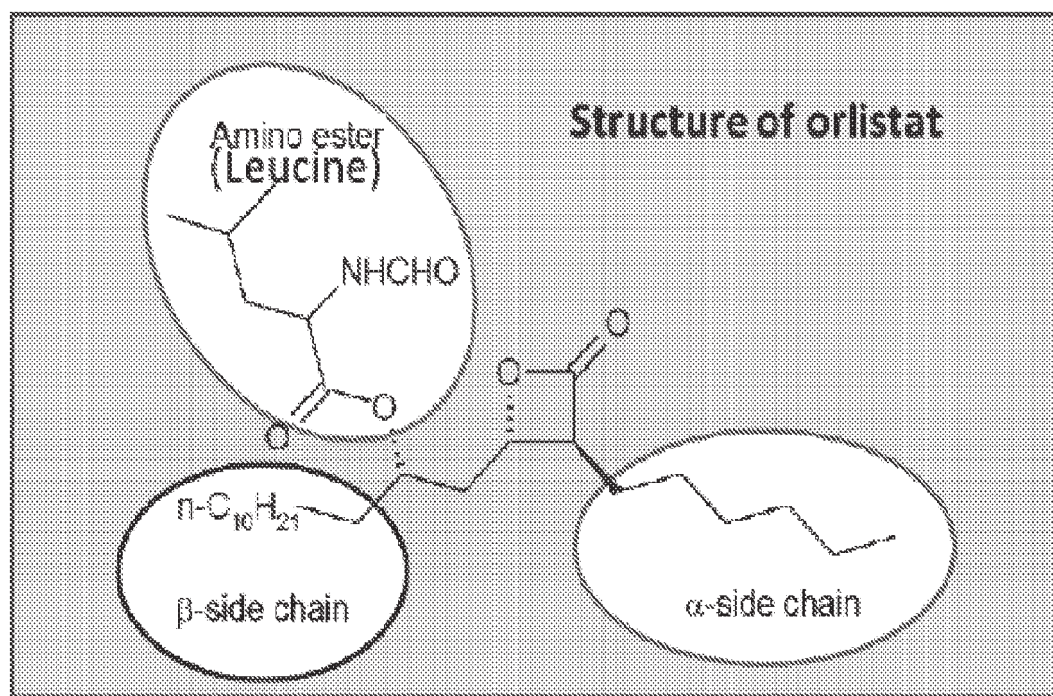
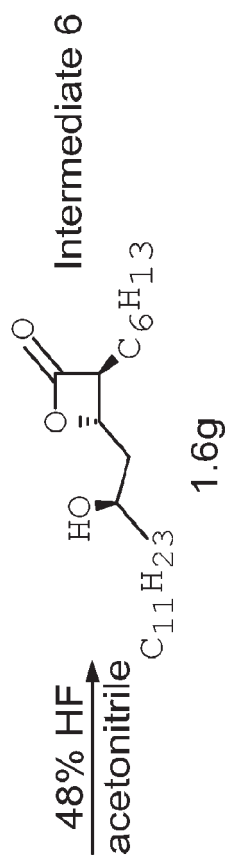
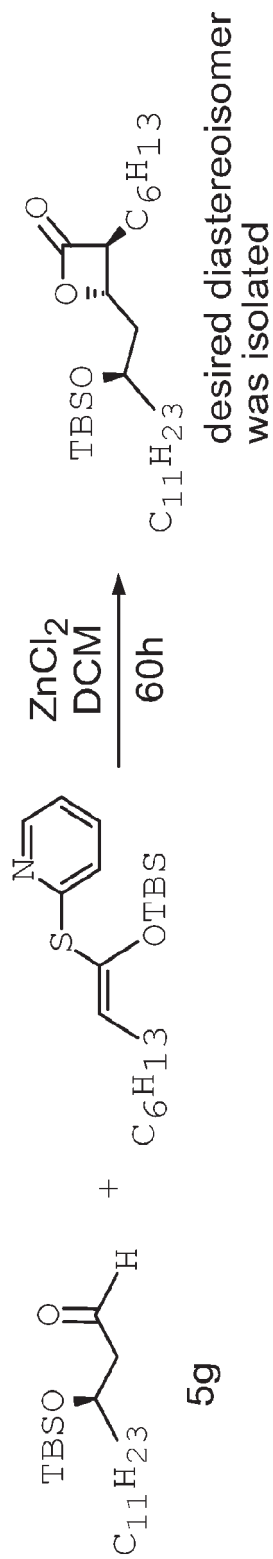


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**FIG. 1**

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Synthesis of intermediate 6 for amino-ester modification:

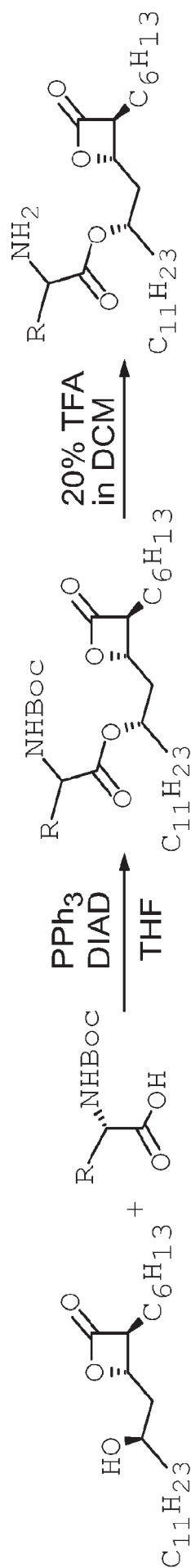


Intermediate 6 was then modified generally as:



FIG. 2

Non-formyl groups were substituted as:



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Formyl groups were substituted as (For details see next page)

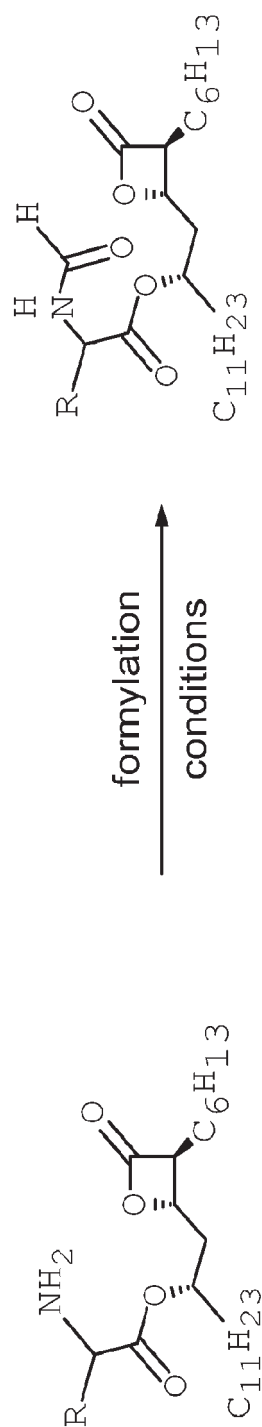


FIG. 2 Cont.

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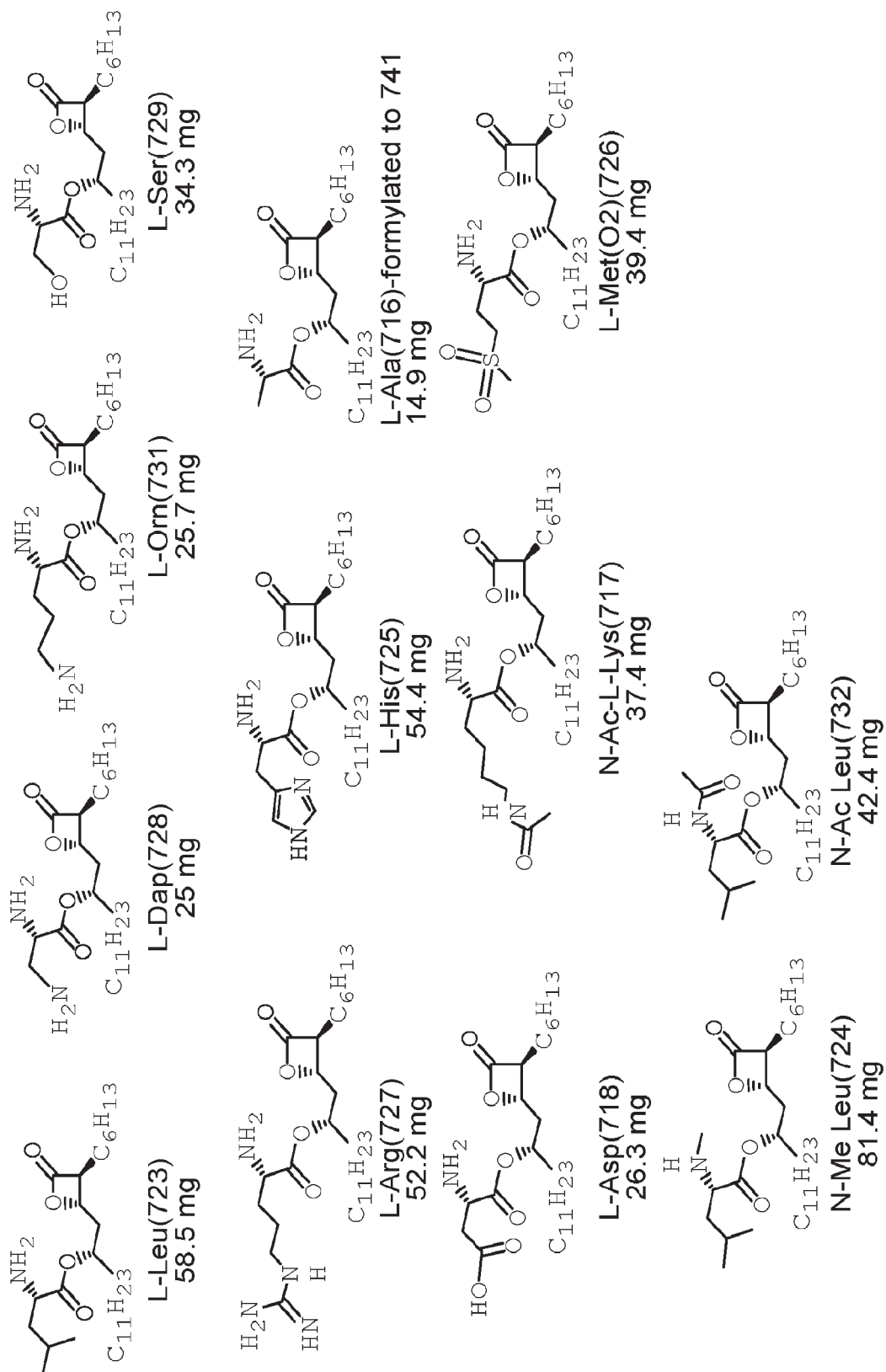


FIG. 3

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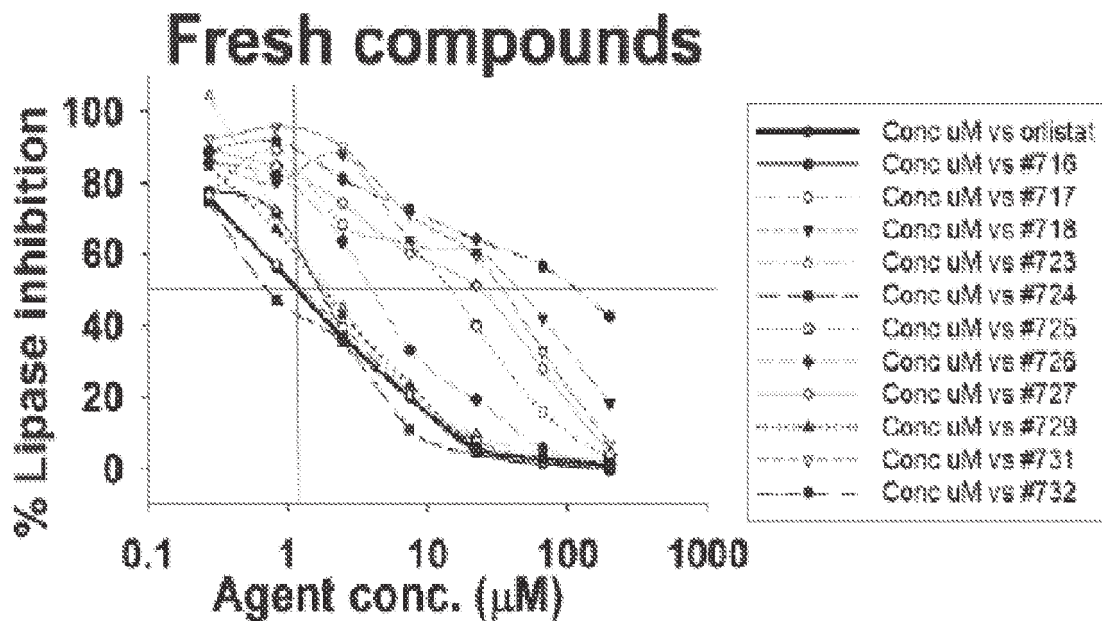


