

THERAPEUTIC COMPOUNDS

BACKGROUND OF THE INVENTION

1. Field of the invention

5 The invention is related to therapeutic compounds, pharmaceutical compositions containing these compounds, manufacturing processes thereof and uses thereof.

Particularly, the present invention is related to compounds that may be effective in treating pain, cancer, multiple sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's disease, anxiety disorders, gastrointestinal disorders and/or cardiovascular disorders.

10 2. Discussion of Relevant Technology

Pain management has been an important field of study for many years. It has been well known that cannabinoid receptor (e.g., CB₁ receptor, CB₂ receptor) ligands including agonists, antagonists and inverse agonists produce relief of pain in a variety of animal models by interacting with CB₁ and/or CB₂ receptors. Generally, CB₁ receptors are located
15 predominately in the central nervous system, whereas CB₂ receptors are located primarily in the periphery and are primarily restricted to the cells and tissues derived from the immune system.

While CB₁ receptor agonists, such as Δ^9 -tetrahydrocannabinol (Δ^9 -THC) and anadamide, are useful in anti-nociception models in animals, they tend to exert undesired
20 CNS side effects, e.g., psychoactive side effects, the abuse potential, drug dependence and tolerance, etc. These undesired side effects are known to be mediated by the CB₁ receptors located in CNS. There are lines of evidence, however, suggesting that CB₁ agonists acting at peripheral sites or with limited CNS exposure can manage pain in humans or animals with much improved overall in vivo profile.

25 Therefore, there is a need for new CB₁ receptor ligands such as agonists that may be useful in managing pain or treating other related symptoms or diseases with reduced or minimal undesirable CNS side effects.

DESCRIPTION OF THE EMBODIMENTS

The present invention provides CB₁ receptor ligands which may be useful in treating pain and/or other related symptoms or diseases.

Unless specified otherwise within this specification, the nomenclature used in this specification generally follows the examples and rules stated in *Nomenclature of Organic Chemistry, Sections A, B, C, D, E, F, and H*, Pergamon Press, Oxford, 1979, which is incorporated by references herein for its exemplary chemical structure names and rules on naming chemical structures.

The term "C_{m-n}" or "C_{m-n} group" used alone or as a prefix, refers to any group having m to n carbon atoms.

The term "hydrocarbon" used alone or as a suffix or prefix, refers to any structure comprising only carbon and hydrogen atoms up to 14 carbon atoms.

The term "hydrocarbon radical" or "hydrocarbonyl" used alone or as a suffix or prefix, refers to any structure as a result of removing one or more hydrogens from a hydrocarbon.

The term "alkyl" used alone or as a suffix or prefix, refers to a saturated monovalent straight or branched chain hydrocarbon radical comprising 1 to about 12 carbon atoms. Illustrative examples of alkyls include, but are not limited to, C₁₋₆alkyl groups, such as methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, and hexyl, and longer alkyl groups, such as heptyl, and octyl. An alkyl can be unsubstituted or substituted with one or two suitable substituents.

The term "alkylene" used alone or as suffix or prefix, refers to divalent straight or branched chain hydrocarbon radicals comprising 1 to about 12 carbon atoms, which serves to links two structures together.

The term "alkenyl" used alone or as suffix or prefix, refers to a monovalent straight or branched chain hydrocarbon radical having at least one carbon-carbon double bond and comprising at least 2 up to about 12 carbon atoms. The double bond of an alkenyl can be unconjugated or conjugated to another unsaturated group. Suitable alkenyl groups include, but are not limited to C₂₋₆alkenyl groups, such as vinyl, allyl, butenyl, pentenyl, hexenyl,

butadienyl, pentadienyl, hexadienyl, 2-ethylhexenyl, 2-propyl-2-butenyl, 4-(2-methyl-3-butene)-pentenyl. An alkenyl can be unsubstituted or substituted with one or two suitable substituents.

The term "alkynyl" used alone or as suffix or prefix, refers to a monovalent straight or branched chain hydrocarbon radical having at least one carbon-carbon triple bond and comprising at least 2 up to about 12 carbon atoms. The triple bond of an alkynyl group can be unconjugated or conjugated to another unsaturated group. Suitable alkynyl groups include, but are not limited to, C₂₋₆alkynyl groups, such as ethynyl, propynyl, butynyl, pentynyl, hexynyl, methylpropynyl, 4-methyl-1-butyne, 4-propyl-2-pentyne, and 4-butyl-2-hexynyl. An alkynyl can be unsubstituted or substituted with one or two suitable substituents.

The term "cycloalkyl," used alone or as suffix or prefix, refers to a saturated monovalent ring-containing hydrocarbon radical comprising at least 3 up to about 12 carbon atoms. Examples of cycloalkyls include, but are not limited to, C₃₋₇cycloalkyl groups, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, and saturated cyclic and bicyclic terpenes. A cycloalkyl can be unsubstituted or substituted by one or two suitable substituents. Preferably, the cycloalkyl is a monocyclic ring or bicyclic ring.

The term "cycloalkenyl" used alone or as suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical having at least one carbon-carbon double bond and comprising at least 3 up to about 12 carbon atoms.

The term "cycloalkynyl" used alone or as suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical having at least one carbon-carbon triple bond and comprising about 7 up to about 12 carbon atoms.

The term "aryl" used alone or as suffix or prefix, refers to a monovalent hydrocarbon radical having one or more polyunsaturated carbon rings having aromatic character, (*e.g.*, $4n + 2$ delocalized electrons) and comprising 5 up to about 14 carbon atoms.

The term "arylene" used alone or as suffix or prefix, refers to a divalent hydrocarbon radical having one or more polyunsaturated carbon rings having aromatic character, (*e.g.*, $4n + 2$ delocalized electrons) and comprising 5 up to about 14 carbon atoms, which serves to link two structures together.

The term "heterocycle" used alone or as a suffix or prefix, refers to a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O, P and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s). Heterocycle may be saturated or unsaturated, containing one or more double bonds, and heterocycle may contain more than one ring. When a heterocycle contains more than one ring, the rings may be fused or unfused. Fused rings generally refer to at least two rings share two atoms therebetween. Heterocycle may have aromatic character or may not have aromatic character.

The term "heteroaromatic" used alone or as a suffix or prefix, refers to a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O, P and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s), wherein the ring-containing structure or molecule has an aromatic character (*e.g.*, $4n + 2$ delocalized electrons).

The term "heterocyclic group," "heterocyclic moiety," "heterocyclic," or "heterocycolo" used alone or as a suffix or prefix, refers to a radical derived from a heterocycle by removing one or more hydrogens therefrom.

The term "heterocyclyl" used alone or as a suffix or prefix, refers a monovalent radical derived from a heterocycle by removing one hydrogen therefrom.

The term "heterocyclylene" used alone or as a suffix or prefix, refers to a divalent radical derived from a heterocycle by removing two hydrogens therefrom, which serves to links two structures together.

The term "six-membered" used as prefix refers to a group having a ring that contains six ring atoms.

The term "five-membered" used as prefix refers to a group having a ring that contains five ring atoms.

A five-membered ring heteroaryl is a heteroaryl with a ring having five ring atoms wherein 1, 2 or 3 ring atoms are independently selected from N, O and S.

Exemplary five-membered ring heteroaryls are thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4-oxadiazolyl.

A six-membered ring heteroaryl is a heteroaryl with a ring having six ring atoms wherein 1, 2 or 3 ring atoms are independently selected from N, O and S.

Exemplary six-membered ring heteroaryls are pyridyl, pyrazinyl, pyrimidinyl, triazinyl and pyridazinyl.

The term "heteroaryl" used alone or as a suffix or prefix, refers to a heterocycl having aromatic character.

5 The term "heterocycloalkyl" used alone or as a suffix or prefix, refers to a monocyclic or polycyclic ring comprising carbon and hydrogen atoms and at least one heteroatom, preferably, 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, and having no unsaturation. Examples of heterocycloalkyl groups include pyrrolidinyl, pyrrolidino, piperidinyl, piperidino, piperazinyl, piperazino, morpholinyl, morpholino, 10 thiomorpholinyl, thiomorpholino, and pyranyl. A heterocycloalkyl group can be unsubstituted or substituted with one or two suitable substituents. Preferably, the heterocycloalkyl group is a monocyclic or bicyclic ring, more preferably, a monocyclic ring, wherein the ring comprises from 3 to 6 carbon atoms and from 1 to 3 heteroatoms, referred to herein as C₃₋₆heterocycloalkyl.

15 Heterocycle includes, for example, monocyclic heterocycles such as: aziridine, oxirane, thiirane, azetidine, oxetane, thietane, pyrrolidine, pyrroline, imidazolidine, pyrazolidine, pyrazoline, dioxolane, sulfolane, 2,3-dihydrofuran, 2,5-dihydrofuran, tetrahydrofuran, thiophane, piperidine, 1,2,3,6-tetrahydro-pyridine, piperazine, morpholine, thiomorpholine, pyran, thiopyran, 2,3-dihydropyran, tetrahydropyran, 1,4-dihydropyridine, 20 1,4-dioxane, 1,3-dioxane, dioxane, homopiperidine, 2,3,4,7-tetrahydro-1*H*-azepine, homopiperazine, 1,3-dioxepane, 4,7-dihydro-1,3-dioxepin, and hexamethylene oxide.

