MICROCOPY RESOLUTION TEST CHART
NATIONAL BUREAU OF STANDARDS - 1983 - 4
Convention Application for a Patent

We hereby apply for the grant of a Patent for an invention entitled

"N-(TETRAZOL-5-YL) PROSTAGLANDIN CARBOXAMIDES"

which is described in the accompanying complete specification.

This application is a Convention Application and is based on the applications numbered 869,569 & 893,731

for a patent or similar protection made in the United States of America

on January 16, 1978 & April 5, 1978, respectively

Our address for service is:

Care: SPRUSON & FERGUSON
PATENT ATTORNEYS
ESSO HOUSE, 127 KENT STREET
SYDNEY. NEW SOUTH WALES.
AUSTRALIA.

Dated this 31st day of October 1978

The Common Seal of
PFIZER INC.
was hereto affixed in the presence of:-

[Signature of Applicant]

To:
The Commissioner of Patents
DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT OR PATENT OF ADDITION

In support of the Convention Application made for a patent for an invention entitled

43359/79

"N-(TETRAZOL-5-YL) PROSTAGLANDIN CARBOXAMIDES"

I. William Gestal McCreery
of 4 School Lane
Scarsdale, N.Y. 10583
U.S.A.
do solemnly and sincerely declare as follows:

1. (or in the case of an application by a body corporate)
1. I am authorised by

the applicant for the purposes of this application to make this declaration on its behalf.

2. The basic applications as defined by Section 141 of the Act were made in the United States of America and on the

16th day of January 1975 and on the 5th day of April 1978 both by

Thomas Ken Schaaf,
35 Colt Lane, Old Lyme, New London County, State of Connecticut, United States of America

3. Thomas Ken Schaaf, 35 Colt Lane, Old Lyme, New London County, State of Connecticut, United States of America

is the actual inventor of the invention and the facts upon which the applicant is entitled to make the application are as follows:

The Applicant Company is the assignee of the said invention from the actual inventor.

4. The basic applications referred to in paragraph 2 of this Declaration were the first applications made in a Convention country in respect of the invention the subject of the application.

Declared at New York, N.Y. this 13 day of November 1978

Signature of Declarant:

To:
The Commissioner of Patents,

SPRUSON & FERGUSON, SYDNEY.
The compounds have anti-ulcer, fertility control and bronchodilator properties.

CLAIM

1. A compound of the formula

```
O

H H H H

C-A-C-C-C-CONH-H H H H

Y...

B-C-C-G : H

HO
```

or a pharmacologically acceptable salt thereof, wherein:

- A is ethylene or cis-vinylene;
- B is ethylene or trans-vinylene;
- Y is hydrogen or hydroxy;
- G is CH₂Ar, CH₂OAr or CR₂(CH₂)₃CH₃;
- Ar is phenyl, fluorophenyl, chlorophenyl, methylphenyl, ethylphenyl, methoxyphenyl, ethoxyphenyl, biphenyl or trifluoromethylphenyl;
- R is hydrogen or methyl; and
- Z is hydrogen or methyl.
The following statement is a full description of this invention, including the best method of performing it known to us:

"N-(TETRAZOL-5-YL) PROSTAGLANDIN CARBOXAMIDES"
N-(Tetrazol-5-yl) Prostaglandin Carboxamides

Abstract

Three classes of N-(tetrazol-5-yl) prostaglandin carboxamides having the bottom side chain substitutions of C-16 phenyl or substituted phenyl (Class 1), C-16 phenoxy or substituted phenoxy (Class 2) and C-15 n-pentyl, 2-hexyl or 2-methyl-2-hexyl (Class 3) have been synthesized using the corresponding acyl imidazole intermediates and 5-amino tetrazole. The three classes of prostaglandins have different and selective biological activities which are antiulcer (Class 1), fertility control (Class 2) and bronchodilator or fertility control (Class 3).
N-(Tetrazol-5-yl) Prostaglandin Carboxamides

The prostaglandins are C-20 unsaturated fatty acids which exhibit diverse physiological effects. Their structure, nomenclature, biological activities and medicinal use have been described in U.S. 3,971,825 and U.S. 3,984,400.

A common problem confronting medical scientists who attempt to make biologically efficacious, synthetic drugs is the modulation of the biological action of an appropriate lead compound. In a traditional approach to drug synthesis the researcher will look for an increase in biological potency. The prostaglandin researcher however frames his design around increased oral activity, increased duration of action and enhancement of one of the diverse physiological effects of the prostaglandin class and diminution of the others. This latter criterion is important because without it a synthetic prostaglandin would exhibit incompatible side effects. For example it would be clinically inadvisable to administer an antiulcer synthetic prostaglandin that also causes diarrhea.

