SUBSTITUTED CHROMAN DERIVATIVES

Field of the Invention

The present invention relates to new piperidinyl- or piperazinyl-substituted 3,4-dihydro-2*H*-1-benzopyran derivatives as *(R)*- enantiomers, *(S)*-enantiomers or racemates in the form of free base or pharmaceutically acceptable salts or solvates thereof, a process for their preparation, pharmaceutical compositions containing said therapeutically active compounds and to the use of said active compounds in therapy.

An object of the invention is to provide compounds for therapeutic use, especially compounds having a selective effect at a subgroup of 5-hydroxytryptamine receptors, designated h5-HT_{1B}-receptor (previously called the 5-$HT_{1D\beta}$-receptor) in mammals including man.

It is also an object of the invention to provide compounds with a therapeutic effect after oral administration.

Background of the Invention

Various central nervous system disorders such as depression, anxiety, etc. appear to involve the disturbance of the neurotransmitters noradrenaline (NA) and 5-hydroxytryptamine (5-HT), the latter also known as serotonin. The drugs most frequently used in the treatment of depression are believed to act by improving the neurotransmission of either or both of these physiological agonists. It appears that the enhancement of 5-HT neurotransmission primarily affects the depressed mood and anxiety, whereas the enhancement of noradrenaline neurotransmission affects the retardation symptoms occurring in depressed patients. The invention concerns compounds which have an effect on 5-HT neurotransmission.

Serotonin, or 5-HT, activity is believed to be involved in many different types of psychiatric disorders. For instance it is believed that an increase in 5-HT activity is

associated with anxiety, while a decrease in 5-HT release has been associated with depression. Serotonin has in addition been implicated in such diverse conditions as eating disorders, gastrointestinal disorders, cardiovascular regulation disorders and sexual disturbances.

The 5-HT Receptors

The various effects of 5-HT may be related to the fact that serotonergic neurons stimulate the secretion of several hormones, e.g. cortisol, prolactin, ß-endorphin, vasopressin and others. The secretion of each of these other hormones appears to be regulated on a specific basis by several different 5-HT (serotonin) receptor subtypes. With the aid of molecular biology techniques, to date these receptors have been classified as 5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6 and 5-HT_7 with the 5-HT_1 receptor further divided into the 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E} and 5-HT_{1F} subtypes. Each receptor subtype is involved in a different serotonin function and has different properties.

Regulation of the 5-HT transmission

The release of 5-HT is feedback-regulated by two different subtypes of 5-HT receptors. Inhibitory 5-HT_{1A} autoreceptors are located on the cell bodies in the raphé nuclei which upon stimulation by 5-HT decrease the impulse propagation in the 5-HT neurons and thereby reducing the 5-HT released at the nerve terminals. Another subtype of inhibitory 5-HT receptors is located on the 5-HT nerve terminals, the h5-HT_{1B} receptors (in rodents the r5-HT_{1B} receptors) which regulate the synaptic concentration of 5-HT by controlling the amount of 5-HT that is released. An antagonist of these terminal autoreceptors thus increases the amount of 5-HT released by nerve impulses which has been shown in both *in vitro* and *in vivo* experiments.

The use of an antagonist of the terminal h5-HT_{1B} autoreceptor will accordingly increase the synaptic 5-HT concentration and enhance the transmission in the 5-HT system. It would thus produce an antidepressant effect making it useful as a medication for depression.

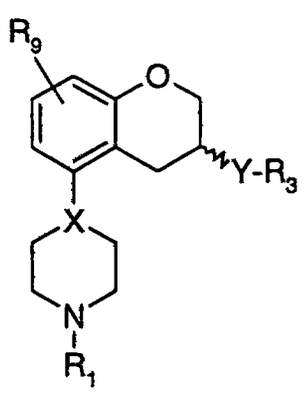
Other localizations of h5-HT_{1B} receptor subtype also exist. A large part of these postsynaptic receptors appear to be located on nerve terminals of other neuronal systems (so called heteroreceptors). Since the h5-HT_{1B} receptor mediates inhibitory responses an antagonist of this receptor subtype might also increase the release of other neurotransmitters than 5-HT.

Compounds having h5-HT_{1B} activity may according to well known and recognised pharmacological tests be divided into full agonists, partial agonists and antagonists.

Disclosure of the Invention

The object of the present invention is to provide compounds having a selective effect at the h5-HT_{1B} receptor, preferably antagonistic properties, as well as having a good bioavailability. The effect on the other receptors chosen from, for example, the 5-HT_{1A}, 5-HT_{2A}, D_1, D_{2A}, D_3, α_1 and α_2 receptor has been investigated.

Accordingly, the present invention provides compounds of the formula I



(I)

wherein

X is N or CH;

Y is NR_2CH_2, CH_2NR_2, NR_2CO, $CONR_2$ or NR_2SO_2

wherein R_2 is H or C_1-C_6 alkyl;

R_1 is H, C_1-C_6 alkyl or C_3-C_6 cycloalkyl;

R_3 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl or $(CH_2)_n$-aryl,

wherein aryl is phenyl or a heteroaromatic ring containing one or two heteroatoms selected from N, O and S and which may be mono- or di-substituted with R_4 and/or R_5;

wherein R_4 is H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halogen, CN, CF_3, OH, C_1-C_6 alkoxy, NR_6R_7, OCF_3, SO_3CH_3, SO_3CF_3, $SO_2NR_6R_7$, phenyl, phenyl-C_1-C_6 alkyl, phenoxy, C_1-C_6 alkylphenyl, an optionally substituted heterocyclic or heteroaromatic ring containing one or two heteroatoms selected from N, O, S, SO and SO_2 wherein the substituent(s) is(are) selected from C_1-C_6 alkyl, C_3-C_6 cycloalkyl and phenyl-C_1-C_6 alkyl; or COR_8;

wherein R_6 is H, C_1-C_6 alkyl or C_3-C_6 cycloalkyl;

R_7 is H, C_1-C_6 alkyl or C_3-C_6 cycloalkyl; and

R_8 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, CF_3, NR_6R_7, phenyl, or a heterocyclic ring containing one or two heteroatoms selected from N, O, S, SO and SO_2;

wherein R_5 is H, OH, CF_3, OCF_3, halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy;

n is 0-4;

R_9 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, OCF_3, $OCHF_2$, OCH_2F, halogen, $CONR_6R_7$, CN, CF_3, OH, C_1-C_6 alkoxy, NR_6R_7, SO_3CH_3, SO_3CF_3, $SO_2NR_6R_7$, an unsubstituted or substituted heterocyclic or heteroaromatic ring containing one or two heteroatoms selected from N and O, wherein the substituent(s) is(are) C_1-C_6 alkyl; or COR_8; wherein R_6, R_7 and R_8 are as defined above,

as *(R)*-enantiomers, *(S)*-enantiomers or a racemate in the form of a free base or a pharmaceutically acceptable salt or solvate thereof which possess a high selective effect at the h5-HT_{1B} receptor and also show sufficient bioavailability after oral administration.

In the present context C_1-C_6 alkyl may be straight or branched. C_1-C_6 alkyl may be methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, t-pentyl, neo-pentyl, n-hexyl or i-hexyl.

In the present context C_1-C_6 alkoxy may be straight or branched. C_1-C_6 alkoxy may be methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, n-pentyloxy, i-pentyloxy, t-pentyloxy, neo-pentyloxy, n-hexyloxy or i-hexyloxy.

In the present context C_3-C_6 cycloalkyl may be cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, preferably cyclohexyl.

In the present context halogen may be fluoro, chloro, bromo or iodo.

In the present context the heteroaromatic ring containing one or two heteroatoms selected from N, O or S preferably is a 5- or 6-membered heteroaromatic ring and may be furyl, imidazolyl, isoxazolyl, isothiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, thiazolyl or thienyl. The heteroaromatic ring can be either substituted or unsubstituted.

In the present context the heterocyclic ring containing one or two heteroatoms selected from N, O, S, SO or SO_2 may optionally contain a carbonyl function and is preferably a 5-, 6- or 7-membered heterocyclic ring and may be imidazolidinyl, imidazolinyl, morpholinyl, piperazinyl, piperidinyl, piperidonyl, pyrazolidinyl, pyrazolinyl, pyrrolidinyl, pyrrolinyl, tetrahydropyranyl, thiomorpholinyl, preferably piperidino, 1-piperazinyl, morpholino, thiomorpholino and 4-piperidon-1-yl.

A preferred embodiment of the invention relates to compounds of formula I wherein Y is NHCO or CONH i.e. amides. Of these compounds, the compounds wherein R_9 is C_1-C_6 alkyl, C_1-C_6 alkoxy, $OCHF_2$ or OCH_2F and R_3 is unsubstituted phenyl, or mono- or di-substituted phenyl, and especially ortho-, meta- or para- substituted phenyl, and particularly these wherein the substituent R_4 is phenyl, phenyl-C_1-C_6 alkyl, cyclohexyl, piperidino,

1-piperazinyl, morpholino, CF_3, 4-piperidon-1-yl, n-butoxy or COR_8 wherein R_8 is phenyl, cyclohexyl, 4-piperidon-1-yl, 1-piperazinyl, morpholino, CF_3, piperidino or NR_6R_7, are preferred.

Examples of combinations of substituents are:

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is OCH_3;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is piperidino, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is piperidino, R_5 is H, R_9 is OCH_3;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_9 is OCH_3;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is morpholino, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is morpholino, R_5 is H, R_9 is OCH_3;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is piperidino, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is OCH_3;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_9 is CH_3, C_2H_5 or C_3H_7;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is piperidino, R_5 is H, R_9 is OCH_3;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is piperidino, R_5 is H, R_9 is OCH_3;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is COR_8, R_8 is cyclohexyl, R_9 is CH_3, C_2H_5 or C_3H_7;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is morpholino, R_5 is H, R_9 is OCH_3;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_9 is CH_3, C_2H_5 or C_3H_7.

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is piperidino, R_5 is H, R_9 is OCH_3;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is piperidino, R_5 is H, R_9 is OCH_3;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is OCH_3;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is morpholino, R_5 is H, R_9 is OCH_3;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is OCH_3;

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X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is morpholino, R_5 is H, R_9 is OCH_3;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is piperidino, R_5 is H, R_9 is OCH_3;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is OCH_3;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_9 is OCH_3;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is morpholino, R_5 is H, R_9 is OCH_3;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is piperidino, R_5 is H, R_9 is OCH_3;

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X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is piperidino, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

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X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is OCH_3;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is OCH_3;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is piperidino, R_5 is H, R_9 is OCH_3;

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X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is COR_8, R_8 is morpholino, R_9 is OCH_3;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is morpholino, R_5 is H, R_9 is OCH_3;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is morpholino, R_5 is H, R_9 is OCH_3;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is OCH_3;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is COR_8, R_8 is morpholino, R_9 is OCH_3;

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X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_9 is CH_3, C_2H_5 or C_3H_7;

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X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_9 is OCH_3;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is COR_8, R_8 is cyclohexyl, R_9 is OCH_3;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_9 is OCH_3;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is COR_8, R_8 is NR_6R_7, $R_6R_7CH_3$, C_2H_5 or C_3H_7, R_9 is OCH_3;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_9 is OCH_3.

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X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is morpholino, R_5 is H, R_9 is OCH_3;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_9 is OCH_3;

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X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is piperidino, R_5 is H, $R_9$is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_9 is CH_3, C_2H_5 or C_3H_7;

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X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is piperidino, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

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X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is COR_8, R_8 is NR_6R_7, $R_6R_7CH_3$, C_2H_5 or C_3H_7, R_9 is CH_3, C_2H_5 or C_3H_7;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is morpholino, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is piperidino, R_5 is H, R_9 is OCH_3;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is morpholino, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is morpholino, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is morpholino, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is piperidino, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is OCH_3;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_9 is OCH_3;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is piperidino, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_9 is CH_3, C_2H_5 or C_3H_7;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is piperidino, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is piperidino, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_9 is CH_3, C_2H_5 or C_3H_7;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is piperidino, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is morpholino, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is morpholino, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is OCH_3;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is COR_8, R_8 is morpholino, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is morpholino, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is morpholino, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is morpholino, R_5 is H, R_9 is OCH_3;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is COR_8, R_8 is morpholino, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is morpholino, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_9 is CH_3, C_2H_5 or C_3H_7;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is morpholino, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is piperidino, R_5 is H, R_9 is OCH_3;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is morpholino, R_5 is H, R_9 is OCH_3;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is piperidino, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7.

Preferred compounds are:

(*S*)-*N*-[8-Methyl-5-(4-methylpiperazin-1-yl)-3,4-dihydro-2*H*-1-benzopyran-3-yl]-4-(dimethylaminocarbonyl)benzamide and

N-(4-Morpholinophenyl)-8-methoxy-5-(4-methylpiperazin-1-yl)-3,4-dihydro-2*H*-1-benzopyran-3-carboxamide

The compounds of the present invention are in the form of the racemate or the *(R)*- or *(S)*-enantiomer in the form of a free base or a pharmaceutically acceptable salt or solvate thereof. Compounds in the form of the (*S*)-enantiomer are considered preferred.

Both organic and inorganic acids can be employed to form non-toxic pharmaceutically acceptable acid addition salts of the compounds of this invention. Illustrative acids are sulfuric, nitric, phosphoric, oxalic, hydrochloric, formic, hydrobromic, citric, acetic, lactic, tartaric, dibenzoyltartaric, diacetyltartaric, palmoic, ethanedisulfonic, sulfamic, succinic, propionic, glycolic, malic, gluconic, pyruvic, phenylacetic, 4-aminobenzoic, anthranilic, salicylic, 4-aminosalicylic, 4-hydroxybenzoic, 3,4-dihydroxybenzoic, 3,5-dihydroxybenzoic, 3-hydroxy-2-naphthoic, nicotinic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, benzenesulfonic, p-toluenesulfonic, sulfanilic, naphthalenesulfonic, ascorbic, cyclohexylsulfamic, fumaric, maleic and benzoic acids. These salts are readily prepared by methods known in the art.

The preferred solvates of the compounds of this invention are the hydrates.

Pharmaceutical Formulations

In a second aspect the present invention provides a pharmaceutical formulation comprising as active ingredient a therapeutically effective amount of the compound of formula I as an enantiomer or a racemate in the form of a free base or a pharmaceutically acceptable salt or solvate thereof, optionally in association with diluents, excipients or inert carriers.

According to the present invention the compound of the invention will normally be administered orally, rectally or by injection, in the form of pharmaceutical formulations comprising the active ingredient either as a free base or a pharmaceutically acceptable non-toxic acid addition salt, e.g. the hydrochloride, hydrobromide, lactate, acetate, phosphate, sulfate, sulfamate, citrate, tartrate, oxalate and the like in a pharmaceutically acceptable dosage form. The dosage form may be a solid, semisolid or liquid preparation. Usually the active substance will constitute between 0.1 and 99% by weight of the preparation, more specifically between 0.5 and 20% by weight for preparations intended for injection and between 0.2 and 50% by weight for preparations suitable for oral administration.

To produce pharmaceutical formulations containing the compound of the invention in the form of dosage units for oral application, the selected compound may be mixed with a solid excipient, e.g. lactose, saccharose, sorbitol, mannitol, starches such as potato starch, corn starch or amylopectin, cellulose derivatives, a binder such as gelatine or poly-vinylpyrrolidone, and a lubricant such as magnesium stearate, calcium stearate, polyethylene glycol, waxes, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain e.g. gum arabic, gelatine, talcum, titanium dioxide, and the like. Alternatively, the tablet can be coated with a polymer known to the person skilled in the art, dissolved in a readily volatile organic solvent or mixture of organic solvents. Dyestuffs may be added to these coatings in order to readily distinguish between tablets containing different active substances or different amounts of the active compound.

For the preparation of soft gelatine capsules, the active substance may be admixed with e.g. a vegetable oil or poly-ethylene glycol. Hard gelatine capsules may contain granules of the active substance using either the above mentioned excipients for tablets e.g. lactose, saccharose, sorbitol, mannitol, starches (e.g. potato starch, corn starch or amylopectin), cellulose derivatives or gelatine. Also liquids or semisolids of the drug can be filled into hard gelatine capsules.

Dosage units for rectal application can be solutions or suspensions or can be prepared in the form of suppositories comprising the active substance in a mixture with a neutral fatty base, or gelatine rectal capsules comprising the active substance in admixture with vegetable oil or paraffin oil. Liquid preparations for oral application may be in the form of syrups or suspensions, for example solutions containing from about 0.1% to about 20% by weight of the active substance herein described, the balance being sugar and mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethyl-cellulose as a thickening agent or other excipients known to the person skilled in the art.

Solutions for parenteral applications by injection can be prepared in an aqueous solution of a water-soluble pharmaceutically acceptable salt of the active substance, preferably in a concentration of from about 0.1% to about 10% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may conveniently be provided in various dosage unit ampoules.

Suitable daily doses of the compound of the invention in therapeutical treatment of humans are about 0.01-100 mg/kg bodyweight at peroral administration and 0.001-100 mg/kg bodyweight at parenteral administration.

