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(54) **Title:** CHROMENONES AND THEIR USE AS MODULATORS OF METABOTROPIC GLUTAMATE RECEPTORS

(57) **Abstract:** The invention relates to chromenone derivatives as well as their pharmaceutically acceptable salts. The invention further relates to a process for the preparation of such compounds. The compounds of the invention are Group I mGluR modulators and are therefore useful for the control and prevention of acute and/or chronic neurological disorders.

WO 2007/045876 A1

CHROMENONES AND THEIR USE AS MODULATORS OF METABOTROPIC GLUTAMATE RECEPTORS

FIELD OF THE INVENTION

The present invention is concerned with novel metabotropic glutamate receptor (mGluR) modulators, methods for their synthesis and the treatment and/or prevention of neurological disorders by administration of such substances.

BACKGROUND OF THE INVENTION

Neuronal stimuli are transmitted by the central nervous system (CNS) through the interaction of a neurotransmitter released by a neuron, which neurotransmitter has a specific effect on a neuroreceptor of another neuron.

L-glutamic acid is considered to be the major excitatory neurotransmitter in the mammalian CNS, consequently playing a critical role in a large number of physiological processes. Glutamate-dependent stimulus receptors are divided into two main groups. The first group comprises ligand-controlled ion channels whereas the second comprises metabotropic glutamate receptors (mGluR). Metabotropic glutamate receptors are a subfamily of G-protein-coupled receptors (GPCR). There is increasing evidence for a peripheral role of both ionotropic and metabotropic glutamate receptors outside of the CNS e.g., in chronic pain states.

At present, eight different members of these mGluRs are known. On the basis of structural parameters such as sequence homology, the second messenger system utilized by these receptors and their different affinity to low-molecular weight compounds, these eight receptors can be divided into three groups: mGluR1 and mGluR5 belong to Group I which couple to phospholipase C and their activation leads to intracellular calcium-ion mobilization. Both mGluR2 and mGluR3 belong to Group II and mGluR4, mGluR6, mGluR7 and mGluR8 belong to Group III, which couple to adenyl

cyclase with their activation causing a reduction in second messenger cAMP and as such a dampening of the neuronal activity.

Group I mGluR modulators have been shown to modulate the effects of the presynaptically released neurotransmitter glutamate via postsynaptic mechanisms. Moreover, as these modulators can be both positive and/or negative Group I mGluR modulators, such modulators may increase or inhibit the effects of these metabotropic receptors. Since a variety of pathophysiological processes and disease states affecting the CNS are thought to be related to abnormal glutamate neurotransmission, and Group I mGluRs are shown to be expressed in several areas of the CNS, modulators of these receptors could be therapeutically beneficial in the treatment of CNS diseases.

Therefore, group I mGluR modulators may be administered to provide neuroprotection in acute and chronic pathological conditions such as: AIDS-related dementia, Alzheimer's disease, Creutzfeld-Jakob's syndrome, bovine spongiform encephalopathy (BSE) or other prion related infections, diseases involving mitochondrial dysfunction, diseases involving ß-amyloid and/or tauopathy such as Down's syndrome, hepatic encephalopathy, Huntington's disease, motor neuron diseases such as amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), olivoponto-cerebellar atrophy, post-operative cognitive deficit (POCD), Parkinson's disease, Parkinson's dementia, mild cognitive impairment, dementia pugilistica, vascular and frontal lobe dementia, cognitive impairment, eye injuries or diseases (e.g. glaucoma, retinopathy, macular degeneration), head and brain and spinal cord injuries / trauma, hypoglycaemia, hypoxia (e.g. perinatal), ischaemia (e.g. resulting from cardiac arrest, stroke, bypass operations or transplants), convulsions, epilepsy, temporal lope epilepsy, glioma and other tumours, inner ear insult (e.g. in tinnitus, sound- or drug-induced), L-Dopa-induced and tardive dyskinesias.

Other indications in this context include a symptomatological effect on the following conditions: abuse and addiction (nicotine, alcohol, opiate, cocaine, amphetamine, obesity and others), amyotrophic lateral sclerosis (ALS), anxiety and panic disorders, attention deficit hyperactivity disorder (ADHD), restless leg syndrome, hyperactivity in children, autism, convulsions, epileptic convulsions, epilepsy, temporal lobe epilepsy, dementia (e.g. in Alzheimer's disease, Korsakoff syndrome, vascular dementia, HIV infections), major depressive disorder or depression (including that resulting from Borna virus infection) and bipolar manic-depressive disorder, drug tolerance (e.g. to opioids), movement disorders, dystonia, dyskinesia (e.g. L-Dopa-induced, tardive dyskinesia or in Huntington's disease), fragile-X syndrome, chorea, Huntington's chorea, irritable bowel syndrome (IBS), migraine, multiple sclerosis (MS), muscle spasms, pain (chronic and acute, e.g. inflammatory pain, neuropathic pain, allodynia, hyperalgesia, nociceptive pain), Parkinson's disease, post traumatic stress disorder, schizophrenia (positive and negative symptoms), spasticity, tinnitus, Tourette's syndrome, urinary incontinence , vomiting, pruritic conditions (e.g. pruritis), sleep disorders, micturition disorders, neuromuscular disorder in the lower urinary tract, gastroesophageal reflux disease (GERD), lower esophageal sphincter (LES) disease, functional gastrointestinal disorders, dyspepsia, regurgitation, respiratory tract infection, bulimia nervosa, chronic laryngitis, asthma (e.g. reflux-related asthma), lung disease, eating disorders, obesity, obesity-related disorders, binge eating disorders, agoraphobia, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, anxiety disorder, posttraumatic stress disorder, social phobia, substance-induced anxiety disorder, delusional disorder, schizoaffective disorder, schizophreniform disorder, substance-induced psychotic disorder and delirium.

Yet further indications for Group I mGluR modulators include those indications wherein a particular condition does not necessarily exist but wherein a particular physiological parameter may be improved through

administration of the instant compounds, for example cognitive enhancement.

Positive modulators may be particularly useful in the treatment of positive and negative symptoms in schizophrenia and cognitive deficits in various forms of dementia and mild cognitive impairment.

THE PRESENT INVENTION

We have determined that certain chromenones are Group I mGluR modulators. Therefore, these substances may be therapeutically beneficial in the treatment of conditions which involve abnormal glutamate neurotransmission or in which modulation of Group I mGluR receptors results in therapeutic benefit. These substances are preferably administered in the form of a pharmaceutical composition, wherein they are present together with one or more pharmaceutically acceptable diluents, carriers, or excipients.

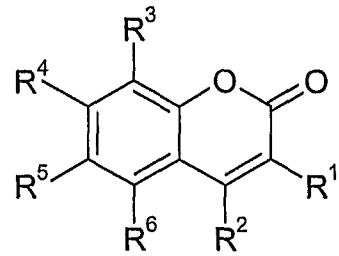
OBJECTS OF THE INVENTION

It is an object of the present invention to provide novel pharmaceutical compounds which are chromenone Group I mGluR modulators and pharmaceutical compositions thereof. It is a further object of the invention to provide a novel method of treating, eliminating, alleviating, palliating, or ameliorating undesirable CNS disorders which involve abnormal glutamate neurotransmission by employing a compound of the invention or a pharmaceutical composition containing the same. An additional object of the invention is the provision of a process for producing the chromenone active principles. Yet additional objects will become apparent hereinafter, and still further objects will be apparent to one skilled in the art.

SUMMARY OF THE INVENTION

What we therefore believe to be comprised by our invention may be summarized inter alia in the following words:

A compound of Formula I



I

wherein

R^1 represents hydrogen, C_{1-6}alkyl, aryl, heteroaryl or $-C(=O)-R^{10}$;

R^2 represents hydrogen, C_{1-6}alkyl, aryl, heteroaryl, arylC_{1-6} alkyl, heteroarylC_{1-6}alkyl, cyano, nitro, halogen, hydroxy or C_{2-6} alkoxy;

or R^1 and R^2 together represent $-W^1-X^1-Y^1-Z^1-$,
wherein
W^1 represents a single bond, oxygen, sulfur, $-NR^7-$ or $-CR^8R^9-$, and
X^1, Y^1 and Z^1 each independently represents oxygen, sulfur, $-NR^7-$ or $-CR^8R^9-$;

R^3 represents hydrogen, C_{1-6}alkyl, aryl, heteroaryl, nitro, amino, C_{1-6} alkoxy, halogen, hydroxy, $-C(=O)-R^{10}$, $-N(R^{11})-C(=O)-R^{10}$, $-N(R^{11})SO_2-R^{10}$, $-N(R^{11})C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C_{1-6}$alkylene-$C(=O)N(R^{11})_2$, $-N(R^{11})C(=S)N(R^{11})_2$, $-N(R^{11})C(=O)N(R^{11})_2$, C_{1-6}alkylamino, di-C_{1-6} alkylamino, cycloC_{3-12}alkylamino, cycloC_{3-12} alkylaminoC_{1-6}alkyl, cycloC_{3-12}alkyl-C_{1-6}alkylamino, di-C_{1-6} alkylaminoC_{1-6}alkyl, C_{1-6}alkoxy-C_{2-6} alkylamino, arylamino, arylC_{1-6} alkylamino, N-cycloC_{3-12} alkyl-N-C_{1-6} alkylamino, N-aryl-N-C_{1-6} alkylamino, N-arylC_{1-6}alkyl-N-C_{1-6} alkylamino, pyrrolidino, piperidino, 4-arylpiperidino, 4-heteroarylpiperidino, morpholino, morpholinoC_{1-6}

alkyl, piperazino, 4-C_{1-6}alkylpiperazino, 4-arylpiperazino, hexamethyleneimino, heteroarylamino or heteroarylC_{1-6} alkylamino;

R^4 represents hydrogen, halogen, nitro, amino, hydroxy, $-OR^{12}$, $-SO_3CF_3$, C_{1-6}alkyl, cycloC_{3-12}alkyl, cycloC_{3-12}alkyl-C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6}alkynyl, aryl, biaryl, arylC_{1-6}alkyl, arylC_{2-6}alkenyl, arylC_{2-6} alkynyl, heteroaryl, heteroarylC_{1-6}alkyl, heteroarylC_{2-6}alkenyl, heteroarylthio, 2,3-dihydro-1H-indenyl, C_{1-6}alkoxyC_{1-6}alkyl, aryloxyarylC_{1-6}alkoxy, C_{1-6}alkylthio, C_{4-6} alkenylthio, cycloC_{3-12} alkylthio, cycloC_{3-12}alkyl-C_{1-6}alkylthio, cycloC_{3-12} alkyl-C_{3-6}alkenylthio, C_{1-6}alkoxyC_{1-6}alkylthio, C_{1-6}alkoxyC_{3-6}alkenylthio, arylC_{3-6}alkenylthio, heteroarylC_{1-6}alkylthio, C_{1-6}alkylsulfonyl, cycloC_{3-12} alkyl-C_{1-6} alkylsulfonyl, arylC_{1-6}alkylsulfonyl, C_{1-6}alkylamino, di-C_{1-6} alkylamino, cycloC_{3-12}alkylamino, C_{1-6}alkoxycycloC_{3-12}alkylamino, cycloC_{3-12} alkylC_{1-6} alkylamino, di-C_{1-6}alkylaminoC$_{1-6}$alkyl, C_{1-6}alkoxy-C_{2-6} alkylamino, arylamino, arylC_{1-6}alkylamino, N-cycloC_{3-12}alkyl-N-C_{1-6}alkylamino, N-aryl-N-C_{1-6}alkylamino, N-arylC_{1-6}alkyl-N-C_{1-6} alkylamino, 2-indanylamino, tetrahydrofuryl, pyrrolidino, piperidino, 4-arylpiperidino, 4-heteroarylpiperidino, morpholino, piperazino, 4-C_{1-6} alkylpiperazino, 4-arylpiperazino, hexamethyleneimino, benzazepinyl, 1,3-dihydro-2H-isoindol-2-yl, heteroarylC_{1-6}alkoxy, heteroarylamino, heteroarylC_{1-6} alkylamino, $-N(R^{11})C(=O)-R^{10}$, $-N(R^{11})SO_2-R^{10}$, $-N(R^{11})C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C_{1-6}$alkylene-$C(=O)N(R^{11})_2$, $-S-C(=O)N(R^{11})_2$ or $-O-C(=O)-R^{10}$;

R^5 represents hydrogen, halogen, nitro, amino, hydroxy, C_{1-6}alkoxy, C_{1-6} alkyl, C_{1-6}alkylamino, hydroxyC_{1-6}alkoxy, aryl, heteroaryl, OCF_3, $-N(R^{11})C(=O)-R^{10}$, $-N(R^{11})SO_2-R^{10}$, $-N(R^{11})C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C_{1-6}$alkylene-$C(=O)N(R^{11})_2$, $-N(R^{11})C(=S)N(R^{11})_2$, $-N(R^{11})C(=O)N(R^{11})_2$, $-O-SO_2R^{10}$ or $-C(=O)R^{10}$;

R^6 represents hydrogen, C_{1-6}alkyl, aryl, heteroaryl, halogen, hydroxy or C_{1-6}alkoxy;

R^7 represents hydrogen, C_{1-6}alkyl, aryl, heteroaryl, arylC_{1-6} alkyl, C_{1-6} alkoxy, halogen, hydroxy, cyano, nitro, hydroxyC_{1-6}alkyl, cycloC_{3-12} alkoxy, C_{1-6}alkylamino, di-C_{1-6}alkylamino, cycloC_{3-12}alkylamino, cycloC_{3-12}alkyl-C_{1-6}alkylamino, di-C_{1-6}alkylaminoC_{1-6}alkyl, arylamino, arylC_{1-6}alkyl, N-aryl-N-C_{1-6}alkylamino, pyrrolidino, piperidino, 4-C_{1-6} alkylpiperazino, morpholino, hexamethyleneimino, pyrrolidinylC_{1-6} alkyl, piperidinylC_{1-6}alkyl, morpholinylC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6} alkylthio, C_{1-6}alkylaminosulfonyl or di-C_{1-6}alkylaminosulfonyl;

R^8 and R^9 each independently represent hydrogen, C_{1-6}alkyl, aryl, heteroaryl, arylC_{1-6} alkyl, C_{1-6}alkoxy, halogen, hydroxy, cyano, nitro, amino or cycloC_{3-12}alkyl;

R^{10} represents hydrogen, C_{1-6}alkyl, cycloC_{3-12}alkyl (e.g. adamantyl), aryl, heteroaryl or carboxyC_{1-6}alkyl;

R^{11} represents hydrogen, C_{1-6}alkyl, cycloC_{3-12}alkyl (e.g. adamantyl), aryl, heteroaryl, carboxyC_{1-6}alkyl or C_{1-6}alkylcarbonyl;

R^{12} represents C_{1-6}alkyl optionally substituted by one or more (e.g. 1, 2, 3, 4 or more) substituents selected from hydroxy, cycloC_{3-12}alkyl, C_{1-6} alkylamino, di-C_{1-6}alkylamino, morpholino, halogen, arylamino and -C(=O)R^{13}; heteroaryl; cycloC_{3-12} alkyl; C_{1-6}alkoxycycloC_{3-12}alkyl; arylC_{1-6} alkyl; aryloxyarylC_{1-6}alkyl and C_{2-6} alkenyl; and

R^{13} represents amino, pyrrolidino or piperidino;

or if R^1 and R^2 represent -W^1-X^1-Y^1-Z^1- and W^1 does not represent a single bond,

R^3 and R^4, R^4 and R^5 or R^5 and R^6 together with the carbon atoms to which they are attached may form a 5-6 membered ring which may be saturated or unsaturated, wherein the ring

may optionally have 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, and wherein the ring may be optionally substituted by one or more (e.g. 1, 2, 3, 4 or more) substituents selected from hydrogen, C_{1-6} alkyl, cycloC_{3-12} alkyl, aryl, heteroaryl, arylC_{1-6}alkyl, carboxyC_{1-6} alkyl, alkylcarbonyl, arylcarbonyl, oxo, thioxo, C_{1-6}alkoxy, C_{1-6} alkylthio, arylC_{1-6} alkylthio, arylC_{1-6}alkoxy, morpholino, C_{3-6} cycloalkylamino, pyrrolidino, piperidino, hexamethyleneimino, piperazinyl, N-C_{1-6} alkylpiperazinyl and arylamino;

wherein the term "C_{1-6}alkyl", unless otherwise specified, denotes straight or branched chain groups which may be unsubstituted or substituted by one or more (e.g. 1, 2, 3, 4 or more) fluorine, chlorine and/or bromine atoms; the term "C_{1-6}alkoxy" denotes straight or branched chain groups which may be unsubstituted or substituted by one or more (e.g. 1, 2, 3, 4 or more) fluorine, chlorine and/or bromine atoms; the term "cycloC_{3-12} alkyl" denotes monocyclic, bicyclic or tricyclic groups which may be unsubstituted or substituted by one or more (e.g. 1, 2, 3, 4 or more) fluorine, chlorine and/or bromine atoms; the term "aryl" denotes phenyl or naphthyl or phenyl substituted by one or more (e.g. 1, 2, 3, 4 or more) substituents, which may be the same or different, selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, cycloC_{3-12}alkyl, hydroxy, halogen, cyano, nitro, C_{1-6}alkoxycarbonyl, amino, C_{1-6}alkylamino, di-C_{1-6}alkylamino, N-cycloC_{3-12}alkyl-N-C_{1-6}alkylamino, azetidinyl, pyrrolyl, piperidinyl, morpholinyl, 4-C_{1-6} alkylpiperazinyl, tetrazolyl, oxazolyl, furyl, thiophenyl, isoxazolyl, thiazolyl, imidazolyl, oxadiazolyl, pyridinyl, pyrimidyl and C_{1-6} alkylenedioxy; and the term "heteroaryl" denotes an aromatic 5-6 membered ring containing from one to four heteroatoms selected from oxygen, sulfur and nitrogen, or a bicyclic group comprising a 5-6 membered ring containing from one to four heteroatoms selected from oxygen, sulfur and nitrogen fused with a benzene ring or a 5-6 membered aromatic ring containing from one to four heteroatoms

selected from oxygen, sulfur and nitrogen, wherein the heteroaryl group may be optionally substitued by one or more (e.g. 1, 2, 3, 4 or more) substituents, which may be the same or different, selected from C_{1-6}alkyl, C_{1-6}alkoxy, cycloC_{3-12}alkyl, hydroxy, halogen, cyano, nitro, C_{1-6}alkoxycarbonyl, amino, C_{1-6}alkylamino, di-C_{1-6}alkylamino, N-cycloC_{3-12}alkyl-N-C_{1-6}alkylamino, azetidinyl, pyrrolyl, piperazinyl, morpholinyl, 4-C_{1-6}alkylpiperazinyl, tetrazolyl, oxazolyl, furyl, thiophenyl, isoxazolyl, thiazolyl, imidazolyl, oxadiazolyl, pyridinyl, pyrimidyl and phenyl;

and optical isomers, pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof;

with the proviso that the compounds of Formula I do not include:
chromen-2-one,
2-chloro-3-isopropoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
3-(2-chlorobenzyloxy)-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-(2-chlorobenzyloxy)-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
3-(1-phenylethoxy)benzo[c]chromen-6-one,
8-hexyl-7-methoxy-2,3-dihydro-1H-cyclopenta[c]chromen-4-one,
2-chloro-3-methoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
3-hydroxy-4-piperidin-1-ylmethyl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-hydroxy-9-methyl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
6-chloro-7-hydroxy-4-trifluoromethylchromen-2-one,
2-chloro-3-hydroxy-4-morpholin-4-ylmethyl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-4-dimethylaminomethyl-3-hydroxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-ethyl-3-hydroxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2,3-dimethoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,

2-hydroxy-3-methoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-(2-methylallyloxy)-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
3-allyloxy-2-chloro-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-hydroxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-hexyl-3-methoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
8-chloro-7-isopropoxy-2,3-dihydro-1H-cyclopenta[c]chromen-4-one,
8-chloro-7-hydroxy-2,3-dihydro-1H-cyclopenta[c]chromen-4-one,
3-(adamantane-1-carbonyl)-6-methoxychromen-2-one,
3-(adamantane-1-carbonyl)-6-bromochromen-2-one,
3-(adamantane-1-carbonyl)chromen-2-one,
3-isopropoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-(3-methylbut-2-enyloxy)-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
8-isopropoxy-1,2,3,4-tetrahydrochromeno[3,4-c]pyridin-5-one,
3-amino-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
3-isopropylamino-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
3-amino-2-chloro-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
6-chloro-3-imidazo[1,2-a]pyridin-2-ylchromen-2-one,
3-pyridin-2-yl-3,4,7,8,9,10-hexahydro-2H-1,5-dioxa-3-azachrysen-6-one or
6-chloro-3-imidazo[1,2-a]pyridin-2-ylchromen-2-one.

Such a compound of Formula I wherein R^1 represents hydrogen or $-C(=O)-R^{10}$.

Such a compound of Formula I wherein R^{10} represents adamantyl.

Such a compound of Formula I wherein R^2 represents hydrogen, aryl, heteroaryl or C_{1-6}alkyl.

Such a compound of Formula I wherein R^2 represents phenyl or pyridyl.

Such a compound of Formula I wherein R^1 and R^2 together represent

$-W^1-X^1-Y^1-Z^1-$,

wherein

W^1 represents a single bond or $-CR^8R^9-$, and X^1, Y^1, and Z^1 each independently represent $-CR^8R^9-$, wherein R^8 and R^9 are each independently selected from hydrogen, C_{1-6}alkyl, aryl and heteroaryl.

Such a compound of Formula I wherein R^8 represents hydrogen and R^9 represents hydrogen, C_{1-6}alkyl, aryl or heteroaryl.

Such a compound of Formula I wherein R^9 represents hydrogen, methyl, ethyl, trifluoromethyl, *t*-butyl, phenyl or pyridyl.

Such a compound of Formula I wherein R^9 represents hydrogen, methyl or trifluoromethyl.

Such a compound of Formula I wherein R^3 represents hydrogen, C_{1-6} alkyl, morpholinoC_{1-6}alkyl, amino, nitro, $-N(R^{11})C(=O)N(R^{11})_2$, $-N(R^{11})SO_2-R^{10}$, C_{1-6} alkylamino or $-N(R^{11})C(=O)-R^{10}$.

Such a compound of Formula I wherein R^4 represents halogen, hydroxy, OR^{12}, $-S-C(=O)N(R^{11})_2$, $-C(=O)N(R^{11})_2$, C_{1-6}alkylthio, C_{1-6} alkylsulfonyl, morpholino, pyrrolidino, arylC_{1-6}alkylamino, $-N(R^{11})C(=O)-R^{10}$, heteroarylthio, $-O-C(=O)-R^{10}$, di-C_{1-6}alkylamino or heteroaryl.

Such a compound of Formula I wherein R^4 represents halogen, OR^{12}, $-S-C(=O)N(R^{11})_2$, $-C(=O)N(R^{11})_2$, C_{1-6}alkylthio or di-C_{1-6} alkylamino.

Such a compound of Formula I wherein R^{12} represents C_{1-6}alkyl optionally substituted by one or more substituents selected from hydroxy, di-C_{1-6} alkylamino, morpholino, halogen, cycloC_{3-12}alkyl, arylamino and $-C(=O)R^{13}$ (e.g. as in CF_3 or CHF_2); cycloC_{3-12}alkyl; C_{1-6}alkoxycycloC_{3-12}alkyl or heteroaryl.

Such a compound of Formula I wherein R^4 represents bromo, methoxy, *iso*-propoxy, -C(=O)N(R^{11})$_2$, *iso*propylsulfanyl, difluoromethoxy, dimethylamino or diethylamino.

Such a compound of Formula I wherein R^{11} represents hydrogen or C_{1-6} alkyl.

Such a compound of Formula I wherein R^{11} represents methyl.

Such a compound of Formula I wherein R^5 represents hydrogen, nitro, halogen, C_{1-6}alkyl, hydroxy C_{1-6}alkoxy, -C(=O)-R^{10}, -N(R^{11})SO_2-R^{10}, -N(R^{11})C(=O)-R^{10} or C_{1-6}alkylamino.

Such a compound of Formula I wherein R^5 represents hydrogen, nitro, chloro or ethyl.

Such a compound of Formula I wherein R^6 represents hydrogen or C_{1-6} alkyl.

Such a compound of Formula I wherein R^3 and R^4 together with the carbon atoms to which they are attached form a 5-6 membered ring which may be saturated or unsaturated, wherein the ring has 1 or 2 heteroatoms selected from oxygen and nitrogen and may optionally be substituted by one or more substituents selected from C_{1-6}alkyl, C_{1-6}alkylthio, C_{1-6}alkoxy, oxo, arylC_{1-6} alkyl, aryl, arylC_{1-6}alkylthio and morpholino.

Such a compound of Formula I wherein R^4 and R^5 together with the carbon atoms to which they are attached form a 5-6 membered ring which may be saturated or unsaturated, wherein the ring has 1 or 2 heteroatoms selected from oxygen and nitrogen and may optionally be substituted by one or more substituents selected from heteroaryl, piperazinyl, N-C_{1-6}alkylpiperazinyl, arylamino, arylC_{1-6}alkylthio, morpholino, C_{1-6}alkylthio, oxo, thioxo, arylcarbonyl, aryl, C_{1-6}alkoxy, arylC_{1-6}alkyl and cycloC_{3-12}alkyl.

Such a compound of Formula I wherein R^5 and R^6 together with the carbon atoms to which they are attached form a 5-6 membered ring which may be saturated or unsaturated, wherein the ring has 1 or 2 heteroatoms selected from oxygen and nitrogen and may optionally be substituted by one or more substituents selected from heteroaryl, oxo, thioxo, aryl, C_{1-6}alkyl and C_{1-6} alkoxy.

Such a compound of Formula I selected from:

N-acetyl-N-(2-chloro-3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-4-yl)acetamide,

N-(2-chloro-3-isopropxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-4-yl)benzamide,

N-(3-isopropxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-2-yl)isobutyramide,

N-(2-chloro-3-isopropxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-4-yl)formamide,

N-(2-chloro-3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-4-yl)succinamic acid,

dimethylthiocarbamic acid 6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-3-yl ester,

S-(N,N-dimethylcarbamoyl)-2-chloro-8-phenyl-3-thio-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,

2-chloro-3-(pyridin-2-ylsulfanyl)-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,

S-(N,N-dimethylcarbamoyl)-8-ethyl-2-chloro-6-oxo-3-thio-7,8,9,10-tetrahydro-6H-benzo[c]chromen-6-one, and

12-chloro-16-isopropylsulfanyl-1,2,3,4-tetrahydro-7,17-dioxa-15-azacyclopenta[a]phenanthren-6-one.

Such a compound of Formula I selected from:

3-(adamantane-1-carbonyl)-7-methoxychromen-2-one,

3-(adamantane-1-carbonyl)-7-dimethylaminochromen-2-one,

3-(adamantane-1-carbonyl)-7-diethylaminochromen-2-one,

3-(adamantane-1-carbonyl)-7-bromochromen-2-one,
2-chloro-3-isopropoxy-9-methyl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-isopropoxy-8-trifluoromethyl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
dimethylthiocarbamic acid S-(2-chloro-9-methyl-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-3-yl) ester,
dimethylthiocarbamic acid S-(2-chloro-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-3-yl) ester,
3-isopropoxy-2-nitro-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-isopropylsulfanyl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-ethyl-3-isopropoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-difluoromethoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
7-isopropoxy-8-nitro-2,3-dihydro-1H-cyclopenta[c]chromen-4-one, and
2-chloro-3-isopropoxy-7-methyl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one.

Moreover, a compound of Formula I as hereinbefore defined or an optical isomer, pharmaceutically acceptable salt, ester, hydrate, solvate or polymorph thereof, subject to the modified proviso that the compound of Formula I may additionally be 2-chloro-3-methoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one, 2-chloro-3-isopropoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one or 8-chloro-7-isopropoxy-2,3-dihydro-1H-cyclopenta[c]chromen-4-one, for use as a medicament.

Moreover, a pharmaceutical composition comprising as active ingredient a compound of the invention as hereinbefore defined, together with one or more pharmaceutically acceptable excipients or vehicles.

Moreover, use of a compound of the invention as hereinbefore defined but not subject to the foregoing proviso to Formula I as or in the manufacture of a medicament for prevention and/or treatment of a condition associated with

abnormal glutamate neurotransmission or in which modulation of Group I mGluR receptors results in therapeutic benefit or for enhancing cognition.

Furthermore, a method for treating or preventing a condition or disease associated with abnormal glutamate neurotransmission or a method for modulating Group I mGluR receptors to achieve therapeutic benefit, or a method for enhancing cognition, such method comprising administering to a living animal, including a human, a therapeutically effective amount of a compound of the invention as hereinbefore defined but not subject to the foregoing proviso to Formula **I**.

Such a use or method wherein the condition associated with abnormal glutamate neurotransmission, or wherein modulation of mGluR receptors results in therapeutic benefit, is selected from: AIDS-related dementia, Alzheimer's disease, Creutzfeld-Jakob´s syndrome, bovine spongiform encephalopathy (BSE) or other prion related infections, diseases involving mitochondrial dysfunction, diseases involving ß-amyloid and/or tauopathy such as Down's syndrome, hepatic encephalopathy, Huntington's disease, motor neuron diseases such as amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), olivoponto-cerebellar atrophy, post-operative cognitive deficit (POCD), Parkinson's disease, Parkinson's dementia, mild cognitive impairment, dementia pugilistica, vascular and frontal lobe dementia, cognitive impairment, eye injuries or diseases (e.g. glaucoma, retinopathy, macular degeneration), head and brain and spinal cord injuries / trauma, hypoglycaemia, hypoxia (e.g. perinatal), ischaemia (e.g. resulting from cardiac arrest, stroke, bypass operations or transplants), convulsions, epileptic convulsions, epilepsy, temporal lobe epilepsy, glioma and other tumours, inner ear insult (e.g. in tinnitus, sound- or drug-induced), L-Dopa-induced and tardive dyskinesias, abuse and addiction (nicotine, alcohol, opiate, cocaine, amphetamine, obesity and others), anxiety and panic disorders, attention deficit hyperactivity disorder (ADHD), restless leg syndrome, hyperactivity in children, autism, convulsions / epilepsy, dementia (e.g. in Alzheimer's disease, Korsakoff syndrome, vascular

dementia, HIV infections), major depressive disorder or depression (including that resulting from Borna virus infection) and bipolar manic-depressive disorder, drug tolerance (e.g. to opioids), movement disorders, dystonia, dyskinesia (e.g. L-Dopa-induced, tardive dyskinesia or in Huntington's disease), fragile-X syndrome, Huntington's chorea, chorea, irritable bowel syndrome (IBS), migraine, multiple sclerosis, muscle spasms, pain (chronic and acute, e.g. inflammatory pain, neuropathic pain, allodynia, hyperalgesia, nociceptive pain), Parkinson's disease, post traumatic stress disorder, schizophrenia (positive and negative symptoms), spasticity, tinnitus, Tourette´s syndrome, urinary incontinence, vomiting, pruritic conditions (e.g. pruritis), sleep disorders, micturition disorders, neuromuscular disorder in the lower urinary tract, gastroesophageal reflux disease (GERD), lower esophageal sphincter (LES) disease, functional gastrointestinal disorders, dyspepsia, regurgitation, respiratory tract infection, bulimia nervosa, chronic laryngitis, asthma (e.g. reflux-related asthma), lung disease, eating disorders, obesity and obesity-related disorders, binge eating disorders, agoraphobia, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, anxiety disorder, posttraumatic stress disorder, social phobia, substance-induced anxiety disorder, delusional disorder, schizoaffective disorder, schizophreniform disorder, substance-induced psychotic disorder, delirium, or for cognitive enhancement and/or neuroprotection.

