

FIG. 1

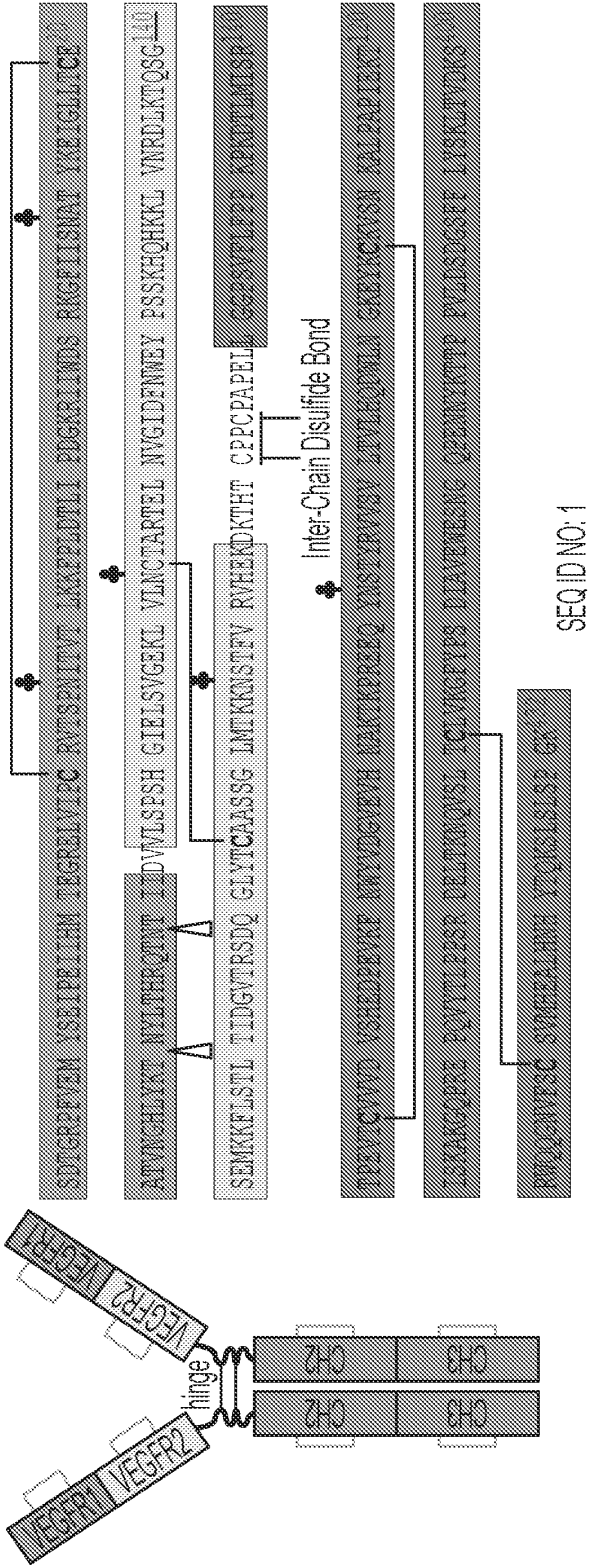
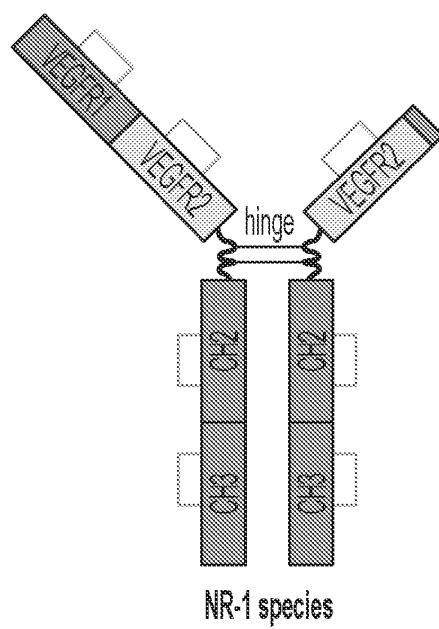


FIG. 2



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FIG. 3

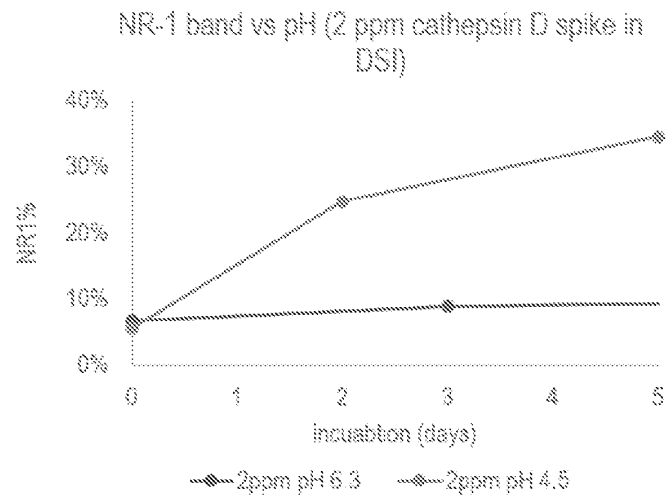


FIG. 4

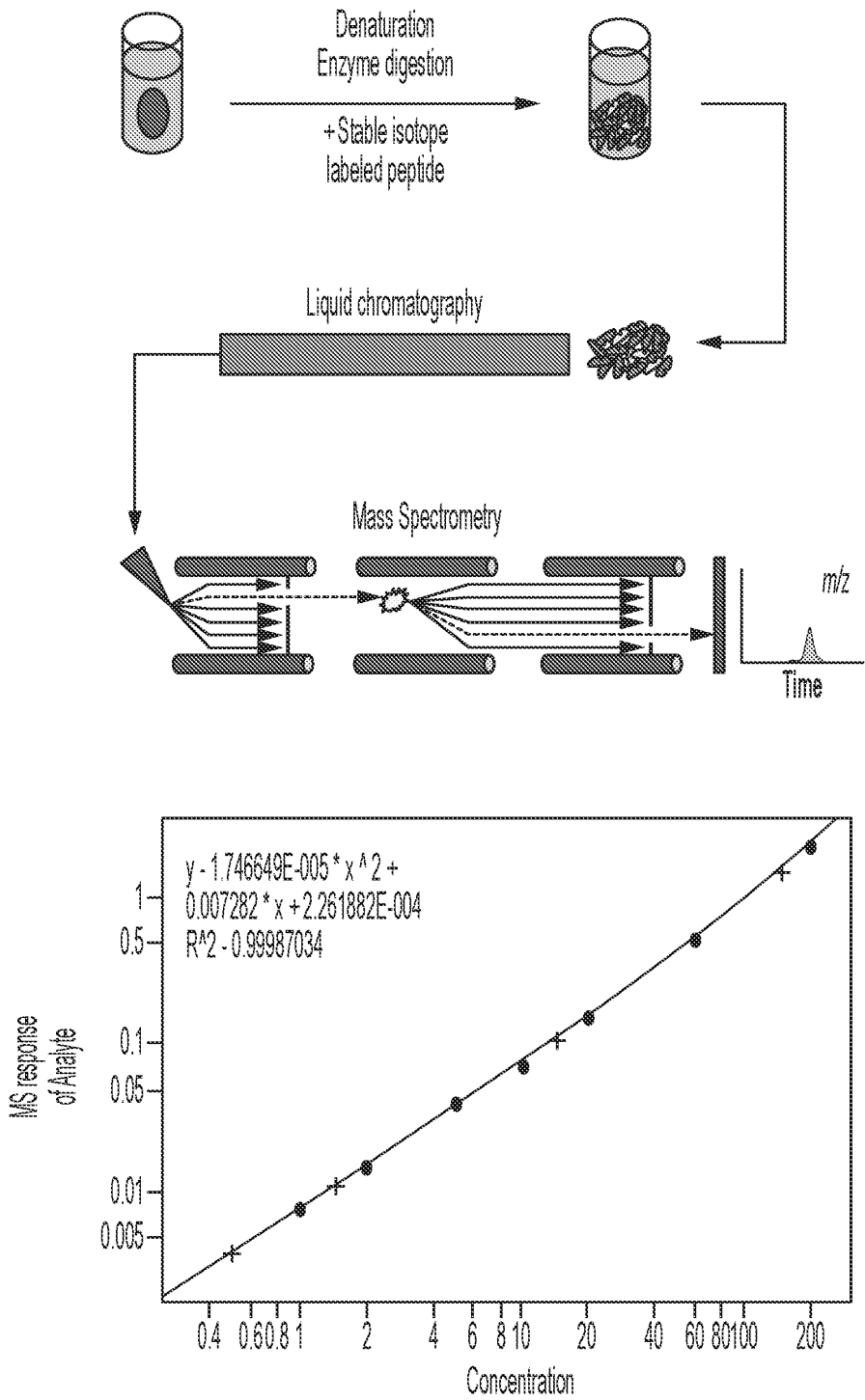


FIG. 5

Method	LC-MRM-MS absolute quantitation
Targets	Cathepsin D
Matrix	VEGF Trap
Processing	Direct enzymatic digestion with Lys-C under non-reduced condition
Sample consumption	50 µg of protein
Dynamic range	0.5 – 200 ppm (1 ppm = 1 ng HCP / mg drug)
QC	LLOQ: 0.5 ppm, LQC: 1.5 ppm, MQC: 15 ppm, HQC: 150 ppm
Instrument time	32 min per sample

LC-MRM-MS (Liquid Chromatography-Multiple Reaction Monitoring-Mass Spectrometry)

FIG. 6

Lot Number	Material Full Name	Site	Cathepsin D concentration-duplicate 1 (ppm)	Cathepsin D concentration-duplicate 2 (ppm)	Average Cathepsin D concentration (ppm) *
I	VEGF Trap DSI	A	1.46	1.38	1.42
II	VEGF Trap DSI	A	1.10	1.23	1.21
III	VEGF Trap DSI	A	1.48	1.47	1.47
I	VEGF Trap DSI	B	0.82	0.85	0.84
II	VEGF Trap DSI	B	1.00	1.08	1.04
III	VEGF Trap DSI	B	0.87	0.86	0.86
IV	VEGF Trap DS	A	BLLQ	BLLQ	BLLQ
V	VEGF Trap DS	A	BLLQ	BLLQ	BLLQ
VI	VEGF Trap DS	A	BLLQ	BLLQ	BLLQ
VII	VEGF Trap DS	A	BLLQ	BLLQ	BLLQ
IV	VEGF Trap DS	B	BLLQ	BLLQ	BLLQ
V	VEGF Trap DS	B	BLLQ	BLLQ	BLLQ
VI	VEGF Trap DS	B	BLLQ	BLLQ	BLLQ

* Levels were calculated as the mean of the duplicate measurements.

