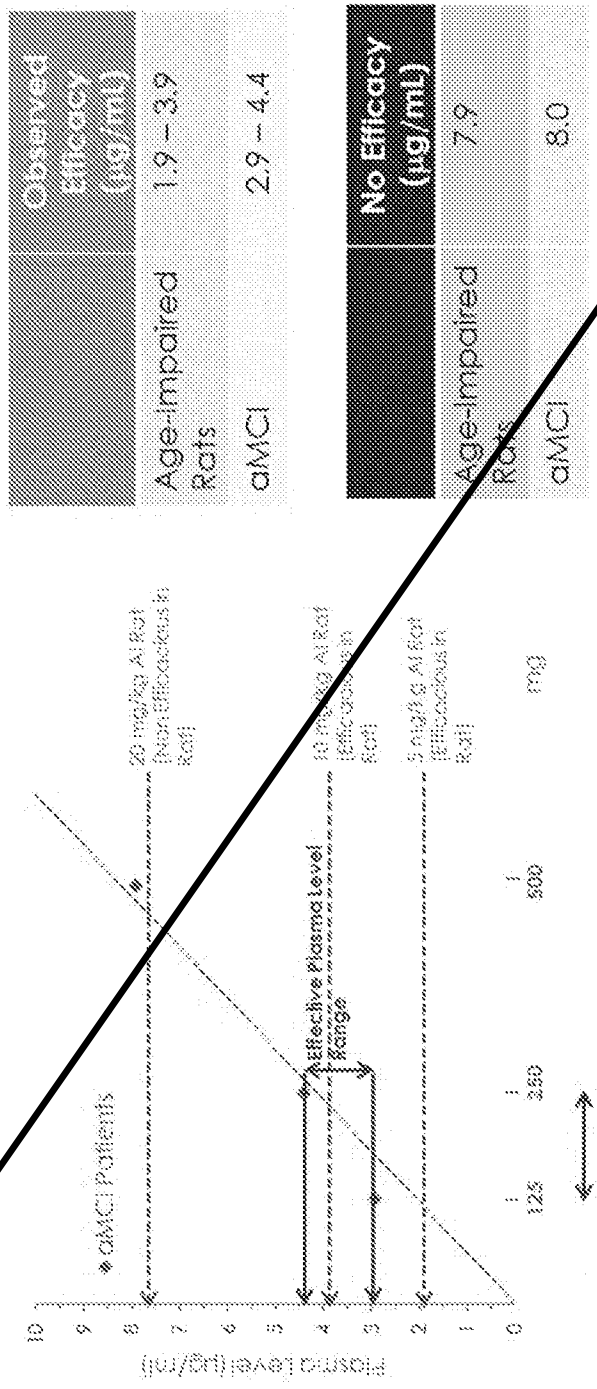

Observed Efficacy (ug/ml)
Age-impaired Rats
1.9 – 3.9
aMCI
2.9 – 4.4
No Efficacy (ug/ml)
Age-Impaired Rats
7.9
aMCI
8.0
Plasma Level (ug/ml)
10
9
8
7
6
5
4
3
2
1
0
aMCI Patients
Effective Plasma Level Range
25 mg/kg Ai Rat [Non-Efficacious in Rat]
10 mg/kg Ai Rat [Efficacious in Rat]
3 mg/kg Ai Rat [Efficacious in Rat]
1/125
1/360
1/600
mg
Efficacy Phase 2 clinical trial

FIG. 1

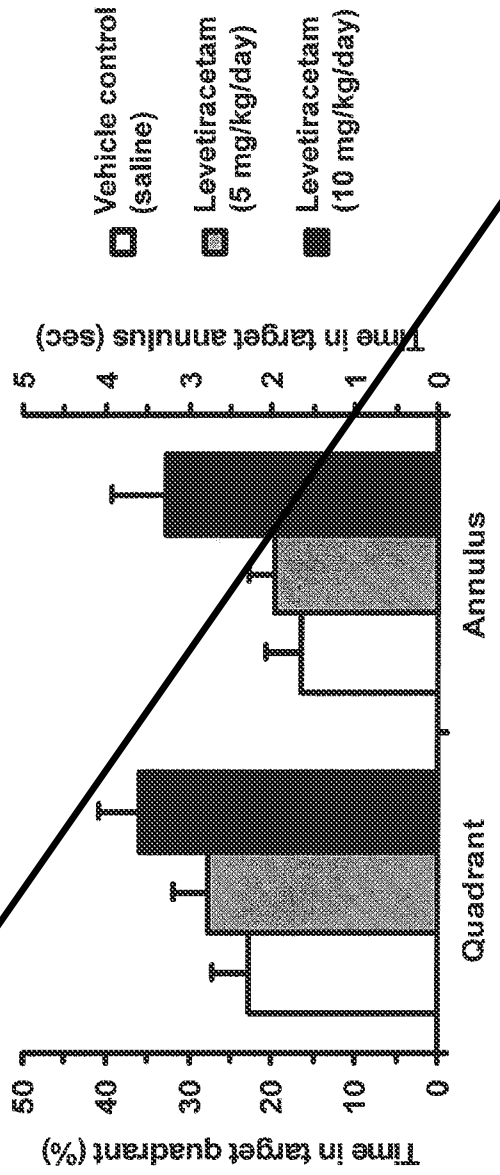
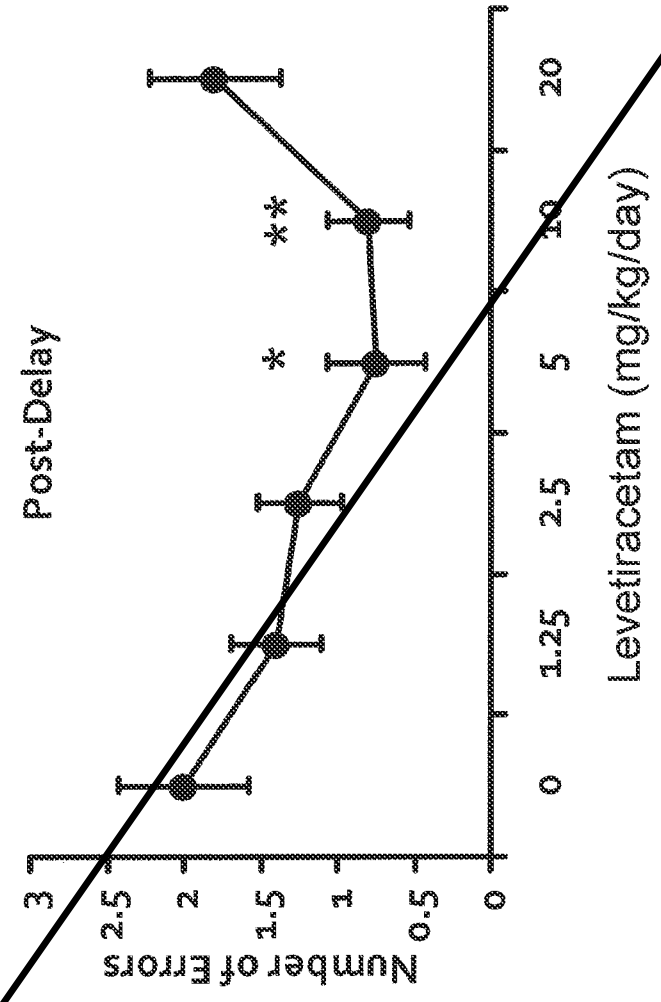

Vehicle control (saline)
Levetiracetam (5 mg/kg/day)
Levetiracetam (10 mg/kg/day)
Time in target annulus (sec)
0
1
2
3
4
5
Annulus
Quadrant
Time in target quadrant (%)
0
10
20
30
40
50

FIG. 2



* t(9) = 2.18, p = 0.057
** t(9) = 2.37, p = 0.042

FIG. 3

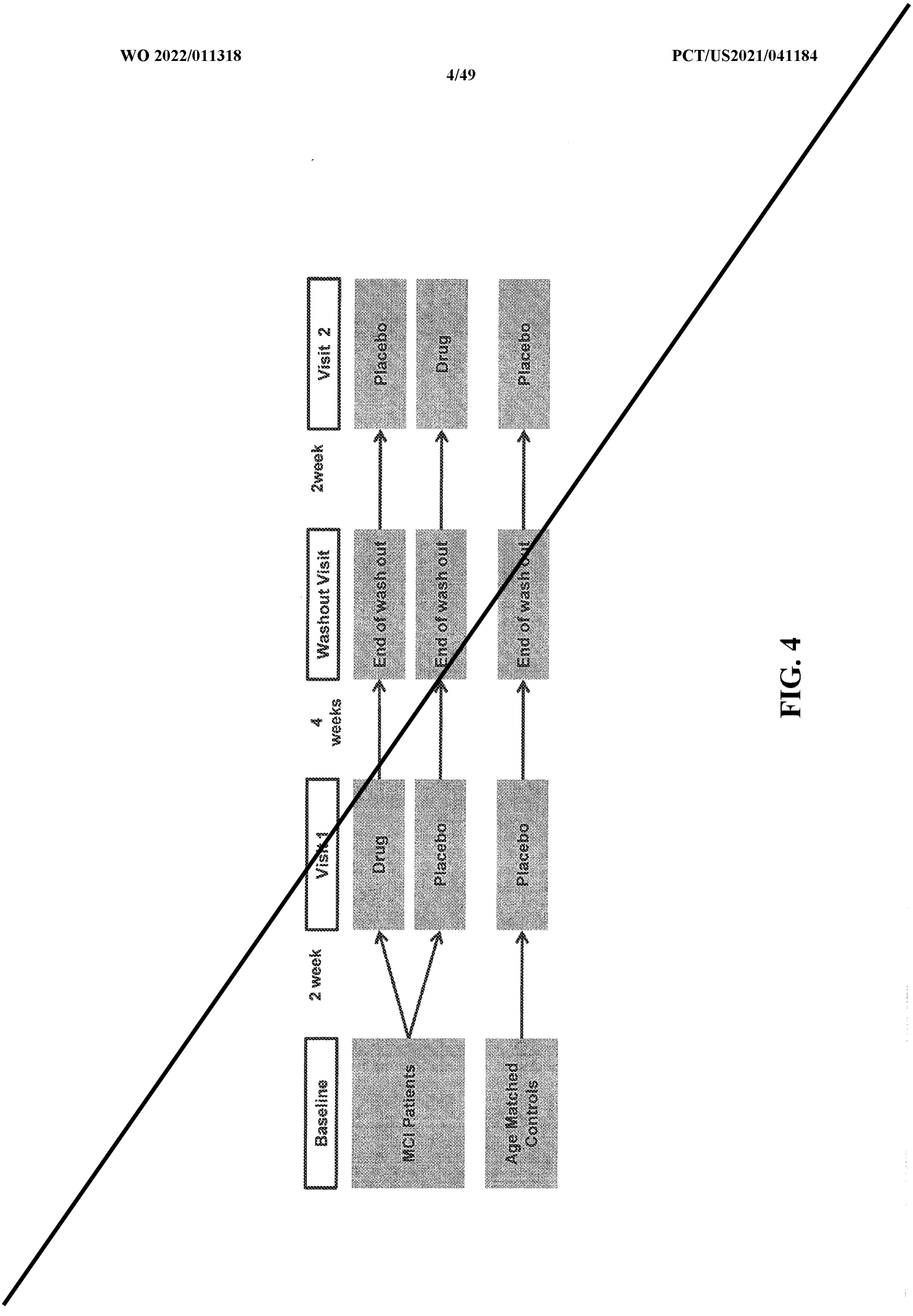

Baseline
2 week
Visit 1
4 weeks
Washout Visit
2week
Visit 2
MCI Patients
Age Matched Controls
Drug
Placebo
Placebo
End of wash out
End of wash out
End of wash out
Placebo
Drug
Placebo

FIG. 4

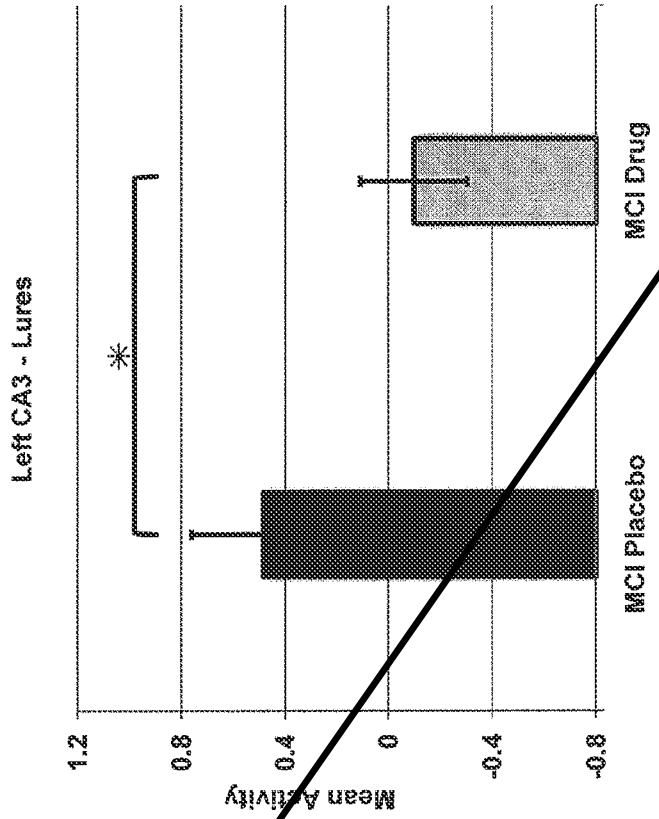

Left CA3 - Lures
Mean Activity
1.2
0.8
0.4
0
-0.4
-0.8
MCI Placebo
MCI Drug
*Paired samples t-test: t = 2.276, p = 0.037

FIG. 5B

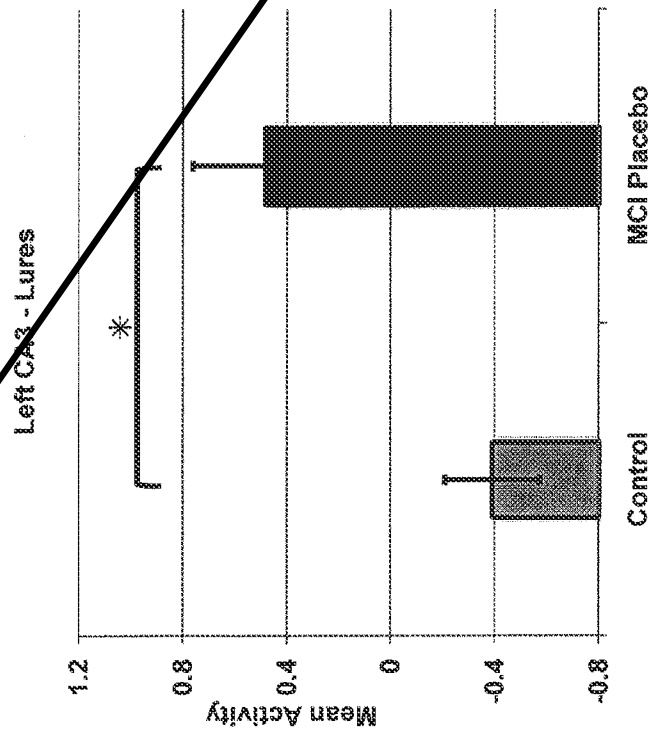

Left CA3 - Lures
Mean Activity
1.2
0.8
0.4
0
-0.4
-0.8
Control
MCI Placebo
*Independent samples t-test: t = -2.636, p = 0.013

FIG. 5A

Left CA3 Lures

Group	Mean Activity	Standard Error
Control	-0.39129	0.182628
MCI Placebo	0.48440	0.277487
MCI Drug	-0.09653	0.205892

FIG. 5C

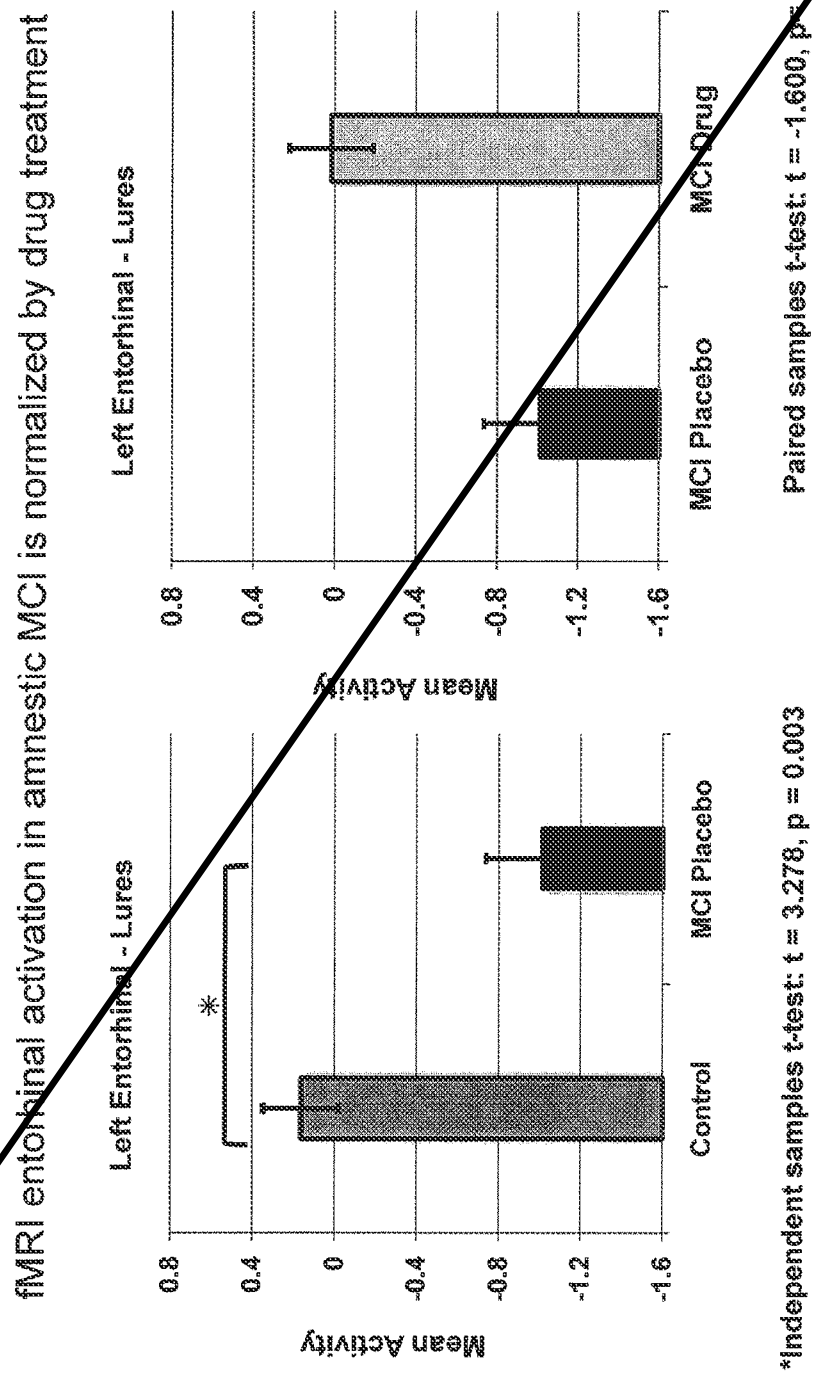

fMRI entorhinal activation in amnestic MCI is normalized by drug treatment
Left Entorhinal - Lures
Mean Activity
0.8
0.4
0
-0.4
-0.8
-1.2
-1.6
Control
MCI Placebo
*
*Independent samples t-test: t = 3.278, p = 0.003
Left Entorhinal - Lures
Mean Activity
MCI Placebo
MCI Drug
Paired samples t-test: t = -1.600, p = 0.129

FIG. 6A

FIG. 6B

Left Entorhinal Lures

Group	Mean Activity	Standard Error
Control	0.16444	0.143864
MCI Placebo	-1.01273	0.329062
MCI Drug	0.016291	0.411762

FIG. 6C

Reduced memory in task that taxes pattern separation
2500 ms
500 ms
ISI
Sample lure pairs

FIG. 7A

FIG. 7B

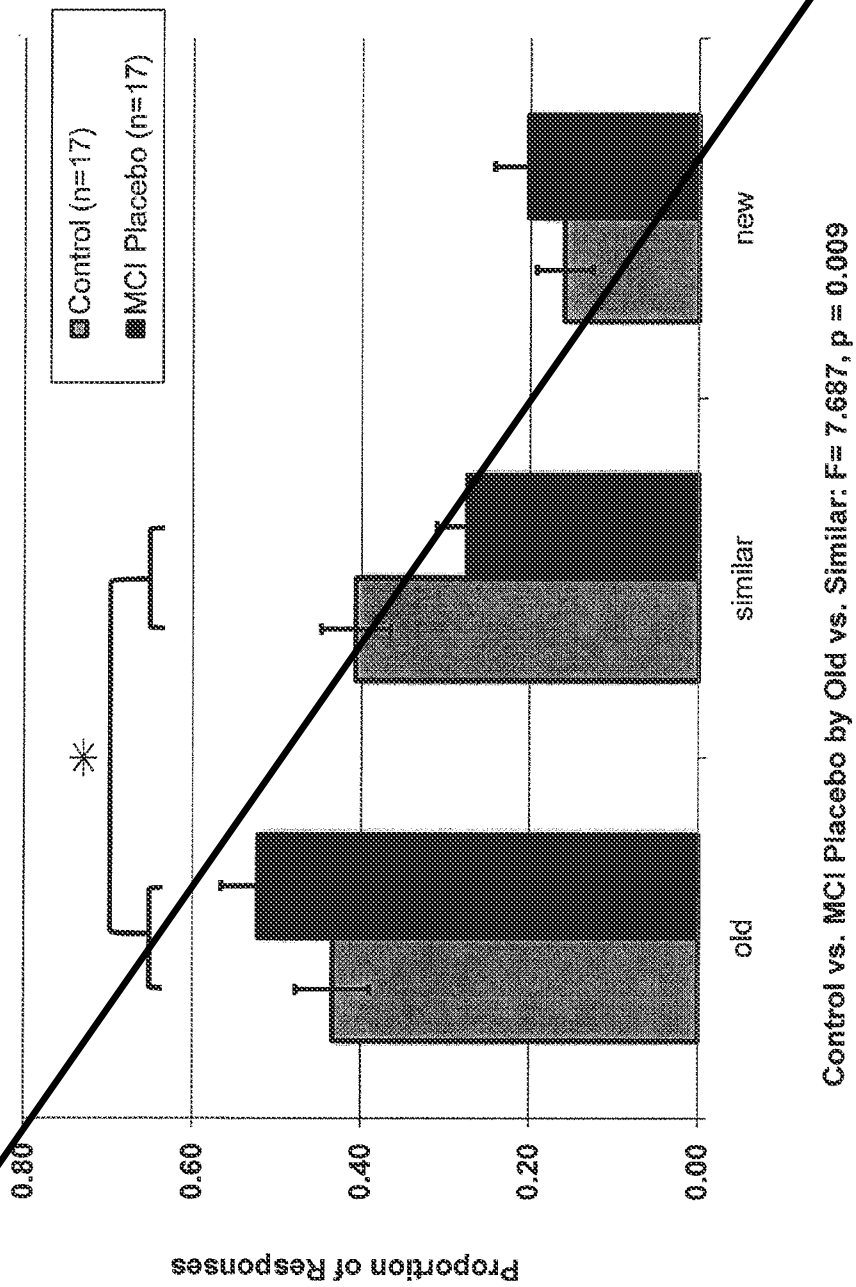

Behavioral Performance
Control (n=17)
MCI Placebo (n=17)
Proportion of Responses
0.00
0.20
0.40
0.60
0.80
old
similar
new
Control vs. MCI Placebo by Old vs. Similar: F= 7.687, p = 0.009

FIG. 8

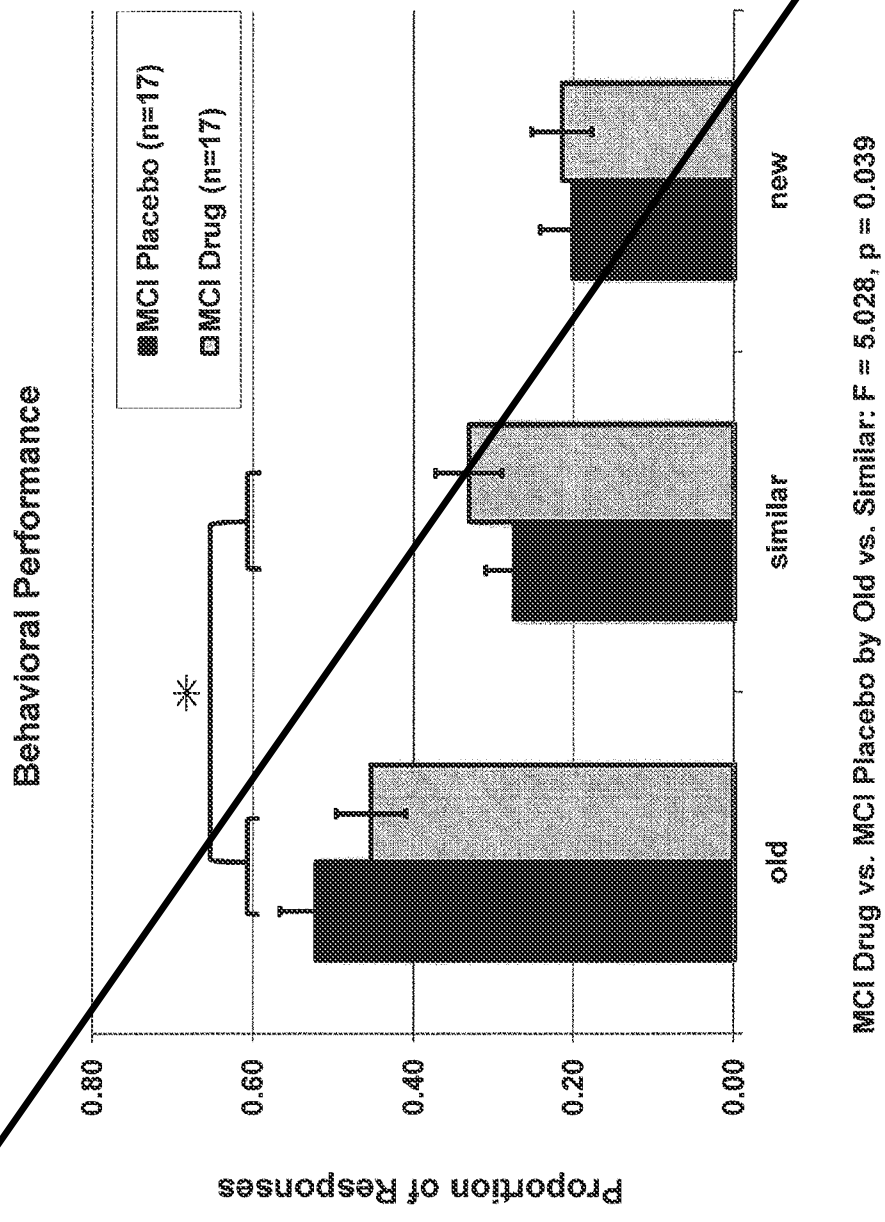

Behavioral Performance
MCI Placebo (n=17)
MCI Drug (n=17)
Proportion of Responses
0.80
0.60
0.40
0.20
0.00
old
similar
new
MCI Drug vs. MCI Placebo by Old vs. Similar: F = 5.028, p = 0.039

FIG. 9

Behavioral Performance

Control Subjects	Proportion of Responses	Standard Error
Old	0.433676	0.04426
Similar	0.406771	0.04135
New	0.159553	0.03312
MCI Placebo Subjects	**Proportion of Responses**	**Standard Error**
Old	0.52262	0.04871
Similar	0.27549	0.03956
New	0.20188	0.04528
MCI Drug Subjects	**Proportion of Responses**	**Standard Error**
Old	0.45361	0.04825
Similar	0.33144	0.04592
New	0.21494	0.04202

FIG. 10

FIG. 11A

Group	Mean	Standard Error	Delayed (p-value)
Control	7.18	0.56	Control vs. Placebo: <0.001
MCI Placebo	3.59	0.59	Control vs. Drug: < 0.001
MCI Drug	3.65	0.53	Placebo vs. Drug: 0.887

FIG. 11B

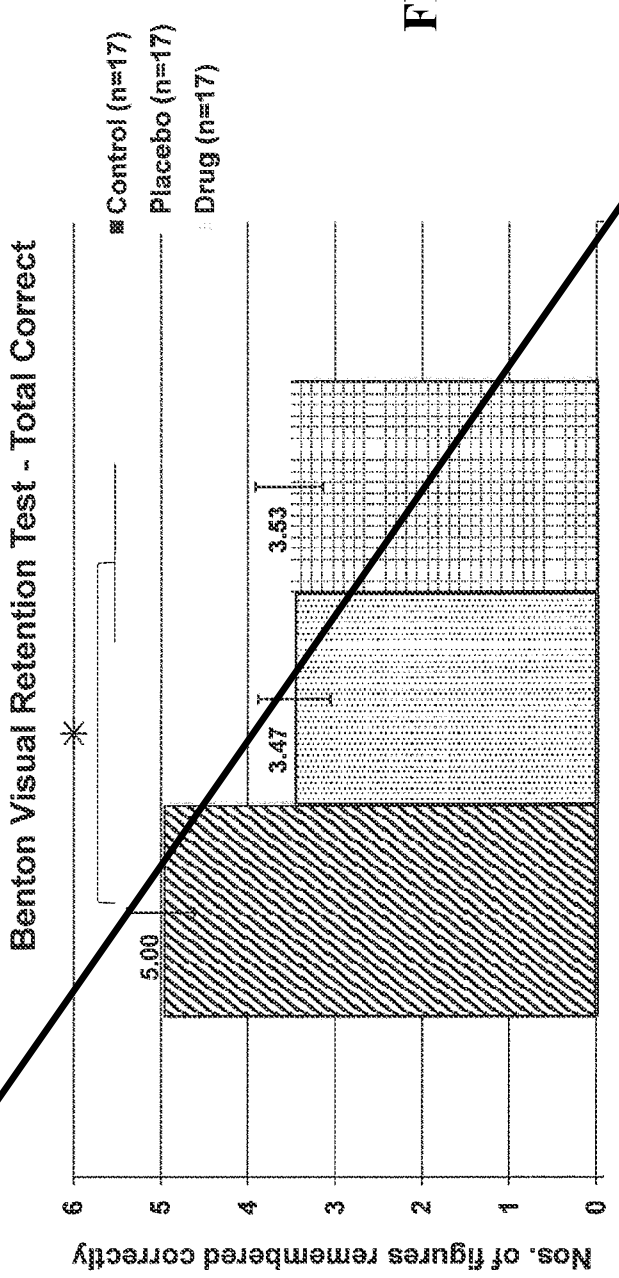


FIG. 12A

Group	Mean	Standard Error	Total Correct (p-value)
Control	5.00	0.38	Control vs. Placebo: 0.011
MCI Placebo	3.47	0.41	Control vs. Drug: 0.011
MCI Drug	3.53	0.38	Placebo vs. Drug: 0.805

FIG. 12B

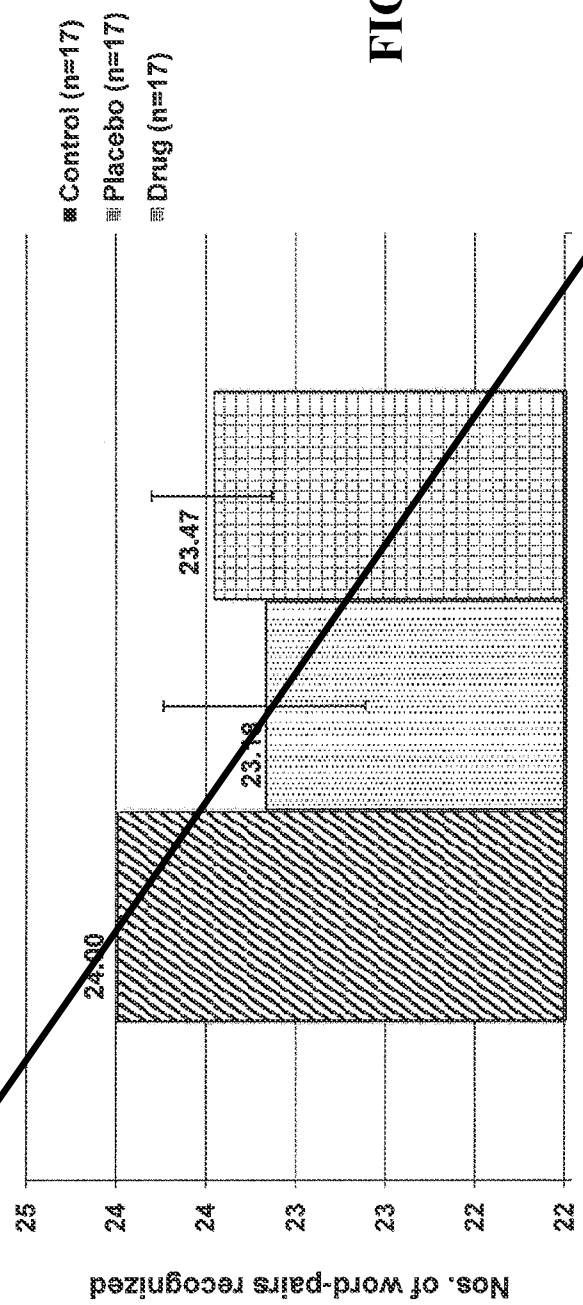


FIG. 13A

Group	Mean	Standard Error	Recognition (p-value)
Control	24.00	0.00	Control vs. Placebo: 0.154
MCI Placebo	23.18	0.56	Control vs. Drug: 0.122
MCI Drug	23.47	0.33	Placebo vs. Drug: 0.428

FIG. 13B

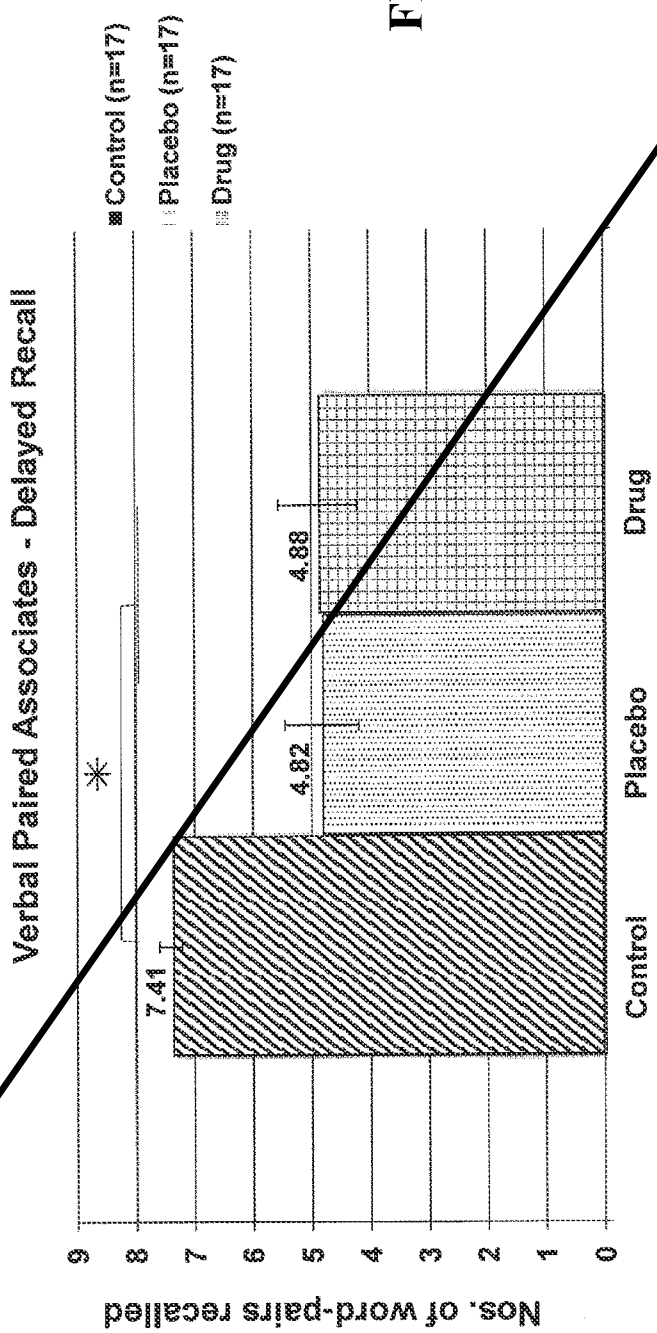


FIG. 14A

Group	Mean	Standard Error	Delayed Recall (p-value)
Control	7.41	0.19	Control vs. Placebo: <0.001
MCI Placebo	4.82	0.63	Control vs. Drug: 0.001
MCI Drug	4.88	0.67	Placebo vs. Drug: 0.848

FIG. 14B

Study Status

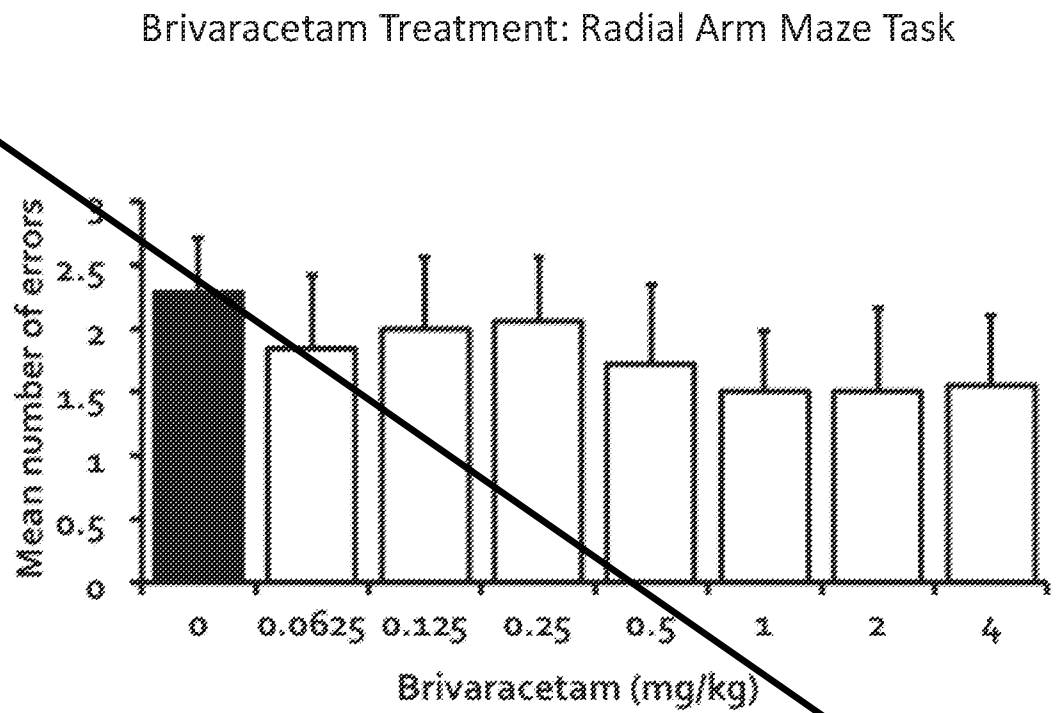
	Control subjects	MCI subjects	Total subjects
Participated in screening	26	32	58
Screening failures	4	9	13
Enrolled	22	23	45
Removed or withdrew from study	5	6	11
Total subjects used in analysis	17	17	34

