

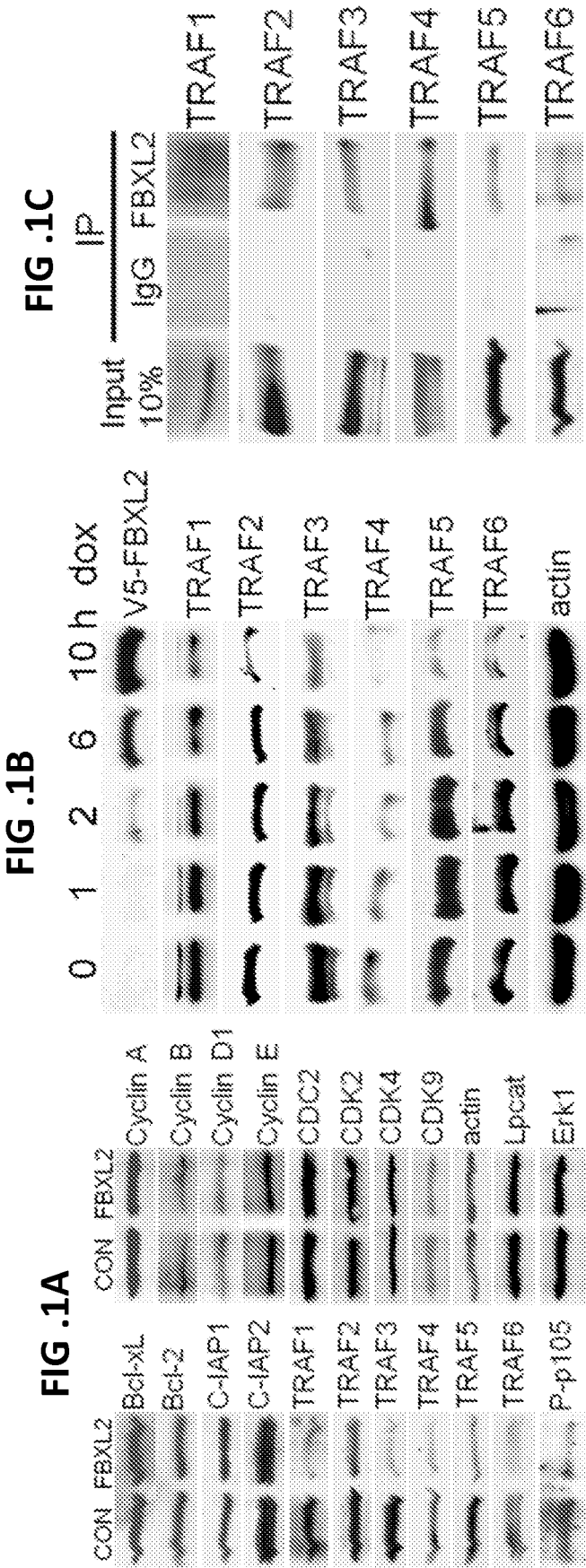


FIG .1E

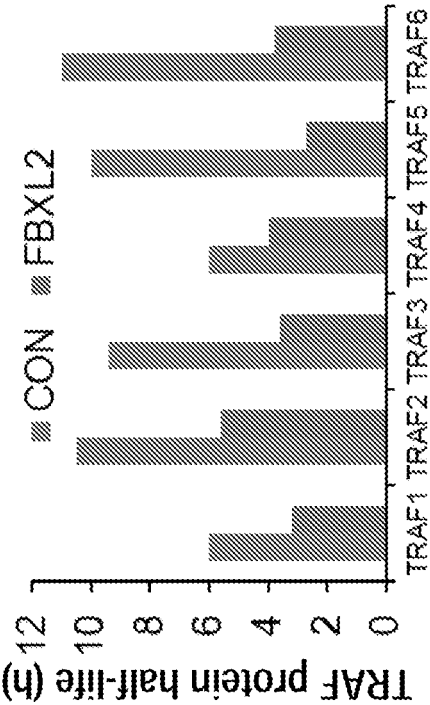


FIG .1D

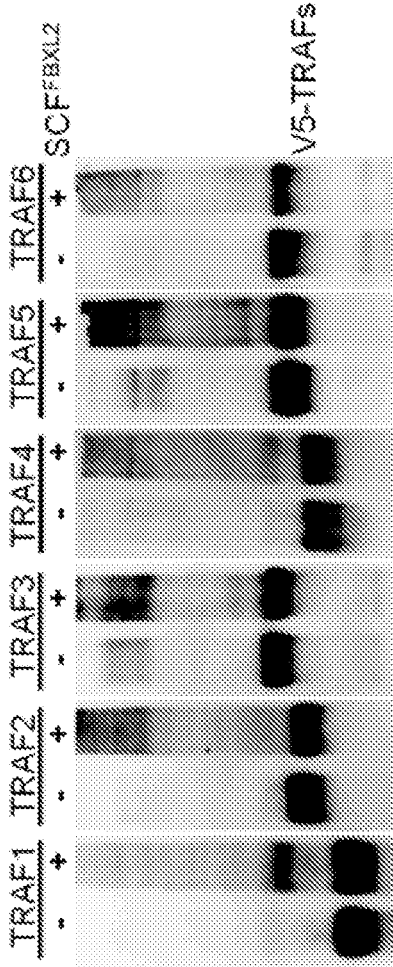


FIG. 2A

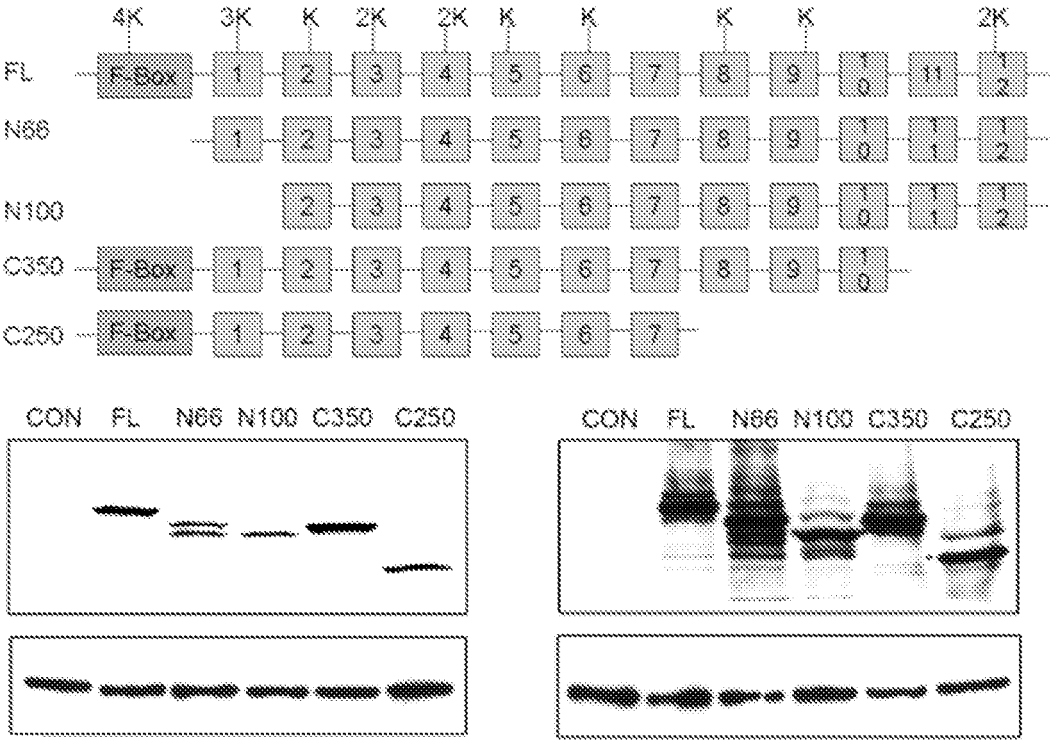


FIG. 2B

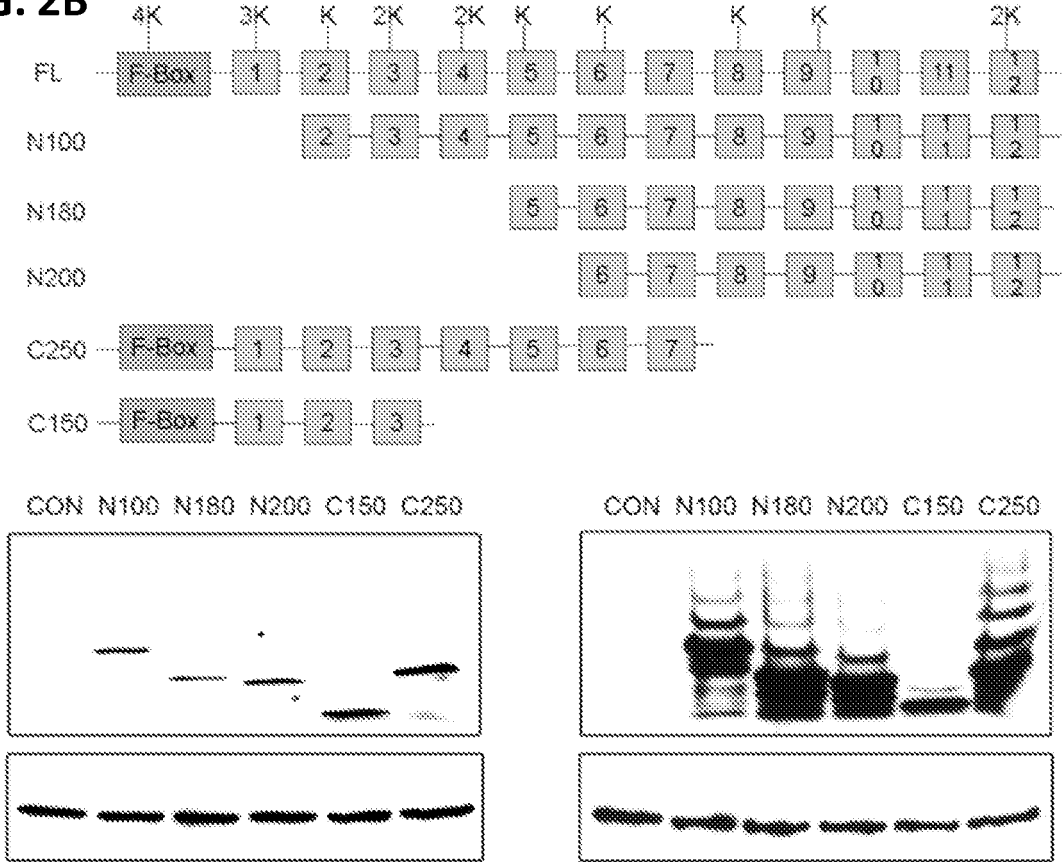


FIG. 2C

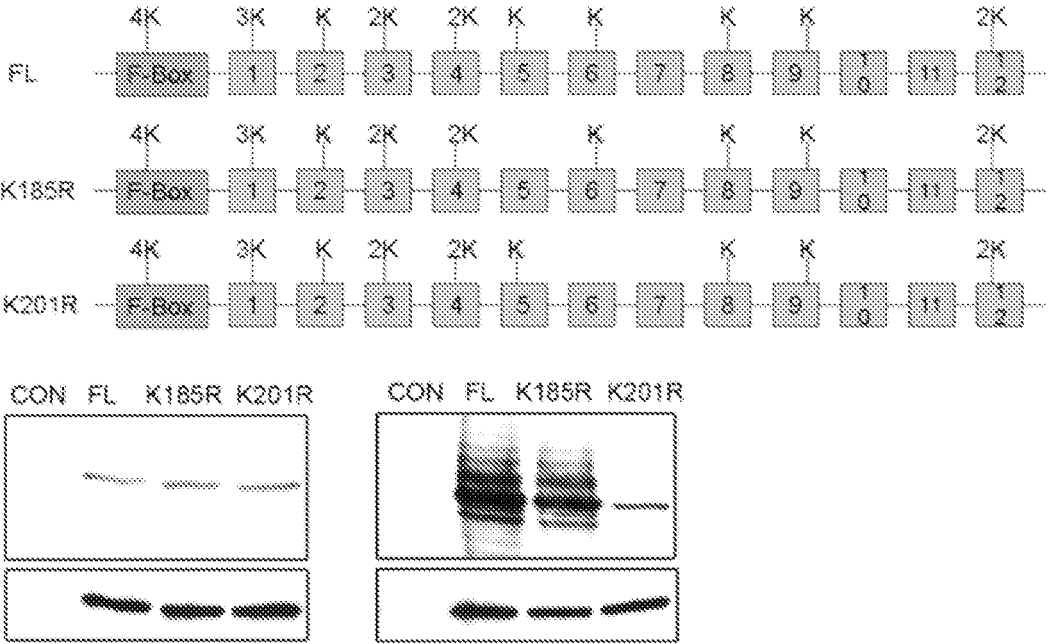


FIG. 2D

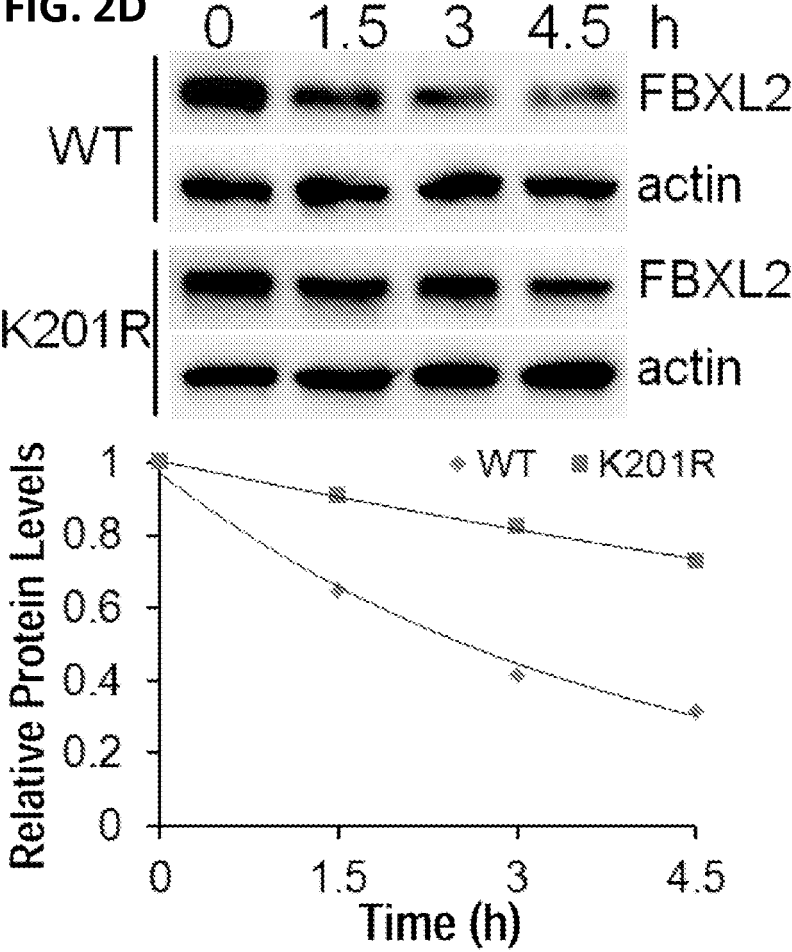


FIG. 3C

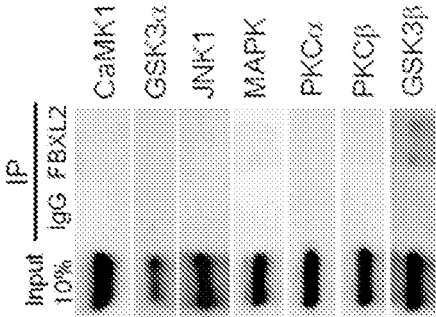


FIG. 3B

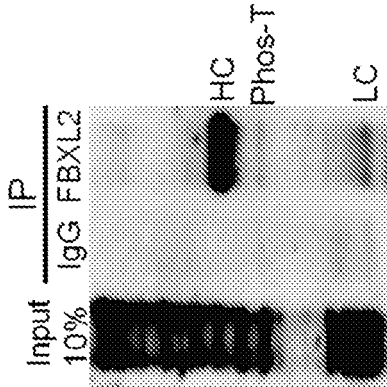


FIG. 3A

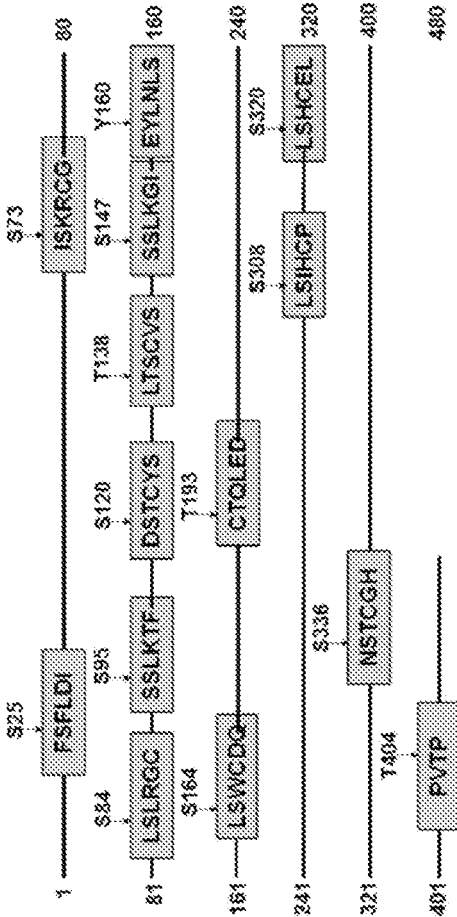


FIG. 3D



FIG. 3E

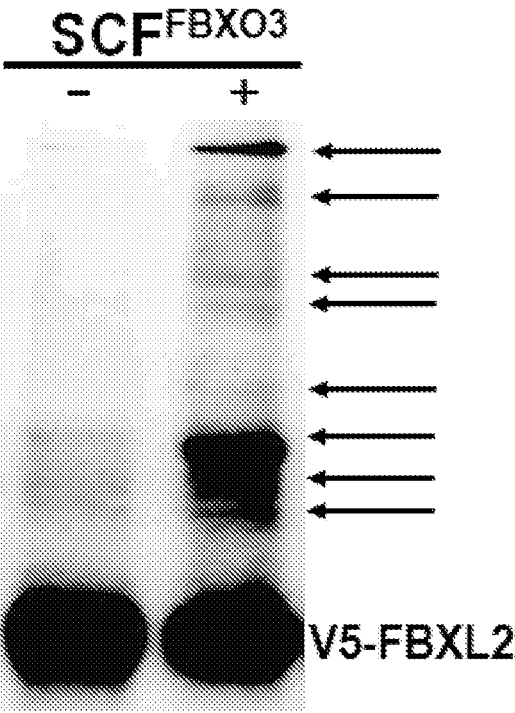


FIG. 3F

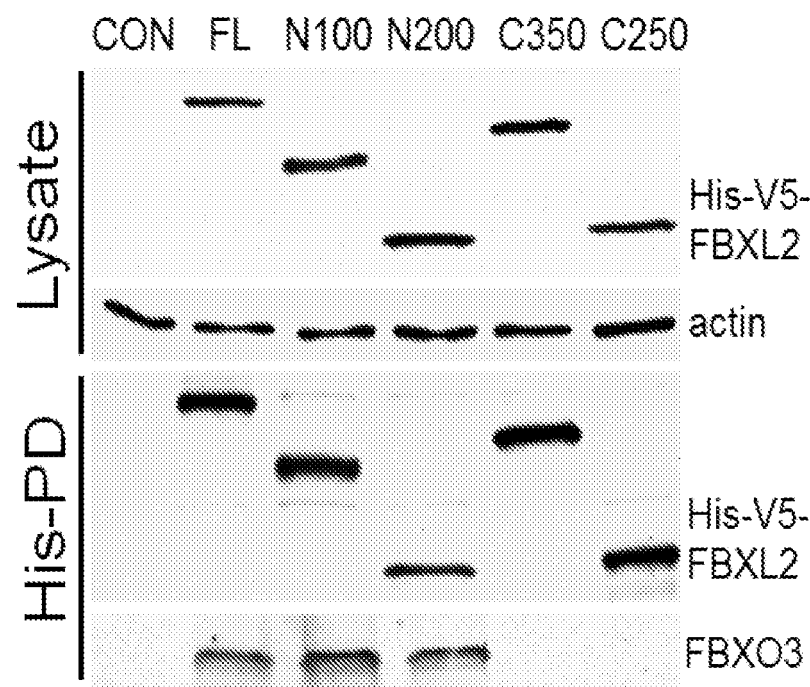


FIG. 3G

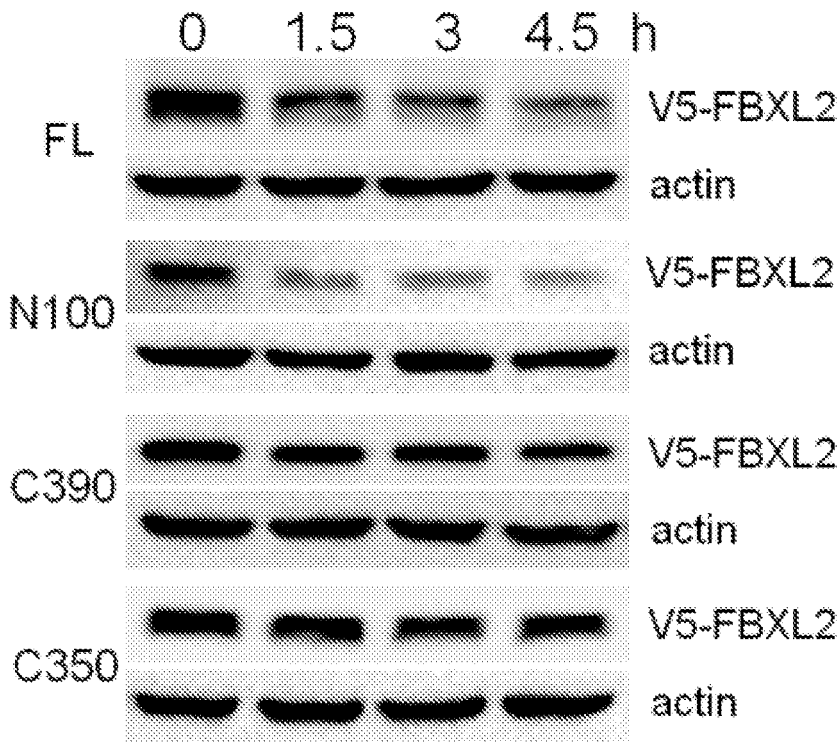


FIG. 3H

GSK3β phosphorylation site

Consensus sequence	PXpTP
FBXL2	402 PVpTP

FIG. 3I

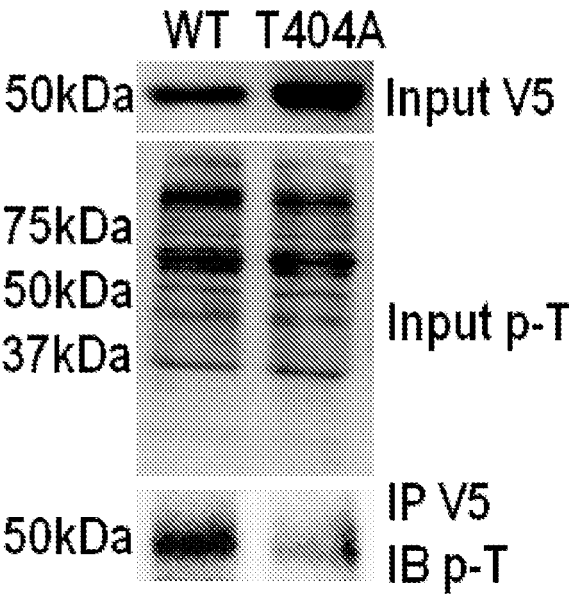


FIG. 3J

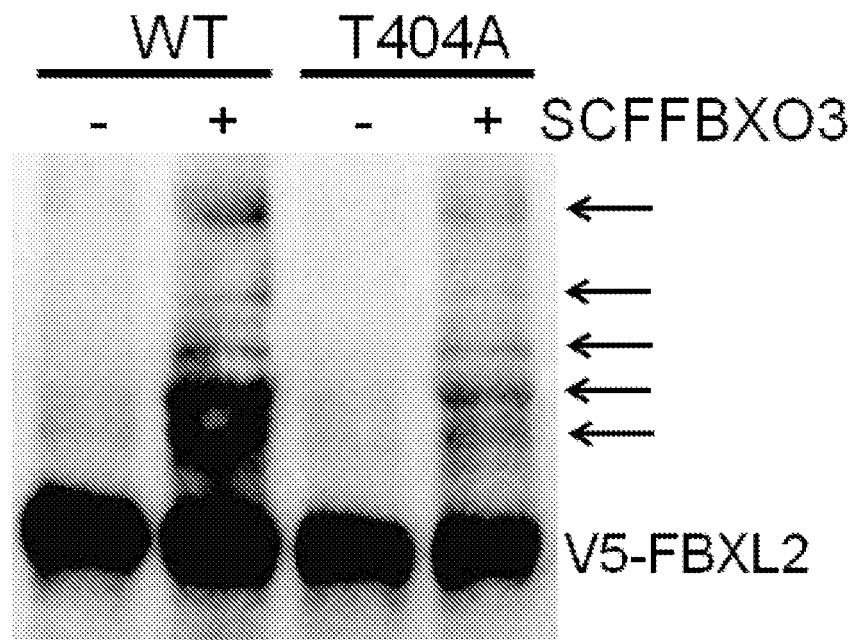


FIG. 3K

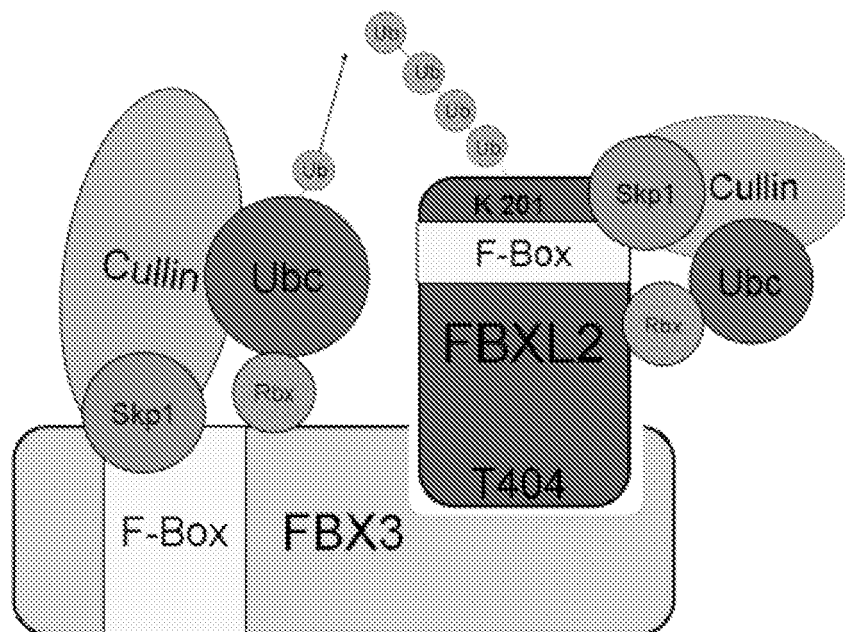


FIG. 4A

SNP ID	Chr	11 pos	Sequence	AA change
rs1403994	3	2777394	TTCATTCTTCTTCC	V223I
Sample Ascertainment				
SNP	Individual Group	Chrom. Sample Size	C	T
rs234492449	European	48	0.875	0.13
	African	46	1	1
	American	48	1	1
	Asian	220	0.945	0.05
rs26683029	European	90	1	1
	Asian	88	1	1
	African	120	1	1
	Italian	174	0.895	0.12
rs69314891	European	120	0.95	0.05
	Asian	90	1	1
	Asian	90	1	1
	African	120	1	1

