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(54) Title: METHOD OF TREATING ANGIOGENESIS-RELATED DISORDERS USING BENZOYL PHENYLACETIC ACID

(57) Abstract: The use of 3-benzolphenylacetic acids and derivatives, including nepafenac, to treat angiogenesis-related disorders, including ophthalmic angiogenesis-related disorders such as diabetic retinopathy and exudative macular degeneration, is disclosed.

METHOD OF TREATING ANGIOGENESIS-RELATED DISORDERS

FIELD OF THE INVENTION

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This invention relates to the use of certain 3-benzoylphenylacetic acids and derivatives to treat or prevent angiogenic diseases.

BACKGROUND OF THE INVENTION

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3-benzoylphenylacetic acid and certain of its derivatives are known to possess anti-inflammatory activity. U.S. Patent Nos. 4,254,146, 4,045,576, 4,126,635, and 4,503,073, and U.K. Patent Application Nos. 2,071,086A and 2,093,027A disclose various 3-benzoylphenylacetic acids, salts and esters, and
15 hydrates thereof, having anti-inflammatory activity. U.S. Patent No. 4,568,695 discloses 2-amino-3-benzoylphenylethyl alcohols having anti-inflammatory activity. U.S. Patent No. 4,313,949 discloses 2-amino-3-benzoylphenylacetamides having anti-inflammatory activity.

20

Certain derivatives of 2-amino-3-benzoylbenzeneacetic acid (amfenac) and 2-amino-3-(4-chloro-benzoyl)benzeneacetic acid have also been evaluated by Walsh et al., J. Med Chem., 33:2296-2304 (1990), in an attempt to discover nonsteroidal anti-inflammatory prodrugs with minimal or no gastrointestinal side effects upon oral administration.

25

U.S. patent No. 4,683,242 teaches the transdermal administration of 2-amino-3-benzoylphenylacetic acids, salts, and esters, and hydrates and alcoholates thereof to control inflammation and alleviate pain.

30

U.S. Patent No. 4,910,225 teaches certain benzoylphenylacetic acids for local administration to control ophthalmic, nasal or otic inflammation. Only acetic acids are disclosed in the '225 patent; no esters or amides are

mentioned or taught as anti-inflammatory agents for local administration to the eyes, nose and ears.

U.S. Patent No. 5,475,034 discloses topically administerable compositions containing certain amide and ester derivatives of 3-benzoylphenylacetic acid, including nepafenac, useful for treating ophthalmic inflammatory disorders and ocular pain. According to the '035 patent at Col. 15, lines 35-39, "[s]uch disorders include, but are not limited to uveitis scleritis, episcleritis, keratitis, surgically-induced inflammation and endophthalmitis."

U.S. Patent No. 6,066,671 discloses the topical use of certain amide and ester derivatives of 3-benzoylphenylacetic acid, including nepafenac, for treating GLC1A glaucoma.

Throughout the description and claims of this specification, use of the word "comprise" and variations of the word, such as "comprising" and "comprises", is not intended to exclude other additives, components, integers or steps.

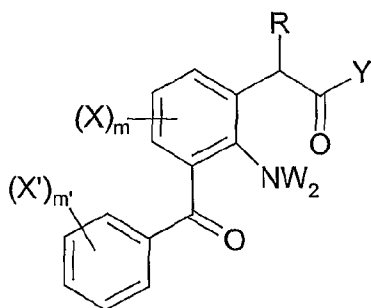
The discussion of documents, acts, materials, devices, articles and the like is included in this specification solely for the purpose of providing a context for the present invention. It is not suggested or represented that any or all of these matters formed part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed in Australia before the priority date of each claim of this application.

SUMMARY OF THE INVENTION

It has now been found that certain 3-benzoylphenylacetic acids and derivatives, including nepafenac (2-amino,3-benzoyl-phenylacetamide), are useful for the treatment of angiogenesis disorders.

