

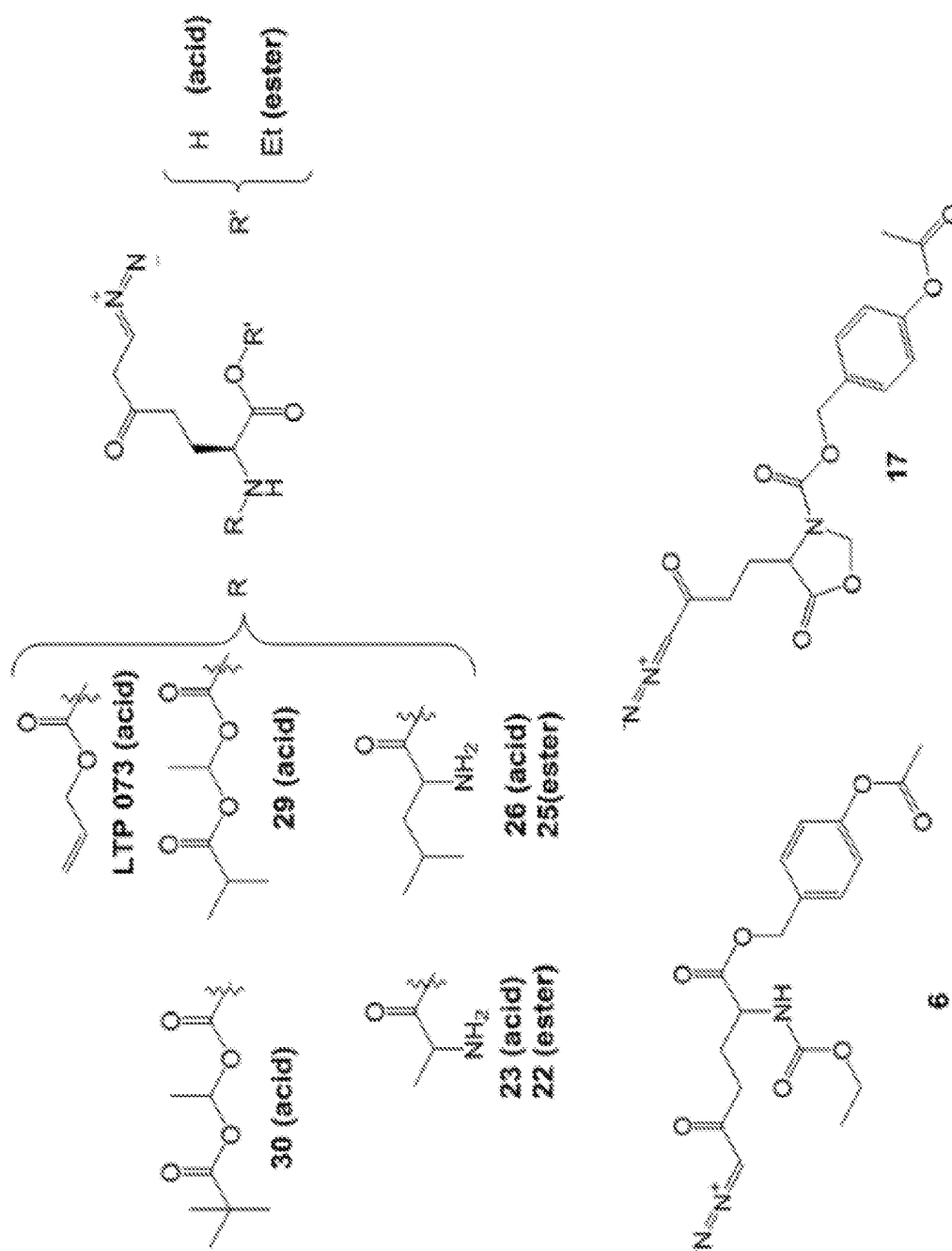
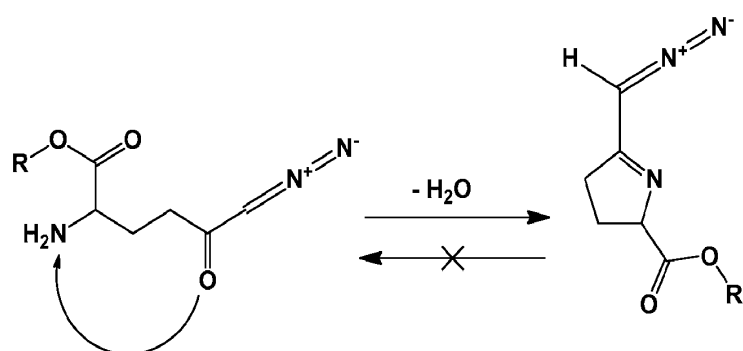
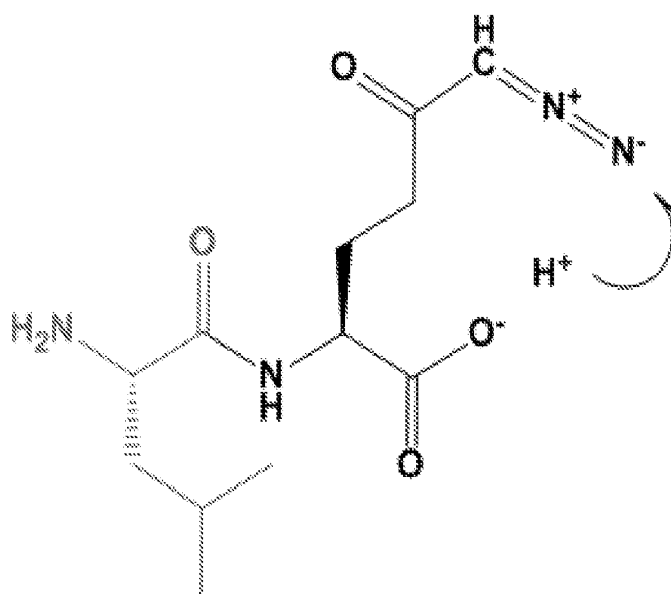
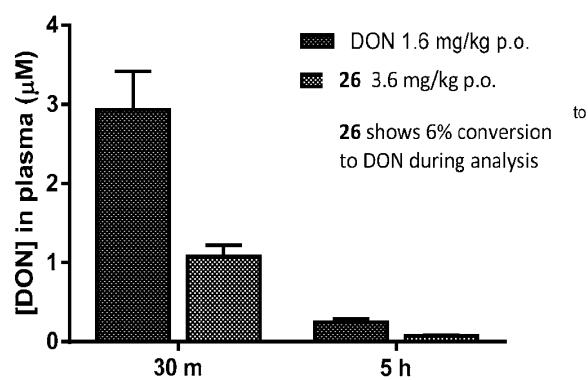
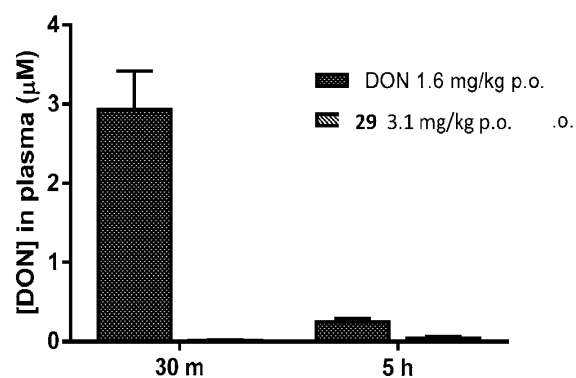


FIG. 1

*FIG. 2A**FIG. 2B*

26 : DON in mouse plasma**FIG. 3A****29 : DON in mouse plasma****FIG. 3B**

23 : DON in mouse plasma

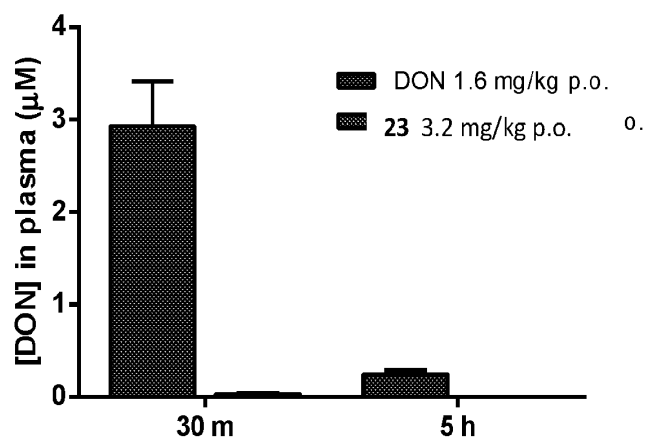


FIG. 3C

30 : DON in mouse plasma

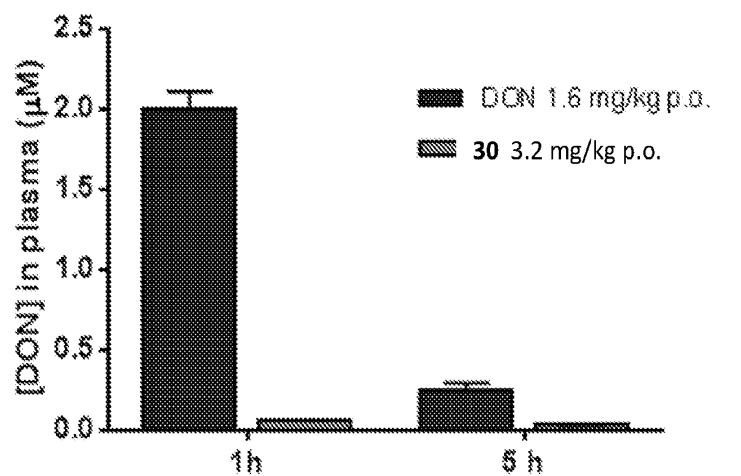
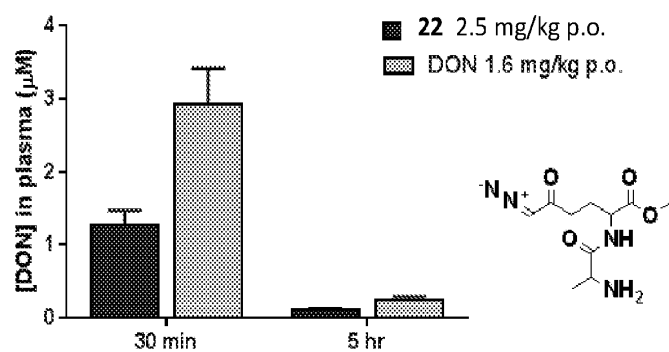


