

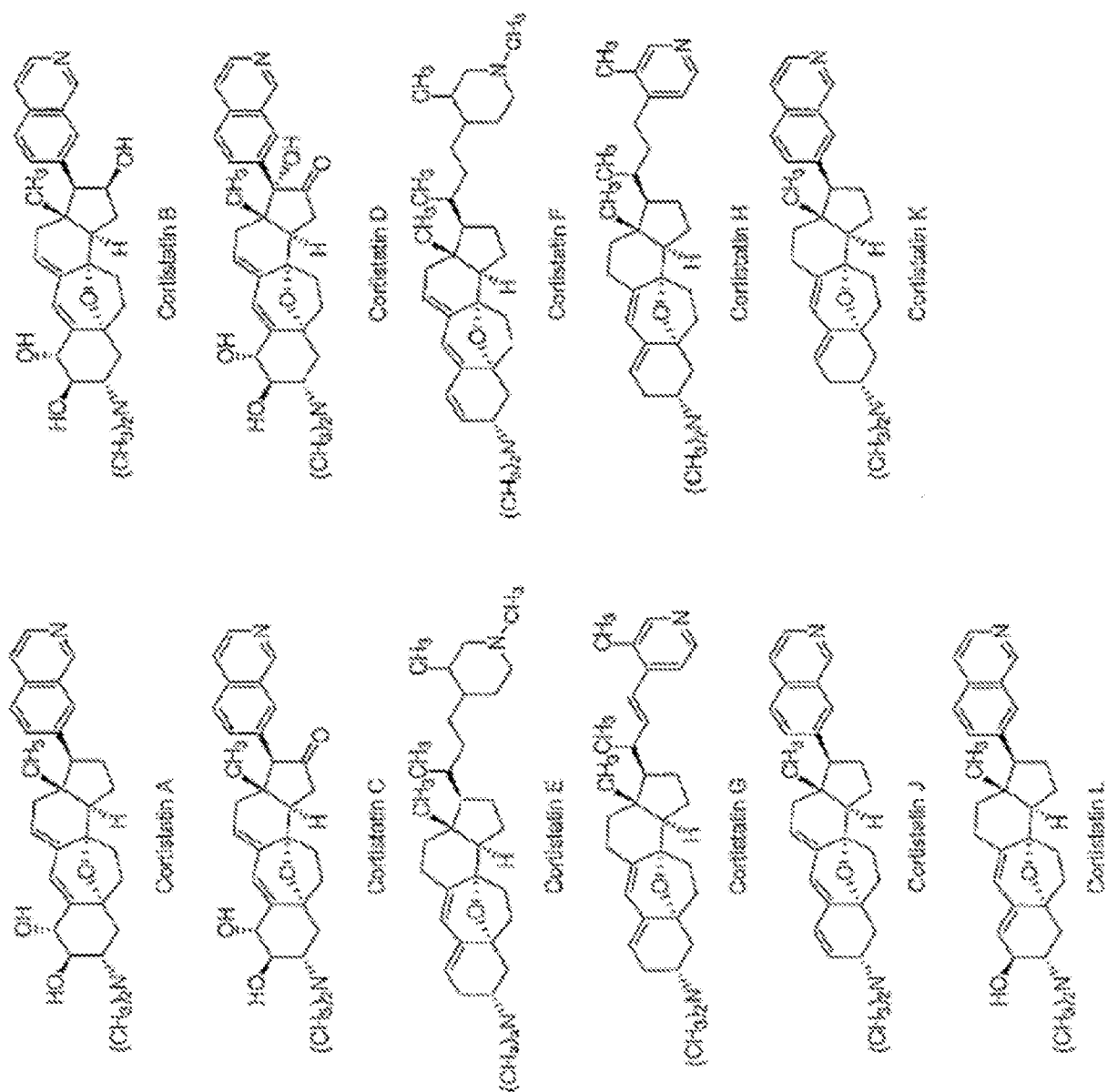
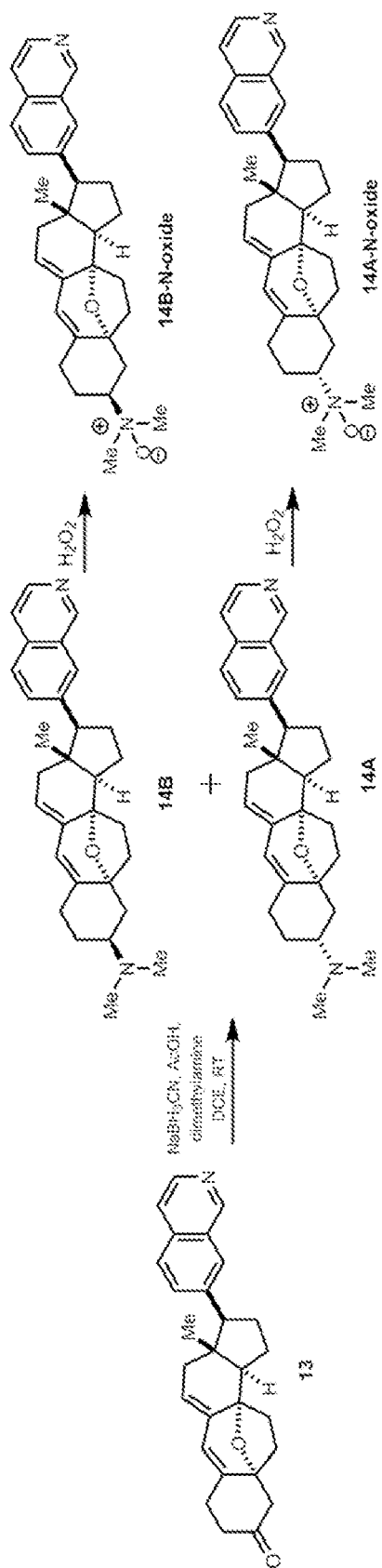
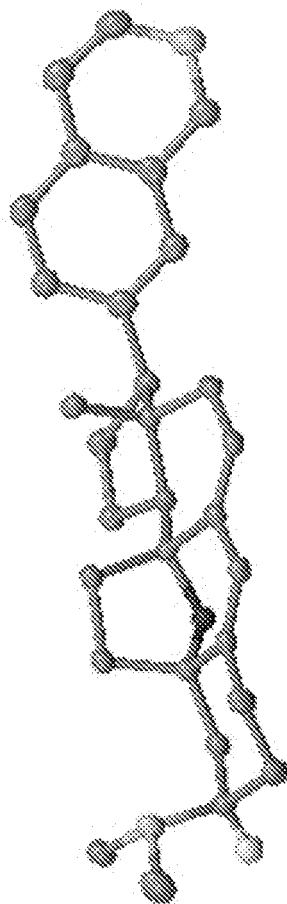


Figure 1

A**B**Molecular structure of ent-dimethylamine (**14B**) in the crystal**Figure 2**

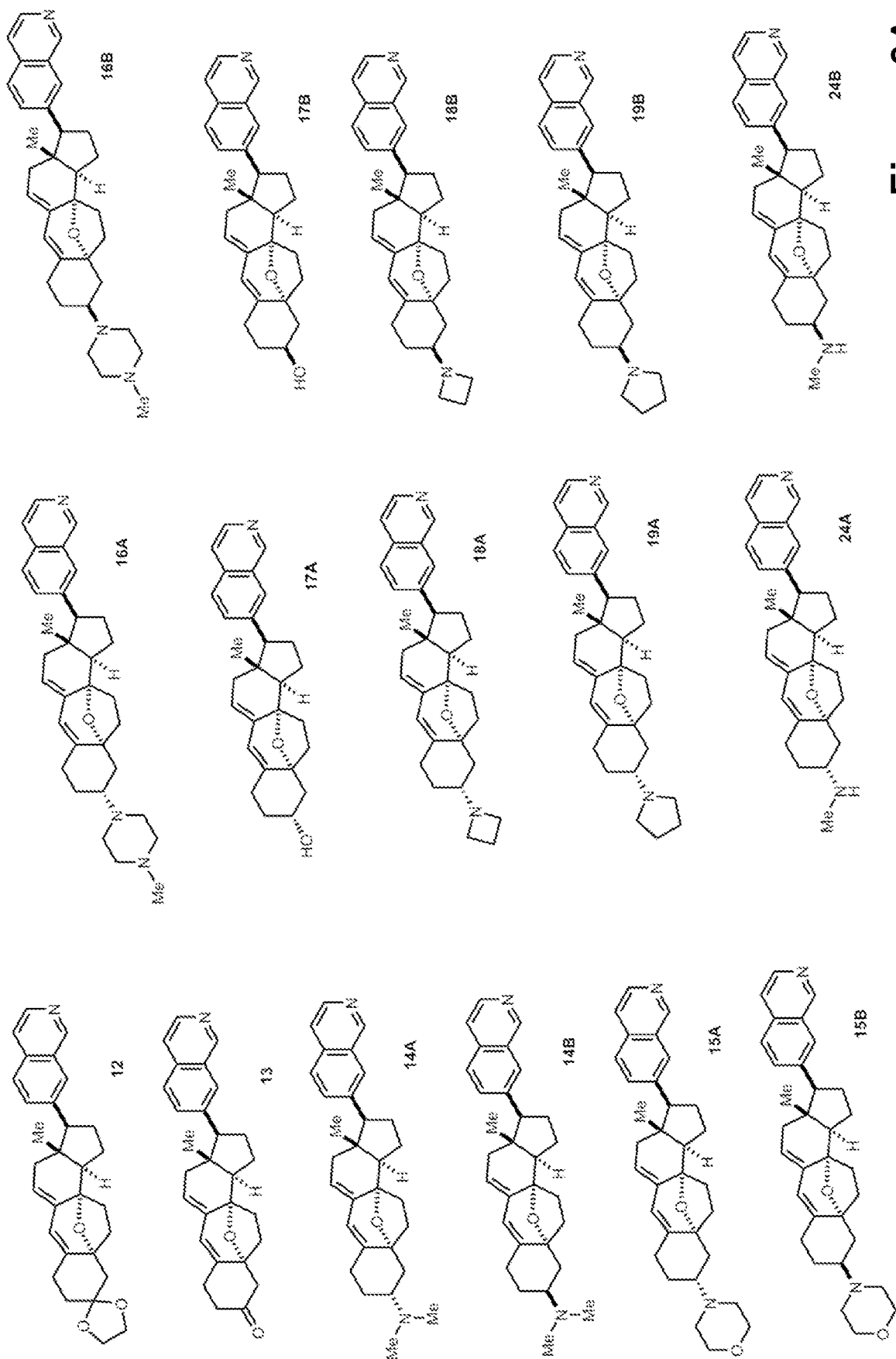
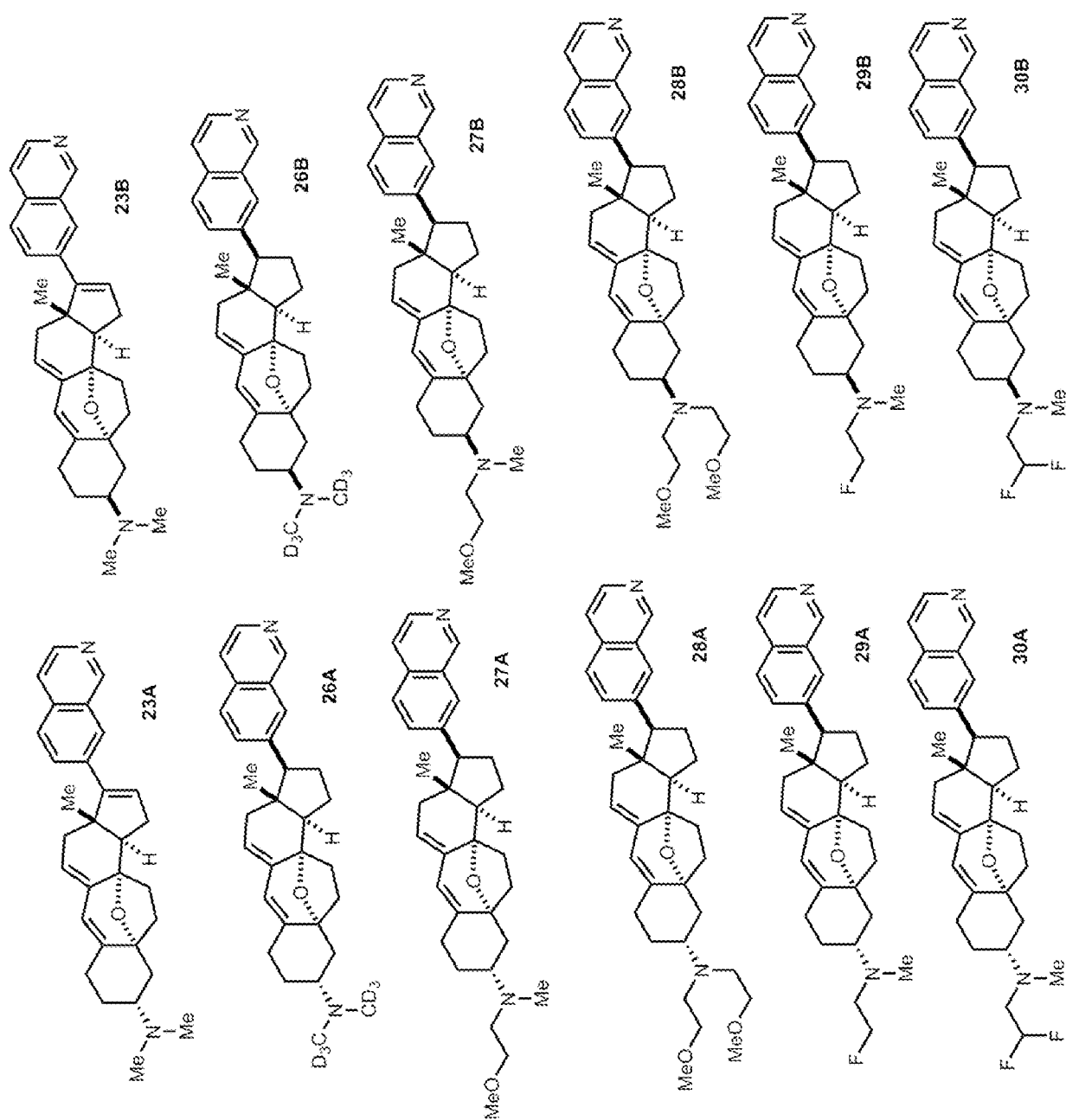


