

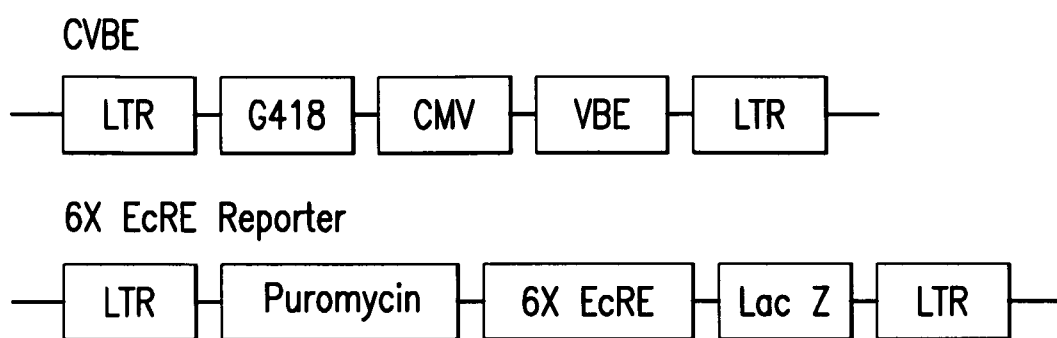


FIG.1

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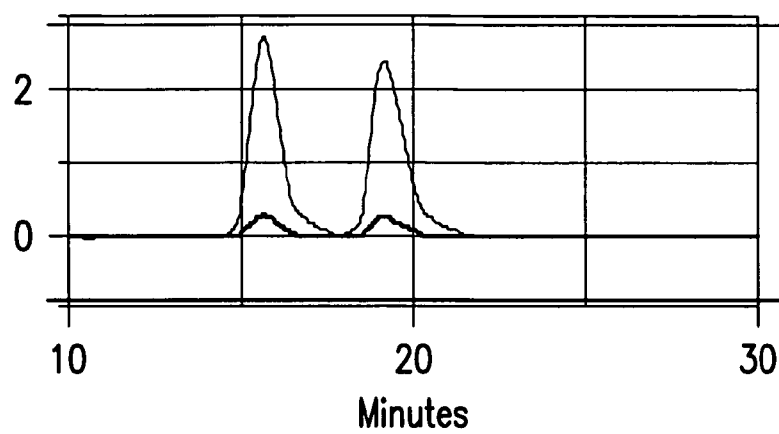


FIG.2A

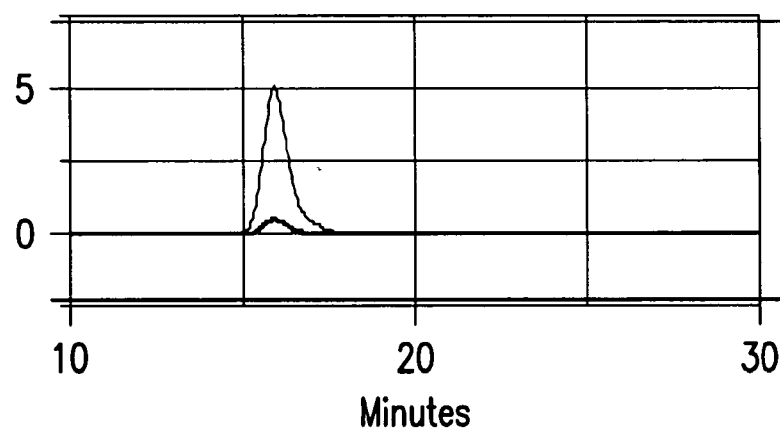


FIG.2B

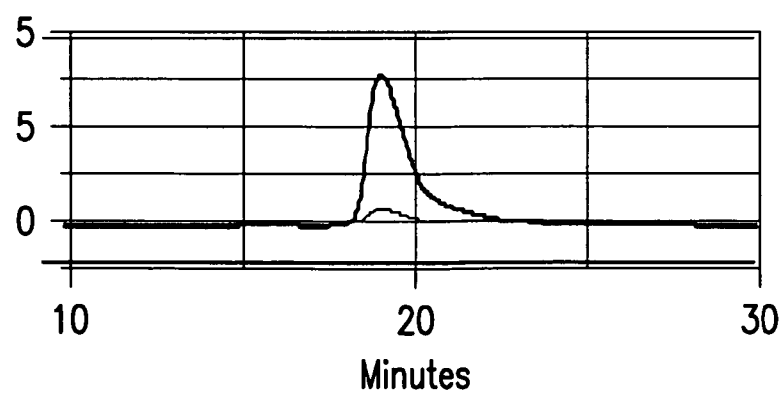


FIG.2C

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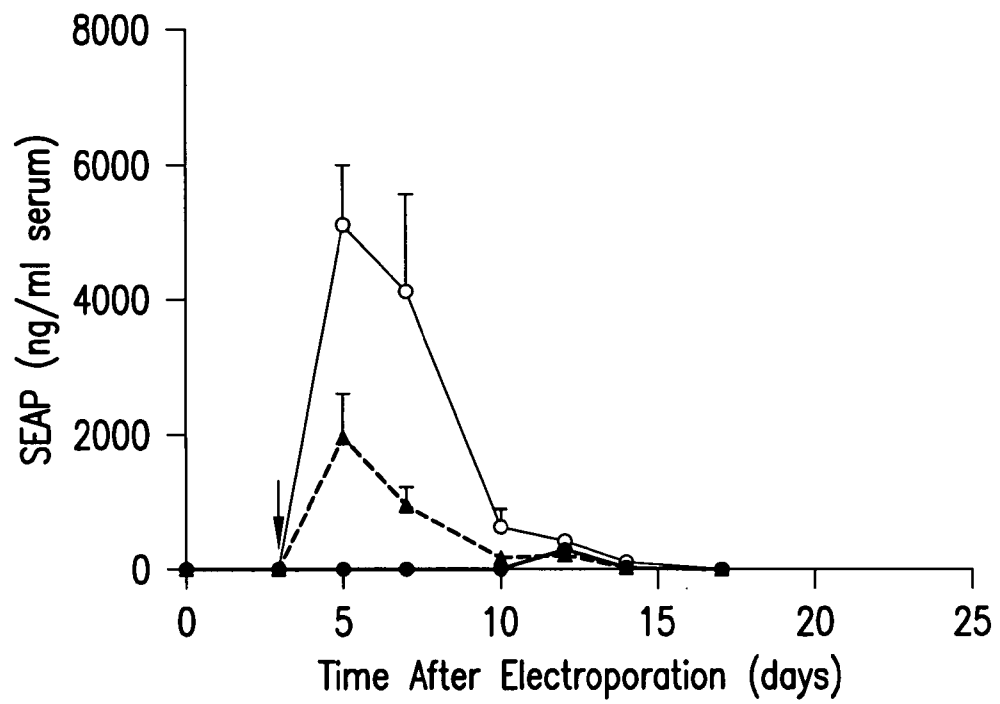