FIG. 4B

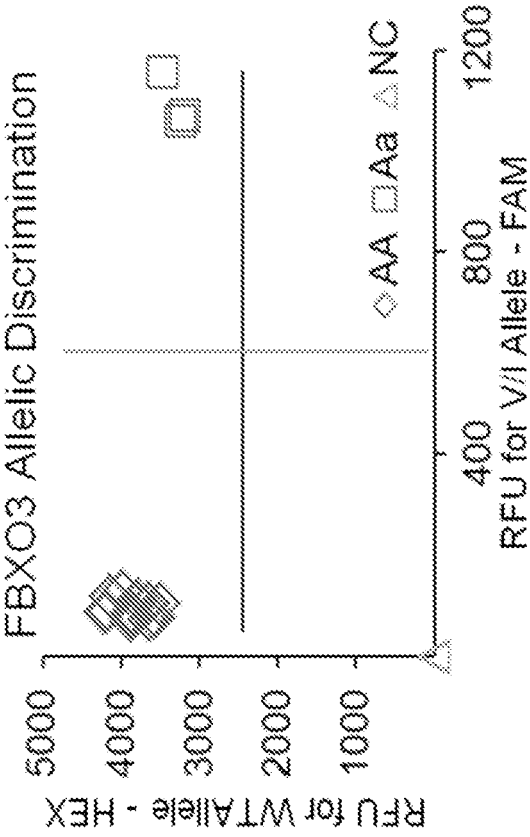


FIG. 4C

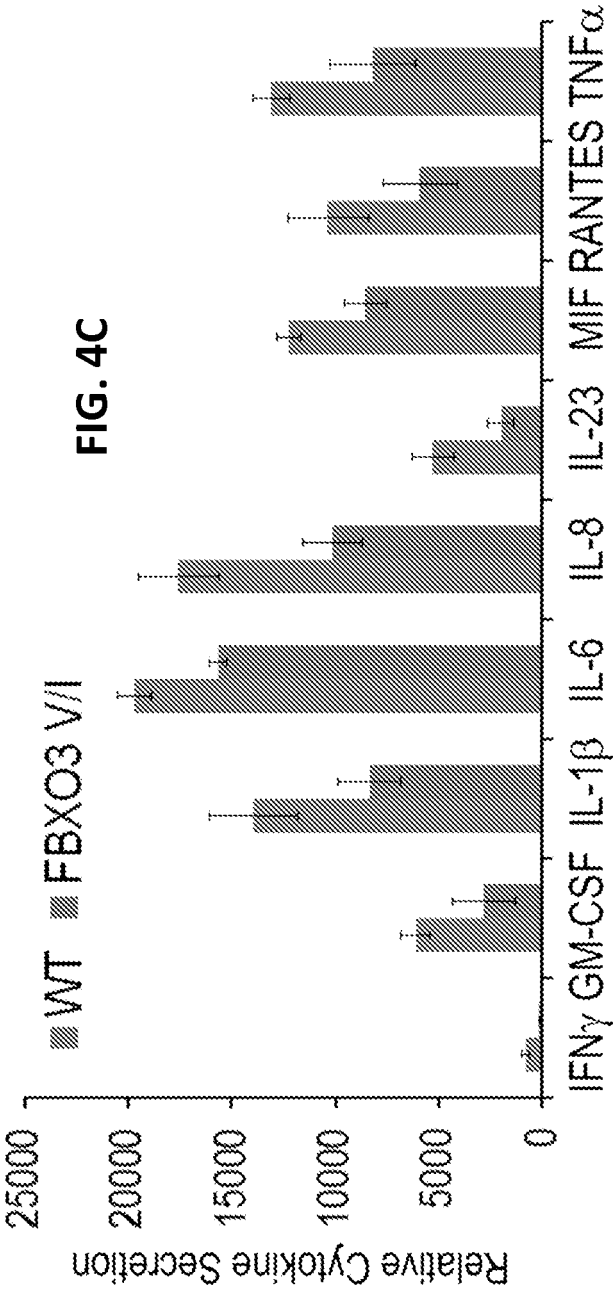


FIG. 4D

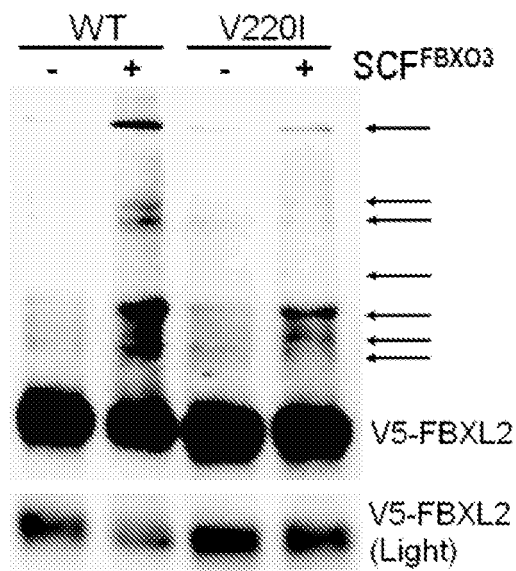


FIG. 4E

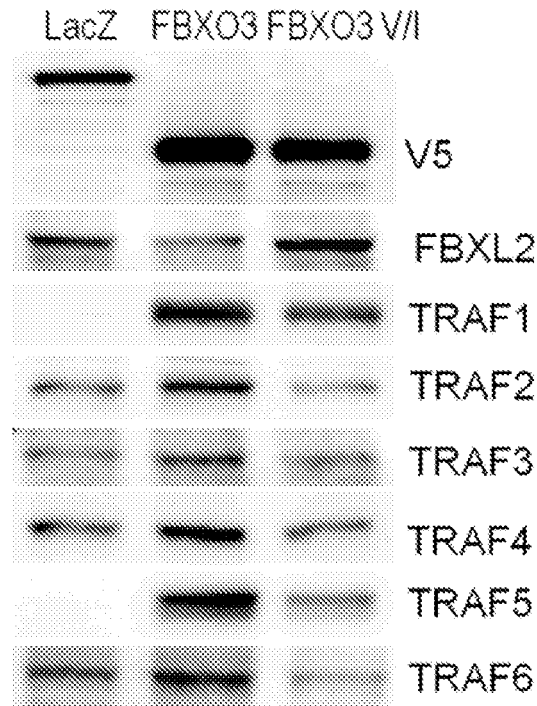


FIG. 4F

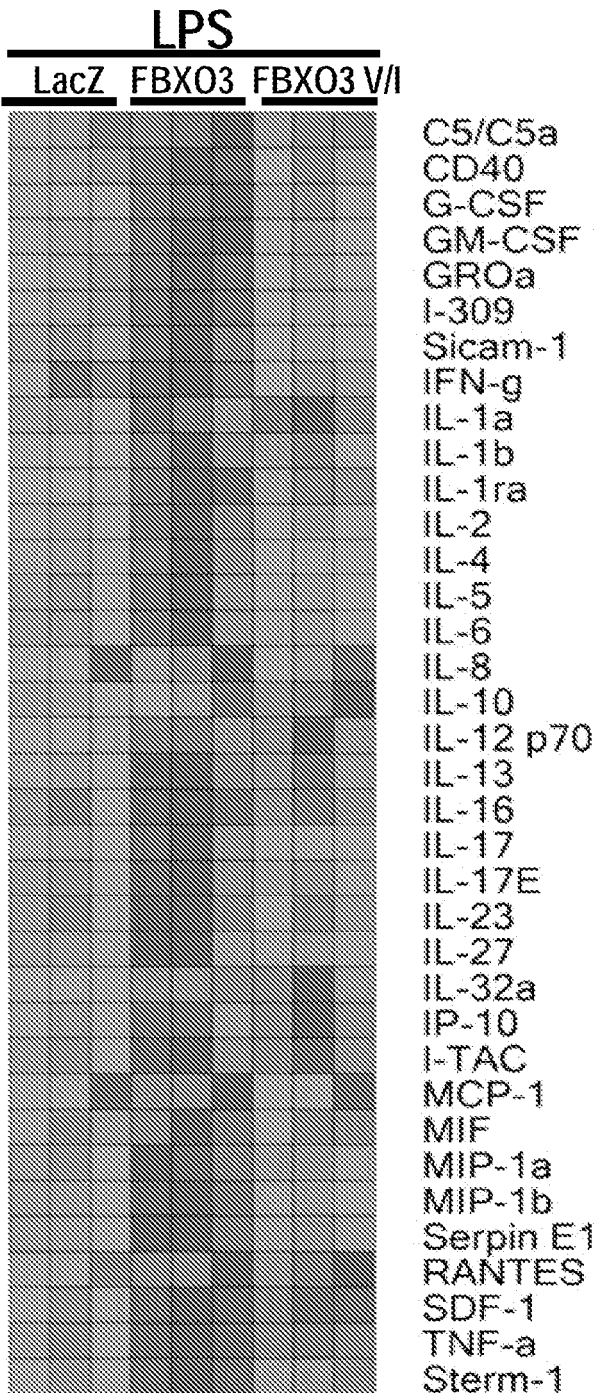


FIG. 5A

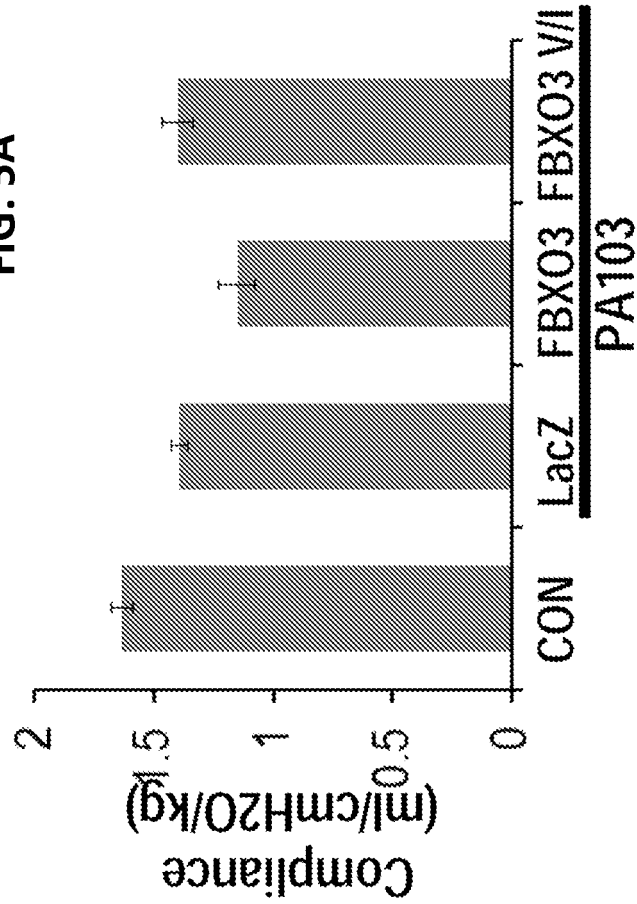
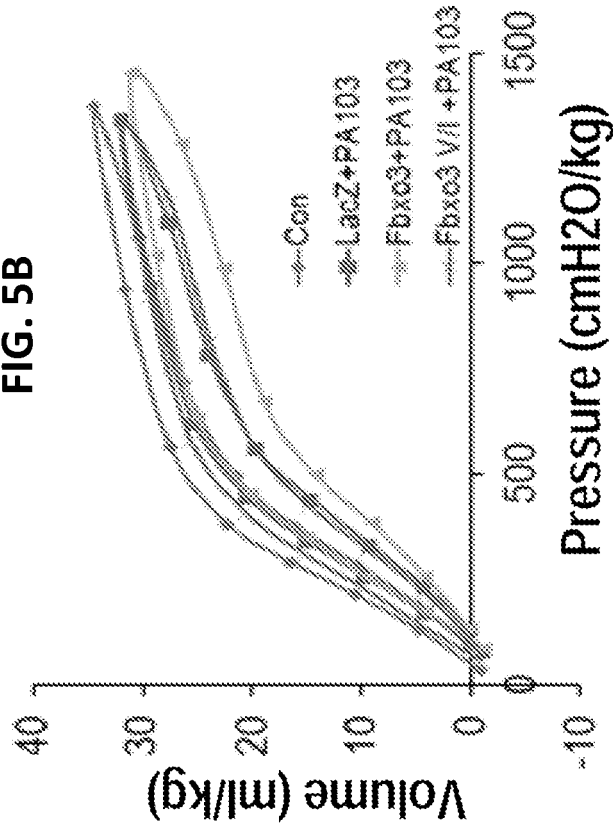
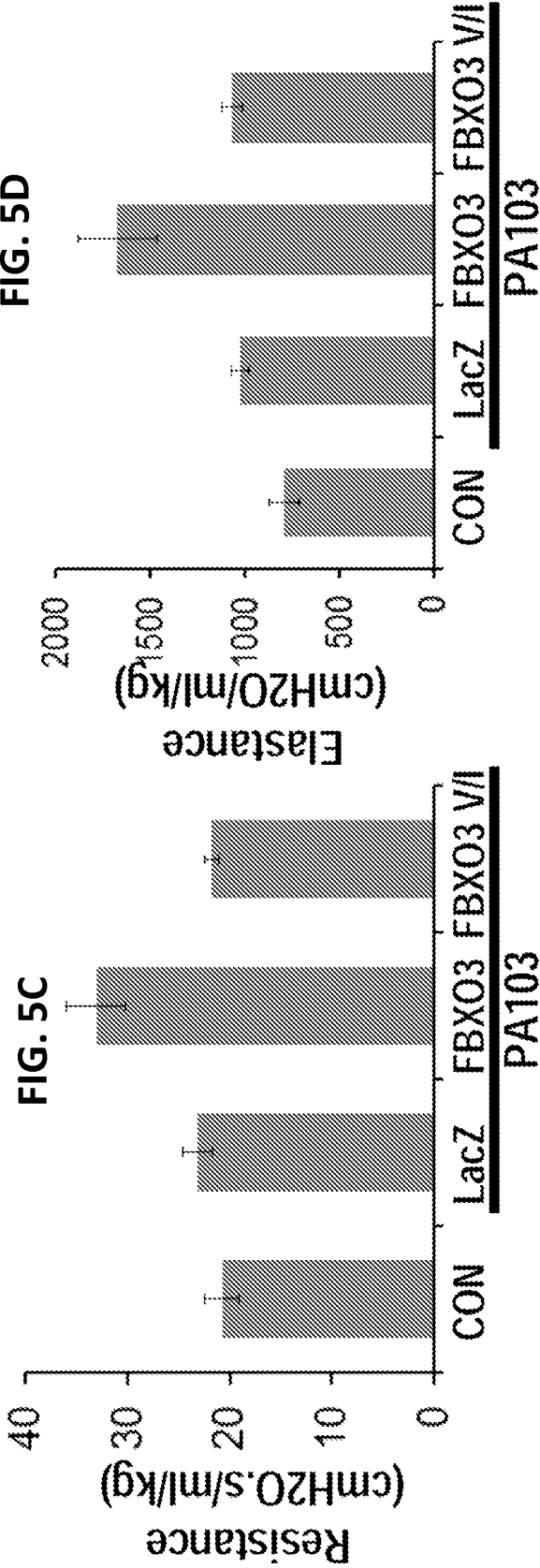


FIG. 5B





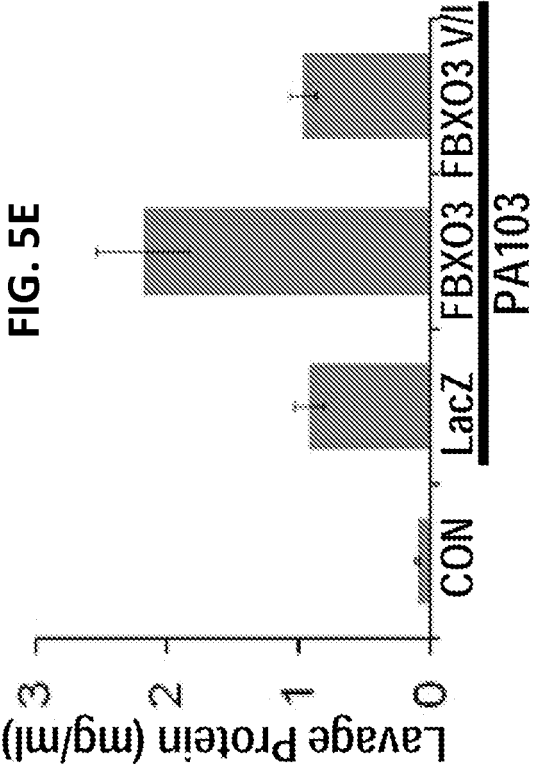
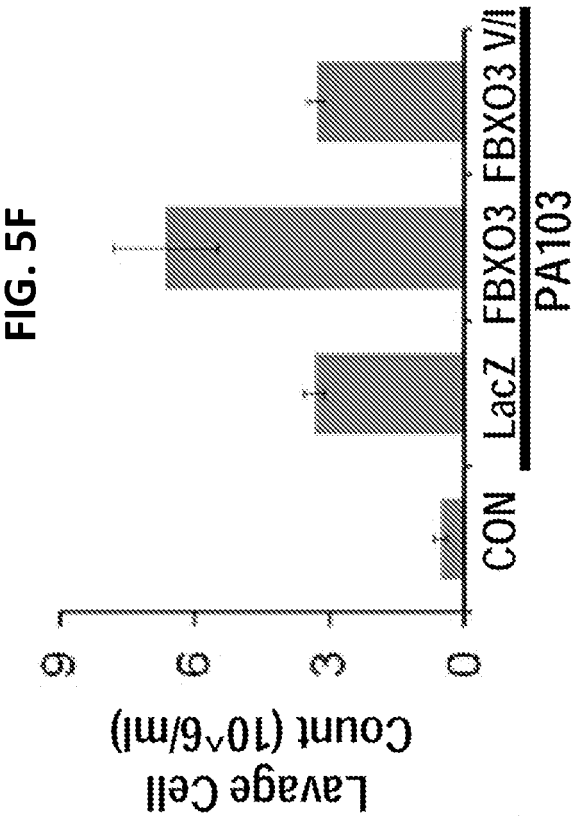
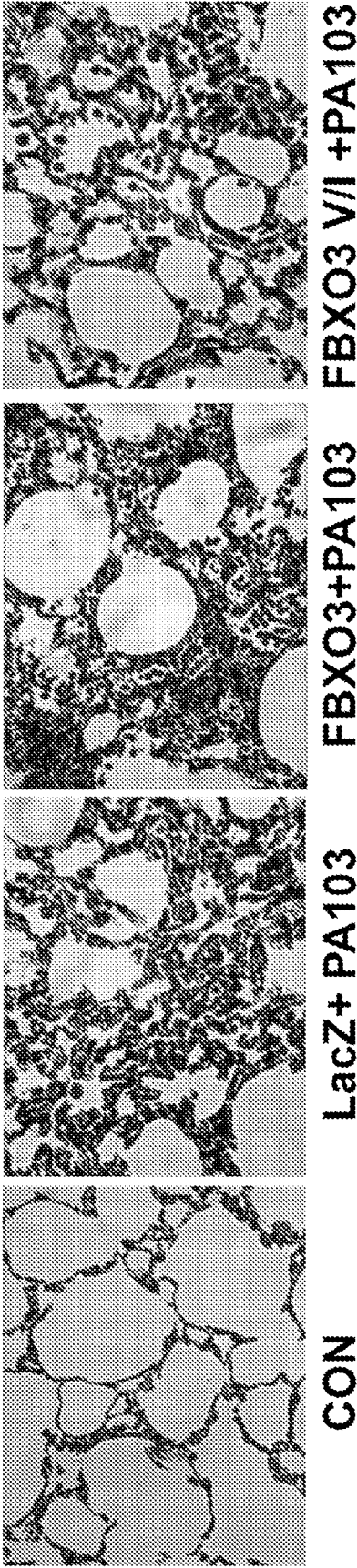


FIG. 5G



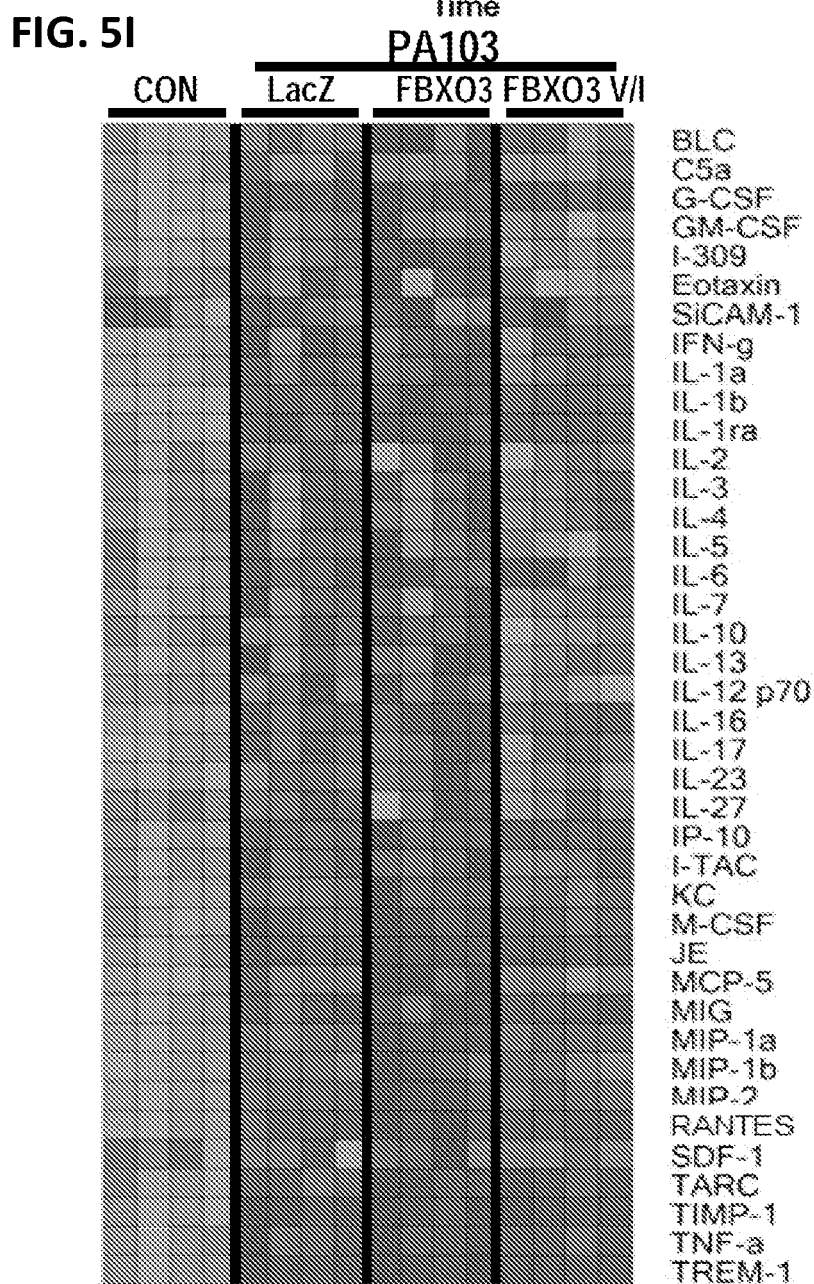
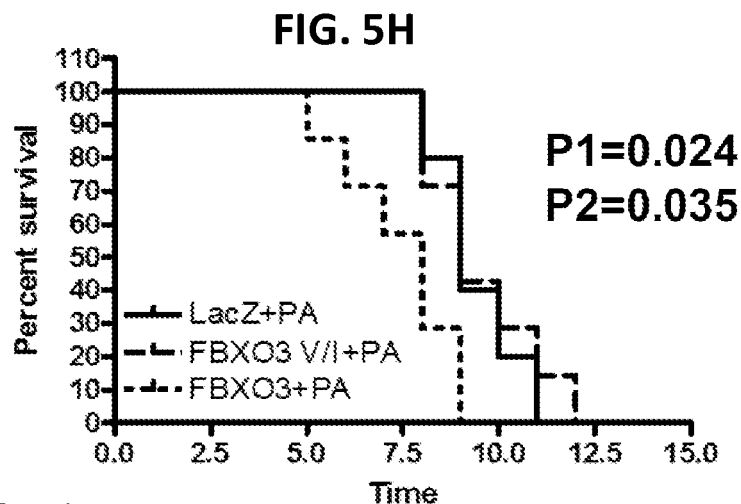


FIG. 6B

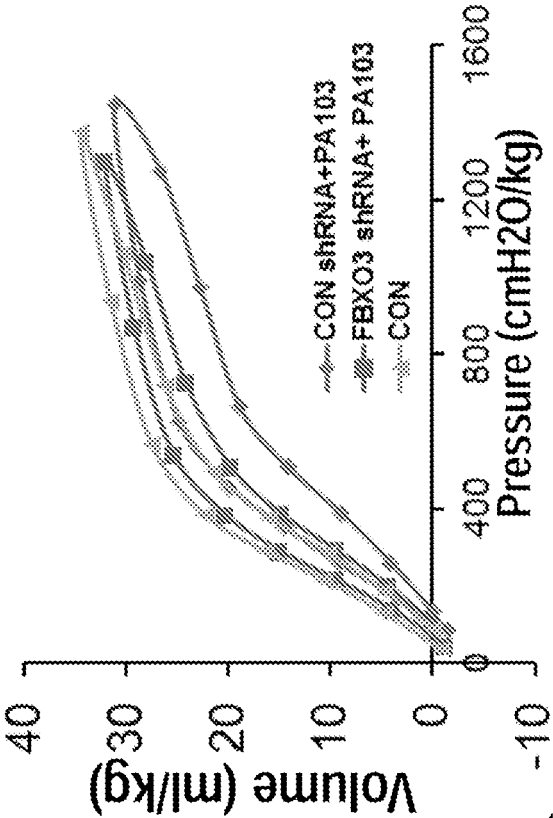
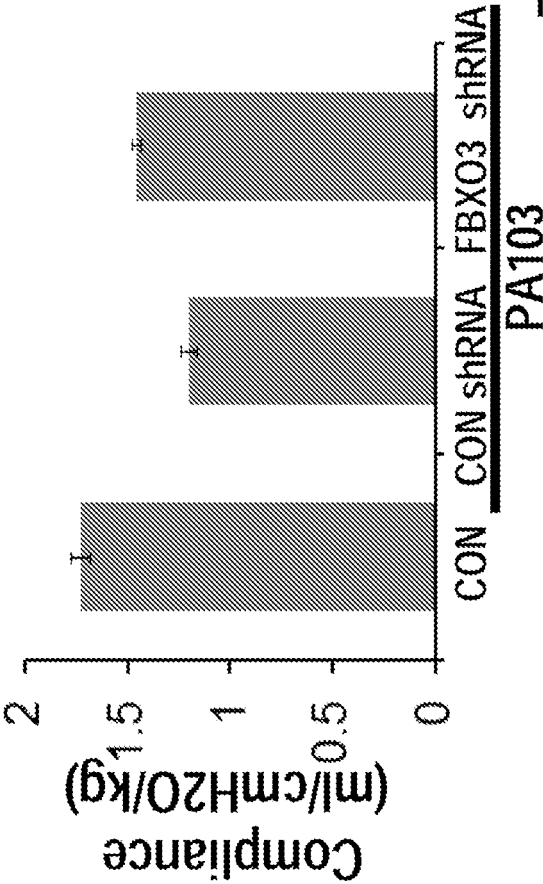
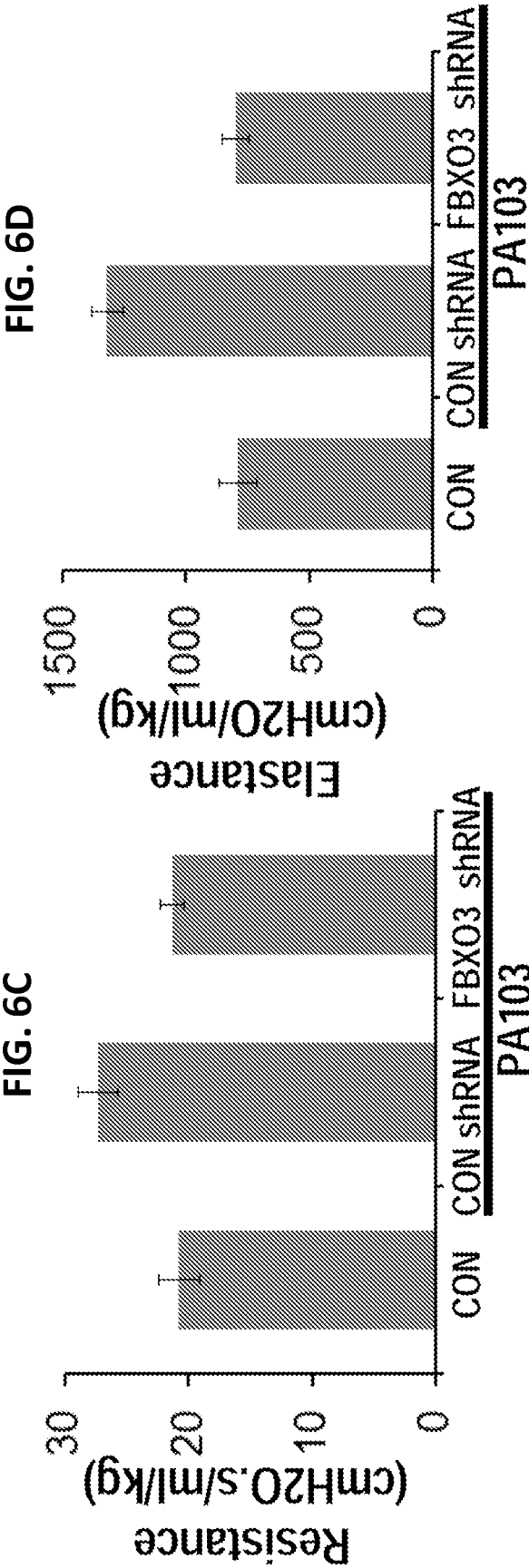


FIG. 6A





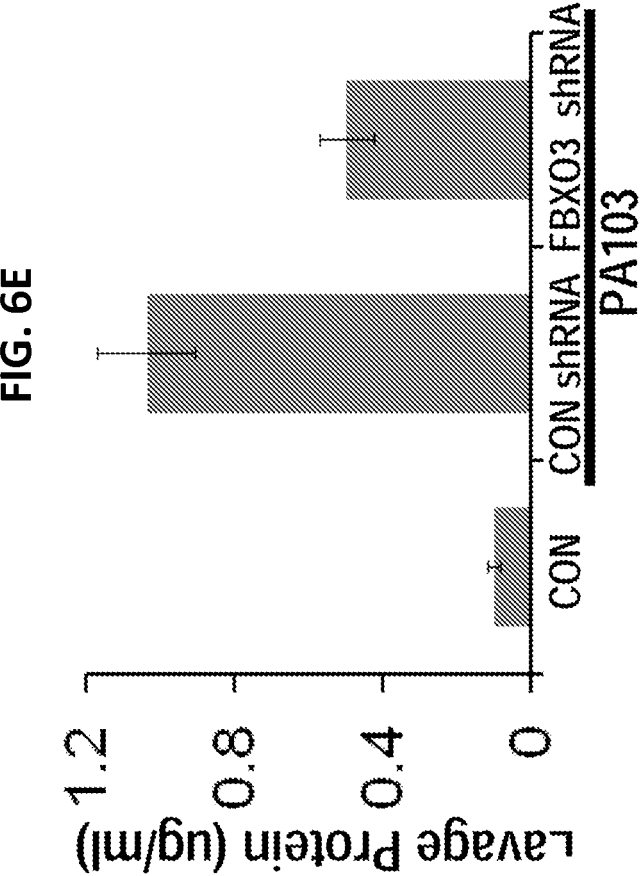
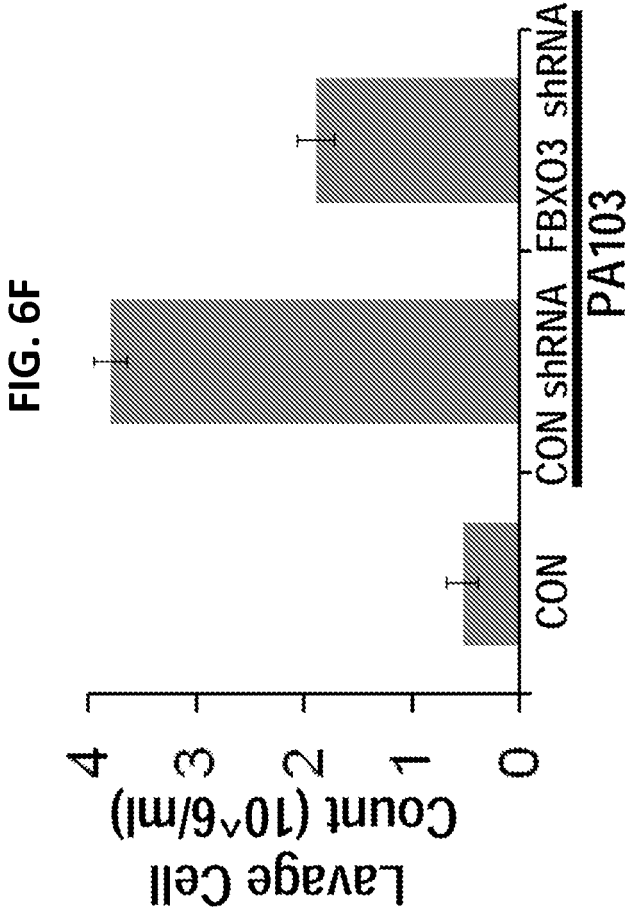


