Table of Contents:

Table S1.

Protein Sample	Ti (°C)
Nsp5 (wild type Mpro)	60.1 ± 0.1
Nsp5 (wild type Mpro) – after 48 h	60.3 ± 0.1
NT650-Nps5 (red Mpro)	60.3 ± 0.1

Table S2.

Compound	GScore (kcal/mol) Replica #1	GScore (kcal/mol) Replica #2	GScore (kcal/mol) Replica #3	GScore (kcal/mol) Replica #4	GScore (kcal/mol) Replica #5	GScore (kcal/mol) Replica #6	Mean ± st. dev.
Myricetin (**2**)	-7.073	-7.073	-7.073	-7.073	-7.073	-7.073	-7.073 ± 0.000
Ellagic Acid (**7**)	-6.085	-6.085	-6.085	-6.085	-6.085	-6.085	-6.085 ± 0.000
Urolithin A (**8**)	-6.343	-6.462	-6.462	-6.462	-6.462	-6.462	-6.44217 ± 0.04858
Urolithin B (**9**)	-5.739	-5.739	-5.739	-5.739	-5.739	-5.739	-5.739 ± 0.000
Urolithin C (**10**)	-6.082	-6.081	-6.081	-6.081	-6.081	-6.081	-6.08117 ± 0.00041
Urolithin D (**11**)	-6.520	-6.518	-6.518	-6.518	-6.518	-6.518	-6.51833 ± 0.00082

Figure S1.