Figure 3A



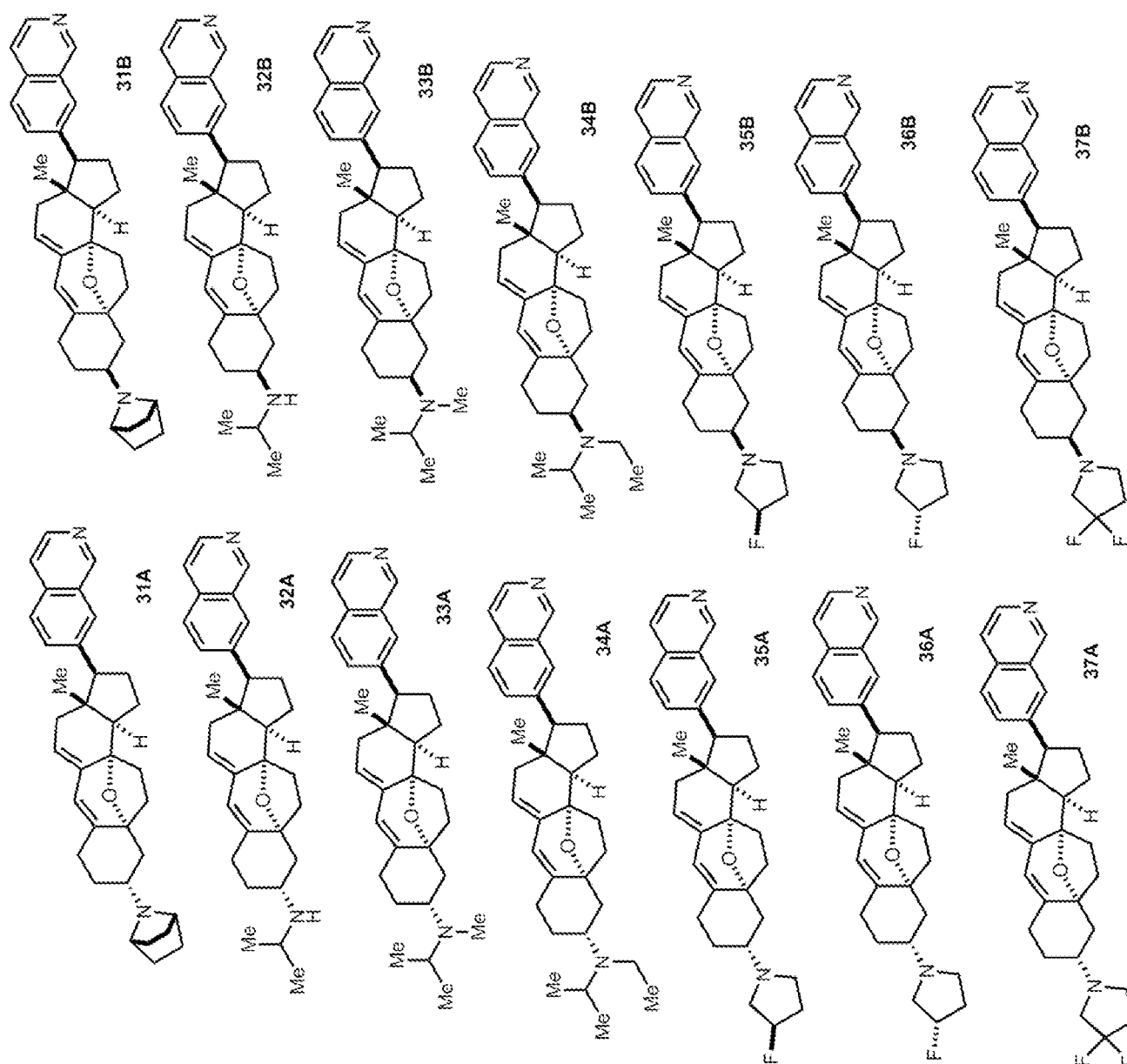


Figure 3C

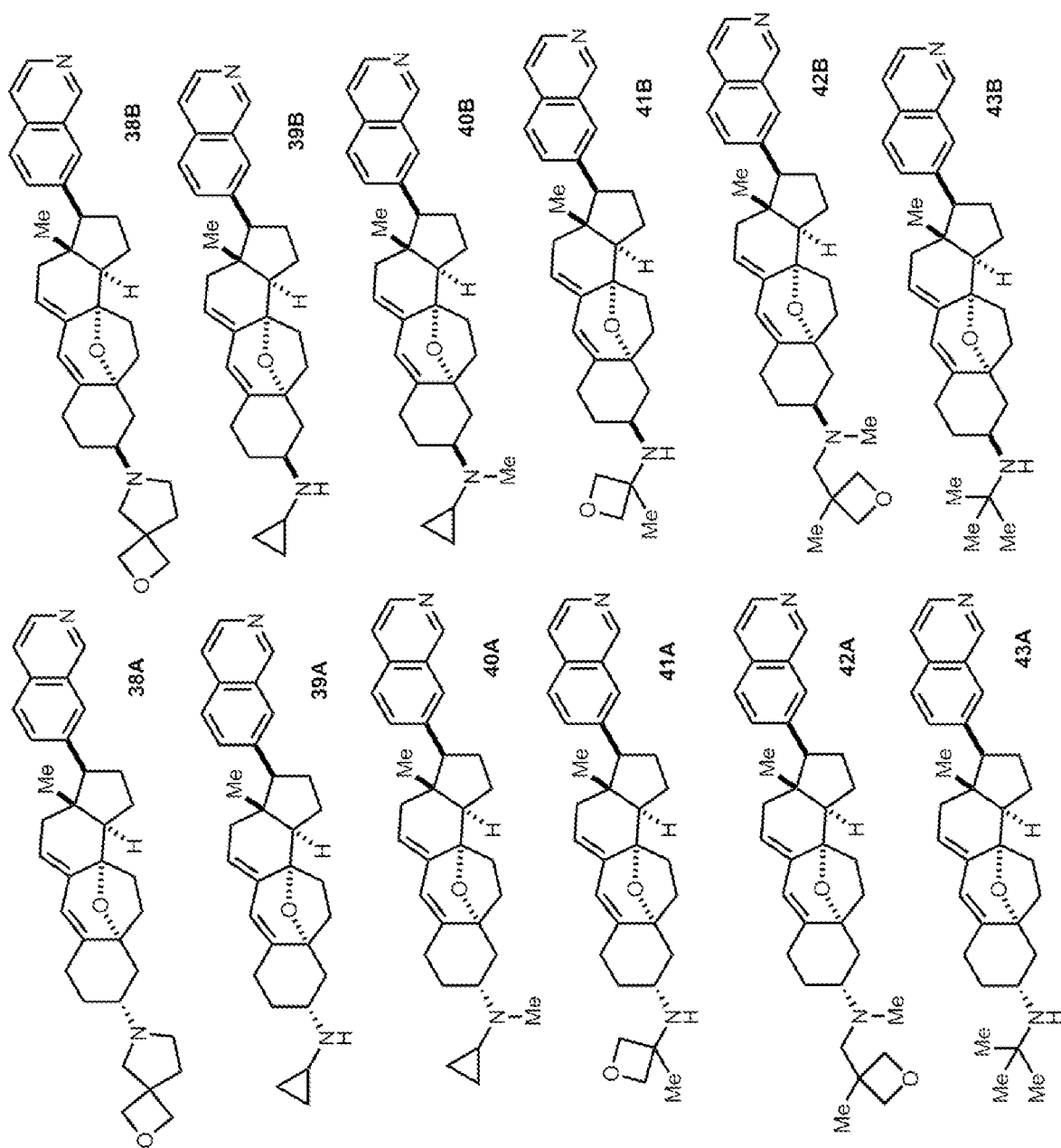


Figure 3D

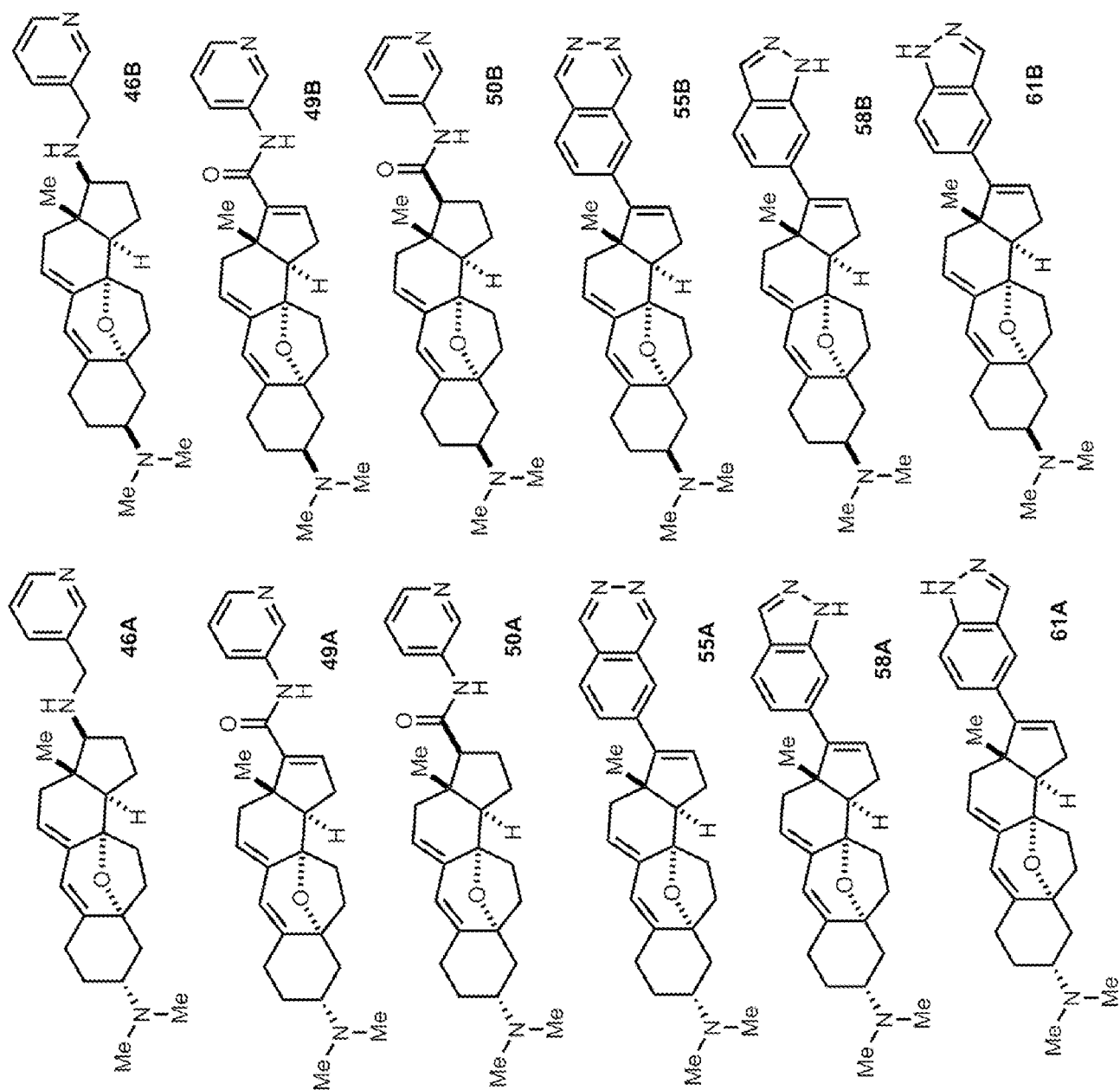


Figure 3E

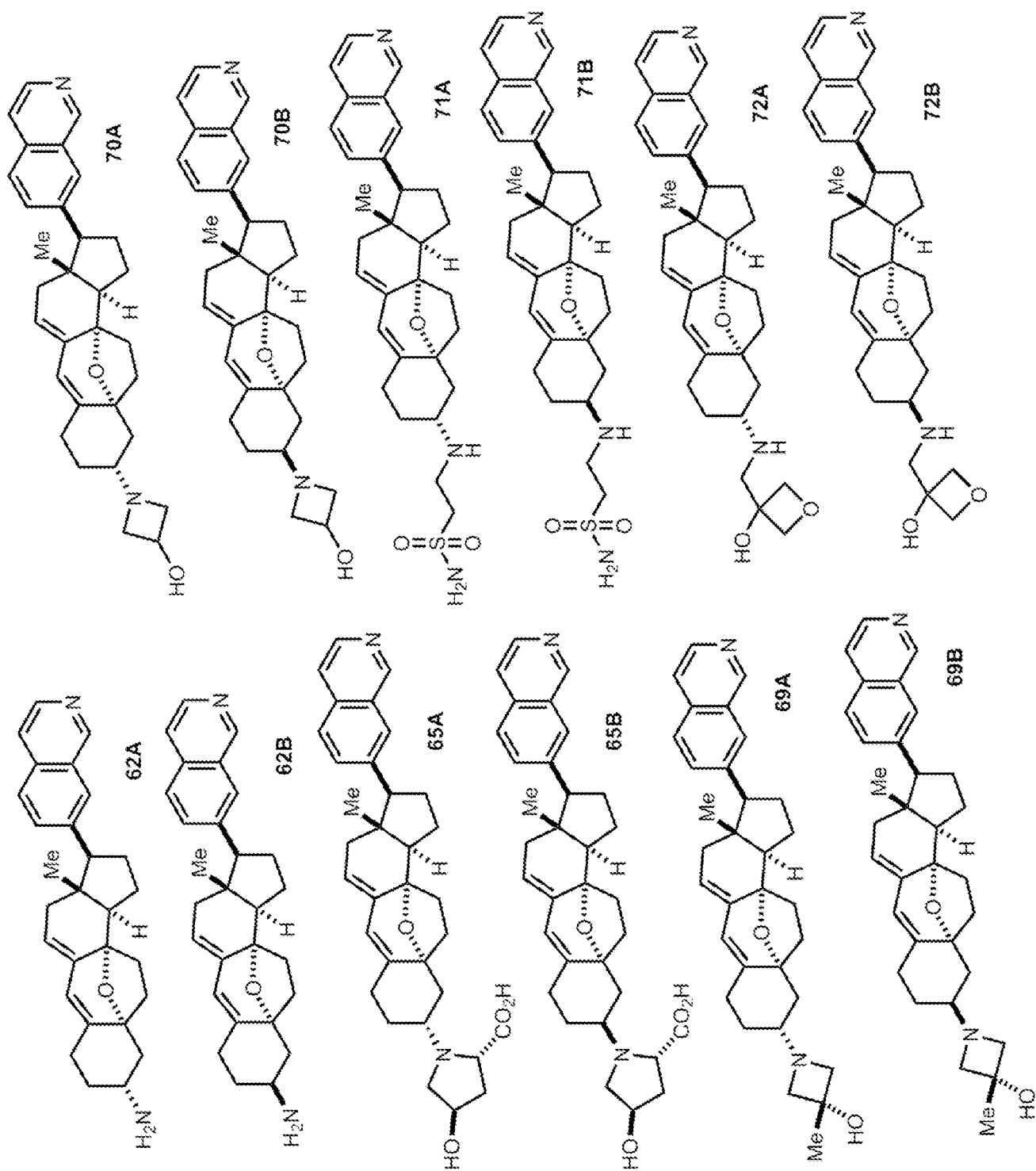


Figure 3F

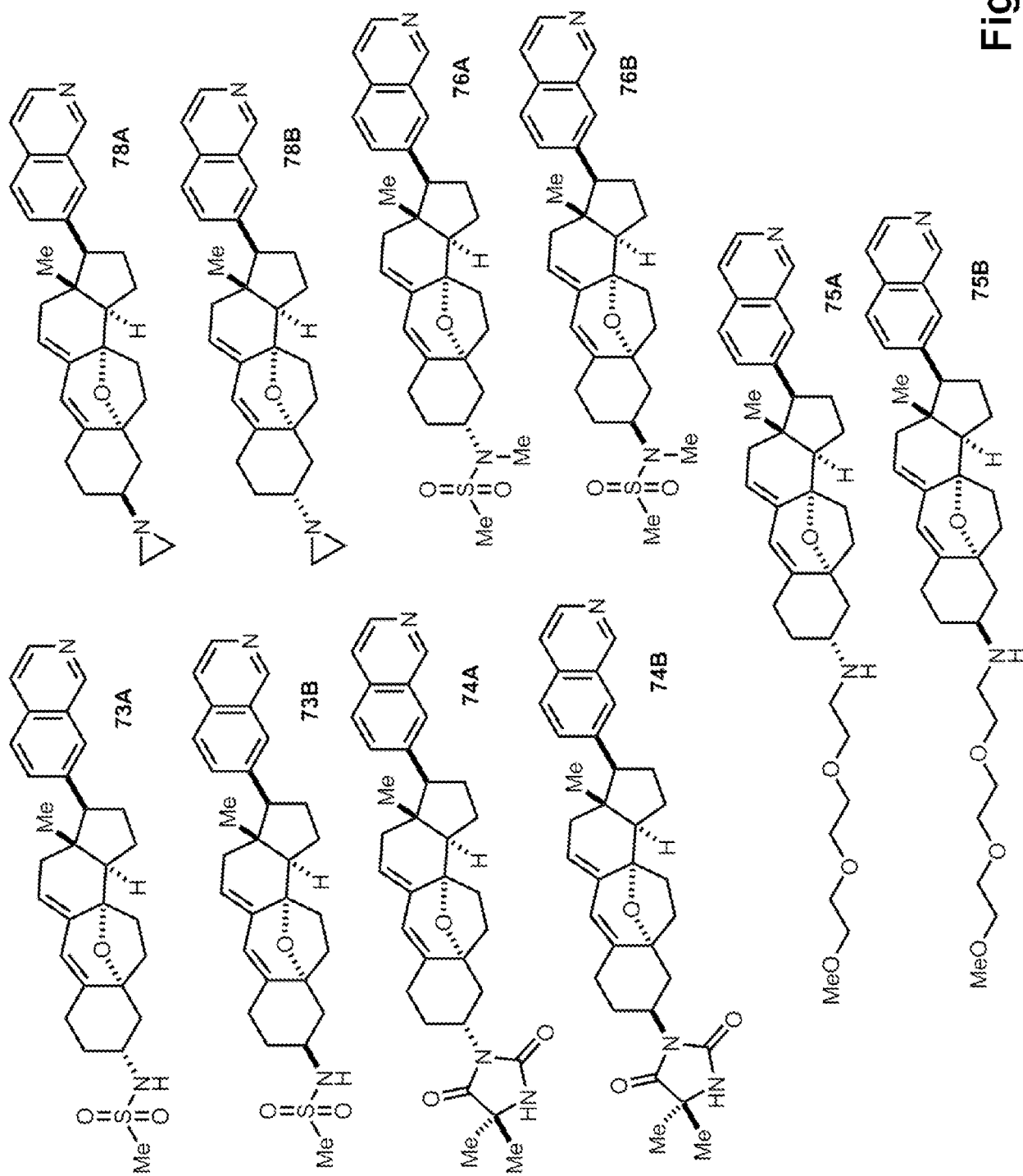


Figure 3G

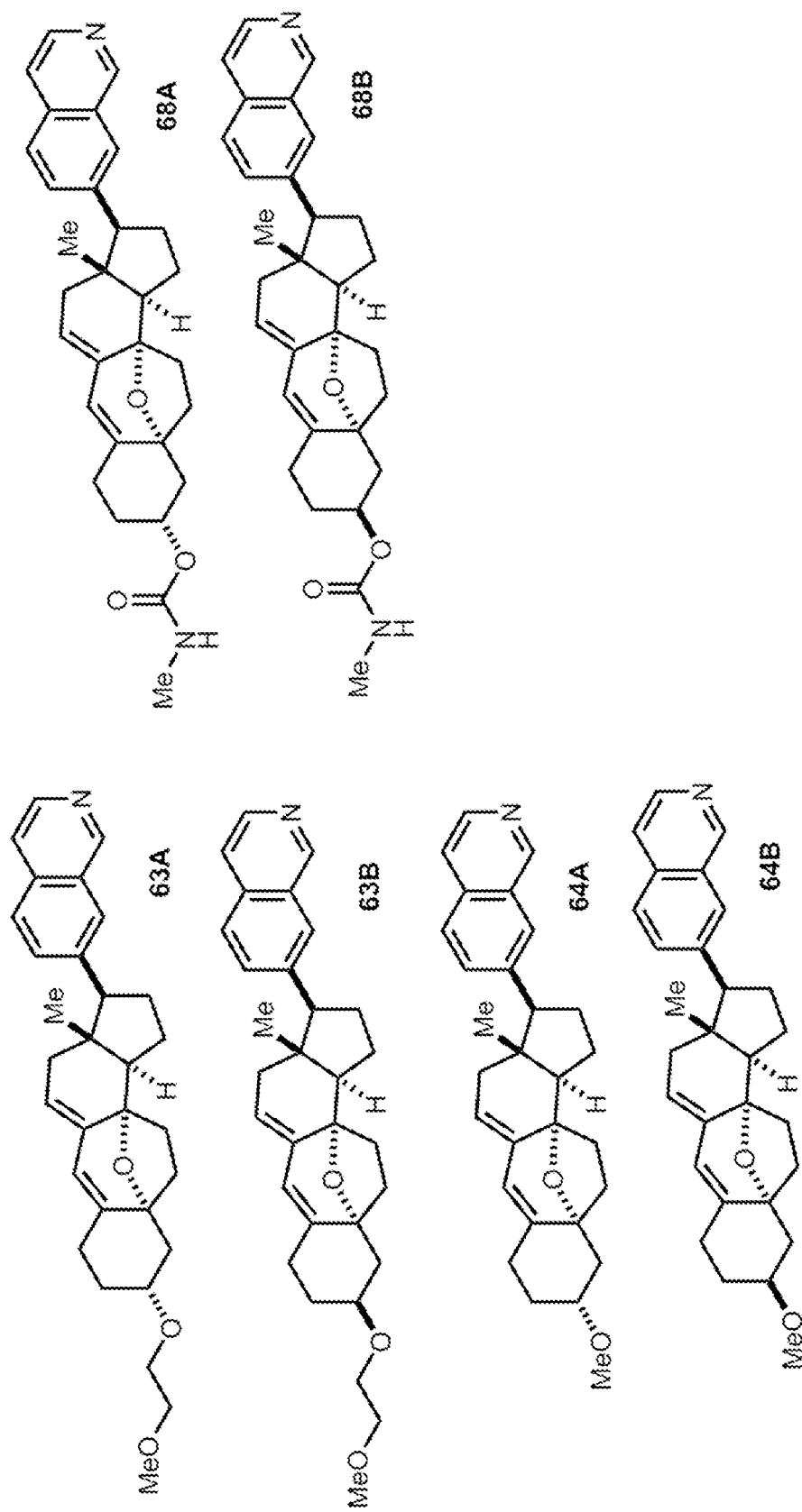


Figure 3H

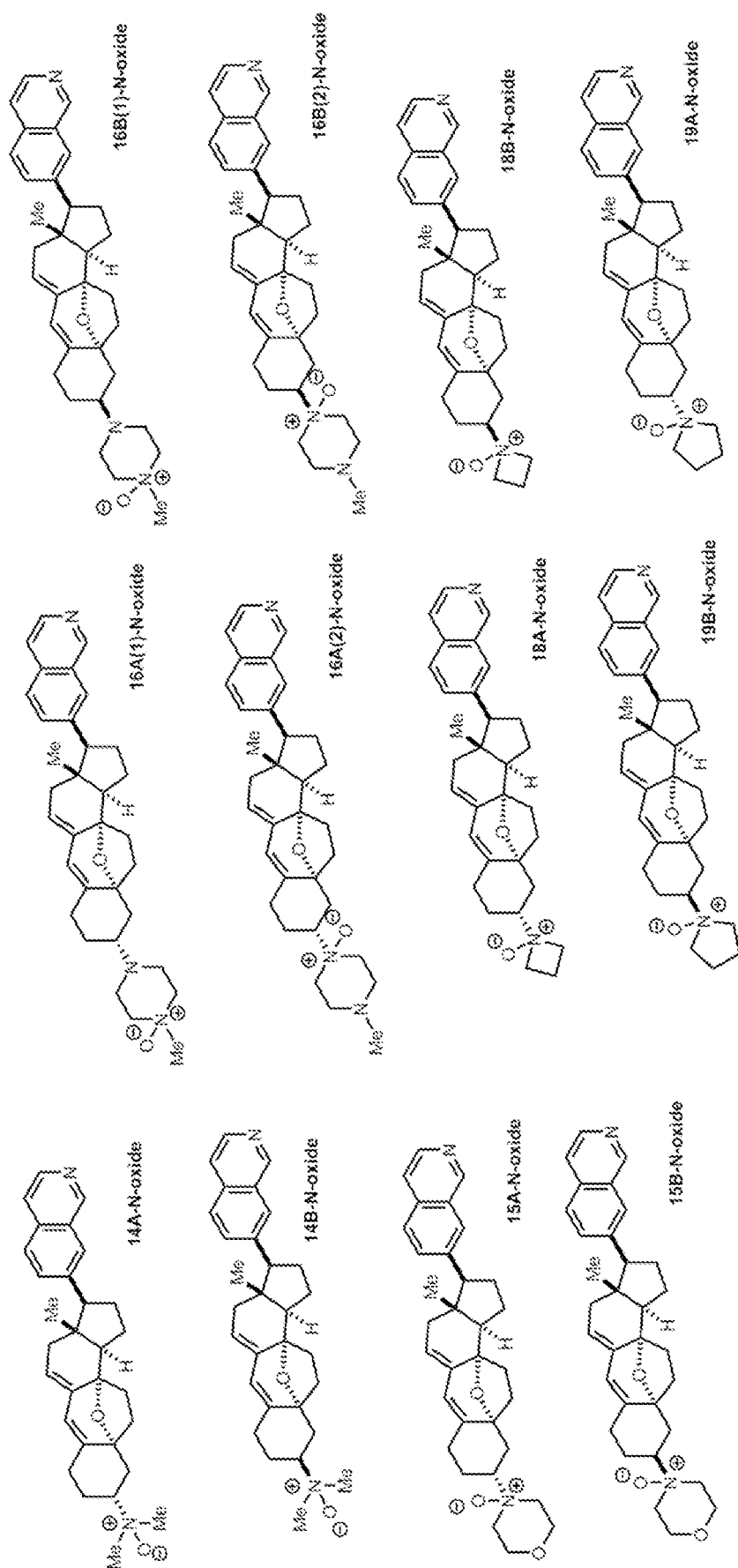


