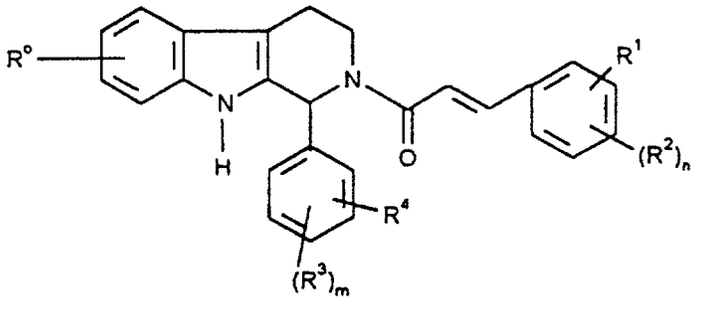
CARBOLINE DERIVATIVES.

This invention relates to a series of carboline derivatives, to processes for their preparation, pharmaceutical compositions containing them, and their use as therapeutic agents. In particular, the invention relates to carboline derivatives which are potent and selective inhibitors of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase (cGMP specific PDE) having utility in a variety of therapeutic areas where such inhibition is thought to be beneficial, including the treatment of cardiovascular disorders.

Thus, according to a first aspect, the present invention provides compounds of formula (I)



(I)

wherein

R^0 represents -hydrogen or -halogen;

R^1 is selected from the group consisting of:

-hydrogen,

$-NO_2$,

-trifluoromethyl,

-trifluoromethoxy,

-halogen,

-cyano,

a 5- or 6- membered heterocyclic group containing at least one heteroatom selected from oxygen, nitrogen and sulphur (optionally substituted by - $C(=O)OR^a$ or C_{1-4}alkyl),

$-C_{1-6}$alkyl optionally substituted by $-OR^a$,

$-C_{1-3}$alkoxy,

$-C(=O)R^a$,

$-O-C(=O)R^a$,

-C(=0)OR^a,
-C_{1-4}alkylene C(=0)OR^a,
-O-C_{1-4}alkylene -C(=0)OR^a,
-C_{1-4}alkylene-0-C_{1-4}alkylene-C(=0)OR^a,
-C(=0)$NR^aSO_2R^c$,
-C(=0)C_{1-4}alkylene Het, wherein Het represents 5- or 6-membered heterocyclic group as defined above,
-C_{1-4}alkylene NR^aR^b,
-C_{2-6}alkenyleneNR^{a}R^b,
-C(=0)NR^aR^b,
-C(=0)NR^aR^c,
-C(=0)NR^aC_{1-4}alkylene OR^b
-C(=0)NR^aC_{1-4}alkylene Het, wherein Het represents a 5- or 6-membered heterocyclic group as defined above,
-OR^a
-OC_{2-4}alkylene NR^aR^b,
-OC_{1-4}alkylene-CH(OR^a)CH_2 NR^aR^b,
-O-C_{1-4}alkylene Het, wherein Het represents a 5- or 6- membered heterocyclic group as defined above,
-O-C_{2-4}alkylene-OR^a,
-O-C_{2-4}alkylene-NR^a-C(=0)-OR^b,
-NR^aR^b,
-NR^aC_{1-4}alkyleneNR^{a}R^b,
-$NR^aC(=0)R^b$,
-$NR^aC(=0)NR^aR^b$,
-N(SO_2C_{1-4}alkyl)$_2$,
-NR^a(SO_2C_{1-4}alkyl),
-$SO_2NR^aR^b$, and
-OSO_2trifluoromethyl;

R^2 is selected from the group consisting of:
-hydrogen,
-halogen,
-OR^a,
-C_{1-6} alkyl,
-NO_2, and

$-NR^aR^b$,

or R^1 and R^2, together form a 3- or 4- membered alkylene or alkenylene chain, optionally containing at least one heteratom ;

R^3 is selected from the group consisting of:

-hydrogen,

-halogen,

$-NO_2$,

-trifluoromethoxy,

$-C_{1-6}$alkyl, and

$-C(=O)OR^a$;

R^4 is hydrogen,

or R^3 and R^4 together form a 3- or 4- membered alkylene or alkenylene chain, optionally containing at least one heteratom;

R^a and R^b, which may be the same or different, are independently selected from hydrogen and C_{1-6}alkyl;

R^c represents phenyl or C_{4-6}cycloalkyl, which phenyl or C_{4-6}cycloalkyl can be optionally substituted by one or more halogen atoms, one or more $-C(=O)OR^a$ or one or more $-OR^a$;

n is an integer selected from 1, 2 and 3;

m is an integer selected from 1 and 2;

and pharmaceutically acceptable salts and solvates (e.g. hydrates) thereof.

The terms alkyl or alkylene as used herein respectively contain the appropriate indicated number of carbon atoms and appropriately include straight chained and branched alkyl or alkylene groups, typically methyl, methylene, ethyl and ethylene groups, and straight chained and branched propyl, propylene, butyl and butylene groups. The term C_{2-6}alkenylene as used herein contains 2 to 6 carbon atoms and appropriately includes straight chained and branched alkenylene groups, in particular ethenylene or the like.

The terms C_{4-6} cycloalkyl denotes cyclic groups containing 4 to 6 carbon atoms, namely cyclobutane, cyclopentane and cyclohexane.

The term halogen as used herein includes fluorine, chlorine, bromine and iodine.

The term 5- or 6-membered heterocyclic group as used herein includes 5- or 6- membered heterocycloalkyl and heteroaryl groups, e.g. tetrahydrofuranyl,

piperidyl, piperazinyl pyrrolidinyl, morpholinyl, pyridyl, imidazolyl, furyl, and tetrazolyl.

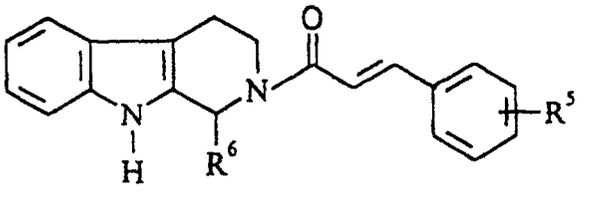
Appropriately, R° represents hydrogen. Alternatively R° may represent halogen, in particular fluorine.

R^1 may represent any of the substituents as hereinbefore described, or more particularly may represent any of $-OR^a$, $-O-C_{2-4}alkyleneNR^aR^b$, $-O-C_{1-4}alkyleneHet$ and $-O-C_{2-4}alkylene-OR^a$. In particular, R^1 represents $-O-C_{2-4}alkylene\ NR^aR^b$, wherein suitably $C_{2-4}alkylene$ may represent ethylene and aptly, R^a and R^b may independently represent methyl.

Particularly suitably R^2 represents hydrogen. Alternatively, in the case where R^1 and R^2 together form a 3- or 4- membered alkylene or alkenylene chain optionally containing at least one heteratom as hereinbefore described, suitably R^1 and R^2 together form a methylenedioxy chain, an ethyleneoxy chain, an ethylenedioxy chain, an ethenyleneoxy chain, a propylene chain, a butylene chain or $-NR^a$ethylene-O-. Aptly, R^1 and R^2 together form methylenedioxy, propylene or $-N(CH_3)-(CH_2)_2-O-$.

Suitably R^3 and R^4, together form a 3- or 4- membered alkylene or alkenylene chain, optionally containing at least one heteratom as hereinbefore described. Particularly suitably R^3 and R^4 together form a methylenedioxy chain, an ethyleneoxy chain, an ethylenedioxy chain, an ethenyleneoxy chain, a propylene chain, a butylene chain or $-NR^a$ethylene-O-. Aptly R^3 and R^4 together form a methylenedioxy chain, an ethyleneoxy chain, an ethylenedioxy chain, an ethenyleneoxy chain or a propylene chain. In particular, R^3 and R^4 together form methylenedioxy or ethyleneoxy, most particularly ethyleneoxy.

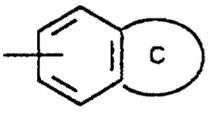
A particular subgroup of compounds according to the present invention can be represented by formula (Ia)



(Ia)

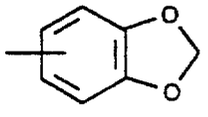
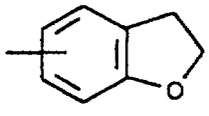
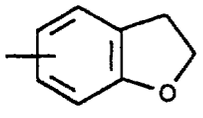
wherein

R^5 is selected from the group consisting of -OH, $-OC_{2-4}alkylene\ NR^aR^b$ and $O-C_{1-4}alkylene$ Het, wherein Het is as hereinbefore described and

R^6 represents  wherein C represents a 5- or 6-membered ring which may be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur and nitrogen, optionally substituted by C_{1-4}alkyl;

and pharmaceutically acceptable salts and solvates (e.g. hydrates thereof).

Typically, R^5 represents -OC_{2-4}alkylene NR^aR^b, in particular -$OCH_2CH_2N(CH_3)_2$. Alternatively, R^5 may represent -O-C_{1-4}alkylene Het, where Het may suitable be piperidyl, pyrrolidinyl (optionally substituted by C_{1-4}alkyl, e.g. methyl) or morpholinyl.

Particularly aptly R^6 represents  or  , especially 

The compounds of formula (I) may contain one or more asymmetric centres and thus can exist as enantiomers or diastereoisomers. It is to be understood that the invention includes both mixtures and separate individual isomers of the compounds of formula (I).

The pharmaceutically acceptable salts of the compounds of formula (I) which contain a basic centre are acid addition salts formed with pharmaceutically acceptable acids. Examples include the hydrochloride, hydrobromide, sulphate or bisulphate, phosphate or hydrogen phosphate, acetate, benzoate, succinate, fumarate, maleate, lactate, citrate, tartrate, gluconate, methanesulphonate, benzenesulphonate and p-toluenesulphonate salts. Compounds of the formula (I) can also provide pharmaceutically acceptable metal salts, in particular alkali metal salts, with bases. Examples include the sodium and potassium salts.

Particular individual compounds of the invention include:

(E)-1-(1-Phenyl-1,3,4,9-tetrahydro-β-carbolin-2-yl)-3-phenylpropene-1-one

(E)-1-(1-Phenyl-1,3,4,9-tetrahydro-β-carbolin-2-yl)-3-(4-nitrophenyl)propene-1-one

(E)-1-(1-Phenyl-1,3,4,9-tetrahydro-β-carbolin-2-yl)-3-(4-trifluoromethylphenyl)-propene-1-one
(E)-1-(1-Phenyl-1,3,4,9-tetrahydro-β-carbolin-2-yl)-3-(4-methoxy-phenyl)propene-1-one
(E)-1-[1-(4-Methoxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-trifluoromethylphenyl)propene-1-one
(E)-N-[4-[3-Oxo-3-(1-phenyl-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]phenyl]-acetamide
(E)-1-[1-(4-Methoxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)-3-phenylpropene-1-one
(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-phenyl-propene-1-one
(E)-1-(1-Phenyl-1,3,4,9-tetrahydro-β-carbolin-2-yl)-3-(4-formylphenyl)propene-1-one
(E)-N-[4-[3-Oxo-3-(1-(4-nitrophenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]-phenyl]acetamide
(E)-1-[1-(4-Nitrophenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-phenylpropene-1-one
(E)-1-[1-(4-Trifluoromethoxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-phenyl-propene-1-one
(E)-1-[1-(4-Methylphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-phenylpropene-1-one
(E)-N-[4-[3-Oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)-propenyl]phenyl]acetamide
(E)-4-[3-Oxo-3-(1-phenyl-1,3,4,9-tetrahydro-β-carbolin-2-yl)-propenyl]benzoic acid, methyl ester
(E)-1-[1-(2-Chlorophenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-phenylpropene-1-one
(E)-1-(1-Phenyl-1,3,4,9-tetrahydro-β-carbolin-2-yl)-3-(3,4-methylenedioxyphenyl)-propene-1-one
(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-bromophenyl)propene-1-one
(E)-1-[1-(4-Chlorophenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-phenylpropene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-ethoxyphenyl)propene-1-one

(E)-4-[3-Oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]acetic acid, phenyl ester

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-hydroxyphenyl)propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-formylphenyl)propene-1-one

(E)-1-[4-[3-Oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)-propenyl]phenyl]-3-phenylurea

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-aminophenyl)propene-1-one

(E)-1-[1-(3,4-Methylenedioxy-phenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-nitro-phenyl)-propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-[(4-bis(methylsulfonyl)aminophenyl]propene-1-one

(E)-4-[3-Oxo-3-[1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-propenyl]benzoic acid, methyl ester

(E)-N-[4-[3-Oxo-3-[1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]propenyl]phenyl]methanesulfonamide

(E)-4-[3-Oxo-3-[1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]propenyl]benzamide]

(E)-4-[3-Oxo-3-[1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-propenyl]benzoic acid

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-cyanophenyl)propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-trifluoromethylphenyl)propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3,4-methylenedioxyphenyl)propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-chlorophenyl)propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-trifluoromethoxyphenyl)propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-methylphenyl)propene-1-one

(E)-[4-[3-Oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]phenyl]urea

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-hydroxymethylphenyl)propene-1-one

(E)-N-Benzyl-4-[3-oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]benzamide

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(2,4-dichlorophenyl)propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-methoxy-4-hydroxyphenyl)propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-hydroxy-4-methoxyphenyl)propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-fluorophenyl)propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-indan-5-yl-1-propene-1-one

(E)-N-[4-[3-Oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]benzoyl]benzenesulfonamide

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3,4-dichlorophenyl)propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3,4-dimethoxyphenyl)propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3,4-dihydroxyphenyl)propene-1-one

(E)-N-Methyl-N-[4-(3-oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]phenyl]acetamide

(E)-2,2-Dimethyl-N-[4-[3-Oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]phenyl]propionamide

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3,5-dimethoxyphenyl)propene-1-one

(E)-(N)-(4-[3-[1-(3,4-Methylenedioxyphenyl)-6-fluoro-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-oxopropenyl]phenyl)-acetamide

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3,4,5-trimethoxyphenyl)propene-1-one

(E)-N-[4-[3-Oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]phenyl]isobutyramide

(E)-1-[1-(3,4-Methylenedioxyphenyl)-6-fluoro-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-phenylpropene-1-one

(E)-N-(2-Methoxyethyl)-4-[3-oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]benzamide

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-hydroxyphenyl)propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-methoxyphenyl)propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-nitrophenyl)propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-[4-(2-dimethylaminoethoxy)phenyl]propene-1-one

(E)-N-(2-Morpholin-4-ylethyl)-4-[3-oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]benzamide

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-[4-(1H-tetrazol-5-yl)phenyl]propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-aminophenyl)propene-1-one

(E)-N-Cyclohexyl-4-[3-oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]benzamide

(E)-N-(Tetrahydrofuran-2-ylmethyl)-4-[3-oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]benzamide

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-cyanophenyl)propene-1-one

(E)-N-(4-Piperidine-4-carboxylic acid, ethyl ester)-4-[3-oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]benzamide

(E)-N-(4-Piperidine-4-carboxylic acid)-4-[3-oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]benzamide

(E)-3-[3-Oxo-3-[1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-propenyl]benzoic acid

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-(4-methylpiperazine-1-carbonyl)phenyl)propene-1-one

(E)-N-(2-Piperazin-1-ylethyl)-3-[3-oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]benzamide

(E)-4-[3-Oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)-propenyl]acetic acid ethyl ester

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-tetrazolophenyl)propene-1-one

(E)-2-[3-Oxo-3-[1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-propenyl]benzoicacid, methyl ester

(E)-3-[3-Oxo-3-[1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-propenyl]benzoic acid, methyl ester

(E)-1-(4-[3-Oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)-propenyl]phenyl)piperidine-4-carboxylic acid, ethyl ester

(E)-N-(1-Ethylpyrrolidin-2-yl-methyl)-3-[3-oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]benzamide

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-(2-dimethylaminoethoxy)phenyl)propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3,5-diterbutyl-4-hydroxyphenyl)propene-1-one

(E)-3-[3-Oxo-3-[1-(4-methoxycarbonylphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]propenyl]benzoic acid, methyl ester

(E)-2-[3-Oxo-3-[1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-propenyl]benzoic acid

(E)-(4-[3-Oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]phenoxy)acetic acid, ethyl ester

(E)-(4-[3-Oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)-propenyl]phenyl)acetic acid

(E)-(4-[3-Oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]phenoxy)acetic acid

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-nitro-4-chlorophenyl)propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(5-nitro-2-chlorophenyl)propene-1-one

(E)-3-Chloro-4-[3-oxo-3-[1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]propenyl]benzoic acid, methyl ester

(E)-(4-[3-Oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]benzyloxy)acetic acid

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(5-amino-2-chlorophenyl)propene-1-one

(E)-3-Chloro-4-[3-oxo-3-[1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]propenyl]benzoic acid

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3,5-dibromo-4-hydroxyphenyl)propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-(2-dimethylaminopropoxy)phenyl)propene-1-one

(E)-2-Chloro-5-[3-oxo-3-[1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]propenyl]benzoic acid, methyl ester

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-(2-diisopropylaminoethoxy)phenyl)propene-1-one

(E)-2-Chloro-5-[3-oxo-3-[1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]propenyl]benzoic acid

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-hydroxy-4-nitrophenyl)propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3,5-dimethyl-4-hydroxyphenyl)propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-(2-dimethylaminoethoxy)-4-nitrophenyl)propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-(2-dimethylaminoethoxy)-4-aminophenyl)propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-nitro-4-hydroxy-5-methoxyphenyl)propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-chlorophenyl)propene-1-one

(E)-1-[1-(4-Methoxy-phenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(2-chloro-5-nitrophenyl)propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(2,6-dichlorophenyl)propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-methylaminomethylphenyl)propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-methylphenyl)-propene-1-one

(E)-N-Methyl-(4-[3-oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]benzenesulfonamide

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-hydroxy-4-acetylphenyl)propene-1-one

(E)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(2-chloro-5-nitrophenyl)propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(2-hydroxyphenyl)propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-nitro-2-piperidin-1-ylphenyl)propene-1-one

(E)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-phenylpropene-1-one

(E)-1-[1-(4-Isopropylphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-nitrophenyl)propene-1-one

(E)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-nitrophenyl)propene-1-one

(E)-(R)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-phenylpropene-1-one

(E)-(S)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-phenylpropene-1-one

(E)-1-[1-(4-Methoxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3(3-nitrophenyl)propene-1-one

(E)-1-[1-(4-Methylphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(2-chloro-5-nitrophenyl)propene-1-one

(E)-N-(Tetrahydrofuran-2-ylmethyl)-3-[3-oxo-3-(1-(3,4-methylenedioxy)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]benzamide

(E)-1-[1-(Indan-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-phenylpropene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-acetylphenyl)propene-1-one

(E)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)]-3-(4-(2-dimethylaminoethoxy)phenyl)propene-1-one

(E)-4-[3-Oxo-3-[1-(4-methoxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]propenyl]-benzoic acid, methyl ester

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(2-hydroxy-5-nitrophenyl)propene-1-one

(E)-4-[3-Oxo-3-[1-(2,3-dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]propenyl]benzoic acid, methyl ester

(E)-4-[3-Oxo-3-[1-(4-methoxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]propenyl]benzoic acid

(E)-4-[3-Oxo-3-[1-(2,3-dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]propenyl]benzoic acid

(E)-1-[1-(Benzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-phenylpropene-1-one

(E)-3-[3-Oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)-propenyl]phenyl)trifluoromethanesulfonic acid, phenyl ester

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-[4-(2-hydroxyethoxy)phenyl]propene-1-one

(E)-1-[1-(Benzofuran-5-yl-1,3,4,9-tetrahydro-β-carbolin-2-yl)]-3-(4-(2-dimethylaminoethoxy)phenyl)propene-1-one

(E)-1-[1(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(2-dimethylaminophenyl)propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(2-piperidin-1-ylphenyl)propene-1-one

(E)-4-[3-Oxo-3-[1-(benzofuran-5-yl-1,3,4,9-tetrahydro-β-carbolin-2-yl]-propenyl]-benzoic acid, methyl ester

(E)-4-[3-(1-Benzofuran-5-yl-1,3,4,9-tetrahydro-β-carbolin-2-yl)-3-oxo-propenyl]-benzoic acid

(E)-4-[3-Oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]phenyl)trifluoromethanesulfonic acid, phenyl ester

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(2-(2-dimethylaminoethoxy)phenyl)propene-1-one

(E)-1-[1-(3-Fluoro-4-methoxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-phenylpropene-1-one

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)]-3-(4-(2-dimethylaminoethoxy)phenyl)propene-1-one

(E)-1-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-phenylpropene-1-one

(E)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)]-3-(4-(2-pyrrolidin-1-ylethoxy)phenyl)propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-[4-pyrrolidin-1-ylphenyl]propene-1-one

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-nitrophenyl)propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-[4-imidazol-1-ylphenyl]propene-1-one

(E)-4-[3-[1-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-oxopropenyl]benzoic acid, methyl ester

(E)-1-[1-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-nitrophenyl)propene-1-one

(E)-1-[1-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)]-3-(4-(2-dimethylaminoethoxy)phenyl)propene-1-one

(E)-1-[1-(3-Fluoro-4-methoxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)]-3-(4-(2-dimethylaminoethoxy)phenyl)propene-1-one

(E)-4-[3-[1-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-oxopropenyl]benzoic acid

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-phenylpropene-1-one

(E)-(S)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)]-3-(4-(2-dimethylaminoethoxy)phenyl)propene-1-one

(E)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-aminophenyl)propene-1-one

(E)-(S)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-phenylpropene-1-one

(E)-(S)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-nitrophenyl)propene-1-one

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)]-3-(4-(1-(S)-methylpyrrolidin-2-yl-methoxy)phenyl)propene-1-one

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-hydroxyphenyl)propene-1-one

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)]-3-(4-(2-dimethylamino-1-methylethoxy)phenyl)propene-1-one

(E)-1-(1-Phenyl-1,3,4,9-tetrahydro-β-carbolin-2-yl)-3-(4-(4-methylpyperazin-1-yl)-phenyl)propene-1-one

(E)-(R)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)]-3-(4-(1-(S)-methylpyrrolidin-2-yl-methoxy)phenyl)propene-1-one

(E)-(R)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)]-3-(4-(2-dimethylamino-1-methylethoxy)phenyl)propene-1-one

(E)-(R)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)]-3-(4-(2-dimethylaminopropoxy)phenyl)propene-1-one

(E)-4-[3-Oxo-3-[1-(3,4-fluorophenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-propenyl]benzoic acid, methyl ester

(E)-(R)-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)]-3-(4-(2-diethylaminoethoxy)phenyl)propene-1-one

(E)-(R)1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)]-3-(4-(2-dimethylaminopropoxy)phenyl)propene-1-one

(E)-4-[3-Oxo-3-[1-(3,4-difluorophenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]propenyl]-benzoic acid

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-aminophenyl)propene-1-one

(E)-(R)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-aminophenyl)propene-1-one

(E)-(R)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)]-3-(4-(2-pyrrolidin-1-ylethoxy)phenyl)propene-1-one

(E)-(R)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)]-3-(4-(2-diethylaminoethoxy)phenylpropene-1-one

(E)-1-[1-(3-Fluoro-4-methoxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)]-3-(3-nitrophenyl)propene-1-one

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-trifluoromethylphenyl)propene-1-one

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-trifluoromethylphenyl)propene-1-one

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-(2-morpholin-4-ylethoxy)phenyl)propene-1-one

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-(2-(ethylmethylamino)ethoxy)phenyl)propene-1-one

(E)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-(3-(dimethylamino)propenyl)phenyl)propene-1-one

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-(3-dimethylamino-2-hydroxypropoxy)phenyl)propene-1-one

(E)-(R)-1-(1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)-3-(4-formylphenyl)propene-1-one

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-propylaminomethyl)phenyl)propene-1-one

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-[4-(2-dimethylaminoethylamino)phenylpropene-1-one

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-(2-aminoethoxy)phenyl)propene-1-one

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-hydroxyphenyl)propene-1-one

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-(4-methylpiperazin-1-yl)phenylpropene-1-one

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-methylaminomethyl)phenyl)propene-1-one

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-isopropylaminomethyl)phenyl)propene-1-one

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-dimethylaminomethyl)phenyl)propene-1-one

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-[4-(3-dimethylaminopropoxy)phenyl]propene-1-one

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-(2-piperidin-1-ylethoxy)phenyl)propene-1-one

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)-3-(4-(2-piperidin-1-ylethoxy)phenyl]propene-1-one

(E)-(R)-[2-(4-{3-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-oxopropenyl}phenoxy)ethyl]methylcarbamic acid, tertbutyl ester

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-[4-(2-methylaminoethoxy)phenyl]propene-1-one
and pharmaceutically acceptable salts and solvates (e.g. hydrates) thereof.

A specific compound of the invention is:
(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)]-3-(4-(2-dimethylaminoethoxy)phenyl)propene-1-one
and pharmaceutically acceptable salts and solvates (e.g. hydrates) thereof.

It has been shown that compounds of the present invention are potent and selective inhibitors of cGMP specific PDE. Thus, compounds of formula (I) are of interest for use in therapy, specifically for the treatment of a variety of conditions where inhibition of cGMP specific PDE is thought to be beneficial.

