Title: TREATMENT OF GLAUCOMA AND OCULAR HYPERTENSION WITH IMIDAZOLE ANGIOTENSIN-II RECEPTOR ANTAGONISTS

Abstract

Substituted imidazoles such as 2-butyl-4-chloro-1-[(2'-{(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-5-(hydroxymethyl)imidazole and 2-butyl-4-chloro-1-[(2'-carboxybiphenyl-4-yl)methyl]-5-(hydroxymethyl)imidazole and pharmaceutically acceptable salts thereof are useful for treating glaucoma and ocular hypertension.
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TREATMENT OF GLAUCOMA AND OCULAR HYPERTENSION
WITH IMIDAZOLE ANGIOTENSIN-II RECEPTOR ANTAGONISTS

BACKGROUND OF THE INVENTION

Glaucome is an ocular disease complex associated with an elevated pressure within the eye, i.e., elevated intraocular pressure (IOP). As a result of the elevated IOP, damage to the optic nerve, resulting in irreversible loss of visual function, may ensue. Untreated, this condition may eventually lead to blindness. Ocular hypertension, i.e., a condition of elevated IOP, without optic nerve damage or characteristic glaucomatous visual field loss, is now believed by the majority of ophthalmologists to represent the earliest phase in the onset of glaucoma. Glaucome is among the leading causes of blindness in the U.S. today.

Drugs currently available for the control of the symptoms of glaucoma and to halt the progressive optic nerve damage are only marginally effective (Yorio (1985) J. Ocular Pharmacol. 1:397-422). Recently, the renin-angiotensin system (RAS) has been suggested as possibly playing a role in the maintenance of intraocular pressure, as the angiotensin-converting enzyme (ACE) inhibitors, captopril and SCH 33861, have been shown to lower IOP in ocular normotensive rabbits (Watkins et al. (1987) J. Ocular Pharmacol. 3:295-307) and in humans with elevated intraocular pressures (Constad et al. (1988) Am. J. Ophthalmol. 105:674-677). More recently, a renin inhibitor identified as Abbott-64662 was found to decrease aqueous humor formation and lower the IOP in
rabbits following topical application (Stein et al. (1989) *The Pharmacologist* 31:124).


Conventional therapy for glaucoma has involved topical administration of pilocarpine and/or epinephrine, and more recently beta-blockers, such as Timolol, administered to the eye several times daily. For example, beta-blockers useful as antiglaucoma agents are disclosed in commonly-assigned U.S. Patent Application 07/285007, filed 12/15/88 (CC-0747).

**SUMMARY OF INVENTION**

According to the present invention there is provided a method of treating glaucoma and intraocular hypertension and promoting retinal blood flow in a mammal comprising the topical ocular administration of an angiotensin II antagonist compound having the formula (I):

![Chemical Structure](I)
wherein

\[ R^1 \text{ is } 4\text{-}CO_2H; \ 4\text{-}CO_2R^9; \ -OSO_3H; \ -SO_3H; \ -C(CF_3)_{2}OH; \]

\[ -OPO_3H_2; \ -PO_3H_2; \ -NHPO_3H_2; \]

\[ 4\text{-}NHSO_2CH_3; \ 4\text{-}NHSO_2CF_3; \ -CONHOR^{12}; \]

\[ -SO_2NH_2; \]

\[ \begin{array}{c}
\text{OH} \\
\text{O} \\
\text{C} \quad \text{P} \quad \text{O} \quad \text{H} \\
\text{R}^{27} \text{OH}
\end{array} \]

\[ \begin{array}{c}
\text{N} \quad \\
\text{N} \\
\text{N} \\
\text{H}
\end{array} \]

\[ 4\text{-}N \]

\[ \begin{array}{c}
\text{N} \quad \text{N} \\
\text{N} \\
\text{N} \\
\text{H}
\end{array} \]

\[ \begin{array}{c}
\text{4-X} \\
\text{R}^{3}
\end{array} \]

\[ \begin{array}{c}
\text{4-X} \\
\text{R}^{3}
\end{array} \]

\[ \begin{array}{c}
\text{4-X} \\
\text{R}^{3}
\end{array} \]

\[ \begin{array}{c}
\text{4-X} \\
\text{R}^{3}
\end{array} \]

\[ \begin{array}{c}
\text{4-X} \\
\text{R}^{3}
\end{array} \]

\[ \begin{array}{c}
\text{4-X} \\
\text{R}^{3}
\end{array} \]

\[ \begin{array}{c}
\text{4-X} \\
\text{R}^{3}
\end{array} \]

\[ \begin{array}{c}
\text{4-X} \\
\text{R}^{3}
\end{array} \]
\[
\begin{align*}
\text{4CONH} & \quad \text{4CONHNHSO}_2\text{CF}_3; \\
\text{4CONH} & \quad \text{4CONH}-\text{CHCH}_2\text{C}_6\text{H}_5 \text{ (l-isomer)}; \\
\text{4-CO-N} & \quad \text{HO}_2\text{C} \quad \text{4}\text{Z} \quad \text{R}^{11}; \\
\text{4} & \quad \text{N} \quad \text{CF}_3; \\
\text{4-CN} & \quad \text{4-CONHCO}_2\text{H} \\
\text{R}^4 & \quad \text{O} \quad \text{-CONHSO}_2(\text{CH}_2)\text{s} \quad \text{R}^{20}; \\
\text{R}^2 & \text{is H; Cl; Br; I; F; NO}_2; \text{CN; alkyl of 1 to 4 carbon atoms; acyloxy of 1 to 4 carbon atoms; alkoxy of 1 to 4 carbon atoms; CO}_2\text{H; CO}_2\text{R}^9; \text{NHSO}_2\text{CH}_3; \text{NHSO}_2\text{CF}_3; \text{CONHOR}^{12}; \text{SO}_2\text{NH}_2; \\
\text{R}^3 & \text{is H; Cl, Br, I or F; alkyl of 1 to 4 carbon atoms or alkoxy of 1 to 4 carbon atoms;} \\
\text{R}^4 & \text{is CN, NO}_2 \text{or CO}_2\text{R}^{11}; \\
\text{R}^5 & \text{is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, alkenyl or alkynyl of 2 to 4 carbon atoms;} \\
\text{R}^6 & \text{is alkyl of 2 to 10 carbon atoms, alkenyl or alkynyl of 3 to 10 carbon atoms or the same groups substituted with F or CO}_2\text{R}^{14}; \text{cycloalkyl of 3 to 8 carbon atoms, cycloalkylalkyl of 4 to 10 carbon atoms;} 
\end{align*}
\]
cycloalkylalkenyl or cycloalkylalkynyl of 5 to 10 carbon atoms; (CH₂)₂Z(CH₂)ₐR₅ optionally substituted with F or CO₂R¹⁴; benzyl or benzyl substituted on the phenyl ring with 1 or 2 halogens, alkoxy of 1 to 4 carbon atoms, alky of 1 to 4 carbon atoms or nitro;
R⁷ is H, F, Cl, Br, I, NO₂, CF₂F₂ν⁺₁, where ν = 1-6; C₆F₅ or CN;  
\[ -\text{CR}^{16} \]
straight or branched alky of 1 to 6 carbon atoms; phenyl or phenylalkyl, where alky is 1 to 3 carbon atoms; or substituted phenyl or substituted phenylalkyl, where alky is 1 to 3 carbon atoms, substituted with one or two substituents selected from alky of 1 to 4 carbon atoms, F, Cl, Br, OH, OCH₃, CF₃, and COOR, where R is H, alky of 1 to 4 carbon atoms, or phenyl; vinyl; alkynyl of 2-10 carbon atoms; phenylalkynyl where the alkynyl portion is 2-6 carbon atoms; heteroaryl selected from 2- and 3-thienyl, 2- and 3-furyl, 2-, 3-, and 4-pyridyl, 2-pyrazinyl, 2-, 4-, and 5-pyrimidinyl, 3- and 4-pyridazinyl, 2-, 4-, and 5-thiazolyl, 2-, 4-, and 5-selenazolyl, 2-, 4-, and 5-oxazolyl; 2- or 3-pyrrolyl, 3-, 4- or 5-pyrazolyl, and 2-, 4- or 5-imidazolyl; o-, m- or p-biphenyl; o-, m- or p-phenoxyphenyl; substituted phenylalkynyl, heteroaryl, biphenyl or phenoxophenyl as defined above substituted on ring carbon with 1 or 2 substituents selected from halogen, alkoxy of 1-5 carbon atoms, alky of 1-5 carbon atoms, -NO₂, -CN, -CF₃, -COR¹⁶, -CH₂OR¹⁷, -NHCOR¹⁷, CONR¹⁸R¹⁹, S(O)₂R¹⁷, and SO₂NR¹⁸R¹⁹; pyrrolyl, pyrazolyl or imidazolyl as defined above substituted on ring nitrogen with alky of 1-5 carbon atoms or benzyl; or substituted alky, alkenyl, or alkynyl of 1 to 10 carbon atoms substituted with a substituted or unsubstituted
heteroaryl, biphenylyl or phenoxyphenyl group as defined above; 1- or 2- naphthyl; 5- or 6-naphthoquinonyl; 3-,
4- or 5-acenaphthyl; 3- 4-, or 5-acenaphthenyl; 1-, 2-or 9-anthracenyl; 1- or 2-anthraquinonyl; 1-, 2-, 3-, 4-, or 9-phenanthrenyl; 2-, 3-, 4-, 5-, 6-, 7- or 8-
quinolinyl; 1-, 3-, 4-, 5-, 6-, 7- or 8-isooquinonyl; 2-, 3-, 4-, 5-, 6- or 7-indolyl which can be substituted on
ring nitrogen with lower alkyl of 1 to 5 carbon atoms or benzyl; 4-, 5-, 6- or 7-indenyl; 2-, 3-, 4-, 5-, 6- or
7-benzofuryl; 2-, 3-, 4-, 5-, 6- or 7-benzothienyl; 1-, 2-, 3- or 4-dibenzofuryl; 1-, 2-, 3- or 4-dibenzo-
thienyl; 1-, 2-, 3- or 4-fluorenyl; any of the foregoing
polycyclic aryl groups substituted with 1 or 2
subsituents selected from halogen, alkoxy of 1-5 carbon
atoms, alkyl of 1-5 carbon atoms, -NO₂, -CN, -CF₃,
-COR₁₆, -CH₂OR₁₇, -NHCOR₁₇, CONR₁₈R₁₉, S(O)ₐR₁₇, and
SO₂NR₁₈R₁₉; the anhydride of 4,5-dicarboxyl-1- or
2-naphthyl; or substituted alkyl of 1 to 10 carbon
atoms, alkenyl or alkylnyl of 2 to 10 carbon atoms
substituted with a substituted or unsubstituted
polycyclic aryl group as defined above;