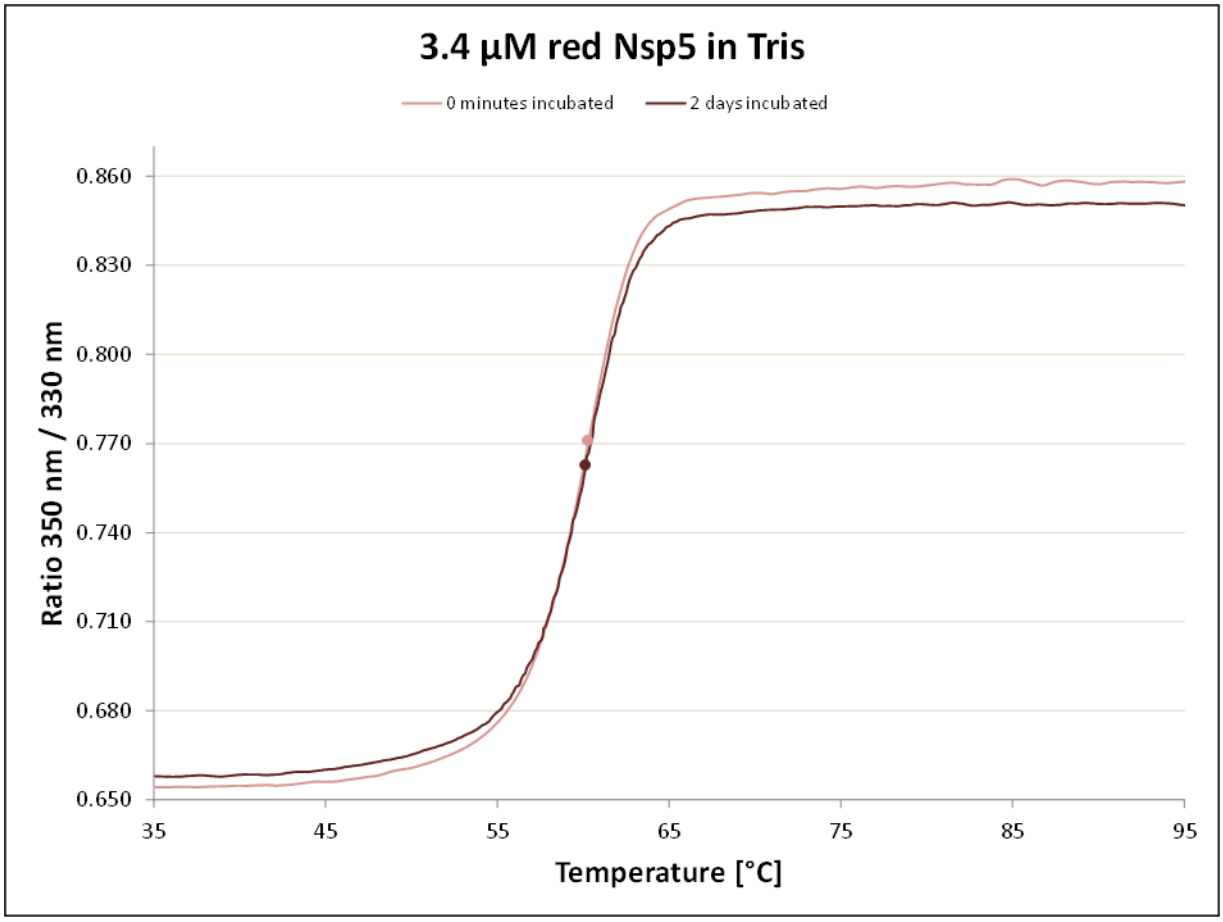

3.4 µM red Nsp5 in Tris
0 minutes incubated
2 days incubated
Ratio 350 nm / 330 nm
0.860
0.830
0.800
0.770
0.740
0.710
0.680
0.650
35
45
55
65
75
85
95
Temperature [°C]

Figure S2.