FIG. 15A

Characteristics of Study Samples

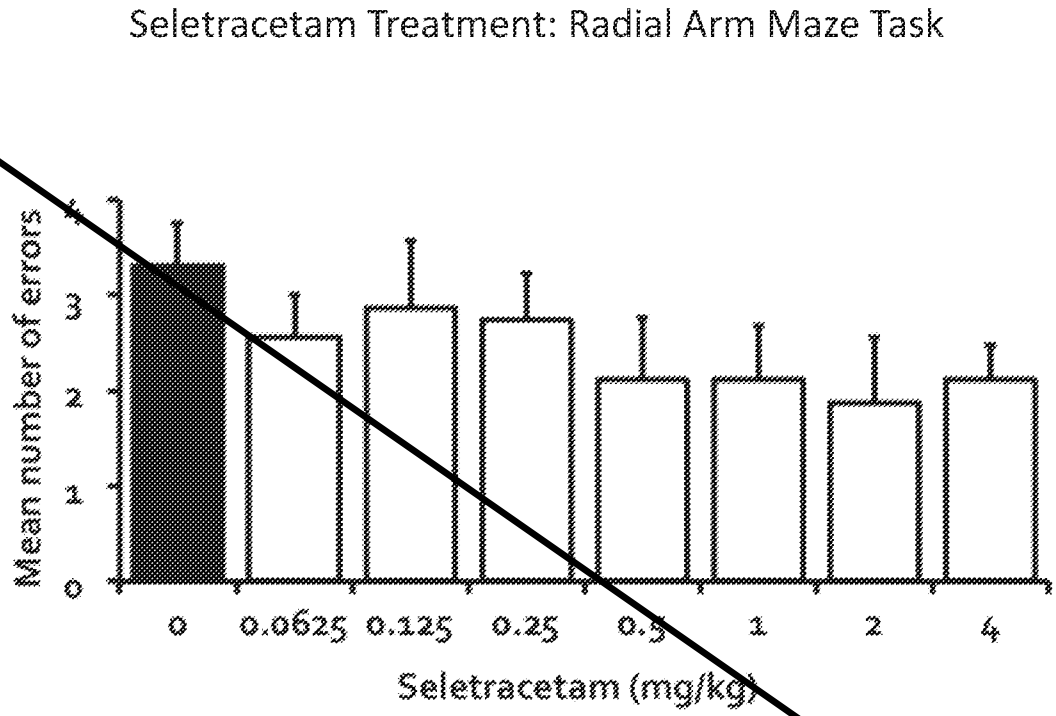
	Control Subjects	MCI Subjects	p
N	17	17	
Sex (M/F)	9/8	6/11	0.307
Age (yrs)	69.3 (7.0)	72.9 (8.9)	0.201
Education (yrs)	15.9 (2.6)	15.8 (2.9)	0.951
Race (Caucasian/African American)	17/0	14/3	0.074
Hispanic or Latino (y/n)	0/17	1/16	0.317

FIG. 15B



Repeated measures ANOVA for within-subject contrasts, $F(1, 8) = 6.046$, $p = 0.039$
Means and SEMs are shown

FIG. 16



Repeated measures ANOVA for within-subject contrasts, F(1, 7) = 12.577, p = 0.009
Means and SEMs are shown

FIG. 17

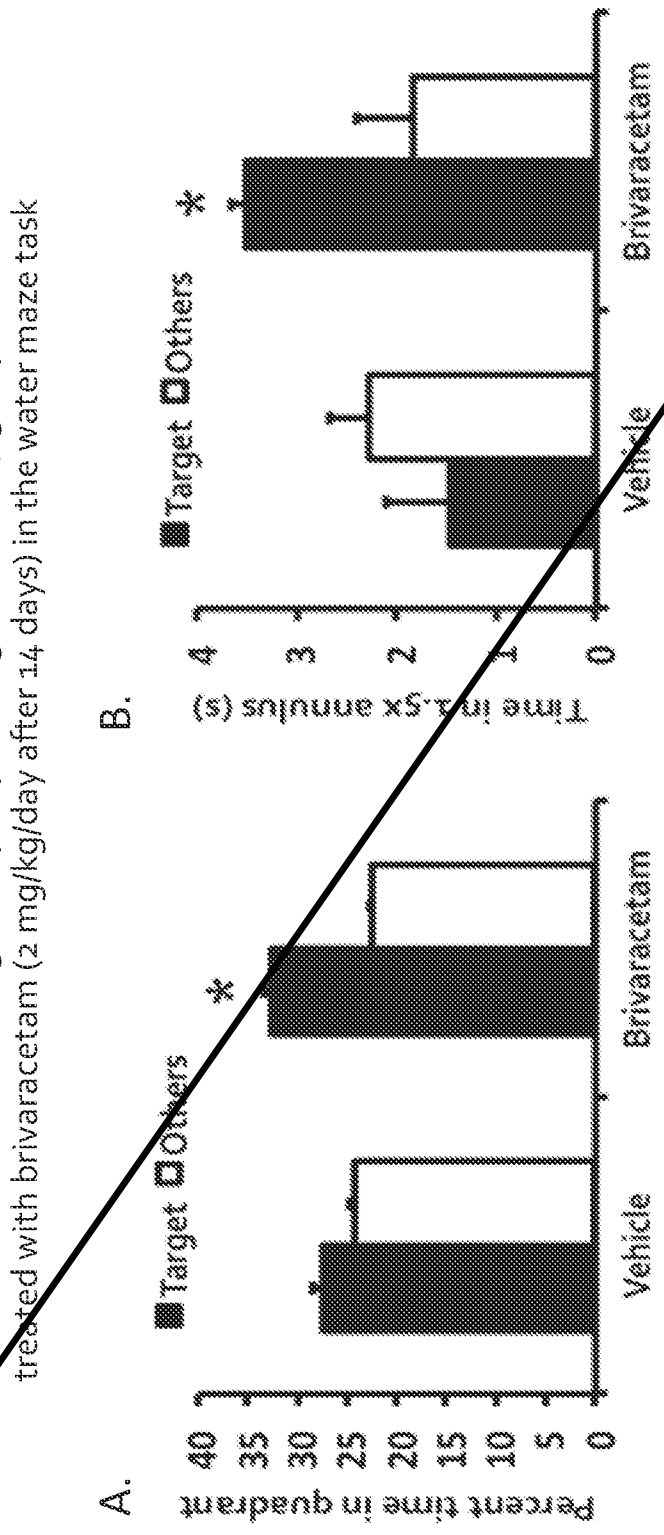


FIG. 18A

FIG. 18B

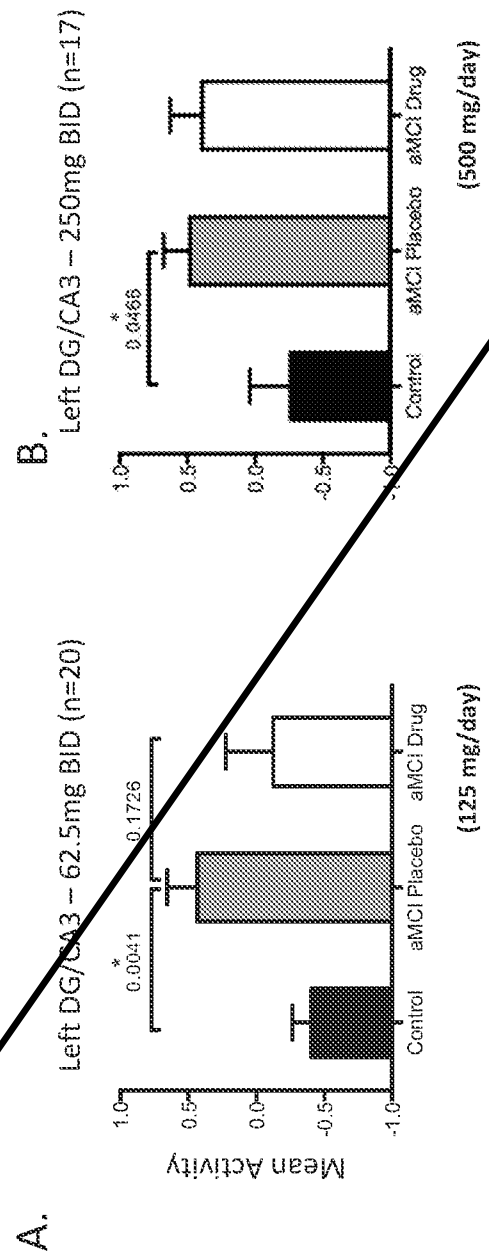


FIG. 19A

FIG. 19B

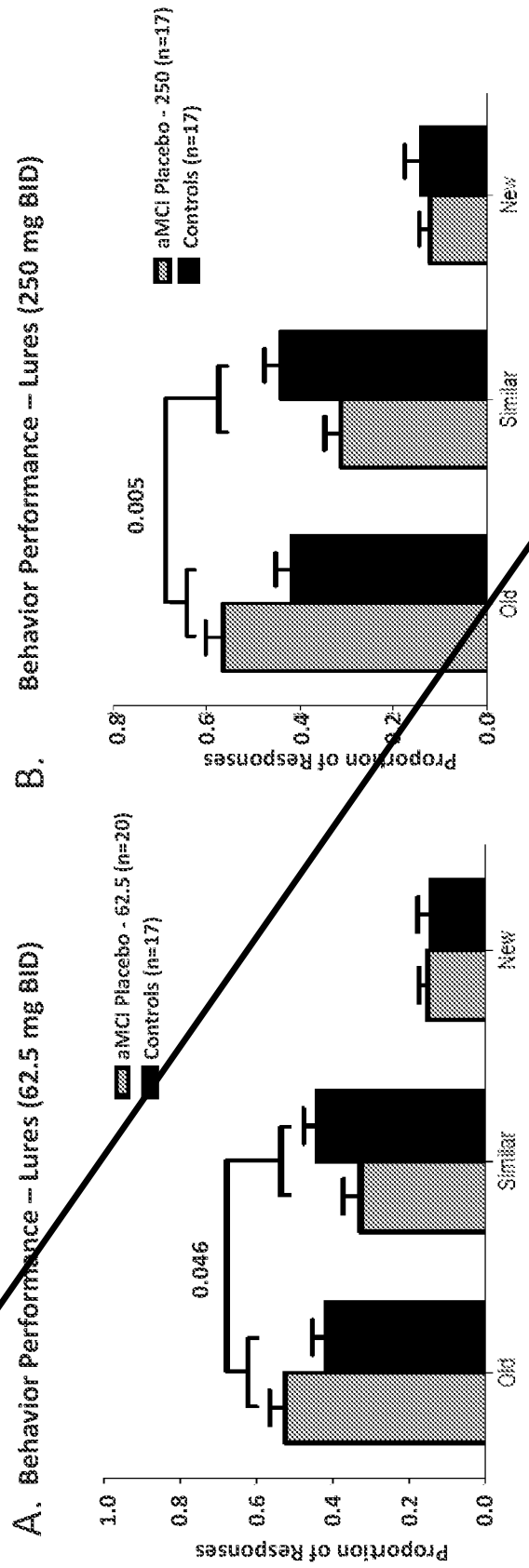


FIG. 20A

FIG. 20B

FIG. 21A

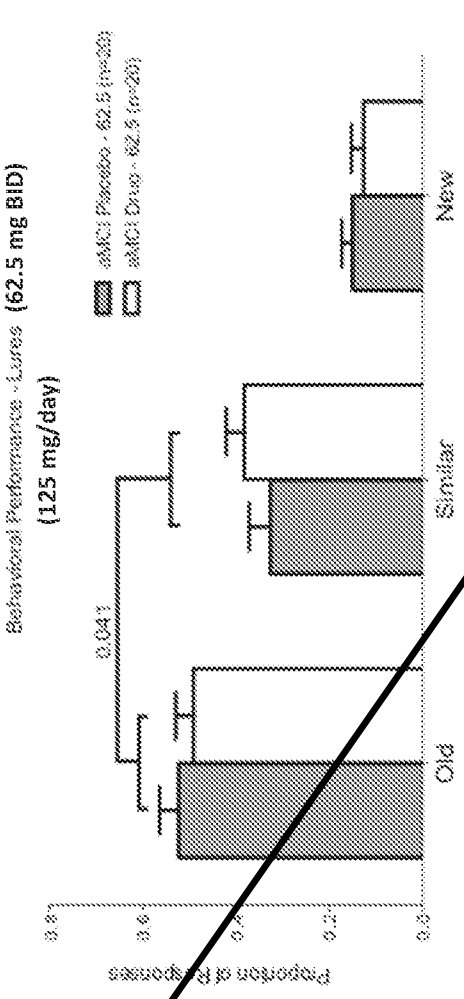
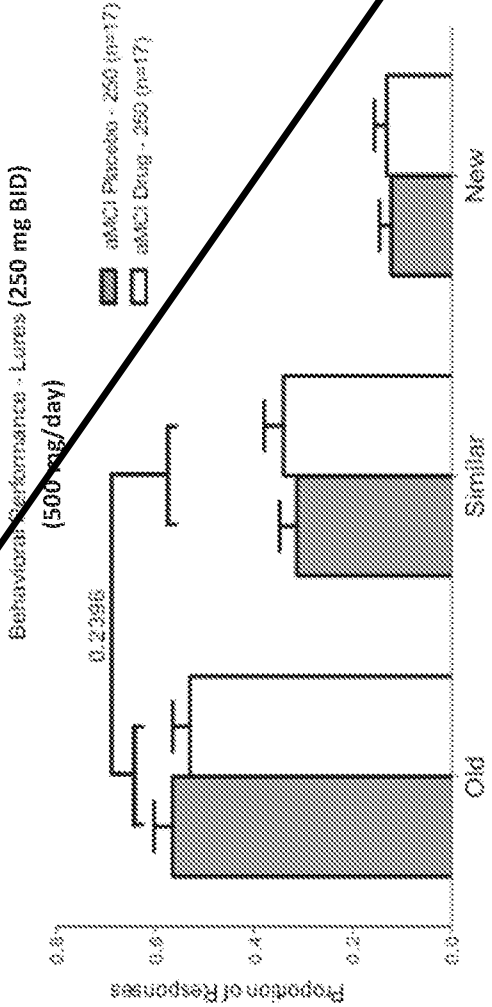


FIG. 21B



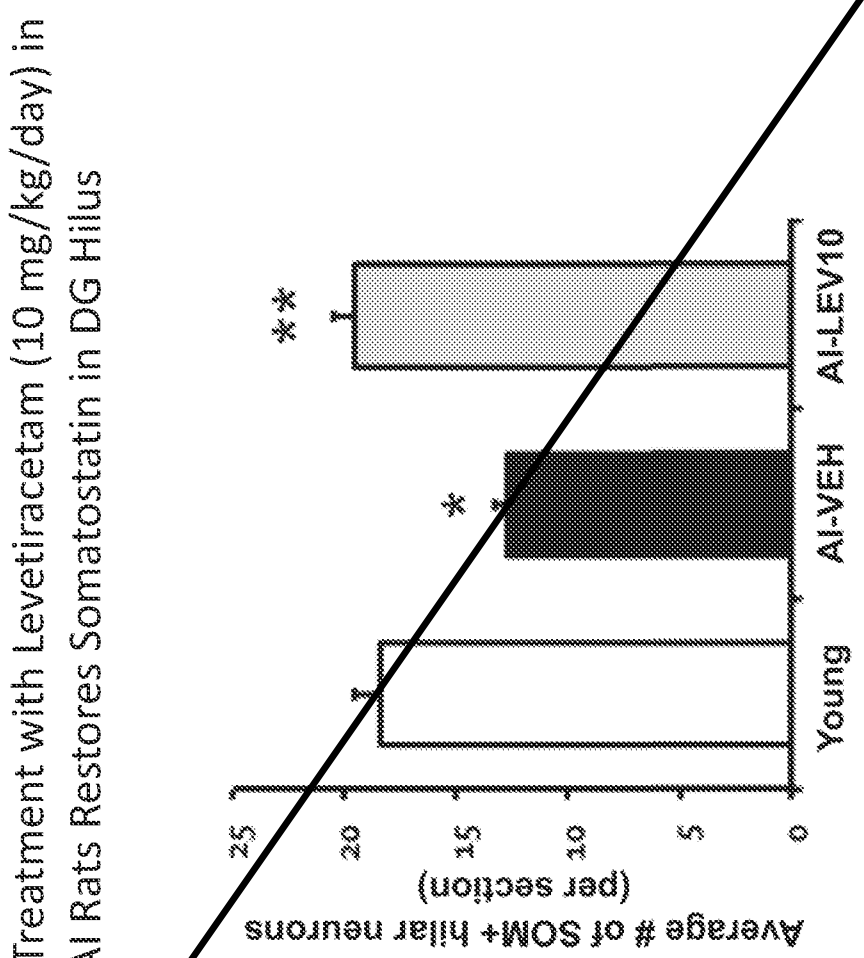

Chronic Treatment with Levetiracetam (10 mg/kg/day) in
AI Rats Restores Somatostatin in DG Hilus
Average # of SOM+ hilar neurons
(per section)
0
5
10
15
20
25
Young
AI-VEH
AI-LEV10
*
**

FIG. 22

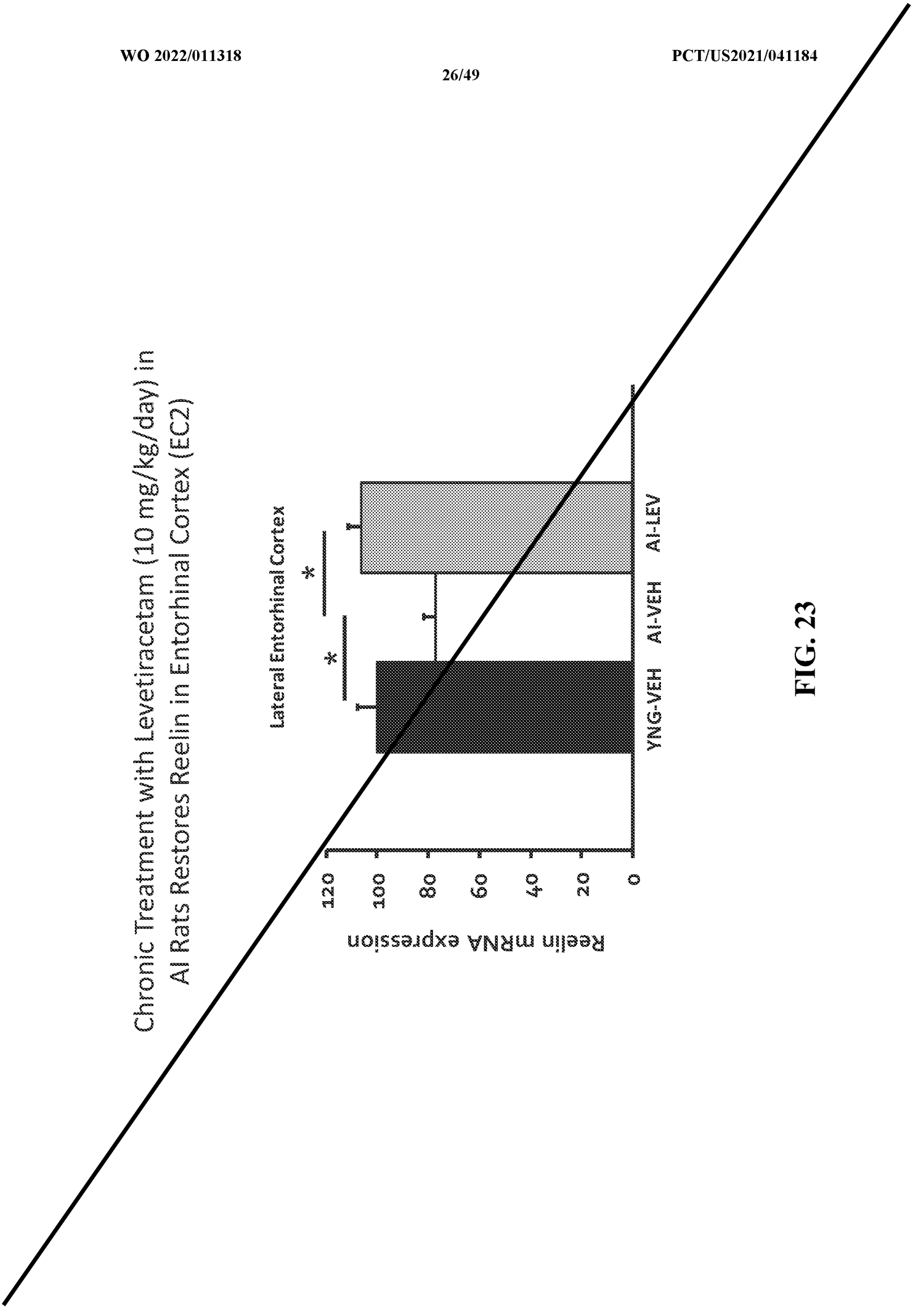

Chronic Treatment with Levetiracetam (10 mg/kg/day) in
AI Rats Restores Reelin in Entorhinal Cortex (EC2)
Lateral Entorhinal Cortex
*
*
Reelin mRNA expression
120
100
80
60
40
20
0
YNG-VEH
AI-VEH
AI-LEV

FIG. 23

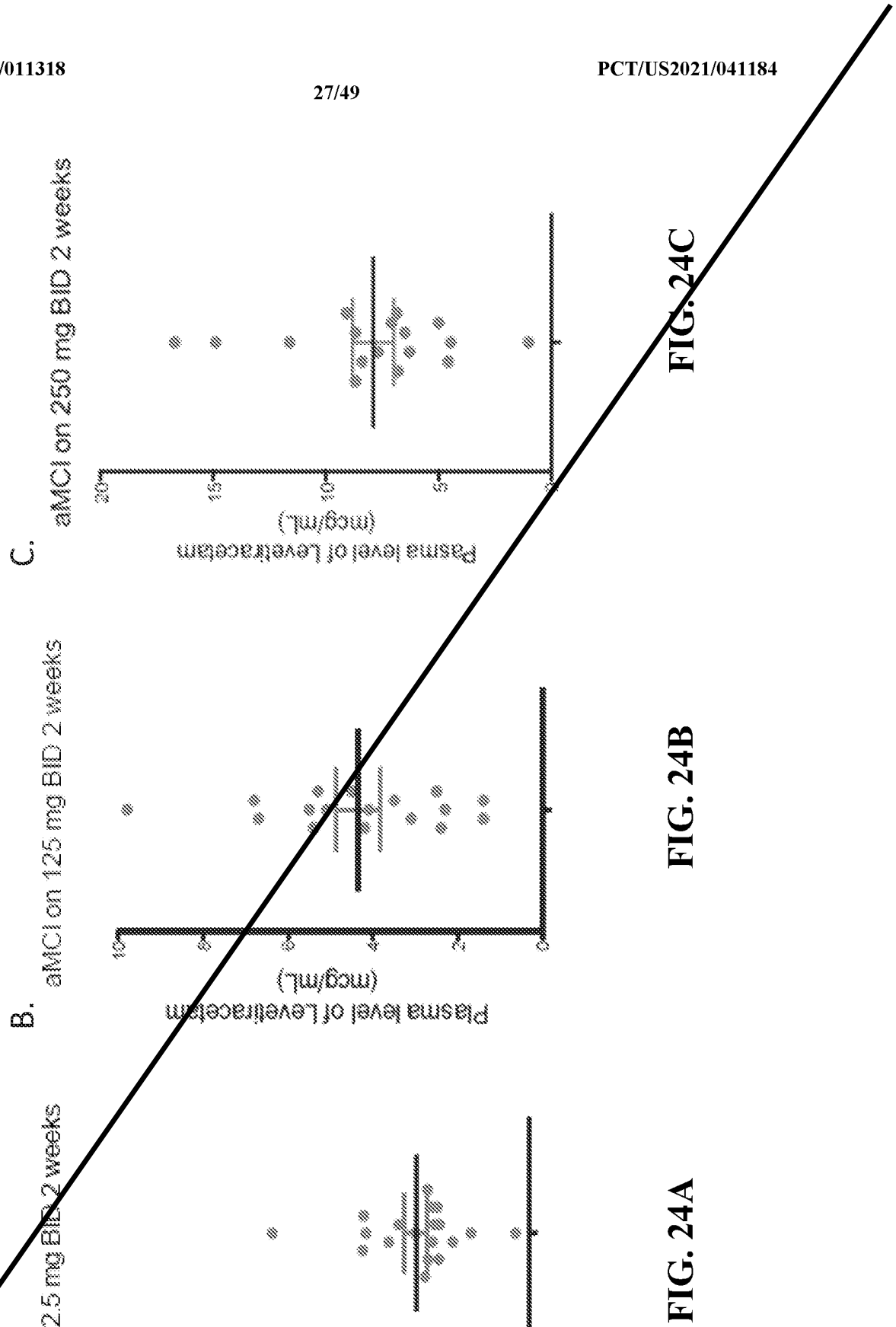


FIG. 24A

FIG. 24B

FIG. 24C

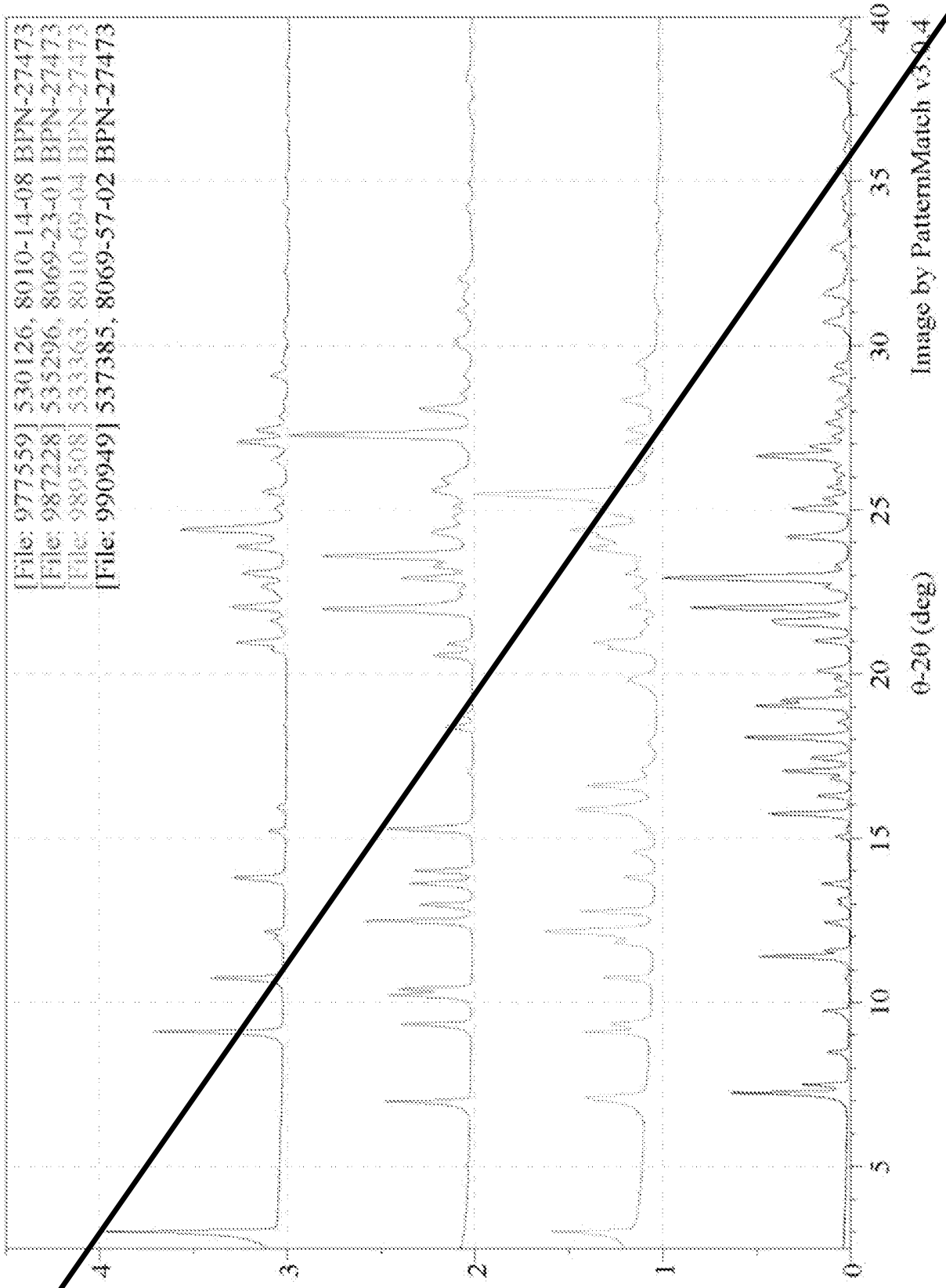

[File: 977559] 530126, 8010-14-08 BPN-27473
[File: 987228] 533296, 8069-23-01 BPN-27473
[File: 980308] 533303, 8010-09-04 BPN-27473
[File: 990949] 537385, 8069-57-02 BPN-27473
Arbitrary y scale
0-2θ (deg)
Image by PatternMatch v3.0.4

FIG. 25

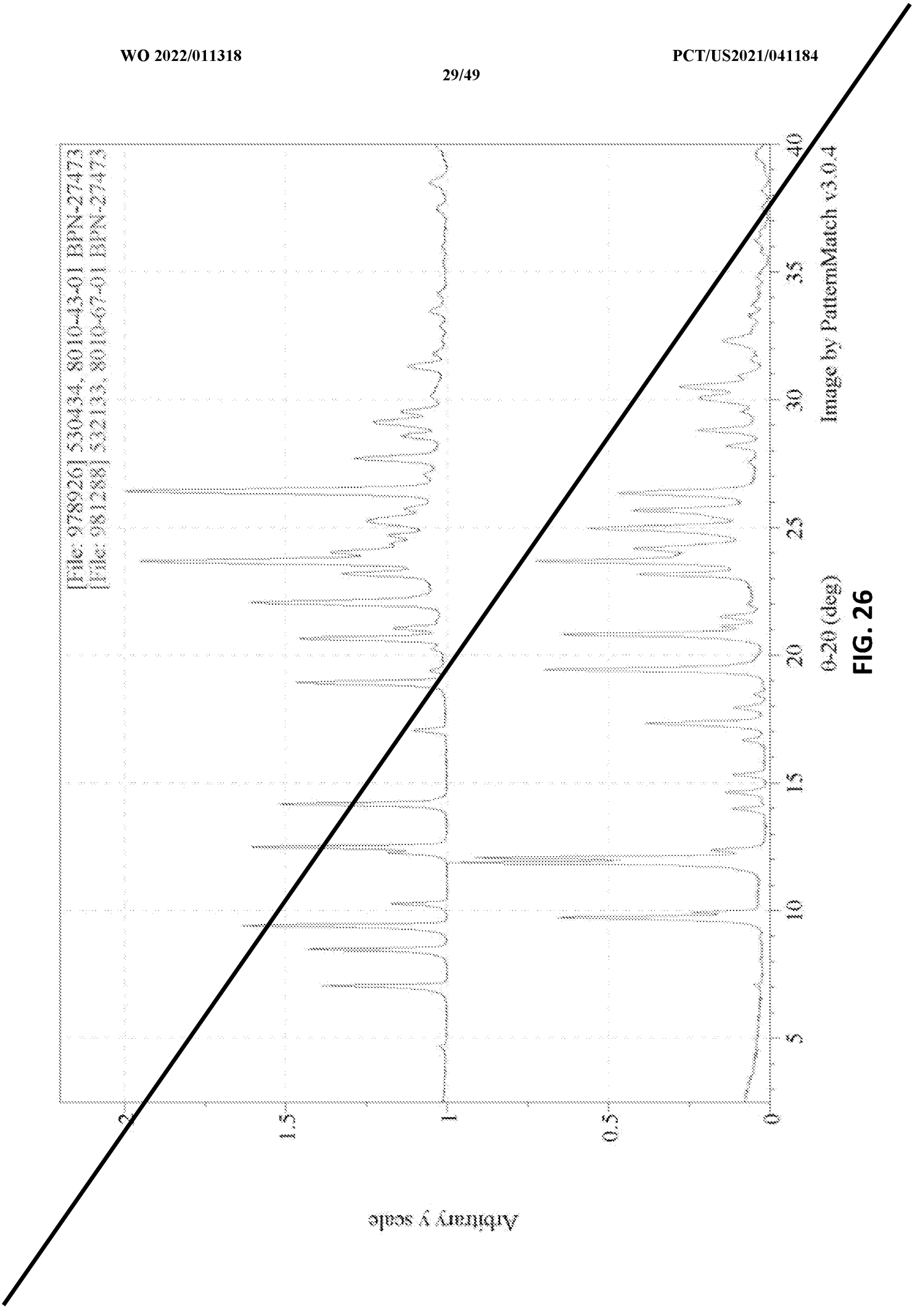

[File: 9789261] 530434, 8010-43-01 BPN-27473
[File: 9813288] 532133, 8010-07-01 BPN-27473
Arbitrary y scale
0
0.5
1
1.5
2
5
10
15
20
25
30
35
40
θ-2θ (deg)
Image by PatternMatch v3.0.4

FIG. 26

FIG. 27A

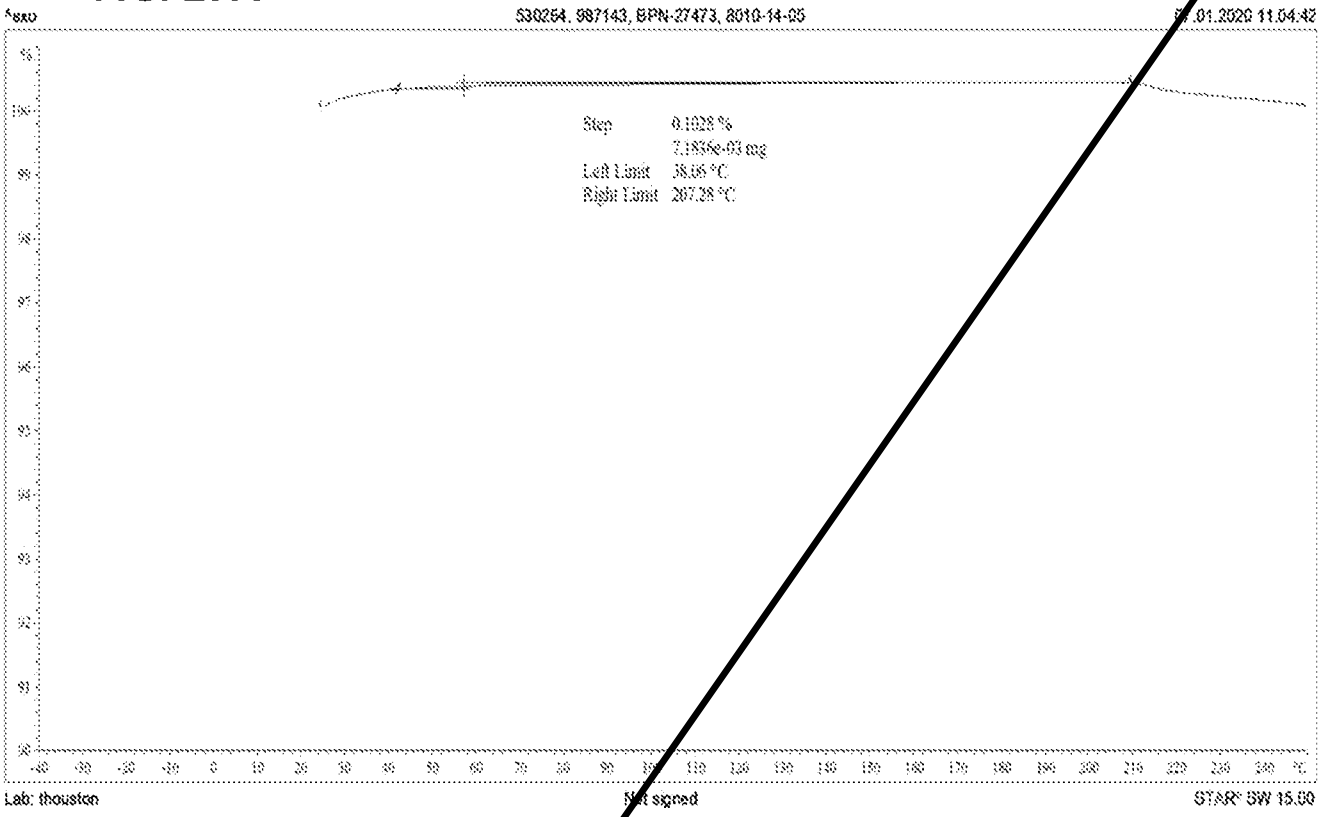
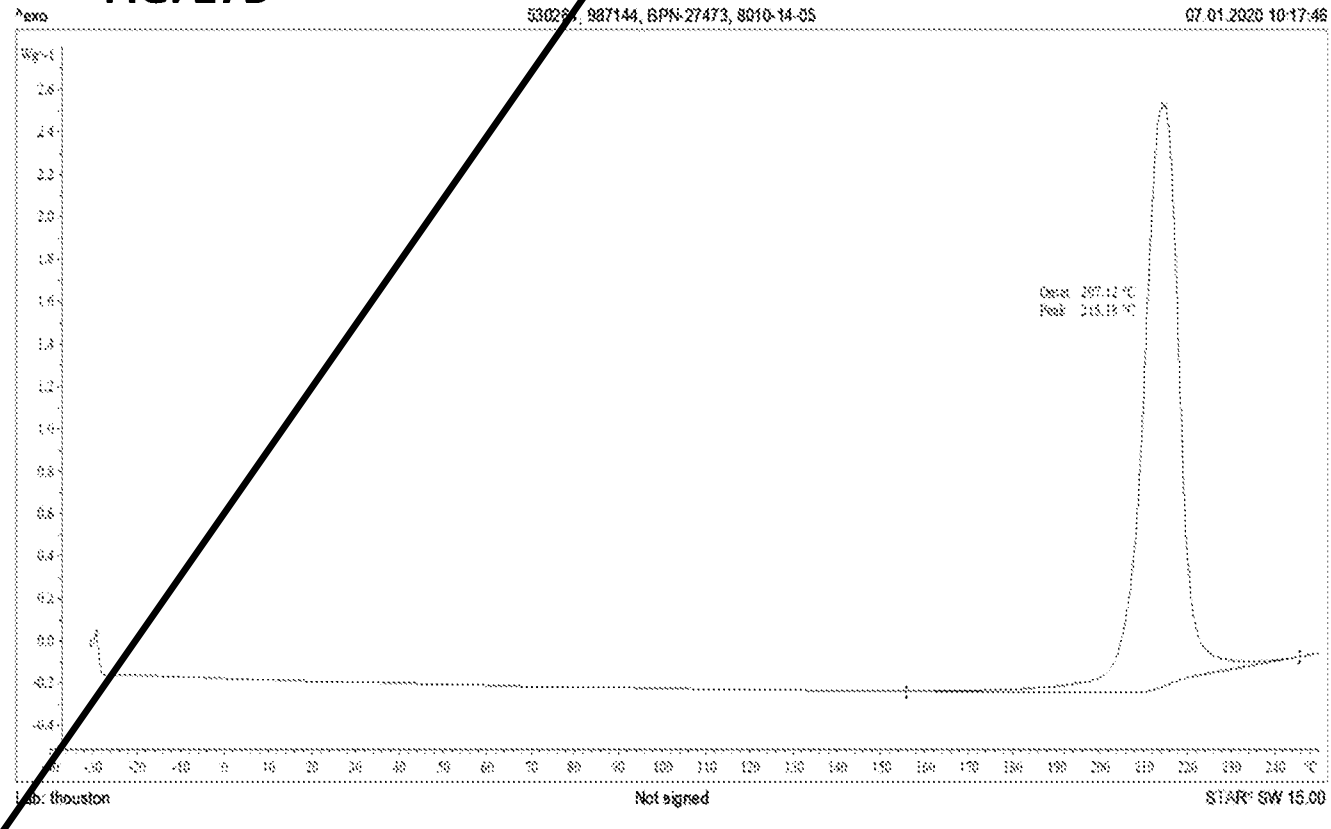