To achieve increased selectivity, researchers have concentrated their efforts on the "active" sites of the natural prostaglandins. In the main, these include the C-1 carboxylic acid group, the C-9 ketone or hydroxyl group, the C-11 hydroxyl group and the lipophilic end of the bottom side chain. Such work is publicized in the following articles and patents: U.S. 4,011,262, U.S.
It has now been surprisingly discovered that an increase in the distance between the C-9 functionality and the top side chain acidic group by juncture of an amide group results in potent biological activity.

Three classes of C-1 amidotetrazole prostaglandins have been invented which have distinctly different profiles of biological activity. Class 1 includes compounds of formula 1, which have antiulcer activity.

Class 2 includes compounds of formula 2, which have fertility control activity.

Class 3 includes compounds of formula 3, which have bronchodilator or fertility control activity depending on the identity of R and Z.
It is apparent that the structural differentiation of the classes is found in the identity of the omega or bottom side chain. However, it is the combination of this functional group with the other important ones such as the amidotetrazole group that causes the different biological activities observed. Nevertheless, these three classes may be structurally combined into one generic formula (4).

In each of the above formulas, the symbol A represents cis-vinylene or ethylene, the symbol B represents trans-vinylene or ethylene, the symbol Y represents hydroxy or hydrogen, the symbol R represents hydrogen or methyl, the symbol Z represents hydrogen or methyl, the symbol Ar represents phenyl, fluorophenyl, chlorophenyl, methylphenyl, ethylphenyl, methoxyphenyl, ethoxyphenyl, biphenyl or trifluoromethylphenyl and the symbol G represents CH₂Ar, CH₂OAr or CR₂(CH₂)₃CH₃.
Especially preferred compounds are as follows:

Class 1, N-(tetrazol-5-yl) 9-oxo-11-alpha, 15-alpha-bishydroxy-16-phenyl-16-omega-tetranor-5-cis-prostenamide;

In addition there is contemplated the PGF type compounds corresponding to the three classes above and the pharmacologically acceptable salts, the acidic tetrazole moiety being neutralized.

According to the process of the invention, each class of N-(tetrazole) prostaglandin carboxamides is synthesized from a similar class of 11,15-bis(hydroxyl protected) or 11-desoxy-15-(hydroxyl protected) PGF compounds. This generic starting material has the same basic structure for all the classes and includes any arrangement of bond type at the C5-C6 and C13-C14 positions which relate to the elements A and B of formulae 1, 2 and 3. In other words, it is the (11),15-hydroxyl protected PGF compound corresponding to the Generic Formula (4) above. Differentiation of the basic structure according to class is determined by the identity of the terminus of the bottom side chain of the respective starting materials. Thus the starting material for class 1 has the substitution 16-aryl-16-omega-tetranor on the above basic PGF structure; the starting material for class 2 has the substitution 16-aryloxy-16-omega-tetranor; and the starting material for class 3 has the 15-n-pentyl, 2-hexyl or 2-methyl-2-hexyl substitution on the bottom side chain of the above basic PGF structure. These structures are shown on Chart 1 and are F1, F2 and F3 respectively.

The starting material PGF compounds for each of the classes are known; the characteristics of the 11-hydroxy starting materials are reported in U.S.
The conversion of starting materials into the classes of products of the invention is illustrated by Scheme A. To transform a starting material into a member of a class of compounds of the invention, the C-1 carboxylic acid group is first converted into a C-1 N-(tetrazol-5-yl) carboxamide group (step 1, Scheme A). Then this N-(tetrazole) carboxamide PGF intermediate is oxidized with Jones reagent to make the corresponding PGE intermediate which is deprotected by removing the 15-mono or 11,15-bis hydroxyl protecting (R') groups (step 2.1, Scheme A) to make an N-(tetrazole) carboxamide prostaglandin of formula 1,2 or 3. Alternatively a PGF type of compound corresponding to PGE compound of formula 1,2 or 3 may be prepared by simple cleavage of the C-11 and/or C-15 hydroxyl (R') protecting groups of the N-(tetrazole) carboxamide intermediate.