FIG. 7

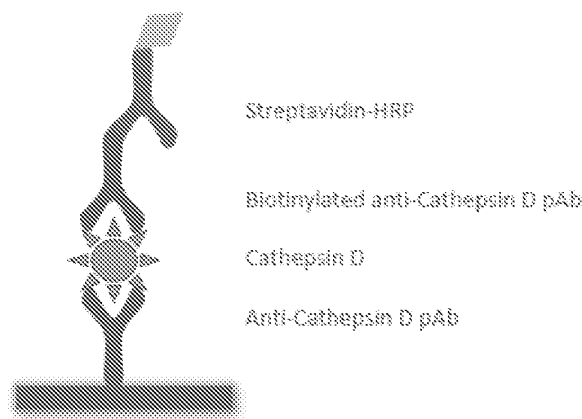


FIG. 8

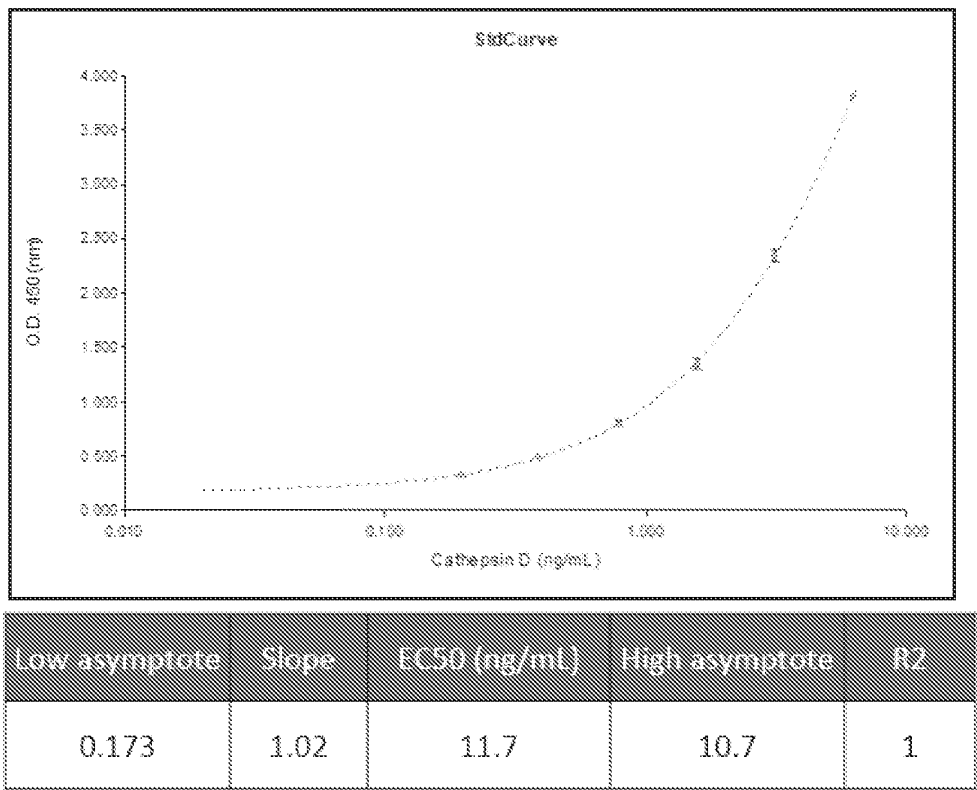


FIG. 9

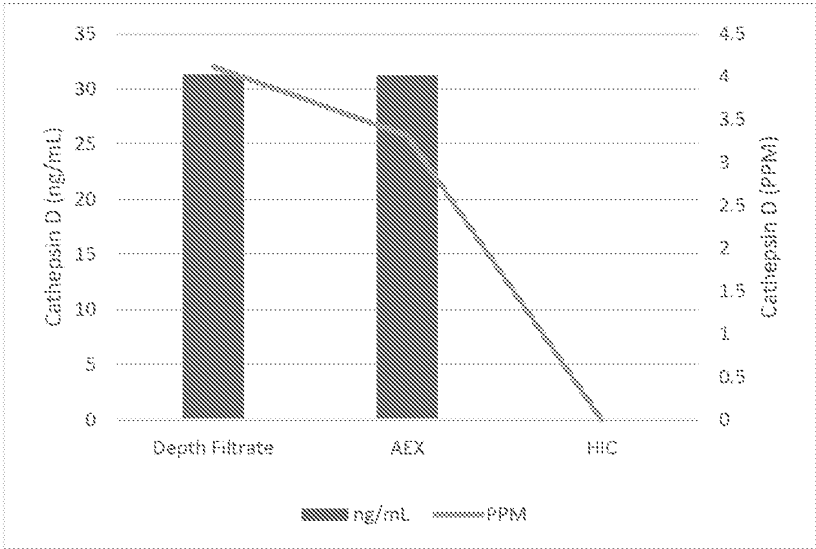


FIG. 10

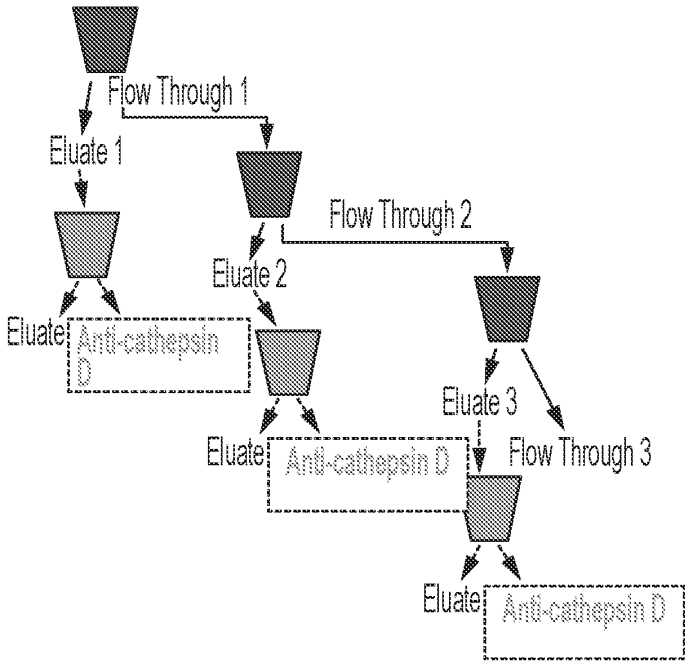


FIG. 11

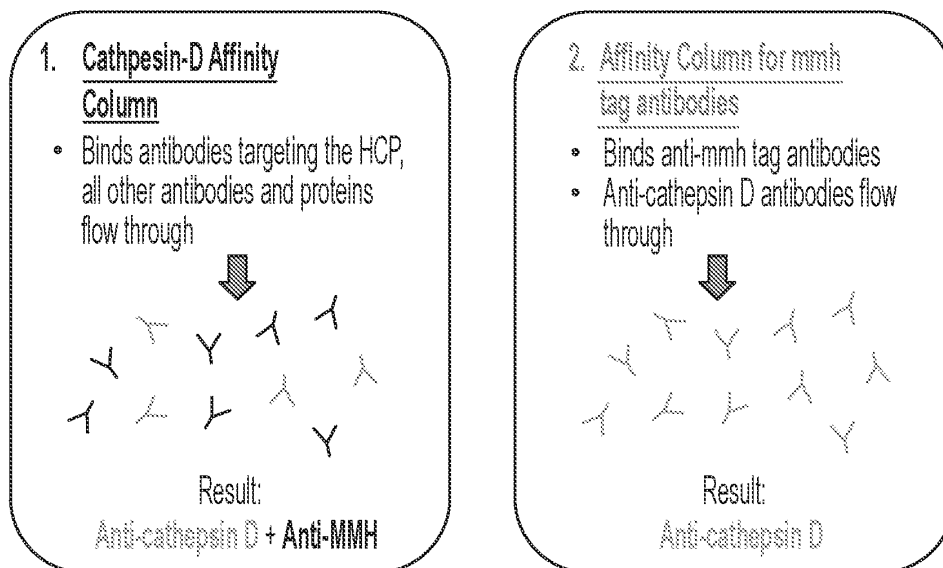


FIG. 12

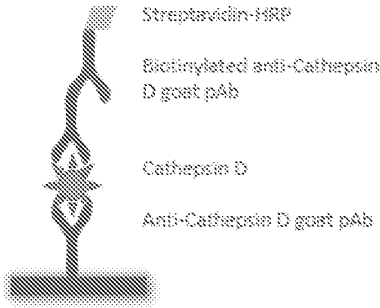
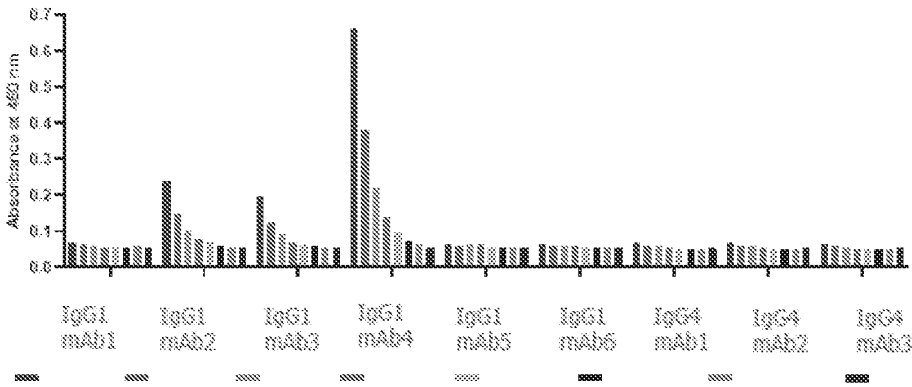


