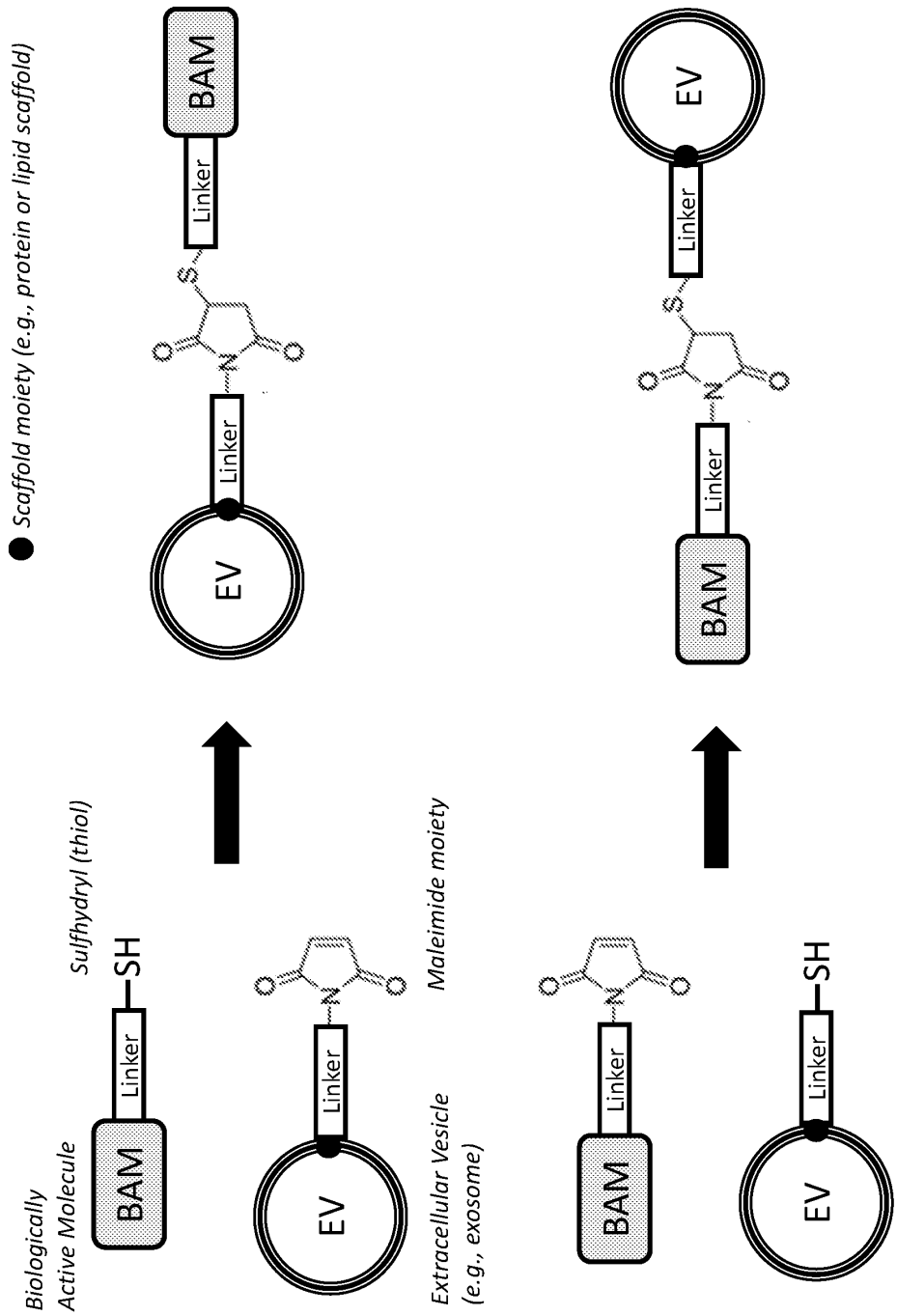

Scaffold moiety (e.g., protein or lipid scaffold)
Biologically Active Molecule
Sulfhydryl (thiol)
Maleimide moiety
Extracellular Vesicle (e.g., exosome)
BAM
Linker
SH
EV
N
O
S

FIG. 1A

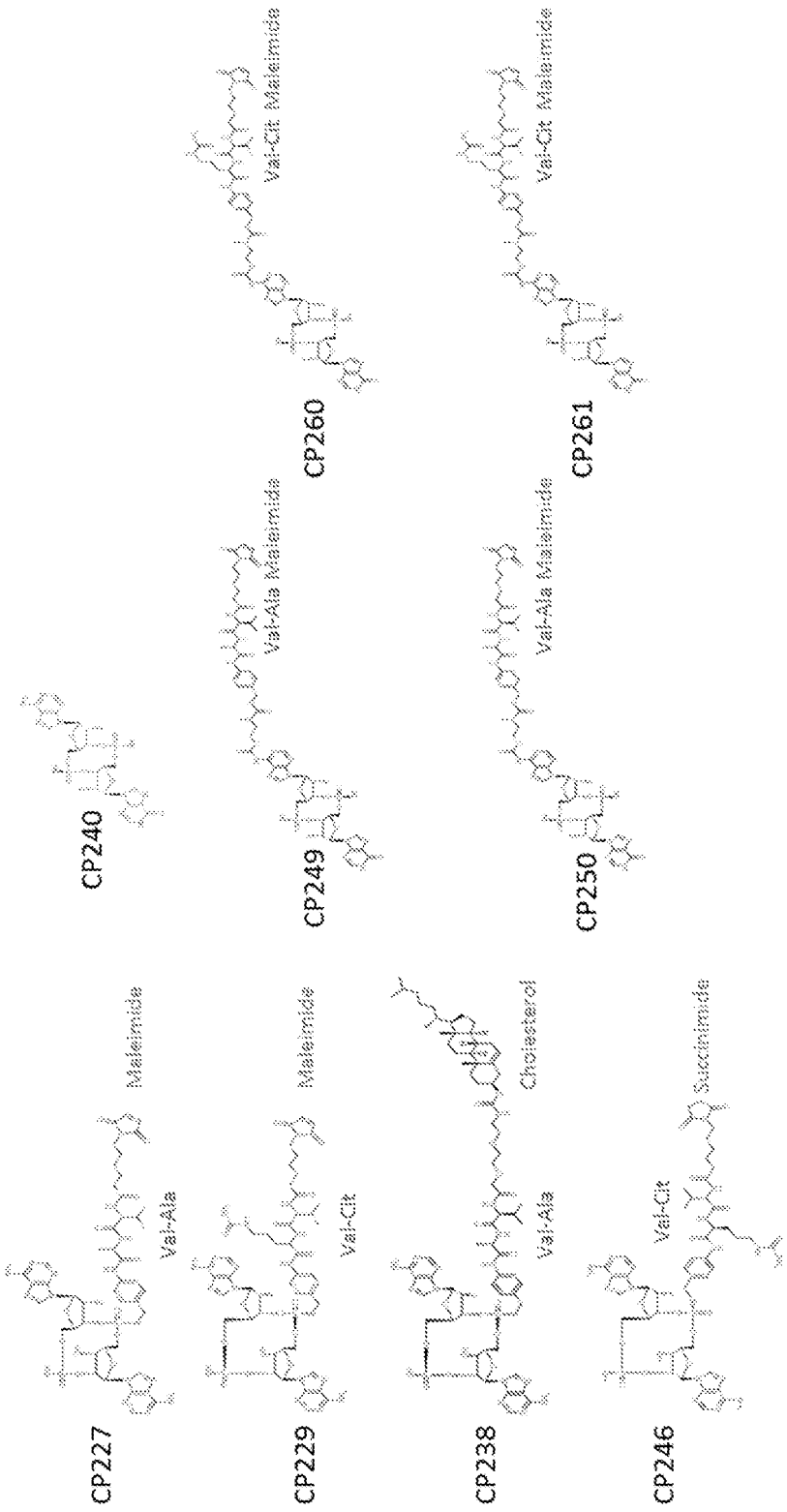

CP227
Val-Ala
Maleimide
CP229
Val-Cit
Maleimide
CP238
Val-Ala
Cholesterol
CP246
Val-Cit
Succinimide
CP240
CP249
Val-Ala Maleimide
CP250
Val-Ala Maleimide
CP260
Val-Cit Maleimide
CP261
Val-Cit Maleimide