The compound of the invention may be used in a combination with a 5-HT reuptake inhibitor, such as fluoxetine, paroxetine, citalopram, clomipramine, sertraline, alaproclate or fluvoxamin, preferably paroxetine or citalopram. Another possible combination is to use the compound of the invention together with a monoamine oxidase inhibitor, such as moclobemide, tranylcypramine, brofaromide or phenelzine, preferably moclobemide or phenelzine . Still another possible combination is the compound of the invention together with a 5-HT_{1A} antagonist, such as the compounds disclosed in WO 96/33710, preferably *(R)*-5-carbamoyl-3-(*N,N*-dicyclobutylamino)-8-fluoro-3,4-dihydro-2*H*-1-benzopyran.

Medical and Pharmaceutical Use

In a further aspect the present invention provides the use of the compounds of formula I in therapy as a h5-HT $_{1B}$ antagonist, partial agonist or full agonist, preferably as an antagonist and the use in the treatment of 5-hydroxytryptamine mediated disorders. Examples of such disorders are disorders in the CNS such as mood disorders (depression, major depressive episodes, dysthymia, seasonal affective disorder, depressive phases of bipolar disorder), anxiety disorders (obsessive compulsive disorder, panic disorder with/without agoraphobia, social phobia, specific phobia, generalized anxiety disorder, posttraumatic stress disorder), personality disorders (disorders of impulse control, trichotellomania), obesity, anorexia, bulimia, premenstrual syndrome, sexual disturbances, alcoholism, tobacco abuse, autism, attention deficit, hyperactivity disorder, migraine, memory disorders (age associated memory impairment, presenile and senile dementia), pathological aggression, schizophrenia, endocrine disorders (e g hyperprolactinaemia), stroke, dyskinesia, Parkinson´s disease, thermoregulation, pain and hypertension. Other examples of hydroxytryptamine mediated disorders are urinary incontinence, vasospasm and growth control of tumors (e g lung carcinoma).

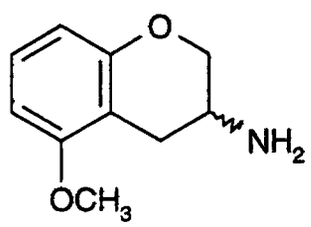
Methods of Preparation

The present invention also relates to processes for preparing the compound of formula I. Throughout the following description of such processes it is understood that, where appropriate, suitable protecting groups will be added to, and subsequently removed from, the various reactants and intermediates in a manner that will be readily understood by one skilled in the art of organic synthesis. Conventional procedures for using such protecting groups as well as examples of suitable protecting groups are described, for example, in "Protective Groups in Organic Synthesis" T.W. Greene, Wiley-Interscience, New York, 1991.

Methods of Preparation of Intermediates

1. In the case where Y is NR_2CO and X is N

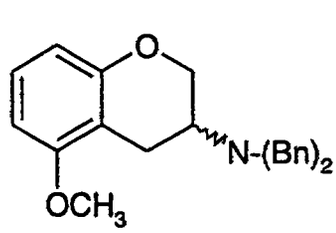
(i) Benzylation of the compound of the formula **II**, either as a racemate (described in: Thorberg, S-O.; Hall, H.; Åkesson, C.; Svensson, K.; Nilsson, J. L. G. *Acta Pharm. Suec.* **1987**, *24(4)*, 169-182) or as an enantiomer (described in: patent application WO 93/07135),



(II)

to obtain a compound of formula **III** by the reaction with a suitable benzylating agent, e.g. benzyl halide such as benzyl bromide, benzyl chloride, or an activated alcohol, e.g. benzyl-mesylate or tosylate. The reaction may be carried out by using the salt or the base of compound **II** in a suitable solvent, e.g. *N,N*-dimethylformamide, acetone or acetonitrile, with a suitable base, e.g. NaOH, $NaHCO_3$, K_2CO_3 or a trialkylamine, such as triethylamine at a reaction temperature within the range of +20 °C to +150 °C. The presence of a suitable catalyst, e.g. alkali metal iodide such as potassium iodide or sodium iodide, may increase the speed of the reaction.

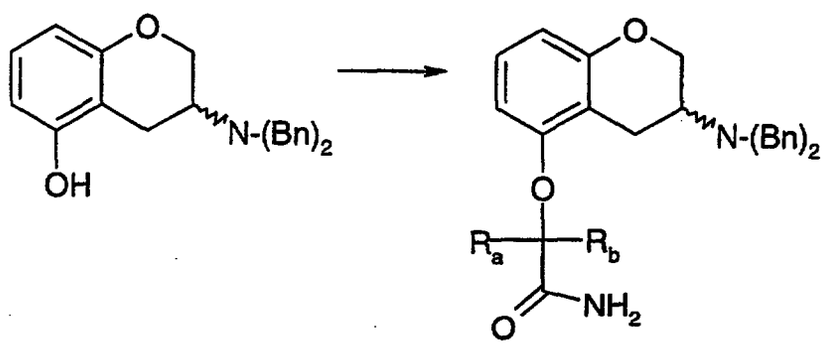
(ii) Demethylation of the compound of formula **III**



(III)

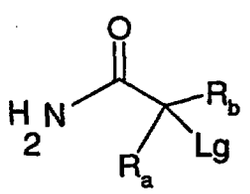
to obtain a compound of formula **IV** may be carried out by treating the compound with an acidic reagent such as aqueous HBr, HI, HBr/CH_3COOH, BBr_3, $AlCl_3$, pyridine-HCl or with a basic nucleophilic reagent such as $CH_3C_6H_4SNa$ or C_2H_5SNa in a suitable solvent. Suitable solvents may be methylene chloride or chloroform and at a reaction temperature between -78 °C and +60 °C.

(iii) Conversion of the compound of formula **IV** to a compound of formula **V**



(IV) **(V)**

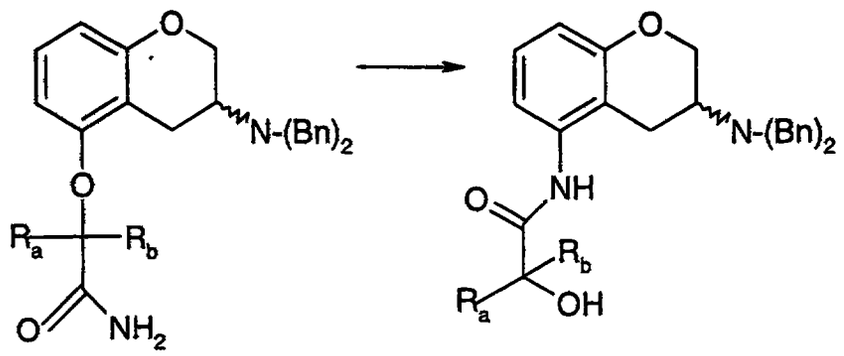
may be carried out by the reaction with a compound of formula **VI**



(VI)

where Lg denotes a leaving group, e.g. a halogen such as chlorine, bromine or iodine or an alkane- or arenesulfonyloxy group such as a p-toluenesulfonyloxy group, and R_a and R_b are hydrogen or a lower alkyl group, e.g. methyl. The process may be carried out with a salt of the compound of formula **IV** obtained by reaction with a base such as K_2CO_3, Na_2CO_3, KOH, NaOH, BuLi or NaH. The reaction may be conducted in a suitable solvent, e.g. an aprotic solvent such as dioxane, *N,N*-dimethylformamide, tetrahydrofuran, toluene, benzene or petroleum ether, and the reaction may occur between +20 °C and +150 °C.

(iv) Rearrangement of a compound of formula **V** to a compound of formula **VII**

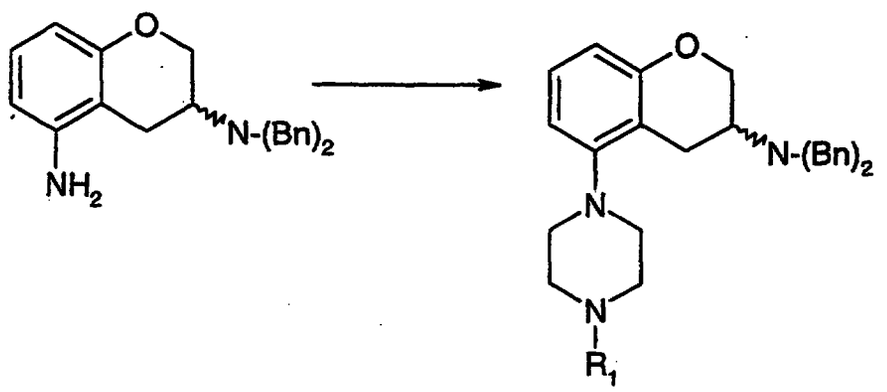


(V) **(VII)**

may be carried out in a suitable solvent, e.g. aprotic solvent such as *N,N* dimethylformamide, dioxane, 1,1,3,3-tetramethylurea, tetrahydrofuran or hexamethylphosphoric triamide, with a suitable base, e.g. K_2CO_3, KOH, potassium *tert*-butoxide or NaH, at a reaction temperature within the range of +20 °C to +150 °C. The presence of a co-solvent such as 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone or hexamethylphosphoric triamide in appropriate concentration in the solvent may increase the speed of the reaction.

(v) Hydrolysis of a compound of formula **VII** to a compound **VIII** may be carried out under acidic conditions using acids such as H_2SO_4, HCl or HBr in a suitable solvent, e.g. H_2O, ethanol, methanol or mixtures thereof, and the reaction may occur between +20 °C and +100 °C or under basic conditions using bases such as NaOH or KOH in a suitable solvent, e.g. H_2O, ethanol, methanol or mixtures thereof, and at a reaction temperature between +20 °C and +100 °C

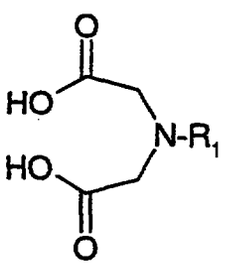
(vi) Conversion of compound of formula **VIII** to a compound of formula **IX**



(VIII) **(IX)**

may be carried out by

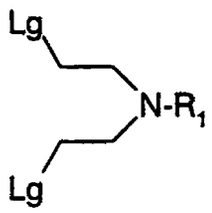
a) reaction with a compound of formula **X**



(X)

where R_1 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl. The process may be carried out in a suitable solvent, e.g. an aprotic/anhydrous solvent such as tetrahydrofuran or *N,N*-dimethylformamide, in the presence of coupling reagent such as *N,N*-carbonyldiimidazole and the reaction may occur between +20 °C and +130 °C. The reaction is followed by the reduction of the imide with a suitable reducing agent, e.g. $LiAlH_4$, in a suitable solvent, e.g. diethyl ether or tetrahydrofuran, at a temperature between +20 °C and reflux, or

b) by reaction with a compound of formula **XI**

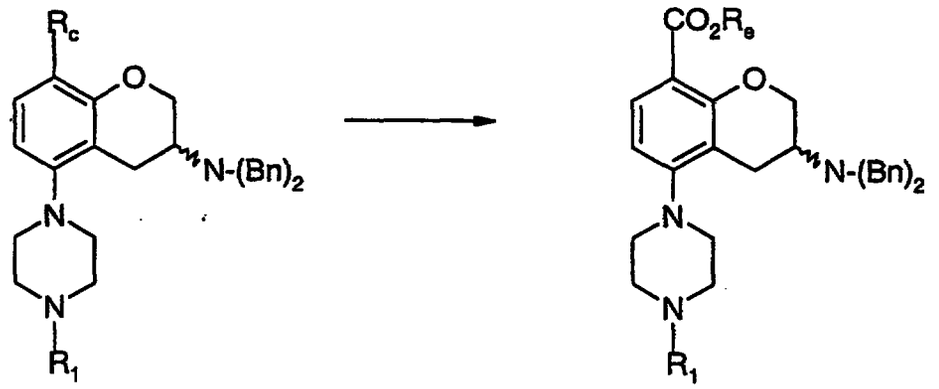


(XI)

where Lg denotes a leaving group, e.g. a halogen such as chlorine, bromine or iodine, or an alkane- or arenesulfonyloxy group such as p-toluenesulfonyloxy group, and R_1 is C_1-C_6-alkyl or C_3-C_6 cycloalkyl. The process may be carried out in a suitable solvent such as ethanol, butanol, *N,N*-dimethylformamide, acetonitrile or a mixture of water and acetonitrile with a suitable base, e.g. K_2CO_3, $NaHCO_3$ or KOH, and at a reaction temperature between +20 °C and +150 °C.

(vii) Halogenation of the compound of formula **IX** to a compound of formula **XII** where R_c denotes bromine, chlorine or iodine may be performed by a reagent such as ICl or Br_2, Cl_2 or SO_2Cl_2 with or without a suitable base such as sodium acetate in a suitable solvent such as acetic acid at a reaction temperature between +20 °C and +50 °C.

(viii) The conversion of a compound of formula **XII** where R_c is a halogen, e.g. bromine or iodine, to a compound of formula **XIII** where R_1 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl and R_e is C_1-C_6 alkyl



(XII) (XIII)

may be carried out by palladium-catalysed carbonylation. The process may be performed by reacting **XII** with an alcohol of formula R_eOH where R_e is C_1-C_6 alkyl at atmospheric or at elevated carbon monoxide pressure in a suitable solvent such as dioxane or *N,N*-dimethylformamide and at a reaction temperature between +20 °C and +120 °C in the presence of a suitable catalyst such as PdX_2, $L_2Pd(0)$, L_2PdX_2 where X denotes a halogen such as chlorine or bromine or for acetate and L denotes a suitable ligand such as triphenylphosphine, 1,3-bis(diphenylphosphinopropane) or 1,1´-bis(diphenylphosphino)ferrocene and a suitable trialkylamine such as triethylamine.

(ix) Conversion of a compound of formula **XIII** to a compound of formula **XIV** where R_1 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl and R_9 is $CONR_6R_7$ wherein R_6 and R_7 are H, C_1-C_6 alkyl or C_3-C_6 cycloalkyl may be performed by,

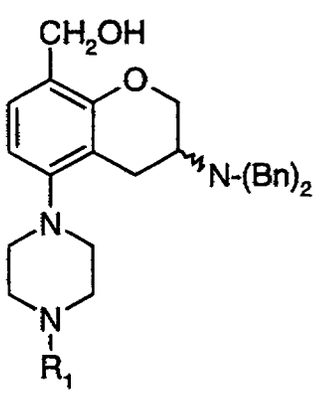
a) hydrolysis under basic conditions with a suitable base such as KOH, LiOH or C_2H_5SNa in a suitable solvent such as methanol, tetrahydrofuran or *N,N*-dimethylformamide, in the presence of water at a reaction temperature between 20 °C and reflux temperature, or under acidic conditions in a suitable solvent such as methanol or ethanol using acids such as aqueous HBr, HI, HBr/CH_3COOH at a reaction temperature between 20 °C and reflux temperature, or

cleavage with a Lewis acid such as BBr_3 or TMSI in a suitable solvent such as methylene chloride or chloroform and at a reaction temperature between -78 °C and + 120 °C .

b) conversion of the above formed acid to a acid chloride with a suitable reagent such as $SOCl_2$ or $(COCl)_2$, neat or in a suitable solvent such as methylene chloride or chloroform with or without a catalytic amount of *N,N*-dimethylformamide at a reaction temperature between -20 °C and reflux temperature.

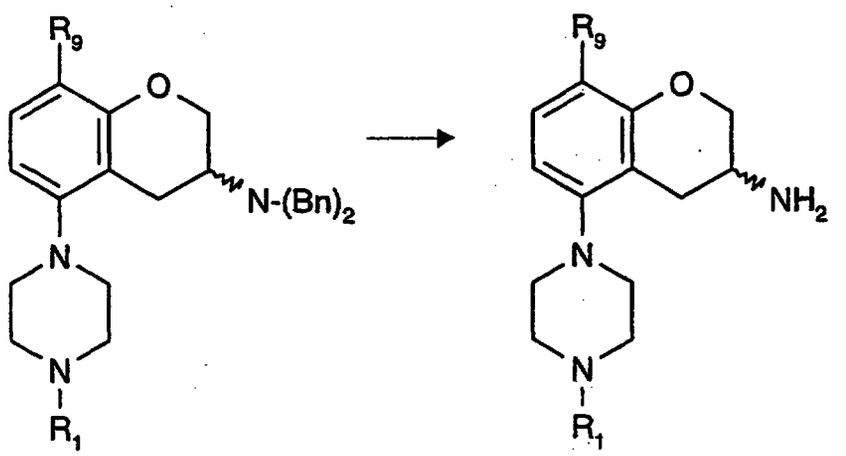
c) reacting the acid chloride with an excess of an amine of formula NHR_6R_7 where R_6 and R_7 are H, C_1-C_6 alkyl or C_3-C_6 cycloalkyl in a suitable solvent such as methylene chloride or dioxane at a reaction temperature between -20 °C and reflux temperature.

(x) Conversion of a compound of formula **XIII** to a compound of formula **XV** where R_1 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl may be performed by reduction with a suitable reducing agent such as $LiAlH_4$ or $LiAlH_2(OCH_2CH_2OCH_3)_2$ in a suitable solvent such as diethyl ether, tetrahydrofuran or toluene at a reaction temperature between +20 °C and reflux temperature.