R₈ is H, CN, alkyl of 1 to 10 carbon atoms,
alkenyl of 3 to 10 carbon atoms, or the same groups
substituted with F; phenylalkenyl wherein the aliphatic
portion is 2 to 6 carbon atoms; -(CH₂)ₘ-imidazol-1-yl;
-(CH₂)ₘ-1,2,3-triazolyl optionally substituted with one
or two groups selected from CO₂CH₃ or alkyl of 1 to 4
carbon atoms; -(CH₂)ₙ-tetrazolyl;
-\((\text{CH}_2)_{n-1}\text{CH-R}^{11}\); 
\(\text{OR}^{17}\)

-\(\text{OR}^{14}\)

-\(\text{CH}=\text{CH}(\text{CH}_2)_s\text{CHOR}^{15}\); 
-\(\text{CH}=\text{CH}(\text{CH}_2)_s\text{CR}^{16}\); 
-\(\text{CR}^{16}\)

-\(\text{CH}=\text{CH}(\text{CH}_2)_s\text{O} \text{CR}^{11}\); 
-\((\text{CH}_2)_m\text{-tetrazolyl}\)

-\(\text{CH}_3\)

-\(\text{CH-COR}^{16}\); 
-\((\text{CH}_2)_n\text{OR}^{16}\); 
-\((\text{CH}_2)_n\text{O} \text{CHNR}^{10}\)

-\((\text{CH}_2)_n\text{NR}^{11}\text{COR}^{10}\); 
-\((\text{CH}_2)_n\text{NR}^{11}\text{CNHR}^{10}\); 
-\((\text{CH}_2)_n\text{NR}^{11}\text{SO}_2\text{R}^{10}\)

or, 
-\((\text{CH}_2)_n\text{NR}^{11}\text{CR}^{10}\);

\(R^9\) is 
\(\text{CH-OCR}^{21}\);

\(R^{10}\) is alkyl of 1 to 6 carbon atoms or
perfluoroalkyl of 1 to 6 carbon atoms, 1-adamantyl,
1-naphthyl, 1-(1-naphthyl)ethyl, or \((\text{CH}_2)_p\text{C}_6\text{H}_5\);

\(R^{11}\) is H, alkyl of 1 to 6 carbon atoms, cycloalkyl
of 3 to 6 carbon atoms, phenyl or benzyl;

\(R^{12}\) is H, methyl or benzyl;
\(R^{13}\) is \(-\text{CO}_2\text{H}; -\text{CO}_2\text{R}^{9}; -\text{CH}_2\text{CO}_2\text{H}, -\text{CH}_2\text{CO}_2\text{R}^{9}\);

-\(\text{O-S-OH}; -\text{O-P-OH}; -\text{SO}_3\text{H}; -\text{NHP-OH}\);

-\(\text{OH}\); 
\(\text{OH}\)
-PO₃H₂; -C(CF₃)₂OH; -NHSO₂CH₃; -NHSO₂CF₃; -NHCOCF₃;
-CONHOR¹²; -SO₂NH₂;

\[
\text{Diagram:}
\]

\[
R^{14} \text{ is } H, \text{ alkyl or perfluoroalkyl of 1 to 8 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, phenyl or benzyl;}
\]

R¹⁵ is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, phenyl, benzyl, acyl of 1 to 4 carbon atoms, phenacyl;

R¹⁶ is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, \((\text{CH₂})p\text{C₆H₅}, \text{ OR}^{17}, \text{ or NR}^{18}\text{R}^{19};
\]

R¹⁷ is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, phenyl or benzyl;

R¹⁸ and R¹⁹ independently are H, alkyl of 1 to 4 carbon atoms, phenyl, benzyl, \(\alpha\)-methylbenzyl, or taken together with the nitrogen form a ring of the formula
Q is NR²⁰, O or CH₂;
R²⁰ is H, alkyl of 1-4 carbon atoms, or phenyl;
R²¹ is alkyl of 1 to 6 carbon atoms, -NR²²R²³, or

-CHCH₂CO₂CH₃;
  \begin{center}
  \text{NH₂}
  \end{center}

R²² and R²³ independently are H, alkyl of 1 to 6
10  carbon atoms, benzyl, or are taken together as (CH₂)ₓ
  where x is 3-6;
R²⁴ is H, CH₃ or C₆H₅;
R²⁵ is NR²⁷R²⁸, OR²⁸, NHCONH₂, NHCSNH₂,  

-NHSO₂-CH₃ or -NHSO₂-CH₃

R²⁶ is hydrogen, alkyl with from 1 to 6 carbon
20  atoms, benzyl, or allyl;
R²⁷ and R²⁸ are independently hydrogen, alkyl with
  from 1 to 5 carbon atoms, or phenyl;
R²⁹ and R³⁰ are independently alkyl of 1-4 carbon
  atoms or taken together are -(CH₂)ₓ⁻;
R³¹ is H, alkyl of 1 to 4 carbon atoms, -CH₂CH=CH₂
  or -CH₂C₆H₄R³₂;
R³² is H, NO₂, NH₂, OH or OCH₃;
X is a carbon-carbon single bond, -CO-, -CH₂-, -O-,  
-S-, -NH-,  
-N-, -CON-, -NCO-

R²⁶ R²³ R²³
-OCH₂⁻, -CH₂O⁻, -SCH₂⁻, -CH₂S⁻, NH(CR²⁷)(R²⁸), NR²³SO₂⁻,
-SO₂NR²³⁻, -C(R²⁷)(R²⁸)NH⁻, -CH=CH⁻, -CF=CF⁻, -CH=CF⁻,
CF=CH⁻, -CH₂CH₂⁻, -CF₂CF₂⁻,

\[ \begin{array}{c}
\text{Y is } 0 \text{ or } S; \\
\text{Z is } 0, \text{NR}^{11}, \text{or } S; \\
\text{m is } 1 \text{ to } 5; \\
\text{n is } 1 \text{ to } 10; \\
\text{p is } 0 \text{ to } 3; \\
\text{q is } 2 \text{ to } 3; \\
\text{r is } 0 \text{ to } 2; \\
\text{s is } 0 \text{ to } 5; \\
\text{t is } 0 \text{ or } 1;
\end{array} \]

and pharmaceutically acceptable salts of these compounds; provided that:

(1) the R¹ group is not in the ortho position;
(2) when R¹ is

\[ \begin{array}{c}
\text{X is a single bond, and } R^{13} \text{ is } CO₂H, \text{ or}
\end{array} \]
then \( R^{13} \) must be in the ortho or meta position; or when \( R^1 \) and \( X \) are as above and \( R^{13} \) is NHSO\(_2\)CF\(_3\) or NHSO\(_2\)CH\(_3\), \( R^{13} \) must be ortho;

(3) when \( R^1 \) is

\[
\begin{array}{c}
\text{R}^1 \\
\text{R}^{13}
\end{array}
\]

and \( X \) is other than a single bond, then \( R^{13} \) must be ortho except when \( X = NR^{23}CO \) and \( R^{13} \) is NHSO\(_2\)CF\(_3\) or NHSO\(_2\)CH\(_3\), then \( R^{13} \) must be ortho or meta;

(4) when \( R^1 \) is 4-CO\(_2\)H or a salt thereof, \( R^6 \) cannot be S-alkyl;

(5) when \( R^1 \) is 4-CO\(_2\)H or a salt thereof, the substituent on the 4-position of the imidazole cannot be CH\(_2\)OH, CH\(_2\)OCOCH\(_3\), or CH\(_2\)CO\(_2\)H;

(6) when \( R^1 \) is

\[
\begin{array}{c}
\text{R}^1 \\
\text{R}^{13}
\end{array}
\]

\( X = -OCH_2- \), and \( R^{13} \) is 2-CO\(_2\)H, and \( R^7 \) is H then \( R^6 \) is not C\(_2\)H\(_5\)S;

(7) when \( R^1 \) is

\[
\begin{array}{c}
\text{CF}_3\text{SO}_2\text{HN}
\end{array}
\]

\( -\text{CONH}- \)

and \( R^6 \) is n-hexyl, then \( R^7 \) and \( R^8 \) are not both hydrogen;

(8) when \( R^1 \) is
R⁶ is not methoxybenzyl;
(9) the R⁶ group is not -F-CHCH₂CH₂CH₃ or CH₂OH;
(10) when r=0, R¹ is

X is -NH-C=O, R¹³ is 2-NHSO₂CF₃, and R⁶ is n-propyl, then R⁷ and R⁸ are not -CO₂CH₃;
(11) when r=0, R¹ is

X is NH-C=O, R¹³ is 2-COOH, and R⁶ is n-propyl, then R⁷ and R⁸ are not -CO₂CH₃;
(12) when r=1, R¹ is

X is a single bond, R⁷ is Cl, and R⁸ is -CHO, then R¹³ is not 3-(tetrazol-5-yl);
(13) when r=1, R¹ is
X is a single bond, $R^7$ is Cl, and $R^8$ is $-\text{CHO}$, then $R^{13}$ is not $4-(\text{tetrazol-5-yl})$.

