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Cameron et al.

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(54) COMPOUNDS AND METHODS FOR

(56) References Cited

INHIBITING CPY26 ENZYMES

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FOREIGN PATENT DOCUMENTS

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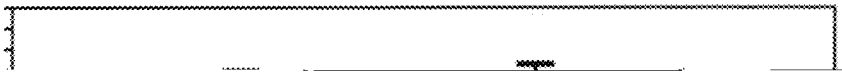
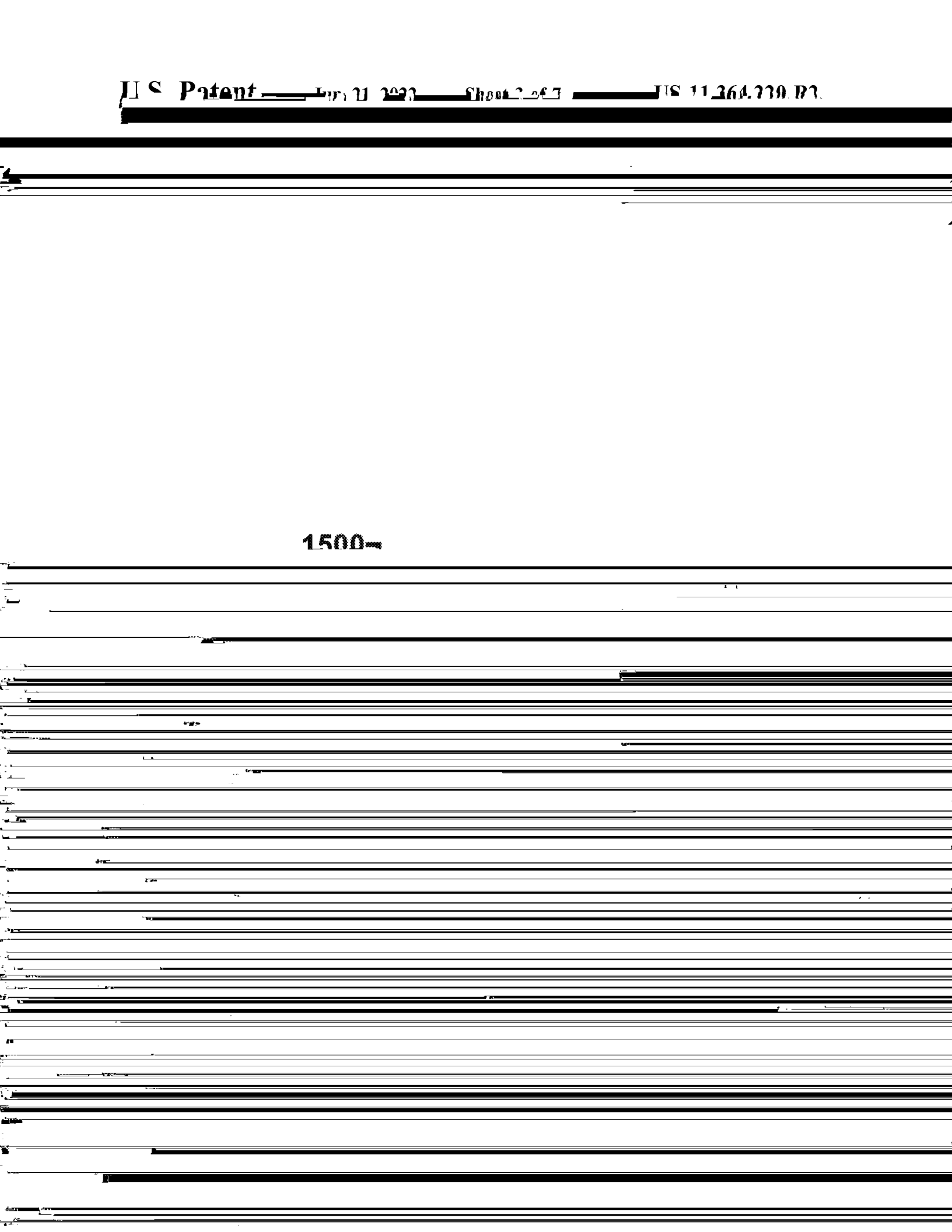
Lu, L., et al., "Critical role of all-trans retinoic acid in stabilizing human natural regulatory T cells under inflammatory conditions"

PNAS, pp. E3432-E3440, (2014).