(XV)

(xi) Conversion of a compound of formula **XIV** where R_9 is $CONR_6R_7$ and R_6 and R_7 are H, C_1-C_6 or C_3-C_6 cycloalkyl to a compound of formula **XVI** where R_1 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl and R_9 is CN or $CONR_6R_7$ where R_6,R_7 are H, C_1-C_6 alkyl or C_3-C_6 cycloalkyl



(XIV) (XVI)

may be carried out by cleavage of the benzyl groups by hydrogenation over a suitable catalyst containing palladium, rhodium, platina or nickel in a suitable solvent, e.g. acetic acid or ethanol, and the reaction may occur between +20 °C and +120 °C or, by debenzylation using ammonium formate and palladium on carbon in a suitable solvent such as methanol at a reaction temperature between +20 °C and +65 °C.

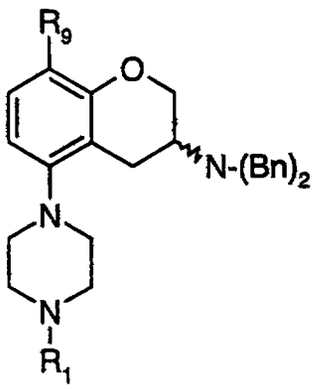
Conversion of a compound of formula **XIV** where R_9 is $CONH_2$ to a compound of formula **XVI** where R_9 is CN may be performed by

a) debenzylation as described above followed by,

b) dehydration with a suitable reagent such as $SOCl_2$ or P_2O_5 in a suitable solvent such as methylene chloride or toluene at a reaction temperature between +20 °C and +110 °C.

(xii) Conversion of a compound of formula **XV** to a compound of formula **XVI** where R_1 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl and R_9 is methyl may be performed by cleavage of the benzyl groups and reduction of the benzyl alcohol under conditions described in method xi above in a suitable solvent such as acetic acid with or without a strong acid such as HCl or HBr.

(xiii) Conversion of a compound of formula **XII** to a compound of formula **XVII** where R_1 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl and R_9 is OH



(XVII)

may be performed by metal-halogen exchange using a suitable alkyllithium or metal such as n-butyllithium or lithium in a suitable solvent such as tetrahydrofuran or diethyl ether, followed by treatment with trimethylborate, a peroxy acid such as peracetic acid or hydrogen peroxide and an acid such as acetic acid. The reaction may be performed at a temperature between -78 °C and +20 °C.

(xiv) Conversion of a compound of the formula **XII** to a compound of the formula **XVII** where R_9 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl or fluorine may be performed by lithium-halogen exchange using a suitable alkyllithium or metal such as n-butyllithium or lithium in a suitable solvent such as tetrahydrofuran or diethyl ether, followed by treatment with an alkyl halide such as methyl iodide or ethyl iodide or by a fluorinating agent such as *N*-fluorobenzenesulfonimide and at a reaction temperature between -78 °C and room temperature.

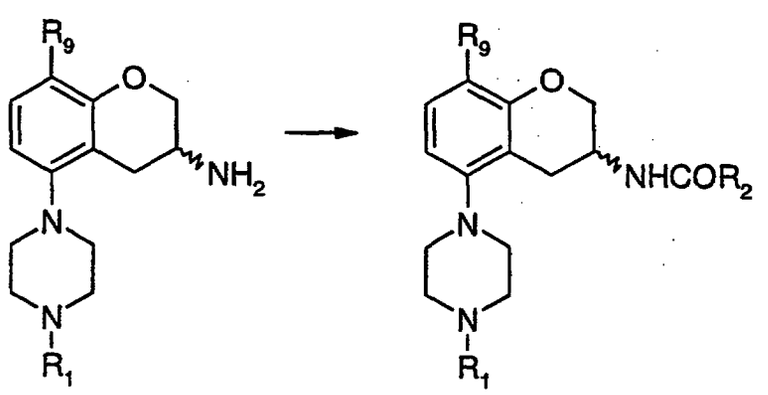
(xv) Conversion of a compound of formula **XVII** to a compound of formula **XVI** where R_9 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, F or OH may be performed by debenzylation under conditions described in method xi above.

(xvi) Conversion of a compound of formula **XVII** where R_9 is OH to a compound of formula **XVI** where R_9 is C_1-C_6 alkoxy or $OCHF_2$ may be performed by alkylation with a suitable alkylating agent such as an alkyl halide, e.g methyl iodide or ethyl iodide or

chlorodifluoromethane, in the presence of a suitable base such as NaH, KOH or NaOH in a suitable solvent such as isopropanol, *N,N*-dimethylformamide or dioxane at a reaction temperature between +20 °C and +80 °C followed by debenzylation under conditions described in method xi above.

(xvii) Conversion of a compound of formula **IX** to a compound of formula **XVI** where R_9 is a halogen such as bromine, chlorine or iodine may be performed by debenzylation under conditions described in method xi above followed by halogenation using a suitable reagent such as Br_2, Cl_2, SO_2Cl_2 or ICl in a suitable solvent such as acetic acid, HCl/ethanol, methylene chloride or toluene with or without a suitable base such as sodium acetate at a reaction temperature between -20 °C and +20 °C.

(xviii) Conversion of a compound of formula **XVI,** to a compound of formula **XVIII,** where R_1 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl, R_2 is H, C_1-C_5 alkyl and R_9 is as in formula **I** above, may be performed by



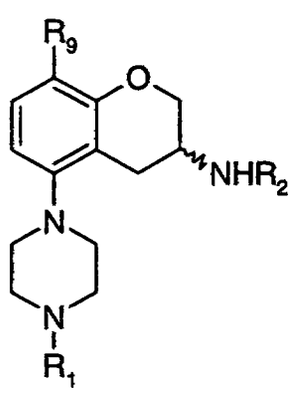
(XVI) **(XVIII)**

acylation with an appropriate activated carboxylic acid of formula R_2COOH where R_2 is H or C_1-C_5 alkyl in a suitable solvent such as methylene chloride or chloroform in the presence of a suitable base such as KOH, NaOH, K_2CO_3 or a trialkylamine e.g. triethylamine.

Activation of the carboxylic acid may be achieved by

a) transforming the carboxylic acid into the corresponding acid chloride using a reagent such as $SOCl_2$ or $(COCl)_2$ in a suitable solvent such as methylene chloride or chloroform with or without a catalytic amount of *N,N*-dimethylformamide at a reaction temperature between +20 °C and +110 °C.

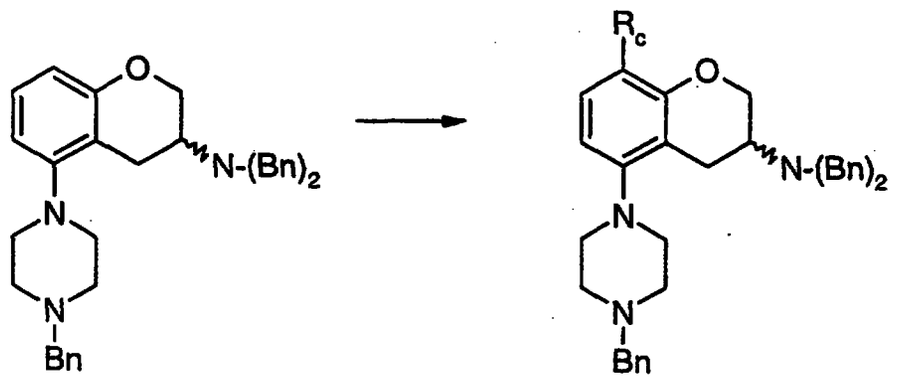
(xix) Conversion of a compound of formula **XVIII** to a compound of formula **XIX** where R_1 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl and R_2 is C_1-C_6 alkyl may be performed by reduction with a suitable reducing agent such as lithium aluminum hydride or diborane in a suitable solvent such as diethyl ether, tetrahydrofuran or dioxane at a reaction temperature between +20 °C and reflux temperature.



(XIX)

(xx) Conversion of a compound of formula **VIII** to a compound of formula **XX** may be performed with for example bis(2-chloroethyl)benzylamine or benzylaminodiacetic acid under conditions described in method vi above.

(xxi) Conversion of a compound of formula **XX** to a compound of formula **XXI** where R_c is bromine, chlorine or iodine may be performed under conditions described in method vii above.



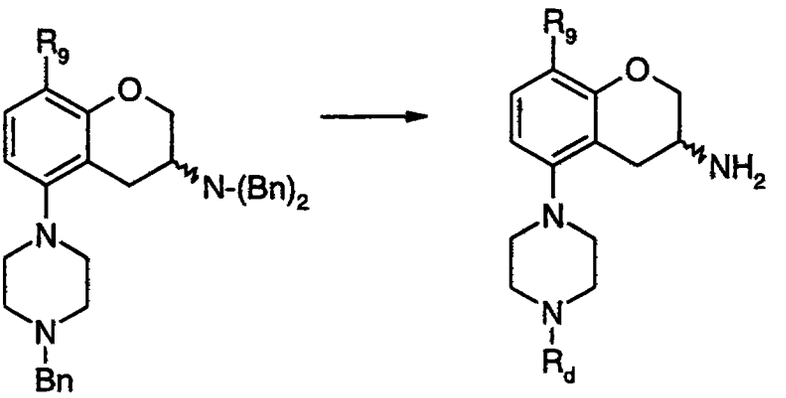
(XX) (XXI)

(xxii) Conversion of a compound of formula **XXI** to a compound of formula **XXII** where R_9 is

a) C_1-C_6 alkyl or fluorine may be performed by litium-halogen exchange and reaction with an appropriate alkyl halide or a fluorinating agent under conditions described in method xiv above.

b) $CONR_6R_7$ wherein R_6 and R_7 are C_1-C_6 alkyl or C_3-C_6 cycloalkyl may be performed by reacting **XXI** with an excess of an amine of the formula NHR_6R_7 wherein R_6 and R_7 are as described above at atmospheric or elevated carbon monoxide-pressure using a suitable catalyst such as L_2PdX_2 where L denotes a suitable ligand such as triphenylphosphine or 1,1´-bis(diphenylphosphino)ferrocene and X denotes chlorine, bromine or acetate, in a suitable solvent such as *N,N*-dimethylformamide or dioxane and at a reaction temperature between +20 °C and +100 °C.

(xxiii) Conversion of a compound of formula **XXII** to a compound of formula **XXIII** where R_9 is C_1-C_6 alkyl or fluorine and R_d is a suitable protecting group such as *tert*-butyloxycarbonyl or benzoyloxycarbonyl may be performed by



(XXII) (XXIII)

debenzylation under conditions described in method xi above followed by reaction with a suitable acylation agent such as di-*tert*-butylcarbonate and a suitable base such as triethylamine in a suitable solvent such as methylene chloride or chloroform and at a reaction temperature between 0 °C and +20 °C.

(xxiv) Conversion of a compound of formula **XX** to a compound of formula **XXIII** where R_9 is a halogen such as bromine, chlorine or iodine may be performed by

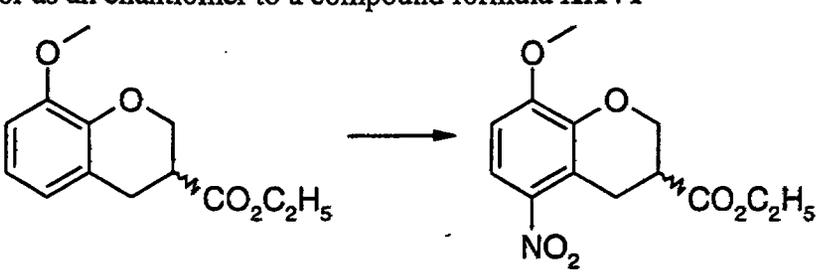
a) debenzylation under conditions described in method xi above

b) halogenation under conditions described in method vii above

c) protection under conditions described in method xxiii above.

2. In the case where Y is $CONR_2$ and X is N

(i) Conversion of a compound of formula **XXV** either as a racemate (described in: Thorberg, S-O.; Hall, H.; Åkesson, C.; Svensson, K.; Nilsson, J. L. G. *Acta Pharm. Suec.* **1987**, *24(4)*, 169-182) or as an enantiomer to a compound formula **XXVI**



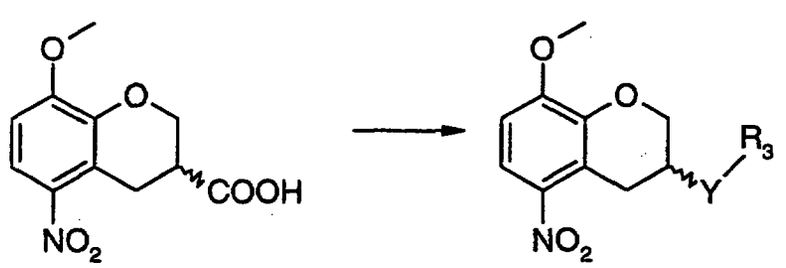
(XXV) (XXVI)

may be performed by electrophilic aromatic substitution using nitric acid in a suitable solvent such as acetic anhydride, methylene chloride or acetic acid at a reaction temperature between -20 °C and room temperature.

(ii) Conversion of a compound of formula **XXVI**, to a compound of formula **XXVII**, where R_9 is methoxy, may be performed by hydrolysis either under acidic conditions using acids such as H_2SO_4, HCl or HBr in a suitable solvent such as water, ethanol, methanol, acetic acid or mixtures thereof and the reaction may occur at temperatures between +20 °C and reflux or,

under basic conditions using bases such as KOH, NaOH or LiOH in a suitable solvent such as water, ethanol, methanol or mixtures thereof and the reaction may occur at temperatures between +20 °C and reflux .

(iii) Conversion of a compound of formula **XXVII** to a compound of formula **XXVIII** where Y is $CONR_2$ wherein R_2 and R_3 is as defined in formula **I** above may be performed by



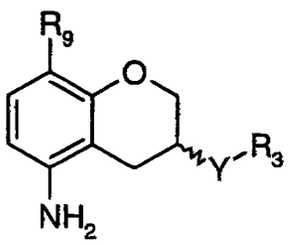
(XXVII) **(XXVIII)**

a) activating the carboxylic acid of formula **XXVII** under conditions described in method **1**, xviii above

b) reacting the formed acid chloride with an amine of formula NHR_2R_3 where R_2 and R_3 are as defined in formula **I** above, in a suitable solvent such as methylene chloride or

chloroform in the presence of a suitable base such as triethylamine or K_2CO_3 at a reaction temperature between -20 °C and reflux temperature.

(iv) Conversion of a compound of formula **XXVIII** to a compound of formula **XXIX**, where R_9 is C_1-C_6 alkyl, C_1-C_6 alkoxy, $CONR_6R_7$ where R_6 and R_7 are C_1-C_6 alkyl or C_1-C_6 cycloalkyl and Y is $CONR_2$ wherein R_2 and R_3 is as defined in formula I above, may be performed by

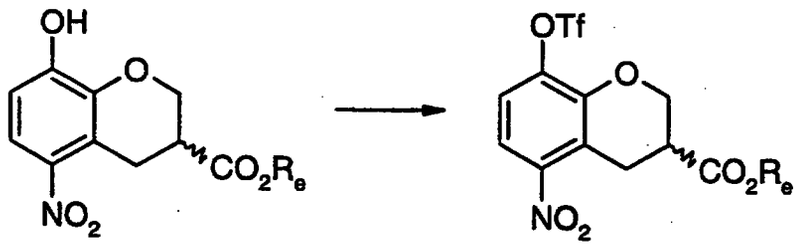


(XXIX)

reduction of the nitro group either using hydrogen at atmospheric or elevated pressure and a catalyst such as palladium, platina or nickel in a suitable solvent such as methanol, ethanol or acetic acid at a reaction temperature between +20 °C and +120 °C or by a reducing agent such as sodium dithionite or stannous chloride or ammonium formate and Pd/C in a suitable solvent such as methanol or ethanol at a reaction temperature between +20 °C and + 80 °C.

(v) Conversion of a compound of formula **XXVI** to a compound of formula **XXX** may be performed by demethylation under conditions described in method **1**, ii above. During the demethylation of **XXVI**, cleavage of the ester may occur and the carboxylic acid could in such case be re-esterified by methods known by a person skilled in the art.

(vi) Conversion of a compound of formula **XXX** to a compound with formula **XXXI** where R_e is C_1-C_6 alkyl may be performed by



(XXX) **(XXXI)**

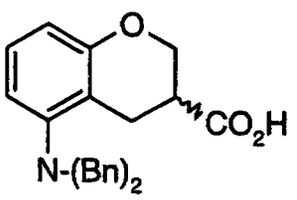
reacting **XXX** with a reagent such as trifluoromethanesulfonic anhydride or *N*-(2-pyridyl)triflimide and a suitable base such as triethylamine or lithium diisopropylamide in a suitable solvent such as methylene chloride or tetrahydrofuran and at a reaction temperature between -78 °C and 0 °C.

