FIG. 1

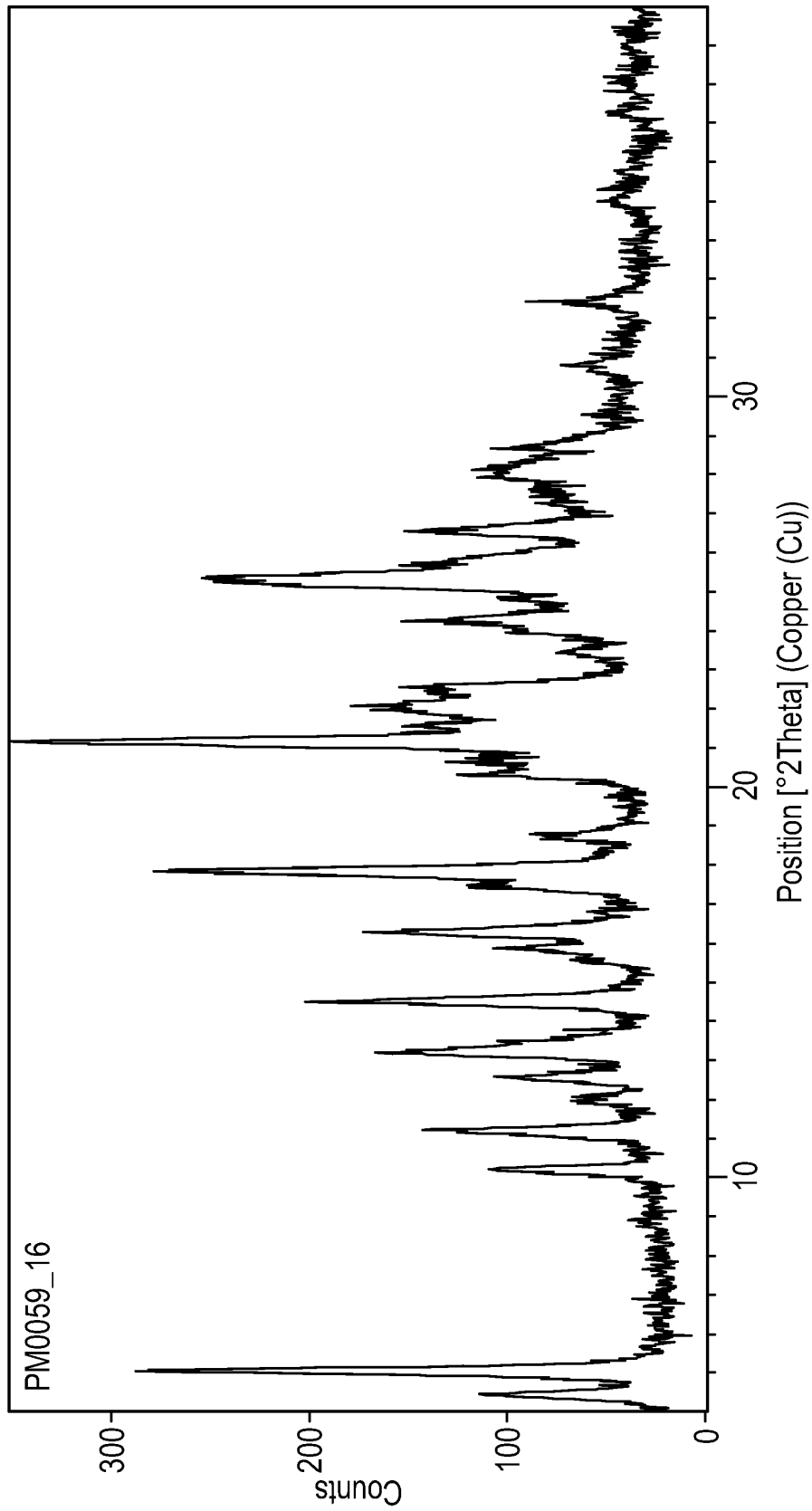

PM0059_16
Counts
0
100
200
300
10
20
30
Position [°2Theta] (Copper (Cu))

FIG. 2A

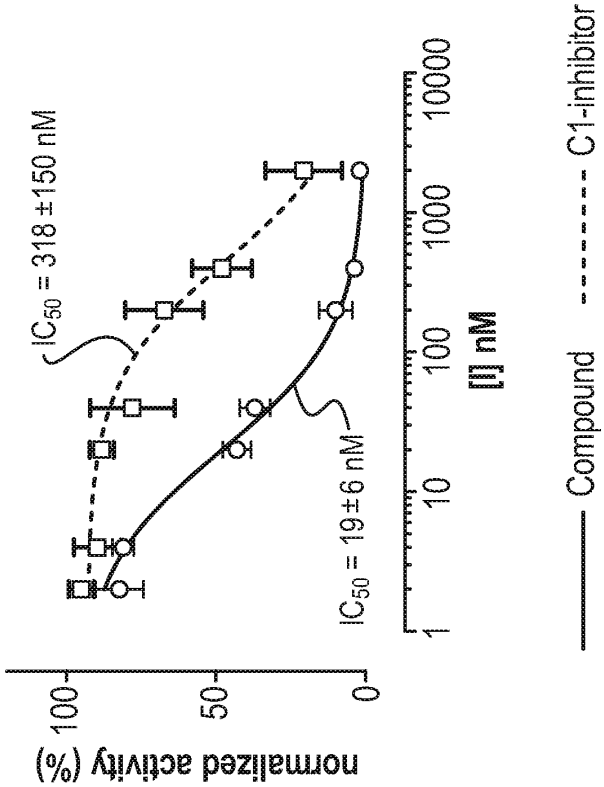

plasma assay (1:4 dilution)
normalized activity (%)
100
50
0
IC50 = 318 ±150 nM
IC50 = 19±6 nM
1
10
100
1000
10000
[I] nM
Compound
C1-inhibitor

FIG. 2B

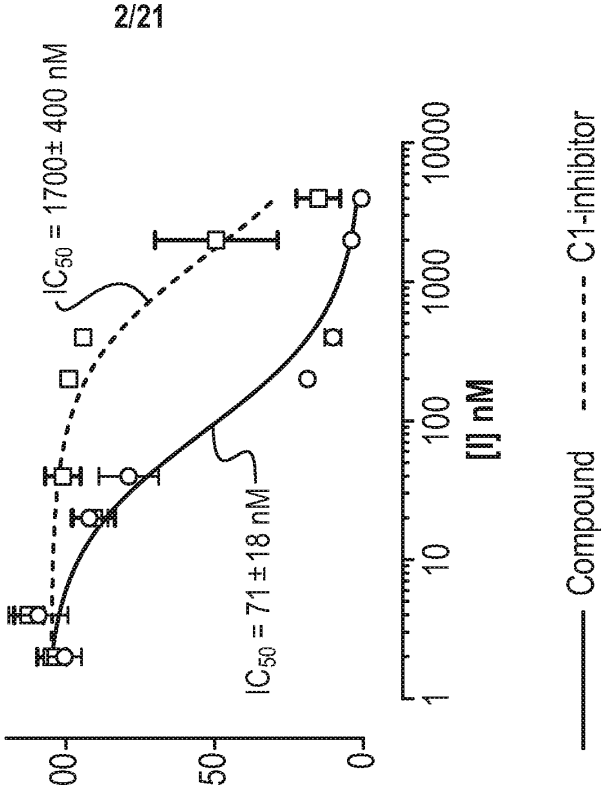

plasma assay (undiluted plasma)
normalized activity (%)
100
50
0
IC50 = 1700± 400 nM
IC50 = 71±18 nM
1
10
100
1000
10000
[I] nM
Compound
C1-inhibitor