FIG. 1B

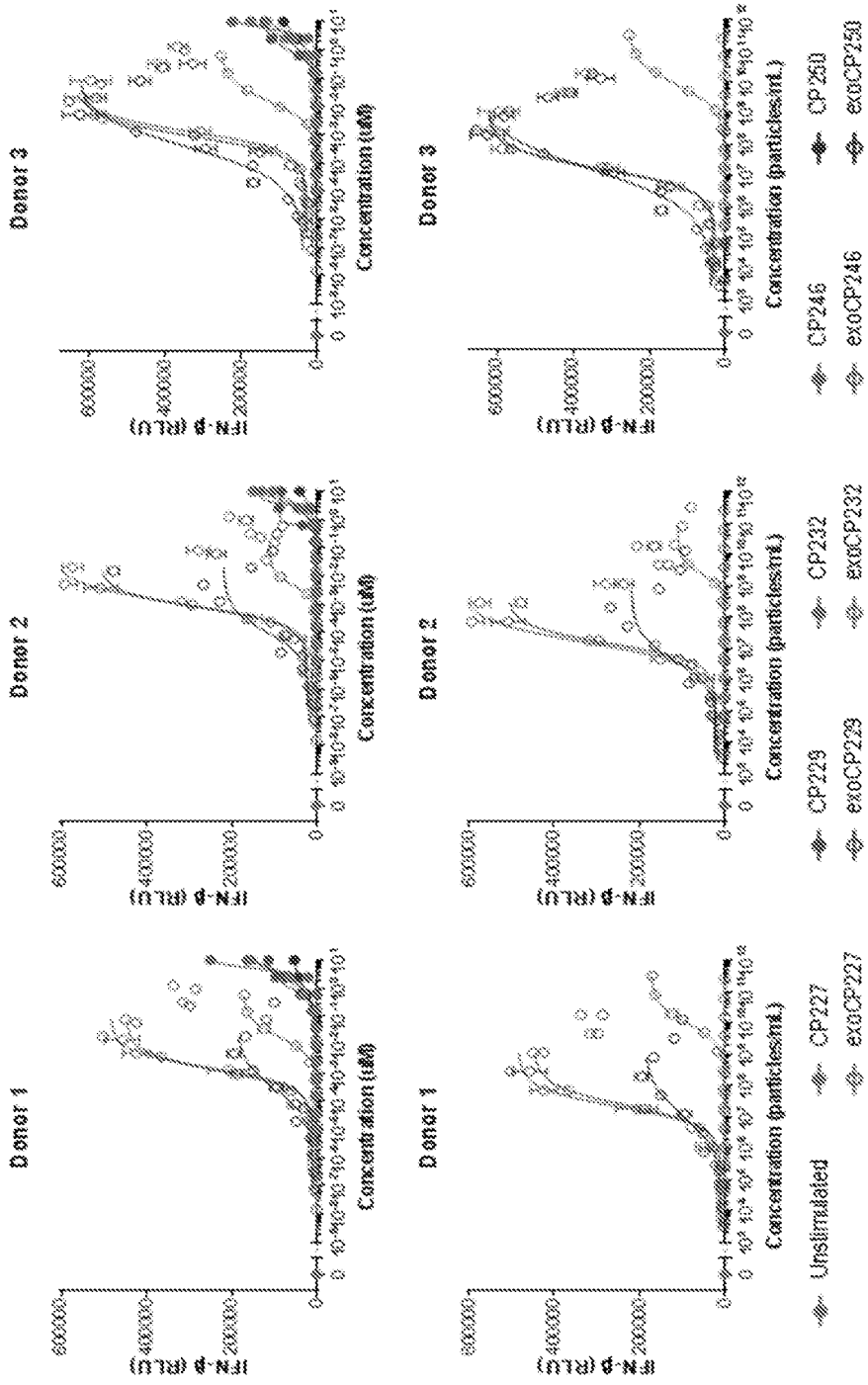
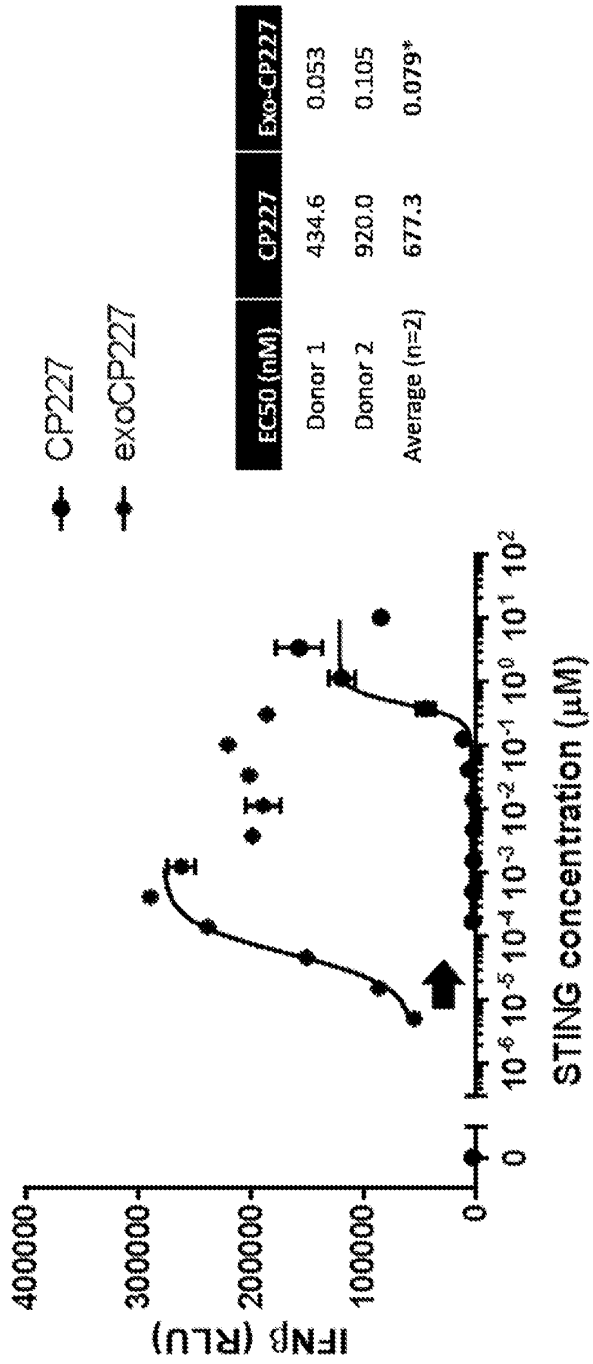
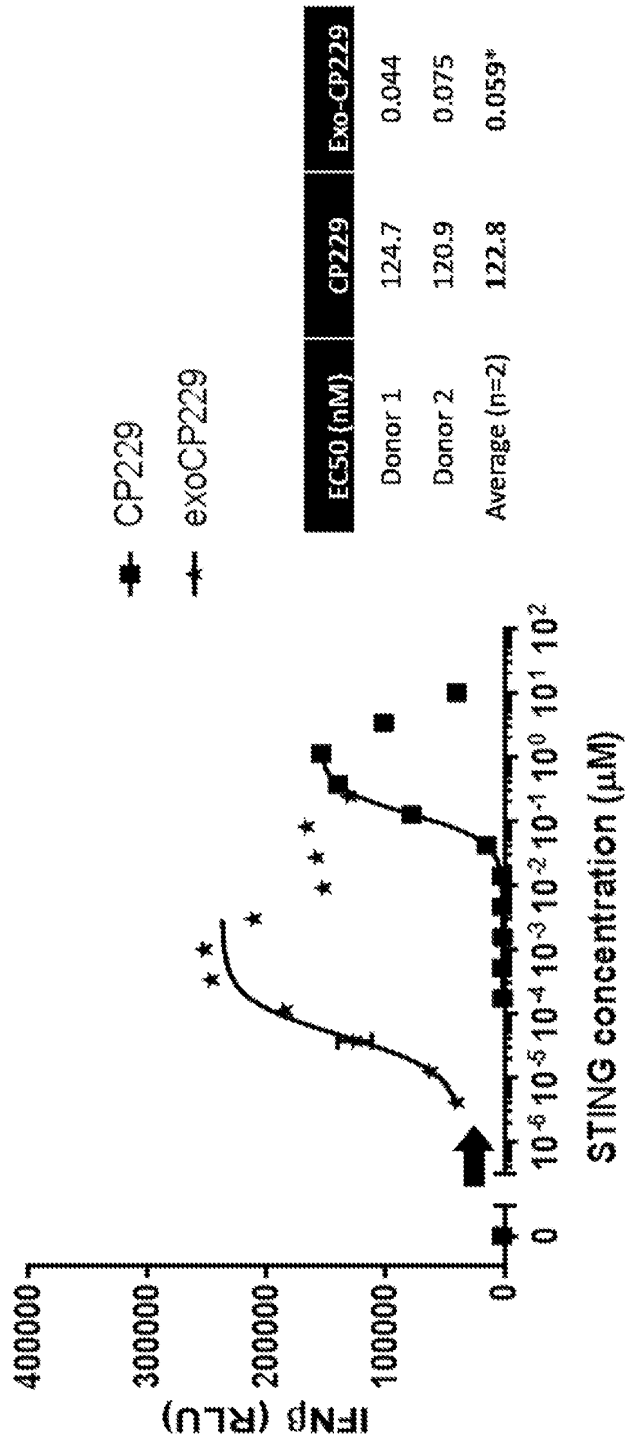

Donor 1
Donor 2
Donor 3
IFN-β (RLU)
Concentration (nM)
Concentration (particles/mL)
Unstimulated
CP227
exoCP227
CP229
exoCP229
CP232
exoCP232
CP246
exoCP246
CP250
exoCP250
Compound: CP227 CP229 CP232 CP246 CP250
Linker: Val-Ala Val-Cit - Val-Cit Val-Cit
Attachment: Mal. Mal. - Succ. Mal.

FIG. 2



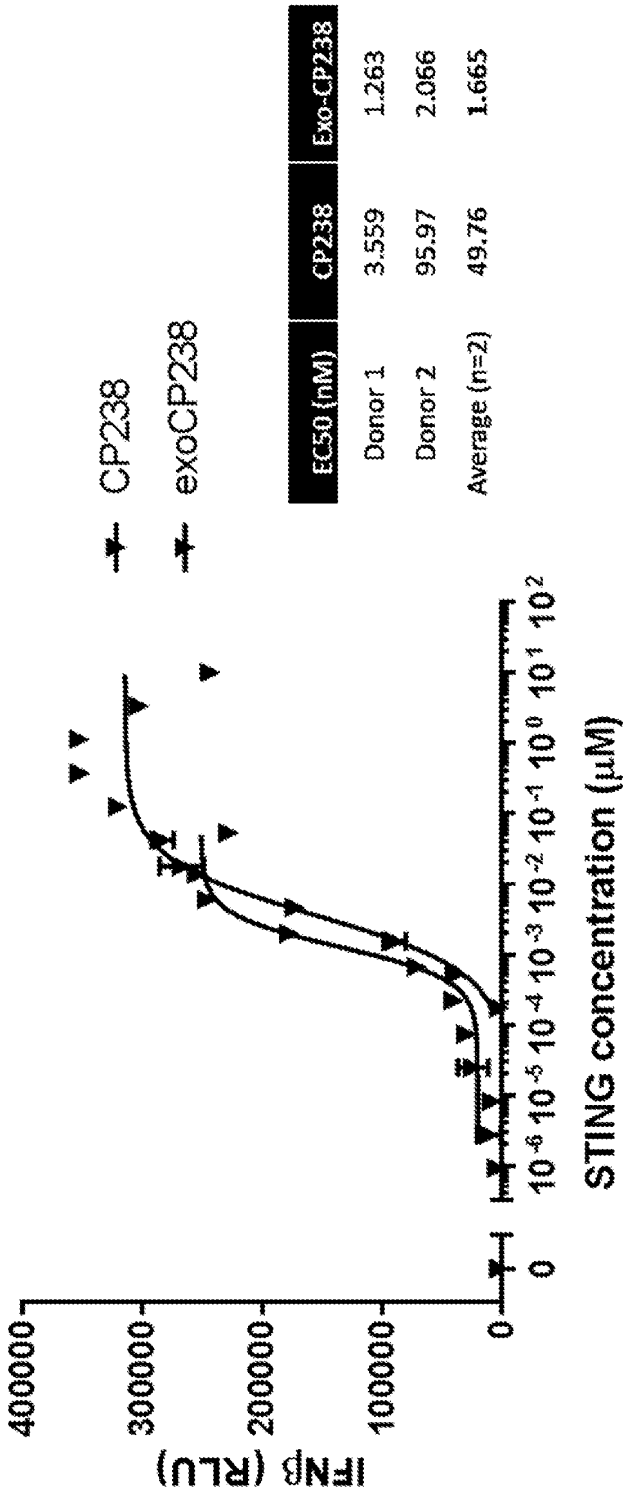
EC50 (nM)	CP227	Exo-CP227
Donor 1	434.6	0.053
Donor 2	920.0	0.105
Average (n=2)	677.3	0.079*

FIG. 3A



EC50 (nM)	CP229	Exo-CP229
Donor 1	124.7	0.044
Donor 2	120.9	0.075
Average (n=2)	**122.8**	**0.059***

FIG. 3B



EC50 (nM)	CP238	Exo-CP238
Donor 1	3.559	1.263
Donor 2	95.97	2.066
Average (n=2)	49.76	1.665