Preferred in the method of this invention are compounds having the formula (II):

\[
\begin{array}{c}
\text{N} \\
\text{R}^6 \\
\text{N} \\
\text{CH}_2 \\
\text{R}^1 \\
\end{array}
\]

(II)

wherein

- $R^1$ is $-\text{CO}_2\text{H}$, $-\text{NHSO}_2\text{CF}_3$;

or

\[
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{N} \\
\text{H} \\
\end{array}
\]

\[
\begin{array}{c}
\text{R}^{13} \\
\text{R}^2 \\
\end{array}
\]

\[
\begin{array}{c}
\text{X} \\
\text{R}^{13} \\
\end{array}
\]

\[
\begin{array}{c}
\text{X} \\
\text{R}^{13} \\
\end{array}
\]
$R_6^3$ is alkyl of 3 to 10 carbon atoms, alkenyl of 3 to 10 carbon atoms, alkynyl of 3 to 10 carbon atoms, cycloalkyl of 3 to 8 carbon atoms, benzyl substituted on the phenyl ring with up to two groups selected from alkoxy of 1 to 4 carbon atoms, halogen, alkyl of 1 to 4 carbon atoms, and nitro; $R_8^8$ is

\[-(CH_2)_n \text{-tetrazolyl}, -(CH_2)_n\text{OR}^{11}, -(CH_2)_n\text{OCR}^{14};\]

\[-\text{CH} = \text{CH(CH}_2)_n\text{CR}^{16}, \text{-CH} = \text{CH(CH}_2)_n\text{CHOR}^{15};\]

\[-(CH_2)_n\text{CR}^{16}, -(CH_2)_n\text{NHCOR}^{10}, -(CH_2)_n\text{NH}_2\text{SO}_2\text{R}^{10};\]

\[-(CH_2)_m\text{F}; \text{ or } -(\text{CR})^{16};\]

phenylalkenyl wherein the aliphatic portion is 2 to 4 carbon atoms; -(CH$_2$)$_m$-imidazol-1-yl; or -(CH$_2$)$_m$-1,2,3-triazolyl optionally substituted with one or two groups selected from -CO$_2$CH$_3$ or alkyl of 1 to 4 carbon atoms;

$R^{13}$ is -CO$_2$H, -CO$_2$R$^9$, NH$_2$SO$_2$CF$_3$; SO$_3$H; or

\[
\begin{array}{c}
\text{N} \\
\text{H} \\
\text{N} \\
\text{N}
\end{array}
\]

$R^{16}$ is H, alkyl of 1 to 5 carbon atoms, OR$^{17}$, or NR$^{18}$R$^{19}$;

$X$ is carbon-carbon single bond, -CO-, CH$_2$CH$_2$-.
-CON-, \(-\text{NCO}^{-}\), \(\text{R}^{23}\), \(\text{R}^{23}\)

-\text{OCH}_2-, -\text{CH}_2\text{O}-, -\text{O}-, -\text{SCH}_2-, -\text{CH}_2\text{S}-, -\text{NH}-\text{CH}_2-, -\text{CH}_2\text{NH}-
or -\text{CH}=\text{CH}-; and pharmaceutically acceptable salts of these compounds.

More preferred in the process of the invention are compounds of the preferred scope where:

- \(\text{R}^{2}\) is \(\text{H}\), alkyl of 1 to 4 carbon atoms, halogen, or alkoxy of 1 to 4 carbon atoms;

- \(\text{R}^{6}\) is alkyl, alkenyl or alkynyl of 3 to 7 carbon atoms;

- \(\text{R}^{7}\) is heteroaryl selected from 2- and 3-thienyl, 2- and 3-furyl, 2-, 3-, and 4-pyridyl, \(\text{H}, \text{Cl}, \text{Br}, \text{I} ; \text{C}_n\text{F}_{2n+1}\), where \(n=1-3\); \(-\text{CR}^{16}\); straight or branched chain alkyl of 1 to 6 carbon atoms; or phenyl;

- \(\text{R}^{8}\) is \(-\text{(CH}_2\text{)}_m\text{OR}^{11}\); \(-\text{(CH}_2\text{)}_m\text{OCR}^{14}\); \(-\text{CH}=\text{CH}_2\text{OR}^{15}\);

- \(-\text{(CH}_2\text{)}_m\text{CR}^{16}\); \(-\text{CH}_2\text{NHCOR}^{10}\); \(-\text{(CH}_2\text{)}_m\text{NHSO}_2\text{R}^{10}\);

- \(\text{N}==\text{N}\)

- \(-\text{CH}_2\text{COR}^{16}\);

- \(\text{R}^{10}\) is \text{CF}_3, alkyl of 1 to 6 carbon atoms or phenyl;

- \(\text{R}^{11}\) is \(\text{H}\), or alkyl of 1 to 4 carbon atoms;

- \(\text{R}^{13}\) is \text{CO}_2\text{H}; \text{CO}_2\text{CH}_2\text{OCOC(CH}_3\text{)}_3; \text{NHSO}_2\text{CF}_3;\)
R\textsubscript{14} is H, or alkyl of 1 to 4 carbon atoms;  
R\textsubscript{15} is H, alkyl of 1 to 4 carbon atoms, or acyl of  
1 to 4 carbon atoms;  
R\textsubscript{16} is H, alkyl of 1 to 5 carbon atoms; OR\textsubscript{17}; or  
m is 1 to 5;  
X = single bond, \(-\text{O}-\); \(-\text{CO}-\); \(-\text{NHCO}-\); or \(-\text{OCH}_2-\); and  
pharmaceutically acceptable salts.  
More preferred in the method of the invention are  
compounds of Formula II, wherein R\textsubscript{1} is  
and X is a single bond; and pharmaceutically suitable  
salts thereof.  
Most preferred in the method of the invention are  
compounds of formula II selected from the following, and  
pharmaceutically acceptable salts thereof.  
• 2-Butyl-4-chloro-1-[(2'--(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-5-(hydroxymethyl)imidazole.  
• 2-Butyl-4-chloro-1-[(2'-carboxybiphenyl-4-yl)-methyl]-5-(hydroxymethyl)imidazole.  
• 2-Butyl-4-chloro-1-[(2'-carboxybiphenyl-4-yl)
yl)-methyl]-5-[(methoxycarbonyl)aminomethyl] imidazole.
  2-Butyl-4-chloro-1-[(2'-carboxybibhenyl-4-yl)-methyl]-5-[(propoxycarbonyl)aminomethyl] imidazole.
  2-Butyl-4-chloro-1-[(2'-carboxybibhenyl-4-yl)methyl]imidazole-5-carboxaldehyde.
  2-Butyl-1-[(2'-carboxybibhenyl-4-yl)methyl]-imidazole-5-carboxaldehyde.
  2-(1E-Butenyl)-4-chloro-1-[(2'-carboxybibhenyl-4-yl)methyl]-5-(hydroxymethyl)imidazole.
  2-(1E-Butenyl)-4-chloro-1-[(2'-carboxybibhenyl-4-yl)methyl]imidazole-5-carboxaldehyde.
  2-Propyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-5-(hydroxymethyl)imidazole.
  2-Propyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxaldehyde.
  2-Butyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxaldehyde.
  2-(1E-Butenyl)-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-5-hydroxymethyl)imidazole.
  2-(1E-Butenyl)-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxaldehyde.
  2-Butyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxylic acid.
  2-Propyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxylic acid.
  2-Propyl-4-trifluoromethyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxylic acid.
  2-Propyl-4-trifluoromethyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-5-(hydroxymethyl)imidazole.
  2-Butyl-4-trifluoromethyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxylic acid.
• 2-Propyl-4-trifluoromethyl-1-[(2'-
  (carboxybiphenyl-4-yl)methyl]imidazole-5-carboxaldehyde.
• 2-Propyl-4-pentafluoroethyl-1-[(2'-
  (1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-5-(hydroxymethyl)-
imidazole.
• 2-Propyl-4-pentafluoroethyl-1-[(2'-
  (1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-
  carboxylic acid.
• 2-Propyl-4-pentafluoroethyl-1-[(2'-
  (1H-tetrazol-
  5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxaldehyde.
• 1-[(2'- (1H-Tetrazol-5-yl)biphenyl-4-
  yl)methyl] -4-phenyl-2-propylimidazole-5-carboxaldehyde.
• 1-[(2'-Carboxybiphenyl-4-yl)methyl]-4-phenyl-
  2-propylimidazole-5-carboxaldehyde.

Throughout the text when an alkyl substituent is
mentioned, the normal alkyl structure is meant (i.e.,
butyl is n-butyl) unless otherwise specified.
Pharmaceutically suitable salts include both the
metallic (inorganic) salts and organic salts; a list of
which is given in Remington's Pharmaceutical Sciences,
17th Edition, pg. 1418 (1985). It is well known to one
skilled in the art that an appropriate salt form is
chosen based on physical and chemical stability,
flowability, hydrosopicity and solubility. Preferred
salts of this invention for the reasons cited above
include potassium, sodium, calcium and ammonium salts.

In the foregoing structural formulae, when a
radical can be a substituent in more than one previously
defined radical, that first radical can be selected
independently in each previously defined radical. For
example, R¹, R² and R³ can each be CONHOR¹². R¹² need
not be the same substituent in each of R¹, R² and R³ but
can be selected independently for each of them.
The invention is also concerned with the use of combinations of the compounds of the foregoing structural formulae with one or more of: a β-blocker such as timolol maleate or betaxalol; a carbonic anhydrase inhibitor such as 5,6-dihydro-4-ethylamino-4H-6-methylthieno[2,3-b]-thiophene-2-sulfonamide-7,7-dioxide; or a para-sympathomimetic agent such as pilocarpine; or an angiotensin converting enzyme (ACE) inhibitor such as enalaprilat.

