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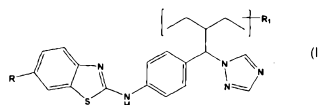
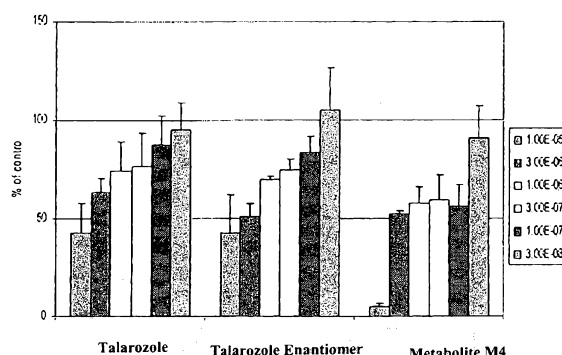
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(54) Title: TALARAZOLE METABOLITES

Talarazole, Talarazole Enantiomer and Metabolite M4

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(57) Abstract: Novel metabolites of talarazole of formula (I) have been isolated and characterized, wherein R = H, OH, OSO₃H or O-gly; R₁ = H, OH, OSO₃H, O-gly or =O; and gly = a glucuronate, or a pharmaceutically acceptable salt thereof. These compounds are targeted for the treatment of various skin-, hair- and nail-associated disorders.

Title: Talarozole Metabolites**Field of the Invention**

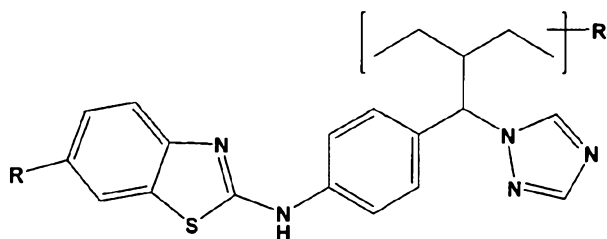
[0001] This application is directed to novel metabolites of talarozole (formerly referred to as rambazole). The application is also directed to the use of these metabolites for the treatment of various skin-, hair- and nail-associated disorders.

Background of the Invention

[0002] Talarozole ((R)-N-[4-[2-ethyl-1-(1H-1,2,4-triazole-1yl)butyl]phenyl]-2-benzothiazolamine) (formerly referred to as rambazole) is a novel enantiomerically pure retinoic acid metabolism-blocking agent (RAMBA). In preclinical in vitro and animal studies, topical talarozole has demonstrated potential effectiveness in the treatment of psoriasis, acne and photo-damage. Oral talarozole is being developed for the treatment of moderate to severe psoriasis and potentially acne. See, *e.g.*, U.S. Patent Nos. 6,833,375; 6,486,187 and 6,124,330, each of which is incorporated by reference in its entirety. Given talarozole's promise as a potent therapeutic agent, its metabolism in selected animal species was investigated and novel talarozole metabolites were isolated and characterized. Select metabolites were evaluated as therapeutic agents, especially in the treatment of keratinization-associated disorders.

Summary of the Invention

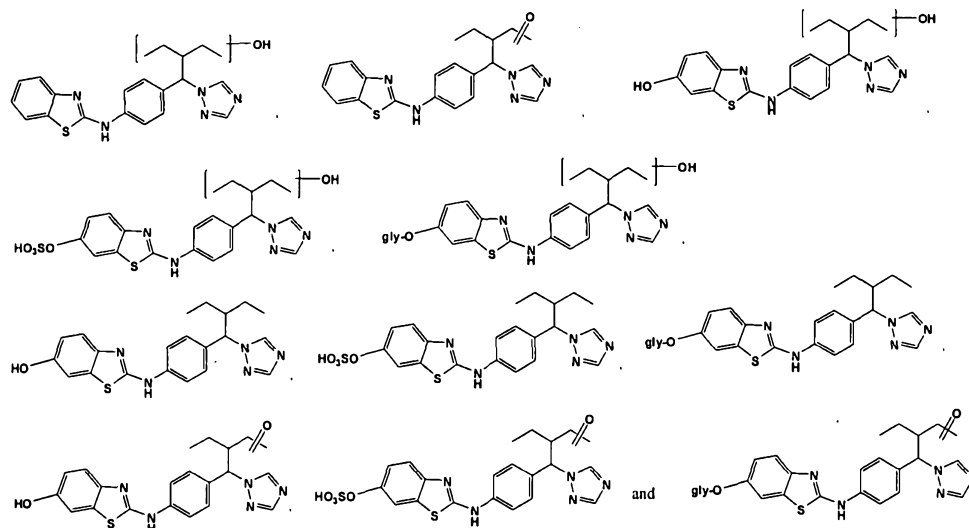
[0003] An aspect of the invention is a novel isolated metabolite of talarozole as represented by Formula I.



Formula I

wherein R = H, OH, OSO₃H or O-gly; R₁ = H, OH, OSO₃H, O-gly or =O; and gly = a glucuronate, or a pharmaceutically acceptable salt thereof, with the proviso that when R = H, R₁ cannot also be H.

[0004] Another aspect of the invention is a compound selected from the group consisting of



[0005] Another aspect of the invention is the treatment of keratinization-associated disorders (*e.g.*, various skin-, hair- and nail-associated disorders) in a warm-blooded mammal in need thereof, comprising administering to the mammal an effective amount of a talarozole metabolite of Formula I.