Chart 1
STARTING MATERIALS FOR THE VARIOUS CLASSES

Fl, starting material for class 1, X is -COOH
F2, starting material for class 2, X is -COOH

F3, starting material for class 3, X is -COOH

Scheme A

Step 1. formation of the N-(tetrazol-5-yl)carboxamide group

1. CDI reagent

2. anhydrous 5-AT reagent
Step 2.1. oxidation with Jones reagent and THP cleavage

\[
\begin{align*}
1. & \quad \text{Oxidation with Jones reagent:} & & \\
& \quad \text{CrO}_3 & & \\
& \quad \text{H}_2\text{SO}_4 & & \\
\text{F1, F2 or F3, } X = -CONHC & & 1, 2, 3
\end{align*}
\]

1. Formula 1, starting material is F1
2. Formula 2, starting material is F2
3. Formula 3, starting material is F3

Step 2.2 cleavage of the THP protecting group to make PGF type compounds

\[
\begin{align*}
& \quad \text{Cleavage of the THP protecting group:} & & \\
& \quad \text{CH}_3\text{COOH} & & \\
& \quad \text{H}_2\text{O} & & \\
\text{F1, F2 or F3, } X = CONHC & & 1, 2, 3
\end{align*}
\]

1. PGF compound corresponding to Formula 1, starting material is F1
2. PGF compound corresponding to Formula 2, starting material is F2
3. PGF compound corresponding to Formula 3, starting material is F3

Reaction Steps 2.1 and 2.2 which embrace cleavage of the C-11 and/or C-15 hydroxyl protecting groups and oxidation of the C-9 hydroxyl to a C-9 oxo (ketone) group are common transformations and are well-known in the art of prostaglandin chemistry. Equivalent methods for C-9 hydroxyl oxidation and for C-11 and/or C-15 hydroxyl protection are also well-known in the art and are applicable here. Prostaglandin researchers have found that selective oxidation methods such as the Pfitzner-Moffett oxidation with dimethyl sulfoxide and dicyclohexylcarbodiimide and the Collins oxidation with chromium trioxide-pyridine complex in methylene chloride may also be used.
to perform the hydroxyl to ketone oxidation. They have also publicized the many methods and groups available for the protection/deprotection of the hydroxyl groups at positions C-11 and/or C-15 of a prostaglandin. Such mild agent labile protecting groups are indicated by $R'$. The tetrahydropyran-yl group is also shown as the preferred group. Some other common mild agent labile protecting groups having utility in the present invention are dimethyl-$t$-butyl silyl which may be removed with tetra-$n$-butyl ammonium fluoride or aqueous acetic acid and 1-methoxyethylen-1-yl which is analogous to tetrahydropyran-2-yl.

Step 1 is novel in that it allows the preparation of a C-1 amide having an acidic group as a substituent. The import of this construct is the fact that the prior art teaches the biologically critical invariance of the C-1 acidic group, C-9 functionality distance while the compounds of the present invention have in fact extended the distance by the length of two of the atoms of the amide group. The N-(tetrazol-5-yl)carboxamide group can be prepared from the carboxylic acid group by first forming a carboxylic acid derivative having an easily displacable leaving group and then performing the amidation with 5-amino tetrazole (5-AT reagent). Any leaving group which can be attached to the prostaglandin intermediate (F1, F2, F3 Chart 1) carboxyl group without destroying the rest of the molecule may be used in the preparation. Some typical leaving groups and the leaving group reagents used to make them include pivaloyloxy/pivaloyl halide which will make the mixed anhydride derivative and ethoxyformyloxy/ethoxyformyl halide which will make the carbonate derivative. The preferred leaving group is imidazol-1-yl which makes an acyl imidazole intermediate. To prepare the N-(tetrazol-5-yl) carboxamide group through the intermediacy of an acyl imidazole group, one first reacts
the prostaglandin carboxylic acid starting material (F1, F2 or F3) with the leaving group reagent 1,1-carbonyl diimidazole in a polar, aprotic solvent such as dimethylformamide, diethylformamide, acetonitrile, tetrahydrofuran or dimethyl sulfoxide to form in situ the acyl imidazole intermediate. The imidazol-1-yl group attached to the C-1 carbonyl is then directly displaced with 5-AT reagent to form the desired N-(tetrazol-5-yl) carboxamide.

A range of reaction temperatures may be employed to both form and displace the acyl imidazole. This range runs from ambient temperature to about 120°C and it is convenient to conduct the reaction at about 90°C or reflux.

After forming the N-(tetrazol-5-yl) carboxamide group, reaction step 2.1 is performed by which a compound of Formula 1, 2 or 3 is prepared or reaction step 2.2 is performed by which a PGF type of compound is prepared.

