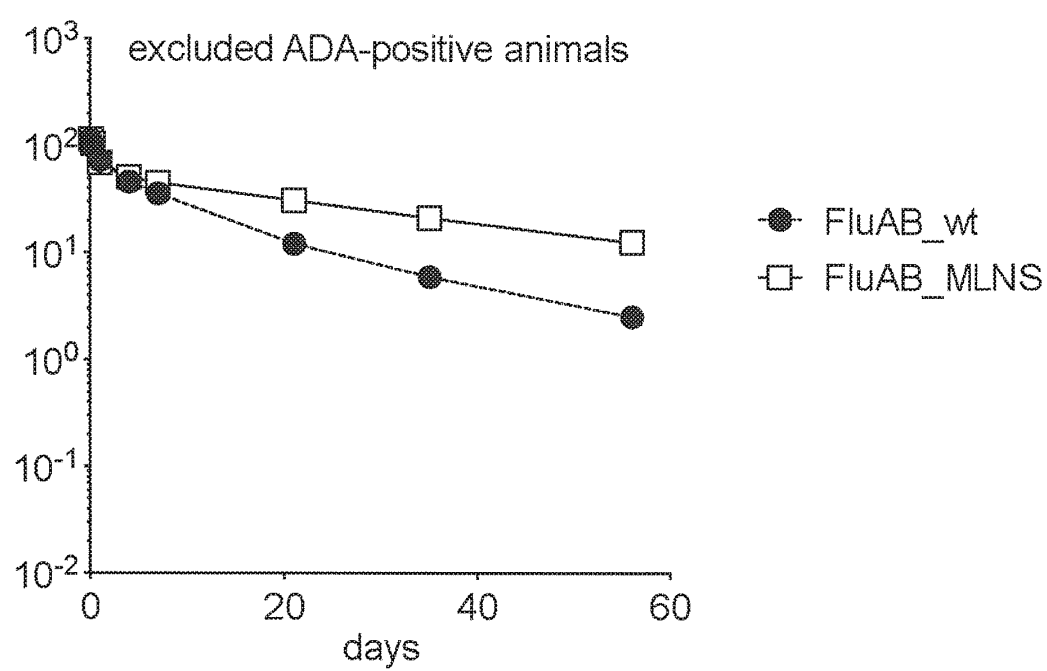


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*FIG. 1*

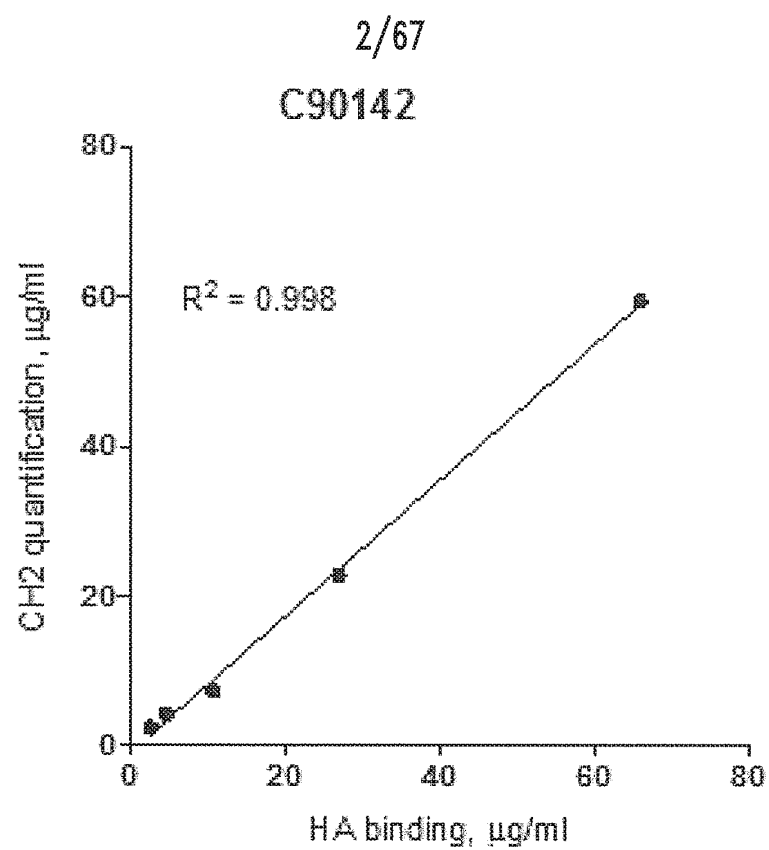


FIG. 2A

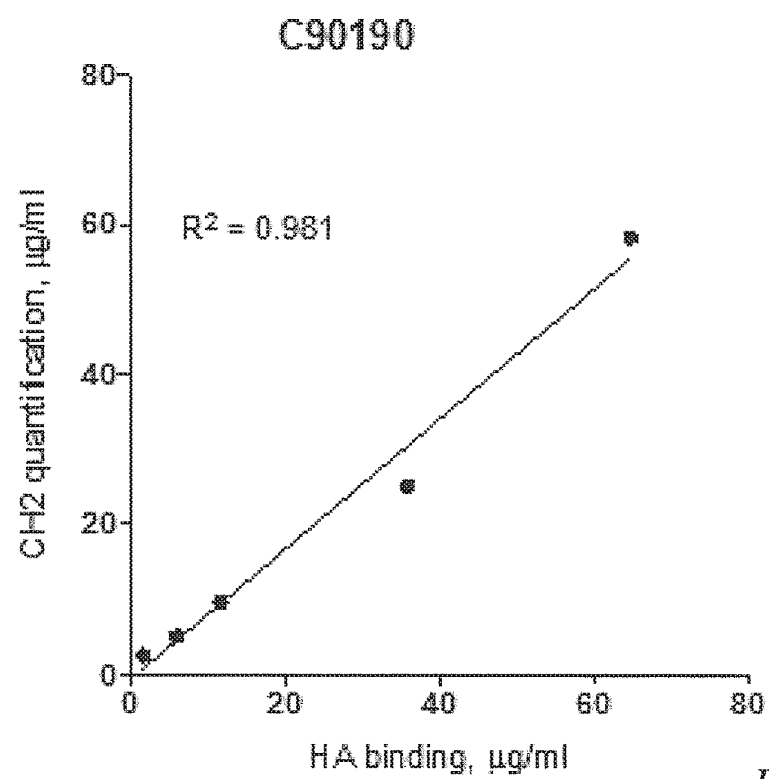


FIG. 2B

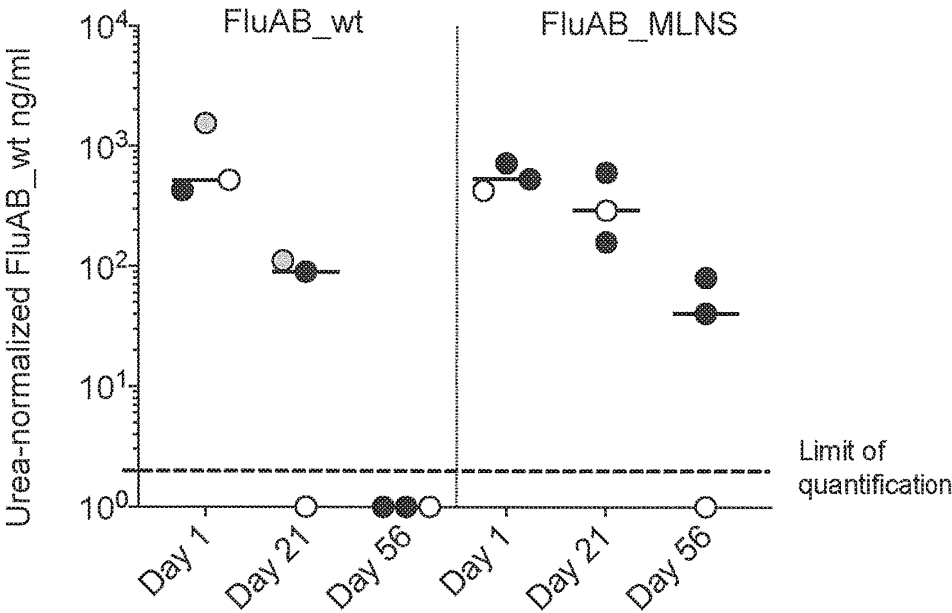


FIG. 3A

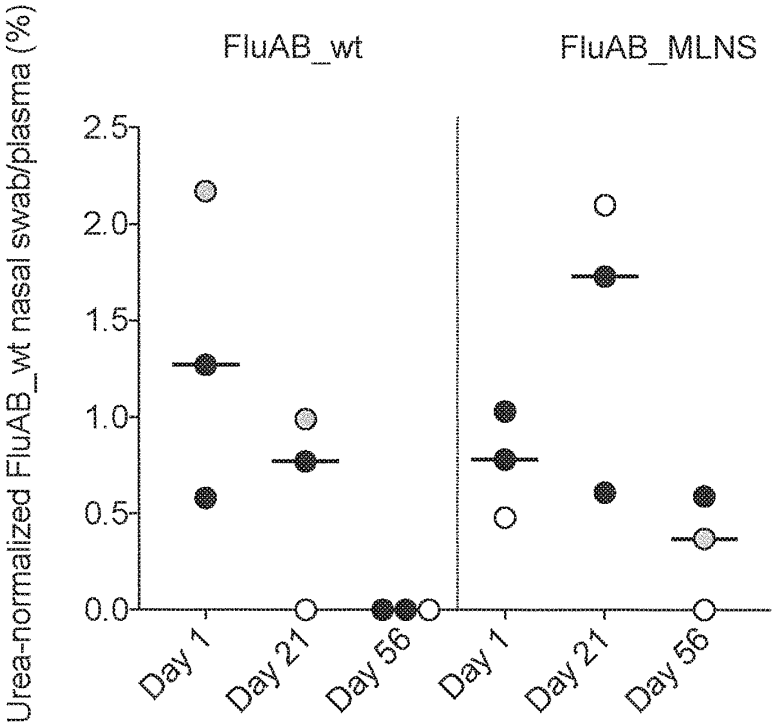
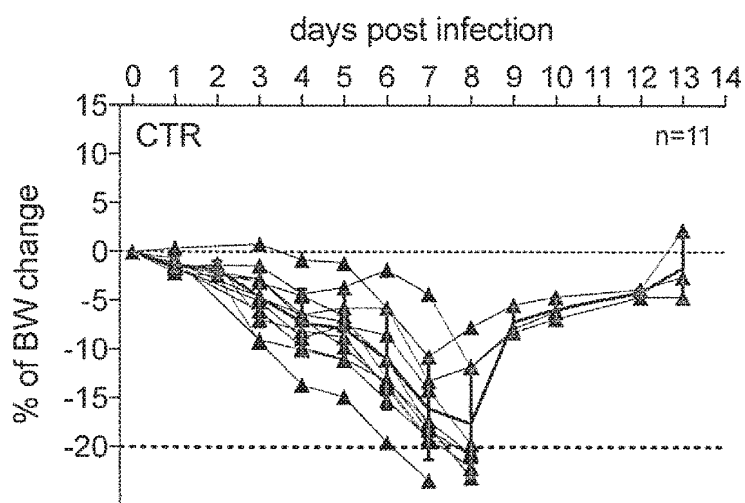
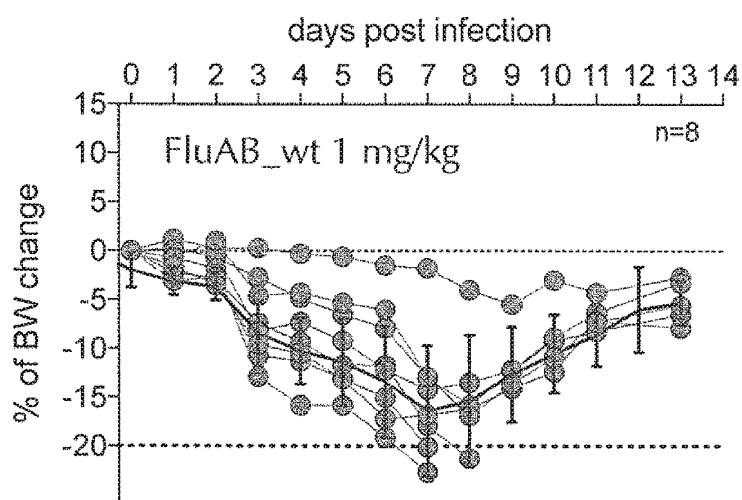


FIG. 3B

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* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$ vs CTR

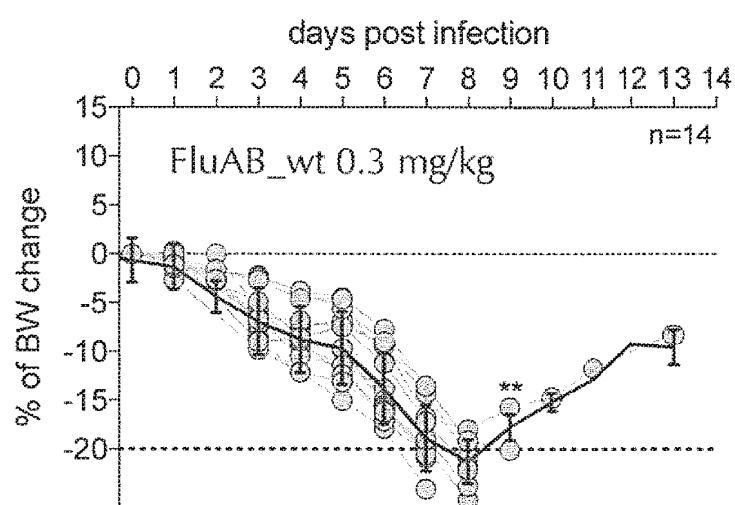
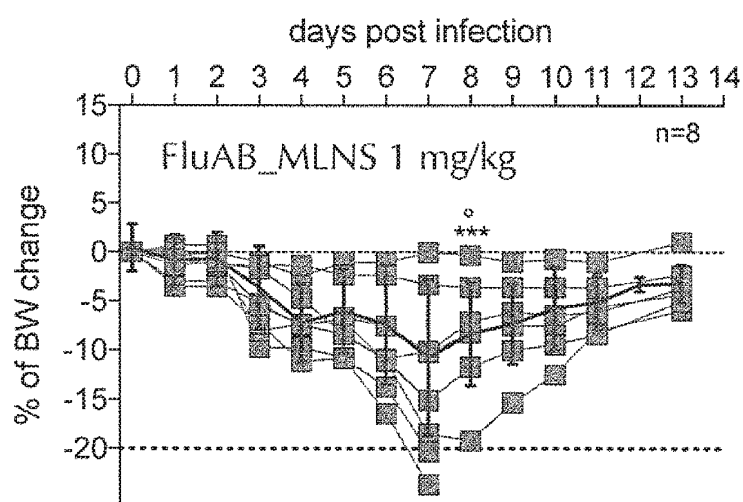
° $p < 0.05$ °° $p < 0.01$ vs. FluAB_wt

*FIG. 4A**FIG. 4B*

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* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$ vs CTR

° $p < 0.05$ °° $p < 0.01$ vs. FluAB_wt

*FIG. 4C**FIG. 4D*

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* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$ vs CTR

° $p < 0.05$ °° $p < 0.01$ vs. FluAB_wt

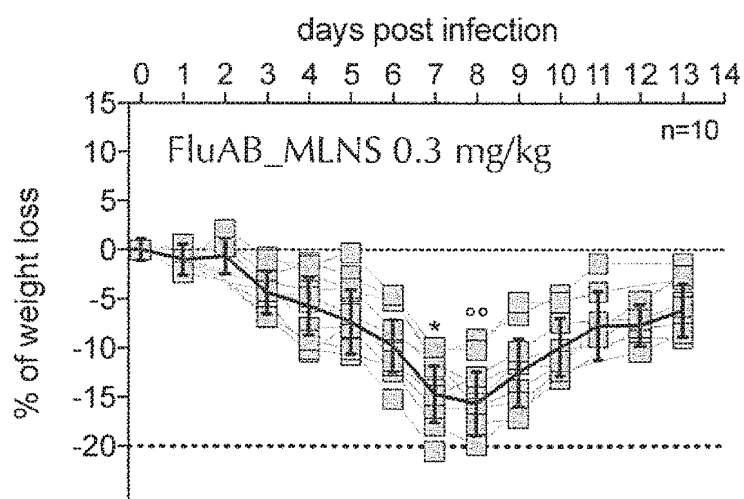


FIG. 4E

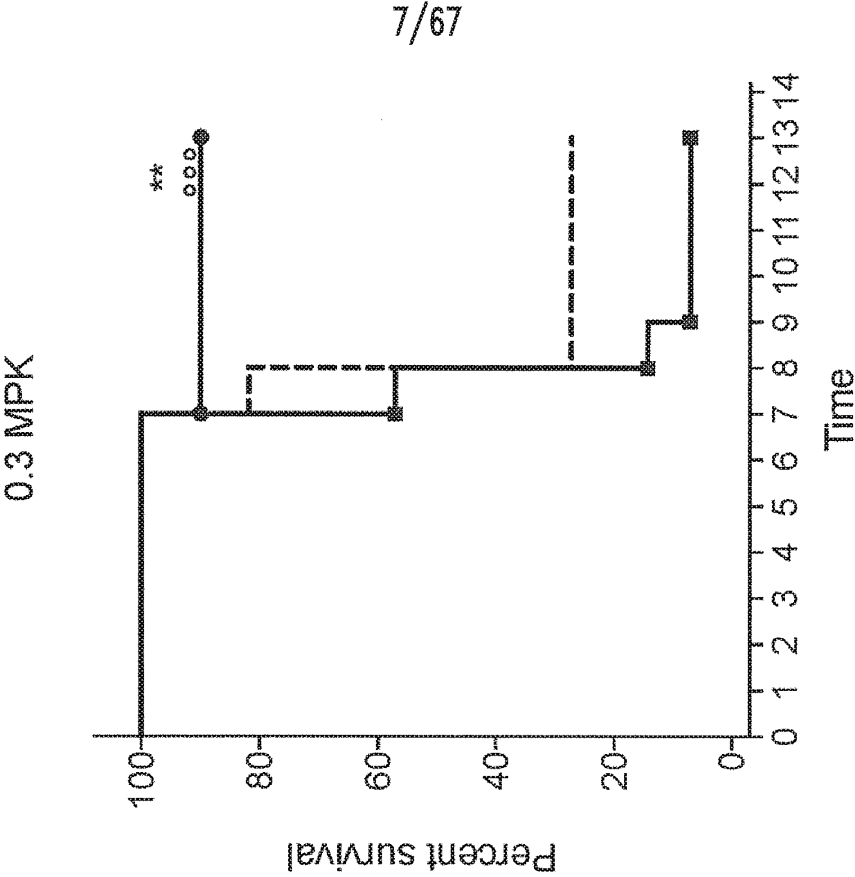


FIG. 5B

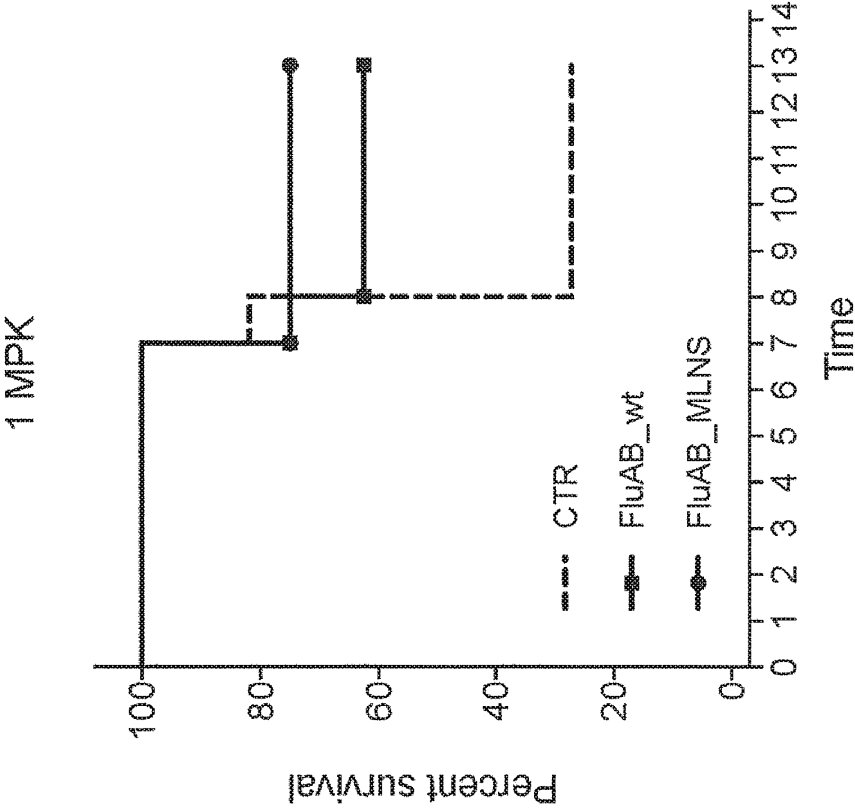


FIG. 5A

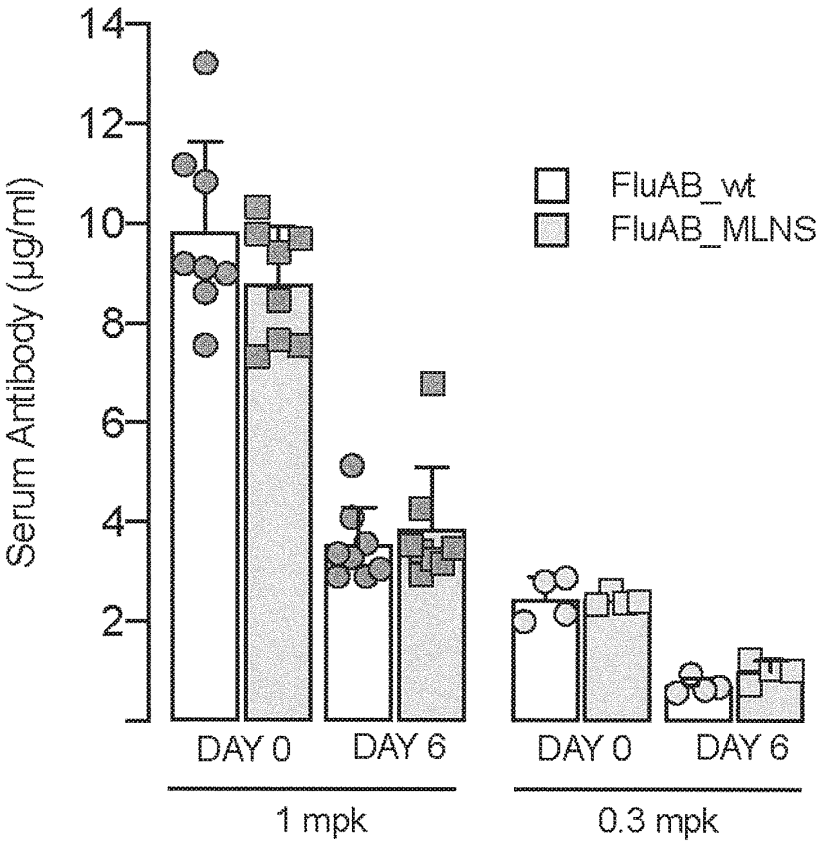


FIG. 6

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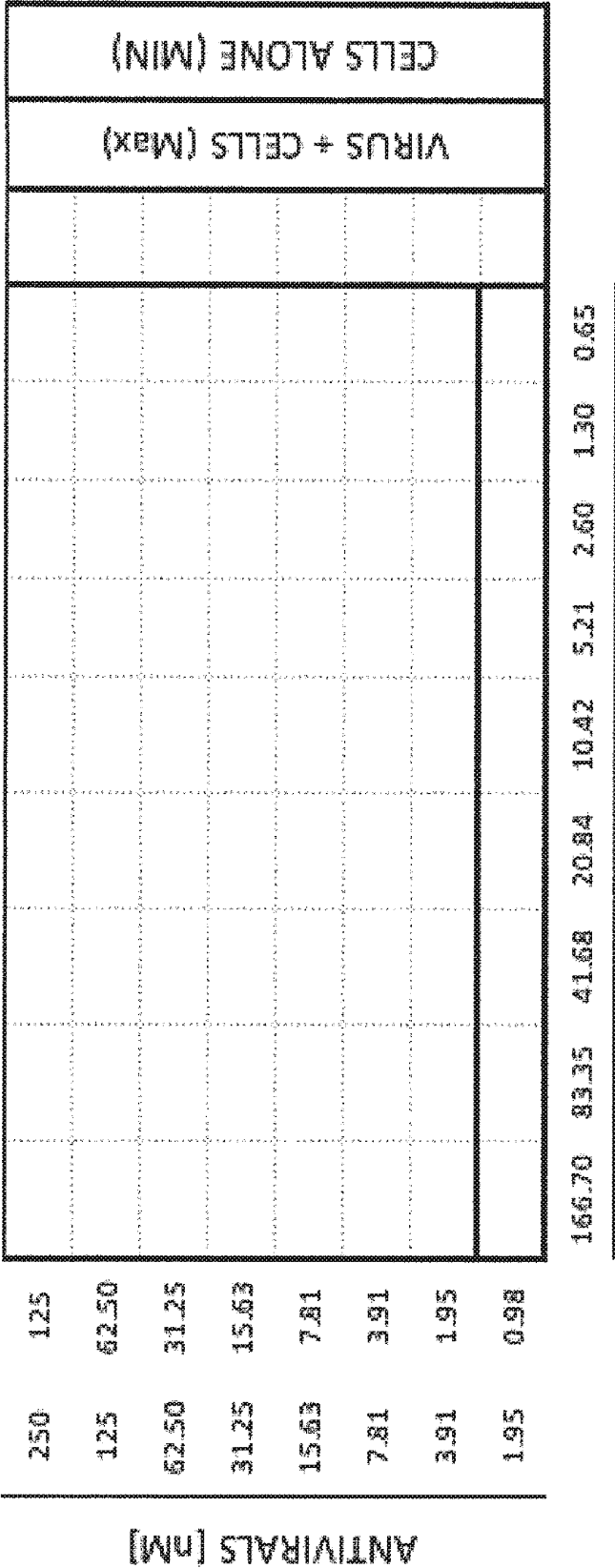


