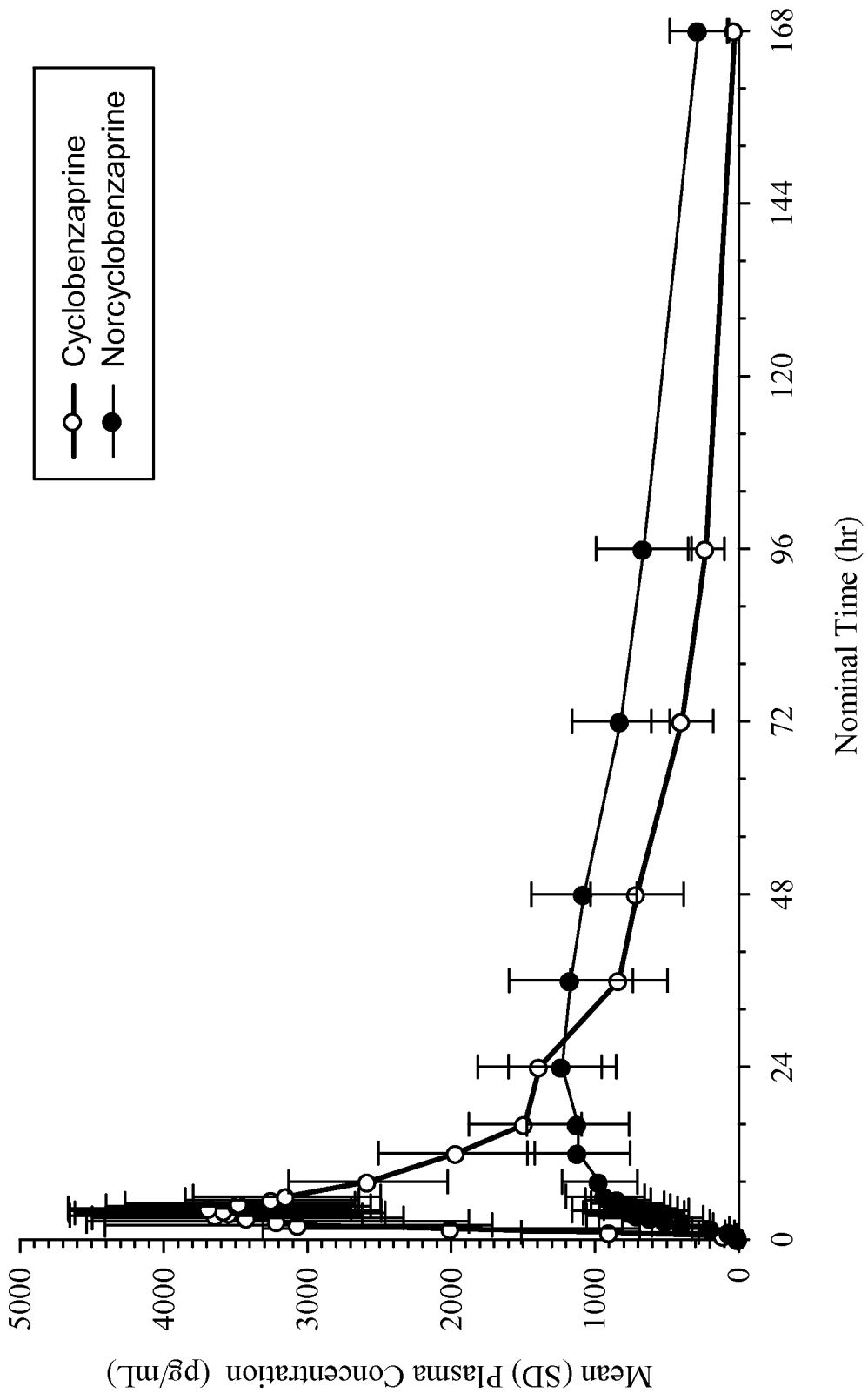

Cyclobenzaprine
Norcyclobenzaprine
Mean (SD) Plasma Concentration (pg/mL)
5000
4000
3000
2000
1000
0
0
24
48
72
96
120
144
168
Nominal Time (hr)

Figure 1a

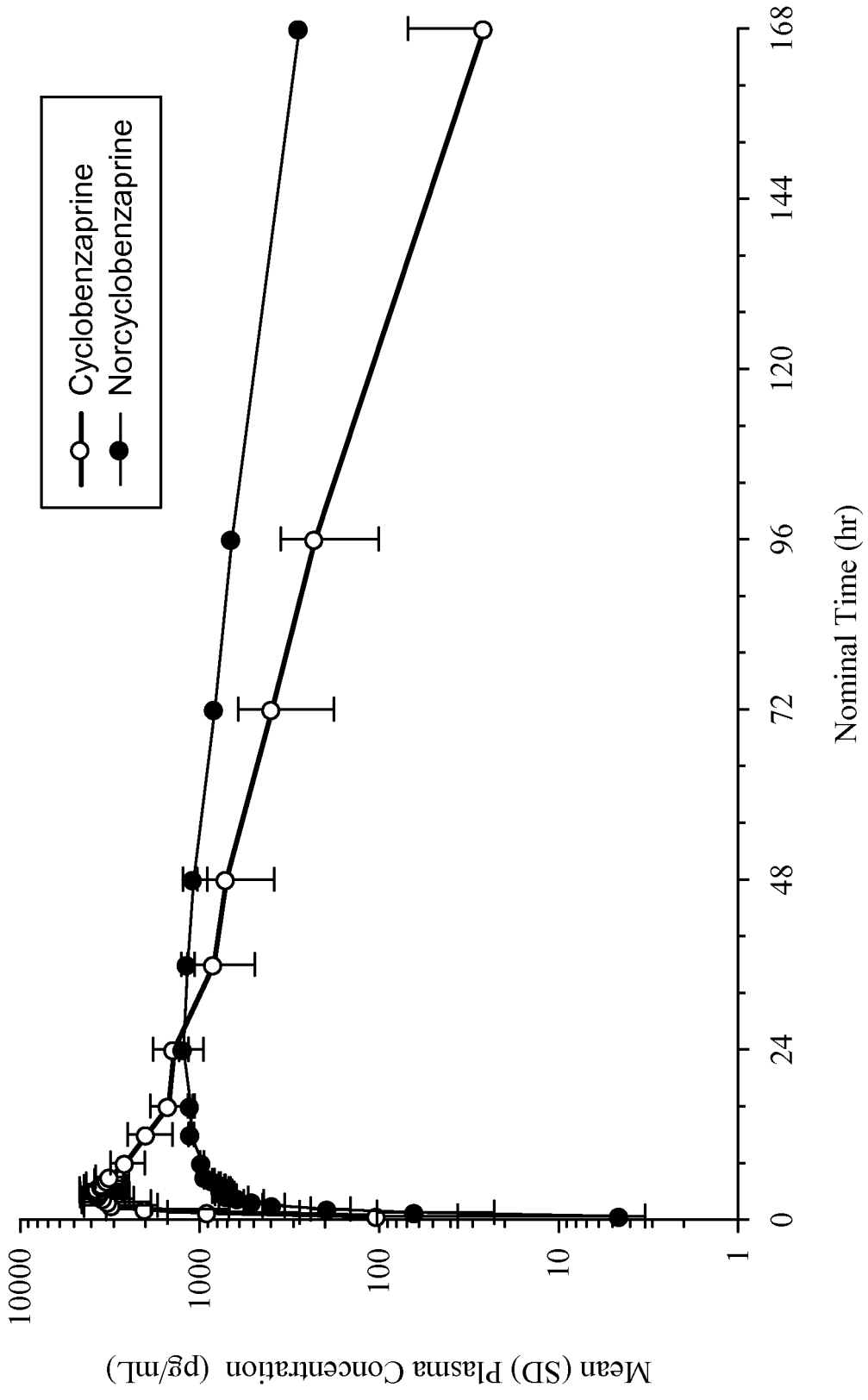

Cyclobenzaprine
Norcyclobenzaprine
Mean (SD) Plasma Concentration (pg/mL)
10000
1000
100
10
1
0
24
48
72
96
120
144
168
Nominal Time (hr)

Figure 1b

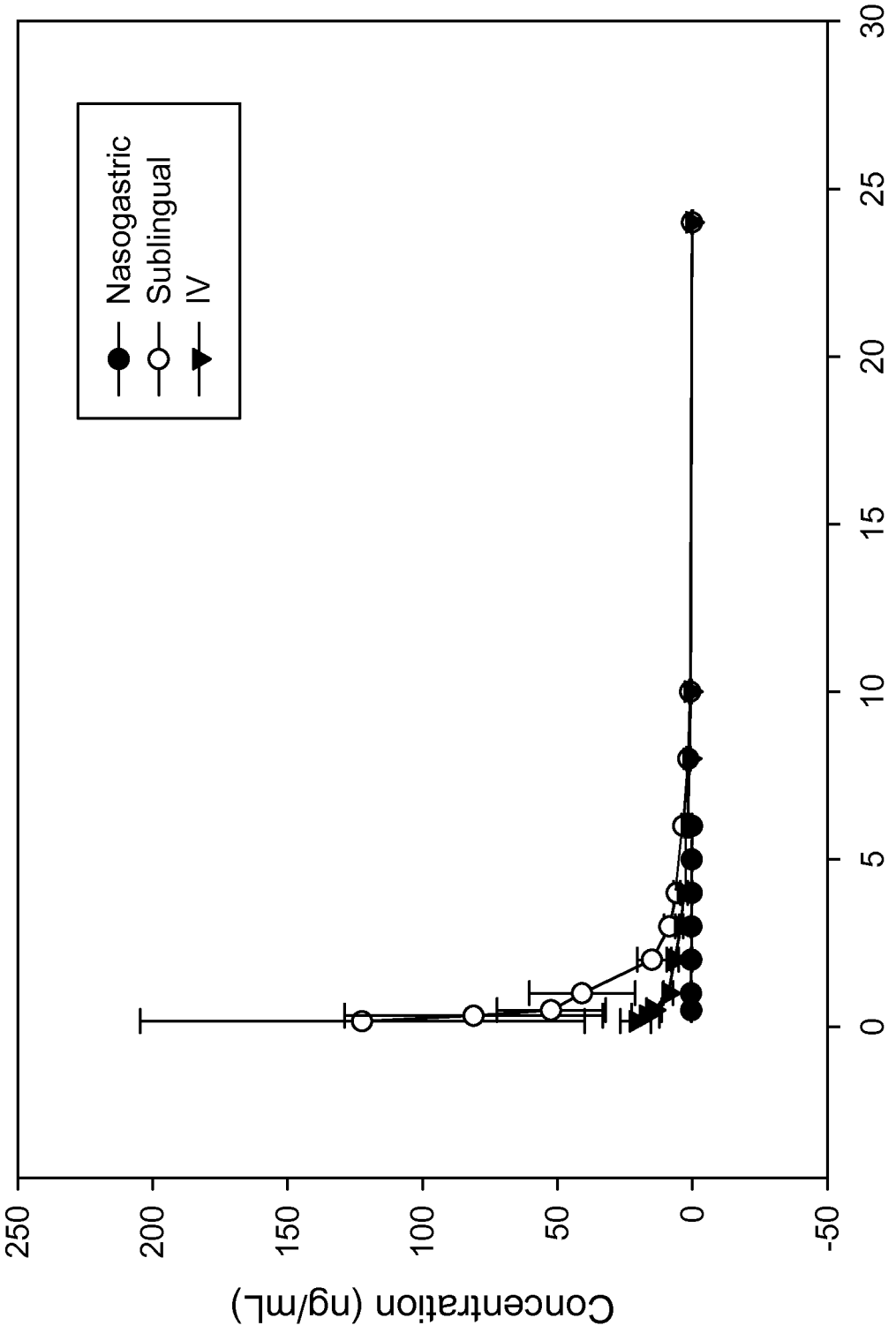

Nasogastric
Sublingual
IV
Concentration (ng/mL)
250
200
150
100
50
0
-50
0
5
10
15
20
25
30
Time (h)

Figure 2

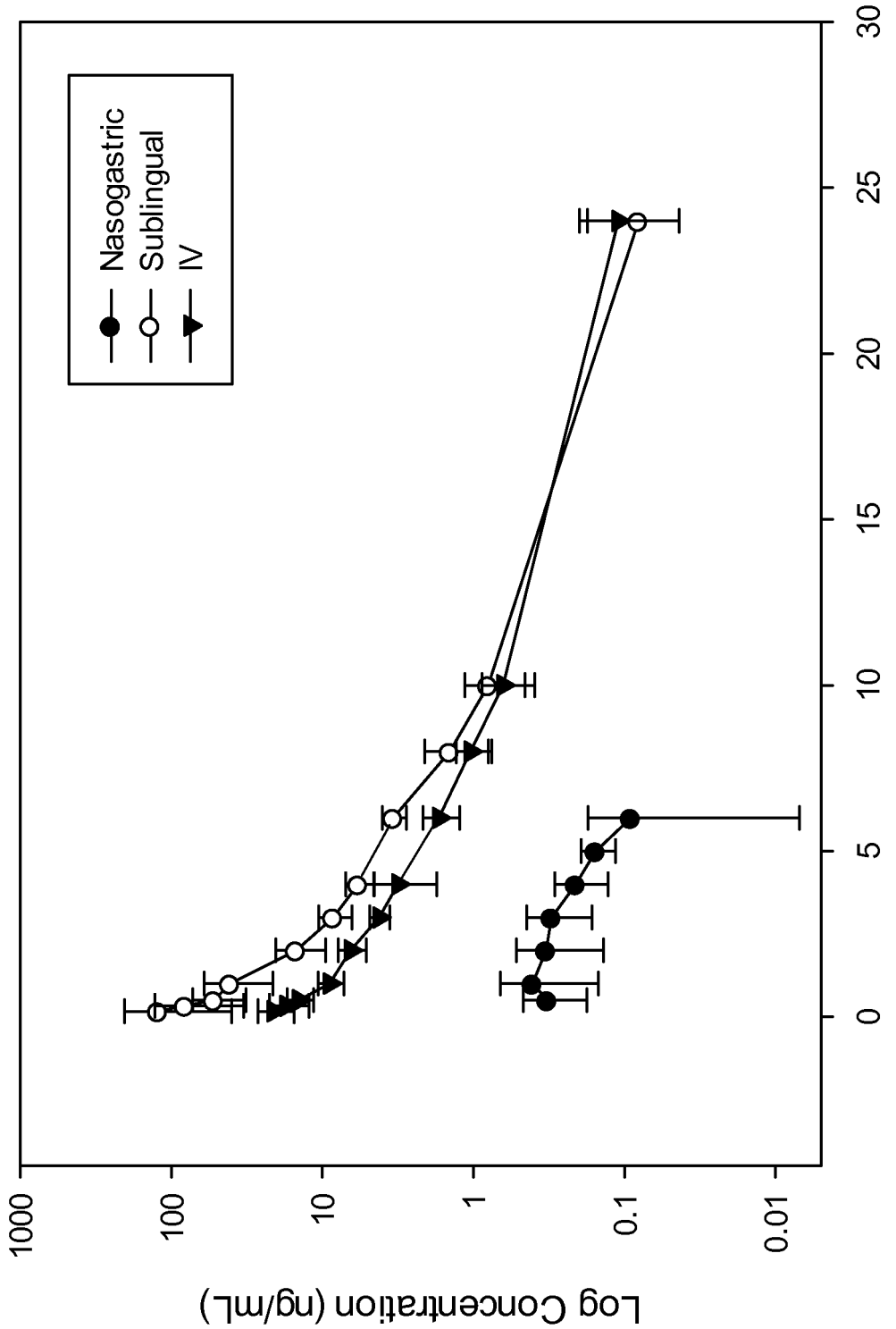

Nasogastric
Sublingual
IV
1000
100
10
1
0.1
0.01
Log Concentration (ng/mL)
0
5
10
15
20
25
30
Time (h)

Figure 3

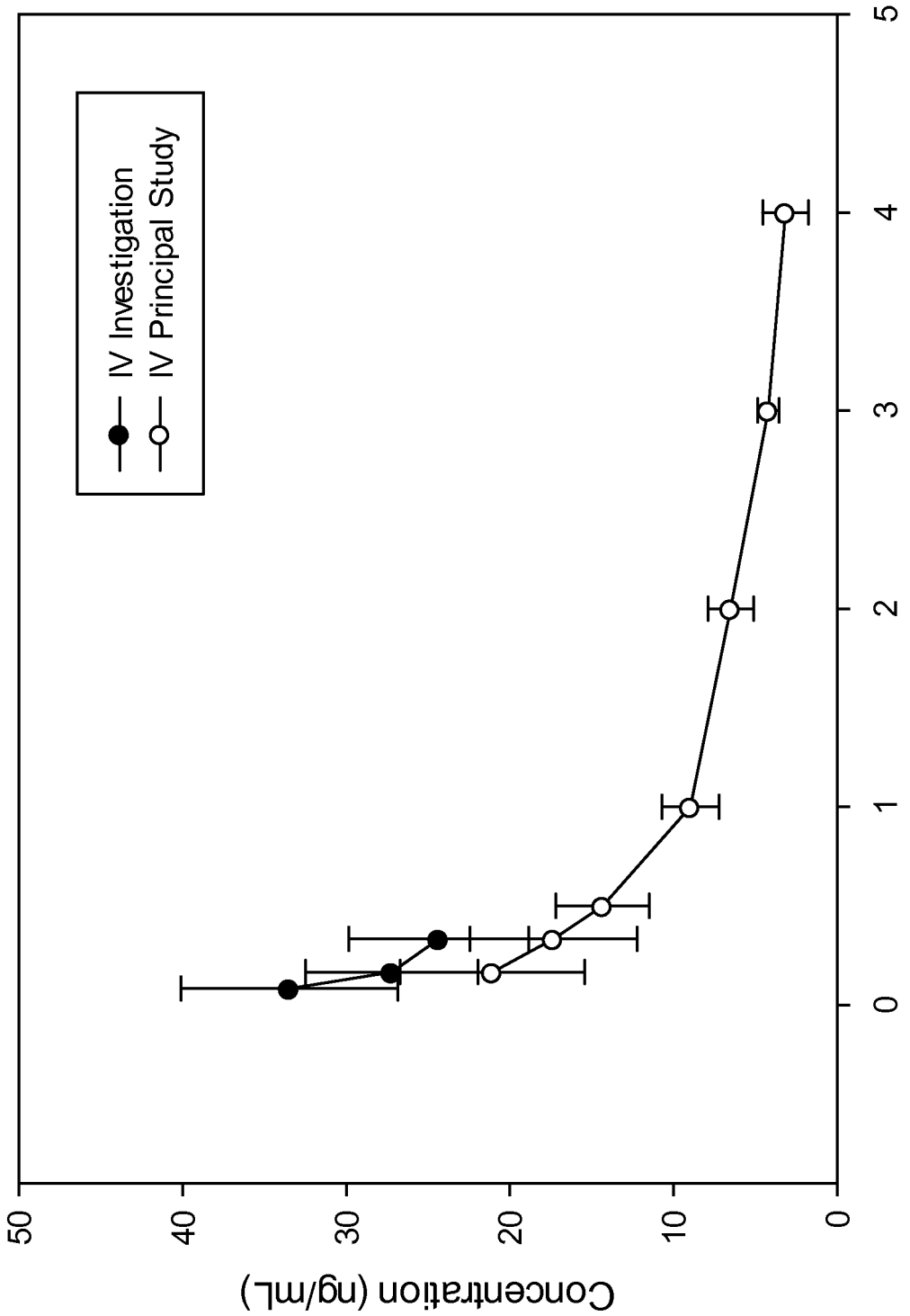

IV Investigation
IV Principal Study
Concentration (ng/mL)
0
10
20
30
40
50
Time (h)
0
1
2
3
4
5