FIG. 3C

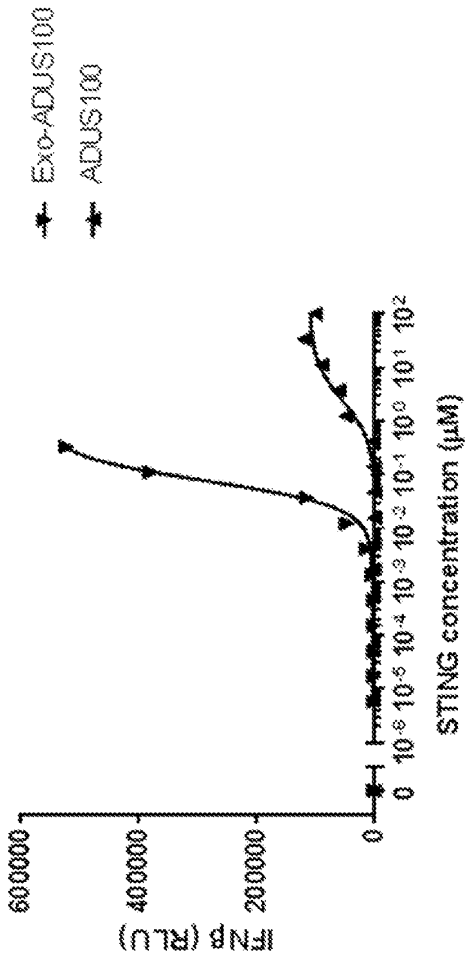


FIG. 4A

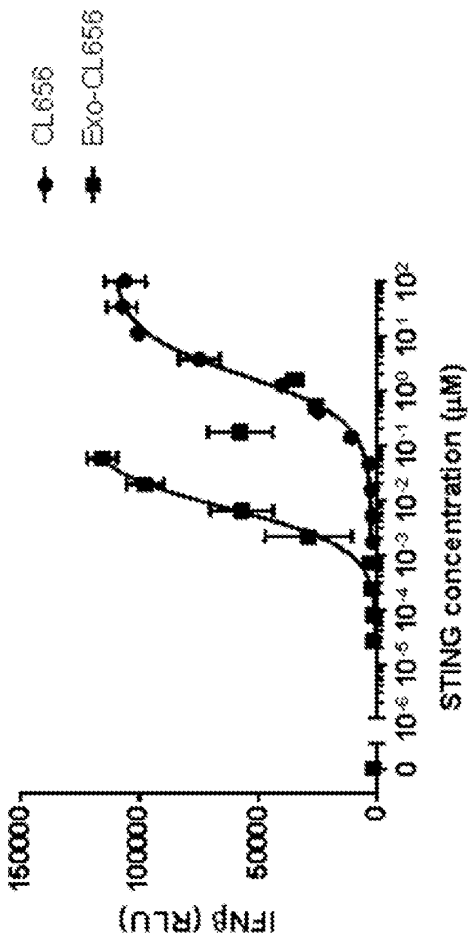


FIG. 4B

	EC50 (nM)	Free Drug	Exo-STING	Fold Increase in potency
ADUS100	2406	75.000	32	
CL656	1899	2.400	791	
CP227	677	0.079	8570	
CP229	122	0.059	2068	
CP238	49	1.665	29	

FIG. 4C

Loading

Sample	Reactive Group	molecules agonist/EV (Exp. 1)	molecules agonist/EV (Exp. 2)
exoCP227	Maleimide	64,700	*42,700
exoCP229	Maleimide	44,500	31,700
exoCP250	Maleimide		15,100
exoCP238	Cholesterol	1,600	
exoCP232	none		1,100
exoCP246	Succinimide		250

*Sample was above ULOQ – likely higher than value listed

FIG. 5A

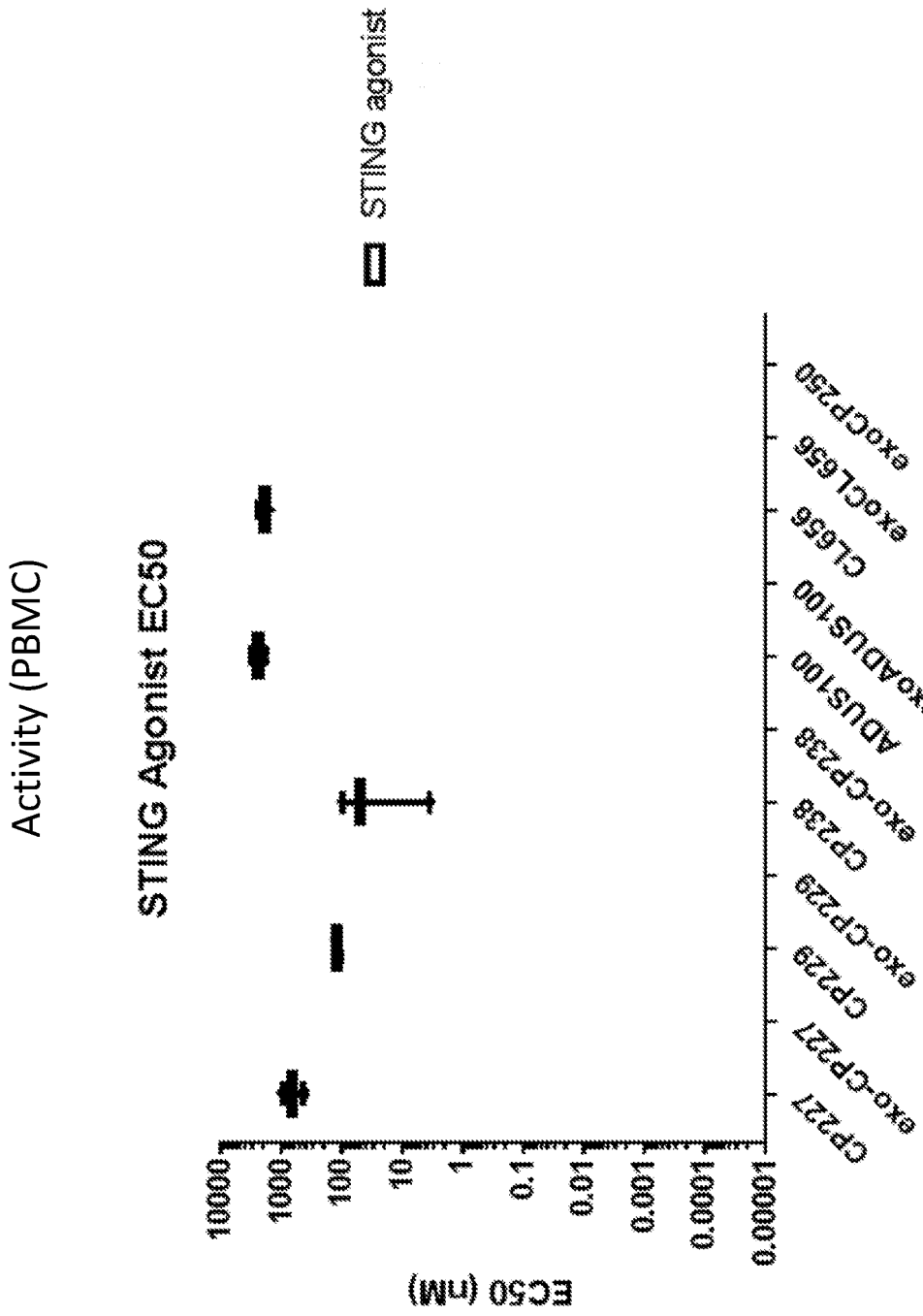
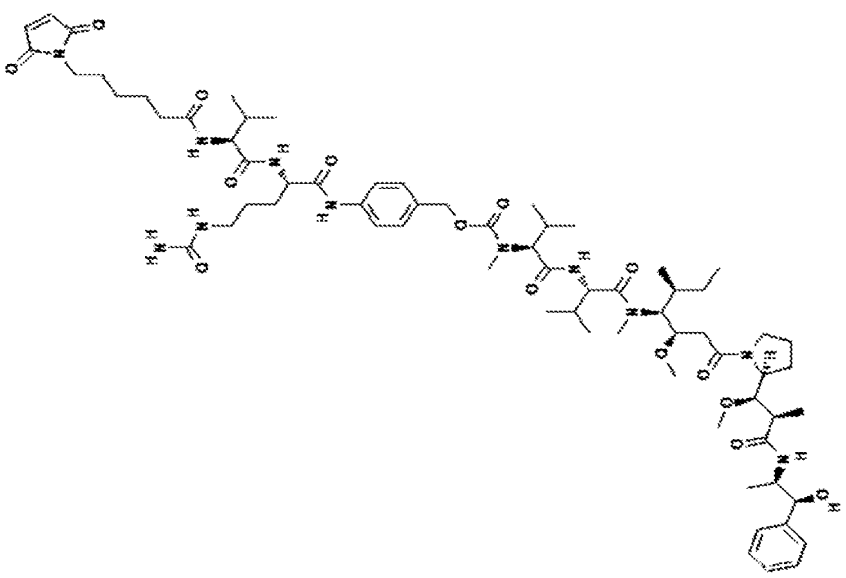

Activity (PBMC)
STING Agonist EC50
STING agonist
EC50 (nM)
10000
1000
100
10
1
0.1
0.01
0.001
0.0001
0.00001
CP22Z
exo-CP22Z
CP229
exo-CP229
CP238
exo-CP238
ADUS100
exoADUS100
CL656
exoCL656
exoCP250

FIG. 5B

mc-vc-PABC-MMAE
Compound CID: 46944733
Molecular Formula: $C_{68}H_{105}N_{11}O_{15}$
Molecular Weight: 1316.65 g/mol



MMAE (monomethyl auristatin E)
PubChem CID: 53297465
Molecular Formula: $C_{39}H_{67}N_5O_7$
Molecular Weight: 717.998 g/mol