FIG. 13



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FIG. 14

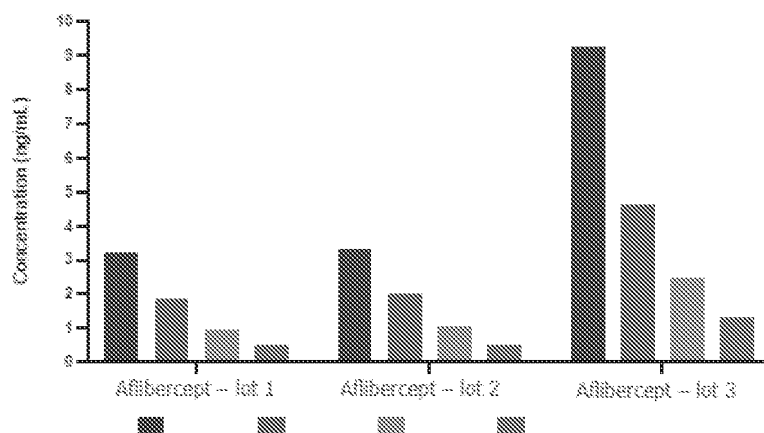


FIG. 15A

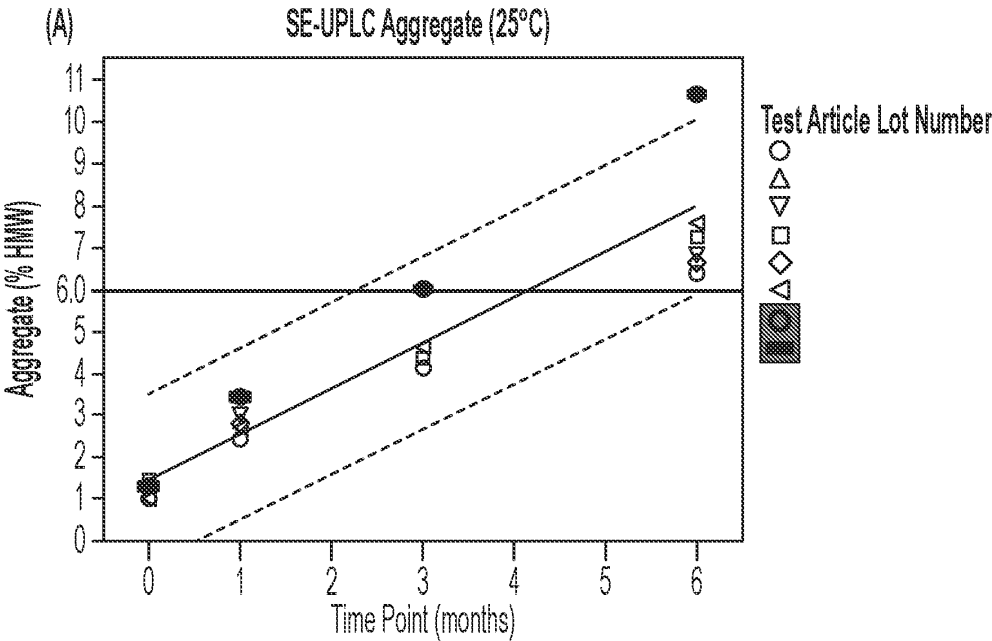
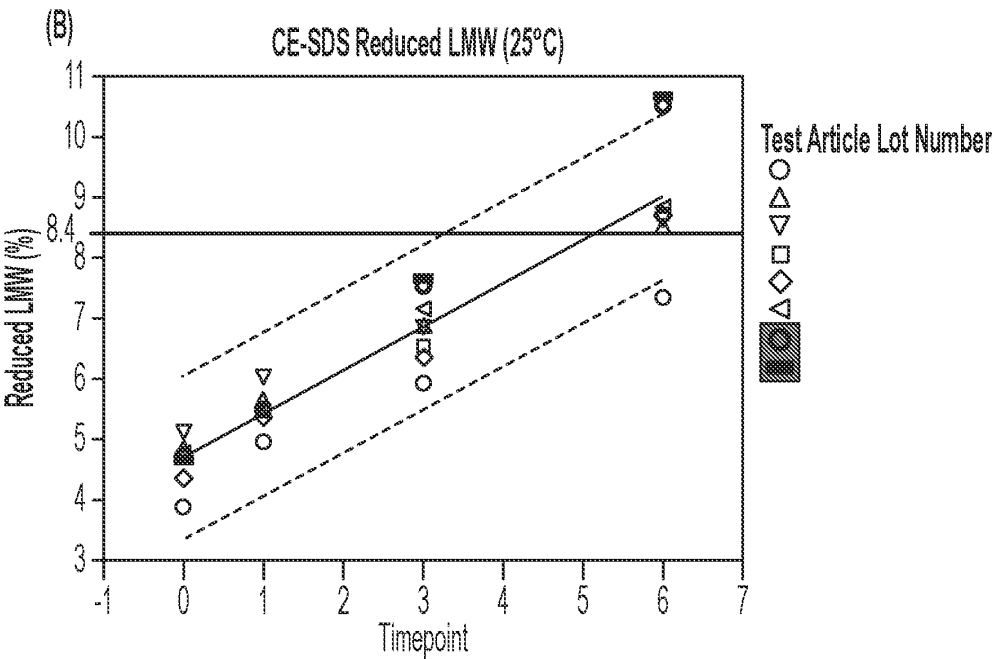
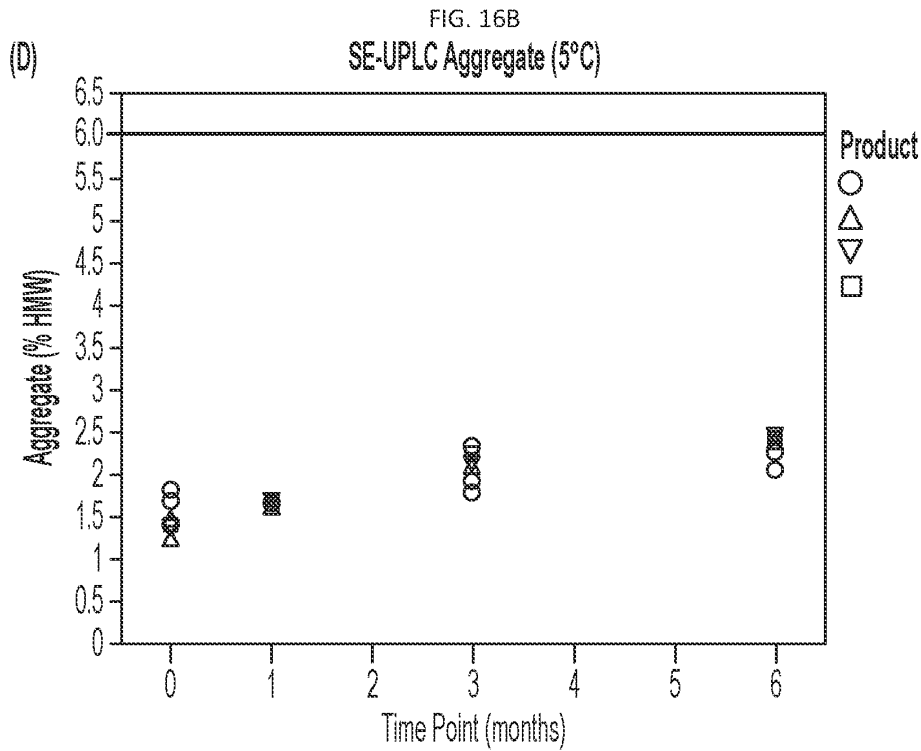
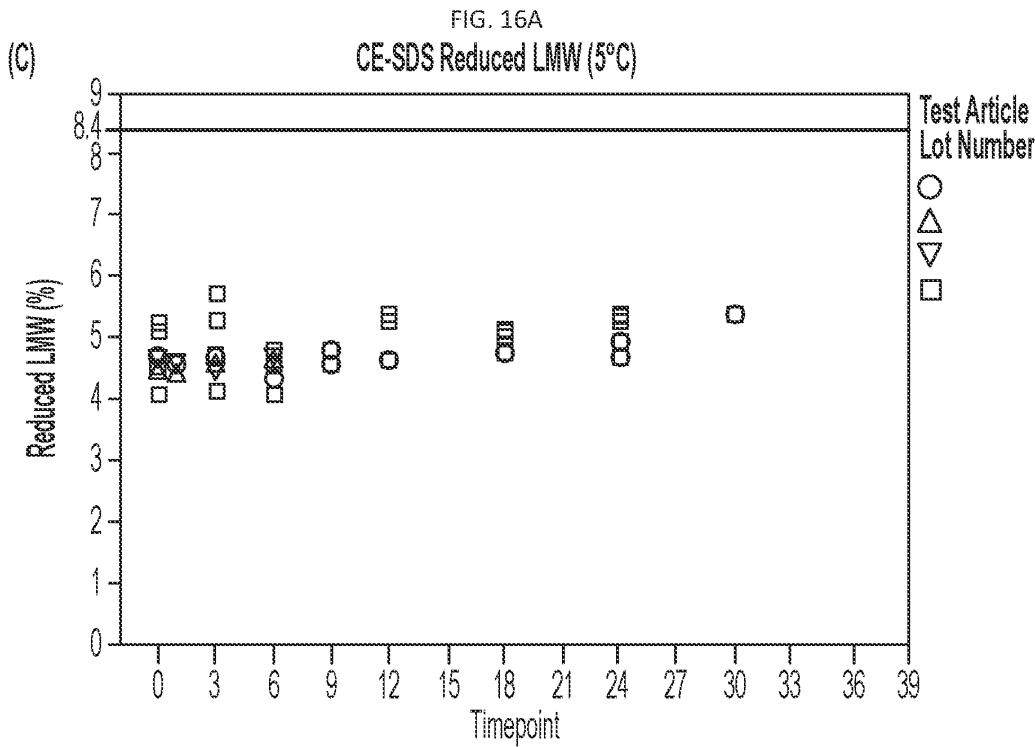


FIG. 15B





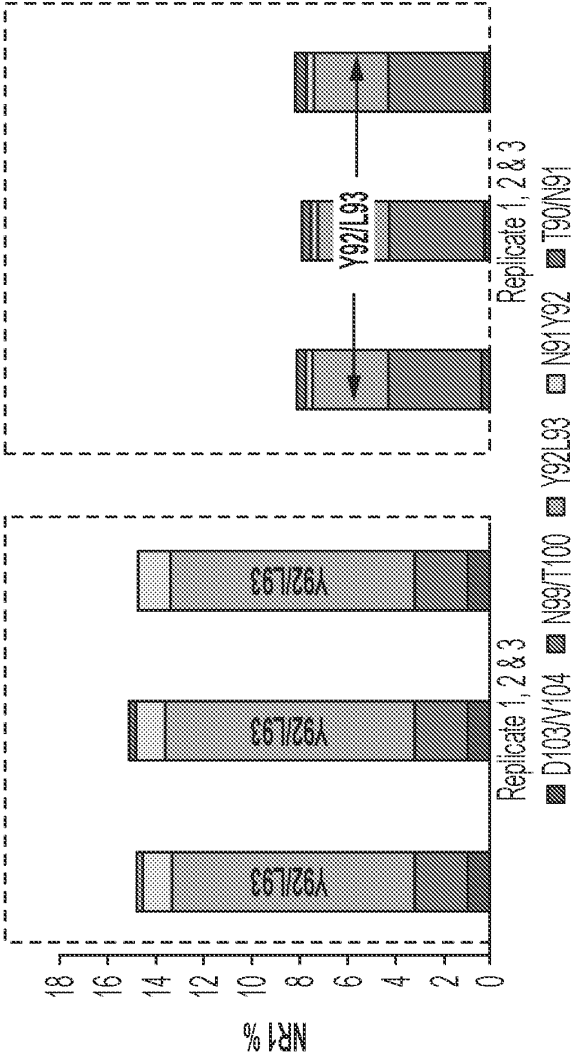
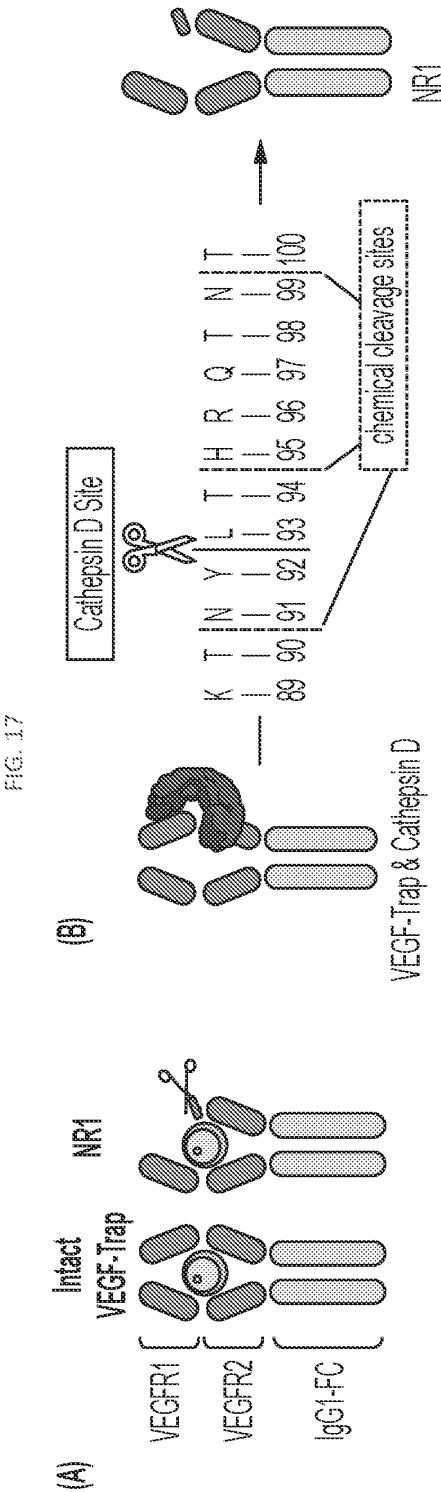