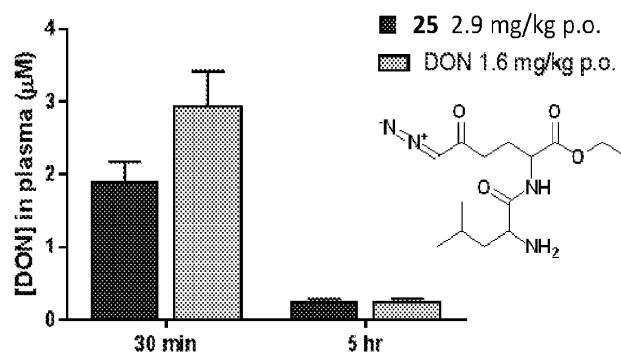
FIG. 3D

5/49



22

0.5 h	5 h
1.3 μM	0.1 μM
43%	45%
percent compared to DON	

FIG. 4A

25

0.5 h	5 h
1.9 μM	0.2 μM
65%	96%
percent compared to DON	

FIG. 4B

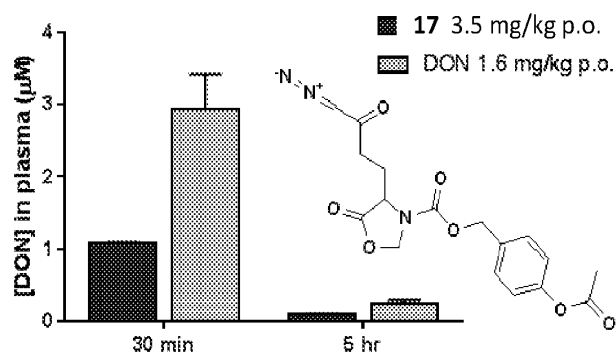


FIG. 4C

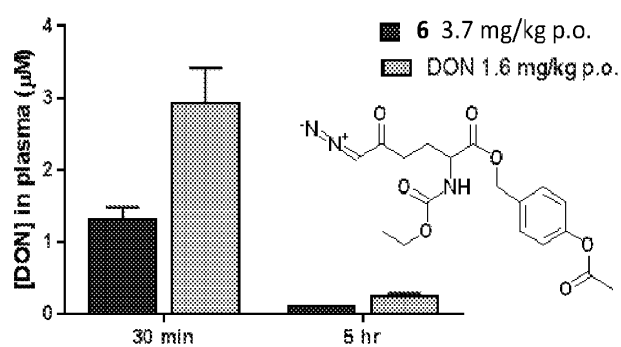
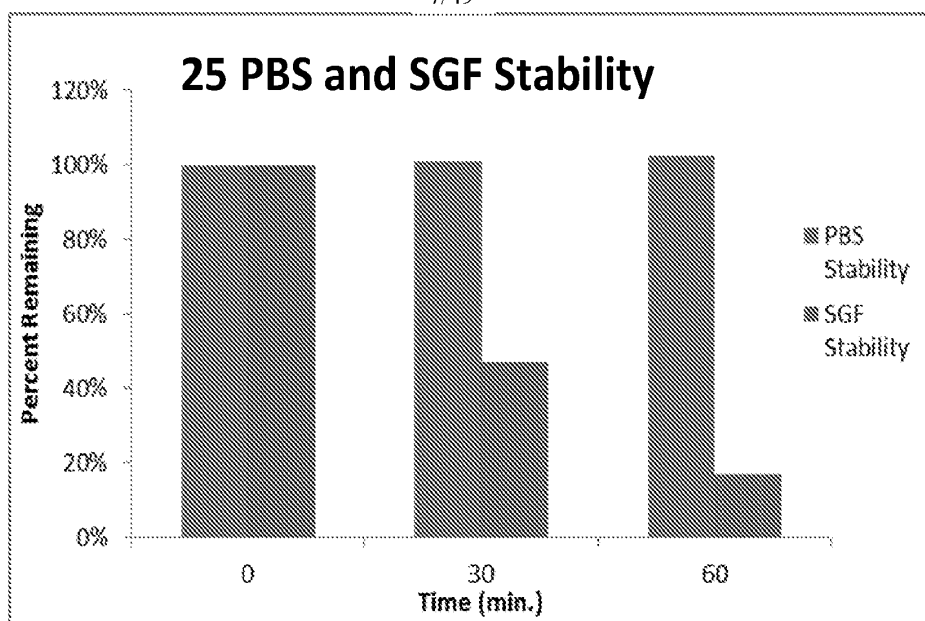


FIG. 4D

7/49

**FIG. 5**

25 Species Plasma Stability

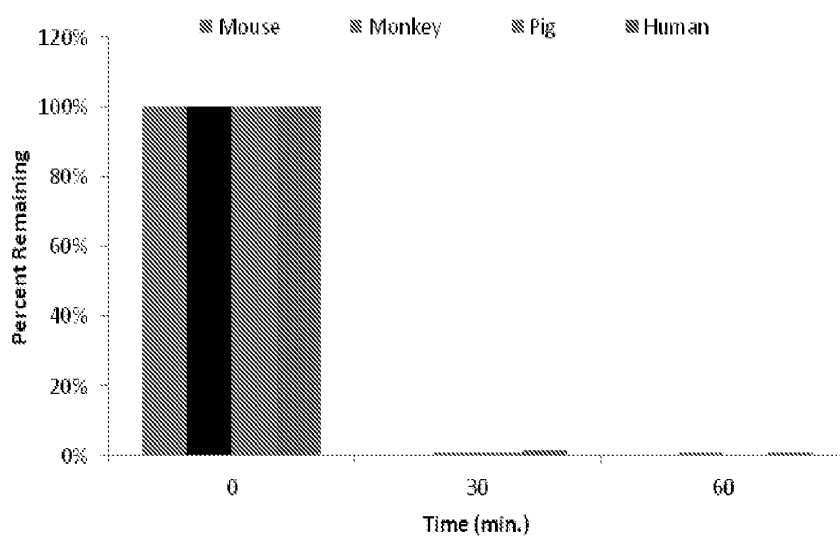
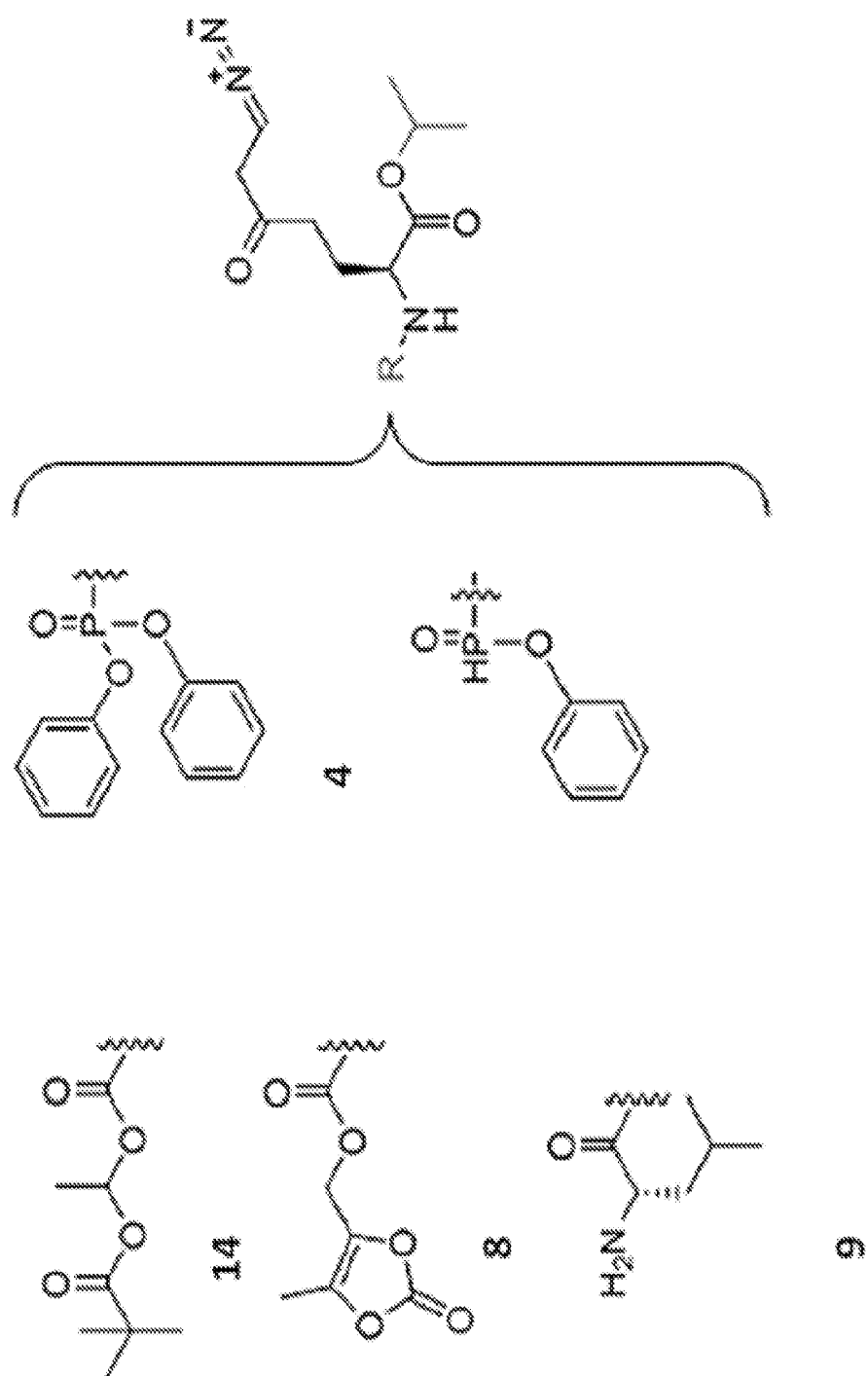
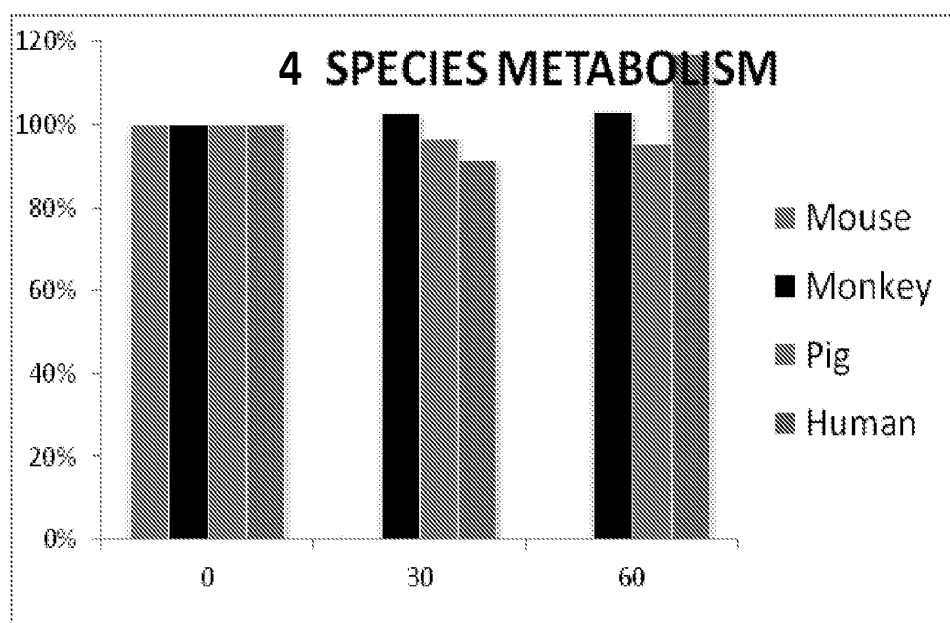
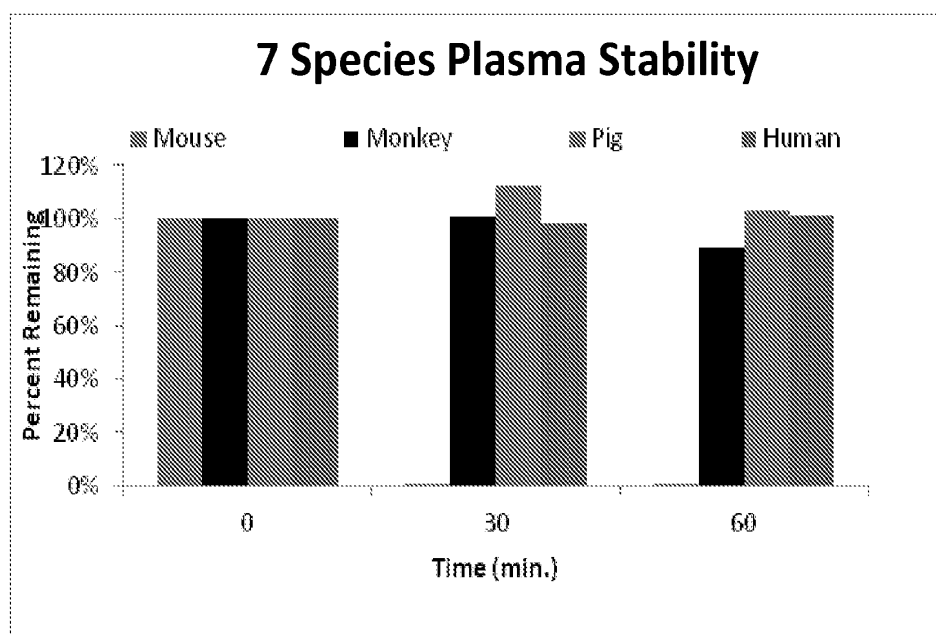