Figure 4

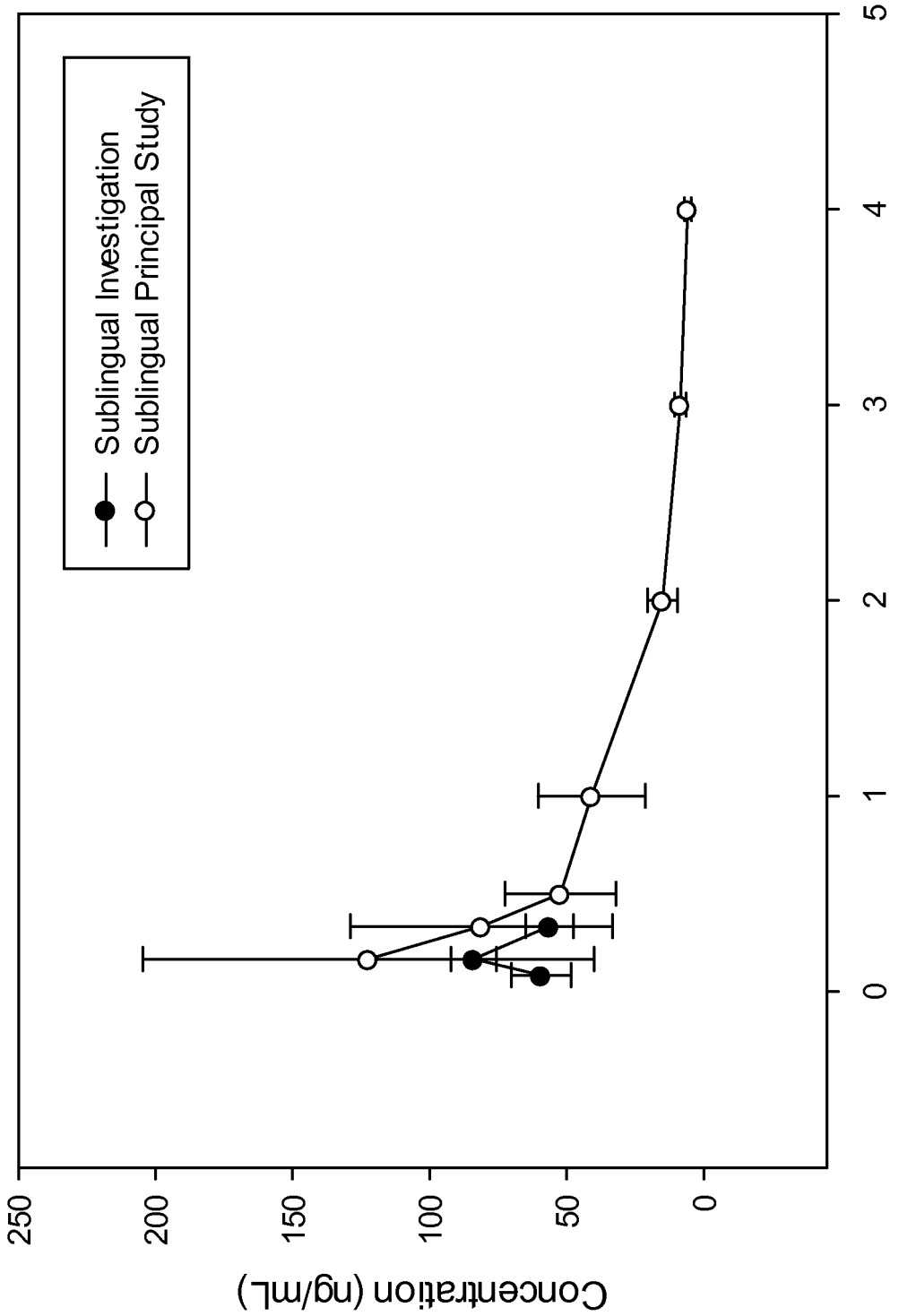

Sublingual Investigation
Sublingual Principal Study
Concentration (ng/mL)
250
200
150
100
50
0
0
1
2
3
4
5
Time (h)

Figure 5

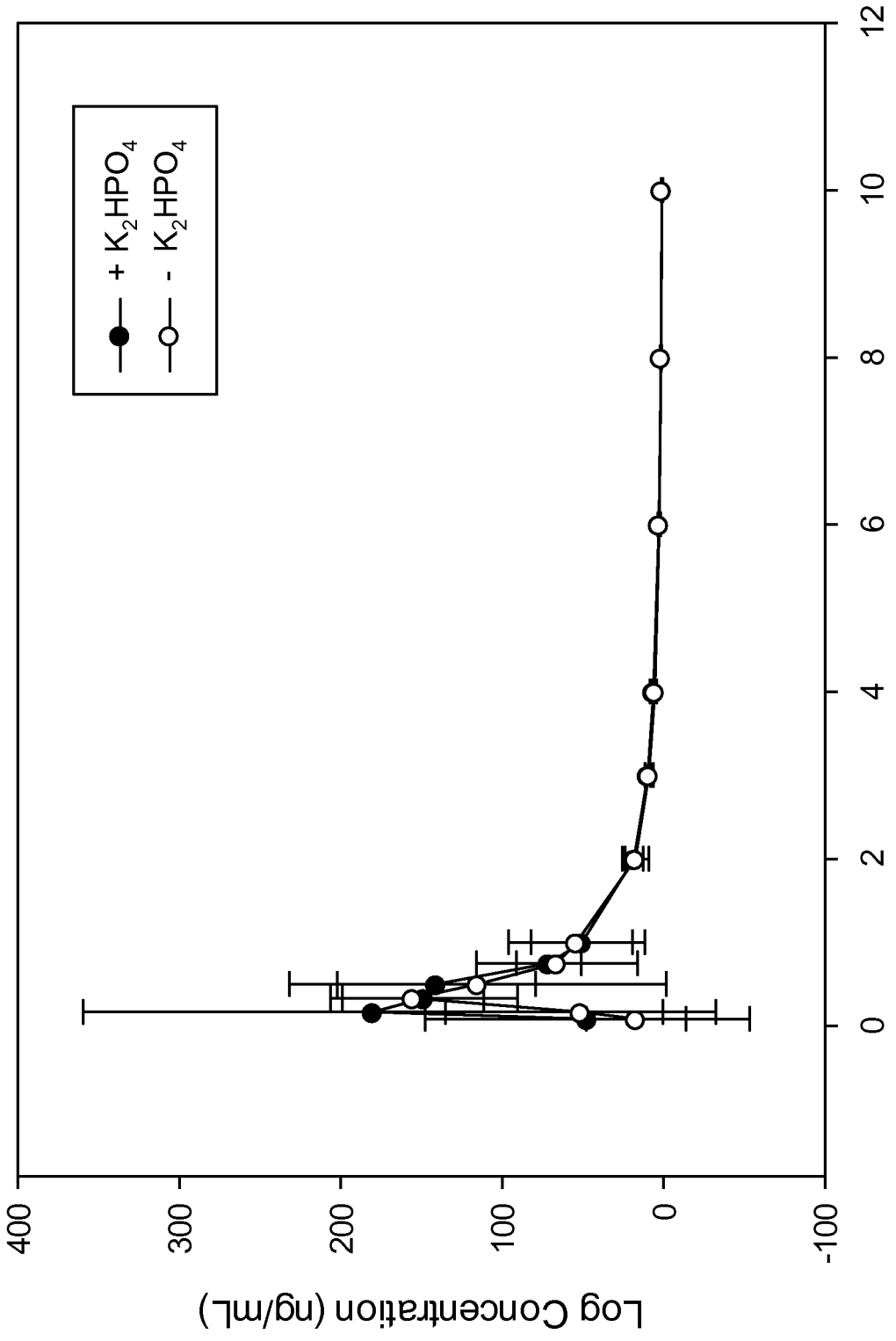

+ K_2HPO_4
- K_2HPO_4
Log Concentration (ng/mL)
400
300
200
100
0
-100
0
2
4
6
8
10
12
Time (h)

Figure 6

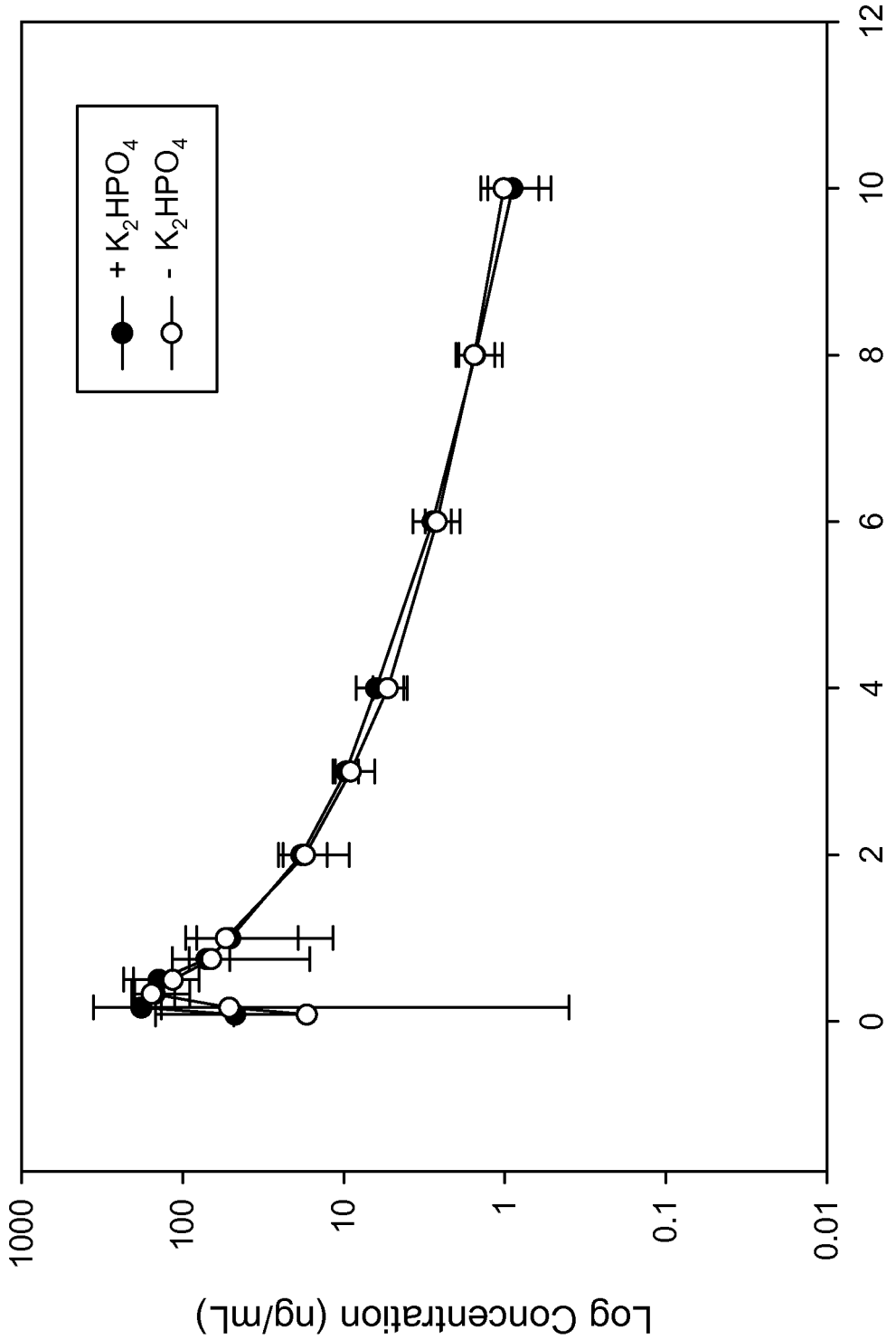

+ K_2HPO_4
- K_2HPO_4
Log Concentration (ng/mL)
1000
100
10
1
0.1
0.01
0
2
4
6
8
10
12
Time (h)

Figure 7

Assessment	Screening, Days -30 to -2	Baseline, Day -1 (On-Site)	Dosing Period (Confined to Study Site)				Follow-up Call, 10 ± 3 Days After Dosing
			Day 1	Day 2	Day 3	Day 4	
Informed consent	x	—	—	—	—	—	—
Medical history	x	—	—	—	—	—	—
Urine β-HCG test (all women)	x	—	—	—	—	x	—
Serum β-HCG test (all women)	—	x	—	—	—	—	—
TSH, HIV, hepatitis B and C	x	—	—	—	—	—	—
Practice sublingual dosing test	—	x	—	—	—	—	—
Alcohol breath test	x	x	—	—	—	—	—
Urine drug screen	x	x	—	—	—	—	—
Urine cotinine	x	x	—	—	—	—	—
Height	x	—	—	—	—	—	—
Physical examination	x	x[a]	—	—	—	x[a]	—
Weight/body mass index	x	x	—	—	—	x	—
Prior/concomitant medications	x	x	x	x	x	x	x
Clinical laboratory tests	x	x	—	—	—	x	—
Vital signs (sitting)[b]	x	x	x	x	x	x	—
12-Lead ECG (supine)	x	x	—	—	—	x	—
Adverse events	x	x	x	x	x	x	x
Administer drug	—	—	x	—	—	—	—
Plasma samples (PK)[c]	—	—	x	x	x	x	—
Urine samples (PK)[d]	—	—	x	x	x	x	—

Abbreviations: ECG, electrocardiogram; HCG, human chorionic gonadotropin; HIV, human immunodeficiency virus; PK, pharmacokinetic; TSH, thyroid-stimulating hormone.

[a] Brief physical examination only.

[b] Vital signs (sitting blood pressure, respiratory rate, oral temperature, and heart rate) will be assessed at screening, upon admission to the study unit, within 1 hour pre-dose, and 1, 3, 6, 8, 12, 24, 48, and 72 hours post-dose. Vital signs will be recorded in advance of other assessments scheduled for a given timepoint, except at the Hour 72 timepoint, when vital signs will be recorded after other assessments have been completed. Otherwise, when another safety measurement coincides with a blood draw, the blood draw will be completed first.

[c] For pharmacokinetic analysis, a total of 25 blood samples will be taken: within 30 minutes pre-dose and 5, 10, 20, 30, and 45 minutes and 1, 2, 2.5, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 8, 12, 16, 24, 36, 48, and 72 hours post-dose.

[d] A single urine sample will be collected within 30 minutes pre-dose (one sample), and urine will be pooled from 0-24, 24-48, and 48-72 hours post-dose. If a subject cannot void his or her bladder within 30 minutes before dosing, a sample from earlier that morning may be used as the pre-dose sample.

Figure 8

SUBSTITUTE SHEET (RULE 26)

SUBSTITUTE SHEET (RULE 26)

Assessment	Time Relative to Dosing, Days 1-4 (Dosing Period)																									
	Day 1																						Day 2		Day 3	Day 4
	Pre-dose[a]	0	5 min	10 min	20 min	30 min	45 min	1 h	2 h	2.5 h	3 h	3.33 h	3.67 h	4 h	4.33 h	4.67 h	5 h	5.5 h	6 h	8 h	12 h	16 h	24 h	36 h	48 h	72 h[b]
Dosing		x																								
Vital signs[c]	x							x			x								x	x	x		x		x	x
Plasma PK	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Urine PK	x	Pooled, 0-24 hours																					24-48 h		48-72 h	
Clinlabs																										x
Urine β-HCG																										x
Brief physical examination																										x
Weight/BMI																										x
12-Lead ECG																										x
AEs	Ongoing																									
Conmeds	Ongoing																									

Abbreviations: Adverse events; AEs; BMI, body mass index; clinlabs, clinical laboratory tests; conmeds, concomitant medications; ECG, electrocardiogram; h, hour(s); HCG, human chorionic gonadotropin; min, minute(s); PK, pharmacokinetics.

[a] Predose evaluations are to be performed within 30 minutes prior to dosing, with the exception of vital signs, which may be recorded within 1 hour prior to dosing. If a subject cannot void his or her bladder within 30 minutes before dosing, a sample from earlier that morning may be used as the predose sample.

[b] Day 4 evaluations will be performed at 72 ± 1.5 hours after dosing. Vital signs will be performed last on Day 4 only.

[c] Vital signs will be recorded in advance of other assessments scheduled for a given timepoint, except at the Hour 72 timepoint, when vital signs will be recorded after other assessments have been completed. Otherwise, when another safety measurement coincides with a blood draw, the blood draw will be completed first.