FIG.3

Material	Lot #	Origin	Micronized	Analysis
R enantiomer	REH-28-4-2	precipitated from CH ₃ OH/H ₂ O, dried in vac oven, then micronized	YES	All ADME analyses except mouse SEAP expression
Racemate	REH-28-9-1 (PYAP-2-8-2-2M)	micronized from PYAP 2-8-2-2	YES	All ADME analyses except mouse PK and mouse SEAP expression
Racemate	PYAP 2-8-2-2	Precipitation from CH ₃ OH and dried in vac oven at ca. 50 °C	NO	Mouse PK

FIG.4

Particle size (μm)	Reading #1	Reading #1	Reading #1	Average
D (V, 0.1)	11.55	11.32	11.34	11.4
D (V, 0.5)	25.26	24.3	25.4	25.0
D (V, 0.9)	50.58	47.99	51.62	50.1

D (V, 0.1): distribution in volume, 10% of the particles is at or below this size.

D (V, 0.5): distribution in volume, 50% of the particles is at or below this size.

D (V, 0.9): distribution in volume, 90% of the particles is at or below this size.

FIG.5

Particle size (μm)	Reading #1	Reading #1	Reading #1	Average
D (V, 0.1)	10.21	9.99	9.96	10.1
D (V, 0.5)	38.4	36.0	35.4	36.6
D (V, 0.9)	89.58	82.15	80.31	84.0

D (V, 0.1): distribution in volume, 10% of the particles is at or below this size.

D (V, 0.5): distribution in volume, 50% of the particles is at or below this size.

D (V, 0.9): distribution in volume, 90% of the particles is at or below this size.

FIG.6

Material	Bulk density (g/mL)	Tapped density (g/mL)	True density (g/mL)
R enantiomer	0.149	0.175	1.1647
racemate	0.193	0.210	1.1522

