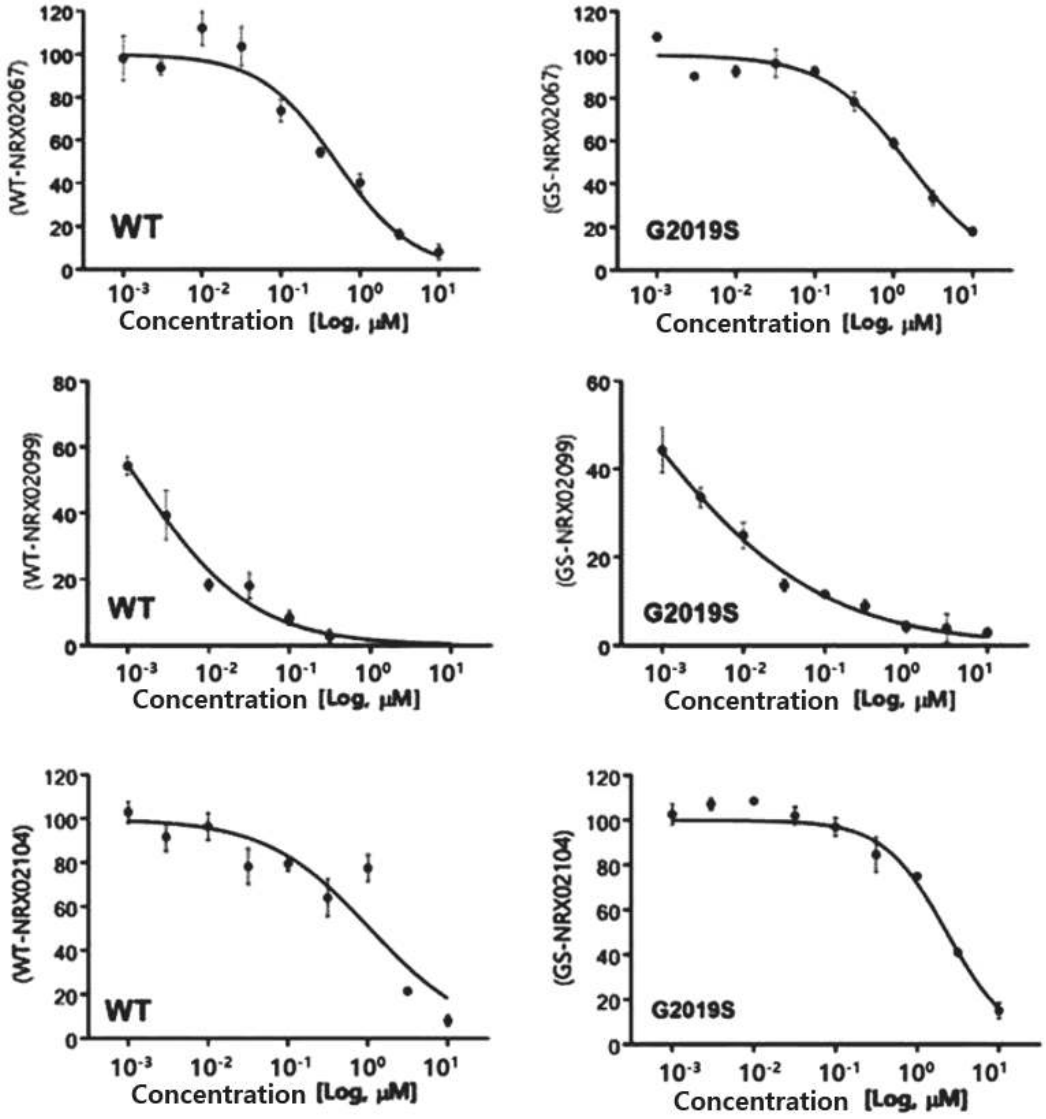
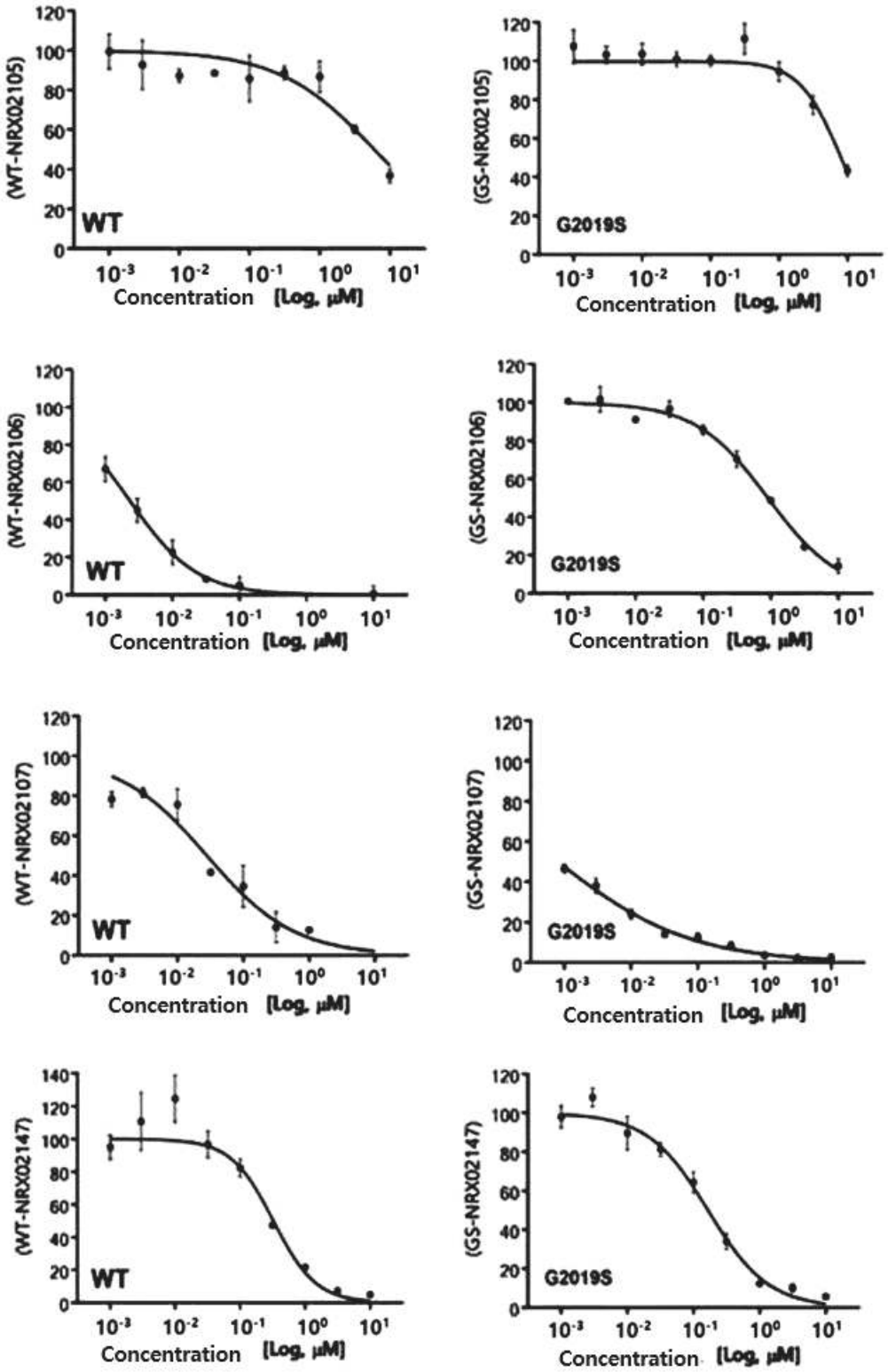
【Drawings】

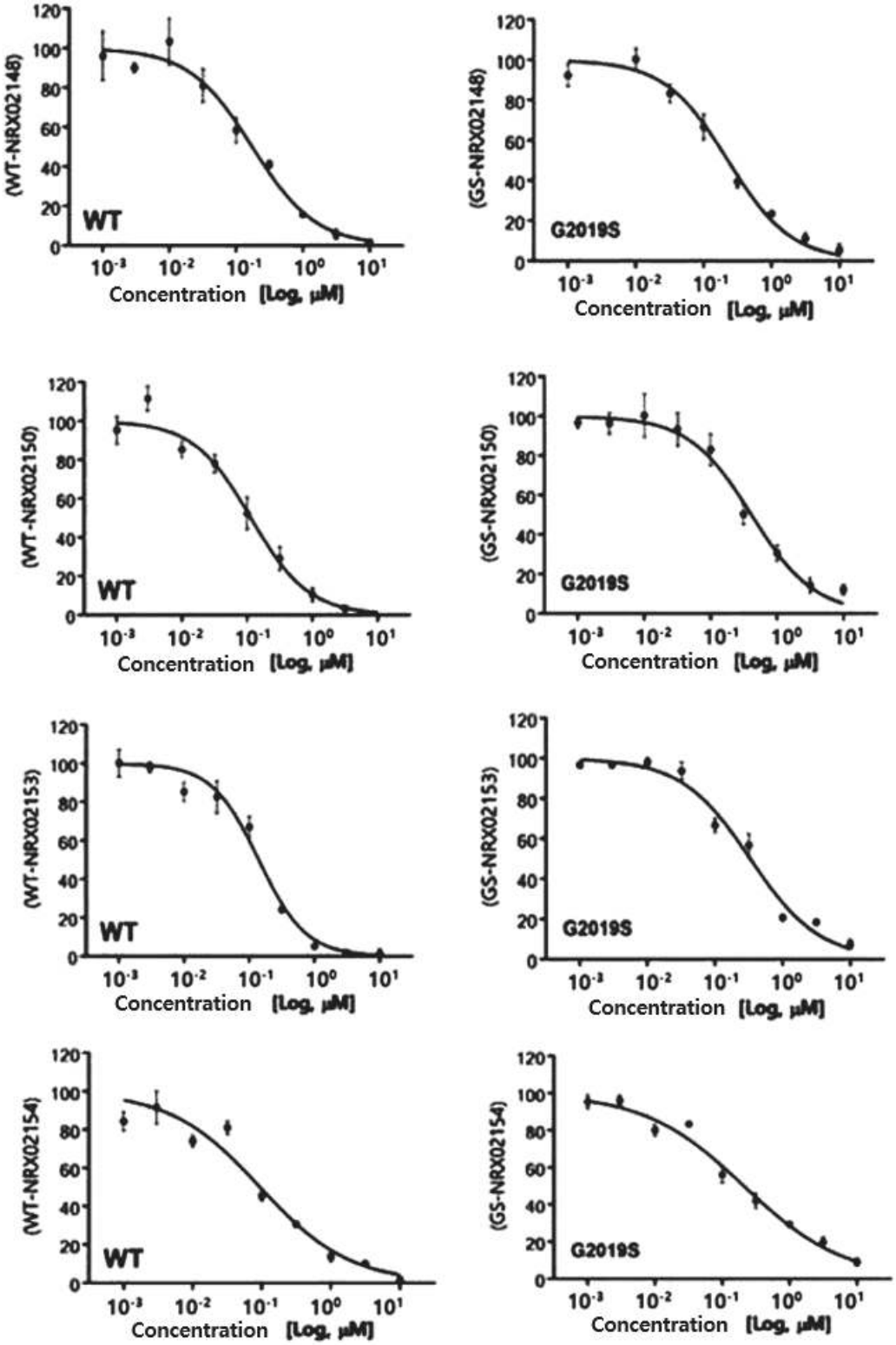
【FIG. 1a】



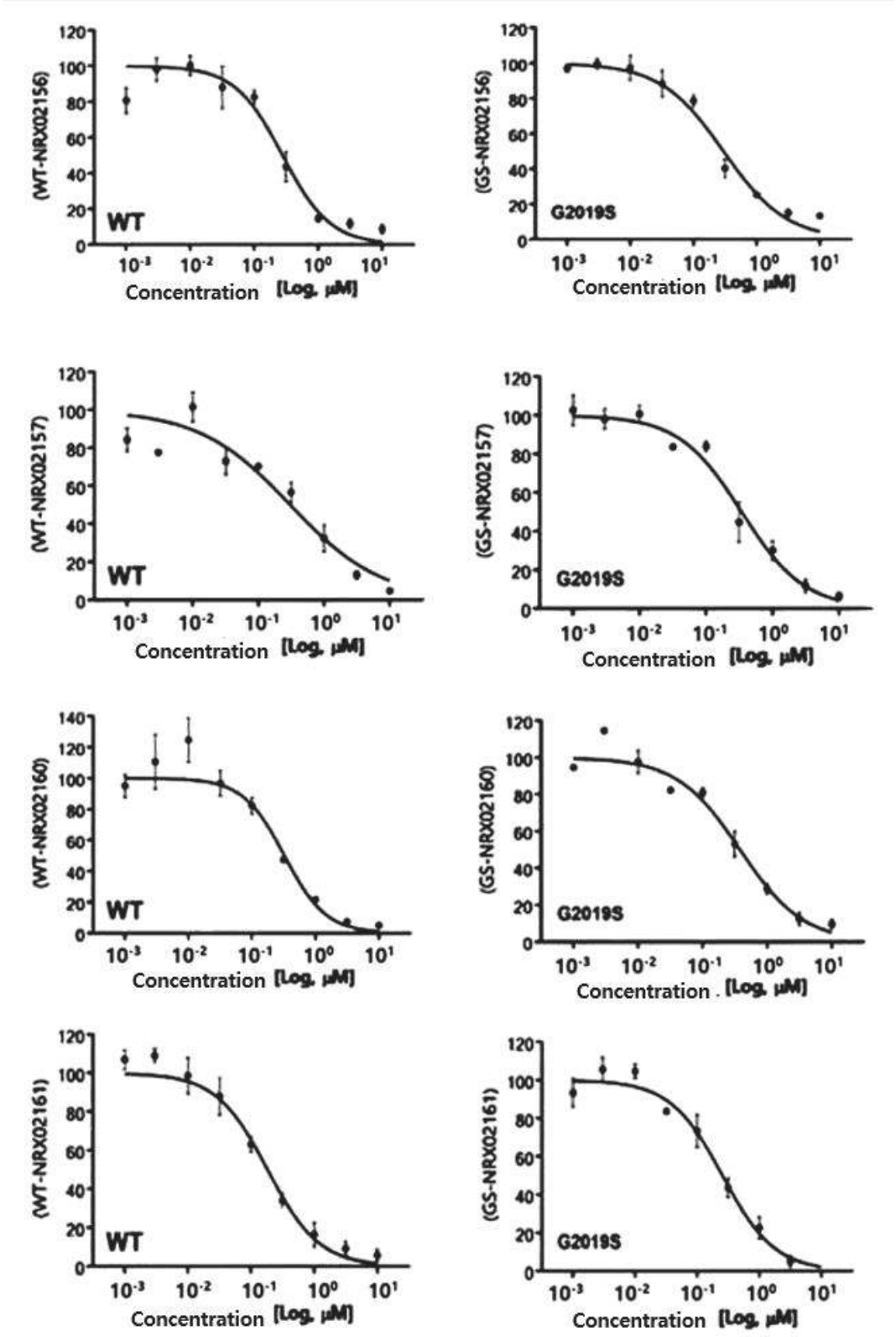
【FIG. 1b】


(WT-NRX02105)
WT
(GS-NRX02105)
G2019S
(WT-NRX02106)
WT
(GS-NRX02106)
G2019S
(WT-NRX02107)
WT
(GS-NRX02107)
G2019S
(WT-NRX02147)
WT
(GS-NRX02147)
G2019S
Concentration [Log, μM]

