

ARYL OR HETEROARYL AMIDES OF TETRAHYDRONAPHTHALENE, CHROMAN, THIOCHROMAN AND 1,2,3,4-TETRAHYDROQUINOLINE CARBOXYLIC ACIDS HAVING RETINOID-LIKE BIOLOGICAL ACTIVITY

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to novel compounds having retinoid-like biological activity. More specifically, the present invention relates to amides formed between aryl or heteroryl amines and tetrahydronaphthalene, chroman, thiochroman and 1,2,3,4-tetrahydroquinoline carboxylic acids where at least one of the aromatic or heteroaromatic moieties of the amide bears an electron withdrawing substituent. The compounds are agonists of RAR retinoid receptors.

2. Background Art

Compounds which have retinoid-like activity are well known in the art, and are described in numerous United States and other 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 skin-related diseases, including, actinic keratoses, arsenic keratoses, inflammatory and non-inflammatory acne, psoriasis, ichthyoses and other keratinization and

1 hyperproliferative disorders of the skin, eczema,
2 atopic dermatitis, Darriers disease, lichen planus,
3 prevention and reversal of glucocorticoid damage
4 (steroid atrophy), as a topical anti-microbial, as
5 skin anti-pigmentation agents and to treat and
6 reverse the effects of age and photo damage to the
7 skin. Retinoid compounds are also useful for the
8 prevention and treatment of cancerous and
9 precancerous conditions, including, premalignant and
10 malignant hyperproliferative diseases such as
11 cancers of the breast, skin, prostate, cervix,
12 uterus, colon, bladder, esophagus, stomach, lung,
13 larynx, oral cavity, blood and lymphatic system,
14 metaplasias, dysplasias, neoplasias, leukoplakias
15 and papillomas of the mucous membranes and in the
16 treatment of Kaposi's sarcoma. In addition,
17 retinoid compounds can be used as agents to treat
18 diseases of the eye, including, without limitation,
19 proliferative vitreoretinopathy (PVR), retinal
20 detachment, dry eye and other corneopathies, as well
21 as in the treatment and prevention of various
22 cardiovascular diseases, including, without
23 limitation, diseases associated with lipid
24 metabolism such as dyslipidemias, prevention of
25 post-angioplasty restenosis and as an agent to
26 increase the level of circulating tissue plasminogen
27 activator (TPA). Other uses for retinoid compounds
28 include the prevention and treatment of conditions
29 and diseases associated with human papilloma virus
30 (HPV), including warts and genital warts, various
31 inflammatory diseases such as pulmonary fibrosis,
32 ileitis, colitis and Krohn's disease,
33 neurodegenerative diseases such as Alzheimer's

1 disease, Parkinson's disease and stroke, improper
2 pituitary function, including insufficient
3 production of growth hormone, modulation of
4 apoptosis, including both the induction of apoptosis
5 and inhibition of T-Cell activated apoptosis,
6 restoration of hair growth, including combination
7 therapies with the present compounds and other
8 agents such as Minoxidil^R, diseases associated with
9 the immune system, including use of the present
10 compounds as immunosuppressants and
11 immunostimulants, modulation of organ transplant
12 rejection and facilitation of wound healing,
13 including modulation of chelosis.

14 United States Patent Nos. 4,740,519 (Shroot et
15 al.), 4,826,969 (Maignan et al.), 4,326,055
16 (Loeliger et al.), 5,130,335 (Chandraratna et al.),
17 5,037,825 (Klaus et al.), 5,231,113 (Chandraratna et
18 al.), 5,324,840 (Chandraratna), 5,344,959
19 (Chandraratna), 5,130,335 (Chandraratna et al.),
20 Published European Patent Application Nos. 0 170 105
21 (Shudo), 0 176 034 A (Wuest et al.), 0 350 846 A
22 (Klaus et al.), 0 176 032 A (Frickel et al.), 0 176
23 033 A (Frickel et al.), 0 253 302 A (Klaus et al.),
24 0 303 915 A (Bryce et al.), UK Patent Application GB
25 2190378 A (Klaus et al.), German Patent Application
26 Nos. DE 3715955 A1 (Klaus et al.), DE 3602473 A1
27 (Wuest et al., and the articles J. Amer. Acad. Derm.
28 15: 756 - 764 (1986) (Sporn et al.), Chem. Pharm.
29 Bull. 33: 404-407 (1985) (Shudo et al.), J. Med
30 Chem. 1988 31, 2182 - 2192 (Kagechika et al.),
31 Chemistry and Biology of Synthetic Retinoids CRC
32 Press Inc. 1990 p 334 - 335, 354 (Dawson et al.),
33 describe or relate to compounds which include a

1 tetrahydronaphthyl moiety and have retinoid-like or
2 related biological activity. United States Patent
3 No. 4,391,731 (Boller et al.) describes
4 tetrahydronaphthalene derivatives which are useful
5 in liquid crystal compositions.

6 United States Patent Nos. 4,980,369, 5,006,550,
7 5,015,658, 5,045,551, 5,089,509, 5,134,159,
8 5,162,546, 5,234,926, 5,248,777, 5,264,578,
9 5,272,156, 5,278,318, 5,324,744, 5,346,895,
10 5,346,915, 5,348,972, 5,348,975, 5,380,877,
11 5,399,561, 5,407,937, (assigned to the same assignee
12 as the present application) and patents and
13 publications cited therein, describe or relate to
14 chroman, thiochroman and 1,2,3,4-tetrahydroquinoline
15 derivatives which have retinoid-like biological
16 activity. Still further, several co-pending
17 applications and recently issued patents which are
18 assigned to the assignee of the present application,
19 are directed to further compounds having
20 retinoid-like activity.

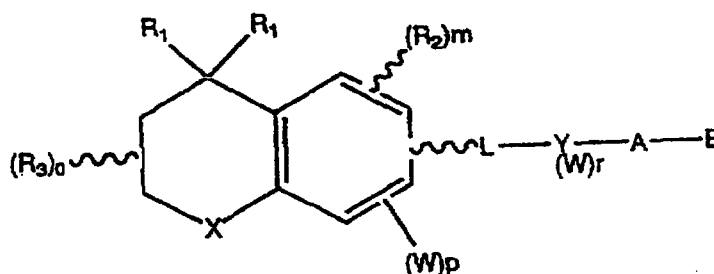
21 It is now general knowledge in the art that two
22 main types of retinoid receptors exist in mammals
23 (and other organisms). The two main types or
24 families of receptors respectively designated the
25 RARs and RXRs. Within each type there are subtypes;
26 in the RAR family the subtypes are designated RAR_α,
27 RAR_β and RAR_γ, in RXR the subtypes are: RXR_α, RXB_β and
28 RXR_γ. It has also been established in the art that
29 the distribution of the two main retinoid receptor
30 types, and of the several sub-types is not uniform
31 in the various tissues and organs of mammalian
32 organisms. Accordingly, among compounds having
33 agonist-like activity at retinoid receptors,

specificity or selectivity for one of the main types or families, and even specificity or selectivity for one or more subtypes within a family of receptors, is considered a desirable pharmacological property.

The present invention provides compounds having retinoid-like biological activity and specifically compounds which are agonists of one or more RAR retinoid receptor subtypes.

SUMMARY OF THE INVENTION

The present invention covers compounds of
Formula 1



Formula 1

wherein X is S, O, NR' where R' is H or alkyl of 1 to 6 carbons, or

X is $[C(R_1)_2]_n$ where n is an integer between 0 and 2;

R₁ is independently H or alkyl of 1 to 6 carbons;

R₂ is hydrogen, or lower alkyl of 1 to 6 carbons;

R₃ is hydrogen, lower alkyl of 1 to 6 carbons or F;

m is an integer having the value of 0 - 2;

o is an integer having the value of 0 - 4;

- 1 p is an integer having the value of 0 - 2;
2 r is an integer having the value 0 - 2 with the
3 proviso that when Z is O the sum of p and r is at
4 least 1;
5 Y is a phenyl or naphthyl group, or heteroaryl
6 selected from a group consisting of pyridyl,
7 thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl,
8 thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said
9 phenyl, naphthyl and heteroaryl groups being
10 optionally substituted with one or two R₂ groups;
11 W is a substituent selected from the group
12 consisting of F, Br, Cl, I, C₁₋₆alkyl, fluoro
13 substituted C₁₋₆ alkyl, NO₂, N₃, OH, OCH₂OCH₃,
14 OC₁₋₁₀alkyl, tetrazol, CN, SO₂C₁₋₆-alkyl, SO₂C₁₋₆-alkyl,
15 SO₂C₁₋₆-fluoro substituted alkyl, SO-C₁₋₆ alkyl,
16 CO-C₁₋₆alkyl, COOR₈, phenyl, phenyl itself substituted
17 with a W group other than with phenyl or substituted
18 phenyl;
19 L is -(C=Z)-NH- or -NH-(C=Z)-
20 Z is O or S;
21 A is (CH₂)_q where q is 0-5, lower branched chain
22 alkyl having 3-6 carbons, cycloalkyl having 3-6
23 carbons, alkenyl having 2-6 carbons and 1 or 2
24 double bonds, alkynyl having 2-6 carbons and 1 or 2
25 triple bonds, and
26 B is COOH or a pharmaceutically acceptable salt
27 thereof, COOR₈, CONR₉R₁₀, -CH₂OH, CH₂OR₁₁, CH₂OCOR₁₁,
28 CHO, CH(OR₁₂)₂, CHOR₁₃O, -COR₇, CR₇(OR₁₂)₂, CR₇OR₁₃O,
29 where R₇ is an alkyl, cycloalkyl or alkenyl group
30 containing 1 to 5 carbons, R₈ is an alkyl group of 1
31 to 10 carbons or trimethylsilylalkyl where the alkyl
32 group has 1 to 10 carbons, or a cycloalkyl group of
33 5 to 10 carbons, or R₈ is phenyl or lower

1 alkylphenyl, R_9 and R_{10} independently are hydrogen,
2 an alkyl group of 1 to 10 carbons, or a cycloalkyl
3 group of 5-10 carbons, or phenyl or lower
4 alkylphenyl, R_{11} is lower alkyl, phenyl or lower
5 alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent
6 alkyl radical of 2-5 carbons.

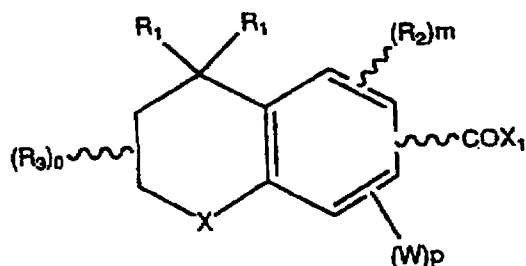
7 In a second aspect, this invention relates to
8 the use of the compounds of Formula 1 for the
9 treatment of skin-related diseases, including,
10 without limitation, actinic keratoses, arsenic
11 keratoses, inflammatory and non-inflammatory acne,
12 psoriasis, ichthyoses and other keratinization and
13 hyperproliferative disorders of the skin, eczema,
14 atopic dermatitis, Darriers disease, lichen planus,
15 prevention and reversal of glucocorticoid damage
16 (steroid atrophy), as a topical anti-microbial, as
17 skin anti-pigmentation agents and to treat and
18 reverse the effects of age and photo damage to the
19 skin. The compounds are also useful for the
20 prevention and treatment of cancerous and
21 precancerous conditions, including, premalignant and
22 malignant hyperproliferative diseases such as
23 cancers of the breast, skin, prostate, cervix,
24 uterus, colon, bladder, esophagus, stomach, lung,
25 larynx, oral cavity, blood and lymphatic system,
26 metaplasias, dysplasias, neoplasias, leukoplakias
27 and papillomas of the mucous membranes and in the
28 treatment of Kaposi's sarcoma. In addition, the
29 present compounds can be used as agents to treat
30 diseases of the eye, including, without limitation,
31 proliferative vitreoretinopathy (PVR), retinal
32 detachment, dry eye and other corneopathies, as well
33 as in the treatment and prevention of various

1 cardiovascular diseases, including, without
2 limitation, diseases associated with lipid
3 metabolism such as dyslipidemias, prevention of
4 post-angioplasty restenosis and as an agent to
5 increase the level of circulating tissue plasminogen
6 activator (TPA). Other uses for the compounds of
7 the present invention include the prevention and
8 treatment of conditions and diseases associated with
9 human papilloma virus (HPV), including warts and
10 genital warts, various inflammatory diseases such as
11 pulmonary fibrosis, ileitis, colitis and Krohn's
12 disease, neurodegenerative diseases such as
13 Alzheimer's disease, Parkinson's disease and stroke,
14 improper pituitary function, including insufficient
15 production of growth hormone, modulation of
16 apoptosis, including both the induction of apoptosis
17 and inhibition of T-Cell activated apoptosis,
18 restoration of hair growth, including combination
19 therapies with the present compounds and other
20 agents such as Minoxidil[®], diseases associated with
21 the immune system, including use of the present
22 compounds as immunosuppressants and
23 immunostimulants, modulation of organ transplant
24 rejection and facilitation of wound healing,
25 including modulation of chelosis.

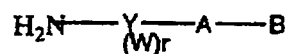
26 This invention also relates to a pharmaceutical
27 formulation comprising a compound of Formula 1 in
28 admixture with a pharmaceutically acceptable
29 excipient.

30 In another aspect, this invention relates to
31 processes for making a compound of Formula 1 which
32 processes comprise reacting, in the presence of an
33 acid acceptor or water acceptor, a compound of

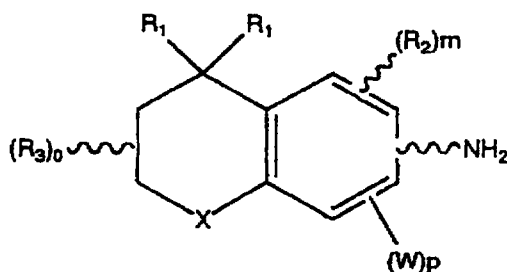
1 Formula 2 with a compound of Formula 3 or a compound
 2 of Formula 2a with a compound of Formula 3a where X_1
 3 is OH, halogen, or other group which renders the
 4 $-COX_1$ group reactive for amide formation, and where
 5 the remaining symbols are defined as in connection
 6 with Formula 1.



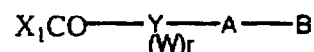
Formula 2



Formula 3



Formula 2a



Formula 3a

Still further, the present invention relates to
 such reactions performed on the compounds of Formula
 1 which cause transformations of the B group while
 the reaction product still remains within the scope
 of Formula 1.

General Embodiments Definitions

1 The term alkyl refers to and covers any and all
2 groups which are known as normal alkyl,
3 branched-chain alkyl and cycloalkyl. The term
4 alkenyl refers to and covers normal alkenyl, branch
5 chain alkenyl and cycloalkenyl groups having one or
6 more sites of unsaturation. Similarly, the term
7 alkynyl refers to and covers normal alkynyl, and
8 branch chain alkynyl groups having one or more
9 triple bonds.

10 Lower alkyl means the above-defined broad
11 definition of alkyl groups having 1 to 6 carbons in
12 case of normal lower alkyl, and as applicable 3 to 6
13 carbons for lower branch chained and cycloalkyl
14 groups. Lower alkenyl is defined similarly having 2
15 to 6 carbons for normal lower alkenyl groups, and 3
16 to 6 carbons for branch chained and cyclo- lower
17 alkenyl groups. Lower alkynyl is also defined
18 similarly, having 2 to 6 carbons for normal lower
19 alkynyl groups, and 4 to 6 carbons for branch
20 chained lower alkynyl groups.

21 The term "ester" as used here refers to and
22 covers any compound falling within the definition of
23 that term as classically used in organic chemistry.
24 It includes organic and inorganic esters. Where B
25 of Formula 1 is -COOH , this term covers the products
26 derived from treatment of this function with
27 alcohols or thioalcohols preferably with aliphatic
28 alcohols having 1-6 carbons. Where the ester is
29 derived from compounds where B is $\text{-CH}_2\text{OH}$, this term
30 covers compounds derived from organic acids capable
31 of forming esters including phosphorous based and
32 sulfur based acids, or compounds of the formula
33 $\text{-CH}_2\text{OCOR}_{11}$, where R_{11} is any substituted or

1 unsubstituted aliphatic, aromatic, heteroaromatic or
2 aliphatic aromatic group, preferably with 1-6
3 carbons in the aliphatic portions.

4 Unless stated otherwise in this application,
5 preferred esters are derived from the saturated
6 aliphatic alcohols or acids of ten or fewer carbon
7 atoms or the cyclic or saturated aliphatic cyclic
8 alcohols and acids of 5 to 10 carbon atoms.
9 Particularly preferred aliphatic esters are those
10 derived from lower alkyl acids and alcohols. Also
11 preferred are the phenyl or lower alkyl phenyl
12 esters.

13 Amides has the meaning classically accorded that
14 term in organic chemistry. In this instance it
15 includes the unsubstituted amides and all aliphatic
16 and aromatic mono- and di- substituted amides.
17 Unless stated otherwise in this application,
18 preferred amides are the mono- and di-substituted
19 amides derived from the saturated aliphatic radicals
20 of ten or fewer carbon atoms or the cyclic or
21 saturated aliphatic-cyclic radicals of 5 to 10
22 carbon atoms. Particularly preferred amides are
23 those derived from substituted and unsubstituted
24 lower alkyl amines. Also preferred are mono- and
25 disubstituted amides derived from the substituted
26 and unsubstituted phenyl or lower alkylphenyl
27 amines. Unsubstituted amides are also preferred.

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

32 A pharmaceutically acceptable salt may be
33 prepared for any compounds in this invention having

1 a functionality capable of forming such-salt, for
2 example an acid functionality. A pharmaceutically
3 acceptable salt is any salt which retains the
4 activity of the parent compound and does not impart
5 any deleterious or untoward effect on the subject to
6 which it is administered and in the context in which
7 it is administered. Pharmaceutically acceptable
8 salts may be derived from organic or inorganic
9 bases. The salt may be a mono or polyvalent ion.
10 Of particular interest are the inorganic ions,
11 sodium, potassium, calcium, and magnesium. Organic
12 salts may be made with amines, particularly ammonium
13 salts such as mono-, di- and trialkyl amines or
14 ethanol amines. Salts may also be formed with
15 caffeine, tromethamine and similar molecules. Where
16 there is a nitrogen sufficiently basic as to be
17 capable of forming acid addition salts, such may be
18 formed with any inorganic or organic acids or
19 alkylating agent such as methyl iodide. Preferred
20 salts are those formed with inorganic acids such as
21 hydrochloric acid, sulfuric acid or phosphoric acid.
22 Any of a number of simple organic acids such as
23 mono-, di- or tri- acid may also be used.

24 Some of the compounds of the present invention
25 may have trans and cis (E and Z) isomers. In
26 addition, the compounds of the present invention may
27 contain one or more chiral centers and therefore may
28 exist in enantiomeric and diastereomeric forms. The
29 scope of the present invention is intended to cover
30 all such isomers per se, as well as mixtures of cis
31 and trans isomers, mixtures of diastereomers and
32 racemic mixtures of enantiomers (optical isomers) as
33 well.

1 With reference to the symbol Y in Formula 1, the
2 preferred compounds of the invention are those where
3 Y is phenyl, pyridyl, 2-thiazolyl, thienyl, or
4 furyl, more preferably phenyl. As far as
5 substitutions on the Y (phenyl) and Y (pyridyl)
6 groups are concerned, compounds are preferred where
7 the phenyl group is 1,4 (para) substituted by the L
8 and A-B groups, and where the pyridine ring is 2,5
9 substituted by the L and A-B groups. (Substitution
10 in the 2,5 positions in the "pyridine" nomenclature
11 corresponds to substitution in the 6-position in the
12 "nicotinic acid" nomenclature.) In the preferred
13 compounds of the invention there is no optional R₂
14 substituent on the Y group.

15 As far as the amide or carbamoyl function "L" is
16 concerned which links the two cyclic portions of the
17 molecule, L is preferably -CZ-NH-; in other words
18 amide or carbamoyl compounds are preferred in
19 accordance with the present invention where the
20 carbonyl (CO-) or thiocarbonyl (CS-) group is linked
21 to the condensed cyclic moiety.

22 With reference to the symbol X in Formula 1,
23 compounds are preferred in accordance with the
24 invention where X is [C(R₁)₂]_n and n is 1, and also
25 where X is O or S (chroman and thiochroman
26 derivatives).

27 The R₁ groups are preferably H or CH₃. The R₂
28 group is preferably hydrogen.

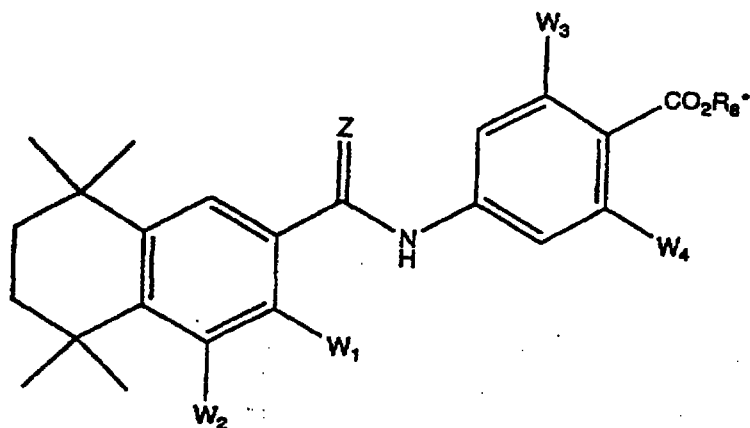
29 The A-B group of the preferred compounds is
30 (CH₂)_n-COOH or (CH₂)_n-COOR₃, where n and R₃ are defined
31 as above. Even more preferably n is zero and R₃ is
32 lower alkyl, or n is zero and B is COOH or a
33 pharmaceutically acceptable salt thereof.

1 Referring now to the W group in Formula 1, this
2 group is, generally speaking, an electron
3 withdrawing group, which is present in the compounds
4 of the invention either in the aromatic portion of
5 the condensed ring system, or as a substituent of
6 the aryl or heteroaryl group Y. Preferably the W
7 group is present in the Y group, or both in the Y
8 group and also in the aromatic portion of the
9 condensed ring system. When the Z group is S
10 (thioamides) a W group does not necessarily have to
11 be present in the compounds of the invention,
12 although preferably at least one W group is
13 nevertheless present. In the aryl or heteroaryl Y
14 moiety the W group is preferably located in the
15 position adjacent to the A-B group; preferably the
16 A-B group is in para position in the phenyl ring
17 relative to the "amide" moiety, and therefore the W
18 group is preferably in meta position relative to the
19 amide moiety. Where the W group is also present in
20 the aromatic portion of the condensed ring system,
21 it preferably occupies the 8 position of the chroman
22 or thiochroman nucleus with the Z=C-NH- group
23 occupying the 6 position. In tetrahydronaphthalene
24 compounds of the invention the Z=C-NH- group is
25 preferably in the 2-position, and the W group is in
26 the 3 or 4 position. Preferred W groups are F, NO₂,
27 Br, I, CF₃, N₃, and OH. The presence of one or two
28 fluoro substituents in the Y group is especially
29 preferred. When the Y group is phenyl, the fluoro
30 substituents preferably are in the ortho and ortho'
31 positions relative to the A-B group, which is
32 preferably COOH or COOR₁.