In addition, heterocycle includes aromatic heterocycles, for example, pyridine, pyrazine, pyrimidine, pyridazine, thiophene, furan, furazan, pyrrole, imidazole, thiazole, oxazole, pyrazole, isothiazole, isoxazole, 1,2,3-triazole, tetrazole, 1,2,3-thiadiazole, 1,2,3-oxadiazole, 1,2,4-triazole, 1,2,4-thiadiazole, 1,2,4-oxadiazole, 1,3,4-triazole, 1,3,4- 25 thiadiazole, and 1,3,4-oxadiazole.

Additionally, heterocycle encompass polycyclic heterocycles, for example, indole, indoline, isoindoline, quinoline, tetrahydroquinoline, isoquinoline, tetrahydroisoquinoline, 1,4-benzodioxan, coumarin, dihydrocoumarin, benzofuran, 2,3-dihydrobenzofuran, 30 isobenzofuran, chromene, chroman, isochroman, xanthene, phenoxathiin, thianthrene, indolizine, isoindole, indazole, purine, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, phenanthridine, perimidine, phenanthroline, phenazine, phenothiazine,

phenoxazine, 1,2-benzisoxazole, benzothiophene, benzoxazole, benzthiazole, benzimidazole, benztriazole, thioxanthine, carbazole, carboline, acridine, pyrolizidine, and quinolizidine.

In addition to the polycyclic heterocycles described above, heterocycle includes polycyclic heterocycles wherein the ring fusion between two or more rings includes more than one bond common to both rings and more than two atoms common to both rings. Examples of such bridged heterocycles include quinuclidine, diazabicyclo[2.2.1]heptane and 7-oxabicyclo[2.2.1]heptane.

Heterocyclyl includes, for example, monocyclic heterocyclyls, such as: aziridinyl, oxiranyl, thiiranyl, azetidiny, oxetanyl, thietanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, dioxolanyl, sulfolanyl, 2,3-dihydrofuranyl, 2,5-dihydrofuranyl, tetrahydrofuranyl, thiophanyl, piperidinyl, 1,2,3,6-tetrahydro-pyridinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, 2,3-dihydropyranyl, tetrahydropyranyl, 1,4-dihydropyridinyl, 1,4-dioxanyl, 1,3-dioxanyl, dioxanyl, homopiperidinyl, 2,3,4,7-tetrahydro-1*H*-azepinyl, homopiperazinyl, 1,3-dioxepanyl, 4,7-dihydro-1,3-dioxepinyl, and hexamethylene oxidyl.

In addition, heterocyclyl includes aromatic heterocyclyls or heteroaryl, for example, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, furyl, furazanyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4 oxadiazolyl.

Additionally, heterocyclyl encompasses polycyclic heterocyclyls (including both aromatic or non-aromatic), for example, indolyl, indolinyl, isoindolinyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, 1,4-benzodioxanyl, coumarinyl, dihydrocoumarinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, isobenzofuranyl, chromenyl, chromanyl, isochromanyl, xanthenyl, phenoxathiinyl, thianthrenyl, indolizinyl, isoindolyl, indazolyl, purinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, phenanthridinyl, perimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxazinyl, 1,2-benzisoxazolyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benzimidazolyl, benztriazolyl, thioxanthinyl, carbazolyl, carbolinyl, acridinyl, pyrolizidinyl, and quinolizidinyl.

In addition to the polycyclic heterocyclyls described above, heterocyclyl includes polycyclic heterocyclyls wherein the ring fusion between two or more rings includes more than one bond common to both rings and more than two atoms common to both rings. Examples of such bridged heterocycles include quinuclidinyl, diazabicyclo[2.2.1]heptyl; and 7-oxabicyclo[2.2.1]heptyl.

The term "alkoxy" used alone or as a suffix or prefix, refers to radicals of the general formula $-O-R$, wherein R is selected from a hydrocarbon radical. Exemplary alkoxy includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, isobutoxy, cyclopropylmethoxy, allyloxy, and propargyloxy.

The term "amine" or "amino" refers to $-NH_2$.

Halogen includes fluorine, chlorine, bromine and iodine.

"Halogenated," used as a prefix of a group, means one or more hydrogens on the group are replaced with one or more halogens.

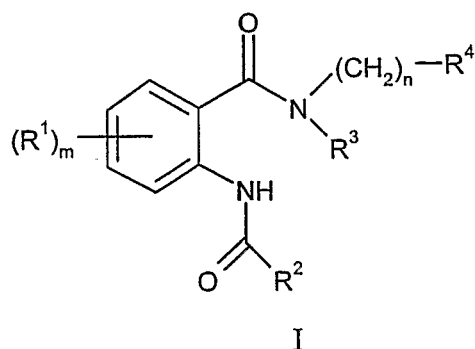
"RT", "r.t." or "rt" means room temperature.

"DMF" refers to dimethyl formamide.

"DIPEA" refers to N,N-diisopropylethylamine.

"HATU" refers to 2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate.

One aspect of the invention is a compound of formula I, a pharmaceutically acceptable salt thereof, diastereomers, enantiomers, or mixtures thereof:



wherein:

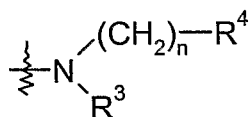
m is selected from 0, 1 and 2;

n is selected from 0, 1, 2, 3, 4 and 5;

R^1 is independently selected from halogen, cyano, amino, nitro, C_{1-6} alkylamino, di C_{1-6} alkylamino, acetylamino, hydroxyl, C_{1-6} alkoxy, C_{1-6} alkyl, halogenated C_{1-6} alkoxy, C_{1-6} alkenyl, and halogenated C_{1-6} alkyl;

R^2 is selected from C_{6-10} aryl and C_{2-10} heterocyclyl; wherein said C_{6-10} aryl and C_{2-10} heterocyclyl used in defining R^2 is optionally substituted by one or more groups selected from halogen, halogenated C_{1-6} alkyl, C_{1-6} alkyl, cyano, nitro, C_{1-6} alkoxy, halogenated C_{1-6} alkoxy, hydroxy, hydroxy- C_{1-6} alkyl, amino, C_{1-6} alkoxy- C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylamino, di C_{1-6} alkyl-amino, amino- C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} heteroaryl, heteroaryl- C_{1-6} alkyl, C_{6-10} aryl, and C_{6-10} aryl- C_{1-6} alkyl; and

R^3 is selected from hydrogen and C_{1-6} alkyl; R^4 is selected from C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, C_{6-10} aryl, C_{2-6} heterocyclyl-amino, C_{2-6} heterocyclyloxy-amino and C_{2-6} heterocyclyl; wherein said C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, C_{6-10} aryl, C_{2-6} heterocyclyl-amino, C_{2-6} heterocyclyloxy-amino and C_{2-6} heterocyclyl used in defining R^4 is optionally substituted by one or more groups selected from halogen, halogenated C_{1-6} alkyl, C_{1-6} alkyl, cyano, nitro, C_{1-6} alkoxy, halogenated C_{1-6} alkoxy, hydroxy, hydroxy- C_{1-6} alkyl, amino, C_{1-6} alkoxy- C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylamino, di C_{1-6} alkyl-amino, amino- C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} heteroaryl, heteroaryl- C_{1-6} alkyl, C_{6-10} aryl, and C_{6-10} aryl- C_{1-6} alkyl; or



is C_{2-10} heterocyclyl, which is optionally substituted by one or more groups selected from halogen, halogen substituted C_{1-6} alkyl, C_{1-6} alkyl, cyano, nitro, C_{1-6} alkoxy, halogenated C_{1-6} alkoxy, hydroxy, hydroxy- C_{1-6} alkyl, amino, C_{1-6} alkoxy- C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylamino, di C_{1-6} alkyl-amino, amino- C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} heteroaryl, heteroaryl- C_{1-6} alkyl, C_{6-10} aryl, and C_{6-10} aryl- C_{1-6} alkyl.

In another embodiment, the compounds of the present invention are those of formula

I,

wherein

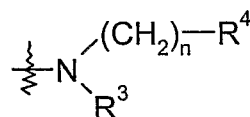
m is selected from 0, 1 and 2;

n is selected from 0, 1, 2, 3 and 4;

R^1 is independently selected from halogen, cyano, amino, nitro, acetylamino, hydroxyl, C_{1-3} alkoxy, C_{1-3} alkyl, halogenated C_{1-3} alkoxy, and halogenated C_{1-3} alkyl;

R^2 is selected from C_{6-10} aryl and C_{2-10} heterocyclyl, wherein said C_{6-10} aryl and C_{2-10} heterocyclyl used in defining R^2 is optionally substituted by one or more groups selected from halogen, halogenated C_{1-3} alkyl, C_{1-3} alkyl, nitro, C_{1-3} alkoxy, halogenated C_{1-3} alkoxy, hydroxy, hydroxy- C_{1-3} alkyl, amino, C_{1-3} alkoxy- C_{1-3} alkyl, C_{2-5} heterocyclyl- C_{1-3} alkyl, C_{1-6} alkoxycarbonyl, C_{1-3} alkylamino, di- C_{1-3} alkyl-amino, and amino- C_{1-3} alkyl; and

R^3 is selected from hydrogen and C_{1-6} alkyl; R^4 is selected from C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-6} heterocyclyl-amino, C_{2-6} heterocyclyloxy-amino, and C_{2-6} heterocyclyl; wherein said C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-6} heterocyclyl-amino, C_{2-6} heterocyclyloxy-amino, and C_{2-6} heterocyclyl used in defining R^4 is optionally substituted by one or more groups selected from halogen, halogenated C_{1-3} alkyl, C_{1-3} alkyl, nitro, C_{1-3} alkoxy, halogenated C_{1-3} alkoxy, hydroxy, hydroxy- C_{1-3} alkyl, amino, C_{1-3} alkoxy- C_{1-3} alkyl, C_{1-6} alkoxycarbonyl, C_{1-3} alkylamino, di- C_{1-3} alkyl-amino, and amino- C_{1-3} alkyl; or



is selected from azepanyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, isoxazolidinyl, triazolyl, morpholinyl, piperidinyl, thiomorpholinyl, pyridazinyl, piperazinyl, triazinyl or 1,4-dioxo-8-azaspiro[4.5]decan-8-yl; wherein said azepanyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, isoxazolidinyl, triazolyl, morpholinyl, piperidinyl, thiomorpholinyl, piperazinyl, triazinyl and 1,4-dioxo-8-azaspiro[4.5]decan-8-yl are optionally substituted by one or more groups selected from halogen, halogenated C_{1-3} alkyl, C_{1-3} alkyl, nitro, C_{1-3} alkoxy, halogenated C_{1-3} alkoxy, hydroxy, hydroxy- C_{1-3} alkyl, amino, C_{1-3} alkoxy- C_{1-3} alkyl, C_{1-6} alkoxycarbonyl, C_{1-3} alkylamino, di- C_{1-3} alkyl-amino, and amino- C_{1-3} alkyl.

