

1,6-DISUBSTITUTED ISOCHROMANS FOR TREATMENT OF
MIGRAINE HEADACHES

BACKGROUND OF THE INVENTION

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1. Field of the Invention

The invention relates to isochroman-alkyl-piperazinyl/piperidinyl-aryl compounds useful for the treatment of headaches, especially migraine and cluster headaches, as analgesics, and also useful as antipsychotics and for the treatment of other CNS and/or cardiovascular disorders.

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2. Description of the Related Art

Chromans (also known as 1-benzopyrans, where the oxygen atom is attached to the aromatic ring) and isochromans (also known as 2-benzopyrans, where the oxygen atom is not attached to the aromatic ring) are known in the art, as are aryl-piperazines (or 4-arylpiperidines). Chromans and aryl piperazines linked together with an alkyl chain are also known. European Patent 300,908 discloses (1-benzopyran)-alkyl-(piperazinyl or aminopiperidine)-aryls useful as antiarrhythmics and anti-fibrillatory agents. The compounds of this invention require -alkyl-piperazinyl (or piperidinyl)-aryl at carbon 1 of a 2-benzopyran ring and also require substitution at the 6-position of the isochroman which are useful for the treatment of vascular (migraine and cluster) headaches and CNS and cardiovascular disorders.

Various isochromans, thioisochromans, benzoxepines, and benzothiepinines with hydroxy, alkoxy, or o-methylenedioxy substitution on their aromatic rings, and linked to aryl piperazines(piperidines) by alkyl chains are known. These compounds are disclosed as being useful as antipsychotics and hypotensives. The compounds of this invention do not permit oxygen substitution on the aromatic ring of the isochroman, thioisochroman, benzoxepin, or benzothiepin ring system for their usefulness in CNS and cardiovascular disorders.

Another group of isochromans, thioisochromans, benzoxepines and benzothiepinines with hydroxy, alkoxy, or o-methylenedioxy functionality attached to their aromatic rings, and linked to aryl piperazines(piperidines) by alkyl chains are known, useful as antipsychotics and hypotensives. The compounds of this invention do not permit oxygen substitution on the aromatic ring of the isochroman, thioisochroman, benzoxepin, or benzothiepin ring system for their usefulness in CNS and cardiovascular disorders.

US Patent 4,179,510 and the many divisionals thereof discloses isochroman-alkyl-piperazinyl (or aminopiperidinyl)-aryls requiring oxygen as a substituent on

the isochroman aromatic ring. These compounds are disclosed as being useful as hypotensive and antipsychotic agents.

Also disclosed are isochroman-, isothiochroman-, 2-benzoxepin-, and -2-benzothiepin-alkyloxyethanols as being useful for preparing the above compounds.

5 More specifically 7,8-dimethoxybenzoxepines are disclosed as are 1-[(6,7-dimethoxyisochroman)alkyl]-4-(aryl)piperazines. Further disclosed are 2-benzoxepine-alkyl-piperazine(aminopiperidine)-aryls, 2-benzothiepins and 2-benzoxepines all requiring an oxygen atom as a substituent on the aromatic ring and useful for the same purposes.

10 Dutch Patent 8,001,981 discloses 1-(2-chlorophenyl)-4-[2-(1,3,4,5-tetrahydro-7,8-dimethoxy-2-benzoxepin-1-yl)ethyl]piperazine useful as an antipsychotic agent.

International Patent Publication WO 92/18089 discloses isochroman-alkyl-piperazinyl (aminopiperidinyl)-aryls, with the requirement that oxygen be present on the aromatic ring of the isochroman which are useful in sensitizing cells against
15 multi-drug resistance.

International Patent Publication WO 88/08424 discloses isochromans-alkyl-piperazinyl (or aminopiperidinyl)-aryls, with the requirement that oxygen be present on the aromatic ring of the isochroman, useful in the treatment of head injury, spinal trauma, and stroke.

20 International Patent Publication WO 90/15056 and US Patent 5,140,040 disclose isochromans, tetralins, and dihydroanaphthalenes substituted with various alkyl amines for the treatment of glaucoma, depression, hypertension, congestive heart failure and vascular spastic conditions.

US Patent 4,994,486 discloses isochroman-alkyl-amines for treating
25 psychoses, Parkinson's disease, and addictive behavior.

Japanese Patent 61083180 discloses isochroman-alkyl-(alkyl)amines as antiulcer agents.

European Patent 404,197 discloses isochroman-alkyl-piperazine-alkyl-keto (alcohol)-aryls with bronchodilator and antiallergy activity.

30 Japanese Patent 51125287 (J 52083846) discloses isochroman-alkyl-amines(piperazine) with antidepressive, analgesic, diuretic, antiinflammatory, and anti-asthma activity.

German Patent DE 2,624,693 and Great Britain Patent GB 1552004 discloses
isochroman-alkyl-amines including aryl piperazines as analgesics, hypotensives,
35 antidepressants, diuretics, antiinflammatories, muscle relaxants, and vasodilators. The compounds differ from the compounds of this invention in that oxygen

substitution is required on the isochroman aromatic ring.

Japanese Patent 57159713 discloses isochroman- and tetralin-(no alkyl spacer)-piperazine-aryls as antiallergics. The compounds of this invention require at least one carbon as a linker.

- 5 US Patents 3,549,656 and 3,467,675 and Belgium Patent 678,035 disclose phthalan-, isochroman-, and isochromen-alkylene-amines for the treatment of depression.

- European Patent 458,387 and US Patent 5,137,911 disclose isochroman-alkylene-piperazine-alkylene-aryls useful as blood platelet aggregation inhibitors, as
10 intracellular calcium antagonists, and for treating cardiac dysrhythmias, angina pectoris, stroke, and myocardial infarction.

German Patent DE 3,409,612 discloses dimethoxyisochroman- and benzoxepine-alkyl-amino-alkyls for prophylaxis of coronary heart disease or hypertension.

- 15 Japanese Patent 6 1083180 discloses isochroman-alkyl-amines useful for treating ulcers. European Patent 457,686 discloses phthalan and indane alkyl aminopiperidinyi ureas or carbamates for the treatment of stress, pain, and schizophrenia.

- J. Med. Chem.*, 25(1), 75-81 (1982) discloses 6,7-dimethoxyisochroman-alkyl-
20 piperazinyl-aryl type compounds which have hypotensive activity.

US Patents 5,032,598 and 5,215,989 generically encompass the isochromans and tetralins of the present invention if the variable substituents are appropriately chosen.

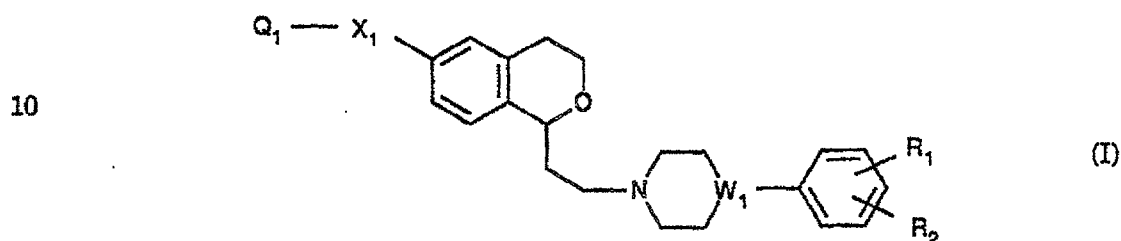
- International Publication No. WO 88/08424 and US Patent 5,120,843 disclose
25 a dialkoxyisochroman containing a substituted pyridinylpiperazinylethyl side chain. However, the compounds of the present invention do not permit alkoxy substitution.

- International Publication No. WO 95/18118 (PCT/US94/13284) discloses various isochromans including 6-(substituted)amino (6-NRR) and 6-(substituted)amide (6-CO-NRR) isochromans which are useful in treating humans
30 who have a central nervous system disorders including psychosis, paraphrenia, psychotic depression, mania, schizophrenia, schizophreniform disorders. These compounds are also useful in the treatment of vascular headaches, particularly migraine headaches. Other central nervous system disorders which can be treated with these compounds include anxiety, drug addiction, convulsive disorders,
35 spectrum disorders, personality disorders, attention deficit disorders in children and adults, post traumatic stress syndrome and dysthymia. WO 95/18118 discloses

racemic 1-(4-methoxyphenyl)-4-[2-(6-aminocarbonylisochroman-1-yl)-ethyl]piperazine (EXAMPLE 138) and 1-(4-methoxyphenyl)-4-[2-(6-methylaminocarbonylisochroman-1-yl)-ethyl]piperazine (EXAMPLE 139).

SUMMARY OF INVENTION

5 Disclosed are 1,6-disubstituted isochromans of formula (I)



15 where:

(I) W_1 is a nitrogen (-N-) or carbon (-CH-) atom;

(II) X_1 is:

(A) $-(CH_2)_{n1}-$ where n_1 is 0 thru 3,

(B) $-CH=CH-$;

20 (III) R_1 is:

(A) -H,

(B) -F, -Cl, -Br, -I,

(C) C_1-C_8 alkyl,

(D) C_2-C_8 alkenyl containing 1 thru 3 double bonds (=),

25 (E) C_2-C_8 alkynyl containing 1 or 2 triple bonds ($\equiv$),

(F) C_3-C_8 cycloalkyl,

(G) $-C_1-C_3$ alkyl- C_3-C_8 cycloalkyl,

(H) $-NO_2$,

(I) $-C\equiv N$,

30 (J) $-CF_3$,

(K) $-O-R_{1-1}$ where R_{1-1} is:

(1) -H,

(2) C_1-C_8 alkyl,

(3) C_2-C_8 alkenyl containing 1 thru 3 double bonds (=),

35 (4) C_2-C_8 alkynyl containing 1 or 2 triple bonds ($\equiv$),

(5) C_3-C_8 cycloalkyl,

- (6) $-C_1-C_3$ alkyl- C_3-C_8 cycloalkyl,
 (7) $-CF_3$,
 (8) $-SO_2-CF_3$,
 (9) $-(CH_2)_{n_2}-\phi$ where n_2 is 0 thru 4 and where $-\phi$ is optionally
 5 substituted with one or two:
- (a) $-F$, $-Cl$, $-Br$, $-I$,
 (b) $-C\equiv N$,
 (c) $-CF_3$,
 (d) C_1-C_3 alkyl,
 10 (e) $-O-R_{1-1A}$ where R_{1-1A} is $-H$, C_1-C_6 alkyl, $-CF_3$ or
 $-CH_2-\phi$,
 (f) $-NR_{1-1A}R_{1-1B}$ where the R_{1-1A} and R_{1-1B} are the
 same or different and where R_{1-1B} is $-H$, C_1-C_6 alkyl, $-CF_3$ or $-CH_2-\phi$, and where
 R_{1-1A} is as defined above,
 15 (g) $-CO-NR_{1-1A}R_{1-1B}$ where R_{1-1A} and R_{1-1B} are as
 defined above,
 (h) $-SO_2-NR_{1-1A}R_{1-1B}$ where R_{1-1A} and R_{1-1B} are as
 defined above,
 (i) $-NR_{1-1A}-SO_2-R_{1-1B}$ where R_{1-1A} and R_{1-1B} are as
 20 defined above,
 (j) $-NO_2$,
 (k) $-O-SO_2-CF_3$,
 (L) $-N(R_{1-1})_2$ where the R_{1-1} can be the same or different and are as
 defined above,
 25 (M) $-CO-N(R_{1-1})_2$ where the R_{1-1} are the same or different and are as
 defined above,
 (N) $-SO_2-R_{1-3}$ where R_{1-3} is:
- (1) $-H$,
 (2) $-CF_3$,
 30 (3) C_1-C_8 alkyl,
 (4) C_2-C_8 alkenyl containing 1 thru 3 double bonds ($=$),
 (5) C_2-C_8 alkynyl containing 1 or 2 triple bonds ($\equiv$),
 (6) C_3-C_8 cycloalkyl,
 (7) $-C_1-C_3$ alkyl- C_3-C_8 cycloalkyl,
 35 (8) $-(CH_2)_{n_2}-\phi$ where n_2 is as defined above and $-\phi$ is optionally
 substituted with one or two:

- (a) -F, -Cl, -Br, -I,
 (b) -C≡N,
 (c) -CF₃,
 (d) C₁-C₆ alkyl,
 5 (e) -O-R_{1-3A} where R_{1-3A} is -H, C₁-C₆ alkyl, -CF₃ or -CH₂-φ,
 (f) -NR_{1-3A}R_{1-3B} where the R_{1-3A} and R_{1-3B} are the same or different and where R_{1-3B} is -H, C₁-C₆ alkyl, -CF₃ or -CH₂-φ, and where R_{1-3A} is as defined above,
 10 (g) -CO-NR_{1-3A}R_{1-3B} where R_{1-3A} and R_{1-3B} are as defined above,
 (h) -SO₂-NR_{1-3A}R_{1-3B} where R_{1-3A} and R_{1-3B} are as defined above,
 (i) -NR_{1-3A}-SO₂-R_{1-3B} where R_{1-3A} and R_{1-3B} are as
 15 defined above,
 (j) -NO₂,
 (k) -O-SO₂-CF₃,
 (9) -O-R_{1-3A} where R_{1-3A} is as defined above,
 (10) -NR_{1-3A}R_{1-3B} where R_{1-3A} and R_{1-3B} are as defined above,
 20 (O) -NR₁₋₁-SO₂-R₁₋₃ where R₁₋₁ and R₁₋₃ may be the same or different and are as defined above,
 (P) -(CH₂)_{n2}-φ where n₂ is as defined above and where -φ is optionally substituted with one or two:
 (1) -F, -Cl, -Br, -I,
 25 (2) -C≡N,
 (3) -CF₃,
 (4) C₁-C₆ alkyl,
 (5) -O-R₁₋₁ where R₁₋₁ is as defined above,
 (6) -N(R₁₋₁)₂ where the R₁₋₁s are the same or different and are
 30 as defined above,
 (7) -CO-N(R₁₋₁)₂ where the R₁₋₁s are the same or different and are as defined above,
 (8) -SO₂-N(R₁₋₁)₂ where the R₁₋₁s are the same or different and are as defined above,
 35 (9) -NR₁₋₁-SO₂-R₁₋₁ where the R₁₋₁s are the same or different and are as defined above,

(10) $-\text{NO}_2$,

(11) $-\text{O}-\text{SO}_2-\text{CF}_3$;

(Q) $-\text{CO}-\text{R}_{1-1}$ where R_{1-1} is as defined above,

(R) $-\text{CO}-\text{O}-\text{Q}_{1-2}$ where Q_{1-2} is defined below;

5 (IV) R_2 is defined the same as R_1 , R_2 can be the same or different than R_1 ;

(V) Q_1 is:

(A) $-\text{CO}-\text{NQ}_{1-1}\text{Q}_{1-2}$ where Q_{1-1} is:

(1) $-\text{H}$,

(2) C_1-C_8 alkyl,

10 (3) C_2-C_8 alkenyl containing 1 thru 3 double bonds ($=$),

(4) C_2-C_8 alkynyl containing 1 or 2 triple bonds ($\equiv$),

(5) C_3-C_8 cycloalkyl,

(6) $-\text{C}_1-\text{C}_3$ alkyl- C_3-C_8 cycloalkyl,

(7) $-\text{CF}_3$,

15 (8) $-\text{SO}_2-\text{CF}_3$,

(9) $-(\text{CH}_2)_{n-7}-\phi$ where n_7 is 0 thru 4 and where ϕ is optionally substituted with one or two:

(a) $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$,

(b) $-\text{C}\equiv\text{N}$,

20 (c) $-\text{CF}_3$,

(d) C_1-C_3 alkyl,

(e) $-\text{O}-\text{Q}_{1-1\text{A}}$ where $\text{Q}_{1-1\text{A}}$ is $-\text{H}$, C_1-C_6 alkyl, $-\text{CF}_3$ or $-\text{CH}_2-\phi$,

(f) $-\text{NQ}_{1-1\text{A}}\text{Q}_{1-1\text{B}}$ where the $\text{Q}_{1-1\text{A}}$ and $\text{Q}_{1-1\text{B}}$ are the same or different and where $\text{Q}_{1-1\text{B}}$ is $-\text{H}$, C_1-C_6 alkyl, $-\text{CF}_3$ or $-\text{CH}_2-\phi$, and where $\text{Q}_{1-1\text{A}}$ is as defined above,

(g) $-\text{CO}-\text{NQ}_{1-1\text{A}}\text{Q}_{1-1\text{B}}$ where $\text{Q}_{1-1\text{A}}$ and $\text{Q}_{1-1\text{B}}$ are as defined above,

30 (h) $-\text{SO}_2-\text{NQ}_{1-1\text{A}}\text{Q}_{1-1\text{B}}$ where $\text{Q}_{1-1\text{A}}$ and $\text{Q}_{1-1\text{B}}$ are as defined above,

(i) $-\text{NQ}_{1-1\text{A}}-\text{SO}_2-\text{Q}_{1-1\text{B}}$ where $\text{Q}_{1-1\text{A}}$ and $\text{Q}_{1-1\text{B}}$ are as defined above,

(j) $-\text{NO}_2$,

(k) $-\text{O}-\text{SO}_2-\text{CF}_3$, and where Q_{1-2} is:

35 (1) $-\text{H}$,

(2) C_1-C_8 alkyl,

- (3) C₂-C₈ alkenyl containing 1 thru 3 double bonds (=),
 (4) C₂-C₈ alkynyl containing 1 or 2 triple bonds (≡),
 (5) C₃-C₈ cycloalkyl,
 (6) -C₁-C₃ alkyl-C₃-C₈ cycloalkyl,
 5 (7) -CF₃,
 (8) -(CH₂)_{n2}-φ where n₂ is as defined above and -φ is optionally substituted with one or two:
- (a) -F, -Cl, -Br, -I,
 (b) -C≡N,
 10 (c) -CF₃,
 (d) C₁-C₆ alkyl,
 (e) -O-Q_{1-2A} where Q_{1-2A} is:
 (i) -H,
 (ii) C₁-C₆ alkyl,
 15 (iii) -CF₃,
 (iv) -(CH₂)_{n9}-Q_{1-2B}(CH₂)_{n10}-Q_{1-2C} where n₉ and n₁₀ are the same or different and are 0 thru 4, where Q_{1-2B} is -O- or -NQ_{1-2D}, where Q_{1-2D} is:
- (a) -H,
 20 (b) C₁-C₈ alkyl,
 (c) C₂-C₈ alkenyl containing 1 thru 3 double bonds,
 (d) C₂-C₈ alkynyl containing 1 or 2 triple bonds,
 (e) C₃-C₈ cycloalkyl,
 (f) -C₁-C₃ alkyl-C₃-C₈ cycloalkyl,
 25 (g) -CF₃,
 (h) -(CH₂)_{n11}-φ where n₁₁ is 0 thru 4 and -φ is optionally substituted with one or two:
- (i) -F, -Cl, -Br, -I,
 (ii) -C≡N,
 30 (iii) -CF₃,
 (iv) C₁-C₃ alkyl,
 (v) -O-Q_{1-2E} where Q_{1-2E} is -H, C₁-C₆ alkyl, -CF₃ or -CH₂-φ,
 (vi) -NQ_{1-2E}Q_{1-2F} where the Q_{1-2E} and Q_{1-2F} are the same or different and where Q_{1-2F} is -H, C₁-C₆ alkyl, -CF₃ or -CH₂-φ, and where Q_{1-2E} is as defined above,
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- (vii) $-\text{CO}-\text{NQ}_{1-2\text{E}}\text{Q}_{1-2\text{F}}$ where $\text{Q}_{1-2\text{E}}$ and $\text{Q}_{1-2\text{F}}$ are as defined above,
- (viii) $-\text{SO}_2-\text{NQ}_{1-2\text{E}}\text{Q}_{1-2\text{F}}$ where $\text{Q}_{1-2\text{E}}$ and $\text{Q}_{1-2\text{F}}$ are as defined above,
- 5 (ix) $-\text{NQ}_{1-2\text{E}}-\text{SO}_2-\text{Q}_{1-2\text{F}}$ where $\text{Q}_{1-2\text{E}}$ and $\text{Q}_{1-2\text{F}}$ are as defined above,
- (x) $-\text{NO}_2$,
- (xi) $-\text{O}-\text{SO}_2-\text{CF}_3$, and where $\text{Q}_{1-2\text{C}}$ is defined the same as $\text{Q}_{1-2\text{D}}$ and the $\text{Q}_{1-2\text{C}}$ and $\text{Q}_{1-2\text{D}}$ can be the same or different, and
- 10 where Q_{1-1} and Q_{1-2} are taken together with the attached nitrogen atom to form a 5 or 6 member ring which can include one additional nitrogen or oxygen atom;
- (B) $-\text{SO}_2-\text{NQ}_{1-1}\text{Q}_{1-2}$ where Q_{1-1} and Q_{1-2} are as defined above,
- (C) $-\text{CO}-\text{O}-\text{Q}_{1-3}$ where Q_{1-3} is:
- 15 (1) $-\text{H}$,
- (2) $-\text{CF}_3$,
- (3) C_1-C_8 alkyl,
- (4) C_2-C_8 alkenyl containing 1 thru 3 double bonds (=),
- (5) C_2-C_8 alkynyl containing 1 or 2 triple bonds ($\equiv$),
- 20 (6) C_3-C_8 cycloalkyl,
- (7) $-\text{C}_1-\text{C}_3$ alkyl- C_3-C_8 cycloalkyl,
- (8) $-(\text{CH}_2)_{n7}-\phi$ where $n7$ is as defined above and ϕ is optionally substituted with one or two:
- (a) $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$,
- 25 (b) $-\text{C}\equiv\text{N}$,
- (c) $-\text{CF}_3$,
- (d) C_1-C_3 alkyl,
- (e) $-\text{O}-\text{Q}_{1-3\text{A}}$ where $\text{Q}_{1-3\text{A}}$ is $-\text{H}$, C_1-C_6 alkyl, $-\text{CF}_3$ or $-\text{CH}_2-\phi$,
- 30 (f) $-\text{NQ}_{1-3\text{A}}\text{Q}_{1-3\text{B}}$ where the $\text{Q}_{1-3\text{A}}$ and $\text{Q}_{1-3\text{B}}$ are the same or different and where $\text{Q}_{1-3\text{B}}$ is $-\text{H}$, C_1-C_6 alkyl, $-\text{CF}_3$ or $-\text{CH}_2-\phi$, and where $\text{Q}_{1-3\text{A}}$ is as defined above,
- (g) $-\text{CO}-\text{NQ}_{1-3\text{A}}\text{Q}_{1-3\text{B}}$ where $\text{Q}_{1-3\text{A}}$ and $\text{Q}_{1-3\text{B}}$ are as defined above,
- 35 (h) $-\text{SO}_2-\text{NQ}_{1-3\text{A}}\text{Q}_{1-3\text{B}}$ where $\text{Q}_{1-3\text{A}}$ and $\text{Q}_{1-3\text{B}}$ are as defined above,

(i) $-NQ_{1-3A}-SO_2-Q_{1-3B}$ where Q_{1-3A} and Q_{1-3B} are as defined above,

(j) $-NO_2$,

(k) $-O-SO_2-CF_3$,

5 (D) $-CO-Q_{1-3}$ where Q_{1-3} is as defined above,

(E) $-CO$ -imidazole,

(F) $-NQ_{1-1}Q_{1-2}$ where Q_{1-1} and Q_{1-2} are as defined above,

(F') $-NQ_{1-1}-CO-Q_{1-2}$ where Q_{1-1} and Q_{1-2} are as defined above,

(G) $-C(Q_{1-3})=N-O-Q_{1-4}$ where Q_{1-4} is defined the same as Q_{1-3} and Q_{1-3} is as defined above, the Q_{1-3} and Q_{1-4} can be the same or different,

(H) $-SO_2-Q_{1-3}$ where Q_{1-3} is as defined above,

(I) $-N(Q_{1-1})-SO_2-Q_{1-3}$ where Q_{1-1} and Q_{1-3} is as defined above,

(J) 5-oxadiazole optionally substituted with one Q_{1-5} where Q_{1-5} is:

(1) $-H$,

15 (2) $-F$, $-Cl$, $-Br$, $-I$,

(3) C_1-C_8 alkyl,

(4) C_2-C_8 alkenyl containing 1 thru 3 double bonds (=),

(5) C_2-C_8 alkynyl containing 1 or 2 triple bonds ($\equiv$),

(6) C_3-C_8 cycloalkyl,

20 (7) $-C_1-C_3$ alkyl- C_3-C_8 cycloalkyl,

(8) $-NO_2$,

(9) $-C\equiv N$,

(10) $-CF_3$,

(11) $-O-Q_{1-5A}$ where Q_{1-5A} is:

25 (a) $-H$,

(b) C_1-C_8 alkyl,

(c) C_2-C_8 alkenyl containing 1 thru 3 double bonds,

(d) C_2-C_8 alkynyl containing 1 or 2 triple bonds,

(e) C_3-C_8 cycloalkyl,

30 (f) $-C_1-C_3$ alkyl- C_3-C_8 cycloalkyl,

(g) $-CF_3$,

(h) $-SO_2-CF_3$,

(i) $-(CH_2)_{n7}-\phi$ where n_7 is 0 thru 4,

(12) $-NQ_{1-5A}Q_{1-5D}$ where Q_{1-5A} is as defined above, Q_{1-5D} is:

35 (a) $-H$,

(b) C_1-C_8 alkyl,

- (c) C₂-C₈ alkenyl containing 1 thru 3 double bonds,
 (d) C₂-C₈ alkynyl containing 1 or 2 triple bonds ($\equiv$),
 (e) C₃-C₈ cycloalkyl,
 (f) -C₁-C₃ alkyl-C₃-C₈ cycloalkyl,
 5 (g) -CF₃,
 (h) -(CH₂)_{n7}- ϕ where n₇ is as defined above,
 (13) -CO-NQ_{1-5A}Q_{1-5D} where Q_{1-5A} and Q_{1-5D} are as defined
 above,
 (14) -SO₂-Q_{1-5K} where Q_{1-5K} is:
 10 (a) -H,
 (b) -CF₃,
 (c) C₁-C₈ alkyl,
 (d) C₂-C₈ alkenyl containing 1 thru 3 double bonds ($=$),
 (e) C₂-C₈ alkynyl containing 1 or 2 triple bonds ($\equiv$),
 15 (f) C₃-C₈ cycloalkyl,
 (g) -C₁-C₃ alkyl-C₃-C₈ cycloalkyl,
 (h) -(CH₂)_{n7}- ϕ where n₇ is as defined above,
 (15) -NQ_{1-5A}-SO₂-Q_{1-5K} where Q_{1-5A} and Q_{1-5K} may be the
 same or different and are as defined above,
 20 (16) -(CH₂)_{n7}- ϕ where n₇ is as defined above and where - ϕ is
 optionally substituted with one or two:
 (a) -F, -Cl, -Br, -I,
 (b) -C $\equiv$ N,
 (c) -CF₃,
 25 (d) C₁-C₈ alkyl,
 (e) -O-Q_{1-5A} where Q_{1-5A} is as defined above,
 (f) -NQ_{1-5A}Q_{1-5D} where Q_{1-5A} and Q_{1-5D} are as defined
 above,
 (g) -CO-NQ_{1-5A}Q_{1-5D} where Q_{1-5A} and Q_{1-5D} are as
 30 defined above,
 (h) -SO₂-NQ_{1-5A}Q_{1-5D} where Q_{1-5A} and Q_{1-5D} are as
 defined above,
 (i) -NQ_{1-5A}-SO₂-Q_{1-5D} where Q_{1-5A} and Q_{1-5D} are as
 defined above,
 35 (j) -NO₂,
 (k) -O-SO₂-CF₃;

(K) 3-oxadiazole optionally substituted with one Q_{1-5} where Q_{1-5} is as defined above,

(L) triazole optionally substituted with one or two Q_{1-5} which may be the same or different, where Q_{1-5} is as defined above,

5 (M) 5-thiadiazole optionally substituted with one Q_{1-5} , where Q_{1-5} is as defined above,

(N) 3-thiadiazole optionally substituted with one Q_{1-5} , where Q_{1-5} is as defined above,

10 (O) 2-oxazole optionally substituted with one or two Q_{1-5} which may be the same or different, where Q_{1-5} is as defined above,

(P) 2-thiazole optionally substituted with one or two Q_{1-5} which may be the same or different, where Q_{1-5} is as defined above,

(Q) 2-imidazole optionally substituted with one, two or three Q_{1-5} which may be the same or different, where Q_{1-5} is as defined above,

15 (R) 1-imidazole optionally substituted with one, two or three Q_{1-5} which may be the same or different, where Q_{1-5} is as defined above,

(S) tetrazole optionally substituted with one Q_{1-5} , where Q_{1-5} is as defined above,

20 (T) cyclobutenedione optionally substituted with one Q_{1-1} and one Q_{1-5} where Q_{1-1} and Q_{1-5} are as defined above,

(U) 1-pyrimidinyl optionally substituted with one Q_{1-5} , where Q_{1-5} is as defined above,

(V) 2-pyridinyl optionally substituted with one Q_{1-5} , where Q_{1-5} is as defined above,

25 (W) 3-pyridinyl optionally substituted with one Q_{1-5} , where Q_{1-5} is as defined above,

(X) 4-pyridinyl optionally substituted with one Q_{1-5} , where Q_{1-5} is as defined above,

30 (Y) $-Z_1-CO-Z_2-Q_{1-2}$ where Q_{1-2} is as defined above and Z_1 is
-O- or

$-N_{Q_{1-1}}$ where Q_{1-1} is as defined above, where Z_2 is

-O- or

$-N_{Q_{1-1}}$ where Q_{1-1} is as defined above,

35 with the proviso that when X_1 is $-(CH_2)_{n1}$, where n_1 is 0 and Q_1 is:

$-CO-N_{Q_{1-1}}Q_{1-2}$,

$-\text{SO}_2-\text{NQ}_{1-1}\text{Q}_{1-2}$ or

$-\text{NQ}_{1-1}\text{Q}_{1-2}$,

$-\text{NQ}_{1-1}-\text{CO}-\text{Q}_{1-2}$ then Q_{1-1} and Q_{1-2} cannot both be selected

from:

5

$-\text{H}$,

$-\text{C}_1-\text{C}_6$ alkyl,

$-\text{C}_3-\text{C}_7$ cycloalkyl,

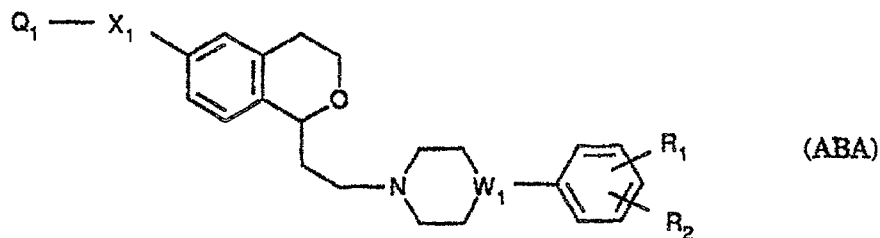
$-\text{C}_1-\text{C}_3$ alkyl- (C_3-C_7) cycloalkyl and pharmaceutically

acceptable salts thereof.

10

Also disclosed are aromatic bicyclic amines of the formula (ABA)

15



20 where:

(I) W_1 is a nitrogen ($-\text{N}-$) or carbon ($-\text{CH}-$) atom;

(II) X_1 is $-(\text{CH}_2)_{n_1}-$, and n_1 is 0,

(III) Q_1 is

(A) $-\text{CO}-\text{NQ}_{1-1}\text{Q}_{1-2}$ where Q_{1-1} is:

25

(1) $-\text{H}$,

(2) C_1-C_8 alkyl,

(3) C_2-C_8 alkenyl containing 1 thru 3 double bonds ($=$),

(4) C_2-C_8 alkynyl containing 1 or 2 triple bonds ($\equiv$),

(5) $-(\text{CH}_2)_{n_7}-\phi$ where n_7 is 0 thru 4 and where $-\phi$ is optionally

30 substituted with one or two:

(a) $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$,

(b) $-\text{C}\equiv\text{N}$,

(c) $-\text{CF}_3$,

(d) C_1-C_3 alkyl,

35

(e) $-\text{O}-\text{Q}_{1-1\text{A}}$ where $\text{Q}_{1-1\text{A}}$ is $-\text{H}$, C_1-C_6 alkyl, $-\text{CF}_3$ or

$-\text{CH}_2-\phi$,

(f) $-NQ_{1-1A}Q_{1-1B}$ where the Q_{1-1A} and Q_{1-1B} are the same or different and where Q_{1-1B} is -H, C_1-C_6 alkyl, $-CF_3$ or $-CH_2-\phi$, and where Q_{1-1A} is as defined above,

5 (g) $-CO-NQ_{1-1A}Q_{1-1B}$ where Q_{1-1A} and Q_{1-1B} are as defined above,

(h) $-SO_2-NQ_{1-1A}Q_{1-1B}$ where Q_{1-1A} and Q_{1-1B} are as defined above,

(i) $-NQ_{1-1A}-SO_2-Q_{1-1B}$ where Q_{1-1A} and Q_{1-1B} are as defined above,

10 (j) $-NO_2$,

(k) $-O-SO_2-CF_3$, and where Q_{1-2} is:

(6) C_1-C_8 alkyl,

(7) C_2-C_8 alkenyl containing 1 thru 3 double bonds (=),

(8) C_2-C_8 alkynyl containing 1 or 2 triple bonds ($\equiv$),

15 (9) $-(CH_2)_{n2}-\phi$ where n_2 is as defined above and ϕ is optionally substituted with one or two:

(a) -F, -Cl, -Br, -I,

(b) $-C\equiv N$,

(c) $-CF_3$,

20 (d) C_1-C_6 alkyl,

(e) $-O-Q_{1-2A}$ where Q_{1-2A} is:

(i) -H,

(ii) C_1-C_6 alkyl,

(iii) $-CF_3$,

25 (iv) $-(CH_2)-\phi$,

(B) $-SO_2-NQ_{1-1}Q_{1-2}$ where Q_{1-1} and Q_{1-2} are as defined above,

(C) $-NQ_{1-1}Q_{1-2}$ where Q_{1-1} and Q_{1-2} are as defined above,

(D) $-NQ_{1-1}-CO-Q_{1-2}$ where Q_{1-1} and Q_{1-2} are as defined above,

(III) R_1 is:

30 (A) -H,

(B) -F, -Cl, -Br, -I,

(C) C_1-C_8 alkyl,

(D) $-C\equiv N$,

(E) $-CF_3$,

35 (F) $-O-R_{1-1}$ where R_{1-1} is:

(1) -H,

(2) C₁-C₈ alkyl,

(3) -CF₃,

(4) -SO₂-CF₃,

(5) -(CH₂)_{n2}-φ where n₂ is 0 thru 4

5 (G) -N(R₁₋₁)₂ where the R₁₋₁ can be the same or different and are as defined above,

(H) -CO-N(R₁₋₁)₂ where the R₁₋₁ are the same or different and are as defined above,

(I) -SO₂-R₁₋₃ where R₁₋₃ is:

10

(1) -CF₃,

(2) C₁-C₈ alkyl,

(3) -O-R_{1-3A} where R_{1-3A} is as defined above,

(4) -NR_{1-3A}R_{1-3B} where R_{1-3A} and R_{1-3B} are as defined above,

(J) -CO-R₁₋₁ where R₁₋₁ is as defined above;

15 (IV) R₂ is defined the same as R₁, R₂ can be the same or different than R₁; and pharmaceutically acceptable salts thereof.

Further disclosed are the aromatic bicyclic amines of EXAMPLES 1, 2, 11, 12, 14, 24, 40, 72, 84, 86 and 88.

DETAILED DESCRIPTION OF THE INVENTION

20 The invention consists of novel compounds, 1,6-disubstituted isochroman (I) and a small group of aromatic bicyclic amines (ABA) which are previously generically disclosed in International Publication WO 95/18118 (PCT/US94/13284) with a unique spectrum of activity, highly active against vascular headaches especially migraine and cluster headaches. The processes used to produce the novel
25 compounds of the claimed invention are known to those skilled in the art. By starting with the appropriate starting materials and organizing the process steps in a particular order (using protective groups where necessary) the novel compounds of the invention are produced. The process of each step of the invention is known to those skilled in the art. One skilled in the art given the chemical structure of any of
30 the 1,6-disubstituted isochroman (I) or aromatic bicyclic amines (ABA), could readily prepare the compounds from known compounds by methods known to those skilled in the art even without the discussion and EXAMPLES below.

35 CHART A describes the construction of the 6-bromoisochroman (VI), which is a useful intermediate for many of the 1,6-disubstituted isochroman (I) and aromatic bicyclic amines (ABA). Reaction of 3-bromophenethanol (II) with ethyl 3,3-diethoxypropionate in the presence of titanium tetrachloride in nitromethane or

dichloromethane gives the isochroman ester (III). Standard hydrolysis using lithium hydroxide in THF-water provides the acid (IV), which can be coupled to a variety of substituted arylpiperazines or 4-arylpiperidines to give the amides (V). The arylpiperazine moiety carries the R₁ and R₂ substituents. It is preferred that the
5 desired R₁ and R₂ substituents be on the aryl group prior to the production of the amide (V). The starting R₁ and R₂ aryl groups are known to those skilled in the art or can be readily prepared by known methods from known compounds. Many of the arylpiperazine moieties are commercially available or known in the chemical literature. Those that are not commercially available or known can readily be
10 prepared as illustrated in CHARTS Q and R. These amides are reduced using borane to provide the bromoisochromans (VI).

CHART B describes the conversion of the 6-bromoisochroman (VI) into the corresponding 6-amide and 6-ester analogs. Conversion of the aryl bromide to the primary amide is accomplished via metal-halogen exchange using t-butyl lithium
15 and quenching the resulting aryl anion with trimethylsilylisocyanate, see *J. Med. Chem.*, 36, 2208 (1993). The aryl anion can also be treated with gaseous carbon dioxide, followed by treatment with oxalyl chloride in DMF and subsequent reaction with amines to provide the amides (IX) directly. Alternatively, the 6-bromoisochroman (VI), can be reacted with carbon monoxide in the presence of
20 palladium (II) acetate, 1,3-bisdiphenylphosphinopropane, diisopropylamine, and hexamethyldisilazane in solvents such as DMF to give the amide (VII). Other palladium catalysts, such as *in situ* prepared palladium(0) with organophosphines, or pre-prepared palladium(0) phosphine catalysts can be utilized. The amide (VII) can be converted into either substituted amides (IX) or esters (X) via the bis-BOC
25 derivative (VIII) using the procedure described in *J. Org. Chem.*, 56, 5482 (1991). The 6-bromoisochroman (VI) can be converted to N-methyl substituted amides (IX) directly by using either methylamine or N-methylformamide in place of hexamethyldisilazane in the palladium-mediated reaction described above (see
EXAMPLES 5 and 6). Alternatively, other patterns of N-substitution can be
30 obtained by using other primary or secondary amines in place of hexamethyldisilazane in the palladium-mediated reaction described above.

CHART C describes the enzymatic resolution of racemic (II). Mixing (II) with an enzyme such as the lipase derived from *Pseudomonas cepacia* in aqueous buffer (preferred pH 5-8) results in selective hydrolysis of the (-)-ester to give the (-)-acid
35 (XI). It is preferred to carry out this reaction at room temperature (20-35°) using 5-20% by weight of the enzyme. The reaction is monitored by known means of

removing an aliquot, acidifying, and examining by HPLC. When the reaction is complete, the products (XI), the (-)-acid, and (XII), the (+)-ester are recovered and separated by acid/base extractive techniques well-known by those skilled in the art. These optically-active compounds can be used when appropriate in any of the
5 illustrated Charts to prepare optically pure versions of the described compounds.

The undesired enantiomer, (+)-ethyl (isochroman-1-yl)acetate (XII), recovered from the *Pseudomonas cepacia* mediated kinetic resolution of enantiomers, can be effectively recycled back to the racemic mixture for subsequent further treatment with the *Pseudomonas* lipase. This iterative process optimizes the overall yield of
10 the desired (-)-isochroman-1-yl-acetic acid (XI). Suitable bases for this racemization are those with pKa's greater than 11, preferably greater than 12. Operable bases include alkali metal amide bases, alkali metal alkoxides, and alkali metal carbonates which can all induce this racemization. It is preferred that the base be alkali metal amide bases or alkali metal alkoxides; it is more preferred that the base
15 be the alkali metal alkoxides, such as sodium or potassium *t*-butoxide or ethoxide. At the completion of the racemization, the reaction is quenched with a proton donor. Virtually any proton donor is operable, for example even water will quench the reaction. However, operationally water is not preferred. Usually the proton donor is an acid. Most common proton donors (hydrochloric acid, ammonium chloride)
20 used to quench enolate anions can be used for this quenching, however, for ease of workup and purification, acetic acid or trifluoroacetic acid is preferred.

CHART D describes the preparation of amides and esters which are linked to the isochroman nucleus by a one-carbon methylene spacer (I, $X_1 = -CH_2-$). Treatment of the aryl bromide (VI) with trimethylsilylacetylene in the presence of
25 palladium (II) acetate, copper(I) iodide, and triethylamine provides the acetylenic isochroman (XIII). Reaction of the acetylenic isochroman (XIII) with a dialkylborane such as dicyclohexylborane followed by an oxidative work-up using basic hydrogen peroxide gives the carboxylic acid (XIV, $Q_{1-3} = H$), from which the generalized esters (XIV) or amides (XV) can be derived by standard techniques known to those skilled
30 in the art.

CHART E describes the preparation of amides and esters which are linked to the isochroman nucleus by a two-carbon spacer which can be either saturated (I, $X_1 = -CH_2CH_2-$) or unsaturated (I, $X_1 = -CH=CH-$). Treatment of the bromide (VI) with
an acrylate ester in the presence of a palladium catalyst, preferably palladium (II)
35 acetate, along with 1,3-bisdiphenylphosphinopropane and diisopropylamine in an organic solvent such as dimethylformamide gives (XVI). Hydrogenation of (XVI) by

standard techniques known to those skilled in the art provides the saturated species (XVII). Similarly, treatment of the bromide (VI) with an acrylamide in the presence of a palladium catalyst, preferably palladium(II) acetate, along with 1,3-bis(diphenylphosphino)propane and diisopropylamine in an organic solvent such as dimethylformamide gives (XVIII). Hydrogenation of (XVIII) by standard techniques known to those skilled in the art provides the saturated species (XIX).

CHART F describes the preparation of amides and esters which are linked to the isochroman nucleus by a three-carbon methylene spacer (I, $X_1 = -CH_2CH_2CH_2-$). Carboxylic acid (X, $Q_{1-3} = H$) is treated with two equivalents of propyl lithium to provide the butyrophenone (XX). Heating to reflux a solution of the butyrophenone (XX) in morpholine with an equivalent of elemental sulfur and morpholine for 10 - 20 hours gives the thiolactam (XXI, see Org. Reactions, Vol III, Chapter 2, pp 83, 1946, John Wiley & Sons, New York.) Hydrolysis of the thiolactam (XXI) with aqueous hydrochloric acid using techniques known to those skilled in the art gives the carboxylic acid (XXII, $Q_{1-3} = H$), from which the esters (XXII) and the amides (XXIII) can be readily obtained using procedures well-known to those skilled in the art.

CHART G describes the preparation of isochromans bearing a 6-acyl substituent such as an acid, an ester, a ketone, or an oxime. Metal-halogen exchange of the arylbromide (VI) generates an aryl-lithium reagent which can be quenched with carbon dioxide to give carboxylic acids (X, $Q_{1-3} = H$). Palladium-mediated carbonylation of the aryl bromide (IV) in the presence of an alcohol generates the corresponding esters (X) via conditions well-documented in the literature. Similarly, palladium-mediated cross-coupling of (VI) with enol-ethers gives rise to ketones (XXIV) following standard acidic hydrolysis of the enol-ether intermediate. Alternatively, treatment of the carboxylic acid (X, $Q_{1-3} = H$) with two equivalents of an alkyl lithium reagent generates the corresponding ketone (XXIV). Condensation of the ketone (XXIV) with either hydroxylamine or any readily-available O-substituted hydroxylamine using toluene as the solvent and a Dean-Stark apparatus for water removal provides the desired oximes (XXV).

CHART H describes the preparation of the sulfonamides (XXVII) and the sulfones (XXIX). Treatment of the aryl bromide (VI) with t-butyl lithium results in metal-halogen exchange, and the resulting aryl lithium can be quenched with sulfur dioxide to afford the lithium salt (XXVI). This salt is then treated with phosphorous pentachloride and the resulting sulfonyl chloride is mixed with the appropriate amine to generate the corresponding sulfonamide (XXVII). Alternatively, aryl

bromide (VI) is converted to the aryl lithium species as described above and quenched with the appropriate disulfide to give the sulfide (XXVIII). This sulfide is then oxidized using standard procedures and oxidants such as m-chloroperbenzoic acid to give the sulfone (XXIX).

5 CHART I describes the preparation of the sulfones (XXXIV) in which the sulfone moiety is linked to the isochroman nucleus with a methylene tether of 1, 2, or 3 carbon atoms. In CHARTs I thru N, the extra carbon atom present (which becomes part of the X_1 linker) in the functionalities illustrated necessitates the "n" to be = 0-2, which corresponds to an n_1 in the 1,6-disubstituted isochromans (I). The
10 carboxylic acids (XXX) can be reduced to the primary alcohols (XXXI) using well-known techniques and reagents such as lithium aluminum hydride or borane. The alcohols (XXXI) can be converted to the corresponding bromides (XXXII) using well-known techniques and reagents such as phosphorous tribromide or carbon tetrabromide and triphenylphosphine. The bromides (XXXII) can be used to alkylate
15 thiols using techniques known to those skilled in the art to provide the sulfides (XXXIII). The sulfides (XXXIII) can be oxidized to the sulfones (XXXIV) by using standard oxidative techniques and reagents such as osmium tetroxide and N-methylmorpholine N-oxide.

CHART J describes the preparation of the sulfonamides (XXXVII) in which
20 the sulfonamide moiety is linked to the isochroman nucleus with a methylene tether of 1, 2, or 3 carbon atoms. The bromides (XXXII) can be treated with sodium sulfite in refluxing 10% aqueous sodium hydroxide solution to provide the sulfonate salts (XXXV). The sulfonate salts are converted to the sulfonyl chlorides (XXXVI) using phosphorous pentachloride and phosphorous oxychloride. Treatment of (XXXVI)
25 with amines ($NQ_{1-1}Q_{1-2}$) gives the sulfonamides (XXXVII).

CHART K describes the preparation of substituted imidazoles and triazoles which are linked to the isochroman nucleus with a methylene tether of 1, 2 or 3 carbon atoms. In CHART K, when the "X" in the substituent is nitrogen the substituent is a triazole and when the "X" is a carbon atom the substituent is an
30 imidazole. These compounds are obtained by alkylating the appropriate imidazole or triazole with the bromides (XXXII). The imidazoles and triazoles are either commercially available or can be prepared as described in the chemical literature using techniques known to those skilled in the art. In this fashion are obtained the compounds (XXXVIII).

35 CHART L describes the preparation of the oxadiazoles (XL) which are linked to the isochroman nucleus with a methylene tether of 1, 2 or 3 carbon atoms. The

requisite oxime amides are prepared from the corresponding nitriles using hydroxylamine hydrochloride and sodium metal in methanol according to the procedure disclosed in *J. Med. Chem.*, 36, 1529 (1993). The nitriles are either commercially available or can be readily prepared as described in the chemical literature using techniques known to those skilled in the art. The oxime amides are treated with either sodium hydride or sodium metal and then further treated with the ester (XXXIX) according to the procedure disclosed in *J. Med. Chem.*, 36, 1529 (1993) to give the heterocyclic products (XL).

CHART M describes the preparation of mono-(XLII) or di-substituted tetrazoles (XLIII) which are linked to the isochroman nucleus with a methylene tether of 1, 2 or 3 carbon atoms. The bromides (XXXII) are converted to the corresponding nitriles (XLI) via a cyanide displacement reaction known to those skilled in the art. These nitriles are then converted to the mono-substituted tetrazoles (XLII) by the action of sodium azide in a solvent such as N-methyl-2-pyrrolidinone according to the procedure disclosed in *J. Med. Chem.*, 38, 1799 (1995). The mono-substituted tetrazoles are converted to the di-substituted tetrazoles (XLIII) by standard alkylation reactions (R-X, acetonitrile, triethylamine).

CHART N describes the preparation of the isomeric triazoles (XLIII) and (XLIV) which are linked to the isochroman nucleus with a methylene tether of 1, 2 or 3 carbon atoms. The nitriles (XLI) can be converted to the imidoesters (XLII) by the action of ethanolic hydrochloric acid according to the procedure disclosed in *J. Med. Chem.*, 38, 1799 (1995). Following this same procedure, treatment of (XLII) with alkyl hydrazines (either commercially available or prepared by means known in the literature) in a solvent such as ethanol and subsequent treatment with formic acid gives a mixture of (XLIII) and (XLIV). This mixture can be separated into its components by standard laboratory techniques such as chromatography or crystallization.

CHART O describes the preparation of substituted triazoles and oxadiazoles from primary carboxamides (VII) using methods known to those skilled in the art, see for example, *J. Org. Chem.*, 44, 4160-4164 (1979). When "X" in (O-2) is nitrogen, the product is a triazole. When "X" in (O-2) is oxygen, the product is a oxadiazole. Treatment of amides (VII) with dimethylamide acetals in non-polar, high boiling solvents such as toluene at 50-100° generates the intermediate (O-1). This intermediate is then reacted with either hydrazine, 1-substituted hydrazines, hydroxylamine, or N-substituted hydroxylamines under acidic conditions (usually acetic acid) at room temperature (20-25°) to give the indicated products (O-2).

CHART P describes the preparation of mono-substituted oxazole derivatives (P-2) from the corresponding propargylic amides (P-1) using methods known to those skilled in the art, see for example, *J. Med. Chem.*, 36, 1529 (1993). Treatment of (P-1) with mercuric acetate in refluxing acetic acid generates the illustrated oxazoles (P-2).

CHART Q discloses the synthesis of piperazine (Q-3) in which R₁ is an electron withdrawing substituent ortho or para to the aniline nitrogen of the piperazine.

Amine (Q-1) and aryl halide (Q-2) where a fluorine or bromine atom is ortho or para to the electron withdrawing substituent are heated without solvent or in a polar solvent such as water, DMF, dimethylacetamide, or other such solvents with a base (either excess (Q-1) or diisopropylethylamine, potassium carbonate or the like) at elevated temperature (60-200°) to give piperazine (Q-3).

CHART R discloses the synthesis of piperazines (R-3). Nitro aryl (R-1) is reduced to aniline (R-2) using hydrogen and a catalyst such as palladium on carbon, Raney nickel, stannous chloride or the like. Alternatively, (R-2) can be purchased commercially. Aniline (R-2) is then heated (about 80 to about 165°) with bis(2-haloethyl)amine hydrochloride with or without added base in solvents such as THF, toluene, ethylene glycol, or chlorobenzene to give piperazine (R-3).

CHART S illustrates an the preparation of an important intermediate useful for the preparation of compounds claimed in this patent. The hydroxy amide (S-3) is conveniently prepared from the hydroxy bromide (S-1; see CHART T) either directly via a palladium-mediated amidation reaction (identical to that illustrated in CHART B) or via the intermediacy of an ester (S-2). This ester is readily synthesized from (S-1) via a palladium-based carbonylation reaction known to those skilled in the art as similar to those already described. The conversion of (S-2) to the amide (S-3) is accomplished by treating (S-2) with an alcoholic solution (typically methanol) containing the appropriate amine reagent in a manner similar to that described in *J. Org. Chem.*, 52, 2033-2036 (1987). This reaction can be carried at at room temperature (20-25°) or preferably at 50-100°.

CHART T illustrates two important alternative approaches to the compounds claimed in this patent. Reduction of the previously described acid (IV) using standard reducing conditions and reagents (preferred is borane) gives the primary alcohol (S-1). This compound is then converted into the hydroxy amide (S-3) as described in CHART S. This hydroxy amide is converted into an alkylating agent (T-2, typical X is a mesylate or a bromide) by standard chemical transformations

and is used to alkylate an appropriate 4-arylpiperazine or 4-arylpiperidine to provide the final compounds (IX). Alternatively, the hydroxy bromide (S-1) is converted into an alkylating agent (T-1, typical X is a mesylate or a bromide) by standard chemical transformations and is used to alkylate an appropriate 4-arylpiperazine or 4-

5 arylpiperidine to provide the bromides (VI). These bromides are then converted into final compounds (IX) as previously illustrated.

CHART U discloses the conversion of chiral bromo acid (U-1) which is (XI) in CHART C to the amide alcohol (U-5) which is (S-3) in CHART T. The bromo acid (U-1) is alkylated to the bromo ester (U-2) using methods known to those skilled in
10 the art. An example is treatment of the bromo acid (U-1) with 1,1'-carbonyldiimidazole in a solvent such as THF to form an activated ester, followed by an alcohol to form the bromo ester (U-2). The bromo ester (U-2) is then treated under the conditions discussed for CHART V for the conversion of (V-1) to (V-2), to give the amide ester (U-3). Hydrolysis of the amide ester (U-3) with aqueous base,
15 taking care not to also hydrolyze the amide group of (U-3), followed by aqueous acid treatment, gives acid amide (U-4). The acid amide (U-4) is then treated with reducing agents such as borane or borane-methyl sulfide in THF as solvent to give the amide alcohol (U-5).

CHART V discloses a method for the conversion of ester (V-1) to diamide (V-
20 4). Ester (V-1) is prepared from bromo isochroman (T-1) and piperazine (Q-3), CHART Q, by methods discussed for CHART T. Ester (V-1) is converted to the amide ester (V-2) using palladium (II) acetate, a co-catalyst such as bis(diphenylphosphino)propane, diisopropylethylamine, carbon monoxide and methyl amine as discussed with regard to CHART B. Solvents for the conversion may be
25 chosen from DMF, dimethylacetamide, N-methylformamide and acetonitrile with dimethylacetamide and N-methylformamide preferred when methyl amine gas is used. Preferred temperatures are 50 to 120°. The amide ester (V-2) is further converted to the corresponding amide acid (V-3) using aqueous base followed by acid neutralization to give (V-3) or a salt thereof. When the ester is the tert-butyl ester,
30 trifluoroacetic acid or hydrochloric acid in solvents such as ether or ethyl acetate are used to convert the amide ester (V-2) to the corresponding amide acid (V-3). The amide acid (V-3) then is treated with a condensing agent and an amine to provide the corresponding diamide (V-4) using methods known to those skilled in the art such as discussed with regard to CHART W.

35 CHART W discloses a synthesis of hydroxamic acid derivatives (W-7) and (W-8). These compounds are also prepared by the processes of CHARTS A and B. The

alcohol group of the ester alcohol (S-2), Chart S, is protected with a suitable protecting group such as a dihydropyranyl group, which is stable to basic conditions, to give tetrahydropyranyl ether (W-2). The ester group of the ether (W-2) is then hydrolyzed with aqueous base and then acidified carefully (so as not to remove the protecting group) to give carboxylic acid (W-3). The carboxylic acid (W-3) is then treated with a condensing agent such as carbonyldiimidazole, diethylcyanophosphonate, dicyclohexylcarbodiimide, or other suitable condensing agents (see, for example, *Major Methods of Peptide Bond Formation*, Volume One of *The Peptides: Analysis, Synthesis, Biology*, E. Gross and J. Meienhofer, eds., Academic Press) in solvents such as dichloromethane or DMF and a base such as triethylamine in the presence of an amine such as an O-alkyl, N-alkylhydroxylamine (itself prepared by the method of Sulsky et al., *Tet. Lett.* 30, 31-34 (1989) to give hydroxamate ether (W-4). The hydroxamate ether (W-4) is then deprotected using methods such as those found in *Protective Groups in Organic Synthesis* by Theodora W. Greene and published by John Wiley and Sons to give the hydroxamate alcohol (W-5). The hydroxyl group of hydroxamate alcohol (W-5) is then converted to a leaving group by one of the many methods known to those skilled in the art, such as forming a mesylate, tosylate, or chloride, bromide, or iodide, to give the hydroxamate (W-6); the hydroxamate (W-6) is then coupled to an amine such as piperazine (Q-3) of CHART Q or piperazine (R-3) of CHART R or commercially available amines to give hydroxamate amine (W-7). The hydroxamate amine (W-7) can be further converted to hydroxamic acid amine (W-8) when alkyl-1 is a protecting group such as benzyl by palladium on carbon or other such methods known to those skilled in the art.

CHART X discloses the synthesis of the carbamate (X-6). The phenol/aniline (X-1) is reacted with alkyl diethoxypropionate in a similar manner as the transformation of the 3-bromophenethanol (II) to the corresponding isochroman ester (III) of CHART A, to give the phenol/aniline ester (X-2). The phenol/aniline ester (X-2) is hydrolyzed to the phenol/aniline acid (X-3) by aqueous base followed by aqueous acid. The phenol/aniline acid (X-3) is then condensed with piperazines (Q-3) of CHART Q or (R-3) of CHART R or commercially available amines to give the phenol/aniline amide (X-4) using methods such as those discussed in CHART W. The phenol/aniline amide (X-4) is then reduced to the phenol/aniline amine (X-5) with reducing agents such as borane or borane-methyl sulfide in solvents such as THF. The phenol/aniline amine (X-5) is then reacted with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or sodium hydride or other such bases and an

isocyanate in dichloromethane or THF as the solvent to give the carbamate/urea (X-6).

CHART Y discloses the synthesis of racemic (Y-5) starting with the phenol (Y-1). The phenol (Y-1) is reacted with chloropropionaldehyde diethyl acetal in the presence of a Lewis acid such as boron trifluoride etherate or titanium tetrachloride, in solvents such as dichloromethane or nitromethane, to give the chloro phenol (Y-2). The phenol of chloro phenol (Y-2) is then converted to a leaving group using trifluoromethanesulfonic anhydride or N-phenyltrifluoromethanesulfonimide in the presence of a base such as triethylamine and optionally adding a catalyst such as 4-dimethylaminopyridine and in a solvent such as dichloromethane, to give the triflate (Y-3). The triflate (Y-3) is then be converted to the amide chloride (Y-4) using palladium (II) acetate, a co-catalyst, diisopropylethylamine, carbon monoxide and methyl amine as discussed with regard to CHART W. Solvents for the conversion include DMF, dimethylacetamide, N-methylformamide, and acetonitrile, with dimethylacetamide and N-methylformamide preferred when methyl amine gas is used. Preferred temperatures are about 50 to about 120°. The amide chloride (Y-4) is then stirred at 60 to 110° in the presence of the piperazine (Q-3) or (R-3) or commercial amines, a base such as triethylamine or diisopropylethylamine, and a solvent such as ethylene glycol, THF, DMF or acetonitrile to give the amide amine (Y-5).

CHART Z describes the preparation of a number of aniline-based derivatives (Z-2), (Z-3), (Z-4), (Z-5), (Z-6) and (Z-7). These compounds arise from standard derivations of the aniline (Z-1), itself prepared from the bromide (VI) via metal-halogen exchange (typically using either *n*-butyllithium or *t*-butyllithium) followed addition of diphenylphosphoryl azide (usually in THF at -78°) and subsequent reduction with bis(2-methoxyethoxy)aluminum hydride. This conversion of (VI) to (Z-1) closely follows known chemistry, see *Tetrahedron Letters*, 25, 429-432 (1984) and *J. Am. Chem. Soc.*, 94, 6203-6205 (1972). The reactions converting (Z-1) into the derivatives (Z-2)-(Z-7) are standard transformations, known to those skilled in the art, and involve acylations (typically with acid chlorides or anhydrides), mesylations, and standard lactam reductions as previously described.

CHART AA illustrates the preparation of one-carbon homologated isochroman-6-carboxamides (AA-5). The sequence involves metal-halogen exchange of the bromide (VI) using alkyl lithium reagents (typically *t*-butyl lithium) followed by quenching of the resulting anion with DMF to give the aldehyde (AA-1). This aldehyde is reduced using standard reagents (such as sodium borohydride in THF),

and the resulting alcohol (AA-2) is converted to the nitrile (AA-3) by activation with methanesulfonyl chloride and displacement of the resulting mesylate with cyanide anion. Hydrolysis of the nitrile is carried out by treating a solution of (AA-3) in DMF with 30% hydrogen peroxide in the presence of potassium carbonate and stirring the reaction mixture at room temperature (20-25°) for 20 hrs. The resulting amide (AA-4) is converted into substituted amides (AA-5) as previously described.

CHART BB illustrates a generalized procedure for the preparation of tethered amines such as (BB-2) by reduction of the corresponding amides (BB-1) utilizing standard amide reduction conditions as previously described (typically either employing borane or lithium aluminum hydride in THF).

CHART CC illustrates that functional groups on the arylpiperazine portion of these molecules (ie, R1 and R2) can be transformed into other functional groups. Depicted is a standard hydrogenolytic debenzylation of the an aryl-ether (CC-1) to provide the corresponding phenol (CC-2). Conversion of the phenol (CC-2) into the corresponding trifluoromethanesulfonate (CC-3) by standard methods is illustrative of typical derivations of phenols such as (CC-2). Conversion of the triflate (CC-3) into numerous derivatives can be accomplished by palladium-mediated couplings. For example, coupling (CC-3) with enol-ethers provides ketone-substituted aryl derivatives. These reactions are typically carried out in DMF or acetonitrile using palladium(II) acetate, 1,3-bis(diphenylphosphino)propane, and triethylamine at elevated temperatures (50-120°).

CHART DD illustrates an alternative preparation of isochroman-6-triazoles (DD-4) and isochroman-6-oxadiazoles (DD-6). The primary alcohol of the previously-described amide (DD-1) is be protected by standard techniques, preferably as the benzyl ether (P = -CH₂-phenyl). This material is be reacted with amide acetals as described in CHART O and the resulting intermediate (DD-2) is treated with hydrazine, substituted hydrazine, hydroxyl amine, or N-substituted hydroxyl amines as described in CHART O to generate the triazoles (DD-3) or oxadiazoles (DD-5). The protecting group "P" is removed using standard conditions (typically hydrogenolysis using a transition metal catalyst such as palladium or platinum) and the resulting alcohol can be activated (usually as a sulfonate ester or halide) and reacted with the appropriate aryl piperazine as described previously in CHART T.

For the 1,6-disubstituted isochromans (I) it is preferred that n₁ is 0 or 1; it is more preferred that n₁ is 0. It is preferred that R₁ is -O-R₁₋₁, -CF₃, -CO-N(R₁₋₁)₂, -CO-R₁₋₁ and it is preferred that R₁₋₁ is C₁-C₃ alkyl. It is preferred that R₂ is -H. It is preferred that Q₁ is selected from the group consisting of -CO-NQ₁₋₁Q₁₋₂, -SO₂-

$NQ_{1-1}Q_{1-2}$ and $-NQ_{1-1}Q_{1-2}$; it is more preferred that Q_1 is $-CO-NQ_{1-1}Q_{1-2}$.

For the aromatic bicyclic amines (ABA) it is preferred that W_1 is nitrogen (-N-) and it is preferred that one of R_1 or R_2 is -H. It is preferred that Q_1 is (A) $-CO-NQ_{1-1}Q_{1-2}$ and that Q_{1-1} is -H and that Q_{1-2} is $-CH_3$ (C_1 alkyl).

- 5 The 1,6-disubstituted isochroman (I) and aromatic bicyclic amines (ABA) contain an asymmetric center and therefore produce two enantiomers one "S" which is (-) and the other "R" which is (+). In some cases both enantiomers (+) and (-) are useful in the same way as the optically impure (racemic, $\pm$) mixture. Hence, they may be utilized in the racemic form without separating them. However, if it is
- 10 desired to utilize one of the enantiomers, the optically impure mixture or intermediate can be resolved by means known to those skilled in the art. It is preferable to resolve the racemic intermediate (II) using the lipase method described in CHART C, alternatively chemical methods known to those skilled in the art can be used, see for example, Optical Resolution Procedures for Chemical Compounds,
- 15 Vol 1, Amines and Related Compounds, Paul Newman, Optical Resolution Information Center, Manhattan College, Riverdale, NY, 10471, 1978. The optically impure mixture can also be separated using chromatographic techniques on chiral stationary phases, see Chromatographic Enantioseparation, 2nd edition, John Wiley & Sons, NY, 1992. These optically pure compounds are then used in the same way
- 20 as the racemic mixture. When used in this patent application the term 1,6-disubstituted isochroman (I) aromatic bicyclic amines (ABA) refers to and includes both enantiomers as well as optically impure forms thereof, the most common of which is a racemic mixture ($\pm$, dl).

- Some 1,6-disubstituted isochroman (I) and aromatic bicyclic amines (ABA)
- 25 contain two asymmetric centers and therefore four stereoisomers (SS, RR, SR, RS) exist producing two diastereomeric pairs of enantiomers, one SS,RR and the other SR,RS. The diastereomeric pairs of enantiomers can be readily separated by means known to those skilled in the art. When used in this patent application the term 1,6-disubstituted isochroman(I) and aromatic bicyclic amines (ABA) includes all four
- 30 enantiomers as well as optically impure forms thereof, the most common of which is a racemic mixture ($\pm$).

- The 1,6-disubstituted isochroman (I) and aromatic bicyclic amines (ABA) are amines, and as such form acid addition salts when reacted with acids of sufficient strength. Pharmaceutically acceptable salts include salts of both inorganic and
- 35 organic acids. The pharmaceutically acceptable salts are sometimes but not always preferred over the corresponding free amines since they produce compounds which

are more water soluble and more crystalline. The preferred pharmaceutically acceptable salts include salts of the following acids methanesulfonic, hydrochloric, hydrobromic, sulfuric, phosphoric, nitric, benzoic, citric, tartaric, fumaric, maleic, $\text{CH}_3(\text{CH}_2)_n\text{-COOH}$ where n is 0 thru 4, $\text{HOOC}(\text{CH}_2)_n\text{-COOH}$ where n is as defined
5 above.

The 1,6-disubstituted isochroman (I) and aromatic bicyclic amines (ABA) of this invention possess selective pharmacological properties and are useful in treating humans with vascular headaches, particularly migraine and cluster headaches. The 1,6-disubstituted isochroman (I) and aromatic bicyclic amines (ABA) are also useful
10 as analgesic agents.

In clinical practice the 1,6-disubstituted isochroman (I) and aromatic bicyclic amines (ABA) of the present invention will normally be administered orally, nasally, rectally, vaginally or by injection in the form of pharmaceutical compositions containing the active ingredient either as a free base or as a pharmaceutically
15 acceptable acid addition salt in association with one or more pharmaceutically acceptable carriers. It is preferred that the 1,6-disubstituted isochroman (I) and aromatic bicyclic amines (ABA) be administered either orally or nasally.

For therapeutical treatment of migraine or cluster headaches and for treatment of pain as analgesic agents the suitable daily doses of the 1,6-
20 disubstituted isochroman (I) and aromatic bicyclic amines (ABA) are from about 0.005 to about 50 mg/kg for oral or nasal application, preferably from about 0.1 to about 30 mg/kg, and from about 0.05 to about 10 mg/kg for parenteral application, preferably from about 0.03 to about 3 mg/kg. The use and administration to a patient to be treated in the clinic would be readily apparent to a person of ordinary
25 skill in the art.

The exact dosage and frequency of administration depends on the particular 1,6-disubstituted isochroman (I) or aromatic bicyclic amine (ABA) used, the particular condition being treated, the severity of the condition being treated, the age, weight, general physical condition of the particular patient, other medication
30 the individual may be taking as is well known to those skilled in the art and can be more accurately determined by measuring the blood level or concentration of the 1,6-disubstituted isochroman (I) and/or aromatic bicyclic amine (ABA) in the patient's blood and/or the patient's response to the particular condition being treated.

DEFINITIONS AND CONVENTIONS

35 The definitions and explanations below are for the terms as used throughout this entire document including both the specification and the claims.

I. CONVENTIONS FOR FORMULAS AND DEFINITIONS OF VARIABLES

The chemical formulas representing various compounds or molecular fragments in the specification and claims may contain variable substituents in addition to expressly defined structural features. These variable substituents are identified by a letter or a letter followed by a numerical subscript, for example, "Z₁" or "R_i" where "i" is an integer. These variable substituents are either monovalent or bivalent, that is, they represent a group attached to the formula by one or two chemical bonds. For example, a group Z₁ would represent a bivalent variable if attached to the formula CH₃-C(=Z₁)H. Groups R_i and R_j would represent monovalent variable substituents if attached to the formula CH₃-CH₂-C(R_i)(R_j)-H. When chemical formulas are drawn in a linear fashion, such as those above, variable substituents contained in parentheses are bonded to the atom immediately to the left of the variable substituent enclosed in parenthesis. When two or more consecutive variable substituents are enclosed in parentheses, each of the consecutive variable substituents is bonded to the immediately preceding atom to the left which is not enclosed in parentheses. Thus, in the formula above, both R_i and R_j are bonded to the preceding carbon atom.

Chemical formulas or portions thereof drawn in a linear fashion represent atoms in a linear chain. The symbol "-" in general represents a bond between two atoms in the chain. Thus CH₃-O-CH₂-CH(R_i)-CH₃ represents a 2-substituted-1-methoxypropane compound. In a similar fashion, the symbol "=" represents a double bond, e.g., CH₂=C(R_i)-O-CH₃, and the symbol "≡" represents a triple bond, e.g., HC≡C-CH(R_i)-CH₂-CH₃. Carbonyl groups are represented in either one of two ways: -CO- or -C(=O)-, with the former being preferred for simplicity.

Chemical formulas of cyclic (ring) compounds or molecular fragments can be represented in a linear fashion. Thus, the compound 4-chloro-2-methylpyridine can be represented in linear fashion by N^{*}=C(CH₃)-CH=CCl-CH=C^{*}H with the convention that the atoms marked with an asterisk (*) are bonded to each other resulting in the formation of a ring. Likewise, the cyclic molecular fragment, 4-(ethyl)-1-piperazinyI can be represented by -N^{*}-(CH₂)₂-N(C₂H₅)-CH₂-C^{*}H₂.

A rigid cyclic (ring) structure for any compounds herein defines an orientation with respect to the plane of the ring for substituents attached to each carbon atom of the rigid cyclic compound. For saturated compounds which have two substituents attached to a carbon atom which is part of a cyclic system, -C(X₁)(X₂)- the two substituents may be in either an axial or equatorial position relative to the ring and may change between axial/equatorial. However, the position of the two substituents

relative to the ring and each other remains fixed. While either substituent at times may lie in the plane of the ring (equatorial) rather than above or below the plane (axial), one substituent is always above the other. In chemical structural formulas depicting such compounds, a substituent (X_1) which is "below" another substituent (X_2) will be identified as being in the alpha (α) configuration and is identified by a broken, dashed or dotted line attachment to the carbon atom, i.e., by the symbol "- - -" or "...". The corresponding substituent attached "above" (X_2) the other (X_1) is identified as being in the beta (β) configuration and is indicated by an unbroken line attachment to the carbon atom.

- 10 When a variable substituent is bivalent, the valences may be taken together or separately or both in the definition of the variable. For example, a variable R_i attached to a carbon atom as $-C(=R_i)-$ might be bivalent and be defined as oxo or keto (thus forming a carbonyl group $(-CO-)$ or as two separately attached monovalent variable substituents $\alpha-R_{i,j}$ and $\beta-R_{i,k}$. When a bivalent variable, R_i , is defined to consist of two monovalent variable substituents, the convention used to define the bivalent variable is of the form " $\alpha-R_{i,j}:\beta-R_{i,k}$ " or some variant thereof. In such a case both $\alpha-R_{i,j}$ and $\beta-R_{i,k}$ are attached to the carbon atom to give $-C(\alpha-R_{i,j})(\beta-R_{i,k})-$. For example, when the bivalent variable R_6 , $-C(=R_6)-$ is defined to consist of two monovalent variable substituents, the two monovalent variable substituents are $\alpha-R_{6,1}:\beta-R_{6,2}$, ..., $\alpha-R_{6,9}:\beta-R_{6,10}$, etc, giving $-C(\alpha-R_{6,1})(\beta-R_{6,2})-$, ..., $-C(\alpha-R_{6,9})(\beta-R_{6,10})-$, etc. Likewise, for the bivalent variable R_{11} , $-C(=R_{11})-$, two monovalent variable substituents are $\alpha-R_{11,1}:\beta-R_{11,2}$. For a ring substituent for which separate α and β orientations do not exist (e.g. due to the presence of a carbon carbon double bond in the ring), and for a substituent bonded to a carbon atom which is not part of a ring the above convention is still used, but the α and β designations are omitted.

- Just as a bivalent variable may be defined as two separate monovalent variable substituents, two separate monovalent variable substituents may be defined to be taken together to form a bivalent variable. For example, in the formula $-C_1(R_i)H-C_2(R_j)H-$ (C_1 and C_2 define arbitrarily a first and second carbon atom, respectively) R_i and R_j may be defined to be taken together to form (1) a second bond between C_1 and C_2 or (2) a bivalent group such as oxa $(-O-)$ and the formula thereby describes an epoxide. When R_i and R_j are taken together to form a more complex entity, such as the group $-X-Y-$, then the orientation of the entity is such that C_1 in the above formula is bonded to X and C_2 is bonded to Y. Thus, by convention the designation "... R_i and R_j are taken together to form $-CH_2-CH_2-O-CO-$..." means a lactone in which the carbonyl is bonded to C_2 . However, when

designated "... R_j and R_i are taken together to form -CO-O-CH₂-CH₂-the convention means a lactone in which the carbonyl is bonded to C₁.

The carbon atom content of variable substituents is indicated in one of two ways. The first method uses a prefix to the entire name of the variable such as "C₁-C₄", where both "1" and "4" are integers representing the minimum and maximum number of carbon atoms in the variable. The prefix is separated from the variable by a space. For example, "C₁-C₄ alkyl" represents alkyl of 1 through 4 carbon atoms, (including isomeric forms thereof unless an express indication to the contrary is given). Whenever this single prefix is given, the prefix indicates the entire carbon atom content of the variable being defined. Thus C₂-C₄ alkoxycarbonyl describes a group CH₃-(CH₂)_n-O-CO- where n is zero, one or two. By the second method the carbon atom content of only each portion of the definition is indicated separately by enclosing the "C₁-C_j" designation in parentheses and placing it immediately (no intervening space) before the portion of the definition being defined. By this optional convention (C₁-C₃)alkoxycarbonyl has the same meaning as C₂-C₄ alkoxy-carbonyl because the "C₁-C₃" refers only to the carbon atom content of the alkoxy group. Similarly while both C₂-C₆ alkoxyalkyl and (C₁-C₃)alkoxy(C₁-C₃)alkyl define alkoxyalkyl groups containing from 2 to 6 carbon atoms, the two definitions differ since the former definition allows either the alkoxy or alkyl portion alone to contain 4 or 5 carbon atoms while the latter definition limits either of these groups to 3 carbon atoms.

When the claims contain a fairly complex (cyclic) substituent, at the end of the phrase naming/designating that particular substituent will be a notation in (parentheses) which will correspond to the same name/designation in one of the CHARTS which will also set forth the chemical structural formula of that particular substituent.

Statement About Nomenclature

Several methods exist for the naming of the compounds of this invention, differing principally in the use of the term "isochroman" or "3,4-dihydro-1H-2-benzopyran" for the bicyclic group within the compound. For example, one name for the compound of example 6 is (S)-(-)-1-[2-[4-[4-(aminocarbonyl)phenyl]-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide or (S)-(-)-1-(benzamide-4-yl)-4-[2-(6-methylaminocarbonylisochroman-1-yl)ethyl]piperazine. Another name is (S)-1-[2-[4-[4-(aminocarbonyl)phenyl]-1-piperazinyl]ethyl]-3,4-dihydro-N-methyl-1H-2-benzopyran-6-carboxamide.

II. DEFINITIONS

All temperatures are in degrees Centigrade.

TLC refers to thin-layer chromatography.

HPLC refers to high pressure liquid chromatography.

5 THF refers to tetrahydrofuran.

DMF refers to dimethylformamide.

DMSO refers to dimethylsulfoxide.

LDA refers to lithium diisopropylamide.

p-TSA refers to p-toluenesulfonic acid monohydrate.

10 TEA refers to triethylamine.

BOC refers to 1,1-dimethylethoxy carbonyl or tert-butoxycarbonyl -CO-O-C(CH₃)₃.

DMAP refers to dimethylaminopyridine, (CH₃)₂N-pyridin-1-yl.

TFA refers to trifluoroacetic acid, CF₃-COOH.

15 Saline refers to an aqueous saturated sodium chloride solution.

Chromatography (column and flash chromatography) refers to purification/separation of compounds expressed as (support; eluent). It is understood that the appropriate fractions are pooled and concentrated to give the desired compound(s).

20 IR refers to infrared spectroscopy.

CMR refers to C-13 magnetic resonance spectroscopy, chemical shifts are reported in ppm (δ) downfield from TMS.

NMR refers to nuclear (proton) magnetic resonance spectroscopy, chemical shifts are reported in ppm (δ) downfield from tetramethylsilane.

25 - ϕ refers to phenyl (C₆H₅).

$[\alpha]_D$ refers to the angle of rotation of plane polarized light (specific optical rotation) at 25° with the sodium D line (589A).

MS refers to mass spectrometry expressed as m/e or mass/charge unit.

30 [M + H]⁺ refers to the positive ion of a parent plus a hydrogen atom. EI refers to electron impact. CI refers to chemical ionization. FAB refers to fast atom bombardment.

HRMS refers to high resolution mass spectrometry.

Ether refers to diethyl ether.

35 Pharmaceutically acceptable refers to those properties and/or substances which are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical

point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

When solvent pairs are used, the ratios of solvents used are volume/volume (v/v).

- 5 Pharmaceutically acceptable anion salts include mesylate, chloride, sulfate, phosphate, nitrate, citrate, $\text{CH}_3(\text{CH}_2)_{n_1}\text{COO}^{-1}$ where n_1 is 0 thru 4, $^{-1}\text{OOC}(\text{CH}_2)_{n_1}\text{COO}^{-1}$ where n is as defined above, $^{-1}\text{OOC-CH=CH-COO}^{-1}$, $\phi\text{-COO}^{-1}$,

EXAMPLES

- Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following detailed examples describe how to prepare the various compounds and/or perform the various processes of the invention and are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques.

