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CHROMANS AND THIOCHROMANS WITH HETEROARYLETHYNYL SUBSTITUENTS AT THE 7-POSITION HAVING RETINOID-LIKE BIOLOGICAL ACTIVITY

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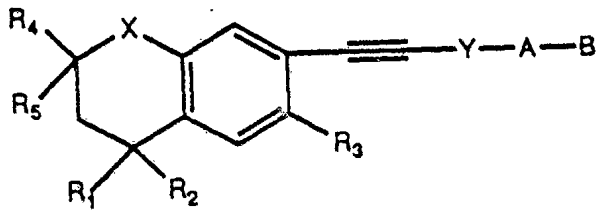
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(57) Claim

1. A compound of the formula



where X is S or O;

R_1-R_5 independently are hydrogen or lower alkyl;

Y is a heteroaryl group or a lower alkyl substituted heteroaryl group where heteroaryl is selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, ~~pirimidinyl~~ pyrimidinyl, pyrazinyl, thiazolyl and oxazolyl;

A is lower branched chain alkyl having 2 to 6 carbons, cycloalkyl having 3 to 6 carbons, alkenyl having 2 to 6 carbons and 1 or 2 double bonds, alkynyl having 2 to 6 carbons and 1 or 2 triple bonds, $(CH_2)_n$

.../2

and where n is an integer from 0 - 5;

B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, $COONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11}, CH_2OCOR_{11}, CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, -COR", $CR"(OR_{12})_2$, or $CR"OR_{13}O$, where R" is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent alkyl radical of 2 - 5 carbons.

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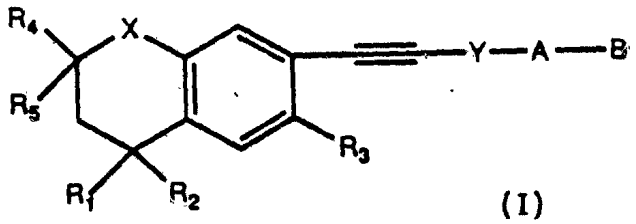
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(I)

(57) Abstract

Novel compounds of formula (I), where X is S, O; R_1-R_5 are hydrogen or lower alkyl; R_6 is lower alkyl, lower alkenyl, lower cycloalkyl having 1 to 6 carbons, or halogen; A is lower branched chain alkyl having 2 to 6 carbons, cycloalkyl having 3 to 6 carbons, alkenyl having 2 to 6 carbons and 1 or 2 double bonds, alkynyl having 2 to 6 carbons and 1 or 2 triple bonds, $(CH_2)_n$ where n is 0-5; and B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, $COONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11}, CH_2OCOR_{11}, CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, -COR", $CR"(OR_{12})_2$, or $CR"OR_{13}O$, where R" is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is a divalent alkyl radical of 2-5 carbons, have retinoic acid like activity.

CHROMANS AND THIOCHROMANS WITH HETEROARYLETHYNYL SUBSTITUENTS AT THE 7-POSITION HAVING RETINOID-LIKE BIOLOGICAL ACTIVITY

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention is directed to novel compounds which have retinoic acid-like biological activity. More specifically, the present invention relates to compounds having an ethynyl heteroaromatic acid portion and a second portion which is a 2-and/or 4-substituted thiochromanyl, or chromanyl group. The acid function may also be converted to an alcohol, aldehyde or ketone, or derivatives thereof, or may be reduced to $-CH_3$.

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 6-chromanyl, 6-thiochromanyl or 6-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 6-chromanyl, 6-thiochromanyl or 6-tetrahydroquinolinyl group. The disubstituted acetylene compounds described and claimed in the aforesaid co-pending applications have significant retinoic acid-like activity.

A published European patent application of the present applicant (Publication No. 0284288, published on September 28, 1988) describes compounds having retinoic acid like activity which are 4,4 disubstituted chroman-6-yl, 4,4 disubstituted - thiochroman-6-yl acetylenes also substituted by a substituted heteroaryl group.

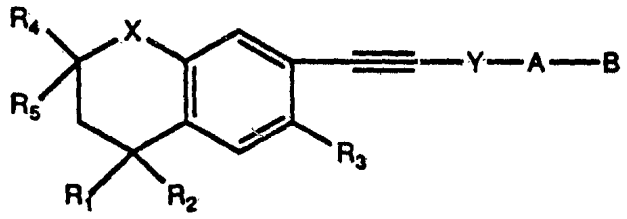
Retinoic acid-like activity has been generally recognized in the art to be associated with useful biological activity. Specifically, compounds having retinoic acid-like activity are useful as regulators of cell proliferation and differentiation, and particularly as agents for treating dermatoses, such as acne, Darier's disease, psoriasis, ichthyosis, 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 and preventing 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 heteroaromatic 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 Eiichi 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

This invention covers compounds of **Formula 1**



Formula 1

wherein **X** is S, or O; R_1-R_5 are hydrogen or lower alkyl; **Y** is a heteroaryl group or a lower alkyl substituted heteroaryl group where heteroaryl is selected from a group consisting of pyridyl, thienyl,

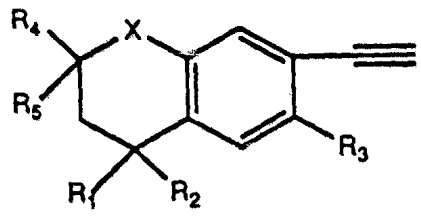
furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl and oxazolyl; A is lower branched chain alkyl having 3 to 6 carbons, cycloalkyl having 3 to 6 carbons, alkenyl having 2 to 6 carbons and 1 or 2 double bonds, alkynyl having 2 to 6 carbons and 1 or 2 triple bonds, or $(CH_2)_n$ where n is 0-5; B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11}, CH_2OCOR_{11}, CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, -COR", $CR"(OR_{12})_2$, or $CR"OR_{13}O$, where R" is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent alkyl radical of 2 - 5 carbons.

In a second aspect, this invention relates to the use of the compounds of **Formula 1** for treating dermatoses, such as acne, Darier's disease, psoriasis, icthyosis, eczema, atopic dermatitis and epithelial cancers. These compounds are also useful in the treatment of arthritic diseases and other immunological disorders (e.g. lupus erythematosus), in promoting wound healing, in treating dry eye syndrome and in reversing the effects of sun damage to skin.

This invention also relates to a pharmaceutical formulation comprising a compound of **Formula 1** in admixture with a pharmaceutically acceptable excipient.

In another aspect, this invention relates to the process for making a compound of **Formula 1** which process comprises reacting a compound of **Formula 2** with

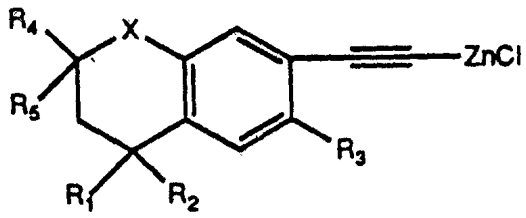
a compound of **Formula 3** in the presence of cuprous iodide and $Pd(PQ_3)_2Cl_2$ (Q is phenyl) or a similar complex





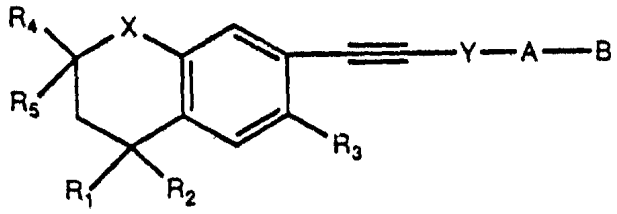
Formula 2 **Formula 3**

where R_1-R_5 are the same as described above, X' is a halogen, preferably I; and **Y** and **A** are the same as defined above; and **B** is H, or a protected acid, alcohol, aldehyde or ketone, giving the corresponding compound of **Formula 1**; or to the process of making a compound of **Formula 1** which consists of reacting a zinc salt of **Formula 4** with a compound of **Formula 3** in the presence of $Pd(PQ_3)_4$ (Q is phenyl) or a similar complex.



Formula 4

where R_1-R_5, and X, are the same as defined above, giving the corresponding compound of **Formula 1**; or homologating a compound of the **Formula 5**



Formula 5

where **A** is $(CH_2)_n$ and **n** is 0-4 to give an acid of **Formula 1**; or

converting an acid of **Formula 1** to a salt; or

forming an acid addition salt;

converting an acid of **Formula 1** to an ester; or

converting an acid of **Formula 1** to an amide; or

reducing an acid of **Formula 1** to an alcohol or aldehyde; or

converting an alcohol of **Formula 1** to an ether or ester; or

oxidizing an alcohol of **Formula 1** to an aldehyde; or

converting an aldehyde of **Formula 1** to an acetal; or

converting a ketone of **Formula 1** to a ketal.

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 **Formula 1**) is -COOH, this term covers the products derived from treatment of this function with alcohols, preferably with aliphatic alcohols having 1-6 carbons. Where the ester is derived from compounds where **B** is

$-CH_2OH$, this term covers compounds of the formula $-CH_2OOCR_{11}$ where R_{11} is any substituted or unsubstituted aliphatic, aromatic or aliphatic-aromatic group, preferably with 1-6 carbons in the aliphatic portions.

Preferred esters are derived from the saturated aliphatic alcohols or acids of ten or fewer carbon 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 and includes straight as well as branched chain alkyl groups. 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 of this invention having 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.

With reference ot the symbol Y in Formula 1, the preferred compounds of the invention are those where Y is pyridyl or thienyl.

Even more preferred compounds of this invention are those where the ethynyl group and the B group are attached to the 2 and 5 positions respectively of a pyridine ring (the 6 and 3 positions of the nicotinic acid nomenclature being equivalent to the 2/5 designation in the pyridine nomenclature) or to the 5

and 2 positions respectively of a thiophene group respectively.

With regard to the side chain (substituent) on the heteroaryl group Y, compounds are preferred where **A** is $(CH_2)_n$ and **n** is 0; and **B** is -COOH, an alkali metal salt or organic amine salt, or a lower alkyl ester thereof, or $-CH_2OH$ and the lower alkyl esters and ethers thereof, (formed with a lower alkanol) or -CHO and acetal derivatives thereof. The most preferred compounds shown in **Formula 6** are:

Ethyl 6-(4,4-dimethyl-7-thiochromanyl)-ethynyl-nicotinate (**Compound 1**, X=S, R_3=H, R_4=H, R_5=H, R_8 = C_2H_5);

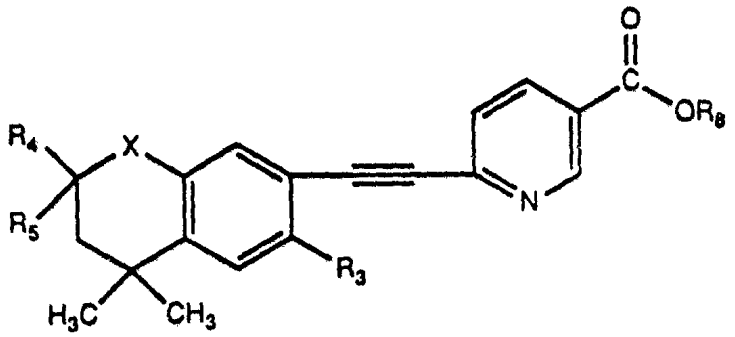
6-[(4-4-dimethyl-7-thiochromanyl)-ethynyl]-nicotinic acid (**Compound 2** , X=S, R_3=H, R_4=H, R_5=H, R_8=H);

Ethyl 6-(2,2,4,4-tetramethyl-7-thiochromanyl)-ethynyl-nicotinate (**Compound 3**, X=S, R_3=H, R_4=CH_3, R_5=CH_3, R_8=C_2H_5);

Ethyl-6-(2,2,4,4-tetramethyl-7-chromanyl)-ethynyl-nicotinate **Compound 4**, X=O, R_3=H, R_4=CH_3, R_5=CH_3, R_8=C_2H_5).

6-(2,2,4,4-tetramethyl-7-thiochromanyl)-ethynyl nicotinic acid (**Compound 49**, X=S, R_3=H, R_4=CH_3, R_5=CH_3, R_8=H).

6-(2,2,4,4-tetramethyl-7-chromanyl)-ethynyl nicotinic acid (**Compound 50**, X=O, R_3=H, R_4=CH_3, R_5=CH_3, R_8=H).



