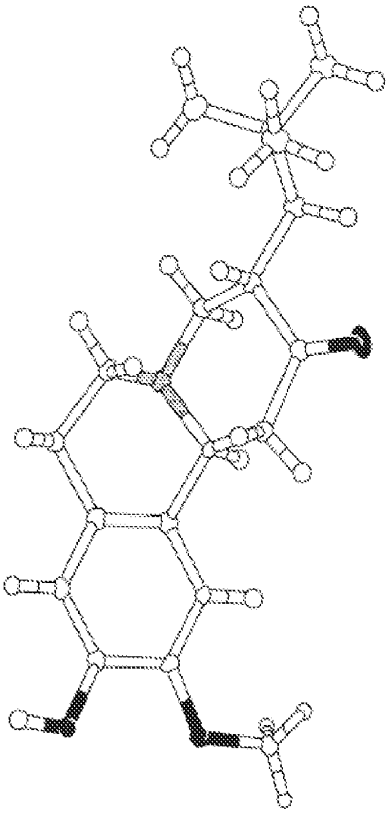
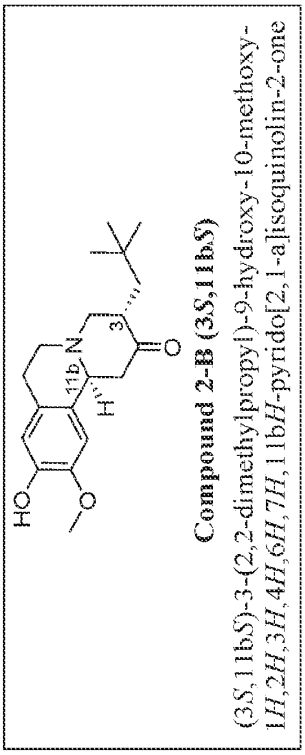
Representation of the crystal structure of Compound 2-B (3S,11bS)



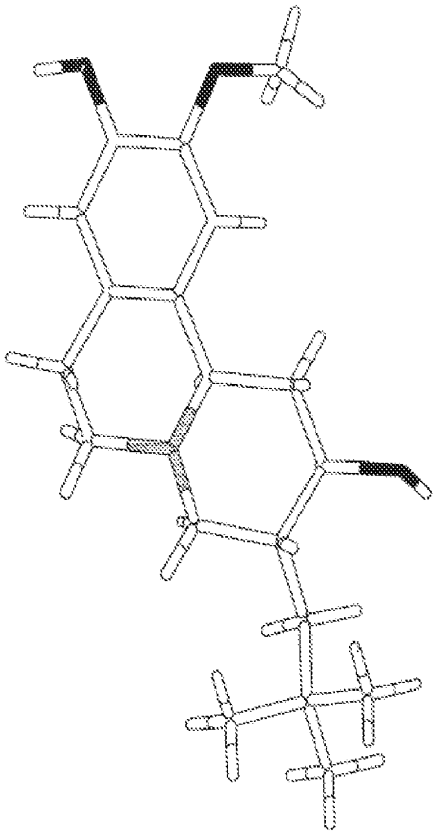


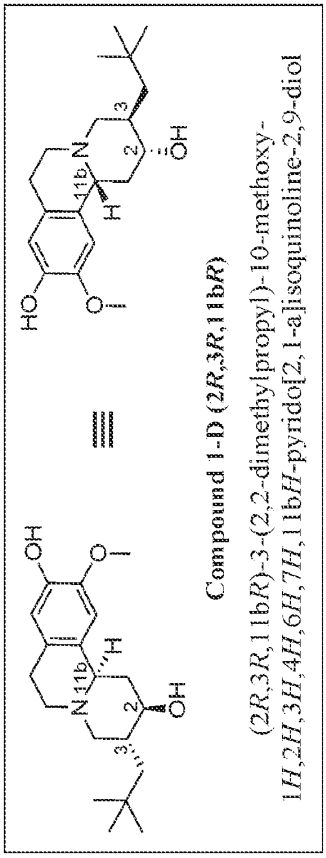
Compound 2-B (3*S*,11b*S*)

(3*S*,11b*S*)-3-(2,2-dimethylpropyl)-9-hydroxy-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinolin-2-one

FIG. 1A

Representation of the crystal structure of Compound 1-D (2*R*,3*R*,11b*R*)





Compound 1-D (2*R*,3*R*,11b*R*)

(2*R*,3*R*,11b*R*)-3-(2,2-dimethylpropyl)-10-methoxy-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,11b*H*-pyrido[2,1-a]isoquinoline-2,9-diol

FIG. 1B

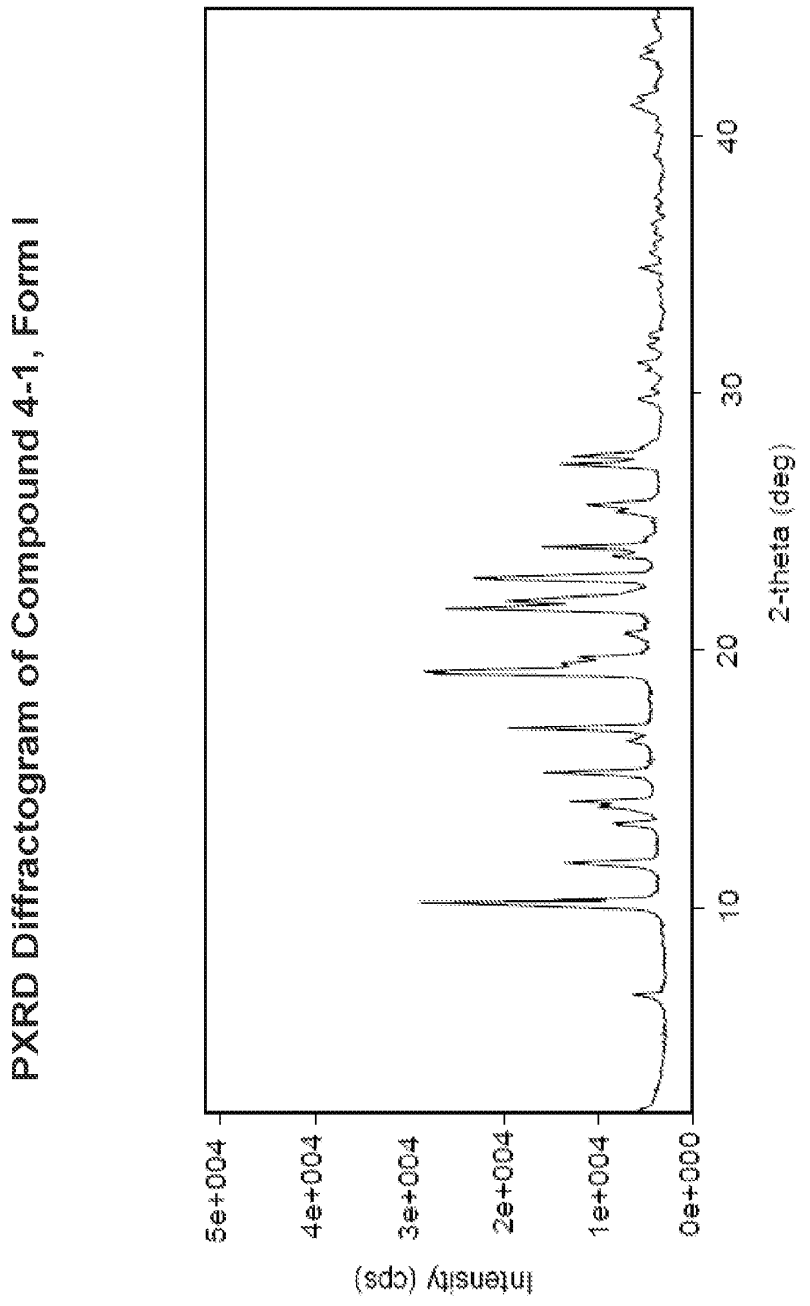

PXRD Diffractogram of Compound 4-1, Form I
Intensity (cps)
5e+004
4e+004
3e+004
2e+004
1e+004
0e+000
10
20
30
40
2-theta (deg)

