638275

COMMONWEALTH of AUSTRALIA
Patents Act 1952

APPLICATION FOR A STANDARD PATENT

I/We

Allergan, Inc.

of

2525 Dupont Drive, Irvine, California, 92715-1599, United States of America

hereby apply for the grant of a Standard Patent for an invention entitled:

Process and intermediates for preparing compounds having a disubstituted acetylene moiety and retinoic acid-like biological activity

which is described in the accompanying complete specification.

Details of basic application(s):-

Number	Convention Country	Date
409477	United States of America	19 September 1989

The address for service is care of DAVIES & COLLISON, Patent Attorneys, of 1 Little Collins Street, Melbourne, in the State of Victoria, Commonwealth of Australia.

DATED this SEVENTEENTH day of SEPTEMBER 1990

To: THE COMMISSIONER OF PATENTS

.....
a member of the firm of
DAVIES & COLLISON for
and on behalf of the
applicant(s)

Davies & Collison, Melbourne

ALLERGAN DOCKET
NO. 16766-ASTPL

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952–1973

DECLARATION IN SUPPORT OF CONVENTION OR NON–CONVENTION APPLICATION FOR A PATENT OR PATENT OF ADDITION

Insert title of invention.

In support of the Application made for a patent / patent of addition for an invention entitled: PROCESS AND INTERMEDIATES FOR PREPARING COMPOUNDS HAVING A DISUBSTITUTED ACETYLENE MOIETY AND RETINOIC ACID-LIKE BIOLOGICAL ACTIVITY

Insert full name(s) and address(es) of declarant(s) being the applicant(s) or person(s) authorized to sign on behalf of an applicant company.

~~We~~ I, Martin A. Voet
28451 Avenida La Mancha
San Juan Capistrano, CA 92675
United States of America

do solemnly and sincerely declare as follows :–

Cross out whichever of paragraphs 1(a) or 1(b) does not apply

1(a) relates to application made by individual(s)
1(b) relates to application made by company; insert name of applicant company.

1. (a) ~~I am / We are the applicant for the patent / patent of addition~~

or (b) I am authorized by

ALLERGAN, INC.

the applicant..... for the patent / patent of addition to make this declaration on its behalf.

Cross out whichever of paragraphs 2(a) or 2(b) does not apply

2(a) relates to application made by inventor(s)
2(b) relates to application made by company(s) or person(s) who are not inventor(s); insert full name(s) and address(es) of inventors.

2. (a) ~~I am / We are the actual inventor / joint inventors of the invention~~

or (b)

ROSHANTHA A. S. CHANDRARATNA of
23015 Ashwood
El Toro, California 92630
United States of America

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

State manner in which applicant(s) derive title from inventor(s)

That said ALLERGAN, INC. is the assignee of the said ROSHANTHA A. S. CHANDRARATNA in respect of the invention.

Cross out paragraphs 3 and 4 for non-convention applications. For convention applications, insert basic country(s) followed by date(s) and basic applicant(s).

3. The basic application..... as defined by Section 141 of the Act was / ~~were~~ made
in United States of America on the September 19, 1989
by Roshantha A. S. Chandraratna
in ..... on the .....
by.....
in ..... on the .....
by.....

4. The basic application..... referred to in paragraph 3 of this Declaration was / ~~were~~ the first application..... made in a Convention country in respect of the invention the subject of the application.

Insert place and date of signature.

Declared at Irvine, California, U.S.A. this 8th day of August, 1990

Signature of declarant(s) (no attestation required)

ALLERGAN, INC.
x Martin A. Voet
MARTIN A. VOET, Associate General Counsel-Intellectual Pty. and Assistant Secretary

Note: Initial all alterations.

DAVIES & COLLISON, MELBOURNE and CANBERRA

AU9062615

(12) PATENT ABRIDGMENT (11) Document No. AU-B-62615/90
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 638275

(54) Title
PROCESS AND INTERMEDIATES FOR PREPARING COMPOUNDS HAVING A DISUBSTITUTED ACETYLENE MOIETY AND RETINOIC ACID-LIKE BIOLOGICAL ACTIVITY

International Patent Classification(s)
(51)[5] C07D 335/06 C07D 215/06 C07D 311/58 C07D 401/06
C07D 405/06 C07D 407/06 C07D 409/06

(21) Application No. : 62615/90 (22) Application Date : 17.09.90

(30) Priority Data

(31) Number	(32) Date	(33) Country
409477	19.09.89	US UNITED STATES OF AMERICA

(43) Publication Date : 28.03.91

(44) Publication Date of Accepted Application : 24.06.93

(71) Applicant(s)
ALLERGAN, INC.

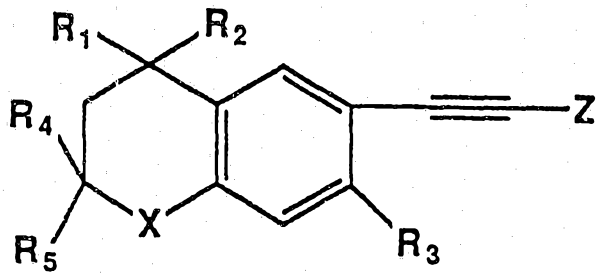
(72) Inventor(s)
ROSHANTHA A.S. CHANDRARATNA

(74) Attorney or Agent
DAVIES COLLISON CAVE , 1 Little Collins Street, MELBOURNE VIC 3000

(56) Prior Art Documents
AU 613608 13732/88 C07D 311/58
AU 62592/90 C07D 311/58
EP 290130

(57) Claim

1. A process of reacting compounds of the formula



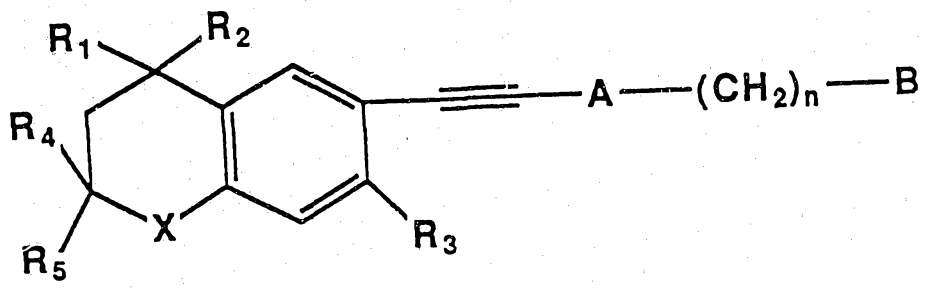
wherein R_1, R_2, R_3, R_4 and R_5 are hydrogen or lower alkyl groups having 1 to 6 carbons and wherein at least one of the R_4 and R_5 groups is not hydrogen and wherein R_1, R_2, R_3, R_4 and R_5 may be otherwise identical or different from one another; X is S , O or NR', wherein R' is hydrogen or lower alkyl; Z is hydrogen, or a metal ion, or a metal ion bound to an anion, said metal ion forming a salt with the ethynyl function of the compound of

.../2

the formula; with compounds of the formula

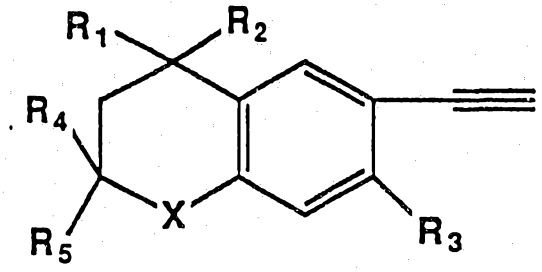
$$X' - A - (CH_2)_n - B$$

wherein X' is a leaving group, A is phenyl or heteroaryl selected from the group consisting of pyridinyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl and oxazolyl, n is an integer between 0 to 5, and B is H, -COOH is a pharmaceutically acceptable salt, ester or amide thereof, $-CH_2OH$ or an ether or ester derivative, or -CHO or an acetal derivative, or $-COR_i$ or a ketal derivative where R_i is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, in the presence of one or more catalysts, to provide compounds of the formula



wherein X, R_1, R_2, R_3, R_4, R_5, A, n and B are defined as above.

46. Compounds of the formula,



wherein

X is S, O or NR' where R' is H or lower alkyl and R_1, R_2, R_3, R_4 and R_5 are hydrogen or lower alkyl having 1 to 6 carbons and at least one of the R_4 and R_5 groups is not hydrogen or salts of the compounds of the formula defined herein.

638275

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

COMPLETE SPECIFICATION

NAME & ADDRESS
OF APPLICANT:

Allergan, Inc.
2525 Dupont Drive
Irvine California 92715-1599
United States of America

NAME(S) OF INVENTOR(S):

Roshantha A.S. CHANDRARATNA

ADDRESS FOR SERVICE:

DAVIES & COLLISON
Patent Attorneys
1 Little Collins Street, Melbourne, 3000.

COMPLETE SPECIFICATION FOR THE INVENTION ENTITLED:

Process and intermediates for preparing compounds having a disubstituted acetylene moiety and retinoic acid-like biological activity

The following statement is a full description of this invention, including the best method of performing it known to me/us:-

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention is directed to the preparation of compounds which have retinoic acid-like biological activity. More specifically, the present invention is directed to processes and intermediates which result in the synthesis of disubstituted acetylene compounds having retinoic acid-like activity.

2. Related Art

European Patent Application 176034A (published April 2, 1986) discloses tetrahydronaphtalene compounds having an ethynylbenzoic group. United States Patent No. 4,739,098 discloses compounds wherein three olefinic units from the acid-containing moiety of retinoic acid are replaced by an ethynylphenyl functionality. These compound have retinoic acid-like biological activity.

United States Patent No. 4,810,804 (issued on March 7, 1989) based on an application of the same inventor and assigned to the same assignee as the present application, discloses such disubstituted acetylene compounds wherein one of the substituents of the acetylene (ethyne) group is a substituted phenyl group, and the second substituent is a

substituted or unsubstituted chromanyl, thiochromanyl or tetrahydroquinolinyl group. The compounds disclosed and claimed in United States Patent No. 4,810,804 have retinoic acid-like biological activity.

Several co-pending applications of the present inventor, which applications are assigned to the assignee of the present application, are directed to further types of disubstituted acetylene compounds wherein one substituent of the acetylene (ethyne) moiety is a substituted phenyl or a substituted heteroaryl group, and the other substituent is a substituted or unsubstituted chromanyl, thiochromanyl or tetrahydroquinolinyl group. The disubstituted acetylene compounds described and claimed in the aforesaid co-pending applications have significant retinoic acid-like activity.

Retinoic acid-like activity has been generally recognized in the art to be associated with useful biological activity. Specifically, compounds having retinoic acid-like activity are useful as regulators of cell proliferation, and particularly as agents for treating dermatoses, such as acne, Darier's disease, psoriasis, icthyosis, eczema, atopic dermatitis and epithelial cancers, for treating arthritic diseases and other immunological disorders (e.g. lupus erythematosus) for promoting wound healing, for treating dry eye syndrome and for reversing the effects of sun damage to skin.

With respect to the synthetic processes of the present

invention which involve either the formation of an acetylenic (ethynyl) function in the compounds of the invention, or the coupling of the compounds of the invention which already have the ethynyl function, with a halogen substituted phenyl or heteroaryl group, the following articles comprise background information: **A General Synthesis of Terminal and Internal Arylalkynes by the Palladium-Catalyzed Reaction of Alkynylzinc Reagents with Aryl Halides** by Anthony O. King and Ei-ichi Negishi, J. Org. Chem. 43 1978 p 358; **Conversion of Methyl Ketones into Terminal Acetylenes and (E)-Trisubstituted Olefins of Terpenoid Origin** by Ei-ichi, Anthony O. King, and William L. Klima, J. Org. Chem. 45 1980 p.2526, and **A Convenient Synthesis of Ethynylarenes and Diethynylarenes** by S. Takahashi, Y. Kuroyama, K. Sonogashira, N. Hagihara, Synthesis 1980 p 627-630.

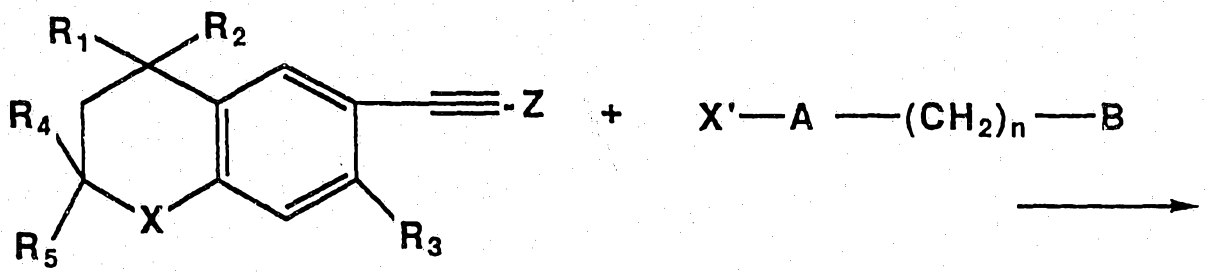
SUMMARY OF THE INVENTION

The present invention is directed to a novel process for making the biologically active and useful disubstituted acetylene compounds having as one of the substituents a substituted or unsubstituted chromanyl, thiochromanyl or tetrahydroquinolinyl group. In another aspect, the present invention covers intermediate compounds which are utilized in the process to make the aforementioned biologically active disubstituted acetylenes.

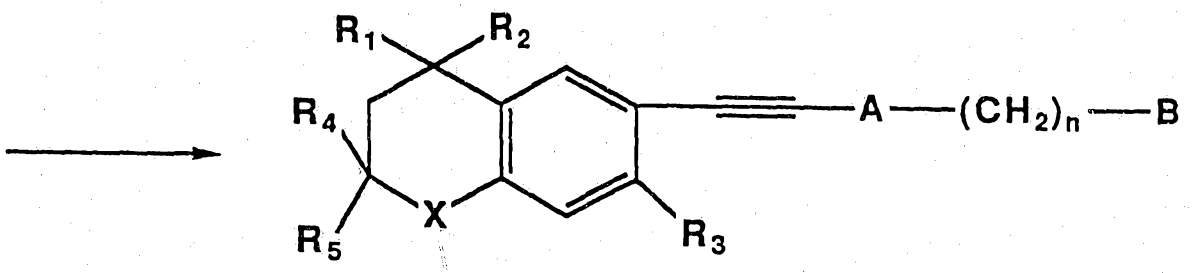
Specifically, in accordance with the present invention

the 6-thiochromanyl-ethyne, 6-chromanyl-ethyne and 6-tetrahydroquinolinyl-ethyne compounds of **Formula 1**, or their suitable metal salts are reacted with a suitable halogensubstituted phenyl or heteroaryl compound of **Formula 2** to provide the compounds of Formula 3. The compounds of Formula 3 either have useful retinoic acid-like activity or are readily converted by routine organic synthetic steps (such as esterification, deesterification, homologation, oxidation, reduction, amide formation or the like) to compounds having the retinoic acid-like activity. (**Formulae 1, 2 and 3** are incorporated in **Reaction Scheme 1**).

Reaction Scheme 1



Formula 1 **Formula 2**



Formula 3

In Formulae 1, 2, and 3, R_1, R_2, R_3, R_4 and R_5 are hydrogen or lower alkyl groups (of 1-6 carbons) and at least one of the R_4 and R_5 groups is not hydrogen where R_1, R_2, R_3, R_4 and R_5 may be otherwise identical or different from one another) X is S, O or NR′ where R′ is hydrogen or lower alkyl, Z represents hydrogen or a metal ion capable of forming a salt with the ethynyl moiety of the molecule, X′ is a leaving group such as a halogeno group, A is phenyl, or heteroaryl such as pyridianyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl or oxazolyl, n is an integer between 0 to 5, and B is H, -COOH or a pharmaceutically acceptable salt, ester or amide thereof, $-CH_2OH$ or an ether or ester derivative, or -CHO or an acetal derivative, or $-COR_i$ or a ketal derivative where R_i is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons.

In a preferred embodiment the reaction shown in Reaction Scheme 1, i.e. the coupling between the compounds of Formula 1 and the compounds of Formula 2, is conducted, in accordance with the invention in the presence of cuprous iodide and in the further presence of $Pd(PQ_3)_2Cl_2$ (Q is phenyl) or similar complex when Z is hydrogen, and in the presence of $Pd(PQ_3)_4$ (Q is phenyl) or similar complex when Z is a metal ion, such as $ZnCl^+$.

The compounds set forth in Formula 1, comprise another aspect of the present invention. These compounds are useful as intermediates for the synthesis of the biologically active and useful retinoic acid-like compounds of Formula 3.

AUSTRALIAN PATENT OFFICE

When the preferred compounds of **Formula 1** are reacted with compounds of **Formula 2**, then, in the resulting compounds of **Formula 3** the X, R_1, R_2, R_3, R_4 and R_5 substituents are defined as for **Compounds 1 through 9**.

The reaction conditions for the coupling of compounds of **Formula 1** with the compounds of **Formula 2**, in accordance with the present invention, as well as the processes for synthesizing the compounds of **Formula 1**, are explained in the ensuing description of Specific Embodoments and examples.

General Embodiments

Definitions

The term "ester" as used here refers to and covers any compound falling within the definition of that term as classically used in organic chemistry. Where B (of **Formulae 1 and 2**) is -COOH, this term covers the products derived from treatment of this function with alcohols. Where the ester is derived from compounds where B is $-CH_2OH$, this term covers compounds of the formula $-CH_2OOCR$ where R is any substituted or unsubstituted aliphatic, aromatic or aliphatic-aromatic group.

Preferred esters are derived from the saturated aliphatic alcohols or acids of ten or fewer carbons atoms or the cyclic or saturated aliphatic cyclic alcohols and acids of 5 to 10 carbon atoms. Particularly preferred aliphatic esters are those derived from lower alkyl acids or alcohols. Here, and

where ever else used, lower alkyl means having 1-6 carbon atoms. Also preferred are the phenyl or lower alkylphenyl esters.

Amide has the meaning classically accorded that term in organic chemistry In this instance it includes the unsubstituted amides and all aliphatic and aromatic mono- and di-substituted amides. Preferred amides are the mono- and di-substituted amides derived from the saturated aliphatic radicals of ten or fewer carbon atoms or the cyclic or saturated aliphatic-cyclic radicals of 5 to 10 carbon atoms. Particularly preferred amides are those derived from lower alkyl amines. Also preferred are mono- and di-substituted amides derived from the phenyl or lower alkylphenyl amines. Unsubstituted amides are also preferred.

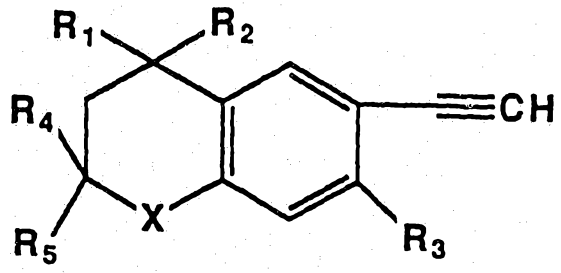
Acetals and ketals include the radicals of the formula -CK where K is $(-OR)_2$. Here, R is lower alkyl. Also, K may be $-OR_1O-$ where R_1 is lower alkyl of 2-5 carbon atoms, straight chain or branched.

A pharmaceutically acceptable salt may be prepared for any compound made in accordance with this invention, provided the compound has a functionality capable of forming such salt, for example an acid or an amine functionality. A pharmaceutically acceptable salt may be any salt which retains the activity of the parent compound and does not impart any deleterious or untoward effect on the subject to which it is

administered and in the context in which it is administered.