FIG. 19

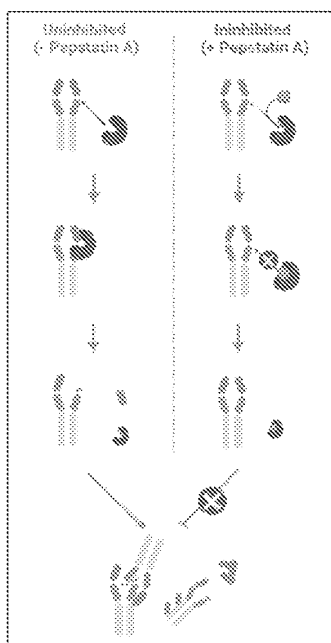


FIG. 20

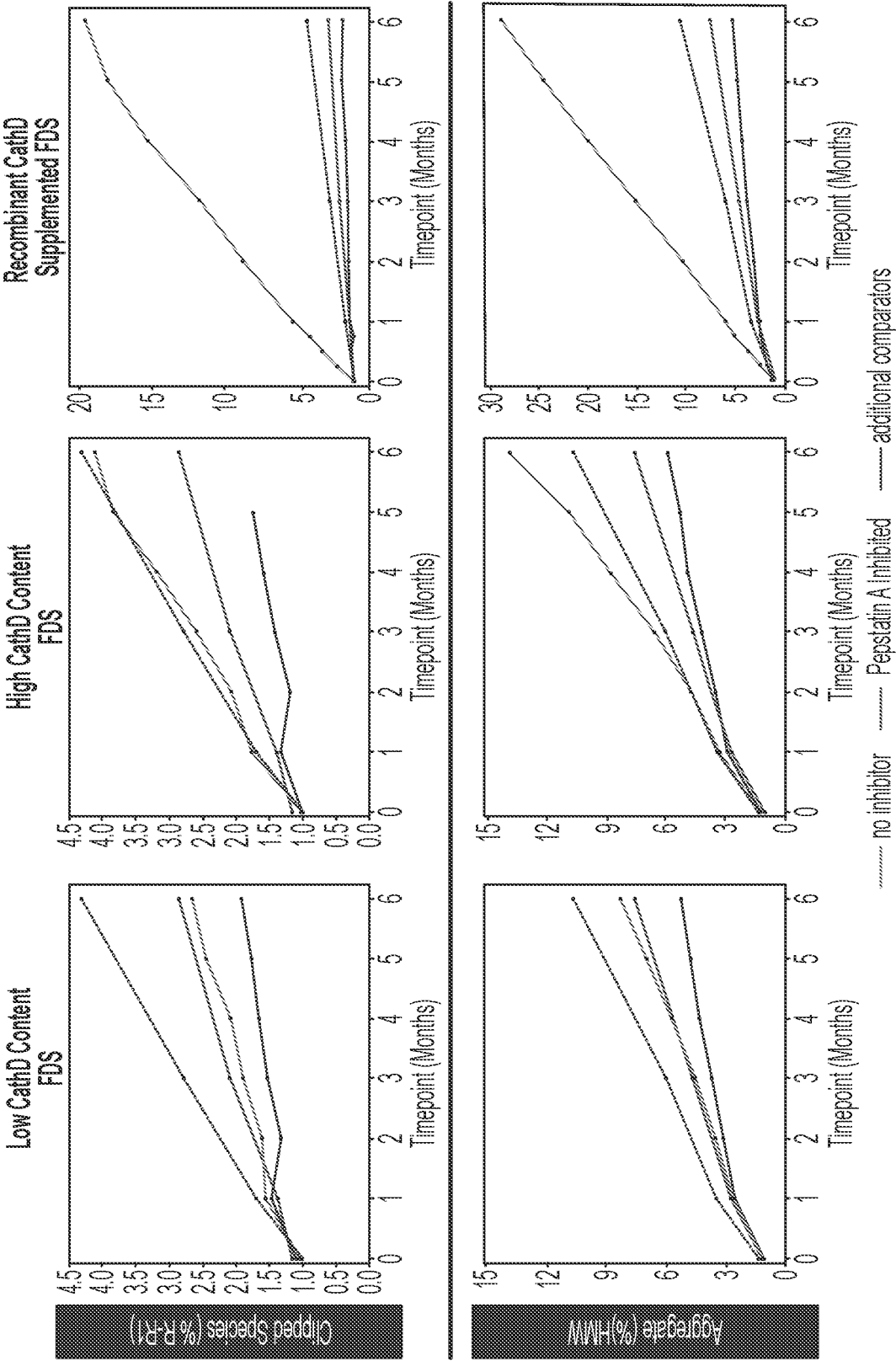
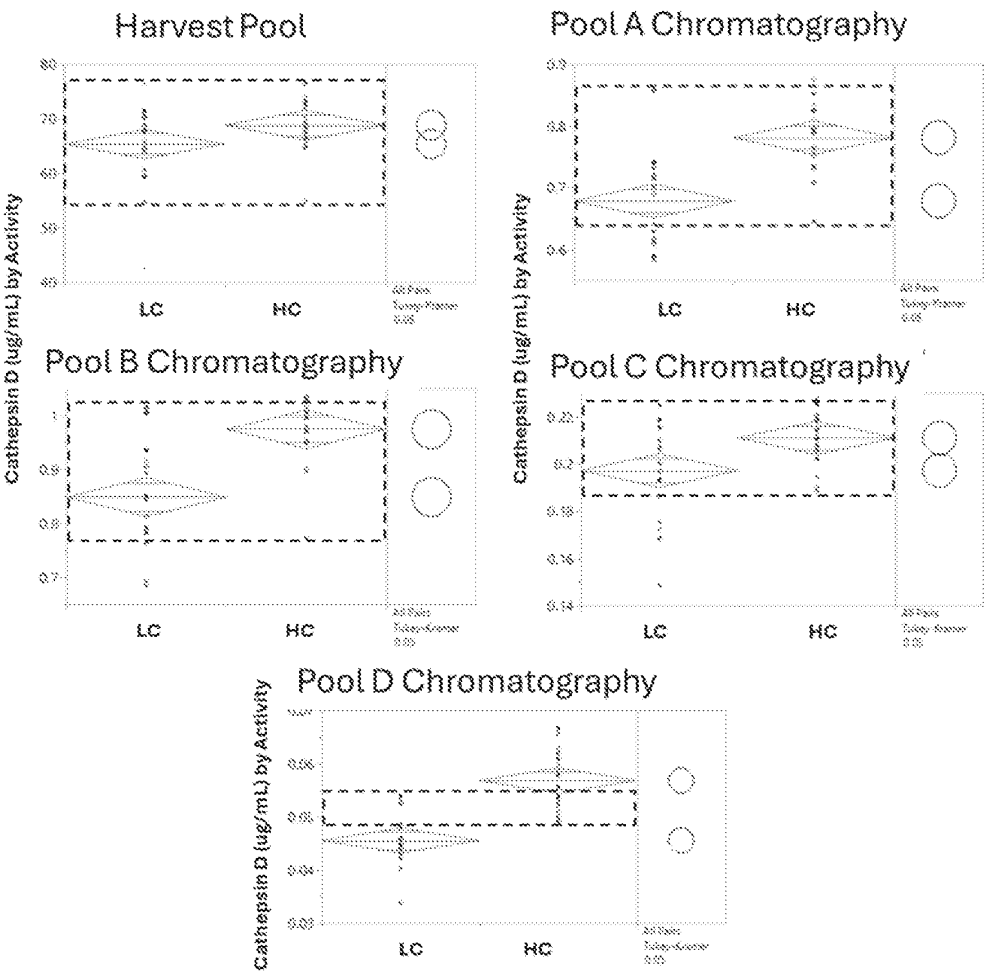