PREPARATION 1 4-(Piperazin-1-yl)benzamide

- A mixture of 4-fluorobenzamide (2.45 g, 17.6 mmol), piperazine (7.56 g, 87.9 mmol) and water (10 mL) is stirred at 100° for 24 hr. After cooling, the solid is collected and washed with water and toluene and then dried under reduced pressure to give the title compound, mp = 240-248°; MS (M/Z) at 205; NMR (DMSO-d₆) 2.59, 2.80, 3.14, 6.90, 7.02, 7.72 and 7.73 δ.

PREPARATION 2 N-[4-(Trifluoromethyl)phenyl]piperazine

- A 100 mL flask equipped with spinbar was charged with 4-bromobenzotrifluoride (19.70 g, 0.088 mol) and piperazine (37.71 g, 0.438 mol). The reactants were heated to 130°. After 48 hours, the mixture contained significant amounts of precipitate and is cooled to 20-25°. During the cooling, the reaction mixture is diluted with sodium hydroxide (3N, 200 mL) resulting in additional amounts of precipitate and is extracted twice with ethyl acetate (200 mL). If the reaction mixture is allowed to cool to 20-25° before adding aqueous base, the reaction becomes a solid mass making further manipulations difficult. The combine organics are washed once with saline (300 mL), dried over magnesium sulfate, filtered, and concentrated to give the product. Recrystallizations from hexanes gives the title compound, mp 87-89° (lit. 86-88°), R_f = 0.20 (methanol/dichloromethane, 7/93).

EXAMPLE 1 (S)-(-)-1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]-

isochroman-6-carboxamide (S)-(VII) also known as (S)-(-)-1-(4-Methoxyphenyl)-4-[2-(6-aminocarbonylisochroman-1-yl)-ethyl]piperazine

Step 1: Ethyl (6-bromoisochroman-1-yl)acetate (III)

5 A mixture of 3-bromophenethyl alcohol (II, 14.8 g) in dichloromethane (37 mL) under argon is cooled to 0° with an ice bath. Ethyl 3,3-diethoxypropionate (90%, 19.1 mL) is added via syringe. A titanium tetrachloride solution (1 M in methylene chloride, 236 mL) is added via a canula to an addition funnel and added semi-dropwise to the reaction mixture over one hr. The reaction is then refluxed for
10 18 hr, after which time it is poured into a mixture of aqueous hydrochloric acid (1N) and saline (1/2) and extracted with methylene chloride. The organic phases are combined, dried over sodium sulfate, filtered, and concentrated. The concentrate is purified by chromatography (silica gel; ethyl acetate/hexane, 10/90) to give ethyl (6-bromoisochroman-1-yl)acetate (III); $R_f = 0.40$ (ethyl acetate/hexane, 25/75); IR (neat)
15 1736, 1483, 1374, 1288, 1280, 1183, 1163, 1110, 1050, 1037 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.30, 7.28, 6.92, 5.17, 4.20, 4.10, 3.79, 3.01-2.91, 2.87-2.65 and 1.28 δ ; CMR (75 MHz, CDCl_3) 170.7, 136.0, 135.5, 131.6, 129.1, 126.0, 120.2, 62.6, 60.5, 41.3, 28.3 and 13.9 δ ; HRMS Calcd for $\text{C}_{13}\text{H}_{15}\text{O}_3\text{Br} = 298.0205$, found = 298.0204.

Step 2: (R)-(+)-Ethyl (6-bromoisochroman-1-yl)acetate (XII) and (S)-(-)-(6-bromoisochroman-1-yl)acetic acid (XI).

Ethyl (6-bromoisochroman-1-yl)acetate (III, Step 1, 29.49 g), Amano P-30 lipase (15 g, lot #LPSAR01520, act = 32,600 u/g), and pH 7 buffer (590 mL) are combined. The reaction is stirred vigorously and the hydrolysis is followed by HPLC as follows. A 100 μL aliquot is added to an opticlear vial containing hydrochloric
25 acid (one drop). Ethyl acetate (1.5 mL) is then added to the vial and the contents are mixed well. The resulting mixture is filtered through celite and assayed by HPLC ($\mu\text{Bondapak C18}$ 3.9 mm x 30 cm reverse-phase column, 10% acetonitrile/90% phosphate buffer (4 L water, 5.22 g sodium dihydrogen phosphate (hydrate), 0.76 mL phosphoric acid) gradient to 85/15 over 15 min, then isocratic at that ratio, 2
30 mL/min, detector at 215 nm), (XI) $R_t = 10.5$ min., (XII) $R_t = 13.5$ min. When the reaction reached the 50% conversion point, it is filtered and the filtrate is rinsed successively with water aqueous hydrochloric acid (1N) and ethyl acetate, several times. The filtrates are combined and extracted (two times) with ethyl acetate. The combined organic extracts are washed with an equal volume of saturated aqueous
35 sodium carbonate (3 x), dried over sodium sulfate, filtered and concentrated to give enantiomerically enriched (XII). The saturated aqueous sodium carbonate washes

are acidified with concentrated hydrochloric acid and extracted three times with methylene chloride, dried over sodium sulfate, filtered and concentrated to give (XI). The acid (XI) was assayed for enantiomeric purity as follows. A mixture of the acid (XI, 15 mg) in THF (0.5 mL) is reduced with borane-THF complex (1M in THF, 0.12 mL) at -5° to 20-25° over 18 hrs. The reaction is cooled to 0°, quenched with methanol (0.1 mL), then warmed to 20-25° and hydrochloric acid (1N, 0.4 mL) are added via pipette. The reaction is then heated to reflux for 10 min., at which point the volatiles are removed under reduced pressure and the residue is partitioned between ethyl acetate and saturated aqueous sodium carbonate. The organic phases are separated, dried over magnesium, filtered, and concentrated. The residue is weighed and diluted to a concentration of 10 mg/mL with a solution of isopropanol in hexane (7%). The mixture is assayed on a Chiracel OJ column using hexane/isopropanol 90/10, 15 min, 1 mL/min, then 80/20 for an additional 10 min (2 mL/min), wavelength 254 nm; (S)-alcohol R_t = 12.46 min, (R)-alcohol R_t = 10.46 min. The ester (XII) could be analyzed in a similar way following hydrolysis (vide infra). If needed, the enantiomerically enriched ester could be re-subjected to another cycle of the enzymatic hydrolysis if indicated by the HPLC analysis. In this manner (R)-(+)-ethyl (6-bromoisochroman-1-yl)acetate (XII) is obtained, (96% ee); R_f = 0.40 (ethyl acetate/hexane, 25/75); $[\alpha]_D^{+72}$ (c = 0.383, ethanol); IR (neat) 1736, 1483, 1374, 1288, 1280, 1183, 1163, 1110, 1050, 1037 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.30, 7.28, 6.92, 5.17, 4.20, 4.10, 3.79, 3.01-2.91, 2.87-2.65 and 1.28; CMR (75 MHz, CDCl_3) 170.7, 136.0, 135.5, 131.6, 129.1, 126.0, 120.2, 62.6, 60.5, 41.3, 28.3, 13.9; HRMS Calcd for $\text{C}_{13}\text{H}_{15}\text{O}_3\text{Br}$ = 298.0205, found = 298.0206. Also, (S)-(-)-(6-bromoisochroman-1-yl)acetic acid (XI) is isolated, (99% ee); mp = 160-161°; R_f = origin (ethyl acetate/hexane, 25/75); $[\alpha]_D^{-90}$ (c = 1, ethanol); IR (neat) 1711, 1482, 1428, 1440, 1330, 1297, 1111, 1101, 1003, 971 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.30, 6.92, 5.17, 4.18-4.11, 3.86-3.78 and 3.04-2.69; CMR (75 MHz, CDCl_3) 175.7, 136.2, 135.1, 132.0, 129.6, 126.2, 120.8, 72.4, 63.1, 45.5, 41.1 and 28.5 δ .

Step 3: (S)-(-)-1-[2-(6-Bromoisochroman-1-yl)acetyl]-4-(4-methoxyphenyl)-piperazine (S)-(V)

(S)-(-)-(6-bromoisochroman-1-yl)acetic acid (XI, Step 2, 3 g), N-(4-methoxyphenyl)piperazine (2.34 g) and dichloromethane (20 mL) are combined and cooled to 0°. Diethylcyanophosphate (2.0 mL) and triethylamine (1.7 mL) are added respectively via syringe. The ice bath is allowed to expire and the mixture is stirred at 20-25° for 18 hours. The reaction mixture is concentrated under reduced pressure to give crude material which is chromatographed (silica gel; ethyl acetate/hexane,

60-80/40-20) to give (S)-(-)-1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(4-methoxyphenyl)-piperazine (S)-(V) (which after recrystallization from ethyl acetate/hexane), mp = 122-123°; R_f = 0.26 (ethyl acetate/hexane, 70/30); $[\alpha]_D^{25}$ = - 86° (c = 0.99, ethanol); IR (mull) 1639, 1512, 1446, 1439, 1249, 1214, 1112, 1030, 1028, 820 cm^{-1} ; NMR (300
 5 MHz, CDCl_3) 7.32-7.26, 7.00, 6.88, 5.27, 4.16-4.07, 3.89, 3.80-3.60, 3.77, 3.05, 2.97-2.90, 2.76 and 2.65 δ ; CMR (75 MHz, CDCl_3) 168.9, 154.3, 145.2, 136.5, 136.2, 131.7, 129.3, 126.4, 120.3, 118.8, 114.4, 73.4, 63.4, 55.5, 51.3, 50.7, 46.1, 41.9, 39.9 and 28.7 δ .

Step 4: (S)-(-)-1-[2-(6-Bromoisochroman-1-yl)ethyl]-4-(4-methoxyphenyl)-
 10 piperazine (S)-(VI)

(S)-(-)-1-[2-(6-Bromoisochroman-1-yl)acetyl]-4-(4-methoxyphenyl)-piperazine ((S)-(V), Step 3, 3.7 g) in THF (84 mL) is cooled to 0° and a mixture of borane-THF complex, (1M in THF, 25 mL) is added via syringe. The ice bath is removed and the mixture is heated to reflux for 18 hrs. The reaction is cooled to 0°
 15 and slowly quenched with aqueous hydrochloric acid (1N, 100 mL), and refluxed for an additional 1.5 hrs. The mixture is cooled to 20-25° and the solvents are removed under reduced pressure, and the aqueous residue is diluted with saline and basified to pH 14 with aqueous sodium hydroxide. The mixture is extracted with dichloromethane and the combined organic phases are dried over sodium sulfate,
 20 filtered, and concentrated. The concentrate is purified by recrystallization from ethyl acetate/hexane to give (S)-(-)-1-[2-(6-bromoisochroman-1-yl)ethyl]-4-(4-methoxyphenyl)-piperazine (S)-(VI), mp = 85-86°; R_f = 0.23 (ethyl acetate); $[\alpha]_D^{25}$ = 48° (c = 0.73, ethanol); IR (neat) 1518, 1479, 1266, 1250, 1155, 1140, 1112, 1103, 1041, 818 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) 7.29, 7.27, 6.97, 6.85, 4.78, 4.14-4.07,
 25 3.76-3.69, 3.76, 3.10, 2.95, 2.70-2.50, 2.13 and 2.02 δ ; CMR (75 MHz, CDCl_3) 153.5, 145.5, 136.8, 136.0, 131.4, 129.0, 126.3, 119.7, 117.9, 114.2, 74.1, 62.5, 55.3, 54.4, 53.3, 50.4, 32.9 and 28.6 δ ; HRMS Calcd for $\text{C}_{22}\text{H}_{27}\text{N}_2\text{O}_2\text{Br}_1$ = 430.1256, found = 430.1270.

Step 5: (S)-(-)-1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]-isochroman-6-
 30 carboxamide (S)-(VII)

(S)-(-)-1-[2-(6-Bromoisochroman-1-yl)ethyl]-4-(4-methoxyphenyl)-piperazine ((S)-(VI), Step 4, 364 mg), palladium(II) acetate (98%, 9.7 mg) and 1,3-bis-diphenylphosphinopropane (97%, 22 mg). A carbon monoxide atmosphere is established in the vial, then into the reaction vessel are introduced via syringe DMF
 35 (2 mL), 1,1,1,3,3,3-hexamethyldisilazane (98%, 1.25 mL) and diisopropylethylamine (0.29 mL). The mixture is heated to 100° for 18 hr. After cooling to 20-25°, the

reaction separated into two phases. The reaction mixture is poured into aqueous hydrochloric acid (1N) and washed two times with ether. The acidic solution is basified with aqueous sodium hydroxide and extracted three times with ethyl acetate. The ethyl acetate phases are combined and concentrated. The is purified
 5 by chromatography (silica gel; methanol/dichloromethane, 5/95) to give (S)-(-)-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-isochroman-6-carboxamide (S)-(VII), mp = 186-187°; R_f = 0.27 (methanol/ethyl acetate, 10/90); $[\alpha]_D$ - 53° (c = 0.92, methylene chloride/methanol (1/1)); IR (mull) 3366, 3198, 1628, 1642, 1602, 1514, 1437, 1245, 1109 and 815 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.61-7.58, 7.18, 6.85, 5.90, 4.86, 4.18-
 10 4.11, 3.80-3.72, 3.76, 3.10, 2.99, 2.73, 2.66-2.49, 2.15 and 2.04 δ ; CMR (75 MHz, CDCl_3) 168.7, 153.5, 145.4, 142.0, 134.3, 131.0, 127.9, 124.8, 124.6, 117.8, 114.1, 74.2, 62.6, 55.2, 54.3, 53.2, 50.3, 32.8, 28.7 and 27.2 δ ; HRMS Calcd for $\text{C}_{29}\text{H}_{29}\text{N}_3\text{O}_3$ = 395.2209, found = 395.2227.

EXAMPLE 2 (R)-(+)-1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]-
 15 isochroman-6-carboxamide (R)-(VII) also known as (R)-(+)-1-(4-Methoxyphenyl)-4-[2-(6-aminocarbonylisochroman-1-yl)-ethyl]piperazine

Step 1: (R)-(+)-6-(Bromoisochroman-1-yl)acetic acid (R)-IV.

A mixture of lithium hydroxide (3M, 150 mL) is added to (R)-(+)-ethyl (6-bromoisochroman-1-yl)acetate (XII, EXAMPLE 1 Step 2, 13.3 g) in THF (150 mL)
 20 and the mixture is stirred at 20-25° for 18 hours. The volatile solvents are removed under reduced pressure, and the residue is acidified with aqueous hydrochloric acid to pH = 1. The resulting mixture is extracted with methylene chloride and the combined organics are dried over sodium sulfate, filtered and concentrated. The
 25 concentrate is purified by recrystallization from dichloromethane/hexane to give (R)-(+)-6-(bromoisochroman-1-yl)acetic acid (R)-IV, mp = 160-161°; R_f = origin (ethyl acetate/hexane, 25/75); $[\alpha]_D$ = +83° (c = 0.99, ethanol); IR (neat) 1711, 1482, 1428, 1440, 1330, 1297, 1111, 1101, 1003 and 971 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.30, 6.92, 5.17, 4.18-4.11, 3.86-3.78 and 3.04-2.69 δ ; CMR (75 MHz, CDCl_3) 175.7, 136.2,
 30 135.1, 132.0, 129.6, 126.2, 120.8, 72.4, 63.1, 45.5, 41.1 and 28.5 δ .

Step 2: (R)-(+)-1-[2-(6-Bromoisochroman-1-yl)acetyl]-4-(4-methoxyphenyl)-piperazine (R)-(V).

Following the general procedure of EXAMPLE 1, Step 3 and making non-critical variations but starting with (R)-(+)-6-(bromoisochroman-1-yl)acetic acid
 35 ((EXAMPLE 2, Step 1, (R)-(IV)), a crude product is obtained which is first purified by silica gel chromatography using a gradient of 60-80% ethyl acetate/hexane, and

the resulting solid is then recrystallized (ethyl acetate/hexane) to give (R)-(+)-1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(4-methoxyphenyl)-piperazine (R)-(V), mp = 122-123°; R_f = 0.26 (ethyl acetate/hexane, 70/30); $[\alpha]_D^{25} = +89^\circ$ (c = 1.00, ethanol); IR (mull) 1639, 1512, 1446, 1439, 1249, 1214, 1112, 1030, 1028 and 820 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.32-7.26, 7.0, 6.88, 5.27, 4.16-4.07, 3.89, 3.80-3.60, 3.77, 3.05, 2.97-2.90, 2.76 and 2.65 δ ; CMR (75 MHz, CDCl_3) 168.9, 154.3, 145.2, 136.5, 136.2, 131.7, 129.3, 126.4, 120.3, 118.8, 114.4, 73.4, 63.4, 55.5, 51.3, 50.7, 46.1, 41.9, 39.9 and 28.7 δ .

Step 3: (R)-(+)-1-[2-(6-Bromoisochroman-1-yl)ethyl]-4-(4-methoxyphenyl)-piperazine (R)-(VI)

Following the general procedure of EXAMPLE 1, Step 4 and making non-critical variations but starting with (R)-(+)-1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(4-methoxyphenyl)-piperazine (R)-(V) (EXAMPLE 2, Step 2), (R)-(+)-1-[2-(6-bromoisochroman-1-yl)ethyl]-4-(4-methoxyphenyl)-piperazine (R)-(VI) is obtained, mp = 85-86°; R_f = 0.23 (ethyl acetate); $[\alpha]_D^{25} = +47^\circ$ (c = 0.94, ethanol); IR (neat) 1518, 1479, 1266, 1250, 1155, 1140, 1112, 1103, 1041 and 818 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.29, 7.27, 6.97, 6.85, 4.78, 4.14-4.07, 3.76-3.69, 3.76, 3.10, 2.95, 2.70-2.50, 2.18 and 2.02 δ ; CMR (75 MHz, CDCl_3) 153.5, 145.5, 136.8, 136.0, 131.4, 129.0, 126.3, 119.7, 117.9, 114.2, 74.1, 62.5, 55.3, 54.4, 53.3, 50.4, 32.9 and 28.6; HRMS Calcd for $\text{C}_{22}\text{H}_{27}\text{N}_2\text{O}_2\text{Br}$ = 430.1256, found = 430.1274.

Step 4: (R)-(+)-1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]-isochroman-6-carboxamide (R)-(VII)

Following the general procedure of EXAMPLE 1, Step 5 and making non-critical variations but starting with (R)-(+)-1-[2-(6-bromoisochroman-1-yl)ethyl]-4-(4-methoxyphenyl)-piperazine (R)-(VI) (EXAMPLE 2, Step 3), a crude material is obtained which is purified by flash chromatography (silica gel, 50 g; methanol/ethyl acetate, 5/95) to give (R)-(+)-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-isochroman-6-carboxamide (R)-(VII), mp = 187-187.5°; R_f = 0.27 (methanol/ethyl acetate, 10/90); $[\alpha]_D^{25} = +52^\circ$ (c = 0.92, methylene chloride/methanol, 1/1); IR (mull) 3366, 3198, 1628, 1642, 1602, 1514, 1437, 1245, 1109 and 815 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.61-7.58, 7.18, 6.85, 5.90, 4.86, 4.18-4.11, 3.80-3.72, 3.76, 3.10, 2.99, 2.73, 2.66-2.49, 2.15 and 2.04 δ ; CMR (75 MHz, CDCl_3) 168.7, 153.5, 145.4, 142.0, 134.3, 131.0, 127.9, 124.8, 124.6, 117.8, 114.1, 74.2, 62.6, 55.2, 54.3, 53.2, 50.3, 32.8, 28.7 and 27.2 δ ; HRMS Calcd for $\text{C}_{23}\text{H}_{29}\text{N}_3\text{O}_3$ = 395.2209, found = 395.2208.

EXAMPLE 3 (S)-(-)-1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]-N-methyl-isochroman-6-carboxamide (S)-(IX) also known as (S)-(-)-1-(4-

Methoxyphenyl)-4-[2-(6-methylaminocarbonylisochroman-1-yl)-
ethylpiperazine

Step 1: (S)-(-)-N,N-Di-*t*-butyloxycarbonyl-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-isochroman-6-carboxamide (S)-(VIII)

- 5 A mixture of (S)-(-)-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-isochroman-6-carboxamide (S)-(VII), EXAMPLE 1, Step 5, 0.71 g), di-*tert*-butyl dicarbonate (0.86 g) and 4-dimethylaminopyridine (0.02 g) in dichloromethane (20 mL) is stirred at 20-25° under argon. After 72 hours, the reaction is concentrated under reduced pressure and the product is purified by column chromatography
- 10 (silica gel, using a gradient eluant starting with 25% ethyl acetate in hexane and progressing to 100% ethyl acetate) to give (S)-(-)-N,N-di-*t*-butyloxycarbonyl-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-isochroman-6-carboxamide (S)-(VIII), $[\alpha]_D = -32^\circ$ ($c = 0.7201$, ethanol); HRMS Calcd for $C_{33}H_{45}N_3O_7 = 595.3257$, found = 595.3282.

- 15 Step 2: (S)-(-)-1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]-N-methyl-isochroman-6-carboxamide (S)-(IX)

- A mixture of (S)-(-)-N,N-di-*t*-butyloxycarbonyl-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-isochroman-6-carboxamide (S)-(VIII) (1.09 g) in dichloromethane (18 mL) in a sealable tube is cooled under nitrogen using acetone and carbon
- 20 dioxide. Into the cold tube is then condensed methylamine (excess; typically 50 equivalents), after which the tube is sealed and allowed to warm to room temperature. After stirring for 16 hr at room temperature, the contents of the tube are concentrated under reduced pressure and the resulting crude product is purified by column chromatography (silica gel; using methanol/dichloromethane 5/95) to give
- 25 (S)-(-)-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N-methyl-isochroman-6-carboxamide (S)-(IX), $[\alpha]_D = -51^\circ$ ($c = 0.9953$, methanol/dichloromethane, 1/1); Anal. Calcd for $C_{24}H_{31}N_3O_3$: C, 70.39; H, 7.63; N, 10.26 - found: C, 70.16; H, 7.84; N, 10.27.

- EXAMPLE 4 (R)-(+)-1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]-N-methyl-
- 30 isochroman-6-carboxamide (R)-(IX) also known as (R)-(+)-1-[4-Methoxyphenyl)-4-[2-(6-methylaminocarbonylisochroman-1-yl)-ethylpiperazine

Step 1: (R)-(+)-N,N-Di-*t*-butyloxycarbonyl-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-isochroman-6-carboxamide (R)-(VIII)

- 35 Following the general procedure of EXAMPLE 3, Step 1 and making non-critical variations, but starting with (R)-(+)-1-[2-[4-(4-methoxyphenyl)-1-

piperazinyl]ethyl]-isochroman-6-carboxamide ((R)-)(VII), EXAMPLE 2, Step 4, 0.60 g) gave (R)-(+)-N,N-di-t-butyloxycarbonyl-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-isochroman-6-carboxamide (R)-(VIII), which was used directly for the next step.

5 Step 2: (R)-(+)-1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]-N-methyl-isochroman-6-carboxamide (R)-(IX)

Following the general procedure of EXAMPLE 3, Step 2 and making non-critical variations, but starting with (R)-(+)-N,N-di-t-butyloxycarbonyl-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-isochroman-6-carboxamide (R)-(VIII) gave (R)-
10 (+)-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N-methyl-isochroman-6-carboxamide (R)-(IX), $[\alpha]_D^{25} = +48^\circ$ ($c = 0.9745$, methanol/dichloromethane, 1/1); HRMS Calcd for $C_{24}H_{31}N_3O_3 = 409.2365$, found = 409.2391.

EXAMPLE 5 (S)-(-)-1-[2-[4-(4-Trifluoromethylphenyl)-1-piperazinyl]ethyl]-N-methyl-isochroman-6-carboxamide (S)-(IX) also known as (S)-(-)-
15 1-(4-Trifluoromethylphenyl)-4-[2-(6-methylaminocarbonylisochroman-1-yl)-ethyl]piperazine

Step 1: (S)-(-)-1-[2-(6-Bromoisochroman-1-yl)acetyl]-4-(4-trifluoromethylphenyl)-piperazine (S)-(V)

(S)-(-)-(6-Bromoisochroman-1-yl)acetic acid (EXAMPLE 1, XI, 542 mg, 2.0
20 mmol), 10 mL dichloromethane, 1-(4-trifluoromethyl)piperazine (507 mg, 3.3 mmol) and diethylcyanophosphonate (0.33 mL, 2.2 mmol) are combined cooled to 0° and treated with triethylamine (0.42 mL, 3.0 mmol) with no visible change followed by warming to $20-25^\circ$. After 16 hours, the reaction mixture is concentrated. The concentrate is purified by LC on 58 g (230-400) silica gel eluting with ethyl
25 acetate/hexane (40/60) to give (S)-(-)-1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(4-trifluoromethylphenyl)-piperazine (S)-(V), $R_f = 0.25$ (ethyl acetate/hexane, 40/60).

Step 2: (S)-(-)-1-[2-(6-Bromoisochroman-1-yl)ethyl]-4-(4-trifluoromethylphenyl)-piperazine (S)-(VI).

(S)-(-)-1-[2-(6-Bromoisochroman-1-yl)acetyl]-4-(4-trifluoromethylphenyl)-
30 piperazine (S)-(V) (Step 1, 876 mg, 1.8 mmol) and 18.0 mL freshly distilled tetrahydrofuran are combined and cooled to 0° . The mixture is drop-wise treated with a 1M solution of borane in tetrahydrofuran (5.4 mL, 5.4 mmol) with foaming. The reaction is warmed to $20-25^\circ$ for 16 hrs. At this time, the reaction is treated with 1M hydrochloric acid (6.0 mL), fitted with a reflux condenser, and heated to
35 reflux for 1 hr. The reaction is cooled to $20-25^\circ$ with the volatiles removed under reduced pressure. The resulting aqueous residue is diluted with water (30 mL),

adjusted to pH > 10, and extracted twice with ethyl acetate (30 mL). The combined organic extracts are washed once with saline (30 mL), dried over magnesium sulfate, filtered, and concentrated. The concentrate is purified by LC on 43 g (230-400) silica gel eluting with ethyl acetate/hexane (40/60) to give (S)-(-)-1-[2-(6-bromoisochroman-1-yl)ethyl]-4-(4-trifluoromethylphenyl)-piperazine (S)-(VI), mp = 104-105°; R_f = 0.30 (ethyl acetate/hexane, 40/60).

Step 3: (S)-(-)-1-[2-[4-(4-Trifluoromethylphenyl)-1-piperazinyl]ethyl]-N-methyl-isochroman-6-carboxamide (S)-(IX)

(S)-(-)-1-[2-(6-Bromoisochroman-1-yl)ethyl]-4-(4-trifluoromethylphenyl)-piperazine (S)-(VI) (Step 2, 703 mg, 1.5 mmol), palladium (II) acetate (17 mg, .075 mmol), 1,3-bis(diphenylphosphino)propane (37 mg, .09 mmol), 3.0 mL dimethylformamide, diisopropylethylamine (0.52 mL, 3.0 mmol), and N-methylformamide (1.8 mL, 30 mmol) are combined and purged six times with carbon monoxide/house vacuum followed by heating to 120°. After 16 hours, the mixture is cooled to 20-25°, treated with 25 mL 1M hydrochloric acid, and stirred for 10 min. This acidic solution is adjusted to pH 12 and extracted three times with ethyl acetate (20 mL). The combined organic extracts are washed once with saline (30 mL), dried over magnesium sulfate, filtered, and concentrated. The concentrate is purified by LC on 33 g (230-400) silica gel eluting with acetone/hexane (40/60) to give (S)-(-)-1-[2-[4-(4-trifluoromethylphenyl)-1-piperazinyl]ethyl]-N-methyl-isochroman-6-carboxamide (S)-(IX), mp = 169-170°; R_f = 0.30 (acetone/hexane, 40/60).

EXAMPLE 6 (S)-(-)-1-[2-[4-[4-(Aminocarbonyl)phenyl]-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide (R)-(IX) also known as (S)-(-)-1-(Benzamide-4-yl)-4-[2-(6-methylaminocarbonylisochroman-1-yl)-ethyl]piperazine

Step 1. (S)-(-)-2-(6-Bromoisochroman-2-yl)ethyl alcohol

(S)-(-)-2-(6-Bromoisochroman-1-yl)acetic acid (XI) (EXAMPLE 1, step 2, 16.27 g, 60 mmol) and 100 mL tetrahydrofuran are combined. This mixture is treated with a 10M solution of borane methyl sulfide (18.0 mL, 0.18 mol) while maintaining 20-25° with a water bath. After 1 hr, the reaction mixture is cooled to 0° and slowly quenched with 160 mL methanol. Note: An induction period of approximately 1-2 minutes is noticed before a rapid and sudden generation of hydrogen. The mixture is warmed to 20-25° and the volatiles are removed under reduced pressure. The resulting solid is diluted with 1M sodium hydroxide (150 mL) and extracted three times with ethyl acetate (100 mL). The combined organic extracts are washed once with saline (100 mL), dried over magnesium sulfate, filtered, and concentrated

to give a solid. This material is recrystallized from ethyl acetate/hexane to give (S)-(-)-2-(6-bromoisochroman-2-yl)ethyl alcohol (S-1), mp 95-96°; R_f = 0.28 (acetone/hexane, 30/70).

Step 2: (S)-(-)-6-Bromo-1-(bromoethyl)isochroman

5 (S)-(-)-2-(6-Bromoisochroman-2-yl)ethyl alcohol (S-1) (Step 1, 14.0 g, 54 mmol) and 91 mL dichloromethane are combined. The resulting mixture is treated with 25 mL tetrahydrofuran. The suspension is treated with carbon tetrabromide (22.6 g, 68 mmol), cooled to 0°, and portion-wise treated with triphenyl phosphine (21.4 g, 82 mmol). The resulting mixture is warmed to 20-25° for three hours followed by
10 concentration under reduced pressure to give a solid. The triphenyl phosphine oxide is removed by recrystallization from ethyl acetate/hexane with the mother liquor giving a solid. This material is absorbed on 70 g silica gel and purified by LC on 700 g (230-400) silica gel eluting with ethyl acetate/hexane (5/95) to give (S)-(-)-6-bromo-1-(bromoethyl)isochroman (IV), R_f = 0.47 (10% acetone/hexane).

15 Step 3: (S)-(-)-4-[4-[2-(6-Bromoisochroman-1-yl)ethyl]-1-piperazinyl]benzamide

A mixture of (S)-(-)-6-bromo-1-(bromoethyl)isochroman (IV) (Step 2, 17.22 g, 53.8 mmol), 14.36 g (67.0 mmol) of 4-(piperazin-1-yl)benzamide (PREPARATION 1, 10.43 g (80.7 mmol) of diisopropylethylamine, and 125 mL of ethylene glycol
20 heated at 85-90° overnight. After cooling, water (300 mL) is added and the resulting solid is collected by filtration. The cake is washed three times with water (for a total of about 200 mL) and then with toluene (for a total of about 200 mL). The filter cake is then dried under reduced pressure. After drying, the crude product is slurried in methanol/dichloromethane and silica gel is added to adsorb the mixture.
25 After removal of the solvents, the silica gel slurry is poured onto the top of a silica gel column equilibrated with dichloromethane/methanol (95/5). Elution is begun using dichloromethane/methanol (95/5) and then changed to dichloromethane/methanol (92/8) to elute (S)-(-)-4-[4-[2-(6-bromoisochroman-1-yl)ethyl]-1-piperazinyl]benzamide (VI), obtained as a solid after pooling of the
30 appropriate fractions and concentration..

Step 4: (S)-(-)-1-[2-[4-[4-(Aminocarbonyl)phenyl]-1-piperazinyl]ethyl]-N-methylisochromanyl-6-carboxamide

(S)-(-)-4-[4-[2-(6-Bromoisochroman-1-yl)ethyl]-1-piperazinyl]benzamide (VI) (Step 3, 3.34g, 7.52 mmol) is slurried in 55 mL of dry DMF and degassed using
35 house vacuum (releasing to argon). The slurry is transferred to a 3-necked round bottom flask (using an additional 10 mL of DMF to rinse the flask) containing

palladium acetate (0.084 g, 0.376 mmol) and 1,3-bis(diphenylphosphino)propane (0.232 g, 0.564 mmol) and the flask is placed in an oil bath. Diisopropylethylamine (2.6 mL, 15.3 mmol) is added and the mixture is again lightly degassed and released to argon. Carbon monoxide is blown onto the surface of the mixture as the
5 temperature of the bath is raised to 60°. As the temperature increased, the mixture became homogeneous and the tip of the needle is then placed slightly below the surface of the solution. After bubbling carbon monoxide into the solution for several minutes, methyl amine gas also is bubbled into the solution. Carbon monoxide and methyl amine addition were continued for 6 hr or until the starting material is
10 consumed, after which the mixture is cooled and DMF removed under reduced pressure. The residue is applied to a silica gel column and eluted with methanol/dichloromethane (8/92) until the less polar impurities were eluted. The eluent is then switched to methanol/dichloromethane (10/90) and (S)-(-)-1-[2-[4-(aminocarbonyl)phenyl]-1-piperazinyl]ethyl-N-methylisochromanyl-6-carboxamide
15 (IX) is obtained after pooling and concentration of the appropriate fractions and crystallization from methanol/dichloromethane, mp 231.5-232.5°.

EXAMPLE 7 1-[2-[4-(4-Methylphenyl)-1-piperazinyl]ethyl]-isochroman-6-carboxamide (VII)

Step 1: 6-Bromoisochroman-1-yl-acetic acid (IV)

20 Following the general procedure of EXAMPLE 2, Step 1 and making non-critical variations but using racemic ethyl 6-bromoisochroman-1-yl-acetate (III), 6-bromoisochroman-1-yl-acetic acid (IV) is obtained, mp 160-161°; NMR (300 MHz, CDCl₃) 7.30, 6.92, 5.17, 4.18-4.11, 3.86-3.78 and 3.04-2.69 δ.

Step 2: 1-[2-(6-Bromoisochroman-1-yl)acetyl]-4-(4-methylphenyl)-
25 piperazine (V)

Following the general procedure of EXAMPLE 1, Step 3 and making non-critical variations but using racemic 6-bromoisochroman-1-yl-acetic acid (IV) and 4-methylphenylpiperazine, 1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(4-methylphenyl)-piperazine (V) is obtained which after flash chromatography (silica gel 80 g; ethyl
30 acetate/hexane, 50/50), R_f = 0.20 (ethyl acetate/hexane, 50/50); IR (neat) 1642, 1515, 1481, 1462, 1443, 1234, 1208, 1107, 1031 and 813 cm⁻¹; NMR (300 MHz, CDCl₃) 7.30, 7.09, 7.01, 6.84, 5.26, 4.13-4.07, 3.95-3.87, 3.82-3.60, 3.12, 3.05-2.89, 2.77, 2.65 and 2.28 δ; CMR (75 MHz, CDCl₃) 168.2, 148.3, 136.5, 136.8, 131.7, 129.6, 129.2, 126.3, 121.2, 116.8, 73.3, 63.3, 60.2, 48.7, 45.9, 41.7, 39.8, 26.6 and 20.3 δ.

35 Step 3: 1-[2-(6-Bromoisochroman-1-yl)-ethyl]-4-(4-methylphenyl)-piperazine (VI)

Following the general procedure of EXAMPLE 1, Step 4 and making non-critical variations but using 1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(4-methylphenyl)-piperazine (V), 1-[2-(6-bromoisochroman-1-yl)-ethyl]-4-(4-methylphenyl)piperazine (VI) is obtained, $R_f = 0.21$ (ethyl acetate/hexane, 50/50); IR (neat) 2941, 2925, 2818, 1515, 1481, 1379, 1239, 1143, 1111 and 813 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.32-7.26, 7.07, 6.97, 6.84, 4.78, 4.14-3.07, 3.78-3.69, 3.16, 2.94, 2.7-2.48, 2.26, 2.15-1.90 δ ; CMR (75 MHz, CDCl_3) 149.0, 136.9, 136.1, 131.4, 129.4, 129.0, 128.9, 126.3, 119.8, 116.1, 74.1, 62.6, 54.4, 53.2, 49.5, 33.0, 28.6 and 20.2 δ .

Step 4: 1-[2-[4-(4-Methylphenyl)-1-piperazinyl]ethyl]-isochroman-6-carboxamide (IX)

Following the general procedure of EXAMPLE 1, Step 5 and making non-critical variations but using 1-[2-(6-bromoisochroman-1-yl)-ethyl]-4-(4-methylphenyl)-piperazine (VI), 1-[2-[4-(4-methylphenyl)-1-piperazinyl]ethyl]-isochroman-6-carboxamide (VII) is obtained, $R_f = 0.2$ (methanol/ethyl acetate, 10/90); IR (mull) 3373, 3180, 1647, 1623, 1571, 1520, 1406, 1242, 1111 and 817 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.59, 7.18, 7.07, 6.84, 6.05, 4.86, 4.13, 3.77, 3.17, 3.00, 2.76-2.45, 2.26, 2.14 and 2.02 δ ; HRMS Calculated for $\text{C}_{23}\text{H}_{29}\text{N}_3\text{O}_2 = 379.2260$, found = 379.2269.

EXAMPLE 8 1-[2-[4-(4-Chlorophenyl)-1-piperazinyl]ethyl]-isochroman-6-carboxamide (VII)

Step 1: 1-[2-(6-Bromoisochroman-1-yl)acetyl]-4-(4-chlorophenyl)piperazine (V)

Following the general procedure of EXAMPLE 1, Step 3 and making non-critical variations but using racemic 6-bromoisochroman-1-yl-acetic acid (IV) and 4-chlorophenylpiperazine, 1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(4-methylphenyl)-piperazine (V) is obtained, $R_f = 0.20$ (ethyl acetate/hexane, 50/50); IR (mull) 1642, 1594, 1496, 1482, 1443, 1275, 1232, 1107, 1030 and 821 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.32-7.21, 7.01, 6.84, 5.26, 4.11, 3.94, 3.79-3.60, 3.14, 3.09-2.89, 2.77 and 2.65 δ ; CMR (75 MHz, CDCl_3) 178.1, 148.5, 136.0, 131.8, 129.1, 128.8, 125.8, 125.0, 120.0, 117.5, 73.0, 63.2, 49.7, 49.2, 55.0, 41.9, 39.6 and 28.5 δ .

Step 2: 1-[2-(6-Bromoisochroman-1-yl)-ethyl]-4-(4-chlorophenyl)piperazine (VI)

Following the general procedure of EXAMPLE 1, Step 4 and making non-critical variations but using 1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(4-chlorophenyl)-piperazine (V), 1-[2-(6-bromoisochroman-1-yl)-ethyl]-4-(4-chlorophenyl)piperazine (VI) is obtained, mp = 94-96°; $R_f = 0.22$ (ethyl acetate/hexane, 50/50); IR (mull) 1500, 1483, 1448, 1248, 1242, 1152, 1144, 1113, 1102 and 815 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.32-7.26, 7.19, 6.97, 6.83, 4.78, 4.14-4.07, 3.78-3.69, 3.16, 3.00-2.90,

2.7-2.48 and 2.15-1.90 δ ; CMR (75 MHz, CDCl_3) 149.6, 137.1, 136.0, 131.4, 129.1, 128.7, 126.3, 124.6, 120.0, 116.9, 74.0, 62.6, 54.3, 53.3, 53.0, 48.9, 33.0 and 28.6 δ .

Step 3: 1-[2-[4-(4-Chlorophenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (IX)

5 Following the general procedure of EXAMPLE 1, Step 5 and making non-critical variations but using 1-[2-(6-bromoisochroman-1-yl)-ethyl]-4-(4-chlorophenyl)-piperazine (VI), 1-[2-[4-(4-chlorophenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VII) is obtained, mp = 169-171°; R_f = 0.22 (methanol/ethyl acetate, 10/90); IR (mull) 3365, 1649, 1661, 1623, 1500, 1403, 1241, 1112, 1096 and 821 cm^{-1} ;
 10 NMR (300 MHz, CDCl_3) 7.59, 7.18, 6.84, 6.05, 4.88, 4.15, 3.77, 3.17, 3.00, 2.76-2.45, 2.14 and 2.02 δ .

EXAMPLE 9 1-[2-[4-(4-Phenylmethyloxyphenyl)-1-piperazinyl]ethyl]-isochroman-6-carboxamide (VII)

Step 1: 1-(4-Phenylmethyloxyphenyl)-4-[2-(6-bromoisochroman-1-yl)acetyl]piperazine (V)
 15

Following the general procedure of EXAMPLE 1, Step 3 and making non-critical variations but using racemic 6-bromoisochroman-1-yl-acetic acid (IV) and 4-phenylmethyloxypiperazine, 1-(4-phenylmethyloxyphenyl)-4-[2-(6-bromoisochroman-1-yl)acetyl]piperazine (V) is obtained, R_f = 0.47 (ethyl acetate); IR (mull) 1510, 1481,
 20 1463, 1458, 1445, 1239, 1231, 1101 and 1027 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.43-7.25, 7.00, 5.27, 5.02, 4.23-4.06, 3.93-3.87, 3.80-3.59, 3.06, 2.98-2.89, 2.76 and 2.65 δ ; CMR (75 MHz, CDCl_3) 168.9, 153.4, 145.3, 137.1, 136.4, 136.2, 131.6, 129.3, 128.4, 127.8, 127.3, 126.4, 120.2, 118.6, 115.5, 73.3, 70.3, 63.4, 51.1, 50.5, 46.0, 41.8, 39.8 and 28.7 δ . Step 2: 1-(4-Phenylmethyloxyphenyl)-4-[2-(6-bromoisochroman-1-yl)-ethyl]piperazine (VI)
 25

Following the general procedure of EXAMPLE 1, Step 4 and making non-critical variations but using 1-(4-phenylmethyloxyphenyl)-4-[2-(6-bromoisochroman-1-yl)acetyl]piperazine (V), 1-(4-phenylmethyloxyphenyl)-4-[2-(6-bromoisochroman-1-yl)-ethyl]piperazine (VI) is obtained, mp = 87-90°; R_f = 0.43 (ethyl acetate); IR (neat)
 30 1578, 1517, 1452, 1258, 1153, 1113, 1054, 1049, 818 and 737 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.43-7.26 (m, 7H, aromatic H's), 6.97 (d, 1H, J =8.2 Hz, aromatic H), 6.90 (s with broad base, 4H, aromatic H's), 5.01 (s, 2H, PhC-H_2), 4.77 (m of d, 1H, J =5.5 Hz, PhC-H), 4.14-4.07 (m, 1H), 3.74 (d of t, 1H, J_a =3.9 Hz, J_b =9.4 Hz), 3.11 (t, 4H, J =4.9 Hz, four of pip-H), 2.95 (m, 1H), 2.7-2.54 (several m's, 7H), 2.11 (m, 1H,
 35 pipCH-H), 2.02 (m, 1H, pipCH-H) δ ; CMR (75 MHz, CDCl_3) 153.0, 145.1, 137.4, 137.1, 136.3, 131.6, 128.5, 127.8, 126.5, 120.0, 118.0, 115.6, 74.3, 70.5, 62.8, 54.6,

53.5, 50.5, 33.1 and 28.9 δ .

Step 3: 1-[2-[4-(4-Phenylmethoxyphenyl)-1-piperazinyl]ethyl]-
isochroman-6-carboxamide (VII)

Following the general procedure of EXAMPLE 1, Step 5 and making non-
critical variations but using 1-(4-phenylmethoxyphenyl)-4-[2-(6-bromoisochroman-
1-yl)-ethyl]piperazine (VI), 1-[2-[4-(4-phenylmethoxyphenyl)-1-piperazinyl]ethyl]-
isochroman-6-carboxamide (VII) is obtained, IR (mull) 3368, 3178, 1647, 1623, 1611,
1570, 1515, 1334, 124.6 and 1111 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.58 (m, 2H,
aromatic H's), 7.43-7.30 (m, 5H, aromatic H's), 7.15 (d, 1H, $J=8.4$ Hz, aromatic H),
6.90 (s, 4H, aromatic H's), 6.20-5.80 (two broad singlets, C(O)N-H_2), 5.0 (s, 2H, $\text{PhC-H}_2\text{-O}$), 4.87 (m of d, 1H, $J=5.8$ Hz), 4.18-4.10 (m, 1H), 3.81-3.73 (m, 1H), 3.10 (t, 4H,
 $J=4.8$ Hz, four of pip-H), 3.0 (m, 1H), 2.75 (m, 1H), 2.650-2.54 (m, 6H), 2.15 (m, 1H),
2.05 (m, 1H) δ ; CMR (75 MHz, CDCl_3) 169.0, 152.9, 145.8, 142.3, 137.3, 134.5,
131.3, 128.5, 128.1, 127.8, 127.4, 125.0, 124.9, 118.0, 115.5, 74.5, 70.4, 62.8, 54.6,
53.4, 50.4, 33.1 and 29.0 δ .

EXAMPLE 10 1-[2-[4-(4-Butoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-
carboxamide (VII)

Step 1: 1-[2-(6-Bromoisochroman-1-yl)acetyl]-4-(4-butoxyphenyl)-
piperazine (V)

Following the general procedure of EXAMPLE 1, Step 3 and making non-
critical variations but using racemic 6-bromoisochroman-1-yl-acetic acid (IV) and 4-
butoxyphenylpiperazine, 1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(4-butoxyphenyl)-
piperazine (V) is obtained, $R_f = 0.24$ (ethyl acetate/hexane, 50/50); IR (mull) 1640,
1513, 1482, 1441, 1422, 1245, 1232, 1103, 1031, 829 cm^{-1} ; NMR (300 MHz, CDCl_3)
7.29, 7.00, 6.90, 5.26, 4.13-4.07, 3.92, 3.93-3.87, 3.80-3.60, 3.06, 2.98-2.89, 2.76, 2.65,
1.74, 1.48, 0.96 δ ; CMR (75 MHz, CDCl_3) 168.8, 153.8, 145.0, 136.4, 136.2, 131.6,
129.3, 126.3, 120.2, 118.7, 115.1, 73.3, 67.9, 63.3, 51.2, 50.7, 46.1, 41.8, 39.8, 31.3,
28.7, 19.1, 17.3 and 13.7 δ .

Step 2: 1-[2-(6-Bromoisochroman-1-yl)-ethyl]-4-(4-butoxyphenyl)-
piperazine (VI)

Following the general procedure of EXAMPLE 1, Step 4 and making non-
critical variations but using 1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(4-butoxyphenyl)-
piperazine (V), 1-[2-(6-bromoisochroman-1-yl)ethyl]-4-(4-butoxyphenyl)piperazine (VI)
is obtained, $R_f = 0.43$ (ethyl acetate); IR (neat) 2957, 2931, 2887, 1511, 1481, 1261,
1243, 1233, 1112, 1057 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.32 (d, 2H, $J=8.3$ Hz, aromatic
H's), 7.06 (d, 1H, $J=8.3$ Hz, aromatic H), 6.85 (q, 4H, $J=9.7$ Hz, aromatic H's), 4.80

(m of d, 1H, J=6.1 Hz), 4.13-4.08 (m, 1H), 3.98-3.89 (m, 3H), 3.71 (d of t, 1H, J_a=3.7 Hz, J_b=13.7 Hz), 3.28 (broad s, 4H), 3.10-2.72 (broad m, 7H), 2.65 (m of d, 1H, J=16.5 Hz), 2.40 (m, 1H), 2.22 (m, 1H), 1.74 (quintet, 2H, J=6.6 Hz), 1.46 (sextet, 2H, J=7.3 Hz), 1.25 (t, 2H, J=7.0 Hz), 0.96 (t, 3H, J=7.3 Hz) δ ; HRMS Calculated for $C_{25}H_{33}N_2O_2Br$ = 473.1804, found = 473.1796.

Step 3: 1-[2-[4-(4-Butoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VII)

Following the general procedure of EXAMPLE 1, Step 5 and making non-critical variations but using 1-[2-(6-bromoisochroman-1-yl)-ethyl]-4-(4-butoxyphenyl)-piperazine (VI), 1-[2-[4-(4-butoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VII) is obtained, R_f = 0.18 (methanol/ethyl acetate, 10/90); IR (mull) 3364, 2820, 1647, 1624, 1570, 1517, 1413, 1260, 1245, 1111 cm⁻¹; NMR (300 MHz, CDCl₃) 7.60 (m, 2H, aromatic H's), 7.18 (d, 1H, J=8.5 Hz, aromatic H), 6.86 (q, 4H, J=9.2 Hz, aromatic H's), 6.20-5.80 (two broad singlets, C(O)N-H₂), 4.85 (m of d, 1H, J=18 Hz), 4.15 (m, 1H), 3.90 (t, 2H, J=6.5 Hz, -O-C-H₂-CH₂CH₂Me), 3.77 (m, 1H), 3.10 (t, 4H, J=4.8 Hz, four of pip-H), 2.96 (m, 1H), 2.80-2.50 (m, 6H), 2.15 (m, 1H), 2.05 (m, 1H), 1.74 (quintet, 2H, J=6.8 Hz, -OCH₂C-H₂-CH₂Me), 1.48 (quintet, 2H, J=7.5 Hz, -OCH₂C-H₂C-H₂-Me), 0.96 (t, 3H, J=7.3 Hz, -OCH₂CH₂CH₂C-H₃) δ ; CMR (75 MHz, CDCl₃) 169.1, 160.8, 153.4, 145.6, 142.4, 134.6, 131.3, 130.3, 128.2, 127.6, 125.1, 125.0, 118.1, 115.1, 74.5, 68.1, 62.9, 54.7, 53.5, 50.6, 41.4, 33.2, 31.5, 29.0, 19.3 and 13.9 δ ; HRMS Calculated for $C_{26}H_{35}N_3O_3$ = 437.2678, found = 437.2678.

EXAMPLE 11 1-[2-[4-(4-Diethylaminophenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VII)

Step 1: 1-[2-(6-Bromoisochroman-1-yl)acetyl]-4-(4-diethylaminophenyl)-piperazine (V)

Following the general procedure of EXAMPLE 1, Step 3 and making non-critical variations, but using racemic 6-bromoisochroman-1-yl-acetic acid (IV) and 4-diethylaminophenylpiperazine, 1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(4-diethylaminophenyl)piperazine (V) is obtained, R_f = 0.21 (acetone/hexane, 30/70); IR (mull) 1633, 1518, 1482, 1446, 1423, 1261, 1232, 1196, 1109, 809 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 7.32-7.26 (m, 2H, aromatic H's), 7.0 (d, 1H, J=8.2 Hz, aromatic H), 6.88 (d, 2H, J=9.0 Hz, aromatic H's), 6.68 (d, 2H, J=9.0 Hz, aromatic H's), 5.27 (m of d, 1H, J=5.9 Hz, ArC-H), 4.16-4.07 (m, 1H), 3.89 (m, 1H), 3.76 (m, 2H), 3.64 (m, 2H), 3.28 (q, 4H, J=7.1 Hz, two of PhNC-H₂), 2.98 (m, 5H), 2.76 (d of d, 1H, J_a=3.7 Hz, J_b=14.9 Hz), 2.65 (m of d, 1H, J=16.4 Hz), 1.12 (t, 6H, J=7.0 Hz, two of NCH₂C-H₃) δ ; CMR (75 MHz, CDCl₃) 168.8, 143.2, 141.6, 136.4, 136.2, 131.6, 129.2, 126.3,

120.2, 119.2, 113.7, 73.3, 63.3, 51.6, 51.0, 46.1, 44.6, 41.9, 39.8, 33.1, 28.6 and 12.4 δ .

Step 2: 1-[2-(6-Bromoisochroman-1-yl)-ethyl]-4-(4-diethylaminophenyl)-piperazine (VI)

5 Following the general procedure of EXAMPLE 1, Step 4 and making non-critical variations but using 1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(4-diethylaminophenyl)piperazine (V), 1-[2-(6-bromoisochroman-1-yl)-ethyl]-4-(4-diethylaminophenyl)piperazine (VI) is obtained, $R_f = 0.26$ (ethyl acetate); IR (neat) 2931, 2965, 2814, 1516, 1374, 1262, 1232, 1144, 1109, 813 cm^{-1} ; NMR (300
10 MHz, CDCl_3) 7.3-7.26 (m, 2H, aromatic H's), 6.98 (d, 1H, $J=8.2$ Hz, aromatic H), 6.88 (d, 2H, $J=9.0$ Hz, aromatic H's), 6.68 (d, 2H, $J=9.0$ Hz, aromatic H's), 4.77 (m of d, 1H, $J=5.9$ Hz, ArC-H), 4.14-4.07 (m, 1H), 3.74 (d of t, 1H, $J_a=3.9$ Hz, $J_b=9.3$ Hz), 3.26 (q, 4H, $J=7.1$ Hz, two of PhNC-H_2), 3.08 (t, 4H, $J=4.8$ Hz, four of pip-H), 2.95 (m, 1H), 2.70-2.53 (m, 7H), 2.11 (m, 1H, pipCH-H), 2.00 (m, 1H, pipCH-H), 1.11 (t,
15 6H, $J=7.0$ Hz, two of $\text{NCH}_2\text{C-H}_3$) δ ; HRMS Calculated for $\text{C}_{25}\text{H}_{34}\text{N}_3\text{O}_1\text{Br}_1$ = 0.152 $\text{C}_4\text{H}_8\text{O}_2 = 472.1964$, found = 472.1956.

Step 3: 1-[2-[4-(4-Diethylaminophenyl)-1-piperazinyl]ethyl]-isochroman-6-carboxamide (VII)

Following the general procedure of EXAMPLE 1, Step 5 and making non-critical variations but using 1-[2-(6-bromoisochroman-1-yl)-ethyl]-4-(4-diethylaminophenyl)piperazine (VI), 1-[2-[4-(4-diethylaminophenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VII) is obtained, $R_f = 0.25$ (methanol/ethyl acetate, 10/90); NMR (300 MHz, CDCl_3) 7.59, 7.18, 6.87, 6.68, 6.1, 5.7, 4.87, 4.13, 3.78, 3.26, 3.06, 2.78-2.57, 2.17, 2.05 and 1.11 δ .

25 EXAMPLE 12 1-[2-[4-(3-Trifluoromethylphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VII)

Step 1: 1-[2-(6-Bromoisochroman-1-yl)acetyl]-4-(3-trifluoromethylphenyl)-piperazine (V)

Following the general procedure of EXAMPLE 1, Step 3 and making non-critical variations but using racemic 6-bromoisochroman-1-yl-acetic acid (IV) and 3-trifluoromethylphenylpiperazine, 1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(3-trifluoromethylphenyl)piperazine (V) is obtained, $R_f = 0.30$ (ethyl acetate/hexane, 40/60); IR (liq.) 1643, 1610, 1592, 1496, 1482, 1448, 1374, 1351, 1320, 1309, 1282, 1233, 1164, 1121, 1076 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.34 (m, 3H, aromatic), 7.08
30 (m, 4H, aromatic), 5.25 (brdd, 1H, $J=5.6$ Hz, methine), 4.11 (m, 1H, OCH_{2a}), 3.94 (m, 1H, O=C-N-CH_{2a}), 3.80-3.65 (m, 4H, O=C-N-CH_{2bcd} , OCH_{2b}), 3.23 (m, 4H, Ph-

NCH_{2s}), 2.95 (m, 2H, Ph-CH_{2a} & N-CO-CH_{2a}), 2.78 (dd, 1H, J=14.8 Hz & J=3.7 Hz, N-CO-CH_{2b}), 2.66 (bd, 1H, J=16.4 Hz, Ph-CH_{2b}) δ ; CMR (75 MHz, CDCl₃) 169.2, 151.1, 136.4, 136.3, 131.8, 131.4, 129.7, 129.5, 126.5, 126.0, 122.4, 120.5, 119.2, 116.6, 112.7, 73.6, 63.6, 49.2, 48.8, 45.8, 41.6, 40.0 and 28.8 δ ; MS (EI, m/z) = 482.

5 Step 2: 1-[2-(6-Bromoisochroman-1-yl)-ethyl]-4-(3-trifluoromethylphenyl)-piperazine (VI)

Following the general procedure of EXAMPLE 1, Step 4 and making non-critical variations but using 1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(3-trifluoromethylphenyl)piperazine (V), the product is obtained. This material is
 10 purified by LC (silica gel, 230-400, 142 g; ethyl acetate/hexane, 30/70) to give 1-[2-(6-bromoisochroman-1-yl)-ethyl]-4-(3-trifluoromethylphenyl)piperazine (VI), R_f = 0.40 (ethyl acetate/hexane, 40/60); IR (liq.) 2824, 1610, 1496, 1481, 1449, 1357, 1319, 1293, 1239, 1164, 1123, 1076, 993, 949 and 695 cm⁻¹; NMR (300 MHz, CDCl₃) 7.32 (m, 3H, aromatic), 7.07 (m, 3H, aromatic), 6.97 (d, 1H, J=8.2 Hz, aromatic), 4.79
 15 (brdd, 1H, J=5.7 Hz, methine), 4.11 (m, 1H, OCH_{2a}), 3.73 (m, 1H, OCH_{2b}), 3.23 (t, 4H, J=5.0 Hz, Ph-NCH_{2s}), 2.93 (m, 1H, Ph-CH_{2a}), 2.58 (m, 7H, Ph-NC(H₂)-CH_{2s}-NCH₂ & Ph-CH_{2b}), 2.10 (m, 1H, C(H)-CH_{2a}), 2.00 (m, 1H, C(H)-CH_{2b}) δ ; CMR (75 MHz, CDCl₃) 151.4, 137.0, 136.3, 131.7, 131.4 (q_{rt}, J_{CF}=36 Hz), 129.5, 129.3, 126.5, 126.2, 120.0, 118.6, 115.7 (d, J_{CF}=4 Hz), 112.1 (d, J_{CF}=4 Hz), 74.2, 62.9, 54.5, 53.2,
 20 48.7, 33.2, 28.9 δ ; MS (EI, m/z) = 468.

Step 3: 1-[2-[4-(3-Trifluoromethylphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VII)

Following the general procedure of EXAMPLE 1, Step 5 and making non-critical variations but using 1-[2-(6-bromoisochroman-1-yl)-ethyl]-4-(3-trifluoromethylphenyl)piperazine (VI) the product is obtained. This material is
 25 purified by LC (silica gel, 230-400, 120 g; acetone/hexane, 50/50) to give 1-[2-[4-(3-trifluoromethylphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VII). This material is recrystallized from ethyl acetate/hexane to give 1-[2-[4-(3-trifluoromethylphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VII), mp =
 30 129-131°; R_f = 0.22 (acetone/hexane, 50/50); IR (mull) 3383, 1647, 1618, 1606, 1567, 1407, 1359, 1322, 1312, 1287, 1161, 1139, 1115, 1098, 952 cm⁻¹; NMR (300 MHz, CDCl₃) 7.60, 7.33, 7.18, 7.07, 6.00, 4.88, 4.14, 3.77, 3.24, 3.01, 2.78-2.48, 2.01 δ ; CMR (75 MHz, CDCl₃) 169.1, 151.4, 142.4, 134.6, 131.5 (q_{rt}, J_{CF}=32 Hz), 131.4, 129.5, 128.2, 125.1, 125.0, 122.5, 118.6, 115.8 (d, J_{CF}=4 Hz), 112.1 (d, J_{CF}=4 Hz),
 35 74.4, 63.0, 54.5, 53.2, 48.7, 33.2, 29.1 δ ; HRMS (EI) calculated for C₂₃H₂₆F₃N₃O₂ = 433.1977, found = 433.1979.

EXAMPLE 13 1-[2-[4-(4-Methylsulfonylphenyl)-1-piperazinyl]ethyl]-
isochroman-6-carboxamide (VII)

Step 1: 1-[2-(6-Bromoisochroman-1-yl)acetyl]-4-(4-
methylsulfonylphenyl)-piperazine (V)

5 Following the general procedure of EXAMPLE 1, Step 3 and making non-critical variations but using racemic 6-bromoisochroman-1-yl-acetic acid (IV) and 4-methylsulfonylphenylpiperazine the product is obtained. This material is purified by LC (silica gel, 230-400, 150 g; ethyl acetate) to give 1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(4-methylsulfonylphenyl)piperazine (V), $R_f = 0.30$ (ethyl acetate); IR (mull) 1639, 1593, 1508, 1481, 1405, 1295, 1239, 1145, 1105, 1096, 1027, 1000, 958, 825, 779 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.77 (d, 2H, $J=8.9$ Hz, aromatic), 7.28 (m, 2H, aromatic), 7.00 (d, 1H, $J=8.2$ Hz, aromatic), 6.91 (d, 2H, $J=9.0$ Hz, aromatic), 5.24 (brdd, 1H, $J=5.7$ Hz, methine), 4.10 (m, 1H, OCH_{2a}), 3.94 (m, 1H, $\text{O}=\text{C}-\text{N}-\text{CH}_{2a}$), 3.78-3.60 (m, 4H, OCH_{2b} , $\text{O}=\text{C}-\text{N}-\text{CH}_{2bcd}$), 3.38 (m, 4H, $\text{Ph}-\text{N}-\text{CH}_{2s}$), 3.00-15 2.88 (m, 5H, $\text{Ph}-\text{CH}_{2a}$, CH_3 , $\text{N}-\text{C}=\text{O}-\text{CH}_{2a}$), 2.78 (dd, 1H, $J=14.7$ Hz & 3.6 Hz, $\text{N}-\text{C}=\text{O}-\text{CH}_{2b}$), 2.65 (brdd, 1H, $J=16.4$ Hz, $\text{Ph}-\text{CH}_{2b}$) δ ; CMR (75 MHz, CDCl_3) 169.3, 153.9, 136.3, 131.8, 129.5, 129.2, 126.4, 120.5, 114.1, 73.7, 63.6, 47.5, 47.2, 45.5, 44.9, 41.3, 40.0 and 28.8 δ ; HRMS (EI) calculated for $\text{C}_{22}\text{H}_{25}\text{BrN}_2\text{O}_4\text{S} = 492.0719$, found = 492.0714.

20 Step 2: 1-[2-(6-Bromoisochroman-1-yl)-1-ethyl]-4-(4-methylsulfonylphenyl)piperazine (VI)

Following the general procedure of EXAMPLE 1, Step 4 and making non-critical variations but using 1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(4-methylsulfonylphenyl)piperazine (V), 1-[2-(6-bromoisochroman-1-yl)-1-ethyl]-4-(4-methylsulfonylphenyl)piperazine (VI) is obtained, $R_f = 0.26$ (ethyl acetate); IR (mull) 25 3586, 1592, 1507, 1481, 1424, 1405, 1296, 1249, 1145, 1109, 1095, 1004, 956, 822, 779 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.75 (d, 2H, $J=9.0$ Hz, aromatic), 7.27 (m, 2H, aromatic), 6.95 (d, 1H, $J=8.3$ Hz, aromatic), 6.90 (d, 2H, $J=9.0$ Hz, aromatic), 4.78 (brdd, 1H, $J=5.7$ Hz, methine), 4.10 (m, 1H, OCH_{2a}), 3.74 (m, 1H, OCH_{2b}), 3.35 (t, 30 4H, $J=5.0$ Hz, $\text{Ph}-\text{NCH}_{2s}$), 3.00 (s, 3H, CH_3), 2.94 (m, 1H, $\text{Ph}-\text{CH}_{2a}$), 2.54 (m, 7H, $\text{Ph}-\text{NC}(\text{H}_2)-\text{CH}_{2s}-\text{NCH}_2$ & $\text{Ph}-\text{CH}_{2b}$), 2.09 (m, 1H, $\text{C}(\text{H})-\text{CH}_{2a}$), 2.01 (m, 1H, $\text{C}(\text{H})-\text{CH}_{2b}$) δ ; CMR (75 MHz, CDCl_3) 154.3, 136.9, 136.4, 131.7, 129.3, 129.1, 128.6, 126.4, 120.1, 113.8, 74.1, 62.9, 54.4, 52.9, 47.3, 45.0, 33.1 and 28.9 δ ; HRMS (EI) calculated for $\text{C}_{22}\text{H}_{27}\text{BrN}_2\text{O}_3\text{S} = 480.0906$, found = 480.0903.

35 Step 3: 1-[2-[4-(4-Methylsulfonylphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VII)

Following the general procedure of EXAMPLE 1, Step 5 and making non-critical variations but using 1-[2-(6-bromoisochroman-1-yl)-1-ethyl]-4-(4-methylsulfonylphenyl)piperazine (VI) the product is obtained. This material is purified by LC (silica gel, 230-400 mesh, 75 g; methanol/dichloromethane, 5/95) to give 1-[2-[4-(4-methylsulfonylphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VII), mp = 217-219°; R_f = 0.17 (methanol/dichloromethane, 5/95); IR (mull) 3483, 1668, 1619, 1587, 1568, 1507, 1288, 1140, 1115, 1105, 1095, 1023, 998, 812, 780 cm^{-1} ; NMR (300 MHz, DMSO- d_6) 7.90 (brds, 1H, NH), 7.66 (m, 4H, aromatic), 7.28 (d, 2H, $J=8.0$ Hz, aromatic & NH), 7.06 (d, 2H, $J=9.1$ Hz, aromatic), 4.79 (brdd, 1H, $J=6.5$ Hz, methine), 4.08 (m, 1H, OCH_{2a}), 3.67 (m, 1H, OCH_{2b}), 3.32 (t, 4H, $J=4.0$ Hz, Ph-N- CH_{2a}), 3.08 (s, 3H, CH_3), 2.88 (m, 1H, Ph- CH_{2a}), 2.71 (dm, 1H, $J=16.4$ Hz, Ph- CH_{2b}), 2.53 (m, 5H, Ph-NC(H_2)- CH_{2a} -N CH_{2a}), 2.37 (m, 1H, N CH_{2b}), 2.13 (m, 1H, C(H)- CH_{2a}), 1.98 (m, 1H, C(H)- CH_{2b}) δ ; CMR (75 MHz, DMSO- d_6) 168.2, 154.3, 141.8, 134.1, 132.6, 129.0, 128.9, 128.5, 125.6, 125.2, 114.0, 74.1, 62.7, 54.6, 53.0, 47.2, 44.7, 32.9 and 29.0 δ ; HRMS (FAB) calculated for $\text{C}_{23}\text{H}_{29}\text{N}_3\text{O}_4\text{S}+\text{H}_1$ = 444.1957, found = 444.1959.

EXAMPLE 14 (S)-(-)-1-[2-[4-(4-Trifluoromethylphenyl)-1-piperazinyl]ethyl]-isochroman-6-carboxamide (S)-(VII)

Following the general procedure of EXAMPLE 1, Step 5 and making non-critical variations but using (S)-(-)-1-[2-(6-bromoisochroman-1-yl)-1-ethyl]-4-(4-trifluoromethylphenyl)piperazine (VI, EXAMPLE 5, Step 2, 13.15 g, 28.0 mmol) the product is obtained. This material is purified by LC (silica gel, 230-400 mesh, 780 g; methanol/dichloromethane, 5/95) to give a crude product which is recrystallized from methanol/ethylacetate to give (S)-(-)-1-[2-[4-(4-trifluoromethylphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (S)-(VII), mp = 166-168°; R_f = 0.20 (methanol/dichloromethane, 5/95); $[\alpha]_D^{25} = -50^\circ$ ($c = 0.8533$, methanol); IR (mull) 3365, 3203, 1654, 1619, 1337, 1317, 1243, 1164, 1149, 1138, 1122, 1114, 1107, 1074, 825 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.57 (m, 2H, aromatic), 7.42 (d, 2H, $J=8.7$ Hz, aromatic), 7.14 (d, 1H, $J=7.8$ Hz, aromatic), 6.87 (d, 2H, $J=8.7$ Hz, aromatic), 4.83 (brdd, 1H, $J=5.8$ Hz, methine), 4.10 (m, 1H, OCH_{2a}), 3.73 (m, 1H, OCH_{2b}), 3.25 (t, 4H, $J=4.9$ Hz, Ph-N- CH_{2a}), 2.97 (m, 1H, Ph- CH_{2a}), 2.68-2.45 (m, 7H, Ph-NC(H_2)- CH_{2a} -N CH_{2a} , Ph- CH_{2b}), 2.13 (m, 1H, C(H)- CH_{2a}), 2.02 (m, 1H, C(H)- CH_{2b}) δ ; CMR (75 MHz, CDCl_3) 169.6, 153.2, 142.1, 134.5, 131.3, 128.2, 126.5, 126.3 (d, $J_{\text{CF}}=4$ Hz), 125.0 (d, $J_{\text{CF}}=4$ Hz), 122.9, 120.5 (qrt, $J_{\text{CF}}=33$ Hz), 114.5, 74.4, 63.0, 54.5, 53.0, 47.8, 32.8 and 29.0 δ ; HRMS (EI) calculated for $\text{C}_{23}\text{H}_{26}\text{F}_3\text{N}_3\text{O}_2 = 433.1977$, found = 433.1978.

EXAMPLE 15 1-[2-[4-(4-Ethoxyphenyl)-1-piperazinyl]ethyl]-N-methyl-
isochroman-6-carboxamide (IX)

Step 1: 1-[2-(6-Bromoisochroman-1-yl)acetyl]-4-(4-ethoxyphenyl)-
piperazine (V)

5 Following the general procedure of EXAMPLE 1, Step 3 and making non-critical variations but using racemic 6-bromoisochroman-1-ylacetic acid (IV) and 4-ethoxyphenylpiperazine, 1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(4-ethoxyphenyl)-piperazine (V) is obtained, $R_f = 0.46$ (ethyl acetate/hexane, 70/30); IR (neat) 1641, 1511, 1480, 1463, 1443, 1278, 1243, 1231, 1108, 1049 cm^{-1} ; NMR (300 MHz, CDCl_3)
10 7.28 (m, 2H, aromatic H's), 7.0 (d, 1H, $J=8.2$ Hz, aromatic H), 6.86 (d, 4H, $J=8.2$ Hz, aromatic H's), 5.25 (m of d, 1H, $J=6.5$ Hz, PhC-H), 4.11 (m, 1H), 3.99 (q, 2H, $J=7.0$ Hz, PhOCH_2), 3.89 (m, 1H), 3.80-3.59 (m, 4H), 3.05 (t, 4H, $J=5.0$ Hz), 3.03-2.89 (m's, 2H), 2.77 (d of d, 1H, $J_a=3.6$ Hz, $J_b=14.9$ Hz), 2.66 (m of d, 1H, $J=16.4$ Hz), 1.39 (t, 3H, $J=7.0$ Hz, $\text{PhOCH}_2\text{C-H}_3$) δ ; CMR (75 MHz, CDCl_3) 168.9, 153.6, 145.0, 136.4,
15 136.2, 131.6, 129.3, 126.4, 120.2, 118.7, 115.1, 73.3, 63.7, 63.55, 63.47, 63.4, 51.2, 50.7, 46.0, 41.8, 39.8, 28.7, 14.8 δ ; HRMS calculated for $\text{C}_{23}\text{H}_{27}\text{N}_2\text{O}_3\text{Br} = 458.1205$, found = 458.1217.

Step 2: 1-[2-(6-Bromoisochroman-1-yl)-ethyl]-4-(4-ethoxyphenyl)-
piperazine (VI)

20 Following the general procedure of EXAMPLE 1, Step 4 and making non-critical variations but using 1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(4-ethoxyphenyl)-piperazine (V), 1-[2-(6-bromoisochroman-1-yl)ethyl]-4-(4-ethoxyphenyl)piperazine (VI) is obtained, $R_f = 0.56$ (ethyl acetate/n-hexane, 70/30); IR (neat) 2850, 2810, 1512, 1482, 1251, 1231, 1153, 1108, 1048, 826 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.29 (d, 1H, $J=8.3$ Hz, aromatic H), 7.27 (s, 1H, aromatic H), 6.97 (d, 1H, $J=8.3$ Hz, aromatic H),
25 6.85 (q, 4H, $J=9.7$ Hz, aromatic H's), 4.78 (m of d, 1H, $J=6.1$ Hz), 4.14-4.07 (m, 1H), 3.97 (q, 2H, $J=7.0$ Hz, PhOCH_2), 3.76-3.69 (m, 1H), 3.10 (t, 4H, $J=4.9$ Hz, four of pip-H), 2.95 (m, 1H), 2.70-2.50 (m's, 7H, four pip-H, two PhCH-H, and NCH-H), 2.13 (m, 1H, PhCHCH-H), 2.02 (m, 1H, PhCHCH-H), 1.38 (t, 3H, $J=6.9$ Hz, $\text{PhOCH}_2\text{C-H}_3$) δ ; CMR (75 MHz, CDCl_3) 153.1, 145.6, 137.1, 136.3, 131.6, 129.3,
30 126.5, 1120.0, 118.1, 115.2, 74.3, 62.8, 55.6, 53.5, 50.6, 33.2, 28.9, 15.0 δ .

Step 3: 1-[2-[4-(4-Ethoxyphenyl)-1-piperazinyl]ethyl]-N-methyl-
isochroman-6-carboxamide (IX)

Following the general procedure of EXAMPLE 5, Step 3 and making non-critical variations but using 1-[2-(6-bromoisochroman-1-yl)ethyl]-4-(4-ethoxyphenyl)-
35 piperazine (VI), 1-[2-[4-(4-ethoxyphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-

carboxamide (IX) is obtained, mp = 148-149°; R_f = 0.22 (methanol/methylene chloride, 5/95); IR (mull) 3334, 1633, 1536, 1515, 1310, 1245, 1237, 1146, 1108, 1050 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.54 (s, 2H, aromatic H's), 7.15 (d, 1H, $J=8.5$ Hz, aromatic H), 6.85 (d of d, 4H, $J_a=9.2$ Hz, $J_b=19.2$ Hz, four aromatic H's), 6.15 (broad d, 1H, C(O)N-H), 4.85 (m of d, 1H, $J=6.0$ Hz, PhC-H), 4.13 (m, 1H, $\text{PhCH}_2\text{CH-H}$), 3.97 (q, 2H, $J=7$ Hz, PhOC-H_2), 3.77 (m, 1H, $\text{PhCH}_2\text{CH-H}$), 3.10 (t, 4H, $J=4.8$ Hz, four of pip-H), 3.00 (d, 3H, $J=4.9$ Hz, C(O)NHC-H₃), 3.00 (m, 1H, NCH-H), 2.76-2.45 (several m's, 7H, four pip-H, two PhCH-H, and NCH-H), 2.14 (m, 1H, PhCHCH-H), 2.02 (m, 1H, PhCHCH-H), 1.37 (t, 3H, $J=7.0$ Hz, $\text{PhOCH}_2\text{C-H}_3$) δ ; CMR (75 MHz, CDCl_3) 168.0, 153.1, 145.6, 141.6, 134.5, 132.7, 127.7, 126.3, 125.0, 124.4, 118.1, 115.2, 74.5, 63.8, 62.9, 54.7, 53.5, 50.6, 33.2, 29.1, 26.8 and 15.0 δ .

EXAMPLE 16 1-[2-[4-(4-Propoxyphenyl)-1-piperazinyl]ethyl]-N-methyl-
isochroman-6-carboxamide (IX)

Step 1: 1-[2-(6-Bromoisochroman-1-yl)acetyl]-4-(4-propoxyphenyl)-
piperazine (V)

Following the general procedure of EXAMPLE 1, Step 3 and making non-critical variations but using racemic 6-bromoisochroman-1-yl-acetic acid (IV) and p-propoxyphenylpiperazine, 1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(4-propoxyphenyl)-piperazine (V) is obtained, R_f = 0.50 (ethyl acetate/hexane, 70/30); IR (neat) 1641, 1511, 1481, 1464, 1443, 1278, 1242, 1230, 1108, 825 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.28 (m, 2H, aromatic H's), 7.0 (d, 1H, $J=8.2$ Hz, aromatic H), 6.87 (d, 4H, $J=8.2$ Hz, aromatic H's), 5.25 (m of d, 1H, $J=6.5$ Hz, PhC-H), 4.11 (m, 1H), 3.87 (t, 2H, $J=7.0$ Hz, PhOC-H_2), 3.86 (m, 1H), 3.80-3.59 (m, 4H), 3.05 (t, 4H, $J=5.0$ Hz), 3.03-2.89 (m's, 2H), 2.77 (d of d, 1H, $J_a=3.6$ Hz, $J_b=14.9$ Hz), 2.66 (m of d, 1H, $J=16.4$ Hz), 1.78 (sextet, 2H, $J=7.0$ Hz, $\text{PhOCH}_2\text{C-H}_2$), 1.02 (t, 3H, $J=7.0$ Hz, $\text{PhOCH}_2\text{CH}_2\text{C-H}_3$) δ ; CMR (75 MHz, CDCl_3) 168.9, 153.6, 145.0, 136.4, 136.2, 131.6, 129.3, 126.4, 118.7, 115.1, 69.8, 63.4, 41.8, 39.8, 28.7, 22.5 and 10.4 δ ; HRMS calculated for $\text{C}_{24}\text{H}_{29}\text{N}_2\text{O}_3\text{Br}$ = 472.1362, found = 472.1356.

Step 2: 1-[2-(6-Bromoisochroman-1-yl)-ethyl]-4-(4-propoxyphenyl)-
piperazine (VI)

Following the general procedure of EXAMPLE 1, Step 4 and making non-critical variations but using 1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(4-propoxyphenyl)-piperazine (V), 1-[2-(6-bromoisochroman-1-yl)-ethyl]-4-(4-propoxyphenyl)piperazine (VI) is obtained, R_f = 0.52 (ethyl acetate/hexane, 70/30); IR (mull) 1516, 1448, 1261, 1244, 1196, 1131, 1117, 1103, 1005, 985 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.29 (d, 1H, $J=8.3$ Hz, aromatic H), 7.27 (s, 1H, aromatic H), 6.97 (d,

1H, J=8.3 Hz, aromatic H), 6.85 (q, 4H, J=9.7 Hz, aromatic H's), 4.78 (m of d, 1H, J=6.0 Hz, PhC-H), 4.13 (m, 1H, PhCH₂CH-H), 3.87 (t, 2H, J=6.6 Hz, PhOC-H₂), 3.77 (m, 1H, PhCH₂CH-H), 3.10 (t, 4H, J=4.8 Hz, four of pip-H), 3.00 (m, 1H, NCH-H), 2.76-2.45 (several m's, 7H, four pip-H, two PhCH-H, and NCH-H), 2.14 (m, 1H, PhCHCH-H), 2.02 (m, 1H, PhCHCH-H), 1.77 (sextet, 2H, J=6.9 Hz, PhOCH₂C-H₂), 1.01 (t, 3H, J=7.6 Hz, PhOCH₂CH₂C-H₃) δ ; CMR (75 MHz, CDCl₃) 153.3, 145.4, 136.8, 136.2, 131.5, 129.2, 126.4, 119.9, 118.1, 115.0, 69.8, 62.7, 54.5, 53.3, 50.4, 32.9, 28.7, 22.6, 10.4 δ ; HRMS calculated for C₂₄H₃₁N₂O₂Br₁ = 458.1561, found = 458.1569.