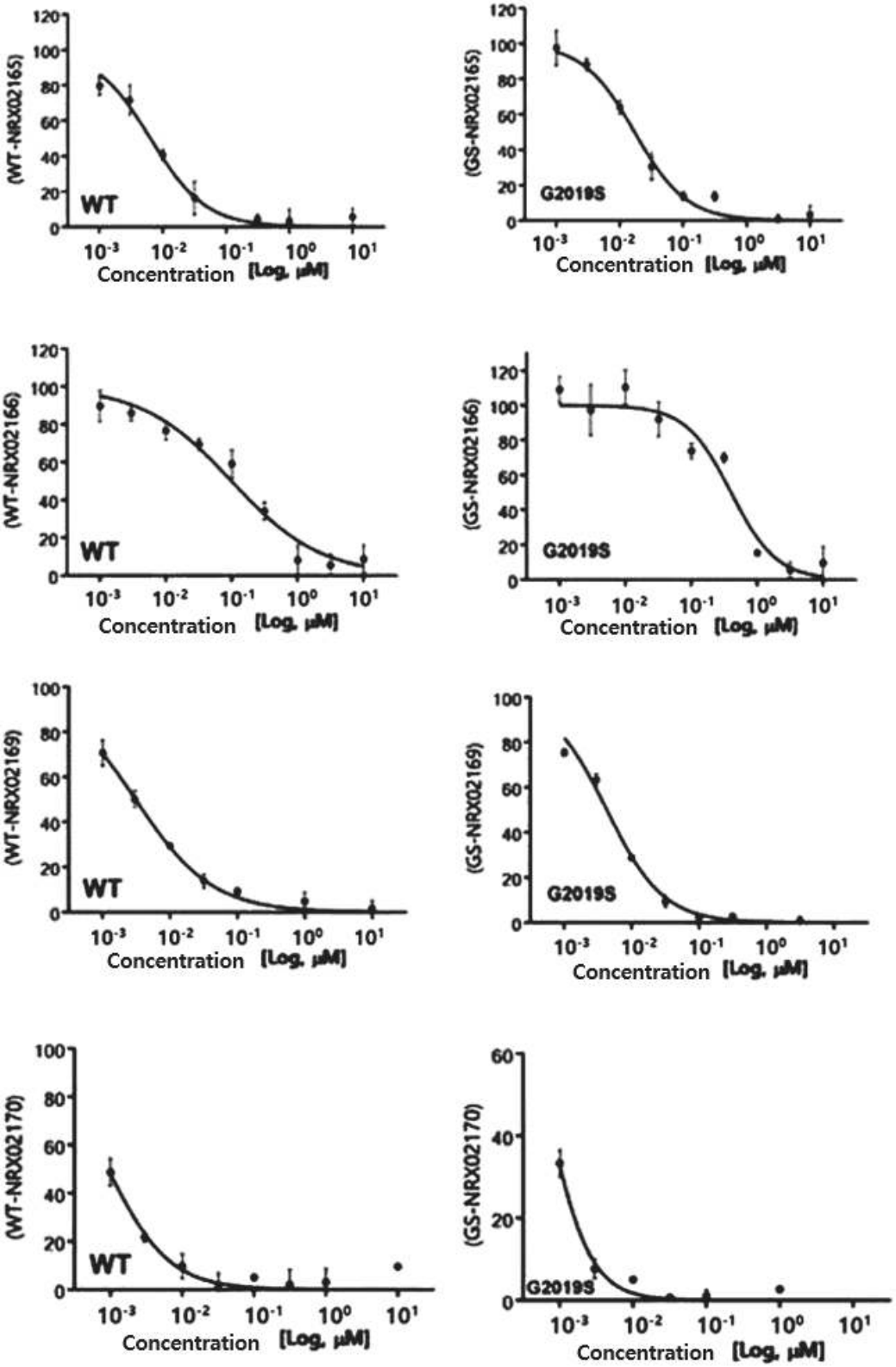
【FIG. 1c】


(WT-NRX02148)
WT
Concentration [Log, μM]
(GS-NRX02148)
G2019S
Concentration [Log, μM]
(WT-NRX02150)
WT
Concentration [Log, μM]
(GS-NRX02150)
G2019S
Concentration [Log, μM]
(WT-NRX02153)
WT
Concentration [Log, μM]
(GS-NRX02153)
G2019S
Concentration [Log, μM]
(WT-NRX02154)
WT
Concentration [Log, μM]
(GS-NRX02154)
G2019S
Concentration [Log, μM]

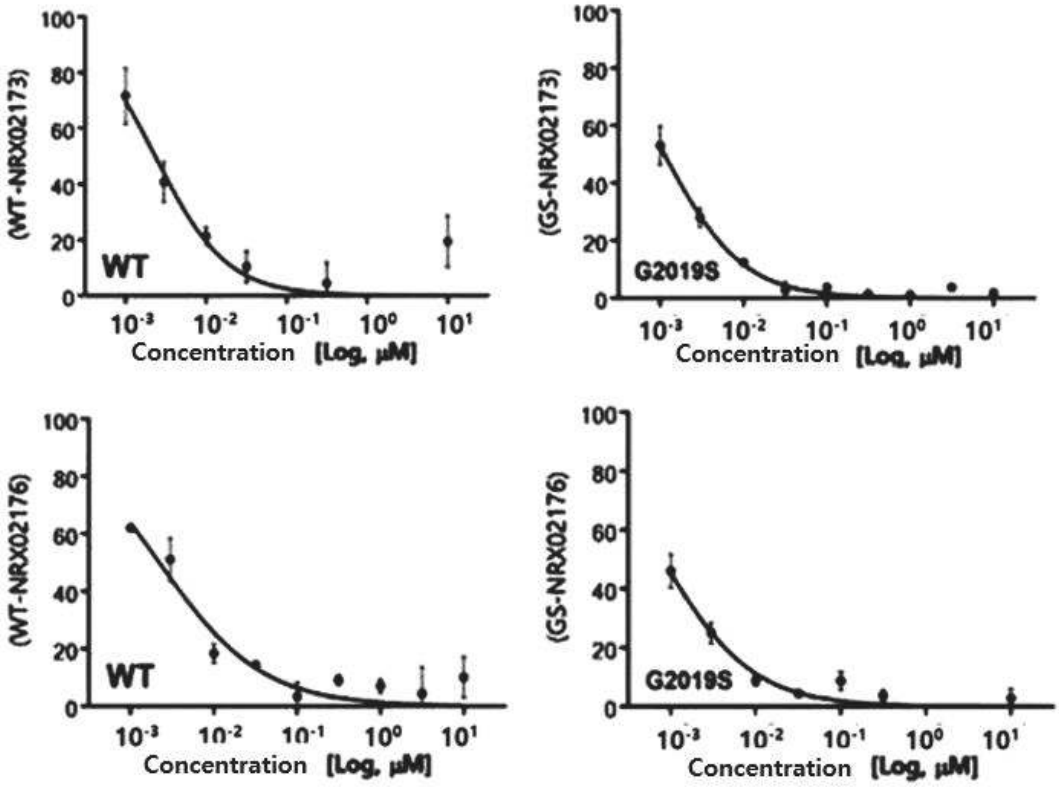
【FIG. 1d】


(WT-NRX02156)
WT
Concentration [Log, μM]
(GS-NRX02156)
G2019S
Concentration [Log, μM]
(WT-NRX02157)
WT
Concentration [Log, μM]
(GS-NRX02157)
G2019S
Concentration [Log, μM]
(WT-NRX02160)
WT
Concentration [Log, μM]
(GS-NRX02160)
G2019S
Concentration [Log, μM]
(WT-NRX02161)
WT
Concentration [Log, μM]
(GS-NRX02161)
G2019S
Concentration [Log, μM]

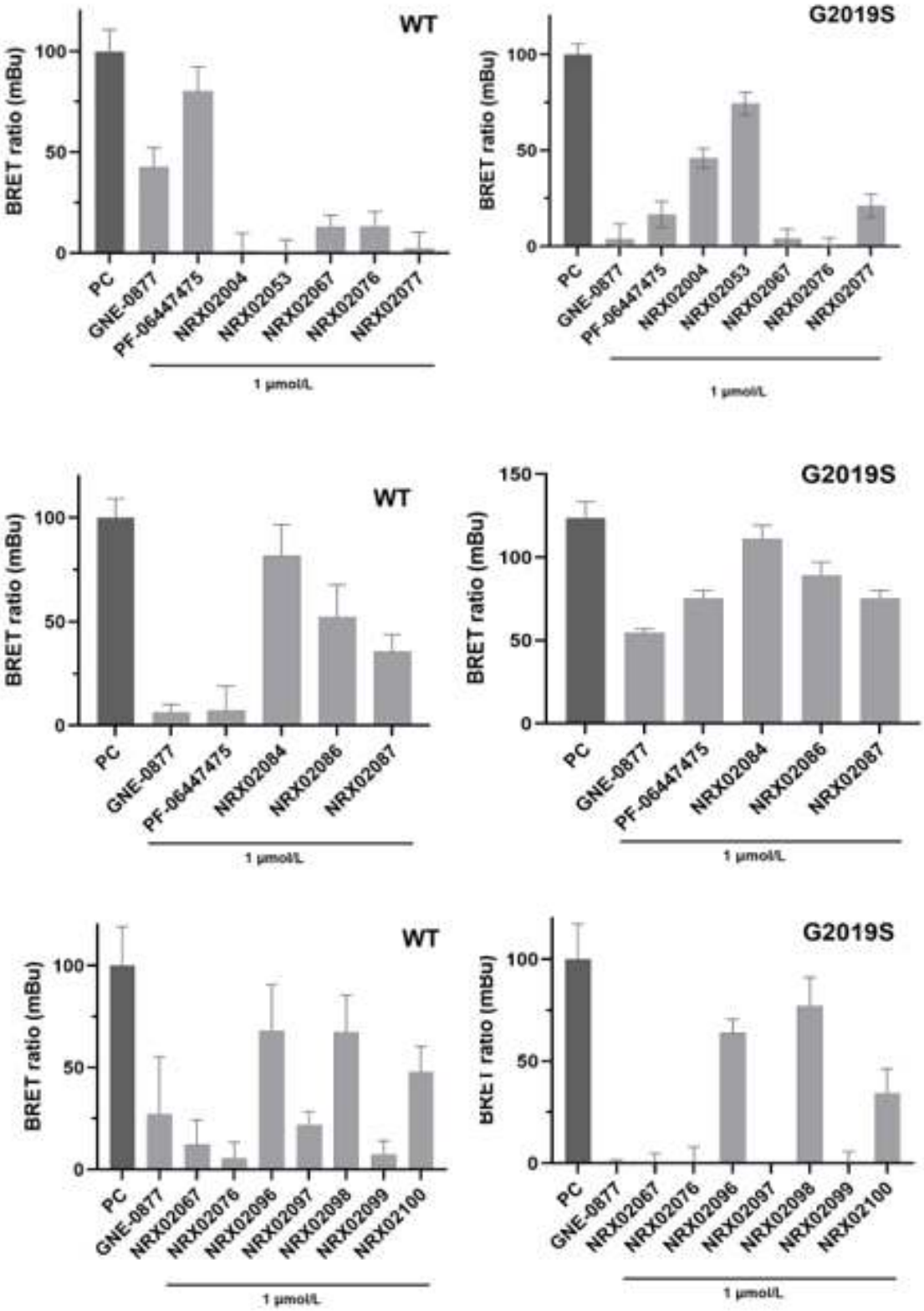
【FIG. 1e】


(WT-NRX02165)
WT
Concentration [Log, μM]
(GS-NRX02165)
G2019S
Concentration [Log, μM]
(WT-NRX02166)
WT
Concentration [Log, μM]
(GS-NRX02166)
G2019S
Concentration [Log, μM]
(WT-NRX02169)
WT
Concentration [Log, μM]
(GS-NRX02169)
G2019S
Concentration [Log, μM]
(WT-NRX02170)
WT
Concentration [Log, μM]
(GS-NRX02170)
G2019S
Concentration [Log, μM]

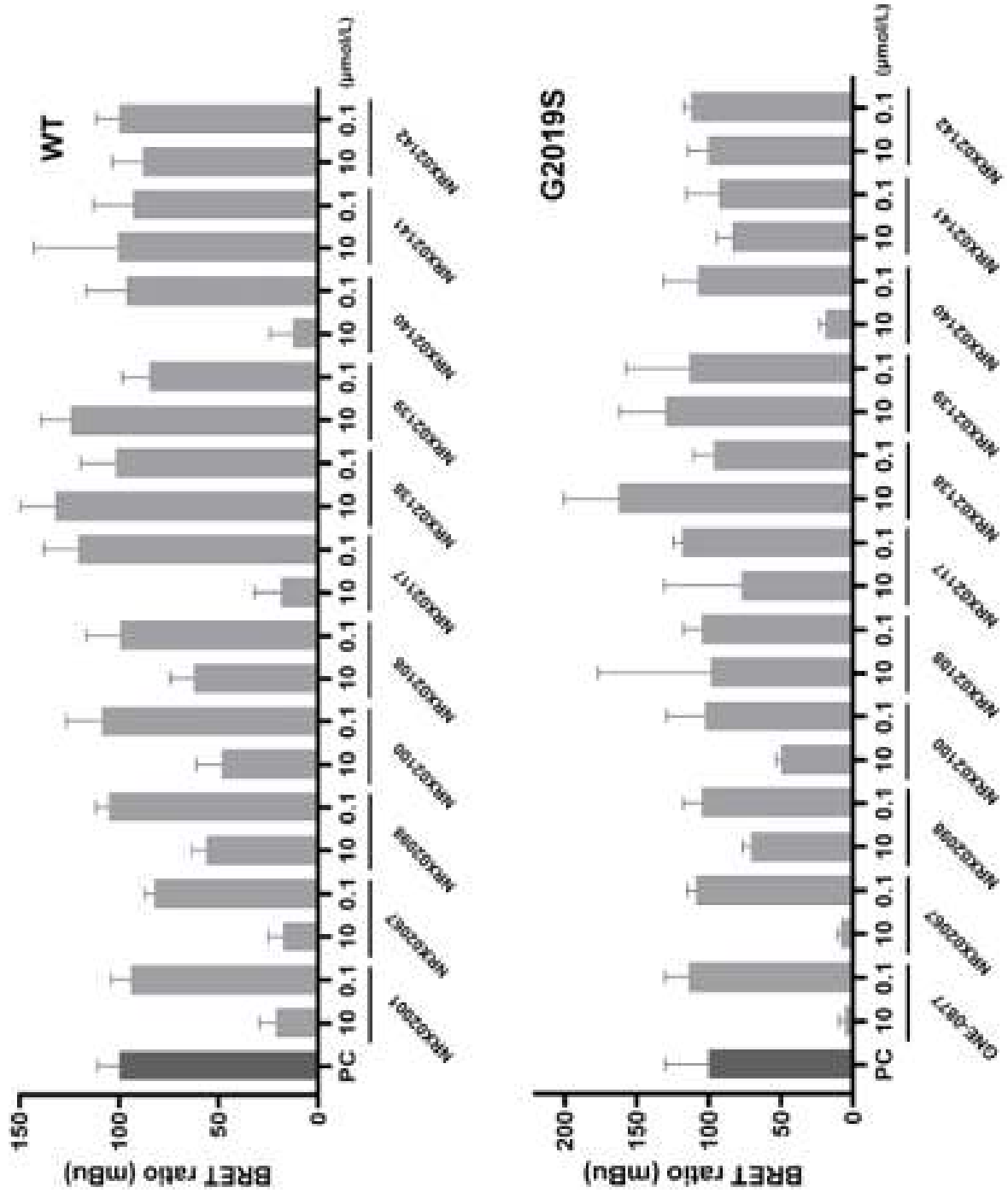
【FIG. 1f】


(WT-NRX02173)
WT
Concentration [Log, μM]
(GS-NRX02173)
G2019S
Concentration [Log, μM]
(WT-NRX02176)
WT
Concentration [Log, μM]
(GS-NRX02176)
G2019S
Concentration [Log, μM]