Alternatively according to the process of the invention, the N-(tetrazole) prostaglandins of each class may be synthesized directly from a corresponding PGE or PGF compound of the formula

```
\[
\begin{align*}
\text{M} & \quad \text{H} \quad \text{H} \quad \text{H} \\
\text{C-A-C-C-C-COOH} & \quad \text{H} \quad \text{H} \quad \text{H} \\
\text{Y...} & \quad \text{B-C-G} \\
\text{HO} &
\end{align*}
\]
```

wherein A, Y, B and G are as defined above and M is oxo or H/"OH. In this route, the PGE or PGF acid is reacted using the method of formation of the N-(tetrazol-5-yl) carboxamide group given in Step 1 above to directly produce an N-(tetrazole)prostaglandin carboxamide of Formula 1,2,3 above or the corresponding PGF carboxamide. The procedure followed is that of Step 1
provided that if M is to be oxo, no basic reagent is used.

In numerous in vivo and in vitro tests, it has been established that the three classes of prostaglandin compounds of the present invention exhibit extreme selectivity. Their biological achievement is the diminution of many of the physiological activities of the natural prostaglandins while maintaining activity in one area. The tests which allow such determination of selectivity include among others, a test for effect on isolated smooth muscle from guinea pig uterus, effect on dog blood pressure, inhibition of histamine induced broncho-constriction in the guinea pig, inhibition of cold, stress-induced ulceration in the rat, antisecretory activity in the dog and diarrheal effect in the mouse.

After comparison to the responses caused by natural prostaglandin in the same tests, the physiological responses caused by the three classes experimental prostaglandins in these tests are helpful in determining their usefulness for the treatment of natural and pathological malconditions. Based upon such comparison, the prostaglandins of Class 1 of the invention have utility as selective antiulcer agents, those of Class 2 have utility as fertility control agents, those of Class 3 wherein R is methyl or hydrogen and Z is hydrogen have utility as bronchodilator agents and those of Class 3 wherein both R and Z are methyl have utility as fertility control agents. Biological test observations for the prostaglandins of Class 1 show that they have potent antiulcer activity while having diminished hypotensive, uterine smooth muscle, diarrheal and bronchodilator activities compared to the test standard natural prostaglandin, PGE₂. The same type of observations show that the prostaglandins of Class 3 having R as methyl or hydrogen and Z as hydrogen exhibit potent
bronchodilator activity and diminished uterine smooth muscle, hypotensive, antiulcer and diarrheal activities. Likewise the prostaglandins of Class 2 exhibit potent uterine smooth muscle activity and diminution of such determined activities as hypotensive activity, diarrheal activity and bronchodilator activity.

The 3 classes of prostaglandins of this invention can be used in a variety of pharmaceutical formulations which contain the prostaglandin, or its pharmaceutically acceptable salts. They may be administered in the same manner as natural prostaglandins by a variety of appropriate routes, such as intravenous, oral and topical including aerosol, intravaginal, intra- and extra-amniotic and intranasal among others. Obviously the selective activity of the particular class of prostaglandins of the invention and their intended use will determine the route to be used. For instance the appropriate routes for the Class 2 prostaglandins are intravenous, oral, intravaginal and intra- and extra-amniotic while the appropriate routes for the Class 3 bronchodilator prostaglandins are aerosol, intranasal, oral and intravenous.

For pharmaceutical formulation and for solid compounding of the 3 classes of prostaglandins the useful, pharmacologically acceptable salts of the acidic tetrazole moiety are those with pharmacologically acceptable metal cations, amine cations, or quaternary ammonium cations.

Especially preferred metal cations are those derived from the alkali metal, e.g., lithium, sodium and potassium, and from the alkaline earth metal, e.g., magnesium and calcium, although cationic forms of other metals, e.g., aluminum, zinc, and iron, are within the scope of this invention.

Pharmacologically acceptable amine cations are those derived from primary, secondary, or tertiary
amines. Examples of suitable amines are methylamine, dimethylamine, triethylamine, ethylamine, benzylamine, alpha-phenylethylamine, beta-phenylethylamine, as well as heterocyclic amines, e.g., piperidine, morpholine, pyrrolidine, and piperazine as well as amines containing water-solubilizing or hydrophilic groups, e.g., mono-, di-, and triethanolamine, ethyldiethanolamine, galactamine, N-methylglucosamine, ephedrine, phenylephrine, epinephrine, procaine, and the like.

Examples of suitable pharmacologically acceptable quaternary ammonium cations are tetramethylammonium, tetraethylammonium, benzyltrimethylammonium, phenyltriethylammonium and the like.

The 3 classes of prostaglandins of this invention can be used in a variety of pharmaceutical preparations which contain the compound or a pharmacologically acceptable salt thereof, and they may be administered by several routes as described above. Although the particular dose, formulation and route of administration are dependent upon each patient's unique condition and the wisdom of his attending physician, the guidelines set forth infra for the classes of prostaglandins of the present invention describe the usefulness of Class 1 as antiulcer agents, of Class 2 as fertility control agents, of Class 3 wherein \( R \) is hydrogen or methyl and \( Z \) is hydrogen as bronchodilator agents, and of Class 3 wherein both \( R \) and \( Z \) are methyl as fertility control agents.