Figure 31

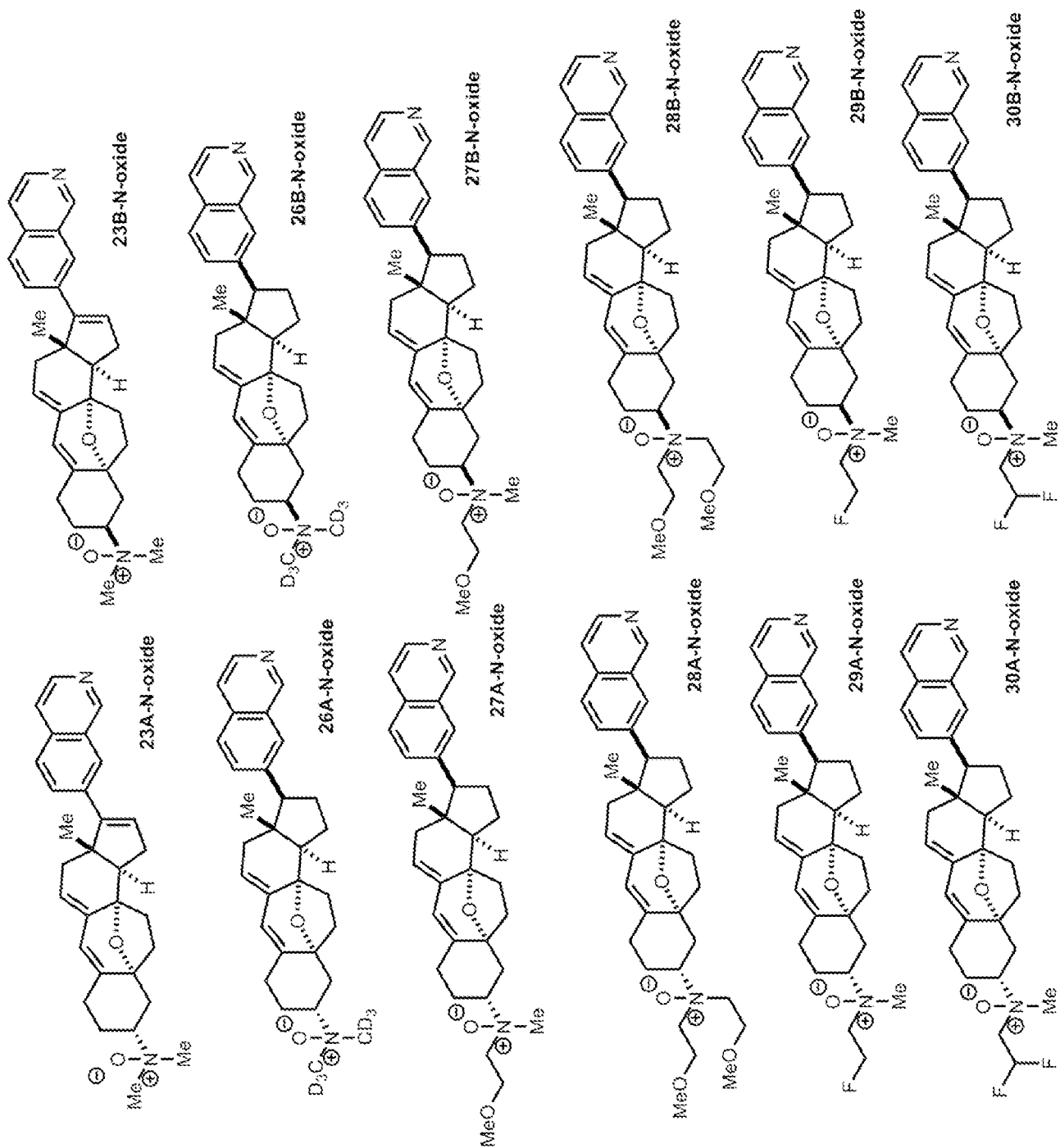


Figure 3J

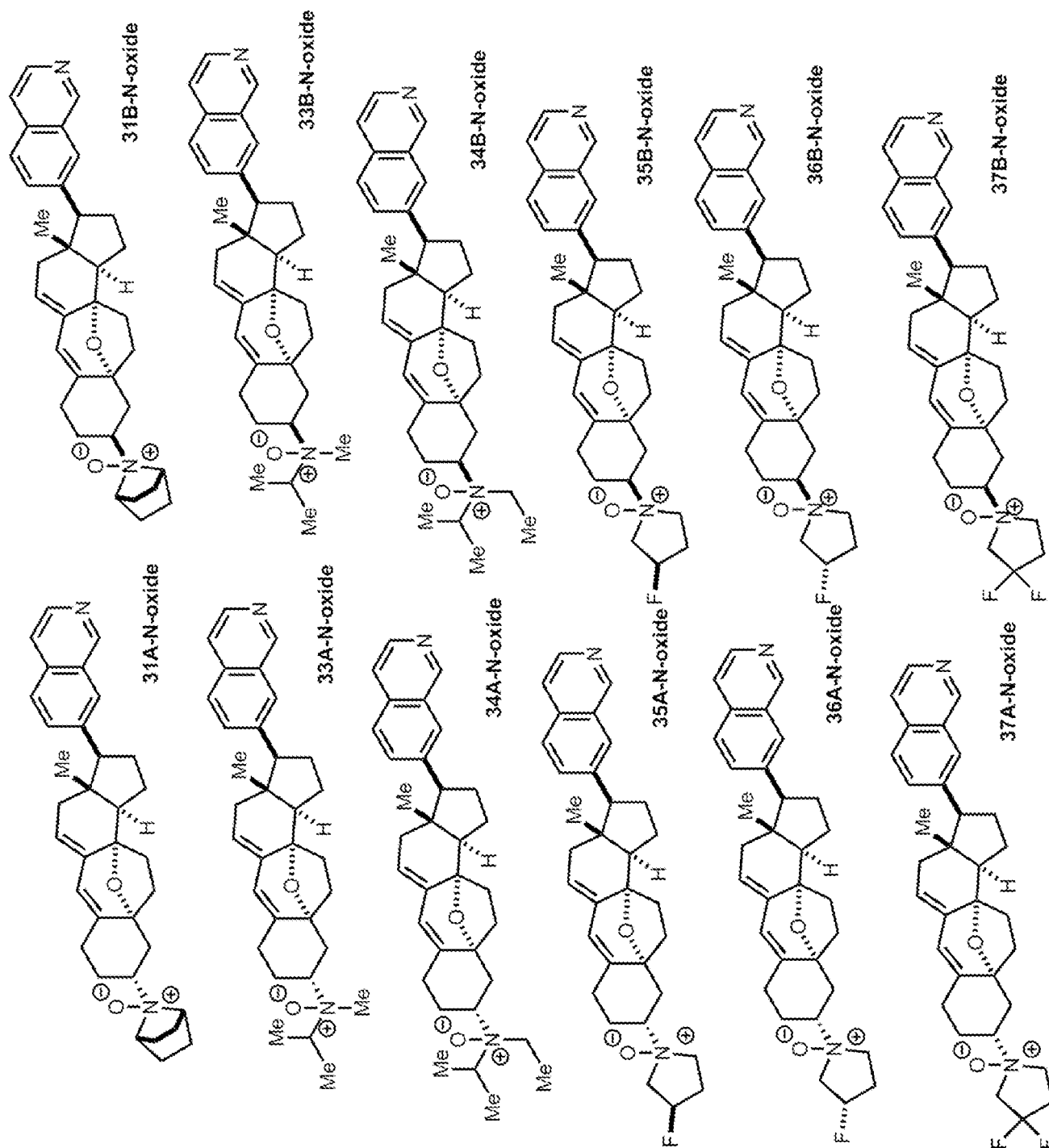


Figure 3K

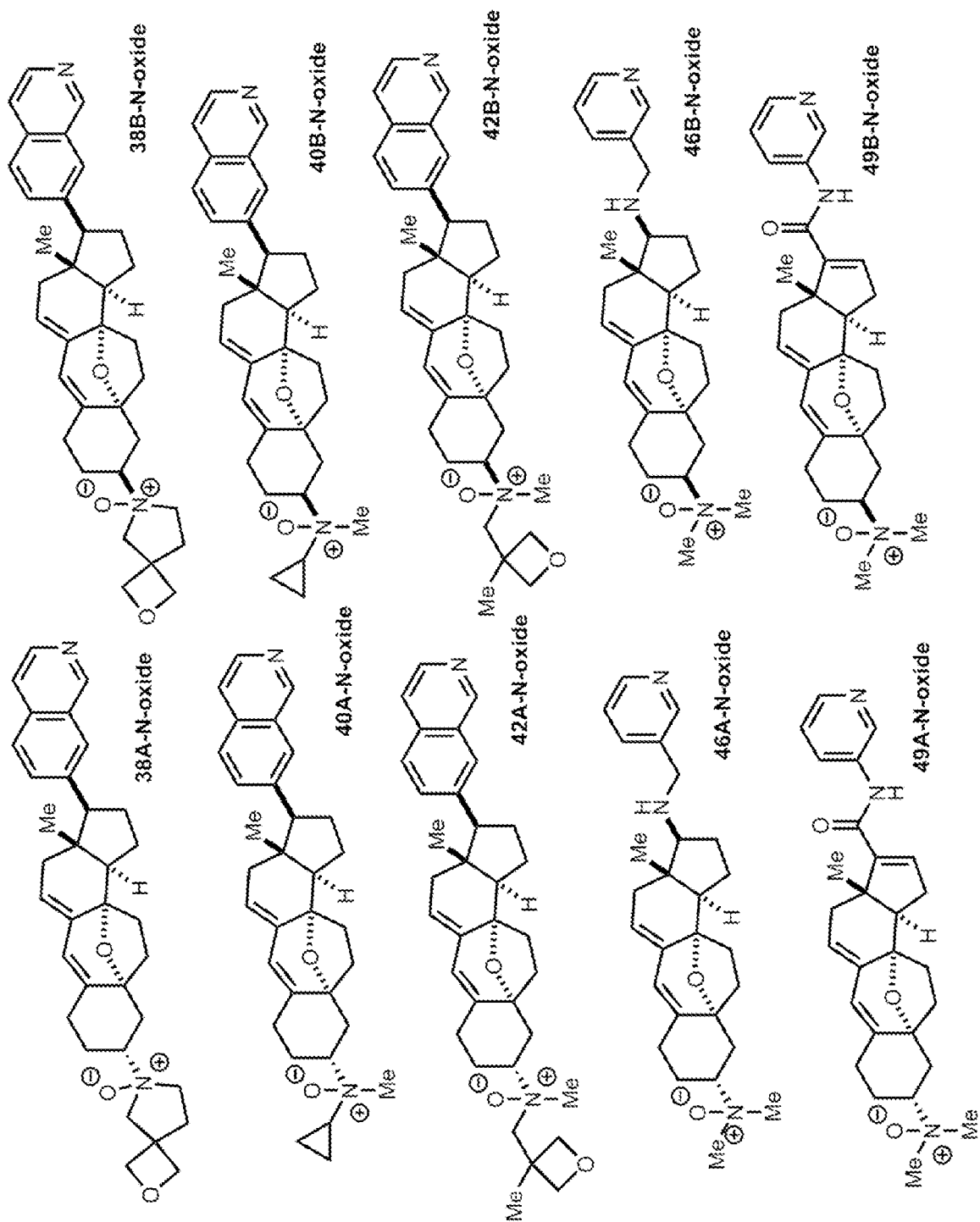


Figure 3L

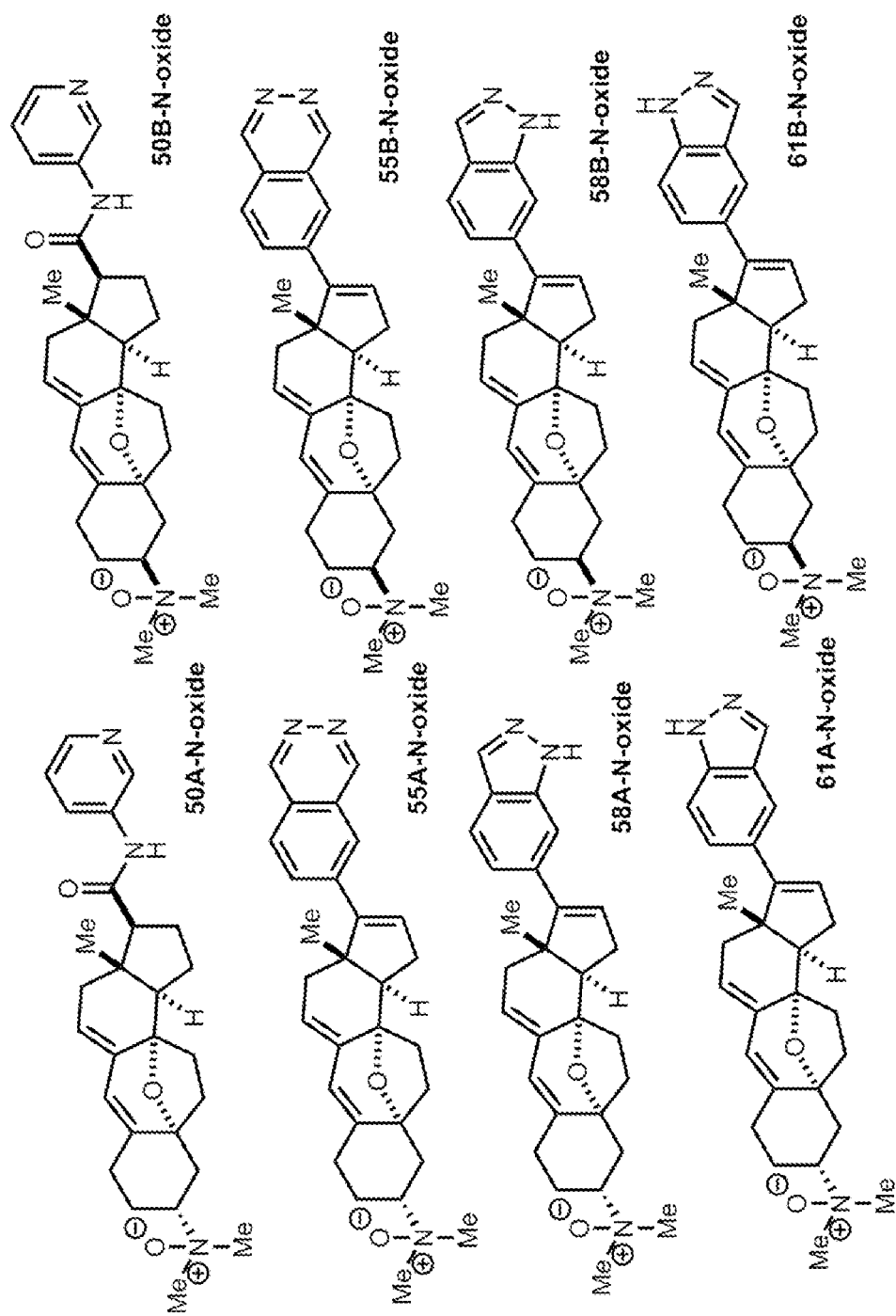


Figure 3M

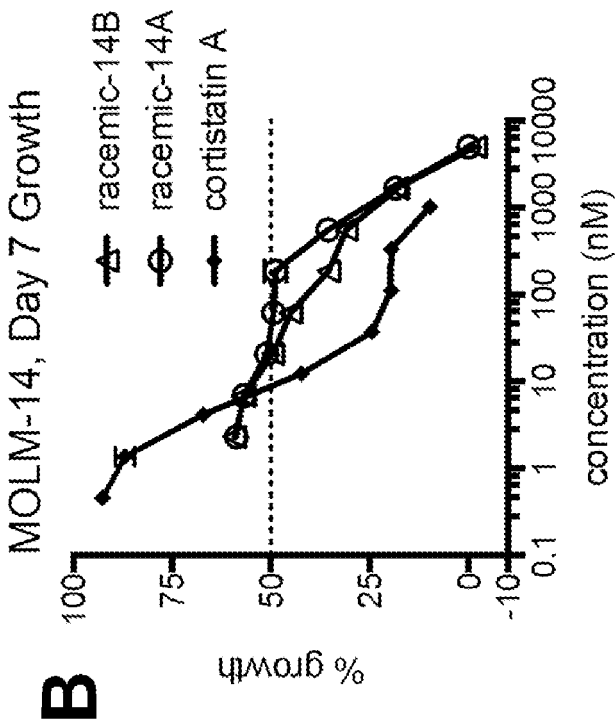
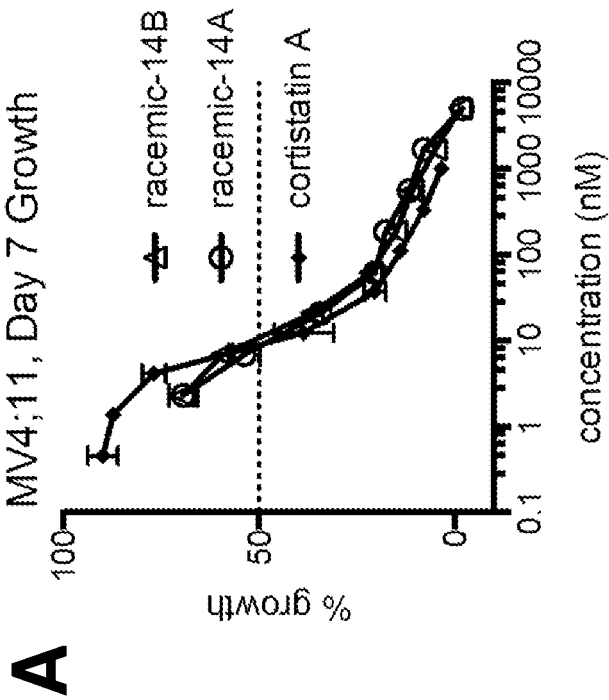


Figure 4

