AU9517256

(12) PATENT ABRIDGMENT (11) Document No. AU-B-17256/95
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 684613

(54) Title
ACETYLENES DISUBSTITUTED WITH A PHENYL OR HETEROARYL GROUP AND A 2-OXOCHROMANYL, 2-OXOTHIOCHROMANYL OR 2-OXO-1,2,3,4-TETRAHYDROQUINOLINYL GROUP HAVING RETINOID-LIKEACTIVITY

International Patent Classification(s)
(51)[6] **C07D 405/06** **A61K 031/35** **C07D 311/20** **A61K 031/455**

(21) Application No. : **17256/95** (22) Application Date : **09.01.95**

(87) PCT Publication Number : **WO95/18803**

(30) Priority Data

(31) Number	(32) Date	(33) Country
178714	**07.01.94**	**US UNITED STATES OF AMERICA**

(43) Publication Date : **01.08.95**

(44) Publication Date of Accepted Application : **18.12.97**

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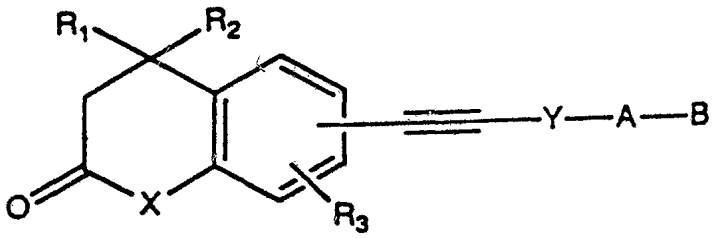
(57) Claim

1. (Amended) A compound of the formula



where R_1 and independently R_2 are hydrogen, lower alkyl of 1 - 6 carbons, or halogen;

R_3 is hydrogen, lower alkyl of 1 - 6 carbons, halogen, OR_{11}, SR_{11}, $OCOR_{11}$, $SCOR_{11}$, NH_2, NHR_{11}, $N(R_{11})_2$, $NHCOR_{11}$ or $NR_{11}COR_{11}$;

X is O, S or NR' where R' is hydrogen or lower alkyl of 1 - 6 carbons;

Y is phenyl or a heteroaryl group selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl and oxazolyl;

A is $(CH_2)_n$ where n is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6

.../2

carbons, alkenyl having 2-6 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds;

B is COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11}, CH_2OCOR_{11}, CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, $-COR_7$, $CR_7(OR_{12})_2$, or $CR_7OR_{13}O$, where R_7 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 5-10 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.

OPI DATE 01/08/95 APPLN. ID 17256/95
AOJP DATE 14/09/95 PCT NUMBER PCT/US95/00268
AU9517256

(51) International Patent Classification 6 : C07D 405/06, 311/20, A61K 31/455, 31/35 — A1

(11) International Publication Number: WO 95/18803

(43) International Publication Date: 13 July 1995 (13.07.95)

(21) International Application Number: PCT/US95/00268

(22) International Filing Date: 9 January 1995 (09.01.95)

(30) Priority Data:
08/178,714 7 January 1994 (07.01.94) US

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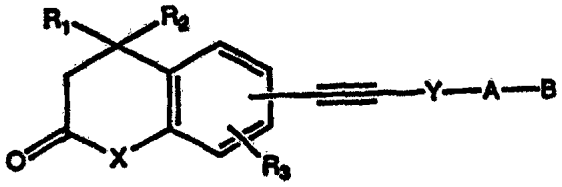
(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

684613

AUSTRALIAN 92 Bis 1/5/96 PATENT OFFICE

(54) Title: ACETYLENES DISUBSTITUTED WITH A PHENYL OR HETEROARYL GROUP AND A 2-OXOCHROMANYL, 2-OXOTHIOCHROMANYL OR 2-OXO-1,2,3,4-TETRAHYDROQUINOLINYL GROUP HAVING RETINOID-LIKE ACTIVITY



(1)

(57) Abstract

Compounds of formula (I) where R_1 and R_2 are hydrogen, lower alkyl of 1-6 carbons, or halogen; R_3 is hydrogen, lower alkyl of 1-6 carbons, halogen, OR_{11}, SR_{11}, $OCOR_{11}$, $SCOR_{11}$, NH_2, NHR_{11}, $N(R_{11})_2$, $NHCOR_{11}$ or $NR_{11}COR_{11}$; X is O, S or NR' where R' is hydrogen or lower alkyl of 1-6 carbons; Y is phenyl or a heteroaryl group selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl and oxazolyl; A is $(CH_2)_n$ where n is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or 2 double bonds; alkynyl having 2-6 carbons and 1 or 2 triple bonds; B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11}, CH_2OCOR_{11}, CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, $-COR_7$, $CR_7(OR_{12})_2$, or $CR_7OR_{13}O$, where R_7 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 5-10 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, have retinoid-like biological activity.

ACETYLENES DISUBSTITUTED WITH A PHENYL OR HETEROARYL GROUP AND A 2-OXOCHROMANYL, 2-OXOTHIOCHROMANYL OR 2-OXO-1,2,3,4-TETRAHYDROQUINOLINYL GROUP HAVING RETINOID-LIKE ACTIVITY

BACKGROUND OF THE INVENTION

AUSTRALIAN PATENT OFFICE

2. Field of the Invention

The present invention is directed to novel compounds which have retinoid-like biological activity. More specifically, the present invention relates to ethyne compounds which have a phenyl or a heteroaryl substituent and also a 2-oxochromanyl, 2-oxothiochromanyl or 2-oxo-1,2,3,4-tetrahydroquinolinyl substituent. The phenyl or heteroaryl group may have an acid or ester function, which may also be converted to an alcohol, aldehyde or ketone, or derivatives thereof, or may be reduced to $-CH_3$.

3. Related Art

Compounds which have retinoid like activity are well known in the art, and are described in numerous United States and foreign patents and in scientific publications. It is generally known and accepted in the art that retinoid like activity is useful for treating animals of the mammalian species, including humans, for curing or alleviating the symptoms and conditions of numerous diseases and conditions. In other words, it is generally accepted in the art that pharmaceutical compositions having a retinoid like compound or compounds as the active ingredient are useful as regulators of cell proliferation and differentiation, and particularly as agents for treating dermatoses, such as acne, Darier's disease, psoriasis, icthyosis, eczema and atopic dermatitis, and for treating and preventing malignant hyperproliferative diseases such as epithelial cancer, breast cancer, prostatic cancer, head and neck cancer and myeloid leukemias, for reversing and preventing atherosclerosis and restenosis resulting from neointimal hyperproliferation, for treating and

preventing other non-malignant hyperproliferative diseases such as endometrial hyperplasia, benign prostatic hypertrophy, proliferative vitreal retinopathy and dysplasias, for treating autoimmune diseases and immunological disorders (e.g. lupus erythematosus) for treating chronic inflammatory diseases such as pulmonary fibrosis, for treating and preventing diseases associated with lipid metabolism and transport such as dyslipidemias, for promoting wound healing, for treating dry eye syndrome and for reversing and preventing the effects of sun damage to skin.

United States Patent No. 4,810,804 discloses such disubstituted acetylene compounds wherein one of the substituents of the acetylene group is a substituted phenyl group, and the second substituent is substitited or unsubstituted 6-chromanyl, 6-thiochromanyl or 6-tetrahydroquinolinyl group. The compounds disclosed and claimed in United States Patent No. 4,810,804 have retinoid acid-like biological activity.

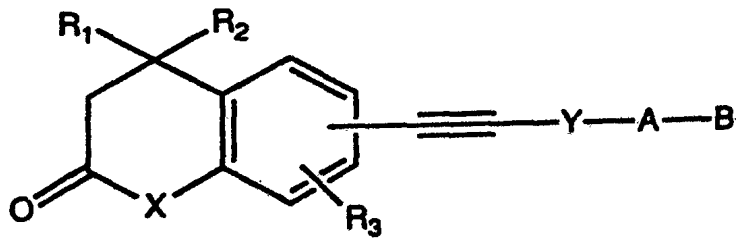
A published European patent application of the present applicant (Publication No. 0284288, published on September 28, 1988) describes compounds having retinoic acid-like activity which are 4,4-disubsituted 6-chromanyl, 4,4-disubsituted 6-thiochromanyl and 4,4-disubsituted 6-tetrahydroquinolinyl acetylenes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

United States Patent Nos. 5,013,744, 5,023,341, 5,053,523, and 5,089,509 describe ethyne compounds substituted with a heteroaromatic or monocyclic aromatic substituent and also with a second monocyclic aromatic or heteroaromatic substituent. The compounds described in these patents have retinoid-like

biological activity.

SUMMARY OF INVENTION

The present invention relates to compounds of **Formula 1**



Formula 1

where R_1 and R_2 are hydrogen, lower alkyl of 1 - 6 carbons, or halogen;

R_3 is hydrogen, lower alkyl of 1 - 6 carbons, halogen, OR_{11}, SR_{11}, $OCOR_{11}$, $SCOR_{11}$, NH_2, NHR_{11}, $N(R_{11})_2$, $NHCOR_{11}$ or $NR_{11}COR_{11}$;

X is O, S or NR' where R' is hydrogen or lower alkyl of 1 - 6 carbons;

Y is phenyl or a heteroaryl group selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl and oxazolyl;

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

B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11}, CH_2OCOR_{11}, CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, $-COR_7$, $CR_7(OR_{12})_2$, or $CR_7OR_{13}O$, where R_7 is an alkyl,

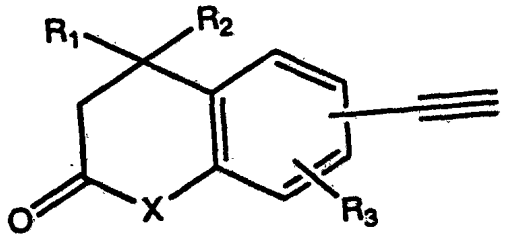
cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl 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** as regulators for cell proliferation and differentiation, and particularly as agents for treating dermatoses, such as acne, Darier's disease, psoriasis, icthyosis, eczema, atopic dermatitis, and for treating and preventing malignant hyperproliferative diseases such as epithelial cancer, breast cancer, prostatic cancer, head and neck cancer and myeloid leukemias, for reversing and preventing artherosclerosis and restenosis resulting from neointimal hyperproliferation, for treating and preventing other non-malignant hyperproliferative diseases such as endometrial hyperplasia, benign prostatic hypertrophy, proliferative vitreal retinopathy and dysplasias, for treating autoimmune diseases and immunological disorders (e.g. lupus erythematosus), for treating chronic inflammatory diseases such as pulmonary fibrosis, for treating and preventing diseases associated with lipid metabolism and transport such as dyslipidemias, for promoting wound healing, for treating dry eye syndrome and in reversing and preventing the effects of sun damage to skin.

This invention also relates to a pharmaceutical

composition 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.

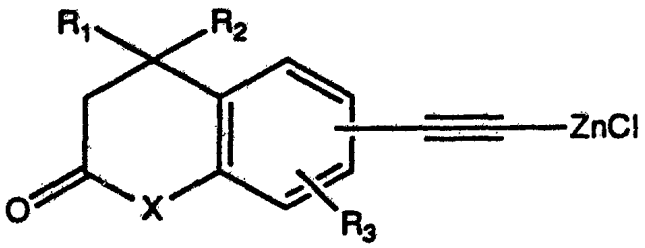


Formula 2



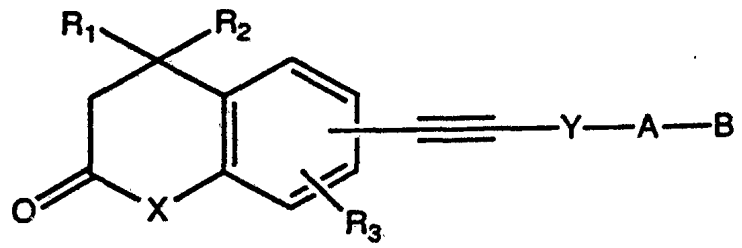
Formula 3

where **X**, **Y**, R_1, R_2 and R_3 are as described above, **X'** is a halogen, preferably I; **A** is 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 **X**, R_1, R_2 and R_3 are the same as defined above, giving the corresponding compound of **Formula 1**; or homologating a compound of **Formula 5**



Formula 5

where A is $(CH2)_n$ 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 akdehyde; 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.