[0006] Another aspect of the invention is a pharmaceutical composition comprising a novel metabolite of talarozole and a diluent or carrier.

[0007] Brief Description of Drawings

[0008] **Figure 1** shows a comparison of the various talarozole metabolites across selected animal species.

[0009] Detailed Description

[0010] Pharmaceutically acceptable salts of the metabolites of the invention include the conventional non-toxic salts that are known in the art and which are formed by the addition of inorganic or organic acids or bases. Examples of acid addition salts include,

but are not limited to, acetate, adipate, benzoate, benzenesulfonate, citrate, camphorate, dodecylsulfate, hydrochloride, hydrobromide, lactate, maleate, methanesulfonate, nitrate, oxalate, pivalate, propionate, succinate, sulfate and tartrate. Base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts and salts with amino acids such as arginine. Also, the basic nitrogen-containing groups may be quaternized with, for example, alkyl halides.

[0011] It is well known in the art that hydroxyl groups on chemical compounds are subject to *in vivo* glycosylation. Selected isolated metabolites of talarozole that contain one or more hydroxyl groups are evidence of this process occurring in the mammals studied, including humans. In an exemplary embodiment, the glycoside is a glucuronide formed by the reaction between glucuronic acid and one or more hydroxyl groups present in the metabolite.

[0012] In addition to carriers, the pharmaceutical compositions of the invention may also include stabilizers and preservatives. For examples of typical carriers, stabilizers and adjuvants known to those of skill in the art, see *Remington: The Science and Practice of Pharmacy*, 21st ed. (Lippincott, Williams & Wilkins (2005)).

[0013] The novel metabolites of this invention may be administered alone or preferably as a pharmaceutical formulation comprising the metabolite together with at least one pharmaceutically acceptable carrier. Optionally, other therapies known to those of skill in the art may be combined with the administration of the metabolites of the invention. More than one metabolite may be present in a single composition.

[0014] The metabolites of the invention are potential biological process modulators that likely impact cell proliferation and differentiation (*e.g.*, keratinocytes, fibroblasts, endothelial cells, sebocytes), immune function (*e.g.*, hemapoeic cells) and may be used in the treatment of skin-, hair- and nail- disorders such as, but not limited to, psoriasis, acne, actinic keratosis, eczema, rosacea, ichthyosis, alopecia and photodamaged skin. Further, the metabolites of the invention may be use in the treatment of cancer, such as prostate cancer, basal and squamous cell carcinomas and melanoma. This invention includes methods for the treatment of keratinization disorders in a mammal, including a human,

comprising administering to said mammal an amount of the compound of the invention or a pharmaceutical composition comprising or consisting of the compound of the invention, that is effective in inhibiting or arresting IP-10 dependent growth of abnormally proliferating epidermal cells, such as keratinocytes, without the addition of other therapeutic agents. In one embodiment of this method, the abnormal cell growth is a type of carcinoma, including but not limited to, basal cell carcinoma, squamous cell carcinoma. In another embodiment the abnormal cell growth is a type of melanoma.

[0015] An “effective amount” is an amount sufficient to effect beneficial or desired results. For example, a therapeutic amount is one that achieves the desired therapeutic effect. In an exemplary embodiment, the daily dose may range from about 0.005 to about 5 mg/kg. This amount may be the same or different from a prophylactically effective amount, which is an amount necessary to prevent the onset of disease or disease symptoms. An effective amount can be administered in one or more administrations, applications or dosages.

[0016] Methods of determining the most effective means and dosage of administration are well known to those of skill in the art and will vary with the composition used for therapy, the purpose of the therapy, the target cell being treated and the subject being treated. Single or multiple administrations can be carried out with the dose level and pattern being selected by the treating physician.

[0017] In an exemplary embodiment, the recipient of the metabolites of the invention is a warm-blooded mammal, preferably a human.

[0018] Pharmaceutical compositions containing the metabolites of the invention can be administered by any suitable route, including oral, rectal, intranasal, topical (including transdermal, aerosol, buccal and sublingual), parenteral (including subcutaneous, intramuscular, intravenous), intraperitoneal and pulmonary. It will be appreciated that the preferred route will vary with the condition and age of the recipient, and the disease being treated.

[0019] Experimental

[0020] Mouse, rat, dog and human were the species used for the safety evaluations of talarozole. More specifically, the disposition of ^{14}C -labeled talarozole was examined in mice, rats, dogs and humans after oral administration to provide information regarding the absorption, metabolism and excretion of talarozole.