FIG. 4A

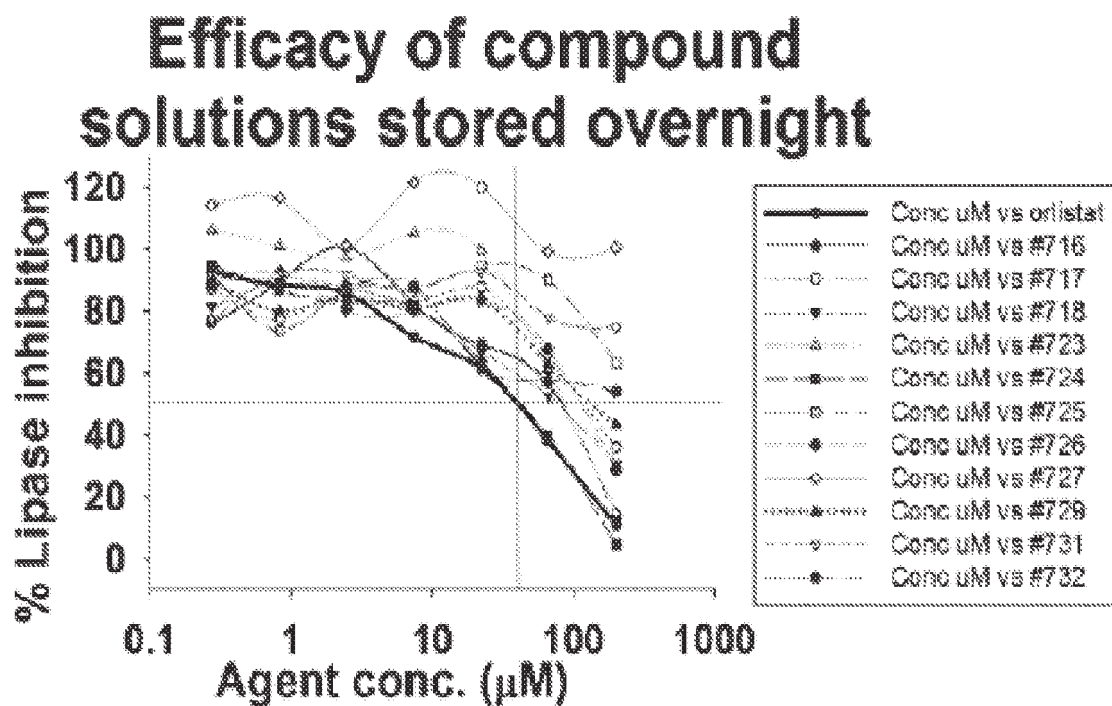


FIG. 4B

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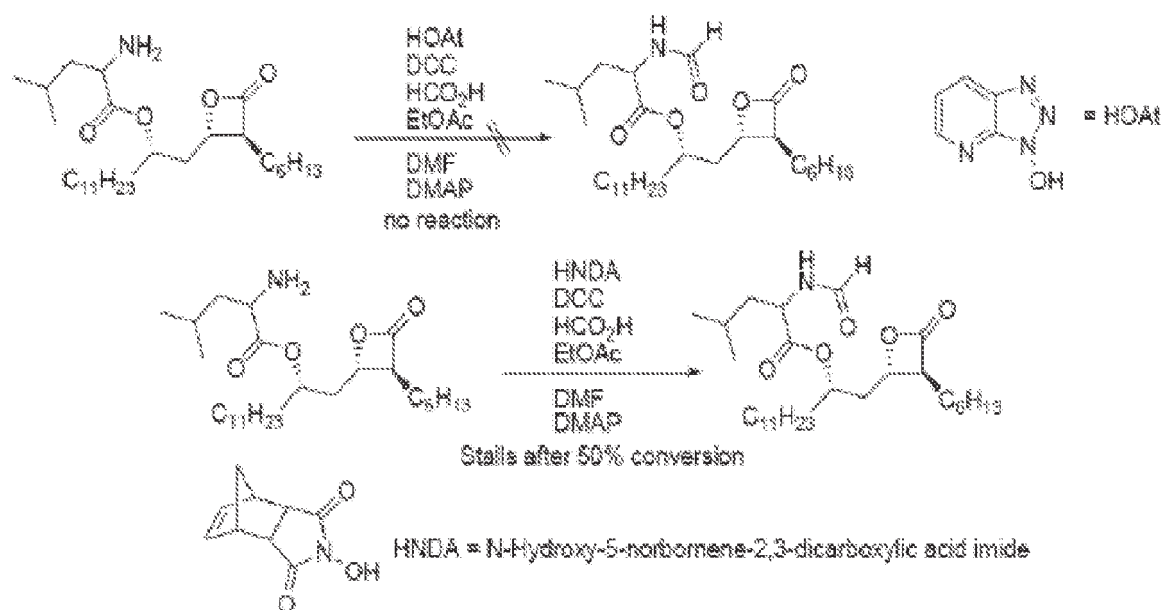


FIG. 5

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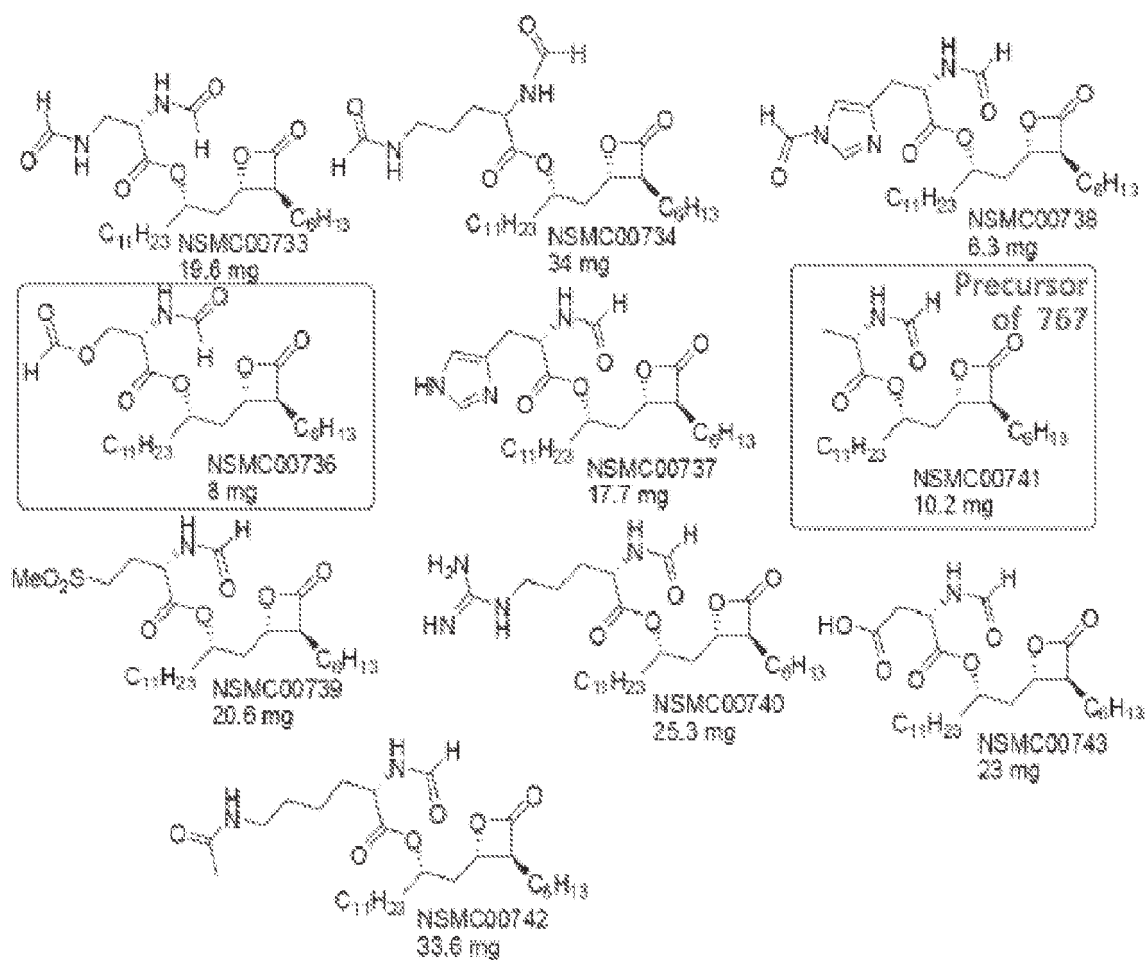


FIG. 6

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Efficacy of Fresh compounds

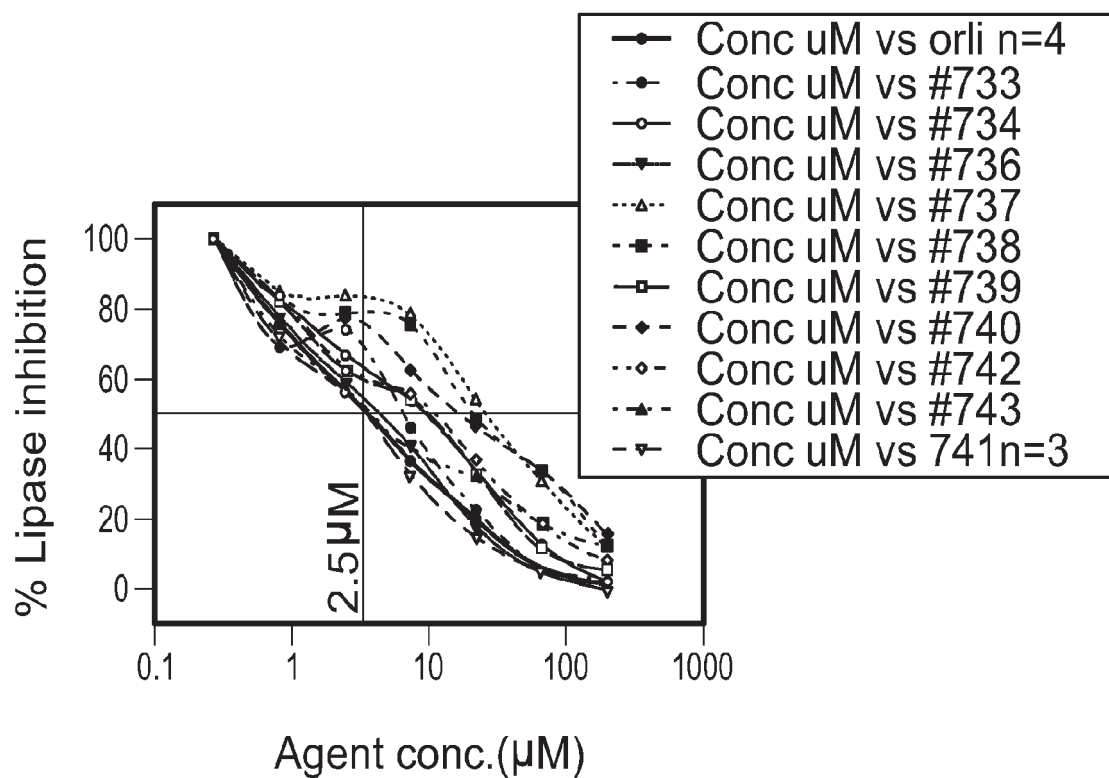


FIG. 7A

Efficacy of compound solutions stored overnight

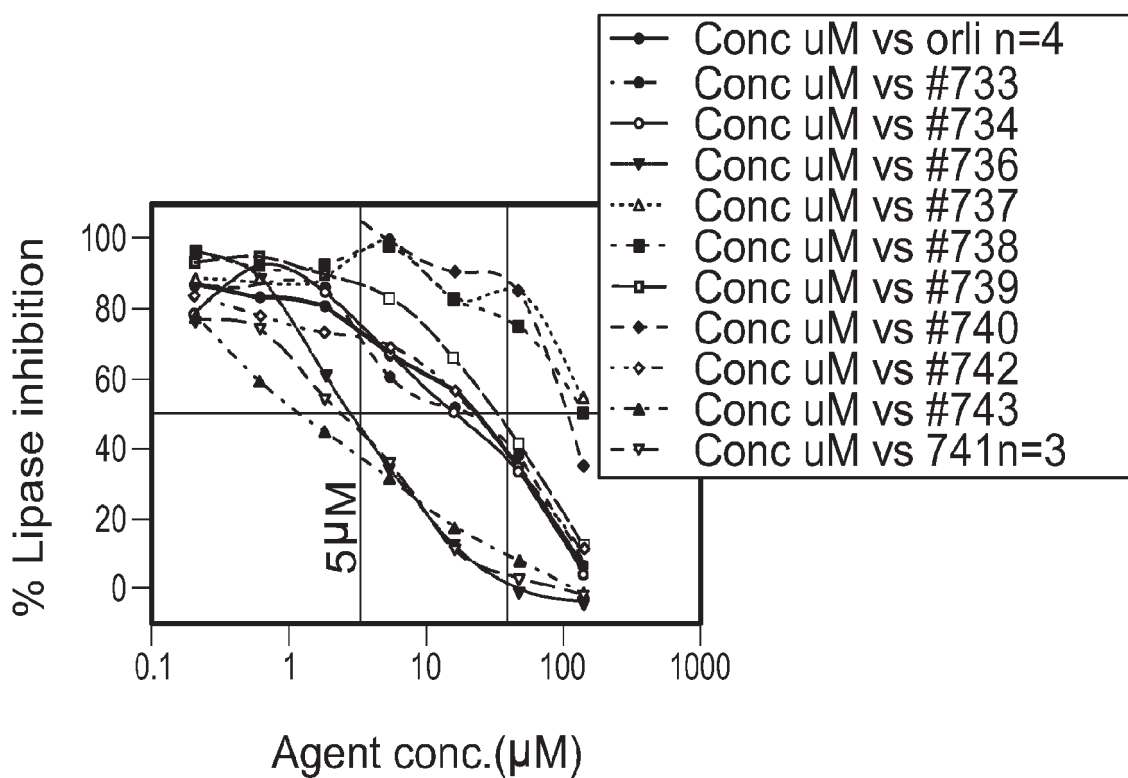


FIG. 7B

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Efficacy of compounds in co-culture