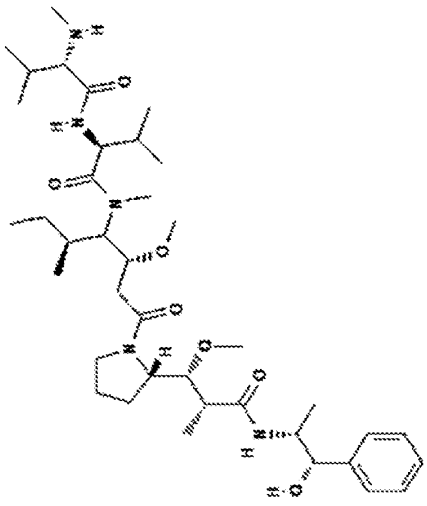


FIG. 6

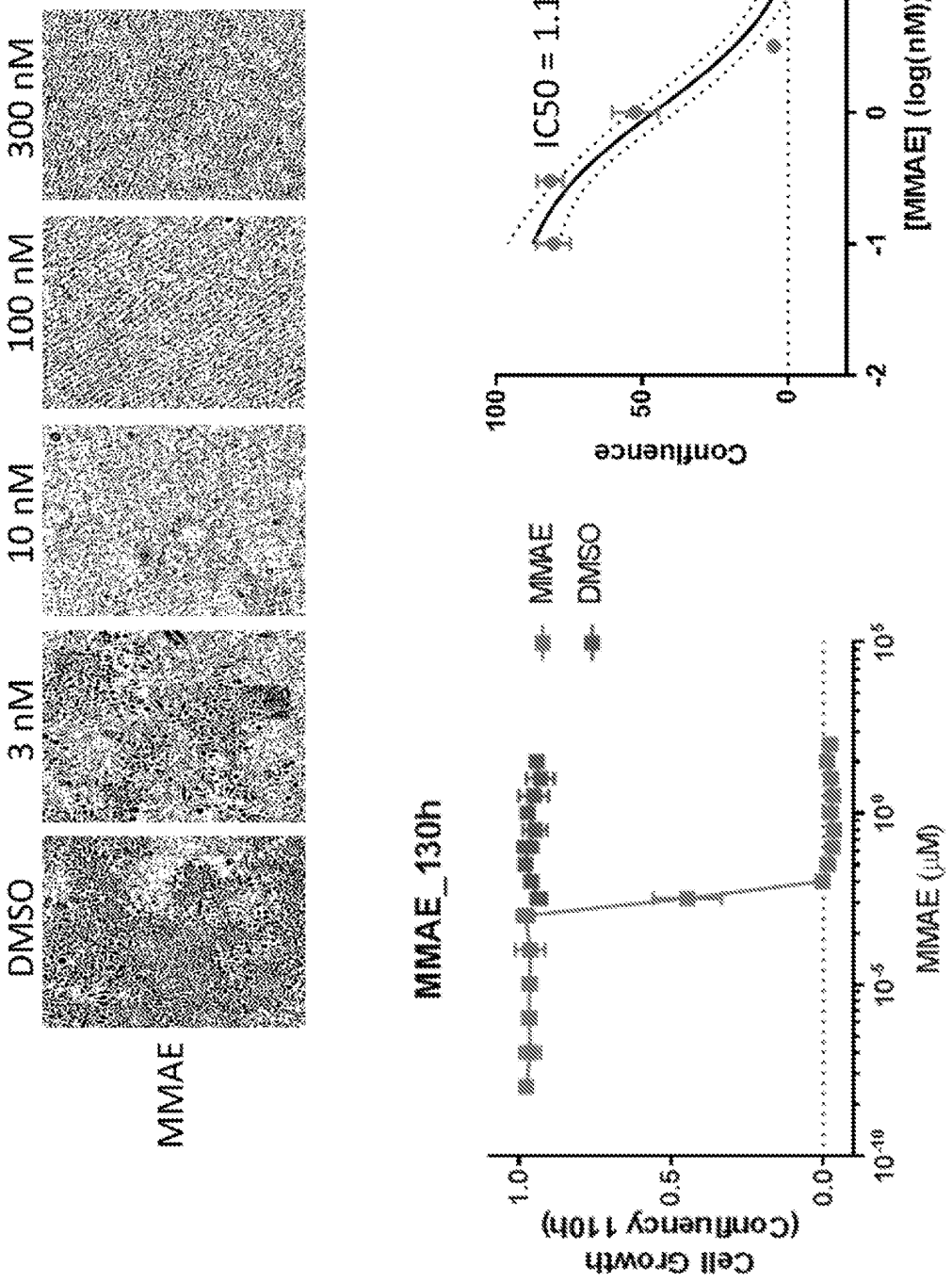

DMSO
3 nM
10 nM
100 nM
300 nM
MMAE
MMAE_130h
MMAE
DMSO
Cell Growth (Confluency 110h)
MMAE (μM)
Confluence
IC50 = 1.1 nM
[MMAE] (log(nM))

FIG. 7

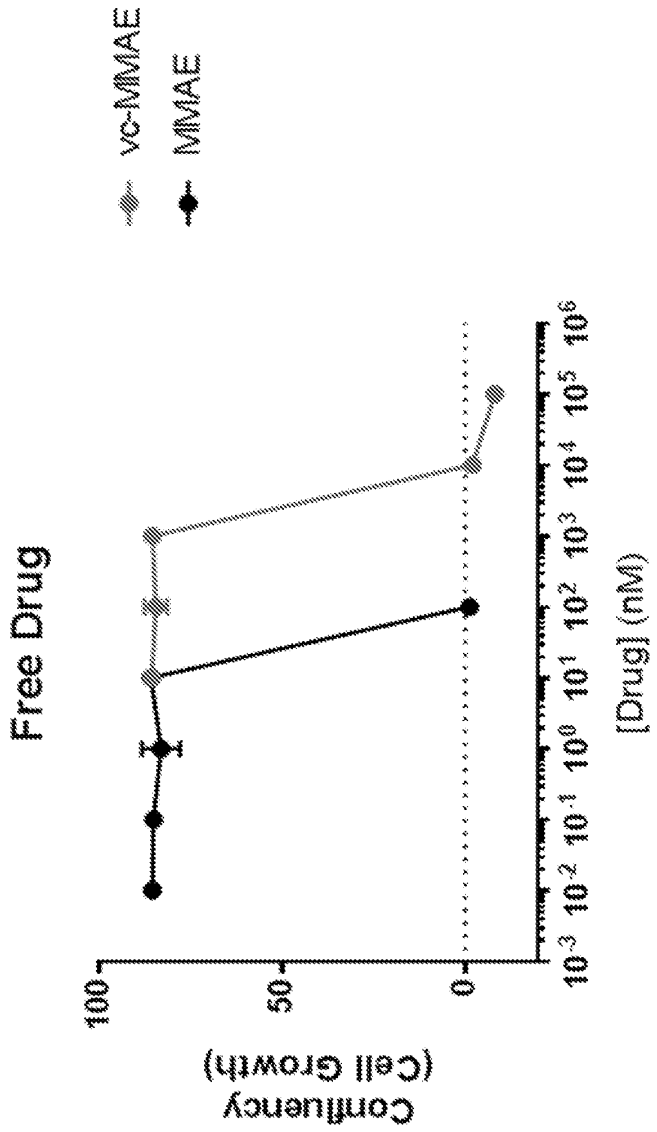

vc-MMAE
MMAE
Free Drug
Confluency
(Cell Growth)
100
50
0
10^{-3} 10^{-2} 10^{-1} 10^{0} 10^{1} 10^{2} 10^{3} 10^{4} 10^{5} 10^{6}
[Drug] (nM)