FIG. 6G

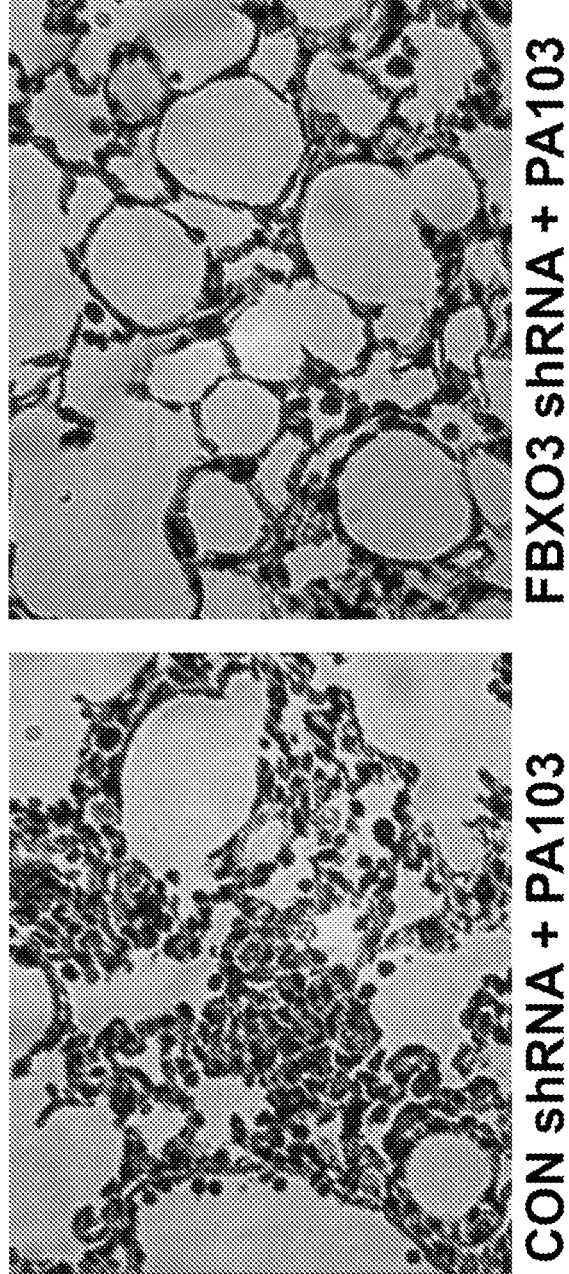


FIG. 6H

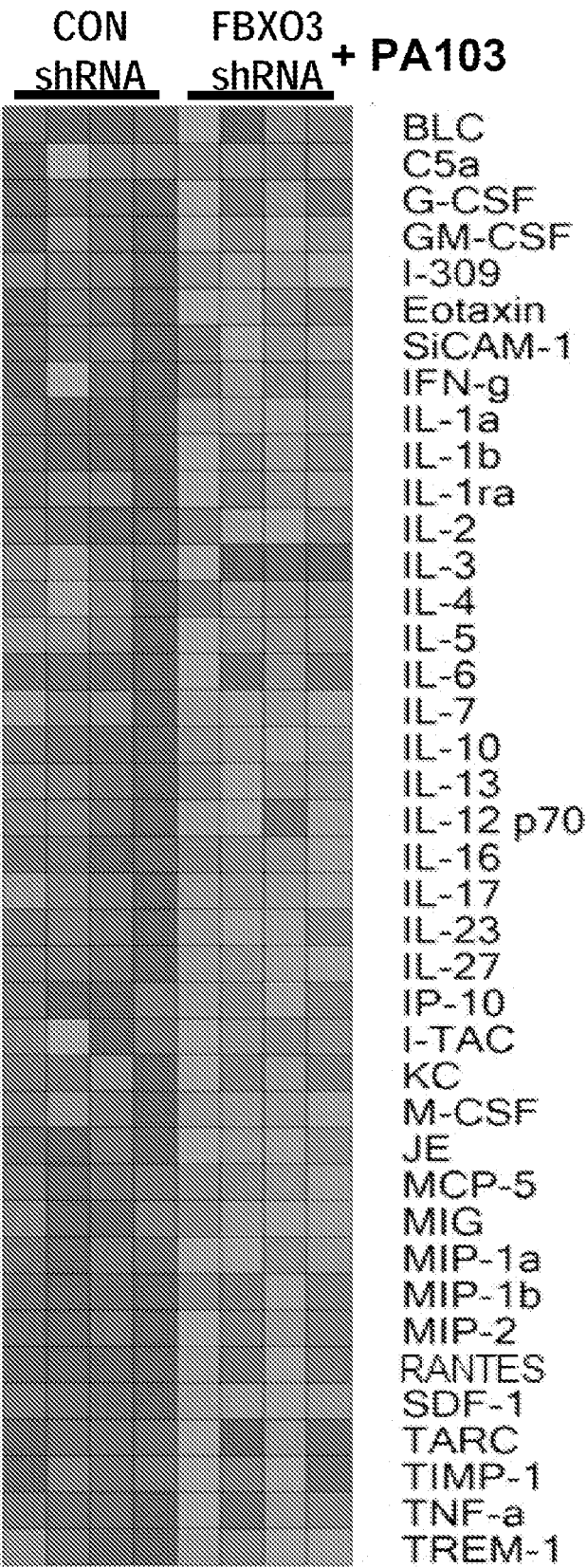


FIG. 6I

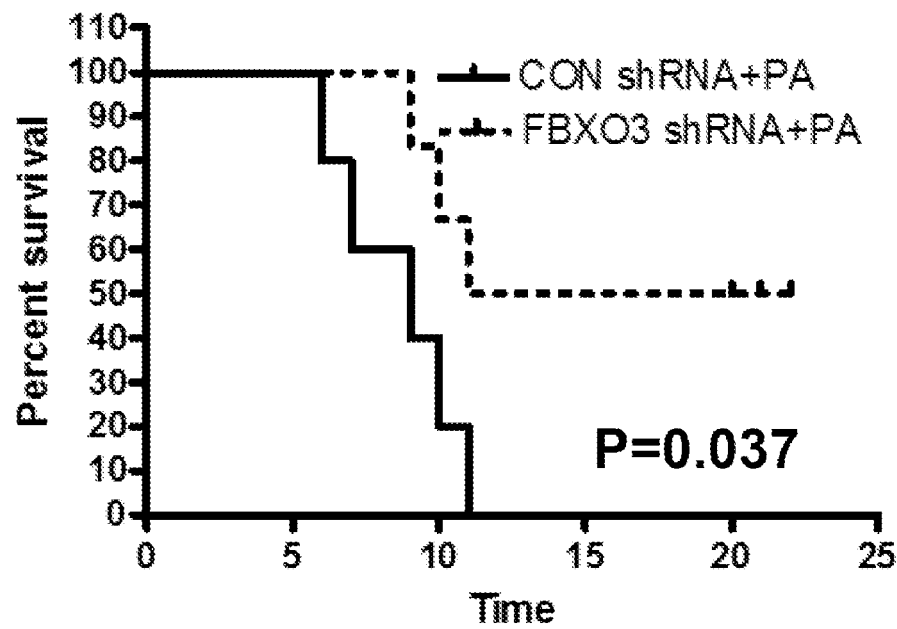


FIG. 7A

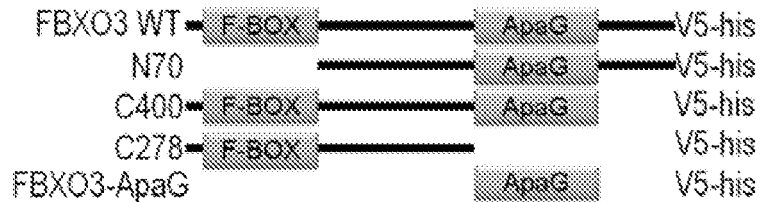


FIG. 7B

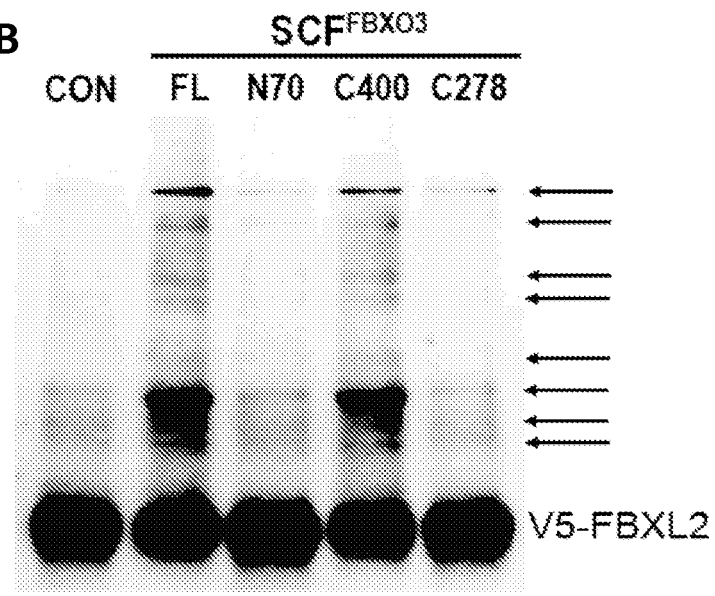


FIG. 7C

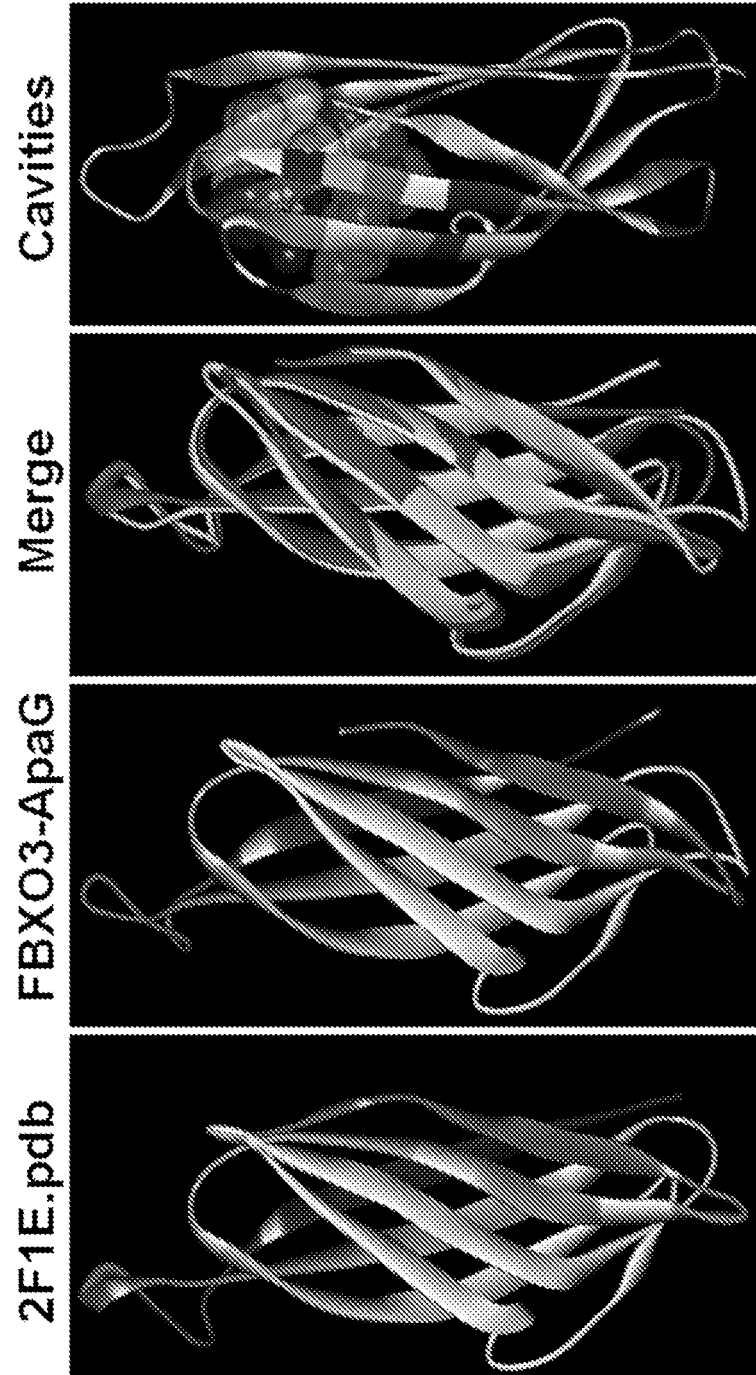




FIG. 7F

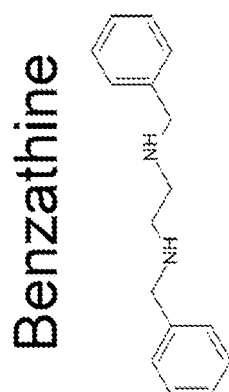


FIG. 7E

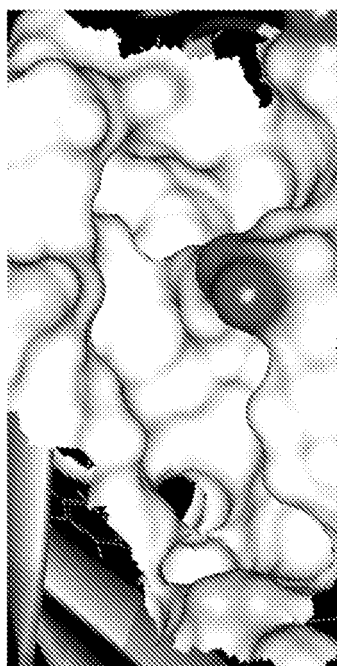
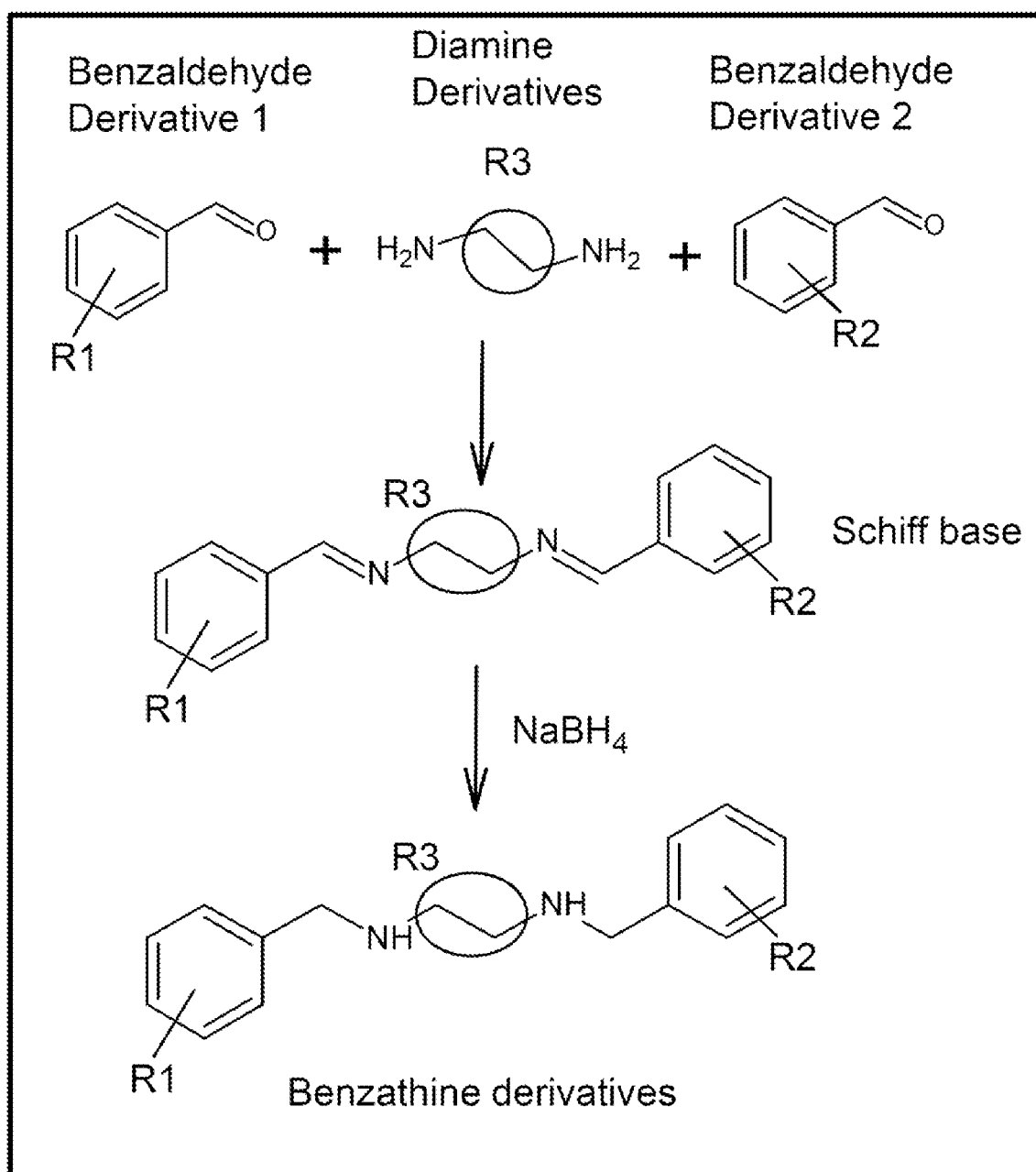


FIG. 7D

FIG. 8A



BC-1215

FIG. 8B

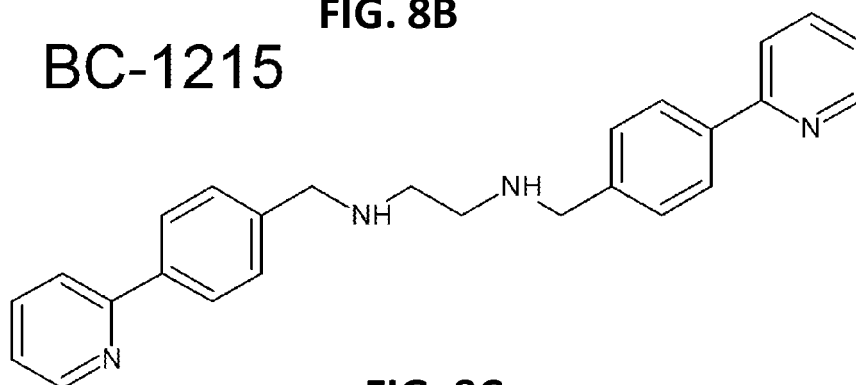


FIG. 8C

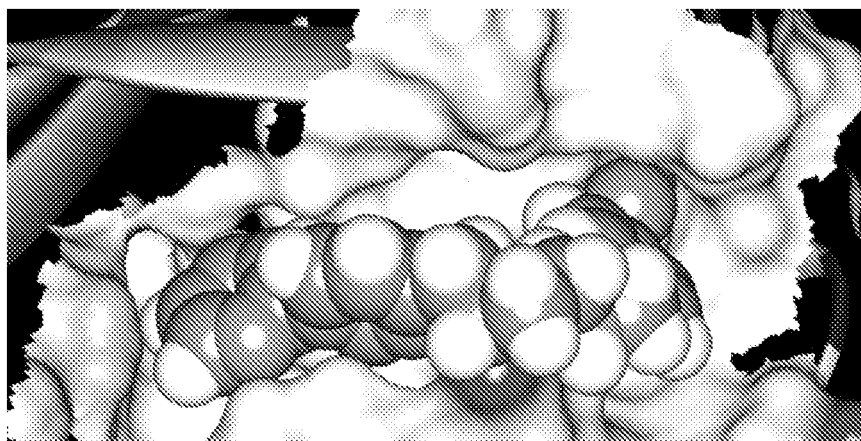
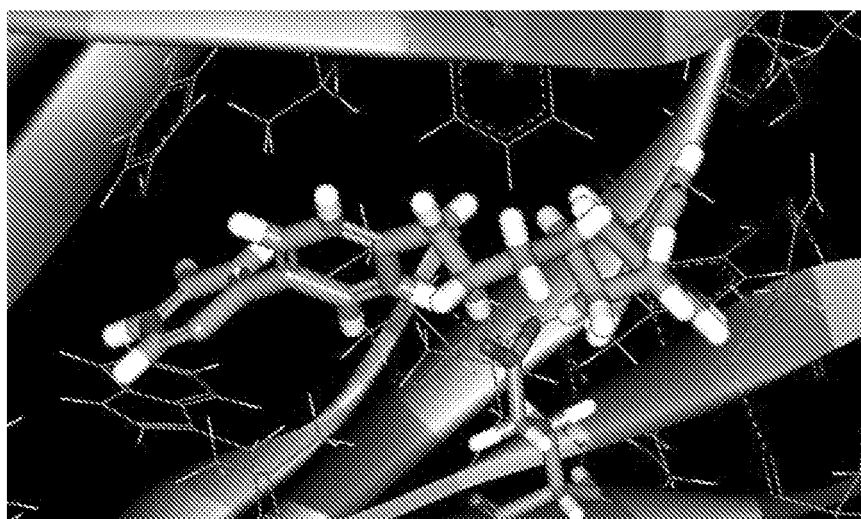


FIG. 8D



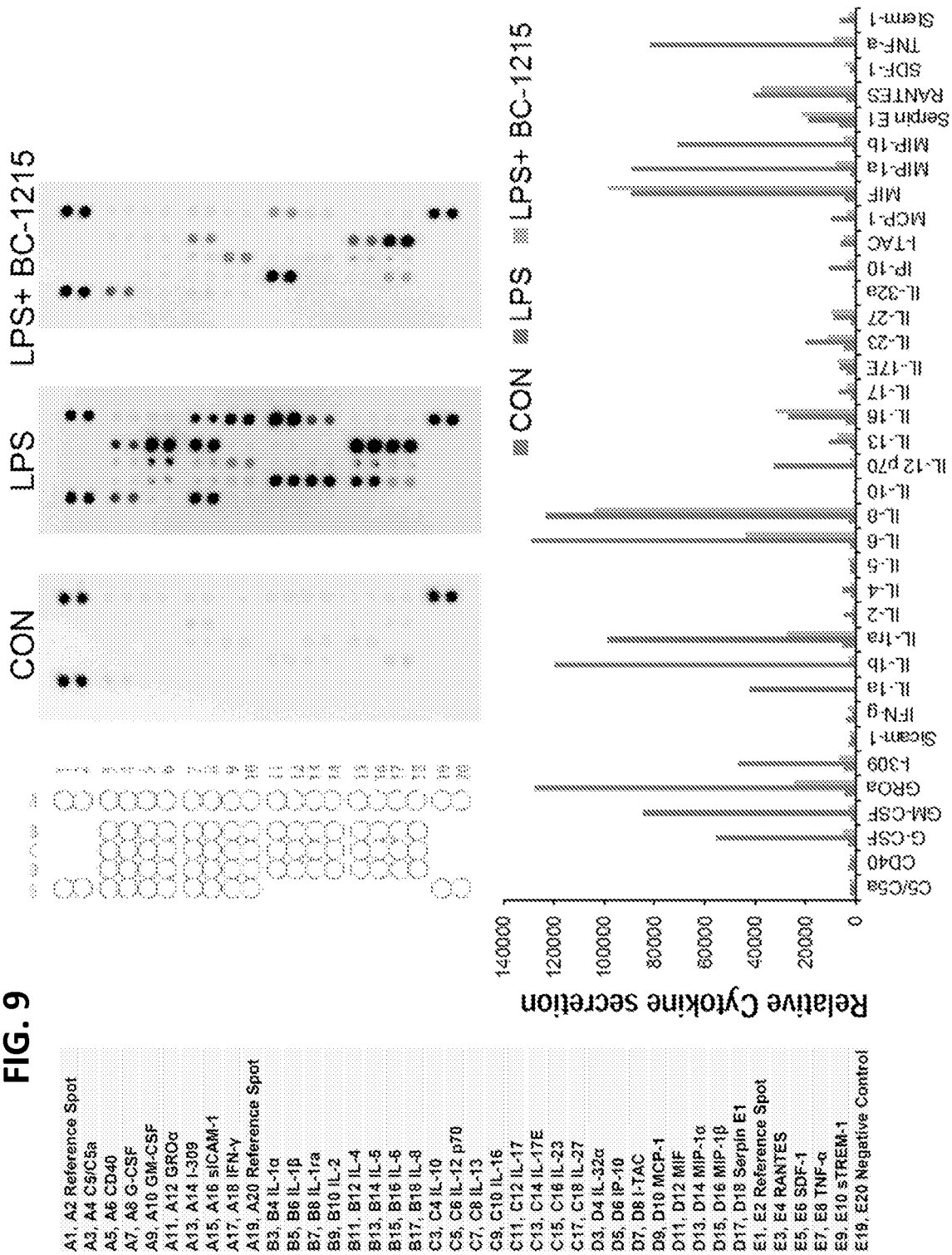


FIG. 10A

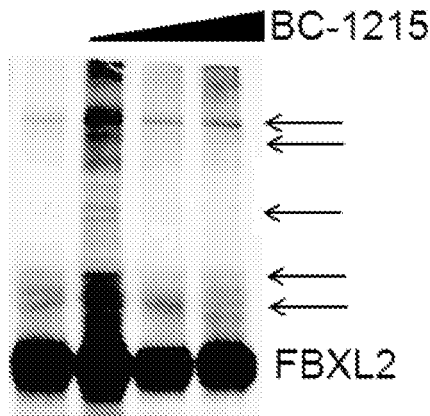
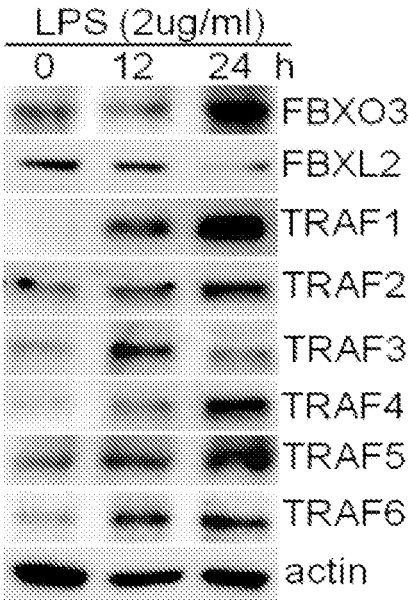


FIG. 10B

FIG. 10C

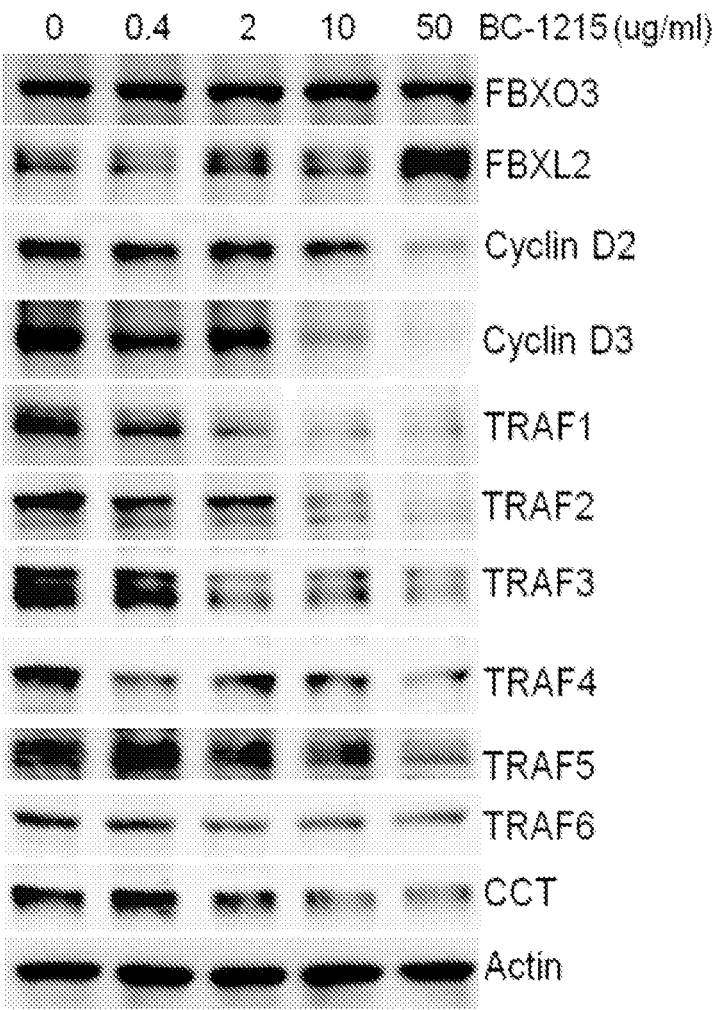


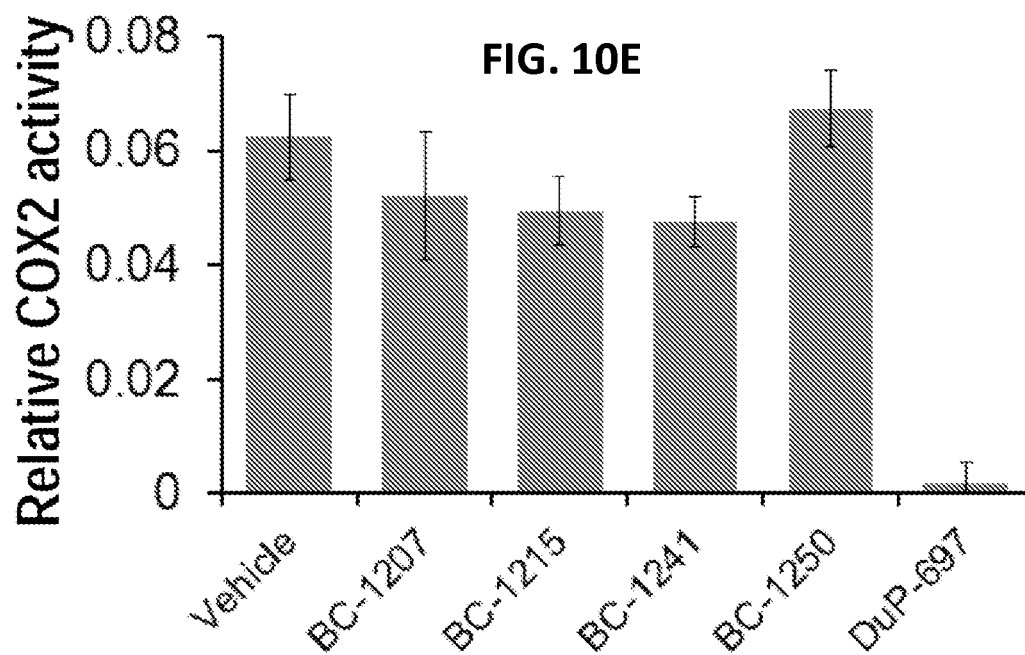
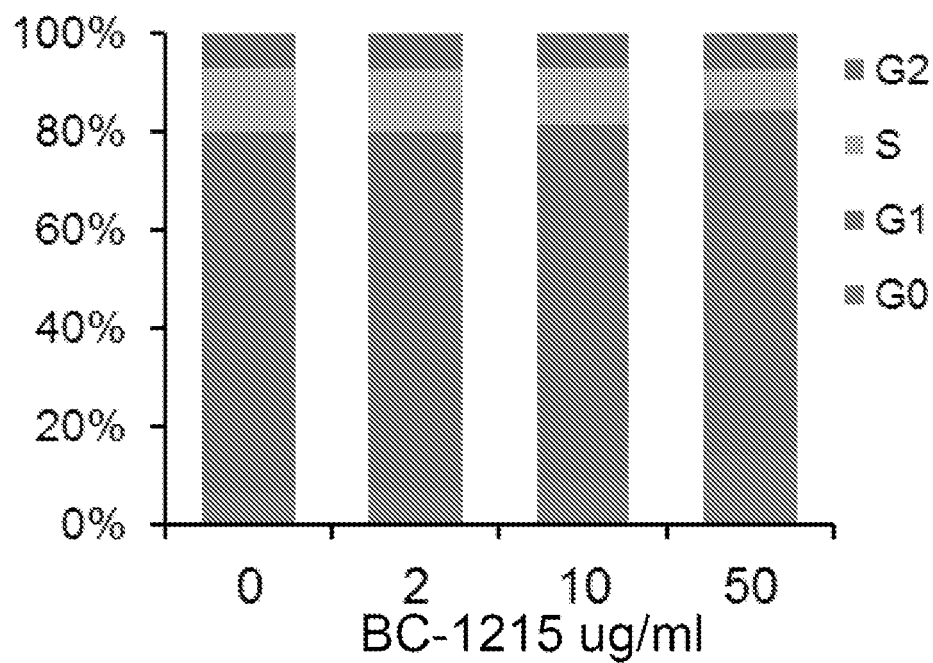
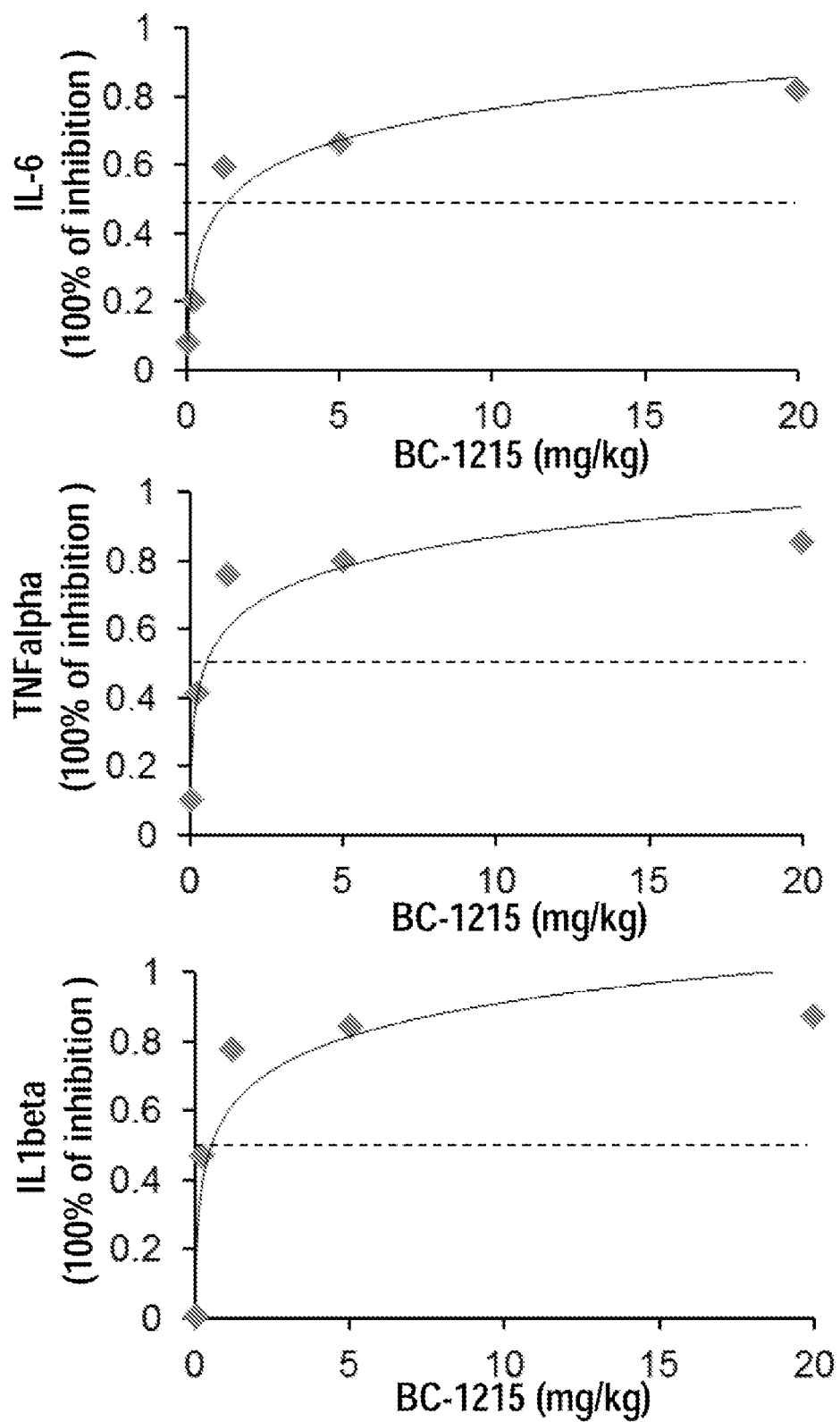
FIG. 10D