FIG. 3A

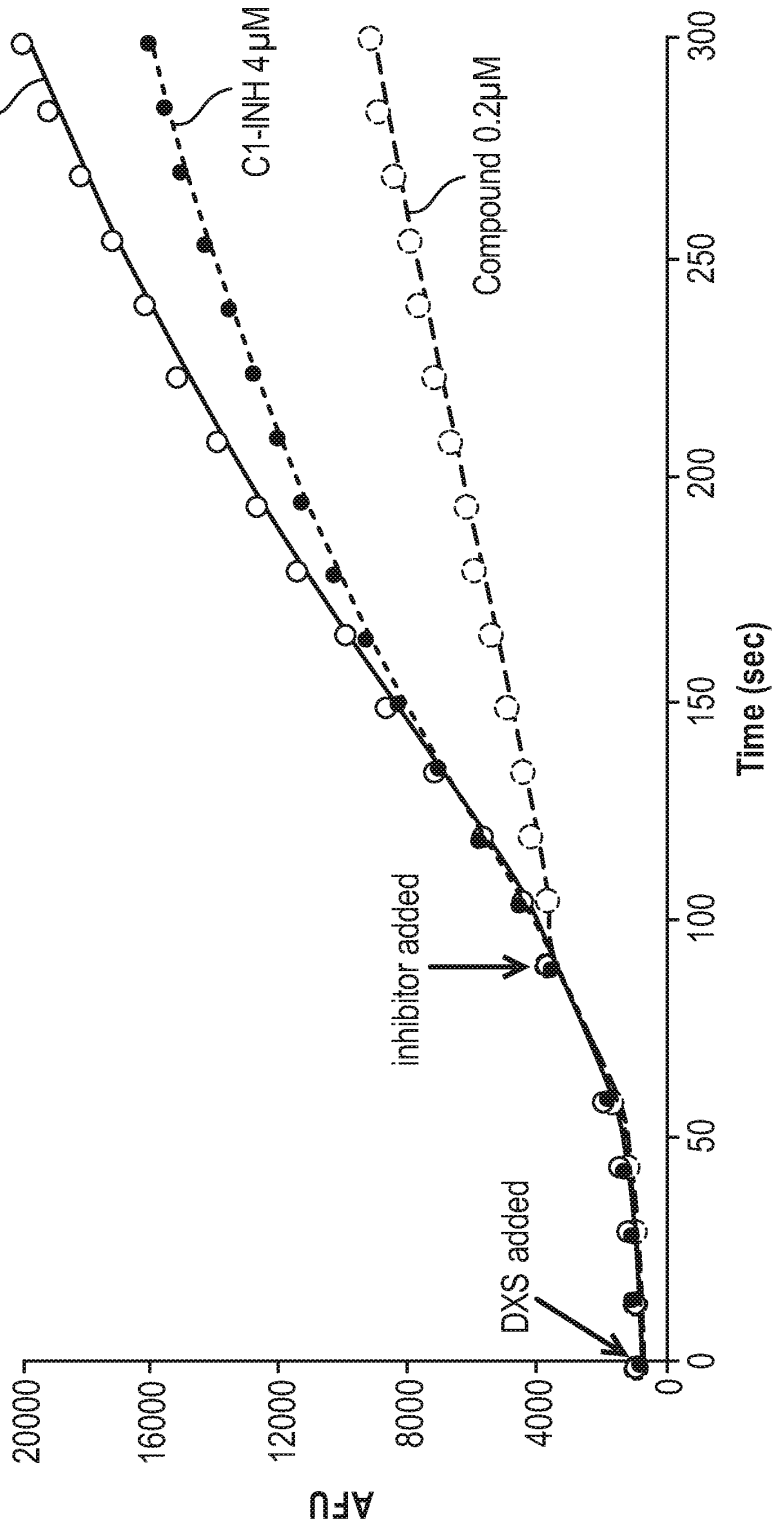

Control
C1-INH 4 µM
Compound 0.2µM
inhibitor added
DXS added
AFU
Time (sec)
0
4000
8000
12000
16000
20000
0
50
100
150
200
250
300

FIG. 3B

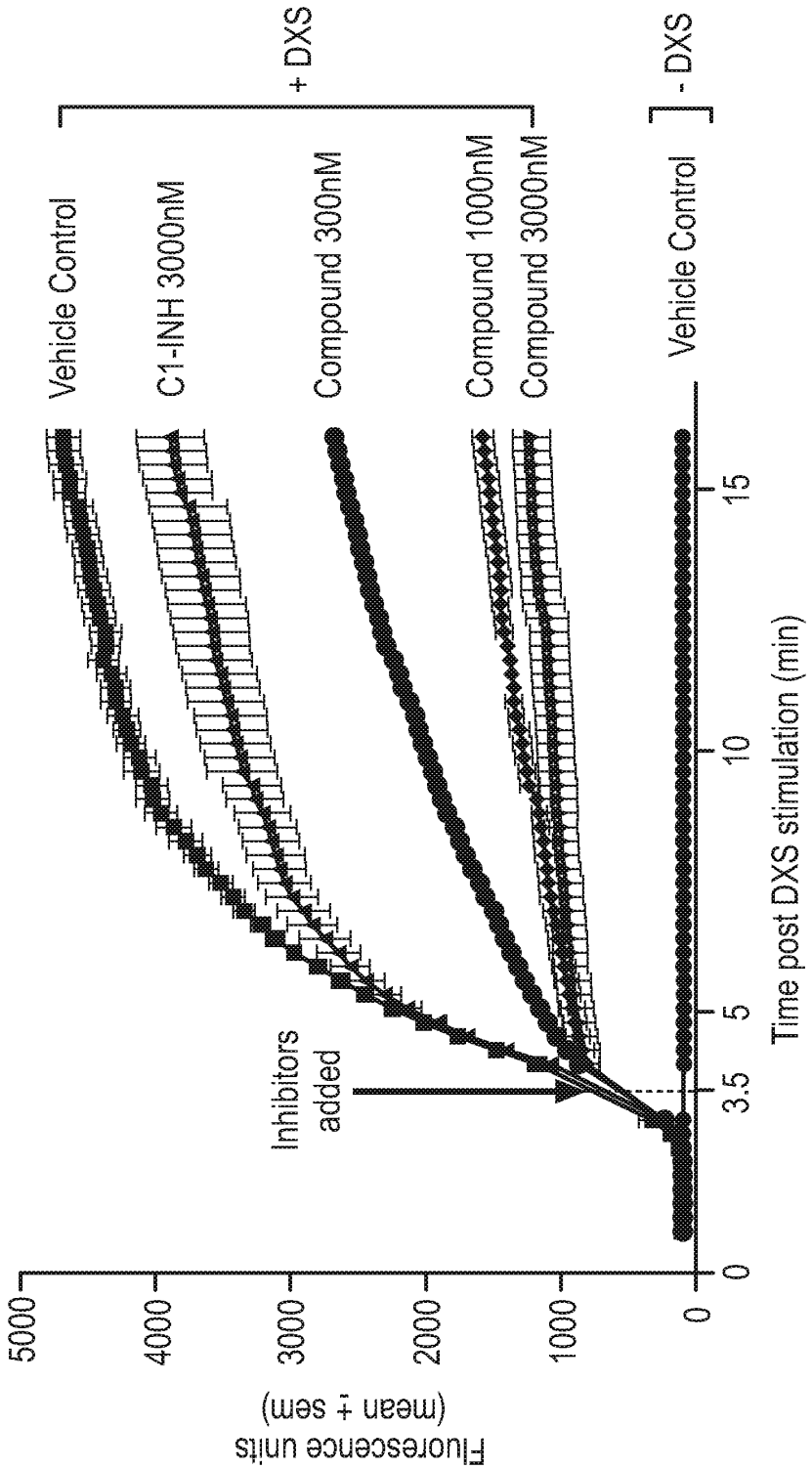

+ DXS
- DXS
Vehicle Control
C1-INH 3000nM
Compound 300nM
Compound 1000nM
Compound 3000nM
Vehicle Control
Inhibitors added
Fluorescence units (mean ± sem)
5000
4000
3000
2000
1000
0
0
3.5
5
10
15
Time post DXS stimulation (min)

FIG. 4A

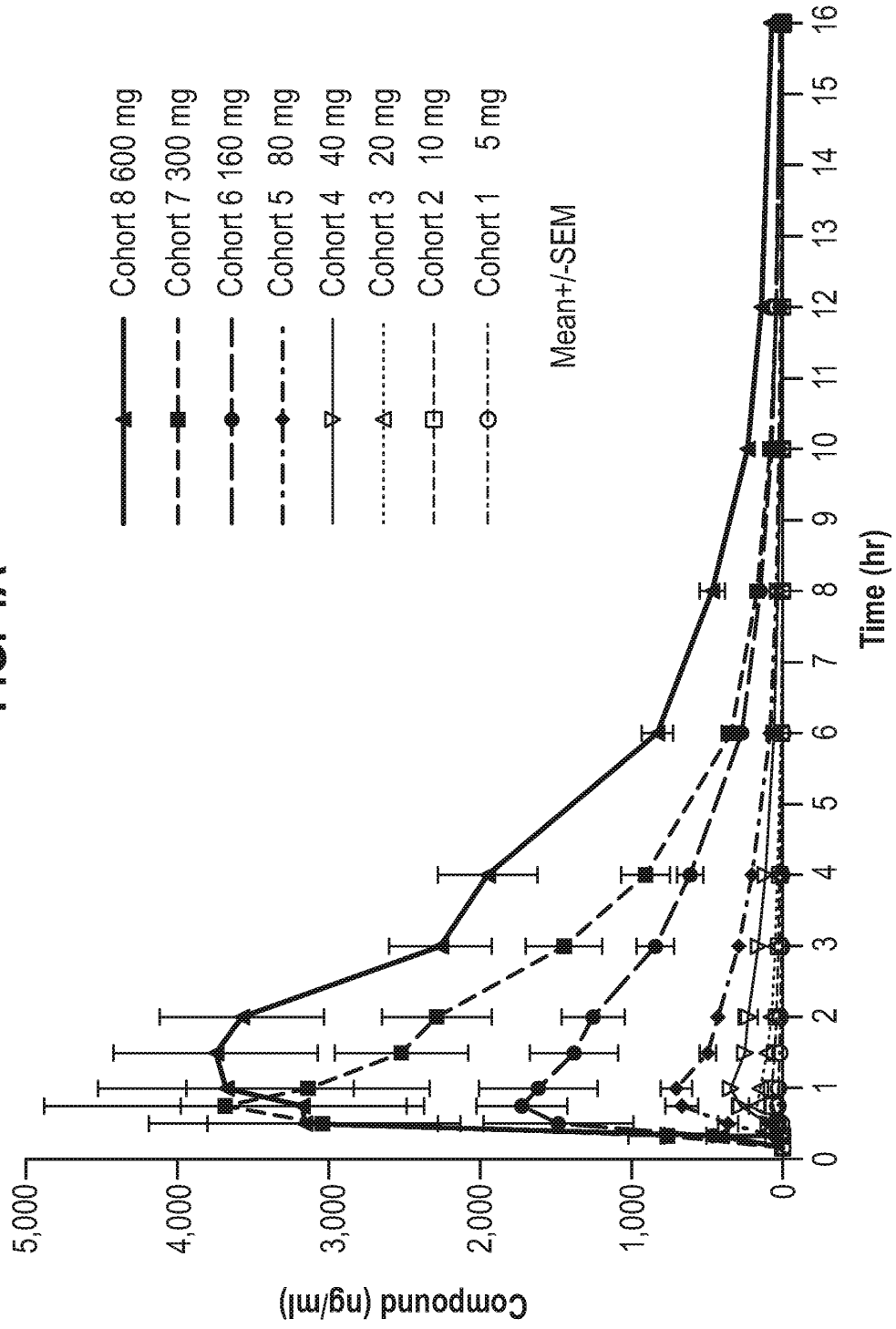

Cohort 8 600 mg
Cohort 7 300 mg
Cohort 6 160 mg
Cohort 5 80 mg
Cohort 4 40 mg
Cohort 3 20 mg
Cohort 2 10 mg
Cohort 1 5 mg
Mean+/-SEM
Compound (ng/ml)
5,000
4,000
3,000
2,000
1,000
0
Time (hr)
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16