FIG. 27B



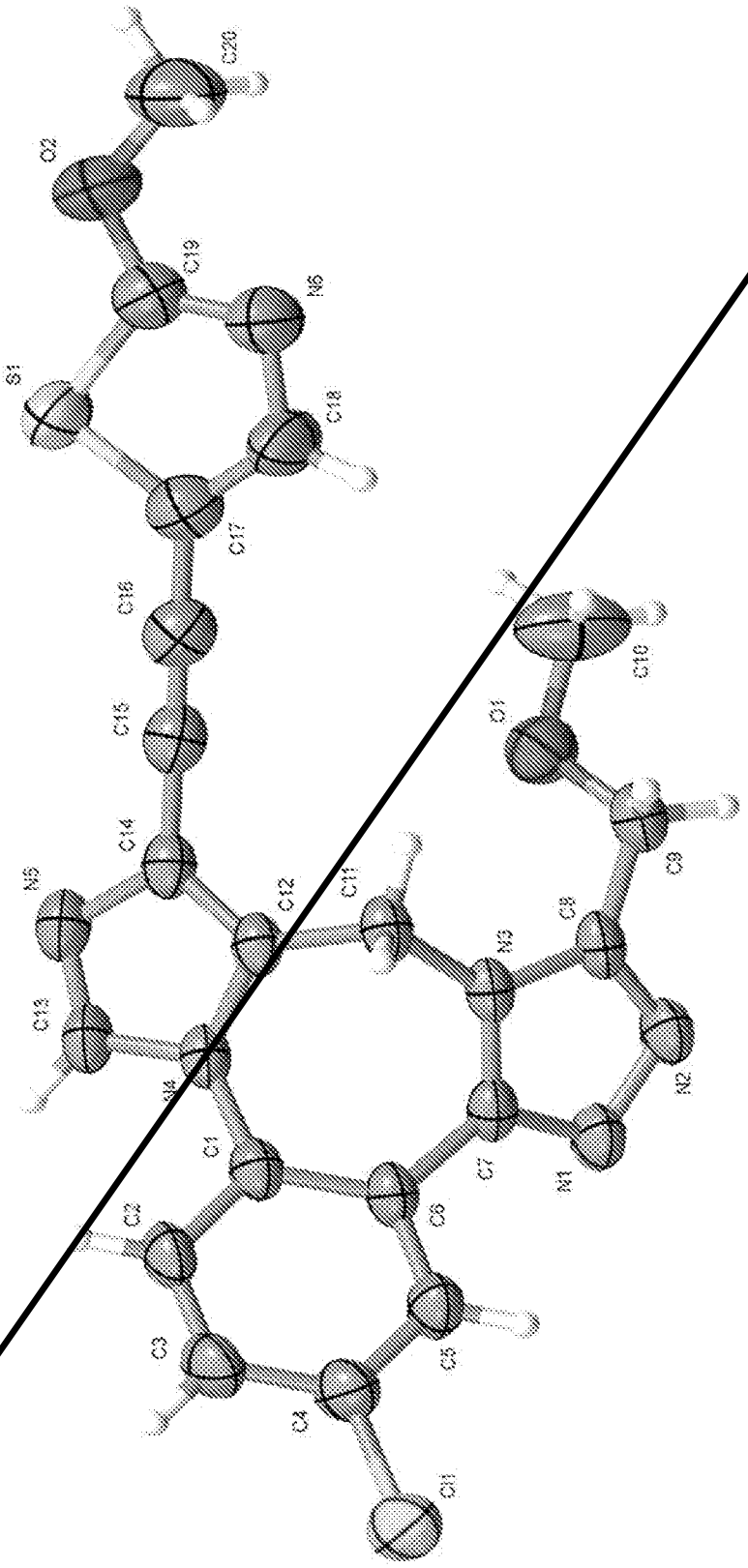

C26
O2
C19
N5
S1
C18
C17
C16
C15
C14
N6
C12
C11
C13
N4
C1
C2
C3
C4
O1
C5
C6
C7
N1
N2
N3
C8
C9
O1
C10

FIG. 28

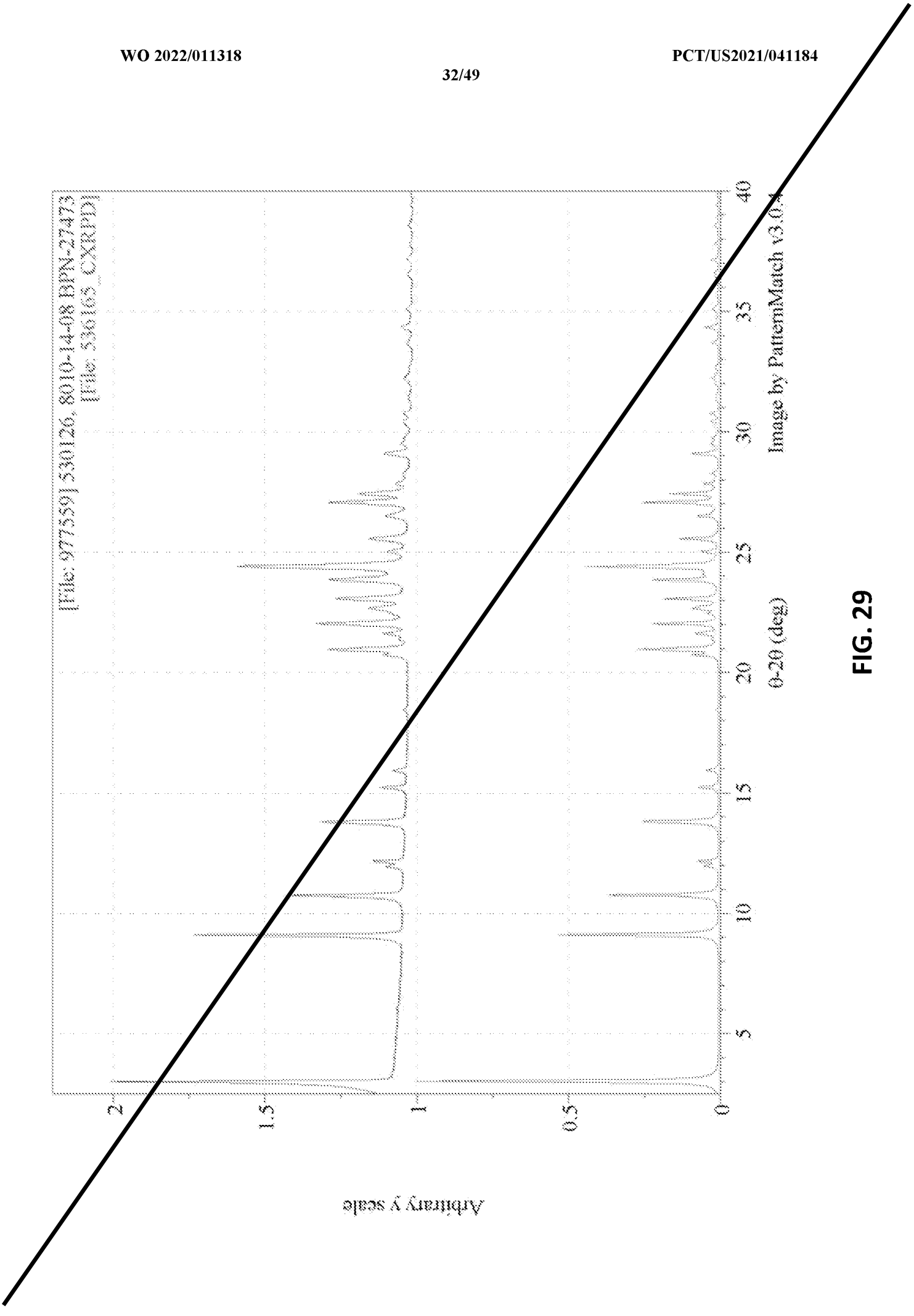

[File: 9775591 530126, 8010-14-08 BPN-27473
[File: 330163_CXRPD]
Arbitrary y scale
0
0.5
1
1.5
2
0
5
10
15
20
25
30
35
40
0-2θ (deg)
Image by PatternMatch v3.0.4

FIG. 29

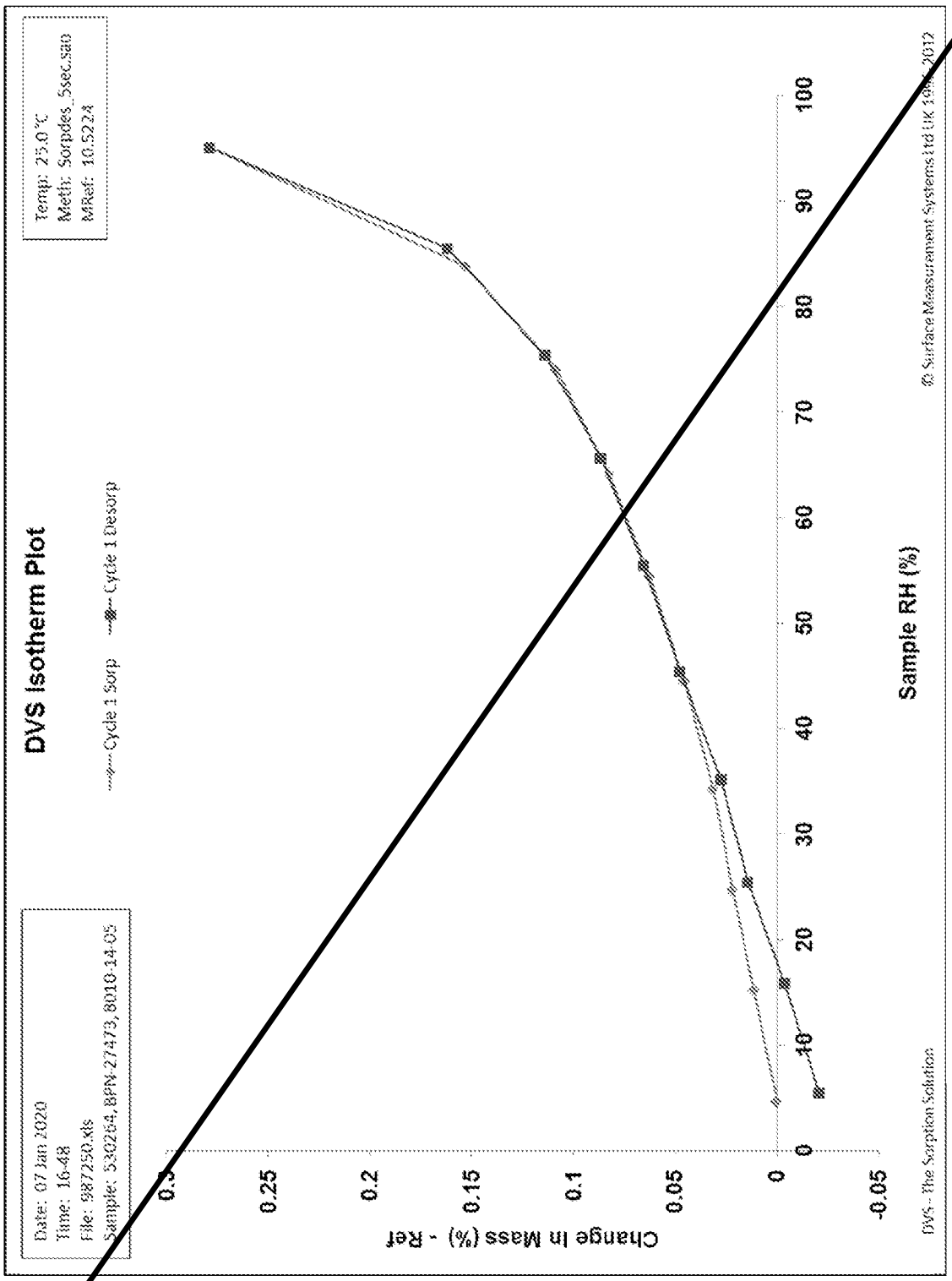
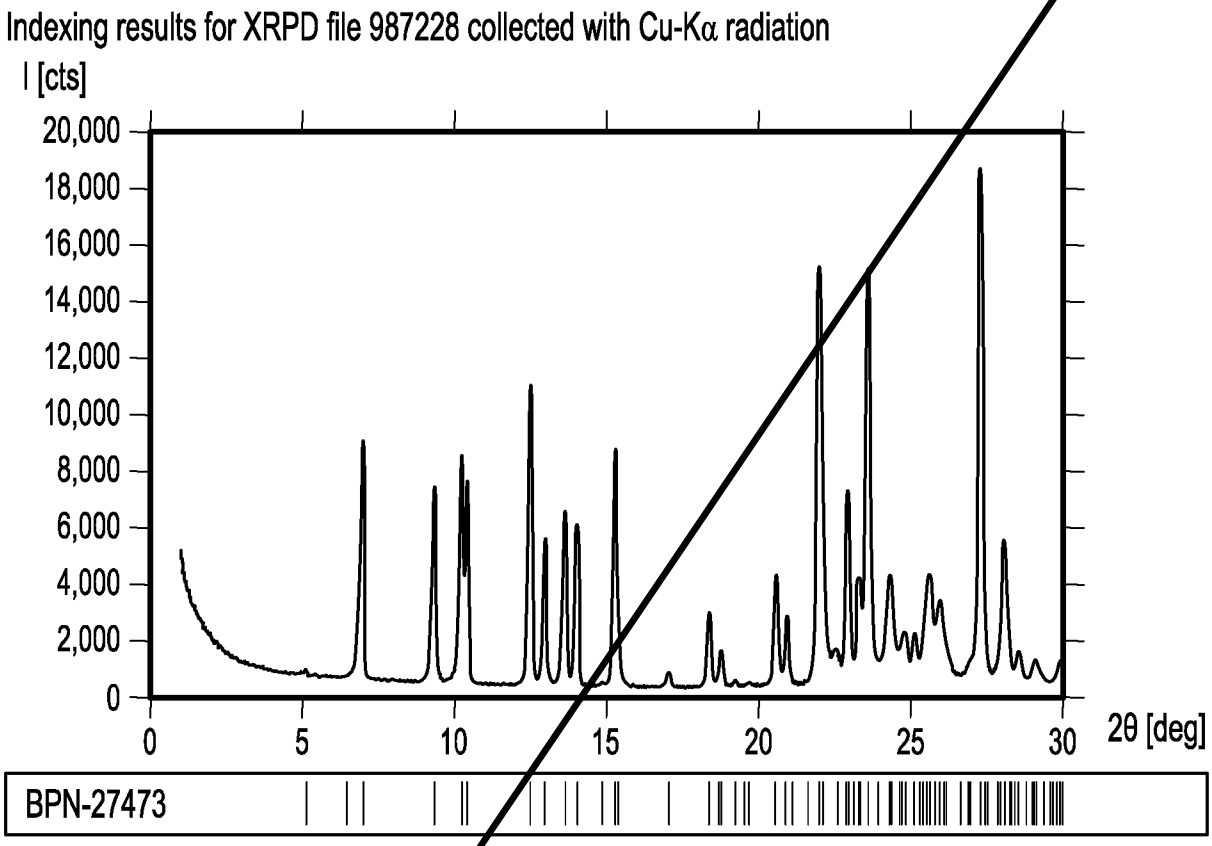

DVS Isotherm Plot
Date: 07 Jan 2020
Time: 16:48
File: 987250.xls
Sample: 330264, BPN-27473, 8010-14-05
Temp: 25.0 °C
Meth: Sorpdes_5sec.sao
MRef: 10.522A
Cycle 1 Sorp
Cycle 1 Desorp
Change In Mass (%) - Ref
Sample RH (%)
0.3
0.25
0.2
0.15
0.1
0.05
0
-0.05
0
10
20
30
40
50
60
70
80
90
100
DVS - The Sorption Solution
© Surface Measurement Systems Ltd UK 1998 - 2012

FIG. 30

34/49



	BPN-27473
Bravais Type	Primitive Monoclinic
a [Å]	14.254
b [Å]	4.041
c [Å]	36.069
α [deg]	90
β [deg]	106.84
γ [deg]	90
Volume [Å^3/cell]	1,988.5
Chiral Contents?	Not Specified
Extinction Symbol	P 1 c 1
Space Group(s)	Pc (7), P2/c (13)
Source	Manual Input

Indexing is a non-cGMP activity

FIG. 31

Output Rendered using Triads v2.1.1

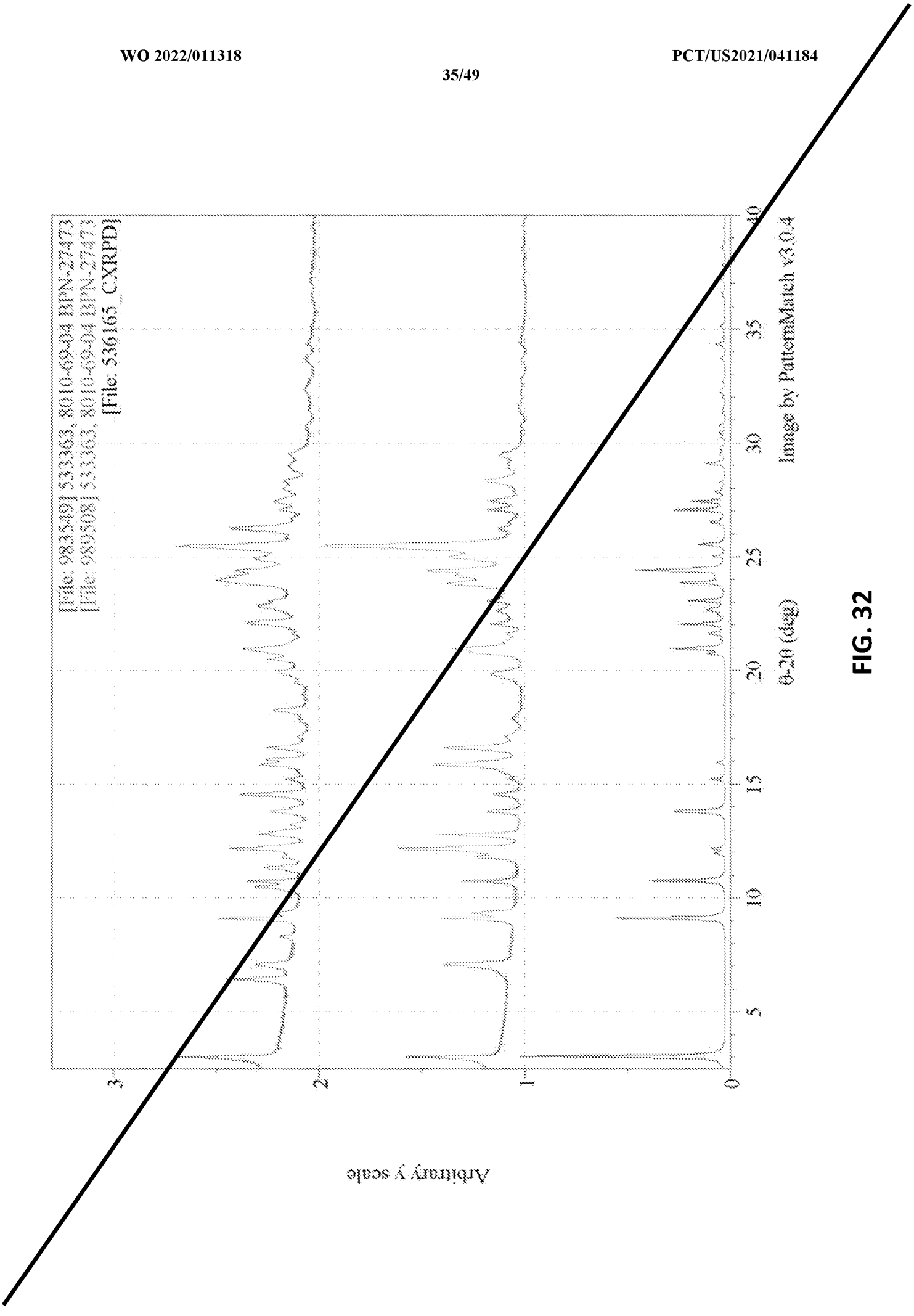

[File: 9835491] 533363, 8010-69-04 BPN-27473
[File: 980508] 533363, 8010-69-04 BPN-27473
[File: 536165_CXRPD]
Arbitrary y scale
0
1
2
3
0
5
10
15
20
25
30
35
40
θ-2θ (deg)
Image by PatternMatch v3.0.4

FIG. 32

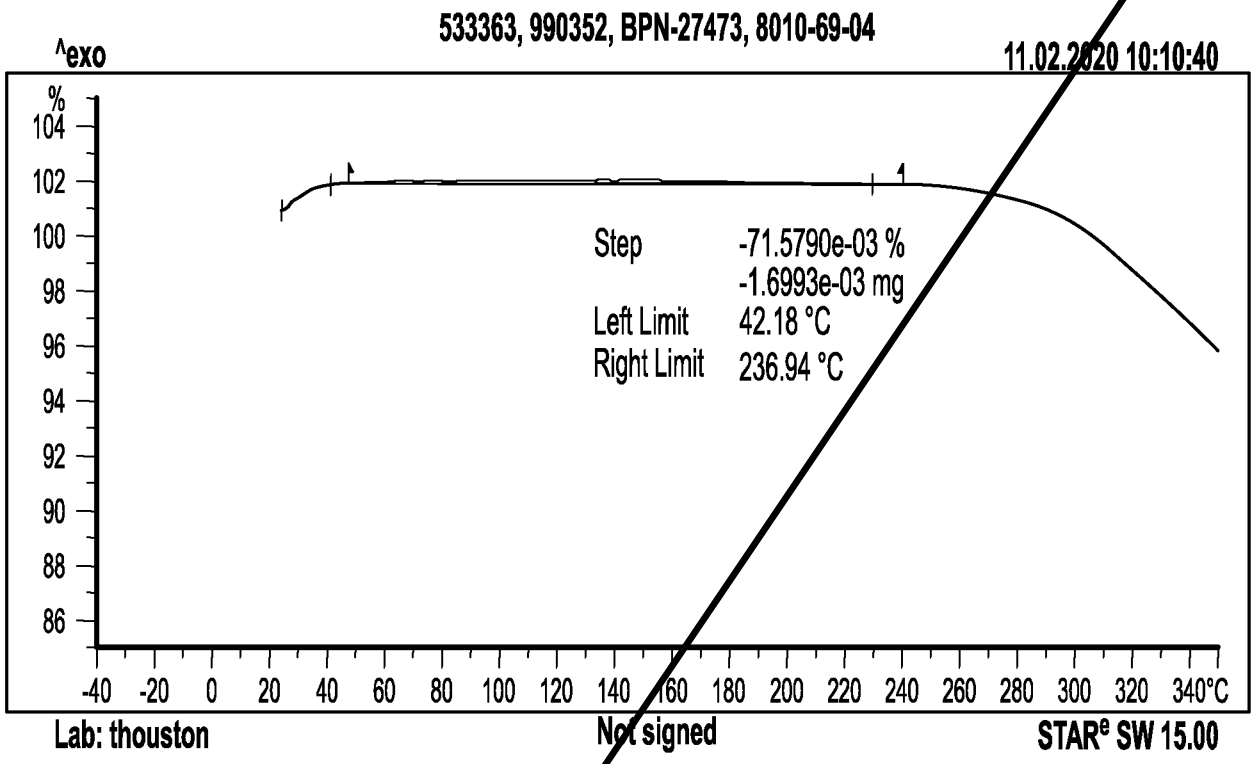


FIG. 33A

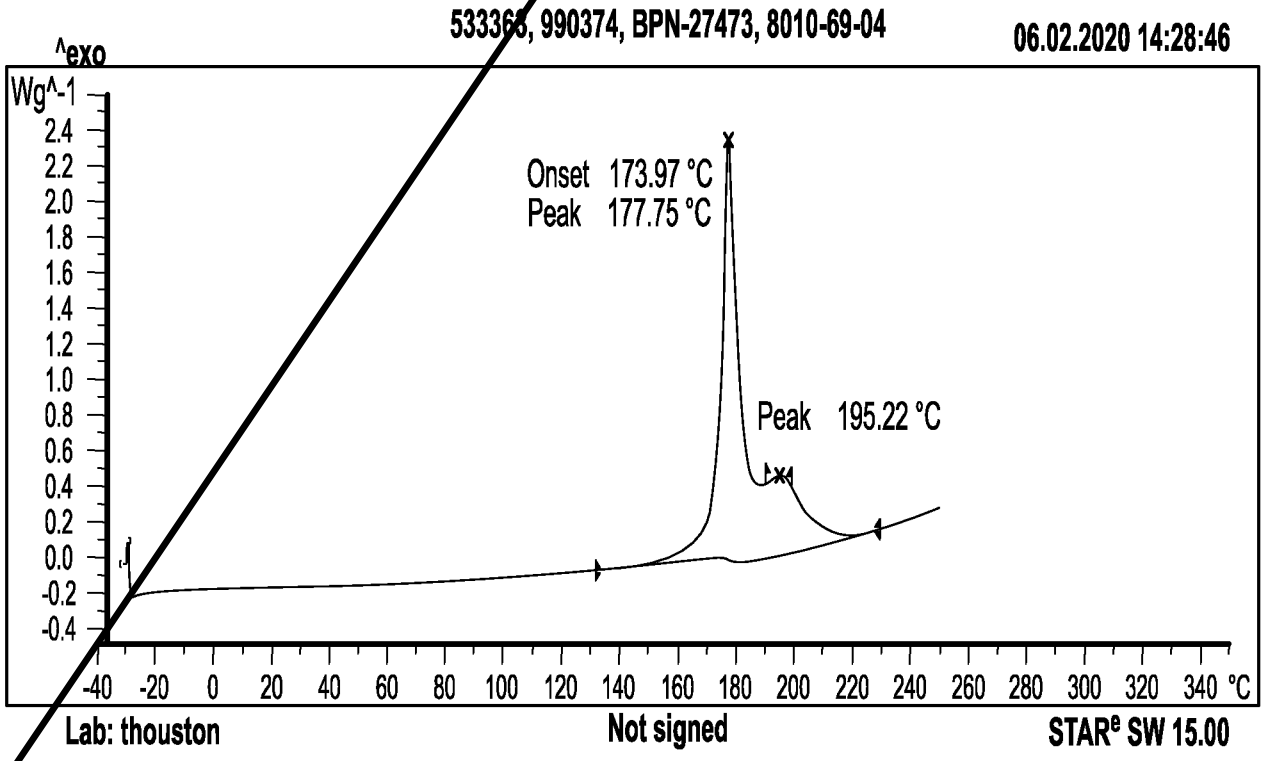


FIG. 33B

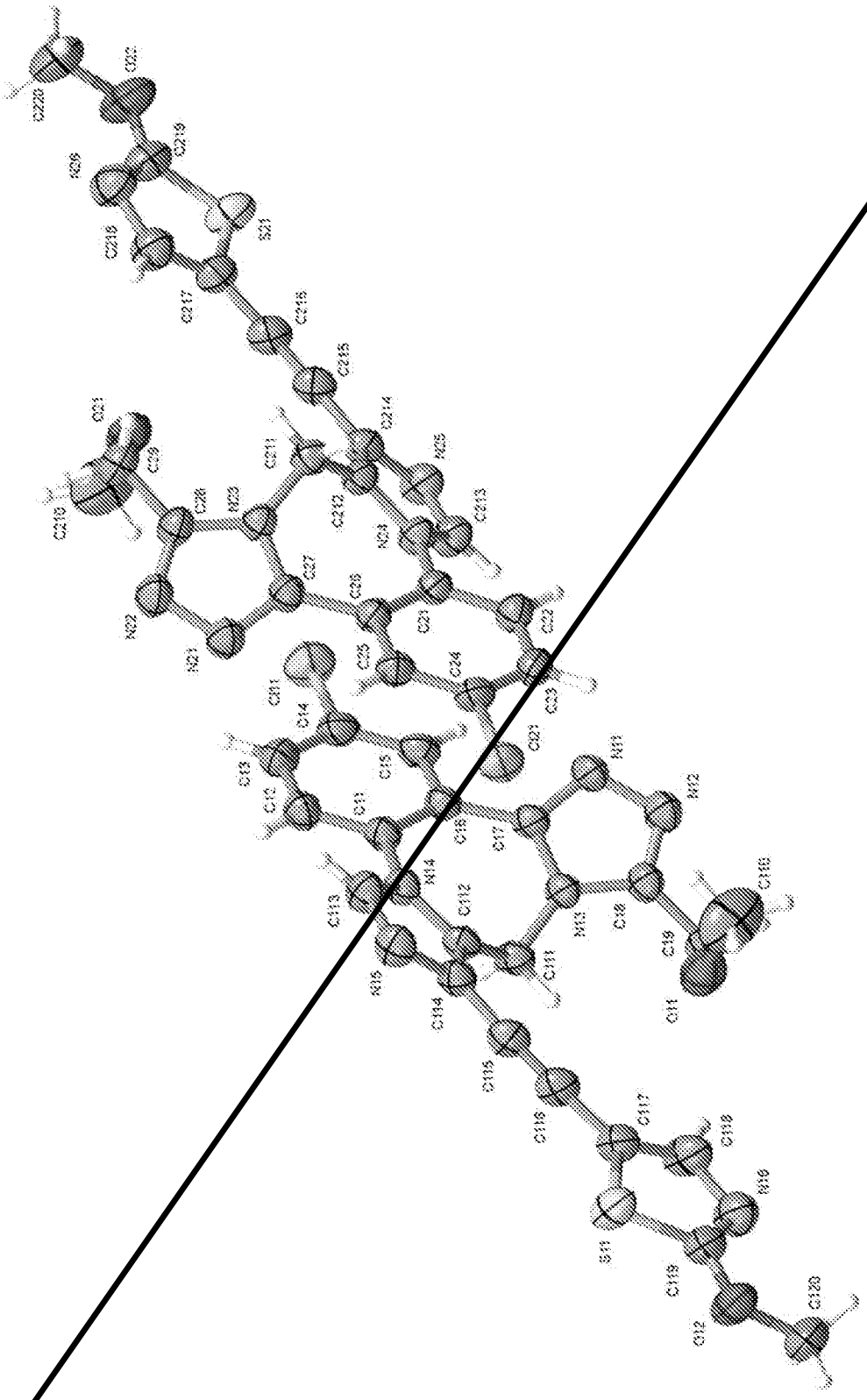


FIG. 34

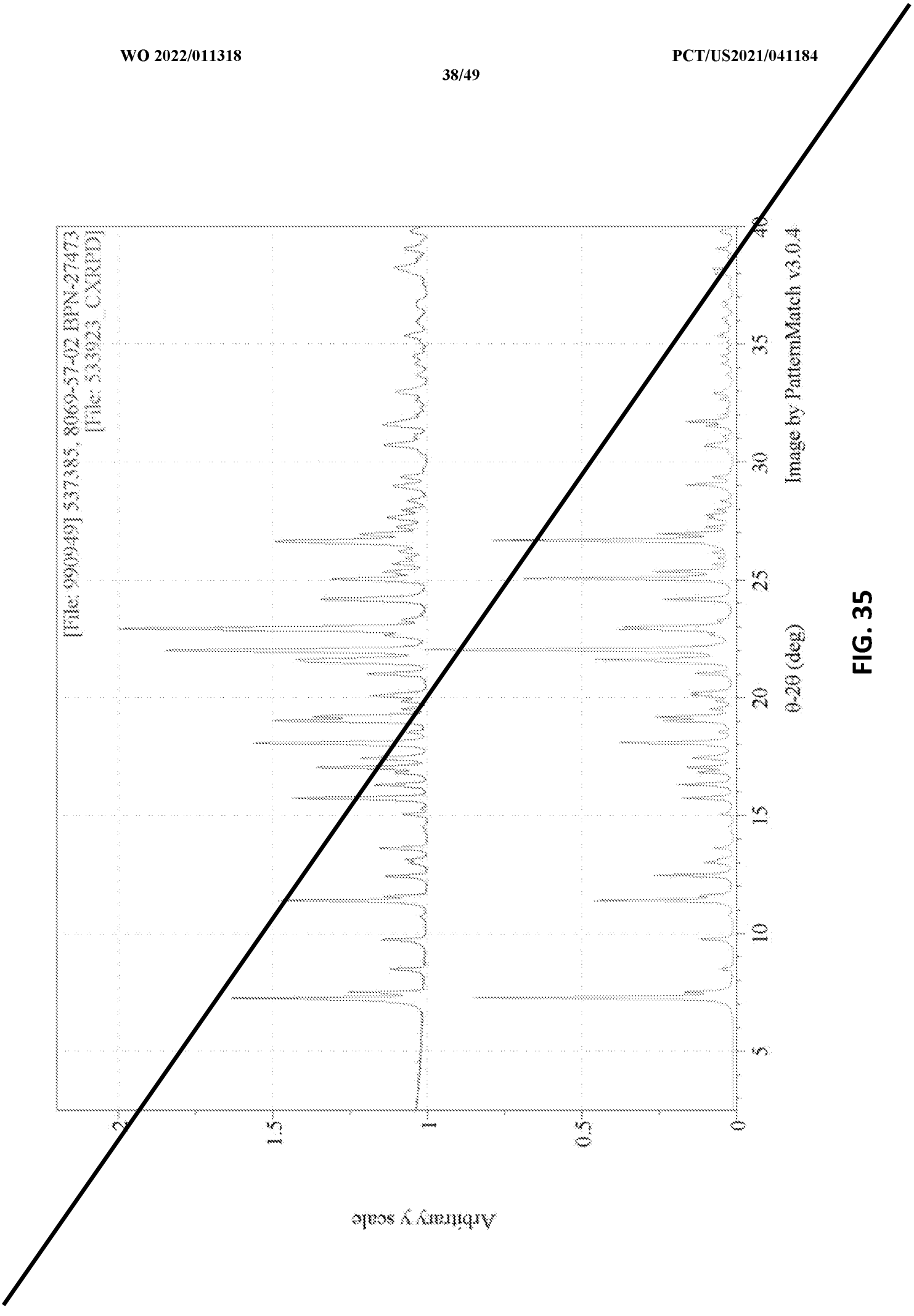

[File: 990491 337385, 8069-57-02 BPN-27473
[File: 333823 CXRPD]
Arbitrary y scale
0
0.5
1
1.5
2
5
10
15
20
25
30
35
40
θ-2θ (deg)
Image by PatternMatch v3.0.4

FIG. 35

FIG. 36A

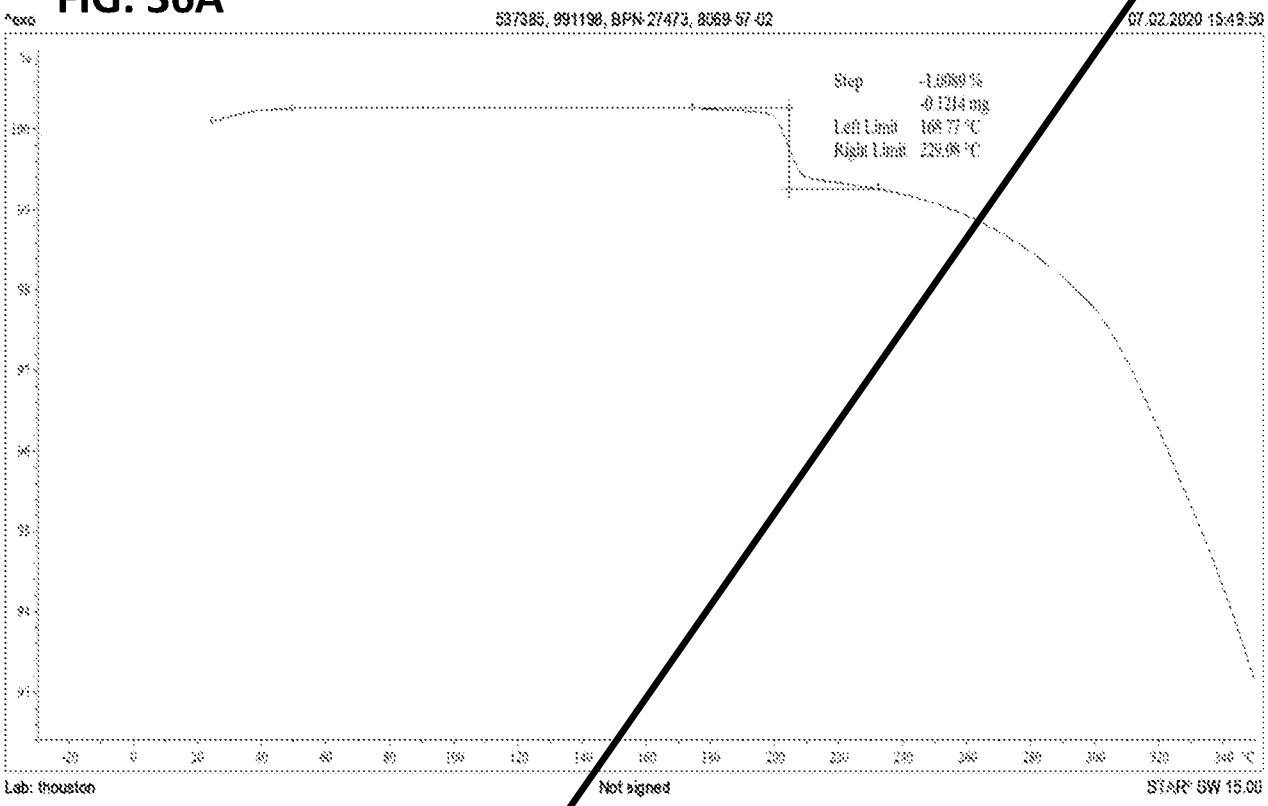
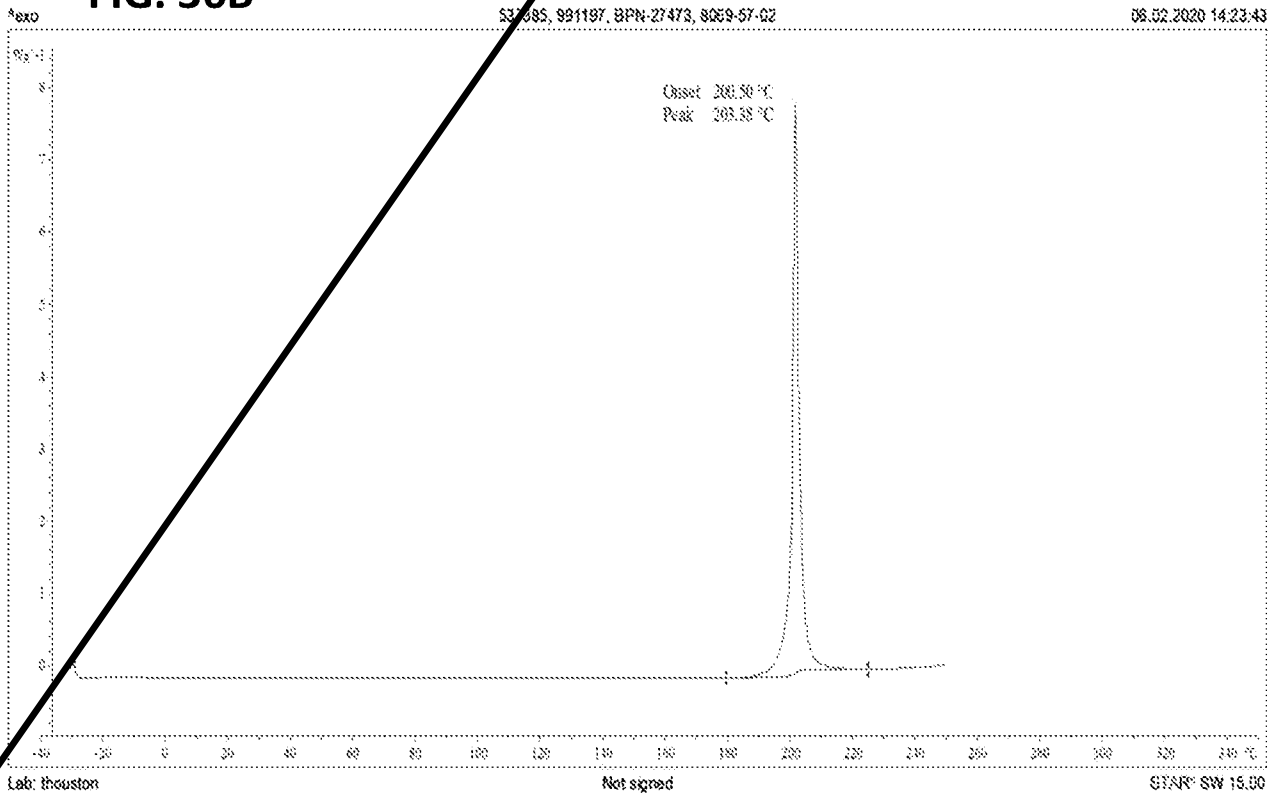


