

Topically Administrable Compositions Containing
3-Benzoylphenylacetic Acid Derivatives for Treatment
of Ophthalmic Inflammatory Disorders

Field of the Invention

5 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

10 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 teach various 3-benzoylphenylacetic acids, salts and esters, and hydrates thereof, having anti-inflammatory activity. U.S. Patent No. 4,568,695 teaches 2-amino-3-benzoylphenylethyl alcohols having
15 anti-inflammatory activity. U.S. Patent No. 4,313,949 teaches 2-amino-3-benzoylphenylacetamides 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
20 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
25 administration is taught by any of the above-listed patents or patent applications.

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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. 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.

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

5 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
10 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.

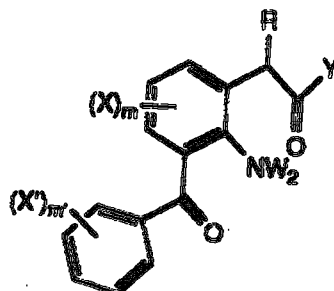
Accordingly, the present invention is directed to novel derivatives of 3-benzoylphenylacetic acid compounds. The present invention is also directed to
15 pharmaceutical compositions suitable for topical ophthalmic administration which contain an anti-inflammatory-effective amount of a 3-benzoylphenylacetic 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

20 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:





W = O, H

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

Y = OR⁵, NR⁵R⁶

5 R⁵ = -(CH₂)_r-Z²-(CH₂)_{r'}-A, -(CH₂)_r-Z²-(CH₂)_{r'}-A'

r = 2-6

r' = 0-6

Z² = O, C=O, OC(=O), C(=O)NR³, NR³C(=O), -S(O)₂CH₂-, S, CHOR³, NR³

Z² = nothing, -CHR⁴-, -CR⁴R⁴-

10 r² = 1, 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, (un)substituted aryl (substitution as defined by X below), (un)substituted
heterocycle, -(CH₂)₃OR³

15 A' = OH, (un)substituted aryl (substitution as defined by X below), (un)substituted
heterocycle (substitution as defined by X below), -(CH₂)₃OR³

R⁴ = C₁₋₆(un)branched alkyl

R⁶ = H, OR⁷

R⁷ = H, C₁₋₆(un)branched alkyl, (un)substituted aryl (substitution as defined by X below)

20 X and X' independently = H, F, Cl, Br, I, OR⁷, CN, OH, S(O)₂R⁴, CF₃, R⁴, NO₂

m = 0-3

m' = 0-5

n² = 0-2



The preferred, novel 3-benzoylphenylacetic acid derivatives are those wherein:

W = H

R = H, CH₃

Y = NR⁵R⁶, -NHOH

5 R⁴ = C₁₋₄ (un)branched alkyl

R⁵ = -(CH₂)_r-Z²-(CH₂)_{r'}-A, -(CH₂)_r-Z²-(CH₂)_{r'}-A'

r = 2-4

r' = 0-2

Z² = O

10 Z³ = nothing

A = H

A' = (un)substituted aryl (substitution as defined by X below)

R⁶ = H, OR⁷

R⁷ = H, C₁₋₂ alkyl

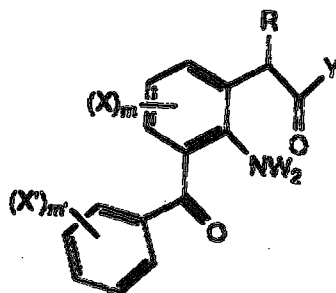
15 X and X' independently = H, F, Cl, Br, CF₃, S(O)₂R⁴, OR⁷

m = 0-2

m' = 0-3

n² = 0

20 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), -

5 $(CH_2)_n Z(CH_2)_m A$

$n = 2-6$

$m = 1-6$

$Z = \text{nothing}, O, C=O, OC(=O), C(=O)O, C(=O)NR^3, NR^3C(=O), S(O)_{2n}, CHOR^3, NR^3$

$n^2 = 0-2$

10 $R^3 = H, C_{1-6}$ (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), $-(CH_2)_k OR^3$

$R'' = H, OH, OR'$

15 X and X' independently = $H, F, Cl, Br, I, OR', CN, OH, S(O)_{2n}R^4, CF_3, R^4, NO_2$

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

$m = 0-3$

$m' = 0-5$

$W = O, H$

20 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

$Y = NR'R''$

$R' = H, C_{1-4}$ (un)branched alkyl, $-(CH_2)_n Z(CH_2)_m A$

25 $Z = \text{nothing}, O, CHOR^3, NR^3$

$R_3 = H$

$A = H, OH$, (un)substituted aryl (substitution as defined by X below)

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

$R'' = H$

30 $R^4 = C_{1-4}$ (un)branched alkyl



$$m = 0-2$$

$$m' = 0-2$$

$$W = H$$

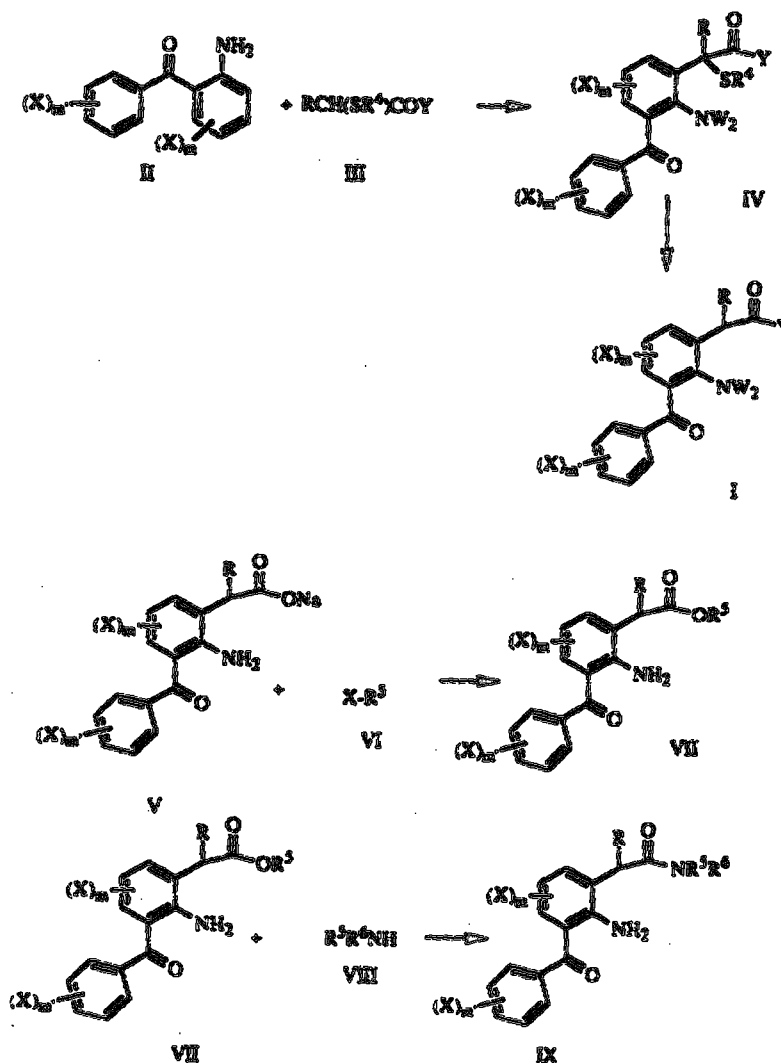
$$n = 2-4$$

$$n' = 0-3$$

5

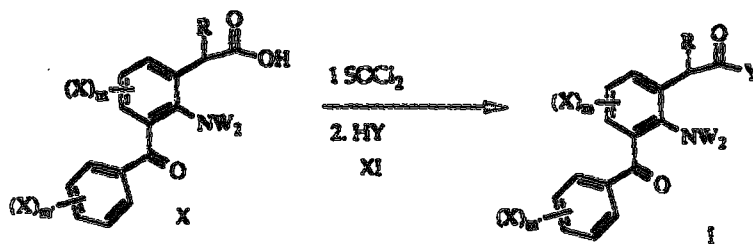
The most preferred compounds for use in the compositions or method of the present invention are 2-Amino-3-(4-fluorobenzoyl)-phenylacetamide; 2-Amino-3-benzoyl-phenylacetamide; and 2-Amino-3-(4-chlorobenzoyl)-phenylacetamide.

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



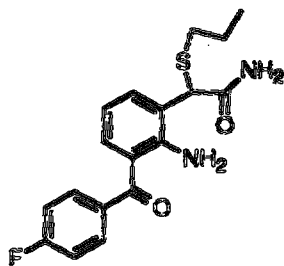
wherein X, Y, R, R⁴, R⁵, R⁶, m, m', and W are as defined above. The general method for the preparation for compounds of Formula I and Formula IV where Y is such that the compound is an amide derivative and W is hydrogen are detailed in U.S. Patent 4,313,949 assigned to A. H. Robins. The general method 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. Patent 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 R⁵ 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. Patent 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.

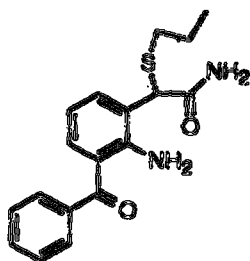


The manipulation of suitable protecting groups and deprotecting steps as employed by one skilled in the art may be necessary for the preparation of compounds of Formula I, Formula IV, Formula VIII, Formula IX and required intermediates.

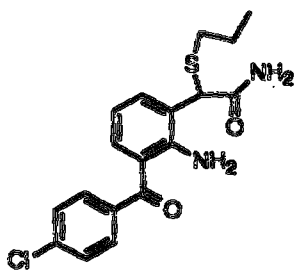
5 The invention will be further illustrated by the following examples which are intended to be illustrative, but not limiting.



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

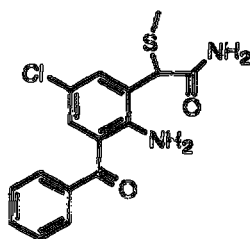


Compound 2
2-Amino-3-benzoyl- α -(n-propylthio)-phenylacetamide

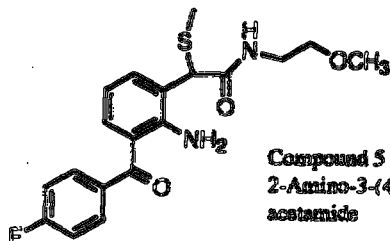


Compound 3
2-Amino-3-(4-chlorobenzoyl)- α -(n-propylthio)-phenylacetamide

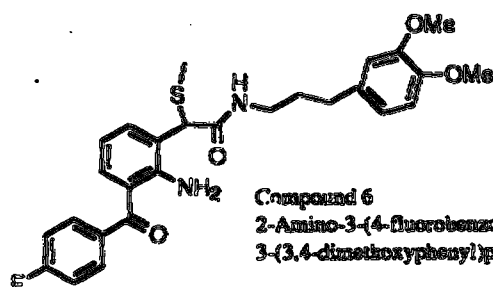




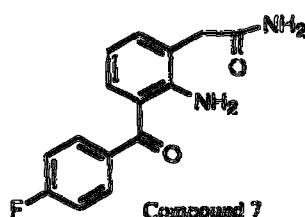
Compound 4

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

Compound 5

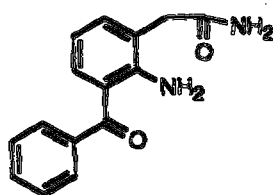
2-Amino-3-(4-fluorobenzoyl)- α -(methylthio)-N-(2-methoxyethyl)acetamide

Compound 6

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

Compound 7

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

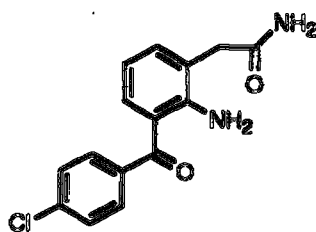


Compound 8

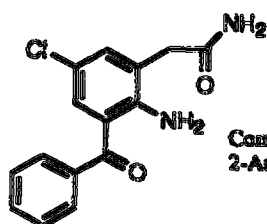
2-Amino-3-benzoyl-phenylacetamide



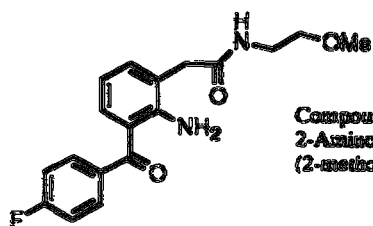
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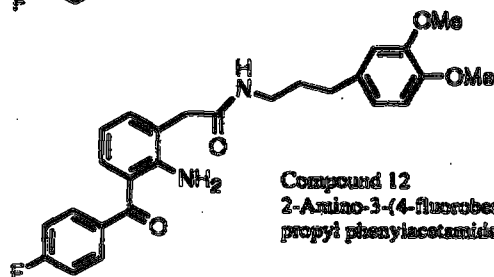
Compound 9
2-Amino-3-(4-chlorobenzoyl)-phenylacetamide