FIG. 4B

Table 2: Compound SAD PK parameters

Dose (mg)	C_{max} (ng/mL) Mean (95% CI)
5	38.7 (28.3, 52.9)
10	80.7 (59.0, 110)
20	169 (124, 231)
40	357 (261, 488)
80	684 (500, 935)
160	1,970 (1440, 2700)
300	3,910 (2860, 5340)
600	4,830 (3530, 6610)

Mean PK parameters of Compound n=6 in each SAD cohort

FIG. 5A

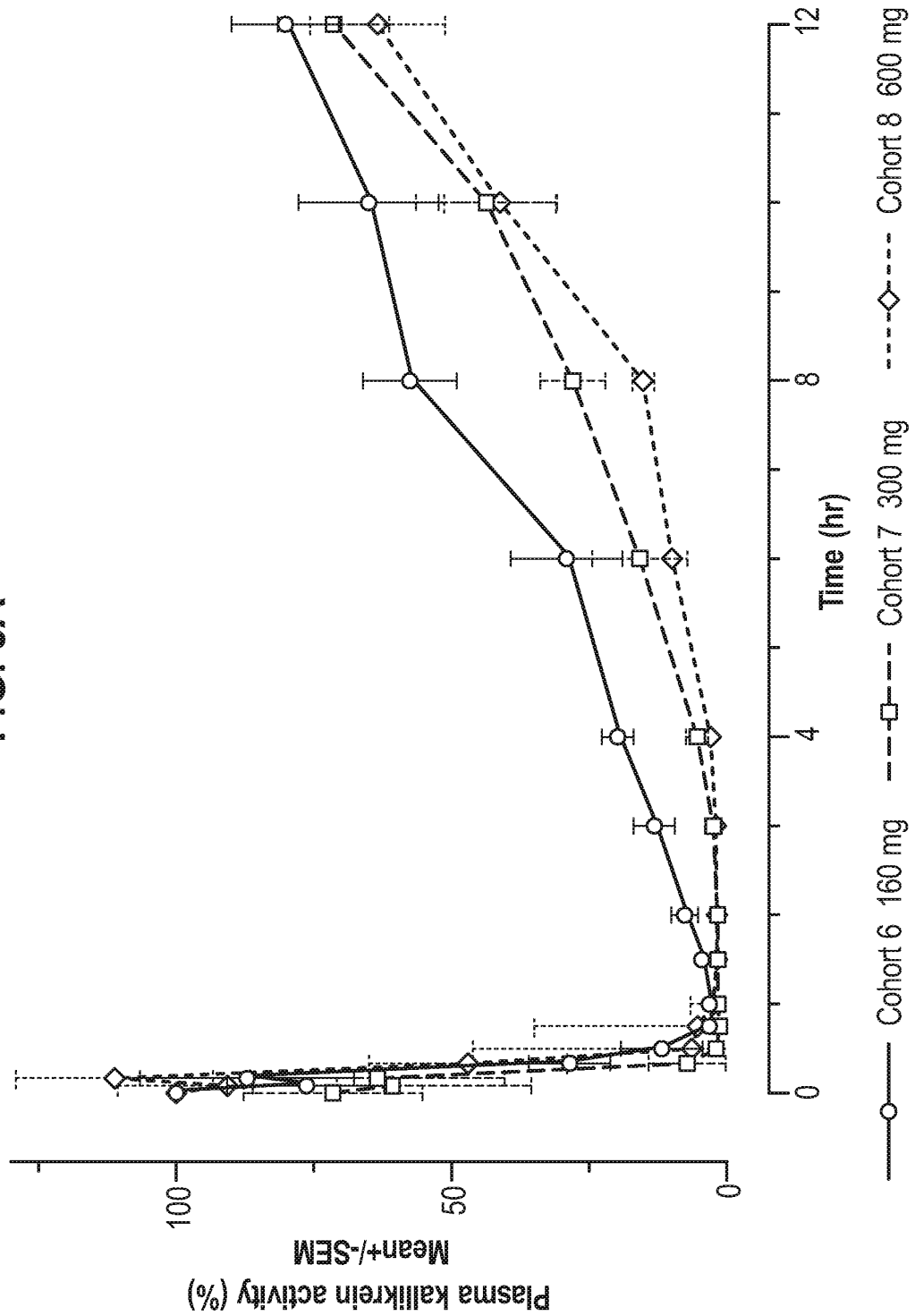

Plasma kallikrein activity (%)
Mean+/-SEM
100
50
0
0
4
8
12
Time (hr)
Cohort 6 160 mg
Cohort 7 300 mg
Cohort 8 600 mg

FIG. 5B

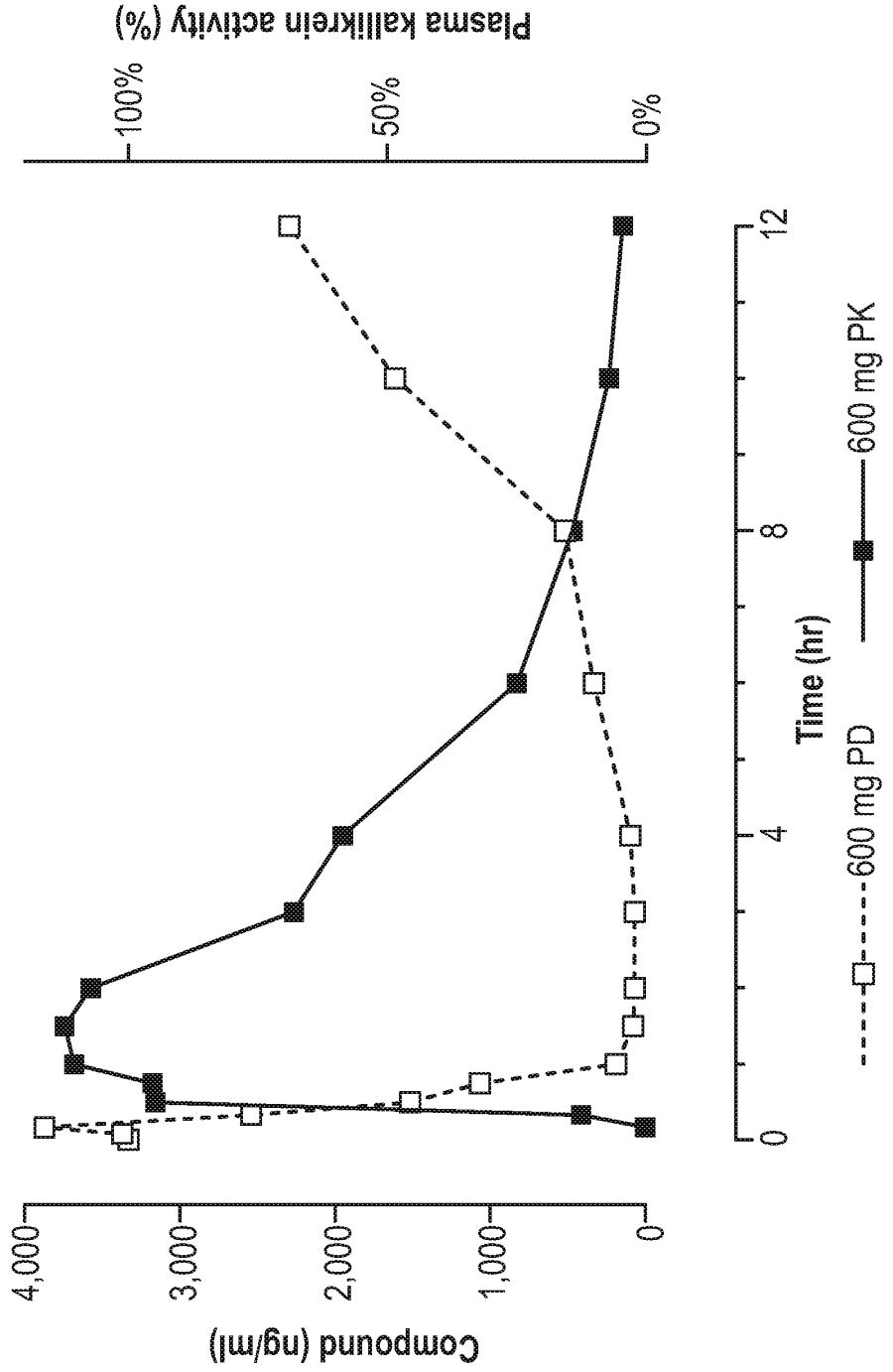

Plasma kallikrein activity (%)
100%
50%
0%
Compound (ng/ml)
4,000
3,000
2,000
1,000
0
0
4
8
12
Time (hr)
600 mg PD
600 mg PK

