INSTRUCTIONS

(a) If Convention application insert 'Convention'.

AMENDED

Reg 76(3)

(a) Convention

AUSTRALIA

Patents Act 633082

(b) Delete one

APPLICATION FOR A (b) STANDARD/~~PETTY~~ PATENT

(c) Insert FULL name(s) of applicant(s)

I/We (c) E.R. SQUIBB & SONS, INC.

(d) Insert FULL address(es) of applicant(s)

of (d) Lawrenceville-Princeton Road, Princeton, New Jersey, UNITED STATES OF AMERICA

(e) Delete one

hereby apply for the grant of a (e) Standard/~~Petty~~ Patent for an invention entitled

(f) Insert TITLE of invention

(f) PYRANYL CYANOGUANIDINE DERIVATIVES

(g) Insert "complete" or "provisional" or "petty patent"

which is described in the accompanying (g) Complete specification.

(*Note: The following applies only to Convention applications)*

Details of basic application(s)

(h) Insert number, country and filing date for the/or each basic application

	Application No.	Country	Filing Date
(h)	359,236	UNITED STATES OF AMERICA	31 May 1989
	493,060	UNITED STATES OF AMERICA	13 March 1990

Address for Service: PHILLIPS ORMONDE AND FITZPATRICK
Patent and Trade Mark Attorneys
367 Collins Street
Melbourne, Australia 3000

(i) Insert date of signing

Dated (i) 29 May, 1990

(j) Signature of applicant(s) (For body corporate see headnote*)

(k) Corporate seal if any

(k)

(j) PHILLIPS ORMONDE & FITZPATRICK
Attorneys for:
E.R. SQUIBB & SONS, INC.

Note: No legalization or other witness required

PHILLIPS ORMONDE AND FITZPATRICK
Patent and Trade Mark Attorneys
367 Collins Street
Melbourne, Australia

P17/2/83

COMMONWEALTH OF AUSTRALIA

Patents Act

DECLARATION FOR A PATENT APPLICATION

▼ INSTRUCTIONS

(a) Insert "Convention" if applicable

(b) Insert FULL name(s) of applicant(s)

(c) Insert "of addition" if applicable

(d) Insert TITLE of invention

(e) Insert FULL name(s) AND address(es) of declarant(s) (See headnote**)

(f) Insert FULL name(s) AND address(es) of actual inventor(s)

(g) Recite how applicant(s) derive(s) title from actual inventor(s) (See headnote**)

(h) Insert country, filing date, and basic applicant(s) for the/or EACH basic application

(k) Insert PLACE of signing

(l) Insert DATE of signing

(m) Signature(s) of declarant(s)

Note: No legalization or other witness required

In support of the (a) convention application made by (b) E.R. SQUIBB & SONS, INC., a corporation duly organized and existing under the laws of the State of Delaware, United States of America, having its offices at Lawrenceville-Princeton Road, Princeton, New Jersey, United States of America, (hereinafter called "applicant(s)") for a patent (c) for an invention entitled (d)

PYRANYL CYANOGUANIDINE DERIVATIVES

I/We (e) Nicholas Patrick Malatestinic of East Windsor, New Jersey, United States of America,

do solemnly and sincerely declare as follows:

1. ~~I am/We are the applicant(s).~~
(or, in the case of an application by a body corporate)
1. I am/~~We are~~ authorized to make this declaration on behalf of the applicant(s).
2. ~~I am/We are the actual inventor(s) of the invention.~~
(or, where the applicant(s) is/are not the actual inventor(s))

2. (f)

Karnail Atwal 92 Valley View Way Newtown, PA, USA	Gary James Grover 101 Bowne Station Rd. Stockton, NJ, USA	Kyoung Soon Kim 11 LeParc Drive Lawrenceville, NJ, USA

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

(g)

Karnail Atwal Gary James Grover Kyoung Soon Kim

By virtue of an Assignment dated: May 30, 1989 (Atwal)
March 13, 1990 (Atwal, Grover and Kim)

*(**Note**: Paragraphs 3 and 4 apply **only** to Convention applications)*

3. The basic application(s) for patent or similar protection on which the application is based is/are identified by ***country, filing date, and basic applicant(s)*** as follows:

(h)

in:	United States of America	on:	May 31, 1989 March 13,1990
By:	Karnail Atwal	Gary James Grover	Kyoung Soon Kim

4. The basic application(s) referred to in paragraph 3 hereof was/were the first application(s) made in a Convention country in respect of the invention the subject of the application.

Declared at (k) Princeton, New Jersey, U.S.A.

Dated (l) March 16, 1990

(m) E.R. Squibb & Sons, Inc.

By [signature]
Nicholas Patrick Malatestinic
Assistant Secretary

(SEAL)

To: The Commissioner of Patents

PHILLIPS ORMONDE & FITZPATRICK
Patent and Trade Mark Attorneys

AU9054552

(12) PATENT ABRIDGMENT (11) Document No. AU-B-54552/90
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 633082

(54) Title
PYRANYL CYANOGUANIDINE DERIVATIVES

International Patent Classification(s)
(51)[5] C07D 311/70 A61K 031/35 C07D 311/68 C07D 405/04
C07D 405/12 C07D 491/052

(21) Application No. : 54552/90 (22) Application Date : 30.04.90

(30) Priority Data

(31) Number	(32) Date	(33) Country
359236	31.05.89	US UNITED STATES OF AMERICA
493060	13.03.90	US UNITED STATES OF AMERICA

(43) Publication Date : 06.12.90

(44) Publication Date of Accepted Application : 21.01.93

(71) Applicant(s)
E.R. SQUIBB & SONS, INC.

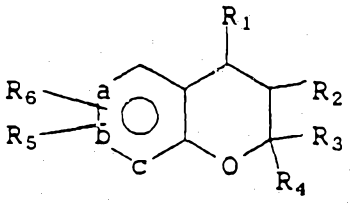
(72) Inventor(s)
KARNAIL ATWAL; GARY JAMES GROVER; KYOUNG SOON KIM

(74) Attorney or Agent
PHILLIPS ORMONDE & FITZPATRICK , 367 Collins Street, MELBOURNE VIC 3000

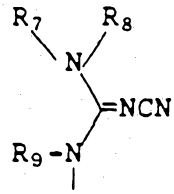
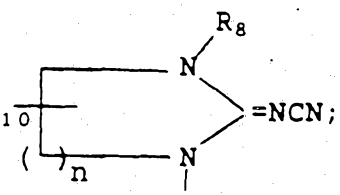
(56) Prior Art Documents
AU 35234/89 C07D

(57) Claim

1. A compound of the formula



wherein a, b, and c are all carbons or one of a, b and c can be nitrogen or -NO- and the others are carbons;

R_1 is  =NCN or  =NCN;

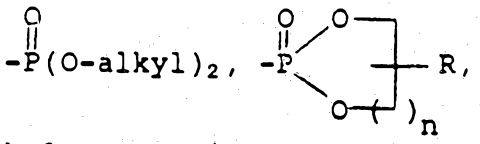
R_2 is hydrogen, hydroxy or $-O\overset{\overset{O}{\|}}{C}CH_3$

R_3 and R_4 are each independently hydrogen, alkyl or arylalkyl, or, R_3 and R_4 taken together with the carbon atom to which they are attached

.../2

form a 5- to 7-membered carbocyclic ring;

R_5 is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, $-NO_2$, -COR, -COOR, -CONHR, $-CONR_2$, $-CF_3$, S-alkyl, -SOalkyl, $-SO_2$alkyl,



halogen, amino, substituted amino, O-alkyl, OCF_3, OCH_2CF_3, -OCOalkyl, -OCONRalkyl, -NRCOalkyl and NRCOOalkyl, $NRCONR_2$ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;

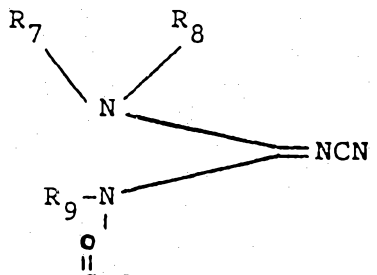
R_6 is selected from H, alkyl, OH, O-alkyl, amino, substituted amino, CN, and NO_2;

R_7 is selected from aryl, arylalkyl, heterocyclo and heterocycloalkyl;

R_8 is selected from hydrogen, alkyl, alkenyl, aryl, heterocyclo, (heterocyclo)alkyl, arylalkyl, cycloalkyl and (cycloalkyl)alkyl, substituted alkyl wherein the substituents include alkoxy, alkylthio and substituted amino, or R_7 and R_8 taken together with the nitrogen atom to which they are attached form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorphilinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl or 4-arylalkyl-1-piperazinyl, wherein each of the so-formed groups can be substituted with alkyl, alkoxy, alkylthio, halogen or trifluoromethyl with the proviso that:

where a, b and c are all carbon atoms,

R_1 is



R_2 is OH or $-OC-CH_3$

R_3 and R_4 are alkyl,

one of R_5 and R_6 is -CN and the other is H,

and R_9 is H or lower alkyl, then

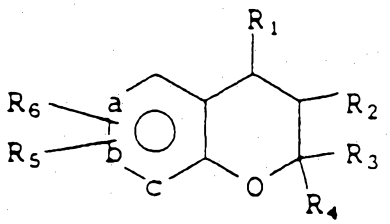
.../3

R_7 and R_8 taken together with the nitrogen atom to which they are attached do not form 1-pyrrolidinyl, 1-piperidinyl or 4-morpholinyl;

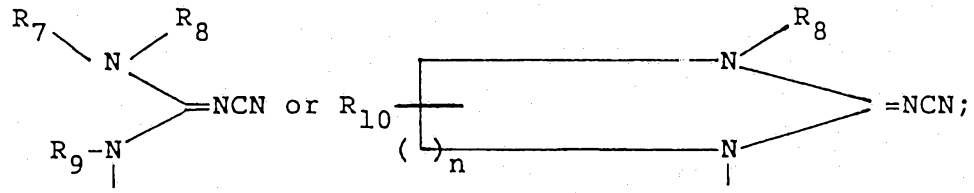
R_9 and R_{10} are selected from hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl or cycloalkylalkyl; and

n is 1, 2 or 3.

38. A method for the treatment of ischemic conditions in a mammalian specie comprising administering to a specie in need thereof an effective amount of a potassium channel activator having little or no vasodilator effect, wherein the potassium channel activator is of the formula:



wherein a, b, and c are all carbons or one of a, b and c can be nitrogen or -NO- and the others are carbons;

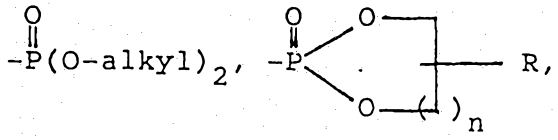
R_1 is  or ;

R_2 is hydrogen, hydroxy or $-O\overset{O}{\overset{\|}{C}}CH_3$

R_3 and R_4 are each independently hydrogen, alkyl or arylalkyl, or, R_3 and R_4 taken together with the carbon atom to which they are attached form a 5- to 7-membered carbocyclic ring;

R_5 is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, $-NO_2$, -COR, -COOR, -CONHR, $-CONR_2$, $-CF_3$, S-alkyl, -SOalkyl, $-SO_2$alkyl,

....4



halogen, amino, substituted amino, O-alkyl, OCF_3, OCH_2CF_3, -OCOalkyl, -OCONRalkyl, -NRCOalkyl and NRCOOalkyl, $NRCONR_2$ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;

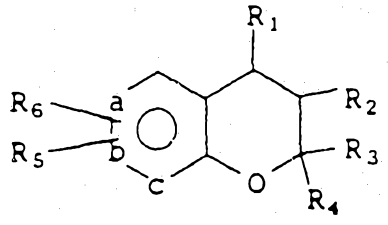
R_6 is selected from H, alkyl, OH, O-alkyl, amino, substituted amino, CN, and NO_2;

R_7 and R_8 are each independently selected from hydrogen, alkyl, alkenyl, aryl, heterocyclo, (heterocyclo)-alkyl, arylalkyl, cycloalkyl and (cycloalkyl)alkyl, substituted alkyl wherein the substituents include alkoxy, alkylthio and substituted amino, or R_7 and R_8 taken together with the nitrogen atom to which they are attached form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorphilinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl or 4-arylalkyl-1-piperazinyl, wherein each of the so-formed groups can be substituted with alkyl, alkoxy, alkylthio, halogen or trifluoromethyl;

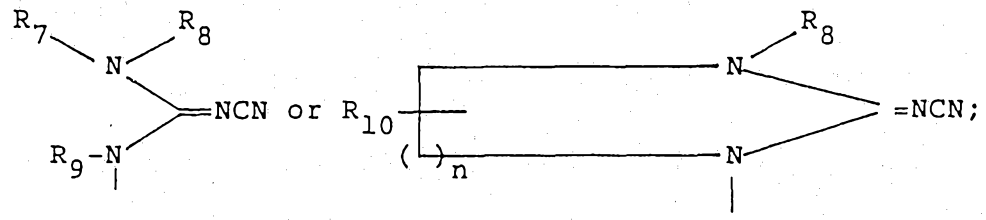
R_9 and R_{10} are selected from hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl or cycloalkylalkyl; and

n is 1, 2 or 3.

39. A pharmaceutical composition for the treatment of ischemic conditions in a mammalian specie comprising an effective amount of a potassium channel activator having little or no vasodilator effect and a pharmaceutically acceptable carrier therefor, wherein the potassium channel activator is of the formula:



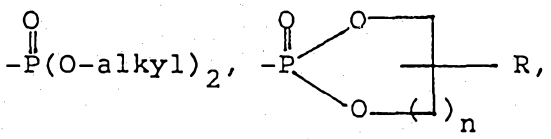
wherein a, b, and c are all carbons or one of a, b and c can be nitrogen or -NO- and the others are carbons;

R_1 is  ;

R_2 is hydrogen, hydroxy or $-OCCH_3$ (O)

R_3 and R_4 are each independently hydrogen, alkyl or arylalkyl, or, R_3 and R_4 taken together with the carbon atom to which they are attached form a 5- to 7-membered carbocyclic ring;

R_5 is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, $-NO_2$, -COR, -COOR, -CONHR, $-CONR_2$, $-CF_3$, S-alkyl, -SOalkyl, $-SO_2$alkyl,



halogen, amino, substituted amino, O-alkyl, OCF_3, OCH_2CF_3, -OCOalkyl, -OCONRalkyl, -NRCOalkyl and NRCOOalkyl, $NRCONR_2$ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;

R_6 is selected from H, alkyl, OH, O-alkyl, amino, substituted amino, CN, and NO_2;

R_7 and R_8 are each independently selected from hydrogen, alkyl, alkenyl, aryl, heterocyclo, (heterocyclo)-alkyl, arylalkyl, cycloalkyl and (cycloalkyl)alkyl, substituted alkyl wherein the substituents include alkoxy, alkylthio and substituted amino, or R_7 and R_8 taken together with the nitrogen atom to which they are attached form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorphilinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl or 4-arylalkyl-1-piperazinyl, wherein each of the so-formed groups can be substituted with alkyl, alkoxy, alkylthio halogen or trifluoromethyl;

.../6

R_9 and R_{10} are selected from hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl or cycloalkylalkyl; and

n is 1, 2 or 3.

AUSTRALIA

Patents Act

633082

COMPLETE SPECIFICATION
(ORIGINAL)

Class Int. Class

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority

Related Art:

Applicant(s):

E.R. Squibb & Sons, Inc.
Lawrenceville-Princeton Road, Princeton, New Jersey, UNITED STATES OF AMERICA

Address for Service is:

PHILLIPS ORMONDE & FITZPATRICK
Patent and Trade Mark Attorneys
367 Collins Street
Melbourne 3000 AUSTRALIA

Complete Specification for the invention entitled:

PYRANYL CYANOGUANIDINE DERIVATIVES

Our Ref : 172106
POF Code: 8448/43804

The following statement is a full description of this invention, including the best method of performing it known to applicant(s):

6006

HA488b

PYRANYL CYANOGUANIDINE DERIVATIVES

This is a continuation-in-part of co-pending application Ser. No. 493,059 filed March 13, 1990, which is a continuation-in-part of co-pending application Ser. No. 359,236 filed May 31, 1989.