[0021] Example 1: Analysis of Talarozole Metabolites

[0022] Male and female CD-1 mice (19-29 g, n = 3/sex/timepoint for blood sampling, n = 3/sex for mass balance), Sprague Dawley rats (0.205-0.237 kg, n = 3/sex/timepoint for blood sampling, n = 3/sex for mass balance) and beagle dogs (7-12 kg, n = 3) were given a single oral dose of ^{14}C -labeled talarozole in 20% hydroxyl propyl B-cyclodextrin at 5 mg/kg. Healthy human male volunteers (76.6-107.9 kg, n = 5) were dosed with a single oral dose of 4 mg ^{14}C -labeled rambazole in ethanol. Blood samples were collected at selected timepoints after dosing and plasma was prepared. Urine and feces were collected for 2, 7 and 8 days. For the human study, up to 288 hours post-dose and semen samples were obtained 2 and 4 hours post-dose. Radioactivity in various matrices were measured by liquid scintillation counting (LSC). Select plasma, urine and fecal samples were subjected to metabolite radioprofiling and characterization, and in the human study, semen samples. Metabolite radioprofiling was accomplished using HPLC with fraction collection followed by solid scintillation counting (Packard TopCount – see representative HPLC run data below). Radioactivity peaks were integrated and the percent distribution of individual metabolites in each sample was determined. Metabolite characterization and identification were accomplished by LC/MS (Finnigan MAT LCQ in positive or negative ESI mode) in conjunction with an appropriate radioactive monitor (RAM). For all species, plasma, urine and fecal samples were pooled across animals and analyzed. Plasma was analyzed at several time-points out to 24 hours. Urine was analyzed over one time-interval (0-24 hours for mouse, 0-48 hours for rat, 0-72 hours for dog, and for in the human study, 0-12, 12-24, 24-48, 0-48 hours. Feces was analyzed over 2-3 time intervals (0-24 and 24-48 hours for mouse and rat; 0-24, 24-48, and 48-72 hours for male dogs; and 24-48, 48-72, and 72-96 hours for female dogs). In the human study, feces were analyzed for 0-48, 48-96, 96-144, 144-192, 192-288, 0-144, 144-288 and 0-288 hours. PK parameters for ^{14}C -labeled talarozole radioactivity was determined from the mean (mouse and rat) or individual (dog and human) plasma concentration

versus time data. PK parameter values were determined by non-compartmental methods using WinNonlin™.

[0023] HPLC data for separations described in Example 1:

LC system: Waters 2695 Separations Module

Analytic column: C18 column, 4.6 x 150 mm, 3 µm

Flow rate: 1.0 mL/min

Mobile phase A: 2% HCOOH in H₂O (pH 3.2)

Mobile phase B: CH₃CN

Gradient:

(min)	(mL/min)	A (%)	B (%)
0	0.7	100	0
3	0.7	100	0
28	0.7	75	25
48	0.7	65	35
78	0.7	30	70
83	0.7	0	100
88	0.7	0	100
90	0.7	100	0
105	0.7	100	0

[0024] Example 2: Effects on Epithelial Differentiation in Rat Vagina: Inhibition of Vaginal Keratinization Induced by Estrogenic Treatment in Ovariectomized Rats by Oral Administration of Talarozole Metabolite M4

[0025] This animal model is based on the observation that retinoic acid (RA) suppresses the keratinization process in the stratified squamous epithelium of the vagina induced by estrogenic treatment in ovariectomized rats (Sietsema & DeLuca, 1982; Geiger & Weiser, 1989). ED₅₀-value for complete suppression (keratinization score = 0) was 1.0 mg/kg/day for talarozole whereas ED₅₀-value for RA was 5.1 mg/kg/day. Oral administration of M4 during 3 days inhibited vaginal keratinization induced by estrogenic treatment in ovariectomized rats in a dose-dependent manner. ED₅₀-value for complete suppression (keratinization score = 0) by M4 was 1.2 mg/kg/day.

[0026] Example 3: Talarozole Metabolites for Suppression of IP-10 Production by IFN γ -Activated Human Epidermal Keratinocytes

[0027] IP-10, a member of the CXC subfamily of chemokines, attracts T-lymphocytes and natural killer cells. IP-10 is upregulated in, for example, psoriasis. In particular, epidermal keratinocytes of psoriatic lesions express elevated levels of IP-10. Suppression of IP-10 expression by activated keratinocytes may represent a novel target for therapeutic intervention of inflammatory skin disorders. Talarozole, its enantiomer and metabolite M4 were observed to down regulate dose-dependently IP-10 expression as shown in Figure 1.

Results and Discussion

[0028] Pharmacokinetics of Radioactivity

[0029] PK parameters for ^{14}C -labeled talarozole are shown in Table 1.

[0030] Table 1: Mean Pharmacokinetic Parameters of ^{14}C -labeled Talarozole Equivalents in Plasma

Species (0-t)	Sex	Cmax (ng equiv/g)	Tmax (hours)	t _{1/2} (hours)	AUC _{0-t} (hr-ng equiv/g)	AUC _{0-∞} (hr-ng equiv/g)
Mouse (0-48 h)	Male	2633	3.0	7.6	10215	10276
	Female	1839	1.0	12.4	6632	6767
Rat (0-48 h)	Male	1130	2.0	17.4	6720	6960
	Female	838	4.0	14.8	7670	7810
Dog (0-168 h)	Male	2533	0.67	55.7	19555	19970
	Female	2719	0.67	49.0	21388	21902
Human (0-48 h)	Male	20.7	3.00	19.4	269	301

Concentrations are ng equivalents of ^{14}C -labeled talarozole

[0031] Excretion of Radioactivity

[0032] In the mouse, rat and dog, over 90% recovery of the radioactive dose was achieved after oral dosing (Table 2). The radioactive dose excreted in feces ranged from 78-89% and 78-92% in male and female animals, respectively.