The invention is also concerned with an ophthalmological formulation for the treatment of ocular hypertension and glaucoma and the promotion of retinal blood flow comprising as active ingredient a compound of the foregoing formulae, either alone or in admixture with one or more of: a β-blocker such as timolol maleate; a carbonic anhydrase inhibitor such as 5,6-dihydro-4-ethylamino-4H-6-methylthieno-[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide; a para-sympathomimetic agent such as pilocarpine; or an ACE inhibitor such as enalaprilat.

**DETAILED DESCRIPTION OF THE INVENTION**

The compounds of the foregoing formulae are described in and prepared by methods set forth in European Patent Application EP 0 324 377, published 7/19/89, (page 17, line 5 through page 212, line 32), copending commonly-assigned U.S. patent application USSN 07/375069, filed 6/30/89, (page 16, line 21 through page 133, line 35), and copending commonly-assigned U.S. patent application USSN 07/373,755, filed 6/30/89, (page 16, line 21 through page 153, line 15), the disclosures of which are hereby incorporated by reference.
The novel pharmaceutical formulation of this invention is a topical ophthalmologically acceptable composition for the treatment of glaucoma, and ocular hypertension associated therewith and the promotion of retinal blood flow which comprises an effective ocular antihypertensive amount of an A-II antagonist, either alone or in combination with a topically effective CA inhibitor or β-blocking and an ophthalmologically acceptable carrier. The A-II antagonist preferably is selected from the previously described compounds.

The novel method of treatment of this invention comprises the topical ocular administration of an effective ocular antihypertensive, retinal blood flow promoting amount of an A-II antagonist either alone or in combination with a topically effective CA inhibitor or β-blocker to a patient in need of such treatment. The A-II antagonist is selected from the previously described compounds.

The compounds of the foregoing formulae are advantageously administered topically to the eye in the form of a solution, ointment, or solid insert, such as is described in U.S. Patent 4,195,085. Formulations may contain the active compound, preferably in the form of a soluble acid addition salt, in amounts ranging from about 0.01% to about 10% by weight, preferably from about 0.5% to about 5% by weight. Unit dosages of the active compound can range from about 0.001 to about 5.0 mg, preferably from about 0.05 to about 2.0 mg, and especially 0.1 to 1.0 mg. The dosage administered to a patient will depend upon the patient's needs and the particular compounds employed.

To prepare suitable dosage forms, the active compounds may be conveniently admixed with a non-toxic pharmaceutically acceptable carrier suitable for topical
ophthalmologic administration. Typical of such 
pharmaceutically acceptable carriers are, for example, 
water, mixtures of water and water miscible solvents 
such as lower alkanols or vegetable oils, petroleum 
based jelly, or including also from 0.5 to 5% by weight 
of water soluble polymers such as cellulose derivatives 
such as methyl cellulose, alkali metal carboxymethyl 
cellulose, hydroxyethyl cellulose, hydroxypropyl 
cellulose, hydroxypropylmethyl cellulose; acrylates such 
as polyacrylic acids salts, ethylacrylates; 
polyacrylamides; natural products such as gelatin, 
alginates, pectins, tragacanth, karaya, chondrus, agar, 
acacia, the starch derivatives such as starch acetate, 
hydroxyethyl starch ethers, hydroxypropyl starch, as 
well as other synthetic derivatives such as polyvinyl 
 alcohol, polyvinyl pyrrolidone polyvinyl methyl ether, 
polyethylene oxide, neutralized carbopol and gums such 
as gellan, rhamson and xanthan gum and mixtures of these 
polymers. The pharmaceutical preparation may also 
contain non-toxic auxiliary substances such as 
emulsifying, preserving, wetting, bodying agents and the 
like, as for example, polyethylene glycols, carbowaxes, 
antibacterial preservative components commonly employed 
in ophthalmic formulations; buffering ingredients; and 
other conventional ingredients.

The method of treatment of this invention 
advantageously involves the topical administration of 
eye drops containing the active compound. Formulations 
for eye drops preferably include the active compound as 
a soluble acid addition salt in a properly buffered, 
sterile, aqueous isotonic solution.

The pharmaceutical preparation may also be in the 
form of a solid insert. For example, one may use a 
solid water soluble polymer as the carrier for the
medicament. Inserts that are known in the art that are suitable for this use include those described in United States Patents 3,993,071; 3,986,510; 3,868,445; and 3,867,510. Solid water insoluble inserts, such as those prepared from ethylene vinyl acetate copolymer, may also be utilized.

The compositions of the invention may include additional therapeutic agents in addition to the A-II antagonist. For example antibiotics, antiinflammatory steroids, and anesthetics as well as other IOP lowering agents such as a carbonic anhydrase inhibitor (CAI), ACE inhibitor or β-blocker may be present.

The preferred CAI is 5,6-dihydro-4-ethylamino-4H-6methyl-thieno[2,3-b]thiopyran-2-sulfonamido-7,7-dioxide, the preferred β-blocker is timolol and the preferred ACE inhibitor is enalaprilat.

If combined with a CAI, ACE inhibitor or β-blocker in a novel formulation of this invention, the A-II antagonist is used in a concentration of about one-half that employed if it were the sole active ingredient, and the CAI, ACE inhibitor or β-blocker is used in a pharmacologically equivalent concentration. In other words each of the A-II antagonists, CAI, ACE inhibitor and β-Blocker in the ophthalmic formulation is present at a concentration of about 0.005 to 2.5% and especially about 0.125 to 1%. As a unit dosage form 0.005 to 1.25 mg, preferably 0.025 to 1.25 mg, and especially 0.05 to 0.5 mg of each active ingredient is applied to the human eye, generally on a daily basis and preferably in divided doses.
EXAMPLE 1
Formulations

A-II antagonist 1 mg 15 mg
Monobasic Sodium phosphate•2H₂O 9.38 mg 6.10 mg
5 Dibasic Sodium phosphate•12H₂O 28.48 mg 16.80 mg
Benzalkonium chloride 0.10 mg 0.10 mg
Water for injection q.s. ad. 1.0 ml 1.0 ml

EXAMPLE 2
Formulations

A-II antagonist 0.5 mg 7.5 mg
CA Inhibitor 0.5 mg 7.5 mg
Monobasic Sodium phosphate•2H₂O 9.38 mg 6.10 mg
Dibasic Sodium phosphate•12H₂O 28.48 mg 16.80 mg
15 Benzalkonium chloride 0.10 mg 0.10 mg
Water for injection q.s. ad. 1.0 ml 1.0 ml

EXAMPLE 3
Formulations

20 A-II antagonist 0.5 mg 7.5 mg
B-blocker 0.5 mg 7.5 mg
Monobasic Sodium phosphate•2H₂O 9.38 mg 6.10 mg
Dibasic Sodium phosphate•12H₂O 28.48 mg 16.80 mg
Benzalkonium chloride 0.10 mg 0.10 mg
25 Water for injection q.s. ad. 1.0 ml 1.0 ml

The active ingredient(s), phosphate buffer salts and benzalkonium chloride are added to and dissolved in water. The pH of the composition is adjusted to 5-6 and diluted to volume. The composition is rendered sterile by exposure to ionizing radiation.

The ability of A-II antagonists to lower intraocular pressure was tested by topical ocular administration of 0.2% and 2% solutions of 2-butyl-4-
chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)-methyl]-5-(hydroxymethyl)imidazole (hereafter referred to as DuP753) to African Green Monkeys. The intraocular pressure was reduced approximately 1.5-2.5 mm Hg for about 2 hours.

The effect of DuP753 on intraocular pressure was also determined in the following Conscious Rabbit Model:

Adult New Zealand white rabbits were placed in a restrainer and their IOP measured using an Alcon Applanation Pneumatonograph, which has both a digital output and recorder for maintaining permanent records. Three consecutive readings per eye were made (duration 10 sec. each) until a constant IOP was recorded. In some instances the peripheral ear artery was cannulated and systemic blood pressure recorded on a physiograph.

Test drugs were applied locally to one eye, either in topical form, or through intracameral administration. Measurements of IOP were made on both the treated eye and vehicle control. A dose comparable to the ocular hypotensive action found in a pilot study was selected as the starting dose and the dose was increased or decreased logarithmically and the effects on IOP were observed. Two to four log doses were tested in order to construct a log dose effect curve, which provided information on efficacy as well as potency. A time course for the drug effect was monitored by measuring the IOP of untreated animals for 60 minutes at 15 minute intervals, to obtain a baseline, and following drug addition (single dose), the IOP was measured at 30 minute intervals for six hours, or until recovery of the IOP. In addition, once a dose-effect curve was generated, the effects of agents on systemic blood pressure (BP) following topical administration was assessed by selecting the ED50 dose for testing. Thus,
both changes in IOP and BP were monitored for each agent.

Table 1 shows results obtained with DuP753 as compared to captopril, an antihypertensive inhibitor of angiotensin-converting enzyme (ACE), in reducing the IOP of ocular normotensive rabbits (N=4). As shown in Table 1, whereas captopril was ineffective in lowering IOP in the present model, DuP753 significantly lowered IOP.

