

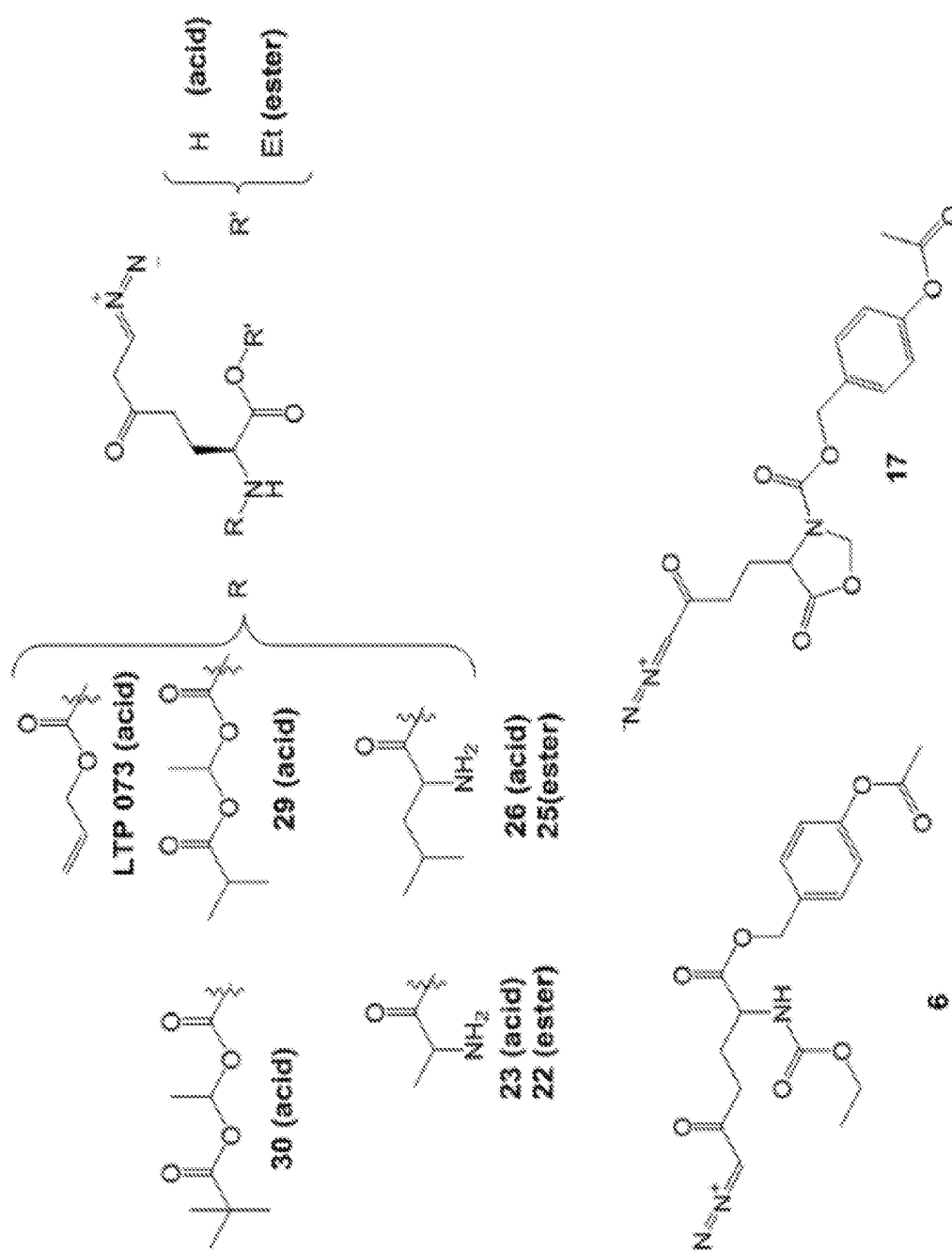
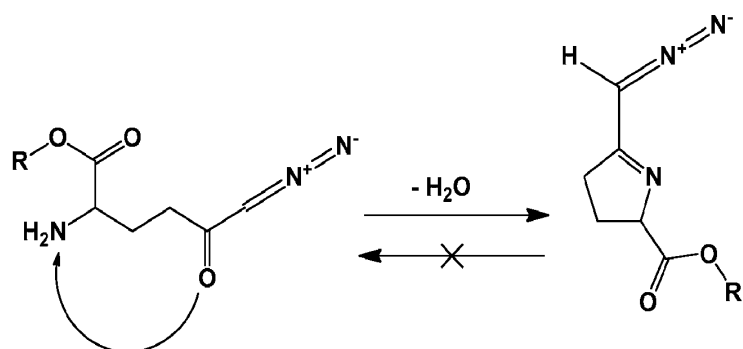
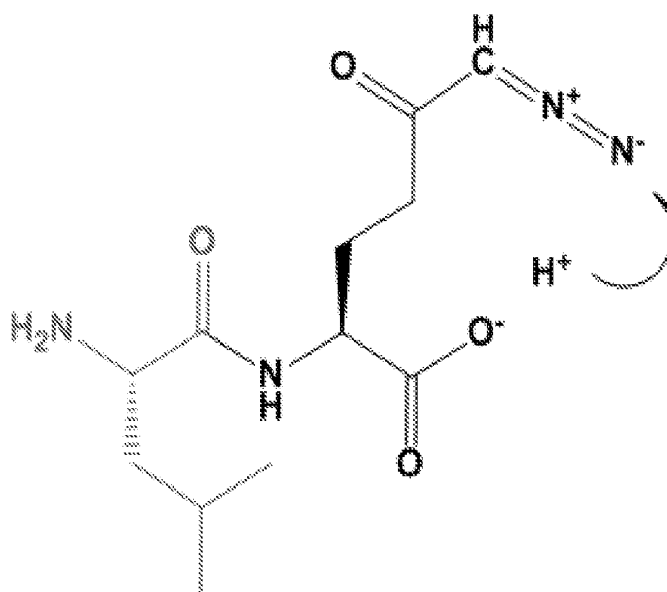
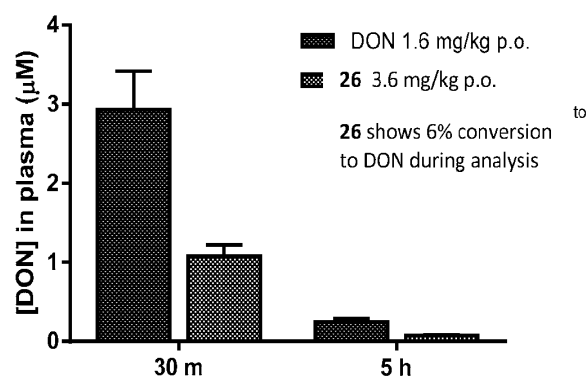
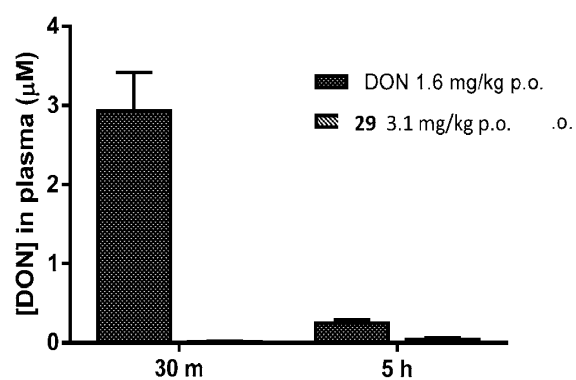
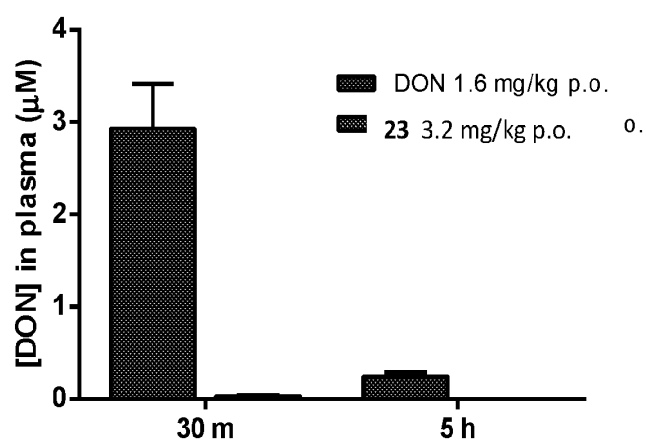


FIG. 1

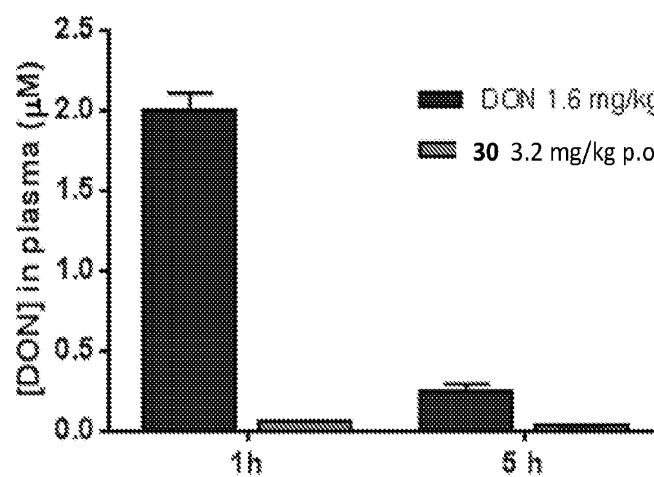
*FIG. 2A**FIG. 2B*

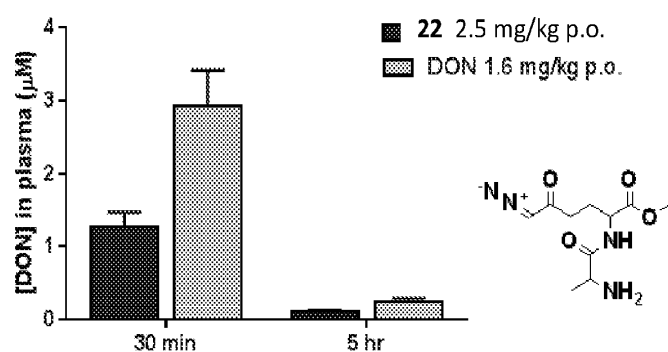
26 : DON in mouse plasma**FIG. 3A****29 : DON in mouse plasma****FIG. 3B**