FIG. 7

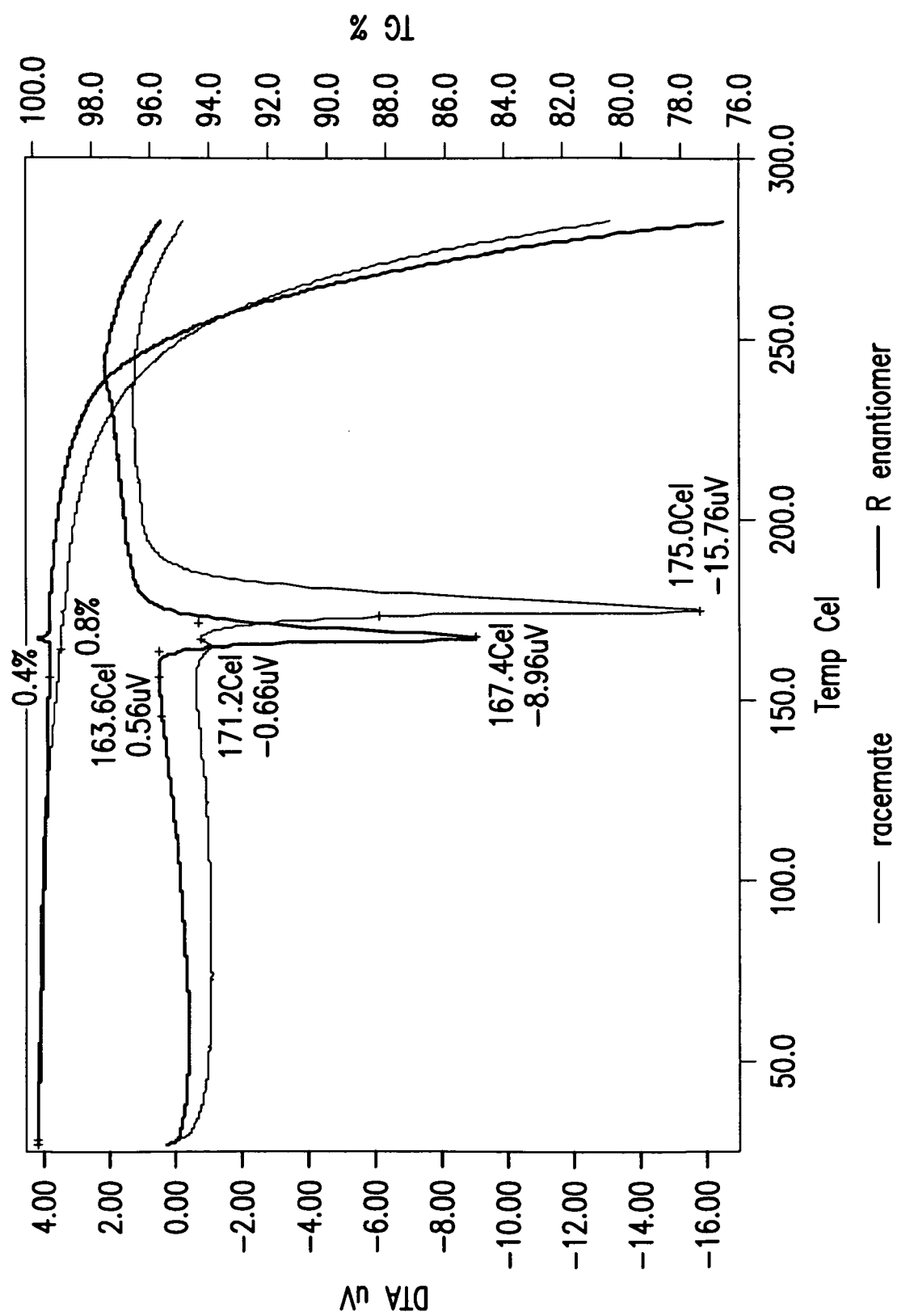


FIG. 8

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Excipient	Color/ viscosity	Vendor	Ligand	Concentration						
				2.5 mg/g	5 mg/g	10 mg/g	15 mg/g	20 mg/g	30 mg/g	50 mg/g
Labrasol	Clear/ fluid	Gattefossé	R enantiomer		soluble	soluble	soluble			
			Racemate		soluble	mostly soluble, opaque	insoluble			
Lauroglycol 90	Clear/ fluid	Gattefossé	R enantiomer			soluble	soluble	soluble		
			Racemate			soluble	soluble	soluble	partly soluble, suspension	insoluble
Phosal 53 MCT	Yellow/ viscous	Phospholi pid GmbH	R enantiomer		Mostly soluble	partly soluble				
			Racemate		insoluble	insoluble				
Miglyol	Clear/ fluid	Sasol	R enantiomer			soluble	soluble			
			Racemate			partly soluble	insoluble			
Cremophor EL	Clear/ viscous	BASF	R enantiomer	Mostly soluble	Mostly soluble	partly soluble				
			Racemate	insoluble	insoluble	insoluble				
polysorbate 80	Clear/ fluid	Croda	R enantiomer		partly soluble	insoluble				
			Racemate		partly soluble, suspension	insoluble				
Crillet 1 HP	Yellow/ viscous	Croda	R enantiomer		mostly soluble	partly soluble				
			Racemate		partly soluble	insoluble				
Isopropyl myristate	Clear/ fluid	Croda	R enantiomer			soluble	soluble			
			Racemate			partly soluble, suspension	insoluble			
Oleic acid	Clear/ fluid	TCI	R enantiomer			soluble	soluble			
			Racemate			partly soluble, suspension	partly soluble, suspension			
PEG 400 NF	Clear/ fluid	Croda	R enantiomer			soluble	partly soluble			
			Racemate			partly soluble, suspension	insoluble			

FIG.9

Excipient	Vendor	Ligand	Conc. mg/g	Appearance		
				Treatment 1	Treatment 2	Comments
Labrasol (PEG-8 caprylic/ capric triglyceride)	Gattefossé	R enantiomer	15	transparent	Transparent (48 hour)	
		Racemate	15	slight precipitate	precipitate (48 hr)	
Lauroglycol 90 (propylene glycol monolaurate)	Gattefossé	R enantiomer	50	transparent	transparent (48 hour)	
		Racemate	50	precipitate	precipitate (48 hr)	
Phosal 53 MCT	Phospholi pid Gmbh	R enantiomer	10	transparent	transparent	
		Racemate	10	precipitate	precipitate	
Miglyol	Sasol	R enantiomer	15	transparent	transparent (24 and 48 hour)	
		Racemate	15	precipitate	Precipitate (24 hour)	
Cremophor EL	BASF	R enantiomer	2.5	transparent	transparent (48 hour)	
		Racemate	2.5	transparent	slight precipitate (48 hour)	(treatment 2) 90 °C for 10 min
polysorbate 80	Croda	R enantiomer	10	transparent	slight precipitate	(treatment 2) 90 °C for 25 min
		Racemate	10	precipitate	slight precipitate	(treatment 2) 90 °C for 25 min
Crillet 1 HP (polysorbate 20)	Croda	R enantiomer	10	transparent	transparent	
		Racemate	10	precipitate	precipitate	(treatment 2) 90 °C for 15 min
Isopropyl myristate	Croda	R enantiomer	15	transparent	transparent	
		Racemate	15	precipitate	precipitate	
Oleic acid	TCI	R enantiomer	15	Translucent/very slight precipitate	Translucent/very slight precipitate	
		Racemate	15	precipitate	precipitate	
PEG 400 NF	Croda	R enantiomer	10	transparent	transparent	
		Racemate	10	precipitate	precipitate	

FIG.10

Solubility (μM) 20% PEG 1000 in distilled water, pH 7.0		
	Filtration	Centrifugation
Racemate	<0.1	1.35
R enantiomer	0.32	7.53

FIG.11

	R enantiomer		Racemate	
Solvent	Solubility (mg/g)	pH	Solubility (mg/g)	pH
Di-water	0.03	6.70	0.1	4.03
0.5% polysorbate 80	2.9	6.33	2.8	4.23
1.0% polysorbate 80	12.3	5.84	4.7	4.39
1.5% polysorbate 80	9.3	5.41	4.5	4.41

FIG.12

Caco-2 Permeability							
Material	%Recovery		Papp (X10 ⁻⁶ cm/s)		Efflux	Permeability Classification ^a	Significant Efflux ^b
	A-B	B-A	A-B	B-A			
Racemate	24	47	1.31	3.42	2.6	High	No
R enantiomer	19	48	12.4	19.1	1.5	High	No

FIG.13

MDR1 –MDCK Permeability						
Material	%Recovery		Papp (X10 ⁻⁶ cm/s)		Efflux	Brain Penetration Classification
	A-B	B-A	A-B	B-A		
Racemate	26	46	0.77	6.90	9.0	Low
R enantiomer	21	50	9.60	37.5	3.9	Moderate