Table 1
Effect of 1% DuP753 and 1%
Captopril on IOP in Rabbits

<table>
<thead>
<tr>
<th>Treatment</th>
<th>IOP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time (hr)</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Control Treated</td>
<td>21</td>
</tr>
<tr>
<td>Control Untreated</td>
<td>21</td>
</tr>
<tr>
<td>Captopril Treated</td>
<td>21</td>
</tr>
<tr>
<td>Captopril Untreated</td>
<td>21</td>
</tr>
<tr>
<td>DuP753 Treated</td>
<td>21.5</td>
</tr>
<tr>
<td>DuP753 Untreated</td>
<td>20</td>
</tr>
</tbody>
</table>
CLAIMS:

1. A method of reducing intraocular pressure and increasing retinal blood flow in a mammal in need of such treatment which comprises topically administering to the eye, in an amount effective to achieve such results, a compound having the formula (I):

$$\begin{align*}
&\begin{array}{c}
\text{N} \\
\mid \\
\text{R}^6 \\
\mid \\
\text{N} \\
\mid \\
\text{R}^8 \\
\mid \\
\text{R}^7 \\
\mid \\
\text{R}^1 \\
\mid \\
\text{R}^2 \\
\mid \\
\text{R}^3 \\
\mid \\
\text{CH}_2 \\
\mid \\
\text{R}^4 \\
\mid \\
\text{R}^5 \\
\end{array} \\
\end{align*}$$

(I)

wherein

R$^1$ is 4-CO$_2$H; 4-CO$_2$R$^9$;

O  O  O
\|  \|  \|
O-S-OH; -SO$_3$H; -C(CF$_3$)$_2$OH; -O-P-OH$_2$; -PO$_3$H$_2$; -NH-P-OH;
\|  \|  \|
O  OH  OH

4-NHSO$_2$CH$_3$; 4-NHSO$_2$CF$_3$; -CONH$_2$$_1$$_2$.
$R^2$ is H; Cl; Br; I; F; NO$_2$; CN; alkyl of 1 to 4 carbon atoms; acyloxy of 1 to 4 carbon atoms; alkoxy of 1 to 4 carbon atoms; CO$_2$H; CO$_2$R$^3$; NH$_2$CO$_2$CH$_3$; NH$_2$CO$_2$CF$_3$; CONHOR$_{12}$; SO$_2$NH$_2$;

$R^3$ is H; Cl, Br, I or F; alkyl of 1 to 4 carbon atoms or alkoxy of 1 to 4 carbon atoms;

$R^4$ is CN, NO$_2$ or CO$_2$R$_{11}$;

$R^5$ is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, alkenyl or alkynyl of 2 to 4 carbon atoms;

$R^6$ is alkyl of 2 to 10 carbon atoms, alkenyl or alkynyl of 3 to 10 carbon atoms or the same groups substituted with F or CO$_2$R$_{14}$; cycloalkyl of 3 to 8 carbon atoms, cycloalkylalkyl of 4 to 10 carbon atoms; cycloalkylalkenyl or cycloalkylalkynyl of 5 to 10 carbon atoms; (CH$_2$)$_z$Z(CH$_2$)$_m$R$^5$ optionally substituted with F or CO$_2$R$_{14}$; benzyl or benzyl substituted on the phenyl ring with 1 or 2 halogens, alkoxy of 1 to 4 carbon atoms, alkyl of 1 to 4 carbon atoms or nitro;

$R^7$ is H, F, Cl, Br, I, NO$_2$, C$_v$F$_{2v+1}$, where $v = 1$-$6$; C$_6$F$_5$; CN; $-OR_{16}$; straight or branched alkyl of 1 to 6 carbon atoms; phenyl or phenylalkyl, where alkyl is 1 to 3 carbon atoms; or substituted phenyl or substituted phenylalkyl, where alkyl is 1 to 3 carbon atoms, substituted with one
or two substituents selected from alkyl of 1 to 4 carbon atoms, F, Cl, Br, OH, OCH₃, CF₃, and COOR, where R is H, alkyl of 1 to 4 carbon atoms, or phenyl; vinyl; alkynyl of 2-10 carbon atoms; phenylalkynyl where the alkynyl portion if 2-6 carbon atoms; heteroaryl selected from 2-and 3-thienyl, 2- and 3-furyl, 2-, 3-, and 4-pyridyl, 2-pyrazinyl, 2-, 4-, and 5-pyrimidinyl, 3- and 4-pyridainyl, 2-, 4- and 5-thiazolyl, 2-, 4-, and 5-selenazolyl, 2-, 4-, and 5-oxazolyl; 2- or 3-pyrazolyl, 3-, 4- or 5-pyrazolyl, and 2-, 4- or 5-imidazolyl; o-, m- or p-biphenylyl; o-, m- or p-phenoxypyphenyl; substituted phenylalkynyl, heteroaryl, biphenylyl or phenoxypyphenyl as defined above substituted on ring carbon with 1 or 2 substituents selected from halogen, alkoxy of 1-5 carbon atoms, alkyl of 1-5 carbon atoms, -NO₂, -CN, -CF₃, -COR¹⁶, -CH₂OR¹⁷, -NHCOR¹⁷, CONR¹⁸R¹⁹, S(O)₂R¹⁷, and SO₂NR¹⁸R¹⁹; pyrrolyl, pyrazolyl or imidazolyl as defined above substituted on ring nitrogen with alkyl of 1-5 carbon atoms or benzyl; or substituted alkyl, alkenyl, or alkynyl of 1 to 10 carbon atoms substituted with a substituted or unsubstituted heteroaryl, biphenylyl or phenoxypyphenyl group as defined above; 1- or 2- naphthyl; 5- or 6-naphthoquinonylnyl; 3-, 4-, or 5-acenaphthyl; 3-, 4-, or 5-acenaphthenyl; 1-, 2- or 9-anthracenyl; 1- or 2-anthraquinonylnyl; 1-, 2-, 3-, 4-, or 9-phenanthrylnyl; 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolinyl; 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolinyl; 2-, 3-, 4-, 5-, 6- or 7-indolyl which can be substituted on ring nitrogen with lower alkyl of 1 to 5 carbon atoms or benzyl; 4-, 5-, 6- or 7-indenyl; 2-, 3-, 4-, 5-, 6- or 7-benzofuranyl; 2-, 3-, 4-, 5-, 6- or 7-benzothienyl; 1-, 2-, 3- or 4-dibenzofuranyl; 1-, 2-, 3- or 4-dibenzo-thienyl; 1-, 2-, 3- or 4-fluorenyl; any of the foregoing polycyclic aryl groups substituted with 1 or 2
substituents selected from halogen, alkoxy of 1-5 carbon atoms, alkyl of 1-5 carbon atoms, -NO₂, -CN, -CF₃, -COR¹⁶, -CH₂OR¹⁷, -NHCOR¹⁷, CONR₁⁸R¹⁹, S(OR)₂R¹⁷, and SO₂NR₁⁸R¹⁹; the anhydride of 4,5-dicarboxyl-1- or 2-naphthyl; or substituted alkyl of 1 to 10 carbon atoms, alkenyl or alkynyl of 2 to 10 carbon atoms substituted with a substituted or unsubstituted polycyclic aryl group as defined above.

R⁸ is H, CN, alkyl of 1 to 10 carbon atoms, alkenyl of 3 to 10 carbon atoms, or the same groups substituted with F; phenylalkenyl wherein the aliphatic portion is 2 to 6 carbon atoms; -(CH₂)ₘ- imidazol-1-yl; -(CH₂)ₘ-1,2,3-triazolyl optionally substituted with one or two groups selected from CO₂CH₃ or alkyl of 1 to 4 carbon atoms; -(CH₂)ₙ-tetrazolyl;

\[
\begin{align*}
-(\text{CH}_2)_{n-1}\text{CH}-\text{R}^{11} &; -(\text{CH}_2)_n\text{OCR}^{14} &; -(\text{CH}_2)_n\text{SR}^{15}; \\
\text{OR}^{17} &; & \\
-\text{CH}=\text{CH}(\text{CH}_2)_{s}\text{CHOR}^{15} &; -\text{CH}=\text{CH}(\text{CH}_2)_{s}\text{CR}^{16} &; -\text{CR}^{16}; \\
-\text{CH}=\text{CH}(\text{CH}_2)_{s}\text{OCR}^{11} &; -(\text{CH}_2)_{s}-\text{CH-COR}^{16} &; -(\text{CH}_2)_n\text{CR}^{16}; \\
\text{CH}_3 & & \\
\end{align*}
\]
\[-(\text{CH}_2)_n-\text{CH-R}^1\] ; \[-(\text{CH}_2)_n\text{OCR}^1\] ; \[-(\text{CH}_2)_n\text{SR}^1\] ; OR raised to a power (\text{OR}^1\)  

\[-\text{CH=CH(\text{CH}_2)_s \text{CHOR}^1}\] ; \[-\text{CH=CH(\text{CH}_2)_s \text{CR}^1}\] ; \[-\text{CR}^1\]  

\[-\text{CH=CH(\text{CH}_2)_s \text{OCR}^1}\] ; \[-(\text{CH}_2)_m\text{-tetrazolyl}\] ;  

\[-(\text{CH}_2)_s\text{-CH-COR}^1\] ; \[-(\text{CH}_2)_n\text{CR}^1\] ; \[-(\text{CH}_2)_n\text{OCH\text{NR}^1}\] ;  

\[-(\text{CH}_2)_n\text{NR}^1\text{COR}^1\] ; \[-(\text{CH}_2)_n\text{NR}^1\text{CNHR}^1\] ; \[-(\text{CH}_2)_n\text{NR}^1\text{SO}_2\text{R}^1\] ;  

or, \[-(\text{CH}_2)_n\text{NR}^1\text{CR}^1\].

R raised to a power (R^9) is \[-\text{R}^{24}\text{-CH-OCR}^{21}\].

R raised to a power (R^10) is alkyl of 1 to 6 carbon atoms or perfluoroalkyl of 1 to 6 carbon atoms, 1-adamantyl, 1-naphthyl, 1-(1-naphthyl)ethyl, or \((\text{CH}_2)_p\text{C}_6\text{H}_5\).