In a further embodiment, the compounds of the present invention are those of formula I, wherein

m is selected from 0 and 1;

n is selected from 0, 1, 2, 3 and 4;

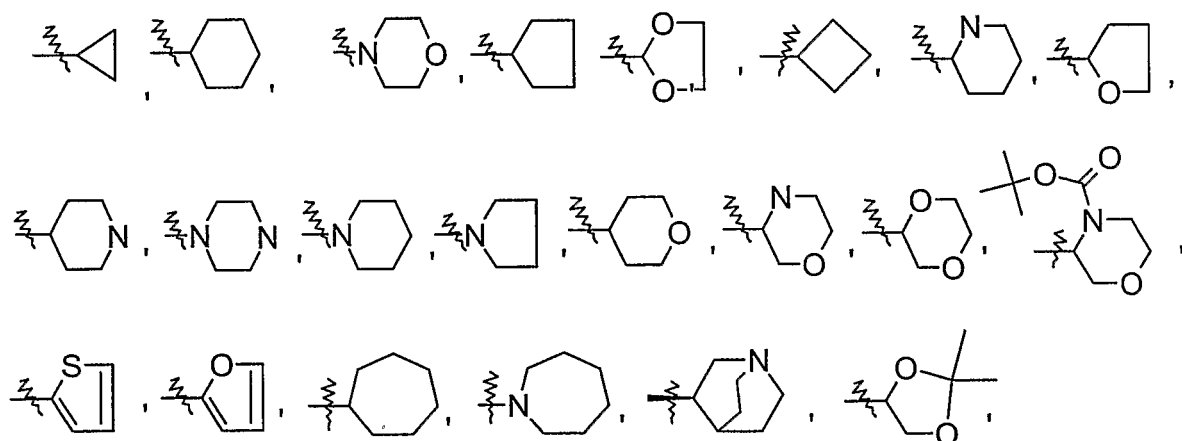
R^1 is independently selected from halogen, amino, nitro, acetylamino, hydroxyl, C_{1-3} alkoxy, C_{1-3} alkyl, halogenated C_{1-3} alkoxy, and halogenated C_{1-3} alkyl;

R^2 is selected from phenyl, naphthyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl,

1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4 oxadiazolyl, indolyl, indolynyl, quinolynyl, tetrahydroquinolynyl, isoquinolynyl, tetrahydroisoquinolynyl, 1,4-benzodioxanyl, coumarin, dihydrocoumarinyl, 2,3-dihydrobenzofuranyl, 1,2-
 5 benzisoxazolyl, 1,3-benzodioxolyl, 2,3-dihydro-1,4-benzodioxinyl, 3,4-dihydro-2H-1,5-benzodioxepinyl, 4H-1,3-benzodioxinyl, benzofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benzimidazolyl, benztriazolyl, thioxanthinyl, carbazolyl, carbolinyl, acridinyl, pyrrolizidinyl, and quinolizidinyl that are optionally substituted by one or more groups selected from halogen, hydroxy, methyl, methoxy, amino, trifluoromethyl,
 10 trifluoromethoxy, methoxymethyl, 1*H*-1,2,3-triazolylmethyl and 1*H*-pyrazolylmethyl;

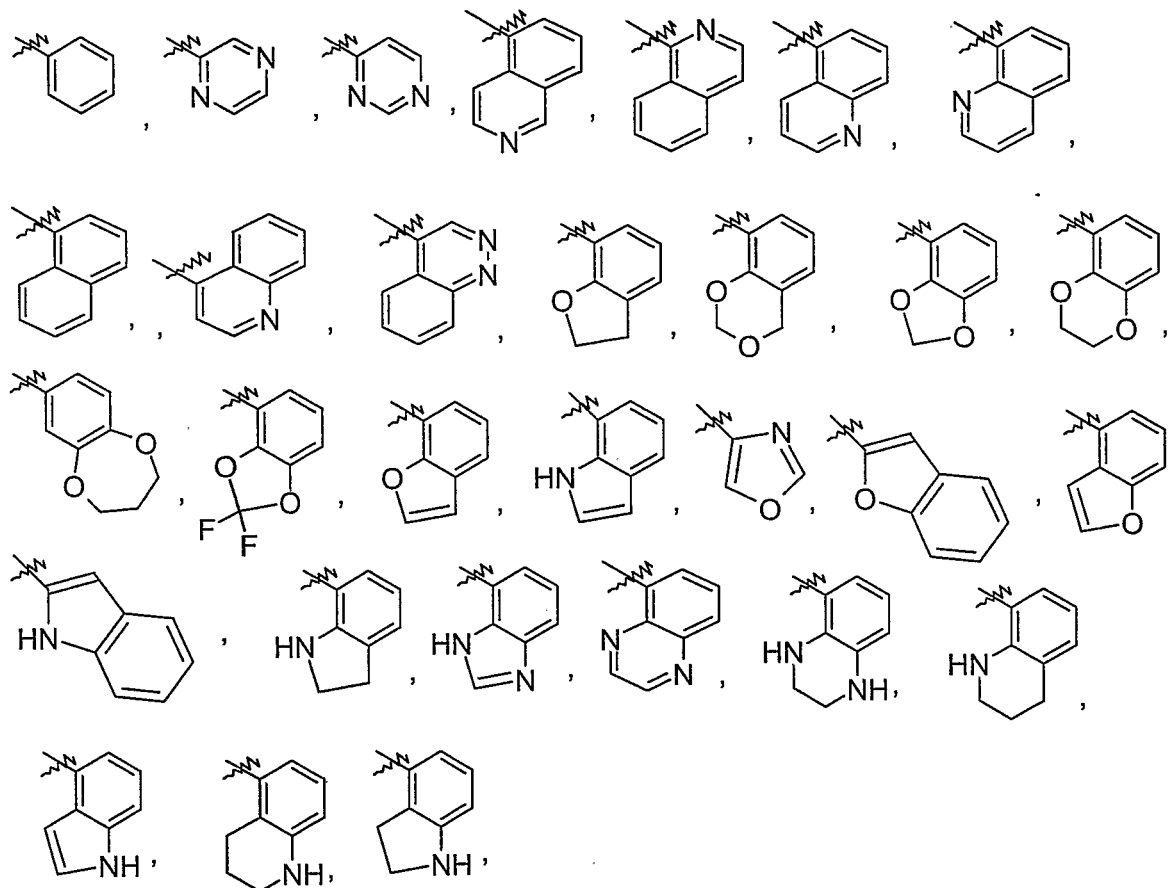
R^3 is selected from hydrogen and C_{1-6} alkyl; and

R^4 is selected from



pyrrolidin-1-amino, piperidin-1-amino, O-cyclohexylhydroxyamino, O-cyclopentylhydroxyamino, O-cyclobutylhydroxyamino, O-cyclopropylhydroxyamino, and C_{1-3} alkyl that are optionally substituted by one or more groups selected from halogen, amino, aminomethyl, 2-aminoethyl, hydroxy, hydroxymethyl, methyl and ethyl.

Particularly, R^2 is selected from



that are optionally substituted with one or more groups selected from halogen, methyl, methoxy, hydroxyl, methoxymethyl, 1*H*-1,2,3-triazolylmethyl and 1*H*-1,2-diazolylmethyl.