[0033] Table 2: Percent of Dose Recovered in Excreta

Species (interval)	Sex	% in Urine	% in Feces	% in Cage Rinse	Total % Recovered
Mouse (0-48 h)	Male	4.3	82.7	4.4	91.4
	Female	3.0	91.6	0.8	95.4
Rat (0-168 h)	Male	6.3	77.5	4.01	95.2
	Female	10.1	77.5	3.88	95.4
Dog (0-192 h)	Male	4.1	88.7	0.8	93.6
	Female	2.9	89.0	0.5	92.4
Human (0-288)	Male	7.3	72.2	--	87.7

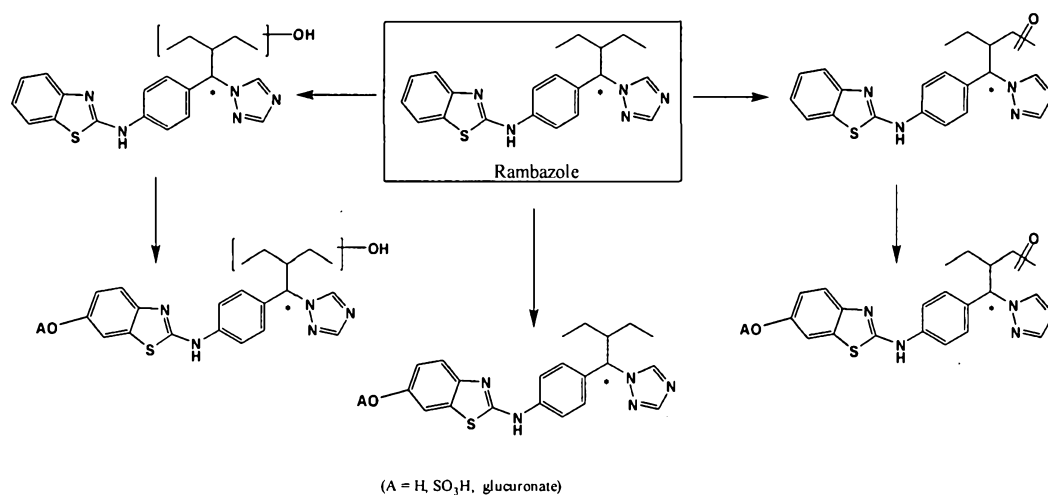
[0034] It was discovered that talarozole was extensively metabolized, with the majority of metabolites excreted in the feces. In addition to uncharged drug, 17, 26 and 19 radioactive components were observed in plasma, urine, and feces from mouse, rat and dog, respectively. Unchanged ^{14}C -labeled talarozole, M3, M4, M9 and M13 were the prominent radioactive components in mouse plasma. Rat had the greatest number of circulating metabolites in plasma. In addition to the metabolites observed in mouse, M11, M12 and M16 were observed in rat plasma. In the dog, only unchanged ^{14}C -labeled talarozole and M4 were characterized. Unchanged ^{14}C -labeled talarozole and M4 were the prominent metabolites in mouse feces, accounting for 6.11 and 10.56% of the dose in male mouse feces and 7.04 and 15.16% of the dose in female mouse feces. Unchanged ^{14}C -labeled talarozole, M4, M14 and M15 were the major metabolites in rat feces, and accounted for 5.34, 4.95, 5.05 and 6.42% of the dose in male rat feces and 4.60, 7.76, 4.82 and 2.38% of the dose in female rat feces. M8 and M4 were the major metabolites in dog feces, and accounted for 11.73 and 19.88% of the dose in male dog feces and 8.86 and 17.01% of the dose in female dog feces. No unchanged ^{14}C -labeled talarozole was detected in mouse urine. Unchanged ^{14}C -labeled talarozole and M4 were observed as minor radio-components in rat urine, accounting for 0.07-1.90% of the dose. Two minor metabolites, M9 and M10, were identified in dog urine, accounting for 0.45-1.34% of the dose. In the human, talarozole was extensively metabolized. In addition to the unchanged talarozole, a total of seven metabolites were characterized or identified. M3 and M4 were identified as monohydroxylated talarozole. M14a and M14b were proposed

as dihydroxylated talarozole. M18 and M19 were characterized as the glucuronides of dihydroxylated talarozole. The protonated molecular ion was determined for M17, but no structure could be proposed based on the available data. The major metabolic routes for (^{14}C)-labeled talarozole in humans were oxidation at multiple sites, followed by glucuronidation. Based on $\text{AUC}_{0-24\text{h}}$, unchanged talarozole accounted for 6.03% of the total plasma radioactivity. Three major circulating metabolites, M4, M14a, and M18, accounted for 27.8%, 12.8% and 10.7% of the total plasma radioactivity, respectively. M19 accounted for 5.60% of the total plasma radioactivity. Unchanged talarozole, M4, M14a, M18, and M19 accounted for 62.9% of the total plasma radioactivity based on $\text{AUC}_{0-24\text{h}}$ values. Metabolite M4 was a major fecal metabolite, accounting for 16% of the dose in the human feces. Unchanged talarozole and all other fecal metabolites were minor, accounting for less than 5% of the dose. Unchanged talarozole was not found in the 0 to 48 hour human urine samples and all urine metabolites accounted for <1% of the dose. Unchanged talarozole and M4 were minor radioactive components in the semen samples and M14a was a major semen metabolite.