As a consequence of the selective PDE 5 inhibition exhibited by compounds of the present invention, cGMP levels are elevated, which in turn can give rise to beneficial anti-platelet, anti-neutrophil, anti-vasospastic, vasodilatory, natriuretic and diuretic activities as well as potentiation of the effects of endothelium-derived relaxing factor (EDRF), nitrovasodilators, atrial natriuretic factor (ANF), brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP) and endothelium-dependent relaxing agents such as bradykinin, acetylcholine and 5-HT_1. The compounds of formula (I) therefore have utility in the treatment of a number of disorders, including stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood vessel patency (e.g. post-percutaneous transluminal coronary angioplasty), peripheral vascular disease, vascular disorders such as Raynaud's disease, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, erectile dysfunction and diseases characterised by disorders of gut motility (e.g. irritable bowel syndrome).

It will be appreciated that references herein to treatment extend to prophylaxis as well as treatment of established conditions.

It will also be appreciated that a compound of formula (I), or a physiologically acceptable salt or solvate thereof can be administered as the raw compound, or as a pharmaceutical composition containing either entity.

There is thus provided as a further aspect of the invention a compound of formula (I) for use in the treatment of stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary

disease, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood vessel patency, (e.g. post-PTCA), peripheral vascular disease, vascular disorders such as Raynaud's disease, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, erectile dysfunction or diseases characterised by disorders of gut motility (e.g. IBS).

According to another aspect of the invention, there is provided the use of a compound of formula (I) for the manufacture of a medicament for the treatment of stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood vessel patency, (e.g. post-PTCA), peripheral vascular disease, vascular disorders such as Raynaud's disease, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, erectile dysfunction or diseases characterised by disorders of gut motility (e.g. IBS).

In a further aspect, the invention provides a method of treating stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood vessel patency, (e.g. post-PTCA), peripheral vascular disease, vascular disorders such as Raynaud's disease, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, erectile dysfunction or diseases characterised by disorders of gut motility (e.g. IBS) in a human or non-human animal body which comprises administering to said body a therapeutically effective amount of a compound with formula (I).

Compounds of the invention may be administered by any suitable route, for example by oral, buccal, sub-lingual, rectal, vaginal, nasal, topical or parenteral (including intravenous, intramuscular, subcutaneous and intracoronary) administration. Oral administration is generally preferred.

For administration to man in the curative or prophylactic treatment of the disorders identified above, oral dosages of a compound of formula (I) will generally be in the range of from 0.5-800mg daily for an average adult patient (70kg). Thus for a typical adult patient, individual tablets or capsules contain from 0.2-400mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier, for administration in single or multiple doses, once or several times per day. Dosages for intravenous, buccal or sublingual administration will

typically be within the range of from 0.1-400 mg per single dose as required. In practice the physician will determine the actual dosing regimen which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can be individual instances in which higher or lower dosage ranges may be merited, and such are within the scope of this invention.

For human use, a compound of the formula (I) can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, the compound may be administered orally, buccally or sublingually, in the form of tablets containing excipients such as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. Such liquid preparations may be prepared with pharmaceutically acceptable additives such as suspending agents (e.g. methylcellulose, a semi-synthetic glyceride such as witepsol or mixtures of glycerides such as a mixture of apricot kernel oil and PEG-6 esters or mixtures of PEG-8 and caprylic/capric glycerides). A compound may also be injected parenterally, for example intravenously, intramuscularly, subcutaneously or intracoronarily. For parenteral administration, the compound is best used in the form of a sterile aqueous solution which may contain other substances, for example salts, or monosaccharides such as mannitol or glucose, to make the solution isotonic with blood.

Thus, the invention provides in a further aspect a pharmaceutical composition comprising a compound of the formula (I) together with a pharmaceutically acceptable diluent or carrier therefor.

There is further provided by the present invention a process of preparing a pharmaceutical composition comprising a compound of formula (I), which process comprises mixing a compound of formula (I) together with a pharmaceutically acceptable diluent or carrier therefor.

A compound of formula (I) may also be used in combination with other therapeutic agents which may be useful in the treatment of the above-mentioned disease states. The invention thus provides, in another aspect, a combination of a compound of formula (I) together with another therapeutically active agent.

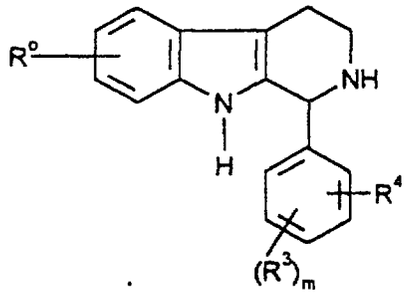
The combination referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical compositions comprising a combination as defined above together with a pharmaceutically acceptable diluent or carrier comprise a further aspect of the invention.

The individual components of such a combination may also be administered either sequentially or simultaneously in separate pharmaceutical formulations.

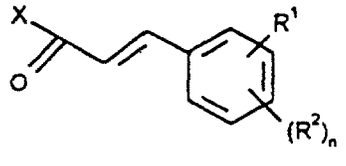
Appropriate doses of known therapeutic agents for use in combination with a compound of formula (I) will be readily appreciated by those skilled in the art.

Compounds of formula (I) may be prepared by any suitable method known in the art or by the following processes which form part of the present invention. In the methods below R^0, R^1,R^2, R^3, and R^4 are are as defined in formula (I) above unless otherwise indicated.

There is a further provided by the present invention a process (A) of preparing a compound of formula (I), which process comprises reacting compounds of formula (II) and (III)



(II)



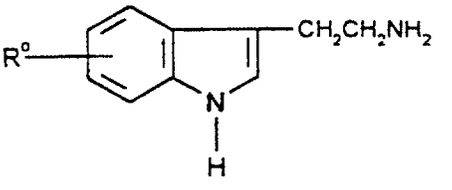
(III)

where X represents a hydroxyl or halogen group.

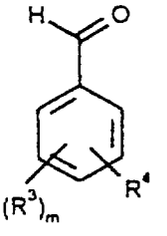
Suitably the reaction is carried out in the presence of 1,3-dicyclohexylcarbodiimide (DCC) or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) and 1-hydroxybenzotriazole (HOBT) in a suitable organic solvent, such as dimethylformamide (DMF) or dichloromethane (DCM) for several hours, e.g. 8 hours to 2 days.

Compounds of formula (I) may be prepared as individual enantiomers from the appropriate enantiomer of formula (II) or as a racemic mixture from the appropriate racemic compound of formula (II). Individual enantiomers of the compounds of the invention may be prepared from racemates by resolution using methods known in the art for the separation of racemic mixtures into their constituent enantiomers, for example using HPLC on a chiral column such as Hypersil naphtyl urea or using separation of salts of diastereoisomers.

A compound of formula (II) may be prepared by Pictet-Spengler cyclization between a tryptamine derivative of formula (IV) and an aldehyde of formula (V)



(IV)



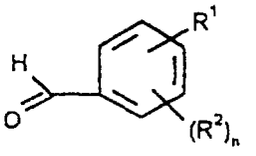
(V)

The reaction may conveniently be effected in a suitable solvent such as a halogenated hydrocarbon (e.g. dichloromethane) or an aromatic hydrocarbon (e.g. toluene) in the presence of an acid such as trifluoroacetic acid (TFA). The reaction may conveniently be carried out at a temperature of from 20 °C to reflux to provide a compound of formula (II) in one step. The reaction may also be carried out in a solvent such as an aromatic hydrocarbon (e.g. toluene) under reflux optionally using a Dean-stark apparatus to trap the water produced.

The reaction provides racemic compounds of formula (II). Enantiomers may be obtained from a resolution with N-acetyl leucine using fractional crystallization in EtOAc:MeOH as solvent. (R) and (S) enantiomers may be isolated as salts depending upon whether N-acetyl-(D) and (L)-leucine was used as the starting material.

Compounds of formulae (IV) and (V) are commercially available compounds or prepared by standard synthetic techniques as hereinafter described in the Examples.

A compound of formula (III) can be prepared from a corresponding aldehyde of formula (VI)



(VI)

suitably by employing a Wittig reaction followed by basic hydrolysis.

Alternatively a compound of formula (III) may be prepared from a compound of formula (VI) by a Knoevenhagel reaction employing malonic acid.

Compounds of formula (VI) can be prepared from known corresponding alcohol, nitrile, or halide derivatives, using techniques well known in the art of synthetic organic chemistry.

According to a further general process (B) compounds of formula (I) can be converted to alternative compounds of formula (I), employing suitable interconversion techniques such as hereinafter described in the Examples.

Compounds of this invention may be isolated in association with solvent molecules by crystallization from or evaporation of an appropriate solvent.

The pharmaceutically acceptable acid addition salts of the compounds of formula (I) which contain a basic centre may be prepared in a conventional manner. For example, a solution of the free base may be treated with a suitable acid, either neat or in a suitable solution, and the resulting salt isolated either by filtration or by evaporation under vacuum of the reaction solvent. Pharmaceutically acceptable base addition salts may be obtained in an analogous manner by treating a solution of a compound of formula (I) with a suitable base. Both types of salt may be formed or interconverted using ion-exchange resin techniques.

Thus, according to a further aspect of the invention, we provide a process for preparing a compound of formula (I) or a salt or solvate (e.g. hydrate) thereof which comprises process (A) or (B) as hereinbefore described followed by

i) salt formation; or

ii) solvate (e.g. hydrate) formation.

The following additional abbreviations are hereinafter used in the accompanying examples: rt (room temperature), DMSO (dimethylsulphoxide), NBS (N-bromosuccinimide), THF (tetrahydrofuran), TFA (trifluoroacetic acid), PTSA (p-toluene sulphonic acid), AIBN (2,2'-azobis isobutyronitrile), and TBDMSCl (tert-butyldimethylsilyl chloride).

Intermediate 1

1-Phenyl-2,3,4,9-tetrahydro-1H-β-carboline

A solution of tryptamine (15 g, 94.0 mmol) and benzaldehyde (10.9 g, 1.1 equiv.) in DCM (800 mL) was treated with TFA (15 mL, 2 equiv.). The resulting mixture was stirred at rt for one day and then neutralized to pH 7 with a saturated aqueous solution of sodium carbonate. After filtration and concentration to dryness the residue was recrystallized from 2-propanol to give the title compound (11.0 g, 47%) as white crystals.

MP: 175-177 °C.

Intermediate 2

1-(4-Methoxyphenyl)-2,3,4,9-tetrahydro-1H-β-carboline

This product was prepared using the same procedure as for Intermediate 1 with tryptamine (15 g, 94.9 mmol), 4-methoxybenzaldehyde (12.9 g, 1.1 equiv.) and TFA (14.6 mL, 2 equiv.) to give the title compound (20.9 g, 80%) as a brownish powder.

MP: 131 °C.

Intermediate 3

1-(4-Nitrophenyl)-2,3,4,9-tetrahydro-1H-β-carboline

This product was prepared using the same procedure as for Intermediate 1 with tryptamine (2.0 g, 12.5 mmol), 4-nitrobenzaldehyde (1.88 g, 1 equiv.) and TFA (1.9 mL, 2 equiv.) to give the title compound (3.1 g, 86%) as a yellow powder.

MP: 190 °C.

Intermediate 4

1-(4-Trifluoromethoxyphenyl)-2,3,4,9-tetrahydro-1H-β-carboline

This product was prepared using the same procedure as for Intermediate 1 with tryptamine (2.0 g, 12.5 mmol), 4-trifluoromethoxybenzaldehyde (2.4 g, 1 equiv.) and TFA (1.9 mL, 2 equiv.) to give the title compound (1.6 g, 38%) as a white powder.
MP: 68-69 °C.

Intermediate 5
1-(4-Chlorophenyl)-2.3.4.9-tetrahydro-1H-β-carboline
This product was prepared using the same procedure as for Intermediate 1 with tryptamine (5.0 g, 30 mmol), 4-chlorobenzaldehyde (4.6 g, 1 equiv.) and TFA (4.6 mL, 2 equiv.) to give the title compound (4.16 g, 49%) as a white powder.
MP: 161 °C.

Intermediate 6
1-(4-Methylphenyl)-2.3.4.9-tetrahydro-1H-β-carboline
This product was prepared using the same procedure as for Intermediate 1 with tryptamine (1.0 g, 6.2 mmol), 4-methylbenzaldehyde (0.74 g, 1 equiv.) and TFA (1 mL, 2 equiv.) to give the title compound (1.6 g, 100%) as a white powder.
MP: 207-209 °C.

Intermediate 7
1-(3.4-Methylenedioxyphenyl)-2.3.4.9-tetrahydro-1H-β-carboline
This product was prepared using the same procedure as for Intermediate 1 with tryptamine (20.0 g, 120 mmol), 3,4-methylenedioxybenzaldehyde (20.6 g, 1.1 equiv.) and TFA (18 mL, 2 equiv.) to give the title compound (22 g, 60%) as white crystals after recrystallization from ethanol.
MP: 178 °C.

Intermediate 8
4-(2,3.4.9-Tetrahydro-1H-β-carbolin-1-yl)benzoic acid, methyl ester
This product was prepared using the same procedure as for Intermediate 1 with tryptamine (2.8 g, 17.4 mmol), 4-formylbenzoic acid, methyl ester (2.87 g, 1.1 equiv.) and TFA (2.7 mL, 2 equiv.) to give the title compound (0.5 g, 9%) as white crystals after recrystallization from isopropanol:H_2O.
MP: 179 °C.

Intermediate 9

1-Indan-5-yl-2,3,4,9-tetrahydro-1H-β-carboline

This product was prepared using the same procedure as for Intermediate 1 with tryptamine (1.28 g, 8.0 mmol), indan-5-carboxaldehyde (1.3 g, 1.1 equiv.) and TFA (1.2 mL, 2 equiv.) to give the title compound (0.36 g, 14%).

^{1}H NMR ($CDCl_3$) δ 7.6 (s, 1H), 7.4 (m, 1H), 6.9-7.2 (m, 6H), 5.1 (s, 1H), 3.3-3.4 (m, 1H), 2.9-3.1 (m, 1H), 2.7-2.9 (m, 6H), 1.9-2.2 (q, 2H).

Intermediate 10

1-(2,3-Dihydrobenzofuran-5-yl)-2,3,4,9-tetrahydro-1H-β-carboline

This product was prepared using a two-step procedure. A solution of tryptamine (32.4 g, 0.2 mol) and 2,3-dihydrobenzofuran-5-carboxaldehyde (30.0 g, 1 equiv.) in toluene (1 L) was heated under reflux for 4 hours. After removal of 4 mL of water and evaporation of toluene the residue was dissolved in DCM (1 L) in the presence of TFA (31 mL, 2 equiv.). The resulting mixture was stirred at rt for 16 hours. Then 1 L of a saturated aqueous solution of $NaHCO_3$ was added. After extraction with DCM and drying over $MgSO_4$, the organic solution was evaporated *in vacuo*. Recrystallization from DCM:iPr_2O (2:30) gave the title compound as white crytals in a 80% yield.

^{1}H NMR ($CDCl_3$) δ 7.6 (s, 1H), 7.5-7.6 (m, 1H), 7-7.3 (m, 5H), 6.7-6.75 (d, 1H), 5.1 (s, 1H), 4.5-4.6 (t, 2H), 3.3-3.45 (m, 1H), 3.05-3.2 (t, 3H), 2.7-3 (m, 2H).

Intermediate 11

1-(4-Isopropylphenyl)-2,3,4,9-tetrahydro-1H-β-carboline

This product was prepared using the same procedure as for Intermediate 1 with tryptamine (5.0 g, 31.2 mmol), 4-isopropylbenzaldehyde (5.08 g, 1.1 equiv.) and TFA (4.8 mL, 2 equiv.) to give the title compound (5.9 g, 67%) as white crystals after recrystallization from iPr_2O.

MP: 146 °C.

Intermediate 12

1-(2,3-Benzofuran-5-yl)-2,3,4,9-tetrahydro-1H-β-carboline

This product was prepared using the same procedure as for Intermediate 1 with tryptamine (2.27 g, 14.1 mmol), 2,3-benzofuran-5-carboxaldehyde (2.1 g, 1

equiv., prepared according to the procedure of Dorn, C.P *et al* **EP 481671A1**) and TFA (2.2 mL, 2 equiv.) to give the title compound (3.0 g, 74%) as white crystals after recrystallization from cyclohexane.
MP: 134-136 °C.

Intermediate 13
1-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-2,3,4,9-tetrahydro-1H-β-carboline
This product was prepared using the same procedure as for Intermediate 1 with tryptamine (4.92 g, 30.7 mmol), 2,3-dihydrobenzo[1,4]dioxin-6-carboxaldehyde (5.05 g, 1.0 equiv.) and TFA (5.0 mL, 2 equiv.) to give the title compound (7.05 g, 75%) as white crystals after recrystallization from iPr_2O.
MP: 144 °C.

Intermediate 14
1-(3-Fluoro-4-methoxyphenyl)-2,3,4,9-tetrahydro-1H-β-carboline
This product was prepared using the same procedure as for Intermediate 1 with tryptamine (4.80 g, 30.0 mmol), 3-fluoro-4-methoxybenzaldehyde (4.86 g, 1.05 equiv.) and TFA (4.6 mL, 2 equiv.) to give the title compound (5.2 g, 59%) as white crystals.
MP: 68 °C.

Intermediate 15
1-(3,4-Difluorophenyl)-2,3,4,9-tetrahydro-1H-β-carboline
This product was prepared using the same procedure as for Intermediate 1 with tryptamine (5.4 g, 33.5 mmol), 3,4-difluorobenzaldehyde (5.0 g, 1.05 equiv.) and TFA (5.2 mL, 2 equiv.) to give the title compound (7.8 g, 82%) as white crystals.
MP: 151 °C.

Intermediate 16
1-(3,4-Methylenedioxyphenyl)-6-fluoro-2,3,4,9-tetrahydro-1H-β-carboline
This product was prepared using the same procedure as for Intermediate 1 with 5-fluorotryptamine (1.59 g, 8.9 mmol), 3,4-methylenedioxybenzaldehyde (1.47 g, 1.1 equiv.) and TFA (1.4 mL , 2 equiv.) to give the title compound (2.34 g, 85%) as white crystals.
MP: 172 °C.

Analysis for $C_{18}H_{15}FN_2O_2$:
Calculated: C,69.67; H,4.87; N,6.12.
Found: C,69.47; H,4.85; N,6.23%

Intermediate 17
1-(2-Chlorophenyl)-2,3,4,9-tetrahydro-1H-β-carboline
This product was prepared using the same procedure as for Intermediate 1 with tryptamine (1.0 g, 6.2 mmol), 2-chlorobenzaldehyde (0.7 mL, 1.0 equiv.) and TFA (1.0 mL, 2 equiv.) to give the title compound (1.2 g, 69%).
^{1}H NMR ($CDCl_3$) δ 7.6 (s, 1H), 7.45 (d, 1H), 7.40 (d, 1H), 6.9-7.2 (m, 6H), 5.6 (s, 1H), 3.2-3.0 (m, 2H), 2.9-2.7 (m, 2H), 2.4 (s, 1H).

Intermediate 18
(S)-1-(3,4-Methylenedioxyphenyl)-2,3,4,9-tetrahydro-1H-β-carboline
(S)-1-(3,4-Methylenedioxyphenyl)-2,3,4,9-tetrahydro-1H-β-carboline was obtained from the resolution of the corresponding racemic amine with N-acetyl-(L)-Leucine (Sigma) in MeOH followed by a recrystallization from MeOH. Treatment of the suspension of the recrystallized material in DCM with a saturated aqueous solution of $NaHCO_3$ gave the enantiomerically pure (S)-1-(3,4-methylenedioxyphenyl)-2,3,4,9-tetrahydro-1H-β-carboline as beige crystals in a 55% yield.
MP: 173 °C.
Analysis for $C_{18}H_{16}N_2O_2$. $0.35H_2O$:
Calculated: C,72.39; H,5.64; N,9.38.
Found: C,72.35; H,5.44; N,9.1%.
$[\alpha]_D^{19.6}$= -35 (c = 0.53, MeOH).

Intermediate 19
(R)-1-(3,4-Methylenedioxyphenyl)-2,3,4,9-tetrahydro-1H-β-carboline
Following the same protocol as for Intermediate 18 (R)-1-(3,4-methylenedioxyphenyl)-2,3,4,9-tetrahydro-1H-β-carboline was obtained from the resolution of the corresponding racemic amine with N-acetyl-(D)-Leucine (Sigma) in MeOH followed by a recrystallization from MeOH. Treatment of the suspension of the recrystallized material in DCM with a saturated aqueous solution of $NaHCO_3$ gave the enantiomerically pure (R)-1-(3,4-

methylenedioxyphenyl)-2,3,4,9-tetrahydro-1H-β-carboline as white crystals in a 59% yield.
MP: 92-94 °C.
Analalysis for $C_{18}H_{16}N_2O_2$:
Calculated: C,73.95; H,5.52; N,9.58.
Found: C,73.72; H,5.52; N,9.52%.
$[\alpha]_D^{21}$ = 34 (c = 0.50, MeOH).

Intermediate 20
(R)-1-(2,3-Dihydrobenzofuran-5-yl)-2,3,4,9-tetrahydro-1H-β-carboline
Following the same protocol as for Intermediate 18 (R)-1-(2,3-dihydrobenzofuran-5-yl)-2,3,4,9-tetrahydro-1H-β-carboline was obtained from the resolution of the corresponding racemic amine with N-acetyl-(D)-Leucine (Sigma) in MeOH:EtOAc followed by a recrystallization from MeOH. Treatment of the suspension of the recrystallized material in DCM with a saturated aqueous solution of $NaHCO_3$ gave the enantiomerically pure (R)-1-(2,3-dihydrobenzofuran-5-yl)-2,3,4,9-tetrahydro-1H-β-carboline as white crystals in a 55% yield.
MP: 98-99 °C.
Analysis for $C_{19}H_{18}N_2O$. $0.15H_2O$:
Calculated: C,77.87; H,6.29; N,9.56.
Found: C,77.83; H,6.33; N,9.44%
$[\alpha]_D^{21}$ = 42 (c = 0.50, MeOH).

Intermediate 21
(S)-1-(4-(2,3-Dihydrobenzo(b)furan)-2,3,4,9-tetrahydro-1H-β-carboline
Following the same protocol as for Intermediate 18 (S)-1-(2,3-dihydrobenzofuran-5-yl)-2,3,4,9-tetrahydro-1H-β-carboline was obtained from the resolution of the corresponding racemic amine with N-acetyl-(L)-Leucine (Sigma) in MeOH/EtOAc followed by a recrystallization from MeOH. Treatment of the suspension of the recrystallized material in DCM with a saturated aqueous solution of $NaHCO_3$ gave the enantiomerically pure (S)-1-(2,3-dihydrobenzofuran-5-yl)-2,3,4,9-tetrahydro-1H-β-carboline as a pale yellow powder in a 45% yield.
MP: 175 °C.

Analalysis for $C_{19}H_{18}N_2O$. $1.0H_2O$:
Calculated: C,74.0; H,6.54; N,9.08.
Found: C,74.01; H,5.88; N,8.92%.
$[\alpha]_D^{19.7}$= -49 (c = 0.50, MeOH).

Intermediate 22
(E)-3-(4-Ureidophenyl)acrylic acid
A stirred solution of (E)-3-(4-aminophenyl)acrylic acid (1.0 g, 5.0 mmol) and potassium isocyanate (2.0 g, 5 equiv.) in a mixture of water and acetic acid (50 mL) was heated at 100 °C for 12 hours. After cooling, a white solid precipitated out. Filtration, washing of the filter cake with a mixture of water and MeOH, and drying it *in vacuo* gave the title compound (0.82 g, 80%) as a white solid.
MP > 350 °C.

Intermediate 23
(E)-3-(4-Acetylmethylaminophenyl)acrylic acid
A stirred solution of N-(4-formylphenyl)-N-methylacetamide (1.0 g, 5.64 mmol), malonic acid (1.06 g, 1.8 equiv.) and piperidine (0.1 g, catalytic amount) in pyridine (3.5 mL) was heated at 60 °C for 12 hours. Pouring the resulting mixture into HCl (1N) gave a precipitate. Filtration gave the title compound (1.2 g, 98%) as a white solid.
MP: 213-215 °C.
Analysis for $C_{12}H_{13}NO_3$. $0.2H_2O$:
Calculated: C,64.68; H,6.06; N,6.29;
Found: C,64.43; H,6.18; N,6.36%.
N-(4-Formylphenyl)-N-methylacetamide (1.0 g, 46%) was obtained as an oil from N-(4-formylphenyl)acetamide (2.0 g, 12.2 mmol) in THF in the presence of iodomethane (1.2 mL, 1.5 equiv.) and NaH (0.73 g, 1.5 equiv., 60% in mineral oil).
^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.0 (s, 3H), 3.4 (s, 3H), 7.4 (d, 2H), 8.0 (d, 2H).

Intermediate 24
(E)-3-[4-(2-Methoxyethylcarbamoyl)phenyl]acrylic acid

The same method was employed as in the preparation of Intermediate 23 but starting from 4-formyl-N-(2-methoxyethyl)benzamide to give the title compound as a white powder in a 57% yield.
MP: 205 °C.

4-Formyl-N-(2-methoxyethyl)benzamide (158 mg, 48%) was obtained by oxidation of 4-hydroxymethyl-N-(2-methoxyethyl)benzamide (330 mg, 1.6 mmol) in DCM in the presence of MnO_2 (3.0 g, 22 equiv.).
^1H NMR ($CDCl_3$, 250 MHz) δ 9.9 (s, 1H), 7.8 (s, 4H), 6.8 (s, 1H), 3.4-3.6 (m, 4H), 3.2 (s, 3H).