DETAILED DESCRIPTION OF THE INVENTION

General Embodiments

Definitions

The term alkyl refers to and covers any and all groups which are known as normal alkyl, branched-chain alkyl and cycloalkyl. The term alkenyl refers to and covers normal alkenyl, branch chain alkenyl and cycloalkenyl groups having one or more sites of unsaturation. Lower alkyl means the above-defined broad definition of alkyl groups having 1 to 6 carbons, and as applicable, 3 to 6 carbons for branch chained

and cyclo-alkyl groups. Lower alkenyl is defined similarly having 2 to 6 carbons for normal alkenyl, and 3 to 6 carbons for branch chained and cycloalkenyl groups.

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. It includes organic and inorganic esters. Where B (of Formula 1) is -COOH, this term covers the products derived from treatment of this function with alcohols or thioalcohols preferably with aliphatic alcohols having 1-6 carbons. Where the ester is derived from compounds where B is $-CH_2OH$, this term covers compounds derived from organic acids capable of forming esters including phosphorous based and sulfur based acids, or compounds of the formula $-CH_2OCOR_{11}$ where R_{11} is defined as above.

The term "amides" 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.

A pharmaceutically acceptable salt may be prepared for any compounds in this invention having a functionality capable of forming such salt, for example an acid functionality. A pharmaceutically acceptable salt is 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.

Pharmaceutically acceptable salts may be derived from organic or inorganic bases. The salt may be a

mono or polyvalent ion. Of particular interest are the inorganic ions, sodium, potassium, calcium, and magnesium. Organic 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 of the present invention may contain one or more double bonds, and therefore may have trans and cis (E and Z) isomers. In adddition, the compounds of the present invention may contain one or more chiral centers and therefore exist in enantiomeric and diastereomeric forms. The scope of the present invention is intended to cover all such isomers per se, as well as mixtures of cis and trans isomers, mixtures of diastereomers and racemic mixtures of enantiomers (optical isomers) as well.

With reference now to **Formula 1**, the preferred compounds of this invention are those where **X** is O or S (chroman and thiochroman derivatives), with the chromans (**X** is O) being particularly preferred.

With reference to the group **Y** in **Formula 1**, compounds are preferred where **Y** is phenyl, pyridyl, thienyl or furyl, with the phenyl and pyridiyl derivatives being particularly preferred. When **Y** is phenyl compounds are preferred where the ethynyl group

and the **A-B** group are attached to the 1 and 4 positions respectively of a benzene ring (i.e., where the phenyl moiety of the compound is <u>para</u> substituted). When the **Y** group is pyridyl or thienyl, compounds are preferred where the ethynyl group and the **A-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 **A-B** side chain (substituent) on the phenyl or heteroaryl group **Y**, compounds are preferred where **A** is $(CH_2)_n$ and **n** is 0. With regard to group **B**, compounds are preferred where and **B** is -COOH, an alkali metal salt or organic amine salt, or a lower alkyl ester therof. The most preferred compounds of the invention are shown in **Formula 6**:

Ethyl 6-[4,4-dimethyl-2-oxo-6-chromanyl]-ethynyl-nicotinate

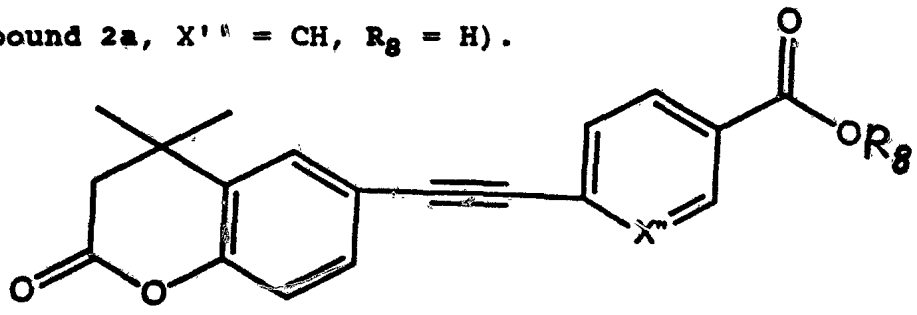
(**Compound 1**, X'' = N, $R_8 = C_2H_5$);

Ethyl 4-[4,4-dimethyl-2-oxo-6-chromanyl]-ethynyl-benzoate

(**Compound 2**, X'' = CH, $R_8 = C_2H_5$), and

4-[4,4-dimethyl-2-oxo-6-chromanyl]-ethynyl-benzoic acid

(**Compound 2a**, X'' = CH, 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 numerous other 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 or psoriasis, 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 suitable 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 by injection. In certain cases, it may be useful to formulate these compounds in suppository form or as extended release formulation for deposit under the skin or intramuscular 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; medicaments for

preventing infection, reducing irritation, inflammation and the like.

Treatment of dermatoses or any other indications known or discovered to be susceptible to treatment by retinoid-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 it expansion. In certain instances, the compound potentially may be used in prophylactic manner to prevent onset of a particular condition. A useful therapeutic or prophylactic 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, no single concentration will be uniformly useful, but will require modification depending on the particularities of the disease being treated. Such concentrations can be arrived at through routine experimentation. However, it is anticipated that in the treatment of, for example, acne, or similar dermatoses, that a formulation containing between 0.01 and 1.0 milligrams per milliliter of formulation will constitute a therapeutically effective concentration for total application. If administered systemically, an amount between 0.01 and 5 mg per kg per day of body weight would be expected to effect a therapeutic result in the treatment of many disease for which these compounds are useful.

The retinoid-like activity of these compounds is confirmed through the classic measure of retinoic acid activity involving the effects of retinoic 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 increases are unknown, it is known that 12-0-tetradecanoylphorbol-13-acetate (TPA) induces ODC activity. Retinoic acid inhibits this induction of ODC activity by TPA. An assay essentially following the procedure set out in Cancer Res: 1662-1670,1975 may be used to demonstrate inhibition of TPA induction of ODC by compounds of this invention. The results of this assay for certain examplary compounds of the invention are shown in **Table 1** below, wherein the percentage of ODC inhibition attained by 30, 100 and 1,000 nanomolar (nmol) concentration of the respective compound is indicated.

Table 1

% inhibition

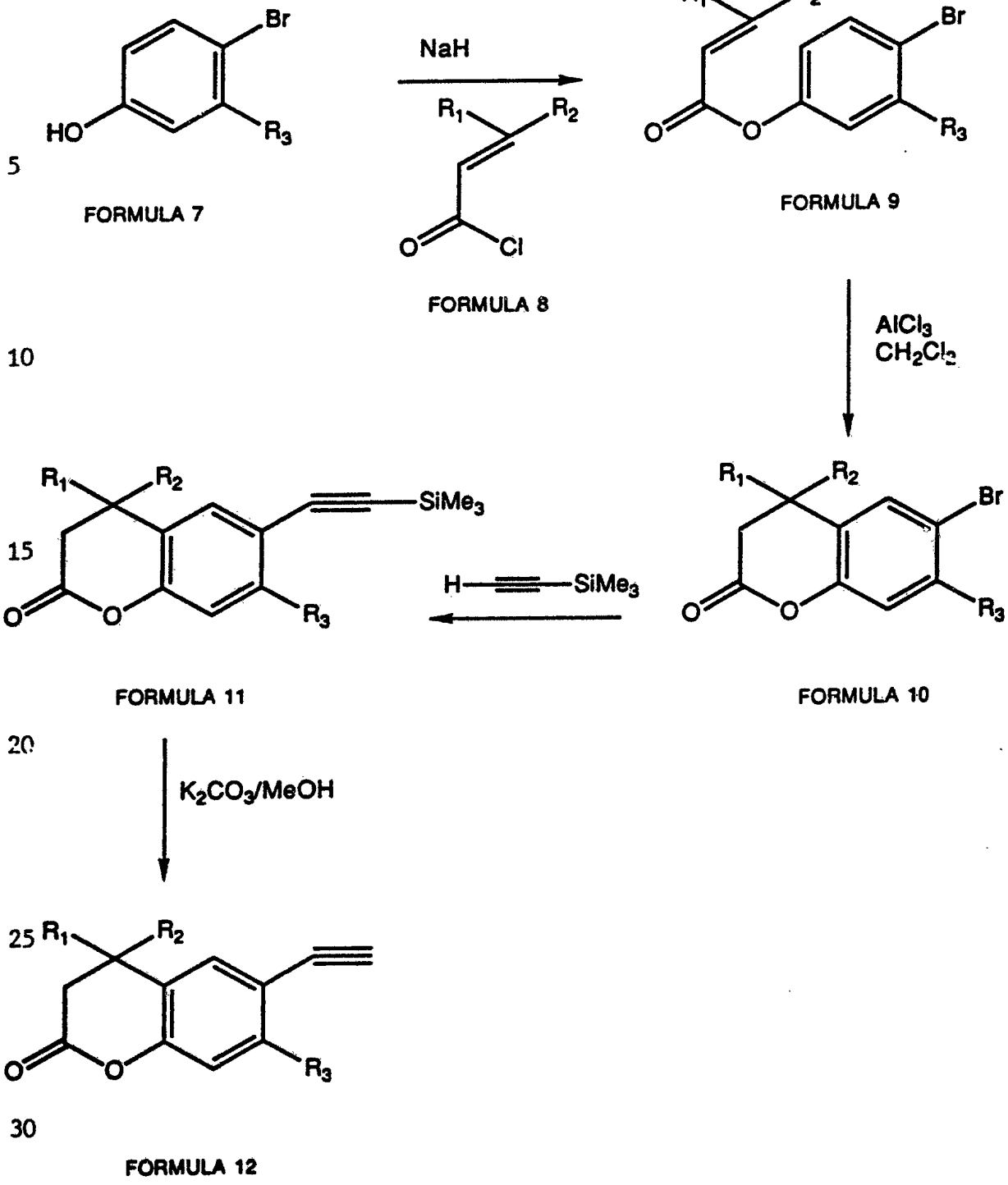
Compound #	30nmol	100nmol	1,000nmol
1	**55%**	**63%**	
2	**80%**	**81%**	
2a	**64%**	--	**78%**

SPECIFIC EMBODIMENTS

Synthetic Processes for Preparing Compounds of the Invention

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 O (chroman derivatives) are prepared as per **Reaction Schemes 1** and **2**.