FIG. 7

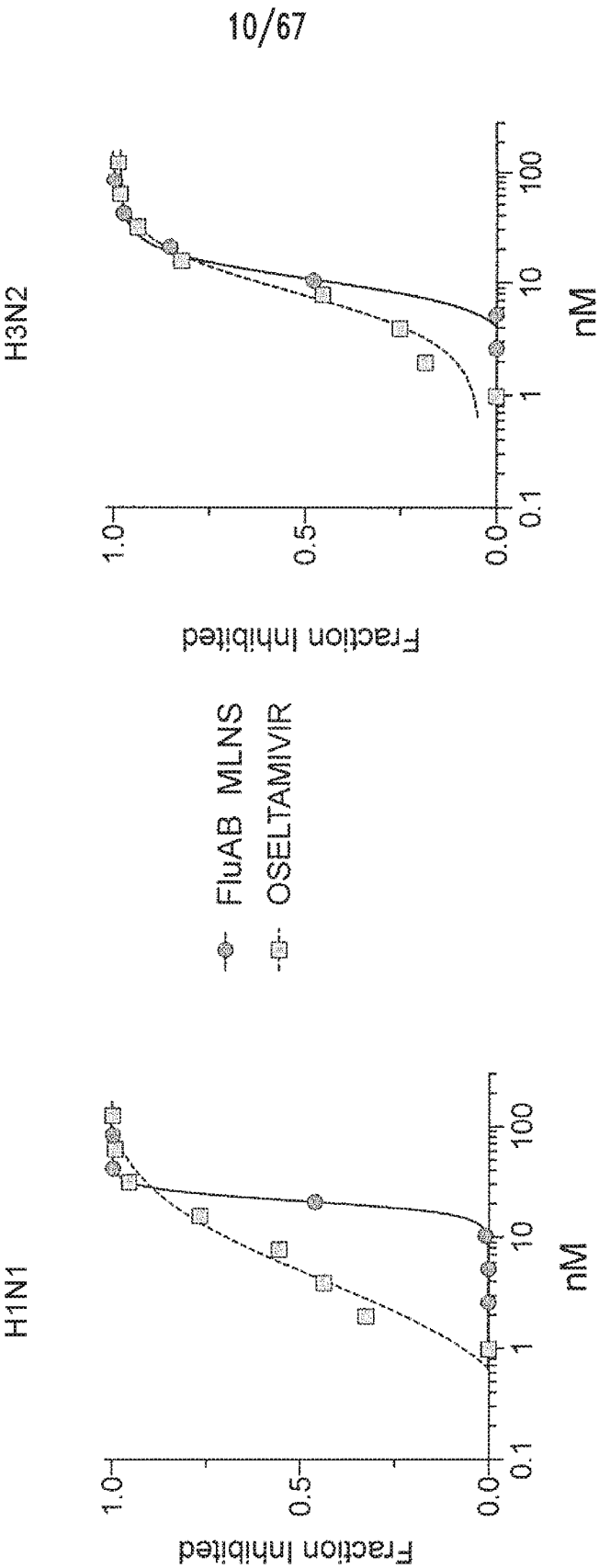


FIG. 8B

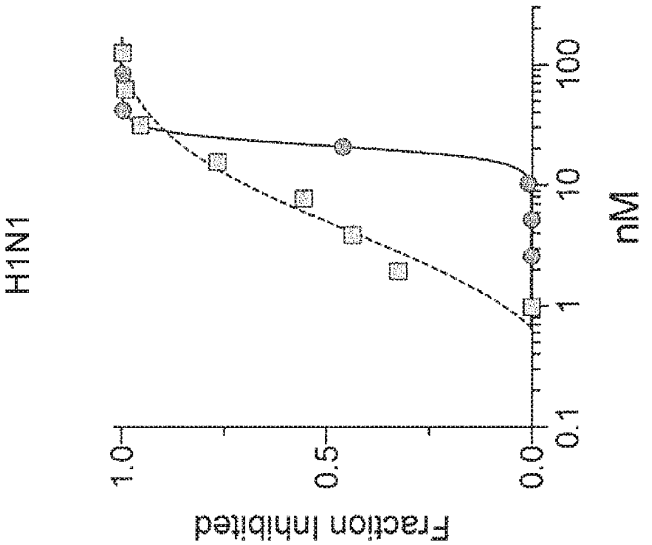


FIG. 8A

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●—● FLUAB MLNS
■—■ OSELTAMIVIR

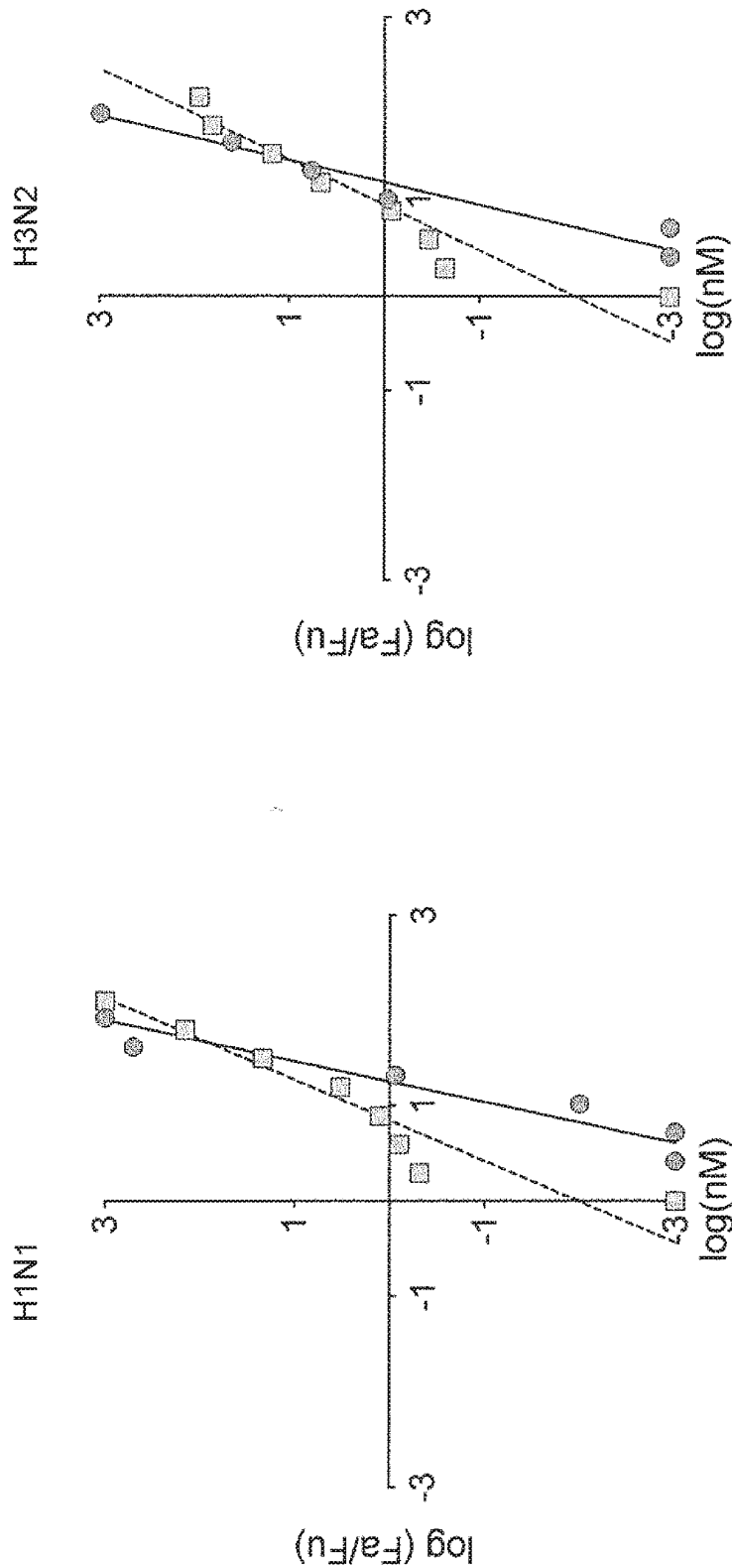


FIG. 8D

FIG. 8C

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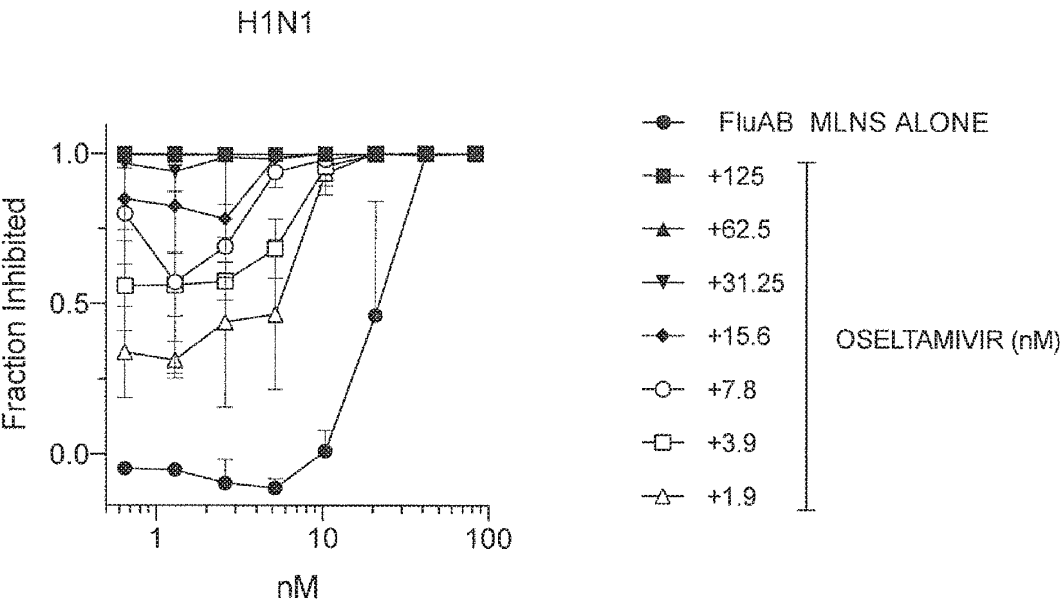


FIG. 9A

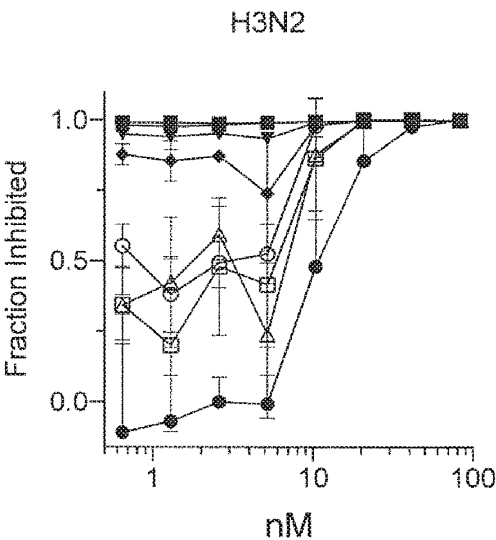


FIG. 9B

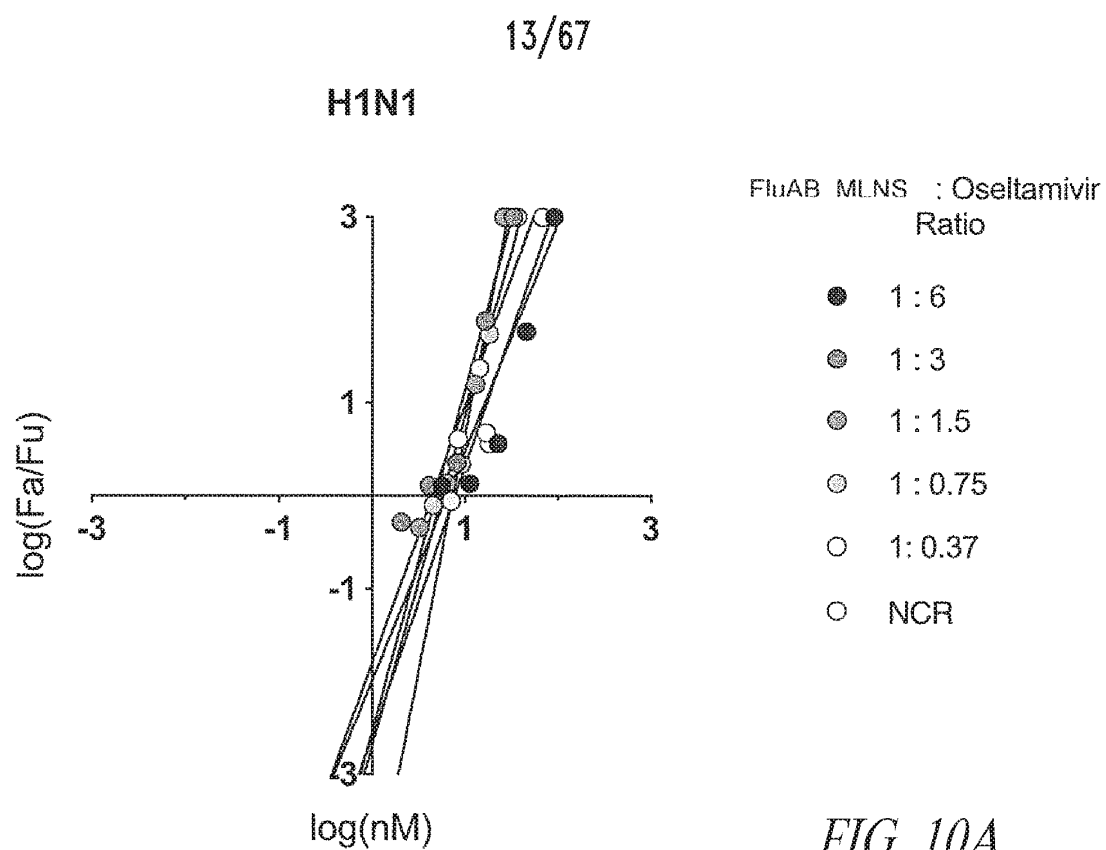


FIG. 10A

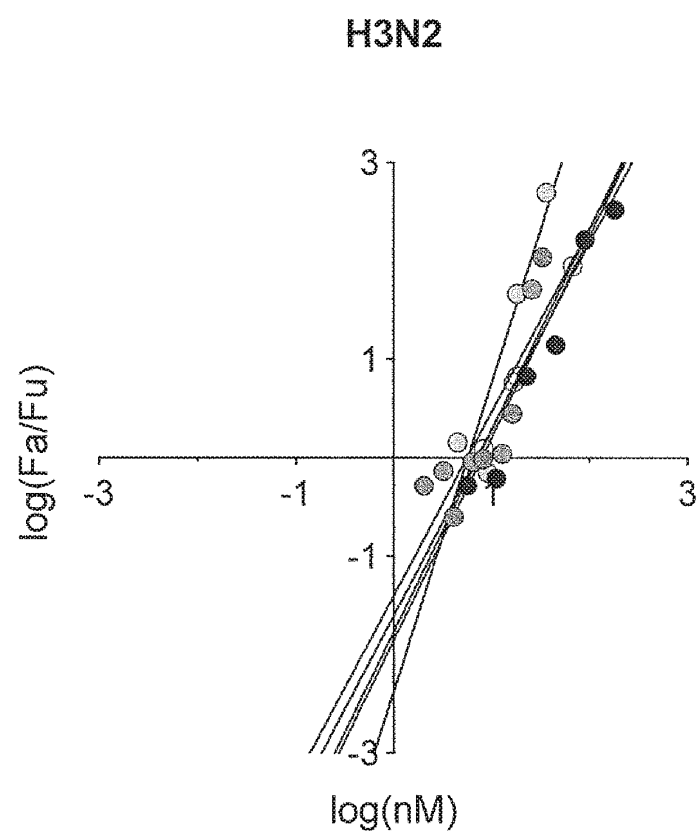


FIG. 10B

H1N1

1:6

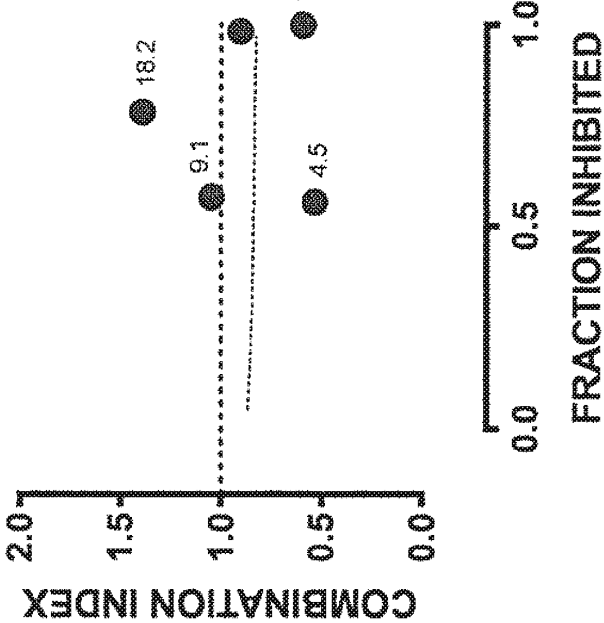


FIG. 11A

1:3

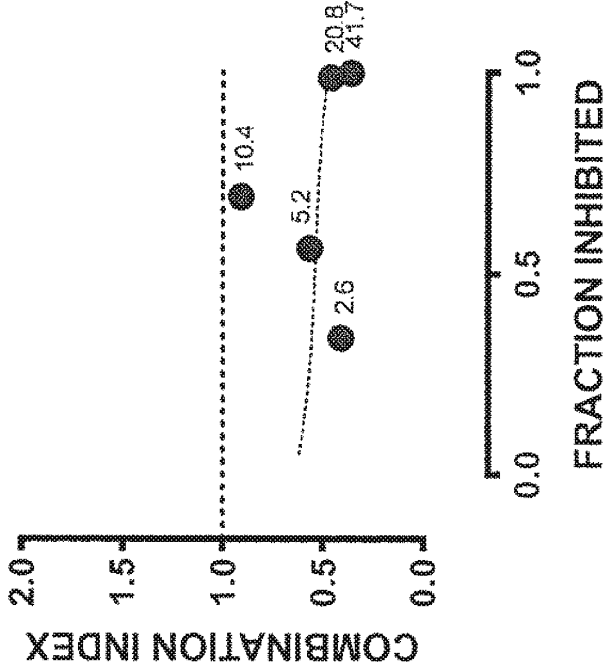


FIG. 11B

H1N1

1:1.5

1:0.37

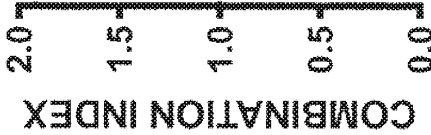
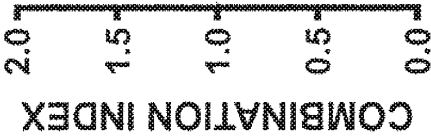
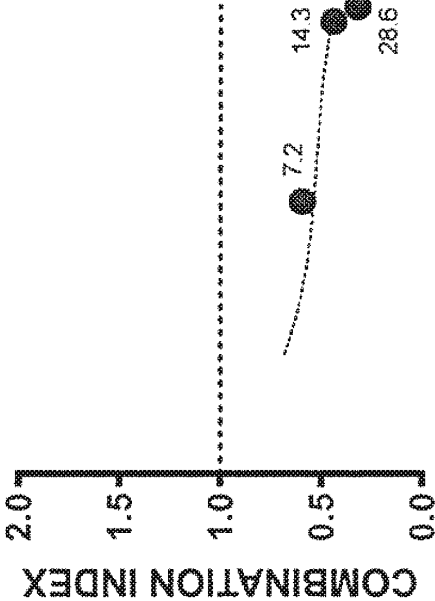