10 Step 3: 1-[2-[4-(4-Propoxyphenyl)-1-piperazinyl]ethyl]-N-methyl-
isochroman-6-carboxamide (IX)

Following the general procedure of EXAMPLE 5, Step 3 and making non-critical variations but using 1-[2-(6-bromoisochroman-1-yl)-ethyl]-4-(4-propoxyphenyl)-piperazine (VI) the product is obtained. Rerystallization from hot ethyl acetate and hexane gives 1-[2-[4-(4-propoxyphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide (IX), R_f = 0.20 (methanol/methylene chloride, 5/95); IR (mull) 3296, 1635, 1569, 1559, 1553, 1512, 1289, 1251, 1242, 1109 cm⁻¹; NMR (300 MHz, CDCl₃) 7.54 (s, 2H, aromatic H's), 7.15 (d, 1H, J=8.5 Hz, aromatic H), 6.85 (d of d, 4H, J_a=9.2 Hz, J_b=19.2 Hz, four aromatic H's), 6.15 (broad d, 1H, C(O)N-H), 4.85 (m of d, 1H, J=6.0 Hz, PhC-H), 4.13 (m, 1H, PhCH₂CH-H), 3.86 (t, 2H, J=6.6 Hz, PhOC-H₂), 3.77 (m, 1H, PhCH₂CH-H), 3.10 (t, 4H, J=4.8 Hz, four of pip-H), 3.00 (d, 3H, J=4.9 Hz, C(O)NHC-H₃), 3.00 (m, 1H, NCH-H), 2.76-2.45 (several m's, 7H, four pip-H, two PhCH-H, and NCH-H), 2.14 (m, 1H, PhCHCH-H), 2.02 (m, 1H, PhCHCH-H), 1.77 (sextet, 2H, J=6.9 Hz, PhOCH₂C-H₂), 1.01 (t, 3H, J=7.4 Hz, PhOCH₂CH₂C-H₃) δ ; CMR (75 MHz, CDCl₃) 167.9, 153.2, 145.4, 141.5, 134.3, 132.5, 127.5, 124.9, 124.3, 118.0, 115.0, 69.8, 62.8, 54.5, 53.4, 50.5, 33.0, 30.5, 28.9, 26.7, 22.5 and 10.4 δ .

EXAMPLE 17 (S)-(-)-1-[2-[4-(4-Trifluoromethoxyphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide (IX)

30 Step 1: (S)-(-)-1-[2-(6-Bromoisochroman-1-yl)acetyl]-4-(4-trifluoromethoxyphenyl)piperazine (S)-(V)

Following the general procedure of EXAMPLE 1, Step 3 and making non-critical variations but using 4-trifluoromethoxyphenylpiperazine, (S)-(-)-1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(4-trifluoromethoxyphenyl)piperazine (S)-(V) is obtained, [α]_D = -70° (c = 0.68, ethanol); R_f = 0.52 (ethyl acetate/hexane, 70/30); IR (neat) 1641, 1511, 1482, 1465, 1445, 1266, 1232, 1211, 1160, 1108 cm⁻¹; NMR (300

MHz, CDCl_3) 7.28 (m, 2H, aromatic H's), 7.14 (d, 2H, $J=8.9$ Hz, aromatic H's), 7.0 (d, 1H, $J=8.2$ Hz, aromatic H), 6.87 (d, 2H, $J=8.9$ Hz, aromatic H's), 5.25 (m of d, 1H, $J=6.5$ Hz, PhC-H), 4.11 (m, 1H), 3.92 (m, 1H), 3.75 (m, 4H), 3.16 (t, 4H, $J=5.0$ Hz), 3.03-2.89 (m's, 2H), 2.77 (d of d, 1H, $J_a=3.6$ Hz, $J_b=14.9$ Hz), 2.66 (m of d, 1H, $J=16.4$ Hz) δ ; CMR (75 MHz, CDCl_3) 168.9, 149.8, 145.0, 136.9, 136.4, 131.6, 129.3, 126.3, 122.0, 120.7, 117.1, 73.4, 63.4, 49.8, 48.2, 45.8, 42.0, 39.8, 28.7 δ ; HRMS calculated for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{F}_3\text{O}_3\text{Br}$ = 498.0766, found = 498.0764.

Step 2: (S)-(-)-1-[2-(6-Bromoisochroman-1-yl)-ethyl]-4-(4-trifluoromethoxyphenyl)-piperazine (S)-(VI)

10 Following the general procedure of EXAMPLE 1, Step 4 and making non-critical variations but using (S)-(-)-1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(4-trifluoromethoxyphenyl)piperazine (S)-(V), (S)-(-)-1-[2-(6-bromoisochroman-1-yl)-ethyl]-4-(4-trifluoromethoxyphenyl)piperazine (S)-(VI) is obtained, $R_f = 0.54$ (ethyl acetate/hexane, 70/30); $[\alpha]_D = -42^\circ$ ($c = 1.1$, ethanol; IR (neat) 2825, 1513, 1281, 1263, 1240, 1204, 1184, 1157, 1112, 1106 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.29 (d, 1H, $J=8.3$ Hz, aromatic H), 7.27 (s, 1H, aromatic H), 7.11 (d, 2H, $J=9$ Hz, aromatic H's), 6.97 (d, 1H, $J=8.2$ Hz, aromatic H), 6.87 (q, 2H, $J=9.1$ Hz, two aromatic H's), 4.78 (m of d, 1H, $J=6.0$ Hz, PhC-H), 4.11 (m, 1H, $\text{PhCH}_2\text{CH-H}$), 3.75 (m, 1H, $\text{PhCH}_2\text{CH-H}$), 3.18 (t, 4H, $J=4.8$ Hz, four of pip-H), 3.00 (m, 1H, NCH-H), 2.76-2.45 (several m's, 7H, four pip-H, two PhCH-H, and NCH-H), 2.14 (m, 1H, PhCHCH-H), 2.02 (m, 1H, PhCHCH-H) δ ; CMR (75 MHz, CDCl_3) 150.0, 136.5, 135.5, 131.5, 129.2, 126.3, 121.9, 120.1, 116.4, 74.1, 62.7, 54.9, 53.1, 49.1, 33.0 and 28.7 δ ; HRMS calculated for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_2\text{F}_3\text{Br}_1$ (+1) = 486.0954, found = 486.0956.

25 Step 3: (S)-(-)-1-[2-[4-(4-Trifluoromethoxyphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide (S)-(IX)

Following the general procedure of EXAMPLE 5, Step 3 and making non-critical variations but using (S)-(-)-1-[2-(6-bromoisochroman-1-yl)-ethyl]-4-(4-trifluoromethoxyphenyl)piperazine (S)-(VI) the product is obtained. Recrystallization from hot ethyl acetate and hexane gives (S)-(-)-1-[2-[4-(4-trifluoromethoxyphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide (S)-(IX), $R_f = 0.20$ (methanol/methylene chloride, 5/95); IR (mull) 1636, 1614, 1572, 1551, 1513, 1450, 1270, 1238, 1157, 1107 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.54 (s, 2H, aromatic H's), 7.15 (d, 1H, $J=8.6$ Hz, aromatic H), 7.11 (d, 2H, $J=8.9$ Hz, two aromatic H's), 6.87 (q, 2H, $J=8.9$ Hz, two aromatic H's), 6.19 (broad d, 1H, C(O)N-H), 4.86 (m of d, 1H, $J=6.0$ Hz, PhC-H), 4.13 (m, 1H, $\text{PhCH}_2\text{CH-H}$), 3.77 (m, 1H, $\text{PhCH}_2\text{CH-H}$), 3.18 (t, 4H, $J=4.8$ Hz, four of pip-H), 3.00 (d, 3H, $J=4.9$ Hz, C(O)NHC-H₃), 3.00 (m, 1H,

NCH-H), 2.76-2.45 (several m's, 7H, four pip-H, two PhCH-H, and NCH-H), 2.14 (m, 1H, PhCHCH-H), 2.02 (m, 1H, PhCHCH-H) δ ; CMR (75 MHz, CDCl_3) 167.8, 149.8, 144.7, 141.3, 134.3, 132.6, 127.5, 124.8, 124.3, 121.8, 116.5, 86.2, 74.3, 62.8, 54.54, 53.4, 48.9, 32.9, 28.9 and 26.7 δ ; HRMS calculated for $\text{C}_{24}\text{H}_{18}\text{O}_3\text{F}_3$ = 463.2083, found = 463.2086.

EXAMPLE 18 (S)-(-)-1-[2-[4-(4-Ethylphenyl)-1-piperazinyl]ethyl]-N-methyl-isochroman-6-carboxamide (S)-(IX)

Step 1: (S)-(-)-1-[2-(6-Bromoisochroman-1-yl)acetyl]-4-(4-ethylphenyl)-piperazine (S)-(V)

Following the general procedure of EXAMPLE 1, Step 3 and making non-critical variations but using 4-ethylphenylpiperazine, (S)-(-)-1-[2-(6-Bromoisochroman-1-yl)acetyl]-4-(4-ethylphenyl)piperazine (S)-(V) is obtained, R_f = 0.70 (ethyl acetate/hexane, 70/30); $[\alpha]_D^{25}$ = -81° (c = 0.7, ethanol); IR (neat) 1640, 1614, 1516, 1482, 1462, 1444, 1428, 1232, 1108 and 826 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.27 (m, 2H, aromatic H's), 7.11 (d, 2H, J=8.4 Hz, aromatic H's), 7.0 (d, 1H, J=8.2 Hz, aromatic H), 6.86 (d, 2H, J=8.2 Hz, aromatic H's), 5.25 (m of d, 1H, J=6.5 Hz, PhC-H), 4.08 (m, 1H), 3.89 (m, 1H), 3.80-3.59 (m, 4H), 3.11 (t, 4H, J=5.0 Hz), 3.03-2.89 (m's, 2H), 2.77 (d of d, 1H, J_a=3.6 Hz, J_b=14.9 Hz), 2.66 (m, 1H), 2.57 (q, 2H, J=7.6 Hz, PhC-H₂), 1.20 (t, 3H, J=7.6 Hz, PhCH₂C-H₃) δ ; CMR (75 MHz, CDCl_3) 169.0, 149.0, 136.5, 136.3, 131.8, 129.4, 128.6, 126.5, 120.4, 116.9, 73.5, 63.5, 50.3, 49.8, 46.1, 41.9, 39.9, 28.8, 27.9 and 15.7 δ .

Step 2: (S)-(-)-1-[2-(6-Bromoisochroman-1-yl)-ethyl]-4-(4-ethylphenyl)-piperazine (S)-(VI)

Following the general procedure of EXAMPLE 1, Step 4 and making non-critical variations but using (S)-(-)-1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(4-ethylphenyl)-piperazine (S)-(V), (S)-(-)-1-[2-(6-Bromoisochroman-1-yl)-ethyl]-4-(4-ethylphenyl)-piperazine (S)-(VI) is obtained, R_f = 0.61 (ethyl acetate/hexane, 30/70); IR (mull) 2960, 2929, 2819, 1516, 1481, 1379, 1237, 1143, 1111 and 822 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.29 (d, 1H, J=8.3 Hz, aromatic H), 7.27 (s, 1H, aromatic H), 7.09 (d, 2H, J=8.6 Hz, aromatic H's), 6.98 (d, 1H, J=8.2 Hz, aromatic H), 6.87 (d, 2H, J=8.6 Hz, aromatic H's), 4.77 (m of d, 1H, J=6.0 Hz, PhC-H), 4.13 (m, 1H, PhCH₂CH-H), 3.75 (m, 1H, PhCH₂CH-H), 3.17 (t, 4H, J=4.8 Hz, four of pip-H), 3.00 (m, 1H, NCH-H), 2.70-2.53 (several m's, 9H, four pip-H, two PhCH-H, PhC-H₂, and NCH-H), 2.14 (m, 1H, PhCHCH-H), 2.02 (m, 1H, PhCHCH-H), 1.20 (t, 3H, J=7.6 Hz, PhCH₂C-H₃) δ ; CMR (75 MHz, CDCl_3) 149.4, 137.1, 136.3, 135.6, 131.6, 129.3, 128.4, 126.5, 120.0, 116.3, 74.3, 62.8, 54.7, 53.5, 49.6, 33.2, 30.3, 28.9, 27.9 and 15.7 δ .

8; HRMS calculated for $C_{23}H_{29}N_2O_1Br_1 = 430.1444$, found = 430.1443.

Step 3: (S)-(-)-1-[2-[4-(4-Ethylphenyl)-1-piperazinyl]ethyl]-N-methyl-
isochroman-6-carboxamide (S)-(IX)

Following the general procedure of EXAMPLE 5, Step 3 and making non-critical variations but using (S)-(-)-1-[2-(6-bromoisochroman-1-yl)-ethyl]-4-(4-ethylphenyl)-piperazine (S)-(VI) the desired product is obtained. Recrystallization from hot ethyl acetate and hexane gives (S)-(-)-1-[2-[4-(4-ethylphenyl)-1-piperazinyl]ethyl]-N-methyl-isochroman-6-carboxamide (S)-(IX), mp = 138-140°; $R_f = 0.28$ (methanol/methylene chloride, 5/95); $[\alpha]_D = -50^\circ$ (c = 0.93, methanol/methylene chloride, 50/50); IR (mull) 3321, 1635, 1614, 1539, 1518, 1405, 1312, 1238, 1107 and 822 cm^{-1} ; NMR (300 MHz, $CDCl_3$) 7.54 (s, 2H, aromatic H's), 7.15 (d, 1H, J=8.6 Hz, aromatic H), 7.09 (d, 2H, J=8.5 Hz, 2 aromatic H's), 6.86 (d, 2H, J=8.5 Hz, 2 aromatic H's), 6.14 (broad d, 1H, C(O)N-H), 4.86 (m of d, 1H, J=6.0 Hz, PhC-H), 4.13 (m, 1H, $PhCH_2CH$ -H), 3.77 (m, 1H, $PhCH_2CH$ -H), 3.17 (t, 4H, J=4.8 Hz, four of pip-H), 3.00 (d, 3H, J=4.9 Hz, C(O)NHC- H_3), 3.00 (m, 1H, NCH-H), 2.76-2.45 (several m's, 9H, four pip-H, two PhCH-H, PhC- H_2 , and NCH-H), 2.14 (m, 1H, $PhCHCH$ -H), 2.02 (m, 1H, $PhCHCH$ -H), 1.20 (t, 3H, J=7.6 Hz, $PhCH_2C$ - H_3) δ ; CMR (75 MHz, $CDCl_3$) 168.0, 149.3, 141.6, 135.7, 134.5, 132.7, 128.4, 127.7, 125.0, 124.4, 116.3, 62.9, 54.7, 53.4, 49.6, 33.1, 29.1, 27.9, 26.8 and 15.7 δ ; HRMS calculated for $C_{25}H_{33}N_3O_3 = 407.2573$, found = 407.2581.

EXAMPLE 19 (S)-(-)-1-[2-[4-(4-Ethoxyphenyl)-1-piperazinyl]ethyl]-N-methyl-
isochroman-6-carboxamide (S)-(IX)

Step 1: (S)-(-)-1-[2-(6-Bromoisochroman-1-yl)acetyl]-4-(4-ethoxyphenyl)-
piperazine (S)-(V)

Following the general procedure of EXAMPLE 1, Step 3 and making non-critical variations but using 4-ethoxyphenylpiperazine, (S)-(-)-1-[2-(6-Bromoisochroman-1-yl)acetyl]-4-(4-ethoxyphenyl)piperazine (S)-(V) is obtained, $R_f = 0.60$ (ethyl acetate/hexane, 70/30); $[\alpha]_D = -78^\circ$ (c = 0.82, ethanol); IR (neat) 1627, 1515, 1478, 1441, 1429, 1250, 1230, 1102, 1031 and 821 cm^{-1} ; NMR (300 MHz, $CDCl_3$) 7.28 (m, 2H, aromatic H's), 7.0 (d, 1H, J=8.2 Hz, aromatic H), 6.86 (d, 4H, J=8.2 Hz, aromatic H's), 5.25 (m of d, 1H, J=6.5 Hz, PhC-H), 4.11 (m, 1H), 3.99 (q, 2H, J=7.0 Hz, PhOC- H_2), 3.89 (m, 1H), 3.80-3.59 (m, 4H), 3.05 (t, 4H, J=5.0 Hz), 3.03-2.89 (m's, 2H), 2.77 (d of d, 1H, $J_a=3.6$ Hz, $J_b=14.9$ Hz), 2.66 (m of d, 1H, J=16.4 Hz), 1.39 (t, 3H, J=7.0 Hz, $PhCH_2C$ - H_3) δ ; CMR (75 MHz, $CDCl_3$) 168.9, 153.5, 145.2, 136.3, 136.2, 131.6, 129.3, 126.4, 118.7, 115.1, 73.3, 63.7, 63.4, 51.2, 50.7, 46.1, 41.9, 39.8, 28.7 and 14.8 δ ; HRMS calculated for $C_{23}H_{27}N_2O_3Br =$

458.1205, found = 458.1203.

Step 2: (S)-(-)-1-[2-(6-Bromoisochroman-1-yl)-ethyl]-4-(4-ethoxyphenyl)-piperazine (S)-(VI)

Following the general procedure of EXAMPLE 1, Step 4 and making non-critical variations but using (S)-(-)-1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(4-ethoxyphenyl)piperazine (S)-(V) gives (S)-(-)-1-[2-(6-bromoisochroman-1-yl)-ethyl]-4-(4-ethoxyphenyl)-piperazine (S)-(VI), mp = 85-87°; R_f = 0.28 (ethyl acetate/n-hexane, 30/70); $[\alpha]_D^{25}$ = -46° (c = 0.60, ethanol); IR (neat) 1516, 1476, 1261, 1246, 1196, 1130, 1117, 1104, 1060 and 932 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.29 (d, 1H, J=8.3 Hz, aromatic H), 7.27 (s, 1H, aromatic H), 6.97 (d, 1H, J=8.3 Hz, aromatic H), 6.85 (q, 4H, J=9.7 Hz, aromatic H's), 4.78 (m of d, 1H, J=6.1 Hz), 4.14-4.07 (m, 1H), 3.97 (q, 2H, J=7.0 Hz, PhOC-H_2), 3.76-3.69 (m, 1H), 3.10 (t, 4H, J=4.9 Hz, four of pip-H), 2.95 (m, 1H), 2.70-2.50 (m's, 7H, four pip-H, two PhCH-H , and NCH-H), 2.13 (m, 1H, PhCHCH-H), 2.02 (m, 1H, PhCHCH-H), 1.38 (t, 3H, J=6.9 Hz, $\text{PhOCH}_2\text{C-H}_3$) δ ; CMR (75 MHz, CDCl_3) 153.1, 145.6, 137.1, 136.3, 131.6, 129.3, 126.5, 1120.0, 118.1, 115.2, 74.3, 62.8, 55.6, 53.5, 50.6, 33.2, 28.9 and 15.0 δ .

Step 3: (S)-(-)-1-[2-[4-(4-Ethoxyphenyl)-1-piperazinyl]ethyl]-N-methyl-isochroman-6-carboxamide (S)-(IX)

Following the general procedure of EXAMPLE 5, Step 3 and making non-critical variations but using (S)-(-)-1-[2-(6-bromoisochroman-1-yl)-ethyl]-4-(4-ethoxyphenyl)piperazine (S)-(VI) gives (S)-(-)-1-[2-[4-(4-ethoxyphenyl)-1-piperazinyl]ethyl]-N-methyl-isochroman-6-carboxamide (S)-(IX). Recrystallization from hot ethyl acetate and hexane gives purified product, mp = 156-157°; R_f = 0.20 (methanol/methylene chloride, 5/95); $[\alpha]_D^{25}$ = -48° (c = 0.94, methanol/methylene chloride, 50/50); IR (mull) 3334, 1633, 1536, 1515, 1310, 1245, 1237, 1146, 1108 and 1050 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.54 (s, 2H, aromatic H's), 7.15 (d, 1H, J=8.5 Hz, aromatic H), 6.85 (d of d, 4H, J_a =9.2 Hz, J_b =19.2 Hz, four aromatic H's), 6.15 (broad d, 1H, C(O)N-H), 4.85 (m of d, 1H, J=6.0 Hz, PhC-H), 4.13 (m, 1H, $\text{PhCH}_2\text{CH-H}$), 3.97 (q, 2H, J=7 Hz, PhOC-H_2), 3.77 (m, 1H, $\text{PhCH}_2\text{CH-H}$), 3.10 (t, 4H, J=4.8 Hz, four of pip-H), 3.00 (d, 3H, J=4.9 Hz, C(O)NHC-H_3), 3.00 (m, 1H, NCH-H), 2.76-2.45 (several m's, 7H, four pip-H, two PhCH-H , and NCH-H), 2.14 (m, 1H, PhCHCH-H), 2.02 (m, 1H, PhCHCH-H), 1.37 (t, 3H, J=7.0 Hz, $\text{PhOCH}_2\text{C-H}_3$) δ ; CMR (75 MHz, CDCl_3) 168.0, 153.1, 145.6, 141.6, 134.5, 132.7, 127.7, 126.3, 125.0, 124.4, 118.1, 115.2, 74.5, 63.8, 62.9, 54.7, 53.5, 50.6, 33.2, 29.1, 26.8 and 15.0 δ ; HRMS calculated for $\text{C}_{25}\text{H}_{33}\text{N}_3\text{O}_3$ = 423.2522, found = 423.2518.

EXAMPLE 20 (S)-(-)-1-[2-[4-(4-Phenylmethoxyphenyl)-1-piperazinyl]ethyl]-N-

methyloisochroman-6-carboxamide (S)-(IX)

Step 1: (S)-(-)-1-[2-(6-Bromoisochroman-1-yl)acetyl]-4-(4-phenylmethyloxyphenyl)piperazine (S)-(V)

Following the general procedure of EXAMPLE 1, Step 3 and making non-critical variations but using 4-phenylmethyloxyphenylpiperazine (3.38 g, 12.6 mmol), the product is obtained. This material is purified by HPLC on a single silica gel cartridge eluting with ethylacetate/hexane (70/30) to give (S)-(-)-1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(4-phenylmethyloxyphenyl)piperazine (S)-(V), $R_f = 0.30$ (ethyl acetate/hexane, 50/50); $[\alpha]_D = -34^\circ$ ($c = 0.50$, methanol); NMR (300 MHz, $CDCl_3$) 7.35 (m, 7H, aromatic), 6.96 (d, 1H, $J=8.2$ Hz, aromatic), 6.90 (m, 4H, aromatic), 5.26 (brdd, 1H, $J=5.4$ Hz, methine), 5.02 (s, 2H, $Ph-CH_2-O$), 4.09 (m, 1H, OCH_{2a}), 3.89 (m, 1H, $O=C-N-CH_{2a}$), 3.81-3.64 (m, 4H, OCH_{2b} , $O=C-N-CH_{2bcd}$), 3.05 (m, 4H, $Ph-N-CH_{2s}$), 3.00-2.89 (m, 2H, $Ph-CH_{2a}$ & $N-C=O-CH_{2a}$), 2.76 (dd, 1H, $J=14.9$ Hz & 3.6 Hz, $N-C=O-CH_{2b}$), 2.66 (brdd, 1H, $J=16.4$ Hz, $Ph-CH_{2b}$) δ ; CMR (75 MHz, $CDCl_3$) 169.0, 153.6, 145.5, 137.3, 136.6, 136.3, 131.8, 129.4, 128.6, 127.9, 127.5, 126.5, 120.4, 118.8, 115.7, 76.7, 73.5, 70.5, 63.5, 51.3, 50.7, 46.2, 42.0, 40.0 and 28.8 δ .

Step 2: (S)-(-)-1-[2-(6-Bromoisochroman-1-yl)-ethyl]-4-(4-phenylmethyloxyphenyl)piperazine (S)-(VI)

Following the general procedure of EXAMPLE 1, Step 4 and making non-critical variations but using (S)-(-)-1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(4-phenylmethyloxyphenyl)piperazine (V, 5.96 g, 11.4 mmol) gives (S)-(-)-1-[2-(6-bromoisochroman-1-yl)-ethyl]-4-(4-phenylmethyloxyphenyl)-piperazine (S)-(VI), $R_f = 0.40$ (ethyl acetate/hexane, 50/50); $[\alpha]_D = -63^\circ$ ($c = 0.925$, methanol); NMR (300 MHz, $CDCl_3$) 7.27 (m, 7H, aromatic), 6.91 (d, 1H, $J=8.3$ Hz, aromatic), 6.83 (s, 4H, aromatic), 4.94 (s, 2H, $Ph-CH_2-O$), 4.73 (brdd, 1H, $J=5.7$ Hz, methine), 4.03 (m, 1H, OCH_{2a}), 3.67 (m, 1H, OCH_{2b}), 3.05 (t, 4H, $J=4.8$ Hz, $Ph-NCH_{2s}$), 2.88 (m, 1H, $Ph-CH_{2a}$), 2.60 (m, 7H, $Ph-NC(H_2)-CH_{2s}-NCH_2$ & $Ph-CH_{2b}$), 2.05 (m, 1H, $C(H)-CH_{2a}$), 1.97 (m, 1H, $C(H)-CH_{2b}$) δ ; CMR (75 MHz, $CDCl_3$) 153.1, 145.8, 137.4, 136.9, 136.3, 131.7, 129.3, 128.5, 127.9, 127.5, 126.5, 120.1, 118.2, 115.6, 70.5, 62.9, 54.6, 53.4, 50.4, 32.9 and 28.9 δ .

Step 3: (S)-(-)-1-[2-[4-(4-Phenylmethyloxyphenyl)-1-piperazinyl]ethyl]-N-methyl-isochroman-6-carboxamide (S)-(IX)

Following the general procedure of EXAMPLE 5, Step 3 and making non-critical variations but using (S)-(-)-1-[2-(6-bromoisochroman-1-yl)-ethyl]-4-(4-phenylmethyloxyphenyl)piperazine (S)-(VI, 5.08 g, 11.4 mmol) gives the product.

This material is purified by LC (silica gel, 230-400 mesh, 270 g; ethyl acetate) and recrystallized from ethyl acetate to give (S)-(-)-1-[2-[4-(4-phenylmethoxyphenyl)-1-piperazinyl]ethyl]-N-methyl-isochroman-6-carboxamide (S)-(IX), mp = 164-167°; R_f = 0.40 (methanol/ethylacetate, 5/95); $[\alpha]_D^{25} = -40^\circ$ ($c = 0.9323$, methanol); IR (mull) 3302, 1639, 1544, 1515, 1498, 1314, 1291, 1272, 1252, 1153, 1138, 1111, 818, 735 and 695 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.53 (m, 2H, aromatic), 7.54 (m, 2H, aromatic), 7.43-7.23 (m, 5H, aromatic), 7.14 (d, 1H, $J=8.6$ Hz, aromatic), 6.89 (s, 4H, aromatic), 6.19 (brdm, 1H, NH), 5.01 (s, 2H, PhO-CH_2), 4.86 (brdd, 1H, $J=5.9$ Hz, methine), 4.14 (m, 1H, OCH_{2a}), 3.76 (m, 1H, OCH_{2b}), 3.10 (t, 4H, $J=4.8$ Hz, Ph-N-CH_{2s}), 3.00 (d, 4H, $J=4.8$ Hz, N-CH_3 & Ph-CH_{2a}), 2.76-2.49 (m, 7H, $\text{Ph-NC(H)}_2\text{-CH}_{2s}\text{-NCH}_{2s}$, Ph-CH_{2b}), 2.14 (m, 1H, C(H)-CH_{2a}), 2.04 (m, 1H, C(H)-CH_{2b}) δ ; CMR (75 MHz, CDCl_3) 168.0, 153.0, 145.9, 141.6, 137.4, 134.5, 132.7, 128.5, 127.9, 127.7, 127.5, 125.0, 124.4, 118.0, 115.6, 74.5, 70.5, 63.0, 54.7, 53.5, 50.5, 33.2, 29.1 and 26.9 δ ; MS (EI, m/z) = 485; HRMS (EI) calculated for $\text{C}_{30}\text{H}_{35}\text{N}_3\text{O}_3$ = 485.2678, found = 485.2675.

EXAMPLE 21 (R)-(+)-1-[2-[4-(4-Ethoxyphenyl)-1-piperazinyl]ethyl]-N-methyl-isochroman-6-carboxamide (R)-(IX)

Step 1: (R)-(+)-1-[2-(6-Bromoisochroman-1-yl)acetyl]-4-(4-ethoxyphenyl)-piperazine (R-V)

Following the general procedure of EXAMPLE 2, Step 2 and making non-critical variations but using 4-ethoxyphenylpiperazine gives (R)-(+)-1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(4-ethoxyphenyl)piperazine (R-V), R_f = 0.60 (ethyl acetate/hexane, 70/30); $[\alpha]_D^{25} = +76^\circ$ ($c = 0.71$, ethanol); IR (neat) 1626, 1515, 1478, 1442, 1249, 1246, 1230, 1102, 1030 and 821 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.28 (m, 2H, aromatic H's), 7.0 (d, 1H, $J=8.2$ Hz, aromatic H), 6.86 (d, 4H, $J=8.2$ Hz, aromatic H's), 5.25 (m of d, 1H, $J=6.5$ Hz, PhC-H), 4.11 (m, 1H), 3.99 (q, 2H, $J=7.0$ Hz, PhOC-H_2), 3.89 (m, 1H), 3.80-3.59 (m, 4H), 3.05 (t, 4H, $J=5.0$ Hz), 3.03-2.89 (m's, 2H), 2.77 (d of d, 1H, $J_a=3.6$ Hz, $J_b=14.9$ Hz), 2.66 (m of d, 1H, $J=16.4$ Hz), 1.39 (t, 3H, $J=7.0$ Hz, $\text{PhCH}_2\text{C-H}_3$) δ ; CMR (75 MHz, CDCl_3) 168.9, 153.6, 145.0, 136.4, 136.2, 131.6, 129.3, 126.4, 120.2, 118.7, 115.1, 73.3, 63.7, 63.55, 63.47, 63.4, 51.2, 50.7, 46.0, 41.8, 39.8, 28.7 and 14.8 δ ; HRMS calculated for $\text{C}_{23}\text{H}_{27}\text{N}_2\text{O}_3\text{Br}$ (on Br 81 ion) = 460.1185, found = 460.1179.

Step 2: (R)-(+)-1-[2-(6-Bromoisochroman-1-yl)-ethyl]-4-(4-ethoxyphenyl)-piperazine (R-VI)

Following the general procedure of EXAMPLE 2, Step 3 and making non-critical variations but using (R)-(+)-1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(4-

ethoxyphenyl)piperazine (R-V) gives (R)-(+)-1-[2-(6-bromoisochroman-1-yl)-ethyl]-4-(4-ethoxyphenyl)piperazine (R-VI), $R_f = 0.25$ (ethyl acetate/n-hexane, 30/70); $[\alpha]_D = +43^\circ$ ($c = 0.73$, ethanol); IR (neat) 2820, 1511, 1478, 1446, 1250, 1225, 1116, 1108, 1047 and 825 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.29 (d, 1H, $J=8.3$ Hz, aromatic H), 7.27 (s, 1H, aromatic H), 6.97 (d, 1H, $J=8.3$ Hz, aromatic H), 6.85 (q, 4H, $J=9.7$ Hz, aromatic H's), 4.78 (m of d, 1H, $J=6.1$ Hz), 4.14-4.07 (m, 1H), 3.97 (q, 2H, $J=7.0$ Hz, PhOC-H_2), 3.76-3.69 (m, 1H), 3.10 (t, 4H, $J=4.9$ Hz, four of pip-H), 2.95 (m, 1H), 2.70-2.50 (m's, 7H, four pip-H, two PhCH-H , and NCH-H), 2.13 (m, 1H, PhCHCH-H), 2.02 (m, 1H, PhCHCH-H), 1.38 (t, 3H, $J=6.9$ Hz, $\text{PhOCH}_2\text{C-H}_3$) δ ; CMR (75 MHz, CDCl_3) 153.1, 145.6, 137.1, 136.3, 131.6, 129.3, 126.5, 1120.0, 118.1, 115.2, 74.3, 62.8, 55.6, 53.5, 50.6, 33.2, 28.9 and 15.0 δ ; HRMS calculated for $\text{C}_{23}\text{H}_{29}\text{N}_2\text{O}_2\text{Br}$ = 444.1413, found = 444.1413.

Step 3: (R)-(+)-1-[2-[4-(4-Ethoxyphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide (R-IX)

Following the general procedure of EXAMPLE 5, Step 3 and making non-critical variations but using (R)-(+)-1-[2-(6-bromoisochroman-1-yl)-ethyl]-4-(4-ethoxyphenyl)piperazine (R-VI) gives (R)-(+)-1-[2-[4-(4-ethoxyphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide (R-IX), $R_f = 0.20$ (methanol/methylene chloride, 5/95); $[\alpha]_D = +49^\circ$ ($c = 0.93$, methanol/methylene chloride, 50/50); IR (mull) 3334, 1633, 1536, 1515, 1310, 1245, 1237, 1146, 1108 and 1050 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.54 (s, 2H, aromatic H's), 7.15 (d, 1H, $J=8.5$ Hz, aromatic H), 6.85 (d of d, 4H, $J_a=9.2$ Hz, $J_b=19.2$ Hz, four aromatic H's), 6.15 (broad d, 1H, C(O)N-H), 4.85 (m of d, 1H, $J=6.0$ Hz, PhC-H), 4.13 (m, 1H, $\text{PhCH}_2\text{CH-H}$), 3.97 (q, 2H, $J=7$ Hz, PhOC-H_2), 3.77 (m, 1H, $\text{PhCH}_2\text{CH-H}$), 3.10 (t, 4H, $J=4.8$ Hz, four of pip-H), 3.00 (d, 3H, $J=4.9$ Hz, C(O)NHC-H_3), 3.00 (m, 1H, NCH-H), 2.76-2.45 (several m's, 7H, four pip-H, two PhCH-H , and NCH-H), 2.14 (m, 1H, PhCHCH-H), 2.02 (m, 1H, PhCHCH-H), 1.37 (t, 3H, $J=7.0$ Hz, $\text{PhOCH}_2\text{C-H}_3$) δ ; CMR (75 MHz, CDCl_3) 168.0, 153.1, 145.6, 141.6, 134.5, 132.7, 127.7, 126.3, 125.0, 124.4, 118.1, 115.2, 74.5, 63.8, 62.9, 54.7, 53.5, 50.6, 33.2, 29.1, 26.8 and 15.0 δ ; HRMS calculated for $\text{C}_{25}\text{H}_{33}\text{N}_3\text{O}_3$ = 423.2522, found = 423.2516.

EXAMPLE 22 1-[2-[4-(3-Trifluoromethylphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide (IX)

Step 1: 1-[2-[4-(3-Trifluoromethylphenyl)-1-piperazinyl]ethyl]-N,N-di-*t*-butyloxycarbonylisochroman-6-carboxamide (VIII)

Following the general procedure of EXAMPLE 3, Step 1 and making non-critical variations but using 1-[2-[4-(3-trifluoromethylphenyl)-1-

piperazinyl]ethyl]-isochroman-6-carboxamide gives crude product. This material is purified by LC (silica gel, 230-400 mesh, 60 g; acetone/hexane, 25/75) to give 1-[2-[4-(3-trifluoromethylphenyl)-1-piperazinyl]ethyl]-N,N-di-t-butyloxycarbonylisochroman-6-carboxamide (VIII), $R_f = 0.37$ (acetone/hexane, 25/75).

5 Step 2: 1-[2-[4-(3-Trifluoromethylphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide (IX)

Following the general procedure of EXAMPLE 3, Step 2 and making non-critical variations but using 1-[2-[4-(3-trifluoromethylphenyl)-1-piperazinyl]ethyl]-N,N-di-t-butyloxycarbonylisochroman-6-carboxamide (VIII, 1.13 g, 1.8 mmol) gives crude product. This material is purified by LC (silica gel, 230-400 mesh, 66 g; acetone/hexane, 50/50) to give 1-[2-[4-(3-trifluoromethylphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide (IX) which is recrystallized from ethylacetate/hexane, mp = 142-143°; $R_f = 0.33$ (acetone/hexane, 50/50); IR (mull) 3307, 1637, 1612, 1606, 1558, 1443, 1311, 1290, 1247, 1151, 1136, 1122, 1109, 1099 and 951 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.55 (m, 2H, aromatic), 7.33 (t, 1H, J=8.0 Hz, aromatic), 7.12 (d, 1H, J=8.6 Hz, aromatic), 7.06 (m, 4H, aromatic), 6.14 (brdm, 1H, NH), 4.87 (brdd, 1H, J=5.9 Hz, methine), 4.14 (m, 1H, OCH_{2a}), 3.76 (m, 1H, OCH_{2b}), 3.24 (t, 4H, J=5.0 Hz, Ph-N-CH_{2s}), 3.00 (d, 4H, J=4.9 Hz, N-CH_3 & Ph-CH_{2a}), 2.76-2.48 (m, 7H, $\text{Ph-NC(H}_2\text{)-CH}_{2s}\text{-NCH}_{2s}$, Ph-CH_{2b}), 2.15 (m, 1H, C(H)- CH_{2a}), 2.05 (m, 1H, C(H)- CH_{2b}) δ ; CMR (75 MHz, CDCl_3) 168.0, 151.4, 141.6, 134.5, 132.7, 131.4 (qrt, $J_{\text{CF}}=32$ Hz), 129.5, 127.7, 125.0, 124.4, 118.6, 115.7 (d, $J_{\text{CF}}=4$ Hz), 112.1 (d, $J_{\text{CF}}=4$ Hz), 74.4, 63.0, 54.6, 53.2, 48.7, 33.2, 29.1 and 26.9 δ ; HRMS (EI) calculated for $\text{C}_{24}\text{H}_{28}\text{F}_3\text{N}_3\text{O}_2 = 447.2133$, found = 447.2132.

25 EXAMPLE 23 1-[2-[4-(4-Methylsulfonylphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide (IX)

Step 1: 1-[2-[4-(4-Methylsulfonylphenyl)-1-piperazinyl]ethyl]-N,N-di-t-butyloxycarbonylisochroman-6-carboxamide (VIII)

Following the general procedure of EXAMPLE 3, Step 1 and making non-critical variations but using 1-[2-[4-(4-methylsulfonylphenyl)-1-piperazinyl]ethyl]-isochroman-6-carboxamide (825 mg, 1.9 mmol) gives crude product. This material is purified by LC (silica gel, 230-400 mesh, 58 g; acetone/hexane, 45/55) to give 1-[2-[4-(4-methylsulfonylphenyl)-1-piperazinyl]ethyl]-N,N-di-t-butyloxycarbonylisochroman-6-carboxamide (VIII), $R_f = 0.20$ (acetone/hexane, 40/60).

35 Step 2: 1-[2-[4-(4-Methylsulfonylphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide (IX)

Following the general procedure of EXAMPLE 3, Step 2 and making non-critical variations but using 1-[2-[4-(4-methylsulfonylphenyl)-1-piperazinyl]ethyl]-N,N-di-t-butyloxycarbonylisochroman-6-carboxamide (VIII, 650 mg, 1.0 mmol) gives crude product. This material is purified by LC (silica gel, 230-400 mesh, 71 g; methanol/dichloromethane, 5/95) to give 1-[2-[4-(4-methylsulfonylphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide (IX), $R_f = 0.30$ (methanol/dichloromethane, 5/95); IR (mull) 1645, 1612, 1593, 1571, 1545, 1508, 1496, 1409, 1296, 1249, 1145, 1106, 1095, 957 and 780 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.73 (d, 2H, $J=8.9\text{ Hz}$, aromatic), 7.55 (m, 2H, aromatic), 7.15 (d, 1H, $J=7.9\text{ Hz}$, aromatic), 6.91 (d, 1H, $J=8.9\text{ Hz}$, aromatic), 6.14 (brdd, 1H, $J=4.4\text{ Hz}$, NH), 4.86 (brdd, 1H, $J=6.2\text{ Hz}$, methine), 4.12 (m, 1H, OCH_{2a}), 3.75 (m, 1H, OCH_{2b}), 3.35 (t, 4H, $J=4.9\text{ Hz}$, Ph- N-CH_{2s}), 2.99 (brds, 7H, N- CH_3 , OCH_3 , Ph- CH_{2a}), 2.75-2.46 (m, 7H, Ph- $\text{NC(H}_2\text{)-CH}_{2s}$ -N CH_{2s} , Ph- CH_{2b}), 2.14 (m, 1H, C(H)- CH_{2a}), 2.02 (m, 1H, C(H)- CH_{2b}) δ ; CMR (75 MHz, CDCl_3) 167.9, 154.3, 141.4, 134.5, 132.7, 129.1, 128.6, 127.7, 124.9, 124.5, 113.8, 74.3, 63.0, 54.5, 52.9, 47.3, 45.0, 33.1, 29.1 and 26.8 δ ; HRMS (EI) calculated for $\text{C}_{24}\text{H}_{31}\text{N}_3\text{O}_4\text{S} = 457.2035$, found = 457.2032; K.F. Water = 0.87%; Melt Solvate = 0.53% ethyl acetate and 0.34% hexane.

EXAMPLE 24 1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VII)

Step 1: 1-[2-(6-Bromoisochroman-1-yl)acetyl]-4-(4-methoxyphenyl)-piperazine (V)

Following the general procedure of EXAMPLE 1, Step 3 and making non-critical variations but using racemic 6-bromoisochroman-1-yl-acetic acid (IV) and 4-methoxyphenylpiperazine gives 1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(4-methoxyphenyl)piperazine (V), $R_f = 0.26$ (ethyl acetate/hexane, 70/30); IR (mull) 1639, 1512, 1446, 1439, 1249, 1214, 1112, 1030, 1028 and 820 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.32-7.26 (m, 2H, aromatic H's), 7.0 (d, 1H, $J=8.2\text{ Hz}$, aromatic H), 6.88 (d, 4H, aromatic H's), 5.27 (m of d, 1H, $J=5.9\text{ Hz}$, ArC-H), 4.16-4.07 (m, 1H), 3.89 (m, 1H), 3.80-3.60 (m, 4H), 3.77 (s, 3H, $-\text{OC-H}_3$), 3.05 (m, 4H, four of pip-H), 2.97-2.90 (m, 2H), 2.76 (d of d, 1H, $J_a=3.7\text{ Hz}$, $J_b=14.9\text{ Hz}$), 2.65 (m of d, 1H, $J=16.4\text{ Hz}$) δ ; CMR (75 MHz, CDCl_3) 168.9, 154.3, 145.2, 136.5, 136.2, 131.7, 129.3, 126.4, 120.3, 118.8, 114.4, 73.4, 63.4, 55.5, 51.3, 50.7, 46.1, 41.9, 39.9, 28.7 δ .

Step 2: 1-[2-(6-Bromoisochroman-1-yl)ethyl]-4-(4-methoxyphenyl)-piperazine (VI)

The general procedure of EXAMPLE 1, Step 4 and making non-critical variations but using 1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(4-methoxyphenyl)-

piperazine (V) gives 1-[2-(6-bromoisochroman-1-yl)ethyl]-4-(4-methoxyphenyl)-
 piperazine (VI), $R_f = 0.23$ (ethyl acetate); IR (neat) 1518, 1479, 1266, 1250, 1155,
 1140, 1112, 1103, 1041 and 818 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.29 (d, 1H, $J=8.3\text{ Hz}$,
 aromatic H), 7.27 (s, 1H, aromatic H), 6.97 (d, 1H, $J=8.3\text{ Hz}$, aromatic H), 6.85 (q,
 5 4H, $J=9.7\text{ Hz}$, aromatic H's), 4.78 (m of d, 1H, $J=6.1\text{ Hz}$), 4.14-4.07 (m, 1H), 3.76-
 3.69 (m, 1H), 3.76 (s, 3H, $-\text{OC}-\text{H}_3$), 3.10 (t, 4H, $J=4.9\text{ Hz}$, four of pip-H), 2.95 (m,
 1H), 2.70-2.50 (m's, 7H), 2.13 (m, 1H, pipCH-H), 2.02 (m, 1H, pipCH-H) δ ; CMR (75
 MHz, CDCl_3) 153.5, 145.5, 136.8, 136.0, 131.4, 129.0, 126.3, 119.7, 117.9, 114.2,
 74.1, 62.5, 55.3, 54.4, 53.3, 50.4, 32.9 and 28.6 δ .

10 Step 3: 1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]-isochroman-6-
 carboxamide (VII)

A dry 100 mL round bottom flask is charged with THF (18 mL) and cooled to
 -78° with a dry ice/acetone bath. *t*-Butyllithium in hexanes (1.7M, 5.4 mL, 9.2
 mmol) is added at once. After stirring for 5 minutes, a mixture 1-[2-(6-
 15 bromoisochroman-1-yl)ethyl]-4-(4-methoxyphenyl)piperazine (VI) in THF (20 mL) is
 added via canula. After stirring for 15 minutes at -78° , trimethylsilyl isocyanate
 (0.88 mL, 6.55 mmol) and dioxane (3.52 mL) are added via syringe respectively. After
 15 min. the cooling bath is removed and the reaction is stirred at $20-25^\circ$ for 1.5 hrs.
 The reaction mixture is quenched with saturated aqueous ammonium chloride, the
 20 volatiles are removed under reduced pressure, and the residue is basified with
 aqueous sodium hydroxide. The crude basic solution is extracted with methylene
 chloride. The organic extracts are combined, dried with sodium sulfate, filtered and
 concentrated. The crude material is purified by flash chromatography (silica gel, 25
 g; using a gradient of 0-10% methanol/ethyl acetate to give 1-[2-[4-(4-
 25 methoxyphenyl)-1-piperazinyl]ethyl]-isochroman-6-carboxamide (VII), mp = $180-182^\circ$;
 $R_f = 0.27$ (methanol/ethyl acetate, 10/90); IR (mull) 3365, 3198, 1628, 1642, 1602,
 1514, 1437, 1245, 1109 and 815 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.61-7.58 (m, 2H,
 aromatic H's), 7.18, (d, 1H, $J=8.6\text{ Hz}$, aromatic H), 6.85 (q, 4H, $J=9.2\text{ Hz}$, aromatic
 H's), 5.90 (very broad d, 2H, $\text{C}(\text{O})\text{N}-\text{H}_2$), 4.86 (m of d, 1H, $J=5.8\text{ Hz}$, PhC-H), 4.18-
 30 4.11 (m, 1H), 3.80-3.72 (m, 1H), 3.76 (s, 3H, $\text{PhOC}-\text{H}_3$), 3.10 (t, 4H, $J=4.8\text{ Hz}$, four of
 pip-H), 2.99 (m, 1H), 2.73 (m of d, 1H, $J=16.4\text{ Hz}$), 2.66-2.49 (m's, 6H), 2.15 (m, 1H,
 pipCH-H), 2.04 (m, 1H, pipCH-H) δ ; CMR (75 MHz, CDCl_3) 168.7, 153.5, 145.4,
 142.0, 134.3, 131.0, 127.9, 124.8, 124.6, 117.8, 114.1, 74.2, 62.6, 55.2, 54.3, 53.2, 50.3,
 32.8, 28.7 and 27.2 δ ; HRMS calculated for $\text{C}_{23}\text{H}_{29}\text{N}_3\text{O}_3 = 395.2209$, found:
 35 395.2219.

EXAMPLE 25 1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]-N-propyl-

isochroman-6-carboxamide (IX)

Step 1: 1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]-N,N-di-t-butylloxycarbonylisochroman-6-carboxamide (VIII)

Following the general procedure of EXAMPLE 3, Step 1 and making non-critical variations but starting with 1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-isochroman-6-carboxamide (VII, EXAMPLE 24), 1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N,N-di-t-butylloxycarbonylisochroman-6-carboxamide (VIII) is obtained.

Step 2: 1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]-N-propylisochroman-6-carboxamide (IX)

An oven-dried 100 mL recovery flask equipped with spinbar is charged with 1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N,N-di-t-butylloxycarbonylisochroman-6-carboxamide (VIII, 566 mg, 0.95 mmol) and 20 mL dichloromethane. This mixture is treated with propylamine (0.78 mL, 9.5 mmol). After 16 hr, the volatiles are removed under reduced pressure to the crude product. This material is purified by LC (silica gel, 230-400 mesh, 30 g; methanol/ethylacetate, 5/95) to give 1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N-propylisochroman-6-carboxamide (IX), mp = 147-149°; R_f = 0.37 (methanol/ethylacetate, 5/95); IR (mull) 3302, 2815, 1639, 1539, 1515, 1320, 1310, 1293, 1278, 1247, 1153, 1112, 1107, 1041 and 824 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.54 (m, 2H, aromatic), 7.16 (d, 1H, J =8.6 Hz, aromatic), 6.87 (m, 4H, aromatic), 6.16 (brdt, 1H, NH), 4.87 (brdd, 1H, J =6.0 Hz, methine), 4.14 (m, 1H, OCH_{2a}), 3.76 (m, 4H, OCH_3 & OCH_{2b}), 3.42 (qrt, 2H, J =6.3 Hz, $\text{N}(\text{H})\text{-CH}_2$), 3.10 (t, 4H, J =4.8 Hz, Ph-N-CH_2), 3.00 (m, 1H, Ph-CH_2), 2.77-2.53 (m, 7H, $\text{Ph-NC}(\text{H}_2)\text{-CH}_2\text{-NCH}_2$, Ph-CH_2), 2.17 (m, 1H, $\text{C}(\text{H})\text{-CH}_2$), 2.05 (m, 1H, $\text{C}(\text{H})\text{-CH}_2$), 1.63 (sxt, 2H, J =7.4 Hz, $\text{C}(\text{H}_3)\text{-CH}_2$), 0.98 (t, 3H, J =7.4 Hz, $\text{CH}_3\text{-C}(\text{H}_2)$); CMR (75 MHz, CDCl_3) 167.1, 153.6, 145.5, 141.3, 134.3, 132.7, 127.4, 124.8, 124.2, 117.9, 114.2, 74.3, 62.8, 55.4, 54.5, 53.3, 50.4, 41.5, 33.0, 28.9, 22.8 and 11.3 δ ; MS (EI, m/z) = 437.

EXAMPLE 26 1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]-N-allyl-isochroman-6-carboxamide (IX)

Following the general procedure of EXAMPLE 25, Step 2 and making non-critical variations but using allylamine (0.69 mL, 9.1 mmol) give crude product. This material is purified by LC (silica gel, 230-400 mesh, 30 g; methanol/ethyl acetate 3/97) to give product which is recrystallized from ethyl acetate/hexane, mp = 146-148°; R_f = 0.34 (methanol/ethylacetate, 5/95); IR (mull) 3295, 2814, 1640, 1536, 1515, 1494, 1443, 1310, 1281, 1246, 1148, 1107, 1037, 923 and 823 cm^{-1} ; NMR (300

5 MHz, CDCl_3) 7.57, 7.17, 6.85, 6.20, 5.92, 5.26, 5.19, 4.87, 4.08, 3.76, 3.11, 3.01, 2.78-2.50, 2.18 and 2.05 δ ; CMR (75 MHz, CDCl_3) 167.1, 153.8, 145.7, 141.8, 134.6, 134.2, 132.5, 127.8, 125.1, 124.5, 118.2, 116.8, 114.4, 74.6, 63.0, 55.6, 54.7, 53.5, 50.7, 42.5, 33.2 and 29.1 δ ; MS (EI, m/z) = 435; HRMS (EI) calculated for $\text{C}_{26}\text{H}_{33}\text{N}_3\text{O}_3$ = 435.2522, found = 435.2516.

EXAMPLE 27 1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]-N-ethyl-
isochroman-6-carboxamide (IX)

Following the general procedure of EXAMPLE 25, Step 2 and making non-critical variations but using ethylamine (approx 2 mL, condensed at 0°) gives crude
10 product. This material is purified by LC (silica gel, 230-400 mesh, 30 g; methanol/ethyl acetate, 5/95) to give product. This material is triturated with ethyl acetate/hexane to give 1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N-ethyl-
isochroman-6-carboxamide (IX), mp = 127-129°; R_f = 0.30 (methanol/ethyl acetate, 5/95); IR (mull) 3308, 2815, 1640, 1540, 1514, 1442, 1359, 1312, 1298, 1283, 1246,
15 1149, 1112, 1037 and 826 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.55 (m, 2H, aromatic), 7.16 (d, 1H, $J=8.6$ Hz, aromatic), 6.87 (m, 4H, aromatic), 6.12 (brdt, 1H, NH), 4.87 (brdd, 1H, $J=8.1$ Hz, methine), 4.15 (m, 1H, OCH_{2a}), 3.77 (m, 4H, OCH_3 & OCH_{2b}), 3.49 (qt, 2H, $J=7.2$ Hz, N(H)-CH_2), 3.11 (t, 4H, $J=4.8$ Hz, Ph-N-CH_{2a}), 3.00 (m, 1H, Ph-CH_{2a}), 2.77-2.50 (m, 7H, $\text{Ph-NC(H}_2\text{)-CH}_{2s}\text{-NCH}_{2s}$, Ph-CH_{2b}), 2.15 (m, 1H, C(H)-CH_{2a}),
20 CH_{2a}), 2.05 (m, 1H, C(H)-CH_{2b}), 1.25 (t, 3H, $J=7.2$ Hz, $\text{CH}_3\text{-C(H}_2\text{)}$); CMR (75 MHz, CDCl_3) 166.9, 153.4, 145.4, 141.2, 134.1, 132.5, 127.3, 124.7, 124.1, 117.8, 114.1, 74.2, 62.6, 55.2, 54.3, 53.2, 50.3, 34.6, 32.9, 28.7 and 14.6 δ ; MS (EI, m/z) = 423.

EXAMPLE 28 1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]-N-propargyl-
isochroman-6-carboxamide (IX)

25 Following the general procedure of EXAMPLE 25, Step 2 and making non-critical variations but using propargylamine (1.6 mL, 23.0 mmol) gives crude product. This material is purified by LC on 75 g (230-400) silica gel eluting with ethyl acetate to give the product which is recrystallized from ethyl acetate/hexane to give 1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N-propargyl-isochroman-6-
30 carboxamide (IX), mp = 162-164°; R_f = 0.40 (methanol/ethyl acetate, 5/95); IR (mull) 3287, 1643, 1636, 1611, 1535, 1515, 1495, 1443, 1303, 1283, 1246, 1147, 1107, 1038 and 822 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.57 (m, 2H, aromatic), 7.17 (d, 1H, $J=8.6$ Hz, aromatic), 6.85 (m, 4H, aromatic), 6.35 (brdt, 1H, NH), 4.88 (brdd, 1H, $J=8.0$ Hz, methine), 4.25 (dd, 2H, $J=5.2$ Hz & $J=2.5$ Hz, N(H)-CH_2), 4.12 (m, 1H, OCH_{2a}), 3.76
35 (m, 4H, OCH_3 & OCH_{2b}), 3.10 (t, 4H, $J=4.8$ Hz, Ph-N-CH_{2a}), 3.01 (m, 1H, Ph-CH_{2a}), 2.78-2.50 (m, 7H, $\text{Ph-NC(H}_2\text{)-CH}_{2s}\text{-NCH}_{2s}$, Ph-CH_{2b}), 2.29 (t, 1H, $J=2.5$ Hz, alkyne),

2.18 (m, 1H, C(H)-CH_{2a}), 2.05 (m, 1H, C(H)-CH_{2b}) δ ; CMR (75 MHz, CDCl₃) 166.7, 153.6, 145.5, 142.0, 134.4, 131.6, 127.6, 124.9, 124.4, 118.0, 114.2, 79.3, 74.3, 71.8, 62.7, 55.4, 54.5, 53.3, 50.4, 33.0, 29.6 and 28.8 δ ; MS (EI, m/z) = 433; HRMS (EI) calculated for C₂₆H₃₁N₃O₃ = 433.2365, found = 433.2367.

5 **EXAMPLE 29** 1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]-N-(4-methoxyphenylmethyl)-isochroman-6-carboxamide (IX)

Following the general procedure of EXAMPLE 25, Step 2 and making non-critical variations but using 4-methoxyphenylmethylamine (1.2 mL, 9.2 mmol) gives crude product. The crude is purified by flash chromatography on 67 g silica gel using methanol/ethyl acetate (10/90) as the eluent to give 1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N-(4-methoxyphenylmethyl)isochroman-6-carboxamide (IX), mp = 162-163°; R_f = 0.40 (methanol/ethyl acetate, 10/90); [α]_D = -40° (c = 0.98, ethanol); IR (mull) 3306, 1642, 1540, 1515, 1313, 1251, 1244, 1235, 1110, 1036 cm⁻¹; NMR (300 MHz, CDCl₃) 7.57 (m, 2H, aromatic H's), 7.28 (d, 2H, J=8.7 Hz, aromatic H), 7.16 (d, 2H, J=8.7 Hz, aromatic H), 6.92-6.82 (m's, 6H, aromatic H's), 6.27 (m, 1H, C(O)N-H), 4.86 (m of d, 1H, J=5.8 Hz, PhC-H), 4.18-4.11 (m, 1H), 3.80 (s, 3H, PhOC-H₃), 3.80-3.72 (m, 1H), 3.76 (s, 3H, PhOC-H₃), 3.10 (t, 4H, J=4.8 Hz, four of pip-H), 2.99 (m, 1H), 2.73 (m of d, 1H, J=16.4 Hz), 2.66-2.49 (m's, 6H), 2.15 (m, 1H, pipCH-H), 2.04 (m, 1H, pipCH-H) δ ; CMR (75 MHz, CDCl₃) 166.9, 145.7, 141.7, 134.5, 132.4, 130.2, 129.3, 127.7, 125.0, 124.5, 118.2, 114.4, 114.2, 74.5, 62.9, 55.5, 55.3, 54.6, 53.5, 50.6, 43.6, 33.1, 29.0 δ ; HRMS calculated for C₃₁H₃₇N₃O₄ = 515.2784, found = 515.2806.

20 **EXAMPLE 30** 1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]-N-phenylmethylisochroman-6-carboxamide (IX)

25 An oven dried 15 mL micro vial, equipped with a claisen condenser, water cooled condenser, and hose adapter, is charged with 1-(2-(6-bromoisochroman-1-yl)-ethyl)-4-(methoxyphenyl)-piperazine (VI, 646 mg, 1.5 mmol), palladium (II) acetate (98%, 17.2 mg, 0.075 mmol) and 1,3-bis-diphenylphosphinopropane (97%, 38.3 mg, 0.09 mmol). Carbon monoxide atmosphere is established in the vial. To the reaction vessel is introduced via syringe DMF (3.75 mL), phenylmethyl amine (1.15 mL, 10.5 mmol) and diisopropylethylamine (0.52 mL, 3 mmol). The mixture is heated to 100° over 10 hours. After cooling to 20-25°, it separated into two phases. The reaction mixture is poured into ethyl acetate. The mixture is washed one time with aqueous sodium hydroxide (1N). The organic layer is then concentrated under reduced pressure to remove excess solvents and reactants to give a crude product which is purified by flash chromatography on 100 g silica gel using ethyl acetate as

the eluent to give 1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N-phenylmethylisochroman-6-carboxamide (IX), mp = 153.0-153.5°; R_f = 0.25 (methanol/ethyl acetate, 10/90); IR (mull) 3263, 2819, 1640, 1543, 1513, 1245, 1234, 1112, 1039 and 826 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.58 (d, 2H, $J=6.9$ Hz, aromatic H's), 7.36-7.28 (m's, 5H, aromatic H's), 7.16, (d, 1H, $J=8.7$ Hz, aromatic H), 6.85 (q, 4H, $J=9.2$ Hz, aromatic H's), 6.42 (t, 1H, C(O)N-H), 4.86 (m of d, 1H, $J=5.8$ Hz, PhC-H), 4.64 (d, 2H, $J=5.7$ Hz, PhC-H₂), 4.17-4.10 (m, 1H), 3.80-3.72 (m, 1H), 3.76 (s, 3H, PhOC-H₃), 3.10 (t, 4H, $J=4.8$ Hz, four of pip-H), 2.99, 2.73 (m of d, 1H, $J=16.4$ Hz), 2.66-2.49 (m's, 6H), 2.15 (m, 1H, pipCH-H), 2.04 (m, 1H, pipCH-H) δ ; CMR (75 MHz, CDCl_3) 189.7, 167.1, 153.8, 145.7, 141.8, 138.2, 134.5, 132.4, 128.8, 127.9, 127.8, 127.6, 125.1, 124.6, 74.5, 62.9, 55.6, 54.6, 53.5, 50.6, 44.1, 33.1, 29.0 δ ; HRMS calculated for $\text{C}_{30}\text{H}_{35}\text{N}_3\text{O}_3$ = 485.2678, found = 485.2664.

EXAMPLE 31 1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]-N-butylisochroman-6-carboxamide (IX)

Following the general procedure of EXAMPLE 30 and making non-critical variations but using n-butylamine (1.04 mL, 10.5 mmol) gives crude product which is purified by flash chromatography on 100 g silica gel using ethyl acetate as the eluent to give product which is recrystallization from hot ethyl acetate to give the title compound, mp = 158.5-159.5°; R_f = 0.28 (ethyl acetate); IR (mull) 3301, 2816, 1637, 1537, 1515, 1444, 1308, 1244, 1111 and 823 cm^{-1} ; NMR (300 MHz, CDCl_3) 5.53, 7.16, 6.87, 6.10, 4.85, 3.80-3.67, 3.76, 3.45, 3.11, 3.10, 2.73, 2.66-2.49, 2.15, 2.04, 1.59, 1.43, 0.96 δ ; CMR (75 MHz, CDCl_3) 167.3, 153.8, 145.7, 141.5, 134.5, 132.9, 127.6, 125.0, 124.4, 118.2, 114.4, 74.5, 63.0, 55.6, 54.7, 53.5, 50.6, 40.0, 39.8, 33.2, 31.8, 29.1, 20.2, 13.8 δ .

EXAMPLE 32 1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]-N-[(R)- α -methylphenylmethyl]-isochroman-6-carboxamide (IX)

Following the general procedure of EXAMPLE 30 and making non-critical variations but using (R)-(+)- α -methylphenylmethylamine (98%, 0.90 mL, 7 mmol) gives crude product which is purified by flash chromatography on 100 g silica gel using a gradient of 0-4% methanol in ethyl acetate. The product is recrystallized from hot methylene chloride/ethyl acetate/hexane to give 1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N-[(R)- α -methylphenylmethyl]isochroman-6-carboxamide (IX) as a mixture of diastereomers, mp = 140.5-141.0°; R_f = 0.28 (ethyl acetate); $[\alpha]_D^{+25}$ (c 0.94, ethanol); IR (mull) 3310, 1636, 1530, 1514, 1495, 1275, 1148, 1110, 700 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.58 (d, 2H, $J=6.9$ Hz, aromatic H's), 7.41-7.28 (m's, 5H, aromatic H's), 7.16, (d, 1H, $J=8.7$ Hz, aromatic H), 6.85 (q, 4H, $J=9.2$ Hz, aromatic

H's), 6.29 (d, 1H, $J=7.8$ Hz, C(O)N-H), 5.84 (quintet, 1H, $J=7.2$ Hz, PhC-H), 4.86 (m of d, 1H, $J=5.8$ Hz, PhC-H), 4.17-4.10 (m, 1H), 3.80-3.72 (m, 1H), 3.76 (s, 3H, PhOC-H₃), 3.10 (t, 4H, $J=4.8$ Hz, four of pip-H), 2.99 (m, 1H), 2.73 (m of d, 1H, $J=16.4$ Hz), 2.66-2.49 (m's, 6H), 2.15 (m, 1H, pipCH-H), 2.04 (m, 1H, pipCH-H), 1.61 (d, 3H, $J=6.9$ Hz, PhC(H)C-H₃) δ ; CMR (75 MHz, CDCl₃) 166.2, 153.7, 145.7, 143.0, 141.7, 134.5, 132.6, 128.7, 127.6, 127.4, 126.2, 125.0, 124.5, 118.1, 114.4, 74.5, 62.9, 55.5, 54.6, 53.4, 50.5, 49.1, 33.1, 29.0, 21.6 δ .

EXAMPLE 33 1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]-N-[(S)- α -methylphenylmethyl]isochroman-6-carboxamide (IX)

Following the general procedure of EXAMPLE 30 and making non-critical variations but using (S)-(-)- α -methylphenylmethylamine (98%, 0.90 mL, 7 mmol) gives crude product which is purified by flash chromatography on 100 g silica gel using a gradient of 0-7% methanol in ethyl acetate. The product is recrystallized from hot methylene chloride/ethyl acetate/hexane to give 1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N-[(S)- α -methylphenylmethyl]isochroman-6-carboxamide (IX) as a mixture of diastereomers, mp = 141.0-141.5°; R_f = 0.28 (ethyl acetate); $[\alpha]_D^{24}$ (c 0.98, ethanol); IR (mull) 3310, 1636, 1530, 1514, 1495, 1275, 1148, 1110, 700 cm⁻¹; NMR (300 MHz, CDCl₃) 7.58 (d, 2H, $J=6.9$ Hz, aromatic H's), 7.41-7.28 (m's, 5H, aromatic H's), 7.16 (d, 1H, $J=8.7$ Hz, aromatic H), 6.85 (q, 4H, $J=9.2$ Hz, aromatic H's), 6.29 (d, 1H, $J=7.8$ Hz, C(O)N-H), 5.84 (quintet, 1H, $J=7.2$ Hz, PhC-H), 4.86 (m of d, 1H, $J=5.8$ Hz, PhC-H), 4.17-4.10 (m, 1H), 3.80-3.72 (m, 1H), 3.76 (s, 3H, PhOC-H₃), 3.10 (t, 4H, $J=4.8$ Hz, four of pip-H), 2.99 (m, 1H), 2.73 (m of d, 1H, $J=16.4$ Hz), 2.66-2.49 (m's, 6H), 2.15 (m, 1H, pipCH-H), 2.04 (m, 1H, pipCH-H), 1.61 (d, 3H, $J=6.9$ Hz, PhC(H)C-H₃) δ ; CMR (75 MHz, CDCl₃) 166.2, 153.7, 145.7, 143.0, 141.7, 134.5, 132.6, 128.7, 127.6, 127.4, 126.2, 125.0, 124.5, 118.1, 114.4, 74.5, 62.9, 55.5, 54.6, 53.4, 50.5, 49.1, 33.1, 29.0, 21.6 δ .

EXAMPLE 34 1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]-N-phenylisochroman-6-carboxamide (IX)

Following the general procedure of EXAMPLE 30 and making non-critical variations but using aniline (0.64 mL, 7 mmol) gives crude product which is purified by LC on 29 g (230-400) silica gel eluting with ethyl acetate/hexane (75/25) to give 1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N-phenylisochroman-6-carboxamide (IX), R_f = 0.25 (ethyl acetate/hexane, 75/25); IR (mull) 2817, 1652, 1599, 1531, 1513, 1442, 1320, 1298, 1246, 1145, 1112, 1038, 823, 754, 693 cm⁻¹; NMR (300 MHz, CDCl₃) 7.87 (s, 1H, NH), 7.63 (m, 4H, aromatic), 7.37 (t, 2H, $J=7.7$ Hz, aromatic), 7.21 (d, 1H, $J=7.9$ Hz, aromatic), 7.18 (t, 1H, $J=6.3$ Hz, aromatic), 6.85 (m, 4H,

aromatic), 4.86 (brdd, 1H, J=6.0 Hz, methine), 4.15 (m, 1H, OCH_{2a}), 3.76 (m, 4H, OCH₃& OCH_{2b}), 3.11 (t, 4H, J=4.9 Hz, Ph-N-CH_{2s}), 3.00 (m, 1H, Ph-CH_{2a}), 2.70-2.50 (m, 7H, Ph-NC(H₂)-CH_{2s}-NCH_{2s}, Ph-CH_{2b}), 2.15 (m, 1H, C(H)-CH_{2a}), 2.05 (m, 1H, C(H)-CH_{2b}) δ ; CMR (75 MHz, CDCl₃) 165.5, 153.8, 145.7, 142.2, 137.9, 134.8, 133.0, 129.1, 127.8, 125.3, 124.6, 124.5, 120.2, 118.2, 114.4, 74.5, 62.9, 55.6, 54.7, 53.5, 50.6, 33.2, 29.1 δ .

EXAMPLE 35 1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]-N-phenylmethyl-N-methyl-isochroman-6-carboxamide (IX)

Following the general procedure of EXAMPLE 30 and making non-critical variations but using phenylmethylmethylamine (1.4 mL, 10.5 mmol) gives crude product which is purified by LC on 77 g (230-400) silica gel eluting with acetone/hexane (40/60) and gradually increasing to acetone/hexane (60/40) to give product. This material is dissolved in ether and treated with gaseous hydrochloric acid resulting in the formation of a solid. Freebase R_f = 0.30 (acetone/hexane, 40/60); bis salt IR (mull) 3423, 2352, 2192, 1627, 1513, 1495, 1400, 1331, 1310, 1294, 1259, 1193, 1106, 1073, 1028 cm⁻¹; NMR of freebase (300 MHz, CDCl₃) 7.26 (m, 8H, aromatic), 6.84 (m, 4H, aromatic), 4.84 (bs, 1H, methine), 4.75 (bs, 1H, Ph-CH_{2a}-N), 4.54 (m, 1H, Ph-CH_{2b}-N), 4.12 (m, 1H, OCH_{2a}), 3.76 (m, 4H, OCH₃& OCH_{2b}), 3.08 (t, 4H, J=4.7 Hz, Ph-N-CH_{2s}), 3.02-2.88 (m, 4H, NCH₃ & Ph-CH_{2a}), 2.64 (m, 7H, Ph-NC(H₂)-CH_{2s}-NCH_{2s}, Ph-CH_{2b}), 2.15 (m, 1H, C(H)-CH_{2a}), 2.05 (m, 1H, C(H)-CH_{2b}) δ ; HRMS (EI) calculated for C₃₁H₃₇N₃O₃ = 499.2835, found = 499.2842.

EXAMPLE 36 1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]-N,N-dimethyl-isochroman-6-carboxamide (IX)

A flame-dried 50 mL flask equipped with spinbar and addition funnel is charged with freshly distilled tetrahydrofuran (6 mL), cooled to -78°, and treated with a 1.7 M solution of tert-butyllithium (3.0 mL, 5.0 mmol). The resulting mixture is treated drop-wise over 10 min. with a solution of 1-(2-(6-bromoisochroman-1-yl)-ethyl)-4-(4-methoxyphenyl)piperazine (VI, 1.08 g, 2.5 mmol) and 7 mL tetrahydrofuran (507 mg, 3.3 mmol). The aryl lithium is stirred 10 min and is treated with carbon dioxide (bone dry). After an addition 10 min, the aryl carboxylate is warmed to 20-25° with the gas addition suspended. The mixture is treated with dimethylformamide (2 drops) followed by oxalyl chloride (0.33 mL, 3.75 mmol) with copious gas evolution and a darkening in color. After 45 min, the mixture is treated with dimethylamine gas. After 20 min, the amine addition is suspended and the reaction mixture is diluted with 40 mL 5M sodium hydroxide and extracted twice with ethyl acetate (40 mL). The combined organics are washed once

with saline (30 mL), dried over magnesium sulfate, filtered, and concentrated to give product which is purified by LC on 63 g (230-400) silica gel eluting with acetone/hexane (50/50) to give 1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N,N-dimethylisochroman-6-carboxamide (IX), mp = 94-96°; R_f = 0.31 (acetone/hexane, 50/50); IR (mull) 2808, 2792, 1624, 1610, 1513, 1488, 1444, 1414, 1275, 1253, 1231, 1152, 1109, 1036, 833 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.19 (m, 2H, aromatic), 7.12 (d, 1H, $J=7.9$ Hz, aromatic), 6.85 (m, 4H, aromatic), 4.85 (brdd, 1H, $J=6.0$ Hz, methine), 4.13 (m, 1H, OCH_{2a}), 3.76 (m, 4H, OCH_3 & OCH_{2b}), 3.13-3.00 (m, 11H, NCH_3 s, Ph- NCH_2 s, Ph- CH_{2a}), 2.65 (m, 7H, Ph- $\text{NC}(\text{H}_2)$ - CH_{2s} - NCH_2 & Ph- CH_{2b}), 2.17 (m, 1H, C(H)- CH_{2a}), 2.05 (m, 1H, C(H)- CH_{2b}) δ ; CMR (75 MHz, CDCl_3) 171.2, 153.5, 145.5, 139.4, 134.2, 134.0, 127.5, 124.6, 124.4, 117.9, 114.2, 74.3, 62.7, 55.3, 54.5, 53.3, 50.4, 39.4, 35.1, 33.0, 28.8 δ ; HRMS (EI) calculated for $\text{C}_{25}\text{H}_{33}\text{N}_3\text{O}_3$ = 423.2522, found = 423.2520.

EXAMPLE 37 1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide (IX)

Following the general procedure of EXAMPLE 36 and making non-critical variations but using methylamine gas and keeping amount of other reagents the same gives 1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide (IX) which is recrystallized from ethyl acetate to give the title compound, mp = 174-176°; R_f = 0.40 (methanol/dichloromethane, 5/95); IR (mull) 3270, 1639, 1543, 1515, 1418, 1319, 1260, 1248, 1235, 1152, 1141, 1112, 1037, 832 and 820 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.53 (m, 2H, aromatic), 7.16 (d, 1H, $J=8.6$ Hz, aromatic), 6.87 (m, 4H, aromatic), 6.19 (brdm, 1H, NH), 4.86 (brdd, 1H, $J=5.9$ Hz, methine), 4.14 (m, 1H, OCH_{2a}), 3.76 (m, 4H, OCH_3 & OCH_{2b}), 3.10 (t, 4H, $J=4.8$ Hz, Ph- N-CH_{2s}), 3.00 (d, 4H, N-CH_3 & Ph- CH_{2a}), 2.77-2.49 (m, 7H, Ph- $\text{NC}(\text{H}_2)$ - CH_{2s} - NCH_2 s, Ph- CH_{2b}), 2.14 (m, 1H, C(H)- CH_{2a}), 2.05 (m, 1H, C(H)- CH_{2b}) δ ; CMR (75 MHz, CDCl_3) 168.0, 153.8, 145.7, 141.6, 134.5, 132.7, 127.7, 125.0, 124.4, 118.2, 114.4, 74.5, 62.9, 55.6, 54.6, 53.5, 50.6, 33.1, 29.1, 26.8 δ ; HRMS (EI) calculated for $\text{C}_{24}\text{H}_{31}\text{N}_3\text{O}_3$ = 409.2365, found = 409.2366.

EXAMPLE 38 1-[2-[4-(4-Chlorophenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide (IX)

Following the general procedure of EXAMPLE 36 and making non-critical variations but using 1-[2-(6-bromoisochroman-1-yl)-ethyl]-4-(4-chlorophenyl)-piperazine (VI, EXAMPLE 8, Step 2, 188 mg, 0.43 mmol) and methylamine gives product which is purified by LC on 10 g (230-400) silica gel eluting with 40% acetone/hexane to give 1-[2-[4-(4-chlorophenyl)-1-piperazinyl]ethyl]-N-methyl-

isochroman-6-carboxamide (IX), mp = 158-160°; R_f = 0.21 (40% acetone/hexane); IR (mull) 3319, 3263, 1639, 1613, 1597, 1571, 1545, 1497, 1334, 1314, 1239, 1150, 1139, 1109, 816 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.54 (brds, 2H, aromatic), 7.16 (m, 3H, aromatic), 6.84 (d, 2H, $J=9.0$ Hz, aromatic), 6.21 (brdm, 1H, NH), 4.86 (brdd, 1H, $J=6.0$ Hz, methine), 4.12 (m, 1H, OCH_{2a}), 3.77 (m, 1H, OCH_{2b}), 3.17 (t, 4H, $J=4.8$ Hz, Ph- N-CH_{2s}), 3.00 (d, 4H, $J=4.9$ Hz, N- CH_3 & Ph- CH_{2a}), 2.77-2.45 (m, 7H, Ph- NCH_2 - CH_{2s} -N CH_2 , Ph- CH_{2b}), 2.18 (m, 1H, C(H)- CH_{2a}), 2.05 (m, 1H, C(H)- CH_{2b}) δ ; CMR (75 MHz, CDCl_3) 167.7, 149.7, 141.3, 134.2, 132.4, 128.7, 127.4, 124.7, 124.2, 124.1, 116.9, 74.2, 62.7, 54.3, 53.0, 48.9, 32.9, 28.8, 26.6 δ ; HRMS (EI) calculated for $\text{C}_{23}\text{H}_{28}\text{ClN}_3\text{O}_2$ = 413.1870, found = 413.1867.

EXAMPLE 39 1-[2-[4-(4-Chlorophenyl)-1-piperazinyl]ethyl]-N,N-dimethylisochroman-6-carboxamide (IX)

Following the general procedure of EXAMPLE 36 and making non-critical variations but using 1-[2-(6-bromoisochroman-1-yl)-ethyl]-4-(4-chlorophenyl)-piperazine (VI, EXAMPLE 8, Step 2, 188 mg, 0.43 mmol) and dimethylamine gave 50 mg (27%) of 1-[2-[4-(4-chlorophenyl)-1-piperazinyl]ethyl]-N,N-dimethylisochroman-6-carboxamide (IX) as product. This material is converted to the bis hydrochloride salt with gaseous hydrochloric acid and recrystallized, mp = 119-122°; R_f = 0.41 (40% acetone/hexane); bis salt IR (mull) 3411, 2507, 2421, 2336, 1628, 1570, 1496, 1397, 1334, 1286, 1263, 1170, 1110, 1095, 1057 cm^{-1} ; free base NMR (300 MHz, CDCl_3) 7.20 (m, 4H, aromatic), 7.12 (d, 1H, $J=7.9$ Hz, aromatic), 6.83 (d, 2H, $J=9.1$ Hz, aromatic), 4.85 (brdd, 1H, $J=6.0$ Hz, methine), 4.13 (m, 1H, OCH_{2a}), 3.76 (m, 1H, OCH_{2b}), 3.18 (t, 4H, $J=4.9$ Hz, Ph-N CH_2), 3.10-3.00 (m, 7H, N CH_3 s & Ph- CH_{2a}), 2.60 (m, 7H, Ph-N CH_2 - CH_{2s} -N CH_2 & Ph- CH_{2b}), 2.14 (m, 1H, C(H)- CH_{2a}), 2.02 (m, 1H, C(H)- CH_{2b}) δ ; CMR (75 MHz, CDCl_3) 171.3, 149.7, 139.3, 134.3, 134.1, 128.8, 127.5, 124.7, 124.5, 124.3, 117.0, 74.3, 62.8, 54.4, 53.0, 48.9, 39.4, 35.2, 32.9, 28.8 δ ; HRMS (EI) calculated for $\text{C}_{24}\text{H}_{30}\text{ClN}_3\text{O}_2$ = 427.2026, found = 427.2020.