In an even further embodiment, the compounds of the present invention are those of formula I and pharmaceutically acceptable salts thereof,

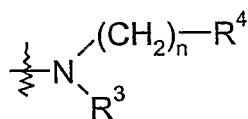
wherein *m* is 1;

n is selected from 0, 1, 2, and 3;

*R*¹ is independently selected from halogen, amino, nitro, acetylamino, hydroxyl, C₁₋₃alkoxy, C₁₋₃alkyl, halogenated C₁₋₃alkoxy, and halogenated C₁₋₃alkyl;

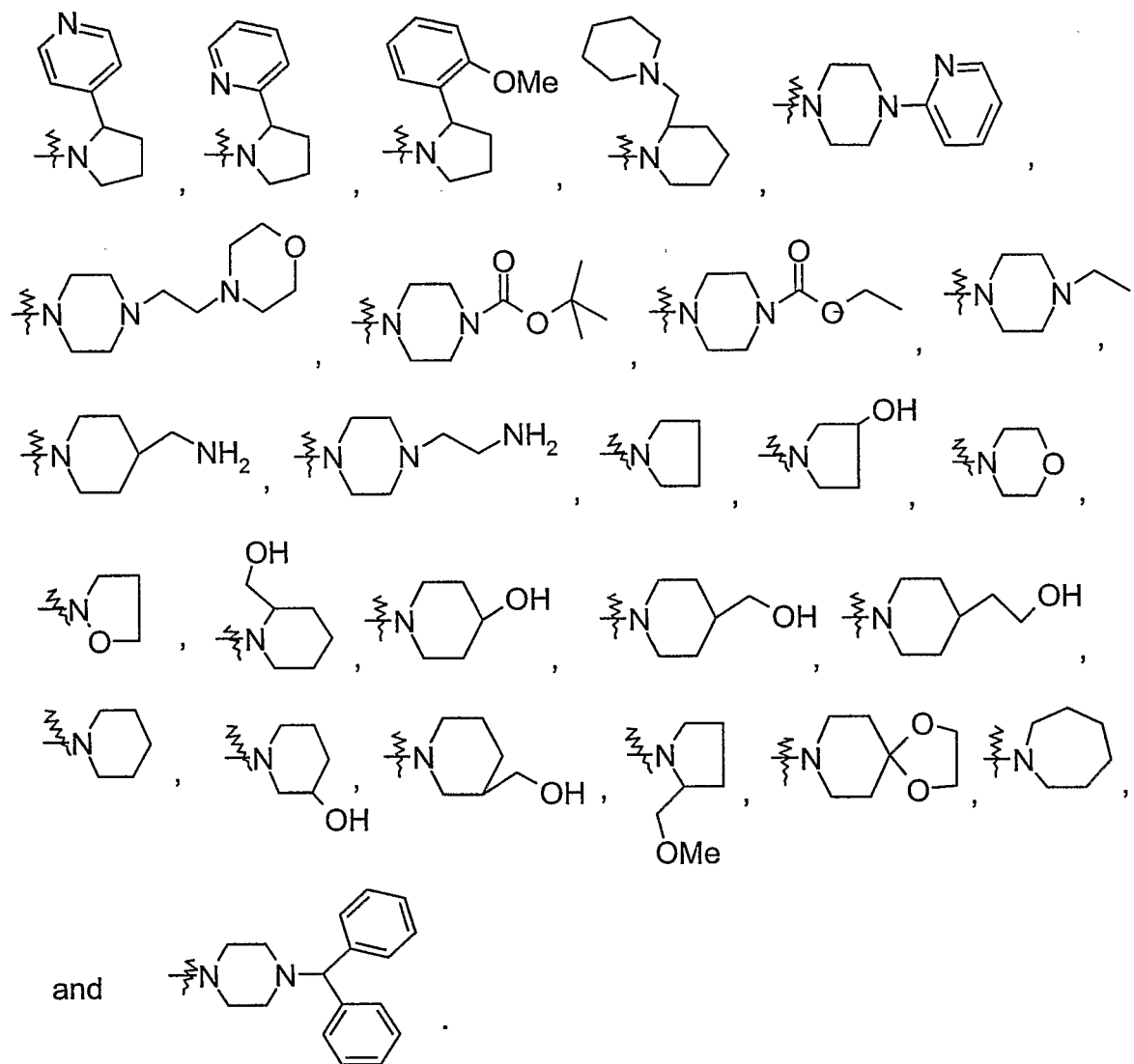
*R*² is selected from phenyl, naphthyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4-oxadiazolyl, indolyl, indolinyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, 1,4-benzodioxanyl, coumarin, dihydrocoumarinyl, 2,3-dihydrobenzofuranyl, 1,2-

benzisoxazolyl, 1,3-benzodioxolyl, 2,3-dihydro-1,4-benzodioxinyl, 3,4-dihydro-2H-1,5-benzodioxepinyl, 4H-1,3-benzodioxinyl, benzofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benzimidazolyl, benztriazolyl, thioxanthinyl, carbazolyl, carbolinyl, acridinyl, pyrrolizidinyl, and quinolizidinyl that are optionally substituted by one or more
 5 groups selected from halogen, hydroxy, methyl, methoxy, amino, trifluoromethyl, trifluoromethoxy, methoxymethyl, 1*H*-1,2,3-triazolylmethyl, 1*H*-pyrazolylmethyl; and

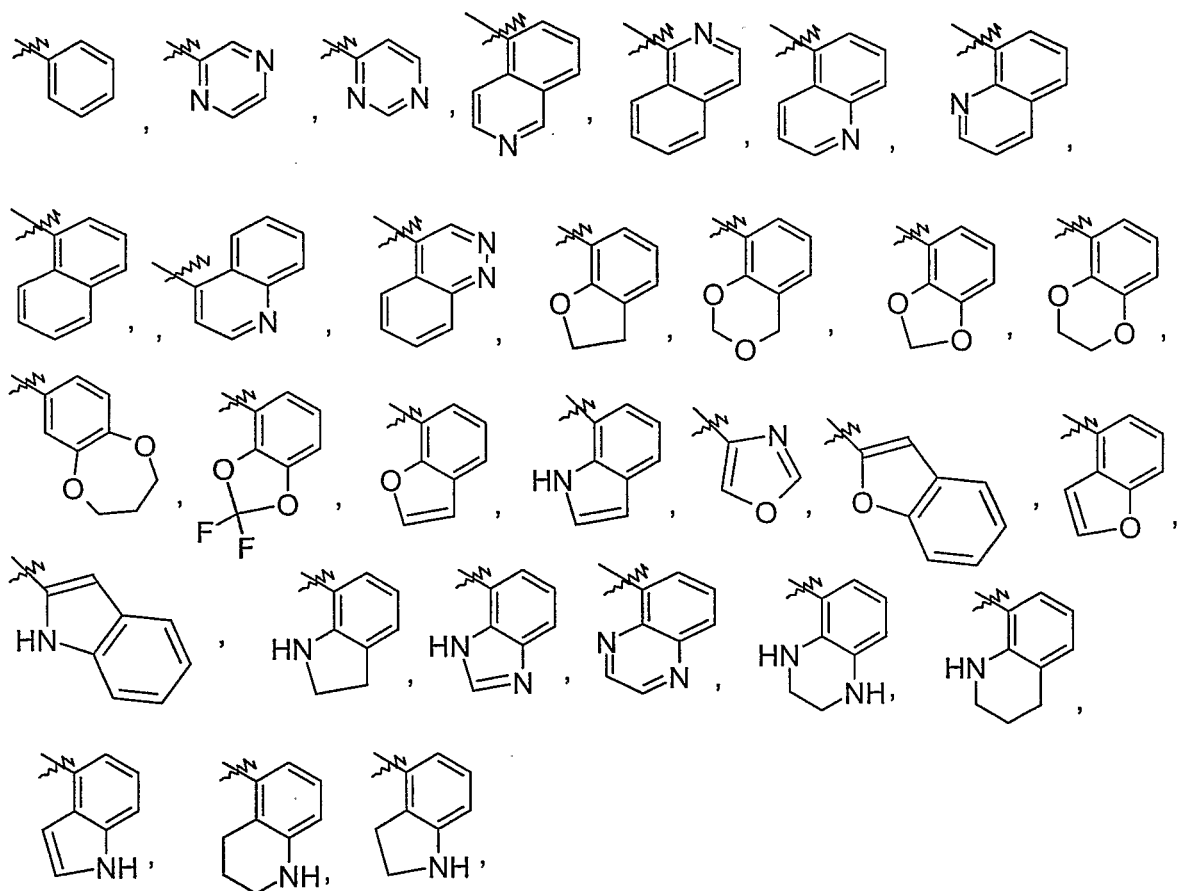


is selected from azetidiny, azepanyl, isoxazolidinyl, morpholinyl, piperazinyl, piperidinyl, pyrrolidinyl, and 1,4-dioxo-8-azaspiro[4.5]decan-8-yl that were optionally substituted with one or more groups selected from halogen, cyano,
 10 nitro, methyl, ethyl, hydroxy, hydroxy-methyl, hydroxy-ethyl, amino-methyl, amino-ethyl, methoxy-methyl, methoxy-phenyl, ethoxycarbonyl, tert-butoxycarbonyl, diphenyl-methyl, morpholinyl-eth-2-yl, piperidinyl-methyl and pyridinyl.

Particularly, $\begin{array}{c} \text{---} \\ \text{---} \end{array} \text{N} \begin{array}{l} \text{---} (\text{CH}_2)_n \text{---} \text{R}^4 \\ \text{---} \text{R}^3 \end{array}$ is selected from



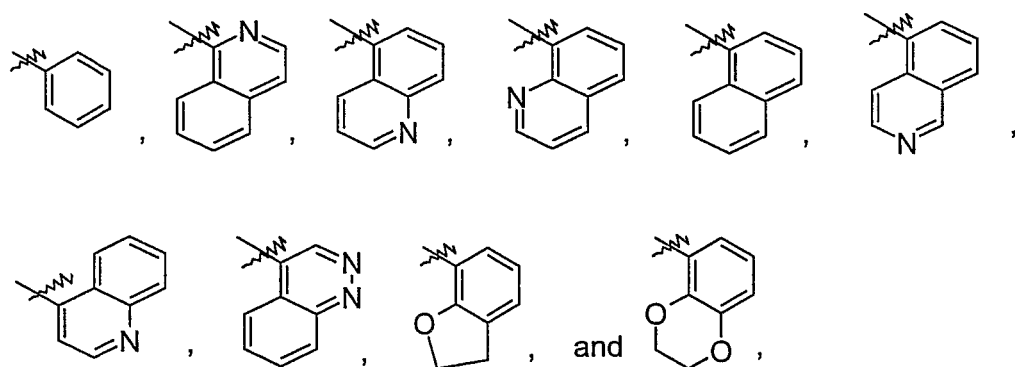
More particularly, R^2 is selected from



that are optionally substituted with one or more groups selected from halogen, methyl, methoxy, hydroxyl, methoxymethyl, 1*H*-1,2,3-triazolylmethyl and 1*H*-pyrazolylmethyl.