DETAILED DESCRIPTION OF THE INVENTION

The 3-benzoylphenylacetic acids and derivatives useful in the methods of the present invention are those of formula (I) below.



(I)

R = H, C₁₋₄ (un)branched alkyl, CF₃, SR⁴;

5 Y = OR', NR''R';

R' = H, C₁₋₁₀ (un)branched alkyl, (un)substituted (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below),

-(CH₂)_nZ(CH₂)_nA;

n = 2-6;

10 n' = 1-6;

Z = nothing, O, C=O, OC(=O), C(=O)O, C(=O)NR³, NR³C(=O), S(O)_{n2}, CHOR³, NR³;

n² = 0-2;

15 R³ = H, C₁₋₆ (un)branched alkyl, (un)substituted aryl (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below);

A = H, OH, optionally (un)substituted aryl (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below), -(CH₂)_nOR³;

R'' = H, OH, OR';

X and X' independently = H, F, Cl, Br, I, OR', CN, OH, S(O)_{n2}R⁴, CF₃, R⁴, NO₂;

20 R⁴ = C₁₋₆ (un)branched alkyl;

m = 0-3;

m' = 0-5;

W = O, H.

25 As used herein, the acid (Y = OH) includes pharmaceutically acceptable salts as well.

Preferred compounds for use in the methods of the present invention are those of Formula I wherein:

- 5 R = H, C₁₋₂ alkyl;
 Y = NR'R";
 R' = H, C₁₋₆ (un)branched alkyl, $-(CH_2)_nZ(CH_2)_nA$;
 Z = nothing, O, CHOR³, NR³;
 R₃ = H;
 10 A = H, OH, (un)substituted aryl (substitution as defined by X below);
 X and X' independently = H, F, Cl, Br, CN, CF₃, OR', SR⁴, R⁴;
 R" = H;
 R⁴ = C₁₋₄ (un)branched alkyl;
 m = 0-2;
 15 m' = 0-2;
 W = H;
 n = 2-4;
 n' = 0-3.

20 The most preferred compounds for use in the compositions or method of the present invention are 2-Amino-3-(4-fluorobenzoyl)-phenylacetamide; 2-Amino-3-benzoyl-phenylacetamide (nepafenac); and 2-Amino-3-(4-chlorobenzoyl)-phenylacetamide.

25 According to the present invention, a therapeutically effective amount of a compound of formula (I) is administered topically, locally or systemically to treat or prevent angiogenesis-related disorders. Such disorders include those that involve the proliferation of tumor cells, such as prostate cancer, lung cancer, breast cancer, bladder cancer, renal cancer, colon cancer, gastric
 30 cancer, pancreatic cancer, ovarian cancer, melanoma, hepatoma, sarcoma and lymphoma. Ophthalmic angiogenesis-related disorders include, but are not limited to exudative macular degeneration; proliferative diabetic retinopathy; ischemic retinopathy (e.g., retinal vein or artery occlusion); retinopathy of

prematurity; neovascular glaucoma; iritis rubeosis; corneal neovascularization; cyclitis; sickle cell retinopathy; and pterygium. Certain disorders, such as sickle cell retinopathy and retinal vein or artery occlusion, can be characterized by both angiogenesis and neurodegenerative components. According to the
5 present invention, a compound of formula (I) is administered to treat or prevent disorders characterized, at least in part, by angiogenesis.

The compounds of formula (I) can be administered in a variety of ways, including all forms of local delivery to the eye, such as subconjunctival
10 injections or implants, intravitreal injections or implants, sub-Tenon's injections or implants, incorporation in surgical irrigating solutions, etc. Additionally, the compounds of formula (I) can be administered systemically, such as orally or intravenously. Suitable pharmaceutical vehicles or dosage forms for injectable compositions, implants, and systemic administration are known. The
15 compounds of formula (I) and especially those wherein $Y = NR'R''$, however, are preferably administered topically to the eye and can be formulated into a variety of topically administrable ophthalmic compositions, such as solutions, suspensions, gels or ointment.

