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(54) Title: METHOD OF TREATING NEURODEGENERATIVE DISORDERS OF THE RETINA AND OPTIC NERVE HEAD

(57) Abstract: The use of 3-benzolphenylacetic acids and derivatives, including nepafenac, to treat neurodegenerative retinal disorders is disclosed.

METHOD OF TREATING NEURODEGENERATIVE DISORDERS OF THE
RETINA AND OPTIC NERVE HEAD

5 FIELD OF THE INVENTION

This invention relates to the treatment of retinopathy. In particular, this invention relates to the use of certain 3-benzoylphenylacetic acids and derivatives to treat or prevent neurodegenerative disorders of the retina and
10 optic nerve head.

BACKGROUND OF THE INVENTION

3-benzoylphenylacetic acid and certain of its derivatives are known to
15 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
20 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
25 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-
30 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
5 eyes, nose and ears.

U.S. Patent No. 5,475,034 discloses topically administrable compositions containing certain amide and ester derivatives of 3-benzoylphenylacetic acid, including nepafenac, useful for treating ophthalmic
10 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."

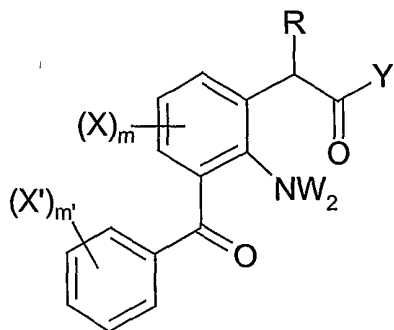
U.S. Patent No. 6,066,671 discloses the topical use of certain amide and
15 ester derivatives of 3-benzoylphenylacetic acid, including nepafenac, for treating GLC1A glaucoma.

SUMMARY OF THE INVENTION

20 It has now been found that certain 3-benzoylphenylacetic acids and derivatives, including nepafenac (2-amino,3-benzoyl-phenylacetamide), are useful in treating neurodegenerative disorders of the retina and optic nerve head.

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.



5

(I)

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)_nA;

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;

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;

R⁴ = C₁₋₆ (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.

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

R = H, C₁₋₂ alkyl;

Y = NR'R'';

10 R' = H, C₁₋₆ (un)branched alkyl, $-(CH_2)_nZ(CH_2)_{n'}A$;

Z = nothing, O, CHOR³, NR³;

R₃ = H;

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;

15 R'' = H;

R⁴ = C₁₋₄ (un)branched alkyl;

m = 0-2;

m' = 0-2;

W = H;

20 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-
25 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
30 treat or prevent neurodegenerative disorders of the retina and optic nerve head.

Such disorders include, but are not limited to atrophic macular degeneration; retinitis pigmentosa; iatrogenic retinopathy; retinal tears and holes; diabetic retinopathy; sickle cell retinopathy; retinal vein and artery occlusion; and optic

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