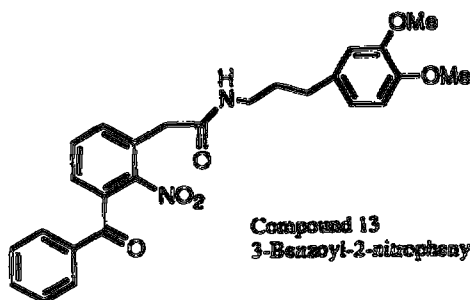
Compound 10
2-Amino-3-benzoyl-5-chlorophenylacetamide



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



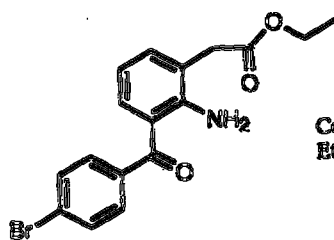
Compound 12
2-Amino-3-(4-fluorobenzoyl)-N-3-(3,4-dimethoxyphenyl)propylphenylacetamide



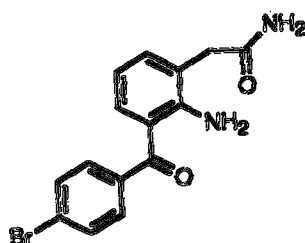
Compound 13
3-Benzoyl-2-nitrophenyl-N-3-(3,4-dimethoxyphenyl)propyl acetamide

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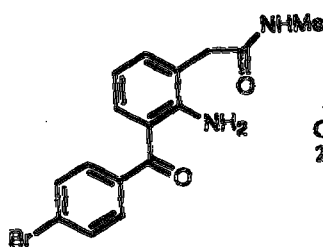




Compound 14
Ethyl 2-amino-3-(4-bromobenzoyl)-benzoate



Compound 15
2-Amino-3-(4-bromobenzoyl)-phenylacetamide



Compound 16
2-Amino-3-(4-bromobenzoyl)-N-methyl-phenylacetamide



Preparation I**2-Amino-3-(4-fluorobenzoyl)- α -(n-propylthio)-phenylacetamide, Compound 1**

A solution of 21.5 g (0.1 mole) of 4'-fluoro-2-aminobenzophenone in 400 mL of methylene chloride was cooled to -70° C and 11.5 g (0.1 mole) of 95% t-butylhypochlorite was added over a period of 15 min, keeping the temperature below -66° C. To this solution was added a solution of 13.3 g of 2-n-propylthioacetamide in 50 mL of methylene chloride over a 10 min period. The solution was stirred for 1 h at -65 to -70° C and then allowed to warm to 0° C at which point 10.2 g (0.1 mole) of triethylamine was added. The solution was stirred for 10 min and then washed with water. The organic solution was dried over magnesium sulfate. After concentrating under reduced pressure, the residue was crystallized from isopropyl alcohol and dried to give 19.5 g (56%) of yellow crystals melting at 140-142° C.

Analysis: Calculated for $C_{15}H_{19}N_2O_2SF$: C, 62.41; H, 5.53; N, 8.09. Found: C, 62.34; H, 5.58; N, 8.04.

Preparation II**2-Amino-3-benzoyl- α -(n-propylthio)-phenylacetamide, Compound 2**

In the same manner as given in Preparation I, 2-amino-3-benzoyl- α -(n-propylthio)-phenylacetamide, Compound 2, is prepared from 2-aminobenzophenone, t-butylhypochlorite and 2-n-propylthioacetamide.

Preparation III**2-Amino-3-(4-chlorobenzoyl)- α -(n-propylthio)-phenylacetamide, Compound 3**

In the same manner as given in Preparation I, 2-amino-3-(4-chlorobenzoyl)- α -(n-propylthio)-phenylacetamide, Compound 3, is prepared from 4'-chloro-2-aminobenzophenone, t-butylhypochlorite and 2-n-propylthioacetamide.

Preparation IV

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

To a cold (-70°C) solution of 12.77 g (0.055 mole) of 2-amino-5-chlorobenzophenone in 300 mL of methylene chloride, under nitrogen atmosphere, was added 6.0 g (0.552 mole) of *t*-butylhypochlorite in 20 mL of methylene chloride. After the reaction was stirred for an additional 15 min, a suspension of 5.8 g (0.055 mole) of α -(methylthio)acetamide in 150 mL of methylene chloride was added. The mixture was stirred at -65°C for 1 h. Triethylamine (5.6 g, 0.055 mole) was added and the solution was allowed to warm to room temperature. The reaction mixture was extracted with water and the organic layer dried over magnesium sulfate. The volume of the solution was reduced in vacuo to about 200 mL and the product crystallized as a yellow solid, m.p. $173.5\text{--}174.5^{\circ}\text{C}$. Yield was 6.86 g (37.3%).

Analysis: Calculated for $\text{C}_{16}\text{H}_{13}\text{N}_2\text{O}_2\text{SCl}$: C, 57.40; H, 4.52; N, 8.36. Found C, 57.38; H, 4.50; n, 8.51

Preparation V**2-Amino-3-(4-fluorobenzoyl)- α -(methylthio)-N-(2-methoxy)ethylacetamide, Compound 5**

To a solution of 21.5 g (0.1 mole) of 2-amino-4'-fluoro-benzophenone in 400 mL of methylene chloride cooled to -70°C is added 11.5 g (0.1 mole) of 95% *t*-butylhypochlorite over 15 min, keeping the temperature below -66°C . To this solution is added a solution of α -(methylthio)-N-(2-methoxyethyl)acetamide (0.1 mole) in 50 mL of methylene chloride over a ten minute period. The solution is stirred for 1 h at -65 to -70°C and then is allowed to warm to 0°C . Triethylamine (0.1 mole) is added and the resulting solution is washed with water. The organic solution is dried with magnesium sulfate, and concentrated in vacuo. The product is isolated using standard conditions.

Preparation VI**2-Amino-3-(4-fluorobenzoyl)- α -(methylthio)-N-3-(3,4-dimethoxyphenyl)propyl acetamide, Compound 6**

To a solution of 21.5 g (0.1 mole) of 2-amino- 4'-fluoro-benzophenone in 400 mL of methylene chloride, cooled to -70° C is added 11.5 g (0.1 mole) of 95% t-butylhypochlorite over 15 min, keeping the temperature below -66° C. To this solution is added a solution of α -(methylthio)-N-3-(3,4-dimethoxyphenyl)propylacetamide (0.1 mole) in 50 mL of methylene chloride over a ten minute period. The solution is stirred for 1 h at -65 to -70° C and then is allowed to warm to 0° C. Triethylamine (0.1 mole) is added and the resulting solution is washed with water. The organic solution is dried with magnesium sulfate, and concentrated in vacuo. The product is isolated using standard conditions.

Preparation VII

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

A solution of 24.2 g (0.07mole) of 2-amino-3-(4-fluorobenzoyl)- α -(n-propylthio)phenylacetamide in 300 mL of tetrahydrofuran was treated with an excess of wet Raney nickel (washed three times with water and three times with tetrahydrofuran). The mixture was stirred for 1 h and filtered. The filtrate was concentrated under reduced pressure and the residue was crystallized from 95% ethanol to afford 14.8 g (78%) of yellow needles melting at 184-186° C.

Analysis: Calculated for $C_{17}H_{15}N_2O_2F$: C, 66.17; H, 4.81; N, 10.29. Found: C, 66.32; H, 4.81; N, 10.48.



Preparation VIII

2-Amino-3-benzoyl-phenylacetamide, Compound 8

In the same manner as given in Preparation VII, 2-amino-3-benzoyl-phenylacetamide is prepared from 2-amino-3-benzoyl- α -(n-propylthio)-phenylacetamide.

5 Preparation IX

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

In the same manner as given in Preparation VII, 2-amino-3-(4-chlorobenzoyl)-phenylacetamide is prepared from 2-amino-3-(4-chlorobenzoyl)- α -(n-propylthio)-phenylacetamide.

10 Preparation X

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

A mixture of 21.34 g (0.0639 mole) of 2-amino-benzoyl-5-chloro- α -(methylthio)-phenylacetamide and excess Raney nickel in a mixture of 900 mL absolute ethanol, and 200 mL dimethylformamide was stirred at room temperature for 45 min. The mixture was
15 filtered through celite to remove Raney nickel. The solvent was removed under reduced pressure to give a yellow solid which was recrystallized to give a solid, m.p. 213.5-215.0° C (d).

Analysis: Calculated for $C_{15}H_{13}N_2O_2Cl$: C, 62.40; H, 4.54; N, 9.70. Found: C, 62.35; H, 4.58; N, 9.74.

20 Preparation XI

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

A mixture of 0.07 mole of 2-amino-3-(4-fluorobenzoyl)- α -(methylthio)-N-(2-methoxy)ethylacetamide in 300 mL of tetrahydrofuran is treated with an excess of wet Raney nickel (washed three times with water and three times with tetrahydrofuran). The



mixture is stirred for 1 h and filtered. The filtrate is concentrated under reduced pressure and the residue is purified by standard procedures to give the product.

Preparation XII

2-Amino-3-(4-fluorobenzoyl)-N-3-(3,4-dimethoxyphenyl)propyl phenylacetamide,

Compound 12

A mixture of 0.07 mole 2-amino-3-(4-fluorobenzoyl)- α -(methylthio)-N-3-(3,4-dimethoxyphenyl)propylacetamide in 300 mL of tetrahydrofuran is treated with an excess of wet Raney nickel (washed three times with water and three times with tetrahydrofuran). The mixture is stirred for 1 h and filtered. The filtrate is concentrated under reduced pressure and the residue is purified by standard procedures to give the product.

Preparation XIII

3-Benzoyl-2-nitrophenyl-N-3-(3,4-dimethoxyphenyl)propyl acetamide, Compound 13

A mixture of 0.028 mole of 3-benzoyl-2-nitrobenzeneacetic acid, 50 mL of thionyl chloride and 50 mL of benzene is heated at reflux. The dark solution is concentrated under vacuum. The residue is diluted with benzene and concentrated under vacuum (twice). A portion of the acid chloride (0.013 mole) in tetrahydrofuran is added to a solution of 3-amino (3,4-dimethoxyphenyl)propane (0.015 mole). The mixture is stirred at room temperature and then added to 200 mL of cold water. The resulting mixture is extracted with diethyl ether. The combined extracts are washed with water, dried over sodium sulfate and concentrated under reduced pressure. The residue is purified using standard procedures to give the product.

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Preparation XIV**Ethyl-2-Amino-3-(4-bromobenzoyl)benzene acetate, Compound 14**

A slurry of 35.6 g (0.1 mole) of 2-amino-3-(bromobenzoyl)benzeneacetic acid in 500 mL of dimethylformamide was treated with 32.0 g (0.2 mole) of ethyl iodide and stirred at ambient temperature for 24 h. The mixture was filtered and the filtrate was poured into 3.5 l of water. The solid which precipitated was collected by filtration, washed with water and recrystallized from absolute ethanol to give 26.8 g (74%) of the title compound, as gold needles, m.p. 107-109° C.

Analysis: Calculated for $C_{17}H_{16}BrNO_2$: C, 56.37; H, 4.45; N, 3.87. Found: C, 56.22; H 4.42; N, 3.87.

Preparation XV**2-Amino-3-(4-bromobenzoyl)-phenylacetamide, Compound 15**

Ammonia is condensed in a tube containing 2-amino-3-(4-bromobenzoyl)benzeneacetic acid, ethyl ester. The tube is sealed and the reaction mixture is warmed. The sealed tube was cooled and opened. Solvent was evaporated and the residue was purified by standard methods to give Compound 15.

Preparation XVI**2-Amino-3-(4-bromobenzoyl)-N-methyl phenylacetamide, Compound 16**

In the same manner as Preparation XV, 2-amino-3-(4-bromobenzoyl)-N-methyl phenylacetamide, Compound 16 is prepared from 2-amino-3-(4-bromobenzoyl)benzeneacetic acid, ethyl ester and methylamine.



