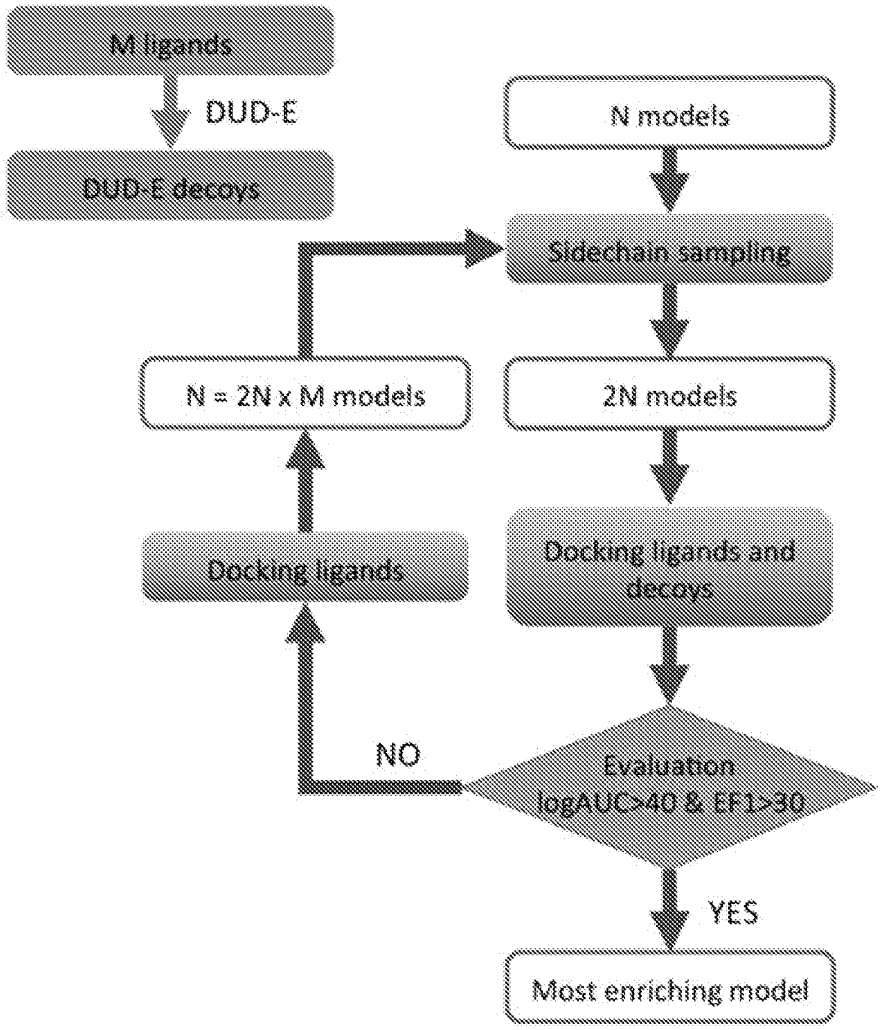

M ligands
DUD-E
DUD-E decoys
N models
Sidechain sampling
2N models
Docking ligands and decoys
Evaluation logAUC>40 & EF1>30
NO
YES
Most enriching model
Docking ligands
N = 2N x M models

FIG. 1

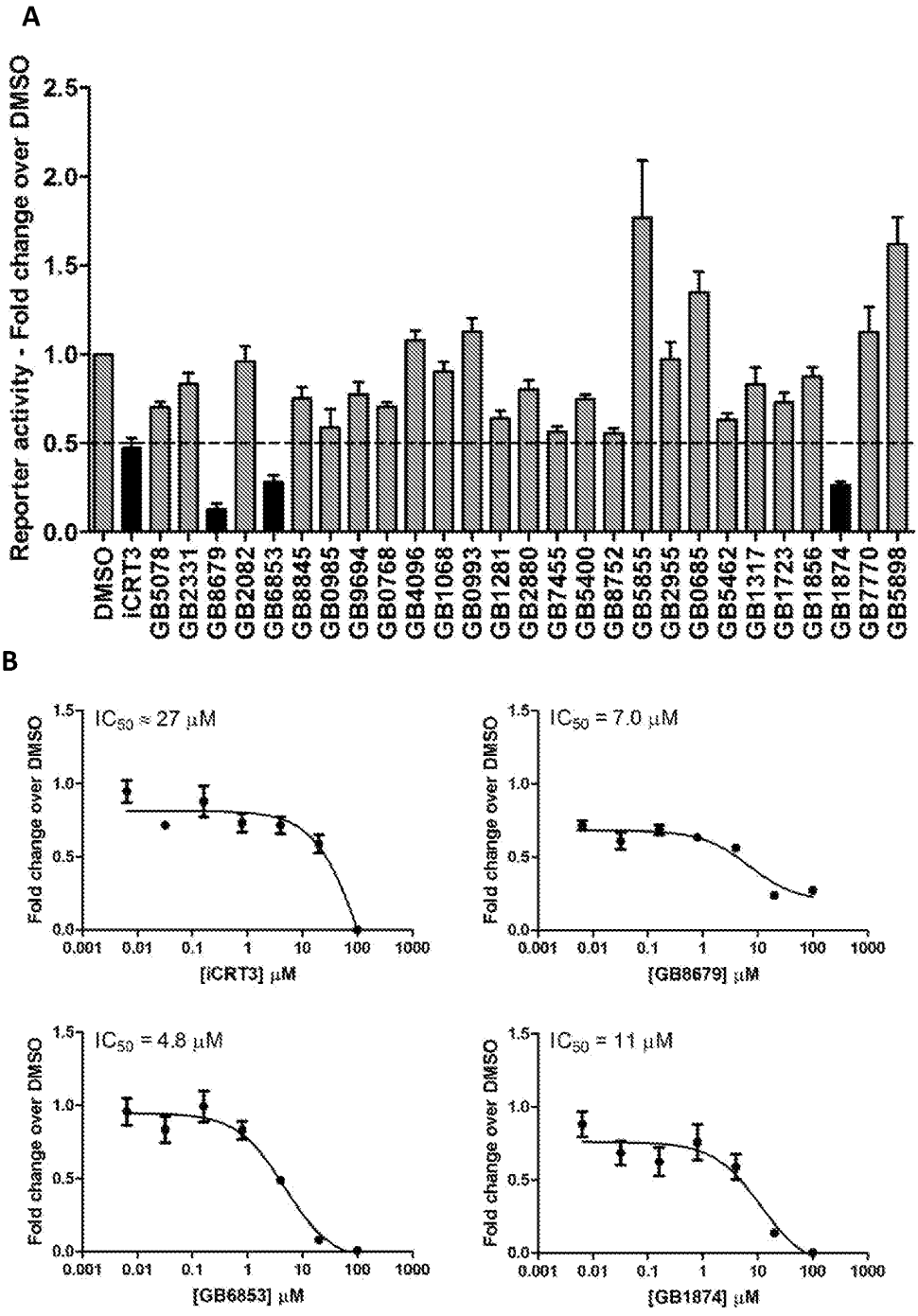
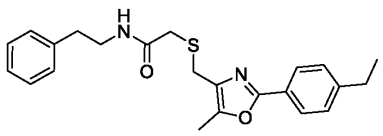
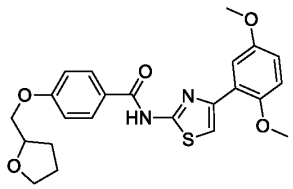