EXAMPLE 40 1-[2-[4-Phenylpiperazinyl]ethyl]isochroman-6-carboxamide (VII)

Step 1: 1-[2-(6-Bromoisochroman-1-yl)acetyl]-4-phenylpiperazine (V)

Following the general procedure of EXAMPLE 1, Step 3 and making non-critical variations, but using racemic 6-bromoisochroman-1-yl-acetic acid (IV, EXAMPLE 7, Step 1) and N-phenylpiperazine gave 1-[2-(6-bromoisochroman-1-yl)acetyl]-4-phenylpiperazine (V), R_f = 0.20 (40% ethyl acetate/hexane); IR (mull) 1641, 1599, 1495, 1482, 1442, 1406, 1329, 1278, 1232, 1171, 1156, 1107, 1027, 760, 694 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.29 (m, 4H, aromatic), 7.00 (d, 1H, $J=8.2$ Hz,

aromatic), 6.91 (m, 3H, aromatic), 5.26 (brdd, 1H, $J=5.8$ Hz, methine), 4.11 (m, 1H, OCH_{2a}), 3.91 (dt, 1H, $J=13.6$ Hz & $J=5.1$ Hz, $\text{O}=\text{C}-\text{N}-\text{CH}_{2a}$), 3.72 (m, 4H, $\text{O}=\text{C}-\text{N}-\text{CH}_{2bcd}$, OCH_{2b}), 3.18 (t, 4H, $J=4.9$ Hz, $\text{Ph}-\text{NCH}_{2s}$), 2.95 (m, 2H, $\text{Ph}-\text{CH}_{2a}$ & $\text{N}-\text{CO}-\text{CH}_{2a}$), 2.76 (dd, 1H, $J=14.8$ Hz & $J=3.7$ Hz, $\text{N}-\text{CO}-\text{CH}_{2b}$), 2.65 (bd, 1H, $J=16.4$ Hz, $\text{Ph}-\text{CH}_{2b}$) δ ; CMR (75 MHz, CDCl_3) 168.8, 150.7, 136.2, 136.1, 131.5, 129.2, 129.0, 126.2, 120.2, 120.1, 116.3, 73.2, 63.3, 49.5, 49.0, 45.8, 41.6, 39.7, 28.5 δ ; HRMS (EI) calculated for $\text{C}_{21}\text{H}_{23}\text{BrN}_2\text{O}_2 = 414.0943$, found = 414.0937.

Step 2: 1-[2-(6-Bromoisochroman-1-yl)-ethyl]-4-phenylpiperazine (VI)

Following the general procedure of EXAMPLE 1, Step 4 and making non-critical variations but using 1-[2-(6-bromoisochroman-1-yl)acetyl]-4-phenylpiperazine (V) gives 1-[2-(6-bromoisochroman-1-yl)-ethyl]-4-phenylpiperazine (VI) which is dissolved in ether (30 mL) and treated with gaseous hydrochloric acid. This crude salt is recrystallized from ethyl acetate/hexane, mp = 241-242°; $R_f = 0.25$ (40% ethyl acetate/hexane); bis salt IR (mull) 2532, 2510, 2482, 2348, 2205, 1596, 1494, 1425, 1407, 1112, 1100, 980, 884, 764, 694 cm^{-1} ; freebase NMR (300 MHz, CDCl_3) 7.26 (m, 4H, aromatic), 6.94 (m, 3H, aromatic), 6.85 (t, 1H, $J=7.3$ Hz, aromatic), 4.78 (brdd, 1H, $J=5.8$ Hz, methine), 4.11 (m, 1H, OCH_{2a}), 3.74 (m, 1H, OCH_{2b}), 3.20 (t, 4H, $J=4.9$ Hz, $\text{Ph}-\text{NCH}_{2s}$), 2.93 (m, 1H, $\text{Ph}-\text{CH}_{2a}$), 2.65 (m, 7H, $\text{Ph}-\text{NC}(\text{H}_2)-\text{CH}_{2s}-\text{NCH}_2$ & $\text{Ph}-\text{CH}_{2b}$), 2.09 (m, 1H, $\text{C}(\text{H})-\text{CH}_{2a}$), 2.00 (m, 1H, $\text{C}(\text{H})-\text{CH}_{2b}$) δ ; CMR (75 MHz, CDCl_3) 151.6, 137.8, 136.3, 131.6, 129.3, 129.1, 126.5, 120.0, 119.6, 116.0, 74.3, 62.8, 54.6, 53.4, 49.1, 33.2, 28.8 δ ; MS (EI, m/z) = 400.

Step 3: 1-[2-[4-Phenylpiperazinyl]ethyl]-isochroman-6-carboxamide (VII).

A flame-dried 10 mL flask equipped with spinbar and addition funnel is charged with freshly distilled tetrahydrofuran (2 mL), cooled to -78°, and treated with a solution of tert-butyllithium (1.7 M, 1.3 mL, 2.3 mmol). The resulting mixture is stirred 5 min and drop-treated with a solution of 1-[2-(6-bromoisochroman-1-yl)-ethyl]-4-phenylpiperazine (VI, 431 mg, 1.1 mmol) in 6 mL tetrahydrofuran. The aryl lithium is stirred 10 min and is added via cannula to a flame-dried 25 mL flask equipped with spinbar containing freshly distilled trimethylsilylisocyanate (0.22 mL, 1.6 mmol) and 2 mL tetrahydrofuran also cooled to -78°. The resulting mixture is warmed to 20-25° for 2 hours, diluted with 25 mL saturated ammonium chloride, the volatiles removed under reduced pressure, adjusted to pH = 13, and extracted twice with ethyl acetate (35 mL). The combined organic extracts are washed once with saline (25 mL), dried over magnesium sulfate, filtered, and concentrated. This material is purified by LC on 27 g (230-400) silica

gel eluting with 5% methanol/ethyl acetate to give 1-[2-[4-phenylpiperazinyl]ethyl]isochroman-6-carboxamide (VII), IR (mull) 3350, 3189, 3057, 1663, 1600, 1570, 1503, 1496, 1427, 1336, 1238, 1143, 1110, 760, 692 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.599 (m, 2H, aromatic), 7.26 (t, 2H, $J=8.2$ Hz, aromatic), 7.18 (d, 1H, $J=8.5$ Hz, aromatic), 6.93 (d, 2H, $J=7.9$ Hz, aromatic), 6.85 (t, 1H, $J=7.2$ Hz, aromatic), 6.10 (brds, 1H, NH), 5.75 (brds, 1H, NH), 4.88 (brdd, 1H, $J=5.9$ Hz, methine), 4.15 (m, 1H, OCH_{2a}), 3.77 (m, 1H, OCH_{2b}), 3.21 (t, 4H, $J=4.9$ Hz, Ph- NCH_{2s}), 3.02 (m, 1H, Ph- CH_{2a}), 2.79-2.50 (m, 7H, Ph- $\text{NC}(\text{H}_2)\text{-CH}_{2s}\text{-NCH}_{2s}$, Ph- CH_{2b}), 2.16 (m, 1H, C(H)- CH_{2a}), 2.05 (m, 1H, C(H)- CH_{2b}) δ ; CMR (75 MHz, CDCl_3) 169.0, 151.3, 142.4, 134.6, 131.3, 129.1, 128.2, 125.1, 124.9, 119.7, 116.0, 74.5, 62.9, 54.6, 53.4, 49.1, 33.1, 29.0 δ ; HRMS (EI) calculated for $\text{C}_{22}\text{H}_{27}\text{N}_3\text{O}_2 = 365.2103$, found = 365.2108.

EXAMPLE 41 1-[2-[4-(3,4-Dichlorophenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VII)

Step 1: 1-[2-(6-Bromoisochroman-1-yl)acetyl]-4-(3,4-dichlorophenyl)-piperazine (V)

Following the general procedure of EXAMPLE 1, Step 3 and making non-critical variations but using racemic 6-bromoisochroman-1-yl-acetic acid (IV, EXAMPLE 7, Step 1) and 3,4-dichlorophenylpiperazine gives 1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(3,4-dichlorophenyl)piperazine (V), IR (mull) 1640, 1592, 1482, 1448, 1406, 1275, 1234, 1206, 1140, 1107 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.32-7.26 (m, 3H, aromatic H's), 7.01 (d, 1H, $J=8.2$ Hz, aromatic H), 6.96 (d, 1H, $J=2.8$ Hz, aromatic H), 6.74 (d of d, 1H, $J_a=2.8$ Hz, $J_b=8.9$ Hz, aromatic H), 5.24 (m of d, 1H, $J=9.6$ Hz), 4.11 (m, 1H), 3.94 (m, 1H), 3.79-3.60 (m's, 4H), 3.16 (m, 4H), 3.09-2.89 (m, 2H), 2.77 (d of d, 1H, $J_a=3.6$ Hz, $J_b=14.8$ Hz), 2.65 (d, 1H, $J=10.3$ Hz) δ ; CMR (75 MHz, CDCl_3) 168.0, 150.1, 136.2, 132.8, 131.7, 130.5, 129.4, 126.4, 123.0, 120.8, 117.7, 115.7, 73.5, 63.5, 48.5, 47.9, 45.2, 41.5, 39.9, 28.7 δ ;

Step 2: 1-[2-(6-Bromoisochroman-1-yl)-ethyl]-4-(3,4-dichlorophenyl)-piperazine (VI)

Following the general procedure of EXAMPLE 1, Step 4 and making non-critical variations but using 1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(3,4-dichlorophenyl)-piperazine (V) gives 1-[2-(6-bromoisochroman-1-yl)-ethyl]-4-(3,4-dichlorophenyl)-piperazine (VI), which after flash chromatography on 100 g of silica gel using a gradient of 40% to 50% ethyl acetate in hexane, $R_f = 0.25$ (ethyl acetate/hexane, 25/75); IR (neat) 2825, 1593, 1483, 1467, 1455, 1449, 1380, 1239, 1142, 1111 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.32-7.24 (m, 2H, aromatic H's), 6.98 (m,

2H, aromatic H), 6.73 (d of d, 1H, $J_a=2.9$ Hz, $J_b=8.9$ Hz, aromatic H's), 4.78 (m of d, 1H, $J=5.8$ Hz), 4.12 (m, 1H), 3.73 (m, 1H), 3.16 (t, 4H, $J=5.0$ Hz), 3.00-2.90 (m, 1H), 2.7-2.48 (m, 7H), 2.12 (m, 1H), 2.02 (m, 1H) δ ; CMR (75 MHz, $CDCl_3$) 150.2, 137.1, 136.0, 132.2, 131.4, 130.1, 129.0, 126.2, 121.8, 120.0, 116.9, 114.9, 73.9, 62.6, 54.2, 52.8, 48.4, 32.9, 28.6 δ ; HRMS calculated for $C_{21}H_{23}N_2O_1Br_1Cl_2$ = 468.0371, found = 418.0363.

Step 3: 1-[2-[4-(3,4-Dichlorophenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VII)

Following the general procedure of EXAMPLE 40, Step 3 and making non-critical variations, but using 1-[2-(6-bromoisochroman-1-yl)-ethyl]-4-(3,4-dichlorophenyl)piperazine (VI) gives 1-[2-[4-(3,4-dichlorophenyl)-1-piperazinyl]ethyl]-isochroman-6-carboxamide (VII), R_f = 0.13 (ethyl acetate); NMR (300 MHz, $CDCl_3$) 7.59 (m, 2H, aromatic H's), 7.24 (2 m, 3H, aromatic H's), 6.94 and 5.74 (two d, 1H, aromatic H) 5.90 (broad d, 2H, $PhC(O)N-H_2$), 4.87 (m of d, 1H, $J=6.0$ Hz, $PhC-H$), 4.15 (m, 1H, $PhCH_2CH-H$), 3.77 (m, 1H, $PhCH_2CH-H$), 3.18 (t, 4H, $J=4.8$ Hz, four of pip-H), 3.00 (m, 1H, $NCH-H$), 2.76-2.45 (several m's, 7H, four pip-H, two $PhCH-H$, and $NCH-H$), 2.15 (m, 1H, $PhCHCH-H$), 2.03 (m, 1H, $PhCHCH-H$) δ ; CMR (75 MHz, $CDCl_3$) 168.3, 152.0, 142.7, 135.2, 133.0, 130.7, 129.0, 125.0, 117.5, 115.0, 74.8, 63.0, 54.5, 53.0, 48.6, 33.0, 28.8 δ ; HRMS calculated for $C_{22}H_{26}N_3F_1O_2$ = 433.1324, found = 433.1325.

EXAMPLE 42 1-[2-[4-(4-Fluorophenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VII)

Step 1: 1-[2-(6-Bromoisochroman-1-yl)acetyl]-4-(4-fluorophenyl)piperazine (V)

Following the general procedure of EXAMPLE 1, Step 3 and making non-critical variations but using racemic 6-bromoisochroman-1-yl-acetic acid (IV, EXAMPLE 7, Step 1) and 4-fluorophenylpiperazine gives 1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(4-fluorophenyl)piperazine (V), IR (neat) 1641, 1510, 1482, 1464, 1444, 1278, 1232, 1107, 827, 817 cm^{-1} ; NMR (300 MHz, $CDCl_3$) 7.32-7.26 (m, 2H, aromatic H's), 6.99 (m, 3H, aromatic H's), 6.92-6.86 (m, 2H, aromatic H's), 5.26 (m of d, 1H, $J=9.6$ Hz), 4.11 (m, 1H), 3.94 (m, 1H), 3.79-3.60 (m's, 4H), 3.08 (m, 4H), 2.99-2.89 (m, 2H), 2.77 (d of d, 1H, $J_a=3.6$ Hz, $J_b=14.8$ Hz), 2.65 (d, 1H, $J=10.3$ Hz) δ ; CMR (75 MHz, $CDCl_3$) 168.0, 147.2, 136.2, 131.7, 129.2, 126.2, 120.2, 118.3, 118.2, 115.6, 115.3, 73.2, 63.3, 50.6, 50.1, 45.2, 41.5, 39.7, 28.5 δ ; HRMS calculated for $C_{21}H_{22}N_2O_2FBr$ = 432.0843, found = 432.0849.

Step 2: 1-[2-(6-Bromoisochroman-1-yl)ethyl]-4-(4-

fluorophenyl)piperazine (VI)

Following the general procedure of EXAMPLE 1, Step 4 and making non-critical variations but using 1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(4-fluorophenyl)-piperazine (V) gives 1-[2-(6-bromoisochroman-1-yl)ethyl]-4-(4-fluorophenyl)piperazine (VI) which after flash chromatography on 100 g of silica gel using a gradient of 40% to 50% ethyl acetate in hexane, $R_f = 0.26$ (25% ethyl acetate in hexane); IR (neat) 2952, 2820, 1510, 1481, 1456, 1379, 1235, 1144, 1109, 817 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.31-7.26 (m, 2H, aromatic H's), 6.98-6.85 (m, 5H, aromatic H's), 4.78 (m of d, 1H, $J=5.8$ Hz), 4.14-4.07 (m, 1H), 3.78-3.69 (m, 1H), 3.16 (t, 4H, $J=5.0$ Hz), 3.00-2.90 (m, 1H), 2.7-2.48 (m, 7H), 2.12 (m, 1H), 2.02 (m, 1H) δ ; CMR (75 MHz, CDCl_3) 158.3, 156.2, 148.2, 137.3, 136.9, 131.7, 129.3, 126.5, 117.8, 117.7, 115.6, 115.4, 74.3, 62.8, 54.6, 53.4, 50.2, 33.2, 28.9 δ ; HRMS calculated for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_1\text{Br}_1\text{F}_1 = 418.1056$, found = 418.1057.

Step 3: 1-[2-[4-(4-Fluorophenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VII)

Following the general procedure of EXAMPLE 40, Step 3 and making non-critical variations but using 1-[2-(6-bromoisochroman-1-yl)ethyl]-4-(4-fluorophenyl)-piperazine (VI) gives 1-[2-[4-(4-fluorophenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VII), $R_f = 0.09$ (ethyl acetate); NMR (300 MHz, CDCl_3) 7.59 (m, 2H, aromatic H's), 7.17 (m, 1H, aromatic H), 6.87 (m, 4H, aromatic H's), 6.21 (broad s, 2H, PhC(O)N-H_2), 4.87 (m of d, 1H, $J=6.0$ Hz, PhC-H), 4.15 (m, 1H, $\text{PhCH}_2\text{CH-H}$), 3.77 (m, 1H, $\text{PhCH}_2\text{CH-H}$), 3.13 (t, 4H, $J=4.8$ Hz, four of pip-H), 3.00 (m, 1H, NCH-H), 2.76-2.45 (several m's, 7H, four pip-H, two PhCH-H , and NCH-H), 2.15 (m, 1H, PhCHCH-H), 2.03 (m, 1H, PhCHCH-H) δ ; CMR (75 MHz, CDCl_3) 169.1, 158.3, 155.5, 147.5, 142.0, 134.4, 131.2, 128.0, 124.9, 124.8, 117.6, 117.5, 115.4, 115.1, 74.3, 62.7, 54.4, 53.1, 499.9, 32.8, 28.8 δ ; HRMS calculated for $\text{C}_{22}\text{H}_{26}\text{N}_3\text{F}_1\text{O}_2 = 383.2009$, found = 383.2010.

EXAMPLE 43 1-[2-[4-(3-Ethoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VII)

Step 1: 1-[2-(6-Bromoisochroman-1-yl)acetyl]-4-(3-ethoxyphenyl)piperazine (V)

Following the general procedure of EXAMPLE 1, Step 3 and making non-critical variations but using racemic 6-bromoisochroman-1-yl-acetic acid (IV, EXAMPLE 7, Step 1) and 3-ethoxyphenylpiperazine give 1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(3-ethoxyphenyl)piperazine (V) which after flash chromatography on 200 g of silica gel using 25% ethyl acetate in hexane, $R_f = 0.28$ (50% ethyl acetate in

hexane); IR (neat) 1641, 1501, 1480, 1445, 1241, 1225, 1108, 1040, 1031, 748 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.32-7.26 (m, 2H, aromatic H's), 7.03-6.98 (m, 2H, aromatic H's), 6.94-6.86 (m, 3H, aromatic H's), 5.28 (m of d, 1H, $J=7.4$ Hz), 4.16-4.05 (m, 4H), 3.98-3.91 (m, 1H), 3.83-3.65 (m, 4H), 3.08-2.91 (m, 6H), 2.80-2.64 (m, 2H), 1.46 (t, 3H, $J=6.9$ Hz, $-\text{CH}_3$) δ ; CMR (75 MHz, CDCl_3) 178.5, 152.0, 140.0, 157.0, 156.5, 131.7, 129.4, 126.5, 123.3, 121.0, 120.0, 118.4, 112.5, 73.4, 63.6, 63.5, 60.0, 51.0, 50.5, 46.4, 42.2, 40.0, 28.8, 14.9 δ ; HRMS calculated for $\text{C}_{23}\text{H}_{27}\text{N}_2\text{O}_3\text{Br}_1 = 458.1205$, found = 458.1215.

Step 2: 1-[2-(6-Bromoisochroman-1-yl)ethyl]-4-(3-ethoxyphenyl)piperazine (VI)

Following the general procedure of EXAMPLE 1, Step 4 and making non-critical variations but using 1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(3-ethoxyphenyl)piperazine (V) gives 1-[2-(6-bromoisochroman-1-yl)ethyl]-4-(3-ethoxyphenyl)piperazine (VI) which after flash chromatography on 100 g of silica gel using a gradient of 40% to 50% ethyl acetate in hexane, $R_f = 0.30$ (50% ethyl acetate in hexane); IR (neat) 2816, 1501, 1480, 1448, 1240, 1143, 1124, 1046, 1110, 748 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.31-7.26 (m, 2H, aromatic H's), 7.00-6.90 (m, 4H, aromatic H's), 6.85-6.83 (m, 1H, aromatic H), 4.78 (m of d, $J=5.9$ Hz, 1H), 4.14-4.03 (m, 3H), 3.78-3.70 (m, 1H), 3.13 (broad s, 4H), 3.00-2.90 (m, 1H), 2.69-2.52 (m, 7H), 2.13 (m, 1H), 1.99 (m, 1H), 1.45 (t, 3H, $J=7.0$ Hz) δ ; CMR (75 MHz, CDCl_3) 151.37, 141.19, 137.0, 136.1, 131.5, 129.1, 126.4, 122.5, 120.8, 119.8, 117.9, 112.2, 74.2, 63.4, 62.6, 54.6, 53.5, 50.4, 33.0, 28.7, 14.8 δ ; HRMS Calculated for $\text{C}_{23}\text{H}_{29}\text{N}_2\text{O}_2\text{Br}_1 = 444.1413$, found = 444.1400.

Step 3: 1-[2-[4-(3-Ethoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VII)

Following the general procedure of EXAMPLE 36 and making non-critical variations, but using 1-[2-(6-bromoisochroman-1-yl)ethyl]-4-(3-ethoxyphenyl)piperazine (VI) gives the product which is converted into the hydrochloride salt using ethereal hydrochloric acid to give 1-[2-[4-(3-ethoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VII), mp = 208-210°; $R_f = 0.14$ (10% methanol in ethyl acetate); IR (mull) 2417, 2365, 1611, 1520, 1489, 1476, 1448, 1260, 1121, 152 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.60 (m, 2H, aromatic H's), 7.18 (d, 1H, $J=8.5$ Hz, aromatic H), 6.94 (m, 3H, aromatic H's), 6.84 (m of d, 1H, $J=8.2$ Hz, aromatic H), 6.00 (broad d, 2H, PhC(O)N-H_2), 4.86 (m of d, 1H, $J=6.0$ Hz, PhC-H), 4.13 (m, 1H, $\text{PhCH}_2\text{CH-H}$), 4.06 (q, 2H, 6.9 Hz, Proc-H_2), 3.77 (m, 1H, $\text{PhCH}_2\text{CH-H}$), 3.13 (broad s, 4H, four of pip-H), 3.00 (m, 1H, NCH-H), 2.76-2.45 (several m's, 7H, four pip-H, two PhCH-H ,

and NCH-H), 2.16 (m, 1H, PhCHCH-H), 2.02 (m, 1H, PhCHCH-H), 1.45 (t, 3H, J=7.0 Hz, PhOCH₂C-H₃) δ ; CMR (75 MHz, CDCl₃) 151.2, 142.0, 141.2, 134.1, 131.3, 147.6, 125.0, 124.9, 121.2, 117.9, 112.2, 74.1, 63.0, 62.8, 54.8, 53.3, 50.3, 32.5, 31.5, 27.2, 22.2, 14.5 δ ; HRMS calculated for C₂₄H₃₁N₃O₃ = 409.2365, found = 409.2364.

5 EXAMPLE 44 (S)-(-)-1-[2-[4-(4-Methoxyphenyl)-1-piperidinyl]ethyl]-N-methylisochroman-6-carboxamide (S)-(IX)

Step 1: (S)-(-)-1-[2-(6-Bromoisochroman-1-yl)acetyl]-4-(4-methoxyphenyl)-piperidine (S)-(V)

Following the general procedure of EXAMPLE 1, Step 3 and making non-critical variations but using 4-methoxyphenylpiperidine (421 mg, 2.2 mmol) gives crude produce which is purified by LC on 53 g (230-400) silica gel eluting with 40% ethyl acetate/hexane to give (S)-(-)-1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(4-methoxyphenyl)piperidine (S)-(V), R_f = 0.26 (50% ethyl acetate/hexane); [α]_D -86 (c 0.4975, methanol); IR (liq.) 2933, 1638, 1612, 1513, 1481, 1463, 1446, 1283, 1268, 1247, 1179, 1106, 1036, 1005, 830 cm⁻¹; NMR (300 MHz, CDCl₃) 7.28 (m, 2H, aromatic), 7.11 (dd, 2H, J=8.6 Hz & J=3.4 Hz, aromatic), 7.03 (m, 1H, aromatic), 6.85 (d, 2H, J=8.6 Hz, aromatic), 5.29 (brds, 1H, O-CH), 4.85 (m, 1H, Ph-CH), 4.10 (m, 2H, OCH_{2a} & O=C-N-CH_{2a}), 3.79 (m, 4H, OCH₃ & OCH_{2b}), 3.15-2.66 (m, 7H, O=C-N-CH_{2bcd}, Ph-CH_{2a}, N-CO-CH_{2s}, Ph-CH_{2b}), 1.90-1.50 (m, 4H, Ph-C(H)-CH_{2s}) δ ; CMR (75 MHz, CDCl₃) 168.9, 168.8, 158.2, 137.5, 136.8, 136.3, 131.7, 129.4, 127.6, 126.6, 126.3, 120.3, 114.0, 73.5, 63.4, 55.3, 46.8, 42.8, 41.9, 40.2, 40.0, 34.2, 33.2, 33.0, 28.9 δ .

Step 2: (S)-(-)-1-[2-(6-Bromoisochroman-1-yl)ethyl]-4-(4-methoxyphenyl)-piperidine (S)-(VI)

Following the general procedure of EXAMPLE 1, Step 4 and making non-critical variations but using (S)-(-)-1-[2-(6-bromoisochroman-1-yl)acetyl]-4-(4-methoxyphenyl)piperidine (S)-(V) gives product which is purified by LC on 47 g (230-400) silica gel eluting with 75% ethyl acetate/hexane to give (S)-(-)-1-[2-(6-bromoisochroman-1-yl)ethyl]-4-(4-methoxyphenyl)piperidine (S)-(VI), R_f = 0.28 (75% ethyl acetate/hexane); [α]_D = -46 (c = 0.6677, methanol); IR (liq.) 2932, 2847, 2832, 2805, 1513, 1481, 1466, 1378, 1274, 1247, 1179, 1127, 1109, 1039, 828 cm⁻¹; NMR (300 MHz, CDCl₃) 7.29 (m, 2H, aromatic), 7.14 (d, 2H, J=8.6 Hz, aromatic), 6.97 (d, 1H, J=8.2 Hz, aromatic), 6.83 (d, 2H, J=8.7 Hz, aromatic), 4.77 (brdd, 1H, J=5.7 Hz, methine), 4.10 (m, 1H, OCH_{2a}), 3.78 (s, 3H, OCH₃), 3.71 (m, 1H, OCH_{2b}), 3.04 (m, 2H, NCH_{2ab}), 2.95 (m, 1H, Ph-CH_{2a}), 2.70-2.40 (m, 4H, Ph-CH, NCH_{2cd}, Ph-CH_{2b}), 2.04 (m, 4H, O-C(H)-CH_{2s}, NCH_{2ef}), 1.79 (m, 4H, Ph-C(H)-CH_{2s}) δ ; CMR (75 MHz,

CDCl₃) 158.2, 140.3, 137.5, 136.4, 136.2, 131.7, 129.5, 127.7, 126.6, 120.2, 113.9, 74.2, 63.1, 55.3, 54.8, 54.5, 53.9, 41.1, 32.5, 32.0, 28.8) δ ; HRMS (EI) calculated for C₂₃H₂₈BrNO₂ = 429.1304, found = 429.1286.

Step 3: (S)-(-)-1-[2-[4-(4-Methoxyphenyl)-1-piperidinyl]ethyl]-N-methyl-
5 isochroman-6-carboxamide (S)-(IX)

Following the general procedure of EXAMPLE 5, Step 3 and making non-critical variations but using (S)-(-)-1-[2-(6-bromoisochroman-1-yl)ethyl]-4-(4-methoxyphenyl)piperidine (S)-(VI, 445 mg, 1.03 mmol) gives product which is purified by LC on 24 g (230-400) silica gel eluting with 75% acetone/hexane to give
10 (S)-(-)-1-[2-[4-(4-methoxyphenyl)-1-piperidinyl]ethyl]-N-methylisochroman-6-carboxamide (S)-(IX), R_f = 0.36 (75% acetone/hexane); IR (liq.) 3291, 2934, 1636, 1612, 1571, 1551, 1514, 1496, 1467, 1315, 1293, 1247, 1179, 1109, 1036 cm⁻¹; NMR (300 MHz, CDCl₃) 7.54 (m, 2H, aromatic), 7.116(m, 3H, aromatic), 6.84 (d, 2H, J=8.7 Hz, aromatic), 6.20 brdm, 1H, NH), 4.85 (m, 1H, O-CH), 4.13 (m, 1H, OCH_{2a}), 3.78
15 (m, 4H, OCH₃ & OCH_{2b}), 3.00 (m, 6H, Ph-CH_{2a}, NCH₃, Ph-CH_{2b}, Ph-CH), 2.77-2.40 (m, 4H, N-CH_{2s}), 2.10-1.94 (m, 4H, N-CH_{2s} & O-C(H)-CH_{2s}), 1.80 (m, 4H, Ph-C(H)-CH_{2s}) δ ; HRMS (EI) calculated for C₂₅H₃₂N₂O₃ = 408.2413, found = 408.2414.

EXAMPLE 45 (S)-(-)-1-[2-[4-(4-Trifluoromethylphenyl)-1-piperazinyl]ethyl]-
N,N-dimethylisochroman-6-carboxamide (S)-(IX)

20 Following the general procedure of EXAMPLE 6, Step 4 and making non-critical variations but using (S)-(-)-1-[2-(6-bromoisochroman-1-yl)-1-ethyl]-4-(4-trifluoromethylphenyl)piperazine (S)-(VI, EXAMPLE 5, Step 2, 21.17 g, 45.1 mmol) gives product which is purified by LC on 780 g (230-400) silica gel eluting with 3%-5% methanol/dichloromethane to give (S)-(-)-1-[2-[4-(4-trifluoromethylphenyl)-1-
25 piperazinyl]ethyl]-N,N-dimethylisochroman-6-carboxamide (S)-(IX), mp = 149-151°; R_f = 0.34 (5% methanol/dichloromethane); [α]_D = -46° (c = 0.988, methanol); IR (mull) 1627, 1617, 1527, 1414, 1337, 1315, 1294, 1241, 1160, 1152, 1143, 1135, 1107, 1072, 824 cm⁻¹; NMR (300 MHz, CDCl₃) 7.46 (d, 2H, J=8.7 Hz, aromatic), 7.20 (m, 2H, aromatic), 7.11 (d, 1H, J=7.9 Hz, aromatic), 6.90 (d, 2H, J=8.7 Hz, aromatic),
30 4.85 (brdd, 1H, J=5.9 Hz, methine), 4.12 (m, 1H, OCH_{2a}), 3.75 (m, 1H, OCH_{2b}), 3.28 (t, 4H, J=5.0 Hz, Ph-N-CH_{2s}), 3.09 (brds, 3H, NCH₃), 2.99 (brds, 4H, NCH₃ & Ph-CH_{2a}), 2.74-2.48 (m, 7H, Ph-NC(H₂)-CH_{2s}-NCH_{2s}, Ph-CH_{2b}), 2.12 (m, 1H, C(H)-CH_{2a}), 2.04 (m, 1H, C(H)-CH_{2b}) δ ; CMR (75 MHz, CDCl₃) 171.4, 153.3, 139.5, 134.5, 134.3, 127.7, 126.6, 126.3 (d, J_{CF}=4 Hz), 126.2, 124.8, 124.6, 120.4 (qrt, J_{CF}=33 Hz),
35 114.4, 74.4, 63.0, 54.6, 53.1, 48.0, 39.6, 35.4, 33.2, 29.0 δ ; MS (EI, m/z) = 461.

EXAMPLE 46 1-(4-Methoxyphenyl)-4-[2-[6-(5-methyloxazole-2-yl)isochroman-1-

yl)ethyl]piperazine (P-2)

An oven-dried 25 mL flask equipped with spinbar and reflux condenser is charged with 1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl-N-propargylisochroman-6-carboxamide (IX, EXAMPLE 28, 433 mg, 1.0 mmol) and mercuric acetate (19 mg, 0.06 mmol). The mixture is diluted with 12 mL acetic acid and heated to reflux. After 3 hr, the reaction is cooled to 20-25°, volatiles removed under reduced pressure, residue diluted with 35 mL 1M sodium hydroxide, and extracted twice with ethyl acetate (30 mL). The combined organic extracts are washed once with saline (20 mL), dried over magnesium sulfate, filtered and concentrated. This material is combined with the crude material from an identical 0.25 mmol scale reaction and purified by LC on 41 g (230-400) silica gel eluting with 25% acetone/hexane to give 1-(4-methoxyphenyl)-4-[2-[6-(5-methyloxazole-2-yl)isochroman-1-yl]ethyl]piperazine (P-2) which is recrystallized from ethyl acetate/hexane, mp = 129-130°; R_f = 0.40 (50% acetone/hexane).

EXAMPLE 47 1-[2-(6-Aminoisochroman-1-yl)-ethyl]-4-(4-methoxyphenyl)-piperazine (Z-1)

A 10 mL oven dried two neck round bottom under argon atmosphere is charged with a solution of 1-[2-(6-bromoisochroman-1-yl)-ethyl]-4-(4-methoxyphenyl)piperazine (VI, 406 mg, 0.94 mmol) in THF (2 mL). The mixture is cooled to -78° and *t*-butyl lithium (1.7 M in pentane, 1.081 mL, 1.83 mmol) is added dropwise. After stirring at -78° for 15 min, the aryl lithium is added dropwise via a canula to a solution of diphenylphosphorylazide (98%, 0.188 mL, 0.85 mmol) in THF (9 mL) at -78°. The reaction mixture is maintained at -78° for two hours then warmed to -20° over 40 min, and then re-cooled to -78°. Sodium bis(2-methoxyethoxy)aluminum hydride (3.4 M in toluene, 1.11 mL, 3.77 mmol) is added slowly via syringe. As the reaction is warmed to 0°, effervescence of nitrogen is observed. The reaction mixture is stirred at 0° for two hours and then at 20-25° for 30 min. After cooling to 0°, the reaction is quenched very slowly with water. After effervescence subsided, the crude is warmed to 20-25°, and filtered on a glass frit, alternatively washing with water and ethyl acetate until no more product is observed by TLC in the filtrate. The combined filtrates were transferred to a separatory funnel, salted out with sodium chloride, shaken and the layers were separated. The organic layer is washed one time with 1% aqueous sodium hydroxide and one time with saline, dried with sodium sulfate, filtered and concentrated. After two flash chromatographies on 20 g silica gel using 5% methanol in methylene chloride as the eluent, 1-[2-(6-aminoisochroman-1-yl)-ethyl]-4-(4-

methoxyphenyl)piperazine (Z-1) is obtained, $R_f = 0.18$ (5% methanol in methylene chloride); IR (neat) 2951, 2828, 1625, 1511, 1456, 1262, 1244, 1104, 1037, 824 cm^{-1} ; NMR (300 MHz, CDCl_3) 6.85 (m, 5H, aromatic H's), 6.53 (d of d, 1H, $J_a=2.4$ Hz, $J_b=8.2$ Hz, aromatic H), 6.43 (d, 1H, $J=2.2$ Hz, aromatic H), 4.75 (m of d, 1H, $J=5.8$ Hz, PhC-H), 4.09 (m, 1H, $\text{PhCH}_2\text{CH-H}$), 3.76 (s, 3H, OC-H_3), 3.71 (m, 1H, $\text{PhCH}_2\text{CH-H}$), 3.57 (broad s, 2H, N-H_2), 3.11 (t, 4H, $J=4.9$ Hz, four pip-H), 2.89 (m, 1H, PhCH-H), 2.60 (m's, 7H, PhCH-H, NC-H_2 and four pip-H), 2.10 (m, 1H, PhCHCH-H), 2.00 (m, 1H, PhCHCH-H) δ ; CMR (75 MHz, CDCl_3) 153.8, 145.7, 144.6, 134.9, 129.6, 128.2, 125.7, 120.2, 118.2, 115.5, 114.9, 114.4, 113.6, 74.6, 63.2, 55.6, 54.9, 53.5, 50.6, 33.3, 29.2 δ ; HRMS calculated for $\text{C}_{22}\text{H}_{29}\text{N}_3\text{O}_2 = 367.2260$, found = 367.2255.

EXAMPLE 48 (S)-(-)-1-[2-(6-Aminoisochroman-1-yl)-ethyl]-4-(4-methoxyphenyl)piperazine (S)-(Z-1)

Following the general procedure of EXAMPLE 47 and making non-critical variations but using (S)-(-)-1-[2-(6-bromoisochroman-1-yl)-ethyl]-4-(4-methoxyphenyl)piperazine (S)-(VI) gives (S)-(-)-1-[2-(6-aminoisochroman-1-yl)-ethyl]-4-(4-methoxyphenyl)piperazine (S)-(Z-1), $R_f = 0.18$ (5% methanol in methylene chloride); $[\alpha]_D = -53^\circ$ ($c = 1.04$, ethanol); IR (neat) 2951, 2828, 2819, 1625, 1511, 1262, 1244, 1104, 1037, 824 cm^{-1} ; NMR (300 MHz, CDCl_3) 6.85 (m, 5H, aromatic H's), 6.53 (d of d, 1H, $J_a=2.4$ Hz, $J_b=8.2$ Hz, aromatic H), 6.43 (d, 1H, $J=2.2$ Hz, aromatic H), 4.75 (m of d, 1H, $J=5.8$ Hz, PhC-H), 4.09 (m, 1H, $\text{PhCH}_2\text{CH-H}$), 3.76 (s, 3H, OC-H_3), 3.71 (m, 1H, $\text{PhCH}_2\text{CH-H}$), 3.57 (broad s, 2H, N-H_2), 3.11 (t, 4H, $J=4.9$ Hz, four pip-H), 2.89 (m, 1H, PhCH-H), 2.60 (m's, 7H, PhCH-H, NC-H_2 and four pip-H), 2.10 (m, 1H, PhCHCH-H), 2.00 (m, 1H, PhCHCH-H) δ ; CMR (75 MHz, CDCl_3) 153.8, 145.7, 144.6, 134.9, 129.6, 128.2, 125.7, 120.2, 118.2, 115.5, 114.9, 114.4, 113.6, 74.6, 63.2, 55.6, 54.9, 53.5, 50.6, 33.3, 29.2 δ ; HRMS calculated for $\text{C}_{22}\text{H}_{29}\text{N}_3\text{O}_2 = 367.2260$, found = 367.2258.

EXAMPLE 49 (S)-(-)-N-[Isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]formamide (S)-(Z-2)

Acetic anhydride (0.32 mL, 3.43 mmol) is cooled to 0° . Acetic formic anhydride is generated by the dropwise addition of 98% formic acid (0.20 mL, 5.2 mmol) to the acetic anhydride. The mixture is heated to 55° for 2 hours and then cooled to 0° . THF (1 mL) is added via syringe, followed by a solution of (S)-(-)-1-[2-(6-aminoisochroman-1-yl)-ethyl]-4-(4-methoxyphenyl)piperazine (S)-(Z-1, 600 mg, 1.63 mmol) in THF (2 mL). The reaction is warmed to $20-25^\circ$ and stirred for 3 hours. The reaction is concentrated and purified by flash chromatography to give

(S)-(-)-N-[isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]formamide (S)-(Z-2), $R_f = 0.20$ (5% methanol in methylene chloride); IR (mull) 1692, 1616, 1539, 1512, 1306, 1292, 1266, 1245, 1107, 825 cm^{-1} ; NMR (300 MHz, CDCl_3) 8.65 (d, 1/2 H (rotomer), $J=11.4$ Hz, NC(O)-H), 8.36 (d, 1/2 H (rotomer), $J=1.7$ Hz, NC(O)-H), 7.91 (broad d, 1/2 H (rotomer), $J=11.4$ Hz, N-H), 7.43 (broad s, 1/2 H (rotomer), N-H), 7.24 (m, 1H, aromatic H), 7.07 (d of d, 1H, $J_a=8.4$ Hz, $J_b=10.9$ Hz, aromatic H), 6.84 (q and m, 5H, $J=9.2$ Hz, aromatic H's), 4.80 (m of d, 1H, $J=5.8$ Hz, PhC-H), 4.10 (m, 1H, $\text{PhCH}_2\text{CH-H}$), 3.76 (s, 3H, OC- H_3), 3.71 (m, 1H, $\text{PhCH}_2\text{CH-H}$), 3.11 (t, 4H, $J=4.9$ Hz, four pip-H), 2.95 (m, 1H, PhCH-H), 2.60 (m's, 7H, PhCH-H, NC- H_2 and four pip-H), 2.18 (m, 1H, PhCHCH-H), 2.06 (m, 1H, PhCHCH-H) δ ; HRMS calculated for $\text{C}_{23}\text{H}_{29}\text{N}_3\text{O}_3 = 395.2209$, found = 395.2210.

EXAMPLE 50 (S)-(-)-N-[isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]acetamide (S)-(Z-2)

A 25 mL round bottom flask is charged with (S)-(-)-1-[2-(6-aminoisochroman-1-yl)-ethyl]-4-(4-methoxyphenyl)piperazine (S)-(Z-1, 200 mg, 0.54 mmol) and 4-dimethylaminopyridine (6.7 mg, 0.054 mmol). Methylene chloride (7 mL) is added via syringe and the reaction vessel is cooled to 0° . Triethylamine (0.114 mL, 0.82 mmol) and acetyl chloride (0.042 mL, 0.60 mmol) are then added respectively via syringe. The ice bath is removed after 15 min. and the reaction is stirred at $20-25^\circ$ for 1.5 hours. The reaction is then partitioned between 0.5 M aqueous sodium hydroxide and methylene chloride. The layers were separated and the aqueous portion is extracted one more time with methylene chloride. The organics were combined, dried with sodium sulfate, filtered and concentrated. The concentrate is chromatographed on 17 g silica gel using 5% methanol in methylene chloride as the eluent to give (S)-(-)-N-[isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]acetamide (S)-(Z-2), $R_f = 0.18$ (5% methanol in methylene chloride); $[\alpha]_D -44^\circ$ (c 0.93, 50% ethanol in methylene chloride); IR (mull) 1667, 1615, 1599, 1546, 1512, 1421, 1333, 1312, 1247, 1036 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.35, 7.21, 7.15, 7.04, 6.80, 4.80, 4.10, 3.76, 3.71, 3.11, 2.95, 2.60, 2.16, 2.10, 2.02 δ ; CMR (75 MHz, CDCl_3) 168.3, 153.8, 145.7, 136.0, 134.9, 134.1, 125.3, 120.1, 118.2, 118.0, 114.5, 74.5, 63.1, 55.6, 54.8, 53.5, 50.6, 33.2, 29.2, 24.6 δ ; HRMS calculated for $\text{C}_{24}\text{H}_{31}\text{N}_3\text{O}_3 = 409.2365$, found = 409.2358.

EXAMPLE 51 (S)-(-)-N-[isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]benzamide (S)-(Z-2)

Following the general procedure of EXAMPLE 50 and making non-critical variations but using benzoyl chloride gives (S)-(-)-N-[isochroman-1-[2-[4-(4-

methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]benzamide (S)-(Z-2), $R_f = 0.30$ (5% methanol in methylene chloride); $[\alpha]_D = -40^\circ$ ($c = 1.0$, 50% ethanol in methylene chloride); IR (mull) 3282, 1651, 1516, 1505, 1389, 1312, 1280, 1244, 1108, 694 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.86 (d, 2H, $J=6.8$ Hz, aromatic H's), 7.80 (broad s, 1H, PhN-H), 7.50 (m, 4H, aromatic H's), 7.36 (d, 1H, $J=8.3$ Hz, aromatic H), 7.10 (d, 1H, $J=8.3$ Hz, aromatic H), 6.86 (q, 4H, $J=9.2$ Hz, aromatic H's), 4.84 (m of d, 1H, $J=5.8$ Hz, PhC-H), 4.13 (m, 1H, $\text{PhCH}_2\text{CH-H}$), 3.76 (s, 3H, OC- H_3), 3.76 (m, 1H, $\text{PhCH}_2\text{CH-H}$), 3.12 (t, 4H, $J=4.6$ Hz, four pip-H), 2.99 (m, 1H, PhCH-H), 2.68 (m's, 7H, PhCH-H, NC- H_2 and four pip-H), 2.10 (m, 1H, PhCHCH-H), 2.02 (m, 1H, PhCHCH-H) δ ; HRMS calculated for $\text{C}_{29}\text{H}_{33}\text{N}_3\text{O}_3 = 471.2522$, found = 471.2525.

EXAMPLE 52 (S)-(-)-N-[Isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]propionamide (S)-(Z-2)

Following the general procedure of EXAMPLE 50 and making non-critical variations but using propionyl chloride (S)-(-)-N-[isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]propionamide (S)-(Z-2) is obtained, $R_f = 0.22$ (5% methanol in methylene chloride); $[\alpha]_D = -44^\circ$ ($c = 0.97$, 50% ethanol in methylene chloride); IR (mull) 3306, 1659, 1590, 1515, 1421, 1245, 1214, 1110, 1036, 821 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.76 (s, 1H, aromatic H), 7.36 (broad s, 1H, PhN-H), 7.24 (d, 1H, $J=8.3$ Hz, aromatic H), 7.00 (d, 1H, $J=8.3$ Hz, aromatic H), 6.80 (q, 4H, $J=9.2$ Hz, aromatic H's), 4.77 (m of d, 1H, $J=5.8$ Hz, PhC-H), 4.06 (m, 1H, $\text{PhCH}_2\text{CH-H}$), 3.76 (s, 3H, OC- H_3), 3.71 (m, 1H, $\text{PhCH}_2\text{CH-H}$), 3.07 (t, 4H, $J=4.9$ Hz, four pip-H), 2.85 (m, 1H, PhCH-H), 2.60 (m's, 7H, PhCH-H, NC- H_2 and four pip-H), 2.33 (q, 2H, $J=7.5$ Hz, PhNHC(O)C-H_2), 2.14 (m, 1H, PhCHCH-H), 2.00 (m, 1H, PhCHCH-H), 1.19 (t, 3H, $J=7.5$ Hz, $\text{PhNHC(O)CH}_2\text{C-H}_3$) δ ; CMR (75 MHz, CDCl_3) 172.5, 153.7, 145.8, 136.3, 134.7, 133.8, 125.2, 120.2, 118.1, 114.5, 74.4, 63.0, 55.6, 54.8, 53.5, 50.6, 33.3, 30.6, 29.2 and 9.8 δ .

EXAMPLE 53 (S)-(-)-N-[Isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]acrylamide (S)-(Z-2)

Following the general procedure of EXAMPLE 50 and making non-critical variations but using acryl chloride gives (S)-(-)-N-[isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]acrylamide (S)-(Z-2), $R_f = 0.22$ (5% methanol in methylene chloride); $[\alpha]_D = -40^\circ$ ($c = 0.79$, 50% ethanol in methylene chloride); IR (mull) 3266, 1661, 1592, 1536, 1512, 1422, 1244, 1218, 1109, 822 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.46 (broad s, 1H, PhN-H), 7.26 (s, 1H, aromatic H), 7.06 (d, 1H, $J=8.4$ Hz, aromatic H), 6.85 (q, 4H, $J=9.2$ Hz, aromatic H's), 6.43 (d of d, 1H, $J_a=1.3$ Hz, $J_b=16.8$ Hz, one acryl-H), 6.23 (m, 1H, one acryl-H), 5.76 (d of d, 1H,

Ja=1.3 Hz, Jb=10 Hz, one acryl-H), 4.81 (m of d, 1H, J=5.8 Hz, PhC-H), 4.11 (m, 1H, PhCH₂CH-H), 3.76 (s, 3H, OC-H₃), 3.75 (m, 1H, PhCH₂CH-H), 3.11 (t, 4H, J=4.9 Hz, four pip-H), 2.96 (m, 1H, PhCH-H), 2.60 (m's, 7H, PhCH-H, NC-H₂ and four pip-H), 2.14 (m, 1H, PhCHCH-H), 2.03 (m, 1H, PhCHCH-H) δ ; CMR (75 MHz, CDCl₃) 163.5, 153.8, 145.8, 135.9, 134.9, 134.4, 131.1, 127.9, 125.4, 120.2, 118.2, 118.0, 114.4, 74.5, 63.0, 55.6, 54.8, 53.5, 50.6, 33.2, 29.2 δ ; HRMS calculated for C₂₅H₃₁N₃O₃ = 421.2365, found = 421.2358.

EXAMPLE 54 (S)-(-)-N-[Isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]isobutyramide (S)-(Z-2)

Following the general procedure of EXAMPLE 50 and making non-critical variations but using i-butyryl chloride gives (S)-(-)-N-[Isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]isobutyramide (S)-(Z-2), R_f = 0.27 (5% methanol in methylene chloride); [α]_D = -42° (c = 0.94, 50% ethanol in methylene chloride); IR (mull) 3289, 1660, 1589, 1524, 1515, 1451, 1422, 1243, 1109, 822 cm⁻¹; NMR (300 MHz, CDCl₃) 7.43 (s, 1H, aromatic H), 7.23 (d, 1H, J=8.4 Hz, aromatic H), 7.13 (broad s, 1H, PhN-H), 7.04 (d, 1H, J=8.3 Hz, aromatic H), 6.84 (q, 4H, J=9.2 Hz, aromatic H's), 4.80 (m of d, 1H, J=5.8 Hz, PhC-H), 4.10 (m, 1H, PhCH₂CH-H), 3.76 (s, 3H, OC-H₃), 3.71 (m, 1H, PhCH₂CH-H), 3.10 (t, 4H, J=4.9 Hz, four pip-H), 2.96 (m, 1H, PhCH-H), 2.60 (m's, 8H, PhCH-H, NC-H₂, PhNHC(O)C-H and four pip-H), 2.14 (m, 1H, PhCHCH-H), 2.00 (m, 1H, PhCHCH-H), 1.24 (d, 6H, J=6.9 Hz, two of PhNHC(O)CHMeC-H₃) δ ; CMR (75 MHz, CDCl₃) 175.2, 153.8, 145.8, 136.2, 134.9, 133.9, 125.3, 120.0, 118.2, 117.8, 114.4, 74.5, 63, 1, 60.8, 55.6, 54.8, 53.5, 50.6, 36.7, 33.2, 29.3, 19.6 δ ; HRMS calculated for C₂₆H₃₅N₃O₃ = 437.2678, found = 437.2680.

EXAMPLE 55 (S)-(-)-1-[2-(6-Ethylaminoisochroman-1-yl)-ethyl]-4-(4-methoxyphenyl)piperazine (S)-(Z-4)

Following the general procedure of EXAMPLE 5, Step 2, and making non-critical variations but using (S)-(-)-N-[isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]acetamide (S)-(Z-2, EXAMPLE 50) as the substrate gives (S)-(-)-1-[2-(6-ethylaminoisochroman-1-yl)-ethyl]-4-(4-methoxyphenyl)piperazine (S)-(Z-4), R_f = 0.32 (5% methanol in methylene chloride); [α]_D = -46° (c = 0.54, 50% ethanol in methylene chloride); IR (neat) 2953, 2825, 2819, 1616, 1512, 1268, 1244, 1147, 11104, 824 cm⁻¹; NMR (300 MHz, CDCl₃) 6.86 (m, 5H, aromatic H's), 6.47 (d of d, 1H, Ja=2.4 Hz, Jb=8.2 Hz, aromatic H), 6.34 (d, 1H, J=2.2 Hz, aromatic H), 4.76 (m of d, 1H, J=5.8 Hz, PhC-H), 4.09 (m, 1H, PhCH₂CH-H), 3.76 (s, 3H, OC-H₃), 3.71 (m, 1H, PhCH₂CH-H), 3.13 (t and q

overlapping, 6H, four pip-H, and PhNC-H₂), 2.91 (m, 1H, PhCH-H), 2.62 (m's, 7H, PhCH-H, NC-H₂ and four pip-H), 2.10 (m, 1H, PhCHCH-H), 2.00 (m, 1H, PhCHCH-H), 1.25 (t, 3H, J=7.1 Hz, PhNHCH₂C-H₃) δ ; CMR (75 MHz, CDCl₃) 153.8, 146.8, 145.8, 134.8, 126.8, 125.6, 118.2, 114.4, 112.2, 111.6, 74.6, 63.4, 55.6, 54.9, 53.5, 50.5, 38.6, 33.3, 29.5, 15.0 δ ; HRMS calculated for C₂₄H₃₃N₃O₂ = 395.2573, found: 395.2573.

EXAMPLE 56 (S)-(-)-1-(4-Methoxyphenyl)-4-[2-(6-propylaminoisochroman-1-yl)-ethyl]piperazine (S)-(Z-4)

Following the general procedure of EXAMPLE 5, Step 2, and making non-critical variations but using (S)-(-)-N-[isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]propionamide (S)-(Z-2, EXAMPLE MDE45) as the substrate gives of (S)-(-)-1-(4-methoxyphenyl)-4-[2-(6-propylaminoisochroman-1-yl)-ethyl]piperazine (S)-(Z-4), R_f = 0.52 (50% acetone in hexane); [α]_D = -41° (c = 0.69, 50% ethanol in methylene chloride); IR (neat) 2812, 2804, 1614, 1514, 1271, 1254, 1247, 1105, 1034, 830cm⁻¹; NMR (300 MHz, CDCl₃) 6.86 (m, 5H, aromatic H's), 6.47 (d of d, 1H, J_a=2.4 Hz, J_b=8.2 Hz, aromatic H), 6.34 (d, 1H, J=2.2 Hz, aromatic H), 4.76 (m of d, 1H, J=5.8 Hz, PhC-H), 4.09 (m, 1H, PhCH₂CH-H), 3.76 (s, 3H, OC-H₃), 3.71 (m, 1H, PhCH₂CH-H), 3.54 (broad s, 1H, PhN-H), 3.09 (t and q overlapping, 6H, four pip-H, and PhNC-H₂), 2.91 (m, 1H, PhCH-H), 2.62 (m's, 7H, PhCH-H, NC-H₂ and four pip-H), 2.10 (m, 1H, PhCHCH-H), 2.00, 1.63, 1.25 δ ; HRMS calculated for C₂₅H₃₅N₃O₂ = 409.2729, found = 409.2722.

EXAMPLE 57 (S)-(-)-1-(4-Methoxyphenyl)-4-[2-(6-methylaminoisochroman-1-yl)-ethyl]piperazine (S)-(Z-4)

Acetic anhydride (0.32 mL, 3.43 mmol) is cooled to 0°. Acetic formic anhydride is generated by the dropwise addition of 98% formic acid (0.20 mL, 5.2 mmol) to the acetic anhydride. The mixture is heated to 55° for 2 hours and then cooled to -15° with an ethylene glycol/carbon dioxide bath. THF (10 mL) is added via syringe, followed by a solution of (S)-(-)-1-[2-(6-aminoisochroman-1-yl)-ethyl]-4-(4-methoxyphenyl)piperazine (S)-(Z-1, EXAMPLE 48, 1.99 g, 5.41 mmol) in THF (10 mL). The reaction stirred for 2 hours at -15°. The reaction warmed to 20-25° and volatiles removed under reduced pressure leaving a yellow oil. A solution of the crude in THF (30 mL) is charged into a 250 mL round bottom equipped with a reflux condenser. The mixture is cooled to 0° and borane methyl sulfide complex (10M, 1.73 mL, 17.3 mmol) is added slowly via syringe. The ice bath is removed when effervescence subsided. The mixture is then heated to gentle reflux for 3 hours, then at 20-25° for three days. The reaction is cooled to 0° and methanol (30 mL) is added

dropwise (effervescence) then stirred for 1 hour at 20-25°, followed by reflux for 2 hours. After cooling to 20-25°, the volatiles are removed under reduced pressure and the aqueous residue is basified with aqueous sodium hydroxide and extracted 80 mL ethyl acetate (three times). The organic extracts are combined, dried with sodium sulfate, filtered and concentrated to give a crude product. The crude material is purified by flash chromatography using 25% acetone in hexane as the eluent to give (S)-(-)-1-(4-methoxyphenyl)-4-[2-(6-methylaminoisochroman-1-yl)-ethyl]piperazine (S)-(Z-4), IR (neat) 2933, 2831, 2817, 1616, 1513, 1275, 1246, 1107, 1038, 826 cm⁻¹; NMR (300 MHz, CDCl₃) 6.86 (m, 5H, aromatic H's), 6.47 (d of d, 1H, Ja=2.4 Hz, Jb=8.2 Hz, aromatic H), 6.35 (d, 1H, J=2.2 Hz, aromatic H), 4.76 (m of d, 1H, J=5.8 Hz, PhC-H), 4.09 (m, 1H, PhCH₂CH-H), 3.76 (s, 3H, OC-H₃), 3.71 (m, 1H, PhCH₂CH-H), 3.58 (broad s, 1H, N-H), 3.11 (t, 4H, four pip-H), 2.92 (m, 1H, PhCH-H), 2.82 (s, 3H, NHC-H₃), 2.62 (m's, 7H, PhCH-H, NC-H₂ and four pip-H), 2.10 (m, 1H, PhCHCH-H), 2.00 (m, 1H, PhCHCH-H) δ ; CMR (75 MHz, CDCl₃) 153.8, 147.7, 145.8, 134.8, 126.9, 125.5, 118.2, 114.4, 111.8, 111.3, 74.64, 63.3, 55.6, 54.9, 53.5, 53.4, 50.6, 33.4, 30.9, 29.5 δ ; HRMS calculated for C₂₃H₃₁N₃O₂: 381.2416. Found: 381.2415.

EXAMPLE 58 (S)-(-)-1-(4-Methoxyphenyl)-4-[2-(6-dimethylaminoisochroman-1-yl)-ethyl]piperazine (S)-(Z-7)

From the preparation described in EXAMPLE 57 is also isolated (S)-(-)-1-(4-methoxyphenyl)-4-[2-(6-dimethylaminoisochroman-1-yl)ethyl]piperazine (S)-(Z-7), R_f = 0.22 (acetone/hexane, 25/75); NMR (300 MHz, CDCl₃) 6.99-6.81 (m's, 5H, aromatic H's), 6.62 (d of d, 1H, Ja=2.4 Hz, Jb=8.2 Hz, aromatic H), 6.46 (d, 1H, J=2.2 Hz, aromatic H), 4.78 (m of d, 1H, J=5.8 Hz, PhC-H), 4.10 (m, 1H, PhCH₂CH-H), 3.76 (s, 3H, OC-H₃), 3.71 (m, 1H, PhCH₂CH-H), 3.11 (q, 4H, four pip-H), 2.95 (m, 1H, PhCH-H), 2.92 (s, 6H, two of NC-H₃), 2.62 (m's, 7H, PhCH-H, NC-H₂ and four pip-H), 2.10 (m, 1H, PhCHCH-H), 2.00 (m, 1H, PhCHCH-H) δ ; CMR (75 MHz, CDCl₃) 153.8, 149.2, 145.8, 134.6, 126.3, 125.4, 118.1, 114.4, 112.5, 112.1, 111.4, 74.6, 63.4, 55.6, 55.0, 53.5, 50.6, 46.8, 40.7, 33.4, 29.7 δ .

EXAMPLE 59 (S)-(-)-1-[2-(6-Ethylmethylaminoisochroman-1-yl)-ethyl]-4-(4-methoxyphenyl)piperazine (S)-(Z-7)

From the process described in EXAMPLE 57 is also isolated (S)-(-)-1-[2-(6-ethylmethylaminoisochroman-1-yl)-ethyl]-4-(4-methoxyphenyl)piperazine (S)-(Z-7), R_f = 0.22 (acetone/hexane, 25/75); [α]_D = -54°(c = 0.83, ethanol/methylene chloride 50/50); IR (mull) 2815, 1611, 1515, 1256, 1245, 1236, 1107, 1095, 1037 and 824 cm⁻¹; NMR (300 MHz, CDCl₃) 6.97-6.81, 6.59, 6.42,

4.77, 4.10, 3.76, 3.71, 3.37, 3.11, 2.95, 2.88, 2.62, 2.10, 2.00 and 1.11 δ ; CMR (75 MHz, CDCl_3) 153.8, 147.6, 145.8, 134.6, 125.7, 125.5, 118.1, 114.4, 112.1, 111.0, 74.7, 63.5, 55.6, 55.0, 53.5, 50.6, 46.8, 37.5, 33.5, 29.7 and 11.3 δ .

EXAMPLE 60 (S)-(-)-N-[Isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]-N-methylacetamide (S)-(Z-5)

5

Following the general procedure of EXAMPLE 50 and making non-critical variations but using (S)-(-)-1-(4-methoxyphenyl)-4-[2-(6-methylaminoisochroman-1-yl)ethyl]piperazine (S)-(Z-4), the title compound is obtained, $R_f = 0.26$

(methanol/methylene chloride 5/95); $[\alpha]_D = -38^\circ$ ($c = 0.69$, ethanol/methylene chloride (50/50)); IR (mull) 1669, 1661, 1513, 1448, 1445, 1275, 1248, 1109, 1036 and 826 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.13, 6.98, 6.86, 4.83, 4.13, 3.76, 3.76, 3.23, 3.10, 2.97, 2.61, 2.14, 2.02 and 1.87 δ ; CMR (75 MHz, CDCl_3) 170.6, 153.8, 145.7, 142.7, 137.8, 135.7, 127.2, 126.1, 124.8, 118.2, 114.4, 74.5, 62.8, 61.2, 55.6, 54.8, 53.5, 50.7, 37.2, 33.3, 29.0 and 22.5 δ .

15 EXAMPLE 61 (S)-(-)-N-[Isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]-N-methylisobutyramide (S)-(Z-5)

Following the general procedure of EXAMPLE 54 and making non-critical variation but using (S)-(-)-1-(4-methoxyphenyl)-4-[2-(6-methylaminoisochroman-1-yl)-ethyl]piperazine (S)-(Z-4) gives (S)-(-)-N-[isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]-N-methylisobutyramide (S)-(Z-5), $R_f = 0.33$ (5% methanol in methylene chloride); $[\alpha]_D = -34^\circ$ ($c = 0.80$, 50% ethanol in methylene chloride); IR (mull) 2962, 1658, 1512, 1468, 1457, 1386, 1245, 1109, 1038, 825 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.13 (d, 1H, $J = 8.2$ Hz, aromatic H), 6.98 (d, 1H, $J = 8.2$ Hz, aromatic H), 6.86 (m and q, 5H, $J = 9.2$ Hz, aromatic H's), 4.83 (m of d, 1H, $J = 5.8$ Hz, PhC-H), 4.13 (m, 1H, $\text{PhCH}_2\text{CH-H}$), 3.76 (s, 3H, OC-H₃), 3.76 (m, 1H, $\text{PhCH}_2\text{CH-H}$), 3.22 (s, 3H, NC-H₃), 3.10 (t, 4H, $J = 4.6$ Hz, four pip-H), 2.97 (m, 1H, PhCH-H), 2.61 (m's, 8H, NC(O)CMe₂-H, PhCH-H, NC-H₂ and four pip-H), 2.14 (m, 1H, PhCHCH-H), 2.02 (m, 1H, PhCHCH-H), 1.03 (d, 6H, $J = 6.5$ Hz, two of NC(O)CHC-H₃) δ ; CMR (75 MHz, CDCl_3) 177.4, 153.8, 145.7, 142.4, 137.8, 135.7, 127.4, 126.1, 125.0, 118.2, 114.5, 74.5, 62.8, 55.6, 54.8, 53.5, 50.7, 37.5, 33.3, 31.0, 29.0, 19.8 δ ; HRMS calculated for $\text{C}_{27}\text{H}_{37}\text{N}_3\text{O}_3 = 451.2835$, found = 451.2827.

30 EXAMPLE 62 (S)-(-)-N-[Isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]-methanesulfonamide (S)-(Z-3)

(S)-(-)-1-[2-(6-aminoisochroman-1-yl)-ethyl]-4-(4-methoxyphenyl)-piperazine (S)-(Z-1) (200 mg, 0.54 mmol) and 4-dimethylaminopyridine (6.7 mg, 0.054 mmol) are mixed. Pyridine (2 mL) is added via syringe, the mixture is cooled to 0° , and

methane sulfonyl chloride (.045 mL, 0.60 mmol) is introduced. The ice bath is removed after 15 min. and the reaction is stirred at 20-25° for 1.5 hours. The reaction is diluted with water and extracted two times with ethyl acetate. The organics were combined, washed one time with an saturated aqueous copper sulfate solution then with water, dried over magnesium sulfate, filtered and concentrated. The concentrate is chromatographed on 25 g silica gel using 50% acetone in hexane as the eluent to give (S)-(-)-N-[isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]-methanesulfonamide (S)-(Z-3), $R_f = 0.21$ (5% methanol in methylene chloride); $[\alpha]_D = -43^\circ$ (c = 0.89, 50% ethanol in methylene chloride); IR (mull) 1512, 1339, 1319, 1295, 1244, 1152, 1106, 1037, 973, 826 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.05 (m's, 3H, aromatic H's), 6.87 (q, 4H, J=9.0 Hz, aromatic H's), 4.80 (m of d, 1H, J=5.8 Hz, PhC-H), 4.11 (m, 1H, $\text{PhCH}_2\text{CH-H}$), 3.76 (s, 3H, OC-H_3), 3.71 (m, 1H, $\text{PhCH}_2\text{CH-H}$), 3.10 (t, 4H, J=4.6 Hz, four pip-H), 3.0 (s, 3H, $\text{NHSO}_2\text{C-H}_3$), 2.95 (m, 1H, PhCH-H), 2.60 (m's, 7H, PhCH-H, NC-H₂ and four pip-H), 2.11 (m, 1H, PhCHCH-H), 2.01 (m, 1H, PhCHCH-H) δ ; CMR (75 MHz, CDCl_3) 153.8, 145.7, 135.8, 135.6, 134.8, 126.1, 121.2, 119.0, 118.2, 114.5, 74.4, 62.9, 55.6, 54.8, 53.5, 50.6, 39.4, 33.2, 29.1 δ ; HRMS calculated for $\text{C}_{23}\text{H}_{31}\text{N}_3\text{O}_4\text{S}_1 = 445.2035$, found = 445.2031.

EXAMPLE 63 (S)-(-)-6-Amino-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]isochroman, methyl urea (S)-(X-6)

(S)-(-)-1-[2-(6-aminoisochroman-1-yl)-ethyl]-4-(4-methoxyphenyl)piperazine (S)-(Z-1, 376 mg, 1.0 mmol) is added to acetonitrile (4 mL). Methyl isocyanate (0.091 mL, 1.53 mmol) is added slowly via syringe. Additional acetonitrile (7 mL) is added and the reaction is stirred for 3 hours at 20-25°. The precipitate is filtered and rinsed successively with ethyl acetate and hexane to give crude product which is purified by flash chromatography using 5% methanol in methylene chloride to give (S)-(-)-6-amino-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]isochroman, methyl urea (S)-(X-6), $R_f = 0.07$ (5% methanol in methylene chloride); $[\alpha]_D = -43^\circ$ (c = 0.75, 50% ethanol in methylene chloride); IR (mull) 3312, 1645, 1614, 1597, 1567, 1512, 1421, 1310, 1244, 1109 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.11 (s, 1H, aromatic H), 7.02 (m, 2H, aromatic H's), 6.84 (q and m, 5H, J=9.2 Hz, aromatic H's), 5.09 (m of d, 1H, J=5.5 Hz, C(O)NMe-H), 4.77 (m of d, 1H, J=5.8 Hz, PhC-H), 4.07 (m, 1H, $\text{PhCH}_2\text{CH-H}$), 3.76 (s, 3H, OC-H_3), 3.71 (m, 1H, $\text{PhCH}_2\text{CH-H}$), 3.09 (t, 4H, J=4.9 Hz, four pip-H), 2.90 (m, 1H, PhCH-H), 2.79 (d, 3H, J=4.7 Hz, C(O)NHC-H₃), 2.60 (m's, 7H, PhCH-H, NC-H₂ and four pip-H), 2.10 (m, 1H, PhCHCH-H), 2.02 (m, 1H, PhCHCH-H) δ ; CMR (75 MHz, CDCl_3) 156.8, 153.8, 145.7, 136.8, 135.0, 133.5, 125.5, 121.2,

119.1, 118.2, 114.5, 74.5, 63.1, 55.6, 54.8, 53.5, 50.6, 33.2, 29.2, 27.0 δ ; HRMS calculated for $C_{24}H_{32}N_4O_3$ = 424.2474, found = 42473.

EXAMPLE 64 (S)-(-)-6-Amino-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]isochroman, *t*-butylcarbamate (S)-(X-6)

- 5 (S)-(-)-1-[2-(6-aminoisochroman-1-yl)-ethyl]-4-(4-methoxyphenyl)piperazine (S)-(Z-1, 200 mg, 0.54 mmol) and sodium hexamethyldisilazane (200 mg, 1.09 mmol) are mixed. THF (2 mL) is added via syringe and the reaction is stirred for 15 min. Di-*t*-butyl pyrocarbonate (108 mg, 0.50 mmol) is added as a solution in THF (2 mL). The mixture is stirred at 20-25° for 20 hours. The reaction is poured into water (40 mL).
- 10 The volatiles are removed under reduced pressure, and the aqueous residue is extracted with ethyl acetate (2 x 50 mL). The organics were combined, dried with sodium sulfate, filtered and concentrated. The concentrate is chromatographed on 30 g silica gel using 5% methanol in methylene chloride as the eluent to give (S)-(-)-6-amino-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]isochroman, *t*-butylcarbamate
- 15 (S)-(X-6), R_f = 0.38 (5% methanol in methylene chloride); $[\alpha]_D^{25}$ = -39° (c = 0.65, 50% ethanol in methylene chloride); IR (mull) 1694, 1522, 1515, 1423, 1367, 1286, 1243, 1167, 1109, 1058 cm^{-1} ; NMR (300 MHz, $CDCl_3$) 7.24 (s, 1H, aromatic H), 7.02 (m, 2H, aromatic H's), 6.86 (q, 4H, J =9.0 Hz, aromatic H's), 6.44 (broad s, 1H, N-H), 4.79 (m of d, 1H, J =5.8 Hz, PhC-H), 4.10 (m, 1H, PhCH₂CH-H), 3.76 (s, 3H, OC-H₃), 3.71
- 20 (m, 1H, PhCH₂CH-H), 3.10 (t, 4H, J =4.6 Hz, four pip-H), 2.94 (m, 1H, PhCH-H), 2.60 (m's, 7H, PhCH-H, NC-H₂ and four pip-H), 2.11 (m, 1H, PhCHCH-H), 2.01 (m, 1H, PhCHCH-H), 1.52 (s, 9H, three of CC-H₃) δ ; CMR (75 MHz, $CDCl_3$) 153.8, 152.8, 145.8, 136.5, 134.8, 132.8, 125.3, 118.6, 118.2, 116.8, 114.4, 80.6, 63.1, 61.1, 55.6, 54.8, 53.5, 50.6, 33.3, 29.3, 28.4 δ .

25 **EXAMPLE 65** 1-(4-Methoxyphenyl)-4-[2-(6-methylaminomethylisochroman-1-yl)ethyl]piperazine (BB-2)

- Following the general procedure of EXAMPLE 1, Step 4 and making non-critical variations but using 1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N-methyl-isochroman-6-carboxamide (IX, EXAMPLE 37) gives crude product. This
- 30 material is purified by LC on 13 g (230-400) silica gel eluting with 5% 3M ammonia in methanol/dichloromethane to give 1-(4-methoxyphenyl)-4-[2-(6-methylaminomethylisochroman-1-yl)ethyl]piperazine (BB-2), mp = 74-76°; R_f = 0.36 (5% 3M NH₃ in methanol/dichloromethane); IR (mull) 2788, 1512, 1291, 1276, 1253, 1232, 1180, 1151, 1132, 1107, 1051, 1035, 1012, 927, 831; NMR (300 MHz, $CDCl_3$)
- 35 7.08 (m, 3H, aromatic), 6.85 (m, 4H, aromatic), 4.85 (brdd, 1H, J =6.0 Hz, methine), 4.15 (m, 1H, OCH_{2a}), 3.77 (m, 4H, OCH₃& OCH_{2b}), 3.71 (s, 2H, Ph-CH₂-N), 3.11 (t,

4H, $J=4.9$ Hz, Ph-N-CH_{2s}), 2.97 (m, 1H, Ph-CH_{2a}), 2.72-2.50 (m, 7H, Ph-NC(H₂)-CH_{2s}-NCH_{2s}, Ph-CH_{2b}), 2.46 (s, 3H, NCH₃), 2.14 (m, 1H, C(H)-CH_{2a}), 2.04 (m, 1H, C(H)-CH_{2b}) δ ; CMR (75 MHz, CDCl₃) 153.6, 145.6, 137.9, 136.7, 133.9, 128.5, 126.0, 124.7, 118.0, 114.3, 74.5, 63.0, 55.6, 55.4, 54.7, 50.5, 35.9, 33.2, 29.0 δ ; HRMS (EI)

5 calculated for C₂₄H₃₃N₃O₂ = 395.2573, found = 395.2573.

EXAMPLE 66 1-(4-Methoxyphenyl)-4-[2-(6-dimethylaminomethylisochroman-1-yl)ethyl]piperazine (BB-2)

Following the general procedure of EXAMPLE 1, Step 4 and making non-critical variations but using 1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N,N-

10 dimethylisochroman-6-carboxamide (IX, EXAMPLE 36) gives crude product which is purified by LC on 13 g (230-400) silica gel eluting with 100% dichloromethane and gradually increasing polarity to 5% 3M ammonia in methanol/dichloromethane to give 1-(4-methoxyphenyl)-4-[2-(6-dimethylaminomethylisochroman-1-yl)ethyl]piperazine (BB-2), mp = 95-98°; R_f = 0.33 (5% 3M ammonia in methanol/dichloromethane); IR (mull) 2809, 2791, 2770, 2762, 1512, 1442, 1277, 1253, 1232, 1179, 1150, 1107, 1045, 15
1037, 832 cm⁻¹; NMR (300 MHz, CDCl₃) 7.07 (m, 3H, aromatic), 6.87 (m, 4H, aromatic), 4.83 (brdd, 1H, $J=6.4$ Hz, methine), 4.11 (m, 1H, OCH_{2a}), 3.76 (m, 4H, OCH₃& OCH_{2b}), 3.40 (s, 2H, Ph-CH₂-N), 3.11 (t, 4H, $J=4.9$ Hz, Ph-NCH_{2s}), 2.97 (m, 1H, Ph-CH_{2a}), 2.65 (m, 7H, Ph-NC(H₂)-CH_{2s}-NCH₂ & Ph-CH_{2b}), 2.26 (s, 6H, 20 NCH_{3s}), 2.18 (m, 1H, C(H)-CH_{2a}), 2.05 (m, 1H, C(H)-CH_{2b}) δ ; CMR (75 MHz, CDCl₃) 153.8, 145.8, 137.0, 136.6, 133.9, 129.5, 127.1, 124.6, 118.2, 114.4, 74.6, 64.0, 63.2, 55.6, 54.9, 53.5, 50.6, 45.3, 33.3, 29.1 δ ; HRMS (EI) calculated for C₂₅H₃₅N₃O₂ = 409.2729, found = 409.2733.

EXAMPLE 67 1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]-isochroman-6-
25 carboxylic acid, ethyl ester (X)

An oven-dried 10 mL flask equipped with spinbar, reflux condenser, and 3-way adapter is charged with 1-[2-(6-bromoisochroman-1-yl)ethyl]-4-(4-methoxyphenyl)-piperazine (VI, EXAMPLE 24, Step 2, 431 mg, 1.0 mmol), palladium II acetate (11 mg, 0.05 mmol), 1,3-bis(diphenylphosphino)propane (25 mg, 0.06
30 mmol), 2.5 mL dimethylformamide, diisopropylethylamine (0.35 mL, 2.0 mmol), and ethanol (1.2 mL, 20 mmol). The resulting mixture is purged six times with carbon monoxide/under reduced pressure followed by heating to 100°. After 18 hours, the mixture is cooled to 20-25°, concentrated under high vacuum, diluted with 20 mL 1M sodium hydroxide, and extracted twice with ethyl acetate (20 mL). The
35 combined organics are washed once with saline (20 mL), dried over magnesium sulfate, filtered, and concentrated to give product. This material is purified by LC

on 22 g (230-400) silica gel eluting with 30% acetone/hexane to give 1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-isochroman-6-carboxylic acid, ethyl ester (X), mp = 117-119°; R_f = 0.45 (35% acetone/hexane); IR (mull) 1712, 1513, 1422, 1286, 1260, 1246, 1187, 1145, 1140, 1108, 1053, 1037, 1023, 818, 767 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.84 (d, 1H, $J=8.2$ Hz, aromatic), 7.80 (s, 1H, aromatic), 7.17 (d, 1H, $J=8.1$ Hz, aromatic), 6.85 (m, 4H, aromatic), 4.85 (brdd, 1H, $J=6.0$ Hz, methine), 4.36 (qrt, 2H, $J=7.1$ Hz, CO_2CH_2), 4.15 (m, 1H, OCH_2), 3.76 (m, 4H, OCH_3 & OCH_2), 3.10 (t, 4H, $J=4.7$ Hz, Ph-N-CH_2), 3.00 (m, 1H, Ph-CH_2), 2.79-2.50 (m, 7H, $\text{Ph-NC(H}_2\text{)-CH}_2\text{-NCH}_2$, Ph-CH_2), 2.15 (m, 1H, C(H)-CH_2), 2.06 (m, 1H, C(H)-CH_2), 1.39 (t, 3H, $J=7.1$ Hz, $\text{C(H}_2\text{)-CH}_3$); CMR (75 MHz, CDCl_3) 166.2, 153.5, 145.4, 142.9, 133.9, 129.8, 128.2, 126.9, 124.5, 117.8, 114.1, 74.3, 62.6, 60.6, 55.2, 54.3, 53.2, 50.3, 32.8, 28.7, 14.0 δ .