FIG. 11C

FIG. 11D

H1N1

0.37



NCR

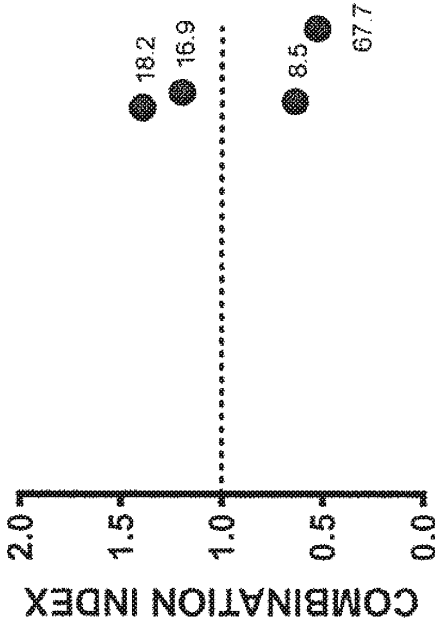


FIG. 11E

FIG. 11F

H3N2

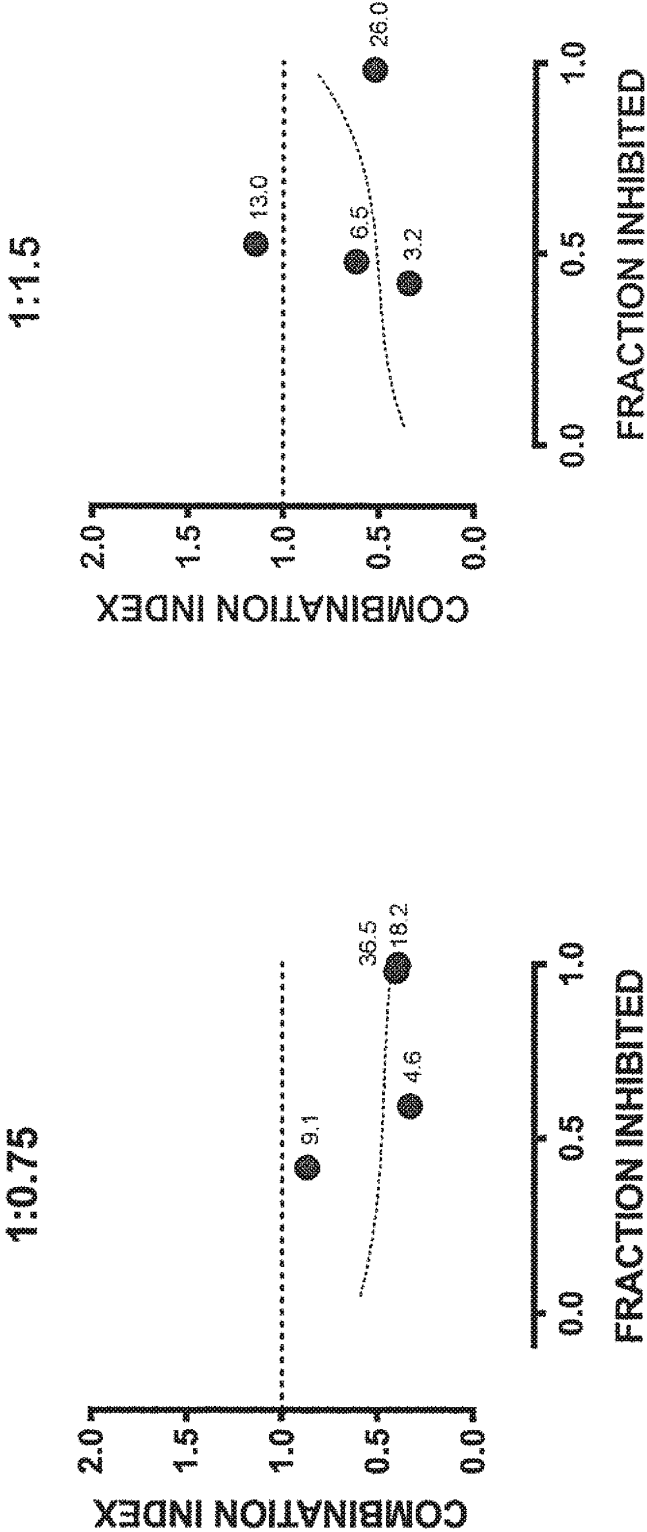


FIG. 12A

FIG. 12B

H3N2

1:3

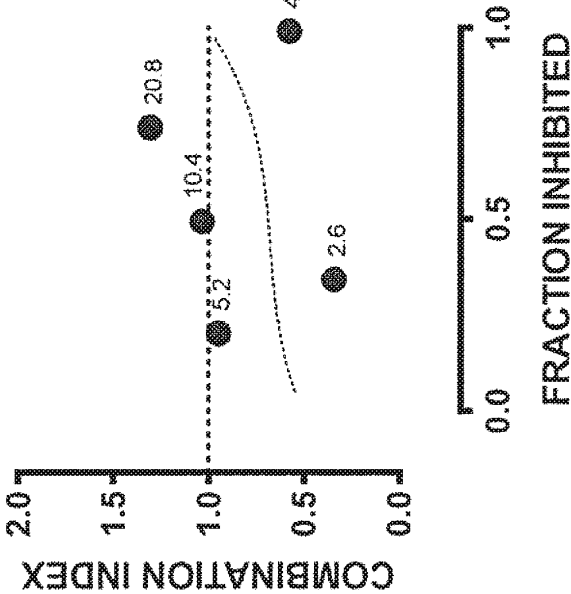


FIG. 12C

1:6

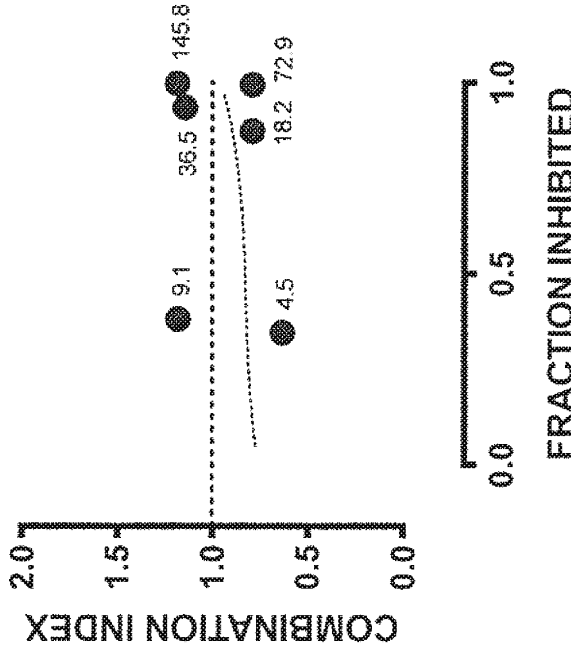


FIG. 12D

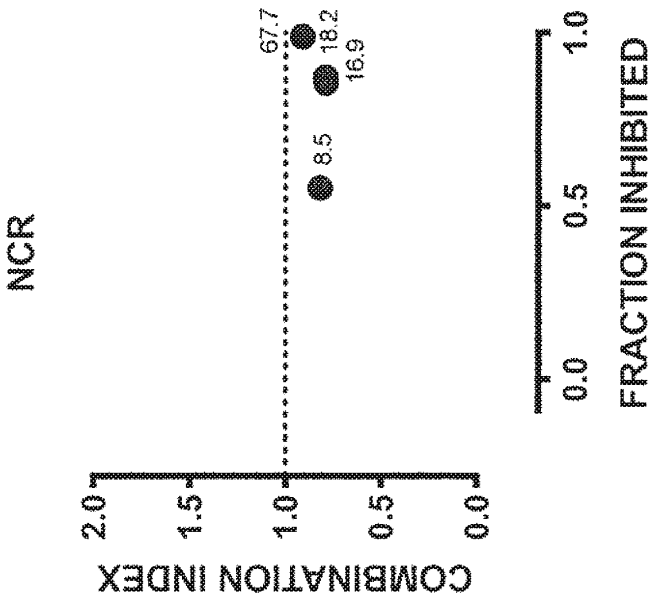


FIG. 12E

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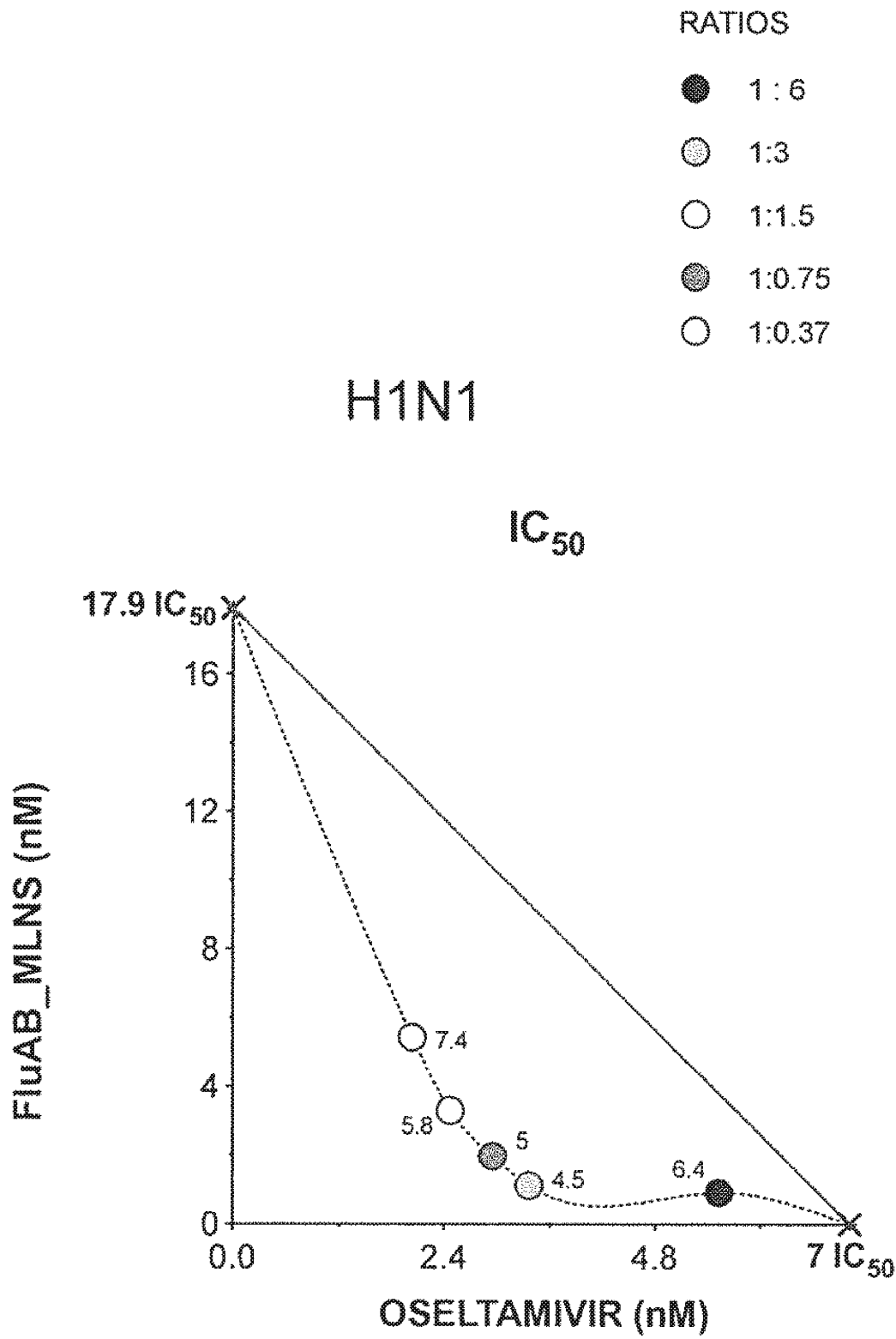


FIG. 13A

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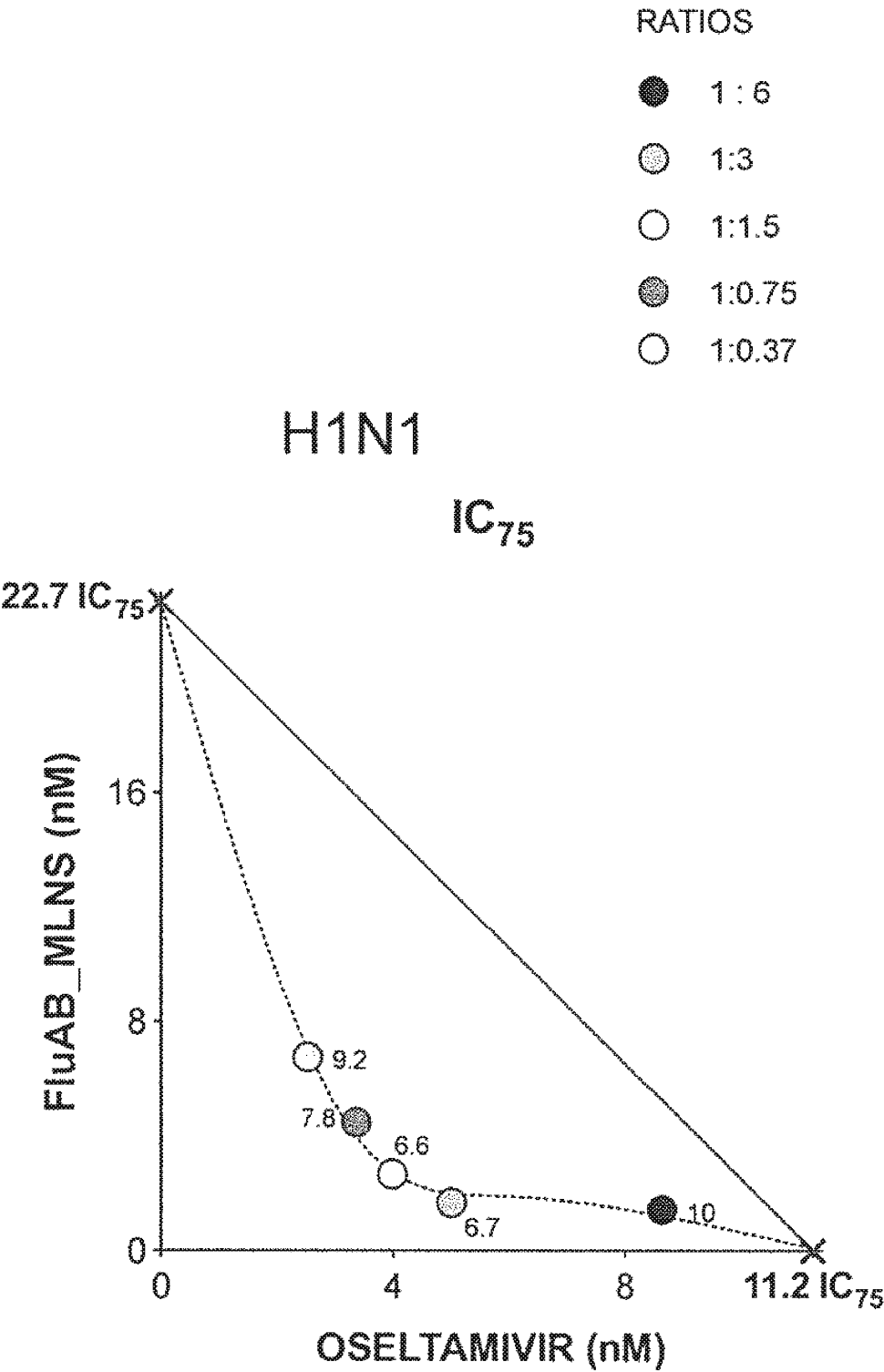


FIG. 13B

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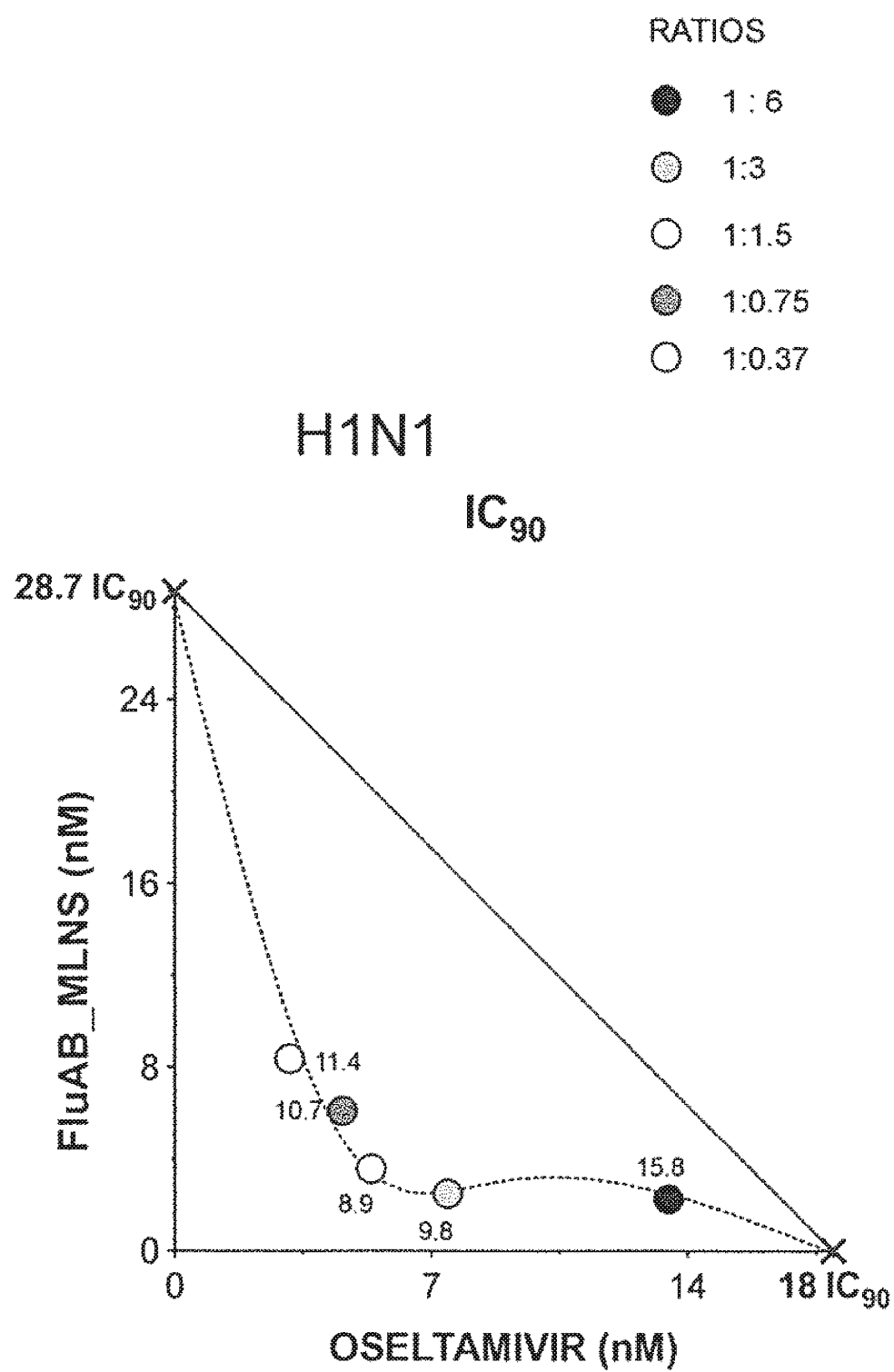