Figure 9

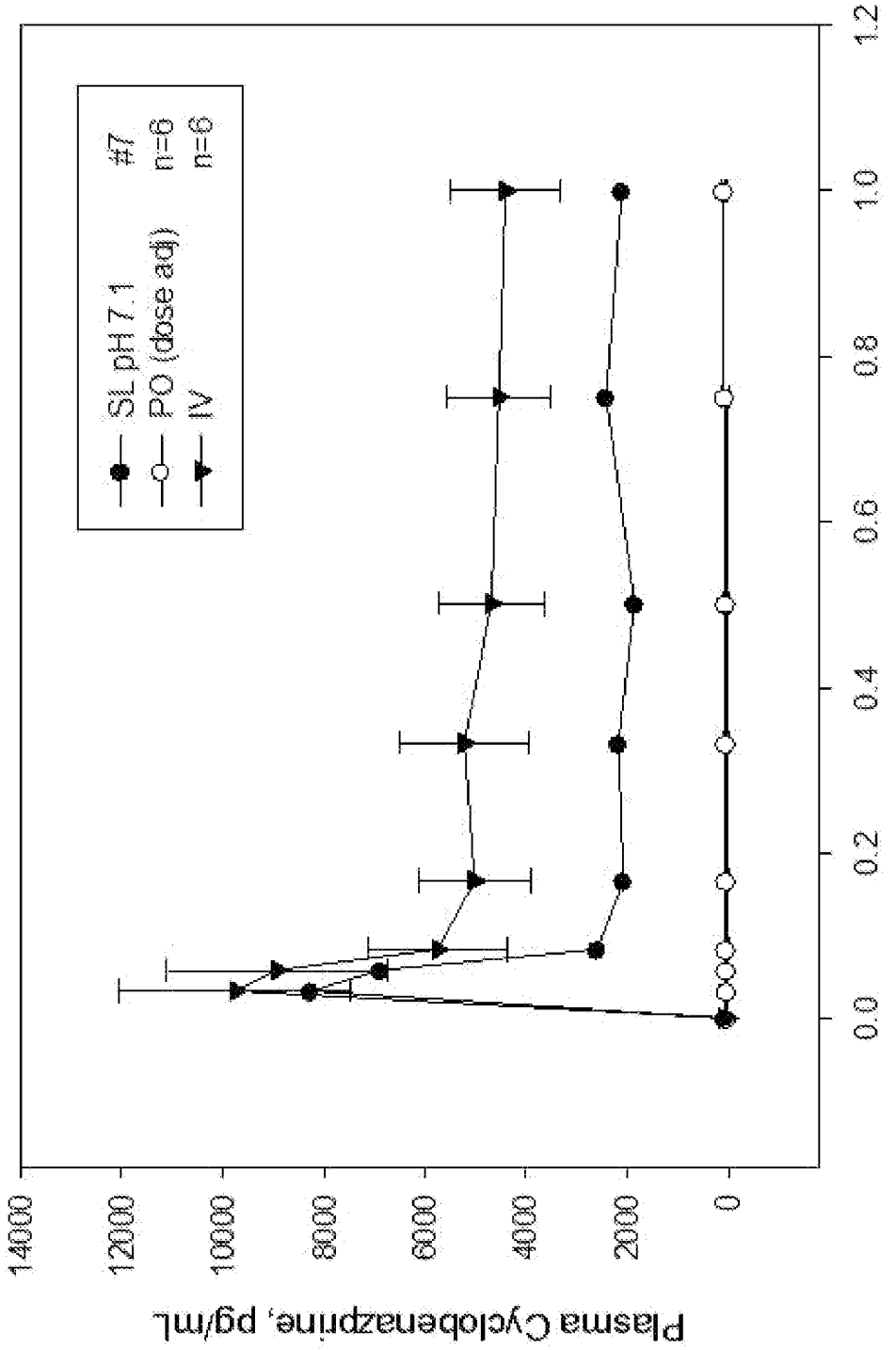

Plasma Cyclobenzaprine, pg/mL
14000
12000
10000
8000
6000
4000
2000
0
0.0
0.2
0.4
0.6
0.8
1.0
1.2
Time, h
SL pH 7.1 #7
PO (dose adj) n=6
IV n=6

Figure 10

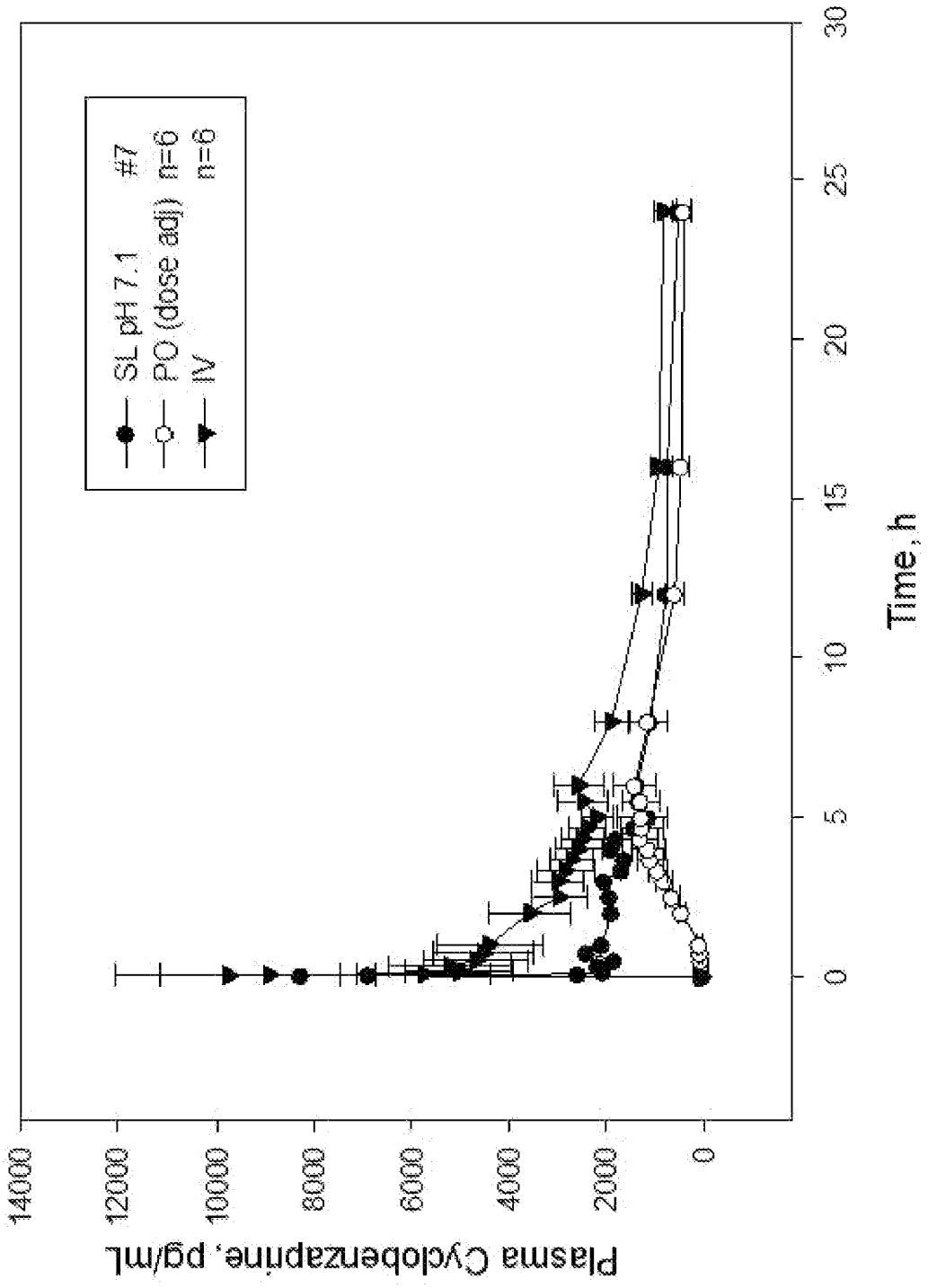

Plasma Cyclobenzaprine, pg/mL
14000
12000
10000
8000
6000
4000
2000
0
Time, h
0
5
10
15
20
25
30
SL pH 7.1 #7
PO (dose adj) n=6
IV n=6

Figure 11

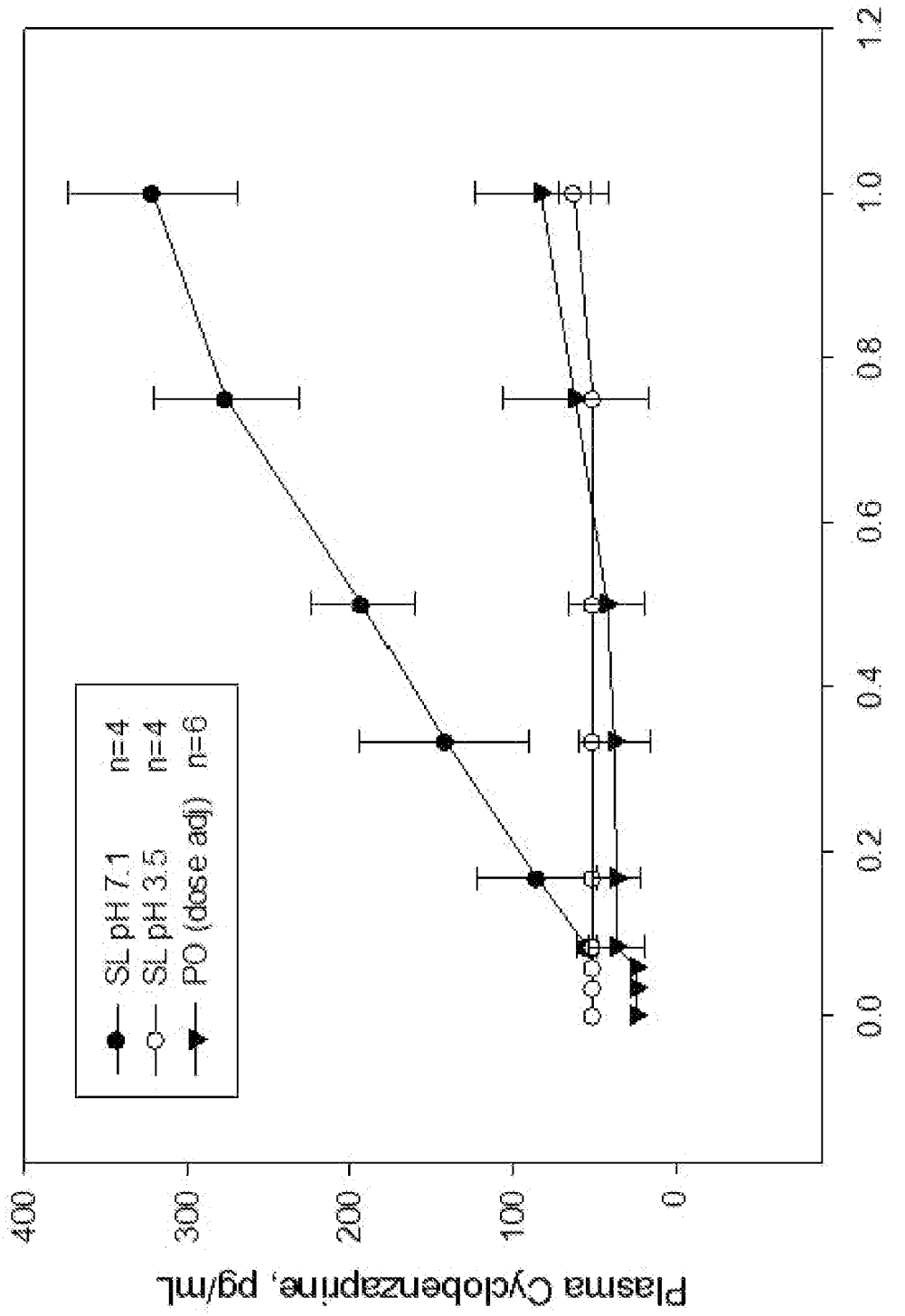

Plasma Cyclobenzaprine, pg/mL
400
300
200
100
0
0.0
0.2
0.4
0.6
0.8
1.0
1.2
Time, h
SL pH 7.1 n=4
SL pH 3.5 n=4
PO (dose adj) n=6

Figure 12

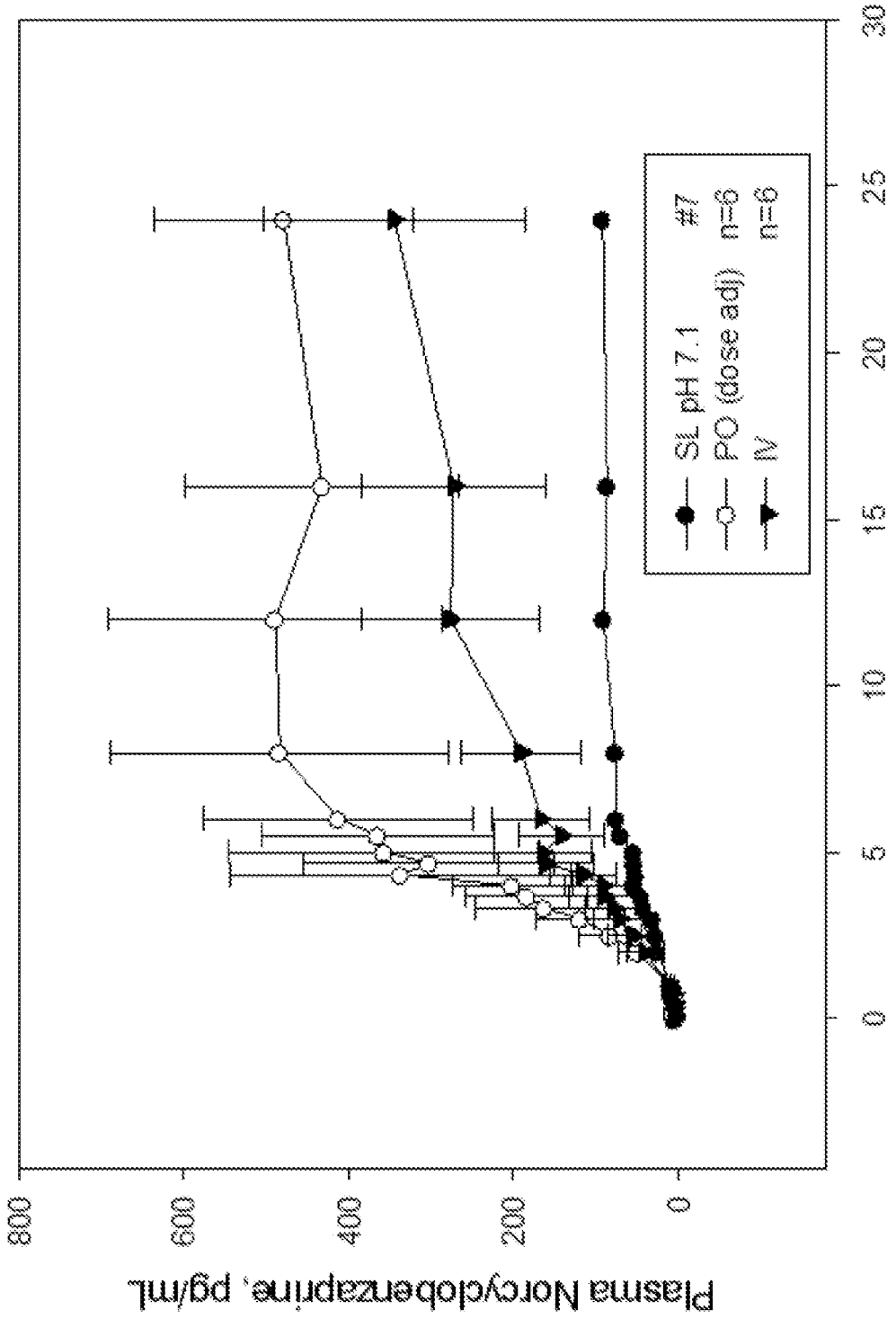

Plasma Norcyclobenzaprine, pg/mL
800
600
400
200
0
0
5
10
15
20
25
30
Time, h
SL pH 7.1 #7
PO (dose adj) n=6
IV n=6

Figure 13

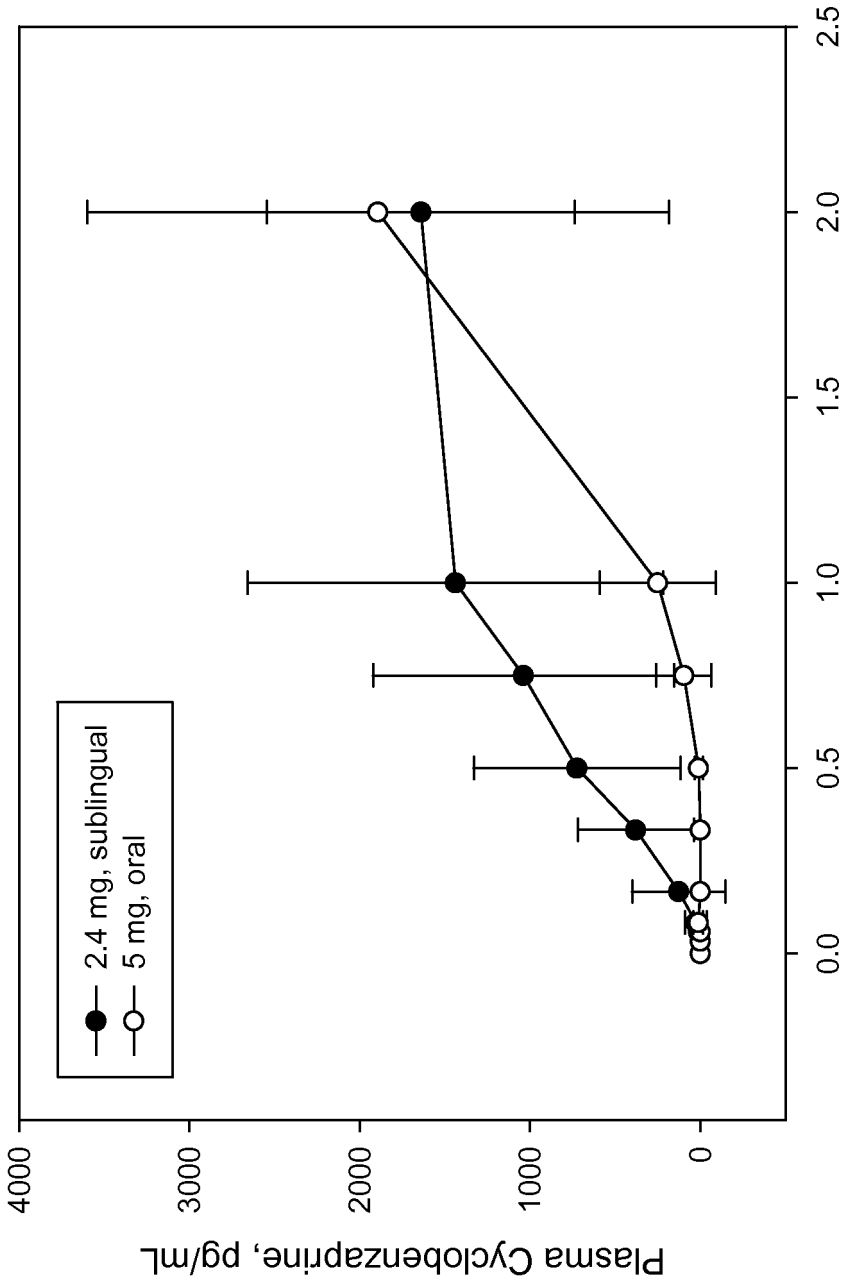

Plasma Cyclobenzaprine, pg/mL
4000
3000
2000
1000
0
0.0
0.5
1.0
1.5
2.0
2.5
Time, hr
2.4 mg, sublingual
5 mg, oral