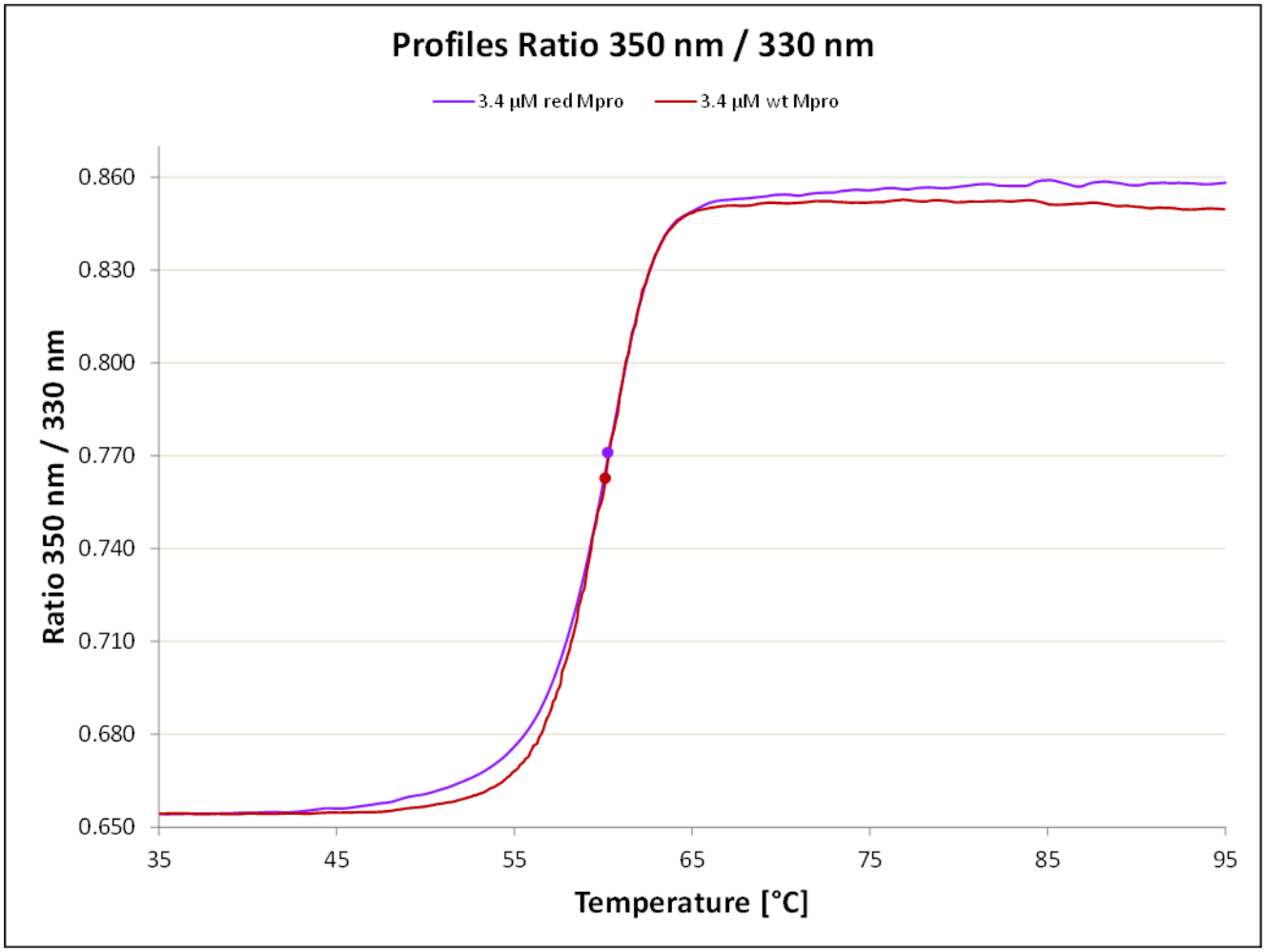

Profiles Ratio 350 nm / 330 nm
3.4 µM red Mpro
3.4 µM wt Mpro
Ratio 350 nm / 330 nm
0.860
0.830
0.800
0.770
0.740
0.710
0.680
0.650
35
45
55
65
75
85
95
Temperature [°C]

Figure S3.

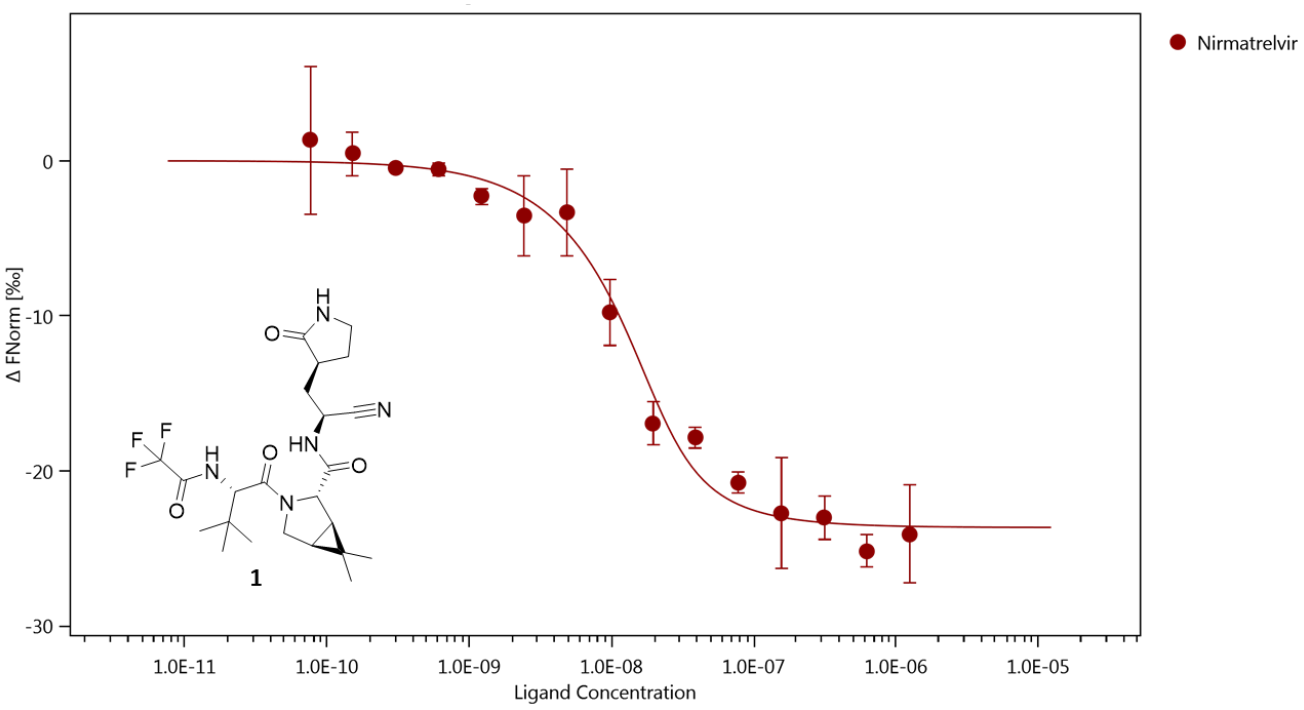

Nirmatrelvir
Δ FNorm [‰]
0
-10
-20
-30
1.0E-11
1.0E-10
1.0E-09
1.0E-08
1.0E-07
1.0E-06
1.0E-05
Ligand Concentration
1

Figure S4.