FIG. 2

DSC and TGA Thermogram of Compound 4-1, Form I

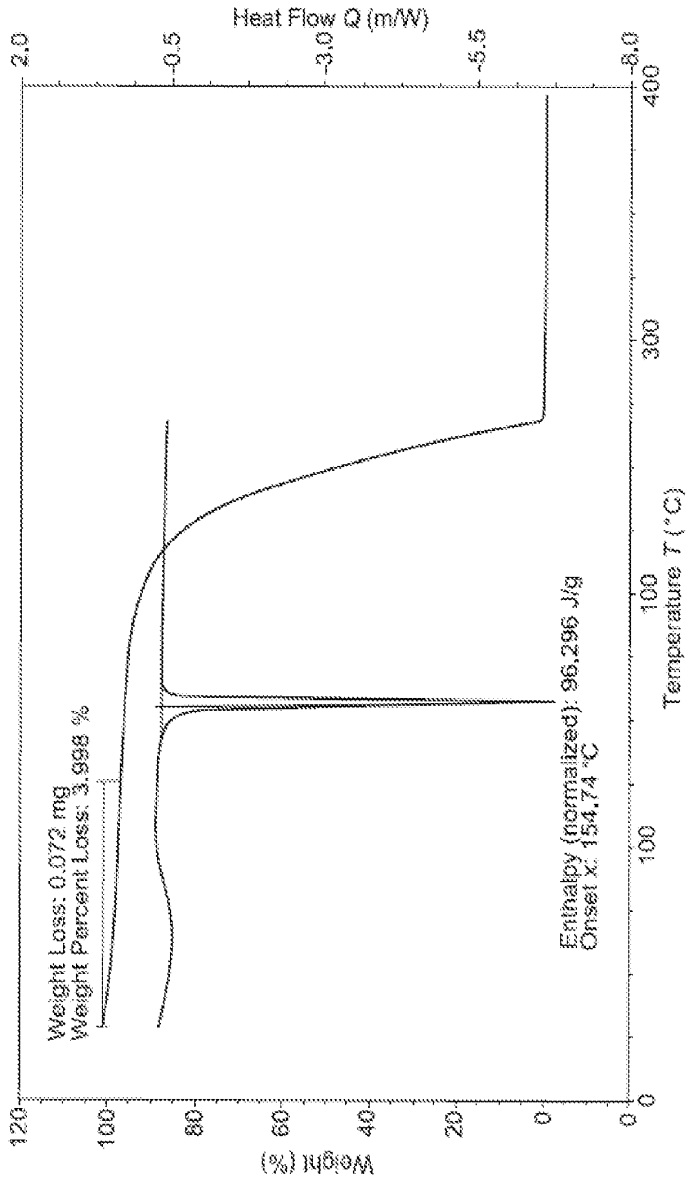


FIG. 3

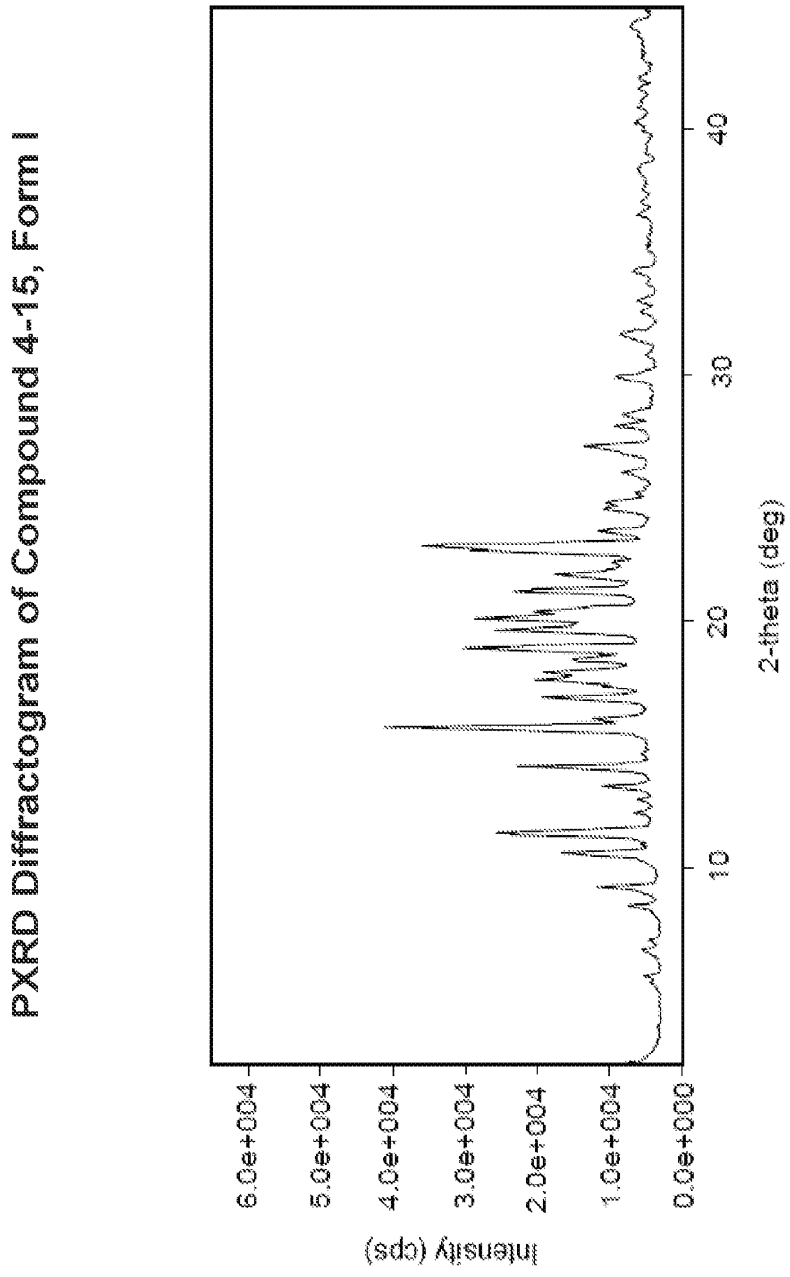

PXRD Diffractogram of Compound 4-15, Form I
Intensity (cps)
6.0e+004
5.0e+004
4.0e+004
3.0e+004
2.0e+004
1.0e+004
0.0e+000
10
20
30
40
2-theta (deg)