R raised to a power (R^11) is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, phenyl or benzyl;

R raised to a power (R^12) is H, methyl or benzyl;

R raised to a power (R^13) is \(-\text{CO}_2\text{H}\); \(-\text{CO}_2\text{R}^9\); \(-\text{CH}_2\text{CO}_2\text{H}\); \(-\text{CH}_2\text{CO}_2\text{R}^9\);
\[ \text{R}^{14} \text{ is } H, \text{ alkyl or perfluoroalkyl of 1 to 8 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, phenyl or benzyl;} \]

\[ \text{R}^{15} \text{ is } H, \text{ alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, phenyl, benzyl, acyl of 1 to 4 carbon atoms, phenacyl;} \]

\[ \text{R}^{16} \text{ is } H, \text{ alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, } (\text{CH}_2)_p\text{C}_6\text{H}_5, \text{ OR}^{17}, \text{ or NR}^{18}\text{R}^{19}; \]
R^{17} is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, phenyl or benzyl;

R^{18} and R^{19} independently are H, alkyl of 1 to 4 carbon atoms, phenyl, benzyl, α-methylbenzyl, or taken together with the nitrogen form a ring of the formula

\[
\text{Q is } NR^{20}, O \text{ or } CH_2;
\]

R^{20} is H, alkyl of 1-4 carbon atoms, or phenyl;

R^{21} is alkyl of 1 to 6 carbon atoms, \(-NR^{22}R^{23}\), or

\[
\text{CHCH}_2CO_2CH_3;
\]

\[
\text{NH}_2
\]

R^{22} and R^{23} independently are H, alkyl of 1 to 6 carbon atoms, benzyl, or are taken together as \((CH_2)_u\) where \(u\) is 3-6;

R^{24} is H, CH_3 or \(-C6H_5\);

R^{25} is \(NR^{27}R^{28}\), OR^{28}, NHCONH_2, NHCSNH_2,

\[
\text{NHSO}_2-\text{CH}_3 \text{ or } -\text{NHSO}_2-
\]

R^{26} is hydrogen, alkyl with from 1 to 6 carbon atoms, benzyl, or allyl.
R²⁷ and R²⁸ are independently hydrogen, alkyl with
from 1 to 5 carbon atoms, or phenyl;

R²⁹ and R³⁰ are independently alkyl of 1-4 carbon
5 atoms or taken together are -(CH₂)q⁻;

R³¹ is H, alkyl of 1 to 4 carbon atoms, -CH₂CH=CH₂
or -CH₂C₆H₄R³²;

10 R³² is H, NO₂, NH₂, OH or OCH₃;

X is a carbon-carbon single bond, -CO-, -CH₂-, -O-, -S-, -NH-, -N-, -CON-, -NCO-
15 R²⁶  R²³  R²³

-OCH₂-, -CH₂O-, -SCH₂-, -CH₂S-, NHC(R²⁷)(R²⁸),
-NR²³SO₂-, -SO₂NR²³-, -C(R²⁷)(R²⁸)NH-, -CH=C=CH-, -CF=CF-, -CH=CF-, -CF=CH-, -CH₂CH₂-, -CF₂CF₂-,
20

\[
\begin{array}{c}
\text{OR}^{14}, \text{OCOR}^{17}, \text{NR}^{25} \\
\text{OR}^{28} \text{OR}^{30}
\end{array}
\]

Y is 0 or S;
25 Z is 0, NR¹¹, or S;

m is 1 to 5;

n is 1 to 10;
p is 0 to 3;

q is 2 to 3;

r is 0 to 2;

s is 0 to 5;

30 t is 0 or 1;
or a pharmaceutically acceptable salt thereof; provided that:

(1) the R¹ group is not in the ortho position;

(2) when R¹ is

\[
\begin{array}{c}
\text{R}^2 \\
\text{R}^3 \\
\text{R}^1 \\
\text{R}^3 \\
\text{R}^2 \\
\text{X}
\end{array}
\]

\[X \text{ is a single bond, and } R^{13} \text{ is } \text{CO}_2\text{H, or}
\]

\[
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{N} \\
\text{H}
\end{array}
\]

then R¹ must be in the ortho or meta position; or when

R¹ and X are as above and R¹ is NHSO₂CF₃ or NHSO₂CH₃, R¹ must be ortho;

(3) when R¹ is

\[
\begin{array}{c}
\text{R}^2 \\
\text{R}^3 \\
\text{R}^1 \\
\text{R}^3 \\
\text{R}^2 \\
\text{X}
\end{array}
\]

and X is other than a single bond, then R¹ must be ortho except when X = NR²³CO and R¹ is NHSO₂CF₃ or NHSO₂CH₃, then R¹ must be ortho or meta;

(4) when R¹ is 4-CO₂H or a salt thereof, R⁶ cannot be S-alkyl;

(5) when R¹ is 4-CO₂H or a salt thereof, the substituent on the 4-position of the imidazole cannot be CH₂OH, CH₂OCH₂CH₃, or CH₂CO₂H;

(6) when R¹ is
X is $-\text{OCH}_2-$, and $R^{13}$ is 2-CO$_2$H, and $R^7$ is H then $R^6$ is not C$_2$H$_5$S;

(7) when $R^1$ is

\[
\begin{align*}
&\text{CF}_3\text{SO}_2\text{HN} \\
&\text{-CONH-} \\
\end{align*}
\]

and $R^6$ is n-hexyl, then $R^7$ and $R^8$ are not both hydrogen;

(8) when $R^1$ is

\[
\begin{align*}
&\text{CF}_3\text{SO}_2\text{HN} \\
&\text{-NHCO-} \\
\end{align*}
\]

$R^6$ is not methoxybenzyl;

(9) the $R^6$ group is not $-\text{F-CHCH}_2\text{CH}_2\text{CH}_3$ or CH$_2$OH;

(10) when $r=0$, $R^1$ is

\[
\begin{align*}
&\text{-X-} \\
&\text{R}^{13} \\
\end{align*}
\]

$X$ is $-\text{NH-C=O}$, $R^{13}$ is 2-NHSO$_2$CF$_3$, and $R^6$ is n-propyl, then $R^7$ and $R^8$ are not $-\text{CO}_2\text{CH}_3$;

(11) when $r=0$, $R^1$ is
X is NH-C=O, R^{13} is 2-COOH, and R^6 is n-propyl, then R^7 and R^8 are not -CO_2CH_3;

(12) when r=1, R^1=

X is a single bond, R^7 is Cl, and R^8 is -CHO, then R^{13} is not 3-(tetrazol-5-yl);

(13) when r=1, R^1=

X is a single bond, R^7 is Cl, and R^8 is -CHO, then R^{13} is not 4-(tetrazol-5-yl).

2. Method of claim 1 wherein the compound of formula (I) is a compound of formula (II):
wherein \( R^1 \) is \(-\text{CO}_2\text{H}; -\text{NHSO}_2\text{CF}_3; \)

\[
\begin{align*}
\text{or} \\
&\text{alkyl of 3 to 10 carbon atoms, alkenyl of 3 to 10 carbon atoms, alkynyl of 3 to 10 carbon atoms, cycloalkyl of 3 to 8 carbon atoms, benzyl substituted on the phenyl ring with up to two groups selected from alkoxy of 1 to 4 carbon atoms, halogen, alkyl of 1 to 4 carbon atoms, and nitro;}
\end{align*}
\]

\( R^8 \) is
42

\[-(CH_2)_n-tetrazolyl, -(CH_2)_nOR^{11}, -(CH_2)_nOCR^{14}, \]

\[-(CH_2)_nCR^{16}, -(CH_2)_nCR^{16} \]

\[-CH=CH(CH_2)_nCR^{16}, -(CH_2)_nCHOR^{15}, \]

\[-(CH_2)_nCR^{16}, -(CH_2)_nNHCOOR^{10}, -(CH_2)_nNHSO_2R^{10}, \]

\[-(CH_2)_mF; \text{ or } -(CH_2)_mCR^{16}; \]

phenylalkenyl wherein the aliphatic portion is 2 to 4 carbon atoms; \(-(CH_2)_m\)-imidazol-1-yl; or \(-(CH_2)_m\)-1,2,3-triazolyl optionally substituted with one or two groups selected from \(-CO_2CH_3\) or alkyl of 1 to 4 carbon atoms;

\[R^{13} \text{ is } -CO_2H, -CO_2R^{9}, NHSO_2CF_3, SO_3H; \text{ or} \]

\[
\text{N}
\text{N}
\text{N}
\text{N}
\text{H}
\]

\[R^{16} \text{ is } H, \text{ alkyl of 1 to 5 carbon atoms, OR}^{17}, \text{ or} \]

\[NR^{18}R^{19}; \]

\[X \text{ is carbon-carbon single bond, } -CO-, CH_2CH_2-, \]

\[-CON-, -NCO-, \]

\[R^{23} \]

\[R^{23} \]

\[-OCH_2-, -CH_2O-, -O-, -SCH_2-, -CH_2S-, -NH-CH_2-, -CH_2NH-, \]

\[\text{or } -CH=CH-; \text{ or a pharmaceutically acceptable salt thereof.} \]

20
3. Method of claim 2 wherein the compound of formula (II) is a compound wherein:

   R² is H, alkyl of 1 to 4 carbon atoms, halogen, or alkoxy of 1 to 4 carbon atoms;

   R⁶ is alkyl, alkenyl or alkynyl of 3 to 7 carbon atoms;

   R⁷ is heteroaryl selected from 2- and 3-thienyl, 2- and 3-furyl, 2-, 3-, and 4-pyridyl, p-biphenylyl; H, Cl, Br, I; CₓF₂ᵥ+₁, where v=1-3; - CR¹⁶ ; straight or branched chain alkyl of 1 to 6 carbon atoms; or phenyl;

   R⁸ is

   \[-(CH₂)ₘOR¹¹; -(CH₂)ₘOCR¹⁴; -CH=CH-CH₂OR¹⁵; \]

   \[-(CH₂)ₘCR¹⁶; -CH₂NHCOR¹₀; -(CH₂)ₘNH₂SO₂R¹₀; \]

   \[-CH₂ \]

   \[\text{or } -COR¹⁶;\]

   R¹₀ is CF₃, alkyl of 1 to 6 carbon atoms or phenyl;

   R¹¹ is H, or alkyl of 1 to 4 carbon atoms;

   R¹₃ is CO₂H; CO₂CH₂OCOC(CH₃)₃; NH₂SO₂CF₃;
R\textsuperscript{14} is H, or alkyl of 1 to 4 carbon atoms;

R\textsuperscript{15} is H, alkyl of 1 to 4 carbon atoms, or acyl of 1 to 4 carbon atoms;

R\textsuperscript{16} is H, alkyl of 1 to 5 carbon atoms; OR\textsuperscript{17}; or

\[
\begin{array}{c}
\text{-N} \\
\text{O}
\end{array}
\]

m is 1 to 5;

X = single bond, -O-; -CO-; -NHCO-; or -OCH\textsubscript{2}-; or a pharmaceutically acceptable salt thereof.