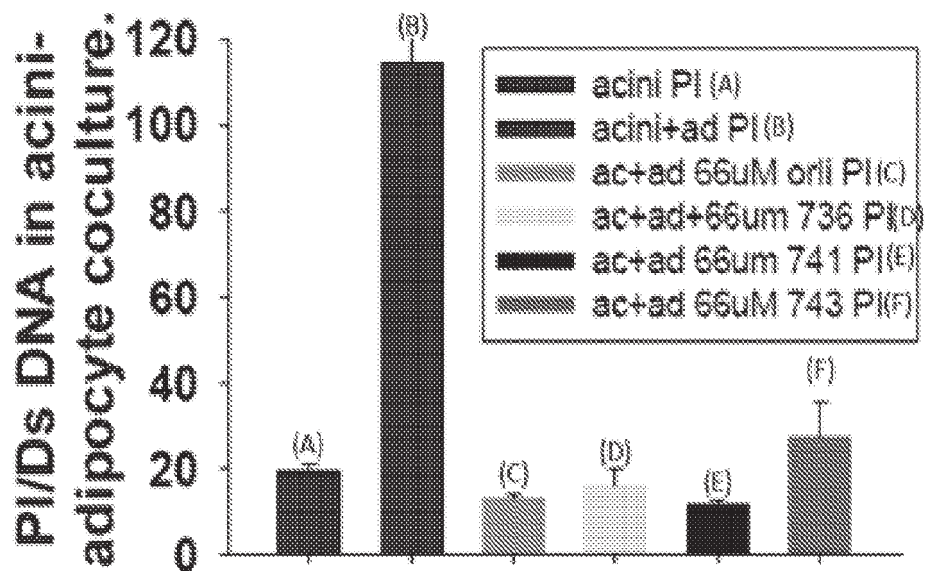


FIG. 8A

Toxicity of compounds to acinar cells

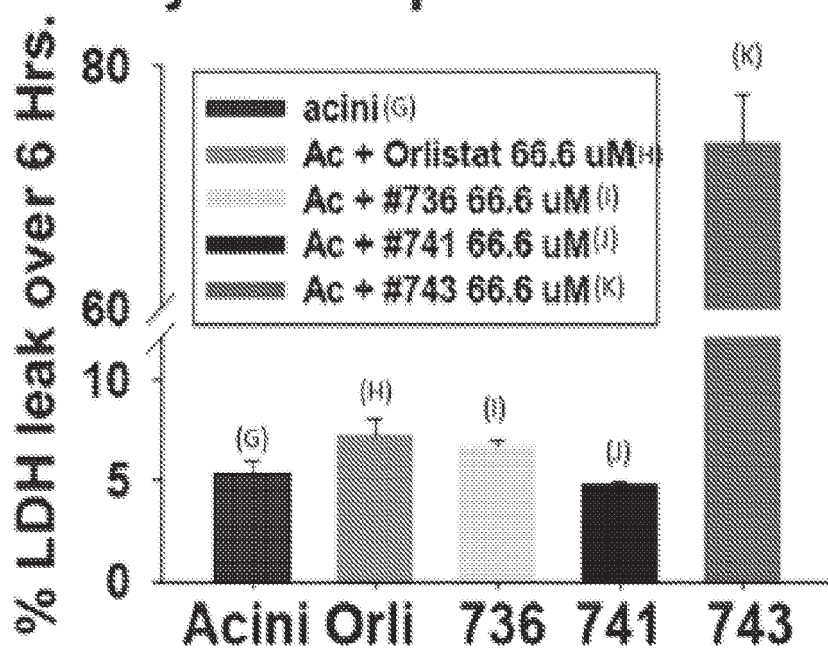


FIG. 8B

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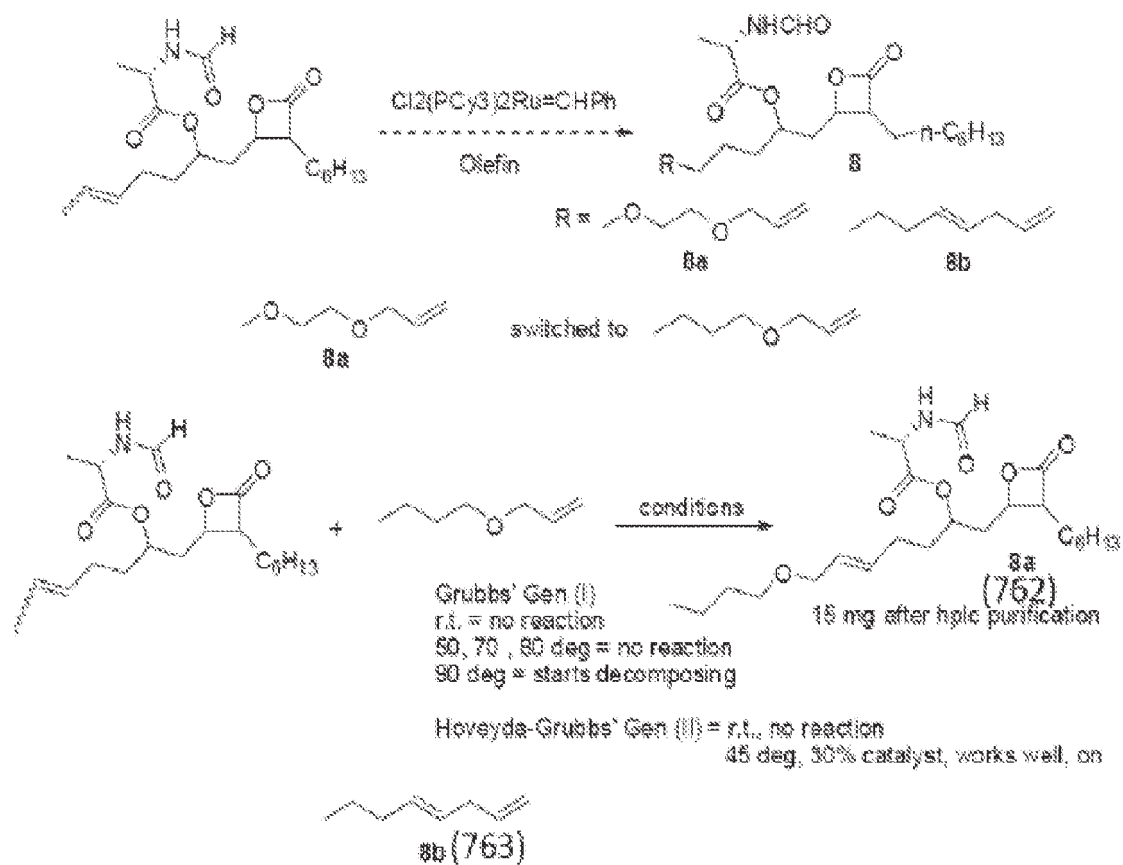


FIG. 9

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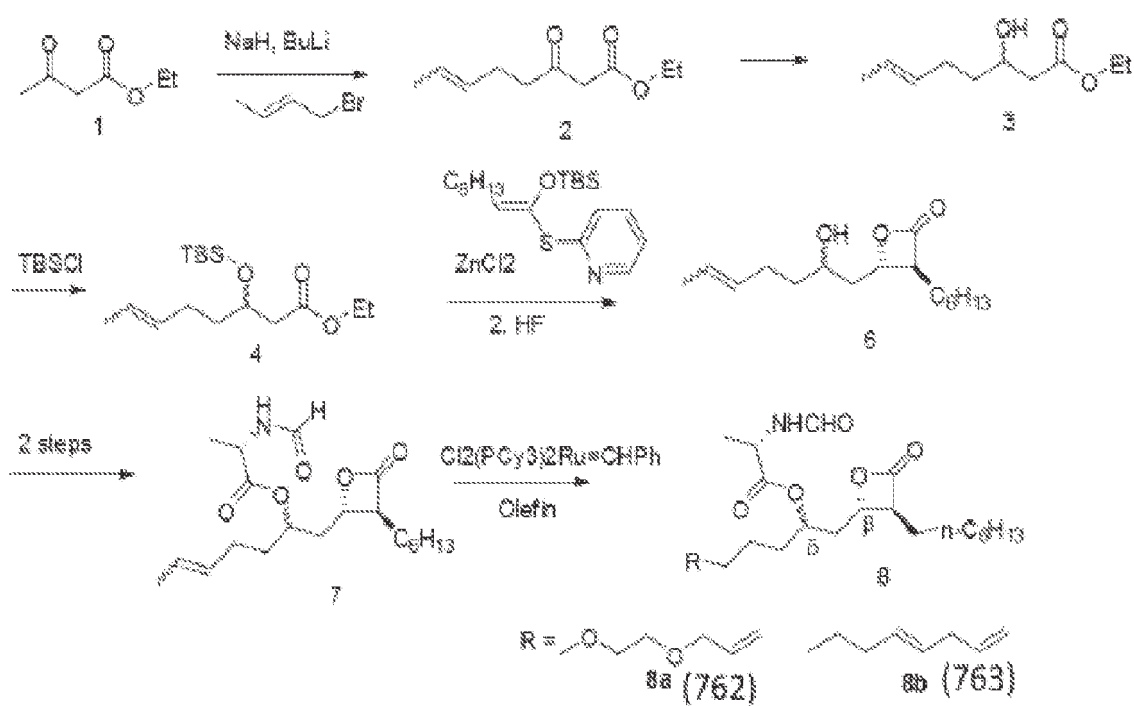


FIG. 10

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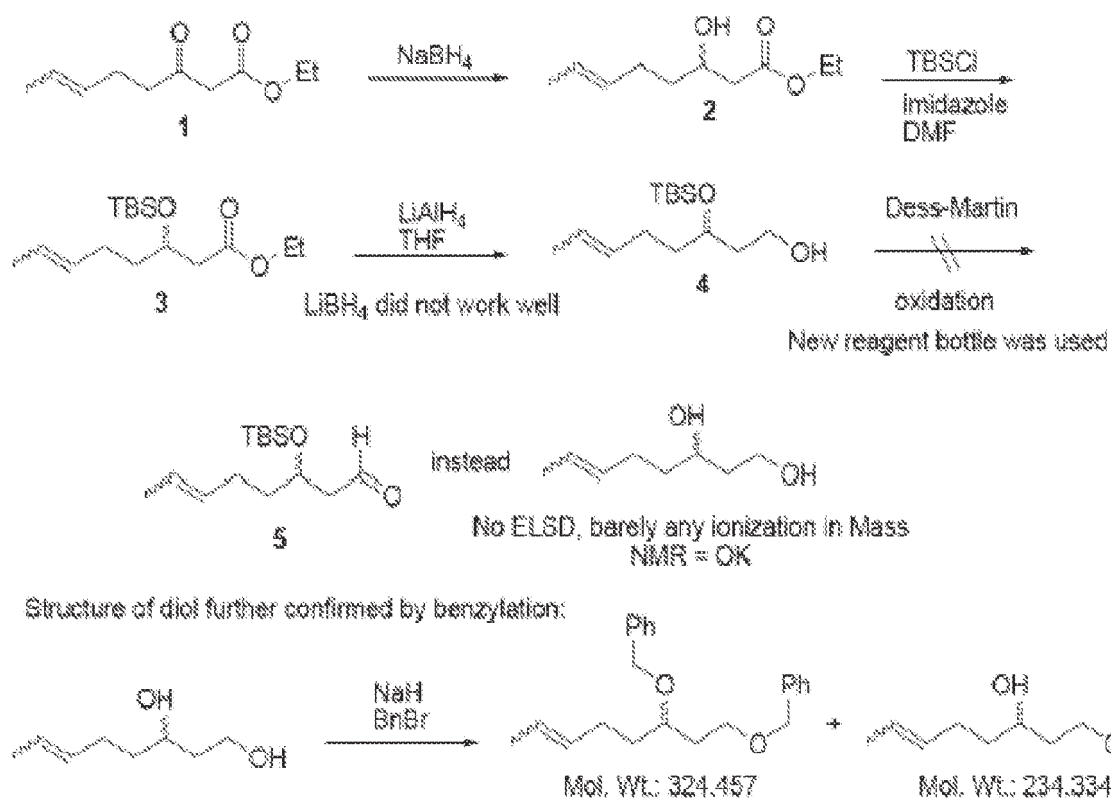