5

In a more particular embodiment, R^2 is selected from



that are

optionally substituted with one or more groups selected from halogen, methyl, methoxy, hydroxyl, methoxymethyl, 1*H*-1,2,3-triazolylmethyl and 1*H*-pyrazolylmethyl.

10 It will be understood that when compounds of the present invention contain one or more chiral centers, the compounds of the invention may exist in, and be isolated as,

enantiomeric or diastereomeric forms, or as a racemic mixture. The present invention includes any possible enantiomers, diastereomers, racemates or mixtures thereof, of a compound of Formula I. The optically active forms of the compound of the invention may be prepared, for example, by chiral chromatographic separation of a racemate, by synthesis
5 from optically active starting materials or by asymmetric synthesis based on the procedures described thereafter.

It will also be appreciated that certain compounds of the present invention may exist as geometrical isomers, for example E and Z isomers of alkenes. The present invention includes any geometrical isomer of a compound of Formula I. It will further be understood
10 that the present invention encompasses tautomers of the compounds of the formula I.

It will also be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It will further be understood that the present invention encompasses all such solvated forms of the compounds of the formula I.

Within the scope of the invention are also salts of the compounds of the formula I.
15 Generally, pharmaceutically acceptable salts of compounds of the present invention may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound, for example an alkyl amine with a suitable acid, for example, HCl or acetic acid, to afford a physiologically acceptable anion. It may also be possible to
20 make a corresponding alkali metal (such as sodium, potassium, or lithium) or an alkaline earth metal (such as a calcium) salt by treating a compound of the present invention having a suitably acidic proton, such as a carboxylic acid or a phenol with one equivalent of an alkali metal or alkaline earth metal hydroxide or alkoxide (such as the ethoxide or methoxide), or a suitably basic organic amine (such as choline or meglumine) in an aqueous
25 medium, followed by conventional purification techniques.

In one embodiment, the compound of formula I above may be converted to a pharmaceutically acceptable salt or solvate thereof, particularly, an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, methanesulphonate or *p*-toluenesulphonate.

30 We have now found that the compounds of the invention have activity as pharmaceuticals, in particular as modulators or ligands such as agonists, partial agonists, inverse agonist or antagonists of CB₁ receptors. More particularly, the compounds of the

invention exhibit activity as agonist of the CB₁ receptors and are useful in therapy, especially for relief of various pain conditions such as chronic pain, neuropathic pain, acute pain, cancer pain, pain caused by rheumatoid arthritis, migraine, visceral pain etc. This list should however not be interpreted as exhaustive. Additionally, compounds of the present invention are useful in other disease states in which dysfunction of CB₁ receptors is present or implicated. Furthermore, the compounds of the invention may be used to treat cancer, multiple sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's disease, anxiety disorders, gastrointestinal disorders and cardiovascular disorders.

Compounds of the invention are useful as immunomodulators, especially for autoimmune diseases, such as arthritis, for skin grafts, organ transplants and similar surgical needs, for collagen diseases, various allergies, for use as anti-tumour agents and anti viral agents.

Compounds of the invention are useful in disease states where degeneration or dysfunction of cannabinoid receptors is present or implicated in that paradigm. This may involve the use of isotopically labelled versions of the compounds of the invention in diagnostic techniques and imaging applications such as positron emission tomography (PET).

Compounds of the invention are useful for the treatment of diarrhoea, depression, anxiety and stress-related disorders such as post-traumatic stress disorders, panic disorder, generalized anxiety disorder, social phobia, and obsessive compulsive disorder, urinary incontinence, premature ejaculation, various mental illnesses, cough, lung oedema, various gastro-intestinal disorders, e.g. constipation, functional gastrointestinal disorders such as Irritable Bowel Syndrome and Functional Dyspepsia, Parkinson's disease and other motor disorders, traumatic brain injury, stroke, cardioprotection following myocardial infarction, spinal injury and drug addiction, including the treatment of alcohol, nicotine, opioid and other drug abuse and for disorders of the sympathetic nervous system for example hypertension.

Compounds of the invention are useful as an analgesic agent for use during general anaesthesia and monitored anaesthesia care. Combinations of agents with different properties are often used to achieve a balance of effects needed to maintain the anaesthetic state (e.g. amnesia, analgesia, muscle relaxation and sedation). Included in this combination are inhaled anaesthetics, hypnotics, anxiolytics, neuromuscular blockers and opioids.

In another aspect of the invention is the use of a compound according to formula I for inhibition of transient lower esophageal sphincter relaxations (TLESRs) and thus for treatment or prevention of gastroesophageal reflux disorder (GERD). The major mechanism behind reflux has been considered to depend on a hypotonic lower esophageal sphincter.

5 However, e.g. Holloway & Dent (1990) *Gastroenterol. Clin. N. Amer.* 19, pp. 517-535, has shown that most reflux episodes occur during transient lower esophageal sphincter relaxations (TLESRs), i.e. relaxations not triggered by swallows. In further embodiments, the compounds according to the present invention are useful for the prevention of reflux, treatment or prevention of regurgitation, treatment or prevention of asthma, treatment or
10 prevention of laryngitis, treatment or prevention of lung disease and for the management of failure to thrive.

A further aspect of the invention is the use of a compound according to formula I for the manufacture of a medicament for the inhibition of transient lower esophageal sphincter relaxations, for the treatment or prevention of GERD, for the prevention of reflux, for the
15 treatment or prevention of regurgitation, treatment or prevention of asthma, treatment or prevention of laryngitis, treatment or prevention of lung disease and for the management of failure to thrive.

An even further aspect of the invention is the use of a compound according to formula I for the manufacture of a medicament for the treatment or prevention of functional
20 gastrointestinal disorders, such as functional dyspepsia (FD). Yet another aspect of the invention is the use of a compound according to formula I for the manufacture of a medicament for the treatment or prevention of irritable bowel syndrome (IBS), such as constipation predominant IBS, diarrhea predominant IBS or alternating bowel movement predominant IBS. Exemplary irritable bowel syndrome (IBS) and functional
25 gastrointestinal disorders, such as functional dyspepsia, are illustrated in Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Mueller-Lissner SA. C. Functional Bowel Disorders and Functional Abdominal Pain. In: Drossman DA, Talley NJ, Thompson WG, Whitehead WE, Corazziari E, eds. *Rome II: Functional Gastrointestinal Disorders: Diagnosis, Pathophysiology and Treatment*. 2 ed. McLean, VA: Degnon Associates, Inc.;
30 2000:351-432 and Drossman DA, Corazziari E, Talley NJ, Thompson WG and Whitehead WE. *Rome II: A multinational consensus document on Functional Gastrointestinal Disorders*. *Gut* 45(Suppl.2), II1-II81.9-1-1999.

Also within the scope of the invention is the use of any of the compounds according to the formula I above, for the manufacture of a medicament for the treatment of any of the conditions discussed above.

A further aspect of the invention is a method for the treatment of a subject suffering
5 from any of the conditions discussed above, whereby an effective amount of a compound according to the formula I above, is administered to a patient in need of such treatment.

Thus, the invention provides a compound of formula I, or pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of formula
10 I, or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The term "therapeutic" and "therapeutically" should be construed accordingly. The term "therapy" within the context of
15 the present invention further encompasses to administer an effective amount of a compound of the present invention, to mitigate either a pre-existing disease state, acute or chronic, or a recurring condition. This definition also encompasses prophylactic therapies for prevention of recurring conditions and continued therapy for chronic disorders.

The compounds of the present invention are useful in therapy, especially for the
20 therapy of various pain conditions including, but not limited to: acute pain, chronic pain, neuropathic pain, back pain, cancer pain, and visceral pain.

In use for therapy in a warm-blooded animal such as a human, the compound of the invention may be administered in the form of a conventional pharmaceutical composition by any route including orally, intramuscularly, subcutaneously, topically, intranasally,
25 intraperitoneally, intrathoracically, intravenously, epidurally, intrathecally, intracerebroventricularly and by injection into the joints.

In one embodiment of the invention, the route of administration may be oral, intravenous or intramuscular.

The dosage will depend on the route of administration, the severity of the disease,
30 age and weight of the patient and other factors normally considered by the attending physician, when determining the individual regimen and dosage level at the most appropriate for a particular patient.

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid and liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

5 A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet-disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided compound of the invention, or the active component. In tablets, the active
10 component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into
15 convenient sized moulds and allowed to cool and solidify.

Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

The term composition is also intended to include the formulation of the active
20 component with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier which is thus in association with it. Similarly, cachets are included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

25 Liquid form compositions include solutions, suspensions, and emulsions. For example, sterile water or water propylene glycol solutions of the active compounds may be liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions for oral administration can be prepared by dissolving the active
30 component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as

natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Depending on the mode of administration, the pharmaceutical composition will preferably include from 0.05% to 99%w (percent by weight), more preferably from 0.10 to 5 50%w, of the compound of the invention, all percentages by weight being based on total composition.

A therapeutically effective amount for the practice of the present invention may be determined, by the use of known criteria including the age, weight and response of the individual patient, and interpreted within the context of the disease which is being treated or 10 which is being prevented, by one of ordinary skills in the art.

Within the scope of the invention is the use of any compound of formula I as defined above for the manufacture of a medicament.

Also within the scope of the invention is the use of any compound of formula I for the manufacture of a medicament for the therapy of pain.

15 Additionally provided is the use of any compound according to Formula I for the manufacture of a medicament for the therapy of various pain conditions including, but not limited to: acute pain, chronic pain, neuropathic pain, back pain, cancer pain, and visceral pain.

A further aspect of the invention is a method for therapy of a subject suffering from 20 any of the conditions discussed above, whereby an effective amount of a compound according to the formula I above, is administered to a patient in need of such therapy.

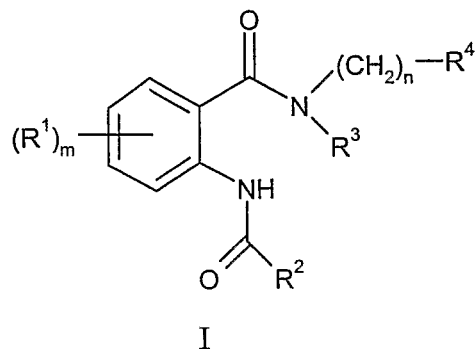
Additionally, there is provided a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

25 Particularly, there is provided a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier for therapy, more particularly for therapy of pain.

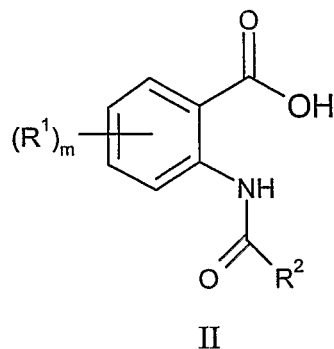
Further, there is provided a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, in association with a 30 pharmaceutically acceptable carrier use in any of the conditions discussed above.

Another aspect of the invention is a method of preparing the compounds of the present invention.

In one embodiment, the method of the invention is a method for preparing a compound of formula I,



5 comprising the step of reacting a compound of formula II,



with a compound of $R^3(CH_2)_nR^4NH$, in the presence of a base, such as an DIPEA, a solvent such as DMF, and optionally a coupling reagent, such as HATU,

10 wherein:

m is selected from 0, 1 and 2;

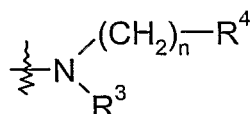
n is selected from 0, 1, 2, 3, 4 and 5;

R^1 is independently selected from halogen, cyano, amino, nitro, C_{1-6} alkylamino, di C_{1-6} alkylamino, acetylamino, hydroxyl, C_{1-6} alkoxy, C_{1-6} alkyl, halogenated C_{1-6} alkoxy, C_{1-6} alkenyl, and halogenated C_{1-6} alkyl;

R^2 is selected from C_{6-10} aryl and C_{2-10} heterocyclyl; wherein said C_{6-10} aryl and C_{2-10} heterocyclyl used in defining R^2 is optionally substituted by one or more groups selected from halogen, halogenated C_{1-6} alkyl, C_{1-6} alkyl, cyano, nitro, C_{1-6} alkoxy, halogenated C_{1-6} alkoxy, hydroxy, hydroxy- C_{1-6} alkyl, amino, C_{1-6} alkoxy- C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylamino, di C_{1-6} alkyl-amino, amino- C_{1-6} alkyl, C_{2-5} heterocyclyl- C_{1-3} alkyl, C_{3-6} cycloalkyl, C_{2-6} heteroaryl, heteroaryl- C_{1-6} alkyl, C_{6-10} aryl, and C_{6-10} aryl- C_{1-6} alkyl; and

R^3 is selected from hydrogen and C_{1-6} alkyl; R^4 is selected from C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, C_{6-10} aryl, C_{2-6} heterocyclyl-amino, C_{2-6} heterocyclyloxy-amino, and C_{2-6} heterocyclyl; wherein said C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, C_{6-10} aryl, C_{2-6} heterocyclyl-amino, C_{2-6} heterocyclyloxy-amino, and C_{2-6} heterocyclyl used in

5 defining R^4 is optionally substituted by one or more groups selected from halogen, halogenated C_{1-6} alkyl, C_{1-6} alkyl, cyano, nitro, C_{1-6} alkoxy, halogenated C_{1-6} alkoxy, hydroxy, hydroxy- C_{1-6} alkyl, amino, C_{1-6} alkoxy- C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylamino, di- C_{1-6} alkyl-amino, amino- C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} heteroaryl, heteroaryl-



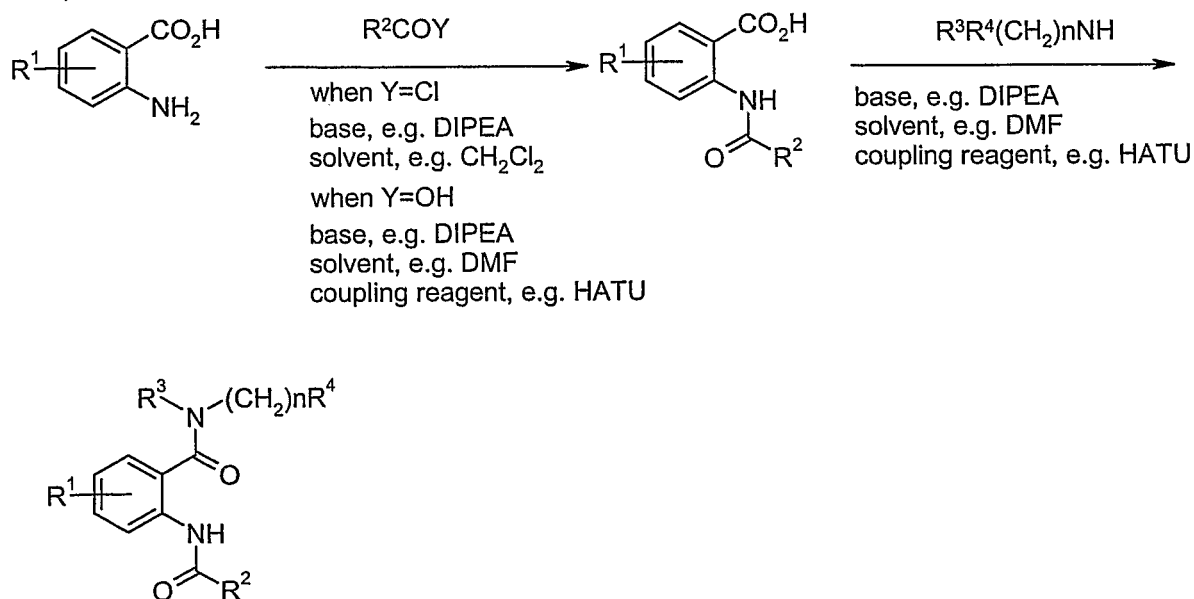
C_{1-6} alkyl, C_{6-10} aryl, and C_{6-10} aryl- C_{1-6} alkyl; or