23 : DON in mouse plasma

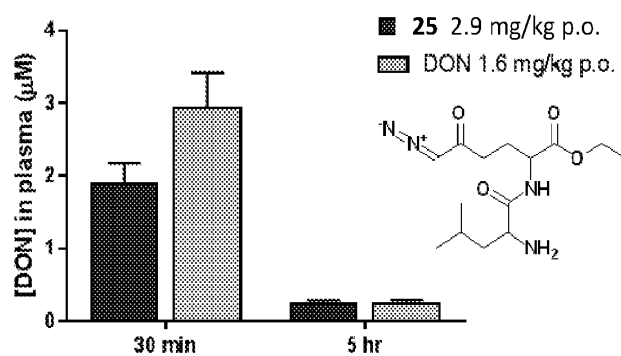
*FIG. 3C*

30 : DON in mouse plasma

*FIG. 3D*

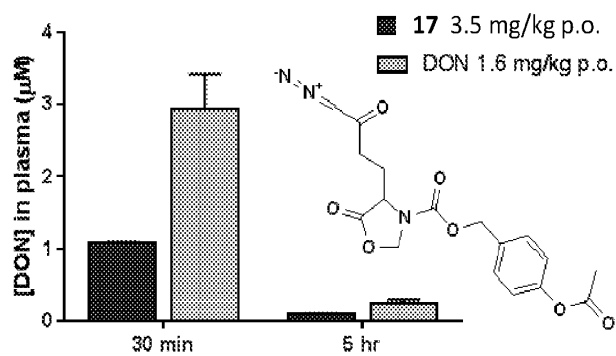


22	0.5 h	5 h	percent compared to DON
	1.3 μM	0.1 μM	
	43%	45%	

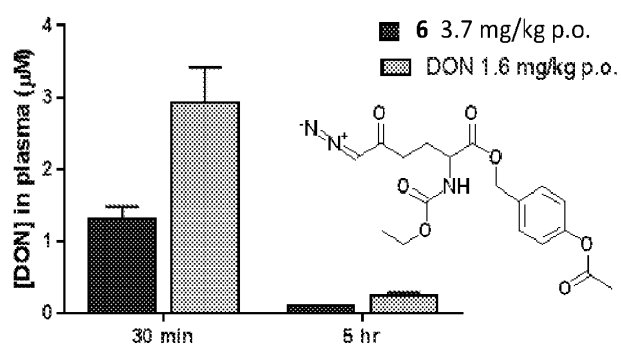
FIG. 4A

25	0.5 h	5 h	percent compared to DON
	1.9 μM	0.2 μM	
	65%	96%	

FIG. 4B

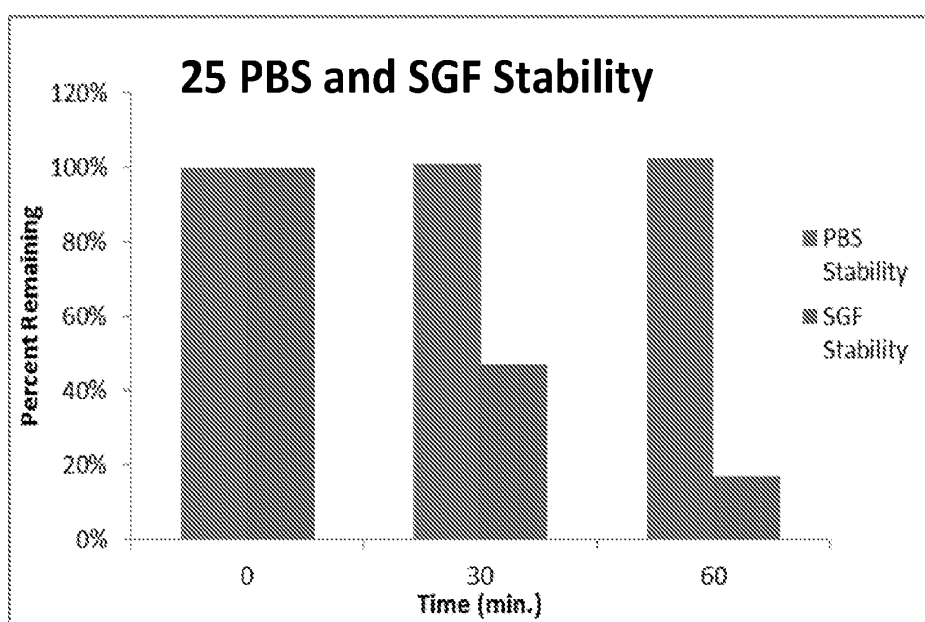


17	0.5 h	5 h	
	1.1 μM	0.1 μM	
	37%	42%	percent compared to DON

FIG. 4C

6	0.5 h	5 h	
	1.3 μM	0.1 μM	
	45%	42%	percent compared to DON

FIG. 4D

*FIG. 5*

25 Species Plasma Stability

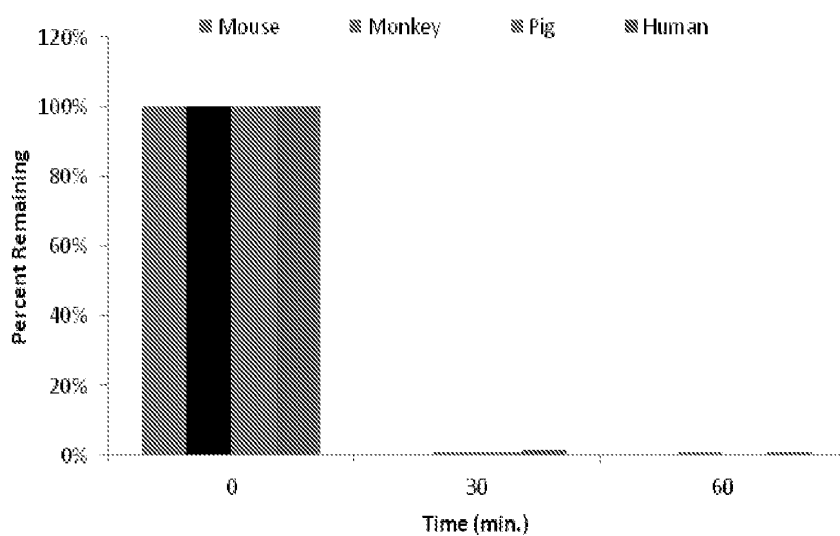
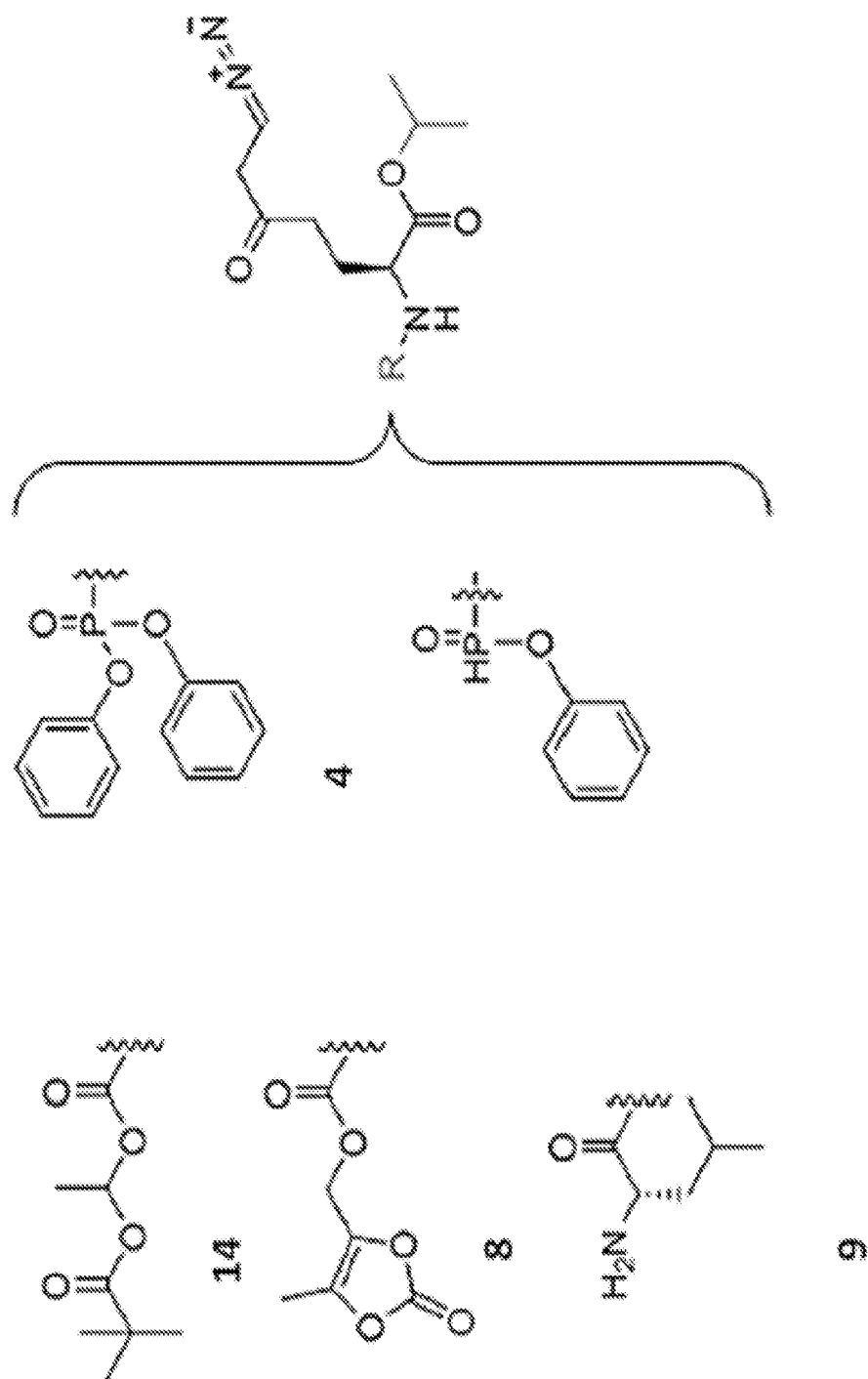
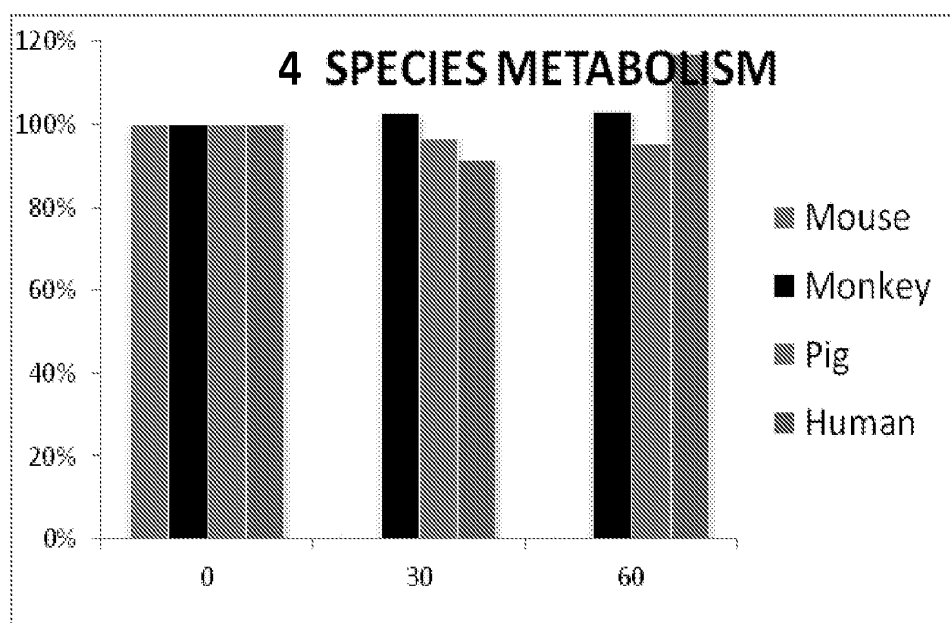
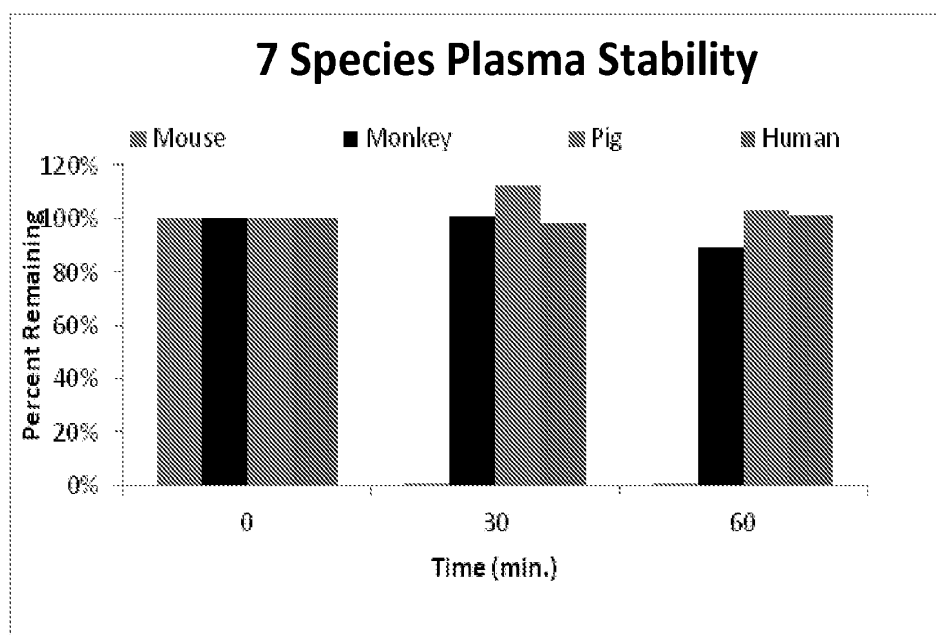
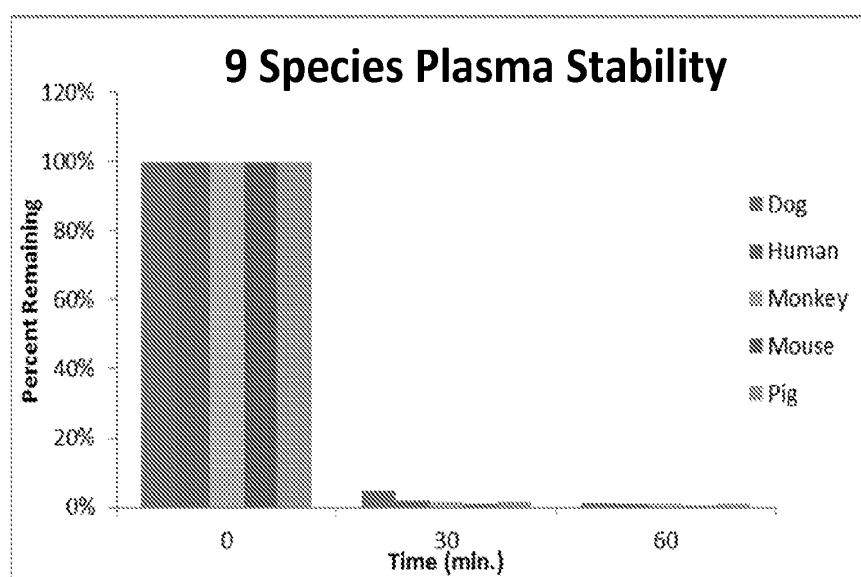


