

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
21 February 2002 (21.02.2002)

PCT

(10) International Publication Number
WO 02/13805 A2

(51) International Patent Classification⁷: **A61K 31/00**

Road 809, Cleburne, TX 76031 (US). **YANNI, John, M.** [US/US]; 2821 Donnybrook Drive, Burseson, TX 76028 (US). **KAPIN, Michael, A.** [US/US]; 3602 Silkwood Trail, Arlington, TX 76016 (US).

(21) International Application Number: PCT/US01/25319

(22) International Filing Date: 13 August 2001 (13.08.2001)

(74) Agents: **RYAN, Patrick, M.** et al.; R & D Counsel Q-148, 6201 South Freeway, Fort Worth, TX 76134-2099 (US).

(25) Filing Language: English

(26) Publication Language: English

(81) Designated States (*national*): AU, BR, CA, CN, JP, KR, MX, PL, US, ZA.

(30) Priority Data:
60/225,132 14 August 2000 (14.08.2000) US

(84) Designated States (*regional*): European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).

(71) Applicant (*for all designated States except US*): **ALCON UNIVERSAL LTD.** [CH/CH]; Bosch 69, P.O. Box 62, CH-6331 Hunenberg (CH).

Published:
— *without international search report and to be republished upon receipt of that report*

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **GAMACHE, Daniel, A.** [US/US]; 5610 Hunterwood Lane, Arlington, TX 76017 (US). **GRAFF, Gustav** [US/US]; 6500 County

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 02/13805 A2

(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-benzoylphenylacetamides 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."

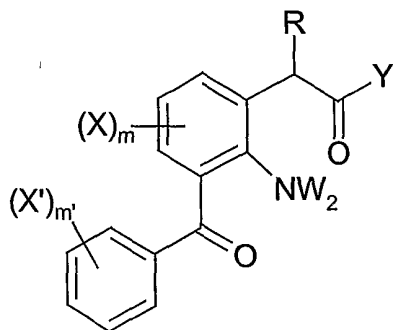
U.S. Patent No. 6,066,671 discloses the topical use of certain amide and
15 ester derivatives of 3-benzoylphenylacetic acid, including nepafenac, for treating GLC1A glaucoma.

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

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.