FIG. 4

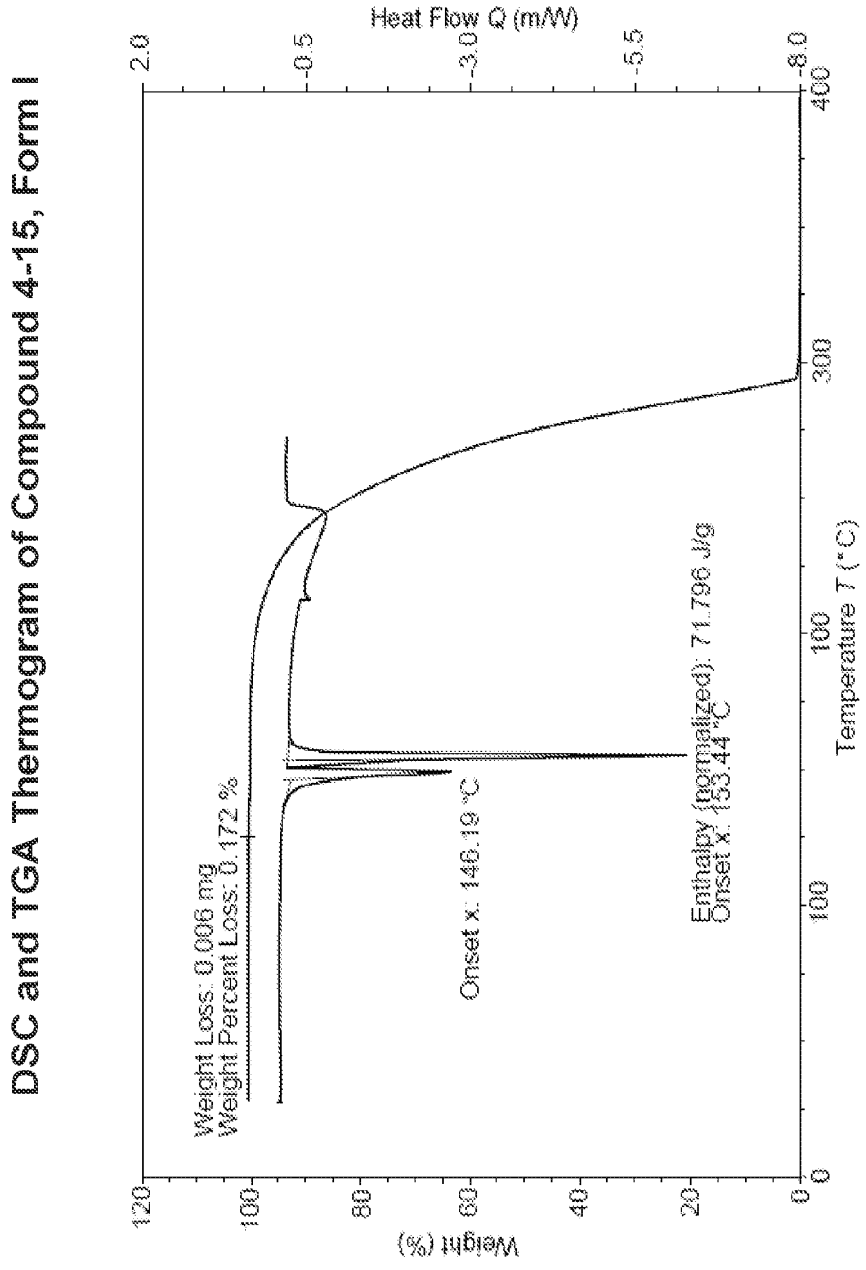

DSC and TGA Thermogram of Compound 4-15, Form I
Heat Flow Q (mW)
2.0
-0.5
-3.0
-5.5
-8.0
Weight (%)
120
100
80
60
40
20
0
Temperature T (°C)
0
100
200
300
400
Weight Loss: 0.006 mg
Weight Percent Loss: 0.172 %
Onset x: 146.19 °C
Enthalpy (normalized): 71.796 J/g
Onset x: 153.44 °C

FIG. 5

General synthetic scheme for preparing Compounds of Formula (I)

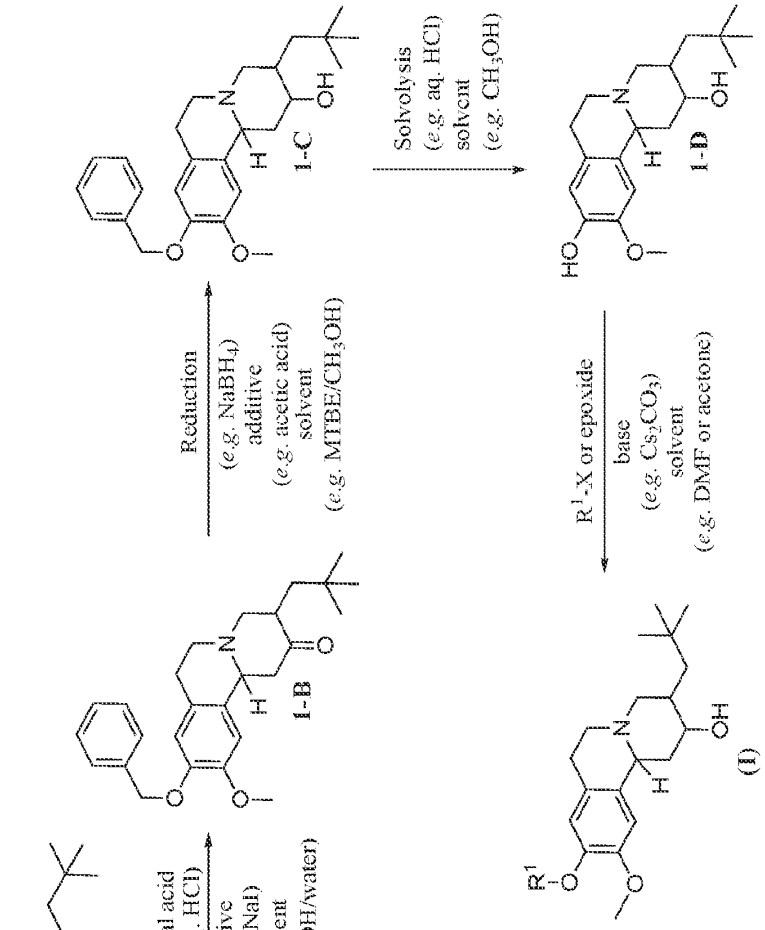


FIG. 6

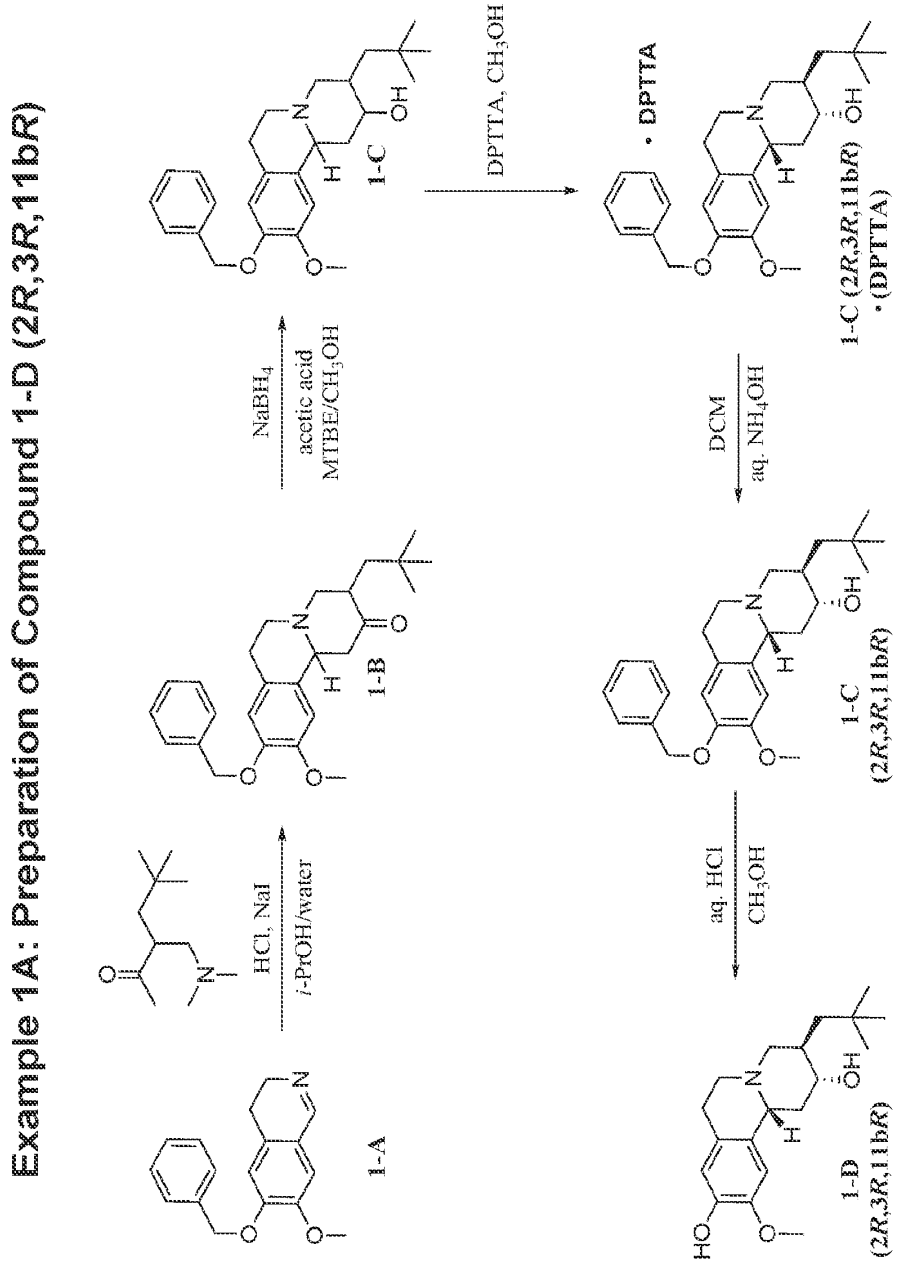

Example 1A: Preparation of Compound 1-D (2R,3R,11bR)
1-A
HCl, NaI
i-PrOH/water
1-B
NaBH4
acetic acid
MTBE/CH3OH
1-C
DPTTA, CH3OH
• DPTTA
1-C (2R,3R,11bR) • (DPTTA)
DCM
aq. NH4OH
1-C (2R,3R,11bR)
aq. HCl
CH3OH
1-D (2R,3R,11bR)