(vii) Conversion of a compound of formula **XXXI**, to a compound of formula **XXVII** where the carboxylic acid has a protection group R_e and R_9 is

a) C_1-C_6 alkyl, may be carried out by a Stille-coupling using an alkyltin reagent such as tetramethyltin and a suitable catalyst such as L_2PdCl_2 wherein L is a suitable ligand such as triphenylphosphine or 1,1´-bis(diphenylphosphino)ferrocene in the presence of LiCl in a suitable solvent such as *N,N*-dimethylformamide or dioxane at a reaction temperature between +20 °C and +100 °C.

b) $CONR_6R_7$ wherein R_6 and R_7 are C_1-C_6 alkyl or C_3-C_6 cycloalkyl, may be performed by reacting **XXXI** with an excess of an amine of the formula NHR_6R_7 wherein R_6 and R_7 are as described above at atmospheric or elevated carbon monoxide-pressure using a suitable catalyst such as L_2PdX_2 where L denotes a suitable ligand such as triphenylphosphine or 1,1´-bis(diphenylphosphino)ferrocene and X denotes chlorine, bromine or acetate, in a suitable solvent such as *N,N*-dimethylformamide or dioxane and at a reaction temperature between +20 °C and +100 °C.

(viii) Conversion of a compound of formula **XXXI** to a compound of formula **XXXII** may be performed by



(XXXII)

a) reduction under conditions described in method **1**, xi above

b) benzylation under conditions described in method **1**, i above

c) hydrolysis of the ester under conditions described in method **1**, ix above.

(ix) Conversion of a compound of formula **XXXII** to a compound of formula **XXIX** where R_9 is a halogen such as bromine, chlorine or iodine may be performed by

a) activating the carboxylic acid under conditions described in method **1**, xviii above

b) reacting with an amine of formula NHR_2R_3 wherein R_2 is hydrogen or C_1-C_6 alkyl, R_3 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl or $(CH_2)_n$-aryl, wherein aryl is phenyl or a heterocyclic ring containing one or two heteroatoms selected from N,O and S and which may be mono- or disubstituted with R_4 and/or R_5;

wherein R_4 is hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, F, CF_3, OH, $SO_2NR_6R_7$, phenyl, phenyl-C_1-C_6 alkyl, phenoxy, C_1-C_6 alkylphenyl, an optionally substituted heterocyclic or heteroaromatic ring containing one or two heteroatoms selected from N, O, S, SO_2 wherein the substituent(s) is (are) selected from C_1-C_6 alkyl or C_3-C_6 cycloalkyl, phenyl-C_1-C_6 alkyl;

wherein R_6 and R_7 are hydrogen, C_1-C_6 alkyl or C_3-C_6 cycloalkyl;

wherein R_5 is hydrogen, OH, F, CF_3, C_1-C_6 alkyl or C_3-C_6 cycloalkyl;

and n is 0-4

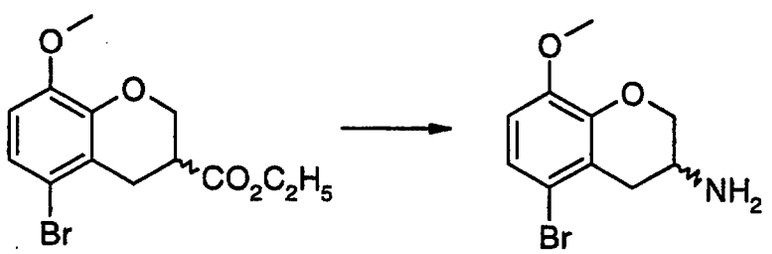
c) debenzylation under conditions described in method **1**, xi above

d) halogenation under conditions described in method vii above.

3. In the case where Y is NR_2CO and X is CH

(i) Conversion of a compound of formula **XXV** to a compound of formula **XXXIII** may be performed by electrophilic aromatic substitution using a halogenating reagent such as Br_2 or *N*-bromosuccinimide and a suitable base such as sodium acetate in a suitable solvent such as acetic acid or acetonitrile and at a reaction temperature between 0 °C and +20 °C.

(ii) Conversion of a compound of formula **XXXIII** to a compound of formula **XXXIV** may be performed by



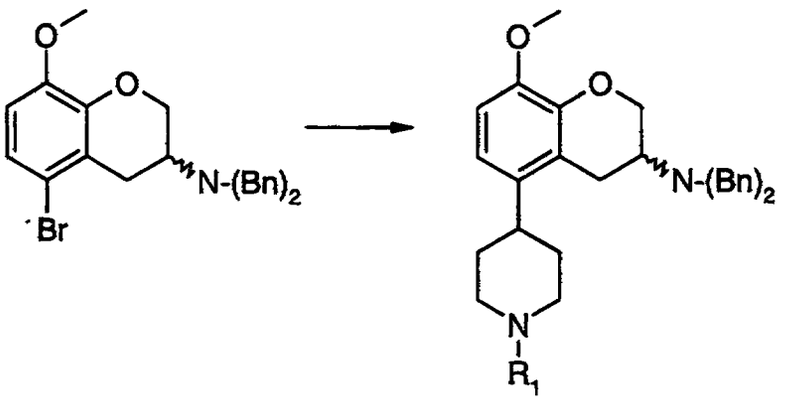
(XXXIII) **(XXXIV)**

a) hydrolysis of the ester under conditions described in method **1**, v above

b) a Curtius rearrangement by transforming the carboxylic acid into an acyl azide with a suitable reagent such as $SOCl_2$ and a suitable base such as triethylamine in a suitable solvent such as methylene chloride or toluene followed by heating the formed acid chloride with sodium azide or by reacting the carboxylic acid with diphenoxyphosphoryl azide in a suitable solvent such as methanol or water at reflux. If methanol is used as the solvent the formed carbamate may be hydrolysed to the amine under conditions described in method **1**, v above.

(iii) Conversion of a compound of formula **XXXIV** to a compound of formula **XXXV** may be performed by benzylation under conditions described in method **1**, i above.

(iv) Conversion of a compound of formula **XXXV** to a compound of formula **XXXVI** where R_1 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl may be performed by



(XXXV) **(XXXVI)**

a) a halogen-metal exchange using an alkyllithium or a metal such as n-butyllithium, lithium or magnesium followed by treatment with an appropriate *N*-alkyl-4-piperidone such as *N*-methyl-4-piperidone in a suitable solvent such as tetrahydrofuran or diethyl ether at a reaction temperature between -78 °C and 0 °C

b) reduction of the formed benzylic alcohol by a suitable reducing agent such as sodium borohydride or triethylsilane and an acid such as CF_3CO_2H or CF_3SO_3H in a suitable solvent such as tetrahydrofuran or diethyl ether at a reaction temperature between 0 °C and +65 °C.

(v) Conversion of a compound of formula **XXXVI** to a compound of formula **XXXVII** where R_1 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl may be performed by

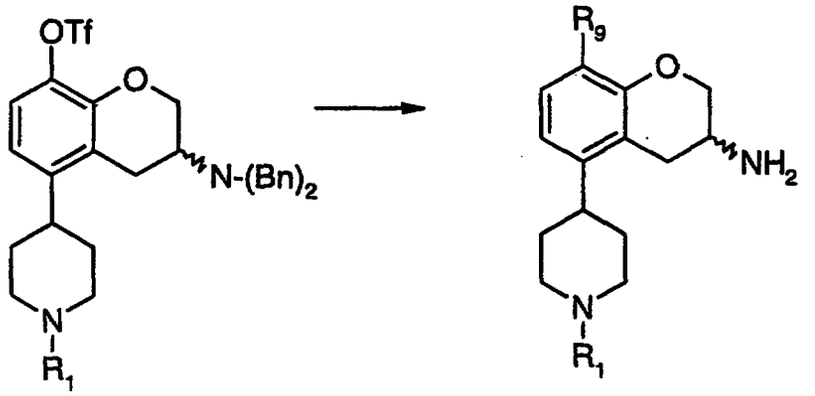
a) demethylation under conditions described in method **1**, ii above

b) triflating the formed phenol under conditions described in method **2**, xxx above.

(vi) Conversion of a compound of formula **XXXVII** to a compound of formula **XXXVIII** where R_9 is

a) C_1-C_6 alkyl, may be carried out by a Stille-coupling under conditions described in method **2**, vii-a

b) $CONR_6R_7$ wherein R_6 and R_7 are C_1-C_6 alkyl or C_3-C_6 cycloalkyl may be performed by



(XXXVII) (XXXVIII)

palladium-catalyzed carbonylation under conditions described in method **1**, xxii-b.

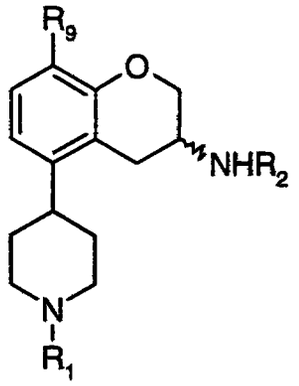
(vii) Conversion of a compound of formula **XXXVI** to a compound of formula **XXXVIII** where R_9 is

a) methoxy, may be performed by debenzylation under conditions described in method **1**, xi above

b) hydroxy, may be performed by demethylation under conditions described in method **1**, ii above followed by debenzylation as described in method **1**, xi above

c) C_2-C_6 alkoxy or $OCHF_2$, may be performed by demethylation as described in method **1**, ii above followed by alkylation under conditions described in method **1**, xvi and debenzylation as described in method **1**, xi above.

(viii) Conversion of a compound of formula **XXXVIII** to a compound of formula **XXXIX** where R_9 is C_1-C_6 alkyl, C_1-C_6 alkoxy, $OCHF_2$ or hydroxy and R_2 is C_1-C_6 alkyl may be performed by

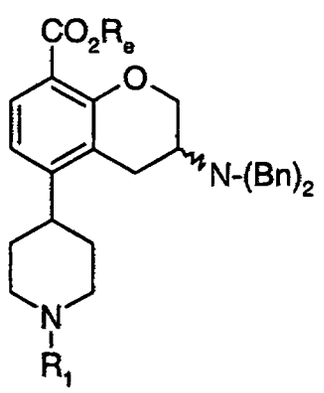


(XXXIX)

a) amidation of **XXXVIII** with a carboxylic acid of the formula R_2CO_2H wherein R_2 is hydrogen or C_1-C_5 under conditions described in method **1**, xviii above

b) reduction under conditions described in method **1**, xix above.

(ix) Conversion of a compound of formula **XXXVII** to a compound of formula **XL** where R_1 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl and R_e is C_1-C_6 alkyl may be performed under conditions described in method **1**, viii above.



(XL)

(x) Conversion of a compound of formula **XL** to a compound of formula **XXXVIII** where R_1 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl and R_9 is CN may be performed by

a) amidation with NH_3 under conditions described in method **1**, ix above

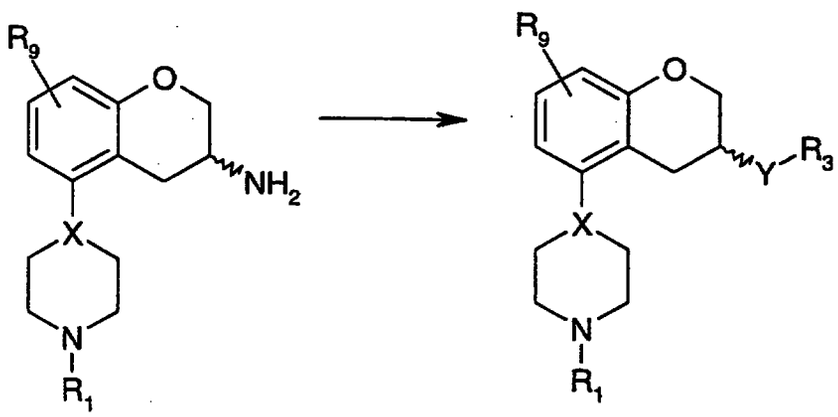
b) dehydration of the primary amide and debenzylation under conditions described in method **1**, xi above.

Method of Preparation of End Products

Another object of the invention is a process **A(i), A(ii), A(iii), B(i), B(ii), C(i), C(ii), D or E** for the preparation of the compound of general formula **I** by

A(i)

acylation, in the case where R_1 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl, Y is NR_2CO, R_2 is hydrogen and X, R_3 and R_9 are as defined in general formula **I** above, of a compound of formula **A**



(A) **(I)**

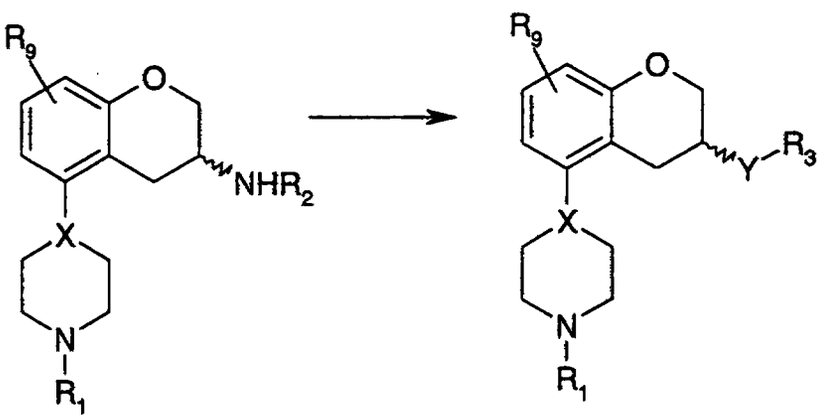
with an activated carboxylic acid R_3-$COLg_1$ where Lg_1 is a leaving group or by using a carboxylic acid R_3-COOH with an activating reagent.

Thus, the acylation according to the process **A(i)** may be carried out with an appropriate activated carboxylic acid, R_3COLg_1 where R_3 is as defined above and Lg_1 is a leaving group, such as halogen, e.g. chlorine, in a suitable solvent such as methylene chloride or chloroform with a suitable base, e.g. a trialkylamine such as triethylamine, at a temperature between -20 °C and reflux temperature or by using an carboxylic acid, R_3COOH wherein R_3 is as defined above with an activating reagent, e.g. *N,N'*-carbonyldiimidazole, *N,N'*-

dicyclohexylcarbodiimide or diphenylphosphinic chloride, with a suitable base such as *N*-methylmorpholine in a suitable solvent such as *N,N*-dimethylformamide or tetrahydrofuran and the reaction may be conducted at a temperature between +20 °C and +150 °C.

Method A (ii):

acylation, in the case where R_1 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl, Y is NR_2CO, R_2 is C_1-C_6 alkyl and X, R_3 and R_9 are as defined in general formula **I** above, of a compound of formula **B,**



(B) **(I)**

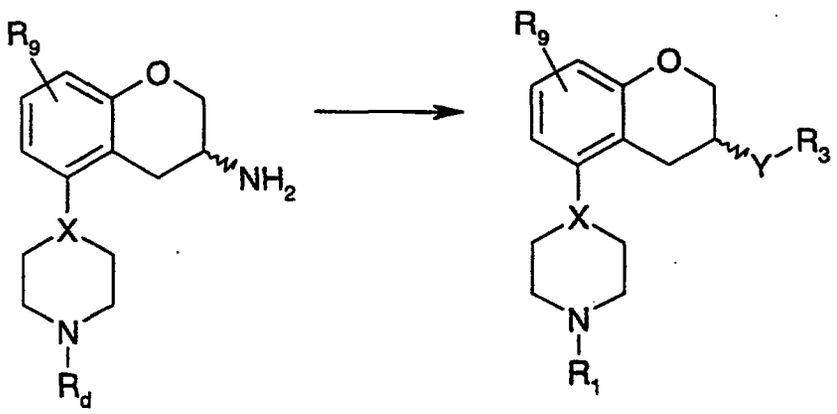
with an activated carboxylic acid R_3-$COLg_1$ where Lg_1 is a leaving group or by using a carboxylic acid R_3-COOH with an activating reagent.

Thus, the acylation according to the process **A(ii)** may be carried out with an appropriate activated carboxylic acid, R_3COLg_1 where R_3 is as defined above and Lg_1 is a leaving group, such as halogen, e.g. chlorine, in a suitable solvent such as methylene chloride or chloroform with a suitable base, e.g. trialkylamine such as triethylamine at a temperature between -20 °C and reflux temperature or by using an carboxylic acid, R_3COOH wherein R_3 is as defined above with an activating reagent, e.g. *N,N'*-carbonyldiimidazole, *N,N'*-

dicyclohexylcarbodiimide or diphenylphosphinic chloride, with a suitable base such as *N*-methylmorpholine in a suitable solvent such as *N,N*-dimethylformamide or tetrahydrofuran and the reaction may be conducted at a temperature between +20 °C and +150 °C.