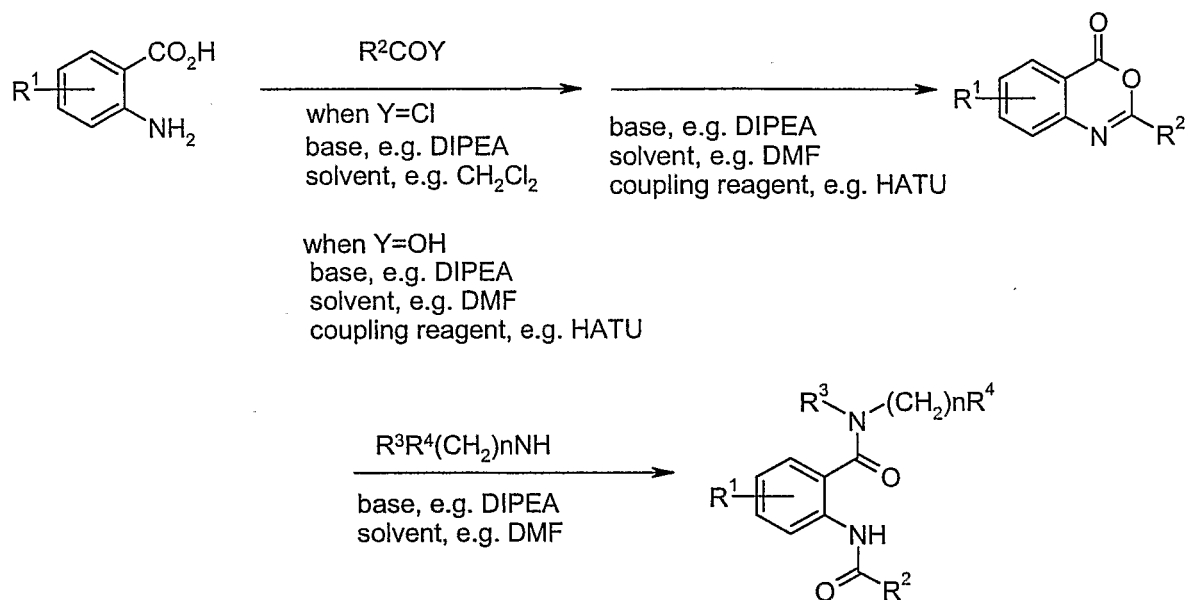
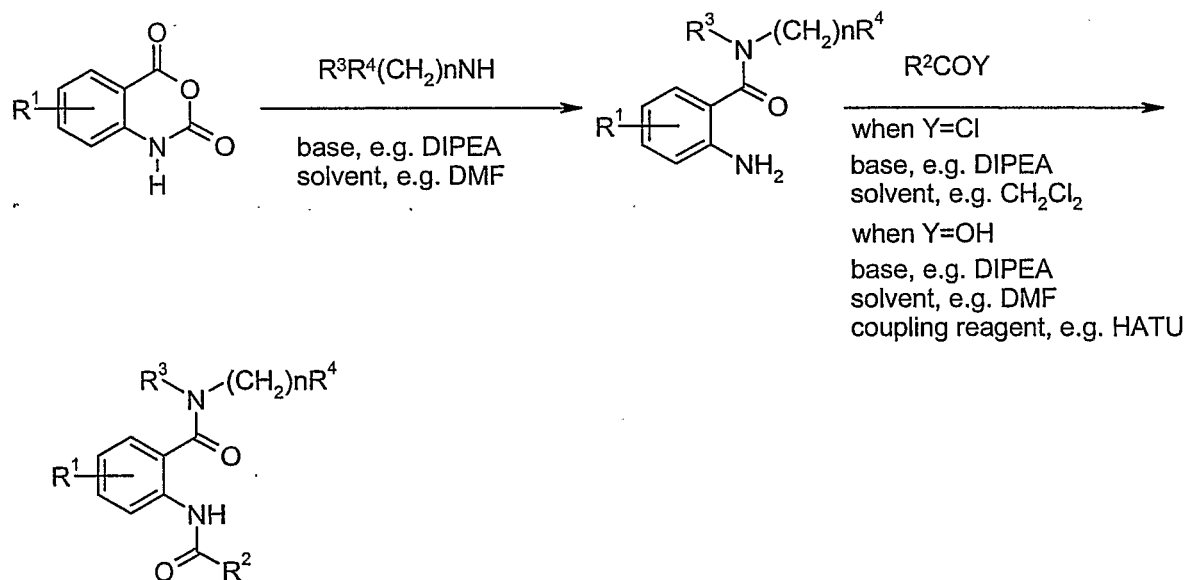
is selected from a C_{2-}

10 $_{10}$ heterocyclyl, which is optionally substituted by one or more groups selected from halogen, halogen substituted C_{1-6} alkyl, C_{1-6} alkyl, cyano, nitro, C_{1-6} alkoxy, halogenated C_{1-6} alkoxy, hydroxy, hydroxy- C_{1-6} alkyl, amino, C_{1-6} alkoxy- C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylamino, di- C_{1-6} alkyl-amino, amino- C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} heteroaryl, heteroaryl- C_{1-6} alkyl, C_{6-10} aryl, and C_{6-10} aryl- C_{1-6} alkyl.

15 Compounds of the present invention may be prepared according to the synthetic routes as depicted in Schemes 1-3.

Scheme 1. A synthetic route used for the synthesis of compounds



Scheme 2. A synthetic route used for the synthesis of compounds**Scheme 3. A synthetic route used for the synthesis of compounds**

Biological Evaluation

hCB₁ and hCB₂ receptor binding

Human CB₁ receptor from Receptor Biology (hCB₁) or human CB₂ receptor from BioSignal (hCB₂) membranes are thawed at 37 °C, passed 3 times through a 25-gauge blunt-end needle, diluted in the cannabinoid binding buffer (50 mM Tris, 2.5 mM EDTA, 5 mM MgCl₂, and 0.5 mg/mL BSA fatty acid free, pH 7.4) and aliquots containing the appropriate amount of protein are distributed into 96-well plates. The IC₅₀ of the compounds of the invention at hCB₁ and hCB₂ are evaluated from 10-point dose-response curves done with ³H-CP55,940 at 20000 to 25000 dpm per well (0.17-0.21 nM) in a final volume of 300 µl. The total and non-specific binding are determined in the absence and presence of 0.2 µM of HU210 respectively. The plates are vortexed and incubated for 60 minutes at room temperature, filtered through Unifilters GF/B (presoaked in 0.1% polyethyleneimine) with the Tomtec or Packard harvester using 3 mL of wash buffer (50 mM Tris, 5 mM MgCl₂, 0.5 mg BSA pH 7.0). The filters are dried for 1 hour at 55 °C. The radioactivity (cpm) is counted in a TopCount (Packard) after adding 65 µl/well of MS-20 scintillation liquid.

hCB₁ and hCB₂ GTPγS binding

Human CB₁ receptor from Receptor Biology (hCB₁) or human CB₂ receptor membranes (BioSignal) are thawed at 37 °C, passed 3 times through a 25-gauge blunt-end needle and diluted in the GTPγS binding buffer (50 mM Hepes, 20 mM NaOH, 100 mM NaCl, 1 mM EDTA, 5 mM MgCl₂, pH 7.4, 0.1% BSA). The EC₅₀ and E_{max} of the compounds of the invention are evaluated from 10-point dose-response curves done in 300µl with the appropriate amount of membrane protein and 100000-130000 dpm of GTPγ³⁵S per well (0.11 –0.14 nM). The basal and maximal stimulated binding is determined in absence and presence of 1 µM (hCB₂) or 10 µM (hCB₁) Win 55,212-2 respectively. The membranes are pre-incubated for 5 minutes with 56.25 µM (hCB₂) or 112.5 µM (hCB₁) GDP prior to distribution in plates (15 µM (hCB₂) or 30 µM (hCB₁) GDP final). The plates are vortexed and incubated for 60 minutes at room temperature, filtered on Unifilters GF/B (presoaked in water) with the Tomtec or Packard harvester using 3 ml of wash buffer (50 mM Tris, 5 mM MgCl₂, 50 mM NaCl, pH 7.0). The filters are dried for 1

hour at 55 °C. The radioactivity (cpm) is counted in a TopCount (Packard) after adding 65 µl/well of MS-20 scintillation liquid. Antagonist reversal studies are done in the same way except that (a) an agonist dose-response curve is done in the presence of a constant concentration of antagonist, or (b) an antagonist dose-response curve is done in the presence of a constant concentration of agonist.

Based on the above assays, the dissociation constant (K_i) for a particular compound of the invention towards a particular receptor is determined using the following equation:

$$K_i = IC_{50} / (1 + [rad] / K_d),$$

Wherein IC_{50} is the concentration of the compound of the invention at which 50% displacement has been observed;

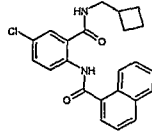
$[rad]$ is a standard or reference radioactive ligand concentration at that moment; and

K_d is the dissociation constant of the radioactive ligand towards the particular receptor.

Using the above-mentioned assays, the K_i towards human CB_1 receptors for most compounds of the invention is measured to be in the range of 7.3-5900 nM. The K_i towards human CB_2 receptors for most compounds of the invention is measured to be in the range of about 4.7-5300 nM. The EC_{50} towards human CB_1 receptors for most compounds of the invention is measured to be in the range of about 40-6500 nM. The E_{max} towards human CB_1 receptors for most compounds of the invention is measured to be in the range of about 17.7-110 %.

The following table shows certain biological activities for some of the exemplified compounds.

COMPOUND	Structures	K_i (hCB1) (nM)	EC_{50} (hCB1) (nM)	E_{max} (hCB1) (%)
Example 49		179	968	109
Example 30		71	304	109

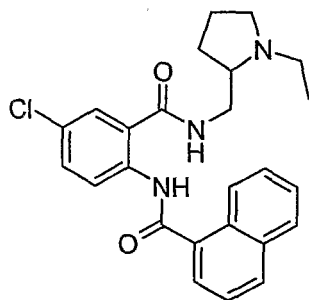
Example 17		7.3	41	95
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EXAMPLES

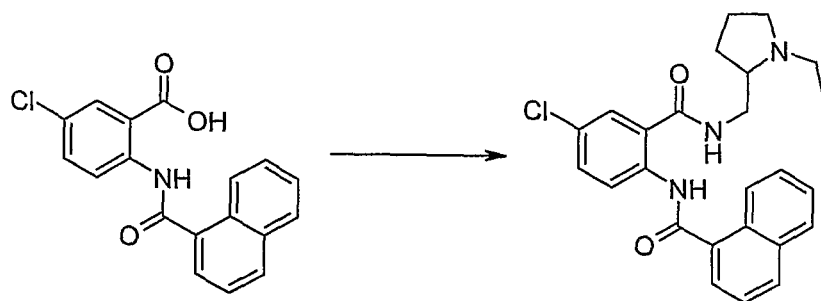
The invention will further be described in more detail by the following Examples which describe methods whereby compounds of the present invention may be prepared, purified, analyzed and biologically tested, and which are not to be construed as limiting the invention.