FIG. 11

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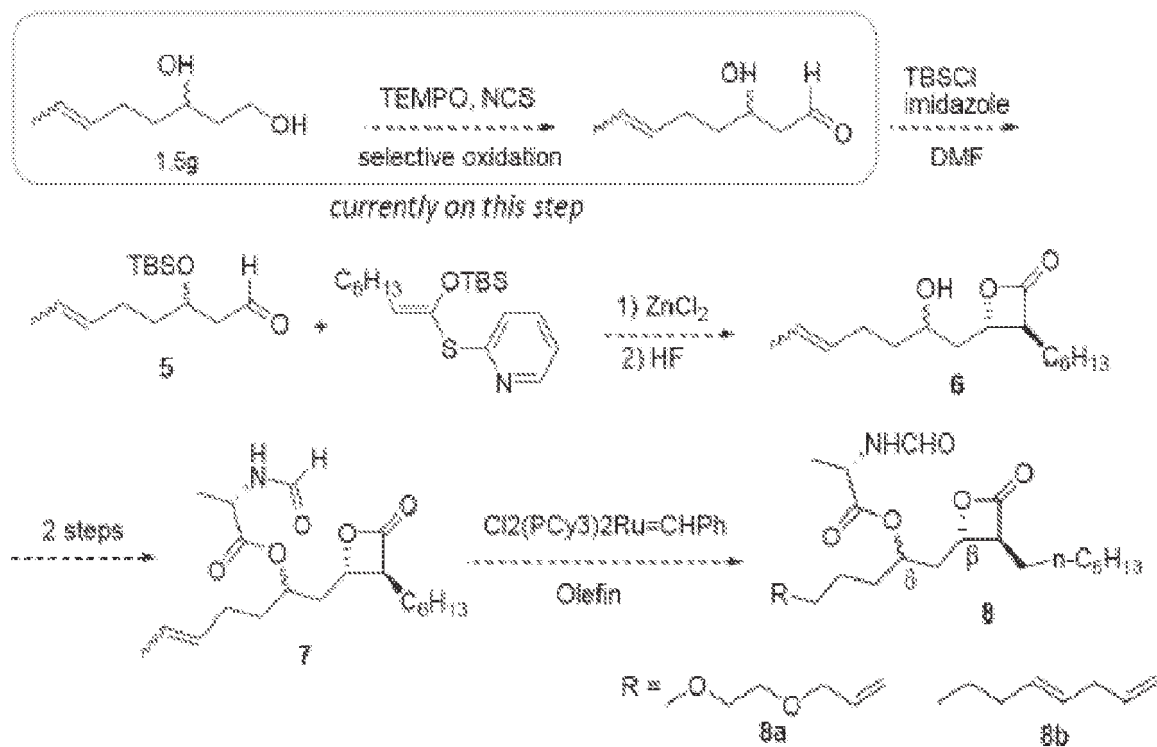


FIG. 12

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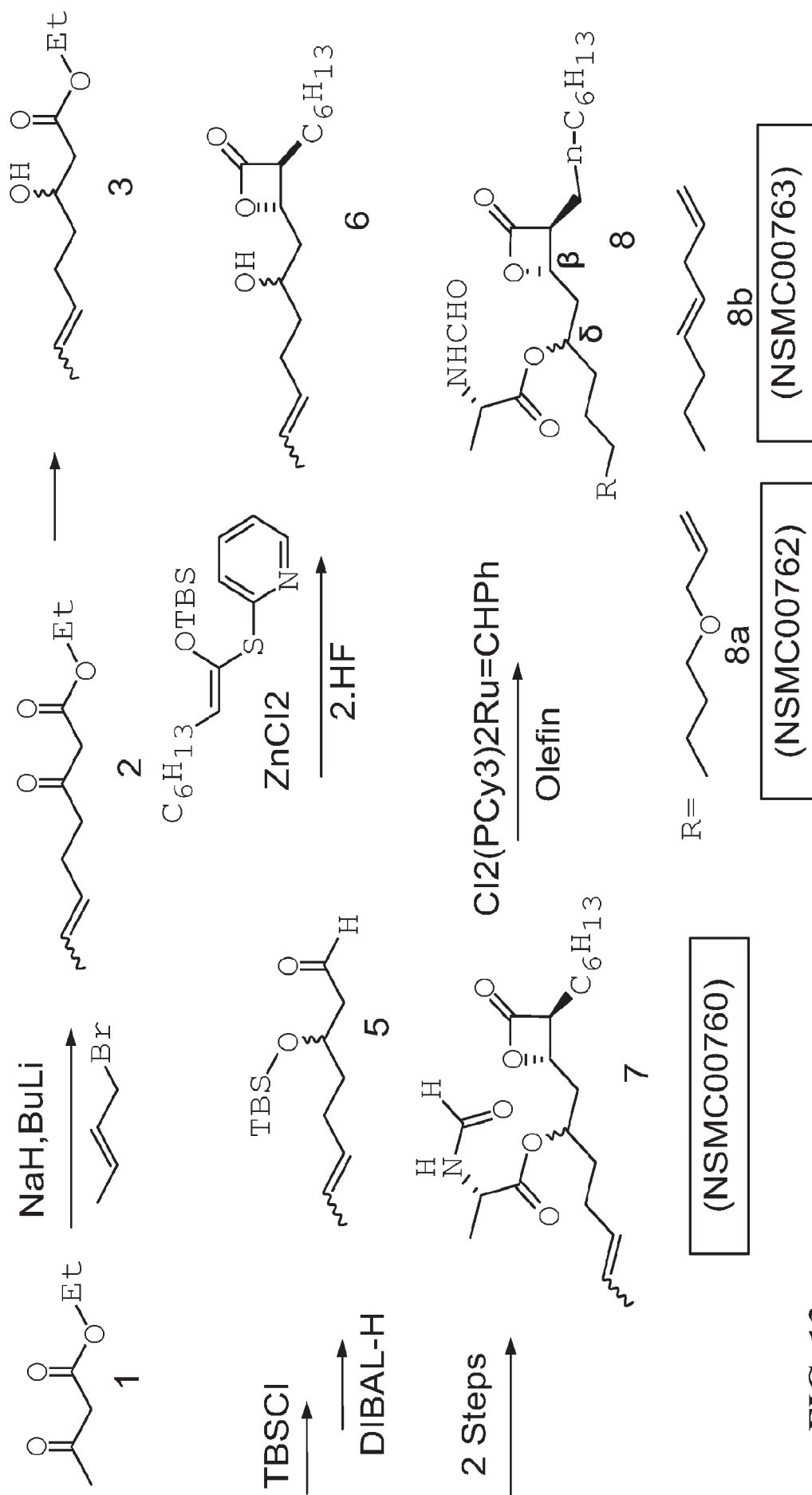
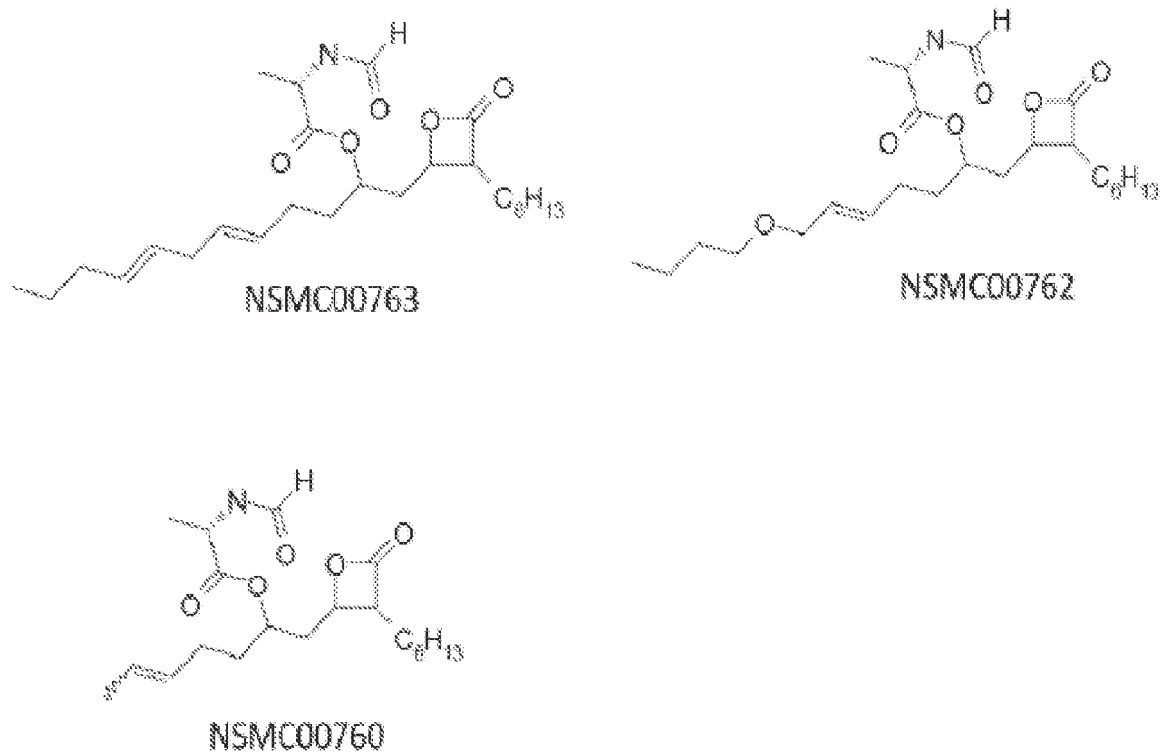


FIG. 13

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**FIG. 14**

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Lipase inhibition by β -chain modifications of 741