Medh, R.D., et al., "Stimulation of Tissue Plasminogen Activator Production by Retinoic Acid: Synergistic Effect on Protein Kinase

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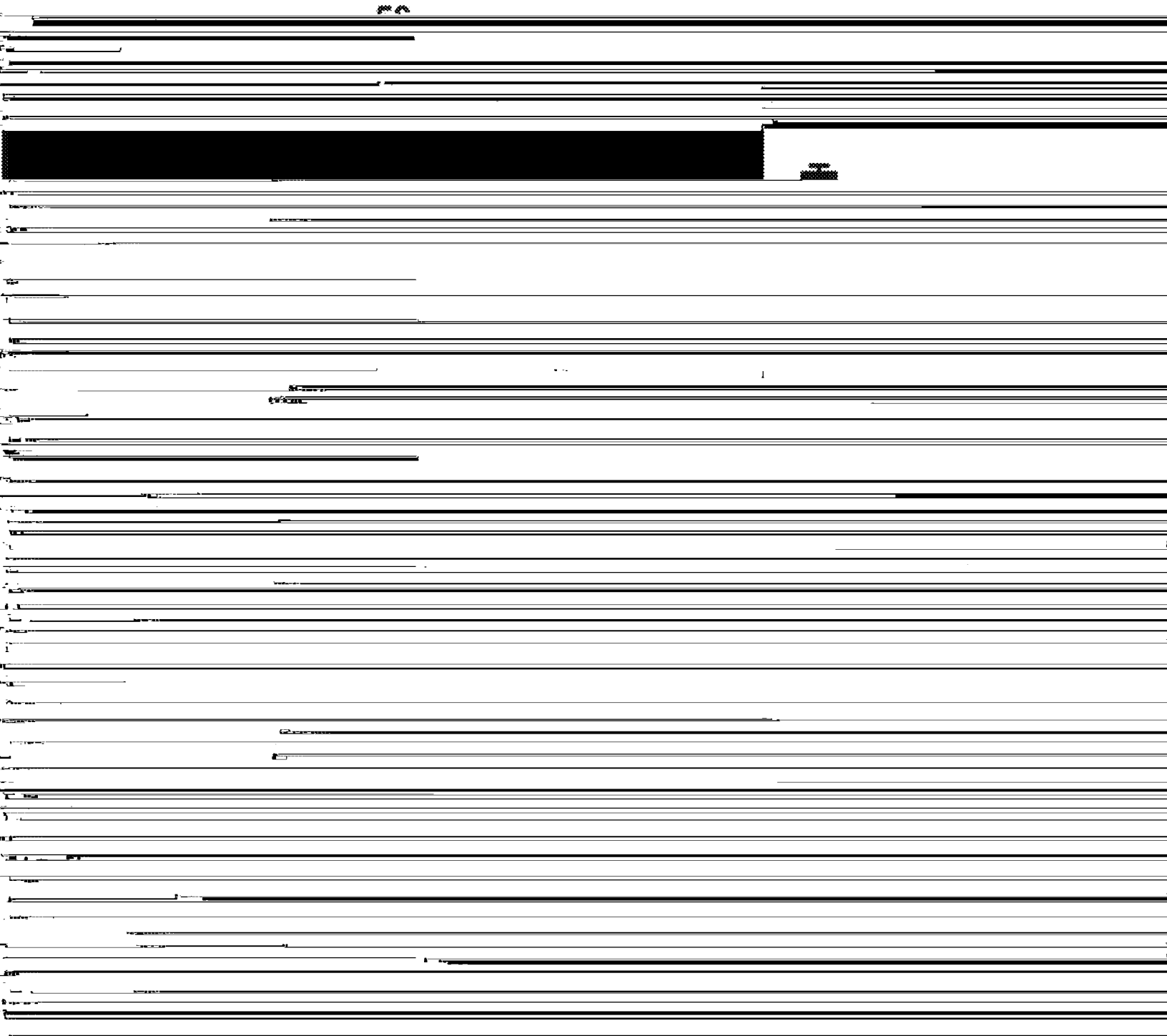
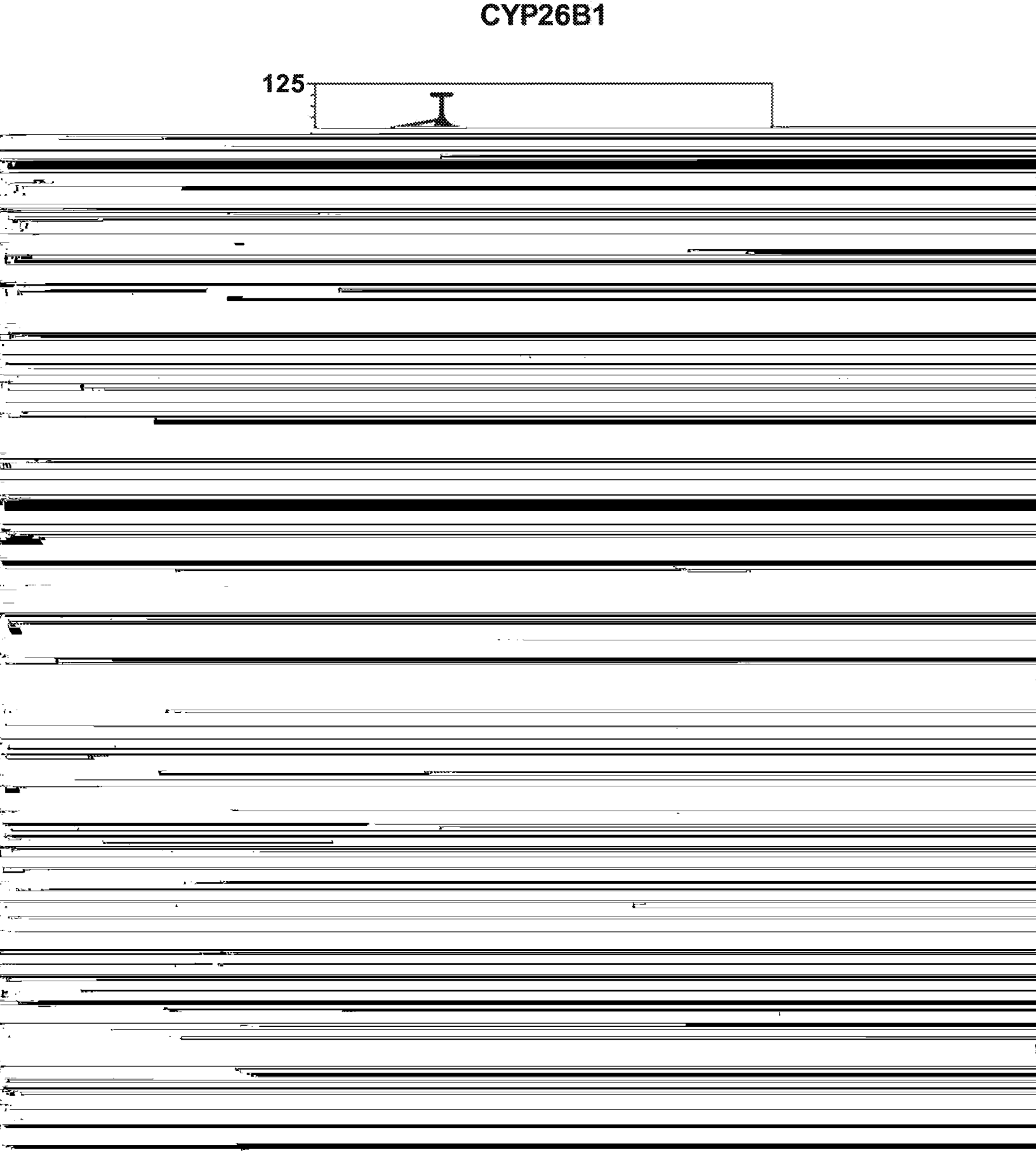