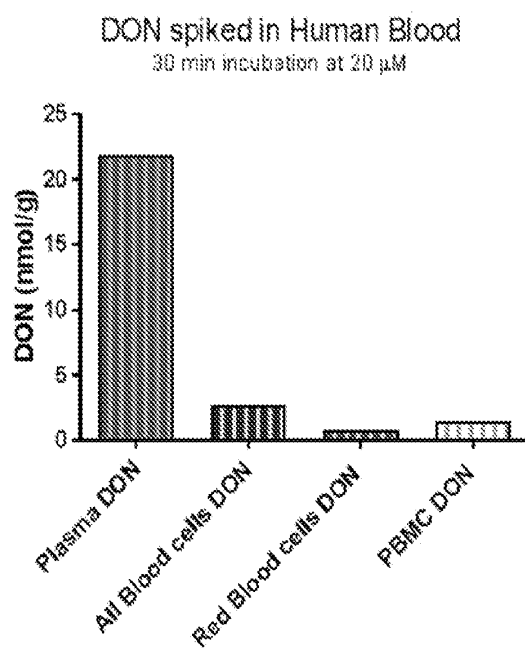
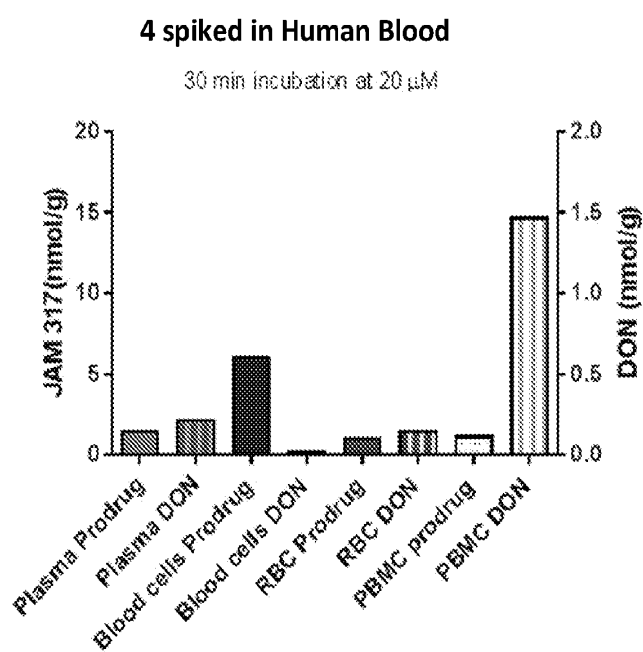
FIG. 6

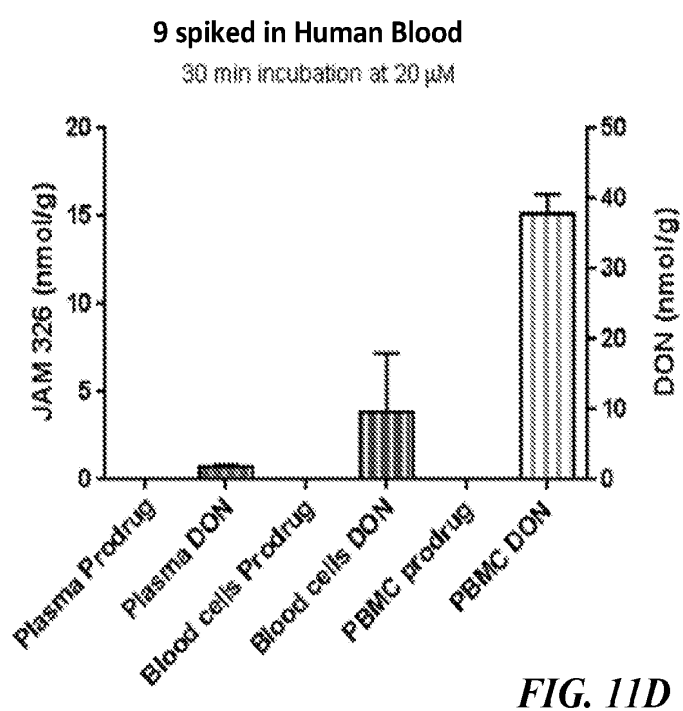
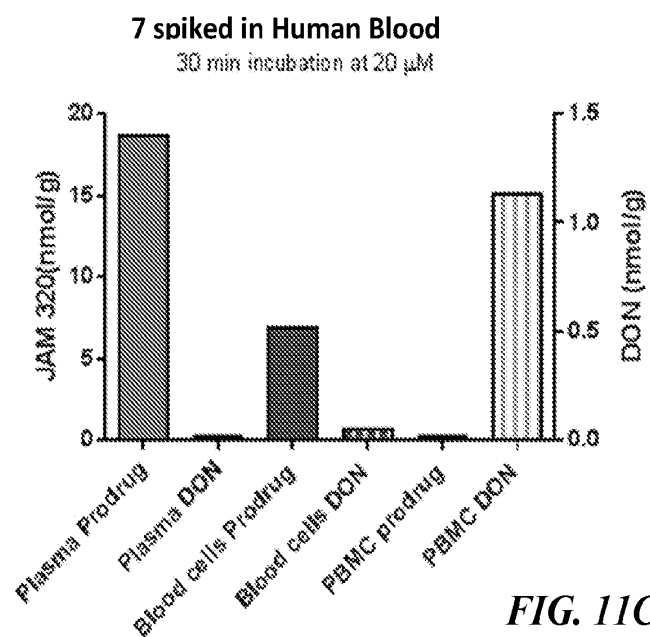
**FIG. 7**

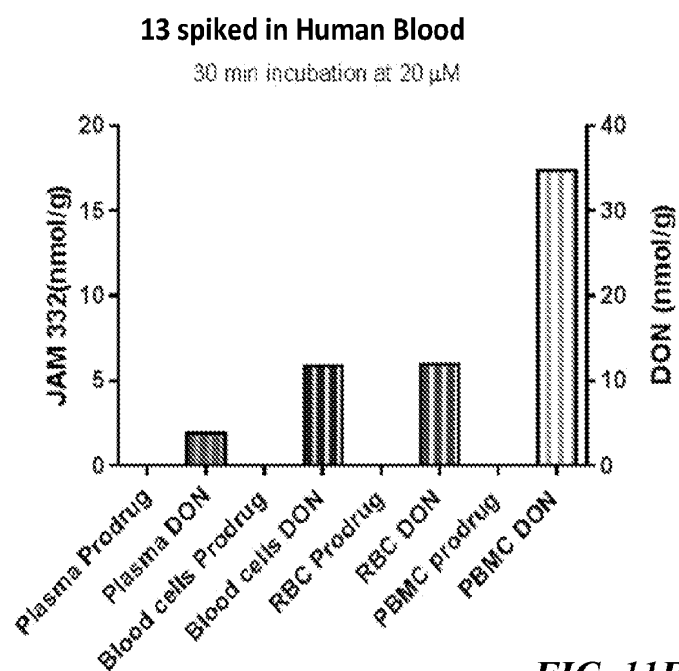
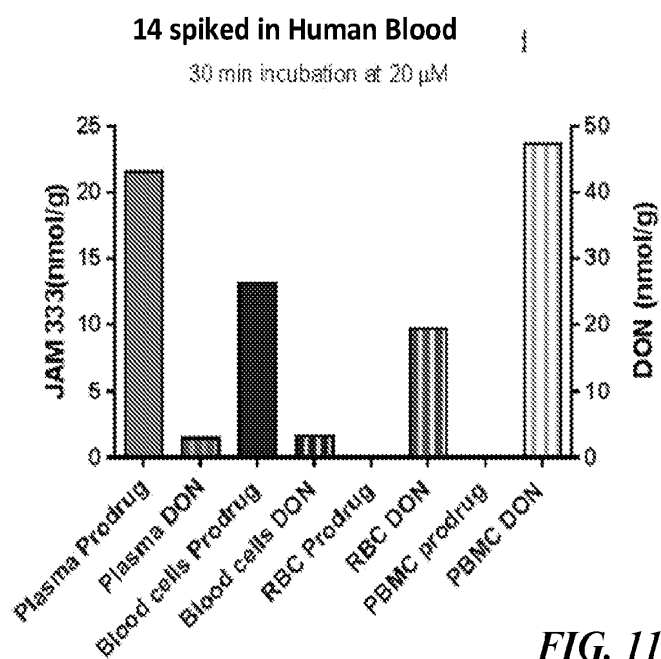
**FIG. 8**

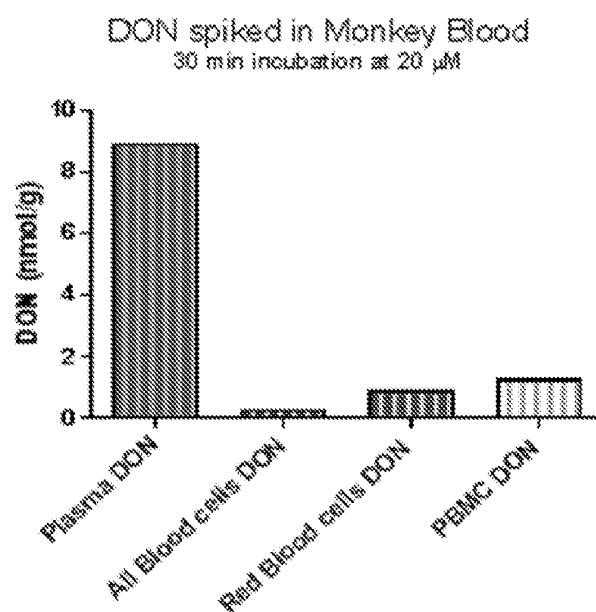
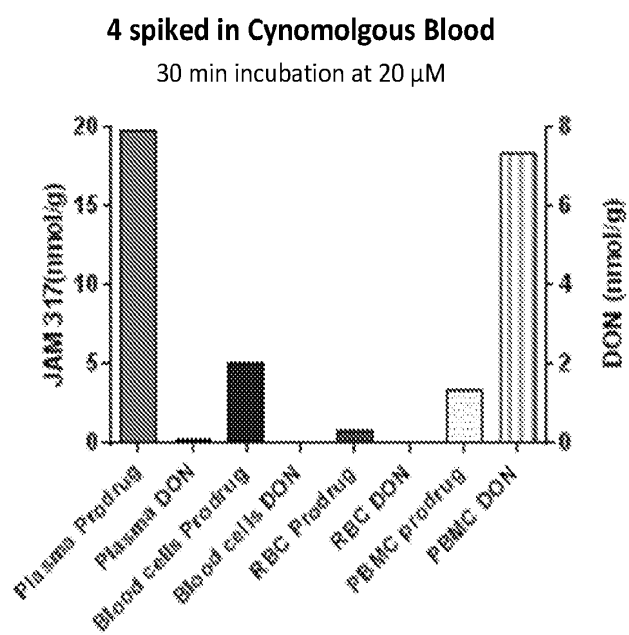
**FIG. 9**