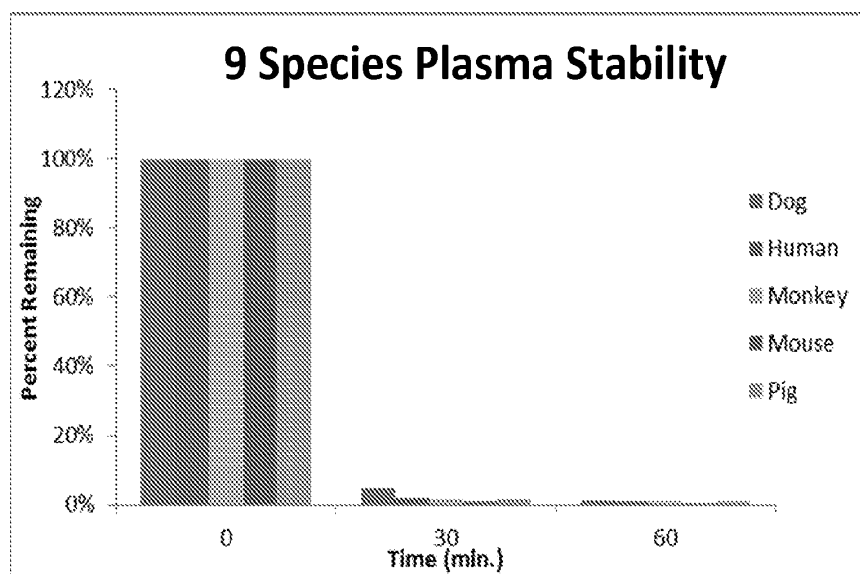
FIG. 6

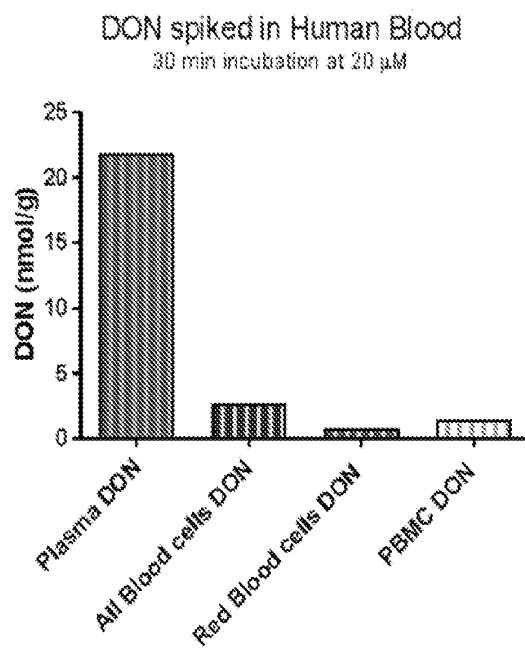
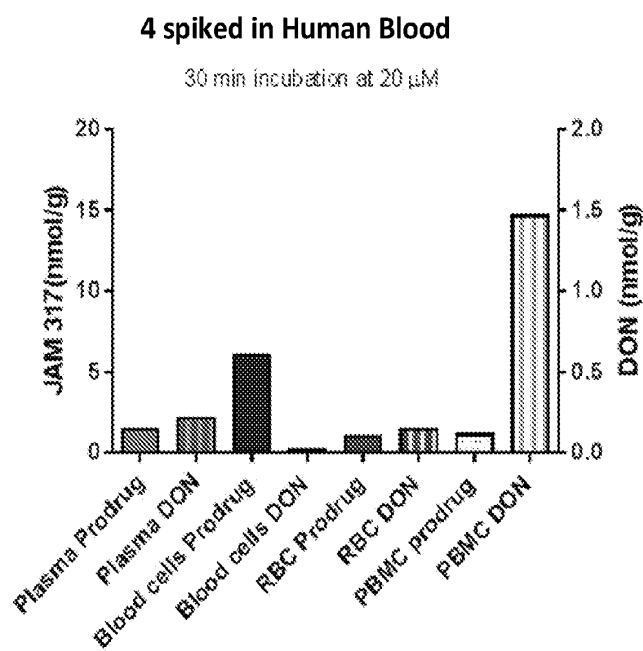
9/49

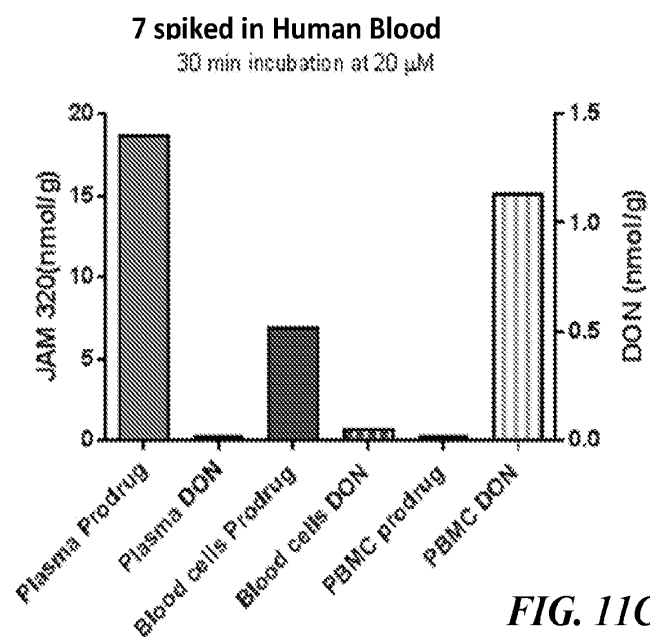
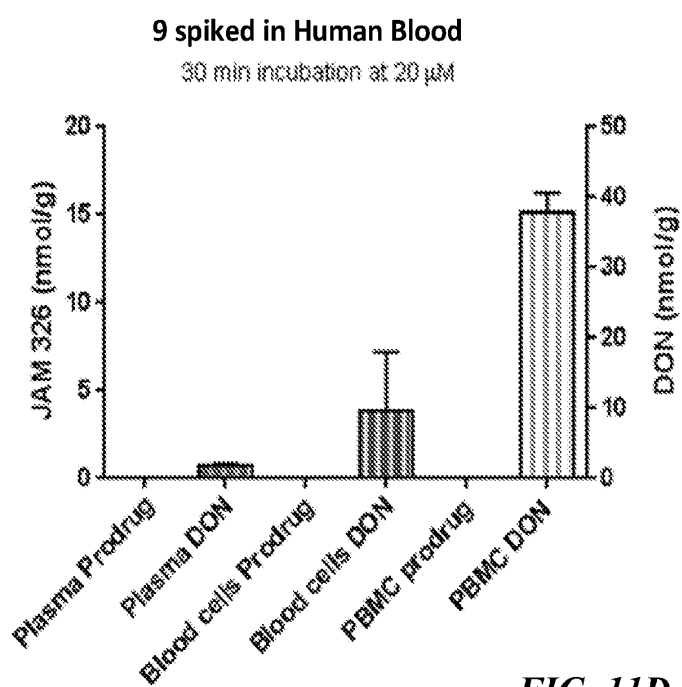
**FIG. 7**

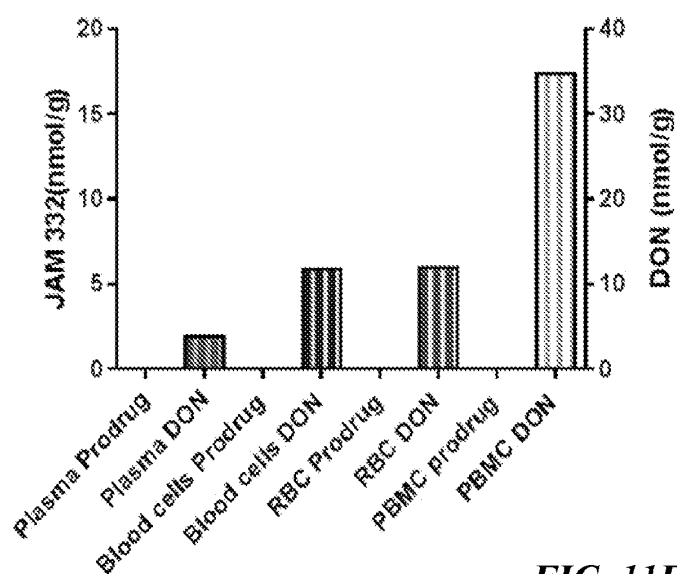
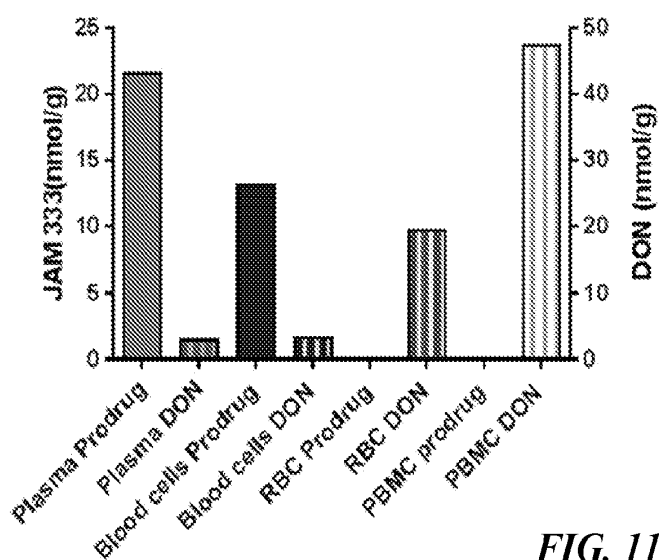
**FIG. 8**

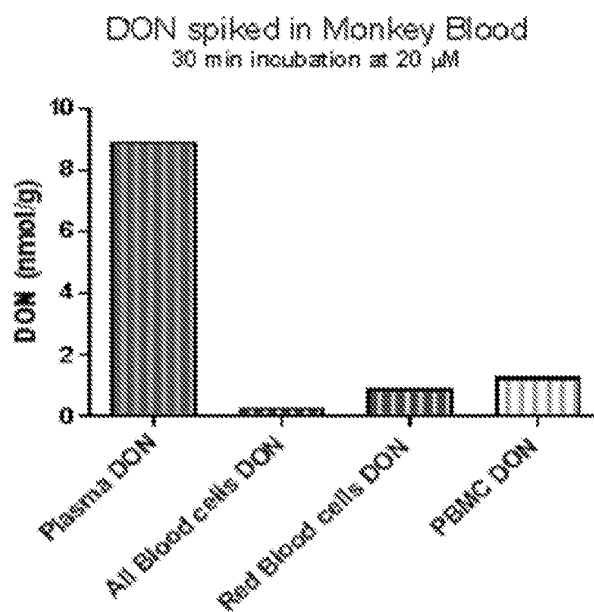
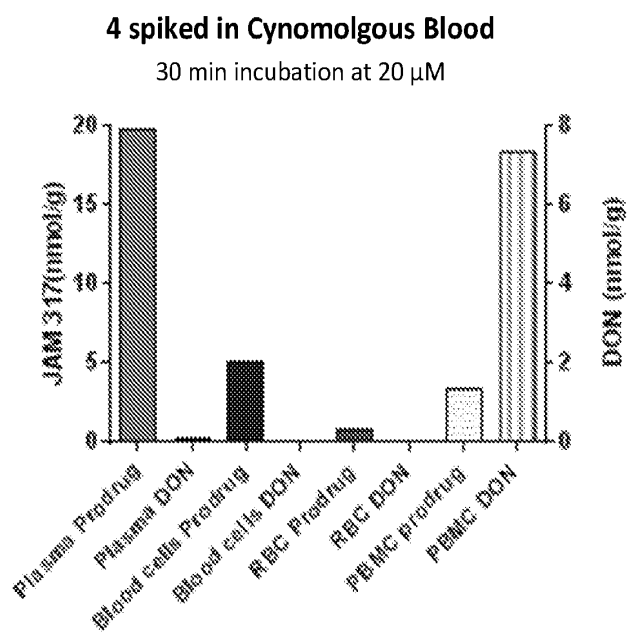
**FIG. 9**

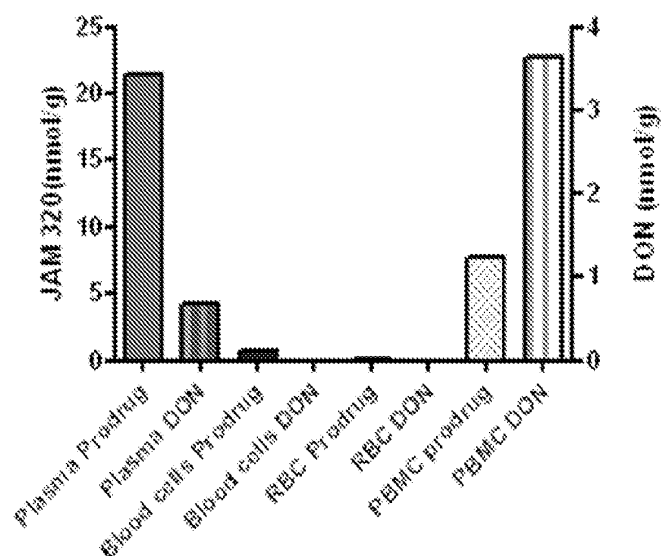
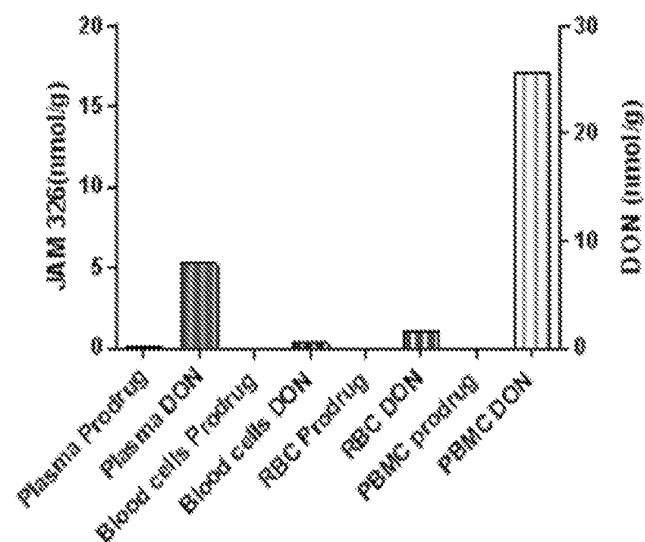
**FIG. 10**