A
Reporter activity - Fold change over DMSO
2.5
2.0
1.5
1.0
0.5
0.0
DMSO
iCRT3
GB5078
GB2331
GB8679
GB2082
GB6853
GB8845
GB0985
GB9694
GB0768
GB4096
GB1068
GB0993
GB1281
GB2880
GB7455
GB5400
GB8752
GB5855
GB2955
GB0685
GB5462
GB1317
GB1723
GB1856
GB1874
GB7770
GB5898
B
IC50 ≈ 27 μM
Fold change over DMSO
[iCRT3] μM
IC50 = 7.0 μM
[GB8679] μM
IC50 = 4.8 μM
[GB6853] μM
IC50 = 11 μM
[GB1874] μM
0.001
0.01
0.1
1
10
100
1000

FIG. 2

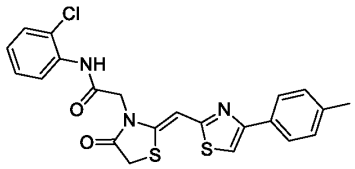
C



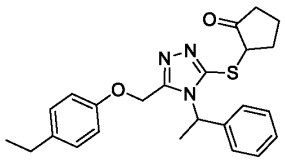
iCRT3



GB8679



GB6853



GB1874

D

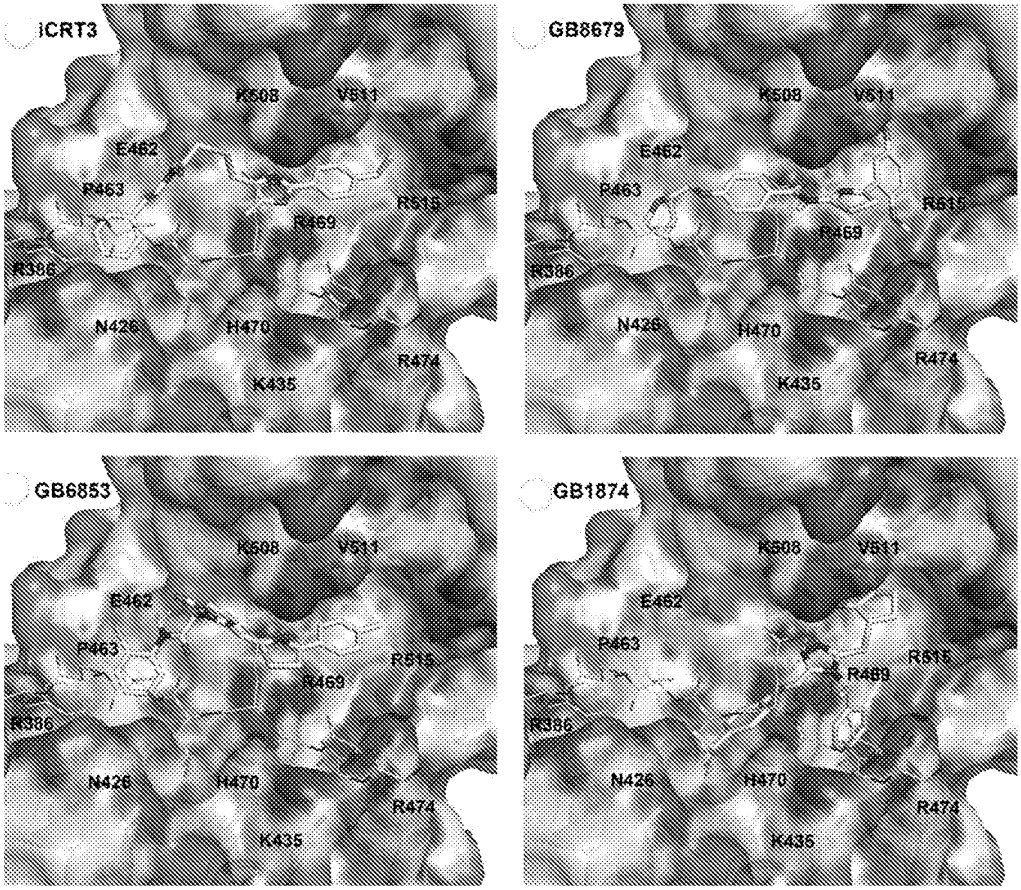


FIG. 2 (Continued)

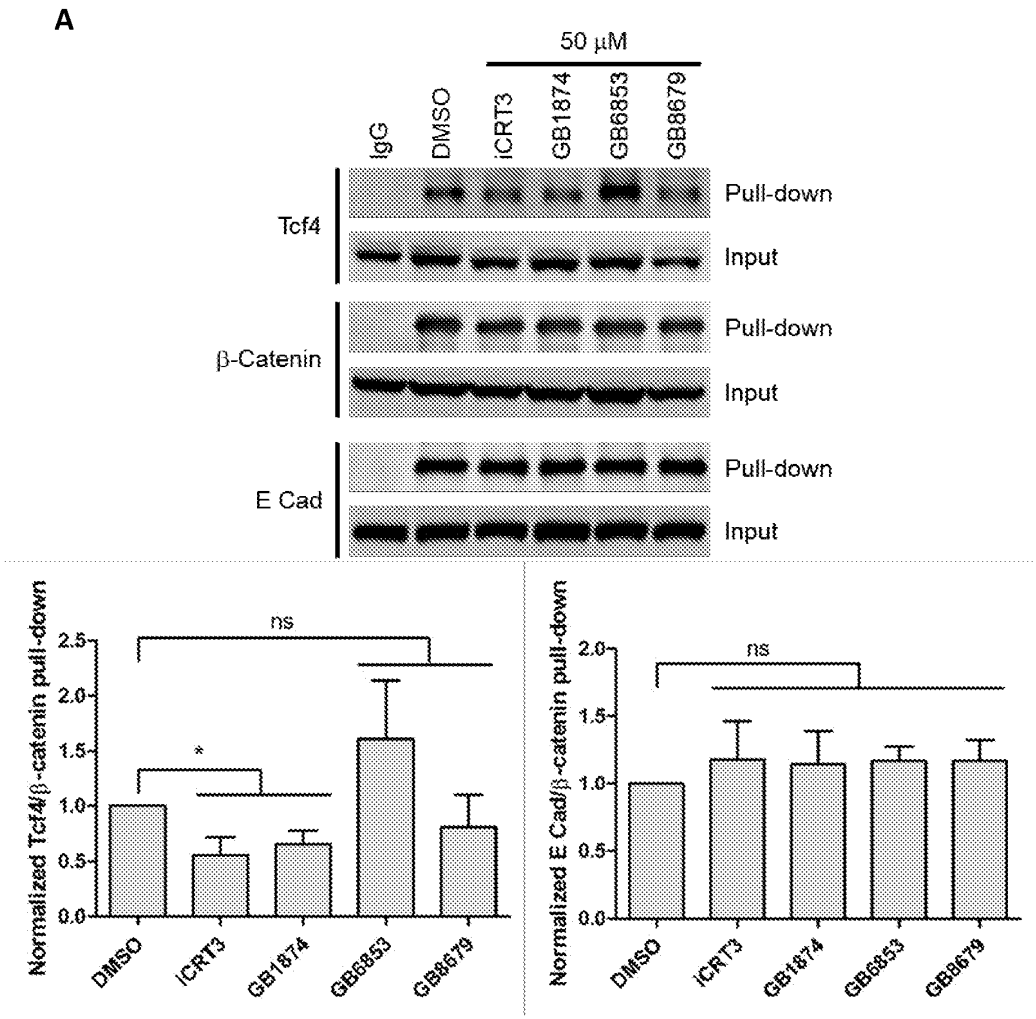

A
50 μM
IgG
DMSO
iCRT3
GB1874
GB6853
GB8679
Tcf4
β-Catenin
E Cad
Pull-down
Input
Normalized Tcf4/β-catenin pull-down
Normalized E Cad/β-catenin pull-down
ns
*
DMSO
iCRT3
GB1874
GB6853
GB8679