Anti-Inflammatory Tests

I. In vitro Anti-Inflammatory Test

In vitro anti-inflammatory activity of 2-amino-3-benzoylbenzeneacetic acid analogues was tested by polarographically monitoring the inhibition in the rate of oxygen consumption (Cook HW., Ford G., and Lands WEM, Anal. Biochem. 96:341, 1979) in the conversion of arachidonic acid to prostaglandin H₂ by prostaglandin H synthase (cyclooxygenase). Cyclooxygenase enzyme was prepared by solubilizing 20 mg of lipid-depleted sheep vesicular gland microsomal powder (Graff G, Stephenson JH, et al., J. Biol. Chem. 253:7662, 1978) in 1.0 mL of buffer containing 50 mM phosphate, 5 mM diethyldithiocarbamic acid, and 2 μ M hematin (pH 7.4). Incubations were carried out at 30°C with a YSI-oxygen monitor (Model 53) in 50 mM phosphate/0.5 mM phenol buffer (pH 7.4) as described elsewhere (Graff G, and Anderson LA, Prostaglandins 38:473, 1989).

II. Ex Vivo Anti-Inflammatory Test

Ex vivo anti-inflammatory activity of 2-amino-3-benzoylbenzeneacetic acid analogues was evaluated in naive New Zealand Albino (NZA) rabbits. In this test animals were dosed bilaterally with a single 50 μ L aliquot of a 0.1 % solution/suspension of vehicle, formulated test or reference compound. After 60 minutes of treatment, animals were euthanized, iris/ciliary body (ICB) quickly excised and placed into ice-cold PBS buffer (pH 7.4). The tissue was then weighed, homogenized in ice-cold 50 mM phosphate/0.5 mM phenol buffer (pH 7.4) and incubated for 10 minutes at 37°C with 10 μ M of [1-¹⁴C]-20:4. Upon termination of the incubations, reaction products (prostaglandins) were isolated by organic solvent extraction (Bligh, E.G. and Dyer, W.J., Can. J. Biochem. Physiol. 37:911, 1959) and quantified by C₁₈-HPLC (Powell, W.S., Anal. Biochem. 148:59 1985).



III. In Vivo Anti-Inflammatory Test

In vivo anti-inflammatory activity of 2-amino-3-benzoylbenzeneacetic acid analogues was evaluated in the model of trauma-induced breakdown of the blood-aqueous-barrier in New Zealand Albino (NZA) rabbits. Animals were anesthetized prior to bilateral administration of a single topical 50 μ L dose of a 0.1 % solution/ suspension of formulated test or reference compound. After 45 minutes of treatment ocular trauma was induced by paracentesis. Thirty minutes post-paracentesis animals were euthanized, and aqueous humor was removed for protein (Bradford MM, Anal. Biochem. 72:248, 1976) and PGE₂ analysis (Radio immune assay, NEN-Research Products, E.I. Du Pont de Nemours, Boston, MA).

Results

The results from in vitro, ex vivo and in vivo anti-inflammatory tests are summarized in Table 1. Non-halogenated and halogenated 2-amino-3-benzoylbenzeneacetic acid analogues with free carboxylic acid functional groups, including the reference compound diclofenac, were potent in vitro inhibitors of sheep vesicular gland cyclooxygenase activity with IC₅₀ values ranging from 0.029 to 0.250 μ M. When tested in vivo, they effectively inhibited trauma-induced accumulation of PGE₂ ($\geq$ 98 %) and plasma protein influx into the aqueous humor in vivo. Similar results were obtained with the reference compound, diclofenac, which was somewhat less effective both in vitro and in vivo than the chloro- or bromo- substituted 2-amino-3-benzoylbenzeneacetic acids.

In contrast, unsubstituted and mono-substituted amide analogues of 2-amino-3-benzoylbenzeneacetic acid (Compounds 7, 8, 9, 15 and 16) were $\geq$ 3 orders of magnitude less effective inhibitors of cyclooxygenase activity in vitro with IC₅₀ values ranging from 16 to >133 μ M. Despite their weak inhibitory effects on cyclooxygenase activity in vitro, they were as effective as, or in one instance (Compound 7) more effective than, free carboxylic acid analogues in inhibiting plasma protein influx into the anterior chamber (62 to 72 %) and aqueous humor PGE₂ accumulation (>93 %). Interestingly, the dimethyl substituted amide analog was inactive in both in vitro and in vivo tests.



Although the in vitro potency was clearly enhanced by halogenation of the 4-position of the benzoyl ring of 2-amino-3-benzoylbenzeneacetic acid, there was little evidence for such a structure related effect in vivo.

5 When tested for ex vivo anti-inflammatory activity, Compound 8 was the most effective inhibitor of iris/ciliary body prostaglandin synthesis. The synthesis of all prostaglandins produced by the iris/ciliary body was inhibited to a similar extent. This spectrum of inhibition is in contrast to the effects of 2-amino-3-benzoylbenzeneacetic acid analogs with free carboxylic acid functional groups which predominately inhibited PGE₂ production.

10 Conversion of the free carboxylic acid functional group of Bromfenac to an ethyl ester (Compound 14) also resulted in a >3 orders of magnitude decline in in vitro cyclooxygenase inhibitory activity. However, when tested for topical ocular anti-inflammatory activity the ethyl ester showed significant inhibitory activity by reducing plasma protein extravasation into the aqueous humor by 60 %.

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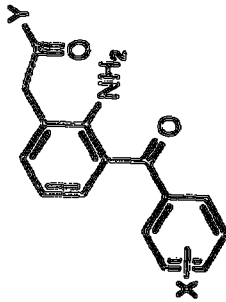


TABLE 1

SUMMARY OF ANTI-INFLAMMATORY TEST RESULTS

Compound	Substituent X	Y	In Vitro Cyclooxygenase Inhibition IC50 (uM)	Ex Vivo Iris/Ciliary Body Total Prostaglandin Synthesis Inhibition (%)***	In Vivo Aqueous Humor PGE2 Accumulation Inhibition (%)**	In Vivo Paracetesis Protein Extravasation Inhibition (%)*
Diclofenac**	-	-	0.120	50	97	84
Amfenac	4'-H	OH	0.25	-	-	41
-	4'-F	OH	0.171	-	-	42
-	4'-Cl	OH	0.070	-	99	72
Bromfenac	4'-Br	OH	0.029	44	98	62
# 15	4'-Br	NH2	19	-	97	64
# 16	4'-Br	NHCH3	16	48	93	62
-	4'-Br	N(CH3)2	>>100	-	-27	2
# 6	H	NH2	64	81	98	61
# 7	4'-F	NH2	133	27	98	72
# 8	4'-Cl	NH2	>>100	29	96	66
# 15	4'-Br	NH2	19	23	97	64
# 14	4'-Br	OCH2CH3	>>25	33	-	60

* Single topical dose of a 0.1 % drug solution/suspension 45 minutes prior to paracetesis

**Diclofenac, also known as Voltaren Optibatic (TM), is used as a reference standard

*** Single topical dose of 0.1 % drug solution/ suspension 60 minutes prior to iris/ciliary body isolation

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The 3-benzoylphenylacetic acid derivative compounds of this invention are useful for controlling ophthalmic inflammatory disorders and ocular pain. Such disorders include, but are not limited to uveitis, scleritis, episcleritis, keratitis, surgically-induced inflammation and endophthalmitis.

5 The 3-benzoylphenylacetic acid derivatives may be formulated into a variety of topically administrable ophthalmic compositions, such as solutions, suspensions, gels or ointment.

10 Pharmaceutical compositions comprising compounds of Formula I in aqueous solution, optionally containing a preservative for multidose use and other conventionally employed ophthalmic adjuvants, including a salt entity to adjust the tonicity of solutions, can be employed. The most preferred form of delivery is by eye drops; however, formulations wherein the final specialty form is a gel or ointment can also be employed and formulated according to conventional technology. The ophthalmic compositions of the present invention will typically contain one or more compounds of Formula I in an
15 amount of from about 0.001 to about 4.0% (w/v), preferably from about 0.01 to about 0.5% (w/v).

20 Further, additional therapeutic agents including steroids, such as, dexamethasone; antibiotics, such as gentamicin; anti-infectives, such as sulfonamides; and anti-allergics, such as antihistamines, may be added to supplement the ophthalmic compositions of the present invention.

25 The compositions may contain preservatives such as thimerosal, chlorobutanol, benzalkonium chloride, Onamer M, or chlorhexidine; buffering agents, such as phosphates, borates, carbonates and citrates; and thickening agents, such as, high molecular weight carboxy vinyl polymers, such as, the ones sold under the name of Carbopol which is a trademark of the B.F. Goodrich Chemical Company, hydroxyethylcellulose, or polyvinyl alcohol, for example.

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The compositions are prepared by dissolving the various ingredients in the required amount of water with stirring to ensure that all the ingredients are dissolved. The aqueous compositions of the invention may be solutions, suspensions, or gels. After preparation of the solution, suspension, or gel the compositions are then packaged in dispensers suitable for delivery of the ophthalmic compositions.

The following examples of ophthalmic compositions typify the manner in which the invention may be practiced. The examples should be construed as illustrative, and not as a limitation upon the overall scope of the invention. The percentages are expressed on a weight/volume basis. "Active Agent" means one or more compounds of Formula I.

Formulation 1

Active agent	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%

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Formulation 2

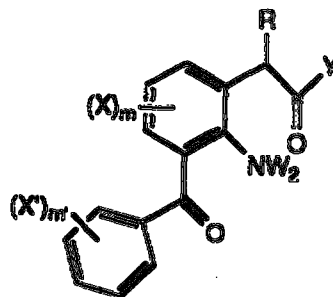
	Active Agent	0.01 - 0.5%
	Hydroxypropyl Methylcellulose	0.5%
	Polysorbate 80	0.01%
5	Benzalkonium Chloride	0.01% + 5% excess
	Disodium EDTA	0.01%
	Dibasic Sodium Phosphate	0.2%
	Sodium Chloride	q.s. 290-300 mOsm/Kg
	pH adjustment with NaOH and/or HCl	pH 4.2 - 7.4
10	Water	q.s. 100%

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We claim:



1. A 3-benzoylphenylacetic acid derivative of the formula:



W = O, H

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

Y = OR⁵, NR⁵R⁶

R¹ = -(CH₂)_r-Z²-(CH₂)_{r'}-A, -(CH₂)_r-Z²-(CH₂)_{r'}-A'

r=2-6

r'=0-6

Z² = O, C=O, OC(=O), C(=O)NR³, NR³C(=O), -S(O)₂CH₂-, S, CHOR³, NR³

Z² = nothing, -CHR⁴-, -CR⁴R⁴-

r²=1, 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, (un)substituted aryl (substitution as defined by X below),

(un)substituted heterocycle, -(CH₂)₃OR³

A' = OH, (un)substituted aryl (substitution as defined by X below),

(un)substituted heterocycle (substitution as defined by X below), -(CH₂)₃OR³

R⁴ = C₁₋₆(un)branched alkyl

R⁶ = H, OR⁷

R⁷ = H, C₁₋₆(un)branched alkyl, (un)substituted aryl (substitution as defined by X below)

X and X' independently = H, F, Cl, Br, I, OR⁷, CN, OH, S(O)₂R⁴, CF₃, R⁴,

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$$m = 0-3$$

$$m' = 0-5$$

$$n^2 = 0-2$$


2. The 3-benzoylphenylacetic acid derivative of Claim 1 wherein:

W = H

R = H, CH₃

Y = NR⁵R⁶, -NHOH

R⁴ = C₁₋₄ (un)branched alkyl

R⁵ = -(CH₂)_r-Z²-(CH₂)_{r'}-A, -(CH₂)_r-Z³-(CH₂)_{r'}-A'

r = 2-4

r' = 0-2

Z² = O

Z³ = nothing

A = H

A' = (un)substituted aryl (substitution as defined by X below)

R⁶ = H, OR⁷

R⁷ = H, C₁₋₂ alkyl

X and X' independently = H, F, Cl, Br, CF₃, S(O)₂R⁴, OR⁷

m = 0-2

m' = 0-3

n² = 0

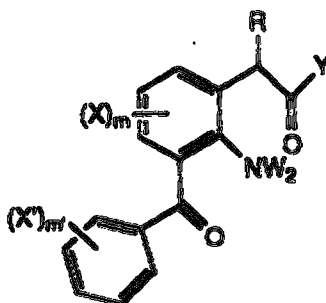
3. The 3-benzoylphenylacetic acid derivative of Claim 1 wherein the derivative is selected from the group consisting of 2-Amino-3-(4-fluorobenzoyl)-α(methylthio)-N-(2-methoxy)ethylacetamide, 2-Amino-3-(4-fluorobenzoyl)-α(methylthio)-N-3-(3,4-dimethoxyphenyl)propylacetamide, 2-Amino-3-(4-fluorobenzoyl)-N-(2-methoxy)ethyl phenylacetamide, 2-Amino-3-(4-fluorobenzoyl)-N-3-(3,4-dimethoxyphenyl)propyl phenylacetamide, and 3-Benzoyl-2-nitrophenyl-N-3-(3,4-dimethoxyphenyl)propyl acetamide.