The prostaglandins of Class 1 are useful as antiulcer agents. For treatment of peptic ulcers, these drugs are appropriately administered orally in the form of aqueous suspensions, ethanolic solutions or preferably in the form of capsules or tablets containing 0.001 to 0.10 mg/kg of prostaglandin per dose with up to 12 doses per day.
For induction of abortion, the prostaglandins of Class 2 and of Class 3 wherein both R and Z are methyl may be orally administered in appropriately formulated tablets, aqueous suspensions or alcoholic solutions containing about 0.05-5 mg, of prostaglandin per dose with 1-7 doses per day being employed. For intravaginal administration a suitable formulation would be lactose tablets or an impregnated tampon containing about 0.1-10 mg of prostaglandin per dose with 1-7 doses being employed. For intra-amniotic administration a suitable formulation would be an aqueous solution containing the prostaglandin at 0.05-5 mg/dose with 1-7 doses being employed. For extra-amniotic administration a suitable formulation would be an aqueous solution containing the prostaglandin at 0.01-1 mg/dose with 1-5 doses being employed. Alternatively, the prostaglandins of Class 2 and of Class 3 wherein both R and Z are methyl can be infused intravenously for induction of abortion at doses of 0.05-50 microgram of prostaglandin per minute for a period of from about 1-24 hours.

Another use for the prostaglandins of Class 2 and of Class 3 wherein both R and Z are methyl is an inducer of labor. For this purpose an ethanol-caline solution of the prostaglandins is employed for an intravenous infusion in the amount of from about 0.1-10 microgram/kg/min of prostaglandin for about 1-24 hours.

Another use for the prostaglandins of Class 2 and of Class 3 wherein both R and Z are methyl is fertility control. For this purpose a tablet is employed for intravaginal or oral administration containing 0.1-10 mg of prostaglandin per dose with 1-7 doses being employed at or following the expected day of menstruation. For synchronization of the estrous cycle in pigs, sheep, cows or horses, a solution or suspension containing 0.3-30 mg/dose of the prostaglandin administered subcutaneously or intramuscularly from 1-4 days.
The prostaglandins of Class 3 wherein R is hydrogen or methyl and Z is hydrogen are useful as bronchodilator agents and to increase nasal patency or accessibility. An appropriate dosage form for this treatment is solution of the prostaglandin in aqueous ethanol or t-butanol or a suspension thereof employed as an aerosol using an inert gas as a propellant wherein the amount of prostaglandin contained is about 5 to 500 microgram per dose.

To prepare any of the above dosage forms or any of the numerous other forms possible, various reaction-inert diluents, excipients or carriers may be employed. Such substances include, for example, water, ethanol, gelatins, lactose, starches, magnesium stearate, talc, vegetable oils, benzyl alcohols, gums, polyalkylene glycols, petroleum jelly, cholesterol and other known carriers for medicaments. If desired, these pharmaceutical compositions may contain auxiliary substances such as preserving agents, wetting agents, stabilizing agents, or other therapeutic agents such as antibiotics.

The following examples are merely illustrative, and in no way limit the scope of the appended claims. The IR spectral data were obtained on a Perkin-Elmer Grating Infrared Spectrometer and are given in microns. The NMR spectral data were obtained on a Varian HA-60 spectrometer and are delta ppm. Melting points are uncorrected and are in °Centigrade. TLC measurements were obtained on silica gel and are recorded as Rf values.

In general, the temperatures of the reactions described in the examples, when unspecified, will be taken to mean ambient or room temperature which varies from 15° to 30°C.

The time requirements of the reactions described in the examples, unless otherwise stated, were determined by monitoring with thin layer chromatography (TLC). The usual TLC system was silica gel on glass (E. Merck-Silica Gel plates, E. Merck, Darmstadt, W. German) with
benzene/ether or methanol/chloroform as diluents and vanillin/ethanol or iodine as developers. ["Introduction to Chromatography" J. M. Bobbitt, A. F. Schwarting, R.J. Gritter, Van Nostrand-Renhold, N.Y. 1968]. As a general rule, the reaction in question was deemed essentially complete when the TLC spot representing the critical starting material disappeared or quit changing appearance. 

