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(54) Title: METHOD OF TREATING ANGIOGENESIS-RELATED DISORDERS

(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

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

BACKGROUND OF THE INVENTION

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 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-benzoyl-phenylacetamides having anti-inflammatory activity.

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.

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.

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 administrable compositions containing certain amide and ester derivatives of 3-benzyolphenylacetic 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."

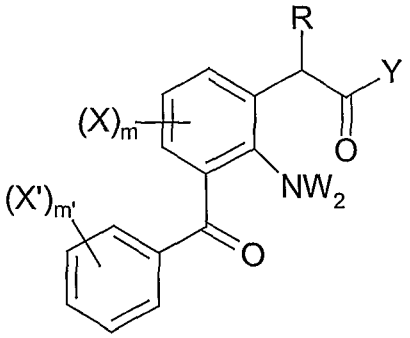
U.S. Patent No. 6,066,671 discloses the topical use of certain amide and ester derivatives of 3-benzoylphenylacetic acid, including nepafenac, for treating GLC1A glaucoma.

SUMMARY OF THE INVENTION

It has now been found that certain 3-benzoylphenlacetic acids and derivatives, including nepafenac (2-amino,3-benzoyl-phenylacetamide), are useful for the treatment of angiogenesis-related 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, C_{1-4} (un)branched alkyl, CF_3, SR^4;

Y = OR', NR"R';

R' = H, C_{1-10} (un)branched alkyl, (un)substituted (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below), $-(CH_2)_nZ(CH_2)_{n'}A$;

n = 2-6;

n'= 1-6;

Z = nothing, O, C=O, OC(=O), C(=O)O, $C(=O)NR^3$, $NR^3C(=O)$, $S(O)_{n2}$, $CHOR^3$, NR^3;

n^2 = 0-2;

R^3 = H, C_{1-6} (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), $—(CH_2)_nOR^3$;

R" = H, OH, OR';

X and X' independently = H, F, Cl, Br, I, OR', CN, OH, $S(O)_{n2}R^4$, CF_3, R^4, NO_2;

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

m = 0-3;

m' = 0-5;

W = O, H.

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:

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

Y = NR'R";

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

Z = nothing, O, $CHOR^3$, NR^3;

R_3 = H;

A = H, OH, (un)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;

n' = 0-3.

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.

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 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

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