20 Pharmaceutical compositions comprising a compound of formula (I) in aqueous solution or suspension, optionally containing a preservative for multidose use and other conventionally employed ophthalmic adjuvants, can be topically administered to the eye. The most preferred form of delivery is by aqueous eye drops, but gels or ointments can also be used. Aqueous eye
25 drops, gels and ointments can be formulated according to conventional technology and would include one or more excipients. For example, topically administrable compositions may contain tonicity-adjusting agents, such as mannitol or sodium chloride; preservatives such as chlorobutanol, benzalkonium chloride, polyquaternium-1, or chlorhexidine; buffering agents,
30 such as phosphates, borates, carbonates and citrates; and thickening agents, such as high molecular weight carboxy vinyl polymers, including those known as carbomers, hydroxyethylcellulose, or polyvinyl alcohol.

The doses of the compounds of formula (I) used in the treatment or prevention of ophthalmic angiogenesis-related disorders will depend on the type of disorder to be prevented or treated, the age and body weight of the patient, and the form of preparation/route of administration. Compositions intended for topical ophthalmic administration will typically contain a compound of formula (I) in an amount of from about 0.001 to about 4.0% (w/v), preferably from about 0.01 to about 0.5% (w/v), with 1-2 drops once to several times a day. Likewise, representative doses for other forms of preparations are approximately 1 – 100 mg/day/adult for injections and approximately 10 – 1000 mg/adult for oral preparations, each administered once to several times a day.

Additional therapeutic agents may be added to supplement the compounds of formula (I).

The following examples are presented to illustrate various aspects of the present invention, but are not intended to limit the scope of the invention in any respect. The percentages are expressed on a weight/volume basis.

Example 1: The following formulations are representative of the topical compositions useful in the present invention.

Formulation 1

Compound of formula (I)	0.01 – 0.5%
Polysorbate 80	0.01%
Benzalkonium Chloride	0.01% + 10% excess
Disodium EDTA	0.1%
Monobasic Sodium Phosphate	0.03%
Dibasic Sodium Phosphate	0.1%
Sodium Chloride	q.s. 290-300 mOsm/Kg
pH adjustment with NaOH and/or HCl	pH 4.2 – 7.4
Water	q.s. 100%

Formulation 2

	Compound of formula (I)	0.01 – 0.5%
	Hydroxypropyl Methylcellulose	0.5%
5	Polysorbate 80	0.01%
	Benzalkonium Chloride	0.01% + 5% excess
	Disodium EDTA	0.01%
	Dibasic Sodium Phosphate	0.2%
	Sodium Chloride	q.s. 290-300 mOsm/Kg
10	pH adjustment with NaOH and/or HCl	pH 4.2 – 7.4
	Water	q.s. 100%

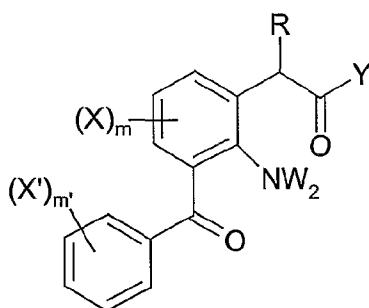
Formulation 3

15	Nepafenac	0.1 + 6% excess
	Carbopol 974P	0.08%
	Tyloxapol	0.01%
	Glycerin	2.4%
	Disodium EDTA	0.01%
20	Benzalkonium Chloride	0.01%
	pH adjustment with NaOH and/or HCl	pH 7.5 ± 0.2
	Water	q.s. 100%

25 This invention has been described by reference to certain preferred
embodiments; however, it should be understood that it may be embodied in
other specific forms or variations thereof without departing from its special or
essential characteristics. The embodiments described above are therefore
considered to be illustrative in all respects and not restrictive, the scope of the
30 invention being indicated by the appended claims rather than by the foregoing
description.