FIG. 3

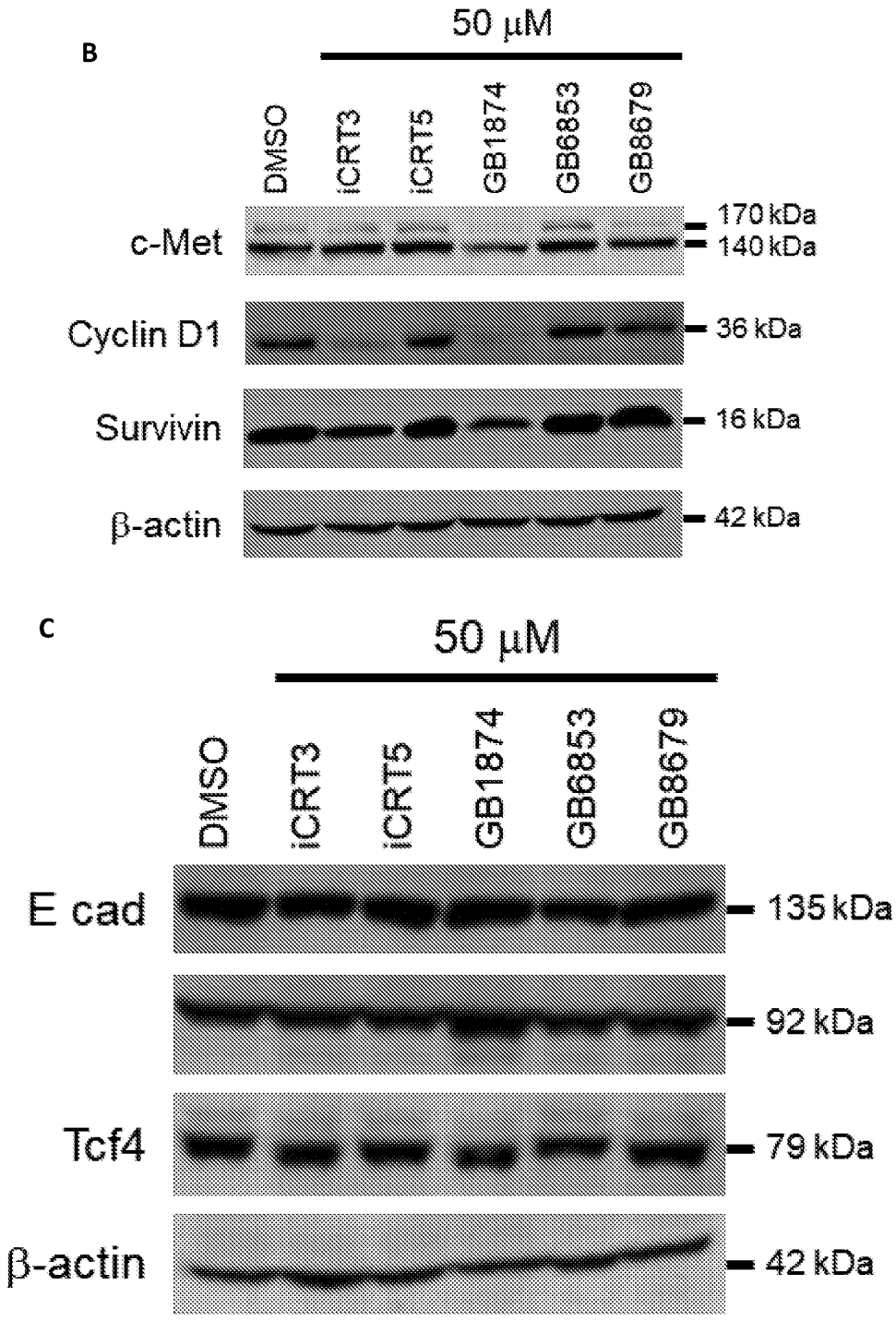
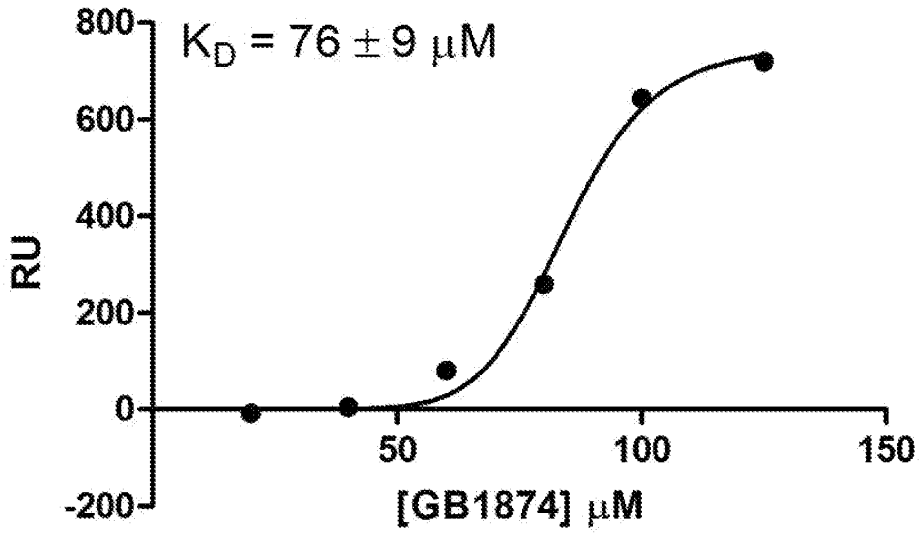


FIG. 3 (Continued)

D



E

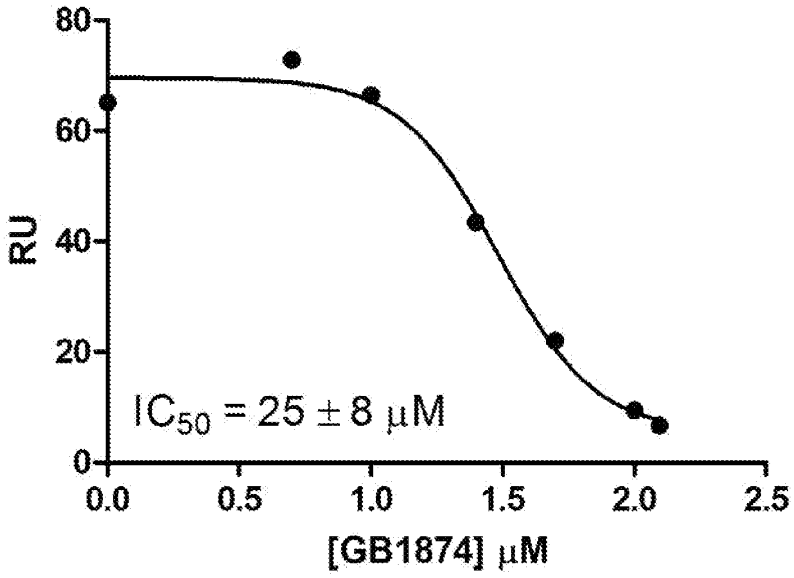


FIG. 3 (Continued)