Formula 6

The compounds of this invention may be administered systemically or topically, depending on such considerations as the condition to be treated, need for site-specific treatment, quantity of drug to be administered, and similar considerations.

In the treatment of dermatoses, it will generally be preferred to administer the drug topically, though in certain cases such as treatment of severe cystic acne, oral administration may also be used. Any common topical formulation such as a solution, suspension, gel, ointment, or salve and the like may be used. Preparation of such topical formulations are well described in the art of pharmaceutical formulations as exemplified, for example, Remington's Pharmaceutical Science, Edition 17, Mack Publishing Company, Easton, Pennsylvania. For topical application, these compounds could also be administered as a powder or spray, particularly in aerosol form.

If the drug is to be administered systemically, it may be confected as a powder, pill, tablet or the like, or as a syrup or elixir for oral administration. For intravenous or intraperitoneal administration, the compound will be prepared as a solution or suspension capable of being administered by injection. In certain

cases, it may be useful to formulate these compounds in suppository form or as an extended release formulation for deposit under the skin or intermuscular injection.

Other medicaments can be added to such topical formulation for such secondary purposes as treating skin dryness, providing protection against light; other medications for treating dermatoses, preventing infection, reducing irritation, inflammation and the like.

Treatment of dermatoses or any other indications known or discovered to be susceptible to treatment by retinoic acid-like compounds will be effected by administration of the therapeutically effective dose of one or more compounds of the instant invention. A therapeutic concentration will be that concentration which effects reduction of the particular condition, or retards its expansion. In certain instances, the drug potentially could be used in a prophylactic manner to prevent onset of a particular condition. A given therapeutic concentration will vary from condition to condition and in certain instances may vary with the severity of the condition being treated and the patient's susceptibility to treatment. Accordingly, a given therapeutic concentration will be best determined at the time and place through routine experimentation. However, it is anticipated that in the treatment of, for example, acne, or other such dermatoses, that a formulation containing between 0.001 and 5 percent by weight, preferably about 0.01 to 1% will usually constitute a therapeutically effective concentration. If administered systemically, an amount between 0.01 and 100 mg per kg body weight per day, but preferably about 0.1 to 10 mg/kg, will effect a therapeutic result

in most instances.

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 retinoic 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 12-0-tetradecanoyl-phorbol-13-acetate (TPA) induces ODC activity. Retinoic 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 retinoic acid-like activity it is noted that in the assay conducted essentially in accordance with the method of Verma & Boutwell, ibid, the following examples of the preferred compounds of the present invention (Compounds 1, 2, 3 and 4) attained an 80% inhibition of TPA induced ODC activity at the following concentrations (IC_{80}):

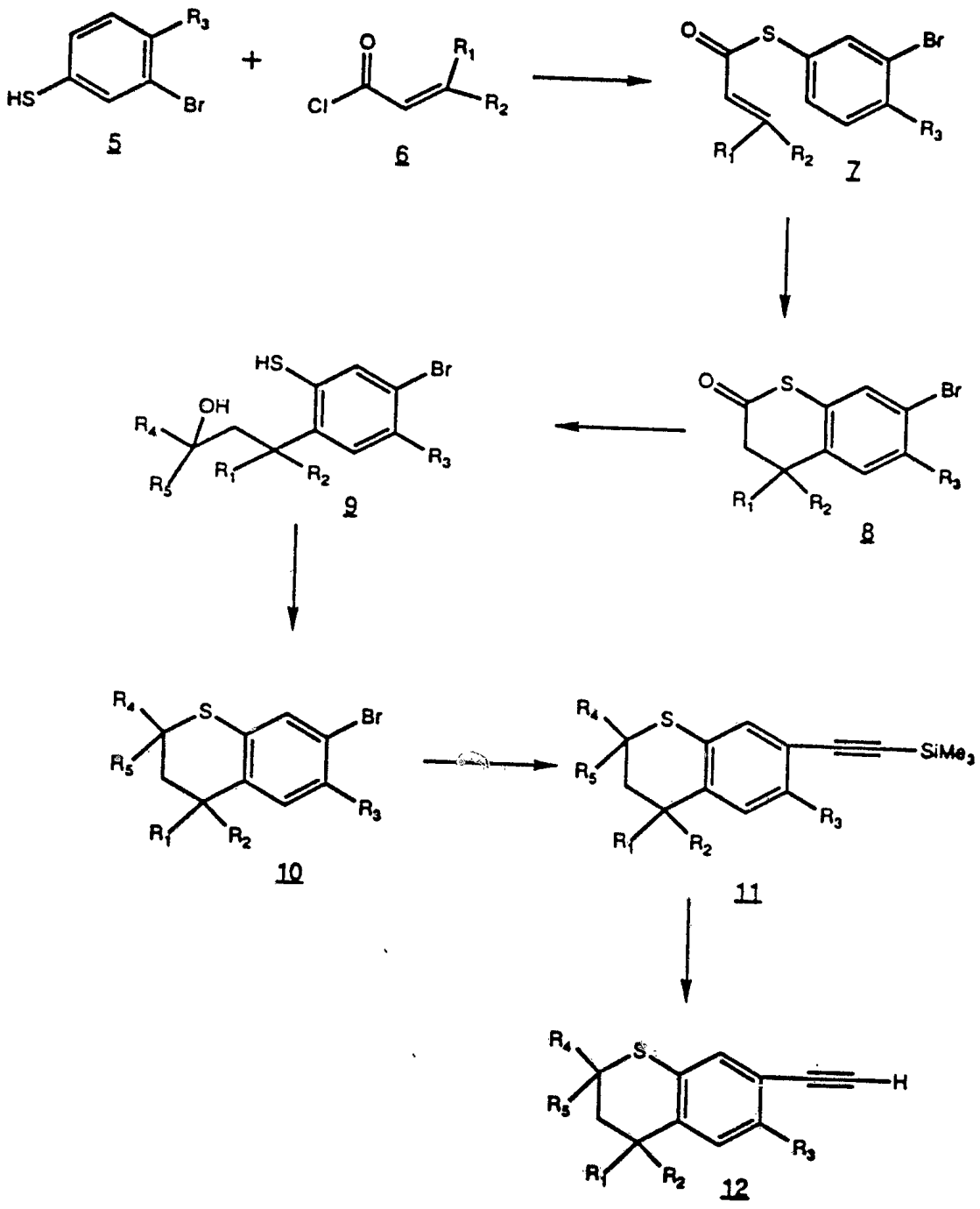
Compound	IC_{80} conc (nmols)
1	1.4
2	14.6
3	2.44

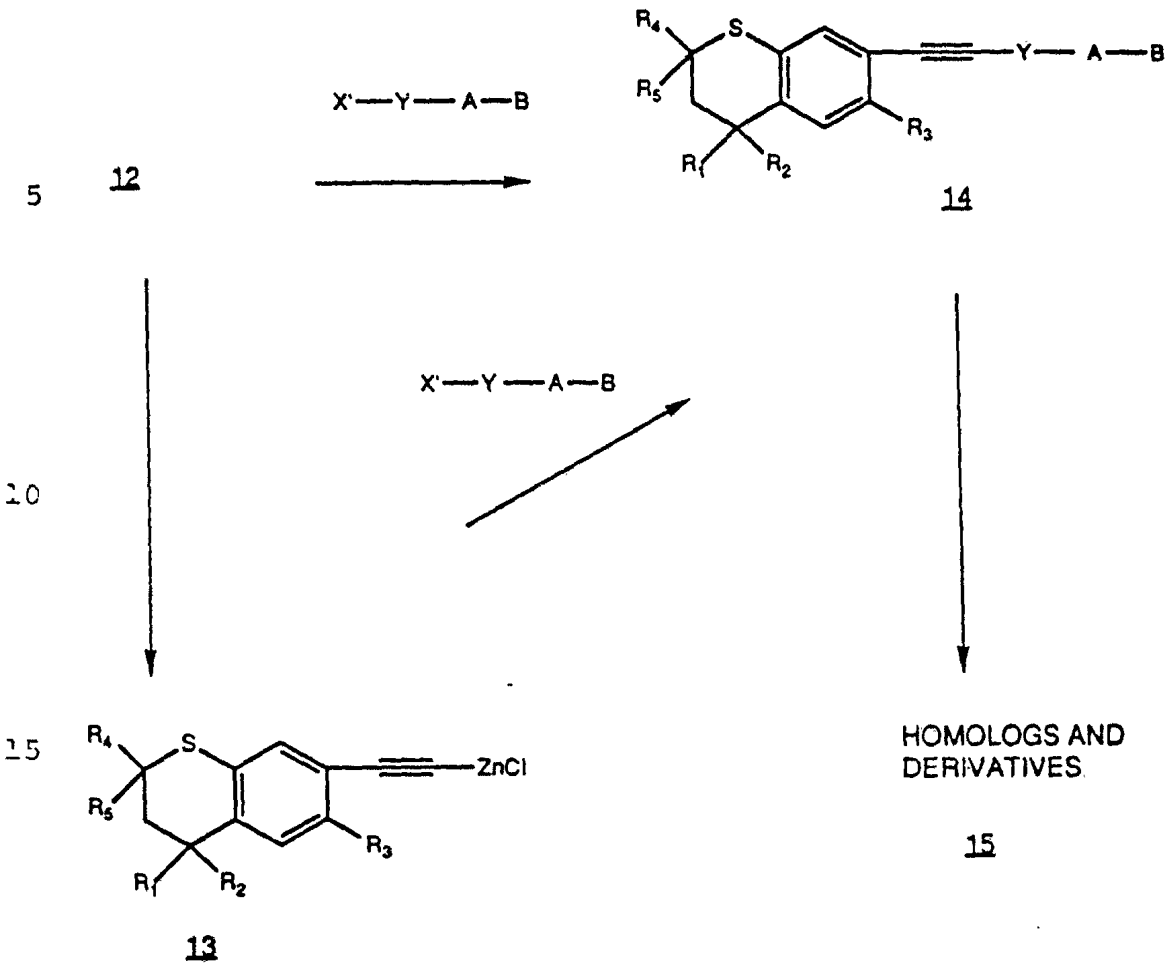
4	1.0
49	0.97

Specific Embodiments

The compounds of this invention 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 **Formula 1** 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 **Formula 1**. 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.

Compounds of **Formula 1** where X is -S- and R_4 and R_5 are identical and are lower alkyl, are prepared as per **Reaction Scheme 1**


HS
Br
R3
5
+
Cl
O
R1
R2
6
O
S
Br
R3
R1
R2
7
O
S
Br
R3
R1
R2
8
HS
Br
OH
R4
R5
R1
R2
R3
9
R4
S
Br
R5
R1
R2
R3
10
R4
S
SiMe3
R5
R1
R2
R3
11
R4
S
H
R5
R1
R2
R3
12