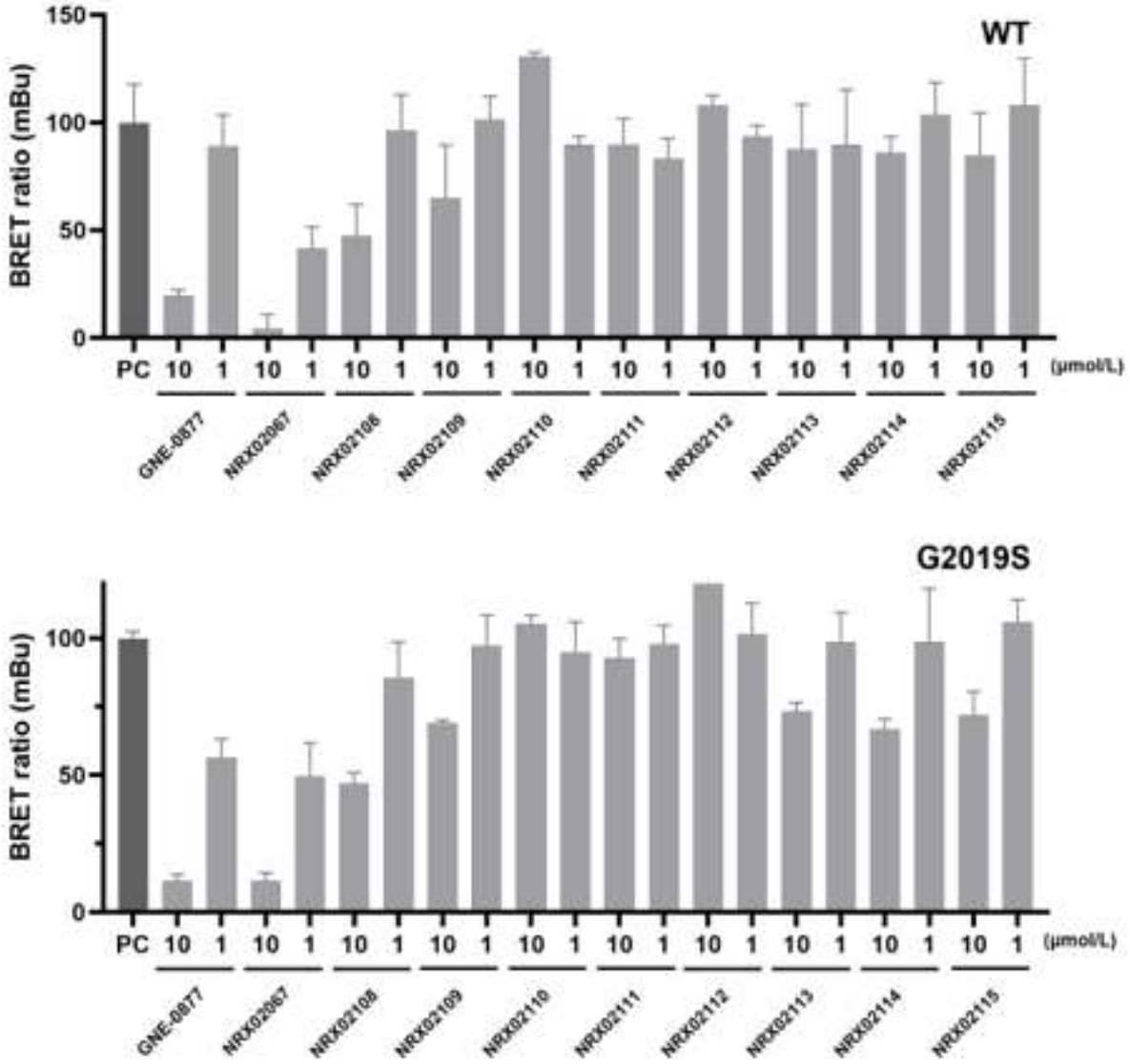
【FIG. 2a】


WT
G2019S
BRET ratio (mBu)
100
50
0
PC
GNE-0877
PF-06447475
NRX02004
NRX02053
NRX02067
NRX02076
NRX02077
1 μmol/L
WT
G2019S
BRET ratio (mBu)
150
100
50
0
PC
GNE-0877
PF-06447475
NRX02084
NRX02086
NRX02087
1 μmol/L
WT
G2019S
BRET ratio (mBu)
100
50
0
PC
GNE-0877
NRX02067
NRX02076
NRX02096
NRX02097
NRX02098
NRX02099
NRX02100
1 μmol/L

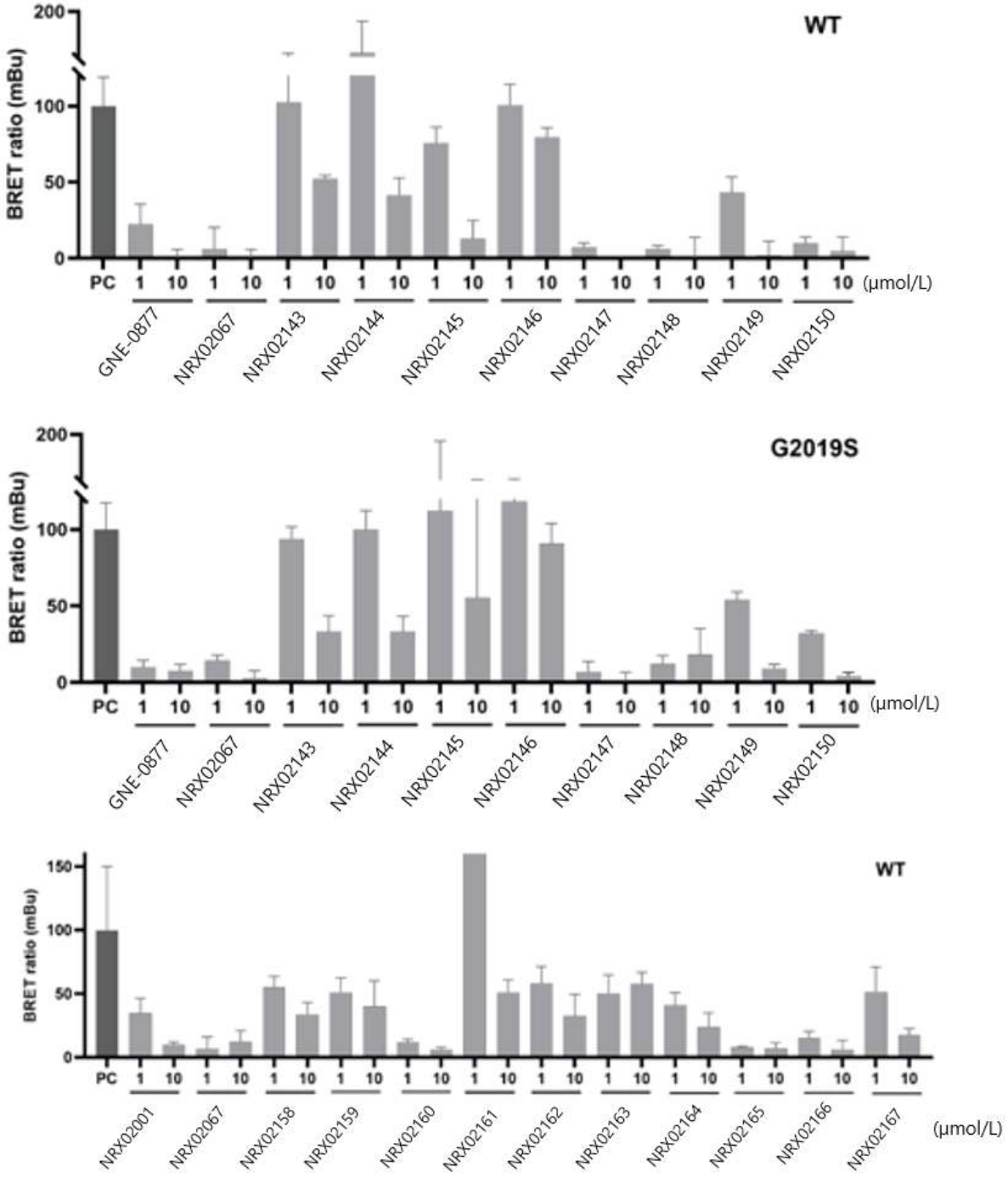
【FIG. 2b】


WT
G2019S
BRET ratio (mBu)
(μmol/L)
PC
10
0.1
NRX02001
NRX02067
NRX02098
NRX02100
NRX02108
NRX02117
NRX02138
NRX02139
NRX02140
NRX02141
NRX02142
GNE-0877

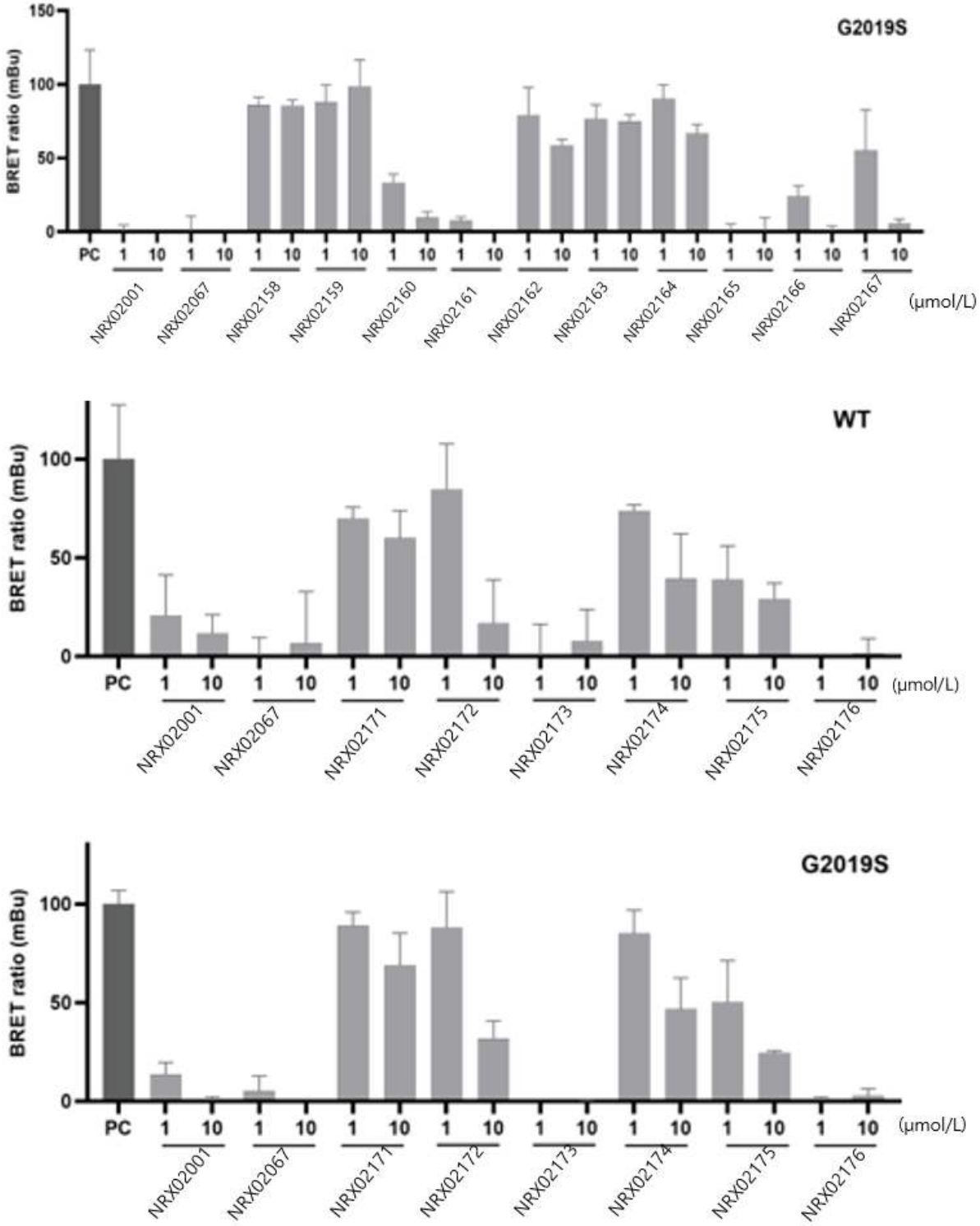
【FIG. 2c】


WT
BRET ratio (mBu)
150
100
50
0
PC 10 1 10 1 10 1 10 1 10 1 10 1 10 1 10 1 10 1 10 1
(μmol/L)
GNE-0877
NRX02067
NRX02108
NRX02109
NRX02110
NRX02111
NRX02112
NRX02113
NRX02114
NRX02115
G2019S
BRET ratio (mBu)
100
50
0
PC 10 1 10 1 10 1 10 1 10 1 10 1 10 1 10 1 10 1 10 1
(μmol/L)
GNE-0877
NRX02067
NRX02108
NRX02109
NRX02110
NRX02111
NRX02112
NRX02113
NRX02114
NRX02115

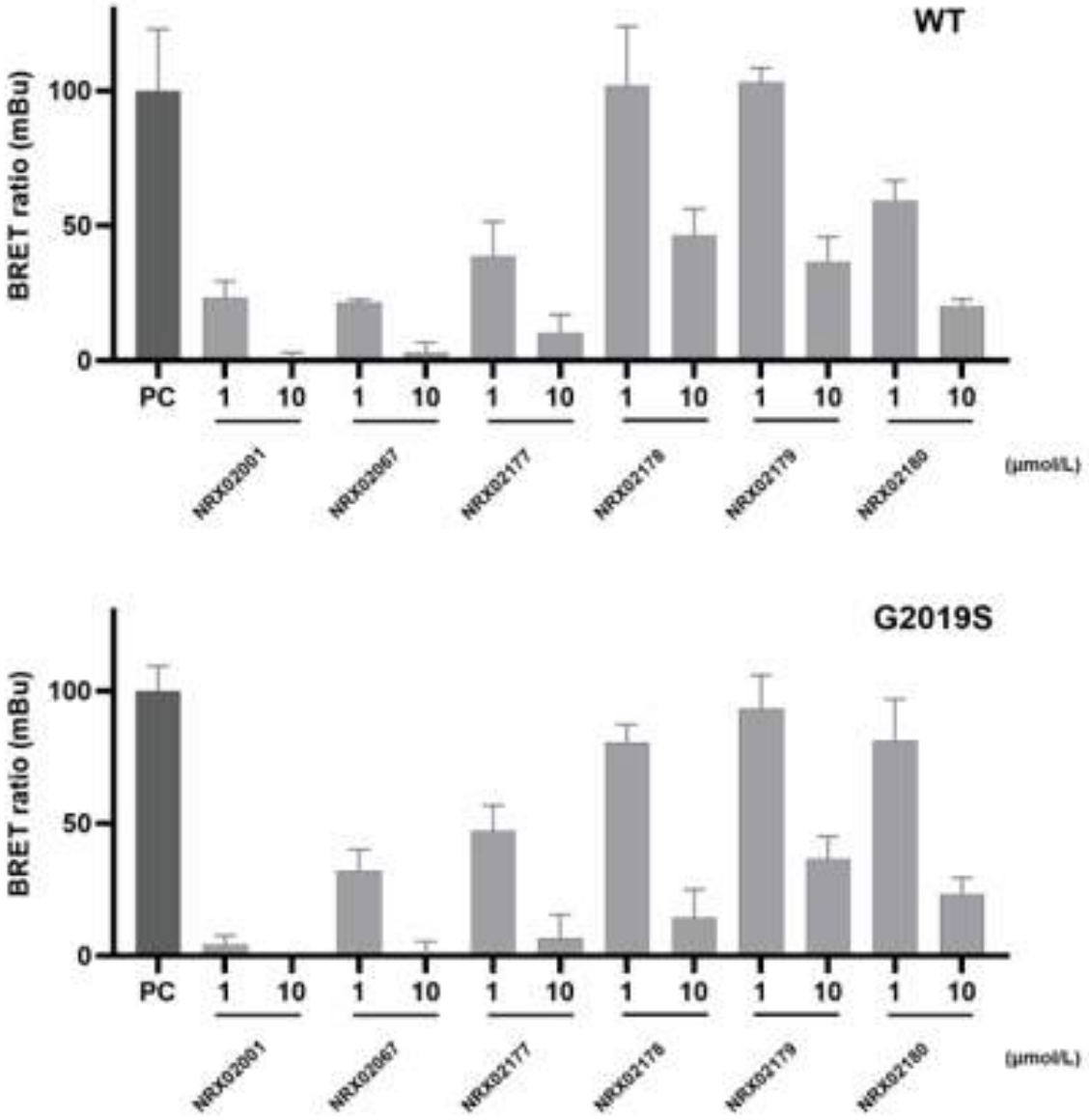
【FIG. 2d】


WT
BRET ratio (mBu)
200
100
50
0
PC
1
10
(μmol/L)
GNE-0877
NRX02067
NRX02143
NRX02144
NRX02145
NRX02146
NRX02147
NRX02148
NRX02149
NRX02150
G2019S
BRET ratio (mBu)
GNE-0877
NRX02067
NRX02143
NRX02144
NRX02145
NRX02146
NRX02147
NRX02148
NRX02149
NRX02150
WT
BRET ratio (mBu)
150
100
50
0
NRX02001
NRX02067
NRX02158
NRX02159
NRX02160
NRX02161
NRX02162
NRX02163
NRX02164
NRX02165
NRX02166
NRX02167
(μmol/L)