FORMULA 7

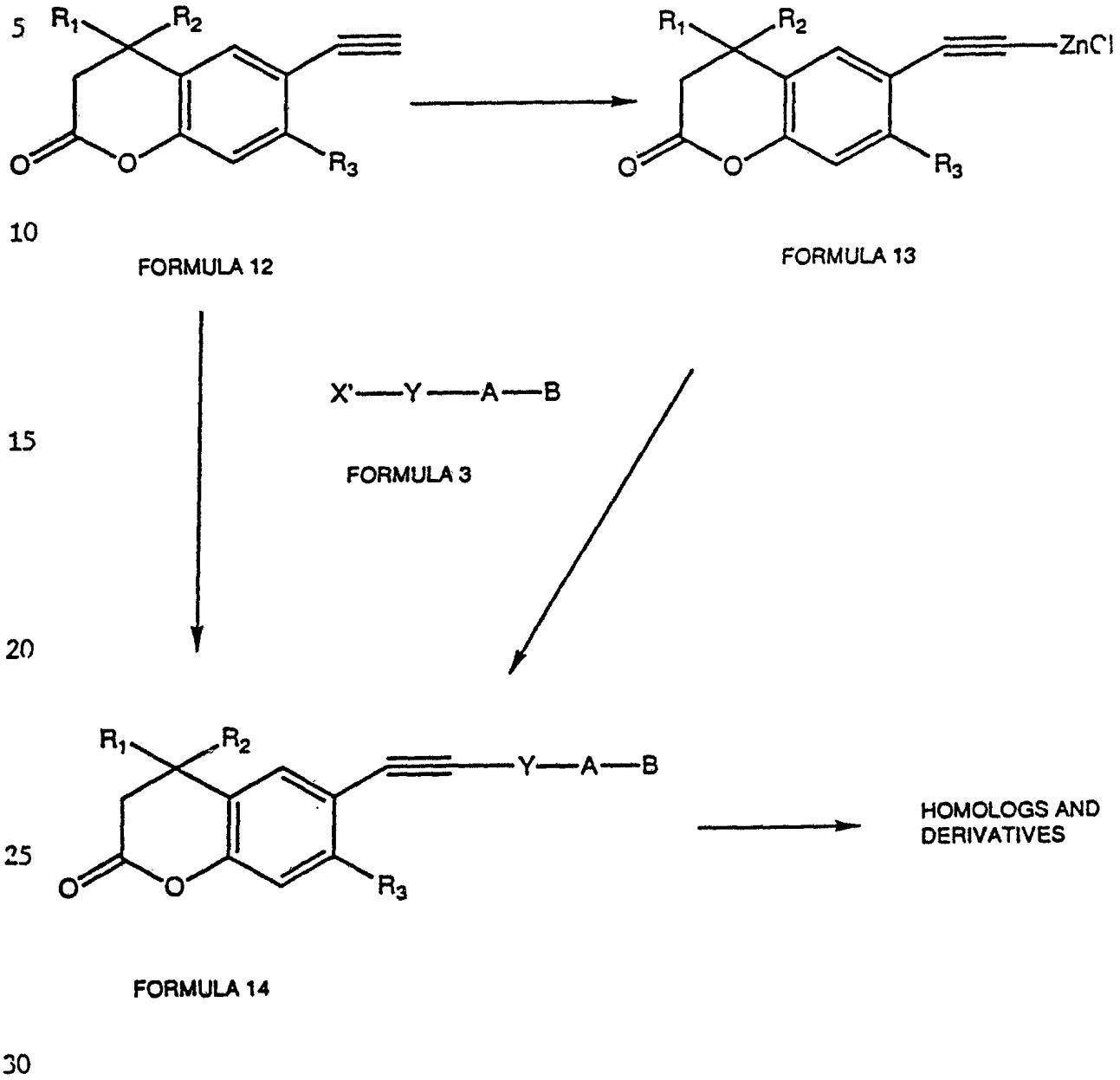
FORMULA 8

FORMULA 9

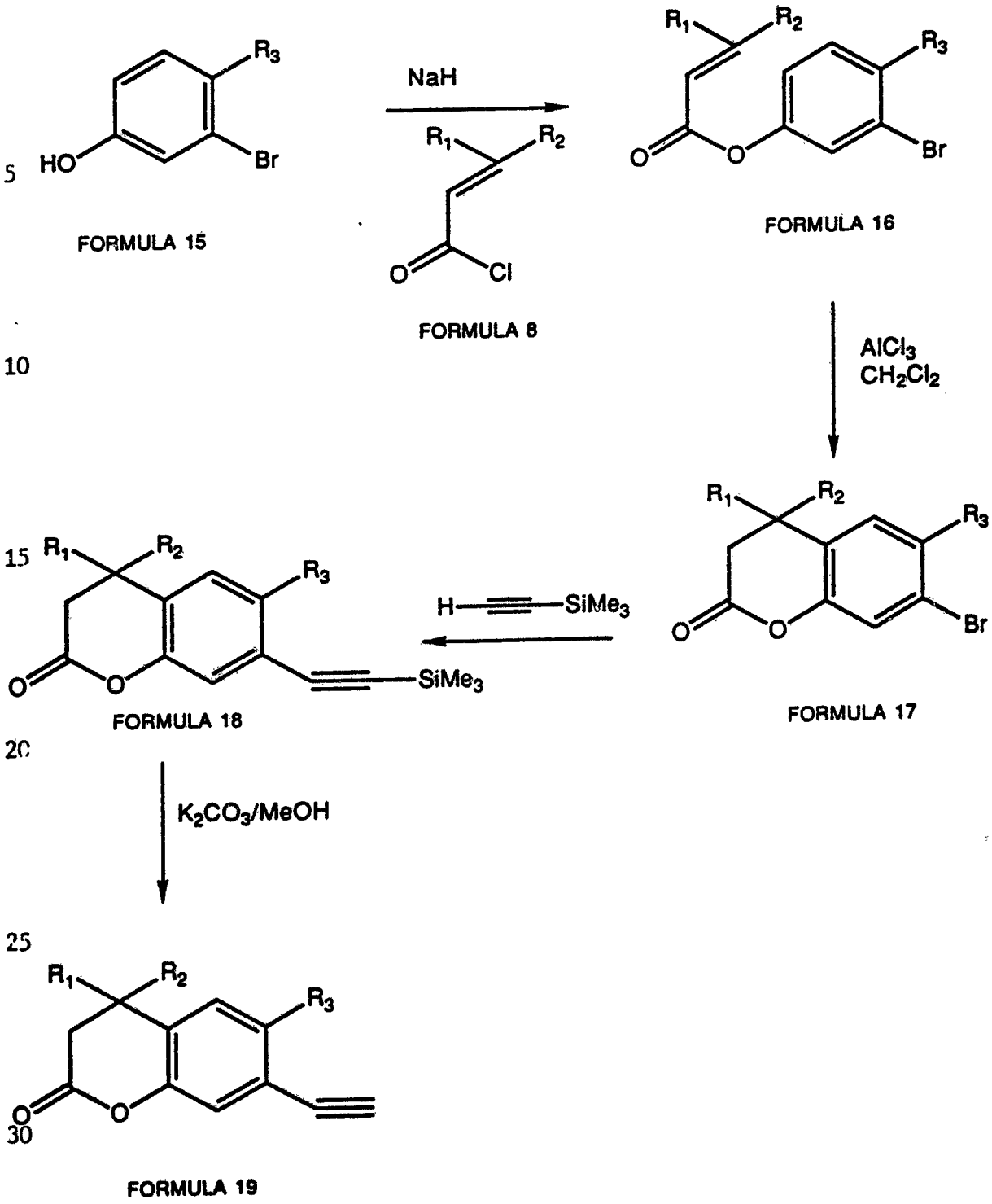
FORMULA 10

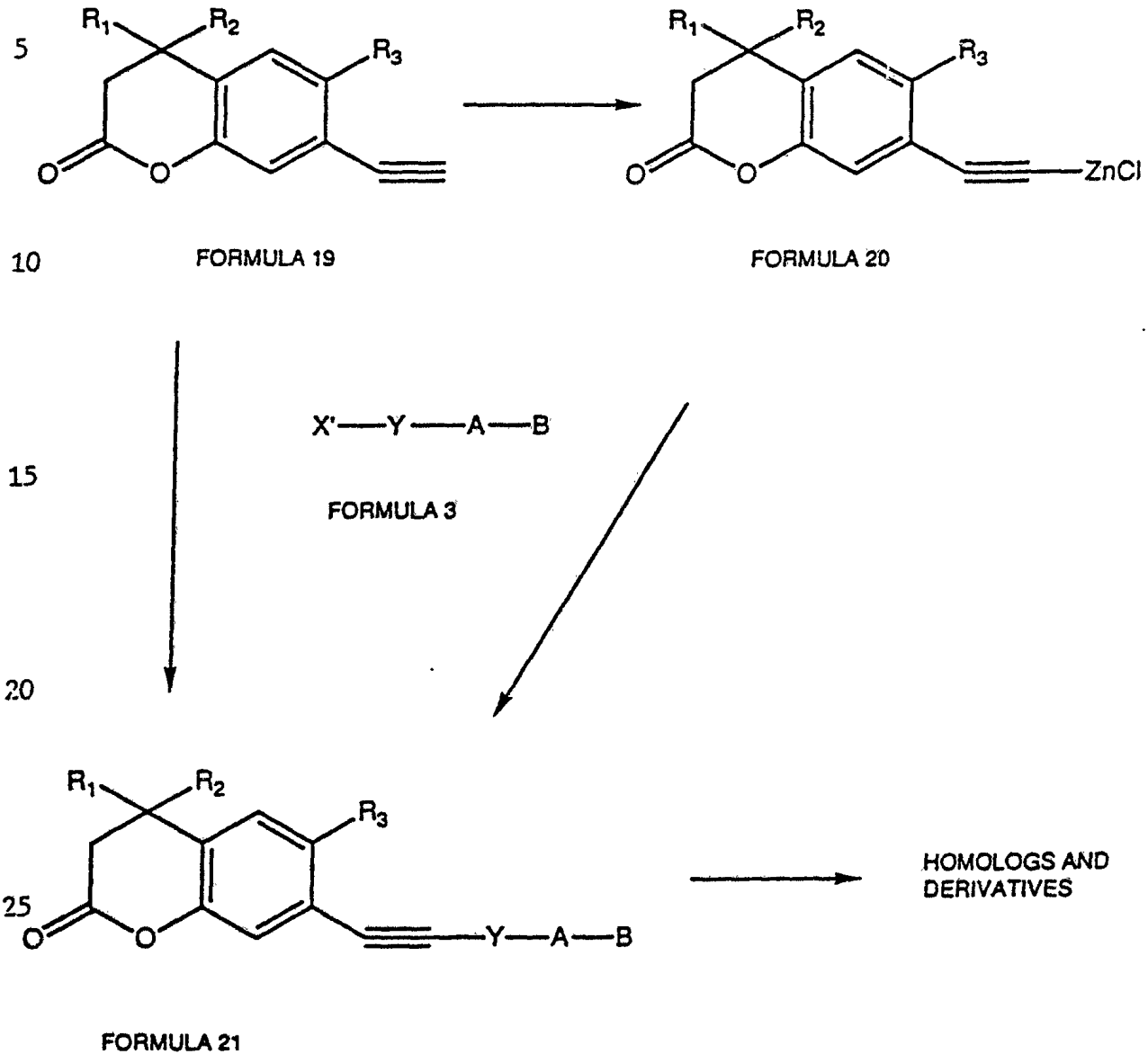
FORMULA 11

FORMULA 12



Reaction Scheme 1


HO
Br
R3
FORMULA 15
NaH
R1
R2
O
Cl
FORMULA 8
O
O
FORMULA 16
AlCl3
CH2Cl2
FORMULA 17
H
SiMe3
FORMULA 18
K2CO3/MeOH
FORMULA 19



Reaction Scheme 2

In **Reaction Schemes 1** and **2** R_1 - R_3 are defined as in connection with **Formula 1**, and **X'**, **Y**, **A** and **B** are defined as in connection with **Formula 3**. As it will become apparent from the schemes, in **Reaction Scheme 1** the ethynyl group is located in the 6-position of the chroman ring, whereas in **Reaction Scheme 2** the ethynyl group is located in the 7-position of the chroman ring. A general description of the synthetic steps outlined in **Reaction Schemes 1** and **2** is as follows.

In **Reaction Scheme 1** 4-bromophenol (**Formula 7**), or a 4-bromophenol substituted in the 3-(meta) position by an alkyl substituent (R_3 in **Formula 7**) is acylated with an acylating agent, such as an acid chloride (**Formula 8**) derived from an appropriately substituted acrylic acid. Thus, the R_1 and R_2 substitutents of the target compound are introduced through this acrylic acid derivative (**Formula 8**). The acylation with the acid chloride (**Formula 8**) 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 1** as **Formula 9**. The substituted phenyl-acrylate (**Formula 9**) 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-6-bromo-chroman (**Formula 10**) which bears, in the 4-position, the R_1 and R_2 substituents and in the 7 positions the R_3 substituent (as applicable). To introduce the acetylene (ethyne) portion into the molecule, the substituted 6-bromo-2-oxo-chroman (**Formula 10**) is reacted with trimethylsilyl acetylene 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 a 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 6-trimethylsilylethynyl-2-oxo-chroman is shown as **Formula 11** in **Reaction Scheme 1.**

As shown in **Reaction Scheme 1**, the trimethylsilyl moiety is removed from the 6-trimethylsilylethynyl-2-oxo-chroman (**Formula 11**) in the next synthetic step, to provide the ring substituted 6-ethynyl-2-oxo-chroman derivative (**Formula 12**). The latter reaction is conducted under basic conditions, preferably under an inert gas atmosphere.

In order to introduce a phenyl or heteroaryl substitutent on the acetylene (ethyne) portion of a compound of **Formula 12**, the latter compound is coupled with the reagent **X'-Y-A-B** (**Formula 3**). In other words, the phenyl or heteroaryl substitutent is introduced into the 6-ethynyl-2-oxo-chroman (**Formula 12**) by reacting the latter with a halogen substituted phenyl or heteroaromatic compound of **Formula 3** in which the phenyl or heteroaromatic nucleus (**Y**) either has the desired substituent [**A-B**] or wherein the actual subsituent **A-B** can be readily converted to the desired substituent by means of organic reactions well known in the art.

Coupling of the 6-ethynyl-2-oxo-chroman (**Formula 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. Alternatively, a metal salt, such as the zinc salt of **Formula 13** derived from the ethynyl compound of **Formula 12** is reacted with the reagent of **Formula 3** in the presence of a palladium complex catalyst having the formula $Pd(PQ_3)_4$ (Q is phenyl) or similar complex.