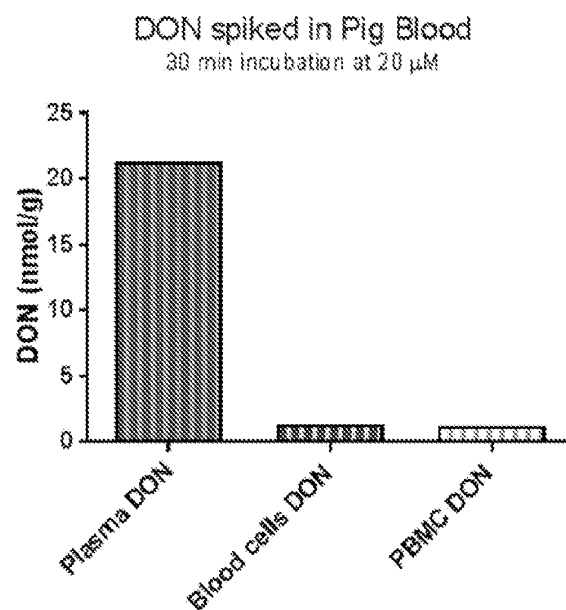
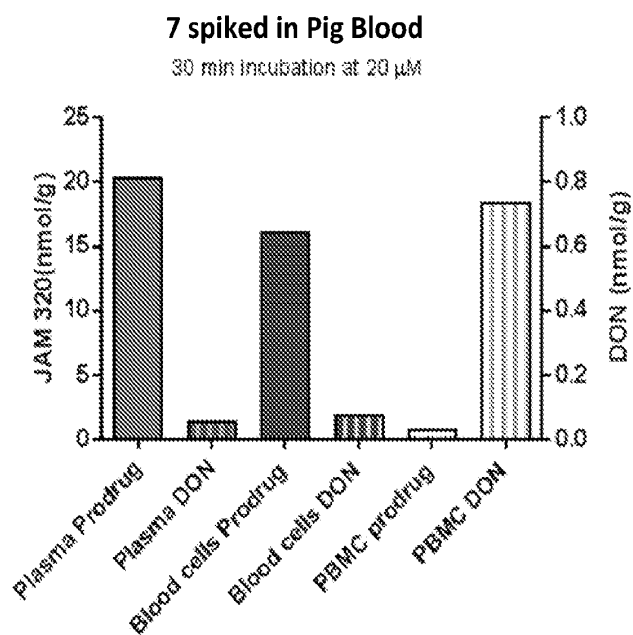
**FIG. 11A****FIG. 11B**

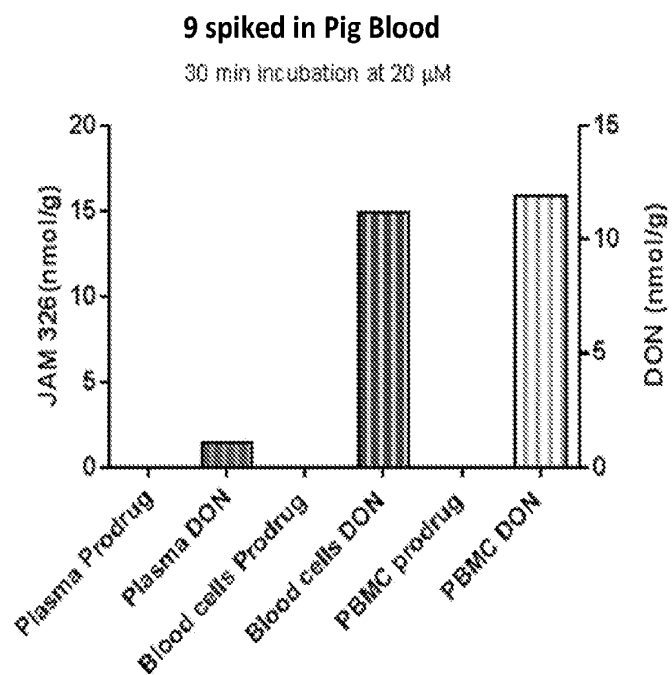
*FIG. 11C**FIG. 11D*

13 spiked in Human Blood30 min incubation at 20 μ M**FIG. 11E****14 spiked in Human Blood**30 min incubation at 20 μ M**FIG. 11F**

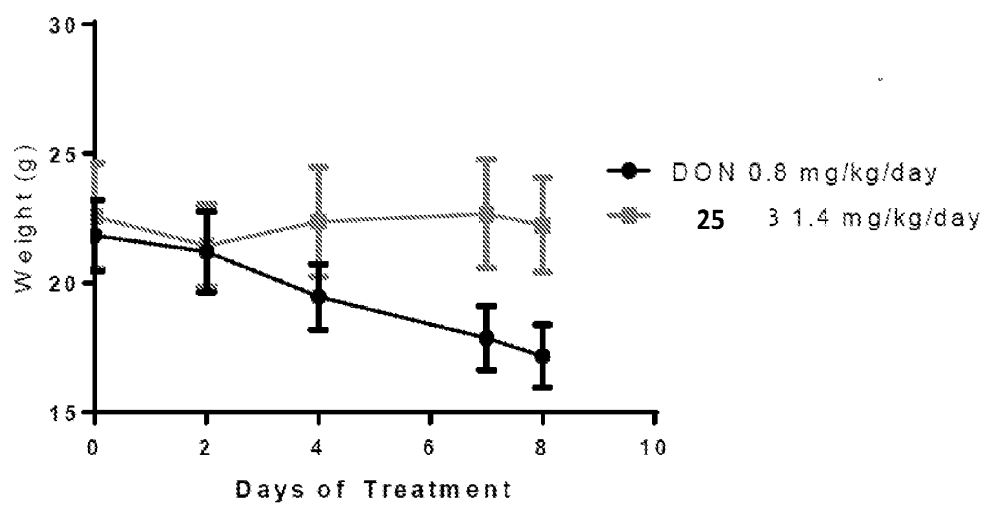
**FIG. 12A****FIG. 12B**

7 spiked in Cynomolgous Blood30 min incubation at 20 μ M**FIG. 12C****9 spiked in Cynomolgous Blood**30 min incubation at 20 μ M**FIG. 12D**

**FIG. 13A****FIG. 13B**

*FIG. 13C*

20/49

*FIG. 14*

	DON	25	Normal Range
WBC	1.06	1.07	4.45-13.96 K/uL
Hgb	11.80	13.87	10.8-19.2 g/dL
Plt	315.67	715.33	841-2159 K/uL

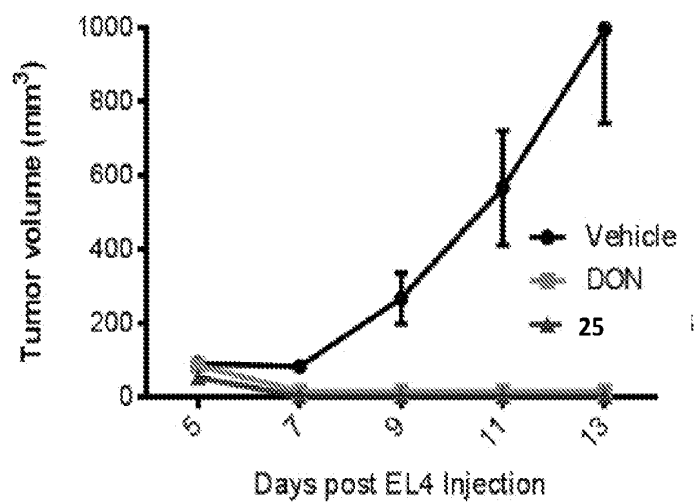
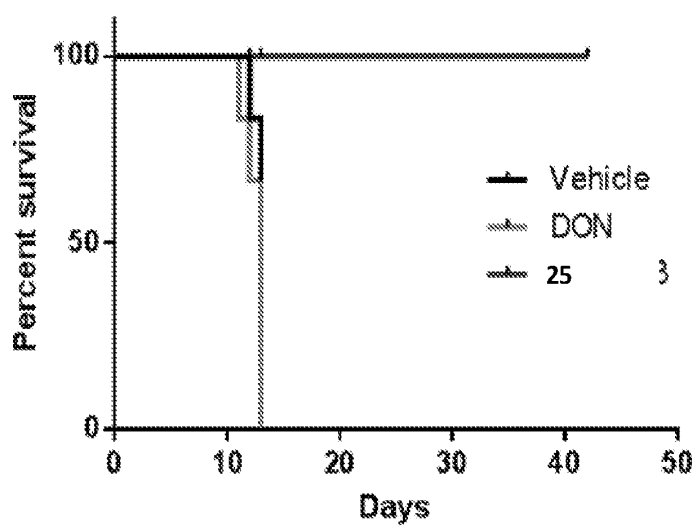
N = 3 mice per group

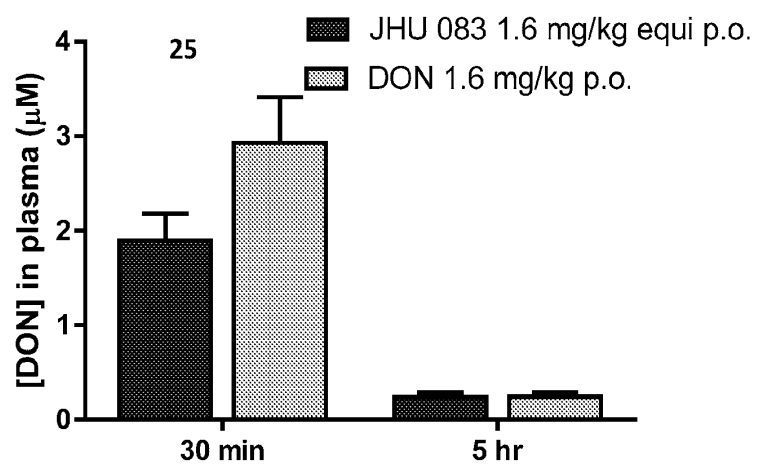
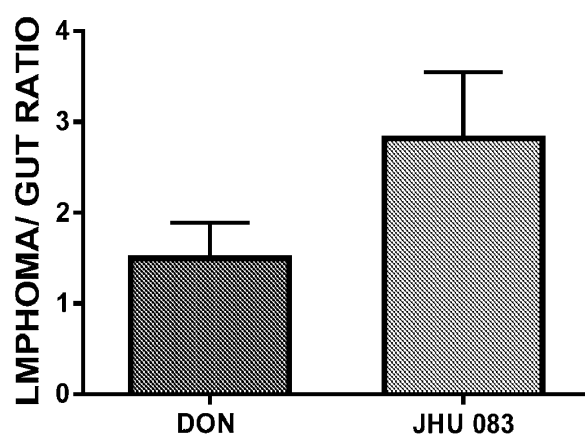
FIG. 15

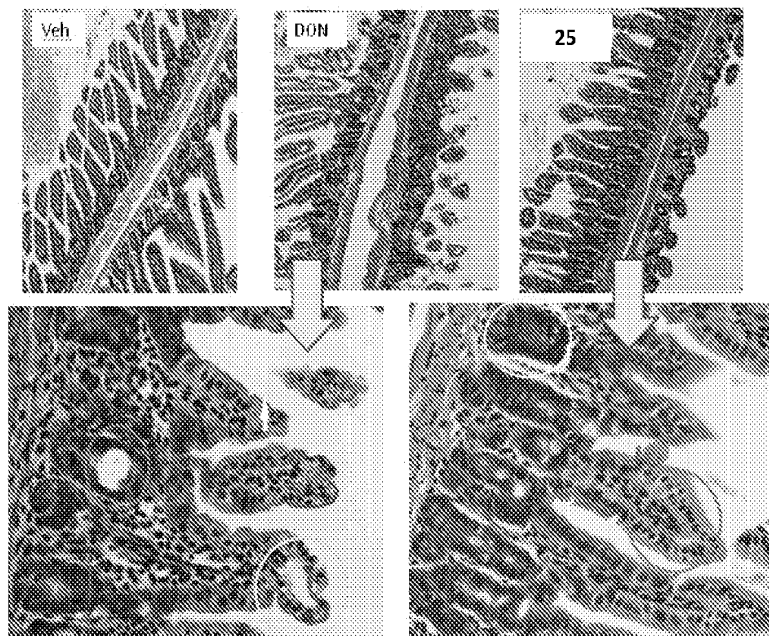
	DON (n=2)	25 (n=3)	Normal Range
AST	158	94	46-392 U/L
ALT	14	22	28-129 U/L
ALP	70	143	111-275 U/L
GGT	7	5	0-8 U/L
Tprot	3.9	4.7	4.8-7.0 g/dL
Albumin	2.3	3.4	2.8-3.8 g/dL
Creatinine	0.30	0.30	0.2-0.5 mg/dL
Calcium	8.6	8.5	9.7-12.5 mg/dL
BUN	26	21	7-28 mg/dL
Tbili	0.7	0.3	0.2-0.6 mg/dL
Glucose	228	391	172-372 mg/dL