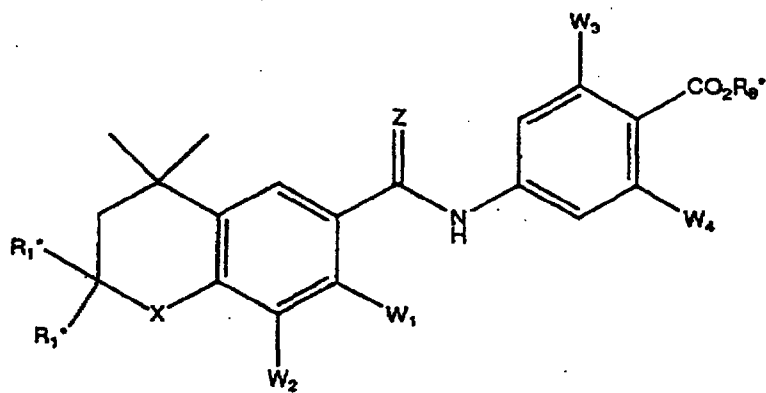
33 The most preferred compounds of the invention

1 are shown in Table 1, with reference to Formulas 4
2 and 5.

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Formula 4



Formula 5

TABLE 1

Compound										
No.	Formula	R ₁ *	X*	W ₁	W ₂	Z	W ₃	W ₄	R8*	
1	1	4	--	--	H	H	O	F	H	Et
2	2	4	--	--	H	H	O	F	H	H
3	3	4	--	--	F	H	O	H	H	Et
4	4	4	--	--	F	H	O	H	H	H
5	5	4	--	--	H	Br	O	F	H	Et
6	6	4	--	--	H	Br	O	F	H	H
7	7	4	--	--	OH	H	O	F	H	Et
8	8	4	--	--	OH	H	O	F	H	H
9	9	5	H	O	H	Br	O	F	H	Et
10	10	5	H	O	H	Br	O	F	H	H
11	11	5	CH ₃	O	H	Br	O	F	H	Et
12	12	5	CH ₃	O	H	Br	O	F	H	H
13	13	5	CH ₃	O	H	CF ₃	O	F	H	Et
14	14	5	CH ₃	O	H	CF ₃	O	F	H	H
15	15	5	CH ₃	O	H	N ₃	O	F	H	Et
16	16	5	CH ₃	O	H	N ₃	O	F	H	H
17	17	5	CH ₃	O	H	CF ₃	O	F	F	CH ₃
18	18	5	CH ₃	O	H	CF ₃	O	F	F	H
19	19	5	CH ₃	O	H	I	O	F	H	Et
20	20	5	CH ₃	O	H	I	O	F	H	H
21	21	5	CH ₃	O	H	CH ₃	O	F	H	Et
22	22	5	CH ₃	O	H	CH ₃	O	F	H	H
23	23	5	CH ₃	S	H	H	O	F	H	Et
24	24	5	CH ₃	S	H	H	O	F	H	H
25	25	4	--	--	H	H	S	H	H	Et
26	26	4	--	--	H	H	S	H	H	H
27	27	4	--	--	H	H	S	F	H	Et
28	28	4	--	--	H	H	S	F	H	H
29	29	4	--	--	H	Br	O	NO ₂	H	CH ₃
30	30	4	--	--	H	Br	O	NO ₂	H	H

1	31	5	CH ₃	O	H	H	O	F	H	Et
2	32	5	CH ₃	O	H	H	O	F	H	H
3	33	4	--	--	OH	Br	O	F	H	Et
4	34	4	--	--	OH	Br	O	F	H	H
5	35	4	--	--	OH	Br	O	F	F	CH ₃
6	36	4	--	--	OH	Br	O	F	F	H
7	37	4	--	--	H	H	O	F	F	CH ₃
8	38	4	--	--	H	H	O	F	F	H

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Modes of Administration

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12 The compounds of this invention may be
 13 administered systemically or topically, depending on
 14 such considerations as the condition to be treated,
 15 need for site-specific treatment, quantity of drug
 16 to be administered, and numerous other
 17 considerations.

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18 In the treatment of dermatoses, it will
 19 generally be preferred to administer the drug
 20 topically, though in certain cases such as treatment
 21 of severe cystic acne or psoriasis, oral
 22 administration may also be used. Any common topical
 23 formulation such as a solution, suspension, gel,
 24 ointment, or salve and the like may be used.
 25 Preparation of such topical formulations are well
 26 described in the art of pharmaceutical formulations
 27 as exemplified, for example, Remington's
 28 Pharmaceutical Science, Edition 17, Mack Publishing
 29 Company, Easton, Pennsylvania. For topical
 30 application, these compounds could also be
 31 administered as a powder or spray, particularly in
 32 aerosol form. If the drug is to be administered
 33 systemically, it may be confected as a powder, pill,
 tablet or the like or as a syrup or elixir suitable

1 for oral administration. For intravenous or
2 intraperitoneal administration, the compound will be
3 prepared as a solution or suspension capable of
4 being administered by injection. In certain cases,
5 it may be useful to formulate these compounds by
6 injection. In certain cases, it may be useful to
7 formulate these compounds in suppository form or as
8 extended release formulation for deposit under the
9 skin or intramuscular injection.

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

16 Treatment of dermatoses or any other indications
17 known or discovered to be susceptible to treatment
18 by retinoic acid-like compounds will be effected by
19 administration of the therapeutically effective dose
20 of one or more compounds of the instant invention.
21 A therapeutic concentration will be that
22 concentration which effects reduction of the
23 particular condition, or retards its expansion. In
24 certain instances, the compound potentially may be
25 used in prophylactic manner to prevent onset of a
26 particular condition.

27 A useful therapeutic or prophylactic
28 concentration will vary from condition to condition
29 and in certain instances may vary with the severity
30 of the condition being treated and the patient's
31 susceptibility to treatment. Accordingly, no single
32 concentration will be uniformly useful, but will
33 require modification depending on the

1 particularities of the disease being treated. Such
2 concentrations can be arrived at through routine
3 experimentation. However, it is anticipated that in
4 the treatment of, for example, acne, or similar
5 dermatoses, that a formulation containing between
6 0.01 and 1.0 milligrams per milliliter of formulation
7 will constitute a therapeutically effective
8 concentration for total application. If
9 administered systemically, an amount between 0.01
10 and 5 mg per kg per day of body weight would be
11 expected to effect a therapeutic result in the
12 treatment of many disease for which these compounds
13 are useful.

14 Assay of Retinoid-like Biological Activity

15 The retinoid-like activity of the compounds of
16 the invention can be confirmed in assays wherein
17 ability of the compound to bind to retinoid
18 receptors is measured. As it is noted in the
19 introductory section of this application for patent
20 two main types of retinoic acid receptors (RAR and
21 RXR) exist in mammals (and other organisms). Within
22 each type there are sub-types (RAR_α, RAR_β, RAR_γ, RXR_α,
23 RXR_β and RXR_γ) the distribution of which is not
24 uniform in the various tissues and organs of
25 mammalian organisms. Selective binding of only one
26 or two retinoid receptor subtypes within one
27 retinoid receptor family can give rise to beneficial
28 pharmacological properties because of the varying
29 distribution of the sub-types in the several
30 mammalian tissues or organs. For the
31 above-summarized reasons, binding of any or all of
32 the retinoid receptors, as well as specific or
33 selective activity in a receptor family, or

1 selective or specific activity in any one of the
2 receptor subtypes, are all considered desirable
3 pharmacological properties.

4 In light of the foregoing the prior art has
5 developed assay procedures for testing the agonist
6 like activity of compounds in the RAR α , RAR β , RAR γ ,
7 RXR α , RXR β and RXR γ receptor subtypes. For example,
8 a chimeric receptor transactivation assay which
9 tests for agonist-like activity in the RAR α , RAR β ,
10 RAR γ , and RXR α receptor subtypes, and which is based
11 on work published by Feigner P. L. and Holm M.
12 (1989) Focus, 11 2 is described in detail in U.S.
13 Patent No. 5,455,265. The specification of United
14 States Patent No. 5,455,265 is expressly
15 incorporated herein by reference.

16 A holoreceptor transactivation assay and a
17 ligand binding assay which measure the ability of
18 the compounds of the invention to bind to the
19 several retinoid receptor subtypes, respectively,
20 are described in published PCT Application No. WO
21 WO93/11755 (particularly on pages 30 - 33 and 37 -
22 41) published on June 24, 1993, the specification of
23 which is also incorporated herein by reference. A
24 description of the ligand binding assay is also
25 provided below.

26 BINDING ASSAY

27 All binding assays were performed in a similar
28 fashion. All six receptor types were derived from
29 the expressed receptor type (RAR α , β , γ and RXR α ,
30 β , γ) expressed in Baculovirus. Stock solutions of
31 all compounds were prepared as 10mM ethanol
32 solutions and serial dilutions carried out into 1:1
33 DMSO; ethanol. Assay buffers consisted of the

1 following for all six receptor assays: 8% glycerol,
2 120mM KCl, 8mM Tris, 5mM CHAPS 4mM DTT and 0.24mM
3 PMSF, pH ~ 7.4@ room temperature.

4 All receptor binding assays were performed in the
5 same manner. The final assay volume was 250 μ l and
6 contained from 10-40 μ g of extract protein depending
7 on receptor being assayed along with 5 nM of [³H]
8 all-trans retinoic acid or 10nM [³H] 9-cis retinoic
9 acid and varying concentrations of competing ligand
10 at concentrations that ranged from 0 - 10⁻⁵ M. The
11 assays were formatted for a 96 well minitube system.
12 Incubations were carried out at 4°C until
13 equilibrium was achieved. Non-specific binding was
14 defined as that binding remaining in the presence of
15 1000nM of the appropriate unlabeled retinoic acid
16 isomer. At the end of the incubation period, 50 μ l
17 of 6.25% hydroxyapatite was added in the appropriate
18 wash buffer. The wash buffer consisted of 100mM
19 KCl, 10mM Tris and either 5mM CHAPS (RXR α , β , γ) or
20 0.5% Triton X-100 (RAR α , β , γ). The mixture was
21 vortexed and incubated for 10 minutes at 4°C,
22 centrifuged and the supernatant removed. The
23 hydroxyapatite was washed three more times with the
24 appropriate wash buffer. The receptor-ligand
25 complex was adsorbed by the hydroxyapatite. The
26 amount of receptor-ligand complex was determined by
27 liquid scintillation counting of hydroxyapatite
28 pellet.

29 After correcting for non-specific binding, IC₅₀
30 values were determined. The IC₅₀ value is defined as
31 the concentration of competing ligand needed to
32 reduce specific binding by 50%. The IC₅₀ value was
33 determined graphically from a loglogit plot of the

1 data. The K_d values were determined by application
2 of the Cheng-Prusoff equation to the IC_{50} values, the
3 labeled ligand concentration and the K_d of the
4 labeled ligand.

5 The results of ligand binding assay are expressed
6 in K_d numbers. (See Cheng et al. Biochemical
7 Pharmacology Vol. 22 pp 3099-3108, expressly
8 incorporated herein by reference.)

9 **Table 2** shows the results of the ligand binding
10 **assay** for certain exemplary compounds of the
11 **invention.**

TABLE 2
Ligand Binding Assay

Compound #	RAR α	RAR β	RAR γ	RXR α	RXR β	RXR γ
2	1.90	480.0	0.00	0.00	0.00	0.00
4	23.00	23.00	96.0	0.00	0.00	0.00
6	1.3	0.00	0.00	0.00	0.00	0.00
8	3.00	0.00	0.00	0.00	0.00	0.00
12	24.0	0.00	0.00	0.00	0.00	0.00
14	14.0	0.00	0.00	0.00	0.00	0.00
16	52.0	0.00	0.00	0.00	0.00	0.00
18	51.0	0.00	0.00	0.00	0.00	0.00
20	16.0	0.00	0.00	0.00	0.00	0.00
22	57.0	0.00	0.00	0.00	0.00	0.00
24	126.0	584	0.00	0.00	0.00	0.00
26	15	0.00	0.00	0.00	0.00	0.00
28	7.5	0.00	0.00	0.00	0.00	0.00
30	245.0	0.00	0.00	0.00	0.00	0.00
32	162.0	0.00	0.00	0.00	0.00	0.00
34	4.00	0.00	0.00	0.00	0.00	0.00
36	2.30	0.00	0.00	0.00	0.00	0.00
38	9.00	0.00	0.00	0.00	0.00	0.00

0.00 indicates value greater than 1000nM (nanomolar)

1 As it can be seen from the test results
2 summarized in Table 2, the therein indicated
3 exemplary compounds of the invention bind
4 specifically or selectively to RAR α receptors.

5 **CANCER CELL LINE ASSAYS**

6 **MATERIALS AND METHODS**

7 **Hormones**

8 All trans-Retinoic acid (t-RA) (Sigma Chemicals
9 Co., St. Louis, MO) was stored at -70°C. Prior to
10 each experiment the compound was dissolved in 100%
11 ethanol at 1 mM and diluted in culture medium
12 immediately before use. All experiments were
13 performed in subdued light. Controls were assayed
14 using the same concentration of ethanol as present
15 in the experimental plates and this concentration of
16 diluent had no effect in either assay.

17 **Cells and Cell Culture**

18 All cell lines, RPMI 8226, ME-180 and AML-193
19 were obtained from the American Type Culture
20 Collection (ATCC, Rockville, MD). RPMI 8226 is a
21 human hematopoietic cell line obtained from the
22 peripheral blood of a patient with multiple myeloma.
23 The cells resemble the lymphoblastoid cells of other
24 human lymphocyte cell lines and secrete α -type light
25 chains of immunoglobulin. RPMI-8226 cells are grown
26 in RPMI medium (Gibco) supplemented with 10% fetal
27 bovine serum, glutamine and antibiotics. The cells
28 were maintained as suspension cultures grown at 37°C
29 in a humidified atmosphere of 5% CO₂ in air. The
30 cells were diluted to a concentration of 1×10^5 /ml
31 twice a week.

32 ME-180 is a human epidermoid carcinoma cell line
33 derived from the cervix. The tumor was a highly
34 invasive squamous cell carcinoma with irregular cell
35 clusters and no significant keratinization. ME-180
36 cells were grown and maintained in McCoy's 5a medium

1 (Gibco) supplemented with 10% fetal bovine serum,
2 glutamine and antibiotics. The cells were
3 maintained as monolayer cultures grown at 37°C in a
4 humidified atmosphere of 5% CO₂ in air. The cells
5 were diluted to a concentration of 1×10^5 /ml twice a
6 week.

7 AML-193 was established from the blast cells
8 classified as M5 Acute Monocyte Leukemia. The
9 growth factor, granulocyte colony-stimulation factor
10 (GM-CSF) was required to establish this cell line
11 and growth factors are necessary for its continuous
12 proliferation in chemically defined medium. AML-193
13 cells were grown and maintained in Iscove's modified
14 Dulbecco's medium supplemented with 10% fetal bovine
15 serum, glutamine and antibiotics with 5µg/ml insulin
16 (Sigma Chemical Co.) and 2 ng/ml rh GM-CSF (R and D
17 Systems). The cells were diluted to a concentration
18 of 3×10^5 /ml twice a week.

19 Incorporation of ³H-Thymidine

20 The method used for determination of the
21 incorporation of radiolabeled thymidine was adapted
22 from the procedure described by Shrivastav et al.
23 RPMI-8226 cells were plated in a 96 well round
24 bottom microtiter plate (Costar) at a density of
25 1,000 cells/well. To appropriate wells, retinoid
26 test compounds were added at the final
27 concentrations indicated for a final volume of 150
28 µl/well. The plates were incubated for 96 hours at
29 37°C in a humidified atmosphere of 5% CO₂ in air.
30 Subsequently, 1 µCi of [5'-³H]-thymidine (Amersham,
31 U.K. 43 Ci/mmol specific activity) in 25 µl culture
32 medium was added to each well and the cells were
33 incubated for an additional 6 hours. The cultures
34 were further processed as described below.

35 ME-180 wells, harvested by trypsinization were
36 plated in a 96 well flat bottom microtiter plate

1 (Costar) at a density of 2,000 cells/well. The
2 cultures were treated as described above for RPMI
3 8226 with the following exceptions. After
4 incubation with thymidine the supernatant was
5 carefully removed, and the cells were washed with a
6 0.5 mM solution of thymidine in phosphate buffered
7 saline. ME180 cells were briefly treated with 50 μ l
8 of 2.5% trypsin to dislodge the cells from the
9 plate. AML-193 cells were plated in a 96 well
10 round bottom microtiter plate (Costar) at a density
11 of 1,000 cells/well. To appropriate wells, retinoid
12 test compounds were added at the final
13 concentrations indicated for a final volume of 150
14 μ l/well. The plates were incubated for 96 hours at
15 37°C in a humidified atmosphere of 5% CO₂ in air.
16 Subsequently, 1 μ Ci of [5'-³H]-thymidine (Amersham,
17 U.K., 43 Ci/mmol specific activity) in 25 μ l culture
18 medium was added to each well and the cells were
19 incubated for an additional 6 hours.

20 All cells lines were then processed as follows:
21 the cellular DNA was precipitated with 10%
22 trichloroacetic acid onto glass fiber filter mats
23 using a SKATRON multi-well cell harvester (Skatron
24 Instruments, Sterling VA). Radioactivity
25 incorporated into DNA, as a direct measurement of
26 cell growth, was measured by liquid scintillation
27 counting. The numbers represent the mean
28 disintegrations per minute of incorporated thymidine
29 from triplicate wells $\pm$ SEM.

30 In the above noted in vitro cell lines exemplary
31 compounds 6, 8, 12, 14 and 20 of the invention
32 caused significant decrease in the proliferation of
33 the tumor cell lines (as measured by incorporation
34 of radioactive labeled thymidine) in the 10⁻¹¹ to 10⁻⁶
35 molar concentration range of the respective test
36 compound.

SPECIFIC EMBODIMENTS

The compounds of this invention can be made by the synthetic chemical pathways illustrated here. 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. Generally speaking the process of preparing compounds of the invention involves the formation of an amide by the reaction of a compound of the general Formula 2 with a compound of general Formula 3, or by the reaction of a compound of general Formula 2a with a compound of general Formula 3a as these formulas are defined in the Summary section of the present application for patent. Thus, as is noted above, a compound of Formula 2 is an acid or an "activated form" of a carboxylic acid attached to the aromatic portion of a tetrahydronaphthalene, ($X = [C(R_1)_2]_n$ and n is 1), dihydroindene ($[C(R_1)_2]_n$ where n is 0), chroman (X is O), thiochroman (X is S), or tetrahydroquinoline (X is NR') nucleus. The carboxylic acid, or its "activated form" is attached to the 2 or 3 position of the tetrahydronaphthalene, and to the 6 or 7 position of the chroman, thiochroman or tetrahydroquinoline moieties. In the preferred compounds of the invention the attachment is to the 2 position of tetrahydronaphthalene and to the 6 position of chroman, thiochroman or tetrahydroquinoline.

The term "activated form" of the carboxylic acid should be understood in this regard as such derivative of the carboxylic acid which is capable of forming an amide when reacted with a primary amine of Formula 3. In case of the "reverse amides" the activated form of a carboxylic acid is a derivative (Formula 3a) that is capable of forming

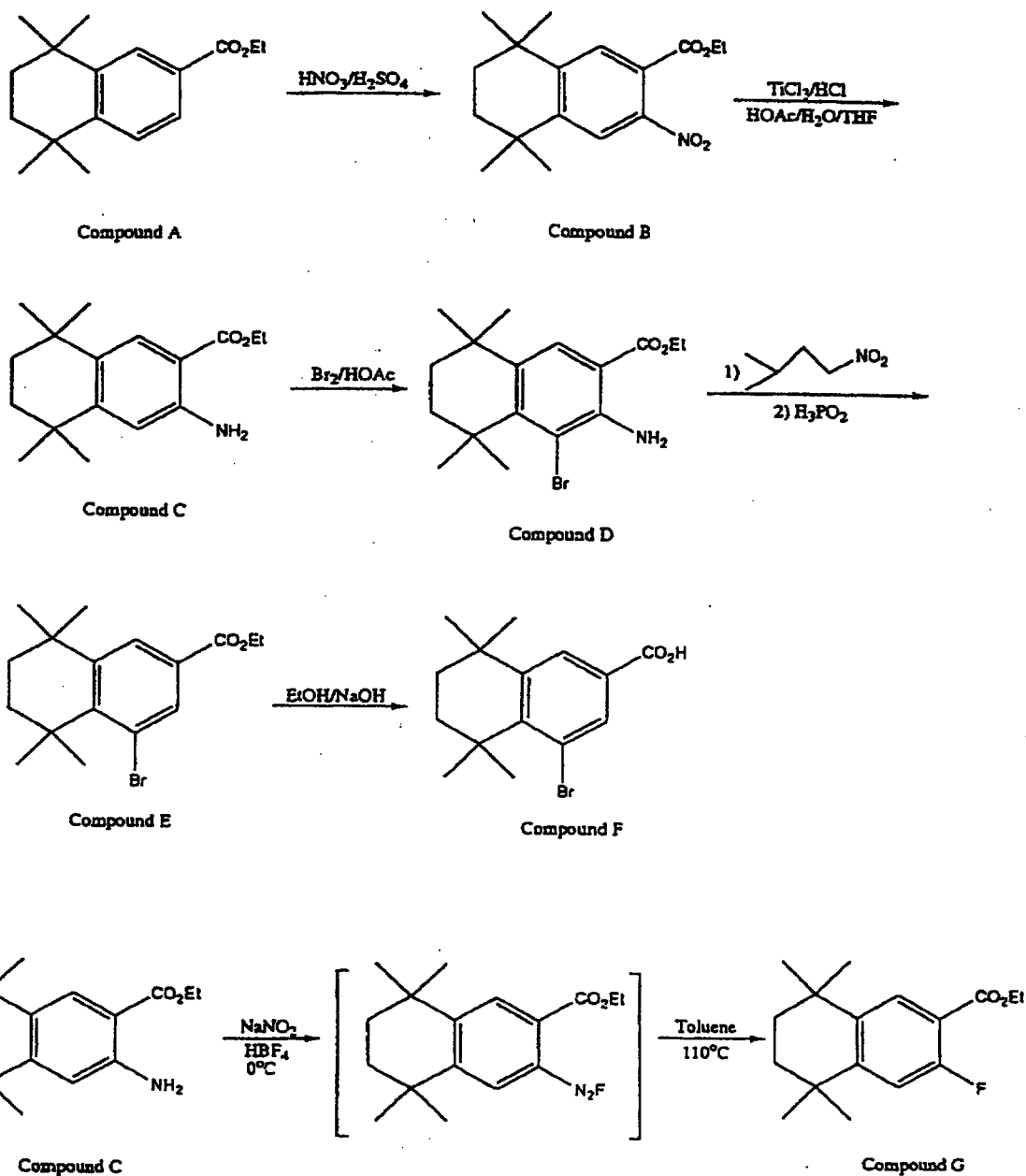
1 an amide when reacted with a primary amine of
2 Formula 2a. This, generally speaking, means such
3 derivatives of a carboxylic acid which are normally
4 known and used in the art to form amide linkages
5 with an amine. Examples of suitable forms or
6 derivatives for this purpose are acid chlorides,
7 acid bromides, and esters of the carboxylic acid,
8 particularly active esters, where the alcohol moiety
9 of the ester forms a good leaving group. Presently
10 most preferred as reagents in accordance with
11 Formula 2 (or Formula 3a) are acid chlorides (X_1 is
12 Cl). The acid chlorides of Formula 2 (or of Formula
13 3a) can be prepared by traditional methods from the
14 corresponding esters (X_1 is for example ethyl) by
15 hydrolysis and treatment with thionyl chloride
16 (SOCl_2). The acid chlorides of Formula 2 (or of
17 Formula 3a) can also be prepared by direct treatment
18 of the carboxylic acids with thionyl chloride, where
19 the carboxylic acid, rather than an ester thereof is
20 available commercially or by a known synthetic
21 procedure. The acid chlorides of Formula 2 (or of
22 Formula 3a) are typically reacted with the amine of
23 Formula 3 (or amine of Formula 2a) in an inert
24 solvent, such as methylene chloride, in the presence
25 of an acid acceptor, such as pyridine.