We Claim:

1. A method of treating or preventing an angiogenesis-related disorder in a patient suffering from or predisposed to such a disorder which comprises
 5 administering to the patient a therapeutically effective amount of 3-benzoylphenylacetic acid or derivative of the formula:



wherein

- 10 R = H, C₁₋₄ (un)branched alkyl, CF₃, SR⁴;
 Y = OR', NR''R';
 R' = H, C₁₋₁₀ (un)branched alkyl, (un)substituted (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below),
 -(CH₂)_nZ(CH₂)_{n'}A;
 15 n = 2-6;
 n' = 1-6;
 Z = nothing, O, C=O, OC(=O), C(=O)O, C(=O)NR³, NR³C(=O), S(O)_{n2},
 CHOR³, NR³;
 n² = 0-2;
 20 R³ = H, C₁₋₆ (un)branched alkyl, (un)substituted aryl (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below);
 A = H, OH, optionally (un)substituted aryl (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below), -(CH₂)_nOR³;
 R'' = H, OH, OR';
 25 X and X' independently = H, F, Cl, Br, I, OR', CN, OH, S(O)_{n2}R⁴, CF₃, R⁴,
 NO₂;

$R^4 = C_{1-6}$ (un)branched alkyl;

$m = 0-3$;

$m' = 0-5$; and

$W = O, H$.

2. The method of Claim 1 wherein

$R = H, C_{1-2}$ alkyl;

$Y = NR'R''$;

$R' = H, C_{1-6}$ (un)branched alkyl, $-(CH_2)_nZ(CH_2)_{n'}A$;

$Z = \text{nothing}, O, CHOR^3, NR^3$;

$R_3 = H$;

$A = H, OH, (\text{un})\text{substituted aryl}$ (substitution as defined by X below);

X and X' independently = H, F, Cl, Br, CN, CF_3 , OR' , SR^4 , R^4 ;

$R'' = H$;

$R^4 = C_{1-4}$ (un)branched alkyl;

$m = 0-2$;

$m' = 0-2$;

$W = H$;

$n = 2-4$; and

$n' = 0-3$.

3. The method of Claim 1 or 2 wherein the 3-benzoylphenylacetic acid or derivative is selected from the group consisting of 2-Amino-3-(4-fluorobenzoyl)-phenylacetamide; 2-Amino-3-benzoyl-phenylacetamide; and 2-Amino-3-(4-chlorobenzoyl)-phenylacetamide.

4. The method of any one of Claims 1 to 3 wherein the angiogenesis-related disorder is an ophthalmic angiogenesis-related disorder.

5. The method of any one of Claims 1 to 4 wherein the 3-benzoylphenylacetic acid or derivative is topically administered to the eye.

6. The method of any one of Claims 1 to 5 wherein the therapeutically effective amount of 3-benzoylphenylacetic acid or derivative is from about 0.001 to about 4.0% (w/v).
7. The method of any one of Claims 1 to 4 wherein the angiogenesis-related disorder is selected from the group consisting of exudative macular degeneration; proliferative diabetic retinopathy; ischemic retinopathy; retinopathy of prematurity; neovascular glaucoma; iritis rubeosis; corneal neovascularization; cyclitis; sickle cell retinopathy; and pterygium.
8. The method of any one of Claims 1 to 7 wherein the 3-benzoylphenylacetic acid or derivative is administered orally, intravenously, in a subconjunctival injection or implant, in a sub-Tenon's injection or implant, in an intravitreal injection or implant, or in a surgical irrigating solution.
9. The method of any one of Claims 1 to 3 or 8 wherein the angiogenesis-related disorder is selected from the group consisting of prostate cancer; lung cancer; breast cancer; bladder cancer; renal cancer; colon cancer; gastric cancer; pancreatic cancer; ovarian cancer; melanoma; hepatoma; sarcoma; and lymphoma.
10. A method according to claim 1 substantially as hereinbefore described, with reference to the Example.

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