FIG. 13C

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OS: FluAB_MLNS

ratio

● 6

○ 3

○ 1.5

● 0.75

H3N2

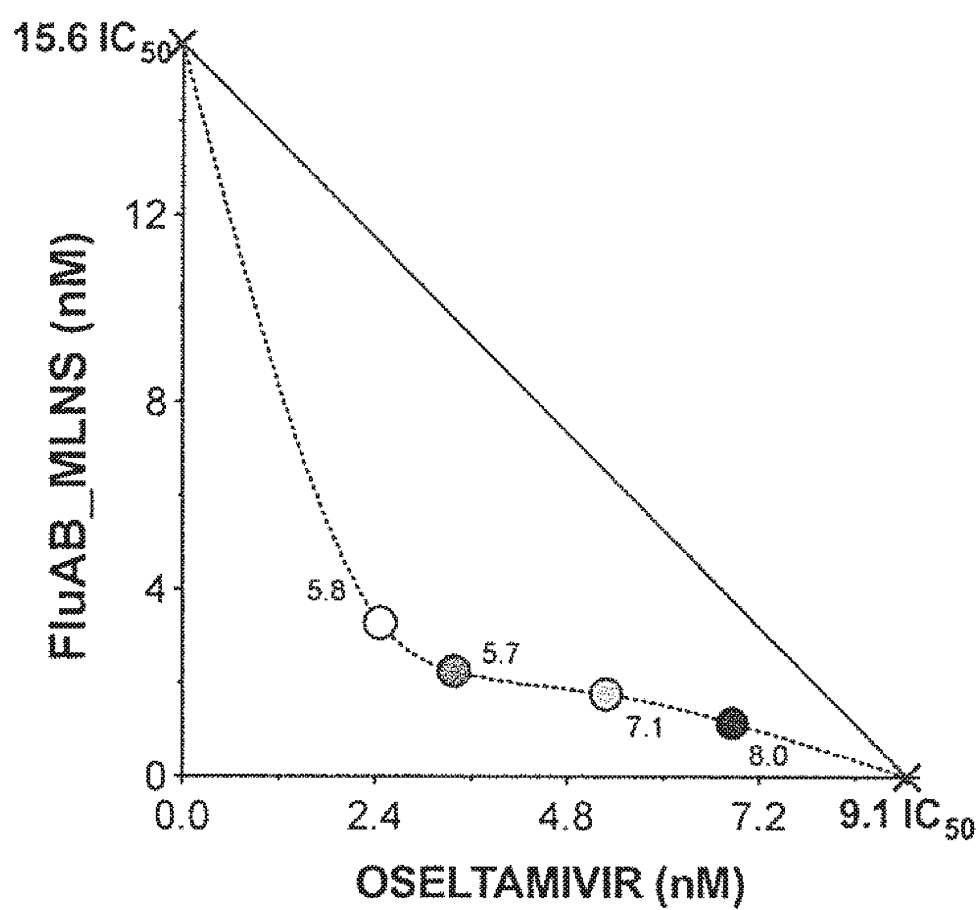
 IC_{50} 

FIG. 14A

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OS: FluAB_MLNS

ratio

● 6

○ 3

○ 1.5

● 0.75

H3N2

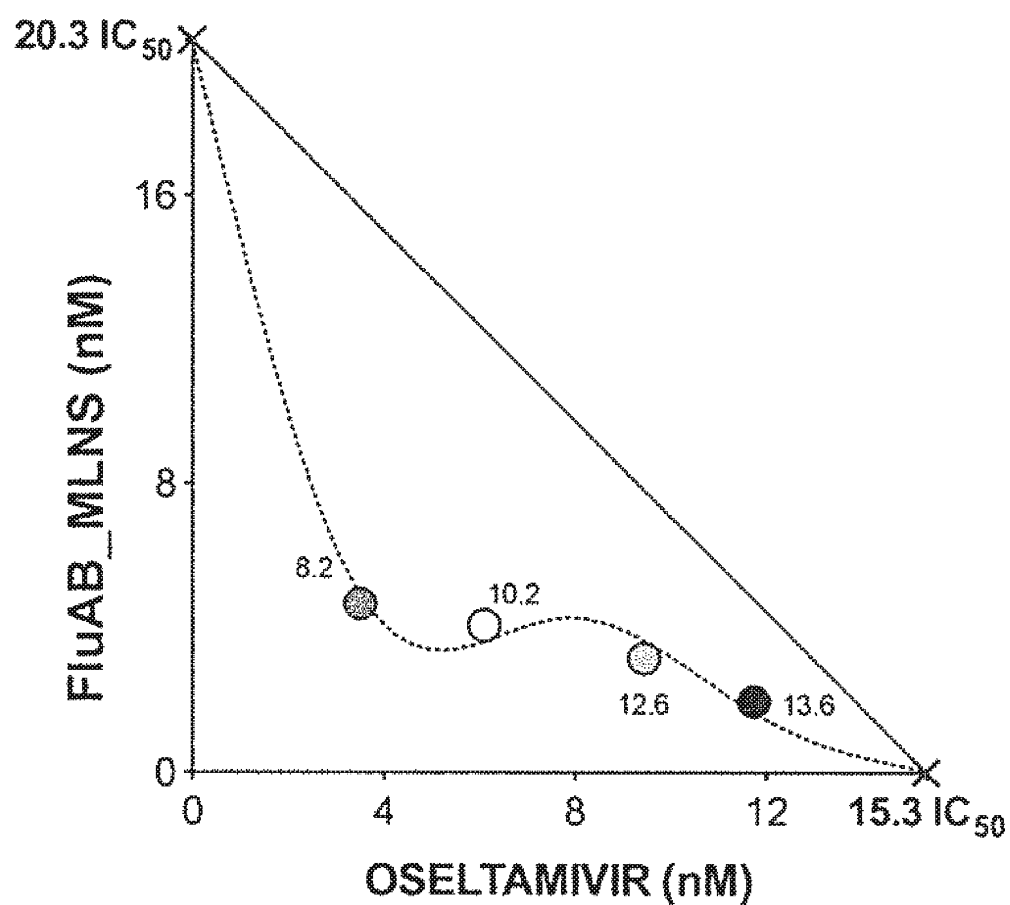
IC₇₅

FIG. 14B

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OS: FluAB_MLNS

ratio

- 6
- 3
- 1.5
- 0.75

H3N2

IC₉₀

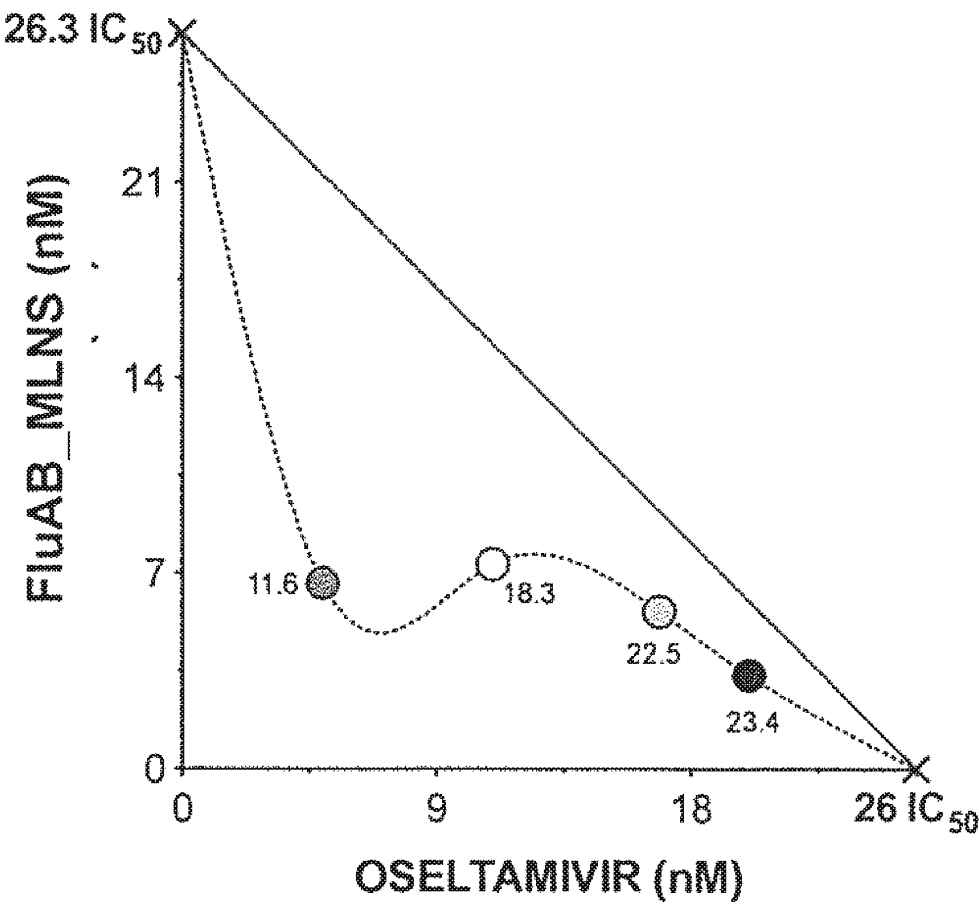


FIG. 14C

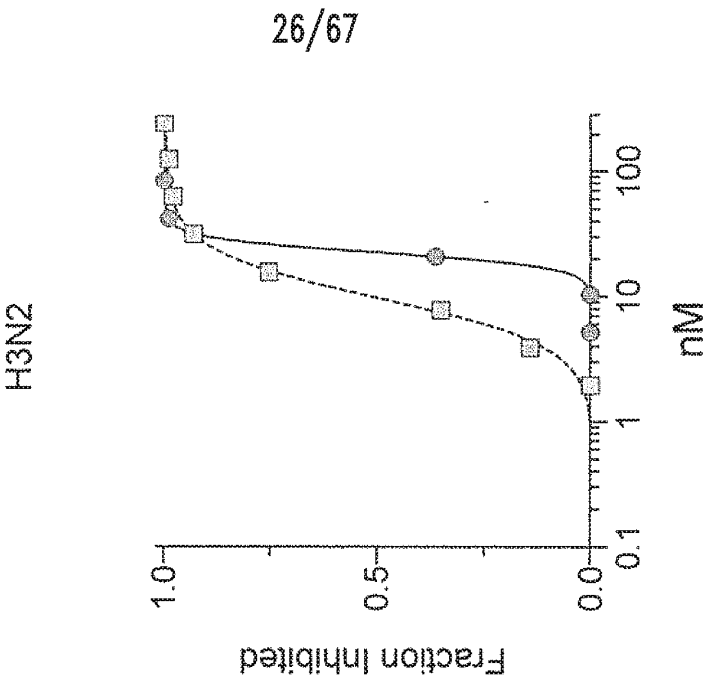


FIG. 15B

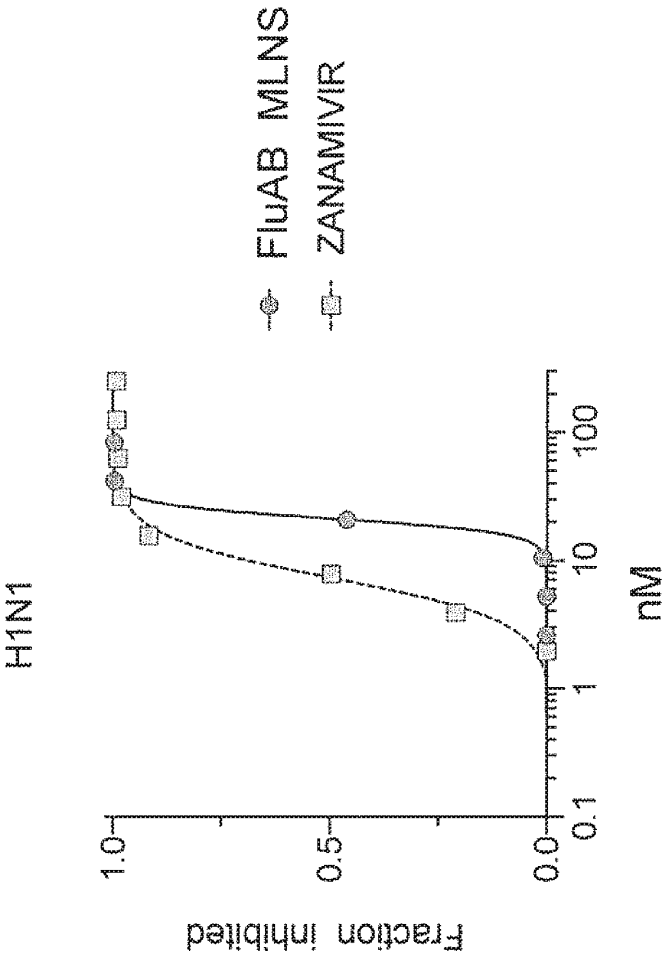


FIG. 15A

●—● FLUAB MLNS
■---■ ZANAMIVIR

H1N1

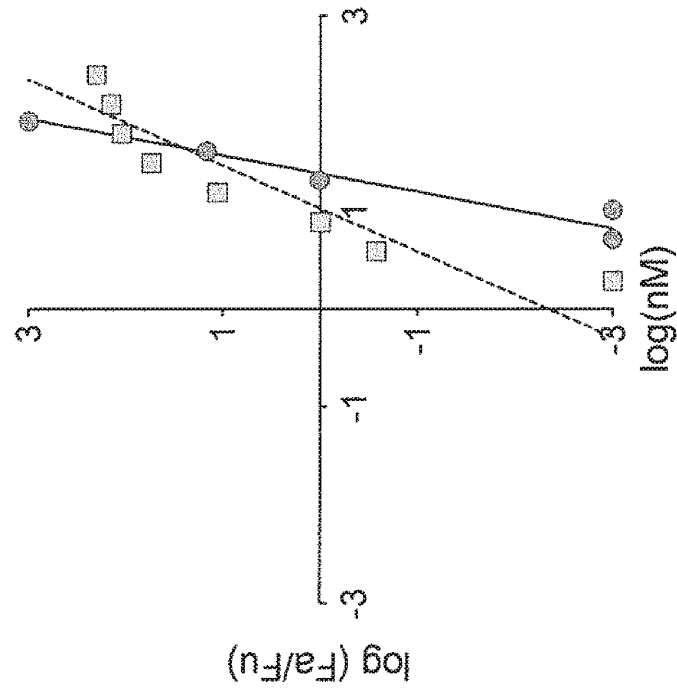


FIG. 15C

H3N2

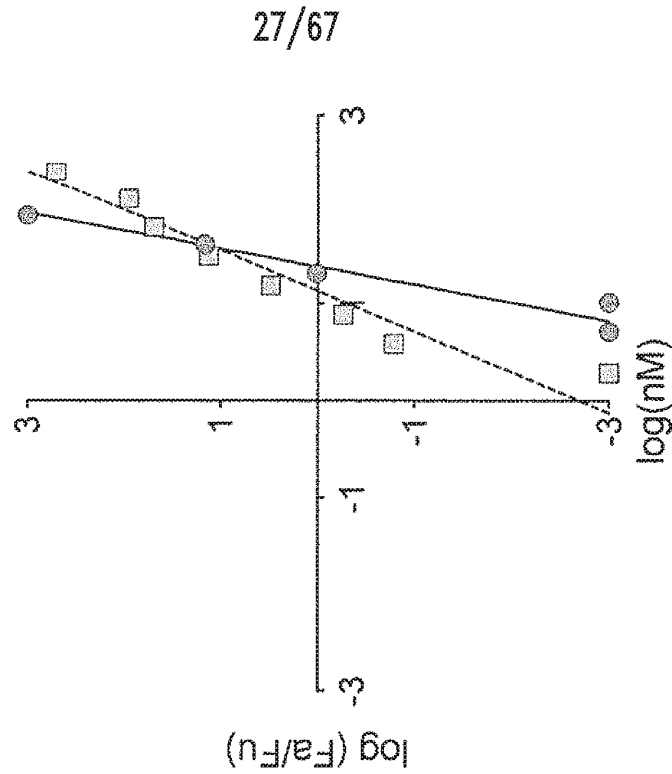


FIG. 15D

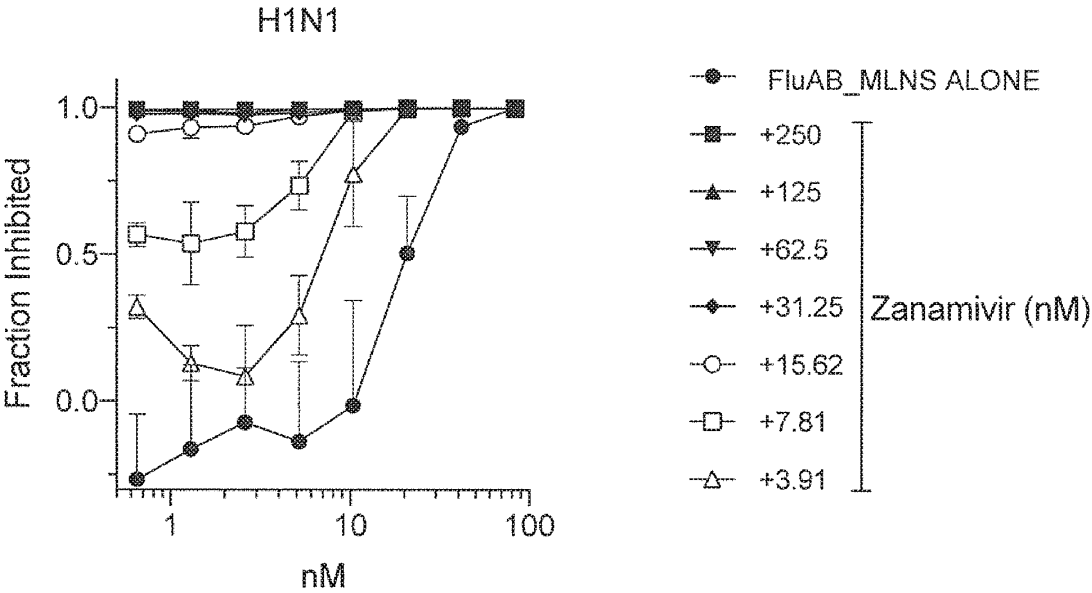


FIG. 16A

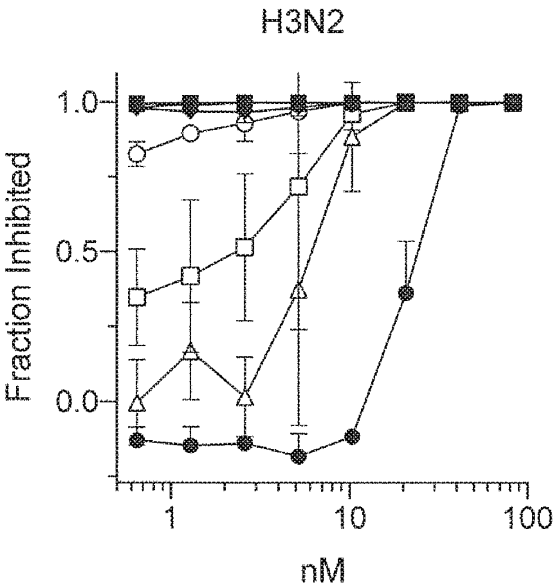


FIG. 16B

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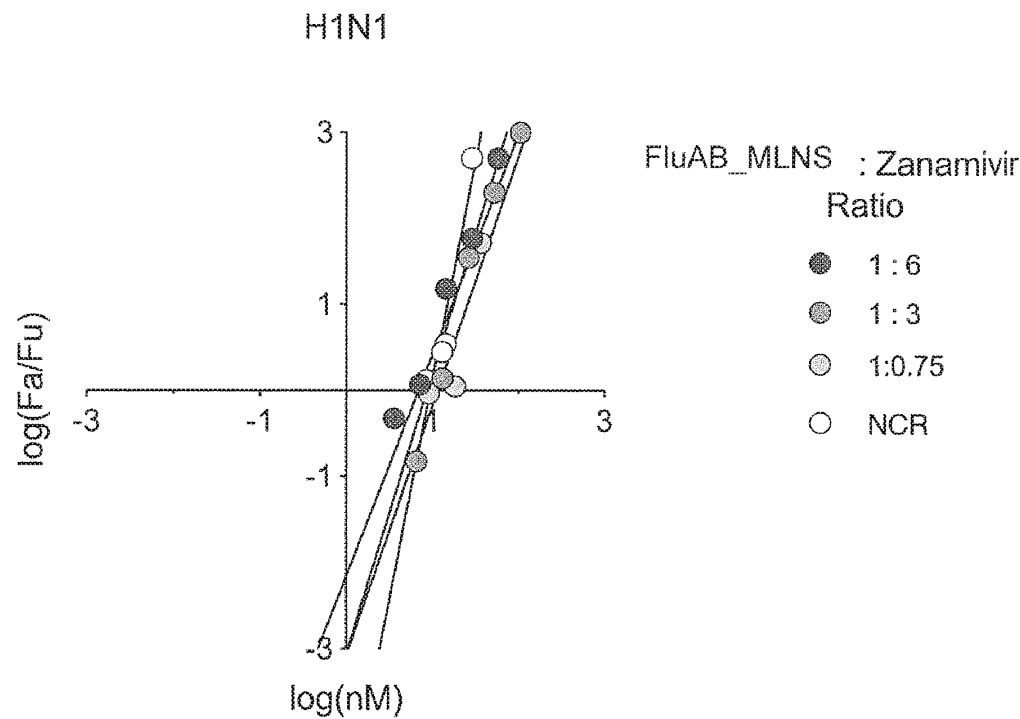