FIG. 8A

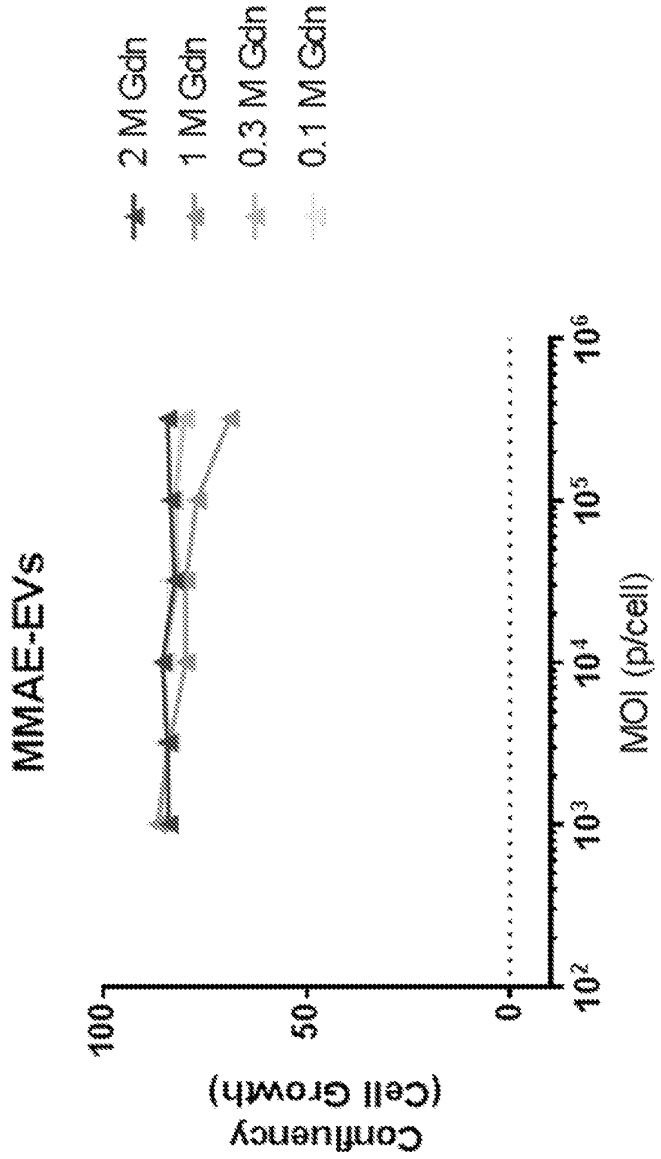

2 M Gdn
1 M Gdn
0.3 M Gdn
0.1 M Gdn
MMAE-EVs
Confluency
(Cell Growth)
100
50
0
10^2
10^3
10^4
10^5
10^6
MOI (p/cell)

FIG. 8B

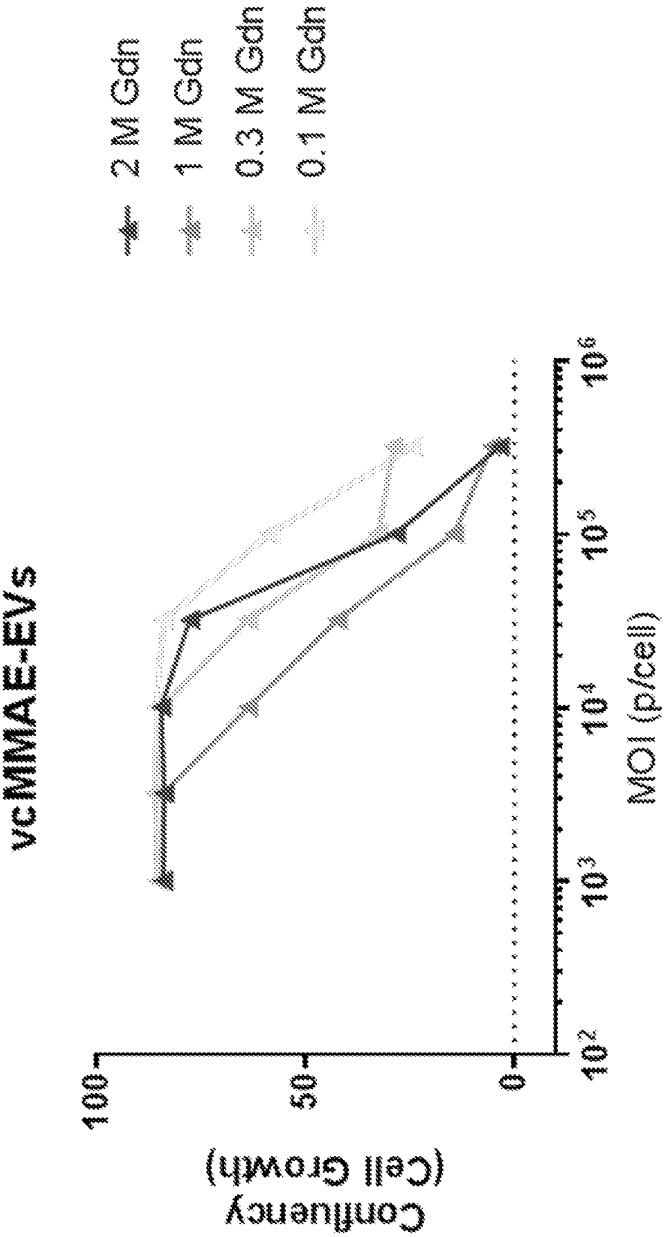

2 M Gdn
1 M Gdn
0.3 M Gdn
0.1 M Gdn
vcMMAE-EVs
Confluency
(Cell Growth)
100
50
0
10^2
10^3
10^4
10^5
10^6
MOI (p/cell)

FIG. 8C

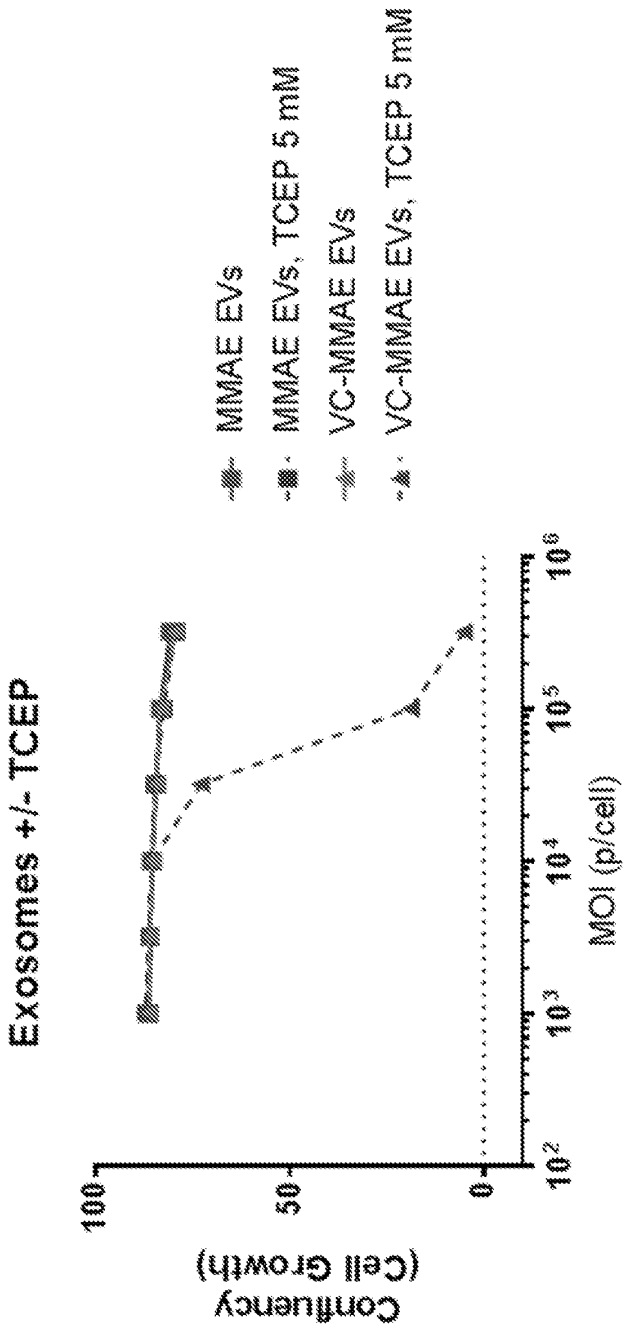

Exosomes +/- TCEP
MMAE EVs
MMAE EVs, TCEP 5 mM
VC-MMAE EVs
VC-MMAE EVs, TCEP 5 mM
Confluency (Cell Growth)
100
50
0
10^2
10^3
10^4
10^5
10^6
MOI (p/cell)

FIG. 8D

FIG. 9A

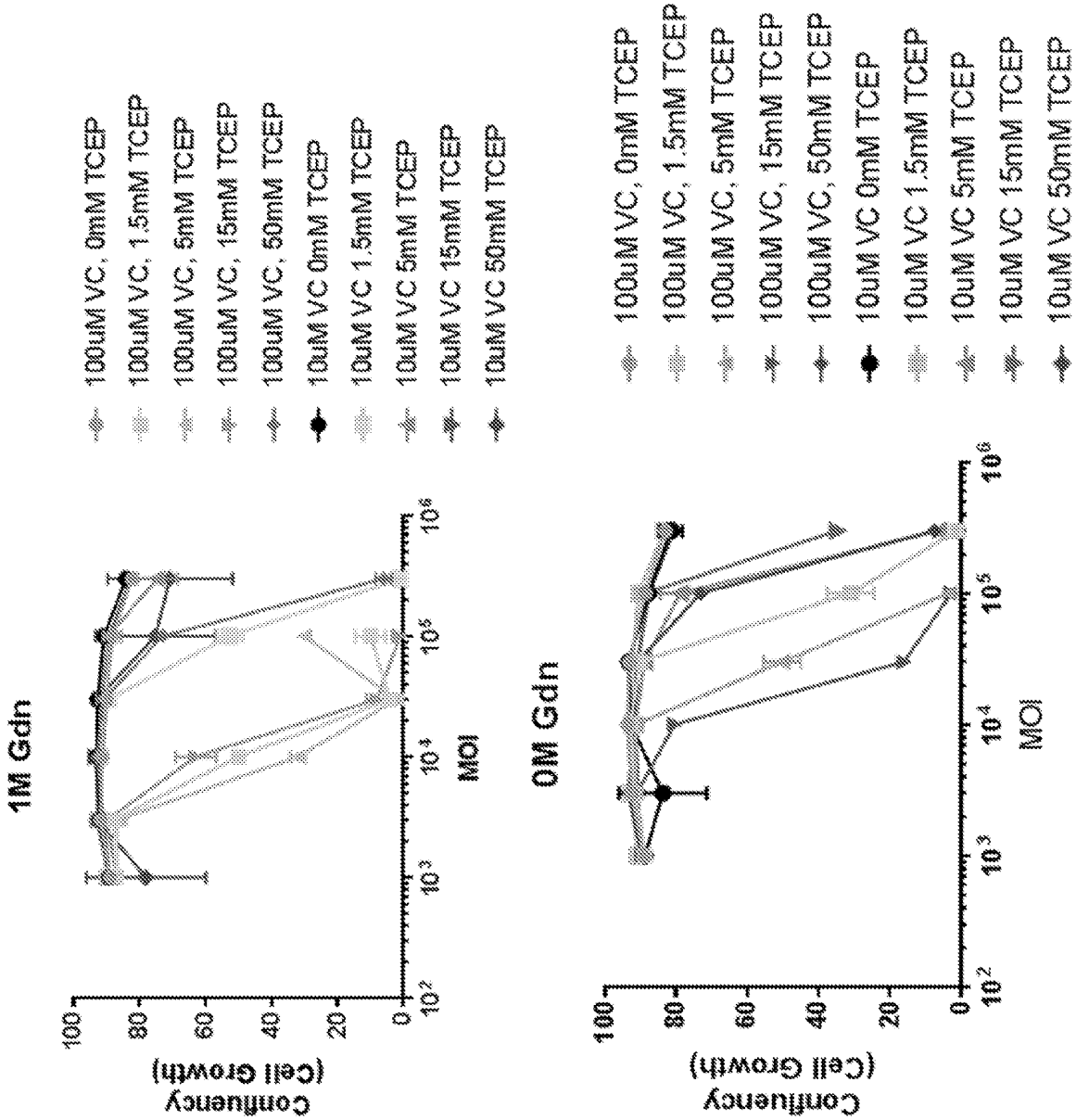
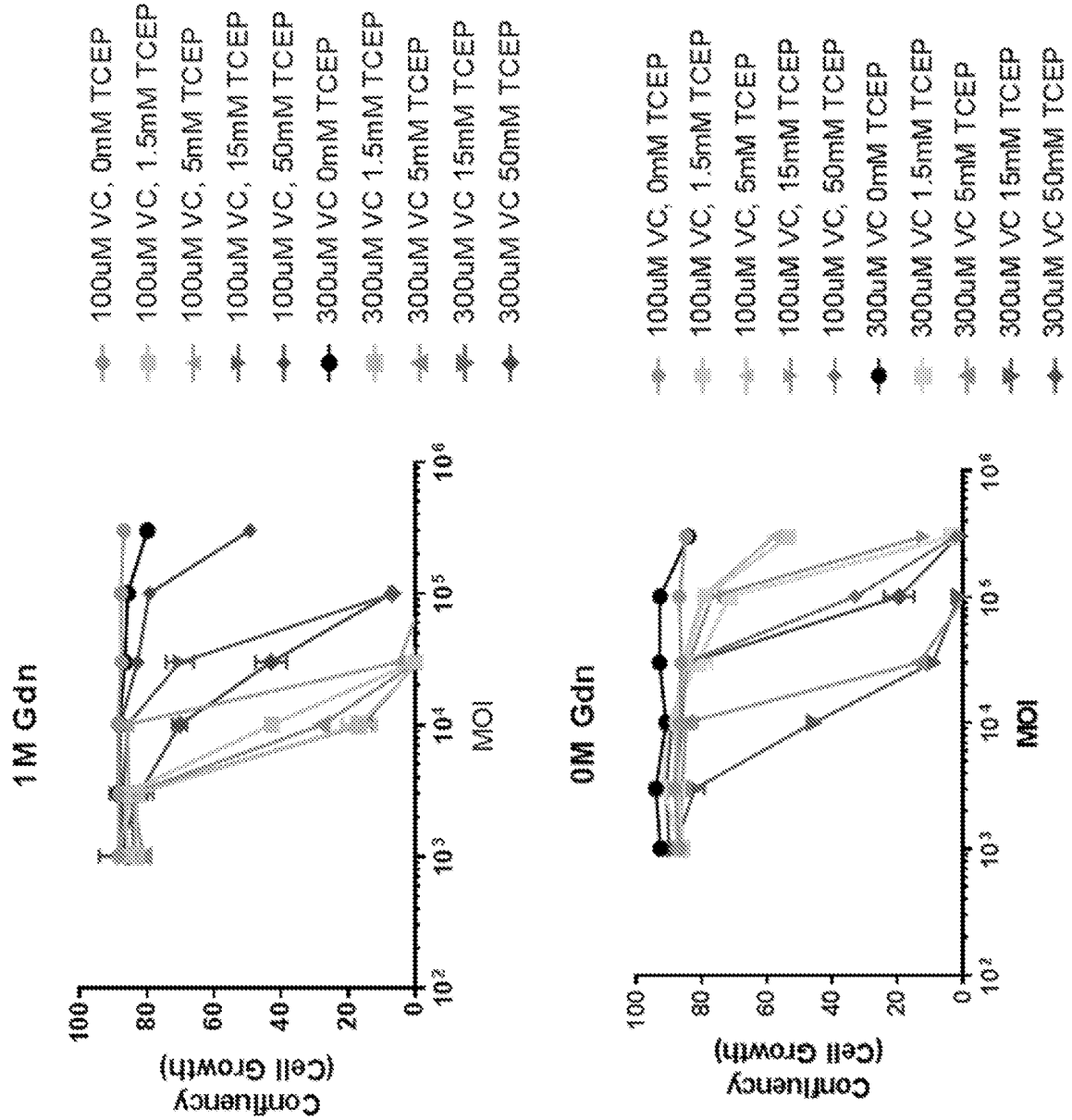

1M Gdn
0M Gdn
Confluency (Cell Growth)
MOI
100uM VC, 0mM TCEP
100uM VC, 1.5mM TCEP
100uM VC, 5mM TCEP
100uM VC, 15mM TCEP
100uM VC, 50mM TCEP
10uM VC 0mM TCEP
10uM VC 1.5mM TCEP
10uM VC 5mM TCEP
10uM VC 15mM TCEP
10uM VC 50mM TCEP

FIG. 9B


1M Gdn
0M Gdn
Confluency (Cell Growth)
MOI
100uM VC, 0mM TCEP
100uM VC, 1.5mM TCEP
100uM VC, 5mM TCEP
100uM VC, 15mM TCEP
100uM VC, 50mM TCEP
300uM VC 0mM TCEP
300uM VC 1.5mM TCEP
300uM VC 5mM TCEP
300uM VC 15mM TCEP
300uM VC 50mM TCEP