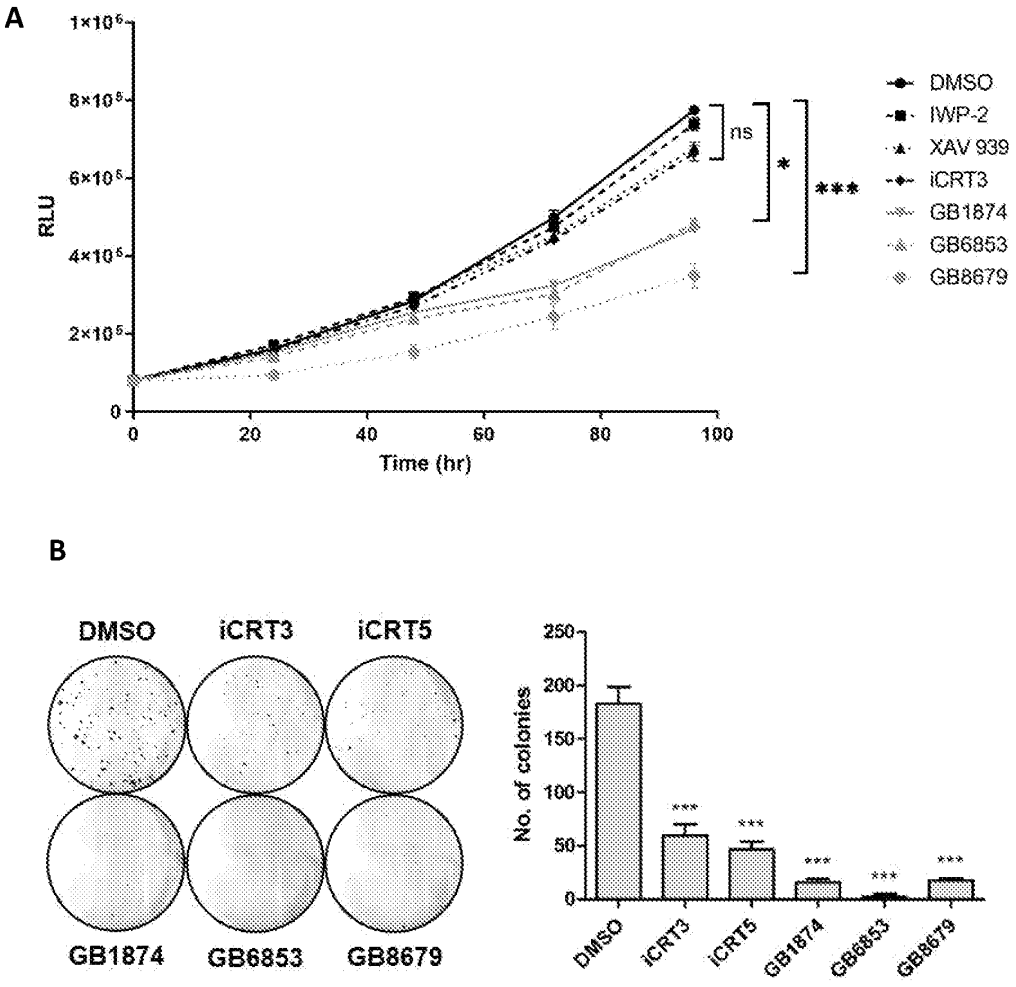
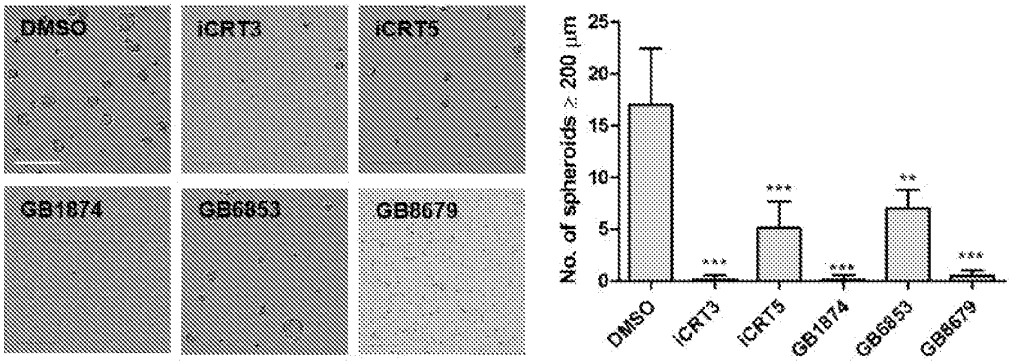

A
1×10⁶
8×10⁵
6×10⁵
4×10⁵
2×10⁵
0
RLU
0
20
40
60
80
100
Time (hr)
ns
*
***
DMSO
IWP-2
XAV 939
iCRT3
GB1874
GB6853
GB8679
B
DMSO
iCRT3
iCRT5
GB1874
GB6853
GB8679
No. of colonies
250
200
150
100
50
0
***
DMSO
iCRT3
iCRT5
GB1874
GB6853
GB8679

FIG. 4

C



D

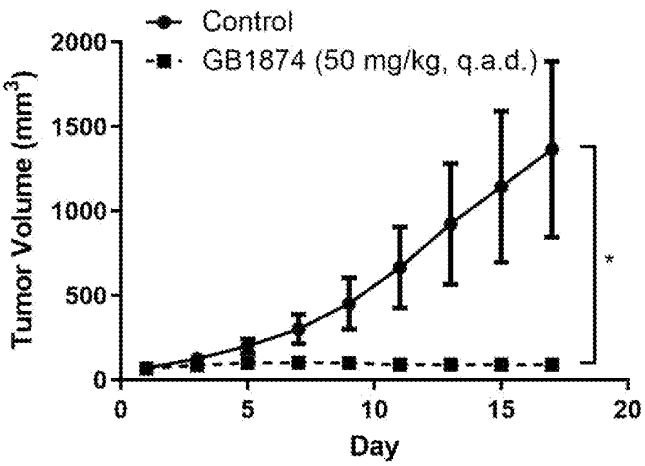


FIG. 4 (Continued)