26 The carboxylic acids themselves in accordance
27 with Formula 2 (or Formula 3a) are also suitable for
28 amide formation when reacted with an amine, a
29 catalyst (4-dimethylaminopyridine) in the presence
30 of a dehydrating agent, such as
31 dicyclohexylcarbodiimide (DCC) or more preferably
32 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
33 hydrochloride (EDC).

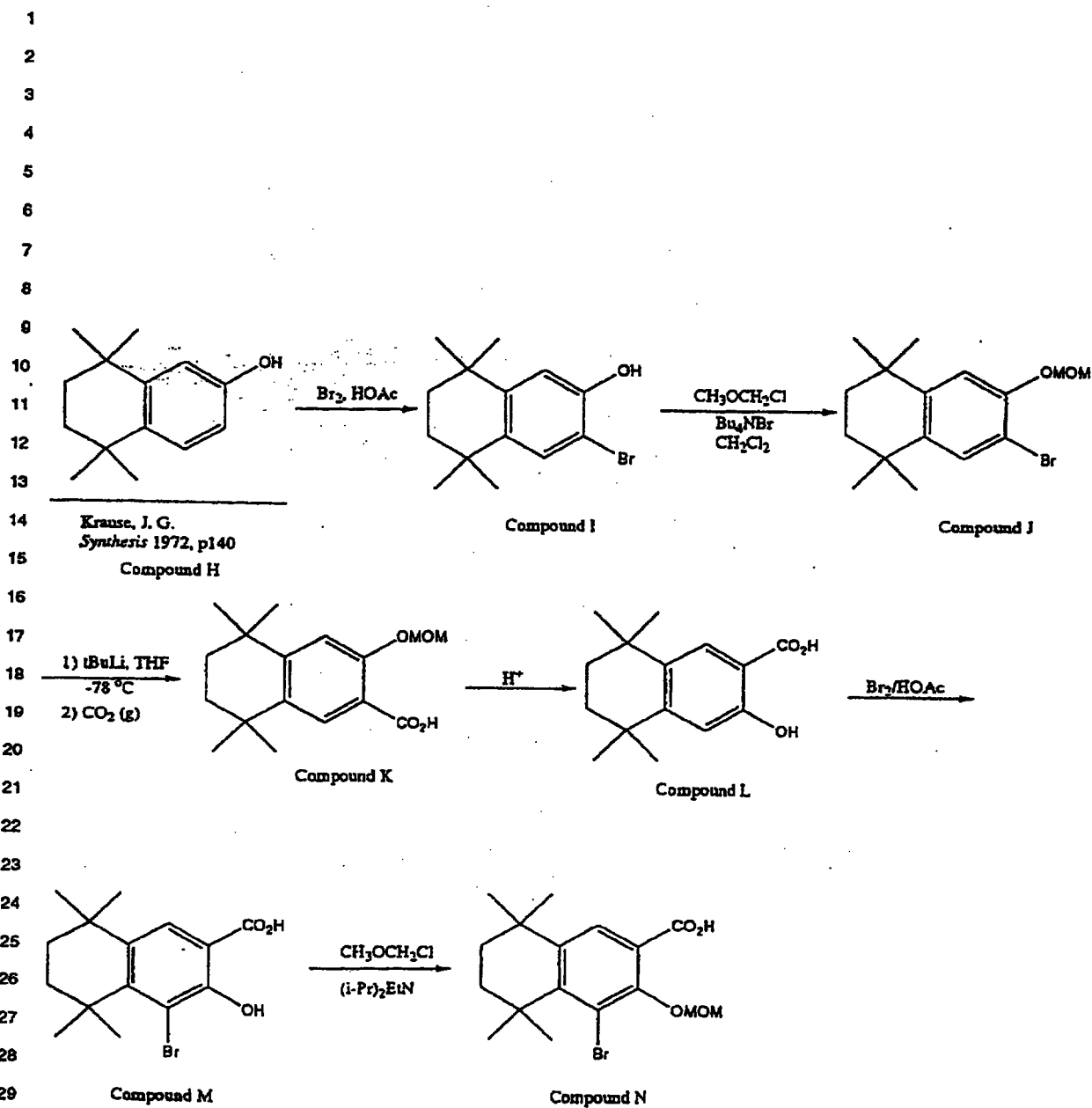
34 The carboxylic acids or the corresponding esters
35 of Formula 2, are generally speaking, prepared as
36 described in the chemical scientific or patent

1 literature and the literature procedures for their
2 preparation may be modified, if necessary, by such
3 chemical reactions or processes which per se are
4 known in the art. For example, generally speaking,
5 2,2, 4,4 and/or 2,2,4,4-substituted chroman
6 6-carboxylic acids and chroman 7-carboxylic acids
7 are available in accordance with the teachings of
8 United States Patent Nos. 5,006,550, 5,314,159,
9 5,324,744, and 5,348,975, the specifications of
10 which are expressly incorporated herein by
11 reference. 2,2, 4,4 and/or 2,2,4,4-substituted
12 thiochroman 6-carboxylic acids are available in
13 accordance with the teachings of United States
14 Patent No. 5,015,658, the specifications of which is
15 expressly incorporated herein by reference.
16 5,6,7,8-Tetrahydronaphthalene-2-carboxylic acids
17 are, generally speaking, available in accordance
18 with the teachings of United States Patent No.
19 5,130,335, the specifications of which is expressly
20 incorporated herein by reference.

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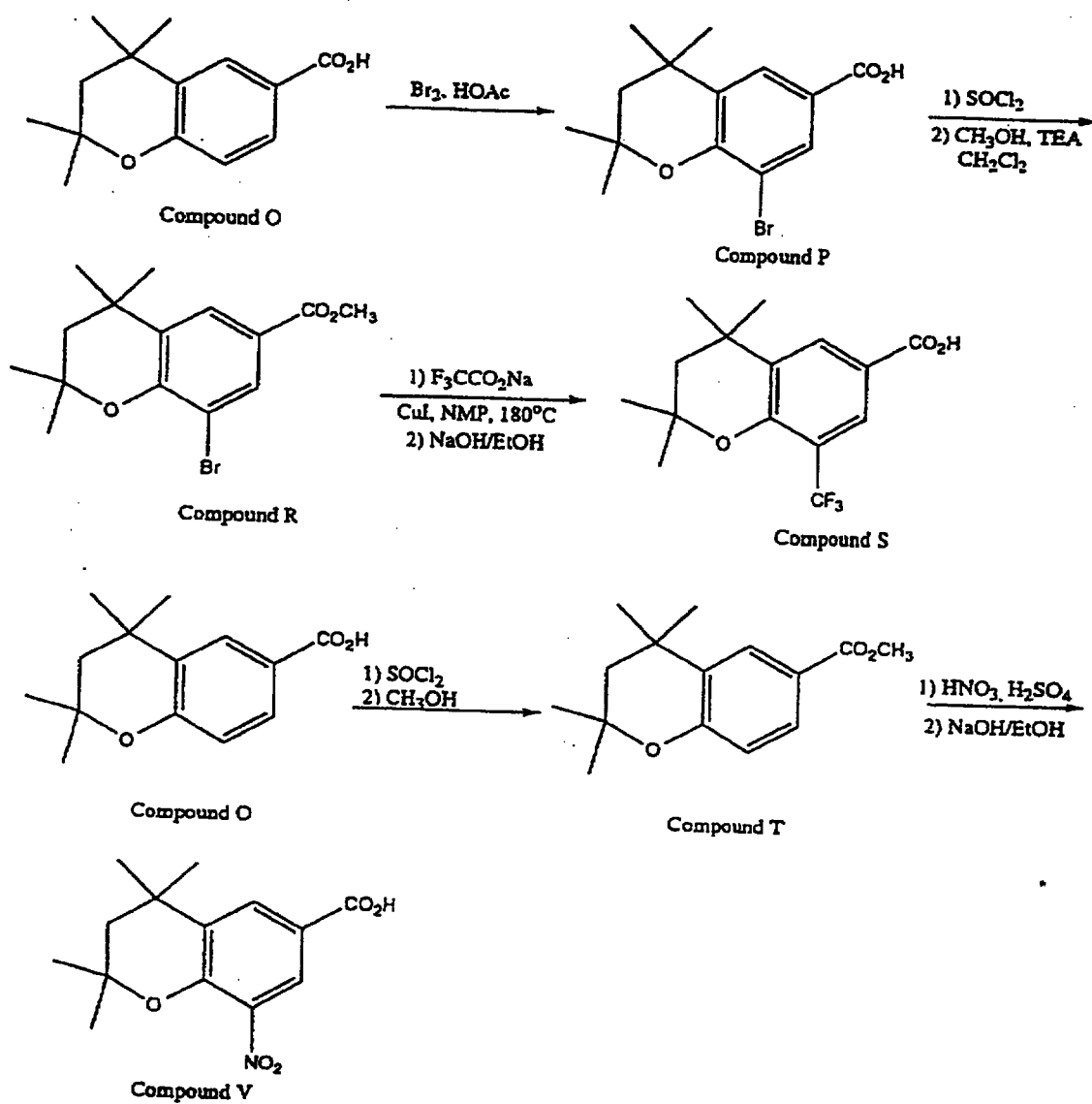
Reaction Scheme 1



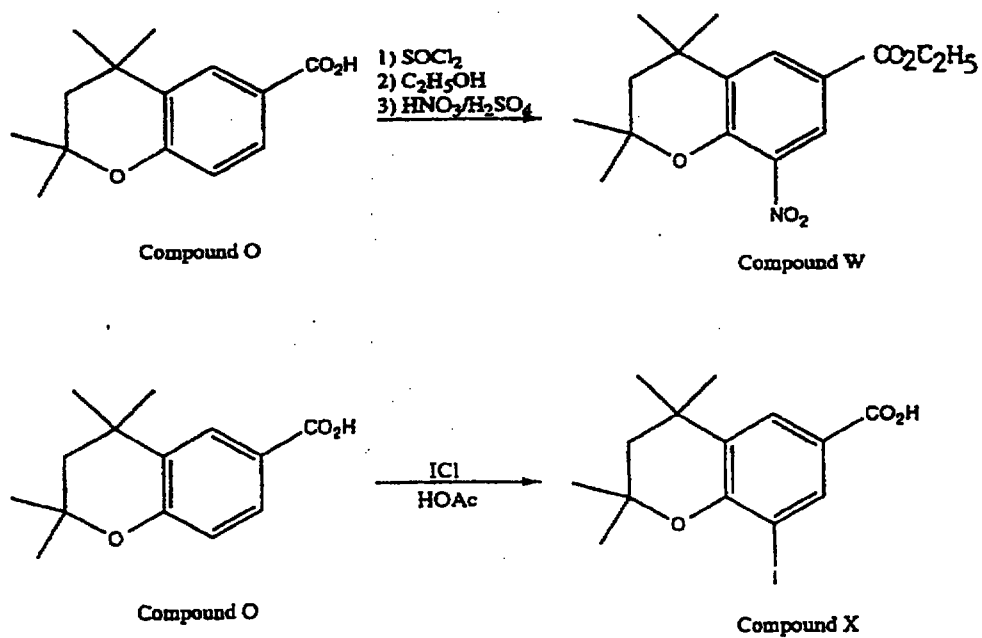
Reaction Scheme 2

1 Reaction Schemes 1 and 2 provide examples for
2 the synthesis of derivatives of
3 5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-
4 carboxylic acid, which are within the scope of
5 Formula 2 and which are reacted with an amine of
6 Formula 3 to provide
7 (5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-naphthalene-
8 2-yl)carbamoyl derivatives within the scope of
9 Formula 1. Thus, as is shown in Reaction Scheme 1,
10 ethyl
11 5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-
12 carboxylate (Compound A) is nitrated to provide the
13 corresponding 3-nitro compound (Compound B). The
14 nitro group of Compound B is reduced to provide the
15 corresponding 3-amino compound (Compound C) which is
16 described in the publication Lehmann et al. Cancer
17 Research, 1991, 51, 4804. Ethyl
18 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-aminonaphth
19 alene-2-carboxylate (Compound C) is brominated to
20 yield the corresponding 4-bromo derivative (Compound
21 D), which is converted by treatment with
22 isoamylnitrite and reduction with H_3PO_2 , to ethyl
23 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-4-bromonaphth
24 alene-2-carboxylate (Compound E). Saponification of
25 Compound E yields
26 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-4-bromonaphth
27 alene-2-carboxylic acid (Compound F) which is used
28 as a reagent in accordance with Formula 2. Ethyl
29 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-aminonaphth
30 alene-2-carboxylate (Compound C) is also diazotized
31 and reacted with HBF_4 to provide ethyl
32 5,6,7,8-tetrahydro-5,5,8,8-tetra-methyl-3-fluoronaph
33 thalene-2-carboxylate (Compound G) which serves
34 either per se or after saponification as a reagent
35 in accordance with Formula 2.

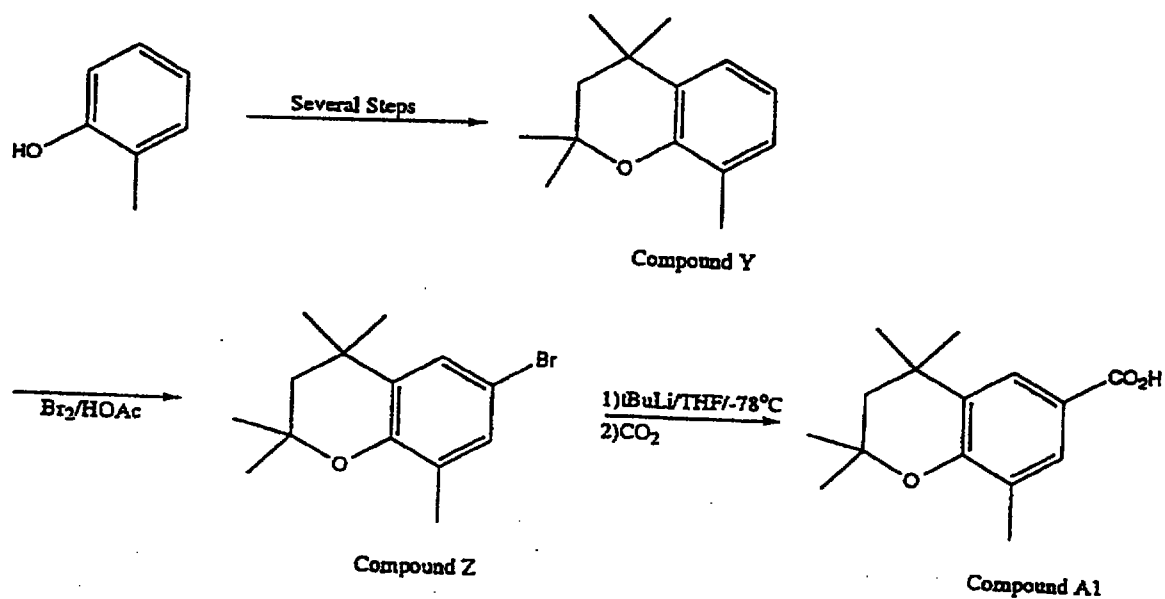
1 5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-hydroxy-
2 naphthalene (Compound H, available in accordance
3 with the publication Krause Synthesis 1972 140), is
4 the starting material in the example shown in
5 Reaction Scheme 2. Compound H is brominated to
6 provide the corresponding 3-bromo compound (Compound
7 I) which is thereafter protected in the hydroxyl
8 function by treatment with methoxymethyl chloride
9 (MOMCl) to yield
10 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-methoxymet-
11 hoxy-2-bromonaphthalene (Compound J). Compound J is
12 reacted with *t*-butyllithium and carbon dioxide to
13 provide the corresponding carboxylic acid (Compound
14 K) from which the methoxymethyl protecting group is
15 removed by acid to give
16 5,6,7,8-tetrahydro-5,5,8,8-tetra-
17 methyl-2-hydroxynaphthalene-3-carboxylic acid
18 (Compound L). Compound L is brominated to yield
19 5,6,7,8-tetrahy-
20 dro-5,5,8,8-tetramethyl-1-bromo-2-hydroxynaphthalene
21 -3-carboxylic acid (Compound M). Compound L and
22 Compound M serve as reagents in accordance with
23 Formula 2. The hydroxy group of Compound M is
24 protected for further transformations with
25 methoxymethyl chloride (MOMCl) in the presence of
26 base, yielding
27 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-1-bromo-2-met-
28 hoxymethoxynaphthalene-3-carboxylic acid (Compound
29 N).



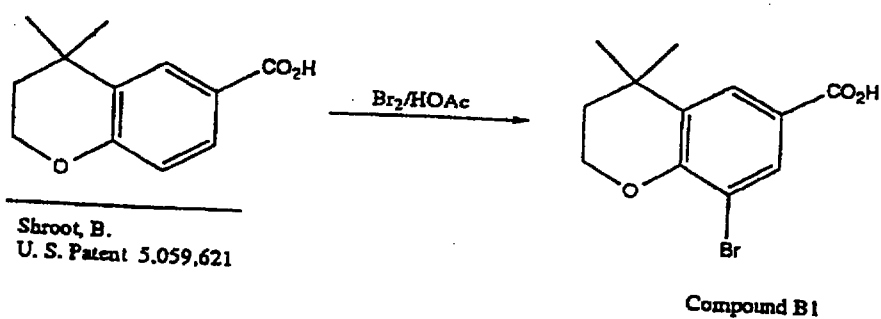
Reaction Scheme 3



35



Reaction Scheme 4



Reaction Scheme 5

1 **Reaction Schemes 3, 4 and 5** provide examples for
2 the synthesis of derivatives of 2,2,4,4 and
3 4,4-substituted chroman-6-carboxylic acids which can
4 serve as reagents in accordance with **Formula 2** for
5 the synthesis of the carbamoyl (amide) compounds
6 within the scope of the present invention. Thus,
7 referring now to **Reaction Scheme 3**,
8 2,2,4,4-tetramethylchroman-6-carboxylic acid
9 (**Compound O**, see U. S. Patent No. 5,006,550) is
10 brominated with bromine in acetic acid to yield the
11 corresponding 8-bromo derivative (**Compound P**).
12 **Compound P** is converted to the acid chloride by
13 treatment with thionyl chloride, and the resulting
14 acid chloride is suitable for reaction with an amine
15 of **Formula 3** to provide the carbamoyl (amide)
16 compounds of the invention. The acid chloride is
17 also reacted with an alcohol (methanol) in the
18 presence of base to yield the corresponding ester,
19 methyl
20 2,2,4,4-tetramethyl-8-bromochroman-6-carboxylate
21 (**Compound R**). The bromo function of **Compound R** is
22 converted to a trifluoromethyl function by treatment
23 with sodium trifluoroacetate in the presence of
24 cuprous iodide catalyst and 1-methyl-2-pyrrolidinone
25 (NMP), and the carboxylate ester group is saponified
26 to yield
27 2,2,4,4-tetramethyl-8-trifluoromethylchroman-6-carbo
28 xylic acid (**Compound S**). **Compound S** is within the
29 scope of **Formula 2** and is suitable per se or as the
30 acid chloride or in other "activated" form to react
31 with the amines of **Formula 3** to yield the carbamoyl
32 (amide) compounds of the invention.
33 2,2,4,4-Tetramethylchro-man-6-carboxylic acid
34 (**Compound O**) is also converted to the methyl ester
35 (**Compound T**) which is then nitrated to yield
36 2,2,4,4-tetramethyl-8-nitrochroman-6-carboxylic acid

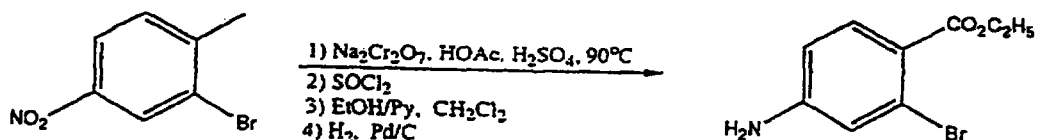
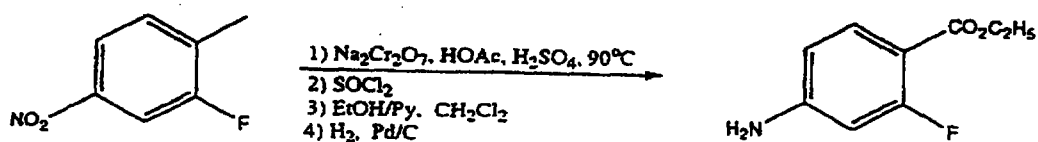
1 (Compound V), still another reagent within the scope
2 of Formula 2. Moreover, in the example further
3 shown in Reaction Scheme 3,
4 2,2,4,4-tetramethylchroman-6-carboxylic acid
5 (Compound O) is converted to the ethyl ester and
6 nitrated thereafter to yield ethyl
7 2,2,4,4-tetramethyl-8-nitrochroman-6-carboxylate
8 (Compound W). Still further, Compound O is reacted
9 with ICl to yield
10 2,2,4,4-tetramethyl-8-iodochroman-6-carboxylic acid
11 (Compound X).

12 In accordance with the example shown in Reaction
13 Scheme 4, 2-methylphenol is subjected to a series of
14 reactions in accordance with the teachings of United
15 States Patent No. 5,045,551 (incorporated herein by
16 reference) to yield 2,2,4,4,8-pentamethylchroman
17 (Compound Y). Compound Y is brominated with bromine
18 in acetic acid to give
19 2,2,4,4,8-pentamethyl-6-bromochroman (Compound Z)
20 which is reacted with t-butyl lithium and thereafter
21 with carbon dioxide to give
22 2,2,4,4,8-pentamethylchroman-6-carboxylic acid
23 (Compound A₁).