Such a use or method wherein the condition associated with abnormal glutamate neurotransmission, or wherein modulation of mGluR receptors results in therapeutic benefit, is selected from: addiction, neuropathic pain, L-Dopa-induced and tardive dyskinesias, ALS, fragile-X syndrome, Parkinson's disease, anxiety disorders, epilepsy, positive and/or negative symptoms of schizophrenia, cognitive impairment, or for cognitive enhancement and/or neuroprotection.

Such a use or method wherein the condition associated with abnormal glutamate neurotransmission, or wherein modulation of mGluR receptors

results in therapeutic benefit, is selected from: neuropathic pain, diabetic neuropathic pain (DNP), cancer pain, pain related to rheumathic arthritis, inflammatory pain, L-Dopa-induced and tardive dyskinesias, Parkinson's disease, anxiety disorders, Huntington's chorea and/or epilepsy.

Such a use or method wherein the compound is administered in the form of a pharmaceutical composition thereof comprising the compound of Formula I in combination with one or more pharmaceutically-acceptable diluents, excipients, or carriers.

Such a use or method wherein the compound of Formula I is selected from:

3-(adamantane-1-carbonyl)-7-methoxychromen-2-one,
3-(adamantane-1-carbonyl)-7-dimethylaminochromen-2-one,
3-(adamantane-1-carbonyl)-7-diethylaminochromen-2-one,
3-(adamantane-1-carbonyl)-7-bromochromen-2-one,
2-chloro-3-isopropoxy-9-methyl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-isopropoxy-8-trifluoromethyl-7,8,9,10-tetrahydro-benzo[c]chromen-6-one,
dimethylthiocarbamic acid S-(2-chloro-9-methyl-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-3-yl) ester,
dimethylthiocarbamic acid S-(2-chloro-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-3-yl) ester,
3-isopropoxy-2-nitro-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-isopropylsulfanyl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-ethyl-3-isopropoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-difluoromethoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
7-isopropoxy-8-nitro-2,3-dihydro-1H-cyclopenta[c]chromen-4-one,
2-chloro-3-isopropoxy-7-methyl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-isopropoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-methoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one, and
8-chloro-7-isopropoxy-2,3-dihydro-1H-cyclopenta[c]chromen-4-one.

Specific compounds of Formula I within the present invention include but are not limited to:

6-chloro-7-(4-fluorobenzyloxy)-4-phenylchromen-2-one,
7-(3-phenoxybenzyloxy)-4-phenylchromen-2-one,
7-(4-fluorobenzyloxy)-4-phenylchromen-2-one,
6-chloro-7-isopropoxy-4-trifluoromethylchromen-2-one,
6-chloro-7-hydroxy-4-pyridin-2-ylchromen-2-one,
6-chloro-7-hydroxy-4-pyridin-3-ylchromen-2-one,
6-chloro-7-hydroxy-4-pyridin-4-ylchromen-2-one,
6-chloro-7-isopropoxy-4-pyridin-4-ylchromen-2-one,
6-chloro-7-isopropoxy-4-pyridin-2-ylchromen-2-one,
6-chloro-7-isopropoxy-4-pyridin-3-ylchromen-2-one,
3-(adamantane-1-carbonyl)-7-methoxychromen-2-one,
3-(adamantane-1-carbonyl)-7-dimethylaminochromen-2-one,
3-(adamantane-1-carbonyl)-7-diethylaminochromen-2-one,
3-(adamantane-1-carbonyl)-7-oxazol-2-ylchromen-2-one,
3-(adamantane-1-carbonyl)-7-bromochromen-2-one,
3-isopropoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
3-hydroxy-2-nitro-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
3-isopropoxy-2-nitro-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-amino-3-isopropoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2,2-dimethylpropionic acid 6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-3-yl ester,
2-chloro-3-(2-oxo-2-pyrrolidin-1-ylethoxy)-7,8,9,10-tetrahydrobenzo[c]chromen-6-onene,
2-chloro-3-(2-oxo-2-piperidin-1-ylethoxy)-7,8,9,10-tetrahydrobenzo[c]chromen-6-onene,
2-chloro-3-isopropoxy-9-methyl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-hydroxy-8-trifluoromethyl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,

2-chloro-3-isopropoxy-8-trifluoromethyl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-(2-hydroxyethoxy)-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
dimethylthiocarbamic acid S-(2-chloro-9-methyl-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-3-yl) ester,
2-chloro-3-(2-dimethylaminoethoxy)-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
dimethylthiocarbamic acid S-(2-chloro-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-3-yl) ester,
2-chloro-3-isopropylsulfanyl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-methylsulfanyl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-methanesulfonyl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-(2-hydroxy-3-morpholin-4-ylpropoxy)-7,8,9,10-tetrahydro-benzo[c]chromen-6-one,
2-chloro-3-isopropoxy-4-morpholin-4-ylmethyl-7,8,9,10-tetrahydro-benzo[c]chromen-6-one,
2-chloro-3-(3-dimethylamino-2-hydroxypropoxy)-7,8,9,10-tetrahydro-benzo[c]chromen-6-one,
2-chloro-3-(3-diethylamino-2-hydroxypropoxy)-7,8,9,10-tetrahydro-benzo[c]chromen-6-one,
2-chloro-3-(2-hydroxy-3-isopropylaminopropoxy)-7,8,9,10-tetrahydro-benzo[c]chromen-6-one,
2-chloro-3-cyclobutylmethoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-ethyl-3-isopropoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-(2-hydroxyethoxy)-3-methoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
4-amino-3-isopropoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-methoxy-3-*iso*propoxy-7,8,9,10-tetrahydro-6H-benzo[c]chromen-6-one,
2-chloro-3-(2-hydroxy-3-isopropylaminopropoxy)-7,8,9,10-tetrahydrobenzo[c]chromen-6-one hydrochloride,
2-chloro-3-hydroxy-4-nitro-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-(3-chloro-2-hydroxypropoxy)-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,

1-(3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-4-yl)-3-phenylurea,

2-chloro-3-(2-hydroxy-3-phenylaminopropoxy)-7,8,9,10-tetrahydro-benzo[c]chromen-6-one hydrochloride,

1-(2,4-dichlorophenyl)-3-(3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-4-yl)thiourea,

3-isopropoxy-4-nitro-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,

N-tosyl-4-amino-3-isopropoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,

2-chloro-3-isopropoxy-4-nitro-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,

4-amino-2-chloro-3-isopropoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,

2-difluoromethoxy-3-methoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,

2-chloro-3-difluoromethoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,

trifluoromethanesulfonic acid 2-chloro-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-3-yl ester,

3-benzyl-8-isopropoxy-1,2,3,4-tetrahydrochromeno[3,4-c]pyridin-5-one,

2-acetyl-3-methoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,

3-isopropoxy-4-methylamino-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,

N-(3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-4-yl) - methanesulfonamide

N-acetyl-N-(3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-4-yl)acetamide,

2-chloro-N-(3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-4-yl)acetamide,

N-(3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-2-yl)methanesulfonamide,

N-(3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-2-yl)-4-methylbenzenesulfonamide,

3-isopropoxy-4-nitro-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,

N-acetyl-N-(3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-2-yl)acetamide,

N-acetyl-N-(2-chloro-3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-4-yl)acetamide,

2-chloro-N-(3-isopropoxy-6-oxo-7,8,9,10-tetrahydrobenzo[c]cromen-2-yl)acetamide,
1-(3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-2-yl)-3-phenylurea,
N-(3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-2-yl)succinamic acid,
N-(3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-2-yl)formamide,
3-isopropoxy-2-methylamino-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-morpholin-4-yl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
3-benzylamino-2-chloro-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
N-(3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]-chromen-2-yl)benzamide,
N-(3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]-chromen-4-yl)benzamide,
N-(2-chloro-3-isopropxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-4-yl)benzamide,
N-(3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-2-yl)isobutyramide,
N-isobutyryl-N-(3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-2-yl)isobutyramide,
N-(3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-4-yl)isobutyramide,
N-(2-chloro-3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-4-yl)formamide,
N-(2-chloro-3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-4-yl)-4-methylbenzesulfonamide,
N-(2-chloro-3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-4-yl)succinamic acid,
N-(2-chloro-3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-4-yl)-acetamide,
2-chloro-3-pyrrolidin-1-yl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,

dimethylthiocarbamic acid 6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-3-yl ester,

acetic acid 2-chloro-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-3-yl ester,

2-chloro-3-ethoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,

2-chloro-3-propoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,

2-(2-chloro-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-3-yloxy)acetamide,

N-(2-chloro-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-3-yl)acetamide,

S-(N,N-dimethylcarbamoyl)-8-tert-butyl-2-chloro-6-oxo-3-thio-7,8,9,10-tetrahydro-6H-benzo[c]chromen-6-one,

S-(N,N-dimethylcarbamoyl)-2-chloro-8-phenyl-3-thio-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,

3-methoxy-2-pyridin-2-yl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,

3-(pyridin-2-yloxy)-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,

2-chloro-3-(pyridin-2-ylsulfanyl)-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,

S-(N,N-dimethylcarbamoyl)-8-ethyl-2-chloro-6-oxo-3-thio-7,8,9,10-tetrahydro-6H-benzo[c]chromen-6-one,

S-(N,N-dimethylcarbamoyl)-10-methyl-2-chloro-6-oxo-3-thio-7,8,9,10-tetrahydro-6H-benzo[c]chromen-6-one,

12-chloro-16-thioxo-1,2,3,4,15,16-hexahydro-7,17-dioxa-15-azacyclopenta[a]phenanthren-6-one,

2-chloro-3-(4-methoxycyclohexyloxy)-7,8,9,10-tetrahydrobenzo[c]chromen-6-one, mixture of cis and trans isomers,

2,2-dimethylpropionic acid 6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-3-yl ester,

12-chloro-16-isopropylsulfanyl-1,2,3,4-tetrahydro-7,17-dioxa-15-azacyclopenta[a]phenanthren-6-one,

12-chloro-16-methylsulfanyl-1,2,3,4-tetrahydro-7,17-dioxa-15-azacyclopenta[a]phenanthren-6-one,

12-chloro-16-ethyl-1,2,3,4-tetrahydro-7,17-dioxa-15-azacyclopenta[a]phenanthren-6-one,

12-chloro-16-methyl-1,2,3,4-tetrahydro-7,17-dioxa-15-azacyclopenta[a]phenanthren-6-one,
15-benzyl-1,2,3,4-tetrahydro-15H-7,17-dioxa-15-azacyclopenta[a]phenanthren-6,16-dione,
15-isopropyl-1,2,3,4-tetrahydro-15H-7,17-dioxa-15-azacyclopenta[a]phenanthren-6,16-dione,
15-methyl-1,2,3,4-tetrahydro-15H-7,17-dioxa-15-azacyclopenta[a]phenanthren-6,16-dione,
16-phenyl-1,2,3,4-tetrahydro-7,17-dioxa-15-azacyclopenta[a]phenanthren-6-one,
16-ethyl-1,2,3,4-tetrahydro-7,17-dioxa-15-azacyclopenta[a]phenanthren-6-one,
1,2,3,4-tetrahydro-15H-7,17-dioxa-15-azacyclopenta[a]phenanthrene-6,16-dione,
1,2,3,4-tetrahydro-7,17-dioxa-15-azacyclopenta[a]phenanthren-6-one,
16-benzylsulfanyl-12-chloro-1,2,3,4-tetrahydro-7,17-dioxa-15-azacyclopenta[a]phenanthren-6-one,
12-chloro-16-morpholin-4-yl -1,2,3,4-tetrahydro-7,17-dioxa-15-azacyclopenta[a]phenanthren-6-one,
9-(6-hydroxypyridin-3yl)-1,2,3,4-tetrahydro-6,8-dioxa-10-azacyclopenta[b]phenanthren-5-one,
9-(4-methylpiperazin-1-yl-1,2,3,4-tetrahydro-6,8-dioxa-10-azacyclopenta[b]phenanthren-5-one,
9-piperazin-1-yl-1,2,3,4-tetrahydro-6,8-dioxa-10-azacyclopenta[b]phenanthren-5-one,
9-phenylamino-1,2,3,4-tetrahydro-6,8-dioxa-10-azacyclopenta[b]phenanthren-5-one,
9-benzylsulfanyl-1,2,3,4-tetrahydro-6,8-dioxa-10-azacyclopenta[b]phenanthren-5-one,
9-morpholin-4-yl-1,2,3,4-tetrahydro-6,8-dioxa-10-azacyclopenta[b]phenanthren-5-one,
9-pyridin-3-yl-1,2,3,4-tetrahydro-6,8-dioxa-10-azacyclopenta[b]phenanthren-5-one,

9-pyridin-4-yl-1,2,3,4-tetrahydro-6,8-dioxa-10-azacyclopenta[b]phenanthren-5-one,
9-methylsulfanyl-1,2,3,4-tetrahydro-6,8-dioxa-10-azacyclopenta[b]phenanthren-5-one,
10-thiophen-2-yl-1,2,3,4-tetrahydro-6,8-dioxa-11-azabenzo[a]anthracene-5,9-dione,
9-isopropylsulfanyl-1,2,3,4-tetrahydro-6,8-dioxa-10-azacyclopenta[b]phenanthren-5-one,
9-benzoyl-1,2,3,4-tetrahydro-6,8-dioxa-10-azacyclopenta[b]phenanthren-5-one,
9-thioxo-1,2,3,4,9,10-hexahydro-6,8-dioxa-10-azacyclopenta[b]phenanthren-5-one,
9-isopropyl-1,2,3,4-tetrahydro-6,8-dioxa-10-azacyclopenta[b]phenanthren-5-one,
9-phenyl-1,2,3,4-tetrahydro-6,8-dioxa-10-azacyclopenta[b]phenanthren-5-one,
10-isopropyl-1,2,3,4-tetrahydro-10H-6,8-dioxa-10-azacyclopenta[b]phenanthrene-5,9-dione,
1,2,3,4-tetrahydro-10H-6,8-dioxa-10-azacyclopenta[b]phenanthrene-5,9-dione,
9-ethyl-1,2,3,4-tetrahydro-6,8-dioxa-10-azacyclopenta[b]phenanthren-5-one,
9-methyl-1,2,3,4-tetrahydro-6,8-dioxa-10-azacyclopenta[b]phenanthren-5-one,
9-ethoxy-1,2,3,4-tetrahydro-6,8-dioxa-10-azacyclopenta[b]phenanthren-5-one,
4-methoxy-2-thioxo-1,2,8,9,10,11-hexahydro-3,6-dioxa-1-azacyclopenta[c]phenanthren-7-one,
12-chloro -1,2,3,4-tetrahydro-7,17-dioxa-15-azacyclopenta[a]phenanthren-6-one,
4-methoxy-2-phenyl- 8,9,10,11-tetrahydro-3,6-dioxa-1-azacyclopenta[c]phenanthren-7-one,
5-methoxy-2-thiophen-2-yl-9,10,11,12-tetrahydro-4,7-dioxa-1-azabenzo[c]phenanthrene-3,8-dione,

4-methoxy-2-methyl- 8,9,10,11-tetrahydro-3,6-dioxa-1-azacyclopenta[c]phenanthren-7-one,
4-methoxy-8,9,10,11-tetrahydro-1H-3,6-dioxa-1-azacyclopenta[c]phenanthren-2,7-dione,
4-methoxy-2-methylsulfanyl- 8,9,10,11-tetrahydro-3,6-dioxa-1-azacyclopenta[c]phenanthren-7-one,
2-ethoxy-4-methoxy- 8,9,10,11-tetrahydro-3,6-dioxa-1-azacyclopenta[c]phenanthren-7-one,
2-chloro-3-pyridin-2-yl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
3-acetyl-2-chloro-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
7-isopropoxy-8-nitro-2,3-dihydro-1H-cyclopenta[c]chromen-4-one,
9-(4-dimethylaminobenzyl)-1,2,3,4-tetrahydro-6,8-dioxa-10-aza-cyclopenta[b]phenanthren-5-one,
4-methoxy-2-pyridin-2-yl-8,9,10,11-tetrahydro-3,6-dioxa-1-aza-cyclopenta[c]phenanthren-7-one,
9-pyridin-2-yl-1,2,3,4-tetrahydro-6,8-dioxa-10-aza-cyclopenta[b]phenanthren-5-one,
2-chloro-3-isopropoxy-8-pyridin-2-yl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-isopropoxy-8-pyridin-3-yl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
10-(3,5-difluorophenyl)-1,2,3,4-tetrahydro-6,8-dioxa-11-azabenzo[a]anthracene-5,9-dione,
4-(5,9-dioxo-1,3,4,5-tetrahydro-2H,9H-6,8-dioxa-11-azabenzo[a]anthracen-10-yl)benzonitrile,
9-phenyl-2,3-dihydro-1H-5,7-dioxa-10-azacyclopenta[a]anthracene-4,8-dione,
10-phenyl-1,2,3,4-tetrahydro-6,8-dioxa-11-azabenzo[a]anthracene-5,9-dione,
10-(4-methoxyphenyl)-1,2,3,4-tetrahydro-6,8-dioxa-11-azabenzo[a]anthracene-5,9-dione,
10-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydro-6,8-dioxa-11-aza-benzo[a]anthracene-5,9-dione,

10-(4-trifluoromethylphenyl)-1,2,3,4-tetrahydro-6,8-dioxa-11-aza-benzo[a]anthracene-5,9-dione,
9-adamantan-1-yl-1,2,3,4-tetrahydro-6,8-dioxa-10-aza-cyclopenta[b]phenanthren-5-one,
10-(4-dimethylaminophenyl)-1,2,3,4-tetrahydro-6,8-dioxa-11-aza-benzo[a]anthracene-5,9-dione,
2-chloro-3-isopropoxy-7-methyl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-isopropoxy-9-pyridin-2-yl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one

and optical isomers, pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof.

DETAILED DESCRIPTION OF THE INVENTION

For the purpose of the present invention, the carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix C_{i-j} indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus, for example, C_{1-3}alkyl refers to alkyl of one to three carbon atoms, inclusive, (i.e., methyl, ethyl, propyl, and isopropyl), straight and branched forms thereof.

As used herein, the following definitions are applicable unless otherwise described. The term "C_{1-6}alkyl" comprises straight or branched chain alkyl groups having 1, 2, 3, 4, 5 or 6 carbon atoms. Said alkyl groups may be unsubstituted and include, e.g., methyl, ethyl, n-propyl, 2-propyl, n-butyl, tert-butyl. Further, these alkyl groups may optionally be substituted by one or more fluorine, chlorine and/or bromine atoms. Examples of these halogenated alkyl moieties include $-CF_3$, $-C_2F_5$, $-CBr_3$, and $-CCl_3$; thus, for example, groups such as R^2, R^4, R^5 and R^7-R^{11} may represent e.g. trifluoromethyl. The term "C_{1-6} alkoxy" comprises straight or branched chain $-O-C_{1-6}$alkyl groups wherein "C_{1-6} alkyl" is defined as given hereinbefore.

Examples of "C_{1-6}alkoxy" include methoxy, ethoxy, n-propoxy, i-propoxy. A C_{1-6}alkoxy group optionally may be substituted by one or more fluorine, chlorine and/or bromine atoms thereby forming, for instance, $-OCF_3$ and $-OC_2F_5$. The term "cycloC_{3-12}alkyl" represents monocyclic, bicyclic or tricyclic alkyl groups having 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 carbon atoms and includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptyl and adamantyl. A cycloC_{3-12}alkyl group optionally may be substituted with one or more fluorine, chlorine and/or bromine atoms. In the context of the present invention the term "di-C_{1-6}alkylamino" refers to an amino moiety in which the nitrogen atom of the amino group is substituted with two C_{1-6} alkyl groups, which may be the same or different, as defined above. Examples of di-C_{1-6}alkylamino groups include dimethylamino, diethylamino and N-methyl-N-isopropylamino. The term "N-cycloC_{3-12}alkyl-N-C_{1-6}alkylamino" comprises amino groups in which the nitrogen atom of the amino group is substituted by one C_{1-6}alkyl group and one N-cycloC_{3-12}alkyl group. Both the C_{1-6}alkyl group and the N-cycloC_{3-12}alkyl group are defined as given hereinbefore. The term "4-C_{1-6}alkyl-piperazinyl" comprises piperazinyl radicals bearing a C_{1-6}alkyl moiety at the nitrogen atom in 4-position of the piperazine ring, said "C_{1-6}alkyl" having the same meaning as given hereinbefore. The term aryl represents phenyl or naphthyl or phenyl substituted by one or more substituents, which may be the same or different, selected from C_{1-6}alkyl, which is optionally substituted with one or more fluorine, chlorine or bromine atoms, C_{2-6}alkenyl, C_{1-6}alkoxy, which is optionally substituted with one or more fluorine, chlorine or bromine atoms, cycloC_{3-12}alkyl, hydroxy, halogen, cyano, nitro, C_{1-6}alkoxycarbonyl, amino, C_{1-6} alkylamino, di-C_{1-6} alkylamino, N-cycloC_{3-12}alkyl-N-C_{1-6}alkylamino, azetidinyl, pyrrolyl, piperidinyl, morpholinyl, 4-C_{1-6}alkyl-piperazinyl, tetrazolyl, oxazolyl, furyl, thiophenyl, isoxazolyl, thiazolyl, imidazolyl, oxadiazolyl, pyridinyl, pyrimidyl, and C_{1-6} alkylenedioxy. The term "heteroaryl" represents an aromatic 5-6 membered ring containing from one to four heteroatoms selected from oxygen, sulfur and nitrogen, or a bicyclic group comprising a 5-6 membered ring containing from one to four heteroatoms selected from oxygen, sulfur and nitrogen fused with a benzene ring or a 5-6 membered ring containing from one to

four heteroatoms selected from oxygen, sulfur and nitrogen, wherein the heteroaryl group may be optionally substitued by one or more substituents, which may be the same or different, selected from C_{1-6}alkyl, which is optionally substituted with one or more fluorine, chlorine or bromine atoms, C_{1-6}alkoxy, which is optionally substituted with one or more fluorine, chlorine or bromine atoms, cycloC_{3-12}alkyl, hydroxy, halogen, cyano, nitro, C_{1-6} alkoxycarbonyl, amino, C_{1-6}alkylamino, di-C_{1-6}alkylamino, N-cycloC_{3-12}alkyl-N-C_{1-6}alkylamino, azetidinyl, pyrrolyl, piperazinyl, morpholinyl, 4-C_{1-6}alkyl-piperazinyl, tetrazolyl, oxazolyl, furyl, thiophenyl, isoxazolyl, thiazolyl, imidazolyl, oxadiazolyl, pyridinyl, pyrimidyl and phenyl. Representative heteroaryl groups include unsubstituted or appropriately substituted pyrroles, oxazoles, thiophens, furans, isoxazoles, imidazoles, oxazoles, oxadiazoles, thiazoles, imidazolines, pyrazoles, oxazolidines, isoxazolidines, thiazolidines, pyridines, pyridazines, pyrimidines, pyrazines, azepines. The term "halogen" represents fluorine, chlorine, bromine and iodine.

The compounds of the present invention are named according to the IUPAC or CAS nomenclature system. Abbreviations which are well known to one of ordinary skill in the art may be used (e.g. "Ph" for phenyl, "Me" for methyl, "Et" for ethyl, "h" for hour or hours, and "rt" for room temperature).

The term "analog" or "derivative" is used herein in the conventional pharmaceutical sense, to refer to a molecule that structurally resembles a reference molecule, but has been modified in a targeted and controlled manner to replace one or more specific substituents of the reference molecule with an alternate substituent, thereby generating a molecule which is structurally similar to the reference molecule. Synthesis and screening of analogs (*e.g.*, using structural and/or biochemical analysis), to identify slightly modified versions of a known compound which may have improved or biased traits (such as higher potency and/or selectivity at a specific targeted receptor type, greater ability to penetrate mammalian blood-brain barriers, fewer side effects, etc.) is a drug design approach that is well known in pharmaceutical chemistry.

In addition, using methods known to those skilled in the art, analogs and derivatives of the compounds of the invention can be created which have improved therapeutic efficacy in controlling neurological conditions including dementia, *i.e.*, higher potency and/or selectivity at a specific targeted receptor type, either greater or lower ability to penetrate mammalian blood-brain barriers (*e.g.*, either higher or lower blood-brain barrier permeation rate), fewer side effects, etc.

The phrase "pharmaceutically acceptable", as used in connection with compositions of the invention, refers to molecular entities and other ingredients of such compositions that are physiologically tolerable and do not typically produce untoward reactions when administered to a mammal (*e.g.*, human). Preferably, as used herein, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in mammals, and more particularly in humans.

Compounds of the present invention may be in the form of pharmaceutically acceptable salts. “Pharmaceutically acceptable salts” refers to those salts which possess the biological effectiveness and properties of the parent compound and which are not biologically or otherwise undesirable. The nature of the salt or isomer is not critical, provided that it is non-toxic and does not substantially interfere with the desired pharmacological activity.

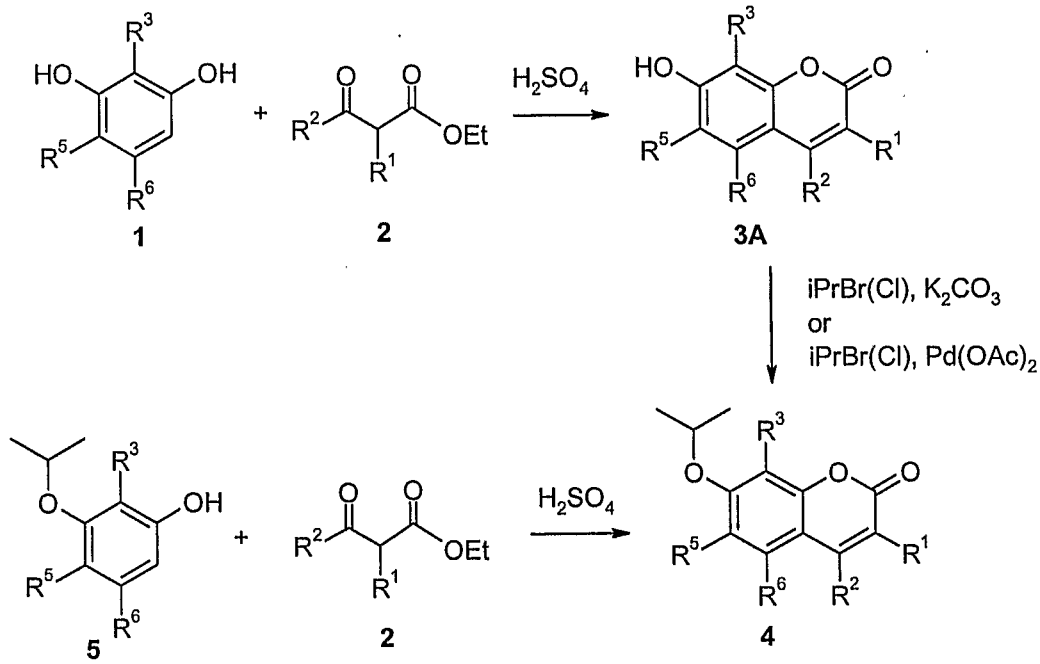
It will be appreciated by those skilled in the art that compounds of the invention having a chiral center may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention ecompasses any racemic, optically-active, polymorphic, tautomeric, or stereoisomeric form, or mixture thereof, of a compound of the invention, which possesses the useful properties described herein.

The following Schemes describe the preparation of compounds of Formula **I** of the present invention. All of the starting materials are prepared by procedures described in these schemes, by procedures well known to one of ordinary skill in organic chemistry or may be obtained commercially. All of the final compounds of the present invention are prepared by procedures described in this chart or by procedures analogous thereto, which would be well known to one of ordinary skill in organic chemistry. All of the variables used in the schemes are as defined in the specification, below or as in the claims.

It will be apparent to those skilled in the art that the described synthetic procedures are merely representative in nature and that alternative synthetic processes are known to one of ordinary skill in organic chemistry.

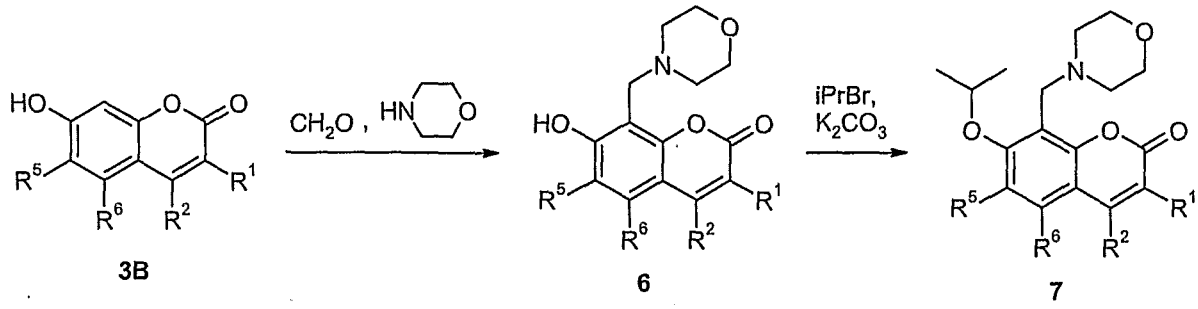
Chromenone **3A** may be prepared by Pechmann condensation of a resorcinol **1** with a substituted β-ketoester **2** according to **Scheme 1**. Compound **4** may be prepared by Pechmann condensation of a mono *O*-alkylated resorcinol **5** with a substituted β-ketoester **2** or, alternatively, by *O*-alkylation, arylation or acylation of chromenone **3A**.