FIG. 6A

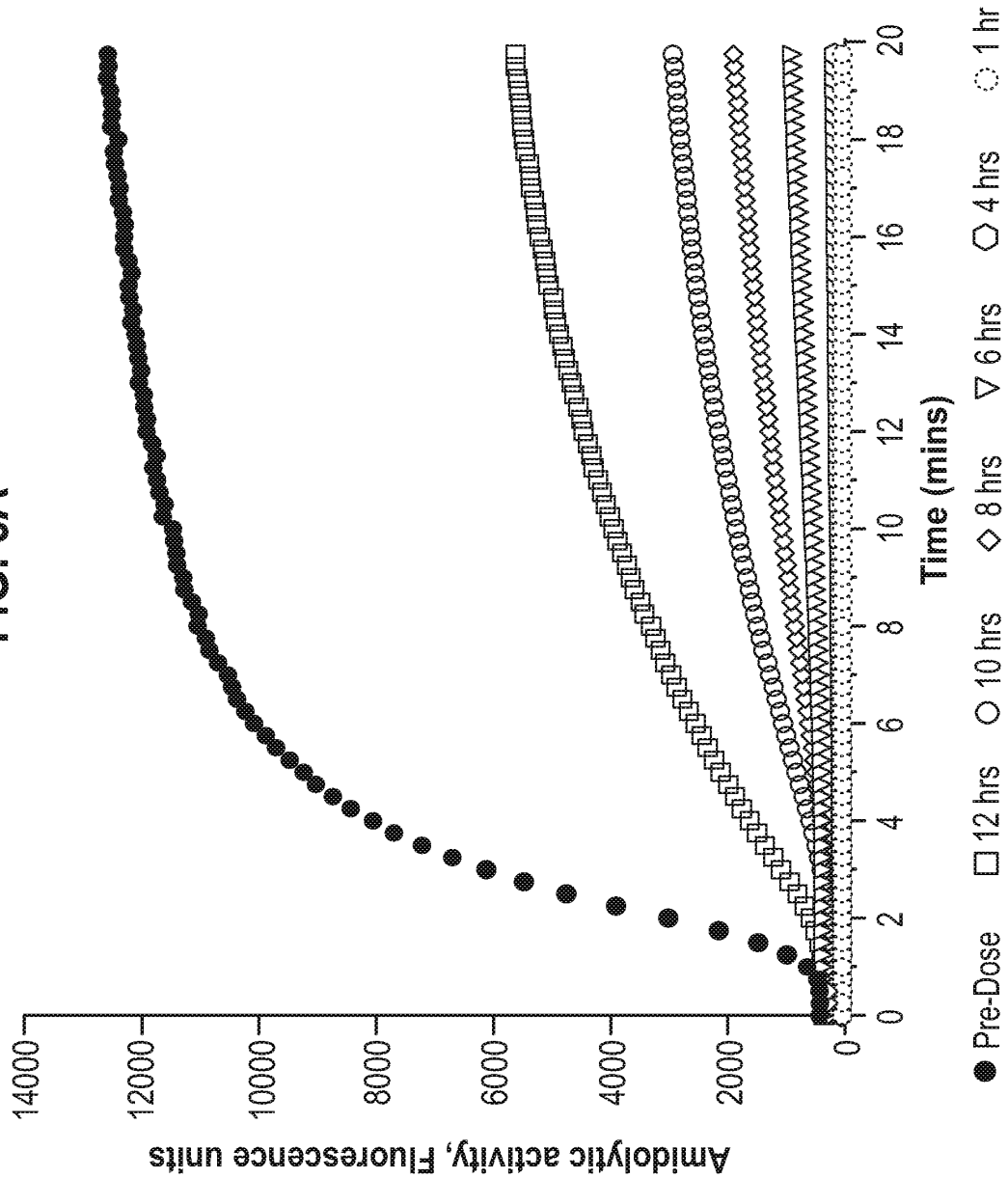
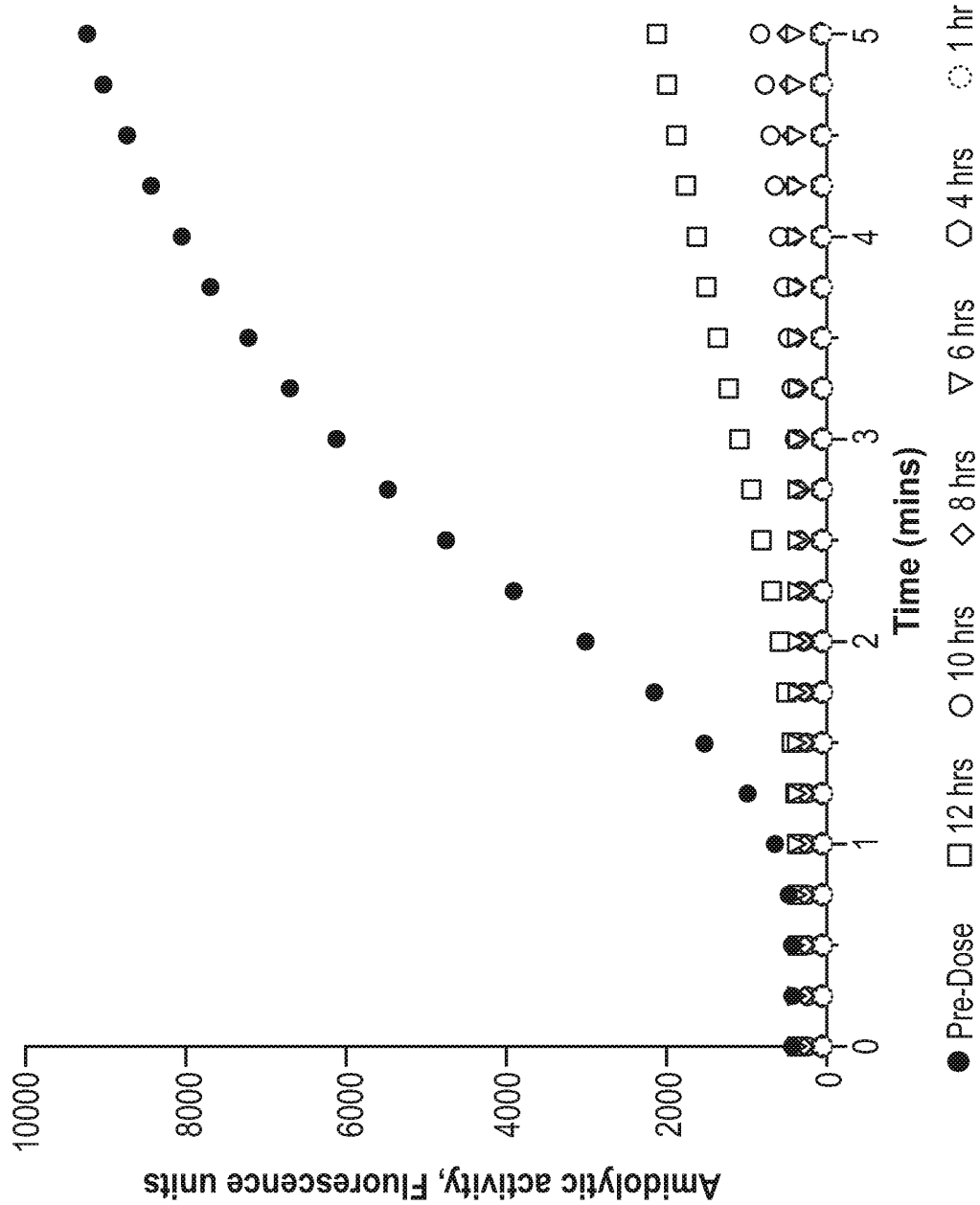

Amidolytic activity, Fluorescence units
14000
12000
10000
8000
6000
4000
2000
0
0
2
4
6
8
10
12
14
16
18
20
Time (mins)
Pre-Dose
12 hrs
10 hrs
8 hrs
6 hrs
4 hrs
1 hr

FIG. 6B


Amidolytic activity, Fluorescence units
10000
8000
6000
4000
2000
0
0
1
2
3
4
5
Time (mins)
Pre-Dose
12 hrs
10 hrs
8 hrs
6 hrs
4 hrs
1 hr

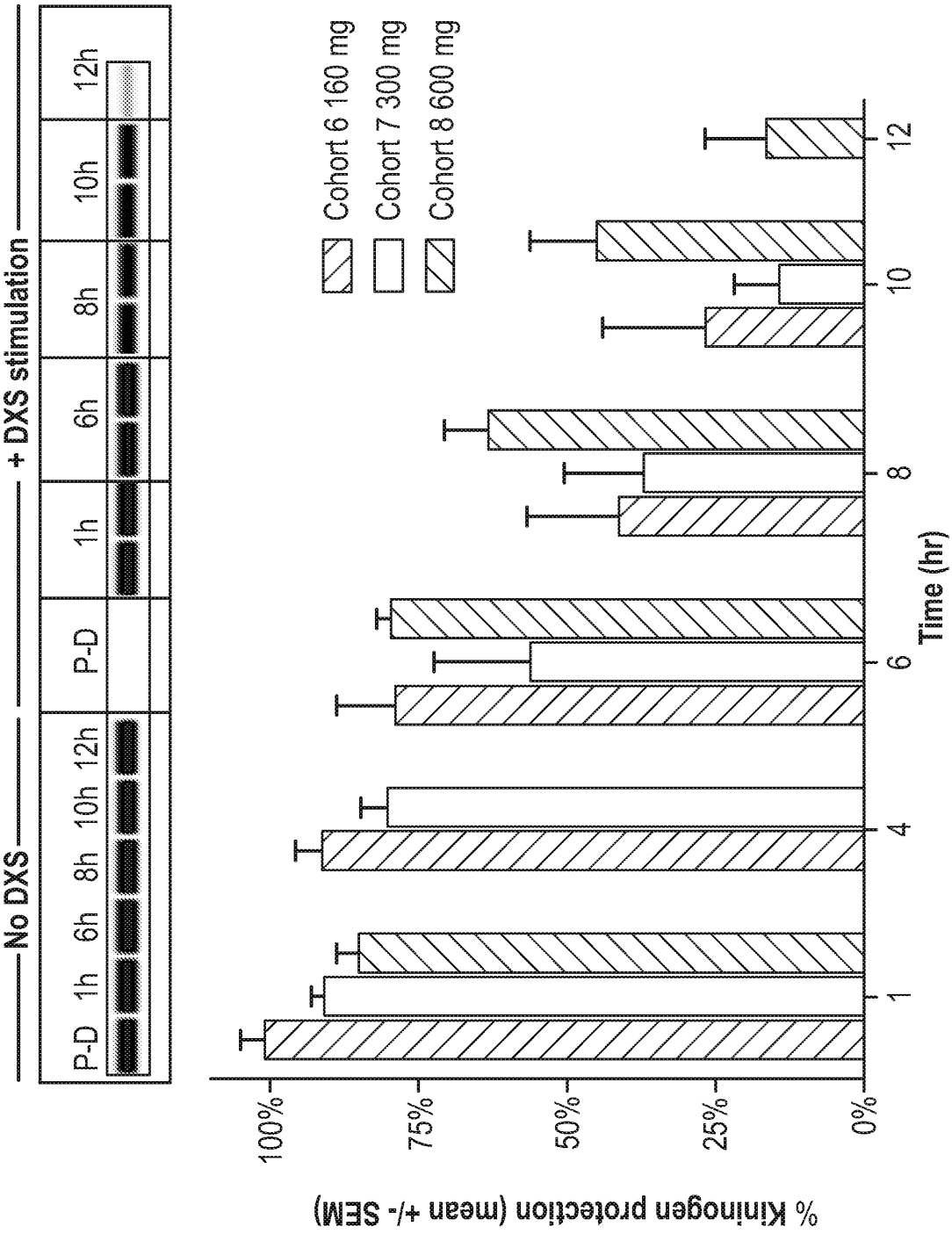

No DXS
+ DXS stimulation
P-D
1h
6h
8h
10h
12h
P-D
1h
6h
8h
10h
12h
Cohort 6 160 mg
Cohort 7 300 mg
Cohort 8 600 mg
% Kininogen protection (mean +/- SEM)
100%
75%
50%
25%
0%
1
4
6
8
10
12
Time (hr)