FIG. 16

23/49

*FIG. 17A**FIG. 17B*

*FIG. 18A**FIG. 18B*

*FIG. 18C*

	Induction and Maintenance	BID Dosing	Reference
WBC	11.25	11.19	4.45-13.96 K/uL
Hgb	14.73	14.57	10.8-19.2 g/dL
Plt	1567.00	1193.67	841-2159 K/uL

N = 3 mice per group

Induction Maintenance dosing: 1.0 mg daily for 5 days followed by 0.3 mg daily for 9 days
BID Dosing: 0.1 mg PO BID for 14 days

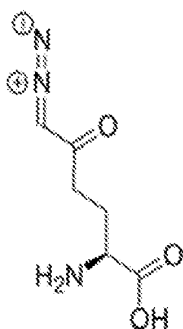
FIG. 19A

	Induction then 0.1 mg/kg/day	Induction then 0.3 mg/kg/day	Reference
WBC	10.16	8.36	4.45-13.96 K/uL
Hgb	13.73	13.90	10.8-19.2 g/dL
Plt	1040.67	1166.00	841-2159 K/uL

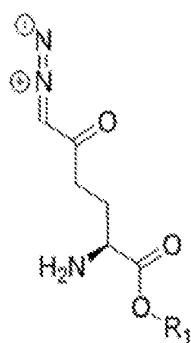
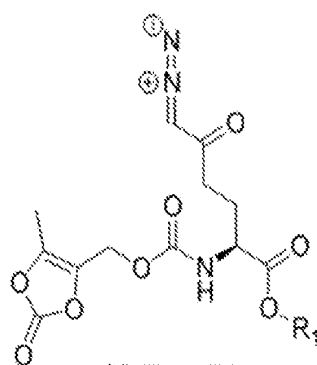
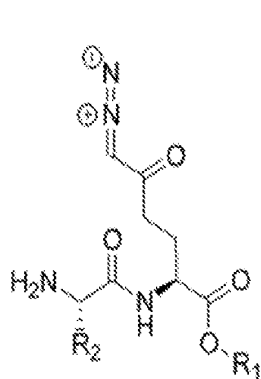
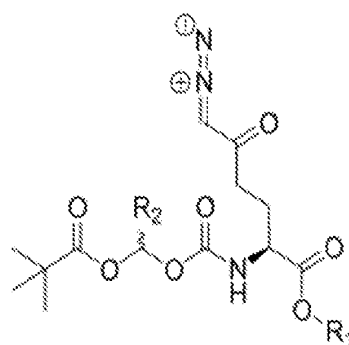
N = 3 mice per group

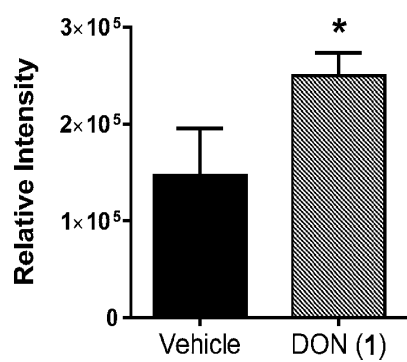
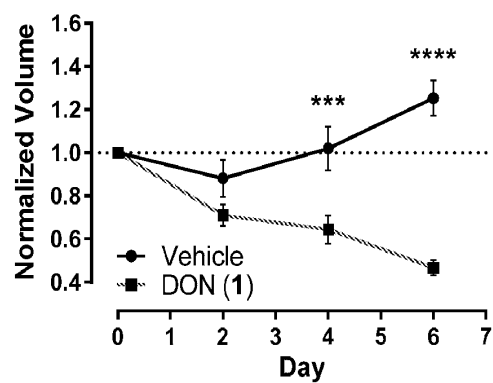
Mice evaluated after 10 days of induction and 38 days of maintenance therapy on JHU-083

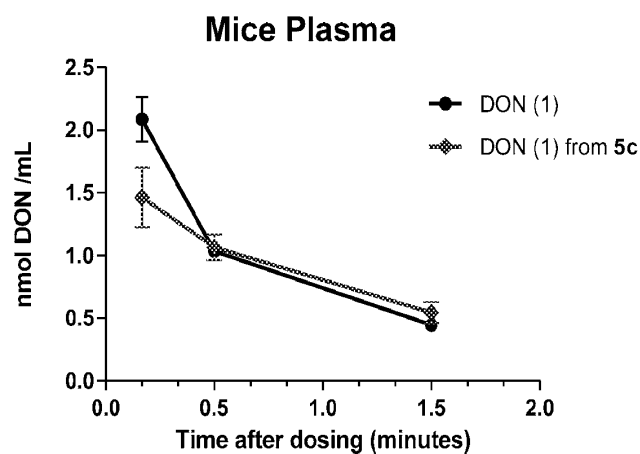
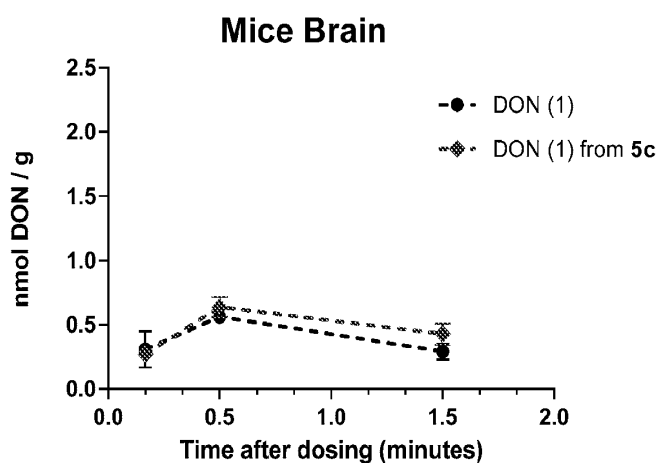
FIG. 19B



1, 6-Diazo-5-oxo-L-norleucine (DON)

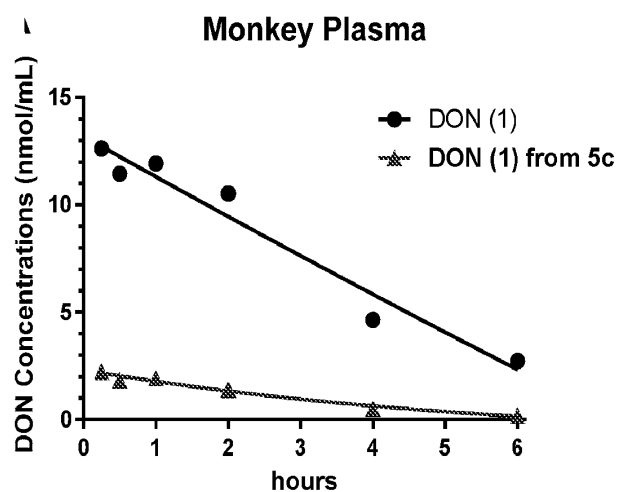
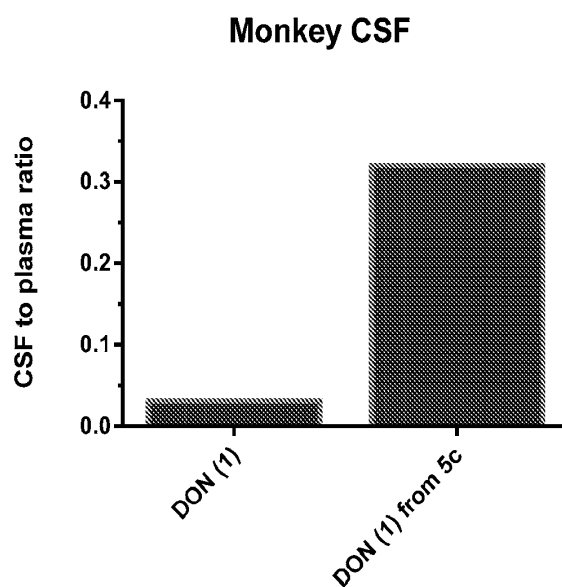
20 (R₁ = Et)
3 (R₁ = iPr)36 (R₁ = Et)
13 (R₁ = iPr)25 (R₁ = Et, R₂ = iBu)
9 (R₁ = iPr, R₂ = iBu)
34 (R₁ = Et, R₂ = -CH₂-3-indolyl)
38 (R₁ = iPr, R₂ = -CH₂-3-indolyl)42 (R₁ = iPr, R₂ = H)
32 (R₁ = Et, R₂ = CH₃)
14 (R₁ = iPr, R₂ = CH₃)**FIG. 20**

*FIG. 21A**FIG. 21B*

**FIG. 22A****FIG. 22B**

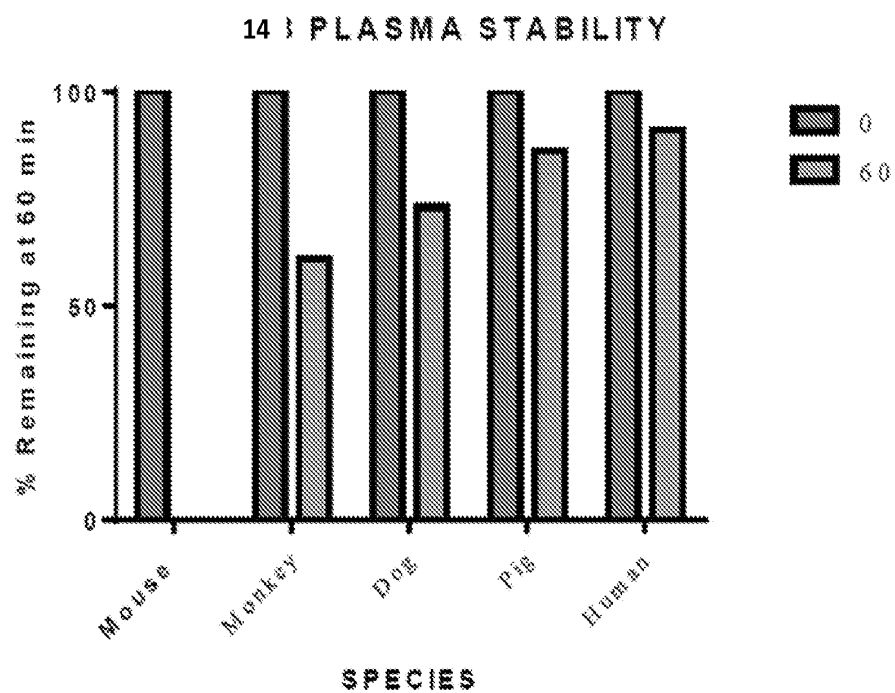
Compound Dosed	Dose (mg/kg equiv)	Tissue	DON C _{max} (ng/mL or nmol/g)	DON T _{max} (hr)	DON AUC _{0-t} (hr*ng/mL or hr*nmol/g)	Brain to plasma ratio
DON (1)	0.8	Plasma	2.2	0.17	1.25	0.46
		Brain	0.56	0.50	0.57	
5c	0.8	Plasma	1.5	1.50	1.22	0.57
		Brain	0.64	30	0.69	