FIG. 21



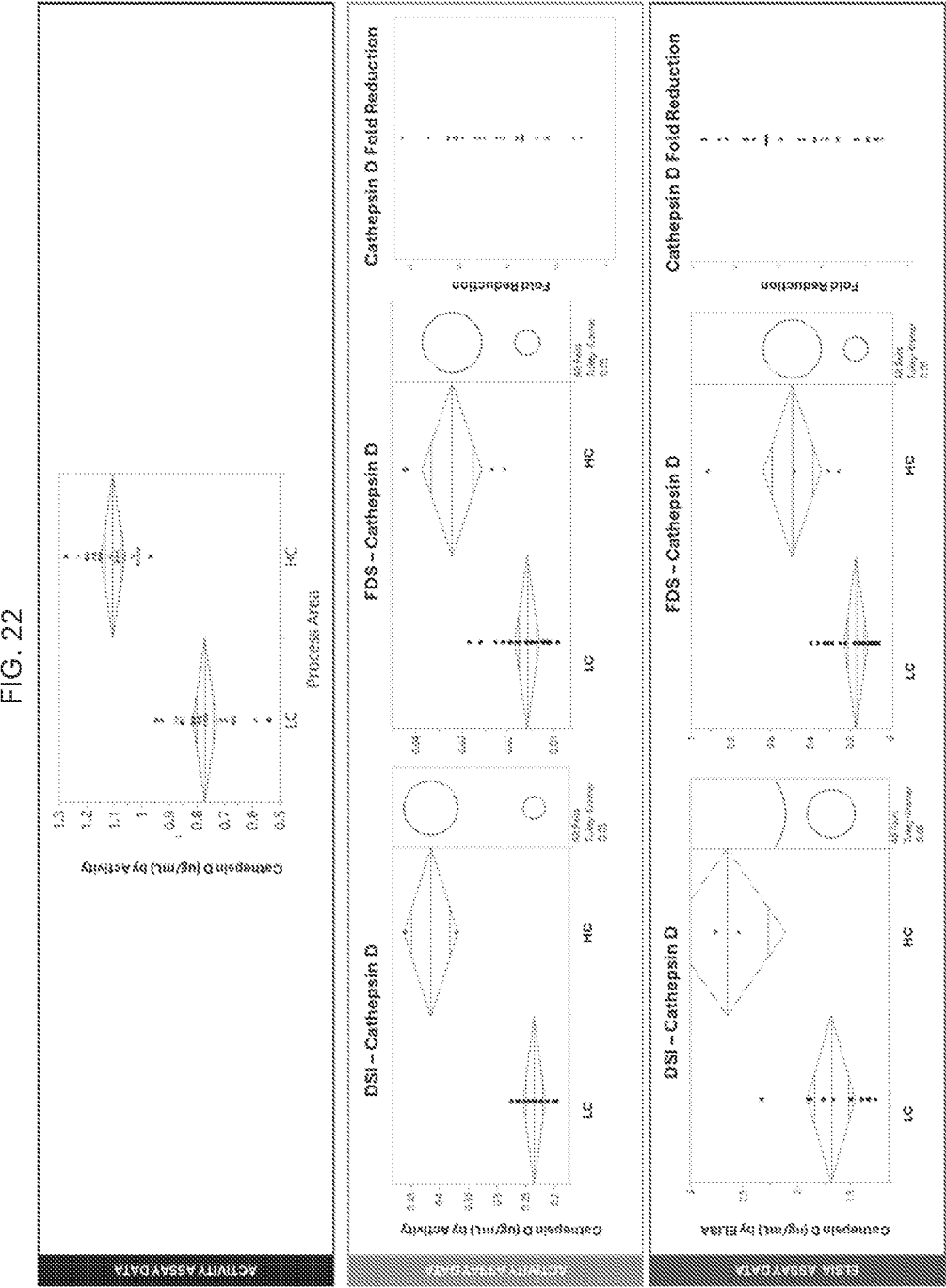


FIG. 23

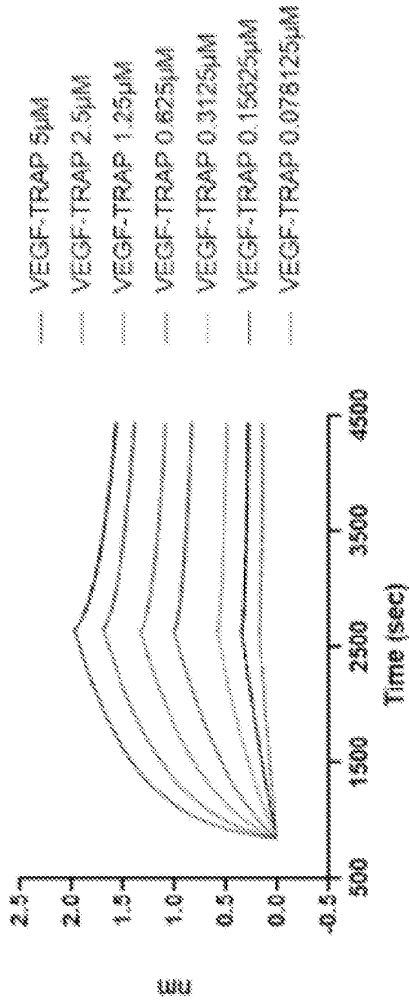


FIG. 24

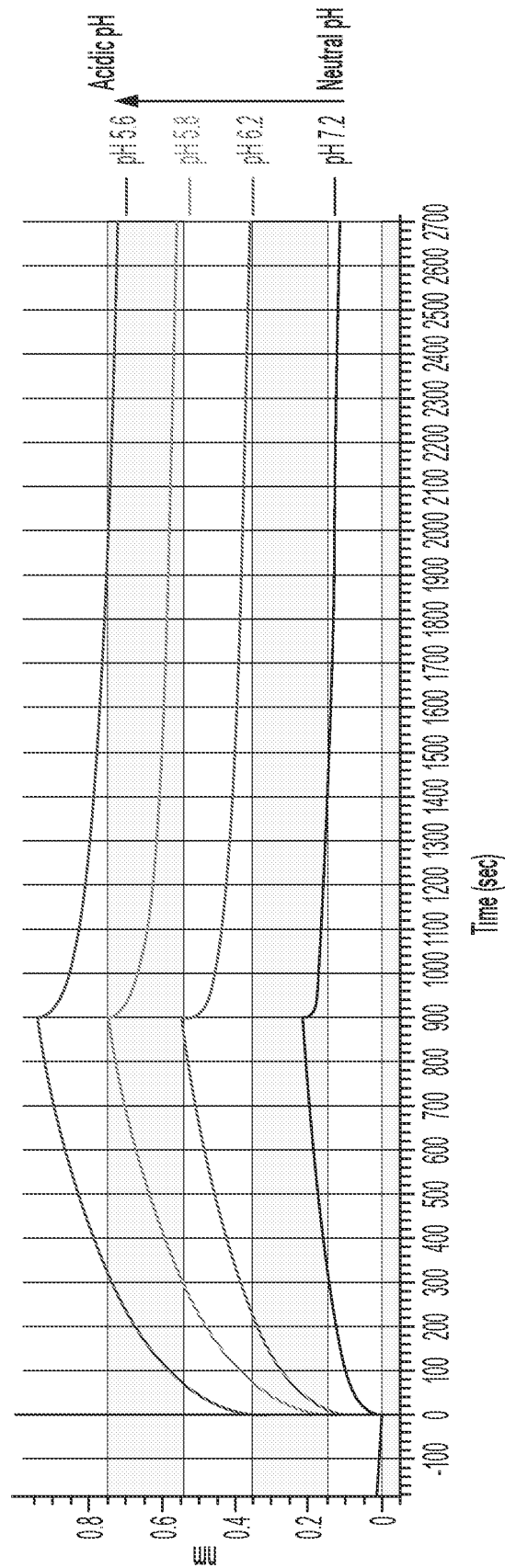
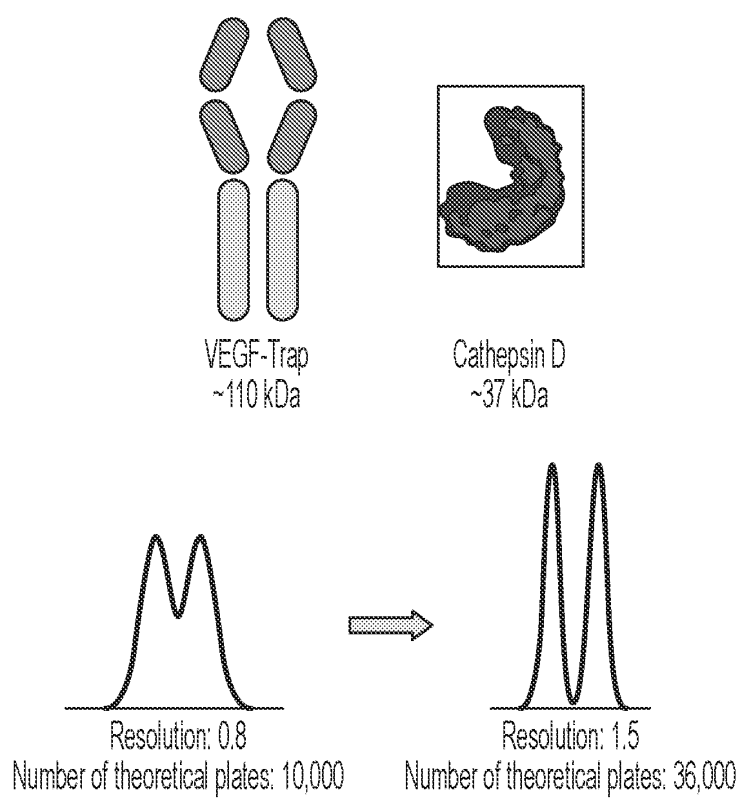
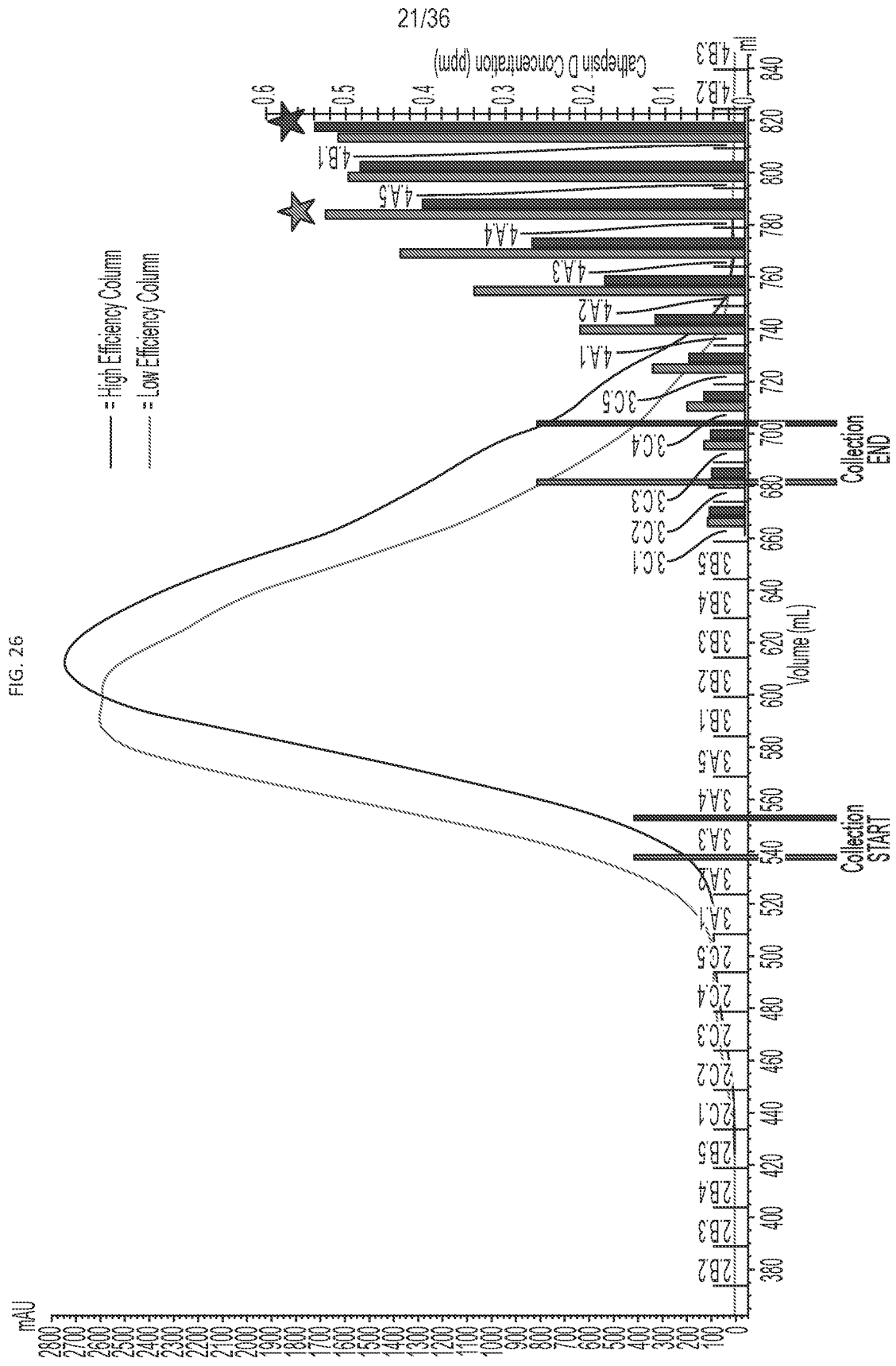