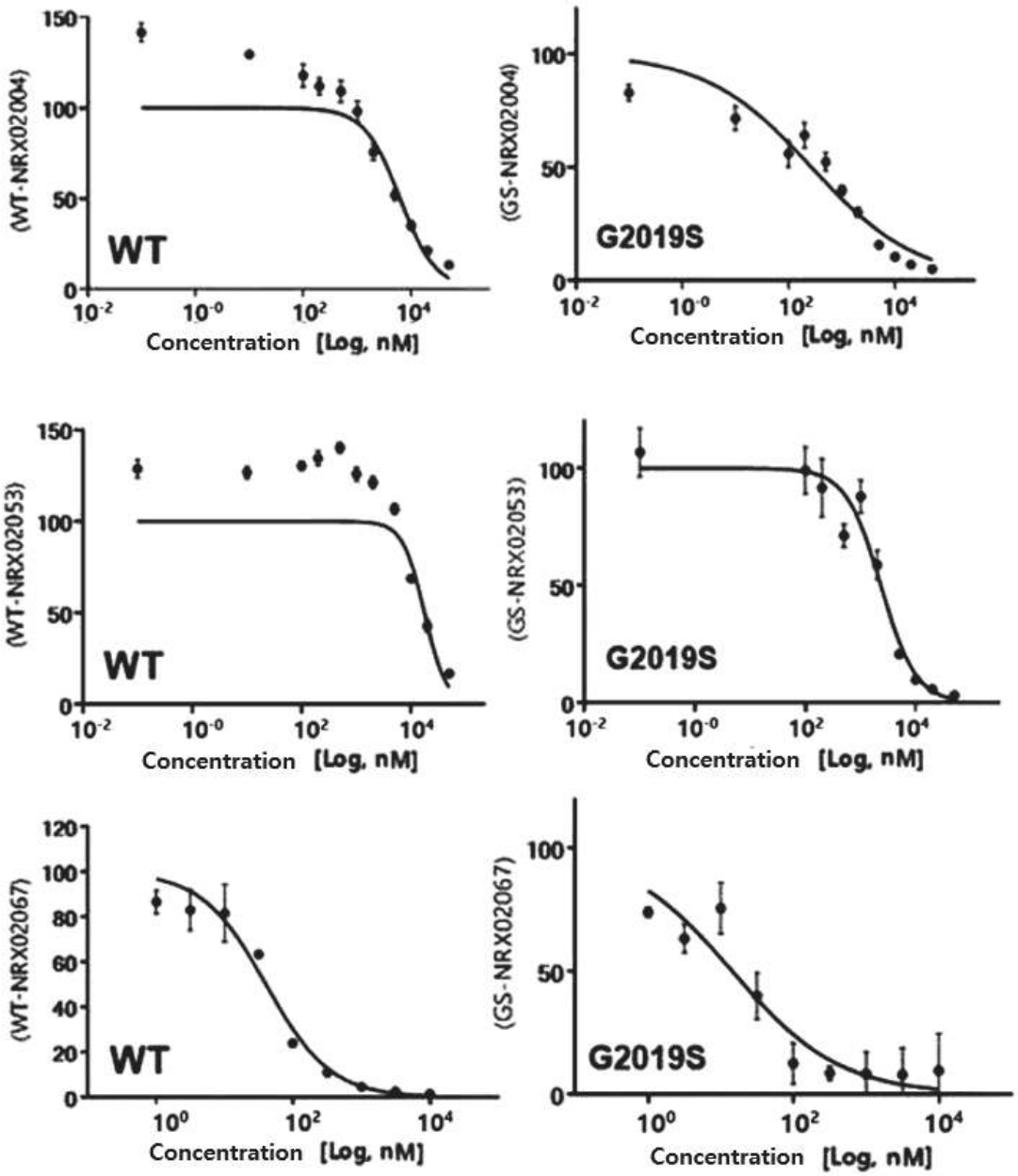
【FIG. 2e】


G2019S
BRET ratio (mBu)
150
100
50
0
PC
1
10
NRX02001
NRX02067
NRX02158
NRX02159
NRX02160
NRX02161
NRX02162
NRX02163
NRX02164
NRX02165
NRX02166
NRX02167
(μmol/L)
WT
BRET ratio (mBu)
100
50
0
PC
1
10
NRX02001
NRX02067
NRX02171
NRX02172
NRX02173
NRX02174
NRX02175
NRX02176
(μmol/L)
G2019S
BRET ratio (mBu)
100
50
0
PC
1
10
NRX02001
NRX02067
NRX02171
NRX02172
NRX02173
NRX02174
NRX02175
NRX02176
(μmol/L)

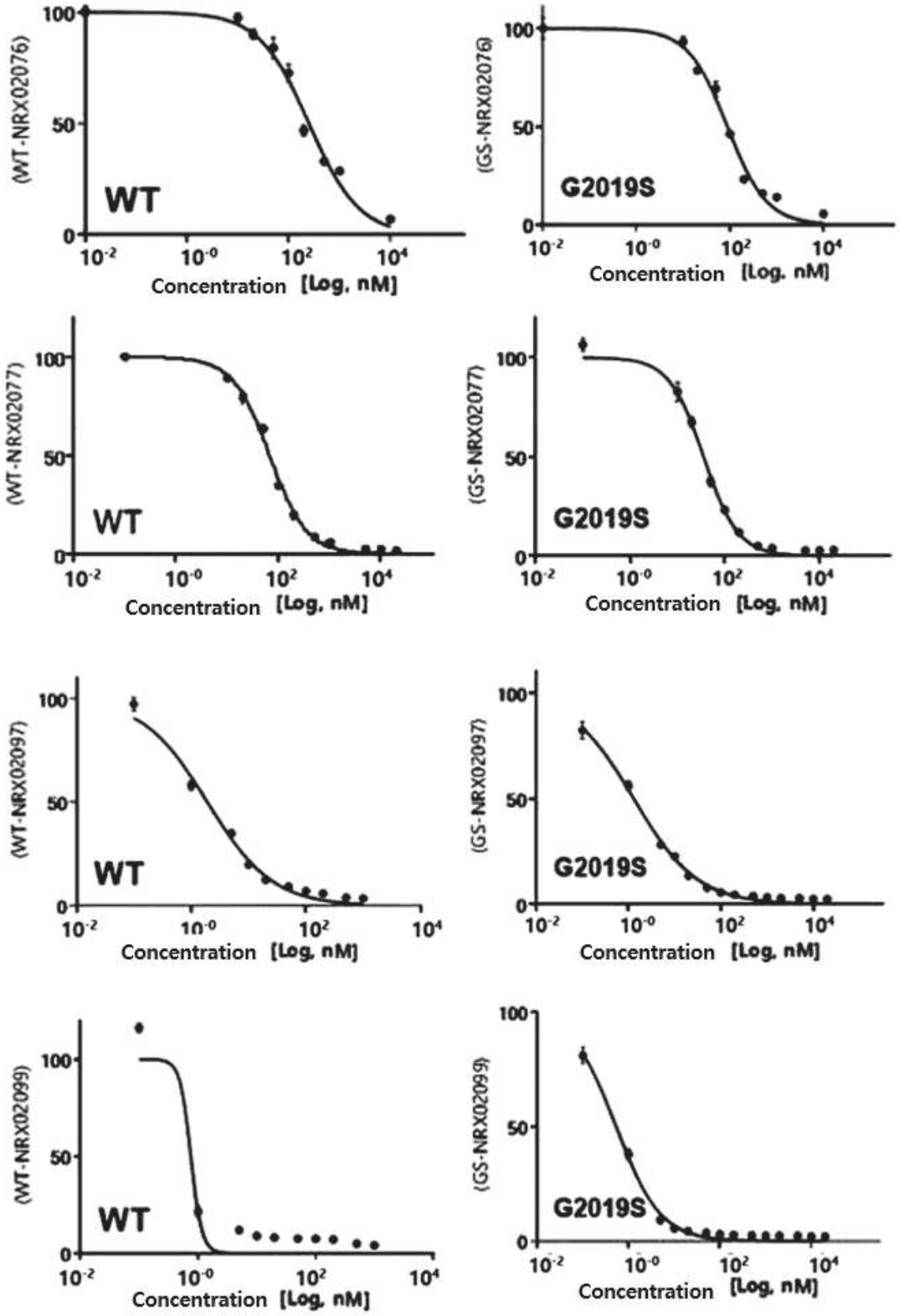
【FIG. 2f】


WT
BRET ratio (mBu)
100
50
0
PC
1
10
NRX02001
NRX02067
NRX02177
NRX02178
NRX02179
NRX02180
(μmol/L)
G2019S
BRET ratio (mBu)
100
50
0
PC
1
10
NRX02001
NRX02067
NRX02177
NRX02178
NRX02179
NRX02180
(μmol/L)

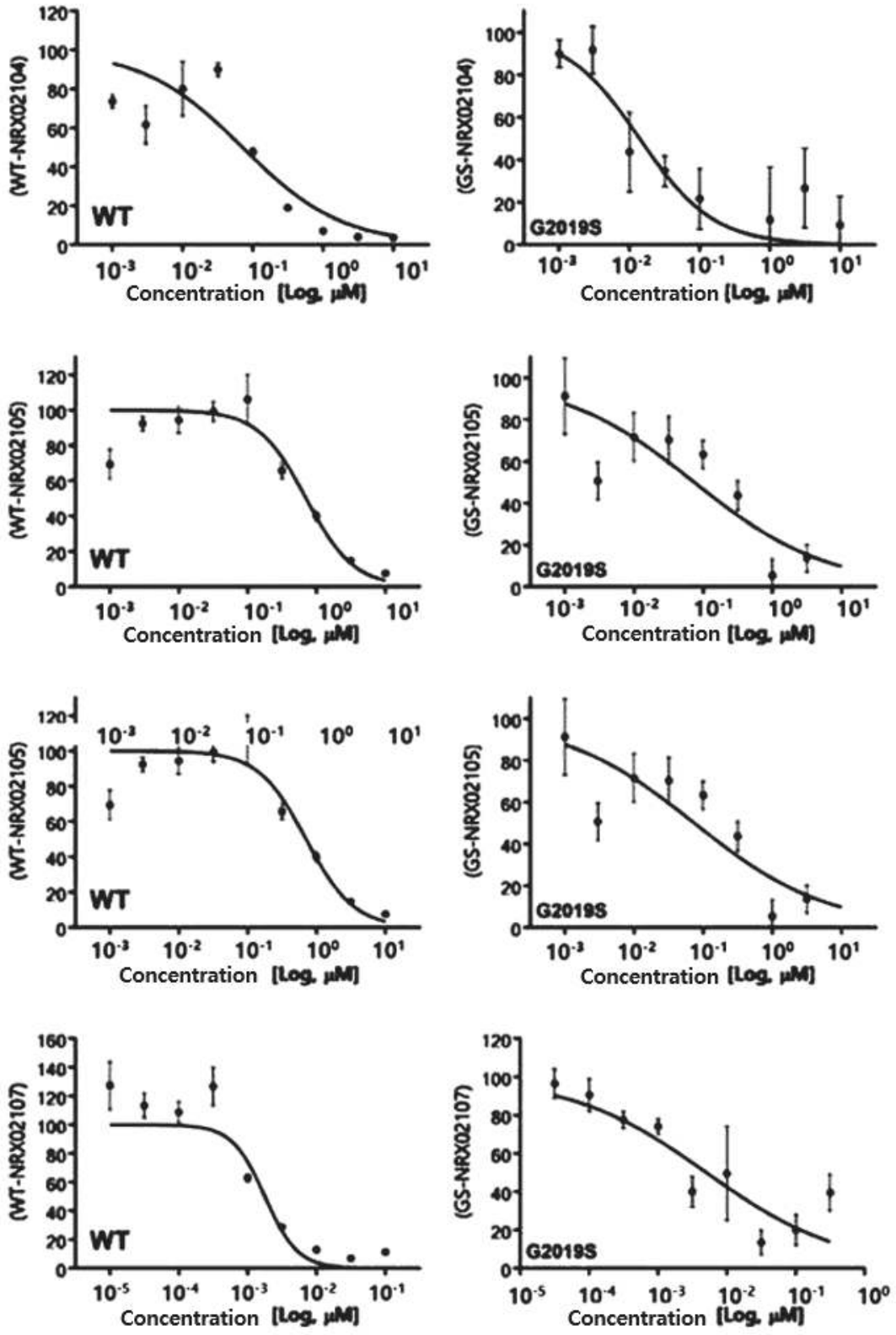
【FIG. 3a】


(WT-NRX02004)
WT
Concentration [Log, nM]
(GS-NRX02004)
G2019S
Concentration [Log, nM]
(WT-NRX02053)
WT
Concentration [Log, nM]
(GS-NRX02053)
G2019S
Concentration [Log, nM]
(WT-NRX02067)
WT
Concentration [Log, nM]
(GS-NRX02067)
G2019S
Concentration [Log, nM]

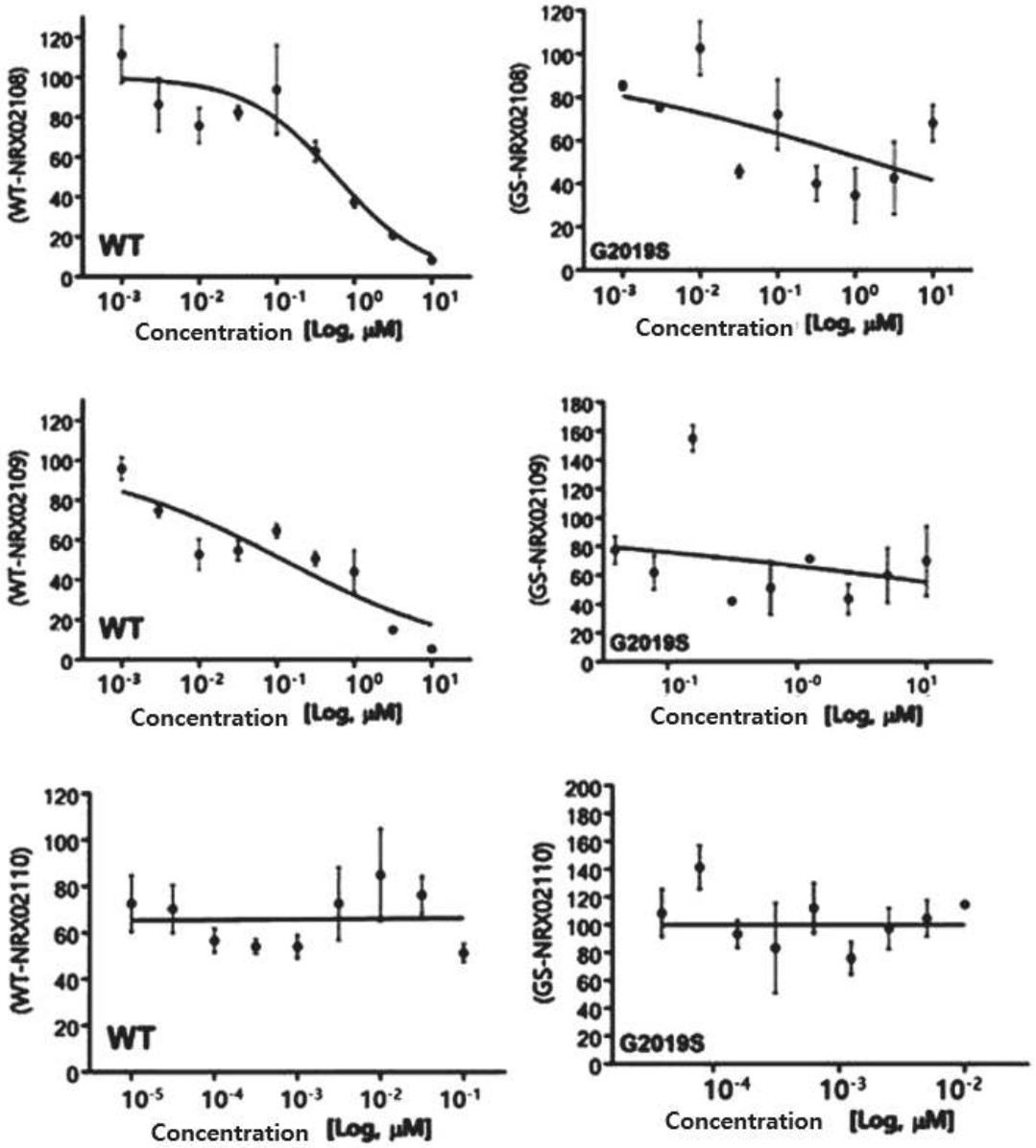
【FIG. 3b】


(WT-NRX02076)
WT
Concentration [Log, nM]
(GS-NRX02076)
G2019S
Concentration [Log, nM]
(WT-NRX02077)
WT
Concentration [Log, nM]
(GS-NRX02077)
G2019S
Concentration [Log, nM]
(WT-NRX02097)
WT
Concentration [Log, nM]
(GS-NRX02097)
G2019S
Concentration [Log, nM]
(WT-NRX02099)
WT
Concentration [Log, nM]
(GS-NRX02099)
G2019S
Concentration [Log, nM]