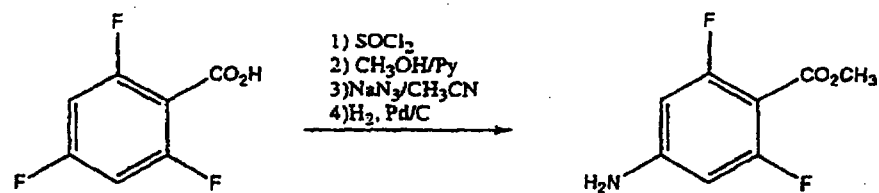
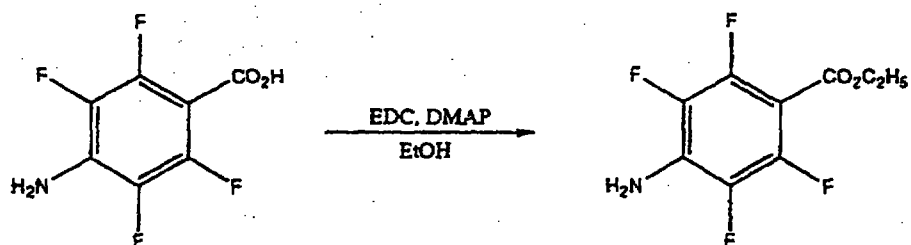
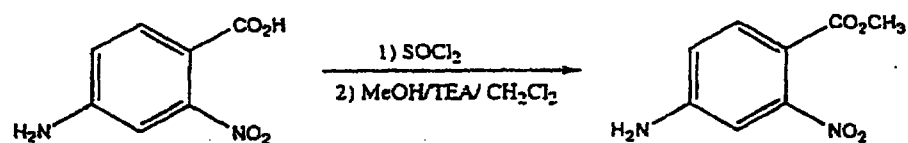
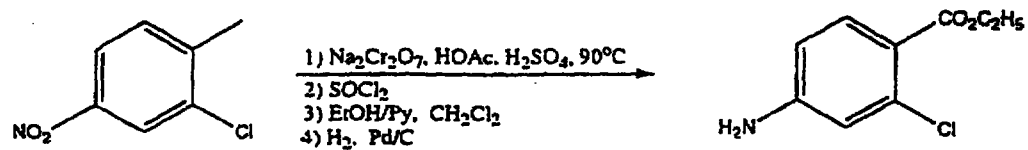
24 Reaction Scheme 5 illustrates the synthesis of
25 4,4-dimethyl-8-bromochroman-6-carboxylic acid
26 (Compound B₁) by bromination of
27 4,4,-dimethyl-chroman-6-carboxylic acid which is
28 available in accordance with the teachings of United
29 States Patent No. 5,059,621, the specification of
30 which is incorporated herein by reference.
31 2,2,4,4,8-Pentamethylchroman-6-carboxylic acid
32 (Compound A₁) and
33 4,4,-dimethyl-8-bromochroman-6-carboxylic acid
34 (Compound B₁) serve as reagents, either per se, or as
35 the corresponding acid chlorides (or other
36 "activated form), in accordance with Formula 2 for

1 the synthesis of the carbamoyl (amide) compounds of
2 the present invention.

3 Referring back now to the reaction between the
4 reagent of Formula 2 with an amine compound of
5 Formula 3 it is noted that the amine compounds are,
6 generally speaking, available in accordance with the
7 state-of-the-art. as described in the scientific and
8 patent literature. More specifically, the amine
9 compounds of Formula 3 can be prepared as described
10 in the scientific and patent literature, or from
11 known compounds of the literature, by such chemical
12 reactions or transformations which are within the
13 skill of the practicing organic chemist. Reaction
14 Scheme 6 illustrates examples for the preparation of
15 amine compounds of Formula 3 (where Y is phenyl)
16 from commercially available starting materials
17 (Aldrich Chemical Company, or Research Plus, Inc.
18 The illustrated compounds of Formula 3 are used for
19 the synthesis of several preferred compounds of the
20 invention.



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Reaction Scheme 6

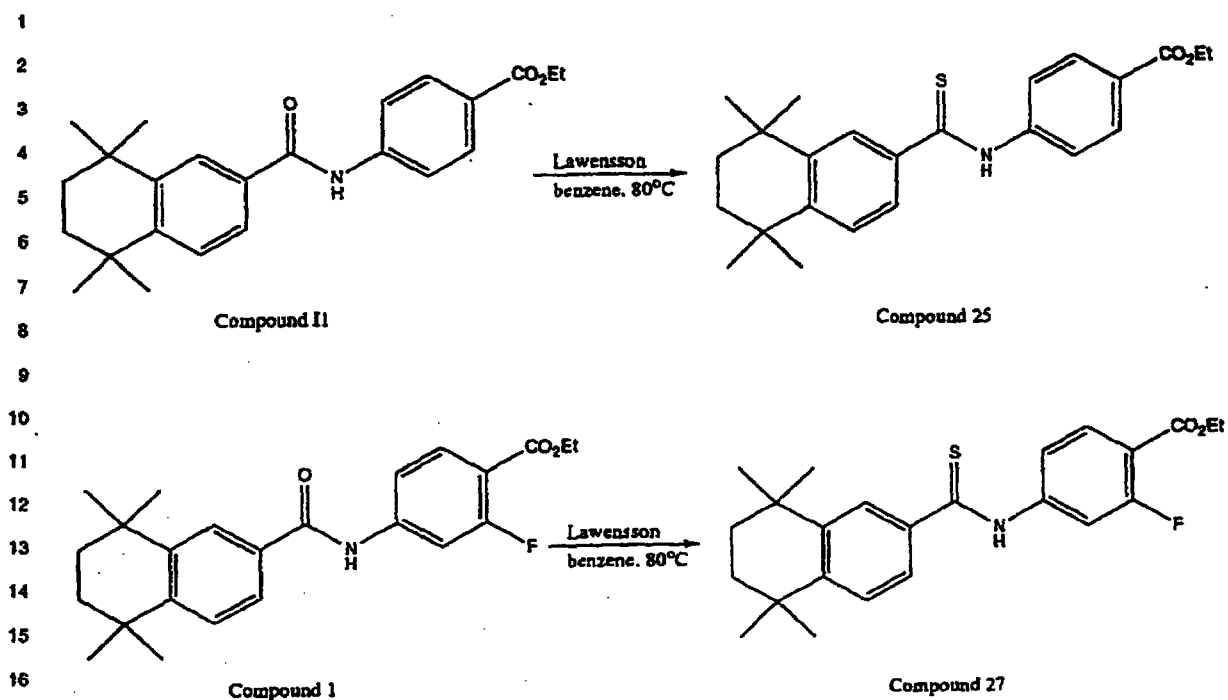


Reaction Scheme 6 -continued-

1 Thus, in accordance with Reaction Scheme 6,
2 3-nitro-6-methyl-fluorobenzene (Aldrich) is
3 subjected to oxidation, conversion of the resulting
4 carboxylic acid to an acid chloride and thereafter
5 to an ethyl ester, followed by reduction of the
6 nitro group, to yield ethyl
7 2-fluoro-4-amino-benzoate (Compound C₁).
8 3-Nitro-6-methyl-bromobenzene (Aldrich) and
9 3-nitro-6-methyl-chlorobenzene (Aldrich) are
10 subjected to essentially to the same series of
11 reactions to yield ethyl 2-bromo-4-amino-benzoate
12 (Compound D₁) and ethyl 2-chloro-4-amino-benzoate
13 (Compound E₁), respectively. 2-Nitro-4-aminobenzoic
14 acid (Research Plus) is converted to its methyl
15 ester (Compound F₁) through the corresponding acid
16 chloride. 2,3,5,6-Tetrafluoro-4-amino-benzoic acid
17 (Aldrich) is esterified by treatment with ethanol in
18 the presence of
19 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
20 hydrochloride (EDC) and 4-dimethylaminopyridine in
21 CH₂Cl₂ to give ethyl
22 2,3,5,6-tetrafluoro-4-amino-benzoate (Compound G₁).
23 2,4,6-Trifluorobenzoic acid (Aldrich) is converted
24 to the methyl ester through the acid chloride, and
25 the 4-fluoro atom is displaced by reaction with
26 sodium azide, followed by hydrogenation, to yield
27 methyl 2,6-difluoro-4-amino benzoate (Compound H₁).
28 Compounds C₁, D₁, E₁, F₁, G₁ and H₁ serve as amine
29 reagents in accordance with Formula 3. Further
30 examples of reagents in accordance with Formula 3
31 are nitro, fluoro, chloro, bromo and trifluoromethyl
32 derivatives of amino substituted heteroaryl
33 carboxylic acids, or their lower alkyl esters, such
34 as ethyl 2-amino-4-chloropyridine 2-carboxylate,
35 ethyl 5-amino-3-chloropyridine 5-carboxylate, and
36 3,4-dibromo-5-aminothiophene-2-carboxylic acid. The

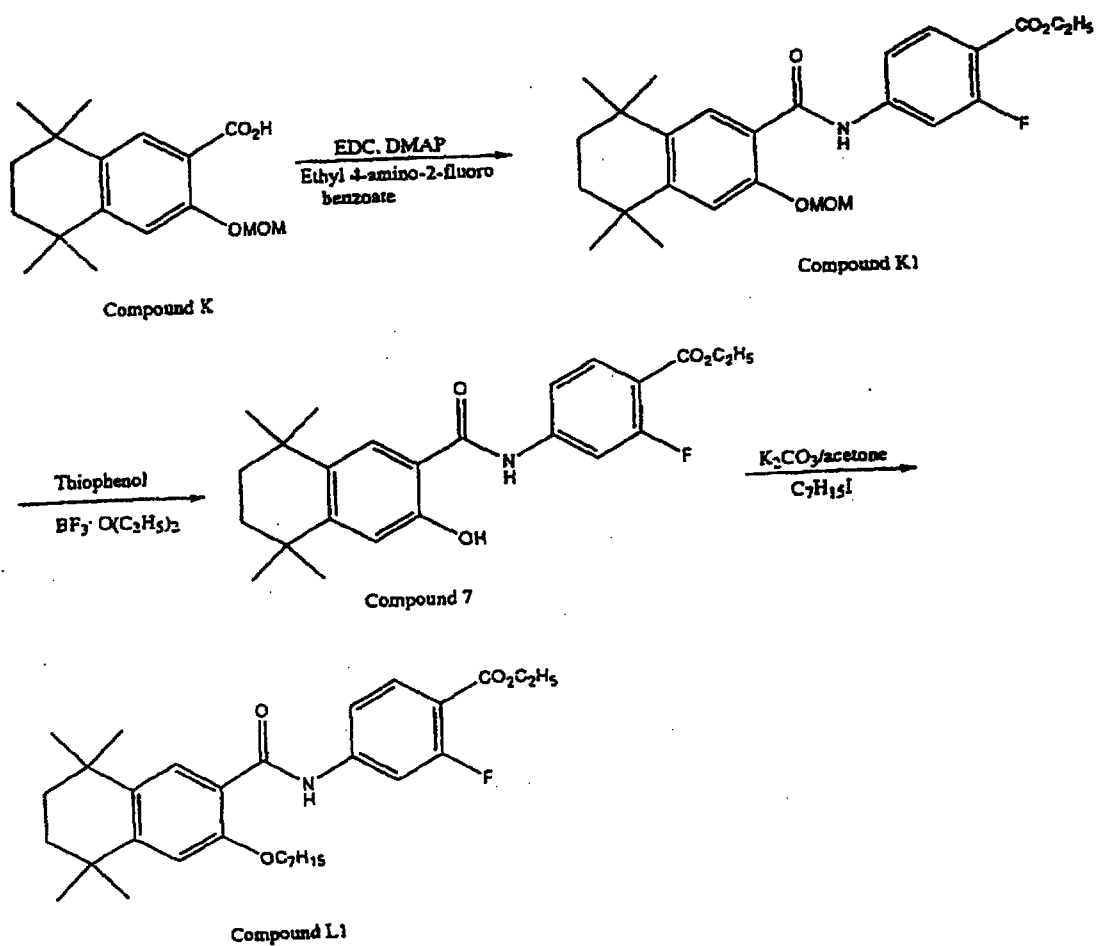
1 latter examples can be prepared by respective
2 chlorination or bromination of
3 2-aminopyridine-5-carboxylic acid or of its ester,
4 3-aminopyridine-6-carboxylic acid or of its ester
5 (described in WO 93/06086) and of
6 2-aminothiophene-5-carboxylic acid (described in
7 PCT/US92/06485).

8 The reaction between the compounds of Formula 2
9 and Formula 3 or between compounds of Formula 2a and
10 3a, described above, comprises the actual synthesis
11 of the carbamoyl (amide) compounds of the invention.
12 Numerous examples of this reaction are described in
13 detail in the experimental section below. The
14 carbamoyl (amide) compounds of the invention can be
15 converted into thiocarbamoyl (thioamide) compounds
16 of the invention where with reference to Formula 1 Z
17 is S, by reacting the carbamoyl (amide) compound
18 with
19 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetan
20 e-2,4-disulfide (Lawesson's reagent). This reaction
21 is illustrated in Reaction Scheme 7 for two specific
22 examples for the compounds of the invention.

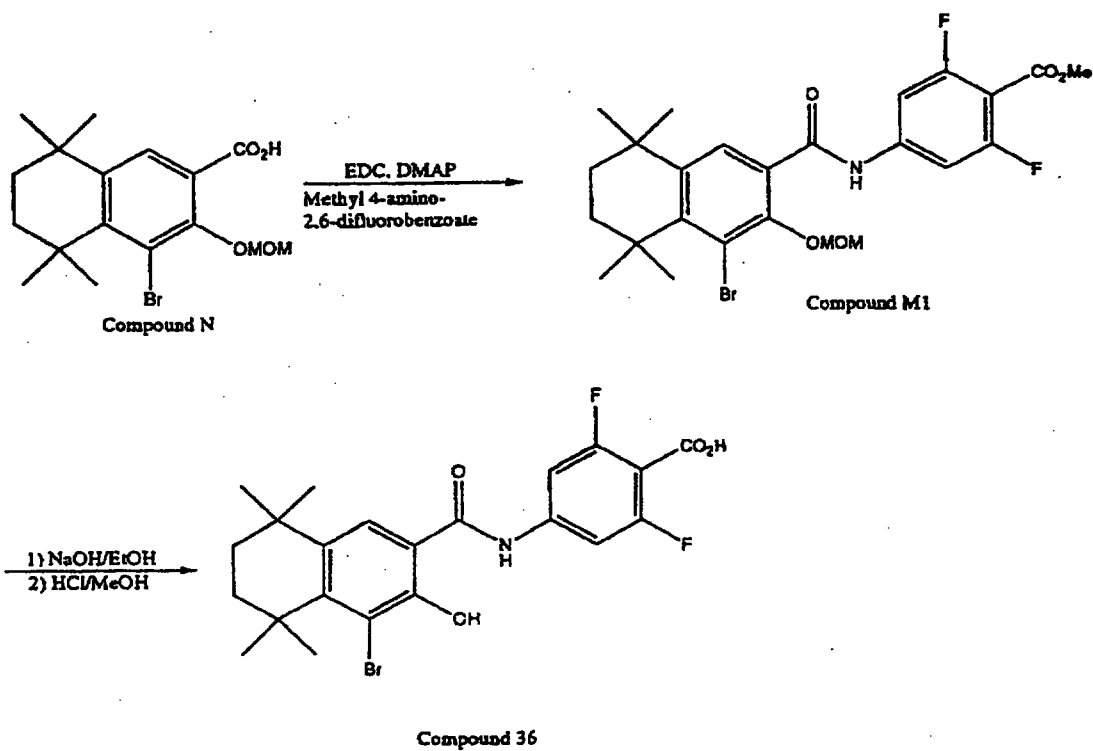


Reaction Scheme 7

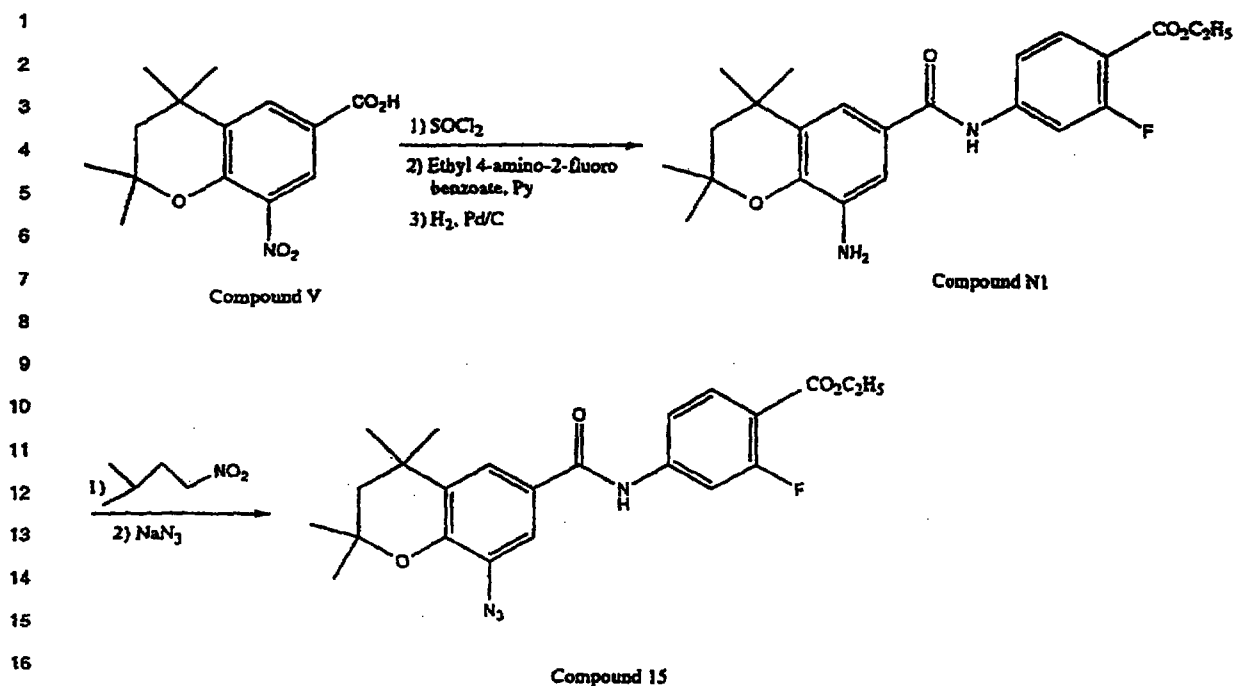
In Reaction Scheme 7 one starting material ethyl 4-[5',6',7',8'-tetrahydro-5',5',8',8'-tetramethylnaphthalen-2-yl)carbamoyl]benzoate (Compound 1,) is obtained in accordance with the teachings of Kagechika et al. J. Med Chem. 1988 31, 2182 - 2192. The other starting material, ethyl 2-fluoro-4-[5',6',7',8'-tetrahydro-5',5',8',8'-tetramethylnaphthalen-2-yl)carbamoyl]benzoate (Compound 1) is obtained in accordance with the present invention.



Reaction Scheme 8



Reaction Scheme 9



Reaction Scheme 10

Reaction Schemes 8, 9 and 10 disclose examples for the preparation of carbamoyl (amide) compounds of the invention, first by a coupling reaction of a compound of Formula 2 with a compound of Formula 3, followed by one or more reactions performed on the carbamoyl (amide) compound that has been first obtained directly in the coupling reaction. Thus, as is shown in Reaction Scheme 8, 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-methoxymethoxynaphthalene-2-carboxylic acid (Compound K) is coupled with ethyl 4-amino-2-fluorobenzoate (Compound C₁) in CH_2Cl_2 in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) and dimethylaminopyridine (DMAP) to give ethyl 2-fluoro-4-[5',6',7',8'-tetrahydro-5',5',8',8'-tetrameth-

1 yl-2'-methoxymethoxy-naphthalen-3'-yl)carbamoyl]benz
2 oate (Compound K₁). The methoxymethyl protecting
3 group is removed from Compound K₁ by treatment with
4 thiophenol and borontrifluoride etherate resulting
5 in ethyl
6 2-fluoro-4-[5',6',7',8'-tetrahydro-5',5',8',8'-tetra
7 methyl-2'-hydroxy-naphthalen-3'-yl)carbamoyl]-
8 benzoate (Compound 7). The hydroxy function of
9 Compound 7 is converted into an n-hexyl ether by
10 treatment with hexyl iodide in the presence of mild
11 base.

12 In accordance with Reaction Scheme 9
13 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-1-bromo-2-met
14 hoxymethoxynaphthalene-3-carboxylic acid (Compound
15 N) is coupled with methyl
16 4-amino-2,6-difluorobenzoate (Compound H₁) in CH₂Cl₂
17 solvent in the presence of ethylcarbodiimide
18 hydrochloride (EDC) and DMAP to provide methyl
19 2,6-difluoro-4-[(5',6',7',8'-tetrahydro-5',5',8',8'-
20 tetramethyl-1'-bromo-2'-methoxymethoxy-naphthalen-3'
21 -yl)carbamoyl]benzoate (Compound M₁), from which the
22 esterifying methyl group and the methoxymethyl
23 protecting group are removed by treatment with base
24 and acid, respectively.

25 Reaction Scheme 10 discloses the example of
26 converting 2,2,4,4-tetramethyl-8-nitrochroman-6-
27 carboxylic acid (Compound V) into the corresponding
28 acid chloride by treatment with thionyl chloride,
29 followed by coupling with ethyl
30 4-amino-2-fluorobenzoate (Compound C₁) and
31 hydrogenation to yield ethyl
32 2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-amino-6'-chr
33 omanyl)carbamoyl]benzoate (Compound N₁). Compound N₁
34 is converted to the corresponding 8-azido compound,
35 ethyl 2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-azido-
36 6'-chromanyl)carbamoyl]benzoate (Compound 15) by

1 treatment of isoamyl nitrate and NaN_3 .