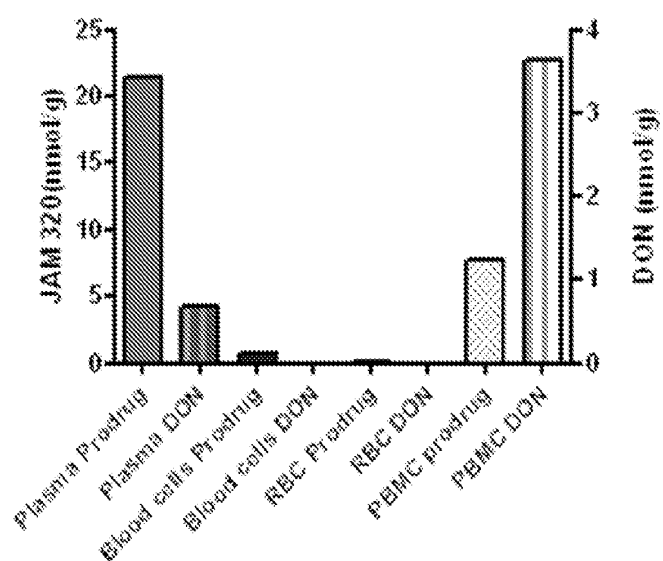
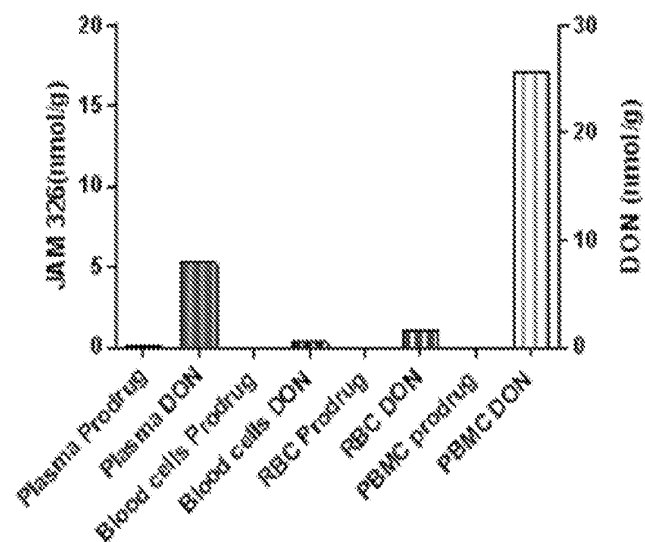
**FIG. 10**

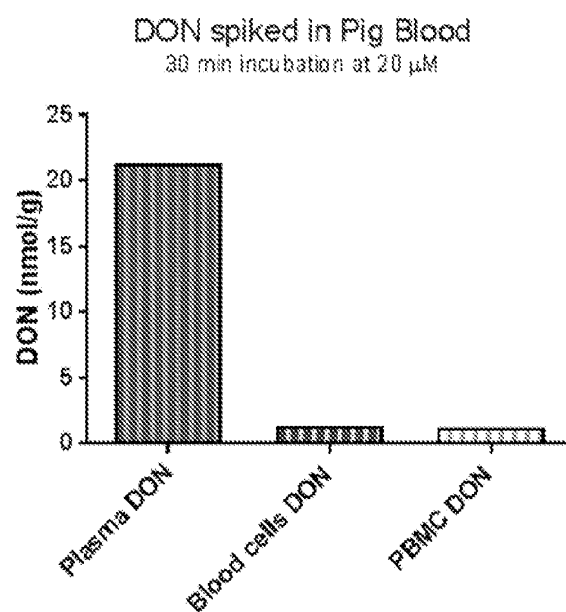
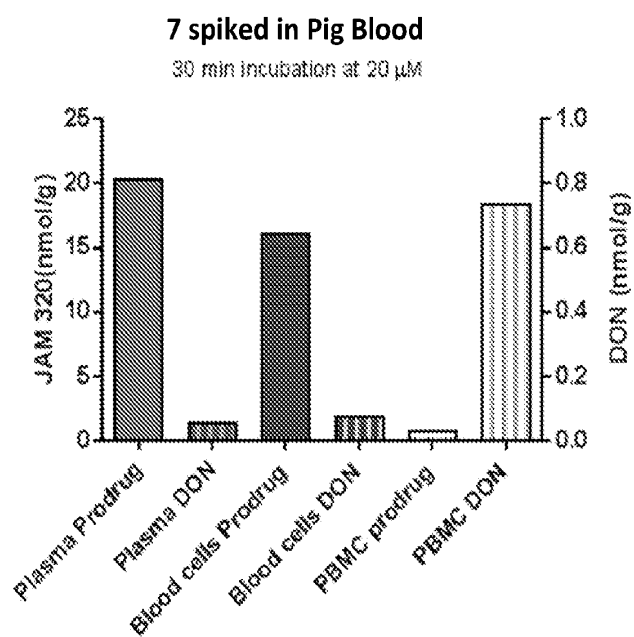
**FIG. 11A****FIG. 11B**

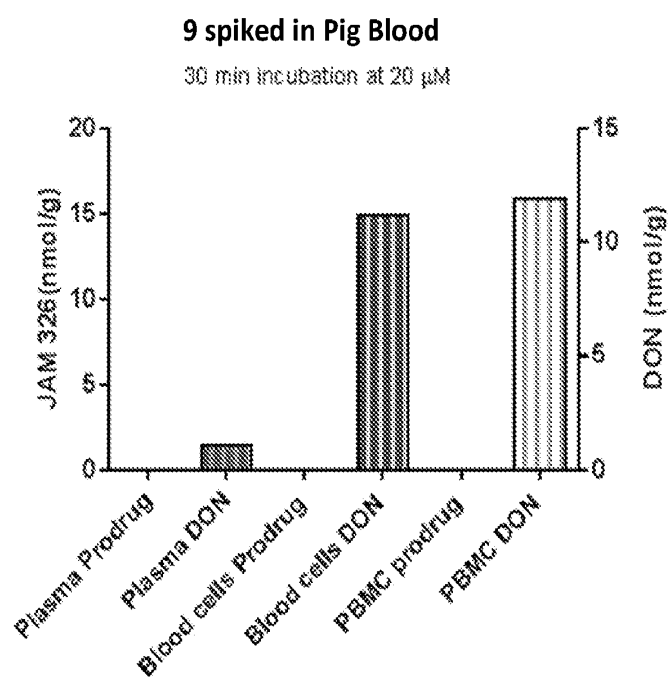


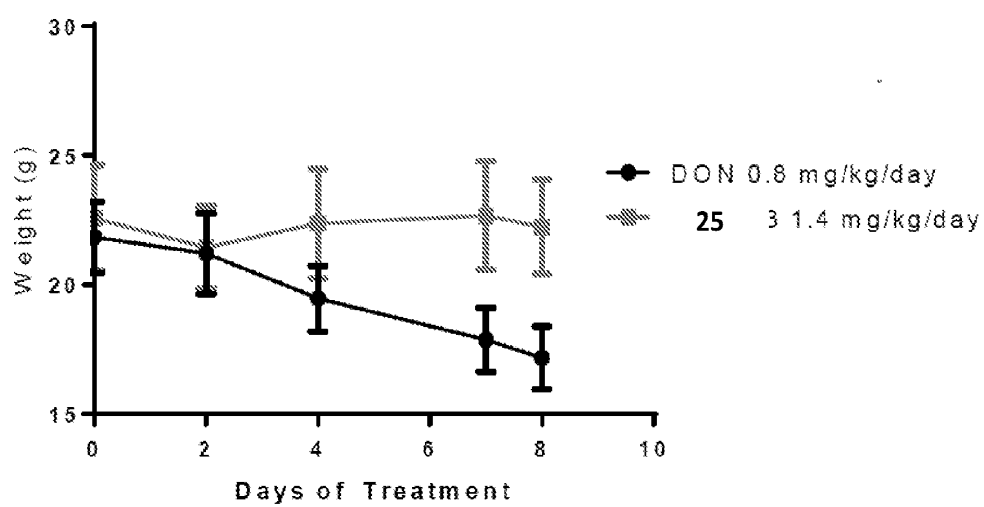
*FIG. 11E**FIG. 11F*

**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*

*FIG. 14*

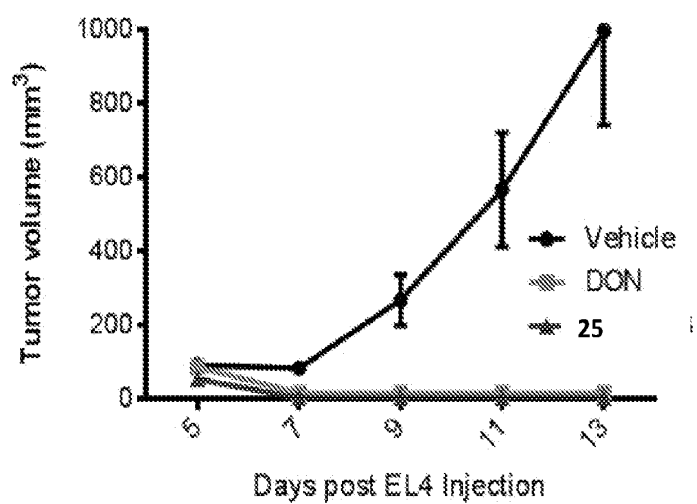
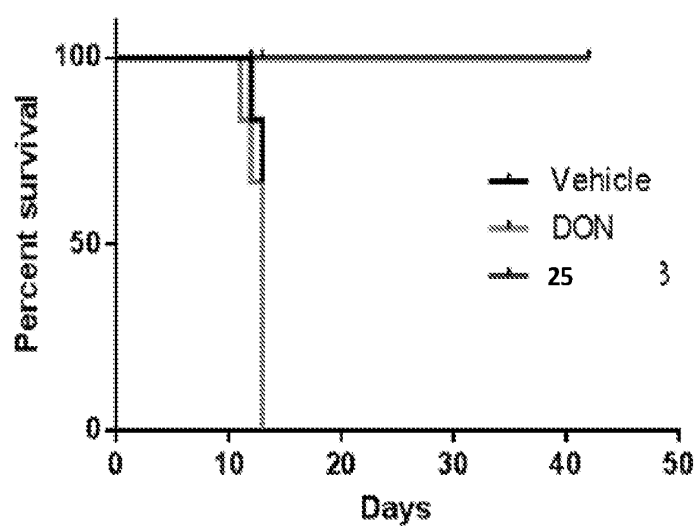
	DON	25	Normal Range
WBC	1.06	1.07	4.45-13.96 K/uL
Hgb	11.80	13.87	10.8-19.2 g/dL
Plt	315.67	715.33	841-2159 K/uL

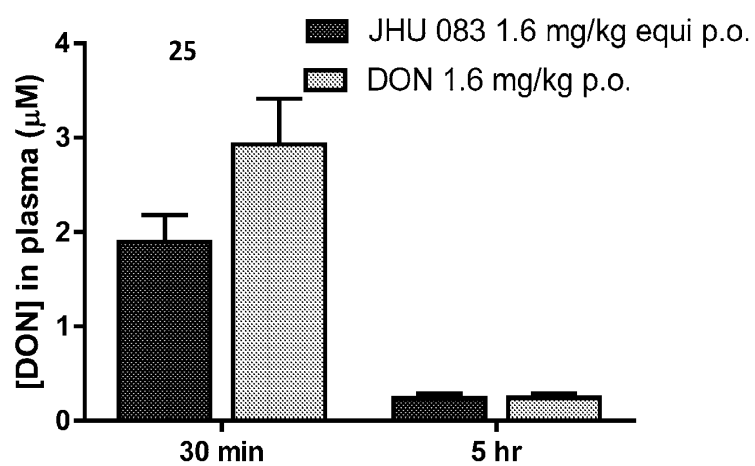
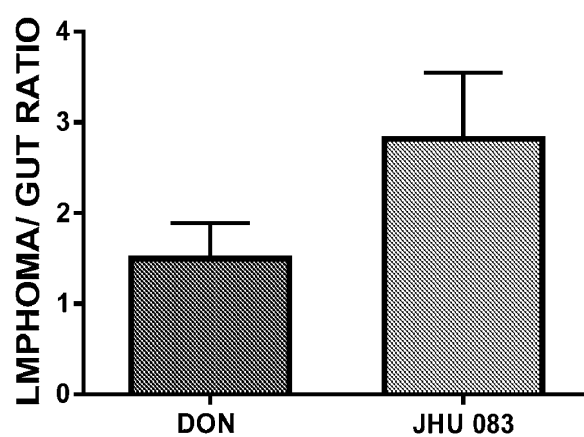
N = 3 mice per group