Method A (iii):

acylation, in the case where R_1 and R_2 are hydrogen, Y is NR_2CO, R_d is a protecting group and X, R_3 and R_9 are as defined in general formula **I** above, of a compound of formula **C**



(C) (I)

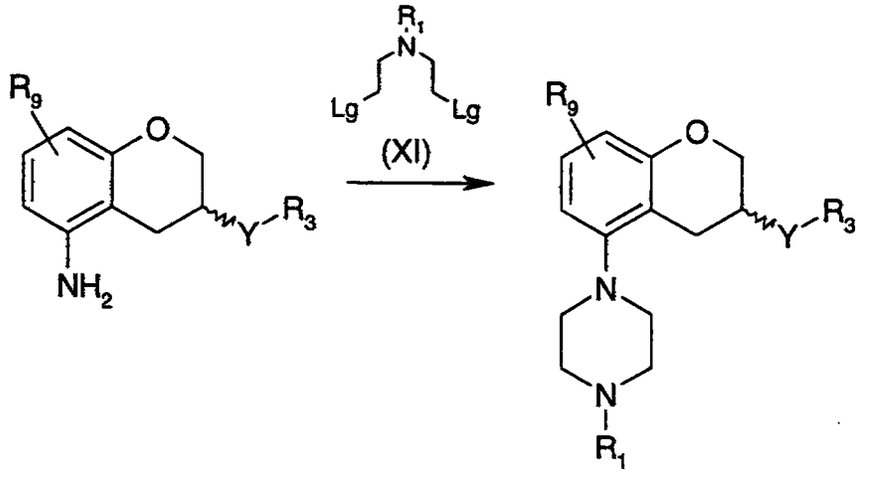
with an activated carboxylic acid R_3-$COLg_1$ where Lg_1 is a leaving group or by using a carboxylic acid R_3-COOH with an activating reagent, followed by the removal of the protecting group R_d;

Thus, the acylation according to the process **A(iii)** may be carried out with an appropriate activated carboxylic acid, R_3COLg_1 where R_3 is as defined above and Lg_1 is a leaving group, such as halogen, e.g. chlorine, in a suitable solvent such as methylene chloride or chloroform with a suitable base, e.g. trialkylamine such as triethylamine, or by using a carboxylic acid, R_3COOH where R_3 is defined as above, with an activating reagent, e.g. *N,N'*-carbonyldiimidazole, *N,N'*-dicyclohexylcarbodiimide or diphenylphosphinic chloride, with a suitable base such as *N*-methylmorpholine in a suitable solvent such as *N,N*-dimethylformamide or tetrahydrofuran and the reaction may be conducted at a temperature between +20 °C and +150 °C, followed by removal of the protecting group R_d by

hydrolysis in a suitable solvent such as methylene chloride or chloroform with a suitable acid such as trifluoroacetic acid at a temperature between +20 °C and +60 °C.

Method B (i):

reacting, in the case where Y is $CONR_2$, R_2, R_3 and R_9 is as defined in general formula **I** above, a compound of formula **D**



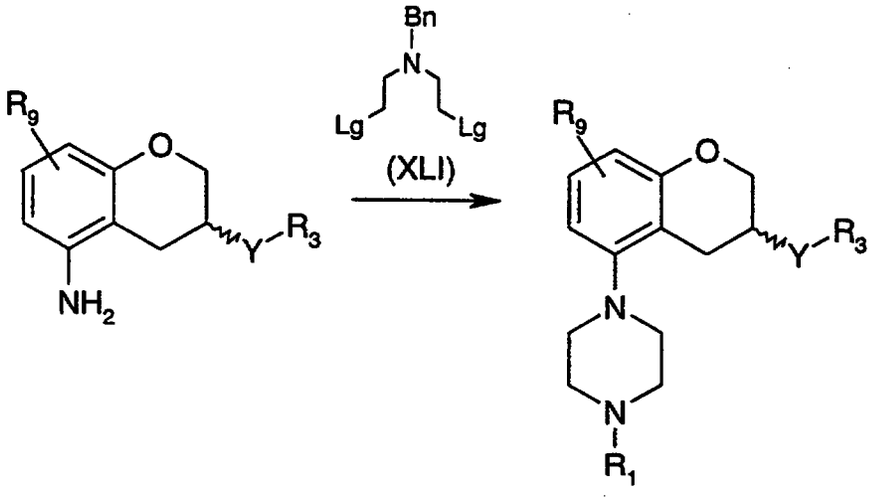
(D) **(I)**

with a compound of formula **XI** wherein Lg is a leaving group.

Thus, the reaction according to the process **B(i)** may be carried out with a compound of formula **XI** wherein R_1 is as defined in general formula **I** and Lg is a leaving group, e.g. a halogen such as chlorine, bromine or iodine, or an alkane- or arenesulfonyloxy group such as p-toluenesulfonyloxy group. The process may be carried out in a suitable solvent such as ethanol, butanol, *N,N*-dimethylformamide, acetonitrile or a mixture of water and acetonitrile with or without a suitable base, e.g. K_2CO_3, $NaHCO_3$ or KOH, and the reaction may occur between +20 °C and +150 °C.

Method B (ii):

reacting, in the case where Y is $CONR_2$, R_1 is H, R_2, R_3 and R_9 is as defined in general formula **I** above with the exception of when R_4 and R_9 are substituents that are susceptible to catalytic hydrogenation known by a person skilled in the art, a compound of formula **D**



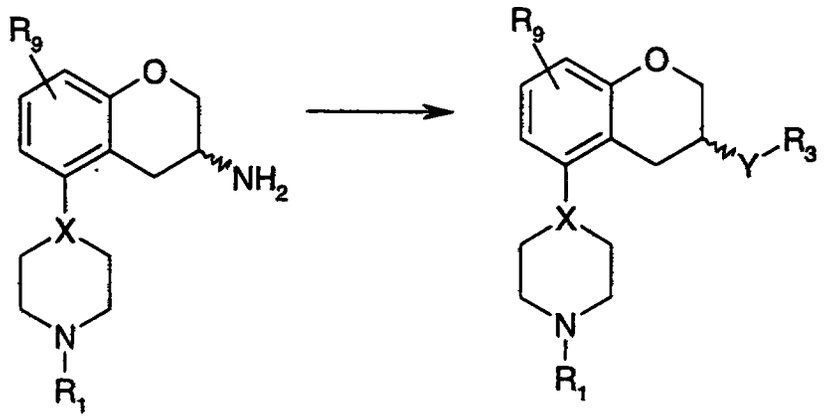
(D) **(I)**

with a compound of formula **XLI** wherein Lg is a leaving group.

Thus, the reaction according to the process **B(ii)** may be carried out with a compound of formula **XLI** where Lg is a leaving group, e.g. a halogen such as chlorine, bromine or iodine, or an alkane- or arenesulfonyloxy group such as p-toluenesulfonyloxy group. The process may be carried out in a suitable solvent such as ethanol, butanol, *N,N*-dimethylformamide, acetonitrile or a mixture of water and acetonitrile with or without a suitable base, e.g. K_2CO_3, $NaHCO_3$ or KOH, and the reaction may occur between +20 °C and +150 °C followed by removal of the benzyl group by catalytic hydrogenation at atmospheric or elevated pressure using a catalyst such as palladium, platina or nickel in a suitable solvent such as methanol, ethanol or acetic acid with or without an acid such as HCl or HBr at a reactiontemperature between +20 °C and +100 °C.

Method C (i):

reacting, in the case where Y is NR_2SO_2, R_2 is hydrogen, R_1, R_3 and R_9 is as defined in general formula **I** above, a compound of formula **E**

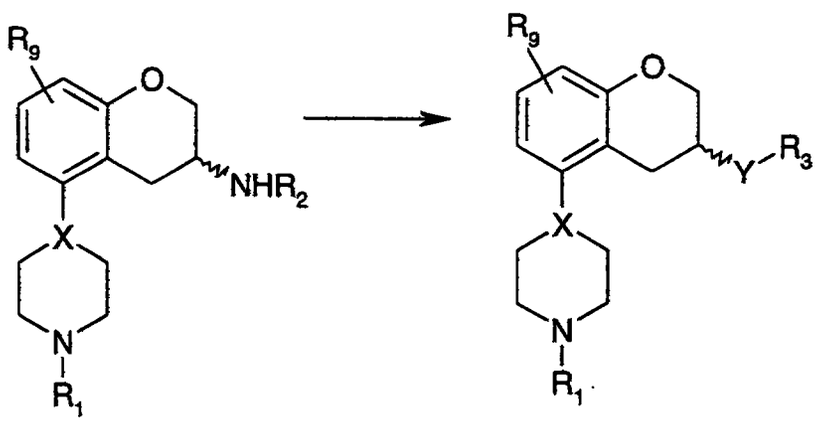


(E) (I)

with an appropriate activated sulfonic acid $R_3SO_2Lg_1$, where Lg_1 is a leaving group such as a halogen, e.g. chlorine, in a suitable solvent such as methylene chloride or chloroform with a suitable base, e.g. a trialkylamine such as triethylamine, and the reaction may be conducted at a temperature between -20 °C and +60 °C.

Method C (ii):

reacting, in the case where Y is NR_2SO_2, R_2 is C_1-C_6 alkyl, R_1, R_3 and R_9 is as defined in general formula **I** above, a compound of formula **E**



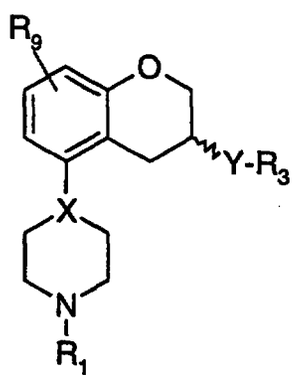
(E) (I)

with an appropriate activated sulfonic acid $R_3SO_2Lg_1$, where Lg_1 is a leaving group such as a halogen, e.g. chlorine, in a suitable solvent such as methylene chloride or chloroform

with a suitable base, e.g. trialkylamine such as triethylamine, and the reaction may be conducted at a temperature between -20 °C and +60 °C.

Method D:

reduction, where Y is NR_2CH_2 or CH_2NR_2, and X, R_1, R_2, R_3 and R_9 are as in formula I above with the exception of when R_4 and R_9 are substituents that are susceptible to certain reducing agents known by a person skilled in the art, of a compound of formula I above where Y is NR_2CO or $CONR_2$, and X, R_1, R_2, R_3 and R_9 are as in formula I above,

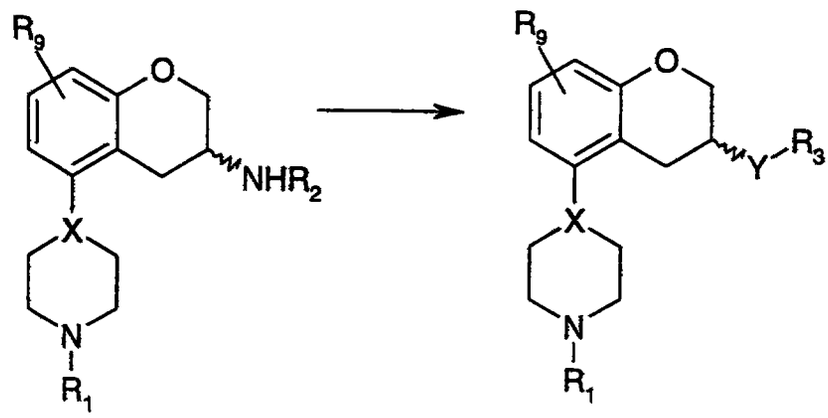


(I)

may be carried out with an appropriate reducing agent such as lithium aluminum hydride, borane or borane-dimethylsulfide in a suitable solvent, e.g. diethyl ether, dioxan or tetrahydrofuran, at a temperature between +20 °C and reflux temperature.

Method E:

alkylation, in the case where R_1 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl, Y is NR_2CH_2 and X, R_2 R_3 and R_9 are as defined in general formula I above with the exception of when R_4 and R_9 are substituents that are susceptible to certain alkylations known by a person skilled in the art, of a compound of formula B,



(B) (I)

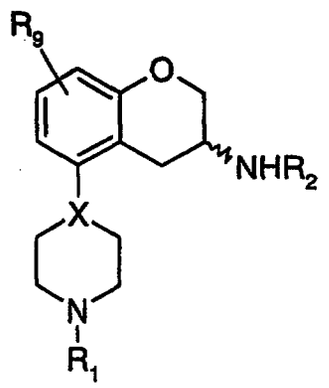
may be carried out with an appropriate alkylating agent.

Thus, alkylation may be carried out with an alkylating reagent of formula R_3Lg where Lg is a leaving group, such as a halogen, e.g. chlorine, bromine or iodine, or an alkane- or arenesulfonyloxy group, such as p-toluenesulfonyloxy group, in the presence of a base such as triethylamine or K_2CO_3 and the reaction may be performed in a suitable solvent such as acetonitrile or *N,N*-dimethylformamide and at a reaction temperature between +20 °C and +100 °C or

by reductive alkylation with an aldehyde of formula R_3CHO and a reducing agent such as sodium cyanoborohydride in a suitable solvent such as methanol or tetrahydrofuran or a mixture thereof and adjustment of pH to slightly acidic by an acid such as acetic acid and the reaction may be performed at a temperature between +10 °C to +50 °C.

Intermediates

The present invention also refers to new intermediates, namely intermediates of formulas



wherein X is N or CH;

R_1 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl;

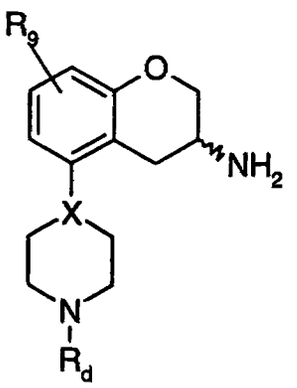
R_2 is hydrogen or C_1-C_6 alkyl;

R_9 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, OCF_3, $OCHF_2$, OCH_2F, halogen, CN, CF_3, OH, C_1-C_6 alkoxy, C_1-C_6 alkoxy-C_1-C_6 alkyl, NR_6R_7, SO_3CH_3, SO_3CF_3, $SO_2NR_6R_7$, an unsubstituted or substituted heterocyclic or heteroaromatic ring containing one or two heteroatoms selected from N and O, wherein the substituent(s) is(are) C_1-C_6 alkyl; or COR_8; wherein

R_6 is H, C_1-C_6 alkyl or C_3-C_6 cycloalkyl;

R_7 is H, C_1-C_6 alkyl or C_3-C_6 cycloalkyl; and

R_8 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, CF_3, NR_6R_7, phenyl, a heteroaromatic ring containing one or two heteroatoms selected from N, O and S or a heterocyclic ring containing one or two heteroatoms selected from N, O, S, SO and SO_2 wherein R_6 and R_7 are as defined above;



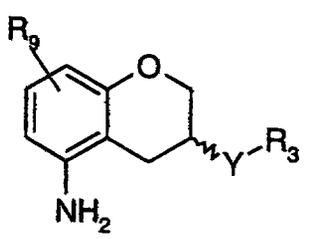
wherein

X is N;

R_9 is as defined above;

R_d is a protecting group;

and



wherein

Y is $CONR_2$;

R_2 is hydrogen or C_1-C_6 alkyl;

R_3 is as defined above; and

R_9 is as defined above.

The invention is illustrated but not restricted to the following working examples.

Working examples

Example 1

(*S*)-3-*N*,*N*-Dibenzylamino-5-methoxy-3,4-dihydro-2*H*-1-benzopyran Hydrochloride. (*S*)-3-Amino-5-methoxy-3,4-dihydro-2*H*-1-benzopyran (45 g, 0.25 mol; described in: WO 93/07135), K_2CO_3 (120 g, 0.87 mol) and benzylbromide (65 mL, 0.55 mol) were mixed in acetonitrile (1000 mL) under nitrogen. The reaction mixture was refluxed for 45 h. The mixture was filtered and the solvent was removed *in vacuo*, and the residue was partitioned between diethyl ether and saturated NaCl (aq). The layers were separated and the organic phase was dried ($MgSO_4$) and filtered followed by precipitation of the hydrochloric salt at room temperature. Yield: 99 gram (99%). An analytical sample was transferred to the base: $[\alpha]^{21}_D$ +116° (*c* 1.0, chloroform). EIMS (70eV) *m/z* (relative intensity) 359 (28, M^+).

Example 2

(*S*)-3-*N*,*N*-Dibenzylamino-5-hydroxy-3,4-dihydro-2*H*-1-benzopyran. (*S*)-3-*N*,*N*-Dibenzylamino-5-methoxy-3,4-dihydro-2*H*-1-benzopyran hydrochloride (67 g, 0.17 mol) was dissolved in methylene chloride (500 mL) under nitrogen, and the solution was cooled to -75 °C. Boron tribromide (32 mL, 0.34 mol) was added dropwise over 5 min. The temperature was then allowed to slowly reach +5 °C, and the reaction was stirred overnight. The reaction mixture was carefully quenched with an 2 M aqueous solution of NH_3 under stirring. The layers were separated and the aqueous phase was extracted two times with methylene chloride. The organic layers were combined, washed with brine, dried ($MgSO_4$), filtered and the solvent was removed *in vacuo* to give a brownish oily residue which was purified by flash chromatography on a silica gel column using methylene chloride as the eluent. Yield: 50 g (86%) of the title compound: $[\alpha]^{21}_D$ +109° (*c* 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 345 (5, M^+).

Example 3

(*S*)-2-(3-*N*,*N*-Dibenzylamino-3,4-dihydro-2*H*-1-benzopyran-5-yloxy)-2-methylpropanamide.