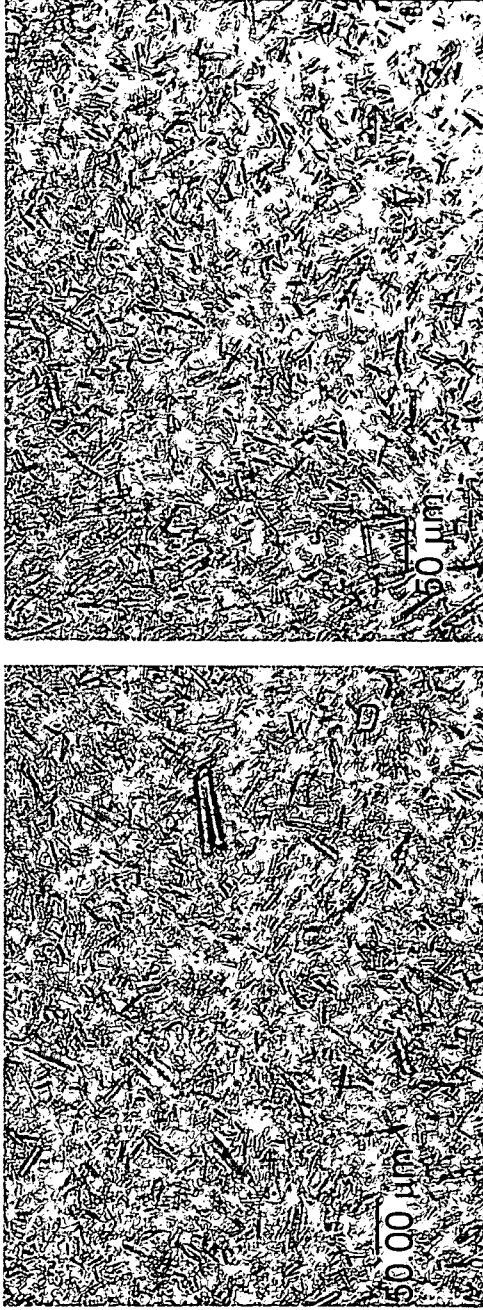
FIG.14

Material	Human Metabolic Stability		
	% Remaining		
	0 Min	15 min	60 min
Racemate	100	--	21
R enantiomer	100	--	28
testosterone	100	21	--

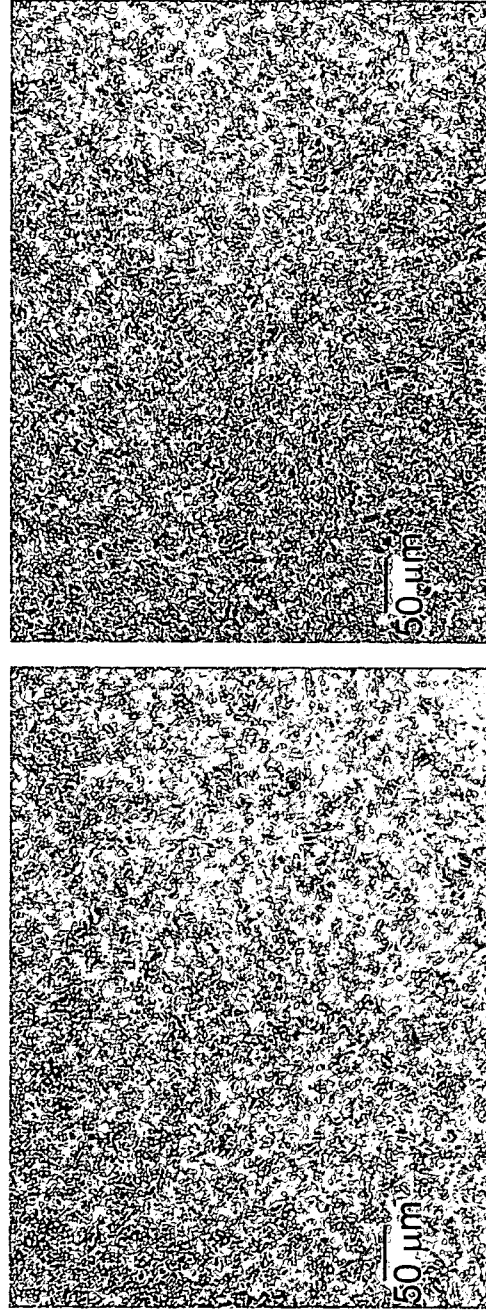
FIG.15

Group	Route	Test Article	Dose (mg/kg/day)	Dose volume (mL/kg/day)	Concentration (mg/mL)	Females ^a
1	Oral	R enantiomer	3	2.5	1.2	36 + 2 ^b
2	Oral	R enantiomer	10	2.5	4	36 + 2 ^b
3	Oral	R enantiomer	30	2.5	12	36 + 2 ^b
4	Oral	R enantiomer	50	2.5	20	36 + 2 ^b
5	Oral	Racemate	3	2.5	1.2	36 + 2 ^b
6	Oral	Racemate	10	2.5	4	36 + 2 ^b
7	Oral	Racemate	30	2.5	12	36 + 2 ^b
8	Oral	Racemate	50	2.5	20	36 + 2 ^b
^a Dose administration will occur for 9 days (first 18 females/group) or 12 days (second 18 females/group). ^b Included as possible replacements						