Compound ID	Name	DOCK [1]	RANK [2]	HUMAN [3]	Final Score[4]	STF IC_{50} (μM)[5]
C00010001	iCRT 3	23	4	1	*	27
B00011001	A01	19	31	-1	*	> 100
B00010002	*A02*	*51*	*24*	*1*	*	*nd*
B00010003	*A03*	*17*	*3*	*1*	***	*62.29*
B00012004	*A04*	*29*	*25*	*1*	*	*> 100*
B00010005	*A05*	*39*	*5*	*1*	*	*nd*
B00010006	*A06*	*22*	*9*	*1*	**	*37.28*
B00011007	*A07*	*12*	*49*	*-1*	*	*> 100*
B00010008	*A08*	*28*	*53*	*-1*		*nd*
B00010009	*A09*	*35*	*2*	*1*	**	*nd*
B00011010	*A10*	*11*	*22*	*-1*	*	*nd*
B00010011	*A11*	*41*	*48*	*-1*		*v*
B00010012	*A12*	*34*	*10*	*1*	*	*9.62*
B00012013	*A13*	*21*	*14*	*1*	**	*nd*
B00010014	*A14*	*42*	*38*	*0*		*> 100*
B00010015	*A15*	*37*	*6*	*1*	*	*nd*
B00011016	*A16*	*26*	*37*	*1*	*	*nd*
B00010017	*A17*	*40*	*63*	*-1*		*nd*
B00010018	*A18*	*57*	*11*	*1*	*	*nd*
B00012019	*A19*	*7*	*21*	*-1*	*	*nd*

FIG. 5

Compound ID	Name	DOCK 1	RANK 2	HUMAN 3	Final Score4	STF IC50 (μM)5
B00010020	A20	52	27	-1		nd
B00010021	A21	55	16	0		nd
B00012022	A22	13	57	0	*	nd
B00010023	A23	50	52	0		nd
B00010024	A24	48	30	-1		nd
B00012025	A25	4	43	-1	*	nd
B00010026	A26	59	39	-1		nd
B00010027	A27	47	35	-1		nd
B00012028	A28	8	40	-1	*	nd
B00010029	A29	60	15	-1		nd
B00010030	A30	56	61	-1		nd
B00012031	A31	16	7	-1	*	nd
B00010032	A32	53	60	-1		nd
B00010033	A33	54	46	-1		nd
B00012034	A34	36	29	-1		nd
B00010035	A35	63	36	-1		nd
B00010036	A36	14	18	-1	*	nd
B00012037	A37	1	17	-1	*	nd
B00010038	A38	46	8	-1		nd
B00010039	A39	25	55	-1		nd
B00012040	A40	2	54	-1	*	nd

FIG. 5 (Continued)

Compound ID	Name	DOCK 1	RANK 2	HUMAN 3	Final Score4	STF IC50 (μM)5
B00010041	A41	45	45	-1		nd
B00010042	A42	62	51	0		nd
B00012043	A43	31	50	-1		nd
B00010044	A44	61	47	0		nd
B00010045	A45	3	23	1	**	0.23
B00011046	A46	18	13	1	**	nd
B00010047	A47	33	64	-1		nd
B00010048	A48	9	32	1	**	2.84
B00011049	A49	43	58	1	*	nd
B00010050	A50	44	19	1	*	nd
B00010051	A51	32	20	1	*	> 100
B00010052	A52	20	44	1	**	> 100
B00010053	A53	27	33	-1		> 100
B00010054	A54	58	34	-1		nd
B00010055	A55	15	12	-1	*	nd
B00010056	A56	38	41	-1		nd
B00010057	A57	10	28	1	**	nd
B00010058	A58	24	42	-1		nd
B00010059	A59	64	56	0		nd
B00010060	A60	49	1	-1	*	nd
B00010061	A61	6	26	0	*	nd
B00010062	A62	5	59	-1	*	nd
B00010063	A63	30	62	-1		nd

FIG. 5 (Continued)

Compound Index	DOCK energy score
GB2880	-59.37
GB8752	-54.84
GB9694	-54.56
GB1068	-53.79
GB5078	-53.39
GB1874	-52.93
GB8845	-51.02
GB2955	-50.47
GB1856	-50.45
GB2082	-50.11
GB0985	-49.85
GB1317	-49.72
GB8679	-48.84
GB1281	-48.78
GB2331	-48.69
GB5400	-48.63
GB0993	-48.54
GB7770	-48.18
GB5462	-47.89
GB1723	-47.83
GB0685	-47.35
GB0768	-47.35
GB7455	-47.21
GB5898	-47.06
GB5855	-47.04
GB6853	-46.56
GB4096	-46.54

FIG. 6A

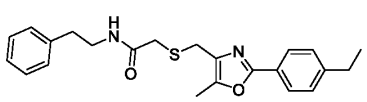
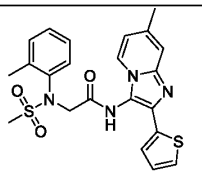
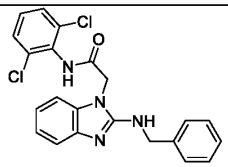
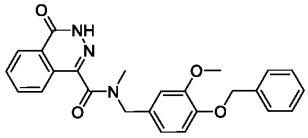
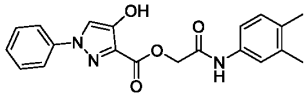
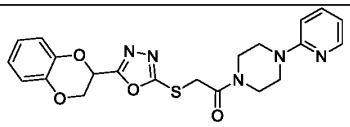
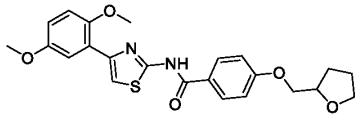
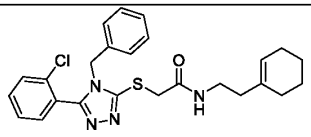
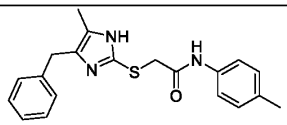
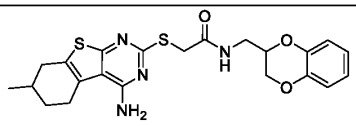
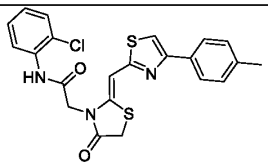
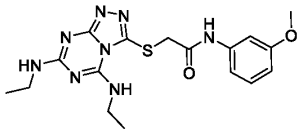
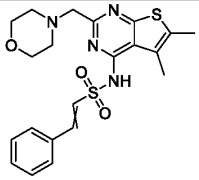
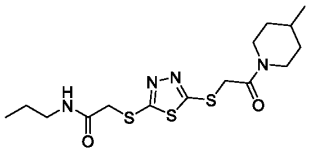
 iCRT3	 GB2880
 GB5078	 GB7455
 GB2331	 GB5400
 GB8679	 GB8752
 GB2082	 GB5855
 GB6853	 GB2955
 GB8845	 GB0685