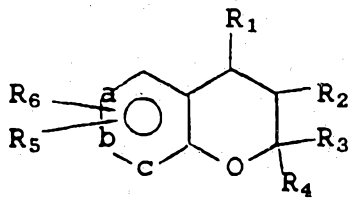
Field of the Invention

The present invention relates to novel compounds having potassium channel activating activity which are therefore useful, for example, as cardiovascular agents.

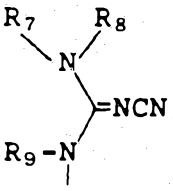
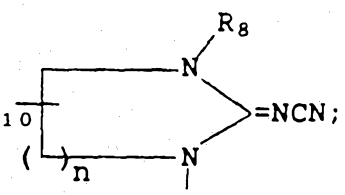
Summary of the Invention

In accordance with the present invention novel compounds having potassium channel activating activity which are useful, for example, as cardiovascular agents, are disclosed. These compounds have the general formula

I

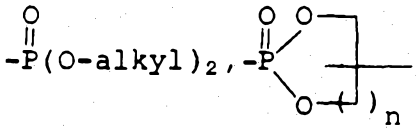


wherein a, b, and c are all carbons or one of a, b and c can be nitrogen or -NO- and the others are carbons;

R_1 is  or  ;

R_2 is hydrogen, hydroxy, $-OCCH_3$;
‖
O

R_3 and R_4 are each independently hydrogen, alkyl or arylalkyl, or, R_3 and R_4 taken together with the carbon atom to which they are attached form a 5- to 7-membered carbocyclic ring;

R_5 is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, $-NO_2$, -COR, -COOR, -CONHR, $-CONR_2$, $-CF_3$, S-alkyl, -SOalkyl, $-SO_2$alkyl, $-P(O\text{-alkyl})_2$,  R, halogen, amino, substituted amino, O-alkyl, OCF_3, OCH_2CF_3, -OCOalkyl, -OCONRalkyl, -NRCOalkyl and NRCOOalkyl, $NRCONR_2$ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;

R_6 is selected from H, alkyl, OH, O-alkyl, amino, substituted amino, CN, and NO_2;

R_7 and R_8 are each independently selected from hydrogen, alkyl, alkenyl, aryl, (heterocyclo)alkyl, heterocyclo, arylalkyl, cycloalkyl and (cycloalkyl)alkyl, substituted alkyl wherein the substituents include alkoxy, alkylthio and substituted amino, or R_7 and R_8 taken together with the nitrogen atom to which they are attached form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorphilinyl, 1-piperazinyl,

4-alkyl-1-piperazinyl or 4-arylalkyl-1-piperazinyl, wherein each of the so-formed groups can be substituted with alkyl, alkoxy, alkylthio, halogen or trifluoromethyl;

R_9 and R_{10} are selected from hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl or cycloalkylalkyl; and

n is 1, 2 or 3.

Detailed Description of the Present Invention

This invention in its broadest aspects relates to the cyanoguanidine compounds of formula I above, to compositions and the methods of using such compounds. The compounds of formula I are useful, for example, as cardiovascular agents. Preferred compounds are those with the 3S, 4R stereochemistry.

The term "alkyl" used in defining various symbols refers to straight or branched chain saturated hydrocarbon radicals having up to eight carbons, preferably from one to five carbons. Similarly, the terms "alkoxy" and "alkylthio" refer to such alkyl groups attached to an oxygen or sulfur.

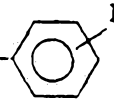
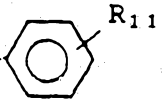
The term "alkenyl" refers to straight or branched chain hydrocarbon radicals having from two to eight carbons and one double bond, preferably three to five carbons. The term "alkynyl" refers to straight or branched chain hydrocarbon radicals having from two to eight carbons and one triple bond, preferably three to five carbons.

The term "cycloalkyl" refers to saturated carbocyclic rings of 3 to 7 carbon atoms with cyclopropyl, cyclopentyl and cyclohexyl being most preferred.

The term "halo" or "halogen" refers to chloro, bromo and fluoro.

The term "halo substituted alkyl" refers to such alkyl groups described above in which one or more hydrogens have been replaced by chloro, bromo or fluoro groups such as trifluoromethyl, which is preferred,pentafluoroethyl, 2,2,2-trichloroethyl, chloromethyl, bromomethyl, etc.

The term "aryl" refers to phenyl, 1-naphthyl, 2-naphthyl or mono substituted phenyl, 1-naphthyl, 2-naphthyl wherein said substituent is alkyl of 1 to 4 carbons, alkylthio of 1 to 4 carbons, alkoxy of 1 to 4 carbons, halo, nitro, cyano, hydroxy, amino, -NH-alkyl wherein alkyl is of 1 to 4 carbons, $-N(alkyl)_2$ wherein alkyl is of 1 to 4 carbons,

$-CF_3$, $-OCHF_2$, $-O-CH_2$—  , 

$-S-CH_2$— (wherein R_{11} is hydrogen, alkyl of 1 to 4 carbons, alkoxy of 1 to 4 carbons, alkylthio of 1 to 4 carbons, halo, hydroxy or CF_3), $-O-CH_2$-cycloalkyl, or $-S-CH_2$- cycloalkyl, and di-substituted phenyl, 1-naphthyl, 2-naphthyl wherein said substituents are selected from methyl, methoxy, methylthio, halo, CF_3, nitro, amino, and $OCHF_2$.

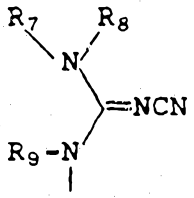
Preferred aryl groups include unsubstituted phenyl and monosubstituted phenyl wherein the substituents are nitro, halo, $-CF_3$, alkyl, cyano or methoxy.

The term "heterocyclo" refers to fully saturated or unsaturated rings of 5 or 6 atoms containing one or two O and S atoms and/or one to four N atoms provided that the total number of hetero atoms in the ring is 4 or less. The hetero ring is attached by way of an available carbon atom. Preferred monocyclic hetero groups include 2- and 3-thienyl, 2- and 3-furyl, 2-, 3- and 4-pyridyl, and imidazolyl. The term hetero also includes bicyclic rings wherein the five or six membered ring containing O, S and N atoms as defined above is fused to a benzene ring and the bicyclic ring is attached by way of an available carbon atom. Preferred bicyclic hetero groups include 4, 5, 6, or 7-indolyl, 4, 5, 6, or 7-isoindolyl, 5, 6, 7 or 8-quinolinyl, 5, 6, 7 or 8-isoquinolinyl, 4, 5, 6, or 7-benzothiazolyl, 4, 5, 6 or 7-benzoxazolyl, 4, 5, 6 or 7-benzimidazolyl, 4, 5, 6 or 7-benzoxadiazolyl, and 4, 5, 6 or 7-benzofuranzanyl.

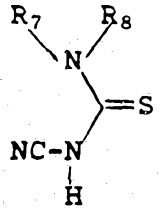
The term heterocyclo also includes such monocyclic and bicyclic rings wherein an available carbon atom is substituted with a lower alkyl of 1 to 4 carbons, lower alkylthio of 1 to 4 carbons, lower alkoxy of 1 to 4 carbons, halo, nitro, keto, cyano, hydroxy, amino, -NH-alkyl wherein alkyl is of 1 to 4 carbons, $-N(alkyl)_2$ wherein alkyl is of 1 to 4 carbons, CF_3, or $OCHF_2$ or such monocyclic and bicyclic rings wherein two or three available carbons have substituents selected from methyl, methoxy, methylthio, halo, CF_3, nitro, hydroxy, amino and $OCHF_2$.

The term "substituted amino" refers to a group of the formula $-NZ_1Z_2$ wherein Z_1 is hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl and Z_2 is alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl or Z_1 and Z_2 taken together with the nitrogen atom to which they are attached are 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorpholinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl, 4-arylalkyl-1-piperazinyl, 4-diarylalkyl-1-piperazinyl, 1-pyrrolidinyl, 1-piperidinyl, or 1-azepinyl substituted with alkyl, alkoxy, alkylthio, halo, trifluoromethyl or hydroxy.

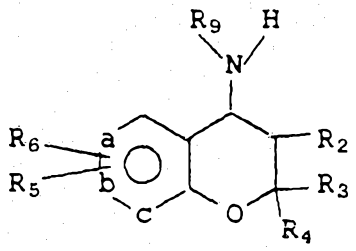
The compounds of formula I wherein R_1 is



can be prepared by treatment of a thiourea of the formula

II 

with an amine of the formula

III 

in the presence of a carbodiimide, preferably 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or dicyclohexylcarbodiimide and an acid source in an organic solvent, such as dimethylformamide, tetrahydrofuran, acetonitrile or dichloromethane.

The thiourea of formula II, wherein R_8 is hydrogen can be prepared by heating an isothiocyanate of the formula

IV $R_7N=C=S$

with either monosodium cyanamide or with cyanamide in the presence of an organic base, such as triethyl amine.

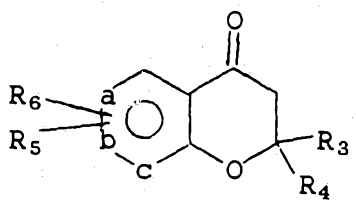
The other thioureas of formula II can be prepared by standard methods described in the literature, such as by C. R. Rasmussen, F. J. Villani, Jr., L. E. Weaner, B. E. Reynolds, A. R. Hood, L. R. Hecker, S. O. Nortey, A. Hanslin, M. J. Costanzo, E. T. Powell, A. J. Molinari, Synthesis, 1988, p. 456, and V. V. Mozolis and S. P. Locubaitite, Russian Chemical Reviews, 1973, 42, 587.

The aminoalcohol of formula III wherein R_2 is hydroxy can be prepared by methods described in the literature, such as by J. M. Evans, C. S. Fake,

T. C. Hamilton, R. H. Poyser, E. A. Watts, J. Med. Chem. 1983, 26, 1582 and J. Med. Chem. 1986, 29, 2194; R. W. Lang, P. F. Wenk, Helvetica Chimica Acta, 1988, 71, 596; EP 0205292 A2 (1986), and WO 87/07607.

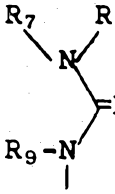
The amine of formula III, wherein R_2 is hydrogen, can be prepared from a ketone of the formula

V

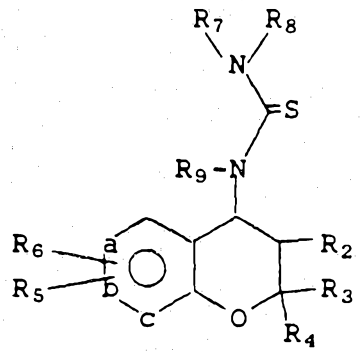


by standard methodology. The ketone of formula V can be obtained by literature procedures, such as disclosed by P. Sebok and T. Timar, Heterocycles, 1988, 27, 2595; P. Teixidor et al., Heterocycles, 1988, 27, 2459; A. Benerji and N. C. Goomer, Tetrahedron Letters, 1979, 3685; G. Ariamala and K. K. Subramanian, Tetrahedron Letters, Vol. 29, No. 28, p. 3487-3488 (1988).

The compounds of formula I wherein R_1 is

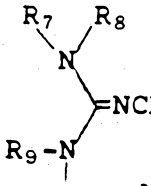


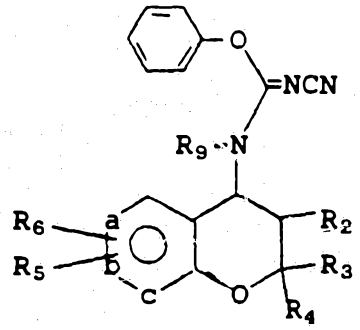
can also be prepared by heating a thiourea of the formula

VI 

with monosodium cyanamide in the presence of a carbodiimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or dicyclohexylcarbodiimide in an organic solvent.

The compounds of formula VI can be prepared from the amino alcohol of formula III by standard methods (i.e., the Rasmussen and Mozolis references above).

The compounds of formula I wherein R_1 is  can also be prepared by reacting a compound of the formula

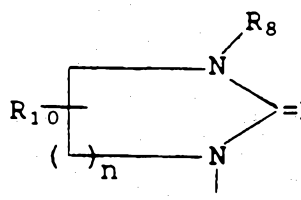
VII 

with an amine of the formula

VIII R_7R_8NH

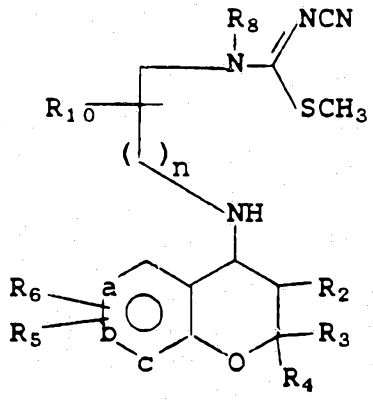
in a polar solvent such as isopropanol. The compounds of formula VII are prepared by reacting an amine of formula III with diphenylcyanocarbonimidate.

The compounds of formula I wherein R_1 is



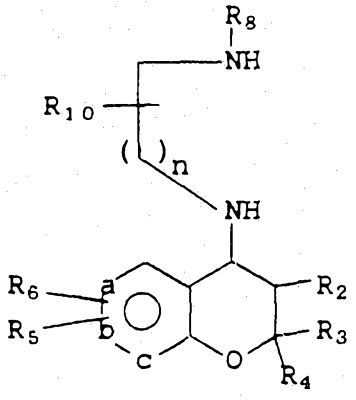
=NCN can be prepared by treating a compound of the formula

IX

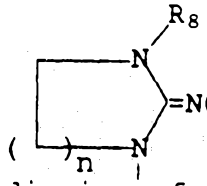


with mercuric acetate in an alcoholic solvent such as methanol.

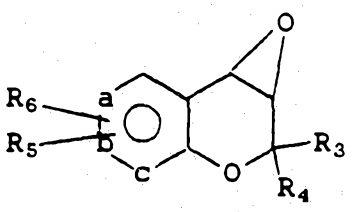
The compounds of formula IX are prepared by treating a diamine of the formula

X 

with dimethyl-N-cyanodithioiminocarbonate.

The compounds of formula I wherein R_1 is  =NCN can also be prepared by treating a diamine of formula X with diphenylcyanocarbonimidate in an alcoholic solvent, such as 2-propanol.

The compound of formula X whrein R_2 is *trans* hydroxyl is obtained by treatment of an epoxide

XI 

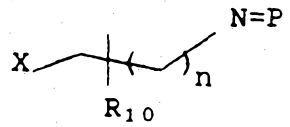
with diamine of the formula

XII 

in an alcoholic solvent, such as ethanol.

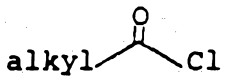
The preparation of the epoxide XI is described by Evans and Lang (references above).

Compounds of formula X can also be prepared from the amino alcohol III and an alkylating agent of the formula

XIII 

wherein P is a protecting group and X is a leaving group, such as Cl, Br and I, in the presence of a base catalyst, followed by deprotection. Compounds of formula X can also be prepared from a ketone or aldehyde of formula XIII (i.e., wherein X is oxo) and amino alcohol III by standard techniques of reductive amination followed by removal of the protection group P.

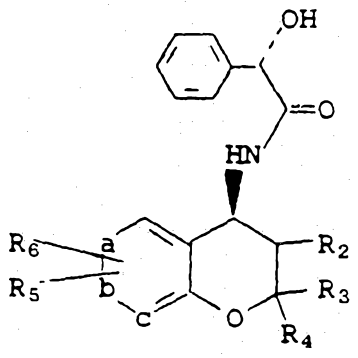
The compounds of the present invention wherein R_2 is OCOalkyl can be prepared by acylation of the alcohol of formula I, wherein R_2 is OH, with an acid chloride of the formula

XIV 

in the presence of a base catalyst, such as pyridine or triethylamine.