(*S*)-3-*N*,*N*-Dibenzylamino-5-hydroxy-3,4-dihydro-2*H*-1-benzopyran (50 g, 0.14 mol) was dissolved in anhydrous 1,4-dioxane (450 mL) under nitrogen. A dispersion of sodium hydride (60-65% in oil, 6.1 g, 0.15 mol) was added in portions. The mixture was stirred for 1 h at room temperature. 2-Bromo-2-methylpropanamide (24 g, 0.14 mol; Coutts, I. G. C.; Southcott, M. R. *J. Chem. Soc. Perkin Trans. 1* **1990**, 767-771) was added to the dark greenish solution and was heated at reflux with stirring for 3 h. An additional amount of sodium hydride (60-65% in oil, 2.8 g, 70 mmol) and 2-bromo-2-methylpropanamide (4.6 g, 28 mmol) was added in portions and heating at 60 °C was continued for 17 h. After cooling, a small amount of methanol (10 mL) was added and the solution was filtered and the solvent was removed *in vacuo*. The residue was partitioned between ethyl acetate (500 mL) and a saturated $NaHCO_3$ solution (50 mL). The organic layer was dried ($MgSO_4$), and the solvent was removed *in vacuo* to give a brownish residue which was crystallized from ethyl acetate/hexane. Yield: 45 g (71%) of the title compound as a white solid: mp 133-134 °C; $[\alpha]^{21}_D$ +99° (*c* 1.0, chloroform).; EIMS (70eV) *m/z* (relative intensity) 430 (9, M^+).

Example 4

(*S*)-5-Amino-3-*N*,*N*-dibenzylamino-3,4-dihydro-2*H*-1-benzopyran. To a solution of (*S*)-2-(3-*N*,*N*-dibenzylamino-3,4-dihydro-2*H*-1-benzopyran-5-yloxy)-2-methylpropanamide (46 g, 0.11 mol) in anhydrous *N*,*N*-dimethylformamide (450 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (45 mL) was added sodium hydride (60-65% in oil, 8.5 g, 0.21 mol) in portions under nitrogen. The reaction mixture was heated at 110 °C with stirring for 13 h. The mixture was then allowed to cool, and the solution was partitioned between ethyl acetate (400 mL) and a 2 M NH_3 solution (200 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (150 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give a brownish oil. EIMS (70eV) *m/z* (relative intensity) 430 (3, M^+).

The obtained material (0.11 mol) was dissolved in ethanol (350 mL). A 6 M HCl solution (250 mL) was added, and the reaction mixture was heated at reflux for 16 h. After stirring, the mixture was allowed to cool to 35 °C, the ethanolic solvent was removed *in vacuo*, and ethyl acetate was added to the aqueous remains. The mixture was cooled on ice, and a solution of conc. NH_3 was slowly added with stirring. The layers were separated, and the aqueous layer was extracted with another portion of ethyl acetate. The combined organic layers were dried ($MgSO_4$), and the solvent was removed *in vacuo* to give a brownish oil which was purified on a short column of silica gel (eluent: hexane/ethyl acetate; 8:2) affording 25 g (68% yield) of the desired compound as a light yellow oil. The product slowly crystallized upon standing in the refrigerator. An analytical sample was recrystallized from diethyl ether/petroleum ether: mp 101-103 °C; $[\alpha]^{21}_D$ +123° (*c* 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 344 (17, M^+).

Example 5

(*S*)-1-(3-*N*,*N*-Dibenzylamino-3,4-dihydro-2*H*-1-benzopyran-5-yl)-4-methylpiperazine-2,6-dione. To a dispersion of *N*-methyliminodiacetic acid (6.90 g, 46.9 mmol) in anhydrous tetrahydrofuran (575 mL) was added 1,1´-carbonyldiimidazole (15.2 g, 93.9 mmol), and the mixture was heated at reflux for 2 h under nitrogen. A solution of (*S*)-5-amino-3-*N*,*N*-dibenzylamino-3,4-dihydro-2*H*-1-benzopyran (15.0 g, 42.7 mmol) in tetrahydrofuran (120 mL) was added with stirring over 0.5 h. The reaction mixture was heated at reflux for 28 h, then allowed to cool, and the solvent was removed *in vacuo*. The residue was purified on a short column of silica gel (eluent: methylene chloride and ethyl acetate) affording 14.1 g (71% yield) of the title compound as a light yellow solid: mp sinters >60 °C; $[\alpha]^{21}_D$ +89° (*c* 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 455 (8, M^+).

Example 6

(*S*)-3-*N*,*N*-Dibenzylamino-5-(4-methylpiperazin-1-yl)-3,4-dihydro-2*H*-1-benzopyran. To a stirred solution of (*S*)-1-(3-*N*,*N*-dibenzylamino-3,4-dihydro-2*H*-1-benzopyran-5-yl)-4-methylpiperazine-2,6-dione (25.4 g, 55.8 mmol) in anhydrous diethyl ether (800 mL) was

added lithium aluminum hydride (9.30 g, 246 mmol) in portions. The reaction mixture was heated to reflux for 6.5 h under nitrogen and was stirred overnight at room temperature. The mixture was cooled (ice-bath), and water (10 mL) was added followed by a 15% aqueous solution of NaOH (10 mL) and another portion of water (30 mL). The precipitate was filtered off and washed with several portions of warm tetrahydrofuran. The organic layers were combined, and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica (eluent: chloroform/ethanol; 95:5 + 0.5% conc. NH_3) affording 13.6 g (57% yield) of the title compound as a light yellow oil: $[\alpha]^{25}_D$ +63° (*c* 1.0, methanol); EIMS (70eV) *m/z* (relative intensity) 427 (5, M^+).

Example 7

(*S*)-3-*N*,*N*-Dibenzylamino-8-iodo-5-(4-methylpiperazin-1-yl)-3,4-dihydro-2*H*-1-benzopyran

(*S*)-3-*N*,*N*-Dibenzylamino-5-(4-methylpiperazin-1-yl)-3,4-dihydro-2*H*-1-benzo-1-pyran (6.9 g, 16 mmol) and sodium acetate (1.5 g, 18 mmol) were dissolved in acetic acid (430 mL). To the solution was added iodine monochloride (18 mL, 1 M, 18 mmol) and the reaction mixture was stirred at room temperature, while protected from light, for 24 h. Additional iodine monochloride (2.5 mL, 1M, 2.5 mmol) was added followed by stirring for 3 h. The solvent was evaporated *in vacuo* and the residue was partitioned between methylene chloride (800 mL) and 2 M NaOH (120 mL). The aqueous phase was extracted with methylene chloride (100 mL) and the combined organic layers were washed with brine (2 x 100 mL) and dried ($MgSO_4$). Evaporation of the solvent gave 8.6 g of a crude product. Purification by column chromatography on silica using ethyl acetate/ethanol (saturated with ammonia) (25:1) as the eluent gave 4.1 g (43% yield) of the title compound (containing about 7% of the starting material) as a yellowish solid: EIMS (70 eV) *m/z* (relative intensity) 553 (15, M^+). The product was used in the next step without further attempts to purification.

Example 8

(*S*)-8-Methoxycarbonyl -3-*N*,*N*-dibenzylamino-5-(4-methylpiperazin-1-yl)-3,4-dihydro-2*H*-1-benzopyran

(*S*)-3-*N*,*N*-Dibenzylamino-8-iodo-5-(4-methylpiperazin-1-yl)-3,4-dihydro-2*H*-1-benzopyran (2.6 g, 4.8 mmol) was dissolved in *N*,*N*-dimethylformamide (100 mL) and flushed with carbon monoxide. To the solution was added palladium acetate (110 mg, 0.48 mmol), 1,3-bis(diphenylphosphino)propane (200 mg, 0.48 mmol), methanol (25 mL) and triethylamine (3.3 mL, 24 mmol). The mixture was reacted with carbon monoxide at 90 °C and at atmospheric pressure for 8 h. The solution was filtered, the solvent was evaporated. The residue was co-evaporated with xylene (2 x 50 mL) and partitioned between methylene chloride (300 mL) and 2 M NH_3 (50 mL). The aqueous phase was extracted with methylene chloride (50 mL) and the combined organic layers were washed with brine (2 x 50 mL) and dried (MgSO4). The solvent was evaporated giving 4.0 g of a crude product. Purification by column chromatography on silica using methylene chloride/ethanol (saturated with ammonia) (50:1) as the eluent gave 1.7 g (68% yield) of the title compound (containing about 5% of the corresponding 8-H analogue) as a yellowish solid: EIMS (70 eV) *m/z* (relative intensity) 485 (8, M^+). The product was used in the next step without further attempts to purification.

Example 9

***(S)*-3-*N*,*N*-Dibenzylamino-8-hydroxymethyl-5-(4-methylpiperazin-1-yl)-3,4-dihydro-2*H*-1-benzopyran**

(*S*)-8- Methoxycarbonyl -3-*N*,*N*-dibenzylamino-5-(methylpiperazin-1-yl)-3,4-dihydro-2*H*-1-benzopyran (490 mg, 1.0 mmol) was dissolved in dry tetrahydrofuran (40 mL) and lithium aluminium hydride (76 mg, 2.0 mmol) was added portionwise. The reaction mixture was stirred at 45 °C for 4 h and cooled to room temperature. The reaction was quenched by the addition of water (76 µL), 15% NaOH (76 µL) and water (225 µL) and stirred for 18h. The white precipitate was filtered off and the solution was dried ($MgSO_4$). The solvent was evaporated *in vacuo* giving 520 mg of a crude product. Purification by column chromatography on silica using chloroform/ethanol (saturated with ammonia)

(15:1) as the eluent gave 390 mg (85% yield) of the title compound containing about 8% of the corresponding 8-methyl analogue) as a yellowish oil: EIMS (70 eV) *m/z* (relative intensity) 457 (15, M^+).

Example 10

(*S*)-3-Amino-8-methyl-5-(4-methylpiperazin-1-yl)-3,4-dihydro-2*H*-1-benzopyran

(*S*)-3-*N*,*N*-Dibenzylamino-8-hydroxymethyl-5-(4-methylpiperazin-1-yl)-3,4-dihydro-2*H*-1-benzopyran (420 mg, 0.90 mmol) was dissolved in methanol (60 mL) and ammonium formate (460 mg, 7.3 mmol) was added. The solution was flushed with nitrogen and palladium on carbon (120 mg, 10%) was added. The reaction mixture was stirred at 50 °C for 16 h. The catalyst was filtered off and the solvent was evaporated *in vacuo* giving 260 mg of a crude product. The residue was dissolved in acetic acid (50 mL) and palladium on carbon (120 mg, 10%) was added. The reaction mixture was hydrogenated at room temperature and at atmospheric pressure for 46 h. The catalyst was filtered off and the solvent was evaporated *in vacuo*. The residue was partitioned between ethyl acetate (120 mL) and 2 M NaOH (10 mL) and the aqueous phase was extracted with ethyl acetate (10 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and the solvent was evaporated *in vacuo* giving 200 mg of a crude product. Purification by preparative TLC on silica using chloroform/ethanol (saturated with ammonia) (10:1) as the eluent afforded 150 mg (64% yield) of the title compound as an oil: EIMS (70 eV) *m/z* (relative intensity) 261 (100, M^+).

Example 11

(*S*)-*N*-[8-Methyl-5-(4-methylpiperazin-1-yl)-3,4-dihydro-2*H*-1-benzopyran-3-yl]-4-methylbenzamide

4-Methylbenzoic acid (22 mg, 0.16 mmol) and 1,1´-carbonyldiimidazole (27 mg, 0.17 mmol) were dissolved in dry *N*,*N*-dimethylformamide (2 mL) and stirred at 75 °C for 1 h. The reaction mixture was cooled to room temperature and a solution of (*S*)-3-amino-8-methyl-5-(methylpiperazin-1-yl)-3,4-dihydro-2*H*-1-benzopyran (40 mg, 0.15 mmol) dissolved in dry *N*,*N*-dimethylformamide (4 mL) was added. The reaction mixture was

stirred at room temperature for 4 days and the solvent was evaporated *in vacuo*. The crude material was partitioned between methylene chloride (40 mL) and water (10 mL). The organic phase was washed with water (10 mL) and brine (5 mL) and dried ($MgSO_4$). The solvent was evaporated *in vacuo* giving 48 mg of a crude product. Purification by preparative TLC on silica using chloroform/ethanol (saturated with ammonia) (15:1) as the eluent afforded 23 mg (40% yield) of the title compound as a white solid: mp 191-192 °C; EIMS (70 eV) *m/z* (relative intensity) 379 (100, M^+); $[\alpha]^{21}_D$ -7° (*c* 0.10, chloroform).

Example 12

(*S*)-8-Carbamoyl-3-*N*,*N*-dibenzylamino-5-(4-methylpiperazin-1-yl)-3,4-dihydro-2*H*-1-benzopyran

(*S*)-8-Methoxycarbonyl-3-*N*,*N*-dibenzylamino-5-(4-methylpiperazin-1-yl)-3,4-dihydro-2*H*-1-benzopyran (800 mg, 1.6 mmol) and potassium hydroxide (500 mg , 8.9 mmol) were dissolved in methanol (50 mL) and stirred at 65 °C for 3 days. The solvent was evaporated *in vacuo* and the residue was co-evaporated with toluene (2 x 100 mL) giving 1.2 g of a crude material. The solid was dispersed in methylene chloride (40 mL) and thionyl chloride (1.2 mL, 16 mml) was added. The reaction mixture was heated to reflux for 1 h followed by evaporation of the solvent and excess thionyl chloride *in vacuo*. The residue was co-evaporated with toluene (100 mL) and dried *in vacuo*. The crude acid chloride was mixed with methylene chloride (40 mL) and cooled on ice. Concentrated ammonia (5 mL, 65 mmol) was added and the reaction mixture was stirred at about 0 °C for 20 min and at room temperature for 40 min. Methylene chloride (100 mL) and water (50 mL) were added and the aqueous layer was extracted with methylene chloride (30 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) followed by evaporation of the solvent *in vacuo* giving 790 mg of a crude product. Purification by preparative TLC on silica using chloroform/ethanol (saturated with ammonia) (15:1) as the eluent gave 460 mg (59% yield) of the title compound as white crystals: mp 173-174 °C; EIMS (70 eV) *m/z* (relative intensity) 470 (4, M^+).

Example 13

(*S*)-3-Amino-8-carbamoyl -5-(4-methylpiperazin-1-yl)-3,4-dihydro-2*H*-1-benzopyran

(*S*)-8-Carbamoyl-3-*N,N*-dibenzylamino-5-(4-methylpiperazin-1-yl)-3,4-dihydro-2*H*-1-benzopyran (120mg mg, 0.95 mmol) was dissolved in methanol (40 mL) and palladium on carbon (480 mg, 10%) was added. The flask was flushed with nitrogen, ammonium formate (480 mg, 7.6 mmol) was added and the reaction mixture was stirred at 50 °C for 18 h. The catalyst was filtered off and the solvent was evaporated *in vacuo*. The residue was co-evaporated with toluene and dried *in vacuo* giving 300 mg (100% yield) of the title compound: EIMS (70 eV) *m/z* (relative intensity) 290 (100, M^+). The crude product was used in the next step without attempts to purification.

Example 14

(*S*)-*N*-[8-Carbamoyl-5-(4-methylpiperazin-1-yl)-3,4-dihydro-2*H*-1-benzopyran-3-yl]-4-benzoylbenzamide

4-Benzoylbenzoic acid (95 mg, 0.42 mmol) and 1,1´-carbonyldiimidazole (71 mg, 0.44 mmol) were dissolved in *N,N*-dimethylformamide (2 mL) and stirred at 75 °C for 1 h. The reaction mixture was cooled to room temperature and a solution of (*S*)-2-amino-8-carbamoyl-5-(4-methylpiperazin-1-yl)-3,4-dihydro-2*H*-1-benzopyran (120 mg, 0.40 mmol) in *N,N*-dimethylformamide (5 mL) was added. The reaction mixture was stirred at room temperature for 4 days and the solvent was evaporated *in vacuo* giving 290 mg of a crude product. Purification by preparative TLC on silica using chloroform/ethanol (saturated with ammonia) (15:1) as the eluent afforded 75 mg (38% yield) of the title compound: mp 259 °C (dec); EIMS (70 eV) *m/z* (relative intensity) 498 (38, M^+); $[\alpha]^{21}_D$ -3 ° (*c* 0.1, chloroform).

Example 15

(*S*)-*N*-[8-Methyl-5-(4-methylpiperazin-1-yl)-3,4-dihydro-2*H*-1-benzopyran-3-yl]-4-(dimethylaminocarbonyl)benzamide

4-(Dimethylaminocarbonyl)benzoic acid (described in: Jurewicz, A.T ; U.S. Patent 3,607,918, **1971**) (38 mg, 0.20 mmol) and 1,1´-carbonyldiimidazole (34 mg , 0.21 mmol)

were dissolved in dry *N,N*-dimethylformamide (4 mL) and stirred at 75 °C for 1.5 h. The reaction mixture was cooled to room temperature and a solution of (*S*)-3-amino-8-methyl-5-(4-methylpiperazin-1-yl)-3,4-dihydro-2*H*-1-benzopyran (49 mg, 0.19 mmol) in dry *N,N*-dimethylformamide (5 mL) was added. The reaction mixture was stirred at 50 °C for 14 h and the solvent was evaporated *in vacuo* giving 120 mg of a crude product. Purification by preparative TLC using chloroform/ methanol/conc. NH_3 (95:5:0.5) as the eluent afforded 40 mg (48% yield) of the title compound as a white foam: EIMS (70 eV) *m/z* (relative intensity) 436 (26, M^+); $[\alpha]^{21}_D$ -9° (*c* 0.20, chloroform).

Example 16

8-Methoxy-5-nitro-3,4-dihydro-2*H*-1-benzopyran-3-carboxylic acid ethyl ester.