Such a salt may be derived from any organic or inorganic acid or base. The salt may be a mono or polyvalent ion. Of particular interest where the acid function is concerned are the inorganic ions, sodium, potassium, calcium, and magnesium. Organic amine salts may be made with amines, particularly ammonium salts such as mono-, di- and trialkyl amines or ethanol amines. Salts may also be formed with caffeine, tromethamine and similar molecules. Where there is a nitrogen sufficiently basic as to be capable of forming acid addition salts, such may be formed with any inorganic or organic acids or alkylating agent such as methyl iodide. Preferred salts are those formed with inorganic acids such as hydrochloric acid, sulfuric acid or phosphoric acid. Any of a number of simple organic acids such as mono-, di- or tri-acid may also be used.

The compounds which are preferably utilized in the synthetic process of the present invention to introduce the substituted chromanyl, substituted thiochromanyl, and substituted tetrahydroquinolinyl moiety as one of the substituents of the ethyne portion of the biologically active compounds, and which therefore are the preferred intermediates in accordance with the invention, are shown in Formula 4.



Formula 4

These preferred compounds and intermediates are:

Compound 1 X=S; $R_1=R_2=CH_3$ $R_3=R_4=R_5=H$

Compound 2 X=S; $R_1=R_2=R_3=CH_3$ $R_4=R_5=H$

Compound 3 X=S $R_1=R_2=R_4=R_5=CH_3$ $R_3=H$

Compound 4 X=O $R_1=R_2=CH_3$ $R_3=R_4=R_5=H$

Compound 5 X=O $R_1=R_2=R_4=R_5=CH_3$ $R_3=H$

Compound 6 X=NH $R_1=R_2=CH_3$ $R_3=R_4=R_5=H$

Compound 7 X=NH $R_1=R_2=R_4=R_5=CH_3$ $R_3=H$

Compound 8 X=S $R_1=R_2=R_3=R_4=R_5=CH_3$

Compound 9 X=O $R_1=R_2=R_3=R_4=R_5-CH_3$

4,4-dimethyl-6-ethynylthiochroman (**Compound 1**)

4,4,7-trimethyl-6-ethynylthiochroman (**Compound 2**)

2,2,4,4-tetramethyl-6-ethynylthiochroman (**Compound 3**)

4,4-dimethyl-6-ethynylchroman (**Compound 4**)

2,2,4,4-tetramethyl-6-ethynylchroman (**Compound 5**)

4,4-dimethyl-6-ethynyl-1,2,3,4-tetrahydroquinoline (**Compound 6**)

2,2,4,4-tetramethyl-6-ethynyl-1,2,3,4-tetrahydroquinoline (**Compound 7**)

2,2,4,4,7-pentamethyl-6-ethynylthiochroman (**Compound 8**)

2,2,4,4,7-pentamethyl-6-ethynylchroman (**Compound 9**)

The metal (preferably zinc) salts of the preferred compounds are also preferred as intermediates in the process of the invention.

Generally speaking the compounds of **Formula 1**, or their metal (such as zinc) salts preferably the compounds of **Formula 4** (or their salts), are reacted with the compounds of **Formula 2** to provide the compounds of **Formula 3**.

When the preferred compounds of **Formula 4** are reacted with compounds of **Formula 2**, then, in the resulting compounds of **Formula 3** the X, R_1, R_2, R_3, R_4 and R_5 substituents are defined as for **Compounds 1 through 9**.

The reaction conditions for the coupling of compounds of **Formula 1** with the compounds of **Formula 2**, in accordance with the present invention as well as the processes for synthesizing the compounds of **Formula 1**, are explained in the ensuing description of Specific Embodiments and Examples.

With respect to biological activity of the compounds of **Formula 3** made in accordance with the process of the present invention (utilizing the intermediates of the invention in the process) the following is noted.

The retionic acid like activity of these compounds was confirmed through the classic measure of retionic acid activity involving the effects of retionic acid on ornithine

decarboxylase. The original work on the correlation between retionic acid and decrease in cell proliferation was done by Verma & Boutwell, Cancer Research, 1977, 37, 2196-2201. That reference discloses that ornithine decarboxylase (ODC) activity increased precedent to polyamine biosynthesis. It has been established elsewhere that increases in polyamine synthesis can be correlated or associated with cellular proliferation. Thus, if ODC activity could be inhibited, cell hyperproliferation could be modulated. Although all causes for ODC activity increase are unknown, it is known that 12-O-tetradecanoylphorbol-13-acetate (TPA) induces ODC activity. Retionic acid inhibits this induction of ODC activity by TPA. The compounds of this invention also inhibit TPA induction of ODC as demonstrated by an assay essentially following the procedure set out in Cancer Res., 35, 1662-1670, 1975.

By way of example of retionic acid-like activity it is noted that in the assay conducted essentially in accordance with the method of Verman & Boutwell, ibid, the following examples of compounds made in accordance with the process of the present invention (**Compounds 10, 11 and 12**) attained an 80% inhibition of TPA induced ODC activity at the following concentrations (IC_{80}):

Compound	IC_{80} conc (mmols)
10	0.69
11	0.13

Compounds 10, 11 and 12 are characterized with reference to **Formula 3** as follows:

Compound 10 X=S $R_1=R_2=R_4=R_5=CH_3$ $R_3=H$, $A-(CH_2)_n-B$=ethyl 6-nicotinate

Compound 11 X=O $R_1=R_2=R_4=R_5=CH_3$ $R_3=H$ $A-(CH_2)_n-B$=ethyl 6-nicotinate.

Compound 12 X=O $R_1=R_2=R_3=R_4=R_5=CH_3$ $A-(CH_2)_n-B$=ethyl 6-nicotinate.

In view of their retinoic acid-like activity the compounds of **Formula 3** may be administered systematically or topically for treatment of a variety of conditions, as is indicated in the introductory section of the present application for patent. For a detailed description of the modes of administration, of various pharmaceutical formulations and dosages in the treatment of mammals (including humans) with the compounds of **Formula 3**, reference is made to United States Patent No, 4,810,804, the specification of which is incorporated herein by reference.

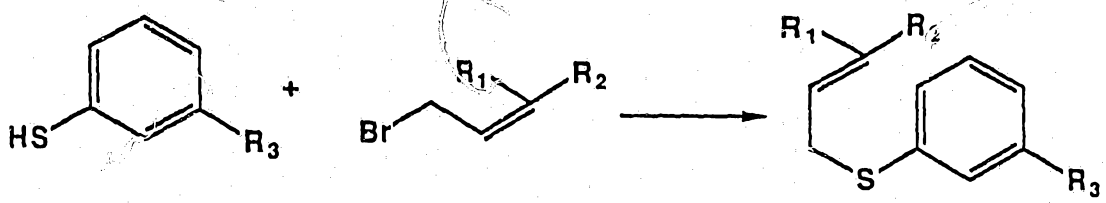
Specific Embodiments

The compounds of the invention which are defined in **Formula 1**, and which serve as key intermediates in the process steps of the invention to make the compounds of **Formula 3**, can be made by a number of different synthetic chemical pathways. To illustrate this invention, there is here outlined a series

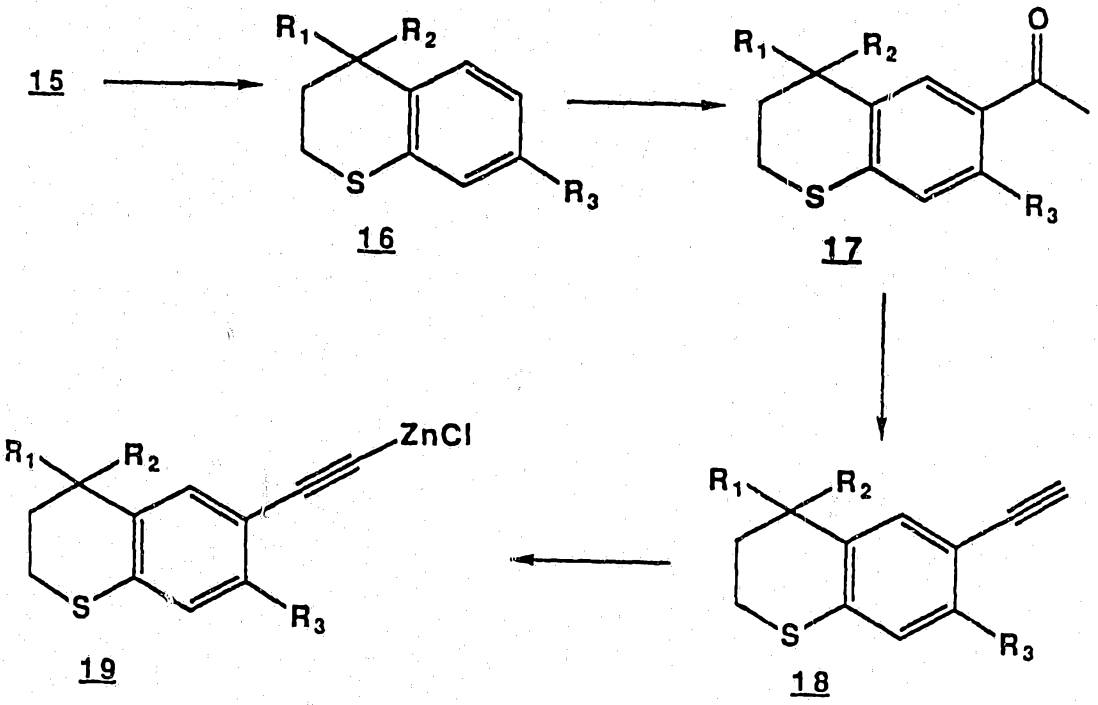
of steps which have been proven to provide the compounds of **Formulae 1 and 3** when such synthesis is followed in fact and in spirit. The synthetic chemist will readily appreciate that the conditions set out here are specific embodiments which can be generalized to any and all of the compounds represented by **Formulae 1 and 3.** Furthermore, the synthetic chemist will readily appreciate that the herein described synthetic steps may be varied and or adjusted by those skilled in the art without departing from the scope and spirit of the invention. Moreover, it should be understood that some of the steps and processes utilized in the hereinbelow given examples of the compounds of **Formula 1,** are novel and innovative on their own right. Such novel steps are described here in sufficient detail to enable the ordinary artisan to duplicate such steps.

With reference to the compounds of **Formula 1, Reaction Scheme 2** illustrates an example of their synthesis when X=S and R_4 and R_5 are both hydrogen.

Reaction Scheme 2



13 14 15



Thus, with reference to **Reaction Scheme 2**, a thiophenol 13 which may be substituted with the R_3 substituent (defined above as hydrogen or lower alkyl) in the 3 position is alkylated, preferably under strongly strongly basic conditions such as NaOH in a polar solvent (acetone, room temp.) with the Compound 14, which is either 1-bromo-3-methyl-2-butene (R_1 and R_2 are methyl, available from Aldrich) or a derivative thereof where either R_1 and R_2 or both are lower alkyl other than methyl. The resulting alkylated thiophenol (sulfide, Compound 15) is thereafter ring closed under Fridel Crafts or like

conditions, typically by refluxing in a inert solvent such as benzene or toluene, in the presence of phosphorous pentoxide and phosphoric acid. The resulting thiochroman **16**, made in accordance with **Reaction Scheme 2**, has no substituents in the 2 position, and preferably in accordance with this reaction scheme R_1 and R_2 are methyl and R_3 is hydrogen.

Compound 16 is acetylated under Fridel Crafts conditions, or the like, preferably with acetyl chloride ($AlCl_3$, CH_2Cl_2, reflux) to provide the 6-acetyl-thiochroman **17**. The acetyl function of **Compound 17** is converted into an acetylenic (ethynyl) function by means of lithium diisopropylamide, or a similar base, at reduced temperature. An intermediate derived from **Compound 17** (presumably a lithium salt of the corresponding enol, not shown on **Reaction Scheme 2**) is esterified by treatment with diethychlorophosphate (or the like) and is again reacted at reduced temperature (e.g. - 78 degrees C) with lithium diisopropylamide, to form the triple bond (presumably by an elimination reaction) and to yield the 6-ethynylthiochroman derivative (**Compound 18**).

It is noted at this point that the present invention is not intended to be limited or bound by the above-mentioned and other theories of reaction mechanisms. Brief description of theory of reaction mechanisms (where applicable) are given to further enable and facilitate the work of a skilled artisan in the field to modify and adjust the synthetic conditions to fit

particular specific intermediates and to make the several compounds of the invention, without departing from the scope and spirit of the invention.

The 6-ethynyl-thiochroman **18** is either utilized directly in the coupling reaction indicated in **Reaction Scheme 1**, or is converted to a metal (zinc) salt (**Compound 19**) before the coupling step.

Generally speaking the zinc chloride salts (**Compounds 19**) are prepared under conditions which exclude water and oxygen. A dry, ether-type solvent such as dialkyl ether or a cyclic ether such as a furan or pyran, particularly a tetrahydrofuran, may be used as the solvent. A solution of **Compound 18** is first prepared under an inert atmosphere (argon or nitrogen) and then a strong base such as n-butyl lithium is added (in about a 10% molar excess). This reaction is begun at a reduced temperature of between -10 degrees and +10 degrees C, preferably about 0 degrees C. The reaction mixture is stirred for a short period, between 30 minutes and 2 hours, and then treated with about a 10% molar excess of fused zinc chloride dissolved in the reaction solvent. This mixture is stirred for an additional 1-3 hours at about the starting temperature, then the temperature is increased to about ambient temperature for 10-40 minutes.

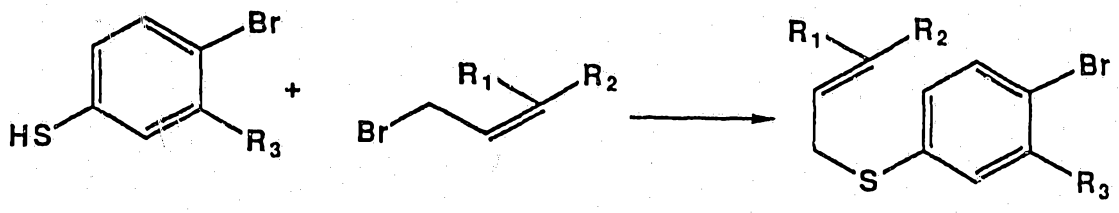
The foregoing general description for the preparation of the ZnCl salts symbolized by **Compound 19**, are also applicable,

with such modifications which will be readily apparent to the skilled artisan in the field, to the preparation of all Zncl salts corresponding to **Formula 1**.

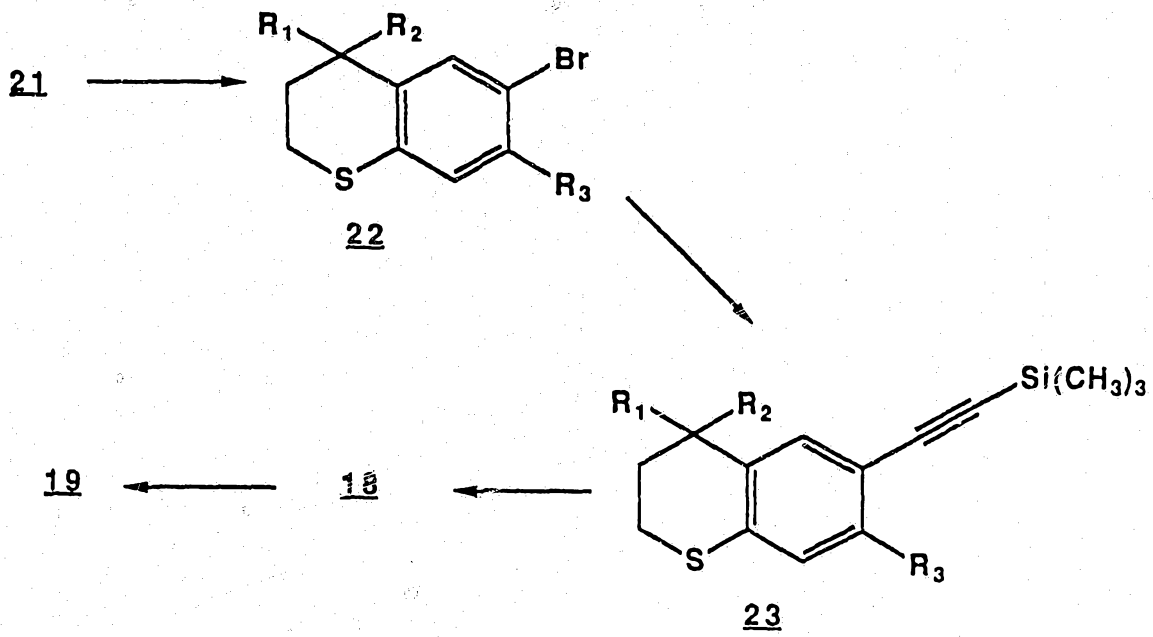
Reaction Scheme 3 shows another method for preparing the compounds of **Formula 1** when X=S and R_4 and R_5 are hydrogen. The synthetic sequence shown in **Reaction Scheme 3** is preferably (but not exclusively) used when R_3 is not hydrogen. In contrast the reactions shown in **Reaction Scheme 2** are preferably (but not exclusively) used when R_3 is hydrogen.

Thus, with reference to **Reaction Scheme 3** the 4-bromothiophenol (**Compound 20**) (which is preferably alkyl substituted in the 3-position) is alkylated with **Compound 14**. The resulting 4-bromo phenyl sulfides **21** are ring closed under conditions analogous to the ring closure of **Compounds 15** described in connection with **Reaction Scheme 2**.

Reaction Scheme 3



20 21



To introduce the acetylene (ethyne) portion into the molecule, the substituted 6-bromothiochroman **22** is reacted with trimethylsilylacetylene in the presence of cuprous iodide and a suitable catalyst, typically having the formula $Pd(PQ_3)_2Cl_2$ (Q is phenyl). The reaction is typically conducted in the presence of bis(triphenylphosphine) palladium (II) chloride catalyst, an acid acceptor, (such as triethylamine) under an inert gas (argon) atmosphere, by heating in a sealed tube. The resulting 6-trimethylsilylethynylthiochroman, is shown as **Compound 23** in **Reaction Scheme 3**.

As is further shown on **Reaction Scheme 3**, the trimethylsilyl moiety is removed from the 6-

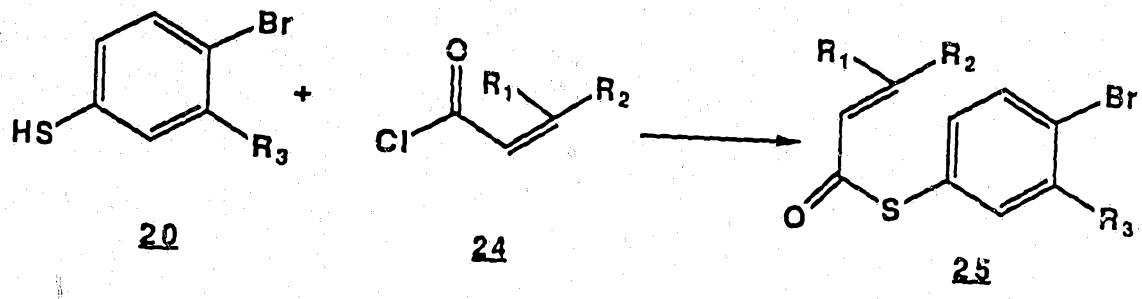
trimethylsilylethynyl-thiochroman **23** in the next synthetic step, to provide the ring substituted 6-ethynyl-thiochroman derivative (**Compound 18**). The latter reaction is conducted under basic conditions, preferably under an inert gas atmosphere.