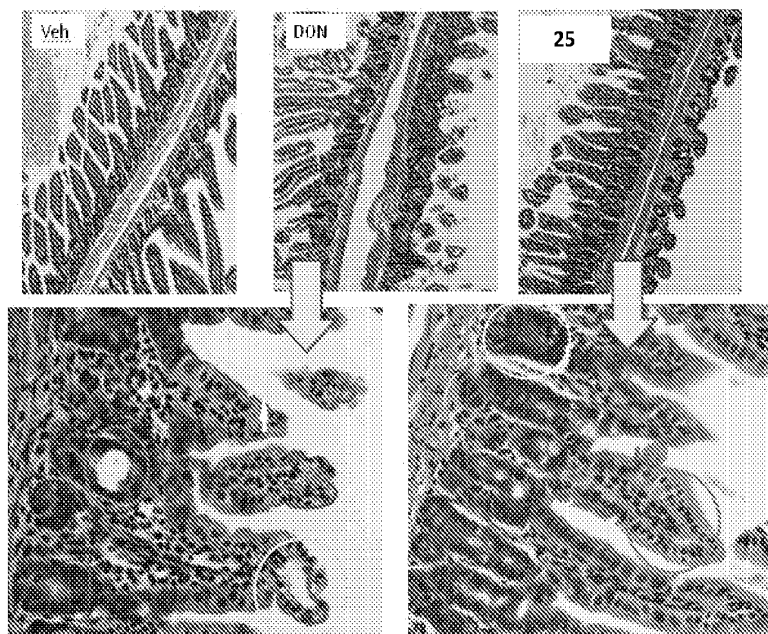
FIG. 15

	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

*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

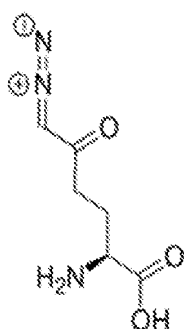
FIG. 19A

	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

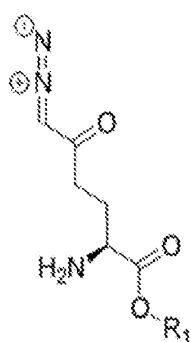
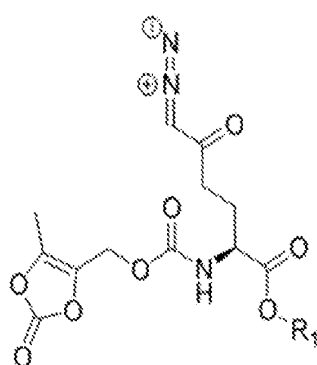
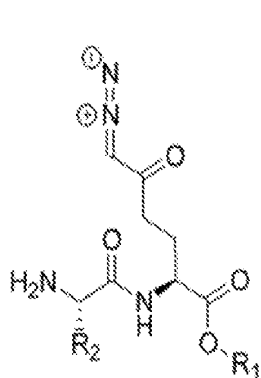
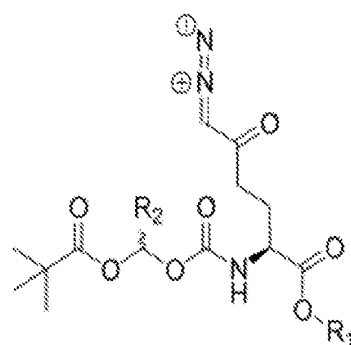
N = 3 mice per group

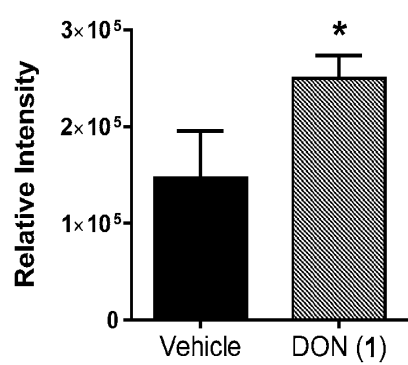
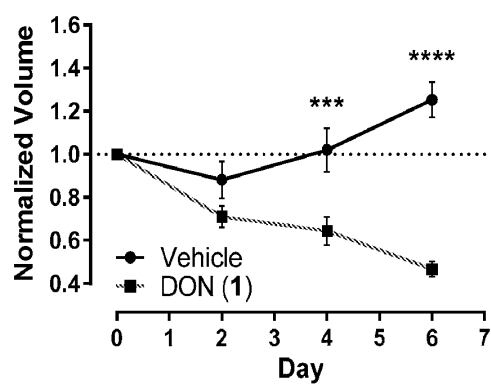
Mice evaluated after 10 days of induction and 38 days of maintenance therapy on JHU-083

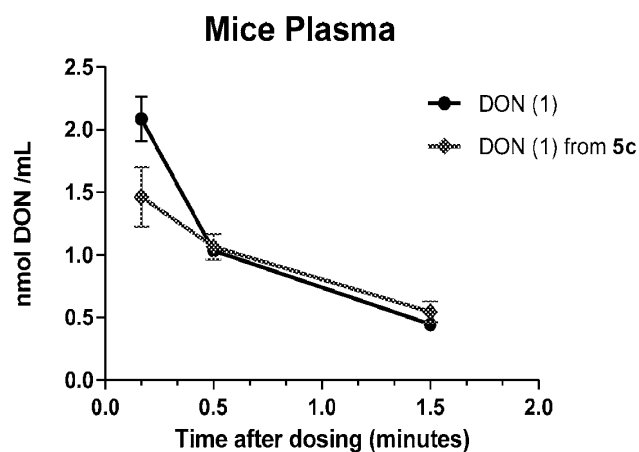
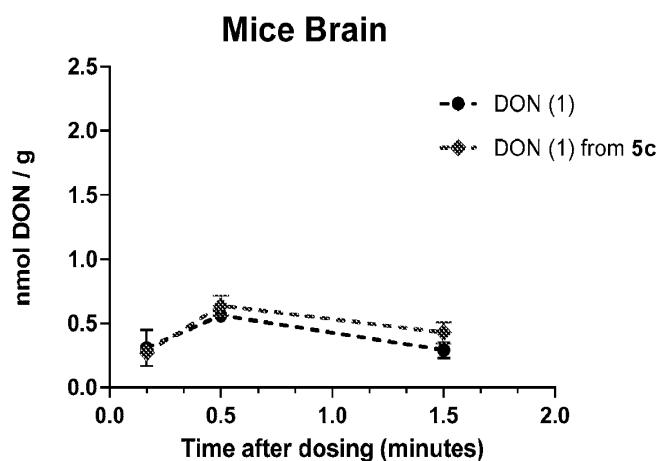
FIG. 19B



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

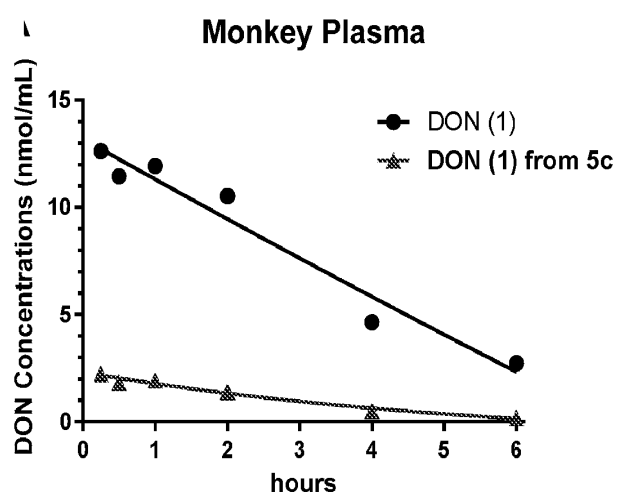
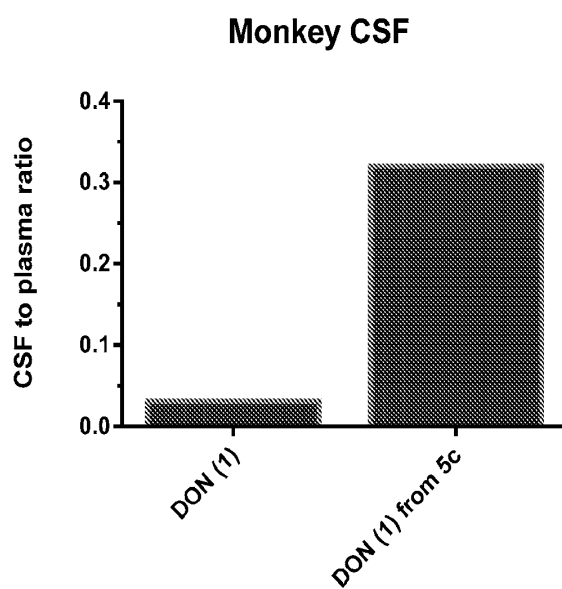
20 (R₁ = Et)
3 (R₁ = iPr)36 (R₁ = Et)
13 (R₁ = iPr)25 (R₁ = Et, R₂ = iBu)
9 (R₁ = iPr, R₂ = iBu)
34 (R₁ = Et, R₂ = -CH₂-3-indolyl)
38 (R₁ = iPr, R₂ = -CH₂-3-indolyl)42 (R₁ = iPr, R₂ = H)
32 (R₁ = Et, R₂ = CH₃)
14 (R₁ = iPr, R₂ = CH₃)**FIG. 20**

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

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

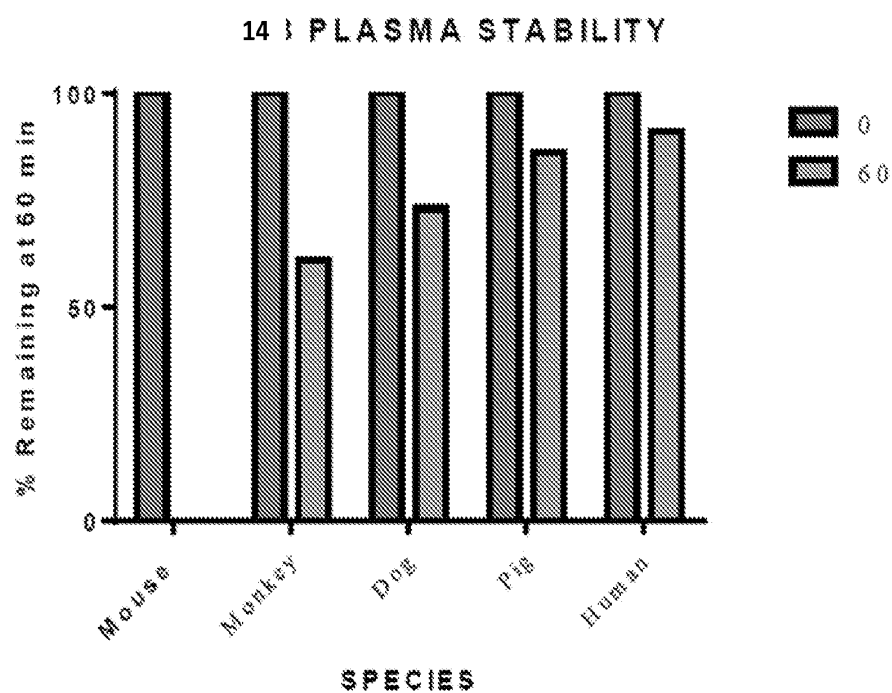
Compound Dosed	Dose (mg/kg equiv)	Tissue	DON C _{max} (ng/mL or nmol/g)	DON T _{max} (hr)	DON AUC _{0-t} (hr*ng/mL or hr*nmol/g)	Brain to plasma ratio
DON (1)	0.8	Plasma	2.2	0.17	1.25	0.46
		Brain	0.56	0.50	0.57	
5c	0.8	Plasma	1.5	1.50	1.22	0.57
		Brain	0.64	30	0.69	