FIG. 36B



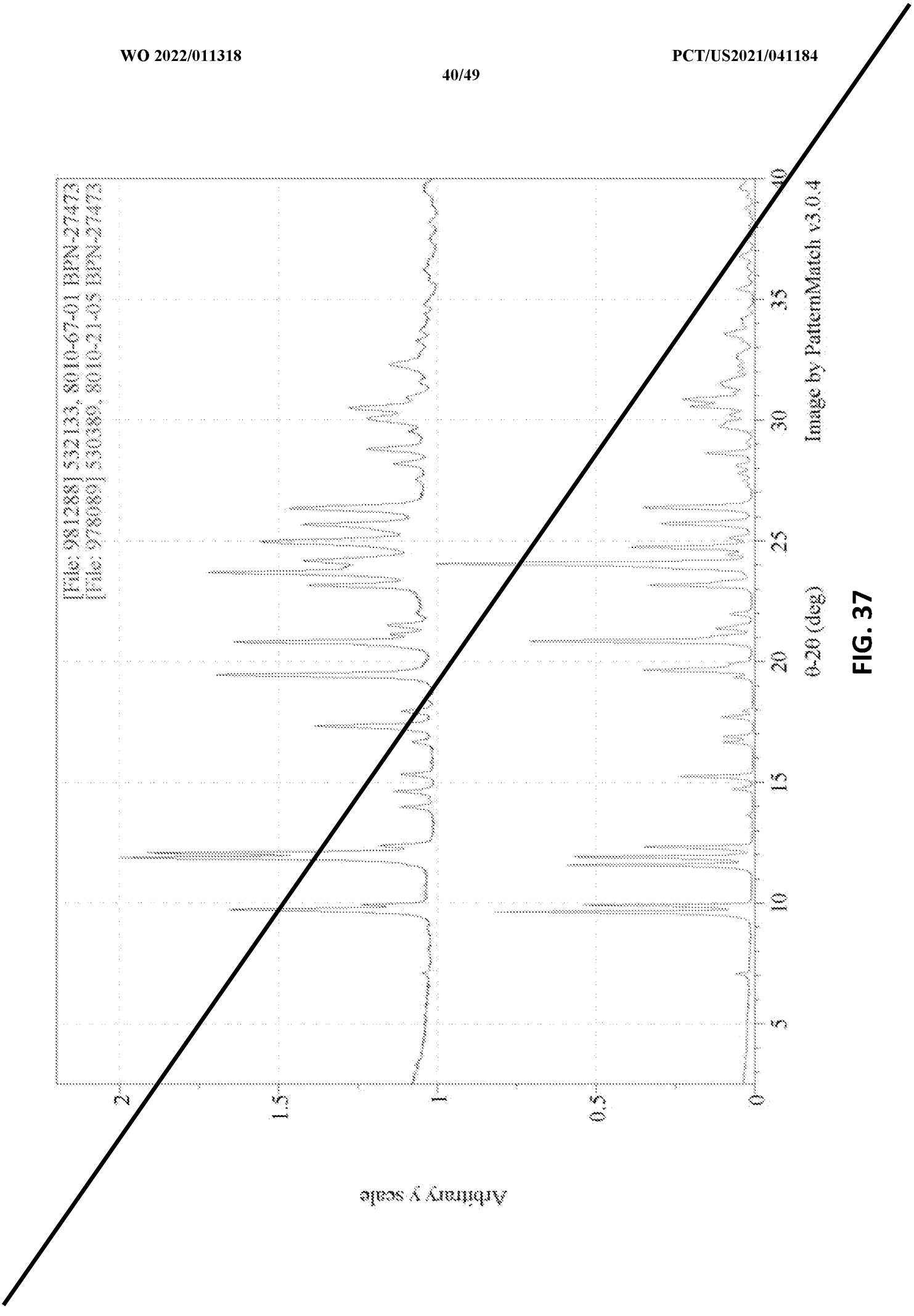
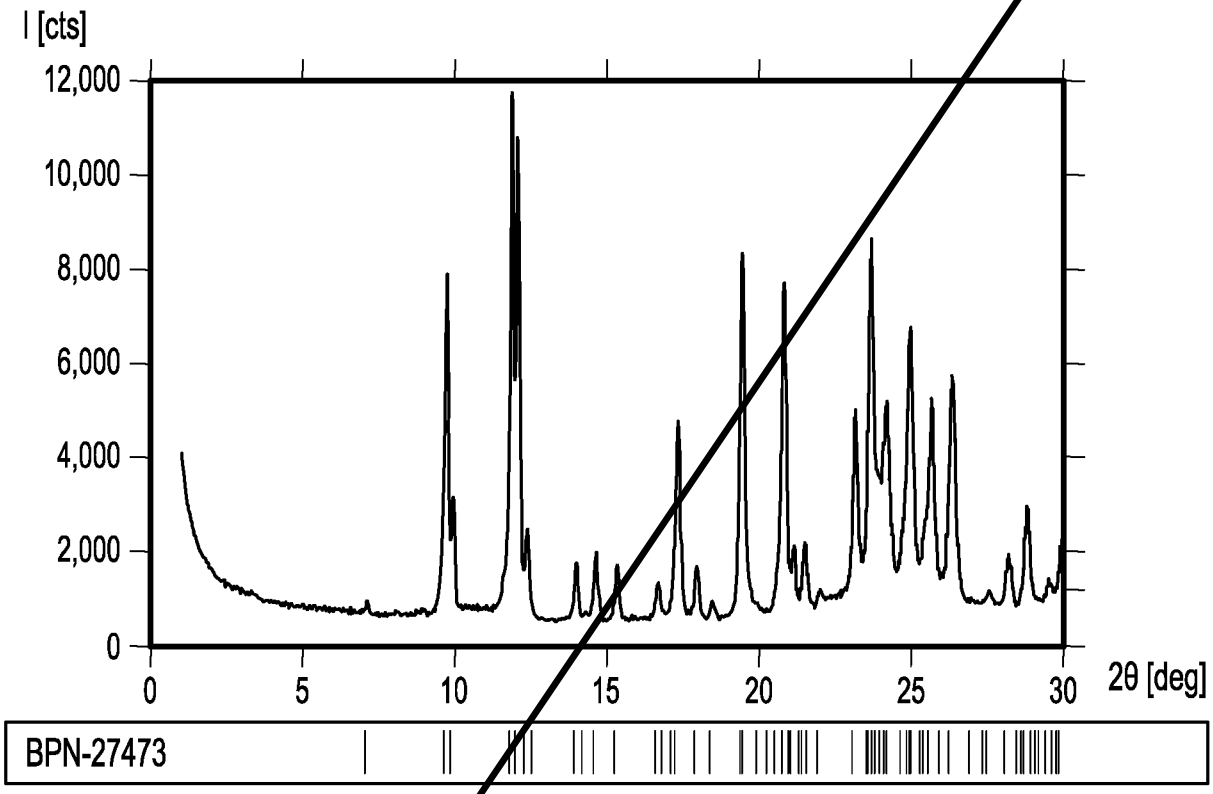

[File: 9812888] 532133, 8010-67-01 BPN-27473
[File: 9780869] 530389, 8010-21-05 BPN-27473
Arbitrary y scale
0
0.5
1
1.5
2
5
10
15
20
25
30
35
40
θ-20 (deg)
Image by PatternMatch v3.0.4

FIG. 37

Indexing results for XRPD file 981288 collected with Cu-Kα radiation.



	BPN-27473
Bravais Type	Triclinic
a [Å]	9.104
b [Å]	9.279
c [Å]	12.416
α [deg]	89.06
β [deg]	86.31
γ [deg]	77.95
Volume [Å^3/cell]	1,023.6
Chiral Contents?	Not Specified
Extinction Symbol	P -
Space Group(s)	Pc (1), P$\bar{1}$ (2)
Source	Triads Algorithm

Indexing is a non-cGMP activity

FIG. 38

Output Rendered using Triads v2.1.1

FIG. 39A

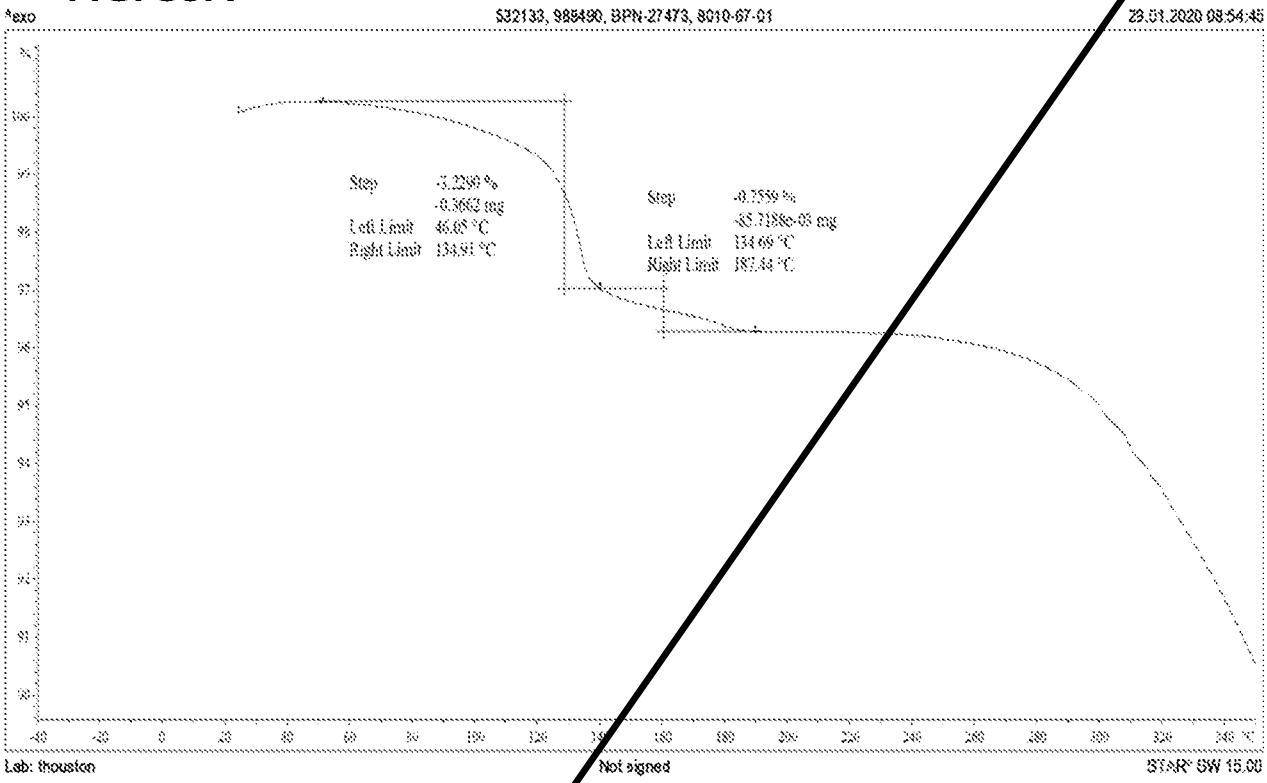
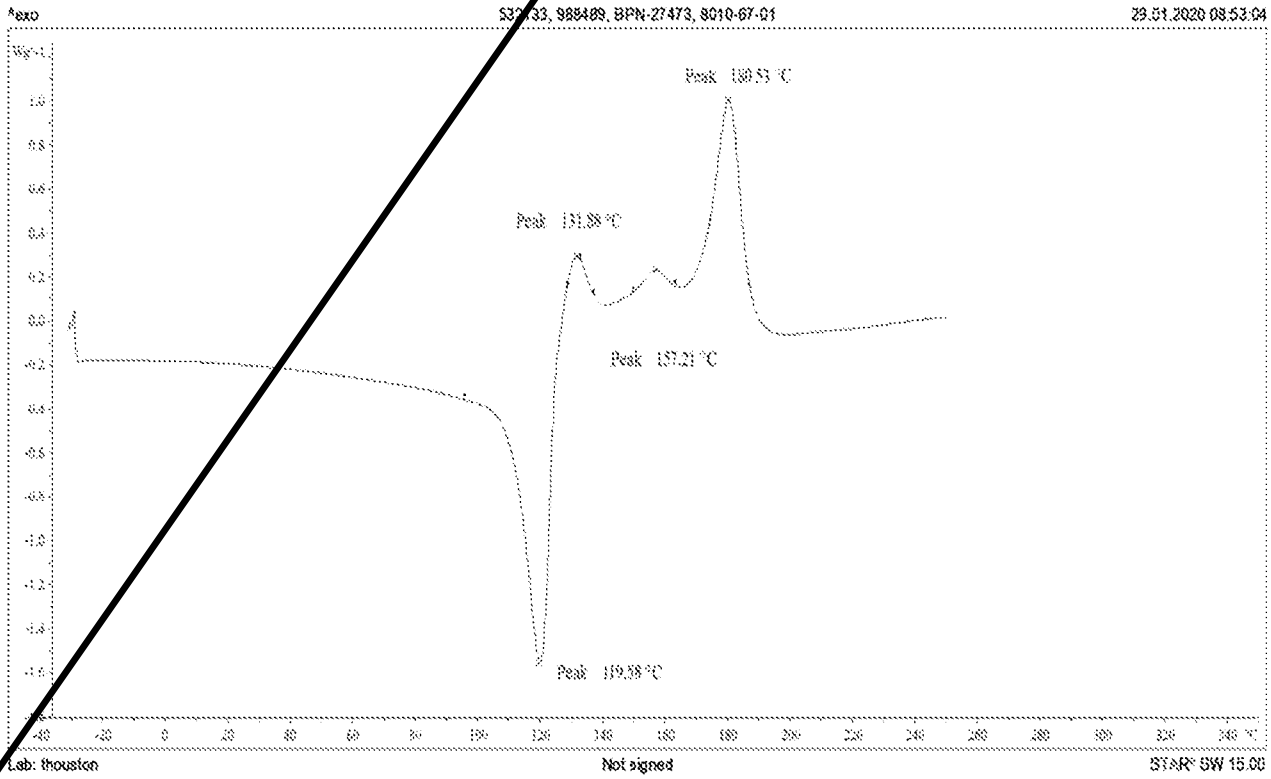


FIG. 39B



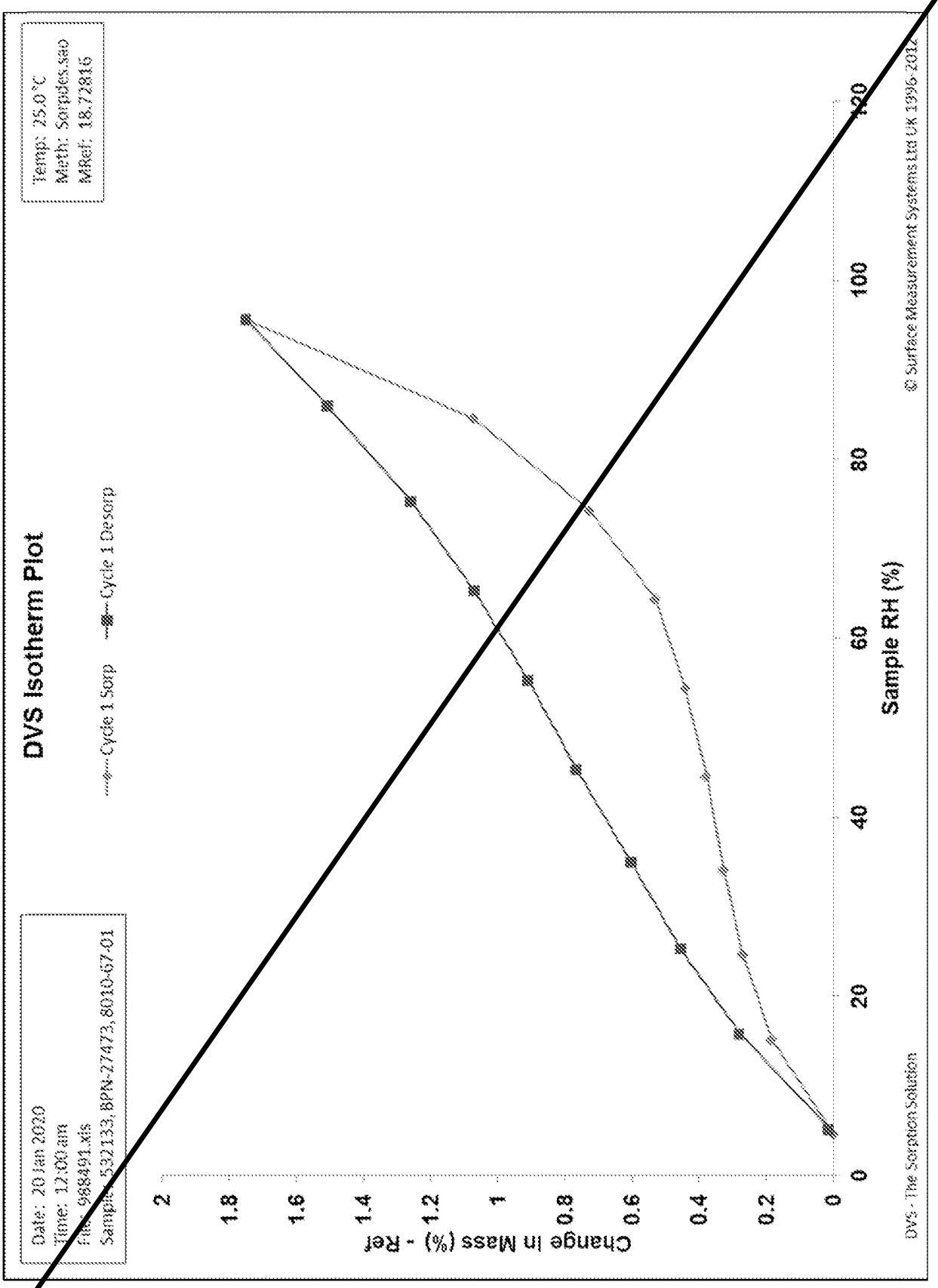
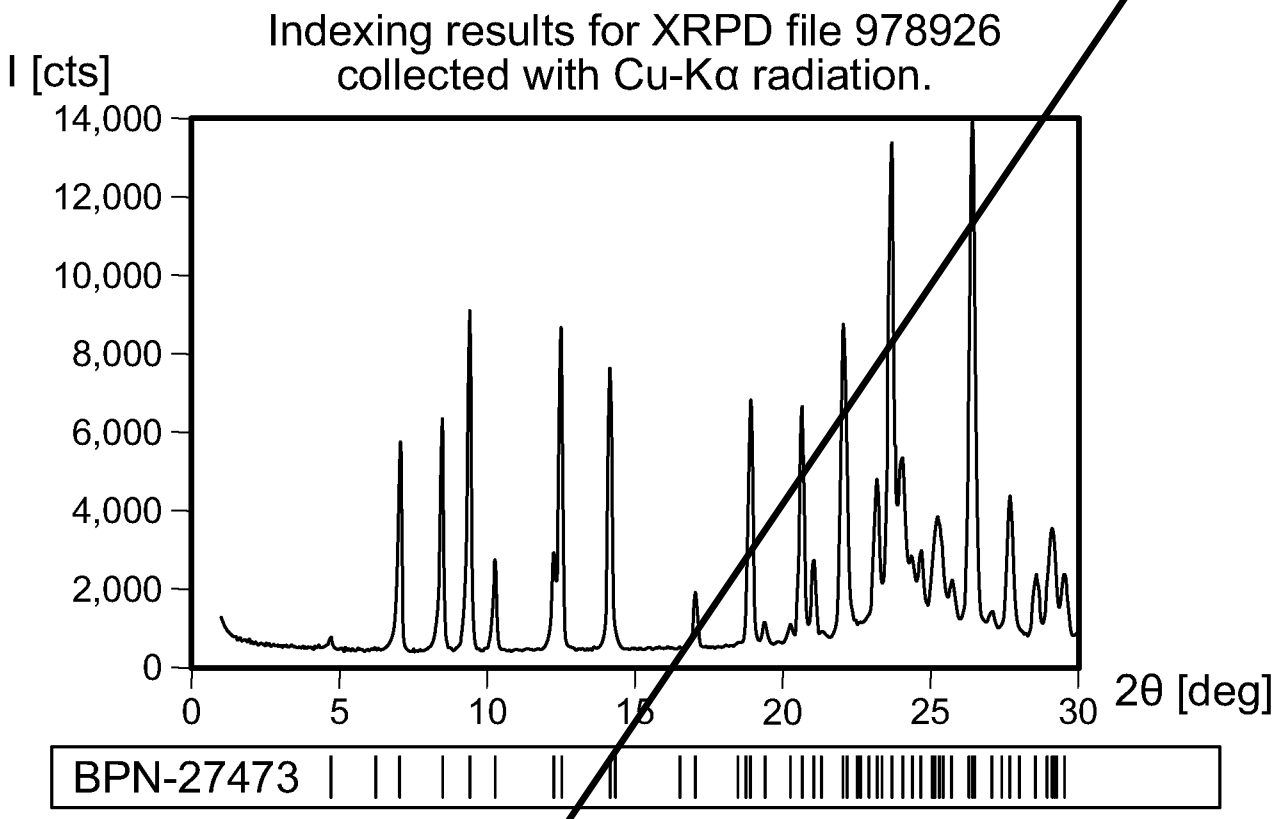

DVS Isotherm Plot
Date: 20 Jan 2020
Time: 12:00 am
File: 988491.xls
Sample: 532133, BPN-27473, 8010-67-01
Temp: 25.0 °C
Meth: Samples.sao
MRef: 18.72816
Cycle 1 Sorp
Cycle 1 Desorp
Change in Mass (%) - Ref
Sample RH (%)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
0
20
40
60
80
100
120
DVS - The Sorption Solution
© Surface Measurement Systems Ltd UK 1996-2012

FIG. 40



	BPN-27473
Bravais Type	Primitive Monoclinic
a [Å]	14.406
b [Å]	4.028
c [Å]	38.206
α [deg]	90
β [deg]	100.94
γ [deg]	90
Volume [Å^3/cell]	2,176.7
Chiral Contents?	Not Specified
Extinction Symbol	P 1 c 1
Space Group(s)	Pc (7), P2/c (13)
Source	Manual Input

FIG. 41

FIG. 42A

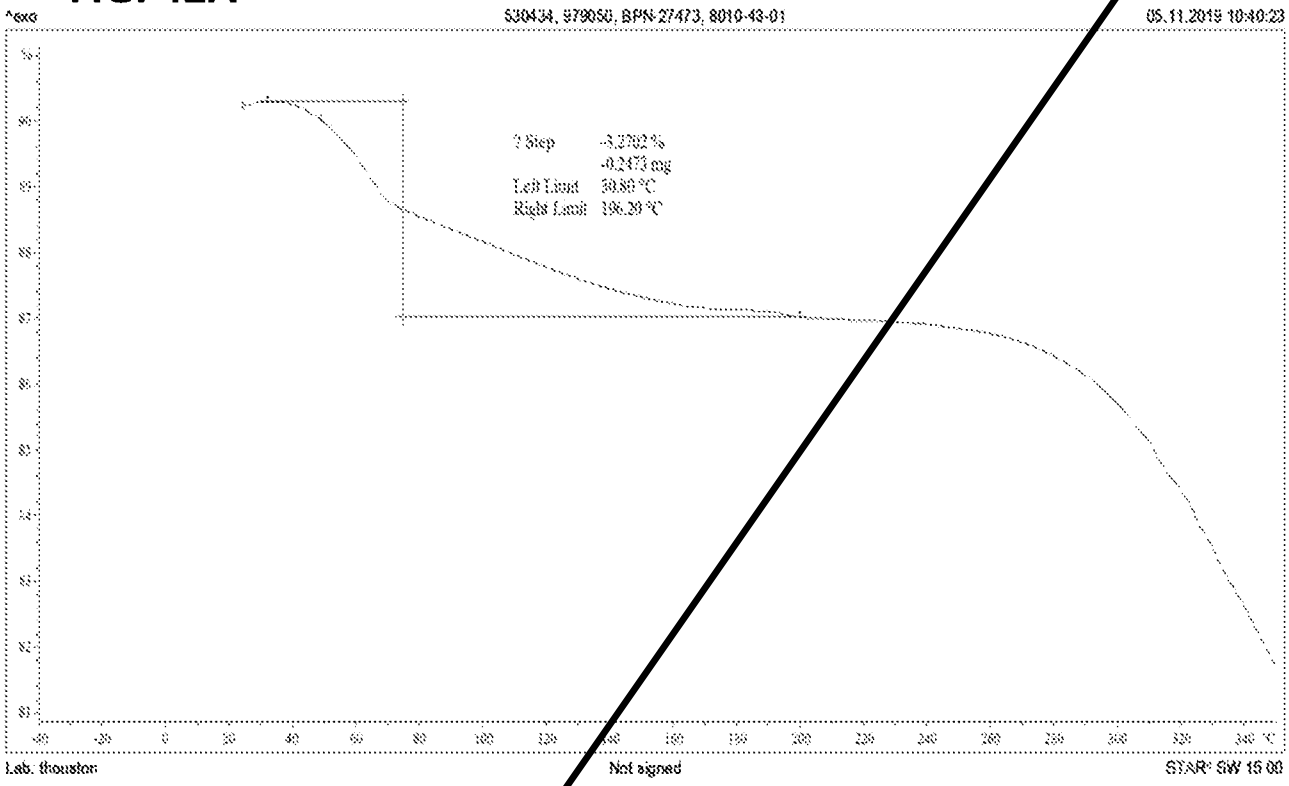
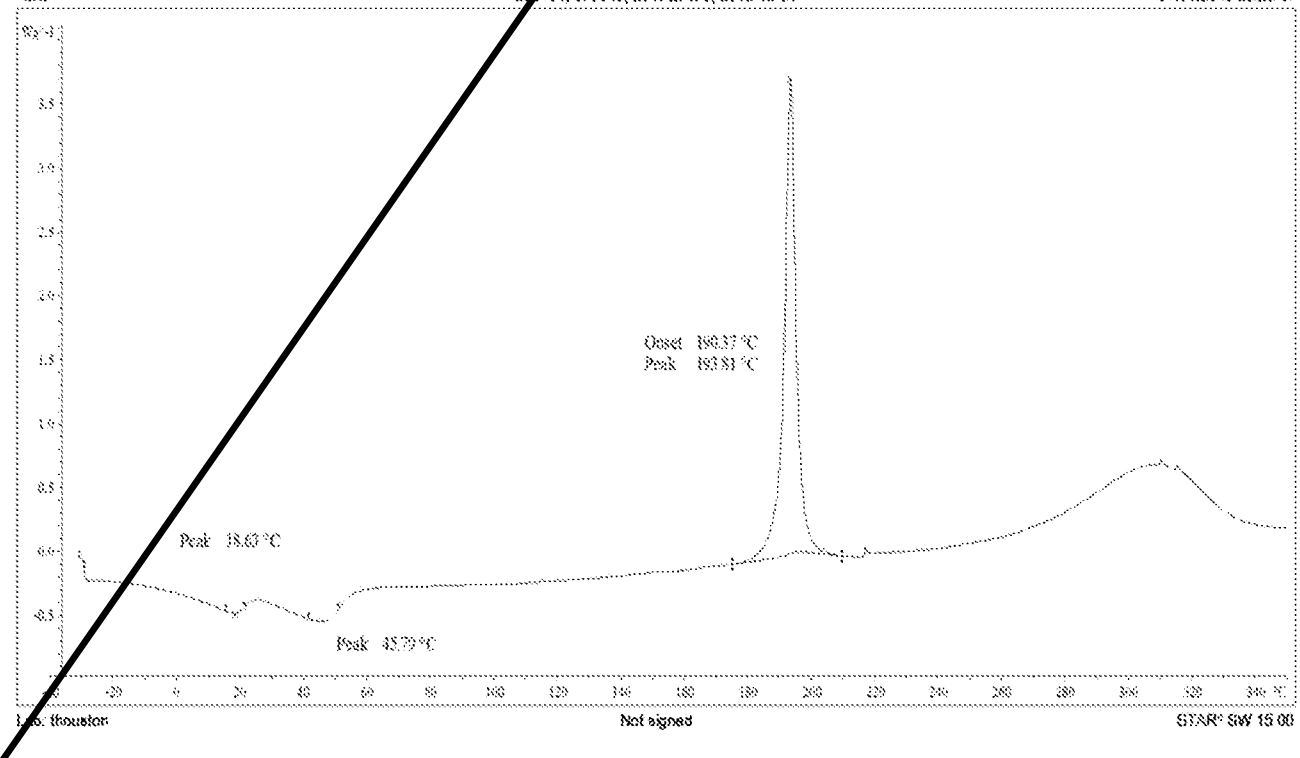


FIG. 42B



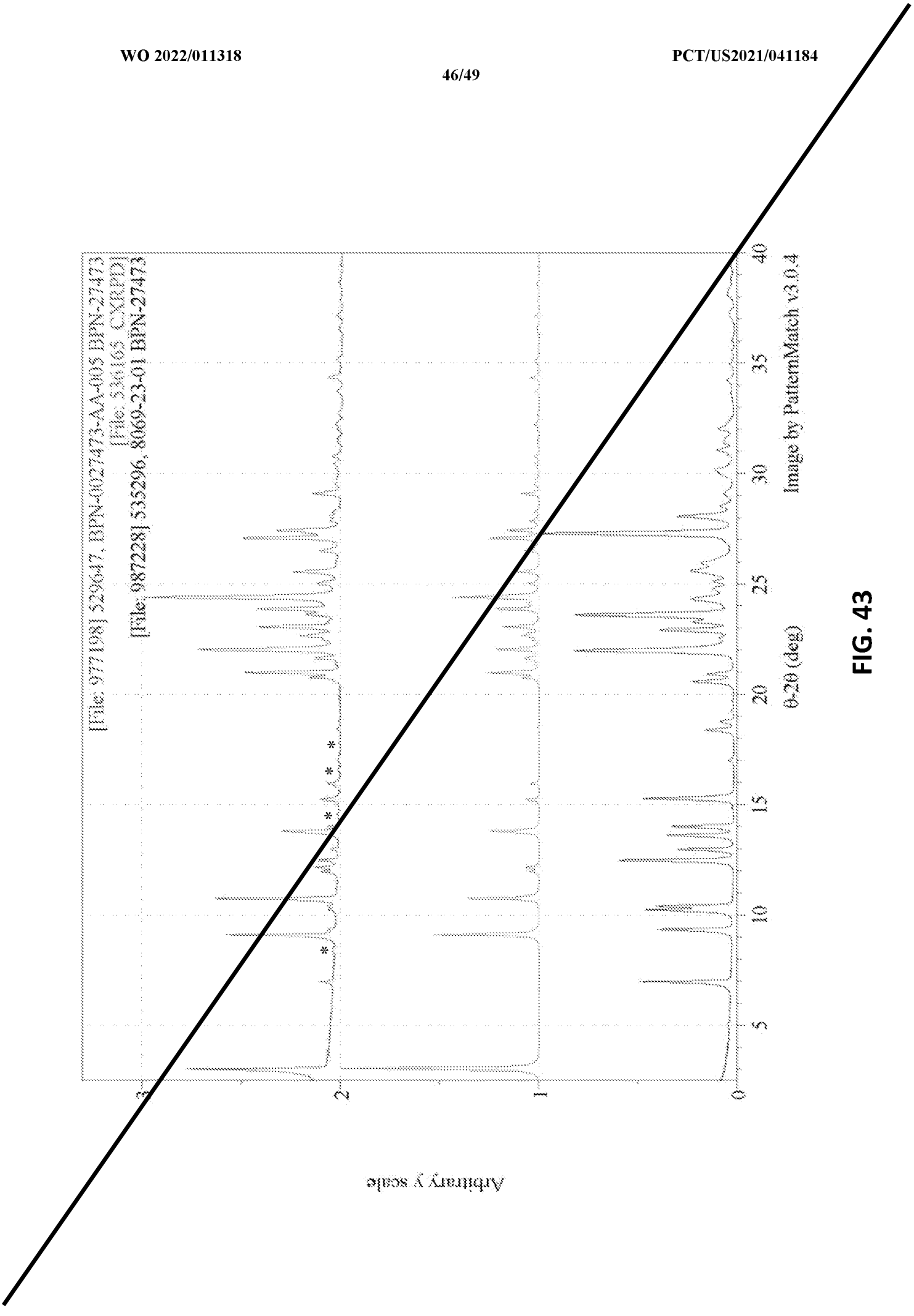

[File: 977198] 529647, BPN-0027473-AA-005 BPN-27473
[File: 536165 CXRPD]
[File: 987228] 535296, 8069-23-01 BPN-27473
Arbitrary y scale
0
1
2
3
5
10
15
20
25
30
35
40
θ-2θ (deg)
Image by PatternMatch v3.0.4

