US005475034A

United States Patent [19]

Yanni et al.

[11] **Patent Number: 5,475,034**

[45] **Date of Patent: Dec. 12, 1995**

[54] **TOPICALLY ADMINISTRABLE COMPOSITIONS CONTAINING 3-BENZOYLPHENYLACETIC ACID DERIVATIVES FOR TREATMENT OF OPHTHALMIC INFLAMMATORY DISORDERS**

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[73] Assignee: **Alcon Laboratories, Inc.**, Fort Worth, Tex.

[21] Appl. No.: **254,090**

[22] Filed: **Jun. 6, 1994**

[51] **Int. Cl.**[6] **A61K 31/165**

[52] **U.S. Cl.** **514/619**; 514/535; 514/570; 514/617; 514/618; 514/621

[58] **Field of Search** 564/169; 514/621, 514/619, 617, 618

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,828,093	8/1974	Bays et al.	260/469
4,045,576	8/1977	Welstead, Jr. et al.	424/309
4,126,635	11/1978	Welstead, Jr. et al.	562/441
4,182,774	1/1980	Welstead, Jr. et al.	424/309
4,254,146	3/1981	Walsh	424/309
4,318,949	2/1982	Shanklin, Jr. et al.	424/248.56
4,503,073	3/1985	Walsh et al.	514/539
4,568,695	2/1986	Moran et al.	514/648
4,683,242	7/1987	Poser	514/539
4,783,487	11/1988	Brune	514/563
4,851,443	7/1989	Brune	514/563
4,910,225	3/1990	Ogawa et al.	514/561

FOREIGN PATENT DOCUMENTS

2071086	9/1981	United Kingdom .
2093027	8/1982	United Kingdom .

OTHER PUBLICATIONS

Sancillo et al., "AHR–10037, a non–steroidal anti–inflammatory compound of low gastric toxicity," *Agents and Actions,* 31:117–126 (1990).

Walsh et al., "Antiinflammatory Agents. 3. Synthesis and Pharmacological Evaluation of 2–Amino–3–benzoylphenylacetic Acid and Analogues," *J. Med. Chem.* 27:1379–1388 (1984).

Walsh et al., "Antiinflammatory Agents. 4. Synthesis and Biological Evaluation of Potential Prodrugs of 2–Amino–3–benzoylbenzeneacetic Acid and 2–Amino–3–(4–chlorobenzoyl)benzeneacetic Acid," *J. Med. Chem.* 33:2296–2304 (1990).

Primary Examiner—Shailendra Kumar
Attorney, Agent, or Firm—Patrick M. Ryan

[57] **ABSTRACT**

Novel ester and amide derivatives of 3-benzoylphenylacetic acid are disclosed. The use of these novel derivatives and certain known derivatives in topically administrable compositions for the treatment of ophthalmic inflammatory disorders is also disclosed.

7 Claims, No Drawings

TOPICALLY ADMINISTRABLE COMPOSITIONS CONTAINING 3-BENZOYLPHENYLACETIC ACID DERIVATIVES FOR TREATMENT OF OPHTHALMIC INFLAMMATORY DISORDERS

FIELD OF THE INVENTION

This invention relates to topically administrable compositions for the treatment of inflammatory disorders. In particular, this invention relates to non-irritating, topically administrable compositions containing 3-benzoylphenylacetic acid derivatives for the treatment of ophthalmic inflammatory disorders.

BACKGROUND OF THE INVENTION

3-benzoylphenylacetic acid and certain of its derivatives are known to possess anti-inflammatory activity. U.S. Pat. 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 teach various 3-benzoylphenylacetic acids, salts and esters, and hydrates thereof, having anti-inflammatory activity. U.S. Pat. No. 4,568,695 teaches 2-amino-3-benzoylphenylethyl alcohols having anti-inflammatory activity. U.S. Pat. No. 4,313,949 teaches 2-amino-3-benzoyl-phenylacetamides having anti-inflammatory activity.