The resulting disubstituted acetylene compound (**Formula 14**) may be the target compound made in accordance with the invention, or may be 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.

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.

A 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 well known Arndt-Eistert method of

homologation, or other known 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 halogenated bicyclic aryl or bicyclic heteroaryl intermediate which is reacted with the ethyne compound or its metal salt, as shown in **Reaction Scheme 1**. Generally speaking, such compounds 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-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 aryl or heteroaryl aldehyde intermediate. Such intermediate can be obtained by reactions well known in the art, for example, by reaction of a corresponding methyl ketone with strong base, such as lithium diisopropyl amide.

The acids and salts derived from compounds of **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 organic 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 dicyclohex-

ylcarbodiimide 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 of **Formula 1** where **B** is H can be prepared from the corresponding halogenated aromatic compounds, preferably where the halogen is I.

Referring now to **Reaction Scheme 2**, 3-bromophenol (**Formula 15**), or a 3-bromophenol substituted the 4-(para) positions by by an alkyl substituent (R_3 in **Formula 15**) is acylated with an acylating agent, such as an acid chloride (**Formula 8**) derived from an appropriately substituted acrylic acid. In **Reaction Scheme 2**, just as in **Reaction Scheme 1**, the R_1 and R_2 substitutents of the target compound are introduced through this acrylic acid derivative (**Formula 8**). The acylation with the acid chloride (**Formula 8**) 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 compound is shown in **Reaction Scheme 2** as **Formula 16**. The substituted phenyl-acrylate (**Formula 16**) is ring closed under Friedel-Crafts type reaction

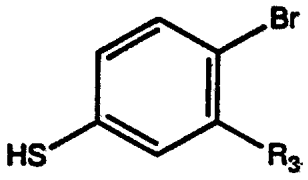
conditions ($AlCl_3$ catalyst, in an inert solvent, such as methylene chloride) to provide the 2-oxo-7-bromo-chroman (**Formula 17**) which bears, in the 4-position, the R_1 and R_2 substituents and in the 6 position the R_3 substituent (as applicable). To introduce the acetylene (ethyne) portion into the molecule, the substituted 7-bromo-2-oxo-chroman (**Formula 17**) is reacted with trimethylsilyl acetylene in the presence of cuprous iodide and a suitable catalyst, typically having the formula $Pd(PQ_3)_2Cl_2$ (Q is phenyl), as defined in **Reaction Scheme 1**. The resulting 7-trimethylsilyl-ethynyl-2-oxo-chroman is shown as **Formula 18** in **Reaction Scheme 2**.

In **Reaction Scheme 2**, just as in **Reaction Scheme 1**, the trimethylsilyl moiety is removed from the 7-trimethylsilylethynyl-2-oxo-chroman (**Formula 18**) under basic conditions, to provide the ring substituted 7-ethynyl-2-oxo-chroman derivative (**Formula 19**).

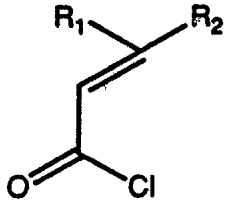
The 7-ethynyl-2-oxo-chroman derivative of **Formula 19** may be converted into the target compounds of the invention in synthetic steps which are analogous to the conversion of 6-ethynyl-2-oxo-chromans (**Formula 12**) into the corresponding target 2-oxo-chroman derivatives (See **Reaction Scheme 1**). Briefly, a compound of **Formula 19** is preferably heated with a reagent **X'-Y-A-B** (**Formula 3**) in the presence of cuprous iodide, a suitable catalysts, 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. This coupling reaction, yields the target chroman compounds of **Formula 21** or such derivatives which are readily converted into the target compounds by protection, deprotection,

esterification, deesterification, homologation and the like, as is discussed in connection with **Reaction Scheme 1.**

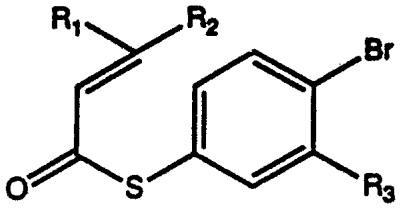
Alternatively, the 7-ethynyl-2-oxo-chroman compounds of **Formula 19** may first be converted to the corresponding metal (zinc) salt of **Formula 20** and thereafter coupled with the reagent **X'-Y-A-B (Formula 3)** under conditions which are similar to the conditions described in **Reaction Scheme 1** for coupling of compounds of **Formula 13** with the same reagent.



FORMULA 22



FORMULA 8



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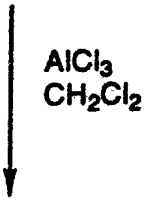

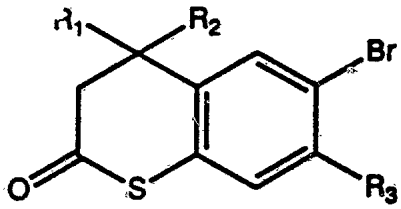

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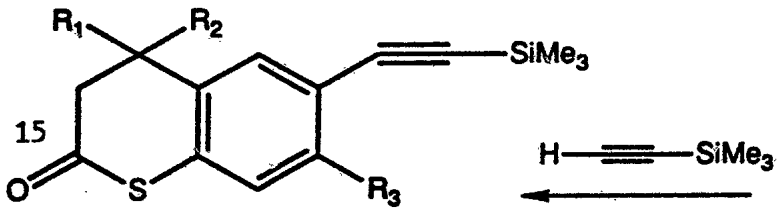

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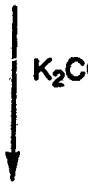
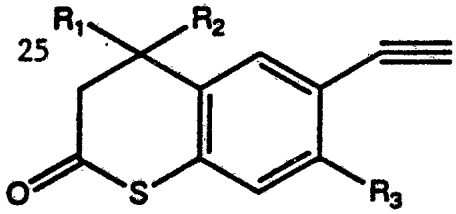
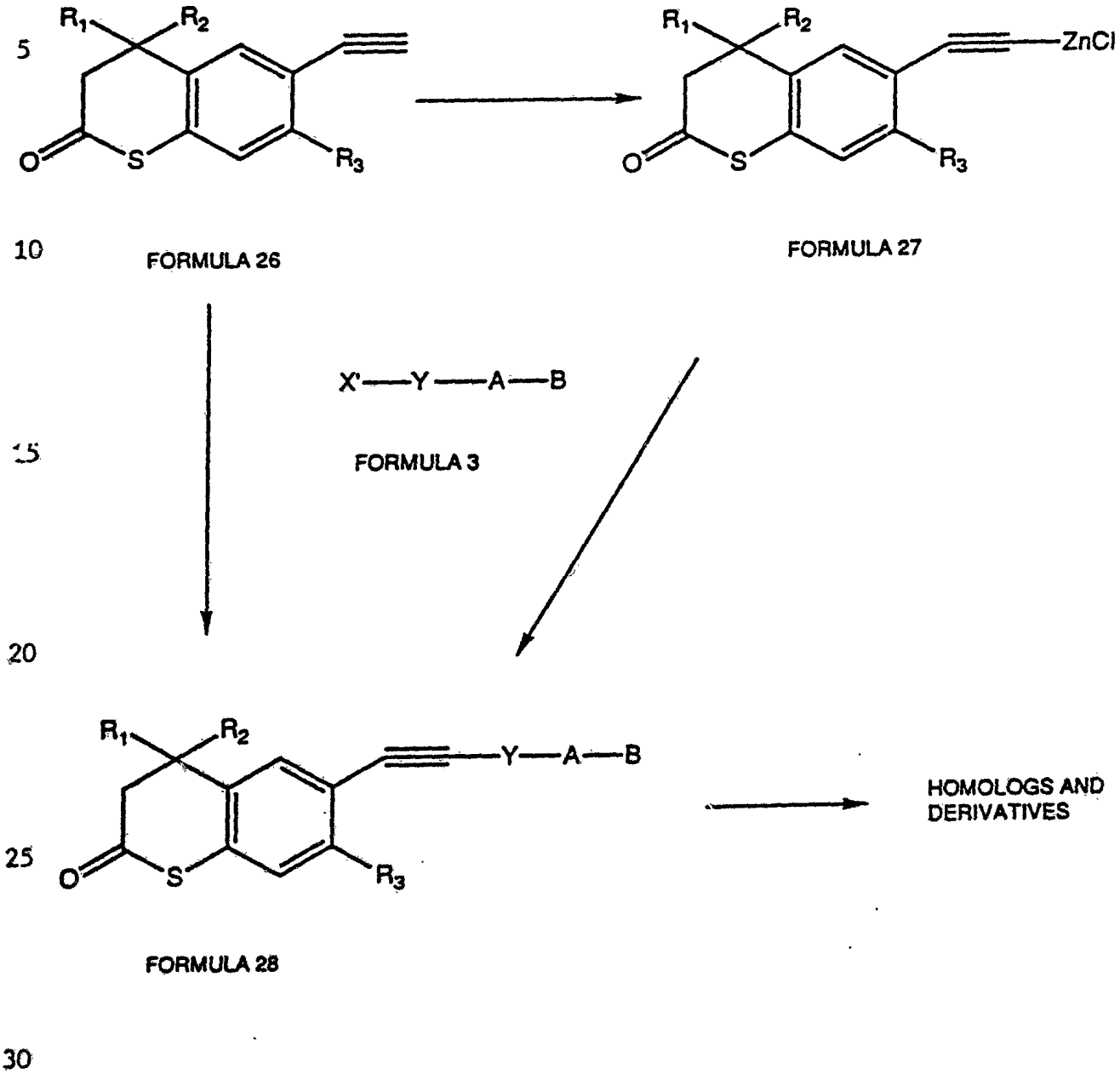
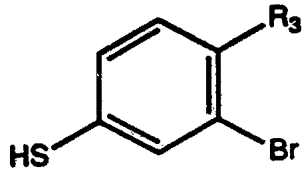




FORMULA 26



Reaction Scheme 3



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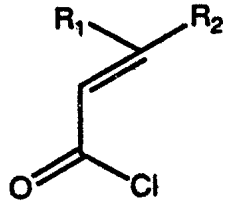
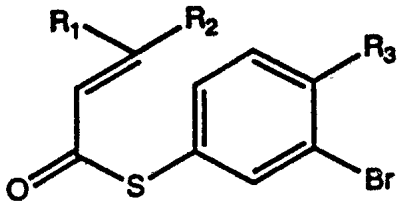
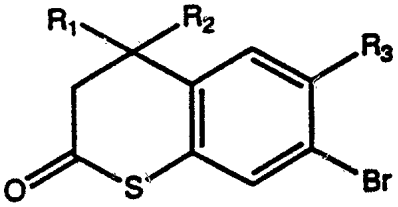