[0035] Metabolite Characterization and Identification

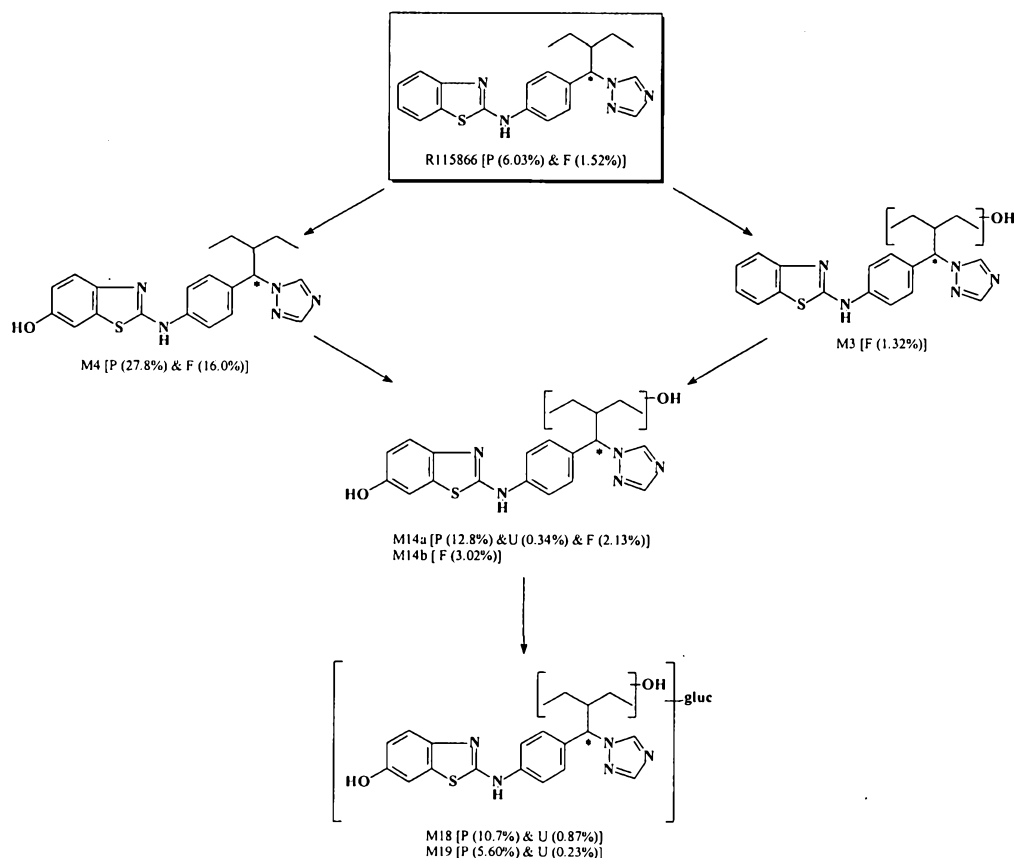
[0036] Table 3 lists the talarozole metabolites characterized and/or identified by LC/MS/MS. ^{14}C -labeled talarozole was observed to metabolize to M4 via oxidation of the benzthiazole ring, and to M3 and M13 via oxidation of the alkyl side chain. Dioxidation of both the benzthiazole ring and the alkyl side chain yielded M14 and M15. Conjugation of M4 with a glucuronyl or sulfate moiety resulted in M9 and M16, respectively. Conjugation of M14 and M15 with a sulfate moiety yielded M11 and M12, respectively. Another metabolite route found only in dogs yielded the addition of 162 atomic mass units (likely, a monosaccharide) to M4 or M9 to provide M8 and M10, respectively.

[0037] Exemplary metabolic pathways of talarozole are proposed in the schematic below.



* denotes position of ¹⁴C label

[0038] The proposed metabolic pathway of talarozole in humans is shown below:



R115866 = talarozole

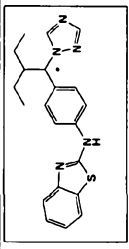
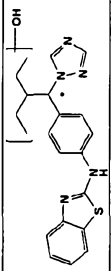
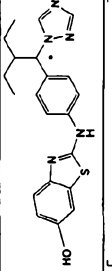
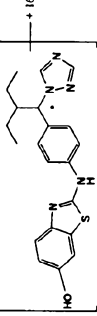
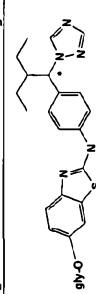
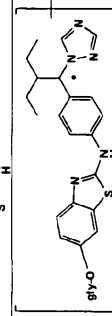
* denotes position of ¹⁴C label

P: plasma (%AUC_{0-24hr}); U: urine (%dose), and F: feces (%dose).

[0039] The above description is not intended to limit the claimed invention in any manner. Furthermore, the disclosed combination of features might not be absolutely necessary for the inventive solution. Disclosures of all publications, patents or published applications cited herein are incorporated by reference in their entirety.