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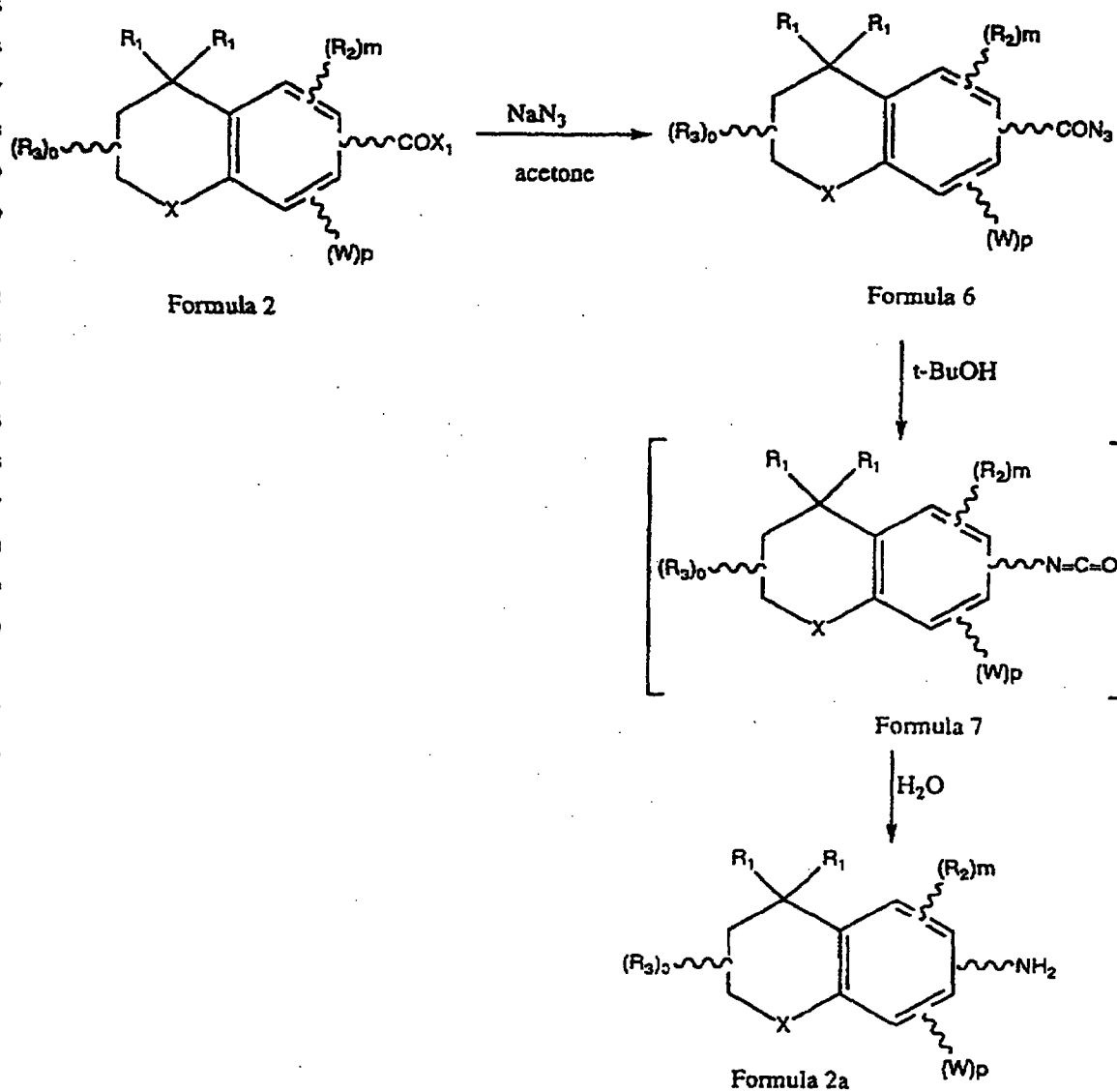
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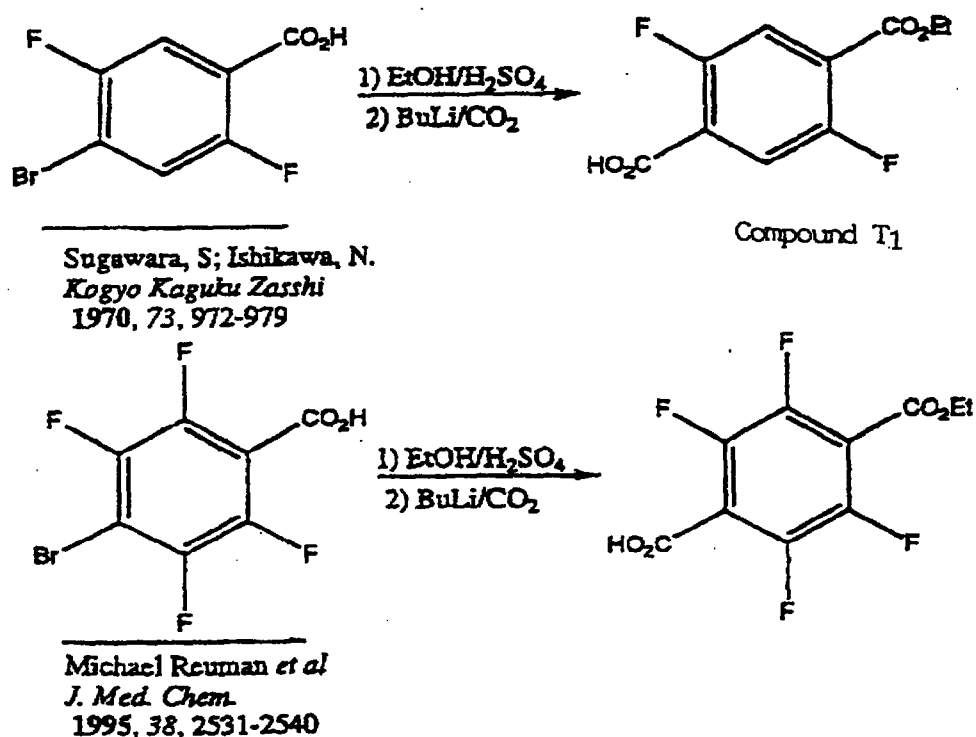
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Reaction Scheme 11

Reaction Scheme 11 illustrates the synthesis of the primary amine compounds of Formula 2a from the acid chlorides ($X_1 = \text{Cl}$) or other form of activated acids of Formula 2 where the primary amine of Formula 2a is not available by a published literature procedure. Thus, substantially in accordance with the step of a Curtius rearrangement, the acid chloride of Formula 2 is reacted with sodium azide in acetone to yield the azide compound of Formula 6. The azide of Formula 6 is heated in a polar high boiling solvent, such as t-butanol, to provide the intermediate isocyanate of Formula 7, which is hydrolyzed to yield a compound of Formula 2a.



Reaction Scheme 12

1 **Reaction Scheme 12** illustrates examples for
2 preparing compounds of **Formula 3a** where such
3 compounds are not available commercially or by a
4 published literature procedure. Thus, by way of
5 example 2,5-difluoro-4-bromobenzoic acid (available
6 by the literature procedure of Sugawara et al. *Kogyo*
7 *Kagaku Zasshi* 1970, 73, 972-979) is first esterified
8 by treatment with ethyl alcohol and acid to yield
9 the corresponding ester, and thereafter is reacted
10 with butyl lithium followed by carbon dioxide to
11 give the monoester of 2,5-difluoro terephthalic acid
12 (**Compound T₁**). A similar sequence of reactions
13 performed on 2,3,5,6-difluoro-4-bromobenzoic acid
14 (available by the literature procedure of Reuman et
15 al. *J. Med. Chem.* 1995, 38, 2531-2540) yields the
16 monoester of 2,3,5,6-tetrafluoroterephthalic acid.
17 The just illustrated sequence of reaction can be,
18 generally speaking, utilized for the synthesis of
19 all compounds of **Formula 3a** with such modification
20 which will become readily apparent to those skilled
21 in the art, where such compounds are not available
22 by a known literature procedure.

23 Numerous other reactions suitable for preparing
24 compounds of the invention, and for converting
25 compounds of **Formula 1** within the scope of the
26 present invention into still further compounds of
27 the invention, and also for preparing the reagents
28 of **Formula 2**, **Formula 3**, **Formula 2a** and **Formula 3a**
29 will become readily apparent to those skilled in the
30 art in light of the present disclosure. In this
31 regard the following general synthetic methodology,
32 applicable for conversion of the compounds of
33 **Formula 1** into further homologs and/or derivatives,
34 and also for preparing the reagents of **Formula 2** and
35 **3**, (as well as **2a** and **3a**) is noted.

36 Carboxylic acids are typically esterified by

1 refluxing the acid in a solution of the appropriate
2 alcohol in the presence of an acid catalyst such as
3 hydrogen chloride or thionyl chloride.
4 Alternatively, the carboxylic acid can be condensed
5 with the appropriate alcohol in the presence of
6 dicyclohexylcarbodiimide and dimethylaminopyridine.
7 The ester is recovered and purified by conventional
8 means. Acetals and ketals are readily made by the
9 method described in March, "Advanced Organic
10 Chemistry," 2nd Edition, McGraw-Hill Book Company, p
11 810). Alcohols, aldehydes and ketones all may be
12 protected by forming respectively, ethers and
13 esters, acetals or ketals by known methods such as
14 those described in McOmie, Plenum Publishing Press,
15 1973 and Protecting Groups, Ed. Greene, John Wiley &
16 Sons, 1981.

17 A means for making compounds where A is $(CH_2)_q$
18 (q is 1 - 5) is to subject the compounds of Formula
19 1, where B is an acid or other function, to
20 homologation, using the well known Arndt-Eistert
21 method of homologation, or other known homologation
22 procedures. Similar homologations (and several of
23 the other herein mentioned synthetic
24 transformations) can be transformed on the reagent
25 of Formula 3. Compounds of the invention, where A
26 is an alkenyl group having one or more double bonds
27 can be made, for example, by having the requisite
28 number of double bonds incorporated into the reagent
29 of Formula 3. Generally speaking, such compounds
30 where A is an unsaturated carbon chain can be
31 obtained by synthetic schemes well known to the
32 practicing organic chemist; for example by Wittig
33 and like reactions, or by introduction of a double
34 bond by elimination of halogen from an
35 alpha-halo-carboxylic acid, ester or like
36 carboxaldehyde. Compounds of the invention where

1 the A group has a triple (acetylenic) bond can be
2 made by using the corresponding aryl or heteroaryl
3 aldehyde intermediate. Such intermediate can be
4 obtained by reactions well known in the art, for
5 example, by reaction of a corresponding methyl
6 ketone with strong base, such as lithium diisopropyl
7 amide.

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

20 The amide (in Formula 1 B is $\text{CONR}_1\text{R}_{10}$) may be
21 formed by any appropriate amidation means known in
22 the art from the corresponding esters or carboxylic
23 acids. One way to prepare such compounds is to
24 convert an acid to an acid chloride and then treat
25 that compound with ammonium hydroxide or an
26 appropriate amine.

27 Alcohols are made by converting the
28 corresponding acids to the acid chloride with
29 thionyl chloride or other means (J. March, "Advanced
30 Organic Chemistry", 2nd Edition, McGraw-Hill Book
31 Company), then reducing the acid chloride with
32 sodium borohydride (March, Ibid, pg. 1124), which
33 gives the corresponding alcohols. Alternatively,
34 esters may be reduced with lithium aluminum hydride
35 at reduced temperatures. Alkylating these alcohols
36 with appropriate alkyl halides under Williamson

1 reaction conditions (March, Ibid, pg. 357) gives the
2 corresponding ethers. These alcohols can be
3 converted to esters by reacting them with
4 appropriate acids in the presence of acid catalysts
5 or dicyclohexylcarbodiimide and
6 dimethylaminopyridine.

7 Aldehydes can be prepared from the corresponding
8 primary alcohols using mild oxidizing agents such as
9 pyridinium dichromate in methylene chloride (Corey,
10 E. J., Schmidt, G., Tet. Lett., 399, 1979), or
11 dimethyl sulfoxide/oxalyl chloride in methylene
12 chloride (Omura, K., Swern, D., Tetrahedron, 1978,
13 34, 1651).

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

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

21 Compounds of Formula 1 where B is H can be
22 prepared from the corresponding halogenated aromatic
23 compounds, preferably where the halogen is I.

24 Specific Examples Ethyl 4-Amino-2-fluorobenzoate
25 (Compound C₁)

26 To a mixture of 2-fluoro-4-nitrotoluene (1.0 g,
27 6.4 mmol, Aldrich) and Na₂Cr₂O₇ (2.74 g, 8.4 mmol) in
28 13.7 ml of HOAc was added slowly 6.83 ml of H₂SO₄.
29 This mixture was slowly heated to 90 °C for 1 h to
30 give a greenish heterogeneous solution. The mixture
31 was cooled to room temperature and diluted with
32 ethyl acetate. The PH of the solution was adjusted
33 to 4 with NaOH (aq.). The mixture was extracted
34 with more ethyl acetate. The organic layer was
35 washed with NaHCO₃ (sat.), then brine and dried over
36 Na₂SO₄. After filtration, the solution was

1 concentrated to dryness which then was dissolved in
2 6 ml of SOCl_2 , and heated at 80 °C for 1 h. The
3 excess of SOCl_2 was removed under reduced pressure
4 and the residue was dissolved in 5 ml of CH_2Cl_2 , 2 ml
5 of EtOH and 2 ml of pyridine. The mixture was
6 stirred at room temperature for 2 h and concentrated
7 to dryness. Ethyl 2-fluoro-4-nitrobenzoate was
8 obtained as a white solid after column
9 chromatography of the residue with ethyl
10 acetate/hexane (1/9). This solid was then dissolved
11 in 10 ml of ethyl acetate, and Pd/C (50 mg) was
12 added. Hydrogenation with a hydrogen balloon
13 converted ethyl 2-fluoro-4-nitrobenzoate into the
14 title compound.

15 ^1H NMR δ 7.77 (t, J = 8.4 Hz, 1H), 6.41 (dd, J_1 =
16 8.6, J_2 = 2.2 Hz, 1H), 6.33 (dd, J_1 = 13.0, J_2 = 2.2
17 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 4.3 (b, 2H), 1.37
18 (t, J = 7.1 Hz, 3H).

19 Methyl 4-Amino-2,6-difluorobenzoate (Compound H₁)

20 A solution of trifluorobenzoic acid (150 mg,
21 0.85 mmol, Aldrich) in 0.5 ml of SOCl_2 was heated
22 under reflux for 2h. The reaction mixture was
23 cooled to room temperature, and excess of SOCl_2 was
24 removed under reduced pressure. The residue was
25 dissolved in 1 ml of pyridine and 0.2 ml of
26 methanol. After stirring at room temperature for 30
27 min, solvent was removed and the residue was
28 purified by column chromatography (ethyl
29 acetate/hexane 1/10) to give methyl trifluoro-
30 benzoate as a colorless oil. This oil was then
31 dissolved in 1 ml of CH_3CN , then a solution of NaN_3
32 (100 mg, 1.54 mmol) in 0.5 ml of water was added.
33 The reaction mixture was refluxed for two days.
34 Salt was filtered and the remaining solution was
35 concentrated to an oil. This oil was then dissolved
36 in 1 ml of methanol, followed by a catalytic amount

1 of Pd/C (10%, w/w). The reaction mixture was
2 hydrogenated under a hydrogen balloon for 12 h.
3 Catalyst was removed and the solution was
4 concentrated to an oil. After column chromatography
5 (ethyl acetate/hexane 1/3), the title product was
6 obtained as colorless crystals.

7 ¹H NMR δ 6.17 (d, J = 10.44 Hz, 2H), 4.2 (b, 2H),
8 3.87 (s, 3H).

9 8-Bromo-2,2,4,4-tetramethyl-6-chromanoic acid
10 (Compound P)

11 To a solution of 2,2,4,4-tetramethyl-6-
12 chromanoic acid (200 mg, 0.85 mmol) in 0.5 ml of
13 AcOH was added Br₂ (0.07 ml, 1.28 mmol). The
14 resulting dark-orange solution was stirred at room
15 temperature for overnight. The excess bromine was
16 removed under reduced pressure. Then the solution
17 was poured into 5 ml of water and extracted with
18 ethyl acetate (3x3ml). The combined ethyl acetate
19 layers were further washed with NaHCO₃ (sat.), brine
20 and dried over MgSO₄. After concentration, the
21 residue was purified by column chromatography
22 (silica gel, ethyl acetate/hexane 1/3) to yield the
23 desired product (170 mg, as white solids).

24 ¹H NMR δ 8.11 (d, J = 2.2 Hz, 1H), 8.00 (d, J = 2.2
25 Hz, 1H), 1.90 (s, 2H), 1.43 (s, 6H), 1.39 (s, 6H).

26 8-Iodo-2,2,4,4-tetramethyl-6-chromanoic Acid
27 (Compound X)

28 To a solution of 2,2,4,4-tetramethyl-6-
29 chromanoic acid (66 mg, 0.28 mmol) in 0.8 ml of AcOH
30 was added ICl (0.07 ml, 1.4 mmol). The resulting
31 colored solution was stirred at room temperature for
32 overnight. Following the same procedure as for the
33 synthesis of 8-bromo-2,2,4,4-tetramethyl-6-
34 chromanoic acid (Compound P), the reaction gave the
35 title compound (107 mg) as white solids.

36 ¹H NMR δ 8.35 (d, J = 2.2 Hz, 1H), 8.03 (d, J = 2.2

1 Hz, 1H), 1.87 (s, 2H), 1.43 (s, 6H), 1.38 (s, 6H).
2 2,2,4,4-Tetramethyl-8-trifluoromethylchroman-6-oic
3 acid (Compound S)

4 A solution of 8-bromo-2,2,4,4-tetramethyl-6-
5 chromanoic acid (Compound R, 150 mg, 0.48 mmol) in 1
6 ml of SOCl₂ was refluxed for 2 h. After cooling to
7 room temperature, the excess of SOCl₂ was removed
8 under reduced pressure and the residue was dissolved
9 in 1 ml of pyridine and 0.2 ml of methanol. The
10 mixture was stirred at room temperature for 30 min.
11 Solvent was removed and the residue was passed
12 through a column (silica gel, ethyl acetate/hexane
13 1/10) to give the methyl 8-bromo-2,2,4,4-tetra-
14 methylchromanoate (158 mg) as a colorless oil. To a
15 solution of this methyl ester in 3 ml of
16 N-methylpyrrolidone (NMP) was added NaCO₃CF₃ (502 mg,
17 3.7 mmol) and CuI (350 mg, 1.84 mmol). The
18 resulting mixture was heated to 175 °C (bath temp)
19 for 2 h. The resulting mixture was cooled to room
20 temperature and poured into ice-water. The product
21 was extracted into ethyl acetate (3x3ml). The
22 combined organic layers were dried and concentrated
23 to dryness. The crude material was purified by
24 column chromatography (ethyl acetate/chloroform
25 1/10) to give the title compound as a colorless oil
26 (120 mg). This was hydrolyzed under standard
27 conditions to give the title compound.

28 ¹H NMR δ 8.21 (d, J = 2.1 Hz, 1H), 8.17 (d, J = 2.1
29 Hz, 1H), 1.92 (s, 2H), 1.41 (s, 12H).

30 Ethyl 8-Nitro-2,2,4,4-tetramethyl-6-chromanoate
31 (Compound W)

32 Ethyl 2,2,4,4-tetramethyl-6-chromanoate (150 mg,
33 0.57 mmol) was slowly added to 0.3 ml of conc. H₂SO₄
34 at 0 °C. To this mixture was added very slowly 0.03
35 ml of HNO₃. The reaction mixture was stirred at 0 °C
36 for 30 min and poured into ice-water. The product

1 was extracted into 5 ml of ethyl acetate, washed
2 with NaHCO₃ (sat.), brine and dried over MgSO₄.
3 After concentration, the product was purified by
4 column chromatography (ethyl acetate/hexane 1/10) to
5 yield 74 mg of light-yellow oil.

6 ¹H NMR δ 8.24 (d, J = 2.1 Hz, 1H), 8.17 (d, J = 2.1
7 Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 1.95 (s, 2H),
8 1.43 (s, 6H), 1.42 (s, 6H), 1.40 (t, J = 7.1 Hz,
9 3H).

10 2-Oxo-4,4,8-trimethylchroman (Compound P₁)

11 In a 500 ml of round bottom flask, NaH (1.66 g,
12 60% suspension in oil, 0.046 mol) was washed with
13 dry hexane. Then, dry THF (22 ml) was added
14 followed by *o*-cresol (5 g, 0.046 mol) in 10 ml of
15 dry THF. The reaction mixture was stirred at 0 °C
16 for 30 min followed by addition of 3,3-dimethyl
17 acryloyl chloride in 10 ml of THF. The resulting
18 white slurry was stirred at room temperature for 12
19 h, then slowly quenched with water. The mixture was
20 then extracted with ethyl acetate. The organic
21 layer was washed with brine, water and dried over
22 MgSO₄. After filtration and removal of the solvent,
23 a yellow oil was obtained (10.44 g). This oil was
24 then dissolved in 50 ml of dry CH₂Cl₂, and was
25 canulated into a solution of AlCl₃ (10.8 g, 0.069
26 mmol) in 10 ml of CH₂Cl₂. The reaction mixture was
27 stirred at room temperature for 12 h. Then
28 ice-water was carefully added and the organic layer
29 was separated, and washed with NaHCO₃ (sat), brine,
30 water and finally dried over MgSO₄. After removal of
31 the drying agent and solvent, the residue was
32 purified by column chromatography (silica gel, ethyl
33 acetate/hexane 1/9) to yield the title compound
34 (4.408 g) as an oil.

35 ¹H NMR δ 7.1 (m, 3H), 2.62 (s, 2H), 2.33 (s, 3H),
36 1.36 (s, 6H).

1 2,4-Dimethyl-4-(2'-hydroxy-3'-methylphenyl)pentan-2-
2 ol (Compound R₁)

3 To a solution of 2-oxo-4,4,8-trimethylchroman
4 (Compound P₁, 2.20 g, 11.5 mmol) in 40 ml of dry
5 ethyl ether was added methyl magnesium bromide
6 (12.67 ml, 38 mmol, 3 M solution in THF). The
7 reaction mixture was stirred at room temperature for
8 12 h, then quenched with NH₄Cl (sat.) until all
9 precipitate dissolved. The mixture was extracted
10 with diethyl ether and the combined organic layers
11 were separated and washed with brine, water and
12 dried over MgSO₄. After filtration and removal of
13 the solvent, the title compound was obtained as a
14 tan solid (2.215 g).

15 ¹H NMR δ 7.16 (d, J = 7.88 Hz, 1H), 7.00 (d, J = 6.72
16 Hz, 1H), 6.81 (t, J = 7.6 Hz, 1H), 5.89 (b, 1H),
17 2.21 (s, 3H), 2.17 (s, 2H), 1.48 (s, 6H), 1.10 (s,
18 6H).

19 2, 2, 4, 4, 8-Pentamethyl-6-bromochroman (Compound
20 Z)

21 A solution of 2,4-dimethyl-4-(2'-hydroxy-3'-
22 methylphenyl)pentan-2-ol (Compound R₁, 2.215 g, 9.98
23 mmol) in 30 ml of 15% of H₂SO₄ was heated to 110 °C.
24 After cooling to room temperature, the reaction
25 mixture was extracted with diethyl ether. The
26 organic layer was washed with NaHCO₃ (sat.), brine
27 and water. After filtration and removal of solvent,
28 the residue was passed through a column (silica gel,
29 pure hexane) to give the title compound as a clear
30 oil (1.636 g). This oil was then dissolved in 1.5
31 ml of HOAc, then Br₂ (0.4113 ml, 7.98 mmol) was
32 added. The reaction mixture was stirred at room
33 temperature for 12 h. Solvent was removed under
34 reduced pressure and to the residue was added ethyl
35 acetate, and the resulting mixture was washed with
36 NaHCO₃ (sat.), brine, water and dried over MgSO₄.