FIG. 17A

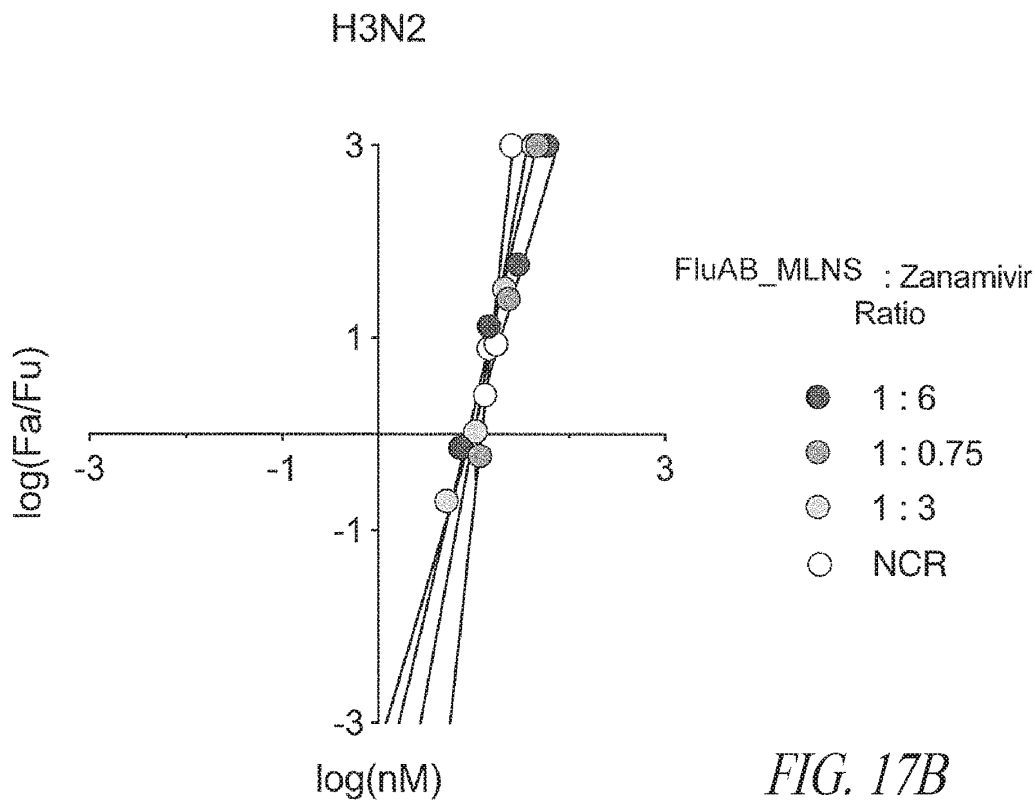


FIG. 17B

H1N1

1:0.75

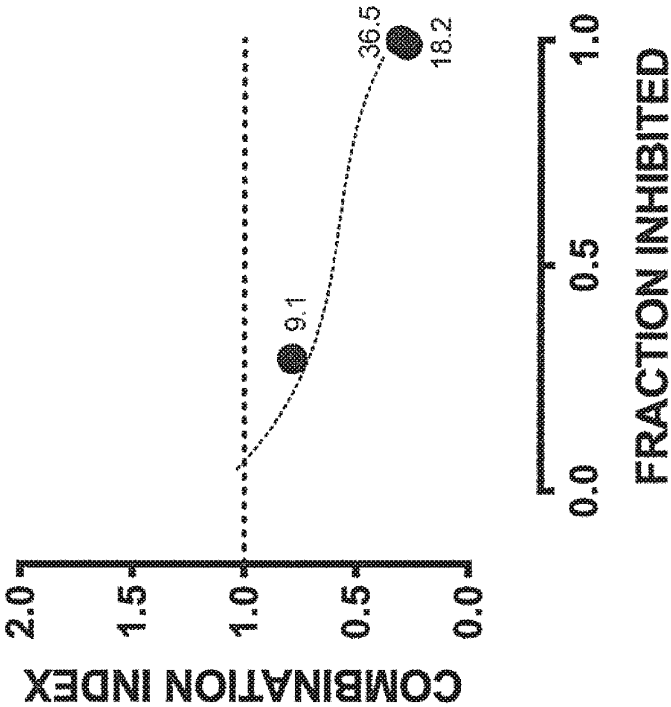


FIG. 18A

1:3

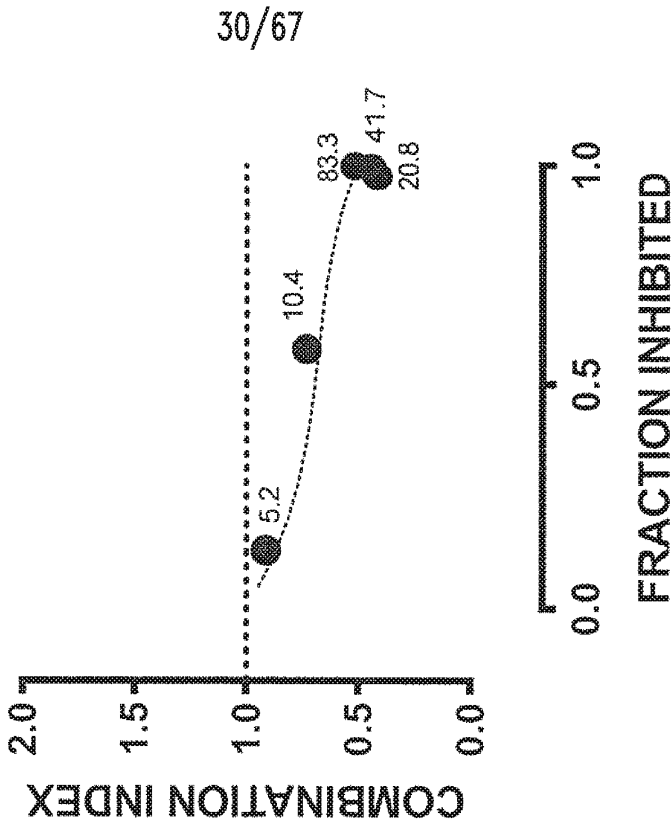


FIG. 18B

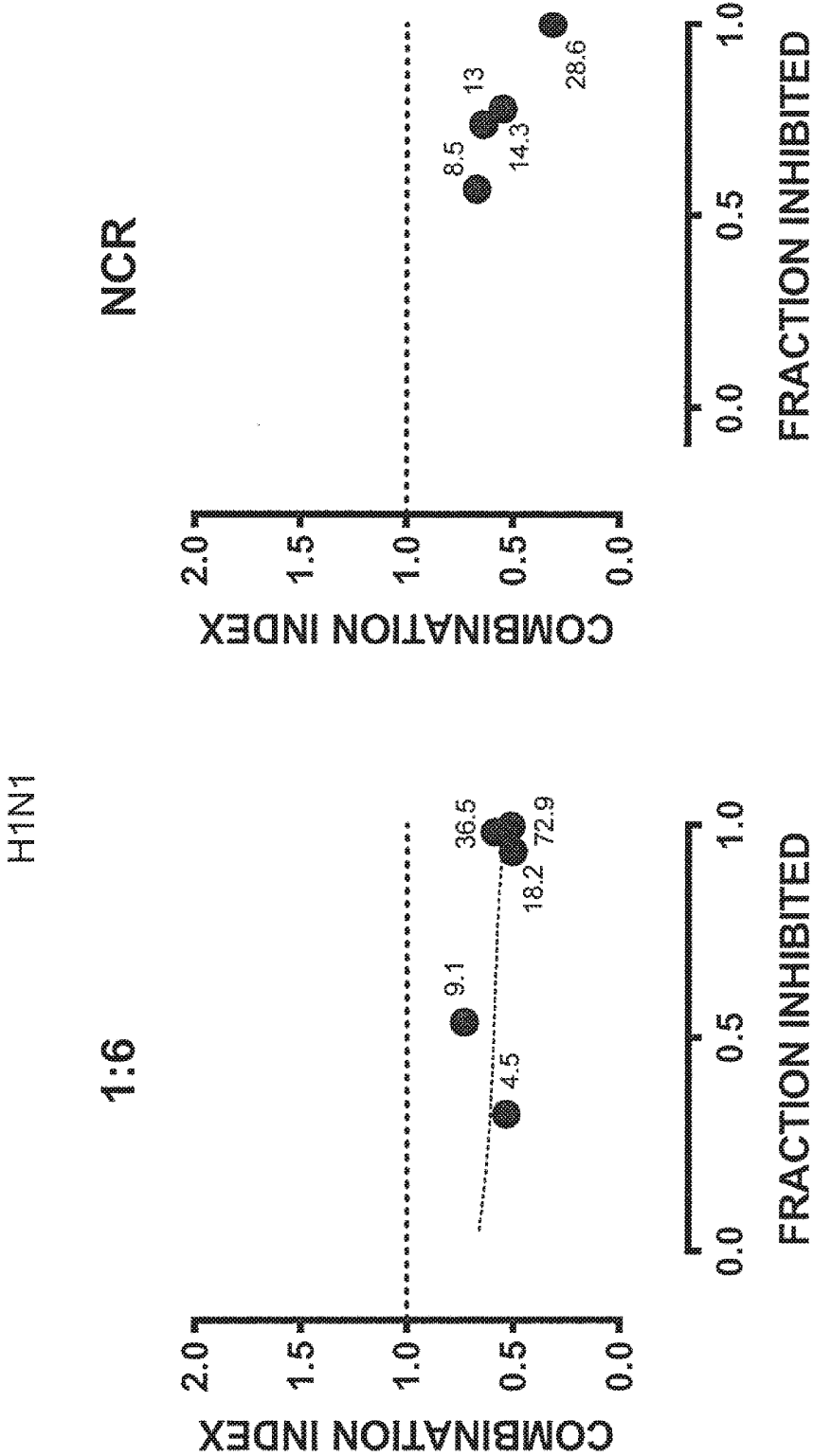


FIG. 18C

FIG. 18D

H3N2

1:0.75

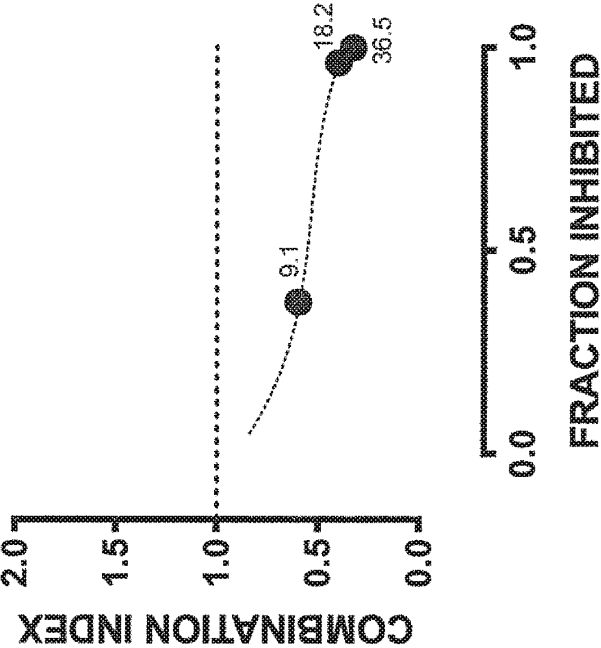


FIG. 19A

1:3

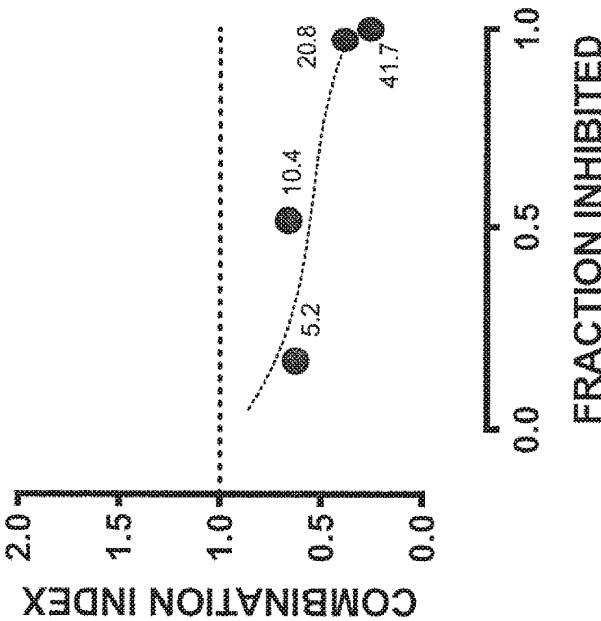


FIG. 19B

H3N2

1:6

NCR

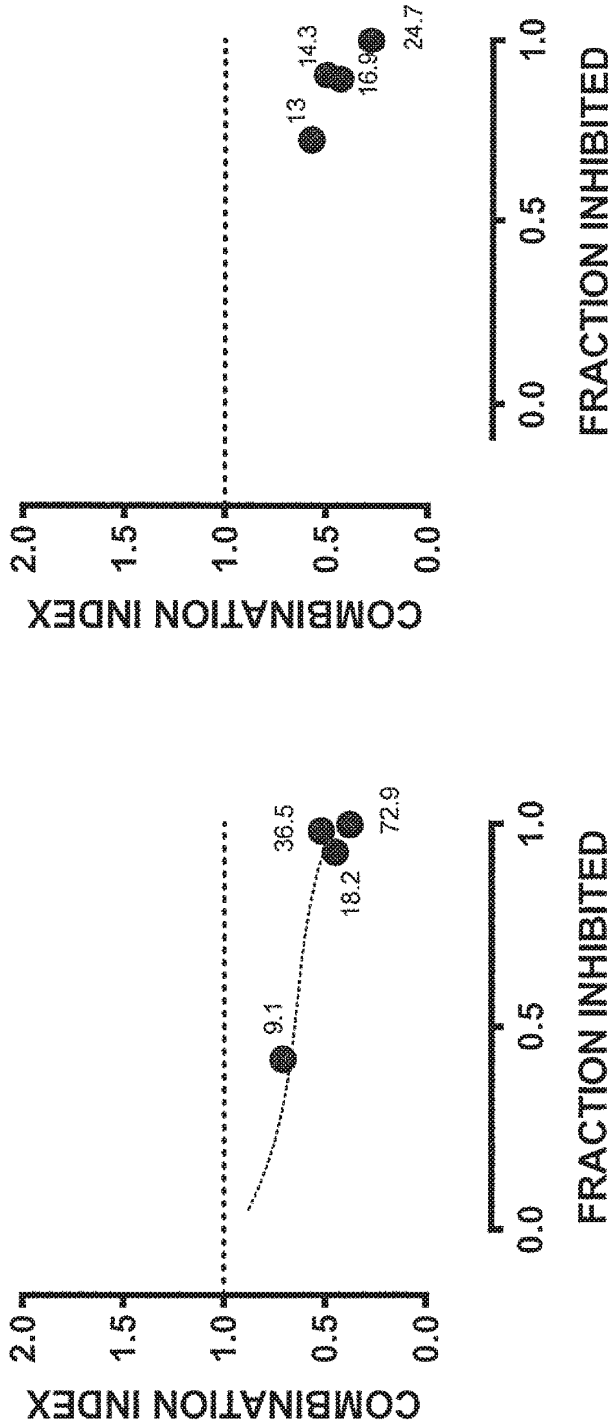


FIG. 19C

FIG. 19D

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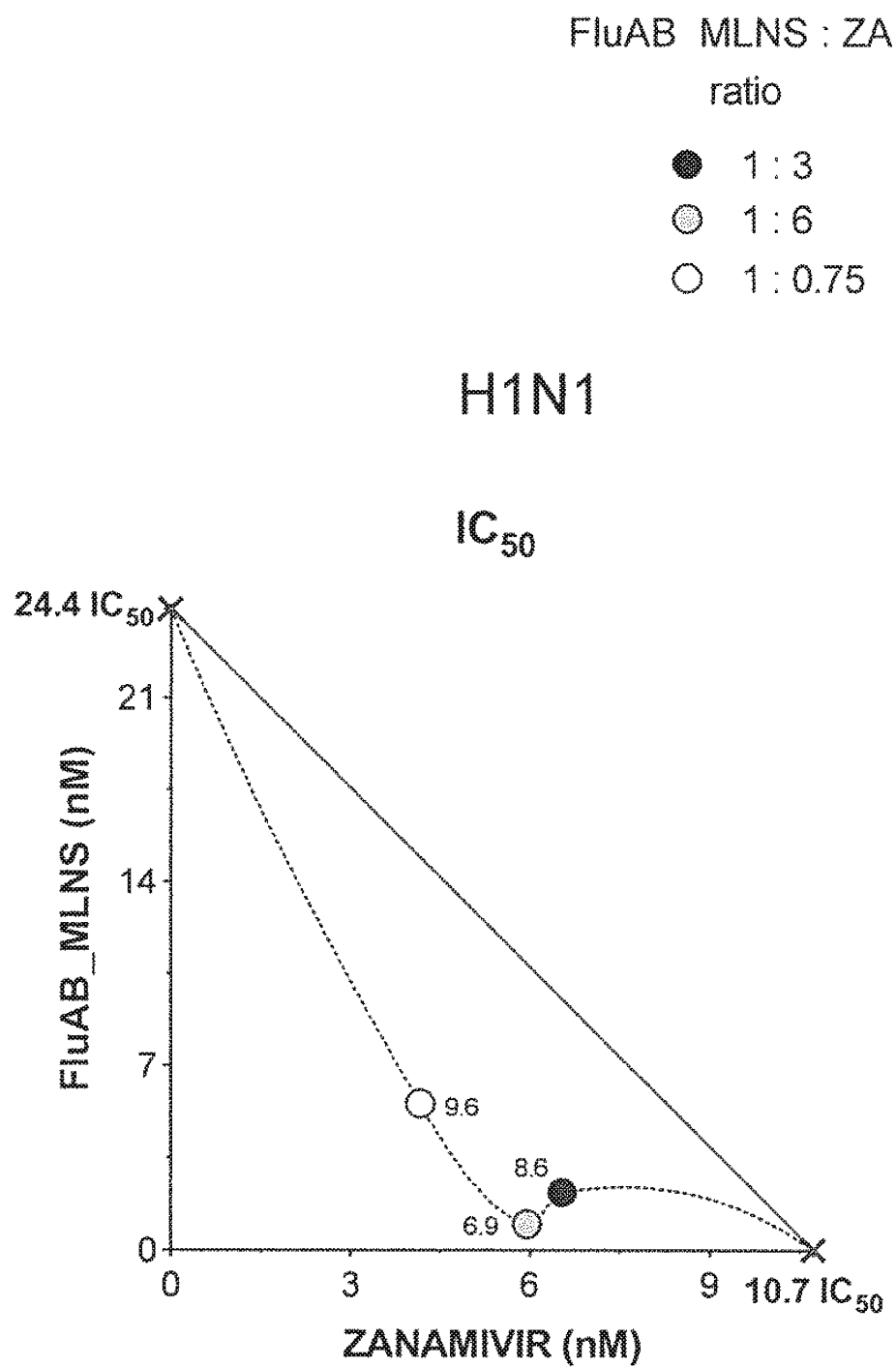


FIG. 20A

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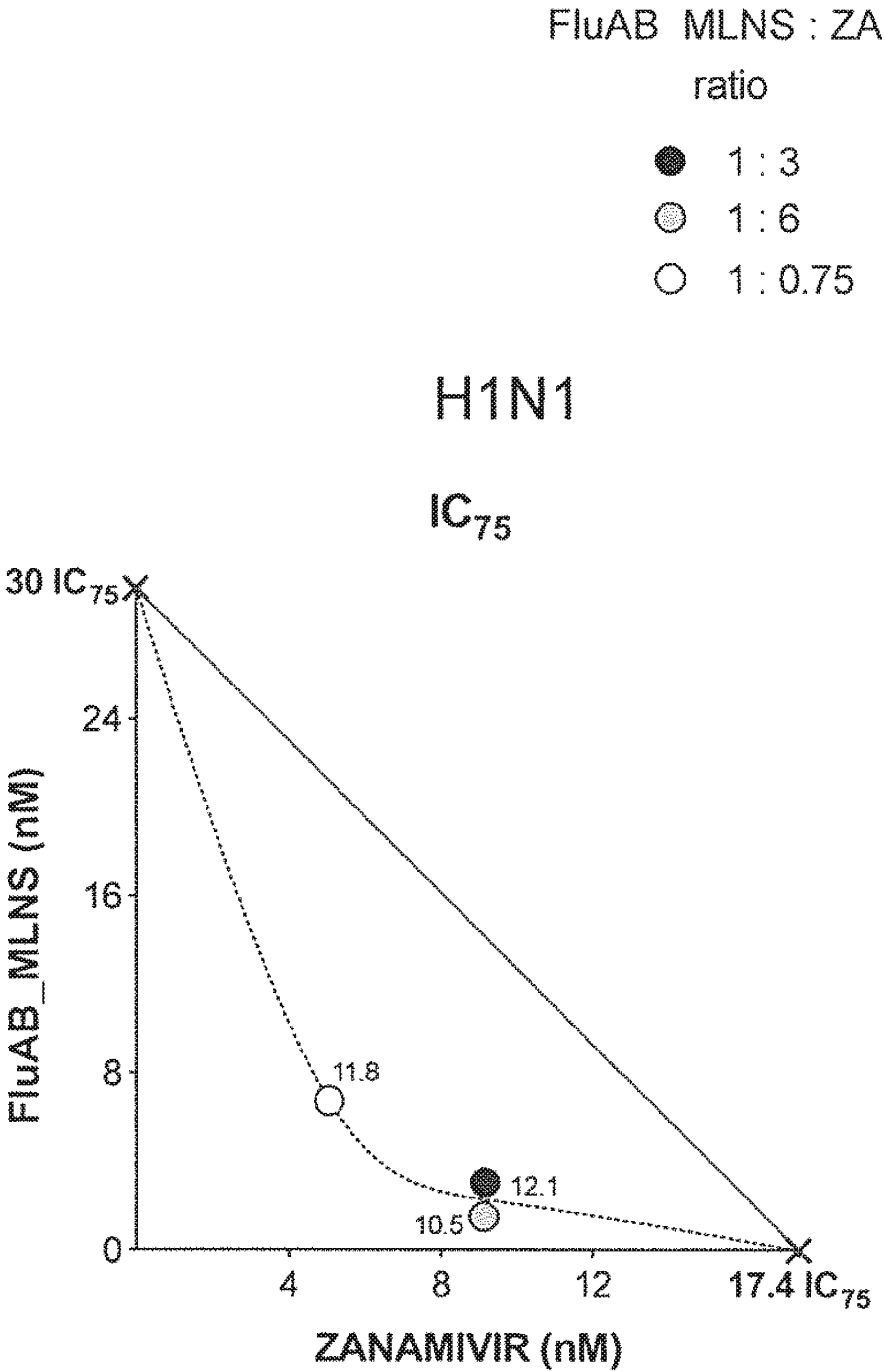


FIG. 20B

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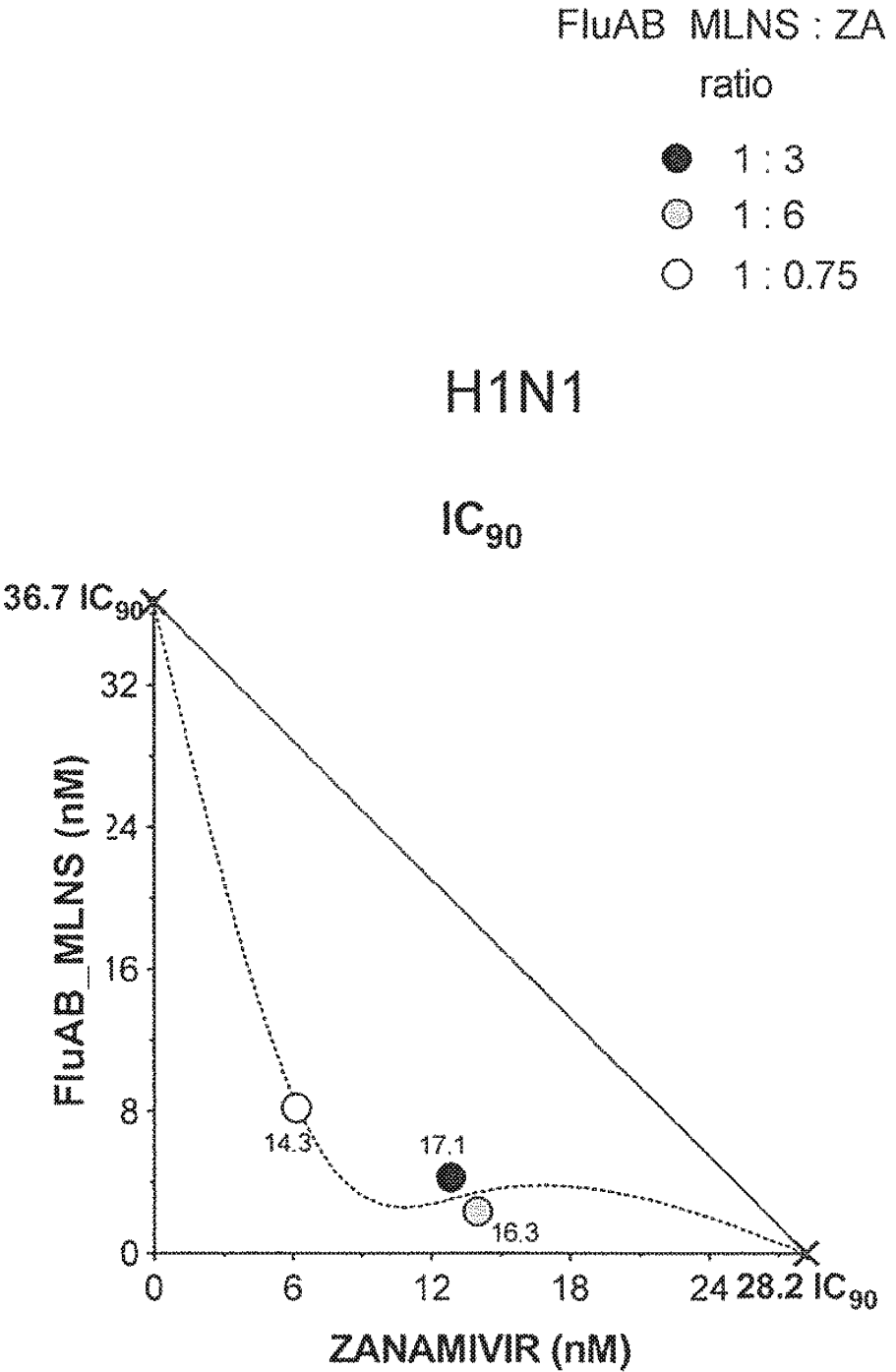