FORMULA 8



FORMULA 30



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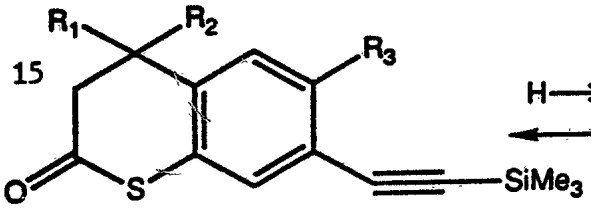
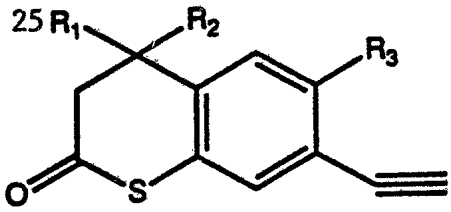
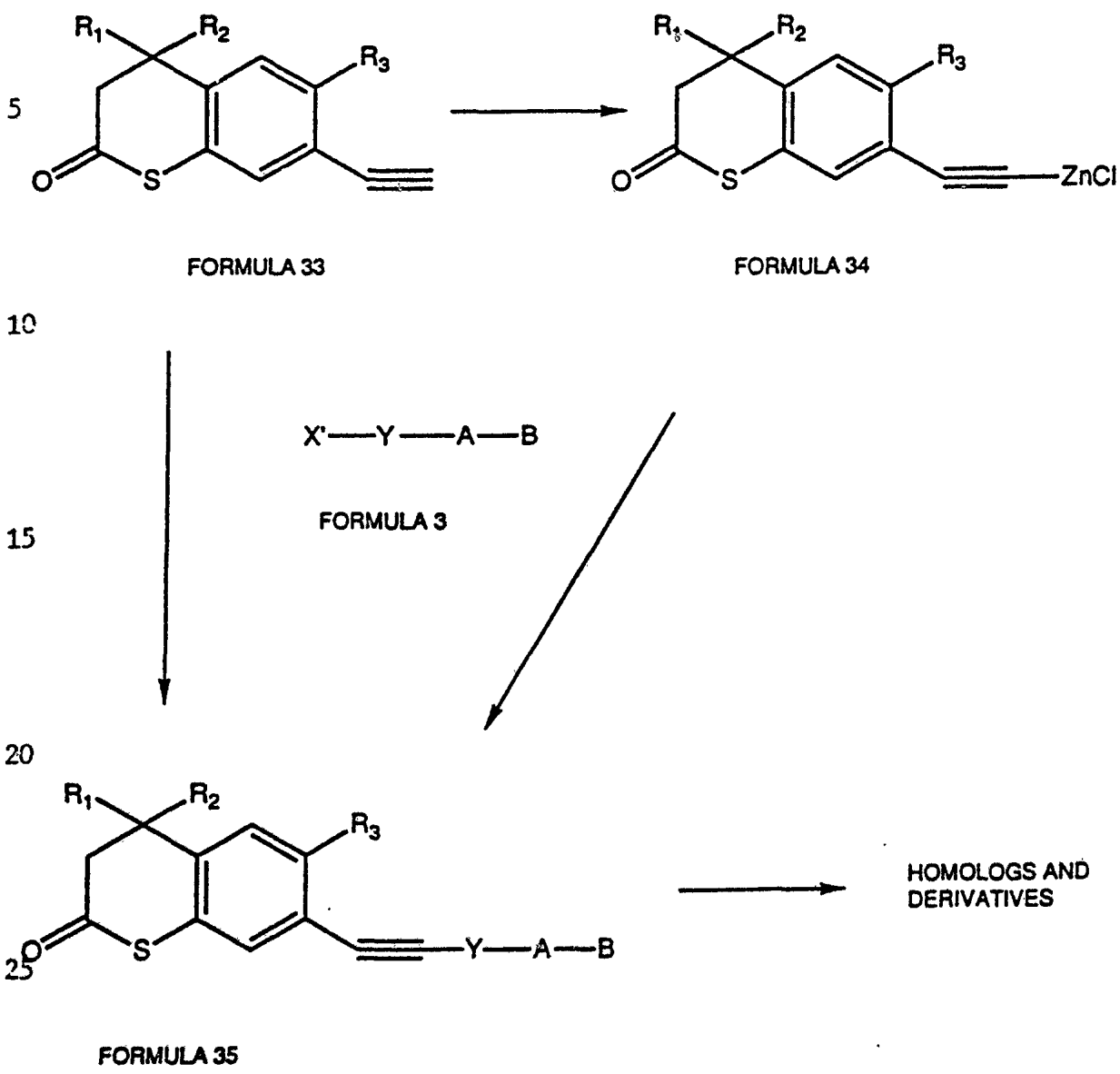


FORMULA 32



FORMULA 33



Reaction Scheme 4

Compounds of **Formula 1** where **X** is S are prepared as per **Reaction Scheme 3** and **4**.

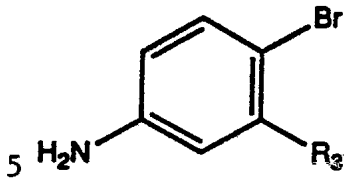
In **Reaction Schemes 3** and **4** the definitions of R_1-R_3, **Y**, **A**, **B**, and **X'** are the same as in **Reaction Schemes 1** and **2**. In **Reaction Scheme 3** the ethynyl group is located in the 6 position of the thiochroman ring. In **Reaction Scheme 4** the ethynyl group is located in the 7 position of the thiochroman ring. Many of the synthetic steps are analogous to the steps described above in connection with **Reaction Schemes 1** and **2**, and these steps are not described in detail again.

Thus, in **Reaction Scheme 3** 4-bromo-thiophenol (**Formula 22**), or a 4-bromo-thiophenol substituted in the 3-(meta) position by an alkyl substituent (R_3) is acylated with the acylating agent of **Formula 8**. The resulting substituted thioester (**Formula 23**) which contains the olefinic bond of the acrylic acid moiety is ring closed in the presence of a Friedel-Crafts type catalysts, as in the preceding reaction schemes. To introduce the acetylene (ethyne) portion into the molecule, the substituted 2-oxo-6-bromo-thiochroman (**Formula 24**) is reacted with trimethylsilyl acetylene as in the preceding reaction schemes to give 6-trimethylsilylethynyl-2-oxo-thiochroman (**Formula 25**). The trimethylsilyl moiety is removed from the 6-trimethylsilylethynyl-2-oxo-thiochroman (**Formula 25**) in the next synthetic step, to provide the ring substituted 6-ethynyl-2-oxo-thiochroman derivative (**Formula 26**).

The compound of **Formula 26** is then coupled with the reagent **X'-Y-A-B** (**Formula 3**) either directly (in the presence of cuprous iodide, and a suitable catalyst, typically of the formula $Pd(PQ_3)Cl_2$, and an

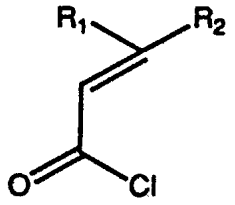
acid acceptor, such as triethylamine) or as its metal (zinc) salt **Formula 27** to yield the compound of **Formula 28**, as described in the preceding reaction schemes.

In accordance with **Reaction Scheme 4**, 3-bromo-thiophenol, or a 3-bromo-thiophenol substituted in the 4-(para) positions by an alkyl substituent (R_3) is acylated with the acylating agent of **Formula 8** to yield the substituted thioester compound of Formula 30. The substituted thioester (**Formula 30**) is ring closed under Friedel-Crafts type reaction conditions, as in the preceding reaction schemes, to provide the 2-oxo-7-bromo-thiochroman (**Formula 31**). The substituted 7-bromo-2-oxo-thiochroman (**Formula 31**) is reacted with trimethylsilyl acetylene, as described above, to yield 7-trimethylsilyl-ethynyl-2-oxo-thiochroman (**Formula 32**). The trimethylsilyl moiety is removed from the 7-trimethylsilylethynyl-2-oxo-thiochroman (**Formula 32**) under basic conditions, to provide the ring substituted 7-ethynyl-2-oxo-thiochroman derivative (**Formula 33**) which is coupled with the reagent **X'-Y-A-B** (**Formula 3**) either directly, or in the form of a metal (zinc) salt (**Formula 34**). This coupling reaction, yields the target 2-oxo-thiochroman compounds of **Formula 35** or such derivatives which are readily converted into the target compounds, as described above.