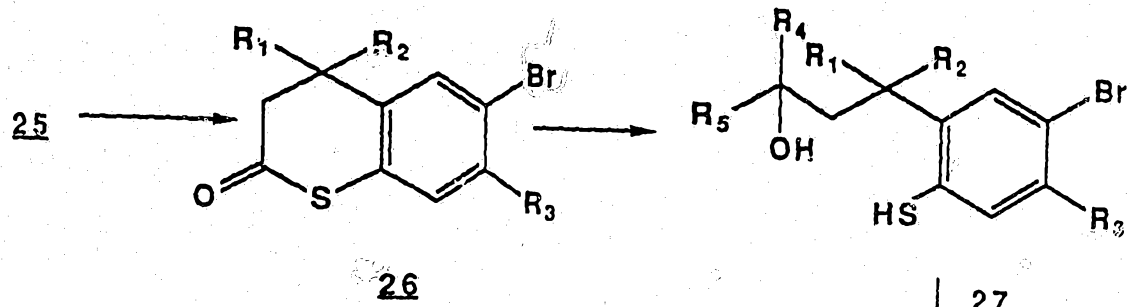
The 6-ethynyl-thiochroman **18** can be utilized directly in the coupling reaction set forth in **Reaction Scheme 1**, or prior to coupling can be converted to the corresponding ZnCl salt, as is described above.

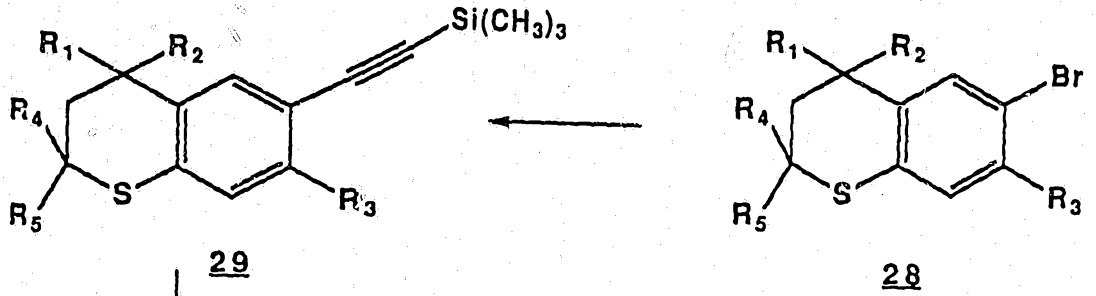
Reaction Scheme 4 shows preparation of the compounds corresponding to **Formula 1** where X=S and at least one of the R_4 and R_5 groups is lower alkyl, preferably where R_4 and R_5 are both lower alkyl, and still more preferably where R_4 and R_5 are identical with one another.

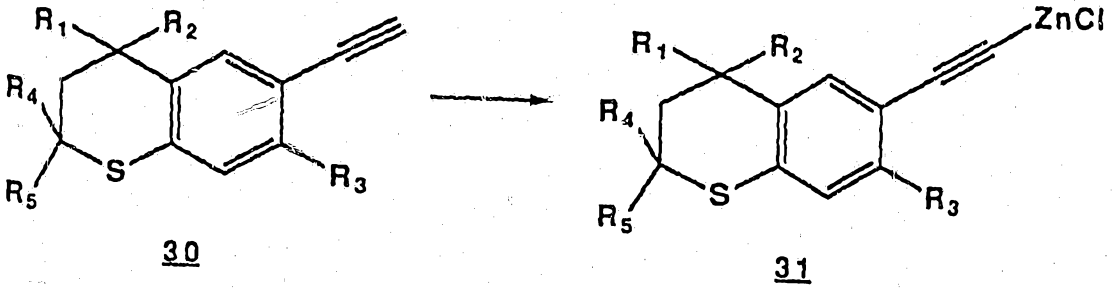
Thus, with specific reference to **Reaction Scheme 4**, the 2 substituted (preferably 2,2 di-substituted) 6-ethynyl thio-chromans can be prepared as follows. The 4-bromo-thio-phenol (**Compound 20**) is acylated with an acylating agent such as an acid chloride (**Compound 24**) derived from an appropriately substituted acrylic acid. The acylation is conducted in an inert solvent (such as tetrahydrofuran) in the presence of strong base (for example sodium hydride). The resulting thioester (**Compound 25**)

Reaction Scheme 4


Br
HS
R3
20
+
O
R1
R2
Cl
24
R1
R2
Br
O
S
R3
25


25
R1
R2
Br
O
S
R3
26
R4
R1
R2
Br
R5
OH
HS
R3
27


Si(CH3)3
R1
R2
R4
R5
S
R3
29
R1
R2
Br
R4
R5
S
R3
28


R1
R2
R4
R5
S
R3
30
ZnCl
R1
R2
R4
R5
S
R3
31

which contains the olefinic bond of the acrylic acid moiety is ring closed in the presence of a Friedel Crafts type catalyst (such as aluminum chloride) by stirring in a suitable solvent such as methylene chloride. The resulting 2-oxo-6-bromo-thiochromane (**Compound 26**) is usually isolated in crystalline form.

The R_4 and/or R_5 substituents (both of which cannot be hydrogen when the steps of **Reaction Scheme 4** are used) and which preferably are identical with one another (for example both are methyl) are introduced by treating the 2-oxo-6-bromo-thiochromane (**Compound 26**) with a Grignard reagent, bearing the alkyl substituents R_4 and R_5 (such as methylmagnesium bromide when R_4 and R_5 are methyl). It will be readily understood by those skilled in the art that depending on the relative molecular ratios of the Grignard reagent and of the oxo-thiochroman compound (**Compound 26**), and also depending on the reaction conditions, the primary products of the reaction may be derivatives where either one or two alkyl groups have been introduced through the Grignard reaction. When the Grignard reagent (such as methylmagnesium bromide) is in excess, the thiochromane ring is opened and the tertiary alcohol derivative of the 4-bromo thiophenol (**Compound 27**) is formed.

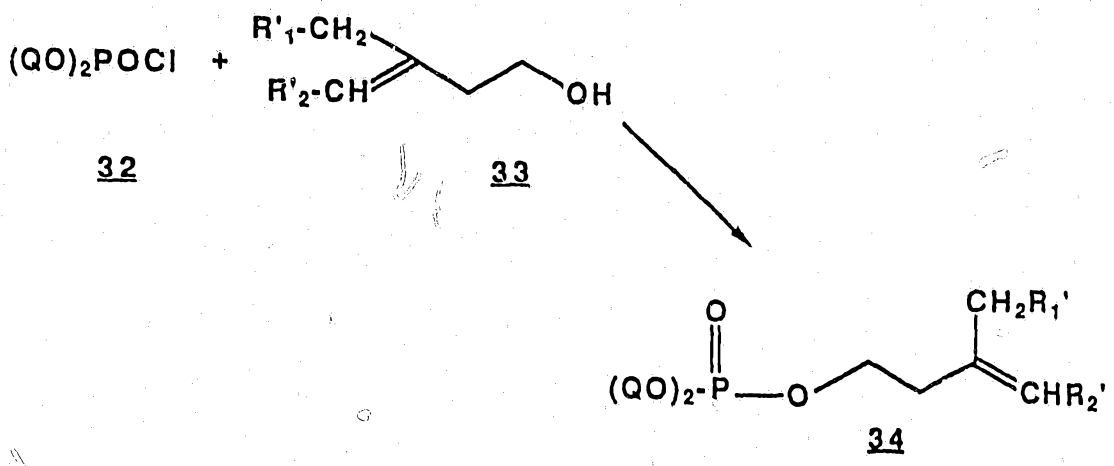
Ring closure of the thiophenol derivative (**Compound 27**) which has the desired R_1, R_2, R_3, R_4 and R_5 substituents, is affected by heating in acidic conditions, preferably by

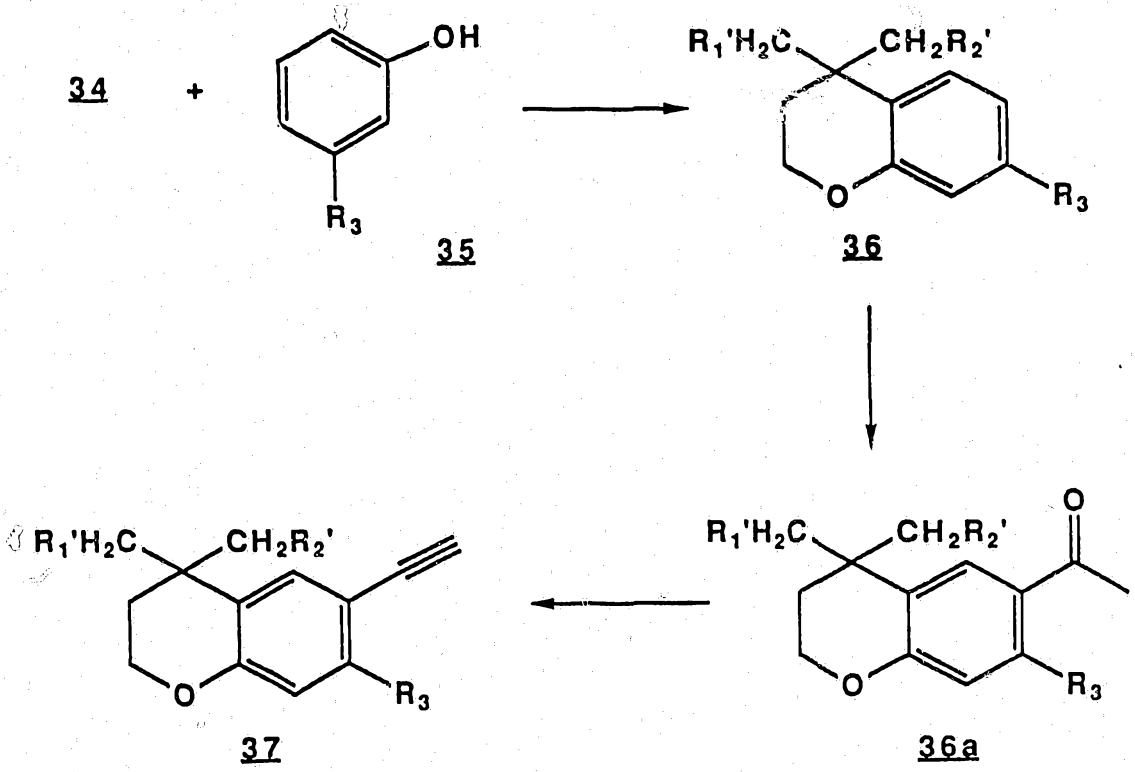
heating **Compound 27** in aqueous acid. The resulting 6-bromothiochroman which bears the desired alkyl (or hydrogen) substituents, R_1, R_2, R_3, R_4 and R_5, is shown as **Compound 28** in **Reaction Scheme 4**

The 6-bromothiochromans **28** (which differs from the 6-bromothiochromans **22** only in that in **Compound 28** the 2 position of the thiochroman ring is substituted) is converted to the 6-(2-trimethylsilyl)-ethynyl derivative **29**, and thereafter into the 6-ethynyl derivative **30**, (and further if desired into the ZnCl salts **31**) in reaction steps which are analogous to the corresponding steps described in connection with **Reaction Scheme 3.**

Turning now to compounds of **Formula 1** where X=O and where R_4 and R_5 are H, (that is turning to chromans substituted in the 4, and possibly in the 7 position) the compounds can be made as indicated in **Reaction Scheme 5.**

Reaction Scheme 5





In **Reaction Scheme 5** Q is phenyl and R_1' and R_2" are hydrogen or lower alkyl having 1 to 5 carbons, and R_3 is defined as above in connection with **Formula 1.** The reaction sequence is hereinafter further described for the preferred case where R_1' and R_2" and R_3 are all hydrogen, i.e. for the synthesis of 4,4-dimethyl-6-ethynylchroman (**Compound 4**).

With reference to **Reaction Scheme 5**, the phosphate (**Compound 34**) is prepared from the corresponding diphenyl chlorophosphate **32** and 3-methyl-3-butene-1-ol (**Compound 33**, R_1' and R_2" are both H) available from Aldrich, or prepared by

means known in the art. It is preferred to prepare Compound 34 by dissolving the alcohol 33 in about a 10% excess of pyridine or the like under an inert atmosphere cooled to approximately -10 degrees to 10 degrees C. This solution is then added drop-wise, under an inert atmosphere, to a solution of diphenyl chlorophosphate 32, in about an equal amount of the reaction solvent. About a 2-5% molar excess of diphenyl chlorophosphate 22 relative to the alcohol 33 is employed. The atmosphere may be argon, nitrogen, or another inert gas. The mixture is heated at reflux for between 1 and 5 hours, preferably about 3, to effect the reaction. The product is then recovered by conventional means. The diphenyl phosphate ester (Compound 34) is then reacted with a phenol 35 to effect formation of chroman (Compound 36). For example, phenol 35 (or R_3 substituted phenol) is added to a flask already containing stannic chloride under argon which has been cooled to between -10 degrees to 10 degrees C. After thorough mixing of this combination for about 15 minutes to an hour at the reduced temperature, the phosphate 34 is added at the reduced temperature. Both of these steps are carried out under an inert atmosphere such as argon or nitrogen. When the addition of the phosphate 34 is completed, the mixture is stirred at about ambient temperature for up to 24 hours. Then the reaction is quenched with a dilute solution of aqueous alkali metal base or the like. The product is recovered by extrac-

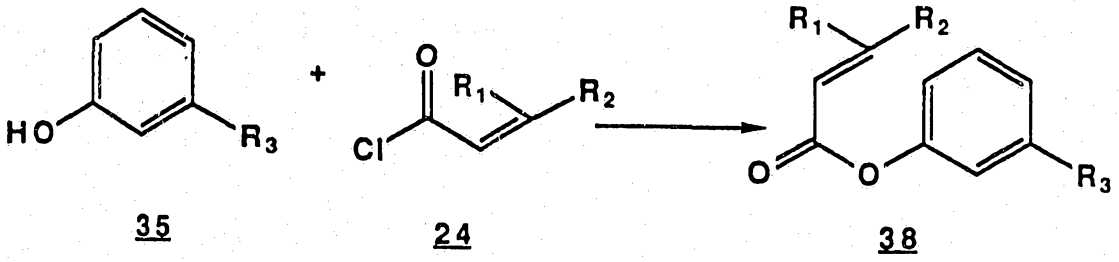
tion and other conventional means.

The acetylenic (ethynyl) function is introduced into the 4,4-disubstituted (and optionaly 7-substituted) chroman **Compound 36** in a sequence of reaction steps which are described in **Reaction Scheme 2** in connection with the analogous thiochroman compounds. Thus, a 6-acetylated chromane (**Compound 36a**) is first obtained, by acetylation with acetyl chloride, and thereafter the acetyl group is converted to the ethynyl group through treatment with lithium diisopropylamide, dialkyl chlorophosphate and another treatment with lithium diisopropylamide.

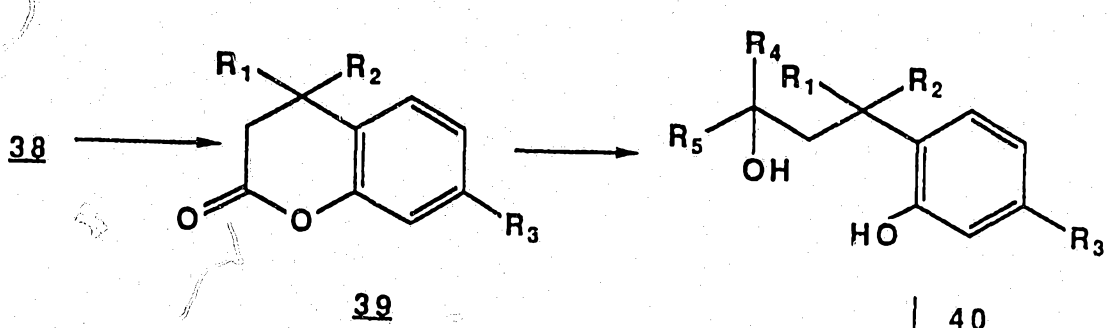
Compound 4 (or its analogs where R_3 is lower alkyl and/or where the 2,2 substituents have 2-6 carbons) can also be converted to the corresponding ZnCl salt (not shown in **Reaction Scheme 5**) prior to a coupling reaction with compounds of **Formula 2**.

Reaction Scheme 6 discloses, in general terms, the preparation of compounds of **Formula 1** where X=O and R_4 and R_5 both are not hydrogen. In other words **Reaction Scheme 6** discloses the preparation of 2 substituted, and preferably of 2,2-disubstituted 6-ethynyl chromanes.

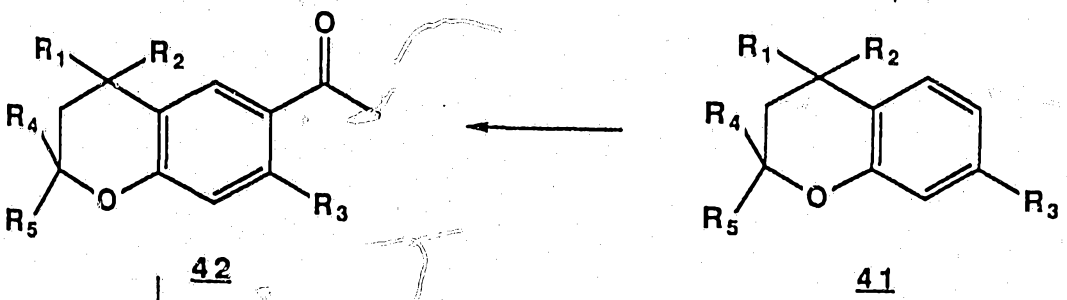
Reaction Scheme 6



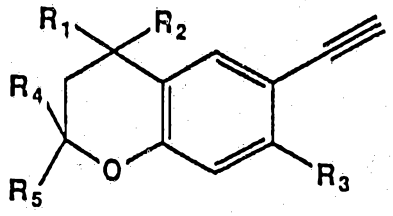
35 24 38



39 40



42 41



43

Thus, in accordance with **Reaction Scheme 6**, phenol, or a phenol substituted in the 3 (meta) position by an alkyl substituent (R_3) (**Compound 35**) is acylated with an acylating agent, such as the acid chloride (**Compound 24**) derived from an appropriately substituted acrylic acid. In **Reaction Scheme 6**, just as in **Reaction Scheme 4**, the R_1 and R_2 substituents of the target compounds are introduced through this acrylic acid derivative **24**. The acylation with the acid chloride **24** is preferably conducted in the presence of a strong base (e.g. sodium hydride) in an inert solvent (such as tetrahydrofuran). The resulting substituted phenyl-acrylate is shown in **Reaction Scheme 6** as **Compound 38**.