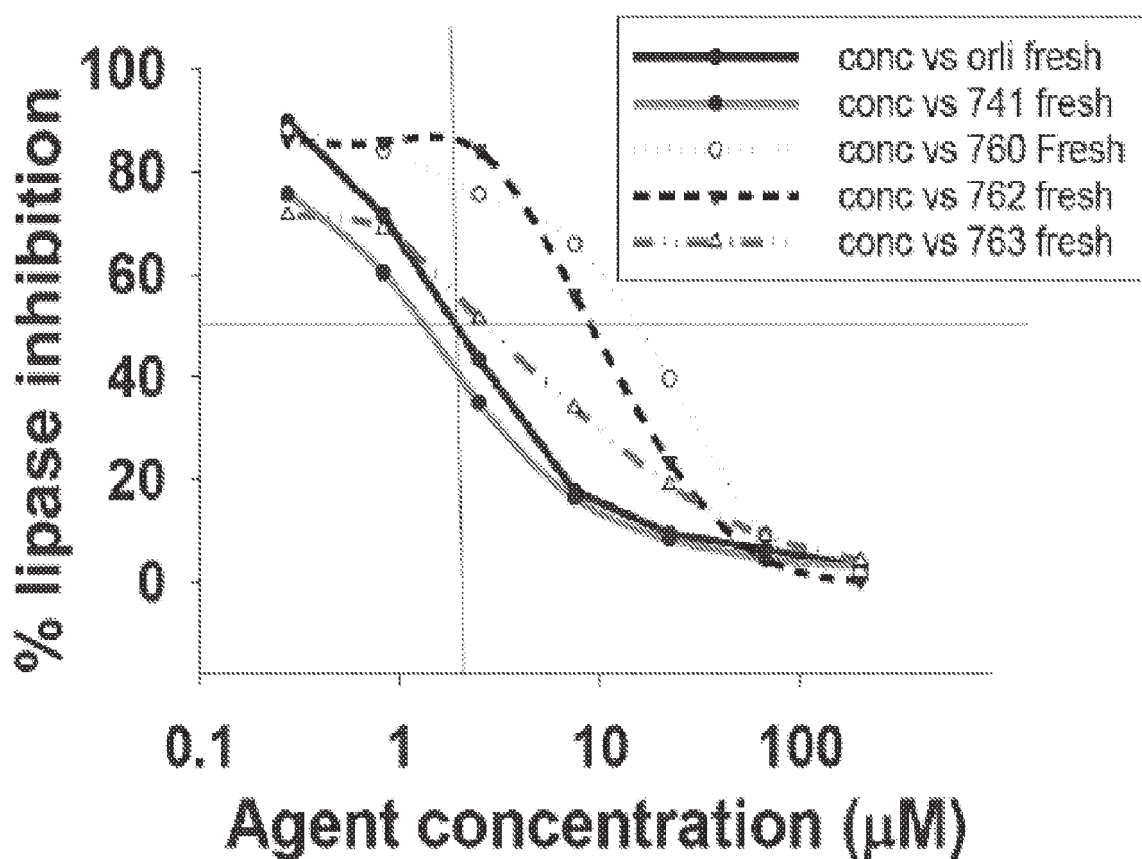


FIG. 15

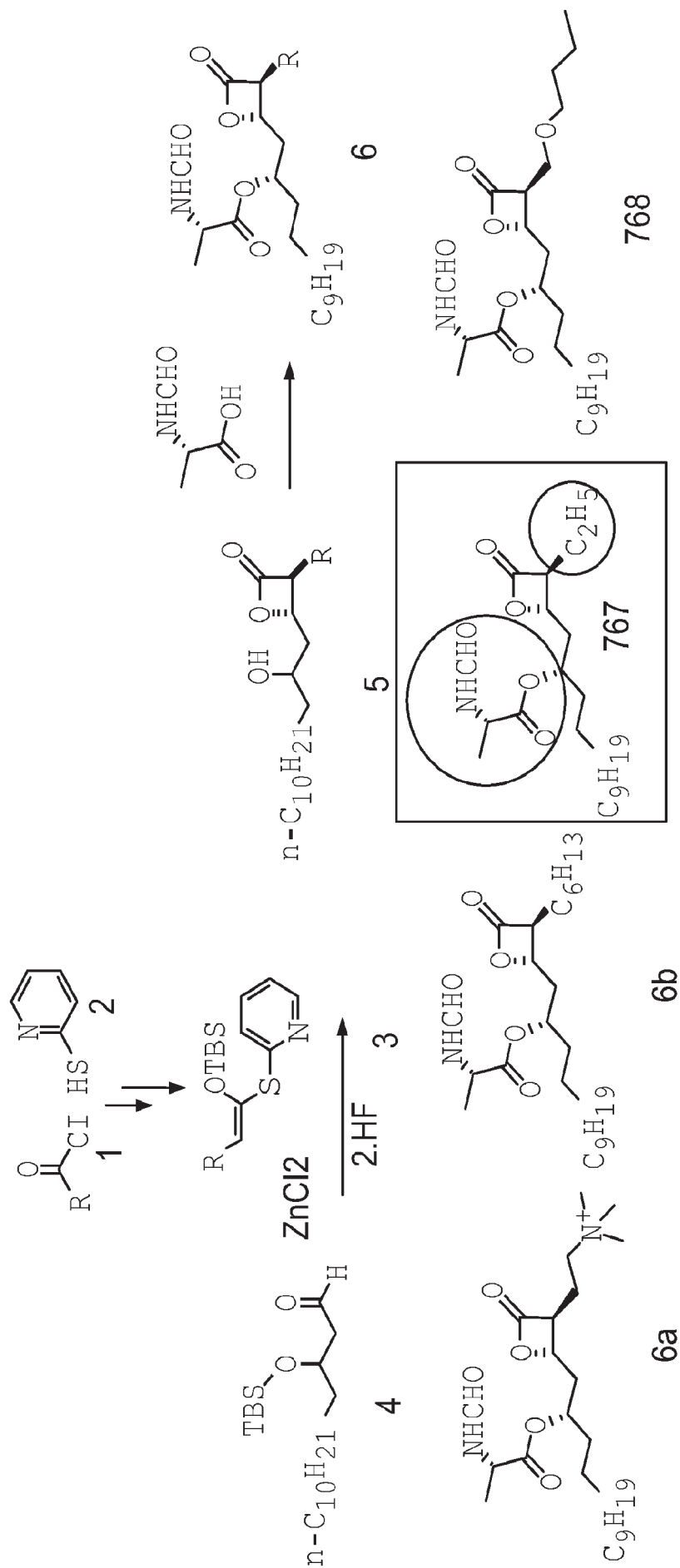


FIG. 16

NSMC00741

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Lipase inhibition by α -chain modifications of 741(FRESH)

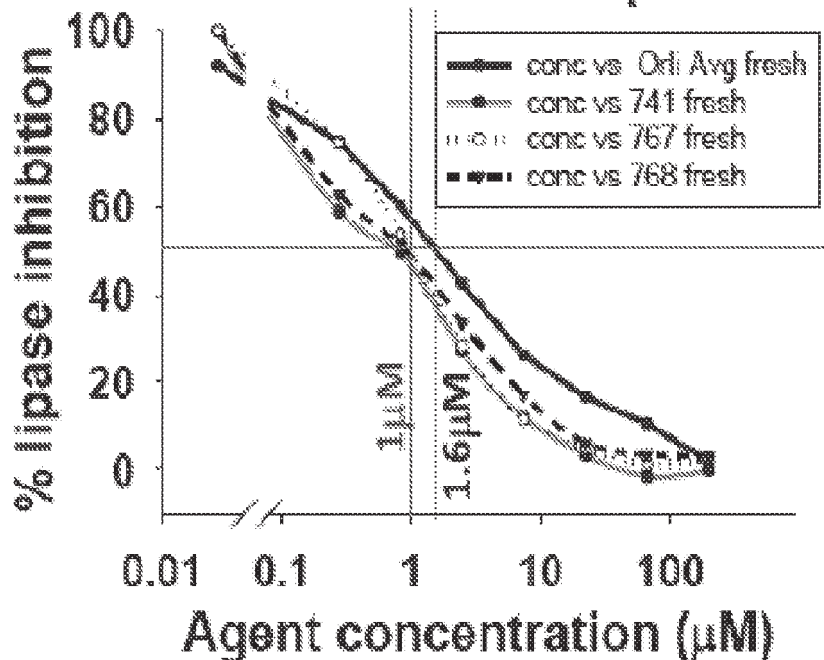


FIG. 17A

Lipase inhibition by α -chain modifications of 741(overnight)

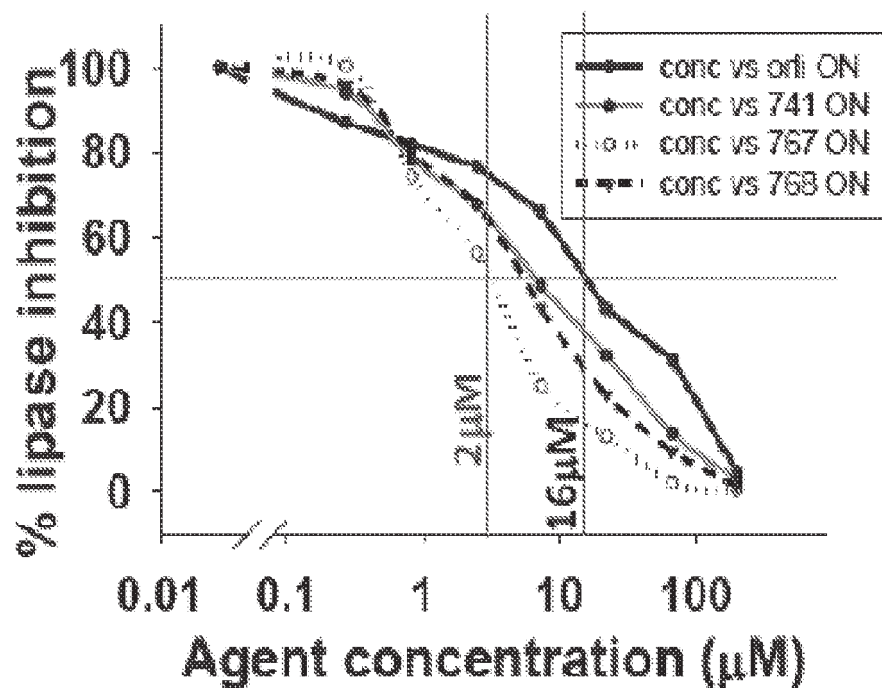


FIG. 17B

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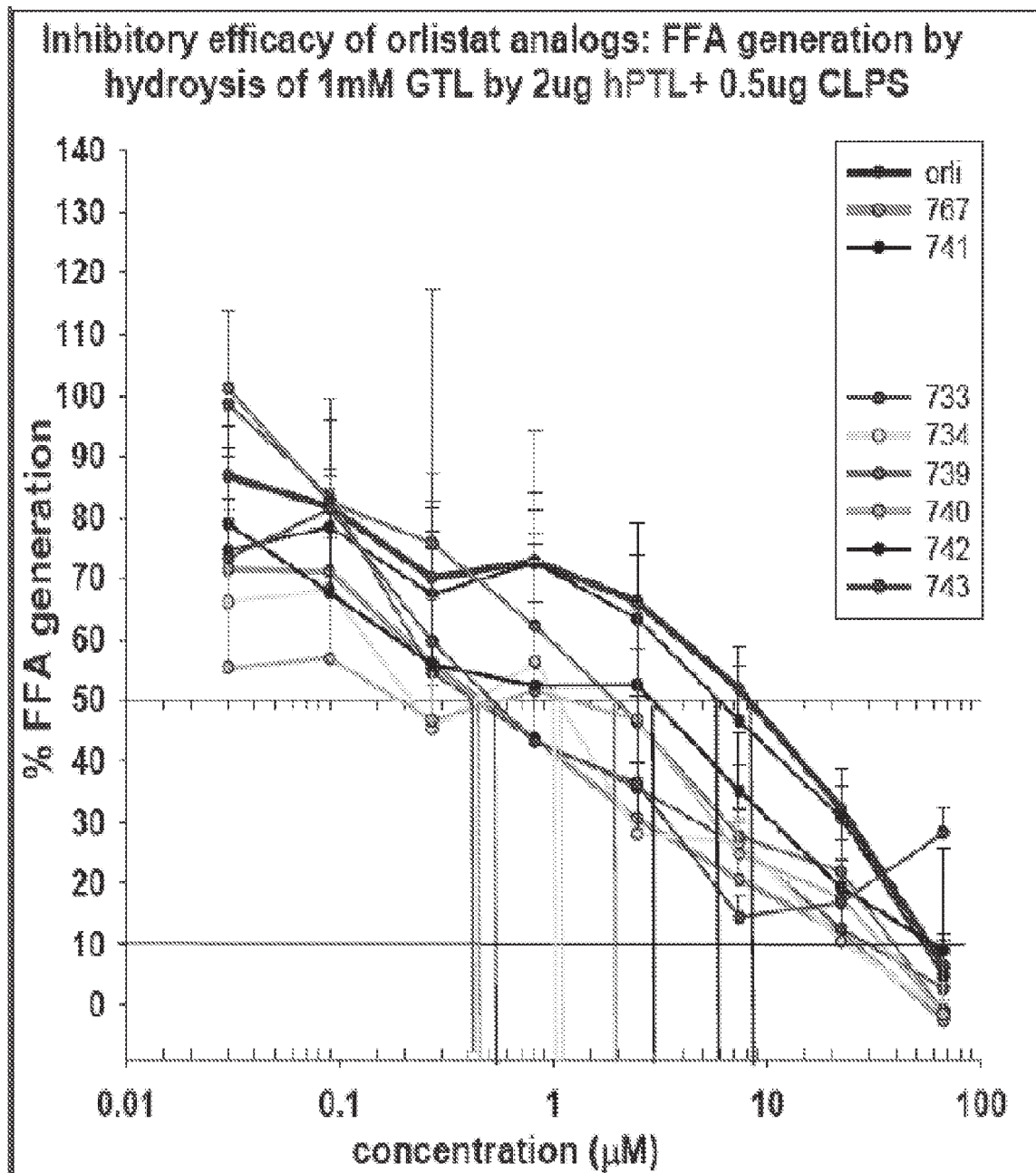