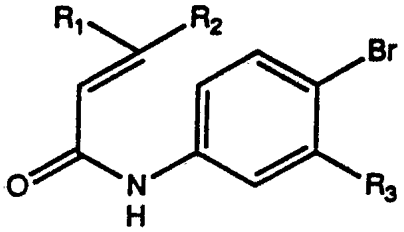


FORMULA 36

NaH

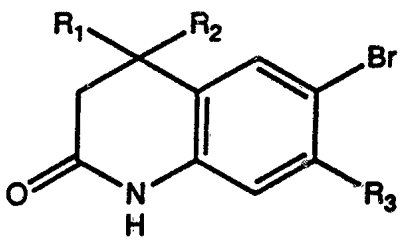


FORMULA 8

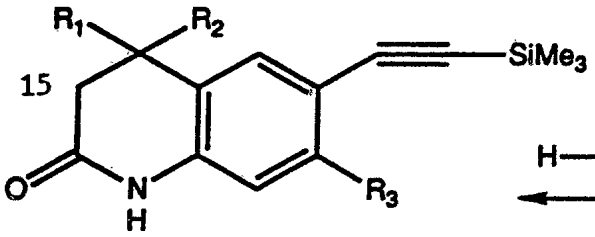


FORMULA 37

$AlCl_3$
CH_2Cl_2

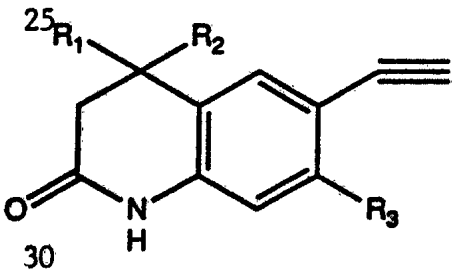


FORMULA 38

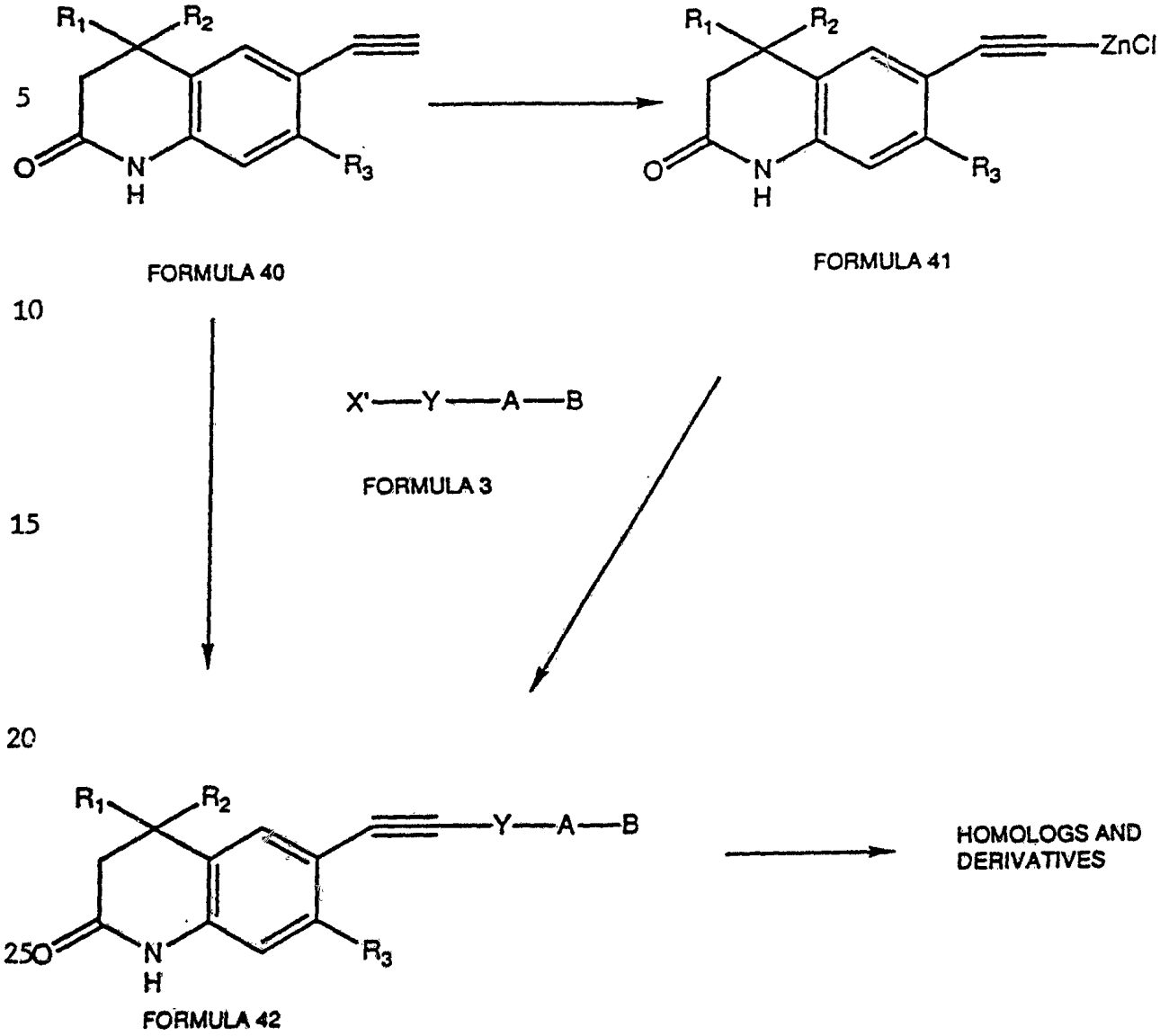


FORMULA 39

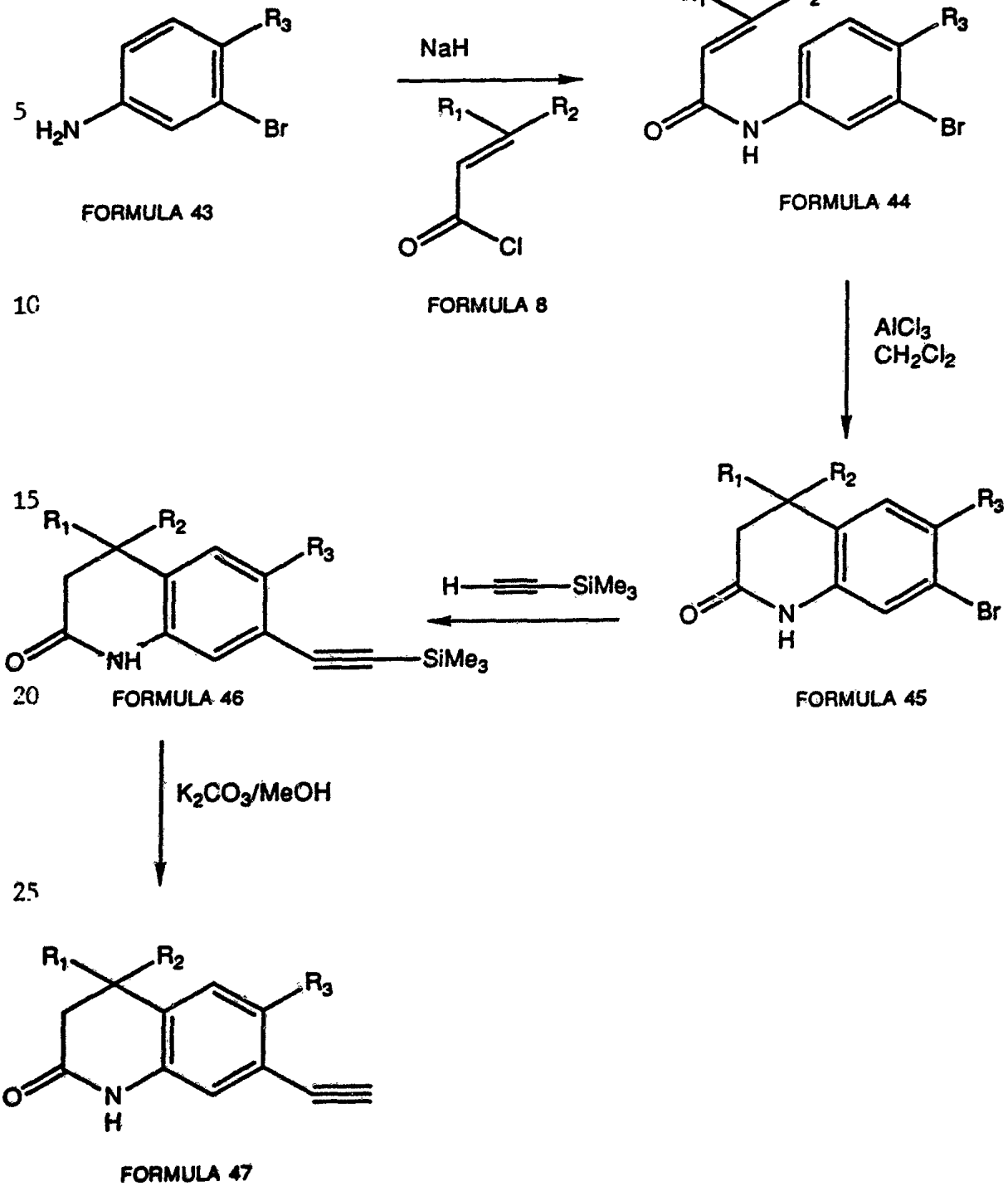
K_2CO_3/MeOH



FORMULA 40



Reaction Scheme 5



FORMULA 43

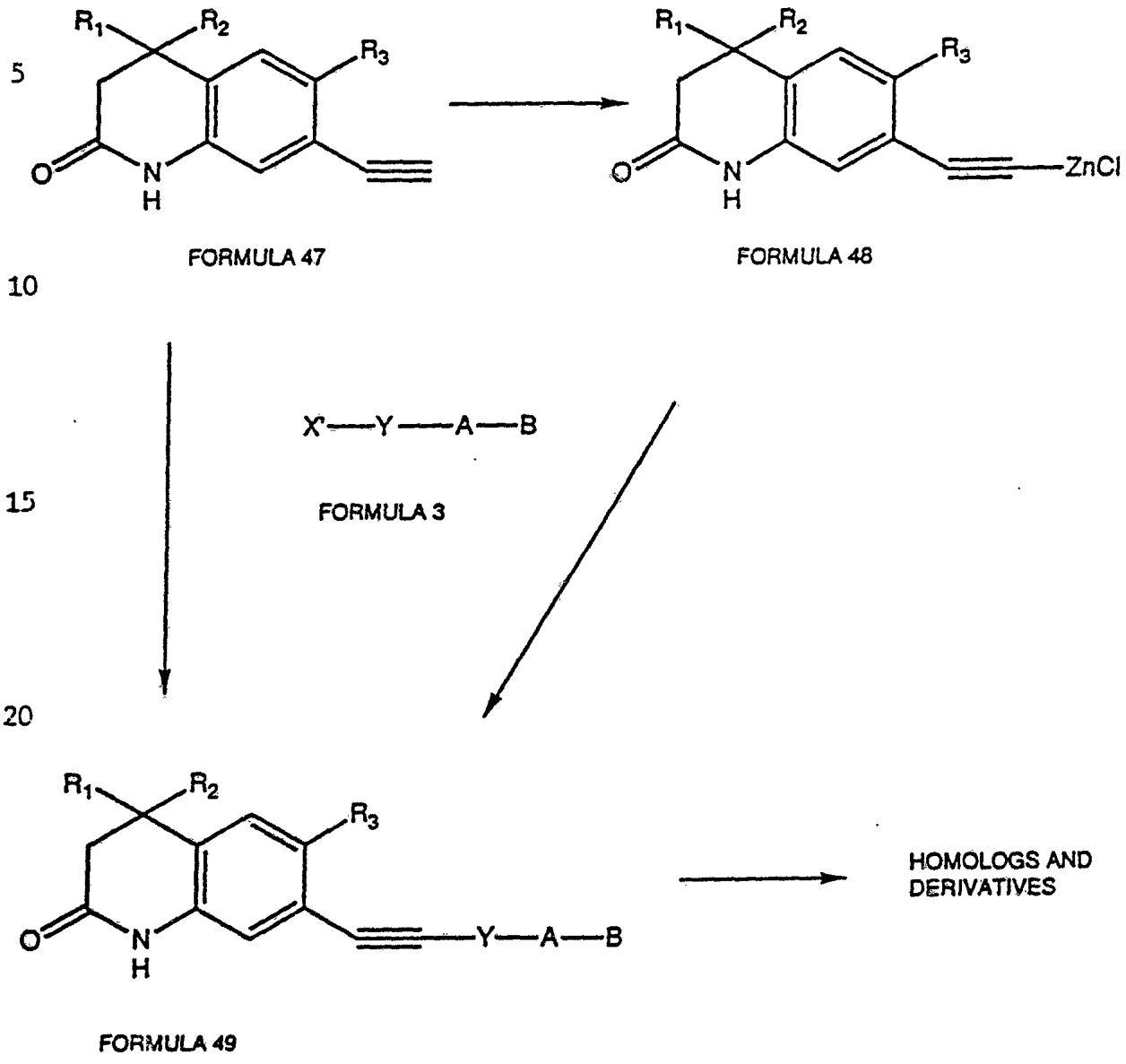
FORMULA 8

FORMULA 44

FORMULA 45

FORMULA 46

FORMULA 47



FORMULA 47

FORMULA 48

FORMULA 3

FORMULA 49

Reaction Scheme 6

Reaction Schemes 5 and 6 illustrate examples of synthesis of the compounds of **Formula 1** where X=NH. In **Reaction Scheme** 5 the ethynyl group is located in the 6 position of the lactame ring, and in **Reaction Scheme 6** the ethynyl group is located in the 7 position of the lactame. The steps shown in **Reaction Schemes** 5 and 6 are analogous to the reaction steps in the preceding schemes, and are described here briefly.

Thus, with reference to **Reaction Scheme** 5, the 4-bromo-aniline, or a 4-bromo-aniline substituted in the 3-(meta) positions by an alkyl substituent (R_3) of **Formula 36** is acylated with the acyl chloride of **Formula 8**. The resulting substituted amide (**Formula 37**) is ring closed under Friedel Crafts conditions to provide the 2-oxo-6-bromo-lactame of **Formula 38**. The acetylene portion is introduced into the substituted 2-oxo-6-bromo-lactame of **Formula 37**, using the same conditions as described above, to give the trimethylsilyl compound of **Formula 39**. The trimethylsilyl moiety is removed from the molecule of **Formula 39** (as e. g. in **Reaction Scheme 1**) to provide the ring substituted 6-ethynyl-2-oxo-lactame (**Formula 40**). The 6-ethynyl-2-oxo-lactame (**Formula 40**), or alternatively the corresponding metal (zinc) salt (**Formula 41**), is subjected to substantially the same reaction procedures as described above (e. g. in **Reaction Scheme 1**) to yield the products of **Formula 42**.

Reaction Scheme 6 discloses substantially the same reaction steps as **Reaction Scheme 5**, except that the starting material is a 3-bromo-aniline (**Formula 43**) which may be alkyl substituted (R_3) in the 4 (para) position. The products of this reaction sequence are the 7-ethynyl substituted 1,2,3,4-tetrahydroquinoline

derivatives of **Formula 49.**

Specific Examples

(4-bromophenyl) 3,3-dimethylacrylate

To an ice bath cooled solution of 1.66 g (69.2 mmol) of NaH (60% suspension in mineral oil) in 25 ml of dry THF was added slowly under argon a solution of 10.0 g (57.8 mmol) of 4-bromophenol in 50 ml of dry THF. The mixture was stirred at 0 degrees C for 30 minutes and then treated with a solution of 6.85 g (6.44 ml, 57.8 mmol) of dimethylacryloyl chloride in 25 ml of dry THF. The cooling bath was then removed and the mixture allowed to warm to room temperature. The organic layer was separated and the aqueous layer was washed with 2 x 25 ml of ether. The combined organic layers were washed with 2 X 50 ml of water, brine and dried ($MgSO_4$). The solvent was removed in-vacuo and the residue purified using flash chromatography (SiO_2; 5% ethyl acetate in hexanes) to give the title compound as a pale yellow oil.

PMR($CDCl_3$): 1.95(3H,d,J-1.5Hz), 2.20(3H,d,J-1.4Hz), 5.88(1H,m), 6.98(2H,d,J-8.9Hz), 7.46(2H,d,J-8.9Hz)

4,4-Dimethyl-6-bromo-2-oxo-chroman

To a stirred, ice cooled suspension of 11.5 g (86.3 mmol) of aluminum chloride in 200 ml of methylene chloride was added a solution of 11.0 g (43.1 mmol) of (4-bromophenyl) 3,3-dimethyl-acrylate in 100 ml of methylene chloride. The mixture was then stirred at room temperature for 20 hours and then poured into ice/brine mixture. The mixture was extracted with methylene chloride and the combined orgainc extracts were washed with water, brine and dried ($MgSO_4$). The solvent was removed in-vacuo and the resulting residue purified using flash chromatography (SiO_2; 4% ethyl

acetate in hexanes) to give the title compound as a yellow oil.

PMR($CDCl_3$): 1.37(6H,s), 2.64(2H,s), 6.96(1H,d,J-8.5Hz), 7.38(1H,dd,J-8.5Hz,J-2.3Hz), 7.45(1H,d,J-2.3Hz).

4,4-dimethyl-6-trimethylsilylethynyl-2-oxo-chroman

The procedure used is substantially in accordance with (Journal of Organic Chemistry, Vol. 46, No. 11, (1981) p 2280-81). To a solution of 2.5 g (9.8 mmol) of 4,4-dimethyl-6-bromo-2-oxo-chroman and 0.087 g (0.3317 mmol) of triphenylphosphine in 36 ml of triethylamine under argon was added 1.74 g (2.5 ml, 17.7 mmol) of trimethylsilylacetylene and 0.027g (0.12 mmol) of palladium(II) acetate. The mixture was refluxed for 20 hours then cooled to room temperature and filtered. The solvent removed in-vacuo and the resulting residue was purified using flash chromatography (SiO_2; 5% ethyl acetate in hexanes) to give the title compound as a yellow oil.