Figure 14a

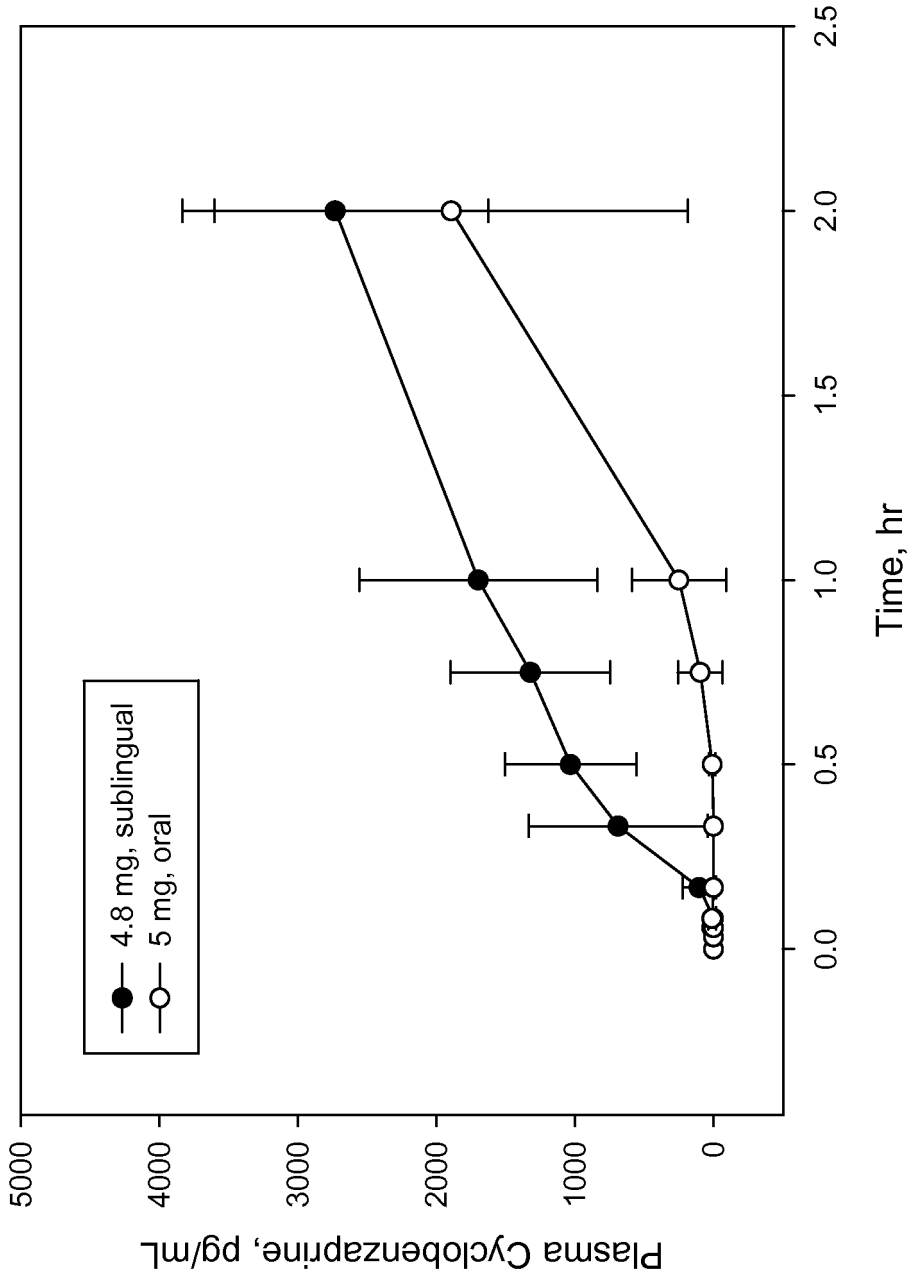

Plasma Cyclobenzaprine, pg/mL
5000
4000
3000
2000
1000
0
0.0
0.5
1.0
1.5
2.0
2.5
Time, hr
4.8 mg, sublingual
5 mg, oral

Figure 14b

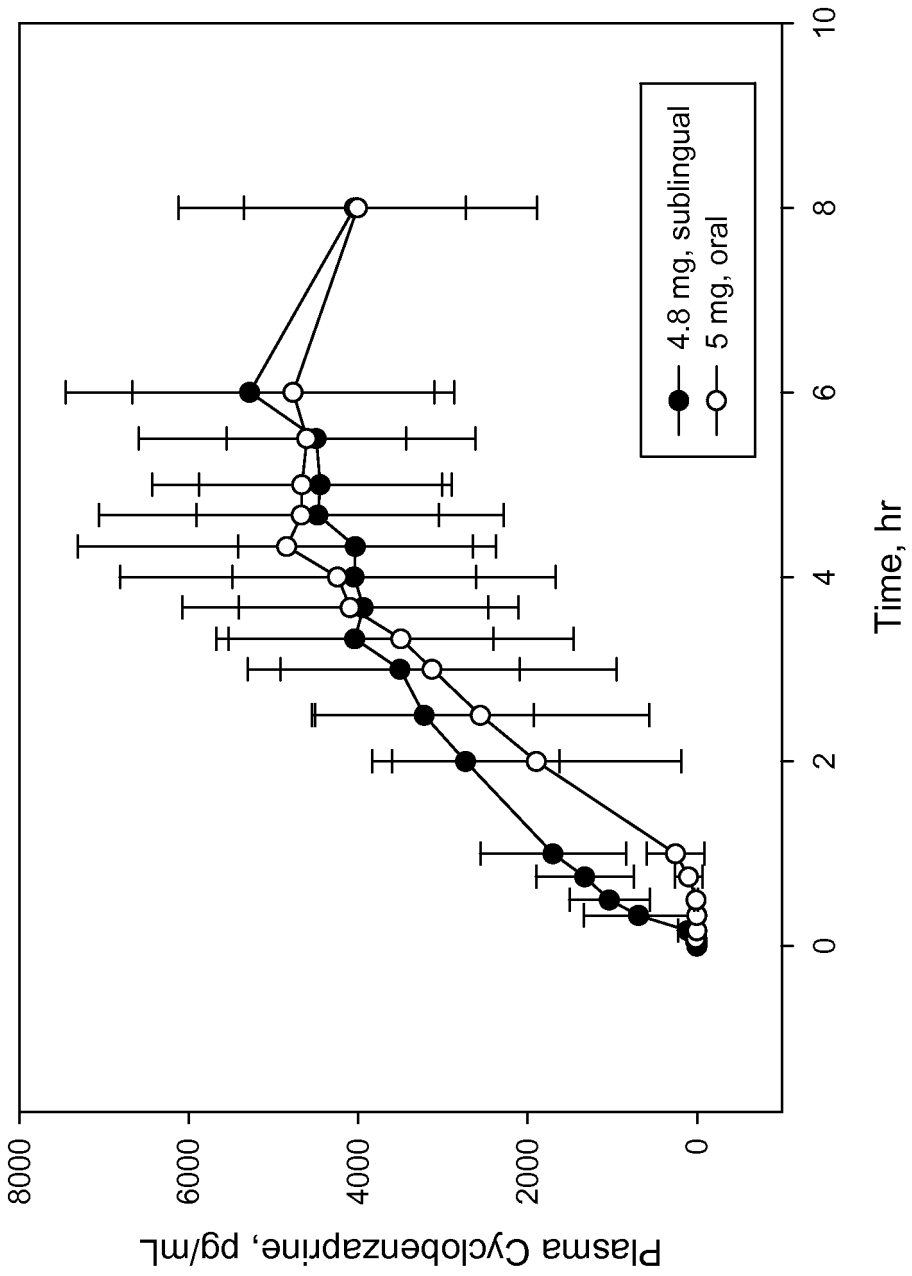

Plasma Cyclobenzaprine, pg/mL
8000
6000
4000
2000
0
0
2
4
6
8
10
Time, hr
4.8 mg, sublingual
5 mg, oral

Figure 15

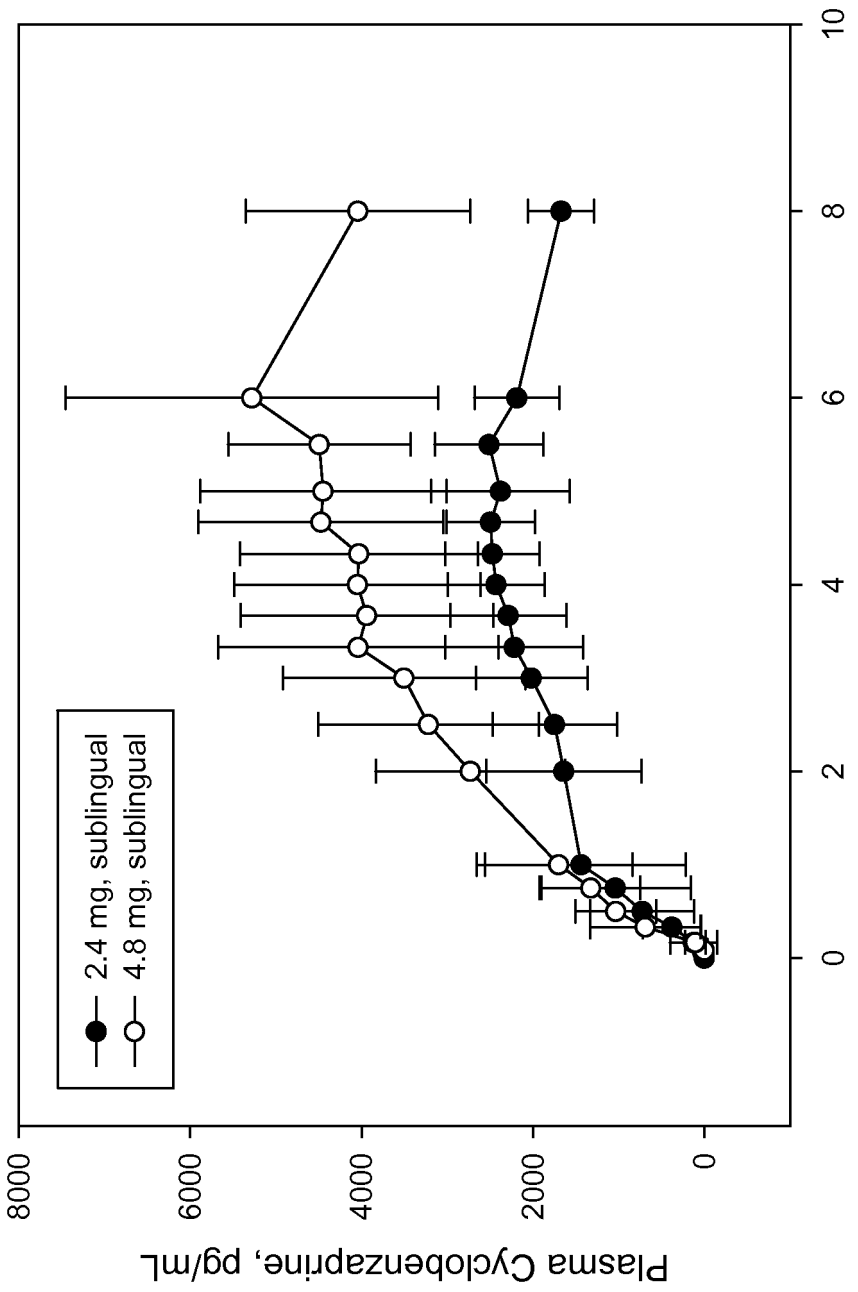

Plasma Cyclobenzaprine, pg/mL
8000
6000
4000
2000
0
Time, hr
0
2
4
6
8
10
2.4 mg, sublingual
4.8 mg, sublingual

Figure 16

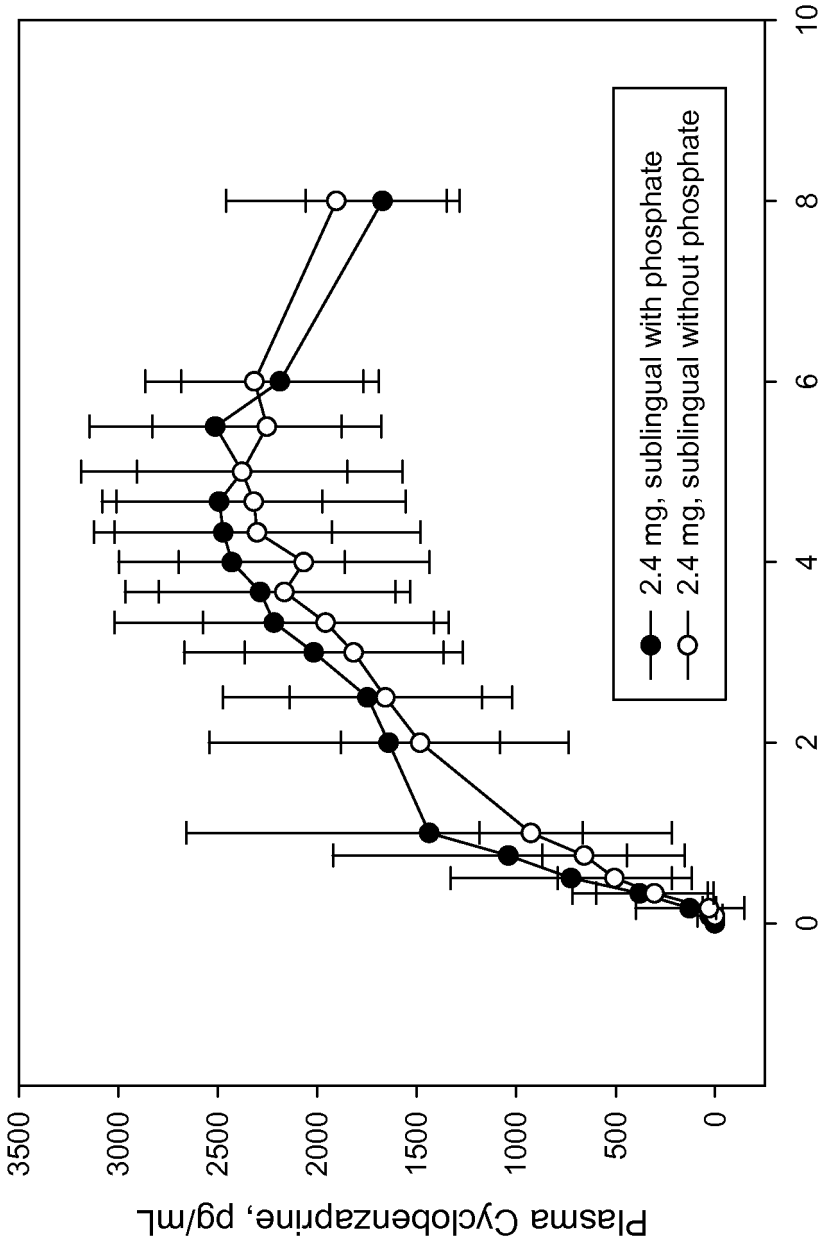

Plasma Cyclobenzaprine, pg/mL
3500
3000
2500
2000
1500
1000
500
0
0
2
4
6
8
10
Time, hr
2.4 mg, sublingual with phosphate
2.4 mg, sublingual without phosphate

Figure 17a

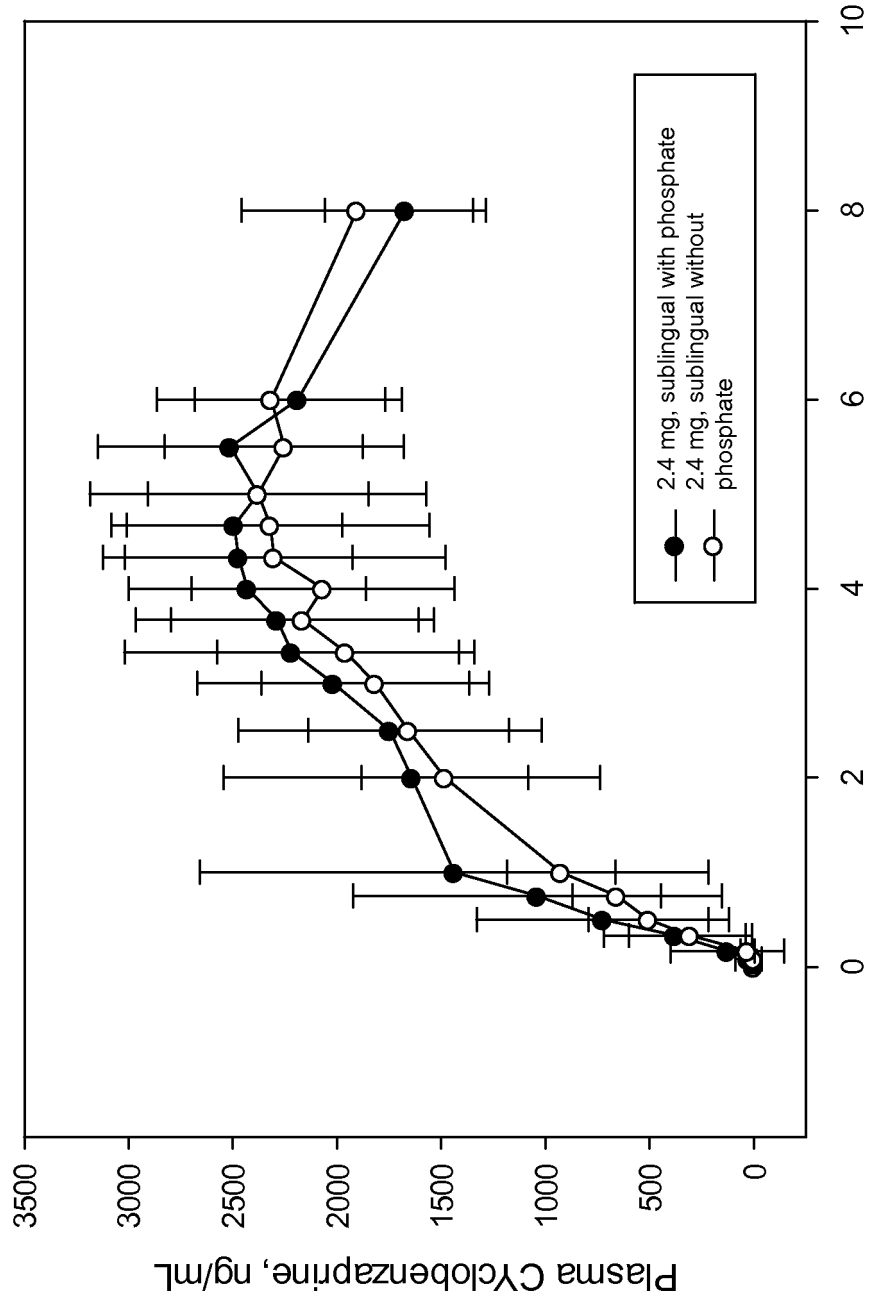

Plasma Cyclobenzaprine, ng/mL
3500
3000
2500
2000
1500
1000
500
0
0
2
4
6
8
10
Time, hr
2.4 mg, sublingual with phosphate
2.4 mg, sublingual without phosphate