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4. A topically administrable, ophthalmic pharmaceutical composition for treating ophthalmic inflammatory disorders and ocular pain which comprises an anti-inflammatory-effective amount of a 3-benzoylphenylacetic acid derivative of the formula:

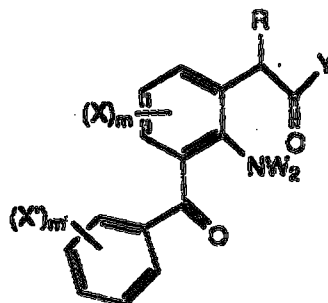


- 5 $R = H, C_{1-4}$ (un)branched alkyl, CF_3 , SR^4
 $Y = OR', NR''R'$
 $R' = H$ (except when $Y = OR'$), C_{1-10} (un)branched alkyl, (un)substituted
(substitution as defined by X below), (un)substituted heterocycle (substitution
as defined by X below), $-(CH_2)_nZ(CH_2)_m A$
10 $n = 2-6$
 $n' = 1-6$
 $Z = \text{nothing}, O, C=O, OC(=O), C(=O)O, C(=O)NR^3,$
 $NR^3C(=O), S(O)_2, CHOR^3, NR^3$
 $n^2 = 0-2$
15 $R^3 = H, C_{1-4}$ (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), $-(CH_2)_n OR^3$
 $R'' = H, OH, OR'$
20 X and X' independently = $H, F, Cl, Br, I, OR', CN, OH, S(O)_2R^4, CF_3, R^4, NO_2$
 $R^4 = C_{1-4}$ (un)branched alkyl
 $m = 0-3$
 $m' = 0-5$
 $W = O, H$





5. The composition of Claim 4 wherein the 3-benzoylphenylacetic acid derivative is of the formula:



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

$Y = NR'R''$

5 $R' = H, C_{1-4} \text{ (un)branched alkyl, } -(CH_2)_n Z (CH_2)_n A$

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

$R_3 = H$

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

$X \text{ and } X' \text{ independently} = H, F, Cl, Br, CN, CF_3, OR', SR', R^4$

10 $R'' = H$

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

$m = 0-2$

$m' = 0-2$

$W = H$

15 $n = 2-4$

$n' = 0-3$

6. The composition of Claim 4 wherein the 3-benzoylphenylacetic acid derivative is selected from the group consisting of 2-Amino-3-(4-fluorobenzoyl)- α -(n-propylthio)-phenylacetamide, 2-Amino-3-benzoyl- α -(n-propylthio)-phenylacetamide, 2-Amino-3-(4-chlorobenzoyl)- α -(n-propylthio)-phenylacetamide, 2-Amino-3-benzoyl-5-chloro- α -(methylthio)-phenylacetamide, 2-Amino-3-(4-fluorobenzoyl)- α -(methylthio)-N-(2-methoxy)ethylacetamide, 2-Amino-3-(4-
- 20





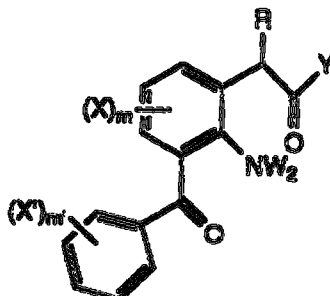
fluorobenzoyl)- α -(methylthio)-N-3-(3,4-dimethoxyphenyl)propylacetamide, 2-Amino-3-(4-fluorobenzoyl)-phenylacetamide, 2-Amino-3-benzoyl-phenylacetamide, 2-Amino-3-(4-chlorobenzoyl)-phenylacetamide, 2-Amino-3-benzoyl-5-chlorophenylacetamide, 2-Amino-3-(4-fluorobenzoyl)-N-(2-methoxy)ethyl phenylacetamide, 2-Amino-3-(4-fluorobenzoyl)-N-3-(3,4-dimethoxyphenyl)propyl phenylacetamide, 3-Benzoyl-2-nitrophenyl-N-3-(3,4-dimethoxyphenyl)propyl acetamide, Ethyl 2-Amino-3-(4-bromobenzoyl)benzene acetate, 2-Amino-3-(4-bromobenzoyl)-phenylacetamide, and 2-Amino-3-(4-bromobenzoyl)-N-methyl phenylacetamide.

- 10 7. The composition of Claim 6 wherein the 3-benzoylphenylacetic acid derivative is selected from the group consisting of 2-Amino-3-(4-fluorobenzoyl)- α -(n-propylthio)-phenylacetamide, 2-Amino-3-(4-chlorobenzoyl)- α -(n-propylthio)-phenylacetamide, 2-Amino-3-(4-chlorobenzoyl)- α -(n-propylthio)-phenylacetamide, 2-Amino-3-benzoyl-5-chloro- α -(methylthio)-phenylacetamide, 2-Amino-3-(4-fluorobenzoyl)-phenylacetamide, 2-Amino-3-benzoyl-phenylacetamide, 2-Amino-3-(4-chlorobenzoyl)-phenylacetamide, 2-Amino-3-benzoyl-5-chlorophenylacetamide, and 2-Amino-3-(4-bromobenzoyl)-phenylacetamide.
- 15 8. The composition of Claim 7 wherein the 3-benzoylphenylacetic acid 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.
- 20 9. The composition of Claim 4 wherein the amount of 3-benzoylphenylacetic acid is from about 0.001 to about 4.0% (w/v).
- 25 10. The composition of Claim 9 wherein the amount of 3-benzoylphenylacetic acid is from about 0.01 to about 0.5% (w/v).
11. A method of treating ophthalmic inflammatory disorders and ocular pain which comprises topically administering to the eye a pharmaceutical composition





comprising an anti-inflammatory-effective amount of a 3-benzoylphenylacetic acid derivative of the formula:



$R = H, C_{1-4}$ (un)branched alkyl, CF_3 , SR^4

$Y = OR', NR''R'$

5 $R' = H$ (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), $-(CH_2)_nZ(CH_2)_{n'}A$

$n = 2-6$

$n' = 1-6$

10 $Z = \text{nothing}, O, C=O, OC(=O), C(=O)O, C(=O)NR^3, NR^3C(=O), S(O)_{n^2}, CHOR^3, NR^3$

$n^2 = 0-2$

$R^3 = H, C_{1-6}$ (un)branched alkyl, (un)substituted aryl (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below)

15 $A = H, OH$, optionally (un)substituted aryl (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below), $-(CH_2)_6OR^3$

$R'' = H, OH, OR'$

X and X' independently = $H, F, Cl, Br, I, OR', CN, OH, S(O)_{n^2}R^4, CF_3, R^4, NO_2$

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

20 $m = 0-3$

$m' = 0-5$

$W = O, H$

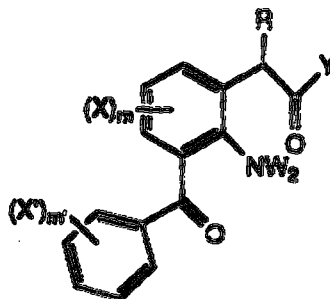
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12. The method of Claim 11 wherein the 3-benzoylphenylacetic acid derivative is of the formula:



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

$Y = NR'R''$

5 $R' = H, C_{1-6} \text{ (un)branched alkyl, } -(CH_2)_n Z (CH_2)_n A$

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

$R_3 = H$

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

$X \text{ and } X' \text{ independently} = H, F, Cl, Br, CN, CF_3, OR^4, SR^4, R^4$

10 $R'' = H$

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

$m = 0-2$

$m' = 0-2$

$W = H$

15 $n = 2-4$

$n' = 0-3$

13. The method of Claim 11 wherein the 3-benzoylphenylacetic acid derivative is selected from the group consisting of 2-Amino-3-(4-fluorobenzoyl)- α -(n-propylthio)-phenylacetamide, 2-Amino-3-benzoyl- α -(n-propylthio)-phenylacetamide, 2-Amino-3-(4-chlorobenzoyl)- α -(n-propylthio)-phenylacetamide, 2-Amino-3-benzoyl-5-chloro- α -(methylthio)-phenylacetamide, 2-Amino-3-(4-fluorobenzoyl)- α -(methylthio)-N-(2-methoxy)ethylacetamide, 2-Amino-3-(4-fluorobenzoyl)- α -(methylthio)-N-3-(3,4-dimethoxyphenyl)propylacetamide, 2-Amino-
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3-(4-fluorobenzoyl)-phenylacetamide, 2-Amino-3-benzoyl-phenylacetamide, 2-Amino-3-(4-chlorobenzoyl)-phenylacetamide, 2-Amino-3-benzoyl-5-chlorophenylacetamide, 2-Amino-3-(4-fluorobenzoyl)-N-(2-methoxy)ethyl phenylacetamide, 2-Amino-3-(4-fluorobenzoyl)-N-3-(3,4-dimethoxyphenyl)propyl phenylacetamide, 3-Benzoyl-2-nitrophenyl-N-3-(3,4-dimethoxyphenyl)propyl acetamide, Ethyl 2-Amino-3-(4-bromobenzoyl)benzene acetate, 2-Amino-3-(4-bromobenzoyl)-phenylacetamide, and 2-Amino-3-(4-bromobenzoyl)-N-methyl phenylacetamide.

14. The method Claim 13 wherein the 3-benzoylphenylacetic acid derivative is selected from the group consisting of 2-Amino-3-(4-fluorobenzoyl)- α -(n-propylthio)-phenylacetamide, 2-Amino-3-(4-chlorobenzoyl)- α -(n-propylthio)-phenylacetamide, 2-Amino-3-(4-chlorobenzoyl)- α -(n-propylthio)-phenylacetamide, 2-Amino-3-benzoyl-5-chloro- α -(methylthio)-phenylacetamide, 2-Amino-3-(4-fluorobenzoyl)-phenylacetamide, 2-Amino-3-benzoyl-phenylacetamide, 2-Amino-3-(4-chlorobenzoyl)-phenylacetamide, 2-Amino-3-benzoyl-5-chlorophenylacetamide, and 2-Amino-3-(4-bromobenzoyl)-phenylacetamide.
15. The method of Claim 14 wherein the 3-benzoylphenylacetic acid 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.
16. The method of Claim 11 wherein the amount of 3-benzoylphenylacetic acid is from about 0.001 to about 4.0% (w/v).
17. The method of Claim 16 wherein the amount of 3-benzoylphenylacetic acid is from about 0.01 to about 0.5% (w/v).

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REPLACEMENT SHEET

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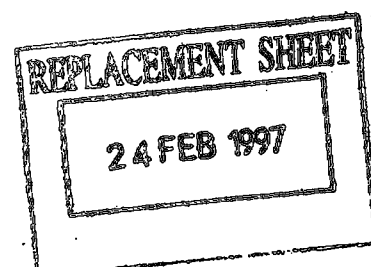
This invention relates to topically administrable compositions for the treatment of inflammatory disorders. In particular, this invention relates to non-irritating, topically administrable compositions containing 3-benzoylphenylacetic acid derivatives for the treatment of ophthalmic inflammatory disorders.

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 teach various 3-benzoylphenylacetic acids, salts and esters, and hydrates thereof, having anti-inflammatory activity. U.S. Patent No. 4,568,695 teaches 2-amino-3-benzoylphenylethyl alcohols having anti-inflammatory activity. U.S. Patent 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.

✓	1	26
✓	27	30
✓	41	-

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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. 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.

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.

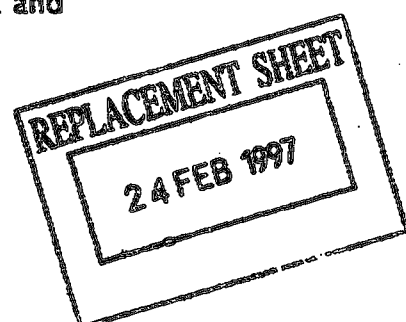
Summary of the Invention

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.