EXAMPLE 68 6-Acetyl-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-isochroman, hydrochloride salt (XXIV)

An oven-dried 10 mL flask equipped with spinbar and reflux condenser is charged with 1-[2-(6-bromoisochroman-1-yl)ethyl]-4-(4-methoxyphenyl)-piperazine (VI, EXAMPLE 24, Step 2, 431 mg, 1.0 mmol), palladium II acetate (11 mg, 0.05 mmol), 1,3-bis(diphenylphosphino)propane (25 mg, 0.06 mmol), thallium II acetate (290 mg, 1.1 mmol), 3.0 mL dimethylformamide, triethylamine (0.28 mL, 2.0 mmol), and vinyl butylether (0.65 mL, 5.0 mmol). The mixture is heated to 100° and after 20 hours, the mixture is cooled to 20-25°, treated with hydrochloric acid (1M, 6 mL) and is stirred for 1 hour. The mixture is concentrated under high vacuum, diluted with 20 mL 5M sodium hydroxide, and extracted twice with ethyl acetate (20 mL). The combined organics are washed once with saline (20 mL), dried over magnesium sulfate, filtered and concentrated. This material is purified by LC on 27 g (230-400) silica gel eluting with 25% acetone/hexane. This material is dissolved in a mixture of ethyl acetate/methanol and is treated with gaseous hydrochloric acid resulting in the formation of a solid that is recrystallized from ethyl acetate/methanol to give 6-acetyl-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-isochroman, hydrochloride salt (XXIV), mp = 195-197°; R_f = 0.15 (30% acetone/hexane); bis salt IR (mull) 2560, 2516, 2487, 2462, 1675, 1511, 1444, 1425, 1359, 1290, 1265, 1245, 1113, 1035, 837 cm^{-1} ; freebase NMR (300 MHz, CDCl_3) 7.78 (d, 1H, $J=8.1$ Hz, aromatic), 7.72 (s, 1H, aromatic), 7.20 (d, 1H, $J=8.1$ Hz, aromatic), 6.87 (m, 4H, aromatic), 4.89 (brdd, 1H, $J=6.0$ Hz, methine), 4.15 (m, 1H, OCH_2), 3.76 (m, 4H, OCH_3 & OCH_2), 3.11 (t, 4H, $J=4.8$ Hz, Ph-N-CH_2), 3.00 (m, 1H, Ph-CH_2), 2.80-2.55 (m, 10H, $\text{Ph-NC(H}_2\text{)-CH}_2\text{-NCH}_2$, Ph-CH_2 , COCH_3), 2.15 (m, 1H, C(H)-CH_2), 2.06 (m, 1H, C(H)-CH_2); δ ;

CMR (75 MHz, CDCl₃) 197.8, 153.7, 145.6, 143.5, 135.2, 134.4, 128.9, 126.1, 125.0, 118.1, 114.3, 74.5, 62.9, 55.5, 54.6, 53.4, 50.5, 33.0, 29.0, 26.5 δ ; HRMS (EI) calculated for C₂₄H₃₀N₂O₃ = 394.2256, found = 394.2262.

EXAMPLE 69 6-Formyl-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-isochroman (AA-1)

1-[2-(6-Bromoisochroman-1-yl)ethyl]-4-(4-methoxyphenyl)piperazine (VI, EXAMPLE 24, Step 2, 2.80 g, 6.5 mmol) and freshly distilled tetrahydrofuran (16 mL) are mixed followed by cooling to -78°. The mixture is treated with a 1.7 M solution of tert-butyllithium (7.7 mL, 13.0 mmol). After 15 min, the aryl lithium is treated with dimethylformamide (1.0 mL, 13 mmol). The reaction is warmed to 20-25° over 1.5 hours then is diluted with 75 mL water and extracted twice with ethyl acetate (75 mL). The combined organics are washed once with saline (50 mL), dried over magnesium sulfate, filtered, and concentrated to give crude product. This material is purified by LC on 160 g (230-400) silica gel eluting with 30% acetone/hexane to give 6-formyl-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-isochroman (AA-1), R_f = 0.28 (30% acetone/hexane); IR (liq.) 2949, 2819, 1698, 1608, 1512, 1464, 1456, 1291, 1285, 1244, 1143, 1124, 1110, 1038, 824 cm⁻¹; NMR (300 MHz, CDCl₃) 9.97 (s, 1H, CHO), 7.69 (d, 1H, J=8.0 Hz, aromatic), 7.60 (s, 1H, aromatic), 7.28 (d, 1H, J=7.7 Hz, aromatic), 6.85 (m, 4H, aromatic), 4.90 (brdd, 1H, J=6.0 Hz, methine), 4.16 (m, 1H, OCH_{2a}), 3.76 (m, 4H, OCH₃ & OCH_{2b}), 3.10 (t, 5H, J=5.0 Hz, Ph-N-CH_{2s} & Ph-CH_{2a}), 2.83-2.50 (m, 7H, Ph-NC(H₂)-CH_{2s}-NCH_{2s}, Ph-CH_{2b}), 2.16 (m, 1H, C(H)-CH_{2a}), 2.07 (m, 1H, C(H)-CH_{2b}) δ ; CMR (75 MHz, CDCl₃) 192.0, 153.8, 145.7, 145.2, 135.0, 134.7, 130.4, 127.4, 125.6, 118.2, 114.4, 74.6, 62.8, 55.6, 54.6, 53.5, 50.6, 33.1, 29.0 δ ; HRMS (EI) calculated for C₂₃H₂₈N₂O₃ = 380.2100, found = 380.2098.

EXAMPLE 70 2-[Isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]acetamide (AA-4)

Step 1: 1-[2-(6-Hydroxymethylisochroman-1-yl)-ethyl]-4-(4-methoxyphenyl)piperazine (AA-2)

6-Formyl-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]isochroman (AA-1, EXAMPLE 71, 2.51 g, 6.6 mmol) and 25 mL methanol are mixed followed by cooling to 0°. The mixture is treated with a single portion of sodium borohydride (500 mg, 13.2 mmol). The reaction is gradually warmed to 20-25° over 2 hours and is diluted with 75 mL water and extracted twice with ethyl acetate (75 mL). The combined organics are washed once with saline (50 mL), dried over magnesium sulfate, filtered and concentrated. This material is purified by LC on 180 g (230-400) silica

gel eluting with methanol/dichloromethane (5/95) to give 1-[2-(6-hydroxymethylisochroman-1-yl)ethyl]-4-(4-methoxyphenyl)piperazine (AA-2), R_f = 0.15 (35% acetone/hexane); IR (mull) 1513, 1445, 1428, 1292, 1279, 1248, 1186, 1152, 1140, 1107, 1057, 1034, 1011, 928, 826 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.17 (d, 1H, J =8.0 Hz, aromatic), 7.09 (m, 2H, aromatic), 6.86 (m, 4H, aromatic), 4.82 (brdd, 1H, J =6.3 Hz, methine), 4.64 (s, 2H, $\text{Ph-CH}_2\text{-O}$), 4.12 (m, 1H, OCH_{2a}), 3.76 (m, 4H, OCH_3 & OCH_{2b}), 3.10 (t, 4H, J =4.8 Hz, Ph-N-CH_{2s}), 2.97 (m, 1H, Ph-CH_{2a}), 2.72-2.50 (m, 7H, $\text{Ph-NC(H)}_2\text{-CH}_{2s}\text{-NCH}_{2s}$, Ph-CH_{2b}), 2.10 (m, 2H, C(H)-CH_{2s}) δ ; MS (EI, m/z) = 382.

10 Step 2: 1-[2-(6-Cyanomethylisochroman-1-yl)ethyl]-4-(4-methoxyphenyl)-piperazine (AA-3)

1-[2-(6-Hydroxymethylisochroman-1-yl)-ethyl]-4-(4-methoxyphenyl)piperazine (AA-2, 2.33 g, 6.1 mmol), 61 mL dichloromethane and triethylamine (1.3 mL, 9.1 mmol) are mixed followed by cooling to 0°. The mixture is treated with
15 methanesulfonylchloride (0.52 mmol, 6.7 mmol). The reaction is warmed to 20-25° over 1.5 hours and concentrated under reduced pressure. The crude mesylate is diluted with 31 mL dimethylsulfoxide and treated with sodium cyanide (896 mg, 18.3 mmol). This mixture is heated to 60°. After 2 hours, the volatiles are removed under high vacuum with the resulting residue diluted with 100 mL water and
20 extracted twice with ethyl acetate (75 mL). The combined organics are washed once with saline (75 mL), dried over magnesium sulfate, filtered and concentrated. This material is purified by LC on 88 g (230-400) silica gel eluting with 35% acetone/hexane to give 1-[2-(6-cyanomethylisochroman-1-yl)ethyl]-4-(4-methoxyphenyl)piperazine (AA-3), mp = 118-119°; R_f = 0.36 (35% acetone/hexane);
25 IR (mull) 2810, 2790, 1512, 1444, 1275, 1253, 1232, 1182, 1151, 1111, 1107, 1058, 1051, 1031 and 831 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.10 (m, 3H, aromatic), 6.87 (m, 4H, aromatic), 4.82 (brdd, 1H, J =6.3 Hz, methine), 4.14 (m, 1H, OCH_{2a}), 3.76 (m, 4H, OCH_3 & OCH_{2b}), 3.74 (s, 2H, NC-CH_2), 3.11 (t, 4H, J =4.8 Hz, Ph-N-CH_{2s}), 2.98 (m, 1H, Ph-CH_{2a}), 2.73-2.50 (m, 7H, $\text{Ph-NC(H)}_2\text{-CH}_{2s}\text{-NCH}_{2s}$, Ph-CH_{2b}), 2.18 (m,
30 1H, C(H)-CH_{2a}), 2.04 (m, 1H, C(H)-CH_{2b}) δ ; CMR (75 MHz, CDCl_3) 153.8, 145.8, 138.1, 135.1, 128.4, 127.9, 125.8, 125.6, 118.2, 117.9, 114.3, 74.462.9, 55.6, 54.7, 53.5, 50.6, 33.3, 29.0, 23.2 δ ; MS (EI, m/z) = 391.

Step 3: 2-[Isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]acetamide (AA-4)

35 1-[2-(6-Cyanomethylisochroman-1-yl)ethyl]-4-(4-methoxyphenyl)piperazine (AA-3, 785 mg, 2.0 mmol), 5.0 mL dimethylformamide and potassium carbonate (39

mg, 0.28 mmol) are mixed. The mixture is treated with a 30% solution of hydrogen peroxide (0.24 mL, 2.3 mmol). After 20 hours, the reaction is diluted with 100 mL dichloromethane and washed once with water (20 mL), once with saline (20 mL), dried over magnesium sulfate, filtered and concentrated. This material is

5 recrystallized from ethyl acetate/hexane to give 2-[isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]acetamide (AA-4), mp = 159-161°; R_f = 0.15 (5% methanol/dichloromethane); IR (mull) 3381, 3208, 2791, 1658, 1633, 1513, 1444, 1293, 1275, 1255, 1231, 1150, 1108, 1032, 833 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.09 (s, 2H, aromatic), 7.02 (s, 1H, aromatic), 6.86 (m, 4H, aromatic), 5.59 (brds, 1H, NH),

10 5.43 (brds, 1H, NH), 4.81 (brdd, 1H, $J=6.0$ Hz, methine), 4.12 (m, 1H, OCH_{2a}), 3.76 (m, 4H, OCH_3 & OCH_{2b}), 3.53 (s, 2H, $\text{O}=\text{C}-\text{CH}_2$), 3.10 (t, 4H, $J=4.9$ Hz, $\text{Ph}-\text{N}-\text{CH}_{2s}$) 2.96 (m, 1H, $\text{Ph}-\text{CH}_{2a}$), 2.72-2.56 (m, 7H, $\text{Ph}-\text{NC}(\text{H}_2)-\text{CH}_{2s}-\text{NCH}_{2s}$, $\text{Ph}-\text{CH}_{2b}$), 2.13 (m, 1H, $\text{C}(\text{H})-\text{CH}_{2a}$), 2.03 (m, 1H, $\text{C}(\text{H})-\text{CH}_{2b}$) δ ; CMR (75 MHz, CDCl_3) 173.4, 153.8, 145.7, 137.4, 134.7, 132.8, 129.8, 127.2, 125.4, 118.1, 114.4, 74.5, 55.6, 54.8,

15 53.5, 50.6, 42.8, 33.2, 29.0 δ ; MS (EI, m/z) = 409.

EXAMPLE 71 2-[Isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]-N-methylacetamide (AA-5)

Following the general procedure of EXAMPLE 3, Step 1 and making non-critical variations but using 2-[isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]acetamide (AA-4, 446 mg, 1.09 mmol) crude product is obtained. This

20 material is purified by LC on 40 g (230-400) silica gel eluting with 50% ethylacetate/hexane to give 2-[isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]-N,N-di-*t*-butyloxycarbonylacetamide, R_f = 0.45 (60% ethylacetate/hexane). This material is reacted with methylamine according to the

25 general procedure of EXAMPLE 3, Step 2 and making non-critical variations to give the desired product which is purified by LC on 13 g (230-400) silica gel eluting with 60% acetone/hexane to give 2-[isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]-N-methylacetamide (AA-5), mp = 147-148°; R_f = 0.20 (50% acetone/hexane); IR (mull) 3309, 1652, 1550, 1515, 1442, 1426, 1412, 1354, 1251,

30 1228, 1153, 1147, 1114, 1036, 826 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.09 (m, 2H, aromatic), 7.01 (s, 1H, aromatic), 6.87 (m, 4H, aromatic), 5.45 (brds, 1H, NH), 4.83 (brdd, 1H, $J=6.0$ Hz, methine), 4.15 (m, 1H, OCH_{2a}), 3.77 (m, 4H, OCH_3 & OCH_{2b}), 3.53 (s, 2H, $\text{O}=\text{C}-\text{CH}_2$), 3.12 (t, 4H, $J=4.8$ Hz, $\text{Ph}-\text{N}-\text{CH}_{2s}$) 2.95 (m, 1H, $\text{Ph}-\text{CH}_{2a}$), 2.77 (d, 3H, $J=4.9$ Hz, NCH_3), 2.72-2.56 (m, 7H, $\text{Ph}-\text{NC}(\text{H}_2)-\text{CH}_{2s}-\text{NCH}_{2s}$, $\text{Ph}-\text{CH}_{2b}$),

35 2.15 (m, 1H, $\text{C}(\text{H})-\text{CH}_{2a}$), 2.04 (m, 1H, $\text{C}(\text{H})-\text{CH}_{2b}$) δ ; CMR (75 MHz, CDCl_3) 171.6, 153.8, 145.7, 137.3, 134.7, 132.9, 130.0, 127.3, 125.4, 118.2, 114.4, 74.5, 63.0, 55.6,

54.9, 53.6, 50.6, 43.3, 33.3, 29.0, 26.5 δ ; MS (EI, m/z) = 423.

EXAMPLE 72 1-[2-[4-(4-Hydroxyphenyl)-1-piperazinyl]ethyl]-isochroman-6-carboxamide (CC-2)

1-[2-[4-(4-Phenylmethyloxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (CC-1, EXAMPLE 9, 0.42 mmol, 200 mg), palladium on carbon (10%, 20 mg), ethanol (5 mL) and methylene chloride (2 mL) are combined. After four days the starting material is consumed. The reaction mixture is filtered on a bed of celite and rinsed several times alternatively with ethanol, methanol, methylene chloride and ethyl acetate. The filtrates are combined and concentrated. The crude material is recrystallized from hot ethanol with some methanol to give 1-[2-[4-(4-hydroxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (CC-2), IR (mull) 3300, 3255, 3206, 1672, 1615, 1513, 1444, 1426, 1366, 1256 cm^{-1} ; NMR (300 MHz, DMSO) 7.85 (d, 1H, $J=8.2$ Hz, aromatic H), 7.82 (s, 1H, aromatic H), 7.43 (d, 1H, $J=8.2$ Hz, aromatic H), 6.96 (d, 2H, $J=8.8$ Hz, aromatic H's), 6.81 (d, 2H, $J=8.8$ Hz, aromatic H's), 5.00 (broad d, 1H), 4.18 (m, 2H), 3.85 (m, 1H), 3.68 (m, 4H), 3.46-3.0 (several broad m, 6H), 2.85 (broad d, 2H, $J=16$ Hz) 2.37 (broad m, 1H) δ ; HRMS calculated for $\text{C}_{22}\text{H}_{27}\text{N}_3\text{O}_3$ = 382.2131, found = 382.2136.

EXAMPLE 73 (S)-(-)-1-[2-[4-(4-Hydroxyphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide (S)-(CC-2)

A Parr flask is charged with (S)-(-)-1-[2-[4-(4-phenylmethyloxyphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide (S)-(CC-1, EXAMPLE 20) 50 mL methanol, 25 mL tetrahydrofuran, and 10% palladium on carbon (200 mg). The resulting black suspension is placed under 40 psi hydrogen and shaken. After 60 hours, the pressure had fallen to 27 psi hydrogen and the reaction mixture is filtered through celite and concentrated. The concentrate is recrystallized from methanol/ethylacetate to give (S)-(-)-1-[2-[4-(4-hydroxyphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide (S)-(CC-2), mp = 154-162 $^{\circ}$; R_f = 0.11 (5% methanol/ethylacetate); $[\alpha]_D^{25}$ = -53 $^{\circ}$ (c = 0.9681, methanol); IR (mull) 3350, 3200, 3174, 2811, 1642, 1573, 1542, 1517, 1300, 1271, 1248, 1243, 1232, 1104, 825, cm^{-1} ; NMR (300 MHz, DMSO- d_6) δ 8.81 (s, 1H, OH), 8.37 (brdd, 1H, $J=4.6$ Hz, NH), 7.61 (m, 3H, aromatic), 7.27 (d, 1H, $J=8.1$ Hz, aromatic), 6.76 (d, 2H, $J=8.9$ Hz, aromatic), 6.63 (d, 2H, $J=8.9$ Hz, aromatic), 4.78 (brdd, 1H, $J=6.0$ Hz, methine), 4.03 (m, 1H, OCH_2), 3.66 (m, 1H, OCH_2), 2.93 (m, 4H, Ph-N-CH_2), 2.76 (d, 4H, $J=4.5$ Hz, N-CH_3 & Ph-CH_2), 2.49 (m, 6H, $\text{Ph-NC(H}_2\text{)-CH}_2\text{-NCH}_2$), 2.35 (m, 1H, Ph-CH_2), 2.15 (m, 1H, C(H)-CH_2), 1.85 (m, 1H, C(H)-CH_2) δ ; CMR (75 MHz, DMSO- d_6) 166.4, 150.8, 144.2, 141.2, 133.7, 132.3, 127.5, 124.8, 124.6, 117.6, 115.4, 73.6, 62.2,

54.2, 53.1, 50.0, 32.5, 28.5, 26.2 δ ; HRMS (EI) calculated for $C_{23}H_{29}N_3O_3$ = 395.2209, found = 395.2212; K.F. Water = 4.28%.

EXAMPLE 74 (S)-(-)-1-[2-[4-(4-Trifluoromethanesulfonyloxyphenyl)-1-piperazinyl]ethyl]-N-methyl-isochroman-6-carboxamide (S)-(CC-3)

(S)-(-)-1-[2-[4-(4-hydroxyphenyl)-1-piperazinyl]ethyl]-N-methyl-isochroman-6-carboxamide (S)-(CC-2, 959 mg, 2.4 mmol), 24 mL dichloromethane, and N-phenyltrifluoromethane-sulfonimide (910 mg, 2.5 mmol) are mixed. The mixture is cooled to 0° and treated with triethylamine (0.51 mL, 3.6 mmol) with no visible change occurring. After 16 hours, the mixture is diluted with 75 mL 1M sodium hydroxide and extracted twice with dichloromethane (75 mL). The combined organics are washed once with saline (50 mL), dried over magnesium sulfate, filtered and concentrated. This material is purified by LC on 88 g (230-400) silica gel eluting with 5% methanol/dichloromethane to give (S)-(-)-1-[2-[4-(4-trifluoromethanesulfonyloxyphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide (S)-(CC-3), R_f = 0.34 (5% methanol/dichloromethane); $[\alpha]_D^{25}$ = -39° (c = 0.9447, methanol); IR (mull) 1641, 1571, 1548, 1505, 1417, 1310, 1297, 1240, 1210, 1209, 1141, 1110, 885, 826, 609 cm^{-1} ; NMR (300 MHz, $CDCl_3$) 7.55 (m, 2H, aromatic), 7.14 (m, 3H, aromatic), 6.87 (d, 2H, J=9.4 Hz, aromatic), 6.18 (brdd, 1H, J=4.6 Hz, NH), 4.85 (brdd, 1H, J=5.8 Hz, methine), 4.13 (m, 1H, OCH_{2a}), 3.75 (m, 1H, OCH_{2b}), 3.22 (t, 4H, J=4.9 Hz, $Ph-N-CH_{2s}$), 3.00 (d, 4H, J=4.9 Hz, $N-CH_3$ & $Ph-CH_{2a}$), 2.75-2.49 (m, 7H, $Ph-NC(H_2)-CH_{2s}-NCH_{2s}$ & $Ph-CH_{2b}$), 2.15 (m, 1H, $C(H)-CH_{2a}$), 2.04 (m, 1H, $C(H)-CH_{2b}$) δ ; CMR (75 MHz, $CDCl_3$) 168.0, 150.9, 142.1, 141.5, 134.5, 132.7, 127.7, 125.0, 124.5, 121.9, 116.3, 74.4, 63.0, 54.5, 53.2, 48.7, 33.2, 29.1, 26.9; HRMS (FAB) calculated for $C_{24}H_{28}F_3N_3O_5S+H_1$ = 528.1780, found = 528.1791.

EXAMPLE 75 (S)-(-)-1-[2-[4-(4-Acetylphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide (S)-(IX)

(S)-(-)-1-[2-[4-(4-Trifluoromethanesulfonyloxyphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide (S)-(CC-3, 527 mg, 1.0 mmol), palladium II acetate (11 mg, .05 mmol), 1,3-bis(diphenylphosphino)propane (25 mg, .06 mmol), 3.5 mL dimethylformamide, triethylamine (0.28 mL, 2.0 mmol), and butylvinylether (0.65 mL, 5.0 mmol) are combined. The resulting mixture is heated to 50°. After 16 hours, the reaction is cooled to 20-25°, treated with 8 mL 1M hydrochloric acid, and is stirred for 1 hour. This acidic mixture is concentrated under reduced pressure, diluted with 15 mL 1M sodium hydroxide, and extracted twice with dichloromethane

(25 mL). The combined organics are washed once with saline (15 mL), dried over magnesium sulfate, filtered, and concentrated. This material is purified by LC on 36 g (230-400) silica gel eluting with 50% acetone/hexane to give (S)-(-)-1-[2-[4-(4-acetylphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide (S)-(CC-4) which upon recrystallization from ethyl acetate/hexane, mp = 156-157°; R_f = 0.20 (50% acetone/hexane); $[\alpha]_D^{25} = -41^\circ$ (c = 0.8481, methanol); IR (mull) 3331, 1662, 1598, 1570, 1550, 1519, 1427, 1415, 1311, 1284, 1239, 1196, 1150, 1107, 609 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.85 (d, 2H, J=8.9 Hz, aromatic), 7.55 (m, 2H, aromatic), 7.14 (d, 1H, J=8.5 Hz, aromatic), 6.84 (d, 2H, J=8.9 Hz, aromatic), 6.24 (brdd, 1H, J=4.6 Hz, NH), 4.86 (brdd, 1H, J=5.8 Hz, methine), 4.12 (m, 1H, OCH_{2a}), 3.76 (m, 1H, OCH_{2b}), 3.35 (t, 4H, J=5.0 Hz, Ph-N-CH_{2a}), 3.00 (d, 4H, J=4.9 Hz, N-CH_3 & Ph-CH_{2a}), 2.75-2.53 (m, 7H, $\text{Ph-NC(H}_2\text{)-CH}_{2a}\text{-NCH}_{2s}$ & Ph-CH_{2b}), 2.50 (s, 3H, O=C-CH_3), 2.16 (m, 1H, C(H)-CH_{2a}), 2.02 (m, 1H, C(H)-CH_{2b}) δ ; CMR (75 MHz, CDCl_3) 196.6, 168.0, 154.2, 141.5, 134.5, 132.7, 130.4, 127.7, 127.6, 125.0, 124.5, 113.4, 74.4, 63.0, 54.5, 53.0, 47.3, 33.2, 29.1, 26.9, 26.1 δ ; HRMS (EI) calculated for $\text{C}_{25}\text{H}_{31}\text{N}_3\text{O}_3$ = 421.2365, found = 421.2365.

EXAMPLE 76 (S)-(-)-3-[Isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]-N,N-dimethylacrylamide (S)-(XVIII)

(S)-(-)-1-[2-(6-Bromoisochroman-1-yl)-ethyl]-4-(4-methoxyphenyl)-piperazine (S)-(VI) (431.4 mg, 1.0 mmol), palladium (II) acetate (98%, 11.4 mg, 0.05 mmol) and 1,3-bis-diphenylphosphinopropane (97%, 24.7 mg, 0.06 mmol) are combined. Argon atmosphere is established. To the reaction vessel is introduced via syringe DMF (4.1 mL), dimethylacrylamide (0.72 mL, 7.0 mmol), and diisopropylethylamine (0.35 mL, 2.0 mmol). The mixture is heated to 100° over 18 hours. After cooling to 20-25°, the reaction is diluted with aqueous sodium hydroxide and extracted three times with ethyl acetate. The organics are combined and concentrated. Residual DMF is removed under high vacuum. The crude material is purified by flash chromatography on 80 g silica gel using 5% methanol in methylene chloride as the eluent to give a solid which is recrystallized from hot ethyl acetate/hexane to give (S)-(-)-3-[isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]-N,N-dimethylacrylamide (S)-(XVIII), mp = 120-121°; R_f = 0.30 (5% methanol in methylene chloride); NMR (300 MHz, CDCl_3) 7.62 (d, 1H, J=15.4 Hz, aromatic H), 7.34 (d, 1H, J=8.0 Hz, aromatic H), 7.10 (d, 1H, J=8.0 Hz, aromatic H), 6.85 (d of d and m, 4H and 1H respectively, $J_a=9.1\text{Hz}$, $J_b=21.4\text{ Hz}$, aromatic H's), 4.83 (m of d, 1H, J=6.0 Hz, PhC-H), 4.13 (m, 1H, $\text{PhCH}_2\text{CH-H}$), 3.75 (m, 1H, $\text{PhCH}_2\text{CH-H}$), 3.75 (s, 3H, PhOC-H_3), 3.17 (s, 3H, NMeC-H_3), 3.10 (t and s, 4H and 3H respectively,

J=4.8 Hz, four of pip-H and one of NMeC-H₃), 2.94 (m, 1H, NCH-H), 2.76-2.45 (several m's, 7H, four pip-H, two PhCH-H, and NCH-H), 2.14 (m, 1H, PhCHCH-H), 2.02 (m, 1H, PhCHCH-H) δ ; CMR (75 MHz, CDCl₃) 166.7, 153.8, 145.7, 142.0, 139.8, 134.5, 133.5, 128.3, 125.5, 125.2, 118.1, 117.1, 114.4, 74.6, 63.0, 55.6, 54.8, 53.5, 50.6, 37.4, 35.9, 33.2 and 29.1 δ .

EXAMPLE 77 (S)-(-)-1-(4-Methoxyphenyl)-4-[2-[6-(1,2,4-triazol-3-yl)-isochroman-1-yl]ethyl]piperazine (S)-(O-2)

Step 1: (S)-(-)-1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]-N-dimethylaminomethyleneisochroman-6-carboxamide (S)-(O-1)

(S)-(-)-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (S)-(VII, 395.5 mg, 1 mmol) and N,N-dimethylformamidedimethylacetal (94%, 0.34 mL, 2.4 mmol) and toluene (1 mL) are combined. The reaction mixture is heated to 90° for 1.5 hours. After cooling to 20-25°, the volatiles are removed under reduced pressure. Purification of the crude material by flash chromatography on 90 g silica gel using 5% methanol in methylene chloride as the eluent gives (S)-(-)-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N-dimethylaminomethyleneisochroman-6-carboxamide (S)-(O-1), mp = 134-135.5°; R_f = 0.28 (5% methanol in methylene chloride); [α]_D = -47° (c = 0.96, 50% methylene chloride in ethanol); IR (mull) 1647, 1608, 1593, 1512, 1446, 1417, 1329, 1259, 1247, 1108 cm⁻¹; NMR (300 MHz, CDCl₃) 8.63 (s, 1H, NMe₂C-H), 8.07 (d, 1H, J=8.1 Hz, aromatic H), 8.02 (s, 1H, aromatic H), 7.14 (d, 1H, J=8.0 Hz, aromatic H), 6.85 (d of d, 4H, J_a=9.2 Hz, J_b=21.6 Hz, aromatic H's), 4.88 (m of d, 1H, J=5.1 Hz, PhC-H), 4.13 (m, 1H, PhCH₂CH-H), 3.76 (m, 1H, PhCH₂CH-H), 3.75 (s, 3H, OC-H₃), 3.21 (s, 3H, NMeC-H₃), 3.18 (s, 3H, NMeC-H₃), 3.10 (t, 4H, J=4.9 Hz, four pip-H), 2.98 (m, 1H, PhCH-H), 2.76 (m of d, 1H, J=16 Hz, PhCH-H), 2.60 (m's, 6H, NC-H₂ and four pip-H), 2.15 (m, 1H, PhCHCH-H), 2.05 (m, 1H, PhCHCH-H) δ ; CMR (75 MHz, CDCl₃) 177.6, 160.8, 153.7, 145.8, 142.0, 134.9, 133.7, 130.3, 127.6, 124.5, 118.1, 114.4, 74.8, 63.1, 55.6, 54.7, 53.5, 50.6, 41.4, 35.3, 33.2 and 29.2 δ .

Step 2: (S)-(-)-1-(4-Methoxyphenyl)-4-[2-[6-(1,2,4-triazol-3-yl)isochroman-1-yl]ethyl]piperazine (S)-(O-2)

(S)-(-)-1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]-N-dimethylaminomethyleneisochroman-6-carboxamide (S)-(O-1, 208 mg, 0.46 mmol) and glacial acetic acid (1 mL) are combined under argon atmosphere. Hydrazine monohydrate (0.045 mL, 0.92 mmol) is added dropwise via syringe with vigorous stirring. It is stirred at 20-25° for 24 hours. The reaction mixture is diluted with water and partitioned between saturated aqueous sodium bicarbonate and

methylene chloride. The organics are combined, dried with sodium sulfate, filtered and concentrated. The concentrate is purified by flash chromatography on 6 g silica gel using 5% methanol in methylene chloride as the eluent to give (S)-(-)-1-(4-methoxyphenyl)-4-[2-[6-(1,2,4-triazol-3-yl)isochroman-1-yl]ethyl]piperazine (S)-(O-2),
 5 mp = 195.5-196°; R_f = 0.11 (5% methanol in methylene chloride); NMR (300 MHz, $CDCl_3$) 8.18 (s, 1H, triazoleC-H), 7.81 (d, 1H, J =7.7 Hz, aromatic H), 7.8 (s, 1H, aromatic H), 7.15 (d, 1H, J =8.0 Hz, aromatic H), 6.85 (d of d, 4H, J_a =9.2 Hz, J_b =21.6 Hz, aromatic H's), 4.87 (m of d, 1H, J =5.1 Hz, PhC-H), 4.13 (m, 1H, $PhCH_2CH$ -H), 3.76 (m, 1H, $PhCH_2CH$ -H), 3.75 (s, 3H, OC- H_3), 3.12 (t, 4H, J =4.9 Hz, four pip-H),
 10 2.98 (m, 1H, $PhCH$ -H), 2.76-2.59 (several m's, 7H, $PhCH$ -H, NC- H_2 and four pip-H), 2.15 (m, 1H, $PhCHCH$ -H), 2.05 (m, 1H, $PhCHCH$ -H) δ ; CMR (75 MHz, $CDCl_3$) 159.4, 153.9, 146.9, 145.6, 139.8, 134.7, 127.3, 127.0, 125.3, 124.2, 118.2, 114.5, 63.1, 55.6, 54.7, 53.4, 50.6, 33.0, 29.0 δ .

EXAMPLE 78 (S)-(-)-1-(4-Methoxyphenyl)-4-[2-[6-(2-methyl-1,2,4-triazol-3-yl)isochroman-1-yl]ethyl]piperazine (S)-(O-2)
 15

Following the general procedure of EXAMPLE 77, Step 2 and making non-critical variations, but using methyl hydrazine gives (S)-(-)-1-(4-methoxyphenyl)-4-[2-[6-(2-methyl-1,2,4-triazol-3-yl)isochroman-1-yl]ethyl]piperazine (S)-(O-2), R_f = 0.17 (5% methanol in methylene chloride); NMR (300 MHz, $CDCl_3$) 8.04, 7.47, 7.46, 7.24,
 20 6.85, 4.89, 4.16, 3.99, 3.80, 3.75, 3.10, 2.98, 2.77, 2.67-2.59, 2.18, 2.07 δ ; CMR (75 MHz, $CDCl_3$) 154.4, 153.8, 150.7, 145.7, 140.4, 134.9, 129.3, 126.2, 125.9, 125.3, 118.1, 114.4, 74.5, 62.9, 55.6, 54.7, 53.5, 50.6, 37.0, 33.2, 29.0 δ .

EXAMPLE 79 (S)-(-)-1-(4-Methoxyphenyl)-4-[2-[6-(2-phenylmethyl-1,2,4-triazol-3-yl)isochroman-1-yl]ethyl]piperazine (S)-(O-2)

25 Following the general procedure of EXAMPLE 77, Step 2 and making non-critical variations but using phenylmethyl hydrazine gives (S)-(-)-1-(4-methoxyphenyl)-4-[2-[6-(2-phenylmethyl-1,2,4-triazol-3-yl)isochroman-1-yl]ethyl]piperazine (S)-(O-3), R_f = 0.28 (5% methanol in methylene chloride); NMR (300 MHz, $CDCl_3$) 8.01 (s, 1H, triazoleC-H), 7.37-7.30 (m's, 5H, aromatic H's), 7.19-
 30 7.15 (m's, 3H, aromatic H's), 6.85 (d of d, 4H, J_a =9.2 Hz, J_b =21.6 Hz, aromatic H's), 5.43 (s, 2H, PhC- H_2), 4.87 (m of d, 1H, J =5.1 Hz, PhC-H), 4.14 (m, 1H, $PhCH_2CH$ -H), 3.79 (m, 1H, $PhCH_2CH$ -H), 3.78 (s, 3H, OC- H_3), 3.10 (t, 4H, J =4.9 Hz, four pip-H), 2.97 (m, 1H, $PhCH$ -H), 2.73-2.52 (several m's, 7H, $PhCH$ -H, NC- H_2 and four pip-H), 2.16 (m, 1H, $PhCHCH$ -H), 2.05 (m, 1H, $PhCHCH$ -H) δ ; CMR (75 MHz, $CDCl_3$)
 35 155.0, 153.8, 151.3, 145.7, 140.5, 135.9, 134.9, 129.4, 129.0, 128.1, 126.9, 126.2, 125.8, 125.3, 118.2, 114.4, 74.4, 62.9, 55.6, 54.7, 53.5, 52.8, 50.6, 33.2, 29.0 δ .

EXAMPLE 80 (S)-(-)-1-(4-Methoxyphenyl)-4-[2-[6-(1,2,4-oxadiazol-5-yl)-
isochroman-1-yl]ethyl]piperazine (S)-(O-2)

Hydroxylamine hydrochloride (83.4 mg, 1.2 mmol) in a mixture of 5N aqueous sodium hydroxide (0.24 mL, 1.2 mmol), 70% acetic acid (1.2 mL) and (S)-(-)-
5 1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N-dimethylaminomethyleneisochroman-6-carboxamide (S)-(O-1, EXAMPLE 77, Step 1, 450.6 mg, 1.0 mmol) are added at once. The mixture is stirred at 20-25° for a total of 70 minutes. The reaction is diluted with water and the pH is raised to 8 with saturated aqueous sodium bicarbonate. The aqueous mixture is extracted twice with
10 methylene chloride. The organics are combined, dried with sodium sulfate, filtered and concentrated. This material (R_f = 0.18 (5% methanol in methylene chloride)) is dissolved in a mixture of anhydrous acetic acid (2 mL) and anhydrous *p*-dioxane (2 mL). Argon atmosphere is established and the reaction is heated to 90° for two hours. After cooling to 20-25°, the reaction is diluted with water and the pH is
15 raised to 8 with saturated aqueous sodium bicarbonate. The aqueous mixture is extracted twice with methylene chloride. The organics were combined, dried with sodium sulfate, filtered and concentrated. Purification of the concentrate by flash chromatography on 50 g silica gel using 4% methanol in methylene chloride as the eluent gives (S)-(-)-1-(4-methoxyphenyl)-4-[2-[6-(1,2,4-oxadiazol-5-yl)isochroman-1-yl]ethyl]piperazine (S)-(O-2), mp = 126-127°; R_f = 0.36 (5% methanol in methylene
20 chloride); NMR (300 MHz, CDCl₃) 8.47 (s, 1H, oxadiazoleC-H), 7.95 (d, 1H, J =8.1 Hz, aromatic H), 7.92 (s, 1H, aromatic H), 7.28 (d, 1H, J =8.1 Hz, aromatic H), 6.86 (d of d, 4H, J_a =9.1 Hz, J_b =21.2 Hz, aromatic H's), 4.90 (m of d, 1H, J =5.1 Hz, PhC-H), 4.17 (m, 1H, PhCH₂CH-H), 3.81 (m, 1H, PhCH₂CH-H), 3.76 (s, 3H, OC-H₃),
25 3.11 (t, 4H, J =4.9 Hz, four pip-H), 3.03 (m, 1H, PhCH-H), 2.80 (m of d, 1H, J =16.4 Hz, PhCH-H), 2.66-2.51 (several m's, 6H, NC-H₂ and four pip-H), 2.18 (m, 1H, PhCHCH-H), 2.07 (m, 1H, PhCHCH-H) δ ; CMR (75 MHz, CDCl₃) 175.3, 157.8, 153.8, 145.7, 143.6, 135.3, 128.7, 125.8, 125.7, 122.0, 118.2, 114.4, 74.5, 62.8, 55.6, 54.6, 53.5, 50.6, 33.1, 29.0 δ .

30 EXAMPLE 81 (S)-(-)-N-Methyl-1-[2-[4-(4-propionylphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (S)-(IX)

Step 1: (S)-(-)-6-Bromo-1-(2-hydroxyethyl)isochroman (S)-(S-1)

(S)-(-)-6-Bromoisochroman-1-yl)acetic acid (S)-(XI, EXAMPLE 1, Step 2, 16.27 g, 60 mmol) and 100 mL tetrahydrofuran are combined. This mixture is treated
35 with a 10M solution of borane methyl sulfide (18.0 mL, 0.18 mol) while maintaining 20-25° with a water bath. After 1 hour, the mixture is cooled to 0° and slowly

quenched with 160 mL methanol. Note: An induction period of approximately 1-2 minutes is noticed before a rapid and sudden generation of hydrogen. The mixture is warmed to 20-25° and volatiles removed under reduced pressure. The resulting mixture is diluted with 1M sodium hydroxide (150 mL) and extracted three times
 5 with ethyl acetate (100 mL). The combined organics are washed once with saline (100 mL), dried over magnesium sulfate, filtered and concentrated. This material is recrystallized from ethyl acetate/hexane to give (S)-(-)-6-bromo-1-(2-hydroxyethyl)-isochroman (S)-(S-1), mp = 95-96°; R_f = 0.28 (30% acetone/hexane); $[\alpha]_D$ = -107° (c = 0.4069, methanol); IR (mull) 3237, 3022, 1482, 1422, 1326, 1277, 1114, 1053, 1026,
 10 972, 905, 894, 880, 816, 788, cm^{-1} ; NMR (300 MHz, CDCl_3) 7.28 (m, 2H, aromatic), 6.92 (d, 1H, $J=8.2$ Hz, aromatic), 4.92 (brdd, 1H, $J=6.8$ Hz, methine), 4.15 (m, 1H, OCH_{2a}), 3.81 (t, 2H, $J=5.5$ Hz, HO-CH_2), 3.74 (m, 1H, OCH_{2b}), 3.00 (m, 1H, Ph-CH_{2a}), 2.66 (dt, 1H, $J=16.4$ Hz & $J=3.1$ Hz, Ph-CH_{2b}), 2.45 (brds, 1H, HO), 2.18 (m, 1H, C(H)-CH_{2a}), 2.02 (m, 1H, C(H)-CH_{2b}) δ ; CMR (75 MHz, CDCl_3) 136.5, 136.1,
 15 131.8, 129.4, 126.3, 120.2, 75.9, 63.4, 60.8, 37.5, 28.8 δ ; MS (EI, m/z) = 256.

Step 2: (S)-(-)-1-(2-Hydroxyethyl)isochroman-6-carboxylic acid, methyl ester (S)-(S-2)

(S)-(-)-6-Bromo-1-(2-hydroxyethyl)isochroman (S)-(S-1, 5.14 g, 20.0 mmol), palladium II acetate (225 mg, 1.0 mmol), 1,3-bis(diphenylphosphino)propane (495
 20 mg, 1.2 mmol), 40.0 mL dimethylformamide, diisopropylethylamine (10.5 mL, 60.0 mmol), and methanol (16 mL, 0.40 mol mmol) are combined. The resulting mixture is purged six times with carbon monoxide/reduced pressure followed by heating to 75° quickly. The reaction mixture is stirred for 19 hours. At this time, the mixture is cooled to 20-25°, diluted with 200 mL water, and extracted twice with
 25 dichloromethane (200 mL). The combined organics are washed once with water (100 mL), once with saline (100 mL), dried over magnesium sulfate, filtered and concentrated. This material is purified by LC on 300 g (230-400) silica gel eluting with 50% ethyl acetate/hexane to give (S)-(-)-1-(2-hydroxyethyl)isochroman-6-carboxylic acid, methyl ester (S)-(S-2), mp = 56-58°; R_f = 0.23 (50% ethyl
 30 acetate/hexane); $[\alpha]_D$ = -114° (c = 0.8773, methanol); IR (mull) 3407, 3336, 1718, 1434, 1418, 1296, 1274, 1261, 1250, 1195, 1112, 1055, 1022, 997, 754 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.79 (m, 2H, aromatic), 7.11 (d, 1H, $J=8.0$ Hz, aromatic), 4.97 (brdd, 1H, $J=6.8$ Hz, methine), 4.15 (m, 1H, OCH_{2a}), 3.88 (s, 3H, CH_3), 3.82 (t, 2H, $J=5.5$ Hz, HO-CH_2), 3.75 (m, 1H, OCH_{2b}), 3.01 (m, 1H, Ph-CH_{2a}), 2.71 (dt, 2H, $J=16.8$ Hz & $J=3.3$ Hz, Ph-CH_{2b} & HO), 2.21 (m, 1H, C(H)-CH_{2a}), 2.03 (m, 1H, C(H)-CH_{2b}) δ ; CMR (75 MHz, CDCl_3) 166.9, 142.8, 134.1, 130.3, 128.3, 127.4, 124.8,

75.8, 63.4, 60.6, 52.1, 37.6, 28.9 δ .

Step 3: (S)-(-)-1-(2-Hydroxyethyl)-N-methylisochroman-6-carboxamide (S)-(S-3)

(S)-(-)-1-(2-Hydroxyethyl)isochroman-6-carboxylic acid, methyl ester (S)-(S-2, 5 473 mg, 2.0 mmol) and 8.0 mL 6M methylamine in methanol are combined. The reaction vessel is sealed with a teflon screwcap and the mixture is heated to 75°. After 20 hours, the reaction mixture is cooled to 20-25°, concentrated under reduced pressure and triturated with hexane to give (S)-(-)-1-(2-hydroxyethyl)-N-methylisochroman-6-carboxamide (S)-(S-3), mp = 99-101°; R_f = 0.20 (5% 10 methanol/dichloromethane); $[\alpha]_D^{25}$ = -119° (c = 0.8674, methanol); IR (mull) 3350, 3274, 1648, 1614, 1572, 1564, 1422, 1336, 1320, 1156, 1107, 1078, 1058, 1045, 718, cm^{-1} ; NMR (300 MHz, CDCl_3) 7.53 (m, 2H, aromatic), 7.08 (d, 1H, J=8.7 Hz, aromatic), 6.32 (brds, 1H, NH), 4.97 (brdd, 1H, J=6.7 Hz, methine), 4.16 (m, 1H, OCH_{2a}), 3.82 (t, 2H, J=5.4 Hz, HO-CH_2), 3.74 (m, 1H, OCH_{2b}), 3.02 (d, 4H, J=4.9 15 Hz, NCH_3 & Ph-CH_{2a}), 2.71 (dt, 2H, J=16.4 Hz & J=3.2 Hz, Ph-CH_{2b} & HO), 2.21 (m, 1H, C(H)-CH_{2a}), 2.03 (m, 1H, C(H)-CH_{2b}) δ .

Step 4: (S)-(-)-1-(2-Methanesulfonyloxyethyl)-N-methylisochroman-6-carboxamide (S)-(T-2)

(S)-(-)-1-(2-Hydroxyethyl)-N-methylisochroman-6-carboxamide (S)-(S-3, 383 20 mg, 1.6 mmol), 16 mL dichloromethane and triethylamine (0.34 mL, 2.4 mmol) are combined followed by cooling to 0°. The mixture is treated with methanesulfonyl chloride (0.15 mL, 1.95 mmol). After 15 min, the reaction is diluted 10 mL dichloromethane and washed once with 15 mL water, once with 15 mL saline, dried over magnesium sulfate, filtered and concentrated to give (S)-(-)-1-(2-methanesulfonyloxyethyl)-N-methylisochroman-6-carboxamide (S)-(T-2), R_f = 0.35 25 (60% acetone/hexane); NMR (300 MHz, CDCl_3) 7.53 (m, 2H, aromatic), 7.11 (d, 1H, J=7.9 Hz, aromatic), 6.23 (brds, 1H, NH), 4.90 (brdd, 1H, J=7.4 Hz, methine), 4.46 (m, 1H, OCH_{2a}), 4.34 (m, 1H, MsO-CH_{2a}), 4.12 (m, 1H, MsO-CH_{2b}), 3.76 (m, 1H, OCH_{2b}), 3.00 (m, 7H, NCH_3 , S-CH_3 , Ph-CH_{2a}), 2.73 (dt, 1H, J=16.1 Hz & J=3.2 Hz, 30 Ph-CH_{2b}), 2.42 (m, 1H, C(H)-CH_{2a}), 2.14 (m, 1H, C(H)-CH_{2b}) δ .

Step 5: (S)-(-)-N-Methyl-1-[2-[4-(4-propionylphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (S)-(IX)

A mixture of (S)-(-)-1-(2-methanesulfonyloxyethyl)-N-methylisochroman-6-carboxamide (S)-(T-2, 509 mg, 1.5 mmol), 4'-piperazinopropiophenone (393 mg, 1.8 35 mmol), and potassium carbonate (622 mg, 4.5 mmol) in acetonitrile (7.5 mL) is heated to 50° overnight, then refluxed for an additional 5 hours. The reaction

mixture is then cooled to 20-25° and concentrated to a residue, which is partitioned between water and dichloromethane. The aqueous layer is extracted twice more with dichloromethane and the combined organic layers are washed once with water, once with saline, dried over magnesium sulfate, filtered and concentrated. This material is purified by LC on 36 g (230-400) silica gel eluting with 60% acetone/hexane. This material is recrystallized from methanol/ethyl acetate to give (S)-(-)-N-methyl-1-[2-[4-(4-propionylphenyl)-1-piperazinyl]ethyl]-isochroman-6-carboxamide (S)-(IX), mp = 160-161°; R_f = 0.20 (60% acetone/hexane); IR (mull) 3274, 1669, 1640, 1607, 1543, 1522, 1415, 1407, 1315, 1233, 1200, 1156, 1142, 1111, 798 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.87 (d, 2H, $J=9.0$ Hz, aromatic), 7.55 (m, 2H, aromatic), 7.14 (d, 1H, $J=8.6$ Hz, aromatic), 6.85 (d, 2H, $J=9.0$ Hz, aromatic), 6.24 (brdd, 1H, $J=4.6$ Hz, NH), 4.86 (brdd, 1H, $J=5.7$ Hz, methine), 4.13 (m, 1H, OCH_{2a}), 3.76 (m, 1H, OCH_{2b}), 3.34 (t, 4H, $J=5.0$ Hz, Ph-N-CH_{2s}), 3.00 (d, 4H, $J=4.9$ Hz, N-CH_3 & Ph-CH_{2a}), 2.90 (qtr, 2H, $J=7.4$ Hz, O=C-CH_2), 2.75-2.46 (m, 7H, $\text{Ph-NC(H)}_2\text{-CH}_{2s}\text{-NCH}_{2s}$ & Ph-CH_{2b}), 2.14 (m, 1H, C(H)-CH_{2a}), 2.02 (m, 1H, C(H)-CH_{2b}), 1.19 (t, 3H, $J=7.4$ Hz, $\text{C(H)}_2\text{-CH}_3$) δ ; CMR (75 MHz, CDCl_3) 199.3, 168.0, 154.1, 141.5, 134.5, 132.7, 130.0, 127.7, 127.3, 125.0, 124.5, 113.5, 74.4, 63.0, 54.5, 53.0, 47.4, 33.2, 31.2, 29.1, 26.8, 8.9 δ ; MS (EI, m/z) 435.

EXAMPLE 82 (S)-(-)-1-[2-[4-(4-Trifluoroacetylphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide (S)-(IX)

Following the general procedure of EXAMPLE 81, Step 5 and making non-critical variations but using 4'-piperazinotrifluoromethylphenone (504 mg, 1.95 mmol) gives crude product. This material is purified by LC on 59 g (230-400) silica gel eluting with 50% acetone/hexane to give (S)-(-)-1-[2-[4-(4-trifluoroacetylphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide (S)-(IX), R_f = 0.20 (60% acetone/hexane).

EXAMPLE 83 1-[1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]-isochroman-6-yl]carbonyl]pyrrolidine (IX)

Following the general procedure of EXAMPLE 30 and making non-critical variations but using pyrrolidine (1.26 mL, 15.0 mmol) gives crude product. The crude is purified by flash chromatography on 100 g silica gel using a gradient of 5-10% methanol in ethyl acetate as the eluent to give purified product. Recrystallization from methylene chloride and hexane gives 1-[1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-isochroman-6-yl]carbonyl]pyrrolidine (IX), mp = 156.0-156.5°; R_f = 0.35 (10% methanol in ethyl acetate); IR (mull) 1615, 1609, 1563, 1514, 1441, 1254, 1234, 1154, 1106, 825 cm^{-1} ; NMR (300 MHz, CDCl_3) 7.32 (d, 1H,

J=8.0 Hz, aromatic H), 7.29 (s, 1H, aromatic H), 7.12 (d, 1H, J=7.9 Hz, aromatic H), 6.85 (q, 4H, J=9.2 Hz, aromatic H's), 4.85 (m of d, 1H, J=5.8 Hz, PhC-H), 4.17-4.10 (m, 1H), 3.80-3.72 (m, 1H), 3.76 (s, 3H, PhOC-H₃), 3.64 (t, 2H, J=6.7 Hz, C(O)NC-H₂), 3.11 (t, 2H, J=6.6 Hz, C(O)NC-H₂), 3.11 (t, 4H, J=4.8 Hz, four of pip-H), 2.99 (m, 1H), 2.73 (m of d, 1H, J=16.4 Hz), 2.66-2.49 (m's, 6H), 2.15 (m, 1H, pipCH-H), 2.04 (m, 1H, pipCH-H), 1.99-1.85 (two slightly overlapping quintets, 4H, J=7.0 Hz, two of C(O)NCH₂C-H₂) δ ; CMR (75 MHz, CDCl₃) 169.4, 153.6, 145.6, 139.7, 135.2, 134.0, 127.7, 124.7, 124.4, 118.0, 114.3, 74.4, 62.9, 55.4, 54.6, 53.4, 50.5, 49.5, 46.1, 33.0, 28.9, 26.3, 24.3 δ .

10 **EXAMPLE 84** (+/-)-1-[2-(4-Phenyl-1-piperidinyl)ethyl]isochroman-6-carboxamide

Step 1. (+/-)-2-(6-Bromoisochroman-1-yl)acetic acid

A mixture of ethyl (+/-)-2-(6-bromoisochroman-1-yl)acetate (III, EXAMPLE 1, step 1; 0.77 g, 2.58 mmol), sodium hydroxide (2N, 1.9 mL) and ethanol (5 mL) is stirred for 75 min, at which time ethanol is removed under reduced pressure. Several milliliters of water are added to the residue, followed by hydrochloric acid (4N) sufficient to bring the pH of the mixture to about 2. The mixture is extracted with ether and the organic layers are dried with magnesium sulfate and concentrated to give (+/-)-2-(6-bromoisochroman-1-yl)acetic acid (IV), NMR (CDCl₃) 2.69 - 2.97, 3.83, 4.16, 5.18, 6.94 and 7.32 δ .

Step 2. (+/-)-2-(6-Bromoisochroman-1-yl)ethyl alcohol

To (+/-)-2-(6-bromoisochroman-1-yl)acetic acid (IV, Step 1; 0.82 g, 3.0 mmol) in dry THF (20 mL) is added borane-methyl sulfide (0.86 g, 9.1 mmol). After stirring for 2.5 hr, methanol is added and the mixture is concentrated under reduced pressure. Methanol is again added and the mixture concentrated twice more. The residue is then partitioned between dichloromethane and aqueous sodium bicarbonate and the organic layers are dried with sodium sulfate and concentrated to give (+/-)-2-(6-bromoisochroman-1-yl)ethyl alcohol (S-1), NMR (CDCl₃) 2.0, 2.2, 2.64, 2.69, 3.02, 3.70-3.79, 3.82-3.86, 4.15, 4.92, 7.28 δ .

30 **Step 3.** (+/-)-1-[2-(6-Bromoisochroman-1-yl)ethyl]-4-phenylpiperidine

Methanesulfonyl chloride (0.22 mL, 2.84 mmol) is added to an ice water-cooled mixture of (+/-)-2-(6-bromoisochroman-1-yl)ethyl alcohol (S-1, step 2; 0.599 g, 2.33 mmol), 4-dimethylaminopyridine (0.016 g, 0.131 mmol), diisopropylethylamine (0.49 mL, 2.81 mmol) and dry THF (7.5 mL). The ice water bath is removed and the mixture is allowed to warm to 20-25°. When the mesylation is complete (by TLC), ethylene glycol (2.4 mL), diisopropylethylamine (1.0 mL, 5.7 mmol) and 4-

phenylpiperidine (0.452 g, 2.80 mmol) are added and the mixture is heated overnight at 80°. After cooling, the mixture is poured into water and extracted with dichloromethane. The combined organic layers are dried over sodium sulfate and concentrated under reduced pressure. The residue is chromatographed (silica gel; 5 methanol/dichloromethane, 2/98) to give (+/-)-1-[2-(6-bromoisochroman-1-yl)ethyl]-4-phenylpiperidine (VI), NMR (CDCl₃) 1.85, 1.99-2.17, 2.46-2.60, 2.65-2.71, 2.95, 3.09, 3.74, 4.10, 4.77, 6.99 and 7.17-7.32 δ.

Step 4. (+/-)-1-[2-(4-Phenyl-1-piperidinyl)ethyl]isochroman-6-carboxamide

A mixture of (+/-)-1-[2-(6-bromoisochroman-1-yl)ethyl]-4-phenylpiperidine (VI, 10 step 1; 0.422 g, 1.05 mmol), DMF (2.7 mL), 1,1,1,3,3,3-hexamethyldisilazane (Aldrich; 1.6 mL, 7.58 mmol), diisopropylethylamine (0.38 mL, 2.18 mmol), palladium (II) acetate (0.012 g, 0.053 mmol) and 1,3-bis(diphenylphosphino)propane (0.026 g, 0.064 mmol) is degassed six times under reduced pressure and released to carbon monoxide each time. The mixture is heated at 90° overnight and then the 15 cooled mixture is poured into hydrochloric acid (1N, 11 mL) and extracted with ether. The pH of the aqueous layer is adjusted to 12 using aqueous sodium hydroxide. The aqueous layer then is extracted three times with ethyl acetate and the combined organic layers are washed with saline, dried over magnesium sulfate and concentrated under reduced pressure. The residue is chromatographed (silica 20 gel; methanol/dichloromethane/ammonium hydroxide, 2/98/0.5) to give (+/-)-1-[2-(4-phenyl-1-piperidinyl)ethyl]isochroman-6-carboxamide (VII), NMR (CDCl₃) 1.83, 1.99-2.22, 2.51-2.62, 2.74-2.79, 2.97-3.08, 3.78, 4.14, 4.87, 5.63, 6.05, 7.19-7.33 and 7.59 δ.

EXAMPLE 85 N-Methyl-1-[2-(4-phenyl-1-piperidinyl)ethyl]isochroman-6-carboxamide, maleic acid salt

25 Step 1. (+/-)-N-Bis(tert-butyloxycarbonyl)-1-[2-(4-phenyl-1-piperidinyl)ethyl]isochroman-6-carboxamide

Following the general procedure of EXAMPLE 3, step 1, and making non-critical variations, (+/-)-1-[2-(4-phenylpiperidin-1-yl)ethyl]isochroman-6-carboxamide (VII, EXAMPLE 84, 0.281 g, 0.634 mmol), 4-dimethylaminopyridine (0.0098 g, 30 0.0802 mmol) and di-tert-butyldicarbonate (0.312 g, 1.43 mmol) give (+/-)-N-bis(tert-butyloxycarbonyl)-1-[2-(4-phenyl-1-piperidinyl)ethyl]isochroman-6-carboxamide (VIII) after chromatography (silica gel; methanol/dichloromethane, 2/98), NMR (CDCl₃) 1.39, 1.84, 2.00-2.20, 2.44-2.63, 2.71-2.81, 2.94-3.15, 3.78, 4.14, 4.89, 7.20-7.30 and 7.60-7.65 δ.

35 Step 2. N-Methyl-1-[2-(4-phenyl-1-piperidinyl)ethyl]isochroman-6-carboxamide, maleic acid salt

Methyl amine gas is condensed into a glass high pressure reaction vessel cooled at -78° (under an argon atmosphere) and containing a mixture of (+/-)-N-bis(tert-butyloxycarbonyl)-1-[2-(4-phenyl-1-piperidinyl)ethyl]isochroman-6-carboxamide (VIII, step 1, 0.2818 g, 0.499 mmol) and dichloromethane (4 mL). After several mLs of methylamine are condensed into liquid, the vessel is sealed and the mixture is allowed to warm to 20-25°, with stirring. After stirring overnight, the vessel is re-cooled to -78° and the seal broken. After again warming to 20-25°, the mixture is concentrated under reduced pressure and the resulting residue is chromatographed (silica gel; methanol/dichloromethane, 3/97 to 5/95) to give N-methyl-1-[2-(4-phenyl-1-piperidinyl)ethyl]isochroman-6-carboxamide (IX).

N-Methyl-1-[2-(4-phenyl-1-piperidinyl)ethyl]isochroman-6-carboxamide is treated with maleic acid (0.0360 g, 0.310 mmol) in dichloromethane/methanol to give N-methyl-1-[2-(4-phenyl-1-piperidinyl)ethyl]isochroman-6-carboxamide, maleic acid salt (B-IX), NMR (CDCl₃) 1.84, 2.05-2.20, 2.52-2.66, 2.72-2.78, 3.01, 3.41, 3.49, 3.78, 4.13, 4.85, 6.12, 7.16-7.32 and 7.53 δ.

EXAMPLE 86 (+/-)-1-[2-[4-(2,4-Dichlorophenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide

Step 1. 1-(2,4-Dichlorophenyl)piperazine

A mixture of 1,3-dichloro-4-fluorobenzene (Q-2) (4.21 g, 25.5 mmol), piperazine (Q-1, 11.0 g, 128 mmol) and dimethylacetamide (15 mL) is heated at 165° for 6.8 hr, at which time the mixture is cooled and partitioned between dichloromethane and aqueous sodium bicarbonate. The organic layers are dried with sodium sulfate and concentrated under high vacuum to give 1-(2,4-dichlorophenyl)piperazine (Q-3), which was sufficiently pure to use in step 2 without further purification.

Step 2. (+/-)-1-[2-(6-Bromoisochroman-1-yl)ethyl]-4-(2,4-dichlorophenyl)piperazine

Following the general procedure of EXAMPLE 84, step 3 and making non-critical variations, (+/-)-2-(6-bromoisochroman-1-yl)ethyl alcohol (S-1) (EXAMPLE 84, step 2; 0.60 g, 2.31 mmol), 4-dimethylaminopyridine (0.018 g, 0.147 mmol), diisopropylethylamine (0.49 mL, 2.81 mmol), methanesulfonyl chloride (0.22 mL, 2.84 mmol) and dry THF (7.5 mL) are converted to the mesylate (T-1). The mesylate is treated with diisopropylethylamine (1.0 mL, 5.7 mmol), 1-(2,4-dichlorophenyl)piperazine (Q-3, step 1; 0.65 g, 2.82 mmol) and ethylene glycol to give, after chromatography (silica gel; methanol/dichloromethane, 2/98) (+/-)-1-[2-(6-bromoisochroman-1-yl)ethyl]-4-(2,4-dichlorophenyl)piperazine (VI), NMR (CDCl₃)

2.01, 2.10, 2.55-2.71, 2.95, 3.05, 3.74, 4.11, 4.78, 6.96, 7.18 and 7.26-7.36 δ .

Step 3. (+/-)-1-[2-[4-(2,4-Dichlorophenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide

Following the general procedure of EXAMPLE 84, step 4, and making non-critical variations, (+/-)-1-[2-(6-bromoisochroman-1-yl)ethyl]-4-(2,4-dichlorophenyl)piperazine (VI, step 1; 0.373 g, 0.794 mmol), gives 0.095 g of (+/-)-1-[2-[4-(2,4-dichlorophenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VII) after chromatography (silica gel; methanol/dichloromethane, 2/98), NMR (CDCl_3) 2.05, 2.15, 2.50-2.80, 3.05, 3.78, 4.15, 4.87, 5.62, 6.04, 6.96, 7.19, 7.35 and 7.60 δ .

10 EXAMPLE 87 (+/-)-N-Methyl-1-[2-[4-(2,4-dichlorophenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide

Step 1. (+/-)-N-Bis(tert-butyloxycarbonyl)-1-[2-[4-(2,4-dichlorophenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide

Following the general procedure of EXAMPLE 3, step 1, and making non-critical variations, (+/-)-1-[2-[4-(2,4-dichlorophenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VI, EXAMPLE 86, step 2; 0.0854 g, 0.198 mmol), 4-dimethylaminopyridine (0.0046 g, 0.0377 mmol) and di-tert-butyl dicarbonate (0.0982 g, 0.450 mmol) give, after chromatography (silica gel; methanol/dichloromethane, 2/98), (+/-)-N-bis(tert-butyloxycarbonyl)-1-[2-[4-(2,4-dichlorophenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VIII), NMR (CDCl_3) 1.40, 2.05, 2.17, 2.51-2.79, 2.95-3.05, 3.78, 4.15, 4.89, 6.96, 7.19, 7.35 and 7.60-7.66 δ .

Step 2. (+/-)-N-Methyl-1-[2-[4-(2,4-dichlorophenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide

25 Following the general procedure of EXAMPLE 85, step 2, and making non-critical variations, (+/-)-N-bis(tert-butyloxycarbonyl)-1-[2-[4-(2,4-dichlorophenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VIII, step 1; 0.104 g, 0.164 mmol) gives after chromatography (silica gel; methanol/dichloromethane, 1.5/98.5 to 3/97 to 5/95) a solid. This material was crystallized from acetonitrile/hexane to give (+/-)-N-methyl-1-[2-[4-(2,4-dichlorophenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (IX), MS (m/z) = 447; IR (mineral oil; most intense peaks) 1637, 1478, 1572, 1558, 1450, 3289 and 1107 cm^{-1} ; NMR (CDCl_3) 2.05, 2.16, 2.52-2.78, 3.03, 3.77, 4.13, 4.86, 6.10, 6.96, 7.17, 7.36 and 7.54 δ .

30 EXAMPLE 88 1-[2-[4-(3-Chloro-4-methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide

Step 1. 1-(3-Chloro-4-methoxyphenyl)piperazine

A mixture of 3-chloro-p-anisidine (R-2, 0.633 g, 4.00 mmol), bis(2-chloroethyl)amine hydrochloride (0.860 g, 4.80 mmol), potassium carbonate (1.11 g, 8.00 mmol) and dimethylacetamide (6 mL) is stirred at 100° for 18 hr and then cooled. The mixture is partitioned between dichloromethane, water and aqueous sodium bicarbonate and the organic layers are dried with sodium sulfate and concentrated. The residue is chromatographed (silica gel; methanol/dichloromethane, 8/92) to give 1-(3-chloro-4-methoxyphenyl)piperazine (R-3), NMR (CDCl₃) 3.05, 3.86, 6.80, 6.87 and 6.99 δ.

Step 2. (+/-)-1-[2-(6-Bromoisochroman-1-yl)ethyl]-4-(3-chloro-4-methoxyphenyl)piperazine

Following the general procedure of EXAMPLE 84, step 3, (+/-)-2-(6-bromoisochroman-1-yl)ethyl alcohol (S-1, EXAMPLE 84, step 3, 0.450 g, 1.75 mmol), 4-dimethylaminopyridine (0.012g, 0.0990 mmol), diisopropylethylamine (0.32 mL, 1.84 mmol), methanesulfonyl chloride (0.14 mL, 1.81 mmol) and dry THF (5.6 mL) are converted to the mesylate. Additional portions of diisopropylethylamine (0.18 mL, 1.03 mmol) and methanesulfonyl chloride (0.08 mL, 1.03 mmol) are added to complete the formation of the mesylate. To the mesylate then is added diisopropylethylamine (0.65 mL, 4.26 mmol), 1-(3-chloro-4-methoxyphenyl)piperazine (step 1; 0.398 g, 1.75 mmol) and ethylene glycol (1.8 mL). The mixture is stirred at 80° for 3 hr and then overnight at 20-25°, after which the mixture again is heated for 4 hr at 80°. Additional 1-(3-chloro-4-methoxyphenyl)piperazine (0.0443 g, 0.195 mmol) is added and the mixture is heated another 3 hr. After cooling, the mixture is partitioned between dichloromethane and aqueous sodium bicarbonate and the organic layers are dried with sodium sulfate and concentrated. The residue is chromatographed (silica gel; methanol/dichloromethane, 2/98) to give (+/-)-1-[2-(6-bromoisochroman-1-yl)ethyl]-4-(3-chloro-4-methoxyphenyl)piperazine (VI), NMR (CDCl₃) 2.01, 2.10, 2.52-2.71, 2.96, 3.10, 3.75, 3.85, 4.10, 4.78, 6.77-6.87, 6.98 and 7.29 δ.

Step 3. (+/-)-1-[2-[4-(3-Chloro-4-methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide

Following the general procedure of EXAMPLE 84, step 4, and making non-critical variations (+/-)-1-[2-(6-bromoisochroman-1-yl)ethyl]-4-(3-chloro-4-methoxyphenyl)piperazine (VI, Step 2; 0.420 g, 0.902 mmol), DMF (2.3 mL), 1,1,1,3,3,3-hexamethyldisilazane (1.4 mL, 6.64 mmol), diisopropylethylamine (0.34 mL, 1.95 mmol), palladium (II) acetate (0.0110 g, 0.049 mmol) and 1,3-bis(diphenylphosphino)propane (0.024 g, 0.0575 mmol) give (+/-)-1-[2-[4-(3-chloro-4-

methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VII). After chromatography (silica gel; methanol/dichloromethane, 2/98), NMR (CDCl₃) 2.05, 2.15, 2.53-2.64, 2.74-2.79, 3.02, 3.11, 3.77, 3.84, 4.14, 4.87, 5.60, 6.04, 6.77-6.87, 6.98, 7.18 and 7.60 δ.

5 EXAMPLE 89 (+/-)-1-[2-[4-(3-Chloro-4-methoxyphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide

Step 1. (+/-)-N-Bis(tert-butyloxycarbonyl)-1-[2-[4-(3-chloro-4-methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide

Following the general procedure of EXAMPLE 3, step 1, and making non-critical variations, (+/-)-1-[2-[4-(3-chloro-4-methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VII, EXAMPLE 88, step 3; 0.153 g, 0.355 mmol), 4-dimethylaminopyridine (0.0086 g, 0.0704 mmol) and di-tert-butylidicarbonate (0.186 g, 0.853 mmol) give, after chromatography (silica gel; methanol/dichloromethane, 2/98), (+/-)-N-bis(tert-butyloxycarbonyl)-1-[2-[4-(3-chloro-4-methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VIII). NMR (CDCl₃) 1.39, 2.03, 2.14, 2.48-2.64, 2.73-2.80, 3.00, 3.11, 3.78, 3.85, 4.14, 4.88, 6.80-6.88, 6.98, 7.20 and 7.60-7.65 δ.

Step 2. (+/-)-N-Methyl-1-[2-[4-(3-chloro-4-methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide

20 Following the general procedure of EXAMPLE 85, step 2, and making non-critical variations, (+/-)-N-bis(tert-butyloxycarbonyl)-1-[2-[4-(3-chloro-4-methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VIII, step 1; 0.183 g, 0.290 mmol) gives 0.118 g of product after chromatography (silica gel; methanol/dichloromethane, 2/98). The product is crystallized from ethyl acetate/methanol/hexane and then from ethyl acetate/dichloromethane to give (+/-)-1-[2-[4-(3-chloro-4-methoxyphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide (IX), MS (m/z) 443; IR (mineral oil, most intense peaks) 1508, 1642, 3266, 1112, 1548, 1274 and 949 cm⁻¹; NMR (CDCl₃) 2.09, 2.21, 2.58-2.77, 3.01, 3.15, 3.76, 3.85, 4.15, 4.88, 6.12, 6.77-6.88, 6.98, 7.17 and, 7.54 δ.

30 EXAMPLE 90 N-(2-Hydroxyethyl)-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide

Step 1. (+/-)-1-2-(6-Bromoisochroman-1-yl)acetyl-4-(4-methoxyphenyl)piperazine

A mixture of (+/-)-2-(6-bromoisochroman-1-yl)acetic acid (IV, EXAMPLE 84, step 1; 4.66 g, 0.0172 mol), dichloromethane (18 mL), DMF (18 mL), diethyl cyanophosphonate (3.4 mL, 0.022 mol), 1-(4-methoxyphenyl)piperazine hydrochloride

(R-3) (Aldrich; 4.78 g, 0.021 mol) and triethylamine (6.5 mL, 0.047 mol) is stirred at 20-25° for 2.5 hours. Saturated sodium bicarbonate (100 mL) is added to the mixture and the mixture is allowed to stir for 20 min, at which time it is extracted with dichloromethane. The combined organic layers are dried over magnesium sulfate and concentrated under reduced pressure. The residue is washed twice with hexane (discard) and the residue again is concentrated under reduced pressure. The residue is chromatographed (silica gel; ethyl acetate/hexane, 50/50) to give (+/-)-1-2-(6-bromoisochroman-1-yl)acetyl-4-(4-methoxyphenyl)piperazine (V), NMR (CDCl₃) 2.63-2.69, 2.74-2.80, 2.90-3.08, 3.59-3.96, 4.11, 5.26, 6.87, 7.01, 7.31 δ.

Step 2. (+/-)-1-[2-(6-Bromoisochroman-1-yl)ethyl]-4-methoxyphenylpiperazine

Following the general procedure of EXAMPLE 1, step 4, but using borane-methyl sulfide (14 mL) in place of borane-THF, (+/-)-1-2-(6-bromoisochroman-1-yl)acetyl-4-(4-methoxyphenyl)piperazine (V, step 1; 5.83 g, 0.013 mol) gives 4.33 g of (+/-)-1-[2-(6-bromoisochroman-1-yl)ethyl]-4-methoxyphenylpiperazine (VI), NMR (CDCl₃) 2.00, 2.12, 2.49-2.71, 2.95, 3.10, 3.75, 4.11, 4.78, 6.87, 6.97 and 7.29 δ.

Step 3. (+/-)-1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide

Following the general procedure of EXAMPLE 84, step 4, (+/-)-1-[2-(6-bromoisochroman-1-yl)ethyl]-4-(methoxyphenyl)piperazine (VI, step 2; 4.29 g, 9.95 mmol) gives (+/-)-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VII), NMR (CDCl₃) 2.06, 2.16, 2.54-2.79, 2.99, 3.11, 3.77, 4.15, 4.87, 5.64, 6.06, 6.87, 7.19 and 7.59 δ.

Step 4. (+/-)-N-Bis(tert-butyloxycarbonyl)-1-[2-[4-(methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide

Following the general procedure of EXAMPLE 3, step 1, (+/-)-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VII, step 3; 1.97 g, 4.97 mmol), 4-dimethylaminopyridine (0.0816 g, 0.668 mmol) and di-tert-butyl-dicarbonate (2.56 g, 0.0117 mol) gives (+/-)-N-bis(tert-butyloxycarbonyl)-1-[2-[4-(methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VIII), NMR (CDCl₃) 1.39, 2.03, 2.15, 2.53-2.78, 2.99, 3.11, 3.77, 4.13, 4.88, 6.85, 7.21 and 7.63 δ.

Step 5. N-(2-hydroxyethyl)-1-[2-[4-(methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide

A mixture of (+/-)-N-bis(tert-butyloxycarbonyl)-1-[2-[4-(methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VIII, step 4; 0.216 g, 0.362 mmol),

dichloromethane (7 mL) and ethanolamine (0.2 mL, 3.31 mmol) is stirred overnight at 20-25°. The mixture is then partitioned between water and dichloromethane. The combined organic layers are dried over sodium sulfate and concentrated under reduced pressure. The residue is chromatographed (silica gel;

- 5 methanol/dichloromethane (4/96) to give product which is crystallized from dichloromethane/hexane/ethyl acetate to give 0.090 g of N-(2-hydroxyethyl)-1-[2-4-(4-methoxyphenyl)-1-piperazinyl]ethylisochromanyl-6-carboxamide (IX), MS (m/z) 439; IR (mineral oil) (most intense peaks) 1514, 1631, 1554, 1031, 3293, 1249 and 1613 cm⁻¹; NMR (CDCl₃) 2.05, 2.15, 2.51-2.78, 3.01, 3.11, 3.63, 3.77, 3.85, 4.13, 4.86, 6.59, 10 6.87, 7.17 and 7.57 δ.

EXAMPLE 91 1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]-N-(phenylmethoxy)isochroman-6-carboxamide

- A mixture of (+/-)-N-bis(tert-butyloxycarbonyl)-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VIII, EXA ret7, step 4; 0.206 g, 0.345 15 mmol), THF (7 mL), O-benzylhydroxylamine hydrochloride (0.0645 g, 0.4041 mmol) and diisopropylethylamine (0.12 mL, 0.689 mmol) is heated at reflux for 7 hours. The mixture then is stirred at 20-25° for two days, at which time additional O-benzylhydroxylamine hydrochloride (0.323 g, 2.03 mmol) and diisopropylethylamine (0.35 mL, 2.01 mmol) are added. After stirring overnight at 85-90°, THF is removed 20 by concentrating under reduced pressure and the residue is partitioned between dichloromethane and water. The combined organic layers are dried over sodium sulfate and concentrated under reduced pressure to give crude material. This material is chromatographed (silica gel; methanol/dichloromethane, 4/96) to give the product which is crystallized from hexane/ethyl acetate/dichloromethane/methanol to 25 give the title compound, MS (m/z) 501; NMR (CDCl₃) 2.03, 2.12, 2.48-2.75, 2.98, 3.10, 3.77, 4.11, 4.84, 5.05, 6.86, 7.14, 7.41 and 8.43 δ.

EXAMPLE 92 (+/-)-1-[1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-yl]-4-methylpiperazine

- A mixture of (+/-)-N-bis(tert-butyloxycarbonyl)-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VIII, EXA ret7, step 4; 0.211 g, 0.355 30 mmol), THF (11 mL), diisopropylethylamine (0.6 mL, 3.44 mmol) and 1-methylpiperazine (0.4 mL, 3.6 mmol) is stirred over a weekend at 20-25°, after which THF is removed under reduced pressure and the residue is partitioned between dichloromethane and water. The combined organic layers are dried over 35 magnesium sulfate and concentrated under reduced pressure to give crude product. The crude product is chromatographed (silica gel; methanol/dichloromethane, 2/98 to

4/96). The product is precipitated from ethyl acetate and hexane to give the title compound, a portion is recrystallized from ethyl acetate, MS (m/z) 478; NMR (CDCl₃) 2.09, 2.32, 2.48-2.75, 2.99, 3.11, 3.47, 3.76, 4.13, 4.86, 6.86 and 7.18 δ.

EXAMPLE 93 (+/-)-N-Hydroxy-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-
5 N-methylisochroman-6-carboxamide

A mixture of (+/-)-N-bis(tert-butyloxycarbonyl)-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide (VIII, EXA ret7, step 4; 0.205 g, 0.344 mmol), dichloromethane (7 mL), N-methylhydroxylamine hydrochloride (0.271 g, 3.25 mmol) and diisopropylethylamine (0.60 mL, 3.44 mmol) are stirred overnight at
10 20-25°. The mixture then is partitioned between dichloromethane and water. The combined organic layers are dried over sodium sulfate and concentrated under reduced pressure. The residue is chromatographed (silica gel; methanol/dichloromethane, 2/98 to 4/96) to give the desired product which is upon crystallization from hexane/methanol/dichloromethane/ethyl acetate gives the title
15 compound, MS (m/z) 425; NMR (CDCl₃) 2.05, 2.17, 2.54-2.77, 3.00, 3.11, 3.42, 3.77, 4.13, 4.85, 6.87, 7.17 and 7.33 δ.