4-Hydroxymethyl-N-(2-methoxyethyl)benzamide (330 mg, 14%) was obtained as an oil (Rf= 0.7, DCM:MeOH (9:1)) by coupling 4-(hydroxymethyl)benzoic acid (1.0 g, 6.5 mmol) with 2-methoxyethylamine (0.6 mL, 6.5 mmol) in the presence of Et_3N (0.95 mL, 1.0 equiv.), EDCI (1.2 g, 1.0 equiv.) and HOBT (0.88 g, 1.0 equiv.).

Intermediate 25
(E)-[4-(2-Dimethylaminoethoxy)phenyl]acrylic acid
The same method was employed as in the preparation of Intermediate 23 but starting from 4-(2-dimethylaminoethoxy)benzaldehyde to give the title compound as a white powder in a 100% yield.
MP: 243 °C.
4-(2-Dimethylaminoethoxy)benzaldehyde (20.6 g, 65%) was obtained by alkylation of 4-hydroxybenzaldehyde (20 g, 164 mmol) in DMF with dimethylaminoethyl chloride (144 g, 8 equiv.) and K_2CO_3 (24.9 g, 1.1 equiv.) for 16 hours at 80 °C.
^1H NMR ($CDCl_3$, 250 MHz) δ 9.85 (s, 1H), 7.9-7.8 (d, 2H), 7-6.9 (d, 2H), 4.2 (t, 2H), 2.7 (t, 2H), 2.3 (s, 6H).

Intermediate 26
(E)-3-[4-(2-Morpholin-4-yl-ethylcarbamoyl)phenyl]acrylic acid
The same method was employed as in the preparation of Intermediate 23 but starting from 4-formyl-N-(2-morpholin-4-yl-ethyl)benzamide to give the title compound as a gummy solid.

4-Formyl-N-(2-morpholin-4-yl-ethyl)benzamide (0.14 g, 55%) was obtained by oxidation of 4-hydroxymethyl-N-(2-morpholin-4-yl-ethyl)benzamide (0.24 g, 0.9 mmol) and MnO_2 (1.73 g, 20 mmol).

^1H NMR ($CDCl_3$, 250 MHz) δ 10 (s, 1H), 7.9 (s, 4H), 6.8 (s, 1H), 3.5 (t, 5H), 2.6 (t, 2H), 2.3 (m, 5H).

4-Hydroxymethyl-N-(2-morpholin-4-yl-ethyl)benzamide (240 mg, 14%) was obtained as a colourless oil (Rf= 0.6, DCM:MeOH (9:1)) by coupling 4-(hydroxymethyl)benzoic acid (1.0 g, 6.5 mmol) with 2-morpholinethylamine (0.85 g (1.0 equiv.) in the presence of Et_3N (0.95 mL, 1.0 equiv.), EDCI (1.2 g, 1.0 equiv.) and HOBT (0.88 g, 1.0 equiv.).

Intermediate 27

(E)-3-(4-Cyclohexylcarbamoylphenyl)acrylic acid

The same method was employed as in the preparation of Intermediate 23 but starting from N-cyclohexyl-4-formylbenzamide to give the title compound as a white powder in a 54% yield.

MP: 214 °C.

N-Cyclohexyl-4-formylbenzamide (0.6 g, 60%) was obtained by oxidation of N-cyclohexyl-4-(hydroxymethyl)benzamide (1.0 g, 4.29 mol) with MnO_2 (0.2 g, 22 equiv.), as a white powder.

MP: 163 °C.

^1H NMR ($CDCl_3$, 250 MHz) δ 10 (s, 1H), 7.95 (s, 4H), 6.6 (s, 1H), 4.1 (m, 1H), 3.9-3.7 (m, 3H), 3.4-3.3 (m, 1H), 2.1-1.9 (m, 2H); 1.8-1.7 (m, 2H).

N-Cyclohexyl-4-(hydroxymethyl)benzamide(1.0 g, 66%) was obtained as white crystals by coupling 4-(hydroxymethyl)benzoic acid with cyclohexylamine (0.75 mL, 1 equiv.) in the presence of Et_3N (0.95 mL, 1.0 equiv.), EDCI (1.2 g, 1.0 equiv.) and HOBT (0.88 g, 1.0 equiv.).

MP: 185 °C.

^1H NMR ($CDCl_3$, 250 MHz) δ 7.8-7.7 (d, 2H), 7.5-7.4 (d, 2H), 6.8 (s, 1H), 4.8 (s, 2H), 4.2 (m, 1H), 4.0-3.75 (m, 2H), 3.4-3.3 (m, 1H), 2.7 (m, 1H), 2-1.9 (m, 2H), 1.6 (m, 1H), 1.1 (m, 1H).

Intermediate 28

(E)-3-{4-[(Tetrahydrofuran-2-ylmethyl)carbamoyl]phenyl}acrylic acid

The same method was employed as in the preparation of Intermediate 23 but starting from 4-formyl-N-(tetrahydrofuran-2-ylmethyl)benzamide to give the title compound as a white powder in a 49% yield.
MP: 215 °C.

4-Formyl-N-(tetrahydrofuran-2-ylmethyl)benzamide (0.36 g, 50%) (Rf= 0.3, DCM:MeOH) was obtained as an oil by oxidation of 4-hydroxymethyl-N-(tetrahydrofuran-2-ylmethyl)benzamide (0.72 g, 3.0 mmol) with MnO_2 (0.36 g, 22 equiv.).

4-Hydroxymethyl-N-(tetrahydrofuran-2-ylmethyl)benzamide (0.72 g, 46%) was obtained as a colourless oil (Rf= 0.6, DCM:MeOH (9:1)) by coupling 4-(hydroxymethyl)benzoic acid (1.0 g, 6.5 mmol) with tetrahydrofuran-2-yl-methylamine (0.67 mL, 1.0 equiv.) in the presence of Et_3N (0.95 mL, 1.0 equiv.), EDCI (1;2 g, 1.0 equiv.) and HOBT (0.88 g, 1.0 equiv.).

Intermediate 29

(E)-1-[4-(2-Carboxyvinyl)benzoyl]piperidine-4-carboxylic acid, ethyl ester

The same method was employed as in the preparation of Intermediate 23 but starting from 1-(4-formylbenzoyl)piperidine-4-carboxylic acid, ethyl ester to give the title compound as a white powder in a 46% yield.
MP: 165 °C.

1-(4-Formylbenzoyl)piperidine-4-carboxylic acid, ethyl ester (960 mg, 49%) (Rf= 0.6, DCM:MeOH(95:5)) was obtained as an oil by oxidation of 1-(4-hydroxymethylbenzoyl)piperidine-4-carboxylic acid, ethyl ester (2.0 g, 6.8 mmol) with MnO_2 (13.1 g, 22 equiv.).

^1H NMR ($CDCl_3$, 250 MHz) δ 10.0 (s, 1H), 7.9 (d, 2H), 7.5 (d, 2H), 4.5 (d, 1H), 4.1 (q, 2H), 3.6 (d, 1H), 3.1 (br s, 2H), 2.5 (m, 1H), 2.1-1.6 (m, 4H), 1.2 (t, 3H).

1-(4-Hydroxymethylbenzoyl)piperidine-4-carboxylic acid, ethyl ester (1.9 g, 100%) was obtained as a colorless oil (Rf= 0.1, DCM:MeOH (95:5)) by coupling 4-(hydroxymethyl)benzoic acid (1.0 g, 6.5 mmol) with 4-piperidine-4-carboxylic acid, ethyl ester (1 mL, 6.5 mmol) in the presence of Et_3N (0.95 mL, 1.0 equiv.), EDCI (1.2 g, 1.0 equiv.) and HOBT (0.88 g, 1.0 equiv.).

^1H NMR ($CDCl_3$, 250 MHz) δ 7.2 (s, 4H), 4.5 (s, 2H), 4.3 (br s, 1H), 4.1 (q, 2H), 3.6 (br s, 1H),3 (t, 2H), 2.5 (m, 1H), 2.1-1.6 (m, 4H), 1.2 (t, 3H).

Intermediate 30

(E)-3-(4-Ethoxycarbonylmethylphenyl)acrylic acid

The same method was employed as in the preparation of Intermediate 23 but starting from (4-formylphenyl)acetic acid, ethyl ester gave the title compound as a yellow gum in a 52% yield.

^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.8-7.6 (m, 3H), 7.4-7.3 (d, 2H), 6.9-6.8 (d, 1H), 4.1-3.9 (q, 2H), 3.55 (s, 2H), 1.2 (t, 3H).

4-(4-Formylphenyl)acetic acid, ethyl ester was prepared according to the procedure of Biagi,G.; Livi,O.; Verugi,E. *Farmaco-Ed. Sc.* **1988**, *43*, 597-611.

Intermediate 31

(E)-1-[4-(2-Carboxyvinyl)phenyl]piperidine-4-carboxylic acid, ethyl ester

The same method was employed as in the preparation of Intermediate 23 but starting from 1-(4-formylphenyl)piperidine-4-carboxylic acid, ethyl ester to give the title compound as a yellow powder in a 86% yield.

MP: 212 °C.

Analysis for $C_{17}H_{21}NO_4$. $0.15H_2O$:

Calculated: C,66.71; H,7.01; N,4.58;

Found: C,66.77; H,7.01; N,4.79%.

1-(4-Formylphenyl)piperidine-4-carboxylic acid, ethyl ester was prepared according to the procedure of Duckworth, D.M. Hindley,R.; Richard,M. **EP 68669A1**.

Intermediate 32

(E)-4-(2-Carboxyvinyl)-3-chlorobenzoic acid, methyl ester

The same method was employed as in the preparation of Intermediate 23 but starting from 3-chloro-4-formylbenzoic acid, methyl ester to give the title compound as a white powder in a 58% yield.

MP: 221 °C.

3-Chloro-4-formylbenzoic acid, methyl ester (4.0 g, 81%) was prepared by reaction of 4-bromomethyl-3-chlorobenzoic acid, methyl ester (6.0 g, 26 mmol) with silver p-toluenesulfonate (15.0 g, 2.0 equiv.) in 100 mL of DMSO in the presence of Et_3N (100 mL, 7 equiv.) at rt for 1 hour. Quenching the resulting mixture with 100 mL of water, extraction with 2 x 100 mL of EtOAc, washing with 50 mL of water, drying over Na_2SO_4 and flash chromatography with

cyclohexane:EtOAc (95:5) as eluting solvent, gave the title compound (2.3 g, 42%) as an oil.

^{1}H NMR ($CDCl_3$, 250 MHz) δ.10.5 (s, 1H), 8.1 (s, 1H), 7.8-7.7 (d, 1H), 7.4-7.3 (d, 1H), 3.8 (s, 3H).

4-Bromomethyl-3-chlorobenzoic acid, methyl ester (6.0 g, 87%) was obtained as an orange oil by refluxing for 12 hours 4-methyl-3-chlorobenzoic acid, methyl ester (5.7 g, 31 mmol) with NBS (6.4 g, 1.2 equiv.) in the presence of a catalytic amount of AIBN in CCl_4.

^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.0 (s, 1H), 7.9-7.8 (d, 1H), 7.45-7.35 (d, 1H), 4.5 (s, 1H), 3.9 (s, 3H).

4-Methyl-3-chlorobenzoic acid, methyl ester (5.7 g, 53%) was obtained as an orange oil by refluxing overnight 4-methyl-3-chlorobenzoic acid (9.9 g, 58 mmol) in MeOH in the presence of PTSA.

^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.0 (d, 1H), 7.85 (dd, 1H), 7.3 (d, 1H), 4.0 (s, 3H), 2.5 (s, 3H).

Intermediate 33

(E)-5-(2-Carboxyvinyl)-2-chlorobenzoic acid, methyl ester

The same method was employed as in the preparation of Intermediate 32 but starting from 2-chloro-5-formylbenzoic acid, methyl ester to give the title compound as a yellow powder in a 76% yield.

MP: 194 °C.

2-Chloro-5-formylbenzoic acid, methyl ester (0.6 g, 25%) was obtained a gum by reaction of 5-bromomethyl-2-chlorobenzoic acid, methyl ester (3.1 g,11.7 mmol) with silver p-toluenesulfonate (6.4 g, 1.75 equiv.) in DMSO in the presence of Et_3N (1.2 mL, 7 equiv.) at rt for 1 hour.

^{1}H NMR ($CDCl_3$, 250 MHz) δ 10 (s, 1H), 8.4 (d, 1H), 7.9 (dd, 1H), 7.7-7.6 (d, 1H), 4.0 (s, 3H).

5-Bromomethyl-2-chlorobenzoic acid, methyl ester (3.1 g, 11.7 mmol) was obtained as a gum in a 45% yield by refluxing for 12 hours 5-methyl-2-chlorobenzoic acid, methyl ester (4.78 g, 25.9 mmol) with NBS (5.56, 1.2 equiv.) in the presence of a catalytic amount of AIBN in CCl_4.

^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.9 (s, 1H), 7.4 (br s, 2H) 4.5 (s, 2H), 3.9 (s, 3H).

5-Methyl-2-chlorobenzoic acid, methyl ester (4.78 g, 90%) was obtained as a brown oil, by refluxing overnight 3-methyl-4-chlorobenzoic acid (5.0 g, 29 mmol) in MeOH in the presence of a catalytic amount of PTSA.
^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.6 (s, 1H), 7.25-7.2 (d, 1H) , 7.15-7.1 (d, 1H), 3.8 (s, 3H), 2.2 (s, 3H).

Intermediate 34
(E)-(3-Hydroxy-4-nitrophenyl)acrylic acid
The same method was employed as in the preparation of Intermediate 23 but starting from 3-hydroxy-4-nitrobenzaldehyde to give the title compound as a white powder in a 88% yield.
MP: 237 °C.

Intermediate 35
(E)-(3,5-Dimethyl-4-hydroxyphenyl)acrylic acid
The same method was employed as in the preparation of Intermediate 23 but starting from 3,5-dimethyl-4-hydroxybenzaldehyde gave the title compound as a white powder in a 94% yield.
MP: 190 °C.

Intermediate 36
(E)-(3-Nitro-4-hydroxy-5-methpxphenyl)acrylic acid
The same method was employed as in the preparation of Intermediate 23 but starting from 3-nitro-4-hydroxy-5-methoxybenzaldehyde to give the title compound as a white powder in a 75% yield.
MP: 248 °C.

Intermediate 37
(E)-3-(3-Nitro-2-piperidin-1-yl-phenyl)acrylic acid
The same method was employed as in the preparation of Intermediate 23 but starting from 2-chloro-3-nitrobenzaldehyde to give the title compound as a yellow powder in a 100% yield.
^{1}H NMR ($CDCl_3$, 250 MHz) δ 10.3 (br s, 1H), 8.1 (d,1H), 7.65 (dd, 1H), 7.55 (dd, 1H), 7.05 (t, 41H). 6.3 (d, 1H), 2.9 (m, 2H), 1.6 (m, 6H).

2-Chloro-3-nitrobenzaldehyde (150 mg, 20%) was prepared by reaction of 1-bromomethyl-2-chloro-3-nitrobenzene (1.0 g, 3.9 mmol) with silver p-toluenesulfonate (1.94 g, 1.75 equiv.) in DMSO in the presence of Et_3N (4 mL, 7 equiv.) at rt for 1 hour.

^1H NMR ($CDCl_3$, 250 MHz) δ.10.5 (s, 1H), 8.1 (dd, 1H), 8.0 (dd, 1H), 7.5 (t, 1H).

1-Bromomethyl-2-chloro-3-nitrobenzene (13.3 g, 68%) was obtained as a yellow oil by refluxing for 2 hours a mixture of 2-chloro-3-nitrotoluene (10 g, 58 mmol) with NBS (10.3 g, 1 equiv.) in the presence of a catalytic amount of AIBN in CCl_4.

^1H NMR ($CDCl_3$, 250 MHz) δ 7.75 (dd, 1H), 7.65 (dd, 1H), 7.45 (m, 1H), 4.6 (s, 2H).

Intermediate 38

(E)-3-(4-Methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)acrylic acid

The same method was employed as in the preparation of Intermediate 23 but starting from 4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-carboxaldehyde (prepared according to the procedure of Kotha,S.; Bindra,V.; Kuki,A. *Heterocyles* **1994,** *38*, 5-8) to give the title compound as a yellow powder in a 61% yield

MP: 190 °C.

Analysis for $C_{12}H_{13}NO_5$:

Calculated: C,65.74; H,5.98; N,6.39;

Found: C,65.85; H,6.04; N,6.33%.

Intermediate 39

(E)-3-(2-Hydroxy-5-nitrophenyl)acrylic acid

The same method was employed as in the preparation of Intermediate 23 but starting from 2-hydroxy-5-nitro benzaldehyde to give the title compound as a yellow powder in a 11% yield.

MP: 265-267.°C

Intermediate 40

(E)-3-[3-(Trifluoromethanesulfonyloxy)phenyl]acrylic acid

The same method was employed as in the preparation of Intermediate 23 but starting from trifluoromethanesulfonic acid, 3-formylphenyl ester (prepared

according to the procedure of Kingsbury,W.D.; Pendrak.I.; Leber,J.D.; Boehm,J.C.; Mallet,B.; Sarau,H.M.; Foley, J.J.; Schmidt, D.B.; Daines,R.A. *J. Med. Chem.* **1993**, *36*, 3308-3320) to give the title compound as pink crystals in a 36% yield.
MP: 107 °C.

Intermediate 41
(E)-3-[4-(Trifluoromethanesulfonyloxy)phenyl]acrylic acid
The same method was employed as in the preparation of Intermediate 23 but starting from trifluoromethanesulfonic acid, 4-formylphenyl ester (prepared according to the procedure of Creary,X.; Benage,B.; Hilton,K. *J. Org. Chem.* **1983**, *48(17)*, 2887-2891) to give the title compound as white crystals in a 61% yield.
MP: 194 °C.

Intermediate 42
(E)-3-[4-(2-Pyrrolidin-1-ylethoxy)phenyl]acrylic acid
The same method was employed as in the preparation of Intermediate 23 but starting from 4-(2-pyrrolidin-1-ylethoxy)benzaldehyde (prepared according to the procedure of Sakaguchi,J.; Nishino, H.; Ogawa,N.; Iwanaga,Y.; Yasuda,S.; Kato,H.; Ito,Y. *Chem. Pharm. Bull.* **1992**, *40*, 202-211) to give the title compound as a yellow solid in a 60% yield.
MP: 183 °C.

Intermediate 43
(E)-3-(4-Pyrrolidin-1-ylphenyl)acrylic acid
The same method was employed as in the preparation of Intermediate 23 but starting from (4-pyrrolidin-1-ylphenyl)benzaldehyde (prepared according to the procedure of Duckworth, D.M. Hindley,R.; Richard,M. **EP 68669A1**) to give the title compound as a yellow solid in a 65% yield.
MP: 265 °C.

Intermediate 44
(E)-3-(4-Imidazol-1-ylphenyl)acrylic acid

The same method was employed as in the preparation of Intermediate 23 but starting from 4-imidazol-1-ylbenzaldehyde (prepared according to the procedure of Sircar,I.; Duell,B.; Bristol,J.A.; Weishaar,R.E.; Evans,D.B. *J. Med. Chem.* **1987**, *30*, 1023-1029) to give the title compound as pink crystals in a 55% yield.
MP: 326-327 °C.

Intermediate 45

(E)-(S)-3-[4-(1-Methylpyrrolidin-2-ylmethoxy)phenyl]acrylic acid

The same method was employed as in the preparation of Intermediate 23 but starting from (S)-4-(1-methylpyrrolidin-2-ylmethoxy)benzaldehyde to give the title compound as a beige powder in a 66% yield.
MP: 251 °C.
$[\alpha]_D^{21}$ = -9 (c = 0.35, pyridine).
(S)-4-(1-Methylpyrrolidin-2-ylmethoxy)benzaldehyde (0.96 g, 44%) was obtained as an orange oil by refluxing for 12 hours at 80°C, 4-hydroxybenzaldehyde (1.22 g, 10 mmol) with (S)-2-chloromethyl-1-methylpyrrolidine, hydrochloride (2.55 g, 1.5 equiv.) in DMF in the presence of K_2CO_3 (3.82 g, 2.8 equiv).
^{1}H NMR ($CDCl_3$, 250 MHz) δ 9.9 (s, 1H), 7.85 (d, 2H), 7.0 (d, 2H), 4.1 (dd, 1H), 4.0 (dd,1H), 3.1 (d tr, 1H), 2.7 (m, 1H), 2.5 (s, 3H), 2.3 (m, 1H), 2 (m, 1H), 1.8 (m, 3H).
(S)-2-Chloromethyl-1-methylpyrrolidine, hydrochloride was prepared according to the procedure of D'Ambra,T.E.; Bacon,E.R.; Edward,R.; Bell,M.R., Carabateas,P.M.; Eissenstat,M.A.; Kumar,V.; Mallamo,J.P.; Ward,S.J. **EP 444451 A2**.

Intermediate 46

(E)-3-[4-(2-Dimethylamino-1-methylethoxy)phenyl]acrylic acid

The same method was employed as in the preparation of Intermediate 23 but starting from 4-(2-dimethylamino-1-methylethoxy)benzaldehyde to give the title compound as a white powder in a 86% yield.
MP: 235 °C.
Analysis for $C_{14}H_{19}NO_3$.HCl:
Calculated: C,58.84; H,7.05; N,4.9;
Found C,58.49; H,7.08; N,5.05%.

4-(2-Dimethylamino-1-methylethoxy)benzaldehyde (2.1 g, 18%) was obtained as an orange oil by refluxing for 12 hours, 4-hydroxybenzaldehyde (7 g, 57 mmol), K_2CO_3 (8.7 g, 1.1 equiv.) and 2-chloropropyldimethylamine, hydrochloride (13.6 g, 1.5 equiv.) in DMF.

^1H NMR ($CDCl_3$, 250 MHz) δ 9.7 (s, 1H), 7.65 (d, 2H), 6.85 (d, 2H), 4.5 (m, 1H), 2.5 (m, 1H), 2.3 (m, 1H), 2.1 (m, 6H), 1.2 (d, 3H).

Intermediate 47

(E)-3-[4-(4-Methylpiperazin-1-yl)phenyl]acrylic acid

The same method was employed as in the preparation of Intermediate 23 but starting from 4-(4-methylpiperazin-1-yl)benzaldehyde (prepared according to the procedure of Sakai,K.; Suzuki,M.; Nunami,K.; Yoneda,N.; Onoda,Y. Iwasawa,Y. *Chem. Pharm. Bull.* **1980**, *28*, 2384-2393) to give the title compound as a white powder in a 65% yield.

MP: 223-226 °C.

Intermediate 48

(E)-3-[4-(2-Dimethylaminopropoxy)phenyl]acrylic acid

The same method was employed as in the preparation of Intermediate 23 but starting from 4-(2-dimethylaminopropoxy)benzaldehyde (prepared according to the procedure of Mizzoni,R.H. **US 3483209**) to give the title compound as a beige powder in a 100% yield.

MP: 231 °C.

Intermediate 49

(E)-3-[4-(2-Morpholin-4-ylethoxy)phenyl]acrylic acid

The same method was employed as in the preparation of Intermediate 23 but starting from 4-(2-morpholin-4-ylethoxy)benzaldehyde (prepared according to the procedure of Naruto,S.; Mizuta,H.; Sawayama,T.; Yoshida,T.; Uno,H.; Kawashima,K.; Sohji,Y.; Kadokawa,T.; Nishimura,H. *J. Med. Chem.* **1982**, *25*, 1240-1245) to give the title compound as a white powder in a 96% yield.

MP: 228 °C.

Intermediate 50

(E)-3-{4-[2-(Ethylmethylamino)ethoxy]phenyl}acrylic acid

The same method was employed as in the preparation of Intermediate 23 but starting from 4-[2-(ethylmethylamino)ethoxy]benzaldehyde to give the title compound as a beige powder in a 73% yield.
MP: 206 °C.
Analysis for $C_{14}H_{19}NO_3$.HCl:
Calculated: C,58.84; H,7.05; N,4.9;
Found C,59.08; H,7.07; N,5.02%.
4-[2-(Ethylmethylamino)ethoxy]benzaldehyde(5.0 g, 59%) was obtained as a brown oil by refluxing for 12 hours 4-hydroxybenzaldehyde (5 g, 41 mmol), K_2CO_3 (6.2 g, 1.1 equiv.) and (2-chloroethyl)ethylmethylamine, hydrochloride (9.7 g , 1.5 equiv.) in DMF.
^{1}H NMR ($CDCl_3$, 250 MHz) δ 9.7 (s, 1H), 7.7 (d, 2H), 6.9 (d, 2H), 4.1 (t, 2H), 2.6 (t, 2H), 2. (s, 6H).

Intermediate 51
(E)-3-[4-(3-Dimethylaminopropenyl)phenyl]acrylic acid
This product was prepared by refluxing for four hours, (E)-3-[4-(3-dimethylaminopropenyl)phenyl]acrylic acid, methyl ester with NaOH (0.16 g, 2 equiv.) in 10 mL of MeOH. After evaporation of the solvent *in vacuo*, treatment with 5 mL of HCl (1N) gave the title compound (0.4 g, 85%) as a gummy orange solid.
^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.6 (d, 2H), 7.4 (d, 1H), 7.2 (d, 2H), 6.6 (d, 1H), 6.4 (d, 1H), 5.8 (m, 1H), 3.7 (d, 2H), 2.6 (s, 6H).
(E)-3-[4-(3-Dimethylaminopropenyl)phenyl]acrylic acid, methyl ester was prepared by the following way: (2-dimethylaminoethyl)triphenylphosphonium bromide (7.2 g, 17.4 mmol) in 30 mL of DMF was treated with KHMDS (27 mL, 1.01 equiv., 0.5 M in toluene) at -78 °C for one hour. At -40 °C, 3-(4-formylphenyl)acrylic acid, methyl ester (2.54 g, 13.3 mmol, prepared according to the procedure of Syper,L.; Miochowski,J. *Synthesis*, **1984**, 9, 747-752) was added dropwise. The resulting mixture was stirred for 12 hours at rt and quenched with water. Extraction with EtOAc, drying over $MgSO_4$ and evaporation *in vacuo* gave a residue that was purified via flash chromatography with DCM:MeOH (90:10) as eluting solvent. The title compound (1.1 g, 34%) was obtained as an orange oil.