FIG. 11
In vivo LPS induced sepsis model



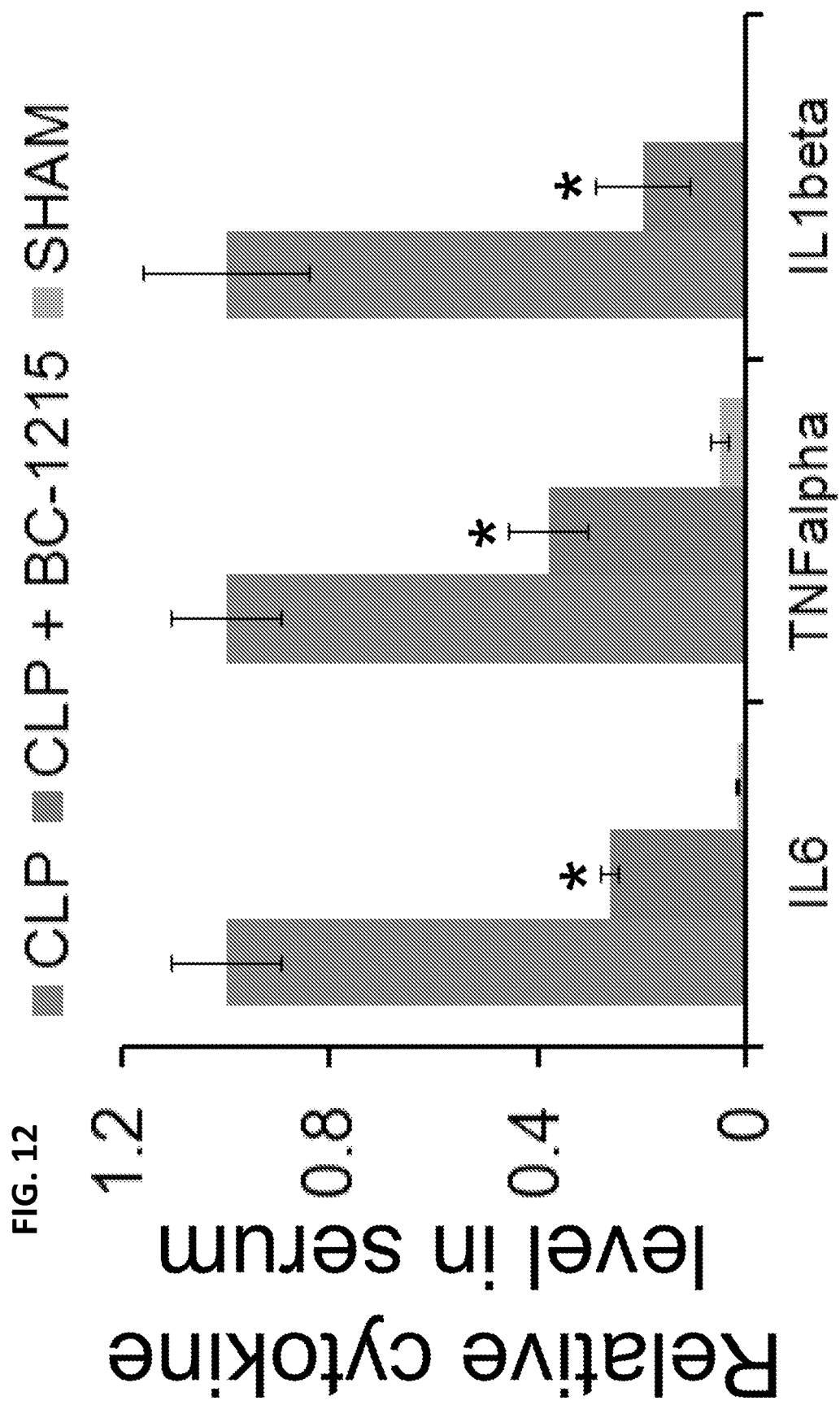


FIG. 13A

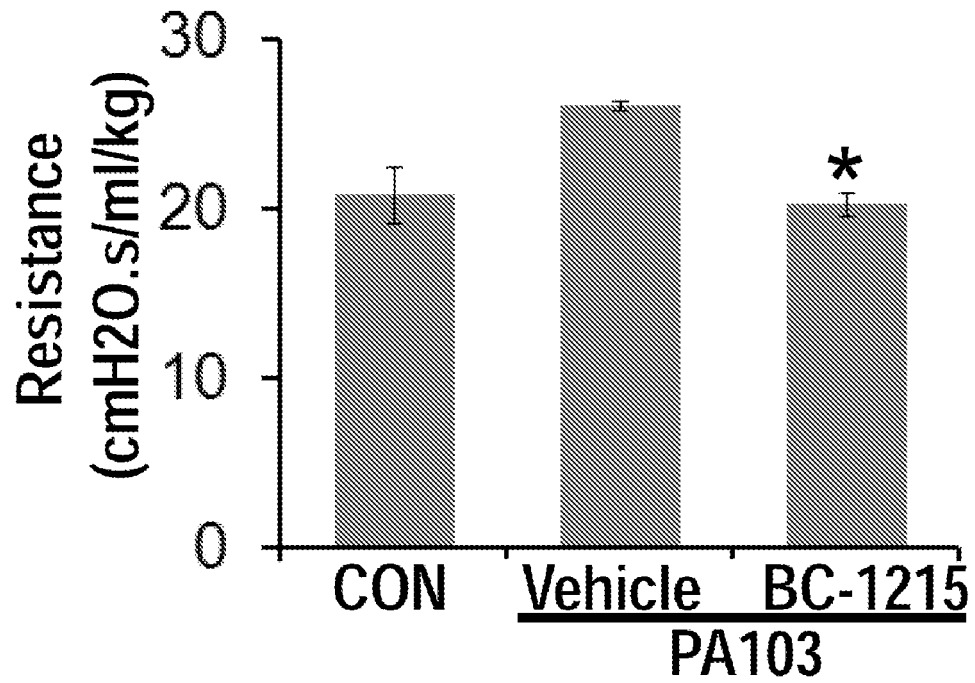
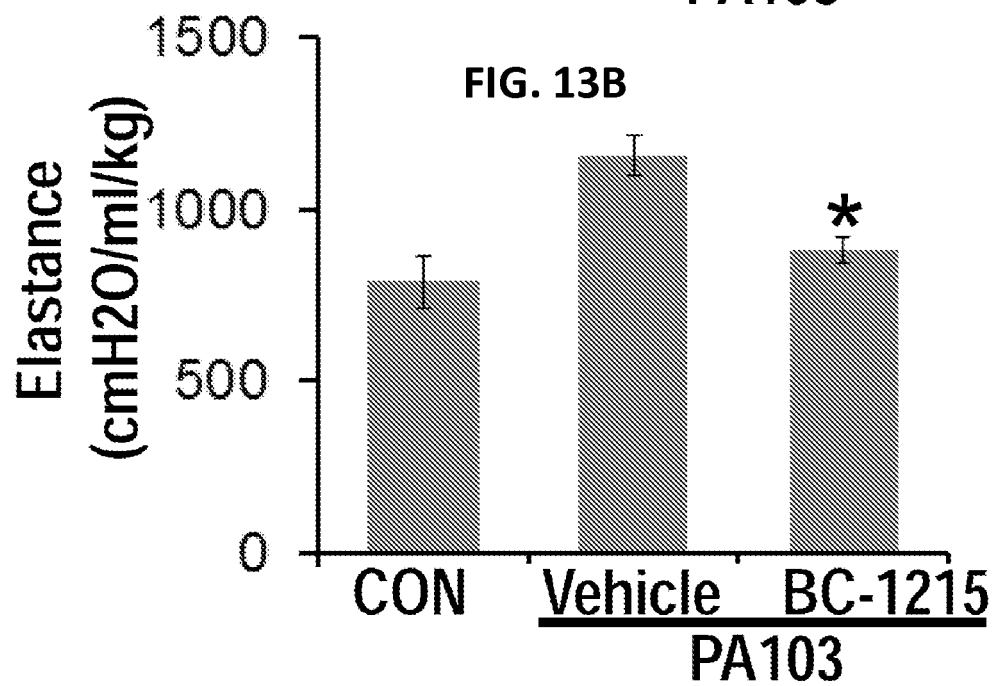
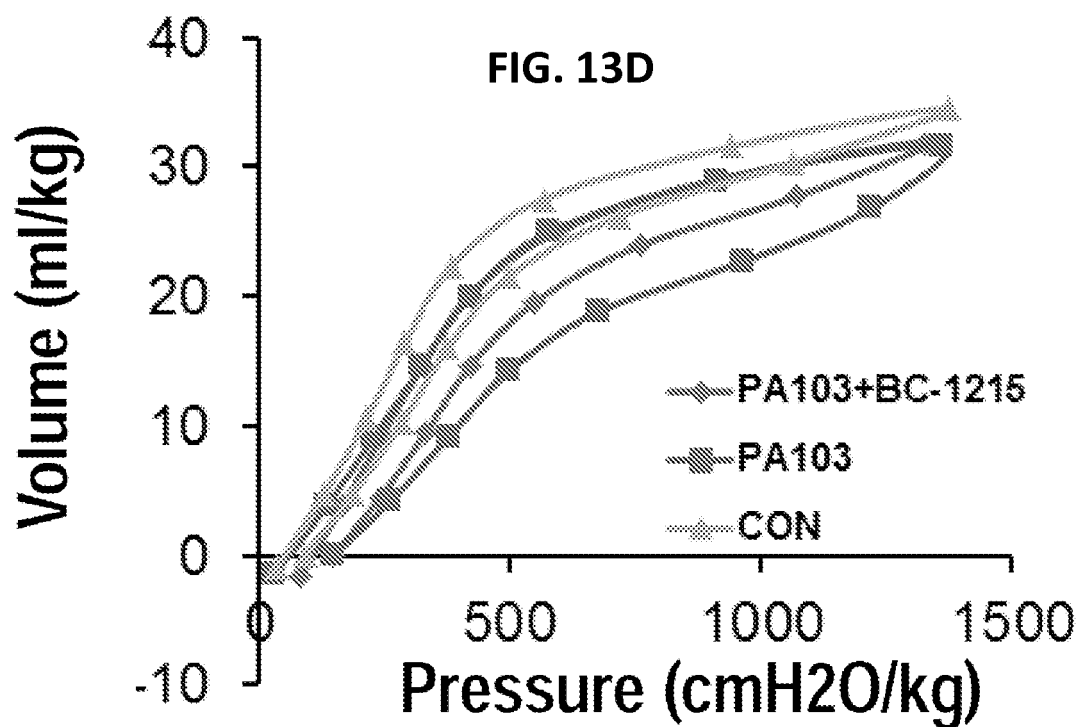
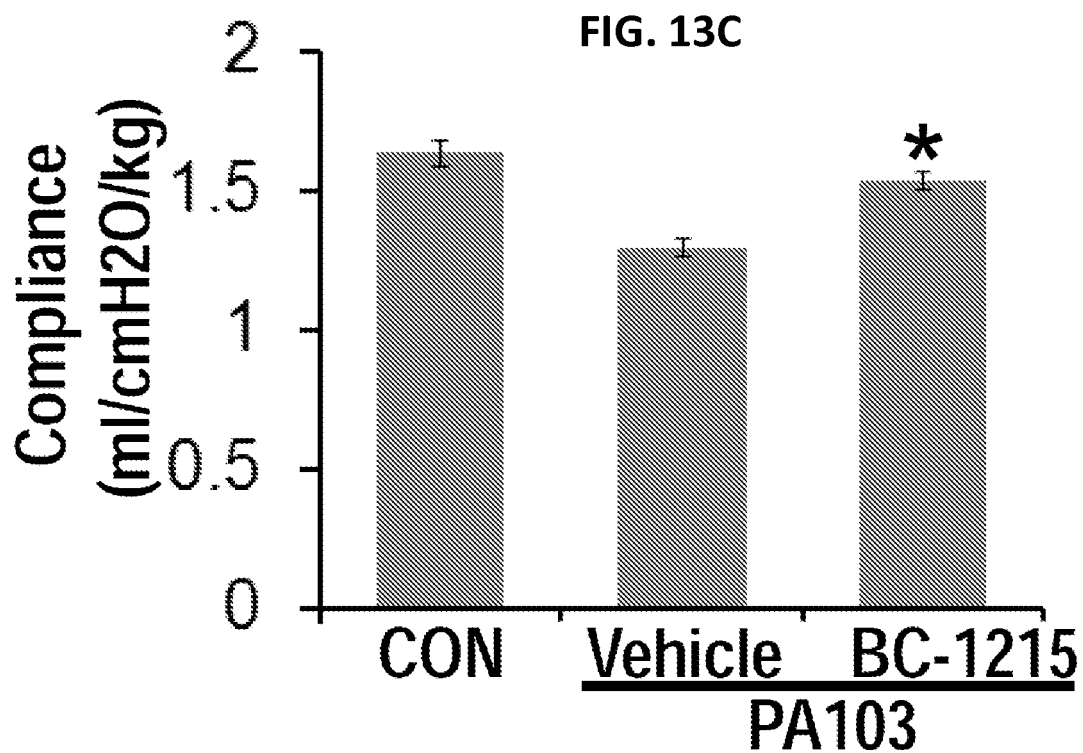


FIG. 13B





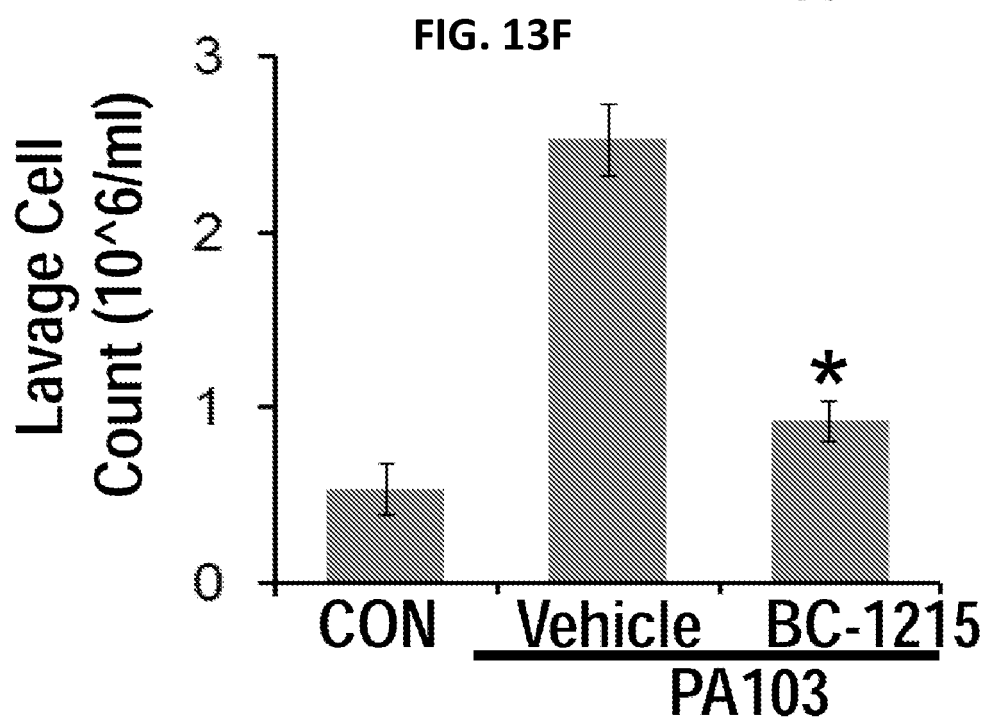
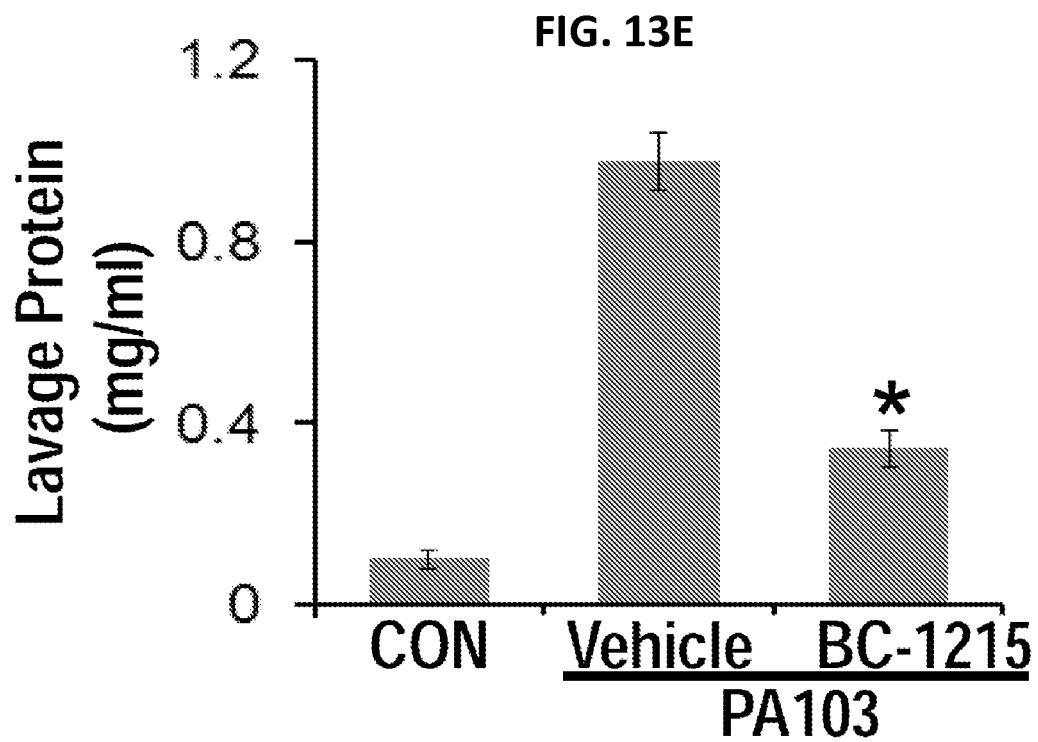