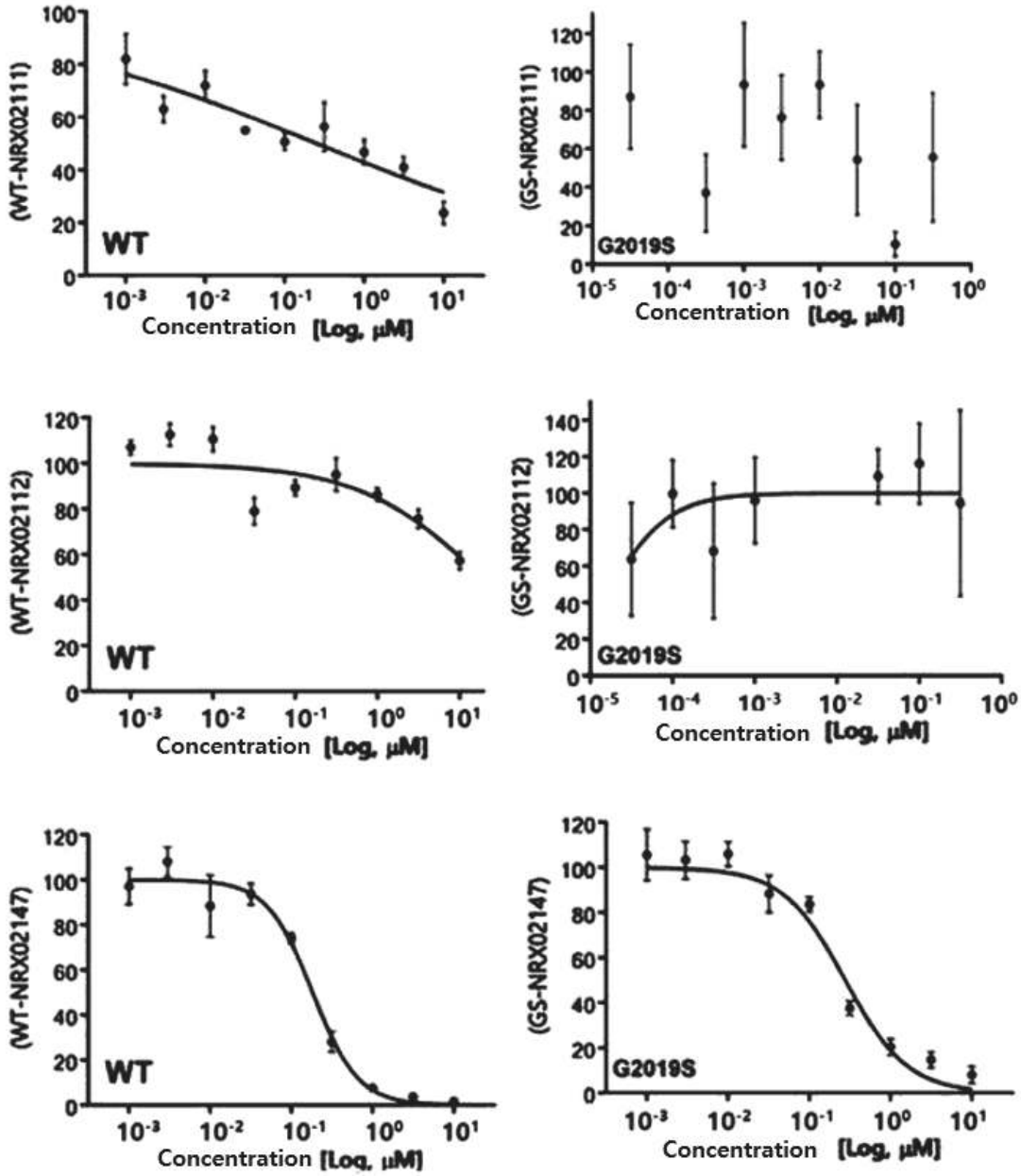
【FIG. 3c】


(WT-NRX02104)
WT
Concentration [Log, μM]
(GS-NRX02104)
G2019S
Concentration [Log, μM]
(WT-NRX02105)
WT
Concentration [Log, μM]
(GS-NRX02105)
G2019S
Concentration [Log, μM]
(WT-NRX02105)
WT
Concentration [Log, μM]
(GS-NRX02105)
G2019S
Concentration [Log, μM]
(WT-NRX02107)
WT
Concentration [Log, μM]
(GS-NRX02107)
G2019S
Concentration [Log, μM]

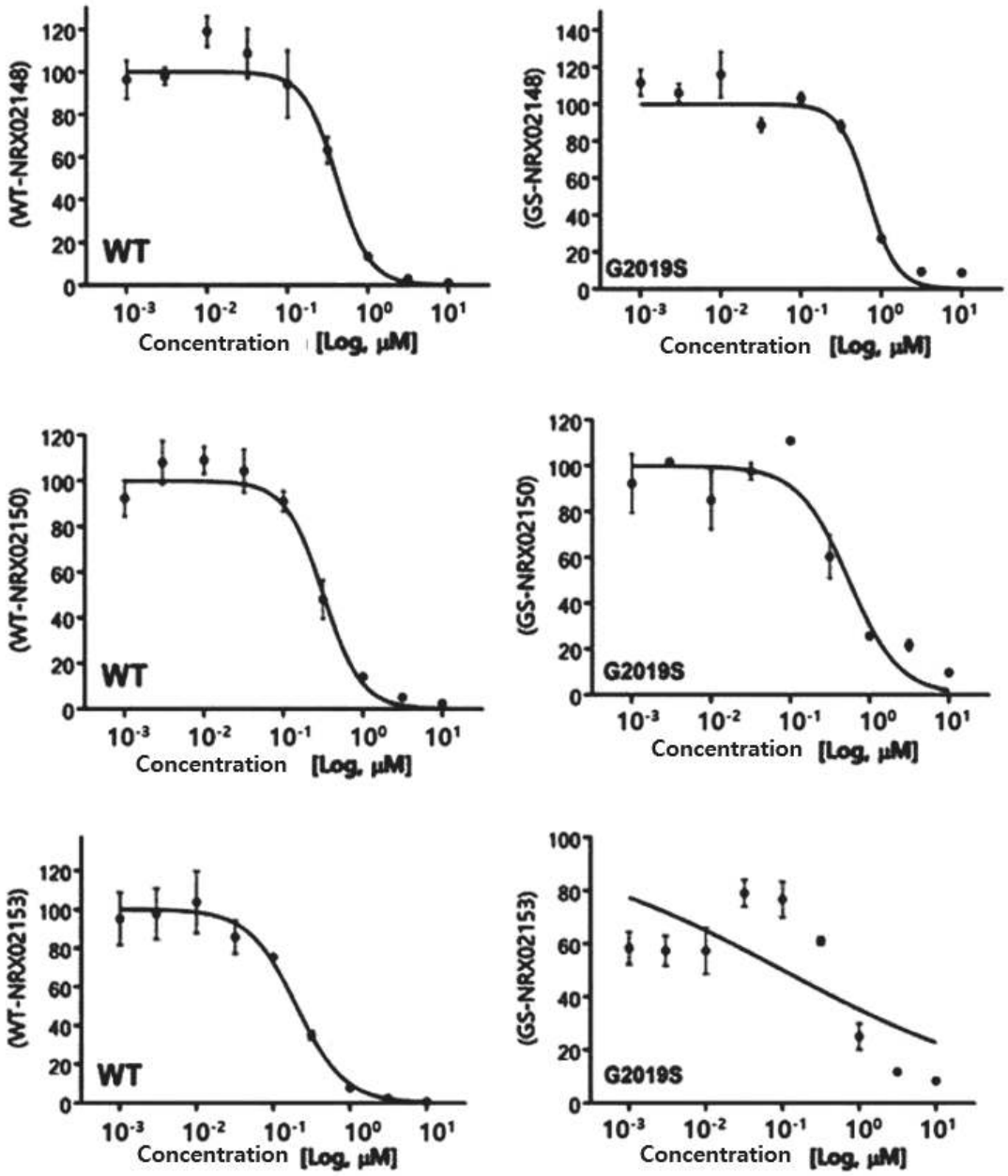
【FIG. 3d】


(WT-NRX02108)
WT
Concentration [Log, μM]
(GS-NRX02108)
G2019S
Concentration [Log, μM]
(WT-NRX02109)
WT
Concentration [Log, μM]
(GS-NRX02109)
G2019S
Concentration [Log, μM]
(WT-NRX02110)
WT
Concentration [Log, μM]
(GS-NRX02110)
G2019S
Concentration [Log, μM]

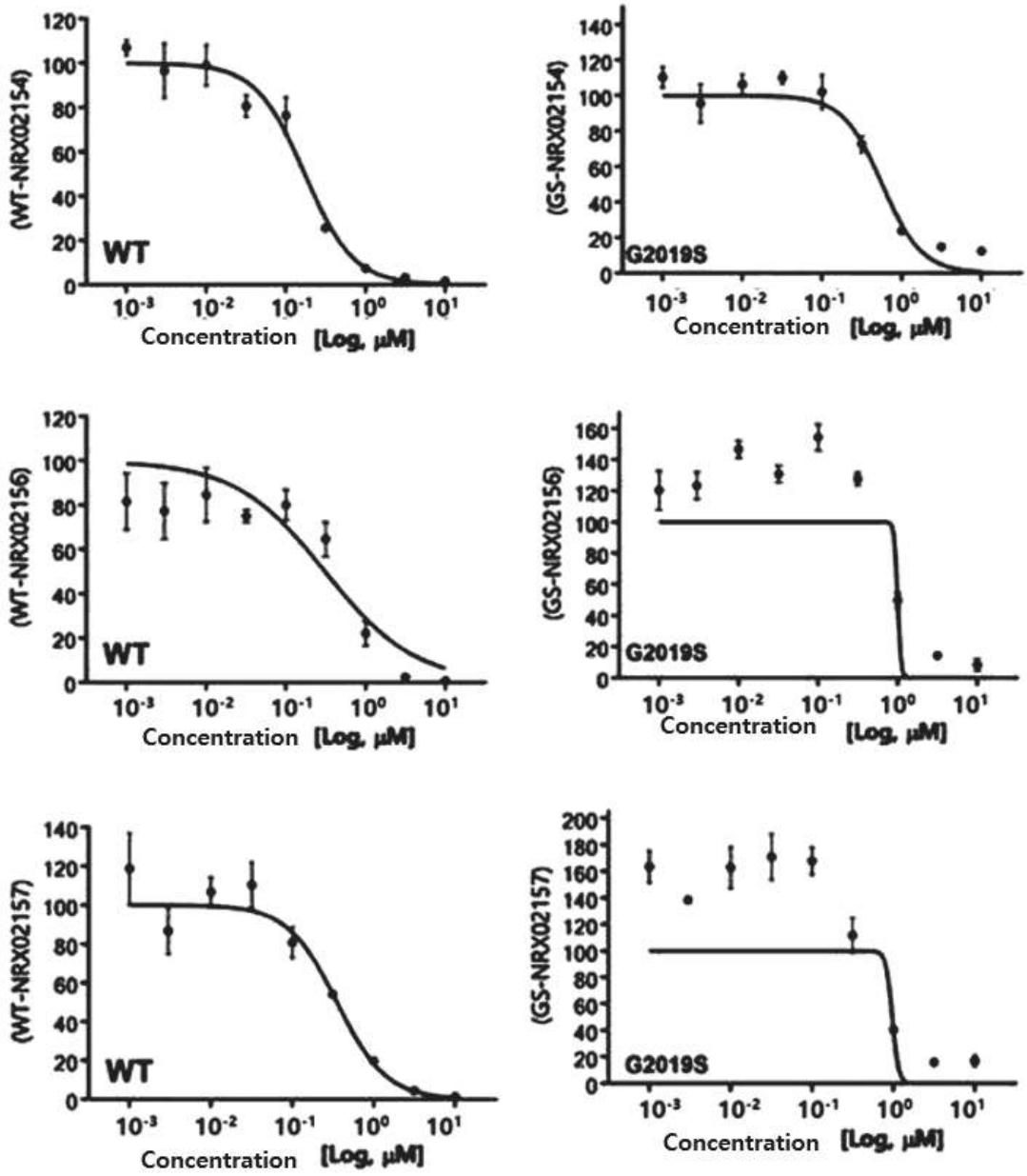
【FIG. 3e】


(WT-NRX02111)
WT
Concentration [Log, μM]
(GS-NRX02111)
G2019S
Concentration [Log, μM]
(WT-NRX02112)
WT
Concentration [Log, μM]
(GS-NRX02112)
G2019S
Concentration [Log, μM]
(WT-NRX02147)
WT
Concentration [Log, μM]
(GS-NRX02147)
G2019S
Concentration [Log, μM]