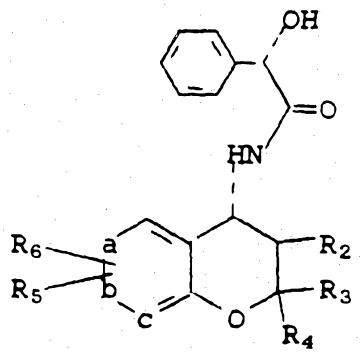
For the preparation of individual enantiomers of compounds of formula I (wherein R_2 =H, OH), compound III (R_2 = =H, OH) is converted to diastereomeric amides of the formula

XV



and

XVI

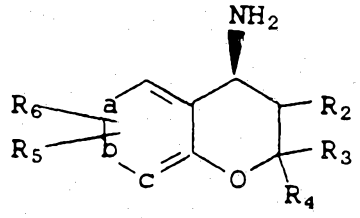


by treatment with chiral nonracemic mandelic acid in the presence of dicyclohexylcarbodiimide.

Compounds XV and XVI are separated by crystallization or chromatography. The enantiomer of mandelic acid that yields crystalline diastereomer with the desired 4R-stereochemistry of benzopyran (as shown in formula XV) is preferred in the resolution step.

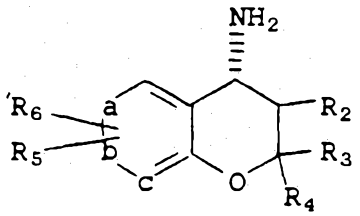
Compounds XV and XVI are then hydrolyzed by heating in the presence of sulfuric acid in dioxane to give enantiomers of the formula

XVII



and

XVIII



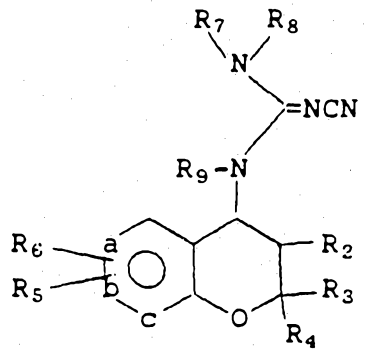
The enantiomers XVII and XVIII are then converted to chiral nonracemic compounds of formula I.

The compounds of the present invention can have asymmetric centers at carbons 2-4 of benzopyran ring. Also, any one of the R's can have an asymmetric carbon. Consequently, compounds of formula I can exist in diastereomeric forms or in mixtures thereof. The above described process can utilize racemates, enantiomers or diastereomers as starting materials. When diastereomeric products are prepared, they can be separated by conventional chromatographic or fractional crystallization methods.

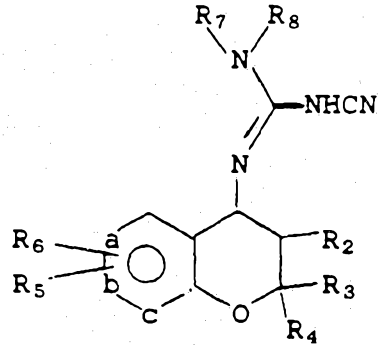
The compounds of the present invention wherein R_9 and/or R_8 is hydrogen, can exist as a mixture of tautomers represented by the following structures. The tautomeric products are obtained in relative amounts that differ from compound to

compound. All forms are included in the scope of formula I.

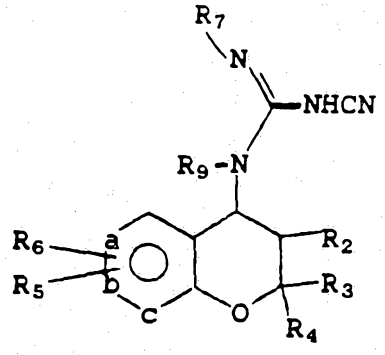
I'



I''



I'''



The compounds of formula I and the pharmaceutically acceptable salts act as potassium channel activators. Thus, compounds of the present invention are useful as anti-arrhythmic agents, antiischemic agents and in the treatment of hypertension.

It has been found that compounds of formula I wherein R_7 is aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, heterocyclo or (heterocyclo)-alkyl are preferred as antiischemic agents, i.e., for the treatment of ischemic conditions such as myocardial ischemia, cerebral ischemia, lower limb ischemia and the like. Especially preferred are those compounds where R_7 is aryl or arylalkyl and R_8 and R_9 are each hydrogen. While any of the compounds of formula I may be used as antiischemic agents, these preferred antiischemic agents have been found to possess little or no vasodilator activity. This means that in the treatment of ischemic heart, these compounds are less likely to cause coronary steal, profound hypotension and coronary underperfusion.

Similarly, the most preferred compounds of formula I for reducing hypertension are those wherein R_7 is hydrogen or alkyl of 1 to 3 carbons, R_7 and R_8 taken together with the nitrogen atom to which they are attached for a 5- or 6-membered ring, such as pyrrolidine or piperidene, R_9 and R_{10} are each hydrogen and n is 1 or 2.

Thus, for example, by the administration of a composition containing one (or a combination) of the compounds of this invention, ischemic conditions of a mammalian (e.g., human) host are reduced. A

single dose, or preferably two to four divided daily doses, provided on a basis of about 0.001 to 100 mg per kilogram of body weight per day, preferably from about 0.1 to about 25 mg per kilogram per day, is appropriate to reduce ischemic conditions. The substance is preferably administered orally, but parenteral routes, such as the subcutaneous, intramuscular, or intravenous routes or any other convenient delivery system, such as inhalation or intranasal solutions or transdermal patches, can also be employed. The above doses are also suitable for the other cardiovascular (e.g., hypertension) and non-cardiovascular uses.

As a result of the potassium channel activating activity of compounds of this invention, these compounds are also useful in the treatment of cardiovascular disorders and any disorders associated with smooth muscle contraction. For example, compounds of the present invention are useful as therapy for congestive heart failure, therapy for peripheral vascular disorders (e.g. Raynaud's Disease), therapy for pulmonary hypertension, as anti-anginal agents, as anti-fibrillatory agents, as thrombolytic agents and in limiting myocardial infarction.

Compounds of the present invention are additionally expected to be useful in the treatment of central nervous system disorders (e.g., Parkinsonism, as anti-tremor agents, epilepsy), in therapy for renal failure, in therapy for urinary incontinence, as anti-diarrheal agents, in therapy for pre-eclampsia, dysmenorrhea and premature labor, as well as for the promotion of hair growth (e.g., in the treatment

of male pattern baldness) and as anti-asthmatic agents.

The compounds of this invention can also be formulated in combination with a diuretic such as, chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlothiazide, trichloromethiazide, polythiazide or benzthiazide as well as ethacrynic acid, tricrynafen, chlorthalidone, furosemide, musolimine, bumetanide, triamterene, amiloride and spironolactone and salts of such compounds, angiotensin converting enzyme inhibitors such as captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril, and salts of such compounds, thrombolytic agents such as tissue plasminogen activator (tPA), recombinant tPA, streptokinase, urokinase, prourokinase, and anisoylated plasminogen streptokinase activator complex (APSAC, Eminase, Beecham Laboratories), or calcium channel blocking agents such as nifedipine or diltiazem. Such combination products if formulated as a fixed dose employ the compounds of this invention within the dose range described above and the other pharmaceutically active agent within its approved dose range.

The compounds of formula I, and combinations thereof, can be formulated, as described above, in compositions such as tablets, capsules or elixirs for oral administration, in sterile solutions or suspensions for parenteral administration, and may also be administered via transdermal patch or nasal inhalation solutions. About 10 to 500 milligrams

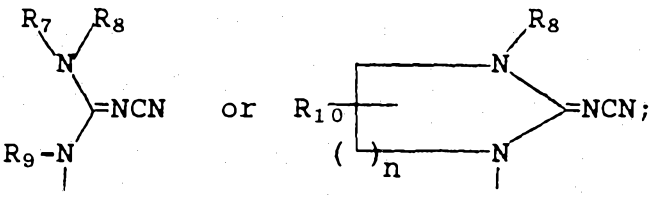
of a compound of formula I is compounded with physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in these compositions or preparations is such that a suitable dosage in the range indicated is obtained.

Preferred compounds are those wherein

a is nitrogen or $-CR_5$;

b and c are each -CH-;

R_1 is



R_2 is hydroxy;

R_3 and R_4 are each alkyl;

R_5 is an electron withdrawing group;

R_6 is hydrogen, alkyl, O-alkyl, amino;

R_7 is hydrogen, alkyl, aryl or arylalkyl;

R_8 is hydrogen;

R_9 is hydrogen or alkyl;

R_{10} is hydrogen; and,

n is 1 or 2.

Most preferred are those compounds wherein

a is nitrogen or $-CR_5$;

b and c are each -CH-;

R_2 is trans-hydroxy;

R_3 and R_4 are each methyl;

R_5 is -CN or $-NO_2$;

R_6 is hydrogen;

R_7 is methyl, ethyl, phenyl or phenylmethyl;

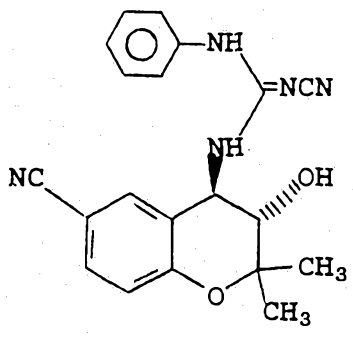
R_8 is hydrogen;

R_9 is hydrogen;

R_{10} is hydrogen; and

n is 1.

The preferred compound of the present invention, which is preferably employed as an antiischemic agent, is



Specific embodiments of the present invention are described hereinafter in the following examples.

Example 1

(*trans*)-N"-Cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-(1,1-dimethylpropyl)guanidine

A. N-Cyano-N'-(1,1-dimethylpropyl)thiourea

To a suspension of monosodium cyanamide (0.64 g, 10 mmol) in absolute ethanol (30 mL), 1,1-dimethylpropylisothiocyanate (1.29 g, 10 mmol) was added slowly at room temperature. Exothermic reaction occurred during addition and near the end of the addition, the initially heterogeneous mixture became a homogeneous solution. It was allowed to stir at room temperature for 2 hours and then heated at 75°C for 1 hour. The reaction mixture was cooled to room temperature and the solid was filtered. The filtrate solution was concentrated to yield the title A compound (1.6 g) as a colorless solid.

B. (*trans*)-N"-Cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-(1,1-dimethylpropyl)guanidine

To a solution of the title A compound (0.94 g, 5.5 mmol) and (*trans*)-4-amino-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile (prepared according to Evans et al., J. Med. Chem., 1983, 26, 1582 and J. Med. Chem., 1986, 29, 2194) (1.0 g, 4.6 mmol) in dimethylformamide (5 mL) under argon, 1-(3-dimethylaminopropyl)-2-ethylcarbodiimide hydrochloride (1.14 g, 5.9 mmol) was added at room temperature. The reaction mixture was stirred at

room temperature for 2 hours and then partitioned between 1N HCl and ethyl acetate. The organic layer was separated and the aqueous phase was reextracted with ethyl acetate and the combined organic phase was washed with water, aqueous sodium bicarbonate and brine. After drying over anhydrous magnesium sulfate, the filtrate was concentrated and the residue was purified by flash chromatography on silica gel (1:1 Hexane/EtOAc). The fractions containing the desired product were combined and concentrated to yield a colorless solid (620 mg). This solid was triturated with isopropyl ether to yield the title compound, m.p. 207-208°C.

Analysis calc'd for $C_{19}H_{25}N_5O_2$:

C, 64.20; H, 7.09; N, 19.71;

Found: C, 64.04; H, 7.11; N, 19.44.

Example 2

(*trans*)-N"-Cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-ethyl guanidine

A. N-Cyano-N'-ethylthiourea

To a suspension of monosodium cyanamide (6.4 g, 100 mmol) in absolute ethanol (30 mL), ethyl-isothiocyanate (9.0 mL, 100 mmol) was added slowly with stirring at room temperature. During addition, exothermic reaction occurred and near the end of the addition the reaction mixture became a homogeneous solution. It was allowed to stir at room temperature for 2 hours and then heated at 75°C for 1 hour. The reaction mixture was cooled to room

temperature and the insoluble material was filtered off (700 mg). The mother liquor was concentrated and the resulting solid was triturated with isopropanol-isopropyl ether to yield the title A compound (11.2 g), m.p. >240°C.

B. (*trans*)-N"-Cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-ethyl guanidine

To a solution of the title A compound (1.15 g, 8.9 mmol) and (*trans*)-4-amino-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile (prepared according to Evans et al., J. Med. Chem., 1983, 26, 1582 and J. Med. Chem., 1986, 29, 2194). (1.5 g, 6.9 mmol) in dimethylformamide (5 mL) under argon was added 1-(3-dimethylaminopropyl)-2-ethyl-carbodiimide hydrochloride (1.71 g, 8.9 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2 hours and then partitioned between 1N HCl and ethyl acetate. The organic phase was separated and the aqueous phase was reextracted with ethyl acetate. The combined organic phase was washed with water, aqueous sodium bicarbonate and brine. After drying over anhydrous magnesium sulfate, the solvent was evaporated and the residue was purified by flash chromatography on silica gel (25% acetone in dichloromethane). The fractions containing the desired product were combined and evaporated to yield a colorless solid (801 mg). This solid product was recrystallized from acetonitrile-ether to yield the title compound, m.p. 185-188°C.

Analysis calc'd for $C_{16}H_{19}N_5O_2$ 0.2 H_2O:
C, 60.64; H, 6.17; N, 22.10;
Found: C, 60,63; H, 6.16; N, 22.25.

Example 3

(*trans*)-N"-Cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-phenyl guanidine

A. N-cyano-N'-phenylthiourea

To a suspension of monosodium cyanamide (6.4 g, 100 mmol) in absolute ethanol (170 mL), phenylisothiocyanate (12.5 mL, 104.5 mmol) was added slowly with stirring at room temperature. The reaction was allowed to stir at room temperature for 1 hour and then heated at 75°C for 4 hours. The reaction was cooled to room temperature and the colorless solid was filtered and washed with ethanol to give the title A compound (13.6 g), m.p. >250°C.

B. (*trans*)-N"-Cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-phenyl guanidine

To a solution of the title A compound (1.06 g, 5.96 mmol) and (*trans*)-4-amino-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile (prepared according to Evans et al., J. Med. Chem., 1983, 26, 1582 and J. Med. Chem., 1986, 29, 2194). (1.0 g, 4.59 mmol) in dimethylformamide (5 mL) under argon, 1-(3-dimethylaminopropyl)-2-ethylcarbodiimide hydrochloride (1.17 g, 5.96 mmol) was

added at room temperature. The reaction mixture was stirred at room temperature for 2 hours and then partitioned between 1N HCl and ethyl acetate. The organic phase was separated and the aqueous phase was reextracted with ethyl acetate and the combined organic phase was washed with water, aqueous sodium bicarbonate and brine. After drying over anhydrous magnesium sulfate, the solvent was evaporated and the colorless residue was triturated with ether to yield the title compound (1.3 g), m.p. 247-249°C (with effervescence).

Analysis calc'd for $C_{20}H_{19}N_5O_2$:

C, 66.46; H, 5.30; N, 19.38;

Found: C, 66.09; H, 5.30; N, 19.35.