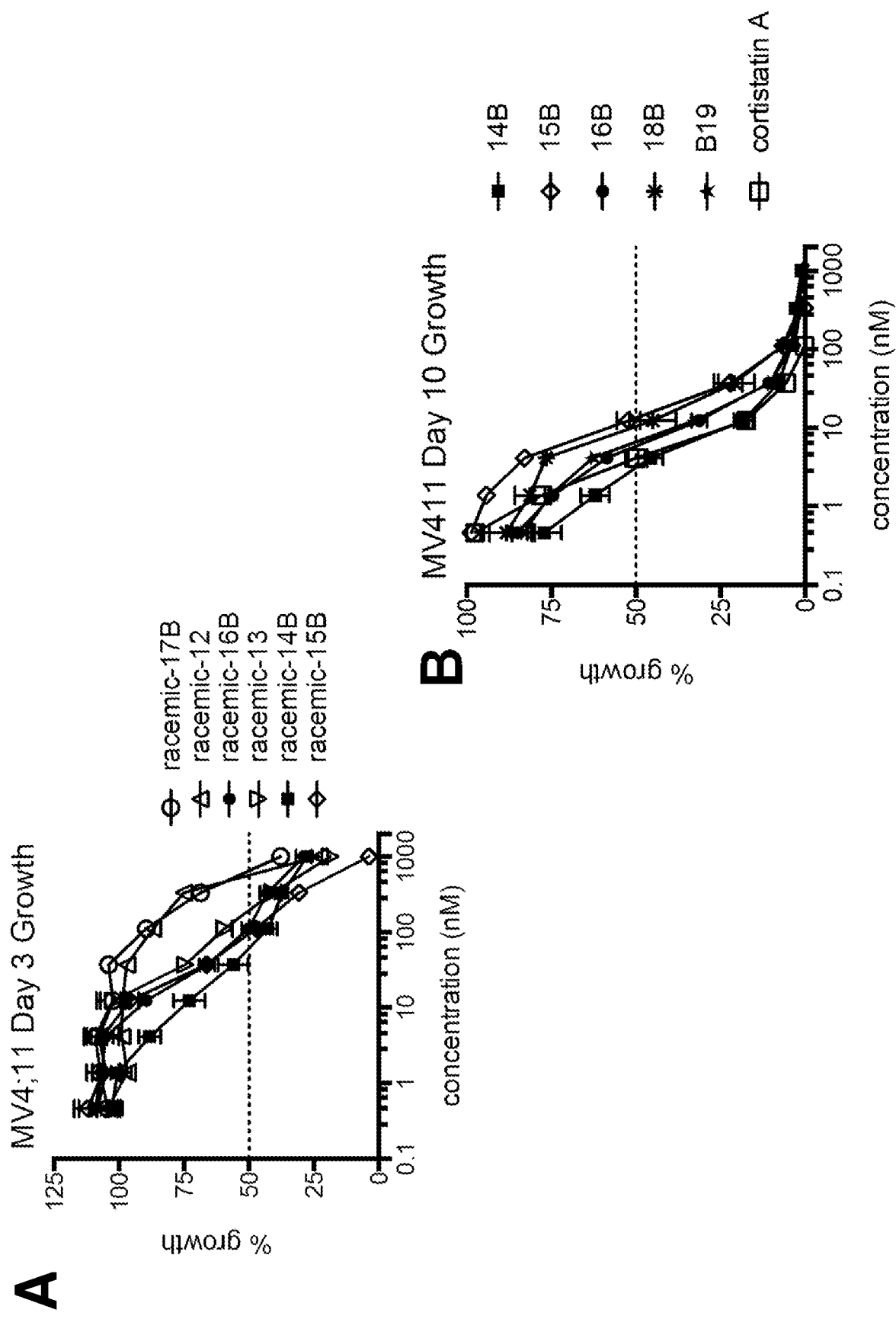


Figure 5

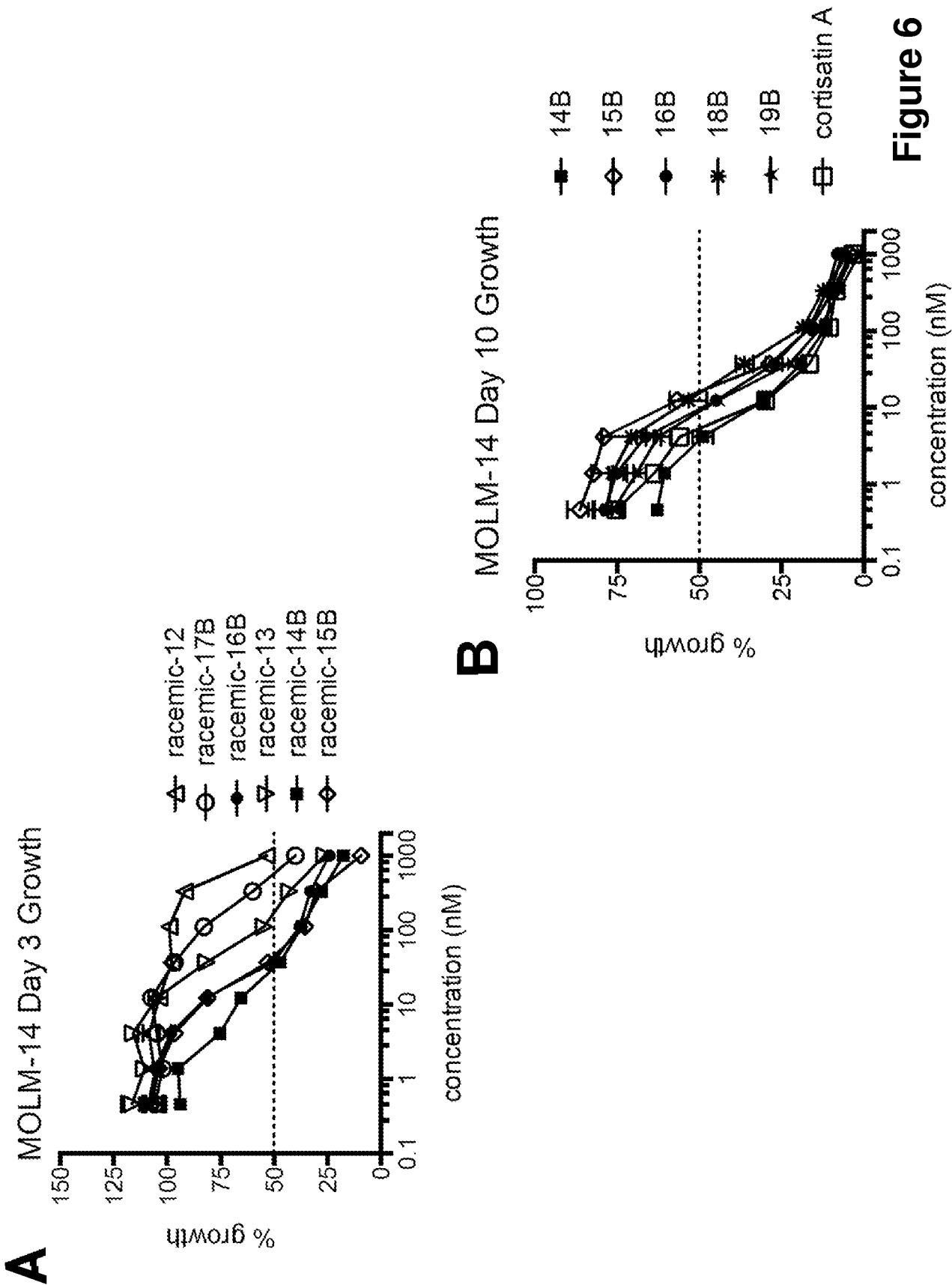


Figure 6

In Cells

IFN γ -stimulated phosphorylation
of STAT1 S727

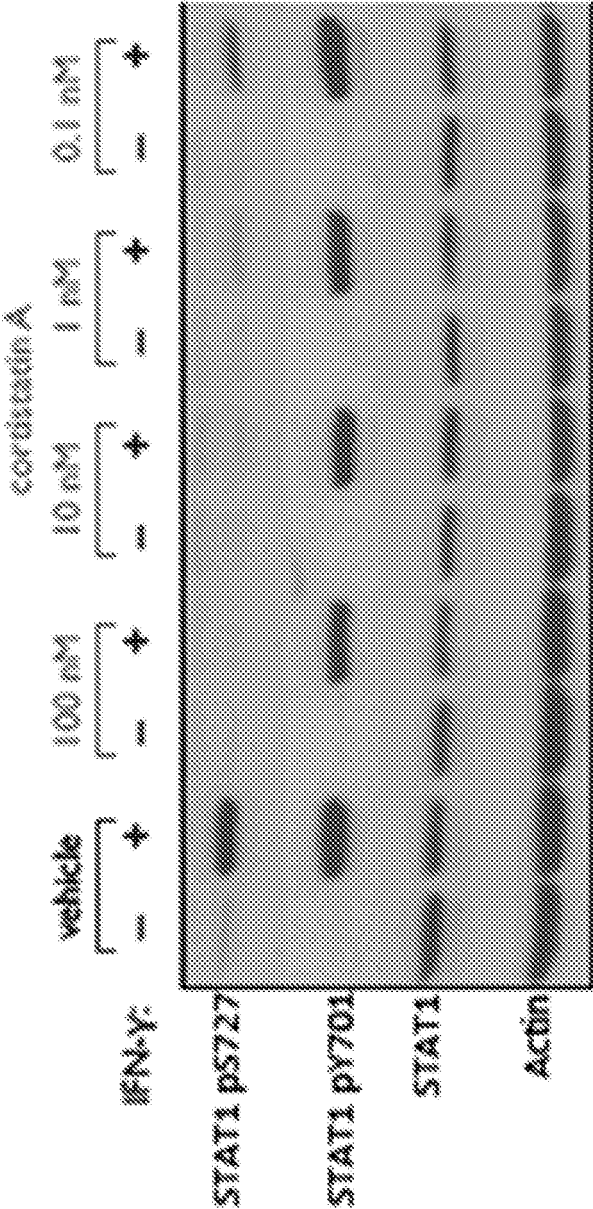
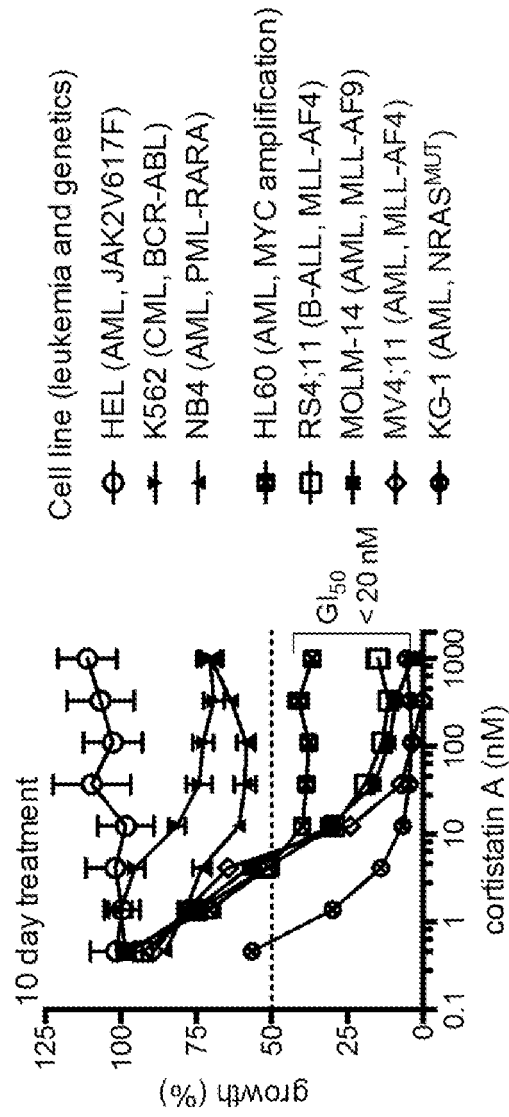


Figure 7

A



B

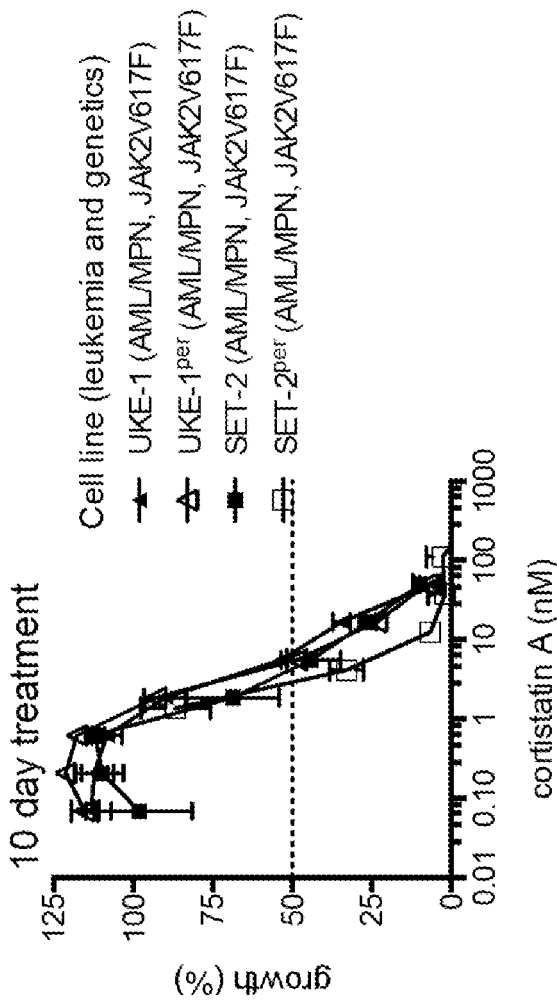


Figure 8

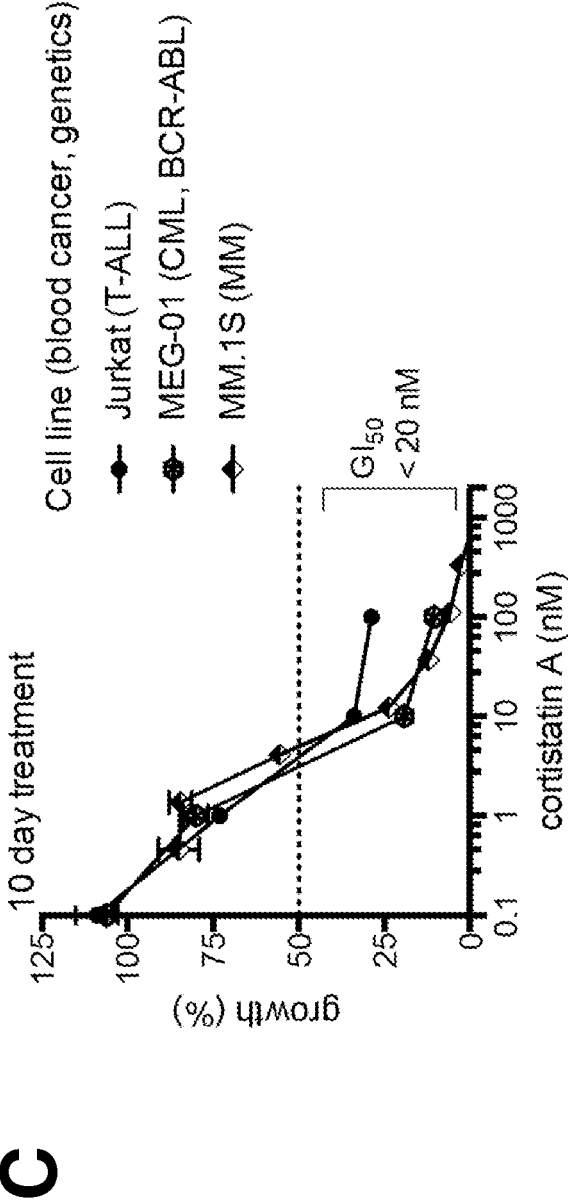


Figure 8 (cont'd)