EXAMPLE 94 (S)-(-)-1-[2-[4-[4-(tert-Butyloxycarbonyl)phenyl]-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide (V-2)

Step 1. 4-Fluorobenzoic acid, tert-butyl ester

20 To a solution of 4-fluorobenzoic acid (18.7 g, 0.133 mol) in DMF (140 mL) is added 1,1-carbonyldiimidazole (21.6 g, 0.134 mol). The mixture is heated for 1 hour at 40°, at which time *t*-butanol (26 mL, 0.272 mol) and DBU (20.5 mL, 0.137 mol) are added. After stirring overnight at 40°, the cooled mixture is poured into ethyl ether (1300 mL) and washed with hydrochloric acid (10%, 250 mL), followed by
25 water (250 mL) and then potassium carbonate (10%, 250 mL). The ether layer is dried over sodium sulfate and concentrated under reduced pressure. The residue is chromatographed (silica gel; ethyl acetate/hexane, 10/90) to give 4-fluorobenzoic acid, tert-butyl ester (Q-2); MS (m/z) 196; NMR (CDCl₃) 1.59, 7.07 and 7.99 δ.

Step 2. 4-(Piperazin-1-yl)benzoic acid, tert-butyl ester

30 A mixture of 4-fluorobenzoic acid, tert-butyl ester (Q-2) (step 1; 20.5 g, 0.105 mol), piperazine (52.8 g, 0.613 mol) and dimethylacetamide (121 mL) is heated at 150-155° for 160 minutes. After cooling, the solid is removed by filtration and washed with hexane. The combined filtrates are concentrated under high vacuum and the residue is partitioned between dichloromethane and water. The combined
35 organic layers are dried over sodium sulfate and concentrated under reduced pressure. The slightly solvent-wet solids are slurried in hexane and the solid is

collected and washed with hexane. The solids are dried at 20-25° under reduced pressure to give the *t*-butyl 4-(piperazin-1-yl)benzoate. Additional product is obtained by concentration of the filtrate and chromatography of the resulting residue (silica gel; methanol/dichloromethane/ammonium hydroxide, 3.5/96.5/0.5 to 7/93/0.5) to give 4-(piperazin-1-yl)benzoic acid, *t*-butyl ester (Q-3); MS (*m/z*) 262; NMR (CDCl₃) 1.57, 3.01, 3.25, 6.84 and 7.87 δ.

Step 3. (S)-(-)-4-[4-[2-(6-bromoisochroman-1-yl)ethyl]-1-piperazinyl]benzoic acid, *tert*-butyl ester (V-1)

Following the general procedure of EXAMPLE 84, step 3, and making non-critical variations, (S)-(-)-2-(6-bromoisochroman-1-yl)ethyl alcohol (S-1) (EXAMPLE 6, step 1; 4.95 g, 0.0193 mol) and 4-(piperazin-1-yl)benzoic acid, *tert*-butyl ester (Q-3) (step 2; 5.42 g, 0.0206 mol) gives the title compound, MS (*m/z*) 500; NMR (CDCl₃) 1.57, 2.02, 2.12, 2.50-2.70, 2.95, 3.32, 3.73, 4.10, 4.79, 6.85, 6.97, 7.29 and 7.86 δ.

Step 4. (S)-(-)-1-[2-[4-[4-(*tert*-Butyloxycarbonyl)phenyl]-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide

A mixture of (S)-(-)-4-[4-[2-(6-bromoisochroman-1-yl)ethyl]-1-piperazinyl]benzoic acid, *tert*-butyl ester (V-1) (step 3; 2.63 g, 5.25 mmol) in dimethylacetamide (45 mL) which has been degassed and released to argon is added to palladium (II) acetate (0.0616 g, 0.274 mmol), 1,3-bis(diphenylphosphino)propane (0.164 g, 0.396 mmol) and diisopropylethylamine (1.8 mL, 0.0103 mol). The mixture is degassed a second time, releasing to argon. The mixture is heated at 60-65° while carbon monoxide is bubbled into the mixture. After several minutes methylamine is also bubbled into the mixture. After heating for 6.5 hours at 60-65°, the mixture is stored overnight in the refrigerator. The mixture then is filtered through diatomaceous earth and additional portions of palladium (II) acetate (0.065 g, 0.290 mmol), 1,3-bis(diphenylphosphino)propane (0.162 g, 0.392 mmol) and diisopropylethylamine (1.8 mL, 0.0103 mol) are added to the filtrate, which is heated at 60° for 4 hr with the addition of carbon monoxide and methylamine gases, after which the mixture is cooled and concentrated under reduced pressure. The residue is partitioned between dichloromethane and water. The combined organic layers are washed with water and saline and dried over sodium sulfate and concentrated under reduced pressure. The residue is chromatographed (silica gel; methanol/dichloromethane, 2/98 to 4/96). Impure fractions are combined and rechromatographed (silica gel; methanol/dichloromethane, 2/98) to give the title compound, MS (*m/z*) 479; NMR (CDCl₃) 1.56, 2.03, 2.16, 2.48-2.79, 3.01, 3.32, 3.76, 4.14, 4.86, 6.08, 6.84, 7.15, 7.53 and 7.86 δ.

EXAMPLE 95 (+/-)-1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-ol, methyl carbamate ester (X-6)

Step 1. (+/-)-2-(6-Hydroxyisochroman-1-yl)acetic acid, ethyl ester

To an ice-cooled mixture of 3-hydroxyphenethyl alcohol (X-1) (2.9 g, 21 mmol) and ethyl 3,3-diethoxypropionate (4.75 g, 25 mmol) in nitromethane (5 mL) is added boron trifluoride etherate (3.44 mL). After the addition is complete (about 5 min) the reaction is stirred for an additional 60 min. The mixture is then partitioned between dichloromethane and aqueous ammonium chloride. The organic layers are dried with sodium sulfate and concentrated. The residue is chromatographed (silica gel; ethyl acetate/hexane, 10/90 to 30/70) to give (+/-)-2-(6-hydroxyisochroman-1-yl)acetic acid, ethyl ester (X-2), NMR (CDCl₃) 1.28, 2.6-3.0, 3.79, 4.09, 4.21, 5.07, 5.19, 6.60, 6.67 and 6.91 δ .

Step 2. (+/-)-2-(6-Hydroxyisochroman-1-yl)acetic acid

To (6-hydroxyisochroman-1-yl)acetic acid, ethyl ester (X-2) (step 1; 2.38 g, 10.1 mmol) in ethanol (10-15 mL) is added sodium hydroxide (2N, 10 mL). The mixture is stirred overnight and ethanol is then removed under reduced pressure. The resulting aqueous mixture is then diluted with several mLs of saline and acidified with hydrochloric acid (3N), and the mixture is extracted with ethyl ether and concentrated. To remove remaining starting material, the residue is partitioned between aqueous sodium bicarbonate and dichloromethane. The organic phase is removed and the aqueous layer is acidified with concentrated hydrochloric acid and then extracted with ether. The ether layer is dried over magnesium sulfate and concentrated. The concentrate is crystallized from THF/hexane/dichloromethane to give (+/-)-2-(6-hydroxyisochroman-1-yl)acetic acid (X-3), NMR (CDCl₃) 2.1-3.0, 3.81, 4.15, 5.2, 6.59, 6.68 and 6.90 δ .

Step 3. (+/-)-1-2-(6-Hydroxyisochroman-1-yl)acetyl-4-(4-methoxyphenyl)piperazine

To a mixture of (+/-)-2-(6-hydroxyisochroman-1-yl)acetic acid (X-3) (step 2; 0.361 g, 1.73 mmol), 1-(4-methoxyphenyl)piperazine dihydrochloride (0.458 g, 1.73 mmol), dichloromethane (5 mL), and DMF (0.5 mL) is added triethylamine (0.80 mL, 5.72 mmol) and then diethyl cyanophosphonate (0.29 mL, 1.91 mmol). After stirring for 50 min, water is added and the mixture is stirred for 1 hour. The mixture is then extracted with dichloromethane and the organic layers are separated, combined and washed with aqueous sodium bicarbonate. The organic layers are dried with sodium sulfate and concentrated. The residue is crystallized from ethyl acetate-dichloromethane-methanol to give (+/-)-1-2-(6-hydroxyisochroman-1-yl)acetyl-4-(4-

methoxyphenyl)piperazine (X-4), NMR (DMSO) 2.57-2.63, 2.73-2.90, 2.97, 3.64, 3.69, 3.95, 5.03, 6.51, 6.57, 6.8-7.0 and 9.27 δ .

Step 4. (+/-)-1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-ol

5 A mixture of (+/-)-1-2-(6-hydroxyisochroman-1-yl)acetyl-4-(4-methoxyphenyl)piperazine (X-4) (step 3; 0.375 g, 0.98 mmol), borane methylsulfide (0.28 mL, 2.9 mmol), and THF (15 mL) is stirred overnight at 20-25° and then at 80° for 2 hr. After cooling, the mixture is treated with methanol and concentrated under reduced pressure. The addition of methanol and concentration is repeated twice
10 more and then the residue is stirred for 3 hr in hydrochloric acid/acetone (4N, 1/9, 5 ml). The acetone is then removed under reduced pressure and the residue is partitioned between dichloromethane and aqueous sodium bicarbonate. The organic layers are dried with sodium bicarbonate and concentrated. The residue is crystallized from dichloromethane/hexane to give (+/-)-1-[2-[4-(4-methoxyphenyl)-1-
15 piperazinyl]ethyl]isochroman-6-ol (X-5), NMR (CDCl₃) 2.05, 2.21, 2.5-2.7, 2.94, 3.13, 3.70, 3.76, 4.10, 4.82, 6.41, 6.57 and 6.80-6.91 δ .

Step 5. (+/-)-1-[2-[4-(4-Methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-ol, methyl carbamate ester

To a mixture of (+/-)-1-[2-[4-(4-methoxyphenyl)-1-
20 piperazinyl]ethyl]isochroman-6-ol (X-5) (step 4; 0.064 g, 0.17 mmol) and DBU (0.032 g, 0.21 mmol) in dichloromethane (2 mL) is added methylisocyanate (0.031 mL; 0.52 mmol). After stirring for 1.5 hr, the mixture is partitioned between dichloromethane and dilute sodium hydroxide. The organic layers are dried with sodium sulfate and concentrated. The residue is chromatographed (silica gel;
25 methanol/dichloromethane, 2/98) to give (+/-)-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-ol, methyl carbamate ester (X-6) which after crystallization from ether/hexane. MS (m/z) at 425; NMR (CDCl₃) 2.04, 2.12, 2.65, 2.90, 3.11, 3.75, 3.77, 4.11, 4.83, 4.98, 6.82-6.95 and 7.08 δ .

EXAMPLE 96 (+/-)-1-[2-[4-[4-(Aminocarbonyl)phenyl]-1-piperazinyl]ethyl]-N-methylisochromanyl-6-carboxamide
30

Step 1. (+/-)-1-(2-Chloroethyl)isochroman-6-ol

To a mixture of 3-hydroxyphenethyl alcohol (Y-1) (0.074 g, 0.537 mmol) and chloropropionaldehyde diethyl acetal (0.107 g, 0.64 mmol) in nitromethane (0.5 mL) is added boron trifluoride-etherate (0.007 mL, 0.054 mmol). After stirring for 100
35 min, water is added and the mixture is partitioned between dichloromethane, water and saline. The organic layers are dried with sodium sulfate and concentrated and

the residue chromatographed (silica gel; ethyl acetate/hexane, 10/90) to give (+/-)-1-(2-chloroethyl)isochroman-6-ol (Y-2) containing a small amount of (+/-)-1-(2-ethoxyethyl)isochroman-6-ol as an impurity. This material is used without further purification in step 2, NMR (CDCl₃) 2.15 - 2.38, 2.62, 2.68, 2.91, 3.6-3.8, 4.10, 4.89, 5.08, 5.59, 6.68 and 6.95 δ .

Step 2. (+/-)-1-(2-Chloroethyl)isochroman-6-ol,
trifluoromethanesulfonate ester

To a mixture of (+/-)-1-(2-chloroethyl)isochroman-6-ol (Y-2, Step 1; 0.079 g, 0.371 mmol), triethylamine (0.0413 g, 0.408 mmol), 4-dimethylaminopyridine (0.0009 g, 0.0074 mmol) and dichloromethane (1 mL) cooled at -78° is added trifluoromethanesulfonic acid anhydride (0.069 g, 0.408 mmol). The cooling bath is then removed and the mixture is allowed to warm slowly to 20-25°. After stirring for a total of 60 min, the mixture is partitioned between dichloromethane and aqueous ammonium chloride. The organic layers are dried with sodium sulfate, concentrated, and the residue chromatographed (silica gel; ethyl acetate/hexane, 10/90) to give (+/-)-1-(2-chloroethyl)isochroman-6-ol, trifluoromethanesulfonate ester (Y-3), NMR (CDCl₃) 2.24, 2.31, 2.73, 2.78, 3.00, 3.67, 3.80, 4.12, 4.94 and 7.05-7.18 δ .

Step 3. (+/-)-1-(2-Chloroethyl)-N-methylisochroman-6-carboxamide

A mixture of (+/-)-1-(2-chloroethyl)isochroman-6-ol, trifluoromethanesulfonate ester (Y-3, Step 2; 0.291 g, 0.844 mmol) in DMF (1.5 mL) is de-gassed under reduced pressure for five minutes, after which palladium (II) acetate (0.019 g, 0.084 mmol) and 1,3-bis(diphenylphosphino)propane (0.52, 0.127 mmol) is added. Carbon monoxide gas is bubbled in and diisopropylethylamine (0.29 mL, 1.69 mmol) is added. Methylamine gas is then bubbled in and the bath temperature is raised to 50°. The addition of methylamine gas and carbon monoxide gas is continued for 1 hR, at which time an additional palladium acetate (0.010 g) and 1,3-bis(diphenylphosphino)propane (0.025 g) are added. After an additional 4 hr the mixture is allowed to cool and then is partitioned between ether, aqueous ammonium chloride, saline-ammonium chloride, and saline. The organic phases are separated, dried over magnesium sulfate and concentrated. Chromatography of the residue (silica gel; methanol/dichloromethane, 2/98), gives (+/-)-1-(2-chloroethyl)-N-methylisochroman-6-carboxamide (Y-4), NMR (CDCl₃) 2.20, 2.33, 2.73, 2.79, 2.97, 3.01, 3.65, 4.12, 4.95, 6.09, 7.14, 7.53 and 7.56 δ .

Step 4. (+/-)-1-[2-[4-[4-(Aminocarbonyl)phenyl]-1-piperazinyl]ethyl]-N-methylisochromanyl-6-carboxamide

A mixture of (+/-)-1-(2-chloroethyl)-N-methylisochroman-6-carboxamide (Y-4, step 3; 0.0937 g, 0.369 mmol), 4-(piperazin-1-yl)benzamide (Q-3, PREPARATION 1, 0.114 g, 0.554 mmol), diisopropylethylamine (0.0716 g, 0.554 mmol), sodium iodide (0.007 g) and ethylene glycol (2 mL) is heated at 100° for 6.5 hr, after which an additional 0.056 g of 4-(piperazin-1-yl)benzamide is added. After stirring for an additional 24 hr at 100°, the mixture is allowed to cool (with stirring for the remainder of the weekend). Water is then added and the mixture is extracted with dichloromethane. The organic extracts are concentrated and combined with the gummy residue (from which the aqueous layer has been decanted). The combined crude product is chromatographed (silica gel; methanol/dichloromethane, 6/94) to give (+/-)-1-[2-[4-[4-(aminocarbonyl)phenyl]-1-piperazinyl]ethyl]-N-methylisochromanyl-6-carboxamide (Y-5), NMR (CDCl₃) 2.05, 2.18, 2.5-2.8, 3.02, 3.32, 3.77, 4.13, 4.88, 4.8-6.0, 6.12, 6.89, 7.16, 7.54 and 7.72 δ.

EXAMPLE 97 (R)-(+)-1-[2-[4-[4-(Aminocarbonyl)phenyl]-1-piperazinyl]ethyl]-N-methylisochromanyl-6-carboxamide

Separation of (+/-)-1-[2-[4-[4-(aminocarbonyl)phenyl]-1-piperazinyl]ethyl]-N-methylisochromanyl-6-carboxamide (Y-5, EXAMPLE 96) into its plus and minus enantiomers is achieved by preparative chromatography on a chiral phase pre-packed column using as solvent ethyl alcohol/isopropyl alcohol/triethylamine in a ratio of 4/1/0.08 (V/V) and using detection at 295 nM. Peak 1, (S)-(-)-1-[2-[4-[4-(aminocarbonyl)phenyl]-1-piperazinyl]ethyl]-N-methylisochromanyl-6-carboxamide (EXAMPLE 6), eluted first, followed by Peak 2, (R)-(+)-1-[2-[4-[4-(aminocarbonyl)phenyl]-1-piperazinyl]ethyl]-N-methylisochromanyl-6-carboxamide (Y-5), MS (m/z) 422.

EXAMPLE 98 (S)-(-)-1-[2-[4-(4-Cyanophenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide

Step 1. 1-(4-Cyanophenyl)piperazine

A mixture of 4-fluorobenzamide (Q-2, 0.700 g, 5.78 mmol), piperazine (2.49 g, 28.9 mmol), and water (5 mL) is heated at 100° for 85 min and then allowed to cool. Water (5-10 mL) is added and the mixture is partitioned between ethyl acetate, aqueous sodium bicarbonate, and saline-aqueous sodium bicarbonate. The organic layers are dried over magnesium sulfate and concentrated to give 1-(4-cyanophenyl)piperazine (Q-3), NMR (CDCl₃) 1.77, 3.02, 3.28, 6.85 and 7.49 δ.

Step 2. (S)-(-)-2-(6-Bromoisochroman-1-yl)ethyl alcohol

Borane-methyl sulfide (3.1 mL, 33.2 mmol) is added to a mixture of (S)-(-)-2-(6-bromoisochroman-1-yl)acetic acid (XI, EXAMPLE 1, step 2; 3.0 g, 11 mmol) and

THF (40 mL). Gas evolution and a moderate exotherm ensue. After stirring for 2.5 hr, methanol is slowly added to quench excess borane-methyl sulfide. The mixture is then concentrated under reduced pressure and methanol is added to the residue. The mixture again is concentrated and methanol again added. After a final
5 concentration from methanol, the residue is partitioned between dichloromethane, aqueous hydrochloric acid, and aqueous sodium bicarbonate. The organic layers are dried over sodium sulfate and concentrated. The residue is chromatographed (silica gel; methanol/dichloromethane, 4/96) to give (S)-(-)-2-(6-bromoisochroman-1-yl)ethyl alcohol (S-1), NMR (CDCl₃) 2.03, 2.20, 2.60-2.70, 3.02, 3.70-3.85, 4.16, 4.93, 6.93 and
10 7.29 δ.

Step 3. (S)-(-)-6-Bromo-1-(2-bromoethyl)isochroman

To a mixture of triphenylphosphine (9.60 g, 36.6 mmol), carbon tetrabromide (6.06 g, 18.3 mmol), and dichloromethane (25 mL, cooled to about 20° to control the exotherm that occurs as the reagents are mixed) is added over 10 min (S)-(-)-2-(6-
15 bromoisochroman-1-yl)ethyl alcohol (S-1, step 2; 2.35 g, 9.1 mmol) in dichloromethane (25 mL). The cooling bath is removed and the mixture is stirred for 40 min, at which time hexane is added dropwise until no more cloudiness appears. The mixture is allowed to stand overnight in the refrigerator and then the solids are removed by filtration. The solids are washed with ether and the combined
20 filtrates are concentrated and the residue is chromatographed (silica gel; ethyl acetate/hexane, 10/90) to give (S)-(-)-6-bromo-1-(2-bromoethyl)isochroman (T-1), NMR (CDCl₃) 2.22 - 2.46, 2.66, 2.71, 2.94, 3.51, 3.62, 4.09, 4.84, 6.94 and 7.29 δ.

Step 4. (S)-(-)-4-[4-[2-(6-Bromoisochroman-1-yl)ethyl]-1-piperazinyl]benzonitrile

A mixture of (S)-(-)-6-bromo-1-(2-bromoethyl)isochroman (T-1, step 3, 1.53 g, 4.79 mmol), 1-(4-cyanophenyl)piperazine (Q-3, step 1, 0.987 g, 5.27 mmol), diisopropylethylamine (0.681 g, 5.27 mmol), and ethylene glycol (5 mL) is heated at 95° for 4 hr and then at 20-25° overnight. The mixture is partitioned between dichloromethane and water and the organic layers are dried over sodium sulfate and
30 concentrated. The residue is chromatographed (silica gel; methanol/dichloromethane, 2/98) to give (S)-(-)-4-[4-[2-(6-bromoisochroman-1-yl)ethyl]-1-piperazinyl]benzonitrile (VI), NMR (CDCl₃) 2.00, 2.12, 2.48-2.72, 2.95, 3.33, 3.73, 4.10, 4.80, 6.85, 6.96, 7.38 and 7.49 δ.

Step 5. (S)-(-)-1-[2-[4-(4-Cyanophenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide

Following the general procedure of EXAMPLE 6, step 4, and making non-

critical variations, (S)-(-)-4-[4-[2-(6-bromoisochroman-1-yl)ethyl]-1-piperazinyl]benzonitrile (VI, step 4, 1.61 g) is converted to (S)-(-)-1-[2-[4-(4-cyanophenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide (IX), MS (m/z) at 404; IR (mineral oil, most intense peaks) 1603, 1635, 2210, 1517 and 1553 cm^{-1} ;
 5 NMR (CDCl_3) 2.05, 2.18, 2.48-2.78, 3.00, 3.01, 3.34, 3.76, 4.12, 4.88, 6.08, 6.85, 7.15, 7.49, 7.53 and 7.54 δ .

EXAMPLE 99 (S)-(-)-1-[2-[4-[4-(Aminocarbonyl)phenyl]-1-piperazinyl]ethyl]-N-methyl-N-(phenylmethoxy)isochroman-6-carboxamide

Step 1. (S)-(-)-1-[2-[(Tetrahydropyran-2-yl)oxy]ethyl]isochroman-6-carboxylic acid, methyl ester
 10

A mixture of (S)-(-)-1-(hydroxyethyl)isochroman-6-carboxylic acid, methyl ester (S-2, EXAMPLE 81, step 2, 1.36 g, 5.76 mmol), dichloromethane (10 mL), p-toluene sulfonic acid monohydrate (0.0142, 0.0747 mmol) and 3,4-dihydro-2H-pyran (1.6 mL, 0.0175 mol) is stirred at 20-25° for 45 minutes. The mixture then is
 15 partitioned between aqueous sodium bicarbonate and dichloromethane. The combined organic layers are dried over sodium sulfate and concentrated under reduced pressure. The residue is chromatographed (silica gel; ethyl acetate/hexane, 5/95 to 15/85) to give (S)-(-)-1-[2-[(tetrahydropyran-2-yl)oxy]ethyl]isochroman-6-carboxylic acid, methyl ester (W-2), NMR (CDCl_3) 1.53, 1.69-1.80, 2.04, 2.23, 2.73-
 20 2.79, 2.98, 3.51-4.13, 4.60, 4.92, 7.18, 7.80 and 7.83 δ .

Step 2. (S)-(-)-1-[2-[(Tetrahydropyran-2-yl)oxy]ethyl]isochroman-6-carboxylic acid

A mixture of (S)-(-)-1-[2-[(tetrahydropyran-2-yl)oxy]ethyl]isochroman-6-carboxylic acid, methyl ester (W-2, step 1, 1.55 g, 4.85 mmol), ethanol (12 mL),
 25 sodium hydroxide (2N, 3.6 mL, 7.2 mmol) and water (1 mL) is stirred for 6.5 hours at 20-25°, at which time the mixture is stored in the refrigerator overnight. The mixture is then stirred an additional 2.5 hours at 20-25° and then is concentrated under reduced pressure. Water (6 mL) is added and the resulting mixture is cooled in an ice/water bath. The pH of the mixture is adjusted to pH 5 using hydrochloric
 30 acid (4N) and the resulting slurry is extracted with dichloromethane. The combined organic layers are dried over magnesium sulfate and concentrated under reduced pressure to give (S)-(-)-1-[2-[(tetrahydropyran-2-yl)oxy]ethyl]isochroman-6-carboxylic acid (W-3), MS (m/z) = 306; NMR (CDCl_3) 1.55, 1.70-1.84, 2.08, 2.26, 2.77-2.82, 3.01, 3.54, 3.66-4.17, 4.63, 4.96, 7.23 and 7.88 δ .

Step 3. (S)-(-)-N-Methyl-N-(phenylmethoxy)-1-[2-[(tetrahydropyran-2-yl)oxy]ethyl]isochroman-6-carboxamide
 35

1,1'-Carbonyldiimidazole (0.064 g, 0.39 mmol) is added to (S)-(-)-1-[2-
 [(tetrahydropyran-2-yl)oxy]ethyl]isochroman-6-carboxylic acid (W-3, step 2; 0.109 g,
 0.356 mmol) and THF (2 mL). The mixture is stirred at 20-25° for 2 hr and then N-
 methyl, O-benzylhydroxylamine (*Tetrahedron Letters*, 30, 31-34 (1989), 0.054 g, 0.39
 5 mmol) is added and the mixture is stirred overnight at 60°. The mixture then is
 concentrated and the residue is partitioned between dichloromethane, water and
 aqueous sodium bicarbonate. The organic layers are dried over sodium sulfate and
 concentrated. The residue is chromatographed (silica gel;
 methanol/dichloromethane, 2/98) to give (S)-(-)-N-methyl-N-(phenylmethoxy)-1-[2-
 10 [(tetrahydropyran-2-yl)oxy]ethyl]isochroman-6-carboxamide (W-4), NMR (CDCl₃)
 1.50 - 1.65, 1.70-1.90, 2.07, 2.28, 2.67, 2.72, 2.92, 3.36, 3.53, 3.66-3.95, 4.02, 4.11,
 4.62, 4.69, 4.92, 7.07-7.14, 7.30, 7.36 and 7.45 δ.

Step 4. (S)-(-)-1-(2-Hydroxyethyl)-N-methyl-N-
 phenylmethoxyisochroman-6-carboxamide
 15 (S)-(-)-N-methyl-N-(phenylmethoxy)-1-[2-[(tetrahydropyran-2-
 yl)oxy]ethyl]isochroman-6-carboxamide (W-4, step 3; 0.131 g, 0.308 mmol) is stirred
 at 20-25° in a mixture of acetic acid/THF/water (4/2/1, 5 mL) for 2 hr and then at
 60° for 4 hr, at which time it is stored in the refrigerator overnight. The solvents
 are then removed and the resulting mixture is partitioned between dichloromethane
 20 and water. The organic layers are dried with sodium sulfate and concentrated and
 the residue is chromatographed (silica gel; methanol/dichloromethane, 2/98) to give
 crude product. NMR of this material indicated the presence of tetrahydropyranyl
 (THP)-like protons, so methanol (2 mL) and *p*-toluenesulfonic acid hydrate (0.006 g)
 are added and the mixture is stirred overnight. The solvent is then removed under
 25 reduced pressure and the residue is partitioned between dichloromethane and
 aqueous sodium bicarbonate. The organic layers are dried over sodium sulfate and
 concentrated to give (S)-(-)-1-(2-hydroxyethyl)-N-methyl-N-
 phenylmethoxyisochroman-6-carboxamide (W-5), NMR (CDCl₃) 2.07, 2.25, 2.64, 2.70,
 3.02, 3.38, 3.77, 3.86, 4.19, 5.01, 7.06, 7.08, 7.31, 7.37 and 7.46 δ.

Step 5. (S)-(-)-1-[2-[4-[4-(Aminocarbonyl)phenyl]-1-piperazinyl]ethyl]-N-
 methyl-N-(phenylmethoxy)isochroman-6-carboxamide

To an ice-cooled mixture of (S)-(-)-1-(2-hydroxyethyl)-N-methyl-N-
 phenylmethoxyisochroman-6-carboxamide (W-5, step 4; 0.099 g, 0.290 mmol),
 diisopropylethylamine (0.049 g, 0.377 mmol) and 4-dimethylaminopyridine (0.0018 g,
 35 0.014 mmol) in dichloromethane (1.5 mL) is added methanesulfonyl chloride (0.043
 g, 0.377 mmol) in dichloromethane (0.5 mL). The mixture is stirred for 1.5 hr and

then partitioned between dichloromethane and aqueous sodium bicarbonate. The organic layers are dried with sodium sulfate and concentrated to give a mesylate (W-6). To the mesylate is added 4-(piperazin-1-yl)benzamide (Q-3, PREPARATION 1, 0.071 g, 0.348 mmol), diisopropylethylamine (0.075 mL, 0.580 mmol), and ethylene glycol (0.3 mL). A small amount of dichloromethane is used to wash down the sides of the flask. The mixture is heated at 85° for 2.5 hr and then cooled. Water is added and the mixture is allowed to stand in the refrigerator overnight. The supernatant is then decanted and the remaining residue is chromatographed (silica gel; methanol/dichloromethane, 4/96 to 6/94) to give the title compound, NMR (CDCl₃) 2.08, 2.20, 2.5-2.75, 2.95, 3.34, 3.37, 3.76, 4.13, 4.69, 4.89, 5.7, 6.89, 7.10, 7.29, 7.47 and 7.72 δ.

EXAMPLE 100 (S)-(-)-1-[2-[4-[4-(Aminocarbonyl)phenyl]-1-piperazinyl]ethyl]-N-hydroxy-N-methylisochroman-6-carboxamide

A mixture of (S)-(-)-1-[2-[4-[4-(aminocarbonyl)phenyl]-1-piperazinyl]ethyl]-N-methyl-N-(phenylmethoxy)isochroman-6-carboxamide (W-7, EXAMPLE 99, step 5, 0.067 g, 0.13 mmol), palladium on charcoal (10%, 0.0068 g) and methanol (3 mL) is stirred under approximately one atmosphere of hydrogen gas for one hour, at which time ethyl acetate (1 mL) is added to aid in dissolving the starting material. Stirring is continued under a hydrogen atmosphere, and after 8 hr an additional palladium on charcoal (10%, 0.0068 g) is added. When the starting material is consumed (about 28 hr) the palladium on charcoal is filtered off and the filtrate is concentrated. The residue is chromatographed (silica gel; methanol/dichloromethane, 8/92 to 15/85) to give (S)-(-)-1-[2-[4-[4-(aminocarbonyl)phenyl]-1-piperazinyl]ethyl]-N-hydroxy-N-methylisochroman-6-carboxamide (W-8), NMR (DMSO) 1.89, 2.10, 2.45, 2.65-2.70, 2.85, 3.21, 3.66, 4.02, 4.77, 6.90, 6.98, 7.22, 7.36, 7.41, 7.68, 7.72 and 9.94 δ.

EXAMPLE 101 (+/-)-1-[2-[4-[4-(Aminosulfonyl)phenyl]-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide

Step 1. 4-(Piperazin-1-yl)benzenesulfonamide

A mixture of 4-fluorobenzenesulfonamide (Q-2, 6.95 g) and piperazine (17.1 g) in water (30 mL) is heated at 100° overnight. The solid is then collected, washed with water and toluene, and dried under reduced pressure to give 4-(piperazin-1-yl)benzenesulfonamide (Q-3), MS (m/z) = 241; IR (mineral oil, most intense peaks) 1160, 822, 1332, 608, 1593 and 1137 cm⁻¹; NMR (DMSO) 2.81, 3.17, 2.3, 7.01, 7.07 and 7.61 δ.

Step 2. (+/-)-1-[2-[4-[4-(Aminosulfonyl)phenyl]-1-piperazinyl]ethyl]-N-

methylochroman-6-carboxamide

Following the general procedure of EXAMPLE 96 and making non-critical variations, (+/-)-1-(2-Chloroethyl)-N-methylochroman-6-carboxamide (Y-4, EXAMPLE 96, step 3, 0.024 g, 0.095 mmol) and 4-(piperaziny-1-

- 5 yl)benzenesulfonamide (Q-3, Step 1) gives (+/-)-1-[2-[4-[4-(aminosulfonyl)phenyl]-1-piperazinyl]ethyl]-N-methylochroman-6-carboxamide (Y-5), NMR (CDCl₃) 2.05, 2.19, 2.5-2.8, 3.01, 3.34, 3.42, 3.79, 4.16, 4.89, 6.41, 6.91, 7.18, 7.54, 7.56 and 7.76 δ.

Following the general procedure of EXAMPLE 94 (CHART V) and making non-critical variations and using the reactants corresponding to the products, the compounds of EXAMPLES 102-104 are obtained:

- EXAMPLE 102 (S)-(-)-N-Methyl-1-[2-[4-[4-(methylaminocarbonyl)phenyl]-1-piperazinyl]ethyl]isochroman-6-carboxamide
 EXAMPLE 103 (S)-(-)-N-Methyl-1-[2-[4-[4-(dimethylaminocarbonyl)phenyl]-1-piperazinyl]ethyl]isochroman-6-carboxamide
 15 EXAMPLE 104 (S)-(-)-N-Methyl-1-[2-[4-[4-(n-propylaminocarbonyl)phenyl]-1-piperazinyl]ethyl]isochroman-6-carboxamide

Following the general procedure of EXAMPLE 100 and making non-critical variations and using the reactants corresponding to the products, the compounds of EXAMPLES 105-108 are obtained:

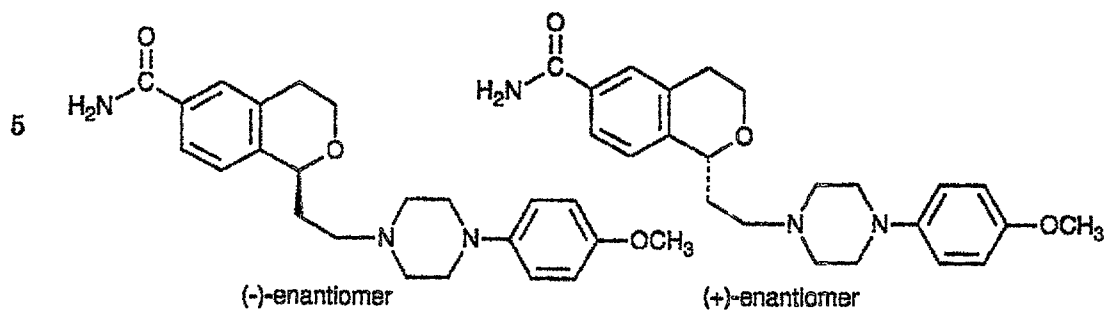
- 20 EXAMPLE 105 (S)-(-)-N-hydroxy-N-methyl-1-[2-[4-[4-(trifluoromethyl)phenyl]-1-piperazinyl]ethyl]isochroman-6-carboxamide
 EXAMPLE 106 (S)-(-)-1-[2-[4-(4-Chlorophenyl)-1-piperazinyl]ethyl]-N-hydroxy-N-methylochroman-6-carboxamide
 EXAMPLE 107 (S)-(-)-1-[2-[4-(4-Cyanophenyl)-1-piperazinyl]ethyl]-N-hydroxy-N-methylochroman-6-carboxamide
 25 EXAMPLE 108 (S)-(-)-N-Hydroxy-N-methyl-1-[2-[4-[4-(methylcarbonyl)phenyl]-1-piperazinyl]ethyl]isochroman-6-carboxamide

Following the procedure of CHART DD and making non-critical variations known to those skilled in the art the compounds of EXAMPLES 109 thru 120 are obtained.

- 30 EXAMPLE 109 (S)-4-[4-[2-[6-(1,2,4-Triazol-3-yl)-isochroman-1-yl]ethyl]-1-piperazinyl]benzamide
 EXAMPLE 110 (S)-4-[4-[2-[6-(2-Methyl-1,2,4-triazol-3-yl)-isochroman-1-yl]ethyl]-1-piperazinyl]benzamide
 35 EXAMPLE 111 (S)-4-[4-[2-[6-(1,2,4-Oxadiazol-5-yl)-isochroman-1-yl]ethyl]-1-piperazinyl]benzamide

- EXAMPLE 112 (S)-1-[2-[6-(1,2,4-Triazol-3-yl)isochroman-1-yl]ethyl]-4-[4-trifluoromethylphenyl]-piperazine
- EXAMPLE 113 (S)-1-[2-[6-(2-Methyl-1,2,4-triazol-3-yl)-isochroman-1-yl]ethyl]-4-[4-trifluoromethylphenyl]piperazine
- 5 EXAMPLE 114 (S)-1-[2-[6-(1,2,4-Oxadiazol-5-yl)isochroman-1-yl]ethyl]-4-[4-trifluoromethylphenyl]-piperazine
- EXAMPLE 115 (S)-1-[4-Acetylphenyl]-4-[2-[6-(1,2,4-triazol-3-yl)isochroman-1-yl]ethyl]piperazine
- EXAMPLE 116 (S)-1-[4-Acetylphenyl]-4-[2-[6-(2-methyl-1,2,4-triazol-3-yl)isochroman-1-yl]ethyl]piperazine
- 10 EXAMPLE 117 (S)-1-[4-Acetylphenyl]-4-[2-[6-(1,2,4-oxadiazol-5-yl)isochroman-1-yl]ethyl]-piperazine
- EXAMPLE 118 3-[1-[2-[4-(4-Aminocarbonylphenyl)piperazin-1-yl]ethyl]isochroman-6-yl]-N,N-dimethylacrylamide
- 15 EXAMPLE 119 3-[1-[2-[4-(4-Trifluoromethylphenyl)piperazin-1-yl]ethyl]isochroman-6-yl]-N,N-dimethylacrylamide
- EXAMPLE 120 3-[1-[2-[4-(4-Acetylphenyl)piperazin-1-yl]-ethyl]isochroman-6-yl]-N,N-dimethylacrylamide

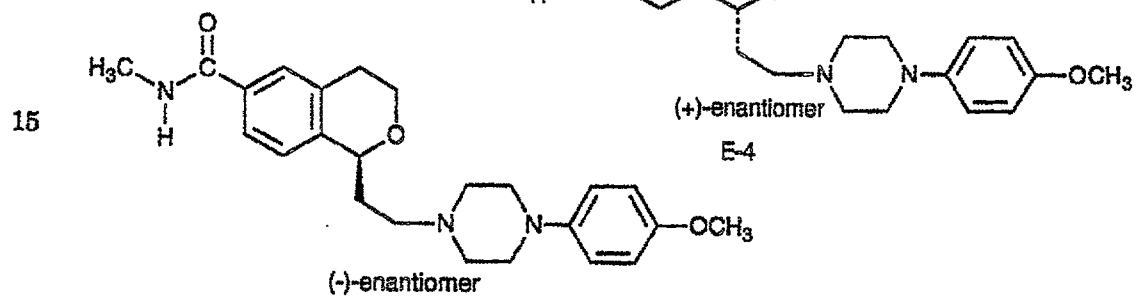
FORMULAS OF THE EXAMPLES (E-#)



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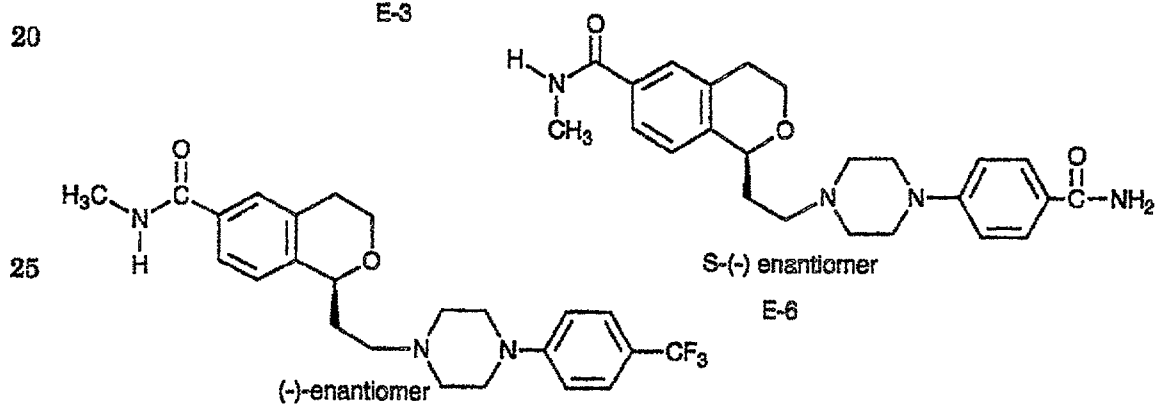
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E-4

E-3

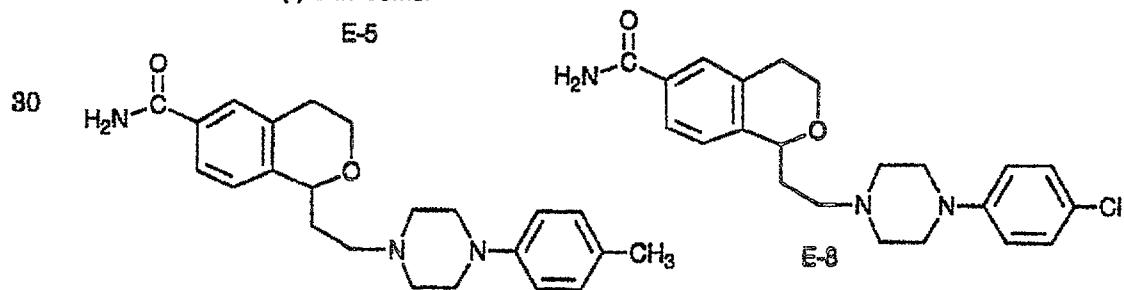
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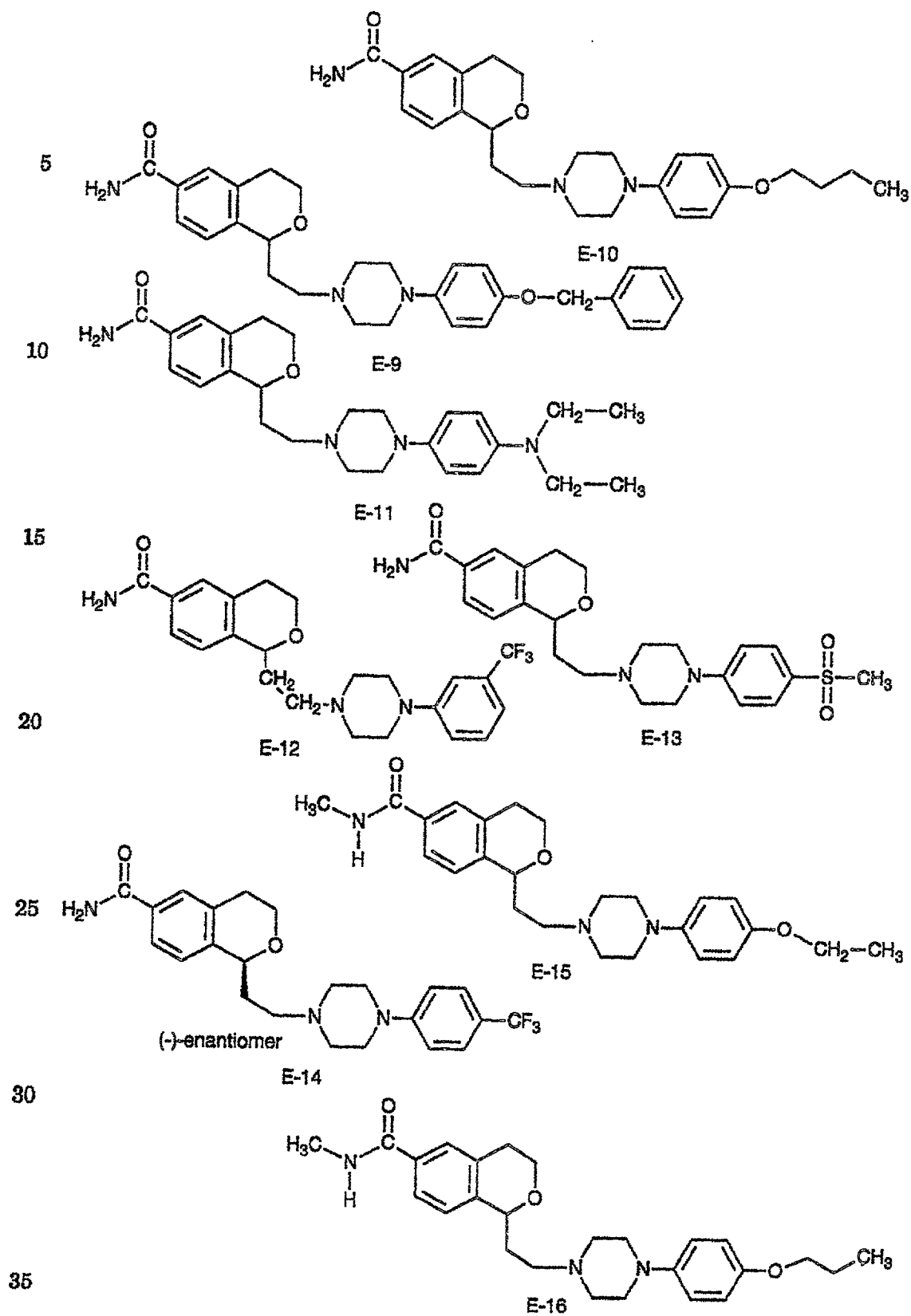
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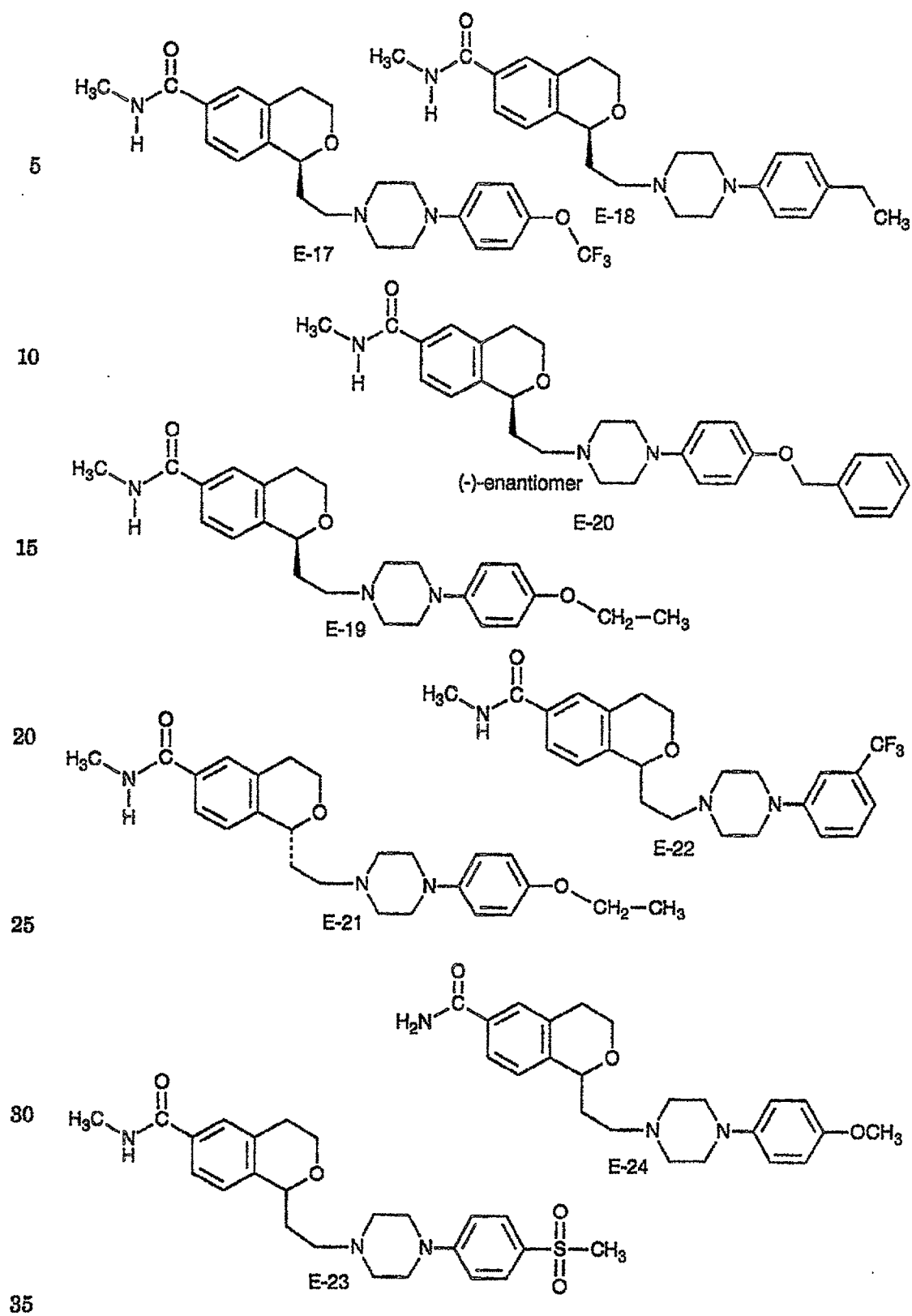
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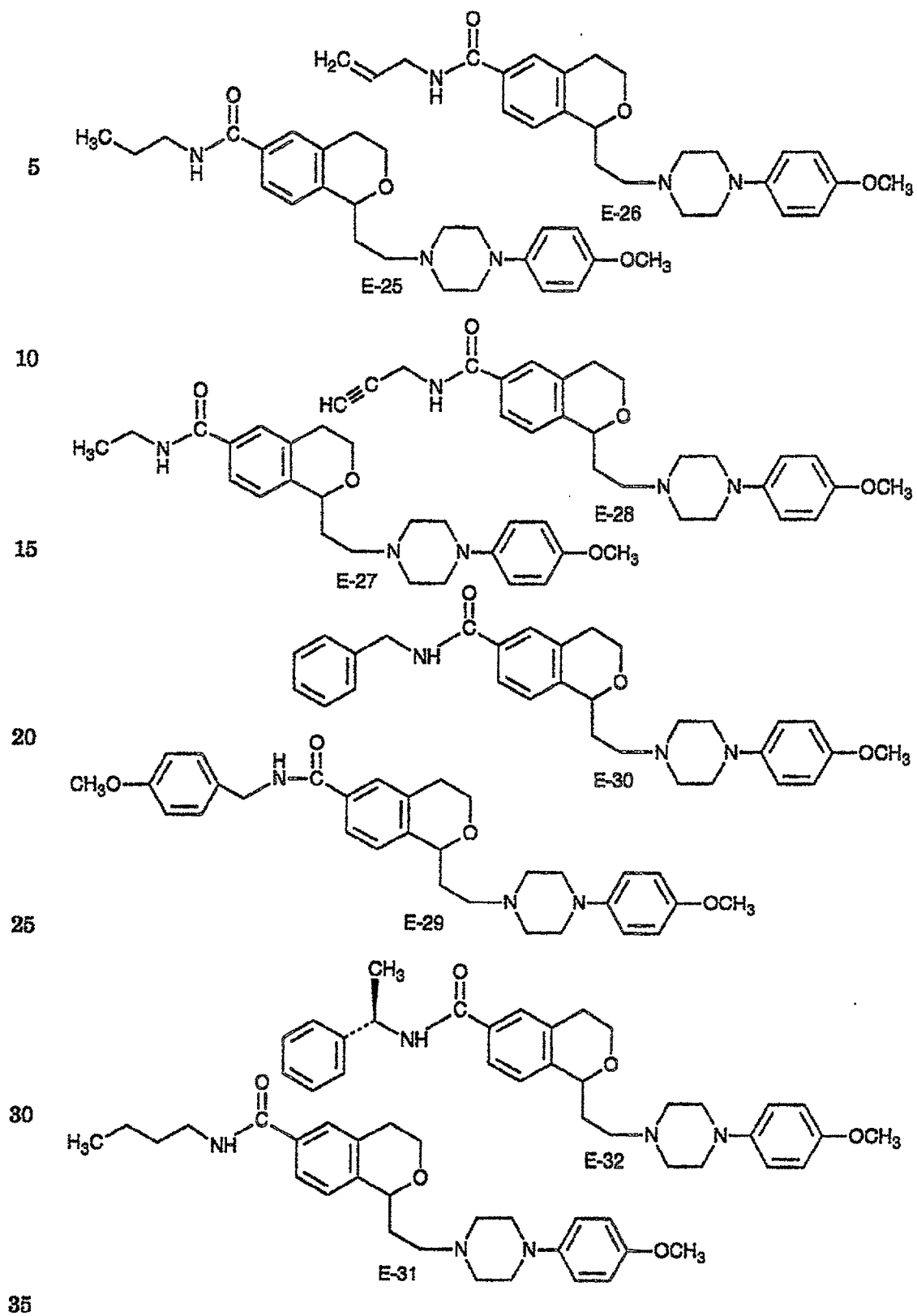


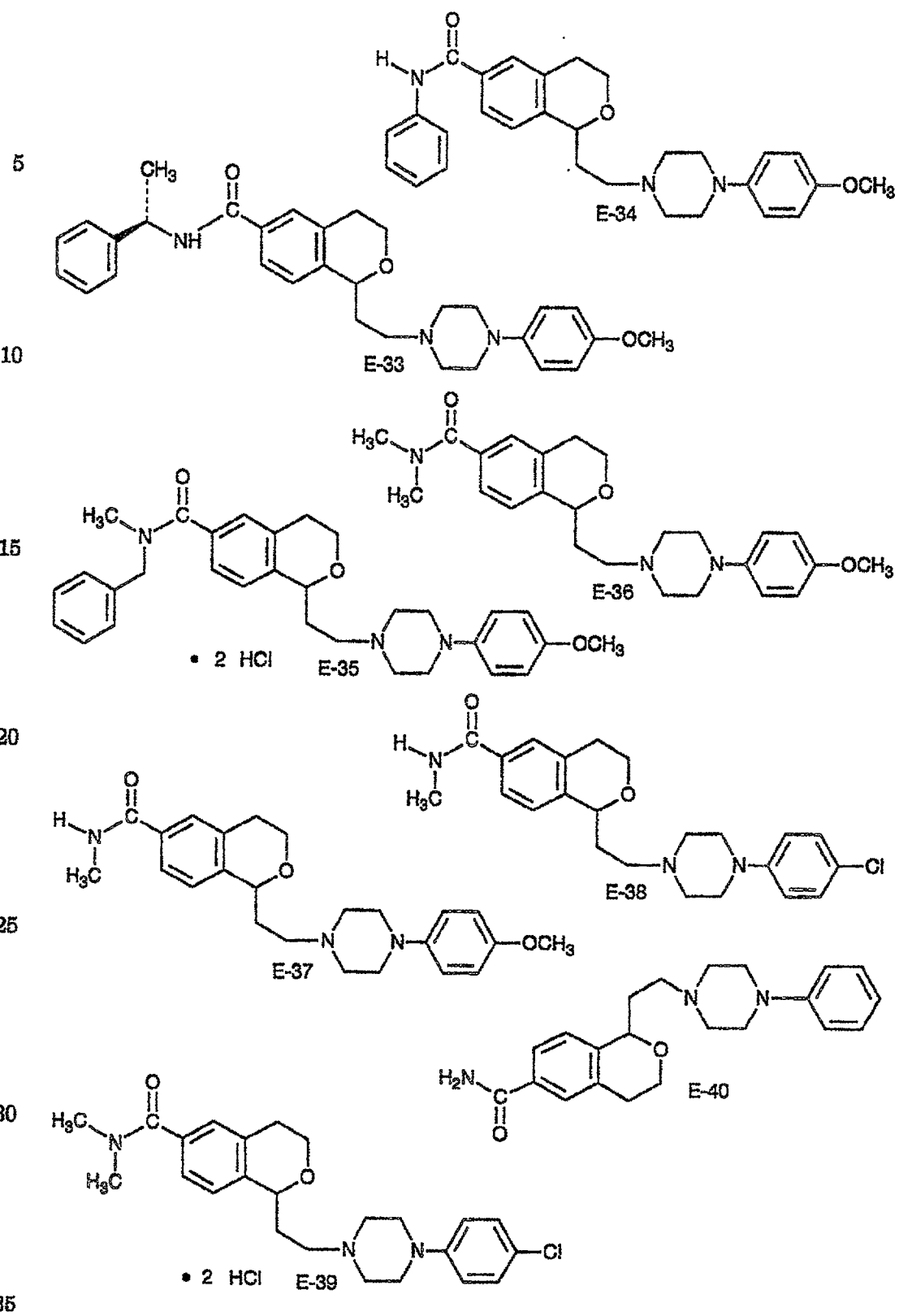
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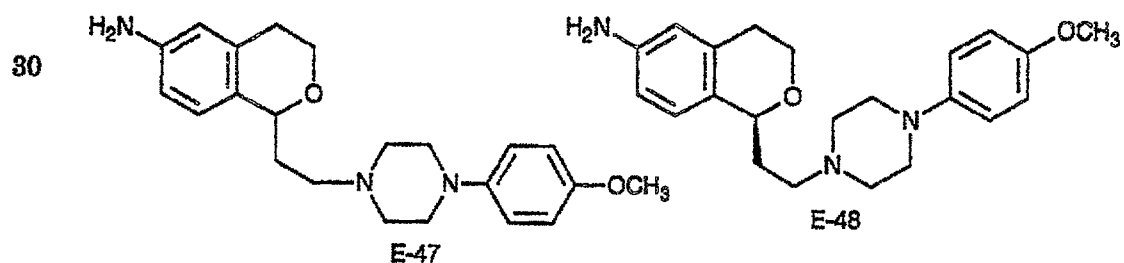
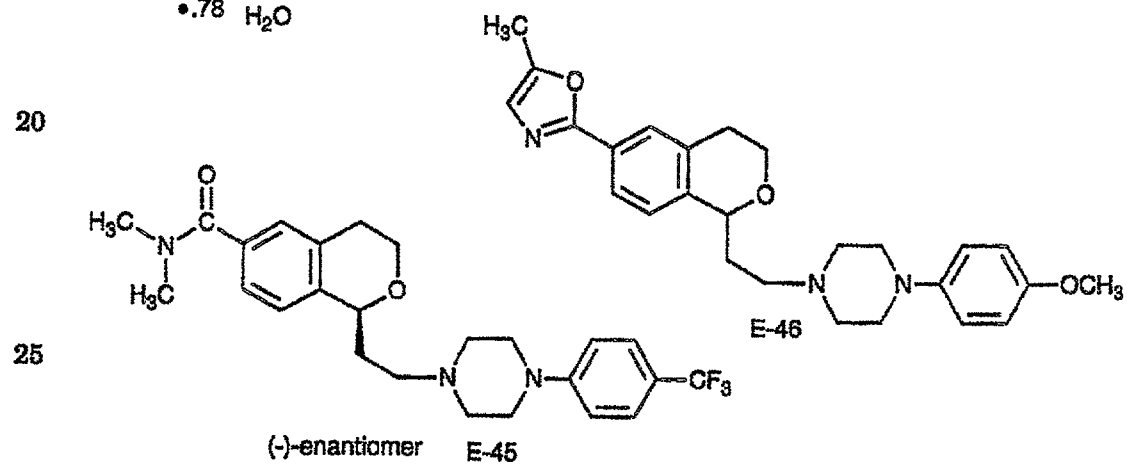
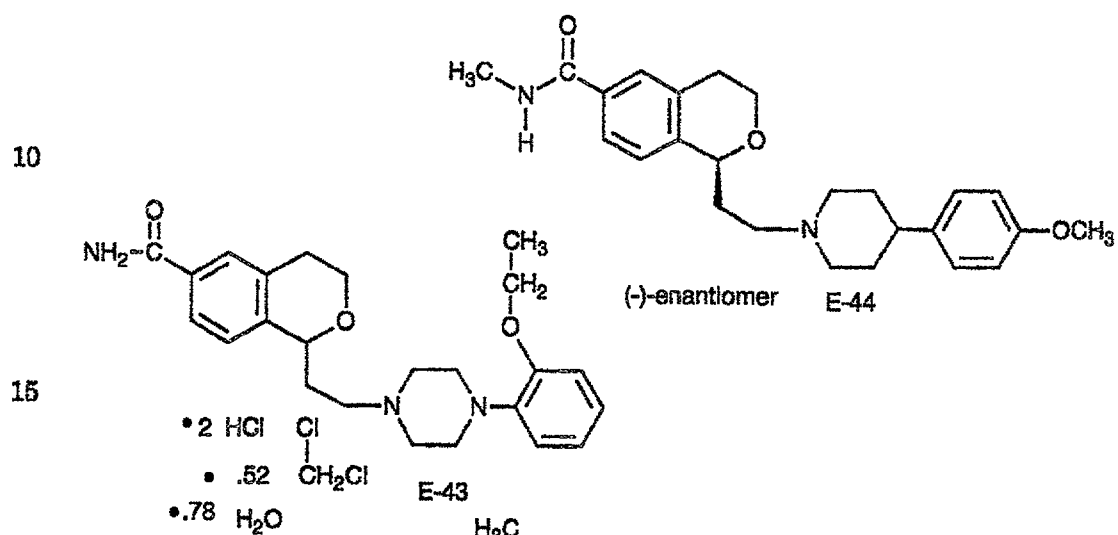
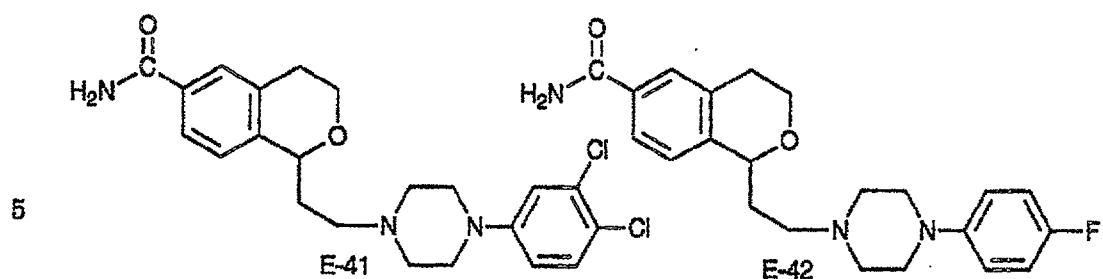
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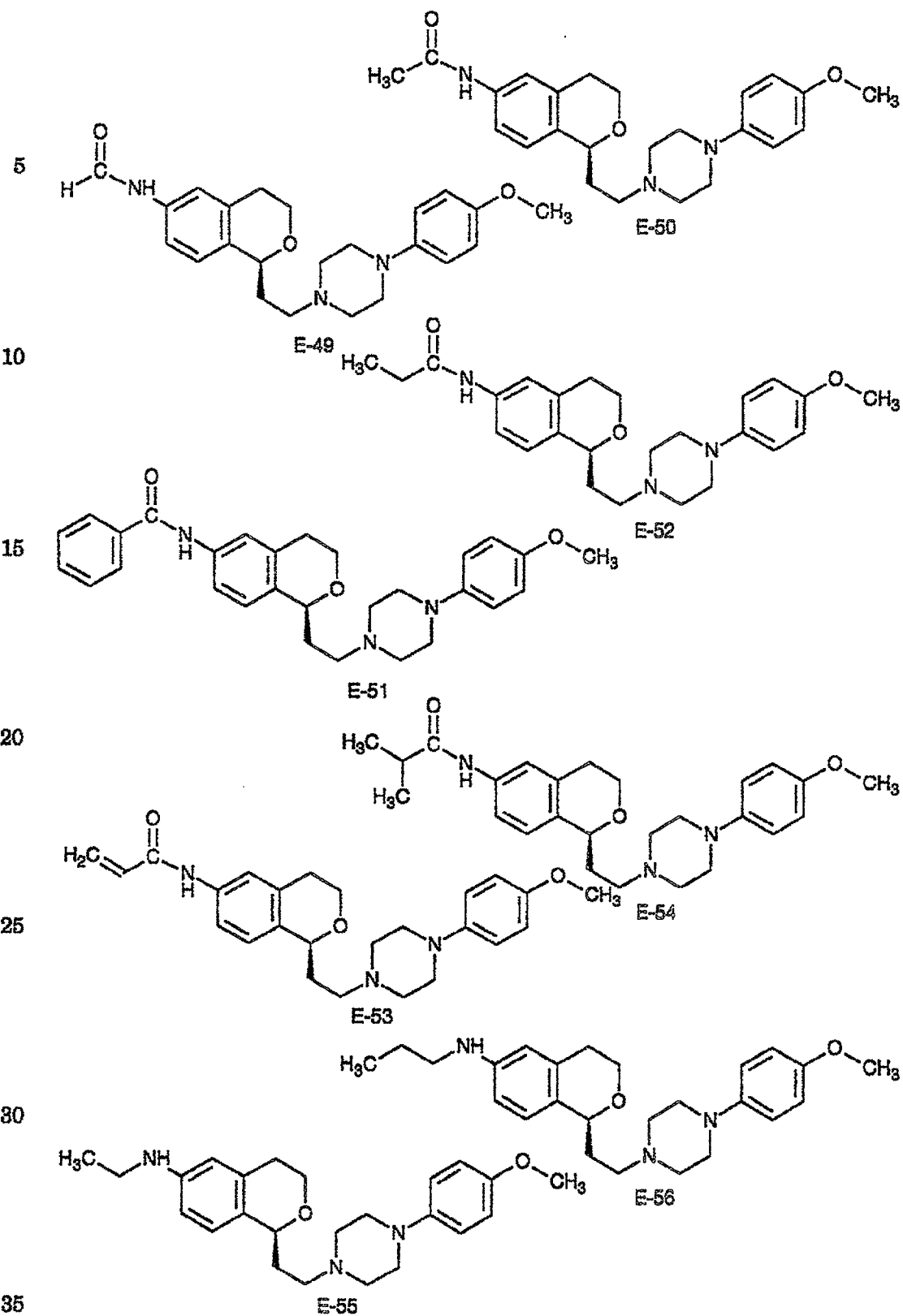


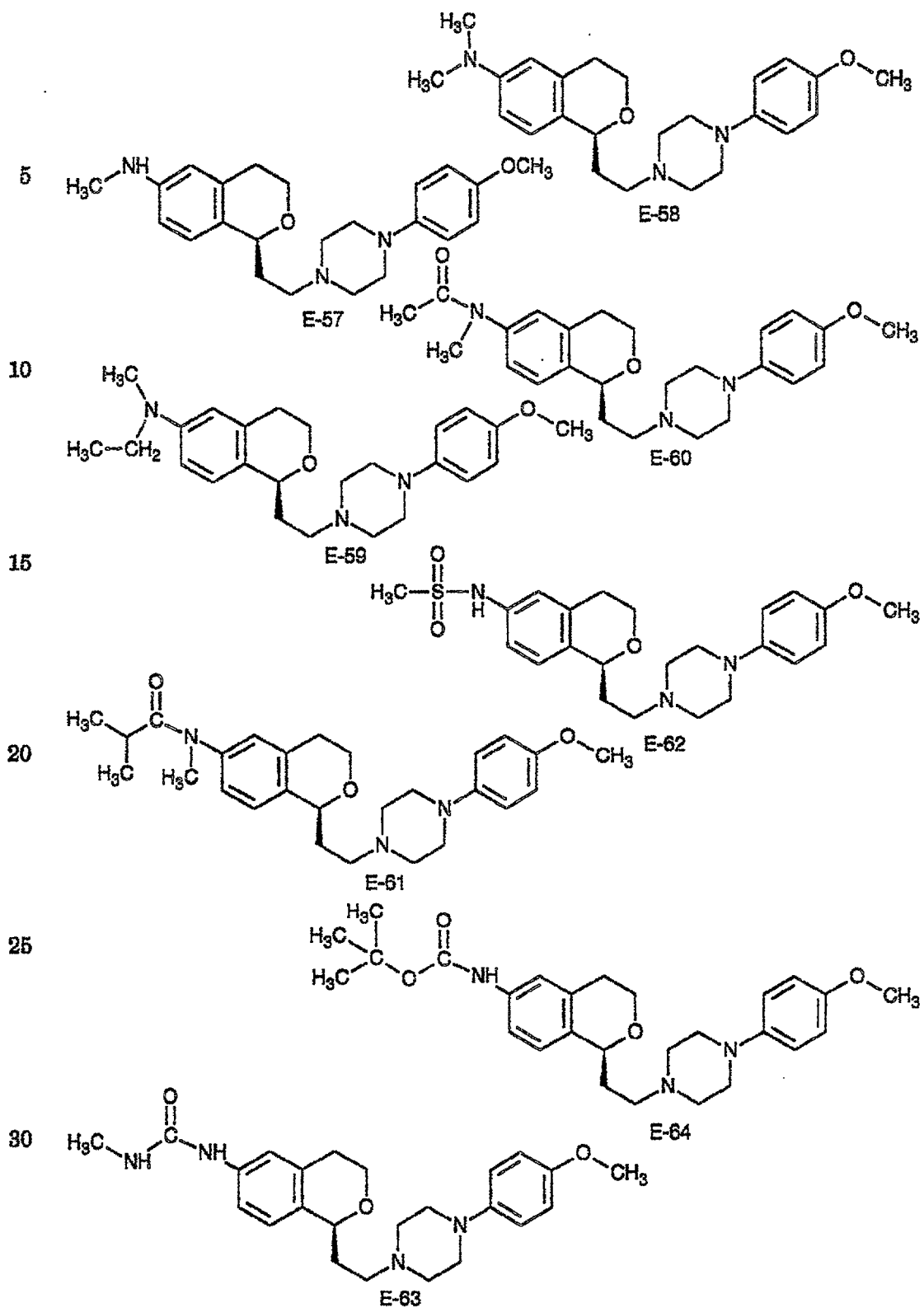


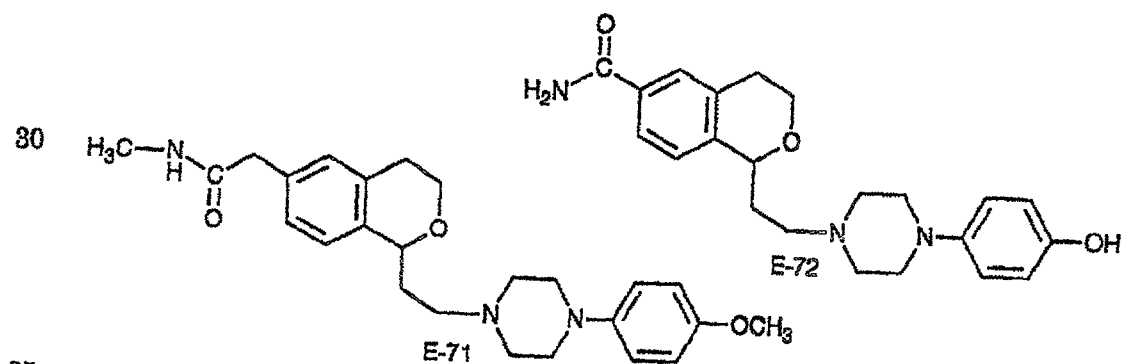
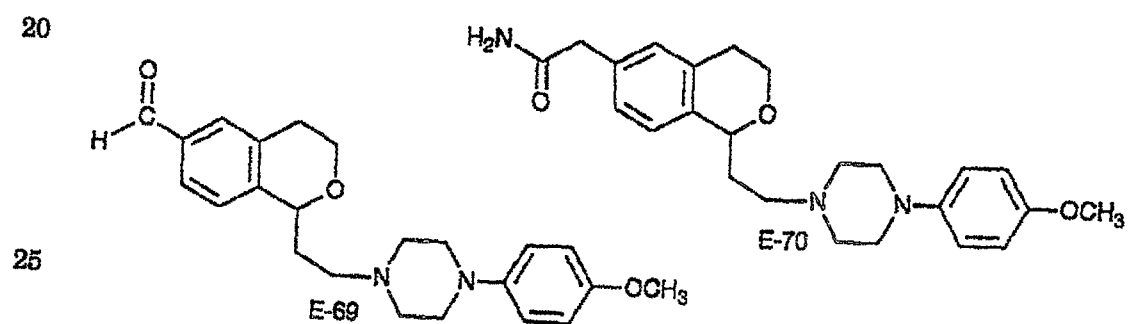
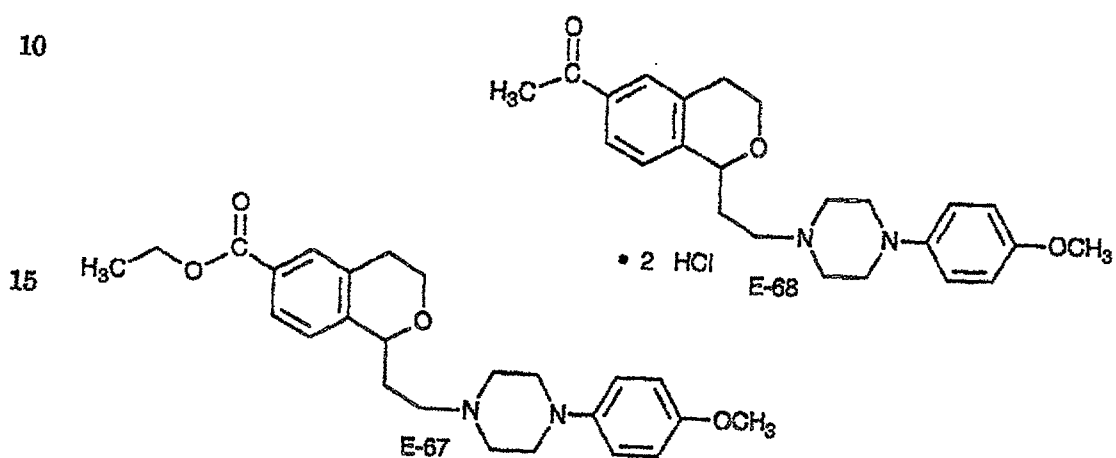
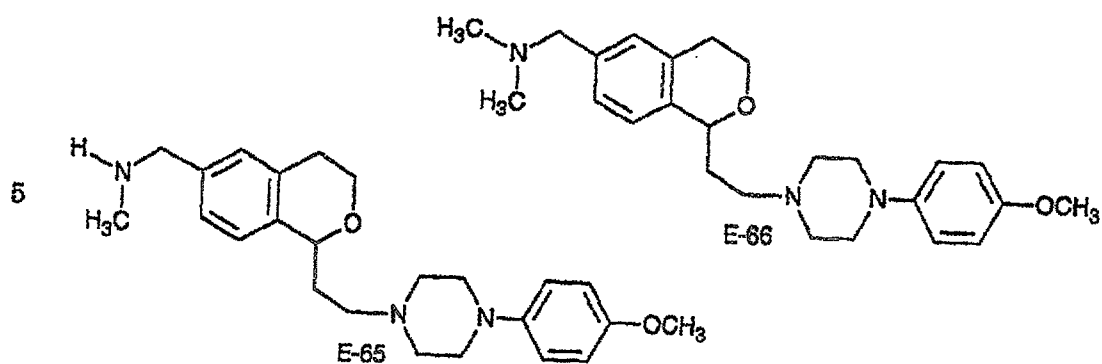