CYP26A1


CYP26B1
125

COMPOUNDS AND METHODS FOR INHIBITING CDK26-ENZYMES

RELATED APPLICATION

This application claims the benefit of the filing date of

methyl. In some embodiments of this aspect, n is 1. In some embodiments, R^4 and R^5 are each C_1 and they form a ring.

In some embodiments of this aspect, the compound of formula (1) is

14 inflammatory acne, psoriasis, ichthyosis and other keratini-

family of enzymes, and the terms "CYP26A1" and "CYP26B1" refer to the enzyme (protein) products of their

Structural formulae for compounds described herein including precursors of compounds of Formula (1) are

for a compound as described herein include the treatment and prevention of conditions and diseases associated with human papilloma virus (HPV) including warts and genital warts, various inflammatory diseases such as pulmonary fibrosis, ileitis, colitis and Crohn's disease, neurodegenera-

dermatoses, treating or preventing infection, or reducing irritation, inflammation, and the like.

Treatment of dermatoses or any other indications known or discovered to be susceptible to treatment by retinoid acid-like compounds, or to control by naturally occurring

slowly for 15 mins. The resulting suspension was left standing for 2 h. It was then filtered and washed with 2×30 mL of water. A resulting solid was dried under high vacuum to afford the title compound T-1 (10.1 g, 81% yield). The analytical data matches those reported in the literature.

was added and the mixture was stirred for 1 h. Then pyridine (1 mL) was added and the mixture stirred for overnight at room temperature. After the reaction was complete, the volatiles were evaporated, CH_2Cl_2 (25 mL) added and the

evaporated to afford T-24 as a beige solid, which was used directly without further purification.