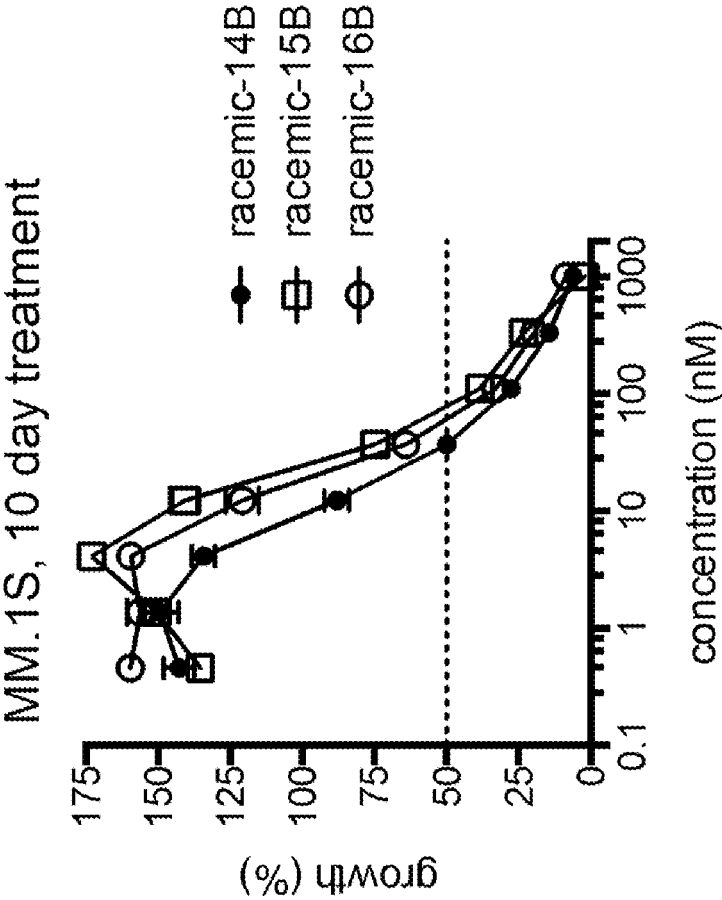
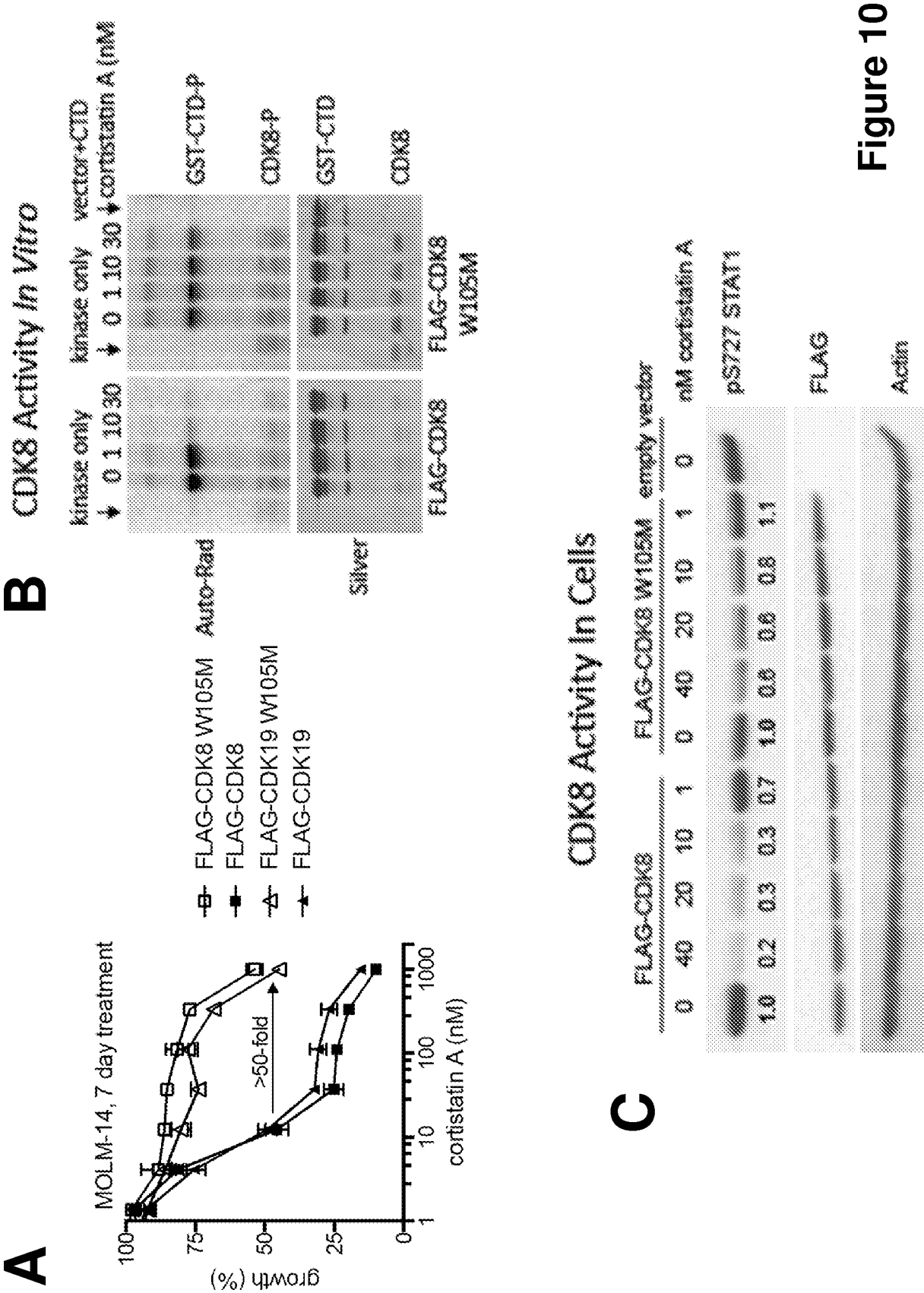
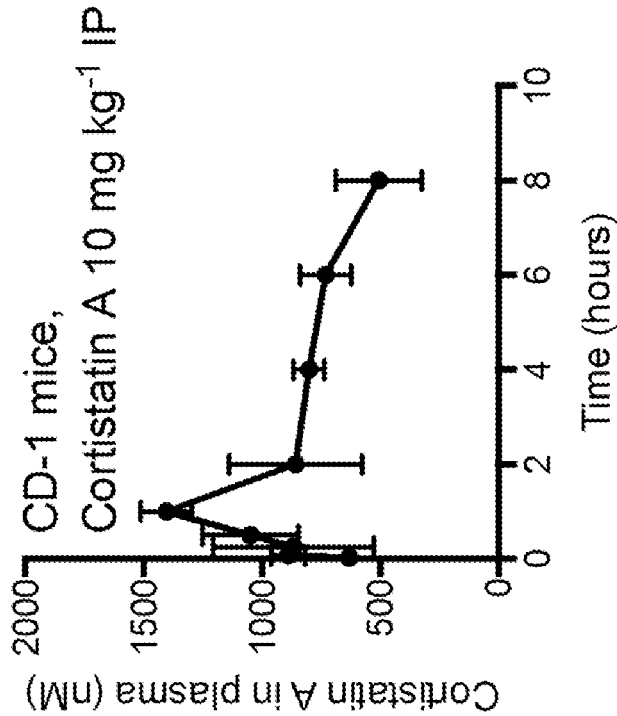


Figure 9





IP Dose of Cortistatin A (10 mg kg ⁻¹)						
Mouse	T 1/2 (hr)	Tmax (hr)	Cmax nM	AUClast (hr*nM)	AUCINF (hr*nM)	Extrapolated (%)
	6.06	1.00	1,406	6,620	11,057	40.1

t_{1/2}= terminal half-life
AUC_{0-∞}= area under a concentration of analyte vs. time calculated using zero to infinity
AUC_{0-last}= computed from time zero to the time of the last positive Y value
Cmax= the peak or maximum concentration
Tmax= the time of peak concentration

Figure 11A

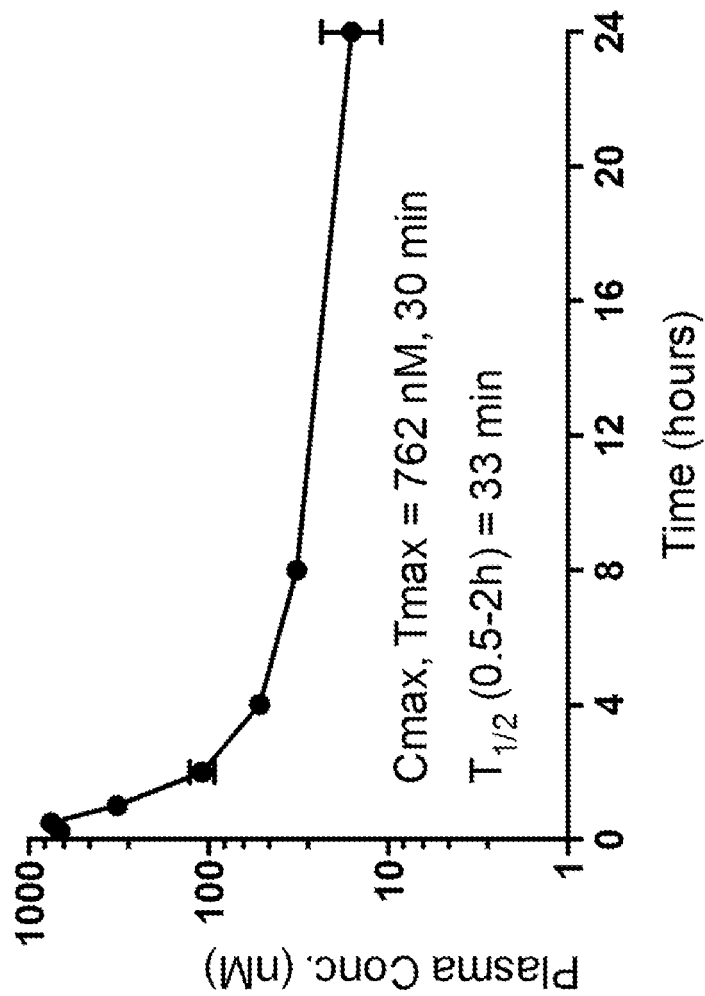


Figure 11B

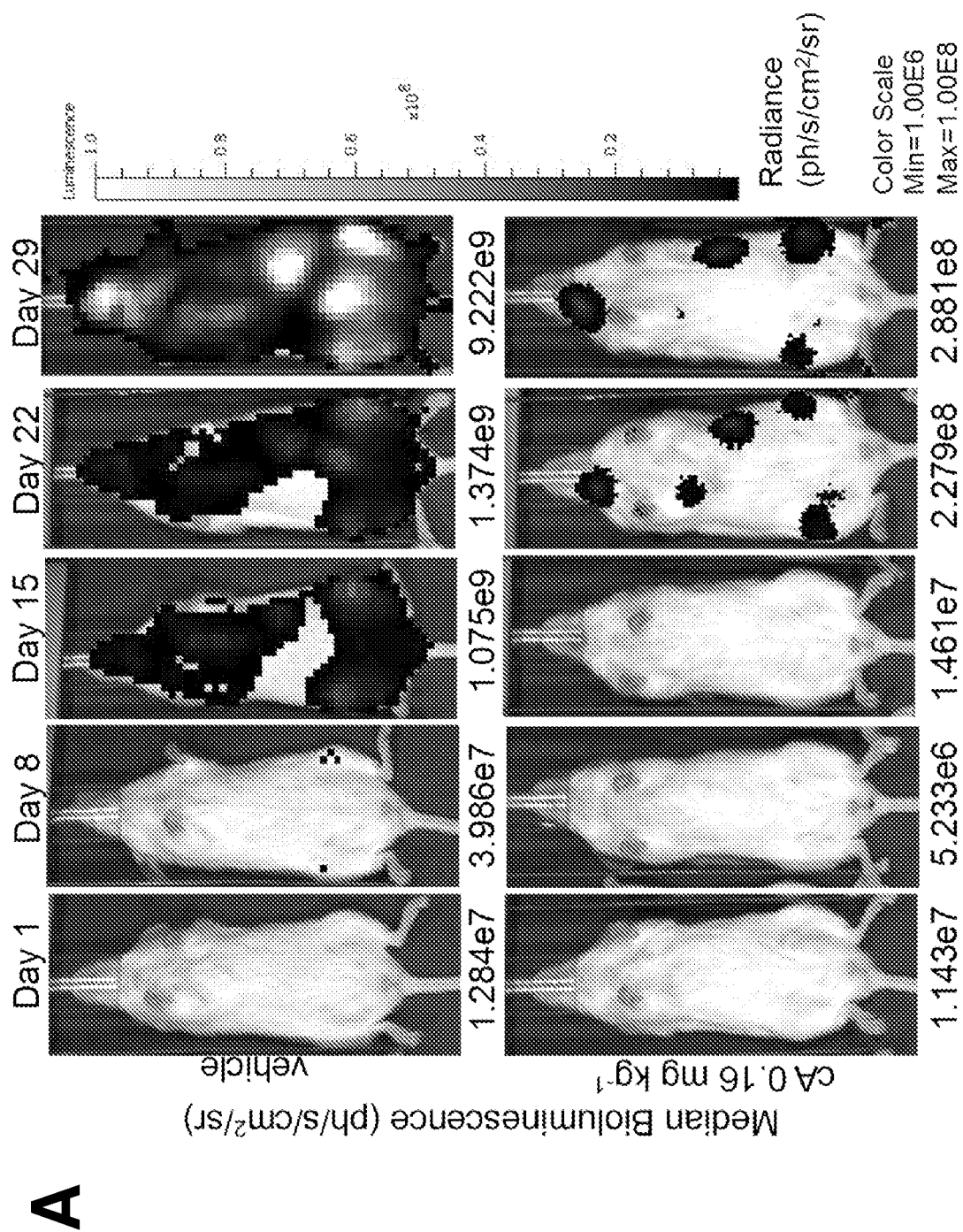
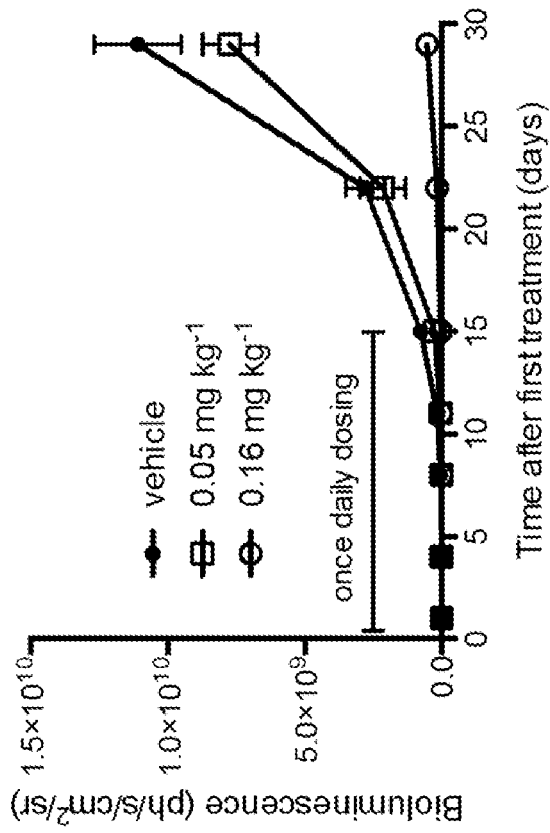


Figure 12

B



C

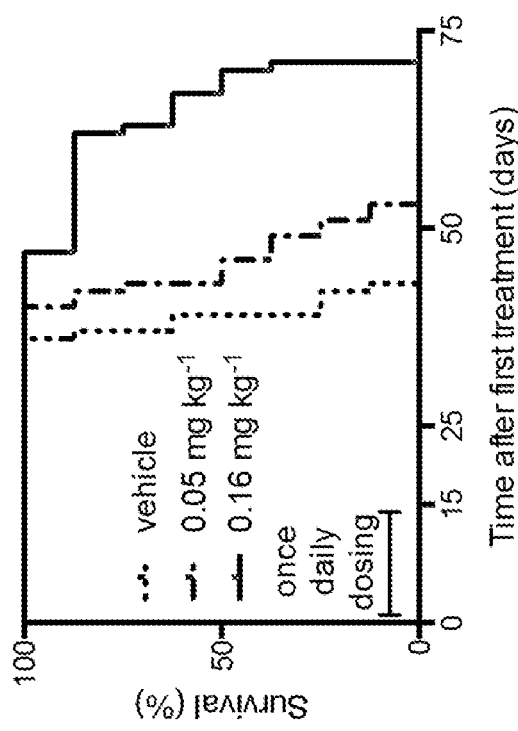


Figure 12 (cont'd)