Example 4

(*trans*)-N"-Cyano-N-(3,4-dihydroxy-3-hydroxy-2,2-dimethyl-6-nitro-2H-1-benzopyran-4-yl)-N'-ethyl-guanidine

To a solution of the title A compound from Example 2 (1.2 g, 9.4 mmol) and (*trans*)-4-amino-3,4-dihydro-2,2-dimethyl-6-nitro-2H-1-benzopyran (1.5 g, 6.3 mmol) (prepared according to Evans et al., J. Med. Chem., 1983, 26, 1582 and J. Med. Chem., 1986, 29, 2194) in dimethylformamide (5 ml) under argon, 1-(3-dimethylaminopropyl)-2-ethylcarbodiimide hydrochloride (2.1 g, 10.7 mmol) was added at room temperature. The reaction mixture was stirred at room temperature for 2 hours and then partitioned between 1N HCl and ethyl acetate. The organic phase was taken and the aqueous phase was reextracted with ethyl acetate and the combined organic phase was washed with water, aqueous sodium bicarbonate

and brine. After drying over anhydrous magnesium sulfate, the solvent was evaporated and the residue was purified by flash chromatography on silica gel (Hexane/Acetone/6:4) to yield a colorless solid (500 mg).
This was triturated with isopropyl ether to provide the title compound, m.p. 204-205°C.
Analysis calc'd for $C_{15}H_{19}N_5O_4 \cdot 0.17\ H_2O$:
C, 53.55; H, 5.79; N, 20.82;
Found: C, 53.89; H, 5.63; N, 20.48.

Example 5

(*trans*)-3,4-Dihydro-3-hydroxy-2,2-dimethyl-4-[2-(cyanoimino)-1-pyrrolidinyl]-2H-1-benzopyran-6-carbonitrile

A. (*trans*)-4-[(2-Aminoethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile

To a suspension of 6-cyano-3,4-epoxy-3,4-dihydro-2,2-dimethyl-2H-benzopyran (1.2 g, 5.97 mmol) (prepared according to Evans et al., J. Med. Chem., 1983, 26, 1582 and J. Med. Chem., 1986, 29, 2194) in ethanol (7.0 mL), ethylenediamine (2.4 mL, 35.8 mmol) was added at room temperature and the reaction mixture was stirred at room temperature for 36 hours. The solvent was removed under reduced pressure and the residue was further dried by use of vacuum pump to yield the title A compound (1.74 g, >100%) as a colorless foam. This material was used for the next reaction without any purification.

B. (*trans*)-3,4-Dihydro-3-hydroxy-2,2-dimethyl-4-[2-(cyanoimino)-1-pyrrolidinyl]-2H-1-benzopyran-6-carbonitrile

To a solution of the title A compound (1.74 g, 5.97 mmol) in ethanol at room temperature, triethylamine (1.7 mL, 11.94 mmol) was added slowly, followed by dimethyl N-cyanodithioimino-carbonate (1.16 g, 11.94 mmol of 90%). The reaction mixture was heated at 80°C for 3 hours and then cooled to ambient temperature. The solvent was evaporated to give a light yellow foam (2.4 g). This material was taken up in methanol (20 mL) and the resulting suspension was treated with mercuric acetate (2.52 g, 7.77 mmol). The reaction mixture was stirred at room temperature for 2 hours and the solvent was evaporated under reduced pressure. The residue was diluted with water, alkalized to pH ~ 9.0 with 5N NaOH and the product was extracted with 5% methanolic chloroform. The combined organic extracts were washed with brine whereby a thick emulsion resulted. The two phase mixture was filtered through a celite pad and the organic layer was separated and dried over magnesium sulfate. The solvent was evaporated and the residue was purified by flash chromatography (5% methanol in chloroform) on silica gel to provide a colorless residue. This residue was triturated with ethyl acetate to yield the desired product (740 mg). The mother liquour was concentrated and triturated with ethyl acetate to provide a second crop (370 mg) for a total of 1.1 g. The combined material was recrystallized from hot ethyl accetate to give the title compound as a white powder, m.p. 254-255°C.

Analysis calc'd for $C_{16}H_{17}N_5O_2$ 0.42 H_2O:
C, 60.27; H, 5.63; N, 21.97;
Found: C, 60.40; H, 5.30; N, 21.84.

Example 6

(*trans*)-N"-Cyano-N-(3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-pyrano[3,2-c]pyridin-4-yl)-phenylguanidine

To a solution of the title A compound from Example 3 (2.2 g, 12.5 mmol) and (*trans*)-4-amino-3,4-dihydro-2,2-dimethyl-2H-pyrano[3,2-c]pyridin-3-ol (1.1 g, 5.7 mmol) (prepared according to EP 0 205 292 A2) in dimethylformamide (5 ml) under argon, 1-(3-dimethylaminopropyl)-2-ethylcarbodiimide hydrochloride (2.2 g, 10.8 mmol) was added at room temperature. The reaction mixture was stirred at room temperature for 2 hours and then partitioned between water (pH ~ 11) and ethyl acetate. The organic phase was separated and the aqueous phase was reextracted with ethyl acetate and the combined organic phase was washed with water, aqueous sodium bicarbonate and brine. After drying over anhydrous magnesium sulfate, the solvent was evaporated and the residue was purified by flash chromatography on silica gel (acetone:dichloromethane/1:4) to yield a colorless solid (470 mg) which was crystallized from acetonitrile to provide the title compound, m.p. 233-236°C.

Analysis calc'd for $C_{18}H_{19}N_5O_2$:
C, 64.08; H, 5.67; N, 20.76;
Found: C, 63.88; H, 5.48; N, 20.76.

Example 7

(*trans*)-N'-Cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-1-pyrrolidine-carboximidamide

A. (*trans*)-4-[[(Cyanoimino)phenoxymethyl]amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile

To a solution of (*trans*)-4-amino-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile (prepared according to Evans et al., J. Med. Chem., 1983, 26, 1582 and J. Med. Chem., 1986, 29, 2194) (5.0 g, 23 mmol) in isopropanol (50 mL), diphenyl-cyanocarbonimidate (5.5 g, 25 mmol) was added at room temperature and the reaction mixture was allowed to stir at room temperature for 16 hours. Most of the isopropanol was evaporated and the residue was dissolved in ethyl acetate. The resulting solution was washed successively with 10% citric acid, 1N sodium hydroxide solution and brine. It was dried over anhydrous magnesium sulfate, concentrated and the residue was crystallized from chloroform-isopropyl ether to yield the title A compound (4.2 g) as a colorless solid, m.p. 186-188°C.

Analysis calc'd for $C_{20}H_{18}N_4O_3 \cdot 0.6H_2O$:
C, 64.37; H, 5.18; N, 15.02;
Found: C, 64.64; H, 4.86; N, 14.75.

B. (*trans*)-N'-Cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-1-pyrrolidine-carboximidamide

To a solution of title A compound (0.8 g, 12.2 mmol) in isopropanol (4 mL), pyrrolidine (0.5

mL) was added at room temperature and the reaction mixture was allowed to stir at room temperature overnight. The suspension was diluted with ether and the colorless solid was filtered and dried to yield the title compound (0.4 g), m.p. 263-264°C.
Analysis calc'd for $C_{18}H_{21}N_5O_2$:
C, 63.70; H, 6.24; N, 20.64;
Found: C, 63.45; H, 6.29; N, 20.88.

Example 8

(*trans*)-N"-Cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-ethyl-N-methylguanidine

A. (*trans*)-N'-Cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N-methylcarbamidic acid, phenyl ester

To a solution of (*trans*)-3,4-dihydro-3-hydroxy-2,2-dimethyl-4-(methylamino)-2H-1-benzopyran-6-carbonitrile (prepared according to Evans et al., J. Med. Chem., 1983, 26, 1582 and J. Med. Chem., 1986, 29, 2194) (1.0 g, 4.3 mmol) in isopropanol (4 mL), diphenylcyanocarbonimidate (1.0 g, 4.3 mmol) was added at room temperature and the reaction mixture was allowed to stir at room temperature for 16 hours. Most of the isopropanol was evaporated and the residue was dissolved in ethyl acetate. The resulting solution was washed successively with 10% citric acid, 1N sodium hydroxide and brine. It was dried over anhydrous magnesium sulfate and concentrated. The resiude was purified by flash

chromatography (ethyl acetate:hexanes 1:1) on silica gel to yield the title A compound. This compound was used for the next step without further purification.

B. (*trans*)-N"-Cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-ethyl-N-methylguanidine

To a solution of the title A compound (0.1 g, 0.27 mmol) in isopropanol (1 mL) and triethyl amine (0.25 mL), ethyl amine hydrochloride (0.1 g, 1.2 mmol) was added at room temperature and the reaction mixture was allowed to stir at room temperature overnight. Most of the solvent was evaporated and the residue was dissolved in ethyl acetate. The solution was washed successively with 10% citric acid, aqueous sodium bicarbonate and brine. After drying over anhydrous magnesium sulfate, the solvent was evaporated and the residue was triturated with ether to yield the title compound as a colorless solid, m.p. 227-228°C.

Example 9

(*trans*)-N"-Cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-[2(dimethylamino)ethyl]guanidine

To a suspension of the compound from Example 7, part A (0.8 g, 2.2 mmol) in isopropanol (3 ml), 95% 1,1-dimethylethylenediamine (0.5 g, 5.7 mmol) was added at room temperature. It was allowed to stir at room temperature for 20 hours and

concentrated *in vacuo*. The residue was triturated with isopropyl ether to give the title compound (0.4 g) as a white solid, m.p. 172-173°C: ^{1}H NMR ($CDCl_3$) δ7.6 (s, 1 H), 7.4 (dd, J = 2.0 & 9.0 Hz, 1H), 6.9 (d, J = 9.0 Hz, 1 H), 6.6 (s, 1 H), 4.9 (t, J = 9.0 Hz, 2 H), 3.5 (d, J = 9.0 Hz, 1 H), 3.4 (s, 2 H), 2.5 (m, 2 H), 2.0 (s, 6 H), 1.5 (s, 3 H), 1.3 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 163.4, 156.8, 133.1, 132.5, 122.8, 118.8, 118.7, 118.0, 103.9, 80.4, 76.2, 69.1, 60.8, 51.8, 44.6, 41.7, 26.4, 18.5; IR (KBr) 1126.9, 1267.0, 1431.4, 1489.0, 1577.0, 1635.8, 2173.3, 3391.9, 3407.6 cm^{-1}.

Analysis calc'd for $C_{18}H_{24}N_6O_2$:

C, 60.65; H, 6.79; N, 23.58;

Found: C, 60.53; H, 6.75; N, 23.62.

Example 10

(*trans*)-N"-Cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-methylguanidine

To a suspension of the compound of Example 7, part A (1.0 g, 2.8 mmol) in isopropanol (6 ml), methylamine (40% solution in methanol, 1 ml) was added at room temperature. The reaction mixture was allowed to stir at room temperature for 20 hours and concentrated *in vacuo*. The crude product obtained was crystallized from isopropanol to give the title compound (0.4 g) as a white solid, m.p. 212-214°C: ^{1}H NMR ($CDCl_3$/DMSO) δ 7.5 (s, 1 H), 7.45 (d, J = 9.0 Hz, 1 H), 6.9 (m, 2 H), 6.8 (d, J = 8.0 Hz, 1 H), 5.55 (br, 1 H), 4.85 (br, 1 H), 3.7 (m, 1

H), 2.88 (d, J = 5.0 Hz, 3 H), 1.48 (s, 3 H), 1.24 (s, 3 H); ^{13}C NMR ($CDCl_3$/DMSO) 160.5, 155.5, 131.6, 131.3, 123.7, 117.9, 117.3, 116.9, 102.2, 79.4, 76.6, 70.9, 27.6, 25.6, 17.7; IR (KBr) 1267, 1419, 1489, 1576, 1608, 2170, 2225, 2977, 3338 cm^{-1}.

Analysis calc'd for $C_{15}H_{17}N_5O_2 \cdot 0.3\ H_2O$:
C, 59.16; H, 5.82; N, 23.01;
Found: C, 59.16; H, 5.57; N, 23.01.

Example 11

(*trans*)-4-[(Cyanoimino)[[4-(phenylmethyl)-1-piperazinyl]methyl]amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile

To a suspension of the compound from Example 7, part A (2.0 g, 5.5 mmol) in isopropanol (5 ml), 4-(phenylmethyl)-1-piperazine (1.0 ml) was added at room temperature. The reaction mixture was allowed to stir at room temperature for 20 hours and concentrated *in vacuo*. The crude product obtained was purified by flash chromatography on silica gel eluting with dichloromethane/acetone (7/3) to give the title compound (0.6 g). It was recrystallized from isopropanol-ether to give the desired product (250 mg) as a white solid, m.p. 205-207°C: ^1H NMR (DMSO-d_6) δ 7.4 (s, 1 H), 7.3 (d, J = 8.0 Hz, 1 H), 7.2 (d, J = 8.0 Hz, 1 H), 7.0 (s, 6 H), 6.6 (d, J = 9.0 Hz, 1 H), 5.6 (d, J = 6.0 Hz, 1 H), 4.6 (t, J = 8.0 & 10.0 Hz, 1 H), 3.2 (m, 5 H), 2.2 (m, 5 H), 1.14 (s, 3 H), 0.88 (s, 3 H); ^{13}C NMR (DMSO-d_6) 161.1, 156.4, 137.6, 133.1, 132.9,

129,1, 128.3, 127.2, 124.6, 117.9, 102.7, 80.6, 71.5, 61.9, 53.0, 52.2, 46.6, 26.7, 18.6; IR (KBr) 1125, 1490, 1524, 1577, 1611, 2170, 2224, 3429 cm^{-1}.

Analysis calc'd for $C_{25}H_{28}N_6O_2$:
C, 67.54; H, 6.35; N, 18.91;
Found: C, 67.29; H, 6.37; N, 18.73.

Example 12

(*trans*)-N"-Cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)guanidine

To a suspension of the compound of Example 7, part A (1.0 g, 2.8 mmol) in isopropanol (6 ml), ammonium hydroxide (1 ml) was added at room temperature. It was allowed to stir at room temperature for 20 hours and concentrated *in vacuo*. The crude product obtained was crystallized from acetone/ethyl acetate to give the title compound (0.31 g) as a white solid, m.p. 250-251°C: ^1H NMR (DMSO-d_6) δ 7.7 (dd, J = 2.0 & 7.0 Hz, 1 H), 7.5 (s, 1 H), 6.9 (m, 2 H), 7.0 (d, J = 9.0 Hz, 1 H), 5.8 (br s, 1 H), 4.8 (br s, 1 H), 3.6 (m, 1 H), 1.48 (s, 3 H), 1.25 (s, 3 H); ^{13}C NMR (DMSO-d_6) 162.3, 156.3, 132.9, 132.6, 124.8, 119.1, 118.1, 102.7, 80.5, 71.3, 26.5, 19.0; IR (KBr) 1064, 1268, 1489.7, 1555, 1635, 2183, 2225, 3432 cm^{-1}.
Analysis calc'd for $C_{14}H_{15}N_5O_2$:
C, 58.93; H, 5.30; N, 24.55;
Found: C, 58.74; H, 5.32; N, 24.23.

Example 13

(*trans*)-N"-Cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-(methylethyl)guanidine

To a suspension of the compound from Example 7, part A (2.0 g, 5.5 mmol) in isopropanol (5 ml), isopropylamine (1.5 ml) was added at room temperature. It was allowed to stir at room temperature for 20 hours and concentrated *in vacuo*. The crude product obtained was purified by flash chromatography on silica gel eluting with 7/3 dichloromethane/acetone to give the title compound (1.2 g). This solid was crystallized from isopropanol-isopropyl ether to give the desired product as a white solid, m.p. 150-152°C: ^{1}H NMR (DMSO-d_6) δ 7.6 (dd, J = 2.0 & 7.0 Hz, 1 H), 7.5 (s, 1 H), 7.2 (d, J = 9.0 Hz, 1 H), 7.0 (d, J = 9.0 Hz, 1 H), 6.8 (d, J = 8.0 Hz, 1 H), 5.9 (d, J = 5.0 Hz, 1 H), 4.8 (t, J = 9.0 Hz, 1 H), 3.9 (m, 1 H), 3.8 (m, 1 H), 1.47 (s, 3 H), 1.24 (s, 3 H), 1.2 (d, J = 3.0 Hz, 6 H); ^{13}C NMR (DMSO-d_6) 159.5, 156.3, 132.7, 132.4, 125.2, 119.1, 118.0, 117.8, 102.7, 80.5, 71.1, 51.5, 43.4, 26.7, 22.6, 22.4, 18.7; IR (KBr) 1268, 1490, 1587.8, 2170, 2226, 2978, 3419 cm^{-1}.