FIG. 20C

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FluAB_MLNS : ZA

ratio

● 1 : 0.75

○ 1 : 6

○ 1 : 3

H3N2

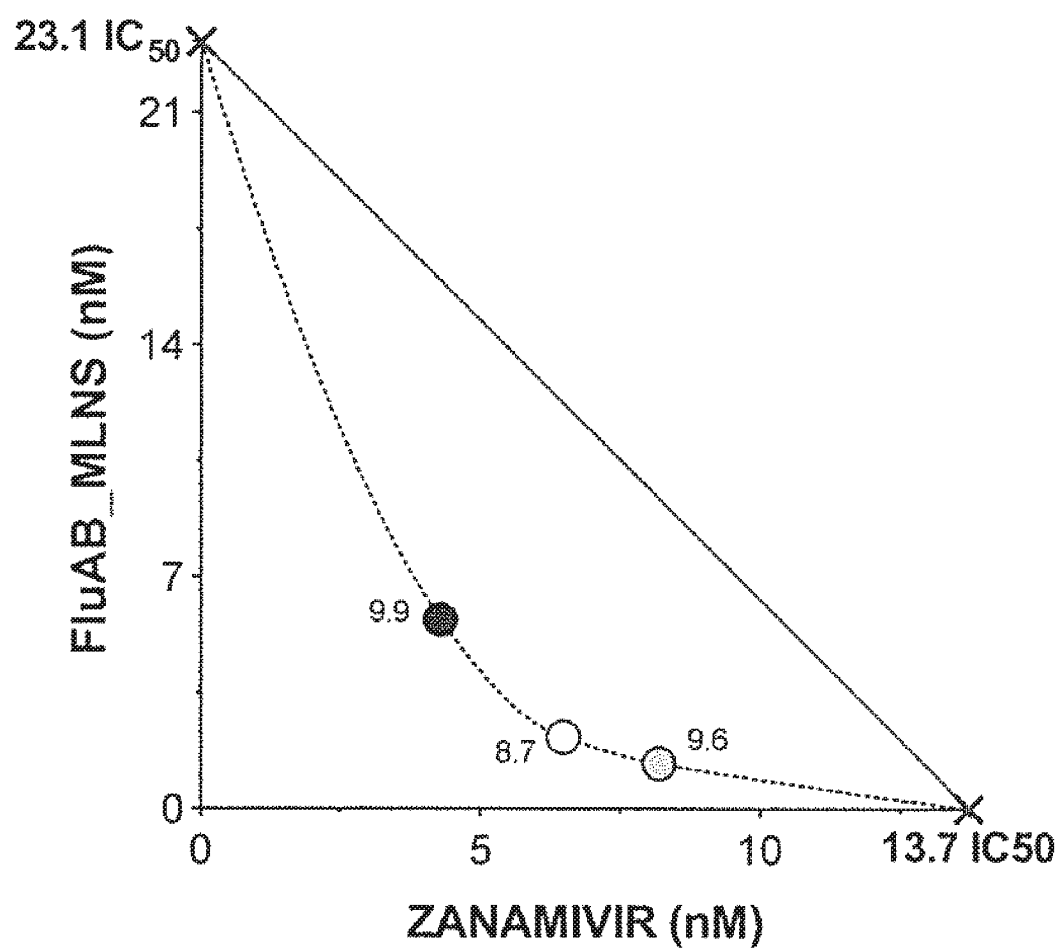
IC₅₀

FIG. 21A

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FluAB_MLNS : ZA

ratio

● 1 : 0.75

○ 1 : 6

○ 1 : 3

H3N2

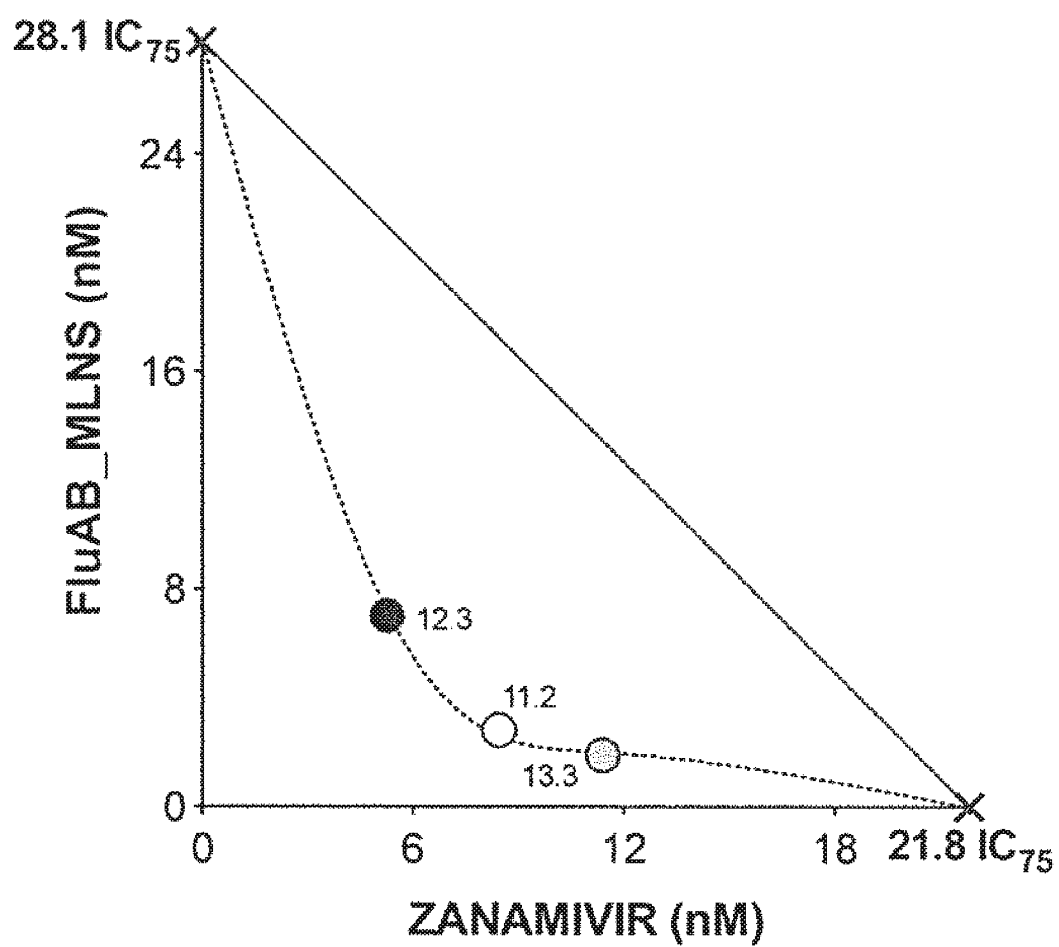
IC₇₅

FIG. 21B

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FluAB_MLNS : ZA

ratio

● 1 : 0.75

○ 1 : 6

○ 1 : 3

H3N2

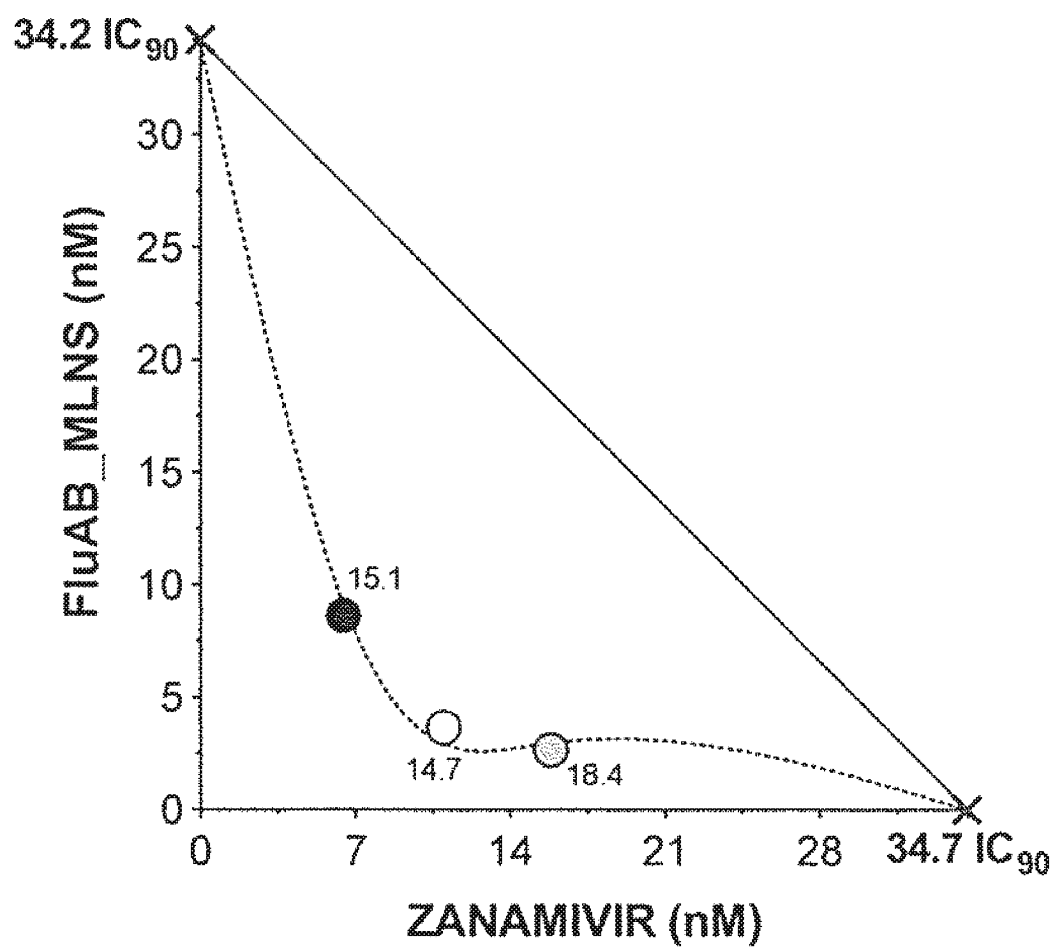
 IC_{90} 

FIG. 21C

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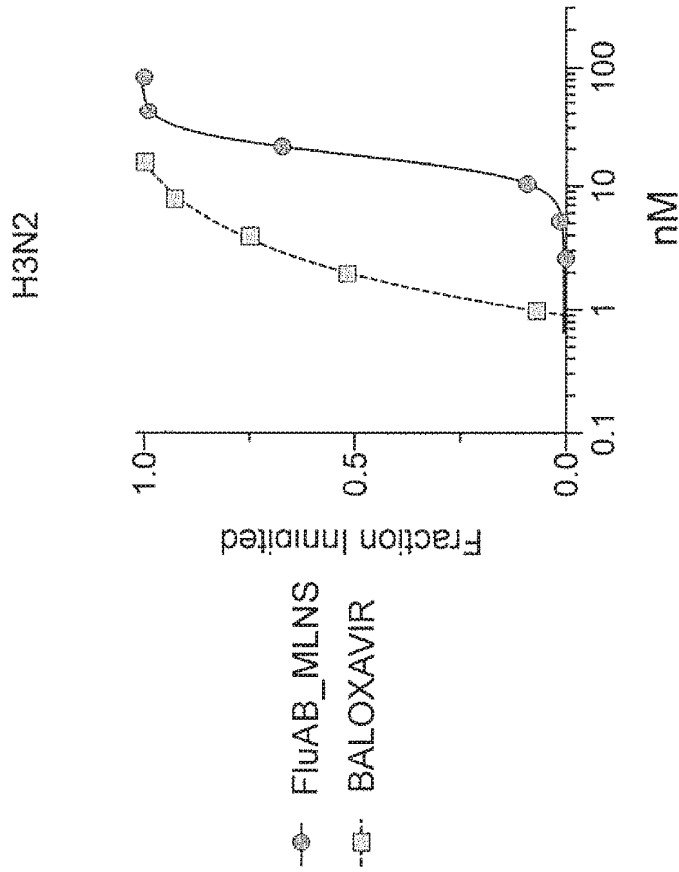


FIG. 22B

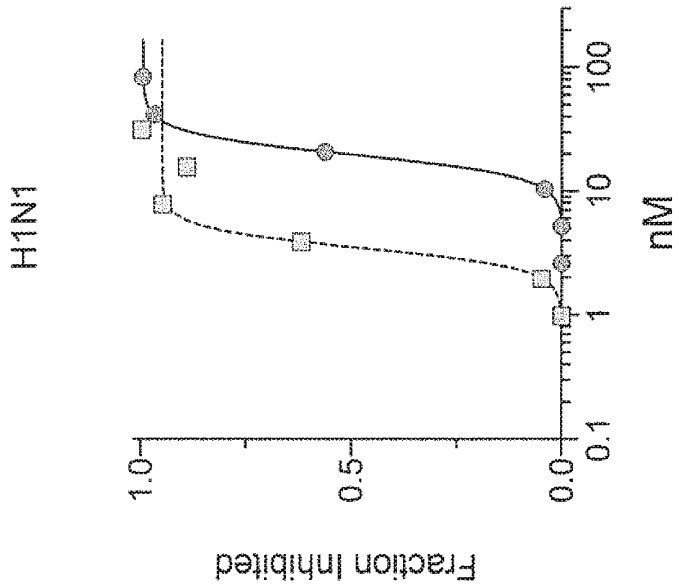


FIG. 22A

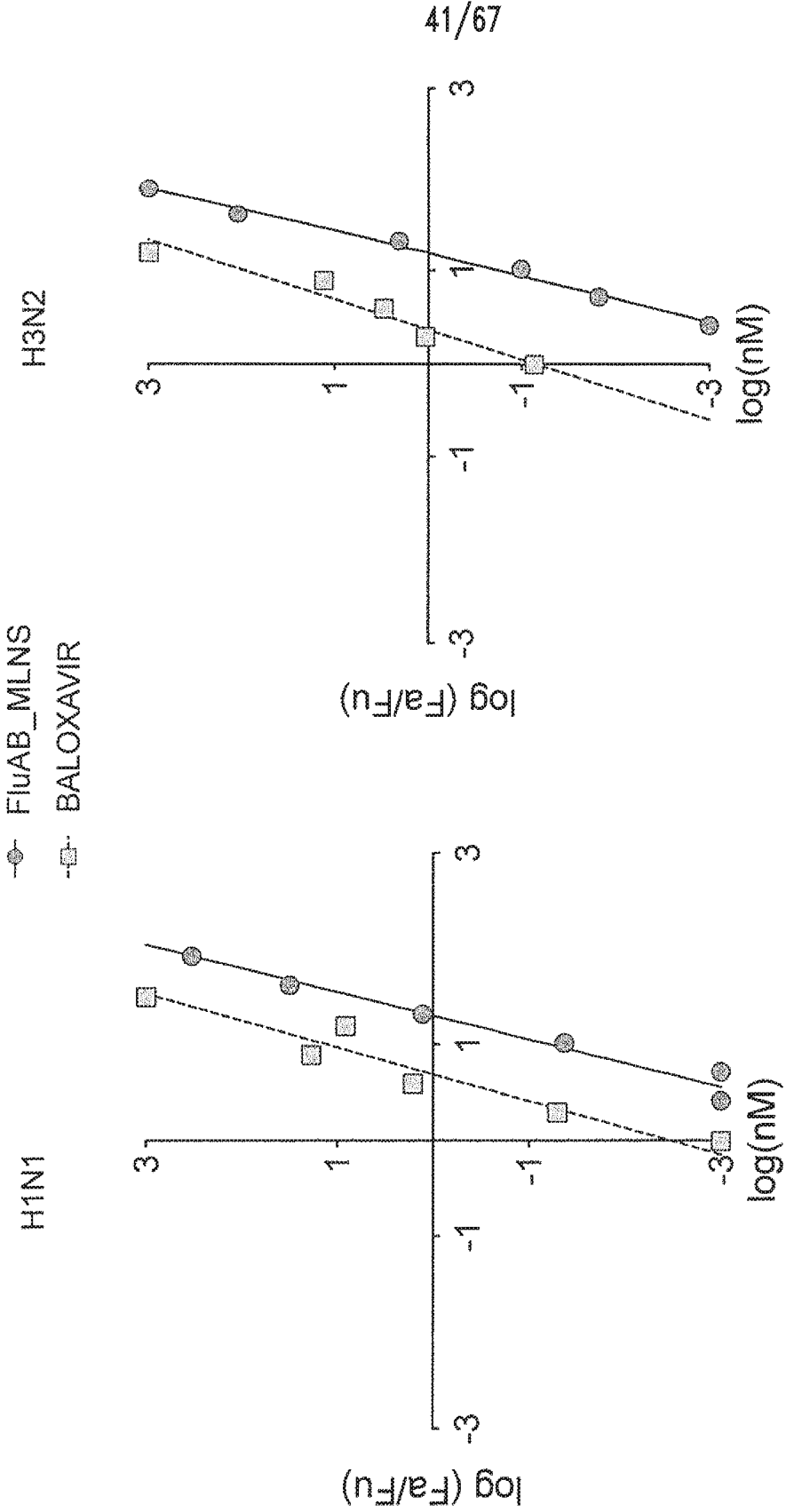


FIG. 22D

FIG. 22C

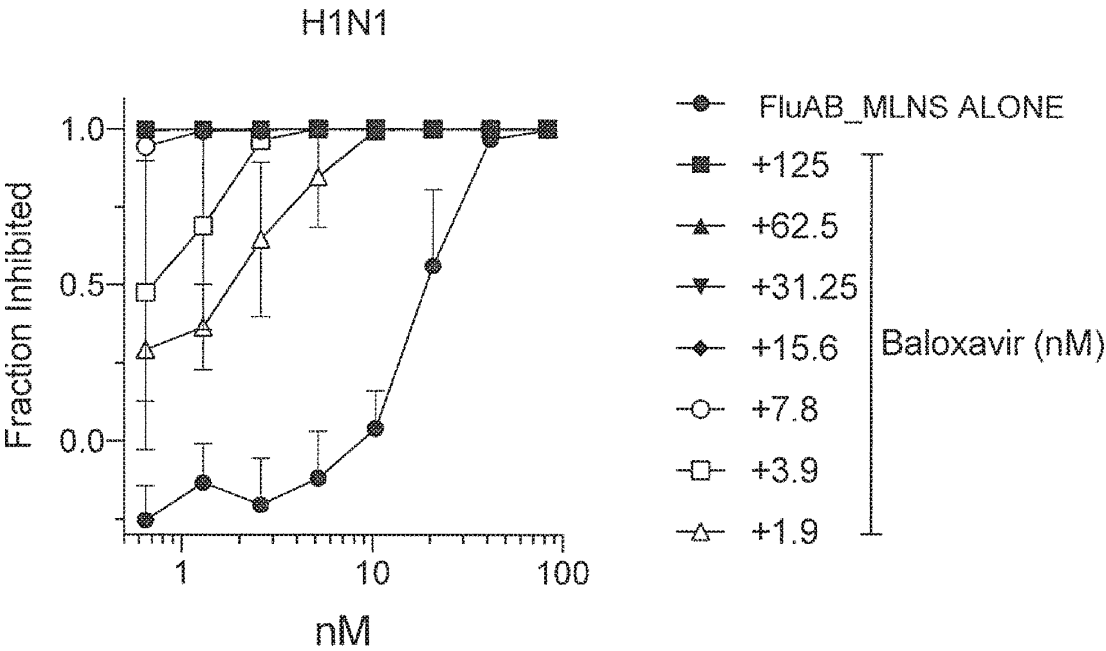


FIG. 23A

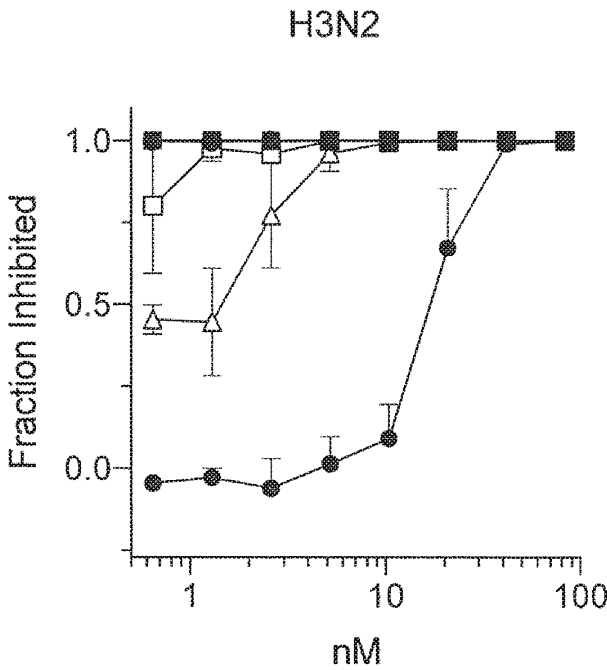


FIG. 23B

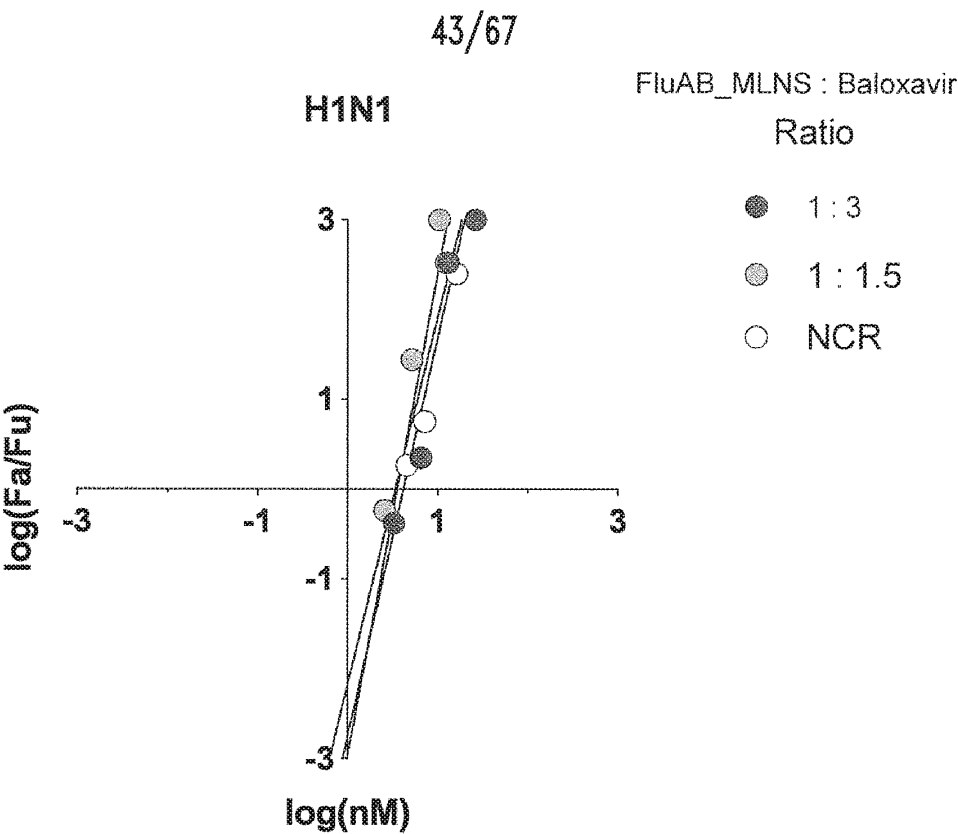


FIG. 24A

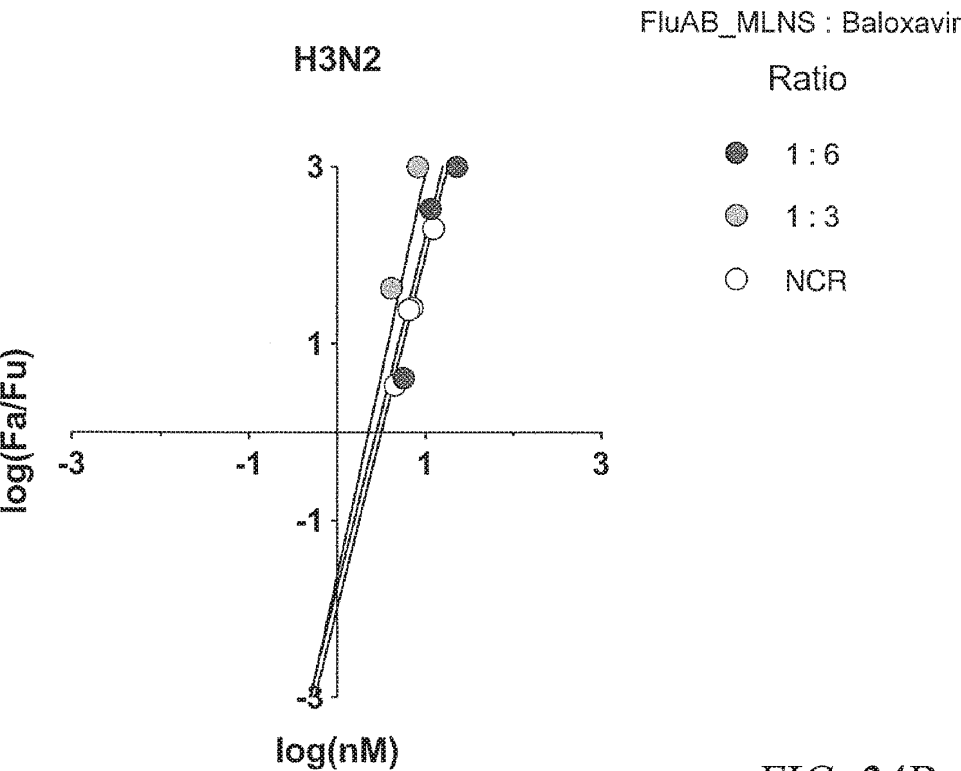


FIG. 24B

H1N1
1:1.5

H3N2
1:3

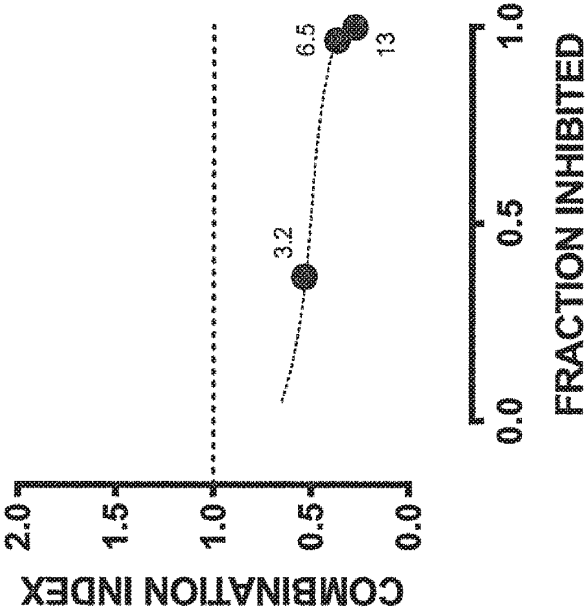


FIG. 25A

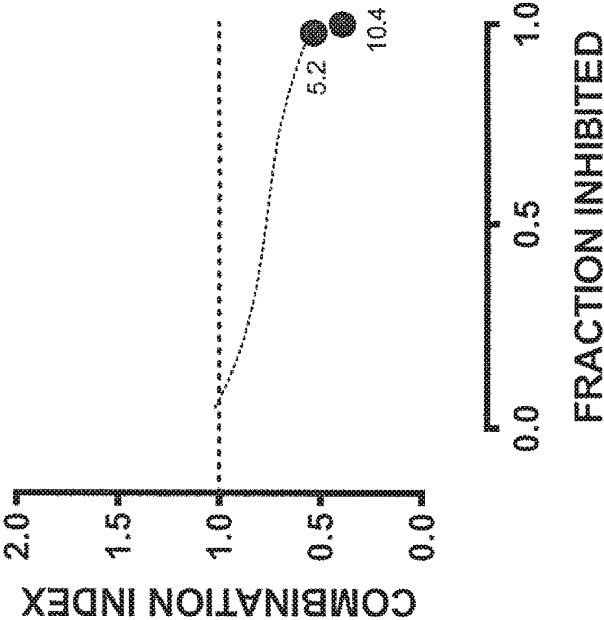
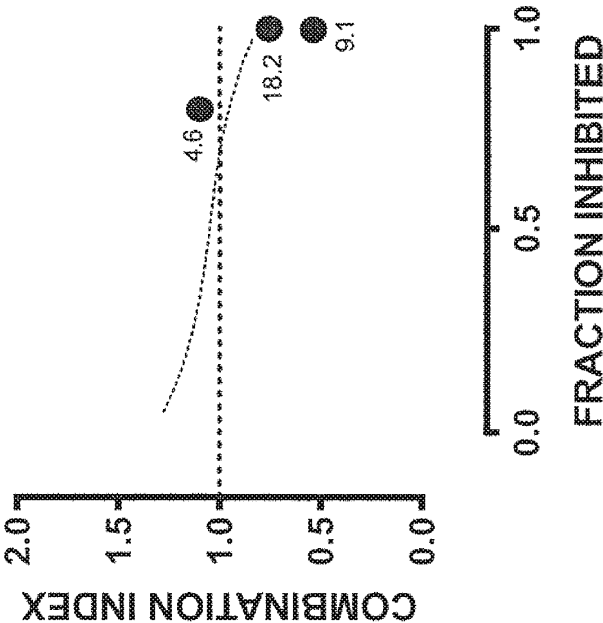