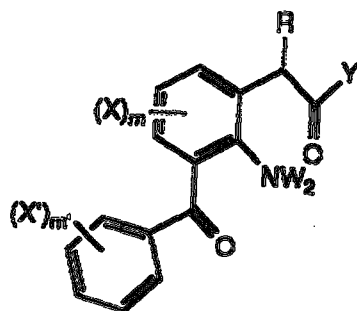
Accordingly, the present invention is directed to novel derivatives of 3-benzoylphenylacetic acid compounds. The present invention is also directed to pharmaceutical compositions suitable for topical ophthalmic administration which contain an anti-inflammatory-effective amount of a 3-benzoylphenylacetic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

Description of Embodiments 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

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

Y = OR⁵, NR⁵R⁶

R⁵ = -(CH₂)_r-Z²-(CH₂)_r-A, -(CH₂)_r-Z³-(CH₂)_r-A'

r = 2-6

r' = 0-6

Z² = O, C=O, OC(=O), C(=O)NR³, NR³C(=O), -S(O)₂CH₂, S, CHOR³, NR³

Z³ = nothing, -CHR⁴-, -CR⁴R⁴-

r² = 1, 2

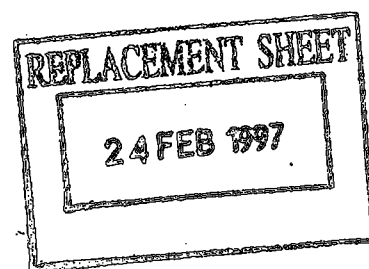
R³ = H, C₁₋₆(un)branched alkyl, (un)substituted aryl (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below)

A = H, OH, (un)substituted aryl (substitution as defined by X below), (un)substituted heterocycle, -(CH₂)_rOR³

A' = OH, (un)substituted aryl (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below), -(CH₂)_rOR³

R⁴ = C₁₋₆(un)branched alkyl

R⁶ = H, OR⁷



$R^7 = H, C_{1-6}(\text{un})\text{branched alkyl}, (\text{un})\text{substituted aryl}$ (substitution as defined by X below)

X and X' independently = H, F, Cl, Br, I, OR⁷, CN, OH, S(O)_{n2}R⁴, CF₃, R⁴, NO₂

m = 0-3

m' = 0-5

n² = 0-2

The preferred, novel 3-benzoylphenylacetic acid derivatives are those wherein:

W = H

R = H, CH₃

Y = NR⁵R⁶, -NHOH

R⁴ = C₁₋₆ (un)branched alkyl

R⁵ = -(CH₂)_r-Z²-(CH₂)_{r'}-A, -(CH₂)_r-Z³-(CH₂)_{r'}-A'

r = 2-4

r' = 0-2

Z² = O

Z³ = nothing

A = H

A' = (un)substituted aryl (substitution as defined by X below)

R⁶ = H, OR⁷

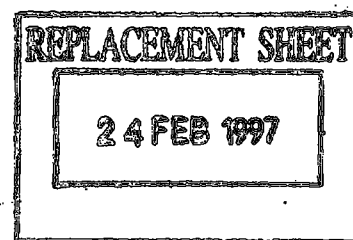
R⁷ = H, C₁₋₂ alkyl

X and X' independently = H, F, Cl, Br, CF₃, S(O)_{n2}R⁴, OR⁷

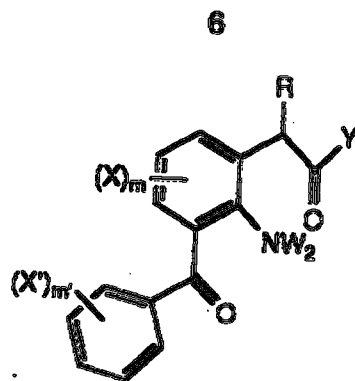
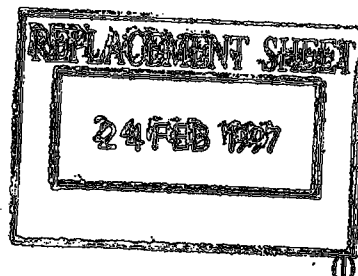
m = 0-2

m' = 0-3

n² = 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:



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$R = H, C_{1-4}$ (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), $-(CH_2)_nZ(CH_2)_nA$

$n = 2-6$

$n' = 1-6$

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

$n^2 = 0-2$

$R^3 = H, C_{1-4}$ (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

$m = 0-3$

$m' = 0-5$

$W = O, H$

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

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$Y = NR'R''$

$R' = H, C_{1-6}$ (un)branched alkyl, $-(CH_2)_nZ(CH_2)_nA$

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

$R_3 = H$

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

$X \text{ and } X' \text{ independently} = H, F, Cl, Br, CN, CF_3, OR', SR^4, R^4$

$R'' = H$

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

$m = 0-2$

$m' = 0-2$

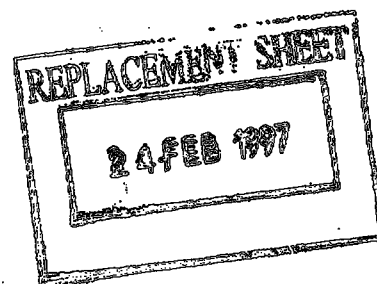
$W = H$

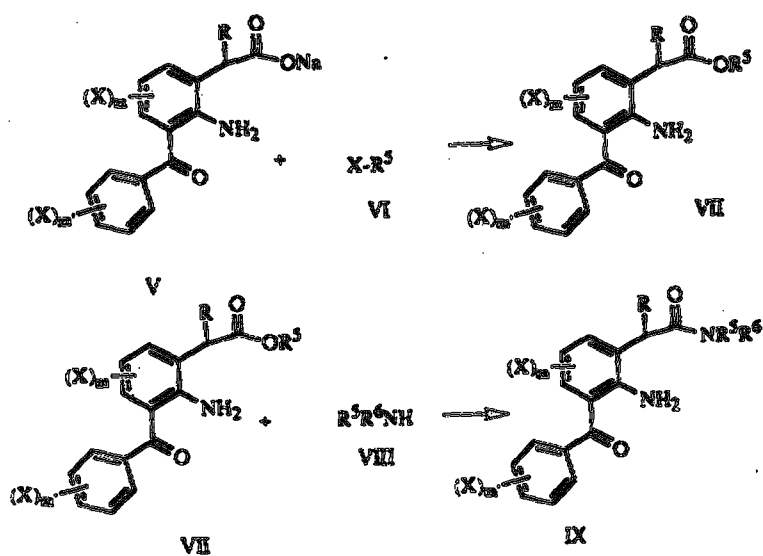
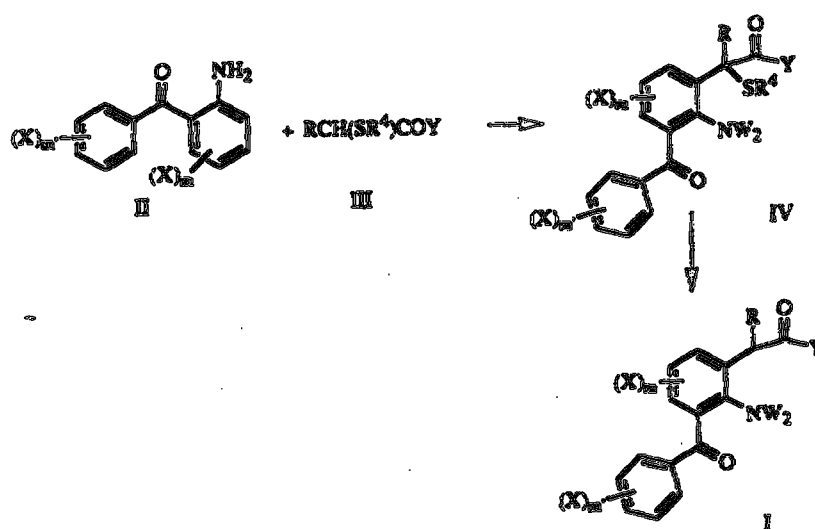
$n = 2-4$

$n' = 0-3$

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:



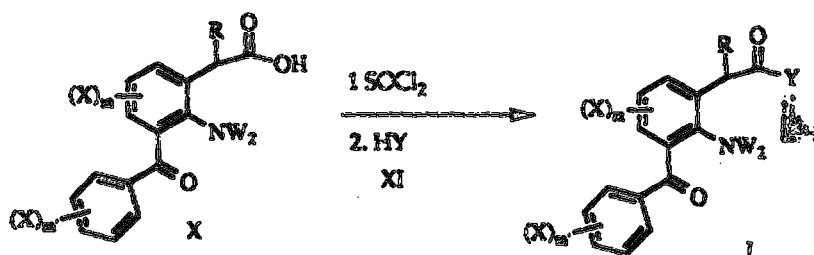


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wherein X, Y, R, R⁴, R⁵, R⁶, m, m', and W are as defined above. The general method for the preparation for compounds of Formula I and Formula IV where Y is such that the compound is an amide derivative and W is hydrogen are detailed in U.S. Patent 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. Patent 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 R⁵ 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. Patent 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.

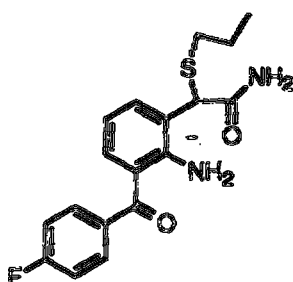


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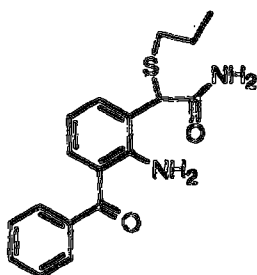
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The manipulation of suitable protecting groups and deprotecting steps as employed by one skilled in the art may be necessary for the preparation of compounds of Formula I, Formula IV, Formula VIII, Formula IX and required intermediates.

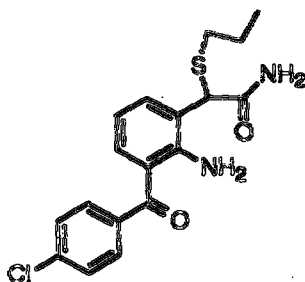
5 The invention will be further illustrated by the following examples which are intended to be illustrative, but not limiting.



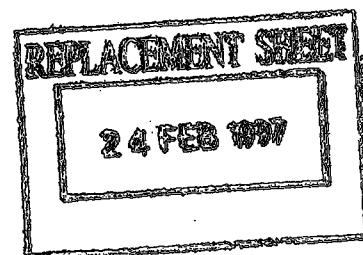
Compound 1
2-Amino-3-(4-fluorobenzoyl)- α -(n-propylthio)-phenylacetamide

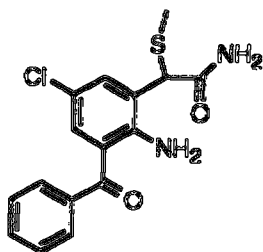


Compound 2
2-Amino-3-benzoyl- α -(n-propylthio)-phenylacetamide

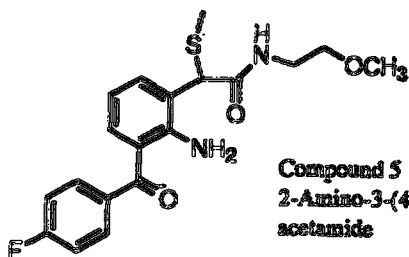


Compound 3
2-Amino-3-(4-chlorobenzoyl)- α -(n-propylthio)-phenylacetamide

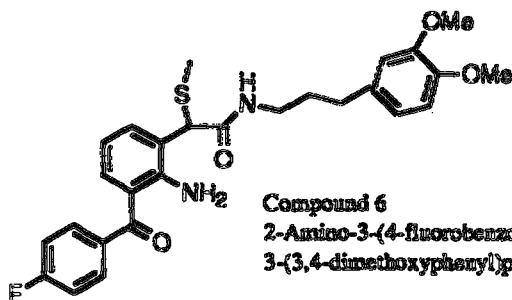




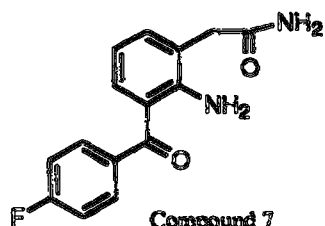
Compound 4
2-Amino-3-benzoyl-5-chloro- α -(methylthio)-phenylacetamide



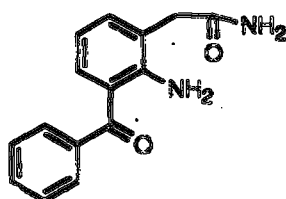
Compound 5
2-Amino-3-(4-fluorobenzoyl)- α -(methylthio)-N-(2-methoxyethyl)acetamide



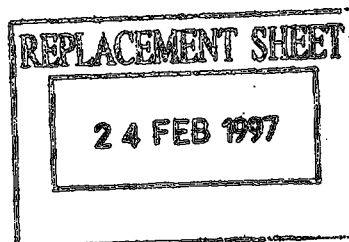
Compound 6
2-Amino-3-(4-fluorobenzoyl)- α -(methylthio)-N-(3-(3,4-dimethoxyphenyl)propyl)phenylacetamide