FIG. 7

FIG. 8

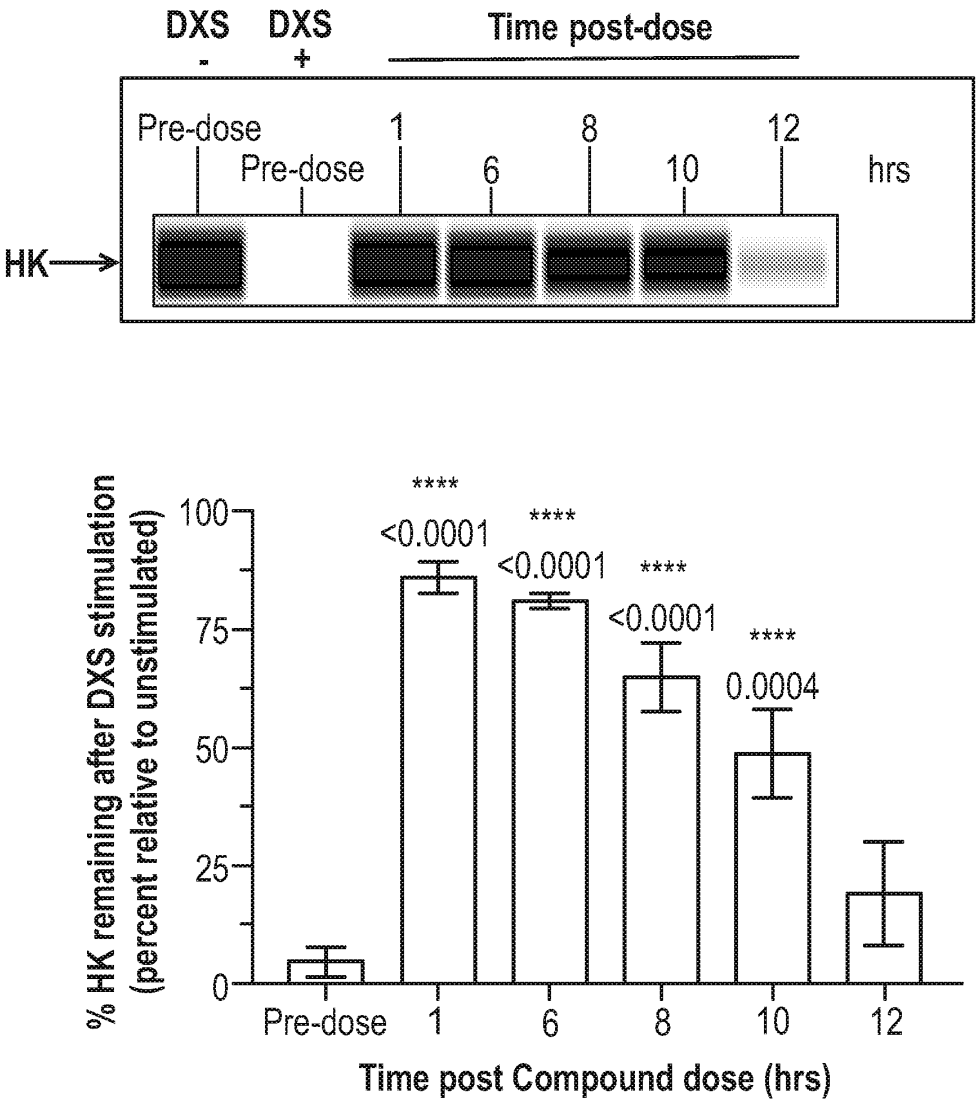

DXS -
DXS +
Time post-dose
Pre-dose
Pre-dose
1
6
8
10
12
hrs
HK
% HK remaining after DXS stimulation (percent relative to unstimulated)
100
75
50
25
0
****
<0.0001
****
<0.0001
****
<0.0001
****
0.0004
Pre-dose
1
6
8
10
12
Time post Compound dose (hrs)

FIG.9

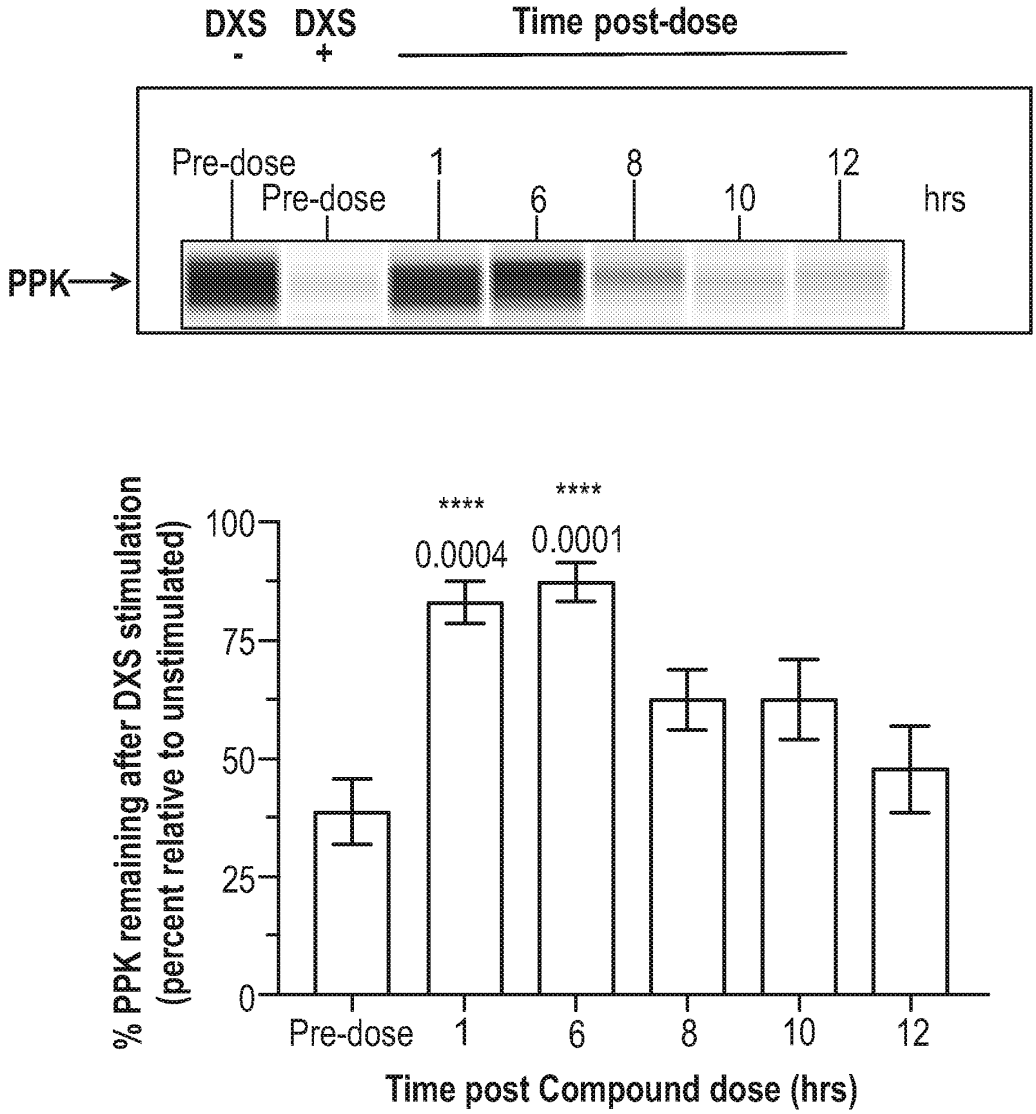

DXS -
DXS +
Time post-dose
Pre-dose
Pre-dose
1
6
8
10
12
hrs
PPK
% PPK remaining after DXS stimulation (percent relative to unstimulated)
100
75
50
25
0
****
****
0.0004
0.0001
Pre-dose
1
6
8
10
12
Time post Compound dose (hrs)