FIG. 7

Example 1B: Preparation of Compound 1-C (2*R*,3*R*,11b*R*)•DPTTA Salt

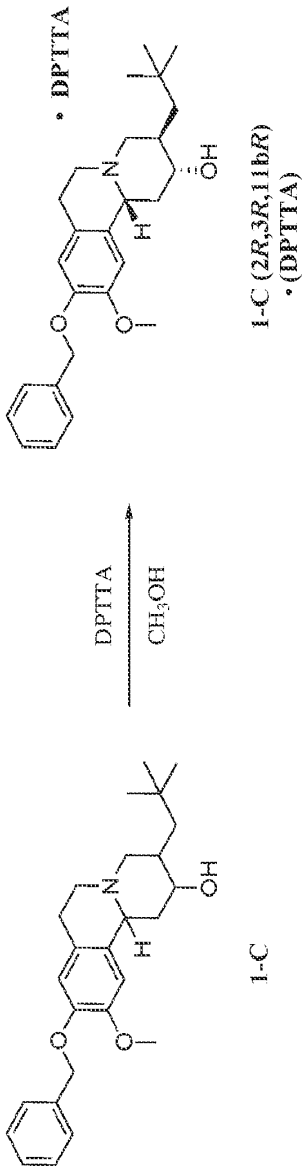


FIG. 8

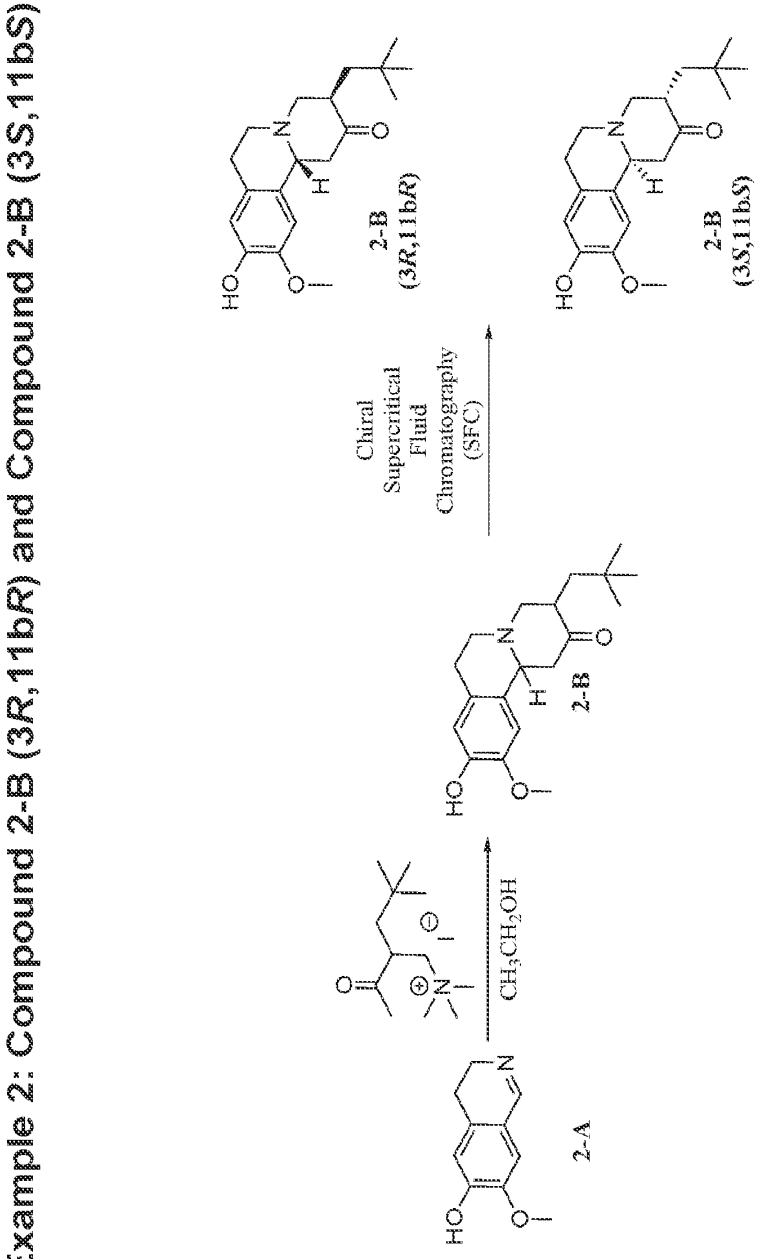

Example 2: Compound 2-B (3R,11bR) and Compound 2-B (3S,11bS)
2-A
CH3CH2OH
2-B
Chiral Supercritical Fluid Chromatography (SFC)
2-B (3R,11bR)
2-B (3S,11bS)

FIG. 9

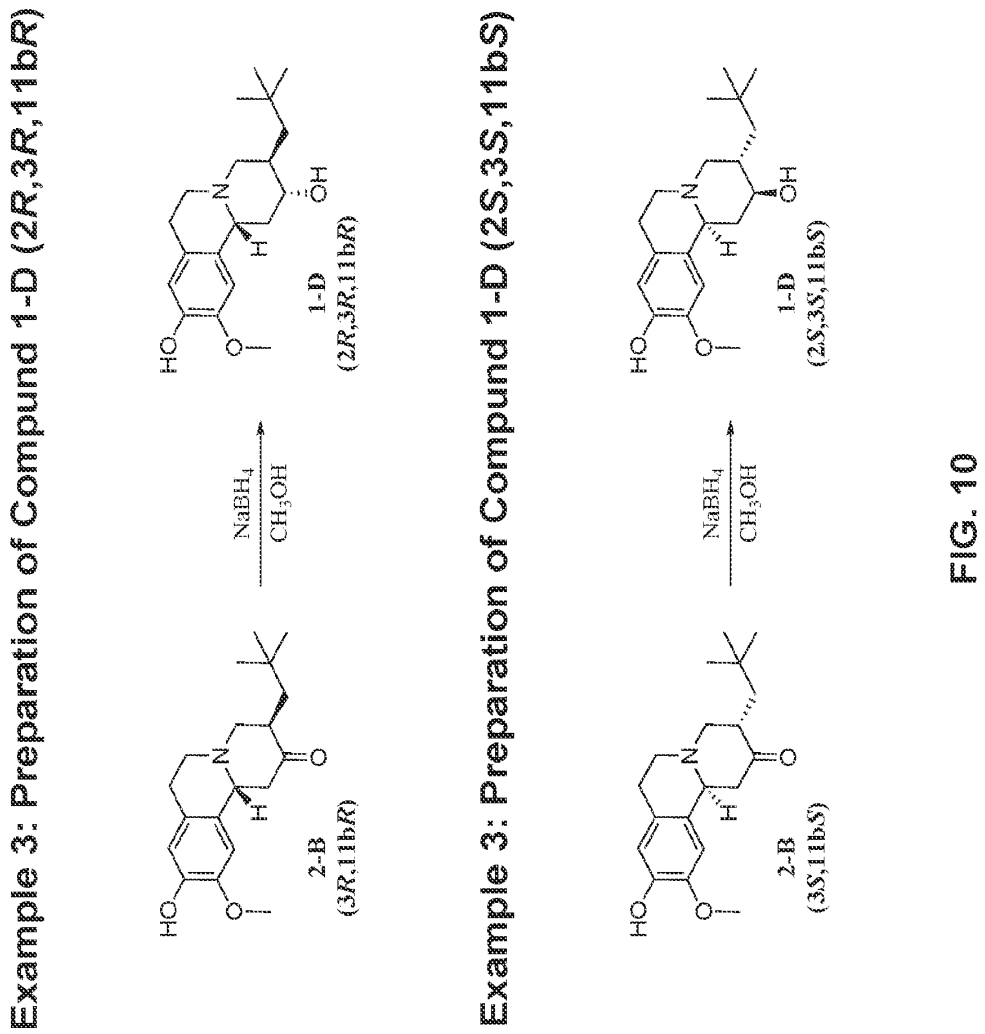

Example 3: Preparation of Compund 1-D (2R,3R,11bR)
2-B
(3R,11bR)
NaBH4
CH3OH
1-D
(2R,3R,11bR)
Example 3: Preparation of Compund 1-D (2S,3S,11bS)
2-B
(3S,11bS)
NaBH4
CH3OH
1-D
(2S,3S,11bS)