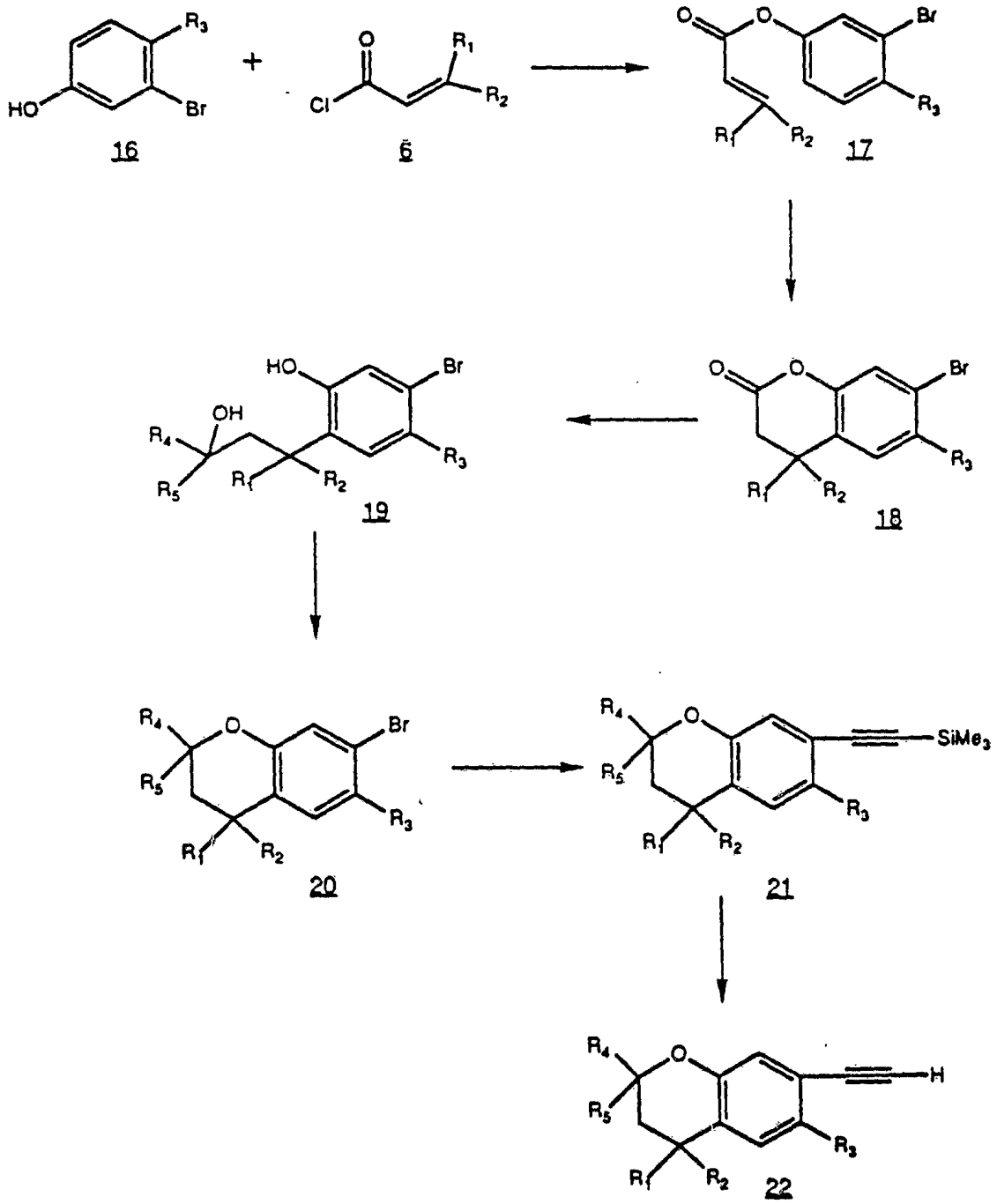


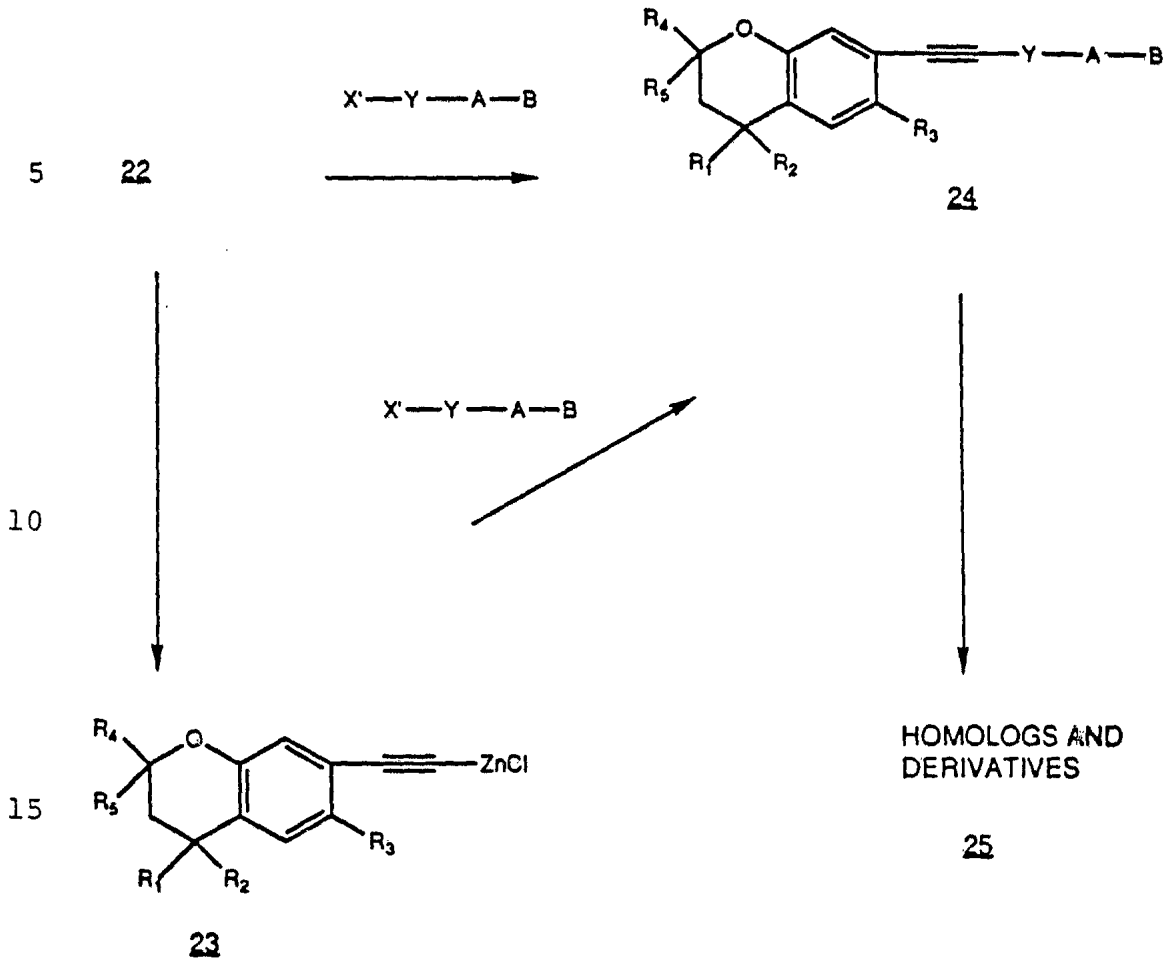
Reaction Scheme 1

In **Reaction Scheme 1**, R_1-R_5 are hydrogen or a lower alkyl group, **Y** is defined as above in connection with **Formula 1**, **A** is lower branched chain alkyl having 3 to 6 carbons, cycloalkyl having 3 to 6 carbons, alkenyl having 2 to 6 carbons and 1 or 2 double bonds, alkynyl having 2 to 6 carbons and 1 or 2 triple bonds, $(CH_2)_n$ where **n** is 0-5 and **B** is H, or a protected acid, alcohol, aldehyde or ketone. **X'** is Cl, Br or I when **n**

is O but preferably is Br or I when **n** is 1-5.

Compounds of **Formula 1** where **X** is oxygen and R_4 and R_5 are hydrogen or lower alkyl, are prepared as per **Reaction Scheme 2.**





Reaction Scheme 2

In **Reaction Scheme 2** the definitions of R_1-R_5, **Y, A, B** and **X'** are the same as in **Reaction Scheme 1.**

A general description of the synthetic steps outlined in **Reaction Schemes 1 and 2** is as follows.

In **Reaction Scheme 1** the 3-bromo-thiophenol (**Compound 5**) is acylated with an acylating agent, such as an acid chloride (**Compound 6**) 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 hydrdride). The resulting thioester

(**Compound 7**) 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-7-bromo-thiochroman (**Compound 8**) is usually isolated in crystalline form.

The R_4 and/or R_5 substituents are introduced by treating the 2-oxo-7-bromo-thiochroman (**Compound 8**) 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) in the presence of $CeCl_3$. When the Grignard reagent (such as methylmagnesium bromide) is in excess, the thiochroman ring is opened and the tertiary alcohol derivative of the 3-bromo thiophenol (**Compound 9**) is formed.

Ring closure of the thiophenol derivative (**Compound 9**) 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 9** in aqueous acid. The resulting 7-bromothiochroman which bears the desired alkyl (or hydrogen) substituents, R_1, R_2, R_3, R_4 and R_5 is shown as **Compound 10** in **Reaction Scheme 1**.

To introduce the acetylene (ethyne) portion into the molecule, the substituted 7-bromothiochroman (**Compound 10**) 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 and an acid acceptor (such as triethylamine) under an inert gas (argon) atmosphere, by heating in a sealed tube. The resulting 7-trimeth-

ylsilylethynylthiochroman is shown as **Compound 11** in **Reaction Scheme 1.**

As is shown on **Reaction Scheme 1**, the trimethylsilyl moiety is removed from the 7-trimethylsilylethynyl-thiochroman (**Compound 11**) in the next synthetic step, to provide the ring substituted 7-ethynyl-thiochroman derivative (**Compound 12**). The latter reaction is conducted under basic conditions, preferably under an inert gas atmosphere.

In order to introduce a heteroaryl substituent on the acetylene (ethyne) portion of **Compound 12**, **Compound 12** is coupled with the reagent **X'-Y-A-B** (**Formula 3**) where the symbols **Y**, **A**, **X'** and **B** have the same meaning as defined in connection with **Formula 3**. In other words, the heteroaryl substituent is introduced into the 7-ethynyl-thiochroman (**Compound 12**) by reacting the latter with a halogen substituted heteroaromatic compound (**Formula 3**) in which the heteroaromatic nucleus (**Y**) either has the desired substituent [**A-B**] or wherein the actual substituent **A-B** can be readily converted to the desired substituent by means of organic reactions well known in the art.

Coupling of the 7-ethynyl-thiochroman (**Compound 12**) with the reagent **X'-Y-A-B** is affected directly in the presence of cuprous iodide, a suitable catalyst, typically 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.

The resulting disubstituted acetylene compound (**Compound 14**) may be the target compound made in accordance with the invention, or maybe readily converted into the target compound by such steps as salt formation, esterification, deesterification,

homologation, amide formation and the like. These steps are further discussed below.

Compound 14 may also be obtained by first converting the 7-ethynyl-thiochroman derivative (**Compound 12**) into a corresponding metal salt, such as a zinc salt, (**Compound 13**) and thereafter coupling the salt (**Compound 13**) with the reagent X'-**Y-A**-B (**Formula 3**) in the presence of a catalyst having the formula $Pd(PQ_3)_4$ (Q is phenyl), or similar complex.

Derivatization of **Compound 14** is indicated in **Reaction Scheme 1** as conversion to "homologs and derivatives", **Compounds 15**.

More specifically with respect to either derivatization or deblocking of protected functionalities in **Compound 14**, or with respect to the preparation of heteroaromatic derivatives of the formula X'-**Y-A**-B, (which after coupling either directly yield the compounds of the invention, or are readily converted into them) the following is noted.

Where a protected heteroaromatic derivative is needed to couple with the compounds of **Formula 2** (**Compounds 12** in **Reaction Scheme 1**), such may be prepared from their corresponding acids, alcohols, ketones or aldehydes. These starting materials, the protected acids, alcohols, aldehydes or ketones, are all available from chemical manufacturers or can be prepared by published methods. Carboxylic acids are typically esterified by refluxing the acid in a solution of the appropriate alcohol in the presence of an acid catalyst such as hydrogen chloride or thionyl chloride. Alternatively, the carboxylic acid can be condensed with the appropriate alcohol in the presence of dicyclohexylcarbodiimide and dimethylaminopyridine.

The ester is recovered and purified by conventional means. Acetals and ketals are readily made by the method described in March, "Advanced Organic Chemistry," 2nd Edition, McGraw-Hill Book Company, p 810). Alcohols, aldehydes and ketones all may be protected by forming respectively, ethers and esters, acetals or ketals by known methods such as those described in McOmie, Plenum Publishing Press, 1973 and Protecting Groups, Ed. Greene, John Wiley & Sons, 1981.

To increase the value of n before effecting a coupling reaction, where such compounds are not available from a commercial source, the heteroaromatic derivatives where B is -COOH are subjected to homologation by successive treatment under Arndt-Eistert conditions or other homologation procedures. Alternatively, heteroaromatic derivatives where B is different from COOH, may also be homologated by appropriate procedures. The homologated acids can then be esterified by the general procedure outlined in the preceding paragraph.

An alternative means for making compounds where A is $(CH_2)_n$ (n is 1 - 5) is to subject the compounds of Formula 1, where B is an acid or other function, to homologation, using the Arndt-Eistert method referred to above, or other homologation procedures.