Figure 17b

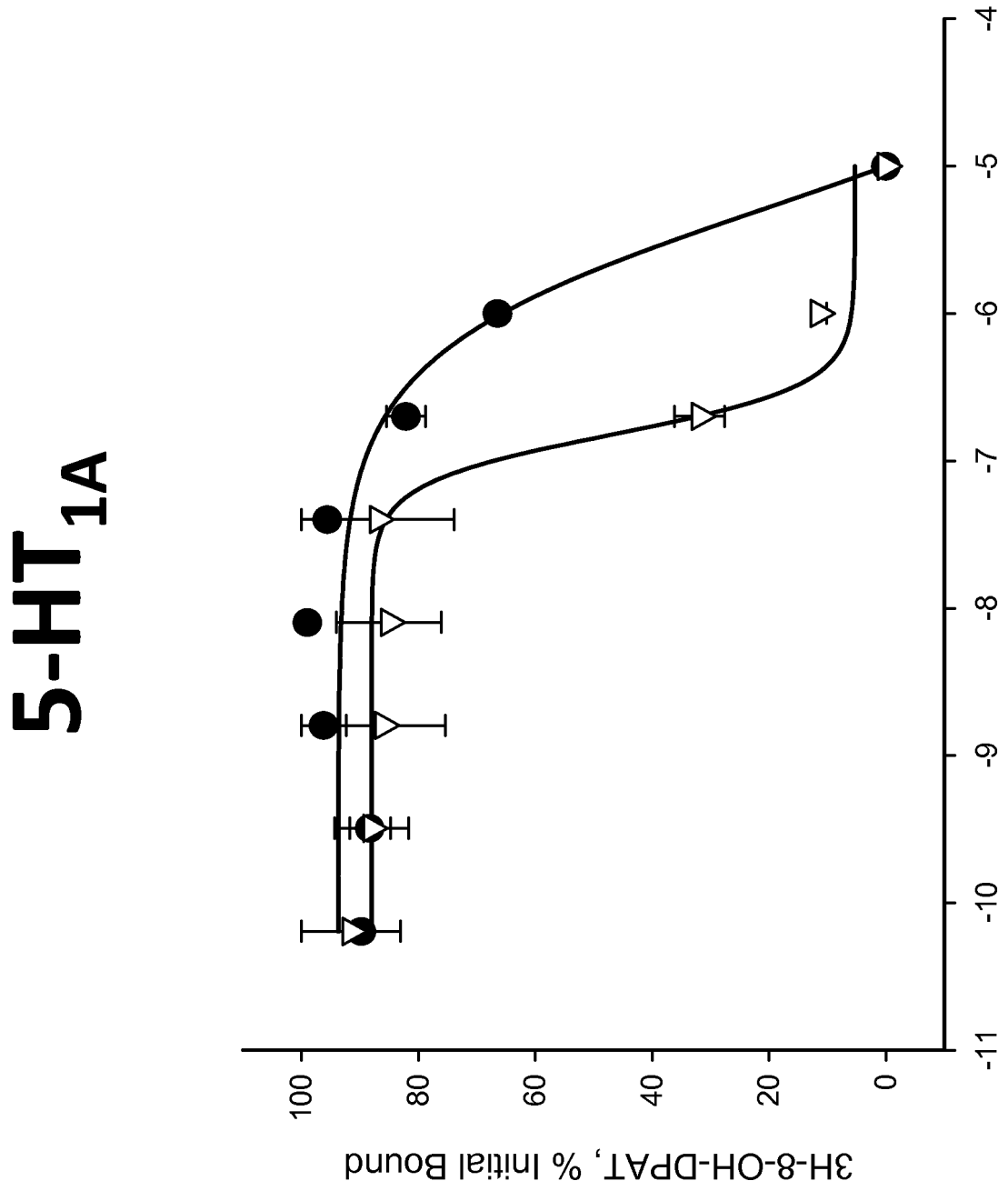

5-HT1A
3H-8-OH-DPAT, % Initial Bound
100
80
60
40
20
0
-4
-5
-6
-7
-8
-9
-10
-11
Log [Compound] (M)

Figure 18a

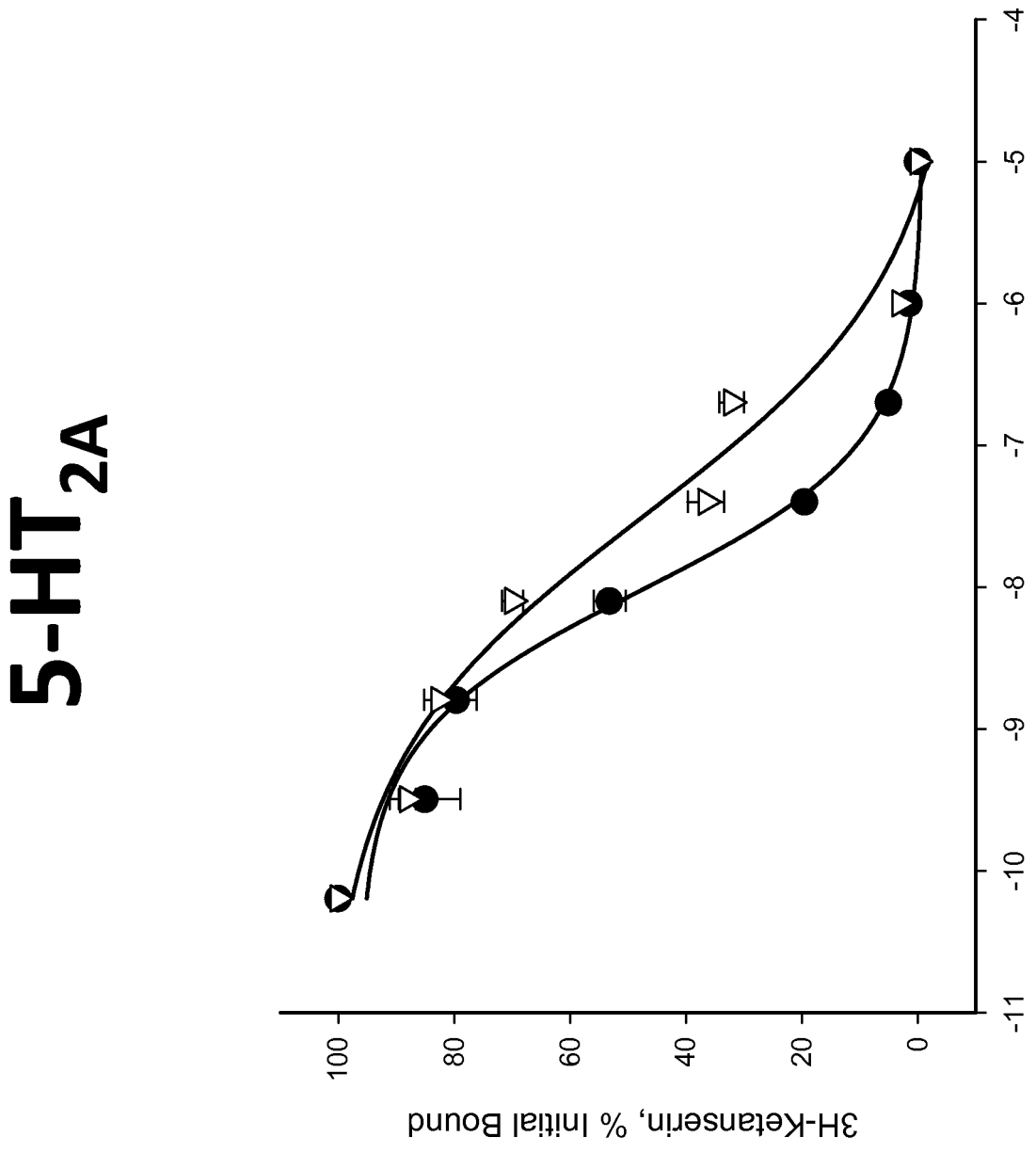

5-HT2A
3H-Ketanserin, % Initial Bound
100
80
60
40
20
0
-11
-10
-9
-8
-7
-6
-5
-4
Log [Compound] (M)

Figure 18b

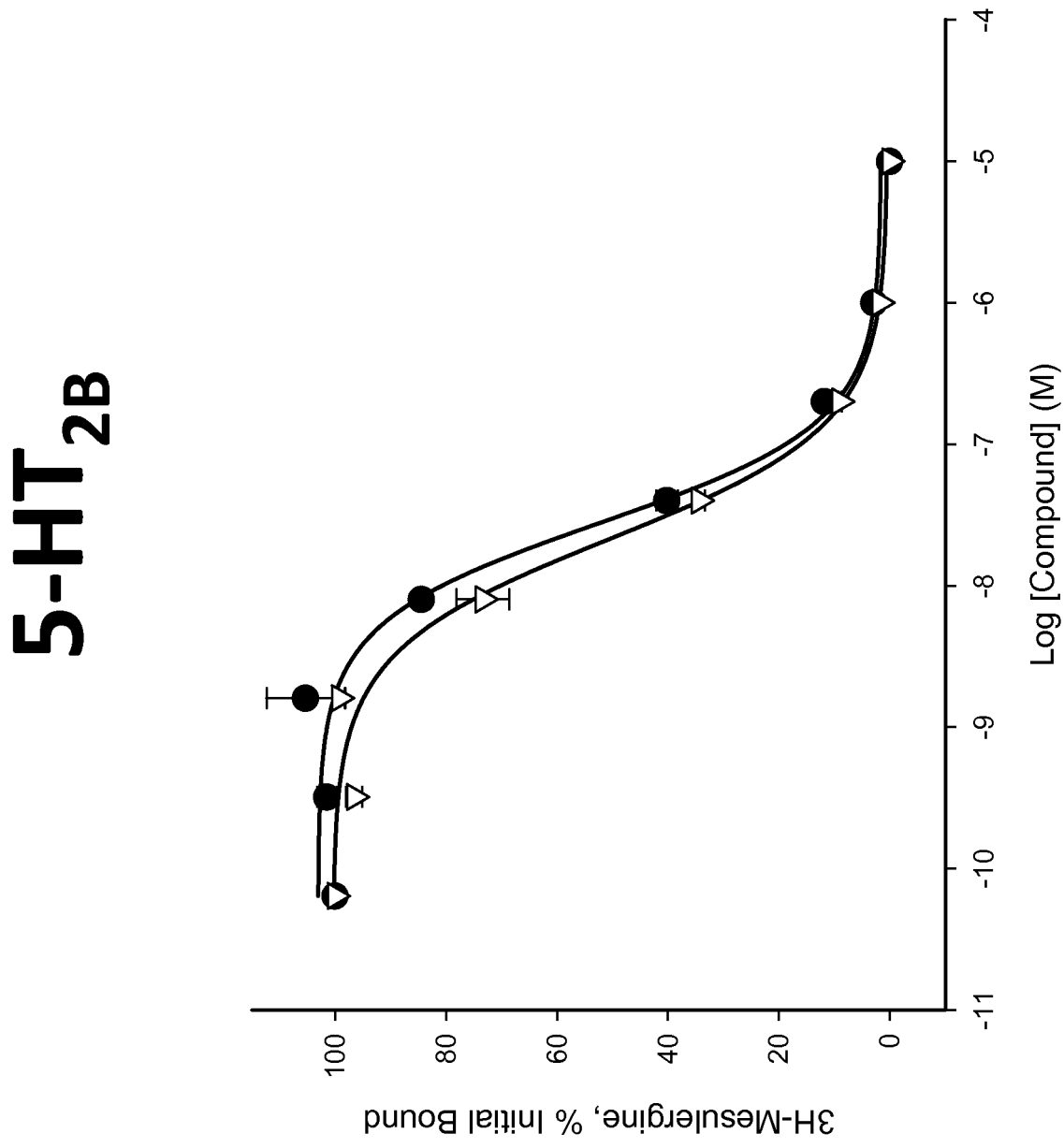

5-HT2B
3H-Mesulergine, % Initial Bound
100
80
60
40
20
0
-11
-10
-9
-8
-7
-6
-5
-4
Log [Compound] (M)

Figure 18c

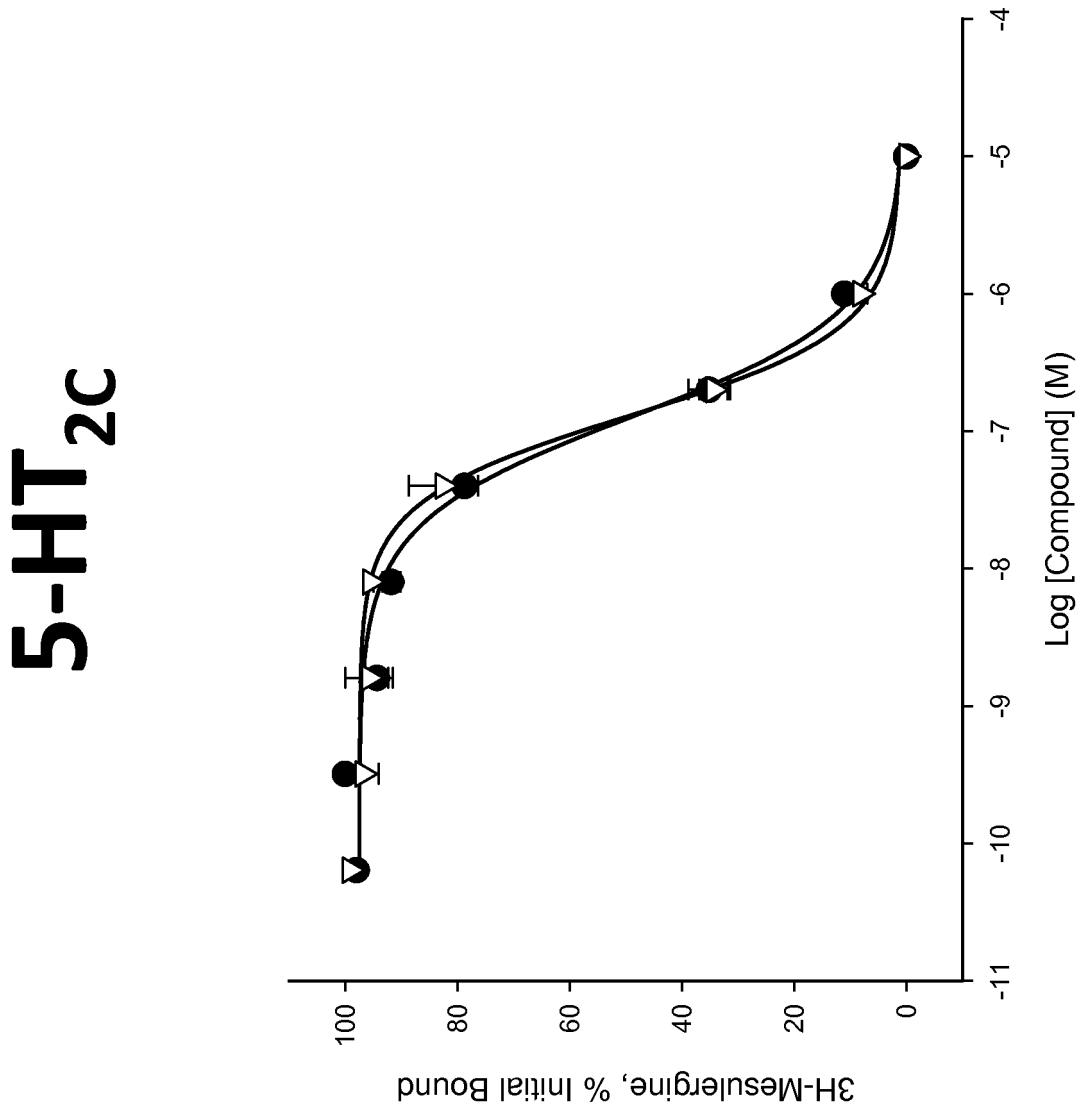

5-HT2C
3H-Mesulergine, % Initial Bound
100
80
60
40
20
0
-11
-10
-9
-8
-7
-6
-5
-4
Log [Compound] (M)