FIG. 25





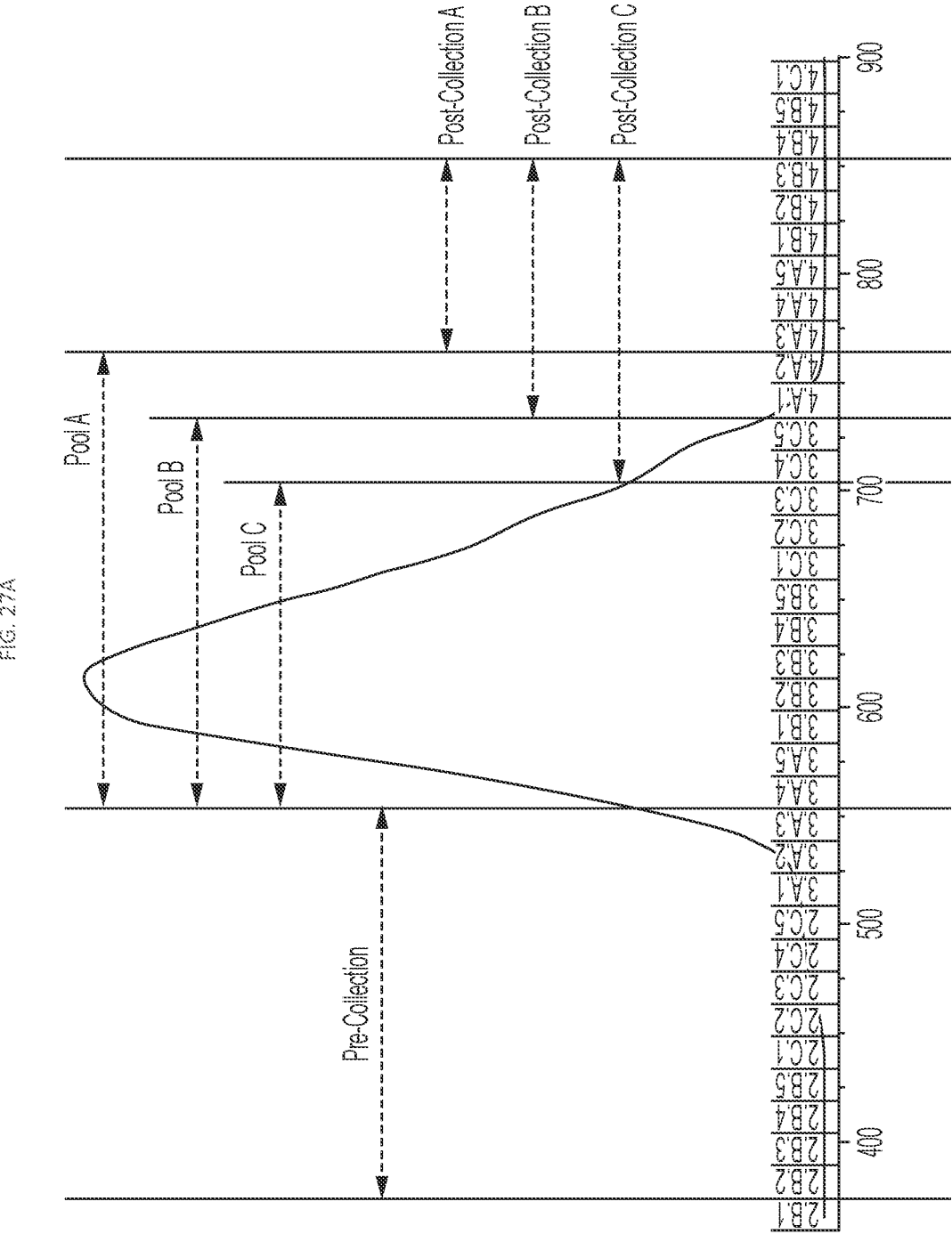


FIG. 27B

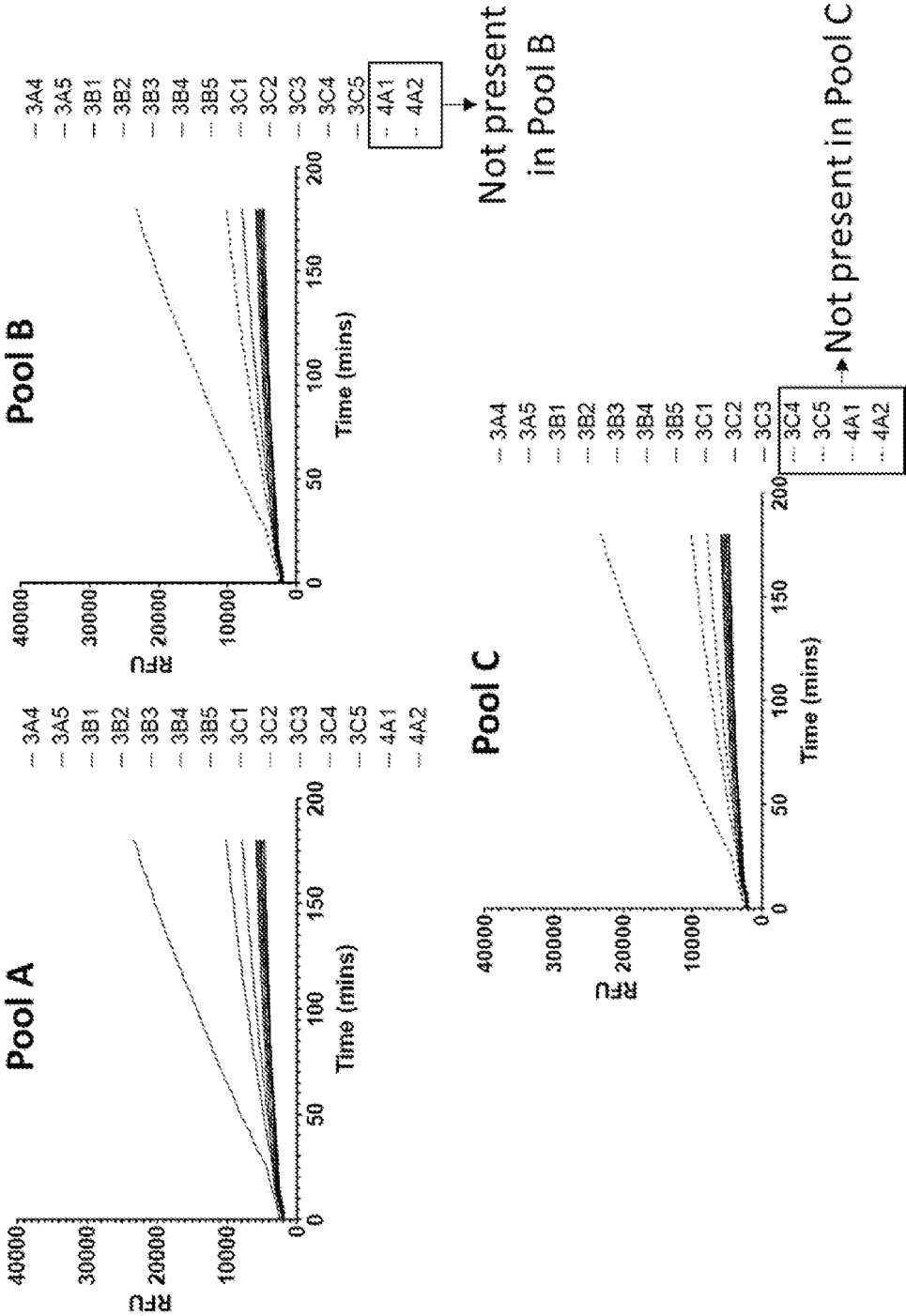
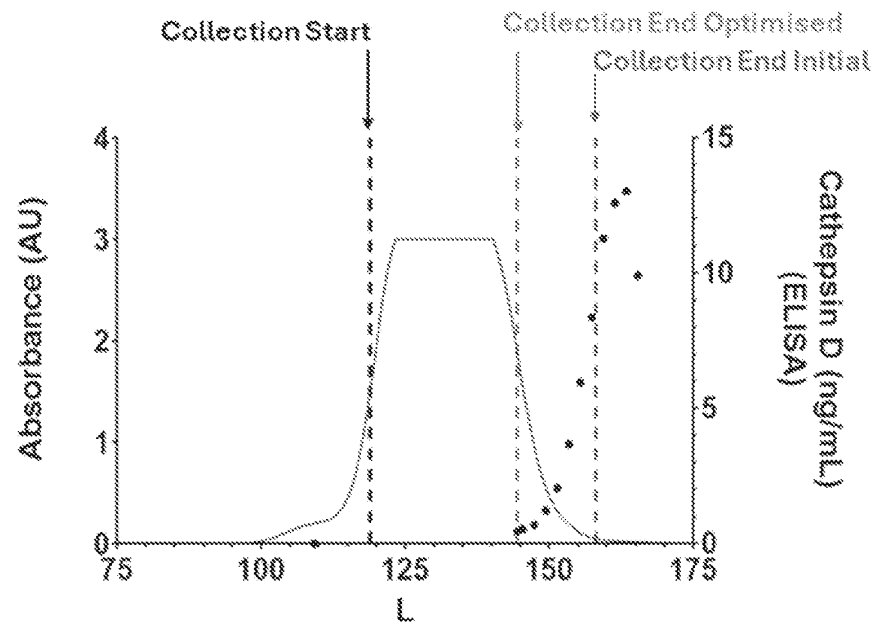