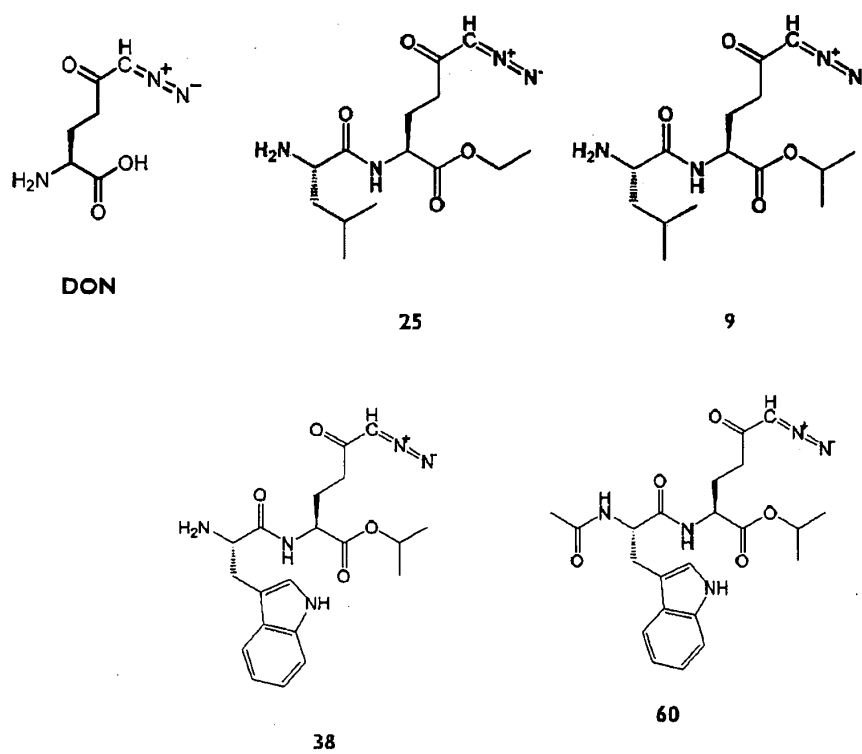
FIG. 22C

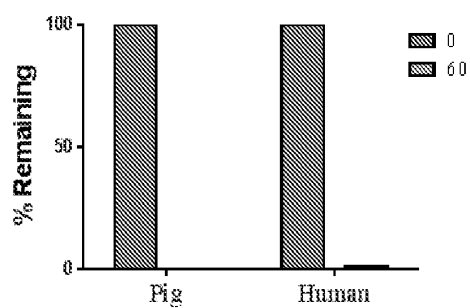
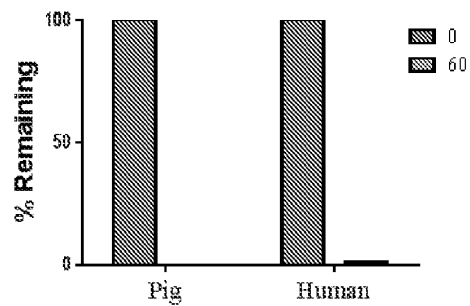
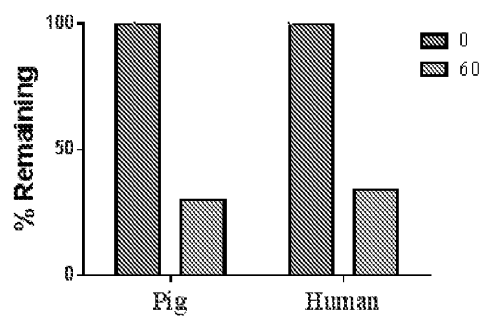
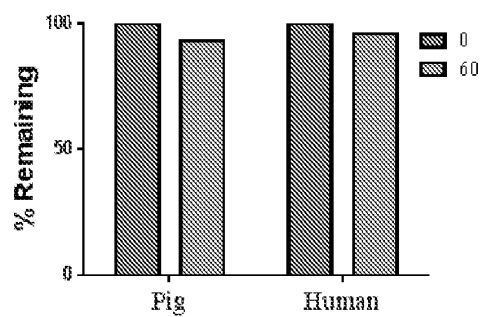
**FIG. 23A****FIG. 23B**

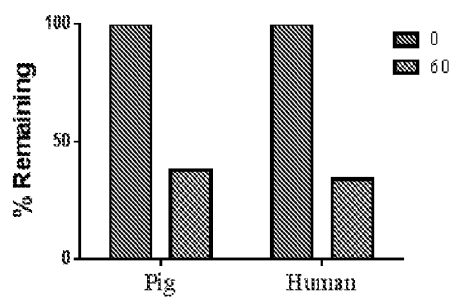
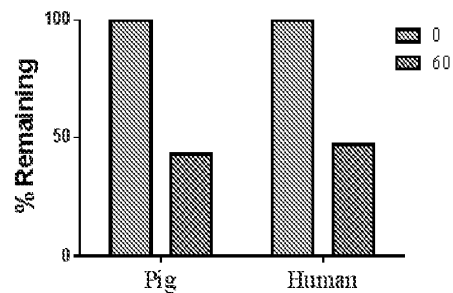
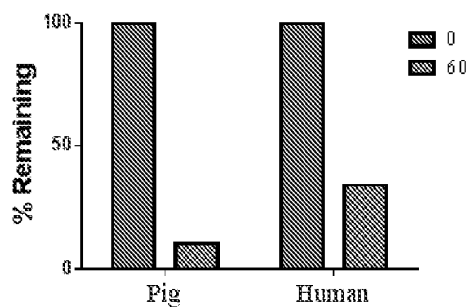
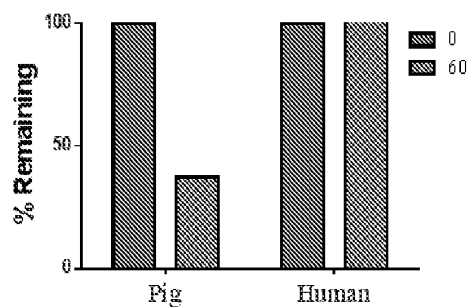
Compound Dosed	Dose (mg/kg qubd)	DON C _{max} (nmol/mL)	DON T _{max} (hr)	DON AUC _{0-t} (hr*nmol/mL)
1	1.6	12.6	0.25	42.7
5c	1.6	2.23	0.25	5.71

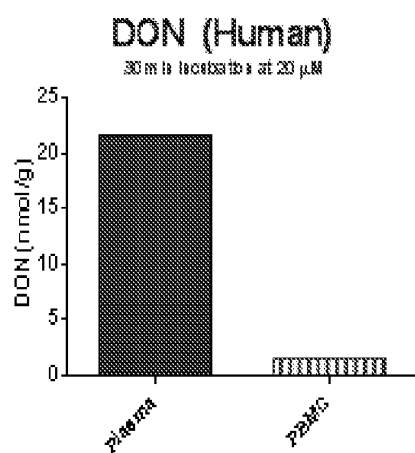
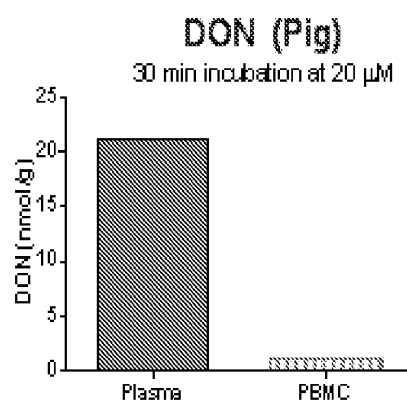
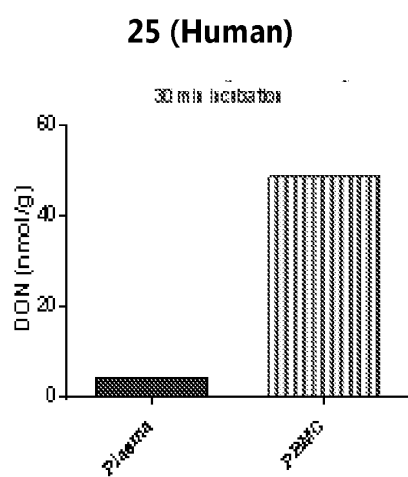
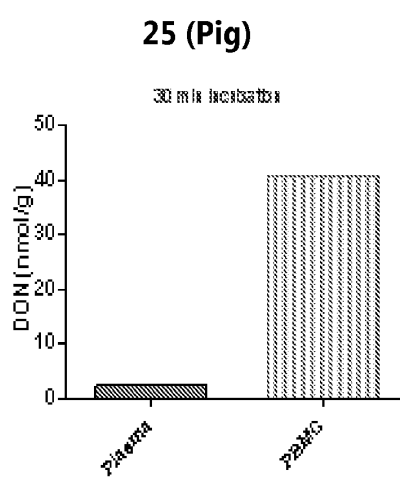
FIG. 23C

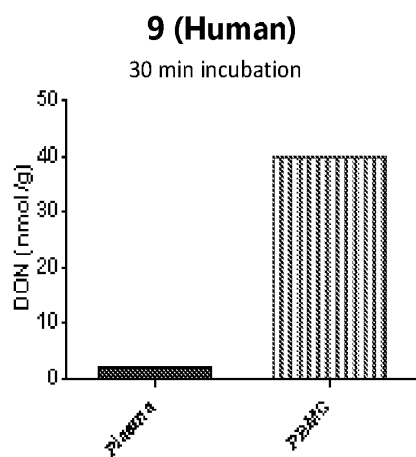
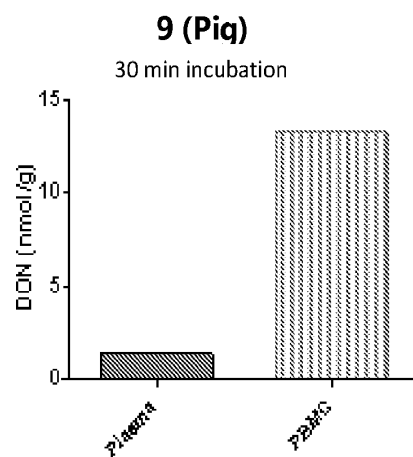
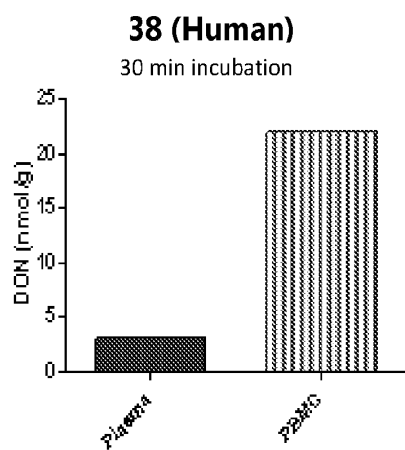
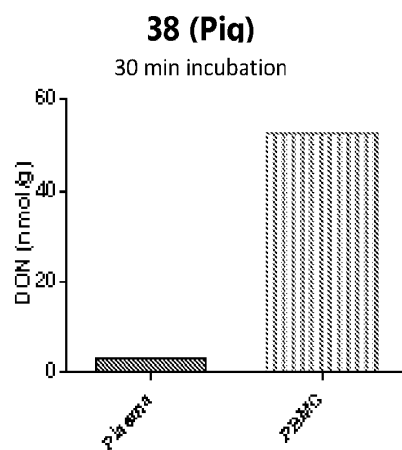
*FIG. 24*

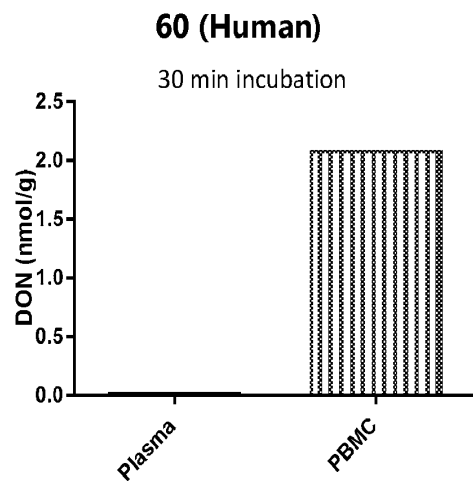
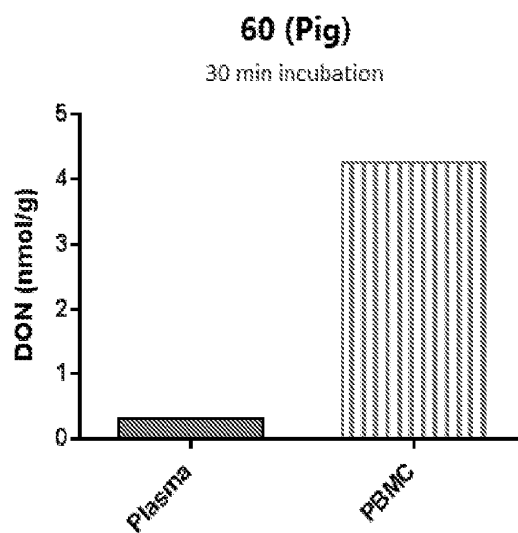
**FIG. 25**

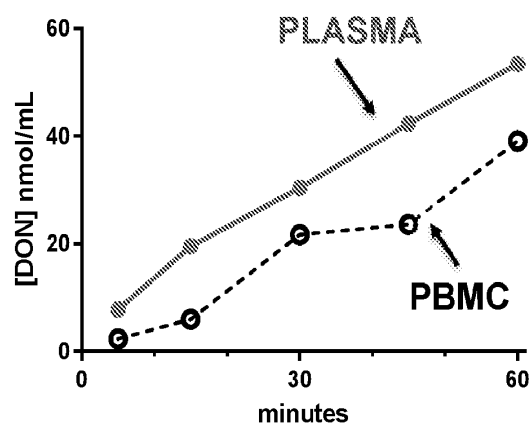
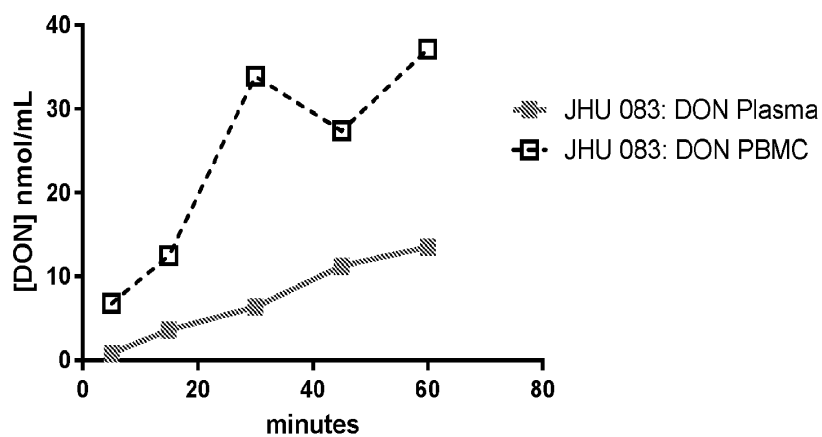
25 3 PLASMA STABILITY**FIG. 26A****9 3 PLASMA STABILITY****FIG. 26B****38 PLASMA STABILITY****FIG. 26C****60 PLASMA STABILITY****FIG. 26D**