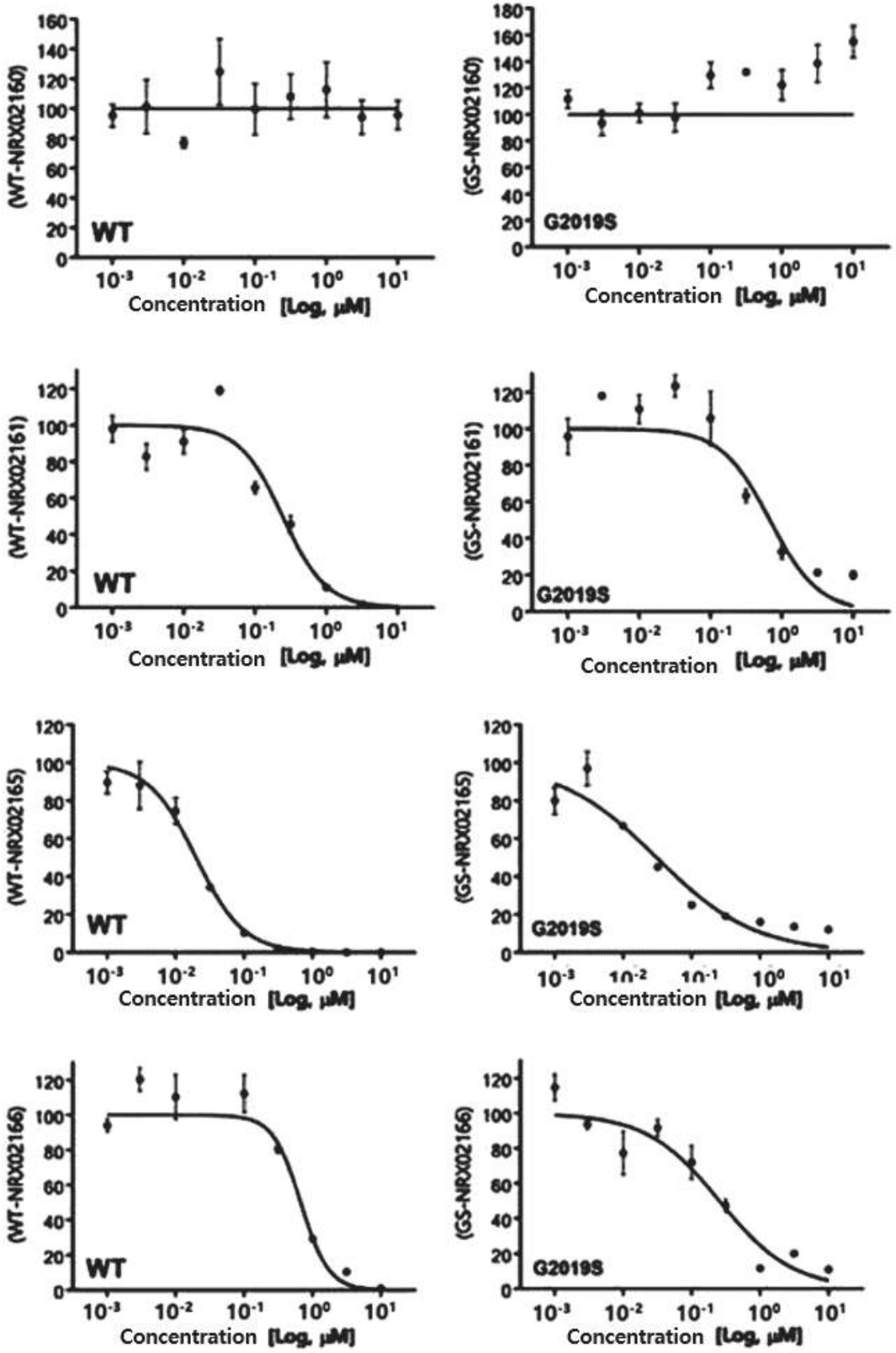
【FIG. 3f】


(WT-NRX02148)
WT
Concentration [Log, μM]
(GS-NRX02148)
G2019S
Concentration [Log, μM]
(WT-NRX02150)
WT
Concentration [Log, μM]
(GS-NRX02150)
G2019S
Concentration [Log, μM]
(WT-NRX02153)
WT
Concentration [Log, μM]
(GS-NRX02153)
G2019S
Concentration [Log, μM]

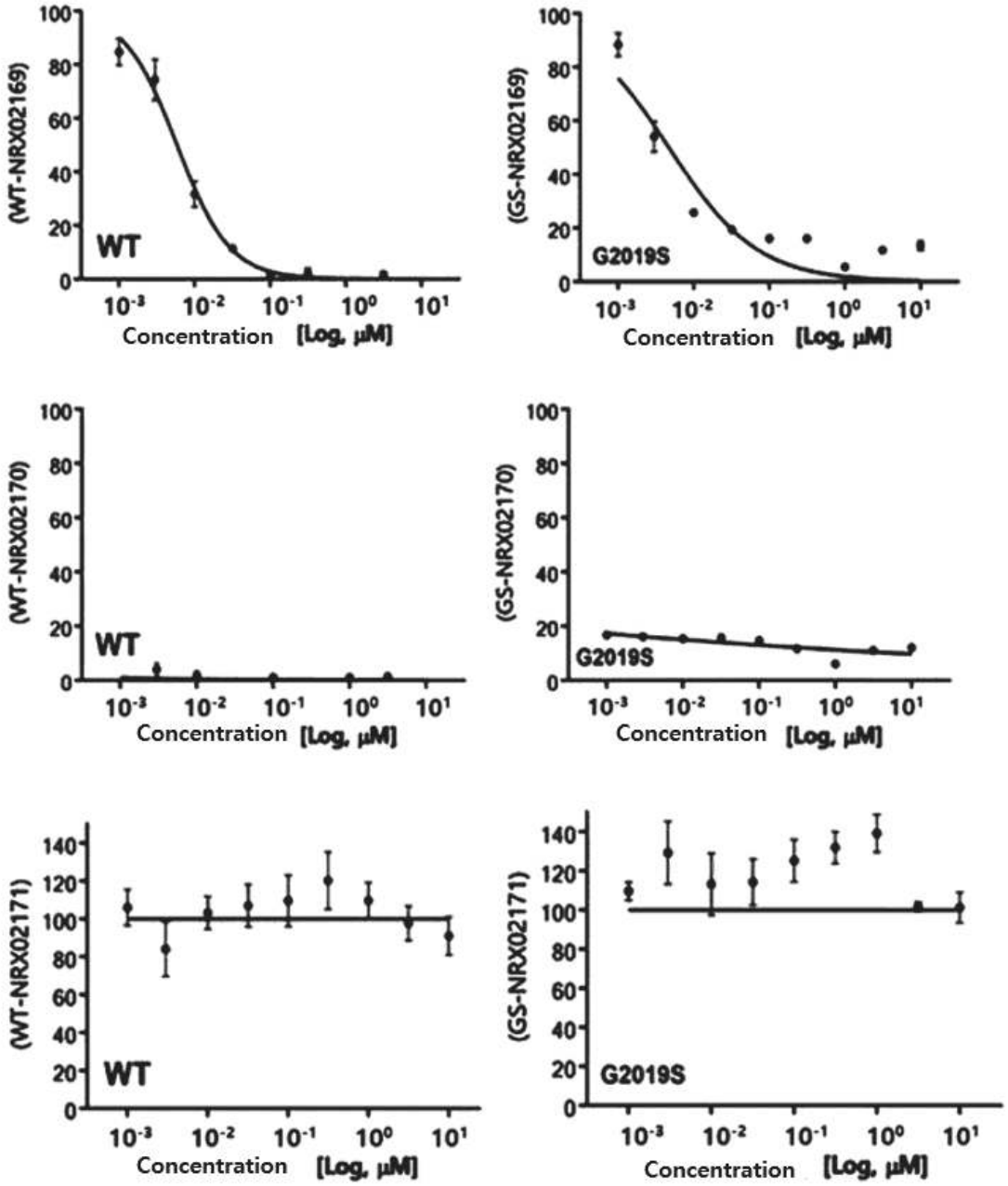
【FIG. 3g】


(WT-NRX02154)
WT
Concentration [Log, μM]
(GS-NRX02154)
G2019S
Concentration [Log, μM]
(WT-NRX02156)
WT
Concentration [Log, μM]
(GS-NRX02156)
G2019S
Concentration [Log, μM]
(WT-NRX02157)
WT
Concentration [Log, μM]
(GS-NRX02157)
G2019S
Concentration [Log, μM]

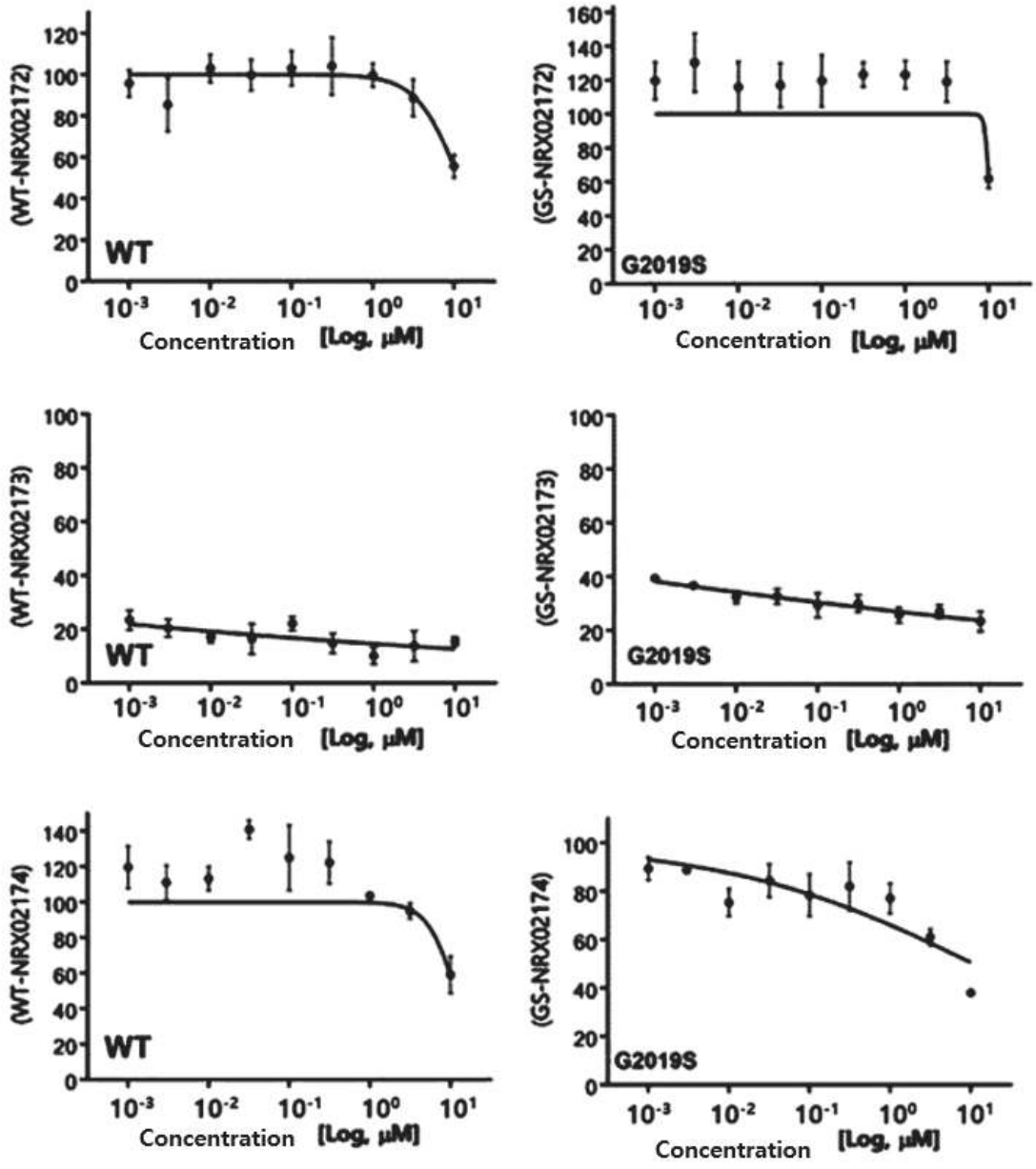
【FIG. 3h】


(WT-NRX02160)
WT
Concentration [Log, μM]
(GS-NRX02160)
G2019S
Concentration [Log, μM]
(WT-NRX02161)
WT
Concentration [Log, μM]
(GS-NRX02161)
G2019S
Concentration [Log, μM]
(WT-NRX02165)
WT
Concentration [Log, μM]
(GS-NRX02165)
G2019S
Concentration [Log, μM]
(WT-NRX02166)
WT
Concentration [Log, μM]
(GS-NRX02166)
G2019S
Concentration [Log, μM]

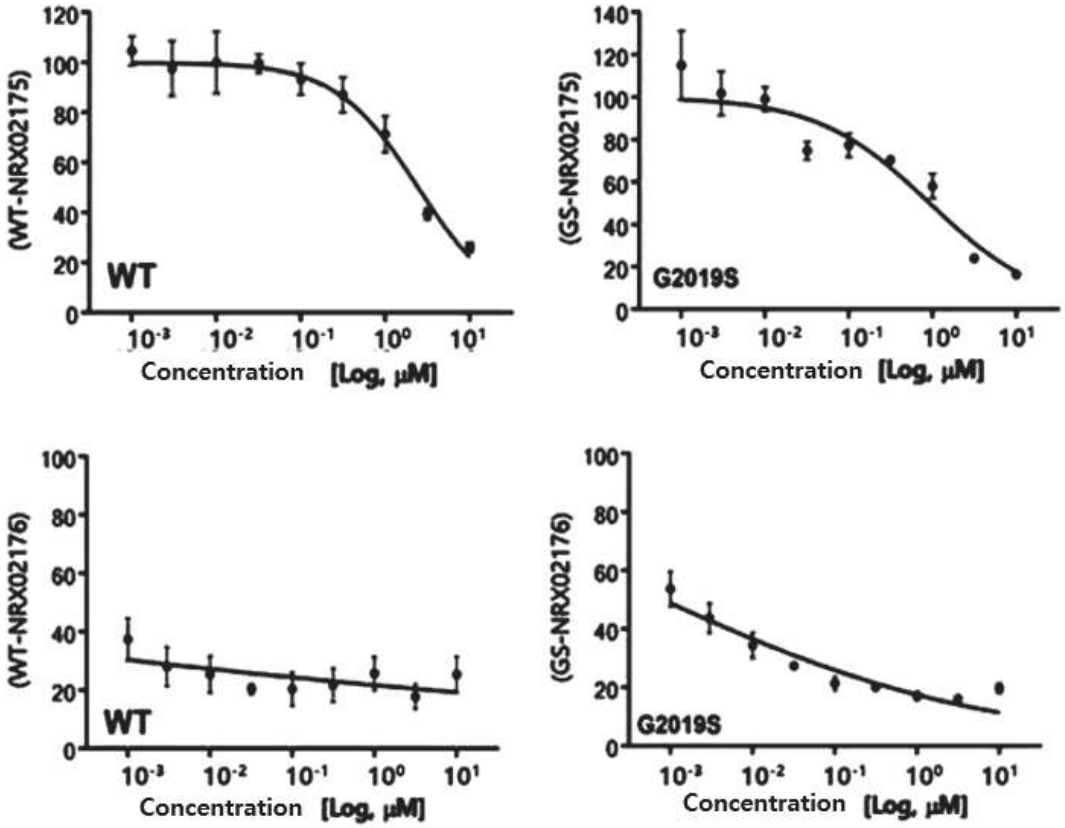
【FIG. 3i】


(WT-NRX02169)
WT
Concentration [Log, μM]
(GS-NRX02169)
G2019S
Concentration [Log, μM]
(WT-NRX02170)
WT
Concentration [Log, μM]
(GS-NRX02170)
G2019S
Concentration [Log, μM]
(WT-NRX02171)
WT
Concentration [Log, μM]
(GS-NRX02171)
G2019S
Concentration [Log, μM]