FIG. 10

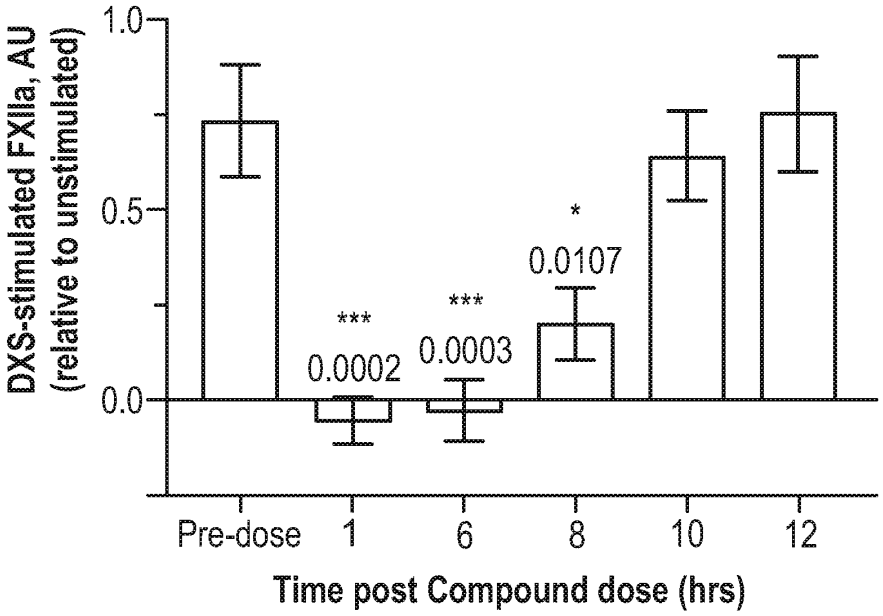

DXS-stimulated FXIIa, AU
(relative to unstimulated)
1.0
0.5
0.0
***
0.0002
***
0.0003
*
0.0107
Pre-dose
1
6
8
10
12
Time post Compound dose (hrs)

FIG. 11

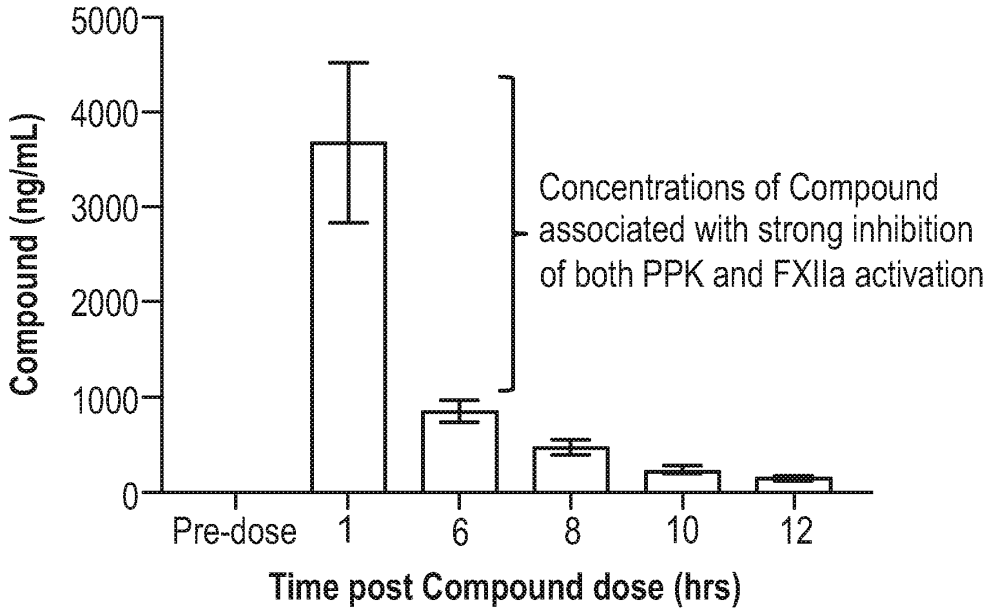

Compound (ng/mL)
5000
4000
3000
2000
1000
0
Concentrations of Compound
associated with strong inhibition
of both PPK and FXIIa activation
Pre-dose
1
6
8
10
12
Time post Compound dose (hrs)

FIG. 12

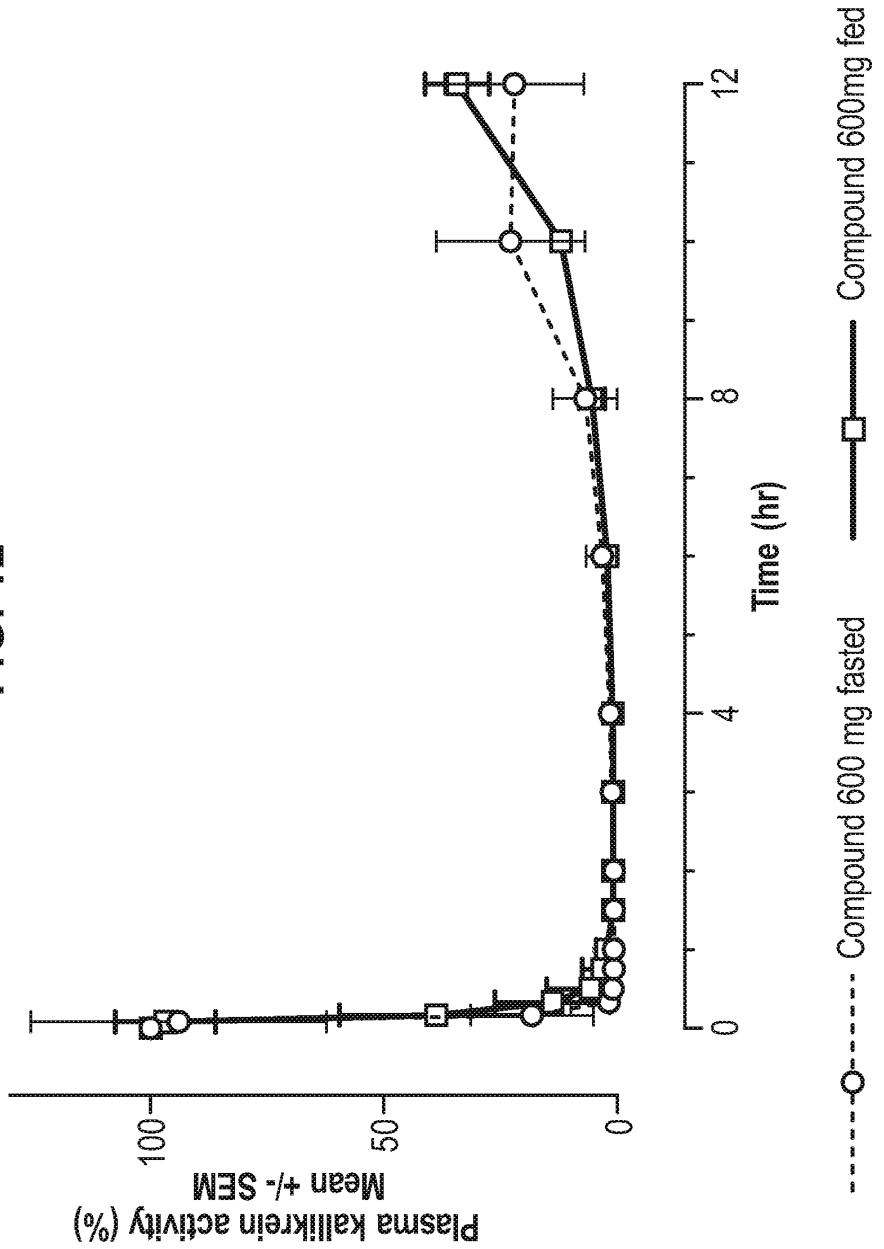

Plasma kallikrein activity (%)
Mean +/- SEM
100
50
0
0
4
8
12
Time (hr)
Compound 600 mg fasted
Compound 600mg fed