FIG. 13H

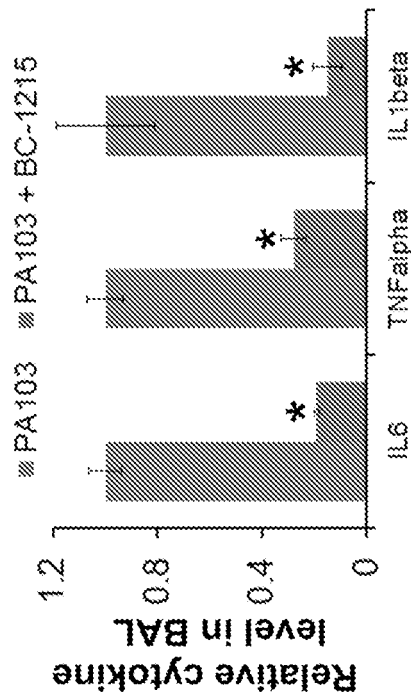


FIG. 13G

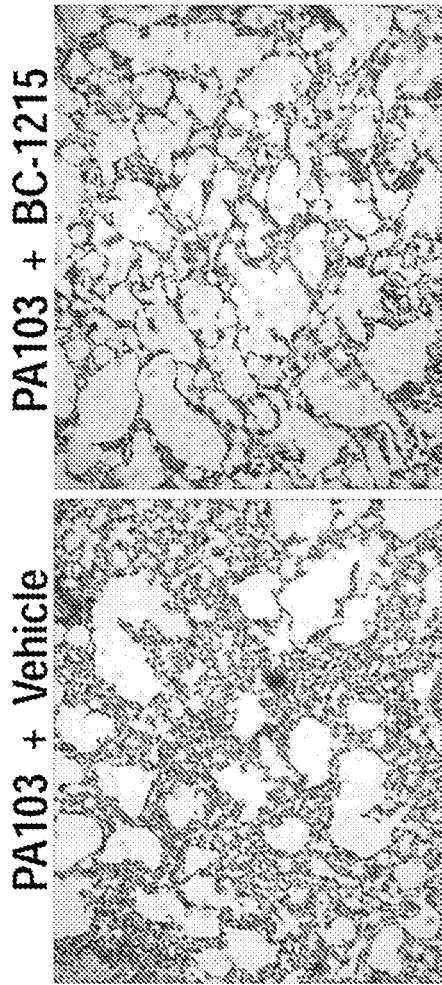


FIG. 14A

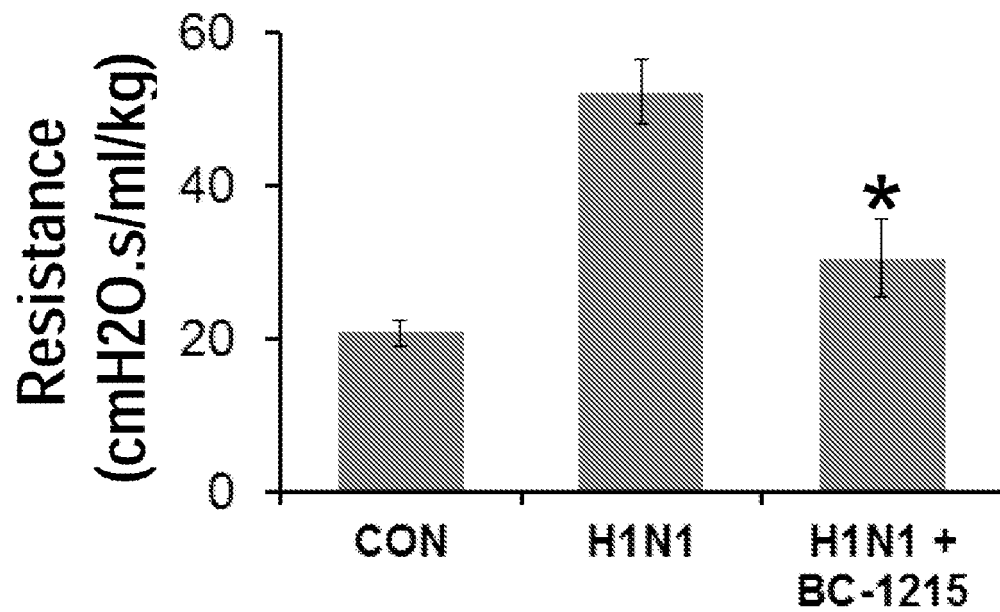


FIG. 14B

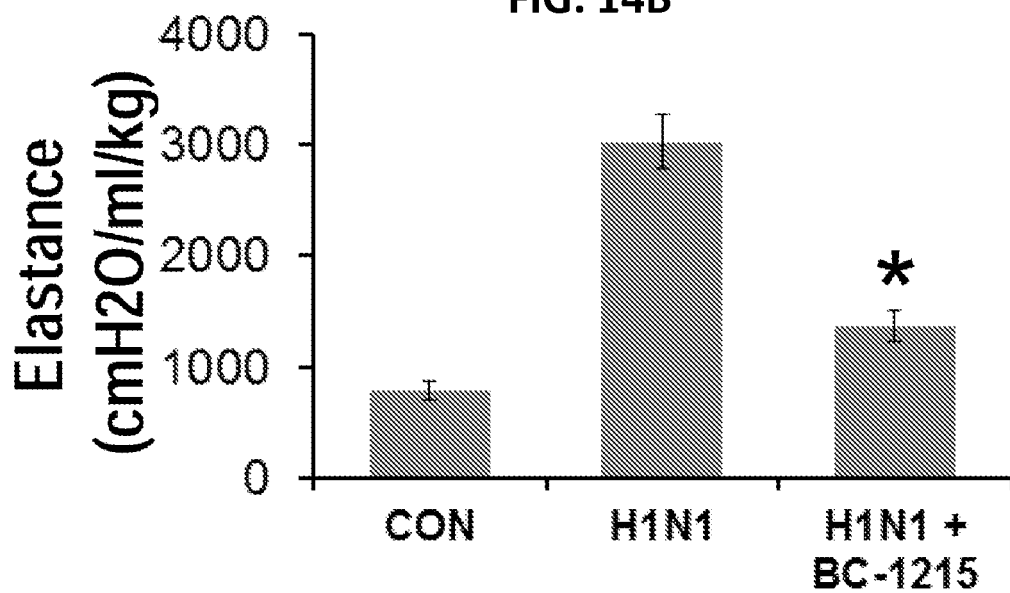


FIG. 14C

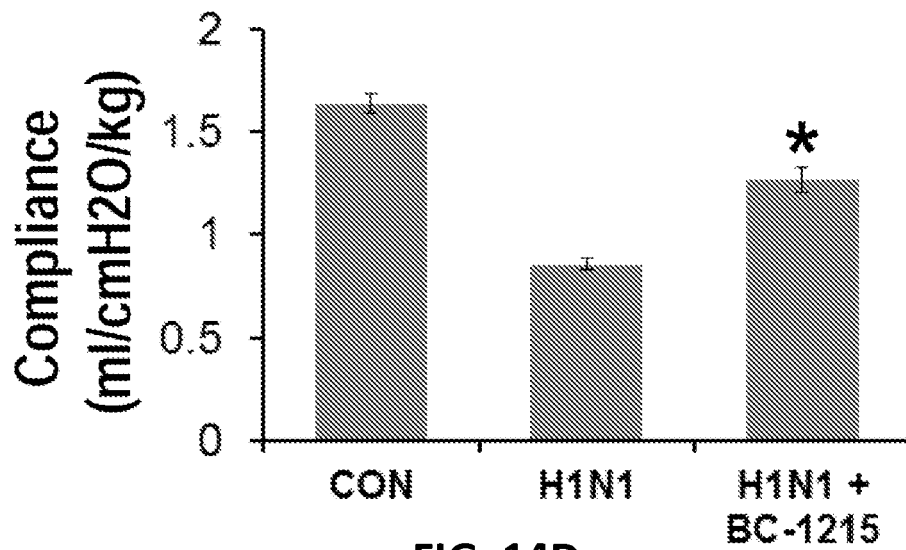


FIG. 14D

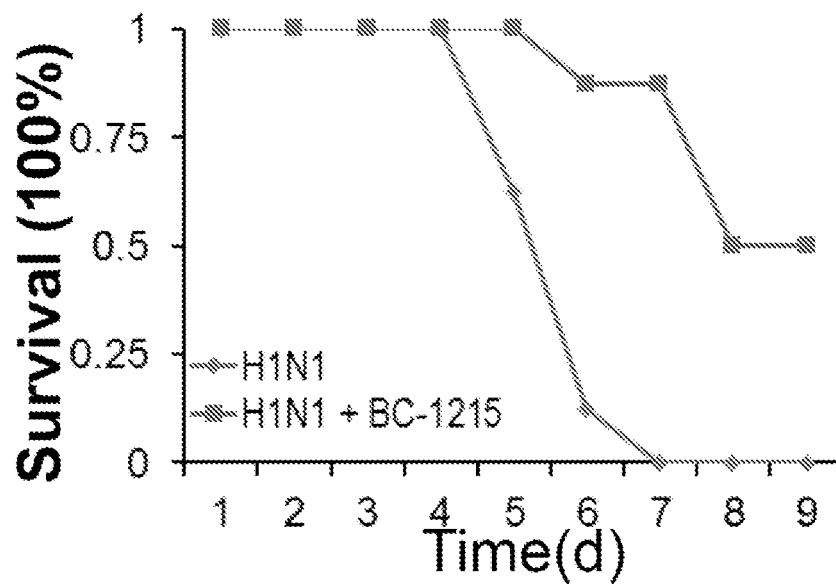


FIG. 14E

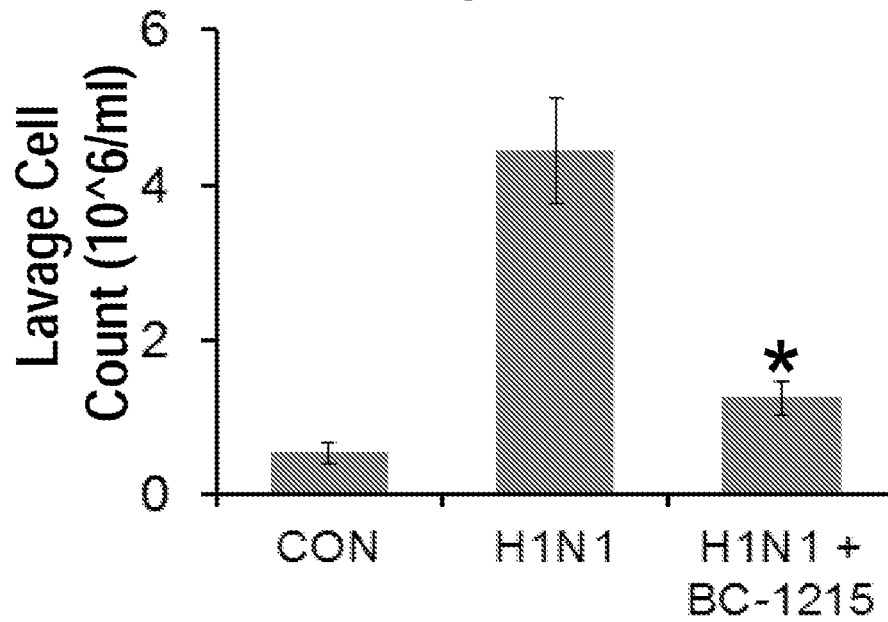


FIG. 14F

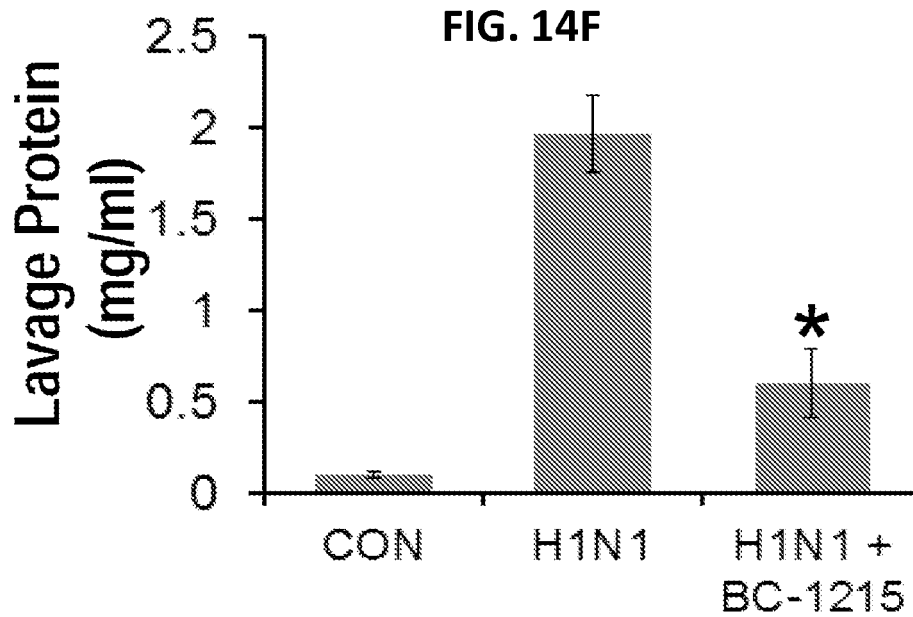


FIG. 14H

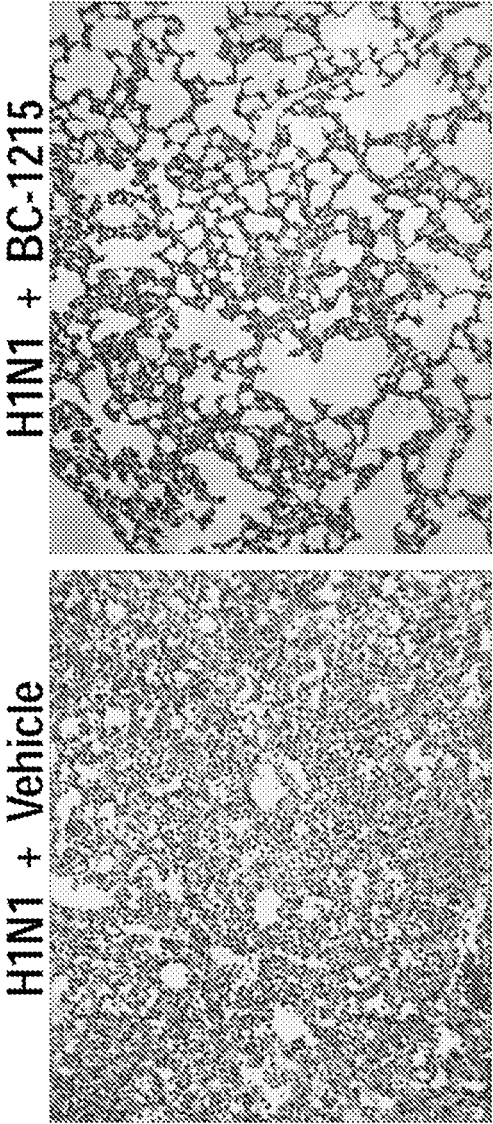


FIG. 14G

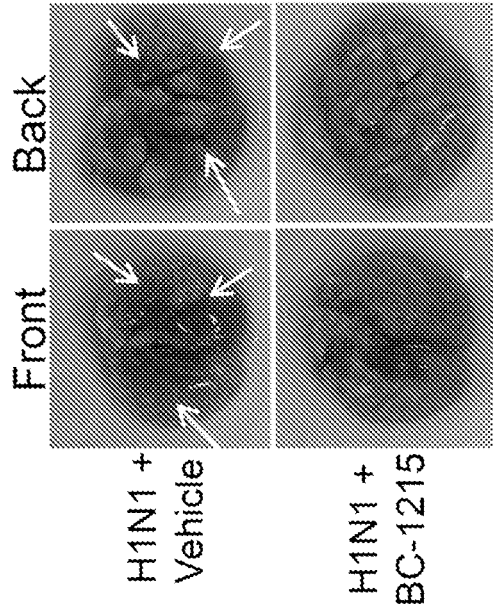


FIG. 15A *In vivo* TPA induced ear edema

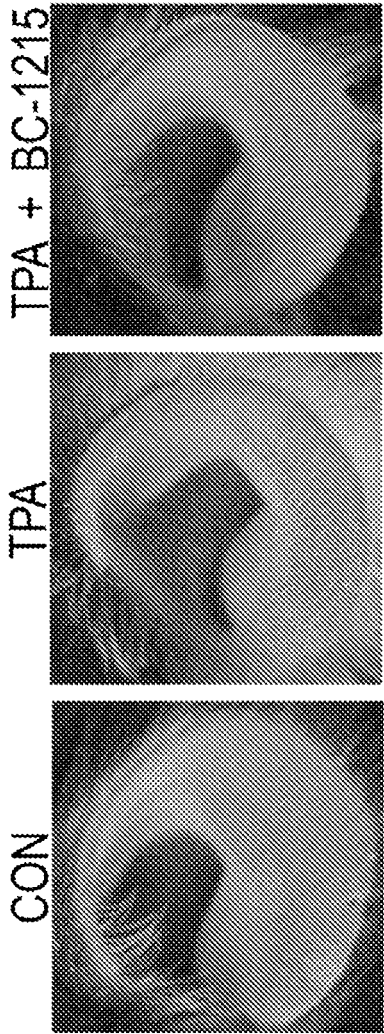


FIG. 15B

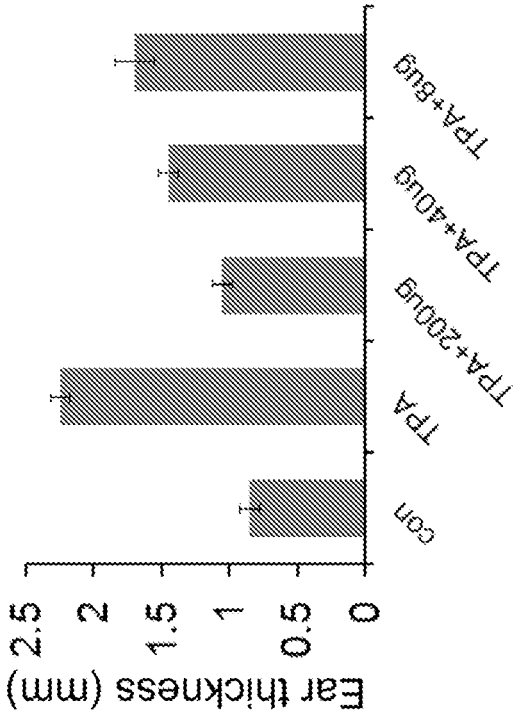


FIG. 15C

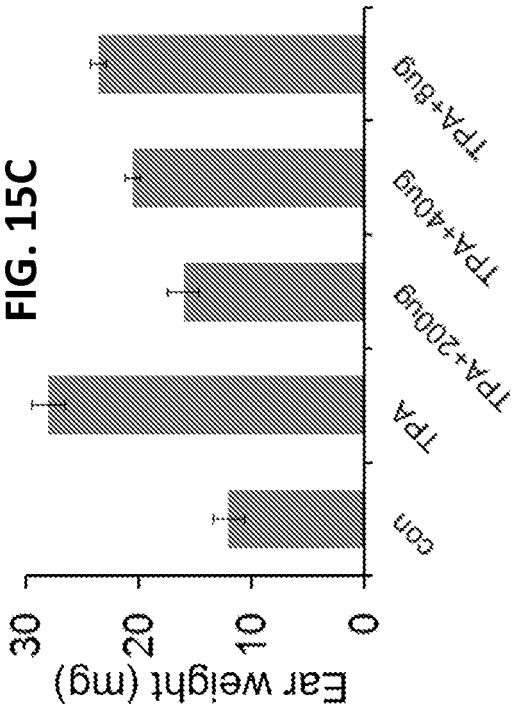
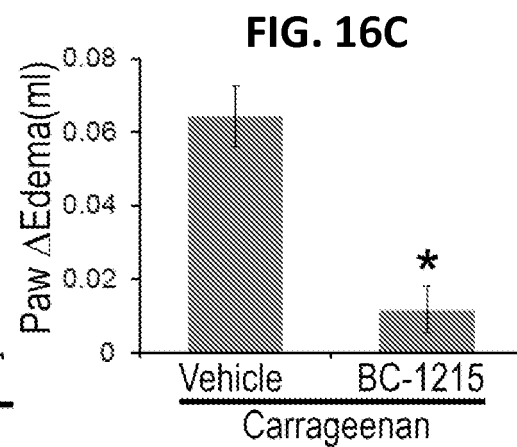
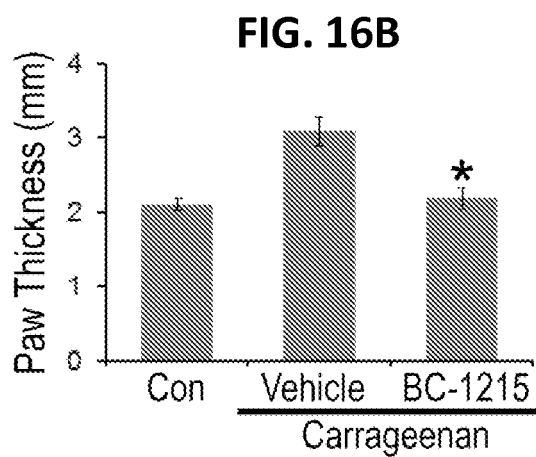
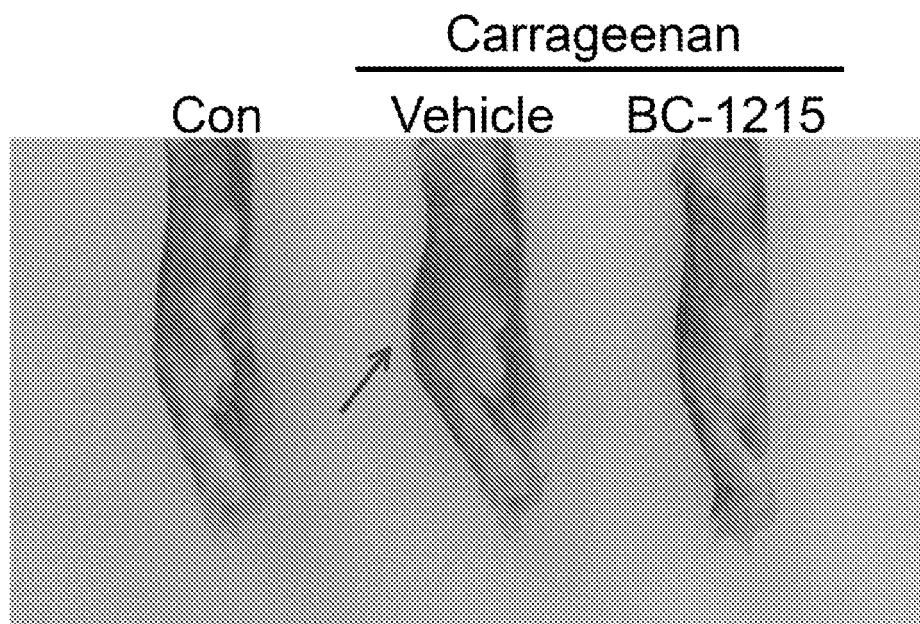


FIG. 16A

In vivo mouse paw edema model



In vivo DSS induced mouse colitis model

FIG. 17A

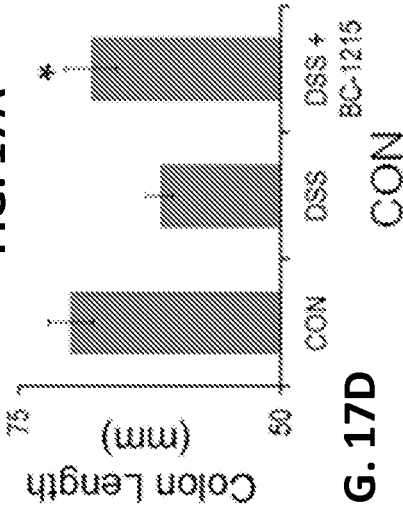


FIG. 17B

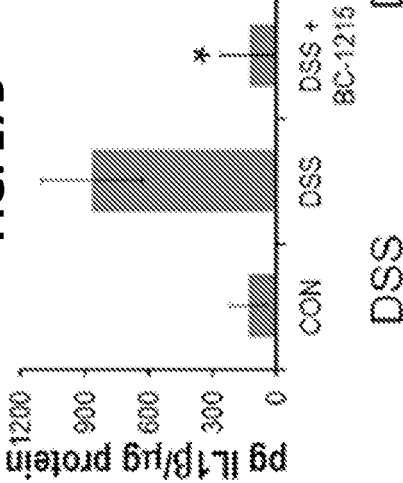


FIG. 17C

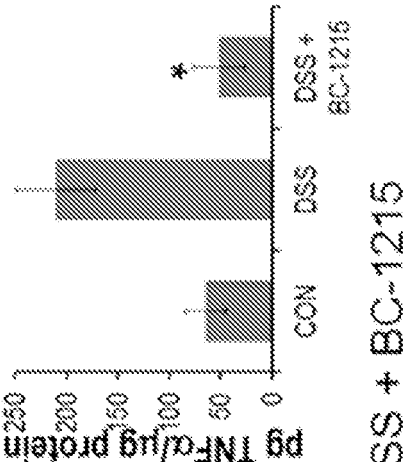


FIG. 17D

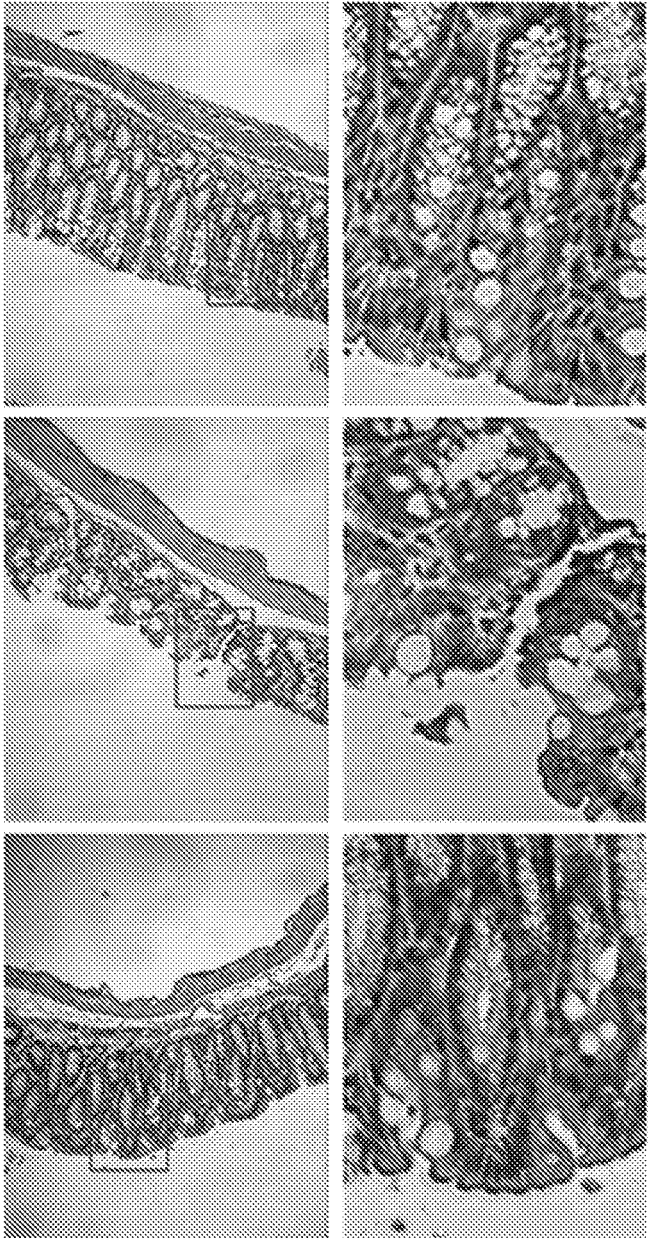


FIG. 18

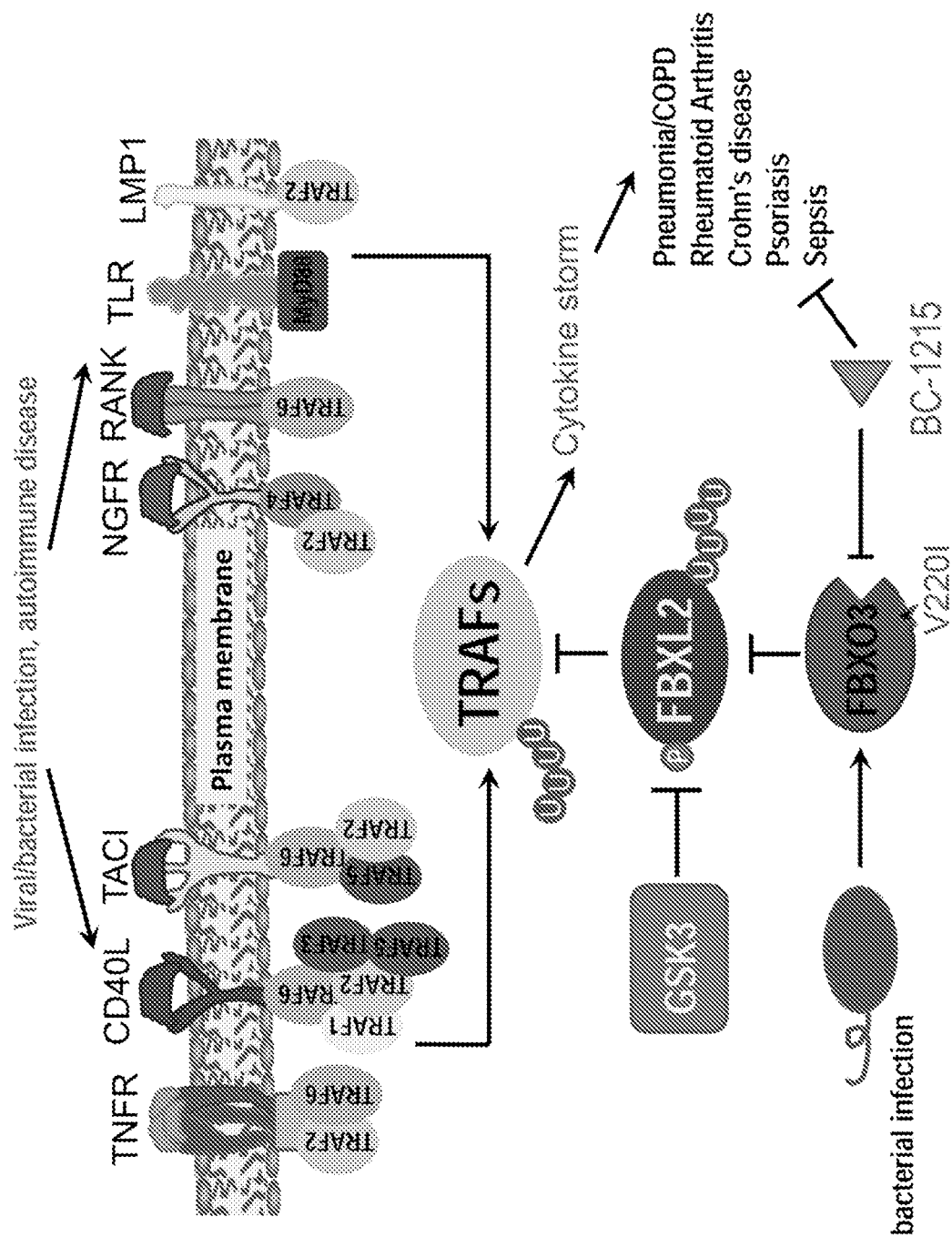
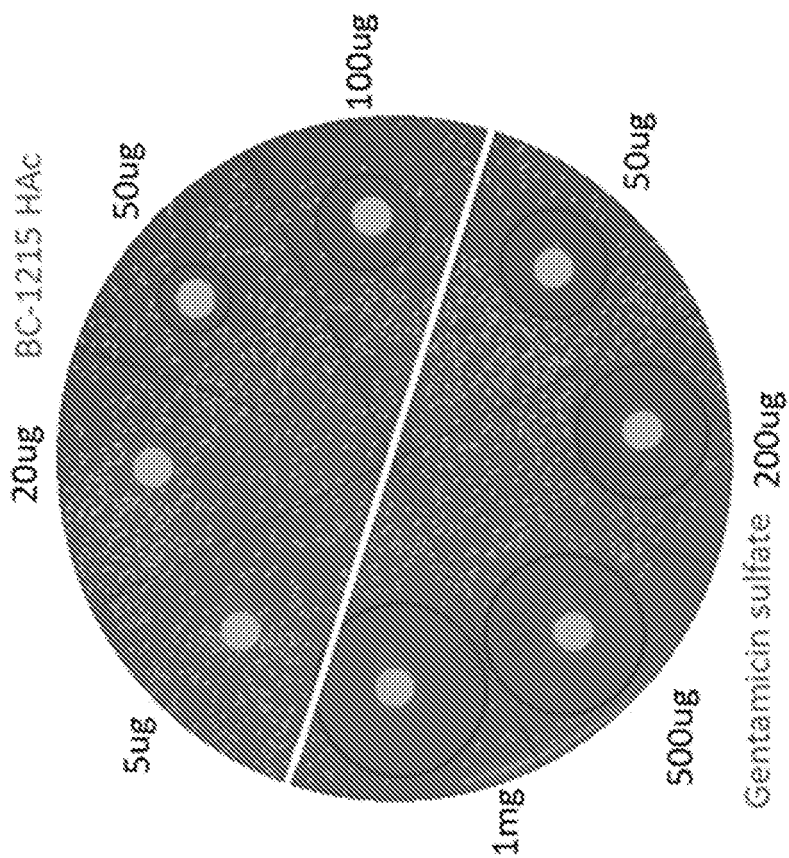


FIG. 19 Kirby-Bauer antibiotic testing



BC-1215 was tested in antibiotic sensitivity test using Mueller-Hinton agar. Briefly, 6mm filter papers containing different amount of BC-1215 or Gentamicin (positive control) were added on the Mueller-Hinton agar pre-exposed to *Staphylococcus aureus*. The plates were incubated at 37 degree for 24h. Zone sizes were measured and marked by red circle indicating positive results.

FIG. 20A

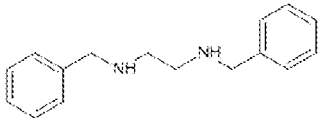
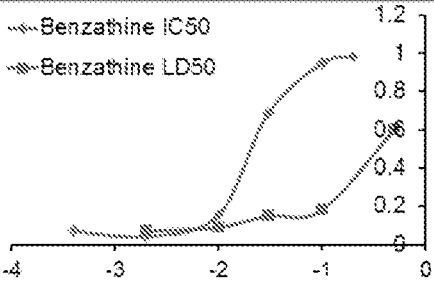
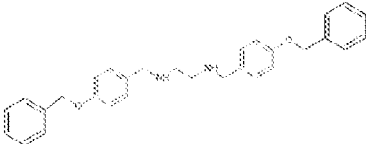
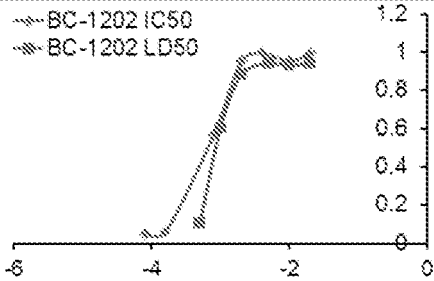
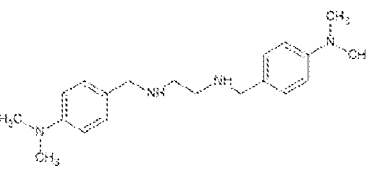
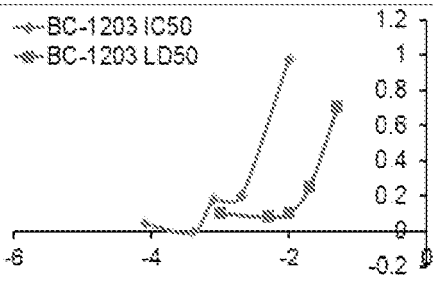
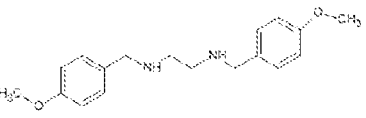
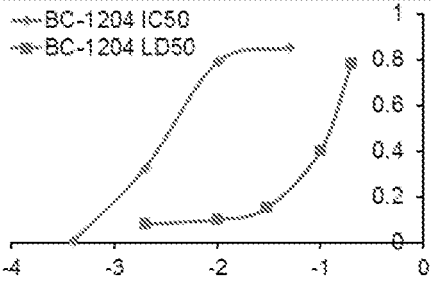
		IL1b assay, Apoptosis	IC50, LD50, TI
Benzathine			IC50 _{IL1β} =25ug/ml LD50 =400ug/ml TI=16
BC-1202			IC50 _{IL1β} =0.8ug/ml LD50 =0.9ug/ml TI=1.1
BC-1203			IC50 _{IL1β} =5ug/ml LD50 =34ug/ml TI=6.8
BC-1204			IC50 _{IL1β} =5ug/ml LD50 =120ug/ml TI=24