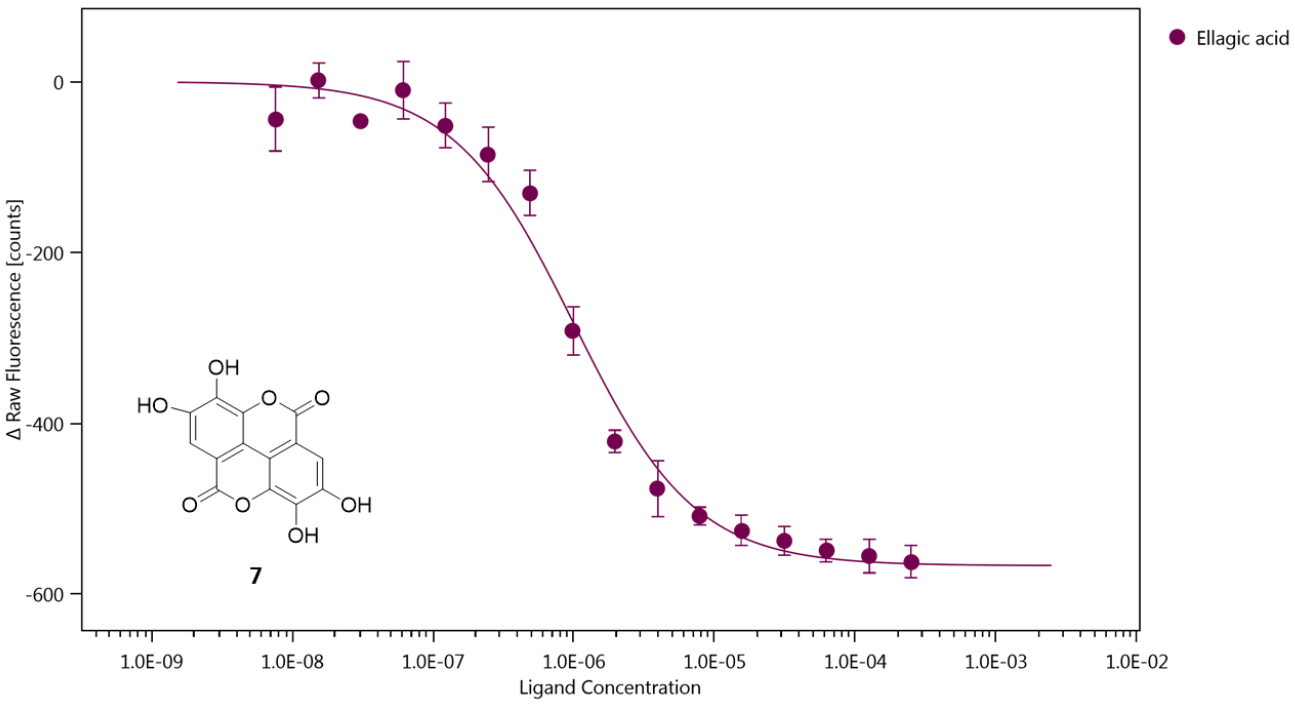

Ellagic acid
0
-200
-400
-600
Δ Raw Fluorescence [counts]
1.0E-09
1.0E-08
1.0E-07
1.0E-06
1.0E-05
1.0E-04
1.0E-03
1.0E-02
Ligand Concentration
OH
HO
O
O
O
O
OH
OH
7

Figure S5.