FIG. 10

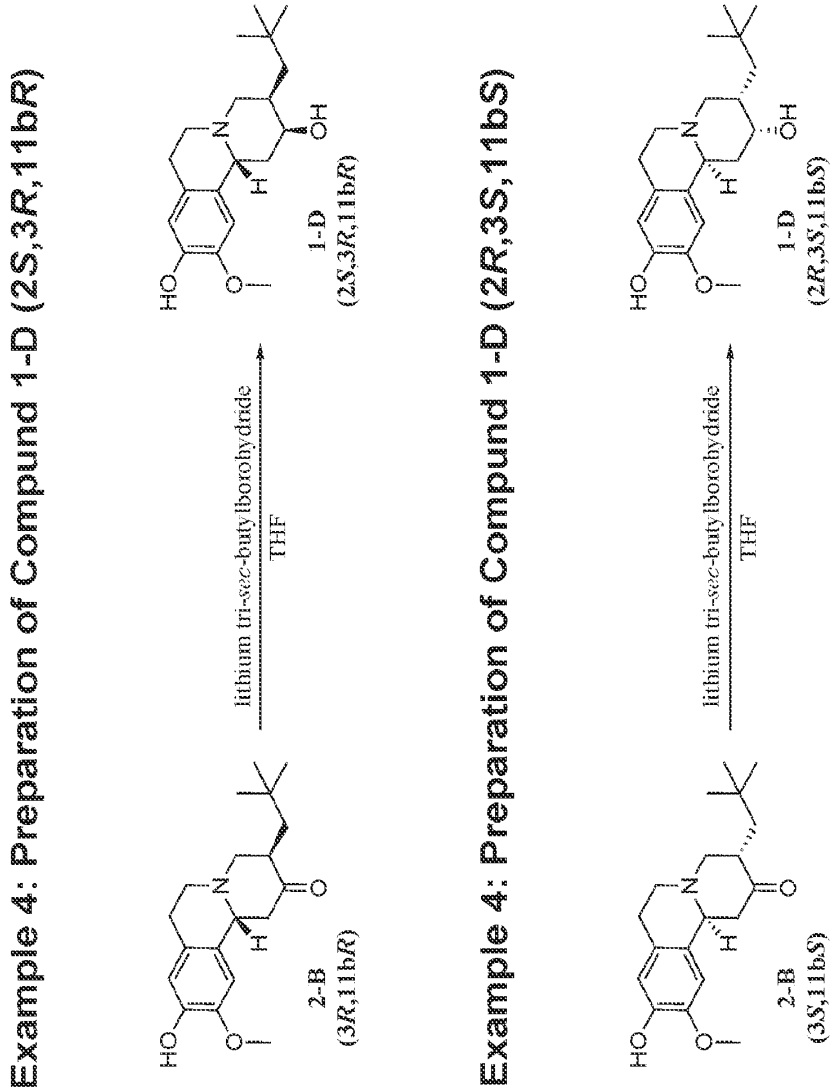

Example 4: Preparation of Compund 1-D (2S,3R,11bR)
2-B
(3R,11bR)
lithium tri-sec-butylborohydride
THF
1-D
(2S,3R,11bR)
Example 4: Preparation of Compund 1-D (2R,3S,11bS)
2-B
(3S,11bS)
lithium tri-sec-butylborohydride
THF
1-D
(2R,3S,11bS)

FIG. 11

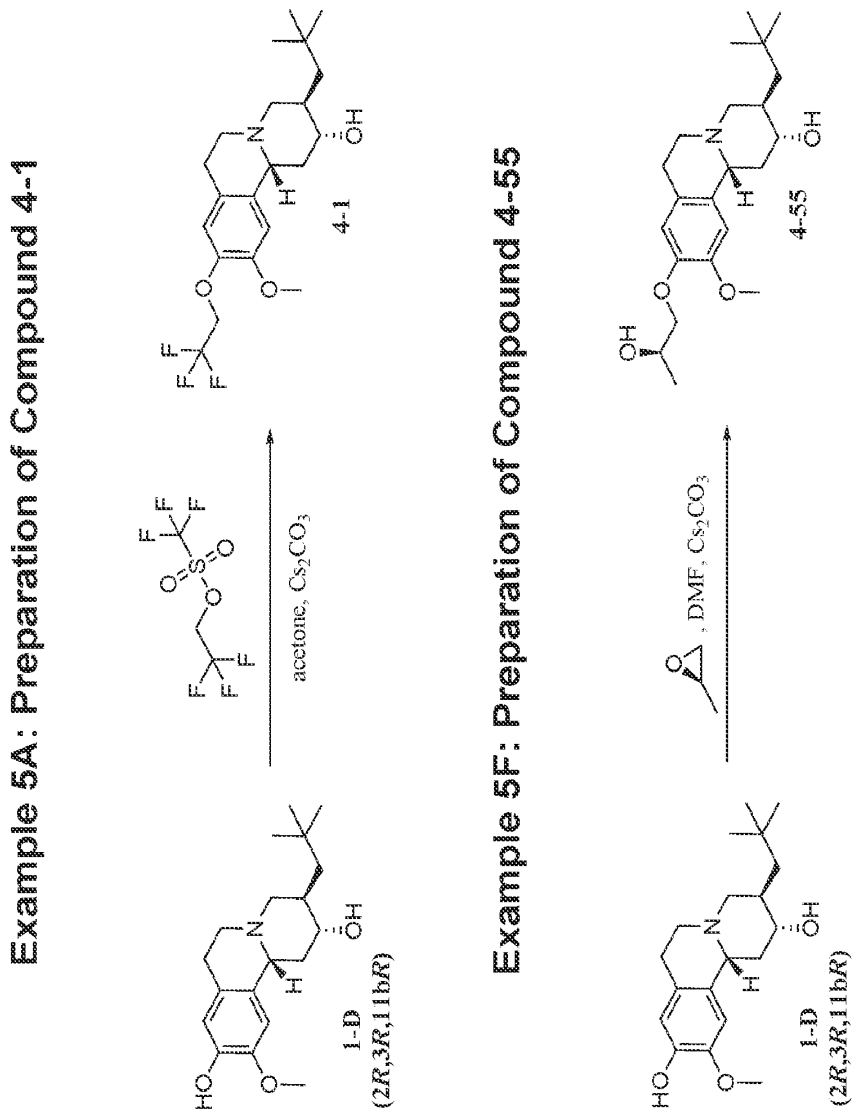

Example 5A: Preparation of Compound 4-1
1-D
(2R,3R,11bR)
acetone, Cs2CO3
4-1
Example 5F: Preparation of Compound 4-55
1-D
(2R,3R,11bR)
, DMF, Cs2CO3
4-55