FIG. 20B

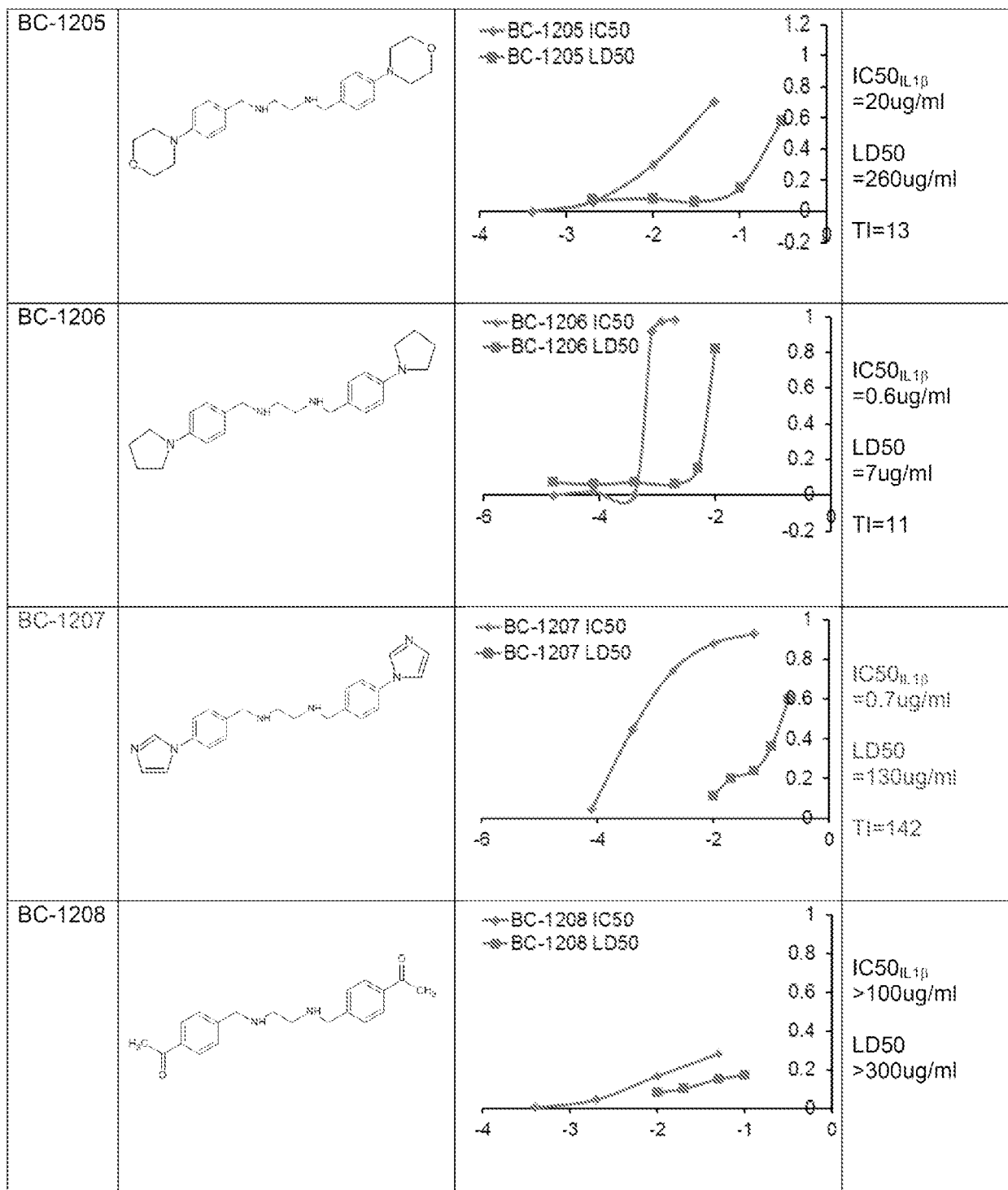


FIG. 20C

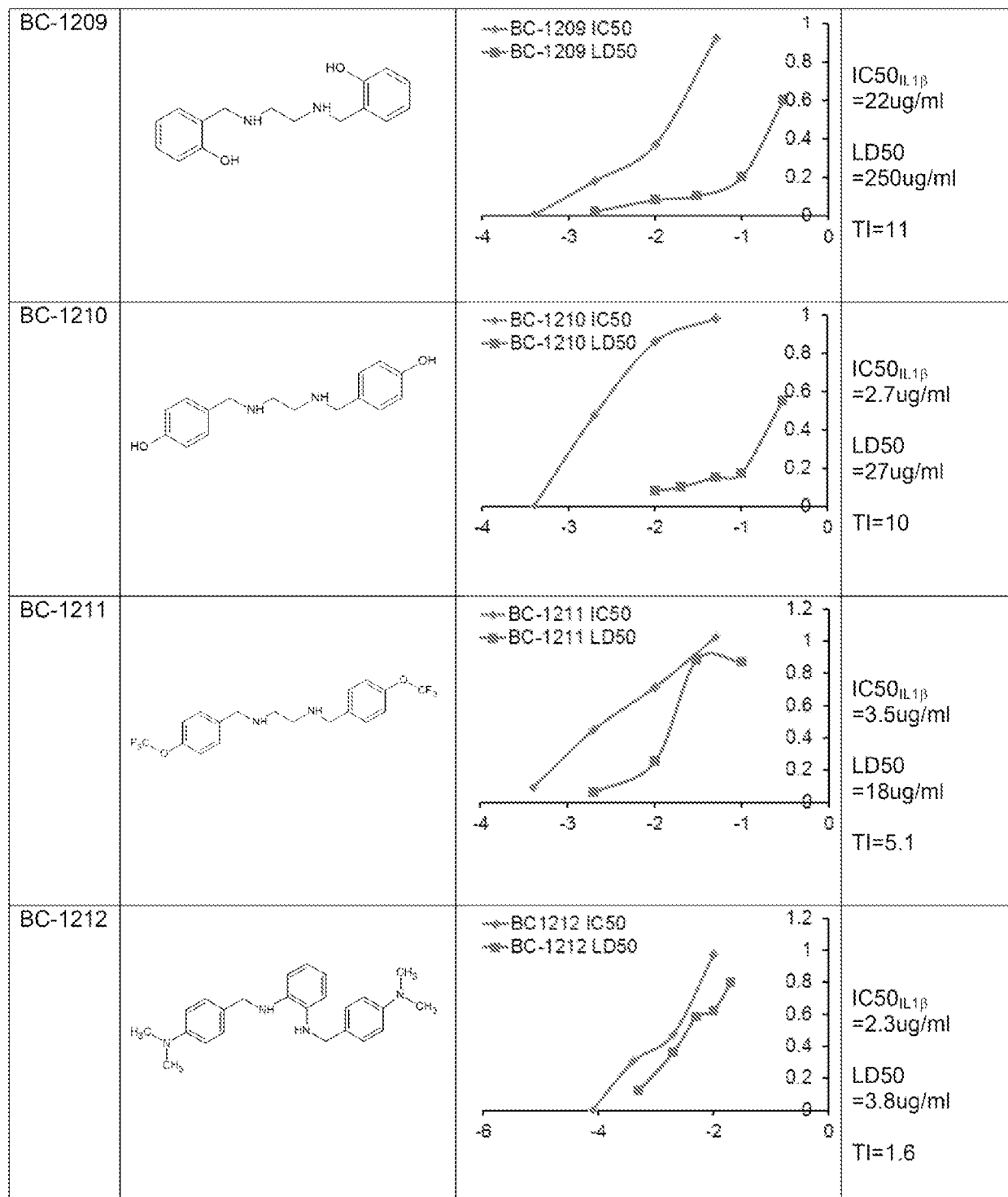


FIG. 20D

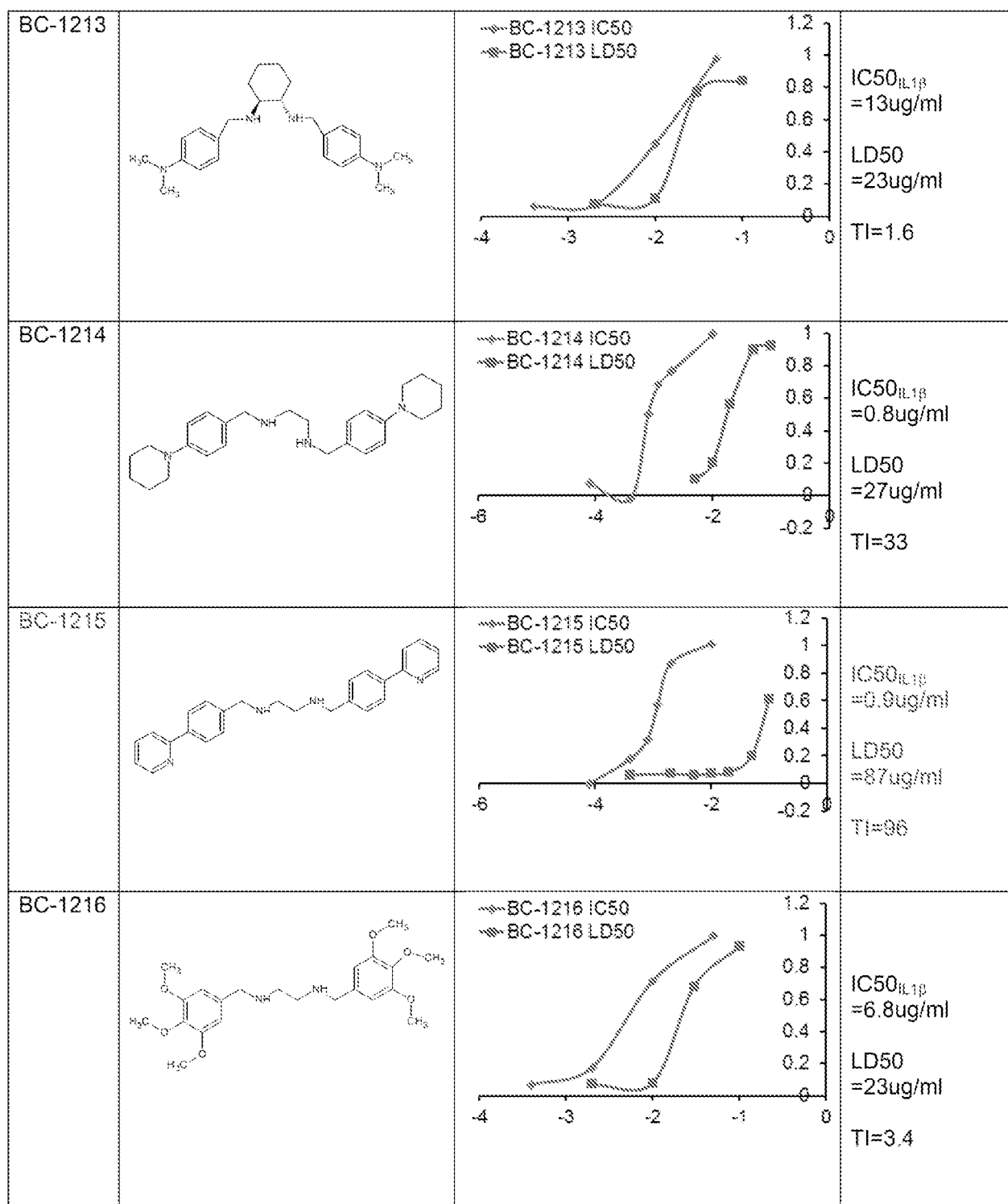


FIG. 20E

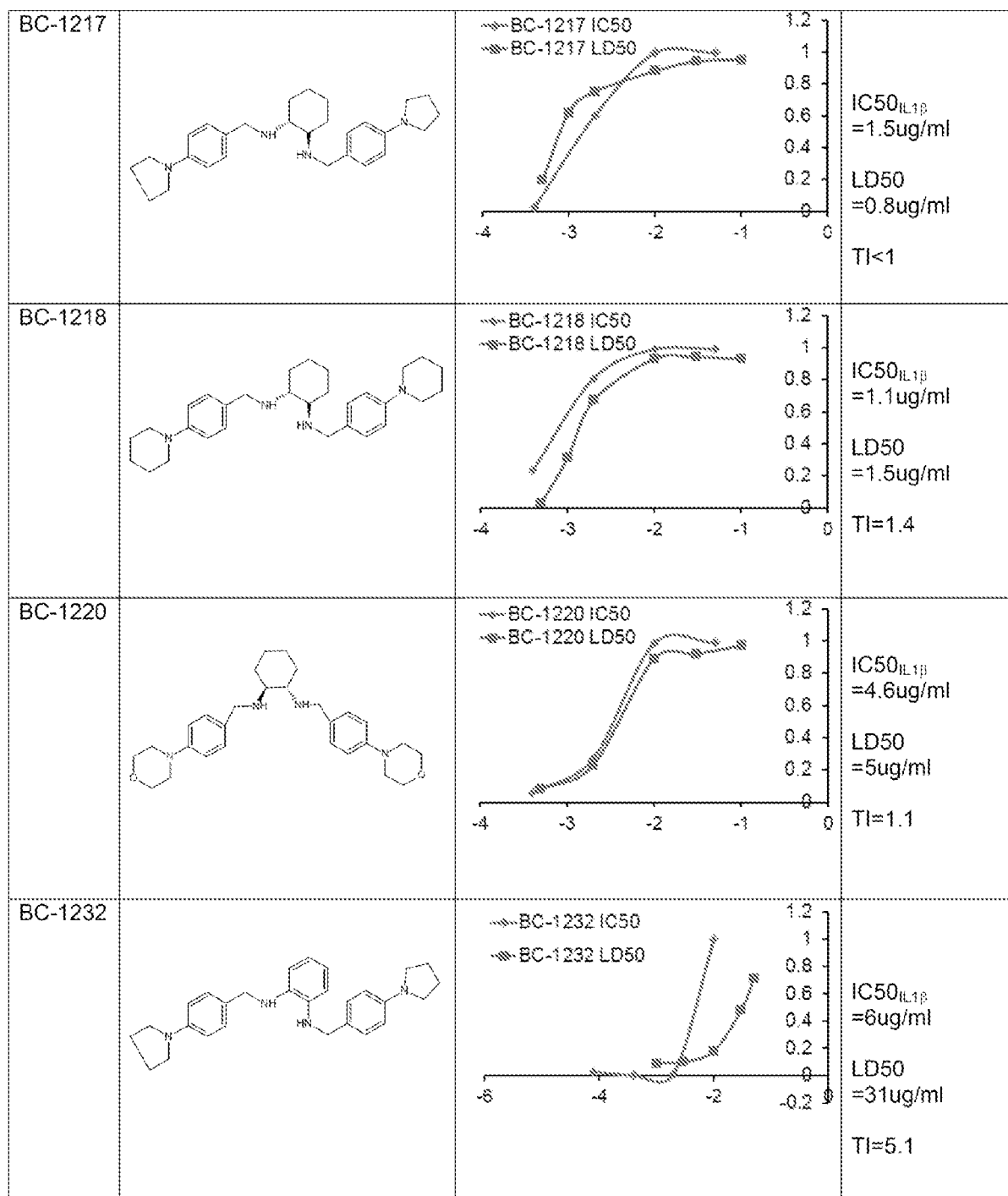


FIG. 20F

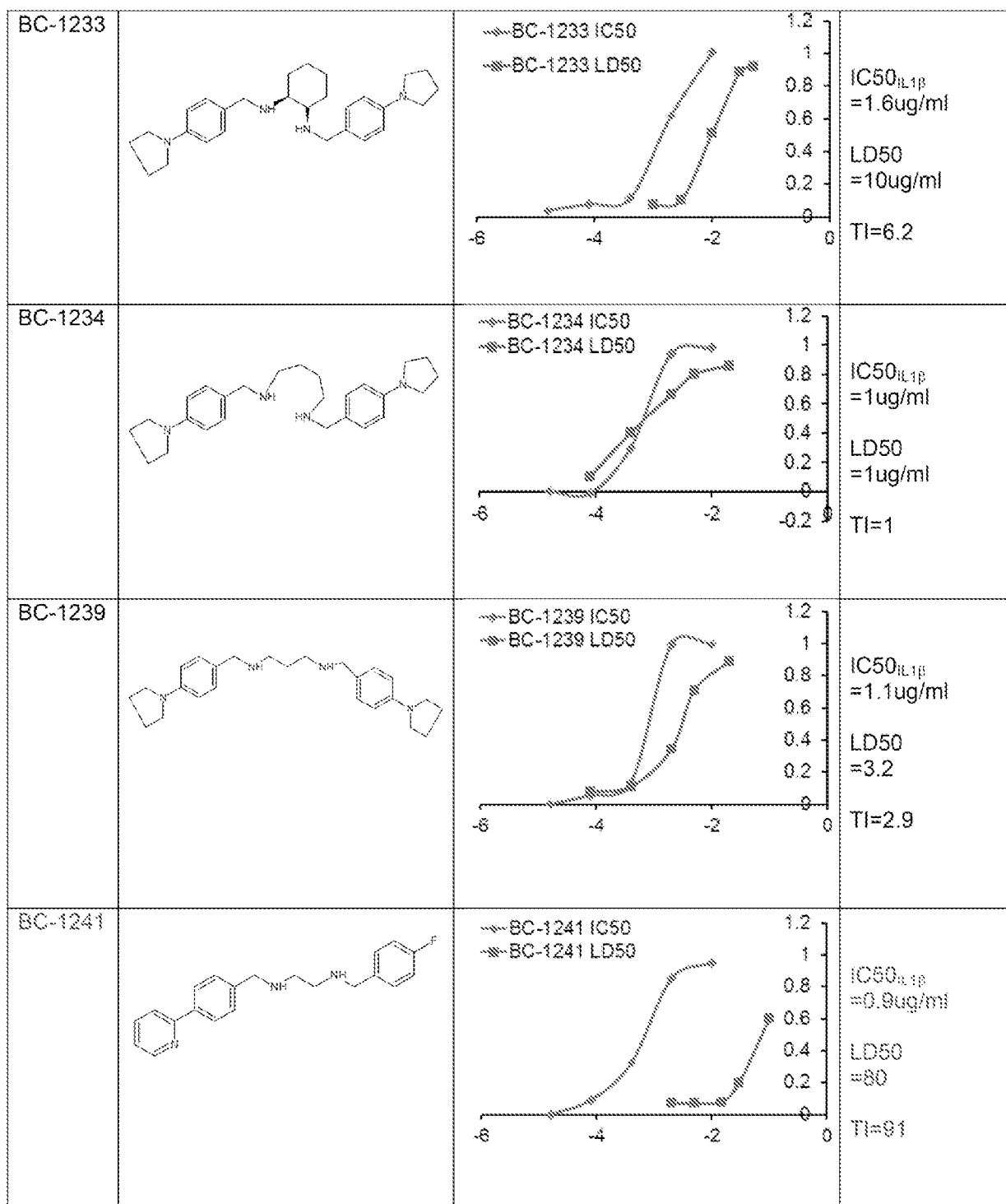


FIG. 20G

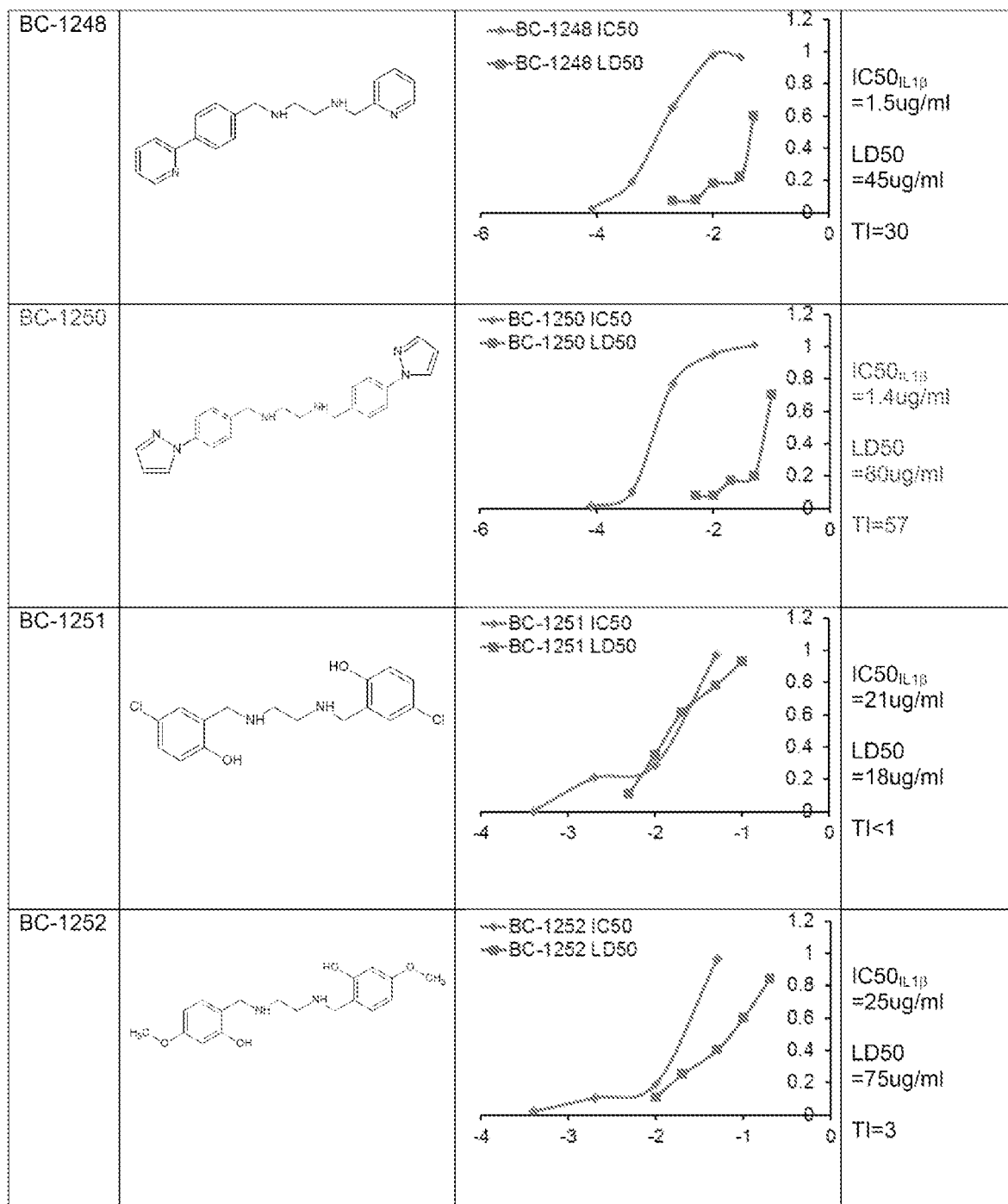


FIG. 20H

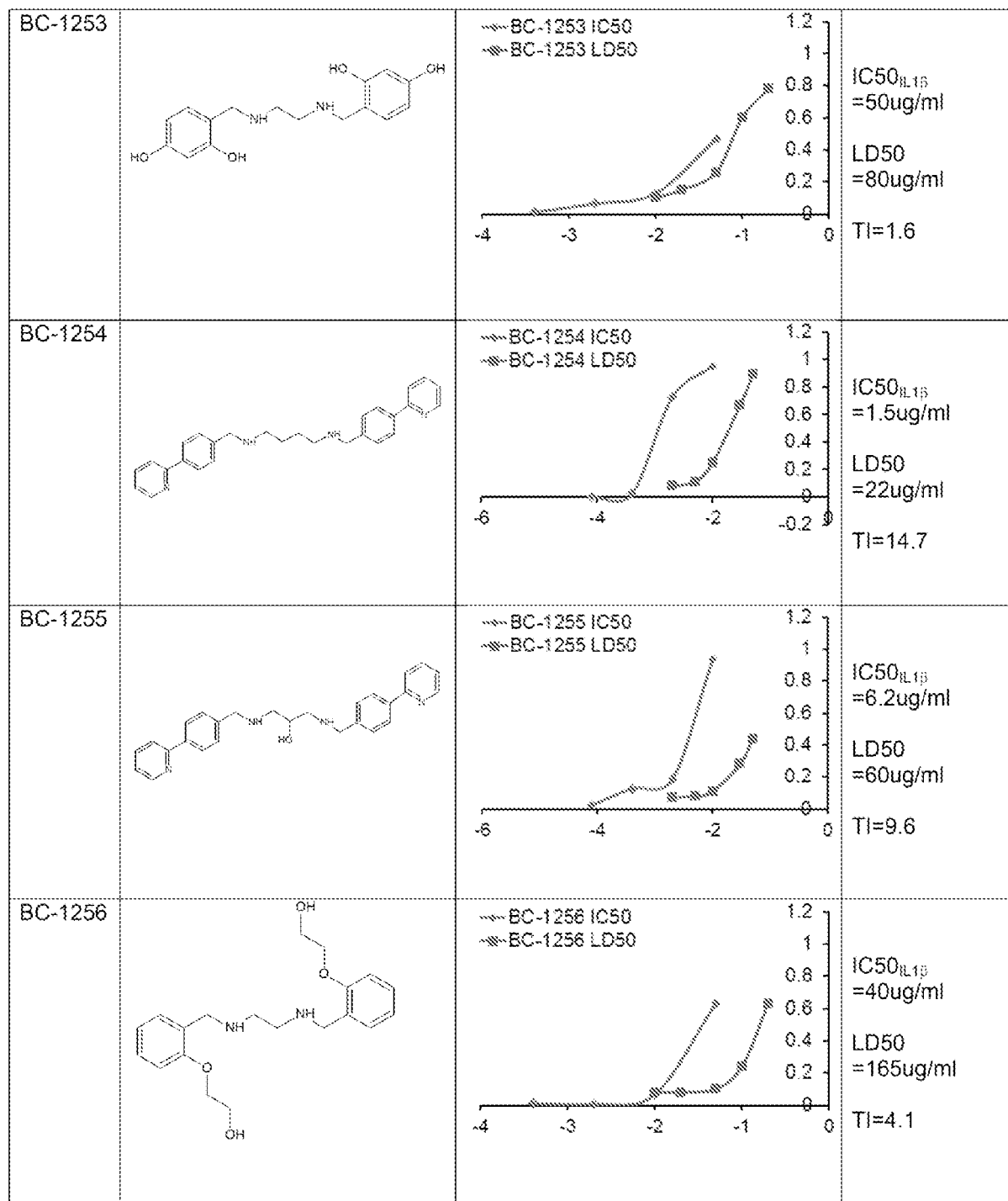


FIG. 20I

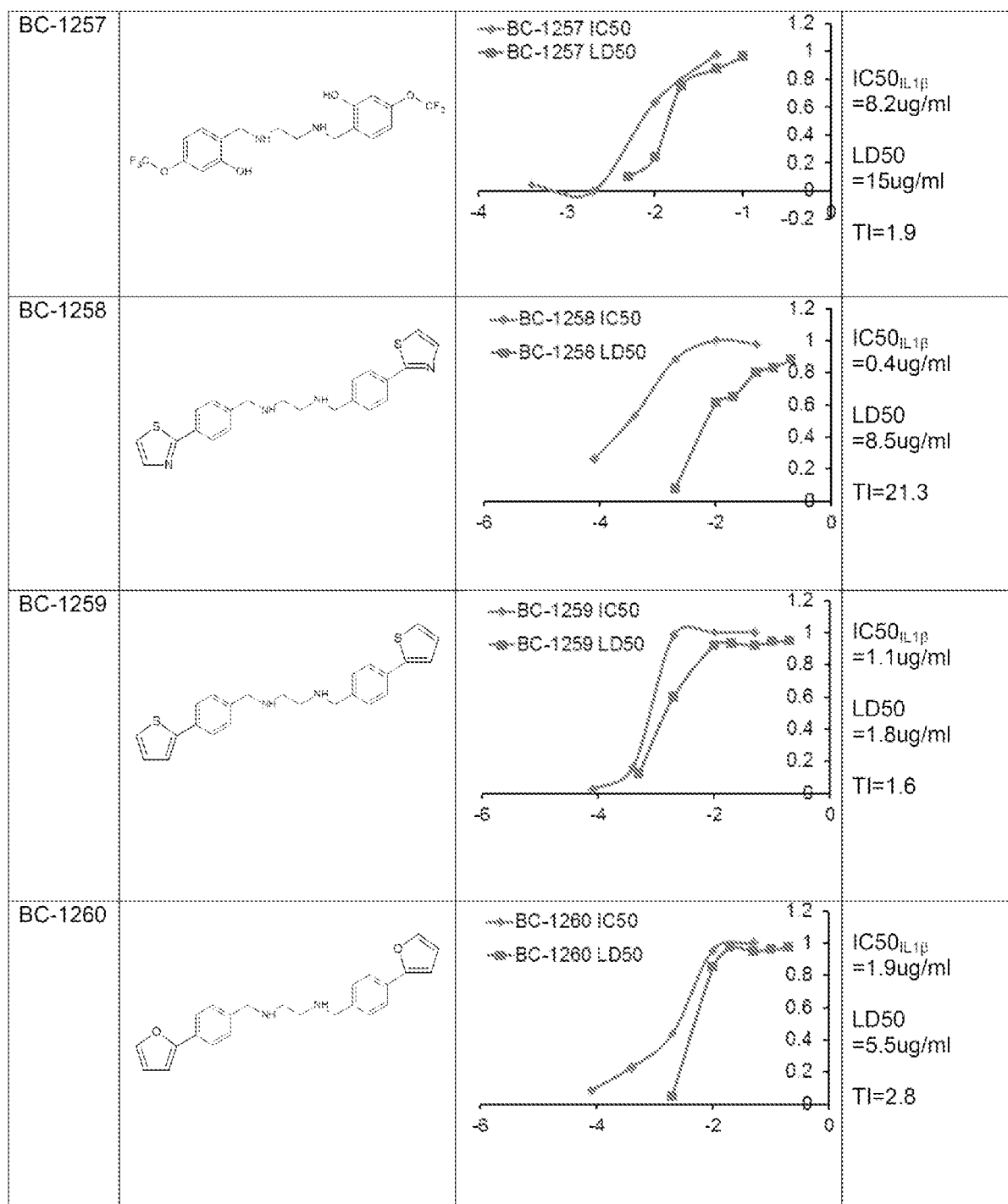


FIG. 20J

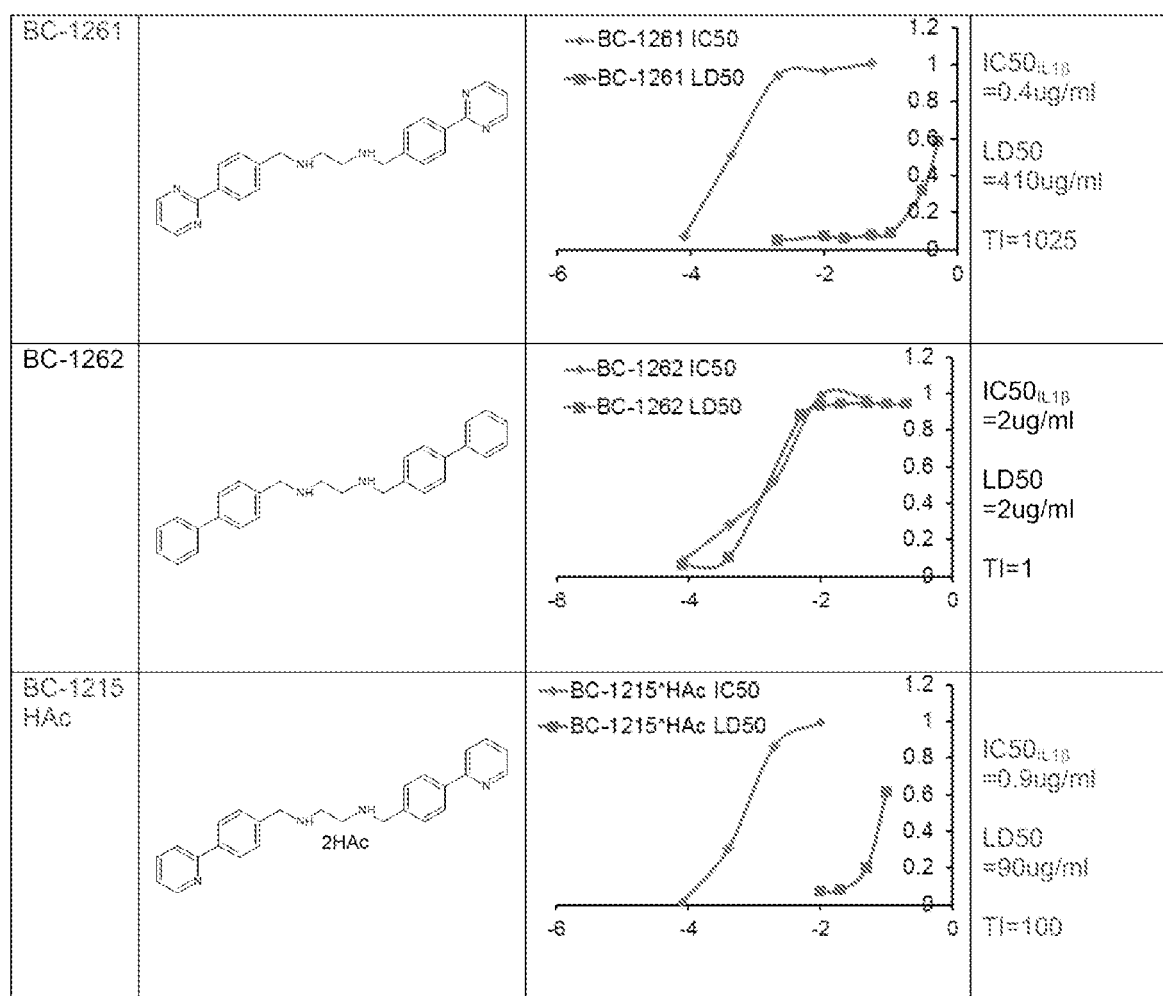


FIG. 21D

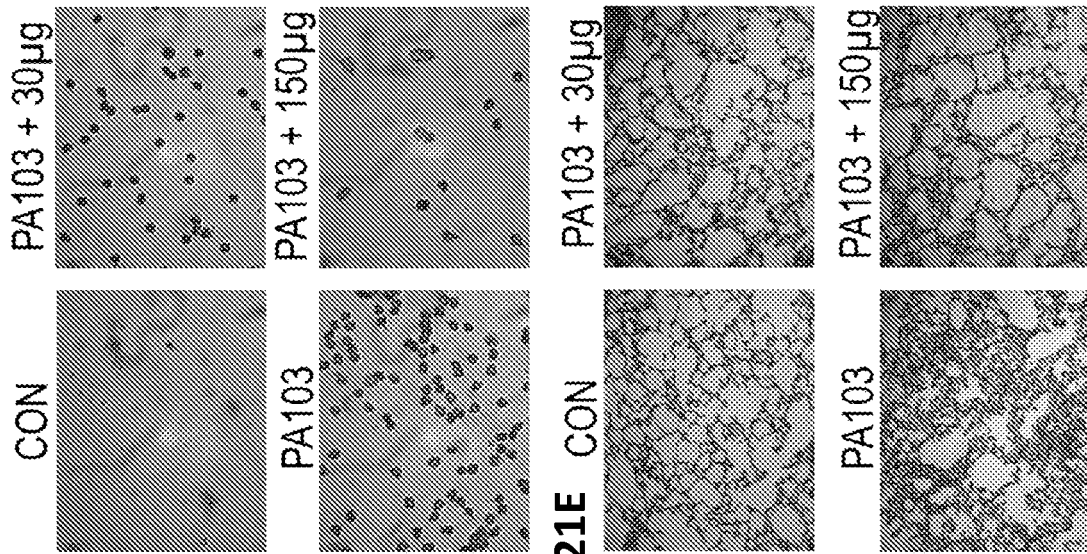


FIG. 21E

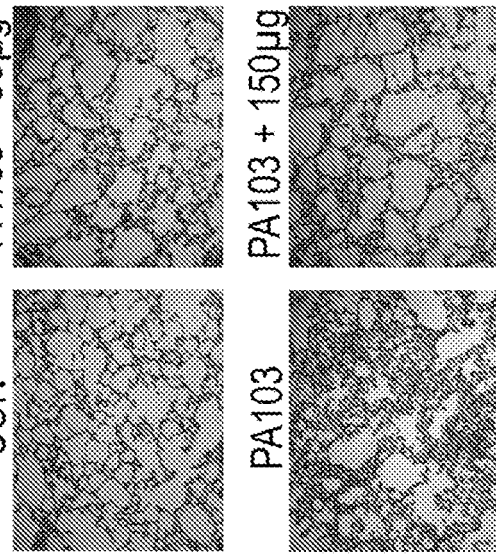


FIG. 21B

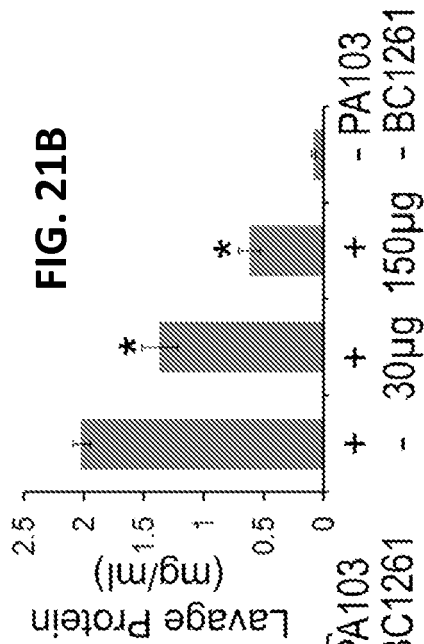


FIG. 21A

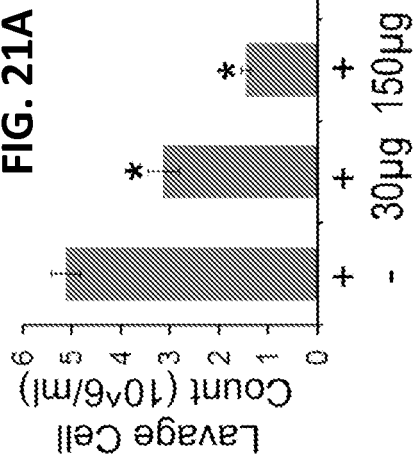


FIG. 21C

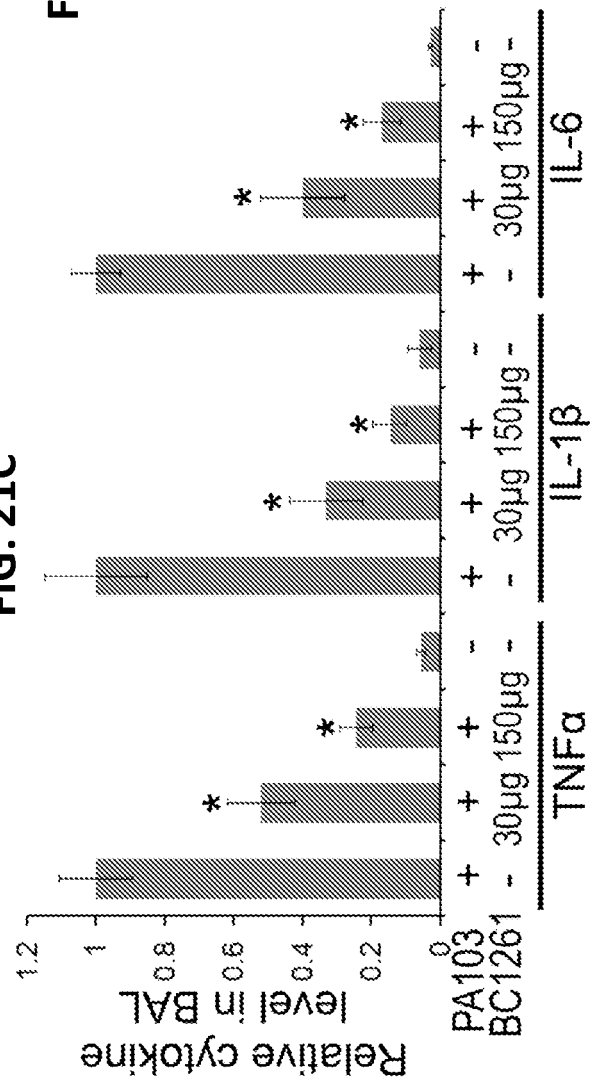


FIG. 22A

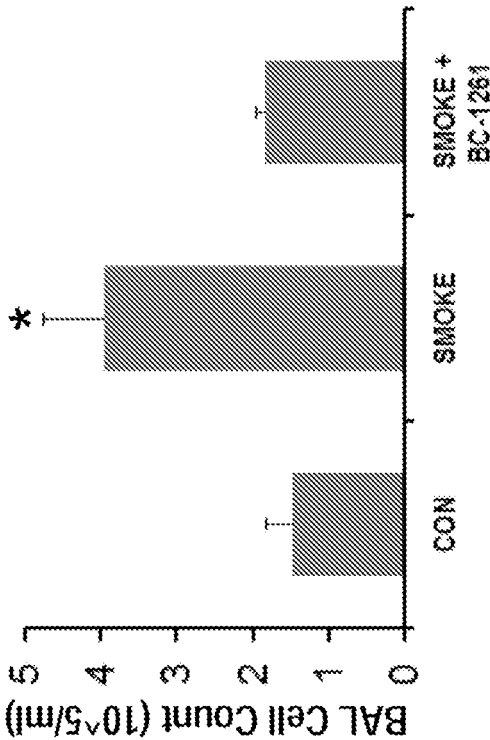


FIG. 22B

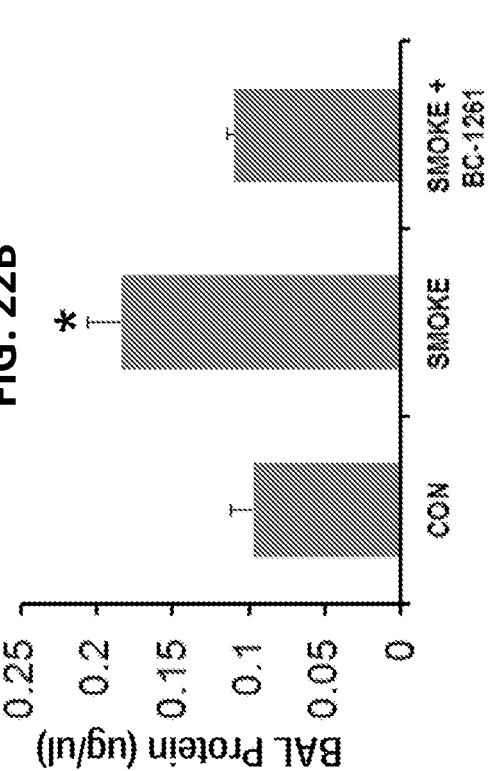


FIG. 22C

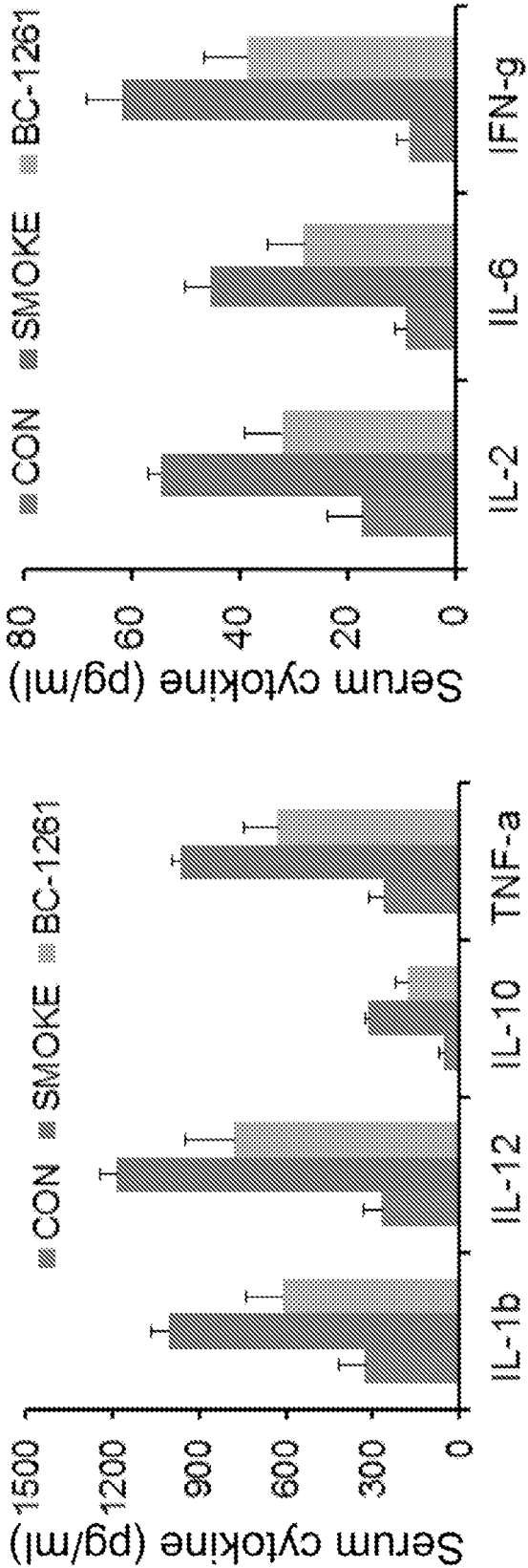


FIG. 23A

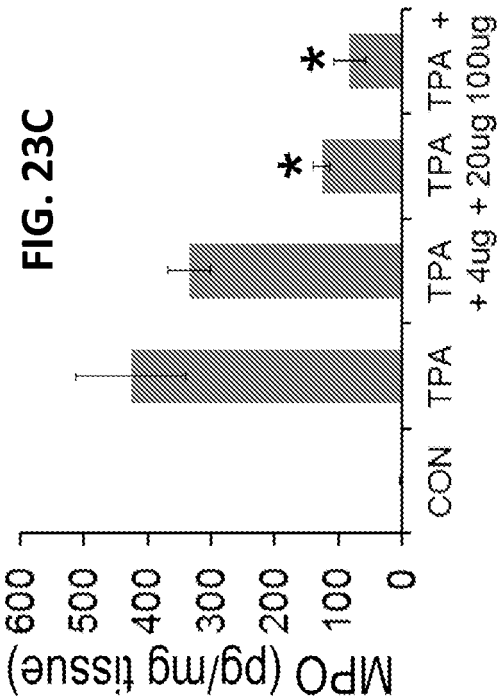
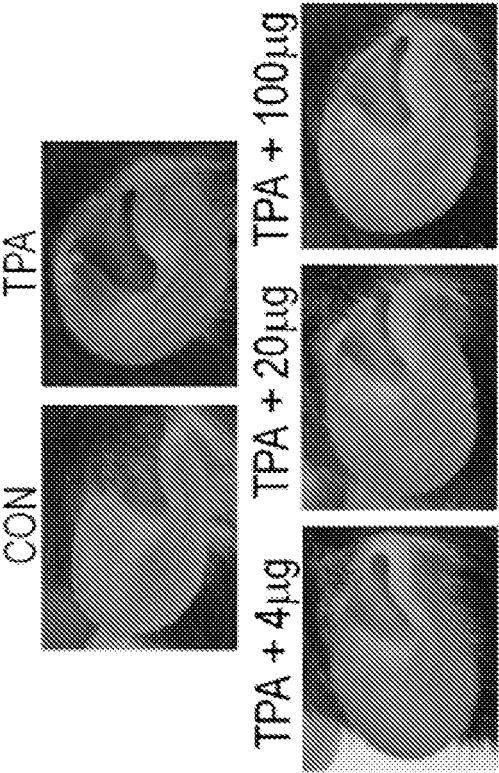