To a stirred solution of 8-methoxy-3,4-dihydro-2*H*-1-benzopyran-3-carboxylic acid ethyl ester (described in Thorberg, S-O et al. *Acta Pharm.Suec.***1987**, *24*, (4), 169-182) (5.5 g, 23 mmol) in methylene chloride (50 mL) at 0 °C was added dropwise 65% HNO_3 (2.0 mL). The solution was stirred at room temperature for 2 h and washed with water. The organic phase was dried and the solvent evaporated *in vacuo*. The residue was treated with diisopropyl ether (30 mL) and ethyl acetate (5 mL) to yield 1.5 g (5.3 mmol) of crystals of the 6-nitro isomer. The mother liquor was purified by column chromatography using diisopropylether as the eluent affording 1.3 g (20% yield) of the title compound: mp 66-68 °C; EIMS (70 eV) *m/z* (relative intensity) 281 (100, M^+).

Example 17

8-Methoxy-5-nitro-3,4-dihydro-2*H*-1-benzopyran-3-carboxylic acid.

A mixture of 8-methoxy-5-nitro-3,4-dihydro-2*H*-1-benzopyran-3-carboxylic acid ethyl ester (5.8 g, 21 mmol) in ethanol (150 mL) and 2 M NaOH (15 mL) was heated to reflux for 30 min. The solvent was evaporated *in vacuo* the residue dissolved in water. Acidification to pH 2 and extraction with ethyl acetate followed by evaporation of the solvent *in vacuo* gave 4.9 g (94 % yield) of the title compound: mp 181-183 °C; EIMS (70 eV) *m/z* (relative intensity) 253 (55, M^+).

Example 18

***N*-(4-Morpholinophenyl)-8-methoxy-5-nitro-3,4-dihydro-2*H*-1-benzopyran-3-carboxamide.**

To a solution of 8-methoxy-5-nitro-3,4-dihydro-2*H*-1-benzopyran-3-carboxylic acid (2.5 g, 10 mmol) in toluene (40 mL) and *N,N*-dimethylformamide (1 mL) was added thionyl chloride (3.6 mL, 50 mmol). The reaction mixture was refluxed for 2 h and the solvent was removed *in vacuo*. The residual acid chloride was added to a solution of 4-(1-morpholino)aniline (described in Devlin, J.P. et. al., *J. Chem. Soc. Perkin Trans, 1*. **1975** 830-841) (1.78 g, 10 mmol) and triethylamine (2.0 g, 20 mmol) in methylene chloride (30 mL) and stirred at 0 °C for 10 min and for 1 h at room temperature. The solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate and washed with 2 M NaOH. Evaporation of the solvent *in vacuo* afforded 1.5 g (36 % yield) of the title compound as white crystals: mp 238-240 °C; EIMS (70 eV) *m/z* (relative intensity) 413 (5, M^+).

Example 19

***N*-(4-Morpholinophenyl)-5-amino-8-methoxy-3,4-dihydro-2*H*-1-benzopyran-3-carboxamide.**

To a solution of *N*-(4-morpholinophenyl)-8-methoxy-5-nitro-3,4-dihydro-2*H*-1-benzopyran-3-carboxamide (1.2 g, 2.9 mmol) in *N,N*-dimethylformamide (10 mL) was added a solution of sodium dithionite (2.1 g, 12 mmol) in water (5 mL). The mixture was stirred at 55 °C for 3 h and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel using ethyl acetate as the eluent affording 273 mg of the title compound (55% yield): EIMS (70 eV) *m/z* (relative intensity) 383 (100, M^+).

Example 20

***N*-(4-Morpholinophenyl)-8-methoxy-5-(4-methylpiperazin-1-yl)-3,4-dihydro-2*H*-1-benzopyran-3-carboxamide.**

A solution of *N*-(4-morpholinophenyl)-5-amino-8-methoxy-3,4-dihydro-2*H*-1-benzopyran-3-carboxamide (270 mg, 0.7 mmol), bis (2-chloroethyl)-methylamine hydrochloride (288

mg, 1.5 mmol) and sodium hydrogen carbonate (126 mg, 1.5 mmol) in n-butanol (10 mL) was stirred at 90 °C for 2.5 h. 2 M ammonia (10 mL) was added at 50 °C, the mixture was cooled and the phases were separated. The organic phase evaporated *in vacuo* and the residue was purified by column chromatography on silica gel using ethyl acetate/triethyl amine (100:8) as the eluent affording 170 mg (50% yield) of the title compound as white crystals: mp 202-204 °C; EIMS (70 eV) *m/z* (relative intensity) 466 (100 M^+).

PHARMACOLOGY

Electrical field stimulation of [^{3}H] -5-HT release from occipital cortex of guinea pigs

[^{3}H]-5-HT is released by electrical field stimulation from slices of occipital cortex of guinea pigs which have been pre-incubated with [^{3}H]-5-HT. This release is similar to that caused by nerve stimulation, i.e. exocytotic release from serotonergic nerve terminals, depending on the presence of Ca^{2+} in the incubation medium. The 5-HT release is regulated at the level of the nerve terminals by autoreceptors, in the guinea pigs (like in humans) belonging to the h5-HT_{1B} receptor subtype. Thus, agonists of h5-HT_{1B} receptors reduce the amount of [^{3}H]-5-HT released by electrical field stimulation whereas the release is increased by antagonists of this receptor type. Testing compounds with this method is accordingly a convenient screening technique for determining the potency and functional effect of new h5-HT_{1B} receptor agonists and antagonists.

Methods and Materials

Buffer composition (mM) $NaHCO_3$ (25), NaH_2PO_4. H_2O (1.2), NaCl (117), KCl(6), $MgSO_4 \times 7H_2O$(1.2), $CaCl_2$(1.3), EDTA Na_2(0.03). The buffer is gassed for at least 30 min before use. The pH of the buffer is about 7.2 in the room temperature but it rises to about 7.4 at 37°C.

Preparation of occipital cortical slices

Guinea pigs (200-250 g) were decapitated and the whole brain was removed. The occipital cortex was dissected and cut to slices 0.4x4 mm with McIlwain chopper machine. The white part of the tissue should be removed carefully with a tweezer before slicing. The

slices were incubated in 5 ml buffer in the presence of 5 mM pargyline chloride. After incubation with 0.1 mM [^{3}H]-5-HT for another 30 min the slices were transferred to a test tube and washed three times with same volume buffer. The slices were transferred to the superfusion chambers with a plastic pipette and were washed for 40 min with the buffer in the presence of uptake inhibitor citalopram 2.5 μM with a flow 0.5 ml/min.

Electrical stimulation of 5-HT release

The superfused buffer was collected in 2 mL/fraction. The slices were stimulated by electricity with a train of pulses of frequency 3 Hz, duration 2 ms and current 30 mA for 3 min at the 4th and 13th fractions. The tested drugs were added from the 8th fraction to the end of experiment.

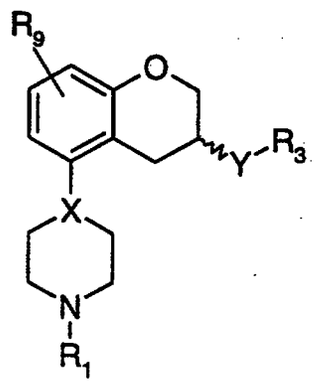
Results

A first electrical (or K^+) stimulation results in a standard amount of [^{3}H] 5-HT released (S_1). Before the first and the second stimulation the h5-HT_{1B} antagonist is added to the media which results in a dose depending increase of the release(S_2) after the second stimulation. See Fig.1.

The S_2/S_1 ratio which is the per cent of released [^{3}H] 5-HT at the second stimulation (S_2) divided by that of the first stimulation (S_1) was used to estimate drug effects on transmitter release.

CLAIMS

1. A compound having the formula I



(I)

wherein

X is N or CH;

Y is NR_2CH_2, CH_2-NR_2, NR_2-CO, CO-NR_2 or NR_2SO_2

wherein R_2 is H or C_1-C_6 alkyl;

R_1 is H, C_1-C_6 alkyl or C_3-C_6 cycloalkyl;

R_3 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl or $(CH_2)_n$-aryl,

wherein aryl is phenyl or a heteroaromatic ring containing one or two heteroatoms selected from N, O and S and which may be mono- or di-substituted with R_4 and/or R_5;

wherein R_4 is H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halogen, CN, CF_3, OH, C_1-C_6 alkoxy, NR_6R_7, OCF_3, SO_3CH_3, SO_3CF_3, $SO_2NR_6R_7$, phenyl, phenyl-C_1-C_6 alkyl, phenoxy, C_1-C_6 alkylphenyl, an optionally substituted heterocyclic or heteroaromatic ring containing one or two heteroatoms selected from N, O, S, SO and SO_2 wherein the substituent(s) is(are) selected from C_1-C_6 alkyl, C_3-C_6 cycloalkyl and phenyl-C_1-C_6 alkyl; or COR_8;

wherein R_6 is H, C_1-C_6 alkyl or C_3-C_6 cycloalkyl;

R_7 is H, C_1-C_6 alkyl or C_3-C_6 cycloalkyl; and

R_8 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, CF_3, NR_6R_7, phenyl, or a heterocyclic ring containing one or two heteroatoms selected from N, O, S, SO and SO_2;

wherein R_5 is H, OH, CF_3, OCF_3, halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy;

n is 0-4;

R_9 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, OCF_3, $OCHF_2$, OCH_2F, halogen, $CONR_6R_7$, CN, CF_3, OH, C_1-C_6 alkoxy, NR_6R_7, SO_3CH_3, SO_3CF_3, $SO_2NR_6R_7$, an unsubstituted or substituted heterocyclic or heteroaromatic ring containing one or two heteroatoms selected from N and O, wherein the substituent(s) is(are) C_1-C_6 alkyl; or COR_8; wherein R_6, R_7 and R_8 are as defined above,

as *(R)*-enantiomers, *(S)*-enantiomers or a racemate in the form of a free base or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1 wherein Y is NR_2CO or $CONR_2$.

3. A compound according to any one of claims 1-2 wherein X is N.

4. A compound according to any one of claims 1-3 wherein R_1 is H or C_1-C_6 alkyl.

5. A compound according to any one of claims 1-4 wherein R_3 is $(CH_2)_n$-aryl.

6. A compound according to any one of claims 1-4 wherein R_3 is $(CH_2)_n$-aryl which is substituted with R_4, which is an optionally substituted heterocyclic or heteroaromatic ring containing one or two heteroatoms selected from N, O and S, or COR_8.

7. A compound according to any one of claims 5 and 6 wherein n is 0.

8. A compound according to claim 6 wherein R_8 is NR_6R_7 or a heterocyclic ring containing two heteroatoms selected from N and O.

9. A compound according to any one of claims 1-8 wherein R_9 is C_1-C_6 alkyl, $OCHF_2$, halogen or C_1-C_6 alkoxy.

10. A compound according to any one of claims 1- 9 wherein X is N, Y is NR_2CO and R_9 is C_1-C_6 alkoxy.

11. A compound according to claim 10 wherein X is N, Y is NR_2CO, R_4 is morpholino or COR_8 and R_9 is C_1-C_6 alkoxy.

12. A compound according to any one of claims 1- 9 wherein X is N, Y is NR_2CO and R_9 is C_1-C_6 alkyl.

13. A compound according to claim 12 wherein X is N, Y is NR_2CO, R_4 is morpholino or COR_8 and R_9 is C_1-C_6 alkyl.

14. A compound according to any one of claims 1- 9 wherein X is N, Y is $CONR_2$ and R_9 is C_1-C_6 alkoxy.

15. A compound according to claim 14 wherein X is N, Y is $CONR_2$, R_4 is morpholino or COR_8 and R_9 is C_1-C_6 alkoxy.

16. A compound according to any one of claims 1- 9 wherein X is N, Y is $CONR_2$ and R_9 is C_1-C_6 alkyl.

17. A compound according to claim 16 wherein X is N, Y is $CONR_2$, R_4 is morpholino or COR_8 and R_9 is C_1-C_6 alkyl.

18. A compound which is
(*S*)-*N*-[8-Methyl-5-(4-methylpiperazin-1-yl)-3,4-dihydro-2*H*-1-benzopyran-3-yl]-4-(dimethylaminocarbonyl)benzamide or
N-(4-Morpholinophenyl)-8-methoxy-5-(4-methylpiperazin-1-yl)-3,4-dihydro-2*H*-1-benzopyran-3-carboxamide
in the form of a free base or pharmaceutical acceptable salt or solvate thereof.

19. A pharmaceutical formulation comprising as active ingredient a therapeutically effective amount of the compound of any one of claims 1-18 as an enantiomer or racemate in the form of a free base or a pharmaceutically acceptable salt or solvate thereof optionally in association with diluents, excipients or inert carriers.

20. A pharmaceutical formulation according to claim 19 for use in the treatment of 5-hydroxytryptamine mediated disorders.

21. A pharmaceutical formulation according to any one of claims 19 or 20 for use in the treatment of mood disorders, anxiety disorders, personality disorders, obesity, anorexia, bulimia, premenstrual syndrome, sexual disturbances, alcoholism, tobacco abuse, autism, attention deficit, hyperactivity disorder, migraine, memory disorders, pathological aggression, schizophrenia, endocrine disorders, stroke, dyskinesia, Parkinson´s disease, thermoregulatory disorders, pain, hypertension, urinary incontinence or vasospasm; or for growth control of tumors.

22. A compound as defined in any of claims 1-18 for use in therapy.

23. A compound as defined in claim 22 for use in the treatment of disorders in the central nervous system.

24. A compound as defined in claim 23 for use in the treatment of mood disorders, anxiety disorders, personality disorders, obesity, anorexia, bulimia, premenstrual syndrome, sexual disturbances, alcoholism, tobacco abuse, autism, attention deficit, hyperactivity disorder, migraine, memory disorders, pathological aggression, schizophrenia, endocrine disorders, stroke, dyskinesia, Parkinson´s disease, thermoregulatory disorders, pain or hypertension.

25. A compound as defined in claim 22 for use in the treatment of urinary incontinence or vasospasm or for growth control of tumors.

26. A compound as defined in claim 22 for use in the treatment of 5-hydroxytryptamine mediated disorders.

27. A compound as defined in claim 26 for use as a h5-HT_{1B} antagonist.

28. The use of a compound defined in any of claims 1-18 in the manufacture of a medicament for the treatment of disorders in the central nervous system and/or urinary incontinence, vasospasm or for growth control of tumors.

29. The use according to claim 28 in the manufacture of a medicament for the treatment of mood disorders, anxiety disorders, personality disorders, obesity, anorexia, bulimia, premenstrual syndrome, sexual disturbances, alcoholism, tobacco abuse, autism, attention deficit, hyperactivity disorder, migraine, memory disorders, pathological aggression, schizophrenia, endocrine disorders, stroke, dyskinesia, Parkinson´s disease, thermoregulatory disorders, pain or hypertension.

30. The use of a compound defined in any of claims 1-18 in the manufacture of a medicament for the treatment of 5-hydroxytryptamine mediated disorders.

31. The use according to claim 30 wherein the compound according to any one of claims 1-18 is used as a h5-HT_{1B} antagonist.

32. A method for the treatment of disorders in the central nervous system and/or urinary incontinence, vasospasm or for growth control of tumors by administering to a mammal including man in need of such a treatment a therapeutically effective amount of a compound defined in any of claims 1-18.

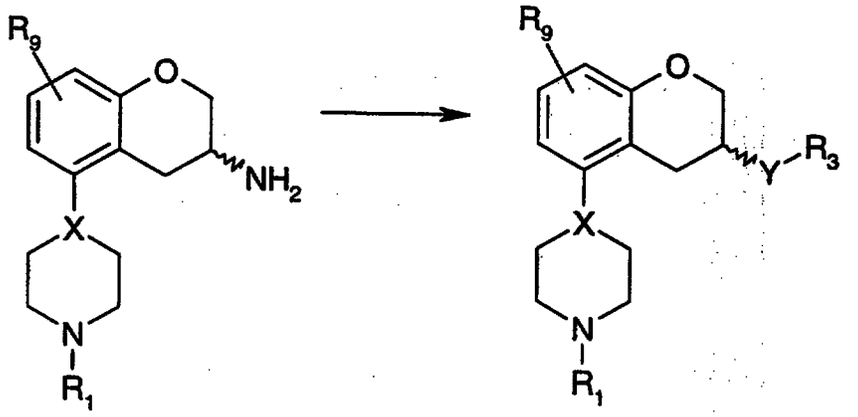
33. A method according to claim 32 for the treatment of mood disorders, anxiety disorders, personality disorders, obesity, anorexia, bulimia, premenstrual syndrome, sexual disturbances, alcoholism, tobacco abuse, autism, attention deficit, hyperactivity disorder, migraine, memory disorders, pathological aggression, schizophrenia, endocrine disorders, stroke, dyskinesia, Parkinson´s disease, thermoregulatory disorders, pain or hypertension.

34. A method for the treatment of 5-hydroxytryptamine mediated disorders by administering to a mammal including man in need of such a treatment a therapeutically effective amount of a compound defined in any of claims 1-18.

35. A method according to claim 34 wherein the compound according to any one of claims 1-18 is used as a h5-HT_{1B} antagonist.