Analysis calc'd for $C_{17}H_{21}N_5O_2 \cdot 0.1\ H_2O$:
C, 62.03; H, 6.49; N, 21.28;
Found: C, 61.75; H, 6.66; N, 21.86.

Example 14

(*trans*)-N"-Cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-dimethyl-guanidine

To a suspension of the compound from Example 7, part A (1.0 g, 2.8 mmol) in isopropanol (6 ml), dimethylamine hydrochloride (0.33 g, 4.2 mmol) was added, followed by powdered potassium carbonate (0.57 g, 4.2 mmol) at room temperature. The reaction mixture was allowed to stir at room temperature for 20 hours and concentrated *in vacuo*. The residue was dissolved in chloroform (150 ml) and washed with water, dried over magnesium sulfate and concentrated *in vacuo*. The crude product obtained was crystallized from dichloromethane-ether to give the title compound (0.44 g) as a white solid. This solid was recrystallized from acetonitrile-chloroform to give colorless solid, m.p. 196-197°C. ^{1}H NMR (DMSO-d_6) δ 7.7 (s, 1 H), 7.6 (dd, J = 3.0 & 8.0 Hz, 1 H), 7.2 (d, J = 9.0 Hz, 1 H), 6.9 (d, J = 9.0 Hz, 1 H), 5.8 (d, J = 6.0 Hz, 1 H), 4.9 (t, J = 9.0 & 10.0 Hz, 1 H), 3.6 (dd, J = 8.0 & 5.0 Hz, 1 H), 3.0 (s, 6 H), 1.42 (s, 3 H), 1.24 (s, 3 H); ^{13}C NMR (DMSO-d_6) 159.3, 154.9, 131.5, 130.8, 123.4, 116.1, 101.4, 78.9, 70.3, 51.5, 25.2, 17.0; IR (KBr) 1143, 1269, 1398, 1489, 1527, 1595, 2168, 2226, 2935, 2980, 3433 cm^{-1}.

Analysis calc'd for $C_{16}H_{19}N_5O_2 \cdot 0.5\ H_2O$:
C, 59.61; H, 6.25; N, 21.73;
Found: C, 59.44; H, 5.95; N, 22.03.

Example 15

(*trans*)-N"-Cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-phenylmethyl-guanidine

To a suspension of the compound from Example 7, part A (0.5 g, 1.4 mmol) in isopropanol (3 ml) was added benzylamine (90% 0.5 ml) at room temperature. The reaction mixture was allowed to stir at room temperature for 20 hours and concentrated *in vacuo*. The residue was combined with another batch of the same material and purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (3:7) to give a white solid (0.8 g). This solid was crystallized from acetonitrile-isopropyl ether to give the title compound as a colorless solid, m.p. 188-189°C: ^{1}H NMR ($CDCl_3$) δ 7.7 (m, 1 H), 7.5 (dd, J = 2.0 & 9.0 Hz, 1 H), 7.4 (m, 6 H), 6.86 (d, J = 9.0 Hz, 1 H), 5.8 (s, 1 H), 4.8 (m, 1 H), 4.5 (d, J = 5.0 Hz, 2 H), 3.7 (dd, J = 6.0 & 4.0 Hz, 1 H), 1.41 (s, 3 H), 1.19 (s, 3 H); ^{13}C NMR ($CDCl_3$) 158.7, 154.5, 136.8, 130.7, 126.5, 125.2, 125.0, 123.0, 116.0, 101.0, 78.6, 42.6, 24.8, 16.9; IR (KBr) 1267, 1491, 1579, 1595, 2175, 2222, 3433 cm^{-1}.

Analysis calc'd for $C_{21}H_{21}N_5O_2$:
C, 67.18; H, 5.64; N, 18.66;
Found: C, 67.14; H, 5.55; N, 18.65.

Example 16

(*trans*)-N"-Cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-[2-[(phenylmethyl)methylamino]ethyl]guanidine

To a suspension of the compound from Example 7, part A (0.5 g, 1.4 mmol) in isopropanol (3 ml), N-methylbenzylethylamine (0.5 ml) was added at room temperature. The reaction mixture was allowed to stir at room temperature for 24 hours. The initially heterogeneous mixture became a homogeneous solution slowly and as the reaction proceeded the product precipitated out of the reaction mixture. Upon completion of reaction, the solid was filtered and triturated with ether to give the title compound (0.45 g) as a colorless solid, m.p. 184-185°C: ^{1}H NMR ($CDCl_3$) δ 9.4 (s, 1 H), 7.59 (d, J = 8.0 Hz, 1 H), 7.2 (m, 4 H), 6.96 (s, 2 H), 6.87 (d, J = 9.0 Hz, 1 H), 6.4 (s, 1 H), 4.9 (m, 2 H), 3.4 (m, 4 H), 2.6 (m, 2 H), 2.1 (s, 3 H), 1.49 (S, 3 H), 1.26 (s, 3 H); ^{13}C NMR ($CDCl_3$) 205.2, 160.7, 155.6, 131.6, 128.0, 127.4, 126.2, 123.5, 118.0, 117.3, 117.1, 102.4, 79.4, 61.3, 55.6, 40.5, 25.7, 17.74; IR (KBr) 1126, 1267, 1489, 1575, 1608, 2172, 2224, 2800, 2976, 3421 cm^{-1}.

Analysis calc'd for $C_{24}H_{28}N_6O_2$:

C, 66.64; H, 6.52; N, 19.43;

Found: C, 66.40; H, 6.52; N, 19.99.

Example 17

(*trans*)-N"-Cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4yl)-N'-(2-methoxyethyl)guanidine

To a suspension of the compound from Example 7, part A (0.5 g, 1.4 mmol) in isopropanol (3 ml), 2-methoxyethylamine (0.12 g, 1.7 mmol, 0.15 ml) was added at room temperature. The reaction mixture was allowed to stir at room temperature for 20 hours and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with ethyl acetate to give the title compound (0.3 g) as a colorless solid, m.p. 94-96°C: ^{1}H NMR ($CDCl_3$) δ 7.5 (s, 1 H), 7.38 (d, J = 7.0 Hz, 1 H), 6.8 (m, 3 H), 4.86 (s, 1 H), 4.0 (m, 1 H), 3.5 (m, 4 H), 3.2 (s, 3 H), 1.9 (s, 1 H), 1.43 (s, 3 H), 1.19 (s, 3 H); ^{13}C NMR ($CDCl_3$) 162.6, 156.8, 133.2, 132.4, 122.5, 119.0, 118.5, 118.1, 103.9, 80.2, 74.7, 60.3, 58.9, 52.2, 26.4, 21.0, 18.7, 14.1; IR (KBr) 1635, 1693, 3404 cm^{-1}. Analysis calc'd for $C_{17}H_{21}N_5O_3 \cdot 0.24\ H_2O$:

C, 58.71; H, 6.23; N, 20.14;

Found: C, 58.81; H, 6.38; N, 20.04.

Example 18

(3S-*trans*)-N"-Cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-phenylguanidine

A. [3R-[3α,4β(S*)]]-N-(6-Cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-α-hydroxybenzeneacetamide

and

[3S-[3α,4β(R*)]]-N-(6-Cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-α-hydroxybenzeneacetamide

To a solution of (*trans*)-4-amino-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile (prepared according to Evans et al., J. Med. Chem., 1983, 26, 1582 and J. Med. Chem., 1986, 29, 2194) (10.0 g, 45.9 mmol), S-(+)-mandelic acid (6.98 g, 45.9 mmol), hydroxybenzotriazole hydrate (6.2 g, 45.9 mmol) in dimethylformamide (60 ml) at 0°C was added dicyclohexylcarbodiimide (9.5 g, 45.9 mmol). It was allowed to stir at room temperature for 20 hours and then cooled in an ice bath. The precipitated solid was filtered and the filtrate was concentrated *in vacuo*. The residue was dissolved in 5 percent methanol in chloroform and washed with 1 N sodium hydroxide, 1 N hydrochloric acid, brine and dried over anhydrous magnesium sulfate. After removing drying agent, the solvent was removed *in vacuo*. The residue was crystallized from ethanol to give [3R-[3α,4β(S*)]]-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-

4-yl)-α-hydroxybenzeneacetamide (6.0 g) as a white solid, m.p. 238-240°C, $[\alpha_D]^{25}$ = +94.6° (c = 1, MeOH): ^{1}H NMR ($CDCl_3$) δ 7.4 (m, 5 H), 7.26 (t, J = 1.0 HZ, 1 H), 6.97 (d, J = 9.0 HZ, 1 H), 6.83 (d, J = 9.0 HZ, 1 H), 5.16 (s, 1 H), 4.98 (t, J = 9.0 HZ, 1 H, 3.8 (d, J = 5.0 HZ, 1 H), 3.55 (dd, J = 4.0 & 5.0 HZ, 1 H), 1.45 (s, 3 H), 1.2 (s, 3 H).

Analysis calc'd for $C_{20}H_{20}N_2O_4$:
C, 68.17; H, 5.72; N, 7.95;
Found: C, 67.92; H, 5.49; N, 8.05.

The residual material of the mother liquor was purified by flash chromatography on silica gel eluting with hexane-ethyl acetate mixture (3:7) and the residue was crystallized from dichloromethane-isopropyl ether to give [3S-[3α,4β(R*)]]-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-α-hydroxybenzeneacetamide (6.0 g) as a white solid, m.p. 100-102°C (foaming); $[\alpha_D]^{25}$ = -26.1° (c = 1, MeOH): ^{1}H NMR (DMSO-d_6) δ 8.45 (d, J = 8.0 Hz, 1 H), 7.5 (m, 4 H), 7.3 (m, 2 H), 7.0 (s, 1 H), 6.88 (d, J = 8.0 Hz, 1 H), 6.2 (s, 1 H), 5.57 (d, J = 5.0 Hz, 1 H), 5.0 (s, 1 H), 4.76 (t, J = 9.0 Hz, 1 H), 3.75 (dd, J = 5.0 & 5.0 Hz, 1 H), 1.40 (S, 3 H), 1.15 (s, 3 H).

Analysis calc'd for $C_{20}H_{20}N_2O_4 \cdot 0.25\ H_2O$:
C, 67.30; H, 5.78; N, 7.84;
Found: C, 67.54; H, 5.95; N, 7.44.

B. (3S-*trans*)-4-Amino-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile

To a solution of [3S-[3α,4β(R*)]]-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-α-hydroxybenzeneacetamide, title A compound (2.8 g, 7.9 mmol) in dioxane (30 ml) was

added a solution of sulfuric acid (2.5 g) in water (12 ml) at room temperature and the reaction mixture was heated at reflux temperature for 24 hours. It was concentrated *in vacuo* and the residue was dissolved in ethyl acetate (200 ml). The organic layer was washed with 1 N sodium hydroxide (50 ml) followed by water (50 ml) and dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give the title B compound (1.6 g) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.74 (s, 1 H), 7.42 (dd, J = 2.0 & 6.0 Hz, 1 H), 6.82 (d, J = 8.0 Hz, 1 H), 3.65 (d, J = 10.0 Hz, 1 H), 3.36 (d, J = 10.0 Hz, 1 H), 1.53 (s, 3 H), 1.23 (s, 3 H).

C. (3S-*trans*)-N"-cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-phenylguanidine

To a solution of N-cyano-N'-phenylthiourea (1.7 g, 9.5 mmol) and the title B compound (1.6 g, 7.3 mmol) in dimethylformamide (7 mL), under argon was added 1-(3-dimethylaminopropyl)-2-ethylcarbodiimide hydrochloride (1.8 g, 9.5 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2 hours and then partitioned between 1N hydrochloric acid and ethyl acetate. The organic phase was separated and the aqueous phase was reextracted with ethyl acetate. The combined extracts were washed with water, aqueous sodium bicarbonate and brine. After drying over anhydrous magnesium sulfate, the solvent was evaporated and the crude product was purified by flash chromatography on silica gel eluting with ethyl acetate/hexanes (7:3) to give a cololess solid (0.7 g). The solid was triturated with ether to yield the title compound (0.35 g) , m.p.

214-216°C; $[\alpha_D]^{25}$ = -34.8° (c = 0.417, MeOH): ^{1}H NMR (DMSO-d_6) d 9.28 (s, 1 H), 7.58 (d, J = 8.0 Hz, 3 H), 7.35 (m, 4 H), 7.15 (m, 1 H), 6.90 (d, J = 8.2 Hz, 1 H), 5.92 (br s, 1 H), 4.92 (t, J = 9.0 Hz, 1 H), 3.72 (br d, J = 5.9 Hz, 1 H), 1.41, 1.18 (s, 3 H each); ^{13}C NMR (DMSO-d_6) 159.2, 156.3, 137.5, 132.6, 132.5, 129.0, 124.8, 124.7, 123.6, 119.0, 117.8, 117.0, 102.6, 80.4, 70.9, 51.9, 26.6, 18.6; IR(KBr) 2226, 2179, 1609, 1582, 1491, 1267 cm^{-1}.

Analysis calc'd for $C_{20}H_{19}N_5O_2 \cdot 0.37\ H_2O$:
C, 65.26; H, 5.40; N, 19.02;
Found: C, 65.62; H, 5.36; N, 18.57.

Example 19

(3R-*trans*-N"-Cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-phenylguanidine

A. (3R-*trans*)-4-amino-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile

To a solution of [3R-[3α,4β(S*)]]-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-α-hydroxybenzeneacetamide, compound of Example 18, part A (2.8 g, 7.9 mmol) in dioxane (30 ml) were added concentrated sulfuric acid (2.5 g) and water (12 ml) at room temperature and the reaction mixture was heated at reflux temperature for 24 hours. It was concentrated *in vacuo* and the residue was combined with another batch of the same material and dissolved in ethyl acetate (400 ml). The resulting solution was washed with 1N sodium hydroxide (50 ml) followed by water (50 ml) and dried over anhydrous magnesium sulfate and

concentrated *in vacuo* to give the title A compound (3.7 g) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.74 (s, 1 H), 7.42 (dd, J = 2.0 & 6.0 Hz, 1 H), 6.82 (d, J = 8.0 Hz, 1 H), 3.65 (d, J = 10.0 Hz, 1 H), 3.36 (d, J = 10.0 Hz, 1 H), 1.53 (s, 3 H), 1.23 (s, 3 H).

B. (3R-*trans*)-N"-Cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-phenylguanidine

To a solution of N-cyano-N'-phenylthiourea (3.9 g, 21.9 mmol) and the title A compound (3.68 g, 16.9 mmol) in dimethylformamide (20 mL) under argon, 1-(3-dimethylaminopropyl)-2-ethylcarbodiimide hydrochloride (4.2 g, 21.9 mmol) was added at room temperature. The reaction mixture was stirred at room temperature for 2 hours and then partitioned between 1N hydrochloric acid and ethyl acetate. The organic phase was separated and the aqueous phase was reextracted with ethyl acetate. The combined extracts were washed with water, aqueous sodium bicarbonate and brine. After drying over anhydrous magnesium sulfate, the solvent was evaporated and the crude product was triturated with ethyl acetate-ether to give a colorless solid (3.5 g). The crude product was purified by flash chromatography on silica gel eluting with ethyl acetate/hexanes (7:3) and the solid, obtained after evaporation of the solvent, was triturated with ether to give the title compound (1.8 g) as a colorless solid, m.p. 215-217°C, $[\alpha_D]^{25}$ = +34.8° (c = 0.417, MeOH): ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 8.8 (s, 1 H), 7.6 (s, 1 H), 7.44 (d, J = 8.0 Hz, 1 H), 7.35 (d, J = 5.0 Hz, 4 H), 7.22 (m, 1 H), 6.85 (d, J = 8.8 Hz, 1 H), 6.7 (br s, 1 H), 5.0 (t, J = 9.0 Hz, 1 H), 3.72 (br d, J =

5.3 Hz, 1 H), 1.48, 1.18 (s, 3 H each); ^{13}C NMR ($CDCl_3$/DMSO-d_6) 159.6, 156.5, 136.6, 132.5, 129.2, 125.7, 124.1, 123.7, 118.9, 118.1, 117.2, 103.4, 80.3, 72.8, 52.4, 26.4, 18.6; IR (KBr) 2226, 2179, 1609, 1582, 1491, 1267 cm^{-1}.