Scheme 1



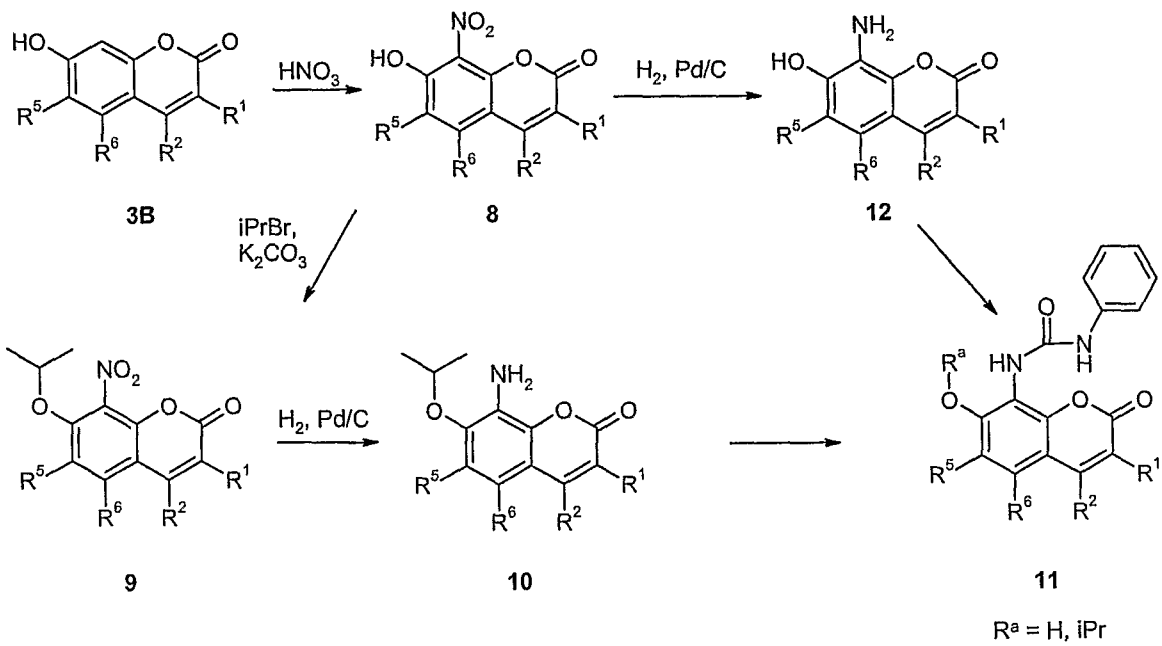
Compound **6** may be prepared from compound **3B** via reaction with an amine derivative (e.g., morpholine) and formaldehyde under acidic conditions (**Scheme 2**). Alkylation of compound **6** at oxygen with an alkyl bromide (e.g. *iso*propyl bromide) yields chromenone derivative **7**.

Scheme 2



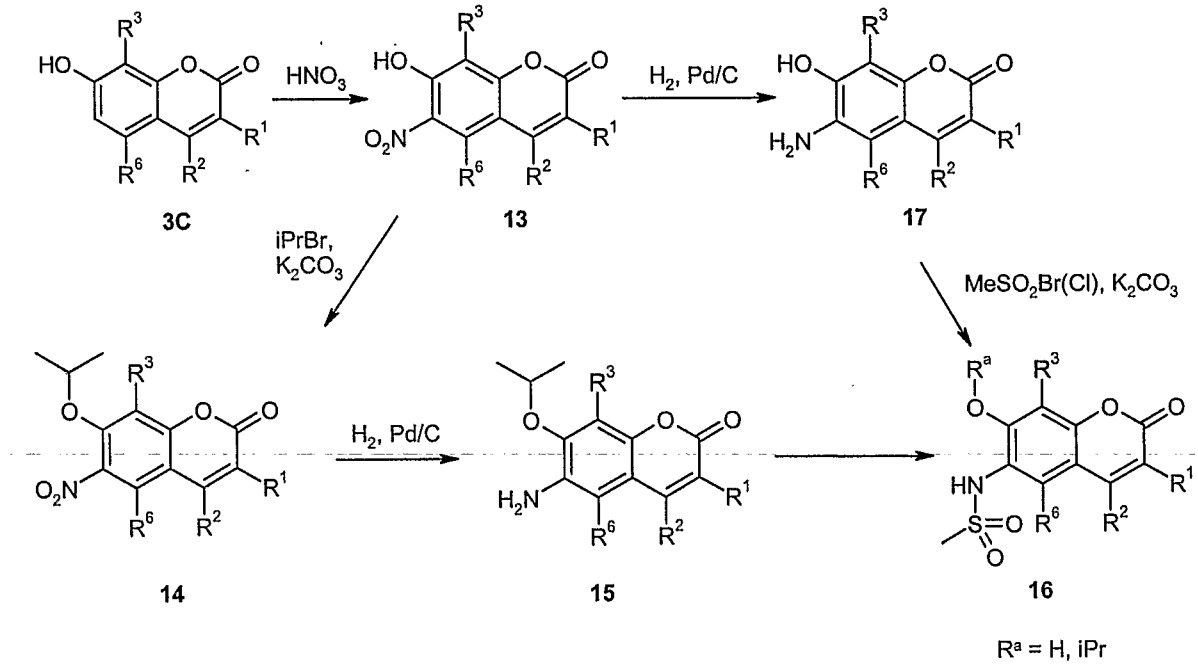
Nitration of compound **3B** yields nitrochromenone **8** (**Scheme 3**). Alkylation of nitro derivative **8** at oxygen yields compound **9**. Reduction of the nitro group of **9** provides aniline **10**. The amino group of **10** may be mono- or bis-alkylated, acylated, sulfonylated, and/or carbamoylated to yield compound **11**. Alternatively, the nitro group in compound **8** may be reduced to yield aniline **12** with a free hydroxy group, the amino group of which may be mono- or bis- acylated, sulfonylated, and/or carbamoylated in the presence of potassium carbonate to yield compound **11**.

Scheme 3



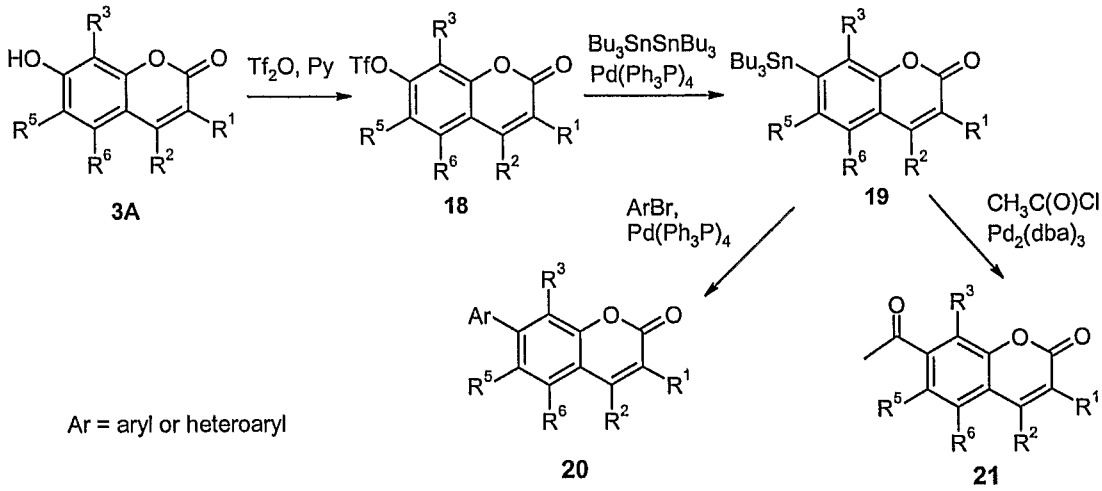
Nitration of compound **3C** yields nitro chromenone **13** (**Scheme 4**). Alkylation of nitro derivative **13** at oxygen yields compound **14**, the nitro group of which may be reduced to provide aniline **15**. The amino group of aniline **15** may be mono- or bis-alkylated, acylated, sulfonylated, and/or carbamoylated to yield compound **16**. Alternatively, the nitro group of compound **13** may be reduced to yield aniline **17** with a free hydroxy group, the amino group of which may be mono- or bis- acylated, sulfonylated, and/or carbamoylated to yield compound **16**.

Scheme 4



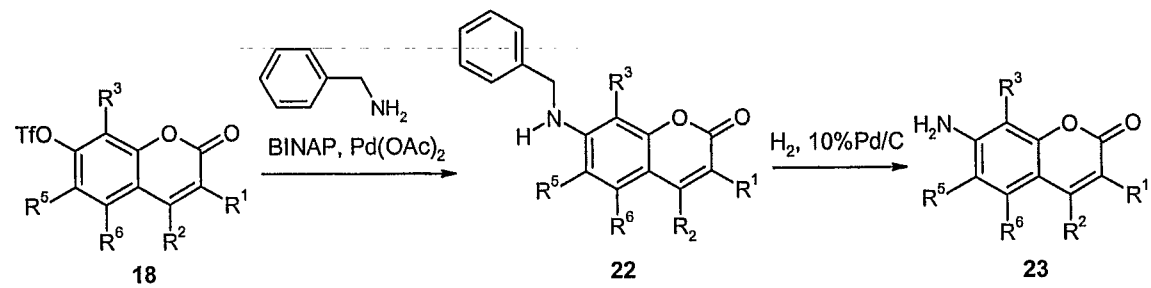
Trifluorosulfonic acid ester **18** may be prepared from chromenone derivative **3A** according to **Scheme 5**. Triflate **18** may be used to prepare stannyl derivative **19** which may be utilized in a palladium catalyzed coupling reaction with an aryl halide to prepare compound **20**, or compound **19** may be coupled with an acyl chloride to prepare compound **21**.

Scheme 5



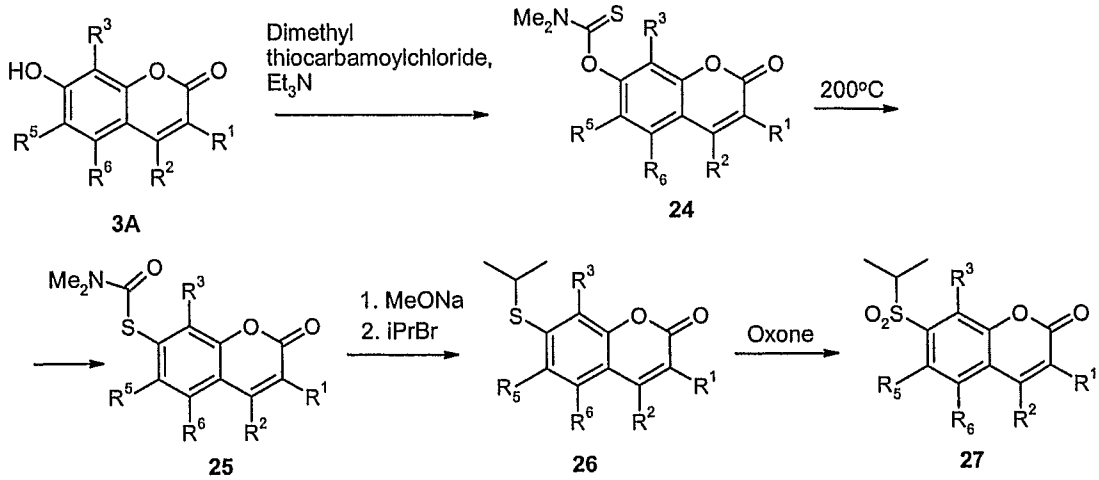
Palladium catalyzed arylation of an amine with triflate **18** yields compound **22**. *N*-Benzyl derivative **22** may be deprotected to yield aniline **23** (**Scheme 6**).

Scheme 6



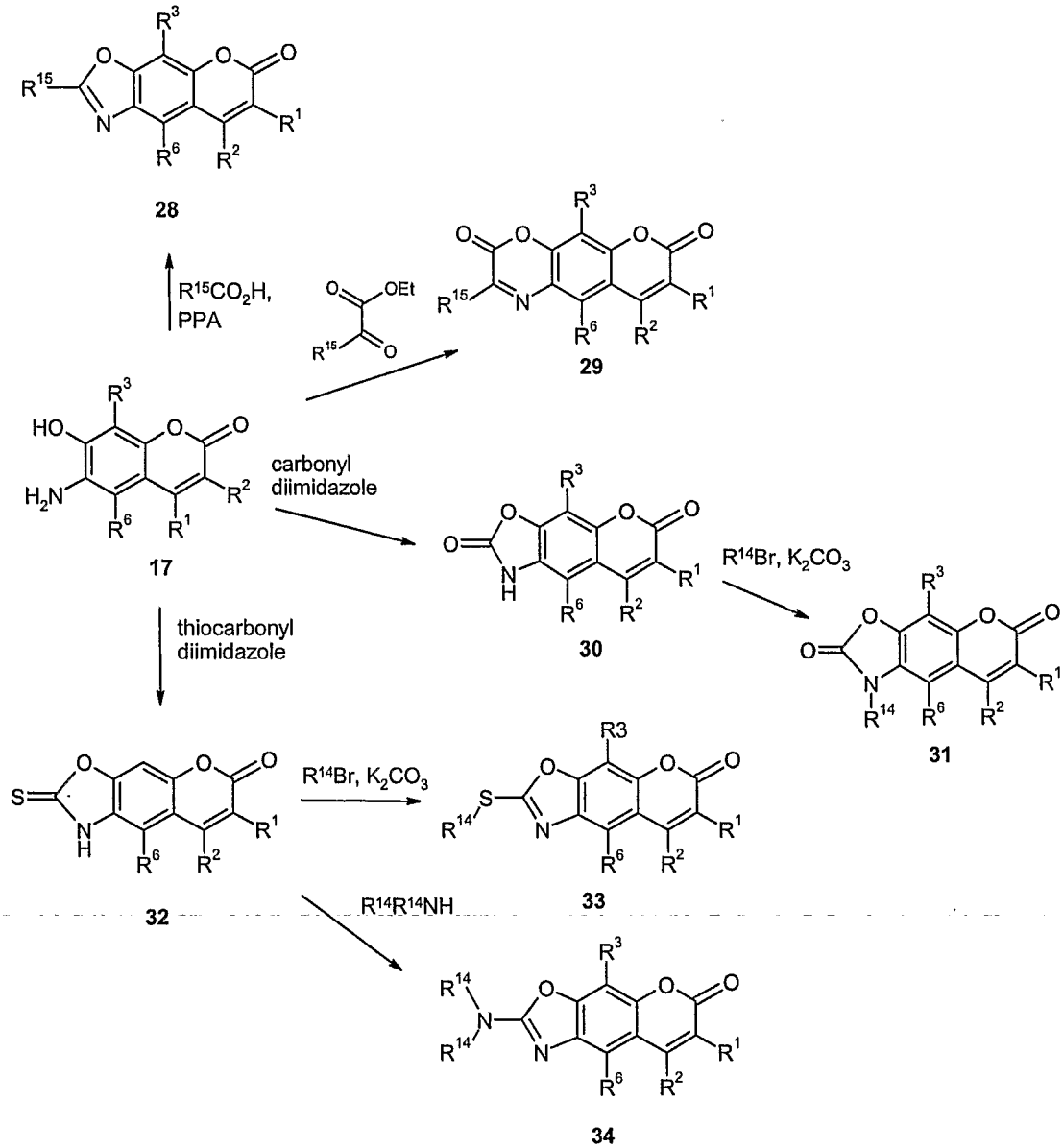
Treatment of 7-hydroxychromenone **3A** with *N,N*-dimethylthiocarbamoyl chloride provides compound **24** which may be subjected to thermal rearrangement to provide carbamoyl protected thiol **25** (**Scheme 7**). Cleavage of the carbamoyl group in compound **25** followed by alkylation or arylation at sulfur yields compound **26**. This compound may be oxidized to sulfone **27**.

Scheme 7



Amino phenol **17** may be condensed with a carboxylic acid to prepare oxazole **28** (**Scheme 8**). Condensation of amino phenol **17** with an α-keto carboxylic acid ester yields compound **29**. Treatment of amino phenol **17** with carbonyldiimidazole provides oxazolidinone **30** which may be alkylated at nitrogen to give compound **31**. Treatment of amino phenol **17** with thiocarbonyldiimidazole provides oxazolidinethione **32** which may be alkylated at sulfur to give compound **33**. Replacement of sulfur with an amine in thione **32** provides compound **34** (wherein R^{14} represents hydrogen, C_{1-6}alkyl, cycloC_{3-12}alkyl, aryl, heteroaryl, carboxyC_{1-6}alkyl, arylC_{1-6}alkyl, alkylcarbonyl or CF_3, and R^{15} represents hydrogen, C_{1-6}alkyl, cycloC_{3-12}alkyl, aryl, heteroaryl, arylC_{1-6}alkyl, carboxyC_{1-6}alkyl, alkylcarbonyl, CF_3, C_{1-6}alkyloxy, C_{1-6}alkylthio, arylC_{1-6}alkylthio, arylC_{1-6}alkyloxy, morpholino, C_{1-6}cycloamino, piperazinyl, N-C_{1-6}alkylpiperazinyl or arylamino).

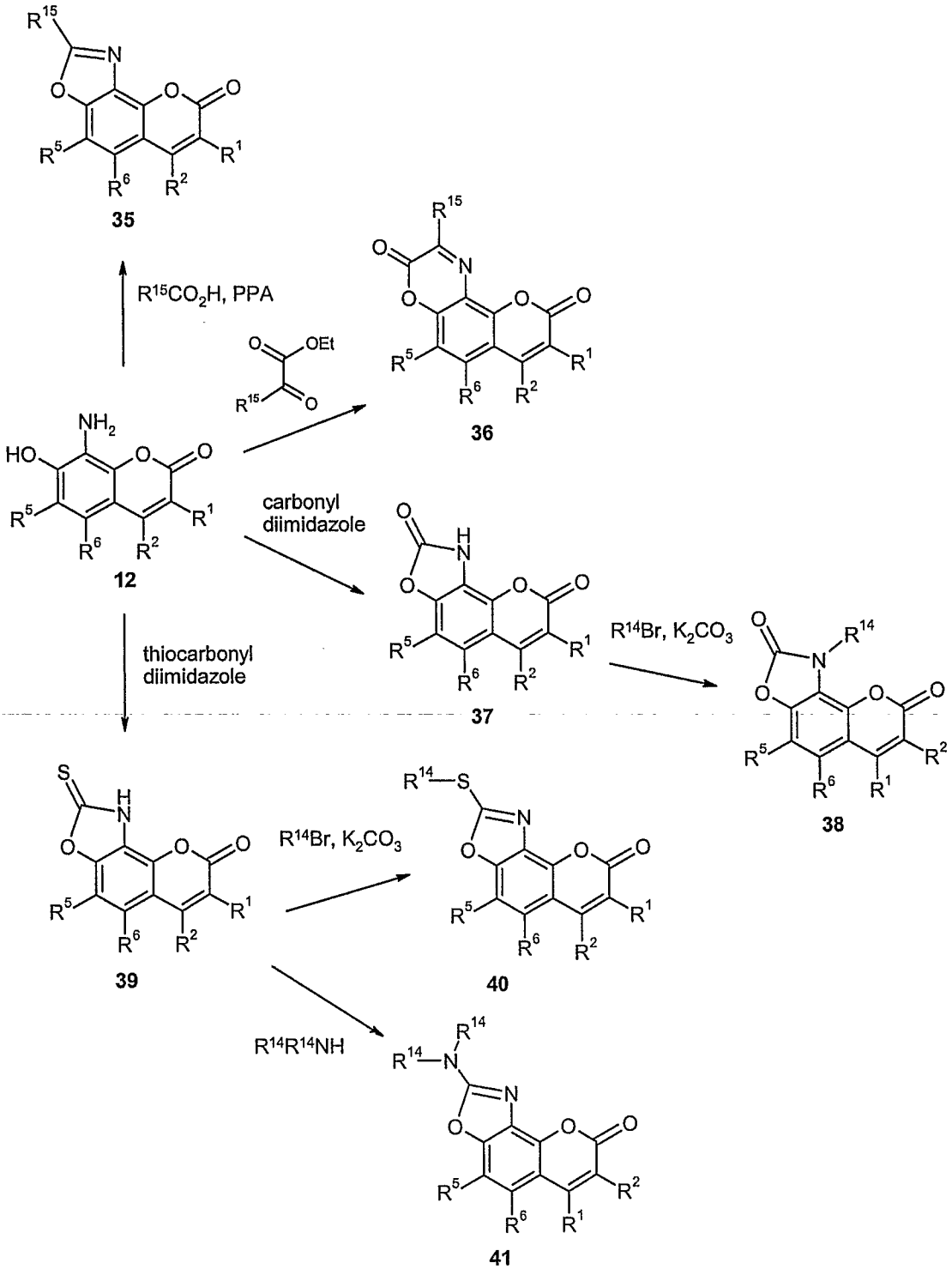
Scheme 8



Amino phenol **12** may be condensed with a carboxylic acid to prepare oxazole **35** (**Scheme 9**). Condensation of amino phenol **12** with an α-keto carboxylic acid ester yields compound **36**. Treatment of amino phenol **12** with carbonyldiimidazole provides oxazolidinone **37** which may be alkylated at nitrogen to provide compound **38**. Treatment of amino phenol **12** with thiocarbonyldiimidazole provides oxazolidinethione **39** which may be alkylated at sulfur to provide compound **40**. Replacement of sulfur with an

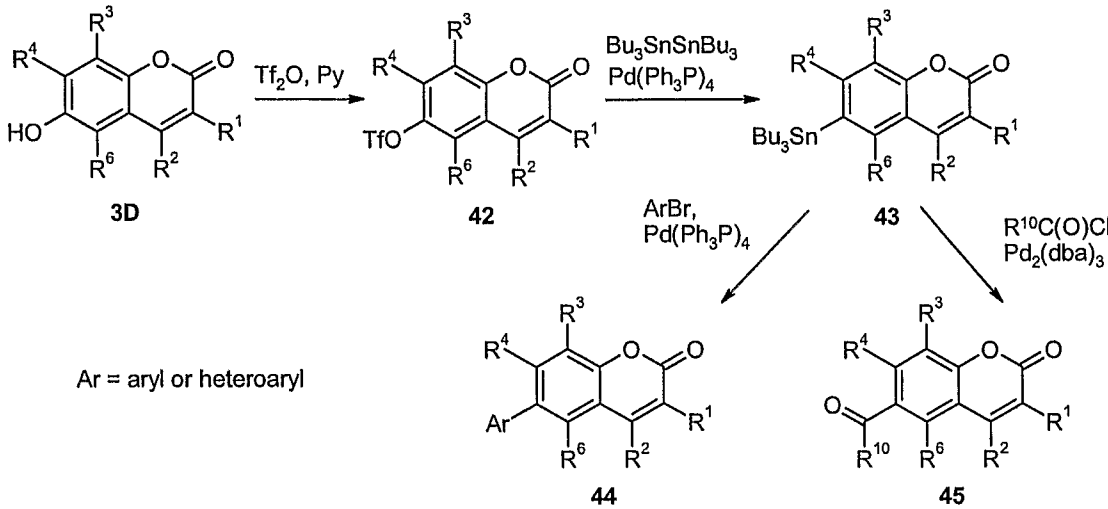
amine in oxazolidinethione **39** yields compound **41** (wherein R^{14} and R^{15} are as previously defined).

Scheme 9



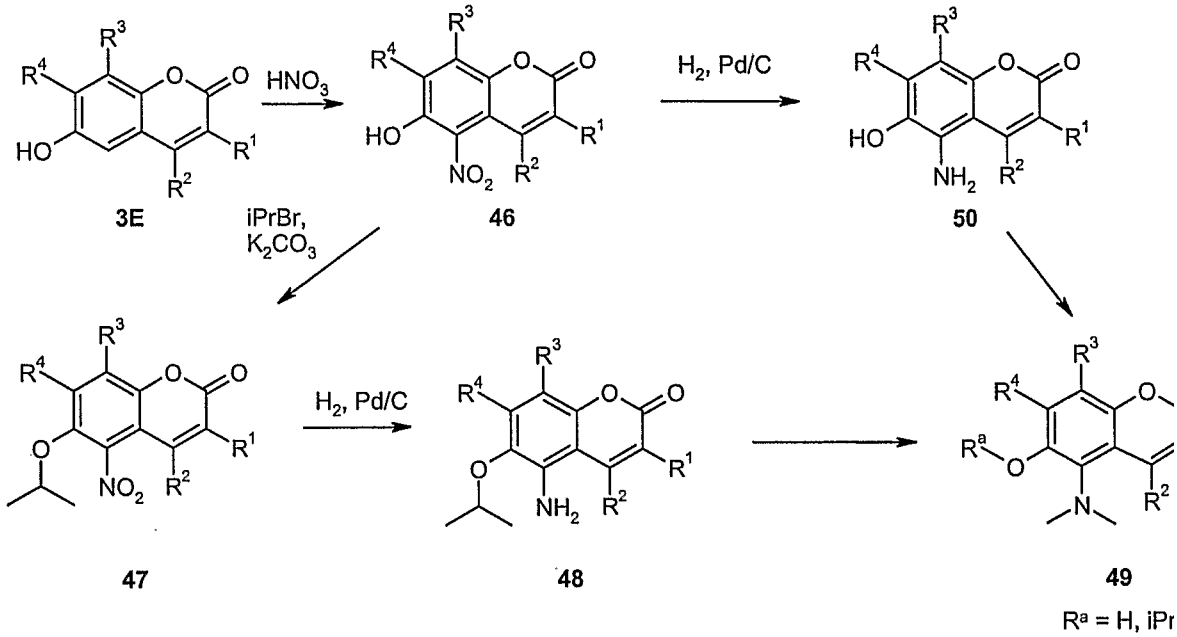
Trifluorosulfonic acid ester **42** may be prepared from chromenone derivative **3D** (**Scheme 10**). Triflate **42** may be used to prepare stannyl derivative **43** which may be utilized for palladium catalyzed coupling with an aryl halide to prepare compound **44**, or compound **43** may be coupled with an acyl chloride to prepare compound **45**.

Scheme 10



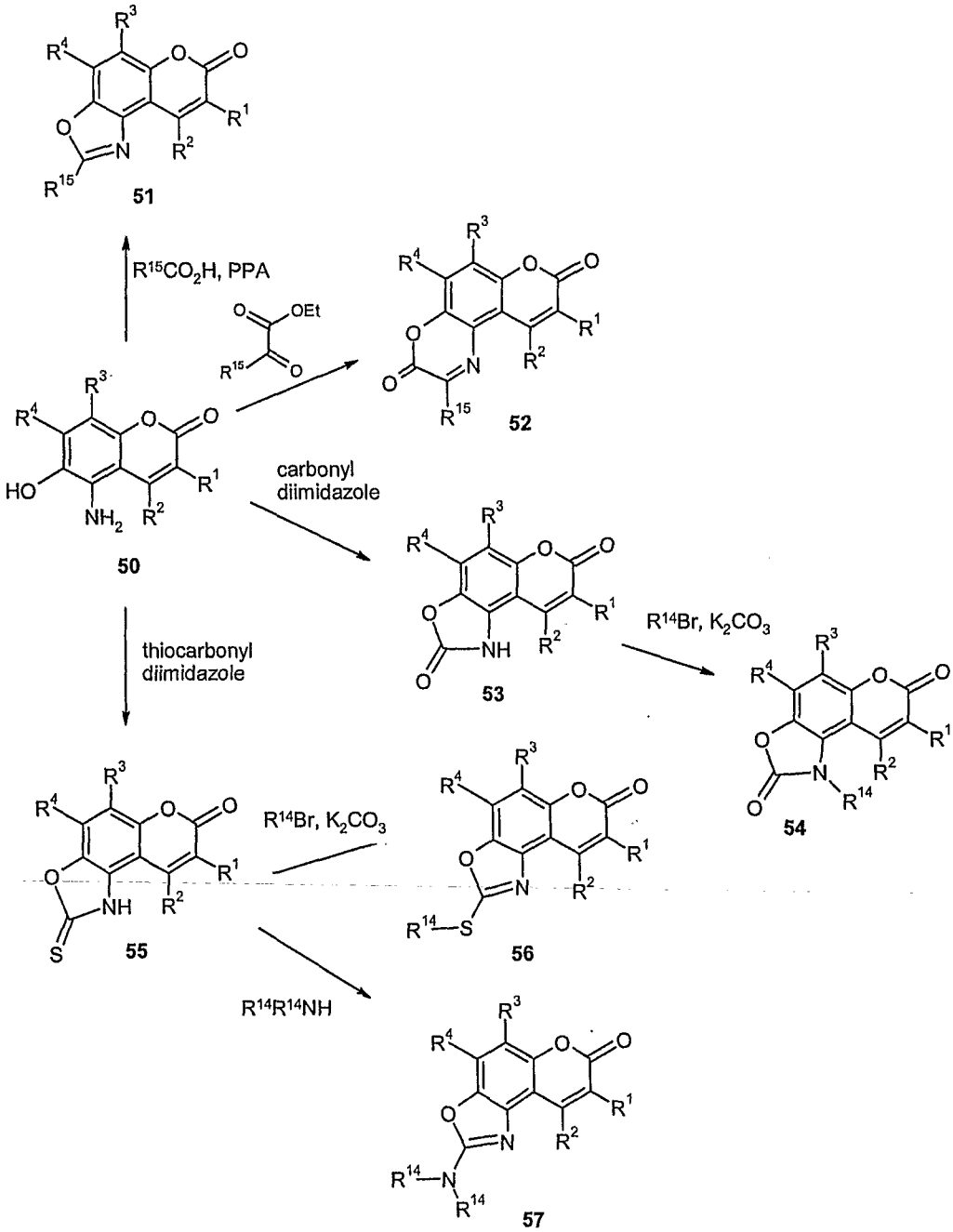
Nitration of compound **3E** yields nitrochromenone **46** (**Scheme 11**). Alkylation of nitro derivative **46** at oxygen yields compound **47**, the nitro group of which may be reduced to yield aniline **48**. The amino group in aniline **48** may be mono- or bis- alkylated, acylated, sulfonylated, and/or carbamoylated to yield compound **49**. Alternatively, the nitro group in compound **46** may be reduced to give aniline **50** with a free hydroxy group, the amino group of which may be mono- or bis- acylated, sulfonylated, and/or carbamoylated to give compound **49**.