1 After filtration and removal of solvent, the residue
2 was passed through a column (silica gel, pure
3 hexane) to give the title compound as a white solid
4 (2.227 g).

5 ^1H NMR δ 7.21 (s, 1H), 7.06 (s, 1H), 2.14 (s, 3H),
6 1.79 (s, 2H), 1.32 (s, 6H), 1.31 (s, 6H).

7 2,2,4,4,8-Pentamethyl-6-chromanoic Acid (Compound A₁)

8 To a solution of 2,2,4,4, 8-pentamethyl-6-bromo-
9 chroman (Compound Z) (1.2 g, 4.24 mmol) in 18 ml of
10 dry THF at -78 °C under argon gas was added slowly
11 5.48 ml of t-BuLi (1.7 M in hexane, 9.33 mmol). The
12 reaction mixture was stirred at -78 °C for 1 h. Then
13 CO₂ was bubbled through the solution for 1 h. After
14 removal of CO₂ stream, the reaction mixture was
15 stirred for an additional hour at -78 °C. Then 10%
16 of HCl was added. After warming up to room
17 temperature, the reaction mixture was extracted with
18 ethyl acetate. The organic layer was further washed
19 with brine and dried over Na₂SO₄. After
20 concentration, the residue was purified by column
21 chromatography (ethyl acetate/hexane 5/95) to yield
22 the title compound as a white solid (774 mg).

23 ^1H NMR δ 7.96 (s, 1H), 7.75 (s, 1H), 2.23 (s, 3H),
24 1.88 (s, 2H), 1.39 (s, 6H).

25 8-Bromo-4,4-dimethyl-6-chromanoic Acid (Compound B₁)

26 Using the same procedure as for the synthesis of
27 8-bromo-2,2,4,4-tetramethylchromanoic acid (Compound
28 P) but using 4,4-dimethylchromanoic acid (100 mg,
29 0.49 mmol), the title compound was obtained as a
30 white solid.

31 ^1H NMR δ 8.10 (d, J = 2.1 Hz, 1H), 7.98 (d, J = 2.1
32 Hz, 1H), 4.39 (t, J = 5.44 Hz, 2H), 1.89 (t, J = 5.4
33 Hz, 1H), 1.38 (s, 6H).

34 Ethyl 2-Amino-1-bromo-5,5,8,8-tetrahydro-
35 5,5,8,8-tetramethylnaphthalene-3-carboxylate
36 (Compound D)

1 To a solution of ethyl 5,6,7,8-tetrahydro-
2 5,5,8,8-tetramethyl-3-aminonaphthalene-2-carboxylate
3 (Compound C, 58 mg, 0.21 mmol) in 2 ml of HOAc was
4 added Br₂ (0.02 ml, 0.42 mmol). The orange solution
5 was stirred at room temperature for 2 days. The
6 excess Br₂ and HOAc were removed under reduced
7 pressure and the residue was passed through a column
8 (silica gel, ethyl acetate/hexane 1/10) to yield the
9 title compound as a light-orange oil (59 mg, 79.5%).
10 ¹H NMR δ 7.90 (s, 1H), 6.41 (b, 2H), 4.36 (q, J = 7.2
11 Hz, 2H), 1.70 (m, 4H), 1.58 (s, 6H), 1.40 (t, J =
12 7.2 Hz, 3H), 1.28 (s, 6H).

13 Ethyl 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl
14 -4-bromonaphthalene-2-carboxylate (Compound E)

15 Ethyl 2-Amino-1-bromo-5,5,8,8-tetrahydro-
16 5,5,8,8-tetramethylnaphthalene-3-carboxylate
17 (Compound D, 59 mg, 0.17 mmol) was dissolved in 2 ml
18 of EtOH at 0°C. To this solution was added 1ml of
19 trifluoroacetic acid and 1 ml of isoamylnitrite.
20 The reaction mixture was stirred at 0°C for 30 min
21 then H₃PO₂ (0.325 ml, 3.14 mmol) was added. The
22 reaction mixture was allowed to warm to room
23 temperature and stirred for 12 h. NaHCO₃ (sat.) was
24 added and the reaction mixture was extracted with
25 ethyl acetate, dried over MgSO₄, filtered and
26 concentrated to give an oil. The product was
27 purified by column chromatography (silica gel, ethyl
28 acetate/hexane 1/10) to give the title compound as a
29 colorless oil.

30 ¹H NMR δ 8.02 (d, J = 2.0 Hz, 1H), 7.95 (d, J = 2.0
31 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 1.71 (m, 4H),
32 1.56 (s, 6H), 1.38 (t, J = 7.1 Hz, 3H), 1.31 (s,
33 6H).

34 Ethyl 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-
35 fluoronaphthalen-2-yl-carboxylate (Compound G)

36 In an ice bath, ethyl 5,6,7,8-tetrahydro-

1 5,5,8,8-tetramethyl-3-aminonaphthalene-2-carboxylate
2 (Compound C, 150 mg, 0.55 mmol) was added 0.24 ml of
3 HBF₄ (48% solution in water), followed by a solution
4 of NaNO₂ (81 mg, 1.16 mmol) in 1 ml of water. The
5 slurry was left in a refrigerator for 3 days. The
6 reaction mixture was washed successively with ethyl
7 acetate until TLC showed no UV visible spot at the
8 baseline. The ethyl acetate layer was dried with
9 MgSO₄ and the solution was concentrated to an oil.
10 The oil was further dissolved in 1 ml of toluene and
11 the mixture was heated under reflux for 2 h. After
12 the reaction cooled to room temperature, solvent was
13 evaporated and the residue was passed through a
14 column (silica gel, ethyl acetate/hexane 1/10) to
15 give the title compound as an oil.

16 ¹H NMR δ 7.85 (d, J = 7.8 Hz, 1H), 7.04 (d, J = 12.3
17 Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 1.69 (s, 4H),
18 1.38 (t, J = 7.1 Hz, 3H), 1.30 (s, 6H), 1.28 (s,
19 6H).

20 2-Bromo-3-hydroxy-5,5,8,8-tetrahydro-5,5,8,8-tetrame
21 thyl naphthalene (Compound I)

22 Using the same procedure as for the synthesis of
23 8-bromo-2,2,4,4-tetramethyl-6-chromanoic acid
24 (Compound P) but using 2-hydroxy-5,5,8,8-tetrahydro-
25 5,5,8,8-tetramethyltetralin (700 mg, 3.43 mmol) and
26 Br₂ (0.177 ml, 3.43 mmol) in 1.5 ml of HOAc, the
27 title compound was obtained as a white solid (747
28 mg).

29 ¹H NMR δ 7.36 (s, 1H), 6.96 (s, 2H), 5.32 (b, 1H),
30 1.66 (s, 4H), 1.25 (s, 12H).

31 5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-3-methoxymet-
32 hoxy-2-bromonaphthalene (Compound J)

33 To a solution of 2-bromo-3-hydroxy-5,5,8,8-tet-
34 rahydro-5,5,8,8-tetramethylnaphthalene (Compound I,
35 600 mg, 2.12 mmol) and catalytic amount of Bu₄NBr in
36 20 ml of dry CH₂Cl₂ at 0 °C was added

1 diisopropylethylamine (1.138 ml, 12.75 mmol),
2 followed by methoxymethyl chloride (0.484 ml, 6.39
3 mmol). The reaction mixture was heated at 45 °C for
4 12 h. The reaction mixture was washed with 10% of
5 citric acid, then NaHCO₃ (sat.), brine and dried over
6 MgSO₄. After filtration and removal of the solvent,
7 the residue was purified by column chromatography
8 (ethyl acetate/hexane 1/9) to yield the title
9 compound (722 mg) as a white solid.

10 ¹H NMR δ 7.43 (s, 1H), 7.06 (s, 1H), 5.21 (s, 2H),
11 3.54 (s, 3H), 1.66 (s, 4H), 1.26 (s, 6H), 1.25 (s,
12 6H).

13 3-Methoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetra-
14 hydronaphthalen-2-yl carboxylic acid (Compound K)

15 Using the same procedure as for the synthesis of
16 2,2,4,4,8-pentamethyl-6-chromanoic acid (Compound A,
17 but using 5,6,7,8-tetrahydro-5,5,8,8-
18 tetramethyl-3-methoxymethoxy-2-bromonaphthalene
19 (Compound J, 722 mg, 2.21 mmol) and 2.86 ml of
20 t-BuLi (4.87 mmol, 1.7 M solution in hexane), the
21 title compound was obtained as a white solid (143
22 mg).

23 ¹H NMR δ 8.12 (s, 1H), 7.19 (s, 1H), 5.40 (s, 2H),
24 3.58 (s, 3H), 1.70 (s, 4H), 1.30 (s, 12H).

25 Ethyl 2-Fluoro-4-[(5',6',7',8'-tetrahydro-
26 5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]be-
27 nzoate (Compound 1)

28 To 5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-
29 2-naphthoic acid (46 mg, 0.2 mmol) was added 1 ml
30 thionyl chloride. This mixture was refluxed for 2
31 h. Excess thionyl chloride was removed under
32 reduced pressure and the residue was dissolved in 2
33 ml of CH₂Cl₂. To this solution was added ethyl
34 4-amino-2-fluorobenzoate ((Compound C₁, 37 mg, 0.2
35 mmol) followed by 0.5 ml of pyridine. The reaction
36 mixture was stirred at room temperature for 4 h and

1 was concentrated under reduced pressure. The
2 residue was purified by column chromatography (ethyl
3 acetate/hexane 1/10) to give the title compound as
4 white solids.

5 ¹H NMR δ 8.06 (b, 1H), 7.93 (t, J = 8.4 Hz, 1H), 7.85
6 (d, J = 2.0 Hz, 1H), 7.78 (dd, J₁ = 2.0 Hz, J₂ = 12.9
7 Hz, 1H), 7.55 (dd, J₁ = 2.0 Hz, J₂ = 8.2 Hz, 1H),
8 7.40 (d, J = 8.3 Hz, 1H), 7.32 (dd, J₁ = 2.02 Hz, J₂
9 = 8.8 Hz, 1H), 4.38 (q, J = 7.2 Hz, 2H), 1.71 (s,
10 4H), 1.40 (t, J = 7.2 Hz), 1.32 (s, 6H), 1.30 (s,
11 6H).

12 Ethyl 4-[(3'-fluoro-5',6',7',8'-tetrahydro-
13 5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]be
14 nzoate (Compound 3)

15 Ethyl 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-
16 3-fluoronaphthalene-2-carboxylate (Compound G, 75
17 mg, 0.27 mmol) was dissolved in a mixture of 3 ml of
18 EtOH and 1 ml of NaOH (1 M in water). The reaction
19 mixture was left overnight at room temperature. The
20 reaction was neutralized with 5% of HCl. Water
21 (2ml) was added and the mixture was extracted with
22 ethyl acetate (3x3ml). The combined layers were
23 washed once with 3 ml of brine and dried over MgSO₄.
24 After filtration, the clear organic solution was
25 concentrated to give 3-fluoro-5,5,8,8-tetrahydro-
26 5,5,8,8-methylnaphthalen-2-yl carboxylic acid.
27 Using the same procedure as for ethyl
28 2-fluoro-4-[(5',6',7',8'-tetrahydro-5',5',8',8'-tetr
29 amethylnaphthalen-2'-yl)carbamoyl]benzoate (Compound
30 1), except using ethyl 4-amino benzoate (45 mg, 0.27
31 mmol), the carboxylic acid was converted to the
32 title compound (white solid).

33 ¹H NMR δ 8.66 (b, 1H), 8.13 (d, J = 7.8 Hz, 1H), 8.05
34 (d, J = 8.3 Hz, 2H), 7.76 (d, J = 8.3 Hz, 2H), 7.07
35 (d, J = 12.3 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 1.70
36 (s, 4H), 1.49 (t, J = 7.1 Hz, 3H), 1.32 (s, 6H),

1 1.30 (s, 6H).

2 Ethyl 2-Fluoro-4-[(5',6',7',8'-tetrahydro-4'-
3 bromo-5',5',8',8'-tetramethylnaphthalen-2'-yl)carbam
4 oyl]benzoate (Compound 5)

5 Using the same procedure as for the synthesis of
6 ethyl 2-fluoro-4-[-5',6',7',8'-tetrahydro-
7 5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]be
8 nzoate (Compound 1), but using 5,6,7,8-tetrahydro-
9 5,5,8,8-tetramethyl-4-bromonaphthalene-2-carboxylic
10 acid (Compound F), the title compound was obtained
11 as a white solid.

12 ¹H NMR δ 8.30 (b, 1H), 7.92 (t, J = 8.4 Hz, 1H), 7.84
13 (d, J = 2.1 Hz, 1H), 7.81 (d, J = 2.1 Hz, 1H), 7.74
14 (dd, J₁ = 2.1 Hz, J₂ = 12.8 Hz, 1H), 7.35 (dd, J₁ =
15 2.0 Hz, J₂ = 8.4 Hz, 1H), 4.36 (q, J = 7.2 Hz, 2H),
16 1.67 (m, 4H), 1.55 (s, 6H), 1.39 (t, J = 7.2 Hz,
17 3H), 1.31 (s, 6H).

18 Ethyl 2-Fluoro-4-[(3'-methoxymethoxy-5',6',7',8'-
19 tetrahydro-5',5',8',8'-tetramethyl-
20 naphthalen-2'-yl)carbamoyl]benzoate (Compound K₁)

21 Using the same procedure as for the synthesis of
22 ethyl 2-fluoro-4-[(3'-methoxymethoxy-4'-bromo-
23 5',6',7',8'-tetrahydro-5',5',8',8'-tetramethylnaphth
24 alen-2'-yl)carbamoyl]benzoate (Compound S₁), but
25 using 3-methoxymethoxy-5,5,8,8-tetramethyl-
26 5,6,7,8-tetrahydronaphthalen-2-yl carboxylic acid
27 (Compound K, 143 mg, 0.49 mmol) and
28 4-amino-2-fluorobenzoate (Compound C₁, 98.5 mg, 0.54
29 mmol), the title compound was obtained as a white
30 solid.

31 ¹H NMR δ 10.1 (b, 1H), 8.20 (s, 1H), 7.93 (t, J = 8.8
32 Hz, 1H), 7.83 (d, J = 13.4 Hz, 1H), 7.29 (d, J = 8.0
33 Hz, 1H), 5.41 (s, 2H), 4.39 (q, J = 7.1 Hz, 2H),
34 3.59 (s, 3H), 1.70 (s, 4H), 1.31 (s, 12H), 1.26 (t,
35 J = 7.1 Hz, 3H).

36 Ethyl 2-Fluoro-4-[(3'-hydroxy-5',6',7',8'-tetra-

1 hydro-5',5',8',8'-tetramethyl-2-naphthalenyl)-
2 carbamoyl]benzoate (Compound 7)

3 A solution of ethyl 2-fluoro-4-[(3'-methoxymet-
4 hoxy-5',6',7',8'-tetrahydro-5',
5 5',8',8'-tetramethyl-
6 naphthalen-2'-yl)carbamoyl]benzoate (Compound K₁,
7 50.7 mg, 0.11 mmol) in 2 ml of CH₂Cl₂ was added
8 thiophenol (0.061 ml, 0.55 mmol). The reaction
9 mixture was stirred at 0 °C for 5 min, then BF₃·Et₂O
10 (0.027 ml, 0.22 mmol) was added. The reaction
11 mixture was stirred at 0 °C for 2 h, then NaHCO₃
12 (sat.) was added. The organic layer was separated,
13 and washed with brine, water and dried over MgSO₄.
14 After filtration and removal of solvent, the residue
15 was passed through a column (silica gel, ethyl
16 acetate/hexane 1/3) to give the title compound as
17 white solid (44.2 mg).

18 ¹H NMR δ 8.61 (b, 1H), 7.94 (t, J = 8.42 Hz, 1H),
19 7.71 (dd, J = 10.8, 2.0 Hz, 1H), 7.53 (s, 1H), 7.35
20 (dd, J = 6.4, 2.0 Hz, 1H), 6.96 (s, 1H), 4.39 (q, J
21 = 7.1 Hz, 2H), 1.69 (s, 4H), 1.40 (t, J = 7.1 Hz,
22 3H), 1.29 (s, 6H), 1.27 (s, 6H).

23 Ethyl

24 2-Fluoro-4-[(4',4'-dimethyl-8'-bromochroman-6'-yl)ca
25 rbamoyl]benzoate (Compound 9) In a 10 ml of round
26 bottom flask, 4,4-dimethyl-8-bromo-6-chromanoic acid
27 (Compound B₁, 139 mg, 0.485 mmol) was added SOCl₂ (1
28 ml, large excess). The resulting solution was
29 heated at 90 °C for 2 h and let cooled to room
30 temperature. The excess of SOCl₂ was evaporated
31 under reduced pressure. The residue was dissolved
32 in CH₂Cl₂ (3 ml). Ethyl 4-amino-2-fluorobenzoate
33 (Compound C₁, 90 mg, 0.49 mmol) was added followed by
34 pyridine (0.5 ml, large excess). The reaction
35 mixture was stirred for overnight and then
36 concentrated to dryness. The residue was purified

1 by column chromatography with ethyl acetate/hexane
2 (1/5) to yield the title compound as a white solid
3 (190 mg).

4 ¹H NMR δ 7.95 (t, J = 8.31 Hz, 1H), 7.88 (b, 1H),
5 7.83 (d, J = 2.2 Hz, 1H), 7.80 (d, J = 2.2 Hz, 1H),
6 7.75 (dd, J = 12.89, 2.0 Hz, 1H), 7.30 (dd, J =
7 8.55, 2.0 Hz, 1H), 4.37 (m, 5H), 1.89 (t, J = 5.49
8 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H), 1.39 (s, 6H).

9 Ethyl 2-Fluoro-4-[(2',2',4',4'-tetramethyl-8'-bromo-
10 chroman-6'-yl)carbamoyl]benzoate (Compound 11)

11 Using the same procedure as for ethyl
12 2-fluoro-4-[(4',4'-dimethyl-8'-bromochroman-6'-yl)ca
13 rbamoyl]benzoate (Compound 9), but using
14 2,2,4,4-tetramethyl-8-bromo-6-chromanoic acid
15 (Compound P, 70 mg, 0.22 mmol) and ethyl
16 4-amino-2-fluorobenzoate (Compound C₁, 38 mg, 0.22
17 mmol), the title compound was obtained as a white
18 solid (80 mg, 76%).

19 ¹H NMR δ 8.25 (b, 1H), 7.92 (t, J = 8.4 Hz, 1H),
20 7.83 (s, 2H), 7.74 (dd, J₁ = 2.0, J₂ = 13.0 Hz, 1H),
21 7.34 (dd, J₁ = 2.0, J₂ = 8.7 Hz, 1H), 4.37 (q, J =
22 7.1 Hz, 2H), 1.88 (s, 2H), 1.41 (s, 6H), 1.39 (t, J
23 = 7.1 Hz, 3H), 1.37 (s, 6H).

24 Ethyl

25 2-Fluoro-4-[(2',2',4',4'-tetramethyl-8'-trifluoromet
26 hylchroman-6'-yl)carbamoyl] benzoate (Compound 13)

27 Using the same procedure as for ethyl
28 2-fluoro-4-[(4',4'-dimethyl-8'-bromochroman-6'-yl)ca
29 rbamoyl]benzoate (Compound 9), but using
30 2,2,4,4-tetramethyl-8-trifluoromethyl-6-chromanoic
31 acid (Compound S, 57 mg, 0.19 mmol) and ethyl
32 4-amino-2-fluorobenzoate (Compound C₁, 35 mg, 0.19
33 mmol), the title compound was obtained as white
34 solids.

35 ¹H NMR δ 8.06 (d, J = 2.2 Hz, 1H), 7.99 (b, 1H), 7.95
36 (t, J = 8.55 Hz, 1H), 7.81 (d, J = 2.2 Hz, 1H), 7.76

1 (dd, J = 12.8, 2.1 Hz, 1H), 7.33 (dd, J = 8.55, 1.9
2 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 1.93 (s, 2H),
3 1.41 (s, 12H), 1.40 (t, J = 7.2 Hz, 3H).

4 Ethyl 2-Fluoro-4-[(2',2',4',4'-tetramethyl-8'-amino-
5 chroman-6'-yl)carbamoyl]benzoate (Compound N₁)

6 Using 8-nitro-2, 2, 4,
7 4-tetramethylchroman-6-carboxylic acid (Compound V)
8 and following the same procedure as for the
9 synthesis of ethyl
10 2-fluoro-4-[(4',4'-dimethyl-8'-bromochroman-6'-yl)ca
11 rbamoyl]benzoate (Compound 9), ethyl
12 2-fluoro-4-[2',2',4',4'-tetramethyl-8'-nitrochroman-
13 6'-yl)]carbamoylbenzoate was obtained as a white
14 solid. This compound (50 mg, 0.12 mmol) was
15 dissolved in 2 ml of methanol. A catalytic amount
16 of Pd/C was added to the solution and the solution
17 was maintained under H₂ atmosphere (hydrogen balloon)
18 for overnight. The catalyst was removed by
19 filtration and the solvent was evaporated to give
20 the title compound as a white solid.

21 ¹H NMR δ 7.93 (t, J = 8.43 Hz, 1H), 7.90 (b, 1H),
22 7.73 (dd, J = 12.9, 2.0 Hz, 1H), 7.29 (dd, J = 8.43,
23 1.96 Hz, 1H), 7.23 (d, J = 2.14 Hz, 1H), 7.01 (d, J
24 = 2.2 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 1.88 (s,
25 2H), 1.39 (s, 6H), 1.38 (t, J = 7.1 Hz, 3H), 1.37
26 (s, 6H).

27 Ethyl 2-Fluoro-4-[(2',2',4',4'-tetramethyl-8'-azido-
28 chroman-6'-yl)carbamoyl]benzoate (Compound 15)

29 To a solution of ethyl
30 2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-aminochroman
31 -6'-yl)carbamoyl]benzoate (Compound N₁, 32 mg, 0.077
32 mmol) in 3 ml of EtOH was added 0.5 ml of
33 trifluoroacetic acid (TFA) and 0.5 ml of
34 isoamylnitrite at 0°C. The reaction was stirred for
35 2 h when a solution of NaN₃ (5 mg,) in 0.2 ml of
36 water was added. The reaction mixture was allowed

1 to warm to room temperature and stirred for
2 overnight. The solvent was removed and the residue
3 was purified by column chromatography (silica gel,
4 ethyl acetate/ hexane 1/10) to give the title
5 compound as a colorless oil.

6 ¹H NMR δ 8.0 (b, 1H), 7.94 (t, J = 7.8 Hz, 1H), 7.73
7 (d, J = 12.1 Hz, 1H), 7.64 (s, 1H), 7.31 (dd, J =
8 8.5, 2.0 Hz, 1H), 7.21 (d, J = 2.0 Hz, 1H), 4.37 (q,
9 J = 7.1 Hz, 2H), 1.90 (s, 2H), 1.39 (t, J = 7.1 Hz,
10 3H), 1.45 (s, 6H), 1.40 (s, 6H).