Compounds of Formula 1 where A is an alkenyl group having one or more double bonds can be made for example, by having the requisite number of double bonds incorporated into the intermediate of Formula 3; that is by using for the intermediate of Formula 3 an unsaturated heteroaromatic compound bearing the X' leaving group (preferably halogen) in the heteroaromatic nucleus. Generally speaking, the

compounds of **Formula 3** where **A** is an unsaturated carbon chain can be obtained by synthetic schemes well known to the practicing organic chemist; for example by Wittig and like reactions, or by introduction of a double bond by elimination of halogen from an alpha-halo-heteroarylalkyl-carboxylic acid, ester or like carboxaldehyde. Compounds of **Formula 1** where the **A** group has a triple (acetylenic) bond can be made by using the corresponding intermediate of **Formula 3**. Such intermediate can be obtained by reactions well known in the art, for example, by reaction of a corresponding heteroaromatic-methyl ketone with strong base, such as lithium diisopropyl amide.

The acids and salts derived from **Formula 1** are readily obtainable from the corresponding esters. Basic saponification with an alkali metal base will provide the acid. For example, an ester of **Formula 1** may be dissolved in a polar solvent such as an alkanol, preferably under an inert atmosphere at room temperature, with about a three molar excess of base, for example, potassium hydroxide. The solution is stirred for an extended period of time, between 15 and 20 hours, cooled, acidified and the hydrolysate recovered by conventional means.

The amide may be formed by any appropriate amidation means known in the art from the corresponding esters or carboxylic acids. One way to prepare such compounds is to convert an acid to an acid chloride and then treat that compound with ammonium hydroxide or an appropriate amine. For example, the acid is treated with an alcoholic base solution such as ethanolic KOH (in approximately a 10% molar excess) at room temperature for about 30 minutes. The solvent is removed and

the residue taken up in an organic solvent such as diethyl ether, treated with a dialkyl formamide and then a 10-fold excess of oxalyl chloride. This is all effected at a moderately reduced temperature between about -10 degrees and +10 degrees C. The last mentioned solution is then stirred at the reduced temperature for 1-4 hours, preferably 2 hours. Solvent removal provides a residue which is taken up in an inert inorganic solvent such as benzene, cooled to about 0 degrees C and treated with concentrated ammonium hydroxide. The resulting mixture is stirred at a reduced temperature for 1 - 4 hours. The product is recovered by conventional means.

Alcohols are made by converting the corresponding acids to the acid chloride with thionyl chloride or other means (J. March, "Advanced Organic Chemistry", 2nd Edition, McGraw-Hill Book Company), then reducing the acid chloride with sodium borohydride (March, Ibid, pg. 1124), which gives the corresponding alcohols. Alternatively, esters may be reduced with lithium aluminum hydride at reduced temperatures. Alkylating these alcohols with appropriate alky halides under Williamson reaction conditions (March, Ibid, pg. 357) gives the corresponding ethers. These alcohols can be converted to esters by reacting them with appropriate acids in the presence of acid catalysts or dicyclohexylcarbodiimide and dimethlaminopyridine.

Aldehydes can be prepared from the corresponding primary alcohols using mild oxidizing agents such as pyridinium dichromate in methylene chloride (Corey, E. J., Schmidt, G., Tet. Lett., 399, 1979), or dimethyl sulfoxide/oxalyl chloride in methylene chloride (Omura, K., Swern, D., Tetrahedron, 1978, 34, 1651).

Ketones can be prepared from an appropriate aldehyde by treating the aldehyde with an alkyl Grignard reagent or similar reagent followed by oxidation.

Acetals or ketals can be prepared from the corresponding aldehyde or ketone by the method described in March, Ibid, p 810.

Compounds where B is H can be prepared from the corresponding halogenated heteroaromatic compounds, preferably where the halogen is I.

With reference to **Reaction Scheme 2**, 3-bromophenol, or a 3-bromophenol substituted in the 4-(para) position by an alkyl substituent (R_3) (**Compound 16**) is acylated with an acylating agent, such as an acid chloride (**Compound 6**) derived from an appropriately substituted acrylic acid. In **Reaction Scheme 2**, just as in **Reaction Scheme 1**, the R_1 and R_2 substituents of the target compounds are introduced through this acrylic acid derivative (**Compound 6**). The acylation with the acid chloride (**Compound 6**) 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 2** as **Compound 17**.

The substituted phenyl-acrylate **17** 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-7-bromo-chroman compound (**Compound 18**) 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 (**Compound 8**) in **Reaction Scheme 1**, the 2-oxo-chroman **18** of **Reaction Scheme 2** is treated

with a Grignard reagent to introduce the R_4 and R_5 substituents. When R_4 and R_5 are methyl, the Grignard reagent is preferably methylmagnesium chloride (dissolved in tetrahydrofuran, THF). A solution of **Compound 18** 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 2** as **Compound 19**.

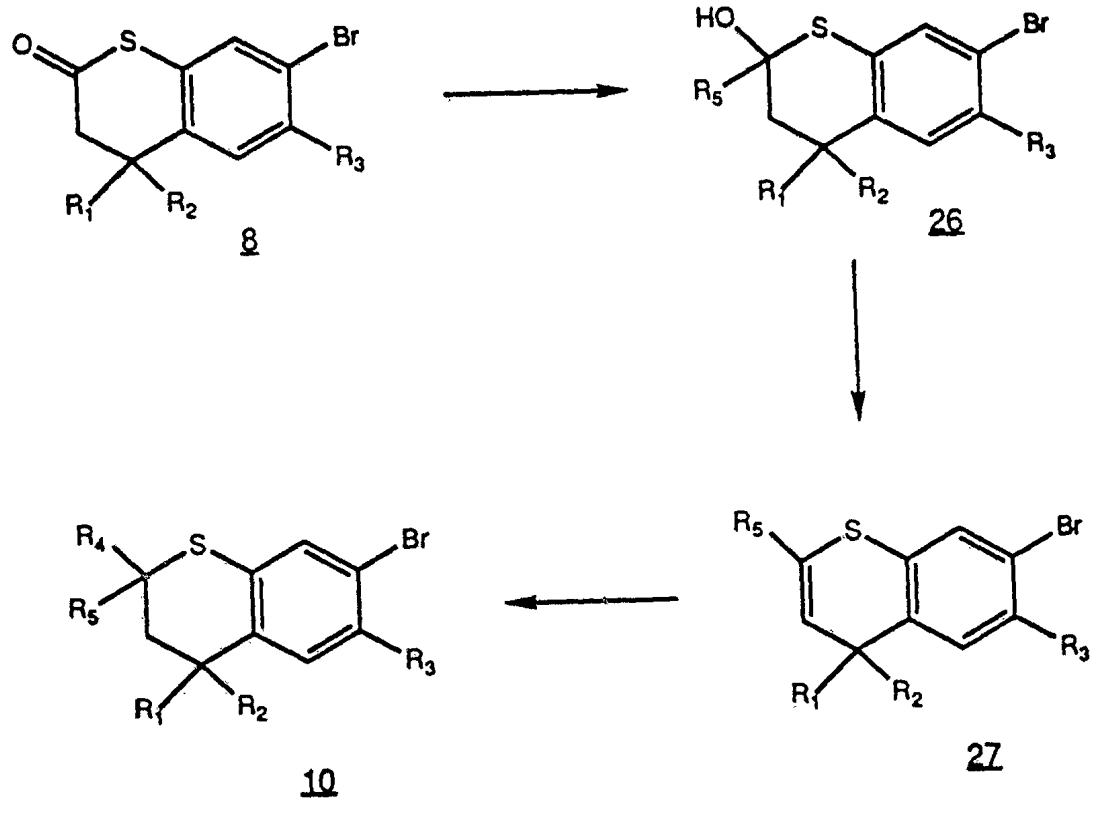
Compound 19 which already has the desired R_1, R_2, R_3, R_4 and R_5 substituents, is ring closed under acidic conditions, (e.g. by heating in aqueous sulfuric acid) to provide the chroman derivative (**Compound 20**). To introduce the acetylene (ethyne) portion into the molecule, the substituted 7-bromo chroman (**Compound 20**) is reacted with trimethylsilyl acetylene in the presence of cuprous iodide and a suitable catalyst, typically having the formula $Pd(PQ_3)_2\ Cl_2$ (Q is phenyl), as defined for the 7-bromo-thiochroman compound in **Reaction Scheme 1**. The resulting 7-trimethylsilyl-ethynyl-chroman is shown as **Compound 21** in **Reaction Scheme 2**.

In **Reaction Scheme 2**, just as in **Reaction Scheme 1**, the trimethylsilyl moiety is removed from the 7-trimethylsilylethynyl-chroman (**Compound 21**) under basic conditions, to provide the ring substituted 7-ethynyl-chroman derivative (**Compound 22**).

Referring still to **Reaction Scheme 2**, the 7-ethynyl-chroman derivative (**Compound 22**) may be converted into the target compounds of the invention in synthetic steps which are analogous to the conversion of 7-ethynyl-thiochromans (**Compound 12**) into the corresponding

target thiochroman derivatives (See **Reaction Scheme 1**). Briefly, **Compound 22** is preferably heated with a reagent **X'-Y-A-B** (**Formula 3**) in the presence of cuprous iodide, a suitable catalyst, typically of the formula $Pd(PQ_3)_2\ Cl_2$ (Q is phenyl or the like) and an acid acceptor, such as triethylamine. This coupling reaction, yields the target chroman compounds, (**Compound 24**) or such derivatives which are readily converted into the target compounds by protection, deprotection, esterification, homologation etc., as is discussed in connection with **Reaction Scheme 1**. The homologs are indicated, as a group, as **Compound 25** in **Reaction Scheme 2**.

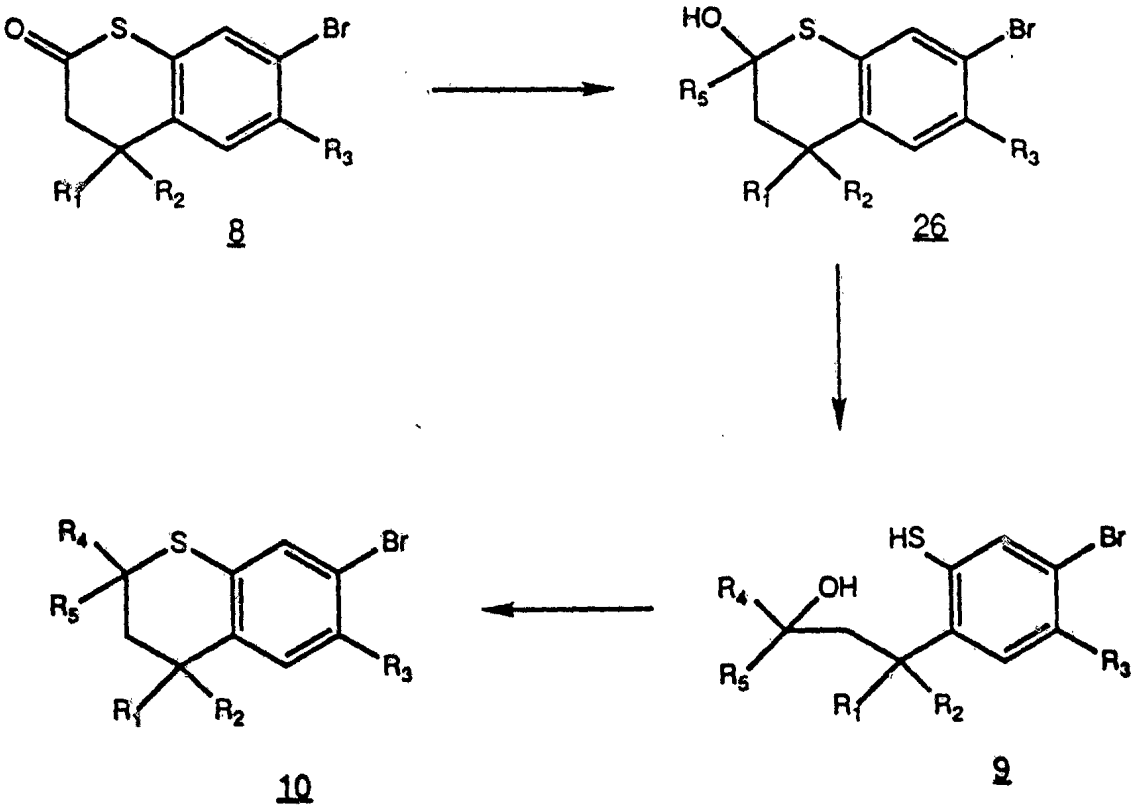
Alternatively, the 7-ethynyl-chroman compounds (**Compound 22**) may first be converted to the corresponding metal (zinc) salt (**Compound 23**) and thereafter coupled with the reagent **X'-Y-A-B** (**Formula 3**) under conditions which are similar to the conditions described in **Reaction Scheme 1** for coupling of **Compounds 13** with the same reagent.