FIG.16



Racemate, Lot #PYAP-2-8-2-2, non-micronized



Racemate, Lot # REH-28-9-1 (PYAP-2-8-2-2M), micronized

FIG.17

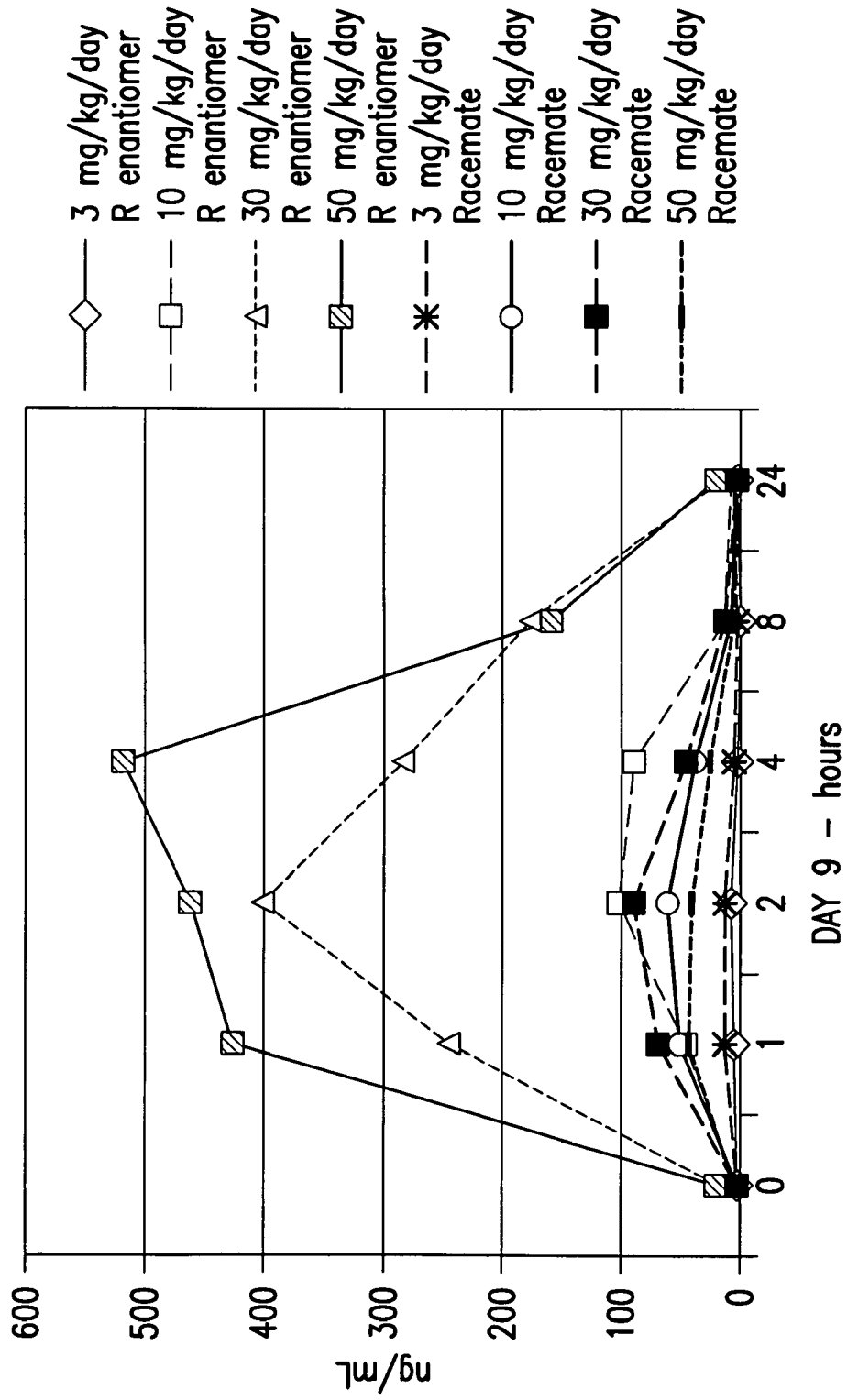


FIG.18

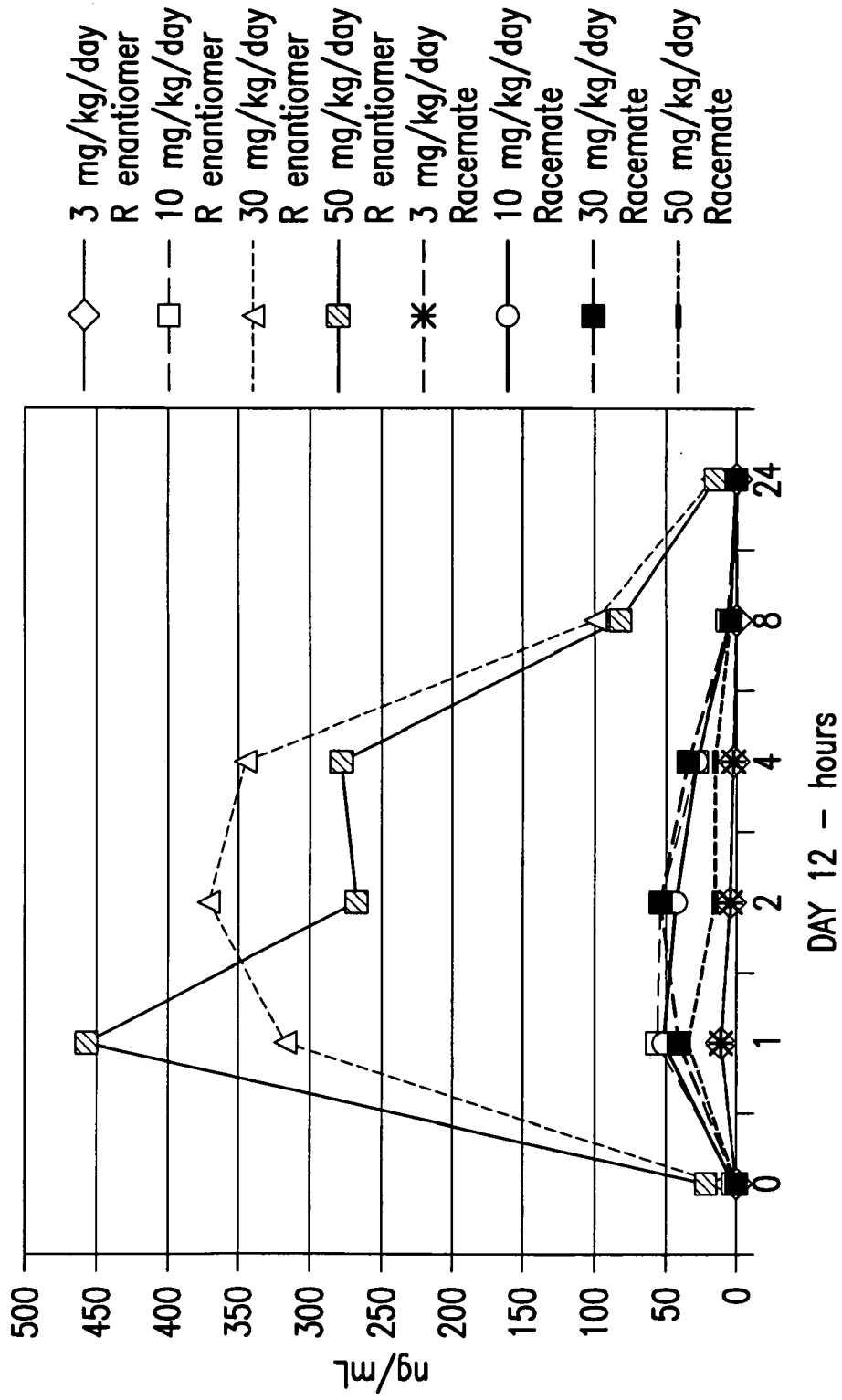


FIG.19

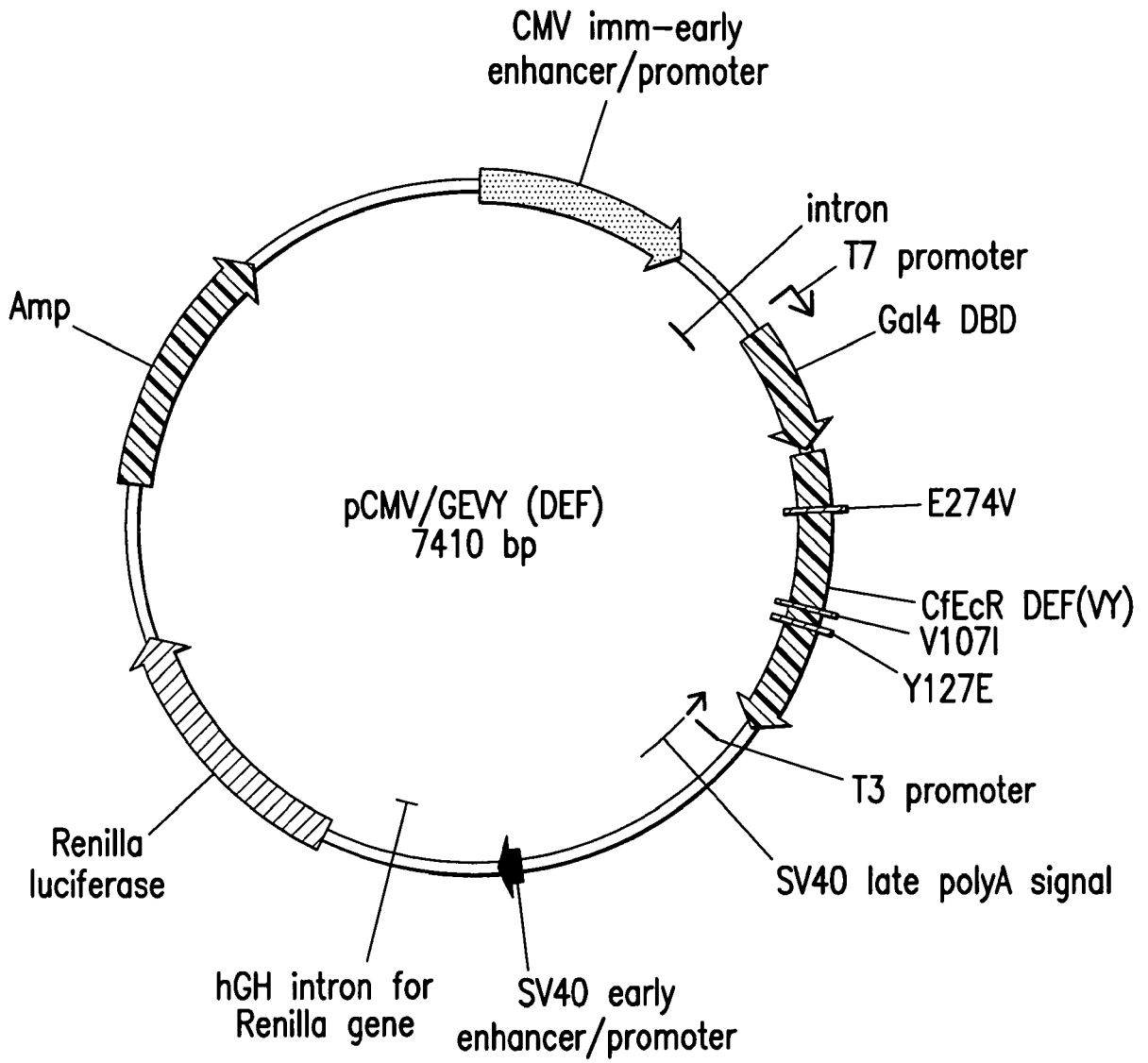