FIG. 25B

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H3N2

1:6

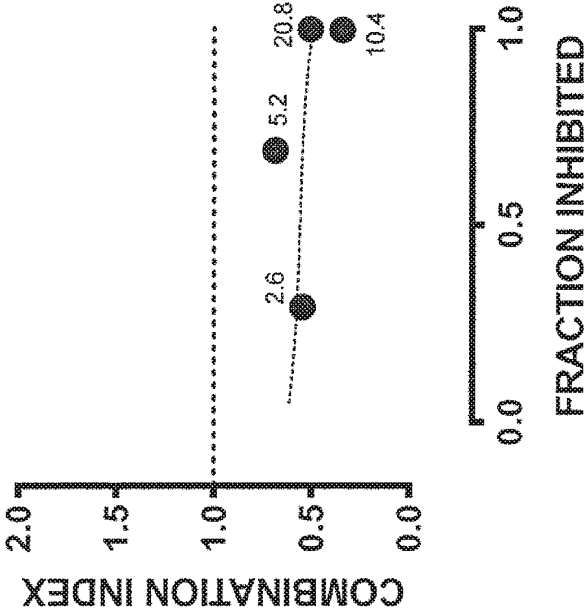


NCR

FIG. 25D

H1N1

1:3



NCR

FIG. 25C

H3N2

NCR

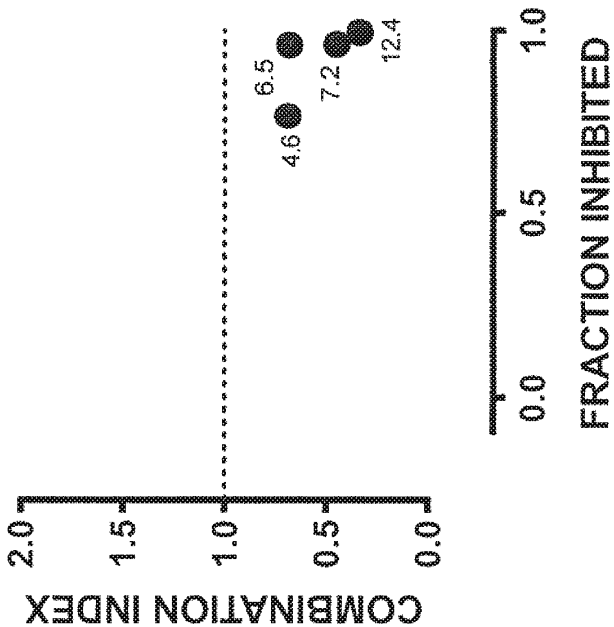


FIG. 25F

H1N1

NCR

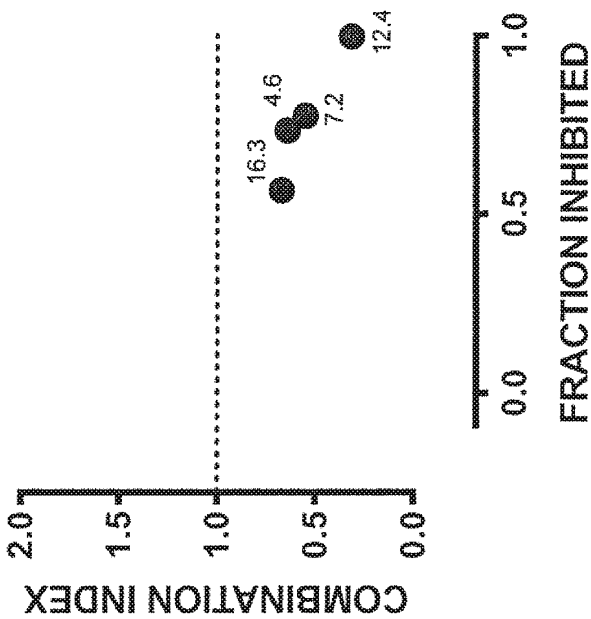


FIG. 25E

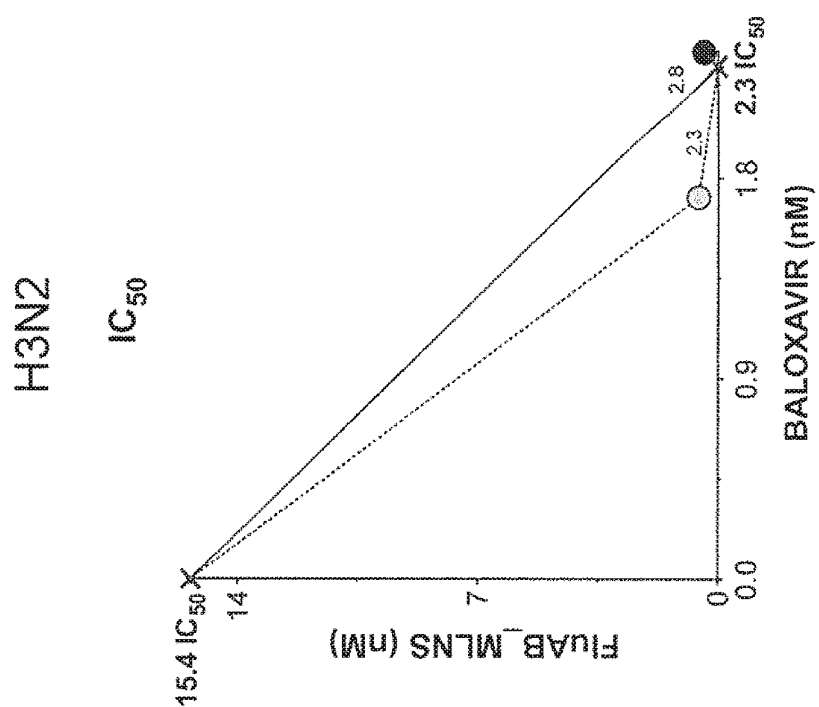


FIG. 26B

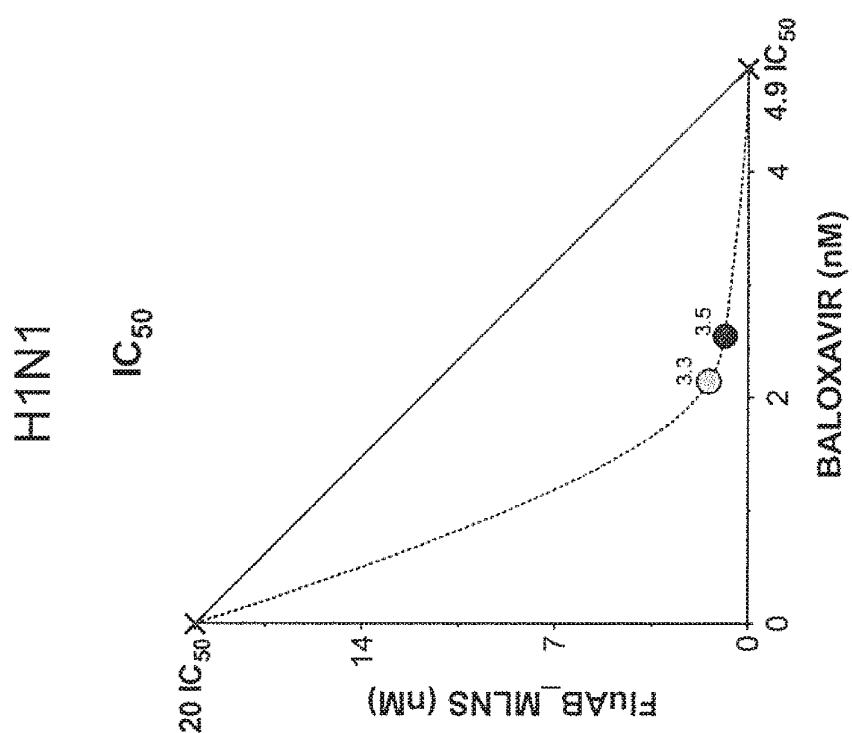


FIG. 26A

H3N2

IC₇₅

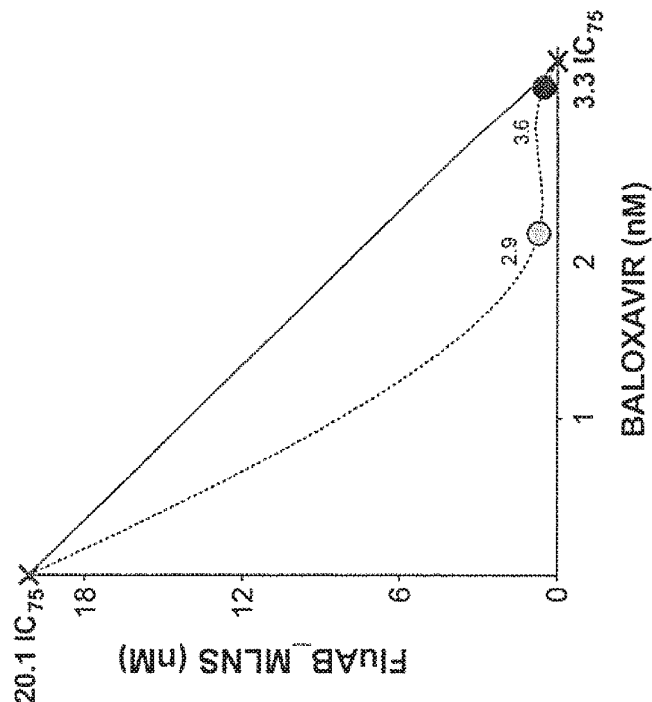


FIG. 26D

H1N1

IC₇₅

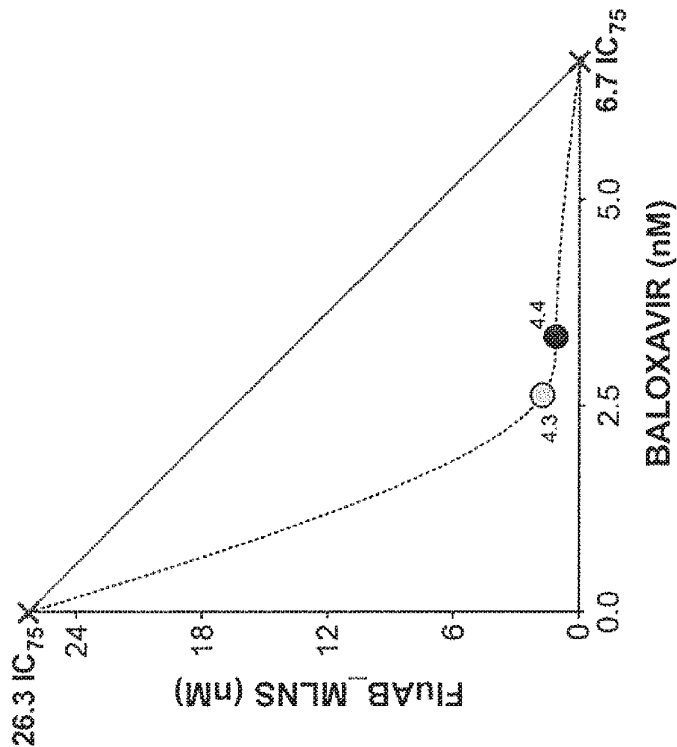
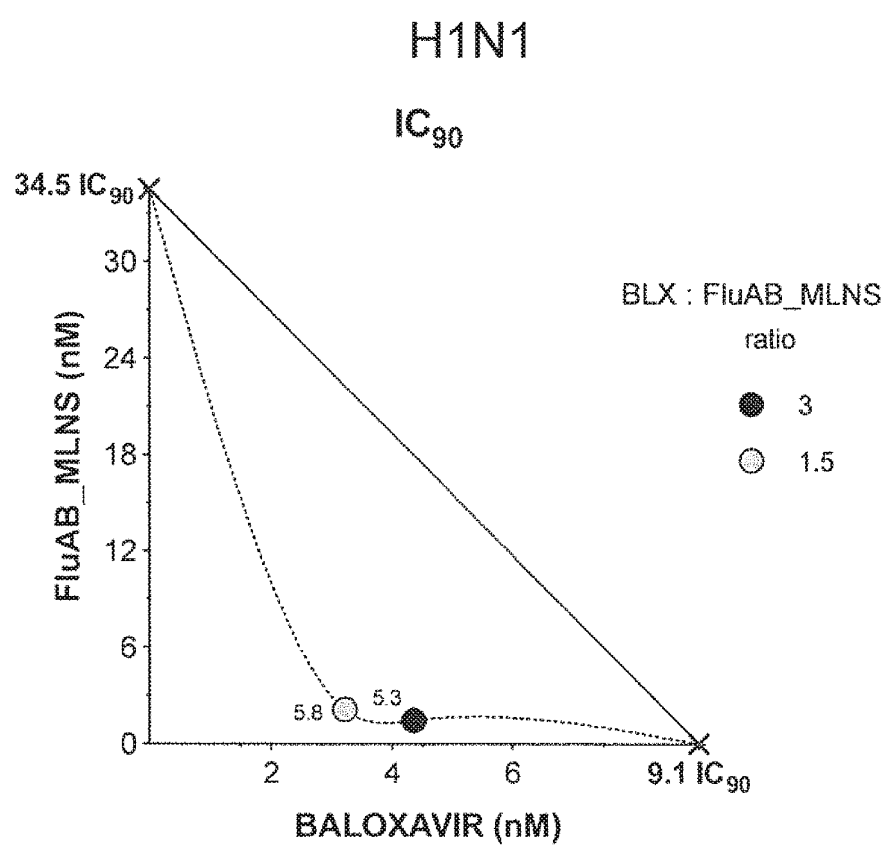


FIG. 26C

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*FIG. 26E*

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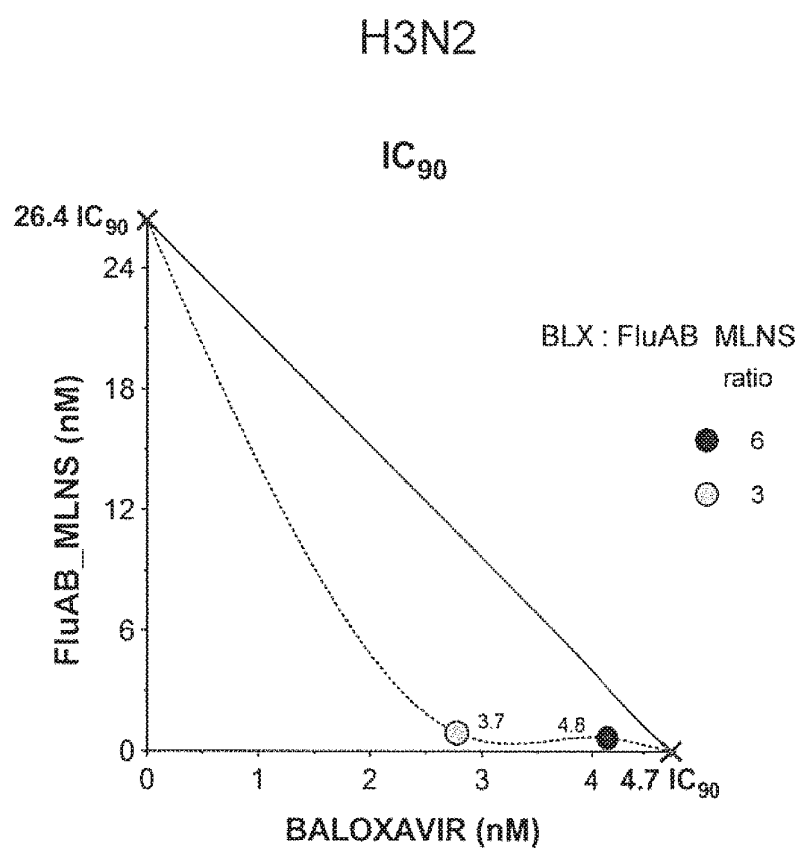


FIG. 26F

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Study Stage	In-patient ^k					Follow-up Period									
	Screening					W1	W2	W4	W6	W8	W12	W20	W34	W52 (EOS)/ET	
Study Visit Week															
Study Visit Day ± Visit Window	D-28 to -2	D-1 ^k	D1	D2	D3	D8±1	D15±2	D29±2	D43±3	D57±4	D85±7	D141±7	D239±7	D365±7	
Informed consent	X														
Demography	X														
Medical history	X														
Inclusion/exclusion criteria	X	X													
Physical examination ^a	X	X ^a	X ^a	X ^a	X ^a	X ^a	X ^a	X ^a	X ^a	X ^a	X ^a	X ^a	X ^a	X	
Body weight, height, and BMI	X														
Nasopharyngeal swab to assess tolerance to procedure	X														
Serology (HBV/HCV/HIV)	X														
Urine for drugs of abuse	X	X													
Vital signs ^b	X		X ^b	X	X	X	X	X	X	X	X	X	X	X	
12 lead ECG ^c	X		X ^c												
Laboratory assessments ^d	X ^d	X				X		X		X		X	X	X	
Pregnancy test ^e	X	X												X	
Randomization			X												
Study drug administration			X												
Local tolerability			X ^f	X	X	X									
BUN analysis (serum) ^g			X ^g	X	X	X	X	X		X	X		X		
Blood sample for PK analysis ^g			X ^g	X	X	X	X	X	X	X	X	X	X	X	
Nasopharyngeal swab for PK analysis ^g			X	X	X	X	X	X		X	X		X		
Anti-drug Antibody (serum)			X ^b				X	X		X		X	X	X	
Anti-influenza A Antibody titer (serum)			X ^b					X							

FIG. 27A

Study Stage	In-patient ^k				Follow-up Period										
	Screening					W1	W2	W4	W6	W8	W12	W20	W34	W52 (EOS)/ET	
Study Visit Week															
Study Visit Day $\pm$ Visit Window	D-28 to-2	D-1 ^k	D1	D2	D3	D8 $\pm$ 1	D15 $\pm$ 2	D29 $\pm$ 2	D43 $\pm$ 3	D57 $\pm$ 4	D85 $\pm$ 7	D141 $\pm$ 7	D239 $\pm$ 7	D365 $\pm$ 7	
ILI symptom surveillance ⁱ											X				
Review/record AEs ^j											X				
Concomitant medications											X				

^aPhysical examinations on Day-1 through W34 (inclusive) will be symptom-directed.

^bOn Day 1, vital signs should be measured within 1 hour pre-dose and 1 hour post-dose.

^cOn Day 1, ECGs will be collected $\leq$ 15 minutes pre-dose and $\leq$ 30 minutes post-dose.

^dSee Example 7 for laboratory tests; INR, PT and PTT to be performed only at screening. Urinalysis to be performed only at screening, Day 1 (pre-dose), and Week 1, 2, 4 and 8 visits.

^eApplicable for women of child bearing potential. Serum pregnancy test will be performed at first screening and urine pregnancy tests will be performed thereafter.

^fLocal tolerability assessment should be done approximately 30 min, 2 hr., 12 hr., 24 hr., and 48 hr. after dose administration.

^gSee Example 7 for PK timepoints.

^hOn Day 1, sample will be collected pre-dose.

ⁱSubjects will begin completing ILL symptom surveillance on Day 3 and continue twice weekly until End of Study.

^jRefer to Example 7 for reporting instructions.

^kSubjects will be admitted on Day-1 and confined at least 12 hours prior to dosing and released following completion of assessments on Day 3.

FIG. 27B

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Study Stage	Screening	Dosing	Follow-up Period				
Study Visit Week			W2	W4	W8	W12	W24 (EOS)/ET
Study Visit Day ± Visit Window	D -28 to -1	D1	D15±2	D29±2	D57±7	D85±7	D169±7
Informed consent	X						
Medical history	X						
Inclusion/exclusion criteria	X	X					
Physical examination ^a	X	X ^a	X ^a	X ^a	X ^a	X ^a	X
Body weight, height, and BMI	X						
Vital signs ^b	X	X ^b	X	X	X	X	X
12 lead-ECG ^c	X	X ^c					
Laboratory assessments ^d	X ^d	X ^f	X	X	X	X	X
Pregnancy test ^e	X	X ^f					X
Anti-influenza A Antibody titer ^f		X ^f		X			
Urine for drugs of abuse	X						
Study drug administration		X					
Blood sample for PK analysis		X ^f	X	X	X	X	X
Anti-drug Antibody (serum)		X ^f	X	X	X	X	X
ILI symptom surveillance ^g			X ^g				
Review/record AEs			X				
Concomitant medications			X				

FIG. 28A

- ^a Physical examination on Day 1 and Weeks 2, 4, 8 and 12 will be symptom-directed.
- ^b On Day 1, vital signs should be measured within 1 hour pre-dose and 1 hour post-dose.
- ^c On Day 1, ECGs will be collected $\leq$ 15 minutes pre-dose and $\leq$ 30 minutes post-dose.
- ^d See Example 7 for laboratory tests; INR, PT and PTT to be performed only at screening, Day 1 (pre-dose), and Week 1, 2, 4 and 8 visits.
- ^e Applicable for women of child bearing potential. Serum pregnancy test will be performed at first screening and urine pregnancy tests will be performed thereafter.
- ^f On Day 1, sample will be collected pre-dose.
- ^g ||| symptom surveillance will continue (same as Part A) twice weekly through End of Study.

FIG. 28B

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Study Stage	Screening	Dosing	Twice weekly	Follow-up Period		
				W4 ±1 week	W12 ±2 weeks	End of season +2 weeks (EOS)/ET
Study Visit ± Visit Window	D -28 to -1	D1				
Informed consent	X					
Demography	X					
Medical history	X					
Inclusion/exclusion criteria	X	X				
Physical examination ^a	X	X ^a		X ^a		X
Body weight, height, and BMI	X					
Vital signs ^b	X	X ^b		X		X
12-lead ECG	X					
Laboratory assessments ^c	X ^c			X		X
Pregnancy test ^d	X	X ^e				X
Anti-influenza A Antibody titer ^e		X ^e				X
Blood sample for PK analysis				X	X	X
Anti-drug Antibody (serum)		X ^e		X	X	X
Genotyping (serum)		X ^e				
Exploratory biomarkers (serum)		X ^e				X
Randomization		X				
Study drug administration		X			X ^f	
ILI symptom surveillance			X			
Review/record AEs ^g						
Concomitant medications				X	X	

FIG. 29A

- ^a Physical examination on Day 1, Week 4, and Week 12 will be symptom-directed.
- ^b On Day 1, vital signs should be measured within 1 hour pre-dose and 1 hour post-dose.
- ^c See Example 7 for laboratory tests; INR, PT and PTT to be performed only during screening.
- ^d Applicable for women of child bearing potential. Serum pregnancy test will be performed at first screening and urine pregnancy tests will be performed locally thereafter.
- ^e On Day 1, sample will be collected pre-dose.
- ^f Only if dose level requires additional injection.
- ^g Refer to Example 7 for reporting instructions.