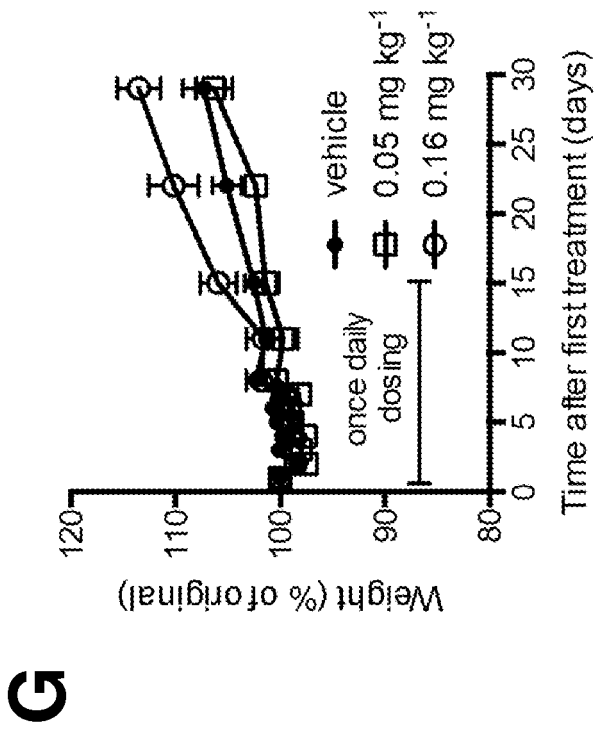
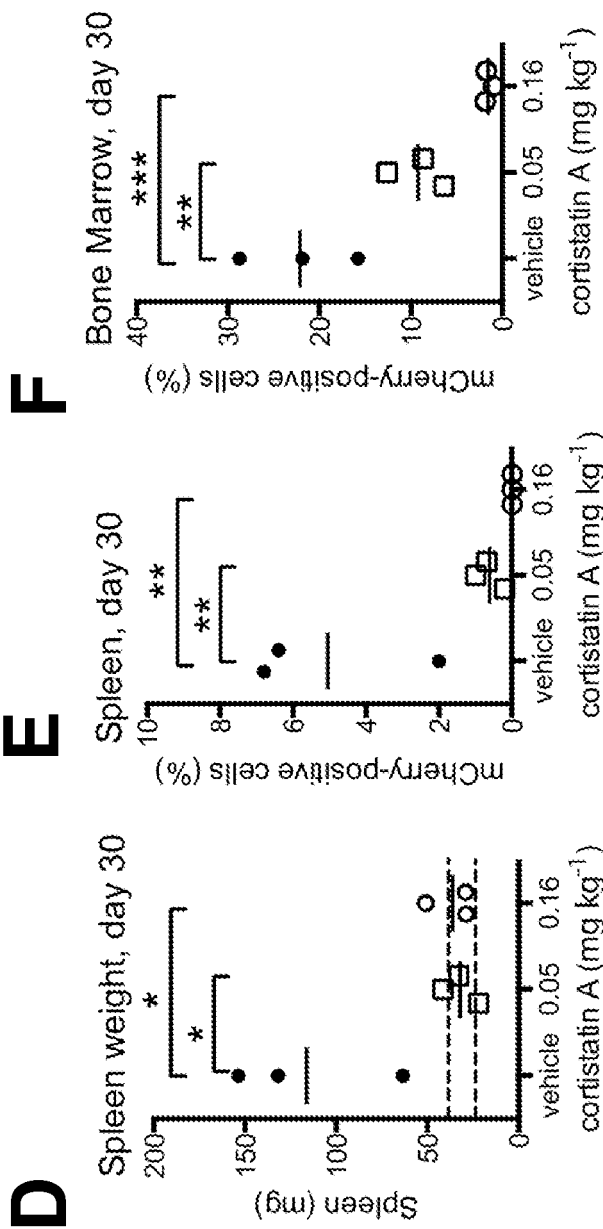
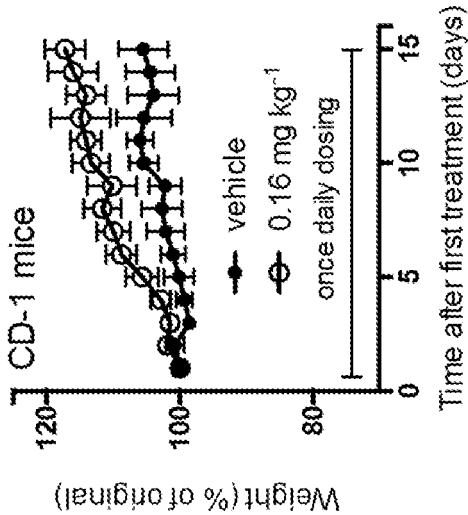


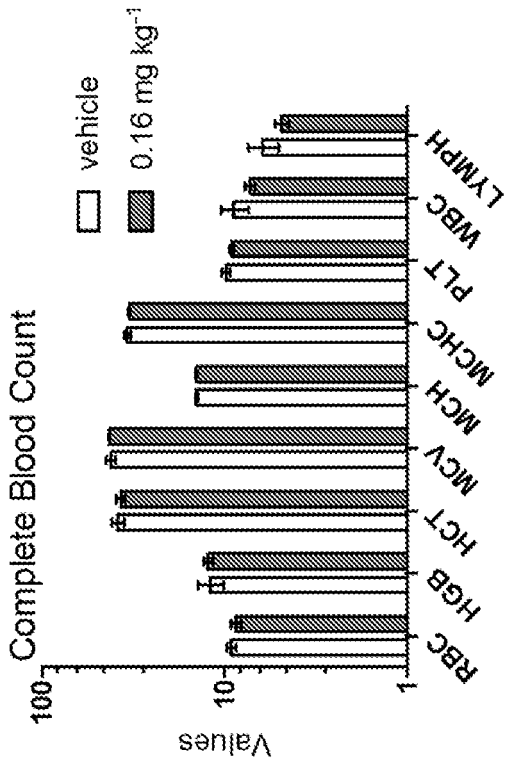
Figure 12 (cont'd)

Figure 13

A



B



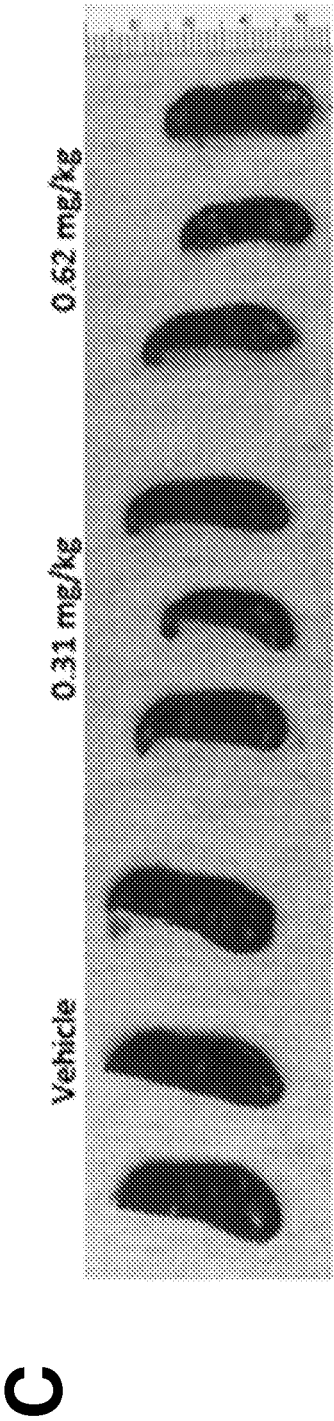
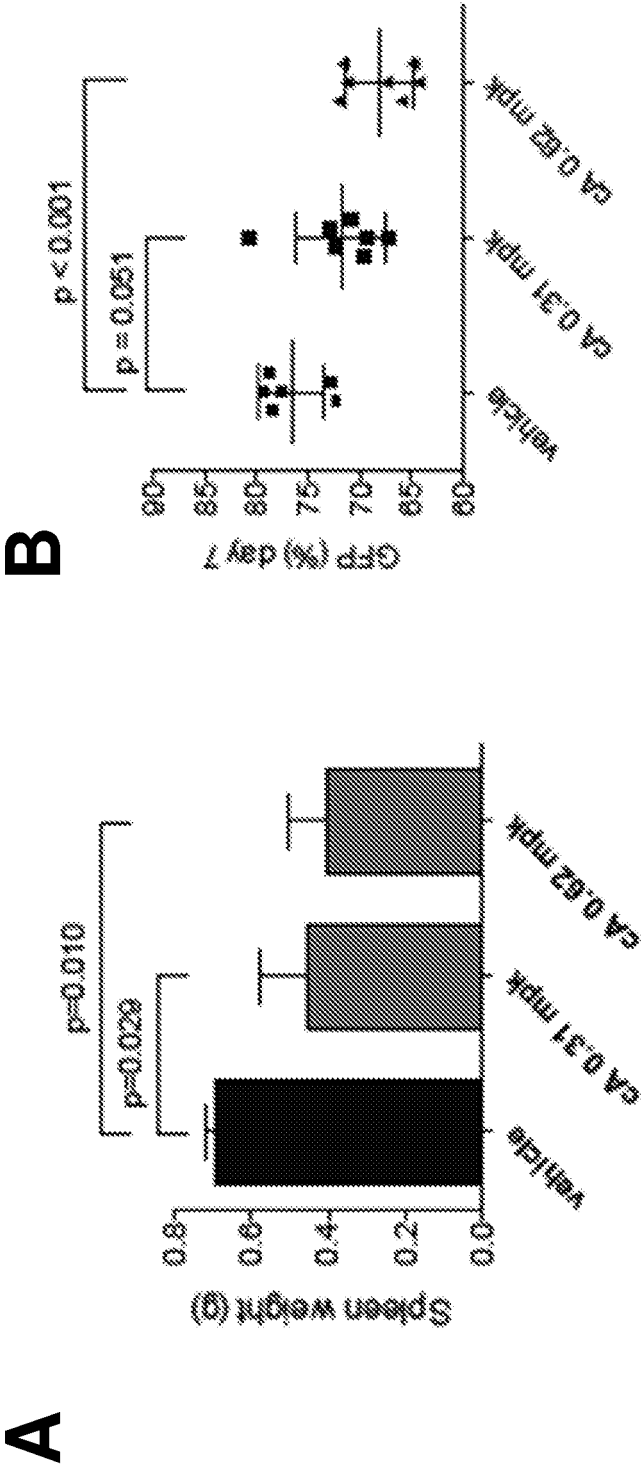
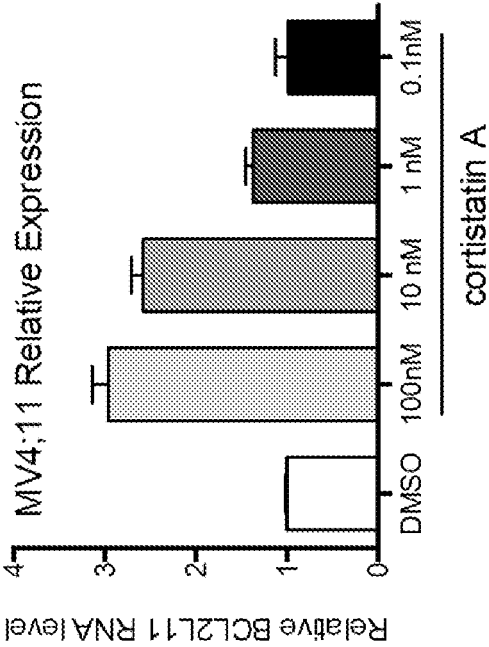


Figure 14

D



E

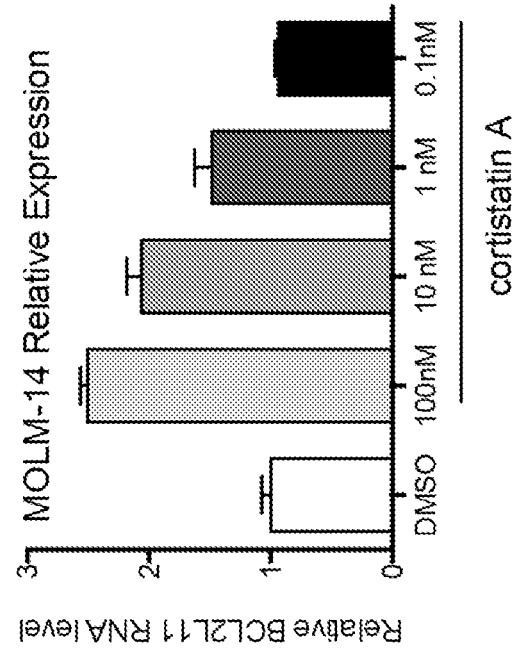


Figure 15 (cont'd)

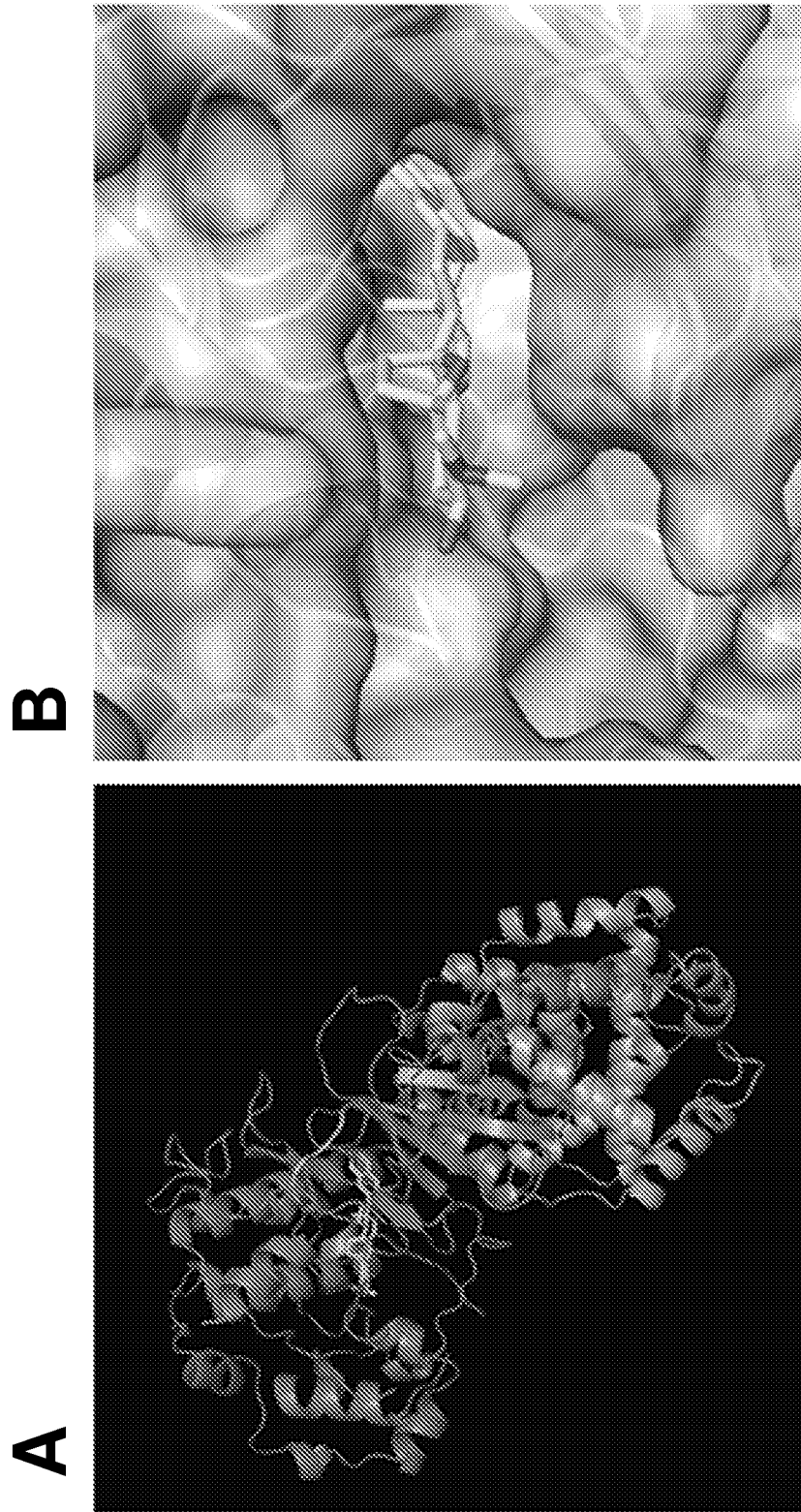


Figure 16

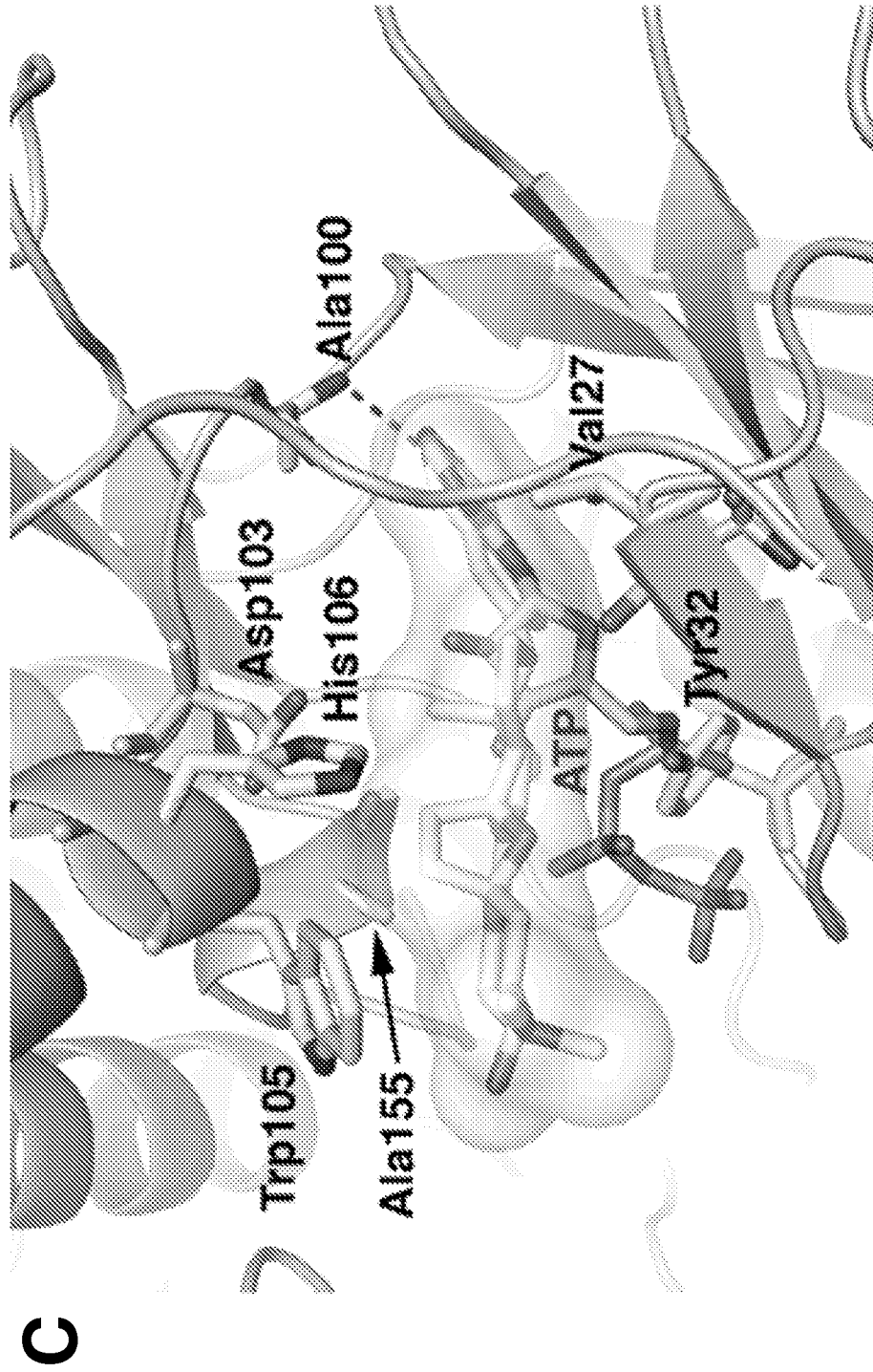


Figure 16 (cont'd)