FIG. 43

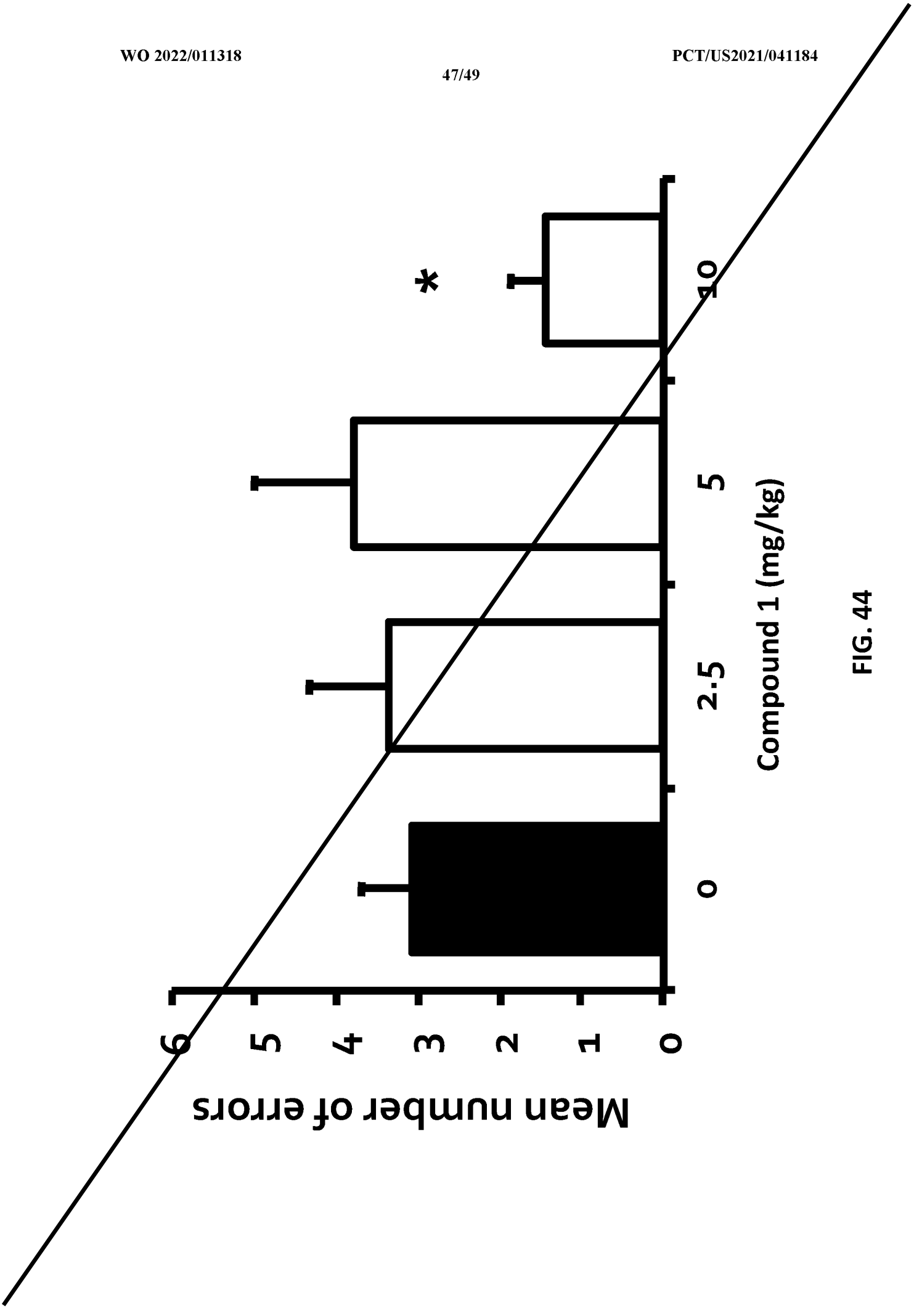


FIG. 44

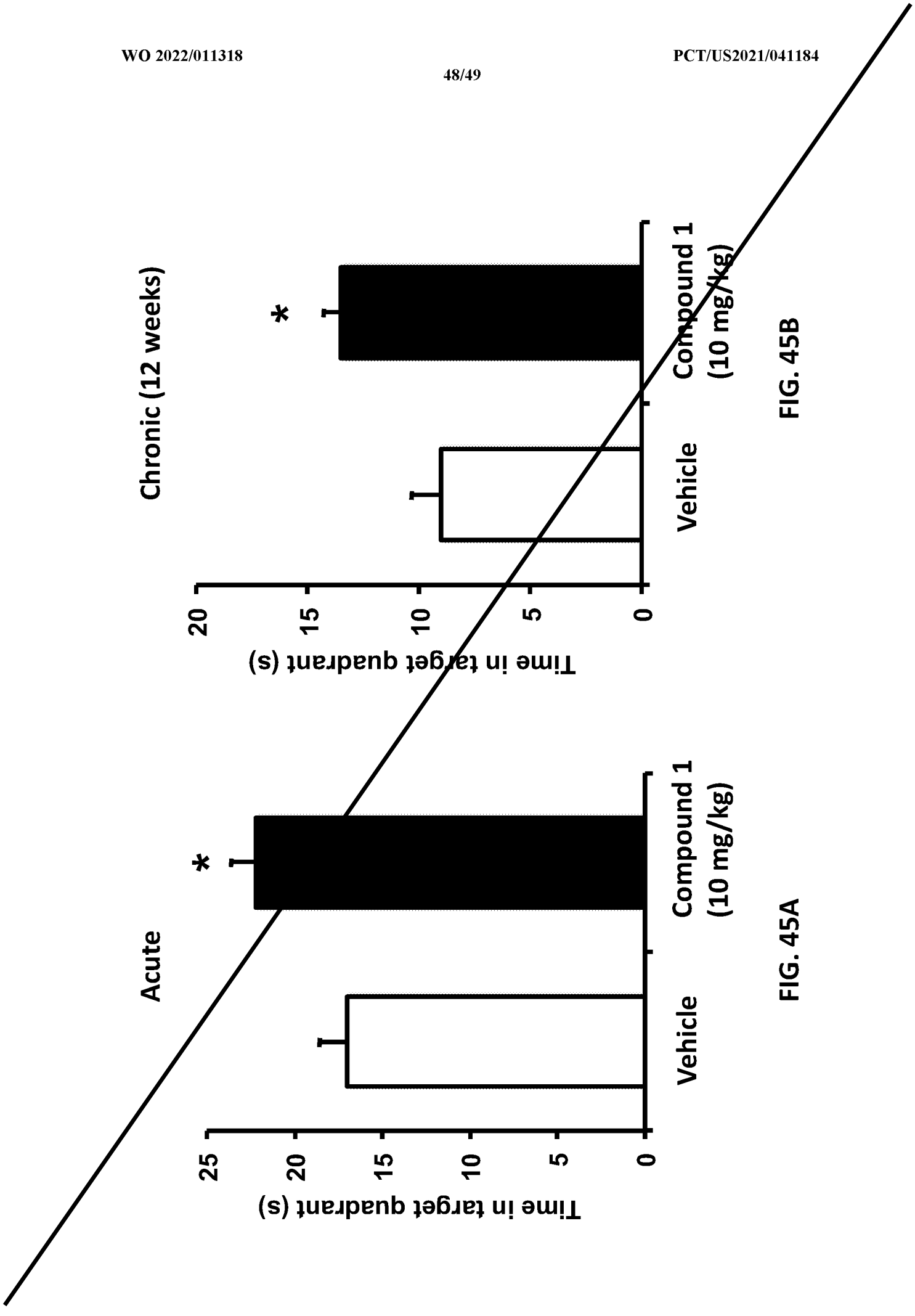


FIG. 45A

FIG. 45B

FIG. 46A

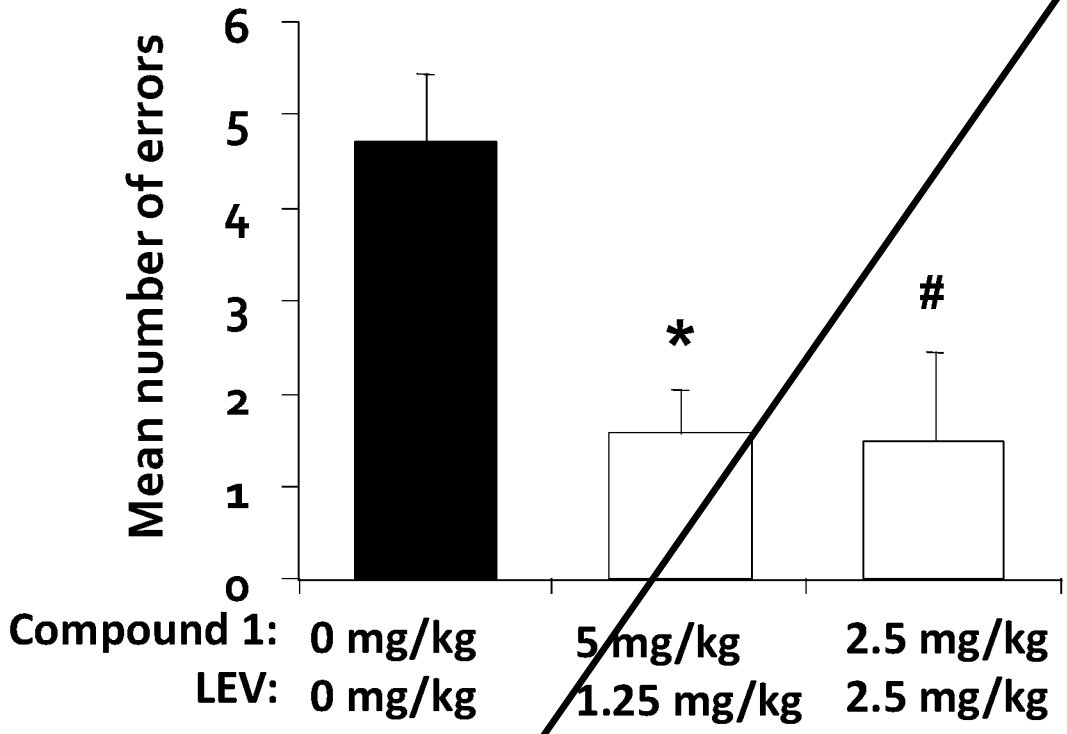
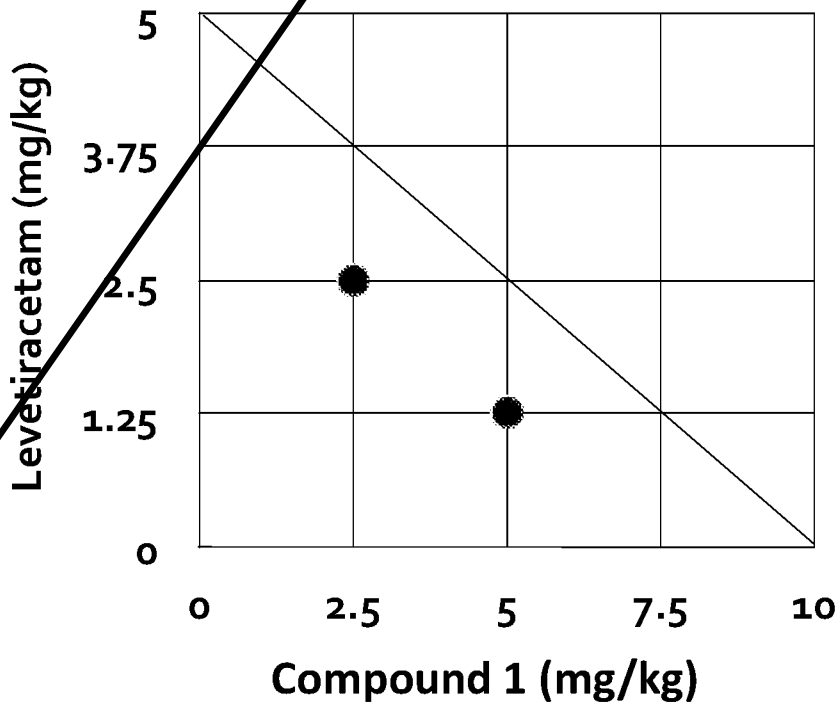
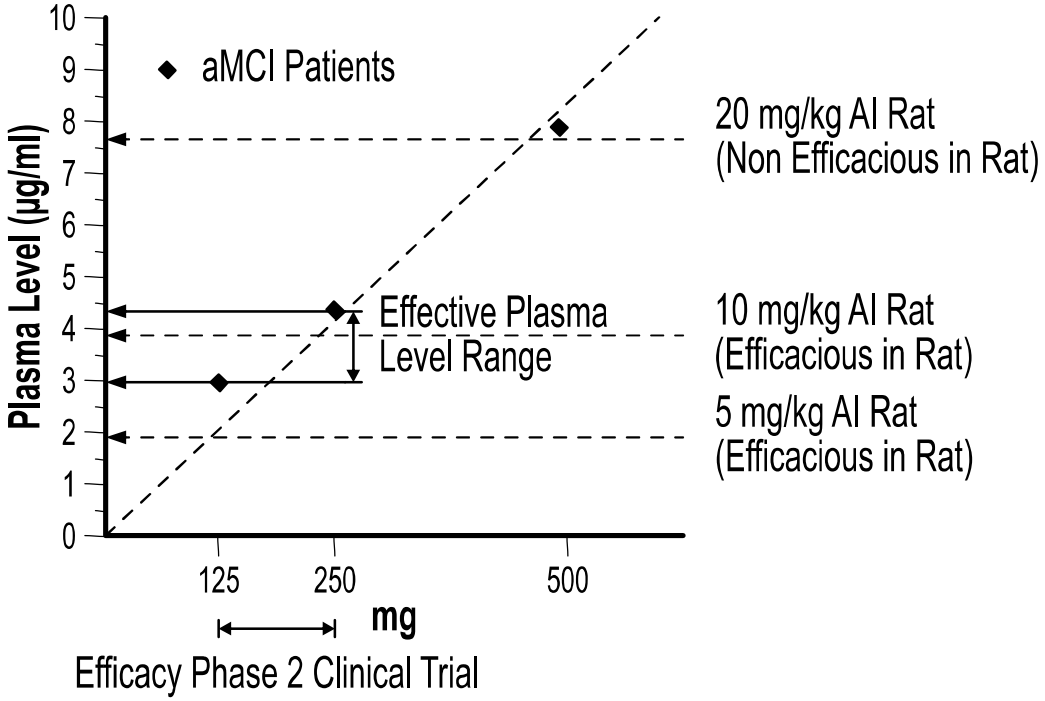


FIG. 46B





	Observed Efficacy (µg/mL)
Age-Impaired Rats	1.9 - 3.9
aMCI	2.9 - 4.4
	No Efficacy (µg/mL)
Age-Impaired Rats	7.9
aMCI	8.0

FIG. 1

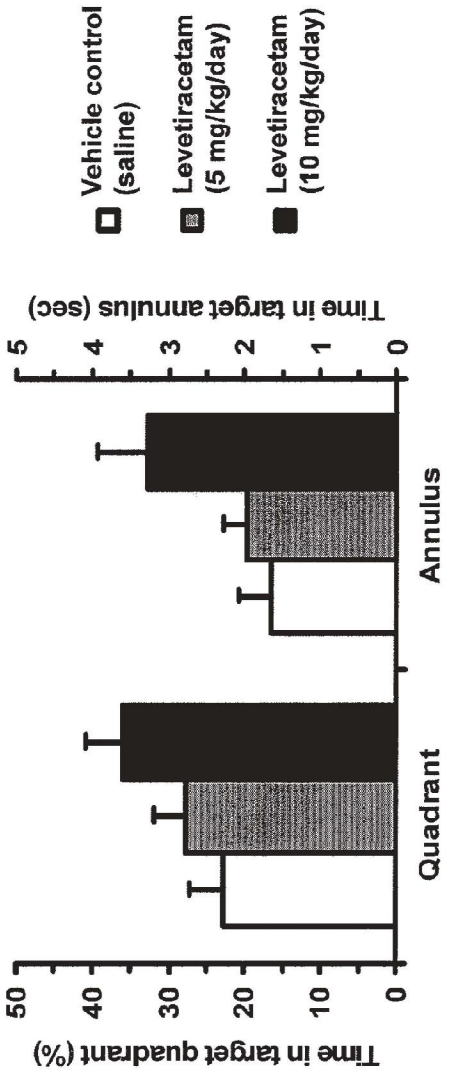
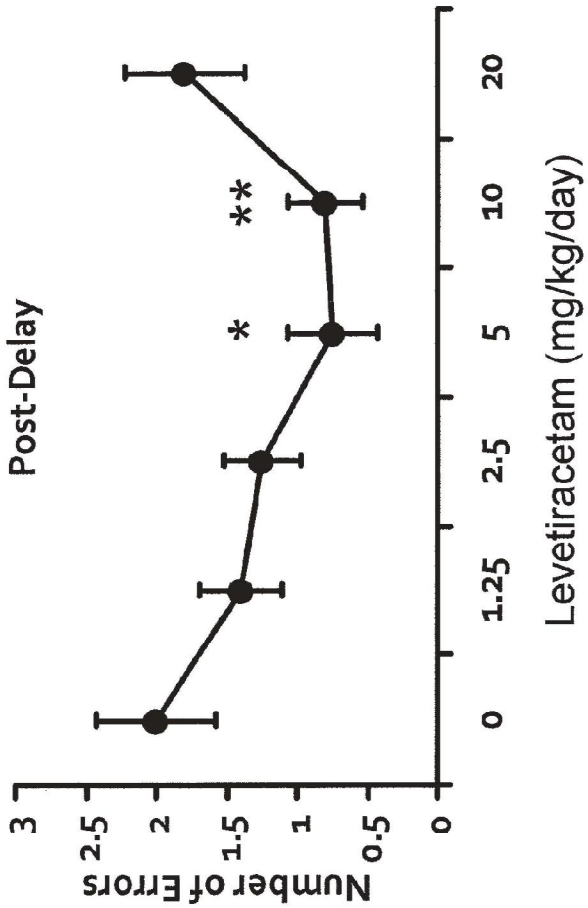

Vehicle control (saline)
Levetiracetam (5 mg/kg/day)
Levetiracetam (10 mg/kg/day)
Time in target annulus (sec)
0
1
2
3
4
5
Time in target quadrant (%)
0
10
20
30
40
50
Quadrant
Annulus

FIG. 2



* t(9) = 2.18, p = 0.057
** t(9) = 2.37, p = 0.042

FIG. 3

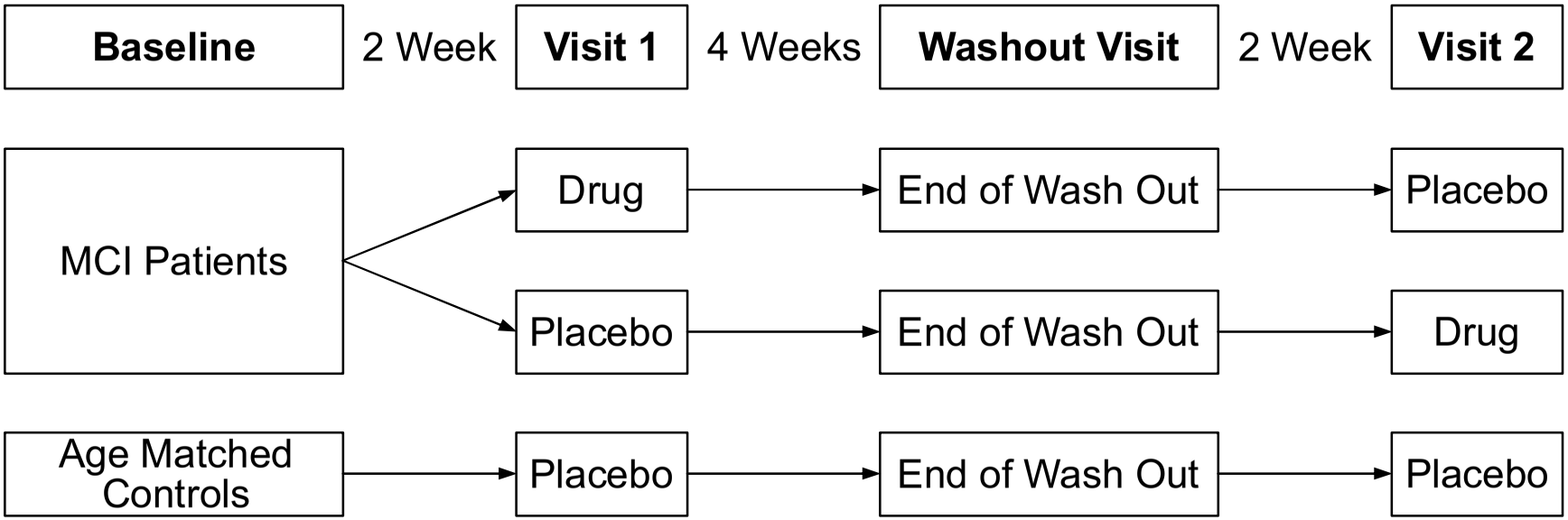
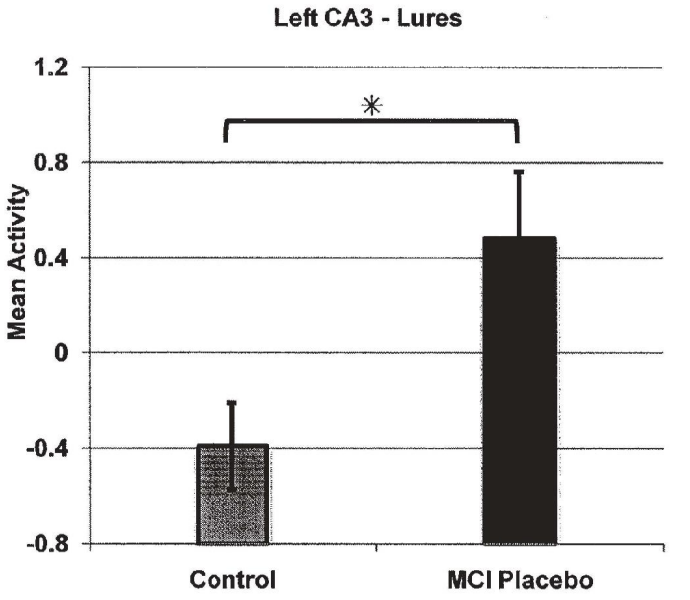
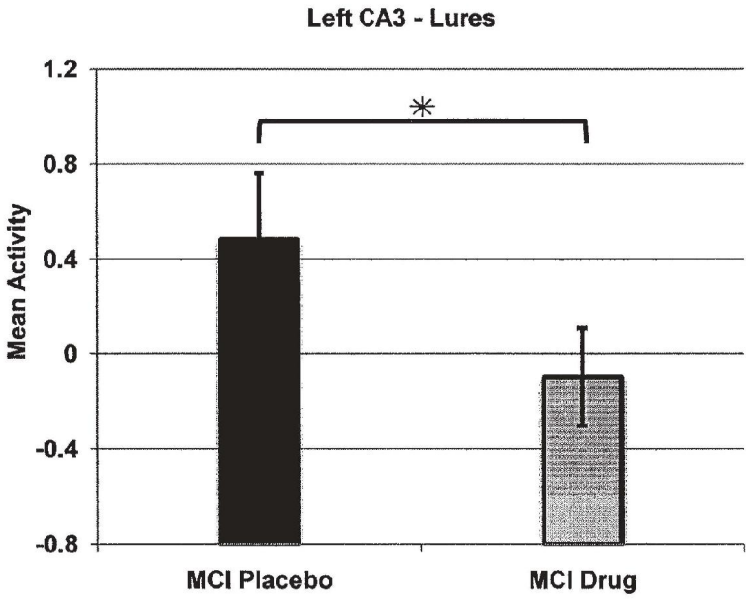

Baseline
2 Week
Visit 1
4 Weeks
Washout Visit
2 Week
Visit 2
MCI Patients
Drug
End of Wash Out
Placebo
Placebo
End of Wash Out
Drug
Age Matched Controls
Placebo
End of Wash Out
Placebo

FIG. 4



*Independent samples t-test: t = -2.636, p = 0.013

FIG. 5A



*Paired samples t-test: t = 2.276, p = 0.037

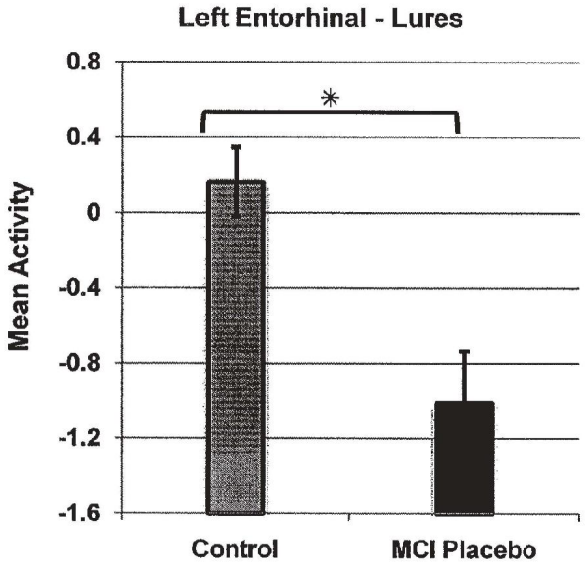
FIG. 5B

Left CA3 Lures

Group	Mean Activity	Standard Error
Control	-0.39129	0.182628
MCI Placebo	0.48440	0.277487
MCI Drug	-0.09653	0.205892

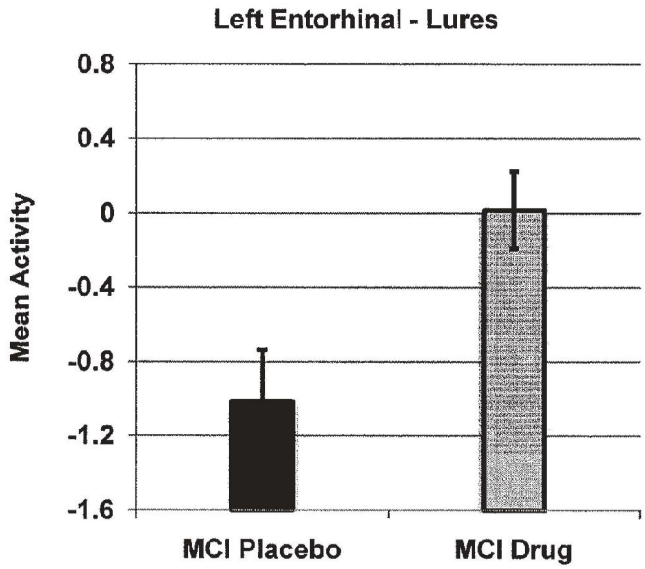
FIG. 5C

fMRI entorhinal activation in amnestic MCI is normalized by drug treatment



*Independent samples t-test: t = 3.278, p = 0.003

FIG. 6A



Paired samples t-test: t = -1.600, p= 0.129

FIG. 6B

Left Entorhinal Lures

Group	Mean Activity	Standard Error
Control	0.16444	0.143864
MCI Placebo	-1.01273	0.329062
MCI Drug	0.016291	0.411762

FIG. 6C

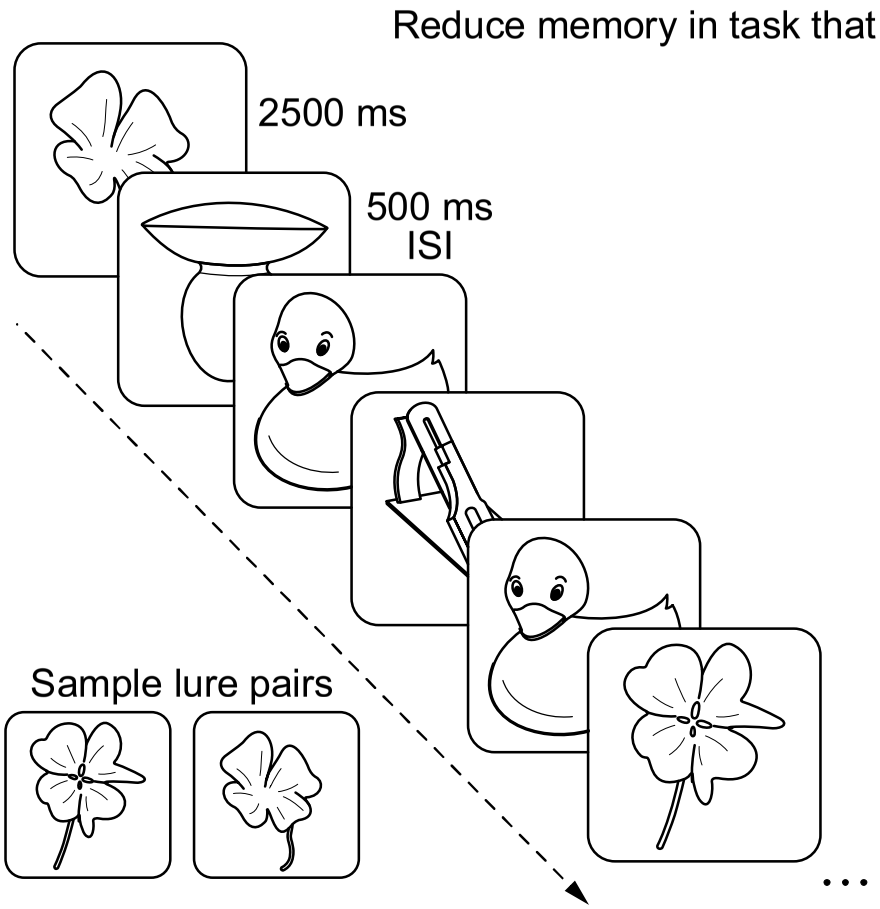

Reduce memory in task that taxes pattern separation
2500 ms
500 ms
ISI
Sample lure pairs

FIG. 7A

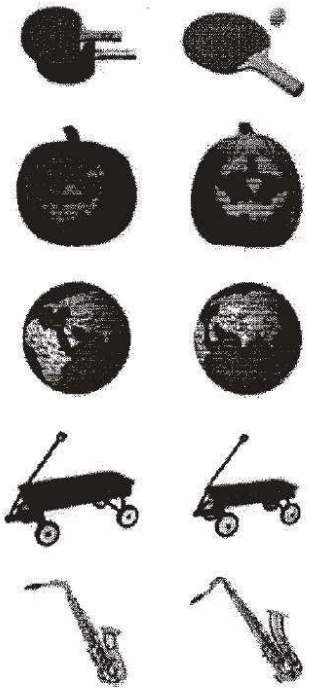


FIG. 7B

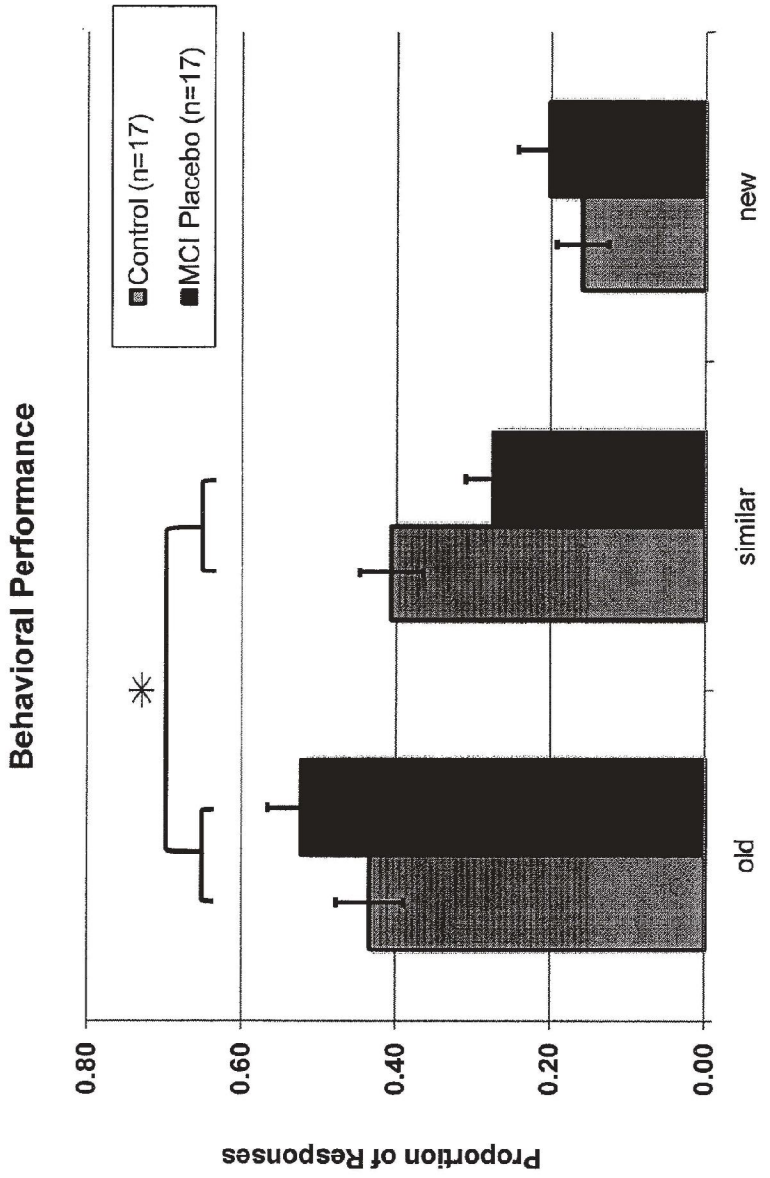

Behavioral Performance
Control (n=17)
MCI Placebo (n=17)
*
Proportion of Responses
0.80
0.60
0.40
0.20
0.00
old
similar
new
Control vs. MCI Placebo by Old vs. Similar: F= 7.687, p = 0.009

FIG. 8

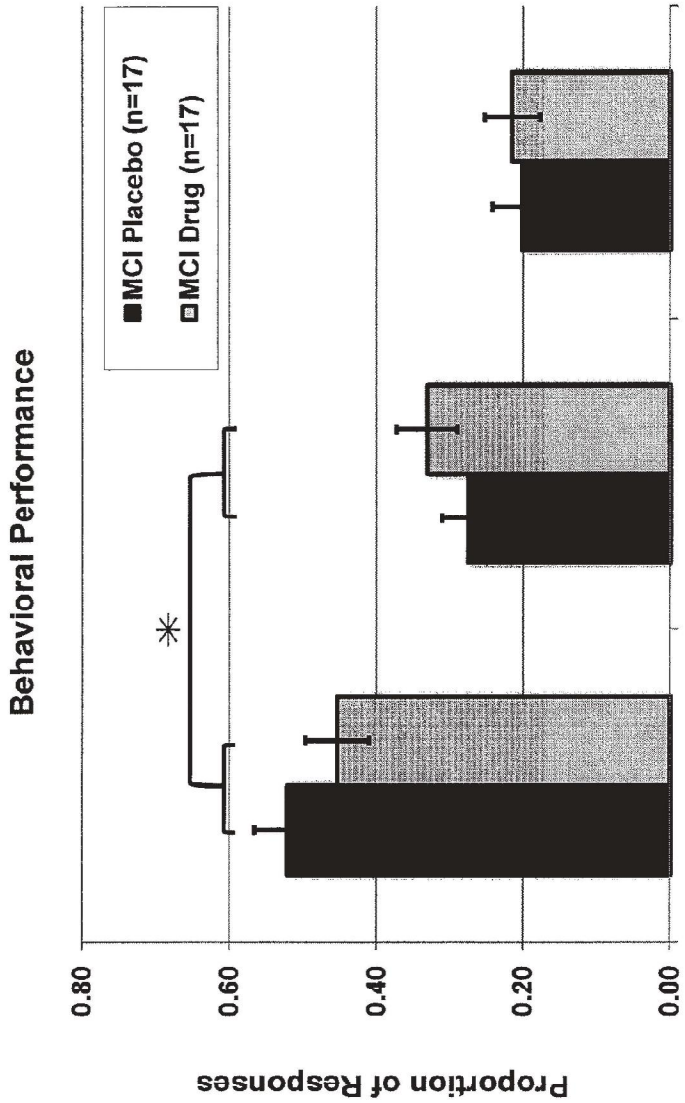

Behavioral Performance
MCI Placebo (n=17)
MCI Drug (n=17)
Proportion of Responses
0.80
0.60
0.40
0.20
0.00
old
similar
new
*
MCI Drug vs. MCI Placebo by Old vs. Similar: F = 5.028, p = 0.039

FIG. 9

Behavioral Performance

Control Subjects	Proportion of Responses	Standard Error
Old	0.433676	0.04426
Similar	0.406771	0.04135
New	0.159553	0.03312
MCI Placebo Subjects	**Proportion of Responses**	**Standard Error**
Old	0.52262	0.04871
Similar	0.27549	0.03956
New	0.20188	0.04528
MCI Drug Subjects	**Proportion of Responses**	**Standard Error**
Old	0.45361	0.04825
Similar	0.33144	0.04592
New	0.21494	0.04202

FIG. 10

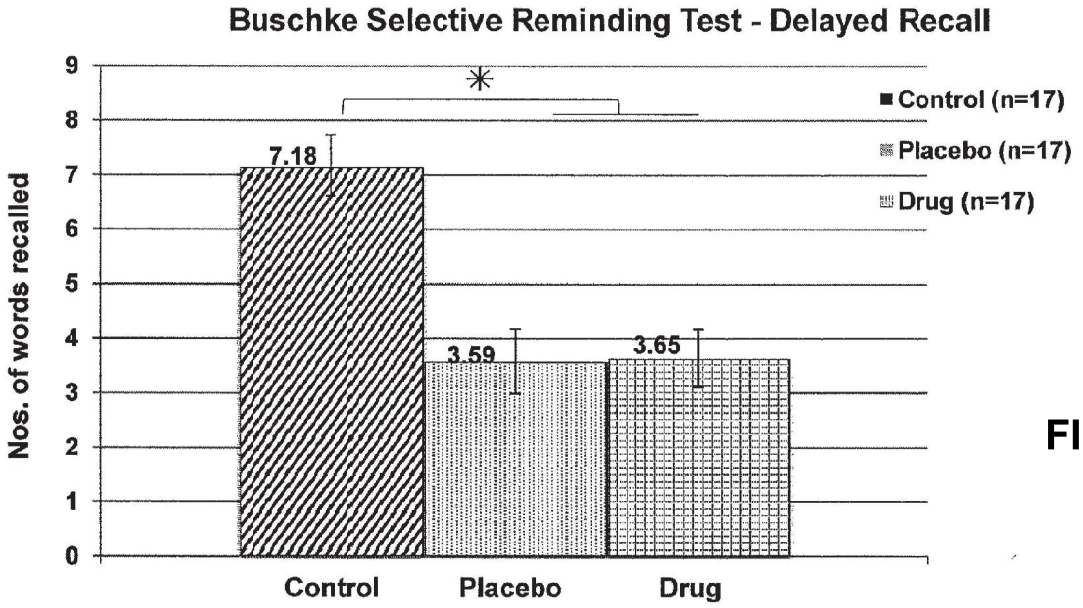


FIG. 11A

Group	Mean	Standard Error	Delayed (p-value)
Control	7.18	0.56	Control vs. Placebo: <0.001
MCI Placebo	3.59	0.59	Control vs. Drug: <0.001
MCI Drug	3.65	0.53	Placebo vs. Drug: 0.887

FIG. 11B

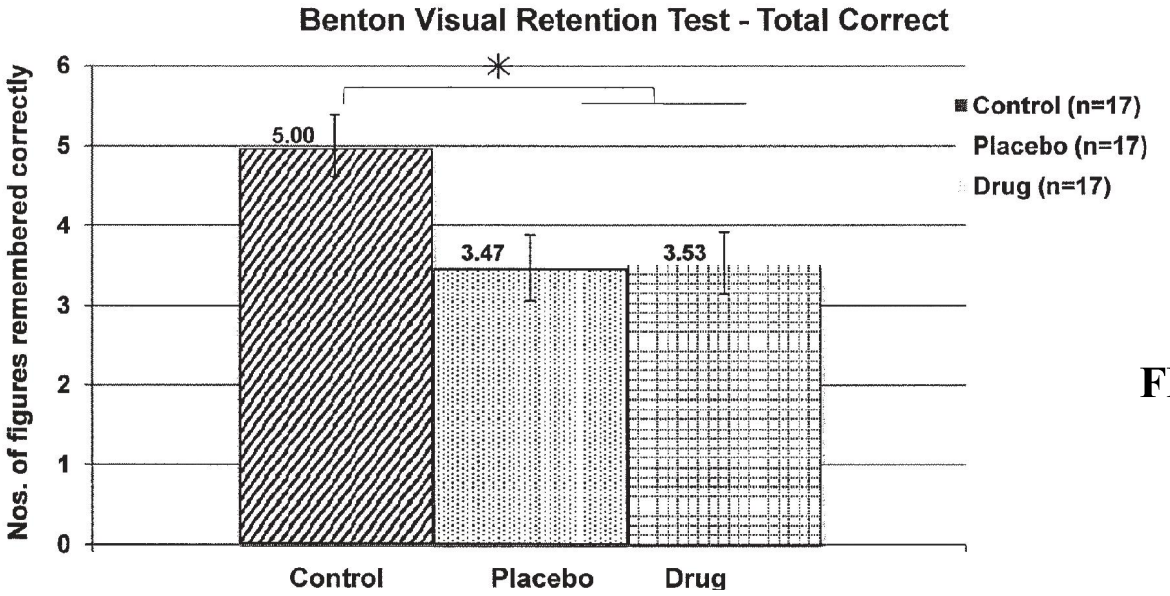


FIG. 12A

Group	Mean	Standard Error	Total Correct (p-value)
Control	5.00	0.38	Control vs. Placebo: 0.011
MCI Placebo	3.47	0.41	Control vs. Drug: 0.011
MCI Drug	3.53	0.38	Placebo vs. Drug: 0.805

FIG. 12B

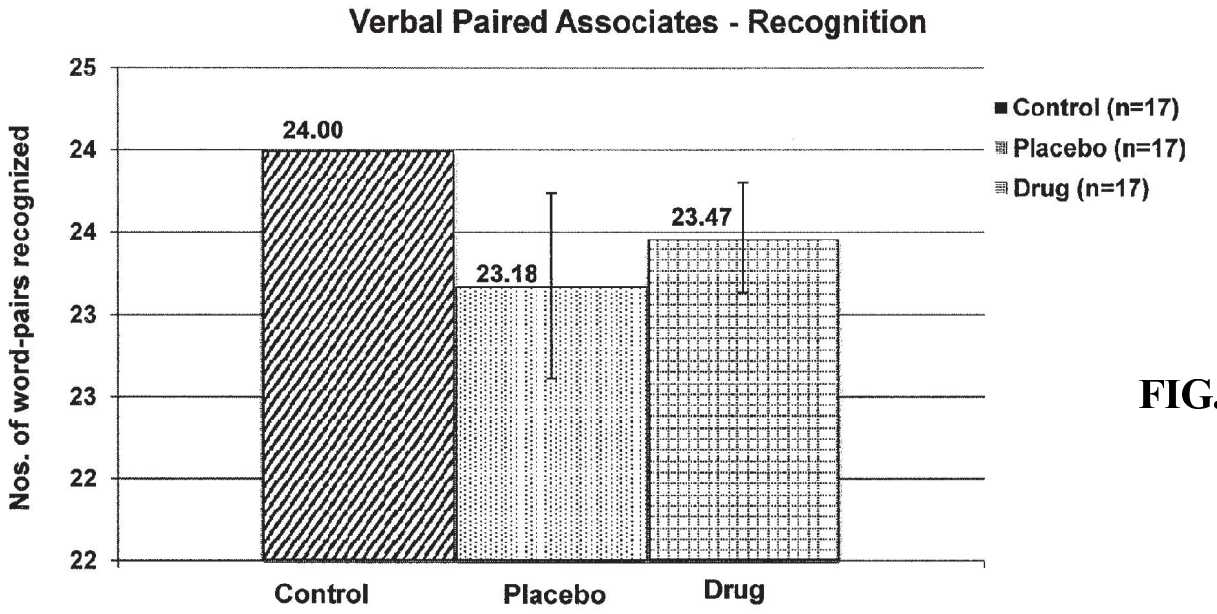


FIG. 13A

Group	Mean	Standard Error	Recognition (p-value)
Control	24.00	0.00	Control vs. Placebo: 0.154
MCI Placebo	23.18	0.56	Control vs. Drug: 0.122
MCI Drug	23.47	0.33	Placebo vs. Drug: 0.428

FIG. 13B

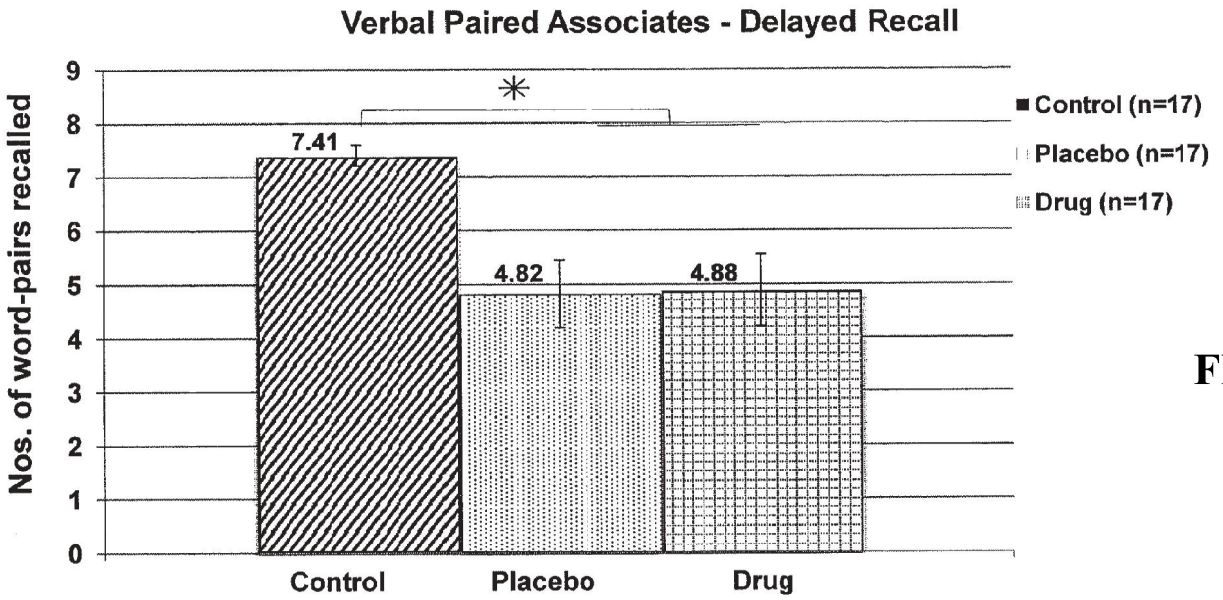


FIG. 14A

Group	Mean	Standard Error	Delayed Recall (p-value)
Control	7.41	0.19	Control vs. Placebo: <0.001
MCI Placebo	4.82	0.63	Control vs. Drug: 0.001
MCI Drug	4.88	0.67	Placebo vs. Drug: 0.848

FIG. 14B

Study Status

	Control Subjects	MCI Subjects	Total Subjects
Participated in Screening	26	32	58
Screening Failures	4	9	13
Enrolled	22	23	45
Removed or Withdrew from Study	5	6	11
Total Subjects Used in Analysis	17	17	34

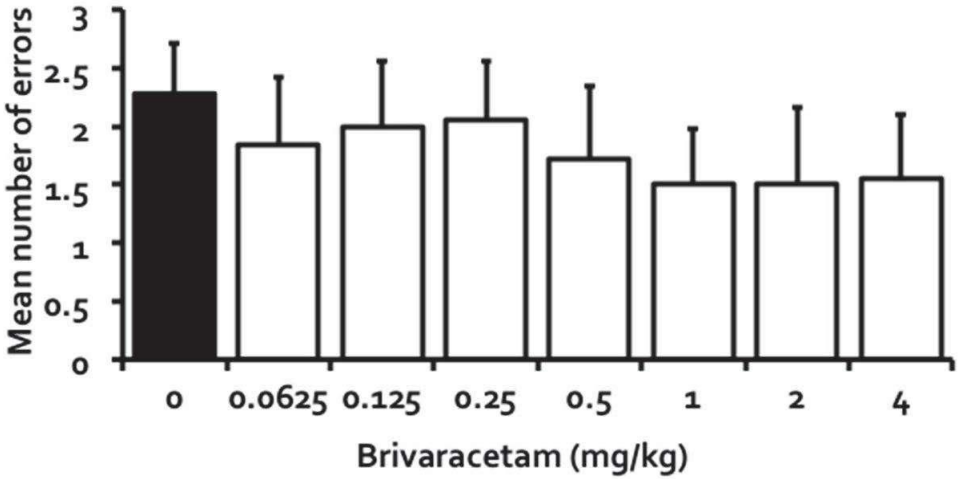
FIG. 15A

Characteristics of Study Samples

	Control Subjects	MCI Subjects	p
N	17	17	
Sex (M/F)	9/8	6/11	0.307
Age (yrs)	69.3 (7.0)	72.9 (8.9)	0.201
Education (yrs)	15.9 (2.6)	15.8 (2.9)	0.951
Race (Caucasian/African American)	17/0	14/3	0.074
Hispanic or Latino (y/n)	0/17	1/16	0.317