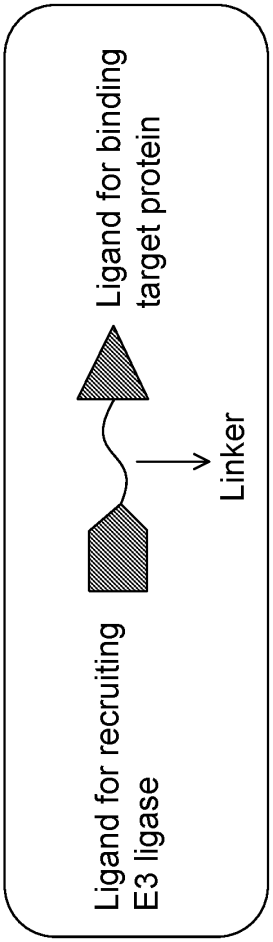


FIG. 10A

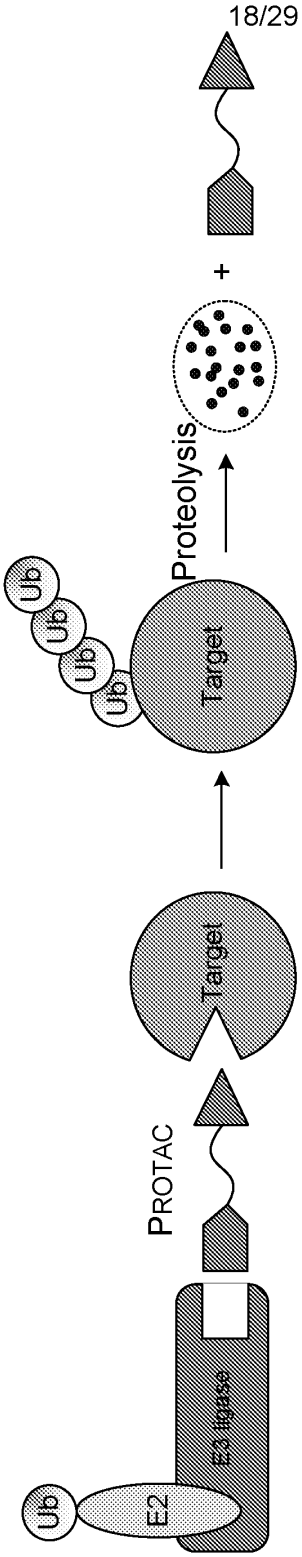


FIG. 10B

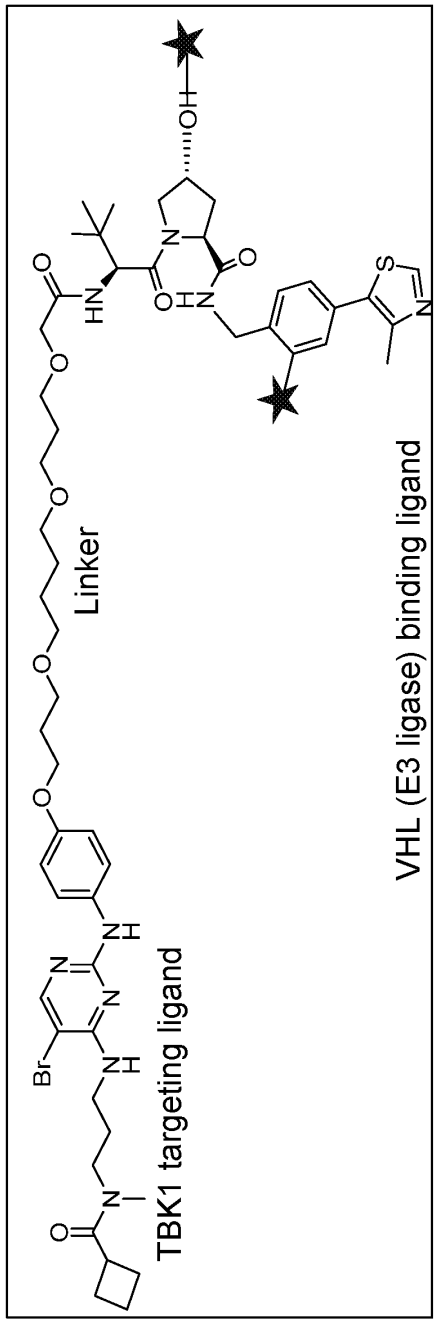


FIG. 10C

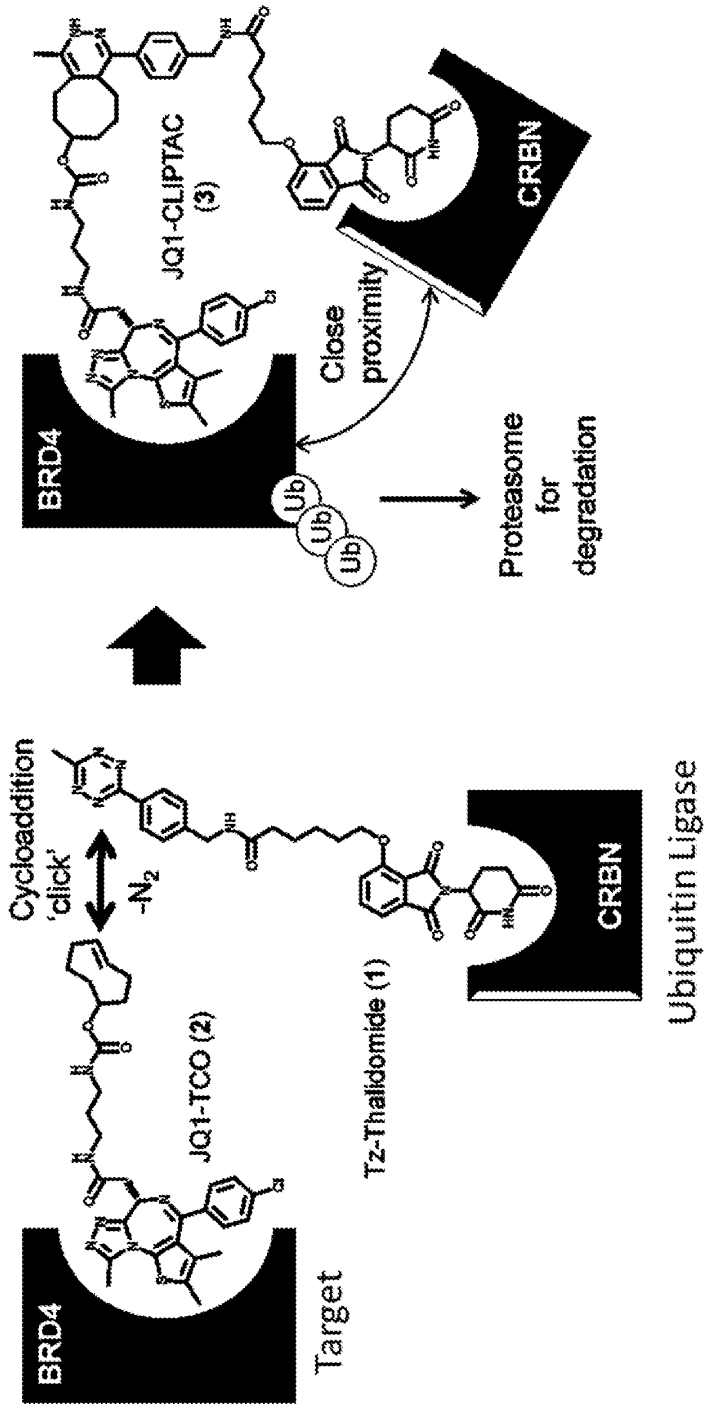

BRD4
JQ1-TCO (2)
Cycloaddition
'click'
$-N_2$
Tz-Thalidomide (1)
CRBN
Ubiquitin Ligase
Target
BRD4
JQ1-CLIPTAC
(3)
CRBN
Close
proximity
Ub
Ub
Ub
Proteasome
for
degradation

FIG. 11



FIG. 12

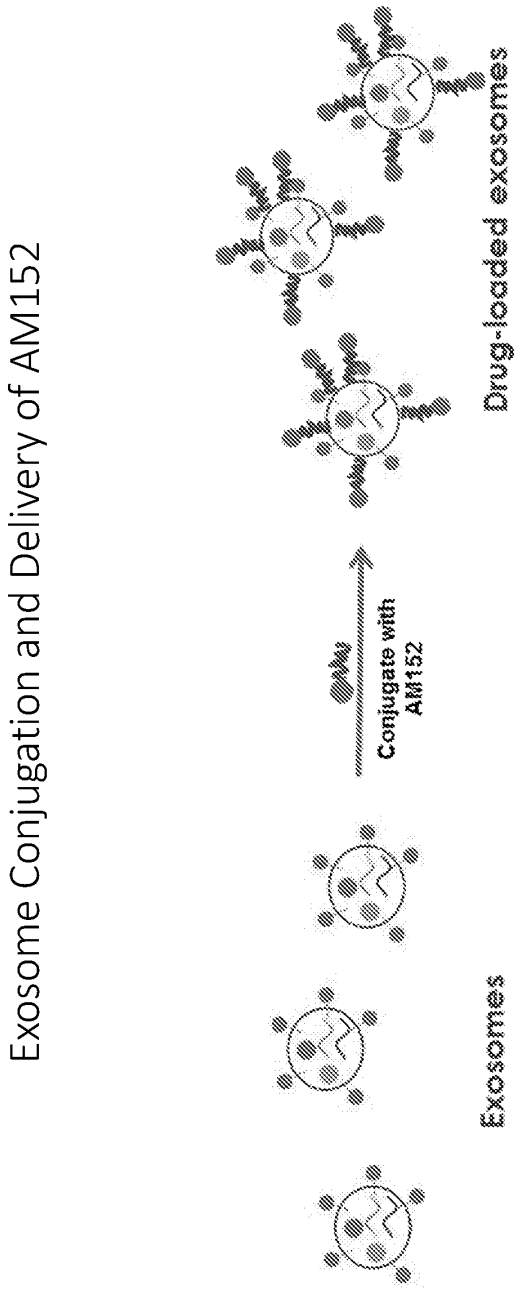

Exosome Conjugation and Delivery of AM152
Exosomes
Conjugate with AM152
Drug-loaded exosomes