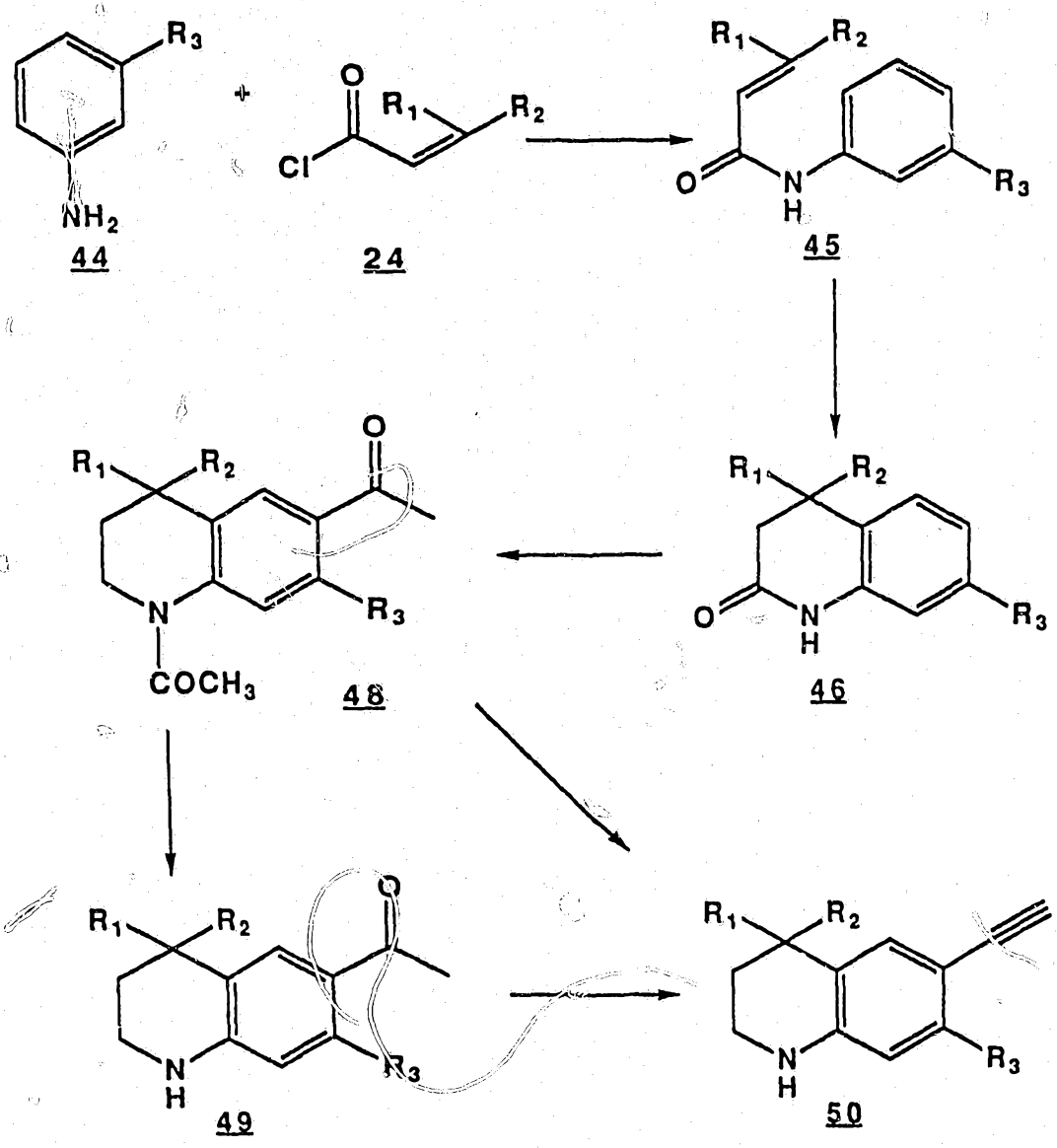
The substituted phenyl-acrylate **38** is ring closed under Friedel Crafts type reaction conditions ($AlCl_3$ catalyst, in an inert solvent, such as methylene chloride) to provide the 2-oxo-chroman compound (**Compound 39**) which bears, in the 4-position, the R_1 and R_2 substituents and in the 6-position the R_3 substituent (as applicable). Just like the analogous 2-oxo-thiochroman **26** in **Reaction Scheme 4**, the 2-oxo-chroman **39** of **Reaction Scheme 6** is treated with a Grignard reagent to introduce the R_4 and R_5 substituents. As it was noted out above, in this Reaction Scheme R_4 and R_5 both cannot be hydrogen, and in the preferred embodiments R_4 and R_5 are identical, for example both are methyl or ethyl. When R_4 and R_5 are methyl, the Grignard reagent is preferably

methylmagnesium chloride (dissolved in tetrahydrofuran, THF). A solution of **Compound 39** in a suitable solvent, for example in dry diethylether is added to this Grignard reagent. The resulting phenol containing a tertiary alcohol side chain, (that is a molecule in which the chroman ring had been opened) is shown in **Reaction Scheme 6** as **Compound 40**.

Compound 40 which already has the desired R_1, R_2, R_3, R_4 and R_5 substituents, is ring closed under acidic conditions, (e.g. by heating in aqueous sulfuric acid) to provide the chroman derivative (**Compound 41**). It should be noted that up to this point in the synthetic sequence similar or analogous steps are involved for making both the 2,2-disubstituted thiochroman (**Reaction Scheme 4**) and the 2,2-disubstituted chroman derivatives (**Reaction Scheme 6**), the only difference being that in **Reaction Scheme 6** the starting phenol derivative does not have a halogen (such as a bromo) substituent.

As is further disclosed in **Reaction Scheme 6**, the ethynyl group is introduced into the 2-substituted (preferably 2,2-disubstituted) chroman in a sequence of steps which is analogous to the steps described in **Reaction Scheme 2** for introducing the ethynyl function into 4-substituted thiochromans. 6-Ethynylchroman **43** can also be utilized directly in the coupling reaction with compounds of **Formula 2**, or can be converted to a suitable metal, preferably ZnCl, salt, in the manner described above.

Compounds of **Formula 1** where X is NR' (R' is H or lower alkyl) and R_4 and 5_5 are both hydrogen can be made in accordance with **Reaction Scheme 7**. The reaction sequence of **Scheme 7** is hereinafter described with primary emphasis to a preferred embodiment where R' is hydrogen, R_1 and R_2 (of **Formula 1**) are both methyl, and R_3 is hydrogen. **Thus**, with reference to **Reaction Scheme 7**, the tetrahydroquinoline



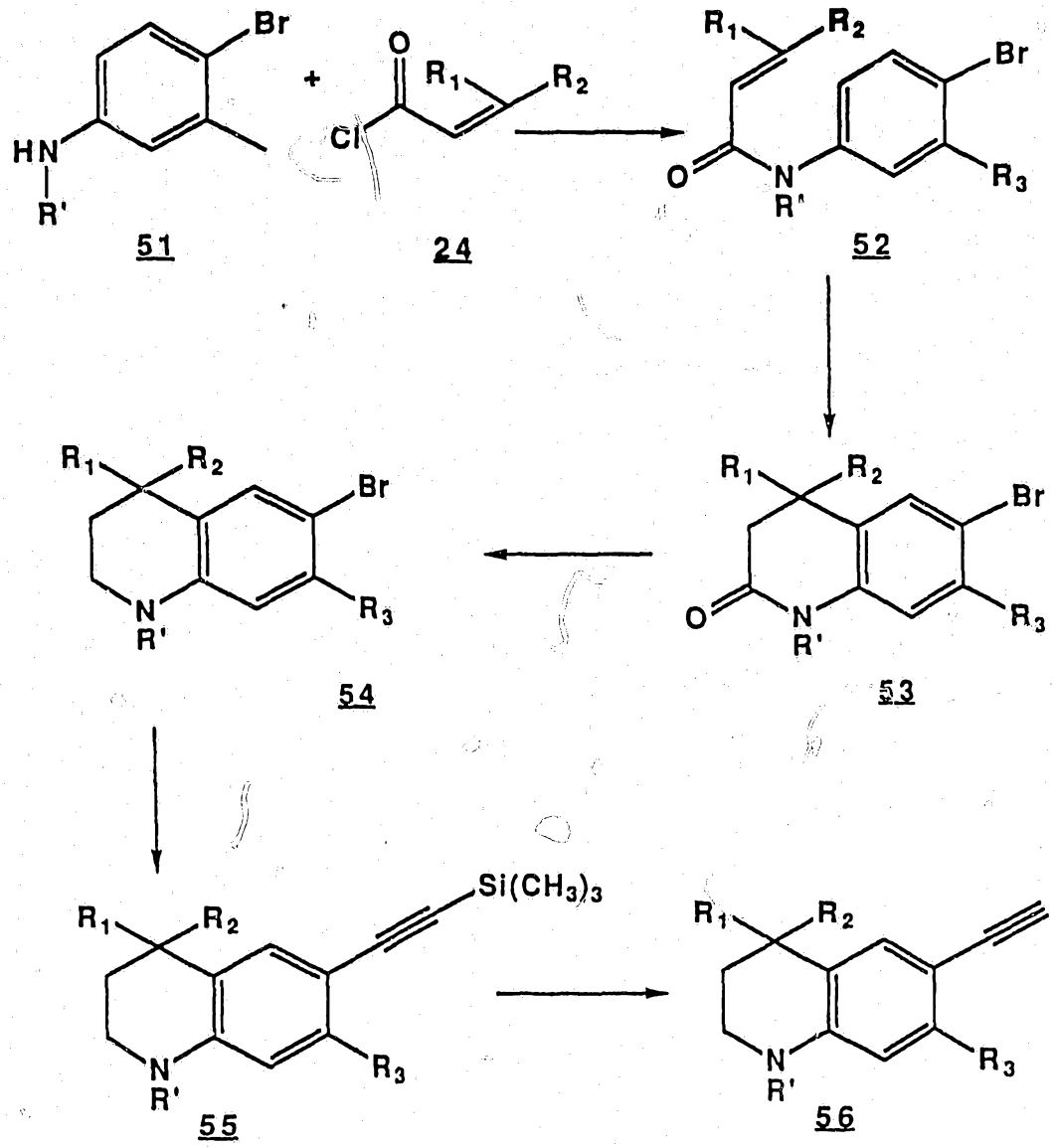
Reaction Scheme 7

moiety, that is where X is nitrogen, is made in part by the method described in European patent application No. 0130795 published September 1, 1985. First, **Compound 24**, 3-methylcrotonoyl chloride (when R_1 and R_2 are both methyl) is reacted with aniline **44** to obtain the amide **45** . This amide **45** is then cyclized using aluminum chloride in the absence of solvent to give **Compound 46**. Lithium aluminum hydride or another acceptable reducing agent of similar type is then used to reduce the 2-oxo-1,2,3,4-tetrahydroquinoline **46**, preferably in inert solvent such as diethyl ether. The resulting amine **47** is then acetylated using acetyl chloride in a polar solvent such as pyridine followed by acetylation in the presence of aluminum chloride to give **Compound 48**. **Compound 48** is then subjected to base hydrolysis to give the secondary amine **49**.

The 6-acetyl group of **Compound 49** is thereafter converted into an ethynyl group in the manner described above for analogous transformation of 6-acetyl chromans or 6-acetyl thiochromans. The 6-ethynyl 1,2,3,4-tetrahydroquinoline (**Compound 50**) may be coupled directly or as the corresponding ZnCl salts, with compounds of **Formula 2**.

Alternatively compounds of **Formula 1** where X= is NR', R_4 and R_5 are H, can also be prepared by the synthetic sequence outlined in **Reaction Scheme 8** (R_1 and R_2 preferably are methyl). **Reaction Scheme 8** will be self-explanatory to those

skilled in the art in light of the analogous reactions disclosed in the present specification (R_3 is defined as above for **Formula 1**).



Reaction Scheme 8

The compounds of **Formula 2** are coupled in accordance with the present invention with the compounds of **Formula 1** to provide the biologically active compounds of **Formula 3**. The compounds of **Formula 2** per se, are not new, and can be made in accordance with well known procedures, or by such adaptation of well known procedures which are within the skill of the practicing synthetic organic chemist.

In accordance with one preferred embodiment of the invention, group A of **Formula 2** is a phenyl group, X' is halogen, preferably bromine or iodine. Ethyl-4-iodobenzoate is one preferred example of a reagent in accordance with **Formula 2**, used in coupling with the compounds of **Formula 1**. Other examples, where A is phenyl, are: ethyl 4-iodophenylacetate, ethyl 4-iodo-phenylpropinoate, ethyl 4-iodo-phenylbutanoate, ethyl 4-iodo-phenylpentanoate. Reagents in accordance with **Formula 2** where the X' and $(CH_2)_n$-B substituents respectively are in meta or ortho position on the phenyl ring, can also be used in the process of the invention. Moreover, the group characterized as B in **Formula 2** may be a suitably protected or unprotected alcohol, aldehyde, ketone, amide, or such other functionality as is set forth in the definition of the group B of **Formula 2**. The preparation of such compounds in accordance with **Formula 2**, suitable for coupling with compounds of **Formula 1**, will be within the skill of the practicing organic chemist in light of the present disclosure.

When group **A** of **Formula 2** is heteroaryl then examples of preferred reagents are: ethyl 6-chloronicotinate,

ethyl 2-(2-chloropyrid-5-yl)acetate;

ethyl 5-(2-chloropyrid-5-yl)pentanoate;

ethyl 2-(2-iodofur-5-yl)acetate;

ethyl 5-(2-iodofur-5-yl)pentanoate;

ethyl 2-(2-iodothien-5-yl)acetate;

ethyl 5-(2-iodothien-5-yl)pentanoate;

ethyl 2-(3-chloropyridazin-6-yl) acetate;

ethyl 5-(3-chloropyridazin-6-yl)pentanoate; and the corresponding chloro, or other halo, substituted pyrimidinyl or pyrazinyl analogues of such esters. In this series also, the B grouping of the compound of **Formula 2** can be protected or unprotected alcohol, aldehyde, ketone, amide or other group, set forth in connection with **Formula 2**.

It is also within the scope of the present invention to couple compounds of **Formula 1** with compounds of **Formula 2**, and thereafter subject the resulting molecule (particularly that portion thereof which is derived from the reagent of **Formula 2**) to such routine synthetic transformations as a blocking and deblocking, homologation, reduction or oxidation, ester formation, saponification, and the like, which results in the formation of further analogs within the scope of **Formula 3** and having retinoic acid-like biological activity.

With respect to the novel coupling reaction of the

process of the present invention, the following is noted. The coupling is affected typically (and preferably) in the presence of cuprous iodide, a suitable catalyst, typically (and preferably) of the formula $Pd(PQ_3)_2Cl_2$ and an acid acceptor, such as triethylamine, by heating in a sealed tube under an inert gas (argon) atmosphere.

Alternatively, the compound of **Formula 1** is first converted to a salt (preferably ZnCl salt) for the coupling. An exemplary generalized process for preparing ZnCl salts of the compounds of **Formula 1** (where Z is converted from H to ZnCl) is described above in connection with **Compounds 19**.

Coupling of the Zncl salts of the 6-thiochromanyl, 6-chromanyl and 6-(1,2,3,4-tetrahydroquinolinyl)-ethyne compounds with compounds of **Formula 2**, is conducted in the presence of $Pd(PQ_3)_4$ catalyst (Q is phenyl). For further details of the conditions of these reactions, reference is made to the following detailed procedures which describe the preparation of specific compounds.

Specific Examples

Phenyl-3-methylbut-2-enylsulfide (**Compound 60**)

A mixture of 14.91g (135.324 mmol) of thiophenol and 5.5g (137.5 mmol) of NaOH in 100 ml acetone was heated at reflux for 2.5 hours and then treated dropwise with a solution of 20 g (134.19 mmol) of 1-bromo-3-methyl-2-butene in 20ml acetone. This solution was refluxed for 40 hours and then stirred at

AUSTRALIAN PATENT OFFICE

room temperature for 24 hours. Solvent was then removed *in vacuo* and the residue was taken up in water and extracted with 3x50ml ether. Ether extracts were combined and washed with 3x30ml of 5% NaOH solution, then water, saturated NaCl solution and dried ($MgSO_4$). Solvent was then removed *in vacuo* and the residue further purified by Kugelrohr distillatin (80 degrees C, 0.75mm) to give the title compound as a pale yellow oil. PMR ($CDCl_3$) :& 1.57 (3H, s), 1.69 (3H, s), 3.52 (2H, d, J-7.7 Hz), 5.29 (1H, t, J-7.7 Hz), 7.14 (1H, t, J-7.0 Hz), 7.24 (2H, t, J-7.0 Hz), 7.32 (2H, d, J-7.0 Hz).

Proceeding in a similar manner, but substituting for thiophenol the appropriate 3-alkylthiophenol, the following compounds can be prepared:

3-methylphenyl-3-methylbut-2-enylsulfide;

3-ethylphenyl-3-methylbut-2-enylsulfide;

3-propylphenyl-3-methylbut-2-enylsulfide;

3-butylphenyl-3-methylbut-2-enylsulfide;

3-pentylphenyl-3-methylbut-2-enylsulfide; and

3-hexylphenyl-3-methylbut-2-enylsulfide.

4,4-Dimethylthiochroman (Compound 61)

To a solution of 15.48g (86.824 mmol) of phenyl-3-methylbut-2-enylsulfide (Compound 60) in 160ml benzene were added successively 12.6g (88.767mmol) of phosphorus pentoxide and 11 ml of 85% phosphoric acid. This solution was refluxed with vigorous stirring under argon for 20 hours, then cooled

to room temperature. The supernatant organic layer was decanted and the syrupy residue extracted with 3x50ml ether. Organic fractions were combined and washed with water, saturated $NaHCO_3$ and saturated NaCl solutions and then dried ($MgSO_4$). Solvent was removed in vacuo and the residue purified by kugelrohr distillation (80 degrees C, 0.5mm) to give the title compound as a pale yellow oil. PMR ($CDCl_3$) :& 1.30 (6H, s), 1.90-1.95 (2H, m), 2.95-3.00 (2H, m), 6.96-7.00 (2H, m), 7.04-7.07 (1H, m), 7.30-7.33 (1H, m).

This method can be used to make 7-position alkyl analogues as exemplified by the following compounds:

4,4,7-trimethylthiochroman ~~(Compound 2)~~

4,4-dimethyl-7-ethylthiochroman;

4,4-dimethyl-7-propylthiochroman;

4,4-dimethyl-7-butylthiochroman; and

4,4-dimethyl-7-hexylthiochroman.

4,4-Dimethyl-6-acetylthiochroman (**Compound 62**)

A solution of 14.3g (80.21 mmol) of 4,4-dimethyl-thiochroman (**Compound 61**) and 6.76g (86.12 mmol) of acetyl chloride in 65 ml benzene was cooled in an ice bath and treated dropwise with 26.712g (102.54 mmol) of stannic chloride. The mixture was stirred at room temperature for 12 hours, then treated with 65 ml water and 33 ml conc. hydrogen chloride and heated at reflux for 0.5 hours. After being cooled to room temperature, the organic layer was separated

AUSTRALIAN PATENT OFFICE

and the aqueous layer extracted with 5x50 ml benzene. The recovered organic fractions were combined and washed with 5% sodium carbonate, water, saturated NaCl and then dried ($MgSO_4$). The solvent was removed in vacuo and the residue purified by flash chromatography (silica; 5% ethyl acetate in hexanes) followed by kugelrohr distillation (150 degrees C, 0.7mm) to give the title compound as a pale yellow oil. PMR ($CDCl_3$): & 1.35 (6H, s), 1.92-1.98 (2H, m) 2.54 (3H, s), 3.02-3.08 (2H, m), 7.13 (1H, d, J-8.6 Hz), 7.58 (1H, dd, J-8.6 Hz, 2Hz), 7.99 (1H, d, J-2Hz).

This procedure serves to acetylate all the compounds which can be made by the process given for the preparation of **Compound 61.**

4,4-Dimethyl-6-ethynylthiochroman **(Compound 1)**

To a solution of 1.441g (14.2405 mmol) of diisopropylamine in 30 ml dry tetrahydrofuran under argon at -78 degrees C was added dropwise 9ml of 1.6M (14.4 mmol) n-butyl lithium in hexane. After stirring this solution at -78 degrees C for 1 hour, it was treated dropwise with a solution of 2.95g (13.389 mmol) of 4,4-dimethyl-6-acetyl-thiochroman (**Compound 62**) in 5ml of dry tetrahydrofuran. After another hour of stirring at -78 degrees C, the solution was treated with 2.507g (14.53 mmol) of diethyl chlorophosphate and brought to room temperature, where it was stirred for 3.75 hours. This solution was then transferred using a double

ended needle to a solution of lithium diisopropylamide [prepared using 2.882g (28.481 mmol) of diisopropylamine and 18ml of 1.6M (28.8 mmol) n-butyllithium in hexane] in 60ml dry tetrahydrofuran at -78 degrees C. The cooling bath was removed and the solution stirred at room temperature for 15 hours, then quenched with water and acidified to pH 1 with 3N hydrogen chloride. The mixture was extracted with 5x50ml pentane and the combined organic fractions washed with 3N hydrogen chloride, water, saturated $NaHCO_3$ and saturated NaCl, then dried ($MgSO_4$). Solvent was then removed in vacuo, and the residu purified by kugelrohr distillation (100 degrees C, 0.7mm) to give the title compound as a pale yellow solid. PMR ($CDCl_3$): & 1.34 (6H, s), 1.94-1.99 (2H, m), 3.04-3.08 (3H, m), 7.06 (1H, d, J-8.4 Hz), 7.17 (1H, dd, J-8.4 Hz, 2.1 Hz), 7.51 (1H, d, J-2.1 Hz).