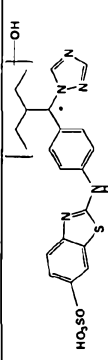
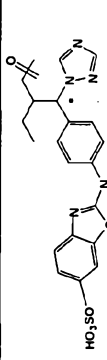
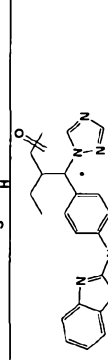
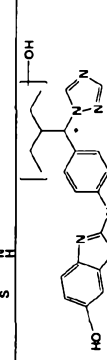
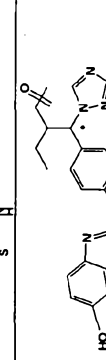
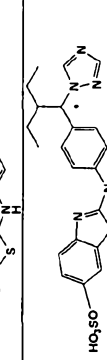
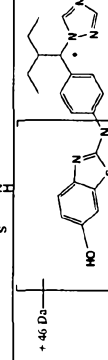
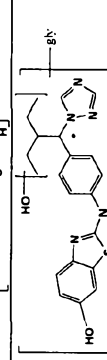

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Table 3 (continued): Talarozole Metabolism Comparison Across Species

Peak Range	Metabolite Code	Proposed Structure	MW	R _t (min)	Rat (5 mg/kg) ^c			Dog (5 mg/kg) ^d		
					Plasma AUC 0-24h (% Sample)	Urine % Dose	Feces % Dose	Plasma AUC 0-24 h ^e (% Sample)	Urine % Dose	Feces % Dose
		Total Radioactivity 14C-Talarozole (Total Collection)			7045.6 ng*hr/g M 8995.6 ng*hr/g F	6.33 M 10.07 F	77.53 M 77.57 F	17047 ng*hr/g M 18225 ng*hr/g F	4.13 M 2.89 F	88.66 M 89.00 F
		Unidentified Metabolites from Radiochromatograms			14 peaks 2505.2 ng*hr/g (35.56%) M 2649.7 ng*hr/g (29.45%) F	11 peaks 3.47 M 5.61 F	22 peaks 48.90 M 52.18 F	16 peaks 9781.7 ng*hr/g (57.39%) M 7739.4 ng*hr/g (42.47%) F	13 peaks 1.80 M 1.68 F	16 peaks 48.95 M 43.94 F
33	Talarozole		377	~74	778.38 ng*hr/g (11.05%) M 3523.2 ng*hr/g (39.17%) F	0.10 M 1.90 F	5.34 M 4.60 F	4132.9 ng*hr/g (24.24%) M 4228.0 ng*hr/g (23.20%) F	ND	1.22 M 1.59 F
28	M3		393	~60	429.53 ng*hr/g (6.10%) M 402.48 ng*hr/g (4.47%) F	ND	DN			
29	M4		393	~62	493.84 ng*hr/g (7.01%) M 331.07 ng*hr/g (3.68%) F	0.07 M 0.29 F	4.95 M 7.76 F	3132.4 ng*hr/g (18.37%) M 6257.6 ng*hr/g (34.33%) F	0.04 M 0.01 F	19.88 M 17.01 F
	M8	 + 162 amu	555	~44				ND	ND	11.73 M 8.86 F
	M9		569	~49	312.30 ng*hr/g (4.43%) M 1084.8 ng*hr/g (12.06%) F	ND	ND	ND	1.35 M 0.45 F	4.31 M 3.09 F
	M10	 + 162 amu	731	~33					0.84 M 0.64 F	ND

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Table 3 (continued): Talarozole Metabolism Comparison Across Species

Peak Range	Metabolite Code	Proposed Structure	MW	R _t (min)	Human (0.067 mg/kg) ^a			Mouse (5 mg/kg) ^b			
					Plasma 0-24h AUC (% Sample)	Urine % Dose	Feces % Dose	Semen	Plasma 0-24 h ^c AUC (% Sample)	Urine % Dose	Feces % Dose
	M11		489	~36							
	M12		487	~41							
	M13		391	~67					406.52 ng*hr/g (4.47%) M 360.47 ng*hr/g (5.45%) F	ND	ND
14	M14a		409	~42	27.10 ng*hr/g (12.83%)	0.34	2.14	X			
15	M14b		409	~44	ND	ND	3.02	X			
	M15		407	~55							
	M16		473	~55							
31	M17		439	~68	ND	ND	2.38	ND			
7	M18		585	~34	22.52 ng*hr/g (10.66%)	0.87	ND	ND			
9	M19		585	~36	11.83 ng*hr/g (5.60%)	0.23	ND	ND			

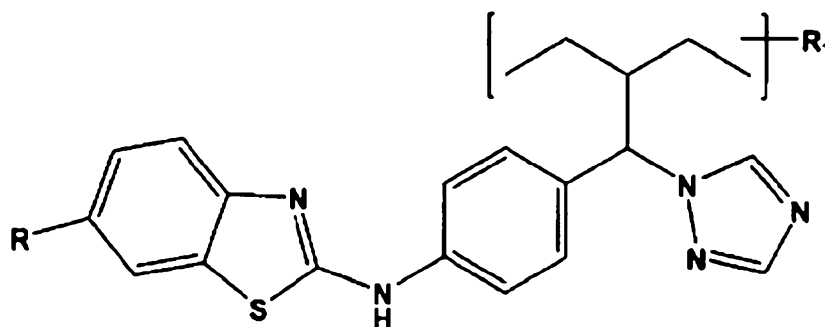
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Table 3 (continued): Talarozole Metabolism Comparison Across Species