FIG. 13

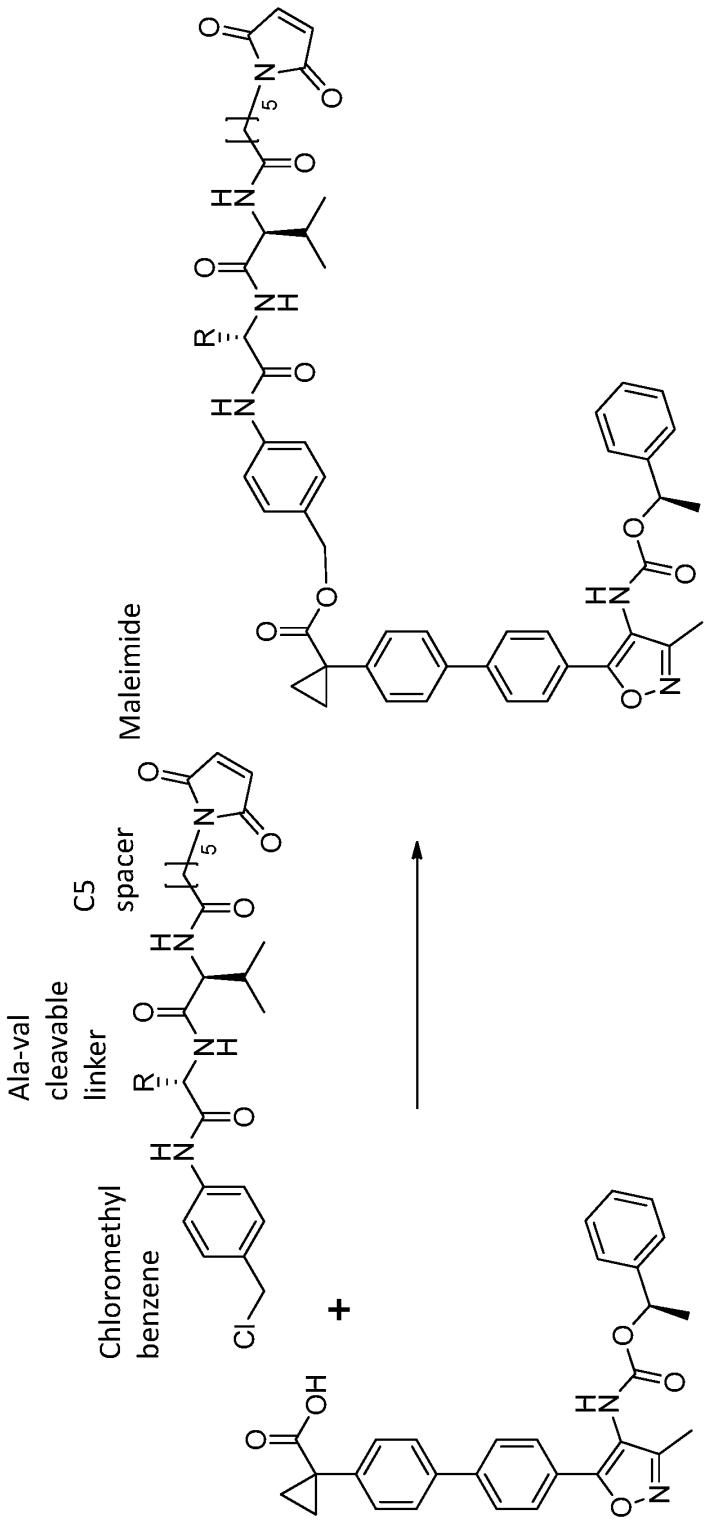

Maleimide
C5 spacer
Ala-val cleavable linker
Chloromethyl benzene
Cl
OH
+

FIG. 14

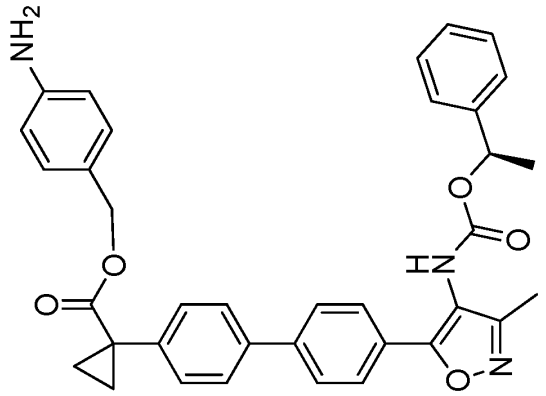


FIG. 16

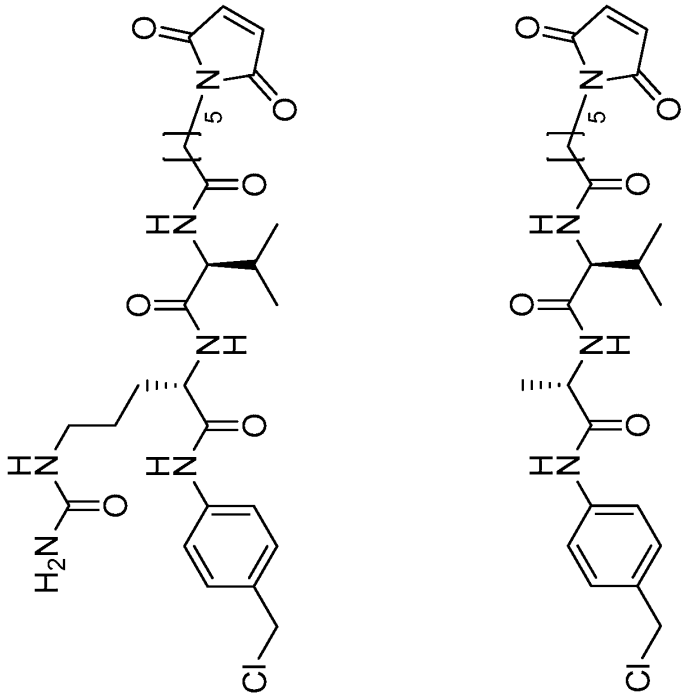


FIG. 15

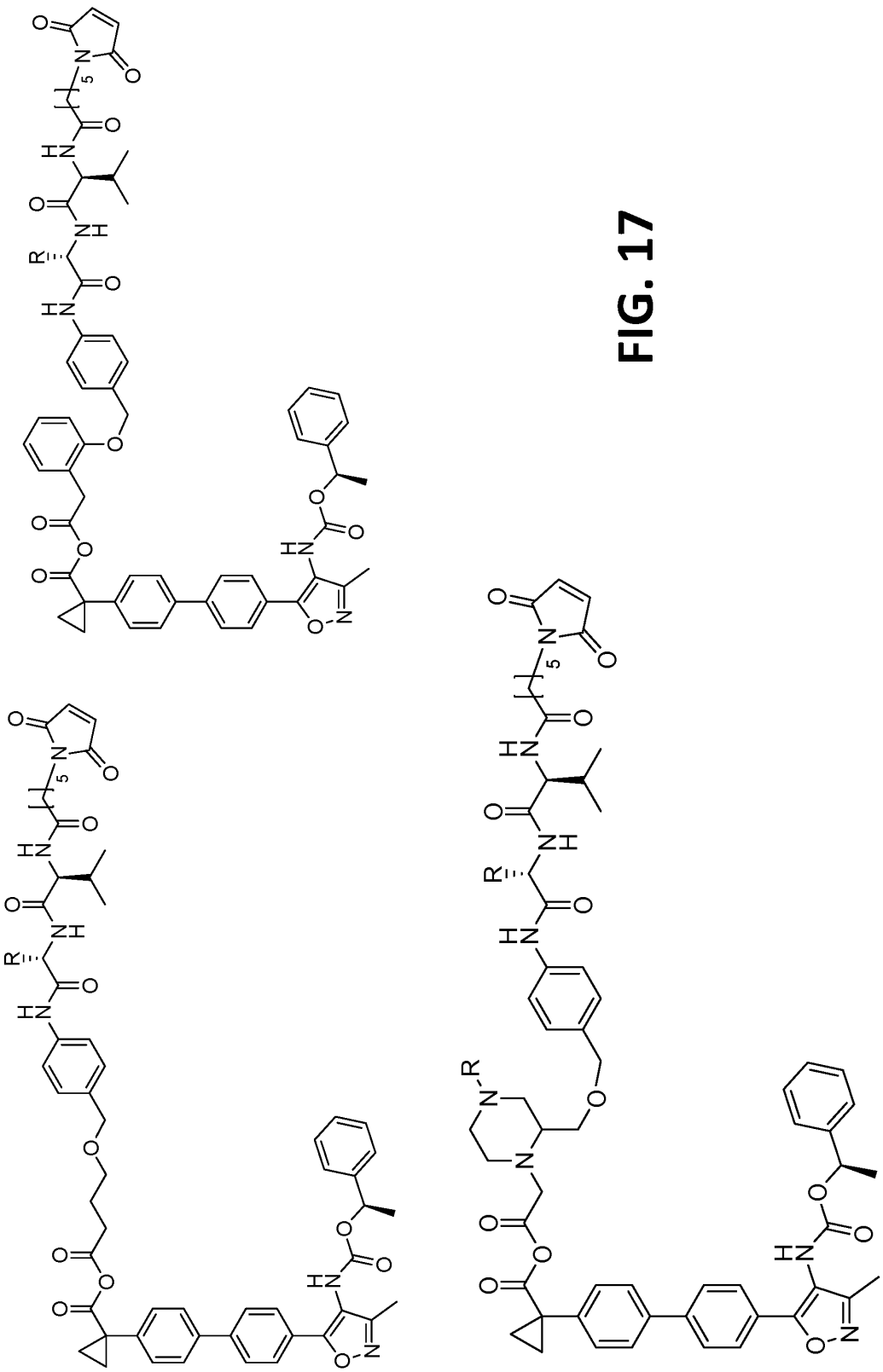


FIG. 17

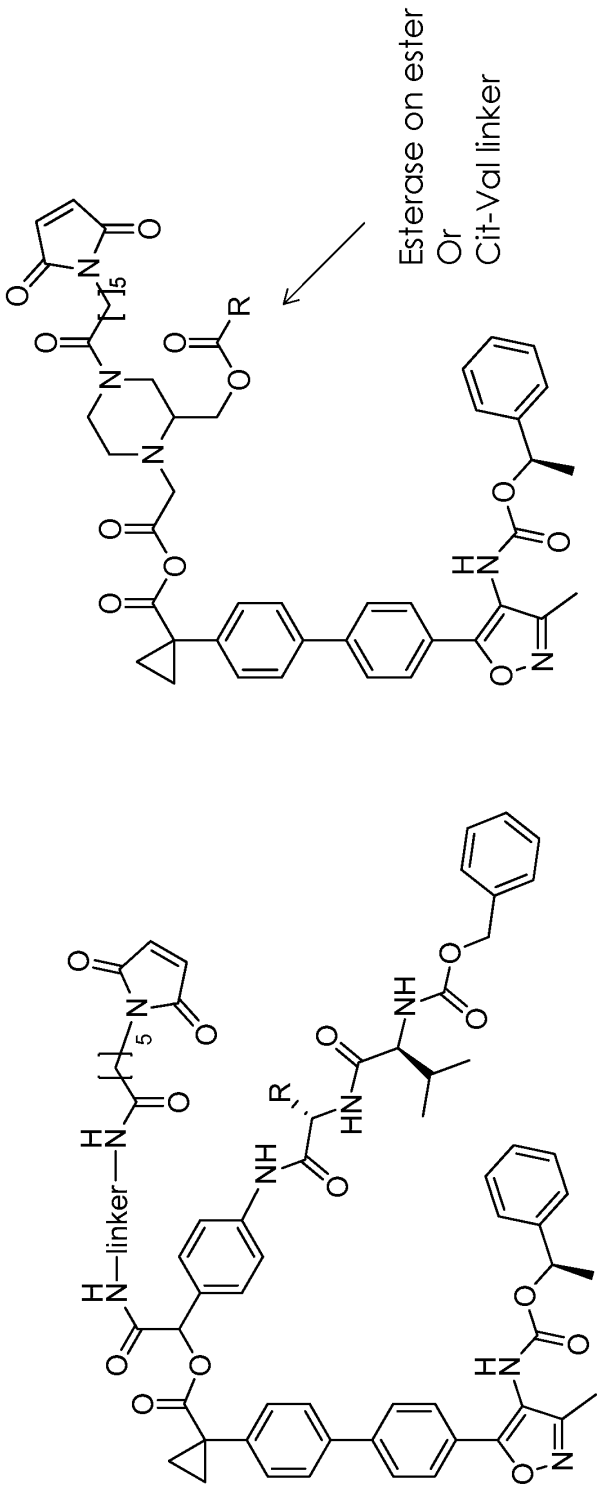