Reaction Scheme 3

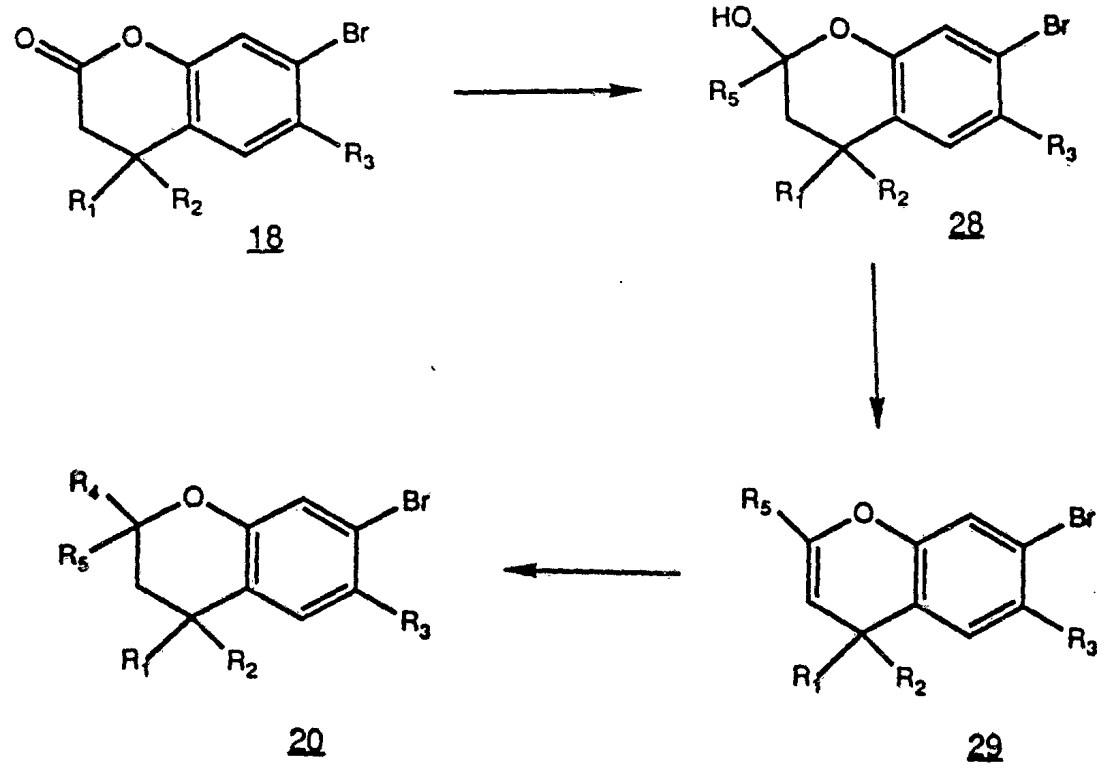
Referring to **Reaction Scheme 3**, the substituted 7-bromothiochroman (**Compound 10**), where one of the R_4 or R_5 substituents is alkyl and the other is hydrogen, can be made by treating the 2-oxo-7-bromo-thiochroman (**Compound 8**) with a Grignard reagent. As in **Reaction Scheme 1** the 2-oxo-thiochroman (**Compound 8**) is subjected to an excess of Grignard reagent, bearing the alkyl substituents R_4 or R_5 (such as methylmagnesium bromide when R_4 or R_5 is methyl). However, the reaction temperature is controlled and maintained at a

relatively low temperature (such as -14 degrees C) and the duration of the reaction is kept relatively short (0.5 hours). A hemiacetal derivative of 3-bromothiophenol (**Compound 26**) is formed in this controlled Grignard reaction, as shown in **Reaction Scheme 3**. **Compound 26** is converted by heating in acidic conditions, preferably with aqueous acid, to the unsaturated derivative (**Compound 27**). **Compound 27** is reduced by hydrogenation in the presence of palladium sulfide-on-carbon catalyst at increased pressure (approximately 30 psi). The resulting 7-bromo-thiochroman which bears the desired hydrogen and alkyl substituents R_1, R_2, R_3, R_4 and R_5 with one of R_4 or R_5 being hydrogen, is shown as **Compound 10**.



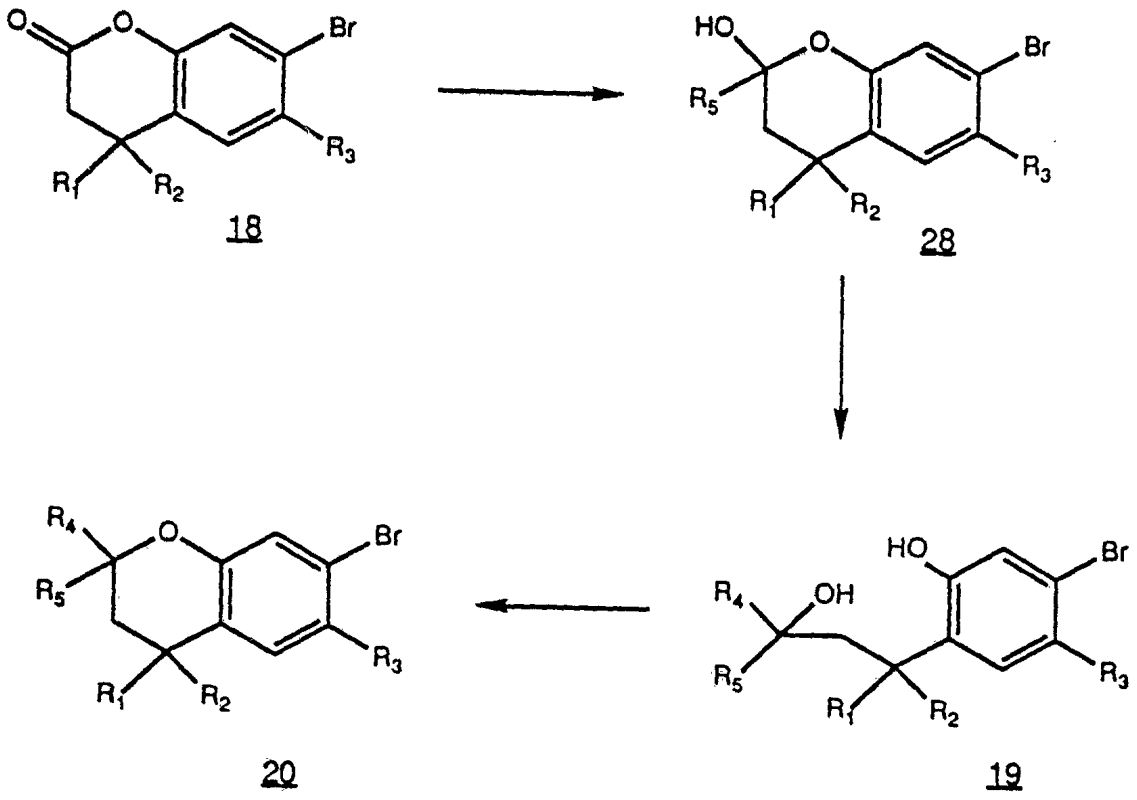
Reaction Scheme 4

To obtain the 7-bromothiochroman (**Compound 10**), (**Reaction Scheme 4**) where the R_4 and R_5 substituents both are alkyl but not identical with one another, the hemiacetal derivative (**Compound 26**) is treated with a different Grignard reagent than previously used, as shown in **Scheme 4**. In this Grignard reaction the thiochroman ring is opened and the tertiary alcohol derivative of 3-bromo-thiophenol (**Compound 9**), is formed. Ring closure of the thiophenol derivative (**Compound 9**) 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 with aqueous acid. The resulting 7-bromo thiochroman which bears the desired alkyl and hydrogen substituents R_1, R_2, R_3, R_4 and R_5 is shown as **Compound 10**.



Reaction Scheme 5

In **Reaction Scheme 5**, just as in **Reaction Scheme 3**, one of the R_4 or R_5 substituents is alkyl and the other is hydrogen. Just like the analogous 2-oxo-thiochroman (**Compound 8**) in **Reaction Scheme 3**, the 2-oxochroman (**Compound 18**) of **Reaction Scheme 5** is treated with a Grignard reagent to introduce the R_4 and R_5 substituents. With controlled reaction temperature and time, the resulting hemiacetal derivative can be isolated as **Compound 28**, as shown in **Reaction Scheme 5**. Under acidic conditions, (e.g. by heating in aqueous acid) the hemiacetal (**Compound 28**) is cyclized to form the corresponding unsaturated derivative (**Compound 29**). The unsaturated derivative can then be reduced using the same conditions as described in connection with **Reaction Scheme 3** for the reduction of **Compound 26**, or by a more general reducing procedure. The resulting chroman derivative is shown as **Compound 20** in **Reaction Scheme 5**.

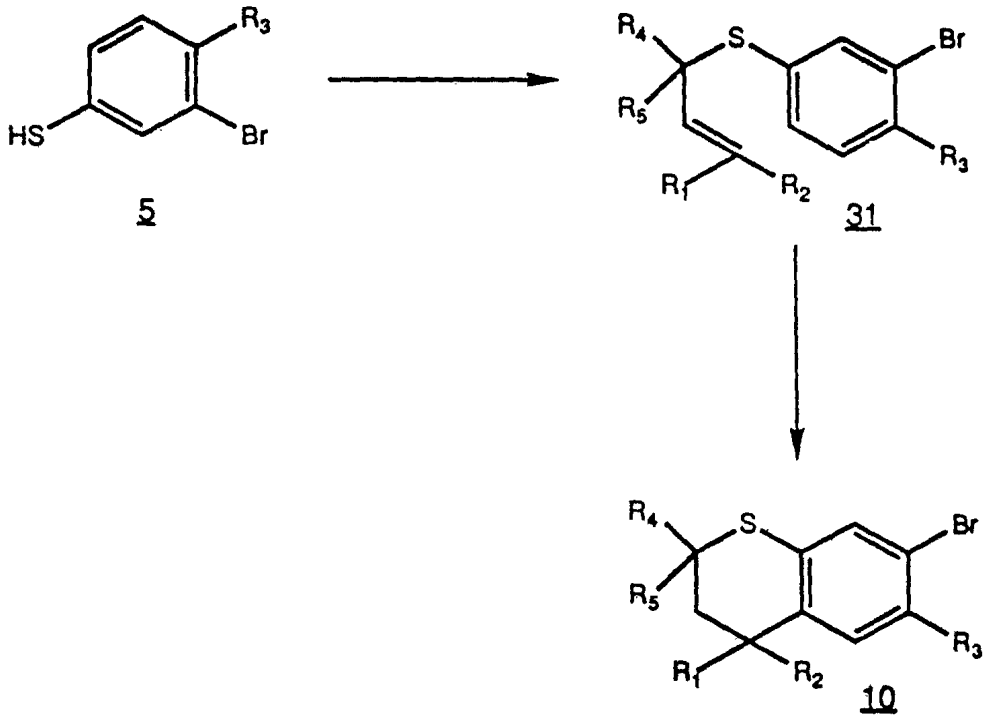


Reaction Scheme 6

Referring to **Reaction Scheme 6**, in **Compound 20** of that scheme the R_4 and R_5 substituents are alkyl but are not identical. The R_4 and R_5 alkyl substituents are introduced by treating **Compound 28** with a different Grignard reagent than previously used, to form the tertiary alcohol (**Compound 19**). The tertiary alcohol (**Compound 19**) which already has the desired R_1, R_2, R_3, R_4 and R_5 substituents, is ring closed under acidic conditions, as described above, to provide the chroman

derivative (**Compound 20**).

With reference to the compounds of **Formula 1**, **Reaction Scheme 7** illustrates an example of the synthesis when X=S and R_4 and R_5 are both hydrogen.