Synthesis of Compound T-25

was added and the mixture was left to warm to room temperature. The dark reaction mixture was stirred for 4 h and then poured on ice-water and extracted with DCM (2×20

Synthesis of Compound T-32

In a 50 mL round-bottomed flask T-31 (830 mg, 3.5 mg) was added. The mixture was hydrogenated with a hydrogen balloon overnight. The mixture was filtered, and

mg, 1.2 mmol, 1.2 equiv) and Et_3N (0.42 mL, 3.0 mmol, 3 equiv) in CH_2Cl_2 (10 mL). The reaction mixture was stirred for 16 h at room temperature. EtOAc (30 mL) was added, was dried ($MgSO_4$) and evaporated. The residue was purified via column chromatography (pentane/EtOAc 9/1 to 1/1)

Synthesis of Compound T-37C

(180 mg, 1.5 equiv, 0.88 mmol) was added and the mixture was stirred for 1 h. Then pyridine (0.5 mL) was added and

structurally related compounds can be prepared in a similar way as the steps described below.

Synthesis of Compound 4 (a.k.a., T-7)

In a 50 mL round-bottomed flask T-6 (400 mg, 0.97 mmol) was dissolved in THF/H_2O (10/5 mL). LiOH (204

Purity (HPLC): >98% (HPLC details: 50:50 MeOH:MeCN, Agilent Zorbax sb-aq 5 μm; 254 nm; 0.5 ml/min), Melting point: >157.5-159.0° C.

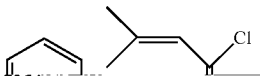
^{1}H-NMR (400 MHz, DMSO-de): 1.18 (s, 6H), 1.22 (s, 6H), 1.62 (s, 4H), 3.48 (s, 2H), 6.86-6.92 (m, 2H), 7.19 (t, J=8.3 Hz, 1H), 7.48-7.54 (m, 2H), 7.68 (d, J=1.6 Hz, 1H), 10.41 (s, 1H), 12.38 (s, 1H) ppm.

and the mixture was stirred for 1 h. Then pyridine (0.7 mL/mmol) was added and the mixture stirred for overnight at room temperature. A standard workup and purification via column chromatography afforded the title compound.

Compound 14 (a.k.a. T-44) was synthesized using 14A (1 equiv) in $Et_2O/THF/H_2O$ (20/4/3 mL/mmol) and KOt-Bu (8.0 equiv). After a standard workup and purification via

Synthesis of Compound 21

The synthetic scheme is presented below.



This retinoid activity assay measures the ability of test

An RA activity assay was used to measure the ability of compounds that inhibit CYP26A1 to enhance activity of

TABLE 1

Compound numbers, names, and structural formulas of compounds described herein

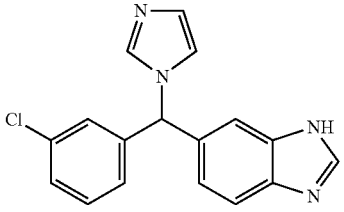
Compound Number	Compound Name	Structural Formula
	Liarozole	
	Ketoconazole	

TABLE 1-continued

Compound numbers, names, and structural formulas of compounds

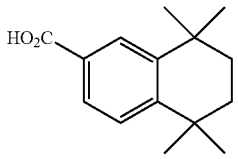
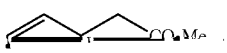
Compound Number	Compound Name	Structural Formula
T-5		
T-6		