FIG. 28



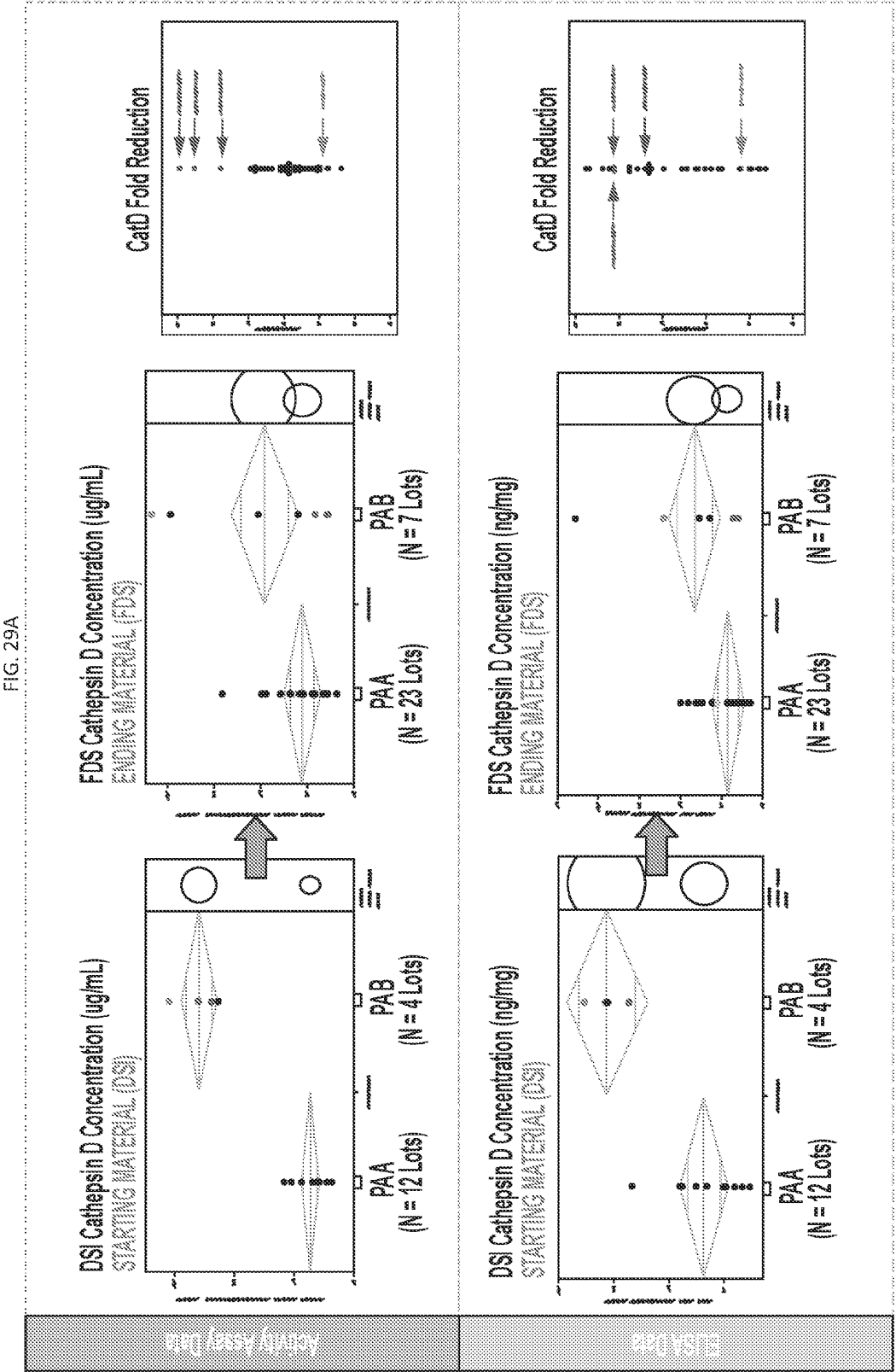


FIG. 29B

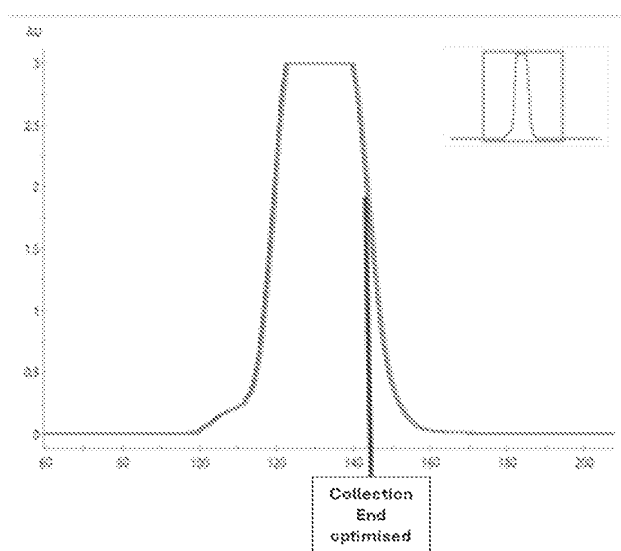


FIG. 29C

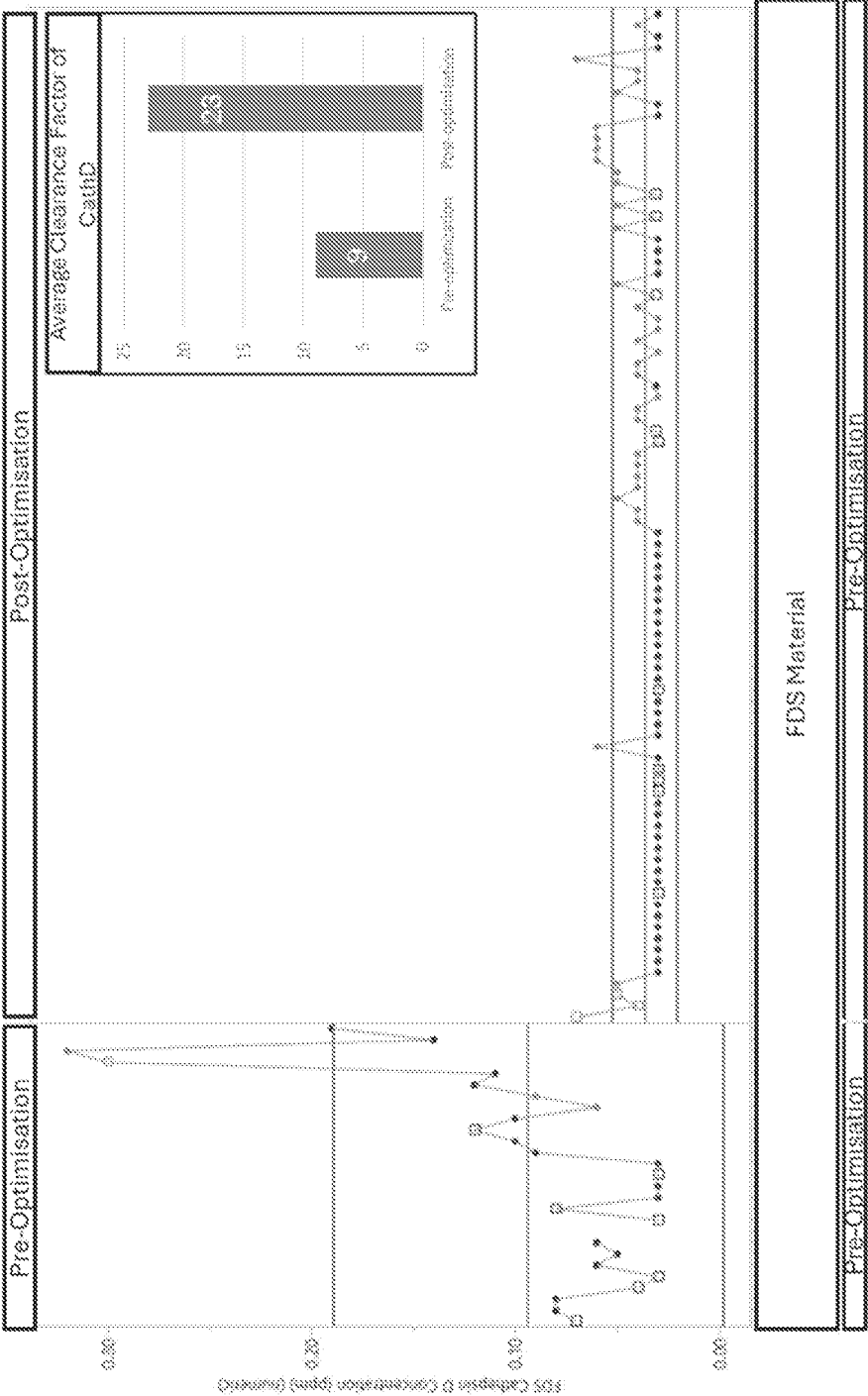


FIG. 30A

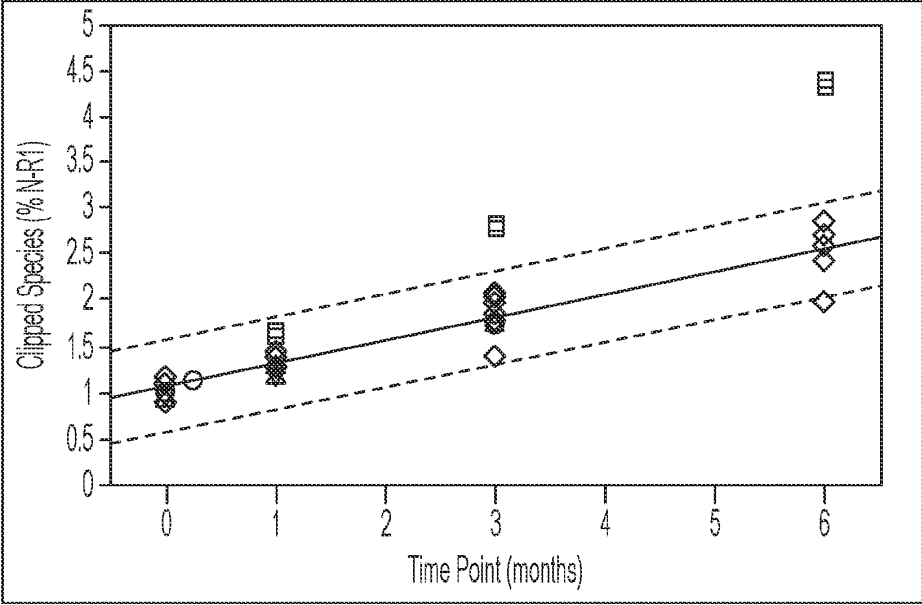
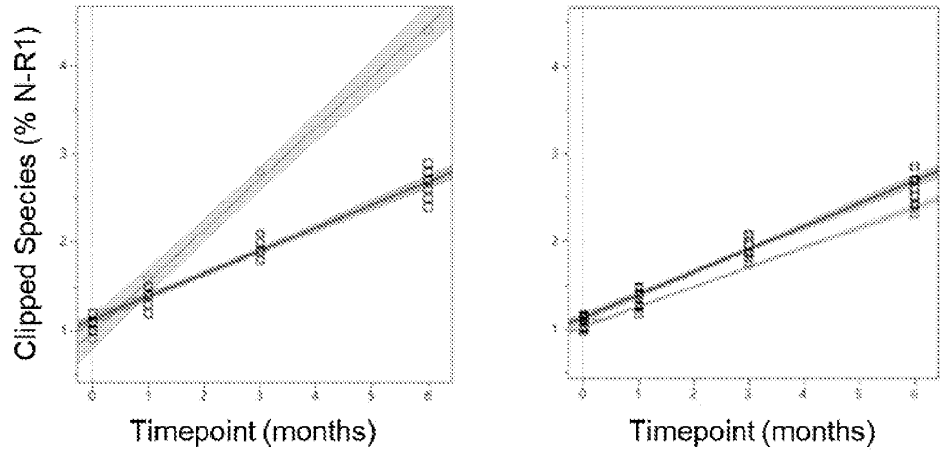