FIG. 23B

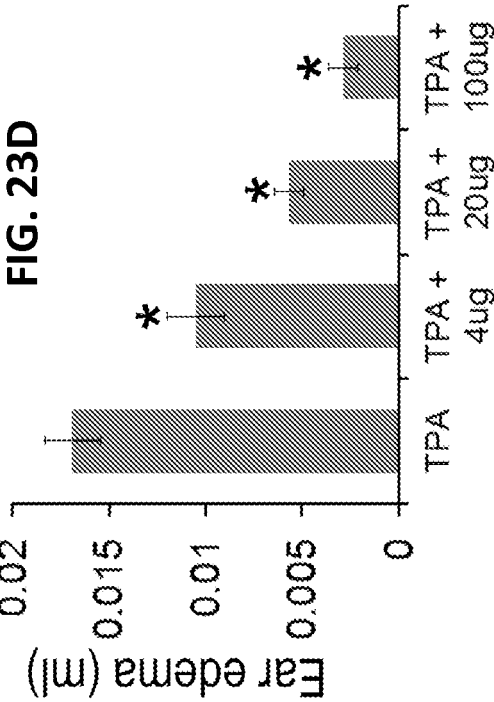
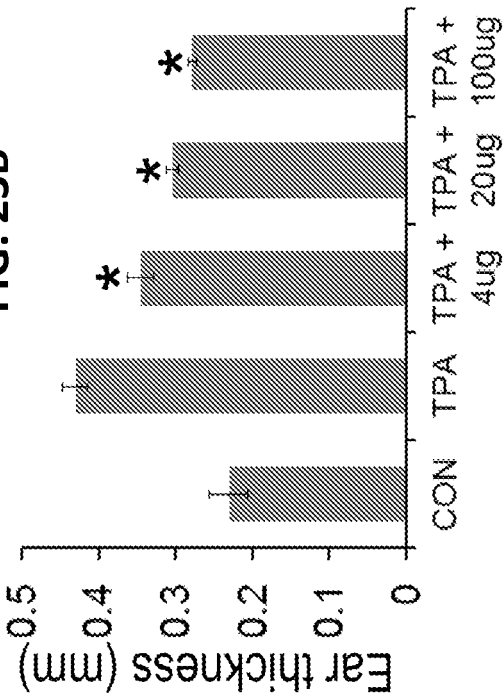


FIG. 24A

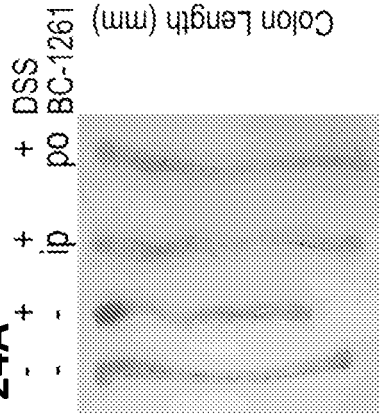


FIG. 24B

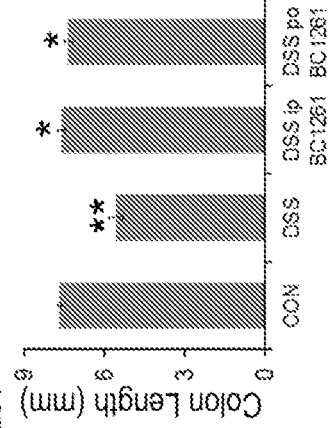


FIG. 24C

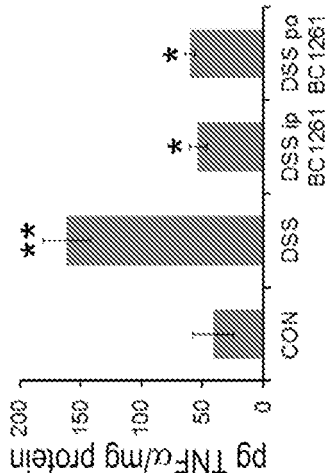
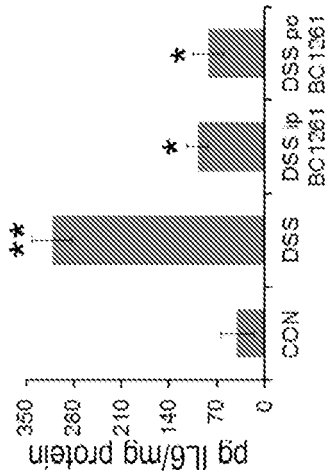
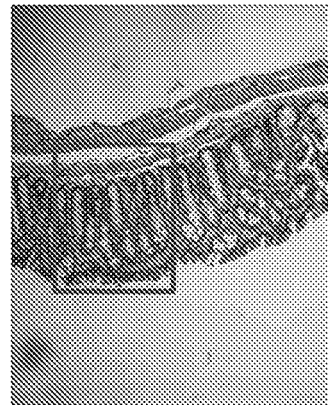


FIG. 24D



CON



DSS

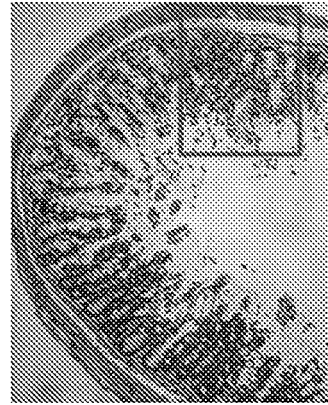
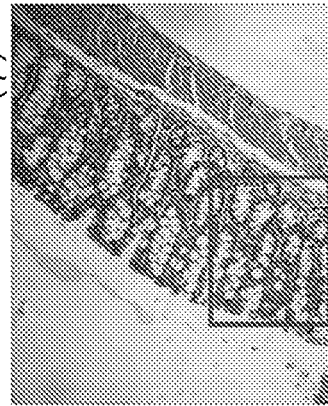
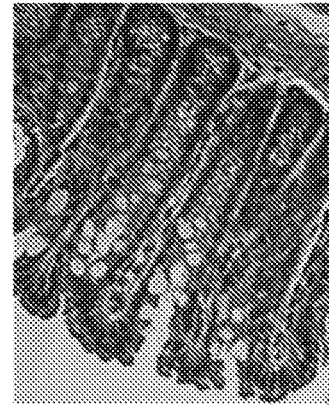
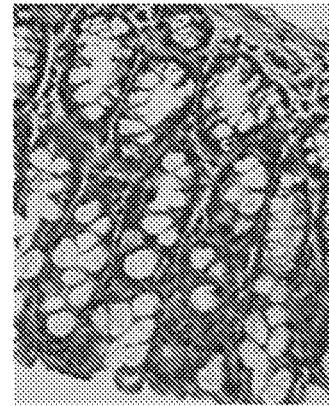
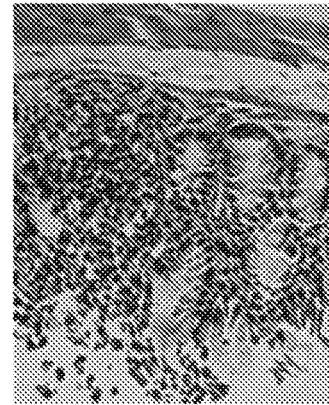
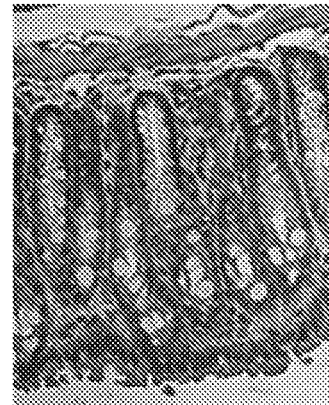
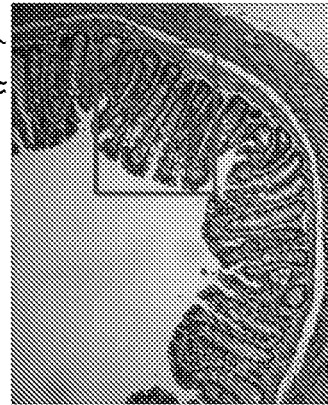


FIG. 24E DSS + BC1261 (ip)



DSS + BC1261 (po)



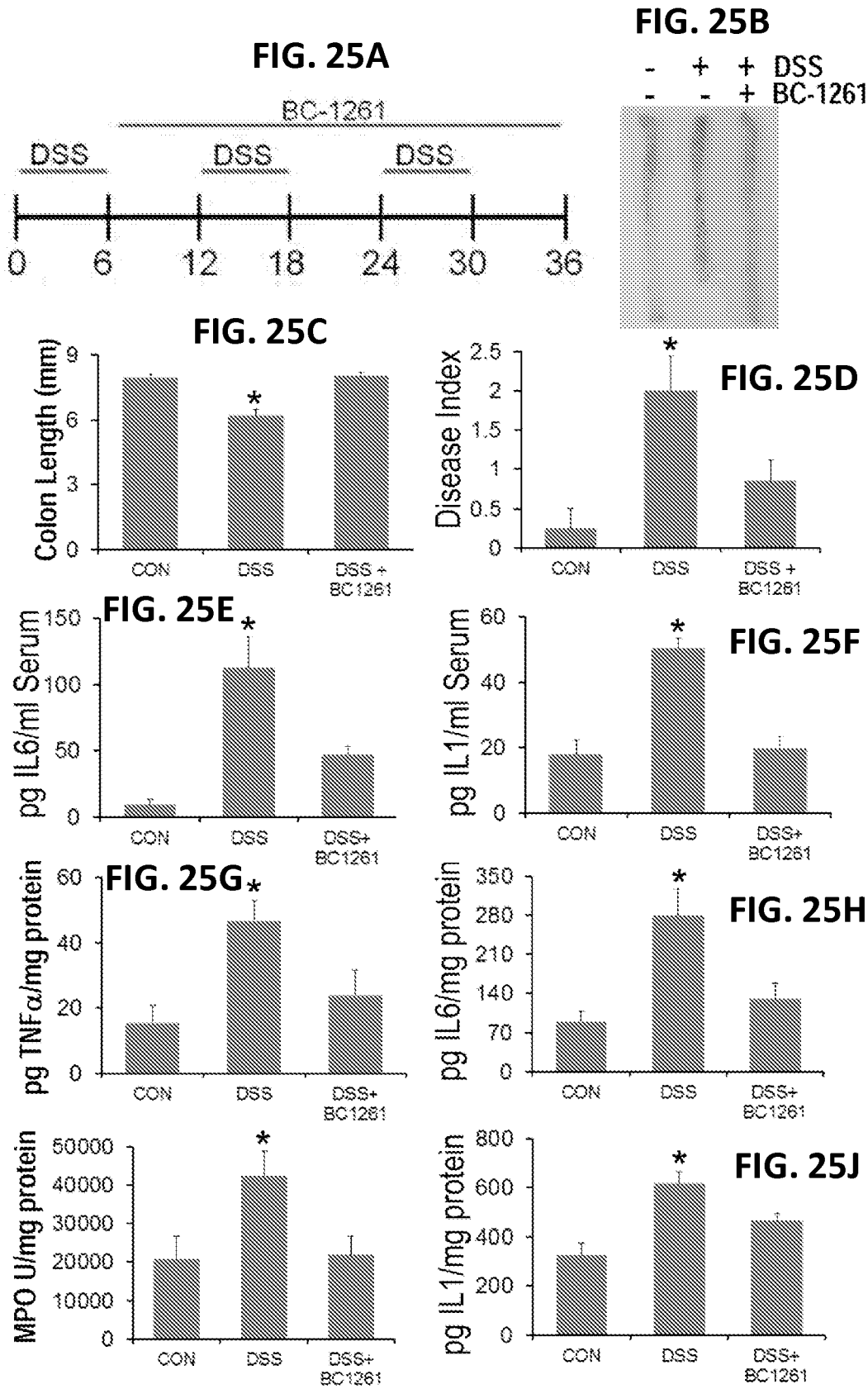


FIG. 26A

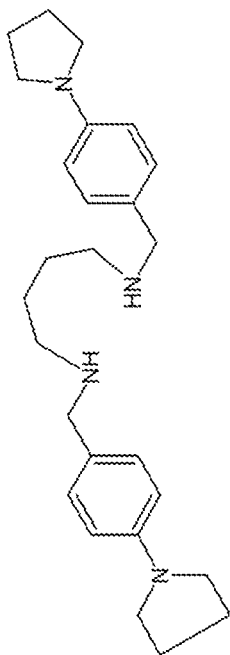


FIG. 26B

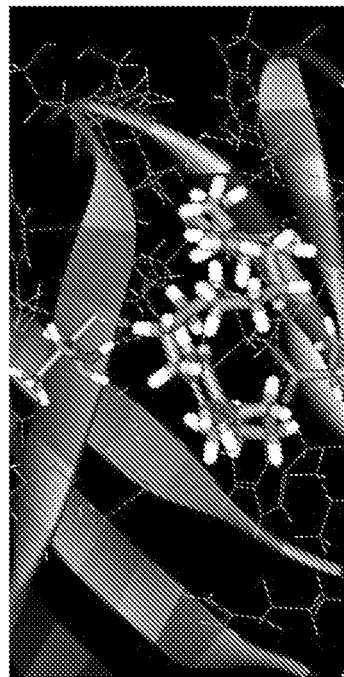
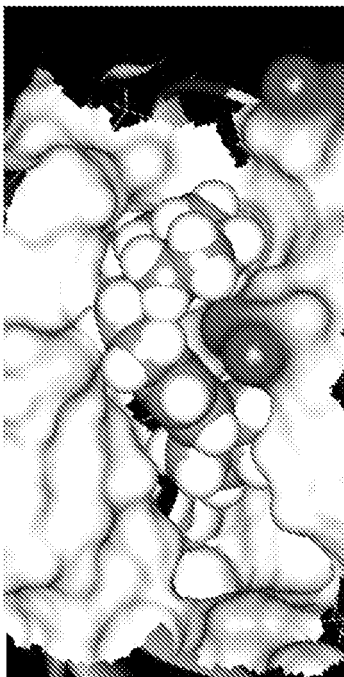


FIG. 26C

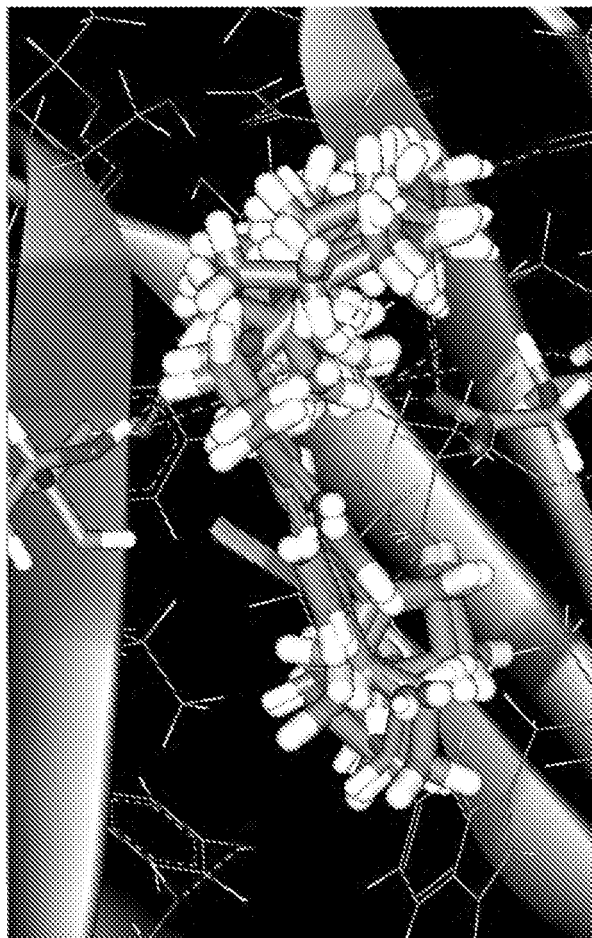


FIG. 26D

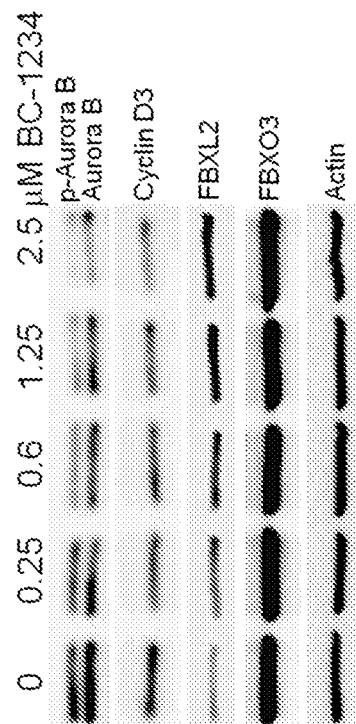


FIG. 27A

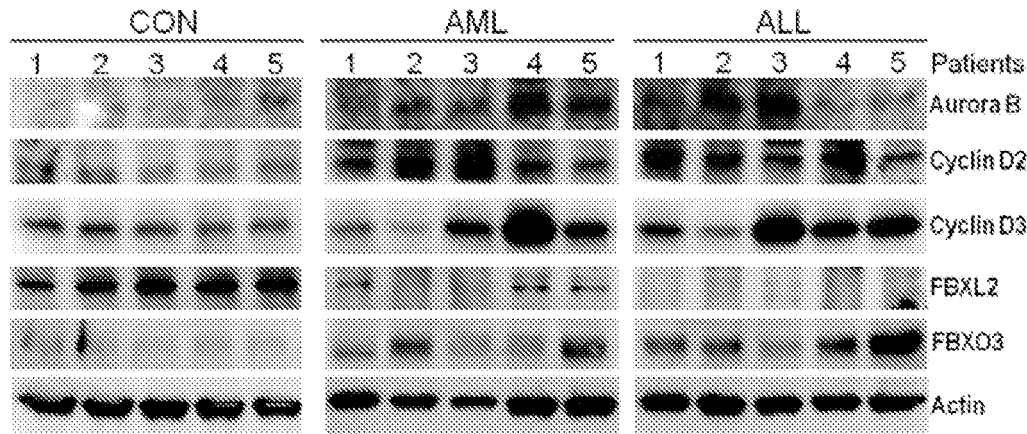


FIG. 27B

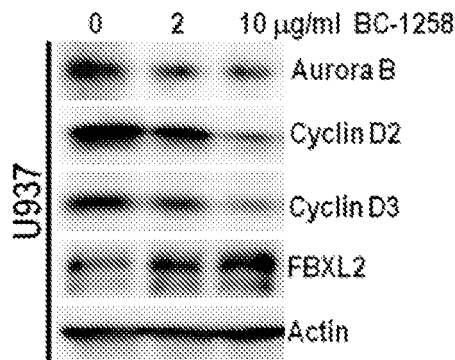


FIG. 27E

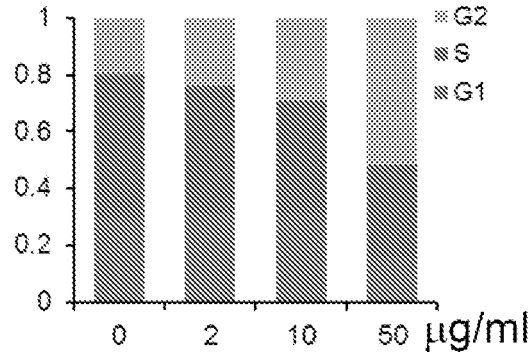


FIG. 27F

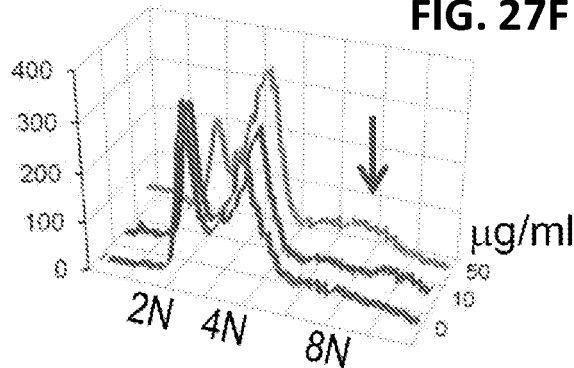


FIG. 27C

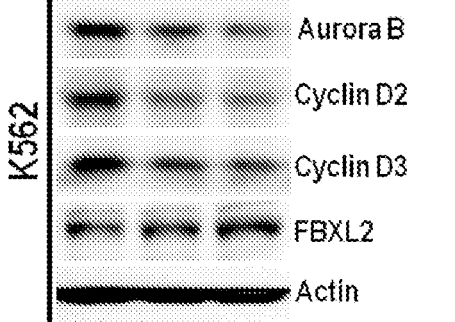


FIG. 27D

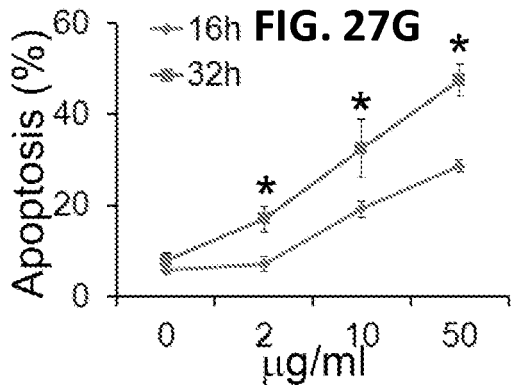
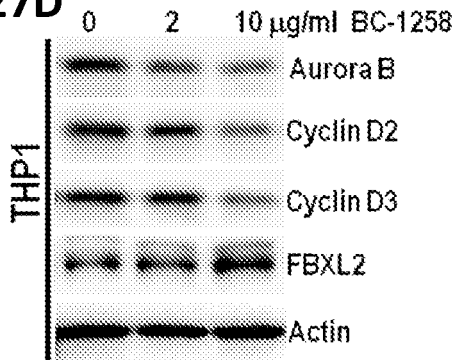


FIG. 27G

FIG. 28A

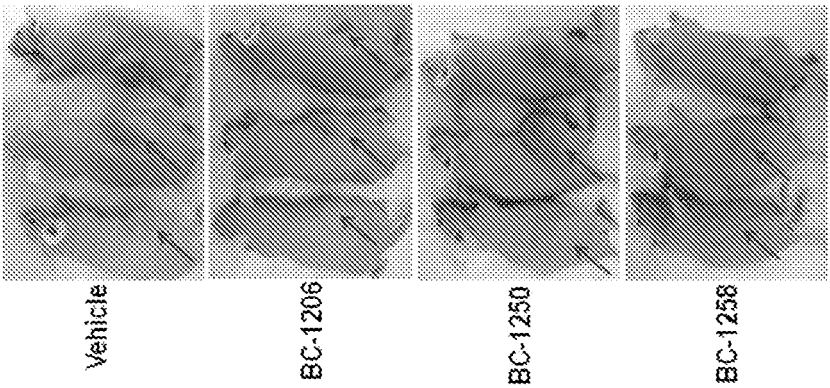


FIG. 28B

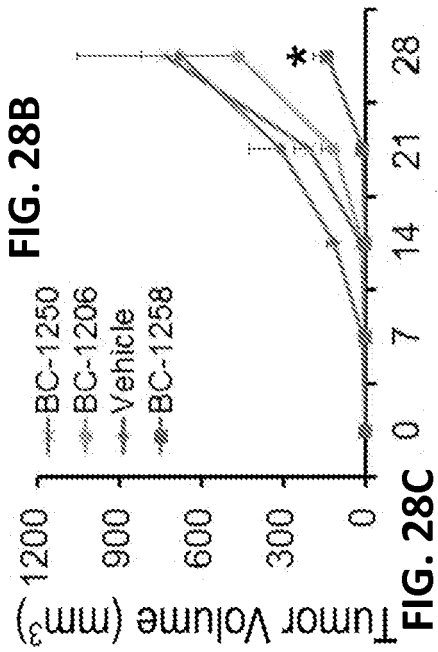


FIG. 28D

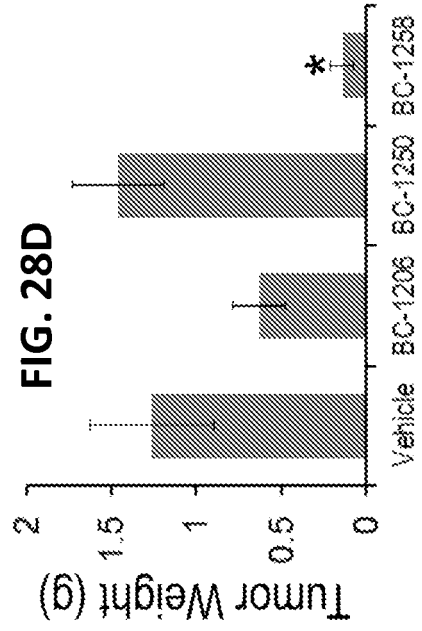


FIG. 28C

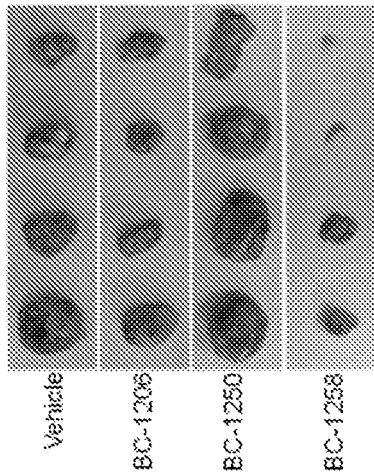


FIG. 28F

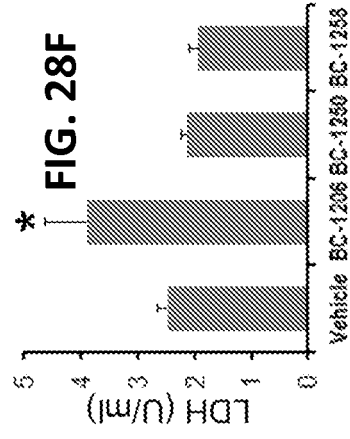


FIG. 28G

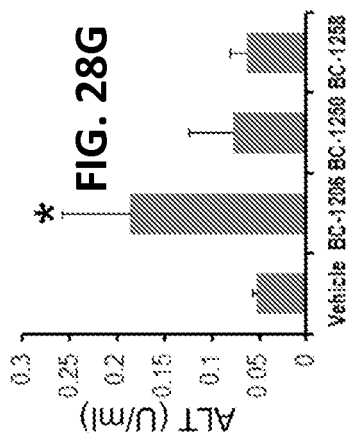


FIG. 28E

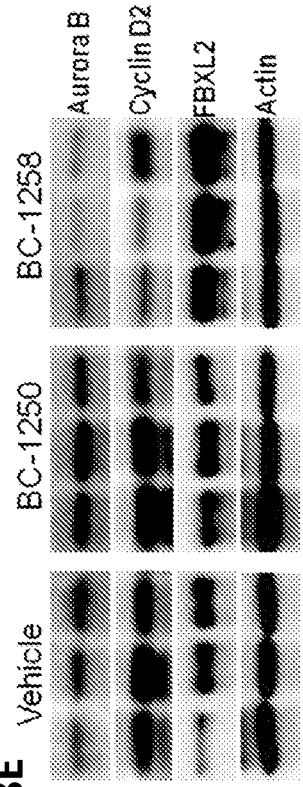


FIG. 28H

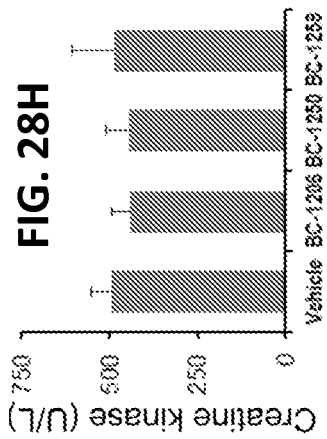
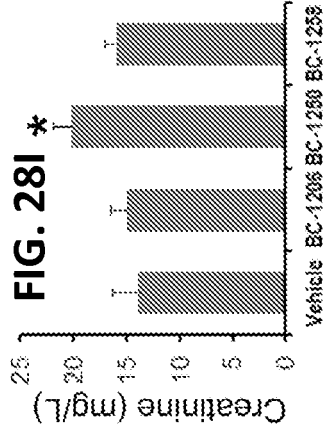
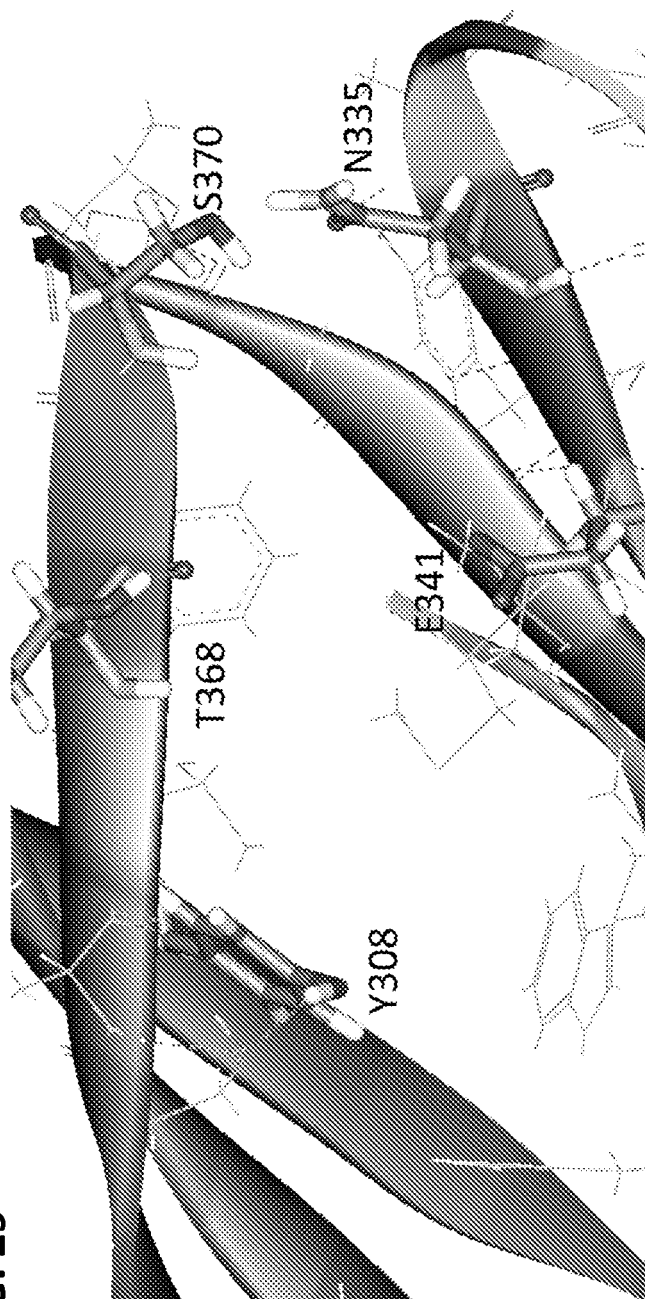


FIG. 28I *



ApaG drug binding motif

FIG. 29



FBXO3 amino acid Y308, N335, E341, T368 and S370 form a drug binding motif.