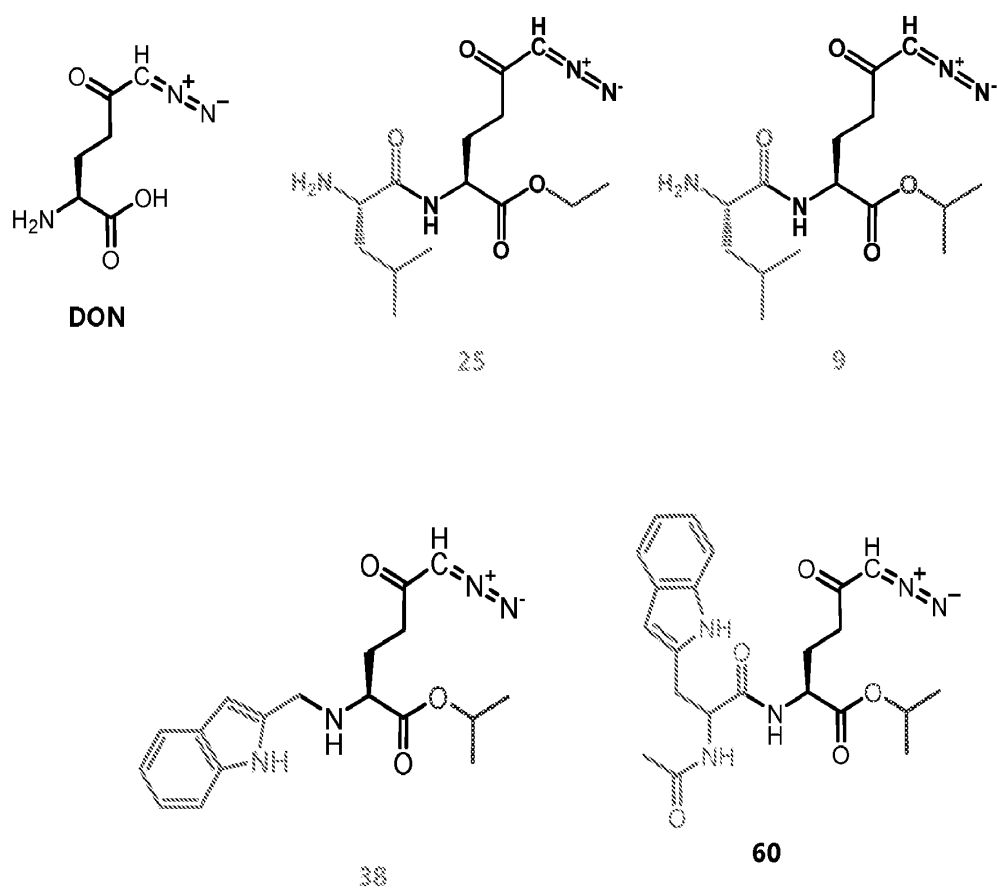
FIG. 22C

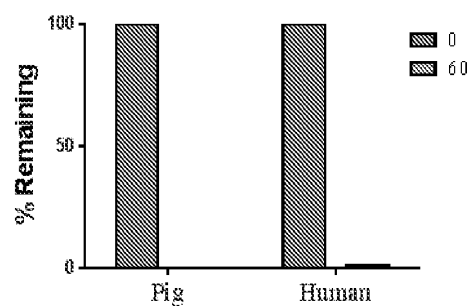
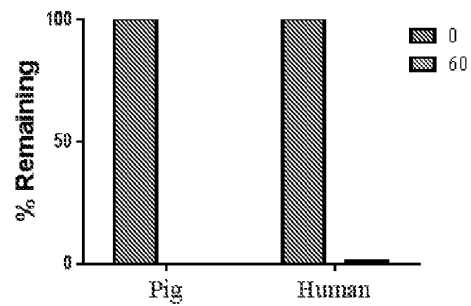
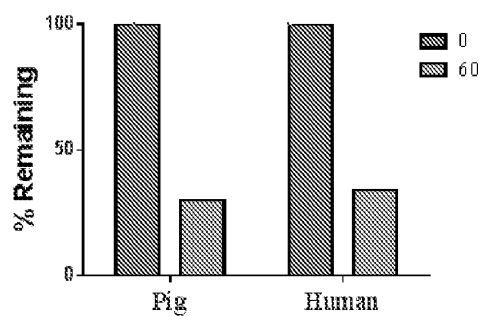
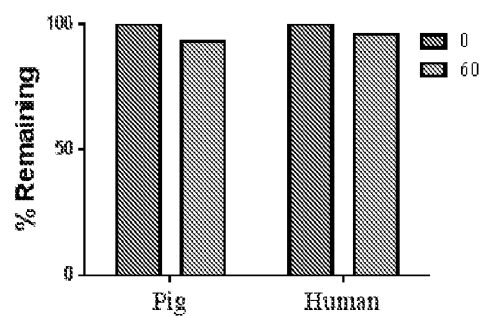
**FIG. 23A****FIG. 23B**

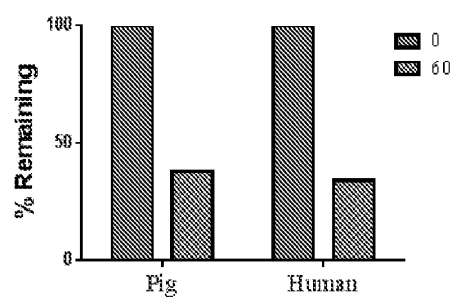
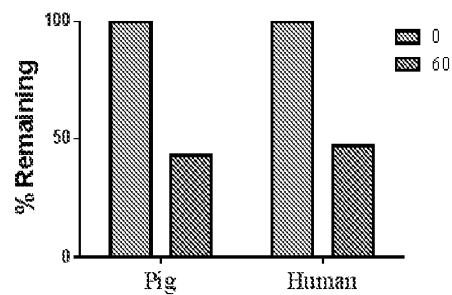
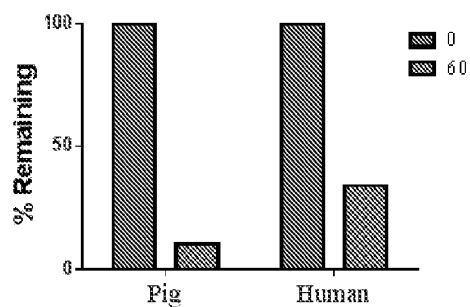
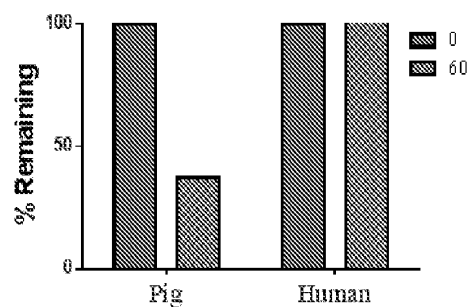
Compound Dosed	Dose (mg/kg equlv)	DON C _{max} (nmol/mL)	DON T _{max} (hr)	DON AUC _{0-t} (hr*nmol/mL)
1	1.6	12.6	0.25	42.7
5c	1.6	2.23	0.25	5.71

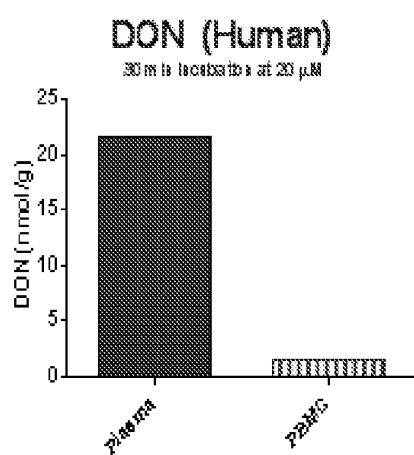
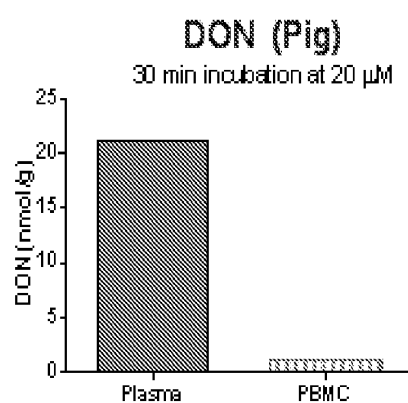
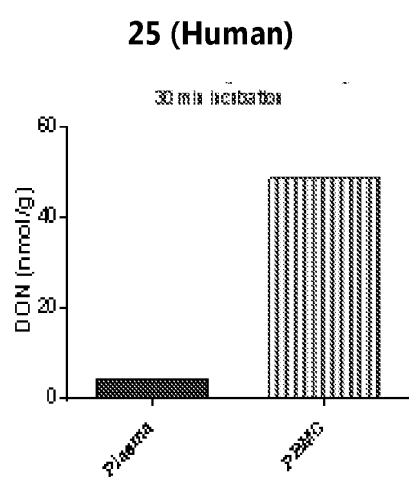
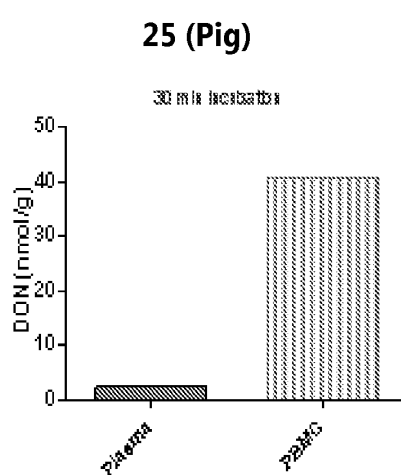
FIG. 23C

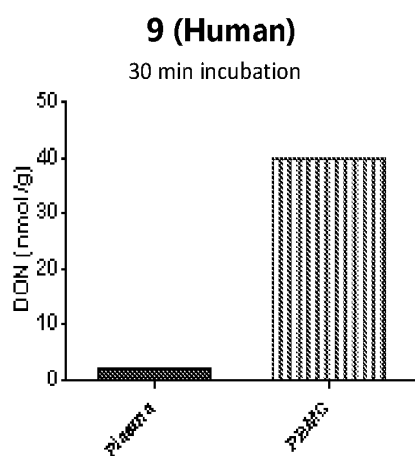
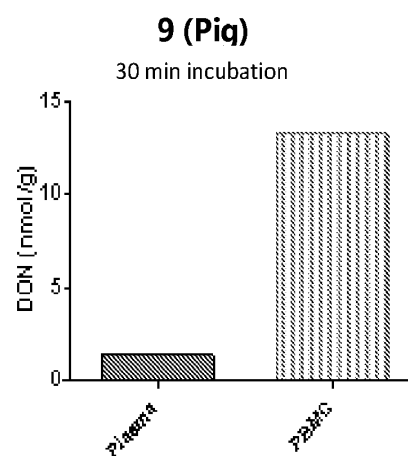
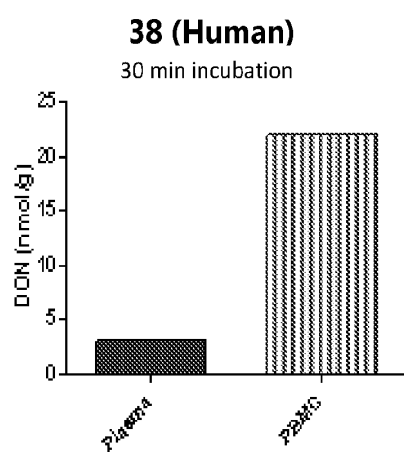
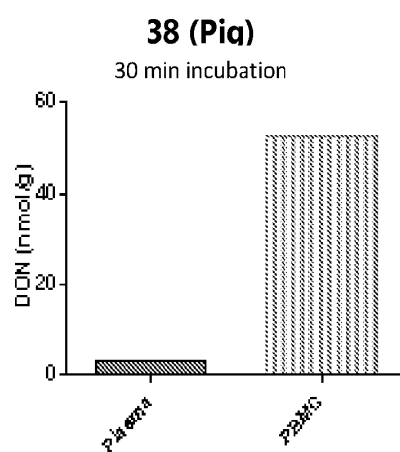
*FIG. 24*