FIG. 18A

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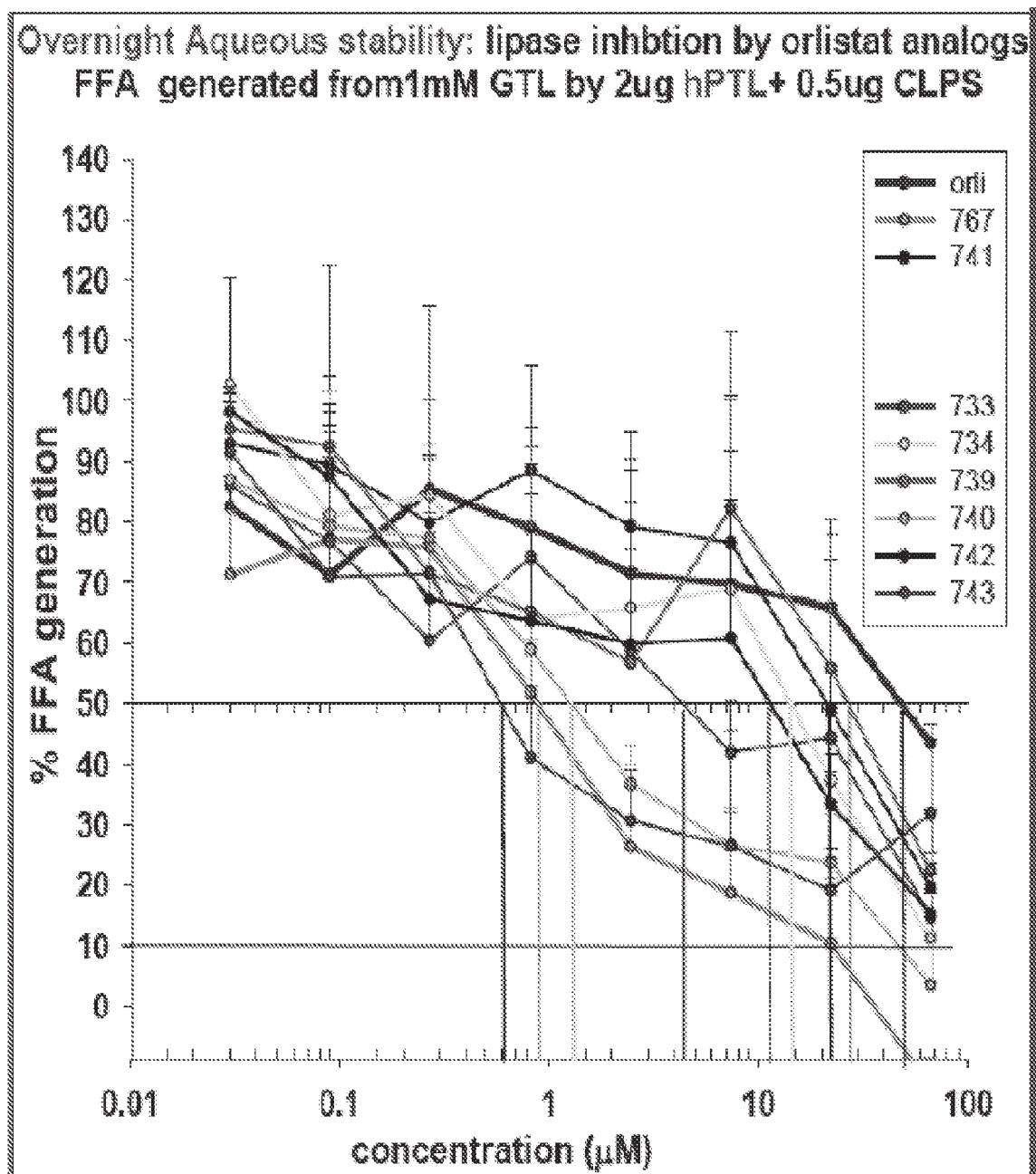


FIG. 18B

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% decrease in ATP over control acini										
Dose (uM)	Orli	767	743	742	741	740	739	734	733	762
200	9.14	4.24	57.37	38.66	3.04	9.30	10.87	23.43	17.48	10.11
66.6	3.02	-9.59	51.86	0.10	4.60	-9.08	-0.24	5.45	10.80	6.92
22.2	1.66	-13.61	30.21	5.33	1.03	-6.36	0.11	4.56	8.31	6.54
7.4	3.48	-6.32	4.72	9.30	-2.40	-0.40	2.39	8.15	6.50	4.13

increase in LDH leakage over 4 hours over controls (19.6%)										
Dose (uM)	Orli	767	743	742	741	740	739	734	733	762
200	13.35	10.97	70.92	34.52	-7.81	-12.02	7.81	8.39	-6.35	-5.94
66.6	10.81	-2.72	60.33	-8.76	-7.54	-14.47	-4.38	-14.16	-13.99	-9.33
22.2	11.02	0.48	26.74	9.28	-4.66	-15.61	7.50	-9.15	-6.38	-3.73
7.4	1.88	2.57	-2.46	19.06	-1.88	-5.78	30.60	1.25	1.88	0.88

FIG. 19

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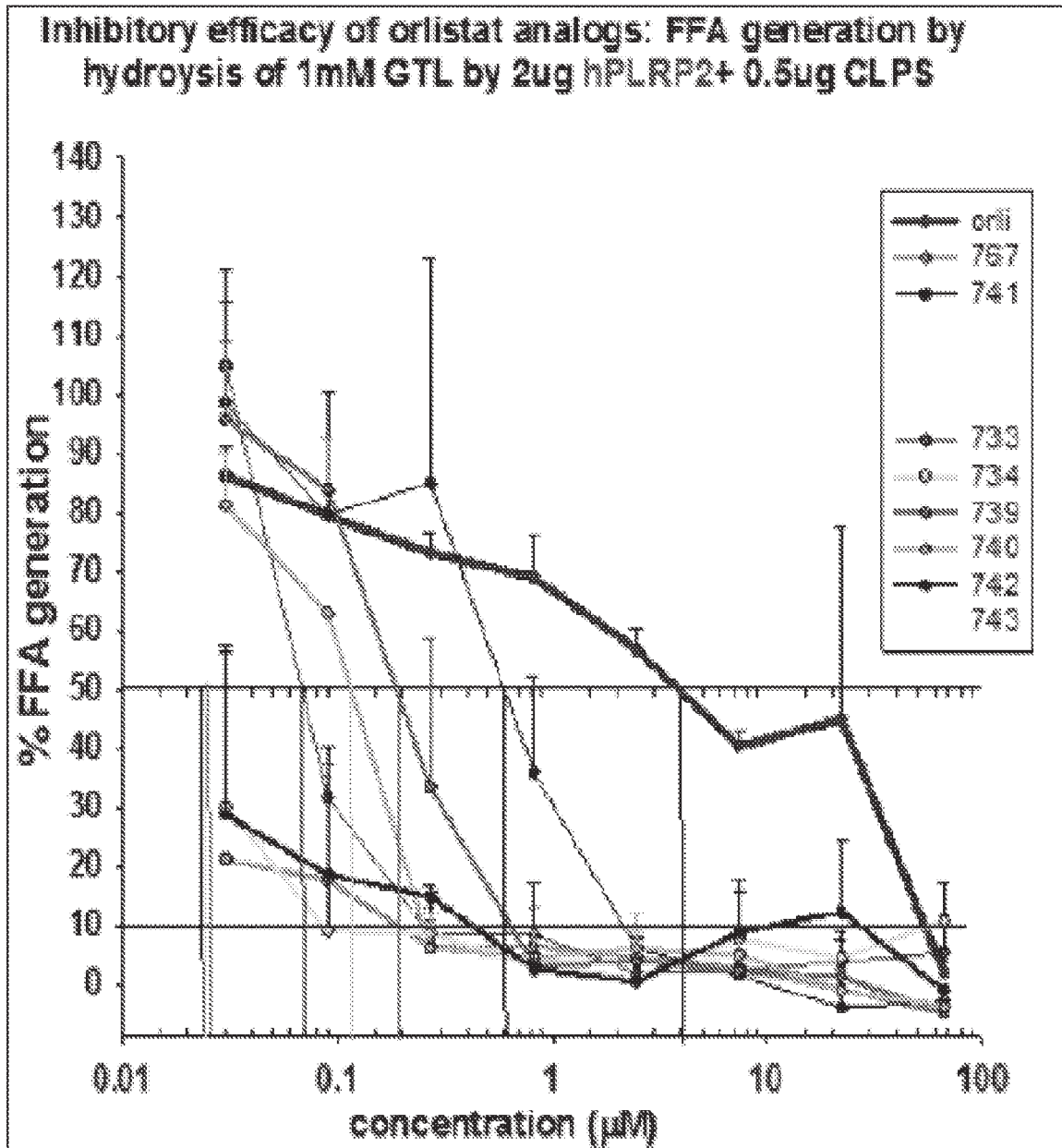


FIG. 20A

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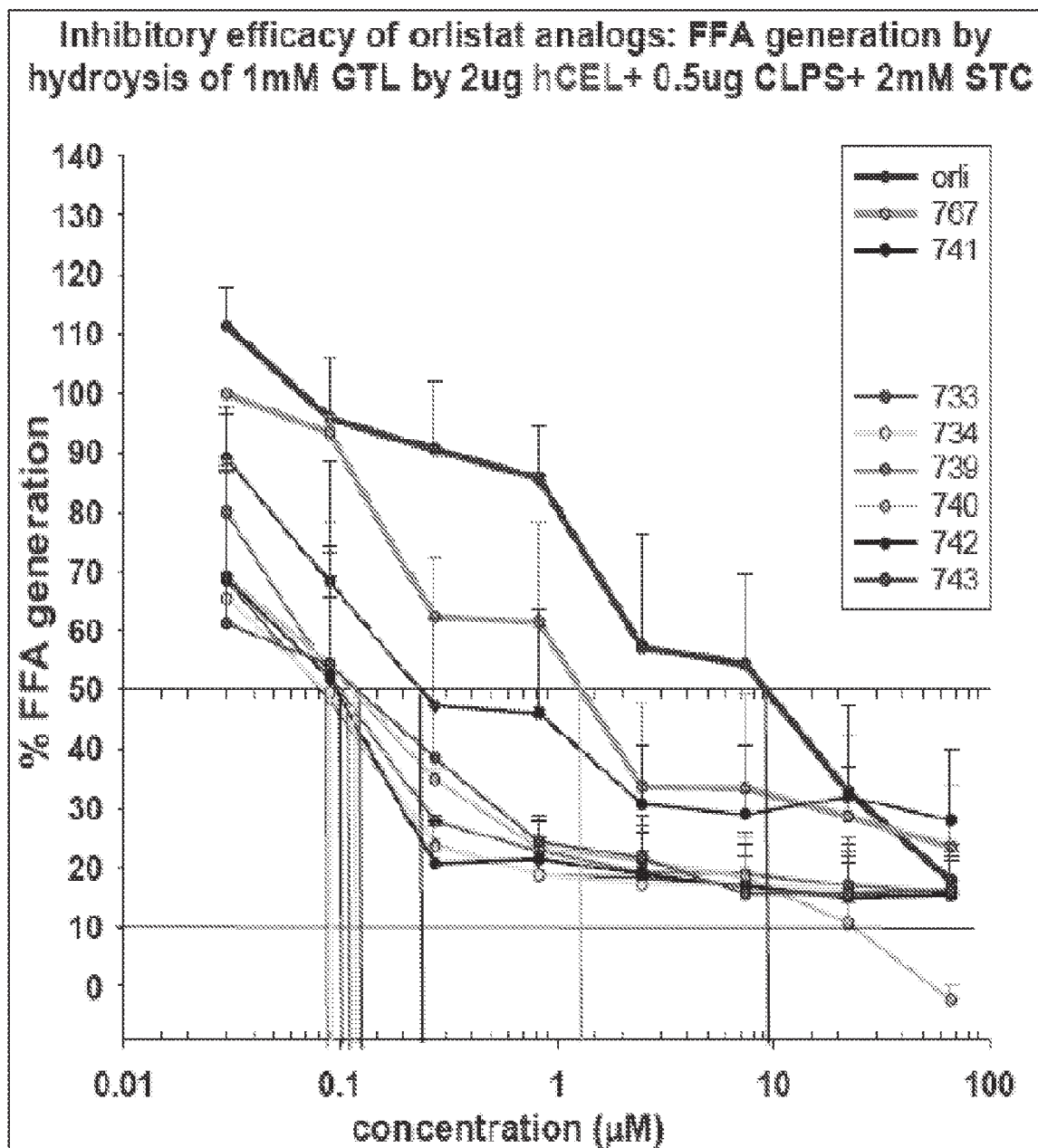


FIG. 20B

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Agent	hPTLIC50 μM Fresh	hPTLIC50 μM overnight	hPLRP2 IC50 μM	hCEL IC50 μM	LDH leak at 20x IC50	ATP drop at 20x IC50
733	0.5	5.5(11x)	0.07	0.1	1.9%	8.3%
767	0.55	1.1(2x)	<0.03	1.5	0.5%	0%
740	0.7	1.05(2x)	0.15	0.1	0% ??	0%
734	1	11(11x)	<0.03	0.1	0% ??	4.5%
739	2	38(19x)	0.3	0.1	8%	0%
741	7	35(5x)	0.7	0.35	0% (??)	3%
orlistat	9	60(7x)	5	10	13.3%	9%

FIG. 21

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Orlistat has 80% efficacy in reducing mortality in severe pancreatitis. If is used as 50 mg/kg/dose, BID, and administered over 2 days. The first dose was given 2 hours after the initiation of pancreatitis

Use of orlistat at this schedule is complicated by hypertriglyceridemia.