Figure 18d

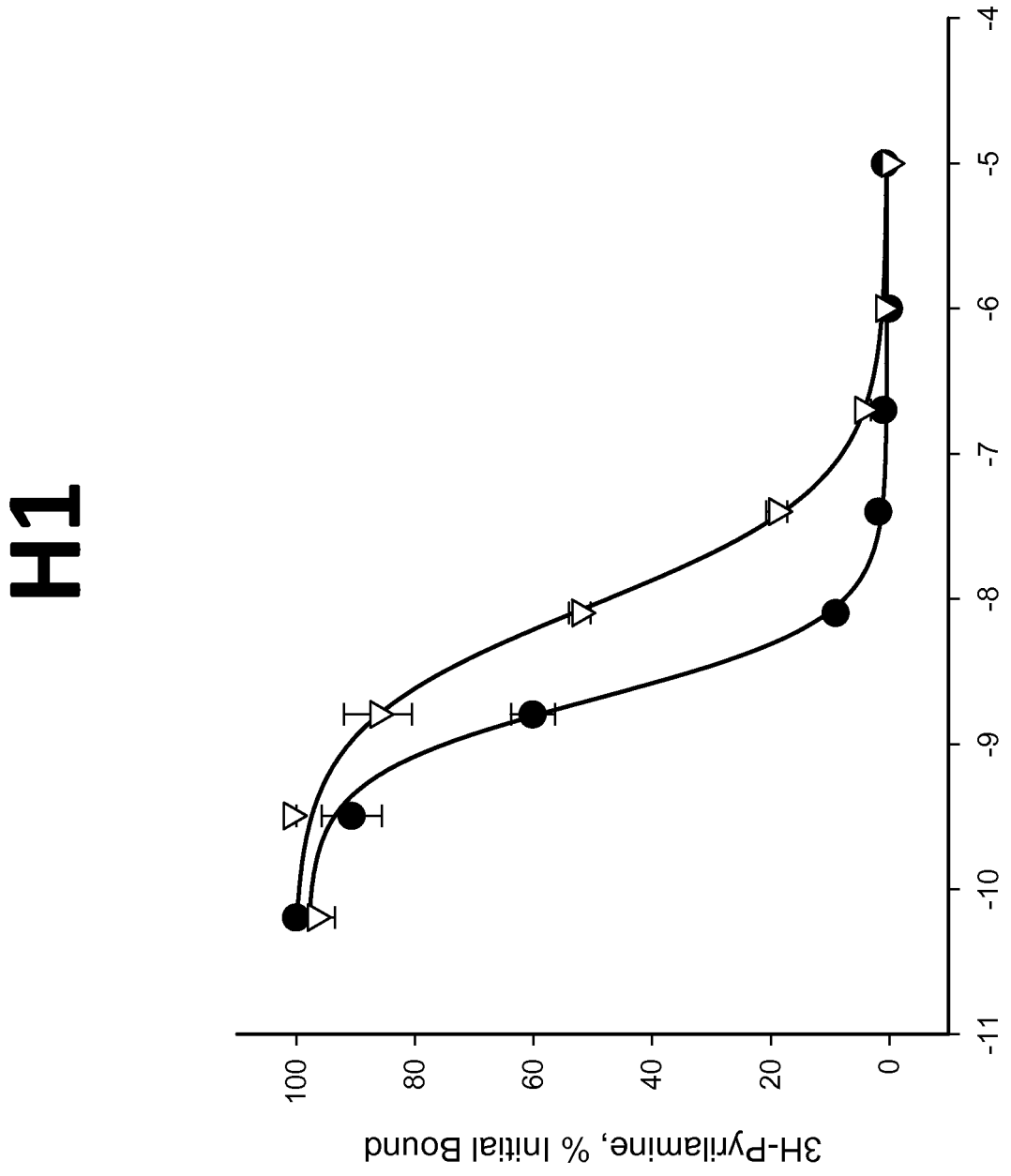

H1
3H-Pyrilamine, % Initial Bound
100
80
60
40
20
0
-11
-10
-9
-8
-7
-6
-5
-4
Log [Compound] (M)

Figure 18e

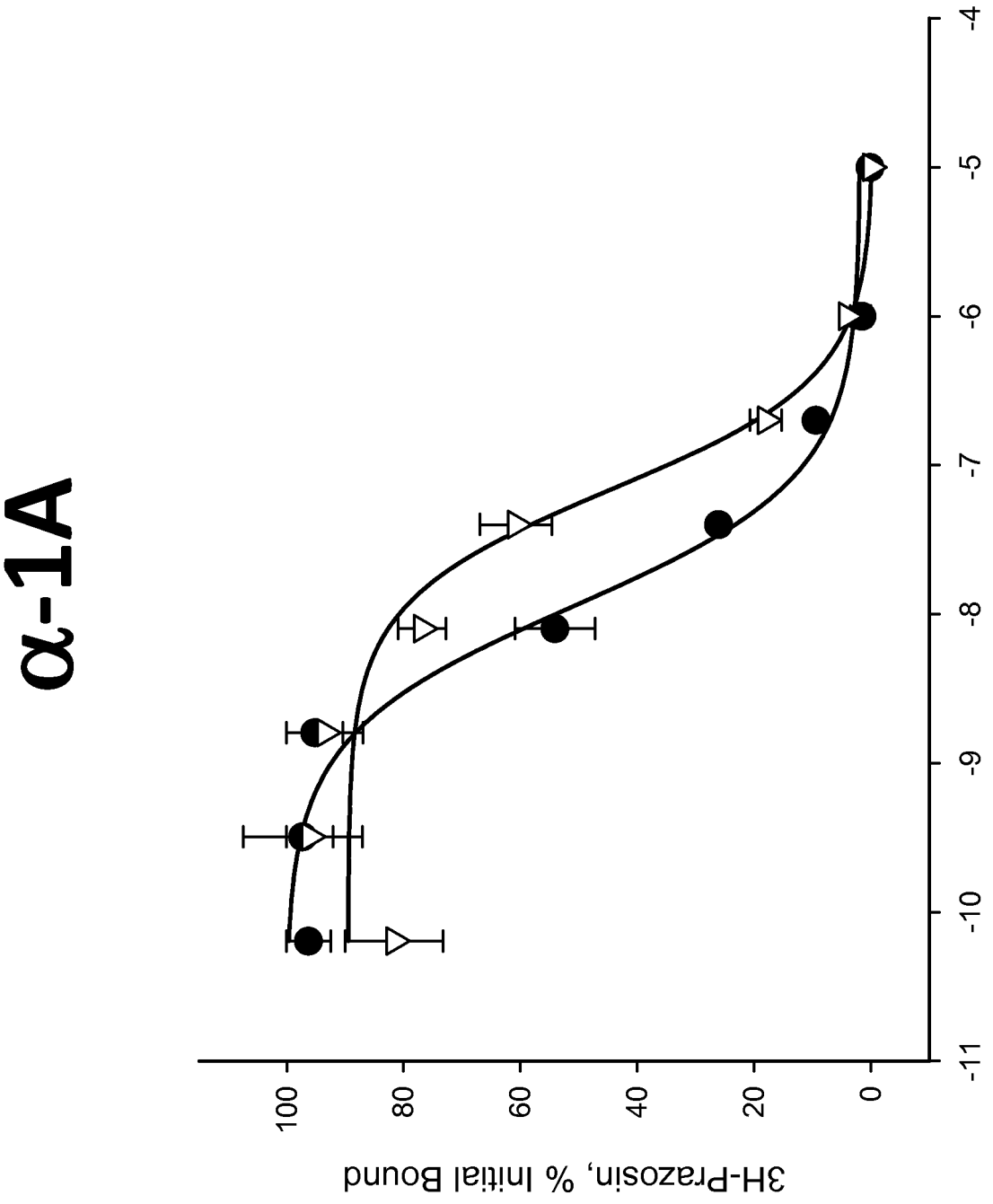

α-1A
3H-Prazosin, % Initial Bound
100
80
60
40
20
0
-11
-10
-9
-8
-7
-6
-5
-4
Log [Compound] (M)

Figure 18f

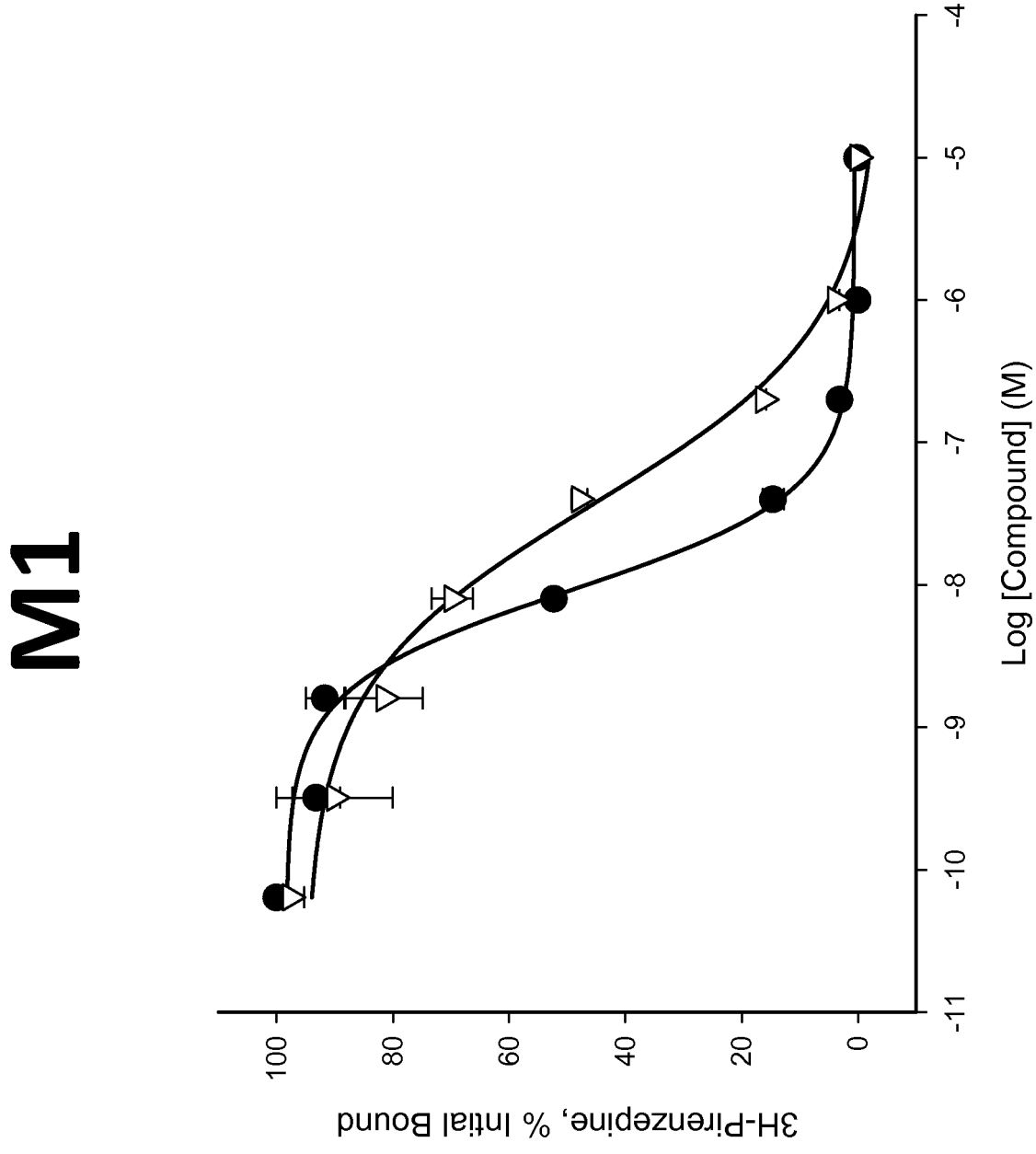

M1
3H-Pirenzepine, % Initial Bound
100
80
60
40
20
0
-11
-10
-9
-8
-7
-6
-5
-4
Log [Compound] (M)

Figure 18g

D1

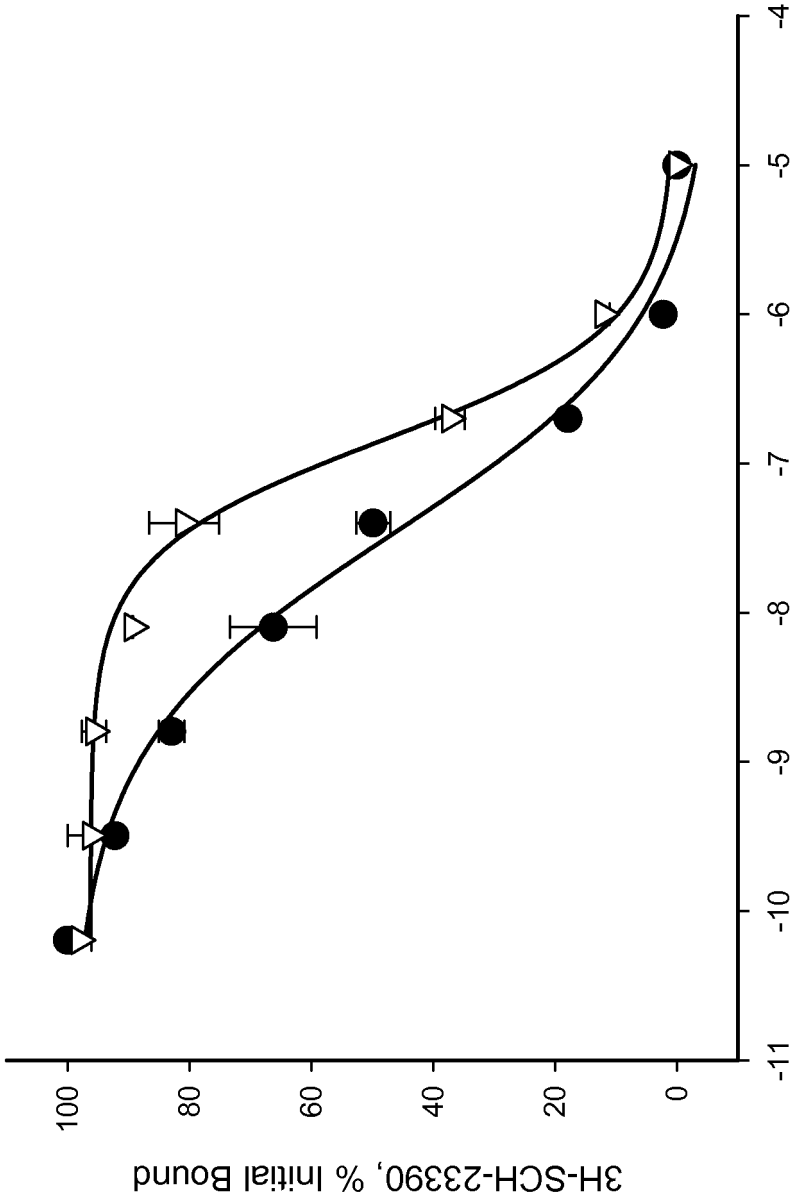


Figure 18h

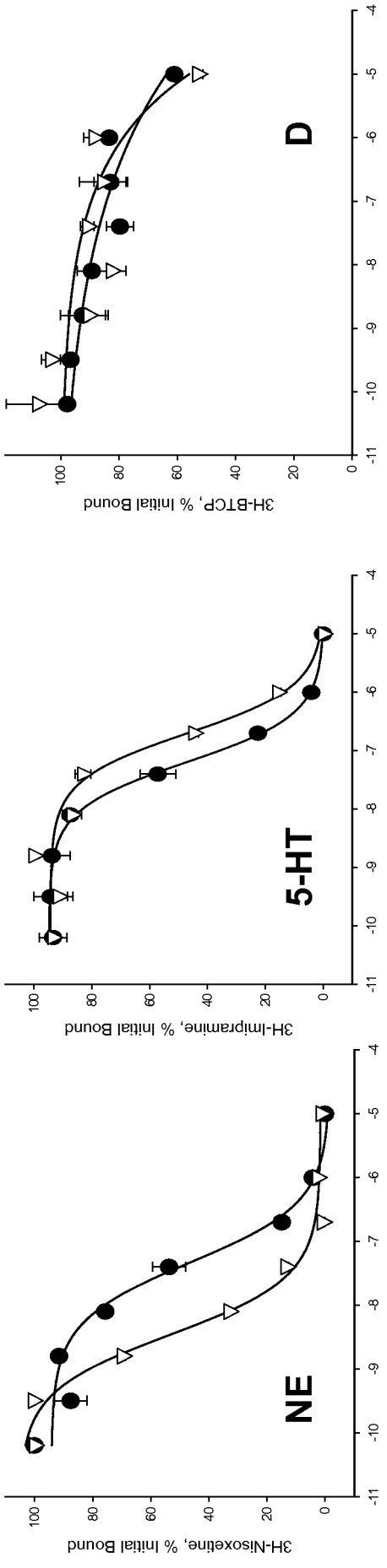

NE
5-HT
D
3H-Nisoxetine, % Initial Bound
3H-Imipramine, % Initial Bound
3H-BTCP, % Initial Bound
100
80
60
40
20
0
-4
-5
-6
-7
-8
-9
-10
-11
Log [Compound] (M)