^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.6 (d, 1H), 7.4 (d, 2H), 7.2 (d, 2H), 6.5 (d, 1H), 6.4 (d, 1H), 5.8 (m, 1H), 3.2 (dd, 2H), 2.1 (s, 6H).

Intermediate 52

(E)-3-[4-(2-(Tertbutyldimethylsilanyloxy)-3-dimethylaminopropenyl)phenyl]acrylic acid

This product was prepared by refluxing for four hours (E)-3-[4-(2-(tertbutyldimethylsilanyloxy)-3-dimethylaminopropanyl]phenyl]acrylic acid, methyl ester (0.8 g, 2.03 mmol) and NaOH (1N) (4 mL, 2 equiv.) in 10 mL of MeOH. Evaporation of the solvent *in vacuo* and treatment with 5 mL of HCl (1N) gave the title compound (0.4 g, 60%) as a beige solid solid.

MP: 207 °C.

(E)-3-[4-(2-(Tertbutyldimethylsilanyloxy)-3-dimethylaminopropoxy)phenyl]acrylic acid, methyl ester (0.8 g, 40%) was obtained as a yellow oil by reaction for 4 hours of (E)-3-[4-(3-dimethylamino-2-hydroxypropoxy)phenyl]acrylic acid, methyl ester (1.35 g, 5.13 mmol) with TBDMSCl (0.93 g, 6.2 mmol) in 50 mL of DMF in the presence of imidazole (0.84 g, 2.4 equiv.). After evaporation *in vacuo*, the residue was taken up in DCM, washed with water, dried over $MgSO_4$, evaporated *in vacuo* and purified via flash chromatography using DCM:MeOH as eluting solvent.

^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.5 (d, 1H), 7.3 (d, 2H), 6.8 (d, 2H), 6.2 (d, 1H), 4.0 (m, 2H), 3.8 (m, 1H), 3.7 (s, 3H), 2.4-2.2 (m, 2H), 2.1 (s, 6H), 0.7 (s, 9H), 0.0 (d, 6H).

(E)-3-[4-(3-Dimethylamino-2-hydroxypropoxy)phenyl]acrylic acid, methyl ester (1.5 g, 60%) was obtained as an oil by reaction of 4-(3-dimethylamino-2-hydroxypropoxy)benzaldehyde (2.0 g, 8.96 mmol) in 80 mL of toluene with triphenylphosphoranylidene methyl acetate (3.6 g, 1.2 equiv.) at 100 °C for one day. After concentration *in vacuo*, the residue was taken up in DCM, washed with water; dried over Na_2SO_4, evaporated *in vacuo* and purified via flash chromatography using DCM:MeOH (95:5) as eluting solvent.

^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.6 (d, 1H), 7.5 (d, 2H), 7.3 (d, 2H), 6.3 (d, 1H), 4.2 (m, 1H), 4.1 (m, 1H), 3.8 (m, 3H), 3.3 (s, 1H), 2.8 (dd, 1H), 2.6 (dd, 1H), 2.4 (s, 6H).

4-(3-Dimethylamino-2-hydroxypropoxy)benzaldehyde (8.2 g, 61%) was obtained as an a yellow oil, by reaction of 4-oxiranylmethoxybenzaldehyde (6 g, 33.6

mmol, prepared according to the procedure of Baldwin,J.J.; Hirchmann,R.; Lumma,W.C.; Ponticello,G.S.; Sweet,C.S.; Scriabine,A. *J. Med. Chem.* **1977**, *20*, 1024-1029) in 100 mL of MeOH with dimethylamine (34 mL, 2 equiv.). The resulting mixture was stirred at reflux for 2 days. Evaporation *in vacuo* gave a residue that was taken up in DCM, washed with brine and dried over $MgSO_4$ and evaporated *in vacuo*.

^1H NMR ($CDCl_3$, 250 MHz) δ 9.7 (s, 1H), 7.6 (d, 2H), 7.0 (d, 2H), 4. (m, 3H), 3.6 (s, 1H), 2.5 (dd, 1H), 2.3 (dd, 1H), 2.25 (s, 6H).

Intermediate 53

(E)-3-[4-(2-(Dimethylaminoethylamino)phenyl]acrylic acid

The same method was employed as in the preparation of Intermediate 23 but starting from 4-[2-(dimethylaminoethyl)amino]benzaldehyde (prepared according to the procedure of Klaus,M.; Mohr,P.; Weiss,E. **EP 331983 A2**) to give the title compound as an oil in a 100% yield.

^1H NMR ($CDCl_3$, 250 MHz) δ 7.5 (d, 1H), 7.2 (d, 2H), 6.5 (d, 2H), 6.1 (d, 1H), 4.6 (s, 1H), 3.0 (m, 2H), 2.5 (t, 2H), 2.2 (s, 6H).

Intermediate 54

(E)-3-{4-[2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)ethoxy]phenyl}acrylic acid

The same method was employed as in the preparation of Intermediate 23 but starting from 4-[2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)ethoxy]benzaldehyde (prepared from the procedure of Hindley,R.M.; Haigh,D.; Cottam,G.P. **WO 9207839 A1**) to give the title compound as an oil in a 99% yield.

^1H NMR ($CDCl_3$, 250 MHz) δ 12.3 (s, 1H), 7.9 (m, 4H), 7.6 (d, 2H), 7.5 (d, 1H), 7.0 (d, 2H), 6.4 (d, 1H), 4.4 (t, 2H), 4.0 (t, 2H).

Intermediate 55

(E)-3-[4-(2-(Piperidin-1-ylethoxy)phenyl]acrylic acid

The same method was employed as in the preparation of Intermediate 23 but starting from 4-(2-piperidin-1-yl-ethoxy)benzaldehyde (which was prepared according to the procedure of Naruto,S.; Mizuta,H.; Sawayama,T.; Yoshida,T.; Uno,H.; Kawashima,K.; Sohji,Y.; Kadokawa,T.; Nishimura,H. *J. Med. Chem.* **1982**, *25*, 1240-1245), to give the title compound as a white powder in a 60% yield.

MP: 231 °C.

Intermediate 56

(E)-3-[4-(2-(Tertbutoxycarbonylmethylamino)ethoxy)phenyl]acrylic acid

(E)-3-[4-(2-Methylaminoethoxy)phenyl]acrylic acid (0.8 g, 3.6 mmol) in dioxane (100 mL) was treated with NaOH (2N) (22 mL, 12 equiv.). After one hour of stirring at 70 °C, ditertbutyldicarbonate (1.6 g, 2 equiv.) was added slowly. The reaction was judged to be complete after 3 hours of stirring at 70 °C. After filtration of the white precipitate, the filtrate was acidified to pH=1 with HCl (1N). A new white solid precipitated out . Filtration and drying *in vacuo* gave the title compound (0.6 g, 50%) as white crystals.

^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.8 (d, 1H), 7.65 (d, 2H), 7.0 (d, 2H), 6.4 (d, 1H), 4.25 (t, 2H), 3.7 (t, 2H), 3.1 (s, 3H), 1.5 (s, 9H).

(E)-3-[4-(2-Methylaminoethoxy)phenyl]acrylic acid (1.1 g, 41%) was obtained as a white solid by hydrolysis of (E)-3-[4-(2-methylaminoethoxy)phenyl]acrylic acid, methyl ester (3.0 g, 12.0 mmol) with NaOH (6.0 g, 12 equiv.) in MeOH/THF at 40 °C.

MP: 245 °C.

(E)-3-[4-(2-Methylaminoethoxy)phenyl]acrylic acid, methyl ester (3.0 g, 70%) was obtained as a yellow oil by reaction of trimethylphosphonoacetate (4.2 g, 23.0 mmol) and n-butyl lithium (9.0 mL, 18.0 mmol, 2.0 M in cyclohexane) at -78 °C, followed by the addition of 4-(2-methylaminoethoxy)benzaldehyde (3.2 g, 18.0 mmol) at - 40 °C. The resulting mixture was stirred at rt for 16 hours, quenched with water, extracted with EtOAc, dried over $MgSO_4$ and concentrated *in vacuo*.

^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.65 (d, 1H), 7.45 (d, 2H). 6.9 (d, 2H), 6.25 (d, 1H), 4.10 (t, 2H), 3.75 (s, 3H), 2.95 (t, 2H), 2.5 (s, 3H).

4-(2-Methylaminoethoxy)benzaldehyde (3.2 g, 51%) was obtained as a yellow oil by reaction of 4-(2-methylaminoethoxy)benzonitrile (7.0 g, 40.0 mmol) with diisobutylaluminum hydride (40 mL, 1.5 equiv., 1.5 M in toluene) in toluene (400 mL) at - 78°C. After 4 hours of stirring at - 78 °C the resulting mixture was treated with a mixture of water/MeOH (4 mL). At rt an additional 20 mL of water was added. The resulting suspension was filtered on a bed of celite. The celite was washed with Et_2O (3 x 200 mL). The filtrate was concentrated *in vacuo* and

purified via flash chromatography of silica gel using MeOH:DCM (1:9) as eluting solvent.

^{1}H NMR ($CDCl_3$, 250 MHz) δ 9.8 (s, 1H), 7.8 (d, 2H), 7.0 (d, 2H), 4.1 (t, 2H), 2.9 (t, 2H), 2.5 (s, 3H).

4-(2-Methylaminoethoxy)benzonitrile (0.6 g, 15%) was obtained as a yellow oil by reaction of 4-(2-chloroethoxy)benzonitrile (2.0 g, 11.0 mmol, prepared according to the procedure of Mizuno,K.; Kimura,Y.; Otsuji,Y. *Synthesis*, **1979**, *9*, 688) with methylamine (4.3 mL, 5 equiv., 40% in water) at 70 °C for 16 hours. The resulting mixture was extracted with DCM, dried over $MgSO_4$, concentrated *in vacuo* and purified via flash chromatography of silica gel using MeOH:DCM (2:8) as eluting solvent, to give the title compound.

^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.6 (d, 2H), 7.0 (d, 2H), 4.1 (t, 2H), 3.0 (t, 2H), 2.5 (s, 3H).

Example 1

(E)-1-(1-Phenyl-1,3,4,9-tetrahydro-β-carboiin-2-yl)-3-phenylpropene-1-one

To a solution of Intermediate 1 (0.2 g, 0.81 mmol) and $NaHCO_3$ (0.08 g, 1.2 equiv.) in 10 mL of DCM was added (E)-cinnamoyl chloride (0.2 g, 1.5 equiv.). After 4 hours of stirring at rt the reaction was judged to be completed by tlc monitoring (SiO_2, DCM:MeOH 98:2) and was quenched with 5 mL of a saturated aqueous solution of $NaHCO_3$. The reaction mixture was extracted with DCM, washed with brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography on a 2 x 20 cm^2 column using DCM:MeOH (98:2) as eluting solvent and removal of the solvent *in vacuo* gave after recrystallization from 2-propanol, the title compound (0.1 g, 33%) as white crystals.

MP: 130-132 °C.

Analysis for $C_{26}H_{22}N_2O$:

Calculated: C,82.51; H,5.86; N,7.40;

Found: C,82.24; H,5.93; N,7.36%.

Example 2

(E)-1-(1-Phenyl-1,3,4,9-tetrahydro-β-carbolin-2-yl)-3-(4-nitrophenyl)propene-1-one

The same method as employed as in the preparation of Example 1 but starting from (E)-4-nitrocinnamoyl chloride gave after recrystallization from iPr_2O:2-propanol (3:1), the title compound as a yellow powder in a 47% yield.
MP: 230-231 °C.
Analysis for $C_{26}H_{21}N_3O_3$:
Calculated: C,73.74; H,5.00; N,9.92;
Found: C,73.89; H,5.12; N,9.86%.

Example 3
(E)-1-(1-Phenyl-1,3,4,9-tetrahydro-β-carbolin-2-yl)-3-(4-trifluoromethylphenyl)-propene-1-one
The same method as employed in the preparation of Example 1 but starting from (E)-4-trifluoromethylcinnamoyl chloride gave after recrystallization from pentane, the title compound as a white powder in a 41% yield.
MP: 211 °C.
Analysis for $C_{27}H_{21}F_3N_2O$. $0.4H_2O$:
Calculated: C,71.48; H,4.84; N,6.17;
Found: C,71.84; H,4.81; N,6.19%.

Example 4
(E)-1-(1-Phenyl-1,3,4,9-tetrahydro-β-carbolin-2-yl)-3-(4-methoxy-phenyl)propene-1-one
The same method as employed in the preparation of Example 1 but starting from (E)-4-methoxycinnamoyl chloride gave after recrystallization from 2-propanol, the title compound as white crystals in a 61% yield.
MP: 160-163 °C.
Analysis for $C_{27}H_{24}N_2O_2$. 0.5(2-propanol):
Calculated: C,78.06; H,6.44; N,6.39;
Found: C,78.04; H,6.02; N,5.97%.

Example 5
(E)-1-[1-(4-Methoxyphenyl)-1.3.4.9-tetrahydro-β-carbolin-2-yl]-3-(4-trifluoromethylphenyl)propene-1-one
The same method as employed in the preparation of Example 1 but starting from Intermediate 2 and (E)-4-trifluoromethylcinnamoyl chloride gave after

recrystallization from pentane, the title compound as a white powder in a 61% yield.
MP: 130-135 °C.
Analysis for $C_{28}H_{23}N_2O_2F_3$. $0.3H_2O$:
Calculated: C,69.79; H,4.94; N,5.81;
Found: C,69.9; H,4.84; N,5.73%.

Example 6
(E)-N-[4-[3-Oxo-3-(1-phenyl-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]phenyl]-acetamide
To a solution of Intermediate 1 (0.2 g, 0.81 mmol) in 40 mL of DCM were added Et_3N (0.13 mL, 1.1 equiv.), DCC (0.18 g, 1.1 equiv.), HOBT (0.12 g, 1.1 equiv.) and (E)-3-(4-acetylaminophenyl)acrylic acid (0.18 g, 1.1 equiv.). After 24 hours of stirring at rt the reaction was judged to be completed by tlc monitoring (SiO_2, DCM:MeOH 95:5) and was quenched with 150 mL of water. A white solid precipitated out and was filtered off. The filtrate was extracted with DCM, washed with brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography on a 2.5 x 25 cm^2 column of silica gel using DCM:MeOH (98:2) as eluting solvent and removal of the solvent *in vacuo* gave the title compound (0.18 g, 51%) as yellow crystals after recrystallization from 2-propanol:pentane.
MP: 177-180 °C.
Analysis for $C_{28}H_{25}N_3O_2.0.7H_2O$:
Calculated: C,75.05; H,5.94; N,9.38;
Found: C,75.01; H,5.81; N,9.22%.

Example 7
(E)-1-[1-(4-Methoxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)-3-phenylpropene-1-one
The same method as employed in the preparation of Example 1 but starting from Intermediate 2 gave the title compound as white crystals in a 56% yield.
MP: 127 °C.
Analysis for $C_{27}H_{24}N_2O_2$. $0.5H_2O$:
Calculated: C,77.67; H,6.04; N,6.71;
Found: C,77.91; H,6.0; N,6.73%.

Example 8

(E)-1-[1-(3.4-Methylenedioxyphenyl)-1.3.4.9-tetrahydro-β-carbolin-2-yl]-3-phenyl-propene-1-one

The same method as employed in the preparation of Example 1 but starting from Intermediate 7 gave after recrystallization from 2-propanol:iPr_2O (2:8), the title compound as white crystals in a 38% yield.

MP: 236-238 °C.

Analysis for $C_{27}H_{24}N_2O_2$. $0.5H_2O$:

Calculated: C,76.76; H,5.25; N,6.63;

Found: C,76.87; H,5.35; N,6.54%.

Example 9

(E)-1-(1-Phenyl-1.3.4.9-tetrahydro-β-carbolin-2-yl)-3-(4-formylphenyl)propene-1-one

The same method as employed in the preparation of Example 6 but starting from (E)-4-formylcinnamic acid gave after recrystallization from acetone:MeOH (10:3), the title compound as yellow crystals in a 60% yield.

MP: 146 °C.

Analysis for $C_{27}H_{22}N_2O_2$. $0.4H_2O$:

Calculated: C,78.39; H,5.55; N,6.77;

Found: C,78.33; H,5.54; N,6.67%.

Example 10

(E)-N-[4-[3-Oxo-3-(1-(4-nitrophenyl)-1.3.4.9-tetrahydro-β-carbolin-2-yl)propenyl]-phenyl]acetamide

The same method as employed in the preparation of Example 6 but starting from Intermediate 3 gave after recrystallization from 2-propanol, the title compound as white crystals in a 51% yield.

MP: 185 °C.

Analysis for $C_{28}H_{24}N_4O_4$. $0.6H_2O$:

Calculated: C,68.45; H,5.17; N,11.4;

Found: C,68.37; H,5.06; N,11.26%.

Example 11

(E)-1-[1-(4-Nitrophenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-phenylpropene-1-one

The same method as employed in the preparation of Example 1 but starting from Intermediate 3 gave after recrystallization from 2-propanol, the title compound as a yellow powder in a 15% yield.

MP: 205-206 °C.

Analysis for $C_{26}H_{21}N_3O_3$. $0.2H_2O$:

Calculated: C,73.12; H,5.05; N,9.84;

Found: C,72.95; H,5.15; N,9.81%.

Example 12

(E)-1-[1-(4-Trifluoromethoxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-phenyl-propene-1-one

The same method as employed in the preparation of Example 1 but starting from Intermediate 4 gave after recrystallization from pentane, the title compound as white crystals in a 44% yield.

MP: 119 °C.

Analysis for $C_{27}H_{21}N_2O_2F_3$:

Calculated: C,70.12; H,4.58; N,6.06;

Found: C,70.02; H,4.58; N,6.02%.

Example 13

(E)-1-[1-(4-Methylphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-phenylpropene-1-one

The same method as employed in the preparation of Example 1 but starting from Intermediate 6 gave after recrystallization from pentane, the title compound as white crystals in a 50% yield.

MP: 125-127 °C.

Analysis for $C_{27}H_{24}N_2O$. $0.6H_2O$:

Calculated: C,80.41; H,6.3; N,6.95;

Found: C,80.49 ; H,6.2 ; N,7.25%.

Example 14

(E)-N-[4-[3-Oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)-propenyl]phenyl]acetamide

The same method as employed in the preparation of Example 6 but starting from Intermediate 7 and (E)-3-(4-acetylaminophenyl)acrylic acid gave after recrystallization from 2-propanol:pentane, the title compound as white crystals in a 85% yield.

MP: 185 °C.

Analysis for $C_{29}H_{25}N_3O_4$. $0.4H_2O$:

Calculated: C,71.56; H,5.34; N,8.63;

Found: C,71.59; H,5.32; 8.66%.

Example 15

(E)-4-[3-Oxo-3-(1-phenyl-1,3,4,9-tetrahydro-β-carbolin-2-yl)-propenyl]benzoic acid, methyl ester

To a solution of Example 9 (0.2 g, 0.49 mmol) in 20 mL of MeOH was added activated MnO_2 (0.59 g, 14 equiv.), sodium cyanide (0.05 g, 2 equiv.) and acetic acid (0.05 g, 1.7 equiv.). The resulting mixture was stirred for 5 hours. Tlc monitoring showed a new compound (SiO_2,DCM:MeOH (95:5), Rf= 0.82). The mixture was filtered through a short column of celite using 150 mL of a mixture of MeOH:EtOAc:$CHCl_3$ (1:25:25). After evaporation *in vacuo* the residue was purified via flash chromatography on a 2 x 20 cm^2 column using DCM as eluting solvent. Evaporation and recrystallization from EtOH gave the title compound (0.15 g, 70%) as yellow crystals.

MP: 222 °C.

Analysis for $C_{28}H_{24}N_2O_3$. $0.03H_2O$:

Calculated: C,76.1; H,5.61; N,6.34;

Found: C,76.05; H,5.68; N,6.15%.

Example 16

(E)-1-[1-(2-Chlorophenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-phenylpropene-1-one

The same method as employed in the preparation of Example 1 but starting from Intermediate 17 gave after recrystallization from EtOH, the title compound as white crystals in a 27% yield.

MP: 220-221 °C.

Analysis for $C_{26}H_{21}N_2OCl$:

Calculated: C,75.63; H,5.13; N,6.78;

Found: C,75.4; H,5.21; N,6.79%.

Example 17

(E)-1-(1-Phenyl-1,3,4,9-tetrahydro-β-carbolin-2-yl)-3-(3,4-methylenedioxyphenyl)-propene-1-one

The same method as employed in the preparation of Example 1 but starting from (E)-(3,4-methylenedioxy)cinnamoyl chloride gave after recrystallization from EtOH, the title compound as a white powder in a 65% yield.

MP: 221 °C.

Analysis for $C_{27}H_{22}N_2O_3$. $0.3H_2O$:

Calculated: C,75.79; H,5.32; N,6.55;

Found: C,75.76; H,5.37; N,6.53%.

Example 18

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-bromophenyl)propene-1-one

The same method as employed in the preparation of Example 1 but starting from Intermediate 7 and (E)-4-bromocinnamoyl chloride gave after recrystallization from EtOH, the title compound as a white powder in a 10% yield.

MP: 188-190 °C.

Analysis for $C_{27}H_{21}N_2O_3Br$. $0.3H_2O$:

Calculated: C,63.99; H,4.3; N,5.53;

Found: C,63.53; H,4.23; N,5.38%.

Example 19

(E)-1-[1-(4-Chlorophenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-phenylpropene-1-one

The same method as employed in the preparation of Example 1 but starting from Intermediate 5 gave after recrystallization from EtOH, the title compound as white crystals in a 72% yield.

MP: 213-214 °C.

Analysis for $C_{26}H_{21}N_2OCl$:

Calculated: C,75.63; H,5.13; N,6.78;

Found: C,75.55; H,5.16; N,6.63%

Example 20

(E)-1-[1-(3.4-Methylenedioxyphenyl)-1,3.4.9-tetrahydro-ß-carbolin-2-yl]-3-(4-ethoxyphenyl)propene-1-one

To a solution of Intermediate 7 (0.2 g,0.68 mmol) in 40 mL of DCM were added Et_3N (0.1 mL, 1.1 equiv.), EDCI (0.14 g, 1.1 equiv.), HOBT (0.12 g, 1.1 equiv.) and (E)-4-ethoxycinnamic acid (0.14 g, 1.1 equiv.). After 48 hours of stirring at rt the reaction was judged to be completed by tlc monitoring (SiO_2, DCM:MeOH (95:5)) and was quenched with 50 mL of water. The reaction mixture was extracted with DCM, washed with brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography on a 2.5 x 25 cm^2 column of silica gel using DCM:MeOH (98:2) as eluting solvent and removal of the solvent *in vacuo* gave the title compound (0.21 g, 67%) as white crystals after recrystallization from EtOH.

MP: 199-200 °C.

Analysis for $C_{29}H_{26}N_2O_4$. $0.3H_2O$:

Calculated: C,73.8; H,5.68; N,5.94;

Found: C,73.72; H,5.68; N,5.97%.

Example 21

(E)-4-[3-Oxo-3-(1-(3.4-methylenedioxyphenyl)-1.3.4.9-tetrahydro-ß-carbolin-2-yl)propenyl]acetic acid, phenyl ester

The same method as employed in the preparation of Example 20 but starting from (E)-4-acetoxycinnamic acid gave after recrystallization from MeOH, the title compound as white crystals in a 54% yield.

MP: 216 °C.

Analysis for $C_{29}H_{24}N_2O_5$:

Calculated: C,72.49; H,5.03; N,5.83;

Found: C,72.3; H,5.11; N,5.84%.

Example 22

(E)-1-[1-(3.4-Methylenedioxyphenyl)-1.3.4.9-tetrahydro-ß-carbolin-2-yl]-3-(4-hydroxyphenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from (E)-4-hydroxycinnamic acid gave after recrystallization from EtOH:pentane the title compound as white crystals in a 57% yield.

MP: 175 °C.
Analysis for $C_{27}H_{22}N_2O_4 .0.3H_2O$:
Calculated: C,73.06; H,5.13; N,6.31;
Found: C,73.14; H,5.36; N,6.44%.

Example 23
(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-formylphenyl)propene-1-one
The same method as employed in the preparation of Example 20 but starting from (E)-4-formylcinnamic acid gave after recrystallization from MeOH the title compound as white crystals in a 100% yield.
MP: 208 °C.
Analysis for $C_{28}H_{22}N_2O_4$. $0.3H_2O$:
Calculated: C,73.77; H,5.00; N,6.15;
Found: C,73.77; H,4.96; N,6.05%.

Example 24
(E)-1-[4-[3-Oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)-propenyl]phenyl]-3-phenylurea
The same method as employed in the preparation of Example 20 but starting from (E)-3-[4-(3-(phenylureido)phenyl]acrylic acid (which was prepared in situ by reaction of phenylisocyanate (1 equiv.), (E)-4-aminocinnamic acid (1 equiv.) and Et_3N (1 equiv.)), gave after recrystallization from EtOH the title compound as white crystals in a 61% yield.
MP: 192 °C.
Analysis for $C_{34}H_{28}N_4O_4$. 0.22(EtOH:H_2O):
Calculated: C,72.48; H,5.26; N,9.82;
Found: C,72.87; H,5.17; N,9.42%.