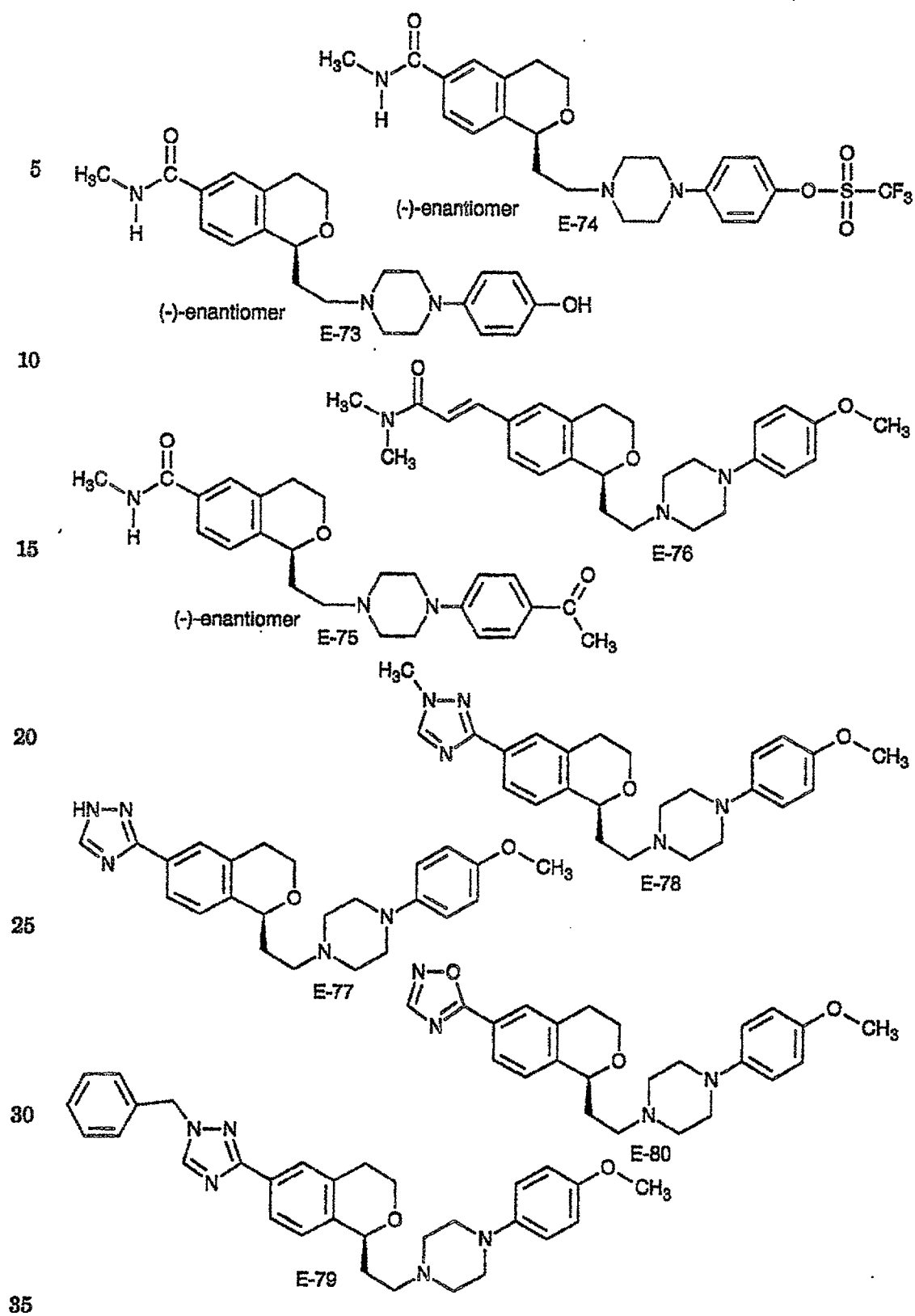


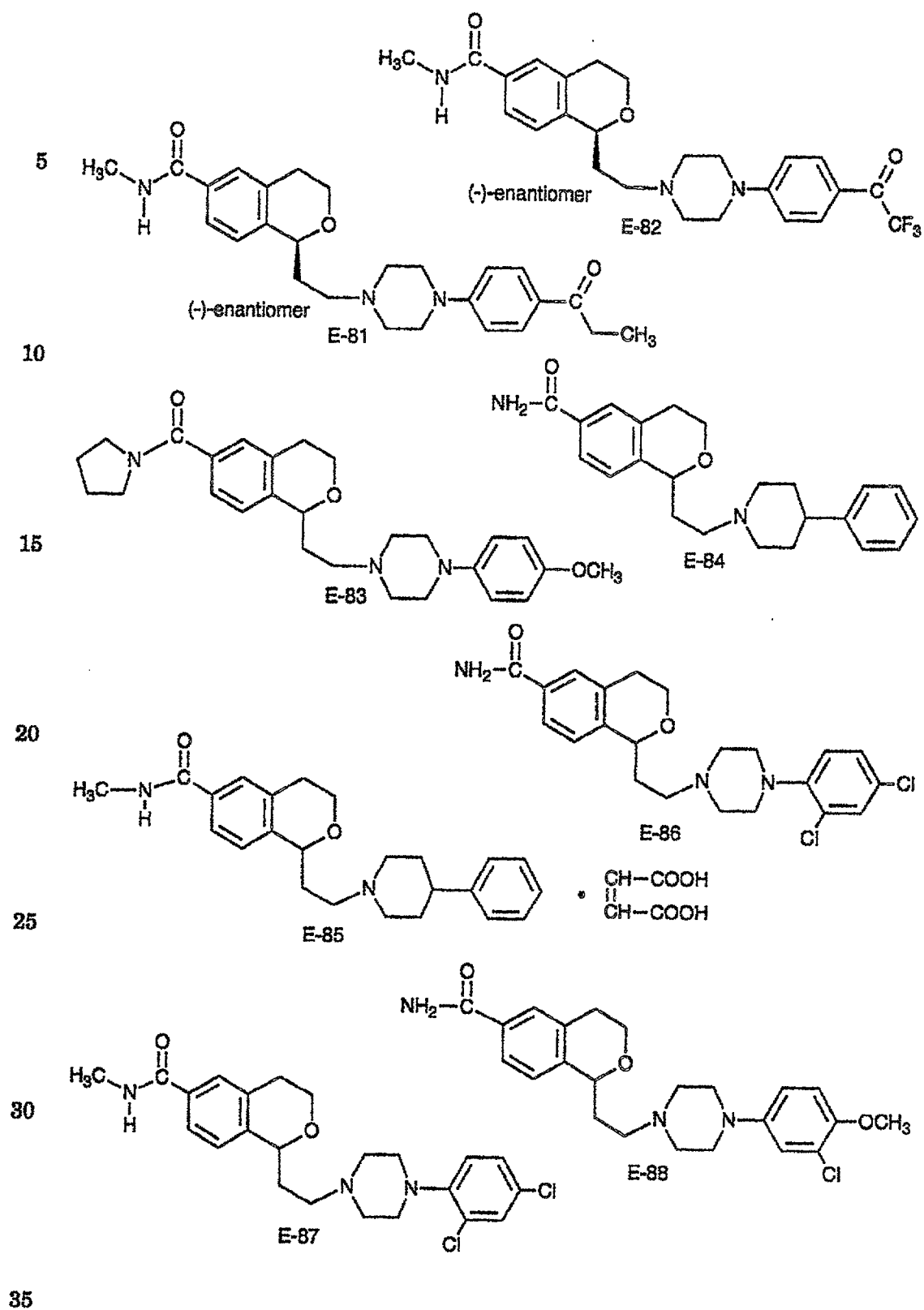
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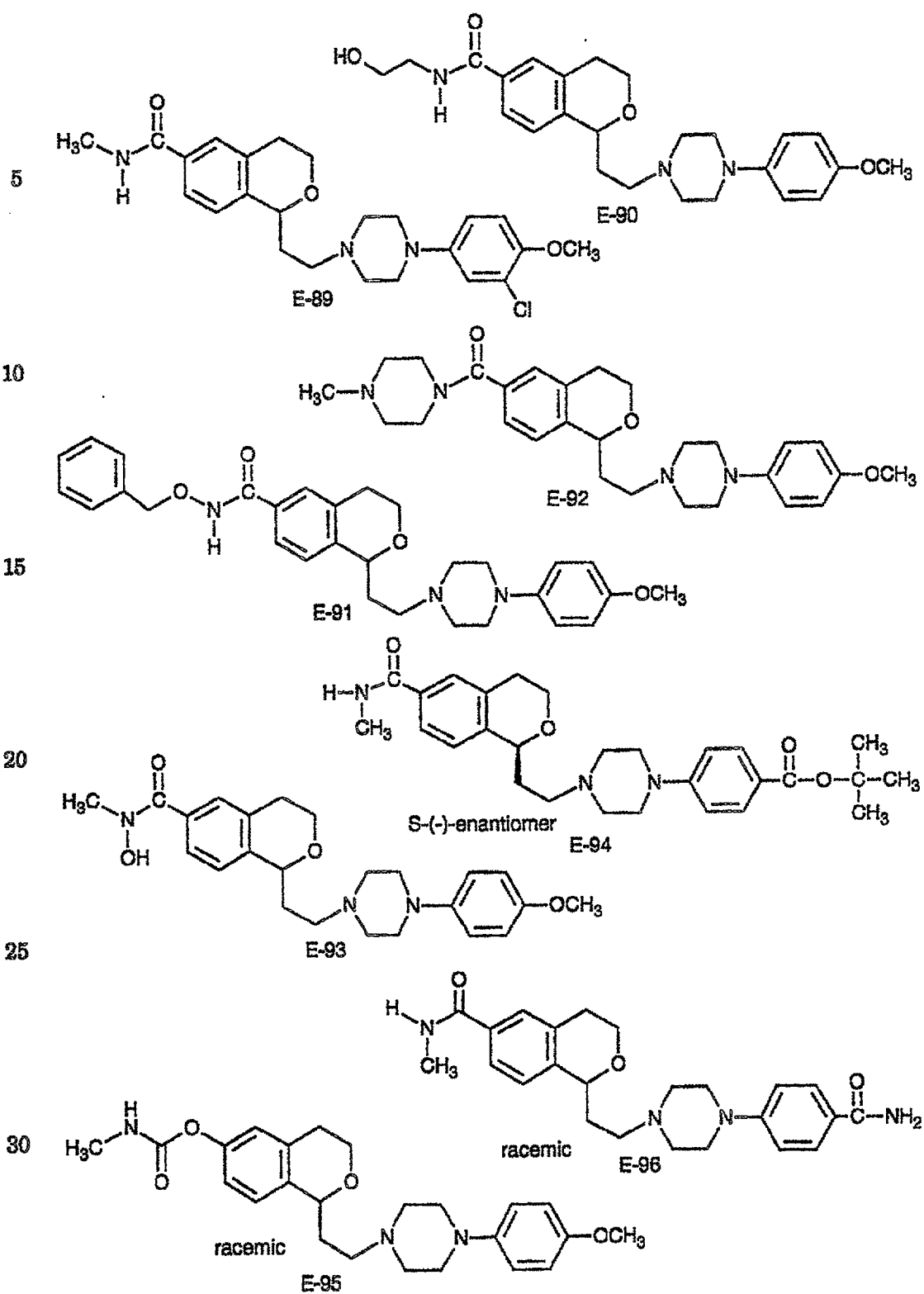












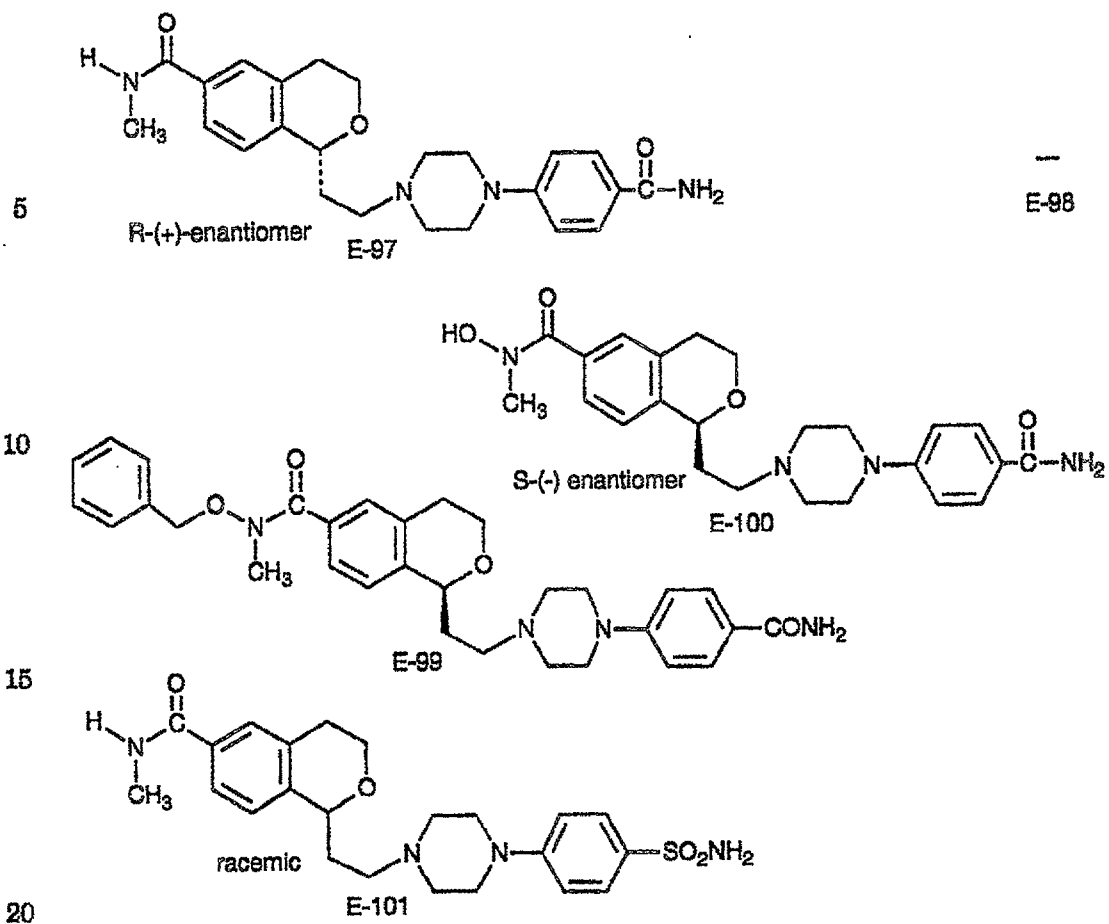


CHART A

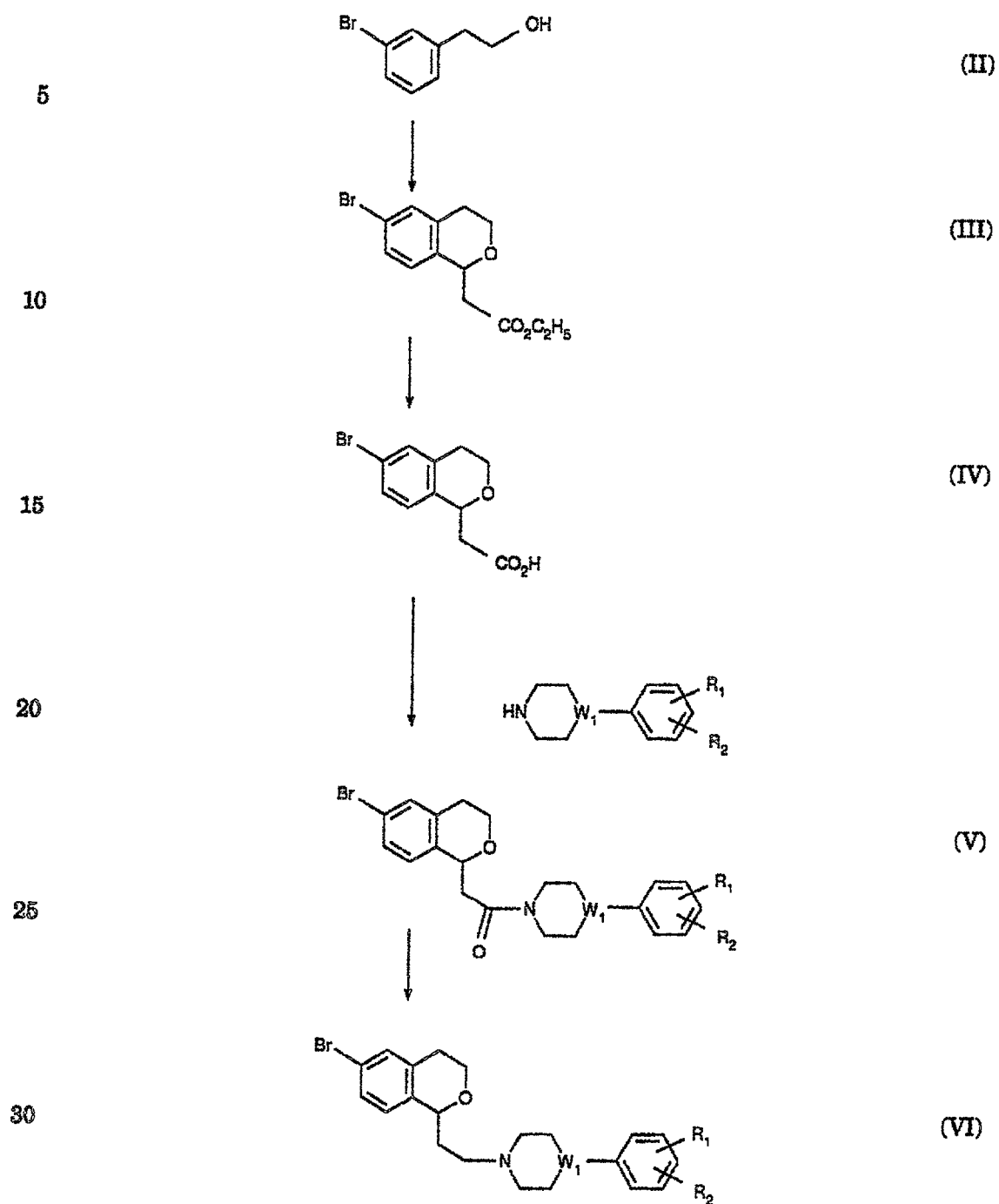


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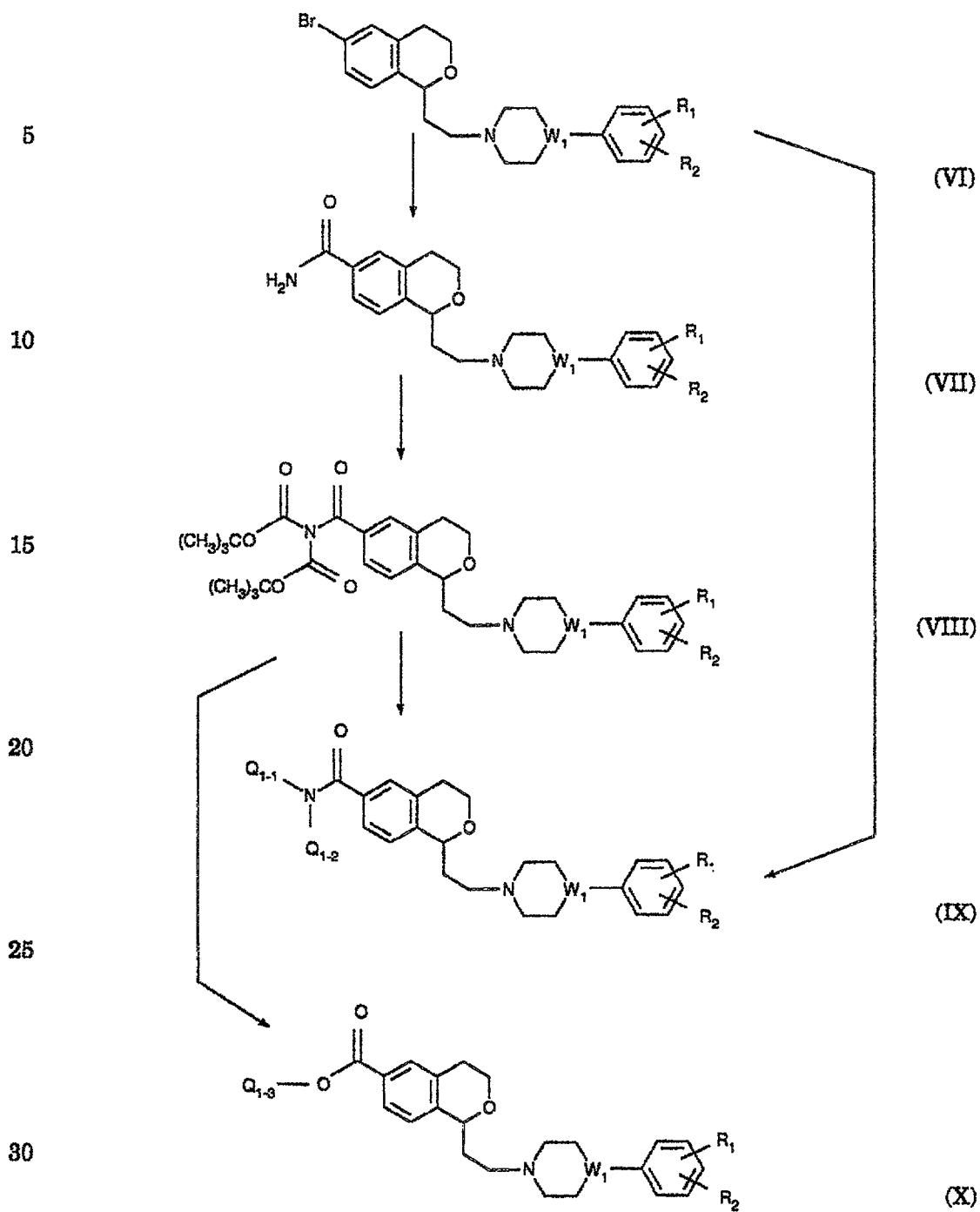


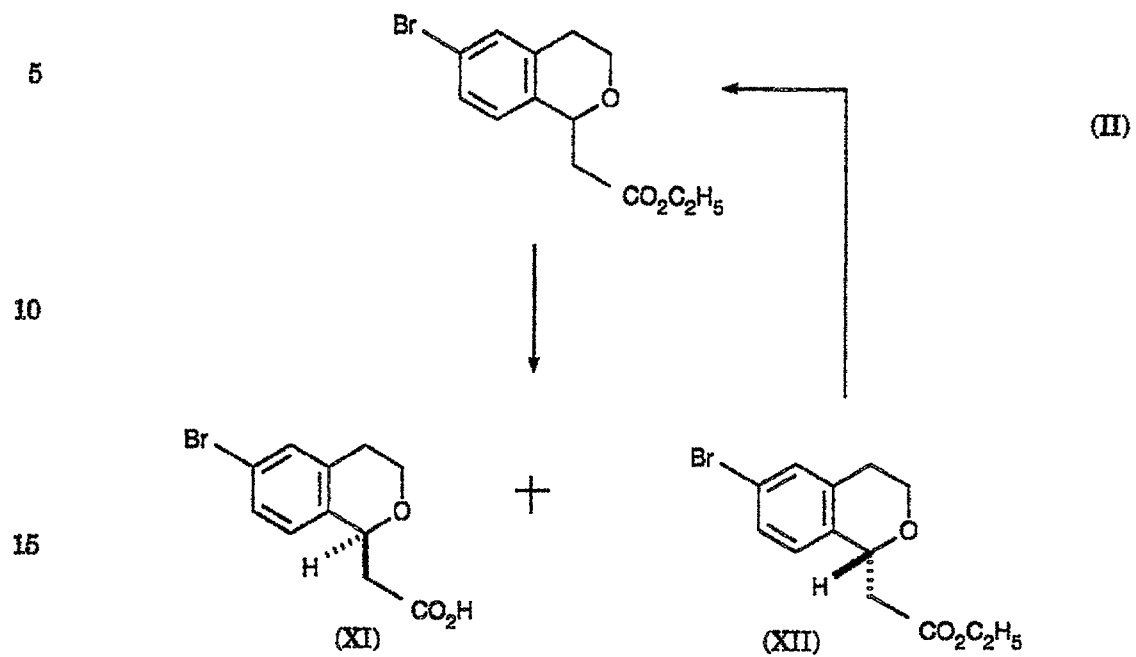
CHART C

CHART D

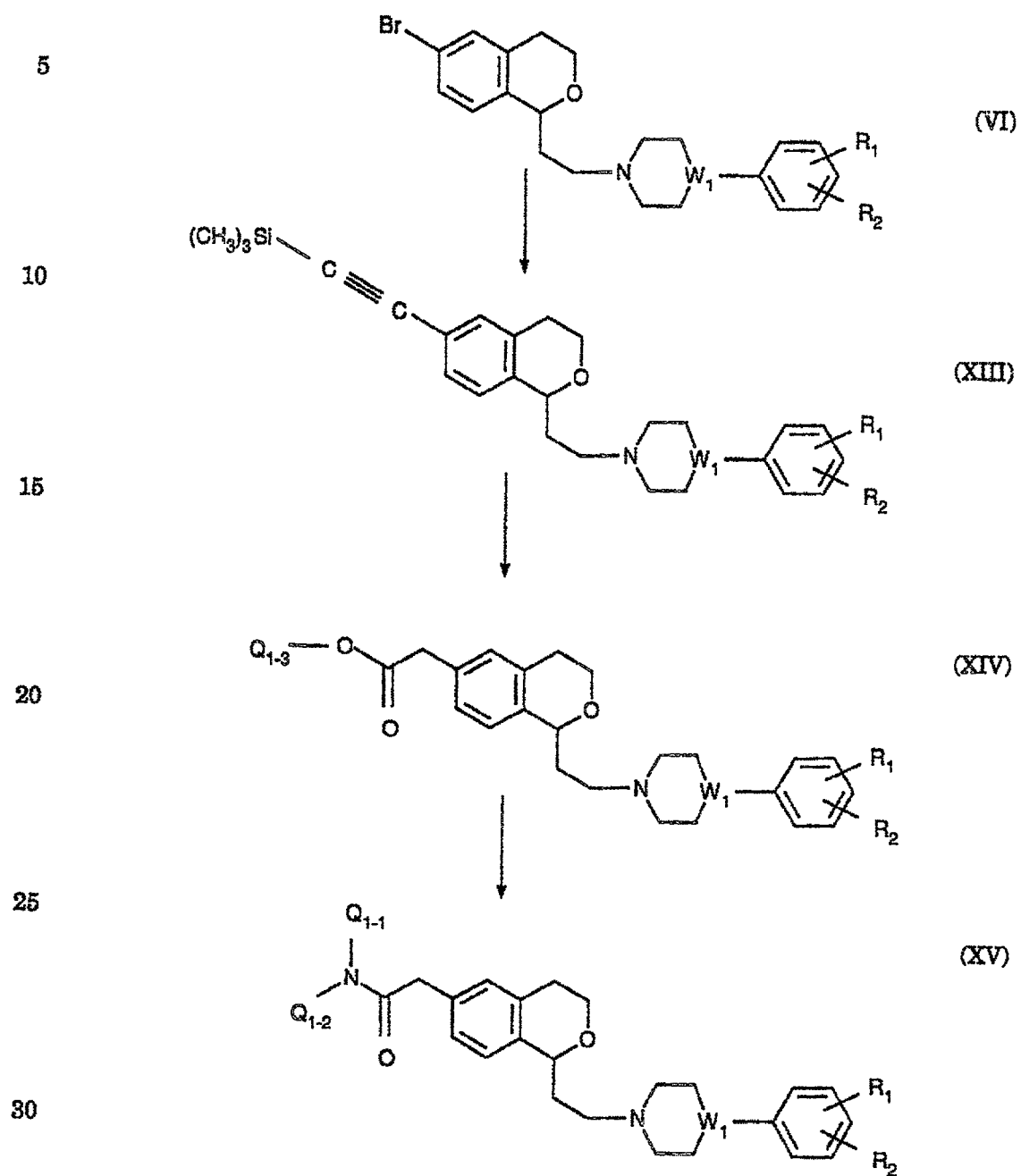


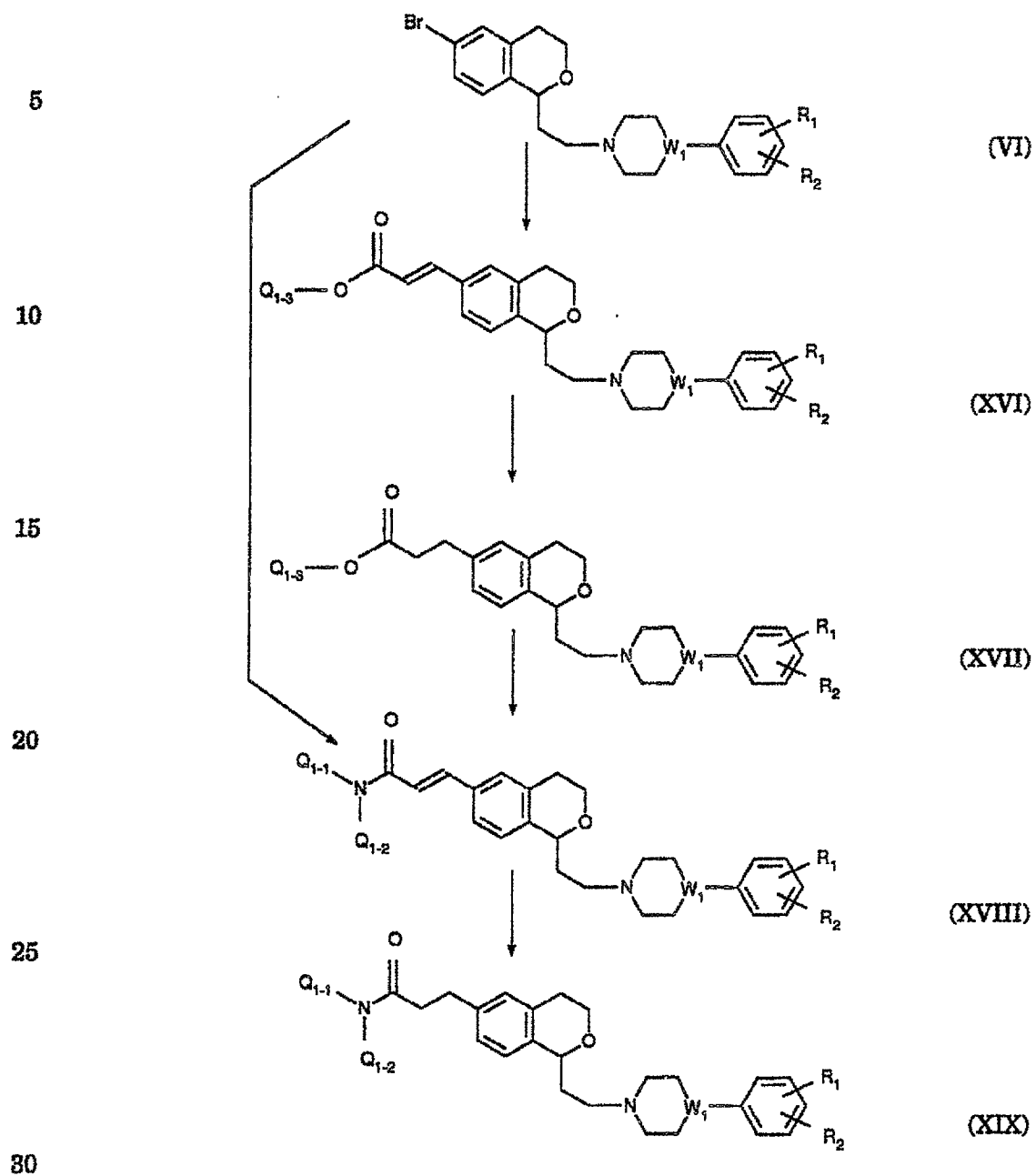
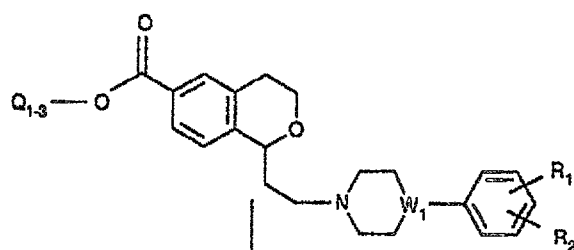
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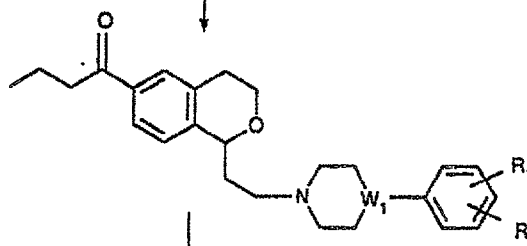
CHART F

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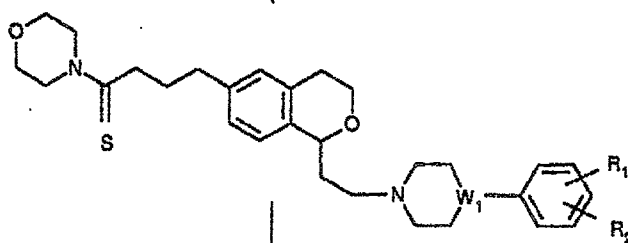
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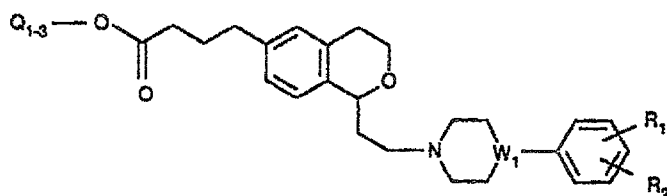
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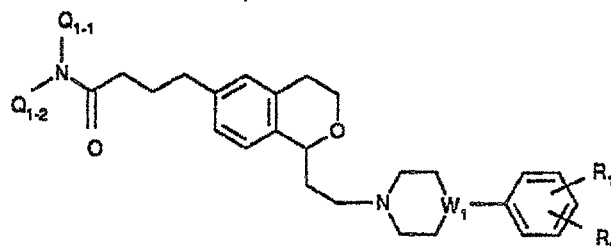
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(XXII)

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(XXIII)

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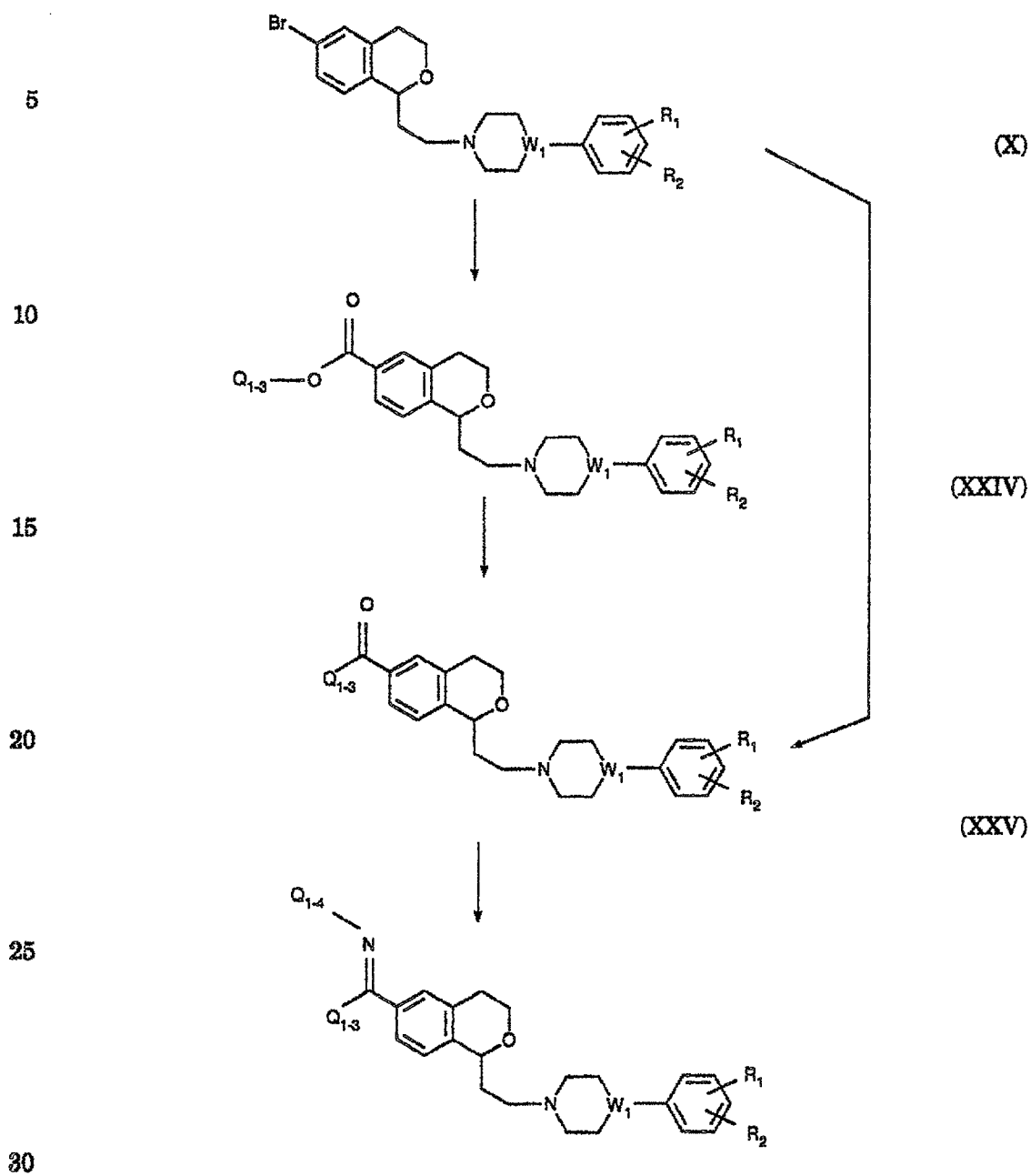
CHART G

CHART H

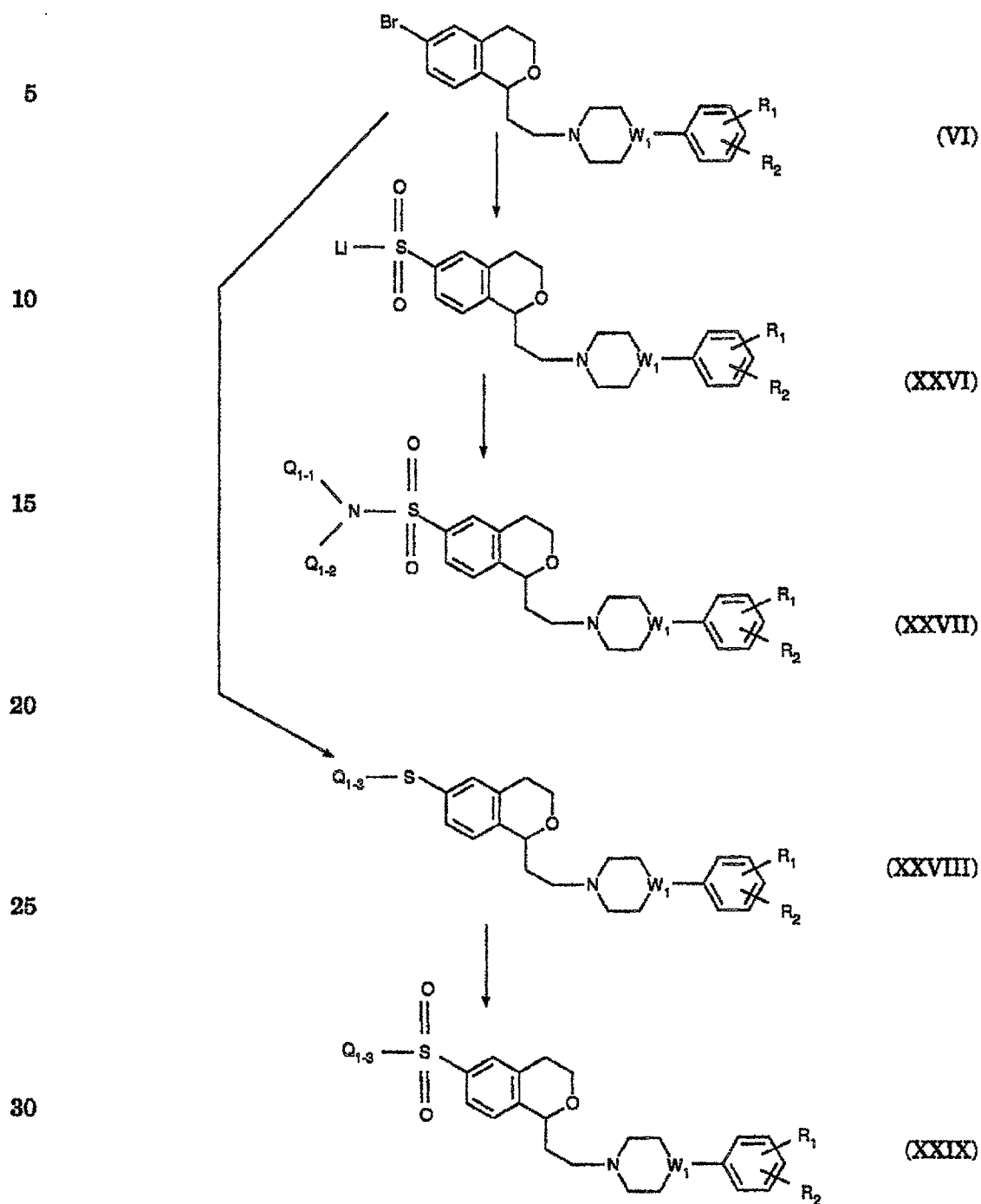


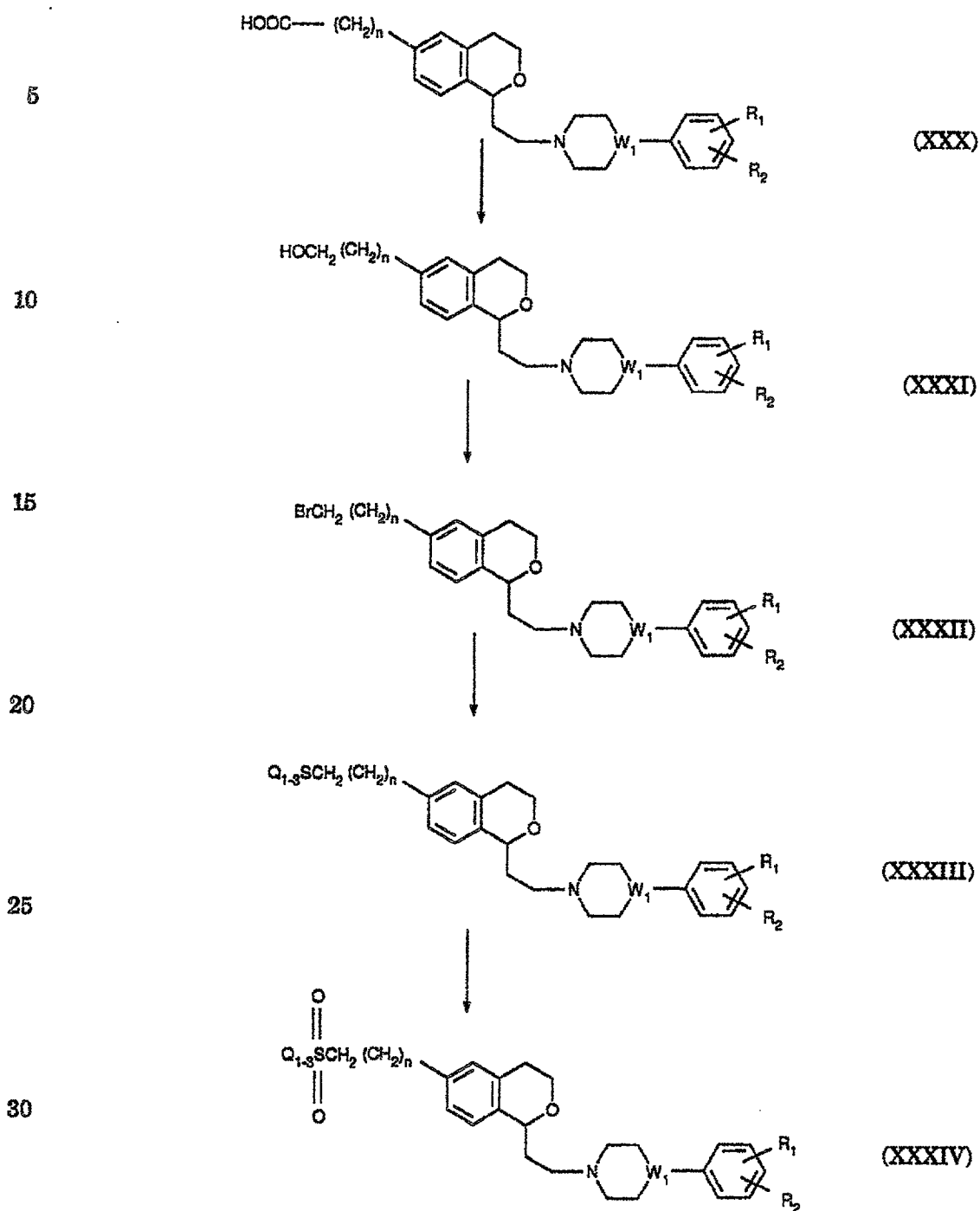
CHART I

CHART J

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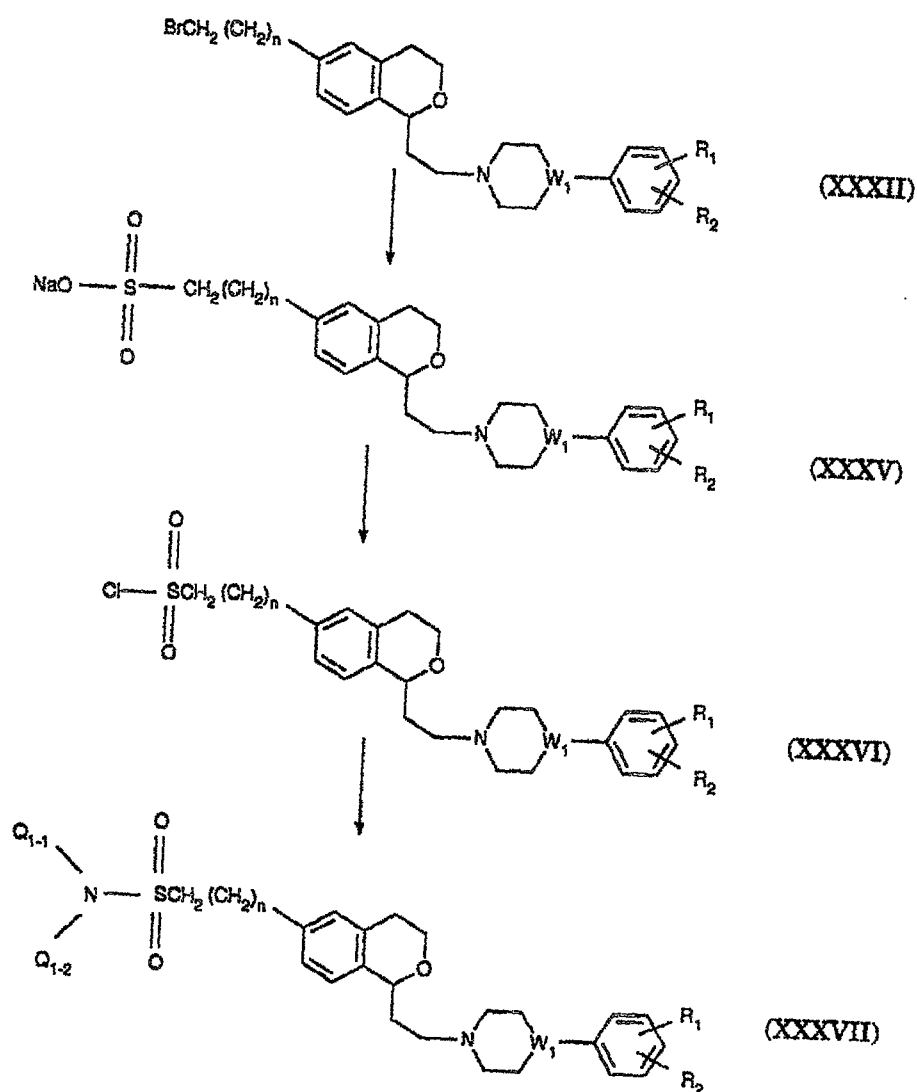
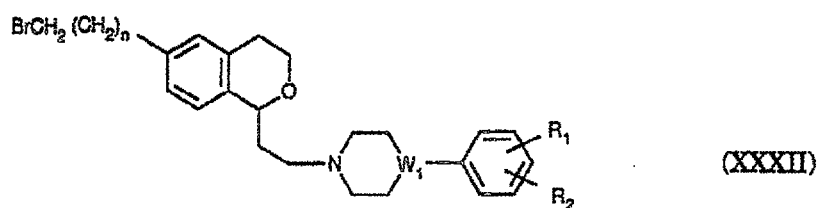
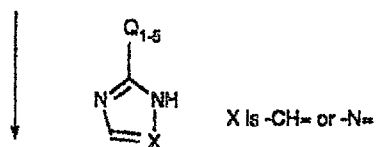


CHART K

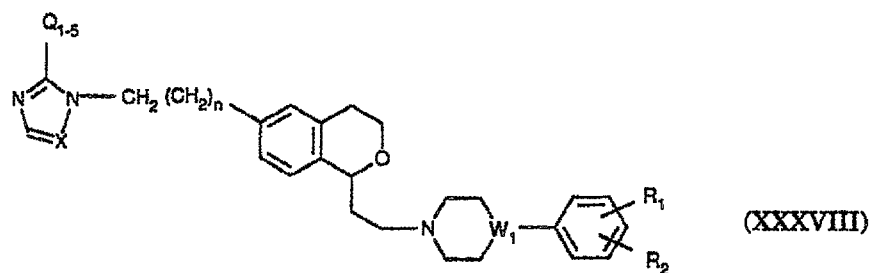
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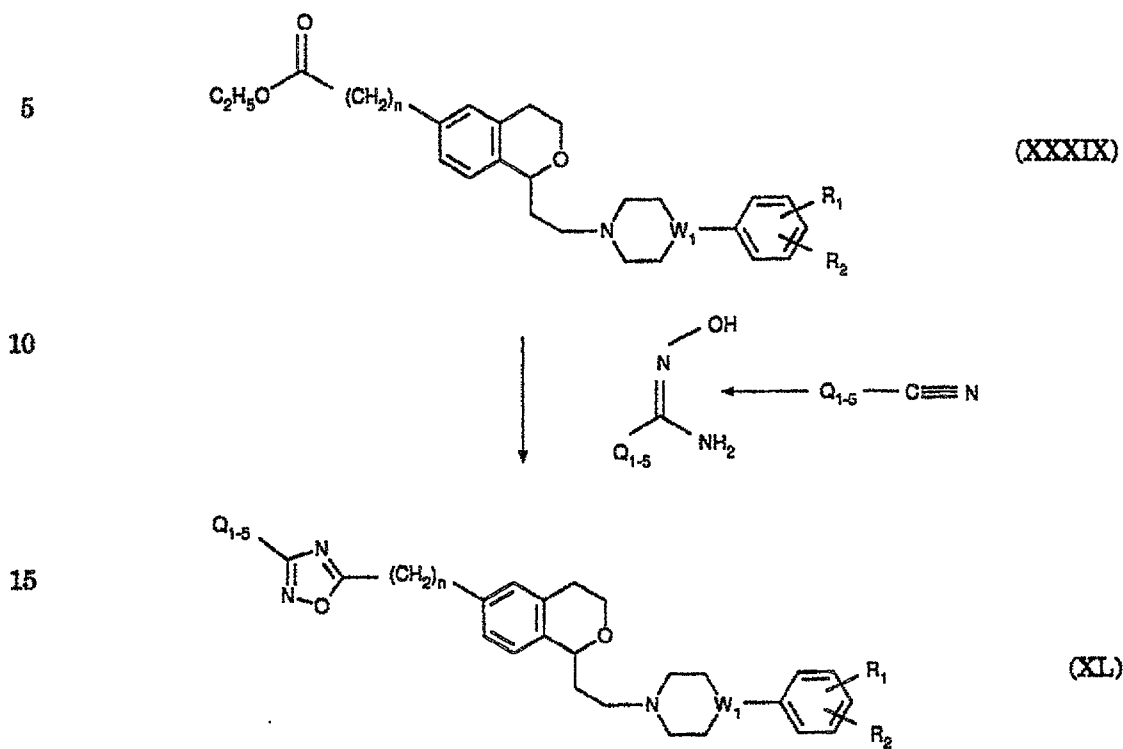
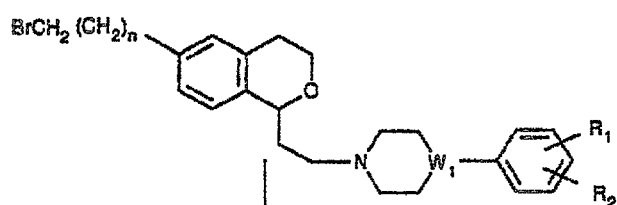
CHART L

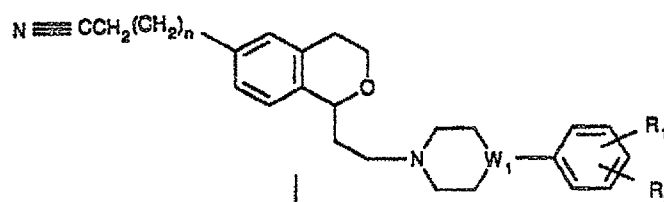
CHART M

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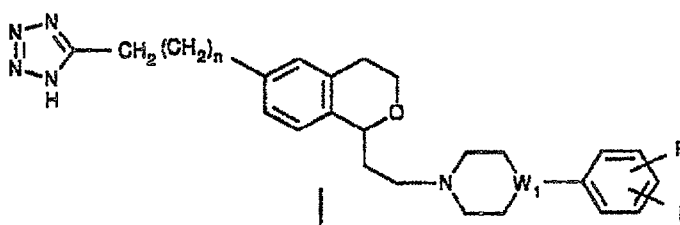
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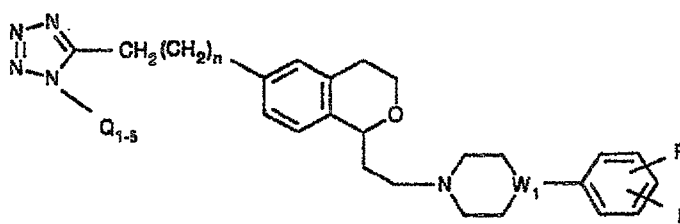
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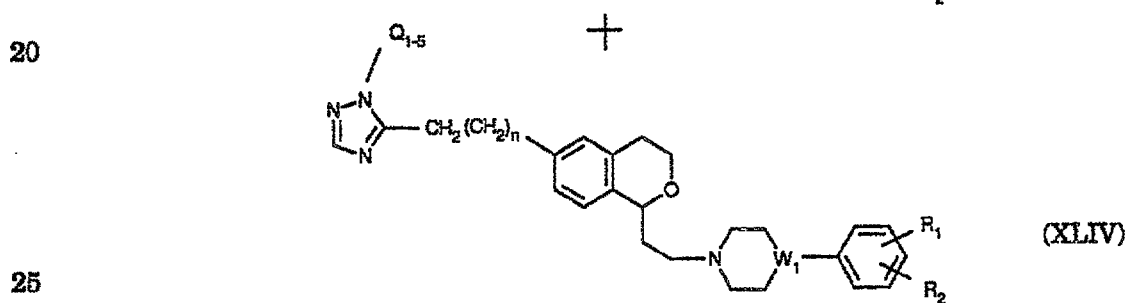
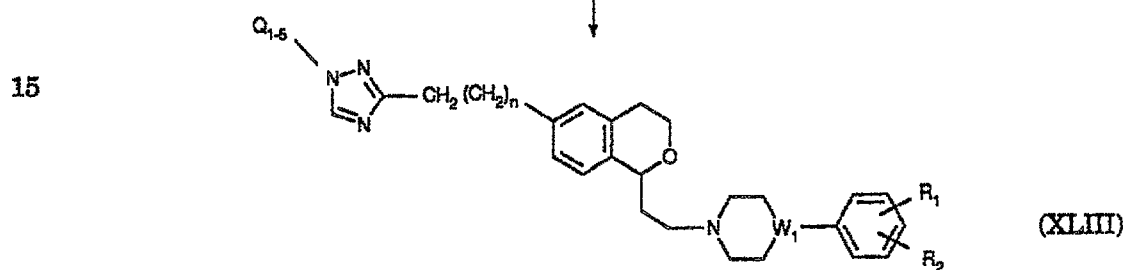
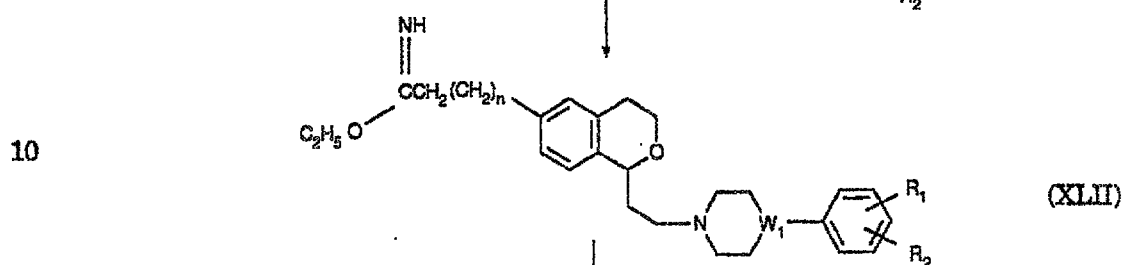
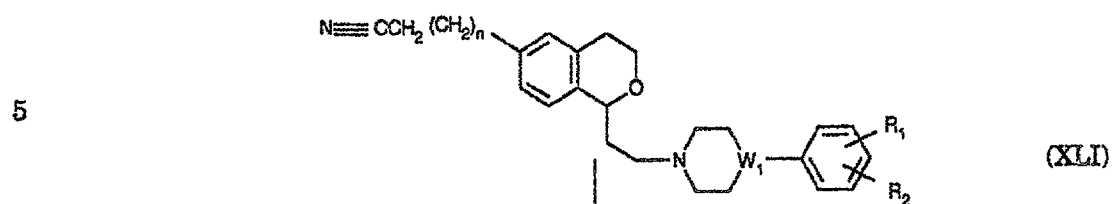
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CHART N

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CHART O

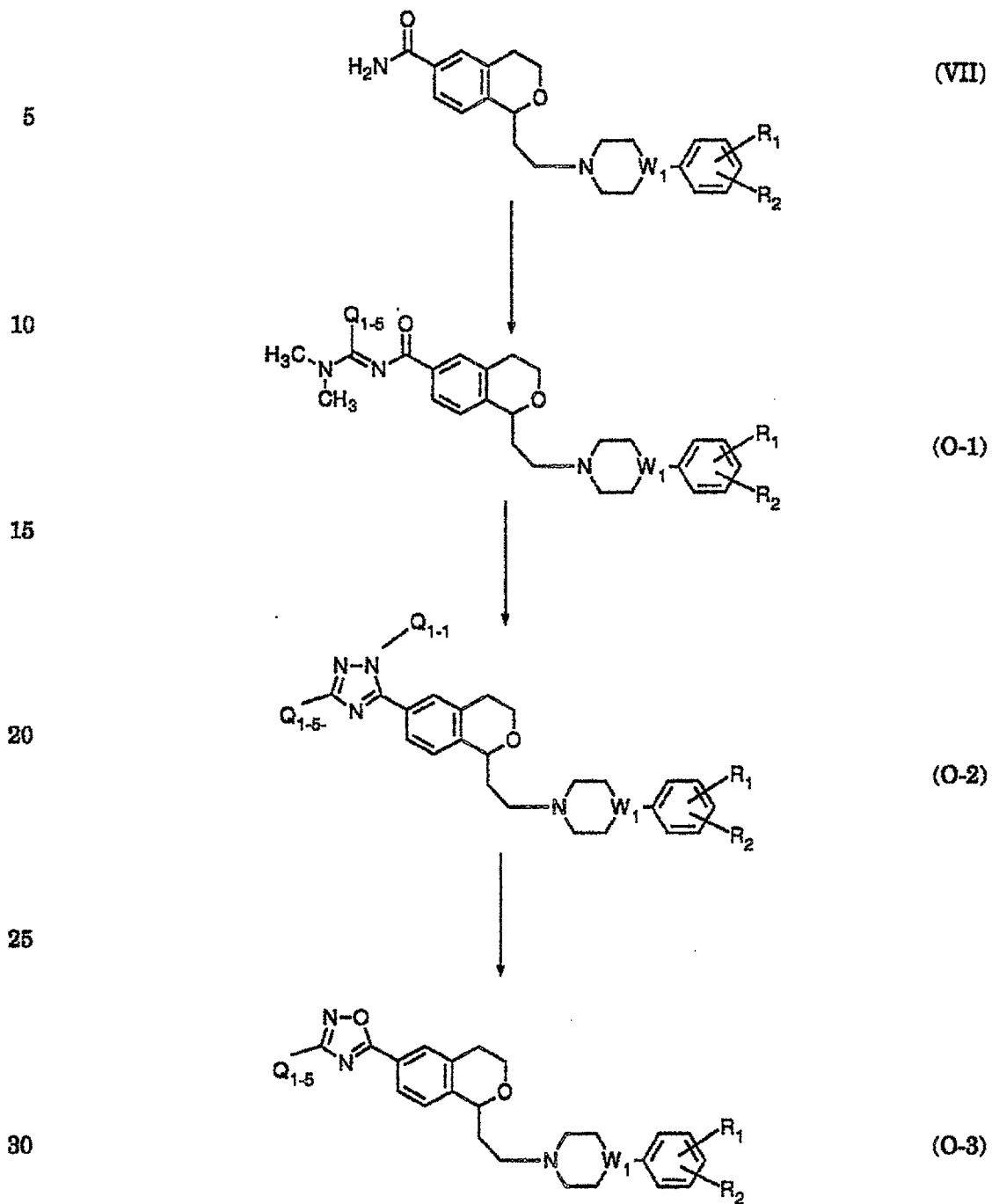
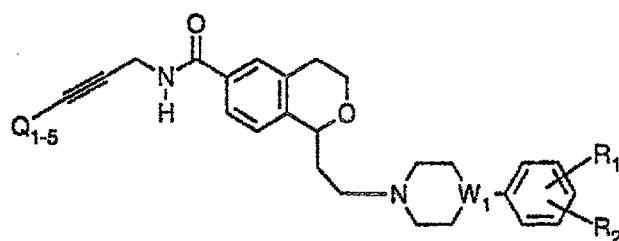


CHART P

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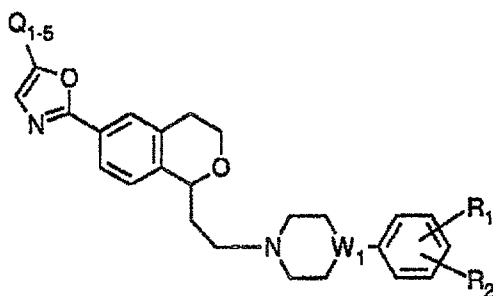


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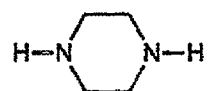


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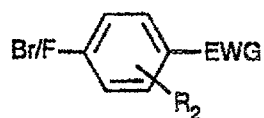
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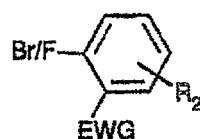
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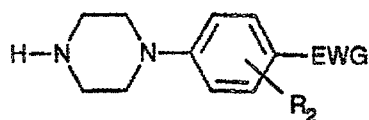
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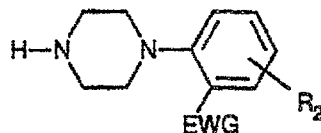
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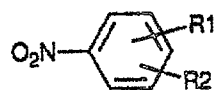
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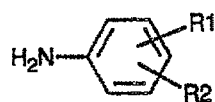
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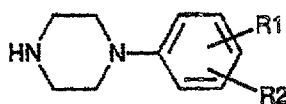
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CHART B

(R-1)



(R-2)



(R-3)

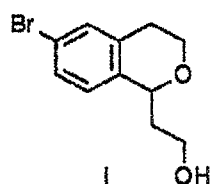
20

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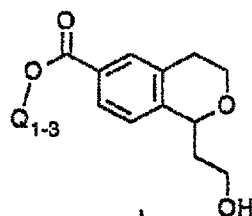
CHART S

5



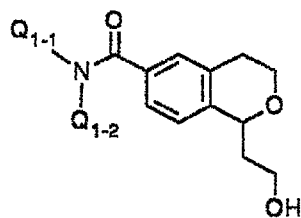
(S-1)

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(S-2)



20

(S-3)

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CHART T

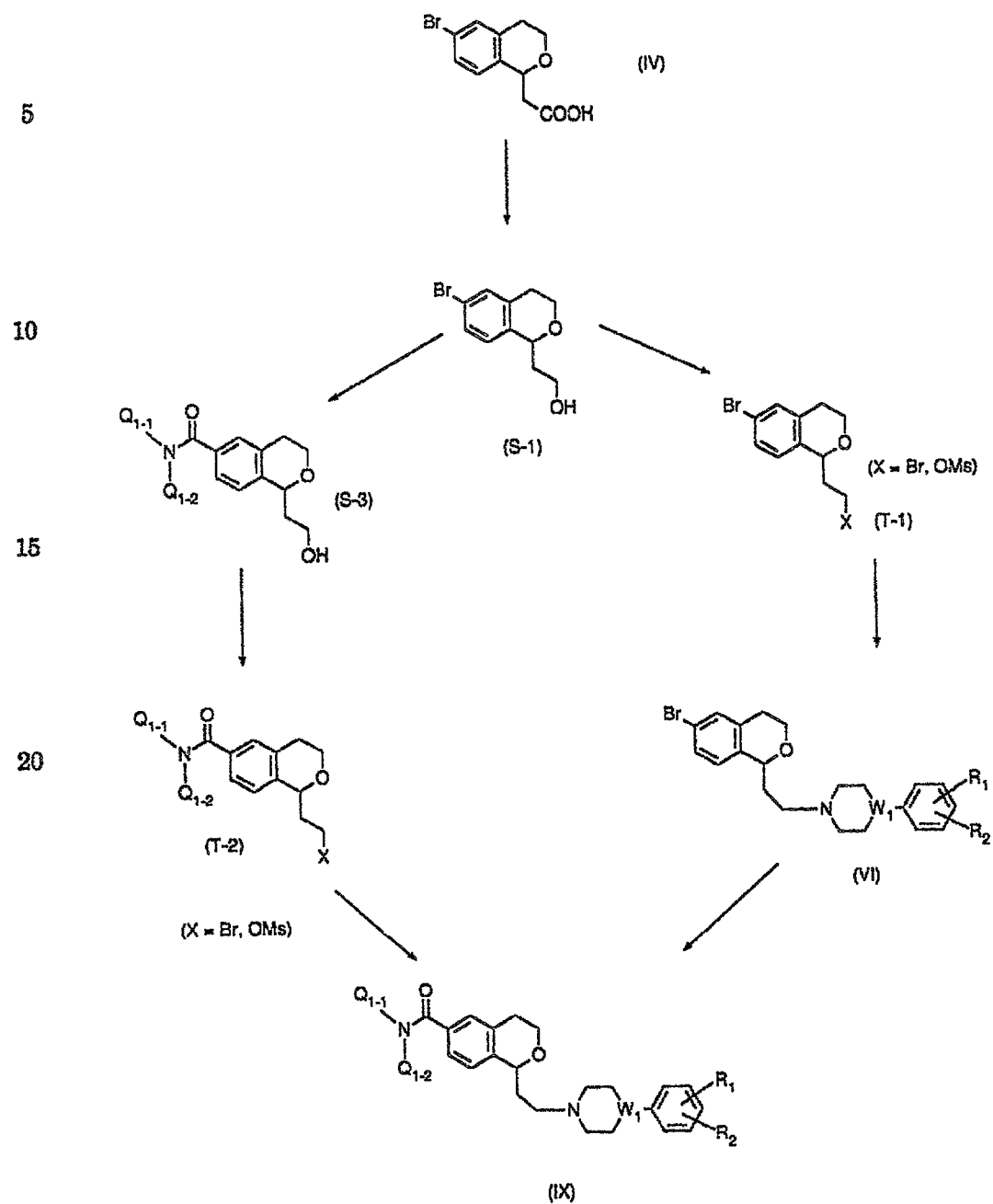


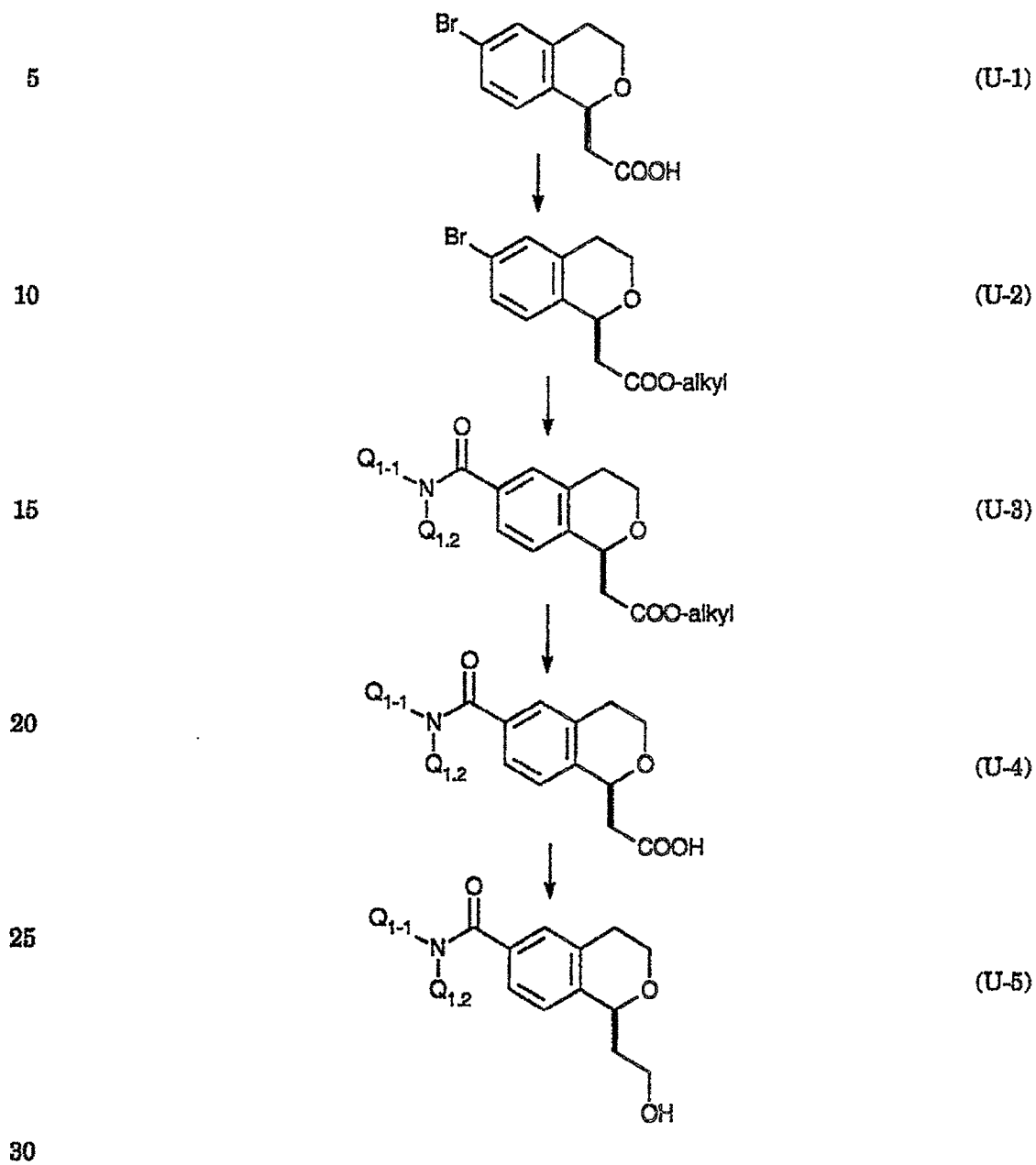
CHART U

CHART V

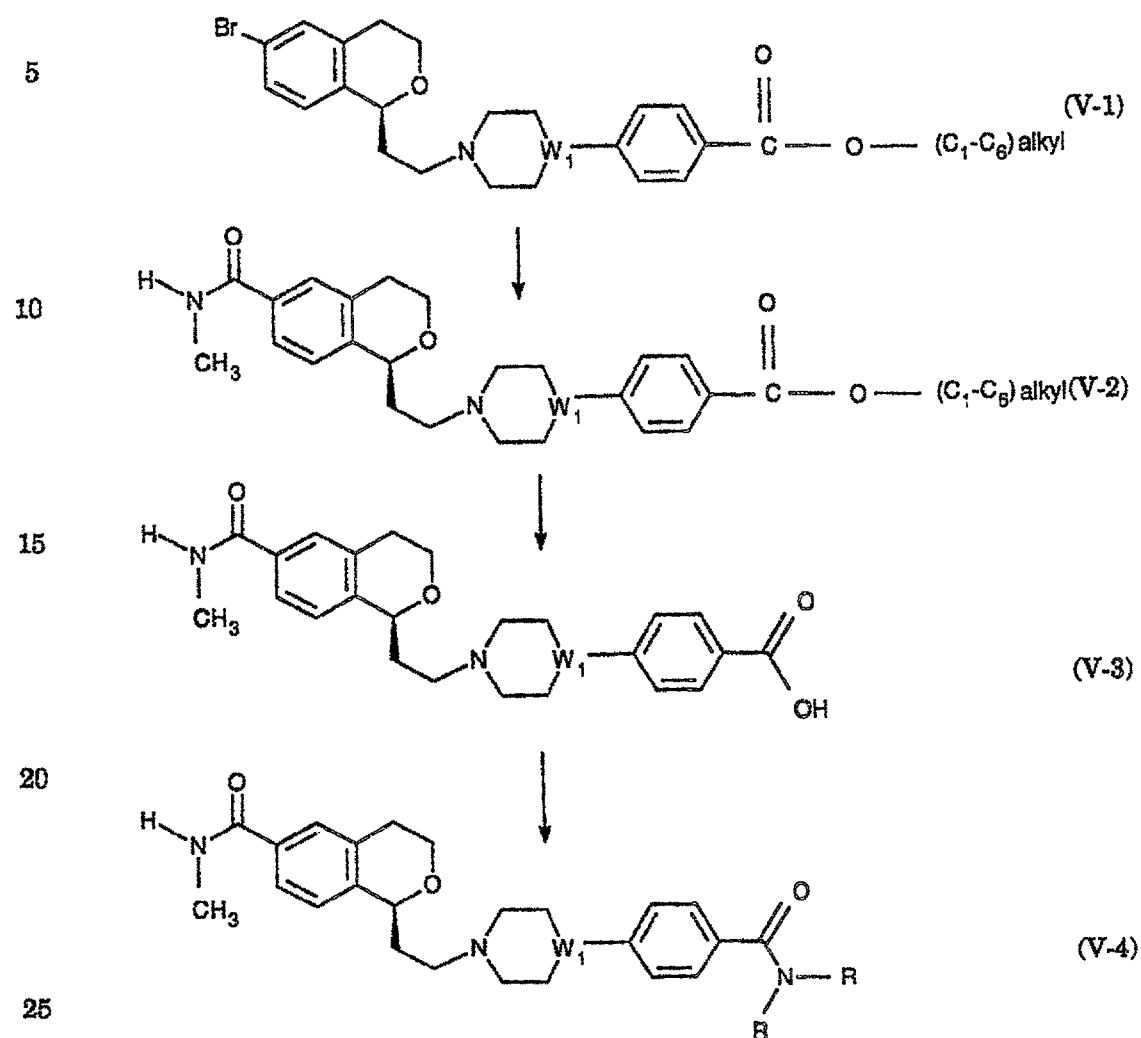
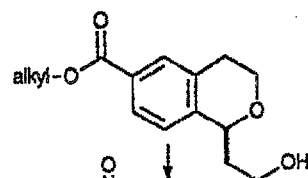
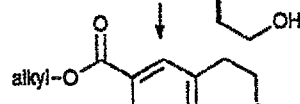
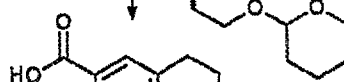


CHART W

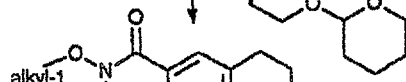
(W-1)



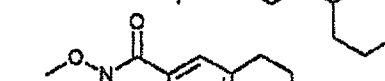
(W-2)



(W-3)



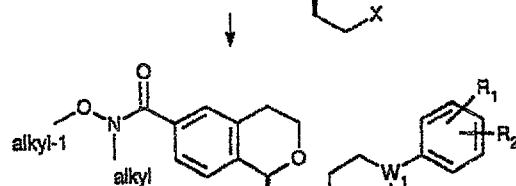
(W-4)



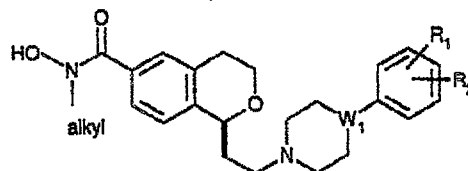
(W-5)



(W-6)



(W-7)



(W-8)

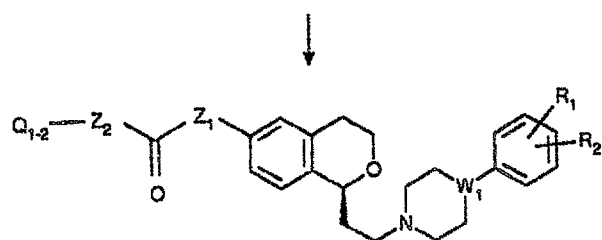
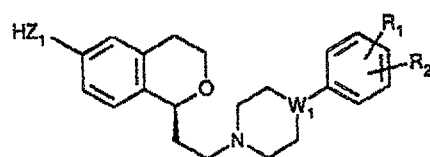
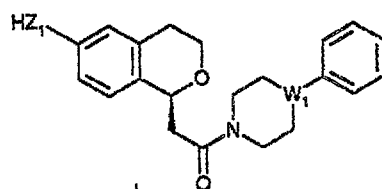
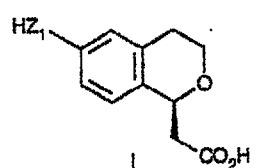
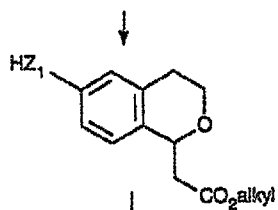
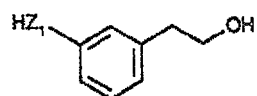
CHART X

CHART Z

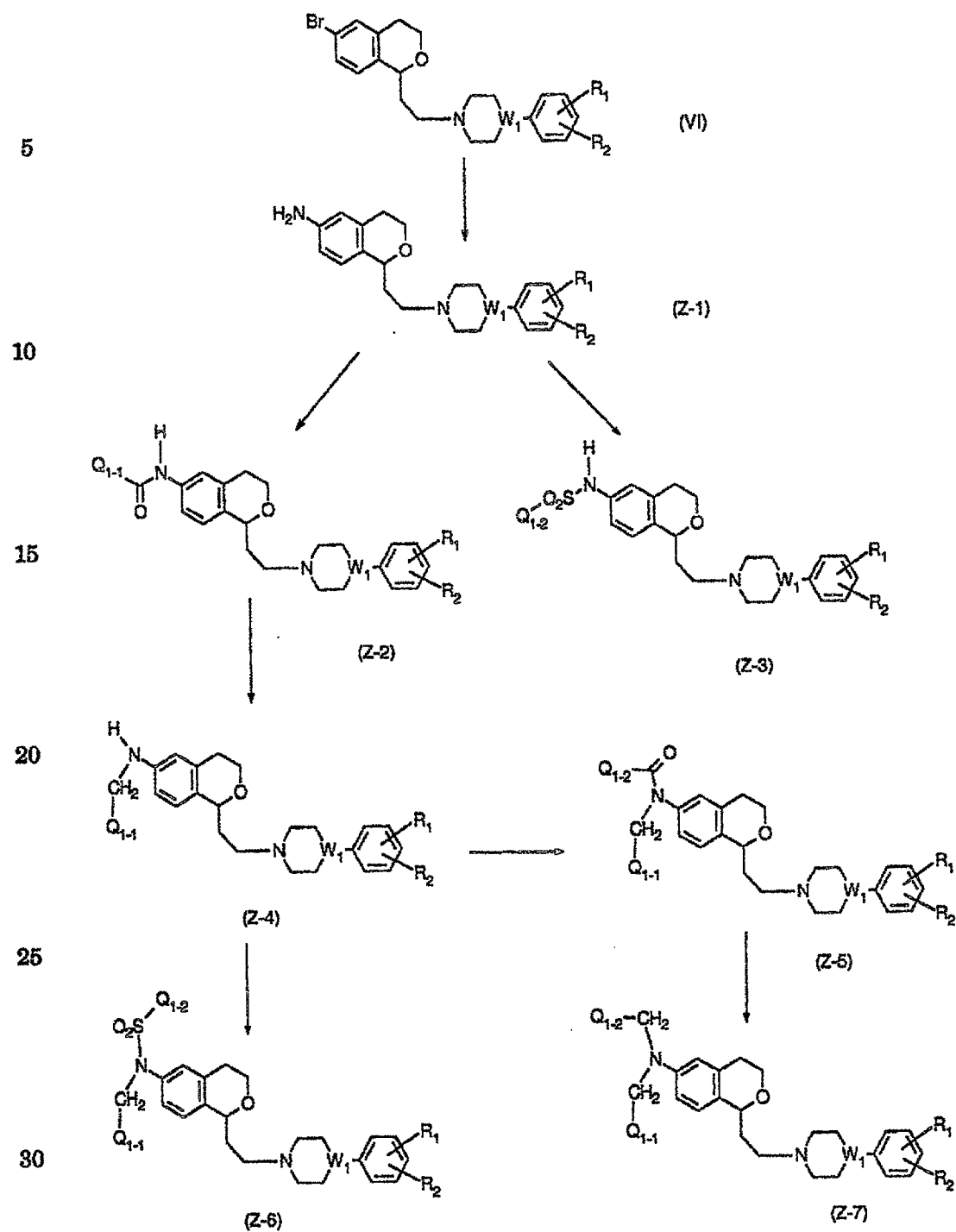
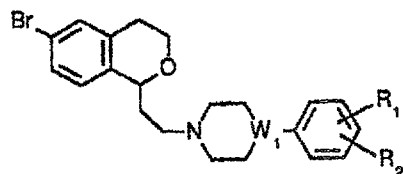
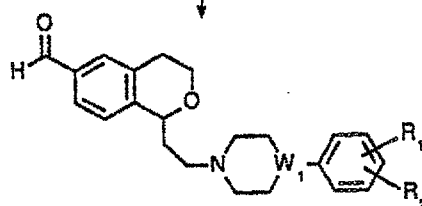
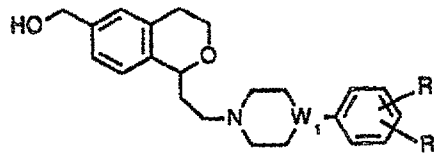