11 Methyl 2,6-Difluoro-4-[(2',2',4',4'-tetramethyl-
12 8'-trifluoromethylchroman-6'-yl)carbamoyl]benzoate
13 (Compound 17)

14 Using the same procedure as for ethyl
15 2-fluoro-4-[(4',4'-dimethyl-8'-bromochroman-6'-yl)ca
16 rbamoyl]benzoate (Compound 9), but using
17 2,2,4,4-tetramethyl-8-trifluoromethylchromanoic acid
18 (Compound S, 11.2 mg, 0.037 mmol) and methyl
19 4-amino-2,6-difluorobenzoate (Compound H₁, 6.6 mg,
20 0.035 mmol), the title compound was obtained as
21 white crystals.

22 ¹H NMR δ 8.21 (b, 1H), 8.05 (s, 1H), 7.82 (s, 1H),
23 7.36 (d, J = 10.20 Hz, 1H), 3.93 (s, 3H), 1.92 (s,
24 2H), 1.40 (s, 12H). Ethyl 2-Fluoro-4-[(2', 2', 4',
25 4'-tetramethyl-8'-iodo-
26 chroman-6'-yl)carbamoyl]benzoate (Compound 19)

27 Using the same procedure as for ethyl
28 2-fluoro-4-[(4',4'-dimethyl-8'-bromochroman-6'-yl)ca
29 rbamoyl]benzoate (Compound 9), but using
30 2,2,4,4-tetramethyl-8-iodochromanoic acid (Compound
31 X, 81 mg, 0.25 mmol) and ethyl
32 4-amino-2-fluorobenzoate ((Compound C₁, 55 mg, 0.30
33 mmol), the title compound was obtained as a white
34 solid.

35 ¹H NMR δ 8.05 (b, 1H), 8.01 (d, J = 2.2 Hz, 1H), 7.94
36 (t, J = 8.4 Hz, 1H), 7.86 (d, J = 2.2 Hz, 1H), 7.75

1 (dd, J = 12.88, 2.1 Hz, 1H), 7.33 (dd, J = 8.8, 2.1
2 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 1.89 (s, 2H),
3 1.42 (s, 6H), 1.38 (s, 6H).

4 Ethyl

5 2-Fluoro-4-[(2',2',4',4',8'-pentamethylchroman-
6 6'-yl)carbamoyl]benzoate (Compound 21)

7 Using the same procedure as for ethyl
8 2-fluoro-4-[(4',4'-dimethyl-8'-bromochroman-6'-yl)ca
9 rbamoyl]benzoate (Compound 9), but using
10 2,2,4,4,8-pentamethyl-6-chromanoic acid (Compound
11 A₁, 92 mg, 0.37 mmol) and ethyl
12 4-amino-2-fluorobenzoate (Compound C₁, 75 mg, 0.41
13 mmol), the title compound was obtained as a white
14 solid (100 mg).

15 ¹H NMR δ 8.31 (b, 1H), 7.90 (t, J = 8.24 Hz, 1H),
16 7.76 (dd, J = 14.29, 1.7 Hz, 1H), 7.74 (s, 1H), 7.43
17 (s, 1H), 7.35 (dd, J = 8.67, 1.7 Hz, 1H), 4.32 (q, J
18 = 7.1 Hz, 2H), 2.18 (s, 3H), 1.84 (s, 2H), 1.38 (t,
19 J = 7.1 Hz, 3H), 1.35 (s, 6H), 1.34 (s, 6H).

20 Ethyl

21 2-Fluoro-4-[(2',2',4',4'-tetramethylthiochroman-6'-y
22 l)carbamoyl]benzoate (Compound 23)

23 Using the same procedure as for the synthesis of
24 ethyl 2-fluoro-4-[(4',4'-dimethyl-8'-bromochroman-
25 6'-yl)carbamoyl]benzoate (Compound 9) but using
26 2,2,4,4-tetramethyl-6-thiochromanoic acid (15 mg,
27 0.06 mmol) and ethyl 2-fluoro-4-aminobenzoate
28 (Compound C₁, 11.2 mg, 0.06 mmol), the title compound
29 was obtained as colorless oil.

30 ¹H NMR δ 7.95 (m, 2H), 7.75 (d, J = 12.75 Hz, 1H),
31 7.58 (m, 2H), 7.50 (d, J = 8.8 Hz, 1H), 7.28 (dd, J
32 = 10.6, 1.9 Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 1.99
33 (s, 2H), 1.44 (s, 6H), 1.42 (s, 6H), 1.40 (t, J =
34 7.1 Hz, 3H).

35 Ethyl 4-[(5',6',7',8'-tetrahydro-5',5',8',8'-
36 tetramethyl-2-naphthalenyl)thiocarbamoyl]benzoate

1 (Compound 25)

2 To a solution of ethyl
3 4-[(5',6',7',8'-tetrahydro-5',5',8',
4 8'-tetramethylnaphthalen-2-yl)carbamoyl]benzoate
5 (Compound I, 61 mg, 0.16 mmol) in 2 ml of anhydrous
6 benzene was added Lawesson's reagent (45 mg, 0.112
7 mmol). The resulting yellow solution was refluxed
8 under N₂ for 2 h. The solvent was removed and the
9 residue was purified by column chromatography
10 (silica gel, ethyl acetate/hexane 1/5) to give the
11 title compound as a yellow solid (55 mg, 87%).
12 ¹H NMR δ 9.04 (b, 1H), 8.11 (d, J = 8.70 Hz, 2H),
13 7.85 (b, 2H), 7.75 (b, 1H), 7.55 (dd, J = 8.2, 1.9
14 Hz, 1H), 7.36 (d, J = 8.3 Hz, 1H), 4.38 (q, J = 7.1
15 Hz, 2H), 1.71 (s, 4H), 1.40 (t, J = 7.1 Hz, 3H),
16 1.30 (s, 12H).

17 Ethyl 2-Fluoro-4-[(5',6',7',8'-tetrahydro-
18 5',5',8',8'-tetramethylnaphthalen-2'-yl)thiocarbamoyl
19 1]benzoate (Compound 27)

20 Using the same procedure as for the synthesis of
21 ethyl
22 4-[(5',6',7',8'-tetrahydro-5',5',8',8'-tetrameth-
23 yl-2-naphthalenyl)thiocarbamoyl]benzoate (Compound
24 25) but using ethyl
25 2-fluoro-4-[(5',6',7',8'-tetrahydro-5',5',8',8'-tetr
26 amethylnaphthalen-2'-yl)carbamoyl]benzoate (Compound
27 1, 167 mg, 0.42 mmol) in 8 ml of benzene and
28 Lawesson's reagent (220 mg, 0.544 mmol), the title
29 compound was obtained as a bright yellow solid
30 (127.5 mg).

31 ¹H NMR δ 9.30 (b, 1H), 8.05 (b, 1H), 7.95 (t, J =
32 8.37 Hz, 1H), 7.77 (d, J = 1.89 Hz, 1H), 7.53 (dd, J
33 = 8.24, 2.1 Hz, 1H), 7.49 (b, 1H), 7.35 (d, J = 8.24
34 Hz, 1H), 4.33 (q, J = 7.1 Hz, 1H), 1.71 (s, 4H),
35 1.32 (s, 6H), 1.30 (s, 6H).

36 3-Hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronap

1 hthalen-2-yl carboxylic acid (Compound L)

2 To a solution of
3 2-bromo-3-methoxymethoxy-5,5,8,8-tetrahydro-5,5,8,8-
4 tetramethylnaphthalene (Compound J, 722 mg, 2.2
5 mmol) in 10 ml of dry THF at -78°C under argon was
6 added slowly 2.86 ml of t-BuLi (1.7 M in hexane, 4.8
7 mmol). The reaction mixture was stirred at -78°C
8 for 1 h. Then CO₂ was bubbled through the solution
9 for 1 h. After removal of CO₂ stream, the reaction
10 mixture was stirred for an additional hour at -78°C.
11 Then 10% of HCl was added. After warming up to room
12 temperature, the reaction mixture was left overnight
13 then extracted with ethyl acetate. The organic
14 layer was washed with brine and dried over Na₂SO₄.
15 After concentration, the residue was purified by
16 column chromatography (ethyl acetate/hexane 1/3) to
17 yield the title compound as a white solid.
18 ¹H NMR d 7.85 (s, 1H), 6.93 (s, 1H), 1.68 (s, 4H),
19 1.28 (s, 12H).

20 4-Bromo-3-hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetra-
21 hydronaphthalen-2-yl carboxylic acid (Compound M)

22 3-Hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetra-
23 hydronaphthalen-2-yl acid (Compound L, 155 mg, 0.62
24 mmol) was dissolved in 1 ml of HOAc. To this
25 solution was added Br₂ (0.033 ml, 0.62 mmol). The
26 reaction mixture was left at room temperature for
27 over night. A stream of air was passed through the
28 reaction mixture to remove the unreacted Br₂. The
29 remaining solid was dissolved in small amount of THF
30 and purified by column chromatography (ethyl
31 acetate/hexane 1/1) to yield the desired product as
32 a cream colored solid.
33 ¹H NMR d 7.91 (s, 1H), 1.75 (m, 2H), 1.64 (m, 2H),
34 1.62 (s, 6H), 1.30 (s, 6H).

35 4-Bromo-3-methoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-
36 -tetrahydronaphthalen-2-yl carboxylic acid (Compound

1 N)

2 To a solution of
3 4-bromo-3-hydroxy-5,5,8,8-tetra-
4 methyl-5,6,7,8-tetrahydronaphthalen-2-yl acid
5 (Compound M), 233 mg, 0.71 mmol) in 6 ml of CH₂Cl₂,
6 was added chloromethyl methyl ether (0.162 ml, 2.1
7 mmol), diisopropylethyl amine (0.764 ml, 4.2 mmol)
8 and a catalytic amount of tetrabutylammonium
9 bromide. The reaction mixture was heated to 45 °C
10 for 2 h. The reaction mixture was concentrated and
11 the residue was purified by column chromatography
12 (ethyl acetate/hexane 1/9) to yield the
13 methoxymethyl ester of the title compound as a white
14 solid (200 mg). This white solid was further
15 dissolved in 20 ml of EtOH. An aqueous solution of
16 NaOH (0.5 ml, 1M) was added. The reaction mixture
17 was stirred at room temperature for over night. The
18 EtOH was removed and the residue was added 2 ml of
19 ethyl acetate and 3 ml of water. This mixture was
20 very slowly acidified with 10% HCl to PH = 7. The
21 ethyl acetate layer was separated and washed with
22 brine, dried over Na₂SO₄. After filtration of the
23 drying agent and removal of solvent, the reaction
24 yielded the title compound as a white solid (155
25 mg). ¹H NMR d 7.99 (s, 1H), 5.20 (s, 2H), 3.66 (s,
26 3H), 1.74 (m, 2H), 1.67 (m, 2H), 1.60 (s, 6H), 1.32
27 (s, 6H). Ethyl
28 2-fluoro-4-[(3'-methoxymethoxy-4'-bromo-5',6',7',8'-
29 tetrahydro-5',5',8',8'-tetramethylnaphtha-
30 len-2'-yl)carbamoyl]benzoate (Compound S₁)

31 To a solution of
32 4-bromo-3-methoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8
33 -tetrahydronaphthalen-2-yl acid (Compound N, 80 mg,
34 0.22 mmol) in 4 ml of CH₂Cl₂, was added DMAP (60 mg,
35 0.26 mmol), ethyl 2-fluoro-4-aminobenzoate (Compound
36 C₁, 43 mg, 0.24 mmol) and EDC (50 mg, 0.26 mmol).

1 The reaction mixture was stirred at room temperature
2 for overnight and then concentrated to dryness. The
3 residue was purified by column chromatography (ethyl
4 acetate/hexane 1/3) to yield the title compound as a
5 clear oil (45 mg).

6 ¹H NMR d 9.92 (b, 1H), 8.10 (s, 1H), 7.94 (t, J = 8.4
7 Hz, 1H), 7.81 (dd, J = 12.9; 1.9 Hz, 1H), 7.35 (dd,
8 J = 8.5; 1.8 Hz, 1H), 5.20 (s, 2H), 4.39 (q, J =
9 7.1 Hz, 2H), 3.61 (s, 3H), 1.74 (m, 2H), 1.64 (m,
10 2H), 1.60 (s, 6H), 1.40 (t, J = 7.1 Hz, 3H), 1.34
11 (s, 6H).

12 Methyl 2,6-Difluoro-4-[(3'-methoxymethoxy-4'-bromo-
13 5',6',7',8'-tetrahydro-5',5',8',8'-tetramethylnaphth
14 alen-2'-yl)carbamoyl]benzoate (Compound M₁)

15 Using the same procedure as for the synthesis of
16 compound ethyl 2-fluoro-4-[(3'-methoxymethoxy-4'-
17 bromo-5',6',7',8'-tetrahydro-5',5',8',8'-tetramethyl
18 naphthalen-2'-yl)carbamoyl]benzoate (Compound S₁) but
19 using 4-bromo-3-methoxymethoxy-5,5,8,8-tetramethyl-
20 5,6,7,8-tetrahydronaphthalen-2-yl acid (Compound N,
21 80 mg, 0.22 mmol), DMAP (60 mg, 0.26 mmol), methyl
22 2,6-difluoro-4-aminobenzoate (Compound E₁, 52 mg,
23 0.24 mmol) and EDC (50 mg, 0.26 mmol), the title
24 compound was obtained as a clear oil.

25 ¹H NMR d 10.01 (b, 1H), 8.11 (s, 1H), 7.42 (d, J =
26 10.0 Hz, 2H), 5.2 (s, 2H), 3.95 (s, 3H), 3.63 (s,
27 3H), 1.75 (m, 2H), 1.65 (m, 2H), 1.61 (s, 6H), 1.35
28 (s, 6H).

29 General procedure for the syntheses of benzoic
30 acid derivatives by hydrolyzing the corresponding
31 methyl or ethyl esters.

32 To a solution of ester (3.0 mmol) in 20 ml of
33 EtOH was added 5 ml of 1 N NaOH in water. The
34 reaction mixture was stirred at room temperature for
35 overnight and neutralized with 10% HCl to pH=5. The
36 alcohol was removed by evaporation and the aqueous

1 layer was extracted with ethyl acetate (3x10ml).
2 The combined ethyl acetate layers were washed with
3 NaHCO₃ (sat.), brine and dried over MgSO₄. After
4 concentration, the desired acid was obtained which
5 could be recrystallized in ethyl acetate or in
6 acetonitrile.

7 2-Fluoro-4-[(5',6',7',8'-tetrahydro-5',5',8',8'-tetra-
8 amethylnaphthalen-2'-yl)carbamoyl]benzoic Acid
9 (Compound 2)
10 ¹H NMR δ (acetone-D₆) 9.86 (b, 1H), 7.95 (m, 3H),
11 7.75 (dd, J = 7.9, 2.2 Hz, 1H), 7.62 (dd, J = 8.5,
12 1.6 Hz, 1H), 7.50 (d, J = 8.3 Hz, 1H), 1.73 (s, 4H),
13 1.32 (s, 6H), 1.30 (s, 6H).

14 4-[(3'-Fluoro-5',6',7',8'-tetrahydro-5',5',8',8'-tetra-
15 ramethylnaphthalen-2'-yl)carbamoyl]benzoic Acid
16 (Compound 4)
17 ¹H NMR δ (acetone-D₆) 9.50 (b, 1H), 8.04 (b, 2H),
18 7.90 (b, 2H), 7.78 (d, J = 7.81 Hz, 1H), 7.19 (d, J
19 = 12.3 Hz, 1H), 1.72 (s, 4H), 1.30 (s, 12H).

20 2-Fluoro-4-[(4'-bromo-5',6',7',8'-tetrahydro-5',5',8',8'-tetra-
21 ramethylnaphthalen-2'-yl)carbamoyl]benzoic
22 Acid (Compound 6)
23 ¹H NMR δ (acetone-D₆) 9.97 (b, 1H), 8.04 (d, J = 1.89
24 Hz, 1H), 8.01 (d, J = 1.90 Hz, 1H), 7.95 (t, J =
25 8.55 Hz, 1H), 7.90 (dd, J = 12.28, 2.0 Hz, 1H), 7.59
26 (dd, J = 8.67, 1.50 Hz, 1H), 1.76 (m, 4H), 1.58 (s,
27 6H), 1.35 (s, 6H).

28 2-Fluoro-4-[(3'-hydroxy-5',6',7',8'-tetrahydro-5',5',8',8'-tetra-
29 ramethylnaphthalen-2'-yl)carbamoyl]benzoic
30 Acid (Compound 8)
31 ¹H NMR (acetone-D₆) δ 11.3 (b, 1H), 10.2 (b, 1H),
32 7.94 (m, 2H), 7.85 (dd, J = 11.4, 1.95 Hz, 1H), 7.53
33 (dd, J = 6.59, 2.08 Hz, 1H), 6.94 (s, 1H), 2.85 (b,
34 1H), 1.70 (s, 4H), 1.29 (s, 6H), 1.28 (s, 12H).

35 2-Fluoro-4-[(8'-bromo-4',4'-dimethylchroman-6'-yl)ca-
36 rbamoyl]benzoic Acid (Compound 10)

1 ¹H NMR (acetone-d₆) δ 9.87 (b, 1H), 8.04 (d, J = 2.1
2 Hz, 1H), 8.03 (d, J = 2.1 Hz, 1H), 7.94 (t, J = 8.66
3 Hz, 1H), 7.91 (dd, J = 13.8, 2.0 Hz, 1H), 7.57 (dd,
4 J = 8.6, 2.0 Hz, 1H), 4.37 (t, J = 5.44 Hz, 2H),
5 1.92 (t, J = 5.44 Hz, 2H), 1.40 (s, 6H).

6 2-Fluoro-4-[(2',2',4',4'-tetramethyl-8'-bromochroman
7 -6'-yl)carbamoyl]benzoic Acid (Compound 12)

8 ¹H NMR δ (acetone-d₆) 9.87 (b, 1H), 8.06 (d, J = 2.2
9 Hz, 1H), 8.04 (d, J = 2.1 Hz, 1H), 7.94 (t, J = 8.54
10 Hz, 1H), 7.91 (dd, J = 14.0, 2.0 Hz, 1H), 7.59 (dd,
11 J = 8.5, 2.3 Hz, 1H), 1.96 (s, 2H), 1.42 (s, 6H),
12 1.41 (s, 6H).

13 2-Fluoro-4-[(2',2',4',4'-tetramethyl-8'-trifluoro-
14 methylchroman-6'-yl)carbamoyl] benzoic Acid
15 (Compound 14)

16 ¹H NMR (acetone-d₆) δ 10.02 (b, 1H), 8.31 (s, 1H),
17 8.09 (s, 1H), 7.92 (m, 2H), 7.56 (d, J = 7.69 Hz,
18 1H), 2.00 (s, 2H), 1.44 (s, 6H), 1.41 (s, 6H).

19 2-Fluoro-4-[(2',2',4',4'-tetramethyl-8'-azidochroman
20 -6'-yl)carbamoyl]benzoic Acid (Compound 16)

21 ¹H NMR δ 8.03 (t, J = 8.4 Hz, 1H), 7.87 (b, 1H), 7.79
22 (dd, J = 13, 2.0 Hz, 1H), 7.64 (d, J = 2.2 Hz, 1H),
23 7.32 (dd, J = 8.66, 1.9 Hz, 1H), 7.22 (d, J = 2.1
24 Hz, 1H), 1.91 (s, 2H), 1.45 (s, 6H), 1.41 (s, 6H).

25 2, 6-Difluoro-4-[(2',2',4',4'-tetramethyl-8'-
26 trifluoromethylchroman-6'-yl)carbamoyl]benzoic acid
27 (Compound 18)

28 ¹H NMR (acetone-d₆) δ 8.30 (d, J = 2.3 Hz, 1H), 8.06
29 (d, J = 2.2 Hz, 1H), 7.59 (d, J = 10.32 Hz, 2H),
30 1.954 (s, 2H), 1.44 (s, 6H), 1.41 (s, 6H).

31 2-Fluoro-4-[(2',2',4',4'-tetramethyl-8'-iodochroman-
32 6'-yl)carbamoyl]benzoic Acid (Compound 20)

33 ¹H NMR δ (acetone-d₆) 10.0 (b, 1H), 8.24 (s, 1H),
34 8.07 (s, 1H), 7.94 (m, 2H), 7.57 (d, J = 8.67 Hz,
35 1H), 1.95 (s, 2H), 1.41 (s, 12H).

36 2-Fluoro-4-[(2',2',4',4',8'-pentamethylchroman-6'-yl

1 l)carbamoyl]benzoic Acid (Compound 22)

2 ¹H NMR δ (acetone-d₆) 9.77 (b, 1H), 7.90 (m, 3H),
3 7.65 (d, J = 2.0 Hz, 1H), 7.56 (dd, J = 8.61, 2.0
4 Hz, 1H), 2.19 (s, 3H), 1.90 (s, 2H), 1.38 (s, 6H),
5 1.37 (s, 6H).

6 2-Fluoro-4-[(2',2',4',4'-tetramethylthiochroman-6'-y
7 l)carbamoyl]benzoic acid (Compound 24)

8 ¹H NMR δ 7.95 (m, 2H), 7.75 (d, J = 12.75 Hz, 1H),
9 7.58 (m, 2H), 7.50 (d, J = 8.8 Hz, 1H), 7.28 (dd, J
10 = 10.6, 1.9 Hz, 1H), 1.99 (s, 2H), 1.44 (s, 6H),
11 1.42 (s, 6H).

12 4-[(5',6',7',8'-tetrahydro-5',5',8',8'-tetramethylna
13 phthalen-2'-yl)thiocarbamoyl]benzoic Acid (Compound
14 26)

15 ¹H NMR δ 9.08 (b, 1H), 8.17 (d, J = 8.61, 2H), 7.95
16 (b, 2H), 7.77 (b, 1H), 7.57 (dd, J = 8.1, 2.1 Hz,
17 1H), 7.37 (d, J = 8.2 Hz, 1H), 1.72 (s, 4H), 1.32
18 (s, 6H), 1.31 (s, 6H).

19 2-Fluoro-4-[(5',6',7',8'-tetrahydro-5',5',8',
20 8'-tetramethylnaphthalen-2'-yl)thiocarbamoyl]benzoic
21 Acid (Compound 28)

22 ¹H NMR δ (acetone-d₆) 11.1 (b, 1H), 8.27 (b, J = 13.2
23 Hz, 1H), 8.02 (t, J = 8.3 Hz, 1H), 7.89 (s, 1H),
24 7.86 (d, J = 10.0 Hz, 1H), 7.62 (d, J = 8.3 Hz, 1H),
25 7.41 (d, J = 8.37 Hz, 1H), 1.72 (s, 4H), 1.30 (s,
26 12H).