Scheme 11



Amino phenol **50** may be condensed with a carboxylic acid to prepare oxazole **51** (**Scheme 12**). Condensation of amino phenol **50** with an α-keto carboxylic acid ester yields compound **52**. Treatment of amino phenol **50** with carbonyldiimidazole provides oxazolidinone **53** which may be alkylated at nitrogen to give compound **54**. Treatment of amino phenol **50** with thiocarbonyldiimidazole provides oxazolidinethione **55** which may be alkylated at sulfur to yield compound **56**. Replacement of sulfur with an amine in thione **55** yields compound **57** (wherein R^{14} and R^{15} are as previously defined).

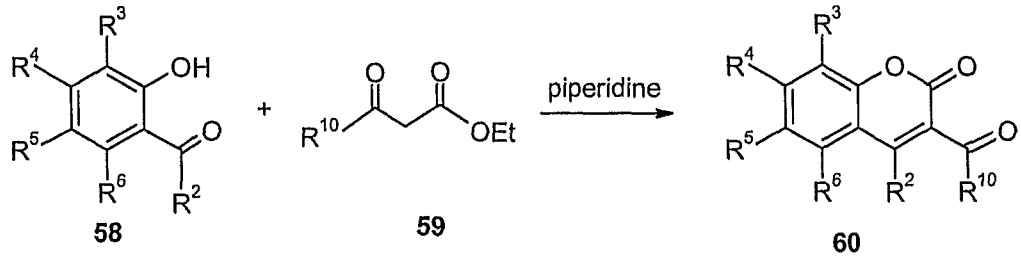
Scheme 12



3-Acylchromenone derivative **60** may be prepared by piperidine catalysed condensation of 2-acylphenol **58** with β-ketoester **59** (**Scheme 13**).

5

Scheme 13



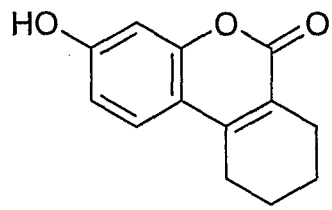
EXPERIMENTAL PART

The compounds and their preparation of the present invention will be better understood in connection with the following examples, which are intended as an illustration of and not a limitation upon the scope of the invention.

Hereinafter, "DMF" is defined as N,N-dimethylformamide, "HCl" as hydrochloric acid, "DMSO" as dimethylsulfoxide and "TMS" as tetramethylsilane.

Preparation 1

3-Hydroxy-7,8,9,10-tetrahydro-benzo[c]chromen-6-one



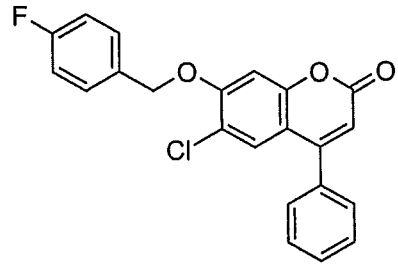
A mixture of resorcinol (1.45 g, 10 mmol) and ethyl 2-oxocyclohexane carboxylate (2.04 g, 12 mmol) is cooled in an ice bath and sulfuric acid (5 ml) is added dropwise. The reaction mixture is stirred for 2.5 h and diluted with ice water (30 ml). The precipitate is collected on a filter and recrystallized from i-PrOH to give the title compound (1.44 g, 67%) as colorless crystals.

Physical characteristics are as follows:

Mp 187-190 °C; ^{1}H NMR (DMSO-d_6, TMS) δ: 1.71, 2.37, 2.72, 6.68, 6.77, 7.52, 10.34; MS: 216 (M^+).

Example 1

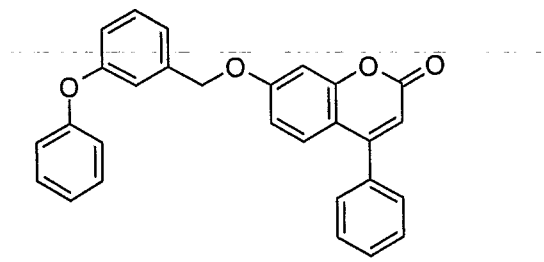
6-Chloro-7-(4-fluoro-benzyloxy)-4-phenyl-chromen-2-one



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 2

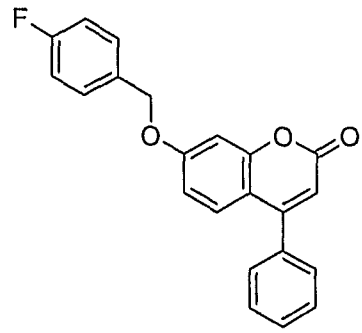
7-(3-Phenoxy-benzyloxy)-4-phenyl-chromen-2-one



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 3

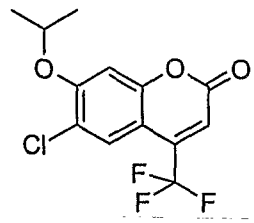
7-(4-Fluoro-benzyloxy)-4-phenyl-chromen-2-one



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 4

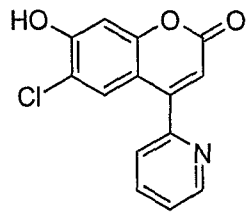
6-Chloro-7-isopropoxy-4-trifluoromethyl-chromen-2-one



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 5

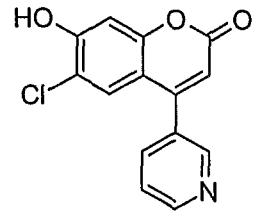
6-Chloro-7-hydroxy-4-pyridin-2-yl-chromen-2-one



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 6

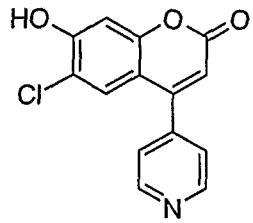
6-Chloro-7-hydroxy-4-pyridin-3-yl-chromen-2-one



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 7

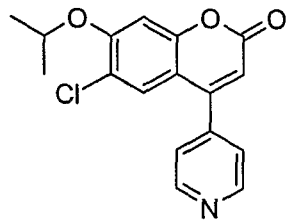
6-Chloro-7-hydroxy-4-pyridin-4-yl-chromen-2-one



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 8

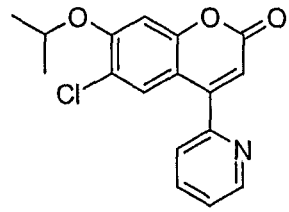
6-Chloro-7-isopropoxy-4-pyridin-4-yl-chromen-2-one



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 9

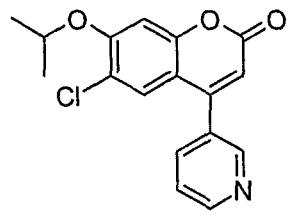
6-Chloro-7-isopropoxy-4-pyridin-2-yl-chromen-2-one



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 10

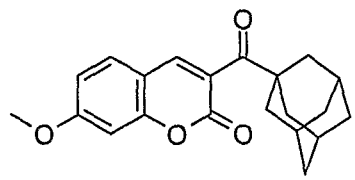
6-Chloro-7-isopropoxy-4-pyridin-3-yl-chromen-2-one



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 11

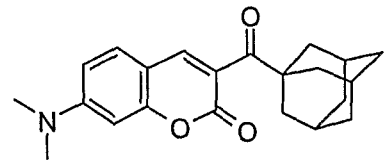
3-(Adamantane-1-carbonyl)-7-methoxy-chromen-2-one



In analogy to the procedure described in **Scheme 13**, the title compound is obtained in moderate yield.

Example 12

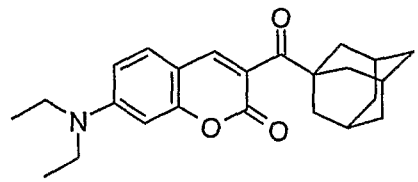
3-(Adamantane-1-carbonyl)-7-dimethylamino-chromen-2-one



In analogy to the procedure described in **Scheme 13**, the title compound is obtained in moderate yield.

Example 13

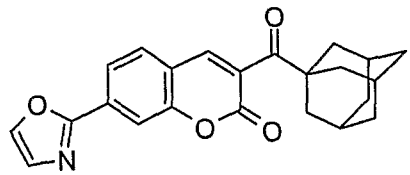
3-(Adamantane-1-carbonyl)-7-diethylamino-chromen-2-one



In analogy to the procedure described in **Scheme 13**, the title compound is obtained in moderate yield.

Example 14

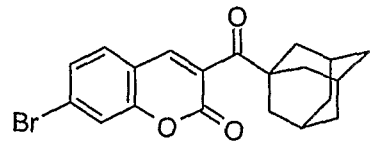
3-(Adamantane-1-carbonyl)-7-oxazol-2-yl-chromen-2-one



In analogy to the procedure described in **Scheme 13**, the title compound is obtained in moderate yield.

Example 15

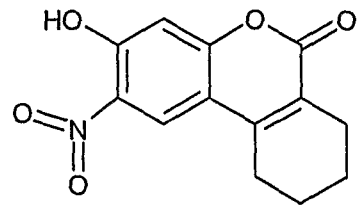
3-(Adamantane-1-carbonyl)-7-bromo-chromen-2-one



In analogy to the procedure described in **Scheme 13**, the title compound is obtained in moderate yield.

Example 16

3-Hydroxy-2-nitro-7,8,9,10-tetrahydrobenzo[c]chromen-6-one



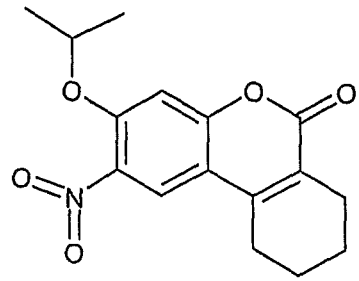
3-Hydroxy-7,8,9,10-tetrahydro-benzo[c]chromen-6-one (**Preparation 1**) (1.0 g, 5.9 mmol) is dissolved in acetic acid (1.5 ml) and the mixture is cooled to 10 °C. Concentrated HNO_3 is added and the reaction mixture is stirred at r.t. for 20 h and diluted with water (15 ml). The precipitate is collected on a filter and recrystallized twice from MeOH to give the title compound (145 mg, 10%) as red crystals.

Physical characteristics are as follows:

Mp 208-210 °C; ^{1}H NMR (DMSO-d_6, TMS) δ: 1.74, 2.41, 2.76, 6.97, 8.19, 11.77.

Example 17

3-Isopropoxy-2-nitro-7,8,9,10-tetrahydrobenzo[c]chromen-6-one



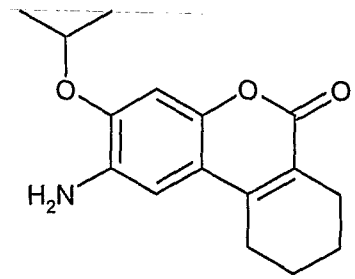
2-Bromopropane (5 ml, 53 mmol) is added to a mixture of 3-Hydroxy-2-nitro-7,8,9,10-tetrahydrobenzo[c]chromen-6-one (**Example 16**) (4.15 g, 13.55 mmol) and K_2CO_3 (5.6 g, 40 mmol) in DMFA (30 ml). The reaction mixture is stirred at 50°C for 24 h, cooled to r.t. and diluted with water (50 ml). The precipitate is collected on a filter and recrystallized from MeOH to give the title compound (154 mg, 30%) as colorless crystals.

Physical characteristics are as follows:

Mp 166-168 °C; ^{1}H NMR (DMSO-d_6, TMS) δ: 1.32, 1.73, 2.41, 2.76, 4.95, 7.41, 8.19.

Example 18

2-Amino-3-isopropoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one



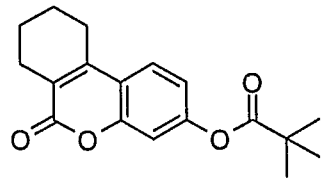
3-Isopropoxy-2-nitro-7,8,9,10-tetrahydrobenzo[c]chromen-6-one (**Example 17**) (1.0 g, 3.3 mmol) is dissolved in EtOH (30 ml) and 10% Pd/C (280 mg) is added. Hydrogen pressure (7 bar) is applied for 6 h. The catalyst is filtered off and the solvent removed *in vacuo*. The residue is purified by flash chromatography on silica gel eluting with mixture of ethyl acetate and light petroleum ether to give the title compound (0.68 g, 75%) as white crystals.

Physical characteristics are as follows:

Mp 95-97 °C; ^{1}H NMR (DMSO-d_6, TMS) δ: 1.30, 1.74, 2.38, 2.65, 4.69, 4.76, 6.85, 6.84.

Example 19

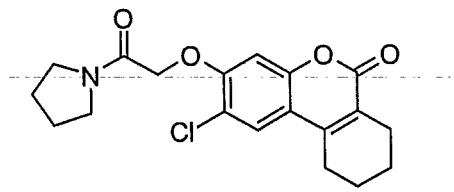
2,2-Dimethyl-propionic acid 6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-3-yl ester



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 20

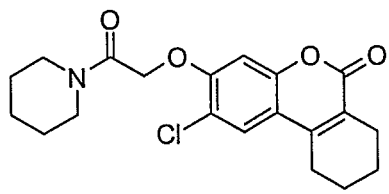
2-Chloro-3-(2-oxo-2-pyrrolidin-1-yl-ethoxy)-7,8,9,10-tetrahydro-benzo[c]chromen-6-onene



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 21

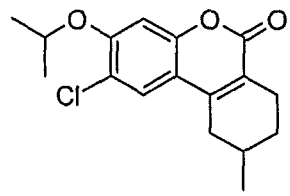
2-Chloro-3-(2-oxo-2-piperidin-1-yl-ethoxy)-7,8,9,10-tetrahydro-benzo[c]chromen-6-onene



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 22

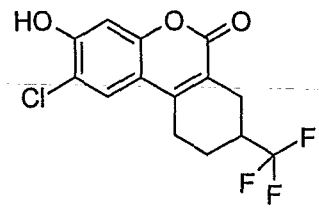
2-Chloro-3-isopropoxy-9-methyl-7,8,9,10-tetrahydro-benzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 23

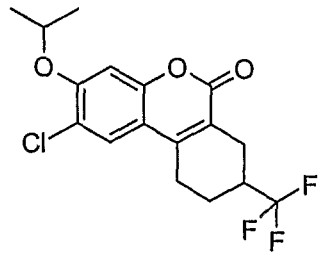
2-Chloro-3-hydroxy-8-trifluoromethyl-7,8,9,10-tetrahydro-benzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 24

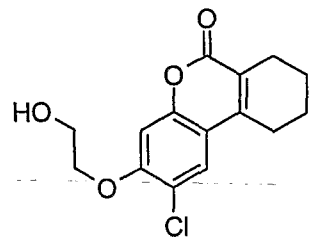
2-Chloro-3-isopropoxy-8-trifluoromethyl-7,8,9,10-tetrahydro-benzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 25

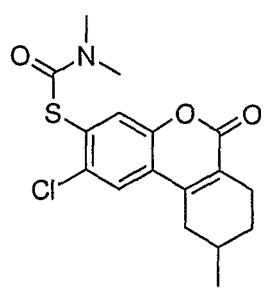
2-Chloro-3-(2-hydroxy-ethoxy)-7,8,9,10-tetrahydro-benzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 26

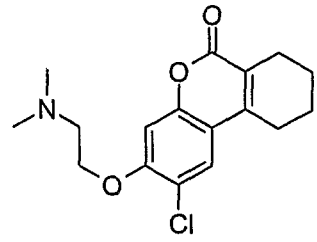
Dimethyl-thiocarbamic acid S-(2-chloro-9-methyl-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-3-yl) ester



In analogy to the procedure described in **Scheme 7**, the title compound is obtained in moderate yield.

Example 27

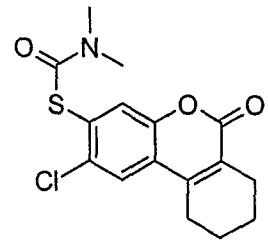
2-Chloro-3-(2-dimethylamino-ethoxy)-7,8,9,10-tetrahydro-benzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 28

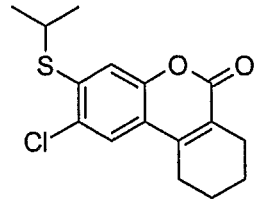
Dimethyl-thiocarbamic acid S-(2-chloro-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-3-yl) ester



In analogy to the procedure described in **Scheme 7**, the title compound is obtained in moderate yield.

Example 29

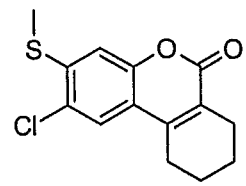
2-Chloro-3-isopropylsulfanyl-7,8,9,10-tetrahydro-benzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 7**, the title compound is obtained in moderate yield.

Example 30

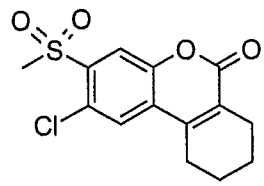
2-Chloro-3-methylsulfanyl-7,8,9,10-tetrahydro-benzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 7**, the title compound is obtained in moderate yield.

Example 31

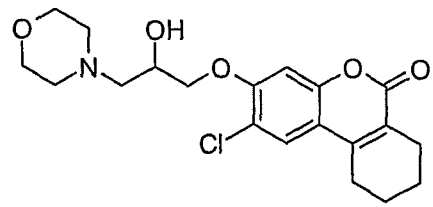
2-Chloro-3-methanesulfonyl-7,8,9,10-tetrahydro-benzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 7**, the title compound is obtained in moderate yield.

Example 32

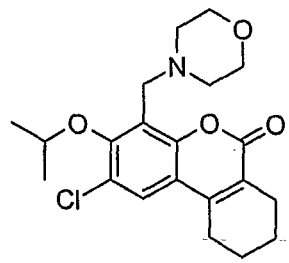
2-Chloro-3-(2-hydroxy-3-morpholin-4-yl-propoxy)-7,8,9,10-tetrahydro-benzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 33

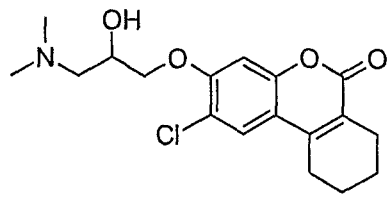
2-Chloro-3-isopropoxy-4-morpholin-4-ylmethyl-7,8,9,10-tetrahydro-benzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 2**, the title compound is obtained in moderate yield.

Example 34

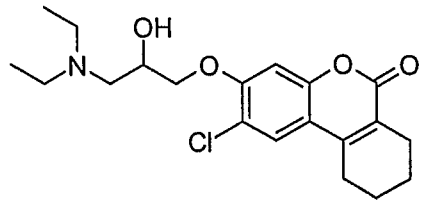
2-Chloro-3-(3-dimethylamino-2-hydroxy-propoxy)-7,8,9,10-tetrahydro-benzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 35

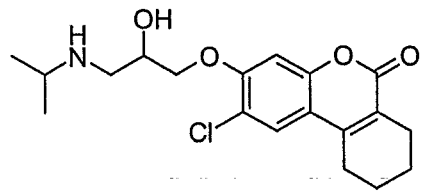
2-Chloro-3-(3-diethylamino-2-hydroxy-propoxy)-7,8,9,10-tetrahydro-benzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 36

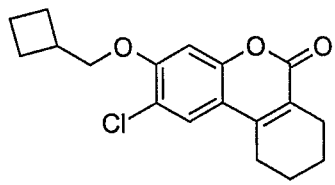
2-Chloro-3-(2-hydroxy-3-isopropylamino-propoxy)-7,8,9,10-tetrahydro-benzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 37

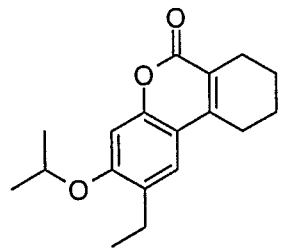
2-Chloro-3-cyclobutylmethoxy-7,8,9,10-tetrahydro-benzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 38

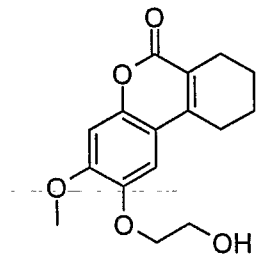
2-Ethyl-3-isopropoxy-7,8,9,10-tetrahydro-benzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 39

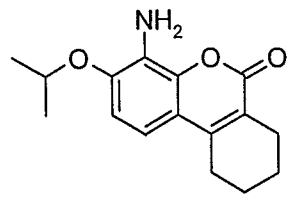
2-(2-Hydroxy-ethoxy)-3-methoxy-7,8,9,10-tetrahydro-benzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 40

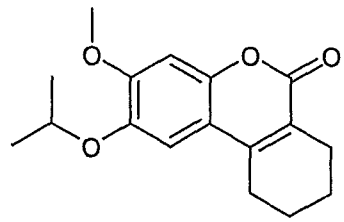
4-Amino-3-isopropoxy-7,8,9,10-tetrahydro-benzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 3**, the title compound is obtained in moderate yield.

Example 41

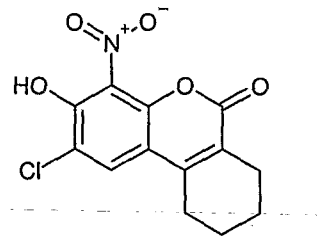
2-Methoxy-3-*iso*propoxy-7,8,9,10-tetrahydro-6H-benzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 42

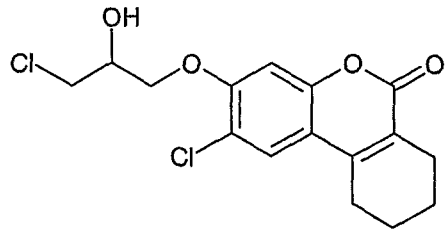
2-Chloro-3-hydroxy-4-nitro-7,8,9,10-tetrahydrobenzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 3**, the title compound is obtained in moderate yield.

Example 43

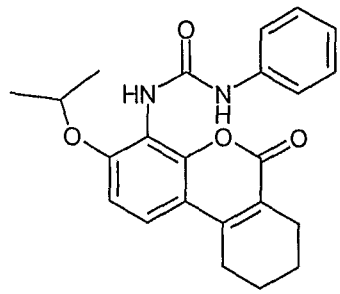
2-Chloro-3-(3-chloro-2-hydroxypropoxy)-7,8,9,10-tetrahydrobenzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 44

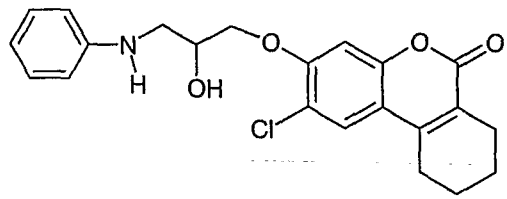
1-(3-Isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-4-yl)-3-phenylurea



In analogy to the procedure described in **Scheme 3**, the title compound is obtained in moderate yield.

Example 45

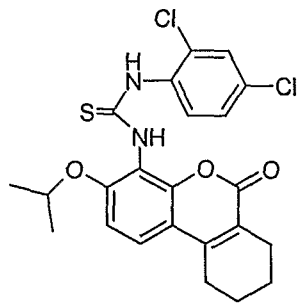
2-Chloro-3-(2-hydroxy-3-phenylaminopropoxy)-7,8,9,10-tetrahydro-benzo[c]chromen-6-one hydrochloride



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 46

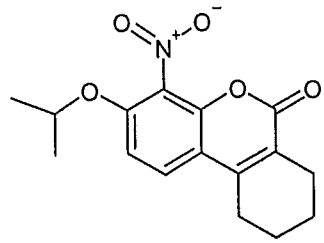
1-(2,4-Dichlorophenyl)-3-(3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-4-yl)thiourea



In analogy to the procedure described in **Scheme 3**, the title compound is obtained in moderate yield.

Example 47

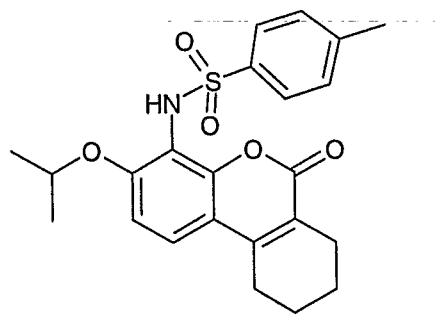
3-Isopropoxy-4-nitro-7,8,9,10-tetrahydrobenzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 3**, the title compound is obtained in moderate yield.

Example 48

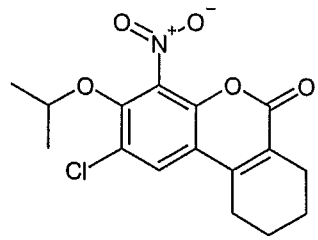
N-Tosyl-4-amino-3-isopropoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 3**, the title compound is obtained in moderate yield.

Example 49

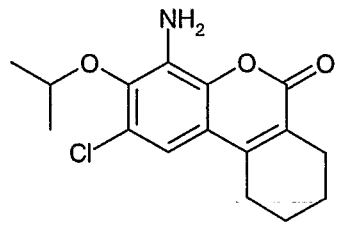
2-Chloro-3-isopropoxy-4-nitro-7,8,9,10-tetrahydrobenzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 3**, the title compound is obtained in moderate yield.

Example 50

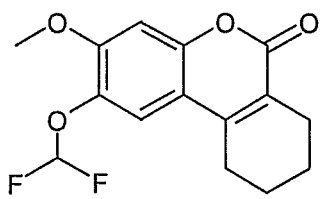
4-Amino-2-chloro-3-isopropoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 3**, the title compound is obtained in moderate yield.

Example 51

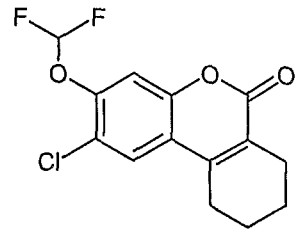
2-Difluoromethoxy-3-methoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 52

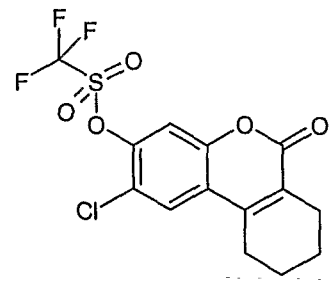
2-Chloro-3-difluoromethoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 53

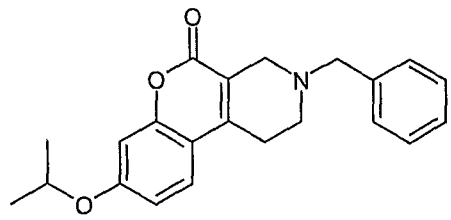
Trifluoromethanesulfonic acid 2-chloro-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-3-yl ester



In analogy to the procedure described in **Scheme 5**, the title compound is obtained in moderate yield.

Example 54

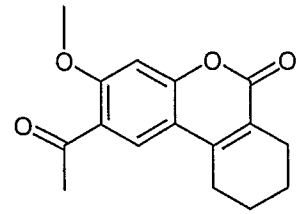
3-Benzyl-8-isopropoxy-1,2,3,4-tetrahydro-chromeno[3,4-c]pyridin-5-one



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 55

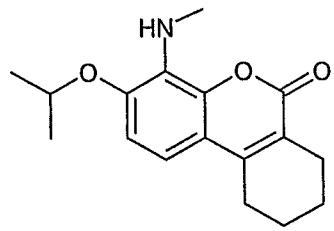
2-Acetyl-3-methoxy-7,8,9,10-tetrahydro-benzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 5**, the title compound is obtained in moderate yield.

Example 56

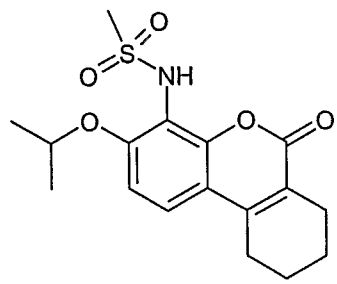
3-Isopropoxy-4-methylamino-7,8,9,10-tetrahydrobenzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 3**, the title compound is obtained in moderate yield.

Example 57

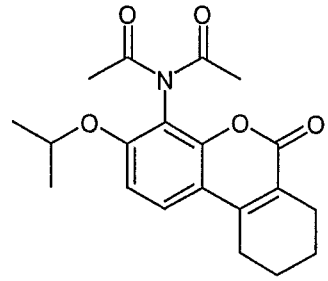
N-(3-Isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-4-yl)-methanesulfonamide



In analogy to the procedure described in **Scheme 3**, the title compound is obtained in moderate yield.

Example 58

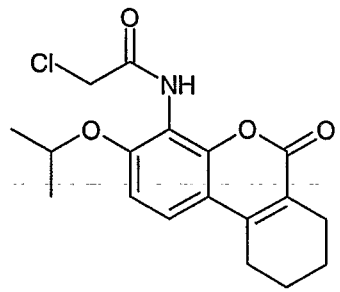
N-Acetyl-N-(3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-4-yl)acetamide



In analogy to the procedure described in **Scheme 3**, the title compound is obtained in moderate yield.

Example 59

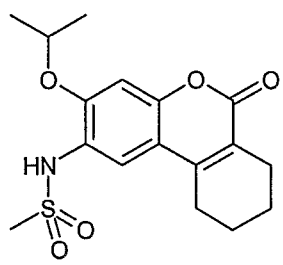
2-Chloro-N-(3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-4-yl)acetamide



In analogy to the procedure described in **Scheme 3**, the title compound is obtained in moderate yield.

Example 60

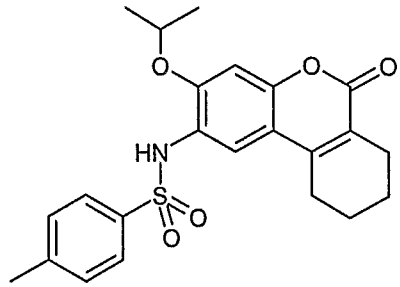
N-(3-Isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-2-yl)methanesulfonamide



In analogy to the procedure described in **Scheme 4**, the title compound is obtained in moderate yield.

Example 61

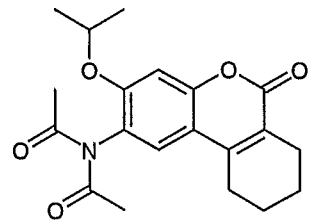
N-(3-Isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-2-yl)-4-methylbenzenesulfonamide



In analogy to the procedure described in **Scheme 4**, the title compound is obtained in moderate yield.