FIG. 12

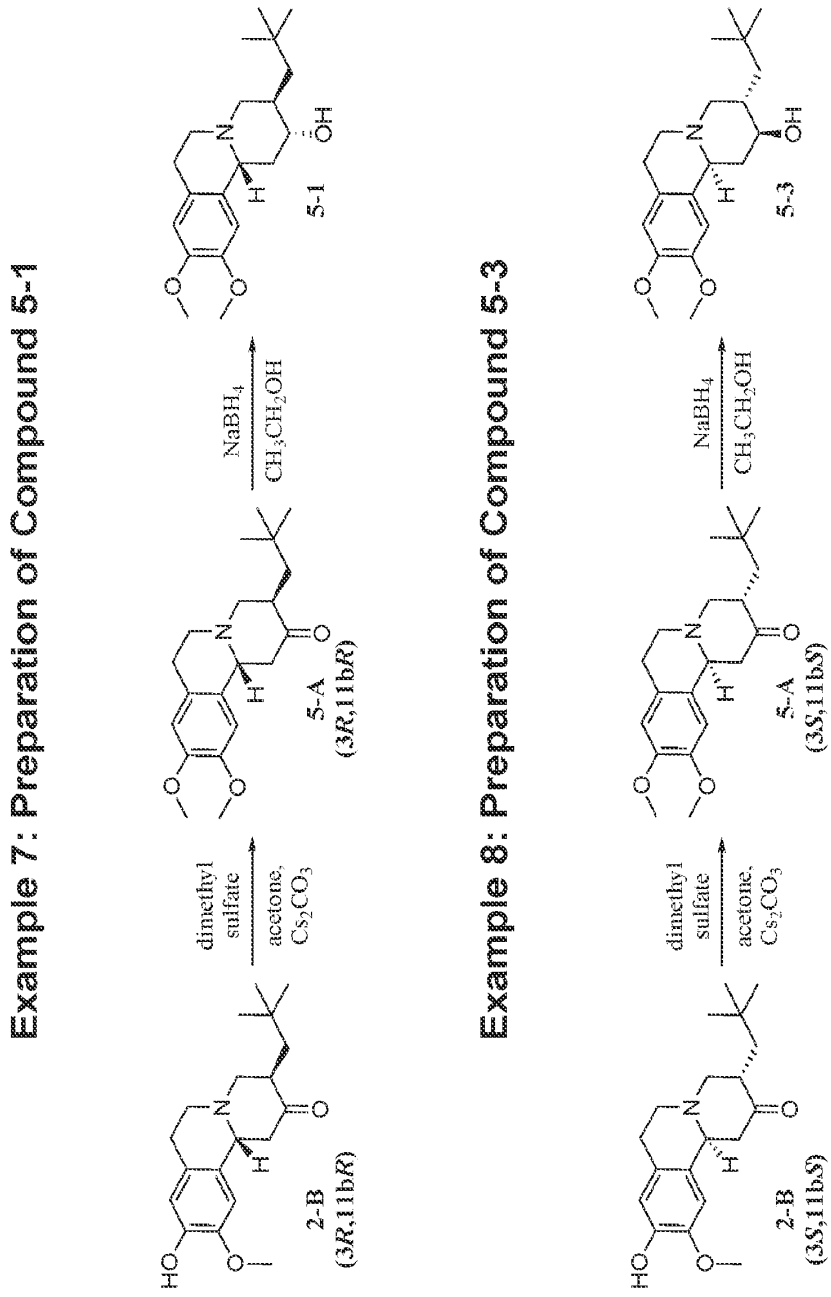

Example 7: Preparation of Compound 5-1
2-B
(3R,11bR)
dimethyl sulfate
acetone, Cs2CO3
5-A
(3R,11bR)
NaBH4
CH3CH2OH
5-1
Example 8: Preparation of Compound 5-3
2-B
(3S,11bS)
dimethyl sulfate
acetone, Cs2CO3
5-A
(3S,11bS)
NaBH4
CH3CH2OH
5-3

FIG. 13

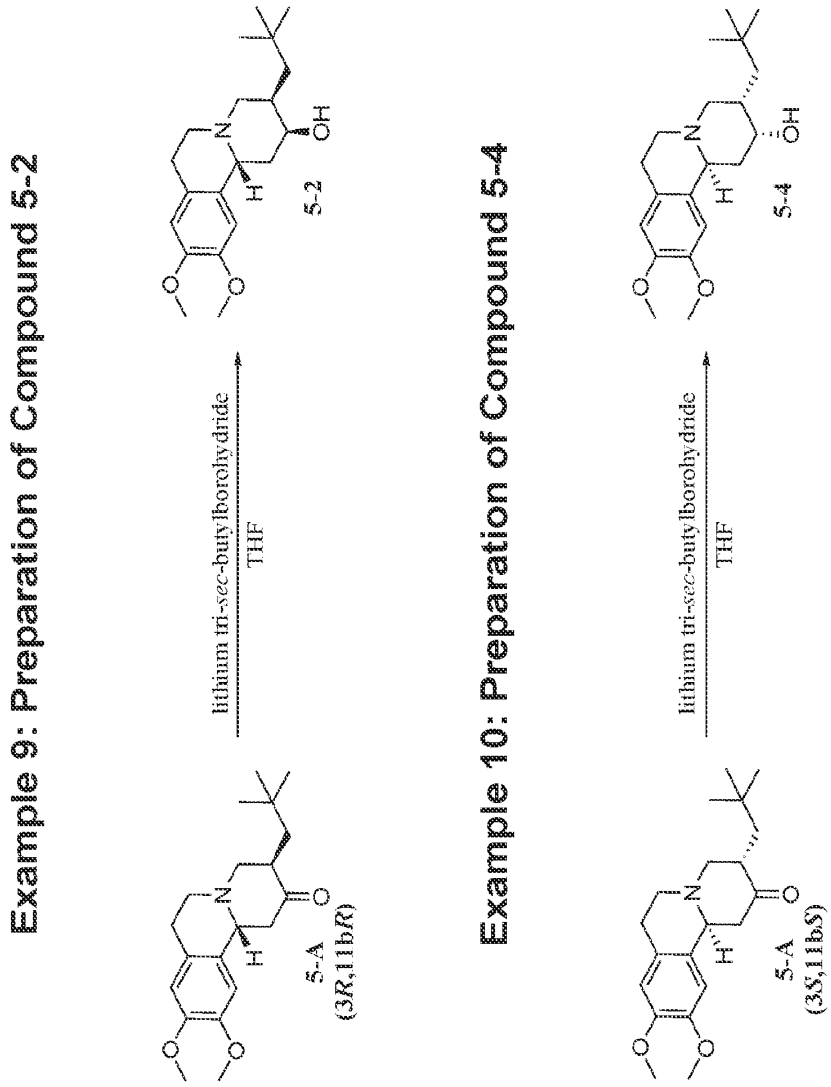

Example 9: Preparation of Compound 5-2
5-A
(3R,11bR)
lithium tri-sec-butylborohydride
THF
5-2
Example 10: Preparation of Compound 5-4
5-A
(3S,11bS)
lithium tri-sec-butylborohydride
THF
5-4

FIG. 14

VMAT2 Ki values (nM) comparison

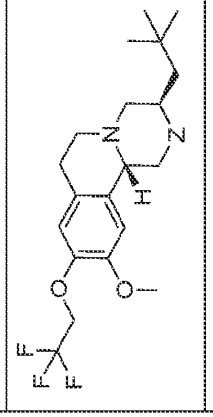
Cmpd of Formula (I) vs Comparator Cmpd	Cmpd No.	Z group	VMAT Ki (nM)	Potency Improvement
	4-1		2.4	6.7x
	4-1C		16	
	4-13		2.2	12.3x
	4-13C		27	
	4-14		2.6	5.8x
	4-14C		15	

FIG. 15

VMAT2 Ki values (nM) comparison

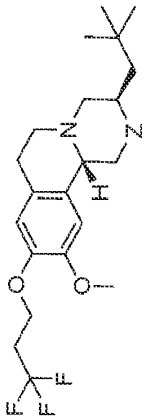
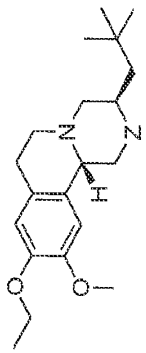
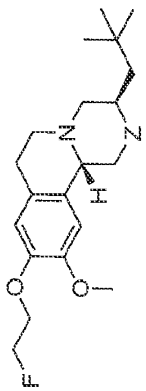
Cmpd of Formula (I) vs Comparator Cmpd	Cmpd No.	Z group	VMAT Ki (nM)	Potency Improvement
	4-15		1.1	10.0x
	4-15C		11	
	4-17		1.1	8.1x
	4-17C		8.9	
	4-18		5.5	5.3x
	4-18C		29	

FIG. 16

VMAT2 Ki values (nM) comparison

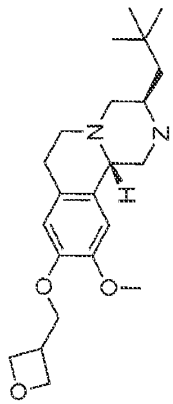
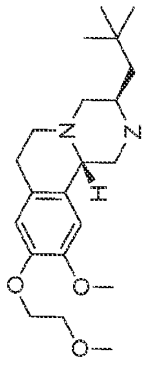
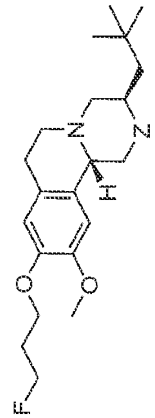
Cmpd of Formula (I) vs Comparator Cmpd	Cmpd No.	Z group	VMAT Ki (nM)	Potency Improvement
	4-22		14	6.6x
	4-22C		93	
	4-26		14	12.1x
	4-26C		169	
	4-28		0.48	7.1x
	4-28C		3.4	