27 2-Fluoro-4-[(3'-hydroxy-4'-bromo-5',6',7',8'-tet-
28 rahydro-5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoic
29 Acid (Compound 34)

31 A solution of ethyl

32 2-fluoro-4-[(3'-methoxymet-hoxy-4'-bromo-5',6',7',8'
33 -tetrahydro-5',5',8',8'-tetramethylnaphthalen-2'-yl)
34 carbamoyl]benzoate (Compound S₁, 45 mg, 0.084 mmol)
35 in 1 ml of EtOH was added 1 ml of aqueous solution
36 of NaOH (1M). The reaction mixture was stirred at

1 room temperature for overnight and acidified to PH =
2 1 with 10% HCl. EtOH was removed and ethyl acetate
3 and more water were added to the solution. The
4 organic layer was separated and washed with NaHCO₃,
5 brine and dried over MgSO₄. After filtration and
6 concentration, the reaction yielded
7 2-fluoro-4-[(3'-methoxymethoxy-4'-bromo-5', 6', 7',
8 8'-tetrahydro-5', 5', 8',
9 8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoic
10 acid as a white solid. The methoxymethyl group was
11 removed by dissolving the white solid in 2 ml of
12 MeOH and 3 drops of HCl (con.). After stirring for
13 overnight, the reaction mixture was concentrated to
14 dryness. The residue was partitioned between ethyl
15 acetate and water. The organic layer was separated,
16 washed with NaHCO₃, brine and dried over MgSO₄.
17 After filtration and concentration, the residual
18 solid was purified in a mini (pipette) column with
19 ethyl acetate /hexane (1/1) to give the title
20 compound as a white solid (5.0 mg).

21 ¹H NMR d (acetone-d₆) 10.19 (b, 1H), 8.01 (s, 1H),
22 7.96 (t, J = 8.6 Hz, 1H), 7.76 (dd, J = 11.2; 2.0
23 Hz, 1H), 7.54 (dd, J = 8.8; 2.0 Hz, 1H), 1.75 (m,
24 2H), 1.65 (m, 2H), 1.61 (s, 6H), 1.32 (s, 6H).

25 2,6-Difluoro-4-[(3'-hydroxy-4'-bromo-5', 6', 7',
26 8'-tetrahydro-5', 5', 8',
27 8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoic
28 Acid (Compound 36)

29 Using the same procedure as for the synthesis of
30 2-fluoro-4-[(3'-hydroxy-4'-bromo-5', 6', 7', 8'-tet-
31 rahydro-5', 5', 8',
32 8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoic
33 acid (Compound 34) the title compound was obtained
34 as a white solid.

35 ¹H NMR d(acetone-d₆) 10.23 (b, 1H), 8.01 (s, 1H),
36 7.52 (d, J = 10.2 Hz, 2H), 4.8 (b, 1H), 1.75 (m,

1 2H), 1.65 (m, 2H), 1.60 (s, 6H), 1.31 (s, 6H).
2 2,6-Difluoro-4-[(5', 6', 7', 8'-tetrahydro-5', 5',
3 8', 8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoic
4 Acid (Compound 38)

5 To 5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-
6 naphthoic acid (43 mg, 0.19 mmol) was added 1 ml of
7 thionyl chloride. This mixture was refluxed for 2
8 h. Excess thionyl chloride was removed under
9 reduced pressure and the residue was dissolved in 2
10 ml of CH₂Cl₂. To this solution was added methyl
11 4-amino-2,6-difluorobenzoate (Compound H₁, 7 mg, 0.2
12 mmol) followed by 0.5 ml of pyridine. The reaction
13 mixture was stirred at room temperature for 4 h and
14 was concentrated under reduced pressure. The
15 residue was purified by column chromatography (ethyl
16 acetate/hexane 1/5) to give the methyl ester of the
17 desired product as a colorless oil.

18 ¹H NMR d 8.11 (d, J = 1.9 Hz, 1H), 8.05 (b, 1H), 7.86
19 (dd, J = 6.2, 2.2 Hz, 1H), 7.41 (m, 3H), 3.93 (s,
20 3H), 1.69 (s, 4H), 1.29 (s, 6H), 1.28 (s, 6H). This
21 colorless oil was hydrolyzed to the desired product
22 with NaOH/H₂O/EtOH according to the general
23 procedure.

24 ¹H NMR d (acetone-d₆) 9.74 (b, 1H), 7.95 (s, 1H),
25 7.70 (d, J = 6.8 Hz, 1H), 7.43 (d, J = 8.4 Hz, 3H),
26 1.71 (s, 4H), 1.29 (s, 6H), 1.28 (s, 6H).

27 Methyl

28 2-nitro-4-[(4'-bromo-5',6',7',8'-tetrahydro-5',5',8'
29 ,8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoate
30 (Compound 29)

31 Using the same procedure as for the synthesis of
32 Compound 1, but using Compound F and Compound F₁, the
33 desired product was obtained as a white solid.

34 ¹H NMR δ 9.24 (b, 1H), 9.23 (d, J = 1.8 Hz, 1H), 7.92
35 (dd, J = 8.4, 2.4, Hz, 1H), 7.87 (d, J = 2.1 Hz,
36 1H), 7.84 (d, 3 = 2.1 Hz, 1H), 7.80 (d, J = 8.7 Hz,

1 1H), 3.91 (s, 3H), 1.75 (m, 2H), 1.65 (m, 2H), 1.58
2 (s, 3H), 1.33 (s, 3H).

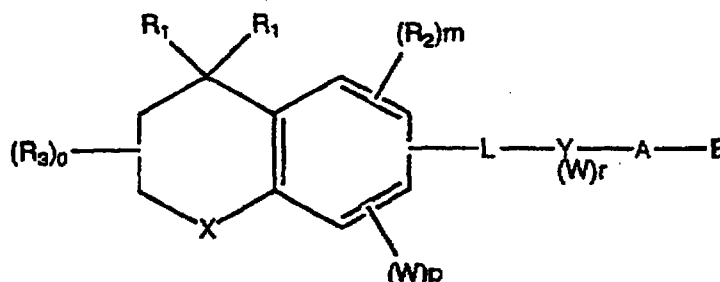
3 2-Nitro-4-[(4'-bromo-5',6',7',8'-tetrahydro-5',5',8'
4 ,8',-tetramethylnaphthalen-2'-yl)carbamoyl]benzoic
5 acid (Compound 30)

6 ¹H NMR δ (acetone-d⁶): 10.16 (b, 1H), 8.42 (d, J =
7 2.0 Hz, 1H), 8.09 (dd, J = 8.6; 2.1 Hz, 1H), 8.06
8 (d, J = 2.2 Hz, 1H), 8.04 (d, J = 2.2 Hz, 1H), 7.93
9 (d, J = 8.6 Hz, 1H), 1.75 (m, 2H), 1.65 (m, 2H),
10 1.57 (s, 3H), 1.34 (s, 3H).
11



WHAT IS CLAIMED IS:

1. A compound of the formula



wherein X is S, O, NR' where R' is H or alkyl of 1 to 6 carbons, or

X is $[C(R_1)_n]_n$ where n is an integer between 0 and 2;

R₁ is independently H or alkyl of 1 to 6 carbons;

R₂ is hydrogen, or lower alkyl of 1 to 6 carbons;

R₃ is hydrogen, lower alkyl of 1 to 6 carbons or F;

m is an integer having the value of 0 - 2;

o is an integer having the value of 0 - 4;

p is an integer having the value of 0 - 2;

r is an integer having the value 0 - 2 with the proviso that when Z is 0 the sum of p and r is at least 1;

Y is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl, naphthyl and heteroaryl groups being optionally substituted with one or two R₂ groups;

W is a substituent selected from the group consisting of F, Br, Cl, I, C₁₋₆ alkyl, fluoro





1 substituted C_{1-6} alkyl, NO_2 , N_3 , OH , OCH_2CH_3 ,
2 OC_{1-10} alkyl, tetrazol, CN , SO_2C_{1-6} -alkyl, SO_2C_{1-6} -alkyl,
3 SO_2C_{1-6} -fluoro substituted alkyl, $SO-C_{1-6}$ alkyl,
4 $CO-C_{1-6}$ alkyl, $COOR_s$, phenyl, phenyl itself substituted
5 with a W group other than with phenyl or substituted
6 phenyl;

7 L is $-(C=Z)-NH-$ or $-HN-(C=Z)-$

8 Z is O or S;

9 A is $(CH_2)_q$ where q is 0-5, lower branched chain
10 alkyl having 3-6 carbons, cycloalkyl having 3-6
11 carbons, alkenyl having 2-6 carbons and 1 or 2
12 double bonds, alkynyl having 2-6 carbons and 1 or 2
13 triple bonds, and

14 B is $COOH$ or a pharmaceutically acceptable salt
15 thereof, $COOR_s$, $CONR_sR_{10}$, $-CH_2OH$, CH_2OR_{11} , CH_2OCOR_{11} ,
16 CHO , $CH(OR_{12})_2$, $CHOR_{13}O$, $-COR_7$, $CR_7(OR_{12})_2$, $CR_7OR_{13}O$,
17 where R_s is an alkyl, cycloalkyl or alkenyl group
18 containing 1 to 5 carbons, R_s is an alkyl group of 1
19 to 10 carbons or trimethylsilylalkyl where the alkyl
20 group has 1 to 10 carbons, or a cycloalkyl group of
21 5 to 10 carbons, or R_s is phenyl or lower
22 alkylphenyl, R_s and R_{10} independently are hydrogen,
23 an alkyl group of 1 to 10 carbons, or a cycloalkyl
24 group of 5-10 carbons, or phenyl or lower
25 alkylphenyl, R_{11} is lower alkyl, phenyl or lower
26 alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent
27 alkyl radical of 2-5 carbons.

28 2. A compound in accordance with Claim 1 where
29 Y is phenyl.

30 3. A compound in accordance with Claim 2 where
31 the phenyl group is 1,4 substituted by the L and the
32 A-B groups.

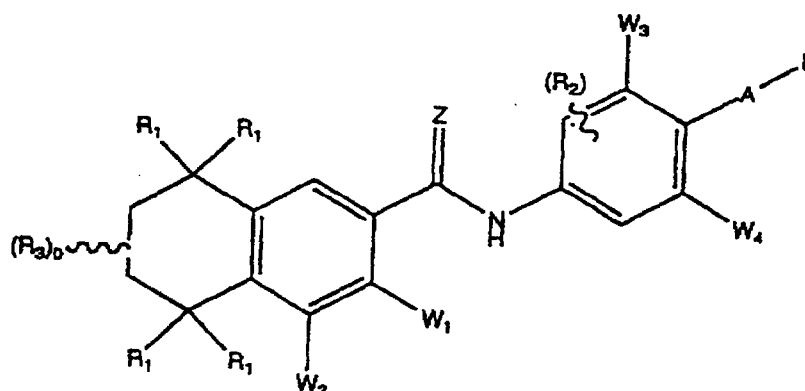
33 4. A compound in accordance with Claim 1 where
34 Y is pyridyl.

35 5. A compound in accordance with Claim 4 where
36 Y is 2,5 substituted by the L and the A-B groups.





- 1 6. A compound in accordance with Claim 1 where
2 X is $[C(R_1)_2]_n$ and n is 1.
3 7. A compound in accordance with Claim 1 where
4 X is O.
5 8. A compound in accordance with Claim 1 where
6 X is S.
7 9. A compound in accordance with Claim 1 where
8 A-B is $(CH_2)_q$ -COOH or a pharmaceutically acceptable
9 salt thereof, $(CH_2)_q$ -COOR₈, or $(CH_2)_q$ -CONR₉R₁₀.
10 10. A compound in accordance with Claim 1 where
11 the Y group has at least one W substituent.
12 11. A compound in accordance with Claim 10
13 where the W substituent is selected from the group
14 consisting of F, NO₂, Br, I, CF₃, N₃, and OH.
15 12. A compound in accordance with Claim 1 where
16 the aromatic portion of the condensed ring has at
17 least one W substituent.
18 13. A compound in accordance with Claim 12
19 where the W substituent is selected from the group
20 consisting of F, NO₂, Br, I, CF₃, N₃, and OH.
21 14. A compound in accordance with Claim 1 where
22 both the Y group and the aromatic portion of the
23 condensed ring have at least one W substituent.
24 15. A compound in accordance with Claim 1 where
25 Z is O.
26 16. A compound of the formula





1 wherein R_1 is independently H or alkyl of 1 to 6
2 carbons;

3 R_2 is hydrogen, or lower alkyl of 1 to 6
4 carbons;

5 R_3 is hydrogen, lower alkyl of 1 to 6 carbons or
6 F;

7 o is an integer having the value of 0 - 4;

8 W_1 , W_2 , W_3 , and W_4 , each is independently
9 selected from the group consisting of H, F, Br, Cl,
10 I, CF_3 , NO_2 , N_3 , OH, OCH_2OCH_3 , OC_{1-10} alkyl and C_{1-6} alkyl,
11 with the proviso that when Z is O then at least one
12 of the W_1 , W_2 , W_3 , and W_4 groups is not H;

13 Z is O or S;

14 A is $(CH_2)_q$ where q is 0-5, lower branched chain
15 alkyl having 3-6 carbons, cycloalkyl having 3-6
16 carbons, alkenyl having 2-6 carbons and 1 or 2
17 double bonds, alkynyl having 2-6 carbons and 1 or 2
18 triple bonds, and

19 B is COOH or a pharmaceutically acceptable salt
20 thereof, $COOR_9$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11} , CH_2OCOR_{11} ,
21 CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, $-COR_7$, $CR_7(OR_{12})_2$, $CR_7OR_{13}O$,
22 where R_7 is an alkyl, cycloalkyl or alkenyl group
23 containing 1 to 5 carbons, R_8 is an alkyl group of 1
24 to 10 carbons or trimethylsilylalkyl where the alkyl
25 group has 1 to 10 carbons, or a cycloalkyl group of
26 5 to 10 carbons, or R_9 is phenyl or lower
27 alkylphenyl, R_9 and R_{10} independently are hydrogen,
28 an alkyl group of 1 to 10 carbons, or a cycloalkyl
29 group of 5-10 carbons, or phenyl or lower
30 alkylphenyl, R_{11} is lower alkyl, phenyl or lower
31 alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent
32 alkyl radical of 2-5 carbons.

33 17. A compound in accordance with Claim 16
34 where A is $(CH_2)_q$ and q is 0, and where B is COOH or
35 a pharmaceutically acceptable salt thereof, $COOR_9$, or
36 $CONR_9R_{10}$.





1 18. A compound in accordance with Claim 17
2 where R_1 is CH_3 , R_2 is H and R_3 is H.

3 19. A compound in accordance with Claim 18
4 where Z is O.

5 20. A compound in accordance with Claim 19
6 where B is $COOR_z$.

7 21. A compound in accordance with Claim 20
8 which is:
9 ethyl 2-fluoro-4-[(5',6',7',8'-tetrahydro-
10 5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]be
11 nzoate;
12 ethyl 4-[(3'-fluoro-5',6',7',8'-tetrahydro-
13 5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]be
14 nzoate;
15 ethyl 2-fluoro-4-[(4'-bromo-5',6',7',8'-tetrahydro-
16 5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]be
17 nzoate;
18 ethyl 2-fluoro-4-[(3'-hydroxy-5',6',7',8'-
19 tetrahydro-5',5',8',8'-tetramethylnaphthalen-2'-yl)c
20 arbamoyl]benzoate;
21 ethyl 2-fluoro-4-[(3'-hydroxy-4'-bromo-5',6',7',8'-
22 tetrahydro-5',5',8',8'-tetramethylnaphthalen-2'-yl)c
23 arbamoyl]benzoate;
24 ethyl 2,6-difluoro-4-[(3'-hydroxy-4'-bromo-
25 5',6',7',8'-tetrahydro-5',5',8',8'-tetramethylnaphth
26 alen-2'-yl)carbamoyl]benzoate; or
27 ethyl 2,6-difluoro-4-[(5',6',7',8'-tetrahydro-
28 5',5',8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]be
29 nzoate.

30 22. A compound in accordance with Claim 19
31 where B is COOH or a pharmaceutically acceptable
32 salt thereof.

33 23. A compound in accordance with Claim 22
34 which is:
35 2-fluoro-4-[(5',6',7',8'-tetrahydro-5',5',8',
36 8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoic

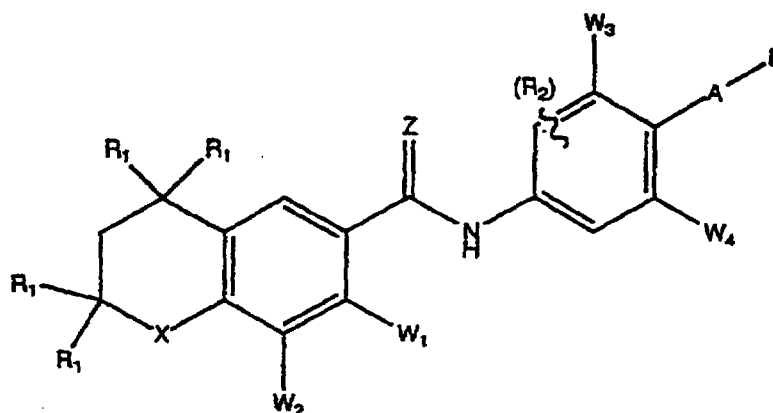




- 1 acid;
2 4-[(3'-fluoro-5',6',7',8'-tetrahydro-5',5',8',8'-tet
3 ramethylnaphthalen-2'-yl)carbamoyl]benzoic acid;
4 2-fluoro-4-[(4'-bromo-5',6',7',8'-tetrahydro-5',5',8
5 ',8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoic
6 acid;
7 2-fluoro-4-[(3'-hydroxy-5',6',7',8'-tetrahydro-5',5'
8 ,8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoic
9 acid;
10 2-fluoro-4-[(3'-hydroxy-4'-bromo-5',6',7',8'-tetrahy
11 -dro-5',5',
12 8',8'-tetramethylnaphthalen-2'-yl)carbamoyl]benzoic
13 acid;
14 2,6-difluoro-4-[(3'-hydroxy-4'-bromo-5',6',7',8'-te
15 trahydro-5',5',8',8'-tetramethylnaphthalen-2'-
16 yl)carbamoyl]benzoic acid; or
17 2,6-difluoro-4-[(5',6',7',8'-tetrahydro-5',5',8',8'-
18 tetramethylnaphthalen-2'-yl)carbamoyl]benzoic acid.
- 19 24. A compound in accordance with Claim 18
20 where Z is S.
- 21 25. A compound in accordance with Claim 24
22 which is:
23 ethyl
24 4-[(5',6',7',8'-tetrahydro-5',5',8',8'-tetramethylna
25 phthalen-2'-yl)thiocarbamoyl]benzoate;
26 ethyl
27 2-fluoro-4-[(5',6',7',8'-tetrahydro-5',5',8',8'-tetr
28 amethylnaphthalen-2'-yl)thiocarbamoyl]benzoate;
29 4-[(5',6',7',8'-tetrahydro-5',5',8',8'-tetramethylna
30 phthalen-2'-yl)thiocarbamoyl]benzoic acid; or
31 2-fluoro-4-[(5',6',7',8'-tetrahydro-5',5',8',8'-tetr
32 amethylnaphthalen-2'-yl)thiocarbamoyl]benzoic acid.

33 26. A compound of the formula
34
35
36





wherein R₁ is independently H or alkyl of 1 to 6 carbons;

R₂ is hydrogen, or lower alkyl of 1 to 6 carbons;

W₁, W₂, W₃, and W₄, each is independently selected from the group consisting of H, F, Br, Cl, I, CF₃, NO₂, N₃, OH, OCH₂OCH₃, OC₁₋₁₀alkyl and C₁₋₆alkyl, with the proviso that when Z is O then at least one of the W₁, W₂, W₃, and W₄ groups is not H;

X is O or S;

Z is O or S;

A is (CH₂)_q where q 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, and

B is COOH or a pharmaceutically acceptable salt thereof, COOR₈, CONR₉R₁₀, -CH₂OH, CH₂OR₁₁, CH₂OCOR₁₁, CHO, CH(OR₁₂)₂, CHOR₁₃O, -COR₇, CR₇(OR₁₂)₂, CR₇OR₁₃O, where R₇ is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R₈ is an alkyl group of 1 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R₈ is phenyl or lower alkylphenyl, R₉ and R₁₀ independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower





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

4 27. A compound in accordance with Claim 26
5 where A is $(CH_2)_q$ and q is 0, and where B is COOH or
6 a pharmaceutically acceptable salt thereof, $COOR_8$, or
7 $CONR_9R_{10}$.

8 28. A compound in accordance with Claim 27
9 where R_1 is independently H or CH_3 , and R_2 is H.

10 29. A compound in accordance with Claim 28
11 where Z is O.

12 30. A compound in accordance with Claim 29
13 where B is $COOR_8$.

14 31. A compound in accordance with Claim 30
15 which is:

16 ethyl 2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-
17 bromochroman-6'-yl)carbamoyl]benzoate;

18 ethyl 2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-
19 trifluoro-methylchroman-6'-yl)carbamoyl] benzoate;

20 ethyl 2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-azido-
21 chroman-6'-yl)carbamoyl]benzoate;

22 ethyl 2,6-difluoro-4-[(2',2',4',4'-tetramethyl-8'-
23 trifluoromethylchroman-6'-yl)carbamoyl]benzoate;

24 ethyl 2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-
25 iodochroman-6'-yl)carbamoyl]benzoate;

26 ethyl 2-fluoro-4-[(2',2',4',4',8'-
27 pentamethylchroman- 6'-yl)carbamoyl]benzoate;

28 ethyl

29 2-fluoro-4-[(2',2',4',4'-tetramethylthiochroman-6'-y
30 l)carbamoyl]benzoate, or

31 ethyl 2-fluoro-4-[(8'-bromo-4',4'-dimethylchroman-
32 6'-yl)carbamoyl]benzoate.

33 32. A compound in accordance with Claim 29
34 where B is COOH or a pharmaceutically acceptable
35 salt thereof.

36 33. A compound in accordance with Claim 32





- 1 which is:
- 2 2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-bromochroman
- 3 - 6'-yl)carbamoyl]benzoic acid;
- 4 2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-trifluoro-
- 5 methylchroman-6'-yl)carbamoyl] benzoic acid;
- 6 2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-azidochroman
- 7 - 6'-yl)carbamoyl]benzoic acid;
- 8 2,6-difluoro-4-[(2',2',4',4'-tetramethyl-8'-trifluor
- 9 omethylchroman-6'-yl)carbamoyl]benzoic acid;
- 10 2-fluoro-4-[(2',2',4',4'-tetramethyl-8'-iodochroman-
- 11 6'-yl)carbamoyl]benzoic acid;
- 12 2-fluoro-4-[(2',2',4',4',8'-pentamethylchroman-6'-yl
- 13)carbamoyl]benzoic acid;
- 14 2-fluoro-4-[(2',2',4',4'-tetramethylthiochroman-6'-y
- 15 l)carbamoyl]benzoic acid, or
- 16 2-fluoro-4-[(8'-bromo-4',4'-dimethylchroman-6'-yl)ca
- 17 rbamoyl]benzoic acid.