Example 25
(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-aminophenyl)propene-1-one
The same method as employed in the preparation of Example 20 but starting from (E)-4-aminocinnamic acid gave after recrystallization from EtOH:DCM:2-propanol (10:2:2) the title compound as white crystals in a 63% yield.

MP: 262-265 °C.
Analysis for $C_{27}H_{23}N_3O_3$. $0.3H_2O$:
Calculated: C,73.22; H,5.37; N,9.49;
Found: C,72.9; H,5.47; 9.32%.

Example 26
(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-nitrophenyl)-propene-1-one

The same method as employed in the preparation of Example 20 but starting from (E)-4-nitrocinnamic acid gave after recrystallization from EtOH, the title compound as yellow crystals in a 69% yield.
MP: 158° C.
Analysis for $C_{27}H_{21}N_3O_5$:
Calculated: C,69.37; H,4.53; N,8.99;
Found: C,69.57; H,4.61; N,8.92%.

Example 27
(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-[(4-bis(methylsulfonyl)aminophenyl]propene-1-one

This product was prepared by refluxing for two hours a solution of Example 25 (0.2 g, 0.6 mmol), mesyl chloride (0.1 mL, 5 equiv.), Et_3N (0.4 mL, 5 equiv.) in 20 mL of THF. The disappearance of the starting material and the formation of a new compound were confirmed by tlc (SiO_2, DCM:MeOH (95:5), Rf= 0.84). After evaporation of THF the residue was dissolved in DCM (15 mL) and washed with H_2O (10 mL). The organic solution was dried over $MgSO_4$ and concentrated *in vacuo* to give a residue which was purified via flash chromatography on a 2.5 x 25 cm^2 column using DCM:MeOH (98:2) as eluting solvent. Recrystallization from EtOH gave the title compound (0.09 g, 25%) as a white powder.
MP: 276 °C.
Analysis for $C_{29}H_{27}N_3O_7S_2$. $0.3H_2O$:
Calculated: C,58.14; H,4.64; N,7.01;
Found: C,57.76; H,4.69; N,6.81%.

Example 28

(E)-4-[3-Oxo-3-[1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-propenyl]benzoic acid, methyl ester

The same method as employed in the preparation of Example 20 but starting from (E)-4-(2-carboxyvinyl)benzoic acid, methyl ester acid (prepared according to the procedure of Taylor,E.C.; Young, W.B.; Chaudhari,R.; Patel,H. *Heterocycles* **1993**, *36*, 1897-1908), gave after recrystallization from MeOH:H_2O (99:1), the title compound as yellow crystals in a 84% yield.

MP: 211 °C.

Analysis for $C_{29}H_{24}N_2O_5$. $0.3H_2O$:

Calculated: C,71.68; H,5.1; N,5.76;

Found: C,71.76; H,5.02; N,5.68%.

Example 29

(E)-N-[4-[3-Oxo-3-[1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]propenyl]phenyl]methanesulfonamide

The same method as employed in the preparation of Example 27 but using 1 equiv. of mesyl chloride gave after recrystallization from EtOH the title compound as an off-white powder in a 10% yield.

MP: 203 °C.

Analysis for $C_{28}H_{25}N_3O_5S$. $0.2H_2O$:

Calculated: C,64.78; H,4.93; N,8.09;

Found: C,64.66; H,5.15; N,7.73%.

Example 30

(E)-4-[3-Oxo-3-[1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]propenyl]benzamide

Into a solution of Example 28 (0.2 g, 0.4 mmol) in 50 mL of MeOH was bubbled ammonia and the resulting mixture was stirred at 35°C for two days. The mixture was concentrated *in vacuo* to give a residue which was washed with 2x30 mL of water. Extraction, drying over $MgSO_4$ and concentration *in vacuo* gave a residue that was purified via radial chromatography using DCM:MeOH (90:10) as eluting solvent and via preparative chromatography (20x20- cm plate, 0.5 mm , SiO_2) using the same eluant. The title compound (0.025 g, 13%) was isolated as white crystals after recrystallization from MeOH:H_2O.

MP: 183 °C.

Analysis for $C_{28}H_{23}N_3O_4$:
Calculated: C,70.07; H,5.17; N,8.76;
Found: C,69.97; H,5.16; N,8.84%.

Example 31
(E)-4-[3-Oxo-3-[1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-propenyl]benzoic acid
This product was prepared by refluxing for four hours a stirred solution of Example 28 (0.5 g, 1.04 mmol) and NaOH (1N) (5.2 mL, 5 equiv.) in 50 mL of MeOH. After evaporation of the solvent *in vacuo*, the residue was treated with 10 mL of HCl (1N). A solid precipitated out and was filtered off. Recrystallization from MeOH gave the title compound (0.35 g, 72%) as white crystals.
MP: 254-256 °C.
Analysis for $C_{28}H_{22}N_2O_5 \cdot 0.2H_2O$:
Calculated: C,72.09; H,4.75; N,6.01;
Found: C,71.60; H,4.84; N,5.88%.

Example 32
(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-cyanophenyl)propene-1-one
The same method as employed in the preparation of Example 20 but starting from (E)-4-cyanocinnamic acid gave after recrystallization from EtOH the title compound as white crystals in a 69% yield.
MP: 167 °C.
Analysis for $C_{28}H_{21}N_3O_3 \cdot 0.1H_2O$:
Calculated: C,74.85; H,4.76; N,9.35;
Found: : C,74.72; H,4.81; N,9.27%.

Example 33
(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-trifluoromethylphenyl)propene-1-one
The same method as employed in the preparation of Example 20 but starting from (E)-4-trifluoromethylcinnamic acid gave after recrystallization from EtOH the title compound as white crystals in a 73% yield.
MP: 233 °C.

Analysis for $C_{28}H_{21}F_3N_2O_3$. $0.2H_2O$:
Calculated: C,68.07; H,4.37; N,5.67;
Found: C,68.04; H,4.32; N,5.65%.

Example 34
(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3,4-methylenedioxyphenyl)propene-1-one
The same method as employed in the preparation of Example 20 but starting from (E)-3,4-methylenedioxycinnamic acid gave after recrystallization from EtOH the title compound as yellow crystals in a 73% yield.
MP: 233 °C.
Analysis for $C_{28}H_{22}N_2O_5$:
Calculated: C,72.09; H,4.75; N,6.01;
Found: C,71.79; H,4.76; N,5.93%.

Example 35
(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-chlorophenyl)propene-1-one
The same method as employed in the preparation of Example 20 but starting from (E)-4-chlorocinnamic acid gave after recrystallization from EtOH the title compound as white crystals in a 55% yield.
MP: 203 °C.
Analysis for $C_{27}H_{21}N_2O_3Cl$:
Calculated: C,70.97; H,4.63; N,6.13;
Found: C,71.04; H,4.76; N,6.04%.

Example 36
(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-trifluoromethoxyphenyl)propene-1-one
The same method as employed in the preparation of Example 20 but starting from (E)-4-trifluoromethoxycinnamic acid (prepared according to the procedure of Yagupol'skii, L.M., Troitskaya, V.I. *Zhurnal Obshchei Khimii* **1960**, *30*, 3102-3104) gave after recrystallization from EtOH the title compound as yellow crystals in a 35% yield.
MP: 203-205°C.

Analysis for $C_{28}H_{21}F_3N_2O_4$:
Calculated: C,66.4; H,4.18; N,5.53;
Found: C,66.23; H,4.26; N,5.54.

Example 37
(E)-1-[1-(3.4-Methylenedioxyphenyl)-1.3.4.9-tetrahydro-β-carbolin-2-yl]-3-(4-methylphenyl)propene-1-one
The same method as employed in the preparation of Example 20 but starting from (E)-4-methylcinnamic acid gave after recrystallization from EtOH:DCM (99:1) the title compound as white crystals in a 67% yield.
MP: 240 °C.
Analysis for $C_{28}H_{24}N_2O_3$. $0.7H_2O$:
Calculated: C,74.88; H,5.7; N,6.24;
Found: C,74.83; H,5.45; N,6.35.%.

Example 38
(E)-[4-[3-Oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]phenyl]urea
The same method as employed in the preparation of Example 20 but starting from Intermediate 22 gave after recrystallization from EtOH the title compound as white crystals in a 49% yield.
MP: 208 °C.
Analysis for $C_{28}H_{24}N_4O_4$. $0.5H_2O$:
Calculated: C,68.7; H,5.15; N,11.44;
Found: C,68.51; H,5.14; N,11.35%.

Example 39
(E)-1-[1-(3.4-Methylenedioxyphenyl)-1.3.4.9-tetrahydro-β-carbolin-2-yl]-3-(4-hydroxymethylphenyl)propene-1-one
This product was prepared by stirring a solution of Example 23 (0.3 g, 0.66 mmol) in 40 mL of MeOH with $NaBH_4$ (0.1 g, 4 equiv.) at rt for two hours. Evaporation of the solvent gave a residue which was dissolved in DCM (100 mL) and washed twice with water (50 mL). Extraction with DCM, drying over $MgSO_4$ and evaporation *in vacuo* gave the title compound (0.2 g, 67%) as white crystals after recrystallization from EtOH.

MP: 206 °C.
Analysis for $C_{28}H_{24}N_2O_4$. 0.3EtOH:
Calculated: C,73.66; H,5.58; N,6.01;
Found: C,73.69; H,5.5; N,6.06%.

Example 40
(E)-N-Benzyl-4-[3-oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]benzamide

This product was prepared by stirring a solution of Example 31 (0.2 g, 0.43 mmol) in 50 mL of THF with benzylamine (0.5 mL, 9 equiv.), Et_3N (1 mL) and diphenylphosphoryl azide (0.5 mL). After two days the reaction mixture was concentrated *in vacuo*. The residue was taken up in 100 mL of DCM and washed with 3 x 50 mL of water. Drying over Na_2SO_4 and evaporation of the solvent gave a residue which was purified via flash chromatography with cyclohexane and Et_2O. Evaporation *in vacuo* and recrystallization from EtOH gave the title compound (0.03 g, 13%) as white crystals.
MP: 203 °C.
Analysis for $C_{35}H_{29}N_3O_4$:
Calculated: C,75.66; H,5.26; N,7.56;
Found: C,75.5; H,5.22; N,7.55%.

Example 41
(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(2,4-dichlorophenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from (E)-2,4-dichlorocinnamic acid gave after recrystallization from EtOH:H_2O the title compound as a white powder in a 66% yield.
MP: 194 °C.
Analysis for $C_{27}H_{20}N_2O_3Cl_2$:
Calculated: C,66.00; H,4.10; N,5.70;
Found: C,65.85; H,4.13; N,5.78%.

Example 42
(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-methoxy-4-hydroxyphenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from (E)-3-methoxy-4-hydroxycinnamic acid gave after recrystallization from EtOH:H_2O (10:1) the title compound as an off-white powder in a 62% yield.
MP: 155 °C.
Analysis for $C_{28}H_{24}N_2O_5$:
Calculated: C,71.78; H,5.16; N,5.98;
Found: C,71.44; H,5.16; N,5.76%.

Example 43

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-hydroxy-4-methoxyphenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from (E)-3-hydroxy-4-methoxycinnamic acid gave after recrystallization from EtOH:H_2O the title compound as an off-white powder in a 47% yield.
MP: 213 °C.
Analysis for $C_{28}H_{24}N_2O_5$. $0.3H_2O$:
Calculated: C,70.96; H,5.23; N,5.91;
Found: C,71.09; H,5.60; N,5.66%.

Example 44

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-fluorophenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from (E)-4-fluorocinnamic acid gave after recrystallization from EtOH the title compound as white crystals in a 74% yield.
MP: 138-139 °C.
Analysis for $C_{27}H_{21}F_3N_2O_3$:
Calculated: C,73.62; H,4.81; N,6.36;
Found: C,73.78; H,4.81; N,5.97%.

Example 45

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-indan-5-yl-1-propene-1-one

The same method as employed in the preparation of Example 20 but starting from (E)-3-indane-5-ylacrylic acid gave, after precipitation, the title compound as a yellow powder in a 22% yield.
MP: 115 °C.
Analysis for $C_{20}H_{26}N_2O_3$. $0.6H_2O$:
Calculated: C,76.12; H,5.79; N,5.92;
Found: C,76.13; H,5.79; N,5.72%.

Example 46

(E)-N-[4-[3-Oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]benzoyl]benzenesulfonamide

The same method as employed in the preparation of Example 20 but starting from Example 31 and benzenesulfonamide gave after recrystallization from EtOH:H_2O the title compound as white crytals in a 20% yield.
MP: 134 °C.
Analysis for $C_{20}H_{26}N_2O_3$. $0.6H_2O$:
Calculated: C,56.13; H,6.67; N,10.91;
Found: C,55.97; H,6.75; N,10.82%.

Example 47

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3,4-dichlorophenyl)propene-1-one .

The same method as employed in the preparation of Example 20 but starting from (E)-3,4-dichlorocinnamic acid gave after recrystallization from EtOH:H_2O (99:1) the title compound as a white powder in a 45% yield.
MP: 212 °C.
Analysis for $C_{27}H_{20}Cl_2N_2O_3$:
Calculated: : C,66.00; H,4.10; N,5.70;
Found: C,65.68; H,4.12; N, 5.68%.

Example 48

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3,4-dimethoxyphenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from (E)-3,4-dimethoxycinnamic acid gave after recrystallization from EtOH:DCM the title compound as a white powder in a 61% yield.
MP: 233 °C.
Analysis for $C_{29}H_{26}N_2O_5$. 0.5 H_2O:
Calculated: C,70.86; H,5.54; N,5.70;
Found: C,70.66; H,5.44; N,5.70%.

Example 49
(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3,4-dihydroxyphenyl)propene-1-one
The same method as employed in the preparation of Example 20 but starting from (E)-3,4-dihydroxycinnamic acid gave after recrystallization from EtOH:DMF the title compound as a white powder in a 41% yield.
MP: 163-165 °C.
Analysis for $C_{27}H_{22}N_2O_5$. 0.3DMF:
Calculated: C,70.34; H,5.10; N,6.76;
Found: C,70.38; H,5.13; N,6.66%.

Example 50
(E)-N-Methyl-N-[4-(3-oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]phenyl]acetamide
The same method as employed in the preparation of Example 20 but starting from Intermediate 23 gave after recrystallization from EtOH:H_2O (10:0.6) the title compound as an off-white powder in a 86% yield EtOH:H_2O.
MP: 165 °C.
Analysis for $C_{30}H_{27}N_3O_4.0.4H_2O$:
Calculated: C,71.96; H,5.6; N,8.39;
Found: C,71.8; H,5.57; N,8.28%.

Example 51
(E)-2,2-Dimethyl-N-[4-[3-Oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]phenyl]propionamide
This product was prepared by condensation of Example 25 (0.2 g, 0.46 mmol) with 2,2-dimethylpropionyl chloride (0.09 mL, 1.5 equiv.) and NaOH (1N) (0.7

mL, 1.5 equiv.) in a mixture of EtOAc:DCM (6:1). When starting material had disappeared, 40 mL of a mixture of DCM:H_2O (2:1) was added. Extraction with DCM, washing with a saturated aqueous solution of NH_4Cl and brine, drying over $MgSO_4$ and evaporation of the solvent *in vacuo* gave the title compound (0.2 g, 83%) after recrystallization from EtOH:H_2O (1:1).
MP: 172-174 °C.
Analysis for $C_{32}H_{31}N_3O_4$. $0.1H_2O$:
Calculated: C,71.23; H,6.16; N,7.79;
Found: C,70.99; H,6.02 ; N.7.84%.

Example 52
(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3,5-dimethoxyphenyl)propene-1-one
The same method as employed in the preparation of Example 20 but starting from (E)-3,5-dimethoxycinnamic acid gave after recrystallization from EtOH the title compound as a white powder in a 61% yield.
MP: 178 °C.
Analysis for $C_{29}H_{26}N_2O_5$:
Calculated: C,72.19; H,5.43; N,5.81;
Found: C,72.3; H,5.48; N,5.63%.

Example 53
(E)-(N)-{4-[3-[1-(3,4-Methylenedioxyphenyl)-6-fluoro-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-oxopropenyl]phenyl}-acetamide
The same method as employed in the preparation of Example 20 but starting from Intermediate 16 and and (E)-3-(4-acetylaminophenyl)acrylic acid gave after recrystallization from MeOH the title compound as a white crystals in a 72% yield.
MP:179-181 °C.
Analysis for $C_{29}H_{24}N_3O_4F.0.4H_2O$:
Calculated: C,69.01; H,4.95; N,8.33;
Found: C,68.97; H,4.91; N.8.34%.

Example 54

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3,4,5-trimethoxyphenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from (E)-3,4,5-trimethoxycinnamic acid gave after recrystallization from MeOH the title compound as a white powder in a 49% yield.

MP: 211 °C.

Analysis for $C_{30}H_{28}N_2O_6$:

Calculated: C,70.3 ; H,5.51; N,5.47;

Found: C,70.49; H,5.59; N,5.34.%.

Example 55

(E)-N-[4-[3-Oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]phenyl]isobutyramide

The same method as employed in the preparation of Example 51 but starting from isobutyryl chloride gave after recrystallization from EtOH the title compound as a white powder in a 85% yield.

MP: 171 °C.

Analysis for $C_{31}H_{29}N_3O_4$. 0.4(H_2O:MeOH):

Calculated: C,72.61; H,6.02; N,7.99;

Found: C,72.33; H,5.77; N,8.33%.

Example 56

(E)-1-[1-(3,4-Methylenedioxyphenyl)-6-fluoro-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-phenylpropene-1-one

The same method as employed in the preparation of Example 1 but starting from Intermediate 16 gave after recrystallization from EtOH the title compound as white crystals in a 71% yield.

MP: 227-228 °C.

Analysis for $C_{27}H_{21}N_2O_3F$:

Calculated: C,73.63; H,4.81; N,6.36;

Found: C,73.72; H,4.77; N,6.43%.

Example 57

(E)-N-(2-Methoxyethyl)-4-[3-oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]benzamide

The same method as employed in the preparation of Example 20 but starting from Intermediate 24 gave after recrystallization from EtOH the title compound as white crystals in a 43% yield.
MP: 170 °C.
Analysis for $C_{27}H_{21}N_2O_3F$. $1.3H_2O$:
Calculated: C,68.07; H,5.82; N,7.68;
Found: C,67.98; H,5.8; N,7.7%.

Example 58
(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-hydroxyphenyl)propene-1-one
The same method as employed in the preparation of Example 20 but starting from (E)-3-hydroxycinnamic acid gave after recrystallization from EtOH:H_2O the title compound as white crystals in a 54% yield.
MP: 248 °C.
Analysis for $C_{27}H_{22}N_2O_4$:
Calculated: C,73.96; H,5.06; N,6.39;
Found: C,74.04; H,5.1; N,6.37%.

Example 59
(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-methoxyphenyl)propene-1-one .
The same method as employed in the preparation of Example 20 but starting from (E)-3-methoxycinnamic acid gave after recrystallization from EtOH the title compound as white crystals in a 49% yield.
MP: 218 °C.
Analysis for $C_{28}H_{24}N_2O_4$:
Calculated: C,74.32; H,5.35; N,6.19;
Found: C,74.37; H,5.61; N,6.32%.

Example 60
(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-nitrophenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from (E)-3-nitrocinnamic acid gave after recrystallization from EtOH:H_2O (20:1) the title compound as white crystals in a 91% yield.
MP: 156-158 °C.
Analysis for $C_{28}H_{24}N_2O_4$:
Calculated: C,69.37; H,4.54; N,8.99;
Found: C,69.12; H,4.77; N,8.81%.

Example 61

(E)-1-[1-(3.4-Methylenedioxyphenyl)-1,3.4,9-tetrahydro-β-carbolin-2-yl]-3-[4-(2-dimethylaminoethoxy)phenyl]propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 25 gave after recrystallization from EtOH:H_2O the title compound as white crystals in a 45% yield.
MP: 157 °C.
Analysis for $C_{31}H_{31}N_3O_4$:
Calculated: C,73.07; H,6.13; N,8.25;
Found: C,72.7 ; H,6.17; N,8.12%.

Example 62

(E)-N-(2-Morpholin-4-ylethyl)-4-[3-oxo-3-(1-(3.4-methylenedioxyphenyl)-1.3.4.9-tetrahydro-β-carbolin-2-yl)propenyl]benzamide

The same method as employed in the preparation of Example 20 but starting from Intermediate 26 gave after recrystallization from EtOH:H_2O the title compound as white crystals in a 13% yield.
MP: 145 °C.
Analysis for $C_{34}H_{34}N_4O_5$. $0.7H_2O$:
Calculated: C,69.07; H,6.03; N9.48;
Found: C,69.08; H, 6.03; N,9.45%.

Example 63

(E)-1-[1-(3.4-Methylenedioxyphenyl)-1,3.4,9-tetrahydro-β-carbolin-2-yl]-3-[4-(1H-tetrazol-5-yl)phenyl]propene-1-one

To a solution of Example 32 (0.25 g, 0.56 mmol) in 10 mL of toluene were added successively trimethylsilylazide (0.30 mL, 4 equiv.) and dibutyltinoxide (0.06 g,

0.4 equiv.). The resulting mixture was stirred at reflux for two days. Tlc monitoring showed formation of a new compound (DCM:MeOH (80:20), Rf=0.35).The reaction mixture was concentrated *in vacuo*. The resulting yellow gum was dissolved in MeOH and concentrated *in vacuo*. The residue was partitioned between EtOAc (25 mL) and an aqueous saturated solution of $NaHCO_3$ (25 mL).The organic phase was extracted with an additional portion of an aqueous saturated solution of $NaHCO_3$ (25 mL). The combined aqueous extracts were acidified to pH= 2 with HCl (1N) and then extracted with EtOAc (2x25 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated to give a yellow powder that was purified via flash chromatography (SiO_2, DCM:MeOH (90:10)). Recrystallization from 2-propanol:iPr_2O (1:1) gave the title compound (0.19 g, 70 %) as white crystals.
MP: 232-233 °C.
Analysis for $C_{28}H_{22}N_6O_3$. $0.4H_2O$:
Calculated: C,67.02; H,4.92; N,16.28;
Found: C,66.83; H,4.53; N,15.96%.

Example 64
(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-aminophenyl)propene-1-one

A solution of Example 60 (1.36 g, 2.9 mmol), $SnCl_2.H_2O$ (2.8 g, 5 equiv.) in EtOH was refluxed overnight. After evaporation of the solvent, the residue was taken up in 50 mL of NaOH (1N). The aqueous phase was extracted with 2 x 100 mL of DCM and 2 x 50 mL of EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (SiO_2, DCM:MeOH (95:5) and recrystallization from EtOH:DCM gave the title compound (0.27 g, 21%) as a pale yellow powder.
MP: 139-141 °C.
Analysis for $C_{27}H_{23}N_3O_3$:
Calculated: C,74.13; H,5.30; N,9.60;
Found: C,73.93; H,5.35; N,9.43%.

Example 65
(E)-N-Cyclohexyl-4-[3-oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]benzamide

The same method as employed in the preparation of Example 20 but starting from Intermediate 27 gave after recrystallization from EtOH:H_2O the title compound as white crystals in a 6% yield.
MP: 214 °C.
Analysis for $C_{28}H_{21}N_3O_3$. $0.1H_2O$:
Calculated: C,72.19; H,6.24; N,7.43;
Found: C,72.28; H,6.19; N,6.93%.

Example 66
(E)-N-(Tetrahydrofuran-2-ylmethyl)-4-[3-oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]benzamide
The same method as employed in the preparation of Example 20 but starting from Intermediate 28 gave after recrystallization from EtOH:H_2O (8:2) the title compound as white crystals in a 61% yield.
MP: 168 °C.
Analysis for $C_{32}H_{29}N_3O_5$. $0.8H_2O$:
Calculated: C,69.88; H,5.61; N,7.64;
Found: C,69.74; H,5.78; N,7.22%.

Example 67
(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-cyanophenyl)propene-1-one .
The same method as employed in the preparation of Example 20 but starting from (E)-cyanocinnamic acid gave after recrystallization from EtOH:H_2O (8:2) the title compound as white crystals in a 46% yield.
MP: 228-230 °C.
Analysis for $C_{28}H_{21}N_3O_3$. $0.8H_2O$:
Calculated: C,72.81; H,4.93; N,9.10;
Found: C,72.74; H,4.69; N,8.99%.

Example 68
(E)-N-(4-Piperidine-4-carboxylic acid, ethyl ester)-4-[3-oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]benzamide

The same method as employed in the preparation of Example 20 but starting from Intermediate 29 gave after recrystallization from iPr_2O the title compound as white crystals in a 28% yield.
MP: 144-145 °C.
Analysis for $C_{36}H_{35}N_3O_6$. $0.7H_2O$:
Calculated: C, 69.93; H,5.93; N,6.8;
Found: C,69.84; H,5.83; N,6.81%.

Example 69

(E)-N-(4-Piperidine-4-carboxylic acid)-4-[3-oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]benzamide

This product was prepared by refluxing a solution of Example 68 (0.21 g, 0.36 mmol) with NaOH (1 N) (0.72 mL, 2 equiv.) in 20 mL of MeOH for 12 hours. After cooling the mixture was poured into H_2O (100 mL) and acidified with HCl (1 N). Extraction with 2 x 50 mL of DCM, drying over Na_2SO_4 and concentration *in vacuo* gave a residue which was recrystallized from MeOH:H_2O to give the title compound (0.05 g, 24%) as white crystals.
MP: 204-205 °C.
Analysis for $C_{34}H_{31}N_3O_6$. $0.4H_2O$:
Calculated: C,68.56; H,5.58; N,7.05;
Found: C,68.58; H,5.12; N,7.06%.