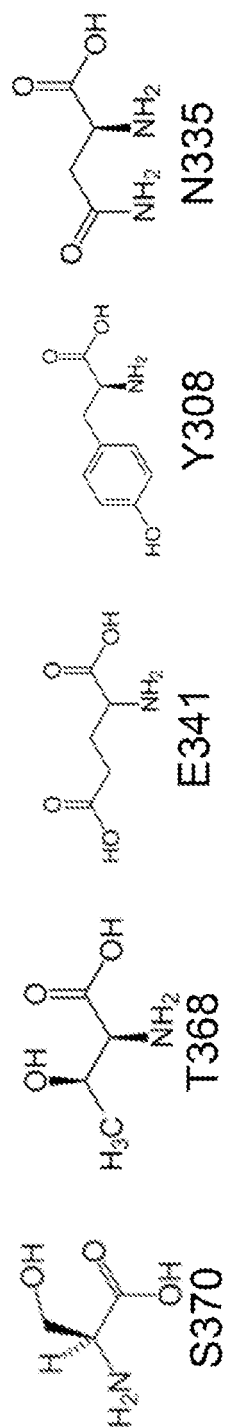
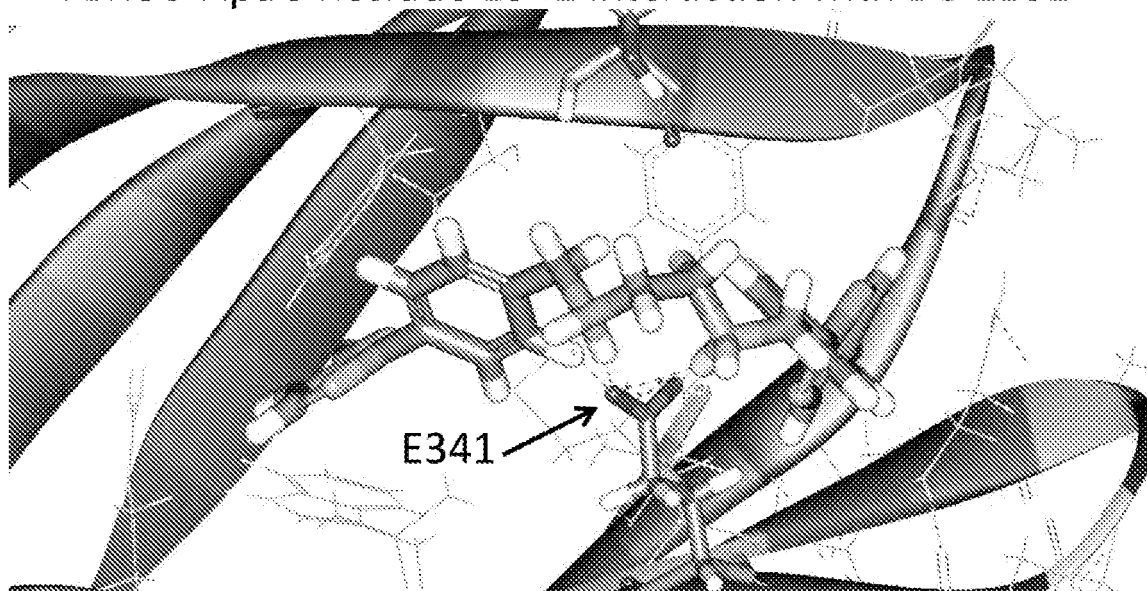
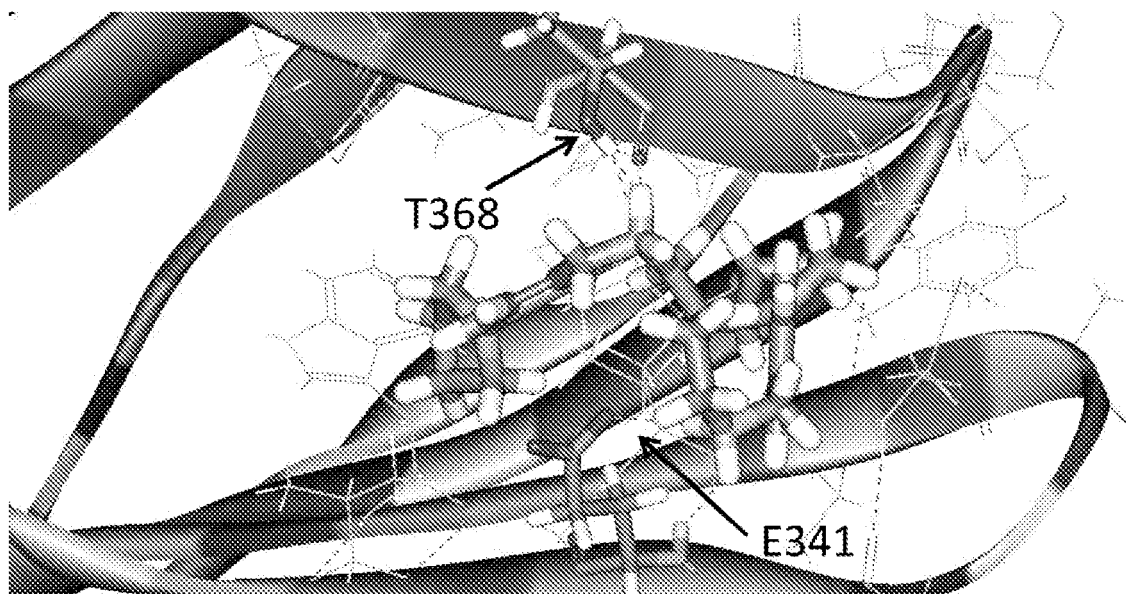


FIG. 30

FBXO3-ApaG Residue E341 interaction with BC-1261

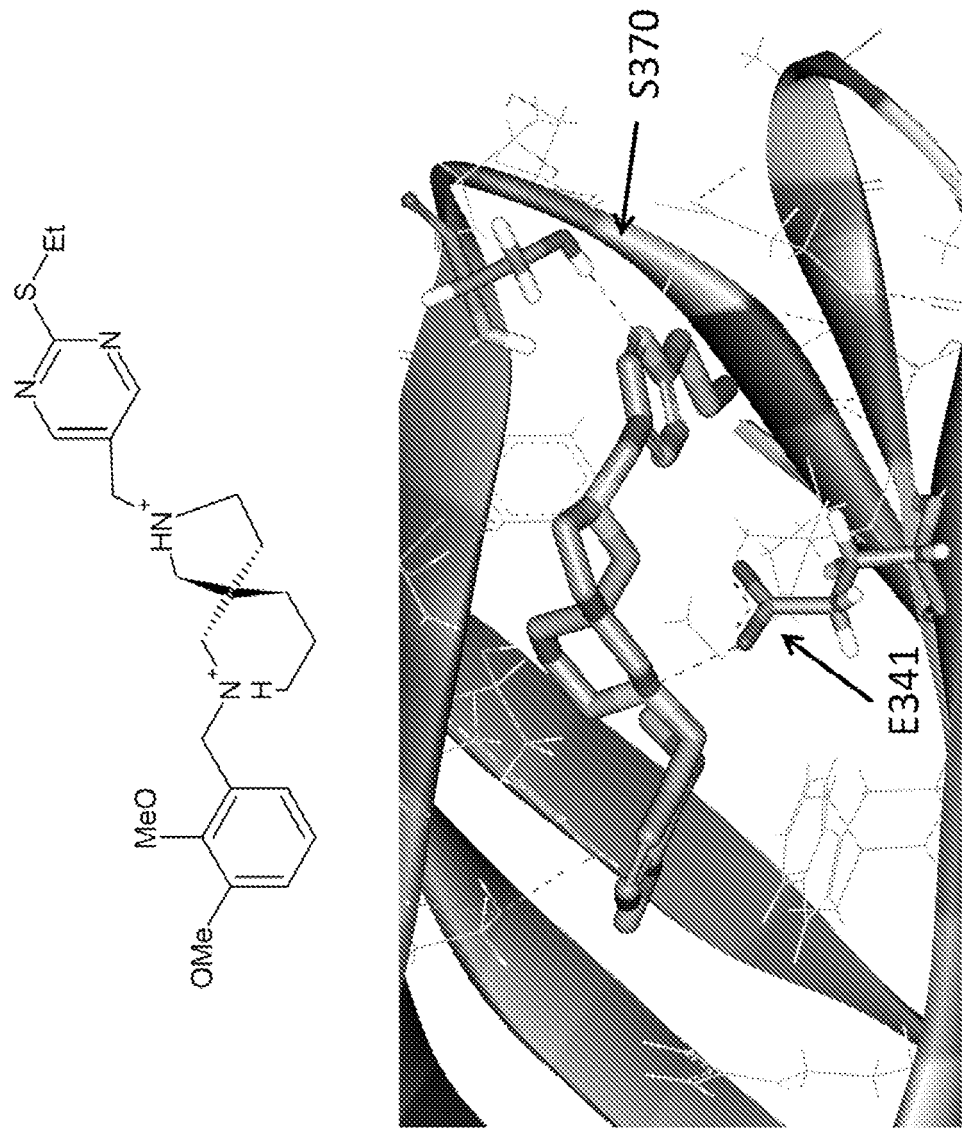


FBXO3-ApaG Residues E341 and T368 interaction with BC-1234



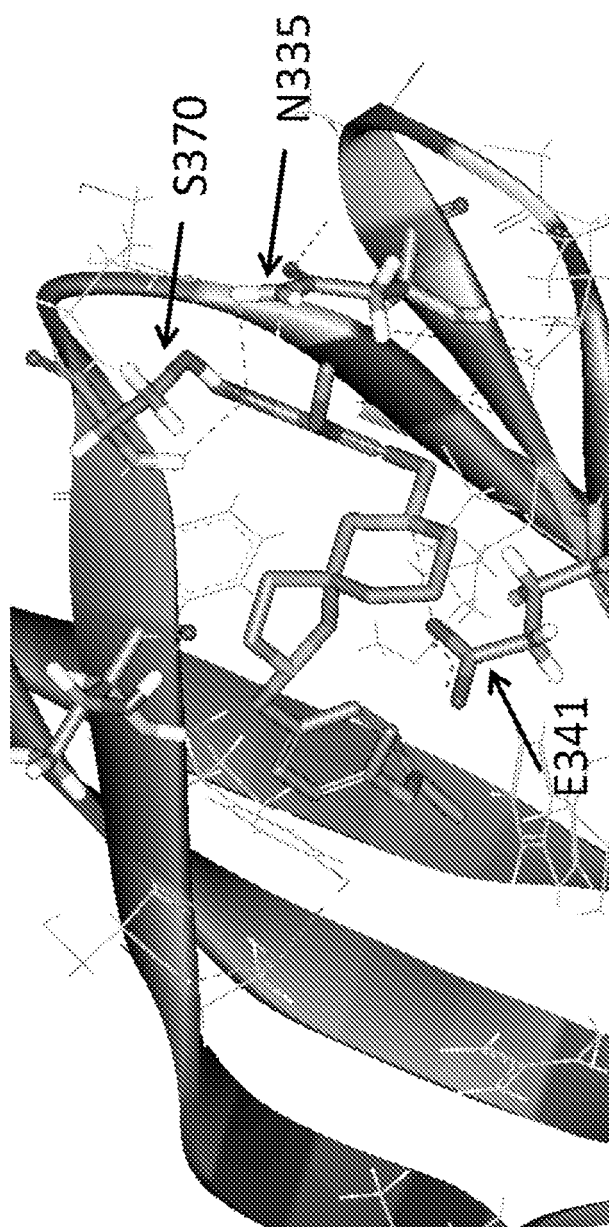
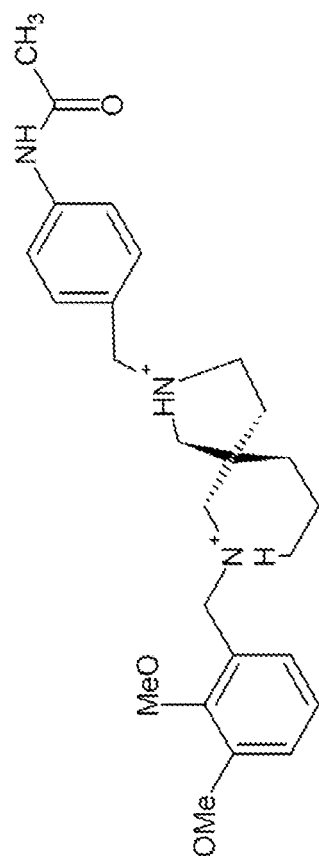
FBXO3-ApaG Residues E341 and T368 interaction with BC-1304

FIG. 31



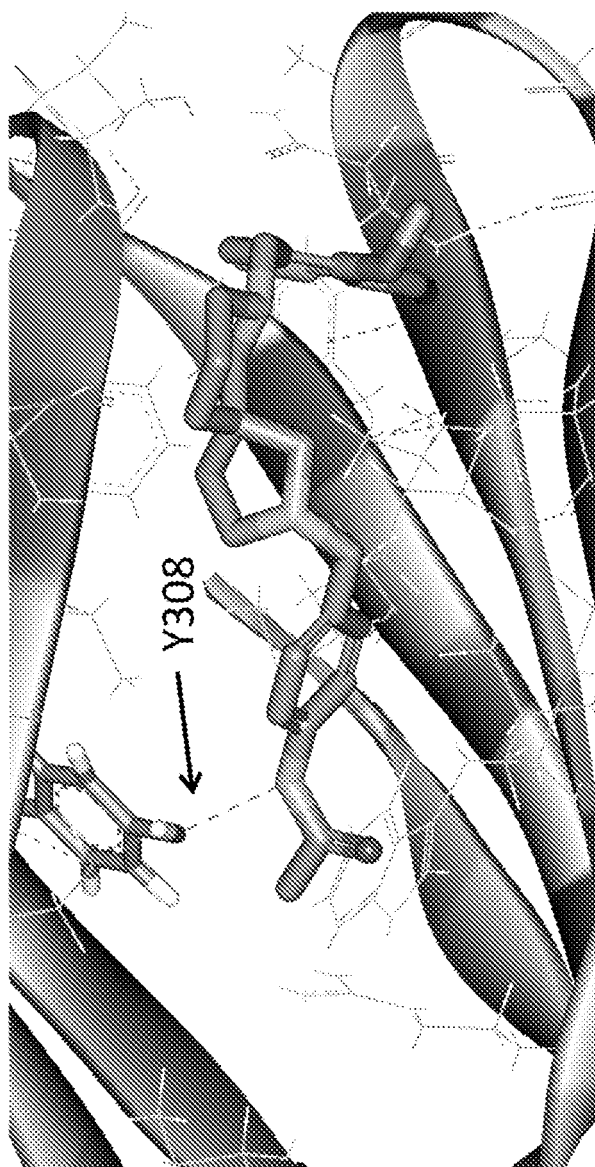
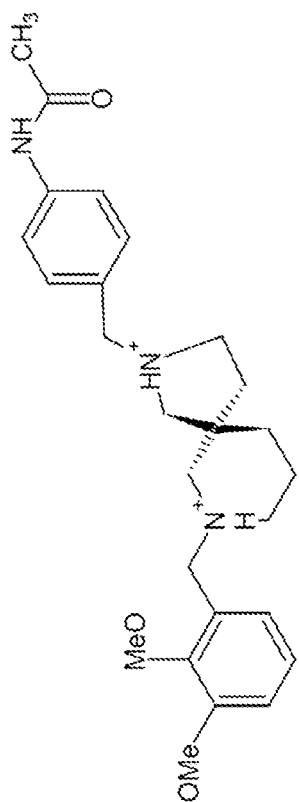
FBXO3-ApaG Residues Y308 with BC-1305

FIG. 32

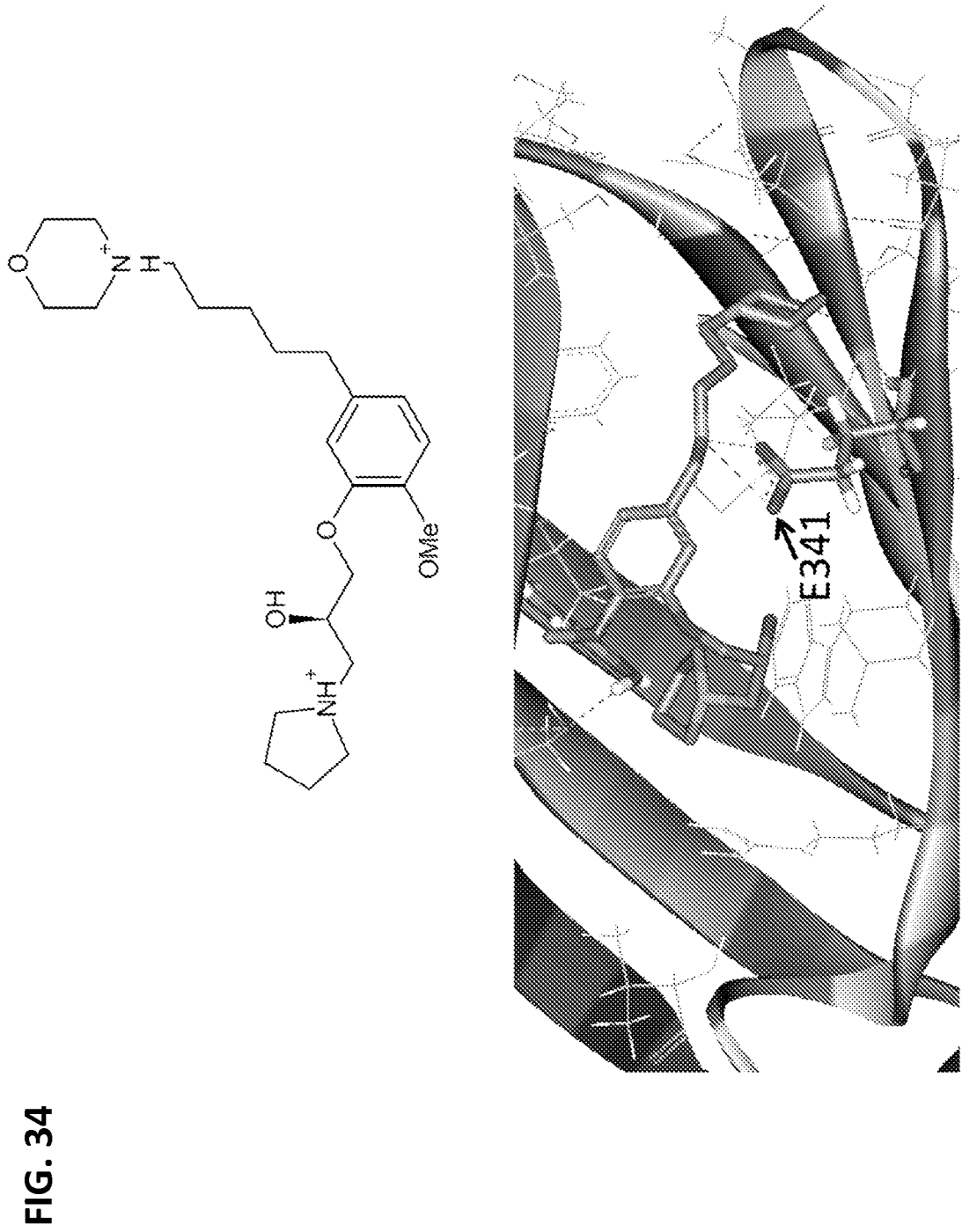


FBXO3-ApaG Residues Y308 with BC-1305 (Secondary position)

FIG. 33

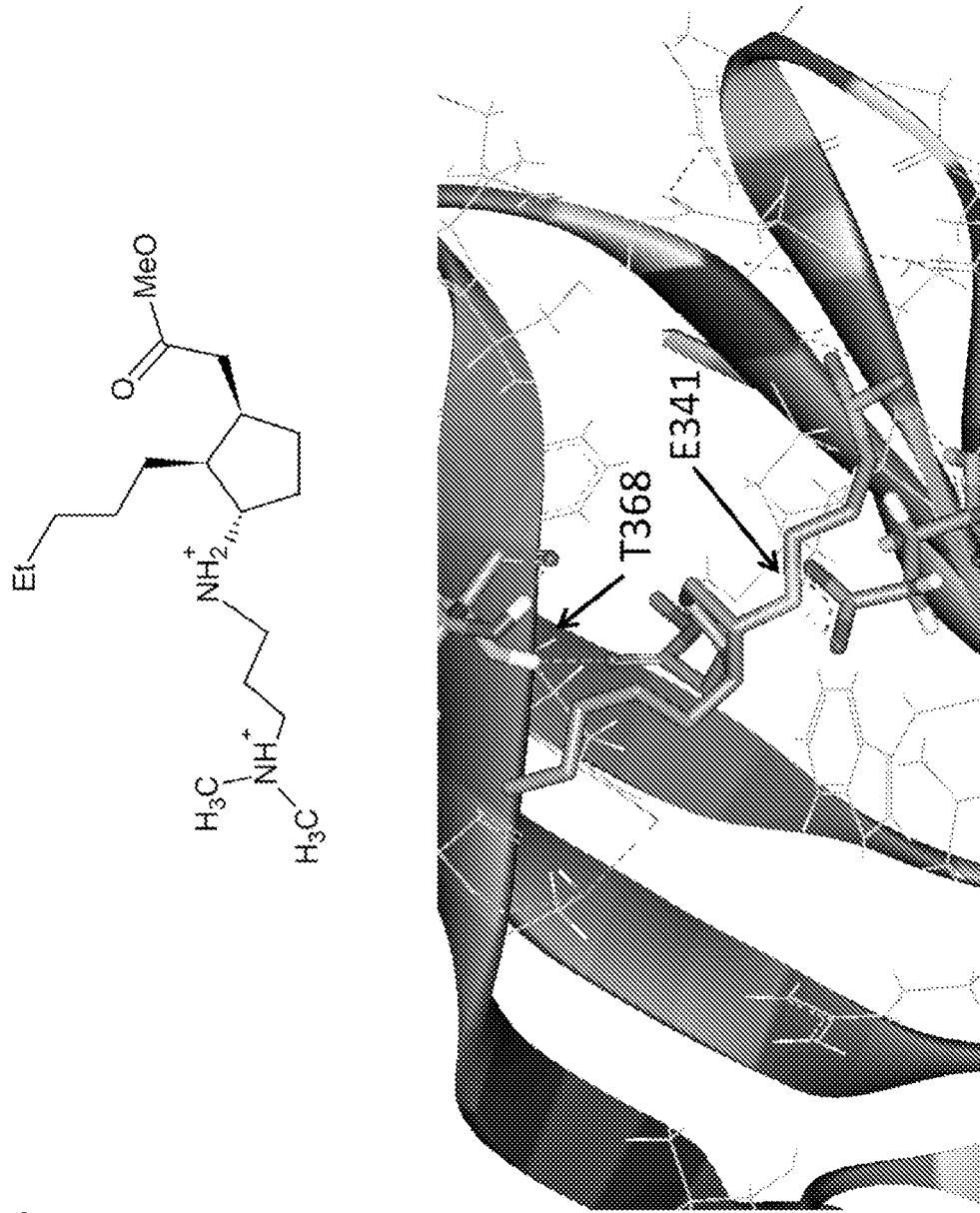


FBXO3-ApaG Residues E341 interaction with BC-1306

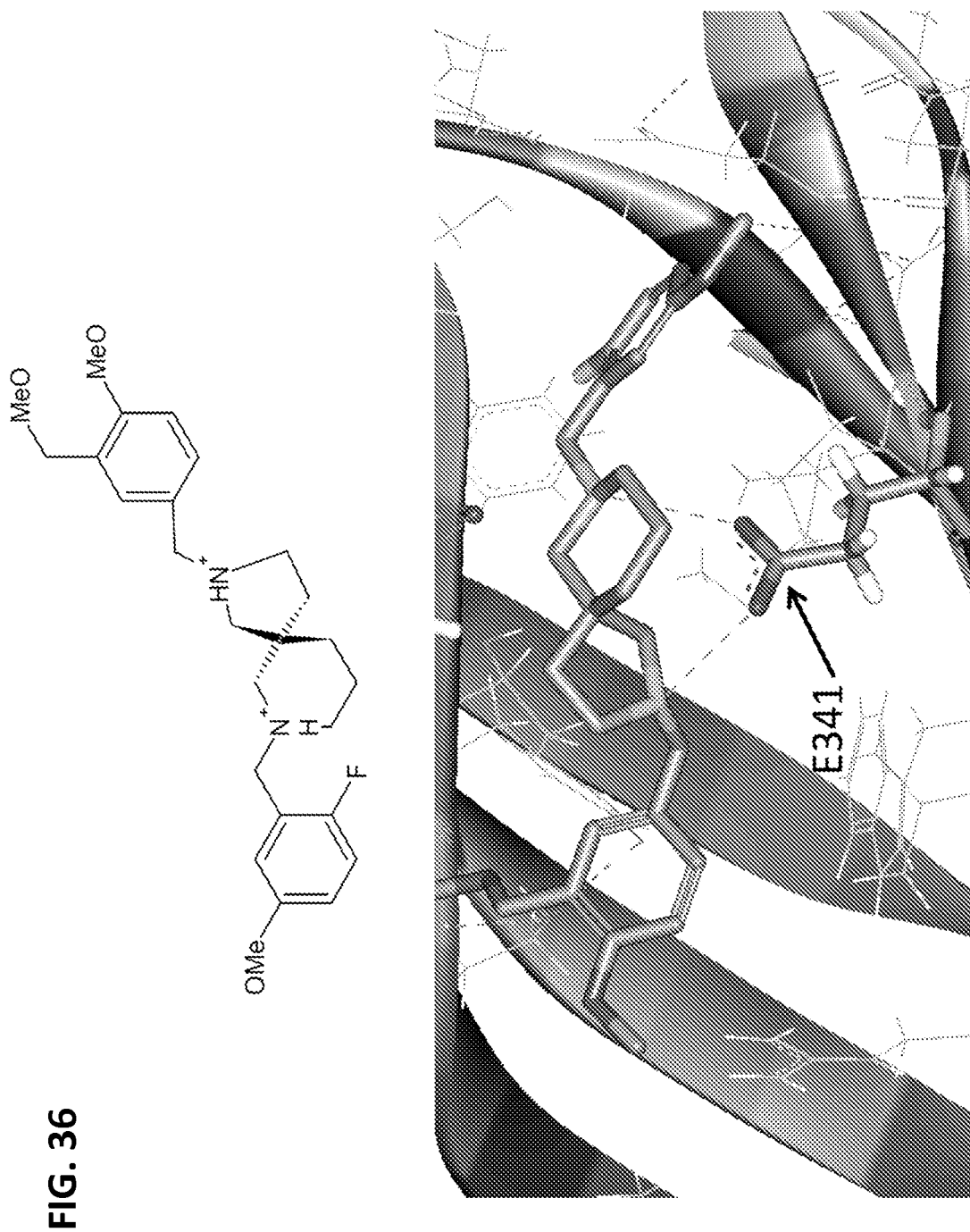


FBXO3-ApaG Residues E341 and T368 interaction with BC-1307

FIG. 35



FBXO3-ApaG Residues E341 interaction with BC-1308



FBXO3-ApaG Residues E341 interaction with BC-1309

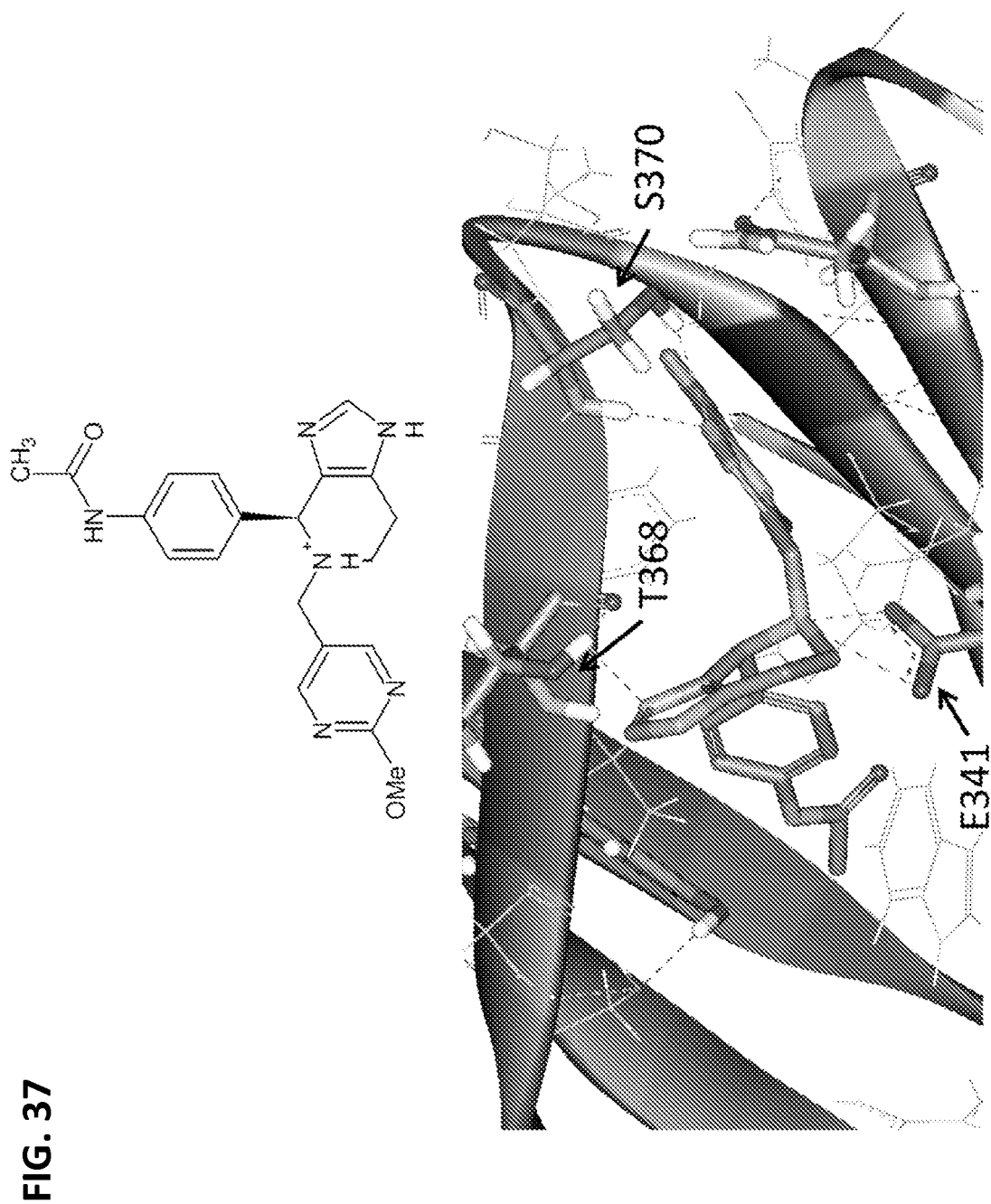


FIG. 38 Summary of In vitro Toxicity/off targeting experiments

Assay	BC-1215 % Inh.	BC-1261 % Inh.
CYP450, 2D6	51	28
CYP450, 3A4	74	46
Nitric Oxide Synthase, Neuronal (nNOS)	83	32
Adrenergic α 1, Non-Selective	55	-4
Adrenergic α 2, Non-Selective	50	36
Calcium Channel L-Type, Phenylalkylamine	72	-2
Opiate μ (OP3, MOP)	44	10
Potassium Channel HERG	55	8
Serotonin (5-Hydroxytryptamine) 5-HT2	57	31
Serotonin (5-Hydroxytryptamine) 5-HT2B	84	20
Serotonin (5-Hydroxytryptamine) 5-HT2C	61	37
Serotonin (5-Hydroxytryptamine) 5-HT4	49	19
Sodium Channel, Site 2	103	43
Transporter, Dopamine (DAT)	81	25
Transporter, Norepinephrine (NET)	86	51
Transporter, Serotonin (5-Hydroxytryptamine) (SERT)	58	6
Histamine H2	84	85
	15/109	2/109

Out of 109 assays tested, BC1215 generates 15 hits (>50% inhibition of activity), whereas BC-1261 only generates 2 hits