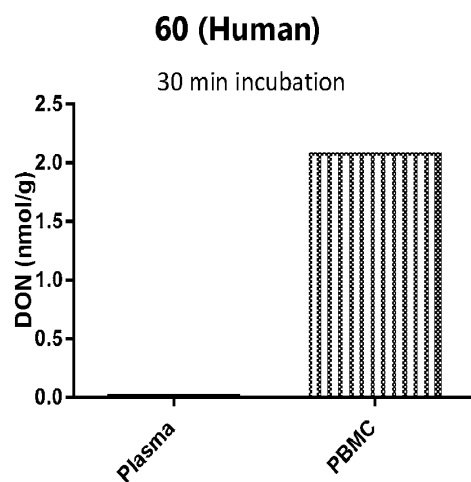
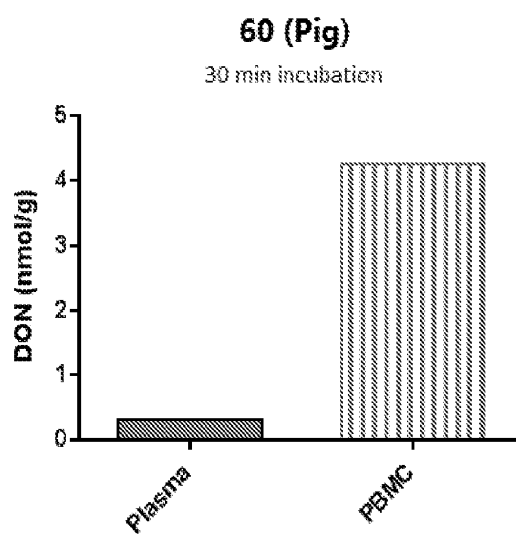
**FIG. 25**

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

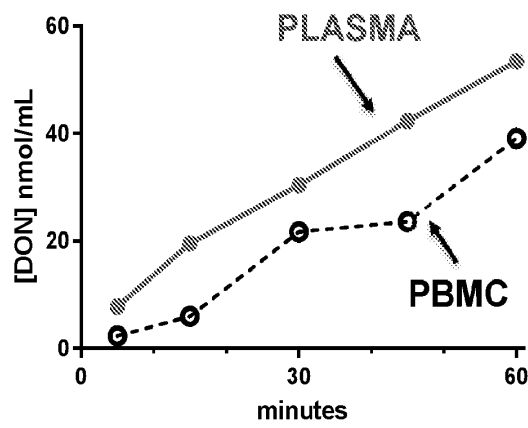


FIG. 29A

25 : 1 hour i.v. infusion

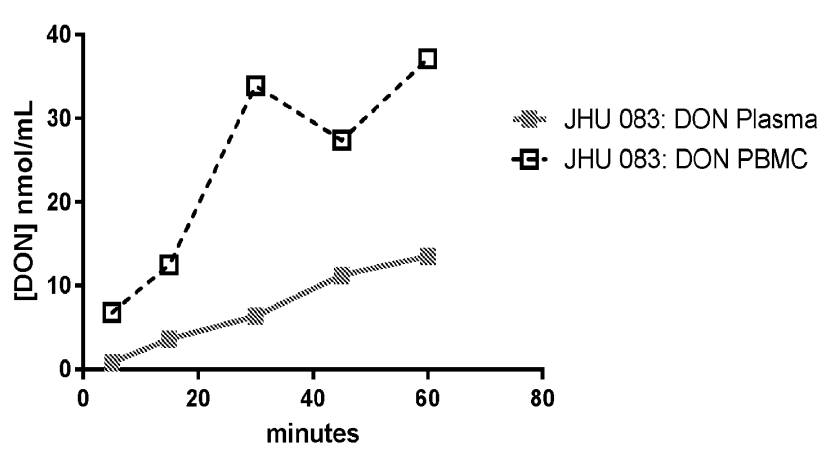
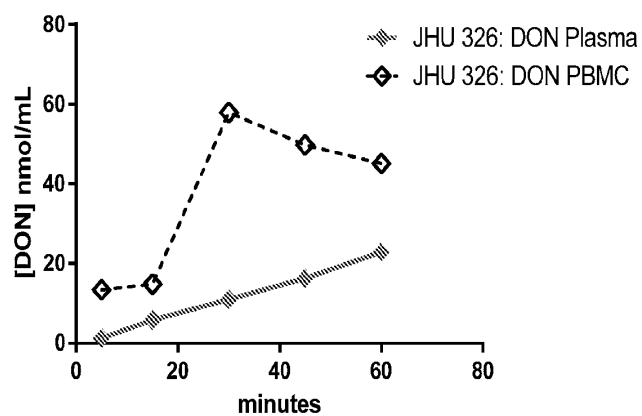
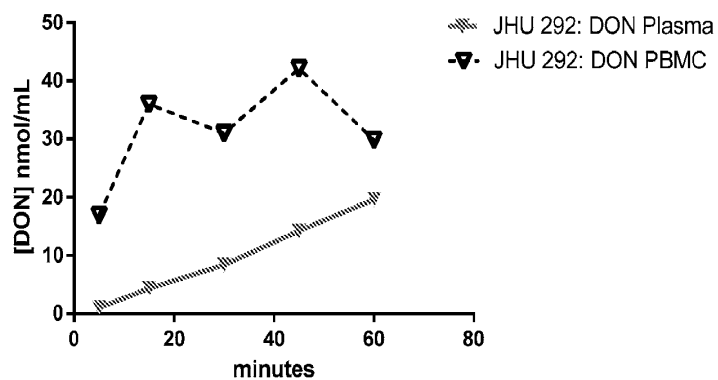
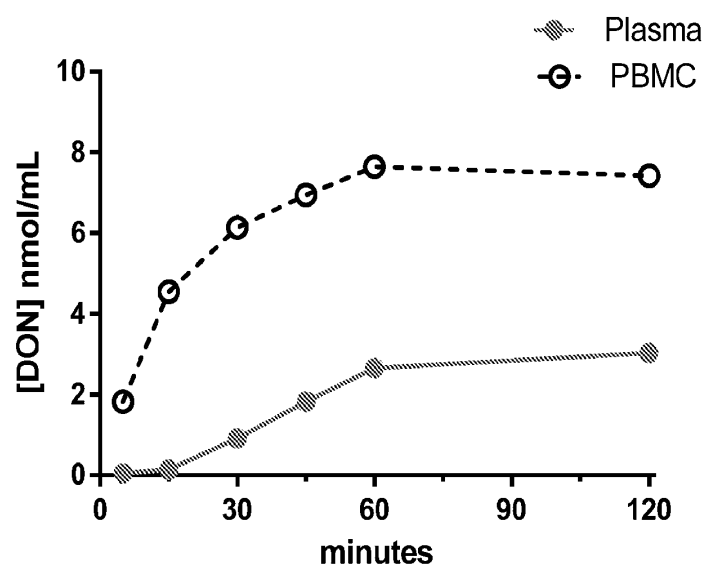


FIG. 29B

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

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

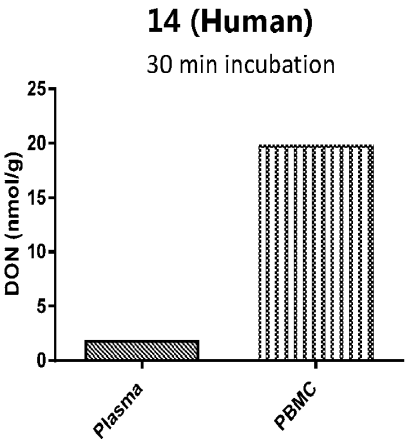


FIG. 30A

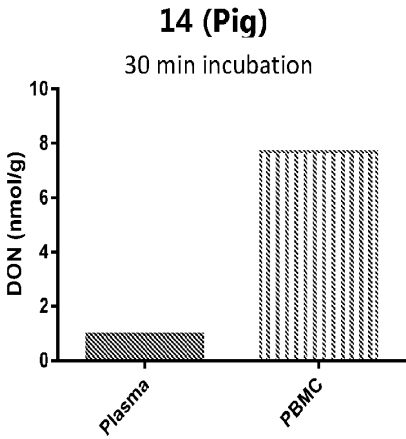
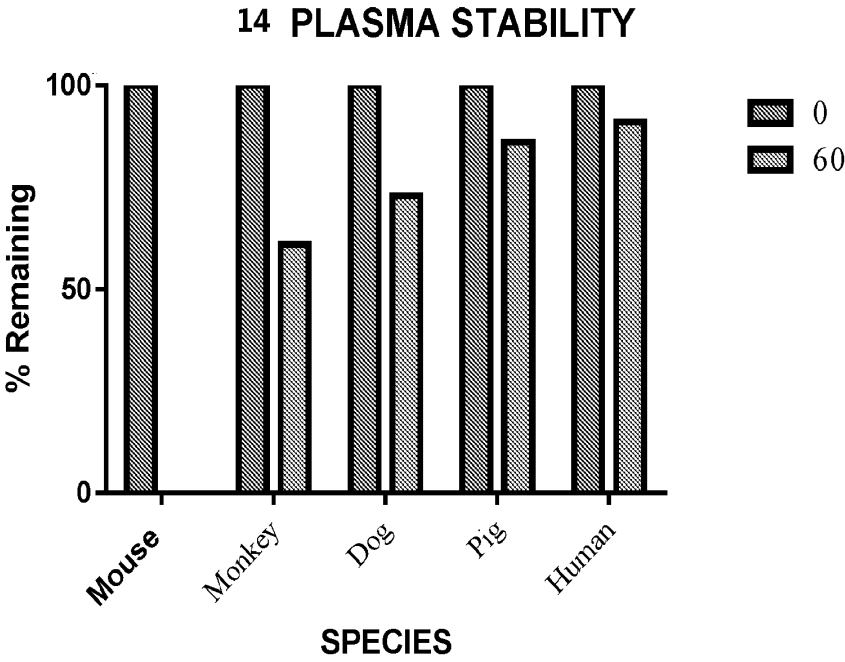
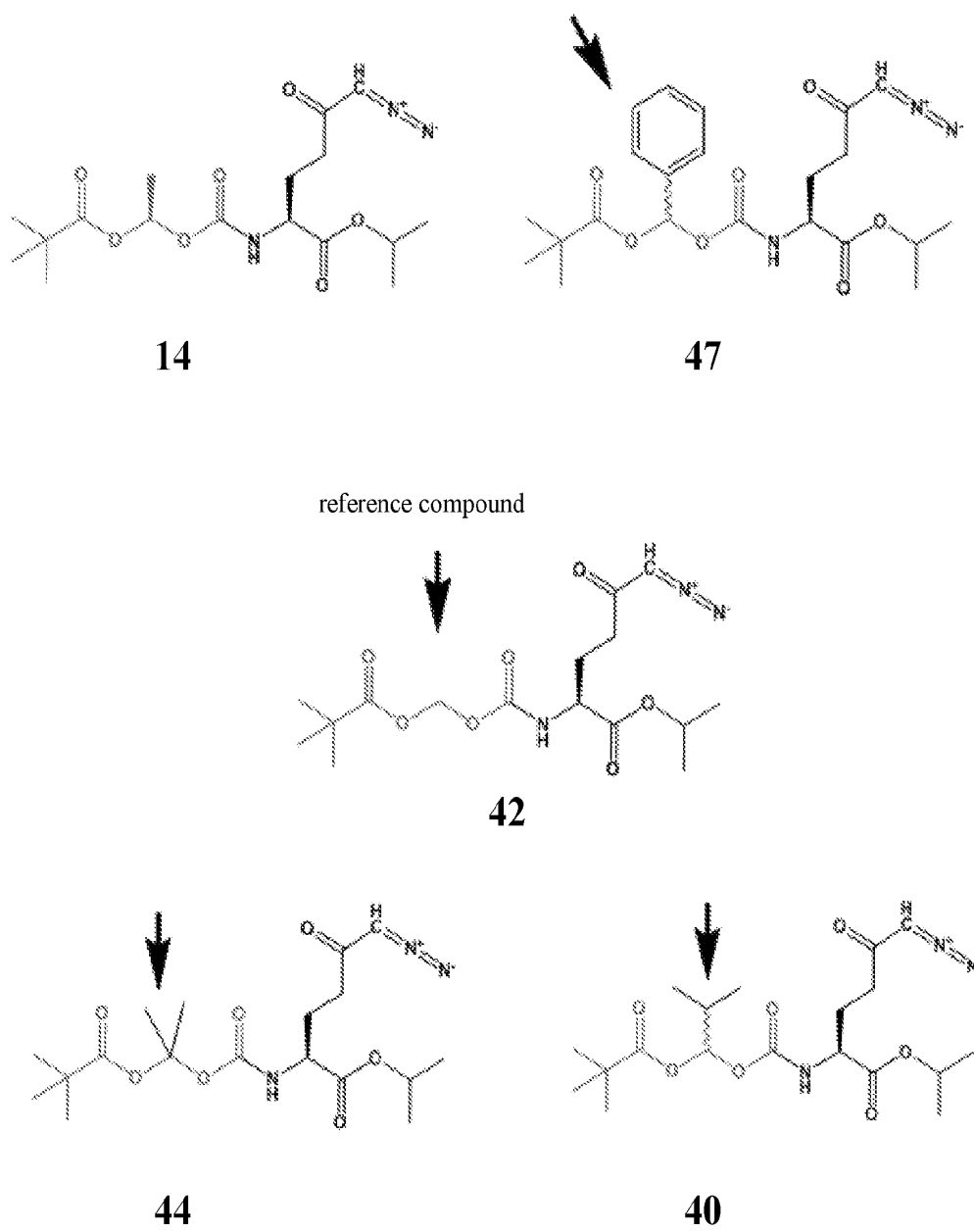