Example 70

(E)-3-[3-Oxo-3-[1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-propenyl]benzoic acid

The same method as employed in the preparation of Example 20 but starting from (E)-3-(2-carboxyvinyl)benzoic acid gave after recrystallization from MeOH, the title compound as a white powder in a 21% yield.
MP: 156-158 °C.
Analysis for $C_{28}H_{22}N_2O_5$. $0.8H_2O$:
Calculated: C,69.93; H,4.95; N,5.83;
Found: C,69.94; H,4.62; N,5.65%.

Example 71

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-(4-methylpiperazine-1-carbonyl)phenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from Example 70 and 4-methylpiperazine gave after recrystallization from MeOH:H_2O, the title compound as a white powder in a 30% yield.

MP: 151 °C.

Analysis for $C_{33}H_{32}N_4O_4$. H_2O:

Calculated: C,69.95; H,6.05; N,9.89;

Found: C,69.63; H,5.93; N,9.99%.

Example 72

(E)-N-(2-Piperazin-1-ylethyl)-3-[3-oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]benzamide

The same method as employed in the preparation of Example 20 but starting from Example 70 and 1-(2-aminoethyl)piperazine gave after recrystallization from iPr_2O, the title compound as a white powder in a 23% yield.

MP: 138-140 °C.

Analysis for $C_{34}H_{35}N_5O_4$. $3.1H_2O$:

Calculated: C,64.46; H,6.55; N,11.05;

Found: C,64.46; H,6.25; N,11.00%.

Example 73

(E)-4-[3-Oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)-propenyl]acetic acid ethyl ester

The same method as employed in the preparation of Example 20 but starting from Intermediate 30 gave after recrystallization from DCM:pentane, the title compound as a white powder in a 17% yield.

MP: 92-95 °C.

Analysis for $C_{31}H_{28}N_2O_5$. $0.9H_2O$:

Calculated: C,70.95; H,5.72; N,5.34;

Found: C,71.32; H,6.0; N,4.93%.

Example 74

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-tetrazolophenyl)propene-1-one

The same method as employed in the preparation of Example 63 but starting from Example 67 gave after recrystallization from MeOH:H_2O, the title compound as a white powder in a 5% yield.
MP: 260-264 °C.
Analysis for $C_{28}H_{22}N_6O_3$. $2.2H_2O$:
Calculated: C,63.43; H,5.02; N,15.85;
Found: C,63.31; H,4.37; N,15.47%.

Example 75

(E)-2-[3-Oxo-3-[1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-propenyl]benzoicacid, methyl ester

The same method as employed in the preparation of Example 20 but starting from (E)-2-(2-carboxyvinyl)benzoic acid, methyl ester (prepared according to the procedure of Alabaster, R.J.; Cottrell, I.F.; Hands, D.; Humphrey, G.R.; Kennedy, D.J.; Wright, S.H.B. *Synthesis* **1989**, *8*, 598-603), gave after recrystallization from MeOH, the title compound as white crystals in a 46% yield.
MP: 203-204 °C.
Analysis for $C_{27}H_{21}N_3O_5$:
Calculated: C,72.49; H,5.03; N,5.83;
Found: C,72.59; H,5.1; N,5.67%.

Example 76

(E)-3-[3-Oxo-3-[1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-propenyl]benzoic acid, methyl ester

The same method as employed in the preparation of Example 20 but starting from (E)-3-(2-carboxyvinyl)benzoicacid, methyl ester (prepared according to the procedure of Baker,S.R.; Jamieson,W.B; Todd,A. **EP 134111 A1**), gave after recrystallization from MeOH, the title compound as yellow crystals in a 61% yield.
MP: 165-167 °C.
Analysis for $C_{29}H_{24}N_2O_5$:
Calculated: C,72.49; H,5.03; N,5.83.;
Found: C,72.53; H,5.02; N,5.93%.

Example 77

(E)-1-(4-[3-Oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)-propenyl]phenyl)piperidine-4-carboxylic acid, ethyl ester

The same method as employed in the preparation of Example 20 but starting from Intermediate 31 gave after recrystallization from MeOH, the title compound as yellow crystals in a 45% yield.

MP: 175 °C.

Analysis for $C_{35}H_{35}N_3O_5$:

Calculated: C,72.77; H,6.11; N,7.27;

Found: C,72.99; H,6.16; N,7.03%.

Example 78

(E)-N-(1-Ethylpyrrolidin-2-yl-methyl)-3-[3-oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]benzamide

The same method as employed in the preparation of Example 20 but starting from Example 70 and 2-pyrrolidin-1-ylethylamine gave after recrystallization from iPr_2O, the title compound as a white powder in a 53% yield.

MP: 128-130 °C.

Analysis for $C_{35}H_{36}N_4O_4$:

Calculated: C,72.9; H,6.29; N,9.72;

Found: C,72.9; H,6.42; N,10.01%.

Example 79

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-(2-dimethylaminoethoxy)phenyl)propene-1-one

To a solution of Example 58 (0.25 g, 0.57 mmol) in 50 mL of DMF was added K_2CO_3 (0.24 g, 3 equiv.) and an excess of dimethylaminodiethyl chloride (about 15 equiv.). The resulting mixture was heated at 60 °C for four hours until disappearance of the starting material (tlc monitoring, DCM:MeOH (90:10). A new compound was formed (Rf= 0.20). After evaporation of DMF, the residue was taken up in 150 mL of DCM, washed with 2x50 mL of water, dried over Na_2SO_4 and recrystallized from EtOH:H_2O.to give the title compound (0.06 g, 22%) as yellow crystals.

MP: 76-78 °C.

Analysis for $C_{31}H_{31}N_3O_4$. $0.6H_2O$:

Calculated: C,71.55; H,6.24; N,8.07;

Found: C,71.34; H,6.45; N,7.8%.

Example 80

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3,5-diterbutyl-4-hydroxyphenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from (E)-3,5-ditertbutyl-4-hydroxycinnamic acid gave after recrystallization from cyclohexane, the title compound as yellow crystals in a 45% yield.

MP: 137 °C.

Example 81

(E)-3-[3-Oxo-3-[1-(4-methoxycarbonylphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]propenyl]benzoic acid, methyl ester

The same method as employed in the preparation of Example 20 but starting from Intermediate 8 and (E)-3-(2-carboxy-vinyl)benzoic acid, methyl ester (prepared according to the procedure of Baker,S.R.; Jamieson,W.B; Todd,A. **EP 134111 A1**), gave after recrystallization from 2-propanol, the title compound as white crystals in a 70% yield.

MP: 182 °C.

Analysis for $C_{30}H_{26}N_2O_5$:

Calculated: C,72.86; H,5.3; N,5.66;

Found: C,72.49 ; H,5.31 ; N,5.68%.

Example 82

(E)-2-[3-Oxo-3-[1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-propenyl]benzoic acid

The same method as employed in the preparation of Example 31 but starting from Example 75 gave after recrystallization from MeOH the title compound as off-white crystals in a 78% yield.

MP: 174 °C.

Analysis for $C_{28}H_{22}N_2O_5$:

Calculated: C,72.09; H,4.75; N,6.01;

Found: C,72.53; H,4.72; N,5.76%.

Example 83

(E)-(4-[3-Oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]phenoxy)acetic acid, ethyl ester

The same method as employed in the preparation of Example 79 but starting from Example 22 and bromoacetic acid, ethyl ester, gave after recrystallization from EtOH:2-propanol the title compound as yellow crystals in a 28% yield.

MP: 99-98 °C.

Analysis for $C_{31}H_{28}N_2O_6$. $2.4H_2O$:

Calculated: C,65.57; H,5.82; N,4.93;

Found: C,65.34; H,5.4; N,5.09%.

Example 84

(E)-(4-[3-Oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)-propenyl]phenyl)acetic acid

The same method as employed in the preparation of Example 31 but starting from a solution of Example 73 in EtOH gave after recrystallization from iPr_2O:2-propanol the title compound as white crystals in a 51% yield.

MP: 231 °C.

Analysis for $C_{29}H_{24}N_2O_5$. 0.25iPrOH:

Calculated: C, 72.11; H, 5.29; N,5.64;

Found: C, 71.9; H, 5.15; N, 5.74%.

Example 85

(E)-(4-[3-Oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]phenoxy)acetic acid

The same method as employed in the preparation of Example 31 but starting from Example 83 gave after recrystallization from iPr_2O:2-propanol the title compound as yellow crystals in a 45% yield.

MP: 158-160 °C.

Analysis for $C_{29}H_{24}N_2O_6$. $0.9H_2O$:

Calculated: C,67.93; H,5.07; N,5.46;

Found: C,68.0; H,4.86; N,5.21%.

Example 86

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-nitro-4-chlorophenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from (E)-3-nitro-4-chlorocinnamic acid gave after recrystallization from EtOH the title compound as yellow crystals in a 56% yield.
MP: 240 °C.
Analysis for $C_{27}H_{20}N_3O_5Cl$:
Calculated: C,64.61; H,4.02; N,8.37;
Found: C,64.5; H,3.97; N,8.28%.

Example 87

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(5-nitro-2-chlorophenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from (E)-5-nitro-2-chlorocinnamic acid gave after recrystallization from EtOH:H_2O the title compound as yellow crystals in a 44% yield.
MP: 146 °C.
Analysis for $C_{27}H_{20}N_3O_5Cl.\ 0.1H_2O$:
Calculated: C,64.38; H,4.04; N,8.34;
Found: C,64.12; H,3.81; N,8.35%.

Example 88

(E)-3-Chloro-4-[3-oxo-3-[1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]propenyl]benzoic acid, methyl ester

The same method as employed in the preparation of Example 20 but starting from Intermediate 32 gave after recrystallization from EtOH the title compound as a white powder in a 57% yield.
MP: 166 °C.
Analysis for $C_{29}H_{23}N_2O_5Cl.\ 0.15EtOH$:
Calculated: C,67.43; H,4.62; N,5.37;
Found: C,67.09; H,4.56; N,5.51%.

Example 89

(E)-(4-[3-Oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]benzyloxy)acetic acid

The same method as employed in the preparation of Example 79 but starting from a solution of (E)-(4-[3-oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-

tetrahydro-β-carbolin-2-yl)propenyl]benzyloxy)acetic acid, ethyl ester in EtOH gave after recrystallization from MeOH:H_2O the title compound as an off-white solid in a 40% yield.

MP: 162-163 °C.

Analysis for $C_{30}H_{26}N_2O_6$. $0.1H_2O$:

Calculated: C,68.17; H,5.13; N,5.49;

Found: C,68.16; H,5.46; N,5.51%.

(E)-(4-[3-Oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]benzyloxy)acetic acid, ethyl ester:

To a solution of Example 39 (0.7 g, 1.5 mmol) in 50 mL of DMF was added K_2CO_3 (0.25 g, 1.2 equiv.) and ethylbromoacetate (0.2 mL, 1.1 equiv.). The resulting mixture was heated at 60 °C for 16 hours until disappearance of the starting material (tlc monitoring, DCM:MeOH (95:5)). A new compound was formed (Rf= 0.8). After evaporation of DMF, the residue was taken up in 150 mL of DCM, washed with 2x50 mL of water, dried over Na_2SO_4 and purified via radial chromatography with DCM to give the title compound (0.85 g, 11%) as a white powder.

^1H NMR ($CDCl_3$) δ 7.8-6.65 (m, 14H), 5.9 (s, 2H), 4.7 (s, 2H), 4.6-4.3 (q, 2H), 4.2-4.0 (m, 4H), 3.6-3.5 (m, 1H), 3.2-2.9 (m, 2H), 1.3-1.2 (t, 3H).

Example 90

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(5-amino-2-chlorophenyl)propene-1-one

The same method as employed in the preparation of Example 64 but starting from Example 87 gave after recrystallization from EtOH:DCM, the title compound as a white powder in a 17% yield.

MP: 251-252 °C.

Analysis for $C_{27}H_{22}ClN_3O_3$. $0.4H_2O$:

Calculated: C,67.68; H,4.8; N,8.77;

Found: C,67.71; H.4.73; N,8.65%.

Example 91

(E)-3-Chloro-4-[3-oxo-3-[1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]propenyl]benzoic acid

The same method as employed in the preparation of Example 31 but starting from Example 88 gave after recrystallization from 2-propanol the title compound as a yellow powder in a 40% yield.
MP: 169 °C.
Analysis for $C_{28}H_{21}N_2O_5$. H_2O:
Calculated: C,64.8; H,4.47; N,5.40;
Found: C,64.47; H,4.13; N,5.60%.

Example 92

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3,5-dibromo-4-hydroxyphenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from (E)-3,5-dibromo-4-hydroxy cinnamic acid gave after recrystallization from EtOH:H_2O the title compound as white crystals in a 13% yield.
MP: 148-150 °C.
Analysis for $C_{27}H_{20}N_2O_4Br_2$. 1.6EtOH:
Calculated: C,54.14; H,4.45; N,4.18;
Found: C,54.1; H,4.15; N,3.77%.

Example 93

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-(2-dimethylaminopropoxy)phenyl)propene-1-one

The same method as employed in the preparation of Example 79 but starting from Example 22 and dimethylaminopropyl chloride gave after recrystallization from cyclohexane:DCM:pentane the title compound as white crystals in a 16% yield.
MP: 106 °C.
Analysis for $C_{32}H_{33}N_3O_4$. $0.3H_2O$:
Calculated: C,72.65; H,6.40; N,7.94;
Found: C,72.74 ; H,6.56; N,7.63%.

Example 94

(E)-2-Chloro-5-[3-oxo-3-[1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]propenyl]benzoic acid, methyl ester

The same method as employed in the preparation of Example 20 but starting from Intermediate 33 gave after recrystallization from MeOH:DCM the title compound as a white powder in a 59% yield.
MP: 228 °C.
Analysis for $C_{29}H_{23}ClN_2O_5$. $1.05H_2O$:
Calculated: C,65.24; H,4.74; N,5.25;
Found: C,64.91; H,4.27; N,5.13%.

Example 95

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-(2-diisopropylaminoethoxy)phenyl)propene-1-one

The same method as employed in the preparation of Example 79 but starting from Example 22 and diisopropylaminodiethyl chloride gave after recrystallization from MeOH:H_2O the title compound as pale yellow crystals in a 12% yield.
MP: 92-93 °C.
Analysis for $C_{35}H_{39}N_3O_4$:
Calculated: C,74.31; H,6.95; N,7.43;
Found: C,74.34; H,7.16; N,7.10%.

Example 96

(E)-2-Chloro-5-[3-oxo-3-[1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]propenyl]benzoic acid

The same method as employed in the preparation of Example 31 but starting from Example 94 gave after recrystallization from MeOH the title compound as white crystals in a 78% yield.
MP: 178 °C.
Analysis for $C_{28}H_{21}N_2O_5$. 0.7MeOH:
Calculated: C,65.86; H,4.58; N,5.35;
Found: C, 65.73 ; H, 4.44 ; N, 5.51%.

Example 97

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-hydroxy-4-nitrophenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 34 gave after recrystallization from EtOH the title compound as yellow crystals in a 77% yield.
MP: 172 °C.

Example 98
(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3,5-dimethyl-4-hydroxyphenyl)propene-1-one
The same method as employed in the preparation of Example 20 but starting from Intermediate 35 gave after recrystallization from MeOH:H_2O the title compound as a white powder in a 71% yield.
MP: 151-152 °C.
Analysis for $C_{29}H_{26}N_2O_4$. $0.4H_2O$:
Calculated: C,73.52; H,5.7; N,5.91;
Found: C,73.56; H,5.59; N 6.29%.

Example 99
(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-(2-dimethylaminoethoxy)-4-nitrophenyl)propene-1-one
The same method as employed in the preparation of Example 79 but starting from Example 97 and dimethylaminodiethyl chloride gave after recrystallization from MeOH the title compound as a pale yellow powder in a 18% yield.
MP: 189 °C.
Analysis for $C_{31}H_{30}N_4O_6$. $1.5H_2O$:
Calculated: C,64.02; H,5.72; N,9.63;
Found: C,64.18; H,5.41; N,9.21%.

Example 100
(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-(2-dimethylaminoethoxy)-4-aminophenyl)propene-1-one
The same method as employed in the preparation of Example 64 but starting from Example 99 gave after recrystallization from iPr_2O the title compound as a pale yellow powder in a 17% yield.
MP: 143 °C.
Analysis for $C_{31}H_{32}N_4O_4$. $0.5H_2O$:

Calculated: C,69.78 ;H,6.23; N,10.5;
Found: C,69.87; H,5.98; N,10.42%.

Example 101

(E)-1-[1-(3.4-Methylenedioxyphenyl)-1.3.4.9-tetrahydro-β-carbolin-2-yl]-3-(3-nitro-4-hydroxy-5-methoxyphenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 36 gave after recrystallization from EtOH:DCM the title compound as pale yellow crystals in a 45% yield.

MP: 172 °C.

Analysis for $C_{28}H_{23}N_3O_7$. $0.8H_2O$:

Calculated: C,63.7; H,4.7; N,7.96;

Found: C,63.71; H,4.31; N,7.98%.

Example 102

(E)-1-[1-(3.4-Methylenedioxyphenyl)-1.3.4.9-tetrahydro-β-carbolin-2-yl]-3-(3-chloro-phenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from (E)-3-chlorocinnamic acid, gave after recrystallization from EtOH the title compound as white crystals in a 48% yield.

MP: 212-213 °C.

Analysis for $C_{27}H_{21}ClN_2O$:

Calculated: C,70.97; H,4.63; N,6.13

Found: C,70.65; H,4.63; N,6.16%.

Example 103

(E)-1-[1-(4-Methoxy-phenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(2-chloro-5-nitrophenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 2 and (E)-2-chloro-5-nitrocinnamic acid gave after recrystallization from 2-propanol the title compound as a yellow powder white in a 18% yield.

MP: 136-138 °C.

Analysis for $C_{27}H_{22}ClN_3O_4$. $0.2H_2O$:

Calculated: C,65.98; H,4.59; N,8.55;

Found: C,65.91; H,4.4; N,8.42%.

Example 104

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(2,6-dichlorophenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from (E)-2,6-dichlorocinnamic acid gave after recrystallization from cyclohexane the title compound as a white powder in a 41% yield.

MP: 118-120 °C.

Analysis for $C_{27}H_{20}Cl_2N_2O_3$. $0.2H_2O$:

Calculated: C,65.52; H,4.15; N,5.66;

Found: C,65.74; H,4.62; N,5.29%.

Example 105

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-methylaminomethylphenyl)propene-1-one

A solution of (E)-1-[1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-methyliminomethylphenyl)propene-1-one (0.46 g, 1.1 mmol), $NaBH_3CN$ (0.14 g, 2.3 mmol) and acetic acid (0.11 mL) in 20 mL of MeOH was stirred at rt for one hour. The reaction mixture was quenched with 50 mL of an aqueous saturated solution of $NaHCO_3$. Extraction with 2x30 mL of DCM, washing with brine, drying over Na_2SO_4 and concentration *in vacuo* gave a residue that was purified via flash chromatography of silica gel using DCM:MeOH (97:3) as eluting solvent. Recrystallization from DCM:cyclohexane gave the title compound (0.05 g, 10%) as a white powder.

MP: 201 °C.

Analysis for $C_{29}H_{27}Cl_2N_3O_3$. $0.5H_2O$:

Calculated: C,73.4; H,5.95; N,8.85;

Found: C,73.66; H,5.82; N,8.57%.

A stirred solution of Example 23 (0.5 g, 1.0 mmol) in MeOH was refluxed with methylamine (1.6 mL, 1.5 equiv., 33% in EtOH) for one hour. Evaporation *in vacuo* gave (E)-1-[1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-methyliminomethylphenyl)propene-1-one (0.46 g, 90%).

^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.2 (d, 1H), 8.1 (s, 1H), 7.8-7.65 (m, 3H), 7.55-7.5 (m, 3H), 7.4-7.1 (m, 3H), 7.0-6.85 (m, 2H), 6.8-6.6 (dd, 2H), 5.9 (s, 2H), 4.2-4.1 (br d, 1H), 3.5 (s+m, 4H), 3.05-2.85 (m, 2H).

Example 106
(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-methylphenyl)-propene-1-one

The same method as employed in the preparation of Example 20 but starting from (E)-3-methylcinnamic acid gave after recrystallization from MeOH the title compound as a white powder in a 67% yield.
MP: 196 °C.
Analysis for $C_{28}H_{24}N_2O_3$:
Calculated: C,77.04; H,5.54; N,6.62;
Found: C,76.76; H,5.56; N,6.33%.

Example 107
(E)-N-Methyl-(4-[3-oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]benzenesulfonamide

The same method as employed in the preparation of Example 20 but starting from (E)-4-(N-methylsulfonamide)cinnamic acid gave after recrystallization from EtOH:H_2O the title compound as white crystals in a 79% yield.
MP: 162 °C.
Analysis for $C_{28}H_{25}N_3O_5$. 0.4EtOH:
Calculated: C,64.78; H,5.17; N,7.87;
Found: C,64.46; H,4.82; N,7.76%.

Example 108
(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-hydroxy-4-acetylphenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from (E)-3-hydroxy-4-acetylcinnamic acid gave after recrystallization from EtOH the title compound as yellow crystals in a 87% yield.
MP: 217-218 °C.
Analysis for $C_{29}H_{24}N_2O_5$:
Calculated: C,72.49; H,5.03; N,5.83:

Found: C,72.24; H,5.25; N,5.53%.

Example 109
(E)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(2-chloro-5-nitrophenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 10 and (E)-2-chloro-5-nitrocinnamic acid gave after recrystallization from EtOH:H_2O (95:5) the title compound as yellow crystals in a 62% yield.

MP: 154 °C.

Analysis for $C_{27}H_{22}ClN_3O_4$. 0.5(H_2O:MeOH):

Calculated: C,66.08; H,4.55; N,8.36;

Found: C,66.3; H,4.52; N,7.94%.

Example 110
(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(2-hydroxyphenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from (E)-2-hydroxy cinnamic acid gave after recrystallization from EtOH:H_2O, the title compound as white crystals in a 47% yield;

MP: 154 °C.

Analysis for $C_{27}H_{22}N_2O_4$. 0.6H_2O:

Calculated: C,72.18; H,5.2; N,6.24;

Found: C,72.19; H,4.93; N,6.13%.

Example 111
(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-nitro-2-piperidin-1-ylphenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 37 gave after recrystallization from MeOH the title compound as yellow crystals in a 31% yield.

MP: 162-163 °C.

Analysis for $C_{32}H_{30}N_4O_5$. 0.2H_2O:

Calculated: C,65.52; H,5.84; N,9.55;

Found: C,65.9; H,5.49; N,9.59%.

Example 112

(E)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-phenylpropene-1-one

The same method as employed in the preparation of Example 1 but starting from Intermediate 10 gave after recrystallization from EtOH the title compound as white crystals in a 52% yield.

MP: 190 °C.

Analysis for $C_{28}H_{24}N_2O_2$:

Calculated: C,79.98; H,5.75; N,6.66;

Found: C,79.94; H.5.86; N,6.62%.

Example 113

(E)-1-[1-(4-Isopropylphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-nitrophenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 11 and (E)-3-nitrocinnamic acid gave after recrystallization from EtOH the title compound as yellow crystals in a 54% yield.

MP: 195 °C.

Analysis for $C_{29}H_{27}N_3O_3$:

Calculated: C,74.82; H,5.85; N,9.03;

Found: C,74.43; H.5.84; N,9.17%.

Example 114

(E)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-nitrophenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 10 and (E)-3-nitrocinnamic acid gave after recrystallization from EtOH the title compound as white crystals in a 35% yield.

MP: 174-176 °C.

Analysis for $C_{28}H_{23}N_3O_4 . 0.1H_2O$:

Calculated: C,71.97; H,5.0; N,8.99;

Found: C,71.78; H.4.89; N,8.83%.

Example 115

(E)-(R)-1-[1-(3,4-Methylenedioxyphenyl)-1.3.4.9-tetrahydro-β-carbolin-2-yl]-3-phenylpropene-1-one

The same method as employed in the preparation of Example 1 but starting from Intermediate 19 gave after recrystallization from EtOH the title compound as white crystals in a 60% yield.

MP: 232-233 °C.

Analysis for $C_{27}H_{22}N_2O_3$. $0.2H_2O$:

Calculated: C,76.11; H,5.3; N,6.57;

Found: C,76.2; H,5.27; N,6.77%

$[\alpha]_D^{21}$ = -336 (c = 0.50, MeOH).

Example 116

(E)-(S)-1-[1-(3,4-Methylenedioxyphenyl)-1.3.4.9-tetrahydro-β-carbolin-2-yl]-3-phenylpropene-1-one

The same method as employed in the preparation of Example 1 but starting from Intermediate 18 gave after recrystallization from iPrOH the title compound as white crystals in a 32% yield.

MP: 235-236 °C.

Analysis for $C_{27}H_{22}N_2O_3$. $0.1H_2O$:

Calculated: C,76.43; H,5.27; N,6.6;

Found: C,76.26; H,5.21; N,6.61%.

$[\alpha]_D^{21}$ = 378 (c = 0.5, MeOH).

Example 117

(E)-1-[1-(4-Methoxyphenyl)-1.3.4.9-tetrahydro-β-carbolin-2-yl]-3(3-nitrophenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 2 and (E)-3-nitrocinnamic acid gave after recrystallization from EtOH the title compound as yellow crystals in a 63% yield.