Each of the above-listed patents or patent applications, all of which are assigned in whole or in part to A. H. Robins, contains an identical disclosure regarding formulations of the 3-benzoylphenylacetic acid or acid derivative. Each of the above also contains the same disclosure regarding administration routes for the drug formulation. The only formulation examples in the A. H. Robins patents or patent applications are capsules, tablets and "injectable-2% sterile solutions," and the only administration routes mentioned are oral (as in capsules or tablets) parenteral (in the form of sterile solutions or suspensions), and, in some cases intravenous (in the form of sterile solutions). No topical or local administration is taught by any of the above-listed patents or patent applications.

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.

In contrast, U.S. Pat. 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. Pat. 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.

Although benzoylphenylacetic acids are effective in suppressing ocular inflammation, their full anti-inflammatory potential has not yet been approached due to their generally slow rate of penetration through the cornea. Relatively high concentrations of these drugs are often needed to achieve corneal penetration rates sufficient to provide effective intraocular drug concentrations. Such high drug concentrations are generally not desirable as they may provoke ocular

irritation and discomfort.

Additionally, the acetic acid compounds taught in the '225 patent are difficult to formulate in stable aqueous solutions. The '225 patent solves this problem by incorporating a water-soluble polymer and sulfite, and adjusting the pH to about 6.0 to 9.0, preferably about 7.5–8.5. Water soluble polymers taught by the '225 patent include polyvinyl pyrrolidone, carboxypropylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, polyvinyl alcohol, sodium salt of polyacrylic acid and so on. Polyvinyl pyrrolidone is preferred. The concentration of water soluble polymer is in the range of 0.1 to 10 w/w %. Sulfite includes sodium, potassium, magnesium, and calcium sulfite salt and so on. The concentration is in the range of about 0.1 to 1.0 w/w %.

What is needed are additional non-steroidal, topically administrable anti-inflammatory agents which are stable, non-irritating at therapeutic doses, and at least as potent as benzoylphenylacetic acids in suppressing ocular inflammation.

SUMMARY OF THE INVENTION

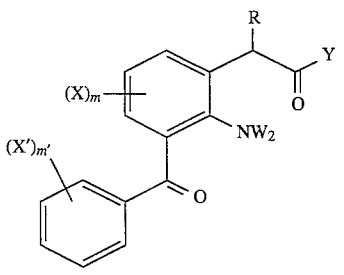
It has now been found that certain novel and certain known 3-benzoylphenylacetic acid derivatives are useful as topically administrable anti-inflammatory compounds for treating ophthalmic inflammatory disorders. Converting the free acetic acid functional group to an ester or an amide enhances compound stability by slowing the rate of lactam formation. Among other factors, the present invention is based on the finding that certain 3-benzoylphenylacetic acid derivatives which show no significant anti-inflammatory activity in vitro are, in fact, as active or even more active than the parent 3-benzoylphenylacetic acids when administered topically to the eye.

Accordingly, the present invention is directed to novel derivatives of 3-benzoylphenylacetic acid compounds. The present invention is also directed to pharmaceutical compositions suitable for topical ophthalmic administration which contain an anti-inflammatory-effective amount of a 3-benzoylphenylacetic acid derivative, and to a method of treating ophthalmic inflammatory disorders which comprises topically administering to the eye a 3-benzoylphenylacetic acid derivative.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, "(un)branched" means optionally branched, and "(un)substituted" means optionally substituted.