TABLE 1-continued

Compound numbers, names, and structural formulae of compounds described herein

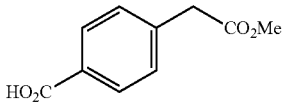
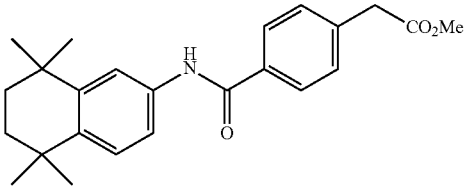
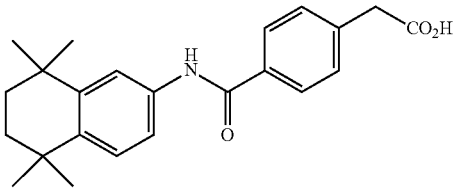
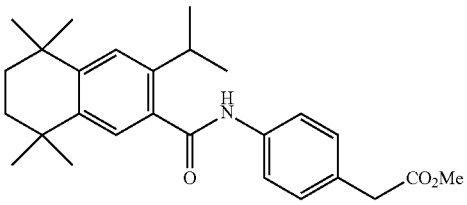
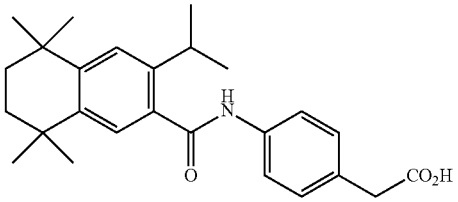
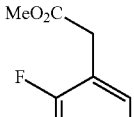
Number	Name	Structural Formula
T-14		
T-16		
T-17		
T-18		
T-19		
T-20		

TABLE 1-continued

Compound numbers, names, and structural formulae of compounds described herein

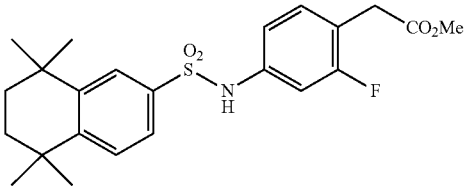
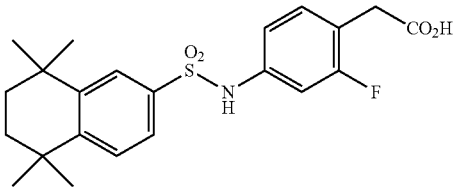
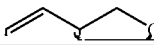
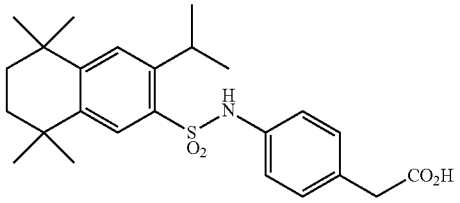
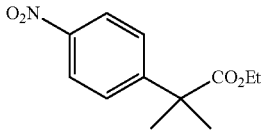
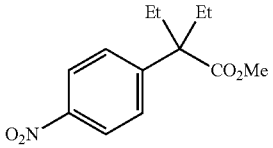
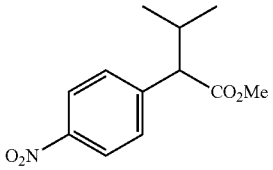
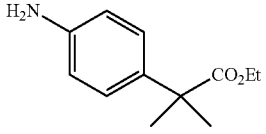
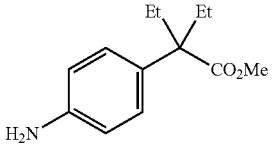
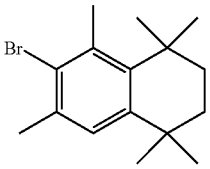
Compound Number	Compound Name	Structural Formula
T-22		
T-23		
T-24		

TABLE 1-continued

Compound numbers, names, and structural formulae of compounds described herein

Compound Number	Compound Name	Structural Formula
T-30		
T-31		
T-31A		
T-31C		
T-32		
T-32A		
T-33		
T-32C		

Compound numbers, names, and structural formulae of compounds described herein

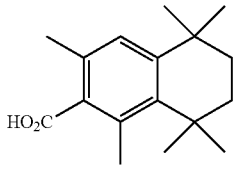
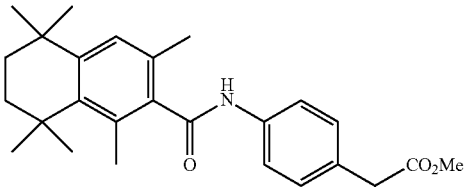
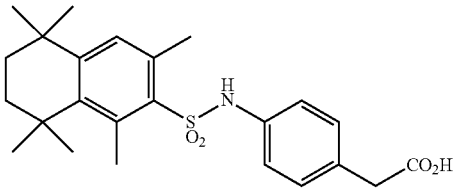
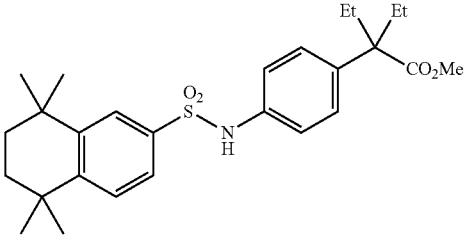
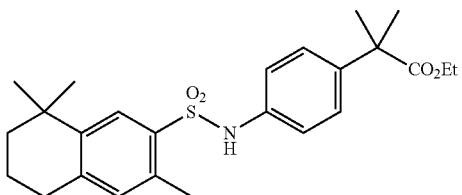
Number	Name	Structural Formula
T-34		
T-35		
T-36		
T-37A		
T-37		