4. Method of claim 3 wherein the compound of formula (II) is a compound wherein \( R^1 \) is

\[
\begin{array}{c}
\text{} \\
\text{R}^1 \\
\text{X} \\
\text{} \\
\text{R}^2
\end{array}
\]

and \( X \) is a single bond; or a pharmaceutically suitable salt thereof.

5. Method of claim 4 wherein the compound of formula II is:

- 2-Butyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl) biphenyl-4-yl)methyl]-5-(hydroxymethyl)imidazole
- 2-Butyl-4-chloro-1-[(2'-carboxybiphenyl-4-yl)-methyl]-5-(hydroxymethyl)imidazole
- 2-Butyl-4-chloro-1-[(2'-carboxybiphenyl-4-yl)-methyl]-5-[(methoxycarbonyl)aminomethyl] imidazole
• 2-Butyl-4-chloro-1-[(2'-carboxybiphenyl-4-yl)-methyl]-
  5-[(propoxycarbonylaminomethyl) imidazole
• 2-Butyl-4-chloro-1-[(2'-carboxybiphenyl-4-
  yl)methyl]imidazole-5-carboxaldehyde
• 2-Butyl-1-[(2'-carboxybiphenyl-4-yl)methyl]-imidazole-5-carboxaldehyde
  5-[(1E-Butenyl)-4-chloro-1-[(2'-carboxybiphenyl-4-
  yl)methyl]imidazole-5-(hydroxymethyl)imidazole
• 2-(1E-Butenyl)-4-chloro-1-[(2'-carboxybiphenyl-4-
  yl)methyl]imidazole-5-carboxaldehyde
• 2-Propyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-
  yl)methyl]-5-(hydroxymethyl)imidazole
• 2-Propyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-
  yl)methyl]imidazole-5-carboxaldehyde
• 2-Butyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-
  yl)methyl]imidazole-5-carboxaldehyde
• 2-(1E-Butenyl)-4-chloro-1-[(2'-(1H-tetrazol-5-
  yl)biphenyl-4-yl)methyl]-5-hydroxymethyl)imidazole
• 2-(1E-Butenyl)-4-chloro-1-[(2'-(1H-tetrazol-5-
  yl)biphenyl-4-yl)methyl]imidazole-5-carboxaldehyde
• 2-Butyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-
  yl)methyl]imidazole-5-carboxylic acid
• 2-Propyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-
  4-yl)methyl]imidazole-5-carboxylic acid
• 2-Propyl-4-trifluoromethyl-1-[(2'-(1H-tetrazol-5-
  yl)biphenyl-4-yl)methyl]imidazole-5-carboxylic acid
• 2-Propyl-4-trifluoromethyl-1-[(2'-(1H-tetrazol-5-
  yl)biphenyl-4-yl)methyl]-5-(hydroxymethyl)imidazole
• 2-Butyl-4-trifluoromethyl-1-[(2'-(1H-tetrazol-5-
  yl)biphenyl-4-yl)methyl]imidazole-5-carboxaldehyde
• 2-Propyl-4-trifluoromethyl-1-[(2'-(carboxybiphenyl-4-
  yl)methyl)]imidazole-5-carboxaldehyde
• 2-Propyl-4-pentafluoroethyl-1-[(2'-(1H-tetrazol-5-
  yl)biphenyl-4-yl)methyl]-5-(hydroxymethyl)imidazole
2-Propyl-4-pentafluoroethyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxylic acid
2-Propyl-4-pentafluoroethyl-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxaldehyde
1-[(2'-(1H-Tetrazol-5-yl)biphenyl-4-yl)methyl]-4-phenyl-2-propylimidazole-5-carboxaldehyde
1-[(2'-Carboxybiphenyl-4-yl)methyl]-4-phenyl-2-propylimidazole-5-carboxaldehyde.

6. An ophthalmological formulation for the treatment of ocular hypertension and increasing retinal blood flow comprising an ophthalmologically acceptable carrier and 0.01% to 5% (w/v) of a compound of formula (II):

![Chemical Structure](image)

wherein
R1 is -CO2H4; -NHSO2CF3;
R\textsuperscript{6} is alkyl of 3 to 10 carbon atoms, alkenyl of 3 to 10 carbon atoms, alkynyl of 3 to 10 carbon atoms, cycloalkyl of 3 to 8 carbon atoms, benzyl substituted on the phenyl ring with up to two groups selected from alkoxy of 1 to 4 carbon atoms, halogen, alkyl of 1 to 4 carbon atoms, and nitro;

R\textsuperscript{7} is H, F, Cl, Br, I, NO\textsubscript{2}, C\textsubscript{v}F\textsubscript{2v+1}, where v = 1–6, C\textsubscript{6}F\textsubscript{5}; CN; \text{} \text{\text{\text{-}\text{R}}\textsuperscript{16}}; straight or branched alkyl of 1 to 6 carbon atoms; phenyl or phenylalkyl, where alkyl is 1 to 3 carbon atoms; or substituted phenyl or substituted phenylalkyl, where alkyl is 1 to 3 carbon atoms, substituted on the phenyl with one or two substituents selected from alkyl of 1 to 4 carbon atoms, F, Cl, Br, OH, OCH\textsubscript{3}, CF\textsubscript{3}, and COOR, where R is H, alkyl of 1 to 4 carbon atoms, or phenyl;

R\textsuperscript{8} is phenylalkenyl wherein the aliphatic portion is 2 to 4 carbon atoms, -(CH\textsubscript{2})\textsubscript{m}-imidazol-1-yl, -(CH\textsubscript{2})\textsubscript{m}-1,2,3-triazolyl optionally substituted with one or two groups selected from CO\textsubscript{2}CH\textsubscript{3} or alkyl of 1 to 4 carbon atoms (CH\textsubscript{2})\textsubscript{m}-tetrazolyl, -(CH\textsubscript{2})\textsubscript{n}OR\textsuperscript{11};
(CH₂)ₙ OR⁺;

-CH=CH(CH₂)ₙ CR⁺;

-CH=CH(CH₂)ₙ COR⁺;

-(CH₂)ₙ CR⁺;

-(CH₂)ₙ NHCO⁻;

-(CH₂)ₙ NHO⁻;

-(CH₂)ₙ NSO₂⁻;

-(CH₂)ₙ F⁻; or -(CR⁺); R² is H; Cl; Br; I; F; NO₂; CN; alkyl of 1 to 4 carbon atoms; acyloxy of 1 to 4 carbon atoms; alkoxy of 1 to 4 carbon atoms; CO₂H; CO₂R³; NSO₂CH₃; NSO₂CF₃; CONHOR¹²; SO₂NH₂;

aryl; or furyl;

R³ is

R¹⁰ is alkyl of 1 to 6 carbon atoms or perfluoroalkyl of 1 to 6 carbon atoms, 1-adamantyl, 1-naphthyl, 1-(1-naphthyl)ethyl, or (CH₂)ₚC₆H₅;

R¹¹ is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, phenyl or benzyl;

R¹² is H, methyl or benzyl;
$R^{13}$ is $-\text{CO}_2\text{H}; -\text{CO}_2R^9; -\text{CH}_2\text{CO}_2\text{H}, -\text{CH}_2\text{CO}_2R^9$;

\[
\begin{array}{cccc}
\text{O} & \text{O} & \text{O} \\
\| & \| & \| \\
\text{O} & \text{OH} & \text{OH}
\end{array}
\]

-PO$_3$H$_2$; -C(CF$_3$)$_2$OH; -NH$_2$SO$_2$CH$_3$; -NH$_2$SO$_2$CF$_3$; -NHCOCF$_3$;

$R^{12}$; -SO$_2$NH$_2$;

\[
\begin{array}{ccc}
\text{N} & \text{N} & \text{N} \\
\text{R}^{27} & \text{O} & \text{C}\text{-P}\text{-OH} \\
\text{OH} & \text{N} & \text{N} \\
\end{array}
\]

-CH$_2$; -CONH; -CONHNOSO$_2$CF$_3$;

\[
\begin{array}{ccc}
\text{N} & \text{N} & \text{N} \\
\text{N} & \text{N} & \text{CF}_3 \\
\text{N} & \text{N} & \text{N} \\
\end{array}
\]

$R^4$ is $-\text{CN}, \text{NO}_2$ or $\text{CO}_2R^n$;

$R^{14}$ is H, alkyl or perfluoroalkyl of 1 to 8 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, phenyl or benzyl;

$R^{15}$ is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, phenyl, benzyl, acyl of 1 to 4 carbon atoms, phenacyl;
$R^{16}$ is $H$, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, $(CH_2)_pC_6H_5$, OR$^{17}$, or NR$^{18}$R$^{19}$;

$R^{17}$ is $H$, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, phenyl or benzyl;

$R^{18}$ and $R^{19}$ independently are $H$, alkyl of 1 to 4 carbon atoms, phenyl, benzyl, $\alpha$-methylbenzyl, or taken together with the nitrogen form a ring of the formula

$$\begin{array}{c}
\text{Q is NR}^{20}, O \text{ or CH}_2; \\
\text{R}^{20} \text{ is } H, \text{ alkyl of } 1-4 \text{ carbon atoms, or phenyl;}
\end{array}$$