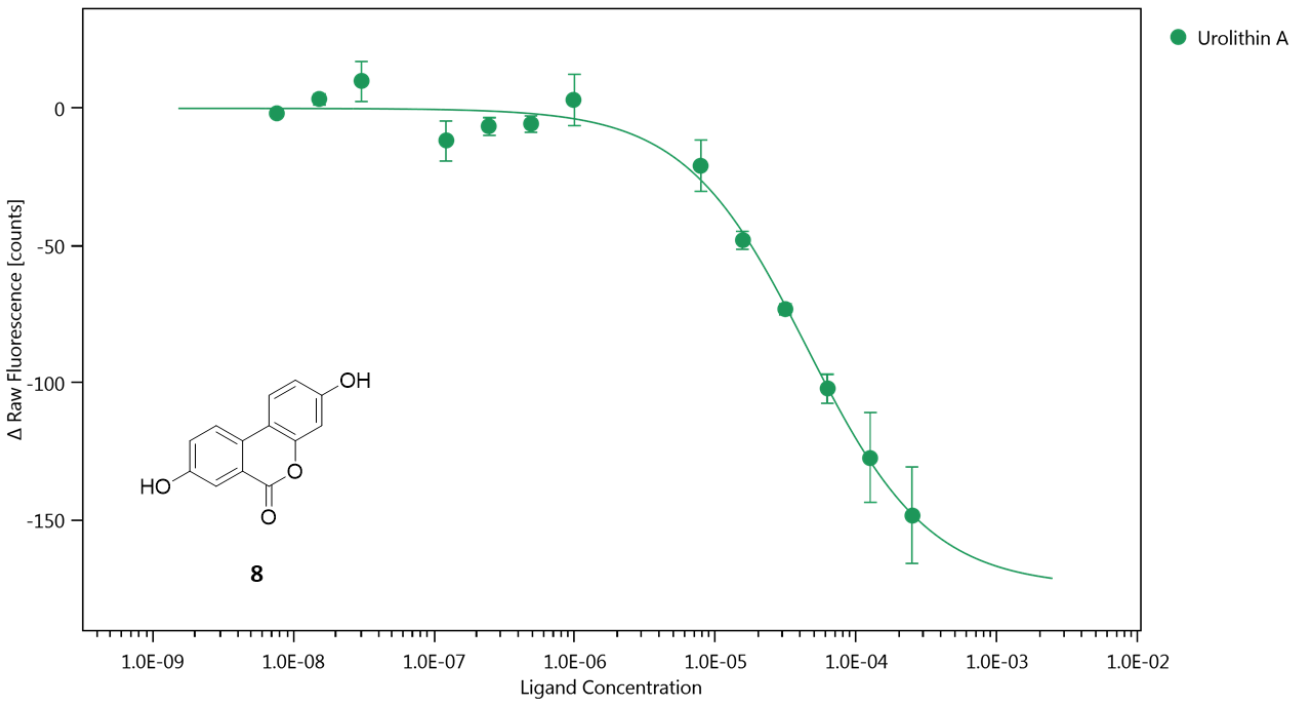

Urolithin A
0
-50
-100
-150
Δ Raw Fluorescence [counts]
OH
HO
O
O
8
1.0E-09
1.0E-08
1.0E-07
1.0E-06
1.0E-05
1.0E-04
1.0E-03
1.0E-02
Ligand Concentration

Figure S6.