The novel 3-benzoylphenylacetic acid derivative compounds of the present invention have the following structural formula:



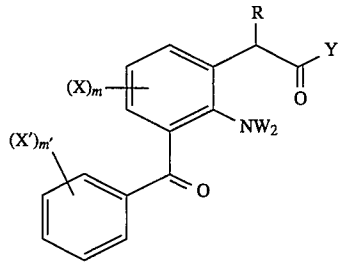
(I)

W=O,H

Y=OR^5, NR^5R^6
R^5=—$(CH_2)_r$—Z^2—$(CH_2)_r$A, —$(CH_2)_r$—Z^3—$(CH_2)_r$ A'
r=2–6
r'=0–6
Z^2O, C=O, OC(=O), C(=O)NR^3, NR^3C(=O), —$S(O)_{r2}CH_2$—, S, $CHOR^3$, NR^3
Z^3=nothing,—CHR^4—, —CR^4R^4—
r^2=1,2
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, (un)substituted aryl (substitution as defined by X below), (un)substituted heterocycle, —$(CH_2)_r$$OR^3$
A'=OH, (un)substituted aryl (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below), —$(CH_2)_r$$OR^3$
R^4=C_{1-6}(un)branched alkyl
R^6=H, OR^7
R^7=H, C_{1-6}(un)branched alkyl, (un)substituted aryl (substitution as defined by X below)
X and X' independently=H, F, Cl, Br, I, OR^7, CN, OH, $S(O)_{n2}R^4$, CF_3, R^4, NO_2
m=0–3
m=0–5
n^2=0–2

The preferred, novel 3-benzoylphenylacetic acid derivatives are those wherein:
W=H
R=H, CH_3
Y=NR^5R^6, —NHOH
R^4=C_{1-4}(un)branched alkyl
R^5=—$(CH_2)_r$—Z^2—$(CH_2)_r$—A, —$(CH_2)_r$—Z^3—$(CH_2)_r$—A'
r=2–4
r'=0–2
Z^2=O
Z^3=nothing
A=H
A'=(un)substituted aryl (substitution as defined by X below)
R^6=H, OR^7
R^7=H, C_{1-2} alkyl
X and X' independently=H, F, Cl, Br, CF_3, $S(O)_{n2}R^4$, OR^7
m=0–2
m'=0–3
n^2=0

The 3-benzoylphenylacetic acid derivative compounds useful in the topically administrable ophthalmic compositions of the present invention are represented by the following structural formula which includes both known derivatives and the novel derivatives of the present invention:



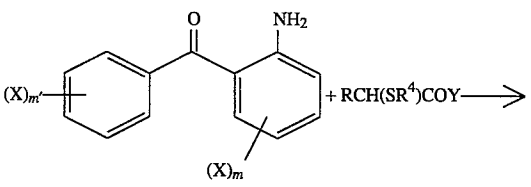
(I)

R=H, C_{1-4} (un)branched alkyl, CF_3, SR^4
Y=OR', NR"R'
R'=H (except when Y=OR'), 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)_n$$Z(CH_2)_{n'}$A
n=2–6
n'=1–6
Z=nothing, O, C=O, OC(=O), C(=O)O, C(=O)NR^3, NR^3C(=O), $S(O)_{n2}$, $CHOR^3$, NR^3
n^2=0–2
R^3=H, C_{1-6} (un)branched alkyl, (un)substituted aryl (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below)
A=H, OH, optionally (un)substituted aryl (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below), —$(CH_2)_n$$OR^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

Preferred compounds for use in the pharmaceutical compositions or method 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; and 2-Amino-3-(4-chlorobenzoyl)-phenylacetamide.

The preparation of the compounds of Formula I, Formula VII and Formula IX may be accomplished by the reactions outlined in the following scheme:



II III

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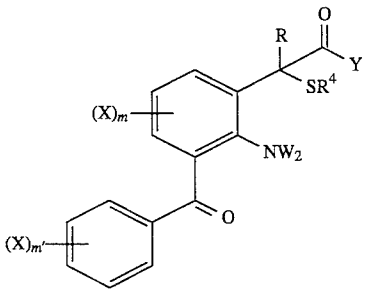
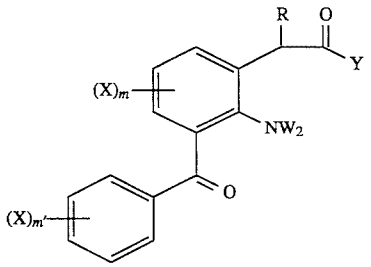
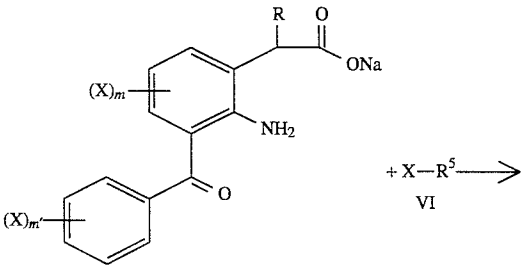


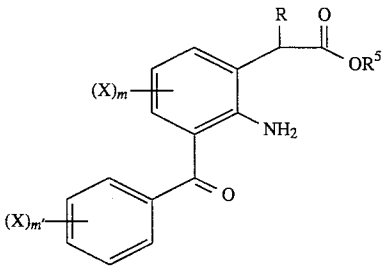
IV



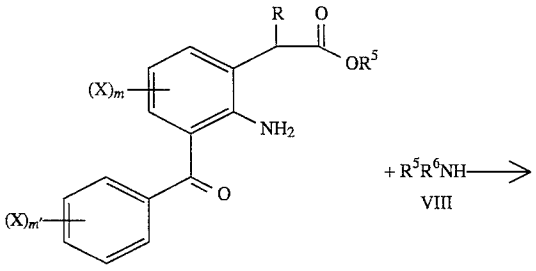
I



V



VII



VII

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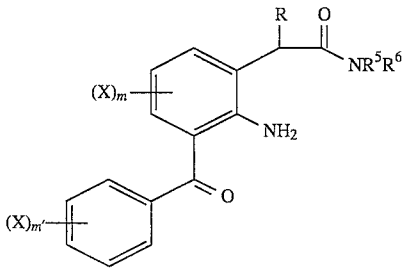
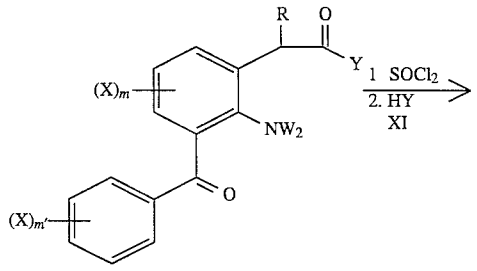


IX

wherein X, Y, R, R^4, R^5, R^6, m, m', and W are as defined above. The general method for the preparation for compounds of Formula I and Formula IV where Y is such that the compound is an amide derivative and W is hydrogen are detailed in U.S. Pat. No. 4,313,949 assigned to A. H. Robins. The general method for preparing compounds of Formula V and detailing the conversion of compounds of Formula V into compounds of the Formula VII are described in U.S. Pat. Nos. 4,045,576, 4,503,073, 4,182,774, and 4,126,635 all assigned to A. H. Robins, and by the methods of Walsh et al., (J. Medicinal Chemistry, volume 27, 1984, pages 1379–88 and J. Medicinal Chemistry, volume 33, 100, pages 2296–2304). Compounds of Formula VI where X' is a suitable leaving group such as Cl, Br, I, or organic sulfonate (mesylate, tosylate) and R^5 is as described above, may be prepared by one skilled in the art. Amides of Formula IX may be formed by reacting esters of Formula VII (preferably ethyl or methyl esters) with the appropriate amine of Formula VIII either neat or in the presence of a solvent such as dimethyl formamide, dimethyl sulfoxide or acetonitrile at temperatures between 0° and 150° C. Amines of Formula VIII, may be prepared by one skilled in the art.

The synthesis of compounds of Formula I and the carboxylic acid of Formula X where W is oxygen is detailed in U.S. Pat. No. 4,254,146 assigned to A. H. Robins and is outlined below. The required amine or alcohol (Formula XI) is commercially available or can be readily prepared by one skilled in the art.