Analysis calc'd for $C_{20}H_{19}N_5O_2 \cdot 0.45\ H_2O$:
C, 65.01; H, 5.42; N, 18.95;
Found: C, 65.18; H, 5.47; N, 18.51.

Example 20 is an alternate procedure to Example 18 and the procedure of this Example 20 is preferred. Additionally, the 3S, 4R enantiomer of Example 20 is the preferred compound of the present invention.

Example 20

(3S-*trans*)-N"-Cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-phenylguanidine

A. [3S-[3α,4β(S*)]]-N-(6-Cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-α-hydroxybenzeneacetamide

and

[3R-[3α,4β(R*)]]-N-(6-Cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-α-hydroxybenzeneacetamide

To a solution of (*trans*)-4-amino-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile (prepared according to Evans et al., J. Med. Chem.,

1983, 26, 1582 and J. Med. Chem., 1986, 29, 2194) (1.64 g, 7.5 mmol), R(-)-mandelic acid (1.14 g, 7.5 mmol), hydroxybenzotriazole hydrate (1.0 g, 7.5 mmol) in dimethylformamide (15 ml) at 0°C was added dicyclohexylcarbodiimide (1.55 g, 7.5 mmol) at room temperature. The reaction mixture was allowed to stir at room temperature for 20 hours and then cooled in an ice bath. The solid was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was dissolved in 5% methanol in chloroform and washed with 1 N sodium hydroxide, 1 N hydrochloric acid, brine followed by drying over anhydrous magnesium sulfate. After removing drying agent the solvent was removed *in vacuo*. The residue was crystallized from ethanol to give [3S-[3α,4β(S*)]]-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-α-hydroxybenzeneacetamide (0.85 g) as a white solid, m.p. 235-237°C: $[\alpha_D]^{25}$ = -94.9° (c = 1, MeOH); ^{1}H NMR (DMSO-d_6) δ 8.45 (d, J = 8.0 Hz, 1 H), 7.5 (m, 4 H), 7.3 (m, 2 H), 7.0 (s, 1 H), 6.88 (d, J = 8.0 Hz, 1 H), 6.2 (s, 1 H), 5.57 (d, J = 5.0 Hz, 1 H), 5.0 (s, 1 H), 4.76 (t, J = 9.0 Hz, 1 H), 3.75 (dd, J = 5.0 & 5.0 Hz, 1 H), 1.40 (s, 3 H), 1.15 (s, 3 H).

Analysis calc'd for $C_{20}H_{20}N_2O_4$:
C, 68.17; H, 5.72; N, 7.95;
Found: C, 68.00; H, 5.52; N, 7.95.

The residual material recovered from the mother liquor was purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (3:7) and the product was crystallized from

dichloromethane-isopropyl ether to give [3R-[3α,4β(R*)]]-N-(6-Cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-α-hydroxy-benzeneacetamide as a white solid, m.p. 100-102°C (foaming): $[\alpha_D]^{25}$ = +25.6° (c = 1, MeOH): ^{1}H NMR ($CDCl_3$) δ 7.4 (m, 5 H), 7.26 (t, J = 1.0 Hz, 1 H), 6.97 (d, J = 9.0 Hz, 1 H), 6.83 (d, J = 9.0 Hz, 1 H), 5.16 (s, 1 H), 4.98 (t, J = 9.0 Hz, 1 H), 3.8 (d, J = 5.0 Hz, 1 H), 3.55 (dd, J = 4.0 & 5.0 Hz, 1 H), 1.45 (s, 3 H), 1.2 (s, 3 H).

Analysis calc'd for $C_{20}H_{20}N_2O_4 \cdot 0.25\ H_2O$:
C, 67.30; H, 5.78; N, 7.84;
Found: C, 67.17; H, 5.87; N, 7.44.

B. (3S-*trans*)-4-Amino-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile

To a solution of [3S-[3α,4β(S*)]]-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-α-hydroxybenzeneacetamide, title A compound (6.09 g, 17.0 mmol) in dioxane (60 ml) was added a solution of sulfuric acid (6.0 g) in water (30 ml) at room temperature and the reaction mixture was heated at reflux temperature for 24 hours. It was then concentrated *in vacuo* and the residue was dissolved in ethyl acetate. The organic layer was washed with 1N sodium hydroxide followed by water and dried over anhydrous magnesium sulfate. The solvent was evaporated to give the title B compound as an oil: ^{1}H NMR ($CDCl_3$) δ 7.74 (s, 1 H), 7.42 (dd, J = 2.0 & 6.0 Hz, 1 H), 6.82 (d, J = 8.0 Hz, 1 H), 3.65 (d, J = 10.0 Hz, 1 H), 3.36 (d, J = 10.0 Hz, 1 H), 1.53 (s, 3 H), 1.23 (s, 3 H).

C. (3S-*trans*)-N"-Cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-phenylguanidine

To a solution of N-cyano-N'-phenylthiourea (2.11 g, 11.9 mmol) and (3S-*trans*)-4-amino-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile (2.0 g, 9.1 mmol), title B compound, in dimethylformamide (20 mL) under argon was added 1-(3-dimethylaminopropyl)-2-ethylcarbodiimide hydrochloride (2.23 g, 11.9 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2 hours and then partitioned between 1N hydrochloric acid and ethyl acetate. The organic phase was separated and the aqueous phase was reextracted with ethyl acetate. The combined organic extracts were washed with water, sodium bicarbonate and brine. After drying over anhydrous magnesium sulfate, the solvent was evaporated and the crude product was purified by flash chromatography on silica gel eluting with ethyl acetate/hexanes (7:3) to give a colorless solid which was triturated with ether to yield the title compound (0.35 g), m.p. 215-216°C: $[\alpha]_D^{25}$ = -33.5° (c = 1, MeOH); ^{1}H NMR (DMSO-d_6) δ 9.28 (s, 1 H), 7.58 (d, J = 8.0 Hz, 3 H), 7.35 (m, 4 H), 7.15 (m, 1 H), 6.90 (d, J = 8.2 Hz, 1 H), 5.92 (br s, 1 H), 4.92 (t, J = 9.0 Hz, 1 H), 3.72 (br d, J = 5.9 Hz, 1 H), 1.41, 1.18 (s, 3 H each); ^{13}C NMR (DMSO-d_6) 159.2, 156.3, 137.5, 132.6, 132.5, 129.0 124.8, 124.7, 123.6, 119.0, 117.8, 117.0, 102.6, 80.4, 70.9, 51.9, 26.6, 18.6; IR (KBr) 2226, 2179, 1609, 1582, 1491, 1267 cm^{-1}.

Analysis calc'd for $C_{20}H_{19}N_5O_2 \cdot 0.24\ H_2O$:
C, 65.26; H, 5.40; N, 19.02;
Found: C, 65.62; H, 5.36; N, 18.57.
HPLC: 99.5% by Chiracel OD column/hexanes (80%), isopropanol (20%), formic acid (0.1%).

Example 21

(*trans*)-4-[2-(Cyanoimino)tetrahydro-1(2H)-pyrimidinyl]-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile

A. (*trans*)-4-[(3-Aminopropyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile

To a suspension of 6-cyano-3,4-expoxy-3,4-dihydro-2,2-dimethyl-2H-benzopyran (prepared according to Evans et al., J. Med. Chem., 1983, 26, 1582 and J. Med. Chem., 1986, 29, 2194) (1.0 g, 5.0 mmol) in ethanol (5.0 mL), 1,3-diaminopropane (2.4 mL, 32.4 mmol) was added at room temperature and the reaction mixture was stirred at room temperature for 36 hours. The solvent was removed under reduced pressure and the residue was dried by use of a vacuum pump for 5 hours to yield the title A compound (1.3 g) as a colorless foam. This material was used for the next step without purification.

B. (*trans*)-4-[2-(Cyanoimino)tetrahydro-1(2H)-pyrimidinyl]-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile

To a solution of the title A compound (1.3 g, 4.7 mmol) in ethanol (5 ml) at room temperature,

triethylamine (1.3 mL, 9.4 mmol) was added followed by dimethyl N-cyanodithioiminocarbonate (1.5 g, 9.4 mmol of 90%) with stirring at room temperature. The reaction mixture was heated at 80°C for 3 hours and then cooled to ambient temperature. The solvent was evaporated to give a light yellow foam (1.5 g). This material was taken up in methanol (20 mL) and the resulting suspension was treated with mercuric acetate (2.0 g, 6.1 mmol). The reaction mixture was stirred at room temperature for 2 hours and the solvent was evaporated under reduced pressure. The residue was diluted with water and alkalized to pH ~9.0 with 2.5N sodium hydroxide and the product was extracted with 10 percent methanolic chloroform (3x). The combined extract was washed with brine whereby a thick emulsion resulted. The two phase mixture was filtered through a celite pad and the organic layer was separated and dried over magnesium sulfate. The solvent was evaporated and the residue was purified by flash chromatography (5% methanol in chloroform) on silica gel to provide a colorless residue (0.5 g) which was crystallized from isopropyl ether-ethyl acetate to yield the title compound as a white powder, m.p. 152-153°C: ^{1}H NMR (DMSO-d_6) δ 7.60 (d, J = 7.0 Hz, 1 H), 7.40 (s, 1 H), 7.0 (d, J = 9.0, 1 H), 5.85 (d, J = 5.2 Hz, 1 H), 5.6 (d, J = 10.5 Hz, 1 H), 3.8 (dd, J = 5.0 Hz, 1 H), 3.2 (m, 4 H), 2.9 (br d, 1H), 1.54, 1.26 (s, 3 H each); ^{13}C NMR (DMSO-d_6) 164.5, 156.8, 133.2, 131.6, 118.9, 118.2, 118.0, 103.1, 80.4, 67.3, 51.2, 40.3, 26.6, 18.6; IR (KBr) 1268.7, 1316.8, 1402.2, 1489.5, 1558.1, 1580.4, 2174.7, 3421.3 cm^{-1}.

Analysis calc'd for $C_{17}H_{19}N_5O_2 \cdot 0.42\ H_2O$:
C, 61.33; H, 6.01; N, 21.04;
Found: C, 61.31; H, 6.02; N, 21.06.

Example 22

(*trans*)-N"-Cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-(4-pyridinylmethyl)guanidine

A suspension of (*trans*)-4[[(cyanoimino)-phenoxymethyl]amino]-3,4-dihydroxy-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile (1.0 g, 2.76 mmol), compound of Example 7, part A, in isopropanol (5 ml) was treated at room temperature with 4-(amino-methyl)pyridine (1.0 ml). The reaction mixture was allowed to stir at room temperature for 4 hours and then heated at reflux temperature for 16 hours. The reaction mixture was cooled to ambient temperature and the precipitated solid was filtered off. The product was recrystallized from ethyl acetate to give the title compound (0.76 g) as a colorless solid, m.p. 156-158°C: ^{1}H NMR (DMSO-d_6) δ 8.53 (d, J = 6.0 Hz, 2 H), 7.9 (m, 1 H), 7.59 (dd, J = 3.0 & 6.0 Hz, 1 H), 7.44 (s, 2 H), 7.31 (d, J = 6.0 Hz, 2 H), 6.91 (d, J = 9.0 Hz, 1 H), 5.9 (s, 1 H), 4.87 (m, 1 H), 4.48 (t, J = 2.0 & 6.0 Hz, 2 H), 3.7 (m, 1 H), 1.99 (s, 3 H), 1.18 (s, 3 H); ^{13}C NMR (DMSO-d_6) 160.4, 156.2, 149.4, 132.6, 132.3, 124.7, 121.7, 117.8, 117.4, 102.6, 80.4, 71.0, 51.5, 43.4, 26.5, 18.6; IR (KBr) 1125.2, 1490.2, 1524.1, 1577.8, 1611.3, 2170.4, 2224.9, 3429.7 cm^{-1}.

Analysis calc'd for $C_{20}H_{20}N_6O_2 \cdot 0.2\ H_2O$:
C, 63.22; H, 5.41; N, 22.12;
Found: C, 63.42; H, 5.17; N, 21.92.

Example 23

(*trans*)-N"-Cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-(3-pyridinylmethyl)guanidine

A suspension of (*trans*)-4-[[(cyanoimino)-phenoxymethyl]amino]-3,4-dihydroxy-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile (1.0 g, 2.76 mmol), compound of Example 7, part A, in isopropanol (5 ml) was treated at room temperature with 3-(aminomethyl)pyridine (1.0 ml). The reaction mixture was allowed to stir at room temperature for 4 hours and then heated under reflux for 16 hours. The reaction mixture was concentrated *in vacuo* and the resulting solid was crystallized from ethyl acetate to give the title compound (0.72 g) as a colorless solid, m.p. 226-228°C: ^{1}H NMR (DMSO-d_6) δ 8.55 (s, 1 H), 8.49 (d, J = 2.0 Hz, 2 H), 7.85 (m, 1 H), 7.75 (d, J = 8.0 Hz, 1 H), 7.59 (d, J = 8.0 Hz, 1 H), 7.40 (m, 3 H), 6.91 (d, J = 8.0 Hz, 1 H), 5.85 (s, 1 H), 4.82 (m, 1 H), 4.48 (m, 2 H), 3.74 (m, 1 H), 1.40 (s, 3 H), 1.17 (s, 3 H); ^{13}C NMR 160.43, 156.2, 148.6, 148.2, 134.6, 134.2, 132.7, 132.2, 124.8, 123.4, 118.9, 117.9, 117.5, 102.6, 80.4, 71.0, 51.5, 42.1, 26.6, 18.7; IR (KBr) 1125.2, 1490.1, 1524.1, 1577.8, 1611.3, 2170.4, 2224.9, 3429.7 cm^{-1}.

Analysis calc'd for $C_{20}H_{20}N_6O_2 \cdot 0.17\ H_2O$:
C, 63.22; H, 5.41; N, 22.12;
Found: C, 63.08; H, 5.32; N, 22.38.

Example 24

(*trans*)-N"-Cyano-N-(6-ethynyl-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-phenylguanidine

A. 1-((1,1-Dimethyl-2-propynyl)oxy)-4-iodobenzene

A solution of 3-chloro-3-methyl-1-butyne (10.0 g, 97.9 mmol), 4-iodophenol (15.0 g, 68.4 mmol), sodium hydroxide (3.90 g, 97.5 mmol) and tetrabutylammonium hydrogen sulfate (9.33 g, 27.5 mmol) in methylene chloride (50 mL) and water (50 mL) was stirred for 19 days at room temperature. After separating the two layers, the organic layer was washed with 1 N sodium hydroxide followed by water, dried over magnesium sulfate and concentrated *in vacuo*. The residue was dissolved in ethyl acetate and washed successively with 1 N hydrochloric acid, 1 N sodium hydroxide, water, brine and dried over anhydrous magnesium sulfate. After removing drying agent, the solvent was removed *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with toluene/hexane (1:10) to give the title compound as an oil (5.78 g, 20.2 mmol) in 30% yield: ^{1}H NMR ($CDCl_3$) δ 7.56 (d, J = 8.7 Hz, 2H), 6.98 (d, J =

8.8 Hz, 2H), 2.56 (s, 1H), 1.63 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 155.4, 137.8, 123.5, 86.0, 85.6, 74.3, 72.6, 29.5.