FIG. 15B

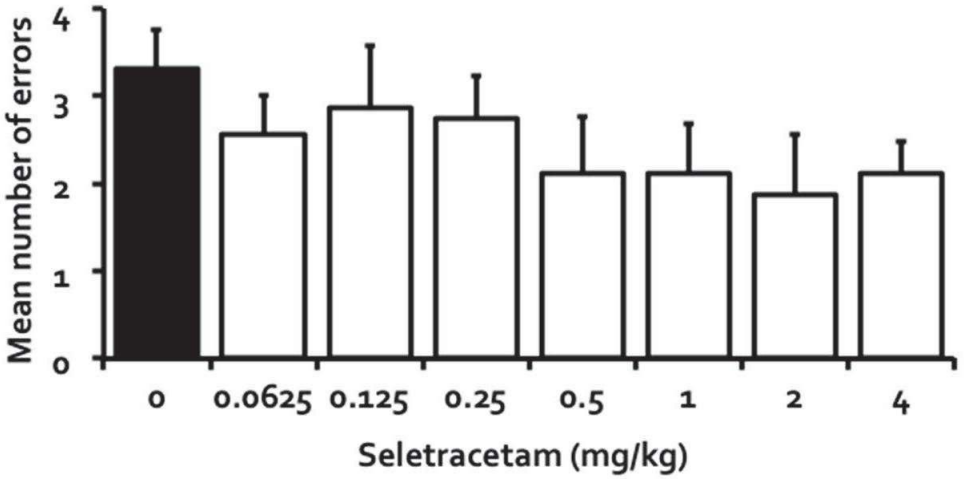
Brivaracetam Treatment: Radial Arm Maze Task



Repeated measures ANOVA for within subject contrasts, $F(1, 8) = 6.046$, $p = 0.039$
Means and SEMs are shown

FIG. 16

Seletracetam Treatment: Radial Arm Maze Task



Repeated measures ANOVA for within subject contrasts, $F(1, 7) = 12.577$, $p = 0.009$
Means and SEMs are shown

FIG. 17

Performance of cognitively impaired aged rats (n = 3/group)
treated with brivaracetam (2 mg/kg/day after 14 days) in the water maze task

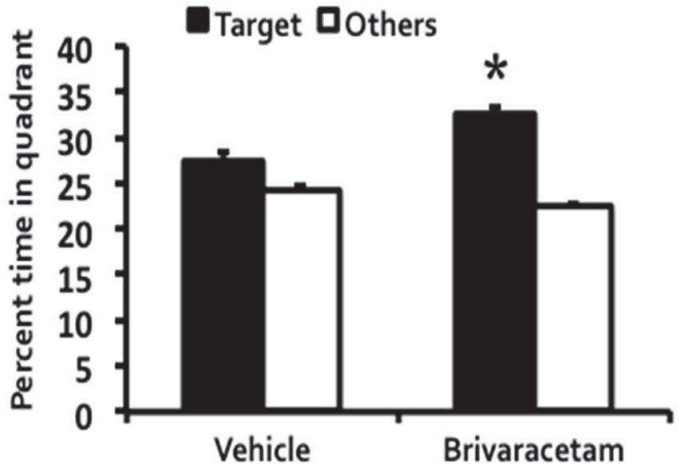


FIG. 18A

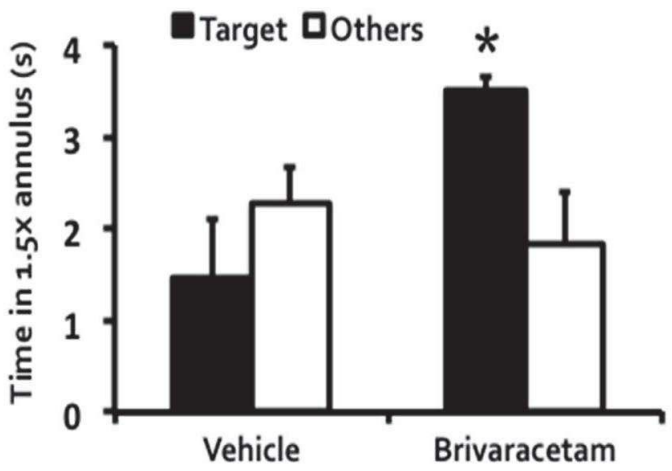


FIG. 18B

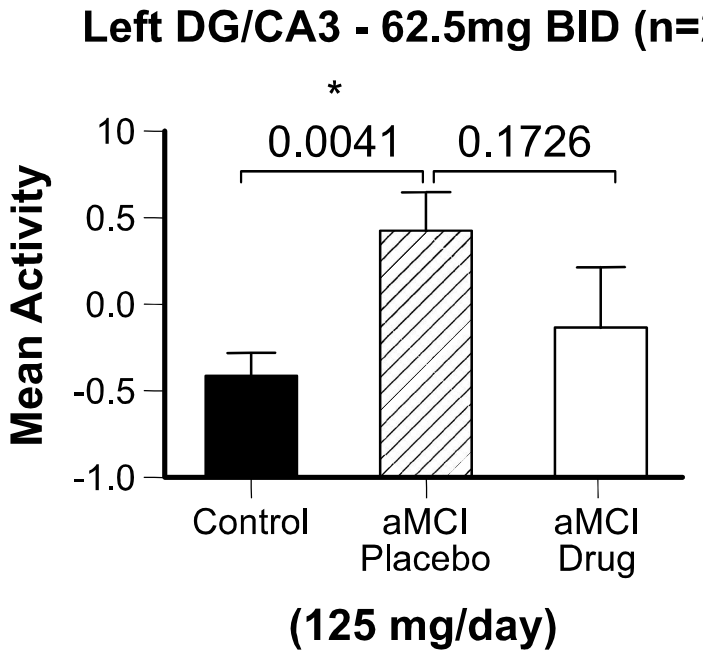


FIG. 19A

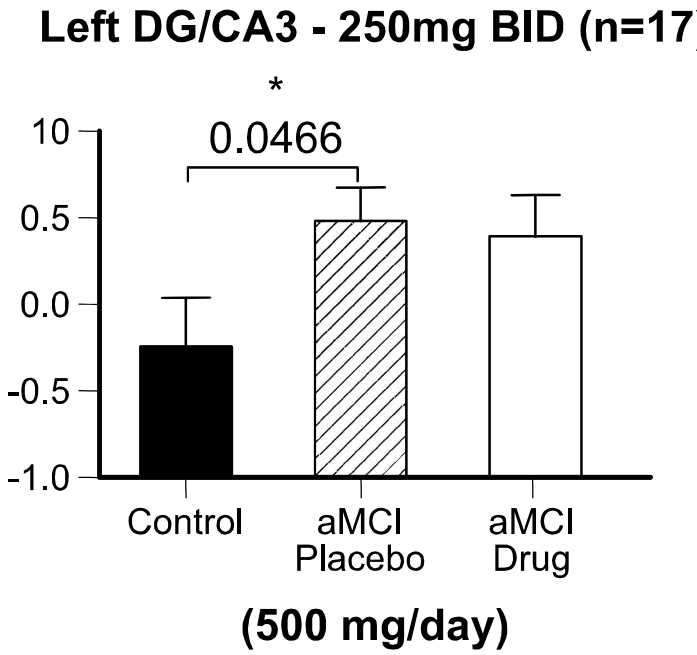


FIG. 19B

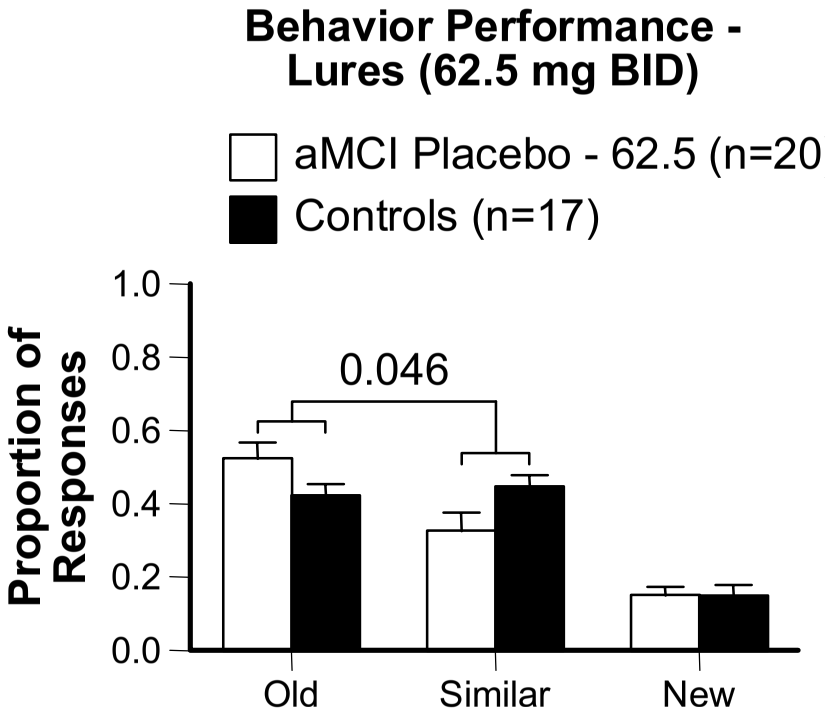


FIG. 20A

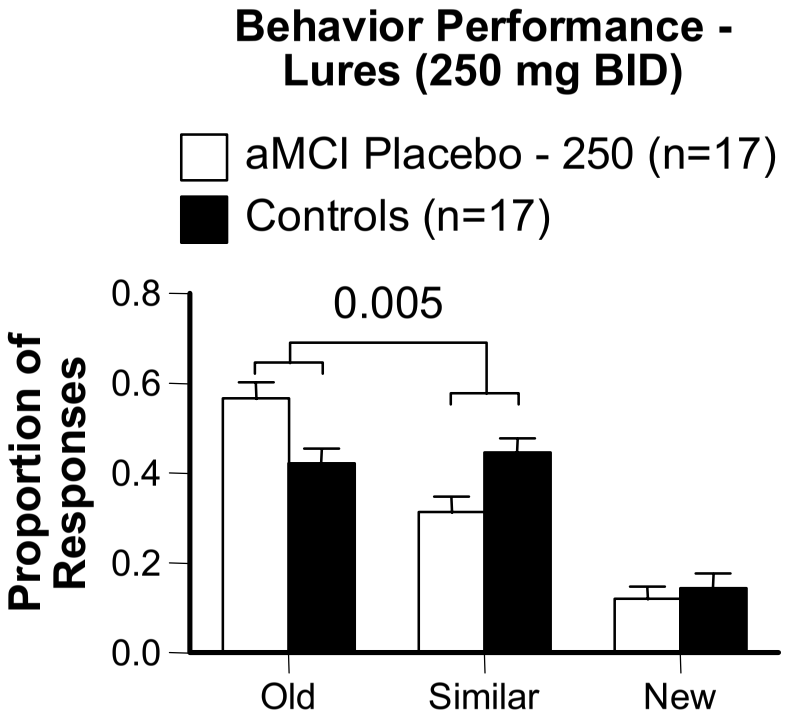


FIG. 20B

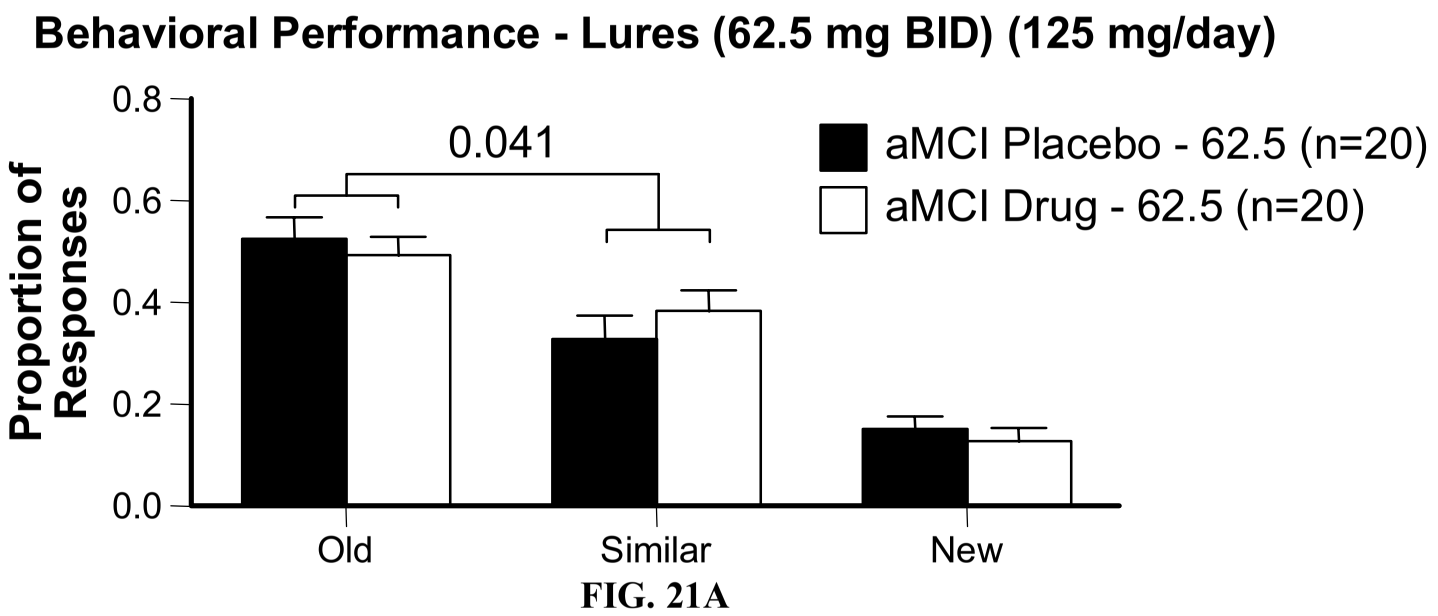


FIG. 21A

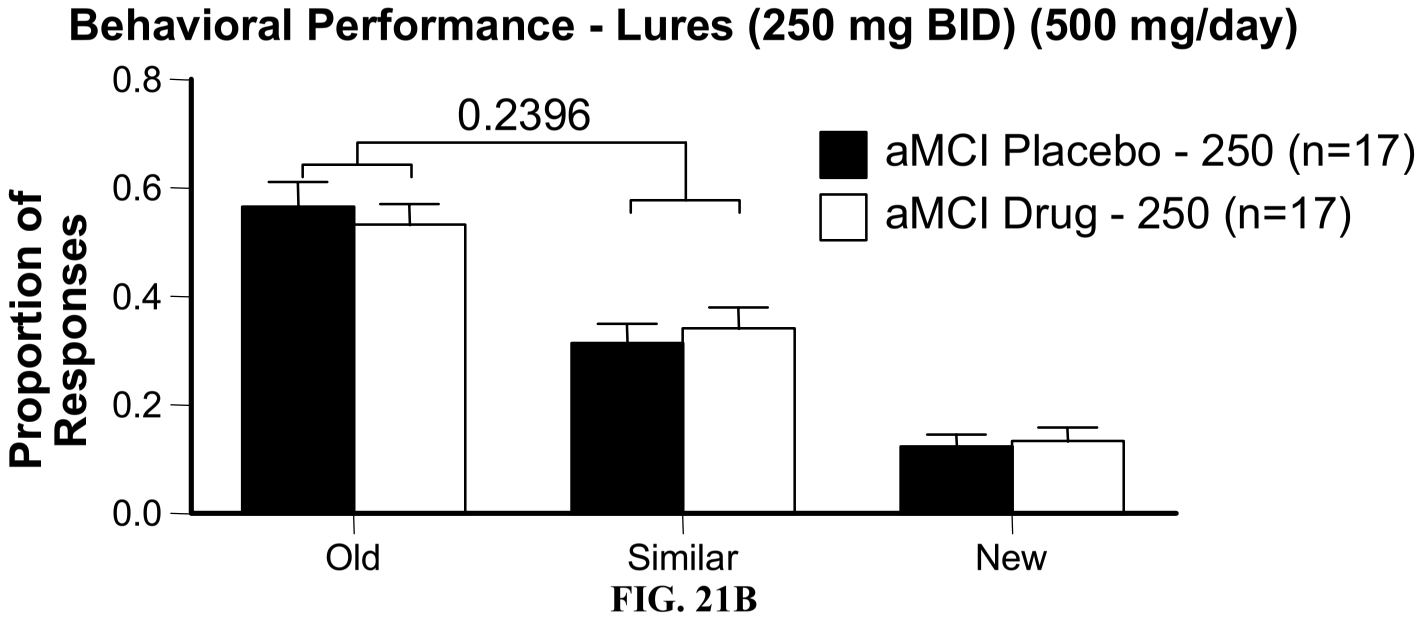


FIG. 21B

Chronic Treatment with Levetiracetam (10 mg/kg/day) in
AI Rats Restores Somatostatin in DG Hilus

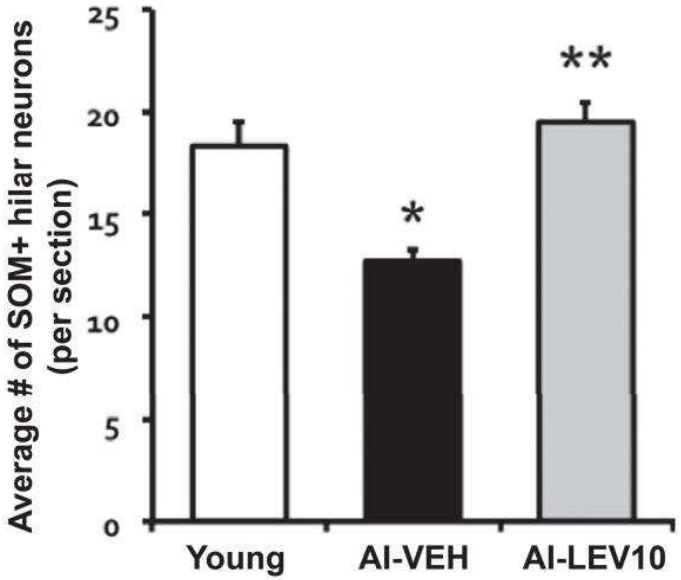


FIG. 22

Chronic Treatment with Levetiracetam (10 mg/kg/day) in AI Rats Restores Reelin in Entorhinal Cortex (EC2)

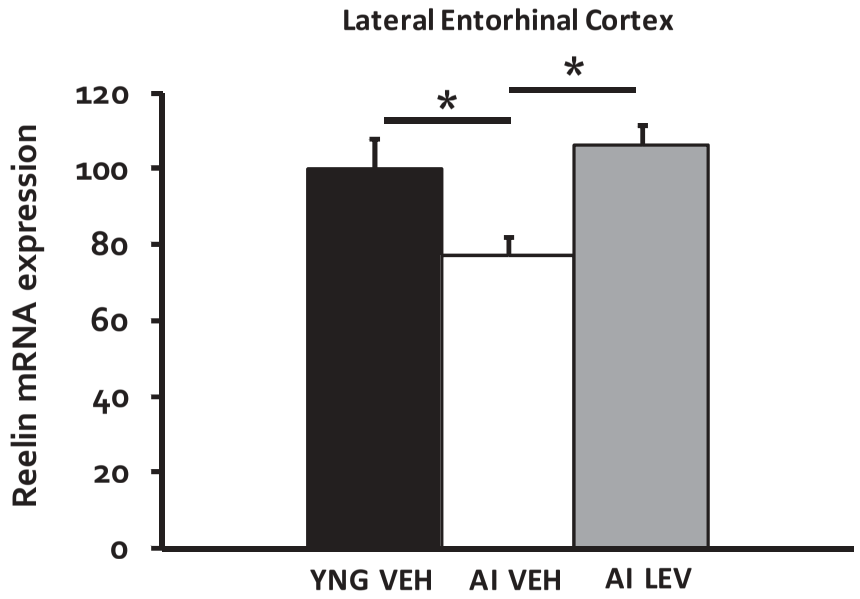


FIG. 23

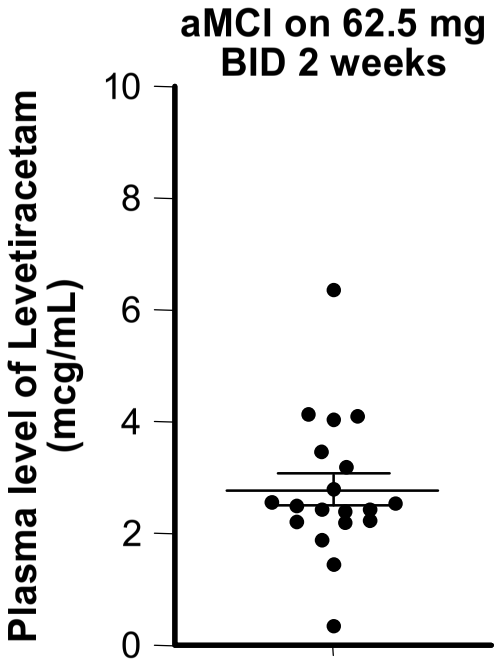


FIG. 24A

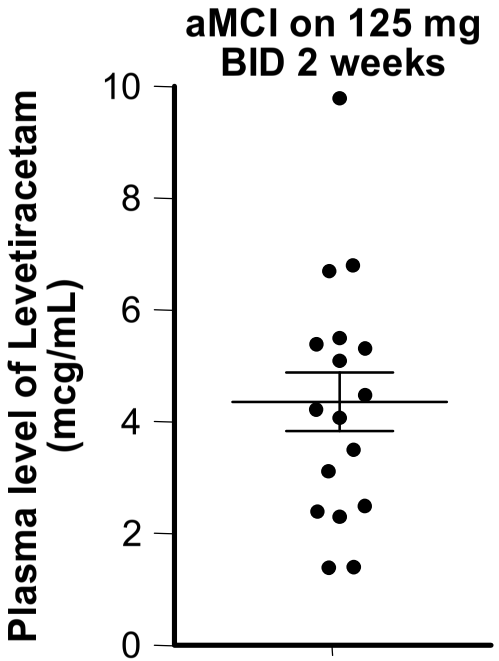


FIG. 24B

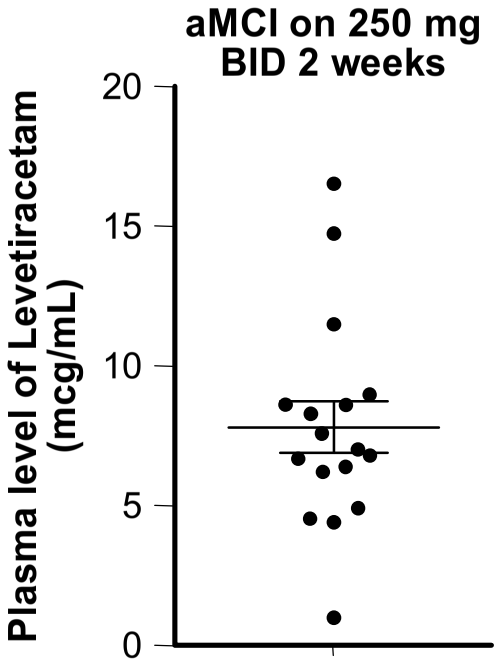


FIG. 24C

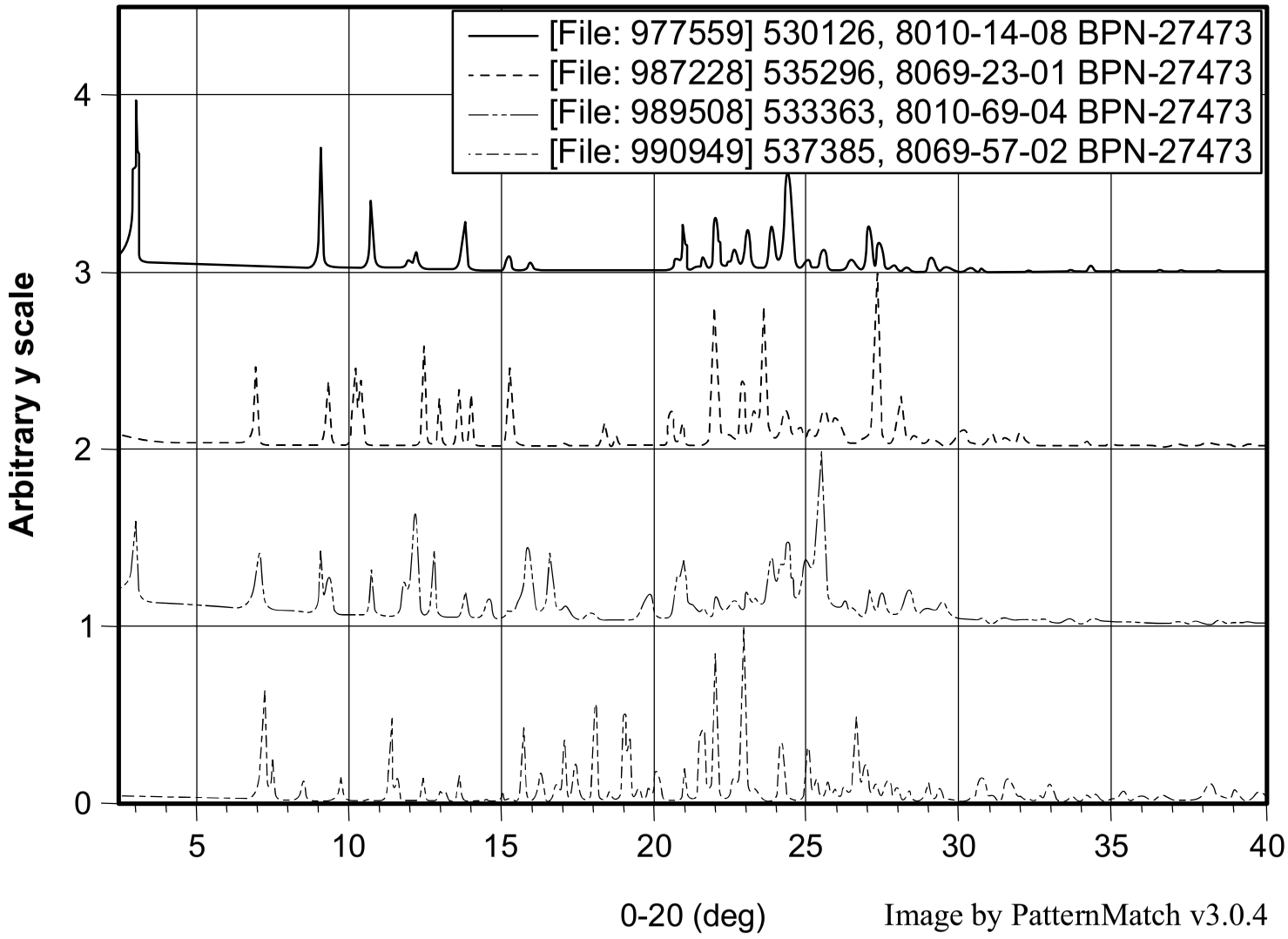

[File: 977559] 530126, 8010-14-08 BPN-27473
[File: 987228] 535296, 8069-23-01 BPN-27473
[File: 989508] 533363, 8010-69-04 BPN-27473
[File: 990949] 537385, 8069-57-02 BPN-27473
Arbitrary y scale
0
1
2
3
4
5
10
15
20
25
30
35
40
0-20 (deg)
Image by PatternMatch v3.0.4

FIG. 25

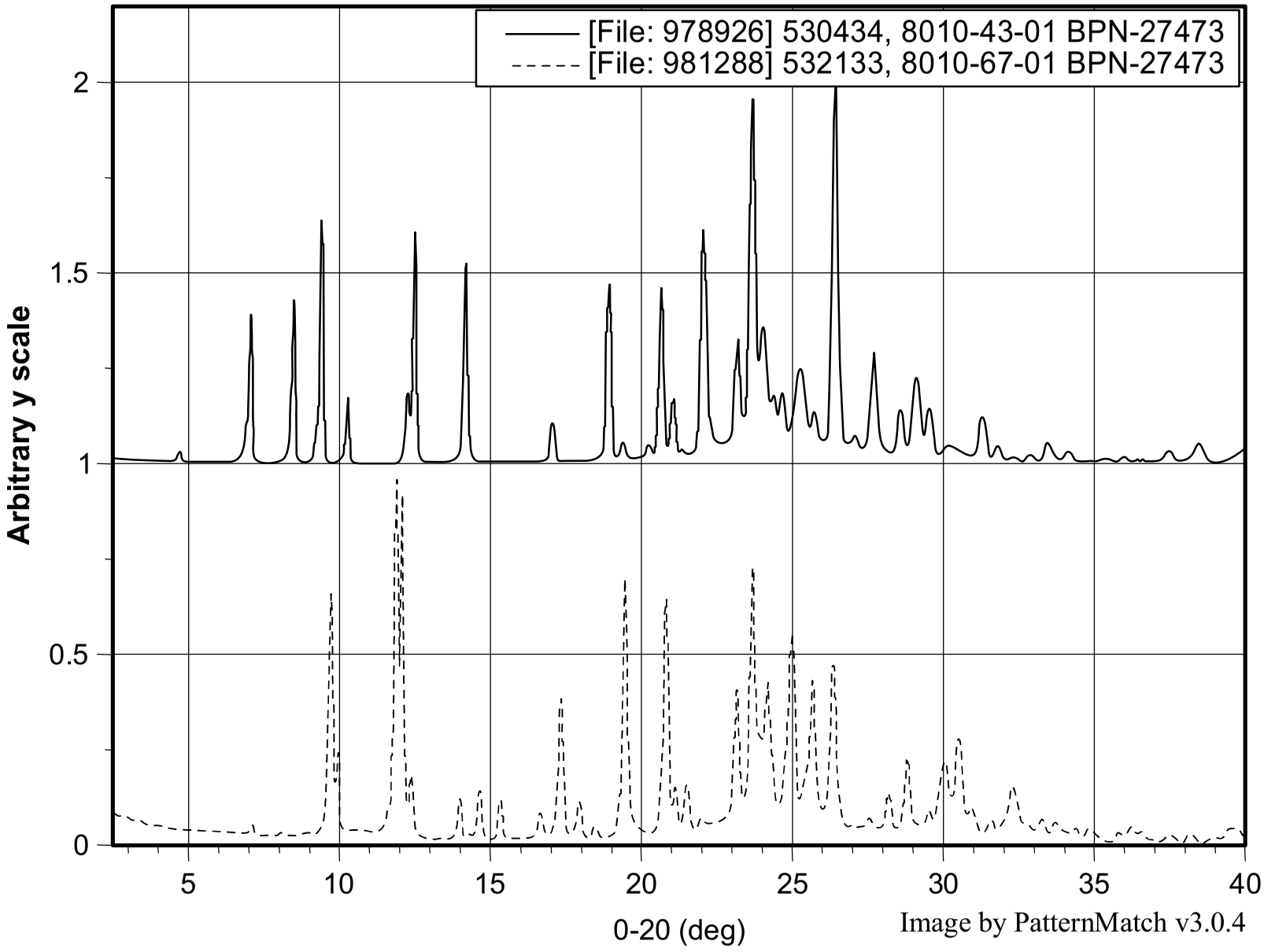

[File: 978926] 530434, 8010-43-01 BPN-27473
[File: 981288] 532133, 8010-67-01 BPN-27473
Arbitrary y scale
0
0.5
1
1.5
2
5
10
15
20
25
30
35
40
0-20 (deg)
Image by PatternMatch v3.0.4