Similarly, the acetyl group of all compounds prepared similar to the preparation of Compound 62, can be converted to an ethynyl function.

4,4-dimethyl-6-ethynylthiochroman ZnCl (Compound 63) and ethyl 4-(4,4-dimethylthiochroman-6-yl-ethynyl) benzoate (Compound 64)

Reaction vessels used in this procedure were flame dried under vacuum and all operations carried out in an oxygen-free, argon or nitrogen atmosphere. To a solution of 533.9 mg (2.6389 mmol) of 4,4-dimethyl-6-ethynyl-thiochroman (Compound

1) in 4ml of dry tetrahydrofuran at 0 degrees C was added dropwise 1.7ml of 1.6M (2.72 mmol) n-butyl lithium in hexane. This was stirred at 0 degrees C for 10 minutes and at room temperature for 15 minutes, cooled again to 0 degrees C and then treated with a solution of 410mg (3.005 mmol) of fused $Zncl_2$ in 4ml dry tetrahydrofuran using a double ended needle. Thereafter, the solution was stirred at 0 degrees C for 45 minutes, then at room temperature for 20 minutes to give **Compound 63**. This product was not isolated but further used as follows: A solution of 724.4mg (2.6243 mmol) of ethyl 4-iodobenzoate in 4ml dry tetrahydrofuran was transferred by double ended needle into a suspension of 520mg (0.45 mmol) of tetrakistriphenylphosphine palladium in 5ml dry tetrahydrofuran and stirred at room temperature for 20 minutes, then treated by double ended needle with the solution of the alkynyl zinc chloride prepared above. This mixture was stirred at room temperature for 18 hours, then quenched with ice and 30 ml 3N hydrogen chloride. Product was recovered by extraction with 3x75ml ether. Ether fractions were combined and washed successively with saturated $NaHCO_3$ and saturated NaCl solutions and dried ($MgSO_4$). Solvent was removed <u>in vacuo</u> and the residue purified by flash chromatography (silica; 5% ethyl acetate in hexane) followed by HPLC (Whatman Partisil M-9 10/50; 4% ethyl acetate in hexane) to give ethyl 4-(4,4-dimethylthiochroman-6-yl-ethynyl) benzoate (**Compound**

64) as a colorless oil. PMR ($CDCl_3$) :& 1.36 (6H), 1.42 (3H, t, J-7 Hz), 1.93-1.99 (2H, m), 3.03-3.08 (2H, m), 4.40 (2H, q, J-7 HZ), 7.09 (1H, d, J-8.4 Hz), 7.22 (1H, dd, J-8.4 Hz, 2.1 Hz), 7.56 (1H, d, J-2.1 Hz), 7.59 (2H, d, J-7.8 Hz), 8.04 (2H, d, J-7.8 Hz).

(3-Methyl-4-bromo-phenyl)-3-methylbut-2-enylsulfide (Compound 65)

To a stirred solution of 9.52 g (68 mmol) of 3-methyl-4-bromo-thiophenol in 80 ml of acetone was added 2.86 g (68 mmol) of powdered sodium hydroxide and mixture stirred until dissolution was complete. The reaction mixture was then heated to reflux, and then treated with a solution of 11.26 g (68 mmol) of 4-bromo-2-methyl-2-butene in 20 ml of acetone. The mixture was heated at reflux for a further 0.5 h, cooled to room temperature and the solvent removed in vacuo. The residue was taken up in 35 ml of water and extracted with ether. The ether extracts were combined and washed successively with water and saturated NaCl solution and then dried ($MgSO_4$). The solvent was removed in vacuo and the residue kugelrohr distilled (140 - 145 degrees C, 0.2 mm) to give the title compound as a colorless oil. PMR ($CDCl_3$): & 1.58 (3H, s), 1.70 (3H, s), 2.33 (3H, s), 3.49 (2H, d, J-7.8 Hz), 5.26 (1H, t, J-7.8 Hz), 6.98 (1H, dd, J-8.3 Hz, 2.3 Hz), 7.17 (1H, d, J-2.3 Hz), 7.38 (1H, d, J-8.3 Hz).

4.4.7-Trimethyl-6-bromothiochroman (Compound 66)

To 40 g of a vigorously stirred mixture of 10% phosphorous pentoxide in methane-sulfonic acid was added slowly 6.0 g(28.8 mmol) of (3-methyl-4-bromophenyl)-3-methylbut-2-enyl-sulfide (**Compound 65**). The mixture was stirred at room temperature for a further 2 h and was then poured onto ice. The mixture was extracted with 2 x 40 ml of ether and the combined ether extracts were washed successively with water and saturated NaCl solution and then dried. The solvent was removed in vacuo and the residue kugelrohr distilled (130 degrees C; 0.07 mm) to give the title compound as a viscous oil. PMR ($CDCl_3$): & 1.28 (6H, s) 1.84-1.93 (2H, m), 2.26 (3H, s), 2.95-3.03 (2H, m), 6.94 (1H, s), 7.46 (1H, s).

4,4,7-Trimethyl-6-trimethylsilylethynyl-thiochroman (**Compound 67**)

A mixture of 624 mg (3.0 mmol) of 4,4,7-trimethyl-6-bromothiochroman (**Compound 66**) 314 mg (3.2 mmol) of trimethylsilyl acetylene, 40 mg (0.21 mmol) of cuprous iodide, 80 mg (0.11 mmol) of bis (triphenylphosphin) palladium (II) chloride and 1 ml of triethylamine was degassed under nitrogen and heated in a sealed tube at 85 degrees C for 15 h. The mixture was then treated with a further 20 mg (0.11 mmol) of cuprous iodide and 40 mg (0.06 mmol) of the palladium (II) catalyst. The mixture was then heated under a nitrogen atmosphere in the sealed tube at 100 degrees C for a further 64 h. The triethylamine was then removed under vacuum and the

residue purified by flash chromatography (silica; hexanes) to give the title compound as a yellow oil. PMR ($CDCl_3$): & 0.28 (9H, s), 1.30 (6H, s), 1.88-1.97 (2H, m), 2.33 (3H, s), 2.97-3.05 (2H, m), 6.92 (1H, s), 7.43 (1H, s).

4,4,7-Trimethyl-6-ethynyl-Thiochroman (**Compound 2**)

A mixture of 380 mg (1.69 mmol) of trimethylsilyl (4,4,7-trimethyl-thiochroman-6-yl) ethyne, (**Compound 67**) 4 ml of isopropanol and 2.5 ml of aqueous 1N potassium hydroxide was degassed under nitrogen and stirred at room temperature for 16 h. The mixture was concentrated under vacuum and extracted with 2 X 10 ml of ether. The ether extracts were combined and washed successively with water and saturated NaCl solution and then dried ($MgSO_4$). The solvent was removed in vacuo to give the title compound as a yellow oil. PMR ($CDCl_3$): & 1.31 (6H, s), 1.88-1.96 (2H, m), 2.35 (3H, s), 3.00-3.08 (2H, m), 3.25 (1H, s), 6.94 (1H, s), 7.47 (1H, s).

S-(4-bromopenyl) 3,3-dimethylthioacrylate (**Compound 69**)

To an ice bath cooled solution of 1.92 g (80 mmol) of NaH (obtained from a 60% suspension in mineral oil by 3 x 15 ml hexane wash) in 30 ml of dry THF was added slowly under argon a solution of 15.1 g (80 mmol) of 4-bromothiophenol in 60 ml of dry THF over 1 h. The mixture was stirred at 0 degrees C for a further 30 min and then treated with a solution of 10.1 g (85 mmol) of dimethylacryloyl chloride in 30 ml of dry THF. The cooling bath was then removed and the mixture then stirred

at room temperature for 40 h. The reaction mixture was poured into 200 ml of water containing 2 ml of glacial acetic acid and the organic layer was separated. The organic layer was washed with 2 x 75 ml of water and then dried ($MgSO_4$). The solvent was removed in vacuo to give the title compound as a yellow oil. PMR ($CDCl_3$): & 1.91 (3H, s), 2.14 (3H, s), 6.03-6.06 (1H, m), 7.28 (2H, d, J-8.6 Hz), 7.53 (2H, d, J-8.6 Hz).

4,4-Dimethyl-6-bromo-2-oxo-thiochroman (**Compound 70**)

To a stirred, ice-cooled suspension of 15.9 g (119 mmol) of aluminum chloride in 140 ml of methylene chloride was added under nitrogen, a solution of 21.64 g (79.9 mmol) of S-(4-bromophenyl) 3,3-dimethyl-thioacrylate (**Compound 69**) in 100 ml of methylene chloride. The mixture was then stirred at room temperature for 72 h and then poured into 250 g of an ice and brine mixture. The mixture was extracted with methylene chloride and the combined organic extracts were washed with saturated NaCl solution and then dried ($MgSO_4$). The solvent was removed in vacuo and the residue recrystallized from hexanes to give the title compound as white crystals. PMR ($CDCl_3$): & 1.40 (6H, s), 2.67 (2H, s), 7.31-7.40 (3H, m). MS exact mass, m/e 269.9714 (calcd. for $C_{11}H_{11}$ SOBr, 269.9714).

4-Bromo-2-(1,1,3-trimethyl-3-hydroxybutyl) thiophenol (**Compound 71**)

To 3.49 g (32.8 mmol) of lithium perchlorate was added under argon 35 ml of 3.0M (105 mmol) methyl magnesium bromide

in ether. The above mixture was treated dropwise with stirring with a solution of 2.961 g (10.926 mmol) of 4,4-dimethyl-6-bromo-2-oxo-thiochroman (**Compound 70**) and the reaction mixture was then heated at reflux for 70 h. The reaction mixture was then allowed to cool and poured onto a mixture of 100 g of ice and 8 ml of conc. H_2SO_4. The organic layer was separated and the aqueous layer was extracted with 2 x 25 ml of ether. The organic layers were combined and washed successively with 2 x 25 ml of saturated $NaHCO_3$ solution, 25 ml of water and 25 ml of saturated NaCl solution and then dried ($MgSO_4$). The solvent was removed <u>in-vacuo</u> and the residue purified by flash chromatography to give the title compound as a pale yellow oil. PMR ($CDCl_3$): & 1.05 (6H, s), 1.52 (6H, s), 2.30 (2H, s), 3.71 (1H, s), 7.22 (1H, dd, J-8.5 Hz, 2.1 Hz), 7.28 (1H, d, J-8.5 Hz), 7.35 (1H, d, J-2.1 Hz)

Using ethyl magnesium bromide, instead of methyl magnesium bromide, provides the corresponding 4-bromo-2- (1,1 dimethyl 3-ethyl-3-hydroxypentyl)-thiophenol.

<u>2,2,4,4-Tetramethyl-6-bromothiochroman</u> (**Compound 72**)

A mixture of 500 mg (1.49 mmol) of 4-bromo-2-(1,1,3-trimethyl-3-hydroxybutyl) thiophenol (**Compound 71**) and 8 ml of 20 percent aqueous H_2SO_4 was heated at reflux for 24 h. The mixture was extracted with hexanes, the organic extracts were combined and washed successively with water, saturated $NaHCO_3$, water again, saturated NaCl and then dried ($MgSO_4$). The

solvent was removed in vacuo and the residue purified by flash chromatography (silica; hexanes) to give the title compound as a clorless oil. PMR ($CDCl_3$): & 1.35 (6H, s), 1.40 (6H, s), 1.93 (2H, s), 7.17 (1H, dd, J-8.4 Hz, 2.1 Hz), 7.23 (1H, d, J-8.4 Hz); 7.26 (1H, d, J-2.1 Hz). MS exact mass, m/e 284.0221 (calcd. for $C_{13}H_{17}$ S Br, 284.0234).

2,2,4,4-Tetramethyl-6-trimethylsilylethynyl-thiochroman (Compound 73)

A solution of 600 mg (2.11 mmol) of 2,2,4,4-tetramethyl-6-bromothiochroman (Compound 72) in 1.5 ml of triethylamine was placed in a heavy-walled tube and degassed and then treated under argon with 1.4 g (14.3 mmol) of trimethylsilylacetylene and a powdered mixture of 75 mg (0.39 mmol) of cuprous iodide and 150 mg (0.21 mmol) of bis(triphenylphosphine) palladium (II) chloride. The reaction mixture was degassed again, then placed under argon and the tube was sealed. The mixture was heated at 100 degrees C for 24 h, allowed to cool to room temperature and then treated with a further 1.4 g (14.3 mmol) of trimethylsilylacetylene and a powdered mixture of 75 mg (0.39 mmol) of cuprous iodide and 150 mg (0.21 mmol) of bis(triphenylphosphine) palladium (II) chloride. The mixture was then degassed, placed under argon and then heated in the sealed tube at 100 degrees C for 96 h. The mixture was cooled to room temperature and extracted with 3 x 10 ml of ether. The organic extracts were combined,

washed successively with 25 ml of water and 25 ml of saturated sodium chloride solution and then dried ($MgSO_4$). The solvent was removed in vacuo and the residue purified by flash chromatography (silica; hexanes followed by 3% ethyl acetate in hexanes) to give the title compound as a yellow, crystalline solid. PMR ($CDCl_3$): & 0.23 (9H, s), 1.36 (6H, s), 1.39 (6H, s), 1.94 (2H, s), 7.17 (1H, dd, J-8.2 Hz, 1.8 Hz), 7.25 (1H, d, J-1.8 Hz), 7.30 (1H, d, J-8.2 Hz). MS exact mass, m/l 302.1519 (calcd. for $C_{18}H_{26}$ S Si, 382.1524).

2,2,4,4-Tetramethyl-6-ethynylthiochroman (Compound 3)

To a solution of 527.6 mg (1.75 mmol) of 2,2,4,4-tetramethyl-6-trimethylsilyl-ethynylthiochroman (Compound 73) in 4 ml of isopropanol was added, under argon, 4 ml of 1N KOH solution. The reaction mixture was stirred at room temperature for 20 h and the isopropanol was then removed under vacuum. The residue was extracted with ether and the combined ether extracts were washed successively with water and saturated NaCl solution and then dried ($MgSO_4$). The solvent was removed in vacuo to give the title compound as a yellow oil. PMR ($CDCl_3$): & 1.34 (6H, s), 1.37 (6H, s), 1.91 (2H, s), 2.99 (1H, s), 7.17 (1H, dd, J-8.1 Hz, 1.8 Hz), 7.26 (1H, d, J-1.8 Hz), 7.30 (1H, d, J-8.1 Hz). MS exact mass, m/e 230.1122 (calcd. for $C_{15}H_{18}S$, 230.1129)

Diphenyl-3-methyl-3-buten-1-yl phosphate (Compound 75)

To an ice-cooled solution of 12.2g (141.65 mmol) of 3-

methyl-3-buten-1-ol (Aldrich) and 11.9g (150.44 mmol) of pyridine in 100ml of tetrahydrofuran was added dropwise under argon a solution of 38.5 g (143.21 mmol) of diphenyl chlorophosphate (**Compound 32**) in 100ml of tetrahydrofuran. The mixture was heated at reflux for 3 hours and then cooled and filtered. The filtrate was concentrated in vacuo and the residue dissolved in 400ml of 1:1 ether and hexane and then washed with 2x200ml water, 75ml saturated NaCl solution and dried ($MgSO_4$). The solvent was removed in vacuo to give the title compound as a pale yellow oil. PMR ($CDCl_3$): δ 1.69 (3H, s), 2.37 (2H, t, J-7 Hz), 4.32 (2H, q, J-7 Hz), 4.72 (1H, s), 4.80 (1H), 7.10-7.35 (10H, m).

4,4-Dimethylchroman (**Compound 76**)

To a dry, ice-cooled flask containing 34.95g (0.134 mol) of stannic chloride was added quickly under argon 63.0g (0.669 mol) of phenol. The mixture was stirred at 0 degrees C for 0.5 hour and then treated with 43.0g (0.135 mol) of diphenyl-3-methyl-3-buten-1-yl phosphate (**Compound 75**), followed by a 5ml carbon disulfide rinse. The mixture was stirred at room temperature for 21 hours and then quenched by pouring onto 700 g ice and 1 liter of 1.5N NaOH. The mixture was extracted with 1x600 ml and 2x300 ml ether. The combined ether fractions were washed with 2N NaOH, saturated NaCl and dried ($MgSO_4$). Solvent was removed in vacuo and the residue purified by flash chromatography (silica; 2% ether in hexane)

to give the title compound as a colorless oil. PMR ($CDCl_3$) &: 1.34 (6H), 1.80-1.85 (2H, m), 4.15-4.20 (2H, m), 6.80 (1H, dd, J-8.1 hz, 1.5 Hz), 6.87 (1H, td, J-8.1 Hz, 1.5 Hz), 7.07 (1H, td, J-8.1 Hz, 1.5 Hz), 7.26 (1H, dd, J-8.1 Hz, 1.5 H).

In a similar manner, but substituting the corresponding 3 alkylphenol for phenol, there may be prepared the following compounds:

4,4,7-trimethylchroman;

4,4-dimethyl-7-ethylchroman;

4,4-dimethyl-7-propylchroman; and

4,4-dimethyl-7-pentylchroman.

4,4-Dimethyl-6-acetylchroman (**Compound 77**)

To a stirred solution of 7.94g (48.9425 mmol) of 4,4-dimethylchroman (**Compound 76**) in 70 ml of nitromethane was added under argon 4.0g (50.96 mmol) of acetyl chloride followed by 6.8g (51 mmol) of aluminum chloride. This was stirred at room temperature for 5.5 hours and then cooled in an ice bath and treated slowly with 70 ml of 6N hydrogen chloride. The resultant mixture was stirred at room temperature for 10 minutes and then treated with 100 ml ether and the organic layer separated. The organic layer was washed with water, saturated $NaHCO_3$ and saturated NaCl solutions and dried ($MgSO_4$). Solvent was removed in vacuo and the residue purified by flash chromatography (silica; 10% ethyl acetate in hexanes). This was followed by kugelrohr distillation (95-100

degrees C; 0.15 mm) to give the title compound as a colorless oil. PMR ($CDCl_3$): & 1.40 (6H), 1.95-2.00 (2H, m), 2.58 (3H), 4.25-4.30 (2H, m), 6.83 (1H, d, J-8.0 Hz), 7.62 (1H, dd, J-8.0 Hz, 1.5 Hz), 8.00 (1H, d, J-1.5 Hz).

Proceeding in the same manner, the other chroman compounds, made similar to **Compound 76**, are converted to their respective acetyl analogs.