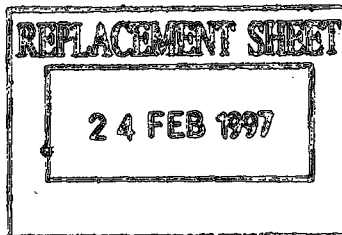


Compound 7
2-Amino-3-(4-fluorobenzoyl)-phenylacetamide

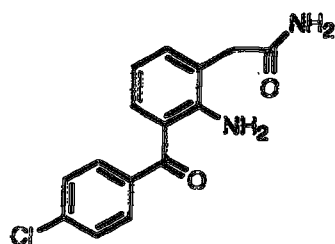


Compound 8
2-Amino-3-benzoyl-phenylacetamide

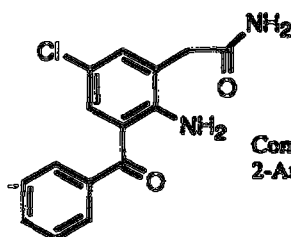




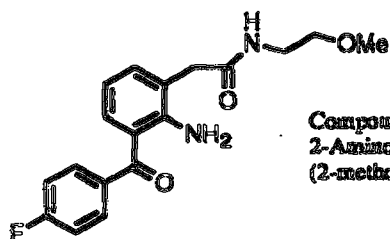
12



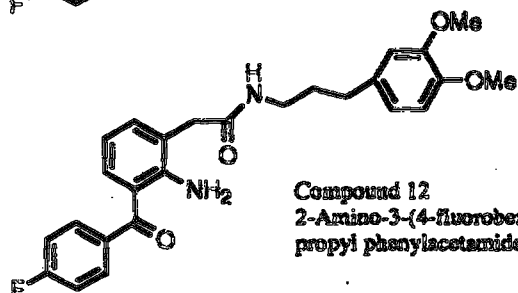
Compound 9
2-Amino-3-(4-chlorobenzoyl)-phenylacetamide



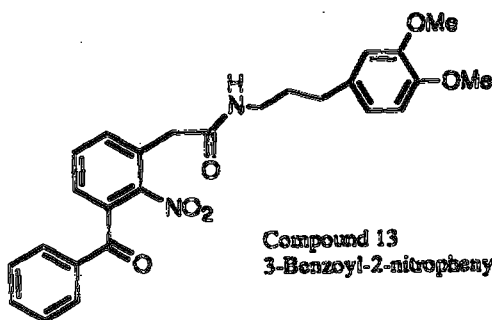
Compound 10
2-Amino-3-benzoyl-5-chlorophenylacetamide



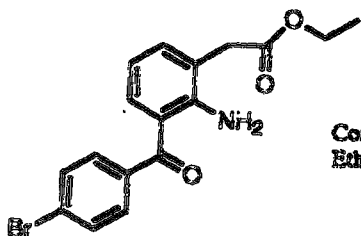
Compound 11
2-Amino-3-(4-fluorobenzoyl)-N-(2-methoxyethyl)phenylacetamide



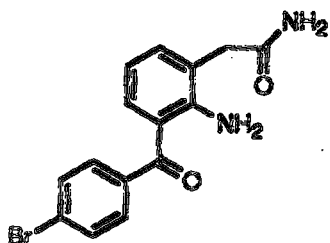
Compound 12
2-Amino-3-(4-fluorobenzoyl)-N-3-(3,4-dimethoxyphenyl)propyl phenylacetamide



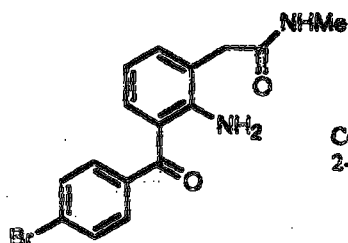
Compound 13
3-Benzoyl-2-nitrophenyl-N-3-(3,4-dimethoxyphenyl)propyl acetamide



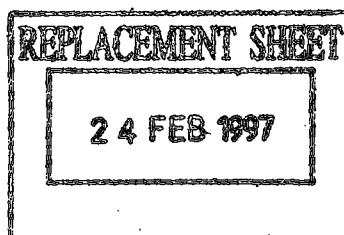
Compound 14
Ethyl 2-amino-3-(4-bromobenzoyl)-benzoate



Compound 15
2-Amino-3-(4-bromobenzoyl)-phenylacetamide



Compound 16
2-Amino-3-(4-bromobenzoyl)-N-methyl-phenylacetamide



Preparation I**2-Amino-3-(4-fluorobenzoyl)- α -(n-propylthio)-phenylacetamide, Compound 1**

A solution of 21.5 g (0.1 mole) of 4'-fluoro-2-aminobenzophenone in 400 mL of methylene chloride was cooled to -70°C and 11.5 g (0.1 mole) of 95% t-butylhypochlorite was added over a period of 15 min, keeping the temperature below -66°C . To this solution was added a solution of 13.3 g of 2-n-propylthioacetamide in 50 mL of methylene chloride over a 10 min period. The solution was stirred for 1 h at -65 to -70°C and then allowed to warm to 0°C at which point 10.2 g (0.1 mole) of triethylamine was added. The solution was stirred for 10 min and then washed with water. The organic solution was dried over magnesium sulfate. After concentrating under reduced pressure, the residue was crystallized from isopropyl alcohol and dried to give 19.5 g (56%) of yellow crystals melting at 140 - 142°C .

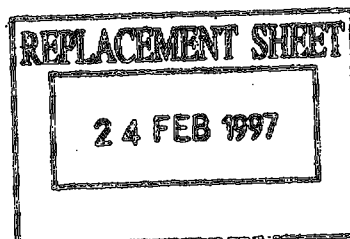
Analysis: Calculated for $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}_2\text{SF}$: C, 62.41; H, 5.53; N, 8.09. Found: C, 62.34; H, 5.58; N, 8.04.

Preparation II**2-Amino-3-benzoyl- α -(n-propylthio)-phenylacetamide, Compound 2**

In the same manner as given in Preparation I, 2-amino-3-benzoyl- α -(n-propylthio)-phenylacetamide, Compound 2, is prepared from 2-aminobenzophenone, t-butylhypochlorite and 2-n-propylthioacetamide.

Preparation III**2-Amino-3-(4-chlorobenzoyl)- α -(n-propylthio)-phenylacetamide, Compound 3**

In the same manner as given in Preparation I, 2-amino-3-(4-chlorobenzoyl)- α -(n-propylthio)-phenylacetamide, Compound 3, is prepared from 4'-chloro-2-aminobenzophenone, t-butylhypochlorite and 2-n-propylthioacetamide.

Preparation IV

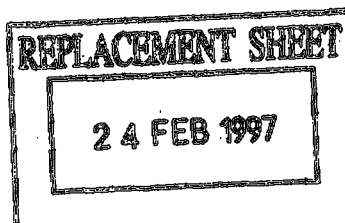
2-Amino-3-benzoyl-5-chloro- α -(methylthio)-phenylacetamide, Compound 4

To a cold (-70°C) solution of 12.77 g (0.055 mole) of 2-amino-5-chlorobenzophenone in 300 mL of methylene chloride, under nitrogen atmosphere, was added 6.0 g (0.552 mole) of t-butylhypochlorite in 20 mL of methylene chloride. After the reaction was stirred for an additional 15 min, a suspension of 5.8 g (0.055 mole) of α -(methylthio)acetamide in 150 mL of methylene chloride was added. The mixture was stirred at -65°C for 1 h. Triethylamine (5.6 g, 0.055 mole) was added and the solution was allowed to warm to room temperature. The reaction mixture was extracted with water and the organic layer dried over magnesium sulfate. The volume of the solution was reduced in vacuo to about 200 mL and the product crystallized as a yellow solid, m.p. $173.5\text{--}174.5^{\circ}\text{C}$. Yield was 6.86 g (37.3%).

Analysis: Calculated for $\text{C}_{16}\text{H}_{15}\text{N}_2\text{O}_2\text{SCl}$: C, 57.40; H, 4.52; N, 8.36. Found C, 57.38; H, 4.50; n, 8.51

Preparation V**2-Amino-3-(4-fluorobenzoyl)- α -(methylthio)-N-(2-methoxy)ethylacetamide, Compound 5**

To a solution of 21.5 g (0.1 mole) of 2-amino-4'-fluoro-benzophenone in 400 mL of methylene chloride cooled to -70°C is added 11.5 g (0.1 mole) of 95% t-butylhypochlorite over 15 min, keeping the temperature below -66°C . To this solution is added a solution of α -(methylthio)-N-(2-methoxyethyl)acetamide (0.1 mole) in 50 mL of methylene chloride over a ten minute period. The solution is stirred for 1 h at -65 to -70°C and then is allowed to warm to 0°C . Triethylamine (0.1 mole) is added and the resulting solution is washed with water. The organic solution is dried with magnesium sulfate, and concentrated in vacuo. The product is isolated using standard conditions.

Preparation VI**2-Amino-3-(4-fluorobenzoyl)- α -(methylthio)-N-3-(3,4-dimethoxyphenyl)propyl acetamide, Compound 6**

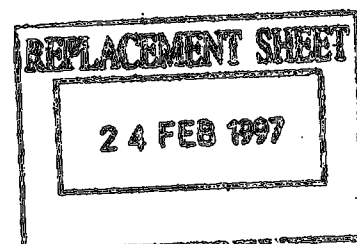
To a solution of 21.5 g (0.1 mole) of 2-amino-4'-fluoro-benzophenone in 400 mL of methylene chloride, cooled to -70°C is added 11.5 g (0.1 mole) of 95% t-butylhypochlorite over 15 min, keeping the temperature below -66°C . To this solution is added a solution of α -(methylthio)-N-3-(3,4-dimethoxyphenyl)propylacetamide (0.1 mole) in 50 mL of methylene chloride over a ten minute period. The solution is stirred for 1 h at -65 to -70°C and then is allowed to warm to 0°C . Triethylamine (0.1 mole) is added and the resulting solution is washed with water. The organic solution is dried with magnesium sulfate, and concentrated in vacuo. The product is isolated using standard conditions.

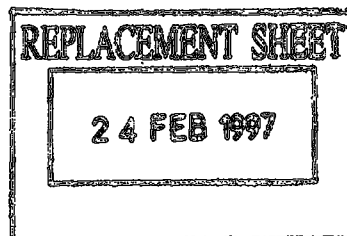
Preparation VII

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

A solution of 24.2 g (0.07mole) of 2-amino-3-(4-fluorobenzoyl)- α -(n-propylthio)phenylacetamide in 300 mL of tetrahydrofuran was treated with an excess of wet Raney nickel (washed three times with water and three times with tetrahydrofuran). The mixture was stirred for 1 h and filtered. The filtrate was concentrated under reduced pressure and the residue was crystallized from 95% ethanol to afford 14.8 g (78%) of yellow needles melting at $184-186^{\circ}\text{C}$.

Analysis: Calculated for $\text{C}_{15}\text{H}_{13}\text{N}_2\text{O}_2\text{F}$: C, 66.17; H, 4.81; N, 10.29. Found: C, 66.32; H, 4.81; N, 10.48.



**Preparation VIII****2-Amino-3-benzoyl-phenylacetamide, Compound 8**

In the same manner as given in Preparation VII, 2-amino-3-benzoyl-phenylacetamide is prepared from 2-amino-3-benzoyl- α -(n-propylthio)-phenylacetamide.

Preparation IX**2-Amino-3-(4-chlorobenzoyl)-phenylacetamide, Compound 9**

In the same manner as given in Preparation VII, 2-amino-3-(4-chlorobenzoyl)-phenylacetamide is prepared from 2-amino-3-(4-chlorobenzoyl)- α -(n-propylthio)-phenylacetamide.

Preparation X**2-Amino-3-benzoyl-5-chlorophenylacetamide, Compound 10**

A mixture of 21.34 g (0.0639 mole) of 2-amino-benzoyl-5-chloro- α -(methylthio)-phenylacetamide and excess Raney nickel in a mixture of 900 mL absolute ethanol, and 200 mL dimethylformamide was stirred at room temperature for 45 min. The mixture was filtered through celite to remove Raney nickel. The solvent was removed under reduced pressure to give a yellow solid which was recrystallized to give a solid, m.p. 213.5-215.0° C (d).

Analysis: Calculated for $C_{15}H_{13}N_2O_3Cl$: C, 62.40; H, 4.54; N, 9.70. Found: C, 62.35; H, 4.58; N, 9.74.

Preparation XI**2-Amino-3-(4-fluorobenzoyl)-N-(2-methoxy)ethyl phenylacetamide, Compound 11**

A mixture of 0.07 mole of 2-amino-3-(4-fluorobenzoyl)- α -(methylthio)-N-(2-methoxy)ethylacetamide in 300 mL of tetrahydrofuran is treated with an excess of wet Raney nickel (washed three times with water and three times with tetrahydrofuran).