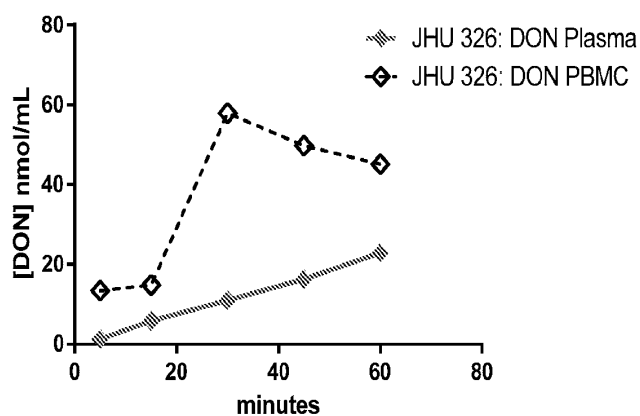
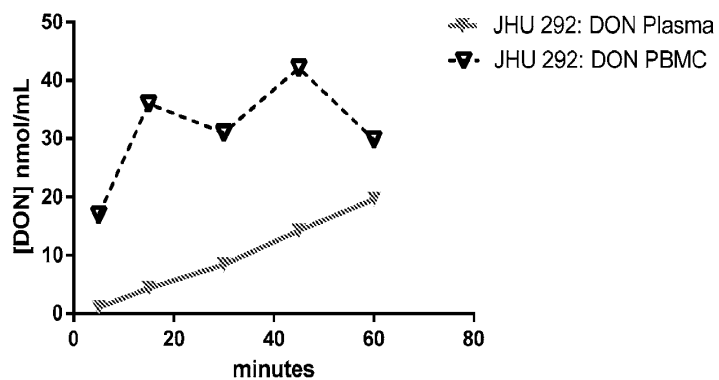
25 MICROSOMAL STABILITY**FIG. 27A****9 MICROSOMAL STABILITY****FIG. 27B****38 MICROSOMAL STABILITY****FIG. 27C****60 MICROSOMAL STABILITY****FIG. 27D**

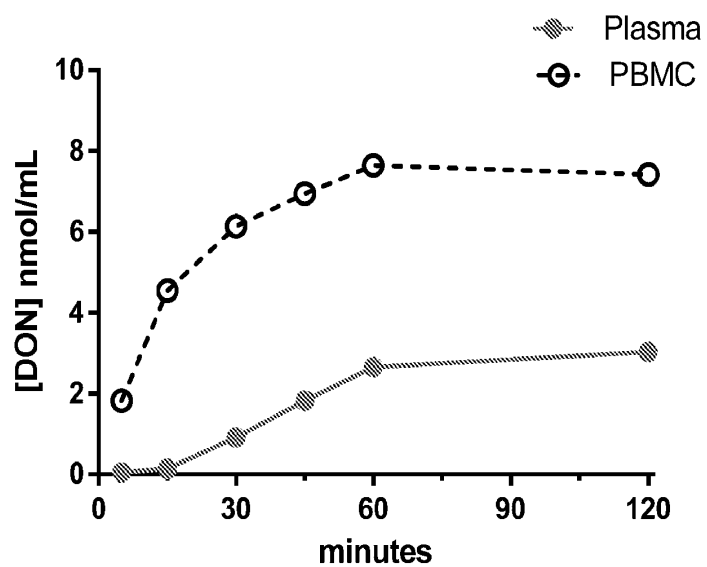
*FIG. 28A**FIG. 28B**FIG. 28C**FIG. 28D*

**FIG. 28E****FIG. 28F****FIG. 28G****FIG. 28H**

*FIG. 28I**FIG. 28J*

DON: 1 hour i.v. infusion**FIG. 29A****25 : 1 hour i.v. infusion****FIG. 29B**

9 : 1 hour i.v. infusion**FIG. 29C****38 : 1 hour i.v. infusion****FIG. 29D**

60 : 1 hour i.v. infusion**FIG. 29E**

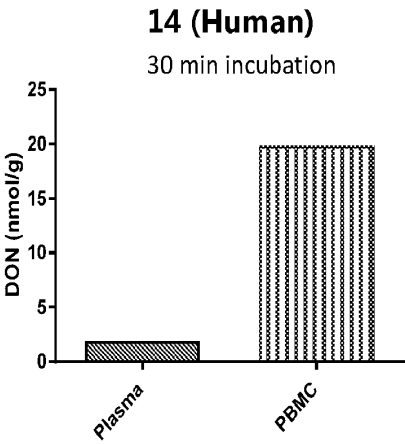


FIG. 30A

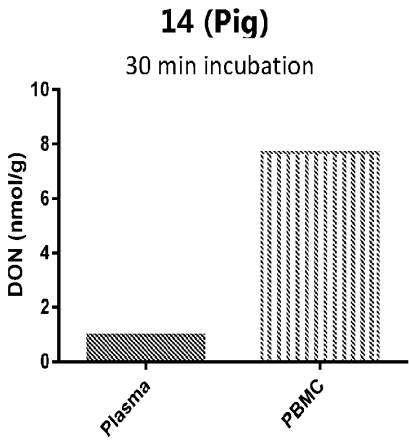
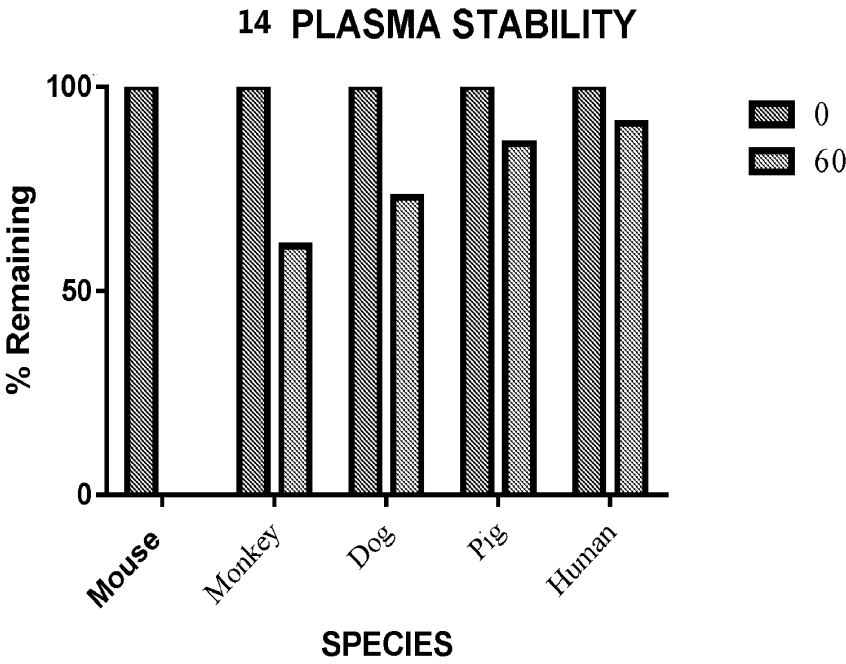
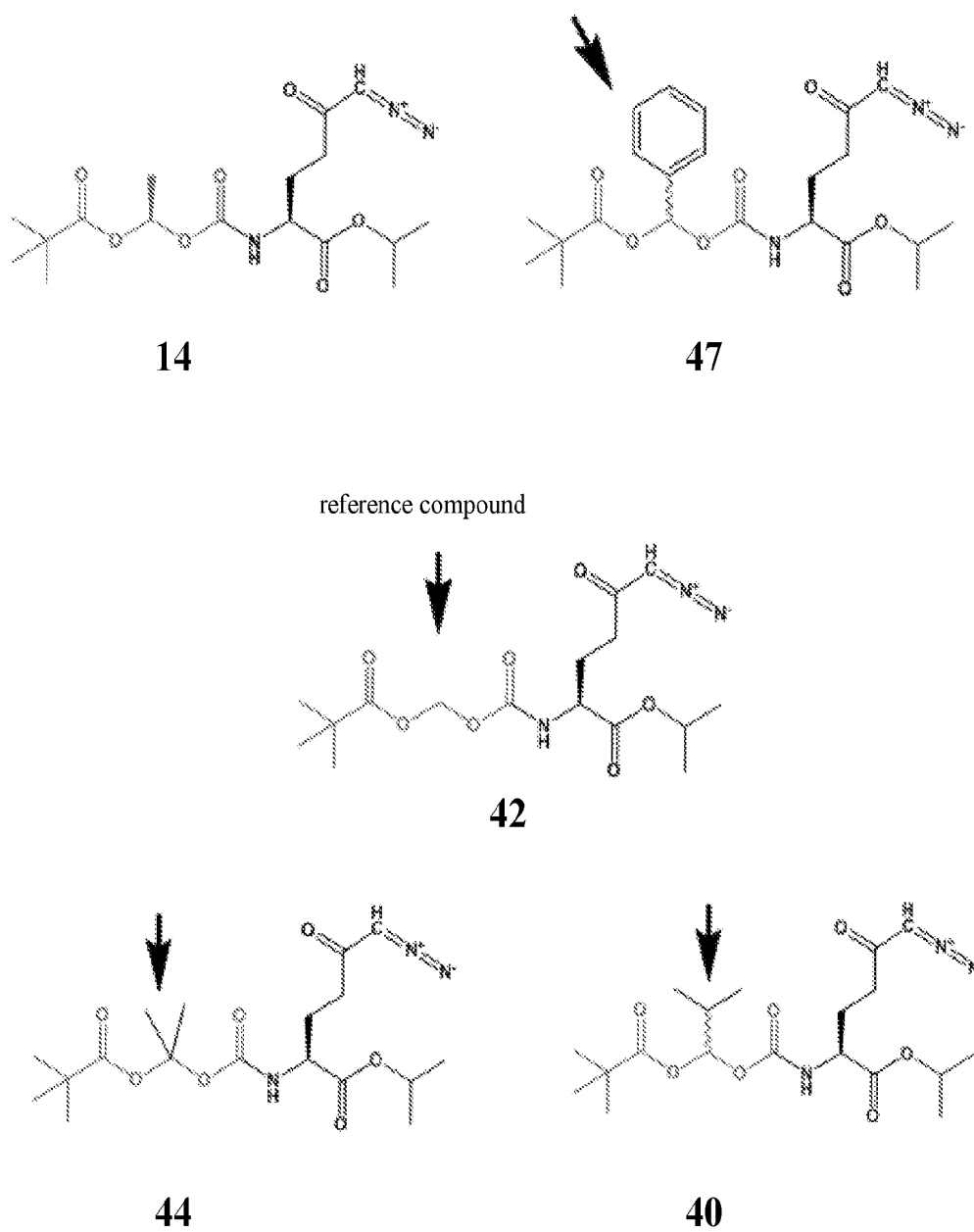