Example 1

N-(Tetrazol-5-yl) 9-alpha-hydroxy-11-alpha, 15-alpha-bis-(tetrahydropyran-2-yloxy)-5-cis-13-trans-prostadienamide (1)

To a solution of 415 mg (0.795 mmole) of 9-alpha-hydroxy-11-alpha, 15-alpha-bis-(tetrahydropyran-2-yloxy)-5-cis-13-trans-prostadienoic acid (SM) in 10 ml of dry dimethylformamide was added 134 mg (0.825 mmole) of 1,1-carbonyldimidazole. The solution was heated under nitrogen at 95° for 4 hours, then 70 mg (0.825 mole) of anhydrous 5-amino-tetrazole was added. The solution was heated under nitrogen for 1.5 hours at 95° then concentrated by rotary evaporation to provide the crude title compound (1) as a viscous oil weighing 823 mg. Its NMR spectrum (CDCl₃) exhibited the following characteristic absorptions (in delta ppm):

5.65 - 5.24 (multiplet) - olefinic

4.81 - 4.62 (multiplet) - CH_O

1.92 (triplet, j = 4 cps) - CH₃

Example 2

N-(Tetrazol-5-yl) 9-alpha,11-alpha,15-alpha-trihydroxy-5-cis-13-trans-prostadienamide (2)

A solution of 200 mg of crude N-(tetrazol-5-yl) 9-alpha-hydroxy-11-alpha,15-alpha-bis-(tetrahydropyran-2-yloxy)-5-cis-13-trans-prostadienamide (1) in 10 ml of a 63-35 mixture of acetic acid:water was stirred at room
temperature for 18 hours under nitrogen; then was concentrated by rotary evaporation. Benzene was added and removed by rotary evaporation (3X). Purification of the crude residue by silica gel column chromatography using mixture of chloroform-ethyl acetate as eluents provided the title compound (2) weighing 6 mg and melting at 168-172° (after recrystallization from ethanol-ether).

TLC Rf was 0.26 (3:2, chloroform:methanol)

Example 3

N-(Tetrazol-5-yl) 9-oxo-11-alpha,15-alpha-bis-(tetrahydropyran-2-yloxy)-5-cis-13-trans-prostaglandinamide (3)

To a solution, cooled to -20°, of 623 mg (1.06 mmols) of N-(tetrazol-5-yl) 9-alpha-hydroxy-11-alpha, 15-alpha-bis-(tetrahydropyran-2-yloxy)-5-cis-13-trans-prostaglandinamide (1) in 15 ml of acetone was added 0.38 ml of Jones reagent. The mixture was stirred for 20 minutes then quenched in the cold by 0.38 ml of isopropyl alcohol. The mixture was stirred for 5 minutes then diluted with ethyl acetate (25 ml), washed with water (3 X 5 ml) and saturated brine (5 ml), dried (magnesium sulfate) and concentrated to provide the title compound (3) as a viscous oil weighing 295 mg.

TLC Rf was 0.48 (9:1, methylene chloride:methanol).

Example 4


A solution of 295 mg of crude N-(tetrazol-5-yl) 9-oxo-11-alpha,15-alpha-bis-(tetrahydropyran-2-yloxy)-5-cis-13-trans-prostaglandinamide (3) in 30 ml of a 65:35 mixture of acetic acid-water was stirred at room temperature under nitrogen for 18 hours. The solution was concentrated by rotary evaporation and benzene was added and concentrated (3X). Purification of the residue by
silica gel column chromatography using mixtures of chloroform - ethyl acetate as eluents provided the title compound (4) weighing 22 mg and melting at 162°. Its IR spectrum (KBr) exhibited the following characteristic absorptions (in microns):

- 5.71 (ketone)
- 5.87 (amide)
- 6.12
- 10.33 (trans olefin)

**Example 5**

The following additional compounds were prepared using the procedures described by Examples 1 through 4 and by substituting the appropriate starting material PGF carboxylic acid for compound (SM) in Example 1.

5A. **N-(tetrazol-5-yl) 9-oxo-11-alpha,15-alpha-dihydroxy-13-trans-prostenamide** m.p. - solid NMR (CD$_3$OD) (in delta ppm): 5.76 5.44 (multiplet) **trans-olefin**: 1.88 (triplet, $j = 4$ cps) CH$_3$

5B. **N-(Tetrazol-5-yl) 9-oxo-11-alpha,15-alpha-dihydroxy-5-cis-16-phenyl-16-omegatetranorprostenamide.** m.p. 75-78° NMR (CD$_3$OD) (in delta ppm): 7.08 (singlet) C$_6$H$_5$: 5.43-0.17(multiplet) **cis-olefin**.