FIG.20

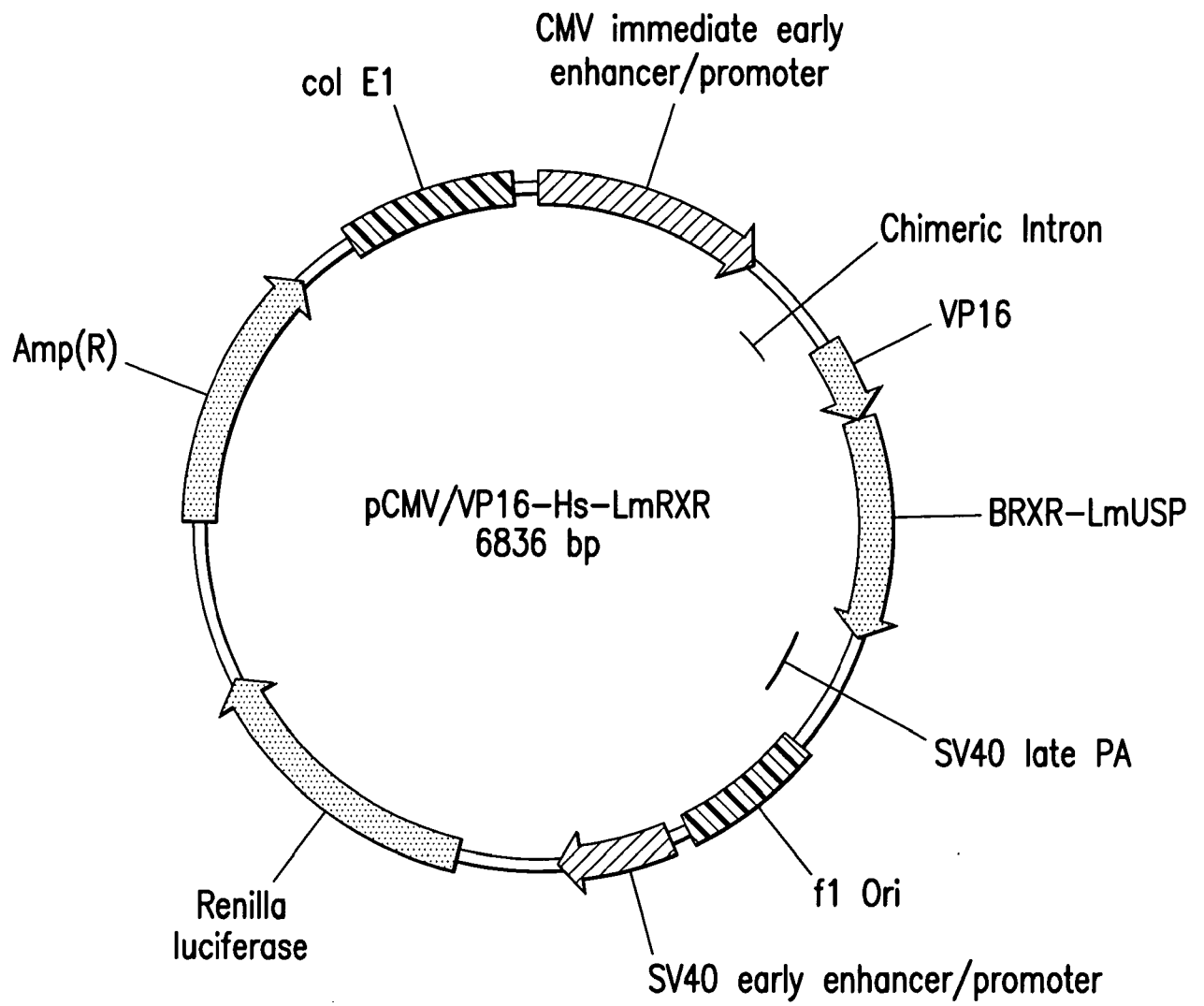


FIG.21

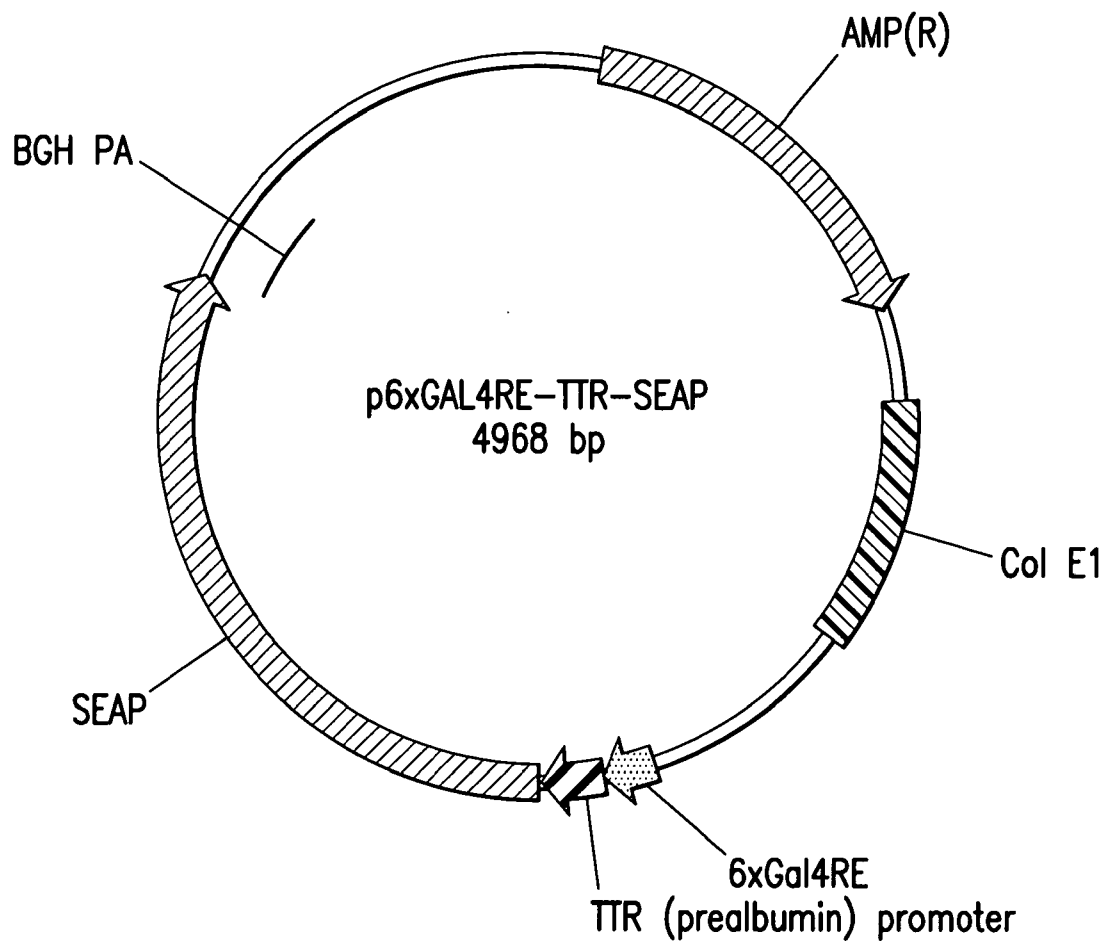


FIG.22

RTS-IL-12