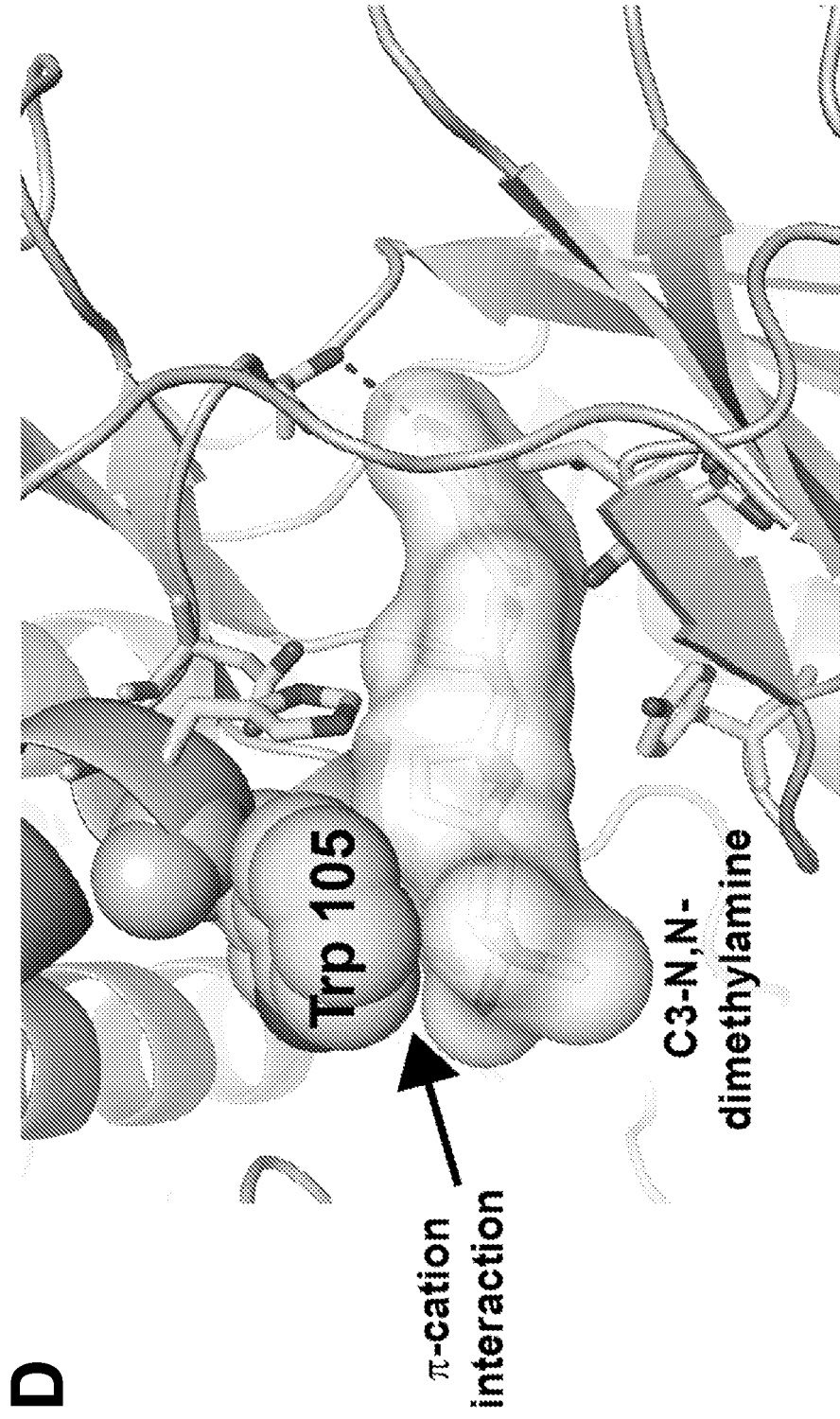


Figure 16 (cont'd)

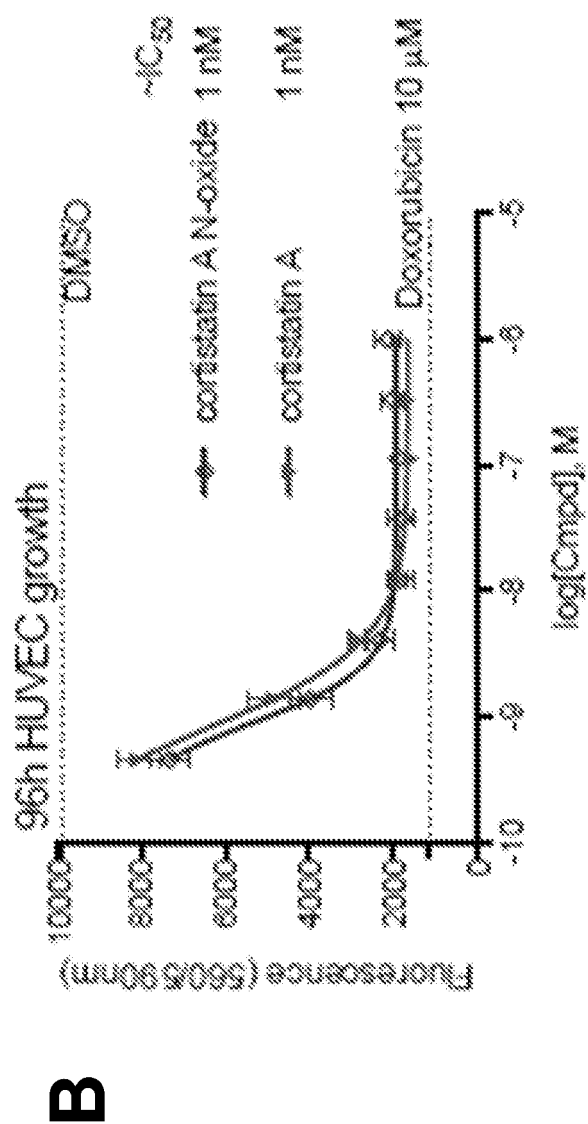
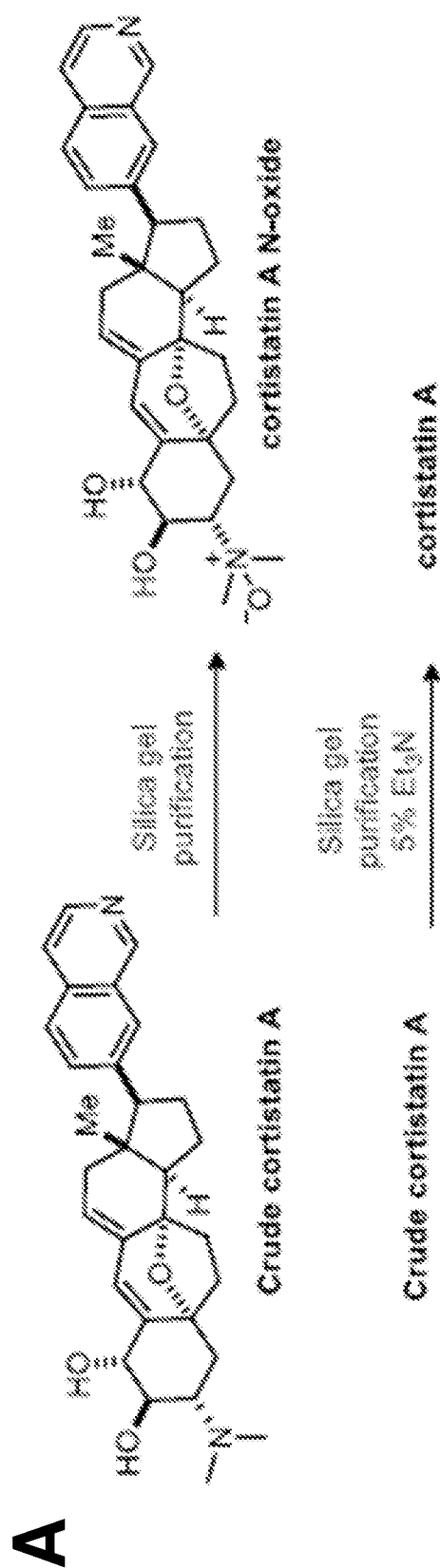


Figure 17

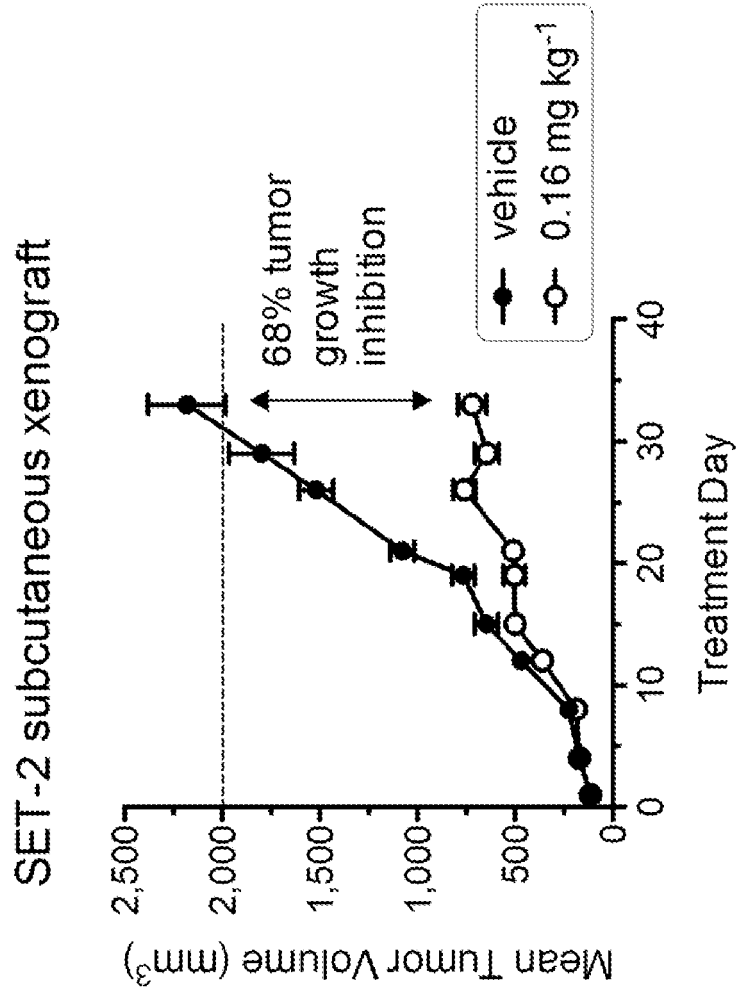
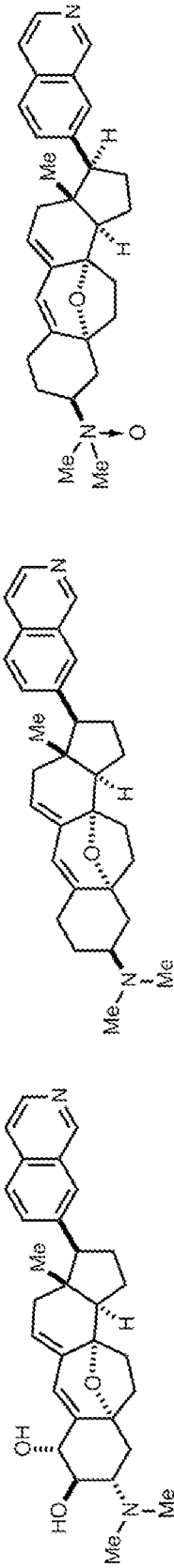


Figure 18



Cortistatin A (CA)

14B

14B-N-oxide (14BNO)

Sample Name	Human Liver Microsome						Rat Liver Microsome					
	R ²	T _{1/2} (min)	CL (μL/min/mg)	CL _{int} (mL/min/kg)	Remaining (T=60min)	Remaining (NCF=60min)	R ²	T _{1/2} (min)	CL (μL/min/mg)	CL _{int} (mL/min/kg)	Remaining (T=60min)	Remaining (NCF=60min)
CA	0.9859	30.3	45.8	45.3	24.9%	112.1%	0.9652	33.5	41.4	74.5	31.1%	73.3%
14B	0.9516	7.2	193.0	191.1	0.5%	80.1%	0.9883	11.2	124.2	223.6	2.8%	86.8%
14BNO	0.9154	46.2	30.0	29.7	44.0%	85.5%	0.9822	15.4	90.2	162.4	5.7%	85.6%

Sample Name	Mouse Liver Microsome						Dog Liver Microsome					
	R ²	T _{1/2} (min)	CL (μL/min/mg)	CL _{int} (mL/min/kg)	Remaining (T=60min)	Remaining (NCF=60min)	R ²	T _{1/2} (min)	CL (μL/min/mg)	CL _{int} (mL/min/kg)	Remaining (T=60min)	Remaining (NCF=60min)
CA	0.9782	27.1	51.2	202.8	22.9%	80.4%	0.9755	29.1	47.6	68.5	25.6%	77.1%
14B	0.9512	19.3	72.0	285.1	13.7%	85.3%	0.9780	7.8	178.2	256.6	0.6%	89.5%
14BNO	0.8467	21.7	64.0	253.4	18.0%	81.5%	-0.0330	77.9	17.8	25.6	65.2%	85.0%

R² is the correlation coefficient of the linear regression for the determination of kinetic constant (see raw data worksheet)

T_{1/2} is half life and CL_{int} is the intrinsic clearance

T_{1/2} and CL of testosterone, propafenone and diclofenac in 4 species are in accordance with the prior results of Wuxi

CL_{int} = CL • 45mg microsome/ g liver • g Liver wt/kg body weight

Liver wt: 22 g/kg relative liver weight for human, 86 g/kg relative liver weight for mouse, 40 g/kg relative liver weight for rat, 32 g/kg relative liver weight for dog