PMR($CDCl_3$): 0.227(9H,s), 1.32(6H,s), 2.56(2H,s), 6.95(1H,d,J-8.3Hz), 7.32(1H,dd,J-8.3Hz, J-1.9Hz), 7.39(1H,J-1.9Hz)

4,4-dimethyl-6-ethynyl-2-oxo-chroman

To a solution of 2.15 g (8.0 mmol) of 4,4-dimethyl-6-trimethylsilylethynyl-2-oxo-chroman in 25 ml of methanol was added, under nitrogen, 1.0 g of potassium carbonate. The reaction mixture was stirred at room temperature for 12 hours and the methanol was then removed under vacuum. The residue was extracted with methylene chloride (2 x 15 ml) and the combined organic layers were washed with dilute HCl, water, brine and dried ($MgSO_4$). The solvent was removed in-vacuo and the residue purified by Kugelrohr distillation to give the title compound as a yellow

oil.

PMR($CDCl_3$): 1.29(6H,s), 2.57(2H,s),3.02(1H,s), 6.94(1H,d,J-8.4Hz), 7.32(1H,dd,J-8.4Hz,J-1.95Hz), 7.39(1H,d,J-1.95Hz).

Ethyl 6-Chloronicotinate

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 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).

Ethyl 6-[4,4-dimethyl-2-oxo-chroman-6-yl] ethynyl-nicotinate (**Compound 1**)

To .305 g (1.5 mmol) of 4,4-dimethyl-6-ethynyl-2-oxo-chroman was added .278 g (1.5 mmol) of ethyl 6-chloronicotinate in 1 ml of triethylamine under bubbling nitrogen in a heavy walled glass tube, degassed under vacuum. Then mixture was then treated with a mixture of 30 mg of cuprous iodide and 60 mg of bis(triphenylphosphine) palladium (II) chloride, and the tube was again degassed under vacuum and flushed with nitrogen. The tube was sealed and the reaction mixture was heated at 60 degrees C for 48 hours. The reaction mixture was cooled and taken up with methylene chloride and silica. Solvent was removed and the resulting residue was purified using flash chromatography (SiO_2; 1L 10% ethyl acetate in hexanes, 1L 12% ethyl acetate in hexanes, 2L 15 % ethyl acetate

in hexanes) to give the title compound as a pale yellow solid.

PMR ($CDCl_3$): 1.38-1.45(9H,m), 2.66(2H,s), 4.43(2H,q), 7.08(1H,d,J-8.3Hz), 7.52(1H,dd,J-8.3Hz, J-1.9Hz), 7.59-7.62(2H,m), 8.3(1H,dd,J-8.25Hz,J-2.1Hz), 9.22(1H,d,J-2.1Hz).

Ethyl 4-iodobenzoate

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 and 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).

Ethyl 4-[4,4-dimethyl-2-oxo-chroman-6-yl] ethynyl-benzoate (Compound 2)

To .322 g (1.6 mmol) of 4,4-dimethyl-6-ethynyl-2-oxo-chroman was added .4 g (1.5 mmol) of ethyl 4-iodobenzoate in 1 ml of triethylamine under bubbling nitrogen in a heavy walled glass tube, degassed under vaccum. The mixture was then treated with a mixture of 30 mg of cuprous iodide and 60 mg of bis(triphenylphosphine) palladium (II) chloride and the tube was again degassed under vacuum and flushed with nitrogen. The tube was sealed and the reaction mixture was heated at 60 degrees C for 48 hours. The reaction mixture was cooled and taken up with methylene chloride and silica. Solvent was removed and the resulting residue was purified using flash chromatography (SiO_2;

10% ethyl acetate in hexanes) to give the title compound as a white solid.

PMR ($CDCl_3$): 1.39-1.43(9H,m), 1.66(2H,s), 4.39(2H,q), 7.07(1H,d,J-8.3Hz), 7.45(1H,dd, J-8.3Hz,J-1.9Hz), 7.52(1H,d,J-1.9Hz), 7.60(1H,d,J-8.4Hz), 8.06(1H,d,J-8.4Hz)

4-[4,4-Dimethyl-2-oxo-chroman-6-yl]ethynyl]benzoic acid (**Compound 2a**)

To a solutiion of 0.21 g (0.6 mmol) of ethyl 4-[4,4-dimethyl-2-oxo-chroman-6-yl]ethynyl]benzoate in 10 ml of anhydrous THF was added 10 ml of 0.5 N lithium hydroxide solution. The reagents were stirred together at ambient temperature until the reaction was complete, as monitored by TLC. The reaction mixture was concentrated in vacuo, diluted with water and washed with diethyl ether. The aqueous phase was diluted with diethyl ether, acidified with conc. HCl (pH-1) and the layers were separated. The aqueous phase was washed three times with ether and then all organic phases were combined, washed with brine solution, dried over Na_2SO_4, filtered and concentrated in vacuo to give the title compound as an off-white solid.

PMR (DMSO-d_6): δ 1.31 (6H, s), 2.78(2H, s), 7.16(1H, d, J=8.4Hz), 7.54(1H, dd, J=8.4, 2 Hz), 7.66(1H, d, J=2 Hz), 7.68(2H, J=8.1 Hz), 7.98(2H, J=8.1 Hz).

S-(4-bromophenyl) 3,3-dimethylthioacrylate

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 hour. 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

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 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).

4,4-Dimethyl-6-trimethylsilylethynyl-2-oxo-thiochroman

A solution of 1.0 g (3.7 mmol) of 4,4-dimethyl-6-bromo-2-oxo-thiochroman in 1 ml of triethylamine was placed in a heavy-walled tube and degassed and then treated under argon with 2.0 g (2.75 ml, 20.0 mmol) of

trimethylsilylacetylene and a powdered mixture of .038g of cuprous iodide and .084 g 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 55 degrees C for 24 hours, allowed to cool to room temperature and taken up with methylene chloride and silica. Solvent was removed in-vacuo and the resulting residual material on silica was purified using flash chromatography (SiO_2; 2% ethyl acetate in hexanes) to give the title compound as a yellow oil.

PMR($CDCl_3$): 0.218(9H,s), 1.34(6H,s), 2.56(2H,s), 7.22(1H,d,J-2Hz), 7.25(1H,dd,J-8.1Hz,J-2.0Hz), 7.33(1H,d,J-8.1Hz.

S-(3-Bromophenyl) 3,3-dimethyl-thio acrylate

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

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-bromophenyl) 3-3 dimethyl-thio acrylate in 100 ml of methylene chloride. The mixture was stirred at room temperature for 24 hours and then poured into 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).

4,4-dimethyl - 7-trimethylsilylethynyl-2-oxo-thiochroman

A solution of 1.0 g (3.7 mmol) of 4,4-dimethyl-7-bromo-2-oxo-thiochroman in 1 ml of triethylamine was placed in a heavy-walled tube and degassed and then treated under argon with 2.0 g (2.75 ml, 20.0 mmol) of trimethylsilylacetylene and a powdered mixture of .038g of cuprous iodide and .084 g 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 55 degrees C for 24 hours, and thereafter allowed to cool to room temperature. Solvent was removed in-vacuo to give the

title compound as a yellow oil.

PMR($CDCl_3$): 0.05(9H,s), 1.40(6H,s), 1.69(2H,s), 7.26-7.42(3H,m).

3-Bromophenyl 3,3-dimethyl acrylate

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).

4,4-dimethyl-7-bromo-2-oxochroman

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 3-bromo-phenyl-3,3-dimethyl acrylate 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 the title compound as an impure yellow oil.

4,4-dimethyl-6-bromo-2-oxo-quinoline

To a solution of 10.0 g (84 mmol) of dimethylacryloyl chloride in 200 ml of dry THF was added a solution of 4-bromo aniline in 250 ml of dry THF. The mixture was stirred at room temperature for 2 hours and extracted with hexane. The combined organic extracts were washed with water, brine and dried ($MgSO_4$). Solvent was removed in-vacuo and the residue was partially purified by recrystallization (20% ethyl acetate in hexanes) to give (4-bromophenyl) 3,3-dimethylacryloylamide as white crystals which was used in the next step without further purification.

To 1.0 g (3.9 mmol) of (4-bromophenyl) 3,3-dimethylacryloylamide heated to 130 degrees C was added .526 g (3.94 mmol) of aluminum chloride over a period of 30 minutes. The reaction mixture was heated for an additional 30 minutes. The mixture was treated again with .079 g (.592 mmol) of aluminum chloride and heated at 130 degrees C for 1 hour and 40 minutes. The reaction mixture was extracted with 20 ml ether and the combined organics washed with 20 ml water, 20 ml brine and dried ($MgSO_4$). Solvent was removed in-vacuo and the residue purified by flash chromatography (SiO_2; 20% ethyl acetate in hexanes) to give the title compound as a light yellow solid.

PMR($CDCl_3$): 1.37(6H,s), 2.52(2H,s), 6.85(1H,d,J-8.2Hz), 7.32(1H,dd,J-8.2Hz, J-2.1Hz), 7.43(1H,J-2.1Hz), 10.2(1H,s).

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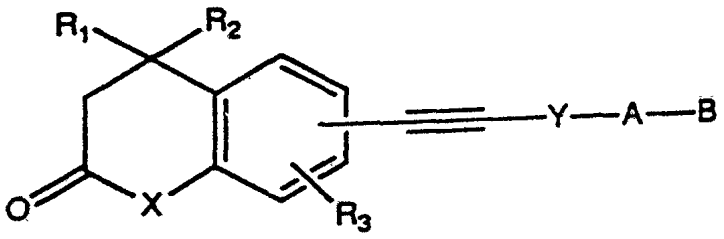
CLAIM REPLACEMENT SHEET

WHAT IS CLAIMED IS:

1. **(Amended)** A compound of the formula



where R_1 and independently R_2 are hydrogen, lower alkyl of 1 - 6 carbons, or halogen;

R_3 is hydrogen, lower alkyl of 1 - 6 carbons, halogen, OR_{11}, SR_{11}, $OCOR_{11}$, $SCOR_{11}$, NH_2, NHR_{11}, $N(R_{11})_2$, $NHCOR_{11}$ or $NR_{11}COR_{11}$;

X is O, S or NR' where R' is hydrogen or lower alkyl of 1 - 6 carbons;

Y is phenyl or a heteroaryl group selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl and oxazolyl;

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

B is COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11}, CH_2OCOR_{11}, CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, $-COR_7$, $CR_7(OR_{12})_2$, or $CR_7OR_{13}O$, where R_7 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

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10 carbons, or a cycloalkyl group of 5-10 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.

2. A compound of claim 1 where **X** is O.

3. **(Amended)** 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 1 where **X** is S.

6. **(Amended)** A compound of claim 5 where **A** is $(CH_2)_n$ and **n** is 0, 1 or 2.

7. A compound of claim 6 where B is COOH or a pharmaceutically acceptable salt, thereof, or **B** is $COOR_8$ or $COONR_9R_{10}$.

8. A compound of claim 1 where **X** is NR'.

9. **(Amended)** A compound of claim 8 where **A** is $(CH_2)_n$ and **n** is 0, 1 or 2.

10. A compound of claim 9 where **B** is COOH or a pharmaceutically acceptable salt, thereof, or **B** is $COOR_8$ or $COONR_9R_{10}$.

11. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and one or more compounds set forth in claim 1 as the active ingredient.

12. A method for treating skin disorders in a mammal which method comprises administering alone or in conjunction with a pharmaceutically acceptable excipient a therapeutically effective amount of one or more compounds set forth in Claim 1.

13. **(Amended)** A compound of the formula

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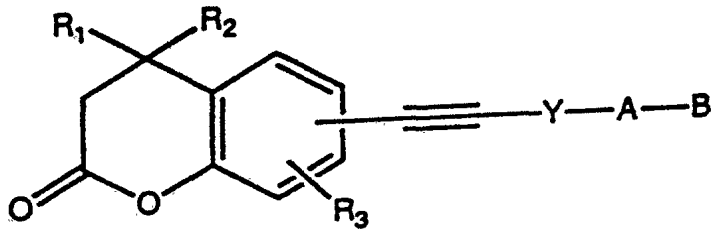

where R_1 and independently R_2 are hydrogen, lower alkyl of 1 - 6 carbons, or halogen;

R_3 is hydrogen, lower alkyl of 1 - 6 carbons, or halogen;

Y is phenyl or a heteroaryl group selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl and oxazolyl;

A is $(CH_2)_n$ where n is 0-5, lower branched chain alkyl having 3-6 carbons, or cycloalkyl having 3-6 carbons;

B is COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11}, CH_2OCOR_{11}, CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, $-COR_7$, $CR_7(OR_{12})_2$, or $CR_7OR_{13}O$, where R_7 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 5-10 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.