TABLE 1-continued

Compound numbers, names, and structural formulae of compounds

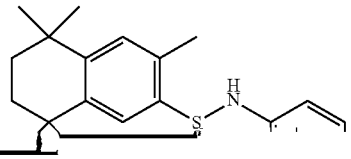
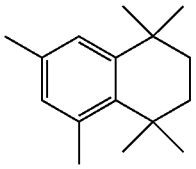
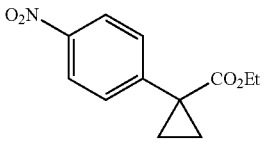
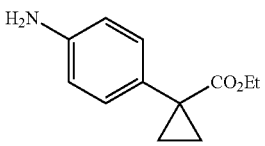
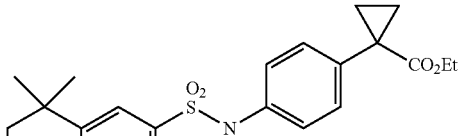
Compound Number	Compound Name	Structural Formula
T-39		
T-40		
T-41		
T-42		
T-43		

TABLE 1-continued

Compound numbers, names, and structural formulae of compounds described herein

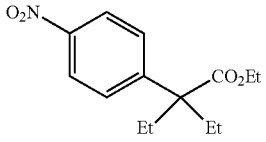
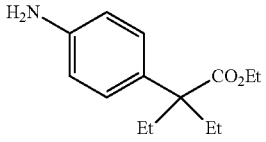
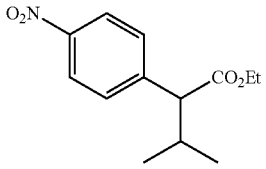
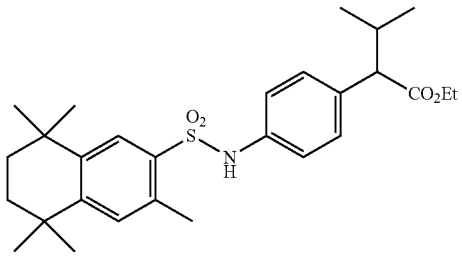
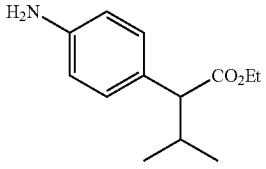
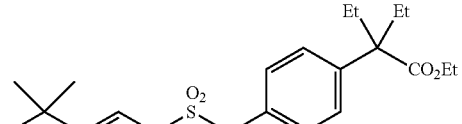
Compound Number	Compound Name	Structural Formula
SS-100		
SS-101		
SS-200		
T-19B		
SS-201		
17A		

TABLE 2

Structure and Activity Results for Compounds of Formula (1)

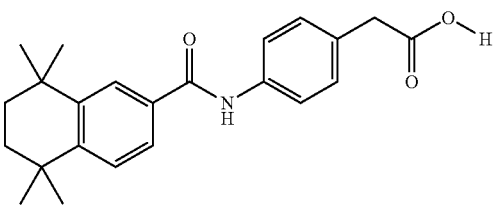
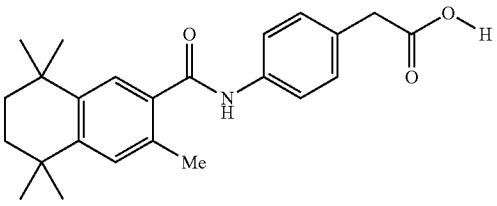
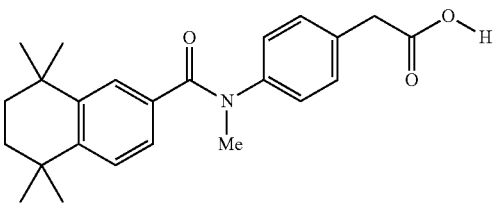
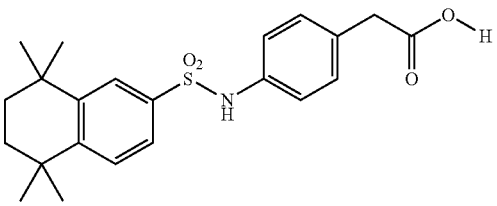
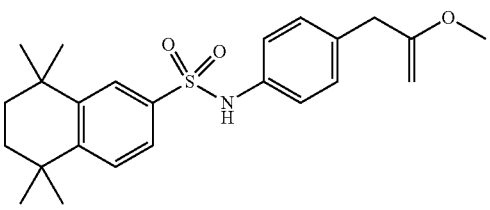
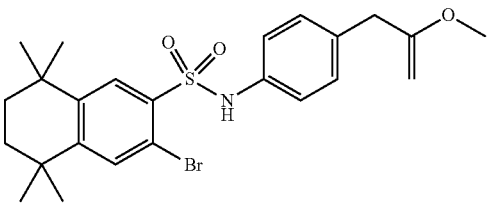
Cmpd No.	Structure	IC50 26A1 (μM)	Keto IC50 (A1)	IC50 relative to keto	IC50 26B1 (μM)	Keto IC50 (B1)	IC50 relative to keto
01		5.66	4.46	1.27	8.807	7.44	1.18
02		0.83	4.46	.19	2.061	7.44	0.28
03		>100	15.66		65.44	4.39	14.9
04 aka T-7		1.14	4.46	0.26	18.87	4.39	4.3
04A		14.02	5.5				
04B		8.24	3.2				
05							