MP: 227 °C.

Analysis for $C_{27}H_{23}N_3O_4$. 0.1EtOH:

Calculated: C,71.32; H,5.19; N,9.17;

Found: C,70.96; H,5.14; N,9.23%.

Example 118

(E)-1-[1-(4-Methylphenyl)-1,3,4,9-tetrahydro-ß-carbolin-2-yl]-3-(2-chloro-5-nitrophenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 6 and (E)-2-chloro-5-nitrocinnamic acid gave after recrystallization from EtOH the title compound as a yellow powder in a 57% yield.

MP: 211-213 °C.

Analysis for $C_{27}H_{23}ClN_3O_3$:

Calculated: : C,68.72; H,4.7; N,8.9;

Found: C,68.42; H,4.73; N,8.91%.

Example 119

(E)-N-(Tetrahydrofuran-2-ylmethyl)-3-[3-oxo-3-(1-(3,4-methylenedioxy)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]benzamide

The same method as employed in the preparation of Example 20 but starting from Example 70 and tetrahydrofurfurylamine gave after recrystallization from EtOH the title compound as a white powder in a 30% yield.

MP: 172-173 °C.

Analysis for $C_{33}H_{31}N_3O_5$. $0.4H_2O$:

Calculated: C,71.18; H,5.76; N,7.55;

Found: C,71.1; H,5.88; N,7.45%.

Example 120

(E)-1-[1-(Indan-5-yl)-1,3,4,9-tetrahydro-ß-carbolin-2-yl]-3-phenylpropene-1-one

The same method as employed in the preparation of Example 1 but starting from Intermediate 9 and tetrahydrofurfurylamine gave after recrystallization from EtOH the title compound as white crystals in a 51% yield.

MP: 223 °C.

Analysis for $C_{29}H_{28}N_2O$. $0.4H_2O$:

Calculated: C,81.81; H,6.34; N,6.58;

Found: C,81.87; H,6.34; N,6.5%.

Example 121

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-ß-carbolin-2-yl]-3-(3-acetylphenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from 3-acetylcinnamic acid (prepared according to the procedure of Cleland,G.H. *J. Org. Chem.* **1969**, *34*, 744-747) gave after recrystallization from EtOH the title compound as a yellow powder in a 42% yield.
MP: 191 °C.
Analysis for $C_{29}H_{24}ClN_2O_4$:
Calculated: C,74.98; H,5.21; N,6.03;
Found: C,74.85; H,5.28; N,6.1%.

Example 122
(E)-1-[1-(2.3-Dihydrobenzofuran-5-yl)-1.3.4.9-tetrahydro-β-carbolin-2-yl)]-3-(4-(2-dimethylaminoethoxy)phenyl)propene-1-one
The same method as employed in the preparation of Example 20 but starting from Intermediate 10 and Intermediate 25 gave after recrystallization from CH_3CN the title compound as white crystals in a 37% yield.
MP: 146 °C.
Analysis for $C_{32}H_{33}N_3O_3$. $1.5H_2O$:
Calculated: C,71.89; H,6.79; N,7.86;
Found: C,72.04; H,7.09; N,7.93%.

Example 123
(E)-4-[3-Oxo-3-[1-(4-methoxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]propenyl]benzoic acid, methyl ester
The same method as employed in the preparation of Example 20 but starting from Intermediate 2 and (E)-4-(2-carboxyvinyl)benzoic acid, methyl ester gave after recrystallization from EtOH the title compound as yellow crystals in a 73% yield.
MP: 189 °C.
Analysis for $C_{29}H_{26}N_2O_4$. 0.1EtOH:
Calculated: C,74.44; H,5.69; N,5.95;
Found: C,74.1; H, 5.65; N,6.01%.

Example 124
(E)-1-[1-(3.4-Methylenedioxyphenyl)-1.3.4.9-tetrahydro-β-carbolin-2-yl]-3-(4-methyl-3.4-dihydro-2H-benzo[1,4]oxazin-6-yl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 38 gave after recrystallization from EtOH the title compound as yellow crystals in a 69% yield.
MP: 231-232 °C.
Analysis for $C_{29}H_{26}N_2O_4$. 0.1EtOH:
Calculated: C,73.01; H,5.51; N, 8.51;
Found: C,72.54; H,5.58; N,8.44%.

Example 125
(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(2-hydroxy-5-nitrophenyl)propene-1-one
The same method as employed in the preparation of Example 20 but starting from Intermediate 39 gave after recrystallization from EtOH the title compound as yellow crystals in a 30% yield.
MP: 205 °C.
Analysis for $C_{27}H_{21}N_3O_6$. 0.6EtOH:
Calculated: C,65.78; H,5.14; N,7.94;
Found: C,65.52; H,4.98; N,8.04%.

Example 126
(E)-4-[3-Oxo-3-[1-(2,3-dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]propenyl]benzoic acid, methyl ester
The same method as employed in the preparation of Example 20 but starting from Intermediate 10 and (E)-4-(2-carboxyvinyl)benzoic acid, methyl ester gave after recrystallization from EtOH the title compound as white needles in a 88% yield.
MP: 186 °C.
Analysis for $C_{30}H_{26}N_2O_4$. 0.2H_2O:
Calculated: C,74.73; H,5.52; N,5.81;
Found: C,75.45; H, 5.38; N,6.07%.

Example 127
(E)-4-[3-Oxo-3-[1-(4-methoxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]propenyl]benzoic acid

The same method as employed in the preparation of Example 31 but starting from Example 123 gave after recrystallization from MeOH:H_2O the title compound as a grey powder in a 43% yield.
MP: 147-149 °C.
Analysis for $C_{28}H_{24}N_2O_4$:
Calculated: C,74.32; H,5.35; N,6.19;
Found: C,74.3; H,5.37; N,6.07%.

Example 128

(E)-4-[3-Oxo-3-[1-(2,3-dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]propenyl]benzoic acid

The same method as employed in the preparation of Example 31 but starting from Example 126 gave after recrystallization from MeOH the title compound as white crystals in a 53% yield.
MP: 222-224 °C.
Analysis for $C_{29}H_{24}N_2O_4$:
Calculated: C,74.98; H,5.21; N,6.03;
Found: C,75.21; H,5.3; N,6.21%.

Example 129

(E)-1-[1-(Benzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-phenylpropene-1-one

The same method as employed in the preparation of Example 1 but starting from Intermediate 12 gave after recrystallization from EtOH the title compound as white crystals in a 35% yield.
MP: 241-242 °C.
Analysis for $C_{28}H_{22}N_2O_2$:
Calculated: C,80.36; H,5.3; N,6.69;
Found: C,80.44; H,5.3; N,6.89%.

Example 130

(E)-3-[3-Oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)-propenyl]phenyl)trifluoromethanesulfonic acid, phenyl ester

The same method as employed in the preparation of Example 20 but starting from Intermediate 40 gave after recrystallization from EtOH the title compound as white crystals in a 38% yield.
MP: 169 °C.
Analysis for $C_{28}H_{21}F_3N_2O_6S$. $0.2H_2O$:
Calculated: C,58.58; H,3.76; N,4.88;
Found: C,58.84; H,3.71; N,4.3%.

Example 131
(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-[4-(2-hydroxyethoxy)phenyl]propene-1-one
The same method as employed in the preparation of Example 20 but starting from (E)-4-(2-hydroxyethoxy)phenyl (prepared according to the procedure of Oku,T.; Kayakiri,H.; Satoh,S.; Abe,Y.; Sawada,Y.; Inoue,T.; Tanaka,H.; **EP 622361**) gave after recrystallization from EtOH the title compound as white crystals in a 57% yield.
MP: 136 °C.
Analysis for $C_{29}H_{26}N_2O_5$. 1.2EtOH:
Calculated: C,58.58; H,3.76; N,4.88;
Found: C,58.84; H,3.71; N,4.3%.

Example 132
(E)-1-[1-(Benzofuran-5-yl-1,3,4,9-tetrahydro-β-carbolin-2-yl)]-3-(4-(2-dimethylaminoethoxy)phenyl)propene-1-one
The same method as employed in the preparation of Example 20 but starting from Intermediate 12 and Intermediate 25 gave after recrystallization from CH_3CN the title compound as white crystals in a 23% yield.
MP: 159 °C.
Analysis for $C_{32}H_{31}N_3O_3$. $0.1H_2O$:
Calculated: C,75.75; H,6.2; N,8.28;
Found: C,75.58; H,5.97; N,8.35%.

Example 133
(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(2-dimethylaminophenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from (E)-2-dimethylaminocinnamic acid (prepared according to the procedure of Suschitzky,H.; Hollywood,F. *Synthesis* **1982**, 662-665) gave after recrystallization from MeOH:H_2O the title compound as a yellow powder in a 51% yield.
MP: 172 °C.
Analysis for $C_{29}H_{27}N_3O_3$:
Calculated: C,74.82; H,5.85; N,9.03;
Found: C,74.75; H,5.85; N,8.9%.

Example 134
(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(2-piperidin-1-ylphenyl)propene-1-one
The same method as employed in the preparation of Example 20 but starting from (E)-2-piperidin-1-ylcinnamic acid (prepared according to the procedure of Suschitzky,H.; Hollywood,F. *Synthesis* **1982**, 662-665) gave after recrystallization from MeOH:H_2O the title compound as a yellow powder in a 37% yield.
MP: 129 °C.
Analysis for $C_{32}H_{31}N_3O_3$:
Calculated: C,76.02; H,6.18; N,8.31;
Found: C,75.66; H,6.18; N,8.29%.

Example 135
(E)-4-[3-Oxo-3-[1-(benzofuran-5-yl-1,3,4,9-tetrahydro-β-carbolin-2-yl]-propenyl]-benzoic acid, methyl ester
The same method as employed in the preparation of Example 20 but starting from Intermediate 12 and (E)-4-(2-carboxyvinyl)benzoic acid methyl ester gave after recrystallization from EtOH the title compound as yellow crystals in a 76% yield.
MP: 221 °C.
Analysis for $C_{30}H_{24}N_2O_4$:
Calculated: C,75.62; H,5.08; N,5.88;
Found: C,75.75; H,5.31; N,5.86%.

Example 136

(E)-4-[3-(1-Benzofuran-5-yl-1,3,4,9-tetrahydro-β-carbolin-2-yl)-3-oxo-propenyl]-benzoic acid

The same method as employed in the preparation of Example 31 but starting from Example 135 gave after recrystallization from CH_3CN the title compound as yellow crystals in a 66% yield.

MP: 283 °C.

Analysis for $C_{29}H_{22}N_2O_4 . 0.6H_2O$:

Calculated: C,73.59; H,4.94; N,5.92;

Found: C,73.48; H,4.78; N,5.93%.

Example 137

(E)-4-[3-Oxo-3-(1-(3,4-methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenyl]phenyl)trifluoromethanesulfonic acid, phenyl ester

The same method as employed in the preparation of Example 20 but starting from Intermediate 41 gave after recrystallization from EtOH the title compound as white crystals in a 51% yield.

MP: 254 °C.

Analysis for $C_{28}H_{21}F_3N_2O_6S$:

Calculated: C,58.95; H,3.71; N,4.91;

Found: C,58.79; H.3.8; N,4.77%.

Example 138

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(2-(2-dimethylaminoethoxy)phenyl)propene-1-one

The same method as employed in the preparation of Example 79 but starting from Example 110 and dimethylaminodiethyl chloride gave after recrystallization from CH_3CN:pentane the title compound as yellow crystals in a 70% yield.

MP: 131 °C.

Analysis for $C_{31}H_{31}N_3O_4 . 1.3H_2O$:

Calculated: C,68.95; H,6.35; N,7.88;

Found: C,69.77; H.6.28; N,7.84%.

Example 139

(E)-1-[1-(3-Fluoro-4-methoxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-phenylpropene-1-one

The same method as employed in the preparation of Example 1 but starting from Intermediate 14 gave after recrystallization from DCM:cyclohexane the title compound as white crystals in a 66% yield.

MP: 122 °C.

Analysis for $C_{27}H_{23}FN_2O_2$. $0.4CH_2Cl_2$:

Calculated: C,71.47; H,5.21; N,6.08;

Found: C,71.46; H,5.27; N,6.12%.

Example 140

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)]-3-(4-(2-dimethylaminoethoxy)phenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 20 and Intermediate 25 gave after recrystallization from CH_3CN the title compound as white crystals in a 85% yield.

MP: 187-189 °C.

Analysis for $C_{32}H_{33}N_3O_3$:

Calculated: C,75.71; H,6.55; N,8.20;

Found: C,75.60; H,6.76; N,8.10%.

$[\alpha]_D^{21}$ = -310 (c = 0.40, $CHCl_3$).

Example 141

(E)-1-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-phenylpropene-1-one

The same method as employed in the preparation of Example 1 but starting from Intermediate 13 gave after recrystallization from EtOH the title compound as white crystals in a 39% yield.

MP: 216 °C.

Analysis for $C_{28}H_{24}N_2O_3$. $0.6H_2O$:

Calculated: C,75.18; H,5.68; N,6.26;

Found: C,75.17; H,5.41; N,6.4%.

Example 142

(E)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)]-3-(4-(2-pyrrolidin-1-ylethoxy)phenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 10 and Intermediate 42 gave after recrystallization from 2-propanol:iPr_2O the title compound as white crystals in a 26% yield.

MP: 152 °C.

Analysis for $C_{34}H_{35}N_3O_3$. $0.5H_2O$:

Calculated: C,75.25; H,6.69; N,7.74;

Found: C,75.31; H,6.6; N,7.69%.

Example 143

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-[4-pyrrolidin-1-ylphenyl]propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 43 gave after recrystallization from EtOH:H_2O the title compound as white crystals in a 73% yield.

MP: 154 °C.

Analysis for $C_{31}H_{29}N_3O_3$. $0.6H_2O$:

Calculated: C,74.11; H,6.06; N,8.36;

Found: C,74.22; H,5.97; N,7.97%.

Example 144

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-nitrophenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 20 and (E)-3-nitrocinnamic acid gave after recrystallization from EtOH the title compound as yellow crystals in a 51% yield.

MP: 155 °C.

Analysis for $C_{28}H_{23}N_3O_4$:

Calculated: C,72.25; H,4.98; N,9.03;

Found: C,72.2; H,5.0; N,9.01%.

$[\alpha]_D^{19}$ = -347 (c = 0.33, MeOH).

Example 145

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-[4-imidazol-1-ylphenyl]propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 44 gave after recrystallization from EtOH the title compound as white crystals in a 69% yield.

MP: 204 °C.

Analysis for $C_{30}H_{24}N_4O_3$. $0.6H_2O$:

Calculated: C,72.68; H,5.04; N,11.3;

Found: C,72.67; H,4.85; N,11.34%.

Example 146

(E)-4-[3-[1-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-oxopropenyl]benzoic acid, methyl ester

The same method as employed in the preparation of Example 20 but starting from Intermediate 13 and (E)-4-(2-carboxyvinyl)benzoic acid, methyl ester gave after recrystallization from MeOH the title compound as a white powder in a 35% yield.

MP: 136 °C.

Analysis for $C_{30}H_{26}N_2O_5$. $0.1H_2O$:

Calculated: C,72.6; H,5.32; N, 5.64;

Found: C,72.31; H,5.26; N,5.74%.

Example 147

(E)-1-[1-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-nitrophenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 13 and (E)-3-nitrocinnamic acid gave after recrystallization from EtOH the title compound as a pale yellow powder in a 93% yield.

MP: 154 °C.

Analysis for $C_{28}H_{23}N_3O_5$. $0.6H_2O$:

Calculated: C,68.31; H,4.95; N,8.54;

Found: C,68.41; H,4.87; N,8.61%.

Example 148

(E)-1-[1-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)]-3-(4-(2-dimethylaminoethoxy)phenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 13 and Intermediate 25 gave after recrystallization from CH_3CN the title compound as a white powder in a 65% yield.

MP: 145 °C.

Example 149

(E)-1-[1-(3-Fluoro-4-methoxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)]-3-(4-(2-dimethylaminoethoxy)phenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 14 and Intermediate 25 gave after recrystallization from iPr_2O the title compound as a white powder in a 60% yield.

MP: 103 °C.

Analysis for $C_{31}H_{32}FN_3O_3$. $0.4H_2O$:

Calculated: C,71.49; H,6.35; N,8.07;

Found: C,71.4; H,6.51; N,8.04%.

Example 150

(E)-4-[3-[1-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-oxopropenyl]benzoic acid

The same method as employed in the preparation of Example 31 but starting from Example 146 gave after recrystallization from MeOH the title compound as a white powder in a 93% yield.

MP: 253 °C.

Analysis for $C_{29}H_{24}N_2O_5$. $0.7H_2O$:

Calculated: C,70.63; H,5.19; N,5.68;

Found: C,70.78; H,5.09; N,5.72%.

Example 151

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-phenylpropene-1-one

The same method as employed in the preparation of Example 1 but starting from Intermediate 20 gave after recrystallization from MeOH the title compound as white crystals in a 100% yield.

MP: 267 °C.
Analysis for $C_{28}H_{24}N_2O_2$:
Calculated: C,79.98; H,5.75; N,6.66;
Found: C,79.86; H,5.89; N,6.72%.
$[\alpha]_D^{22}$ = -362 (c = 0.35, $CHCl_3$).

Example 152
(E)-(S)-1-[1-(2.3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)]-3-(4-(2-dimethylaminoethoxy)phenyl)propene-1-one
The same method as employed in the preparation of Example 20 but starting from Intermediate 21 and Intermediate 25 gave after recrystallization from CH_3CN the title compound as beige crystals in a 79% yield.
MP: 153 °C.
Analysis for $C_{32}H_{33}N_3O_3$. $0.5H_2O$:
Calculated: C, ,74.39; H,6.63; N,8.13;
Found: C,74.36; H,6.69; N,8.44%.
$[\alpha]_D^{21}$ = 314 (c = 0.40, $CHCl_3$).

Example 153
(E)-1-[1-(2.3-Dihydrobenzofuran-5-yl)-1,3.4,9-tetrahydro-β-carbolin-2-yl]-3-(4-aminophenyl)propene-1-one
The same method as employed in the preparation of Example 20 but starting from Intermediate 10 and (E)-4-aminocinnamic acid gave after recrystallization from iPrOH the title compound as white crystals in a 43% yield.
MP: 183 °C.
Analysis for $C_{30}H_{31}N_3O_2$. $1.6H_2O$:
Calculated: C,76.59; H,5.83; 9.57;
Found: C,76.62; H,5.82; N,9.59%.

Example 154
(E)-(S)-1-[1-(2.3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-phenylpropene-1-one
The same method as employed in the preparation of Example 1 but starting from Intermediate 21 gave after recrystallization from EtOH the title compound as white crystals in a 98% yield.

MP: 266 °C.
Analysis for $C_{28}H_{24}N_2O_2$. $0.2H_2O$:
Calculated: C,79.30; H,5.80; N,6.61;
Found: C,79.24; H,5.92; N,6.48%.
$[\alpha]_D^{20}$ = 356 (c = 0.35, $CHCl_3$).

Example 155
(E)-(S)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-nitrophenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 21 and (E)-3-nitrocinnamic acid gave after recrystallization from 2-propanol the title compound as yellow crystals in a 77% yield.
MP: 143 °C.
Analysis for $C_{28}H_{23}N_3O_4$. $0.3H_2O$:
Calculated: C,71.42; H,5.05; N,8.92;
Found: C,71.51; H,4.98; N,9.23%.
$[\alpha]_D^{19}$ = 294 (c = 0.30, $CHCl_3$).

Example 156
(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)]-3-(4-(1-(S)-methylpyrrolidin-2-yl-methoxy)phenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 20 and Intermediate 45 gave after recrystallization from 2-propanol the title compound as white crystals in a 73% yield.
MP: 167 °C.
Analysis for $C_{34}H_{35}N_3O_3$:
Calculated: C,76.52; H,6.61; N,7.87;
Found: C,76.13; H, 6.71; N,7.96%.
$[\alpha]_D^{20}$ = -344 (c = 0.30, $CHCl_3$).

Example 157
(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-hydroxyphenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 20 and (E)-3-hydroxycinnamic acid gave after recrystallization from EtOH the title compound as white crystals in a 93% yield.
MP: 251 °C.
Analysis for $C_{28}H_{24}N_2O_3$. $0.8H_2O$:
Calculated: C,74.58; H,5.72; N,6.21;
Found: C,74.58; H,5.65; N,6.17%.
$[\alpha]_D^{21}$ = -342 (c = 0.53, $CHCl_3$).

Example 158
(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)]-3-(4-(2-dimethylamino-1-methylethoxy)phenyl)propene-1-one
The same method as employed in the preparation of Example 20 but starting from Intermediate 20 and Intermediate 46 gave after recrystallization from CH_3CN the title compound as white crystals in a 100% yield.
MP: 193 °C.
Analysis for $C_{33}H_{35}N_3O_3$. $0.45H_2O$:
Calculated: C,74.82; H,6.83; N,7.93;
Found: C,74.85; H, 6.76; N,8.21%.

Example 159
(E)-1-(1-Phenyl-1,3,4,9-tetrahydro-β-carbolin-2-yl)-3-(4-(4-methylpyperazin-1-yl)-phenyl)propene-1-one
The same method as employed in the preparation of Example 20 but starting from Intermediate 1 and Intermediate 47 gave after recrystallization from EtOH the title compound as pale yellow crystals in a 26% yield.
MP: 223-226 °C.
Analysis for $C_{32}H_{32}N_4O_3$. $0.4H_2O$:
Calculated: C,72.82; H,6.26; N,10.61;
Found C,72.77; H,6.31; N,10.52%.

Example 160
(E)-(R)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)]-3-(4-(1-(S)-methylpyrrolidin-2-yl-methoxy)phenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 19 and Intermediate 45 gave after recrystallization from iPr_2O the title compound as white crystals in a 83% yield.
MP: 164 °C.
Analysis for $C_{33}H_{33}N_3O_4$. $0.9H_2O$:
Calculated: C,71.82; H,6.36; N,7.61;
Found C,72.05; H,6.57; N,7.24%.
$[\alpha]_D^{21}$ = -285 (c = 0.40, $CHCl_3$).

Example 161
(E)-(R)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)]-3-(4-(2-dimethylamino-1-methylethoxy)phenyl)propene-1-one
The same method as employed in the preparation of Example 20 but starting from Intermediate 19 and Intermediate 46 gave after recrystallization from iPr_2O the title compound as white crystals in a 56% yield.
MP: 107 °C.
Analysis for $C_{32}H_{33}N_3O_4$. $0.7H_2O$:
Calculated: C,71.67; H,6.47; N,7.84;
Found: C,71.6; H, 6.53; N,7.97 %.

Example 162
(E)-(R)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)]-3-(4-(2-dimethylaminopropoxy)phenyl)propene-1-one
The same method as employed in the preparation of Example 20 but starting from Intermediate 19 and Intermediate 48 gave after recrystallization from iPr_2O the title compound as white crystals in a 78% yield.
MP: 193 °C.
Analysis for $C_{32}H_{33}N_3O_4$. $1.6H_2O$:
Calculated: : C,69.57; H,6.6; N,7.61;
Found: C,69.46; H, 6.59; N,7.33%.
$[\alpha]_D^{21}$ = -266 (c = 0.40, $CHCl_3$).

Example 163
(E)-4-[3-Oxo-3-[1-(3,4-fluorophenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-propenyl]benzoic acid, methyl ester

The same method as employed in the preparation of Example 20 but starting from Intermediate 15 and (E)-4-(2-carboxyvinyl)benzoic acid, methyl ester gave after recrystallization from EtOH:H_2O the title compound as a yellow powder in a 100% yield.

MP: 200 °C.

Analysis for $C_{28}H_{22}F_2N_2O_3$:

Calculated: C,71.18; H,4.69; N,5.93;

Found: C,71.21; H,4.77; N,6.03%.

Example 164

(E)-(R)-[1-(2.3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)]-3-(4-(2-diethylaminoethoxy)phenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 20 and (E)-3-(4-(2-diethylaminoethoxy)phenyl)acrylic acid (prepared according to the procedure of Sharpe,C.J.; Shabolt,R.S.; Brown, G.R.; Ashford,A.; Ross,J.W. *J. Med. Chem.* **1971**, *14*, 836-842), gave after recrystallization from CH_3CN the title compound as white crystals in a 80% yield.

MP: 193 °C.

Analysis for $C_{34}H_{37}N_3O_3$. $0.6H_2O$:

Calculated: C,74.73; H,7.05; N,7.69;

Found: C,74.53; H, 6.91; N,7.68%.

$[\alpha]_D^{20}$ = -311 (c = 0.30, $CHCl_3$).

Example 165

(E)-(R)-1-[1-(2.3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)]-3-(4-(2-dimethylaminopropoxy)phenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 20 and Intermediate 48 gave after recrystallization from CH_3CN the title compound as white crystals in a 79% yield.

MP: 193 °C.

Analysis for $C_{33}H_{35}N_3O_3$:

Calculated: C,75.98; H,6.76; N,8.06;

Found: C,76.24; H, 6.76; N,8.21%.

$[\alpha]_D^{20}$ = -293 (c = 0.40, $CHCl_3$).

Example 166

(E)-4-[3-Oxo-3-[1-(3,4-difluorophenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]propenyl]benzoic acid

The same method as employed in the preparation of Example 31 but starting from Example 163 gave after recrystallization from MeOH:H_2O the title compound as a white powder in a 100% yield.

MP: 172 °C.