X

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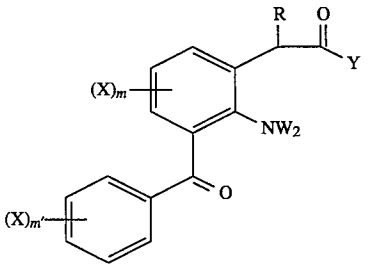
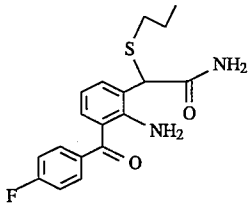


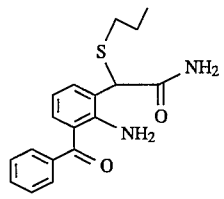
I

The manipulation of suitable protecting groups and deprotecting steps as employed by one skilled in the art may be necessary for the preparation of compounds of Formula I, Formula IV, Formula VIII, Formula IX and required intermediates.

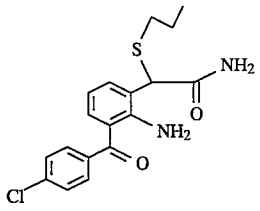
The invention will be further illustrated by the following examples which are intended to be illustrative, but not limiting.



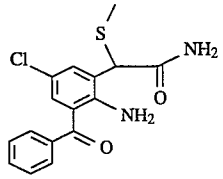
Compound 1
2-Amino-3-(4-fluorobenzoyl)-α-(n-propylthio)-phenylacetamide



Compound 2
2-Amino-3-benzoyl-α-(n-propylthio)-phenylacetamide



Compound 3
2-Amino-3-(4-chlorobenzoyl)-α-(n-propylthio)-phenylacetamide



Compound 4
2-Amino-3-benzoyl-5-chloro-α-(methylthio)-phenylacetamide

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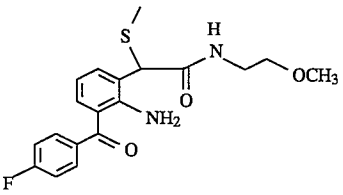
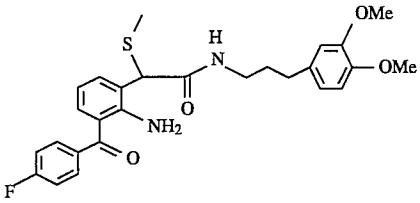
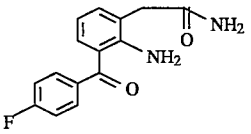


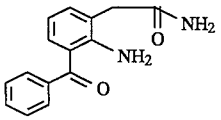
Compound 5
2-Amino-3-(4-fluorobenzoyl)-α-(methylthio)-N-(2-methoxy)ethyl acetamide



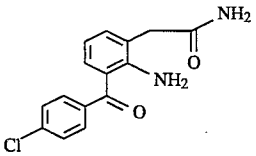
Compound 6
2-Amino-3-(4-fluorobenzoyl)-α-(methylthio)-N-3-(3,4-dimethoxyphenyl)propyl phenylacetamide



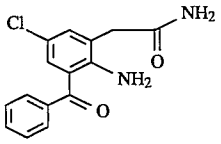
Compound 7
2-Amino-3-(4-fluorobenzoyl)-phenylacetamide



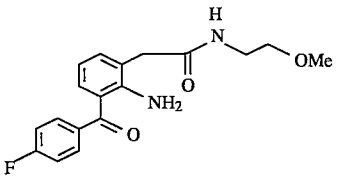
Compound 8
2-Amino-3-benzoyl-phenylacetamide



Compound 9
2-Amino-3-(4-chlorobenzoyl)-phenylacetamide



Compound 10
2-Amino-3-benzoyl-5-chlorophenylacetamide



Compound 11
2-Amino-3-(4-fluorobenzoyl)-N-(2-methoxy)ethyl phenylacetamide

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