TABLE 2-continued

Structure and Activity Results for Compounds of Formula (1)

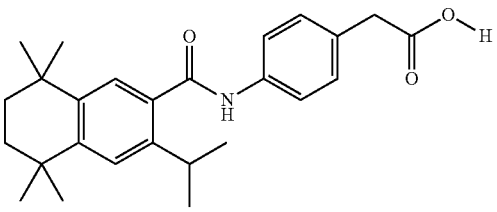
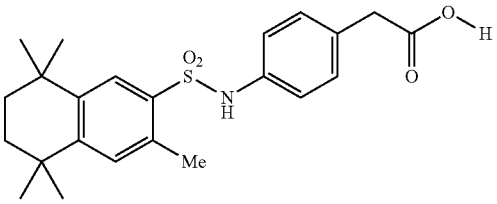
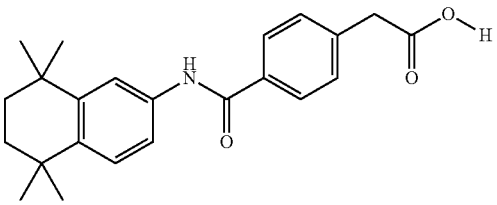
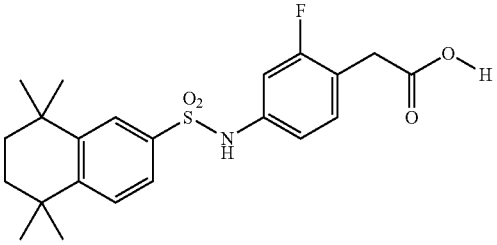
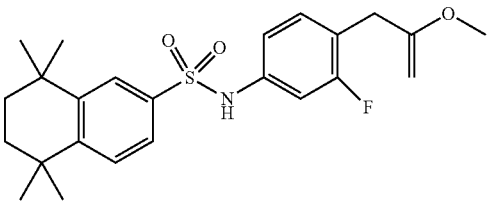
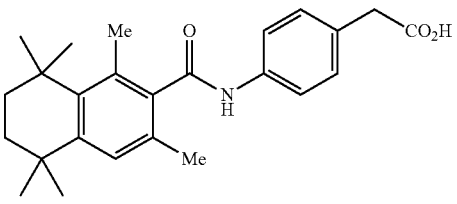
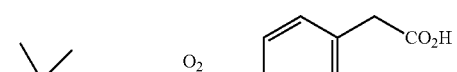
Cmpd No.	Structure	IC50 26A1 (μM)	Keto IC50 (A1)	IC50 relative to keto	IC50 26B1 (μM)	Keto IC50 (B1)	IC50 relative to keto
06		1.29	2.38	0.54	42.28	6.64	6.37
07 aka T-13		0.47	2.38	0.2	>1000	4.39	
08		3.17	2.38	1.33	19.17	4.39	4.36
09 aka T-23		2.2	1.33	1.65	14.24	6.64	2.14
09A		80.52	31.7				
10		8.23	1.33	6.19	0.55	6.64	0.08
11 aka T-30		20.01	1.33	15.05	>1000	6.64	

TABLE 2-continued

Structure and Activity Results for Compounds of Formula (1)

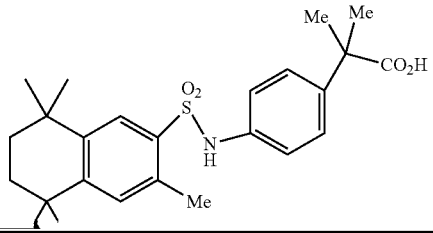
Cmpd No. Structure	IC50 26A1 (μM)	Keto IC50 (A1)	IC50 relative to keto	IC50 26B1 (μM)	Keto IC50 (B1)	IC50 relative to keto
12 aka T-39 	0.1	1.33	.08	>1000	6.64	