Figure 19

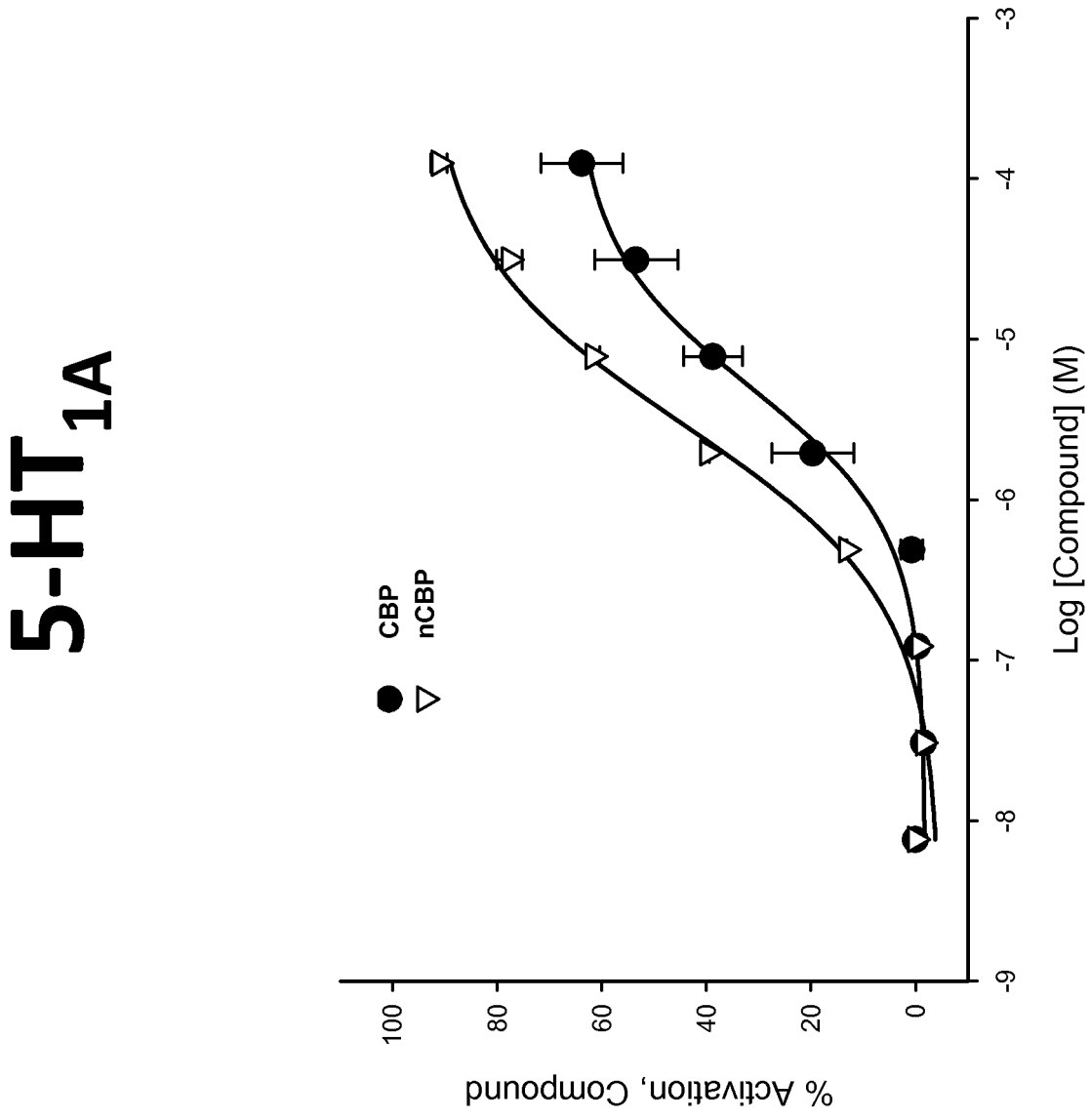

5-HT1A
CBP
nCBP
% Activation, Compound
100
80
60
40
20
0
-9
-8
-7
-6
-5
-4
-3
Log [Compound] (M)

Figure 20a

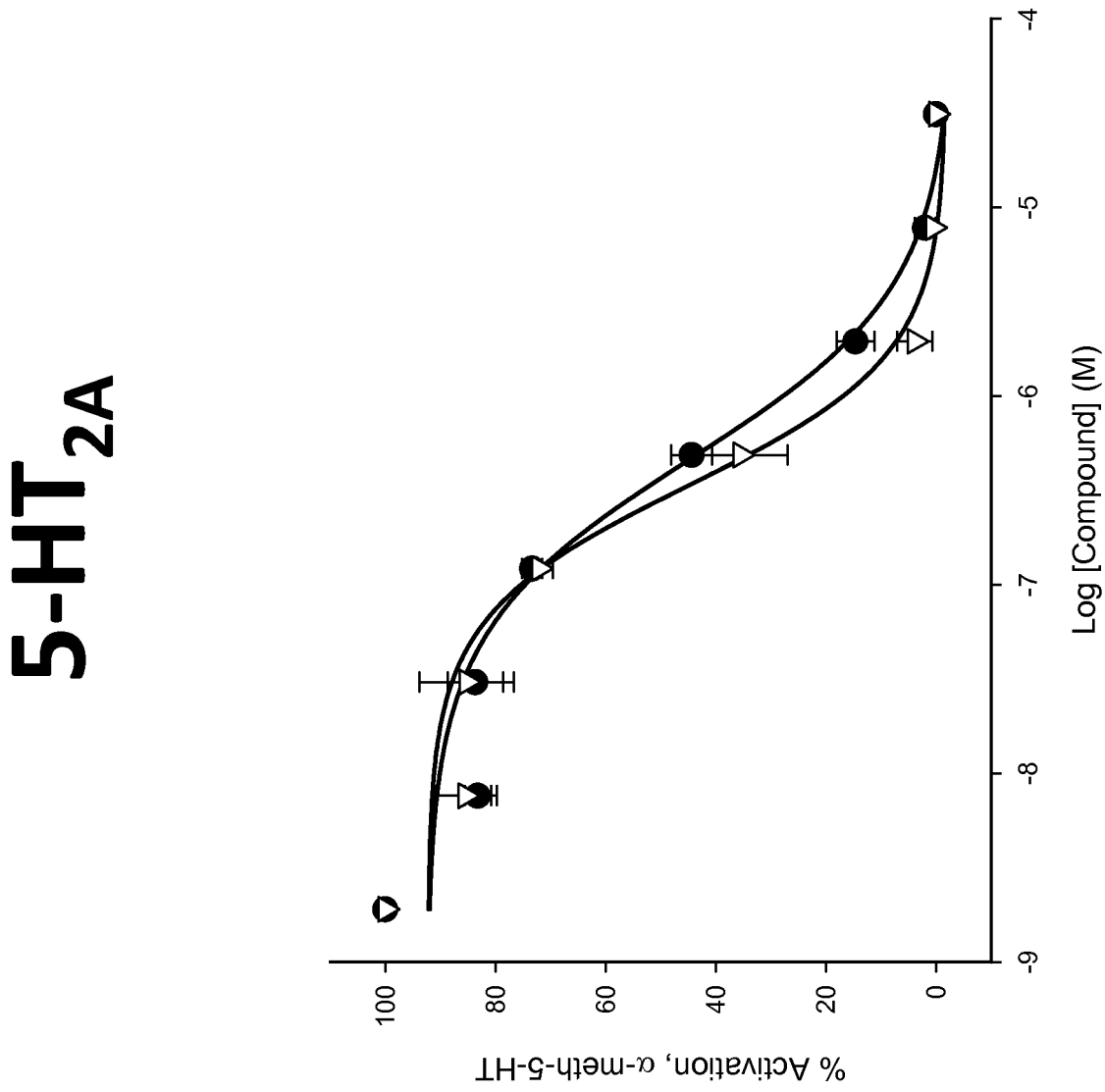

5-HT2A
% Activation, α-meth-5-HT
100
80
60
40
20
0
-9
-8
-7
-6
-5
-4
Log [Compound] (M)

Figure 20b

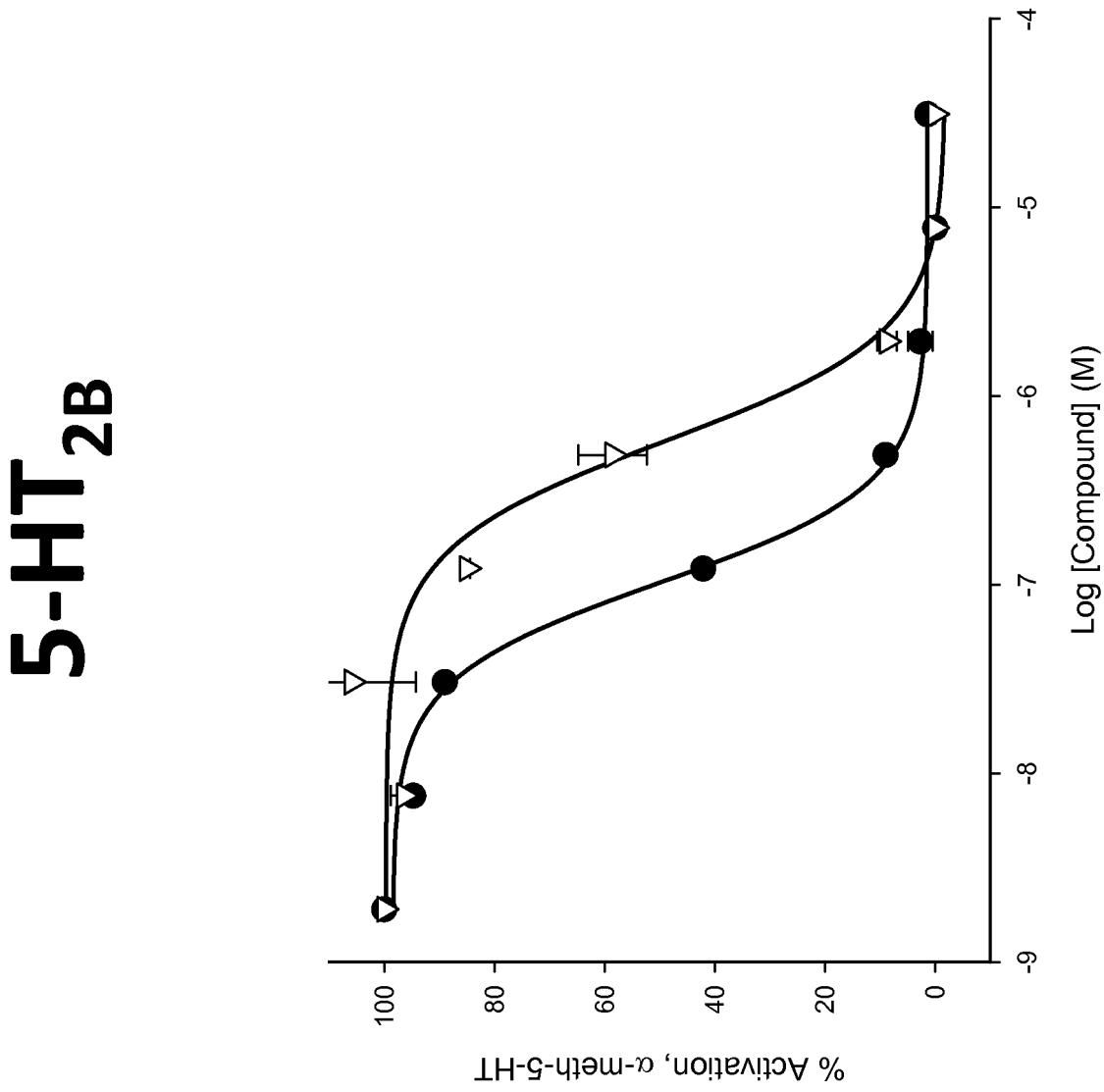

5-HT2B
% Activation, α-meth-5-HT
100
80
60
40
20
0
-9
-8
-7
-6
-5
-4
Log [Compound] (M)

Figure 20c

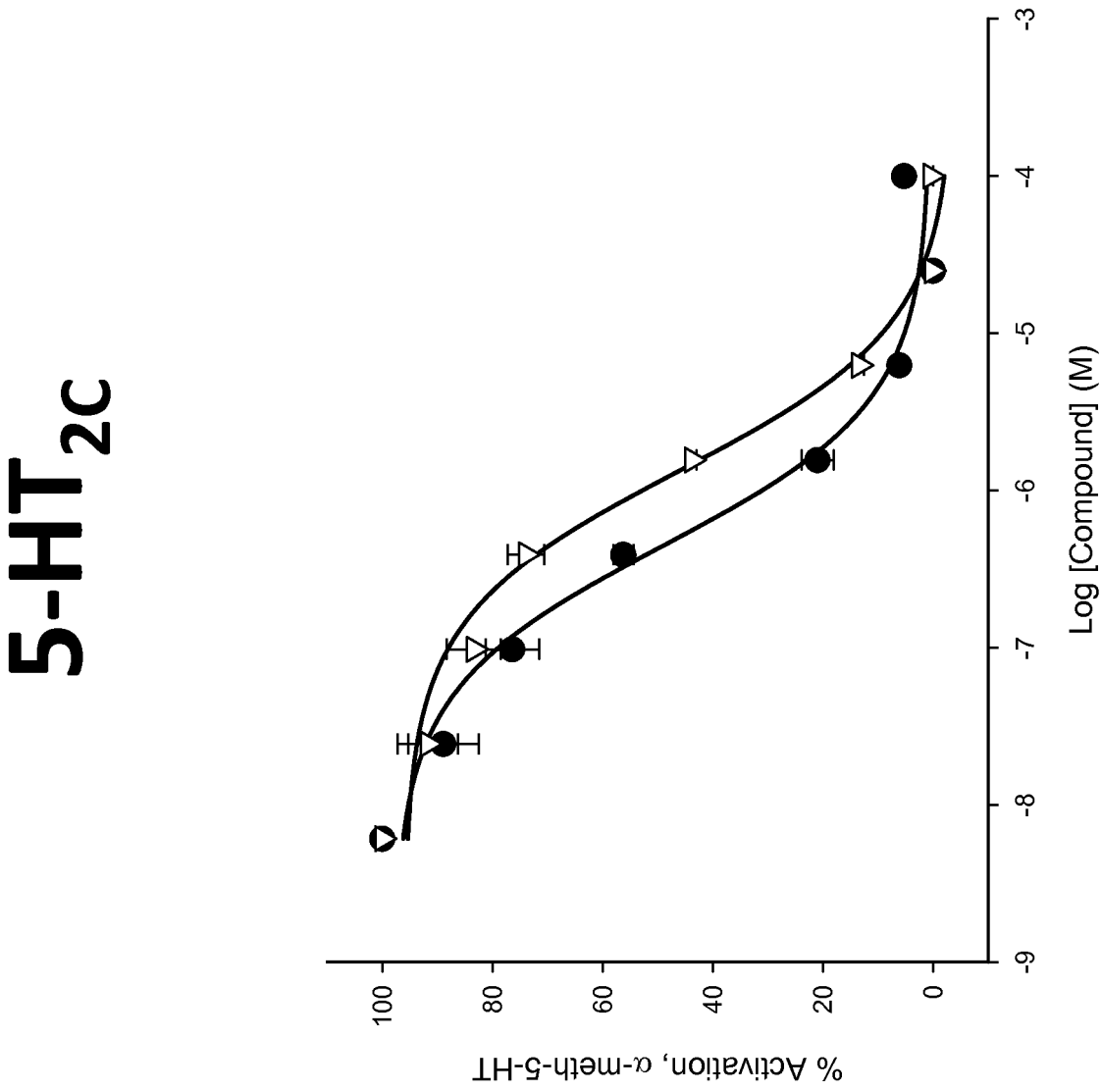

5-HT2C
% Activation, α-meth-5-HT
100
80
60
40
20
0
-9
-8
-7
-6
-5
-4
-3
Log [Compound] (M)