Example 62

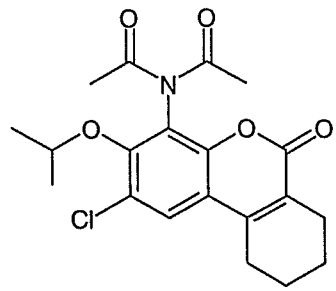
N-Acetyl-N-(3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-2-yl)acetamide



In analogy to the procedure described in **Scheme 4**, the title compound is obtained in moderate yield.

Example 63

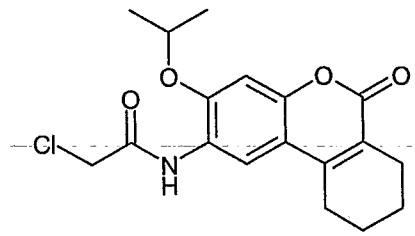
N-Acetyl-N-(2-chloro-3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-4-yl)acetamide



In analogy to the procedure described in **Scheme 3**, the title compound is obtained in moderate yield.

Example 64

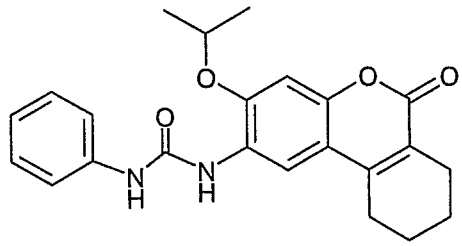
2-Chloro-N-(3-isopropoxy-6-oxo-7,8,9,10-tetrahydrobenzo[c]cromen-2-yl)acetamide



In analogy to the procedure described in **Scheme 4**, the title compound is obtained in moderate yield.

Example 65

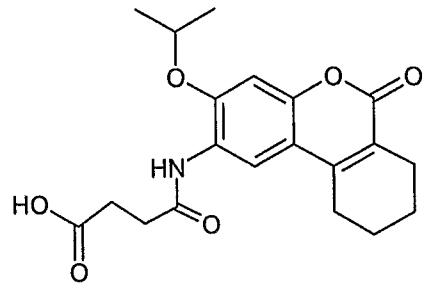
1-(3-Isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-2-yl)-3-phenylurea



In analogy to the procedure described in **Scheme 4**, the title compound is obtained in moderate yield.

Example 66

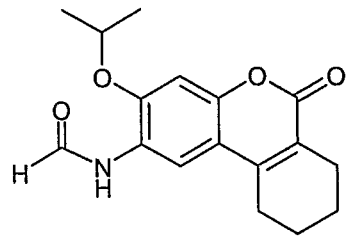
N-(3-Isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-2-yl)succinamic acid



In analogy to the procedure described in **Scheme 4**, the title compound is obtained in moderate yield.

Example 67

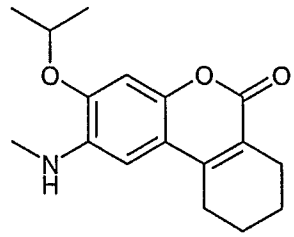
N-(3-Isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-2-yl)formamide



In analogy to the procedure described in **Scheme 4**, the title compound is obtained in moderate yield.

Example 68

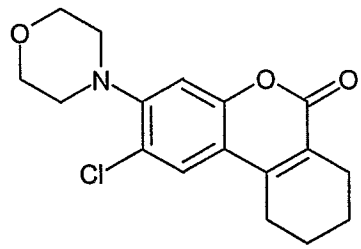
3-Isopropoxy-2-methylamino-7,8,9,10-tetrahydrobenzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 4**, the title compound is obtained in moderate yield.

Example 69

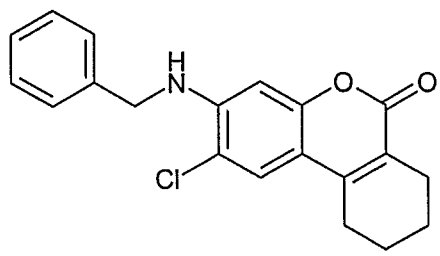
2-Chloro-3-morpholin-4-yl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 6**, the title compound is obtained in moderate yield.

Example 70

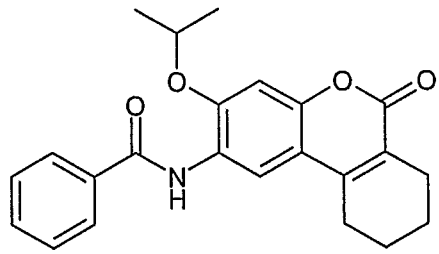
3-Benzylamino-2-chloro-7,8,9,10-tetrahydrobenzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 6**, the title compound is obtained in moderate yield.

Example 71

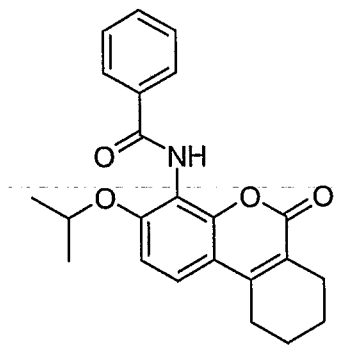
N-(3-Isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]-chromen-2-yl)benzamide



In analogy to the procedure described in **Scheme 4**, the title compound is obtained in moderate yield.

Example 72

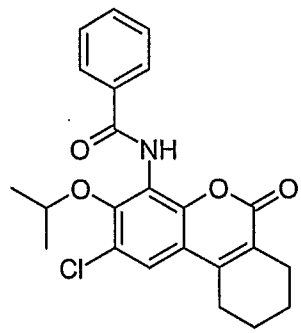
N-(3-Isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]-chromen-4-yl)benzamide



In analogy to the procedure described in **Scheme 3**, the title compound is obtained in moderate yield.

Example 73

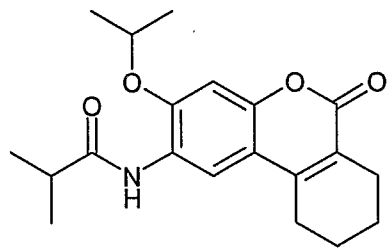
N-(2-Chloro-3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-4-yl)benzamide



In analogy to the procedure described in **Scheme 3**, the title compound is obtained in moderate yield.

Example 74

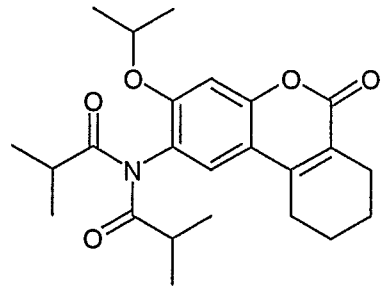
N-(3-Isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]-chromen-2-yl)isobutyramide



In analogy to the procedure described in **Scheme 4**, the title compound is obtained in moderate yield.

Example 75

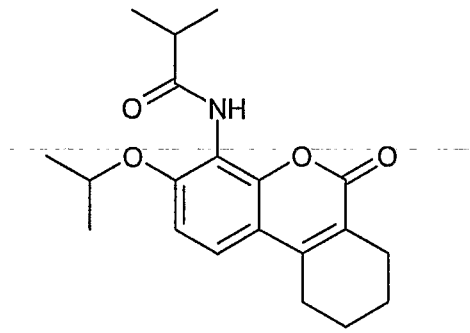
N-Isobutyryl-N-(3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-2-yl)isobutyramide



In analogy to the procedure described in **Scheme 4**, the title compound is obtained in moderate yield.

Example 76

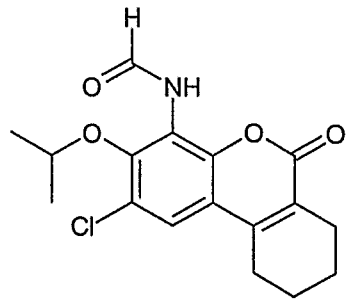
N-(3-Isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]-chromen-4-yl)isobutyramide



In analogy to the procedure described in **Scheme 3**, the title compound is obtained in moderate yield.

Example 77

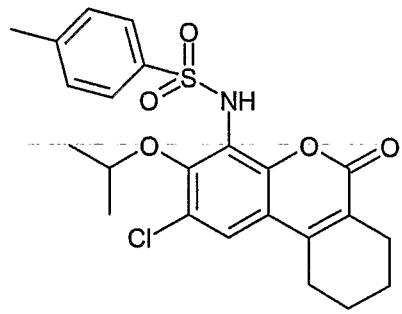
N-(2-Chloro-3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-4-yl)formamide



In analogy to the procedure described in **Scheme 3**, the title compound is obtained in moderate yield.

Example 78

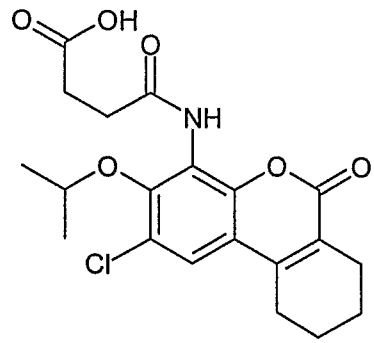
N-(2-Chloro-3-isopropxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-4-yl)-4-methylbenzesulfonamide



In analogy to the procedure described in **Scheme 3**, the title compound is obtained in moderate yield.

Example 79

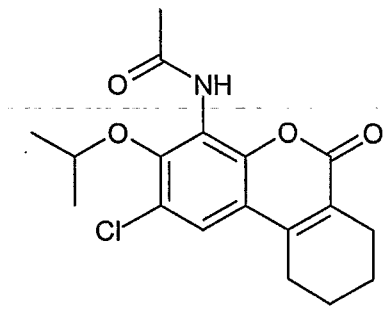
N-(2-Chloro-3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-4-yl)succinamic acid



In analogy to the procedure described in **Scheme 3**, the title compound is obtained in moderate yield.

Example 80

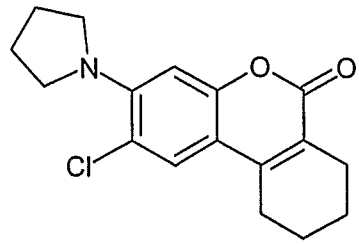
N-(2-Chloro-3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-4-yl)-acetamide



In analogy to the procedure described in **Scheme 3**, the title compound is obtained in moderate yield.

Example 81

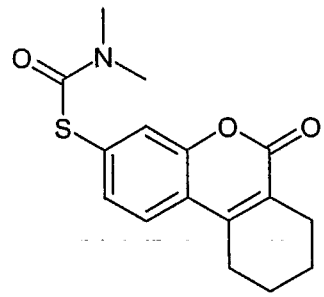
2-Chloro-3-pyrrolidin-1-yl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 6**, the title compound is obtained in moderate yield.

Example 82

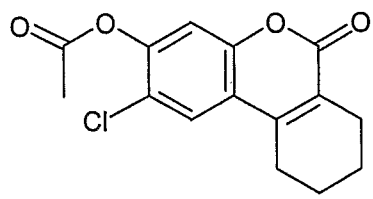
Dimethyl-thiocarbamic acid 6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-3-yl ester



In analogy to the procedure described in **Scheme 7**, the title compound is obtained in moderate yield.

Example 83

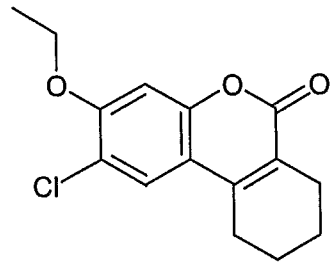
Acetic acid 2-chloro-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-3-yl ester



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 84

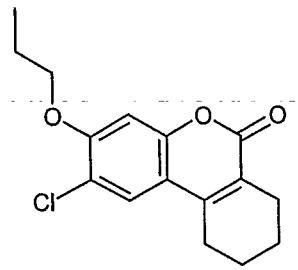
2-Chloro-3-ethoxy-7,8,9,10-tetrahydro-benzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 85

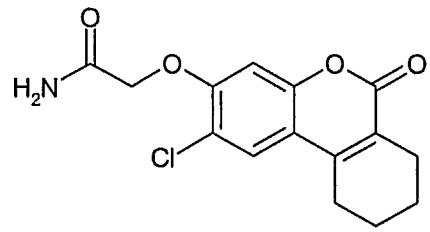
2-Chloro-3-propoxy-7,8,9,10-tetrahydro-benzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 86

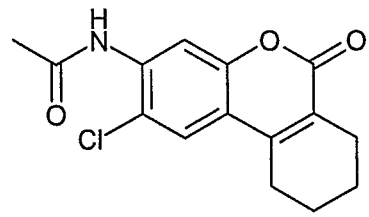
2-(2-Chloro-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-3-yloxy)-acetamide



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 87

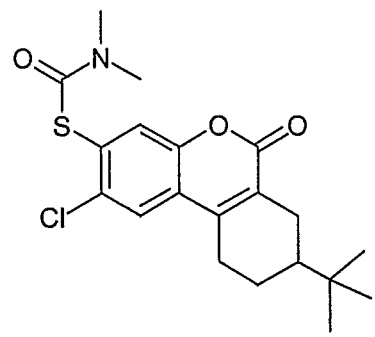
N-(2-Chloro-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-3-yl)-acetamide



In analogy to the procedure described in **Scheme 6**, the title compound is obtained in moderate yield.

Example 88

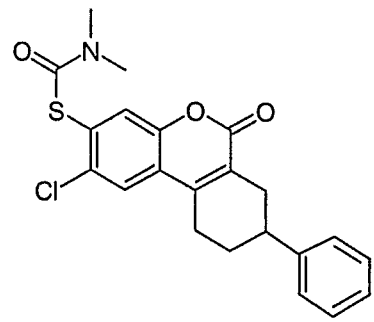
S-(N,N-Dimethylcarbamoyl)-8-tert-butyl-2-chloro-6-oxo-3-thio-7,8,9,10-tetrahydro-6H-benzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 7**, the title compound is obtained in moderate yield.

Example 89

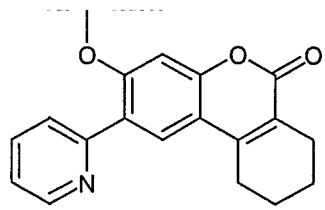
S-(N,N-Dimethylcarbamoyl)-2-chloro-8-phenyl-3-thio-7,8,9,10-tetrahydrobenzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 7**, the title compound is obtained in moderate yield.

Example 90

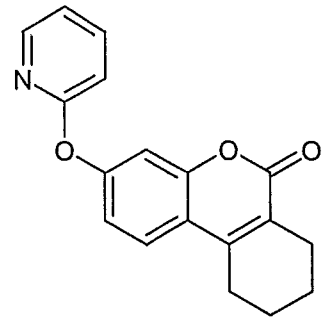
3-Methoxy-2-pyridin-2-yl-7,8,9,10-tetrahydro-benzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 10**, the title compound is obtained in moderate yield.

Example 91

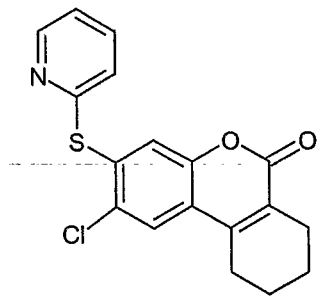
3-(Pyridin-2-yloxy)-7,8,9,10-tetrahydrobenzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 92

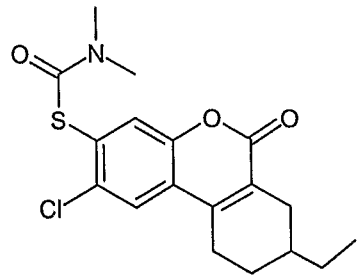
2-Chloro-3-(pyridin-2-ylsulfanyl)-7,8,9,10-tetrahydrobenzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 7**, the title compound is obtained in moderate yield.

Example 93

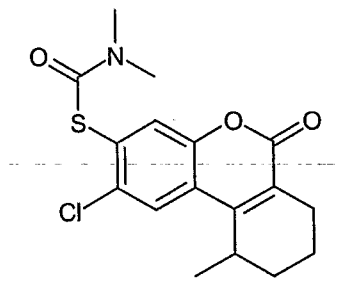
S-(N,N-Dimethylcarbamoyl)-8-ethyl-2-chloro-6-oxo-3-thio-7,8,9,10-tetrahydro-6H-benzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 7**, the title compound is obtained in moderate yield.

Example 94

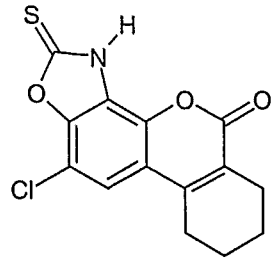
S-(N,N-Dimethylcarbamoyl)-10-methyl-2-chloro-6-oxo-3-thio-7,8,9,10-tetrahydro-6H-benzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 7**, the title compound is obtained in moderate yield.

Example 95

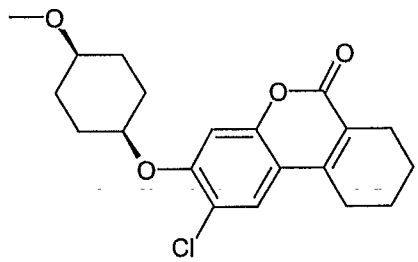
12-Chloro-16-thioxo-1,2,3,4,15,16-hexahydro-7,17-dioxa-15-azacyclopenta[a]phenanthren-6-one



In analogy to the procedure described in **Scheme 9**, the title compound is obtained in moderate yield.

Example 96

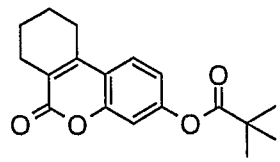
2-Chloro-3-(4-methoxycyclohexyloxy)-7,8,9,10-tetrahydro-benzo[c]chromen-6-one, mixture of cis and trans isomers



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 97

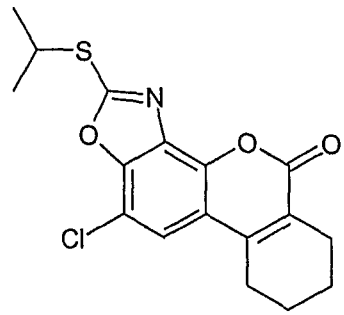
2,2-Dimethyl-propionic acid 6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-3-yl ester



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 98

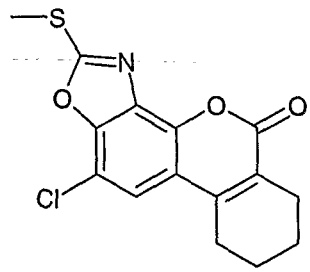
12-Chloro-16-isopropylsulfanyl-1,2,3,4-tetrahydro-7,17-dioxa-15-azacyclopenta[a]phenanthren-6-one



In analogy to the procedure described in **Scheme 9**, the title compound is obtained in moderate yield.

Example 99

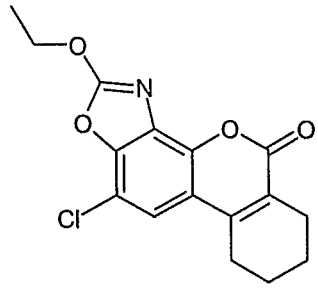
12-Chloro-16-methylsulfanyl-1,2,3,4-tetrahydro-7,17-dioxa-15-azacyclopenta[a]phenanthren-6-one



In analogy to the procedure described in **Scheme 9**, the title compound is obtained in moderate yield.

Example 100

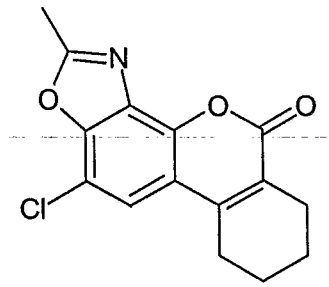
12-Chloro-16-ethyl-1,2,3,4-tetrahydro-7,17-dioxa-15-azacyclopenta[a]phenanthren-6-one



In analogy to the procedure described in **Scheme 9**, the title compound is obtained in moderate yield.

Example 101

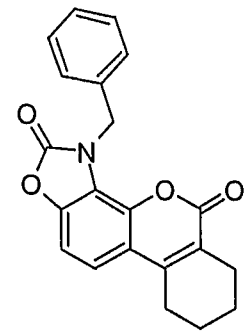
12-Chloro-16-methyl-1,2,3,4-tetrahydro-7,17-dioxa-15-azacyclopenta[a]phenanthren-6-one



In analogy to the procedure described in **Scheme 9**, the title compound is obtained in moderate yield.

Example 102

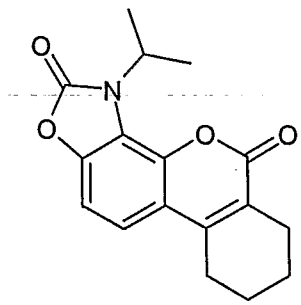
15-Benzyl-1,2,3,4-tetrahydro-15H-7,17-dioxa-15-azacyclopenta[a]phenanthren-6,16-dione



In analogy to the procedure described in **Scheme 9**, the title compound is obtained in moderate yield.

Example 103

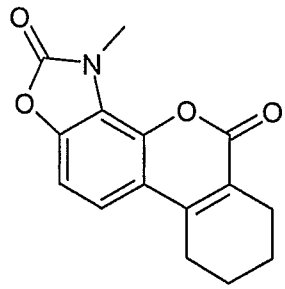
15-Isopropyl-1,2,3,4-tetrahydro-15H-7,17-dioxa-15-azacyclopenta[a]phenanthren-6,16-dione



In analogy to the procedure described in **Scheme 9**, the title compound is obtained in moderate yield.

Example 104

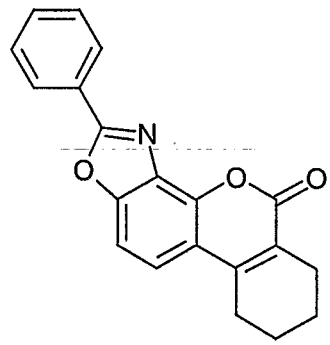
15-Methyl-1,2,3,4-tetrahydro-15H-7,17-dioxa-15-azacyclopenta[a]phenanthren-6,16-dione



In analogy to the procedure described in **Scheme 9**, the title compound is obtained in moderate yield.

Example 105

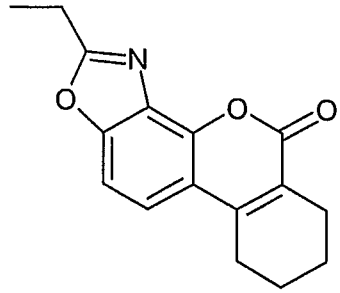
16-Phenyl-1,2,3,4-tetrahydro-7,17-dioxa-15-azacyclopenta[a]phenanthren-6-one



In analogy to the procedure described in **Scheme 9**, the title compound is obtained in moderate yield.

Example 106

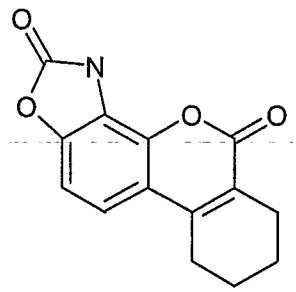
16-Ethyl-1,2,3,4-tetrahydro-7,17-dioxa-15-azacyclopenta[a]phenanthren-6-one



In analogy to the procedure described in **Scheme 9**, the title compound is obtained in moderate yield.

Example 107

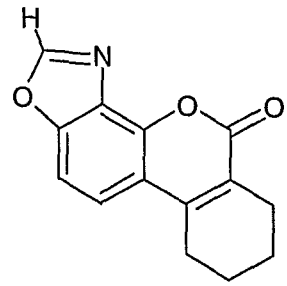
1,2,3,4-Tetrahydro-15H-7,17-dioxa-15-azacyclopenta[a]phenanthrene-6,16-dione



In analogy to the procedure described in **Scheme 9**, the title compound is obtained in moderate yield.

Example 108

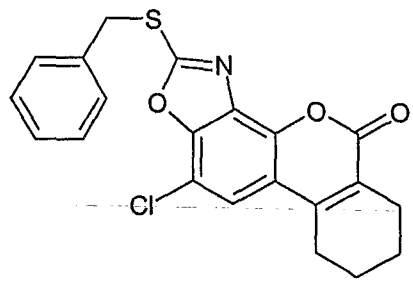
1,2,3,4-Tetrahydro-7,17-dioxa-15-azacyclopenta[a]phenanthren-6-one



In analogy to the procedure described in **Scheme 9**, the title compound is obtained in moderate yield.

Example 109

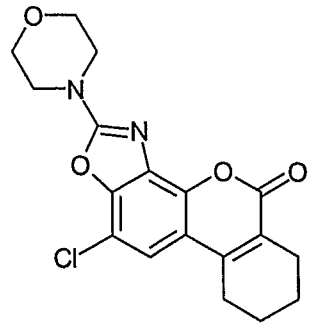
16-Benzylsulfanyl-12-chloro-1,2,3,4-tetrahydro-7,17-dioxa-15-azacyclopenta[a]phenanthren-6-one



In analogy to the procedure described in **Scheme 9**, the title compound is obtained in moderate yield.

Example 110

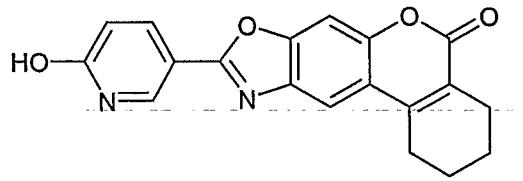
12-Chloro-16-morpholin-4-yl -1,2,3,4-tetrahydro-7,17-dioxa-15-azacyclopenta[a]phenanthren-6-one



In analogy to the procedure described in **Scheme 9**, the title compound is obtained in moderate yield.

Example 111

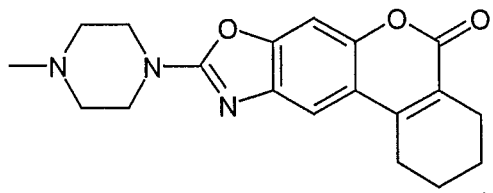
9-(6-Hydroxypyridin-3yl)-1,2,3,4-tetrahydro-6,8-dioxa-10-azacyclopenta[b]phenanthren-5-one



In analogy to the procedure described in **Scheme 8**, the title compound is obtained in moderate yield.

Example 112

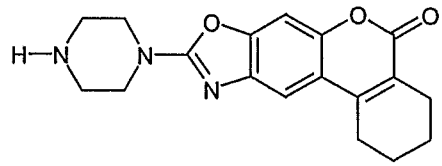
9-(4-Methylpiperazin-1-yl-1,2,3,4-tetrahydro-6,8-dioxa-10-azacyclopenta[b]phenanthren-5-one



In analogy to the procedure described in **Scheme 8**, the title compound is obtained in moderate yield.

Example 113

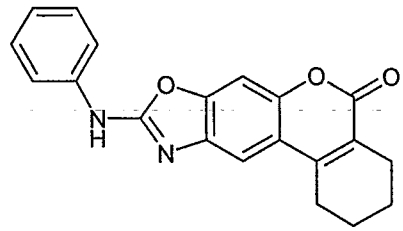
9-Piperazin-1-yl-1,2,3,4-tetrahydro-6,8-dioxa-10-azacyclopenta[b]phenanthren-5-one



In analogy to the procedure described in **Scheme 8**, the title compound is obtained in moderate yield.

Example 114

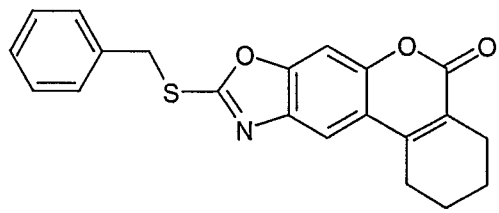
9-Phenylamino-1,2,3,4-tetrahydro-6,8-dioxa-10-azacyclopenta[b]phenanthren-5-one



In analogy to the procedure described in **Scheme 8**, the title compound is obtained in moderate yield.

Example 115

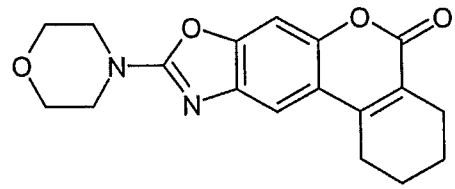
9-Benzylsulfanyl-1,2,3,4-tetrahydro-6,8-dioxa-10-azacyclopenta[b]phenanthren-5-one



In analogy to the procedure described in **Scheme 8**, the title compound is obtained in moderate yield.

Example 116

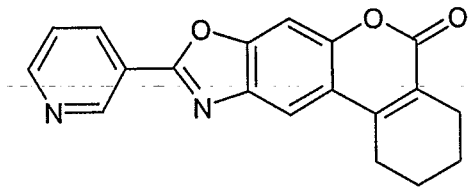
9-Morpholin-4-yl-1,2,3,4-tetrahydro-6,8-dioxa-10-azacyclopenta[b]phenanthren-5-one



In analogy to the procedure described in **Scheme 8**, the title compound is obtained in moderate yield.

Example 117

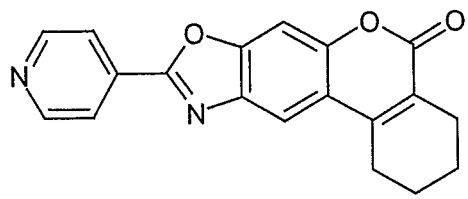
9-Pyridin-3-yl-1,2,3,4-tetrahydro-6,8-dioxa-10-azacyclopenta[b]phenanthren-5-one



In analogy to the procedure described in **Scheme 8**, the title compound is obtained in moderate yield.

Example 118

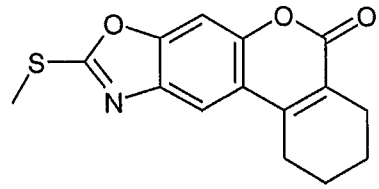
9-Pyridin-4-yl-1,2,3,4-tetrahydro-6,8-dioxa-10-azacyclopenta[b]phenanthren-5-one



In analogy to the procedure described in **Scheme 8**, the title compound is obtained in moderate yield.

Example 119

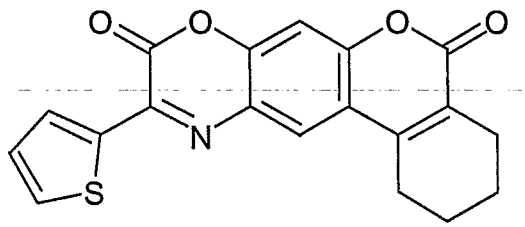
9-Methylsulfanyl-1,2,3,4-tetrahydro-6,8-dioxa-10-azacyclopenta[b]phenanthren-5-one



In analogy to the procedure described in **Scheme 8**, the title compound is obtained in moderate yield.