FIG. 6B

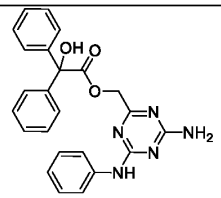
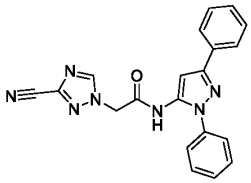
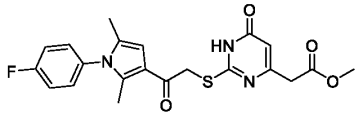
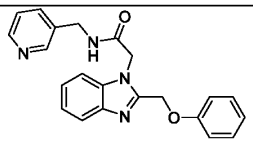
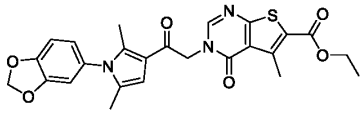
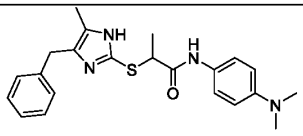
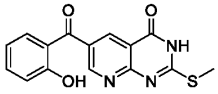
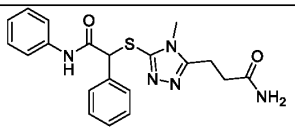
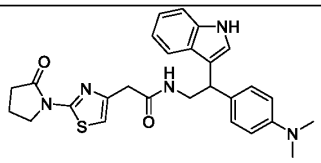
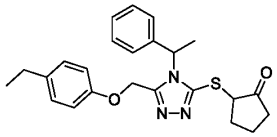
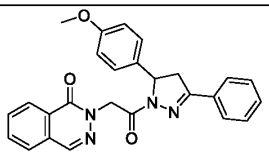
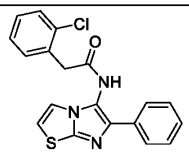
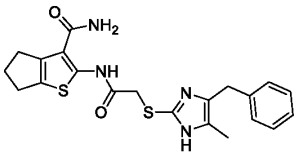
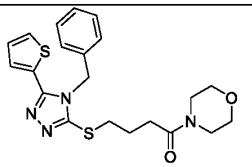
 GB0985	 GB5462
 GB9694	 GB1317
 GB0768	 GB1723
 GB4096	 GB1856
 GB1068	 GB1874
 GB0993	 GB7770
 GB1281	 GB5898

FIG. 6B (Continued)

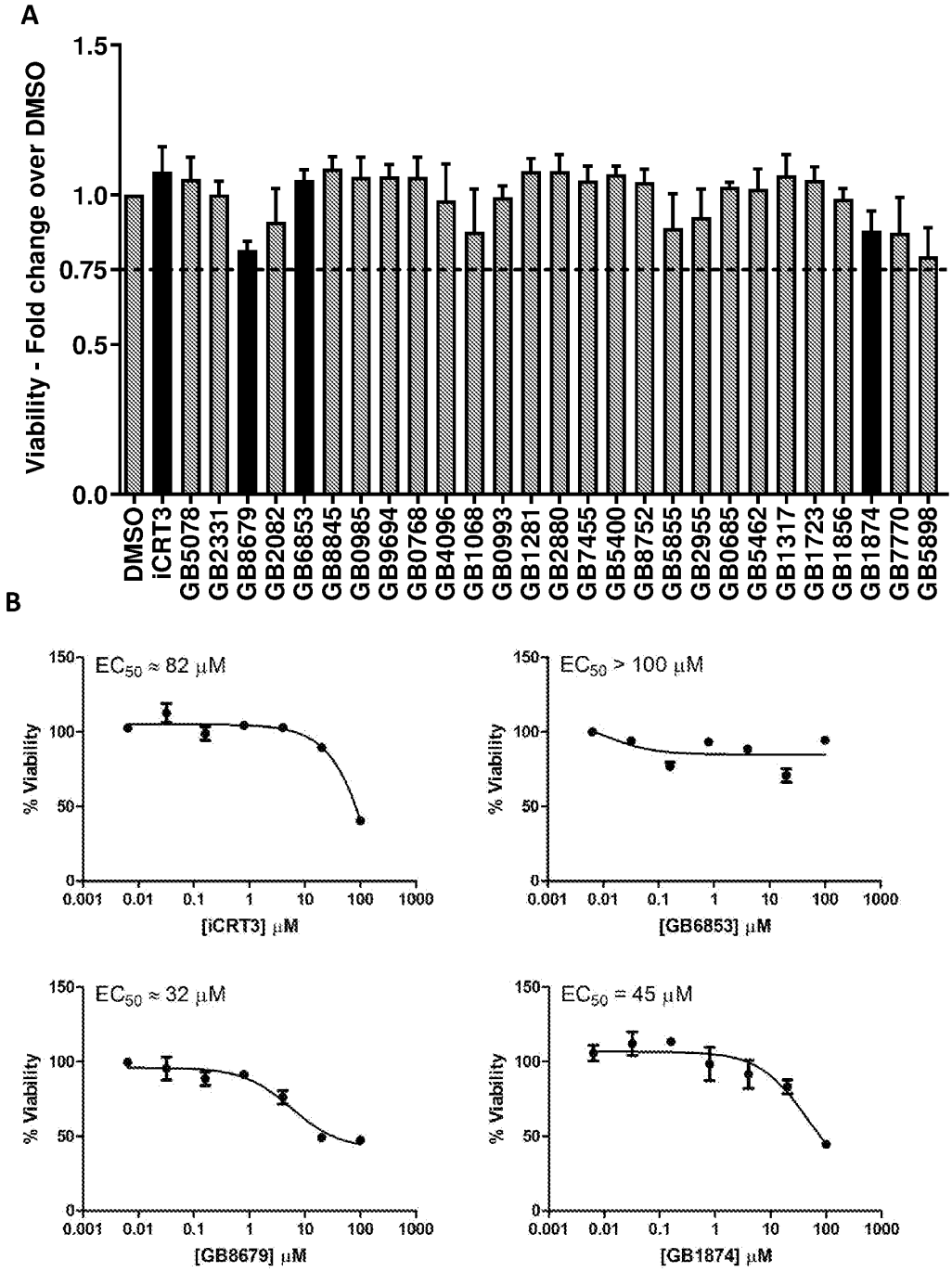

A
Viability - Fold change over DMSO
1.5
1.0
0.75
0.5
0.0
DMSO
iCRT3
GB5078
GB2331
GB8679
GB2082
GB6853
GB8845
GB0985
GB9694
GB0768
GB4096
GB1068
GB0993
GB1281
GB2880
GB7455
GB5400
GB8752
GB5855
GB2955
GB0685
GB5462
GB1317
GB1723
GB1856
GB1874
GB7770
GB5898
B
EC50 ≈ 82 μM
% Viability
[iCRT3] μM
EC50 > 100 μM
[GB6853] μM
EC50 ≈ 32 μM
[GB8679] μM
EC50 = 45 μM
[GB1874] μM
0.001
0.01
0.1
1
10
100
1000