Peak Range	Metabolite Code	Proposed Structure	MW	R _t (min)	Rat (5 mg/kg) ^c		Feces % Dose	Dog (5 mg/kg) ^d	
					Plasma 0-24h AUC (% Sample)	Urine % Dose		Plasma 0-24 h ^c AUC (% Sample)	Urine % Dose
	M11		489	~36	1177.6 ng*hr/g (16.71%) M 298.32 ng*hr/g (3.32%) F	ND	ND		
	M12		487	~41	583.62 ng*hr/g (8.28%) M 268.42 ng*hr/g (2.98%) F	ND	ND		
	M13		391	~67	557.70 ng*hr/g (7.92%) M 219.16 ng*hr/g (2.44%) F	ND	ND		
14	M14a		409	~42	ND	ND	5.05 M 4.82 F		
15	M14b		409	~44					
	M15		407	~55	ND	ND	6.42 M 2.38 F		
	M16		473	~55	207.48 ng*hr/g (2.94%) M 218.47 ng*hr/g (2.43%) F	0.16 M 0.31 F Rt not confirmed	1.42 M 1.33 F Rt not confirmed		
31	M17		439	~68					
7	M18		585	~34					
9	M19		585	~36					

We claim:

1. A compound of Formula I



Formula I

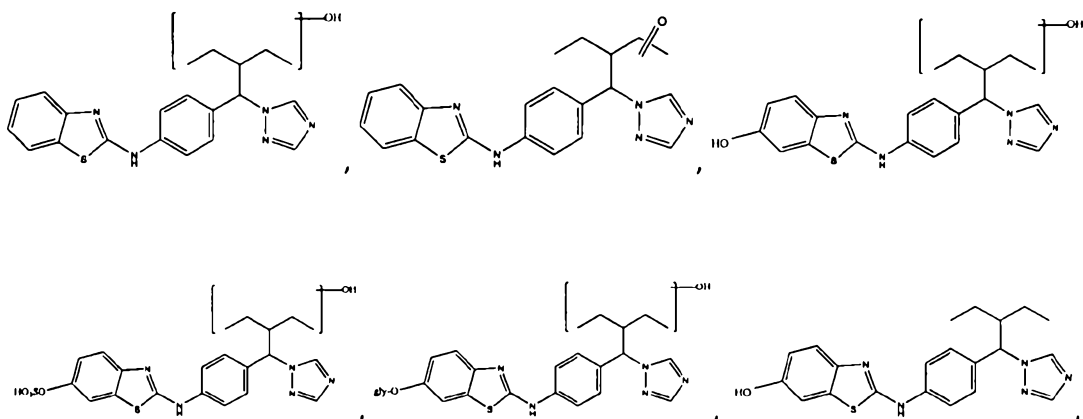
wherein

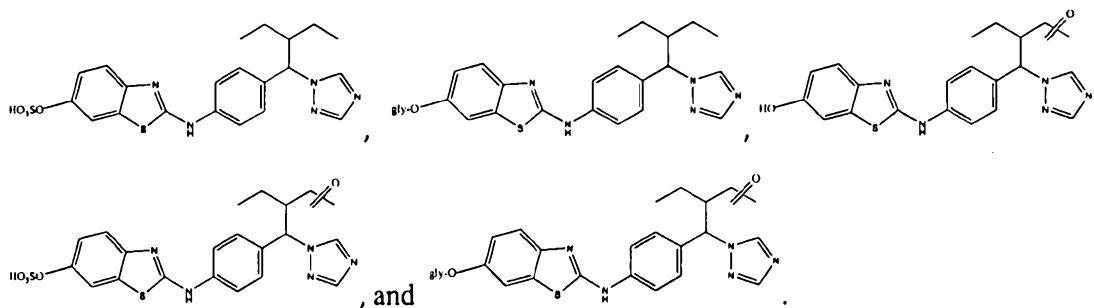
R is H, OH, OSO₃H or O-glucuronate;

R₁ is H, OH, OSO₃H, O-glucuronate or =O;

or a pharmaceutically acceptable salt thereof, with the proviso that when R is H, R₁ cannot also be H.

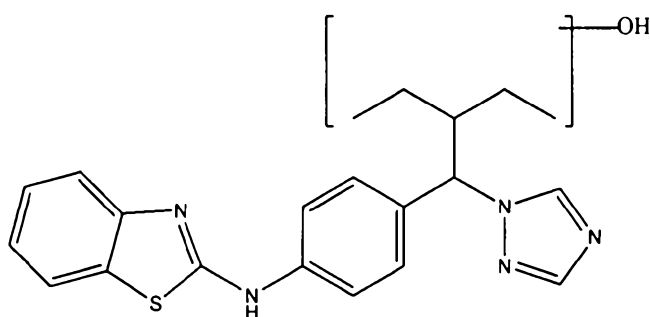
2. A compound according to claim 1, selected from the group consisting of





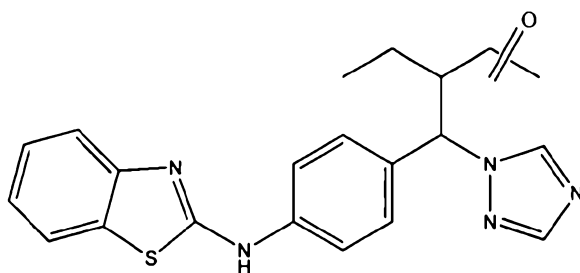
or a pharmaceutically acceptable salt thereof, wherein gly is glucuronate.