Figure 19

N,N-Dimethylamine (14B) Undergoes N-Demethylation in Human Liver Microsomes

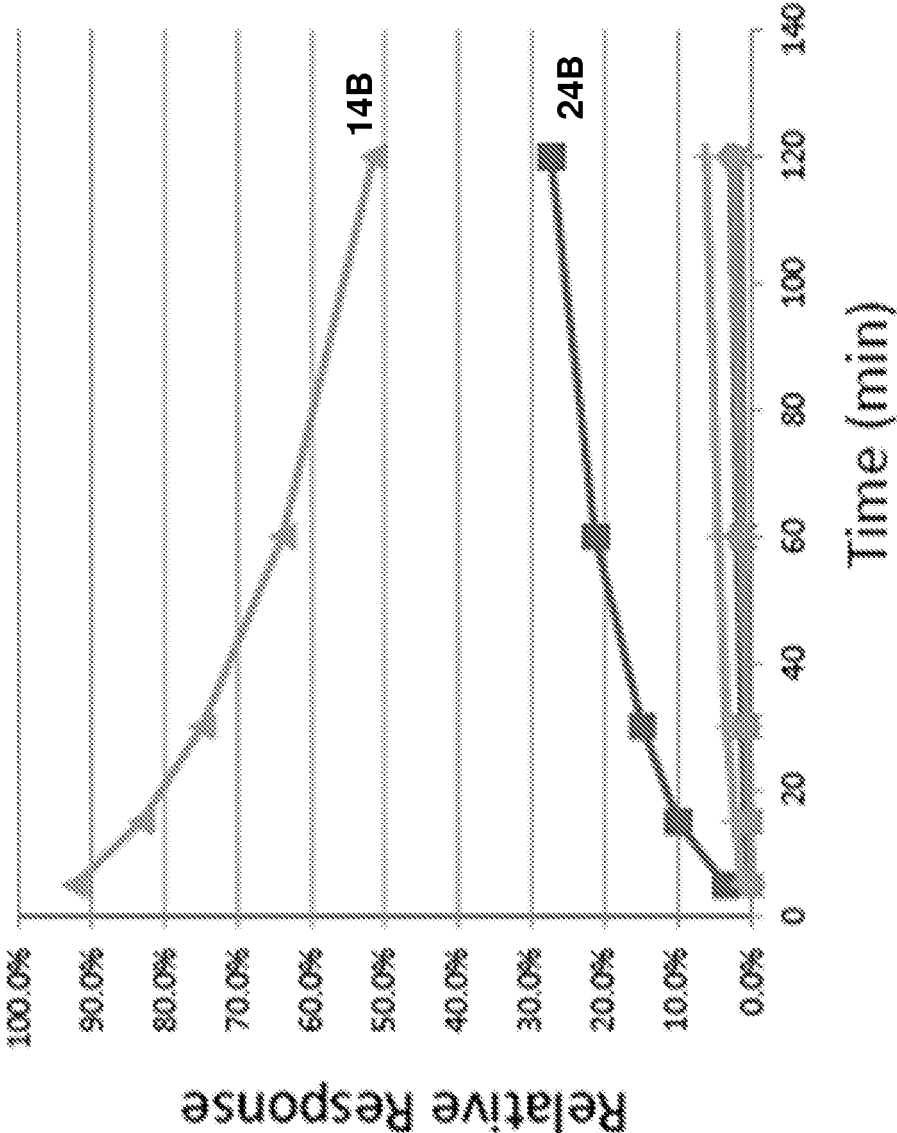


Figure 20

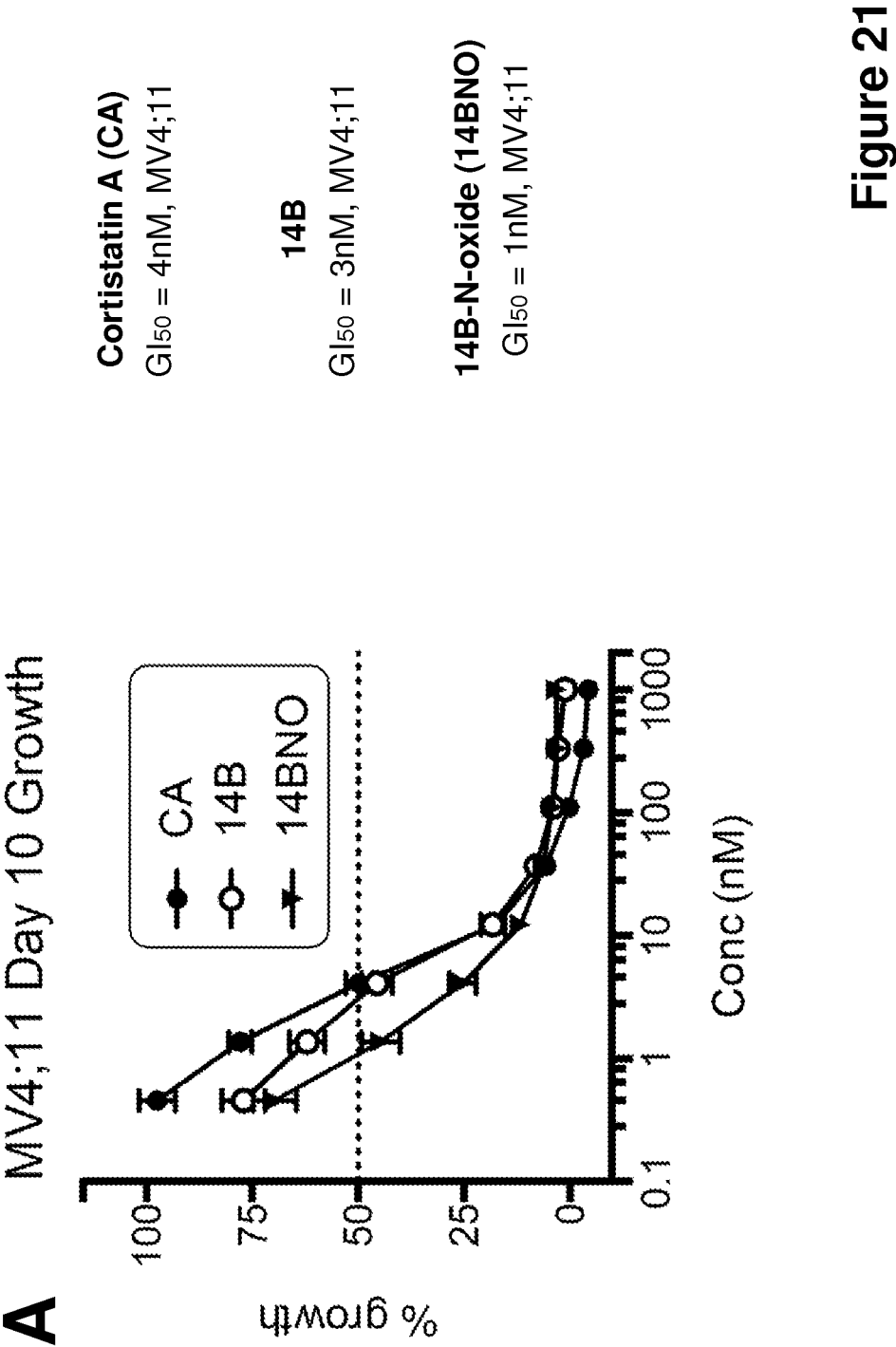


Figure 21

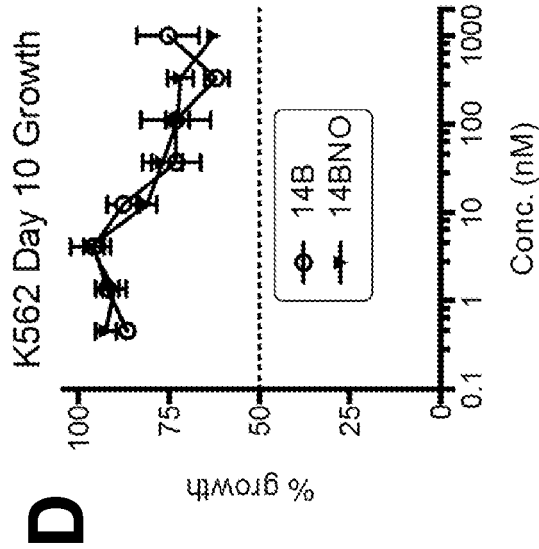
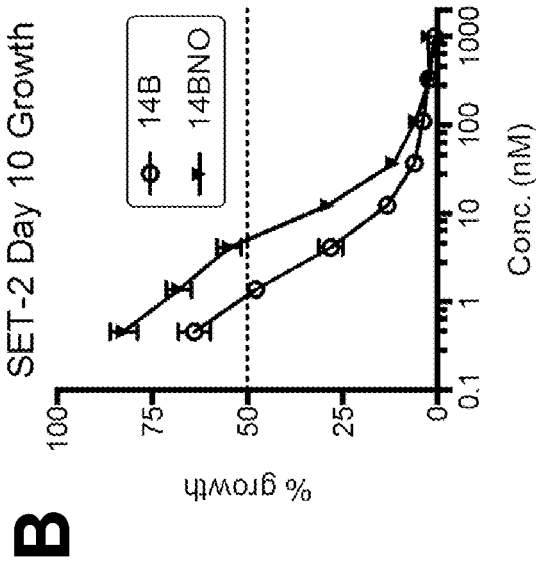
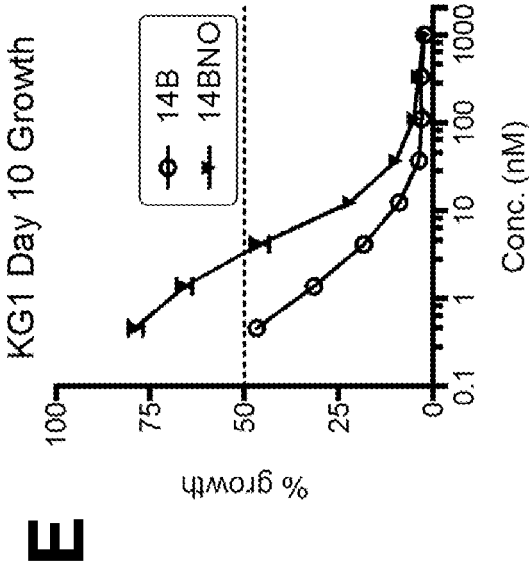
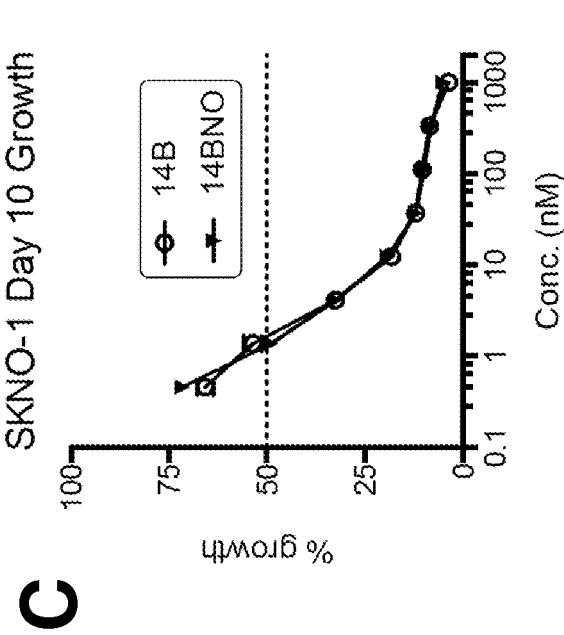


Figure 21 (cont'd)

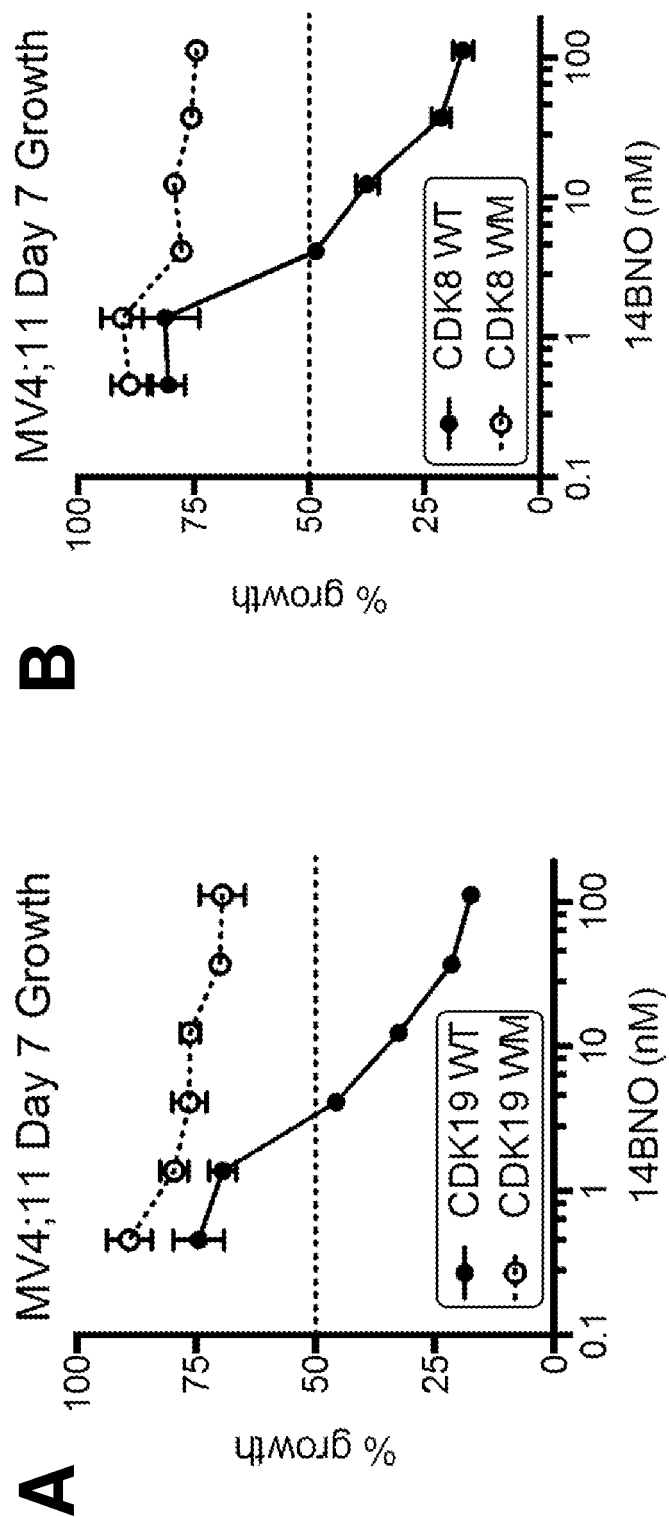


Figure 22

Test Article	Species	CL _{int} (μL/min/ 10 ⁶ cells) ^a	T _{1/2} (min) ^b	% remaining parent at last time point
verapamil	Human	7.3	95.3	41.8%
warfarin	Human	0.46	> 240	94.6%
14BNO	Human	0.50	> 240	88.8%
14BNO	Human (Heat-Inactivated)	N/A	N/A	100%

^aHepatocyte Intrinsic Clearance

^bHalf-life

Figure 23

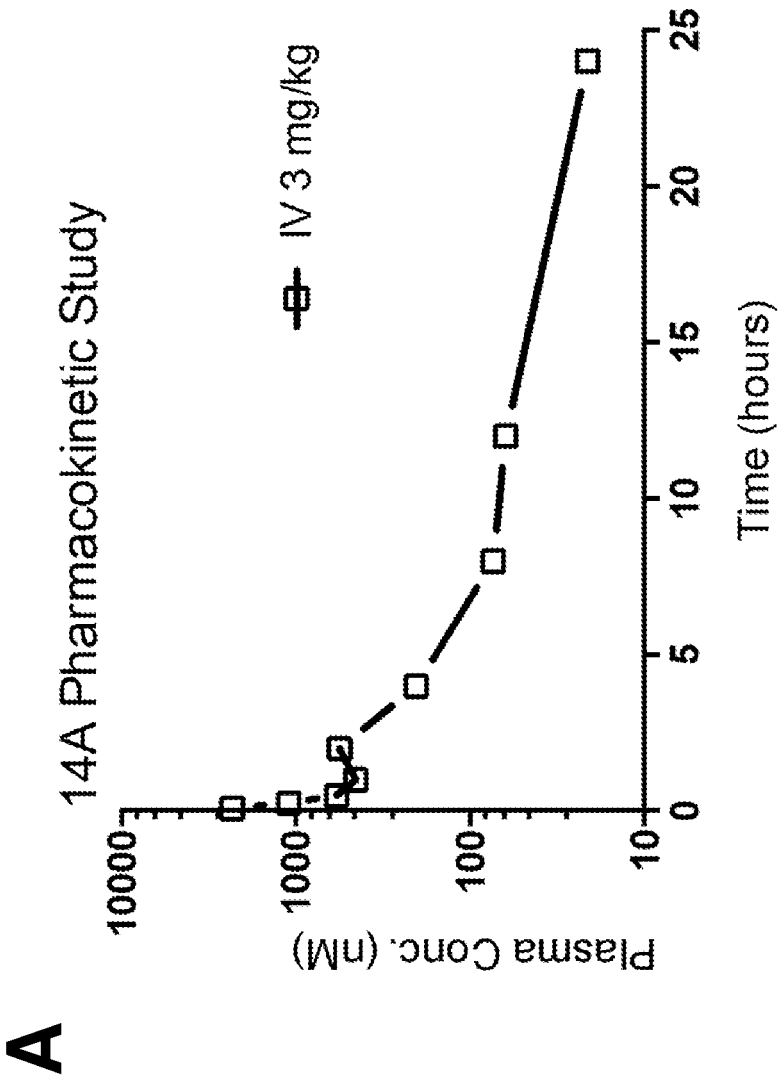


Figure 24

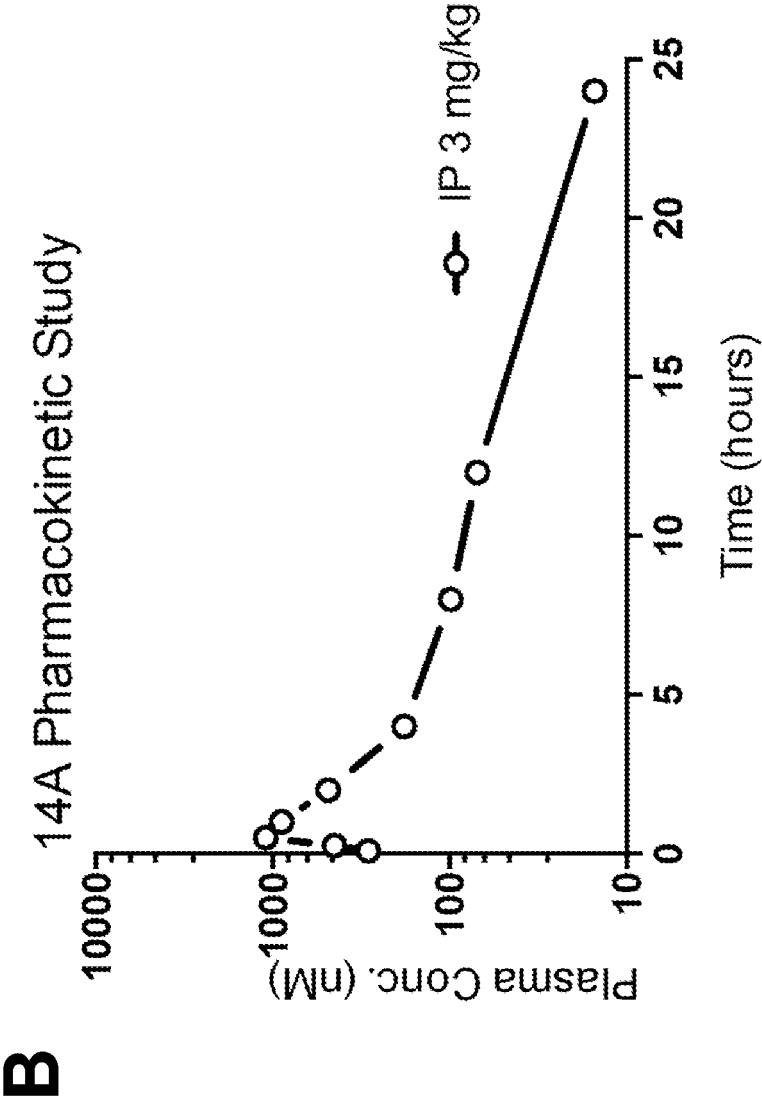


Figure 24 (cont'd)

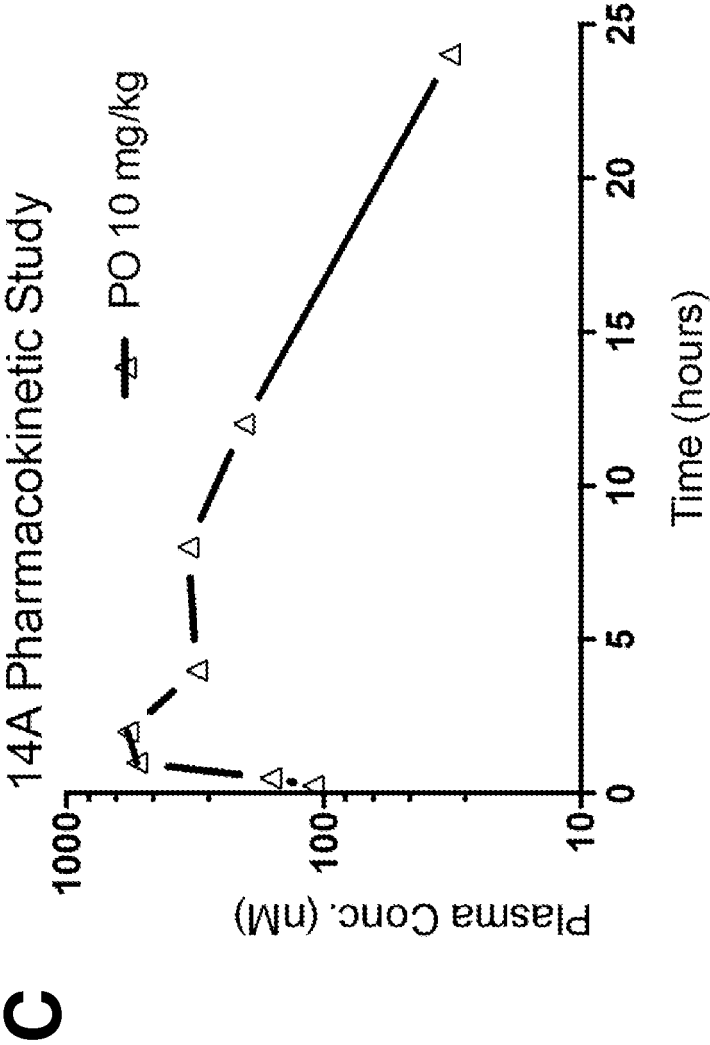


Figure 24 (cont'd)