5C. **N-(tetrazol-5-yl) 9-oxo-11-alpha,15-alpha-dihydroxy-13-trans-16-phenyl-16-omegatetranorprostenamide.** m.p. - 149-150° IR (KBr) (in microns): 5.67 (ketone), 5.83 and 6.10 (amide), 10.28 (**trans-olefin**).

5D. **N-(tetrazol-5-yl) 9-alpha,11-alpha,15-alpha-trihydroxy-5-cis-13-trans-16-phenoxy-16-omegatetranorprostadienamide.** m.p. - 87-90° IR (KBr) (in microns): 5.97 and 6.25 (amide), 10.35 (**trans-olefin**).

5E. **N-(tetrazol-5-yl) 9-oxo-11-alpha,15-alpha-dihydroxy-5-cis-13-trans-16-phenoxy-16-omegatetranorprostadienamide.** m.p. 105-107° IR (KBr) (in microns): 5.68 (ketone), 5.85 and 6.10 (amide), 10.28 (**trans-olefin**).
The synthesis of the compounds of Examples 1 through 5 demonstrates that the 11-hydroxy prostaglandins of classes 1, 2 and 3 of the invention and the corresponding DGF type compounds may be synthesized using the chemical methods described in Examples 1 through 4 by substituting the appropriate 11,15-bis-(tetrahydropyran-2-yl) PGF₂, 13,14-dihydro PGF₂, PGF₁ or PGF₀ wherein the substituent at the C-16 position is phenyl or substituted phenyl for class 1 preparation, phenoxy or substituted phenoxy for class 2 preparation and n-butyl or both methyl and n-butyl for class 3 preparation, for the PGF intermediate labeled (SM) in Example 1, the substituents for the substituted phenyl and phenoxy classes being fluoro, chloro, methyl, ethyl, methoxy, ethoxy, phenyl and trifluoromethyl.

Example 6


To a solution of 0.795 mmole of 9-alpha-hydroxy-15-alpha-(tetrahydropyran-2-yloxy)-16-phenoxy-16-omega-tetranor-13-trans-prostenoic acid (DSM) in 10 ml of dry dimethylformamide is added 134 mg (0.825 mmole) of 1,1-carbonyldimidazole. The solution is heated under nitrogen at 95° for 4 hours, then 70 mg (0.825 mole) of anhydrous 5-amino-tetrazole is added. The solution is heated under nitrogen for 1.5 hours at 95° and then can be concentrated by rotary evaporation to provide the crude title compound (6).

Example 7


10 ml of a 65:35 mixture of acetic acid:water is stirred at room temperature for 18 hours under nitrogen and then is concentrated by rotary evaporation. Benzene is added and removed by rotary evaporation (3X). Purification of the crude residue by silica gel column chromatography using mixture of chloroform-ethyl acetate as eluents may be employed to purify the title compound (7).

**Example 8**


To a solution, cooled to -20°, of 1.06 mmoles of N-(tetrazol-5-yl) 9-alpha-hydroxy-15-alpha-(tetrahydropropyran-2-yloxy)-16-phenoxy-16-omegatetranor-13-trans-prostenamide (6) in 15 ml of acetone is added 0.38 ml of Jones reagent. The mixture is stirred for about 20 minutes then quenched in the cold by 0.38 ml of isopropyl alcohol. The mixture is stirred for 5 minutes then it is diluted with ethyl acetate (25 ml), washed with water (3 x 5 ml) and saturated brine (5 ml), dried (magnesium sulfate) and concentrated to provide the title compound (8).

**Example 9**


A solution of 295 mg of crude N-(tetrazol-5-yl)9-alpha-hydroxy-15-alpha-(tetrahydropropyran-2-yloxy)-16-phenoxy-16-omegatetranor-13-trans-prostenamide (3) in 30 ml of a 65:35 mixture of acetic acid-water is stirred at room temperature under nitrogen for 18 hours. The solution is concentrated by rotary evaporation and benzene is then added and removed in the same way (3X). Purification of the residue by silica gel column chromatography using mixtures of chloroform - ethyl acetate as eluents will provide the title compound (9).
The synthesis of the compounds of Examples 6 through 9 demonstrates that the 11-desoxy prostaglandins of classes 1, 2 and 3 of the invention and the corresponding PGF type compounds may be synthesized using the chemical methods described in Examples 6 through 9 by substituting the appropriate 11-desoxy-15-tetrahydro-pyran-2-yl PGF₂, 13,14-dihydro PGF₂, PGF₃ or PGF₀ starting material wherein the substituent at the C-16 position is phenyl or substituted phenyl for class 1 preparation, phenoxy or substituted phenoxy for class 2 preparation and n-butyl or both methyl and n-butyl for class 3 preparation, for the PGF intermediate labeled (DSM) in Example 6, the substituents for the substituted phenyl and phenoxy classes being fluoro, chloro, methyl, ethyl methoxy, ethoxy, phenyl and trifluoromethyl.