FIG. 7

A

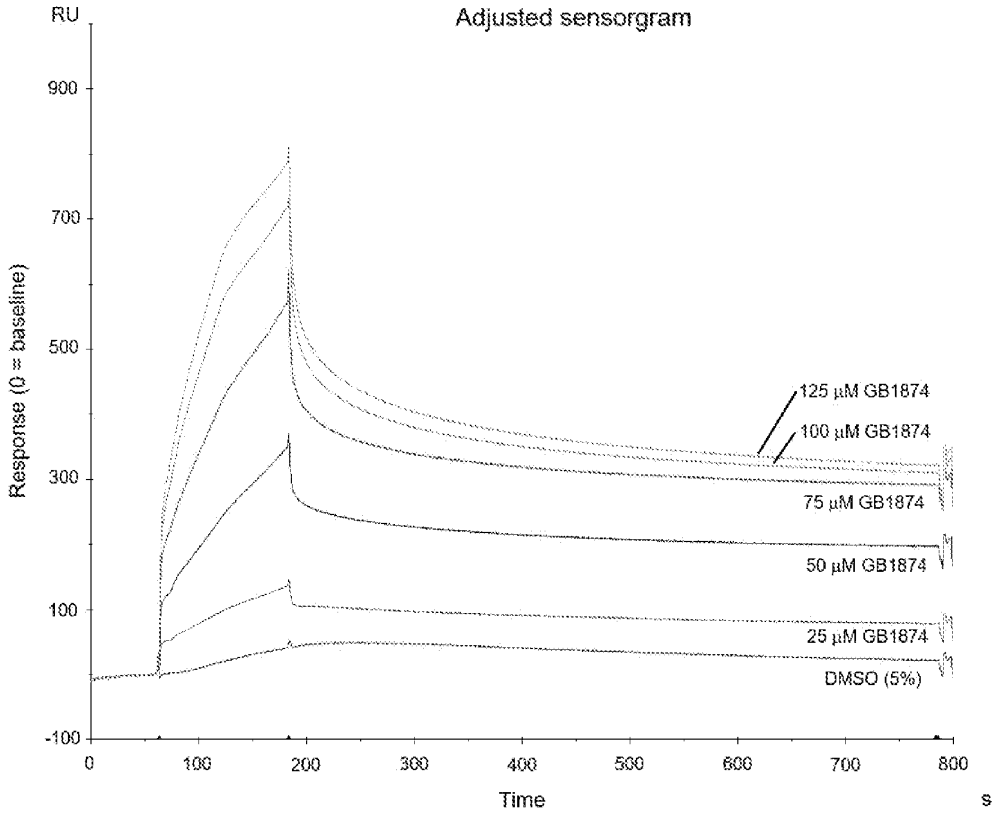

RU
Adjusted sensorgram
900
700
500
300
100
-100
Response (0 = baseline)
125 µM GB1874
100 µM GB1874
75 µM GB1874
50 µM GB1874
25 µM GB1874
DMSO (5%)
0
100
200
300
400
500
600
700
800
Time
s

FIG. 8

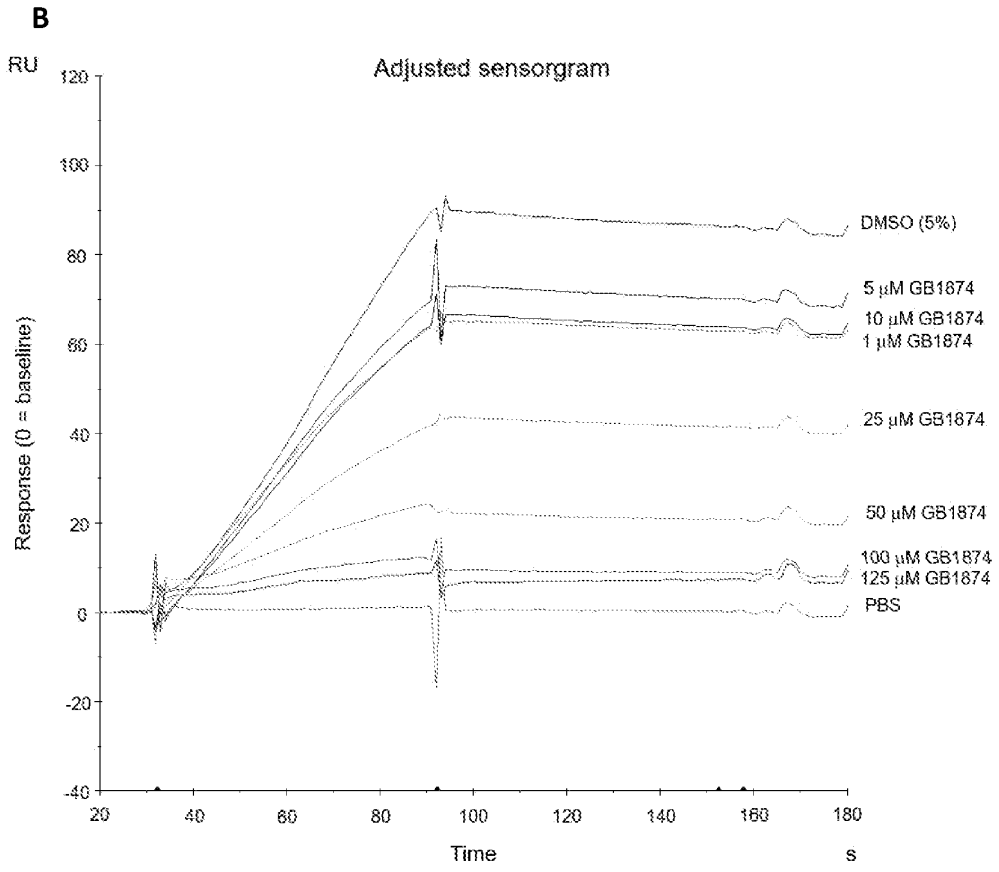
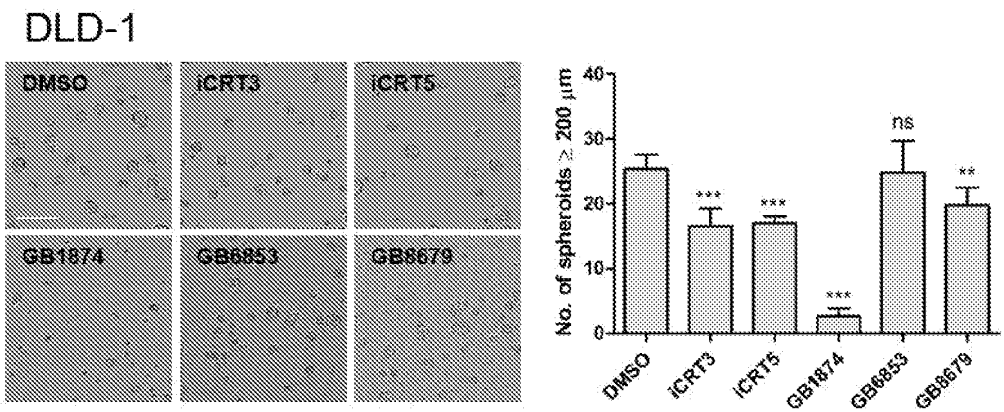


FIG. 8 (Continued)

A


DLD-1
DMSO
iCRT3
iCRT5
GB1874
GB6853
GB8679
No. of spheroids ≥ 200 µm
0
10
20
30
40
***
***
***
ns
**
DMSO
iCRT3
iCRT5
GB1874
GB6853
GB8679

B

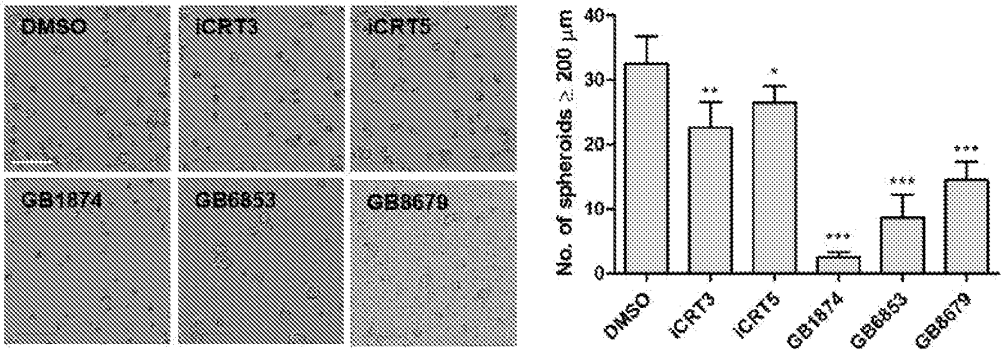

SW480
DMSO
iCRT3
iCRT5
GB1874
GB6853
GB8679
No. of spheroids ≥ 200 µm
0
10
20
30
40
**
*
***
***
DMSO
iCRT3
iCRT5
GB1874
GB6853
GB8679