The mixture is stirred for 1 h and filtered. The filtrate is concentrated under reduced pressure and the residue is purified by standard procedures to give the product.

Preparation XII

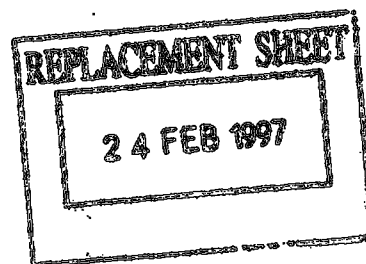
2-Amino-3-(4-fluorobenzoyl)-N-3-(3,4-dimethoxyphenyl)propyl phenylacetamide,
5 Compound 12

A mixture of 0.07 mole 2-amino-3-(4-fluorobenzoyl)- α -(methylthio)-N-3-(3,4-dimethoxyphenyl)propylacetamide in 300 mL of tetrahydrofuran is treated with an excess of wet Raney nickel (washed three times with water and three times with tetrahydrofuran). The mixture is stirred for 1 h and filtered. The filtrate is
10 concentrated under reduced pressure and the residue is purified by standard procedures to give the product.

Preparation XIII

3-Benzoyl-2-nitrophenyl-N-3-(3,4-dimethoxyphenyl)propyl acetamide, Compound 13

A mixture of 0.028 mole of 3-benzoyl-2-nitrobenzeneacetic acid, 50 mL of thionyl chloride and 50 mL of benzene is heated at reflux. The dark solution is concentrated
15 under vacuum. The residue is diluted with benzene and concentrated under vacuum (twice). A portion of the acid chloride (0.013 mole) in tetrahydrofuran is added to a solution of 3-amino (3,4-dimethoxyphenyl)propane (0.015 mole). The mixture is stirred at room temperature and then added to 200 mL of cold water. The resulting
20 mixture is extracted with diethyl ether. The combined extracts are washed with water, dried over sodium sulfate and concentrated under reduced pressure. The residue is purified using standard procedures to give the product.



Preparation XIV**Ethyl-2-Amino-3-(4-bromobenzoyl)benzene acetate, Compound 14**

A slurry of 35.6 g (0.1 mole) of 2-amino-3-(bromobenzoyl)benzeneacetic acid in 500 mL of dimethylformamide was treated with 32.0 g (0.2 mole) of ethyl iodide and stirred at ambient temperature for 24 h. The mixture was filtered and the filtrate was poured into 3.5 l of water. The solid which precipitated was collected by filtration, washed with water and recrystallized from absolute ethanol to give 26.8 g (74%) of the title compound, as gold needles, m.p. 107-109° C.

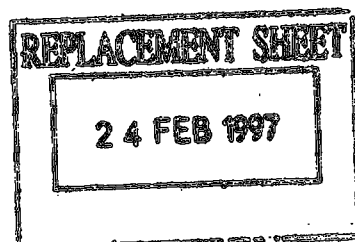
Analysis: Calculated for $C_{17}H_{16}BrNO_3$: C, 56.37; H, 4.45; N, 3.87. Found: C, 56.22; H 4.42; N, 3.87.

Preparation XV**2-Amino-3-(4-bromobenzoyl)-phenylacetamide, Compound 15**

Ammonia is condensed in a tube containing 2-amino-3-(4-bromobenzoyl)benzeneacetic acid, ethyl ester. The tube is sealed and the reaction mixture is warmed. The sealed tube was cooled and opened. Solvent was evaporated and the residue was purified by standard methods to give Compound 15.

Preparation XVI**2-Amino-3-(4-bromobenzoyl)-N-methyl phenylacetamide, Compound 16**

In the same manner as Preparation XV, 2-amino-3-(4-bromobenzoyl)-N-methyl phenylacetamide, Compound 16 is prepared from 2-amino-3-(4-bromobenzoyl)benzeneacetic acid, ethyl ester and methylamine.



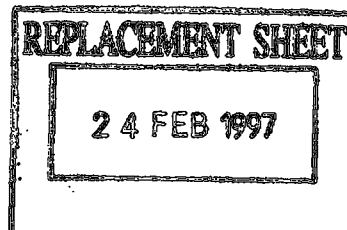
Anti-Inflammatory Tests

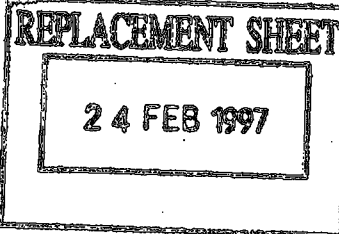
I. in vitro Anti-Inflammatory Test

In vitro anti-inflammatory activity of 2-amino-3-benzoylbenzeneacetic acid analogues was tested by polarographically monitoring the inhibition in the rate of oxygen consumption (Cook HW., Ford G., and Lands WEM, Anal. Biochem. 96:341, 1979) in the conversion of arachidonic acid to prostaglandin H₂ by prostaglandin H synthase (cyclooxygenase). Cyclooxygenase enzyme was prepared by solubilizing 20 mg of lipid-depleted sheep vesicular gland microsomal powder (Graff G, Stephenson JH, et al., J. Biol. Chem. 253:7662, 1978) in 1.0 mL of buffer containing 50 mM phosphate, 5 mM diethyldithiocarbamic acid, and 2 μ M hematin (pH 7.4). Incubations were carried out at 30°C with a YSI-oxygen monitor (Model 53) in 50 mM phosphate/0.5 mM phenol buffer (pH 7.4) as described elsewhere (Graff G, and Anderson LA, Prostaglandins 38:473, 1989).

II. Ex Vivo Anti-Inflammatory Test

Ex vivo anti-inflammatory activity of 2-amino-3-benzoylbenzeneacetic acid analogues was evaluated in naive New Zealand Albino (NZA) rabbits. In this test animals were dosed bilaterally with a single 50 μ L aliquot of a 0.1 % solution/suspension of vehicle, formulated test or reference compound. After 60 minutes of treatment, animals were euthanized, iris/ciliary body (ICB) quickly excised and placed into ice-cold PBS buffer (pH 7.4). The tissue was then weighed, homogenized in ice-cold 50 mM phosphate/0.5 mM phenol buffer (pH 7.4) and incubated for 10 minutes at 37°C with 10 μ M of [1-¹⁴C]-20:4. Upon termination of the incubations, reaction products (prostaglandins) were isolated by organic solvent extraction (Bligh, E.G. and Dyer, W.J., Can. J. Biochem. Physiol. 37:911, 1959) and quantified by C₁₈-HPLC (Powell, W.S., Anal. Biochem. 148:59 1985).





III. In Vivo Anti-Inflammatory Test

In vivo anti-inflammatory activity of 2-amino-3-benzoylbenzeneacetic acid analogues was evaluated in the model of trauma-induced breakdown of the blood-aqueous-barrier in New Zealand Albino (NZA) rabbits. Animals were anesthetized prior to bilateral administration of a single topical 50 μ L dose of a 0.1 % solution/suspension of formulated test or reference compound. After 45 minutes of treatment ocular trauma was induced by paracentesis. Thirty minutes post-paracentesis animals were euthanized, and aqueous humor was removed for protein (Bradford MM, Anal. Biochem. 72:248, 1976) and PGE₂ analysis (Radio immune assay, NEN-Research Products, E.I. Du Pont de Nemours, Boston, MA).

Results

The results from in vitro, ex vivo and in vivo anti-inflammatory tests are summarized in Table 1. Non-halogenated and halogenated 2-amino-3-benzoylbenzeneacetic acid analogues with free carboxylic acid functional groups, including the reference compound diclofenac, were potent in vitro inhibitors of sheep vesicular gland cyclooxygenase activity with IC₅₀ values ranging from 0.029 to 0.250 μ M. When tested in vivo, they effectively inhibited trauma-induced accumulation of PGE₂ ($\geq$ 98 %) and plasma protein influx into the aqueous humor in vivo. Similar results were obtained with the reference compound, diclofenac, which was somewhat less effective both in vitro and in vivo than the chloro- or bromo- substituted 2-amino-3-benzoylbenzeneacetic acids.

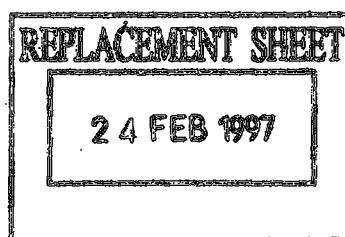
In contrast, unsubstituted and mono-substituted amide analogues of 2-amino-3-benzoylbenzeneacetic acid (Compounds 7, 8, 9, 15 and 16) were $\geq$ 3 orders of magnitude less effective inhibitors of cyclooxygenase activity in vitro with IC₅₀ values ranging from 16 to > 133 μ M. Despite their weak inhibitory effects on cyclooxygenase activity in vitro, they were as effective as, or in one instance (Compound 7) more effective than, free carboxylic acid analogues in inhibiting plasma protein influx into the anterior chamber (62 to 72 %) and aqueous humor PGE₂

accumulation (>93 %). Interestingly, the dimethyl substituted amide analog was inactive in both in vitro and in vivo tests.

Although the in vitro potency was clearly enhanced by halogenation of the 4-position of the benzoyl ring of 2-amino-3-benzoylbenzeneacetic acid, there was little evidence for such a structure related effect in vivo.

When tested for ex vivo anti-inflammatory activity, Compound 8 was the most effective inhibitor of iris/ciliary body prostaglandin synthesis. The synthesis of all prostaglandins produced by the iris/ciliary body was inhibited to a similar extent. This spectrum of inhibition is in contrast to the effects of 2-amino-3-benzoylbenzeneacetic acid analogs with free carboxylic acid functional groups which predominately inhibited PGE₂ production.

Conversion of the free carboxylic acid functional group of Bromfenac to an ethyl ester (Compound 14) also resulted in a >3 orders of magnitude decline in in vitro cyclooxygenase inhibitory activity. However, when tested for topical ocular anti-inflammatory activity the ethyl ester showed significant inhibitory activity by reducing plasma protein extravasation into the aqueous humor by 60 %.



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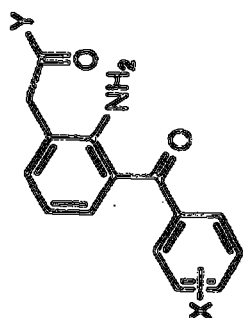


TABLE 1

SUMMARY OF ANTI-INFLAMMATORY TEST RESULTS

Compound	Substituent X	Y	In Vitro Cyclooxygenase Inhibition IC ₅₀ (uM)	Ex Vivo Iris/Ciliary Body Total Prostaglandin Synthesis Inhibition (%)***	In Vivo Aqueous Humor PGE ₂ Accumulation Inhibition (%)*	In Vivo Paracetesis Protein Extravasation Inhibition (%)*
Diclofenac**	-	-	0.120	50	97	54
Amfenac	4'-H	OH	0.25	-	-	41
-	4'-F	OH	0.171	-	-	42
-	4'-Cl	OH	0.070	-	99	72
Bromfenac	4'-Br	OH	0.029	44	98	62
# 15	4'-Br	NH ₂	19	-	97	64
# 16	4'-Br	NHCH ₃	16	48	93	62
-	4'-Br	N(CH ₃) ₂	>>100	-	-27	2
# 8	H	NH ₂	64	61	98	61
# 7	4'-F	NH ₂	133	27	98	72
# 9	4'-Cl	NH ₂	>>100	29	96	65
# 16	4'-Br	NH ₂	19	23	97	64
# 14	4'-Br	OCH ₂ CH ₃	>>25	33	-	60

* Single topical dose of 0.1 % drug solution/suspension 45 minutes prior to paracetesis

**Diclofenac, also known as Voltaren Ophthalmic (TM), is used as a reference standard

*** Single topical dose of 0.1 % drug solution/suspension 60 minutes prior to iris/ciliary body isolation

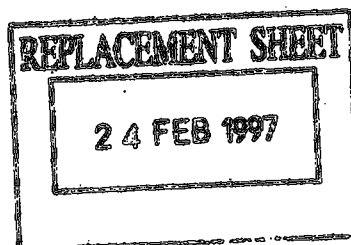
The 3-benzoylphenylacetic acid derivative compounds of this invention are useful for controlling ophthalmic inflammatory disorders and ocular pain. Such disorders include, but are not limited to uveitis, scleritis, episcleritis, keratitis, surgically-induced inflammation and endophthalmitis.

5 The 3-benzoylphenylacetic acid derivatives may be formulated into a variety of topically administrable ophthalmic compositions, such as solutions, suspensions, gels or ointment.