Figure 20d

H1

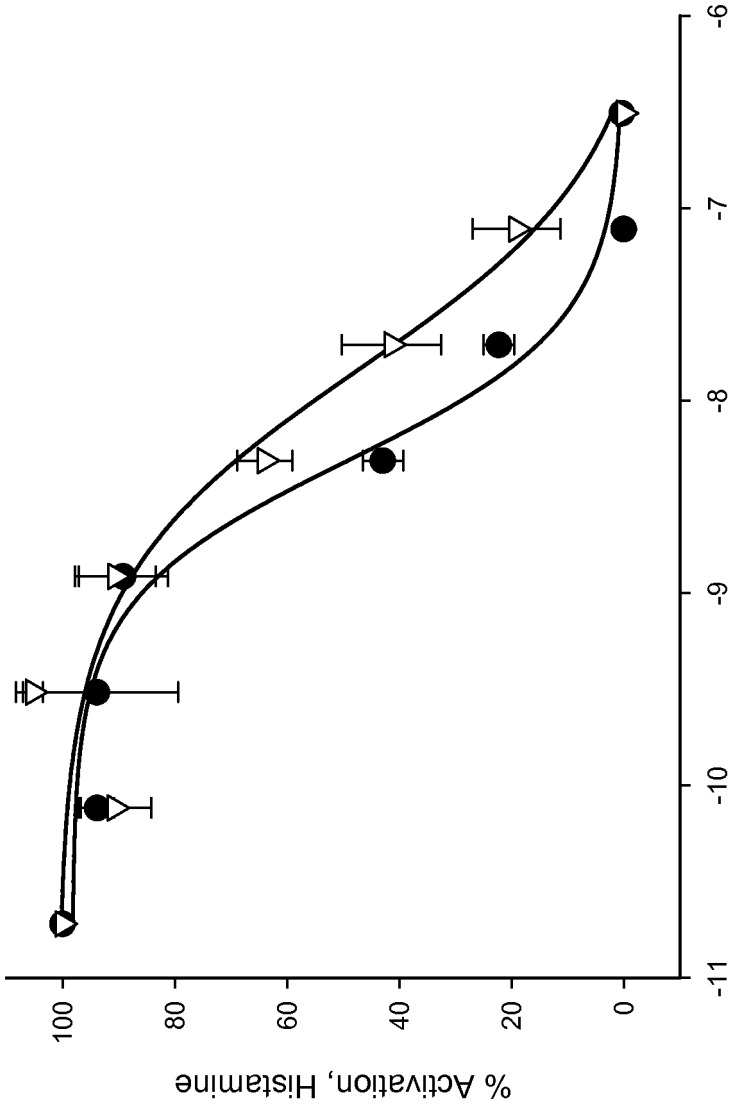


Figure 20e

α-1A

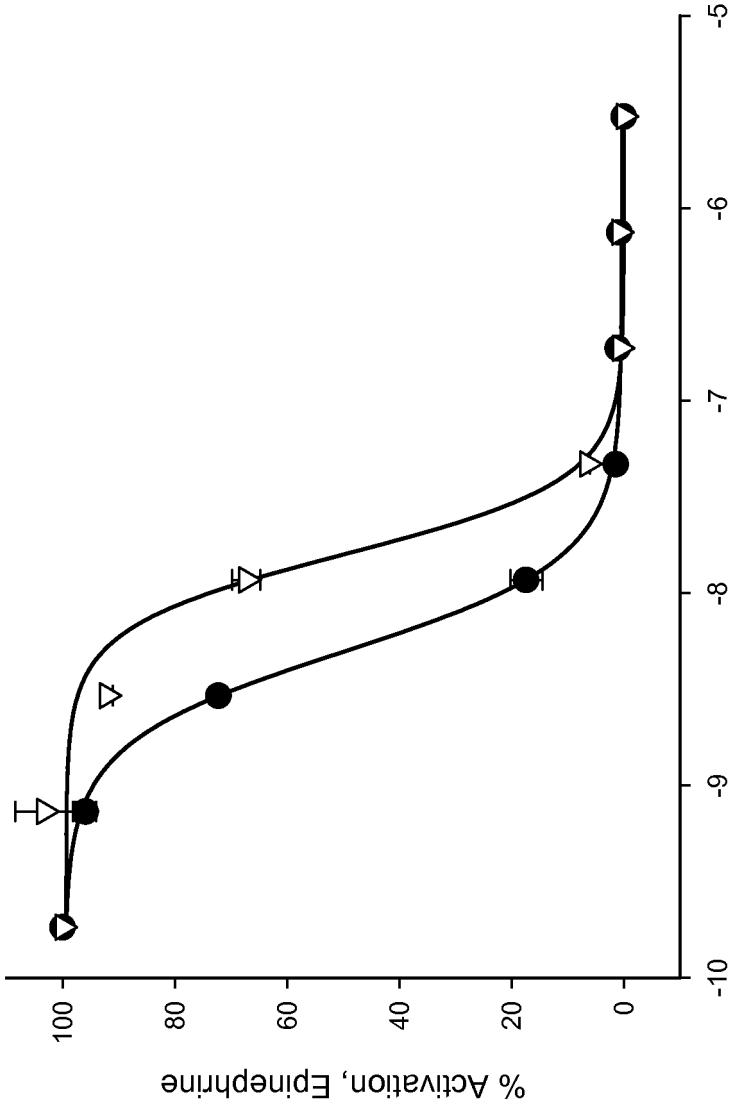


Figure 20f

M1

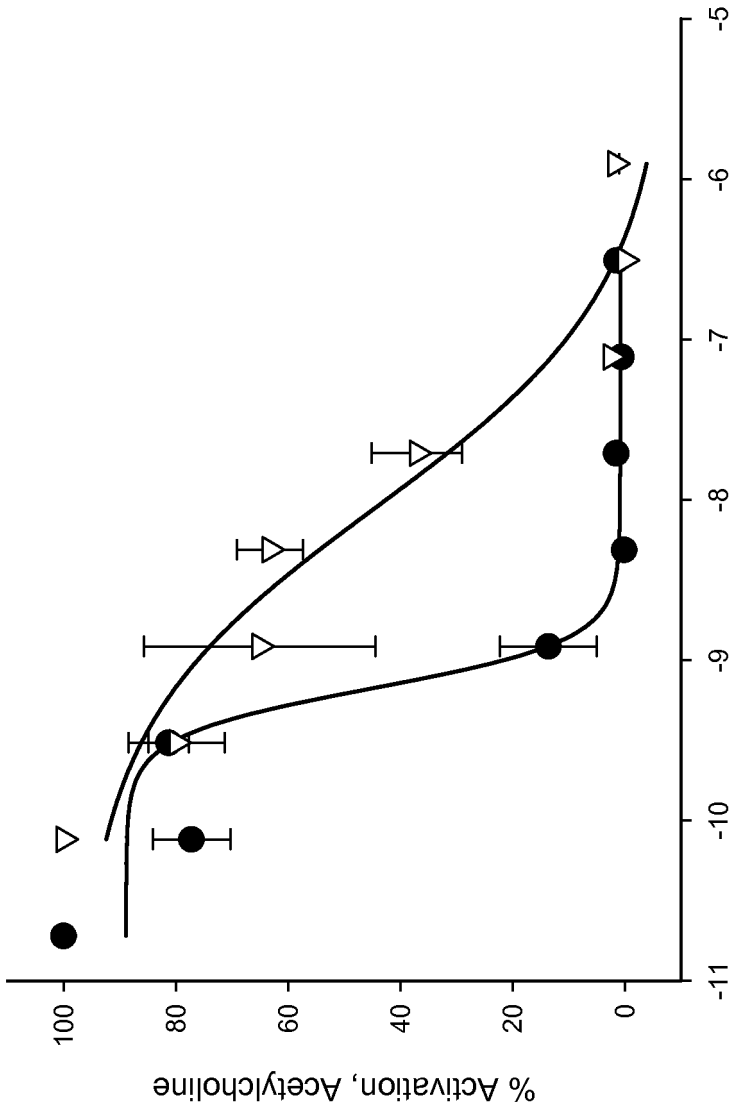


Figure 20g

D1

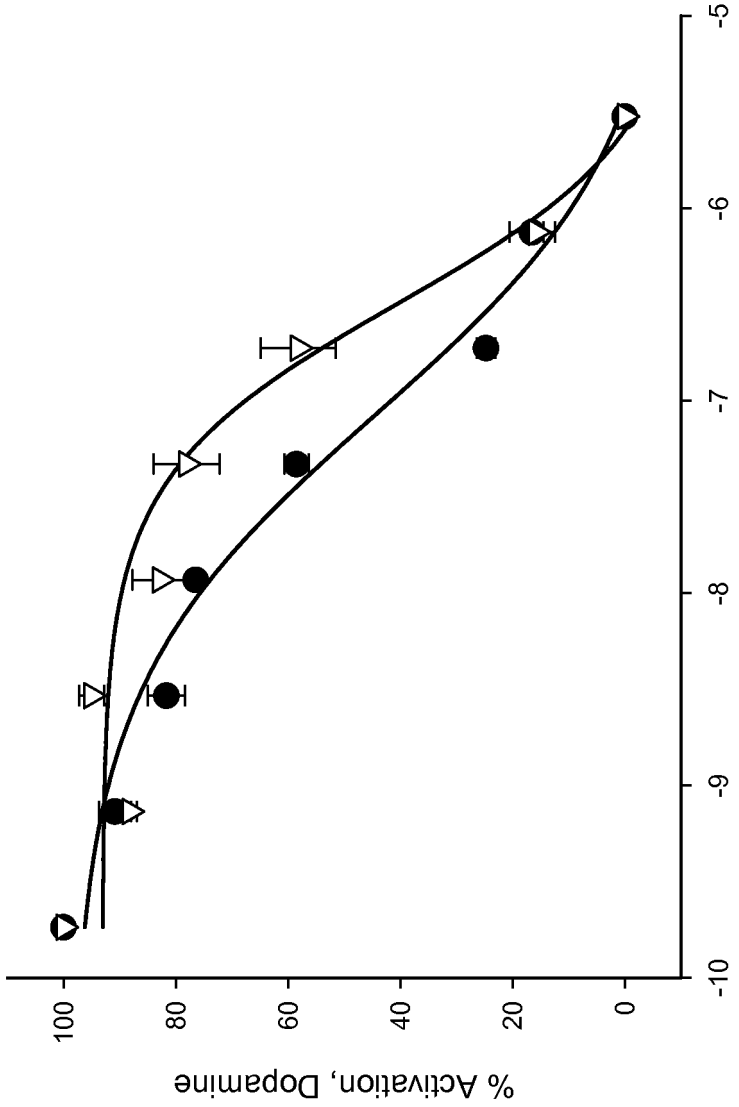


Figure 20h

H1

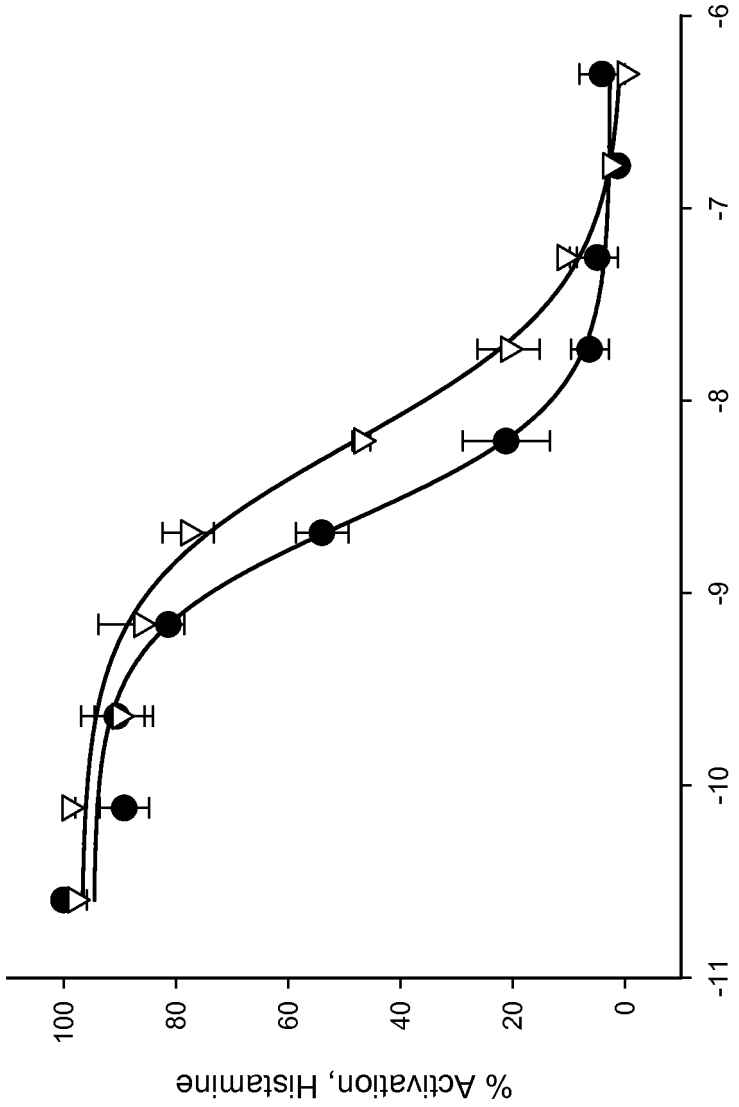


Figure 21a

α-1B

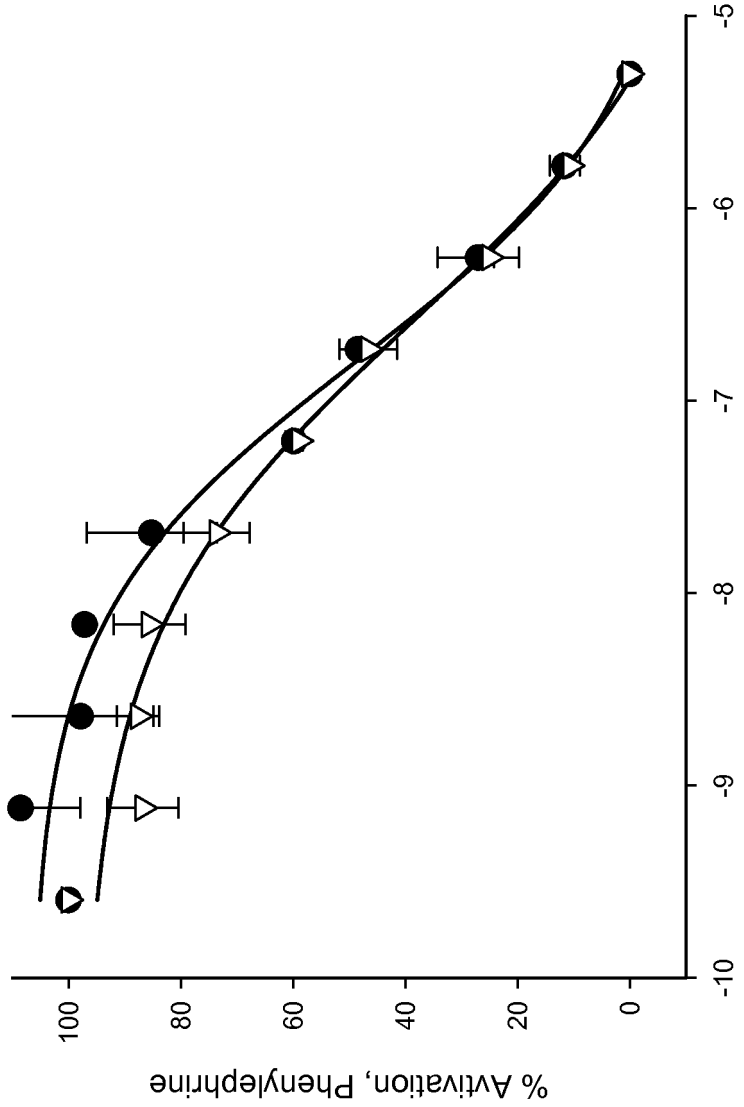


Figure 21b

M1

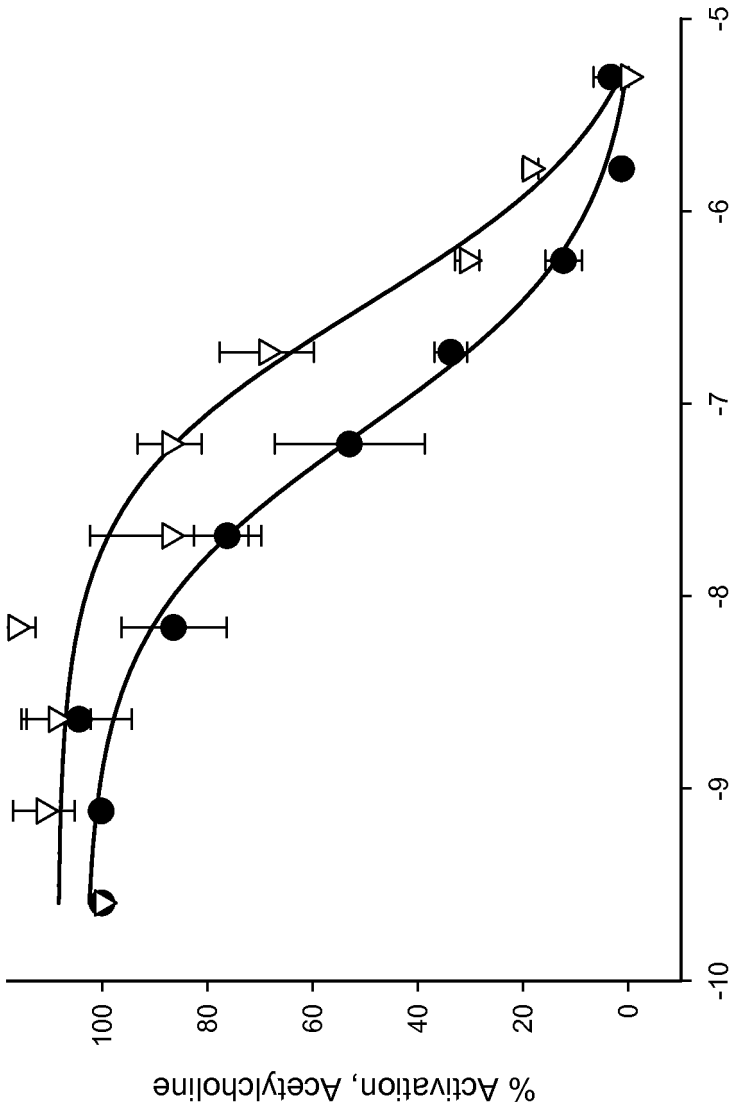


Figure 21c

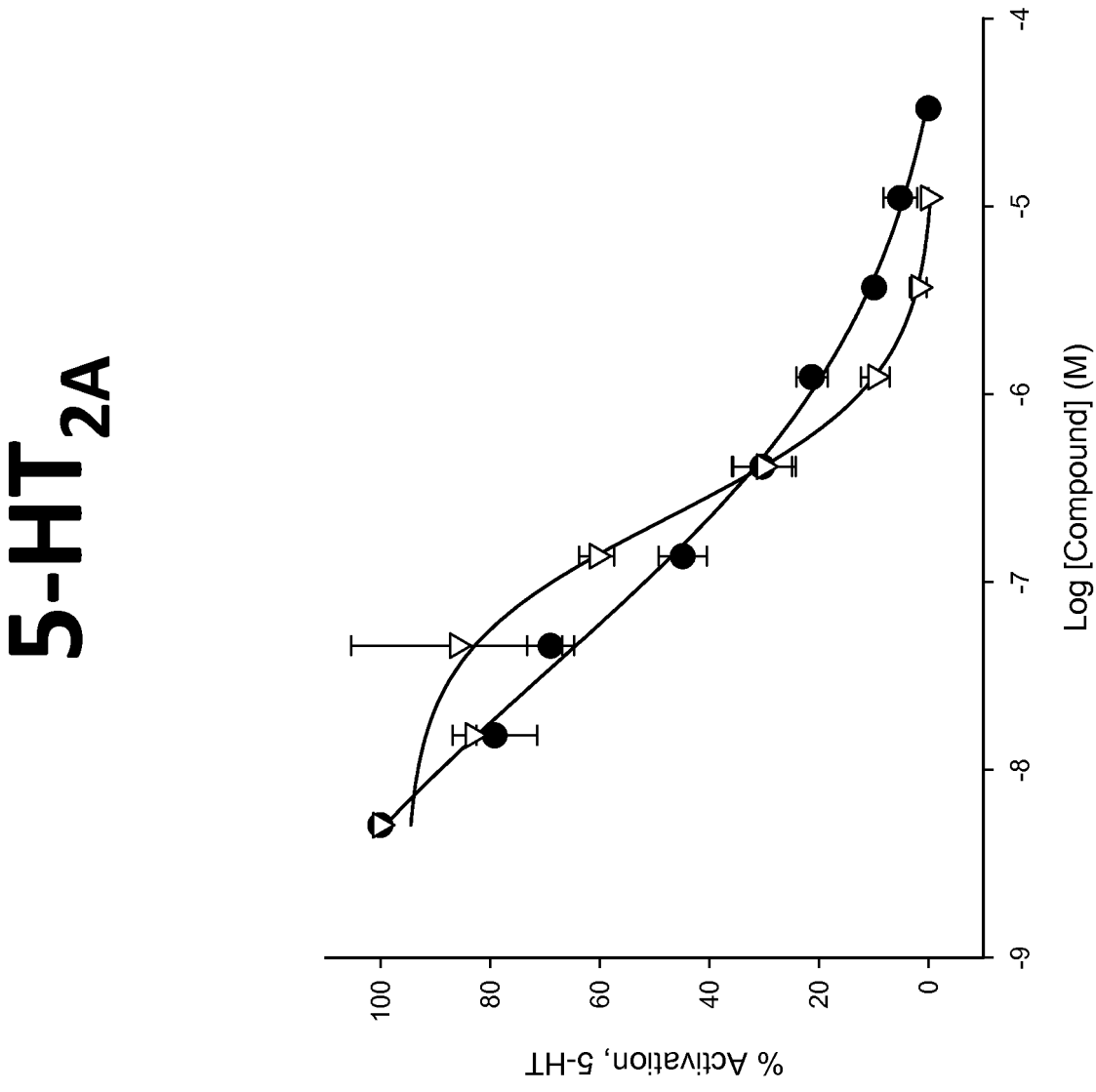


Figure 21d