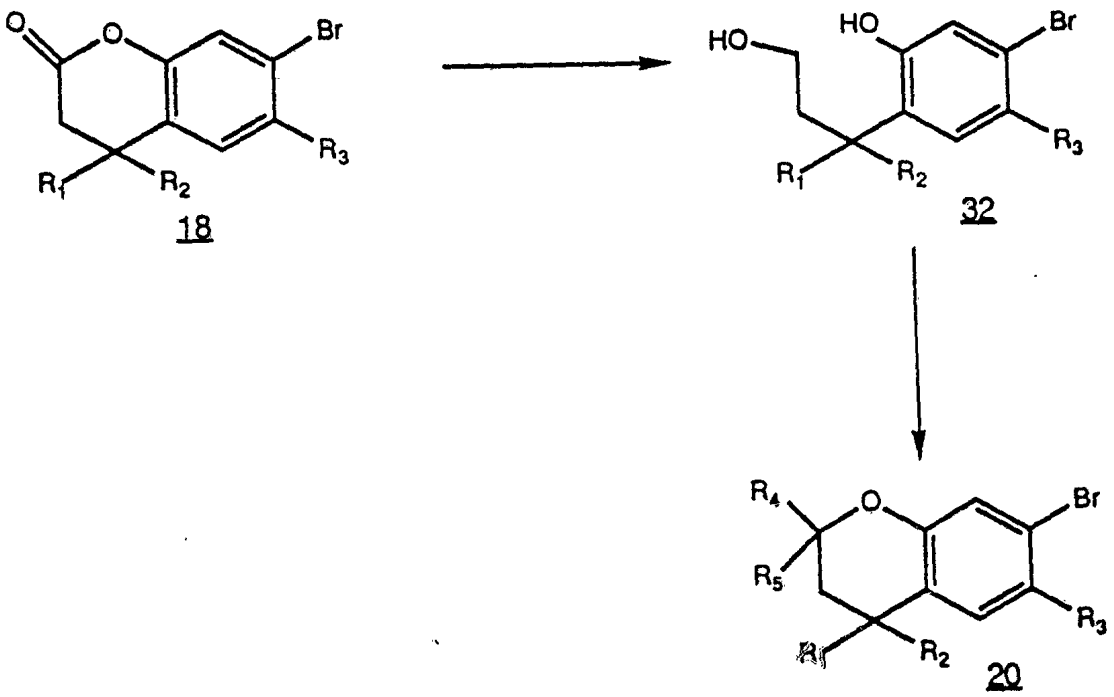


Reaction Scheme 7

Thus, with reference to Reaction Scheme 7, the 3-bromothiophenol (Compound 5) (which maybe alkyl substituted in the 4-position) is alkylated with Compound 30. The resulting 3-bromo phenyl sulfides (Compound 31) are ring closed under Friedel-Crafts (or like) conditions by refluxing in an inert solvent such as benzene or toluene, in the presence of phosphorus pentoxide and phosphoric acid. The resulting thiochroman (Compound 10) made in accordance with Reaction Scheme 7 has R_4

and R_5 as hydrogen, and preferably in accordance with this reaction scheme, R_1 and R_2 are methyl and R_3 is hydrogen.

Turning 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 6 position) the compounds can be made as indicated in **Reaction Scheme 8.**



Reaction Scheme 8

In **Reaction Scheme 8**, R_1 and R_2 are hydrogen or lower alkyl having 1 to 6 carbons, and R_3 is defined as above in connection with **Formula 1.**

The 2-oxo-chroman (**Compound 18**) of **Reaction Scheme**

2 is reduced with lithium aluminum hydride (or by a similar reducing agent) to provide the diol (**Compound 32**). The primary hydroxyl group of **Compound 32** is mesylated (selectively over the phenolic hydroxyl) followed by intramolecular displacement of the mesylate group under basic conditions, to give a 7-bromo-chroman derivative (**Compound 20**) which bears the desired alkyl substituents at R_1 and R_2 and where R_4 and R_5 are both hydrogen. The 7-bromochroman and thiochroman derivatives (**Compound 10** and **Compound 20**) synthesized as per **Reaction Schemes 3 - 8** are subjected to substantially the same reaction procedures as described in **Reaction Scheme 1** and **Reaction Scheme 2** to obtain the final acetyler.c products.

Specific Examples

S-(3-Bromophenyl) 3,3-dimethyl-thio acrylate (**Compound 33**)

To an ice-bath cooled solution of 4.5 g (112.5 mmol) of sodium hydride (60% suspension in mineral oil) in 50 ml of dry THF was added slowly under argon a solution of 20 g (105.8 mmol) of 3-bromothiophenol in 80 ml of dry THF. The mixture was stirred at 0° C for 30 minutes and then treated with a solution of 14 g (118 mmol) of dimethylacryloyl chloride in 30 ml of dry THF. The reaction mixture was allowed to stir at room temperature for 24 hours. The reaction mixture was poured onto 300 ml of water containing 5 ml of glacial acetic acid and the organic layer was separated. The aqueous layer was extracted with 2 X 200 ml ether. The organic extracts were combined and washed with 100 ml of water and 100 ml of saturated NaCl solution and then dried ($MgSO_4$). The solvent was removed in vacuo and the residue was kugelrohr distilled to give the

title compound as a pale yellow oil.

PMR ($CDCl_3$); & 1.90 (3H, s), 2.14 (3H, s), 6.04 (1H, s), 7.26 (1H, t, J - 7.8 Hz), 7.36 (1H, d, J - 4 Hz), 7.5 (1H, dd, J - 7.8 Hz, J - 1.7 Hz), 7.59 (1H, d, J - 1.7 Hz)

4,4 Dimethyl-7-bromo-2-oxo-thiochroman (**Compound 34**)

To a stirred, ice cooled suspension of 20g (150 mmol) of aluminum chloride in 250 ml of methylene chloride was added a solution of 17 g (89.5 mmol) of S-(3-bromopenyl) 3-3 dimethyl-thio acrylate (**Compound 33**) in 100 ml of methylene chloride. The mixture was stirred at room temperature for 24 hours and then poured nto 200 ml of an ice and brine mixture. The organic layer was separated and the aqueous layer was extracted with 150 ml of ether. The organic extracts were combined and then washed with water and saturated NaCl solution and dried ($MgSO_4$). The solvent was removed in vacuo and the residue purified by flash column chromatography (silica; 2% ethyl acetate, hexanes) to give the title compound as a white solid.

PMR ($CDCl_3$); & 1.38 (6H, s), 2.65 (2H, s) 7.33 (3H, s).

5-Bromo-2-(1,1,3-trimethyl-3 hydroxy butyl)-thiophenol (**Compound 35**)

To 132 g (354.3 mmol) of Cerium chloride (dried under vacuum at 135° C for 2 days) was added 200 ml of dry THF, and the suspension was stirred at room temperature for 20 hours. The reaction mixture was then cooled to 0° C and treated with 103 ml (309 mmol) of a 3.0 M solution of methyl magnesium chloride in THF. The mixture was stirred at room temperature for 4 hours, cooled to 0° C, and treated with a solution of 9.6 g (35.4 mmol) of 4,4-dimethyl-7-bromo-2-oxo-thio-

chroman (**Compound 34**) in 60 ml of dry THF. The reaction mixture was allowed to stir at room temperature for 18 hours and then poured into 200 ml of ice containing 2 ml of sulfuric acid. The mixture was extracted with 500 ml of ether. The ether extracts were combined and washed with 300 ml of water and 300 ml of saturated NaCl solution and then dried ($MgSO_4$). The solvent was removed in vacuo to give the title compound as a pale yellow oil.

PMR ($CDCl_3$); & 1.08 (6H, s), 1.54 (6H, s), 2.31 (2H, s), 7.24 (1H, dd, J - 8.5 Hz, J - 2 Hz), 7.30 (1H, d, J - 8.5 Hz) 7.34, (1H, d, J - 2 Hz).

2,2,4,4 Tetramethyl-7-bromo-thiochroman (**Compound 36**)

A mixture of 10 g (33 mmol) of 5-bromo-2-(1,1,3-trimethyl-3-hydroxybutyl) thiophenol (**Compound 35**) and 100 ml of 20 percent aqueous sulfuric acid was heated at reflux for 48 hours. The mixture was cooled to room temperature and extracted with 2 x 50 ml of ether. The ether extracts were combined and washed with 25 ml of saturated sodium bicarbonate solution and 25 ml of saturated NaCl solution and dried ($MgSO_4$). The solvent was removed in vacuo and the residue purified by flash column chromatography (silica: 2% ethyl acetate in hexanes) followed by kugelrohr distillation to give the title compound as a clear oil.

PMR ($CDCl_3$); & 1.810 (6H, s), 1.282 (6H, s), 1.234 (2H, s), 7.047 (1H, dd, J - 2 Hz, J - 8.8 Hz) 7.114 (1H, d J - 8.8 Hz) 7.16 (1H, d, J - 2 Hz).

2,2,4,4 Tetramethyl-7-trimethylsilyl-ethynyl-thiochroman (**Compound 37**)

A solution of 3 g (10.5 mmol) of 2,2,4,4 tetramethyl-7-bromo-thiochroman (**Compound 36**) and 5.16 g (52.6 mmol) of trimethylsilylacetylene in 5 ml of

triethylamine was placed in a heavy walled glass tube and degassed under nitrogen. The mixture was then treated, under nitrogen, with 184 mg (.966 mmol) of cuprous iodide and 368 mg (.524 mmol) of bis (triphenylphosphine) palladium (II) chloride, the reaction mixture was degassed again and placed under nitrogen and the tube was sealed. The mixture was heated at 60° C for 24 hours, cooled to room temperature, and then filtered through celite. The solvent was removed in vacuo and the residue purified by flash column chromatography (silica; 100% hexanes) to give the title compound as a pale yellow solid.

PMR ($CDCl_3$); & 0.22 (9H, s), 1.35 (6H, s), 1.38 (6H, s), 1.93 (2H, s), 7.16 (1H, dd, J - 8.1 Hz, J - 1.74 Hz), 7.24 (1H, d, J - 1.74 Hz) 7.30 (1H, J - 8.1 Hz)

2,2,4,4-Tetramethyl-7-ethynyl-thiochroman (**Compound 38**)

To a solution of 1.04 g (3.4 mmole) of 2,2,4,4 tetramethlyl-7-trimethylsilylethynyl thiochroman (**Compound 37**) in 3 ml of isopropanol was added 5 ml of ethanolic KOH solution. The reaction mixture was stirred at room temperature for 24 hours and the alcohol was then removed in vacuo. The residue was extracted with ether (20 ml) and the combined ether layers were washed with water (15 ml) and saturated NaCl solution (20 ml) and dried ($MgSO_4$). The solvent was removed in vacuo and the residue purified by kugelhohr distillation to give the title compound as a clear oil.

PMR ($CDCl_3$); & 1.38 (6H, s), 1.42 (6H, s), 1.95 (2H, s), 3.02 (1H, s), 7.20 (1H, dd, J - 8.1 Hz, 2.1 Hz), 7.29 (1H, d, J - 2.1 Hz), 7.34 (1H, d, J - 8.1 Hz)

Ethyl-6-(2,2,4,4-tetramethyl-7-thiochromanyl)ethynyl)nicotinate (Compound 3)

A solution of 410 mg (1.78 mmol) of 2,2,4,4-tetramethyl-7-ethynyl thio-chroman (Compound 38) and 375 mg (2.02 mmol) of ethyl 6-chloronicotinate in 3 ml of triethylamine was placed in a heavy walled glass tube and degassed under a nitrogen atmosphere. The mixture was treated with 18 mg (.0256 mmol) of bis(triphenylphospheine) palladium (II) chloride and 8 mg (.042 mmol) of cuprous iodide under nitrogen and stirred for 5 minutes. The mixture was then treated with a further 18 mg of bis(triphenylphosphine) palladium (II) chloride and 8 mg of cuprous iodide, and the mixture was degassed again. The tube was then sealed and the reaction mixture was heated at 45 degrees C for 70 hours. The mixture was then cooled to room temperature and filtered through celite. The solvent was removed in vacuo and the residue was purified by flash chromatography (silica: 5% ethylacetate/hexanes) to give the title compound as a brown solid.