Pharmaceutical compositions comprising compounds of Formula I in aqueous solution, optionally containing a preservative for multidose use and other
10 conventionally employed ophthalmic adjuvants, including a salt entity to adjust the tonicity of solutions, can be employed. The most preferred form of delivery is by eye drops; however, formulations wherein the final specialty form is a gel or ointment can also be employed and formulated according to conventional technology. The ophthalmic compositions of the present invention will typically contain one or more
15 compounds 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).

Further, additional therapeutic agents including steroids, such as, dexamethasone; antibiotics, such as gentamicin; anti-infectives, such as sulfonamides; and anti-allergics, such as antihistamines, may be added to supplement the
20 ophthalmic compositions of the present invention.

The compositions may contain preservatives such as thimerosal, chlorobutanol, benzalkonium chloride, Onamer M, or chlorhexidine; buffering agents, such as phosphates, borates, carbonates and citrates; and thickening agents, such as, high molecular weight carboxy vinyl polymers, such as, the ones sold under the name of
25 Carbopol which is a trademark of the B.F. Goodrich Chemical Company, hydroxyethylcellulose, or polyvinyl alcohol, for example.

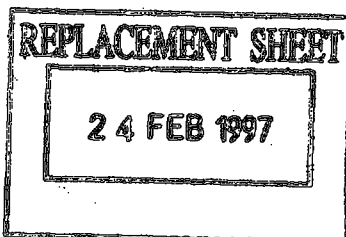


The compositions are prepared by dissolving the various ingredients in the required amount of water with stirring to ensure that all the ingredients are dissolved. The aqueous compositions of the invention may be solutions, suspensions, or gels. After preparation of the solution, suspension, or gel the compositions are then packaged in dispensers suitable for delivery of the ophthalmic compositions.

The following examples of ophthalmic compositions typify the manner in which the invention may be practiced. The examples should be construed as illustrative, and not as a limitation upon the overall scope of the invention. The percentages are expressed on a weight/volume basis. "Active Agent" means one or more compounds of Formula I.

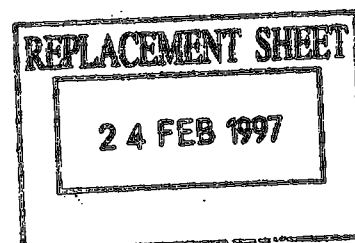
Formulation 1

Active agent	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%



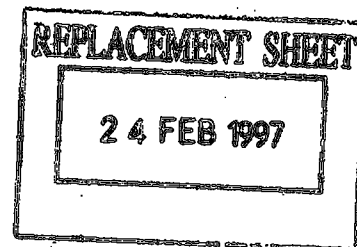
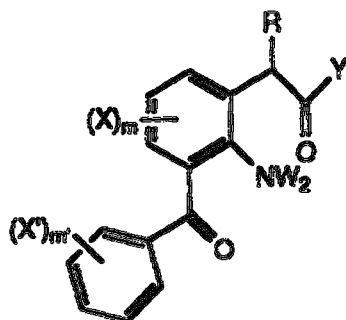
Formulation 2

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



THIS SHEET HAS BEEN
REPLACEDWe claim:

1. A topically administrable, ophthalmic pharmaceutical composition for treating ophthalmic inflammatory disorders and ocular pain which comprises a tonicity-adjusting agent and an anti-inflammatory-effective amount of a 3-benzoylphenylacetic acid derivative of the formula:



$R = H, C_{1-4}$ (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), $-(CH_2)_nZ(CH_2)_nA$

$n = 2-6$

$n' = 1-6$

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

$n^2 = 0-2$

$R^3 = H, C_{1-6}$ (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), $-(CH_2)_nOR^3$

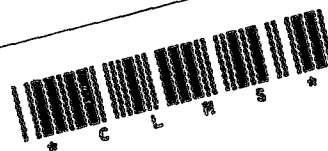
$R'' = H, OH, OR'$

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

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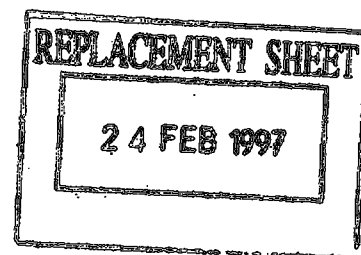
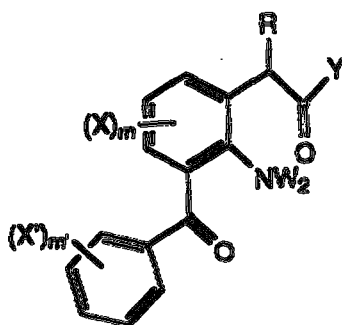


$m = 0-3$

$m' = 0-5$

$W = O, H$

2. The composition of Claim 1 wherein the 3-benzoylphenylacetic acid derivative is of the formula:



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

$Y = NR'R''$

$R' = H, C_{1-6}$ (un)branched alkyl, $-(CH_2)_nZ(CH_2)_nA$

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

$R_3 = H$

$A = H, OH, (un)substituted$ aryl (substitution as defined by X below)

X and X' independently = H, F, Cl, Br, CN, CF₃, OR', SR⁴, R⁴

$R'' = H$

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

$m = 0-2$

$m' = 0-2$

$W = H$

$n = 2-4$

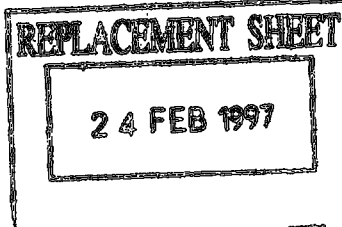
$n' = 0-3$

3. The composition of Claim 1 wherein the 3-benzoylphenylacetic acid derivative is selected from the group consisting of 2-Amino-3-(4-fluorobenzoyl)- α -(n-



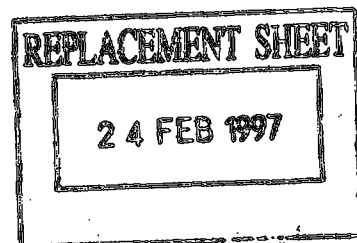
propylthio)-phenylacetamide, 2-Amino-3-benzoyl- α -(n-propylthio)-phenylacetamide, 2-Amino-3-(4-chlorobenzoyl)- α -(n-propylthio)-phenylacetamide, 2-Amino-3-benzoyl-5-chloro- α -(methylthio)-phenylacetamide, 2-Amino-3-(4-fluorobenzoyl)- α -(methylthio)-N-(2-methoxy)ethylacetamide, 2-Amino-3-(4-fluorobenzoyl)- α -(methylthio)-N-3-(3,4-dimethoxyphenyl)propylacetamide, 2-Amino-3-(4-fluorobenzoyl)-phenylacetamide, 2-Amino-3-benzoyl-phenylacetamide, 2-Amino-3-(4-chlorobenzoyl)-phenylacetamide, 2-Amino-3-benzoyl-5-chlorophenylacetamide, 2-Amino-3-(4-fluorobenzoyl)-N-(2-methoxy)ethylphenylacetamide, 2-Amino-3-(4-fluorobenzoyl)-N-3-(3,4-dimethoxyphenyl)propyl phenylacetamide, 3-Benzoyl-2-nitrophenyl-N-3-(3,4-dimethoxyphenyl)propyl acetamide, Ethyl 2-Amino-3-(4-bromobenzoyl)benzene acetate, 2-Amino-3-(4-bromobenzoyl)-phenylacetamide, and 2-Amino-3-(4-bromobenzoyl)-N-methyl phenylacetamide.

4. The composition of Claim 3 wherein the 3-benzoylphenylacetic acid derivative is selected from the group consisting of 2-Amino-3-(4-fluorobenzoyl)- α -(n-propylthio)-phenylacetamide, 2-Amino-3-(4-chlorobenzoyl)- α -(n-propylthio)-phenylacetamide, 2-Amino-3-(4-chlorobenzoyl)- α -(n-propylthio)-phenylacetamide, 2-Amino-3-benzoyl-5-chloro- α -(methylthio)-phenylacetamide, 2-Amino-3-(4-fluorobenzoyl)-phenylacetamide, 2-Amino-3-benzoyl-phenylacetamide, 2-Amino-3-(4-chlorobenzoyl)-phenylacetamide, 2-Amino-3-benzoyl-5-chlorophenylacetamide, and 2-Amino-3-(4-bromobenzoyl)-phenylacetamide.
5. The composition of Claim 4 wherein the 3-benzoylphenylacetic acid 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.
6. The composition of Claim 1 wherein the amount of 3-benzoylphenylacetic acid is from about 0.001 to about 4.0% (w/v).





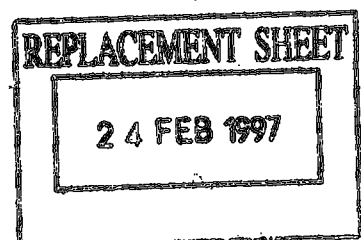
7. The composition of Claim 6 wherein the amount of 3-benzoylphenylacetic acid is from about 0.01 to about 0.5% (w/v).
8. Use of a composition according to any one of Claims 1 - 7 for the manufacture of a medicament for the treatment of ophthalmic inflammatory disorders and ocular pain.

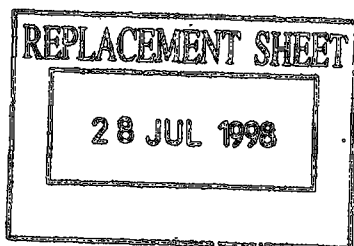


TOPICALLY ADMINISTRABLE COMPOSITIONS CONTAINING
3-BENZOYLPHENYLACETIC ACID DERIVATIVES FOR TREATMENT
OF OPHTHALMIC INFLAMMATORY DISORDERS

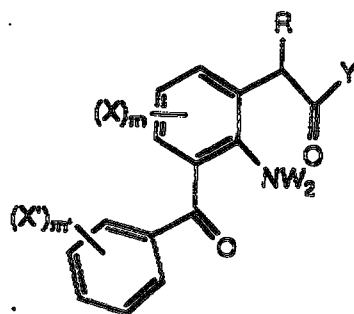
ABSTRACT

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.

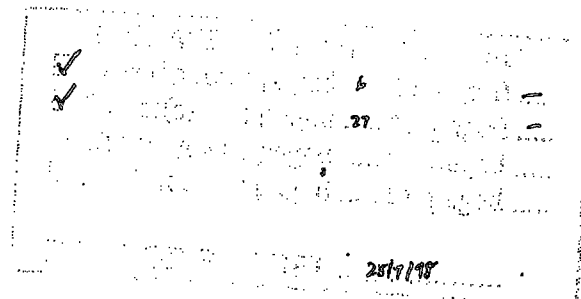




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(1)



$R = H, C_{1-4}$ (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 aryl (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below), $-(CH_2)_nZ(CH_2)_nA$

$n = 2-6$

$n' = 1-6$

$Z =$ 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

$m = 0-3$

$m' = 0-5$

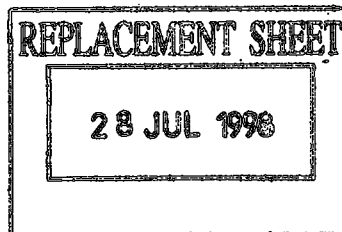
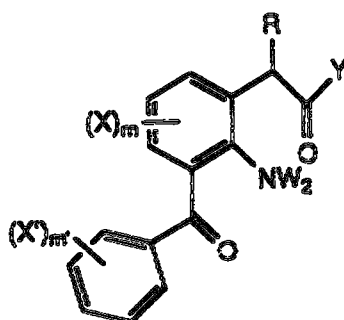
$W = O, H$

Preferred compounds for use in the pharmaceutical compositions or method of the present invention are those of Formula 1 wherein:

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

We claim:

1. A topically administrable, ophthalmic pharmaceutical composition for treating ophthalmic inflammatory disorders and ocular pain which comprises a tonicity-adjusting agent and an anti-inflammatory-effective amount of a 3-benzoylphenylacetic acid derivative of the formula:



$R = H, C_{1-4}$ (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 aryl (substitution as defined by X below), (un)substituted heterocycle (substitution as defined by X below), $-(CH_2)_nZ(CH_2)_nA$

$n = 2-6$

$n' = 1-6$

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

$n^2 = 0-2$

$R^3 = H, C_{1-6}$ (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

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

PCT

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(74) Agents: RYAN, Patrick, M. et al.; Alcon Laboratories, Inc., Patent Dept. Q-148, 6201 South Freeway, Fort Worth, TX 76134 (US).			
(54) Title: TOPICALLY ADMINISTRABLE COMPOSITIONS CONTAINING 3-BENZOYLPHENYLACETIC ACID DERIVATIVES FOR TREATMENT OF OPHTHALMIC INFLAMMATORY DISORDERS			
(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.			

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