FIG. 26

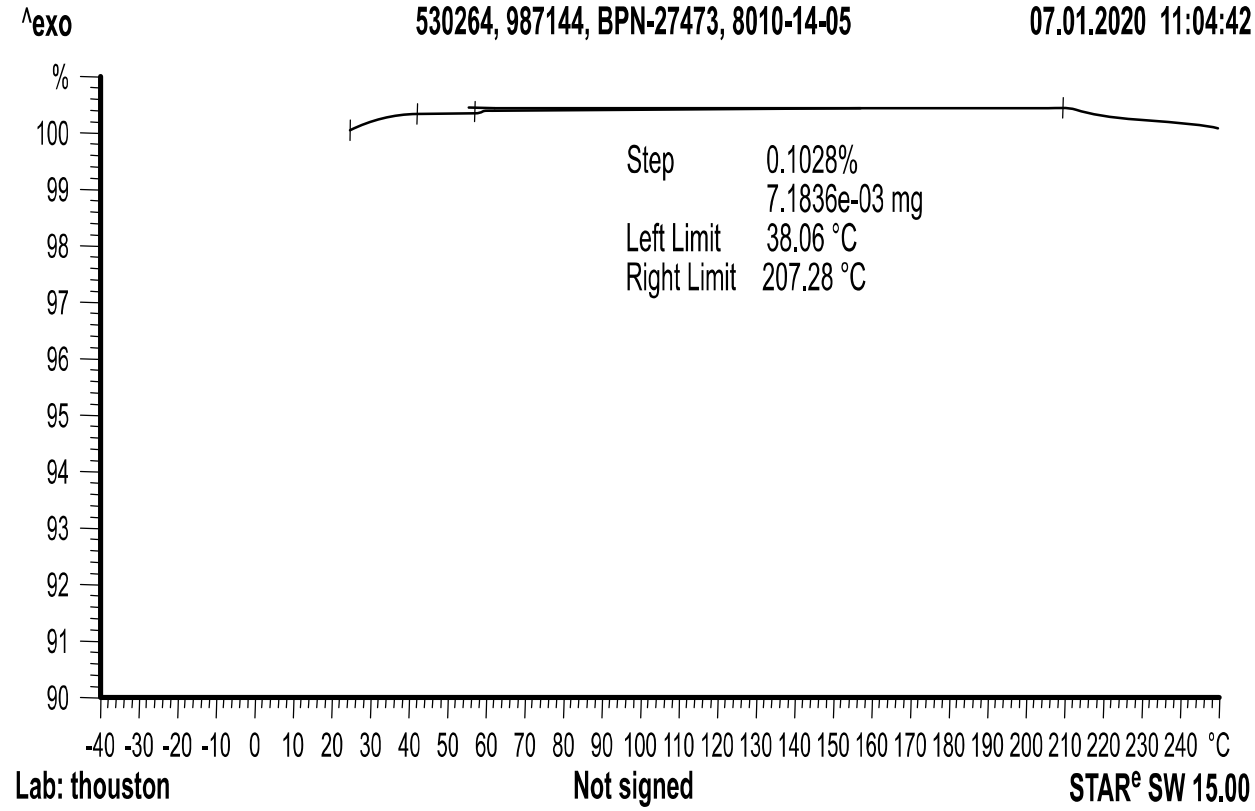


FIG. 27A

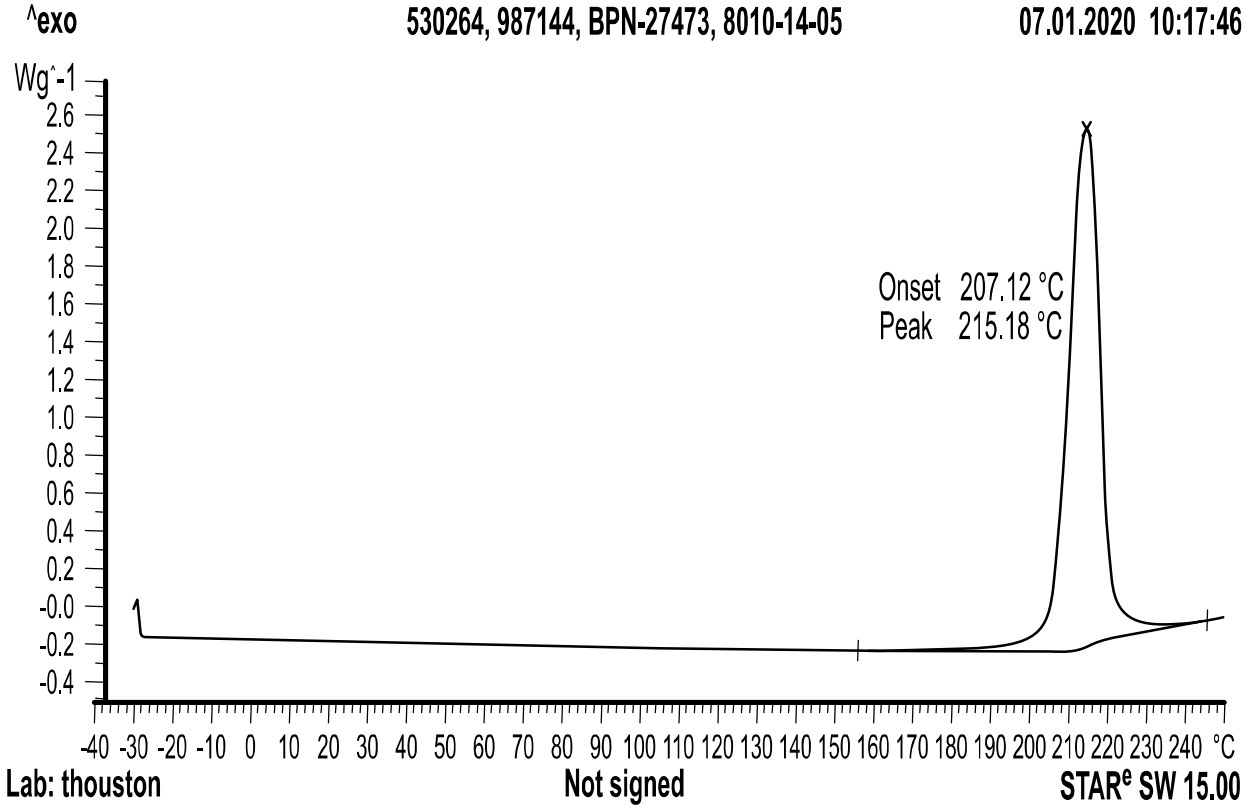


FIG. 27B

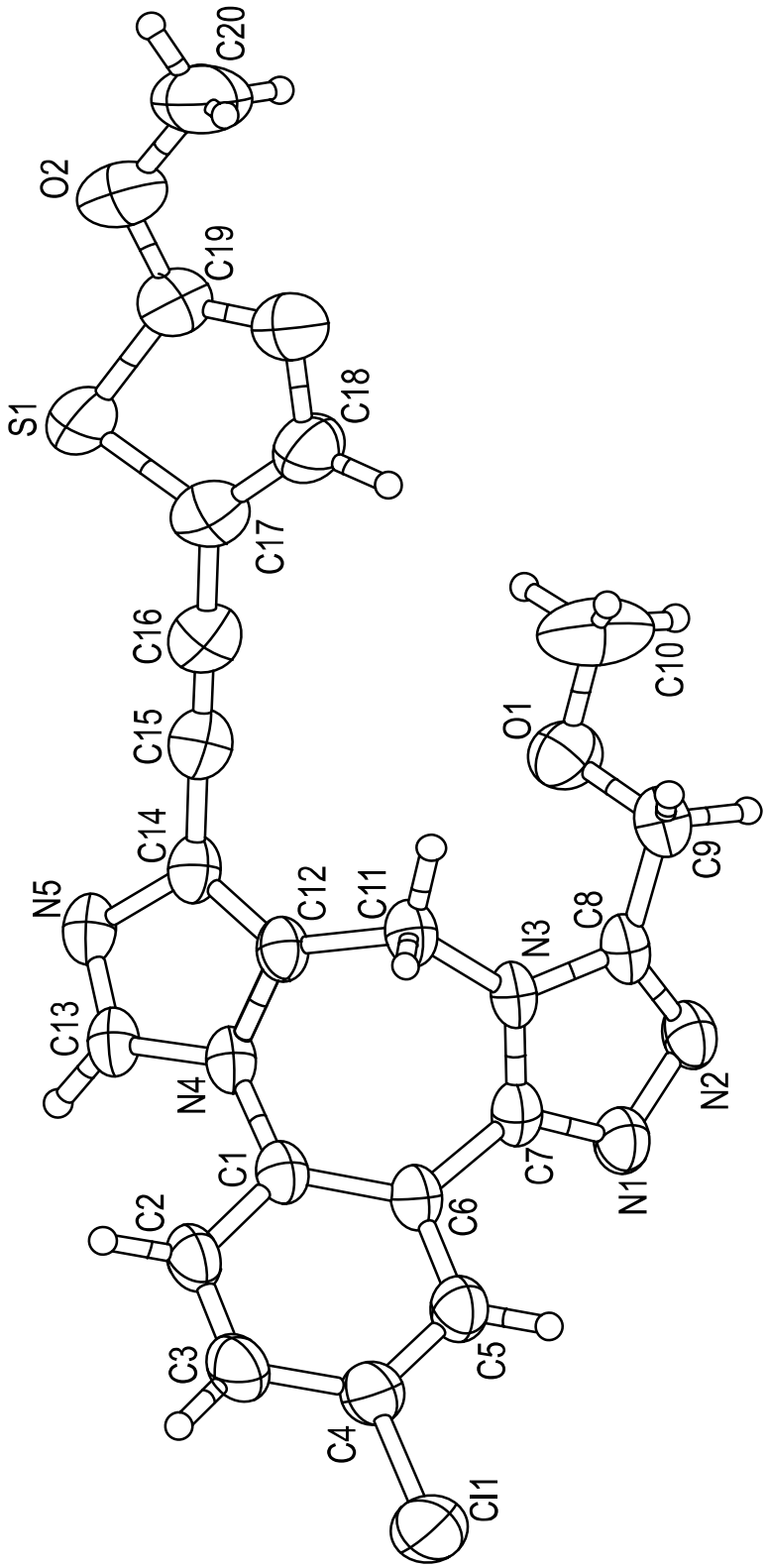

C20
O2
C19
S1
C18
C17
C16
C15
C14
N5
C12
C11
N3
C8
C9
O1
C10
C13
N4
C1
C7
N2
C2
C6
N1
C3
C5
C4
Cl1

FIG. 28

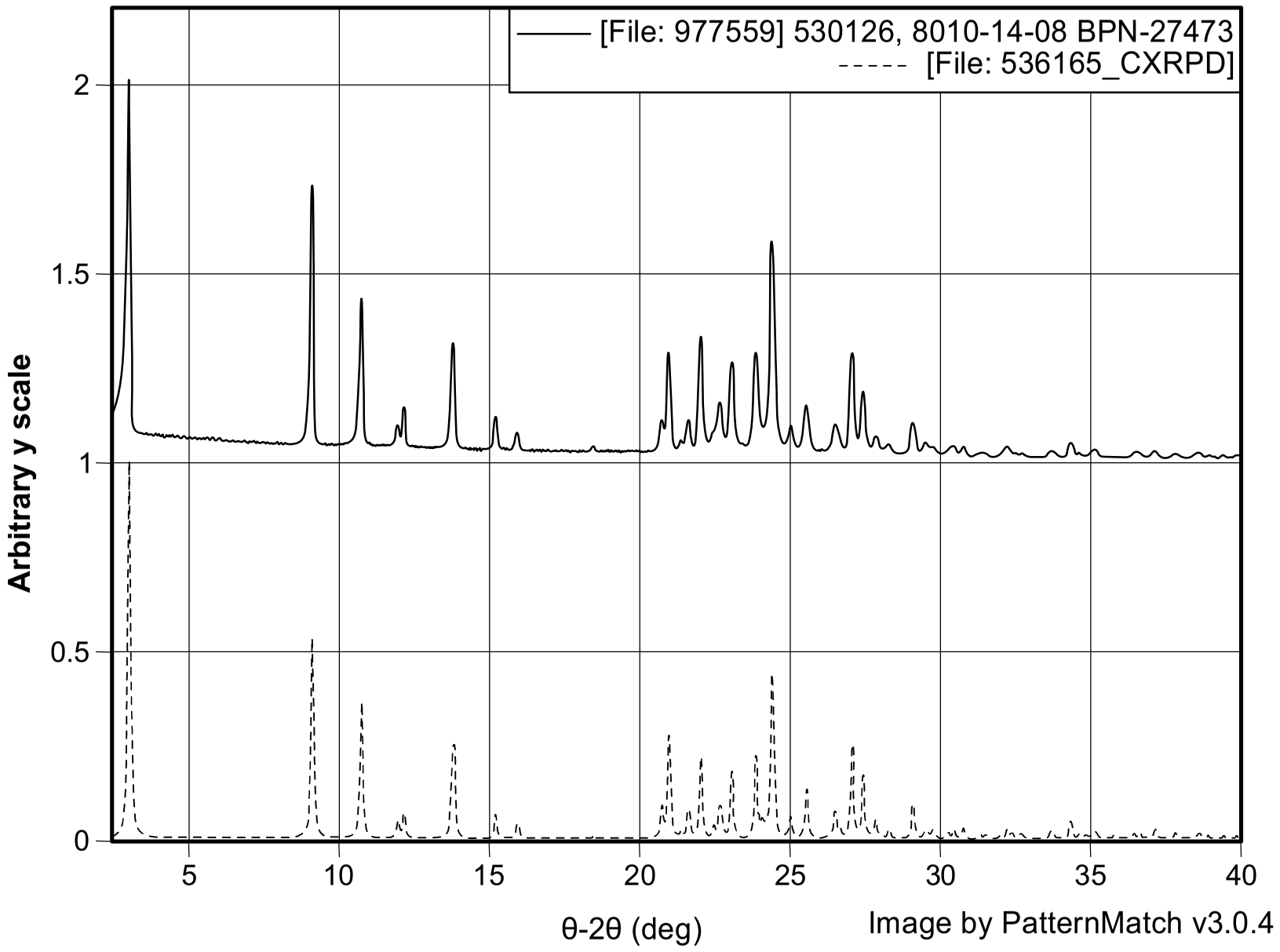

[File: 977559] 530126, 8010-14-08 BPN-27473
[File: 536165_CXRPD]
Arbitrary y scale
2
1.5
1
0.5
0
5
10
15
20
25
30
35
40
θ-2θ (deg)
Image by PatternMatch v3.0.4

FIG. 29

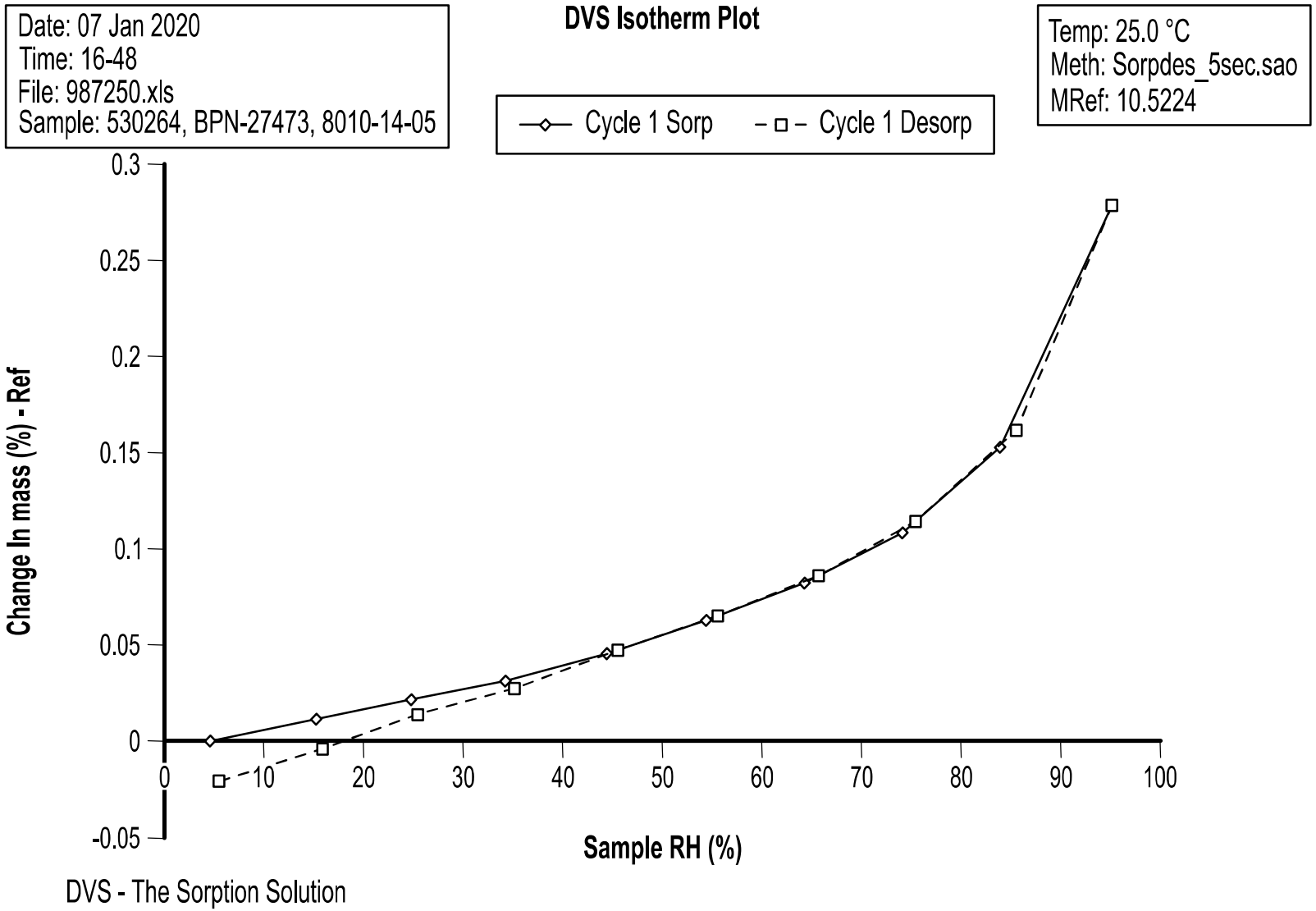
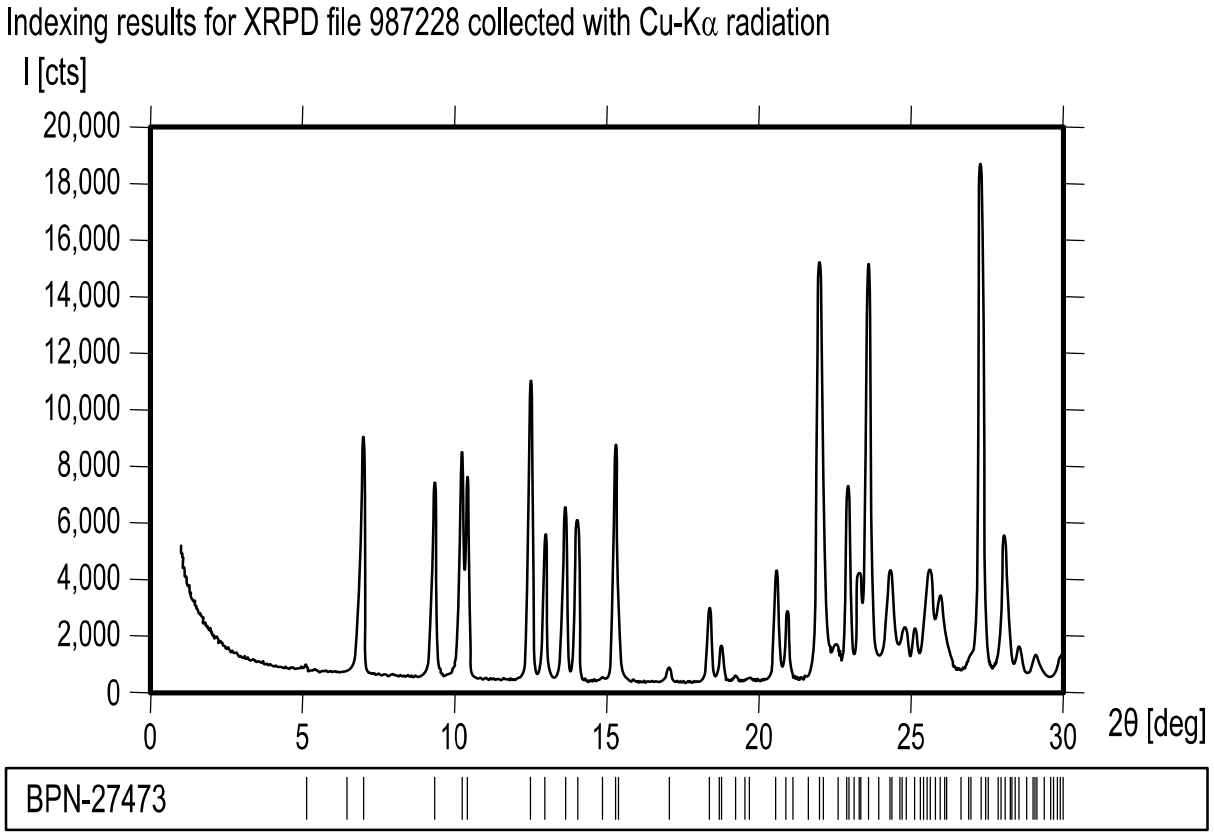

Date: 07 Jan 2020
Time: 16-48
File: 987250.xls
Sample: 530264, BPN-27473, 8010-14-05
DVS Isotherm Plot
Temp: 25.0 °C
Meth: Sorpdes_5sec.sao
MRef: 10.5224
Cycle 1 Sorp
Cycle 1 Desorp
Change In mass (%) - Ref
0.3
0.25
0.2
0.15
0.1
0.05
0
-0.05
0
10
20
30
40
50
60
70
80
90
100
Sample RH (%)
DVS - The Sorption Solution

FIG. 30



	BPN-27473
Bravais Type	Primitive Monoclinic
a [Å]	14.254
b [Å]	4.041
c [Å]	36.069
α [deg]	90
β [deg]	106.84
γ [deg]	90
Volume [Å^3/cell]	1,988.5
Chiral Contents?	Not Specified
Extinction Symbol	P 1 c 1
Space Group(s)	Pc (7), P2/c (13)
Source	Manual Input

Indexing is a non-cGMP activity

FIG. 31

Output Rendered using Triads v2.1.1

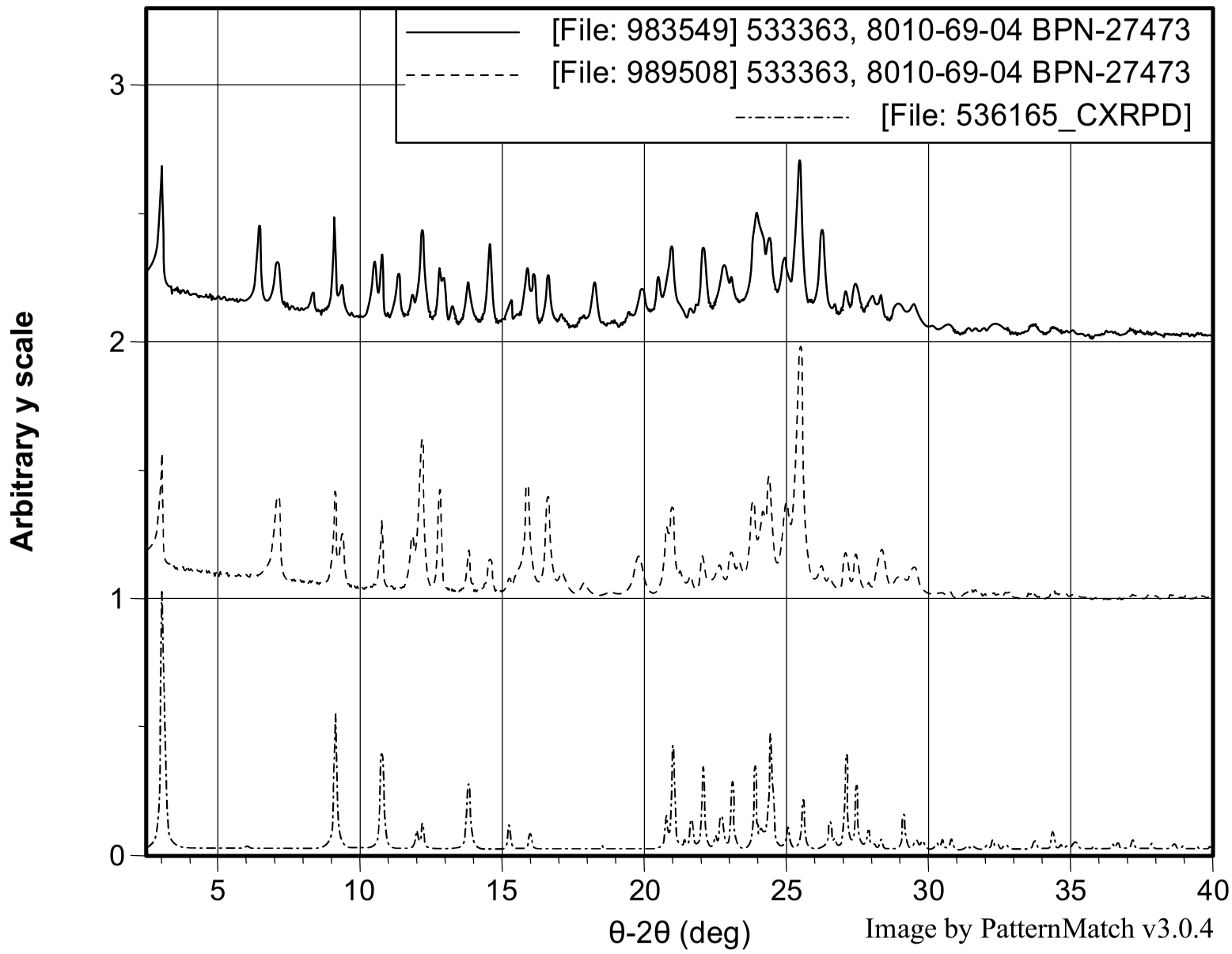

[File: 983549] 533363, 8010-69-04 BPN-27473
[File: 989508] 533363, 8010-69-04 BPN-27473
[File: 536165_CXRPD]
Arbitrary y scale
0
1
2
3
5
10
15
20
25
30
35
40
θ-2θ (deg)
Image by PatternMatch v3.0.4

FIG. 32

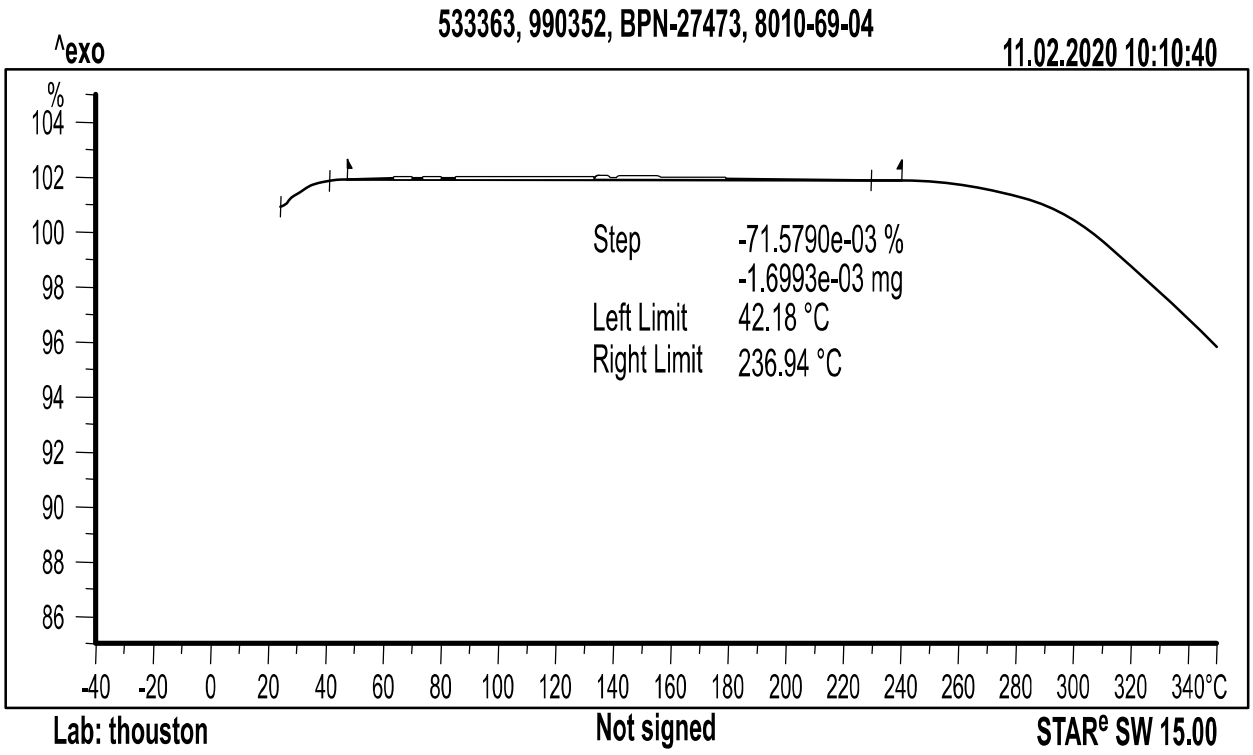


FIG. 33A

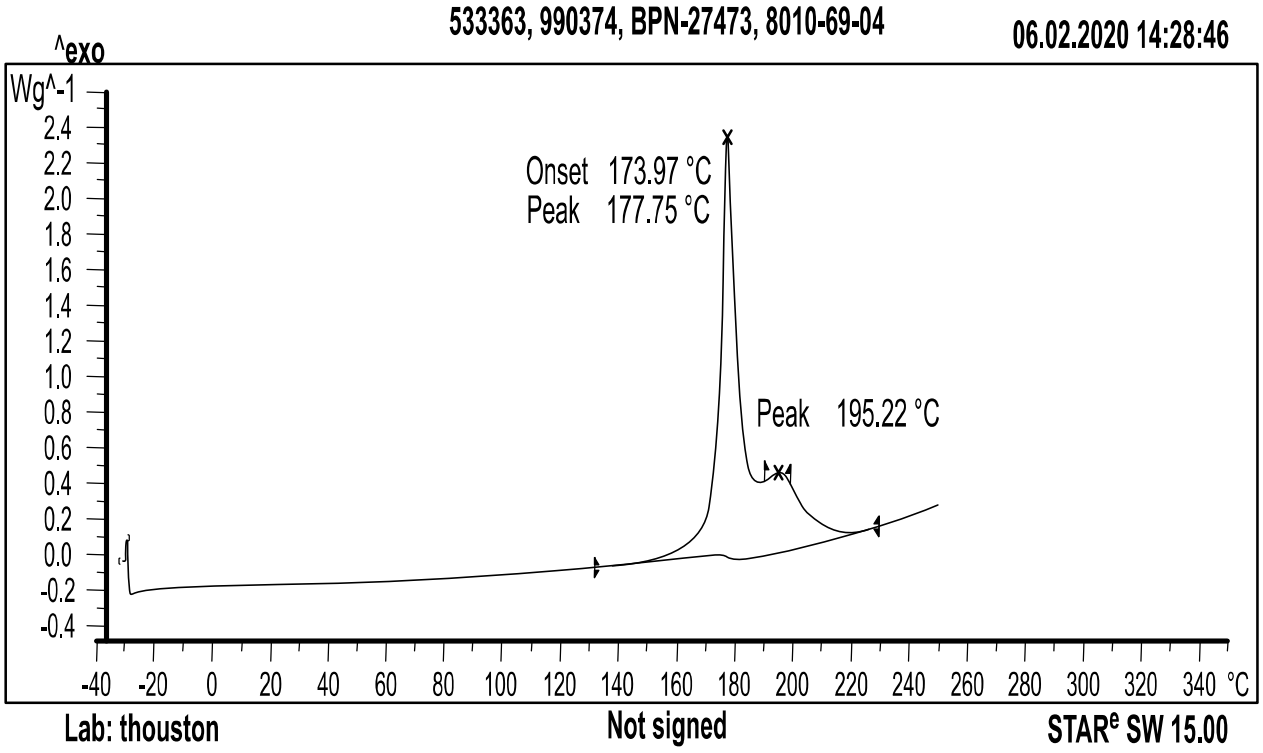


FIG. 33B

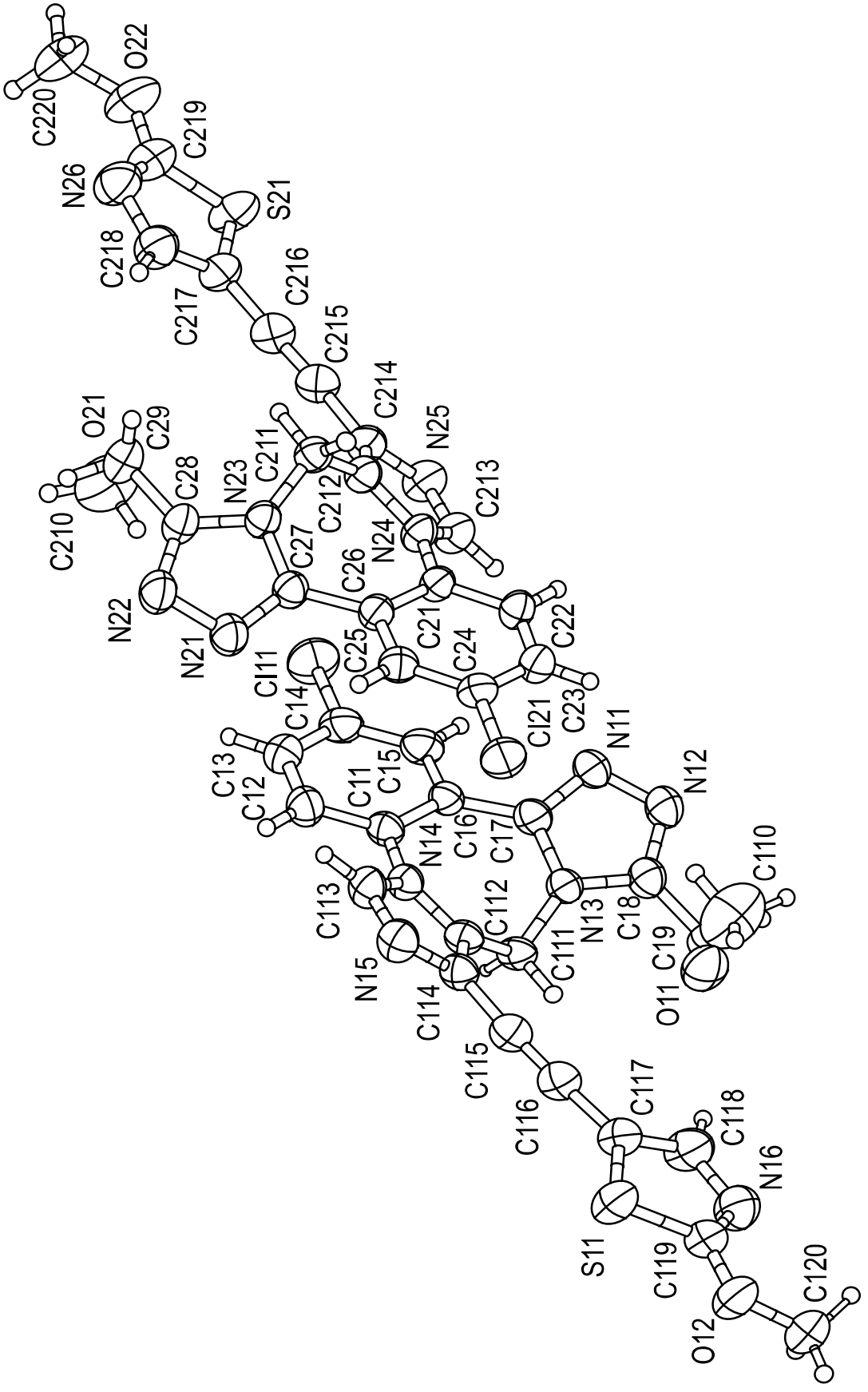

C220
O22
C219
N26
S21
C218
C216
C217
C215
C214
O21
C29
C211
N25
C28
N23
C212
C213
C210
C27
N24
C26
N22
C21
C22
N21
C25
C24
Cl11
C14
Cl21
C23
C13
N11
C12
C11
C15
N12
C16
C17
N14
C110
C113
C112
C18
N13
C111
C19
N15
O11
C114
C115
C117
C116
C118
N16
S11
C119
C120
O12

FIG. 34

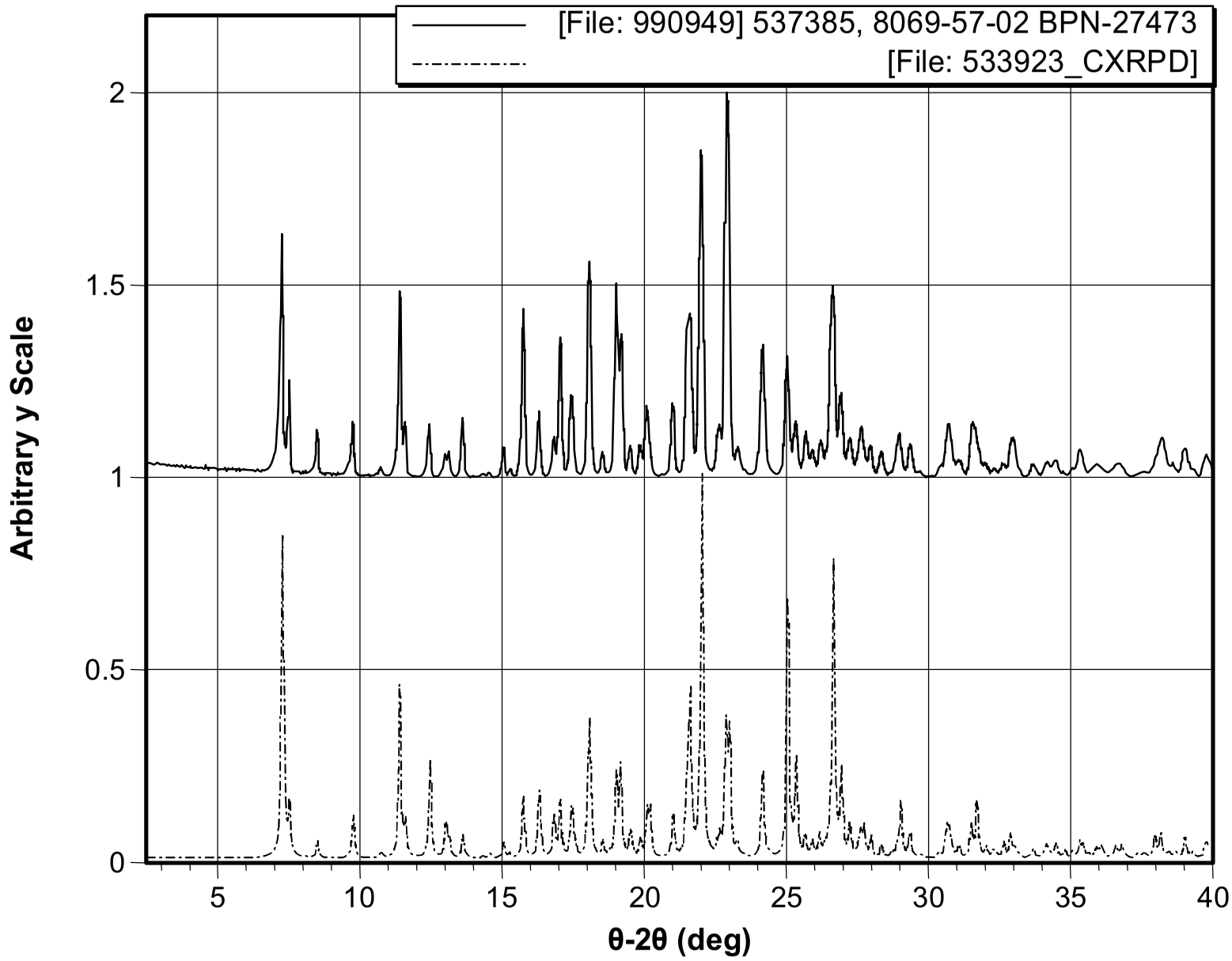

[File: 990949] 537385, 8069-57-02 BPN-27473
[File: 533923_CXRPD]
Arbitrary y Scale
θ-2θ (deg)
0
0.5
1
1.5
2
5
10
15
20
25
30
35
40

FIG. 35

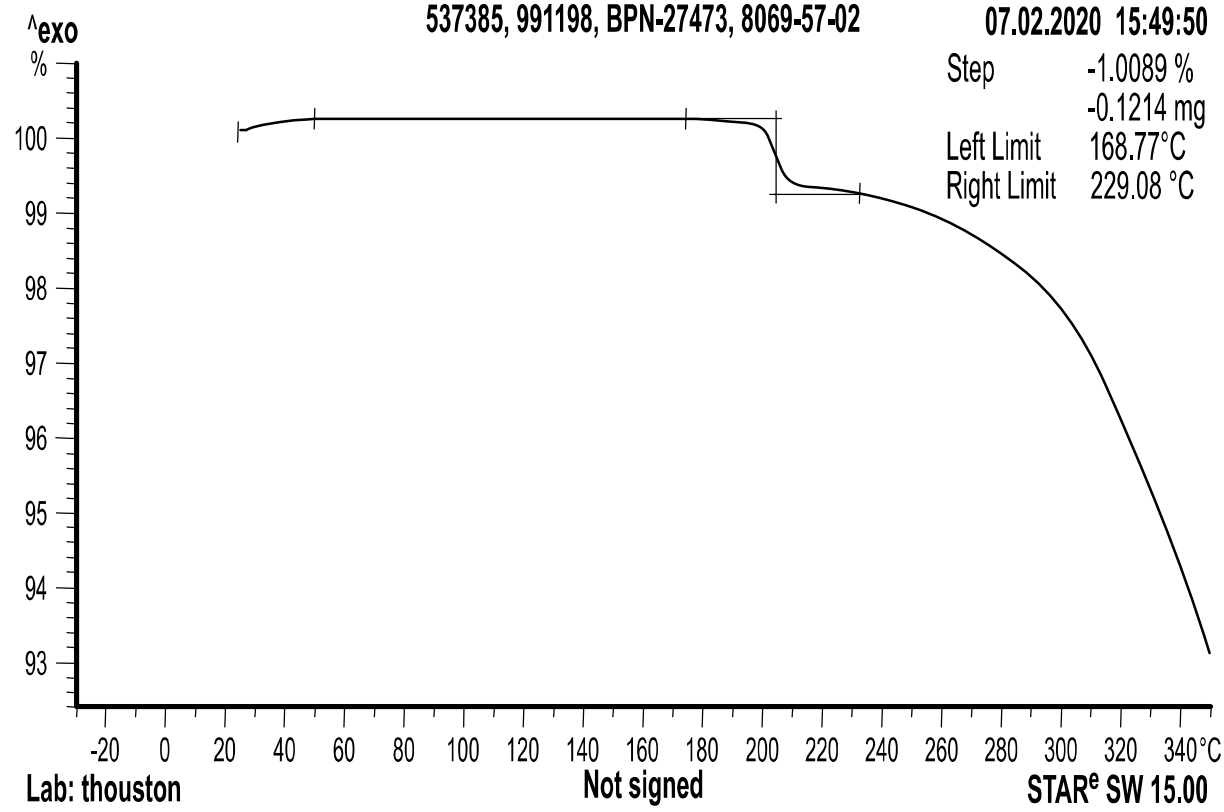


FIG. 36A

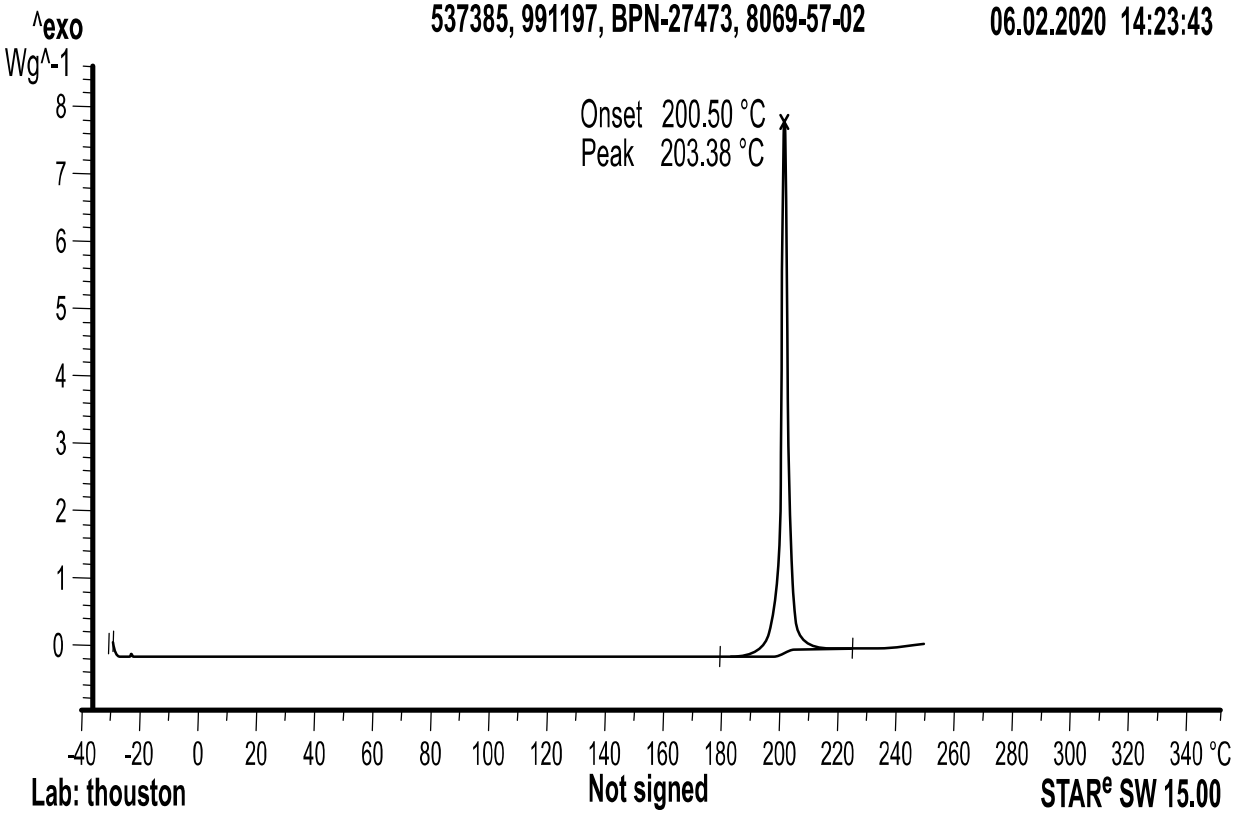


FIG. 36B

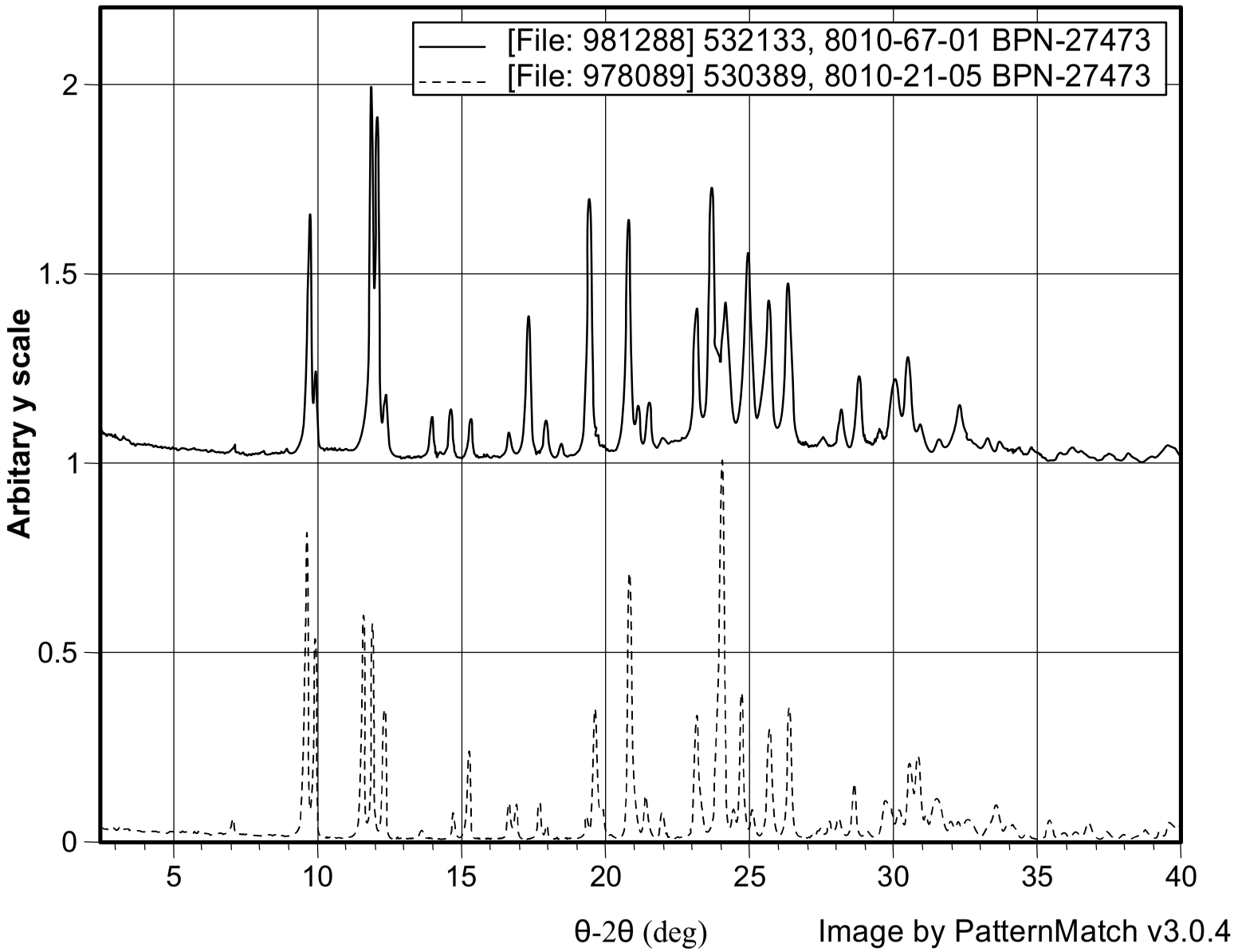
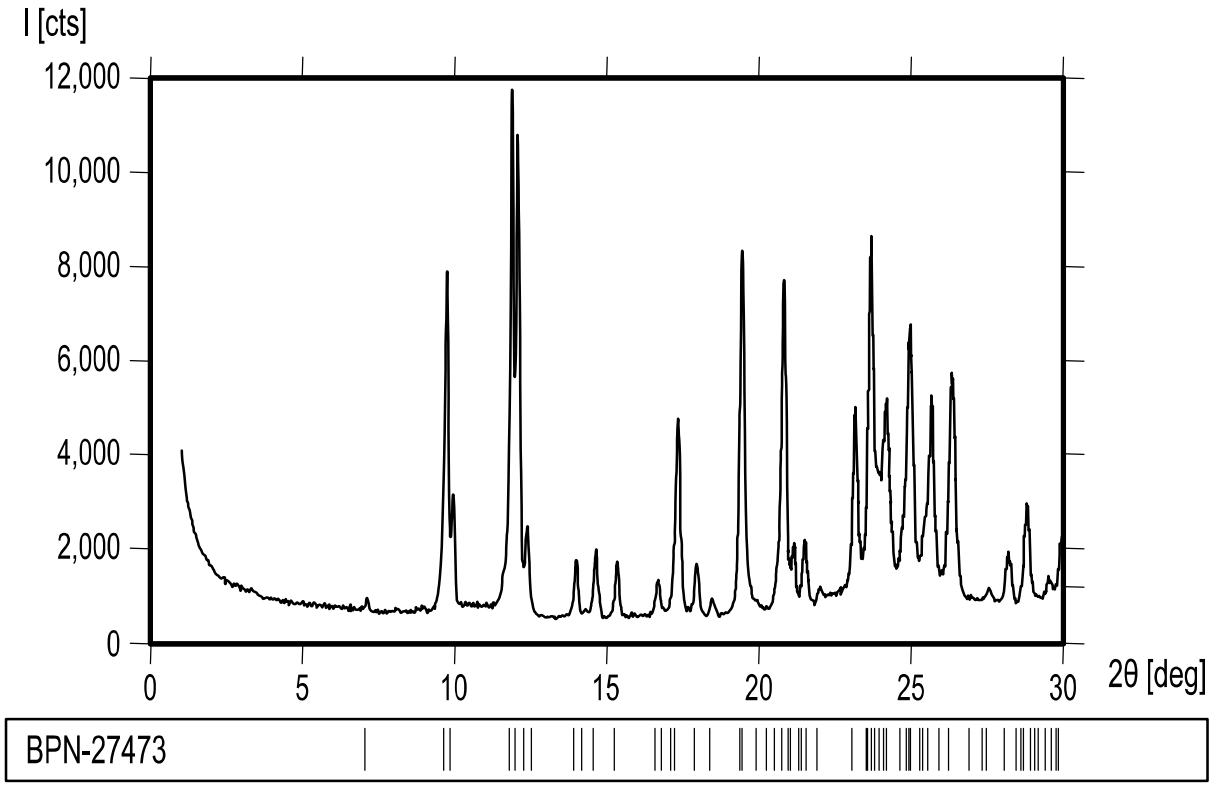

[File: 981288] 532133, 8010-67-01 BPN-27473
[File: 978089] 530389, 8010-21-05 BPN-27473
Arbitary y scale
2
1.5
1
0.5
0
5
10
15
20
25
30
35
40
θ-2θ (deg)
Image by PatternMatch v3.0.4

FIG. 37

Indexing results for XRPD file 981288 collected with Cu-Kα radiation.