FIG. 17

VMAT2 Ki values (nM) comparison

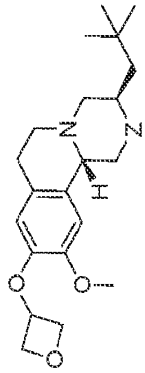
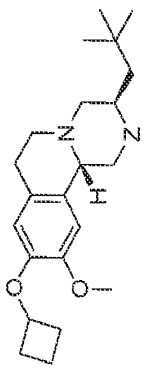
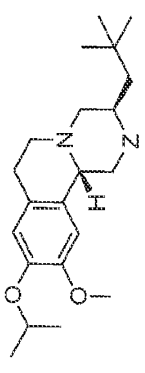
Cmpd of Formula (I) vs Comparator Cmpd	Cmpd No.	Z group	VMAT Ki (nM)	Potency Improvement
	4-30		12	20.9x
	4-30C		251	
	4-32		0.59	5.8x
	4-32C		3.4	
	4-38		3.7	7.0x
	4-38C		26	

FIG. 18

VMAT2 Ki values (nM) comparison

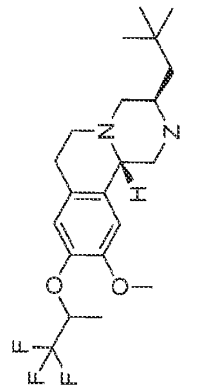
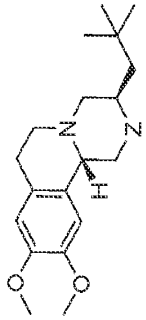
Cmpd of Formula (I) vs Comparator Cmpd	Cmpd No.	Z group	VMAT Ki (nM)	Potency Improvement
	4-39		12	15.1x
	4-39C		181	
	5-1		6.6	4.4x
	5-1C		29	

FIG. 19

VMAT2 Ki values (nM) comparison

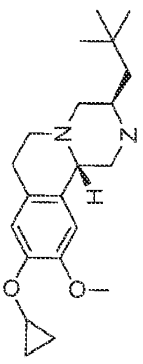
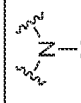
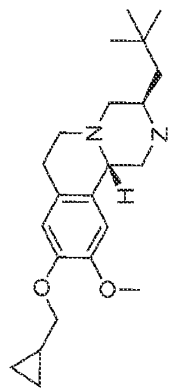
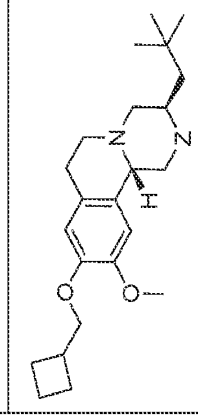
Cmpd of Formula (I) vs Comparator Cmpd	Cmpd No.	Z group	VMAT Ki (nM)	Potency Improvement
	4-27		1.0	4.4x
	4-27C		4.4	
	4-88		0.68	4.1x
	4-88C		2.8	
	4-119		0.29	9.7x
	4-119C		2.8	

FIG. 20

VMAT2 Ki values (nM) comparison

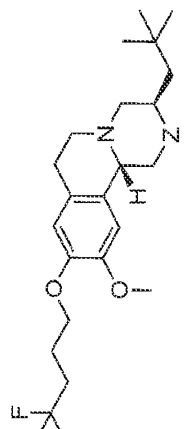
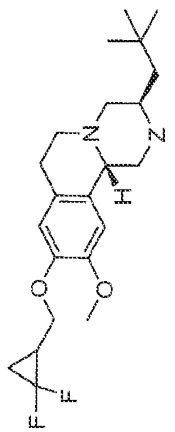
Cmpd of Formula (I) vs Comparator Cmpd	Cmpd No.	Z group	VMAT Ki (nM)	Potency Improvement
	4-120		1.5	13.3x
	4-120C		20	
	4-121		0.82	6.0x
	4-121C		4.9	

FIG. 21

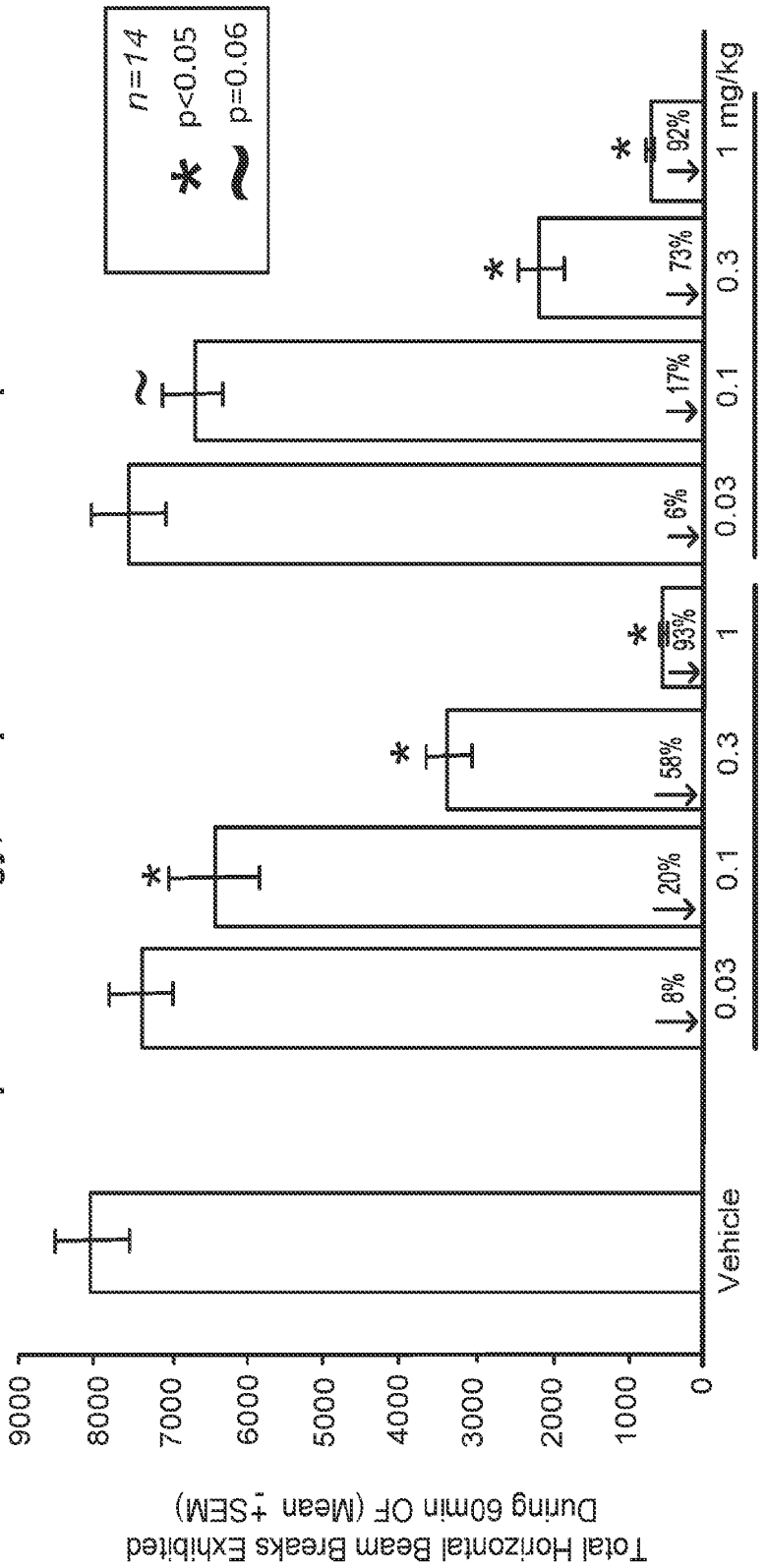

In vivo pharmacology, Compound 4-1 and Compound 4-15
Total Horizontal Beam Breaks Exhibited
During 60min OF (Mean +SEM)
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
n=14
* p<0.05
~ p=0.06
Vehicle
0.03
0.1
0.3
1
0.03
0.1
0.3
1 mg/kg
8%
20%
58%
93%
6%
17%
73%
92%
Cmpd. 4-1
ED50 = 0.24 mg/kg
Cmpd. 4-15
ED50 = 0.18 mg/kg