FIG. 13A

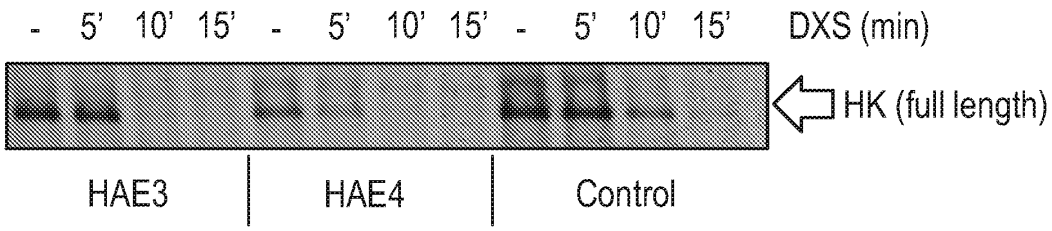


FIG. 13B

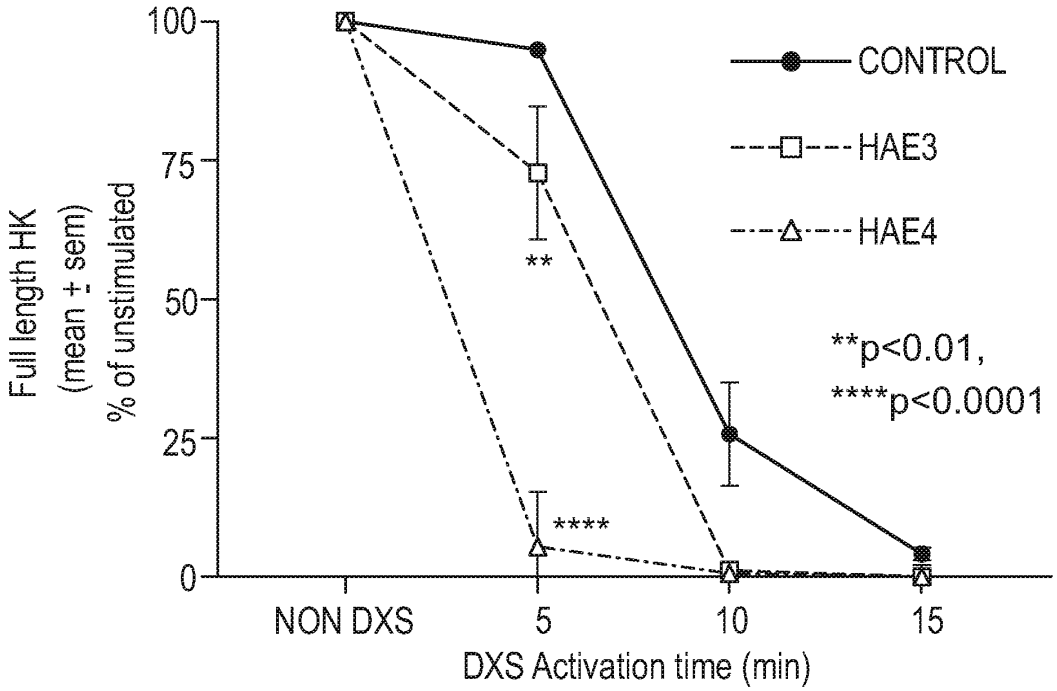


FIG. 14A

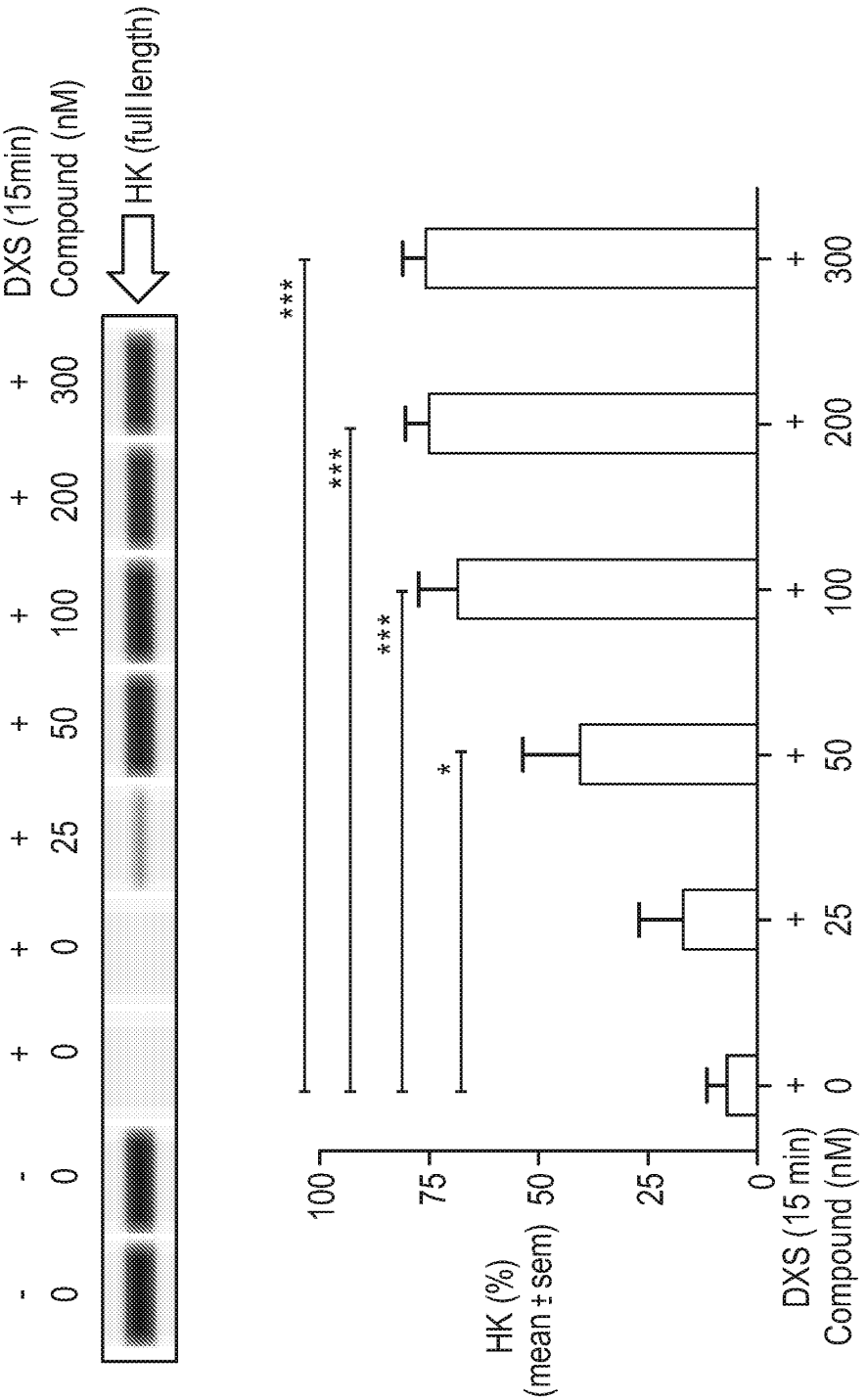

DXS (15min)
Compound (nM)
HK (full length)
- - + + + + + +
0 0 0 0 25 50 100 200 300
HK (%)
(mean ± sem)
100
75
50
25
0
***
***
***
*
DXS (15 min)
Compound (nM)
+ + + + + + +
0 25 50 100 200 300

FIG. 14B

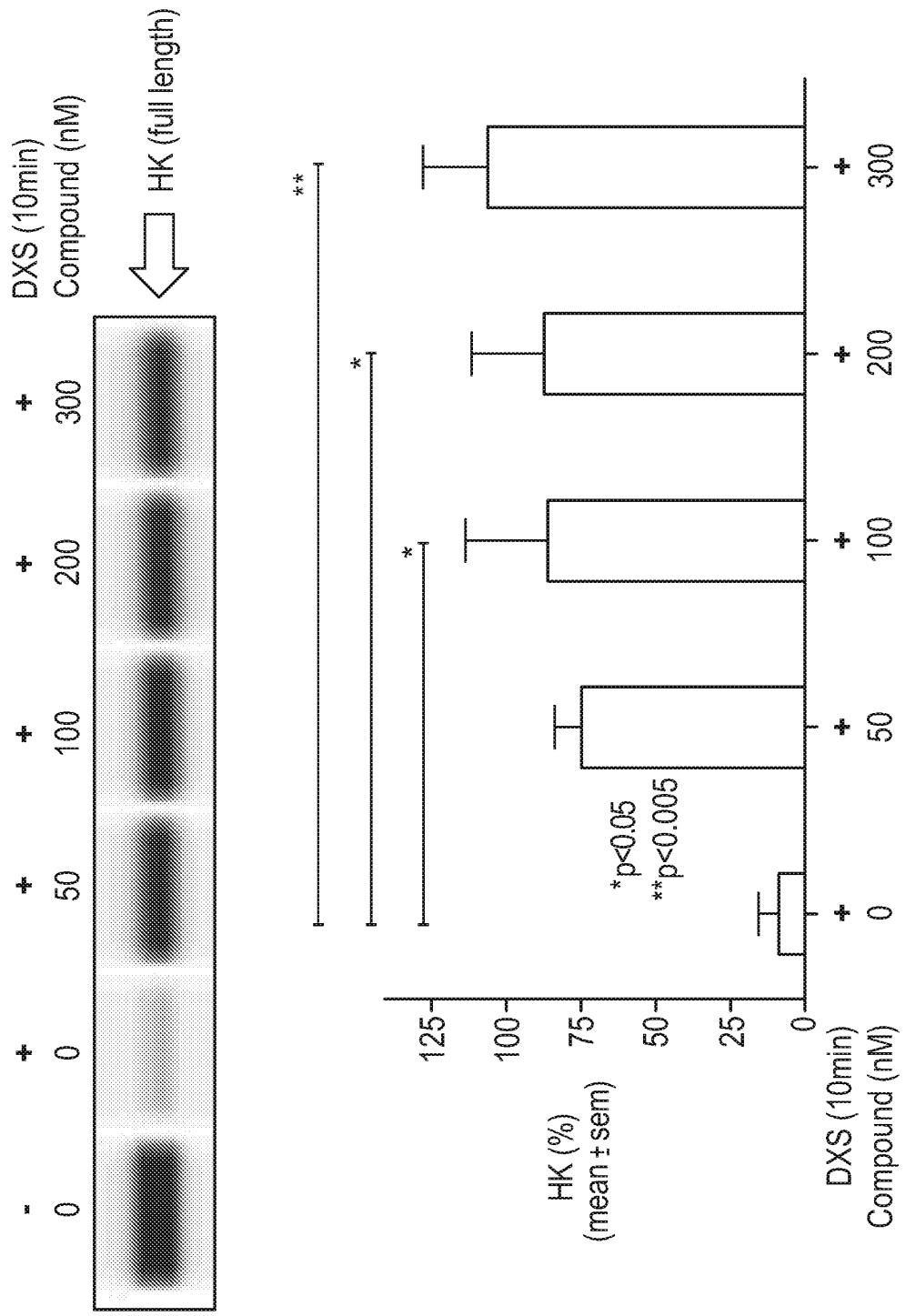

DXS (10min)
Compound (nM)
HK (full length)
- + + + + +
0 0 50 100 200 300
HK (%)
(mean ± sem)
125
100
75
50
25
0
*p<0.05
**p<0.005
*
*
**
DXS (10min)
Compound (nM)
+ + + + +
0 50 100 200 300