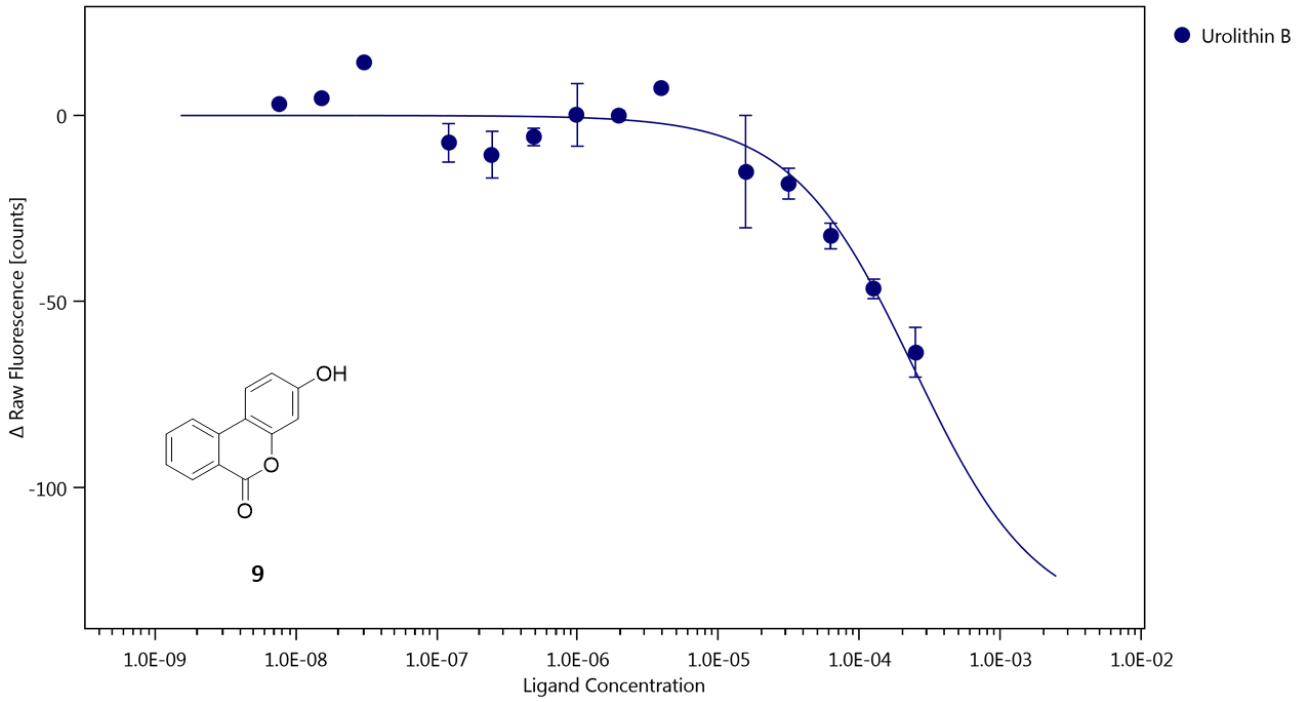

Urolithin B
0
-50
-100
Δ Raw Fluorescence [counts]
OH
O
O
9
1.0E-09
1.0E-08
1.0E-07
1.0E-06
1.0E-05
1.0E-04
1.0E-03
1.0E-02
Ligand Concentration

Figure S7.