TABLE 2-continued

Structure and Activity Results for Compounds of Formula (1)

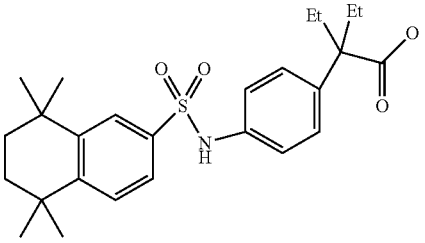
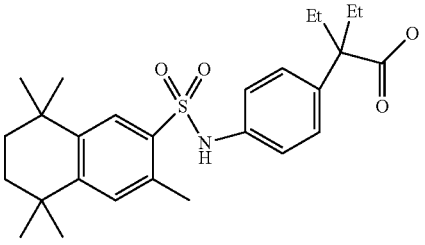
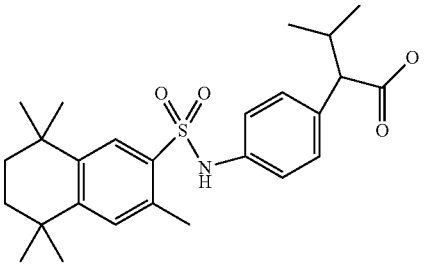
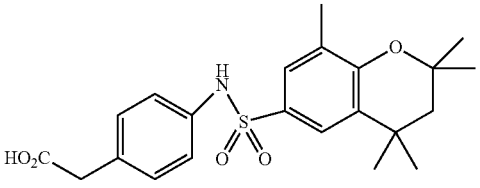
Cmpd No.	Structure	IC50 (μM)	Keto (A1)	IC50 to keto	IC50 (μM)	Keto (B1)	IC50 to keto
17		38.66	3.07	12.6	0.29	8.25	.035
18		>1000	7.49		9.066	6.57	1.38
19		0.7414	4.77	0.16	>100	12.16	
21		1.9	4.8	0.4	21.8	2	10.8

TABLE 3

TABLE 3-continued

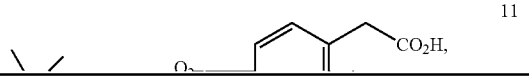
	Luciferase Activity							
Treatment	RLU Avg	SD	0.1 μM RLU Avg	SD	1 μM RLU Avg	SD	10 μM RLU Avg	SD
Cmpd 08			0.0025	0.0007	0.0019	0.0006	0.0028	0.0001
Cmpd 09			0.0018	0.0004	0.0017	0.0004	0.0012	0.0001
DMSO	0.074	0.003						
RA			0.12	0.039	0.132	0.006	0.279	0.021
Cmpd 010			0.073	0.019	0.076	0.004	0.084	0.008
Cmpd 011			0.064	0.005	0.062	0.002	0.044	0.016
Cmpd 012			0.067	0.007	0.082	0.012	0.041	0.002
DMSO	0.087	0.014						
RA			0.088	0.016	0.162	0.017	0.193	0.045
Cmpd 013			0.113	0.026	0.07	0.01	0.04	0.003
DMSO	0.133	0.011						
RA			0.26	0.037	0.327	0.005	0.747	0.118
Cmpd 014			0.111	0.004	0.125	0.01	0.134	0.007
Cmpd 015			0.129	0.018	0.212	0.03	0.816	0.133
DMSO	0.211	0.041						
RA			0.26	0.037	0.327	0.005	0.747	0.118
Cmpd 016			0.166	0.036	0.183	0.03	0.155	0.036
DMSO	0.0293	0.0021						
RA			0.0353	0.0025	0.059	0.0026	0.1277	0.0093
Cmpd 017			0.023	0.0035	0.026	0.0035	0.038	0.0062
DMSO	0.0853	0.0196						
RA			0.1073	0.006	0.1653	0.015	0.528	0.0701
Cmpd 018			0.0683	0.0083	0.0597	0.0042	0.05	0.0053
DMSO	0.0248	0.0087						
RA			0.0214	0.0027	0.0309	0.0027	0.126	0.0178
Cmpd 019			0.0244	0.0052	0.019	0.0102	0.0076	0.003

The invention claimed is:

cer of the breast, skin, prostate, cervix, uterus, colon, blad-

administered by injection, suppository, extended release formulation for deposit under the skin or intramuscular injection.

-continued



11