Example 120

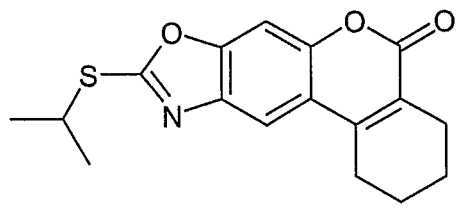
10-Thiophen-2-yl-1,2,3,4-tetrahydro-6,8-dioxa-11-azabenzo[a]anthracene-5,9-dione



In analogy to the procedure described in **Scheme 8**, the title compound is obtained in moderate yield.

Example 121

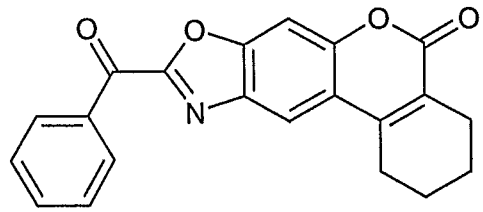
9-Isopropylsulfanyl-1,2,3,4-tetrahydro-6,8-dioxa-10-azacyclopenta[b]phenanthren-5-one



In analogy to the procedure described in **Scheme 8**, the title compound is obtained in moderate yield.

Example 122

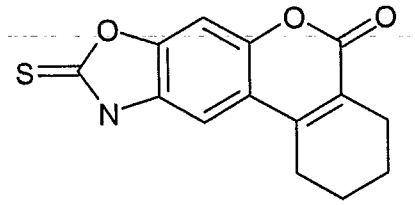
9-Benzoyl-1,2,3,4-tetrahydro-6,8-dioxa-10-azacyclopenta[b]phenanthren-5-one



In analogy to the procedure described in **Scheme 8**, the title compound is obtained in moderate yield.

Example 123

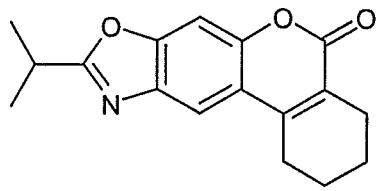
9-Thioxo-1,2,3,4,9,10-hexahydro-6,8-dioxa-10-azacyclopenta[b]phenanthren-5-one



In analogy to the procedure described in **Scheme 8**, the title compound is obtained in moderate yield.

Example 124

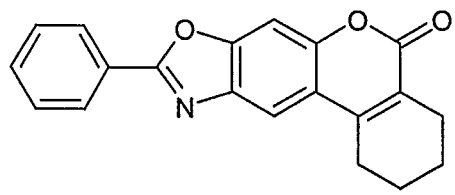
9-Isopropyl-1,2,3,4-tetrahydro-6,8-dioxa-10-azacyclopenta[b]phenanthren-5-one



In analogy to the procedure described in **Scheme 8**, the title compound is obtained in moderate yield.

Example 125

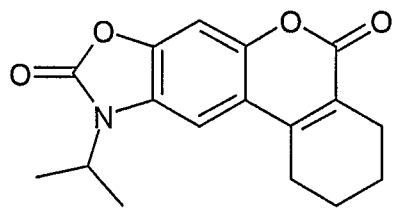
9-Phenyl-1,2,3,4-tetrahydro-6,8-dioxa-10-azacyclopenta[b]phenanthren-5-one



In analogy to the procedure described in **Scheme 8**, the title compound is obtained in moderate yield.

Example 126

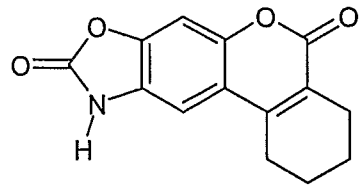
10-Isopropyl-1,2,3,4-tetrahydro-10H-6,8-dioxa-10-azacyclopenta[b]phenanthrene-5,9-dione



In analogy to the procedure described in **Scheme 8**, the title compound is obtained in moderate yield.

Example 127

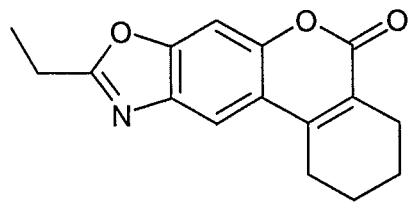
1,2,3,4-Tetrahydro-10H-6,8-dioxa-10-azacyclopenta[b]phenanthrene-5,9-dione



In analogy to the procedure described in **Scheme 8**, the title compound is obtained in moderate yield.

Example 128

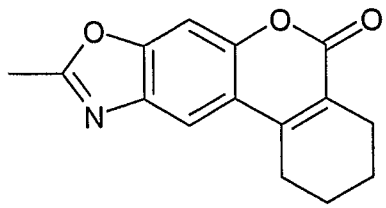
9-Ethyl-1,2,3,4-tetrahydro-6,8-dioxa-10-azacyclopenta[b]phenanthren-5-one



In analogy to the procedure described in **Scheme 8**, the title compound is obtained in moderate yield.

Example 129

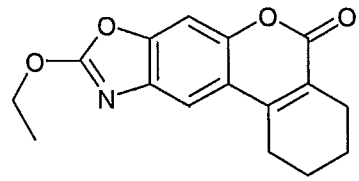
9-Methyl-1,2,3,4-tetrahydro-6,8-dioxa-10-azacyclopenta[b]phenanthren-5-one



In analogy to the procedure described in **Scheme 8**, the title compound is obtained in moderate yield.

Example 130

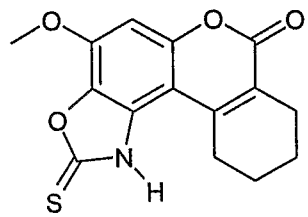
9-Ethoxy-1,2,3,4-tetrahydro-6,8-dioxa-10-azacyclopenta[b]phenanthren-5-one



In analogy to the procedure described in **Scheme 8**, the title compound is obtained in moderate yield.

Example 131

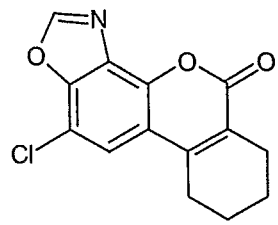
4-Methoxy-2-thioxo-1,2,8,9,10,11-hexahydro-3,6-dioxa-1-azacyclopenta[c]phenanthren-7-one



In analogy to the procedure described in **Scheme 12**, the title compound is obtained in moderate yield.

Example 132

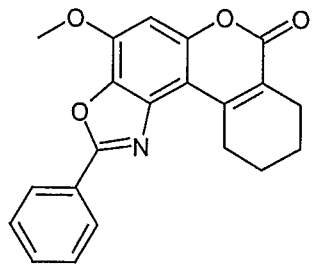
12-Chloro -1,2,3,4-tetrahydro-7,17-dioxa-15-azacyclopenta[a]phenanthren-6-one



In analogy to the procedure described in **Scheme 9**, the title compound is obtained in moderate yield.

Example 133

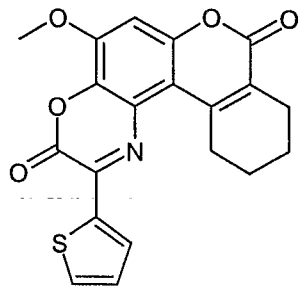
4-Methoxy-2-phenyl- 8,9,10,11-tetrahydro-3,6-dioxa-1-azacyclopenta[c]phenanthren-7-one



In analogy to the procedure described in **Scheme 12**, the title compound is obtained in moderate yield.

Example 134

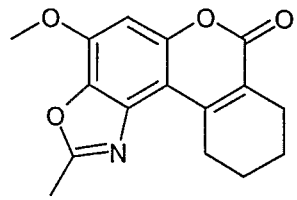
5-Methoxy-2-thiophen-2-yl-9,10,11,12-tetrahydro-4,7-dioxa-1-azabenzo[c]phenanthrene-3,8-dione



In analogy to the procedure described in **Scheme 12**, the title compound is obtained in moderate yield.

Example 135

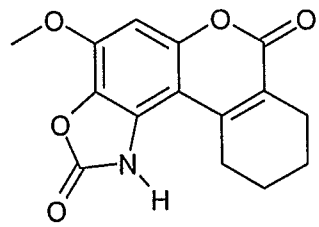
4-Methoxy-2-methyl- 8,9,10,11-tetrahydro-3,6-dioxa-1-azacyclopenta[c]phenanthren-7-one



In analogy to the procedure described in **Scheme 12**, the title compound is obtained in moderate yield.

Example 136

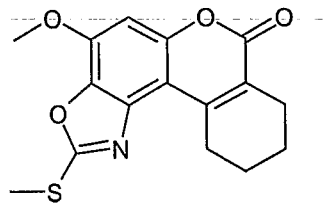
4-Methoxy-8,9,10,11-tetrahydro-1H-3,6-dioxa-1-azacyclopenta[c]phenanthren-2,7-dione



In analogy to the procedure described in **Scheme 12**, the title compound is obtained in moderate yield.

Example 137

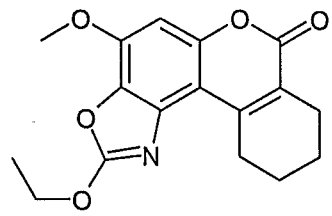
4-Methoxy-2-methylsulfanyl- 8,9,10,11-tetrahydro-3,6-dioxa-1-azacyclopenta[c]phenanthren-7-one



In analogy to the procedure described in **Scheme 12**, the title compound is obtained in moderate yield.

Example 138

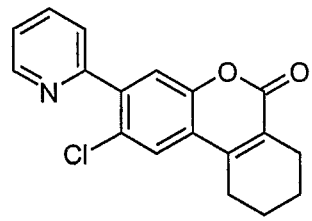
2-Ethoxy-4-methoxy- 8,9,10,11-tetrahydro-3,6-dioxa-1-azacyclopenta[c]phenanthren-7-one



In analogy to the procedure described in **Scheme 12**, the title compound is obtained in moderate yield.

Example 139

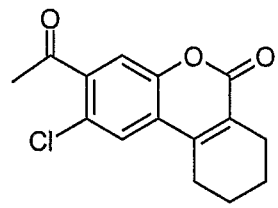
2-Chloro-3-pyridin-2-yl-7,8,9,10-tetrahydro-benzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 5**, the title compound is obtained in moderate yield.

Example 140

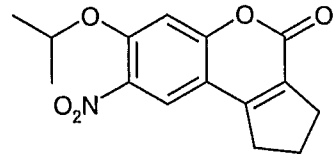
3-Acetyl-2-chloro-7,8,9,10-tetrahydro-benzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 5**, the title compound is obtained in moderate yield.

Example 141

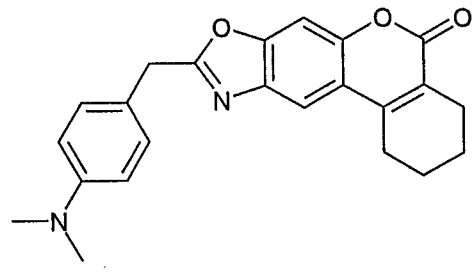
7-Isopropoxy-8-nitro-2,3-dihydro-1H-cyclopenta[c]chromen-4-one



In analogy to the procedure described in **Scheme 4**, the title compound is obtained in moderate yield.

Example 142

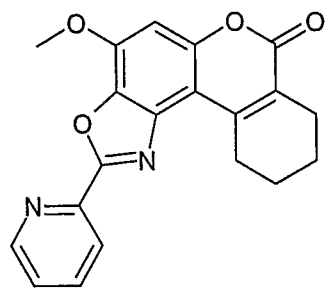
9-(4-Dimethylamino-benzyl)-1,2,3,4-tetrahydro-6,8-dioxa-10-aza-cyclopenta[b]phenanthren-5-one



In analogy to the procedure described in **Scheme 8**, the title compound is obtained in moderate yield.

Example 143

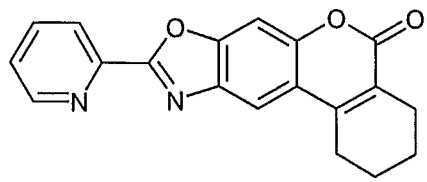
4-Methoxy-2-pyridin-2-yl-8,9,10,11-tetrahydro-3,6-dioxa-1-aza-cyclopenta[c]phenanthren-7-one



In analogy to the procedure described in **Scheme 12**, the title compound is obtained in moderate yield.

Example 144

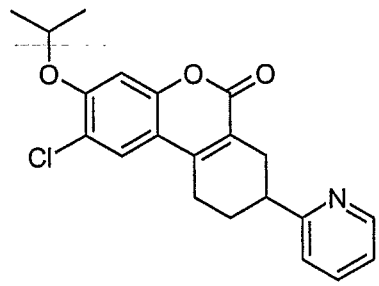
9-Pyridin-2-yl-1,2,3,4-tetrahydro-6,8-dioxa-10-aza-cyclopenta[b]phenanthren-5-one



In analogy to the procedure described in **Scheme 8**, the title compound is obtained in moderate yield.

Example 145

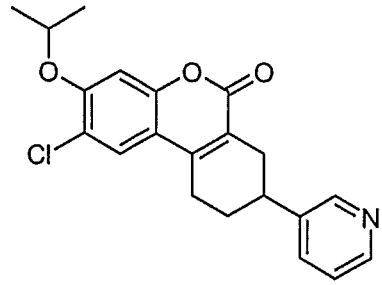
2-Chloro-3-isopropoxy-8-pyridin-2-yl-7,8,9,10-tetrahydro-benzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 146

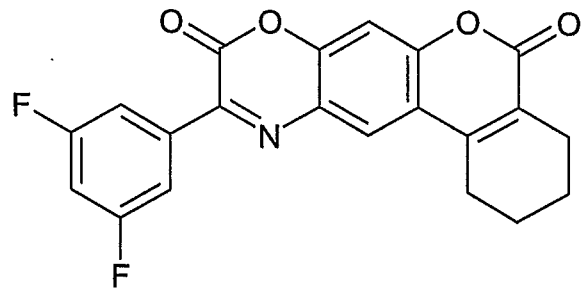
2-Chloro-3-isopropoxy-8-pyridin-3-yl-7,8,9,10-tetrahydro-benzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 147

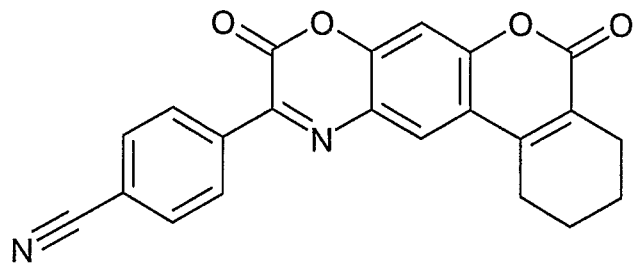
10-(3,5-Difluoro-phenyl)-1,2,3,4-tetrahydro-6,8-dioxa-11-aza-benzo[a]anthracene-5,9-dione



In analogy to the procedure described in **Scheme 8**, the title compound is obtained in moderate yield.

Example 148

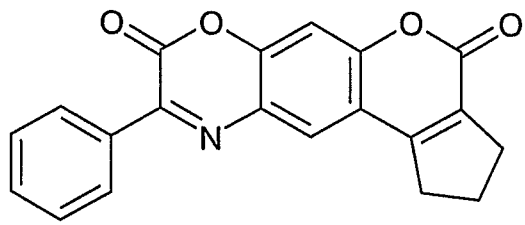
4-(5,9-Dioxo-1,3,4,5-tetrahydro-2H,9H-6,8-dioxa-11-aza-benzo[a]anthracen-10-yl)-benzonitrile



In analogy to the procedure described in **Scheme 8**, the title compound is obtained in moderate yield.

Example 149

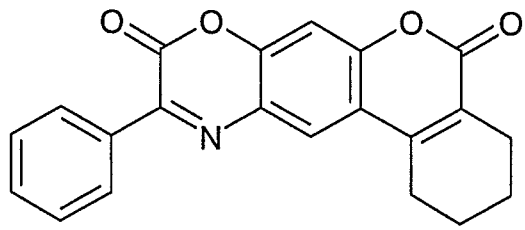
9-Phenyl-2,3-dihydro-1H-5,7-dioxa-10-aza-cyclopenta[a]anthracene-4,8-dione



In analogy to the procedure described in **Scheme 8**, the title compound is obtained in moderate yield.

Example 150

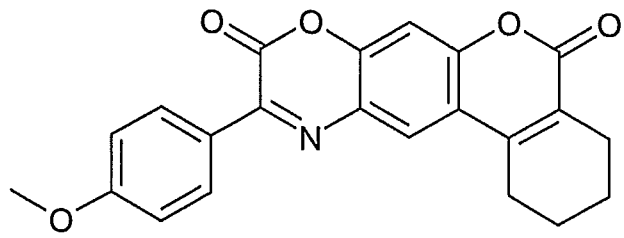
10-Phenyl-1,2,3,4-tetrahydro-6,8-dioxa-11-aza-benzo[a]anthracene-5,9-dione



In analogy to the procedure described in **Scheme 8**, the title compound is obtained in moderate yield.

Example 151

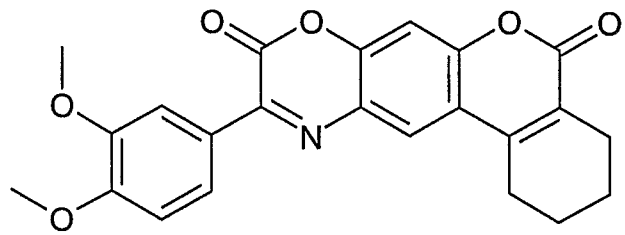
10-(4-Methoxy-phenyl)-1,2,3,4-tetrahydro-6,8-dioxa-11-aza-benzo[a]anthracene-5,9-dione



In analogy to the procedure described in **Scheme 8**, the title compound is obtained in moderate yield.

Example 152

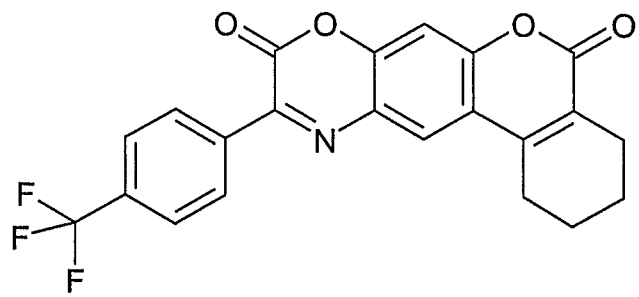
10-(3,4-Dimethoxy-phenyl)-1,2,3,4-tetrahydro-6,8-dioxa-11-aza-benzo[a]anthracene-5,9-dione



In analogy to the procedure described in **Scheme 8**, the title compound is obtained in moderate yield.

Example 153

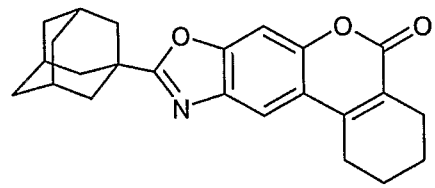
10-(4-Trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-6,8-dioxa-11-aza-benzo[a]anthracene-5,9-dione



In analogy to the procedure described in **Scheme 8**, the title compound is obtained in moderate yield.

Example 154

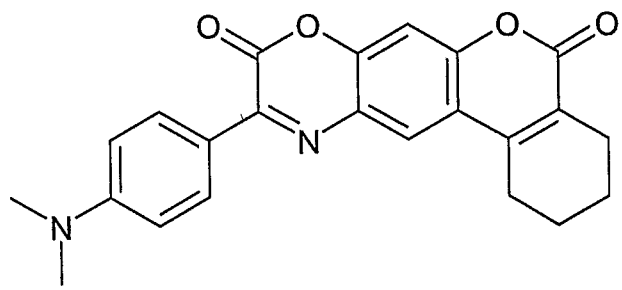
9-Adamantan-1-yl-1,2,3,4-tetrahydro-6,8-dioxa-10-aza-cyclopenta[b]phenanthren-5-one



In analogy to the procedure described in **Scheme 8**, the title compound is obtained in moderate yield.

Example 155

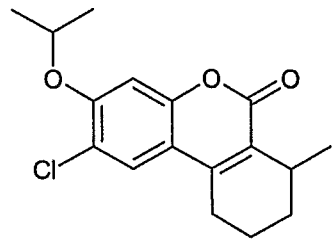
10-(4-Dimethylamino-phenyl)-1,2,3,4-tetrahydro-6,8-dioxa-11-aza-benzo[a]anthracene-5,9-dione



In analogy to the procedure described in **Scheme 8**, the title compound is obtained in moderate yield.

Example 156

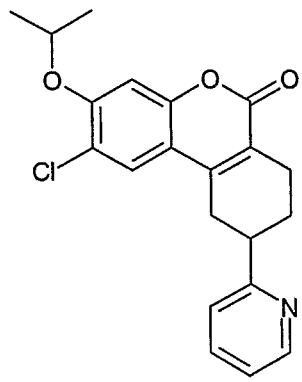
2-Chloro-3-isopropoxy-7-methyl-7,8,9,10-tetrahydro-benzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Example 157

2-Chloro-3-isopropoxy-9-pyridin-2-yl-7,8,9,10-tetrahydro-benzo[c]chromen-6-one



In analogy to the procedure described in **Scheme 1**, the title compound is obtained in moderate yield.

Pure stereoisomeric forms of the compounds and the intermediates of this invention may be obtained by the application of art-known procedures. Diastereomers may be separated by physical separation methods such as

selective crystallization and chromatographic techniques, e.g. liquid chromatography using chiral stationary phases. Enantiomers may be separated from each other by selective crystallization of their diastereomeric salts with optically active acids. Alternatively, enantiomers may be separated by chromatographic techniques using chiral stationary phases. Said pure stereoisomeric forms may also be derived from the corresponding pure stereoisomeric form of appropriate starting materials, provided that the reaction occurs stereoselectively. Stereoisomeric forms of Formula I are obviously intended to be included within the scope of this invention.

ADDITION SALTS

For therapeutic use, salts of the compounds of Formula I are those wherein the counterion is pharmaceutically acceptable. However, salts of acids and bases which are non-pharmaceutically acceptable may also find use, for example, in the preparation and purification of pharmaceutically acceptable compounds. All salts whether pharmaceutically acceptable or not are included within the ambit of the present invention. The pharmaceutically acceptable salts as mentioned above are meant to comprise the therapeutically active non-toxic salt forms which the compounds of Formula I are able to form. The latter can conveniently be obtained by treating the base form with such appropriate acids as inorganic acids, e.g. hydrohalic acids such as hydrochloric, hydrobromic and the like; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids such as acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, oxopropanoic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfonic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely, the salt form can be converted by treatment with alkali into the free base form.

PHARMACEUTICAL COMPOSITIONS

The active ingredients of the invention, together with one or more conventional adjuvants, carriers, or diluents, may be placed into the form of

pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as coated or uncoated tablets or filled capsules, or liquids, such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use; in the form of suppositories or capsules for rectal administration or in the form of sterile injectable solutions for parenteral (including intravenous or subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional or new ingredients in conventional or special proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. Tablets containing one (1) to one hundred (100) milligrams of active ingredient or zero point five (0.5) to five hundred (500) milligrams per tablet, are accordingly suitable representative unit dosage forms.

The term "carrier" applied to pharmaceutical compositions of the invention refers to a diluent, excipient, or vehicle with which an active compound is administered. Such pharmaceutical carriers can be sterile liquids, such as water, saline solutions, aqueous dextrose solutions, aqueous glycerol solutions, and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin, 18th Edition.

METHOD OF TREATING

Due to their high degree of activity and their low toxicity, together presenting a most favorable therapeutic index, the active principles of the invention may be administered to a subject, e.g., a living animal (including a human) body, in need thereof, for the treatment, alleviation, modulation, amelioration, palliation, or elimination of an indication or condition which is susceptible thereto, or representatively of an indication or condition set forth elsewhere in this application, optionally concurrently, simultaneously, or together with one or more pharmaceutically-acceptable excipients, carriers, or diluents,

and optionally in the form of a pharmaceutical composition thereof, whether by oral, rectal, or parental (including intravenous and subcutaneous) or in some cases even topical route, in an effective amount. Suitable dosage ranges are 1-1000 milligrams daily, 10-500 milligrams daily, and 50-500 milligrams daily, depending as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and the preference and experience of the physician or veterinarian in charge.

The term "therapeutically effective" applied to dose or amount refers to that quantity of a compound or pharmaceutical composition that is sufficient to result in a desired activity upon administration to a living animal body in need thereof.

The active agents of the present invention may be administered orally, topically, parenterally, or mucosally (*e.g.*, buccally, by inhalation, or rectally) in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers. It is usually desirable to use the oral route. The active agents may be administered orally in the form of a capsule, a tablet, or the like (*see* Remington: The Science and Practice of Pharmacy, 20th Edition (2000), Philadelphia, PA). The orally administered medicaments may be administered in the form of a time-controlled release vehicle, including diffusion-controlled systems, osmotic devices, dissolution-controlled matrices, and erodible/degradable matrices.

For oral administration in the form of a tablet or capsule, the active drug component can be combined with a non-toxic, pharmaceutically acceptable excipients such as binding agents (*e.g.,* pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (*e.g.,* lactose, sucrose, glucose, mannitol, sorbitol and other reducing and non-reducing sugars, microcrystalline cellulose, calcium sulfate, or calcium hydrogen phosphate); lubricants (*e.g.*, magnesium stearate, talc, or silica, steric acid,

sodium stearyl fumarate, glyceryl behenate, calcium stearate, and the like); disintegrants (*e.g.*, potato starch or sodium starch glycolate); or wetting agents (*e.g.*, sodium lauryl sulphate), coloring and flavoring agents, gelatin, sweeteners, natural and synthetic gums (such as acacia, tragacanth or alginates), buffer salts, carboxymethylcellulose, polyethyleneglycol, waxes, and the like. For oral administration in liquid form, the drug components can be combined with non-toxic, pharmaceutically acceptable inert carriers (*e.g.*, ethanol, glycerol, water), suspending agents (*e.g.*, sorbitol syrup, cellulose derivatives or hydrogenated edible fats), emulsifying agents (*e.g.*, lecithin or acacia), non-aqueous vehicles (*e.g.*, almond oil, oily esters, ethyl alcohol or fractionated vegetable oils), preservatives (*e.g.*, methyl or propyl-p-hydroxybenzoates or sorbic acid), and the like. Stabilizing agents such as antioxidants (BHA, BHT, propyl gallate, sodium ascorbate, citric acid) can also be added to stabilize the dosage forms.

The tablets can be coated by methods well known in the art. The compositions of the invention can be also introduced in microspheres or microcapsules, *e.g.*, fabricated from polyglycolic acid/lactic acid (PGLA). Liquid preparations for oral administration can take the form of, for example, solutions, syrups, emulsions or suspensions, or they can be presented as a dry product for reconstitution with water or other suitable vehicle before use. Preparations for oral administration can be suitably formulated to give controlled or postponed release of the active compound.

The active drugs can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines, as is well known.

Drugs of the invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. Active drugs may also be coupled with soluble polymers as

targetable drug carriers. Such polymers can include polyvinyl-pyrrolidone, pyran copolymer, polyhydroxy-propyl methacrylamide-phenol, polyhydroxy-ethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, active drug may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxybutyric acid, polyorthoesters, polyacetals, polyhydropyrans, polycyanoacrylates, and cross-linked or amphipathic block copolymers of hydrogels.

For administration by inhalation, the therapeutics according to the present invention can be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, *e.g.,* dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. In the case of a pressurized aerosol, the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, *e.g.,* gelatin for use in an inhaler or insufflator can be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The formulations of the invention can be delivered parenterally, *i.e.*, by intravenous (i.v.), intracerebroventricular (i.c.v.), subcutaneous (s.c.), intraperitoneal (i.p.), intramuscular (i.m.), subdermal (s.d.), or intradermal (i.d.) administration, by direct injection, via, for example, bolus injection or continuous infusion. Formulations for injection can be presented in unit dosage form, *e.g.,* in ampoules or in multi-dose containers, with an added preservative. The compositions can take such forms as excipients, suspensions, solutions, or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient can be in powder form for reconstitution with a suitable vehicle, *e.g.,* sterile pyrogen-free water, before use.

Compositions of the present invention can also be formulated for rectal administration, *e.g.*, as suppositories or retention enemas (*e.g.,* containing conventional suppository bases such as cocoa butter or other glycerides).

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient, optionally at various dosage levels to act as a titration pack. The pack may, for example, comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. Compositions of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

As disclosed herein, the dose of the components in the compositions of the present invention is determined to ensure that the dose administered continuously or intermittently will not exceed an amount determined after consideration of the results in test animals and the individual conditions of a patient. A specific dose naturally varies depending on the dosage procedure, the conditions of a patient or a subject animal such as age, body weight, sex, sensitivity, feed, dosage period, drugs used in combination, seriousness of the disease. The appropriate dose and dosage times under certain conditions can be determined by the test based on the above-described indices but may be refined and ultimately decided according to the judgment of the practitioner and each patient's circumstances (age, general condition, severity of symptoms, sex, etc.) according to standard clinical techniques.

Toxicity and therapeutic efficacy of the compositions of the invention can be determined by standard pharmaceutical procedures in experimental animals, *e.g.*, by determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between therapeutic and toxic effects is the therapeutic index and

it can be expressed as the ratio ED_{50}/LD_{50}. Compositions that exhibit large therapeutic indices are preferred.

EXAMPLES OF REPRESENTATIVE PHARMACEUTICAL COMPOSITIONS

With the aid of commonly used solvents, auxiliary agents and carriers, the reaction products can be processed into tablets, coated tablets, capsules, drip solutions, suppositories, injection and infusion preparations, and the like and can be therapeutically applied by the oral, rectal, parenteral, and additional routes. Representative pharmaceutical compositions follow.

(a) Tablets suitable for oral administration which contain the active ingredient may be prepared by conventional tabletting techniques.

(b) For suppositories, any usual suppository base may be employed for incorporation thereinto by usual procedure of the active ingredient, such as a polyethyleneglycol which is a solid at normal room temperature but which melts at or about body temperature.

(c) For parental (including intravenous and subcutaneous) sterile solutions, the active ingredient together with conventional ingredients in usual amounts are employed, such as for example sodium chloride and double-distilled water q.s., according to conventional procedure, such as filtration, aseptic filling into ampoules or IV-drip bottles, and autoclaving for sterility.

Other suitable pharmaceutical compositions will be immediately apparent to one skilled in the art.

FORMULATION EXAMPLES

The following examples are again given by way of illustration only and are not to be construed as limiting.