FIG. 30B



SPECIES

FIG. 30C

**FIG. 31**

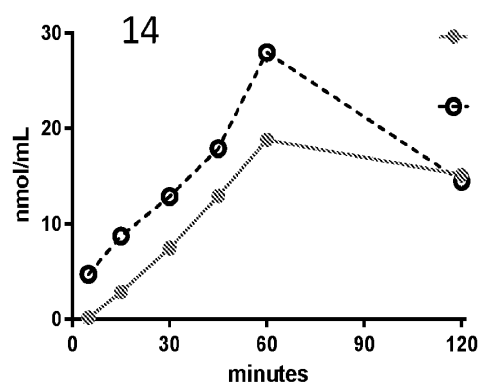


FIG. 32A

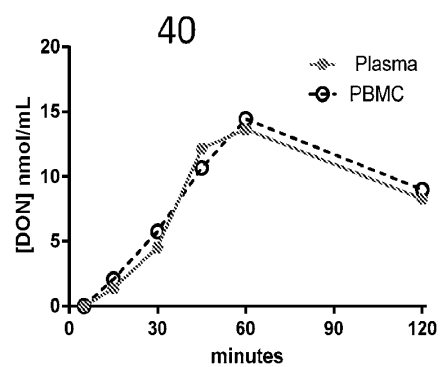


FIG. 32B

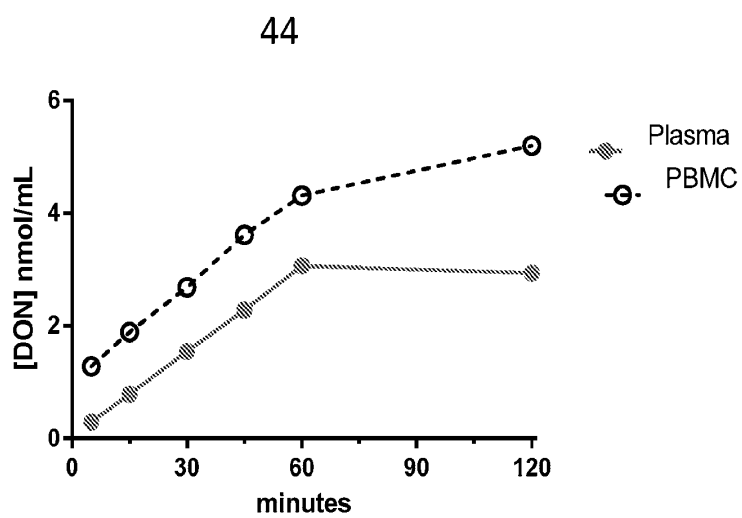
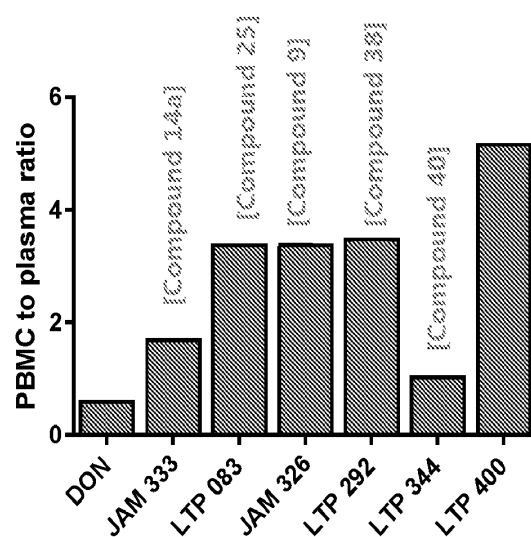


FIG. 32C

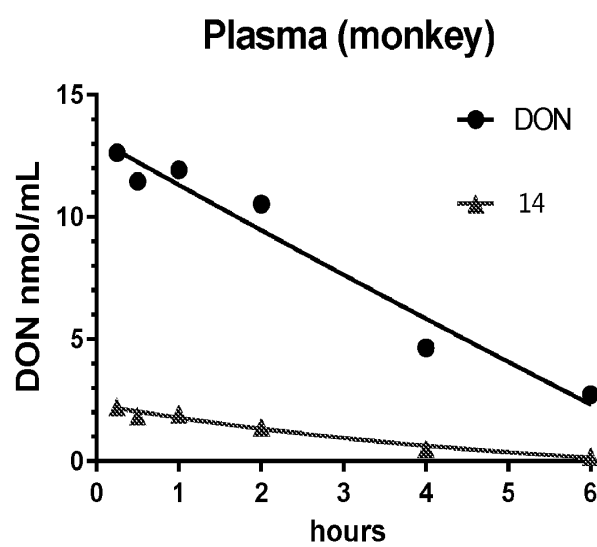
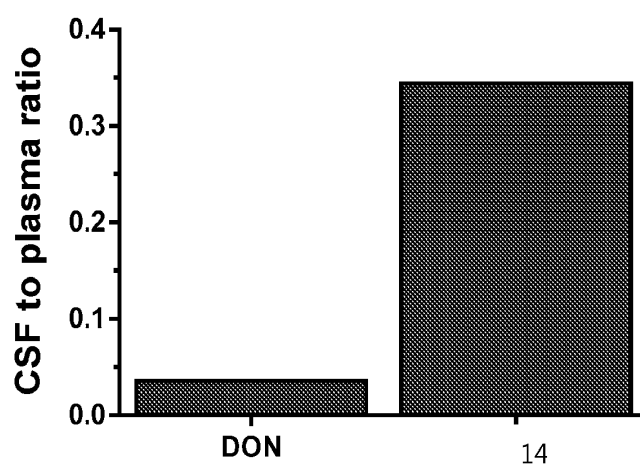


	DON	JAM 333	LTP 083	JAM 326	LTP 292	LTP 344	LTP 400	LTP 387
plasma	29.9	8.0	6.9	11.1	9.1	6.2	1.4	1.5
PBMC	17.7	13.6	23.4	37.3	31.6	6.3	7.2	2.7

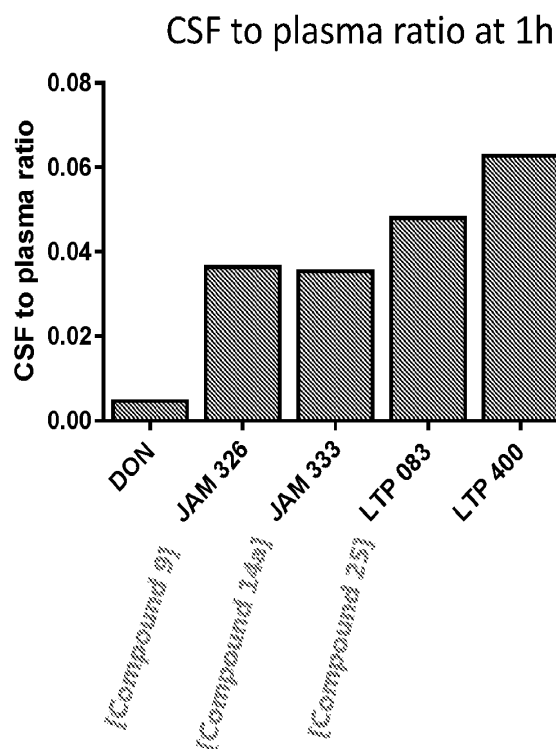
PBMC/Plasma ratio	0.59	1.69	3.37	3.37	3.47	1.03	5.15	1.73
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FIG. 33

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)

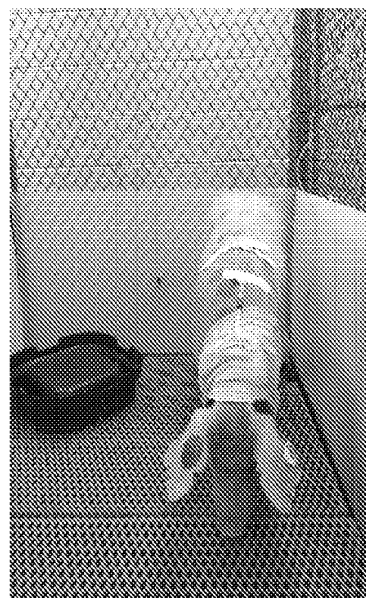
**FIG. 35**

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

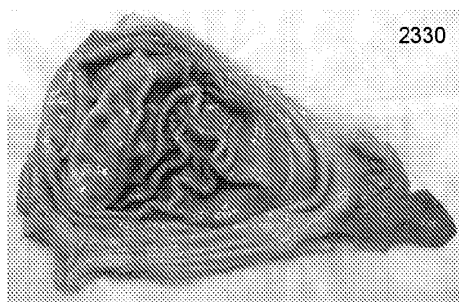
WNL (within normal limits)

Anorexia = no food consumption

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

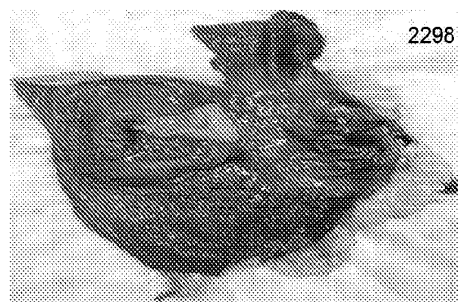
- blue ears and snout
- lowered head
- reduced activity in the cage
- reduced social interaction
- diarrhea

DON



moderate localized
FIG. 37A

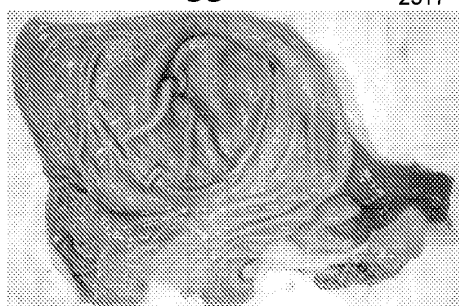
DON



severe generalized
FIG. 37B

38

2317



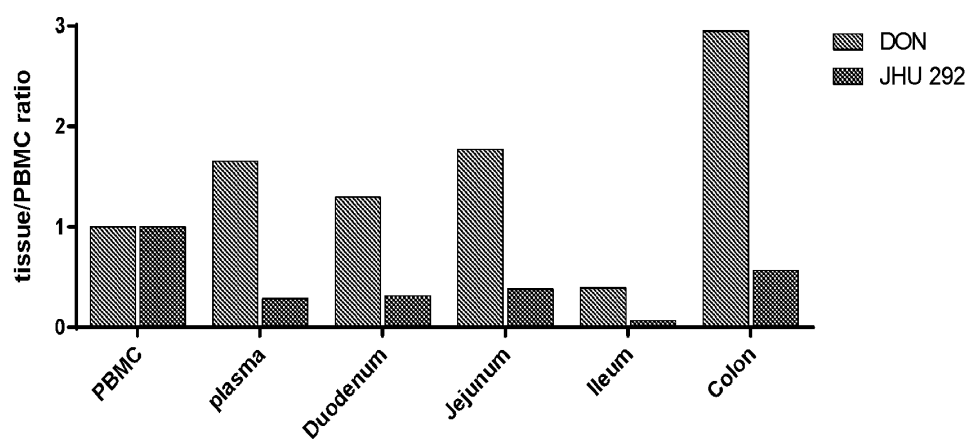
normal appearing gastric
FIG. 37C

38

2319



normal appearing gastric
FIG. 37D

*FIG. 38*