PMR ($CDCl_3$): δ 1.38 - 1.43 (15H, m), 1.96 (2H, s), 4.42 (2H, q, J - 7.0 Hz), 7.32 (1H, dd, J - 8.1 Hz, 1.7 Hz), 7.36 - 7.42 (2H, m), 7.57 (1H, d, J - 8.3 Hz), 8.28 (1H, dd, J - 8.3 Hz, 2.3 Hz), 9.20 (1H, d, J - 2.3 Hz).

6-(2,2,4,4-Tetramethyl-7-thiochromanyl)-ethynyl)nicotinic acid (Compound 49)

To 167 mg (.4756 mmol) of ethyl-6-(2,2,4,4-tetramethyl-7-thiochromanyl)ethynyl-nicotinate (Compound 3) was added 5 ml of ethanolic KOH solution. The reaction mixture was stirred at room temperature for 48 hours. The ethanol was then removed in vacuo and the residue was taken up in water and ether. The layers were

separated and the aqueous layer was acidified to Ph=2 with 1 N HCl and then extracted with ether. The organic extracts were combined and washed successively with water and saturated sodium chloride solution and then dried ($MgSO_4$). The solvent was removed in vacuo to give the title compound as a yellow solid.

PMR ($CDCl_3$): & 1.38 (6H, s), 1.42 (6H, s), 1.97 (2H, s), 7.30 - 7.42 (3H, m), 7.62 (1H, d, J - 8.2 Hz), 8.40 (1H, dd, J - 8.2 Hz, 2.1 Hz), 9.35 (1H, d, J - 2.1 Hz).

3-Bromophenyl 3,3-dimethyl acrylate (**Compound 39**)

To an ice-cooled suspension of 4g (100 mmol) of sodium hydride (60% in mineral oil) in 50 ml of dry THF was added dropwise a solution of 15.7 g(90.7 mmol) of 3-bromo phenol in 25 ml of dry THF. The mixture was stirred at 0 degrees C for 0.5 hours and then treated with a solution of 10.65 g (90.0 mmol) of dimethyl acryloyl chloride in 30 ml of dry THF. The mixture was allowed to warm to room temperature and stirred for 24 hours. The reaction mixture was poured onto 200 ml of ice water containing 3 ml of glacial acetic acid. The mixture was extracted with 2 x 250 ml ether and the combined ether extracts were washed with 200 ml of water and 100 ml saturated NaCl solution and dried ($MgSO_4$). The solvent was removed in vacuo and the residue purified by kugelrohr distillation to give the title compound as a clear oil.

PMR ($CDCl_3$): & 2.02 (3H, s), 2.28 (3H, s), 5.94 (1H, broad s), 7.06 - 7.12 (1H, m), 7.28 (1H, t, J - 8.0 Hz), 7.34 (1H, t, J - 2.0 Hz), 7.37 - 7.42 (1H, m).

5-Bromo-2-(1,1,3-Trimethyl-3-hydroxybutyl)phenol (**Compound 41**)

To a stirred, ice-cooled suspension of 21 g (158

mmol) of aluminum chloride in 200 ml of methylene chloride was added slowly a solution of 23.74 g (93.1 mmol) of 5-bromo-phenyl-3,3-dimethyl acrylate (**Compound 39**) in 100 ml of methylene chloride. The mixture was warmed to room temperature and stirred for 52 hours. The mixture was poured into a mixture of ice and brine and the organic layer was separated. The aqueous layer was extracted with 2 X 100 ml ether. The organic extracts were combined and washed with 2 X 250 ml of water and 50 ml of saturated NaCl solution and dried ($MgSO_4$). The solvent was removed in vacuo and the residue was partially purified by flash column chromatography, (silica; 5% ethyl acetate/hexane) to give impure 4,4-dimethyl-7-bromo-2-oxochroman (**Compound 40**) as a yellow oil which was used in the next step without further purification. To an ice-cooled solution of 10 g of this impure 4,4,dimethyl-7-bromo-2-oxo-chroman (**Compound 40**) in 200 ml of dry THF was added under argon 39.2 ml of 3.0 M methyl magnesium chloride (117.6 mmol) in THF. The reaction mixture was allowed to warm to room temperature and stirred for 5 hours. The reaction mixture was then poured into ice water containing 2 ml of sulfuric acid and the organic layer was separated. The aqueous layer was extracted with 200 ml of ether. The organic extracts were combined and washed with 200 ml of water and 200 ml of brine and dried ($MgSO_4$). The solvent was removed in vacuo and the residue purified by flash column chromatography (silica; 10% ethylacetate/hexanes) to give the title compound as a pale yellow oil.

PMR ($CDCl_3$): & 0.98 (6H, s), 1.36 (6H, s), 2.15 (2H, s), 6.82 (1H, d, J - 1.9 Hz), 6.86 (1H, dd, J - 8.3 Hz, 1.9 Hz), 7.04 (1H, d, J - 8.3 Hz).

2,2,4,4-tetramethyl-7-bromochroman (**Compound 42**)

A mixture of 5.42 (18.9 mmol) of 3-bromo-2(1,1,3 trimethyl-3-hydroxy-butyl) phenol (**Compound 41**) and 50 ml of 20 percent aqueous sulfuric acid was heated at reflux for 24 hours. The reaction mixture was cooled to room temperature and treated with 100 ml of ether. The organic layer was separated and the aqueous layer was extracted with 50 ml of ether. The ether extracts were combined and washed with 100 ml of water and 100 ml saturated NaCl solution and dried ($MgSO_4$). The solvent was removed in vacuo and the residue was purified by Kugelrohr distillation to give the impure title compound as a pale yellow oil.

PMR ($CDCl_3$): & 1.22 (6H, s), 1.24 (6H, s), 1.72 (2H, s), 6.87 (1H, d, J - 2.0 Hz), 6.92 (1H, dd, J - 8.3 Hz, 2.0 Hz), 7.02 (1H, d, J - 8.3 Hz).

2,2,4,4-Tetramethyl-7-trimethylsilylethynyl-chroman (**Compound 43**)

A solution of 2 g (7.4 mmol) of 2,2,4,4 tetramethyl-7-bromochroman (**Compound 42**) and 3.63 g (37.0 mmol) of trimethylsilylacetylene in 5 ml of triethylamine was placed in a heavy walled glass tube and degassed under nitrogen. The mixture was then treated, under nitrogen, with 130 mg (.6826 mmol) of cuprous iodide and 260 mg (.3704 mmol) of bis (triphenyl phosphine) palladium (II) chloride. The reaction mixture was degassed again and placed under nitrogen and the tube was sealed. The mixture was heated to 60 degrees C for 24 hours and then cooled to room temperature and filtered through celite. The solvent was removed in vacuo and the residue purified by flash column chromatography (silica; 2% ethyl acetate/hexane) to give the title compound as a pale yellow solid.

PMR ($CDCl_3$): & 0.23 (9H, s), 1.32 (12H, s), 1.82 (2H, s), 6.92 (1H, d, J - 1.6 Hz) 7.00 (1H, dd, J - 8.6 Hz, 1.6 Hz), 7.19 (1H, J - 8.6 Hz)

2,2,4,4-tetramethyl-7-ethynyl chroman (**Compound 44**)

To a solution of 1.16 g (4.1 mmol) of 2,2,4,4-tetramethyl-7-trimethylsilylethynyl-chroman (**Compound 43**) in 3 ml of isopropanol was added 5 ml of ethanolic KOH solution. The reaction mixture was stirred at room temperature for 24 hours and the alcohol was then removed under vacuum. The residue was extracted with 2 X 10 ml of ether and the combined ether extracts were washed with 15 ml of water and 20 ml of saturated NaCl solution and then dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue purified by Kugelrohr distillation to give the title compound as a white crystalline solid.

PMR ($CDCl_3$): & 1.33 (6H, s), 1.34 (6H, s), 1.83 (2H, s), 2.99 (1H, s), 6.94 (1H, d, J - 1.7 Hz), 7.04 (1H, dd, J - 8.0 Hz, 1.7 Hz), 7.21 (1H, d, J - 8.0 Hz).

Ethyl-6-(2,2,4,4-tetramethyl-7-chromanyl)ethynyl)nicotinate (**Compound 4**)

A solution of 300 mg (1.4 mmoles) of 2,2,4,4-tetramethyl-7-ethynyl chroman (**Compound 44**) and 279.0 mg (1.5 mmoles) of ethyl 6-chloro nicotinate in 4 ml of triethylamine was placed in a heavy walled glass tube and degassed under nitrogen atmosphere. The mixture was treated with 14.7 mg (.021 mmoles) of bis(triphenylphosphine) palladium (II) chloride and 6.6 mg (.035 mg) of cuprous iodide under nitrogen and stirred for 5 minutes. The mixture was then treated with a further 18 mg of bis(triphenylphosphine, palladium (II) chloride and 8 mg of cuprous iodide and the mixture was

degassed again. The tube was then sealed and the reaction mixture was heated at 45 degrees C for 70 hours. The mixture was then cooled to room temperature and filtered through celite. The solvent was removed in vacuo and the residue was purified by flash chromatography (silica: 5% EtOAC/Hexanes) to give the title compound as a yellow solid.

PMR ($CDCl_3$): & 1.35 (12 H, s), 1.42 (3H, t, J - 7.1 Hz), 1.84 (2H, s), 4.42 (2H, d, J - 7.1 Hz), 7.05 (1H, d, J - 1.7 Hz), 7.16 (1H, dd, J - 8.1 Hz, 1.7 Hz), 7.56 (1H, d, J - 8.3 Hz), 8.27 (1H, dd, J - 8.3 Hz, 1.8 Hz), 9.20 (1H, d, J - 1.8 Hz)

6-(2,2,4,4-Tetramethyl-7-chromanyl)-ethynyl nicotinic acid (**Compound 50**)

To 102.2 mg (.3047 mmol) of ethyl-6-(2,2,4,4-tetramethyl-7-chromanyl)-ethynyl nicotinate (**Compound 4**) was added 5 ml of aqueous ethanolic KOH solution. The reaction mixture was stirred at room temperature for 48 hours. The ethanol was then removed in vacuo and the residue was taken up with water and ether. The layers were separated and the aqueous layer was acidified to Ph - 2 with 1 N HCl and then extracted with ether. The organic layers were combined and washed successively with water and saturated sodium chloride solution and dried ($MgSO_4$). The solvent was then removed in vacuo to give the title compound as a yellow solid.

PMR ($CDCl_3$): & 1.37 (12H, s), 1.87 (2H, s), 7.02 (1H, d, J - 1.7 Hz), 7.16 (1H, dd, J - 8.1 Hz, 1.7 Hz), 7.30 (1H, d, J - 8.1 Hz), 7.59 (1H, d, J - 8.1 Hz), 8.30 (1H, dd, J - 8.1 Hz, 2.0 Hz), 9.19 (1H, d, J - 2.0 Hz).

3-Bromophenyl-3-methyl-but-2-enylsulfide (**Compound 45**)

A solution of 25 g (132 mmol) of 3-bromothiophenol in 100 ml of acetone was heated to reflux and then treated with 5.56 g (139 mmol) of powdered NaOH. The mixture was refluxed for a further 0.5 hour. The refluxing mixture was then treated with a solution of 19.7 g (132 mmol) of 1-bromo-3-methyl-2-butene in 30 ml of acetone and refluxed for a further 1.5 hours. The mixture was cooled and then solvent was removed in-vacuo. The residue was extracted with ether and the ether extract was washed with dilute NaOH solution, water, and saturated NaCl solution and thereafter dried ($CaCl_2$). After evaporation of the solvent, the residue was purified by vacuum distillation to give the title compound as a white crystalline solid.

PMR ($CDCl_3$): & 1.61 (3H, s), 1.72 (3H, s), 3.52 (2H, d, J - 7.8 Hz), 5.27 (1H, t, J - 7.8 Hz) 7.10 (1H, t, J - 7.8 Hz), 7.21 (1H, dt, J - 7.8 Hz, J - 1.8 Hz), 7.27 (1H, dt, J - 7.8 Hz, J - 1.8 Hz), 7.44 (1H, t, J - 1.8 Hz).