FIG. 30B

Clipped Species Formation at 25°C



Red: Pre-optimisation,
Green: Post Optimisation,
Black: Comparators

FIG. 31

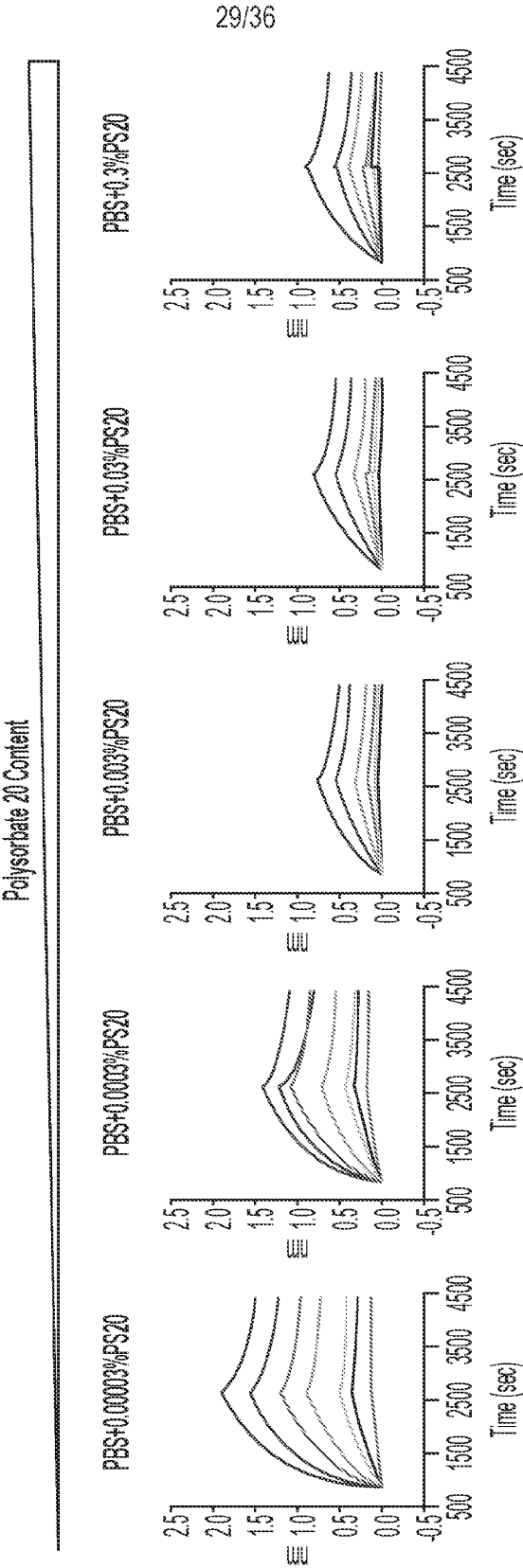


FIG. 32

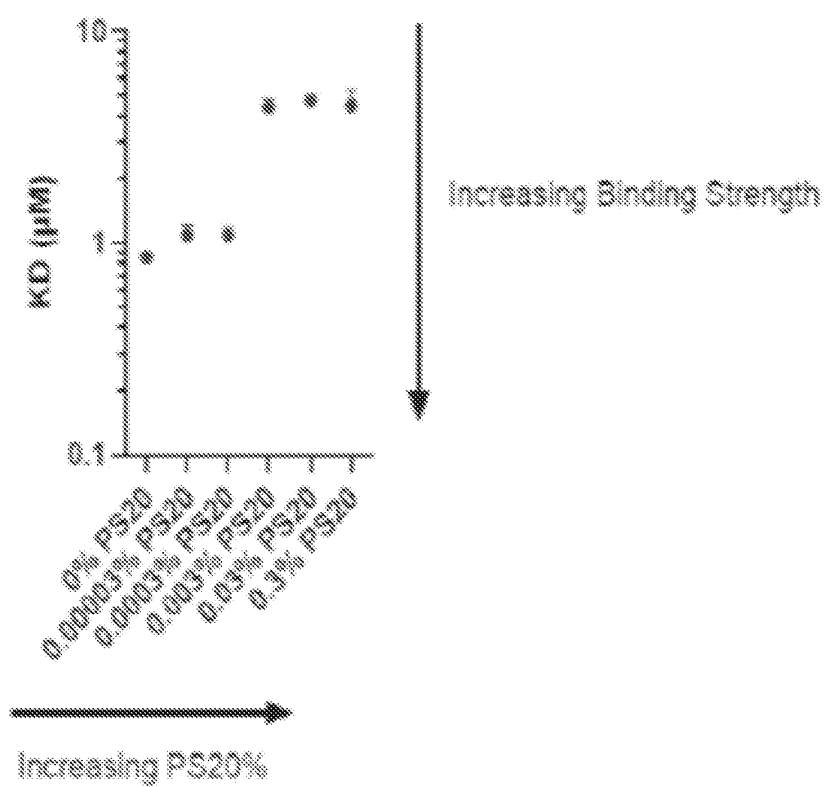


FIG. 33B

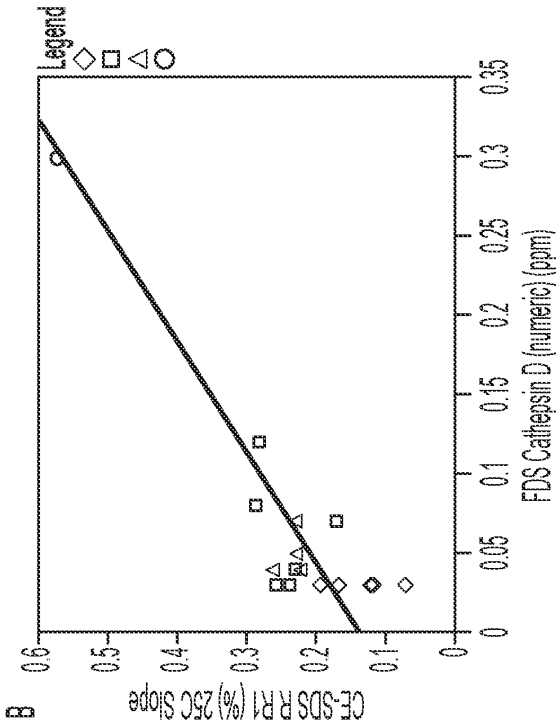


FIG. 33A

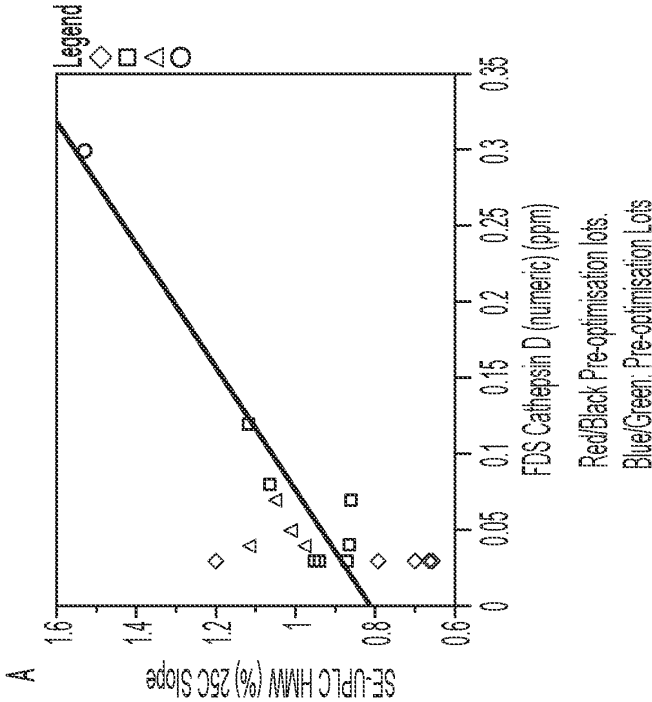
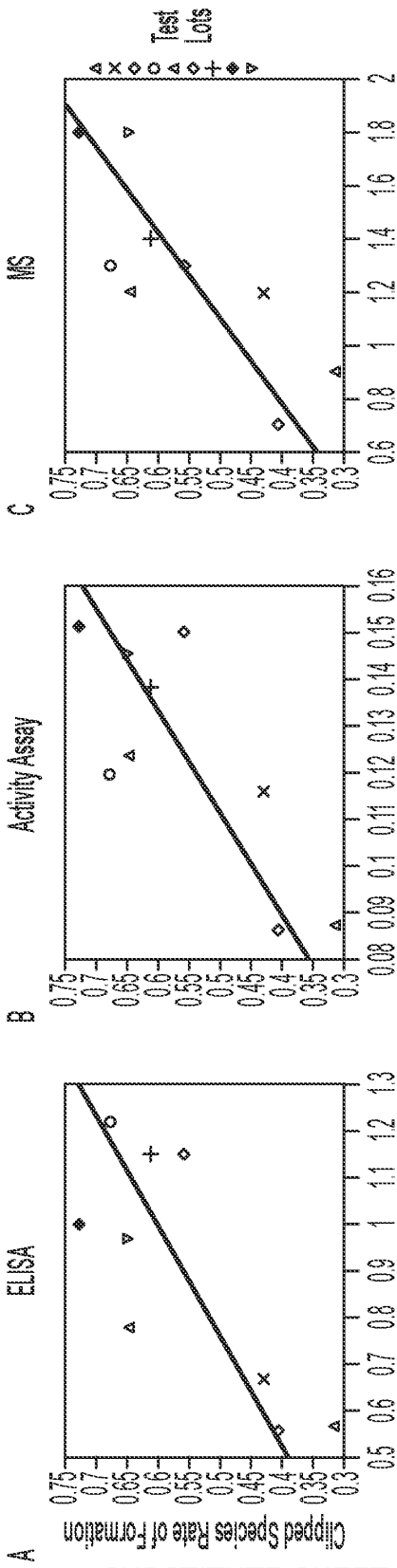


FIG. 34



Cathepsin D level by Assay

Assay	Description	R2	Assay Variability at DSI
ELISA	Total Content	0.59	17.1% n=8 (AV) to 30% (SOP)
Activity	Activity	0.63	6% n=6 (TD - within a run)
MS	Total Content	0.63	NA

FIG. 35A

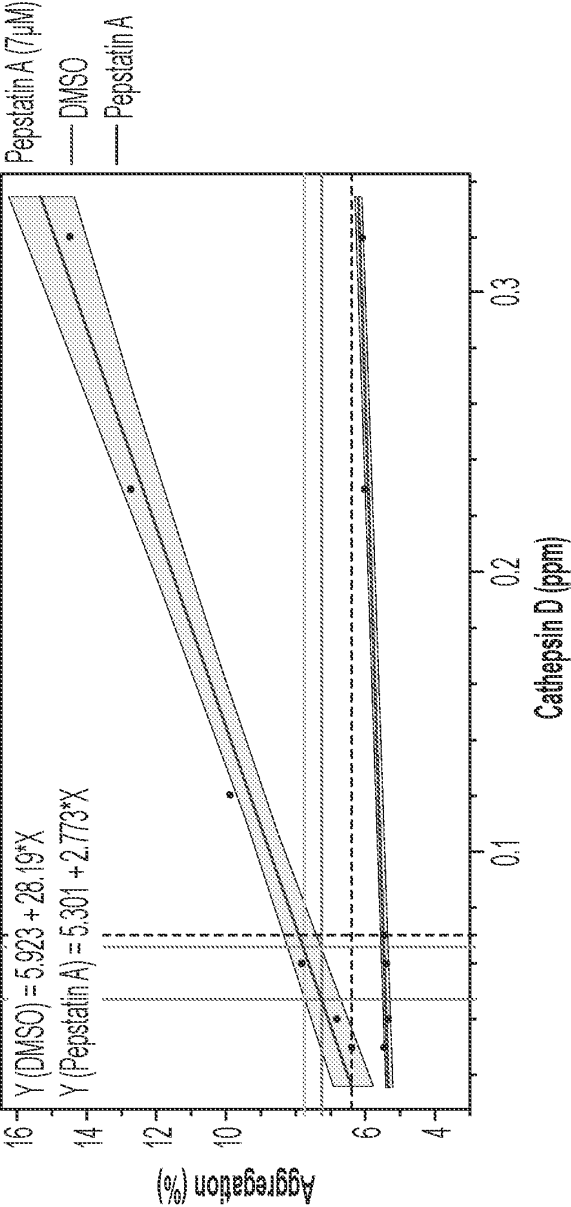


FIG. 35B

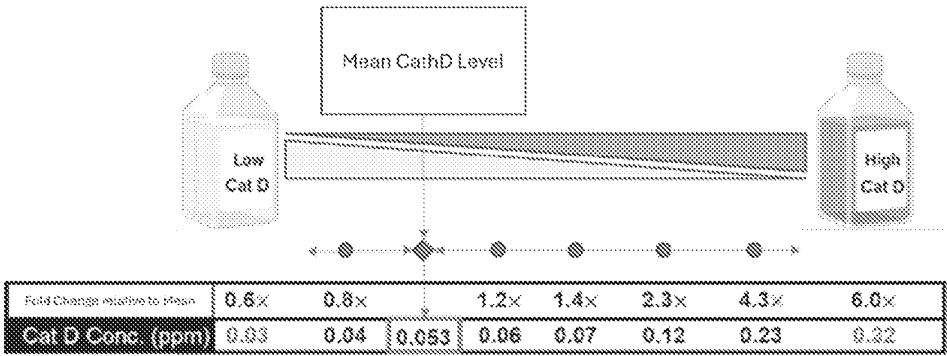


FIG. 36A

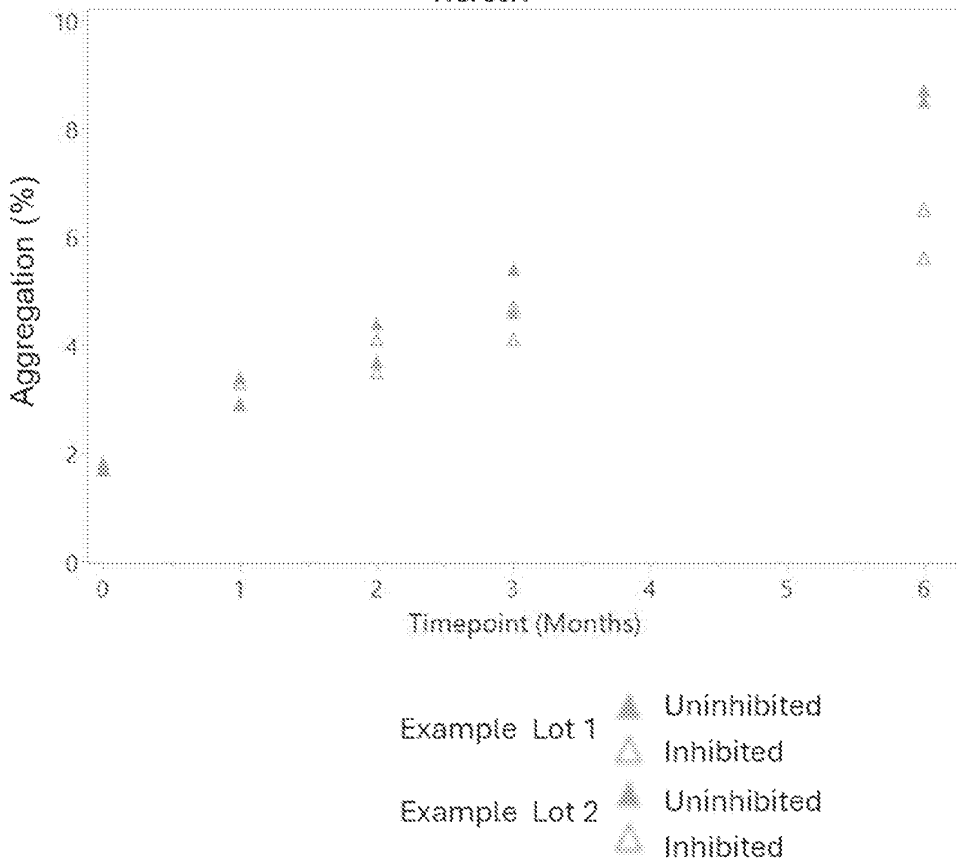


FIG. 36B

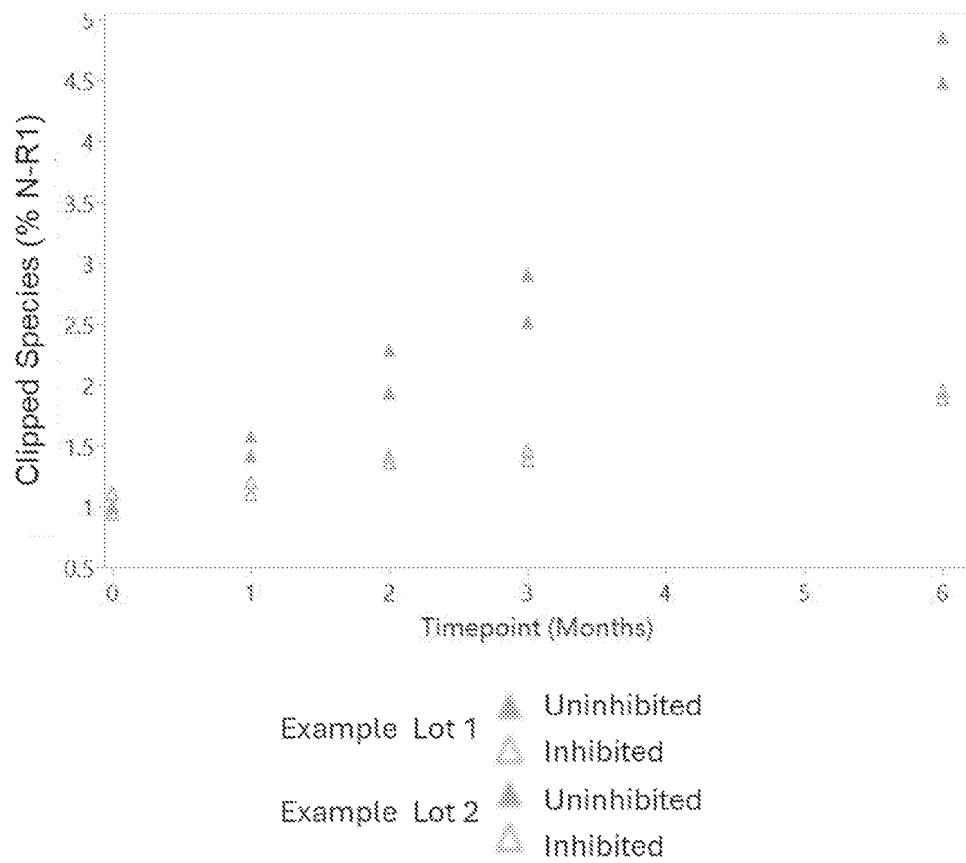


FIG. 37