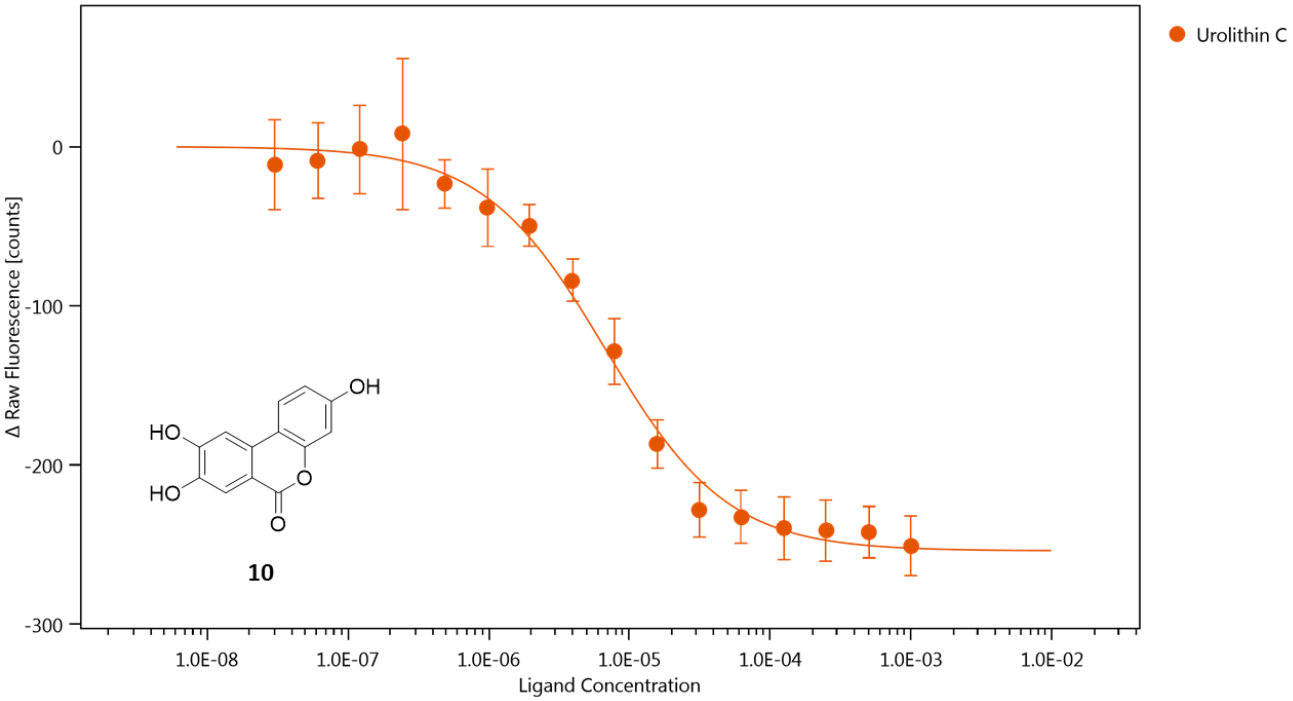
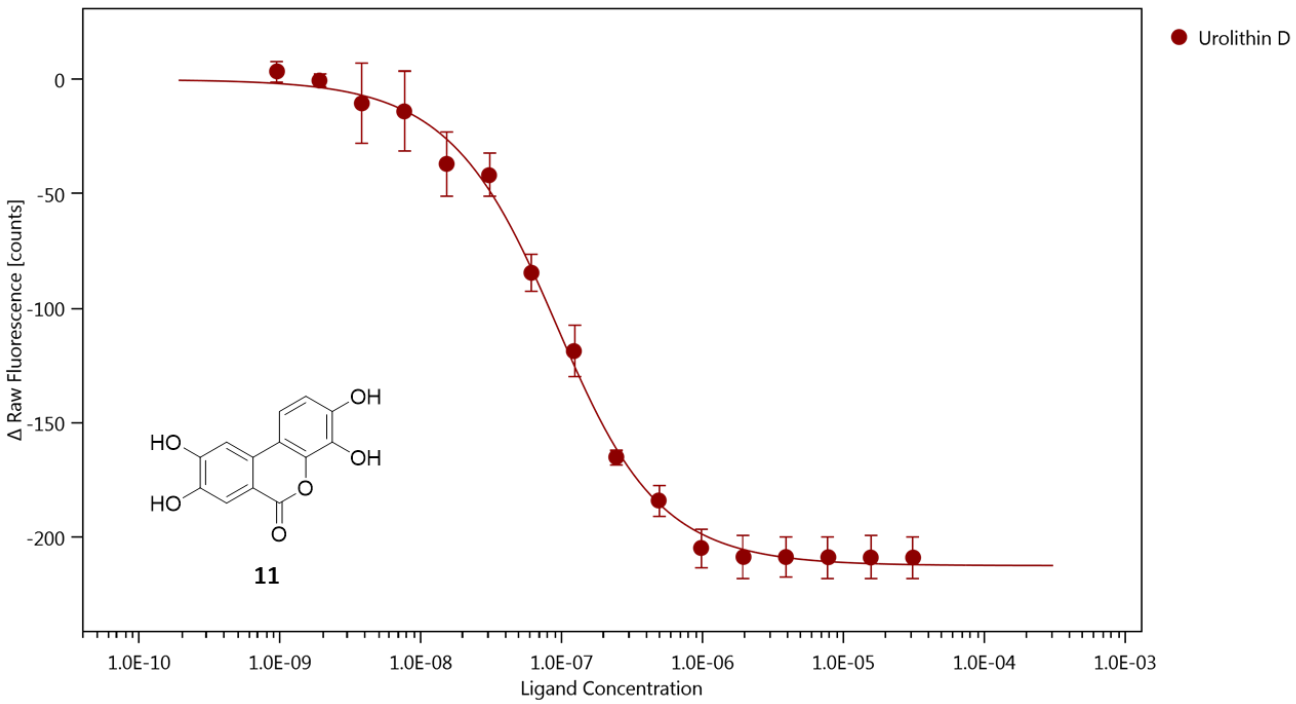

Urolithin C
Δ Raw Fluorescence [counts]
0
-100
-200
-300
1.0E-08
1.0E-07
1.0E-06
1.0E-05
1.0E-04
1.0E-03
1.0E-02
Ligand Concentration
HO
HO
OH
O
O
10

Figure S8.


Urolithin D
0
-50
-100
-150
-200
Δ Raw Fluorescence [counts]
1.0E-10
1.0E-09
1.0E-08
1.0E-07
1.0E-06
1.0E-05
1.0E-04
1.0E-03
Ligand Concentration
HO
HO
OH
OH
O
O
11