FIG. 18

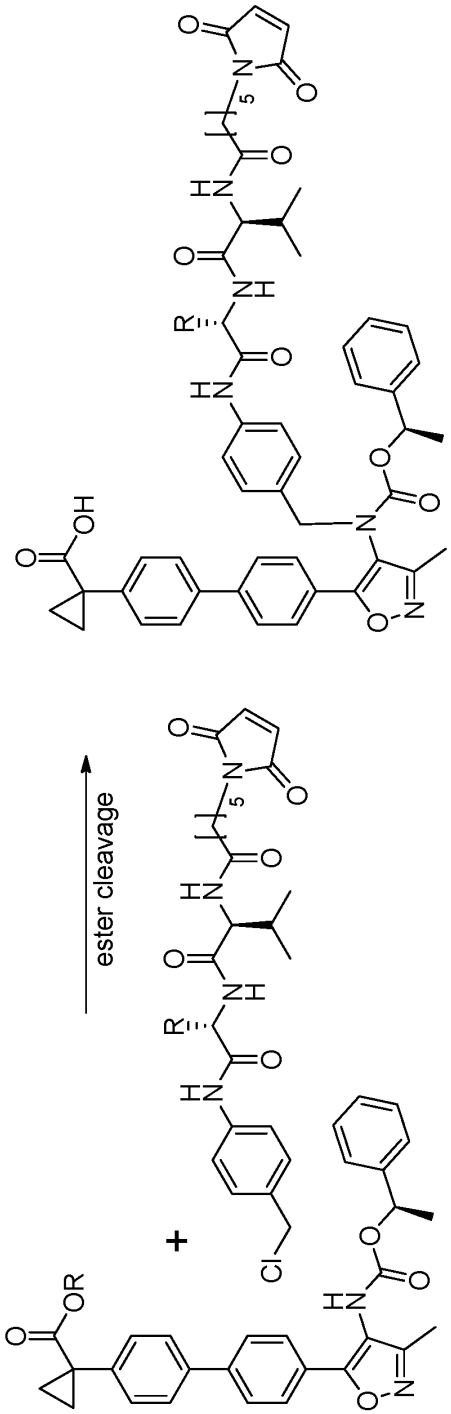


FIG. 19

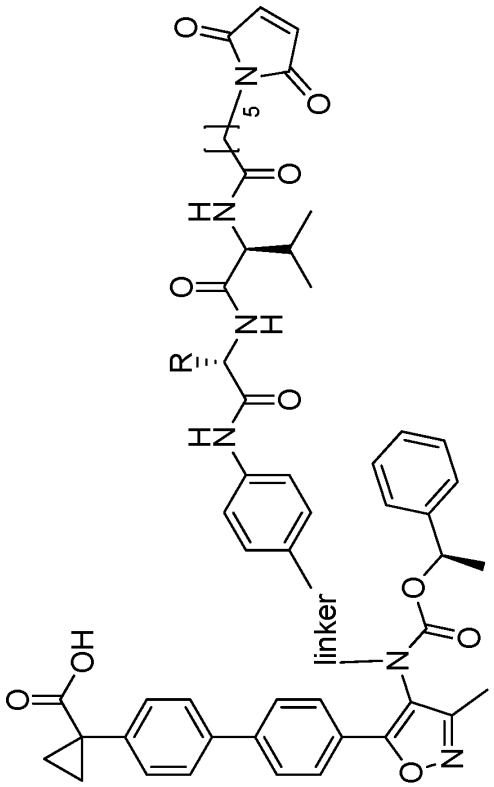


FIG. 20

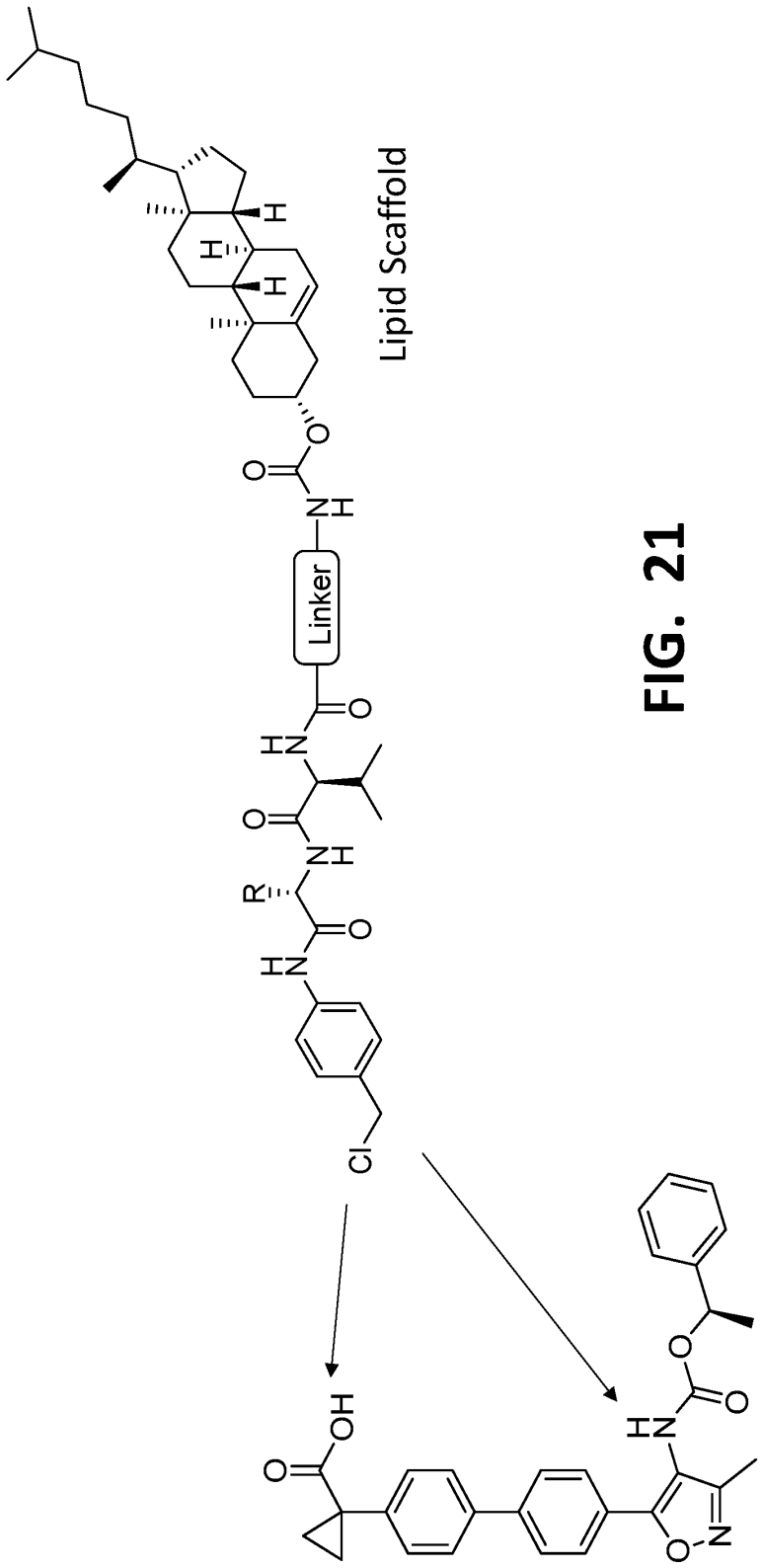


FIG. 21

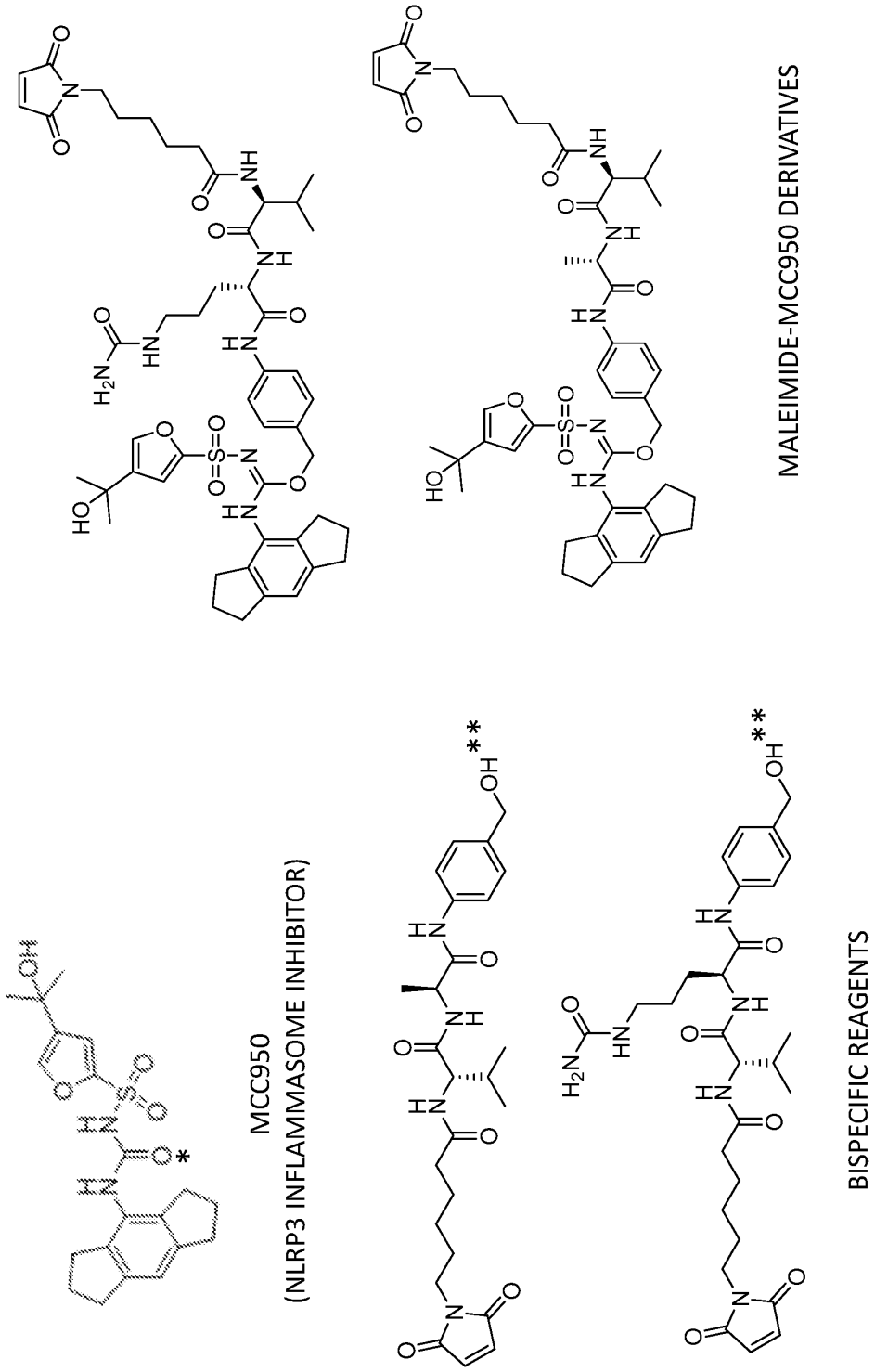

MALEIMIDE-MCC950 DERIVATIVES
MCC950
(NLRP3 INFLAMMASOME INHIBITOR)
BISPECIFIC REAGENTS

FIG. 22