FIG. 22

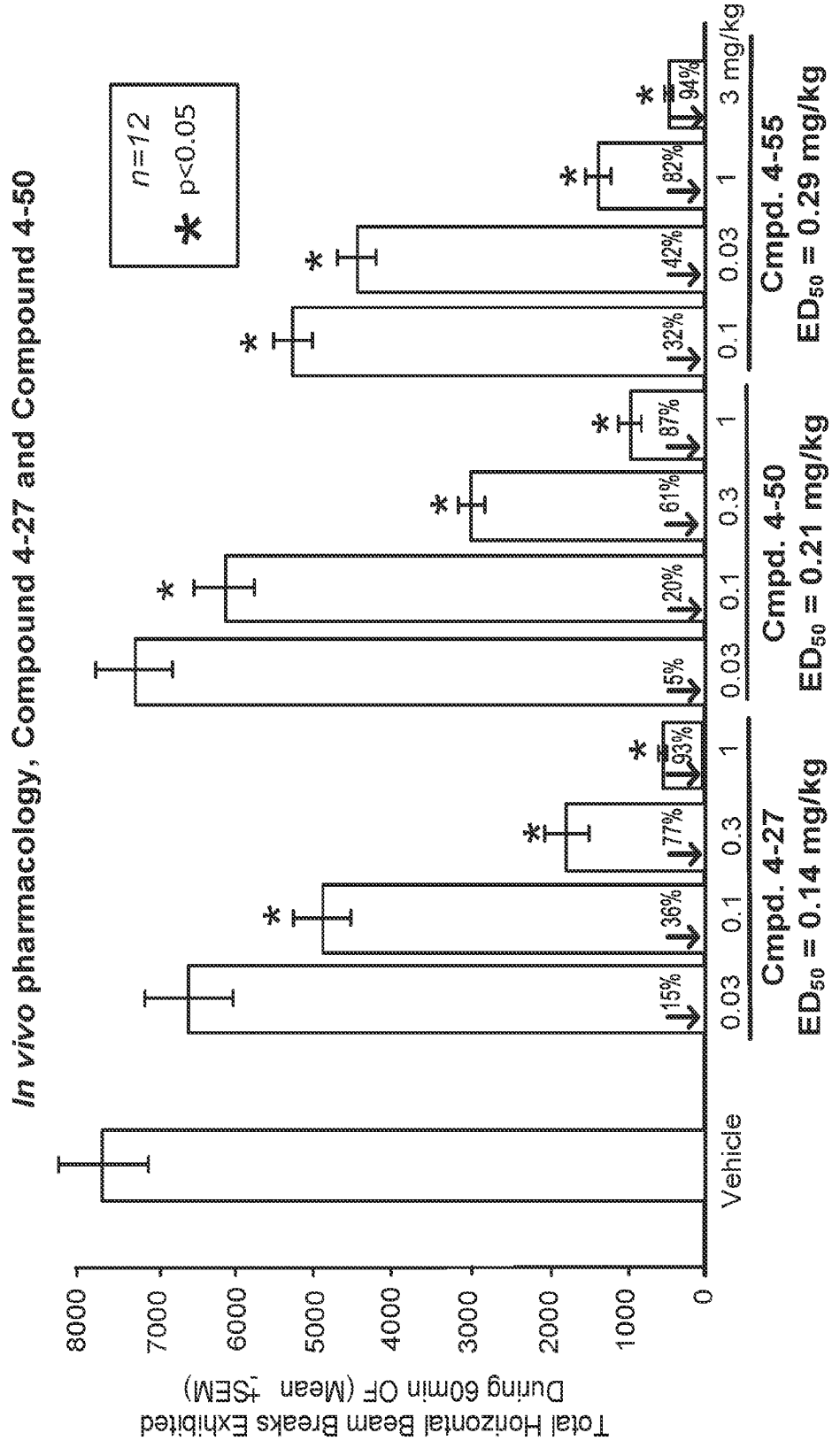

In vivo pharmacology, Compound 4-27 and Compound 4-50
n=12
* p<0.05
Total Horizontal Beam Breaks Exhibited During 60min OF (Mean ±SEM)
8000
7000
6000
5000
4000
3000
2000
1000
0
Vehicle
0.03
0.1
0.3
1
0.03
0.1
0.3
1
0.03
0.1
1
3 mg/kg
15%
36%
77%
93%
5%
20%
61%
87%
32%
42%
82%
94%
Cmpd. 4-27
ED50 = 0.14 mg/kg
Cmpd. 4-50
ED50 = 0.21 mg/kg
Cmpd. 4-55
ED50 = 0.29 mg/kg

FIG. 23

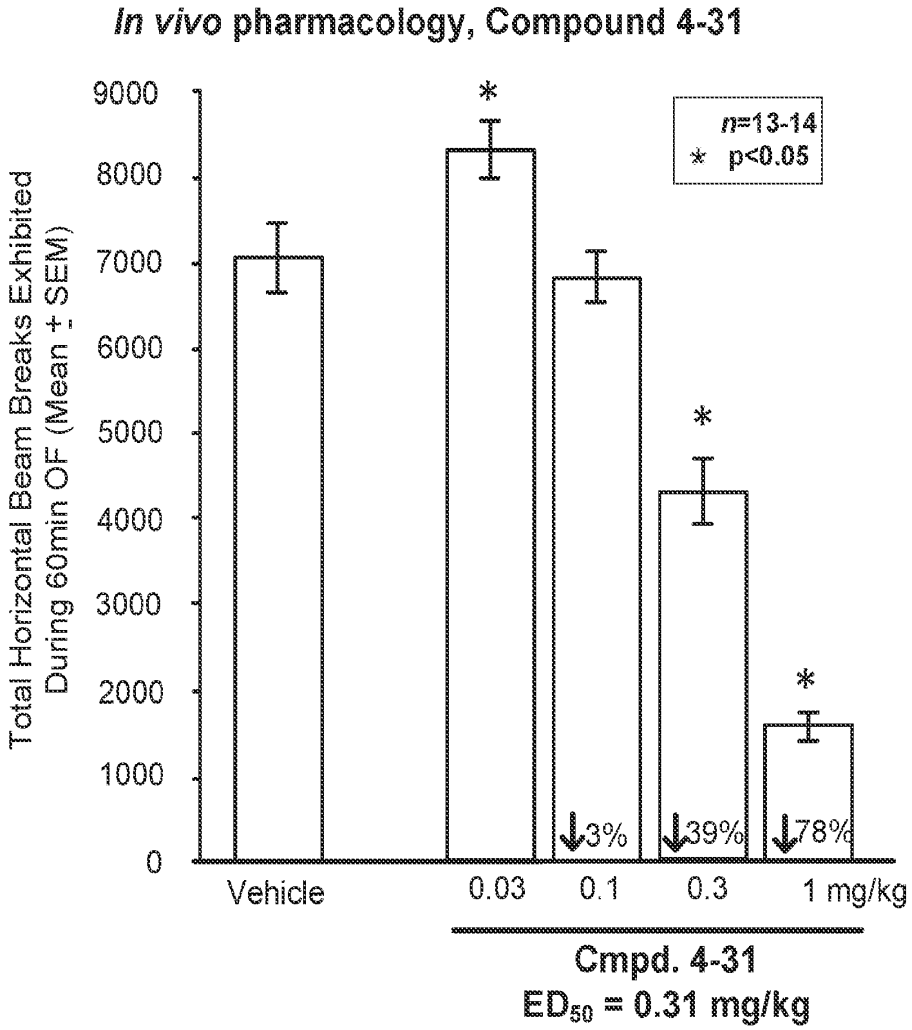

In vivo pharmacology, Compound 4-31
Total Horizontal Beam Breaks Exhibited During 60min OF (Mean ± SEM)
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
n=13-14
* p<0.05
*
*
*
↓3%
↓39%
↓78%
Vehicle
0.03
0.1
0.3
1 mg/kg
Cmpd. 4-31
ED50 = 0.31 mg/kg

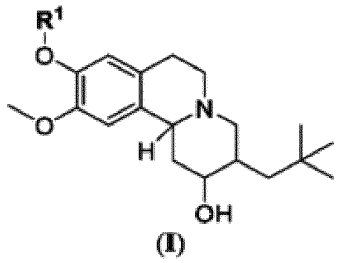
FIG. 24

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/021 080

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

This disclosure relates generally to VMAT2 inhibitor compounds of formula (I), compositions, and methods related thereto.



(I)