4,4-Dimethyl-6-ethynylchroman (**Compound 4**)

To a solution of 2.47g (24.41 mmol) of diisopropylamine in 40ml dry tetrahydrofuran under argon at -78 degrees C was added dropwise 15.2ml of 1.6M (24.32 mmol) n-butyl lithium in hexane. This mixture was stirred at -78 degrees C for 1 hour and then treated dropwise with a solution of 4.98g (24.38 mmol) of 4,4-dimethyl-6-acetylchroman (**Compound 77**) in 1 ml dry of tetrahydrofuran. After stirring at -78 degrees C for 1 hour, the solution was treated with 4.2g (24.36 mmol) of diethyl chlorophosphate. The cooling bath was then removed and the reaction mixture stirred at room temperature for 2.75 hours. This solution was then transferred using a double ended needle to a solution of lithium diisopropyl amide [prepared using 4.95g (48.92 mmol) of diisopropylamine and 30.5 ml of 1.6M (48.8 mmol) n-butyllithium in hexane] in 80 ml dry tetrahydrofuran at -78 degrees C. The cooling bath was removed and mixture stirred at room temperature for 18 hours and then quenched with 50ml water and 25ml of 3N hydrogen

chloride. The mixture was extracted with 2x100ml and 3x50ml of pentane and the combined organic fractions washed with 3N hydrogen chloride, water, saturated $NaHCO_3$ and saturated NaCl solutions and then dried ($MgSO_4$). Solvent was then removed in vacuo and the residue purified by flash chromatography (silica; 10% ethyl acetate in hexane) followed by kugelrohr distillation (70 degrees C; 0.35mm) to give the title compound as a colorless crystalline solid. PMR ($CDCl_3$): & 1.33 (6H), 1.81-1.86 (2H, m), 3.00 (1H, s), 4.19-4.24 (2H, m), 6.75 (1H, d, J-8.5 Hz), 7.22 (1H, dd, J-8.5 Hz, 2.3 Hz), 7.44 (1H, d, J-2.3 Hz).

Using this method, the acetyl derivatives, made similar to Compound 77, are converted to the ethynyl form.

4,4-dimethyl-6-ethynylchroman ZnCl (Compound 79) and ethyl 4-(4,4-dimethylchroman-6-yl-ethynyl) benzoate (Compound 80)

Reaction vessels used in this procedure were flame dried under vacuum and all operations were carried out in an oxygen-free, argon or nitrogen atmosphere. To a solution of 509.4 mg (2.74 mmol) of 4,4-dimethyl-6-ethynyl chroman (Compound 78) in 4 ml of dry tetrahydrofuran at 0 degrees C was added dropwise 1.72 ml of 1.6M (2.75 mmol) of n-butyl lithium in hexane. Stirring was commenced at 0 degrees C for 30 minutes and at room temperature for 15 minutes, after which the solution was cooled again to 0 degrees C and then treated with a solution

of 380 mg (2.79 mmol) of fused zinc chloride in 5 ml of dry tetrahydrofuran using a double ended needle. The resulting solution was stirred at 0 degrees C for 1 hour and then at room temperature for 15 minutes to give Compound 79.

This product was not isolated but further used as follows: A solution of 628.6 mg (2.74 mmol) of ethyl 4-bromobenzoate in 4 ml of dry tetrahydrofuran was transferred by double ended needle into a suspension of 380 mg (0.33 mmol) of tetrakistriphenylphosphine palladium in 5 ml dry tetrahydrofuran and stirred at room temperature for 15 minutes, then treated by double ended needle with the solution of alkynyl zinc chloride prepared above. The mixture was stirred at room temperature for 20 hours and then quenched with ice and 30 ml of 3N hydrogen chloride. The mixture was then extracted with 3x75 ml ether and ether extracts were combined and washed successively with saturated $NaHCO_3$ and saturated NaCl solutions and then dried ($MgSO_4$). Solvent was removed in vacuo and the residue further purified by flash chromatography (silica; 10% ethyl acetate in hexane) to obtain ethyl 4-(4,4-dimethylchroman-6-yl-ethynyl) benzoate (Compound 80) as a white solid. PMR ($CDCl_3$): & 1.36 (6H), 1.42 (3H, t, J-7.3 Hz), 1.82-1.86 (2H, m), 4.21-4.25 (2H, m), 4.40 (2H, q, J-7.3 Hz), 6.79 (1H, d, J-8.1 Hz), 7.28 (1H, dd, J-8.1 Hz, 2.2 Hz), 7.50 (1H, d, J-2.2 Hz), 7.58 (2H, d, J-8.7 Hz), 8.03 (2H, d, J-8.7 Hz).

Phenyl 3,3-dimethylacrylate (Compound 81)

To an ice bath cooled solution of 1.29 g (54 mmol) of NaH (obtained from a 60% suspension in mineral oil by 3x10 ml hexane wash) in 20 ml of dry THF was added slowly under oxygen a solution of 5 g (53 mmol) of phenol in 50 ml of dry THF. The mixture was then treated with a solution of 7 g (59 mmol) of dimethylacryloyl chloride in 30 ml of dry THF. The cooling bath was then removed and the mixture was stirred for a further 2.5 h. The reaction mixture was then poured into 150 ml of water containing 1 ml of glacial acetic acid. The mixture was extracted with 150 ml ether and the ether extract washed with saturated NaCl solution and then dried ($MgSO_4$). The solvent was removed in vacuo and the residue purified by flash chromatography (silica; 5% ether in hexanes) to give the title compound as a yellow oil. PMR ($CDCl_3$)): δ 1.99 (3H, s), 2.24 (3H, s), 5.93 (1H, broad s), 7.10 (2H, d, J-7.8 Hz) 7.22 (1H, t, J-7.8 Hz), 7.38 (2H, t, J-7.8 Hz).

4,4-Dimethyl-2-oxo-chroman (Compound 82)

To a stirred, ice-cooled suspension of 10.4 g (78 mmol) of aluminum chloride in 160 ml of methylene chloride was added slowly under argon a solution of 7 g (39.8 mmol) of phenyl 3,3-dimethylacrylate (Compound 81) in 40 ml of methylene chloride. The cooling bath was removed and the mixture stirred for a further 42 h. The mixture was poured into a mixture of ice and brine and the organic layer separated. The aqueous

layer was extracted with methylene chloride and the organic extracts were combined and washed with saturated NaCl solution and then dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue purified by flash chromatography (silica; 10% ether in hexane) to give the title compound as a colorless oil. PMR ($CDCl_3$: δ 1.30 (6H, s), 2.56 (2H, s), 7.06 (1H, dd, J-8.0 Hz, 1.4 Hz), 7.16 (1H, td, J-8.0 Hz, 1.4 Hz), 7.26 (1H, td, J-8.0 Hz, 1.7 Hz), 7.33 (1H, dd, J-8.0 Hz, 1.7 Hz). MS exact mass, m/e 176.0852 (calcd. for $C_{11}H_{12}O_2$, 176.0837.

2-(1,1,3-Trimethyl-3-hydroxybutyl)phenol (Compound 83)

To 11 ml of 3.0 M (33 mmol) methyl magnesium chloride in THF, cooled in an ice bath, was added, under nitrogen, a solution of 1.96 g (11.1 mmol) of 4,4-dimethyl-2-oxo-chroman (Compound 82) in 35 ml of dry ether. The cooling bath was then removed and the mixture stirred at room temperature for 72 h. The reaction mixture was then poured onto a mixture of 100 g of ice and 3 ml of conc. H_2SO_4 and stirred until the magnesium salts were dissolved. The organic layer was separated and the aqueous layer extracted with 2x50 ml of ether. The organic layers were combined and washed successively with water, saturated $NaHCO_3$ and saturated NaCl solutions and then dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was purified by flash chromatography (silica; 20% ethyl acetate in hexanes) to give the title compound as a pale yellow solid. PMR ($CDCl_3$):

& 1.13 (6H, s), 1.48 (6H, s), 1.89 (1H, s), 2.23 (2H, s), 6.60 (1H, dd, J-7.9 Hz, 1.4 Hz), 6.83 (1H, s), 6.84 (1H, td, J-7.9 Hz, 1.4 Hz), 7.07 (1H, td, J-7.9 Hz, 1.6 Hz), 7.31 (1H, dd, J-7.9 Hz, 1.6 Hz). MS exact mass, m/l 20.1458 (calcd. for $C_{13}H_{20}O_2$, 208.1464).

2,2,4,4-Tetramethyl-chroman (**Compound 84**)

A mixture of 2.98 g (14.3 mmol) of 2-(1,1,3-trimethyl-3-hydroxybutyl) phenol (**Compound 83**) and 40 ml of 20% aqueous H_2SO_4 was heated at reflux, under nitrogen, for 4 h. The mixture was stirred at room temperature for a further 72 h and then diluted with 50 ml of water. The mixture was extracted with 3x20 ml of hexanes. The organic extracts were then combined and washed successively with water and saturated NaCl solution and then dried ($MgSO_4$). The solvent was then removed in vacuo to give the title compound as a colorless oil. PMR ($CDCl_3$):

& 1.36 (6H, s), 1.37 (6H, s), 1.83 (2H, s), 6.71 (1H, dd, J-8.2 Hz, 1.5 Hz) 6.92 (1H, td, J-8.2 Hz, 1.5 Hz), 7.09 (1H, td, J-8.2 Hz, 1.5 Hz), 7.29 (1H, dd, J-8.2 Hz, 1.5 Hz).

2,2,4,4-Tetramethyl-6-acetyl-chroman (**Compound 85**)

To an ice bath cooled solution of 2 g (10.53 mmol) of 2,2,4,4-tetramethylchroman (**Compound 84**) in 25 ml of nitromethane was added, under nitrogen, 941 mg (11.99 mmol) of acetyl chloride followed by 1.59 g (11.92) mmol) of aluminum chloride. The cooling bath was then removed and the mixture

stirred at room temperature for 16 h. The mixture was then cooled again in an ice bath and treated with 25 ml of conc. HCl. The mixture was then filtered and the residue washed with methylene chloride. The filtrate was concentrated in vacuo and the resultant residue was purified by flash chromatography (silica; 10% ethyl acetate in hexanes) to give the title compound as a yellow oil. PMR ($CDCl_3$): δ 1.38 (6H, s), 1.39 (6H, s), 1.87 (2H, s), 2.56 (3H, s), 6.83 (1H, d, J-8.7 Hz), 7.71 (1H, dd, J-8.7 Hz, 2.1 Hz), 7.98 (1H, d, J-2.1 Hz). MS exact mass, m/e 232.1468 (calcd. for $C_{13}H_{20}O_2$, 232.1464).

2,2,4,4-Tetramethyl-6-ethynyl-chroman (**Compound 5**)

To a cooled (-78 degrees C) solution of 522 mg (5.17 mmol) of diisopropylamine in 8 ml of dry THF was added slowly, under nitrogen, 3.23 ml of 1.6 M (5.17 mmol) n-butyl lithium in hexane. The mixture was stirred at - 78 degrees C for 40 minutes and then treated with a solution of 1.24 g (5.17 mmol) of 2,2,4,4-tetramethyl-6-acetylchroman (**Compound 85**) in 2 ml of dry THF. The mixture was stirred at - 78 degrees C for a further 1 h and then treated with 895 mg (5.19 mmol) of diethylchlorophosphate. The reaction mixture was allowed to warm to room temperature and transferred by double-ended needle into a solution of lithium diisopropylamide in THF at -78 degrees C [prepared as described above from 1.04 g (10.34 mmol) of diisopropylamine and 6.46 ml of 1.6 M (10.34 mmol) n-butyl lithium in hexane]. The cooling bath was removed and

the mixture was stirred at room temperature for 16 h. The mixture was then treated with 10 ml of ice water and acidified to a pH of 2 with 10% HCl. The organic layer was separated and the aqueous layer was extracted with 3x30 ml of pentane. The organic extracts were combined and washed successively with 2.30 ml of dilute HCl, water, 3x30 ml of saturated $NaHCO_3$ solution and saturated NaCl solution and then dried ($MgSO_4$). The solvent was removed in vacuo and the residue was purified by flash chromatography (silica; 2% ethyl acetate in hexane) to give the title compound as a pale yellow oil. PMR ($CDCl_3$): δ 1.31 (6H, s), 1.32 (6H, s), 1.50 (2H, s), 3.00 (1H, s), 6.72 (1H, d, J-8.4 Hz), 7.20 (1H, dd, J-8.4 Hz, 2.1 Hz), 7.42 (1H, d, J-2.1 Hz). MS exact mass, m/e 214.1251 (calcd. for $C_{15}H_{18}O$, 214.1357).

3-Methyl-phenyl-3,3-dimethylacrylate (Compound 87)

A 60% suspension of sodium hydride (3.22 g; 81 mmol) in mineral oil was washed with 3x10 ml of hexane and then treated with 30 ml of dry THF. This mixture was cooled in an ice-bath and then treated with a solution of 8.6 g (79.5 mmol) of m-cresol in 80 ml of dry THF. The reaction mixture was stirred for 10 min and then treated with a solution of 10.5 g (88.5 mmol) of dimethylacryloyl chloride in 40 ml of dry THF. The reaction mixture was stirred at room temperature for 96 h and then poured into a mixture of 150 ml of water and 1 ml of glacial acetic acid. The mixture was stirred for 10 min and

the organic layer was separated. The aqueous layer was extracted with 2x50 ml of ether. The organic layers were combined and washed successively with water and saturated NaCl solution and then dried ($MgSO_4$). The solvent was removed in vacuo and the residue was purified by flash chromatography (silica; 10% ethyl acetate in hexane) to give the title compound as a pale yellow oil. PMR ($CDCl_3$): & 1.95 (3H, d, J-1.3 Hz), 2.21 (3H, d, J-1.2 Hz), 2.34 (3H, s), 5.90 (1H, broad S), 6.86 - 6.93 (2H, m), 7.01 (1H, d, J-7.2 Hz), 7.24 (1H, t, J-7.2 Hz).

2-(1,1,3-Trimethyl-3-hydroxybutyl) 5-methyl-phenol (**Compound 88**)

To an ice-bath cooled suspension of 13 g (97.5 mmol) of aluminum chloride in 200 ml of methylene chloride was added dropwise under argon a solution of 9.0 g (47.4 mmol) of 3-metyl-phenyl-3,3-dimethylacrylate (**Compound 87**) in 100 ml of methylene chloride. The reaction mixture was stirred at 0 degrees C for a further 30 min and then at room temperature for 15 h. The reaction mixture was poured into 200 ml of an ice water/salt mixture and the organic layer was separated. The aqueous layer was extracted with 50 ml of ether. The organic layers were combined and washed successively with water and saturated NaCl solution and then dried ($MgSO_4$). The solvent was removed in vacuo and the residue purified by flash chromatography (silica; 5% ethyl acetate in hexane) to give an

approximately 2.5:1 mixture of isomeric products, 4,4,7-trimethyl-2-oxo-chroman and 4,4,5-trimethyl-2-oxo-chroman as a pale yellow oil. To a solution of 3.8 g (20 mmol) of this mixture of isomeric 2-oxo-chromans in 60 ml of ether at 0 degrees C was added under argon 20 ml of 3.0 M (60 mmol) of methyl magnesium bromide in ether. The reaction mixture was stirred at room temperature for 48 h and then poured onto a mixture of ice and 1 ml of conc. H_2SO_4. The organic layer was separated and the aqueous layer extracted with 2x50 ml of ether. The organic layers were combined and washed successively with water, saturated $NaHCO_3$ solution, water again and then saturated NcCl solution and then dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was purified by flash chromatography (silica; 15 % ethyl acetate in hexanes) to give the title compound as a colorless oil. PMR ($CDCl_3$): & 1.14 (6H, s), 1.45 (6H, s), 2.19 (3H, s), 2.21 (2H, s), 6.39 (1H, d, J-1.8 Hz), 6.67 (1H, dd, J-7.9 Hz, 1.8 Hz), 7.16 (1H, d, J-7.9 Hz), 7.44 (1H, s).

2,2,4,4,7-Pentamethyl-chroman (**Compound 89**)

To 2.16 g (11.7 mmol) of 2-(1,1,3-trimethyl-3-hydroxybutyl) 5-methyl-phenol (**Compound 88**) was added under nitrogen 50 ml of 20% aqueous sulfuric acid. The reaction mixture was heated at reflux for 13 h and then cooled. The organic layer was separated and the aqueous layer was extracted with ether. The organic extracts were combined and washed

successively with water, saturated $NaHCO_3$ solution, water again and saturated NaCl solution and then dried ($MgSO_4$). The solvent was removed *in vacuo* to give the title compound as a yellow oil. PMR ($CDCl_3$): δ 1.32 (6H, s), 1.34 (6H, s), 1.81 (2H, s), 2.26 (3H, s), 6.63 (1H, s), 6.72 (1H, d, J-7.9 Hz), 7.15 (1H, d, J-7.9 Hz).

2,2,4,4,7-Pentamethyl-6-acetyl-chroman (**Compound 90**)

To an ice-bath cooled solution of 1.96 g (9.6 mmol) of 2,2,4,4,7-pentamethyl-chroman (**Compound 89**) in 30 ml of nitromethane was added under argon 1.059 g (13.5 mmol) of acetyl chloride followed by 1.9 g (14.3 mmol) of aluminum chloride. The reaction mixture was stirred at room temperature for 14 h and then cooled in an ice-bath and treated with 25 ml of conc. HCl. The mixture was warmed to room temperature and diluted with ether and water. The organic layer was separated and the aqueous layer extracted with ether. The organic extracts were combined and washed successively with water, saturated $NaHCO_3$ solution, water again, and saturated NaCl solution, and then dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was purified by flash chromatography (silica; 5% ethyl acetate in hexanes) to give the title compound as a pale yellow oil. PMR ($CDCl_3$): 1.36 (6H, s), 1.37 (6H, s), 1.86 (2H, s), 2.49 (3H, s), 2.56 (3H, s), 6.65 (1H, s), 7.74 (1H, s).

2,2,4,4,7-Pentamethyl-6-ethynyl-chroman (**Compound 9**)

To a solution of 455 mg (4.5 mmol) of disopropylamine in 5 ml of dry THF at -78 degrees C was added under argon 3 ml of 1.5 M n-BuLi in hexane. The mixture was stirred at -78 degrees C for a further 45 min and then treated with a solution of 1.07 g (4.3 mmol) of 2,2,4,4,7-pentamethyl-6-acetyl-chroman (**Compound 90**) in 4 ml of dry THF. The reaction mixture was stirred at -78 degrees C for 1 h and then treated with 776 mg (4.5 mmol) of diethyl chlorophosphate. The mixture was allowed to warm to room temperature and then transferred by a double-ended needle into a solution of lithium diisopropyl amide in 10 ml dry THF at -78 degrees C which was prepared as described above using 910 mg (9.0 mmol) of diisopropylamine and 6 ml of 1.5 M (9.0 mmol) n-BuLi in hexane. The mixture was stirred at room temperature for 15 h and then poured into 10 ml of iced water. The mixture was acidified to pH=2 with 10% HCl solution. The organic layer was separated and the aqueous layer extracted with pentane. The organic extracts were combined and washed successively with water, saturated $NaHCO_3$ and saturated NaCl solutions and then dried ($MgSO_4$). The solvent was removed in vacuo and the residue purified by Kugelrohr distillation (82 degrees C, 0.3 mm) to give the title compound as a pale yellow oil. PMR ($CDCl_3$): & 1.32 (6H, s), 1.34 (6H, s), 1.81 (2H, s), 2.36 (3H, s), 3.18 (1H, s), 6.64 (1H, s), 7.40 1H (s). MS exact mass, m/e 228.1520 (calcd. for $C_{16}H_{20}O$, 228.1514).

N-(4-Bromophenyl)3,3-dimethylacrylamide (**Compound 92**)

To a solution of 9.48 g (80 mmol) of 3,3-dimethylacryloyl chloride in 200 ml of dry THF was added with vigorous shaking a solution of 13.76 g (80 mmol) of 4-bromoaniline in 300 ml of dry THF. The mixture was stood at room temperature for 2 h and then treated with 80 g of ice followed by 200 ml of hexane. The organic layer was separated and the aqueous layer was extracted with 2x50 ml of hexanes. The organic layers were combined and washed successively with 30 ml of water and 2x30 ml of saturated NaCl solution and then dried ($MgSO_4$). The solvent was removed in vacuo and the residue purified by recrystallization from an ethyl acetate and hexanes mixture to give the title compound as colorless crystals. PMR ($CDCl_3$): & 1.91 (3H, s), 2.23 (3H, s), 5.73 (1H, broad s), 7.38-7.55 (5H, m).