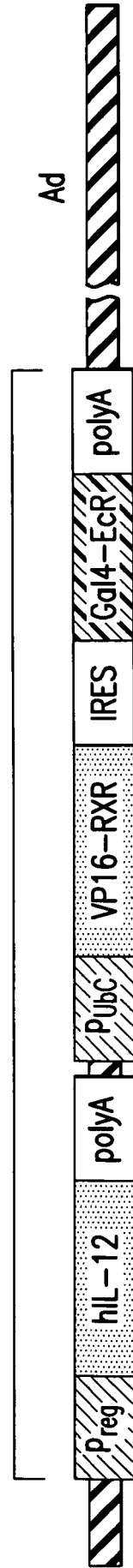


FIG. 23

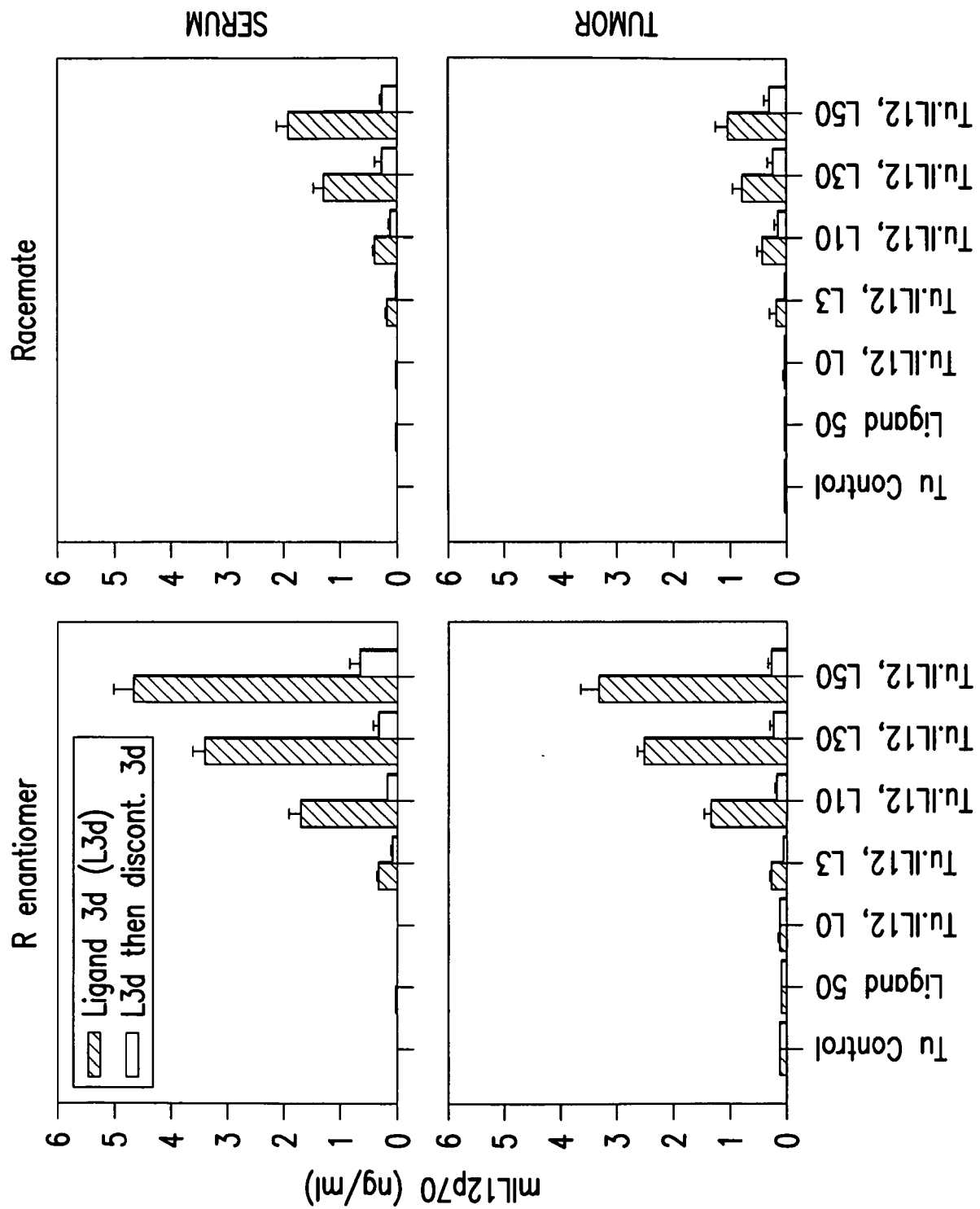


FIG.24

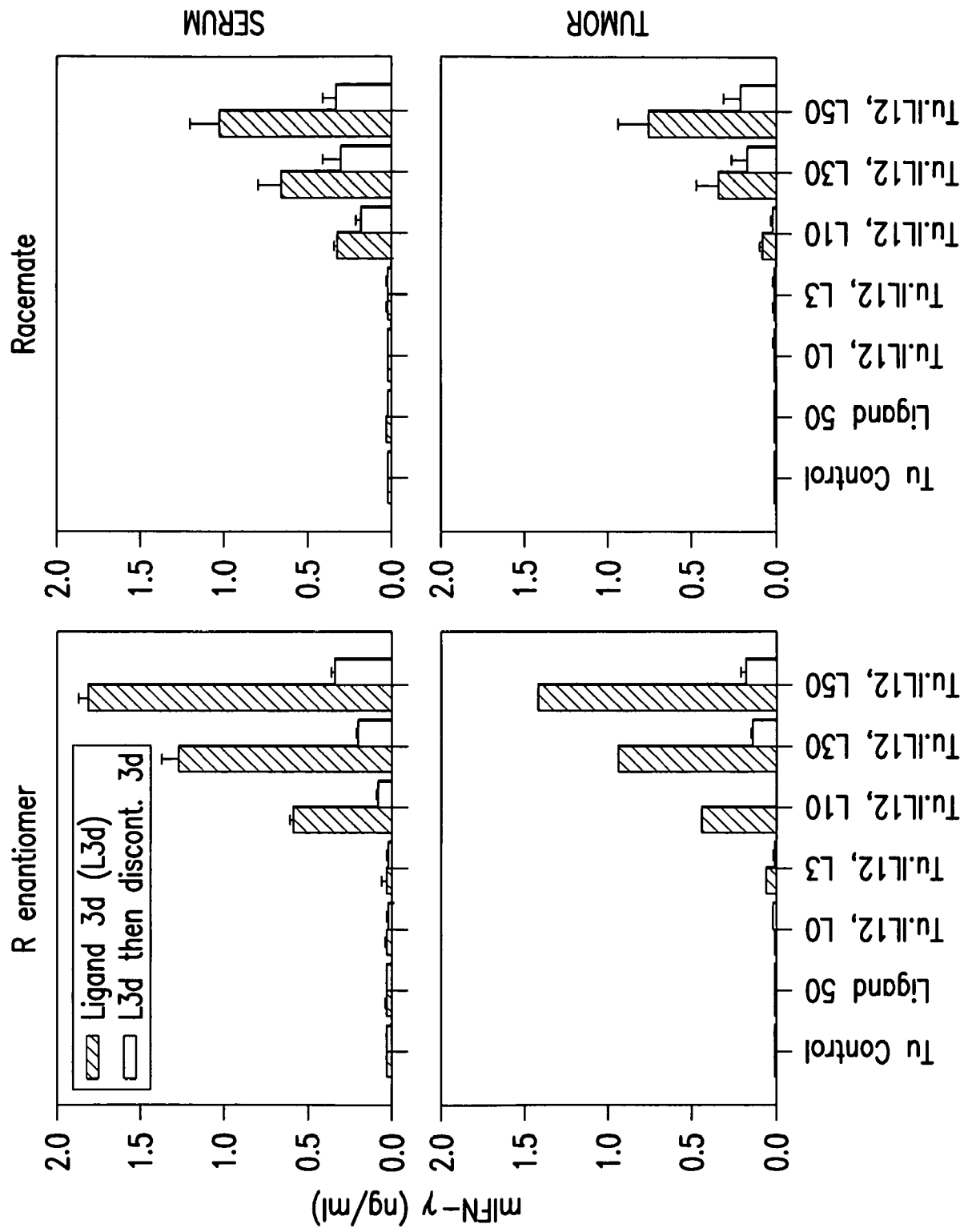


FIG.25