EXAMPLE 1

Tablet Formulation

A suitable formulation for a tablet containing 10 milligrams of active ingredient is as follows:

	mg
Active Ingredient	10
Lactose	61
Microcrystalline Cellulose	25
Talcum	2
Magnesium stearate	1
Colloidal silicon dioxide	1

5

EXAMPLE 2

Tablet Formulation

Another suitable formulation for a tablet containing 100 mg is as follows:

	mg
Active Ingredient	100
Polyvinylpyrrolidone, crosslinked	10
Potato starch	20
Polyvinylpyrrolidone	19
Magnesium stearate	1
Microcrystalline Cellulose	50
Film coated and colored.	

The film coating material consists of:

Hypromellose	10
Microcryst. Cellulose	5
Talcum	5
Polyethylene glycol	2
Color pigments	5

EXAMPLE 3

Capsule Formulation

A suitable formulation for a capsule containing 50 milligrams of active ingredient is as follows:

	mg
Active Ingredient	50
Corn starch	26
Dibasic calcium phosphate	50
Talcum	2
Colloidal silicon dioxide	2

filled in a gelatin capsule.

EXAMPLE 4

Solution for injection

A suitable formulation for an injectable solution is as follows:

Active Ingredient	mg	10
Sodium chloride	mg	q.s.
Water for Injection	mL	add 1.0

EXAMPLE 5

Liquid oral formulation

A suitable formulation for 1 liter of a an oral solution containing 2 milligrams of active ingredient in one milliliter of the mixture is as follows:

	mg
Active Ingredient	2
Saccharose	250
Glucose	300
Sorbitol	150
Orange flavor	10
Colorant	q.s.
Purified water	add 1000 mL

EXAMPLE 6

Liquid oral formulation

Another suitable formulation for 1 liter of a liquid mixture containing 20 milligrams of active ingredient in one milliliter of the mixture is as follows:

	G
Active Ingredient	20.00
Tragacanth	7.00
Glycerol	50.00
Saccharose	400.00
Methylparaben	0.50
Propylparaben	0.05
Black currant-flavor	10.00
Soluble Red color	0.02
Purified water	add 1000 mL

EXAMPLE 7

Liquid oral formulation

Another suitable formulation for 1 liter of a liquid mixture containing 2 milligrams of active ingredient in one milliliter of the mixture is as follows:

	G
Active Ingredient	2
Saccharose	400
Bitter orange peel tincture	20
Sweet orange peel tincture	15
Purified water	add 1000 mL

EXAMPLE 8

Aerosol formulation

180 g aerosol solution contain:

	G
Active Ingredient	10
Oleic acid	5
Ethanol	81
Purified Water	9
Tetrafluoroethane	75

15 ml of the solution are filled into aluminum aerosol cans, capped with a dosing valve, purged with 3.0 bar.

EXAMPLE 9

TDS formulation

100 g solution contain:

	G
Active Ingredient	10.0
Ethanol	57.5
Propyleneglycol	7.5
Dimethylsulfoxide	5.0
Hydroxyethylcellulose	0.4
Purified water	19.6

1.8 ml of the solution are placed on a fleece covered by an adhesive backing foil. The system is closed by a protective liner which will be removed before use.

EXAMPLE 10

Nanoparticle formulation

10 g of polybutylcyanoacrylate nanoparticles contain:

	G
Active Ingredient	1.00
Poloxamer	0.10
Butylcyanoacrylate	8.75
Mannitol	0.10
Sodium chloride	0.05

Polybutylcyanoacrylate nanoparticles are prepared by emulsion polymerization in a water/0.1 N HCl/ethanol mixture as polymerizsation medium. The nanoparticles in the suspension are finally lyophilized under vacuum.

PHARMACOLOGY - SUMMARY

The active principles of the present invention, and pharmaceutical compositions thereof and method of treating therewith, are characterized by unique and advantageous properties, rendering the "subject matter as a whole", as claimed herein, unobvious. The compounds and pharmaceutical compositions thereof exhibit, in standard accepted reliable test procedures, the following valuable properties and characteristics:

METHODS

BINDING ASSAYS FOR THE CHARACTERIZATION OF MGLUR5 ANTAGONIST PROPERTIES

[^{3}H]MPEP (2-methyl-6-(phenylethynyl)pyridine) binding to transmembrane allosteric modulatory sites of mGluR5 receptors in cortical membranes

Preparation of rat cortical membranes:

Male Sprague-Dawley rats (200-250 g) are decapitated and their brains are removed rapidly. The cortex is dissected and homogenized in 20 volumes of ice-cold 0.32 M sucrose using a glass-Teflon homogenizer. The homogenate is centrifuged at 1000xg for 10 min. The pellet is discarded and the supernatant centrifuged at 20,000xg for 20 min. The resulting pellet is re-suspended in 20 volumes of distilled water and centrifuged for 20 min at 8000xg. Then the supernatant and the buffy coat are centrifuged at 48,000xg for 20 min in the presence of 50 mM Tris-HCl, pH 8.0. The pellet is then re-suspended and centrifuged two to three more times at 48,000xg for 20 min in the presence of 50 mM Tris-HCl, pH 8.0. All centrifugation steps are carried out at 4°C. After resuspension in 5 volumes of 50 mM Tris-HCl, pH 8.0 the membrane suspension is frozen rapidly at -80°C.

On the day of assay the membranes are thawed and washed four times by resuspension in 50 mM Tris-HCl, pH 8.0 and centrifugation at 48,000xg for 20 min. and finally re-suspended in 50 mM Tris-HCl, pH 7.4. The amount of protein in the final membrane preparation (250-500 µg/mL) is determined according to the method of Lowry (Lowry O. H. et al., 1951. J. Biol. Chem. 193, 256-275).

[^{3}H]MPEP Assay

Incubations are started by adding (^{3}H)-MPEP (50.2 Ci/mmol, 5nM, Tocris) to vials with 125-250µg protein (total volume 0.5 ml) and various concentrations of the agents. The incubations are continued at room temperature for 60 min (equilibrium is achieved under the conditions used).

Non-specific binding is defined by the addition of unlabeled MPEP (10 µM). Incubations are terminated using a Millipore filter system. The samples are rinsed twice with 4 mL of ice cold assay buffer over glass fibre filters (Schleicher & Schuell) under a constant vacuum. Following separation and rinse, the filters are placed into scintillation liquid (5 mL Ultima Gold) and radioactivity retained on the filters is determined with a conventional liquid scintillation counter (Hewlett Packard, Liquid Scintillation Analyser).

Characterization

Specific binding is extremely high i.e. normally > 85% and essentially independent of buffer (Tris or HEPES oth 50 mM) and pH (6.8-8.9). There is a clear saturable protein dependence and the chosen protein concentration used for subsequent assays (250-500 µg/mL) is within the linear portion of this dependence. Cold MPEP displaces hot ligand with an IC_{50} of 18.8 ± 4.1nM. The Kd of (^{3}H)-MPEP of 13.6 nM is determined by Scatchard analysis and used according to the Cheng Prussoff relationship to calculate the affinity of displacers as Kd values (IC_{50} of cold MPEP equates to a Ki of 13.7 nM). B_{max} is 0.56 pm / mg protein.

FUNCTIONAL ASSAY OF MGLUR5 RECEPTORS

Materials and Methods

Astrocyte culture

Primary astrocyte cultures are prepared from cortices of newborn rats as described by Booher and Sensenbrenner (1972). Briefly, Sprague-Dawley rat pups (2 - 4 d old) are decapitated and neocortices are dissected, disintegrated with a nylon filter (poresize 80 µm) and carefully triturated. The cell suspension is plated on poly-D-lysine precoated flasks (Costar) and cultivated in Dulbecco's Modified Eagle's Medium (DMEM, InVitrogen) supplemented with 10% heat inactivated fetal calf serum (FCS_i, Sigma), 4 mM glutamine (Biochrom) and 50 µg/mL gentamycin (Biochrom) at 37°C in a humidified atmosphere of 5% CO_2/95% air for 7 d with exchanging the medium at day 2.

After 7 DIV, cells are shaken overnight at 250 rpm to remove oligodendrocytes and microglia. The next day, astrocytes are rinsed twice with CMF-PBS, trypsinized and subplated on poly-D-lysine precoated 96-well plates (Becton Dickinson #6516 or #6640) at a density of 40,000 – 45,000 cells/well. 24 h after establishing the secondary culture the astrocytes are rinsed with PBS^{++} and fed with astrocyte-defined medium (ADM) consisting of DMEM containing 1x G5-supplement (InVitrogen), 0.5 µg/mL heparan sulfate (Sigma), and 1.5 µg/ mL fibronectin (Sigma) (Miller et al., 1993). 3 d later the medium is exchanged and the cells incubated for another 2-3 d, so that at the time of experiments astrocytes are 14-15 DIV.

Immunocytochemistry

Immunostaining is performed to confirm the presence of classical astrocytic markers such as GFAP as well the expression of mGluR5 receptors.

Accumulation of [^{3}H]-Inositol Phosphates

After astrocytes are cultured for 12 d ADM is removed and inositol-free DMEM (MP Biomedicals) supplemented with [^{3}H]myo-inositol (0.5 µCi / well; Perkin Elmer), and the ADM chemicals is added. After 48 h the medium is replaced with 100 µL Locke´s buffer (plus 20 mM Li^+, pH 7.4) and incubated for 15 min at 37°C before replacement with agonists / antagonists in Locke´s buffer. The incubation (45 min at 37 °C) is terminated by replacing the Locke's solutions with 100 µL 0.1 M HCl (10 min on ice). The 96 well plates can be frozen at -20°C at this stage until further analysis. Home made resin exchange columns (AG1-X8 Biorad, 140-14444) are used to separate labeled inositol phosphates by elution with 1 mL of 1 M ammonium formate / 0.1 M formic acid into 24-well visiplates (Perkin Elmer). Scintillation liquid (UltimaFlow AF, Perkin Elmer) is added, the plate sealed and vortexed before radioactivity is determined by conventional liquid scintillation counting (Microbeta,Perkin Elmer) as disintegration per minute (DPM).

Alternatively, on the day of assay, columns are washed with 1 mL of 0.1M formic acid followed by 1 mL of distilled water. The contents of each assay

well are then added to one column and washed with 1 mL distilled water followed by 1 mL of 5 mM sodium tetraborate / 60 mM sodium formate. The retained radioactive inositol phosphates are then eluted with 2 X 1mL of 1M ammonium formate / 0.1M formic acid into 24-well visiplates. Scintillation liquid (UltimaFlow AF, Perkin Elmer) is added, the plate sealed and vortexed before radioactivity is determined by conventional liquid scintillation counting (Microbeta,Perkin Elmer) as disintegration per minute (DPM).

Calcium FLIPR studies

Cultured astrocytes express mGluR5 receptors as shown by immunostaining. The increase of intracellular calcium after stimulation with the mGluR5 agonist DHPG or L-quisqualate is measured using the fluorometric imaging plate reader (FLIPR) and the Ca-Kit (both Molecular Devices, CA). Prior to addition of agonist or antagonist the medium is aspirated and cells are loaded for 2 h at RT with 150 µL of loading buffer consisting of Ca-sensitive dye (MD # R8033) reconstituted in sodium chloride (123 mM), potassium chloride (5.4 mM), magnesium chloride (0.8 mM), calcium chloride (1.8 mM), D-glucose (15 mM), and HEPES (20 mM), pH 7.3. Subsequently, plates are transferred to FLIPR to detect calcium increase with the addition of DHPG (300 µM) or L-quisqualate (100 nM) measured as relative fluorescence units (RFU). If antagonists are tested, these compounds are pre-incubated for 10 min at RT before addition of the respective agonist.

For positive modulators, concentration-response curves for quisqualate are performed in the presence and absence of 10 µM modulator to determine the extent of potentiation / agonist potency increase. Thereafter, concentration-response curves for the positive modulator are performed in the presence of a fixed concentration of quisqualate showing the biggest window for potentiation (normally 10-30 nM).

Data analysis

The fluorescence signal increase after addition of agonist reflects the increase of intracellular calcium. Inconsistencies in the amount of cells per well are normalised by using the spatial uniformity correction of the FLIPR software. The mean of replicated temporal data (n=5) is calculated and used for graphical representation. For the evaluation of the pharmacology, the calcium changes in response to different concentrations of agonist or antagonist are determined using a maximum minus minimum (MaxMin) calculation.

All responses (DPM- or RFU-values) are determined as percentage of control (= maximum response at 100 nM quisqualate).

EC_{50} and IC_{50} are calculated according the logistic equation using GraFit 5.0 (Erithacus Software).

FUNCTIONAL ASSAY OF mGluR1 RECEPTORS IN CEREBELLAR GRANULE CELLS – RADIOACTIVE ASSAY FOR CHANGES IN IP3 LEVELS

Preparation of cerebellar granule cells

Cerebellar cortici are obtained from P8 postnatal Sprague Dawley rats, mechanically disrupted into small pieces with forceps and then transferred to Ca^{2+} and Mg^{2+} free Hank's buffered salt solution (HBSS-CMF) on ice. After three washes in HBSS-CMF, the tissue pieces are incubated at 37°C for 8 minutes in the presence of 0.25% trypsin / 0.05% DNase. The enzymatic reaction is stopped with 0.016% DNAase / 0.1% ovomucoid before centrifugation at 800 rpm for 5 minutes. The supernatant is replaced twice with $NaHCO_3$/HEPES-buffered basal Eagle medium (BME) plus 20 mM KCl. Cells are mechanically dissociated in 2 ml of BME by trituration through three Pasteur pipettes of successively decreasing tip diameter and then filtered through a 48 µM gauge filter. Cells are plated at a density of 150,000 cells in 50 µl in each well of poly-L-Lysin pre-coated 96 well plates (Falcon). The cells are nourished with BEM supplemented with 10% foetal calf serum, 2 mM glutamine (Biochrom), 20 mM KCl and gentamycin (Biochrom) and

incubated at 36 °C with 5% CO_2 at 95% humidity. After 24 h, cytosine-ß-D-arabinofuranoside (AraC, 10 µM) is added to the medium.

IP_3 assay with [^{3}H]myo-inositol

After 6 DIV the culture medium is replaced completely with inositol free DMEM (ICN) containing [^{3}H]myo-inositol (Perkin Elmer) at a final concentration of 0.5 µCi / 100 µl / well and incubated for a further 48 hours. The culture medium in each well is replaced with 100 µL Locke's buffer (containing in (mM) NaCl (156), KCl (5.6), $NaHCO_3$ (3.6), $MgCl_2$ (1.0), $CaCl_2$ (1.3), Glucose (5.6), HEPES (10)) with additional (20 mM Li^+, pH 7.4) and incubated for 15 min at 37°C. Locke's buffer is replaced with agonists / antagonists / putative mGluR1 ligands in Locke's buffer and incubated for 45 min. These solutions are then replaced by 100 µL 0.1M HCl in each well and incubated for a further 10 mins on ice. The 96 well plates can be frozen at -20°C at this stage until further analysis. Home made resin exchange columns (AG1-X8 Biorad, 140-14444) are used to separate labeled inositol phosphates. On the day of assay, columns are washed with 1 ml of 0.1M formic acid followed by 1 ml of distilled water. The contents of each assay well are then added to one column and washed with 1 ml distilled water followed by 1 ml of 5 mM sodium tetraborate / 60 mM sodium formate. The retained radioactive inositol phosphates are then eluted with 2 * 1ml of 1M ammonium formate / 0.1M formic acid into 24-well visiplates. Scintillation liquid (UltimaFlow AF, Perkin Elmer) is added, the plate sealed and vortexed before radioactivity is determined by conventional liquid scintillation counting (Microbeta,Perkin Elmer) as disintegration per minute (DPM).

Chemicals

Unless otherwise stated all chemicals are purchased from Sigma.

References

Booher and Sensenbrenner (1972) *Neurobiology* **2(3)**:97-105

Miller et al., (1993) *Brain Res.* **618(1)**:175-8

Compounds of the present invention have a potency (EC_{50} or IC_{50}, respectively) range of about 0.5 nM to about 100 μM.

CONCLUSIONS

In conclusion, from the foregoing, it is apparent that the present invention provides novel, valuable, and unpredictable applications and uses of the compounds of the present invention, which compounds comprise the active principle according to the present invention, as well as novel pharmaceutical compositions thereof and methods of preparation thereof and of treating therewith, all possessed of the foregoing more specifically-enumerated characteristics and advantages.

The high order of activity of the active agent of the present invention and compositions thereof, as evidenced by the tests reported, is indicative of utility based on its valuable activity in human beings as well as in lower animals. Clinical evaluation in human beings has not been completed, however. It will be clearly understood that the distribution and marketing of any compound or composition falling within the scope of the present invention for use in human beings will of course have to be predicated upon prior approval by governmental agencies, such as the U.S. Federal Food and Drug Administration, which are responsible for and authorized to pass judgment on such questions.

The instant chromenone derivatives represent a novel class of Group I mGluR modulators. In view of their potency, they will be useful therapeutics in a wide range of CNS disorders which involve abnormal glutamate induced excitation.

These compounds accordingly find application in the treatment of the following disorders of a living animal body, especially a human: AIDS-related dementia, Alzheimer's disease, Creutzfeld-Jakob´s syndrome, bovine spongiform encephalopathy (BSE) or other prion related infections,

diseases involving mitochondrial dysfunction, diseases involving ß-amyloid and/or tauopathy such as Down's syndrome, hepatic encephalopathy, Huntington's disease, motor neuron diseases such as amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), olivoponto-cerebellar atrophy, post-operative cognitive deficit (POCD), Parkinson's disease, Parkinson's dementia, mild cognitive impairment, dementia pugilistica, vascular and frontal lobe dementia, cognitive impairment, eye injuries or diseases (e.g. glaucoma, retinopathy, macular degeneration), head and brain and spinal cord injuries / trauma, hypoglycaemia, hypoxia (e.g. perinatal), ischaemia (e.g. resulting from cardiac arrest, stroke, bypass operations or transplants), convulsions, glioma and other tumours, inner ear insult (e.g. in tinnitus, sound- or drug-induced), L-Dopa-induced and tardive dyskinesias.

These compounds also find application in the treatment of the following disorders of a living animal body, especially a human: abuse and addiction (nicotine, alcohol, opiate, cocaine, amphetamine, obesity and others), amyotrophic lateral sclerosis (ALS), anxiety and panic disorders, attention deficit hyperactivity disorder (ADHD), restless leg syndrome, hyperactivity in children, autism, convulsions / epilepsy, dementia (e.g. in Alzheimer's disease, Korsakoff syndrome, vascular dementia, HIV infections), major depressive disorder or depression (including that resulting from Borna virus infection) and bipolar manic-depressive disorder, drug tolerance (e.g. to opioids), movement disorders, dystonia, dyskinesia (e.g. L-Dopa-induced, tardive dyskinesia or in Huntington's disease), fragile-X syndrome, Huntington's chorea, irritable bowel syndrome (IBS), migraine, multiple sclerosis, muscle spasms, pain (chronic and acute, e.g. inflammatory pain, neuropathic pain, allodynia, hyperalgesia, nociceptive pain), Parkinson's disease, post traumatic stress disorder, schizophrenia (positive and negative symptoms), spasticity, tinnitus, Tourette's syndrome, urinary incontinence, vomiting, pruritic conditions (e.g. pruritis), sleep disorders, micturition disorders, neuromuscular disorder in the lower urinary tract, gastroesophageal reflux disease (GERD), lower esophageal sphincter (LES) disease, functional gastrointestinal disorders, dyspepsia, regurgitation,

respiratory tract infection, bulimia nervosa, chronic laryngitis, asthma (e.g. reflux-related asthma), lung disease, eating disorders, obesity, obesity-related disorders, agoraphobia, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, social phobia, substance-induced anxiety disorder, delusional disorder, schizoaffective disorder, schizophreniform disorder, substance-induced psychotic disorder, delirium, or for cognitive enhancement and/or neuroprotection.

These compounds also find application in the treatment of indications in a living animal body, especially a human, wherein a particular condition does not necessarily exist but wherein a particular physiological parameter may be improved through administration of the instant compounds, including cognitive enhancement.

The method-of-treating a living animal body with a compound of the invention, for the inhibition of progression or alleviation of the selected ailment therein, is as previously stated by any normally-accepted pharmaceutical route, employing the selected dosage which is effective in the alleviation of the particular ailment desired to be alleviated.

Use of the compounds of the present invention in the manufacture of a medicament for the treatment of a living animal for inhibition of progression or alleviation of selected ailments or conditions, particularly ailments or conditions susceptible to treatment with a Group I mGluR modulator is carried out in the usual manner comprising the step of admixing an effective amount of a compound of the invention with a pharmaceutically-acceptable diluent, excipient, or carrier, and the method-of-treating, pharmaceutical compositions, and use of a compound of the present invention in the manufacture of a medicament.

Representative pharmaceutical compositions prepared by admixing the active ingredient with a suitable pharmaceutically-acceptable excipient, diluent, or carrier, include tablets, capsules, solutions for injection, liquid oral formulations, aerosol formulations, TDS formulations, and nanoparticle formulations, thus to produce medicaments for oral, injectable, or dermal use, also in accord with the foregoing.

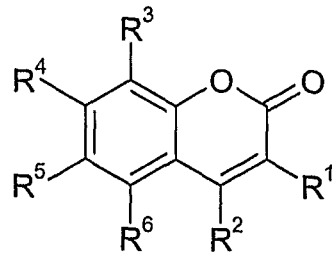
* * * * *

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description.

All patents, applications, publications, test methods, literature, and other materials cited herein are hereby incorporated by reference.

CLAIMS

1. A compound selected from those of Formula I



I

wherein

R^1 represents hydrogen, C_{1-6}alkyl, aryl, heteroaryl or -C(=O)-R^{10};

R^2 represents hydrogen, C_{1-6}alkyl, aryl, heteroaryl, arylC_{1-6}alkyl, heteroarylC_{1-6}alkyl, cyano, nitro, halogen, hydroxy or C_{2-6}alkoxy;

or R^1 and R^2 together represent -W^1-X^1-Y^1-Z^1-,
wherein
W^1 represents a single bond, oxygen, sulfur, -NR^7- or -CR^8R^9- and X^1, Y^1 and Z^1 each independently represent oxygen, sulfur, -NR^7- or -CR^8R^9-;

R^3 represents hydrogen, C_{1-6}alkyl, aryl, heteroaryl, nitro, amino, C_{1-6} alkoxy, halogen, hydroxy, -C(=O)-R^{10}, -N(R^{11})-C(=O)-R^{10}, -N(R^{11})SO_2-R^{10}, -N(R^{11})C(=O)OR^{11}, -C(=O)N(R^{11})$_2$, -C_{1-6}alkylene-C(=O)N(R^{11})$_2$, -N(R^{11})C(=S)N(R^{11})$_2$, -N(R^{11})C(=O)N(R^{11})$_2$, C_{1-6} alkylamino, di-C_{1-6} alkylamino, cycloC_{3-12}alkylamino, cycloC_{3-12} alkylaminoC_{1-6}alkyl, cycloC_{3-12}alkyl-C_{1-6}alkylamino, di-C_{1-6} alkylaminoC_{1-6}alkyl, C_{1-6}alkoxy-C_{2-6}alkylamino, arylamino, arylC_{1-6} alkylamino, N-cycloC_{3-12} alkyl-N-C_{1-6}alkylamino, N-aryl-N-C_{1-6}

alkylamino, N-arylC_{1-6}alkyl-N-C_{1-6} alkylamino, pyrrolidino, piperidino, 4-arylpiperidino, 4-heteroarylpiperidino, morpholino, morpholinoC_{1-6} alkyl, piperazino, 4-C_{1-6}alkylpiperazino, 4-arylpiperazino, hexamethyleneimino, heteroarylamino or heteroarylC_{1-6} alkylamino;

R^4 represents hydrogen, halogen, nitro, amino, hydroxy, -OR^{12}, SO_3CF_3, C_{1-6}alkyl, cycloC_{3-12}alkyl, cycloC_{3-12}alkyl-C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6}alkynyl, aryl, biaryl, arylC_{1-6}alkyl, arylC_{2-6}alkenyl, arylC_{2-6} alkynyl, heteroaryl, heteroarylC_{1-6}alkyl, heteroarylC_{2-6}alkenyl, heteroarylthio, 2,3-dihydro-1H-indenyl, C_{1-6}alkoxyC_{1-6}alkyl, aryloxyarylC_{1-6}alkoxy, C_{1-6}alkylthio, C_{4-6} alkenylthio, cycloC_{3-12} alkylthio, cycloC_{3-12}alkyl-C_{1-6}alkylthio, cycloC_{3-12} alkyl-C_{3-6}alkenylthio, C_{1-6}alkoxyC_{1-6}alkylthio, C_{1-6}alkoxyC_{3-6}alkenylthio, arylC_{3-6}alkenylthio, heteroarylC_{1-6}alkylthio, C_{1-6}alkylsulfonyl, cycloC_{3-12} alkyl-C_{1-6} alkylsulfonyl, arylC_{1-6}alkylsulfonyl, C_{1-6}alkylamino, di-C_{1-6} alkylamino, cycloC_{3-12}alkylamino, C_{1-6}alkoxy-cycloC_3-C_{12}alkylamino, cycloC_{3-12} alkyl-C_{1-6}alkylamino, di-C_{1-6}alkylaminoC_{1-6}alkyl, C_{1-6}alkoxy-C_{2-6} alkylamino, arylamino, arylC_{1-6}alkylamino, N-cycloC_{3-12}alkyl-N-C_{1-6} alkylamino, N-aryl-N-C_{1-6}alkylamino, N-arylC_{1-6}alkyl-N-C_{1-6}alkylamino, 2-indanylamino, tetrahydrofuryl, pyrrolidino, piperidino, 4-arylpiperidino, 4-heteroarylpiperidino, morpholino, piperazino, 4-C_{1-6} alkylpiperazino, 4-arylpiperazino, hexamethyleneimino, benzazepinyl, 1,3-dihydro-2H-isoindol-2-yl, heteroarylC_{1-6}alkoxy, heteroarylamino, heteroarylC_{1-6} alkylamino, -$N(R^{11})C(=O)$-R^{10}, -$N(R^{11})SO_2$-R^{10}, -$N(R^{11})C(=O)OR^{11}$, -$C(=O)N(R^{11})_2$, -C_{1-6}alkylene-$C(=O)N(R^{11})_2$, -S-$C(=O)N(R^{11})_2$ or -O-$C(=O)$-R^{10};

R^5 represents hydrogen, halogen, nitro, amino, hydroxy, C_{1-6}alkoxy, C_{1-6} alkyl, C_{1-6}alkylamino, hydroxyC_{1-6}alkoxy, aryl, heteroaryl, OCF_3, -$N(R^{11})C(=O)$-R^{10}, -$N(R^{11})SO_2$-R^{10}, -$N(R^{11})C(=O)OR^{11}$, -$C(=O)N(R^{11})_2$, -C_{1-6}alkylene-$C(=O)N(R^{11})_2$, -$N(R^{11})C(=S)N(R^{11})_2$, -$(R^{11})C(=O)N(R^{11})_2$, -O-$SO_2R^{10}$ or -$C(=O)R^{10}$;

R^6 represents hydrogen, C_{1-6}alkyl, aryl, heteroaryl, halogen, hydroxy or C_{1-6}alkoxy;

R^7 represents hydrogen, C_{1-6}alkyl, aryl, heteroaryl, arylC_{1-6}alkyl, C_{1-6} alkoxy, halogen, hydroxy, cyano, nitro, hydroxyC_{1-6}alkyl, cycloC_{3-12} alkoxy, C_{1-6}alkylamino, di-C_{1-6}alkylamino, cycloC_{3-12}alkylamino, cycloC_{3-12}alkyl-C_{1-6}alkylamino, di-C_{1-6}alkylaminOC_{1-6}alkyl, arylamino, arylC_{1-6}alkyl, N-aryl-N-C_{1-6}alkylamino, pyrrolidino, piperidino, 4-C_{1-6} alkylpiperazino, morpholino, hexamethyleneimino, pyrrolidinylC_{1-6} alkyl, piperidinylC_{1-6}alkyl, morpholinylC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6} alkylthio, C_{1-6}alkylaminosulfonyl or di-C_{1-6}alkylaminosulfonyl;

R^8 and R^9 each independently represent hydrogen, C_{1-6}alkyl, aryl, heteroaryl, arylC_{1-6}alkyl, C_{1-6}alkoxy, halogen, hydroxy, cyano, nitro, amino or cycloC_{3-12}alkyl;

R^{10} represents hydrogen, C_{1-6}alkyl, cycloC_{3-12}alkyl, aryl, heteroaryl or carboxyC_{1-6}alkyl;

R^{11} represents hydrogen, C_{1-6}alkyl, cycloC_{3-12}alkyl, aryl, heteroaryl, carboxyC_{1-6}alkyl or C_{1-6}alkylcarbonyl;

R^{12} represents C_{1-6}alkyl optionally substituted by one or more substituents selected from hydroxy, cycloC_{3-12}alkyl, C_{1-6}alkylamino, di-C_{1-6}alkylamino, morpholino, halogen, arylamino and -C(=O)R^{13}; heteroaryl; cycloC_{3-12} alkyl; C_{1-6}alkoxycycloC_{3-12}alkyl; arylC_{1-6}alkyl; aryloxyarylC_{1-6}alkyl or C_{2-6} alkenyl; and

R^{13} represents amino, pyrrolidino or piperidino;

or if R^1 and R^2 represent -W^1-X^1-Y^1-Z^1- and W^1 does not represent a single bond,

R^3 and R^4, R^4 and R^5 or R^5 and R^6 together with the carbon atoms to which they are attached may form a 5-6 membered ring which may be saturated or unsaturated, wherein the ring may optionally have 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, and wherein the ring may be optionally substituted by one or more substituents selected from hydrogen, C_{1-6}alkyl, cycloC_{3-12}alkyl, aryl, heteroaryl, arylC_{1-6} alkyl, carboxyC_{1-6}alkyl, alkylcarbonyl, arylcarbonyl, oxo, thioxo, C_{1-6}alkoxy, C_{1-6}alkylthio, arylC_{1-6} alkylthio, arylC_{1-6}alkoxy, morpholino, C_{3-6}cycloalkylamino, pyrrolidino, piperidino, hexamethyleneimino, piperazinyl, N-C_{1-6} alkylpiperazinyl and arylamino;

wherein the term "C_{1-6}alkyl", unless otherwise specified, denotes straight or branched chain groups which may be unsubstituted or substituted by one or more fluorine, chlorine and/or bromine atoms; the term "C_{1-6}alkoxy" denotes straight or branched chain groups which may be unsubstituted or substituted by one or more fluorine, chlorine and/or bromine atoms; the term "cycloC_{3-12}alkyl" denotes monocyclic, bicyclic or tricyclic groups which may be unsubstituted or substituted by one or more fluorine, chlorine and/or bromine atoms; the term "aryl" denotes phenyl or naphthyl or phenyl substituted by one or more substituents, which may be the same or different, selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, cycloC_{3-12}alkyl, hydroxy, halogen, cyano, nitro, C_{1-6}alkoxycarbonyl, amino, C_{1-6}alkylamino, di-C_{1-6}alkylamino, N-cycloC_{3-12}alkyl-N-C_{1-6}alkylamino, azetidinyl, pyrrolyl, piperidinyl, morpholinyl, 4-C_{1-6} alkylpiperazinyl, tetrazolyl, oxazolyl, furyl, thiophenyl, isoxazolyl, thiazolyl, imidazolyl, oxadiazolyl, pyridinyl, pyrimidyl and C_{1-6} alkylenedioxy; and the term "heteroaryl" denotes an aromatic 5-6 membered ring containing from one to four heteroatoms selected from oxygen, sulfur and nitrogen, or a bicyclic group comprising a 5-6 membered ring containing from one to four heteroatoms selected

from oxygen, sulfur and nitrogen fused with a benzene ring or a 5-6 membered aromatic ring containing from one to four heteroatoms selected from oxygen, sulfur and nitrogen, wherein the heteroaryl group may be optionally substituted by one or more substituents, which may be the same or different, selected from C_{1-6}alkyl, C_{1-6} alkoxy, cycloC_{3-12}alkyl, hydroxy, halogen, cyano, nitro, C_{1-6} alkoxycarbonyl, amino, C_{1-6}alkylamino, di-C_{1-6}alkylamino, N-cycloC_{3-12} alkyl-N-C_{1-6}alkylamino, azetidinyl, pyrrolyl, piperazinyl, morpholinyl, 4-C_{1-6} alkylpiperazinyl, tetrazolyl, oxazolyl, furyl, thiophenyl, isoxazolyl, thiazolyl, imidazolyl, oxadiazolyl, pyridinyl, pyrimidyl and phenyl;

and optical isomers, pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof;

with the proviso that the compounds of Formula I do not include:
chromen-2-one,
2-chloro-3-isopropoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
3-(2-chlorobenzyloxy)-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-(2-chlorobenzyloxy)-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
3-(1-phenylethoxy)benzo[c]chromen-6-one,
8-hexyl-7-methoxy-2,3-dihydro-1H-cyclopenta[c]chromen-4-one,
2-chloro-3-methoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
3-hydroxy-4-piperidin-1-ylmethyl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-hydroxy-9-methyl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
6-chloro-7-hydroxy-4-trifluoromethylchromen-2-one,
2-chloro-3-hydroxy-4-morpholin-4-ylmethyl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-4-dimethylaminomethyl-3-hydroxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-ethyl-3-hydroxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,

2,3-dimethoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-hydroxy-3-methoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-(2-methylallyloxy)-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
3-allyloxy-2-chloro-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-hydroxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-hexyl-3-methoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
8-chloro-7-isopropoxy-2,3-dihydro-1H-cyclopenta[c]chromen-4-one,
8-chloro-7-hydroxy-2,3-dihydro-1H-cyclopenta[c]chromen-4-one,
3-(adamantane-1-carbonyl)-6-methoxychromen-2-one,
3-(adamantane-1-carbonyl)-6-bromochromen-2-one,
3-(adamantane-1-carbonyl)chromen-2-one,
3-isopropoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-(3-methylbut-2-enyloxy)-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
8-isopropoxy-1,2,3,4-tetrahydrochromeno[3,4-c]pyridin-5-one,
3-amino-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
3-isopropylamino-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
3-amino-2-chloro-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
6-chloro-3-imidazo[1,2-a]pyridin-2-ylchromen-2-one,
3-pyridin-2-yl-3,4,7,8,9,10-hexahydro-2H-1,5-dioxa-3-azachrysen-6-one or
6-chloro-3-imidazo[1,2-a]pyridin-2-ylchromen-2-one.