4,4-Dimethyl-6-bromo-2-oxo-1,2,3,4-tetrahydroquinoline (**Compound 93**)

To 6.7 g (26.02 mmol) of molten N-(4-bromophenyl)3,3-dimethylacrylamide (**Compound 92**) (heated to 135 degrees C) was added 4.15 g (31.09) of aluminum chloride over 25 min. The reaction mixture was stirred at 130 degrees C for 16 h and then treated with a further 1 g (7.5 mmol) of aluminum chloride. The reaction mixture was heated at 130 degrees C for a further 9 h and then cooled to room temperature: The reaction was then quenched by the slow addition of 100 ml of

ice cold water with slight warming of flask to facilitate mixing. The mixture was extracted with 1x100 ml and 4x50 ml of ether. The organic extracts were combined and washed with 25 ml of saturated NaCl solution and then dried ($MgSO_4$). The solvent was removed in vacuo and the residue purified by flash chromatography (silica; 30% ethyl acetate in hexanes) to give the title compound as a pale yellow solid. PMR ($CDCl_3$): δ 1.37 (6H, s), 2.53 (2H, s), 6.85 (1H, d, J~8.4 Hz), 7.32 (1H, dd, J~8.4 Hz, 2.1 Hz), 7.43 (1H, d, J~2.1 Hz), 10.12 (1H, broad s).

4,4-Dimethyl-6-bromo-1,2,3,4-tetrahydroquinoline (**Compound 94**)

To 23.5 ml of 1.0 M (23.5 mmol) lithium aluminum hydride in THF, heated to reflux under nitrogen, was added a solution of 4.95 g (19.48 mmol) of 4,4-dimethyl-6-bromo-2-oxo-1,2,3,4-tetrahydroquinoline (**Compound 93**) in 50 ml of dry THF and 100 ml of dry ether via a double-ended needle The mixture was heated at reflux for 2 h and then cooled to room temperature. The reaction mixture was then quenched by the slow addition of 25 ml of water followed by 50 ml of 5% NaOH solution. The mixture was extracted with 2x25 ml of ether, the organic extracts were combined and washed successively with 25 ml each of water and saturated NaCl solution and then dried ($MgSO_4$). The solvent was removed in vacuo and the residue purified by flash chromatography (silica; 15% ethyl acetate in hexanes) to give the title compound as a brown oil. PMR ($CDCl_3$): δ 1.27

(6H, s), 1.67-1.74 (2H, m), 3.23-3.32 (2H, m) [illegible] broad s), 6.33 (1H, d, J-8.4 Hz), 7.10 (1H, dd, J-8.4 Hz, [illegible]), 7.25 (1H, d, J-2.3 Hz).

4,4-Dimethyl-6-trimethylsilylethynyl-1,2,3,4-tetrahydroquinoline (**Compound 95**)

A solution of 1.608 g (6.7 mmol) of 4,4-dimethyl-6-bromo-1,2,3,4-tetrahydroquinoline (**Compound 94**) in 1.5 ml of triethylamine in a heavy-walled tube was degassed under argon and then treated with 75 mg (0.39 mmol) of cuprous iodide and 150 mg (0.21 mmol) of bis(triphenylphosphine) palladium (II) chloride. The mixture was degassed again under argon, treated with 2.09 g (21.2 mmol) of trimethylsilylacetylene and the tube was sealed. The mixture was heated at 50 degrees C for 48 h. After cooling to room temperature methylene chloride was added to the reaction mixture and the mixture filtered. The filtrate was concentrated in vacuo and the residue purified by flash chromatography (silica; 10% ethyl acetate in hexanes) to give the title compound as a yellow oil. PMR ($CDCl_3$): & 0.20 (9H, s), 1.20 (6H, s), 1.57-1.63 (2H, m), 3.16-3.25 (2H, m), 4.02 (1H, broad s), 6.24 (1H, d, J-8.2 Hz), 7.00 (1H, dd, J-8.2 Hz, 1.8 Hz), 7.26 (1H, d, J-1.8 Hz).

4,4-Dimethyl-6-ethynyl-1,2,3,4-tetrahydroquinoline (**Compound 6**).

To a solution of 569 mg (2.21 mmol) of 4,4-dimethyl-6-trimethylsilylethynyl-1,2,3,4-tetrahydroquinoline (**Compound**

95) in 3 ml of isopropanol was added, under argon, 1 ml of 1N aqueous KOH solution. The reaction mixture was stirred at room temperature for 36 h and the isopropanol was removed under vacuum. The residue was extracted with ether and the ether extract was washed successively with water and saturated NaCl solution and then dried ($MgSO_4$). The solvent was removed in vacuo and the residue was purified by flash chromatography (silica; 10% ethyl acetate in hexanes) to give the title compound as a brown oil. PMR ($CDCl_3$): & 1.26 (6H, s), 1.65-1.72 (2H, m), 2.96 (1H, s), 3.27-3.34 (2H, m), 6.34 (1H, d, J~8.3 Hz), 7.08 (1H, dd, J~8.3 Hz, 1.6 Hz), 7.33 (1H, d, J~1.6 Hz).

Ethyl-4-iodobenzoate (Compound 97)

To a suspension of 10 g (40.32 mmol) of 4-iodobenzoic acid in 100 ml absolute ethanol was added 2 ml thionyl chloride and the mixture was then heated at reflux for 3 hours. Solvent was removed in vacuo and the residue was dissolved in 100 ml ether. The ether solution was washed with saturated $NaHCO_3$ and saturated NaCl solutions and dried ($MgSO_4$). Solvent was then removed in vacuo an the residue kugelrohr distilled (100 degrees C; 0.55 mm) to give the title compound as a colorless oil, PMR ($CDCl_3$): & 1.42 (3H, t, J~7 Hz), 4,4 (2H, q, J~7 Hz), 7.8 (4H).

In the same manner, but substituting for 4-iodobenzoic acid the appropriate acid, the following compounds can be

prepared:

ethyl 4-iodophenylacetate;

ethyl 3-(4-iodophenyl)propionate;

ethyl 4-(4-iodophenyl)butanoate; and

ethyl 5-(4-iodophenyl)pentanoate.

Ethyl 6-chloronicotinate (**Compound 98**)

A mixture of 15.75 g (0.1 mol) 6-chloronicotinic acid, 6.9 g (0.15 mol) ethanol, 22.7 g (0.11 mol) dicyclohexylcarbodiimide and 3.7 g dimethylaminopyridine in 200 ml methylene chloride was heated at reflux for 2 hours. The mixture was allowed to cool, solvent removed in vacuo and the residue subjected to flash chromatography to give the title compound as a low-melting white solid. PMR ($CDCl_3$): & 1.44 (3H, t, J-6.2 Hz) 4.44 (2H, q, J-4.4 Hz), 7.44 (1H, d, J-8.1 Hz), 8.27 (1H, dd, J-8.1 Hz, 3 Hz), 9.02 (1H, d, J-3 Hz).

The foregoing procedure may be used to esterify any of the other halo-substituted acids employed in the making of these compounds such as:

ethyl 2-(2-chloropyrid-5-yl)acetate;

ethyl 5-(2-chloropyrid-5-yl)pentanoate;

ethyl 2-(2-iodofur-5-yl)acetate;

ethyl 5-(2-iodofur-5-yl)pentanoate;

ethyl 2-(2-iodothien-5-yl)acetate;

ethyl 5-(2-iodothien-5-yl)pentanoate;

ethyl 2-(3-chloropyridazin-6-yl)acetate;

ethyl 5-(3-chloropyridazin-6-yl)pentanoate; and the corresponding chloro, or other halo, substituted pyrimidinyl or pyrazinyl analogues of such esters.

Ethyl 6-[4(4,4-dimethylthiochroman-6-yl)-ethynyl]nicotinate (Compound 99)

Reaction vessels used in this procedure were flame dried under vacuum and all operations carried out in an oxygen-free, argon or nitrogen atmosphere. To a solution of 465.7 mg (2.3019 mmol) of 4,4-dimethyl-6-ethynyl-thiochroman (Compound 1) in 4 ml of dry tetrahydrofuran at 0 degrees C was added dropwise 1.5 ml of 1.6 M (2.4 mmol) n-butyllithium in hexane. This was stirred at 0 degrees C for 10 minutes and at room temperature for 10 minutes, cooled again to 0 degrees C and then treated with a solution of 330 mg (2.4215 mm) of fused $ZnCl_2$ in 4 ml dry tetrahydrofuran using a double ended needle. Thereafter the solution was stirred at 0 degrees C for 30 minutes, then at room temperature for 10 minutes. A solution of 426.3 mg (2.2967 mmol) of ethyl 6-chloronicotinate (Compound 98) in 4 ml dry tetrahydrofuran was transferred by double ended needle into a suspension of 430 mg (0.37 mmol) of tetrakistriphenylphosphine palladium in 4 ml dry tetrahydrofuran and stirred at room temperature for 10 minutes, then treated by double ended needle with the solution of the alkynyl zinc prepared above. This mixture was stirred

at room temperature for 18 hours, then quenched with 100 ml water. Product was recovered by extraction with 3x75 ml ether. Ether fractions were combined and washed with saturated NaCl solutions and dried ($MgSO_4$). Solvent was removed in vacuo and the residue purified by flash chromatography (silica; 5% ethyl acetate in hexane) followed by HPLC (Whatman Partisil M-9 10/50; 4% ethyl acetate in hexane) to give the title compound as a white solid.

PMR ($CDCl_3$): δ 1.36 (6H, s), 1.45 (3H, t, J-7 Hz), 1.96-2.00 (2H, m), 3.05-3.09 (2H, m), 4.45 (2H, q, J-7 Hz), 7.11 (1H, d, J-8.4 Hz), 7.29 (1H, dd, J-8.4 Hz, 2.2 Hz), 7.59 (1H, d, J-7.8 Hz), 7.66 (1H, d, J-2.2 Hz), 8.30 (1H, dd, J-7.8 Hz, 2.3 Hz), 9.22 (1H, d, J-2.3 Hz).

Alternative synthesis: Ethyl 6-[(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate (**Compound 99**) was also prepared as follows.

A solution of 15.4 g (76.2 mmol) of 4,4-dimethyl-6-ethynyl-thiochroman (**Compound 1**) and 14.0 g (75.5 mmol) of ethyl-6-chloronicotinate (**Compound 98**) in 35 ml of freshly distilled triethylamine was degassed and then treated under nitrogen with a finely powdered mixture of 1 g (5.25 mmol) of high purity cuprous iodide and 2 g (2.85 mmol) of bis(triphenylphosphine) palladium (II) chloride. The mixture was heated under nitrogen at 55 degrees C for 20 hours and then cooled to room temperature. The triethylamine was then

removed under vacuum and the residue was diluted with 200 ml of a 1:4 mixture of ethyl acetate and hexanes. This mixture was filtered through silica and the filtrate concentrated in vacuo. The resultant residue was purified by flash chromatography (silica gel; 15% ethyl acetate in hexanes) and recrystallized from a mixture of ethyl acetate and hexanes to give the title compound as a pale yellow solid.

Ethyl 6-[(4,4,7-trimethylthichroman-6-yl)ethynyl]nicotinate (Compound 100)

A mixture of 86 mg (0.4 mmol) of 4,4,7-trimethyl-6-ethynyl-thiochroman (Compound 2), 85 mg (0.46 mmol) of ethyl 6-chloronicotinate (Compound 98) and 0.8 ml of triethylamine was degassed under nitrogen and then treated with a mixture of 10 mg (0.05 mmol) of cuprous iodide and 20 mg (0.03 mmol) of bis(triphenylphosphine) palladium (II) chloride. The reaction mixture was heated at 55 degrees C under a nitrogen atmosphere for 18 hours. The mixture was then extracted with 1.5 ml of 40% ethyl acetate in hexanes and purified by flash chromatography (silica; 10% ethyl acetate in hexanes) to give the title compound as a yellow solid.

PMR ($CDCl_3$): & 1.32 (6H, s), 1.43 (3H, t, J-7.2 Hz), 2.44 (3H, s), 3.01-3.05 (2H, m), 4.42 (2H, q, J-7.2 Hz), 6.98 (1H, s), 7.54-7.63 (2H, m), 8.27 (1H, dd, J-8.3 Hz, 2.3 Hz), 9.21 (1H, d, J-2.3 Hz).

Ethyl 6-[(4,4-dimethylchroman-6-yl)ethynyl]nicotinate

(**Compound 101**)

Reaction vessels used in this procedure were flame dried under vacuum and all operations were carried out in an oxygen-free, argon or nitrogen atmosphere. To a solution of 509.4 mg (2.74 mmol) of 4,4-dimethyl-6-ethynylchroman (**Compound 4**) in 4 ml of dry tetrahydrofuran at 0 degrees C was added dropwise 1.72 ml of 1.6 M (2.75 mmol) of n-butyl lithium in hexane. Stirring was commenced at 0 degrees C for 30 minutes and at room temperature for 15 minutes, after which the solution was cooled again to 0 degrees C and then treated with a solution of 380 mg (2.79 mmol) of fused zinc chloride in 5 ml of dry tetrahydrofuran using a double ended needle. The resulting solution was stirred at 0 degrees C for 1 hour and then at room temperature for 15 minutes. A solution of 628.6 mg (2.74 mmol) of ethyl 6-chloronicotinate (**Compound 98**) in 4 ml of dry tetrahydrofuran was transferred by double ended needle into a suspension of 380 mg (0.33 mmol) of tetrakistriphenylphosphine palladium in 5 ml dry tetrahydrofuran and the mixture was stirred at room temperature for 15 minutes and then treated by double ended needle with the solution of alkynyl zinc prepared above. The mixture was stirred at room temperature for 20 hours and then quenched with ice and 30 ml of 3N hydrogen chloride. The mixture was extracted with 3x75 ml ether and ether extracts were combined and washed successively with saturated $NaHCO_3$ and saturated NaCl and then dried ($MgSO_4$).

Solvent was removed in vacuo and the residue further purified by flash chromatography (silica; 10% ethyl acetate in hexane) to give the title compound as a yellow solid.

PMR ($CDCl_3$): δ 1.36 (6H, s), 1.44 (3H, t, J-7.1 Hz), 1.83-1.87 (2H, m), 4.22-4.26 (2H, m), 4.44 (2H, q, J-7.1 Hz), 6.80 (1H, d, J-7.6 Hz), 7.35 (1H, d, J-8.9 Hz), 7.58 (1H, d, J-7.6 Hz), 7.60 (1H, m), 8.28 (1H, d, J-8.9 Hz), 9.21 (1H, s).

Ethyl 6-[(2,2,4,4-tetramethyl-thiochroman-6-yl)-ethynyl]nicotinate (**Compound 102**)

A solution of 232 mg (1.01 mmol) of 2,2,4,4-tetramethyl-6-ethynylthiochroman (**Compound 3**) and 190 mg (1.03 mmol) of ethyl 6-chloro-nicotinate (**Compound 98**) in 2 ml of triethylamine was placed in a heavy-walled glass tube, degassed, placed under argon and then treated with a powdered mixture of 53 mg (0.28 mmol) of cuprous iodide and 84 mg (0.12 mmol) of bis(triphenylphosphine) palladium (II) chloride. The mixture was degassed again, placed under argon and the tube was sealed. The reaction mixture was heated at 55 degrees C for 60 h and then cooled to room temperature. The mixture was treated with water and ether and the organic layer was separated. The aqueous layer was extracted with ether. The organic layers were then combined and washed with saturated NaCl solution and then dried ($MgSO_4$). The solvent was removed in vacuo and the resultant residue was purified by flash chromatograhy (silica; 10% ethyl acetate in hexanes) to give

the title compound as a dark yellow oil. PMR ($CDCl_3$): & 1.32-1.43 (15H, m), 1.92 (2H, s), 4.38 (2H, q, J-7.1 Hz), 7.28 (1H, dd, J-8.3 Hz, 1.8 Hz), 7.32-7.38 (2H, m), 7.53 (1H, d, J-8.3 Hz), 8.24 (1H, dd, J-8.2 Hz, 2.2 Hz), 9.16 (1H, d, J-2.2 Hz). MS exact mass, m/e 379.1594 (calcd. for C_{23} H_{25} NO_2S, 379.1606).

Ethyl 6-[(2,2,4,4-tetramethylchroman-6-yl)-ethynyl]nicotinate (**Compound 103**)

A solution of 233 mg (1.09 mmol) of 2,2,4,4-tetramethyl-6-ethynylchroman (**Compound 5**) and 209 mg (1.09 mmol) of ethyl 6-chloronicotinate (**Compound 98**) in 1 ml of triethylamine was degassed and then treated under argon with a powdered mixture of 50 mg (0.26 mmol) of cuprous iodide and 100 mg (0.14 mmol) of bis(triphenylphosphine) palladium (II) chloride. The reaction mixture was heated under argon at 55 degrees C for 80 h and then cooled to room temperature. The triethylamine was then removed under vacuum and the residue purified by flash chromatography (silica; 5% ethyl acetate in hexanes) to give the title compound as a yellow oil. PMR ($CDCl_3$): & 1.36 (12H, s), 1.42 (3H, t, J-7.2 Hz), 1.85 (2H, s), 4.37 (2H, q, J-7.2 Hz), 6.79 (1H, d, J-.4 Hz), 7.34 (1H, dd, J-8.4 Hz, 2.1 Hz), 7.56 (1H, d, J-8.7 Hz), 7.60 (1H, d, J-2.1 Hz), 8.27 (1H, dd, J-8.7 Hz, 2.4 Hz), 9.19 (1H, d, J-2.4 Hz). MS exact masss, m/e 363.1837 (calcd. for $C_{23}H_{25}O_3N$, 363.1834).

Ethyl-6-[(2,2,4,4,7-pentamethyl-6-chromanyl)-ethynyl] nicotinate (**Compound 104**)

A solution of 300 mg (1.316 mmol) of 2,2,4,4,7-pentamethyl-6-ethynyl-chroman (**Compound 9**) and 245.6 mg (1.3276 mmol) of ethyl 6-chloro-nicotinate (**Compound 98**) in 2 ml of triethylamine was placed in a pressure tube and a stream of nitrogen was bubbled through the solution for 15 min. The tube was then flushed with argon and a finely ground mixture of 100 mg (0.1425 mmol) of bis (triphenylphosphine) palladium (II) chloride and 50 mg (0.2625 mmol) of cuprous iodide was added to the solution. The pressure tube was then sealed and the reaction mixture heated at 60 degrees C for 72 h. The mixture was cooled to room temperature and the triethylamine removed under vacuum. The residue was purified by flash chromatography (silica; 10% ethyl acetate in hexane) to give the title compound as a yellow solid. PMR ($CDCl_3$): & 1.37 (6H, s), 1.38 (6H, s), 1.44 (3H, t, J-7.2 Hz), 1.85 (2H, s), 2.49 (3H, s), 4.43 (2H, q, J-7.2 Hz), 6.70 (1H, s), 7.55 - 7.61 (2H, m), 8.28 (1H, dd, J-8.2 Hz, 2.1 Hz), 9.22 (1H, d, J-2.1 Hz). MS exact mass, m/e 377.1982 (calcd. for $C_{24}H_{27}O_3N$, 377.1991).