4,4,Dimethyl-7-trimethylsilylethynyl-thiochroman (**Compound 47**)

To 3.63 g (14 mmol) of 3-bromophenyl-3-methyl-but-2-enyl sulfide (**Compound 45**) was added 15 g of a 1:10 P_2O_5, $MeSO_3H$ mixture, and stirred at room temperature for 4 hours. The mixture was treated with cool water followed by boiling water. The mixture was stirred for 10 minutes and cooled to room temperature. The reaction mixture was then extracted with ether and the combined ether extracts were washed with water and then saturated NaCl solution and dried ($CaCl_2$). The solvent was removed in vacuo and the residue purified by Kugelrohr distillation (140 degrees C/0.2 mm) to give

impure 4,4-dimethyl-7-bromo-thiochroman (**Compound 46**) as a pale yellow solid. This was used in the next step without further purification. A solution of 2.03 g of this impure 4,4 dimethyl-7-bromo thiochroman (**Compound 46**) in 2 ml of triethylamine was placed in a heavy-walled tube and degassed and then treated under argon with 3.8 g (38.9 mmol) of trimethylsilylacetylene and a powdered mixture of 100 mg of bis (triphenylphosphine) palladium (II) chloride and 50 mg of cuprous iodide. The reaction mixture was degassed again, then placed under argon and the tube was sealed. The mixture was heated at 60° C for 12 hours. The mixture was cooled to room temperature and then filtered through celite. The solvent was removed in vacuo and the residue purified by flash chromatography (silica; hexanes) to give the title compound as a yellow oil.

PMR ($CDCl_3$): & 0.22 (9H, s), 1.3 (6H, s), 1.91 - 1.98 (2H, t, J - 6.0 Hz), 2.99-3.2 (2H, t, J - 6.0 Hz) 7.09 (1H, dd, J - 1.8, J - 8.2 Hz) 7.20 (1H, d, J - 1.8 Hz) 7.26 (1H, d, J - 8.2 Hz).

Ethyl-6-(4,4-dimethyl-7-thiochromanyl)-ethynyl-nicotinate (**Compound 1**)

To a solution of 1 g (3.6 mmol) of 4,4-dimethyl-7-trimethylsilylethynyl-thio-chroman (**Compound 47**) in 10 ml of isopropyl alcohol was added 5 ml of 1 N KOH solution. The reaction mixture was stirred at room temperature for 18 hours and the isopropanol was then removed under vacuum. The residue was extracted with ether and the ether extracts were combined and washed with dilute HCl solution, water and saturated NaCl solution, and were thereafter dried ($MgSO_4$). The solvent was removed in vacuo to give impure 4,4-dimethyl-7-ethynyl-thiochroman (**Compound 48**) as a pale yellow

oil. This mixture was used in the next step without further purification.

A solution of 720 mg (3.56 mmol) of 4,4-dimethyl)-7-ethynyl thiochroman (**Compound 48**) and 666 mg (3.6 mmol) of ethyl 6-chloronicotinate in 3 ml of triethylamine was placed in a heavy walled glass tube and degassed under argon. The mixture was then treated with a mixture of 350 mg (1.8378 mmol) of cuprous iodide and 250 mg (.356 mmol) of bis(triphenylphosphine) palladium (II) chloride and the tube was sealed. The reaction mixture was stirred at 50 degrees for 20 hours, cooled to room temperature, and then filtered through celite. The solvent was removed in-vacuo and the residue was purified by flash chromatography (silica: 5% EtOAC/Hexane) to give the title compound as a yellow oil.

PMR ($CDCl_3$): & 1.32 (6H, s), 1.41 (3H, t, J - 7.1 Hz), 1.92 - 2.00 (2H, m), 3.00 - 3.08 (2H, m), 4.42 (2H, q, J - 7.1 Hz), 7.25 (1H, dd, J - 8.3 Hz, 2.0 Hz), 7.32 - 7.38 (2H, m), 7.56 (1H, d, J - 8.4 Hz), 8.27 (1H, dd, J - 8.4 Hz, 2.2 Hz), 9.20 (1H, d, J - 2.2 Hz).

6-[(4,4,dimethyl-7-thiochromanyl)-ethynyl]-nicotinic acid (**Compound 2**)

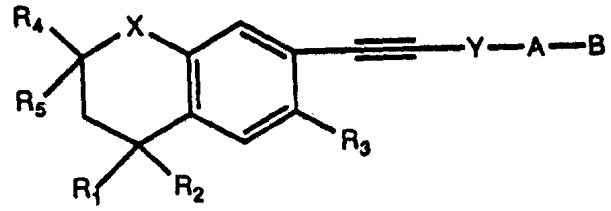
To 200 mg (.5696 mmol) of ethyl-6-(4,4-dimethyl-7-thiochromanyl)-ethynyl-nicotinate (**Compound 1**) was added 5 ml of ethanolic KOH solution. The reaction mixture was stirred at room temperature for 24 hours. The ethanol was removed in vacuo and the residue was taken up in 3 ml of water and 3 ml of ether. The layers were separated and the aqueous layer was washed with ether. The aqueous layer was then acidified to Ph=2 with 1 N HCl and the mixture was extracted with 2x20 ml ether. The ether extracts were combined and

washed successively with water and saturated sodium chloride solution and then dried ($MgSO_4$). The solvent was removed in vacuo to give the title compound as a yellow solid.

PMR ($CDCl_3$): 1.35 (6H, s), 1.93 - 2.02 (2H, s), 3.00 - 3.09 (2H, m), 7.26 (1H, d, J - 8.0 Hz), 7.32 - 7.40 (2H, m), 8.30 (1H, dd, J - 8.0 Hz, 2.0 Hz), 9.22 (1H, d, J - 2.0 Hz).

WHAT IS CLAIMED IS:

1. A compound of the formula



where **X** is S or O;

R_1-R_5 independently are hydrogen or lower alkyl;

Y is a heteroaryl group or a lower alkyl substituted heteroaryl group where heteroaryl is selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, ~~pirimidinyl~~ pyrimidinyl, pyrazinyl, thiazolyl and oxazolyl;

A is lower branched chain alkyl having 2 to 6 carbons, cycloalkyl having 3 to 6 carbons, alkenyl having 2 to 6 carbons and 1 or 2 double bonds, alkynyl having 2 to 6 carbons and 1 or 2 triple bonds, $(CH_2)_n$ and where n is an integer from 0 - 5;

B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11}, CH_2OCOR_{11}, CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, -COR", $CR"(OR_{12})_2$, or $CR"OR_{13}O$, where R" is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or phenyl or lower

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alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent alkyl radical of 2 - 5 carbons.

2. A compound of Claim 1 where X is S.

3. A compound of Claim 2 where A is $(CH_2)_n$ and n is 0, 1, or 2.

4. A compound of Claim 3 where B is COOH or a pharmaceutically acceptable salt, thereof, or B is $COOR_8$ or $COONR_9R_{10}$.

5. A compound of Claim 3 where R_4 is H and R_5 is lower alkyl.

6. A compound of Claim 3 where R_4 is the same alkyl group as R_5.

7. A compound of Claim 3 where R_4 is lower alkyl and R_5 is lower alkyl and R_4 and R_5 are different.

8. A compound of Claim 3 where R_4 and R_5 are both hydrogen.

9. A compound of Claim 1 where X is O.

10. A compound of Claim 9 where A is $(CH_2)_n$ and n is 0, 1, or 2.

11. A compound of Claim 10 where B is COOH or a pharmaceutically acceptable salt, thereof, or B is $COOR_8$ or $COONR_9R_{10}$.

12. A compound of Claim 10 where R_4 is H and R_5 is lower alkyl.

13. A compound of Claim 10 where R_4 is lower alkyl and R_5 is lower alkyl and R_4 and R_5 are different.

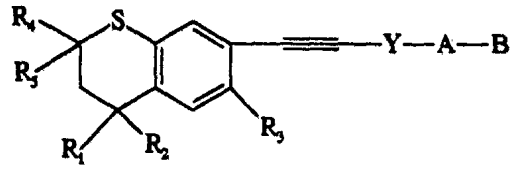
14. A compound of Claim 10 where R_4 is the same alkyl group as R_5.

15. A compound of Claim 12 where R_4 and R_5 are both H.

16. A pharmaceutical composition comprising one

or more compounds set forth in Claim 1, the composition including a pharmaceutically acceptable excipient.

17. A compound of the formula



where R_1, R_2, R_3, R_4 and R_5 independently are hydrogen or lower alkyl;

A is lower branched chain alkyl having 2 to 6 carbons, cycloalkyl having 3 to 6 carbons, alkenyl having 2 to 6 carbons and 1 or 2 double bonds, alkynyl having 2 to 6 carbons and 1 or 2 triple bonds, $(CH_2)_n$ where n is an integer between 0 to 5;

B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, $COONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11}, CH_2OCOR_{11}, CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, -COR", $CR"(OR_{12})_2$, or $CR"OR_{13}O$, where R" is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylpehnyl, R_{12} is lower alkyl, R_{13} is divalent alkyl radical of 2 - 5 carbons; and

Y is a heteroaryl group or a lower alkyl substituted heteroaryl group where heteroaryl is selected from the group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl and oxazolyl.

18. A compound of Claim 17 wherein A is $(CH_2)_n$

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and n is 0.

19. A compound of Claim 17 where B is COOH or a pharmaceutically acceptable salt thereof, or B is $COOR_8$ or $COONR_9R_{10}$.

20. A compound of Claim 19 where R_1-R_5 are independently H or methyl.

21. A compound of Claim 20 where B is $COOC_2H_5$.

22. The compound of Claim 21 where R_3 is H and R_1, R_2, R_4 and R_5 are methyl.

23. The compound of Claim 21 where R_1, R_2 are methyl and R_3, R_4 and R_5 are hydrogen.

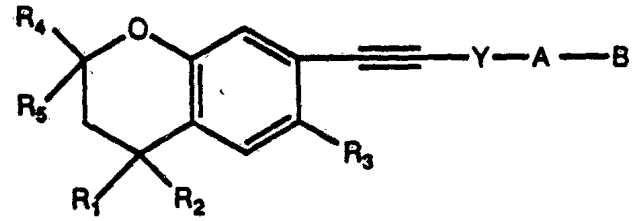
24. A compound of Claim 20 where B is COOH.

25. A compound of Claim 24 where R_3 is H and R_1, R_2, R_4 and R_5 are methyl.

26. A compound of Claim 24 where R_1 and R_2 are methyl and R_3, R_4 and R_5 are H.

27. The compound of Claim 19 where B is COOH or a pharmaceutically acceptable salt thereof, R_1, R_2 are methyl, and R_3, R_4 and R_5 are hydrogen.

28. A compound of the formula



where R_1, R_2, R_3, R_4 and R_5 are hydrogen or lower alkyl;

A is lower branched chain alkyl having 2 to 6 carbons, cycloalkyl having 3 to 6 carbons, alkenyl

having 2 to 6 carbons and 1 or 2 double bonds, alkynyl having 2 to 6 carbons and 1 or 2 triple bonds, $(CH_2)_n$ where n is an integer between 0 to 5;

B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, $COONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11}, CH_2OCOR_{11}, CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, -COR", $CR"(OR_{12})_2$, or $CR"OR_{13}O$, where R" is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylpehnyl, R_{12} is lower alkyl, and R_{13} is divalent alkyl radical of 2 - 5 carbons; and

Y is a heteroaryl group or a lower alkyl substituted heteroaryl group where heteroaryl is selected from the group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl and oxazolyl.

29. A compound of Claim 28 where A is (CH_2) and n is O.

30. A compound of Claim 29 where B is COOH or a pharmaceutically acceptable salt thereof, or B is $COOR_8$ or $COONR_9R_{10}$.

31. A compound of Claim 30 where B is $COOC_2H_5$.

32. The compound of Claim 31 where R_3 is hydrogen, R_1, R_2, R_4 and R_5 are methyl.

33. A compound of Claim 30 where B is COOH.

34. A compound of Claim 33 where R_3 is hydrogen, R_1, R_2, R_4 and R_5 are methyl.

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INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/02349

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

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

Int.Cl.5 C 07 D 409/06 C 07 D 405/06 A 61 K 31/455
C 07 D 401/06 C 07 D 413/06 C 07 D 417/06

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	EP,A,0284288 (ALLERGAN) 28 September 1988, see pages 2-3 (cited in the application)	1,16

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
29-06-1992	11. 08. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Natalie Weinberg

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/02349

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet) see annex

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 17-34
because they relate to subject matter not required to be searched by this Authority, namely:

The variable Y in the formulae of claims 17 and 28 is not defined, so that the claims 17-34 do not define the compounds for which patent protection is sought.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.