B. 2,2-Dimethyl-6-iodo-2H-1-benzopyran

The title A compound (3.91 g, 13.7 mmol) was heated in an oil bath at 170° for 2 hours. After cooling, the crude product was purified by flash chromatography on silica gel eluting with toluene/hexane (1:20) to give the title compound as an oil (3.26 g, 11.4 mmol) in 83% yield: ^1H NMR ($CDCl_3$) δ 7.34 (dd, J_1 = 1.8, J_2 = 2.4 Hz, 1H), 7.24 (d, J = 0.9 Hz, 1H), 6.52 (d, J = 8.8 Hz, 1H), 6.21 (d, J = 10.0 Hz, 1H), 5.58 (d, J = 10.0 Hz, 1H), 1.40 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 152.8, 137.5, 134.7, 131.6, 123.6, 121.1, 118.6, 82.4, 76.4, 27.9.

C. 2,2-Dimethyl-6-(trimethylsilyl)ethynyl)-2H-1-benzopyran

A solution of the title B compound (1.32 g, 4.61 mmol), trimethyl((trimethylstannyl)ethynyl)-silane (1.60 g, 5.69 mmol), lithium chloride (0.62 g, 14.6 mmol) and tetrakis(triphenylphosphine) palladium (0.69 g, 0.60 mmol) in dioxane (16.5 mL) was stirred under argon for 5 hours in an oil bath at 65°. The reaction mixture was cooled to room temperature and concentrated *in vacuo* to give a residue that was combined with the material prepared in a similar manner on a 2.42 mmol scale. The combined material was rinsed with toluene/hexane (1:10) and the filtrate was

concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with toluene/hexane (1:10) to give the title C cmpound as an oil (1.82 g, 7.00 mmol) in 100% yield: ^{1}H NMR ($CDCl_3$) δ 6.98 (dd, J_1 = 2.3, J_2 = 8.2 Hz, 1H), 6.87 (d, J = 1.8 Hz, 1H), 6.44 (d, J = 8.2 Hz, 1H), 6.02 (d, J = 9.4 Hz, 1H), 5.38 (d, J = 10.0 Hz, 1H), 1.20 (s, 6H), 0.00 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 153.4, 133.0,131.2, 130.0,121.6, 121.0, 116.3, 115.2, 105.2, 92.1, 76.7, 28.1, 0.1.

Analysis calc'd for $C_{16}H_{20}OSi$:
C, 74.94; H, 7.86;
Found: C, 75.19; H, 7.61.

D. (*cis*)-1a,7b-Dihydro-2,2-dimethyl-6-((trimethylsilyl)ethynyl)-2H-oxireno(c)-(1)-benzopyran

To a solution of the title C compound (1.37 g, 5.34 mmol) and sodium bicarbonate (2.33 g, 27.7 mmol) in methylene chloride (27 mL) and water (27 mL) at 0° was added 3-chloroperoxybenzoic acid (1.51 g of 80-85% purity, 7.01 mmol). After a few minutes of stirring, the ice bath was removed and the reaction mixture was stirred at room temperature for 9 hours. After adding methylene chloride to the reaction mixture, the organic layer was separated and washed with water followed by brine, dried over magnesium sulfate and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with hexane/ethyl acetate (10:1) to give recovered starting material (0.47 g) and the title copound as an oil

(0.53 g, 1.95 mmol) in 36% yield: ^{1}H NMR ($CDCl_3$) δ 7.24 (d, J = 1.8 Hz, 1H), 7.11 (dd, J_1 = 1.78, J_2 = 2.3 Hz, 1H), 6.49 (d, J = 8.2 Hz, 1H), 3.62 (d, J = 4.1 Hz, 1H), 3.25 (d, J = 4.1 Hz, 1H), 1.34 (s, 3H), 1.00 (s, 3H), 0.00 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 152.9, 134.1, 133.4, 120.0, 118.1, 103.6, 92.9, 73.6, 62.5, 50.5, 25.6, 22.7, 0.00.

E. (*trans*)-4-Amino-6-ethynyl-3,4-dihydro-2H-1-benzopyran-3-ol

A solution of the title D compound (0.53 g, 1.95 mmol) in ethanol (15 mL) and concentrated aqueous ammonium hydroxide (30 mL) was stirred at room temperature for 4 days. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel eluting with hexane/ethyl acetate/methanol (5:5:1) to give a partially purified product. This material was triturated with diethyl ether to give the title compound as a white solid (0.42 g, 1.93 mmol) in 99% yield, m.p. 132-134°C: ^{1}H NMR ($CDCl_3$) δ 7.62 (s, 1H), 7.38 (dd, J_1 = 1.2, J_2 = 1.8 Hz, 1H), 6.82 (d, J = 8.2, Hz, 1H), 3.73 (d, J = 10.0 Hz, 1H), 3.45 (d, J = 9.4 Hz, 1 H), 3.10 (s, 1H), 2.56 (br s, 3H), 1.59 (s, 3H), 1.30 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 153.0, 132.6, 131.0, 125.7, 117.2, 114.0, 83.6 78.6, 75.9, 75.8, 51.1, 26.9, 18.7.
Analysis calc'd for $C_{13}H_{15}NO_2 \cdot 0.06\ H_2O$:
C, 71.52; H, 6.98; N, 6.42;
Found: C, 71.47; H, 6.95; N, 6.47.

F. (*trans*)-N"-Cyano-N-(6-ethynyl-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-phenylguanidine

To a solution of the title E compound (0.150 g, 0.69 mmol) and N-cyano-N'-phenylthiourea (0.180 g, 1.0 mmol) in dimethylformamide (5 mL) was added 1-(3-dimethylaminopropyl)-2-ethyl-carbodiimide hydrochloride (0.200 g, 1.0 mmol) at room temperature. The reaction mixture was stirred overnight at room temperature and the solvent was removed *in vacuo*. The residue was partitioned between water and ethyl acetate. The organic layer was separated and dried over sodium sulfate. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel eluting with hexane/ethyl acetate/ethanol (30:10:5) to give a partially pure product. This material was triturated with diethyl ether to give the title compound (0.12 g, 0.34 mmol) in 49% yield, m.p. 220-222°C (dec); ^{1}H NMR ($CDCl_3$) δ 7.20-7.40 (m, 7H), 6.70 (d, J = 8.2 Hz, 1H), 5.00 (d, J = 10.0 Hz, 1H), 3.67 (d, J = 9.4 Hz, 1H), 3.34 (s, 1H), 1.44 (s, 3H), 1.24 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 161.6, 154.6, 138.2, 133.7, 132.8 130.5, 127.2, 125.7, 123.9, 118.9, 118.3, 116.0, 84.3, 80.5, 77.2, 74.6, 54.0, 27.1, 18.6.

Analysis calc'd for $C_{21}H_{20}N_4O_2 \cdot 0.32\ H_2O$:
C, 68.89; H, 5.68; N, 15.31;
Found: C, 69.11; H, 5.55; N, 15.09.

Example 25

(*trans*)-N"-Cyano-N-(3,4-dihydro-6-(phenylethynyl)-2H-1-benzopyran-4-yl)-N'-phenylguanidine

A. 2,2-Dimethyl-6-(phenylethynyl)-2H-1-benzopyran

To a solution of the title B compound from Example 24 (1.69 g, 5.91 mmol) and phenylacetylene (2.0 mL, 18.1 mmol) in diethylamine (30 mL) at room temperature were added bis(triphenylphosphine)-palladium(II)chloride (0.40 g, 0.572 mmol) and copper(I) iodide (0.22 g, 1.41 mmol) under argon atmosphere. After stirring for 1 hour at room temperature, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate and the insoluble material was filtered. The filtrate was concentrated *in vacuo*. The residue was again dissolved in toluene/hexane (1:10) and the insoluble material was filtered. The filtrate was concentrated *in vacuo* and the crude product was purified by flash chromatography on silica gel eluting with toluene/hexane (1:10) to give the title compound as an oil (1.43 g, 5.49 mmol) in 92% yield: ^{1}H NMR ($CDCl_3$) δ 7.47-7.50 (m, 2H), 7.24-7.31 (m, 4H), 7.14 (d, J = 2.4 Hz, 1H), 6.72 (d, J = 8.2 Hz, 1H), 6.26 (d, J = 10.0 Hz, 1H), 5.58 (d, J = 9.4 Hz, 1H), 1.40 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 153.2, 132.5, 131.3, 131.2, 129.5, 128.2, 127.8, 123.6, 121.6, 121.1, 116.4, 115.2, 89.4, 87.8, 76.7, 28.0.

B. 2,2-Dimethyl-6-(phenylethynyl)-2H-oxireno-(c)-(1)-benzopyran

To a solution of the title A compound (1.14, 4.38 mmol) and sodium bicarbonate (1.86 g, 22.1 mmol) in methylene chloride (15 mL) and water (15 mL) at 0° was added 3-chloroperoxybenzoic acid (1.21 g of 80-85% purity, 5.62 mmol). After 5 minutes, the ice bath was removed and the reaction mixture was stirred at room temperature for 8 hours. It was diluted with methylene chloride and the organic layer was taken. It was washed with water followed by brine and dried over magnesium sulfate. The solvent was concentrated *in vacuo* and the material was purified by flash chromatography on silica gel eluting with hexane/ethyl acetate (10:1) to give recovered starting material (0.17 g) and the title compound as an oil (0.74 g, 2.68 mmol) in 61% yield: ^{1}H NMR ($CDCl_3$) δ 7.42-7.64 (m, 7H), 6.90 (d, J = 8.8 Hz, 1H), 3.99 (d, J = 4.7 Hz, 1H), 3.60 (d, J = 4.7 Hz, 1H), 1.69 (s, 3H), 1.38 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 152.8, 133.7, 132.9, 131.4, 128.3, 128.0, 123.4, 120.2, 118.2, 115.9, 88.9, 88.3, 73.6 62.5, 50.6, 48.2, 22.7.

C. (*trans*)-4-Amino-3,4-dihydro-2,2-dimethyl-6-(phenylethynyl)-2H-1-benzopyran-3-ol

A solution of the title B compound (0.71 g, 2.55 mmol) in absolute ethanol (20 mL) and concentrated aqueous ammonium hydroxide (40 mL) was stirred for 7 days and the solvents were removed *in vacuo*. The crude product was triturated with hexane and diisopropyl ether to give the title compound as a white solid (0.64 g, 2.18 mmol) in 86% yield, m.p. 162-164°C; ^{1}H NMR

($CDCl_3$) δ 7.36-7.67 (m, 7H), 6.86 (d, J = 8.2 Hz, 1H), 3.78 (d, J = 10.0 Hz, 1H), 3.48 (d, J = 10.0 Hz, 1H), 2.51 (br s, 3H), 1.62 (s, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 152.7, 132.1, 131.4, 130.4, 128.3, 128.0, 125.6, 122.8, 117.3, 115.0, 88.6, 87.1, 78.5, 76.0, 51.2, 26.9, 18.7.

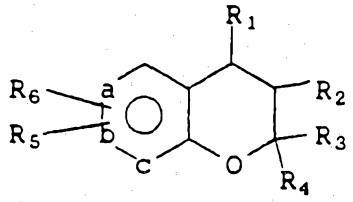
Analysis calc'd for $C_{19}H_{19}O_2N \cdot 0.28\ H_2O$:
C, 76.46; H, 6.61; N, 4.69;
Found: C, 76.39; H, 6.52; N, 4.76.

D. (*trans*)-N"-Cyano-N-(3,4-dihydro-6-(phenylethynyl)-2H-1-benzopyran-4-yl)-N'-phenylguanidine

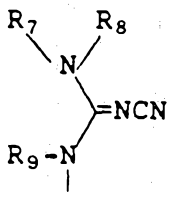
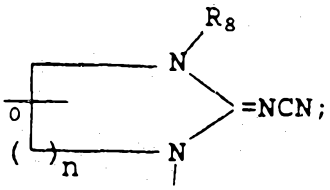
To a solution of the title C compound (0.64 g, 2.18 mmol) and N-cyano-N'-phenylthiourea (0.56 g, 3.16 mmol) in dimethylformamide (16 mL) was added 1-(3-dimethylaminopropyl)-2-ethyl-carbodiimide hydrochloride (0.60 g, 3.49 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2 days and the solvent was removed *in vacuo*. The residue was partitioned between ethyl acetate and water. The organic layer was taken and it was washed with water followed by brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with hexane/ethyl acetate/ethanol (10:10:1) to give a partially purified material. This material was triturated with diisopropyl ether to give the title compound as a white solid (0.46 g, 1.05 mmol) in 48% yield, m.p. 175-177°C: ^1H NMR (DMSO-d_6) δ 9.42 (s, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.20-7.75 (m, 14H), 6.88 (d, J = 9.4 Hz, 1H), 5.59 (br s, 1H), 5.02 (dd, J_1 = 8.8, J_2 = 9.4 Hz, 1H), 3.80 (br d, J = 9.4 Hz, 1H), 1.50 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 159.5, 153.2, 138.0, 132.2, 131.6, 131.3, 129.3, 129.0, 128.0, 124.9, 124.1, 123.7, 122.9, 117.4, 114.3, 89.7, 88.3, 79.9, 71.6, 52.5, 27.1, 18.8.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of the formula

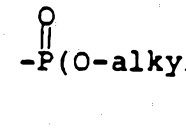


wherein a, b, and c are all carbons or one of a, b and c can be nitrogen or -NO- and the others are carbons;

R_1 is  or  ;

R_2 is hydrogen, hydroxy or $-OCCH_3$ (with O);

R_3 and R_4 are each independently hydrogen, alkyl or arylalkyl, or, R_3 and R_4 taken together with the carbon atom to which they are attached form a 5- to 7-membered carbocyclic ring;

R_5 is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, $-NO_2$, -COR, -COOR, -CONHR, $-CONR_2$, $-CF_3$, S-alkyl, -SOalkyl, $-SO_2$alkyl, $-P(O\text{-alkyl})_2$,  , halogen, amino, substituted amino, O-alkyl, OCF_3, OCH_2CF_3, -OCOalkyl, -OCONRalkyl, -NRCOalkyl and NRCOOalkyl, $NRCONR_2$ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;

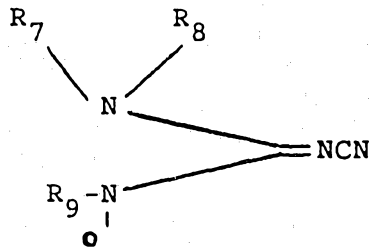
R_6 is selected from H, alkyl, OH, O-alkyl, amino, substituted amino, CN, and NO_2;

R_7 is selected from aryl, arylalkyl, heterocyclo and heterocycloalkyl;

R_8 is selected from hydrogen, alkyl, alkenyl, aryl, heterocyclo, (heterocyclo)alkyl, arylalkyl, cycloalkyl and (cycloalkyl)alkyl, substituted alkyl wherein the substituents include alkoxy, alkylthio and substituted amino, or R_7 and R_8 taken together with the nitrogen atom to which they are attached form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorphilinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl or 4-arylalkyl-1-piperazinyl, wherein each of the so-formed groups can be substituted with alkyl, alkoxy, alkylthio, halogen or trifluoromethyl with the proviso that:

where a, b and c are all carbon atoms,

R_1 is



R_2 is OH or $-OC-CH_3$

R_3 and R_4 are alkyl,

one of R_5 and R_6 is -CN and the other is H,

and R_5 is H or lower alkyl, then

R_7 and R_8 taken together with the nitrogen atom to which they are attached do not form 1-pyrrolidinyl, 1-piperidinyl or 4-morpholinyl;

R_9 and R_{10} are selected from hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl or cycloalkylalkyl; and

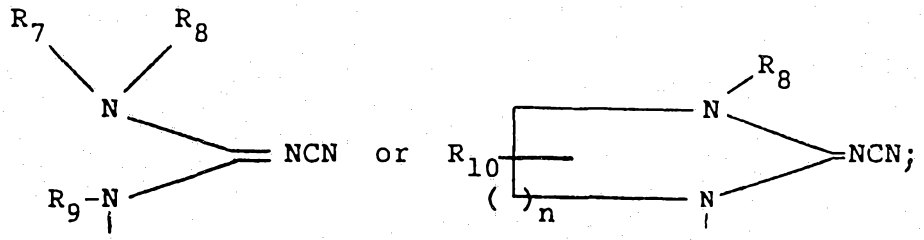
n is 1, 2 or 3.