2. A compound as claimed in Claim 1 wherein R^1 represents hydrogen or -C(=O)-R^{10}.

3. A compound as claimed in Claim 2 wherein R^{10} represents adamantyl.

4. A compound as claimed in any of Claims 1 to 3 wherein R^2 represents hydrogen, aryl, heteroaryl or C_{1-6}alkyl.

5. A compound as claimed in Claim 4 wherein R^2 represents phenyl or pyridyl.

6. A compound as claimed in Claim 1 wherein R^1 and R^2 together represent

$-W^1-X^1-Y^1-Z^1-$,

wherein

W^1 represents a single bond or $-CR^8R^9-$, and X^1, Y^1 and Z^1 each independently represent $-CR^8R^9-$, wherein R^8 and R^9 are each independently selected from hydrogen, C_{1-6}alkyl, aryl and heteroaryl.

7. A compound as claimed in Claim 6 wherein R^8 represents hydrogen and R^9 represents hydrogen, C_{1-6}alkyl, aryl or heteroaryl.

8. A compound as claimed in Claim 7 wherein R^9 represents hydrogen, methyl, ethyl, trifluoromethyl, *t*-butyl, phenyl or pyridyl.

9. A compound as claimed in Claim 8 wherein R^9 represents hydrogen, methyl or trifluoromethyl.

10. A compound as claimed in any of Claims 1 to 9 wherein R^3 represents hydrogen, C_{1-6}alkyl, morpholinoC_{1-6}alkyl, amino, nitro, $-N(R^{11})C(=O)N(R^{11})_2$, $-N(R^{11})SO_2-R^{10}$, C_{1-6}alkylamino or $-N(R^{11})C(=O)-R^{10}$.

11. A compound as claimed in any of Claims 1 to 10 wherein R^4 represents halogen, hydroxy, OR^{12}, $-S-C(=O)N(R^{11})_2$, $-C(=O)N(R^{11})_2$, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, morpholino, pyrrolidino, arylC_{1-6}alkylamino, $-N(R^{11})C(=O)-R^{10}$, heteroarylthio, $-O-C(=O)-R^{10}$, di-C_{1-6}alkylamino or heteroaryl.

12. A compound as claimed in Claim 11 wherein R^4 represents halogen, OR^{12}, $-S-C(=O)N(R^{11})_2$, $-C(=O)N(R^{11})_2$, C_{1-6}alkylthio or di-C_{1-6}alkylamino.

13. A compound as claimed in Claim 12 wherein R^{12} represents C_{1-6}alkyl optionally substituted by one or more substituents selected from hydroxy, di-C_{1-6} alkylamino, morpholino, halogen, cycloC_{3-12}alkyl, arylamino and -C(=O)R^{13}; cycloC_{3-12}alkyl; C_{1-6}alkoxycycloC_{3-12}alkyl or heteroaryl.

14. A compound as claimed in Claim 12 wherein R^4 represents bromo, methoxy, *iso*-propoxy, -C(=O)N(R^{11})$_2$, *iso*propylthio, difluoromethoxy, dimethylamino or diethylamino.

15. A compound as claimed in Claim 12 wherein R^{11} represents hydrogen or C_{1-6}alkyl.

16. A compound as claimed in Claim 15 wherein R^{11} represents methyl.

17. A compound as claimed in any of Claims 1 to 16 wherein R^5 represents hydrogen, nitro, halogen, C_{1-6}alkyl, hydroxy C_{1-6}alkoxy, -C(=O)-R^{10}, -N(R^{11})SO_2-R^{10}, -N(R^{11})C(=O)-R^{10} or C_{1-6}alkylamino.

18. A compound as claimed in Claim 17 wherein R^5 represents hydrogen, nitro, chloro or ethyl.

19. A compound as claimed in any of Claims 1 to 18 wherein R^6 represents hydrogen or C_{1-6}alkyl.

20. A compound as claimed in Claim 1 wherein R^3 and R^4 together with the carbon atoms to which they are attached form a 5-6 membered ring which may be saturated or unsaturated, wherein the ring has 1 or 2 heteroatoms selected from oxygen and nitrogen and may optionally be substituted by one or more substituents selected from C_{1-6}alkyl, C_{1-6}alkylthio, C_{1-6}alkoxy, oxo, arylC_{1-6}alkyl, aryl, arylC_{1-6}alkylthio and morpholino.

21. A compound as claimed in Claim 1 wherein R^4 and R^5 together with the carbon atoms to which they are attached form a 5-6 membered ring

which may be saturated or unsaturated, wherein the ring has 1 or 2 heteroatoms selected from oxygen and nitrogen and may optionally be substituted by one or more substituents selected from heteroaryl, piperazinyl, N-C_{1-6}alkylpiperazinyl, arylamino, arylC_{1-6}alkylthio, morpholino, C_{1-6}alkylthio, oxo, thioxo, arylcarbonyl, aryl, C_{1-6}alkoxy, arylC_{1-6}alkyl and cycloC_{3-12}alkyl.

22. A compound as claimed in Claim 1 wherein R^5 and R^6 together with the carbon atoms to which they are attached form a 5-6 membered ring which may be saturated or unsaturated, wherein the ring has 1 or 2 heteroatoms selected from oxygen and nitrogen and may optionally be substituted by one or more substituents selected from heteroaryl, oxo, thioxo, aryl, C_{1-6}alkyl and C_{1-6}alkoxy.

23. A compound as claimed in Claim 1 selected from:
N-acetyl-N-(2-chloro-3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-4-yl)acetamide,
N-(2-chloro-3-isopropxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-4-yl)benzamide,
N-(3-isopropxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]-chromen-2-yl)isobutyramide,
N-(2-chloro-3-isopropxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-4-yl)formamide,
N-(2-chloro-3-isopropoxy-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-4-yl)succinamic acid,
dimethylthiocarbamic acid 6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-3-yl ester,
S-(N,N-dimethylcarbamoyl)-2-chloro-8-phenyl-3-thio-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-(pyridin-2-ylsulfanyl)-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,

S-(N,N-dimethylcarbamoyl)-8-ethyl-2-chloro-6-oxo-3-thio-7,8,9,10-tetrahydro-6H-benzo[c]chromen-6-one and
12-chloro-16-isopropylsulfanyl-1,2,3,4-tetrahydro-7,17-dioxa-15-azacyclopenta[a]phenanthren-6-one.

24. A compound as claimed in Claim 1 selected from:
3-(adamantane-1-carbonyl)-7-methoxychromen-2-one,
3-(adamantane-1-carbonyl)-7-dimethylaminochromen-2-one,
3-(adamantane-1-carbonyl)-7-diethylaminochromen-2-one,
3-(adamantane-1-carbonyl)-7-bromochromen-2-one,
2-chloro-3-isopropoxy-9-methyl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-isopropoxy-8-trifluoromethyl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
dimethylthiocarbamic acid S-(2-chloro-9-methyl-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-3-yl) ester,
dimethylthiocarbamic acid S-(2-chloro-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-3-yl) ester,
3-isopropoxy-2-nitro-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-isopropylsulfanyl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-ethyl-3-isopropoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-difluoromethoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
7-isopropoxy-8-nitro-2,3-dihydro-1H-cyclopenta[c]chromen-4-one and
2-chloro-3-isopropoxy-7-methyl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one.

25. A compound of Formula I as defined in claim 1 or an optical isomer, pharmaceuctically acceptable salt, hydrate, solvate or polymorph thereof, subject to the modified proviso that the compound of Formula I may additionally be 2-chloro-3-methoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one, 2-chloro-3-isopropoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one or 8-chloro-7-isopropoxy-2,3-dihydro-1H-cyclopenta[c]chromen-4-one, for use as a medicament.

26. A pharmaceutical composition comprising as active ingredient a compound as claimed in any preceding claim, together with one or more pharmaceutically acceptable excipients or vehicles.

27. Use of a compound as defined in Claim 1 but not subject to the proviso thereof as or in the manufacture of a medicament for prevention and/or treatment of a condition associated with abnormal glutamate neurotransmission or in which modulation of Group I mGluR receptors results in therapeutic benefit or for enhancing cognition.

28. A method of treating a living animal body, including a human, afflicted with a condition associated with abnormal glutamate neurotransmission or in which modulation of Group I mGluR receptors results in therapeutic benefit, comprising the step of administering to said body a compound as defined in Claim 1 but not subject to the proviso thereof in an amount which is effective for alleviation of the condition.

29. The use of Claim 27 or method of Claim 28 wherein the condition associated with abnormal glutamate neurotransmission or in which modulation of Group I mGluR receptors results in therapeutic benefit is selected from: AIDS-related dementia, Alzheimer's disease, Creutzfeld-Jakob´s syndrome, bovine spongiform encephalopathy, prion related infections, diseases involving mitochondrial dysfunction, diseases involving ß-amyloid and/or tauopathy, Down's syndrome, hepatic encephalopathy, Huntington's disease, motor neuron diseases, amyotrophic lateral sclerosis, multiple sclerosis, olivoponto-cerebellar atrophy, post-operative cognitive deficit, Parkinson's disease, Parkinson's dementia, mild cognitive impairment, dementia pugilistica, vascular and frontal lobe dementia, cognitive impairment, eye injuries, eye disorders, glaucoma, retinopathy, macular degeneration, head and brain and spinal cord injuries, trauma, hypoglycaemia, hypoxia, perinatal hypoxia, ischaemia, ischaemia resulting from cardiac arrest, stroke, bypass operations or transplants, convulsions,

epileptic convulsions, epilepsy, temporal lobe epilepsy, glioma and other tumours, inner ear insult, inner ear insult in tinnitus, sound- or drug-induced tinnutis, L-Dopa-induced dyskinesias, tardive dyskinesias, abuse and addiction, nicotine addiction, nicotine abuse, alcohol addiction, alcohol abuse, opiate addiction, opiate abuse, cocaine addiction, cocaine abuse, amphetamine addiction, amphetamine abuse, anxiety and panic disorders, attention deficit hyperactivity disorder, restless leg syndrome, hyperactivity in children, autism, dementia, dementia in Alzheimer's disease, dementia in Korsakoff syndrome, Korsakoff syndrome, vascular dementia, dementia related to HIV infections, major depressive disorder, depression, depression resulting from Borna virus infection, bipolar manic-depressive disorder, drug tolerance, drug tolerance to opioids, movement disorders, dystonia, dyskinesias, L-Dopa-induced dyskinesias, tardive dyskinesias, dyskinesias in Huntington's disease, fragile-X syndrome, Huntington's chorea, chorea, irritable bowel syndrome, migraine, multiple sclerosis, muscle spasms, pain, chronic pain, acute pain, inflammatory pain, neuropathic pain, allodynia, hyperalgesia, nociceptive pain, post traumatic stress disorder, schizophrenia, positive or cognitive or negative symptoms of schizophrenia, spasticity, tinnitus, Tourette´s syndrome, urinary incontinence, vomiting, pruritic conditions, pruritis, sleep disorders, micturition disorders, neuromuscular disorder in the lower urinary tract, gastroesophageal reflux disease, lower esophageal sphincter disease, functional gastrointestinal disorders, dyspepsia, regurgitation, respiratory tract infection, bulimia nervosa, chronic laryngitis, asthma, reflux-related asthma, lung disease, eating disorders, obesity and obesity-related disorders, binge eating disorders, agoraphobia, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, social phobia, substance-induced anxiety disorder, delusional disorder, schizoaffective disorder, schizophreniform disorder, substance-induced psychotic disorder and delirium.

30. The use of Claim 27 or method of Claim 28 wherein the condition associated with abnormal glutamate neurotransmission or in which

modulation of Group I mGluR receptors results in therapeutic benefit is selected from: addiction, neuropathic pain, L-Dopa-induced and tardive dyskinesias, amyotrophic lateral sclerosis, fragile-X syndrome, Parkinson's disease, anxiety disorders, epilepsy, positive and/or negative symptoms of schizophrenia and cognitive impairment.

31. The use of Claim 27 or method of Claim 28 wherein the condition associated with abnormal glutamate neurotransmission or wherein negative modulation of Group I mGluR receptors results in therapeutic benefit, is selected from: neuropathic pain, diabetic neuropathic pain, cancer pain, pain related to rheumathic arthritis, inflammatory pain, L-Dopa-induced and tardive dyskinesias, Parkinson's disease, anxiety disorders, Huntington's chorea and epilepsy.

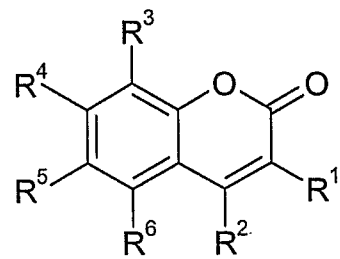
32. The use of Claim 27 or method of Claim 28 wherein the condition associated with abnormal glutamate neurotransmission or wherein positive modulation of Group I mGluR receptors results in therapeutic benefit, is selected from Alzheimer's disease, positive and/or negative symptoms of schizophrenia and cognitive impairment, or is for cognitive enhancement and/or neuroprotection.

33. The use or method as claimed in any of Claims 27 to 32 wherein the compound as defined in Claim 1 but not subject to the proviso thereof is selected from:

3-(adamantane-1-carbonyl)-7-methoxychromen-2-one,
3-(adamantane-1-carbonyl)-7-dimethylaminochromen-2-one,
3-(adamantane-1-carbonyl)-7-diethylaminochromen-2-one,
3-(adamantane-1-carbonyl)-7-bromochromen-2-one,
2-chloro-3-isopropoxy-9-methyl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-isopropoxy-8-trifluoromethyl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,

dimethylthiocarbamic acid S-(2-chloro-9-methyl-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-3-yl) ester,
dimethylthiocarbamic acid S-(2-chloro-6-oxo-7,8,9,10-tetrahydro-6H-benzo[c]chromen-3-yl) ester,
3-isopropoxy-2-nitro-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-isopropylsulfanyl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-ethyl-3-isopropoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-difluoromethoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
7-isopropoxy-8-nitro-2,3-dihydro-1H-cyclopenta[c]chromen-4-one,
2-chloro-3-isopropoxy-7-methyl-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-isopropoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one,
2-chloro-3-methoxy-7,8,9,10-tetrahydrobenzo[c]chromen-6-one and
8-chloro-7-isopropoxy-2,3-dihydro-1H-cyclopenta[c]chromen-4-one.

34. A method for treating or preventing a condition or disease associated with abnormal glutamate neurotransmission or a method for modulating Group I mGluR receptors to achieve therapeutic benefit, or a method for enhancing cognition, such method comprising administering to a living animal, including a human, a therapeutically effective amount of a compound selected from those of Formula I



I

wherein

R^1 represents hydrogen, C_{1-6}alkyl, aryl, heteroaryl or -C(=O)-R^{10};

R^2 represents hydrogen, C_{1-6}alkyl, aryl, heteroaryl, arylC_{1-6}alkyl, heteroarylC_{1-6}alkyl, cyano, nitro, halogen, hydroxy or C_{2-6}alkoxy;

or R^1 and R^2 together represent -W^1-X^1-Y^1-Z^1-,
wherein
W^1 represents a single bond, oxygen, sulfur, -NR^7- or -CR^8R^9- and X^1, Y^1 and Z^1 each independently represent oxygen, sulfur, -NR^7- or -CR^8R^9-;

R^3 represents hydrogen, C_{1-6}alkyl, aryl, heteroaryl, nitro, amino, C_{1-6} alkoxy, halogen, hydroxy, -C(=O)-R^{10}, -N(R^{11})-C(=O)-R^{10}, -N(R^{11})SO_2-R^{10}, -N(R^{11})C(=O)OR^{11}, -C(=O)N(R^{11})$_2$, -C_{1-6}alkylene-C(=O)N(R^{11})$_2$, -N(R^{11})C(=S)N(R^{11})$_2$, -N(R^{11})C(=O)N(R^{11})$_2$, C_{1-6} alkylamino, di-C_{1-6} alkylamino, cycloC_{3-12}alkylamino, cycloC_{3-12} alkylaminoC_{1-6}alkyl, cycloC_{3-12}alkyl-C_{1-6}alkylamino, di-C_{1-6} alkylaminoC_{1-6}alkyl, C_{1-6}alkoxy-C_{2-6}alkylamino, arylamino, arylC_{1-6} alkylamino, N-cycloC_{3-12} alkyl-N-C_{1-6}alkylamino, N-aryl-N-C_{1-6} alkylamino, N-arylC_{1-6}alkyl-N-C_{1-6} alkylamino, pyrrolidino, piperidino, 4-arylpiperidino, 4-heteroarylpiperidino, morpholino, morpholinoC_{1-6} alkyl, piperazino, 4-C_{1-6}alkylpiperazino, 4-arylpiperazino, hexamethyleneimino, heteroarylamino or heteroarylC_{1-6} alkylamino;

R^4 represents hydrogen, halogen, nitro, amino, hydroxy, -OR^{12}, SO_3CF_3, C_{1-6}alkyl, cycloC_{3-12}alkyl, cycloC_{3-12}alkyl-C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6}alkynyl, aryl, biaryl, arylC_{1-6}alkyl, arylC_{2-6}alkenyl, arylC_{2-6} alkynyl, heteroaryl, heteroarylC_{1-6}alkyl, heteroarylC_{2-6}alkenyl, heteroarylthio, 2,3-dihydro-1H-indenyl, C_{1-6}alkoxyC_{1-6}alkyl, aryloxyarylC_{1-6}alkoxy, C_{1-6}alkylthio, C_{4-6} alkenylthio, cycloC_{3-12} alkylthio, cycloC_{3-12}alkyl-C_{1-6}alkylthio, cycloC_{3-12} alkyl-C_{3-6}alkenylthio, C_{1-6}alkoxyC_{1-6}alkylthio, C_{1-6}alkoxyC_{3-6}alkenylthio, arylC_{3-6}alkenylthio, heteroarylC_{1-6}alkylthio, C_{1-6}alkylsulfonyl, cycloC_{3-12} alkyl-C_{1-6}

alkylsulfonyl, arylC_{1-6}alkylsulfonyl, C_{1-6}alkylamino, di-C_{1-6} alkylamino, cycloC_{3-12}alkylamino, C_{1-6}alkoxy-cycloC_3-C_{12}alkylamino, cycloC_{3-12} alkyl-C_{1-6}alkylamino, di-C_{1-6}alkylaminOC_{1-6}alkyl, C_{1-6}alkoxy-C_{2-6} alkylamino, arylamino, arylC_{1-6}alkylamino, N-cycloC_{3-12}alkyl-N-C_{1-6} alkylamino, N-aryl-N-C_{1-6}alkylamino, N-arylC_{1-6}alkyl-N-C_{1-6}alkylamino, 2-indanylamino, tetrahydrofuryl, pyrrolidino, piperidino, 4-arylpiperidino, 4-heteroarylpiperidino, morpholino, piperazino, 4-C_{1-6} alkylpiperazino, 4-arylpiperazino, hexamethyleneimino, benzazepinyl, 1,3-dihydro-2H-isoindol-2-yl, heteroarylC_{1-6}alkoxy, heteroarylamino, heteroarylC_{1-6} alkylamino, -N(R^{11})C(=O)-R^{10}, -N(R^{11})SO_2-R^{10}, -N(R^{11})C(=O)OR^{11}, -C(=O)N(R^{11})$_2$, -C_{1-6}alkylene-C(=O)N(R^{11})$_2$, -S-C(=O)N(R^{11})$_2$ or -O-C(=O)-R^{10};

R^5 represents hydrogen, halogen, nitro, amino, hydroxy, C_{1-6}alkoxy, C_{1-6} alkyl, C_{1-6}alkylamino, hydroxyC_{1-6}alkoxy, aryl, heteroaryl, OCF_3, -N(R^{11})C(=O)-R^{10}, -N(R^{11})SO_2-R^{10}, -N(R^{11})C(=O)OR^{11}, -C(=O)N(R^{11})$_2$, -C_{1-6}alkylene-C(=O)N(R^{11})$_2$, -N(R^{11})C(=S)N(R^{11})$_2$, -(R^{11})C(=O)N(R^{11})$_2$, -O-SO_2R^{10} or -C(=O)R^{10};

R^6 represents hydrogen, C_{1-6}alkyl, aryl, heteroaryl, halogen, hydroxy or C_{1-6}alkoxy;

R^7 represents hydrogen, C_{1-6}alkyl, aryl, heteroaryl, arylC_{1-6}alkyl, C_{1-6} alkoxy, halogen, hydroxy, cyano, nitro, hydroxyC_{1-6}alkyl, cycloC_{3-12} alkoxy, C_{1-6}alkylamino, di-C_{1-6}alkylamino, cycloC_{3-12}alkylamino, cycloC_{3-12}alkyl-C_{1-6}alkylamino, di-C_{1-6}alkylaminOC_{1-6}alkyl, arylamino, arylC_{1-6}alkyl, N-aryl-N-C_{1-6}alkylamino, pyrrolidino, piperidino, 4-C_{1-6} alkylpiperazino, morpholino, hexamethyleneimino, pyrrolidinylC_{1-6} alkyl, piperidinylC_{1-6}alkyl, morpholinylC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6} alkylthio, C_{1-6}alkylaminosulfonyl or di-C_{1-6}alkylaminosulfonyl;

R^8 and R^9 each independently represent hydrogen, C_{1-6}alkyl, aryl, heteroaryl, arylC_{1-6}alkyl, C_{1-6}alkoxy, halogen, hydroxy, cyano, nitro, amino or cycloC_{3-12}alkyl;

R^{10} represents hydrogen, C_{1-6}alkyl, cycloC_{3-12}alkyl, aryl, heteroaryl or carboxyC_{1-6}alkyl;

R^{11} represents hydrogen, C_{1-6}alkyl, cycloC_{3-12}alkyl, aryl, heteroaryl, carboxyC_{1-6}alkyl or C_{1-6}alkylcarbonyl;

R^{12} represents C_{1-6}alkyl optionally substituted by one or more substituents selected from hydroxy, cycloC_{3-12}alkyl, C_{1-6}alkylamino, di-C_{1-6}alkylamino, morpholino, halogen, arylamino and $-C(=O)R^{13}$; heteroaryl; cycloC_{3-12} alkyl; C_{1-6}alkoxycycloC_{3-12}alkyl; arylC_{1-6}alkyl; aryloxyarylC_{1-6}alkyl or C_{2-6} alkenyl; and

R^{13} represents amino, pyrrolidino or piperidino;

or if R^1 and R^2 represent $-W^1-X^1-Y^1-Z^1-$ and W^1 does not represent a single bond,

R^3 and R^4, R^4 and R^5 or R^5 and R^6 together with the carbon atoms to which they are attached may form a 5-6 membered ring which may be saturated or unsaturated, wherein the ring may optionally have 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, and wherein the ring may be optionally substituted by one or more substituents selected from hydrogen, C_{1-6}alkyl, cycloC_{3-12}alkyl, aryl, heteroaryl, arylC_{1-6} alkyl, carboxyC_{1-6}alkyl, alkylcarbonyl, arylcarbonyl, oxo, thioxo, C_{1-6}alkoxy, C_{1-6}alkylthio, arylC_{1-6} alkylthio, arylC_{1-6}alkoxy, morpholino, C_{3-6}cycloalkylamino, pyrrolidino, piperidino, hexamethyleneimino, piperazinyl, N-C_{1-6} alkylpiperazinyl and arylamino;

wherein the term "C_{1-6}alkyl", unless otherwise specified, denotes straight or branched chain groups which may be unsubstituted or substituted by one or more fluorine, chlorine and/or bromine atoms; the term "C_{1-6}alkoxy" denotes straight or branched chain groups which may be unsubstituted or substituted by one or more fluorine, chlorine and/or bromine atoms; the term "cycloC_{3-12}alkyl" denotes monocyclic, bicyclic or tricyclic groups which may be unsubstituted or substituted by one or more fluorine, chlorine and/or bromine atoms; the term "aryl" denotes phenyl or naphthyl or phenyl substituted by one or more substituents, which may be the same or different, selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, cycloC_{3-12}alkyl, hydroxy, halogen, cyano, nitro, C_{1-6}alkoxycarbonyl, amino, C_{1-6}alkylamino, di-C_{1-6}alkylamino, N-cycloC_{3-12}alkyl-N-C_{1-6}alkylamino, azetidinyl, pyrrolyl, piperidinyl, morpholinyl, 4-C_{1-6} alkylpiperazinyl, tetrazolyl, oxazolyl, furyl, thiophenyl, isoxazolyl, thiazolyl, imidazolyl, oxadiazolyl, pyridinyl, pyrimidyl and C_{1-6} alkylenedioxy; and the term "heteroaryl" denotes an aromatic 5-6 membered ring containing from one to four heteroatoms selected from oxygen, sulfur and nitrogen, or a bicyclic group comprising a 5-6 membered ring containing from one to four heteroatoms selected from oxygen, sulfur and nitrogen fused with a benzene ring or a 5-6 membered aromatic ring containing from one to four heteroatoms selected from oxygen, sulfur and nitrogen, wherein the heteroaryl group may be optionally substitued by one or more substituents, which may be the same or different, selected from C_{1-6}alkyl, C_{1-6} alkoxy, cycloC_{3-12}alkyl, hydroxy, halogen, cyano, nitro, C_{1-6} alkoxycarbonyl, amino, C_{1-6}alkylamino, di-C_{1-6}alkylamino, N-cycloC_{3-12} alkyl-N-C_{1-6}alkylamino, azetidinyl, pyrrolyl, piperazinyl, morpholinyl, 4-C_{1-6} alkylpiperazinyl, tetrazolyl, oxazolyl, furyl, thiophenyl, isoxazolyl, thiazolyl, imidazolyl, oxadiazolyl, pyridinyl, pyrimidyl and phenyl;

and optical isomers, pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2006/003888

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D311/74 C07D498/04 C07D311/80 A61K31/353 A61P25/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	EP 1 408 042 A1 (BANYU PHARMA CO LTD [JP]) 14 April 2004 (2004-04-14) the whole document	1-34
A	US 2005/197361 A1 (JIRGENSONS AIGARS [LV] ET AL) 8 September 2005 (2005-09-08) the whole document	1-34

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 December 2006	02/01/2007

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

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INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2006/003888

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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X	P.N. CONFALONE; D. L. CONFALONE: "The design and synthesis of monofunctional psoralens structurally related to methoxalen and trioxalen" TETRAHEDRON, vol. 39, no. 8, 1983, pages 1265-1271, XP002411670 examples	1-26
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2006/003888

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US 2005197361 A1	08-09-2005	US 2005288284 A1	29-12-2005
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