FIG. 30B



SPECIES

FIG. 30C

*FIG. 31*

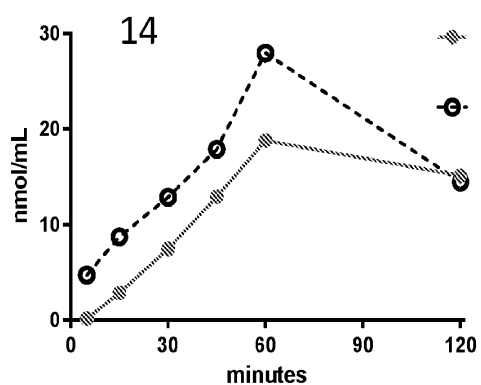


FIG. 32A

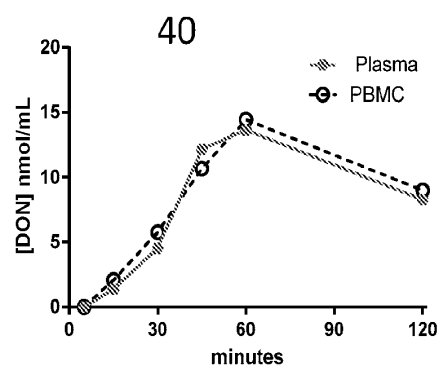


FIG. 32B

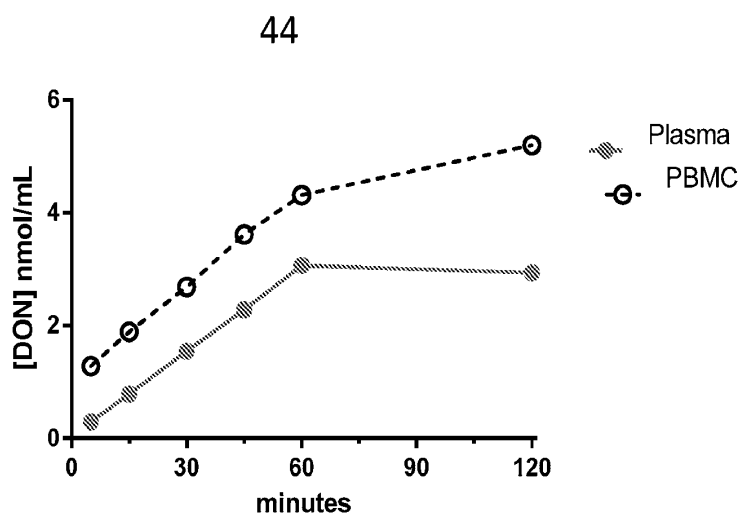


FIG. 32C

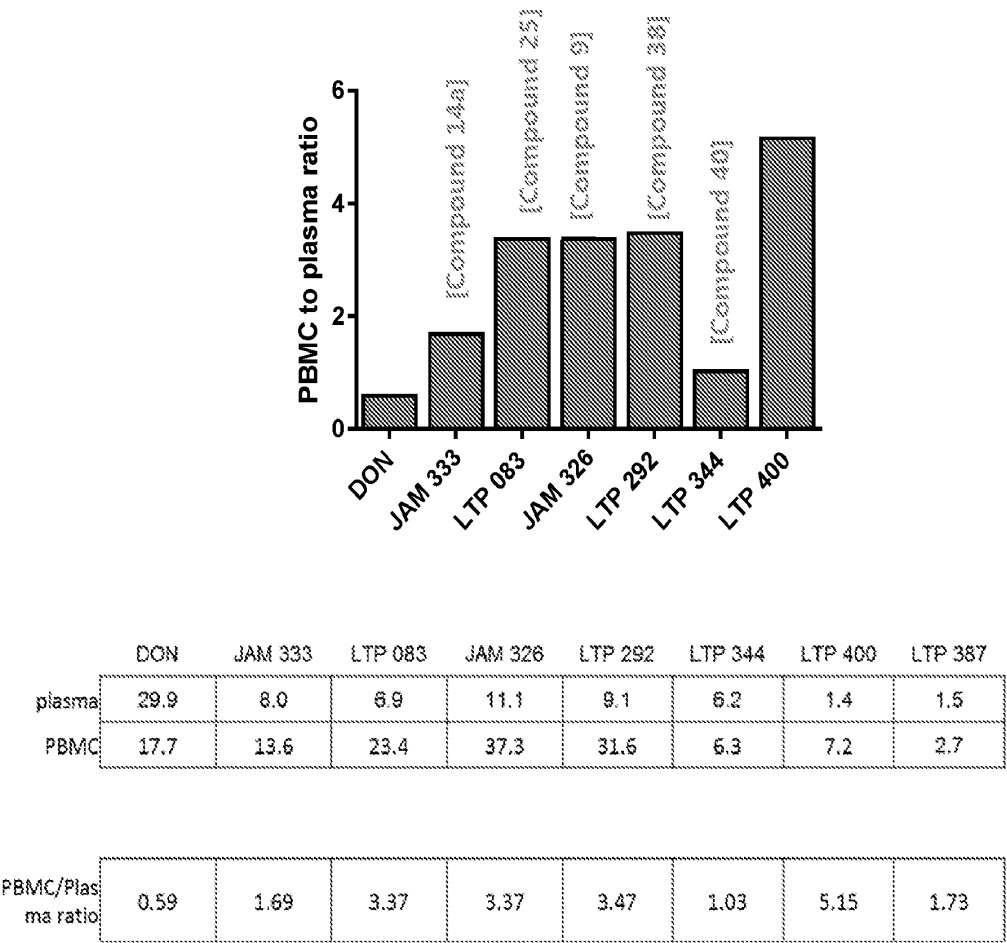


FIG. 33

14

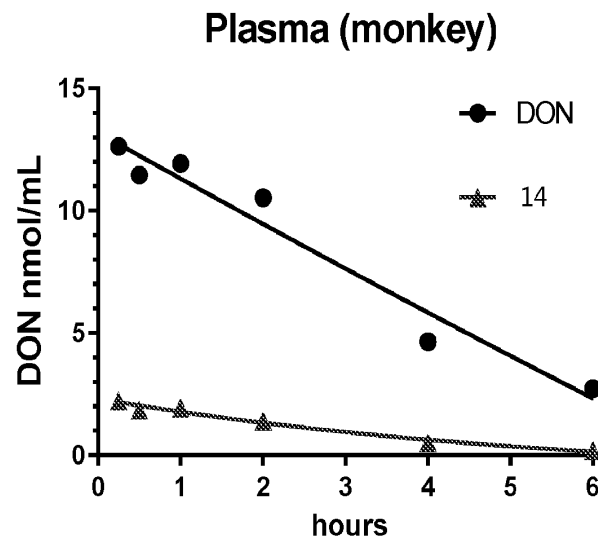


FIG. 34A

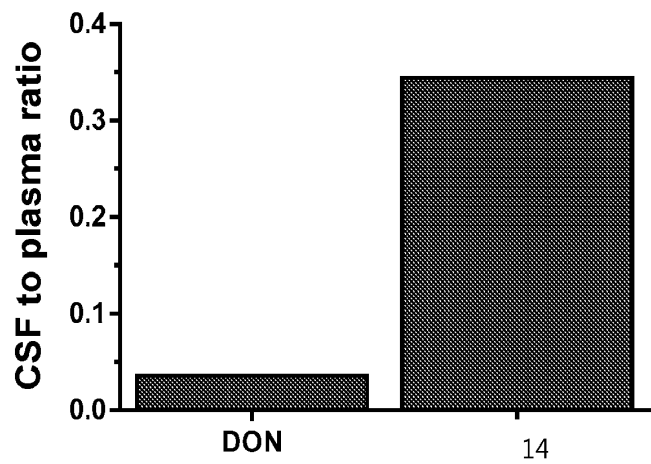
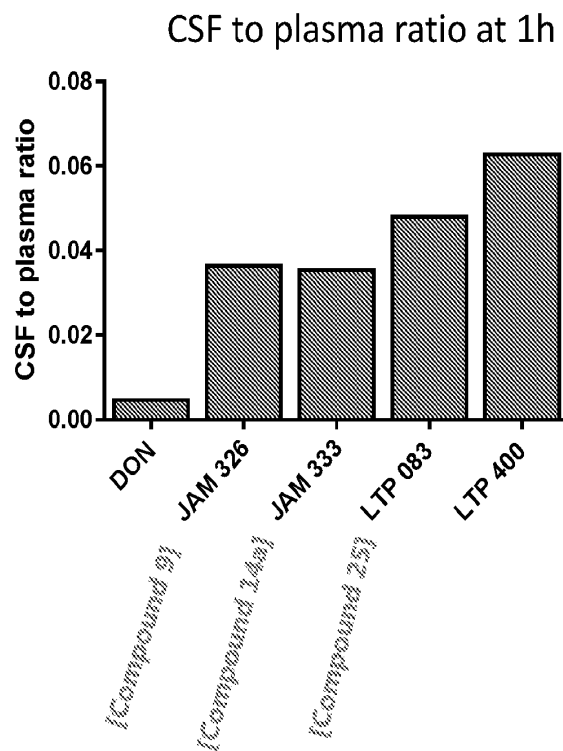


FIG. 34B

- CSF BLQ (<30nM) at 10 and 30 minutes after LTP 400 infusion
- ≈ 170 nM at 1 h (last time-point for CSF)

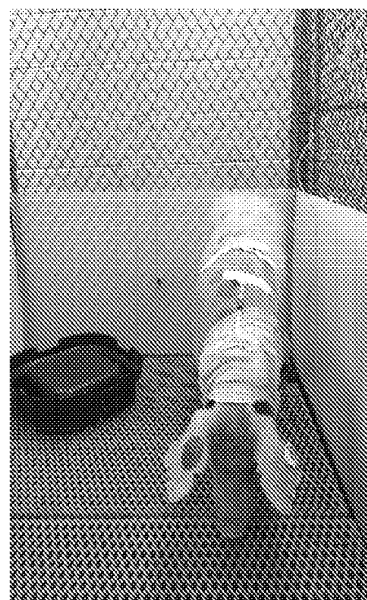
**FIG. 35**

Clinical findings over 5 day observation period

	DON		38	
	Pig 22987	Pig 23302	Pig 23172	Pig 23199
Day 1	WNL	WNL	WNL	WNL
Day 2	WNL	WNL	WNL	WNL
Day 3	WNL	WNL	WNL	WNL
Day 4	anorexia lethargy	anorexia, lethargy, no bowel movement	reduced appetite	WNL
Day 5	anorexia, lethargy, mild diarrhea	anorexia, no bowel movement	WNL	reduced appetite

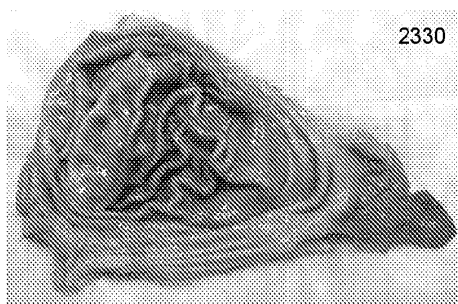
WNL (within normal limits)

Anorexia = no food consumption

**DON TREATED PIG
#22987****FIG. 36**

- blue ears and snout
- lowered head
- reduced activity in the cage
- reduced social interaction
- diarrhea

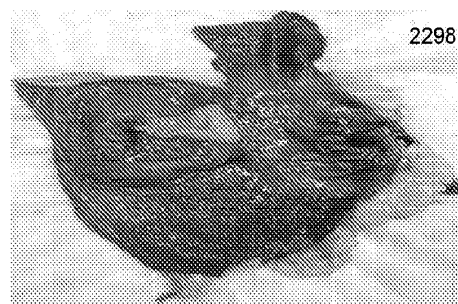
DON



moderate localized

FIG. 37A

DON

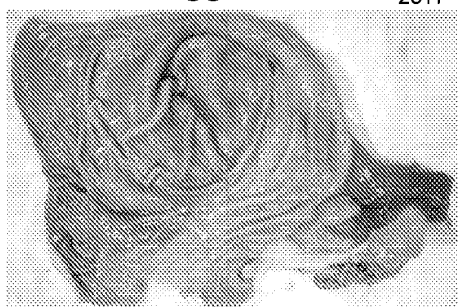


severe generalized

FIG. 37B

38

2317



normal appearing gastric

FIG. 37C

38

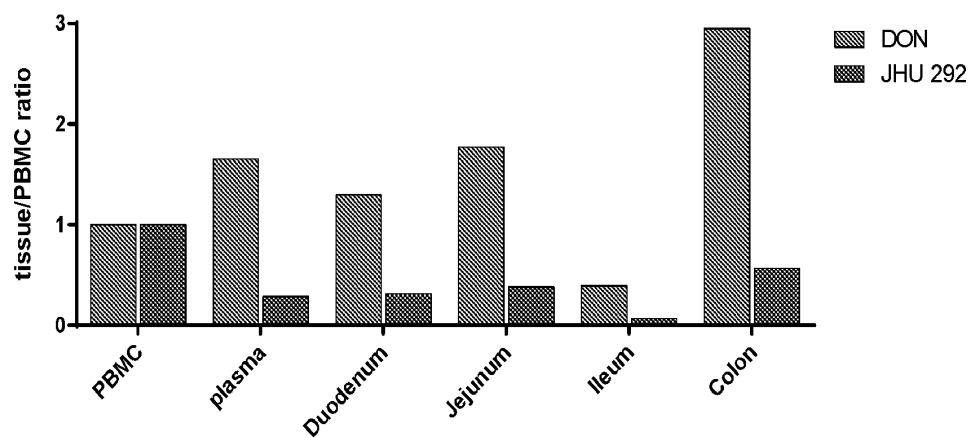
2319



normal appearing gastric

FIG. 37D

49/49

*FIG. 38*