2. A compound in accordance with claim 1 wherein

a is nitrogen or $-CR_5$;

b and c are each -CH-;

R_1 is



R_2 is hydroxy or -OCOalkyl;
R_3 and R_4 are each alkyl;
R_5 is an electron withdrawing group
R_6 is hydrogen, alkyl, O-alkyl, amino;
R_7 is aryl or arylalkyl;
R_8 is hydrogen;
R_9 is hydrogen or alkyl;
R_{10} is hydrogen; and
n is 1 or 2.

3. A compound in accordance with claim 1 wherein
a is nitrogen or $-CR_5$;
b and c are each -CH-;
R_2 is transhydroxy;
R_3 and R_4 are each methyl;
R_5 is -CH or $-NO_2$;
R_6 is hydrogen;
R_7 is phenyl or phenylmethyl;
R_8 is hydrogen;
R_9 is hydrogen;
R_{10} is hydrogen; and
n is 1.

4. A compound in accordance with claim 1 which is (trans)-N"-cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-(1,1-dimethylpropyl)guanidine.

5. A compound in accordance with claim 1 which is (trans)-N"-cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-ethylguanidine.

6. A compound in accordance with claim 1 which is (trans)-N"-cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-phenylguanidine.

7. A compound in accordance with claim 1 which is (trans)-N"-cyano-N-(3,4-dihydro-3-hydroxy-2,2-dimethyl-6-nitro-2H-1-benzopyran-4-yl)-N'-ethylguanidine.

8. A compound in accordance with claim 1 which is (trans)-3,4-dihydro-3-hydroxy-2,2-dimethyl-4-[2-(cyanoimino)-1-pyrrolidinyl]-2H-1-benzopyran-6-carbonitrile.

9. A compound in accordance with claim 1 which is (trans)-N"-cyano-N-(3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-pyrano[3,2-c]pyridin-4-yl)phenylguanidine.

10. A compound in accordance with claim 1 which is (trans)-N'-cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-1-pyrrolidine-carboximidamide.

11. A compound in accordance with claim 1 which is (trans)-N"-cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-ethyl-N-methylguanidine.

12. A compound in accordance with claim 1 which is (trans)-N"-cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-[2(dimethylamino)ethyl]guanidine.

13. A compound in accordance with claim 1 which is (trans)-4[[(cyanoimino)(1-pyrrolidinyl)-methyl]amino]-3,4-dihydroxy-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile.

14. A compound in accordance with claim 1 which is (trans)-N"-cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-methylguanidine.

15. A compound in accordance with claim 1 which is (trans)-4-[(cyanoimino)[[4-(phenylmethyl)-1-piperazinyl]-

methyl]-amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile.

16. A compound in accordance with claim 1 which is (trans)-N"-cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-guanidine.

17. A compound in accordance with claim 1 which is (trans)-N"-cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-(methylethyl)guanidine.

18. A compound in accordance with claim 1 which is (trans)-N"-cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-dimethylguanidine.

19. A compound in accordance with which 1 which is (trans)-N"-cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-phenylmethylguanidine.

20. A compound in accordance with claim 1 which is (trans)-N"-cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-[2-[(phenylmethyl)methylamino]ethyl]-guanidine.

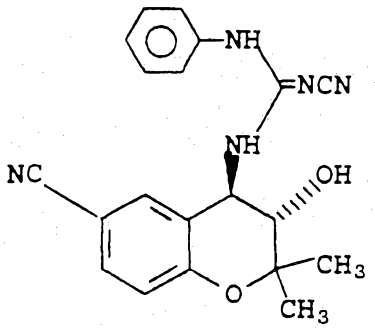
21. A compound in accordance with claim 1 which is (trans)-N"-cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-(2-methoxyethyl)guanidine.

22. A compound in accordance with claim 1 which is (3S-trans)-N"-cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-phenylguanidine.

23. A compound in accordance with claim 1 which is (3R-trans)-N"-cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-phenylguanidine.

24. A compound in accordance with claim 1 which is (*trans*)-4-[2-(cyanoimino)tetrahydro-1(2H)-pyrimidinyl]-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-6-carbonitrile.

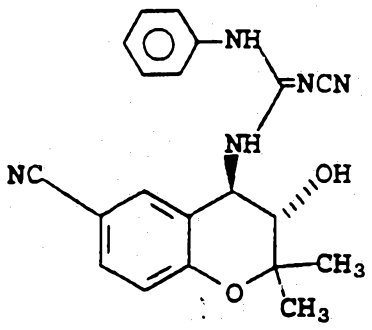
25. A compound in accordance with claim 1 having the structure



26. A method for the treatment of myocardial ischemia which comprises administering to a mammalian specie in need thereof, a therapeutically effective amount of a compound as defined in claim 1.

27. The method of claim 26 wherein said compound is further defined in that R_7 is selected from aryl and arylalkyl, and R_8 and R_9 are each hydrogen.

28. The method of claim 26 wherein said compound has the structure



29. A method of treating hypertension which comprises administering to a mammalian specie in need thereof, a therapeutically effective amount of a compound of claim 1.

30. The method of claim 29 wherein said compound is further defined in that R_7 is selected from hydrogen and alkyl of 1 to 3 carbons, or R_7 and R_8 together form pyrrolidine or piperidine, R_9 and R_{10} are each hydrogen and n is 1 or 2.

31. A compound in accordance with claim 1 which is (trans)-N"-cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-(2-methoxyethyl)guanidine.

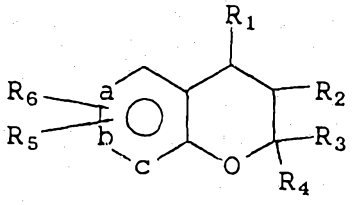
32. A compound in accordance with claim 1 which is (trans)-N"-cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-(4-pyridinylmethyl)guanidine.

33. A compound in accordance with claim 1 which is (trans)-N"-cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-(3-pyridinylmethyl)guanidine.

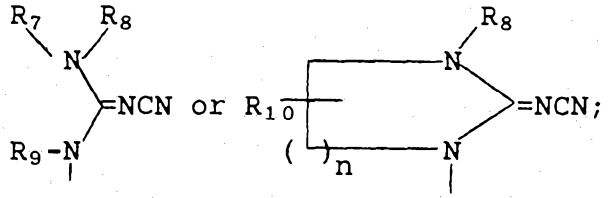
34. A compound in accordance with claim 1 which is (trans)-N"-cyano-N-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N'-phenylguanidine.

35. A compound in accordance with claim 1 which is (trans)-N"-cyano-N-(3,4-dihydro-6-(phenylethynyl)-2H-1-benzopyran-4-yl)-N'-phenylguanidine.

36. A compound of the formula



wherein a, b, and c are all carbons or one of a, b and c can be nitrogen or -NO- and the others are carbons;

R_1 is  ;

R_2 is hydrogen, hydroxy or -OCCH$_3$ (O)

R_3 and R_4 are each independently hydrogen, alkyl or arylalkyl, or, R_3 and R_4 taken together with the carbon atom to which they are attached form a 5- to 7-membered carbocyclic ring;

R_5 is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, -NO_2, -COR, -COOR, -CONHR, -$CONR_2$, -CF_3, S-alkyl, -SOalkyl, -SO_2alkyl, halogen, amino, substituted amino, O-alkyl, -OCOalkyl, -OCONRalkyl, -NRCOalkyl and NRCOOalkyl, $NRCONR_2$ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or cycloalkylalkyl;

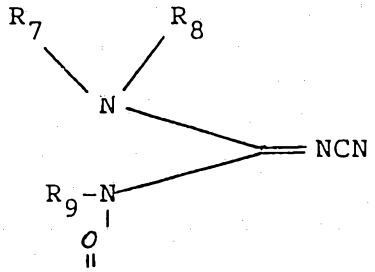
R_6 is selected from H, alkyl, OH, O-alkyl, amino, substituted amino, CN, and NO_2;

R_7 is selected from aryl, arylalkyl, heterocyclo and heterocycloalkyl;

R_8 is selected from hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl and cycloalkylalkyl, or R_7, and R_8 taken together with the nitrogen atom to which they are attached form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorphilinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl or 4-arylalkyl-1-piperazinyl, wherein each of the so-formed groups can be substituted with alkyl, alkoxy, alkylthio, halogen or trifluoromethyl with the proviso that:

where a, b and c are all carbon atoms,

R_1 is



R_2 is OH or $-OC-CH_3$

R_3 and R_4 are alkyl,

one of R_5 and R_6 is -CN and the other is H,

and R_9 is H or lower alkyl, then

R_7 and R_8 taken together with the nitrogen atom to which they are attached do not form 1-pyrrolidinyl, 1-piperidinyl or 4-morpholinyl;

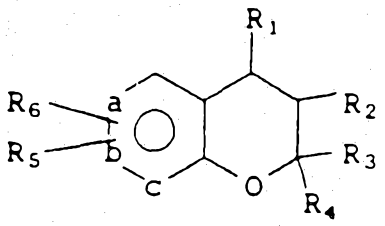
R_9 and R_{10} are selected from hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl or cycloalkylalkyl; and

n is 1, 2 or 3.

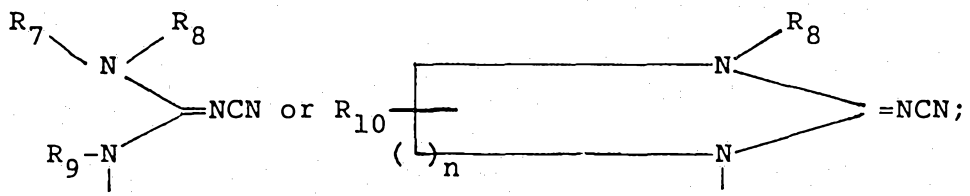
37. A pharmaceutical composition for the treatment of myocardial ischemia in a mammalian species comprising a therapeutically effective amount of a compound as defined in claim 1 and a pharmaceutically acceptable carrier therefor.

38. A method for the treatment of ischemic conditions in a mammalian specie comprising administering to a specie in need thereof an effective amount of a potassium channel activator having little or no vasodilator effect.

38. A method for the treatment of ischemic conditions in a mammalian specie comprising administering to a specie in need thereof an effective amount of a potassium channel activator having little or no vasodilator effect, wherein the potassium channel activator is of the formula:



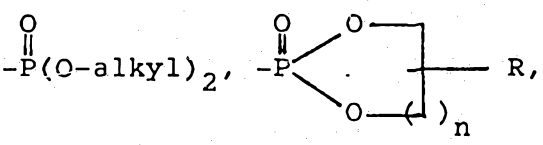
wherein a, b, and c are all carbons or one of a, b and c can be nitrogen or -NO- and the others are carbons;

R_1 is  or =NCN;

R_2 is hydrogen, hydroxy or $-OCCH_3$ (=O)

R_3 and R_4 are each independently hydrogen, alkyl or arylalkyl, or, R_3 and R_4 taken together with the carbon atom to which they are attached form a 5- to 7-membered carbocyclic ring;

R_5 is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, $-NO_2$, -COR, -COOR, -CONHR, $-CONR_2$, $-CF_3$, S-alkyl, -SOalkyl, $-SO_2$alkyl,



halogen, amino, substituted amino, O-alkyl, OCF_3, OCH_2CF_3, -OCOalkyl, -OCONRalkyl, -NRCOalkyl and NRCOOalkyl, $NRCONR_2$ wherein R in each of the above groups

can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;

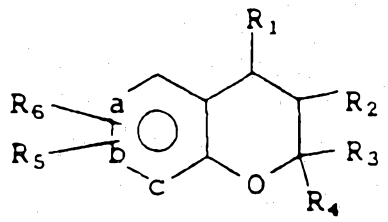
R_6 is selected from H, alkyl, OH, O-alkyl, amino, substituted amino, CN, and NO_2;

R_7 and R_8 are each independently selected from hydrogen, alkyl, alkenyl, aryl, heterocyclo, (heterocyclo)-alkyl, arylalkyl, cycloalkyl and (cycloalkyl)alkyl, substituted alkyl wherein the substituents include alkoxy, alkylthio and substituted amino, or R_7 and R_8 taken together with the nitrogen atom to which they are attached form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorphilinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl or 4-arylalkyl-1-piperazinyl, wherein each of the so-formed groups can be substituted with alkyl, alkoxy, alkylthio, halogen or trifluoromethyl;

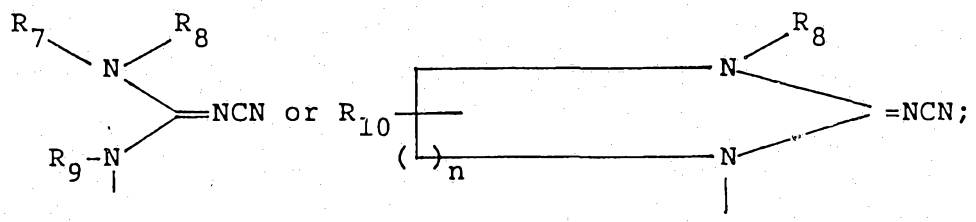
R_9 and R_{10} are selected from hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl or cycloalkylalkyl; and

n is 1, 2 or 3.

39. A pharmaceutical composition for the treatment of ischemic conditions in a mammalian specie comprising an effective amount of a potassium channel activator having little or no vasodilator effect and a pharmaceutically acceptable carrier therefor, wherein the potassium channel activator is of the formula:



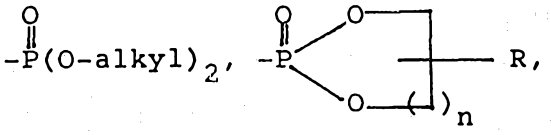
wherein a, b, and c are all carbons or one of a, b and c can be nitrogen or -NO- and the others are carbons;

R_1 is  or ;

R_2 is hydrogen, hydroxy or $-OCCH_3$ (O)

R_3 and R_4 are each independently hydrogen, alkyl or arylalkyl, or, R_3 and R_4 taken together with the carbon atom to which they are attached form a 5- to 7-membered carbocyclic ring;

R_5 is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, $-NO_2$, -COR, -COOR, -CONHR, $-CONR_2$, $-CF_3$, S-alkyl, -SOalkyl, $-SO_2$alkyl,



halogen, amino, substituted amino, O-alkyl, OCF_3, OCH_2CF_3, -OCOalkyl, -OCONRalkyl, -NRCOalkyl and NRCOOalkyl, $NRCONR_2$ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;

R_6 is selected from H, alkyl, OH, O-alkyl, amino, substituted amino, CN, and NO_2;

R_7 and R_8 are each independently selected from hydrogen, alkyl, alkenyl, aryl, heterocyclo, (heterocyclo)-alkyl, arylalkyl, cycloalkyl and (cycloalkyl)alkyl, substituted alkyl wherein the substituents include alkoxy, alkylthio and substituted amino, or R_7 and R_8 taken together with the nitrogen atom to which they are attached form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorphilinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl or 4-arylalkyl-1-piperazinyl, wherein each of the so-formed groups can be substituted with alkyl, alkoxy, alkylthio, halogen or trifluoromethyl;

R_9 and R_{10} are selected from hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl or cycloalkylalkyl; and

n is 1, 2 or 3.

DATED: 17 November 1992

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