14. A compound of claim 13 where Y is phenyl.

15. **(Amended)** A compound of claim 14 where A is

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$(CH_2)_n$ and n is 0.

16. A compound of claim 15 where the ethynyl group is in the 6 position of the chroman ring.

17. A compound of Claim 16 where R_1 and R_2 are methyl, and R_3 is H.

18. (Amended) A compound of claim 17 where the ethynyl and B groups are in 1,4 positions of the phenyl ring.

19. The compound of claim 18 where B is $COOC_2H_5$.

20. The compound of claim 18 where B is COOH, or a pharmaceutically acceptable salt thereof.

21. A compound of claim 13 where Y is pyridyl.

22. (Amended) A compound of claim 21 where A is $(CH_2)_n$ and n is 0.

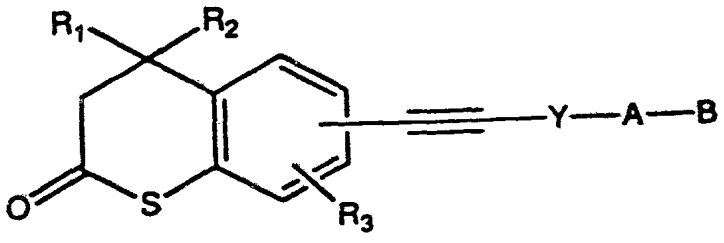
23. A compound of claim 22 where the ethynyl group is in the 6 position of the chroman ring.

24. A compound of Claim 23 where R_1 and R_2 are methyl, and R_3 is H.

25. (Amended) A compound of claim 24 where the ethynyl and B groups are in 2,5 positions of the pyridine ring.

26. The compound of claim 25 where B is $COOC_2H_5$.

27. A compound of the formula



AMENDED SHEET

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CLAIM REPLACEMENT SHEET

where R_1 and R_2 are hydrogen, lower alkyl of 1 - 6 carbons, or halogen;

R_3 is hydrogen, lower alkyl of 1 - 6 carbons, or halogen;

Y is phenyl or a heteroaryl group selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl and oxazolyl;

A is $(CH_2)_n$ where n is 0-5, lower branched chain alkyl having 3-6 carbons, or cycloalkyl having 3-6 carbons;

B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11}, CH_2OCOR_{11}, CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, $-COR_7$, $CR_7(OR_{12})_2$, or $CR_7OR_{13}O$, where R_7 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 5-10 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.

28. A compound of claim 27 where the Y group is phenyl.

29. A compound of claim 27 where the Y group is selected from a group consisting of pyridyl, thienyl and furyl.

30. **(Amended)** A compound of the formula

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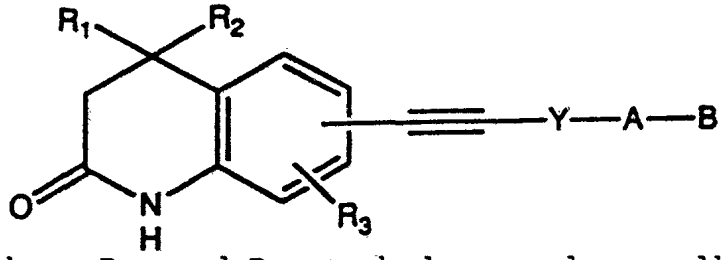

where R_1 and R_2 are hydrogen, lower alkyl of 1 - 6 carbons, or halogen;

R_3 is hydrogen, lower alkyl of 1 - 6 carbons, or halogen;

Y is phenyl or a heteroaryl group selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl and oxazolyl;

A is $(CH_2)_n$ where n is 0-5, lower branched chain alkyl having 3-6 carbons, or cycloalkyl having 3-6 carbons;

B is COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11}, CH_2OCOR_{11}, CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, $-COR_7$, $CR_7(OR_{12})_2$, or $CR_7OR_{13}O$, where R_7 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 5-10 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.

31. A compound of claim 30 where the Y group is phenyl.

32. A compound of claim 30 where the Y group is selected from a group consisting of pyridyl, thienyl and furyl.

AMENDED SHEET

AUSTRALIAN PATENT OFFICE

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/US 95/00268

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D405/06 C07D311/20 A61K31/455 A61K31/35

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. ORGANOMET. CHEM., vol. 387, no. 3, 1990 pages 381-390, DAVIES S.G. ET AL. 'Synthesis of 6-substituted 3,4-dihydro-2H-1-benzopyran-2-ones (dihydrocoumarins) via palladium catalyzed coupling reactions' see compound 11, pages 383 and 388 --- -/--	1-3,11, 13-16

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

"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

Date of the actual completion of the international search	Date of mailing of the international search report
4 May 1995	30. 05. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Hartrampf, G

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 95/00268

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. MED. CHEM., vol. 35,no. 4, 21 February 1992 pages 620-628, MARTINEZ G.R. ET AL. '3,4-Dihydroquinolin-2(1H)-ones as combined inhibitors of thromboxane A2 synthase and cAMP phosphodiesterase' see compound 18, page 622 see page 623; table I	1,8,9, 11,30,32
Y	EP,A,0 176 034 (BASF AKTIENGESELLSCHAFT) 2 April 1986 see the whole document	1-11, 13-32
Y	EP,A,0 284 261 (ALLERGAN INC) 28 September 1988 see the whole document	1-11, 13-32
Y	EP,A,0 284 288 (ALLERGAN INC.) 28 September 1988 cited in the application see the whole document	1-11, 13-32
Y	EP,A,0 290 130 (ALLERGAN INC.) 9 November 1988 see the whole document & US,A,4 810 804 (CHANDRARATNA R.A.S.) 7 March 1989 cited in the application	1-11, 13-32
Y	EP,A,0 419 130 (ALLERGAN, INC.) 27 March 1991 see the whole document & US,A,5 045 551 (CHANDRARATNA R.A.S.) 3 September 1991 cited in the application & US,A,5 183 827 (CHANDRARATNA R.A.S.) 2 February 1993 cited in the application & US,A,5 272 156 (CHANDRARATNA R.A.S.) 21 December 1993 cited in the application	1-11, 13-32
Y	EP,A,0 419 131 (ALLERGAN, INC.) 27 March 1991 see the whole document & US,A,4 980 369 (CHANDRARATNA R.A.S.) 25 December 1990 cited in the application	1-11, 13-32
E,L	US,A,5 399 561 (CHANDRARATNA R.A.) 21 March 1995 see the whole document	1-11, 13-32

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/00268

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

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.: 12
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 12 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition. ./.

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.

For the assessment of the present Claim 12 on the question whether it is industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

1. PRIOR ART

The following documents cited in the International search report were taken into consideration

J. ORGANOMET. CHEM. (1990) 387(3), PP.381-390 (D1)
J. MED. CHEM. (1992) 35(4), PP. 620-628 (D2)
EP-A-0 176 034 (D3)
EP-A-0 284 261 (D4)
EP-A-0 284 288 (D5)
EP-A-0 290 130 (D6)
EP-A-0 419 130 (D7)
EP-A-0 419 131 (D8).

2. NOVELTY

Having regard to the compounds disclosed in the above prior art documents the subject-matter of the present application, i.e. acetylenes disubstituted with a phenyl or a heteroaryl and a 2-oxo(thio)chroman or a 2-oxo-tetrahydroquinoline according to formula (1) in Claim 1 showing retinoid-like activity, does not appear

to fulfil the requirements of novelty, Article 33(2) PCT.

2.1. Documents D1 and D2 disclose compounds which are comprised by the present claims. Compound 11 of D1 and compound 18 of D2 are considered to be novelty destroying to present Claims 1-3, 11, 13-16 (see D1) and to Claims 1, 8, 9, 11, 30, 32 (see D2).

2.2. Documents D3 and D4 describe acetylenes disubstituted with a phenyl or a heteroaryl and a (tetra,di)hydronaphthalene or a 2-oxo-tetrahydronaphthalene (D3).
Documents D5 to D8 comprise acetylenes disubstituted with a phenyl or a heteroaryl and a (thio)chroman or a tetrahydroquinoline.
Additionally the compounds of D3 to D8 exhibit retinoid-like activity.

3. INVENTIVE STEP

The Applicant appears to have set himself the task of making available compounds which show retinoid-like activity and are thus useful in the treatment of cell-proliferation disorders and/or diseases.
For those prior art compounds of D1 and D2 which are structurally identical to the present compounds no use (D1) or a different pharmaceutical use (D2) has been described.

However, with regard to those compounds known from D3 to D8 the problem which the Applicant set out to solve is to be seen in the provision of improved disubstituted acetylene derivatives which show an unexpected effect (brought about by the novel structural feature, ie. the

2-oxo group introduced) with regard to the compounds already evaluated for the same purpose in this pharmaceutical field.

The present compounds, i.e. acetylenes disubstituted with a phenyl or a heteroaryl and a 2-oxo(thio)chroman or a 2-oxo-tetrahydroquinoline appear to be merely distinguished from those compounds known from D5 to D8 by the present 2-oxo group.
For the skilled person it was clearly evident that the desired properties would be retained since the same measure, ie. the introduction of a 2-oxo group has already been successfully employed in the closely related compounds of D3 and D4 which also show retionid-like activity, see in D3 the definition of A which is either $-CH_2-CH_2-$ or $-CO-CH_2-$.

Therefore an inventive step according to Article 33(3) PCT could only be acknowledged if the Applicant is able to demonstrate that the problem of providing compounds with improved and thus unexpected properties, when compared with the structurally closest compounds of the pertinent prior art, has been solved.

4. INDUSTRIAL APPLICABILITY

Insofar the presently claimed compounds exhibit said retinoid-like activity no objection arises, cf. Article 33(4) PCT.

Certain documents

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 4

US-A-5 399 561

The priority documents pertaining to the present application were not available at the time of establishing this first written opinion. Hence, it is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the E-document cited in the international search report could become relevant to assess whether the claims satisfy the criteria set forth in Article 33(1) PCT.

Certain defects of the description

1. To meet the requirements of Rule 5.1(a) PCT, all of the documents cited above should be identified in the description and the relevant background art disclosed therein should be briefly discussed.

2. According to the requirements of Rule 11.13(m) PCT the same feature shall be denoted by the same reference sign throughout the application. This requirement is not met in view of the use of "°C" and "degrees C" in the examples. Preferably "°C" should be used.

3. The units "mm" for the pressure expressed on page 41, line 16 do not meet the requirements of Rule 10.1 PCT and should be replaced by the appropriate SI units. The present expressions should, however, be retained in parentheses after the replacement expressions.

Certain defects in the claims

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 5

1. At present it appears that the breadth of the claims is not reasonable with regard to only 3 working examples in the description. Thus the Applicant is requested to explain on what basis the present claims have been drafted. In the absence of any explanation and/or further test data the breadth appears to be speculative and goes beyond that what could be considered equivalents of those meanings shown in the examples so far.
However, if the Applicant is able to convincingly demonstrate an inventive step, prferably by the way of comparative test data, the breadth already shown therein could in principle be accepted, too.

2. The terms "alkyl" and "lower alkyl" used in Claims 1, 13, 27 and 30 are vague and indefinite and, as such, render the scope of the claims unclear; accordingly, the claims requires amendment to remove this defect (Article 6 PCT).
In the description page 7, the terms "alkyl" and "lower alkyl" are defined as covering not only straight- and branched-chain alkyl, but also cycloalkyl. However, in said claims radicals A, R^7, R^8, R^9 and R^{10} additionally define "cycloalkyl", although according to the description it should be covered by "alkyl" already.

3. Independent Claims 13, 27 and 30 include all the features of independent Claim 1. Hence said claims should be reformulated as claims dependent on Claim 1, cf. Rule 6.4(a) PCT.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int tional Application No
PCT/US 95/00268

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ational Application No
PCT/US 95/00268

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INTERNATIONAL SEARCH REPORT

Information on patent family members

In tional Application No
PCT/US 95/00268

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