$R^{21}$ is alkyl of 1 to 6 carbon atoms, $-\text{NR}^{22}R^{23}$, or $-\text{CHCH}_2\text{CO}_2\text{CH}_3$;

$R^{22}$ and $R^{23}$ independently are $H$, alkyl of 1 to 6 carbon atoms, benzyl, or are taken together as $(CH_2)_u$ where $u$ is 3–6;

$R^{24}$ is $H$, CH$_3$ or $-C_6H_5$;

$R^{25}$ is NR$^{27}$R$^{28}$, OR$^{28}$, NHCONH$_2$, NHCSNH$_2$,

-NHSO$_2$-CH$_3$ or -NHSO$_2$-
R\textsuperscript{26} is hydrogen, alkyl with from 1 to 6 carbon atoms, benzyl, or allyl;

R\textsuperscript{27} and R\textsuperscript{28} are independently hydrogen, alkyl with from 1 to 5 carbon atoms, or phenyl;

R\textsuperscript{29} and R\textsuperscript{30} are independently alkyl of 1-4 carbon atoms or taken together are -(CH\textsubscript{2})\text{q}-;

R\textsuperscript{31} is H, alkyl of 1 to 4 carbon atoms, -CH\textsubscript{2}CH=CH\textsubscript{2} or -CH\textsubscript{2}C\textsubscript{6}H\textsubscript{4}R\textsuperscript{32};

R\textsuperscript{32} is H, NO\textsubscript{2}, NH\textsubscript{2}, OH or OCH\textsubscript{3};

X is a carbon-carbon single bond, -CO-, -CH\textsubscript{2}-, -O-, -S-, -NH-, -N-, -CON-, -NCO-

\begin{array}{c}
\text{OR}\textsuperscript{14}, \text{OCOR}\textsuperscript{17}, \text{NR}\textsuperscript{25}
\end{array}
\begin{array}{c}
\text{R}\textsuperscript{29}O \text{OR}\textsuperscript{30}
\end{array}

\begin{array}{c}
\text{-CH-} \quad \text{-CH-} \quad \text{OR}\textsuperscript{14}
\end{array}
\begin{array}{c}
\text{-C-}
\end{array}
\begin{array}{c}
\text{-C-}
\end{array}

\begin{array}{c}
m \text{ is 1 to 5;}
\end{array}
\begin{array}{c}
n \text{ is 1 to 10;}
\end{array}
\begin{array}{c}
p \text{ is 0 to 3;}
\end{array}
\begin{array}{c}
q \text{ is 2 to 3;}
\end{array}
\begin{array}{c}
r \text{ is 0 to 2;}
\end{array}
\begin{array}{c}
s \text{ is 0 to 5;}
\end{array}
\begin{array}{c}
t \text{ is 0 or 1;}
\end{array}

or a pharmaceutically acceptable salt thereof.
7. The formulation of Claim 6 wherein:
   R² is H, alkyl of 1 to 4 carbon atoms, halogen, or
   alkoxy of 1 to 4 carbon atoms;
   R⁶ is alkyl, alkenyl or alkynyl of 3 to 7 carbon
   atoms;
   R⁷ is H, Cl, Br, I; CᵥF₂ᵥ₊₁, where v = 1–3; or
   \[ -\text{CR}^{16} \]
   R⁸ is
   \[ -(\text{CH}_₂)ₘ\text{OR}^{11}; -(\text{CH}_₂)ₘ\text{OCR}^{14}; \text{CH}²\text{CH}·\text{CHR}^{15}; \]
   \[ -(\text{CH}_₂)ₘ\text{CR}^{16}; \text{CH}_₂\text{NHCOR}^{10}; -(\text{CH}_₂)ₘ\text{NHSO}_₂\text{R}^{10}; \]
   \[ \text{CH}_₂\text{NNH} \]
   \[ \text{H} \]
   or \[ -\text{COR}^{16}; \]
   R¹⁰ is CF₃, alkyl of 1 to 6 carbon atoms or phenyl;
   R¹¹ is H, or alkyl of 1 to 4 carbon atoms;
   R¹³ is CO₂H; CO₂CH₂OCOC(CH₃)₃; NHSO₂CF₃;
   R¹⁴ is H, or alkyl of 1 to 4 carbon atoms;
R^{15} is H, alkyl of 1 to 4 carbon atoms, or acyl of 1 to 4 carbon atoms;

R^{16} is H, alkyl of 1 to 5 carbon atoms; OR^{17}; or

m is 1 to 5;

X = single bond, -O--; -CO--; -NHCO--; or -OCH_{2}--; or a pharmaceutically acceptable salt thereof.

8. The formulation of Claim 7 wherein R^{2} is H, alkyl of 1 to 4 carbon atoms, halogen, or alkoxy of 1 to 4 carbon atoms;

R^{6} is alkyl, alkenyl or alkynyl of 3 to 7 carbon atoms;

R^{7} is C_{v}F_{2v+1}, where v=1-3; OR^{16}; or Cl;

R^{8} is
-(CH₂)ₘOR¹¹; -(CH₂)ₘOCH₂R¹⁴; -COOH or CHO;

R¹⁴

-CH=CH-CHOR¹⁵; -(CH₂)ₘCR¹⁶; -CH₂NHCOR¹⁰;

-(CH₂)ₘNH₂SO₂R¹⁰; -CH₂

R¹⁰ is CF₃, alkyl of 1 to 6 carbon atoms or phenyl;

R¹¹ is H, or alkyl of 1 to 4 carbon atoms;

R¹³ is CO₂H; CO₂CH₂OCOC(CH₃)₃; NH₂SO₂CF₃;

R¹⁴ is H, or alkyl of 1 to 4 carbon atoms;

R¹⁵ is H, alkyl of 1 to 4 carbon atoms, or acyl of 1 to 4 carbon atoms;

R¹⁶ is H, alkyl of 1 to 5 carbon atoms; OR¹⁷; or

m is 1 to 5;

X = single bond, -O--; -CO--; -NHCO--; or -OCH₂--; or a pharmaceutically acceptable salt thereof.
9. The formulation of Claim 8 wherein the compound is:

- 2-Butyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-y1)methyl]-5-(hydroxymethyl)imidazole
- 2-Butyl-4-chloro-1-[(2'-carboxybiphenyl-4-yl)methyl]-5-(hydroxymethyl)imidazole
- 2-Butyl-4-chloro-1-[(2'-carboxybiphenyl-4-yl)methyl]-5-[(methoxycarbonyl)aminomethyl] imidazole
- 2-Butyl-4-chloro-1-[(2'-carboxybiphenyl-4-yl)methyl]imidazole-5-carboxaldehyde
- 2-Butyl-1-[(2'-carboxybiphenyl-4-yl)methyl]-imidazole-5-carboxaldehyde
- 2-(1E-Butenyl)-4-chloro-1-[(2'-carboxybiphenyl-4-yl)methyl]-5-(hydroxymethyl)imidazole
- 2-(1E-Butenyl)-4-chloro-1-[(2'-carboxybiphenyl-4-yl)methyl]imidazole-5-carboxaldehyde
- 2-Propyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-5-(hydroxymethyl)imidazole
- 2-Propyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxaldehyde
- 2-Butyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxaldehyde
- 2-(1E-Butenyl)-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-5-hydroxymethyl)imidazole
- 2-(1E-Butenyl)-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxaldehyde
- 2-Butyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxylic acid
- 2-Propyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxylic acid
• 2-Propyl-4-trifluoromethyl-1-[(2'-H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxylic acid
• 2-Propyl-4-trifluoromethyl-1-[(2'-H-tetrazol-5-yl)biphenyl-4-yl)methyl]-5-(hydroxymethyl)imidazole
• 2-Butyl-4-trifluoromethyl-1-[(2'-H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxylic acid
• 2-Propyl-4-trifluoromethyl-1-[(2'-carboxybiphenyl-4-yl)methyl]imidazole-5-carboxaldehyde
• 2-Propyl-4-pentafluoroethyl-1-[(2'-H-tetrazol-5-yl)biphenyl-4-yl)methyl]-5-(hydroxymethyl)imidazole
• 2-Propyl-4-pentafluoroethyl-1-[(2'-H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxylic acid
• 2-Propyl-4-pentafluoroethyl-1-[(2'-H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxaldehyde

5
10
15

• 1-[(2'-carboxybiphenyl-4-yl)methyl]-4-phenyl-2-propylimidazole-5-carboxaldehyde
# INTERNATIONAL SEARCH REPORT

**International Application No.** PCI/US91/02119

## I. CLASSIFICATION OF SUBJECT MATTER

According to International Patent Classification (IPC) or both National Classification and IPC

<table>
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<th>IPC</th>
<th>U.S. CL</th>
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<td>A61K 31/41</td>
<td>514/381, 382</td>
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## II. FIELDS SEARCHED

### Minimum Documentation Searched

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Documentation Searched other than Minimum Documentation to the extent that such documents are included in the fields searched:

*Cas on line: structure search*

## III. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<th>Relevant to Claim No.</th>
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<tr>
<td>Y</td>
<td>Biosis, volume 90, no 181852, issued 1989. B.P. VOGH, &quot;Effects of of Inhibition of Angilinsin converting enzyme and carbonic anhydrase on fluid production by ciliary process choroid plexus and pancreas&quot;. See the whole abstract.</td>
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* Special categories of cited documents:

- **A** document defining the general state of the art which is not considered to be of particular relevance
- **E** earlier document but published on or after the international filing date
- **L** document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- **O** document referring to an oral disclosure, use, exhibition or other means
- **P** document published prior to the international filing date but later than the priority date claimed

- **T** later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- **X** document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step
- **Y** document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- **A** document member of the same patent family

## IV. CERTIFICATION

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**International Searching Authority**

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