FIG. 9

C

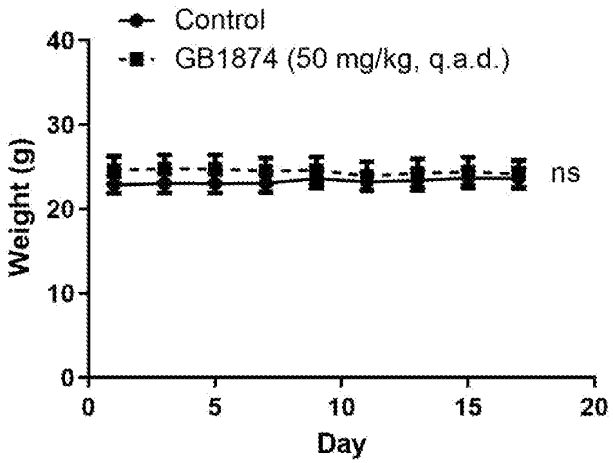


FIG. 9 (Continued)

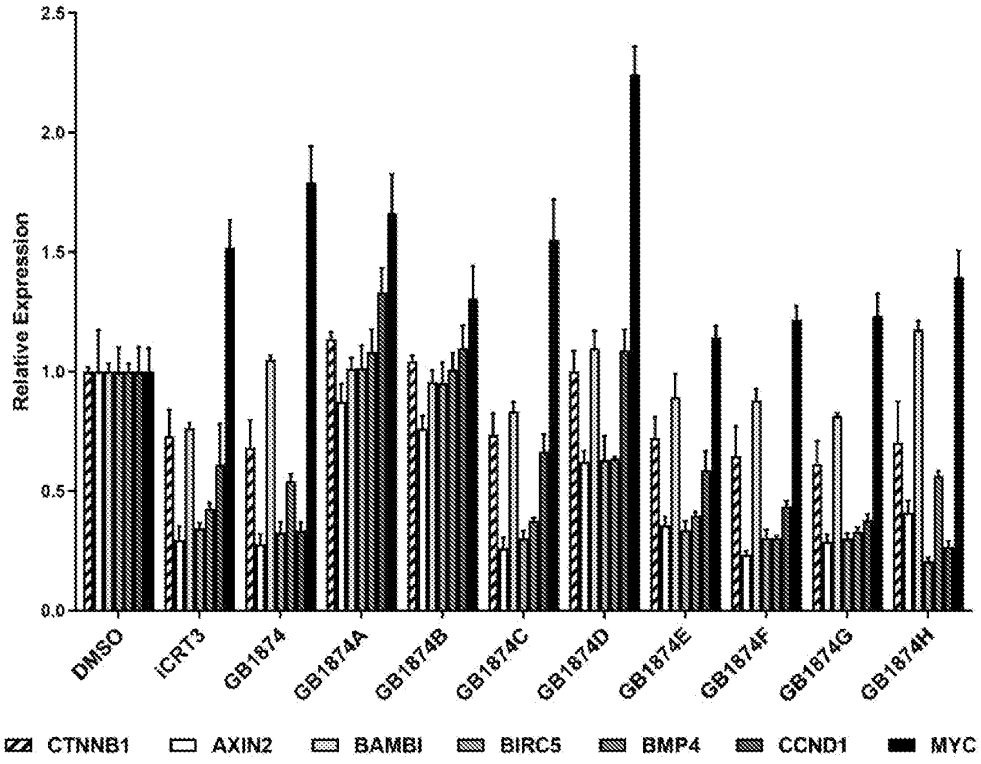

Relative Expression
2.5
2.0
1.5
1.0
0.5
0.0
DMSO
iCRT3
GB1874
GB1874A
GB1874B
GB1874C
GB1874D
GB1874E
GB1874F
GB1874G
GB1874H
CTNNB1
AXIN2
BAMBI
BIRC5
BMP4
CCND1
MYC

FIG. 10

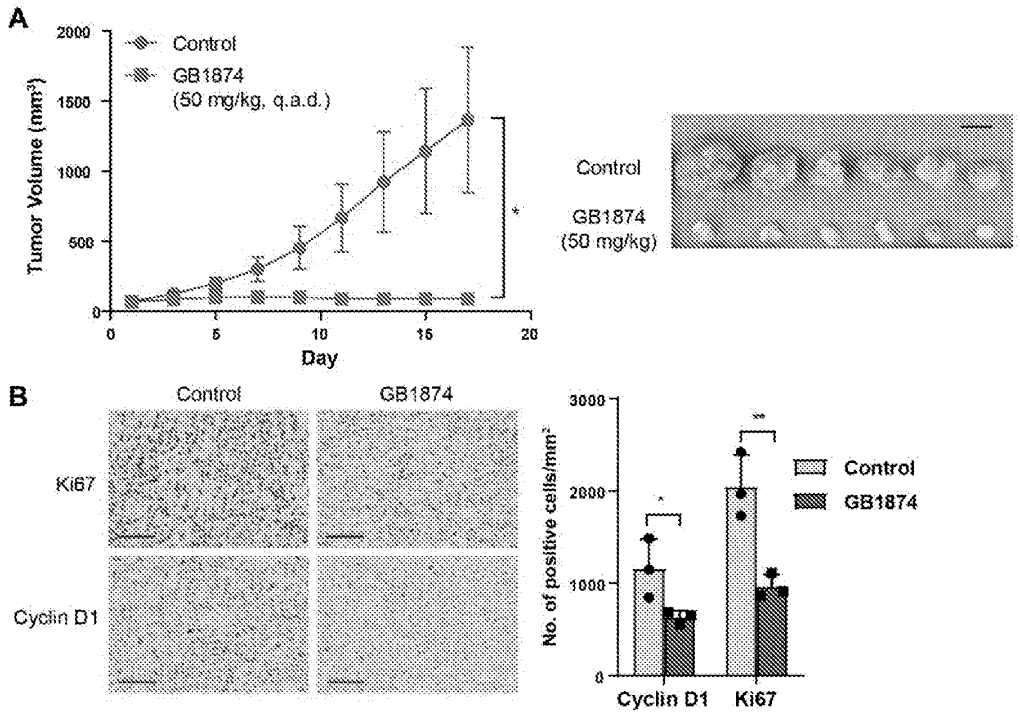

A
Control
GB1874
(50 mg/kg, q.a.d.)
Tumor Volume (mm³)
2000
1500
1000
500
0
0
5
10
15
20
Day
*
Control
GB1874
(50 mg/kg)
B
Control
GB1874
Ki67
Cyclin D1
No. of positive cells/mm²
3000
2000
1000
0
Control
GB1874
Cyclin D1
Ki67

FIG. 11