3. A compound according to claim 1 or 2 which is



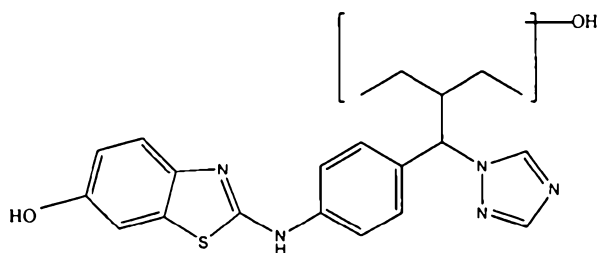
or a pharmaceutically acceptable salt thereof.

4. A compound according to claim 1 or 2 which is



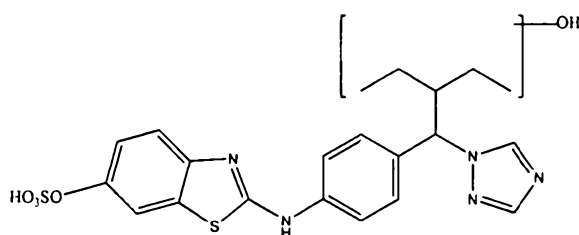
or a pharmaceutically acceptable salt thereof.

5. A compound according to claim 1 or 2 which is



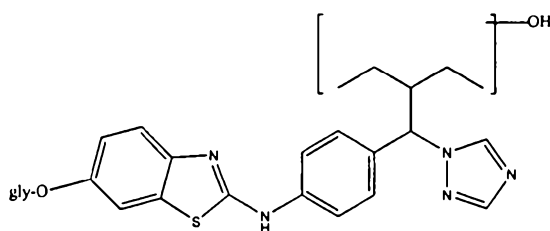
or a pharmaceutically acceptable salt thereof.

6. A compound according to claim 1 or 2 which is



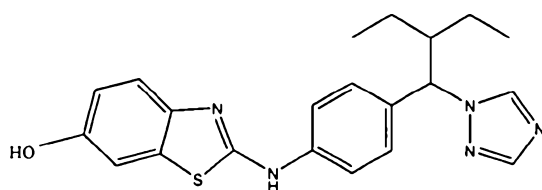
or a pharmaceutically acceptable salt thereof.

7. A compound according to claim 1 or 2 which is



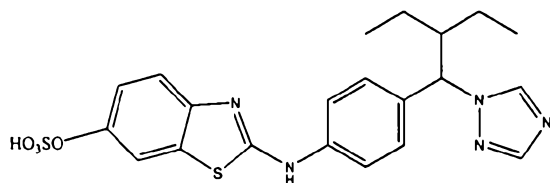
or a pharmaceutically acceptable salt thereof.

8. A compound according to claim 1 or 2 which is



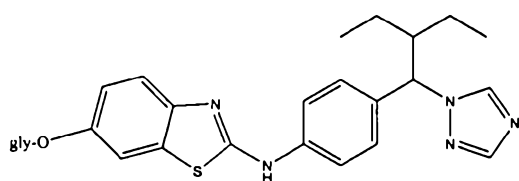
or a pharmaceutically acceptable salt thereof.

9. A compound according to claim 1 or 2 which is



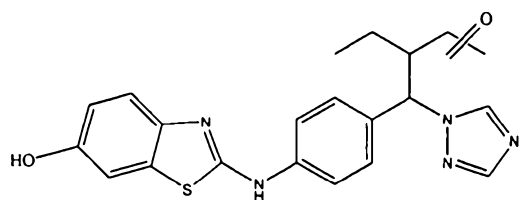
or a pharmaceutically acceptable salt thereof.

10. A compound according to claim 1 or 2 which is



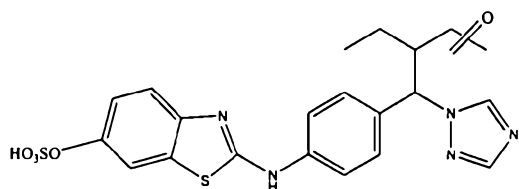
or a pharmaceutically acceptable salt thereof.

11. A compound according to claim 1 or 2 which is



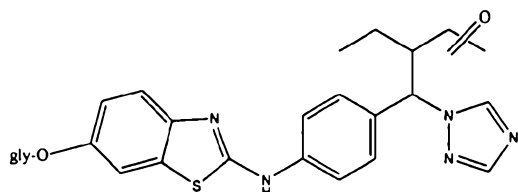
or a pharmaceutically acceptable salt thereof.

12. A compound according to claim 1 or 2 which is



or a pharmaceutically acceptable salt thereof.

13. A compound according to claim 1 or 2 which is



or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition comprising a compound according to any one of claims 1 to 13 and a pharmaceutically acceptable carrier.

15. A method of treating a keratinization-associated disorder, comprising administering to a mammal in need thereof an effective amount of a compound according to any one of claims 1 to 13.

16. The method according to claim 15, wherein the keratinization-associated disorder is a skin, hair or nail disorder.

17. The method according to claim 16, wherein the disorder is psoriasis, acne, actinic keratosis, eczema, rosacea, ichthyosis, alopecia or photodamaged skin.

18. A method of treating basal cell carcinoma or squamous cell carcinoma, comprising administering to a mammal in need thereof an effective amount of a compound according to any one of claims 1 to 13.