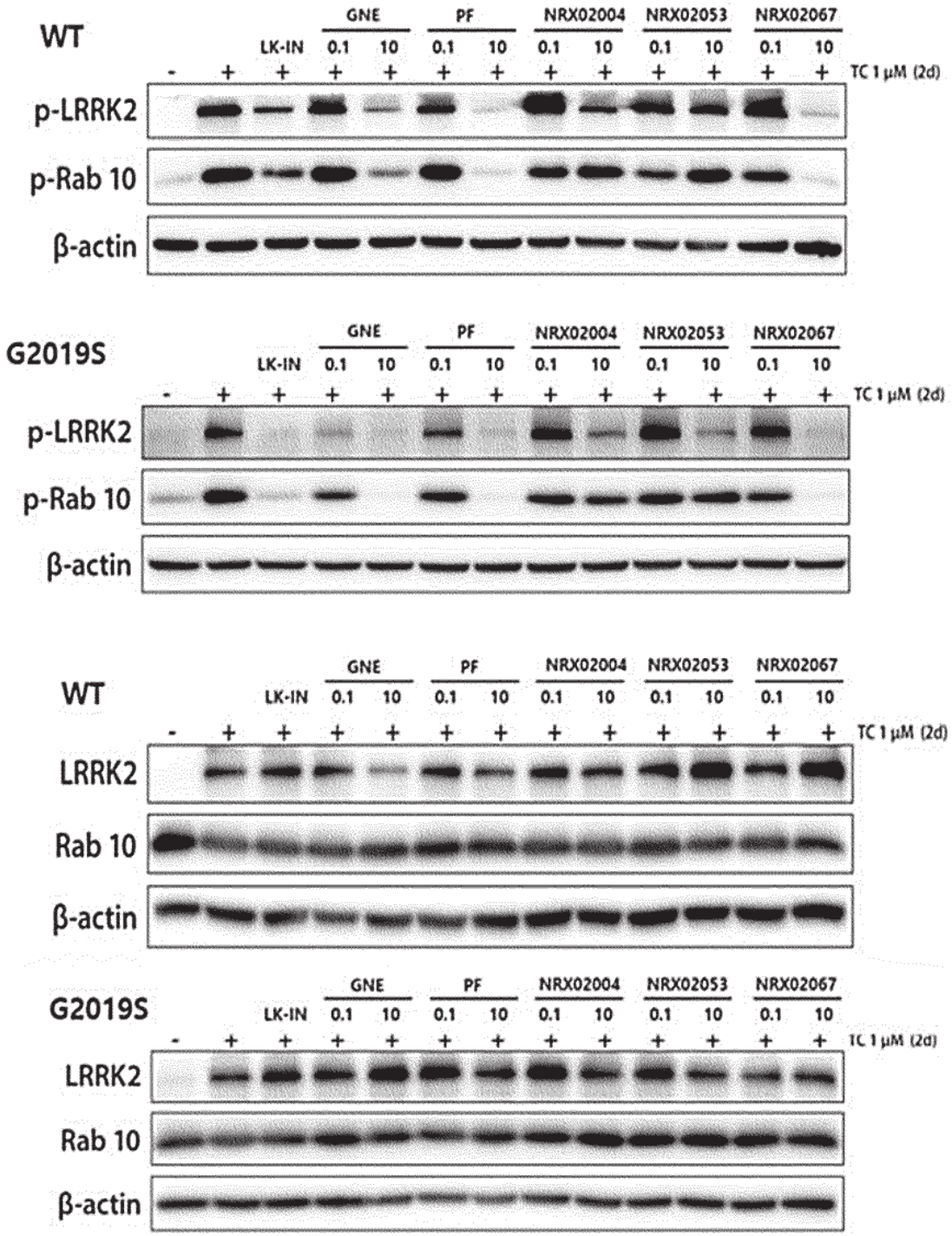
【FIG. 3j】


(WT-NRX02172)
WT
Concentration [Log, μM]
(GS-NRX02172)
G2019S
Concentration [Log, μM]
(WT-NRX02173)
WT
Concentration [Log, μM]
(GS-NRX02173)
G2019S
Concentration [Log, μM]
(WT-NRX02174)
WT
Concentration [Log, μM]
(GS-NRX02174)
G2019S
Concentration [Log, μM]

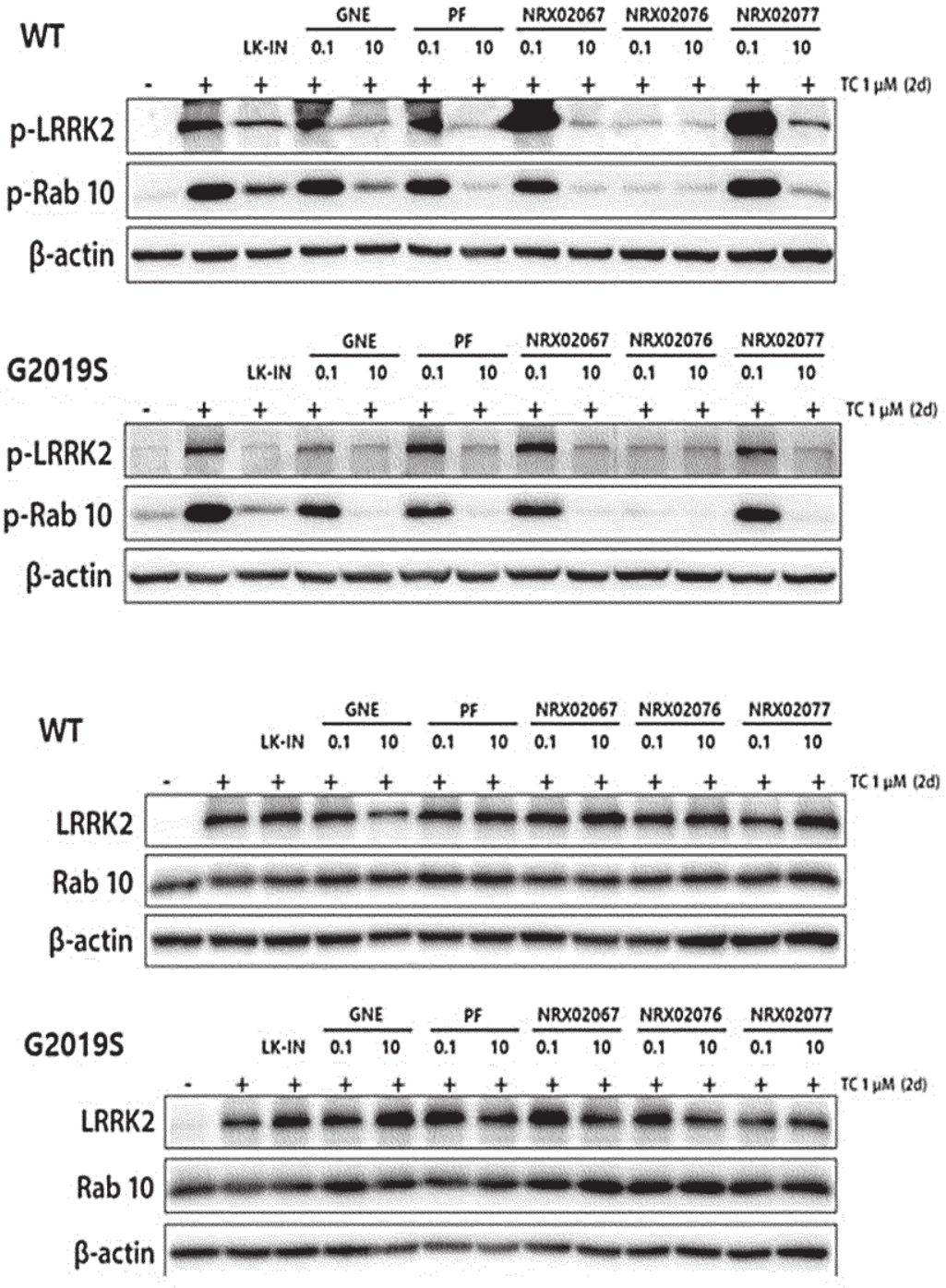
【FIG. 3k】


(WT-NRX02175)
WT
Concentration [Log, μM]
(GS-NRX02175)
G2019S
Concentration [Log, μM]
(WT-NRX02176)
WT
Concentration [Log, μM]
(GS-NRX02176)
G2019S
Concentration [Log, μM]

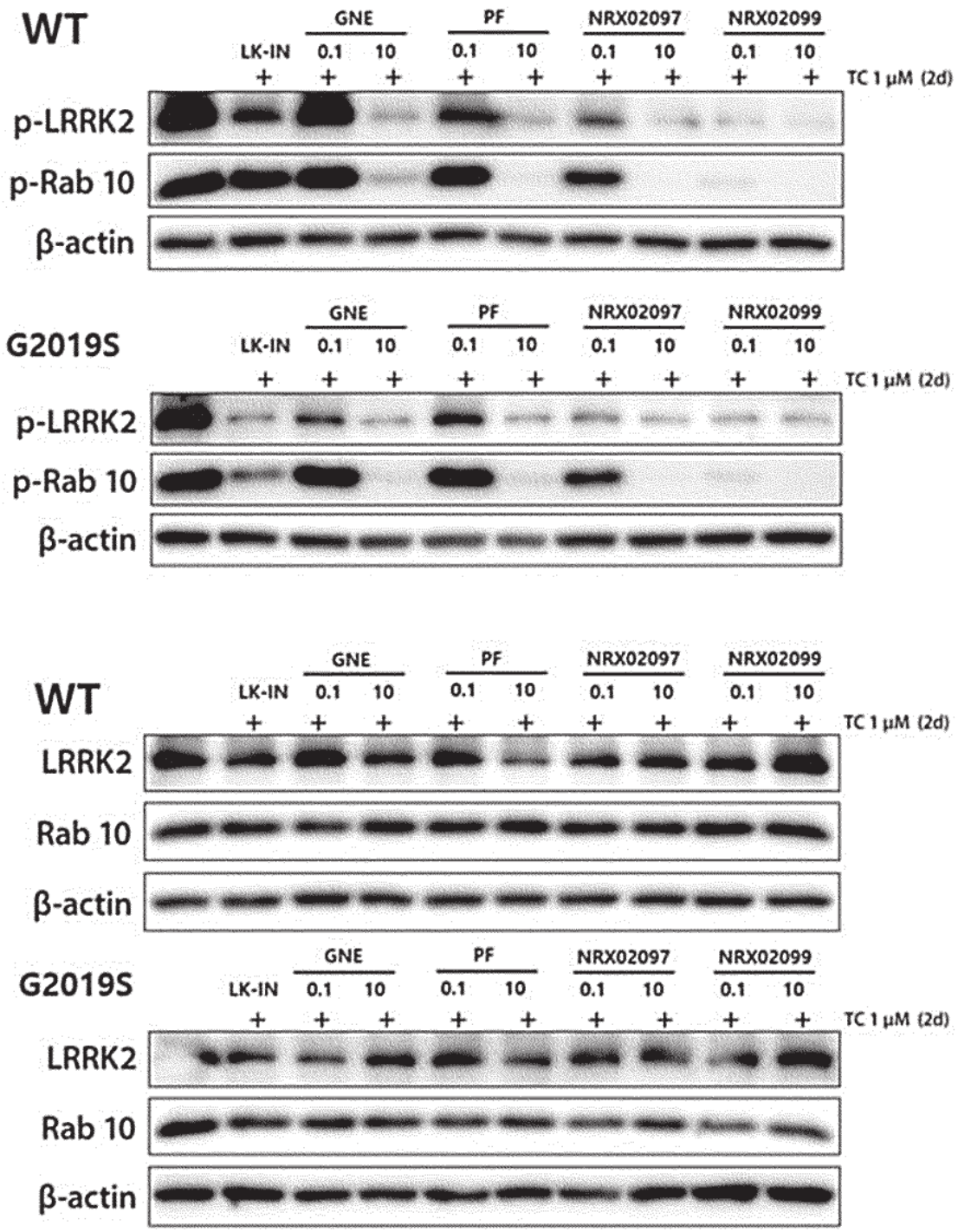
【FIG. 4a】


WT
GNE
PF
NRX02004
NRX02053
NRX02067
LK-IN
0.1
10
TC 1 μM (2d)
p-LRRK2
p-Rab 10
β-actin
G2019S
LRRK2
Rab 10

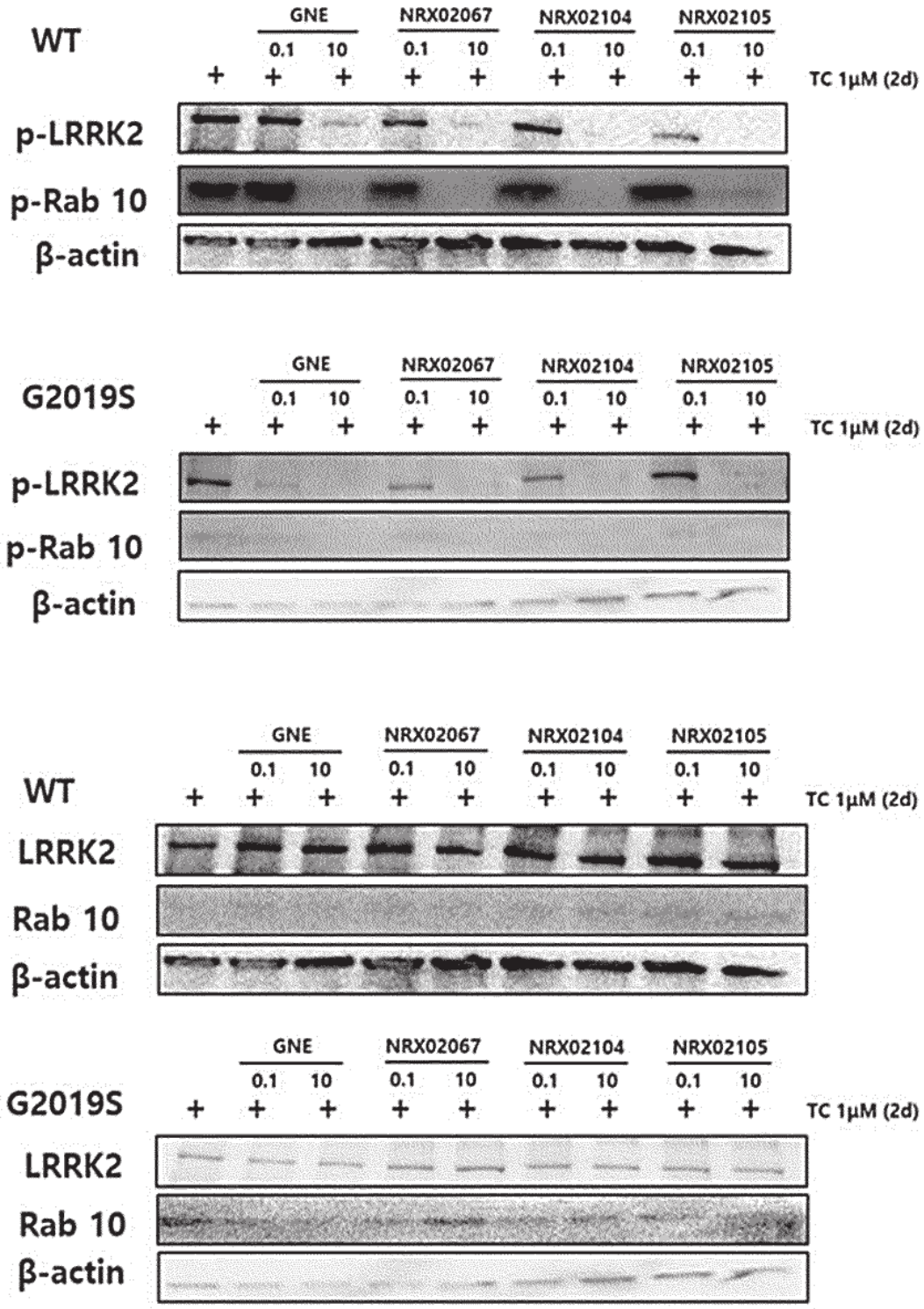
【FIG. 4b】


WT
GNE
PF
NRX02067
NRX02076
NRX02077
LK-IN
0.1
10
TC 1 μM (2d)
p-LRRK2
p-Rab 10
β-actin
G2019S
LRRK2
Rab 10