FIG. 29B

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Days After ILI Symptoms Onset	ILI-D1	ILI-D2	ILI-D3	ILI-D4	ILI-D5	ILI-D6	ILI-D7	ILI-D8	ILI-D9	ILI-D10	ILI-D28 ±3 days
Symptom-directed PE	X										X
Vital signs	X										
Anti-influenza A Antibody titer	X										X
Nasopharyngeal swab virology	X										
Confirmation of influenza A	X										
Blood sample for PK	X										
Anti-drug Antibody (serum)	X										
Laboratory assessment ^a	X										
Exploratory Biomarkers (serum)	X										X
Self-measured oral temperature ^b	X	X	X	X	X	X	X	X	X	X	
WPAI Questionnaire ^c	X							X			
Influenza Symptom severity Questionnaire ^c	X	X	X	X	X	X	X	X	X	X	
Subject contact follow-up (phone call from site) ^d	X	X	X	X	X	X	X	X	X	X	
Review/record AEs						X					
Concomitant medications						X					

^a Only hematology, chemistry, and liver function panels from laboratory tests listed in Example 7.^b Temperature should be measured and recorded in the electronic device twice daily.^c Influenza Symptom Assessment Questionnaire will be completed in the electronic device twice daily up to and including ILI-D10. WPAI Questionnaire will be completed on ILI-D1 and ILI-D28 in the electronic device.^d Subjects will be asked if they have received medically attended healthcare for ILI outside of the clinical study site via phone and during in-clinic visits on ILI-D1 and ILI-D28

FIG. 30

Study Day/Week	Protocol Time	Blood PK (serum)	BUN Analysis (serum)	Nasopharyngeal swab for PK
Day 1	Pre-dose (≤ 5 min)	X		
	1 hr post-dose	X		
	2 hr post-dose	X	X	X
	6 hr post-dose	X		
	12 hr post-dose	X		X
Day 2	24 hr post-dose	X	X	X
Day 3	48 hr post-dose	X	X	X
Week 1		X	X	X
Week 2		X	X	X
Week 4		X	X	X
Week 6		X		
Week 8		X	X	X
Week 12		X	X	X
Week 20		X		
Week 34		X	X	X
Week 52		X		

FIG. 31

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<u>Hematology</u> Complete blood cell count (white blood cells, red blood cells, hemoglobin, hematocrit, Platelets) with differential (lymphocyte, monocyte, segmented neutrophils, eosinophils, basophils)	
<u>Chemistry</u> Albumin Blood urea nitrogen (BUN) Calcium Carbon dioxide bicarbonate Calcium Creatine kinase Creatinine	Creatinine clearance Gamma glutamyl transferase (GGT) Glucose Lactate dehydrogenase (LDH) Potassium Sodium
<u>Liver Function tests</u> Alkaline phosphatase (ALP) Alanine Aminotransferase (ALT)	Aspartate Aminotransferase (AST) Bilirubin (total and direct)
<u>Coagulation Parameters (screening only)</u> International Normalized ratio (INR) time Prothrombin time (PT) Partial thromboplastin time (PTT)	
<u>Urinalysis</u> Bilirubin Glucose Ketones Leukocytes Microscopy (if clinically indicated) color Nitrite pH (dipstick)	Proteins Red blood cells (RBCs) Specific gravity Urobilinogen Visual inspection for appearance and Screen for drugs of abuse
<u>Pregnancy Testing (WOCBP only)</u> Beta-human chorionic gonadotropin (serum) Urine pregnancy test	
<u>Serology</u> Part A screening only: HBV (HBsAg) HCV (anti-HCV) with reflex testing if positive HIV (screen)	

FIG. 32

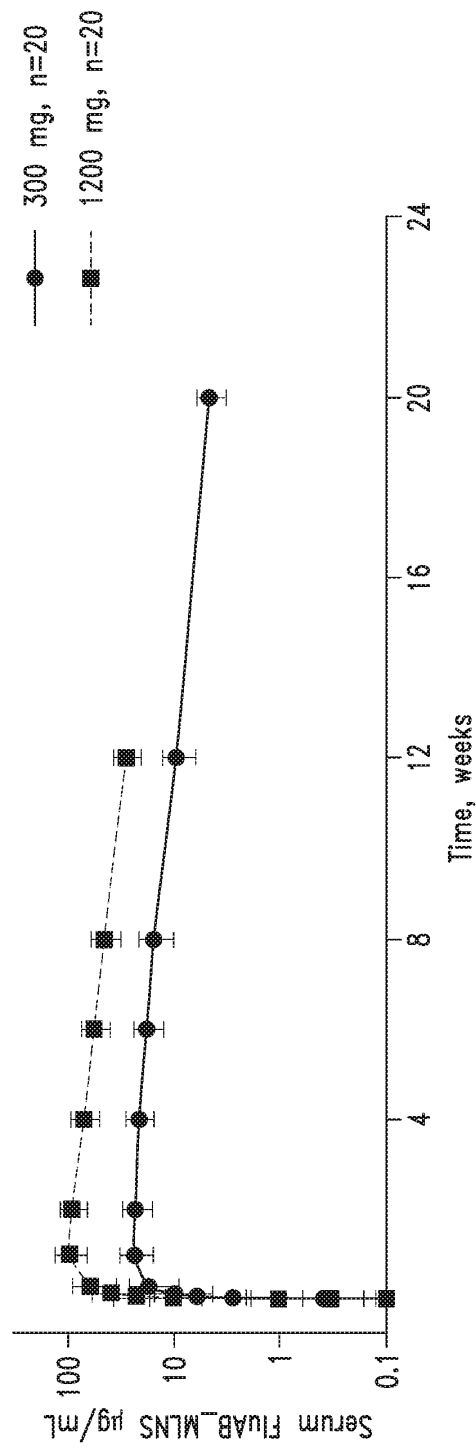
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- Residents of nursing homes and other long-term care facilities

Established diagnosis of:

- Asthma
- Neurological and neurodevelopmental conditions (such as cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability, moderate to severe developmental delay, muscular dystrophy, or spinal cord injury)
- Chronic lung disease (such as chronic obstructive pulmonary disease [COPD], emphysema, and cystic fibrosis)
- Heart disease (such as congenital heart disease, congestive heart failure and coronary artery disease)
- Blood disorders (such as sickle cell disease and Thalassemia)
- Endocrine disorders (such as diabetes and adrenal insufficiency)
- Chronic kidney disease
- Chronic liver disease
- Metabolic disorders (such as inherited metabolic disorders and mitochondrial disorders)
- weakened immune system due to disease or medication (such as individuals with HIV or AIDS, or cancer, or those on chronic steroids)
- People younger than 19 years of age who are receiving long-term aspirin therapy

FIG. 33



Dose mg	C _{max} µg/mL	C _{max} /D µg/mL/mg	T _{max} day	AUC _{inf} day*µg/mL	AUC _{inf} /D day*µg/mL/mg	CL/F mL/day	V/F L	t _{1/2} day
300 (N=20)	24.6 (31.5)	0.08 (31.5)	7.0 (7.0, 14.0)	2260 (30.9)		149 (39.1)	10.6 (38.3)	50.3 (47.7, 51.3)
1200 (N=20)	98.9 (32.0)	0.08 (32.0)	7.0 (7.0, 8.8)					

Data are presented as mean (%CV) except for t_{max} and t_{1/2}, which are presented as median (Q1, Q3)

FIG. 34

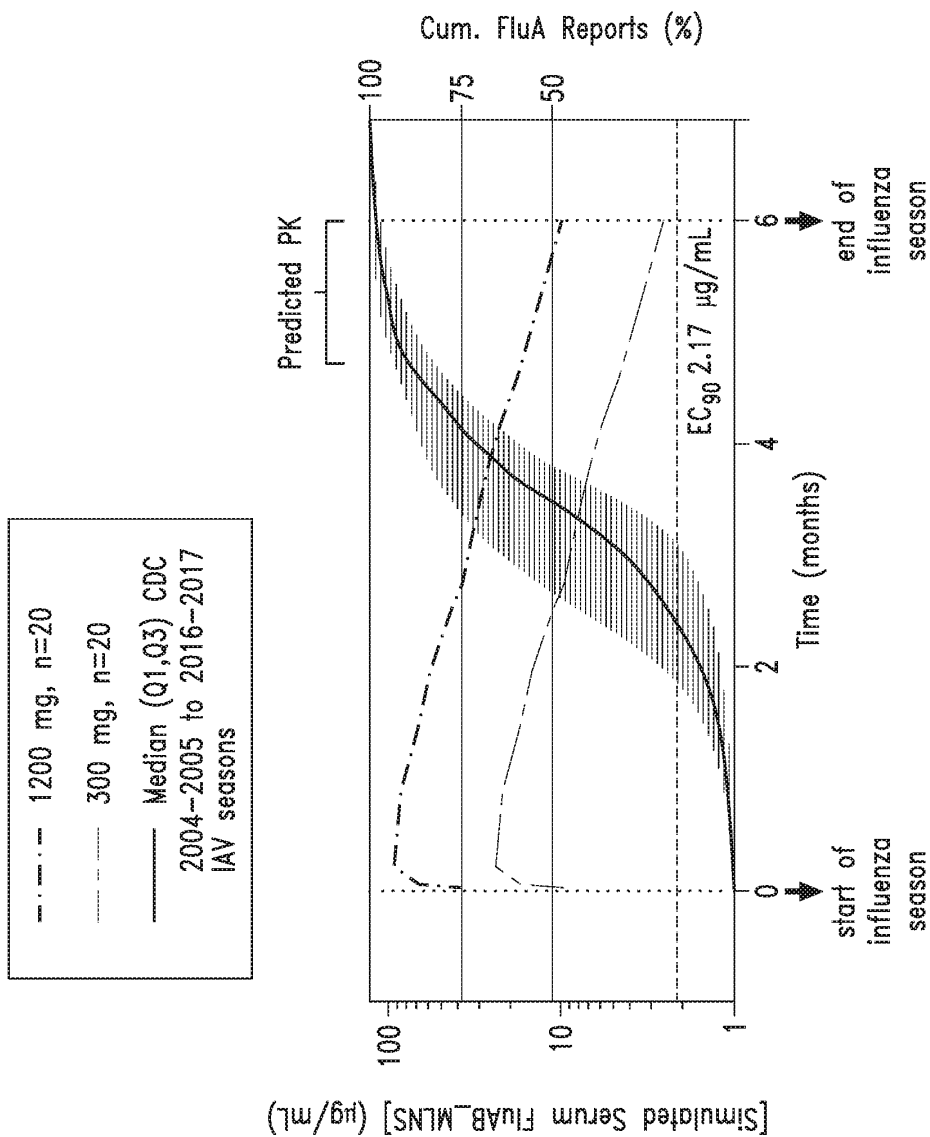


FIG. 35

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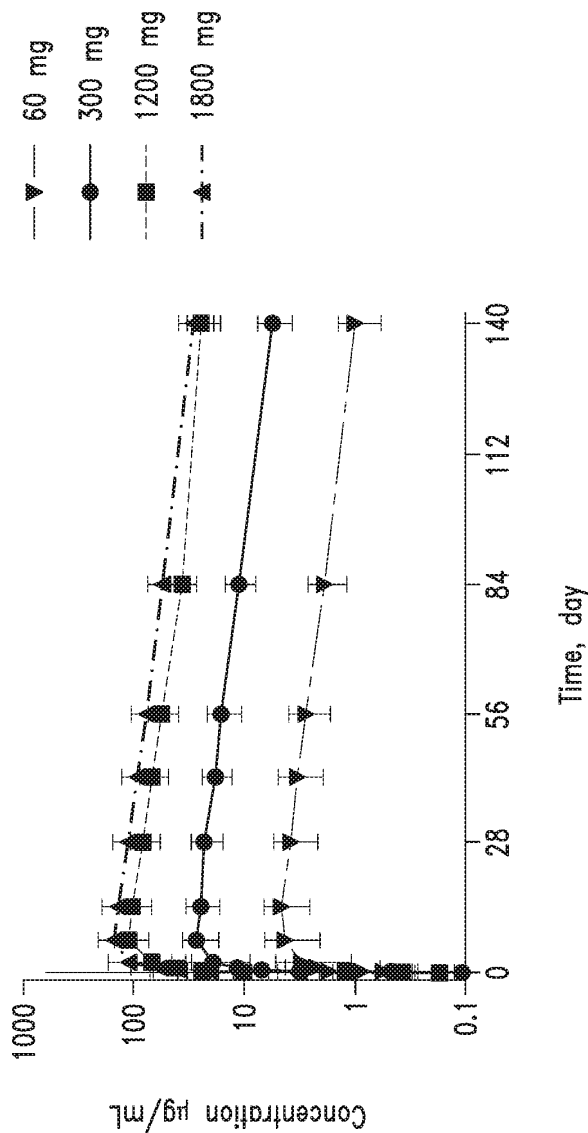


FIG. 36

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Parameter	Dose (mg)			
	300 (N=20)	1200 (N=20)	1800 (N=20)	60 (N=20)
C _{max} , µg/mL	26.6 (35.2)	110 (32.9)	152 (38.4)	4.52 (45.4)
C _{max} /D, µg/mL/mg	0.088 (35.2)	0.091 (32.9)	0.084 (38.4)	0.075 (45.4)
T _{max} , day	7.0 (7.0, 14.0)	7.0 (7.0, 7.0)	7.0 (7.0, 14.0)	14 (7, 17.5)
C _{last} , µg/mL	5.57 (33.7)	27.2 (54.2)	33.5 (71.5)	1.01 (53.1)
T _{last} , day	140	140	140	140
AUC _{last} , day*µg/mL	2010 (32.3)	7180 (32.7)	9930 (38.7)	343 (41.5)
AUC % Extrapolated	18.8 (19.3)	21.4 (22.2)	19.3 (17.8)	19.0 (24.5)
AUC _{inf} , day*µg/mL	2470 (32.3)	9750 (30.0)	12700 (34.8)	455 (34.1)
AUC _{inf} /D, day*µg/mL/mg	8.24 (32.3)	8.12 (30.1)	7.05 (34.8)	7.59 (34.1)
CL/F (mL/day)	137 (39.1)	134 (29.5)	164 (47.0)	157 (58.0)
V/F, L	11.1 (36.1)	11.7 (30.6)	14.1 (55.4)	12.8 (63.1)
t _{1/2} , day	58.7 (53.3, 61.4)	60.1 (56.7, 67.9)	57.8 (54.6, 63.4)	58.1 (49.6, 62.5)

FIG. 37

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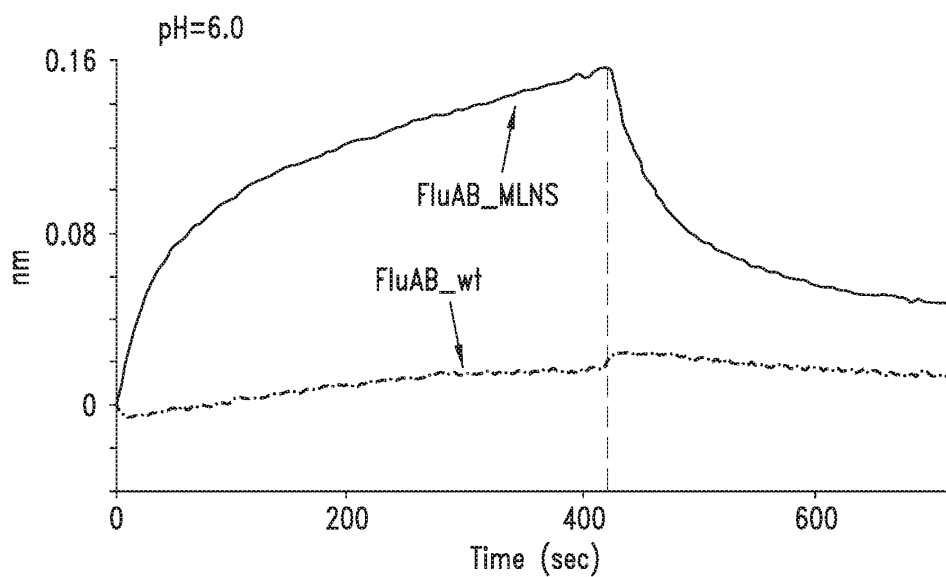


FIG. 38A

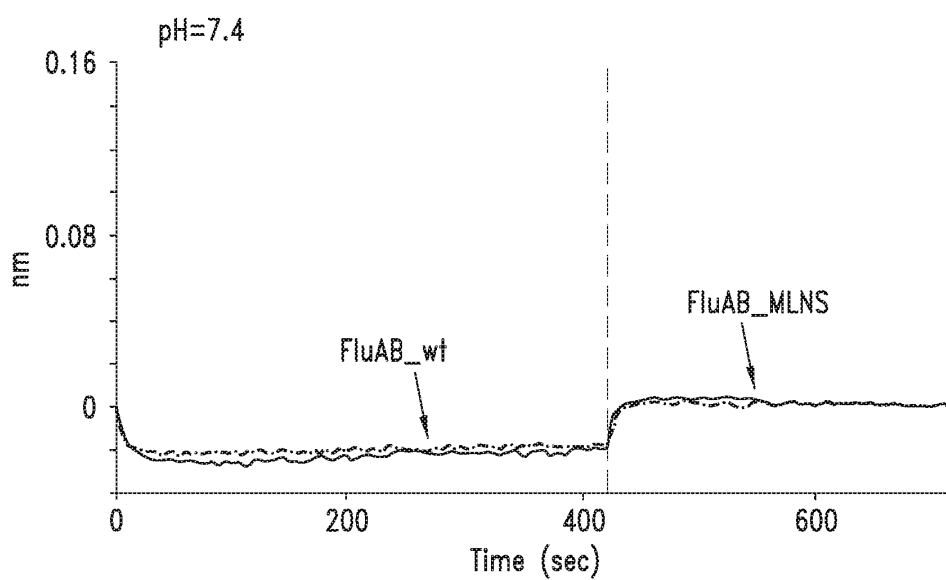


FIG. 38B

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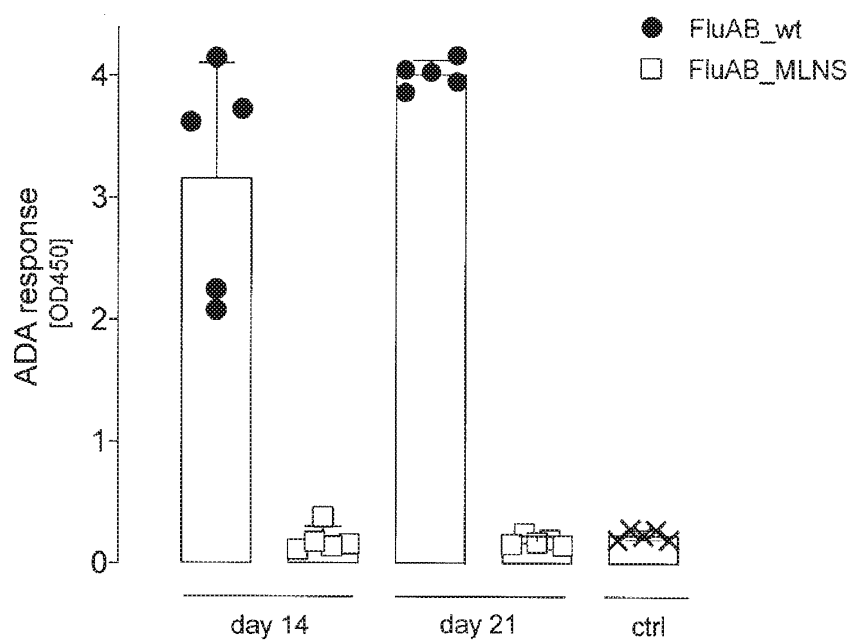


FIG. 39A

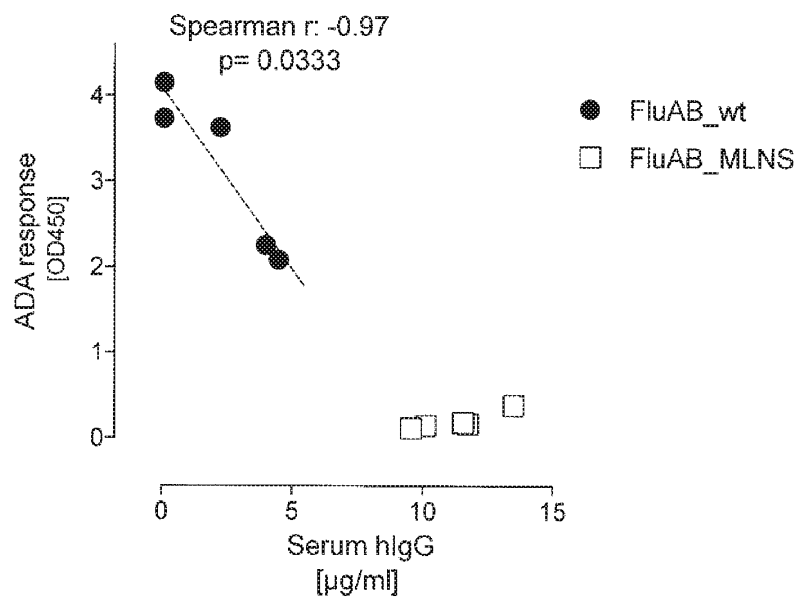


FIG. 39B

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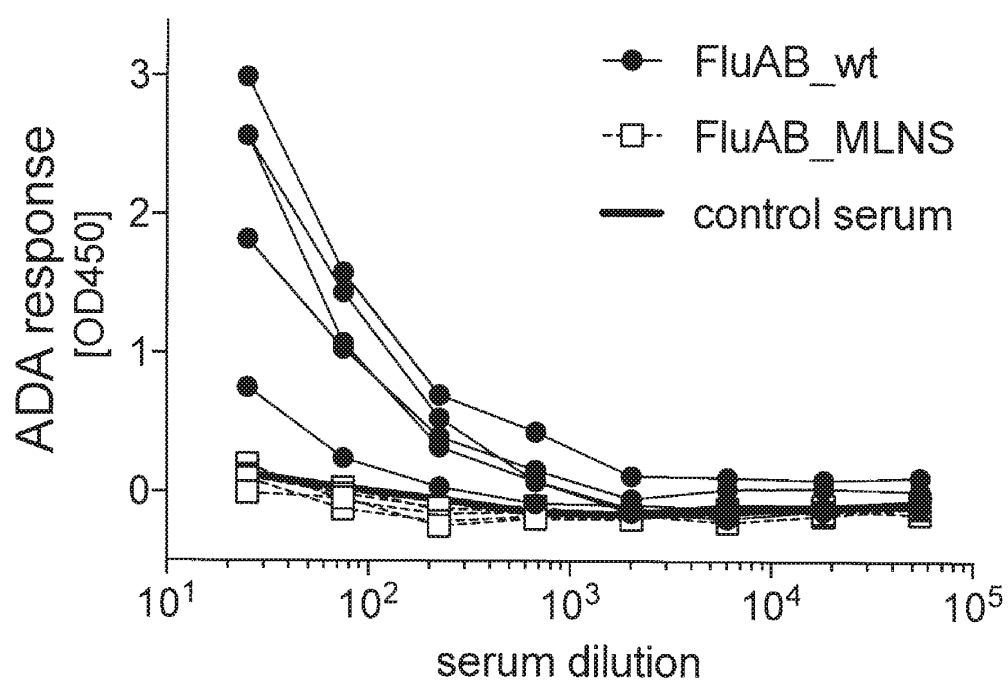


FIG. 40