	BPN-27473
Bravais Type	Triclinic
a [Å]	9.104
b [Å]	9.279
c [Å]	12.416
α [deg]	89.06
β [deg]	86.31
γ [deg]	77.95
Volume [Å^3/cell]	1,023.6
Chiral Contents?	Not Specified
Extinction Symbol	P -
Space Group(s)	Pc (1), $P\bar{1}$ (2)
Source	Triads Algorithm

Indexing is a non-cGMP activity

FIG. 38

Output Rendered using Triads v2.1.1

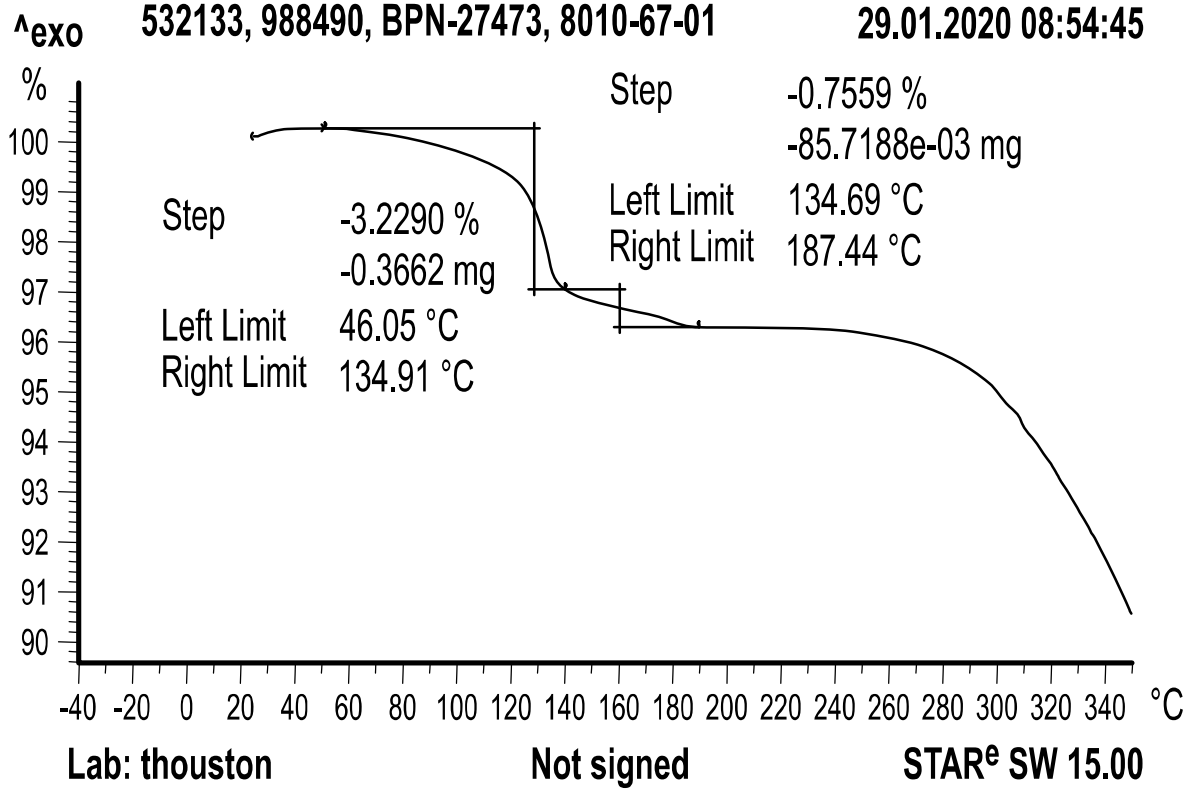


FIG. 39A

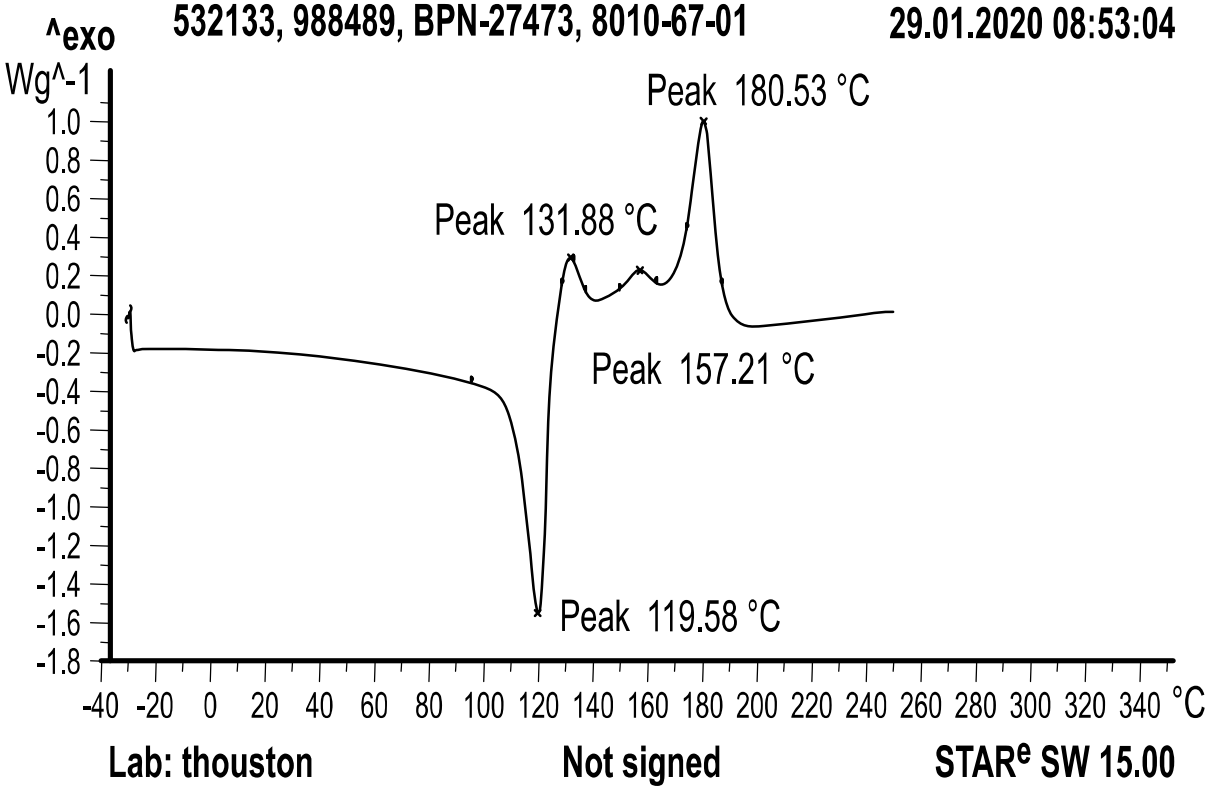


FIG. 39B

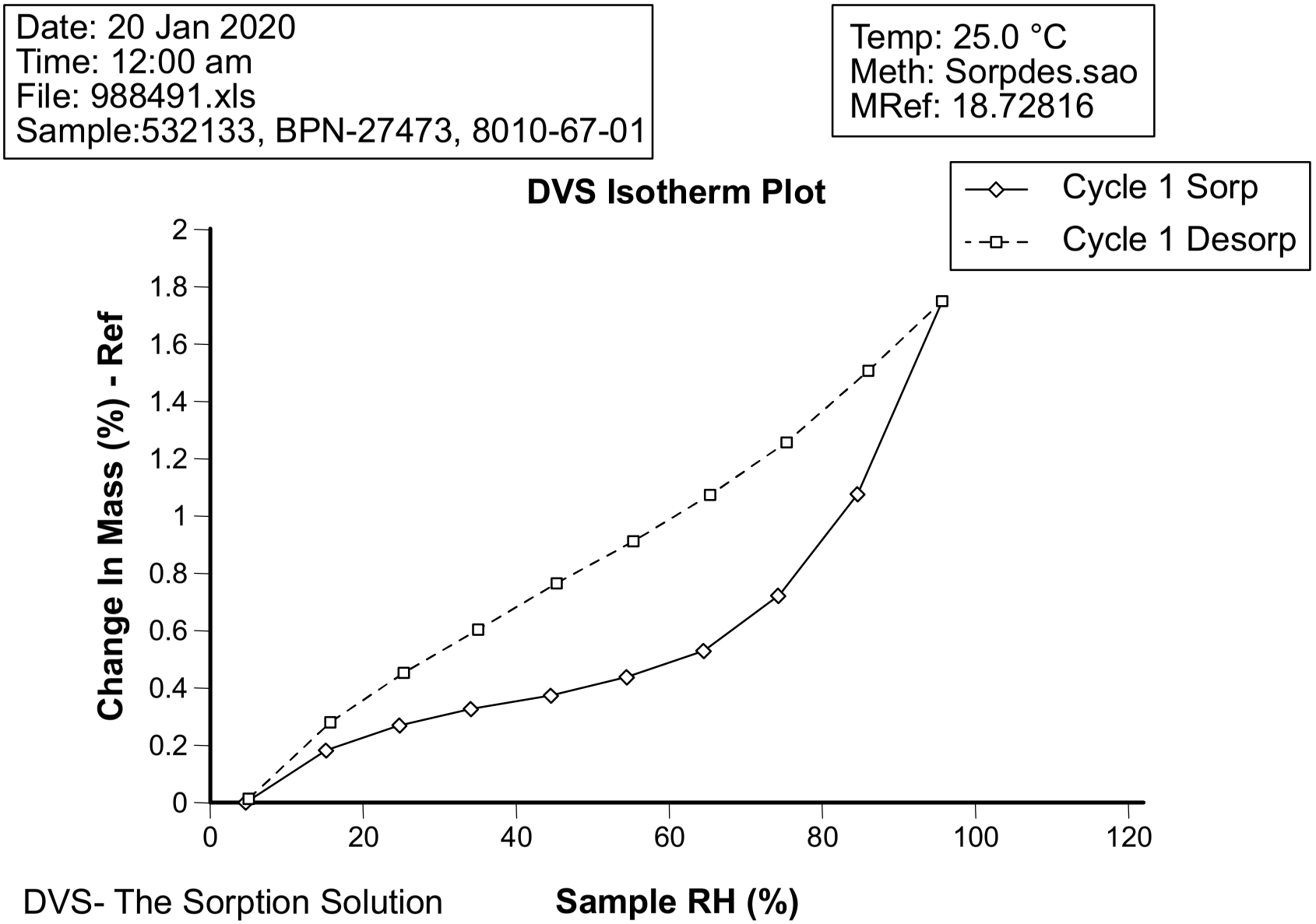
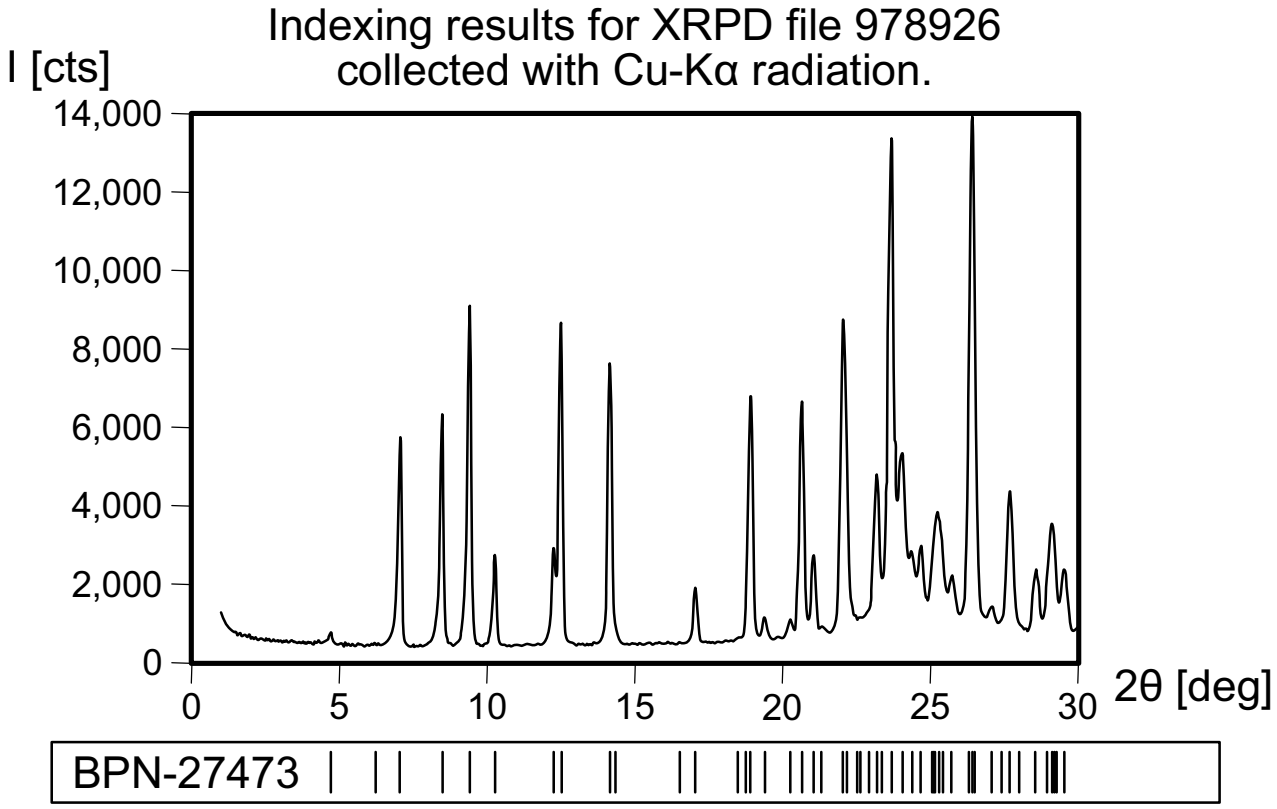

Date: 20 Jan 2020
Time: 12:00 am
File: 988491.xls
Sample:532133, BPN-27473, 8010-67-01
Temp: 25.0 °C
Meth: Sorpdes.sao
MRef: 18.72816
DVS Isotherm Plot
Cycle 1 Sorp
Cycle 1 Desorp
Change In Mass (%) - Ref
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0
20
40
60
80
100
120
DVS- The Sorption Solution
Sample RH (%)

FIG. 40



	BPN-27473
Bravais Type	Primitive Monoclinic
a [Å]	14.406
b [Å]	4.028
c [Å]	38.206
α [deg]	90
β [deg]	100.94
γ [deg]	90
Volume [Å^3/cell]	2,176.7
Chiral Contents?	Not Specified
Extinction Symbol	P 1 c 1
Space Group(s)	Pc (7), P2/c (13)
Source	Manual Input

FIG. 41

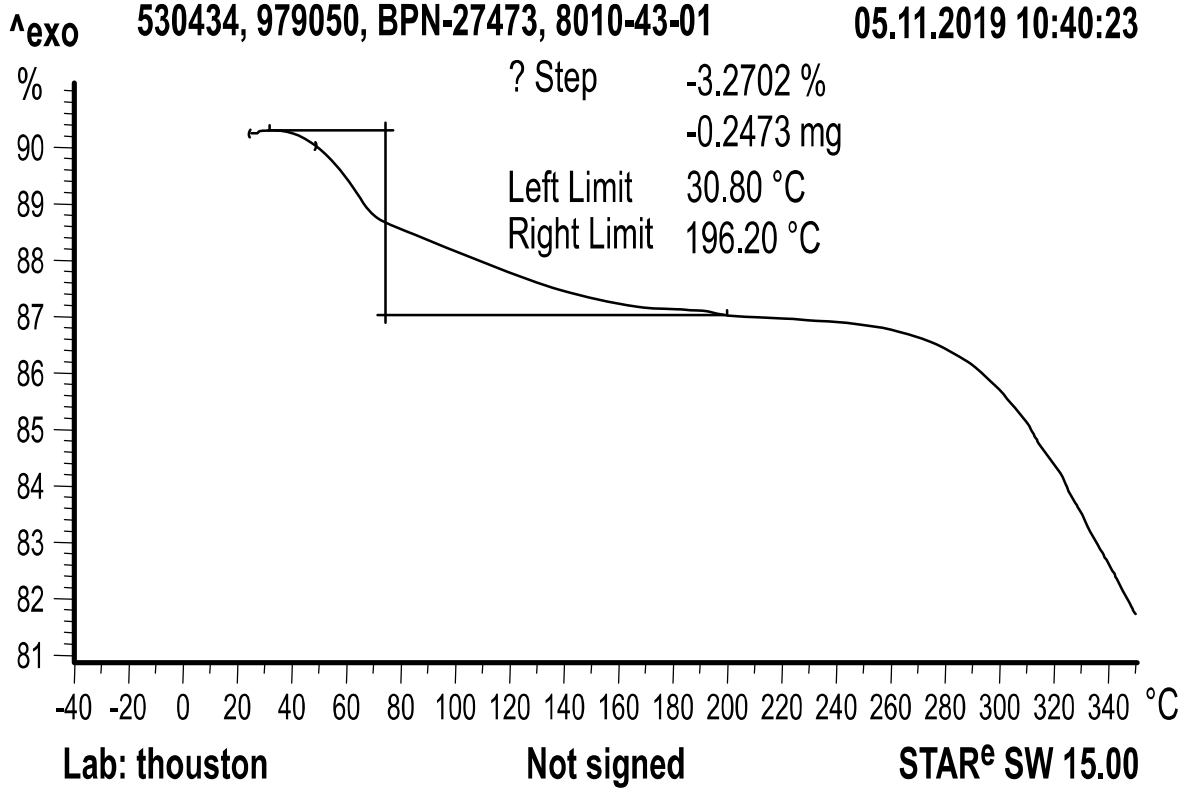


FIG. 42A

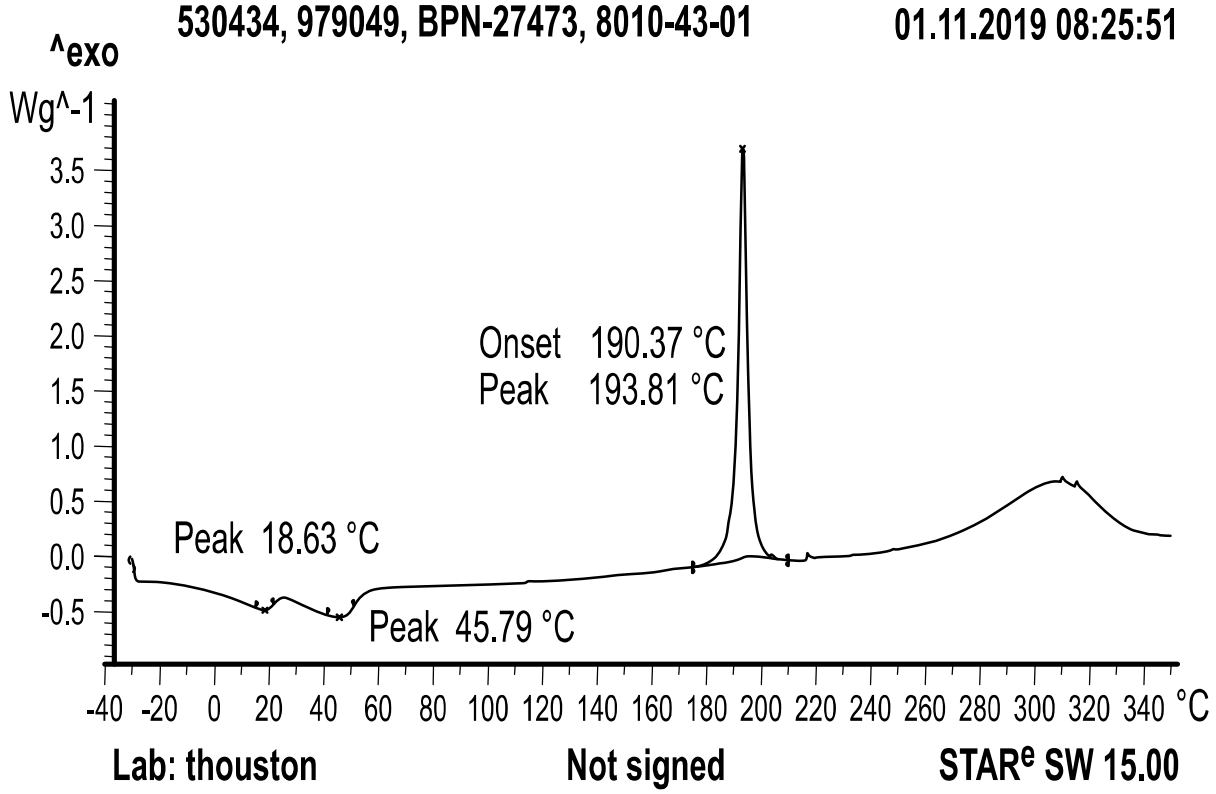


FIG. 42B

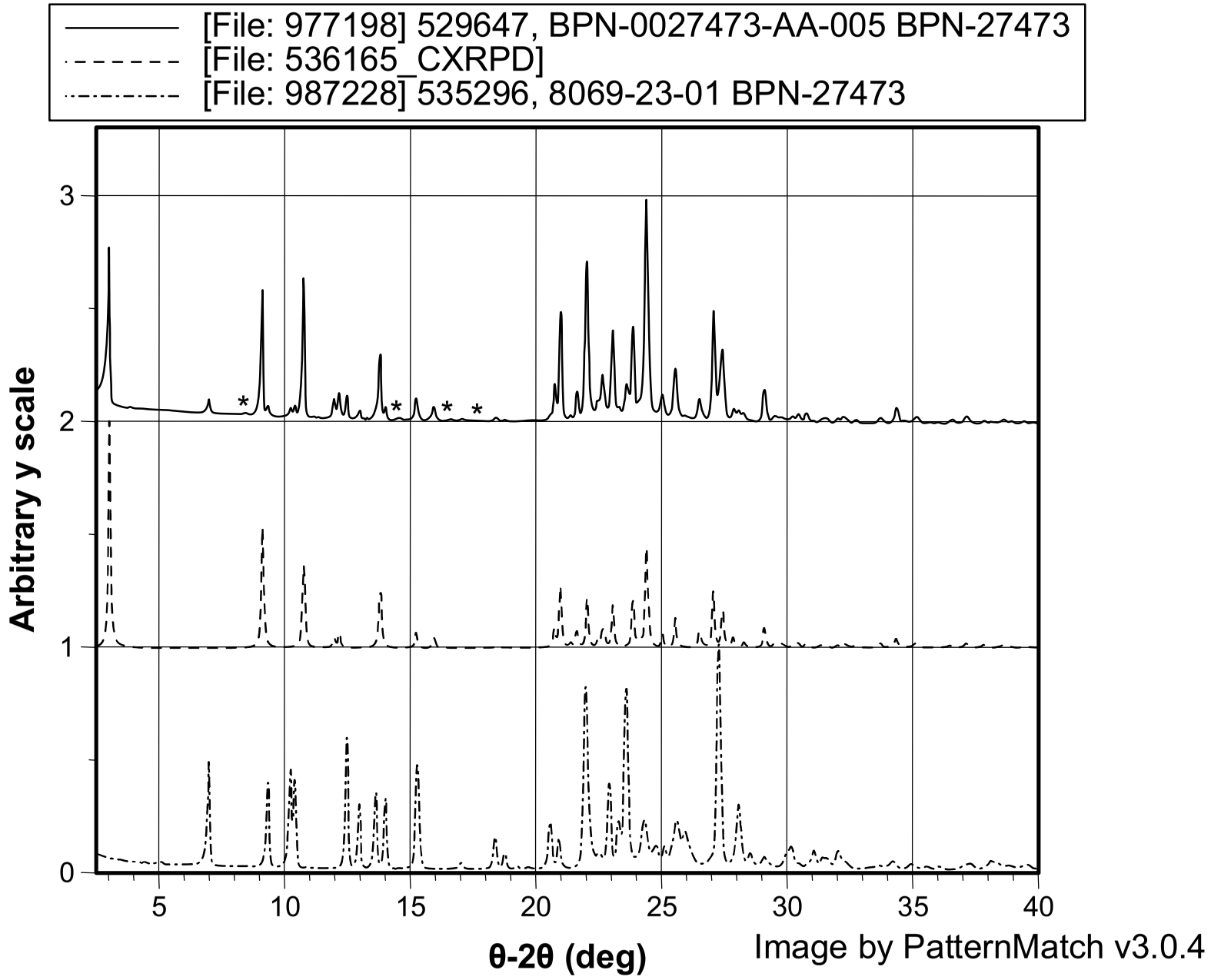

[File: 977198] 529647, BPN-0027473-AA-005 BPN-27473
[File: 536165_CXRPD]
[File: 987228] 535296, 8069-23-01 BPN-27473
Arbitrary y scale
0
1
2
3
5
10
15
20
25
30
35
40
θ-2θ (deg)
Image by PatternMatch v3.0.4

FIG. 43

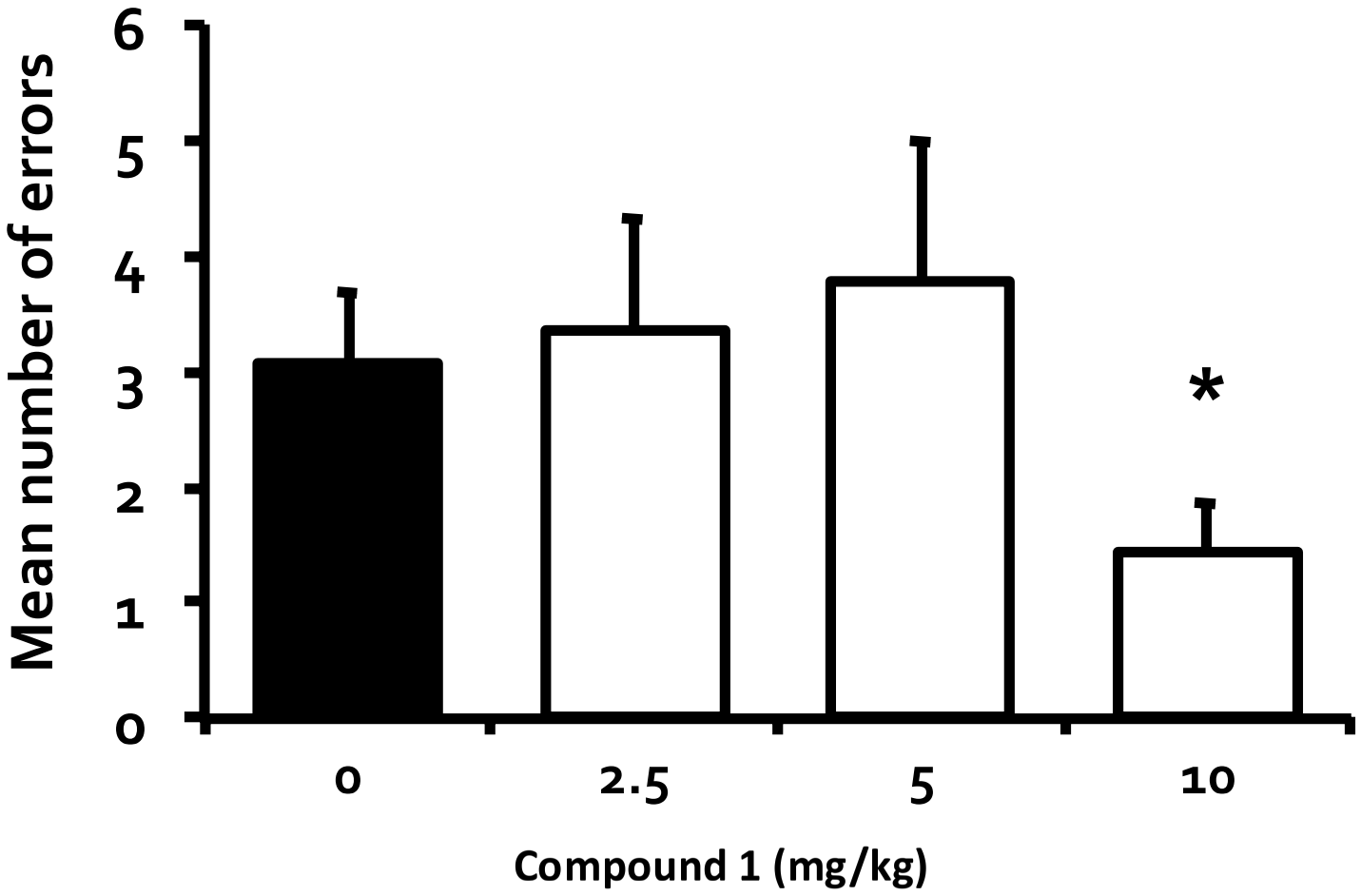


FIG. 44

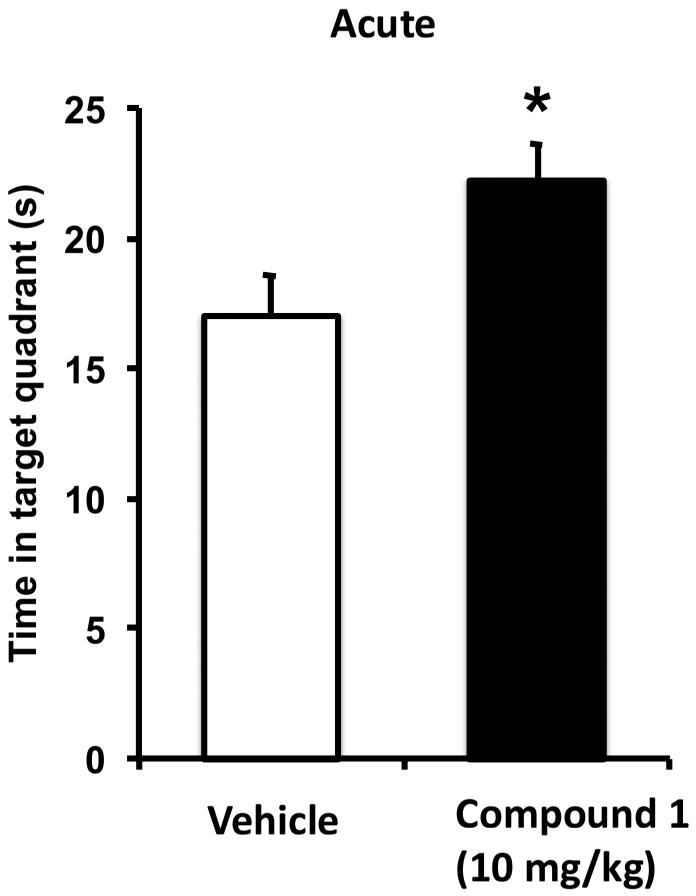


FIG. 45A

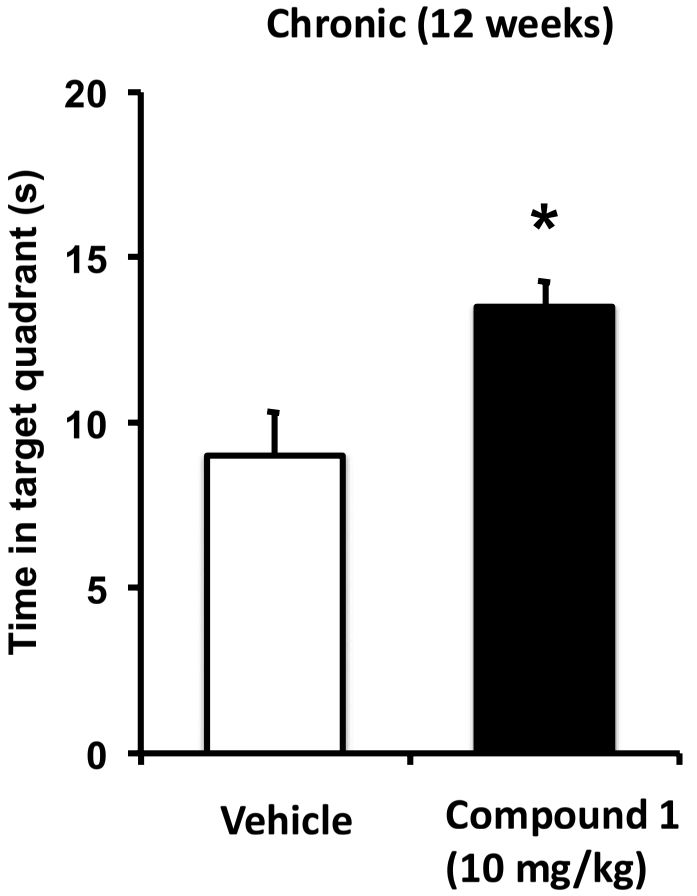


FIG. 45B

FIG. 46A

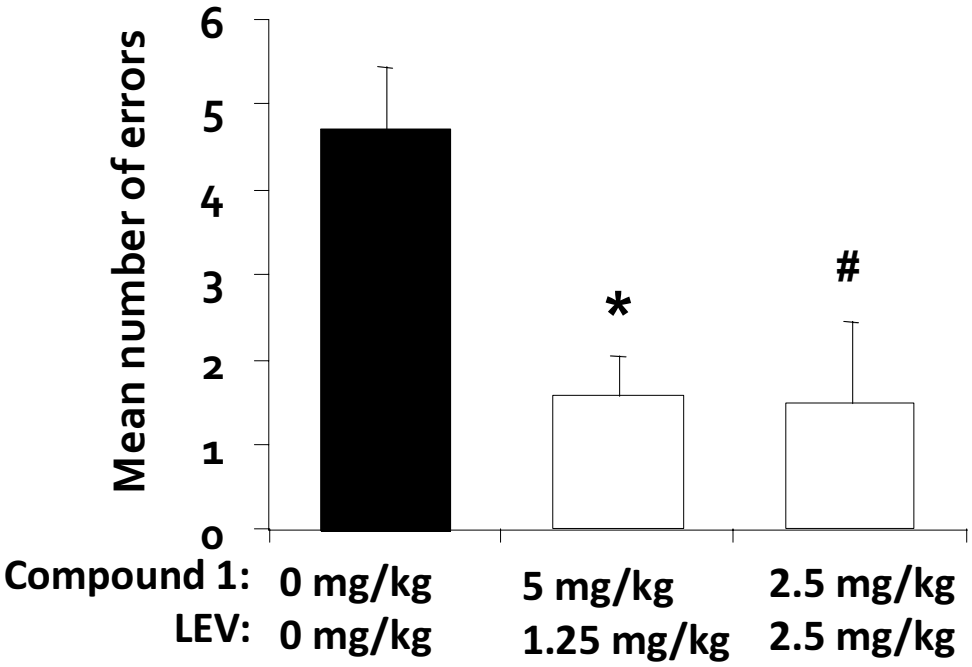


FIG. 46B