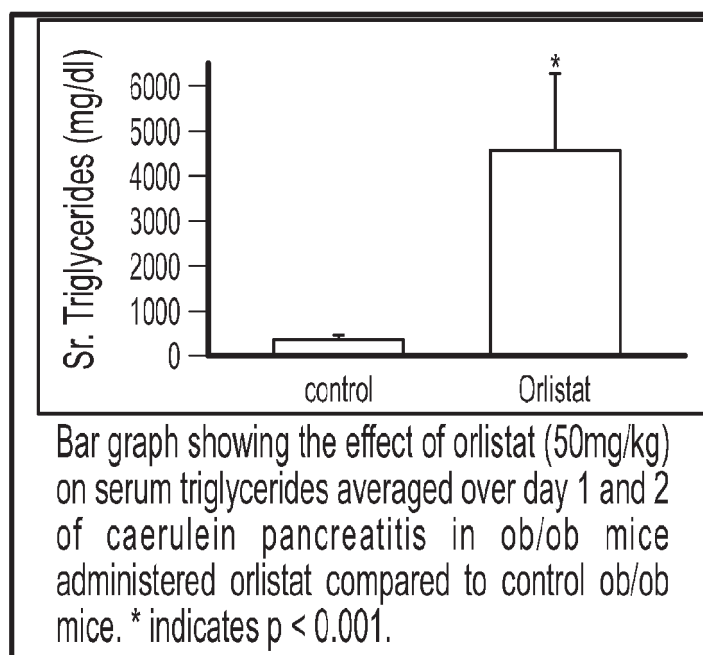
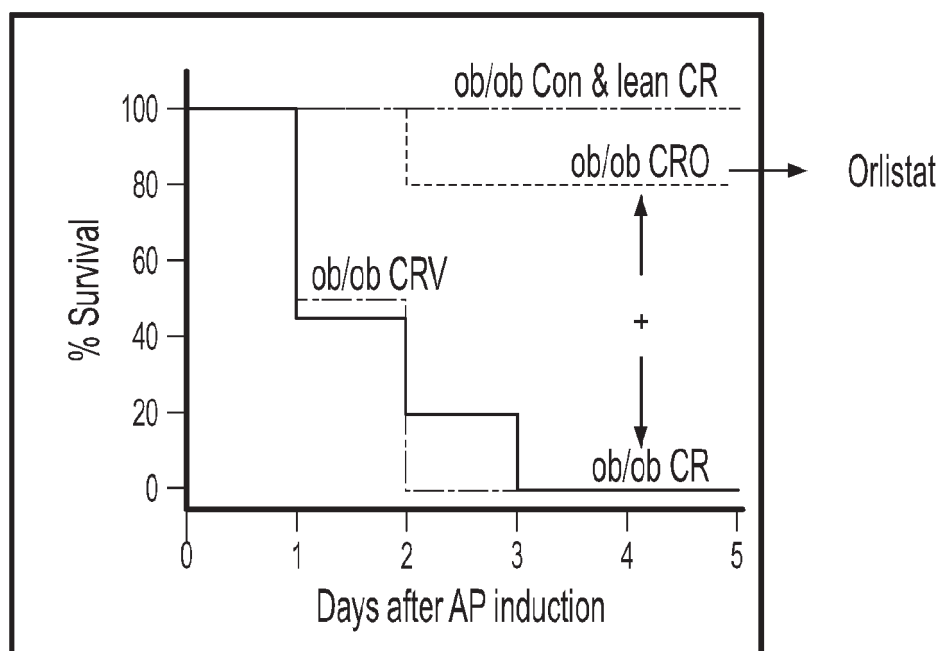


FIG. 22

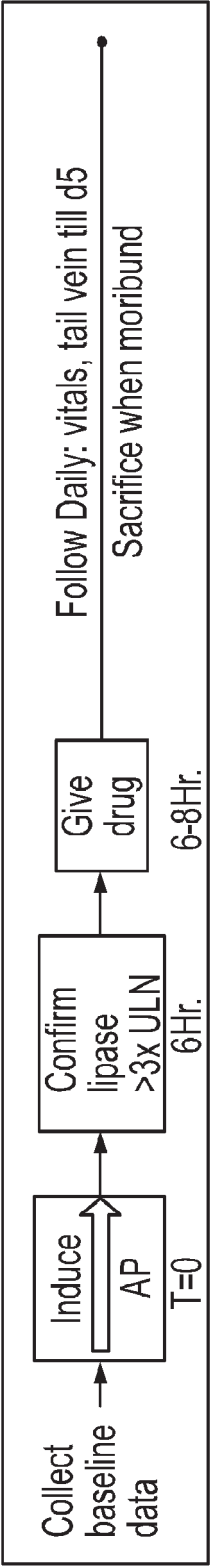


FIG. 23A

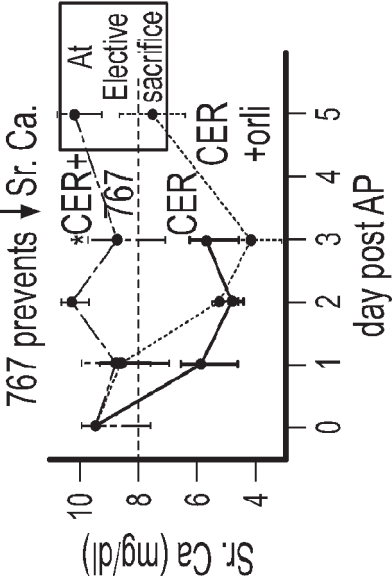
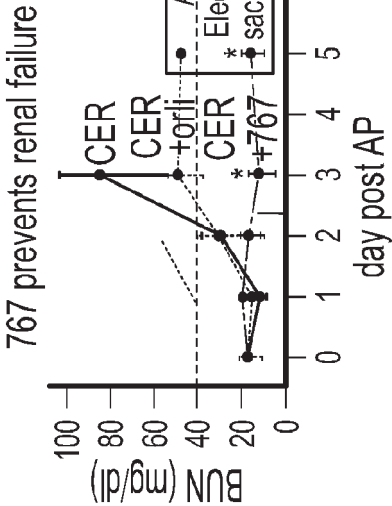
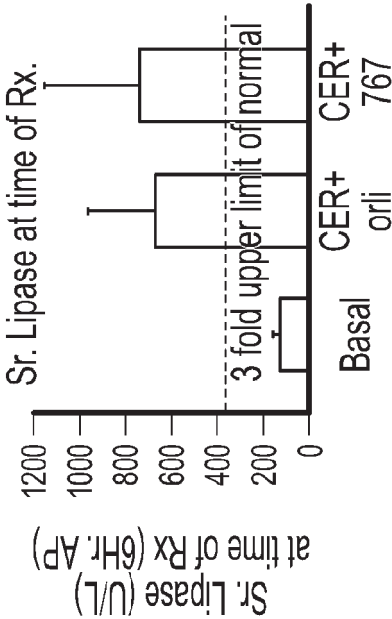


FIG. 23B

FIG. 23C

FIG. 23D

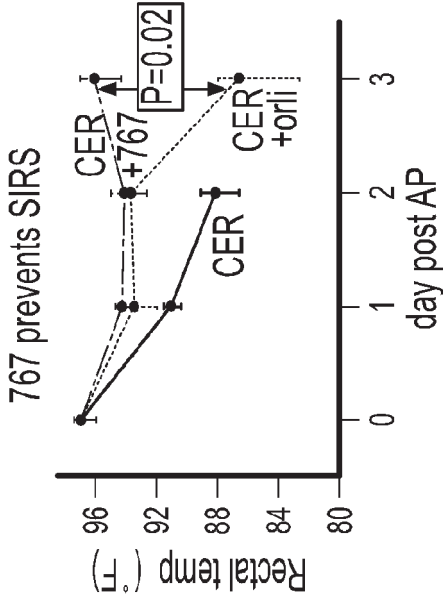


FIG. 23E

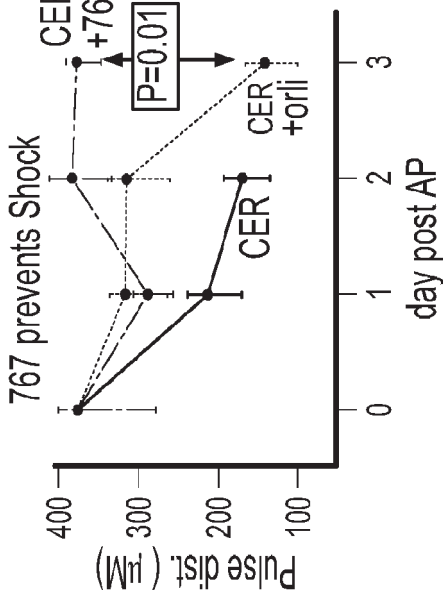


FIG. 23F

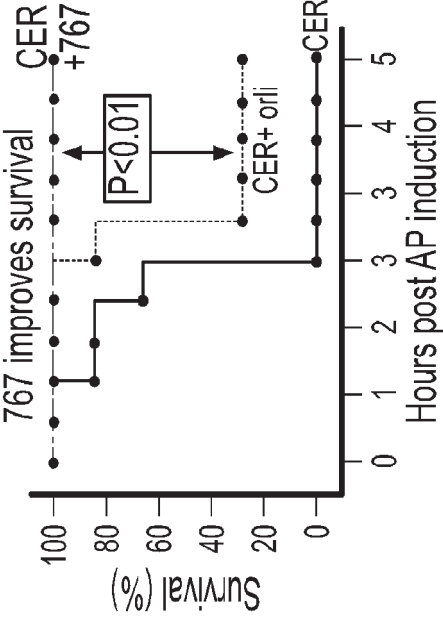
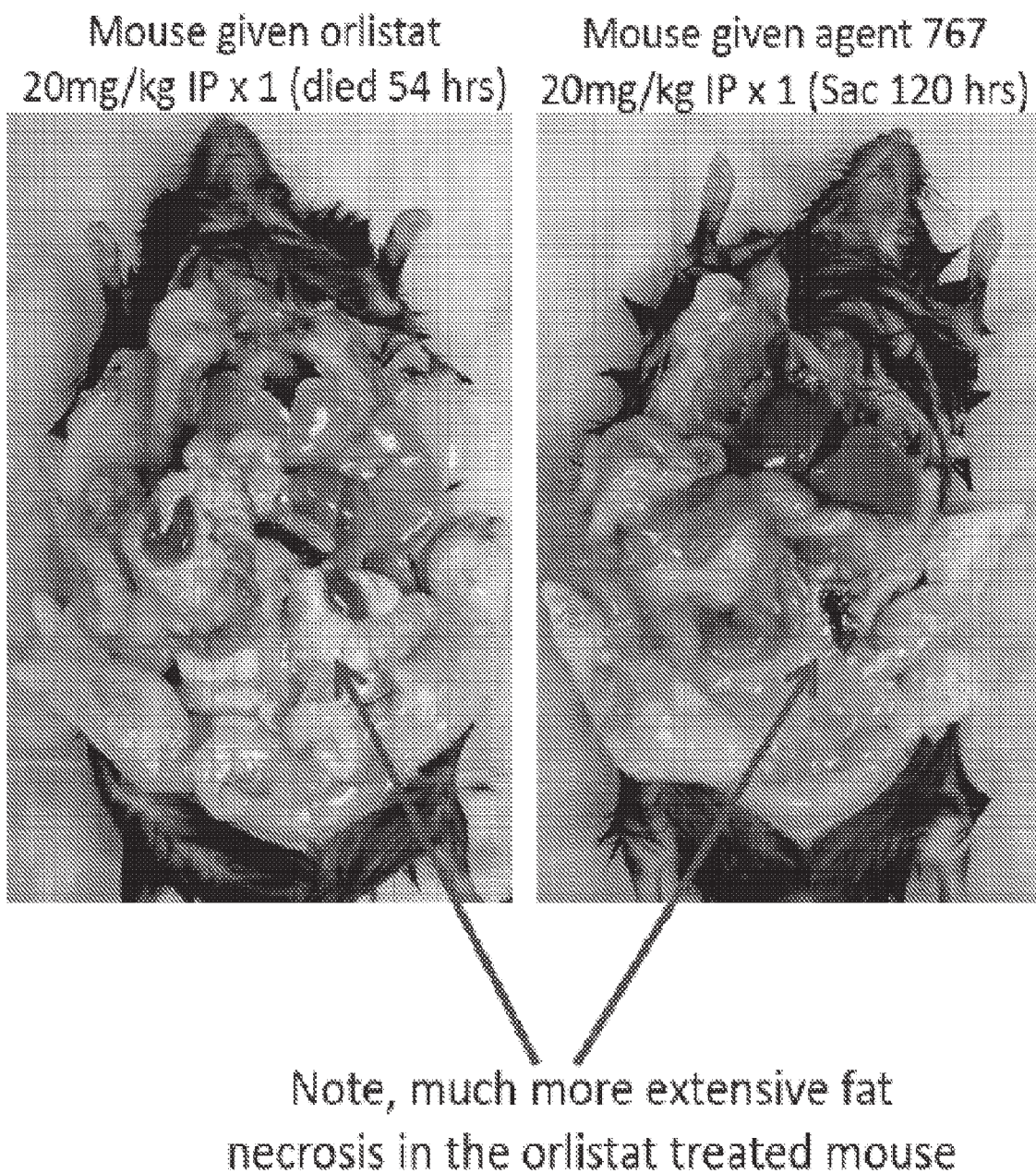