CHART AA

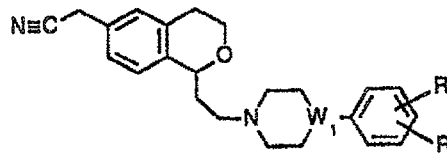
(vi)



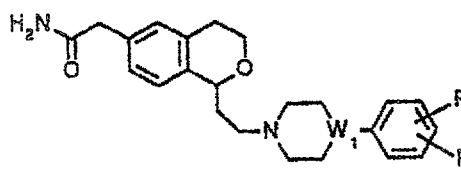
(AA-1)



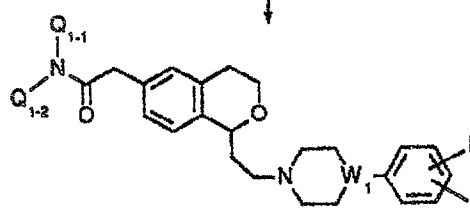
(AA-2)



(AA-3)



(AA-4)



(AA-5)

CHART BB

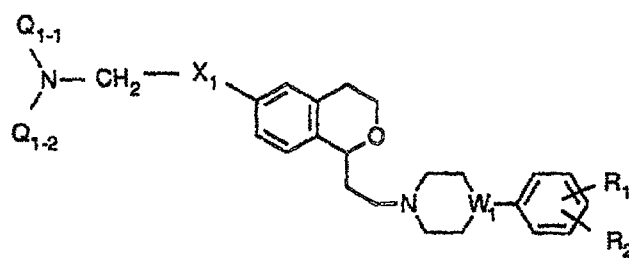
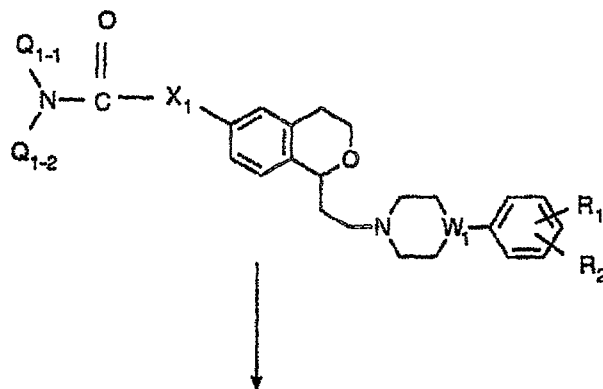


CHART CC

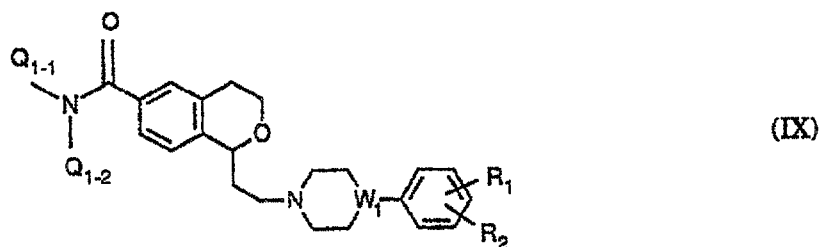
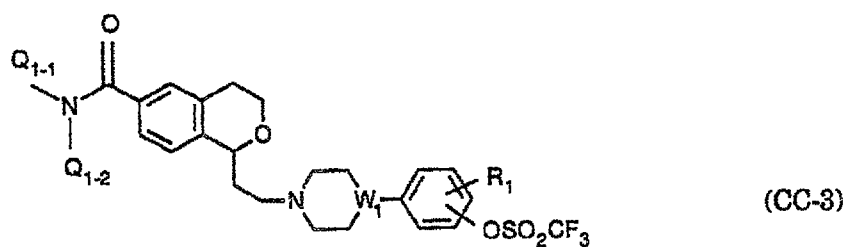
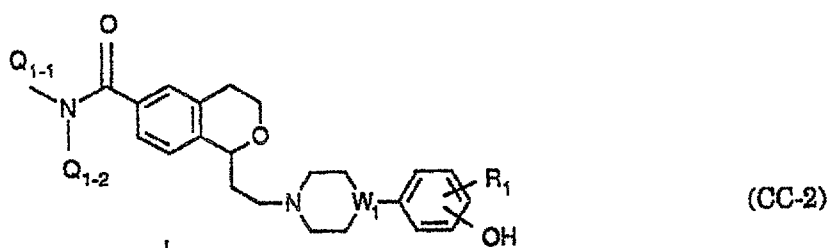
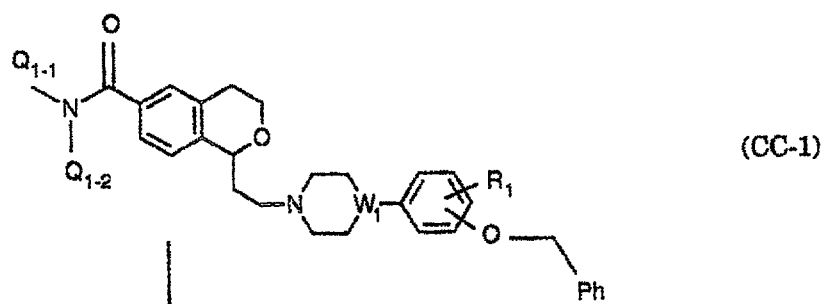
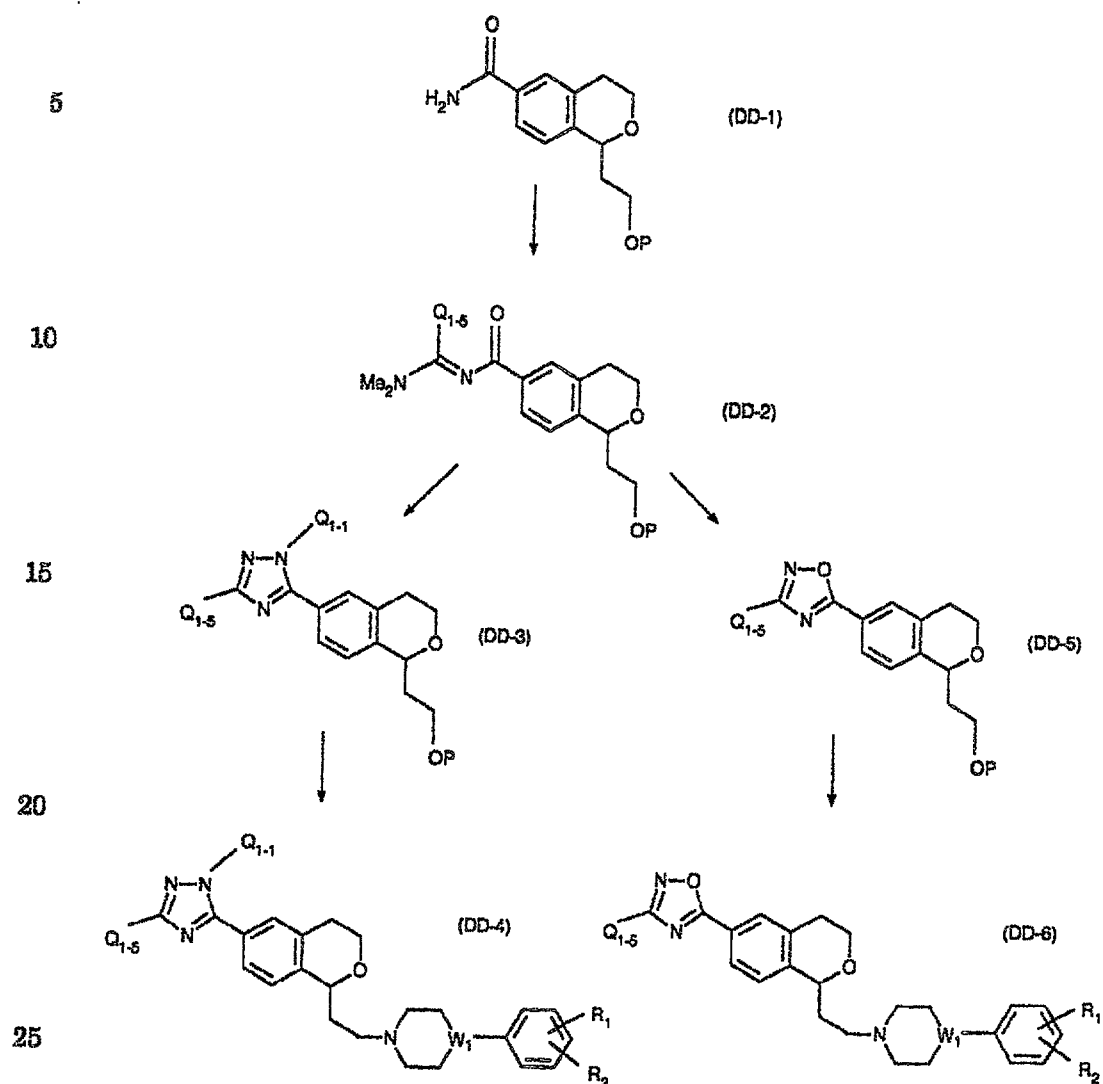


CHART DD

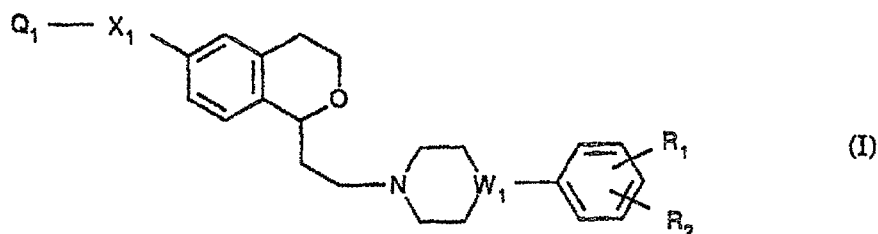


CLAIMS

1. A 1,6-disubstituted isochroman of formula (I)

5

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where:

- (I) W_1 is a nitrogen (-N-) or carbon (-CH-) atom;
- (II) X_1 is:
- (A) $-(CH_2)_{n_1}-$ where n_1 is 0 thru 3,
- (B) $-CH=CH-$;
- (III) R_1 is:
- (A) -H,
- (B) -F, -Cl, -Br, -I,
- (C) C_1-C_8 alkyl,
- (D) C_2-C_8 alkenyl containing 1 thru 3 double bonds ($=$),
- (E) C_2-C_8 alkynyl containing 1 or 2 triple bonds ($\equiv$),
- (F) C_3-C_8 cycloalkyl,
- (G) $-C_1-C_3$ alkyl- C_3-C_8 cycloalkyl,
- (H) $-NO_2$,
- (I) $-C\equiv N$,
- (J) $-CF_3$,
- (K) $-O-R_{1-1}$ where R_{1-1} is:
- (1) -H,
- (2) C_1-C_8 alkyl,
- (3) C_2-C_8 alkenyl containing 1 thru 3 double bonds ($=$),
- (4) C_2-C_8 alkynyl containing 1 or 2 triple bonds ($\equiv$),
- (5) C_3-C_8 cycloalkyl,
- (6) $-C_1-C_3$ alkyl- C_3-C_8 cycloalkyl,



(7) $-\text{CF}_3$,(8) $-\text{SO}_2-\text{CF}_3$,(9) $-(\text{CH}_2)_{n_2}-\phi$ where n_2 is 0 thru 4 and where $-\phi$ is optionally substituted with one or two:5 (a) $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$,(b) $-\text{C}\equiv\text{N}$,(c) $-\text{CF}_3$,(d) C_1-C_3 alkyl,(e) $-\text{O}-\text{R}_{1-1A}$ where R_{1-1A} is $-\text{H}$, C_1-C_6 alkyl, $-\text{CF}_3$ or10 $-\text{CH}_2-\phi$,(f) $-\text{NR}_{1-1A}\text{R}_{1-1B}$ where the R_{1-1A} and R_{1-1B} are the same or different and where R_{1-1B} is $-\text{H}$, C_1-C_6 alkyl, $-\text{CF}_3$ or $-\text{CH}_2-\phi$, and where R_{1-1A} is as defined above,15 (g) $-\text{CO}-\text{NR}_{1-1A}\text{R}_{1-1B}$ where R_{1-1A} and R_{1-1B} are as defined above,(h) $-\text{SO}_2-\text{NR}_{1-1A}\text{R}_{1-1B}$ where R_{1-1A} and R_{1-1B} are as defined above,(i) $-\text{NR}_{1-1A}-\text{SO}_2-\text{R}_{1-1B}$ where R_{1-1A} and R_{1-1B} are as defined above,20 (j) $-\text{NO}_2$,(k) $-\text{O}-\text{SO}_2-\text{CF}_3$,(L) $-\text{N}(\text{R}_{1-1})_2$ where the R_{1-1} can be the same or different and are as defined above,25 (M) $-\text{CO}-\text{N}(\text{R}_{1-1})_2$ where the R_{1-1} are the same or different and are as defined above,(N) $-\text{SO}_2-\text{R}_{1-3}$ where R_{1-3} is:(1) $-\text{H}$,(2) $-\text{CF}_3$,(3) C_1-C_8 alkyl,30 (4) C_2-C_8 alkenyl containing 1 thru 3 double bonds ($=$),(5) C_2-C_8 alkynyl containing 1 or 2 triple bonds ($\equiv$),(6) C_3-C_8 cycloalkyl,(7) $-\text{C}_1-\text{C}_3$ alkyl- C_3-C_8 cycloalkyl,35 (8) $-(\text{CH}_2)_{n_2}-\phi$ where n_2 is as defined above and $-\phi$ is optionally substituted with one or two:

- (a) -F, -Cl, -Br, -I,
 (b) -C≡N,
 (c) -CF₃,
 (d) C₁-C₆ alkyl,
 5 (e) -O-R_{1-3A} where R_{1-3A} is -H, C₁-C₆ alkyl, -CF₃ or -CH₂-φ,
 (f) -NR_{1-3A}R_{1-3B} where the R_{1-3A} and R_{1-3B} are the same or different and where R_{1-3B} is -H, C₁-C₆ alkyl, -CF₃ or -CH₂-φ, and where R_{1-3A} is as defined above,
 10 (g) -CO-NR_{1-3A}R_{1-3B} where R_{1-3A} and R_{1-3B} are as defined above,
 (h) -SO₂-NR_{1-3A}R_{1-3B} where R_{1-3A} and R_{1-3B} are as defined above,
 (i) -NR_{1-3A}-SO₂-R_{1-3B} where R_{1-3A} and R_{1-3B} are as
 15 defined above,
 (j) -NO₂,
 (k) -O-SO₂-CF₃,
 (9) -O-R_{1-3A} where R_{1-3A} is as defined above,
 (10) -NR_{1-3A}R_{1-3B} where R_{1-3A} and R_{1-3B} are as defined above,
 20 (O) -NR₁₋₁-SO₂-R₁₋₃ where R₁₋₁ and R₁₋₃ may be the same or different and are as defined above,
 (P) -(CH₂)_{n₂}-φ where n₂ is as defined above and where -φ is optionally substituted with one or two:
 (1) -F, -Cl, -Br, -I,
 25 (2) -C≡N,
 (3) -CF₃,
 (4) C₁-C₆ alkyl,
 (5) -O-R₁₋₁ where R₁₋₁ is as defined above,
 (6) -N(R₁₋₁)₂ where the R₁₋₁s are the same or different and are
 30 as defined above,
 (7) -CO-N(R₁₋₁)₂ where the R₁₋₁s are the same or different and are as defined above,
 (8) -SO₂-N(R₁₋₁)₂ where the R₁₋₁s are the same or different and are as defined above,
 35 (9) -NR₁₋₁-SO₂-R₁₋₁ where the R₁₋₁s are the same or different



and are as defined above,

(10) $-\text{NO}_2$,

(11) $-\text{O}-\text{SO}_2-\text{CF}_3$;

(Q) $-\text{CO}-\text{R}_{1-1}$ where R_{1-1} is as defined above,

5 (R) $-\text{CO}-\text{O}-\text{Q}_{1-2}$ where Q_{1-2} is defined below;

(IV) R_2 is defined the same as R_1 , R_2 can be the same or different than R_1 ;

(V) Q_1 is:

(A) $-\text{CO}-\text{NQ}_{1-1}\text{Q}_{1-2}$ where Q_{1-1} is:

(1) $-\text{H}$,

10 (2) C_1-C_8 alkyl,

(3) C_2-C_8 alkenyl containing 1 thru 3 double bonds (=),

(4) C_2-C_8 alkynyl containing 1 or 2 triple bonds ($\equiv$),

(5) C_3-C_8 cycloalkyl,

(6) $-\text{C}_1-\text{C}_3$ alkyl- C_3-C_8 cycloalkyl,

15 (7) $-\text{CF}_3$,

(8) $-\text{SO}_2-\text{CF}_3$,

(9) $-(\text{CH}_2)_{n7}-\phi$ where n_7 is 0 thru 4 and where ϕ is optionally substituted with one or two:

(a) $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$,

20 (b) $-\text{C}\equiv\text{N}$,

(c) $-\text{CF}_3$,

(d) C_1-C_3 alkyl,

(e) $-\text{O}-\text{Q}_{1-1\text{A}}$ where $\text{Q}_{1-1\text{A}}$ is $-\text{H}$, C_1-C_6 alkyl, $-\text{CF}_3$ or

$-\text{CH}_2-\phi$,

25 (f) $-\text{NQ}_{1-1\text{A}}\text{Q}_{1-1\text{B}}$ where the $\text{Q}_{1-1\text{A}}$ and $\text{Q}_{1-1\text{B}}$ are the same or different and where $\text{Q}_{1-1\text{B}}$ is $-\text{H}$, C_1-C_6 alkyl, $-\text{CF}_3$ or $-\text{CH}_2-\phi$, and where $\text{Q}_{1-1\text{A}}$ is as defined above,

(g) $-\text{CO}-\text{NQ}_{1-1\text{A}}\text{Q}_{1-1\text{B}}$ where $\text{Q}_{1-1\text{A}}$ and $\text{Q}_{1-1\text{B}}$ are as defined above,

30 (h) $-\text{SO}_2-\text{NQ}_{1-1\text{A}}\text{Q}_{1-1\text{B}}$ where $\text{Q}_{1-1\text{A}}$ and $\text{Q}_{1-1\text{B}}$ are as defined above,

(i) $-\text{NQ}_{1-1\text{A}}-\text{SO}_2-\text{Q}_{1-1\text{B}}$ where $\text{Q}_{1-1\text{A}}$ and $\text{Q}_{1-1\text{B}}$ are as defined above,

(j) $-\text{NO}_2$,

35 (k) $-\text{O}-\text{SO}_2-\text{CF}_3$, and where Q_{1-2} is:



- (1) -H,
 (2) C₁-C₈ alkyl,
 (3) C₂-C₈ alkenyl containing 1 thru 3 double bonds (=),
 (4) C₂-C₈ alkynyl containing 1 or 2 triple bonds (≡),
 5 (5) C₃-C₈ cycloalkyl,
 (6) -C₁-C₃ alkyl-C₃-C₈ cycloalkyl,
 (7) -CF₃,
 (8) -(CH₂)_{n2}-φ where n₂ is as defined above and -φ is optionally
 substituted with one or two:
- 10 (a) -F, -Cl, -Br, -I,
 (b) -C≡N,
 (c) -CF₃,
 (d) C₁-C₆ alkyl,
 (e) -O-Q_{1-2A} where Q_{1-2A} is:
- 15 (i) -H,
 (ii) C₁-C₆ alkyl,
 (iii) -CF₃,
 (iv) -(CH₂)_{n9}-Q_{1-2B}(CH₂)_{n10}-Q_{1-2C} where n₉ and n₁₀ are the
 20 same or different and are 0 thru 4, where Q_{1-2B} is -O- or -NQ_{1-2D}, where Q_{1-2D} is:
- (a) -H,
 (b) C₁-C₈ alkyl,
 (c) C₂-C₈ alkenyl containing 1 thru 3 double bonds,
 (d) C₂-C₈ alkynyl containing 1 or 2 triple bonds,
 25 (e) C₃-C₈ cycloalkyl,
 (f) -C₁-C₃ alkyl-C₃-C₈ cycloalkyl,
 (g) -CF₃,
 (h) -(CH₂)_{n11}-φ where n₁₁ is 0 thru 4 and -φ is optionally
 substituted with one or two:
- 30 (i) -F, -Cl, -Br, -I,
 (ii) -C≡N,
 (iii) -CF₃,
 (iv) C₁-C₃ alkyl,
 (v) -O-Q_{1-2E} where Q_{1-2E} is -H, C₁-C₆ alkyl, -CF₃
 35 or -CH₂-φ,



(vi) $-NQ_{1-2E}Q_{1-2F}$ where the Q_{1-2E} and Q_{1-2F} are the same or different and where Q_{1-2F} is $-H$, C_1-C_6 alkyl, $-CF_3$ or $-CH_2-\phi$, and where Q_{1-2E} is as defined above,

5 (vii) $-CO-NQ_{1-2E}Q_{1-2F}$ where Q_{1-2E} and Q_{1-2F} are as defined above,

(viii) $-SO_2-NQ_{1-2E}Q_{1-2F}$ where Q_{1-2E} and Q_{1-2F} are as defined above,

(ix) $-NQ_{1-2E}-SO_2-Q_{1-2F}$ where Q_{1-2E} and Q_{1-2F} are as defined above,

10 (x) $-NO_2$,

(xi) $-O-SO_2-CF_3$, and where Q_{1-2C} is defined the same as Q_{1-2D} and the Q_{1-2C} and Q_{1-2D} can be the same or different, and where Q_{1-1} and Q_{1-2} are taken together with the attached nitrogen atom to form a 5 or 6 member ring which can include one additional nitrogen or oxygen atom;

(B) $-SO_2-NQ_{1-1}Q_{1-2}$ where Q_{1-1} and Q_{1-2} are as defined above,

(C) $-CO-O-Q_{1-3}$ where Q_{1-3} is:

- (1) $-H$,
- (2) $-CF_3$,
- 20 (3) C_1-C_8 alkyl,
- (4) C_2-C_8 alkenyl containing 1 thru 3 double bonds (=),
- (5) C_2-C_8 alkynyl containing 1 or 2 triple bonds ($\equiv$),
- (6) C_3-C_8 cycloalkyl,
- (7) $-C_1-C_3$ alkyl- C_3-C_8 cycloalkyl,
- 25 (8) $-(CH_2)_{n-7}-\phi$ where n_7 is as defined above and $-\phi$ is optionally substituted with one or two:

- (a) $-F$, $-Cl$, $-Br$, $-I$,
- (b) $-C\equiv N$,
- (c) $-CF_3$,
- 30 (d) C_1-C_3 alkyl,
- (e) $-O-Q_{1-3A}$ where Q_{1-3A} is $-H$, C_1-C_6 alkyl, $-CF_3$ or $-CH_2-\phi$,

(f) $-NQ_{1-3A}Q_{1-3B}$ where the Q_{1-3A} and Q_{1-3B} are the same or different and where Q_{1-3B} is $-H$, C_1-C_6 alkyl, $-CF_3$ or $-CH_2-\phi$, and where Q_{1-3A} is as defined above,



(g) $-\text{CO}-\text{NQ}_{1-3\text{A}}\text{Q}_{1-3\text{B}}$ where $\text{Q}_{1-3\text{A}}$ and $\text{Q}_{1-3\text{B}}$ are as defined above,

(h) $-\text{SO}_2-\text{NQ}_{1-3\text{A}}\text{Q}_{1-3\text{B}}$ where $\text{Q}_{1-3\text{A}}$ and $\text{Q}_{1-3\text{B}}$ are as defined above,

5 (i) $-\text{NQ}_{1-3\text{A}}-\text{SO}_2-\text{Q}_{1-3\text{B}}$ where $\text{Q}_{1-3\text{A}}$ and $\text{Q}_{1-3\text{B}}$ are as defined above,

(j) $-\text{NO}_2$,

(k) $-\text{O}-\text{SO}_2-\text{CF}_3$,

(D) $-\text{CO}-\text{Q}_{1-3}$ where Q_{1-3} is as defined above,

10 (E) $-\text{CO}-\text{imidazole}$,

(F) $-\text{NQ}_{1-1}\text{Q}_{1-2}$ where Q_{1-1} and Q_{1-2} are as defined above,

(F') $-\text{NQ}_{1-1}-\text{CO}-\text{Q}_{1-2}$ where Q_{1-1} and Q_{1-2} are as defined above,

(G) $-\text{C}(\text{Q}_{1-3})=\text{N}-\text{O}-\text{Q}_{1-4}$ where Q_{1-4} is defined the same as Q_{1-3} and Q_{1-3} is as defined above, the Q_{1-3} and Q_{1-4} can be the same or different,

15 (H) $-\text{SO}_2-\text{Q}_{1-3}$ where Q_{1-3} is as defined above,

(I) $-\text{N}(\text{Q}_{1-1})-\text{SO}_2-\text{Q}_{1-3}$ where Q_{1-1} and Q_{1-3} is as defined above,

(J) 5-oxadiazole optionally substituted with one Q_{1-5} where Q_{1-5} is:

(1) $-\text{H}$,

(2) $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$,

20 (3) C_1-C_8 alkyl,

(4) C_2-C_8 alkenyl containing 1 thru 3 double bonds (=),

(5) C_2-C_8 alkynyl containing 1 or 2 triple bonds ($\equiv$),

(6) C_3-C_8 cycloalkyl,

(7) $-\text{C}_1-\text{C}_3$ alkyl- C_3-C_8 cycloalkyl,

25 (8) $-\text{NO}_2$,

(9) $-\text{C}\equiv\text{N}$,

(10) $-\text{CF}_3$,

(11) $-\text{O}-\text{Q}_{1-5\text{A}}$ where $\text{Q}_{1-5\text{A}}$ is:

(a) $-\text{H}$,

30 (b) C_1-C_8 alkyl,

(c) C_2-C_8 alkenyl containing 1 thru 3 double bonds,

(d) C_2-C_8 alkynyl containing 1 or 2 triple bonds,

(e) C_3-C_8 cycloalkyl,

(f) $-\text{C}_1-\text{C}_3$ alkyl- C_3-C_8 cycloalkyl,

35 (g) $-\text{CF}_3$,



- (h) $-\text{SO}_2-\text{CF}_3$,
 (i) $-(\text{CH}_2)_{n7}-\phi$ where n_7 is 0 thru 4,
 (12) $-\text{NQ}_{1-5A}\text{Q}_{1-5D}$ where Q_{1-5A} is as defined above, Q_{1-5D} is:
 (a) $-\text{H}$,
 5 (b) C_1-C_8 alkyl,
 (c) C_2-C_8 alkenyl containing 1 thru 3 double bonds,
 (d) C_2-C_8 alkynyl containing 1 or 2 triple bonds ($\equiv$),
 (e) C_3-C_8 cycloalkyl,
 (f) $-\text{C}_1-\text{C}_3$ alkyl- C_3-C_8 cycloalkyl,
 10 (g) $-\text{CF}_3$,
 (h) $-(\text{CH}_2)_{n7}-\phi$ where n_7 is as defined above,
 (13) $-\text{CO}-\text{NQ}_{1-5A}\text{Q}_{1-5D}$ where Q_{1-5A} and Q_{1-5D} are as defined
 above,
 (14) $-\text{SO}_2-\text{Q}_{1-5K}$ where Q_{1-5K} is:
 15 (a) $-\text{H}$,
 (b) $-\text{CF}_3$,
 (c) C_1-C_8 alkyl,
 (d) C_2-C_8 alkenyl containing 1 thru 3 double bonds ($\equiv$),
 (e) C_2-C_8 alkynyl containing 1 or 2 triple bonds ($\equiv$),
 20 (f) C_3-C_8 cycloalkyl,
 (g) $-\text{C}_1-\text{C}_3$ alkyl- C_3-C_8 cycloalkyl,
 (h) $-(\text{CH}_2)_{n7}-\phi$ where n_7 is as defined above,
 (15) $-\text{NQ}_{1-5A}-\text{SO}_2-\text{Q}_{1-5K}$ where Q_{1-5A} and Q_{1-5K} may be the
 same or different and are as defined above,
 25 (16) $-(\text{CH}_2)_{n7}-\phi$ where n_7 is as defined above and where $-\phi$ is
 optionally substituted with one or two:
 (a) $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$,
 (b) $-\text{C}\equiv\text{N}$,
 (c) $-\text{CF}_3$,
 30 (d) C_1-C_6 alkyl,
 (e) $-\text{O}-\text{Q}_{1-5A}$ where Q_{1-5A} is as defined above,
 (f) $-\text{NQ}_{1-5A}\text{Q}_{1-5D}$ where Q_{1-5A} and Q_{1-5D} are as defined
 above,
 (g) $-\text{CO}-\text{NQ}_{1-5A}\text{Q}_{1-5D}$ where Q_{1-5A} and Q_{1-5D} are as
 35 defined above,



(h) $-\text{SO}_2\text{-NQ}_{1-5\text{A}}\text{Q}_{1-5\text{D}}$ where $\text{Q}_{1-5\text{A}}$ and $\text{Q}_{1-5\text{D}}$ are as defined above,

(i) $-\text{NQ}_{1-5\text{A}}\text{-SO}_2\text{-Q}_{1-5\text{D}}$ where $\text{Q}_{1-5\text{A}}$ and $\text{Q}_{1-5\text{D}}$ are as defined above,

5

(j) $-\text{NO}_2$,

(k) $-\text{O-SO}_2\text{-CF}_3$;

(K) 3-oxadiazole optionally substituted with one Q_{1-5} where Q_{1-5} is as defined above,

(L) triazole optionally substituted with one or two Q_{1-5} which may be the same or different, where Q_{1-5} is as defined above,

(M) 5-thiadiazole optionally substituted with one Q_{1-5} , where Q_{1-5} is as defined above,

(N) 3-thiadiazole optionally substituted with one Q_{1-5} , where Q_{1-5} is as defined above,

15

(O) 2-oxazole optionally substituted with one or two Q_{1-5} which may be the same or different, where Q_{1-5} is as defined above,

(P) 2-thiazole optionally substituted with one or two Q_{1-5} which may be the same or different, where Q_{1-5} is as defined above,

(Q) 2-imidazole optionally substituted with one, two or three Q_{1-5} which may be the same or different, where Q_{1-5} is as defined above,

(R) 1-imidazole optionally substituted with one, two or three Q_{1-5} which may be the same or different, where Q_{1-5} is as defined above,

(S) tetrazole optionally substituted with one Q_{1-5} , where Q_{1-5} is as defined above,

25

(T) cyclobutenedione optionally substituted with one Q_{1-1} and one Q_{1-5} where Q_{1-1} and Q_{1-5} are as defined above,

(U) 1-pyrimidinyl optionally substituted with one Q_{1-5} , where Q_{1-5} is as defined above,

(V) 2-pyridinyl optionally substituted with one Q_{1-5} , where Q_{1-5} is as defined above,

(W) 3-pyridinyl optionally substituted with one Q_{1-5} , where Q_{1-5} is as defined above,

(X) 4-pyridinyl optionally substituted with one Q_{1-5} , where Q_{1-5} is as defined above,

35

(Y) $-\text{Z}_1\text{-CO-Z}_2\text{-Q}_{1-2}$ where Q_{1-2} is as defined above and Z_1 is



-O- or

-N_{Q1-1}- where Q₁₋₁ is as defined above, where Z₂ is

-O- or

-N_{Q1-1}- where Q₁₋₁ is as defined above,

5

with the proviso that when X₁ is -(CH₂)_{n1}-, where n₁ is 0 and Q₁ is:

-CO-NQ₁₋₁Q₁₋₂,

-SO₂-NQ₁₋₁Q₁₋₂ or

-NQ₁₋₁Q₁₋₂,

10

-NQ₁₋₁-CO-Q₁₋₂ then Q₁₋₁ and Q₁₋₂ cannot both be selected

from:

-H,

-C₁-C₆ alkyl,

-C₃-C₇ cycloalkyl,

15

-C₁-C₃ alkyl-(C₃-C₇) cycloalkyl and pharmaceutically

acceptable salts thereof.

2. A 1,6-disubstituted isochroman (I) according to claim 1 where:

(I) W₁ is a nitrogen (-N-) or carbon (-CH-) atom;

20

| |

(II) X₁ is:

(A) -(CH₂)_{n1}- where n₁ is 0 thru 3,

(B) -CH=CH-;

(III) R₁ is:

25

(A) -H,

(B) -F, -Cl, -Br, -I,

(C) C₁-C₈ alkyl,

(D) C₂-C₈ alkenyl containing 1 thru 3 double bonds (=),

(E) C₂-C₈ alkynyl containing 1 or 2 triple bonds (≡),

30

(F) C₃-C₈ cycloalkyl,

(G) -C₁-C₃ alkyl-C₃-C₈ cycloalkyl,

(H) -NO₂,

(I) -C≡N,

(J) -CF₃,

35

(K) -O-R₁₋₁ where R₁₋₁ is:



* C L M S *

- (1) -H,
 (2) C₁-C₈ alkyl,
 (3) C₂-C₈ alkenyl containing 1 thru 3 double bonds (=),
 (4) C₂-C₈ alkynyl containing 1 or 2 triple bonds (≡),
 5 (5) C₃-C₈ cycloalkyl,
 (6) -C₁-C₃ alkyl-C₃-C₈ cycloalkyl,
 (7) -CF₃,
 (8) -SO₂-CF₃,
 (9) -(CH₂)_{n2}-φ where n₂ is 0 thru 4 and where φ is optionally
 10 substituted with one or two:

- (a) -F, -Cl, -Br, -I,
 (b) -C≡N,
 (c) -CF₃,
 (d) C₁-C₃ alkyl,
 15 (e) -O-R_{1-1A} where R_{1-1A} is -H, C₁-C₆ alkyl, -CF₃ or
 -CH₂-φ,
 (f) -NR_{1-1A}R_{1-1B} where the R_{1-1A} and R_{1-1B} are the
 same or different and where R_{1-1B} is -H, C₁-C₆ alkyl, -CF₃ or -CH₂-φ, and where
 R_{1-1A} is as defined above,
 20 (g) -CO-NR_{1-1A}R_{1-1B} where R_{1-1A} and R_{1-1B} are as
 defined above,
 (h) -SO₂-NR_{1-1A}R_{1-1B} where R_{1-1A} and R_{1-1B} are as
 defined above,
 (i) -NR_{1-1A}-SO₂-R_{1-1B} where R_{1-1A} and R_{1-1B} are as
 25 defined above,
 (j) -NO₂,
 (k) -O-SO₂-CF₃,

(L) -N(R₁₋₁)₂ where the R₁₋₁ can be the same or different and are as
 defined above,

30 (M) -CO-N(R₁₋₁)₂ where the R₁₋₁ are the same or different and are as
 defined above,

(N) -SO₂-R₁₋₃ where R₁₋₃ is:

- (1) -H,
 (2) -CF₃,
 35 (3) C₁-C₈ alkyl,



- (4) C₂-C₈ alkenyl containing 1 thru 3 double bonds (=),
 (5) C₂-C₈ alkynyl containing 1 or 2 triple bonds (≡),
 (6) C₃-C₈ cycloalkyl,
 (7) -C₁-C₃ alkyl-C₃-C₈ cycloalkyl,
 5 (8) -(CH₂)_{n2}-φ where n₂ is as defined above and -φ is optionally substituted with one or two:

- (a) -F, -Cl, -Br, -I,
 (b) -C≡N,
 (c) -CF₃,
 10 (d) C₁-C₃ alkyl,
 (e) -O-R_{1-3A} where R_{1-3A} is -H, C₁-C₆ alkyl, -CF₃ or -CH₂-φ,
 (f) -NR_{1-3A}R_{1-3B} where the R_{1-3A} and R_{1-3B} are the same or different and where R_{1-3B} is -H, C₁-C₆ alkyl, -CF₃ or -CH₂-φ, and where
 15 R_{1-3A} is as defined above,
 (g) -CO-NR_{1-3A}R_{1-3B} where R_{1-3A} and R_{1-3B} are as defined above,
 (h) -SO₂-NR_{1-3A}R_{1-3B} where R_{1-3A} and R_{1-3B} are as defined above,
 20 (i) -NR_{1-3A}-SO₂-R_{1-3B} where R_{1-3A} and R_{1-3B} are as defined above,
 (j) -NO₂,
 (k) -O-SO₂-CF₃,
 (9) -O-R_{1-3A} where R_{1-3A} is as defined above,
 25 (10) -NR_{1-3A}R_{1-3B} where R_{1-3A} and R_{1-3B} are as defined above,
 (O) -NR₁₋₁-SO₂-R₁₋₃ where R₁₋₁ and R₁₋₃ may be the same or different and are as defined above,
 (P) -(CH₂)_{n2}-φ where n₂ is as defined above and where -φ is optionally substituted with one or two:
 30 (1) -F, -Cl, -Br, -I,
 (2) -C≡N,
 (3) -CF₃,
 (4) C₁-C₆ alkyl,
 (5) -O-R₁₋₁ where R₁₋₁ is as defined above,
 35 (6) -N(R₁₋₁)₂ where the R₁₋₁s are the same or different and are



as defined above,

(7) $-\text{CO}-\text{N}(\text{R}_{1-1})_2$ where the R_{1-1} s are the same or different and are as defined above,

(8) $-\text{SO}_2-\text{N}(\text{R}_{1-1})_2$ where the R_{1-1} s are the same or different and are as defined above,

(9) $-\text{NR}_{1-1}-\text{SO}_2-\text{R}_{1-1}$ where the R_{1-1} s are the same or different and are as defined above,

(10) $-\text{NO}_2$,

(11) $-\text{O}-\text{SO}_2-\text{CF}_3$;

(IV) R_2 is defined the same as R_1 , R_2 can be the same or different than R_1 ;

(V) Q_1 is:

(A) $-\text{CO}-\text{NQ}_{1-1}\text{Q}_{1-2}$ where Q_{1-1} is:

(1) $-\text{H}$,

(2) C_1-C_8 alkyl,

(3) C_2-C_8 alkenyl containing 1 thru 3 double bonds (=),

(4) C_2-C_8 alkynyl containing 1 or 2 triple bonds ($\equiv$),

(5) C_3-C_8 cycloalkyl,

(6) $-\text{C}_1-\text{C}_3$ alkyl- C_3-C_8 cycloalkyl,

(7) $-\text{CF}_3$,

(8) $-\text{SO}_2-\text{CF}_3$,

(9) $-(\text{CH}_2)_{n7}-\phi$ where $n7$ is 0 thru 4 and where ϕ is optionally substituted with one or two:

(a) $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$,

(b) $-\text{C}\equiv\text{N}$,

(c) $-\text{CF}_3$,

(d) C_1-C_3 alkyl,

(e) $-\text{O}-\text{Q}_{1-1\text{A}}$ where $\text{Q}_{1-1\text{A}}$ is $-\text{H}$, C_1-C_6 alkyl, $-\text{CF}_3$ or $-\text{CH}_2-\phi$,

(f) $-\text{NQ}_{1-1\text{A}}\text{Q}_{1-1\text{B}}$ where the $\text{Q}_{1-1\text{A}}$ and $\text{Q}_{1-1\text{B}}$ are the same or different and where $\text{Q}_{1-1\text{B}}$ is $-\text{H}$, C_1-C_6 alkyl, $-\text{CF}_3$ or $-\text{CH}_2-\phi$, and where $\text{Q}_{1-1\text{A}}$ is as defined above,

(g) $-\text{CO}-\text{NQ}_{1-1\text{A}}\text{Q}_{1-1\text{B}}$ where $\text{Q}_{1-1\text{A}}$ and $\text{Q}_{1-1\text{B}}$ are as defined above,

(h) $-\text{SO}_2-\text{NQ}_{1-1\text{A}}\text{Q}_{1-1\text{B}}$ where $\text{Q}_{1-1\text{A}}$ and $\text{Q}_{1-1\text{B}}$ are as defined above,



(i) $-NQ_{1-1A}-SO_2-Q_{1-1B}$ where Q_{1-1A} and Q_{1-1B} are as defined above,

(j) $-NO_2$,

(k) $-O-SO_2-CF_3$, and where Q_{1-2} is:

5

(1) $-H$,

(2) C_1-C_8 alkyl,

(3) C_2-C_8 alkenyl containing 1 thru 3 double bonds ($=$),

(4) C_2-C_8 alkynyl containing 1 or 2 triple bonds ($\equiv$),

(5) C_3-C_8 cycloalkyl,

10

(6) $-C_1-C_3$ alkyl- C_3-C_8 cycloalkyl,

(7) $-CF_3$,

(8) $-(CH_2)_{n_2}-\phi$ where n_2 is as defined above and ϕ is optionally substituted with one or two:

15

(a) $-F$, $-Cl$, $-Br$, $-I$,

(b) $-C\equiv N$,

(c) $-CF_3$,

(d) C_1-C_6 alkyl,

(e) $-O-Q_{1-2A}$ where Q_{1-2A} is:

20

(i) $-H$,

(ii) C_1-C_6 alkyl,

(iii) $-CF_3$,

(iv) $-(CH_2)-\phi$,

(9) $-(CH_2)_{n_9}-Q_{1-2B}(CH_2)_{n_{10}}-Q_{1-2C}$ where n_9 and n_{10} are the same or different and are 0 thru 4, where Q_{1-2B} is $-O-$ or $-NQ_{1-2D}$, where Q_{1-2D} is:

25

(a) $-H$,

(b) C_1-C_8 alkyl,

(c) C_2-C_8 alkenyl containing 1 thru 3 double bonds,

(d) C_2-C_8 alkynyl containing 1 or 2 triple bonds,

(e) C_3-C_8 cycloalkyl,

30

(f) $-C_1-C_3$ alkyl- C_3-C_8 cycloalkyl,

(g) $-CF_3$,

(h) $-(CH_2)_{n_{11}}-\phi$ where n_{11} is 0 thru 4 and ϕ is optionally substituted with one or two:

35

(i) $-F$, $-Cl$, $-Br$, $-I$,

(ii) $-C\equiv N$,



- (iii) $-\text{CF}_3$,
 (iv) $\text{C}_1\text{-C}_3$ alkyl,
 (v) $-\text{O-Q}_{1-2\text{E}}$ where $\text{Q}_{1-2\text{E}}$ is $-\text{H}$, $\text{C}_1\text{-C}_6$ alkyl, $-\text{CF}_3$
 or $-\text{CH}_2\text{-}\phi$,
 5 (vi) $-\text{NQ}_{1-2\text{E}}\text{Q}_{1-2\text{F}}$ where the $\text{Q}_{1-2\text{E}}$ and $\text{Q}_{1-2\text{F}}$ are
 the same or different and where $\text{Q}_{1-2\text{F}}$ is $-\text{H}$, $\text{C}_1\text{-C}_6$ alkyl, $-\text{CF}_3$ or $-\text{CH}_2\text{-}\phi$, and
 where $\text{Q}_{1-2\text{E}}$ is as defined above,
 (vii) $-\text{CO-NQ}_{1-2\text{E}}\text{Q}_{1-2\text{F}}$ where $\text{Q}_{1-2\text{E}}$ and $\text{Q}_{1-2\text{F}}$
 are as defined above,
 10 (viii) $-\text{SO}_2\text{-NQ}_{1-2\text{E}}\text{Q}_{1-2\text{F}}$ where $\text{Q}_{1-2\text{E}}$ and $\text{Q}_{1-2\text{F}}$
 are as defined above,
 (ix) $-\text{NQ}_{1-2\text{E}}\text{-SO}_2\text{-Q}_{1-2\text{F}}$ where $\text{Q}_{1-2\text{E}}$ and $\text{Q}_{1-2\text{F}}$
 are as defined above,
 (x) $-\text{NO}_2$,
 15 (xi) $-\text{O-SO}_2\text{-CF}_3$, and where $\text{Q}_{1-2\text{C}}$ is defined the
 same as $\text{Q}_{1-2\text{D}}$ and the $\text{Q}_{1-2\text{C}}$ and $\text{Q}_{1-2\text{D}}$ can be the same or different,
 (B) $-\text{SO}_2\text{-NQ}_{1-1}\text{Q}_{1-2}$ where Q_{1-1} and Q_{1-2} are as defined above,
 (C) $-\text{CO-O-Q}_{1-3}$ where Q_{1-3} is:
 (1) $-\text{H}$,
 20 (2) $-\text{CF}_3$,
 (3) $\text{C}_1\text{-C}_8$ alkyl,
 (4) $\text{C}_2\text{-C}_8$ alkenyl containing 1 thru 3 double bonds ($=$),
 (5) $\text{C}_2\text{-C}_8$ alkynyl containing 1 or 2 triple bonds ($\equiv$),
 (6) $\text{C}_3\text{-C}_8$ cycloalkyl,
 25 (7) $-\text{C}_1\text{-C}_3$ alkyl- $\text{C}_3\text{-C}_8$ cycloalkyl,
 (8) $-(\text{CH}_2)_{n7}\text{-}\phi$ where $n7$ is as defined above and ϕ is optionally
 substituted with one or two:
 (a) $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$,
 (b) $-\text{C}\equiv\text{N}$,
 30 (c) $-\text{CF}_3$,
 (d) $\text{C}_1\text{-C}_3$ alkyl,
 (e) $-\text{O-Q}_{1-3\text{A}}$ where $\text{Q}_{1-3\text{A}}$ is $-\text{H}$, $\text{C}_1\text{-C}_6$ alkyl, $-\text{CF}_3$ or
 $-\text{CH}_2\text{-}\phi$,
 (f) $-\text{NQ}_{1-3\text{A}}\text{Q}_{1-3\text{B}}$ where the $\text{Q}_{1-3\text{A}}$ and $\text{Q}_{1-3\text{B}}$ are the
 35 same or different and where $\text{Q}_{1-3\text{B}}$ is $-\text{H}$, $\text{C}_1\text{-C}_6$ alkyl, $-\text{CF}_3$ or $-\text{CH}_2\text{-}\phi$, and where



Q_{1-3A} is as defined above,

(g) $-CO-NQ_{1-3A}Q_{1-3B}$ where Q_{1-3A} and Q_{1-3B} are as defined above,

5 (h) $-SO_2-NQ_{1-3A}Q_{1-3B}$ where Q_{1-3A} and Q_{1-3B} are as defined above,

(i) $-NQ_{1-3A}-SO_2-Q_{1-3B}$ where Q_{1-3A} and Q_{1-3B} are as defined above,

(j) $-NO_2$,

(k) $-O-SO_2-CF_3$,

10 (D) $-CO-Q_{1-3}$ where Q_{1-3} is as defined above,

(E) $-CO$ -imidazole,

(F) $-NQ_{1-1}Q_{1-2}$ where Q_{1-1} and Q_{1-2} are as defined above,

(G) $-C(Q_{1-3})=N-O-Q_{1-4}$ where Q_{1-4} is defined the same as Q_{1-3} and Q_{1-3} is as defined above, the Q_{1-3} and Q_{1-4} can be the same or different,

15 (H) $-SO_2-Q_{1-3}$ where Q_{1-3} is as defined above,

(I) $-N(Q_{1-1})-SO_2-Q_{1-3}$ where Q_{1-1} and Q_{1-3} is as defined above,

(J) 5-oxadiazole optionally substituted with one Q_{1-5} where Q_{1-5} is:

(1) $-H$,

(2) $-F$, $-Cl$, $-Br$, $-I$,

20 (3) C_1-C_8 alkyl,

(4) C_2-C_8 alkenyl containing 1 thru 3 double bonds ($=$),

(5) C_2-C_8 alkynyl containing 1 or 2 triple bonds ($\equiv$),

(6) C_3-C_8 cycloalkyl,

(7) $-C_1-C_3$ alkyl- C_3-C_8 cycloalkyl,

25 (8) $-NO_2$,

(9) $-C\equiv N$,

(10) $-CF_3$,

(11) $-O-Q_{1-5A}$ where Q_{1-5A} is:

(a) $-H$,

30 (b) C_1-C_8 alkyl,

(c) C_2-C_8 alkenyl containing 1 thru 3 double bonds,

(d) C_2-C_8 alkynyl containing 1 or 2 triple bonds,

(e) C_3-C_8 cycloalkyl,

(f) $-C_1-C_3$ alkyl- C_3-C_8 cycloalkyl,

35 (g) $-CF_3$,

- (h) $-\text{SO}_2\text{-CF}_3$,
 (i) $-(\text{CH}_2)_{n7}\text{-}\phi$ where n_7 is 0 thru 4,
 (12) $-\text{NQ}_{1-5A}\text{Q}_{1-5D}$ where Q_{1-5A} is as defined above, Q_{1-5D} is:
 (a) $-\text{H}$,
 5 (b) $\text{C}_1\text{-C}_8$ alkyl,
 (c) $\text{C}_2\text{-C}_8$ alkenyl containing 1 thru 3 double bonds,
 (d) $\text{C}_2\text{-C}_8$ alkynyl containing 1 or 2 triple bonds ($=$),
 (e) $\text{C}_3\text{-C}_8$ cycloalkyl,
 (f) $-\text{C}_1\text{-C}_3$ alkyl- $\text{C}_3\text{-C}_8$ cycloalkyl,
 10 (g) $-\text{CF}_3$,
 (h) $-(\text{CH}_2)_{n7}\text{-}\phi$ where n_7 is as defined above,
 (13) $-\text{CO-NQ}_{1-5A}\text{Q}_{1-5D}$ where Q_{1-5A} and Q_{1-5D} are as defined
 above,
 (14) $-\text{SO}_2\text{-Q}_{1-5K}$ where Q_{1-5K} is:
 15 (a) $-\text{H}$,
 (b) $-\text{CF}_3$,
 (c) $\text{C}_1\text{-C}_8$ alkyl,
 (d) $\text{C}_2\text{-C}_8$ alkenyl containing 1 thru 3 double bonds ($=$),
 (e) $\text{C}_2\text{-C}_8$ alkynyl containing 1 or 2 triple bonds ($=$),
 20 (f) $\text{C}_3\text{-C}_8$ cycloalkyl,
 (g) $-\text{C}_1\text{-C}_3$ alkyl- $\text{C}_3\text{-C}_8$ cycloalkyl,
 (h) $-(\text{CH}_2)_{n7}\text{-}\phi$ where n_7 is as defined above,
 (15) $-\text{NQ}_{1-5A}\text{-SO}_2\text{-Q}_{1-5K}$ where Q_{1-5A} and Q_{1-5K} may be the
 same or different and are as defined above,
 25 (16) $-(\text{CH}_2)_{n7}\text{-}\phi$ where n_7 is as defined above and where ϕ is
 optionally substituted with one or two:
 (a) $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$,
 (b) $-\text{C}\equiv\text{N}$,
 (c) $-\text{CF}_3$,
 30 (d) $\text{C}_1\text{-C}_6$ alkyl,
 (e) $-\text{O-Q}_{1-5A}$ where Q_{1-5A} is as defined above,
 (f) $-\text{NQ}_{1-5A}\text{Q}_{1-5D}$ where Q_{1-5A} and Q_{1-5D} are as defined
 above,
 (g) $-\text{CO-NQ}_{1-5A}\text{Q}_{1-5D}$ where Q_{1-5A} and Q_{1-5D} are as
 35 defined above,



(h) $-\text{SO}_2\text{-NQ}_{1-5\text{A}}\text{Q}_{1-5\text{D}}$ where $\text{Q}_{1-5\text{A}}$ and $\text{Q}_{1-5\text{D}}$ are as defined above,

(i) $-\text{NQ}_{1-5\text{A}}\text{-SO}_2\text{-Q}_{1-5\text{D}}$ where $\text{Q}_{1-5\text{A}}$ and $\text{Q}_{1-5\text{D}}$ are as defined above,

5 (j) $-\text{NO}_2$,

(k) $-\text{O-SO}_2\text{-CF}_3$;

(K) 3-oxadiazole optionally substituted with one Q_{1-5} where Q_{1-5} is as defined above,

(L) triazole optionally substituted with one or two Q_{1-5} which may be the same or different, where Q_{1-5} is as defined above,

10 (M) 5-thiadiazole optionally substituted with one Q_{1-5} , where Q_{1-5} is as defined above,

(N) 3-thiadiazole optionally substituted with one Q_{1-5} , where Q_{1-5} is as defined above,

15 (O) 2-oxazole optionally substituted with one or two Q_{1-5} which may be the same or different, where Q_{1-5} is as defined above,

(P) 2-thiazole optionally substituted with one or two Q_{1-5} which may be the same or different, where Q_{1-5} is as defined above,

(Q) 2-imidazole optionally substituted with one, two or three Q_{1-5} which may be the same or different, where Q_{1-5} is as defined above,

(R) 1-imidazole optionally substituted with one, two or three Q_{1-5} which may be the same or different, where Q_{1-5} is as defined above,

(S) tetrazole optionally substituted with one Q_{1-5} , where Q_{1-5} is as defined above,

25 (T) cyclobutenedione optionally substituted with one Q_{1-1} and one Q_{1-5} where Q_{1-1} and Q_{1-5} are as defined above,

(U) 1-pyrimidinyl optionally substituted with one Q_{1-5} , where Q_{1-5} is as defined above,

(V) 2-pyridinyl optionally substituted with one Q_{1-5} , where Q_{1-5} is as defined above,

(W) 3-pyridinyl optionally substituted with one Q_{1-5} , where Q_{1-5} is as defined above,

(X) 4-pyridinyl optionally substituted with one Q_{1-5} , where Q_{1-5} is as defined above, with the proviso that when X_1 is $-(\text{CH}_2)_{n1}$, where n_1 is 0 and Q_{1-5} is:

35 $-\text{CO-NQ}_{1-1}\text{Q}_{1-2}$,



-SO₂-NQ₁₋₁Q₁₋₂ or

-NQ₁₋₁Q₁₋₂,

-NQ₁₋₁-CO-Q₁₋₂ then Q₁₋₁ and Q₁₋₂ cannot both be selected

from:

5

-H,

-C₁-C₆ alkyl,

-C₃-C₇ cycloalkyl,

-C₁-C₃ alkyl-(C₃-C₇) cycloalkyl and pharmaceutically

acceptable salts thereof.

10

3. A 1,6-disubstituted isochroman (I) according to claim 1 where W₁ is a nitrogen atom.

4. A 1,6-disubstituted isochroman (I) according to claim 1 where W₁ is a carbon

15 atom.

5. A 1,6-disubstituted isochroman (I) according to claim 1 where X₁ is -(CH₂)_{n1}.

6. A 1,6-disubstituted isochroman (I) according to claim 5 where n₁ is 0 or 1.

20 7. A 1,6-disubstituted isochroman (I) according to claim 1 where X₁ is -CH=CH-.

8. A 1,6-disubstituted isochroman (I) according to claim 1 where R₁ is -O-R₁₋₁,
-CF₃, -CO-N(R₁₋₁)₂ and -CO-R₁₋₁.

25 9. A 1,6-disubstituted isochroman (I) according to claim 7 where R₁₋₁ is C₁-C₃ alkyl.

10. A 1,6-disubstituted isochroman (I) according to claim 1 where R₂ is -H.

11. A 1,6-disubstituted isochroman (I) according to claim 1 where Q₁ is selected
30 from the group consisting of -CO-NQ₁₋₁Q₁₋₂, -SO₂-NQ₁₋₁Q₁₋₂ and -NQ₁₋₁Q₁₋₂.

12. A 1,6-disubstituted isochroman (I) according to claim 10 where Q₁ is
-CO-NQ₁₋₁Q₁₋₂.

35 13. A 1,6-disubstituted isochroman (I) according to claim 11 where the



pharmaceutically acceptable anion salt is selected from the group consisting of methanesulfonic, hydrochloric, hydrobromic, sulfuric, phosphoric, nitric, benzoic, citric, tartaric, fumaric, maleic, $\text{CH}_3(\text{CH}_2)_n\text{-COOH}$ where n is 0 thru 4, $\text{HOOC}(\text{CH}_2)_n\text{-COOH}$ where n is as defined above.

5

14. A 1,6-disubstituted isochroman (I) according to claim 1 where R_1 is (Q) $-\text{CO}-R_{1-1}$ or $-\text{CO}-O-Q_{1-2}$.

15. A 1,6-disubstituted isochroman (I) according to claim 14 where the 1,6-disubstituted isochroman is

(S)-(-)-1-[2-[4-(4-trifluoroacetylphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide.

16. A 1,6-disubstituted isochroman (I) according to claim 1 where Q_1 is (Y) $-\text{Z}_1\text{-CO-Z}_2\text{-Q}_{1-2}$.

17. A 1,6-disubstituted isochroman (I) according to claim 16 where the 1,6-disubstituted isochroman is selected from the group consisting of:

(S)-(-)-6-amino-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]isochroman methyl urea,

(S)-(-)-6-amino-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]isochroman *t*-butylcarbamate and

(+/-)-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-ol methyl carbamate ester.

25

18. A 1,6-disubstituted isochroman (I) according to claim 1 where Q_1 is (Fⁿ) $-\text{NQ}_{1-1}\text{-CO-Q}_{1-2}$.

19. A 1,6-disubstituted isochroman (I) according to claim 18 where the 1,6-disubstituted isochroman (I) is selected from the group consisting of:

(S)-(-)-N-[isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]benzamide and

(S)-(-)-N-[isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]acrylamide.

35



20. A 1,6-disubstituted isochroman (I) according to claim 1 where Q_{1-1} and Q_{1-2} are taken together with the attached nitrogen atom to form a 5 or 6 member ring.

21. A 1,6-disubstituted isochroman (I) according to claim 20 where the 5 or 6 member ring is selected from the group consisting of pyrrolidine, piperidine, piperazine and morpholine.

22. A 1,6-disubstituted isochroman (I) according to claim 20 which is
(+/-)-1-[1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-yl]-4-methylpiperazine.

23. A 1,6-disubstituted isochroman (I) according to claim 1 which is selected from the group consisting of:

- 1-[2-[4-(4-methylsulfonylphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide,
(S)-(-)-1-[2-[4-(4-trifluoromethoxyphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide,
1-[2-[4-(4-methylsulfonylphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide,
1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N-allylisochroman-6-carboxamide,
1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N-propargylisochroman-6-carboxamide,
1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N-(4-methoxyphenylmethyl)isochroman-6-carboxamide,
1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N-phenylmethylisochroman-6-carboxamide,
1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N-[(R)- α -methylphenylmethyl]isochroman-6-carboxamide,
1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N-[(S)- α -methylphenylmethyl]isochroman-6-carboxamide,
1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N-phenylisochroman-6-carboxamide,
1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N-phenylmethyl-N-methylisochroman-6-carboxamide,



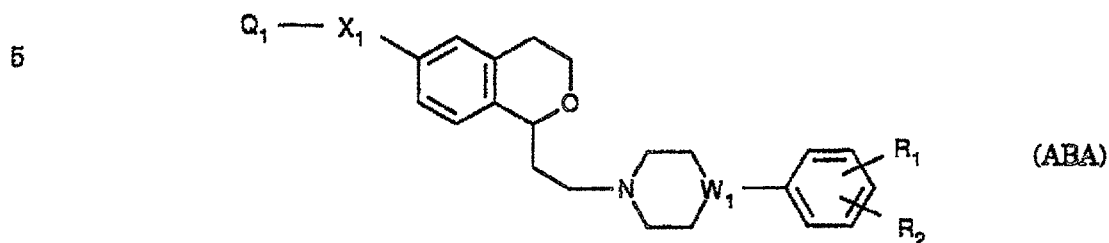
- 1-(4-methoxyphenyl)-4-[2-[6-(5-methyloxazole-2-yl)isochroman-1-yl]ethyl]piperazine,
(S)-(-)-N-[isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]-methanesulfonamide,
- 5 1-(4-methoxyphenyl)-4-[2-(6-methylaminomethylisochroman-1-yl)ethyl]piperazine,
1-(4-methoxyphenyl)-4-[2-(6-dimethylaminomethylisochroman-1-yl)ethyl]piperazine,
1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxylic acid
10 ethyl ester,
6-acetyl-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]isochroman,
6-formyl-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]isochroman,
2-[isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]acetamide,
2-[isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]-N-
15 methylacetamide,
(S)-(-)-3-[isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]-N,N-dimethylacrylamide,
(S)-(-)-1-(4-methoxyphenyl)-4-[2-[6-(1,2,4-triazol-3-yl)-isochroman-1-yl]ethyl]piperazine,
20 (S)-(-)-1-(4-methoxyphenyl)-4-[2-[6-(2-methyl-1,2,4-triazol-3-yl)-isochroman-1-yl]ethyl]piperazine,
(S)-(-)-1-(4-methoxyphenyl)-4-[2-[6-(2-phenylmethyl-1,2,4-triazol-3-yl)-isochroman-1-yl]ethyl]piperazine,
(S)-(-)-1-(4-methoxyphenyl)-4-[2-[6-(1,2,4-oxadiazol-5-yl)-isochroman-1-yl]ethyl]piperazine,
25 1-[1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-yl]carbonyl]pyrrolidine,
N-(2-hydroxyethyl)-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide,
30 1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N-(phenylmethoxy)isochroman-6-carboxamide,
(+/-)-N-hydroxy-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide,
(S)-(-)-1-[2-[4-[4-(aminocarbonyl)phenyl]-1-piperazinyl]ethyl]-N-methyl-N-
35 (phenylmethoxy)isochroman-6-carboxamide,



- (S)-(-)-1-[2-[4-[4-(aminocarbonyl)phenyl]-1-piperazinyl]ethyl]-N-hydroxy-N-methylisochroman-6-carboxamide,
- (S)-(-)-N-hydroxy-N-methyl-1-[2-[4-[4-(trifluoromethyl)phenyl]-1-piperazinyl]ethyl]isochroman-6-carboxamide,
- 5 (S)-(-)-1-[2-[4-(4-chlorophenyl)-1-piperazinyl]ethyl]-N-hydroxy-N-methylisochroman-6-carboxamide,
- (S)-(-)-1-[2-[4-(4-cyanophenyl)-1-piperazinyl]ethyl]-N-hydroxy-N-methylisochroman-6-carboxamide,
- (S)-(-)-N-hydroxy-N-methyl-1-[2-[4-[4-(methylcarbonyl)phenyl]-1-piperazinyl]ethyl]isochroman-6-carboxamide,
- 10 (S)-4-[4-[2-[6-(1,2,4-triazol-3-yl)isochroman-1-yl]ethyl]-1-piperazinyl]benzamide,
- (S)-4-[4-[2-[6-(2-methyl-1,2,4-triazol-3-yl)isochroman-1-yl]ethyl]-1-piperazinyl]benzamide,
- 15 (S)-4-[4-[2-[6-(1,2,4-oxadiazol-5-yl)isochroman-1-yl]ethyl]-1-piperazinyl]benzamide,
- (S)-1-[2-[6-(1,2,4-triazol-3-yl)isochroman-1-yl]ethyl]-4-[4-trifluoromethylphenyl]piperazine,
- (S)-1-[2-[6-(2-methyl-1,2,4-triazol-3-yl)isochroman-1-yl]ethyl]-4-[4-trifluoromethylphenyl]piperazine,
- 20 (S)-1-[2-[6-(1,2,4-oxadiazol-5-yl)isochroman-1-yl]ethyl]-4-[4-trifluoromethylphenyl]piperazine,
- (S)-1-[4-acetylphenyl]-4-[2-[6-(1,2,4-triazol-3-yl)isochroman-1-yl]ethyl]piperazine,
- 25 (S)-1-[4-acetylphenyl]-4-[2-[6-(2-methyl-1,2,4-triazol-3-yl)isochroman-1-yl]ethyl]piperazine,
- (S)-1-[4-acetylphenyl]-4-[2-[6-(1,2,4-oxadiazol-5-yl)isochroman-1-yl]ethyl]piperazine,
- 30 3-[1-[2-[4-(4-aminocarbonylphenyl)piperazin-1-yl]ethyl]isochroman-6-yl]-N,N-dimethylacrylamide,
- 3-[1-[2-[4-(4-trifluoromethylphenyl)piperazin-1-yl]ethyl]isochroman-6-yl]-N,N-dimethylacrylamide,
- 3-[1-[2-[4-(4-acetylphenyl)piperazin-1-yl]ethyl]isochroman-6-yl]-N,N-dimethylacrylamide.



24. An aromatic bicyclic amine of the formula (ABA)



10

where:

(I) W_1 is $(-N-)$ or $(-CH-)$

(II) X_1 is $-(CH_2)_{n_1}-$, and n_1 is 0,

(III) Q_1 is

15

(A) $-CO-NQ_{1-1}Q_{1-2}$ where Q_{1-1} is:

(1) $-H$,

(2) C_1-C_8 alkyl,

(3) C_2-C_8 alkenyl containing 1 thru 3 double bonds ($=$),

(4) C_2-C_8 alkynyl containing 1 or 2 triple bonds ($\equiv$),

20

(5) $-(CH_2)_{n_7}-\phi$ where n_7 is 0 thru 4 and where $-\phi$ is optionally

substituted with one or two:

(a) $-F$, $-Cl$, $-Br$, $-I$,

(b) $-C\equiv N$,

(c) $-CF_3$,

25

(d) C_1-C_3 alkyl,

(e) $-O-Q_{1-1A}$ where Q_{1-1A} is $-H$, C_1-C_6 alkyl, $-CF_3$ or

$-CH_2-\phi$,

(f) $-NQ_{1-1A}Q_{1-1B}$ where the Q_{1-1A} and Q_{1-1B} are the same or different and where Q_{1-1B} is $-H$, C_1-C_6 alkyl, $-CF_3$ or $-CH_2-\phi$, and where

30 Q_{1-1A} is as defined above,

(g) $-CO-NQ_{1-1A}Q_{1-1B}$ where Q_{1-1A} and Q_{1-1B} are as defined above,

(h) $-SO_2-NQ_{1-1A}Q_{1-1B}$ where Q_{1-1A} and Q_{1-1B} are as defined above,

35

(i) $-NQ_{1-1A}-SO_2-Q_{1-1B}$ where Q_{1-1A} and Q_{1-1B} are as



defined above,

(j) $-\text{NO}_2$,

(k) $-\text{O}-\text{SO}_2-\text{CF}_3$, and where Q_{1-2} is:

(6) C_1-C_8 alkyl,

(7) C_2-C_8 alkenyl containing 1 thru 3 double bonds ($=$),

(8) C_2-C_8 alkynyl containing 1 or 2 triple bonds ($\equiv$),

(9) $-(\text{CH}_2)_{n_2}-\phi$ where n_2 is as defined above and ϕ is optionally substituted with one or two:

(a) $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$,

(b) $-\text{C}\equiv\text{N}$,

(c) $-\text{CF}_3$,

(d) C_1-C_6 alkyl,

(e) $-\text{O}-\text{Q}_{1-2A}$ where Q_{1-2A} is:

(i) $-\text{H}$,

(ii) C_1-C_6 alkyl,

(iii) $-\text{CF}_3$,

(iv) $-(\text{CH}_2)-\phi$,

(B) $-\text{SO}_2-\text{NQ}_{1-1}\text{Q}_{1-2}$ where Q_{1-1} and Q_{1-2} are as defined above,

(C) $-\text{NQ}_{1-1}\text{Q}_{1-2}$ where Q_{1-1} and Q_{1-2} are as defined above,

(D) $-\text{NQ}_{1-1}-\text{CO}-\text{Q}_{1-2}$ where Q_{1-1} and Q_{1-2} are as defined above,

(III) R_1 is:

(A) $-\text{H}$,

(B) $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$,

(C) C_1-C_8 alkyl,

(D) $-\text{C}\equiv\text{N}$,

(E) $-\text{CF}_3$,

(F) $-\text{O}-\text{R}_{1-1}$ where R_{1-1} is:

(1) $-\text{H}$,

(2) C_1-C_8 alkyl,

(3) $-\text{CF}_3$,

(4) $-\text{SO}_2-\text{CF}_3$,

(5) $-(\text{CH}_2)_{n_2}-\phi$ where n_2 is 0 thru 4

(G) $-\text{N}(\text{R}_{1-1})_2$ where the R_{1-1} can be the same or different and are as defined above,

(H) $-\text{CO}-\text{N}(\text{R}_{1-1})_2$ where the R_{1-1} are the same or different and are as



defined above,

(I) $-\text{SO}_2\text{-R}_{1-3}$ where R_{1-3} is:

(1) $-\text{CF}_3$,

(2) $\text{C}_1\text{-C}_8$ alkyl,

5 (3) $-\text{O-R}_{1-3A}$ where R_{1-3A} is as defined above,

(4) $-\text{NR}_{1-3A}\text{R}_{1-3B}$ where R_{1-3A} and R_{1-3B} are as defined above,

(J) $-\text{CO-R}_{1-1}$ where R_{1-1} is as defined above;

(IV) R_2 is defined the same as R_1 , R_2 can be the same or different than R_1 ; and pharmaceutically acceptable salts thereof.

10

25. An aromatic bicyclic amine (ABA) according to claim 24 where W_1 is $(-\text{N}-)$.

26. An aromatic bicyclic amine (ABA) according to claim 24 where one of R_1 and R_2 is $-\text{H}$.

15

27. An aromatic bicyclic amine (ABA) according to claim 24 where Q_1 is (A) $-\text{CO-NQ}_{1-1}\text{Q}_{1-2}$.

28. An aromatic bicyclic amine (ABA) according to claim 27 where Q_{1-1} is $-\text{H}$.

20

29. An aromatic bicyclic amine (ABA) according to claim 27 where Q_{1-2} is $-\text{CH}_3$.

30. An aromatic bicyclic amine (ABA) according to claim 27 where the pharmaceutically acceptable anion salt is selected from the group consisting of
25 methanesulfonic, hydrochloric, hydrobromic, sulfuric, phosphoric, nitric, benzoic, citric, tartaric, fumaric, maleic, $\text{CH}_3\text{-(CH}_2)_n\text{-COOH}$ where n is 0 thru 4, $\text{HOOC-(CH}_2)_n\text{-COOH}$ where n is as defined above.

31. An aromatic bicyclic amine (ABA) according to claim 27 where the substituted
30 amino compound is selected from the group consisting of

(S)-(-)-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide,

(R)-(+)-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide,

35 (S)-(-)-1-[2-[4-(4-trifluoromethylphenyl)-1-piperazinyl]ethyl]-N-methyl-



- isochroman-6-carboxamide,
(S)-(-)-1-[2-[4-[4-(aminocarbonyl)phenyl]-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide,
1-[2-[4-(4-ethoxyphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide,
5 carboxamide,
1-[2-[4-(4-propoxyphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide,
(S)-(-)-1-[2-[4-(4-ethylphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide,
10 (S)-(-)-1-[2-[4-(4-ethoxyphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide,
(S)-(-)-1-[2-[4-(4-phenylmethoxyphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide,
(R)-(+)-1-[2-[4-(4-ethoxyphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide,
15 carboxamide,
1-[2-[4-(3-trifluoromethylphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide,
1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N-propylisochroman-6-carboxamide,
20 1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N-ethylisochroman-6-carboxamide,
1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N-butylisochroman-6-carboxamide,
1-[2-[4-(4-chlorophenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide,
25 carboxamide,
(S)-(-)-1-[2-[4-(4-methoxyphenyl)-1-piperidinyl]ethyl]-N-methylisochroman-6-carboxamide,
(S)-(-)-1-[2-[4-(4-hydroxyphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide,
30 (S)-(-)-1-[2-[4-(4-trifluoromethanesulfonyloxyphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide,
(S)-(-)-1-[2-[4-(4-acetylphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide,
(S)-(-)-N-methyl-1-[2-[4-(4-propionylphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide,
35 carboxamide,



- N-methyl-1-[2-(4-phenyl-1-piperidinyl)ethyl]isochroman-6-carboxamide,
 (+/-)-N-methyl-1-[2-[4-(2,4-dichlorophenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide,
 (+/-)-1-[2-[4-(3-chloro-4-methoxyphenyl)-1-piperziny]ethyl]-N-methylisochroman-6-carboxamide,
 5 (S)-(-)-1-[2-[4-[4-(tert-butyloxycarbonyl)phenyl]-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide,
 (+/-)-1-[2-[4-[4-(aminocarbonyl)phenyl]-1-piperazinyl]ethyl]-N-methylisochromanyl-6-carboxamide,
 10 (R)-(+)-1-[2-[4-[4-(aminocarbonyl)phenyl]-1-piperazinyl]ethyl]-N-methylisochromanyl-6-carboxamide,
 (+/-)-1-[2-[4-[4-(aminosulfonyl)phenyl]-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide,
 (S)-(-)-N-methyl-1-[2-[4-[4-(methylaminocarbonyl)phenyl]-1-piperazinyl]ethyl]isochroman-6-carboxamide,
 15 (S)-(-)-N-methyl-1-[2-[4-[4-(dimethylaminocarbonyl)phenyl]-1-piperazinyl]ethyl]isochroman-6-carboxamide,
 (S)-(-)-N-methyl-1-[2-[4-[4-(n-propylaminocarbonyl)phenyl]-1-piperazinyl]ethyl]isochroman-6-carboxamide.
 20
32. An aromatic bicyclic amine (ABA) according to claim 31 where the substituted amino compound is
 (S)-(-)-1-[2-[4-(4-trifluoromethylphenyl)-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide and
 25 (S)-(-)-1-[2-[4-[4-(aminocarbonyl)phenyl]-1-piperazinyl]ethyl]-N-methylisochroman-6-carboxamide.
33. An aromatic bicyclic amine (ABA) according to claim 27 where the substituted amino compound is selected from the group consisting of
 30 1-[2-[4-(4-chlorophenyl)-1-piperazinyl]ethyl]-N,N-dimethylisochroman-6-carboxamide and
 (S)-(-)-1-[2-[4-(4-trifluoromethylphenyl)-1-piperazinyl]ethyl]-N,N-dimethylisochroman-6-carboxamide.
- 35 34. An aromatic bicyclic amine (ABA) according to claim 24 where the substituted

amino compound is selected from the group consisting of

1-[2-(6-aminoisochroman-1-yl)-ethyl]-4-(4-methoxyphenyl)piperazine,
 (S)-(-)-1-[2-(6-aminoisochroman-1-yl)-ethyl]-4-(4-methoxyphenyl)piperazine,
 (S)-(-)-1-[2-(6-ethylaminoisochroman-1-yl)-ethyl]-4-(4-

5 methoxyphenyl)piperazine,

(S)-(-)-1-(4-methoxyphenyl)-4-[2-(6-propylaminoisochroman-1-yl)ethyl]piperazine,

(S)-(-)-1-(4-methoxyphenyl)-4-[2-(6-methylaminoisochroman-1-yl)ethyl]piperazine,

10 (S)-(-)-1-(4-methoxyphenyl)-4-[2-(6-dimethylaminoisochroman-1-yl)ethyl]piperazine and

(S)-(-)-1-[2-(6-ethylmethylaminoisochroman-1-yl)ethyl]-4-(4-methoxyphenyl)piperazine.

15 35. An aromatic bicyclic amine (ABA) according to claim 24 where the substituted amino compound is selected from the group consisting of

(S)-(-)-N-[isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]formamide,

20 (S)-(-)-N-[isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]acetamide,

(S)-(-)-N-[isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]propionamide,

(S)-(-)-N-[isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]isobutyramide,

25 (S)-(-)-N-[isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]-N-methylacetamide and

(S)-(-)-N-[isochroman-1-[2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl]-6-yl]-N-methylisobutyramide.

30 36. An aromatic bicyclic amine selected from the group consisting of:

(S)-(-)-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide,

(R)-(+)-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide,

35 1-[2-[4-(4-diethylaminophenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide,



1-[2-[4-(3-trifluoromethylphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide,

(S)-(-)-1-[2-[4-(4-trifluoromethylphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide,

5 1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide,

1-[2-[4-phenylpiperazinyl]ethyl]isochroman-6-carboxamide,

1-[2-[4-(4-hydroxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide,

(+/-)-1-[2-(4-phenyl-1-piperidiny)]ethyl]isochroman-6-carboxamide,

(+/-)-1-[2-[4-(2,4-dichlorophenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide,

10 1-[2-[4-(3-chloro-4-methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide.

37. An aromatic bicyclic amine according to claim 36 which is:

15 (S)-(-)-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide,

(R)-(+)-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]isochroman-6-carboxamide.

20 38. An aromatic bicyclic amine according to claim 36 where the pharmaceutically acceptable anion salt is selected from the group consisting of methanesulfonic, hydrochloric, hydrobromic, sulfuric, phosphoric, nitric, benzoic, citric, tartaric, fumaric, maleic, $\text{CH}_3(\text{CH}_2)_n\text{-COOH}$ where n is 0 thru 4, $\text{HOOC}(\text{CH}_2)_n\text{-COOH}$ where n is as defined above.

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* C L M S *