36. A process for the preparation of the compound of formula **I** according to claim 1 by

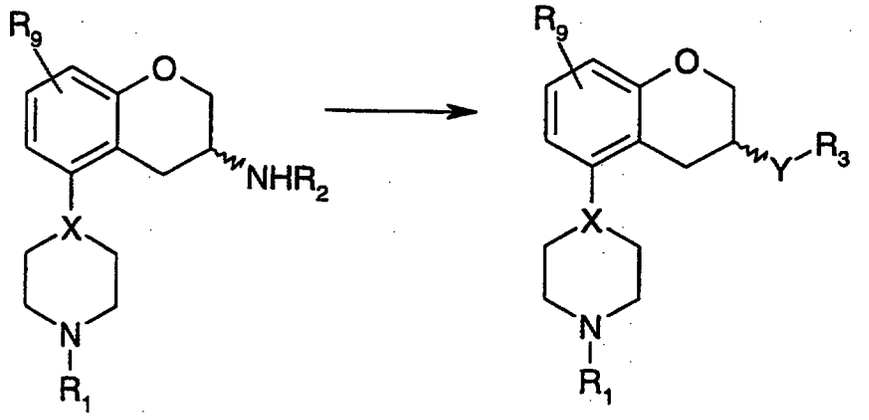
<u>A(i)</u>
acylation, in the case where R_1 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl, Y is NR_2CO, R_2 is hydrogen and X, R_3 and R_9 are as defined in general formula **I** above, of a compound of formula **A**



(A) (I)

with an activated carboxylic acid R_3-$COLg_1$ where Lg_1 is a leaving group or by using a carboxylic acid R_3-COOH with an activating reagent;

A (ii)
acylation, in the case where R_1 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl, Y is NR_2CO, R_2 is C_1-C_6 alkyl and X, R_3 and R_9 are as defined in general formula **I** above, of a compound of formula **B,**

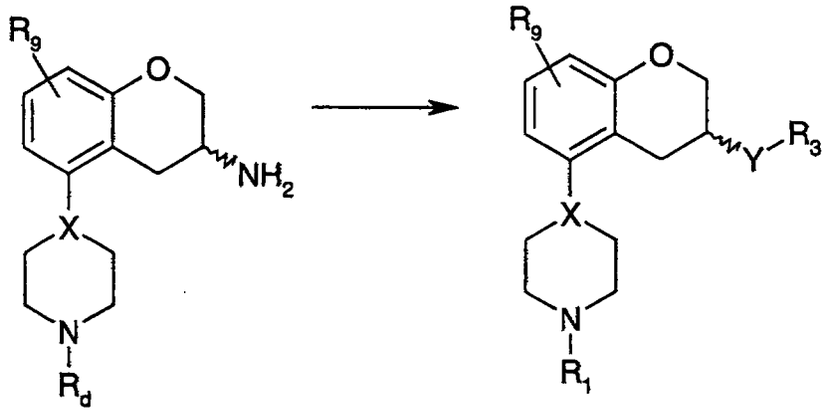


(B) (I)

with an activated carboxylic acid R_3-$COLg_1$ where Lg_1 is a leaving group or by using a carboxylic acid R_3-COOH with an activating reagent;

A (iii)

acylation, in the case where R_1 and R_2 are hydrogen, Y is NR_2CO, R_d is a protecting group and X, R_3 and R_9 are as defined in general formula **I** above, of a compound of formula **C**

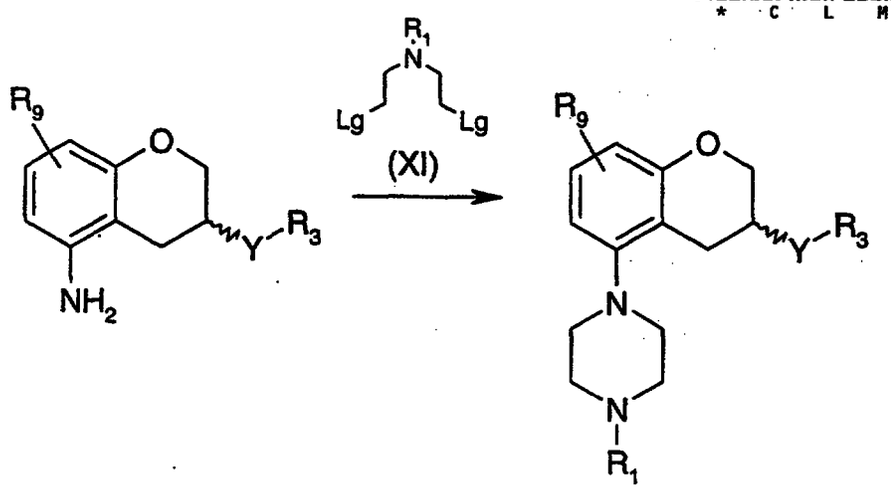


(C) **(I)**

with an activated carboxylic acid R_3-$COLg_1$ where Lg_1 is a leaving group or by using a carboxylic acid R_3-COOH with an activating reagent, followed by the removal of the protecting group R_d;

B (i)

reacting, in the case where Y is $CONR_2$, R_2, R_3 and R_9 is as defined in general formula **I** above, a compound of formula **D**

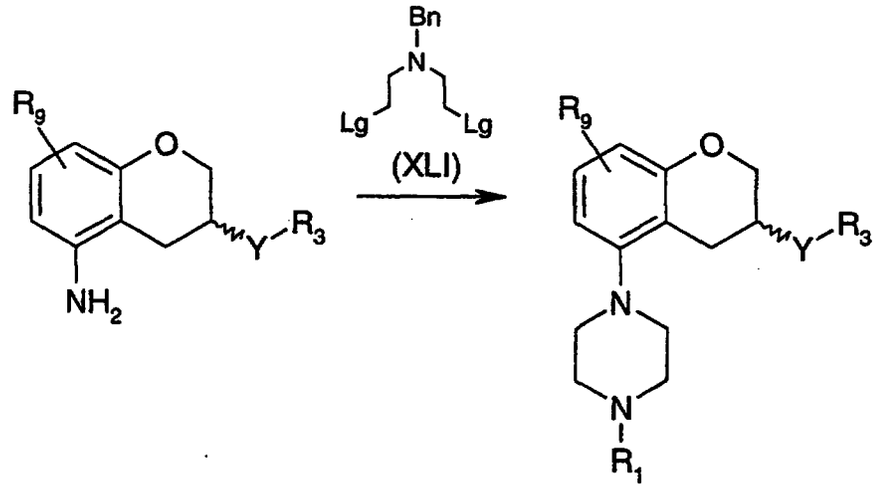


(D) (I)

with a compound of formula **XI** wherein Lg is a leaving group;

B (ii)

reacting, in the case where Y is $CONR_2$, R_1 is H, R_2, R_3 and R_9 is as defined in general formula **I** above with the exception of when R_4 and R_9 are substituents that are susceptible to catalytic hydrogenation known by a person skilled in the art, a compound of formula **D**

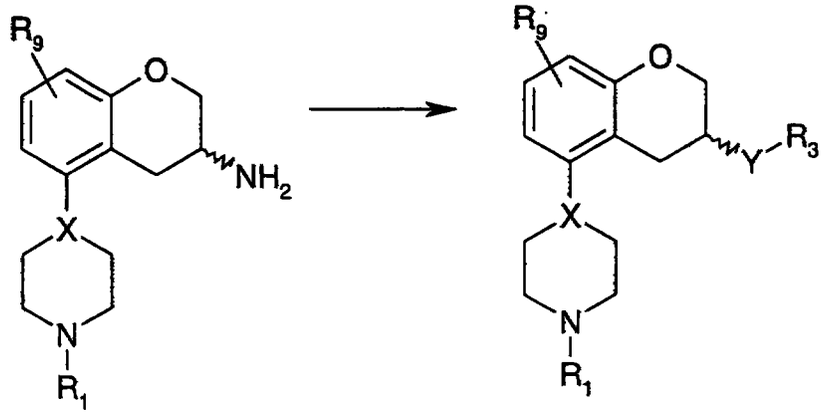


(D) (I)

with a compound of formula **XLI** wherein Lg is a leaving group;

C (i)

reacting, in the case where Y is NR_2SO_2, R_2 is hydrogen, R_1, R_3 and R_9 is as defined in general formula **I** above, a compound of formula **E**

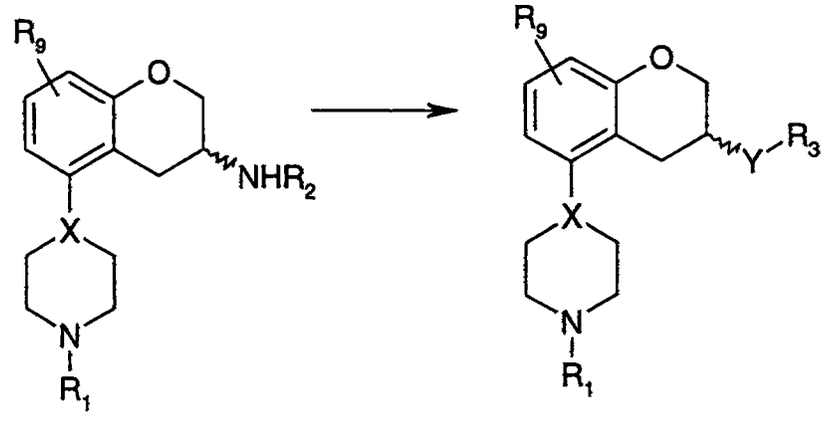


(E) (I)

with an appropriate activated sulfonic acid $R_3SO_2Lg_1$, where Lg_1 is a leaving group;

C (ii)

reacting, in the case where Y is NR_2SO_2, R_2 is C_1-C_6 alkyl, R_1, R_3 and R_9 is as defined in general formula **I** above, a compound of formula **E**

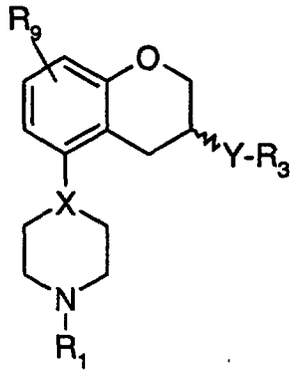


(E) (I)

with an appropriate activated sulfonic acid $R_3SO_2Lg_1$, where Lg_1 is a leaving group;

D

reduction, where Y is NR_2CH_2 or CH_2NR_2, and X, R_1, R_2, R_3 and R_9 are as in formula **I** above with the exception of when R_4 and R_9 are substituents that are susceptible to certain reducing agents known by a person skilled in the art, of a compound of formula **I** above where Y is NR_2CO or $CONR_2$, and X, R_1, R_2, R_3 and R_9 are as in formula **I** above,

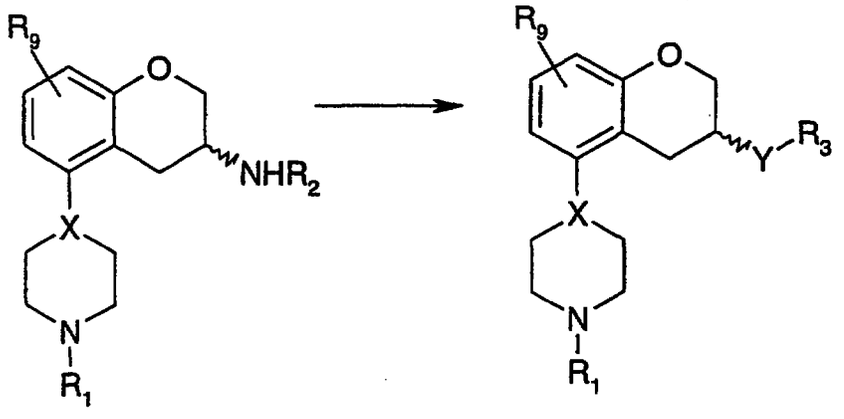


(I)

by a appropriate reducing agent; or

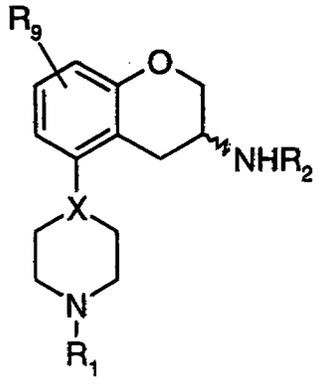
E

alkylation, in the case where R_1 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl, Y is NR_2CH_2 and X, R_2 R_3 and R_9 are as defined in general formula **I** above with the exception of when R_4 and R_9 are substituents that are susceptible to certain alkylations known by a person skilled in the art, of a compound of formula **B**,



(B) **(I)**

37. A compound having the formula



wherein X is N or CH;

R_1 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl;

R_2 is hydrogen or C_1-C_6 alkyl; and

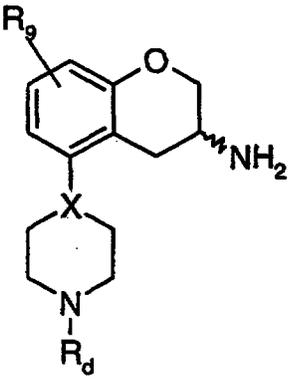
R_9 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, OCF_3, $OCHF_2$, OCH_2F, halogen, CN, CF_3, OH, C_1-C_6 alkoxy, C_1-C_6 alkoxy-C_1-C_6 alkyl, NR_6R_7, SO_3CH_3, SO_3CF_3, $SO_2NR_6R_7$, an unsubstituted or substituted heterocyclic or heteroaromatic ring containing one or two heteroatoms selected from N and O, wherein the substituent(s) is(are) C_1-C_6 alkyl; or COR_8; wherein

R_6 is H, C_1-C_6 alkyl or C_3-C_6 cycloalkyl;

R_7 is H, C_1-C_6 alkyl or C_3-C_6 cycloalkyl; and

R_8 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, CF_3, NR_6R_7, phenyl, a heteroaromatic ring containing one or two heteroatoms selected from N, O and S or a heterocyclic ring containing one or two heteroatoms selected from N, O, S, SO and SO_2 wherein R_6 and R_7 are as defined above.

38. A compound having the formula



wherein

X is N;

R_9 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, OCF_3, $OCHF_2$, OCH_2F, halogen, CN, CF_3, OH, C_1-C_6 alkoxy, C_1-C_6 alkoxy-C_1-C_6 alkyl, NR_6R_7, SO_3CH_3, SO_3CF_3, $SO_2NR_6R_7$, an unsubstituted or substituted heterocyclic or heteroaromatic ring containing one or two heteroatoms selected from N and O, wherein the substituent(s) is(are) C_1-C_6 alkyl; or COR_8; wherein

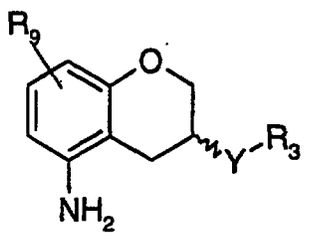
R_6 is H, C_1-C_6 alkyl or C_3-C_6 cycloalkyl;

R_7 is H, C_1-C_6 alkyl or C_3-C_6 cycloalkyl;

R_8 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, CF_3, NR_6R_7, phenyl, a heteroaromatic ring containing one or two heteroatoms selected from N, O and S or a heterocyclic ring containing one or two heteroatoms selected from N, O, S, SO and SO_2 wherein R_6 and R_7 are as defined above; and

R_d is a protecting group.

39. A compound having the formula





wherein

Y is $CONR_2$; wherein R_2 is hydrogen or C_1-C_6 alkyl;

R_3 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl or $(CH_2)_n$-aryl,

wherein aryl is phenyl or a heteroaromatic ring containing one or two heteroatoms selected from N, O and S and which may be mono- or di-substituted with R_4 and/or R_5;

wherein R_4 is H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halogen, CN, CF_3, OH, C_1-C_6 alkoxy, NR_6R_7, OCF_3, SO_3CH_3, SO_3CF_3, $SO_2NR_6R_7$, phenyl, phenyl-C_1-C_6 alkyl, phenoxy, C_1-C_6 alkylphenyl, an optionally substituted heterocyclic or heteroaromatic ring containing one or two heteroatoms selected from N, O, S, SO and SO_2 wherein the substituent(s) is(are) selected from C_1-C_6 alkyl, C_3-C_6 cycloalkyl and phenyl-C_1-C_6 alkyl; or COR_8;

wherein R_6 is H, C_1-C_6 alkyl or C_3-C_6 cycloalkyl;

R_7 is H, C_1-C_6 alkyl or C_3-C_6 cycloalkyl; and

R_8 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, CF_3, NR_6R_7, phenyl, or a heterocyclic ring containing one or two heteroatoms selected from N, O, S, SO and SO_2;

wherein R_5 is H, OH, CF_3, OCF_3, halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy;

n is 0-4; and

R_9 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, OCF_3, $OCHF_2$, OCH_2F, halogen, $CONR_6R_7$, CN, CF_3, OH, C_1-C_6 alkoxy, NR_6R_7, SO_3CH_3, SO_3CF_3, $SO_2NR_6R_7$, an unsubstituted or substituted heterocyclic or heteroaromatic ring containing one or two heteroatoms selected from N and O, wherein the substituent(s) is(are) C_1-C_6 alkyl; or COR_8; wherein R_6, R_7 and R_8 are as defined above.