FIG. 23G

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**FIG. 24**

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Parameter	orlistat	767		
Effective Dosing schedule	2/day x 3 day -repeated dosing	Single dose		
Dose	50mg/kg/dose	20 mg/kg		
Stability in aqueous environment for 24 hours	Unstable- requires fresh formulation	Stable		
Vehicle	• Liposomal- Harmful? • Phospholipases cleave phospholipid→lipotoxic Fatty acids • TG emulsion • Cyclodextrins are ineffective	0.3% ethanol. 767 makes its own micelles		
Complication	Hypertriglyceridemia > 5000	Triglycerides <500.		
Mortality	20% at high repeated dose,71% (5/7) at 20mg/kg	0% (0/8) at 5 days		
SIRS MSOF	WBC counts < 4000/mm ³	4/7	0/8	
	Hypothermia (Temp < 93F)	As a Single 20 mg/kg dose	7/7	0/8
	Shock (pulse distention <50%)		7/7	0/8
	Renal failure (BUN > 40 mg/dl)		7/7	0/8

SIRS: Systemic inflammatory response syndrome. MSOF: Multi-system organ failure

FIG. 25

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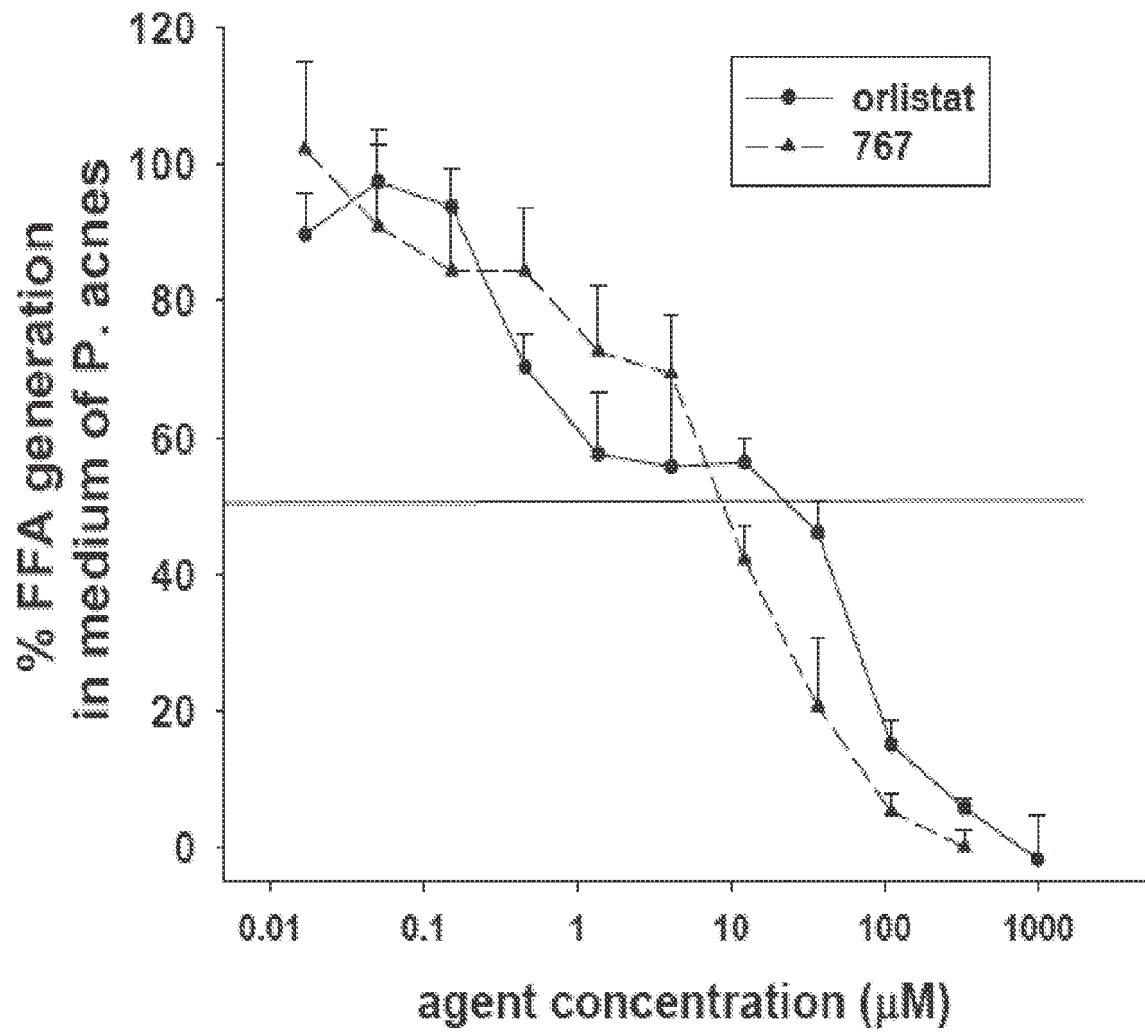
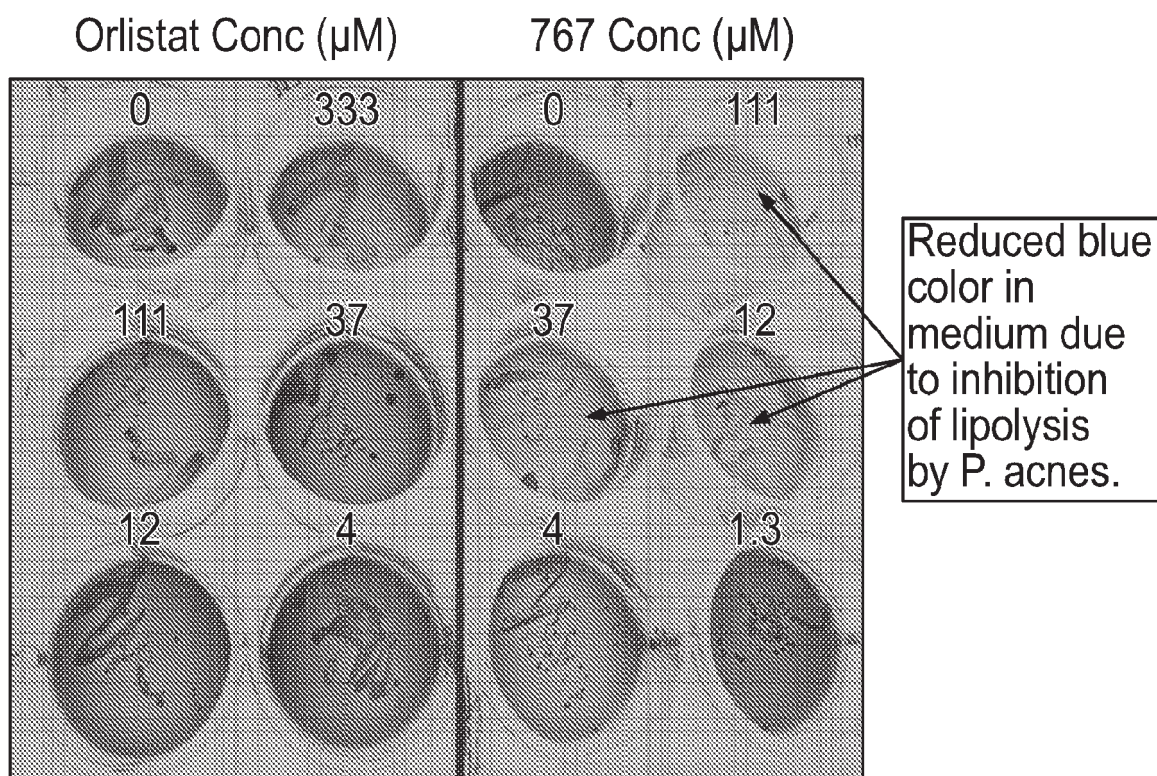


FIG. 26

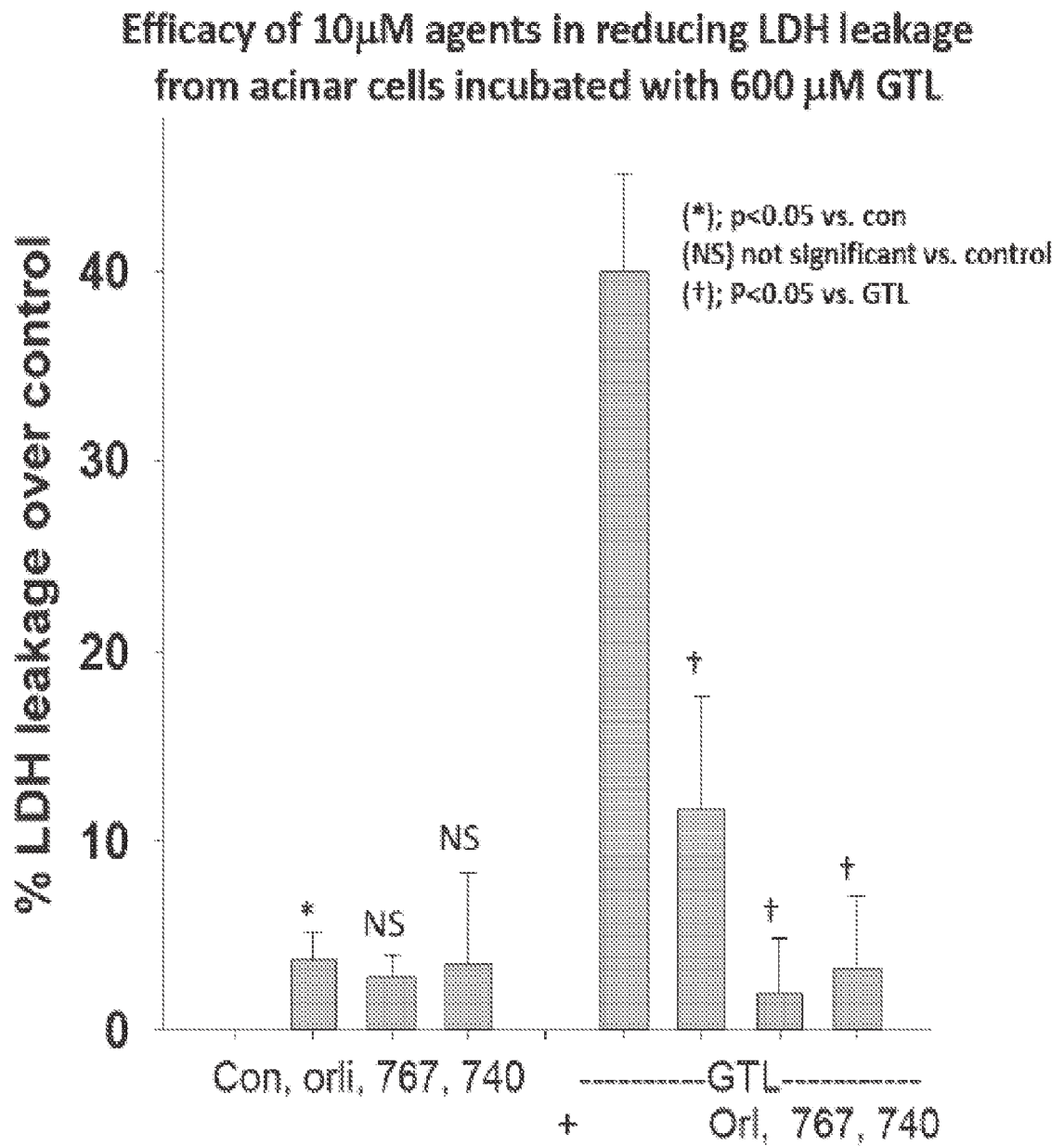
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Color of spirit blue agar with *P. acnes* grown for 6 days under anaerobic conditions

FIG. 27

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**FIG. 28**