Analysis for $C_{27}H_{20}F_2N_2O_3$:

Calculated: C,68.06; H,4.65; N,5.88;

Found: C,68.15; H,4.55; N,5.99%.

Example 167

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-aminophenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 20 and (E)-4-aminocinnamic acid gave after recrystallization from 2-propanol the title compound as white crystals in a 80% yield.

MP: 176 °C.

Analysis for $C_{28}H_{25}N_3O_2$. $0.23H_2O$:

Calculated: C,76.49; H,5.84; N,9.56;

Found: C,76.21; H, 5.61; N,9.96%.

$[\alpha]_D^{21}$ = -375.3 (c = 0.0.35, $CHCl_3$).

Example 168

(E)-(R)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-aminophenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 19 and (E)-4-aminocinnamic acid gave after recrystallization from 2-propanol:H_2O the title compound as white crystals in a 63% yield.

MP: 264 °C.

Analysis for $C_{27}H_{23}N_3O_3$. $0.6H_2O$:

Calculated: C,72.34; H,5.44; N,9.37;

Found: C,72.06; H,5.48; 9.55%.

$[\alpha]_D^{21}$ = -266 (c = 0.3, MeOH).

Example 169

(R)-(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)]-3-(4-(2-pyrrolidin-1-ylethoxy)phenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 19 and Intermediate 42 gave after recrystallization from iPr_2O the title compound as brown crystals in a 4% yield.

MP: 116 °C.

Analysis for $C_{33}H_{33}N_3O_4$. $1.7H_2O$:

Calculated: C,69.99; H,6.48; N,7.42;

Found: C,70.02; H, 6.47; N,7.59%.

Example 170

(E)-(R)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)]-3-(4-(2-diethylaminoethoxy)phenylpropene-1-one

The same method as employed in the preparation of Example 20 but starting from 1 Intermediate 19 and (E)-3-(4-(2-diethylaminoethoxy)phenyl)acrylic acid (prepared according to the procedure of Sharpe,C.J.; Shabolt,R.S.; Brown, G.R.; Ashford,A.; Ross,J.W. *J. Med. Chem.* **1971**, *14(9)*, 836-842) gave after recrystallization from iPr_2O the title compound as white crystals in a 67% yield.

MP: 94 °C.

Analysis for $C_{33}H_{35}N_3O_4$. $0.5H_2O$:

Calculated: C,72.5; H,6.64; N,7.69;

Found: C,72.48; H,6.64; N,7.58%.

$[\alpha]_D^{21}$ = -287 (c = 0.3, $CHCl_3$).

Example 171

(E)-1-[1-(3-Fluoro-4-methoxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)]-3-(3-nitrophenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 14 and (E)-3-nitrocinnamic acid gave after recrystallization from DCM:2-propanol the title compound as a yellow powder in a 90% yield.

MP: 141 °C.

Analysis for $C_{27}H_{22}FN_3O_4$. $0.9CH_2Cl_2$:

Calculated: C,61.16; H,4.38; N,7.67;

Found: C,61.1; H,4.39; N,7.56%.

Example 172

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-trifluoromethylphenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 20 and (E)-4-trifluoromethylcinnamic acid gave after recrystallization from 2-propanol the title compound as white crystals in a 91% yield.

MP: 141 °C.

Analysis for $C_{29}H_{23}F_3N_2O_2$:

Calculated: C,71.3; H,4.75; N,5.73;

Found: C,71.37; H,4.79; N,5.86%.

$[\alpha]_D^{20}$ = -326 (c = 0.3, $CHCl_3$).

Example 173

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(3-trifluoromethylphenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 20 and (E)-3-trifluoromethylcinnamic acid gave after recrystallization from 2-propanol:H_2O the title compound as white crystals in a 80% yield.

MP: 223 °C.

Analysis for $C_{29}H_{23}F_3N_2O_2$:

Calculated: C,71.3; H,4.75; N,5.73;

Found: C,71.44; H,4.73; N,5.85%.

$[\alpha]_D^{20}$ = -326 (c = 0.3, $CHCl_3$).

Example 174

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-(2-morpholin-4-ylethoxy)phenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 20 and Intermediate 49 gave after recrystallization from 2-propanol:H_2O the title compound as white crystals in a 66% yield.

MP: 148 °C.

Analysis for $C_{34}H_{35}N_3O_4$:

Calculated: C,71.3; H,4.75; N,5.73;
Found: C,71.44; H,4.73; N,5.85%.
$[\alpha]_D^{19}$ = -288 (c = 0.3, $CHCl_3$).

Example 175
(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-(2-(ethylmethylamino)ethoxy)phenyl)propene-1-one
The same method as employed in the preparation of Example 20 but starting from Intermediate 20 and Intermediate 50 gave after recrystallization from iPr_2O the title compound as a white powder in a 66% yield.
MP: 107 °C.
Analysis for $C_{33}H_{35}N_3O_3$. $0.8H_2O$:
Calculated: C,73.94; H,6.88; N,7.84;
Found: C,74.09; H,7.15; N,7.48%.
$[\alpha]_D^{21}$ = -253 (c = 0.3, $CHCl_3$).

Example 176
(E)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-(3-(dimethylamino)propenyl)phenyl)propene-1-one
The same method as employed in the preparation of Example 20 but starting from Intermediate 20 and Intermediate 51 gave after recrystallization from EtOH the title compound as a white powder in a 45% yield.
MP: 216 °C.
Analysis for $C_{33}H_{33}N_3O_2$. $0.2H_2O$:
Calculated: C,78.14; H,6.88; N,7.84;
Found: C,78.03; H,6.74; N,8.21%.
$[\alpha]_D^{19.8}$ = -312 (c = 0.29, $CHCl_3$).

Example 177
(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-(3-dimethylamino-2-hydroxypropoxy)phenyl)propene-1-one
At 0 °C to a solution (E)-(R)-1-[1-(2,3-dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-(2-(tertbutyldimethylsilanyloxy)-3-dimethylamino-2-hydroxy-propoxy)phenyl)propene-1-one (0.4 g, 0.6 mmol) in 50 mL of anhydrous THF was added tetrabutylammonium fluoride (0.6 mL, 1 equiv., 1 M

in THF). The resulting mixture was stirred at rt for one day. Quenching with water, extraction with DCM, washing with brine, drying over $MgSO_4$ and concentration *in vacuo* gave an oil. Recrystallization from iPrOH:H_2O gave the title compound (0.2 g, 62%) as an off-white powder.

MP: 138 °C.

Analysis for $C_{33}H_{35}N_3O_4$. $0.5H_2O$:

Calculated: C,72.5; H,6.64; N,7.69;

Found: C,72.21; H,6.75; N,7.48%.

$[\alpha]_D^{20}$ = -283 (c = 0.6, $CHCl_3$).

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-(2-(tertbutyldimethylsilanyloxy)-3-dimethylamino-2-hydroxypropoxy)phenyl)-propene-1-one was obtained in a 89% yield as a yellow oil from the same method as employed in the preparation of Example 20 but starting from Intermediate 20 and Intermediate 52.

^{1}H NMR ($CDCl_3$,250 MHz) δ 8.1 (s, 1H), 7.5-7.3 (m, 2H), 6.9-7.2 (m, 7H), 6.8-6.5 (m, 3H), 4.5 (t, 2H), 4.2 (m, 1H), 4.0 (m, 3H), 3.8 (m, 1H), 3.3 (m, 1H), 3.0 (t, 2H), 2.7-2.9 (m, 3H), 2.3-2.15 (m, 2H), 2.1 (s, 6H), 0.8 (s,9H), 0.05 (d, 6H).

Example 178

(E)-(R)-1-(1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)-3-(4-formylphenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 20 and (E)-4-formylcinnamic acid gave after recrystallization from EtOH the title compound as a white powder in a 53% yield.

MP: 175 °C.

Analysis for $C_{29}H_{24}N_2O_3$. $0.8H_2O$:

Calculated: C,75.24; H,5.57; N,6.05;

Found: C,75.54; H,5.78; N,6.11%.

$[\alpha]_D^{20}$ = -340 (c = 0.33, $CHCl_3$).

Example 179

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-propylaminomethyl)phenyl)propene-1-one

To a solution of a solution of Example 178 (0.5 g, 1.1 mmol) in 50 mL of MeOH was added propylamine (14 mL, 1.5 equiv.). The resulting mixture was stirred at

50 °C for 4 hours. At rt polymer-supported borohydride (1.2 g, 1.2 equiv., 2.5 mmol/g) was added and the resulting mixture was stirred at 50 °C for 6 hours. After evaporation *in vacuo*, the residue was washed with 2x50 mL of DCM. After filtration, the filtrate was washed with 2x50 mL of water. Drying over Na_2SO_4, evaporation *in vacuo* and recrystallization from MeOH gave the title compound (0.4 g, 81%) as a pale yellow powder.
MP: 170 °C.
Analysis for $C_{32}H_{33}N_3O_2$. $0.4H_2O$:
Calculated: C,77.05; H,6.83; N,8.42;
Found: C,77.04; H,6.78; N,8.29%.
$[\alpha]_D^{19}$ = -330 (c = 0.4, MeOH).

Example 180
(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-[4-(2-dimethylaminoethylamino)phenylpropene-1-one
The same method as employed in the preparation of Example 20 but starting from Intermediate 20 and Intermediate 53 gave after recrystallization from EtOH the title compound as yellow crystals in a 12% yield.
MP: 160 °C.
Analysis for $C_{32}H_{34}N_4O_2$. $0.2H_2O$:
Calculated: C,75.33; H,6.8; N,10.98;
Found C,75.06; H,6.83; N,10.98%.
$[\alpha]_D^{20}$ = -214 (c = 0.1, MeOH).

Example 181
(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-(2-aminoethoxy)phenyl)propene-1-one
To a solution of (E)-(R)-2-[2-(4-{3-[1-(2,3-dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-oxo-propenyl}-phenoxy)ethyl]isoindole-1,3-dione (0.85 g, 1.4 mmol) in 50 mL of MeOH:THF was added hydrazine (0.38 mL, 3 equiv., 35% in water). The resulting mixture was stirred at 45 °C for 4 hours. Evaporation *in vacuo* and flash chromatography with DCM:MeOH (80:20) as eluting solvent gave the title compound (0.17 g, 26%) as yellow powder.
MP: 186 °C.
Analysis for $C_{30}H_{29}N_3O_3$. $0.3CH_2Cl_2$:

Calculated: C,72.06; H,5.91; N,8.32;
Found C,72.12; H,6.08; N,8.67%.
$[\alpha]_D^{20}$ = -285 (c = 0.29, MeOH).

(E)-(R)-2-[2-(4-{3-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-oxo-propenyl}phenoxy)ethyl]isoindole-1,3-dione was obtained after recrystallization from EtOH, as a gummy solid in a 90% yield using the same method as employed in the preparation of Example 20 but starting from Intermediate 20 and Intermediate 54.

^{1}H NMR ($CDCl_3$ 250 MHz) δ 8.0-6.7 (m, 19H), 4.5 (t, 2H), 4.2-4.0 (m, 5H), 3.4 (m, 1H), 3.0 (t, 2H), 2.9 (m, 2H).

Example 182

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-hydroxyphenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 20 and (E)-4-hydroxycinnamic acid gave after recrystallization from DMF:MeOH the title compound as a white powder in a 90% yield.
MP: 189 °C.
Analysis for $C_{28}H_{24}N_2O_3$. 0.5DMF:
Calculated: C,75.51; H,5.77; N,7.12;
Found: C,75.31; H.5.84; N,6.81%.
$[\alpha]_D^{20}$ = -310 (c = 0.32, MeOH).

Example 183

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-(4-methylpiperazin-1-yl)phenylpropene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 20 and Intermediate 47 gave after recrystallization from DMF:EtOH the title compound as pale yellow crystals in a 48% yield.
MP: 193 °C.
Analysis for $C_{33}H_{34}N_4O_2$. 1.0DMF:
Calculated: C,73.07; H,6.98; N,11.83;
Found C,72.67; H.7.05; N,11.55%.
$[\alpha]_D^{20}$ = -330 (c = 0.3, $CHCl_3$).

Example 184

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-methylaminomethyl)phenyl)propene-1-one

The same method as employed in the preparation of Example 179 but starting from methylamine gave after recrystallization from MeOH:H_2O the title compound as a white powder in a 52% yield.

MP: 129 °C.

Analysis for $C_{30}H_{29}N_3O_2.1.1H_2O$:

Calculated: C,74.54; H,6.51; N,8.69;

Found: C,74.68; H,6.57; N,8.59%.

$[\alpha]_D^{21}$ = -288 (c = 0.4, $CHCl_3$).

Example 185

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-isopropylaminomethyl)phenyl)propene-1-one

The same method as employed in the preparation of Example 179 but starting from isopropylamine gave after recrystallization from MeOH:H_2O the title compound as a white powder in a 47% yield.

MP: 158 °C.

Analysis for $C_{32}H_{33}N_3O_2$. $0.3H_2O$:

Calculated: C,77.33; H,6.81; N,8.45;

Found: C,77.42; H,6.74; N,8.26%.

$[\alpha]_D^{21}$ = -319 (c = 0.3, MeOH).

Example 186

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-dimethylaminomethyl)phenyl)propene-1-one

The same method as employed in the preparation of Example 179 but using dimethylamine gave after recrystallization from iPrOH:H_2O the title compound as a white powder in a 34% yield.

MP: 153-154 °C.

Analysis for $C_{31}H_{31}N_3O_2.0.2H_2O$:

Calculated: C,77.38; H,6.58; N,8.73;

Found: C,77.4; H,6.49; N,8.61%.

$[\alpha]_D^{21}$ = -336 (c = 0.3, MeOH).

Example 187

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-[4-(3-dimethylaminopropoxy)phenyl]propene-1-one

The same method as employed in the preparation of Example 79 but starting from Example 182 and dimethylaminopropyl chloride gave after recrystallization from CH_3CN the title compound as a white powder in a 53% yield.

MP: 186 °C.

Analysis for $C_{33}H_{35}N_3O_2$. $0.6H_2O$:

Calculated: C,74.44; H,6.85; N,7.89;

Found: C,74.36; H,6.63; N,7.98%.

$[\alpha]_D^{20}$ = -326 (c = 0.3, MeOH).

Example 188

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-(4-(2-piperidin-1-ylethoxy)phenyl)propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 20 and Intermediate 55 gave after recrystallization from CH_3CN the title compound as white crystals in a 50% yield.

MP: 210 °C.

Analysis for $C_{35}H_{37}N_3O_3$:

Calculated: C,76.75; H,6.81; N,7.67;

Found: C,76.68; H,7.11; N,7.93%.

$[\alpha]_D^{18.9}$ = -290 (c = 0.4, $CHCl_3$).

Example 189

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)-3-(4-(2-piperidin-1-ylethoxy)phenyl]propene-1-one

The same method as employed in the preparation of Example 20 but starting from Intermediate 55 gave after recrystallization from MeOH:H_2O the title compound as a beige solid in a 32% yield.

MP: 102 °C.

Analysis for $C_{34}H_{35}N_3O_4$. 0.6MeOH:

Calculated: C,73.05; H,6.63; N,7.39;

Found: C,73.24; H,6.87; N,7.02%.

Example 190

(E)-(R)-[2-(4-{3-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-oxopropenyl}phenoxy)ethyl]methylcarbamic acid, tertbutyl ester

The same method as employed in the preparation of Example 20 but starting from Intermediate 20 and Intermediate 56 gave the title compound as a yellow powder in a 95% yield.

MP: 110 °C.

Analysis for $C_{36}H_{39}N_3O_5$. $0.3H_2O$:

Calculated: C,72.17; H,6.66; N,7.01;

Found; C,71.9; H,6.86; N,7.17%.

Example 191

(E)-(R)-1-[1-(2,3-Dihydrobenzofuran-5-yl)-1,3,4,9-tetrahydro-β-carbolin-2-yl]-3-[4-(2-methylaminoethoxy)phenyl]propene-1-one

A solution of Example 190 (0.33 g, 0.55 mmol) in DCM (30 mL) was treated with zinc bromide (0.63 g, 5 equiv.) for 16 hours at 30 °C. A gummy solid was formed. Extraction with DCM:MeOH, washing with water, drying over Na_2SO_4 and recrystallization from iPrOH gave the title compound as white crystals in a 98% yield.

MP: 145 °C.

Analysis for $C_{31}H_{31}N_3O_3$. $0.2H_2O$:

Calculated: C,74.89; H,6.37; N,8.45;

Found: C,74.90; H,6.70; N,8.49%.

$[\alpha]_D^{20}$= -337 (c = 0.4, MeOH).

Example 192

(E)-1-[1-(3,4-Methylenedioxyphenyl)-1,3,4,9-tetrahydro-β-carbolin-2-yl)-3-(4-(2-piperidin-1-ylethoxy)phenyl]propene-1-one

The same method as employed in the preparation of Example 1 but starting from Intermediate 13 gave after recrystallization from MeOH:H_2O the title compound as a beige solid in a 32% yield.

MP: 102 °C.

Analysis for $C_{34}H_{35}N_3O_4$. 0.6MeOH:

Calculated: C,73.05; H,6.63; N,7.39;

Found: C,73.24; H,6.87; N,7.02%.

Inhibitory effect on cGMP-PDE

cGMP-PDE activity of compounds of the present invention was measured using a one-step assay adapted from Wells at al. (Wells, J. N., Baird, C. E., Wu, Y. J. and Hardman, J. G., Biochim. Biophys. Acta 384, 430 (1975)). The reaction medium contained 50mM Tris-HCl,pH 7.5, 5mM Mg-acetate, 250µg/ml 5'-Nucleotidase, 1mM EGTA and 0.15µM 8-[H^3]-cGMP. The enzyme used was a human recombinant PDE 5 (ICOS, Seattle USA).

Compounds of the invention were dissolved in DMSO finally present at 2% in the assay. The incubation time was 30 minutes during which the total substrate conversion did not exceed 30%.

The IC_{50} values for the compounds examined were determined from concentration-response curves using typically concentrations ranging from 10nM to 10µM. Tests against other PDE enzymes using standard methodology also showed that compounds of the invention are highly selective for the cGMP specific PDE enzyme.

cGMP level measurements

Rat aortic smooth muscle cells (RSMC) prepared according to Chamley et al. in Cell Tissue Res. 177, 503 - 522 (1977) were used between the 10th and 25th

passage at confluence in 24-well culture dishes. Culture media was aspirated and replaced with PBS (0.5ml) containing the compound tested at the appropriate concentration. After 30 minutes at 37°C, particulates guanylate cyclase was stimulated by addition of ANF (100nM) for 10 minutes. At the end of incubation, the medium was withdrawn and two extractions were performed by addition of 65% ethanol (0.25ml). The two ethanolic extracts were pooled and evaporated until dryness, using a Speed-vac system. cGMP was measured after acetylation by scintillation proximity immunoassay (AMERSHAM). The EC_{50} values are expressed as the dose giving half of the stimulation at saturating concentrations

Biological data

The compounds according to the present invention were typically found to exhibit an IC_{50} value of less than 500 nM and an EC_{50} value of less than 5 µM. In vitro test data for representative compounds of the invention is given in the following table:

Table 1. *In vitro* results

Example No.	IC_{50} nM	EC_{50} µM
14	5	0.45
25	72	0.3
28	55	0.3
31	4	1
55	40	0.4
61	20	1.8
140	2	0.1
142	18	1.5
156	15	< 1
164	11	1.5
165	9	< 1
177	12	< 1
184	44	3
180	25	3.5
181	9	2
183	24	2
182	2	< 1
188	24	< 1
191	8	< 1

The hypotensive effects of compounds according to the invention as identified in Table 2 were studied in conscious spontaneously hypertensive rats (SHR). The compounds were admnistered orally at a dose of 5 mg/kg in a mixture of 5% DMF and 95% olive oil. Blood pressure was measured from a catheter inserted in the carotid artery and recorded for 5 hours after administration. The results are expressed as Area Under the Curve (AUC from 0 to 5 hours, mmHg.hour) of the fall in blood pressure over time.

Table 2. *In vivo* results

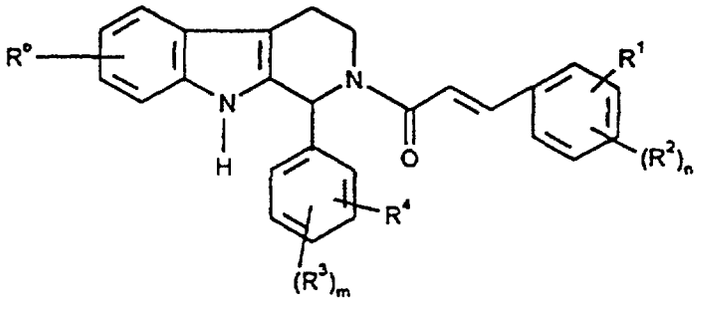
Example No.	AUC PO (mmHg.h)
14	128
25	72
26	102
28	114
31	86
55	97
61	95
112	71
122	76
140	105
142	74
156	57
175	52
177	100
181	77
188	86
191	84

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any novel feature or combination of features described herein. They may take the form of product, composition, process or use claims and may include, by way of example and without limitation, the following claim:

* C L M S *

CLAIM

1. A compound of formula (I)



(I)

wherein

R^0 represents -hydrogen or -halogen;

R^1 is selected from the group consisting of:

-hydrogen,

$-NO_2$,

-trifluoromethyl,

-trifluoromethoxy,

-halogen,

-cyano,

a 5- or 6- membered heterocyclic group containing at least one heteroatom selected from oxygen, nitrogen and sulphur (optionally substituted by - $C(=O)OR^a$ or C_{1-4}alkyl),

-C_{1-6}alkyl optionally substituted by -OR^a,

-C_{1-3}alkoxy,

-$C(=O)R^a$,

-O-$C(=O)R^a$,

-$C(=O)OR^a$,

-C_{1-4}alkylene $C(=O)OR^a$,



-O-C_{1-4}alkylene -C(=O)OR^a,
-C_{1-4}alkylene-O-C_{1-4}alkylene-C(=O)OR^a,
-C(=O)$NR^aSO_2R^c$,
-C(=O)C_{1-4}alkylene Het, wherein Het represents 5- or 6-membered heterocyclic group as defined above,
-C_{1-4}alkylene NR^aR^b,
-C_{2-6}alkenyleneNR^aR^b,
-C(=O)NR^aR^b,
-C(=O)NR^aR^c,
-C(=O)NR^aC_{1-4}alkylene OR^b
-C(=O)NR^aC_{1-4}alkylene Het, wherein Het represents a 5- or 6-membered heterocyclic group as defined above,
-OR^a
-⊖C_{2-4}alkylene NR^aR^b,
-OC_{1-4}alkylene-$CH(OR^a)CH_2$ NR^aR^b,
-O-C_{1-4}alkylene Het, wherein Het represents a 5- or 6- membered heterocyclic group as defined above,
-O-C_{2-4}alkylene-OR^a,
-O-C_{2-4}alkylene-NR^a-C(=O)-OR^b,
-NR^aR^b,
-NR^aC_{1-4}alkyleneNR$^aR^b$,
-$NR^aC(=O)R^b$,
-$NR^aC(=O)NR^aR^b$,
-$N(SO_2C_{1-4}alkyl)_2$,
-$NR^a(SO_2C_{1-4}alkyl)$,
-$SO_2NR^aR^b$, and
-OSO_2trifluoromethyl;
R^2 is selected from the group consisting of:
-hydrogen,
-halogen,
-OR^a,
-C_{1-6} alkyl,
-NO_2, and
-NR^aR^b,



or R^1 and R^2, together form a 3- or 4- membered alkylene or alkenylene chain, optionally containing at least one heteratom ;

R^3 is selected from the group consisting of:

-hydrogen,

-halogen,

$-NO_2$,

-trifluoromethoxy,

$-C_{1-6}$alkyl, and

$-C(=O)OR^a$;

R^4 is hydrogen,

or R^3 and R^4 together form a 3- or 4- membered alkylene or alkenylene chain, optionally containing at least one heteratom;

R^a and R^b, which may be the same or different, are independently selected from hydrogen and C_{1-6}alkyl;

R^c represents phenyl or C_{4-6}cycloalkyl, which phenyl or C_{4-6}cycloalkyl can be optionally substituted by one or more halogen atoms, one or more $-C(=O)OR^a$ or one or more $-OR^a$;

n is an integer selected from 1, 2 and 3;

m is an integer selected from 1 and 2;

and pharmaceutically acceptable salts and solvates thereof.

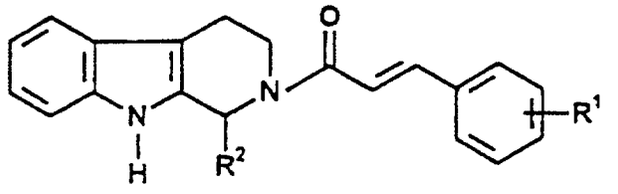
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* C L M S *

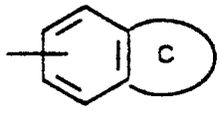
2. A compound represented by formula (I)



(I)

wherein

R^1 is selected from the group consisting of -OH, -OC_{2-4}alkylene NR^aR^b and -O-C_{1-4}alkylene Het, wherein Het represents a 5- or 6- membered heterocyclic group containing at least one heteroatom selected from oxygen, nitrogen, and sulphur, optionally substituted by C_{1-4}alkyl;

R^2 represents  wherein C represents a 5- or 6-membered ring which may be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur and nitrogen, optionally substituted by C_{1-4}alkyl;

R^a and R^b, which may be the same or different, are independently selected from hydrogen and C_{1-6}alkyl;

and pharmaceutically acceptable salts and solvates thereof.

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