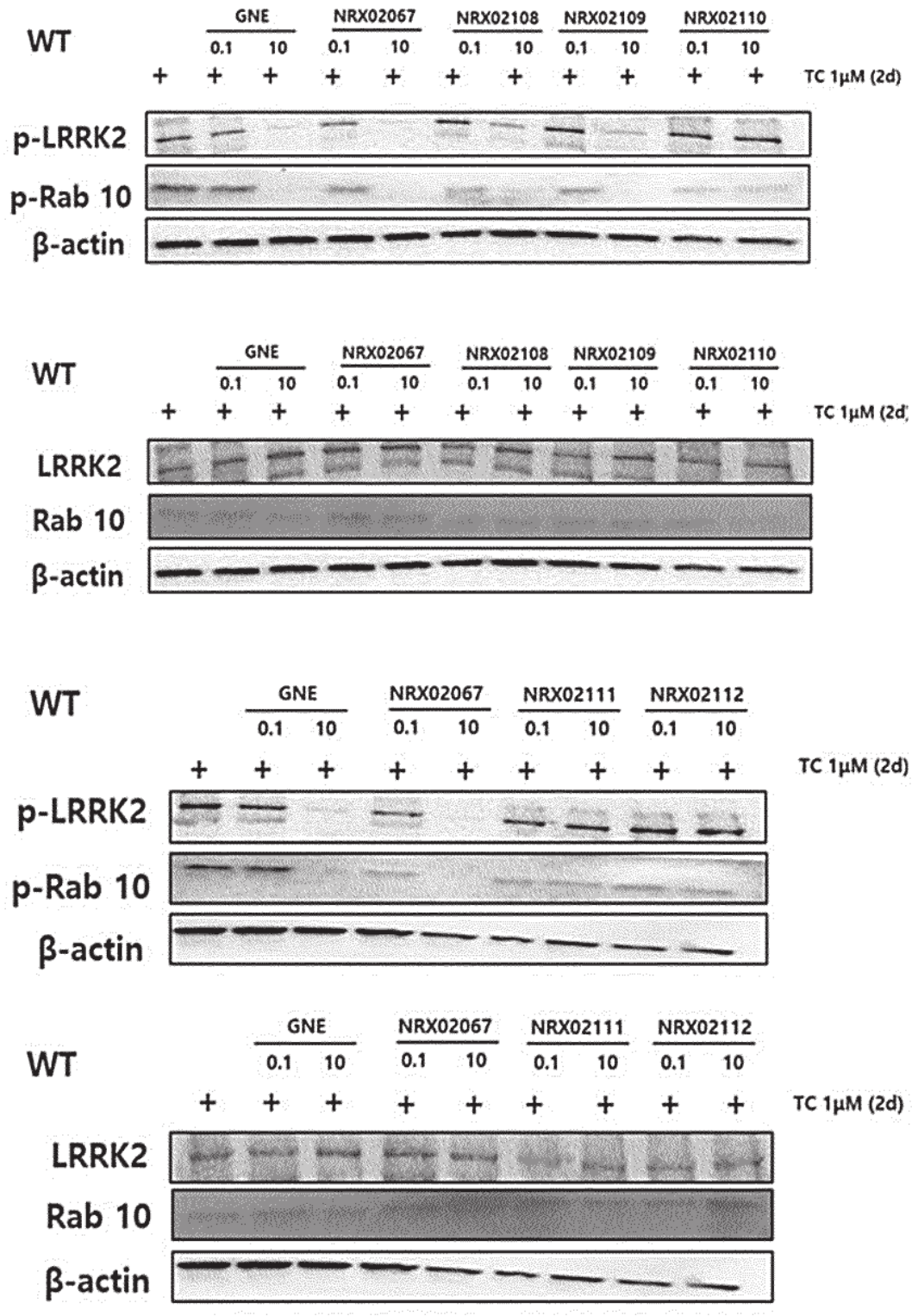
【FIG. 4c】


WT
GNE
PF
NRX02097
NRX02099
LK-IN
0.1
10
TC 1 μM (2d)
p-LRRK2
p-Rab 10
β-actin
G2019S
LRRK2
Rab 10

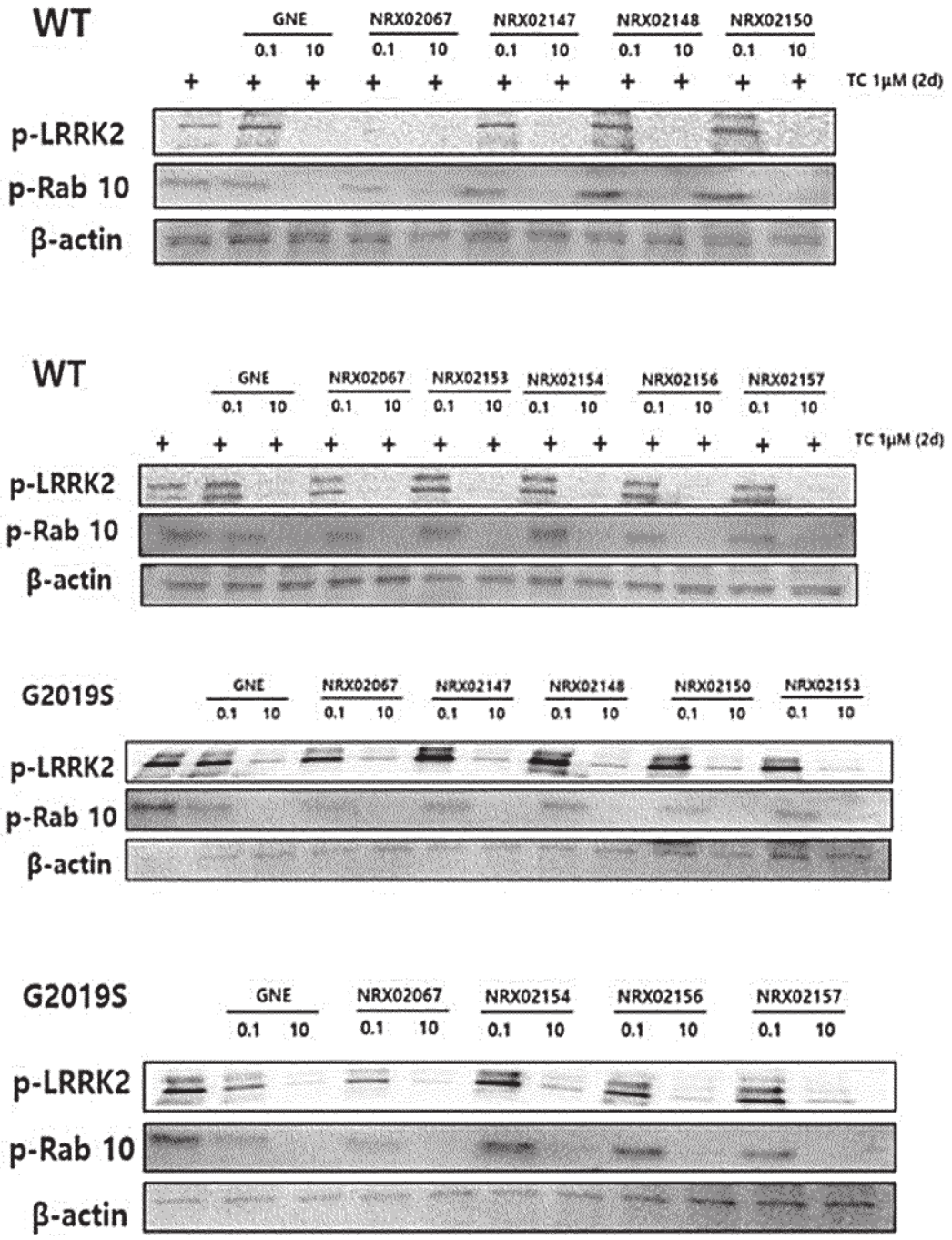
【FIG. 4d】


WT
GNE
NRX02067
NRX02104
NRX02105
0.1
10
TC 1μM (2d)
p-LRRK2
p-Rab 10
β-actin
G2019S
LRRK2
Rab 10

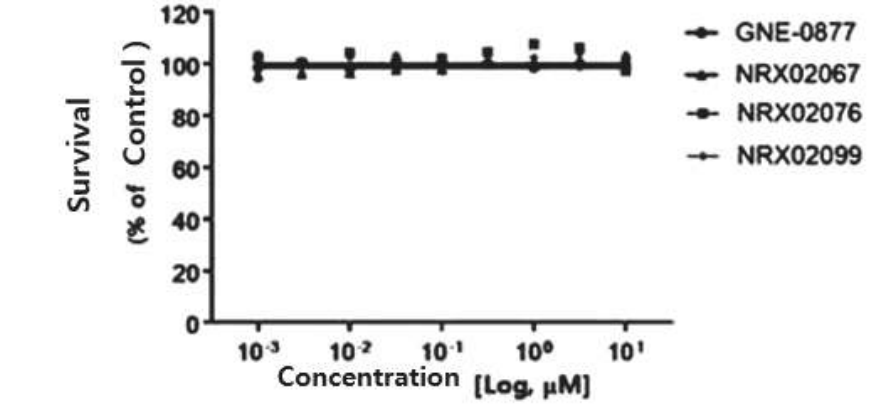
【FIG. 4e】

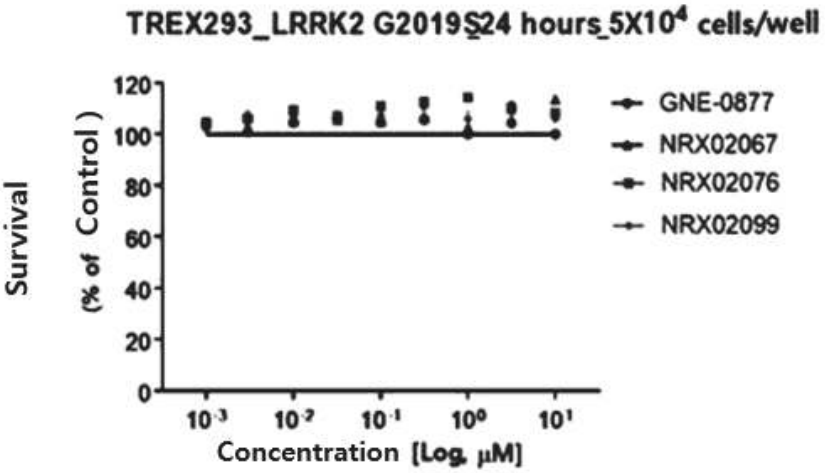

WT
GNE
NRX02067
NRX02108
NRX02109
NRX02110
0.1
10
TC 1μM (2d)
p-LRRK2
p-Rab 10
β-actin
WT
GNE
NRX02067
NRX02108
NRX02109
NRX02110
TC 1μM (2d)
LRRK2
Rab 10
β-actin
WT
GNE
NRX02067
NRX02111
NRX02112
TC 1μM (2d)
p-LRRK2
p-Rab 10
β-actin
WT
GNE
NRX02067
NRX02111
NRX02112
TC 1μM (2d)
LRRK2
Rab 10
β-actin

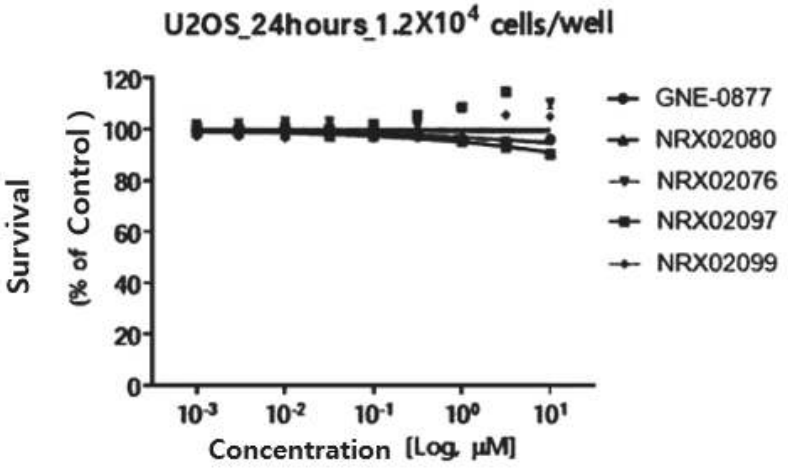
【FIG. 4f】


WT
GNE
NRX02067
NRX02147
NRX02148
NRX02150
0.1 10 0.1 10 0.1 10 0.1 10 0.1 10
+ + + + + + + + + + +
TC 1μM (2d)
p-LRRK2
p-Rab 10
β-actin
WT
GNE
NRX02067
NRX02153
NRX02154
NRX02156
NRX02157
0.1 10 0.1 10 0.1 10 0.1 10 0.1 10 0.1 10
+ + + + + + + + + + + +
TC 1μM (2d)
p-LRRK2
p-Rab 10
β-actin
G2019S
GNE
NRX02067
NRX02147
NRX02148
NRX02150
NRX02153
0.1 10 0.1 10 0.1 10 0.1 10 0.1 10 0.1 10
p-LRRK2
p-Rab 10
β-actin
G2019S
GNE
NRX02067
NRX02154
NRX02156
NRX02157
0.1 10 0.1 10 0.1 10 0.1 10 0.1 10
p-LRRK2
p-Rab 10
β-actin

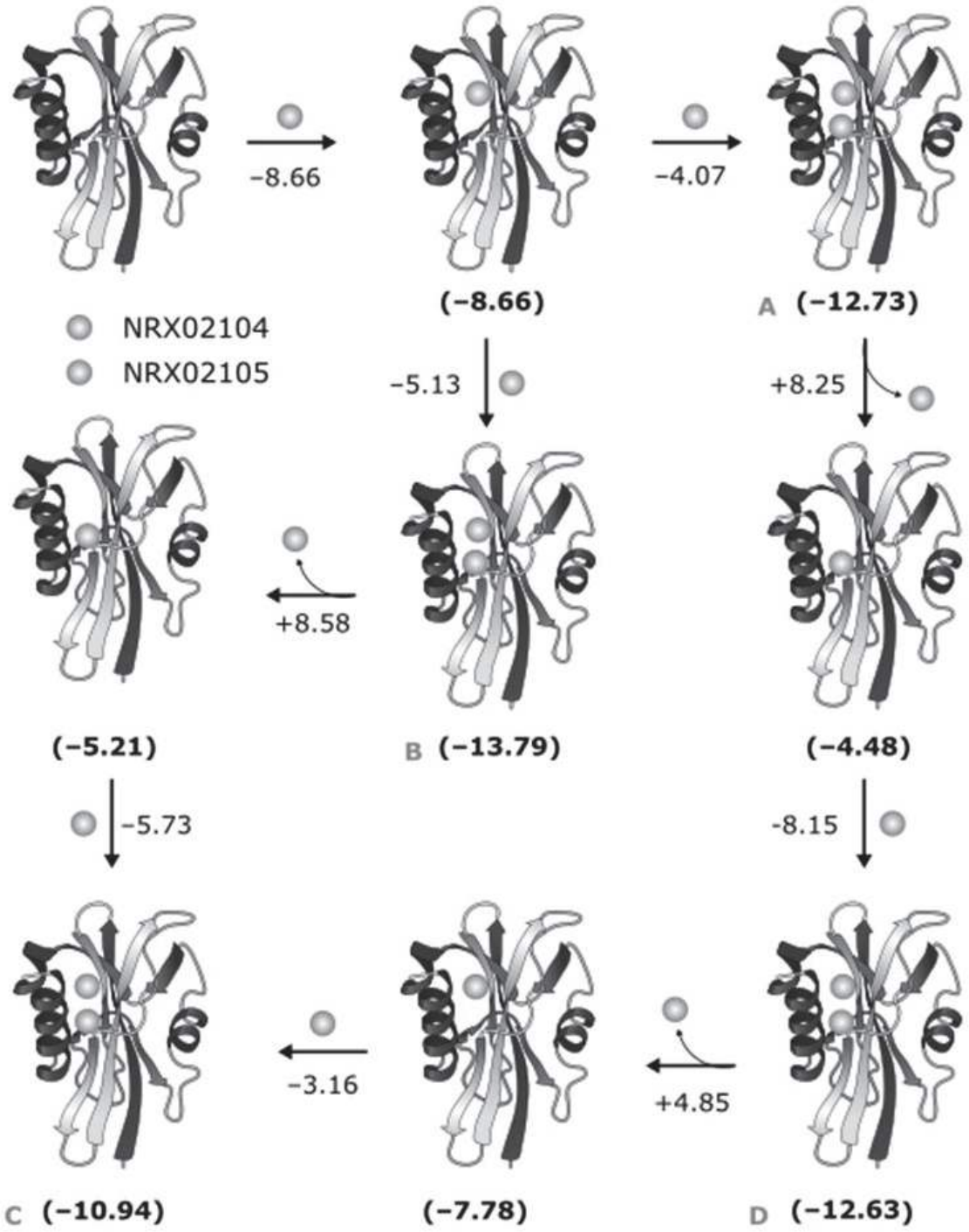
【FIG. 5】


Survival
(% of Control)
120
100
80
60
40
20
0
10^{-3}
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration [Log, μM]
GNE-0877
NRX02067
NRX02076
NRX02099


TREX293_LRRK2 G2019S_24 hours_5X10^4 cells/well
Survival
(% of Control)
120
100
80
60
40
20
0
10^{-3}
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration [Log, μM]
GNE-0877
NRX02067
NRX02076
NRX02099


U2OS_24hours_1.2X10^4 cells/well
Survival
(% of Control)
120
100
80
60
40
20
0
10^{-3}
10^{-2}
10^{-1}
10^{0}
10^{1}
Concentration [Log, μM]
GNE-0877
NRX02080
NRX02076
NRX02097
NRX02099

【FIG. 6】


−8.66
−4.07
(−8.66)
A (−12.73)
NRX02104
NRX02105
−5.13
+8.25
+8.58
(−5.21)
B (−13.79)
(−4.48)
−5.73
−8.15
−3.16
+4.85
C (−10.94)
(−7.78)
D (−12.63)