Example 10

To a solution of 0.795 mmole of 9-alpha-hydroxy-11-alpha,15-alpha-bis-(tetrahydropyran-2-yloxy)-16,16-dimethyl-5-cis-13-trans-prostadienoic acid (RSM) in 10 ml of dry dimethylformamide is added 134 mg (0.825 mmole) of 1,1-carbonyldimidazole. The solution is heated under nitrogen at 95° for 4 hours, then 70 mg (0.825 mole) of anhydrous 5-amino-tetrazole is added. The solution is heated under nitrogen for 1.5 hours at 95° then concentrated by rotary evaporation to provide the crude title compound (10) as viscous oil.

Example 11

is stirred at room temperature for 18 hours under nitrogen; then is concentrated by rotary evaporation. Benzene is added and removed by rotary evaporation (3X). Purification of the crude residue by silica gel column chromatography using mixture of chloroform-ethyl acetate as eluents may be carried out to provide the title compound (11).

**Example 12**


To a solution, cooled to -20°C, of 623 mg (1.06 mmole) of N-(tetrazol-5-yl) 9-alpha-hydroxy-11-alpha,15-alpha-bis-(tetrahydro-pyran-2-yloxy)-16,16-dimethyl-5-cis-13-trans-prostadienamide (10) in 15 ml of acetone is added 0.38 ml of Jones reagent. The mixture is stirred for about 20 minutes then quenched in the cold by 0.38 ml of isopropyl alcohol. The mixture is stirred for 5 minutes and then diluted with ethyl acetate (25 ml), washed with water (3 X 5 ml) and saturated brine (5 ml), dried (magnesium sulfate) and concentrated to provide the title compound (12).

**Example 13**

**N-(Tetrazol-5-yl) 9-oxo-11-alpha,15-alpha-dihydroxy-16,16-dimethyl-5-cis-13-trans-prostadienamide (13)**

A solution of 295 mg of crude N-(tetrazol-5-yl) 9-oxo-11-alpha,15-alpha-bis-(tetrahydropyran-2-yloxy)-16,16-dimethyl-5-cis-13-trans-prostadienamide (12) in 30 ml of a 65:35 mixture of acetic acid-water is stirred at room temperature under nitrogen for 18 hours. The solution is concentrated by rotary evaporation and benzene is added and concentrated (3X). Purification of the residue by silica gel column chromatography using mixtures of chloroform - ethyl acetate as eluents may be carried out to provide the title compound (13).
The synthesis of the compounds of Examples 10 through 13 demonstrates that the 11-hydroxy or 11-desoxy 16,16-dimethyl prostaglandins of the invention and the corresponding PGF type compounds may be synthesized using the chemical methods described in Examples 10 through 13 by substituting the appropriate 11,15-bis(tetrahydropyran-2-yl) or 11-desoxy-15-(tetrahydropyran-2-yl)-16,16-dimethyl PGF$_2$, 13,14-dihydro PGF$_2$, PGF$_1$ or PGF$_0$ for the PGF intermediate labeled (RSM) in Example 10.
The claims defining the invention are as follows:

1. A compound of the formula

\[
\begin{align*}
\text{H} & \text{H} \text{H} \text{H} \\
\text{C} & \text{A}-\text{C}-\text{C}-\text{C}-\text{C}-\text{CO}_{\text{H}} \\
\text{H} & \text{H} \text{H} \text{H} \\
\text{Y} & \text{B}-\text{C}-\text{C}-\text{G} \\
\text{H} & \text{H} \\
\text{HO} & 
\end{align*}
\]

or a pharmacologically acceptable salt thereof, wherein:
- A is ethylene or cis-vinylene;
- B is ethylene or trans-vinylene;
- Y is hydrogen or hydroxy;
- G is \( \text{CH}_2\text{Ar}, \text{CH}_2\text{OAr} \) or \( \text{CR}_2(\text{CH}_2)_3\text{CH}_3 \);
- Ar is phenyl, fluorophenyl, chlorophenyl, methylphenyl, ethylphenyl, methoxyphenyl, ethoxyphenyl, biphenyl or trifluoromethylphenyl;
- R is hydrogen or methyl; and
- Z is hydrogen or methyl.


DATED this TWENTY-THIRD day of NOVEMBER, 1978
PFIZER INC.

Patent Attorneys for the Applicant
SPRUSON & FERGUSON