FIG. 15

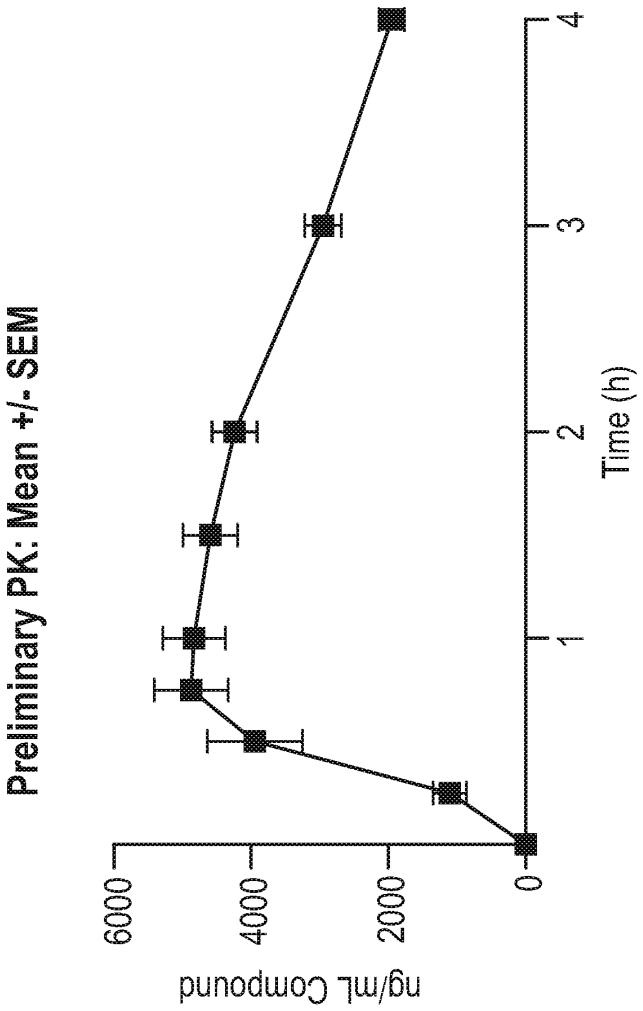

Preliminary PK: Mean +/- SEM
ng/mL Compound
6000
4000
2000
0
1
2
3
4
Time (h)

FIG. 16A

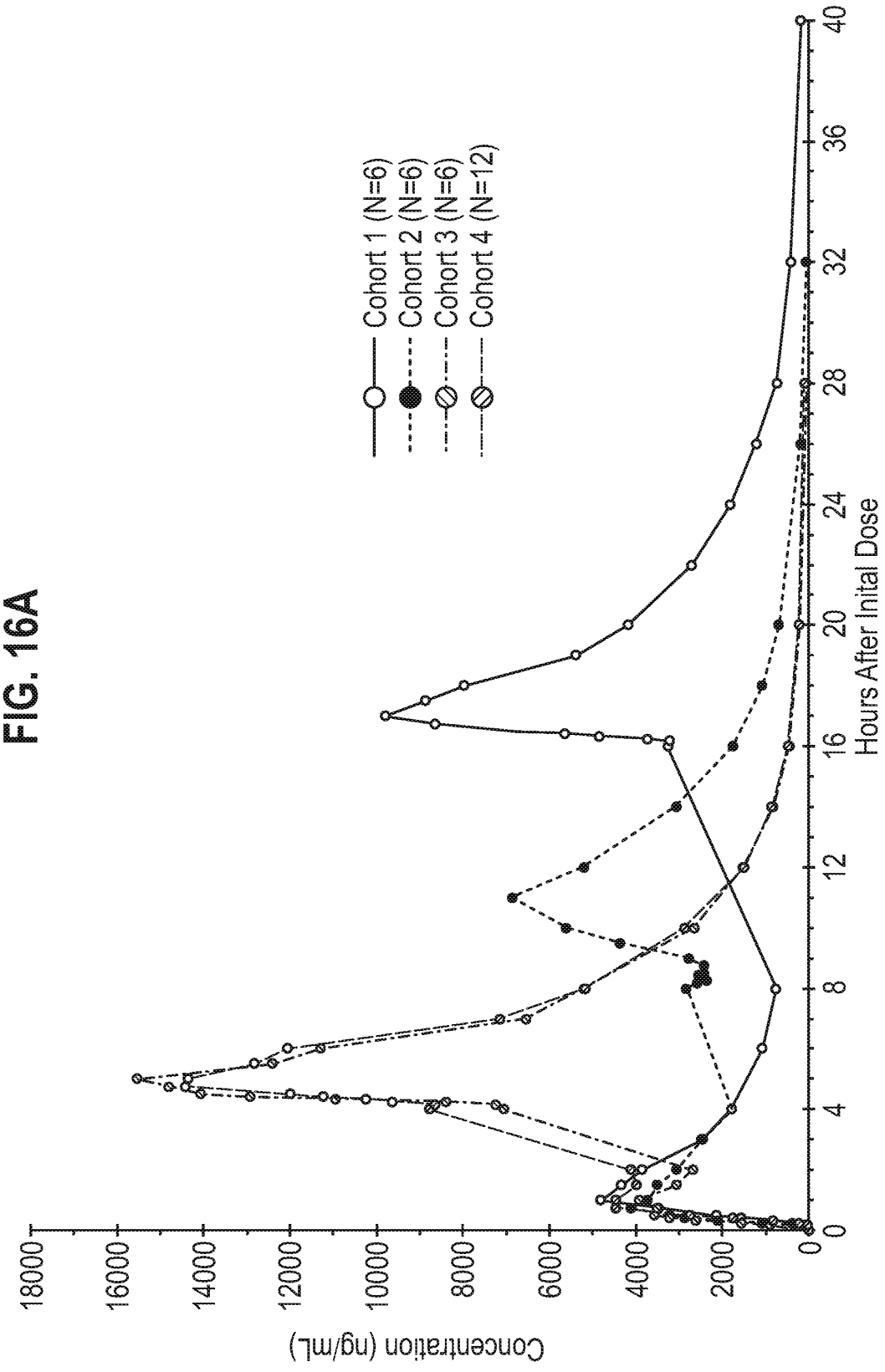
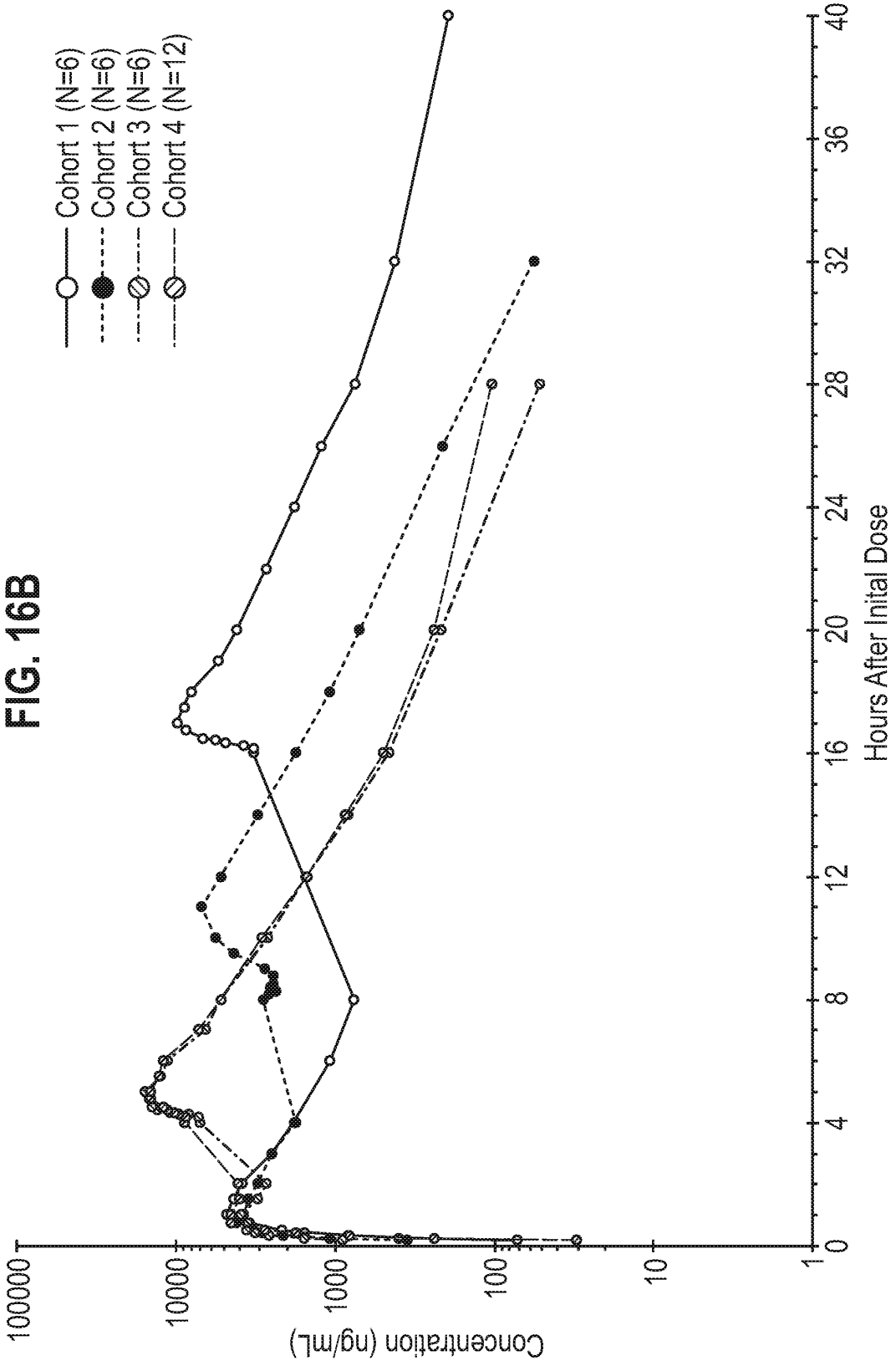

Cohort 1 (N=6)
Cohort 2 (N=6)
Cohort 3 (N=6)
Cohort 4 (N=12)
Concentration (ng/mL)
Hours After Inital Dose
0
2000
4000
6000
8000
10000
12000
14000
16000
18000
0
4
8
12
16
20
24
28
32
36
40

FIG. 16B


Cohort 1 (N=6)
Cohort 2 (N=6)
Cohort 3 (N=6)
Cohort 4 (N=12)
Concentration (ng/mL)
100000
10000
1000
100
10
1
0
4
8
12
16
20
24
28
32
36
40
Hours After Inital Dose