Ethyl 4-[(2,2,4,4,7-pentamethylchroman-6- yl)-ethynyl] benzoate (**Compound 105**)

Nitrogen was bubbled for 15 min through a solution of 200 mg. (0.877 mmol) of 2,2,4,4,7-pentamethyl-6-ethynylchroman

(**Compound 9**) and 245.3 mg (0.888 mmol) of ethyl 4-iodobenzoate (**Compound 97**) in 2 ml of triethylamine. The mixture was then placed under an argon atmosphere and treated with a finely ground mixture of 50 mg (0.2625 mmol) of cuprous iodide and 100 mg (0.1425 mmol) of bis(triphenylphosphine) palladium (II) chloride. The reaction vessel was then fitted with a reflux condenser and the mixture was heated at 55 degrees C under argon for 72 hours. The triethylamine was then removed under vacuum and the residue purified by flash chromatography (silica, 5% ethyl acetate in hexane) to give the title compound as a yellow oil. PMR ($CDCl_3$) : & 1.32 (12H, s), 1.37 (3H, t, J-7.0 Hz), 1.80 (2H, s) 2.40 (3H, s), 4.36 (2H, q, J-7.0 Hz), 6.66 (1H, s, 7.42 (1H, s), 7.54 (2H, d, J-8.6 Hz), 7.99 (2H, d, J-8.6 Hz). MS exact mass, m/e 376.2 038 (calcd. for $C_{25}H_{28}O_3$, 376.2038).

Ethyl 4-[(2,2,4,4-tetramethylchroman-6-yl-ethynyl]benzoate **Compound 106**)

A solution of 233 mg (1.088 mmol) of 2,2,4,4-tetramethyl-6-ethynyl-chroman (**Compound 9**) and 308 mg (1.087 mmol) of ethyl 4-iodo-benzoate (**Compound 97**) in 1 ml of triethylamine was placed in a heavy-walled tube and degassed under argon. The mixture was treated with a finely ground mixture of 50 mg (0.263 mmol) of cuprous iodide and 100 mg (0.142 mmol) of bis (triphenylphosphine) palladium (II) chloride and the tube was then sealed. The reaction mixture was then heated at 55

degrees C for 48 hours. The triethylamine was removed in vacuo and the residue was purified by flash chromatography (silica, 5% ethyl acetate in hexans) to give the title compound as yellow oil. PMR ($CDCl_3$) : & 1.33 (6H, s), 1.34 (6H, s), 1.37 (3H, t, J-7.2 Hz), 1.83 (2H, s), 4.35 (2H, q, J-7.2 Hz), 6.75 (1H, d, J-8.4 Hz), 7.24 (1H, dd, J-8.4 Hz, 2.1 Hz), 7.46 (1H, d, J-2.1 Hz), 7.54 (2H, d, J-8.1 Hz), 7.99 (2H, d, J-8.1 Hz) MS exact mass, m/e 362.1880 (calcd. for $C_{24}H_{26}O_3$, 362.1881).

Ethyl 4-[(2,2,4,4-tetramethyl-thiochroman-6-yl)-ethynyl] benzoate (Compound 107)

A solution of 110.7 mg (o.481 mmol) of 2,2,4,4-tetramethyl-6-ethynylthiochroman (Compound 3) and 142.3 mg (0.516 mmol) of ethyl 4-iodobenzoate (Compound 97) in 2 ml of triethylamine was placed in a heavy walled glass tube and degassed under argon. The mixture was then treated with a finely ground mixture of 42 mg (0.221 mmol) of cuprous iodide and 63 mg (0.09 mmol) of bis (triphenylphosphine) palladium (II) chloride. The reaction mixture was degassed under argon again and the tube was sealed. The mixture was stirred at room temperature for 40 hours. The triethylamine was removed under vacuum and the residue purified by flash chromatography (silica, 3% ethyl acetate in hexanes) to give the title compound as a pale yellow solid. PMR ($CDCl_3$) : & 1.37-1.42 (15H, m), 1.96 (2H, s), 4.38 (2H, q, J-7.0 Hz), 7.25 (1H, dd, J-8.2

Hz, 1.8 Hz), 7.33 (1H, d, J-1.8 Hz), 7.37 (1H, d, J-8.2 Hz), 7.65 (2H, d, J-8.6 Hz), 8.01 (2H, d, J-8.6 Hz). MS exact mass, m/e 378.1636 (calcd. for $C_{24}H_{26}O_2S$, 378.165.3).

Ethyl 4-(4,4-dimethyl-1,2,3,4-tetrahydroquinolin-6-yl)-ethynyl]benzoate (**Compound 108**)

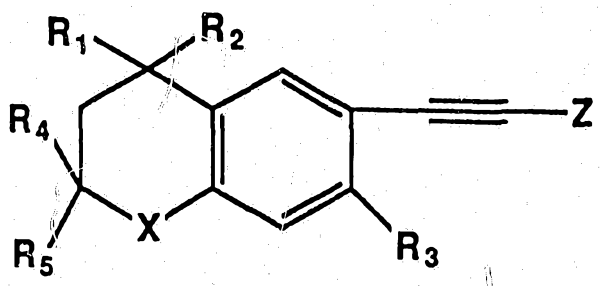
Nitrogen gas was bubbled for 15 minutes through a solution of 145mg (0.7838 mmol) of 4,4-dimethyl-6-ethynyl-1,2,3,4-tetrahydroquinoline (**Compound 6**) and 220 mg (0.797 mmol) of ethyl 4-iodobenzoate (**Compound 97**) in 2 ml of triethylamine placed in a heavy-walled tube. The solution was then treated with a finely ground mixture of 31 mg (0.163 mmol) of cuprous iodide and 62 mg (0.088 mmol) of bis (triphenylphosphine) palladium (II) chloride. The tube was then flushed with argon and sealed. The reaction mixture was heated at 55 degrees C for 72 h. The mixture was allowed to cool and then treated with 1 ml of triethylamine. The mixture was further treated with a ground mixture of 15 mg (0.079 mmol) cuprous iodide and 30 mg (0.003 mmol) of bis(triphenylphosphine) palladium (II) chloride. The tube was flushed with argon and sealed and the mixture was heated at 55 degrees C for a further 24 h. The mixture was cooled and treated with ether and water and the organic layer was separated. The aqueous layer was extracted with ether and the combined organic extracts were washed successively with water and saturated NaCl solution and then dried ($MgSO_4$). The

solvent was removed in-vacuo and the residue was purified by flash chromatography (silica; 10% ethyl acetate in hexane) to give the title compound as a yellow oil. PMR ($CDCl_3$) : δ 1.31 (6H, s), 1.40 (3H, t, J-7.2 Hz), 1.68-1.78 (2H, m), 3.32-3.40 (2H, m), 4.17 (1H, broad s), 4.38 (2H, q, J-7.2 Hz), 6.41 (1H, d, J-8.2 Hz), 7.15 (1H, dd, J-8.2 Hz, 1.9 Hz), 7.39 (1H, d, J-1.9 Hz), 7.54 (2H, d, J-8.4 Hz), 8.00 (2H, d, J-8.4 Hz). MS exact mass, m/e 333.1729 (calcd. for $C_{22}H_{23}O_2N$, 333.1728).

Several modifications of the above described compounds and processes, and application of the herein disclosed processes to numerous compounds beyond the specific examples set forth above, may be practiced by those skilled in the art without departing from the scope and spirit of the present invention. Therefore, the scope of the present invention should be interpreted solely from the following claims, as such claims are read in light of the present disclosure.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A process of reacting compounds of the formula



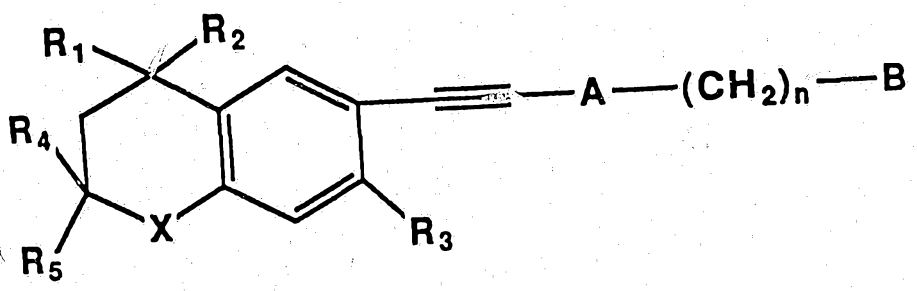
wherein R_1, R_2, R_3, R_4 and R_5 are hydrogen or lower alkyl groups having 1 to 6 carbons and wherein R_1, R_2, R_3, R_4 and R_5 may be identical or different from one another; X is S , O or NR', wherein R' is hydrogen or lower alkyl; Z is hydrogen, or a metal ion, or a metal ion bound to an anion, said metal ion forming a salt with the ethynyl function of the compound of the formula; with compounds of the formula

$$X' - A - (CH_2)_n - B$$

wherein X' is a leaving group, A is phenyl or heteroaryl selected from the group consisting of pyridinyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl and oxazolyl, n is an integer between 0 to 5, and B is H, -COOH is a pharmaceutically acceptable salt, ester or amide thereof, $-CH_2OH$ or an ether or ester derivative, or -CHO or an acetal derivative, or $-COR_i$ or a ketal derivative where R_i is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons,

AUSTRALIAN PATENT OFFICE

in the presence of one or more catalysts, to provide compounds of the formula



wherein X, R_1, R_2, R_3, R_4, R_5, A, n and B are defined as above.

2. The process of Claim 1 wherein Z is H and the catalyst comprises cuprous iodide and $Pd(PQ_3)_2$ Cl_2 where Q is phenyl.

3. The process of Claim 2 wherein Z is $ZnCl^+$ and the catslyst comprises Pd $(PQ_3)_4$ where Q is phenyl.

4. The process of Claim 1 wherein A is phenyl, pyridyl, or thienyl.

5. The process of Claim 1 wherein B is an esterified carboxylic acid group.

6. The process of Claim 1 wherein n is zero.

7. The process of Claim 1 wherein ~~R_4 and R_5 both are hydrogen and~~ R_1 and R_2 both are lower alkyl.

8. The process of Claim 1 wherein R_4 and R_5 both are lower alkyl.

9. The process of Claim 1 wherein R_1, R_2, R_4 and R_5 all

AUSTRALIAN PATENT OFFICE

are lower alkyl.

10. The process of Claim 1 wherein A is phenyl and X is S, O, or NH.

11. The process of Claim 10 wherein R_1 and R_2 both are methyl and R_4 and R_5 both are hydrogen.

12. The process of Claim 11 wherein n is zero.

13. The process of Claim 12 wherein B is an esterified carboxylic acid group.

14. The process of Claim 13 wherein R_3 is hydrogen or methyl.

15. The process of Claim 10 wherein R_1, R_2, R_4 and R_5 all are methyl.

16. The process of Claim 15 wherein n is zero.

17. The process of Claim 16 wherein B is an esterified carboxylic acid group.

18. The process of Claim 17 wherein R_3 is hydrogen or methyl.

19. The process of Claim 1 wherein A is pyridyl and X is S, O or NH.

20. The process of Claim 19 wherein R_1 and R_2 both are methyl and R_4 and R_5 both are hydrogen.

21. The process of Claim 20 wherein n is zero.

22. The process of Claim 21 wherein B is an esterified carboxylic acid group.

23. The process of Claim 22 wherein R_3 is hydrogen or

methyl.

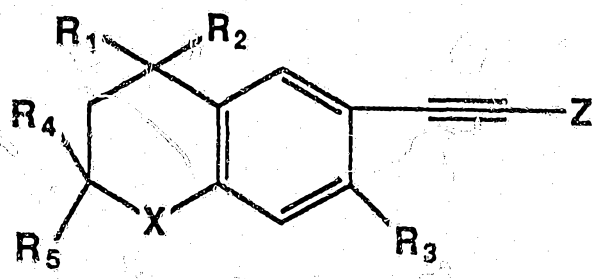
24. The process of Claim 19 wherein R_1, R_2, R_4 and R_5 all are methyl.

25. The process of Claim 24 wherein n is zero.

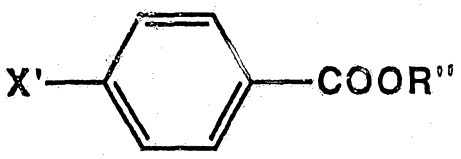
26. The process of Claim 25 wherein B is an esterified carloxylic acid group.

27. The process of Claim 26 wherein R_3 is hydrogen or methyl.

28. A process of reacting compounds of the formula

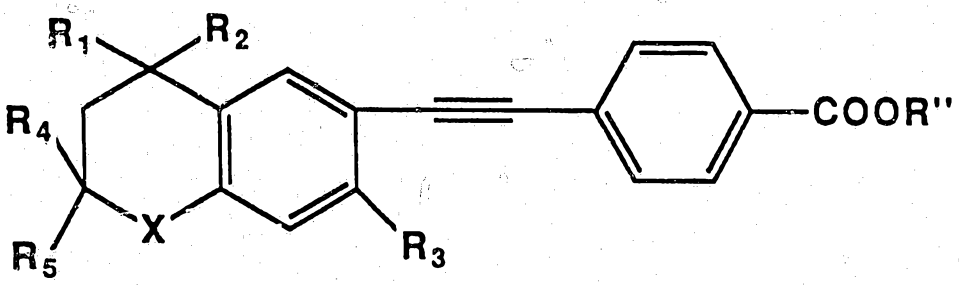


wherein X is S, O or NR' where R' is lower alkyl, R_1, R_2, R_4 and R_5 are hydrogen or methyl and R_3 is lower alkyl, Z is hydrogen or a metal ion, with compounds of the formula



where X' is Cl, Br or I, and R" is an alkyl or cycloalkyl group, in the presence of one or more catalysts, to obtain compounds of the formula

AUSTRALIAN PATENT OFFICE



29. The process of Claim 28 where Z is H and the catalyst comprises cuprous iodide and $Pd(PQ_3)_2Cl_2$ where Q is phenyl.

30. The process of Claim 28 where Z is $ZnCl^+$ and the catalyst comprises $Pd(PQ_3)_4$ where Q is phenyl.

31. The process of Claim 28 where X is S.

32. The process of Claim 28 where X is O.

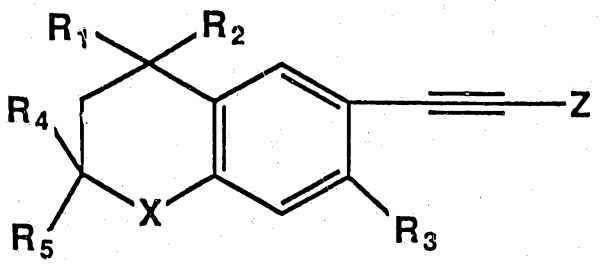
33. The process of Claim 28 where X is NH.

34. The process of Claim 28 wherein R_1 and R_2 both are methyl ~~and R_4 and R_5 both are H.~~

35. The process of Claim 28 wherein R_1, R_2, R_4 and R_5 all are methyl.

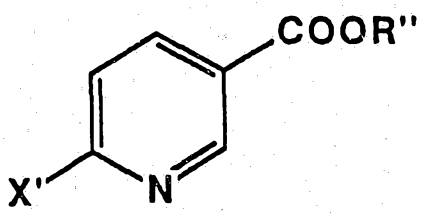
36. The process of Claim 28 wherein R" is C_2H_5.

37. A process of reacting compounds of the formula

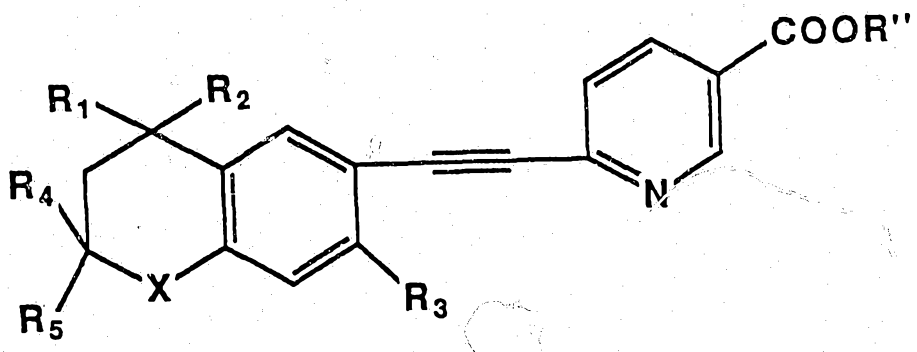


AUSTRALIA D28 PATENT OFFICE

wherein X is S, O or NR' where R' is H or lower alkyl, R_1, R_2, R_4 and R_5 are hydrogen or methyl but R_4+R_5 are not both hydrogen and R_3 is lower alkyl, Z is hydrogen or metal ion, with compounds of the formula



where X' is Cl, Br or I, and R'' is an alkyl or cycloalkyl group, in the presence of one or more catalysts, to obtain compounds of the formula



38. The process of Claim 37 where Z is H and the catalyst comprises cuprous iodide and $Pd(PQ_3)_2Cl_2$ where Q is phenyl.

39. The process of Claim 37 where Z is $ZnCl^+$ and the catalyst comprises $Pd(PQ_3)_4$ where Q is phenyl.

40. The process of Claim 37 where X is S.

41. The process of Claim 37 where X is O.

42. The process of Claim 37 where X is NH.

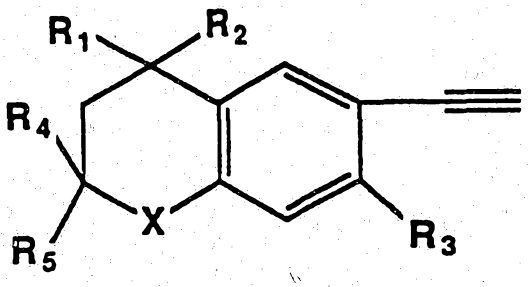
AUSTRALIAN PATENT OFFICE

43. The process of Claim 37 wherein R_1 and R_2 both are methyl.

44. The process of Claim 37 wherein R_1, R_2, R_4 and R_5 all are methyl.

45. The process of Claim 37 wherein R'' is C_2H_5.

46. Compounds of the formula,



wherein

X is S, O or NR' where R' is H or lower alkyl and R_1, R_2, R_3, R_4 and R_5 are hydrogen or lower alkyl having 1 to 6 carbons and at least one of the R_4 and R_5 groups is not hydrogen or salts of the compounds of the formula defined herein.

47. Compounds of Claim 46 wherein X = S.

48. Compounds of Claim 47 wherein R_1 and R_2 both are methyl.

49. The compound of Claim 48 wherein R_3 is methyl.

50. The compound of Claim 48 wherein R_3 is hydrogen.

51. Compounds of Claim 47 wherein R_4 and R_5 both are methyl.

52. Compounds of Claim 51 wherein R_1 and R_2 both are methyl.

53. The compounds of Claim 52 wherein R_3 is methyl.

54. The compound of Claim 52 wherein R_3 is hydrogen.

55. Compounds of Claim 46 wherein X = O.

56. Compounds of Claim 55 wherein R_1 and R_2 both are methyl.

57. The compound of Claim 56 wherein R_3 is methyl.

58. The compound of Claim 56 wherein R_3 is hydrogen.

59. Compounds of Claim 55 wherein R_4 and R_5 both are methyl.

60. Compounds of Claim 59 wherein R_1 and R_2 both are methyl.

61. The compound of Claim 60 wherein R_3 is methyl.

62. The compound of Claim 60 wherein R_3 is hydrogen.

63. Compounds of Claim 46 wherein X = NH.

64. Compounds of Claim 63 wherein R_1 and R_2 both are methyl.

AUSTRALIAN PATENT OFFICE

65. The compound of Claim 64 wherein R_3 is methyl.

66. The compound of Claim 64 wherein R_3 is hydrogen.

67. Compounds of Claim 63 wherein R_4 and R_5 both are methyl.

68. Compounds of Claim 67 wherein R_1 and R_2 both are methyl.

69. The compound of Claim 68 wherein R_3 is methyl.

70. The compound of Claim 68 wherein R_3 is hydrogen.

71. A process of claim 1 or claim 28 or claim 37, or compounds of claim 46 substantially as hereinbefore described with reference to the Examples.

DATED this 14th day of April 1993

Allergan, Inc.

By Its Patent Attorneys

DAVIES COLLISON CAVE

AUSTRALIAN PATENT OFFICE