Example 1

N-[4-Chloro-2-[[[(1-ethyl-2-pyrrolidinyl)methyl]amino]carbonyl]phenyl]-1-naphthalenecarboxamide



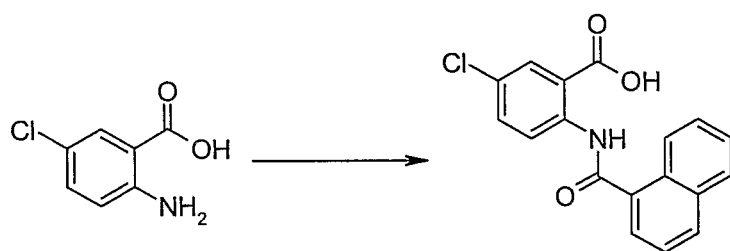
Step A. *N*-[4-Chloro-2-[[[(1-ethyl-2-pyrrolidinyl)methyl]amino]carbonyl]phenyl]-1-naphthalenecarboxamide



1-Ethyl-2-pyrrolidinemethanamine (156.0 mg, 1.22 mmol) was added to a DMF (5 mL) solution of 5-chloro-2-[(1-naphthalenylcarbonyl)amino]benzoic acid (200.0 mg, 0.61 mmol, see Step B for its preparation) and HATU (257.0 mg, 0.68 mmol) at room temperature. The reaction mixture was stirred overnight, and was then concentrated *in*

vacuo. The residue was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized to provide the title compound as the corresponding TFA salt (76 mg, 23 %). ¹H NMR (400 MHz, CDCl₃) δ 1.31 (t, J=7.23 Hz, 3 H), 1.86 (m, 1 H), 2.07 (m, 2 H), 2.19 (m, 1 H), 2.95 (m, 4 H), 3.20 (s, 1 H), 3.57 (m, 1 H), 3.81 (m, 1 H), 7.55 (m, 4 H), 7.83 (d, J=6.25 Hz, 1 H), 7.87 (m, 2 H), 7.97 (d, J=8.20 Hz, 1 H), 8.49 (s, 1 H), 8.92 (d, J=8.98 Hz, 1 H), 9.54 (s, 1 H), 12.04 (s, 1 H). MS (ESI) (M+H)⁺ 436.1.

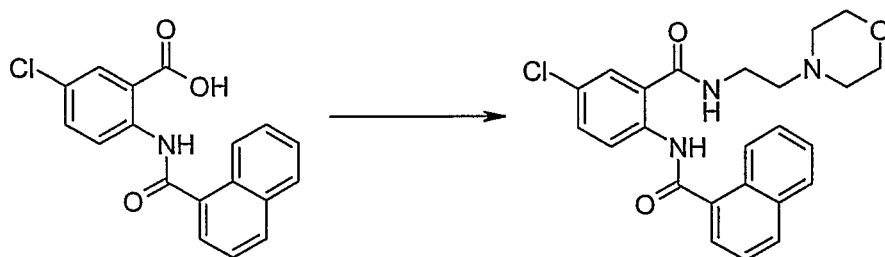
Step B. 5-Chloro-2-[(1-naphthalenylcarbonyl)amino]- benzoic acid



A solution of 1-naphthalenecarbonyl chloride (97 μl, 0.64 mmol) in CH₂Cl₂ (mL) was added to a mixture of 2-amino 5-chlorobenzoic acid (110 mg, 0.64 mmol) and triethylamine (90 μl, 0.64 mmol) in CH₂Cl₂ (3.5 mL) at 0 °C. The reaction mixture was then stirred overnight at room temperature. After removal of solvents, the solids were washed with H₂O, were collected and dried *in vacuo* to provide the title compound (200 mg, 95 %). ¹H NMR (400 MHz, CDCl₃) δ 7.59 (m, 2 H), 7.67 (m, 1 H), 7.75 (d, J=8.59 Hz, 1 H), 7.81 (m, 1 H), 7.94 (d, J=8.20 Hz, 1 H), 8.07 (d, J=8.20 Hz, 1 H), 8.26 (d, J=2.15 Hz, 1 H), 8.33 (d, J=7.23 Hz, 1 H), 9.13 (d, J=8.79 Hz, 1 H). MS (ESI) (M+H)⁺ 326.

Example 2

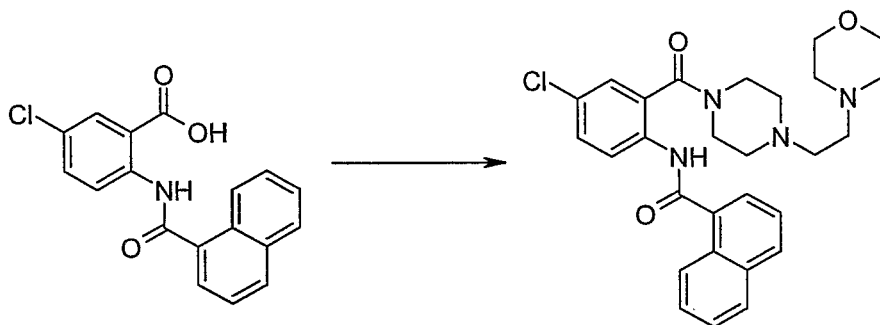
N-[4-Chloro-2-[[[2-(4-morpholinyl)ethyl]amino]carbonyl]phenyl]- 1-naphthalenecarboxamide



Following the procedure for Step A in Example 1, using 5-chloro-2-[(1-naphthalenylcarbonyl)amino]-benzoic acid (200.0 mg, 0.61 mmol), HATU (257.0 mg, 0.68 mmol) and 4-morpholineethanamine (160 μ l, 1.22 mmol) in DMF (5 ml). The product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized to provide the title compound as the corresponding TFA salt (58 mg, 17 %). ¹H NMR (400 MHz, CDCl₃) δ 3.24 (m, 2 H), 3.81 (m, 2 H), 3.93 (m, 8 H), 7.56 (m, 3 H), 7.68 (d, J=2.34 Hz, 2 H), 7.85 (dd, J=7.13, 1.07 Hz, 1 H), 7.89 (d, J=1.76 Hz, 2 H), 7.98 (d, J=8.20 Hz, 1 H), 8.50 (s, 1 H), 8.87 (d, J=8.59 Hz, 1 H), 11.68 (s, 1 H). MS (ESI) (M+H)⁺ 438.1.

Example 3

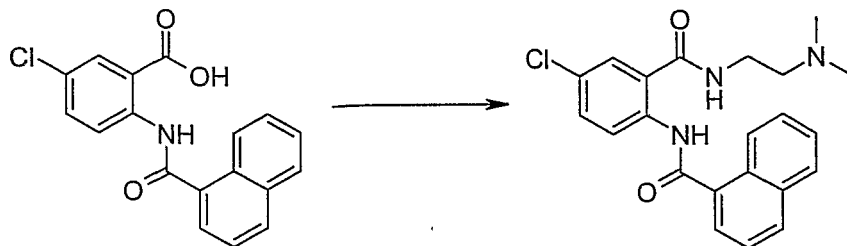
N-[4-Chloro-2-[[4-[2-(4-morpholinyl)ethyl]-1-piperazinyl]carbonyl]phenyl]-1-naphthalenecarboxamide



Following the procedure for Step A in Example 1, using 5-chloro-2-[(1-naphthalenylcarbonyl)amino]-benzoic acid (200.0 mg, 0.61 mmol), HATU (257.0 mg, 0.68 mmol) and 4-[2-(1-piperazinyl)ethyl]-morpholine (243 mg, 1.22 mmol) in DMF (5 ml). The product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized to provide the title compound as the corresponding TFA salt (67 mg, 18 %). ¹H NMR (400 MHz, CDCl₃) δ 2.32 (m, 8 H) 3.14 (m, 4 H), 3.29 (m, 2 H), 3.37 (m, 2 H), 3.89 (m, 4 H), 7.20 (d, J=2.15 Hz, 1 H), 7.38 (m, 1 H), 7.50 (m, 1 H), 7.56 (m, 2 H), 7.71 (d, J=7.03 Hz, 1 H), 7.79 (m, 1 H), 7.90 (m, 1 H), 7.98 (d, J=8.20 Hz, 1 H), 8.32 (s, 1 H), 8.88 (s, 1 H). MS (ESI) (M+H)⁺ 507.1.

Example 4

N-[4-Chloro-2-[[[2-(dimethylamino)ethyl]amino]carbonyl]phenyl]-1-naphthalenecarboxamide



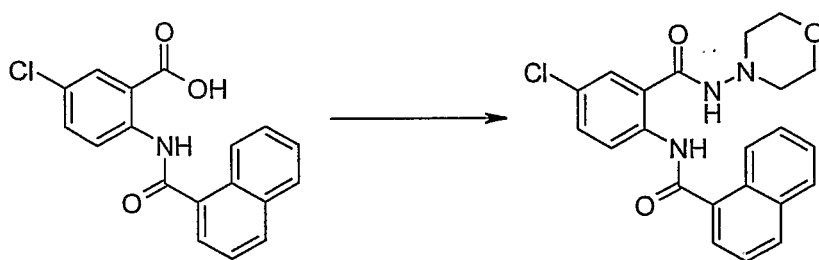
Following the procedure for Step A in Example 1, using 5-chloro-2-[(1-

naphthalenylcarbonyl)amino]-benzoic acid (200.0 mg, 0.61 mmol), HATU (257.0 mg, 0.68 mmol) and *N,N*-dimethyl-1,2-ethanediamine (136 μ l, 1.22 mmol) in DMF (5 ml). The product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized to provide the title compound as the corresponding TFA salt (48 mg, 15 %).

¹H NMR (400 MHz, DMSO-D₆) δ 2.75 (s, 6 H), 3.18 (m, 2 H), 3.51 (q, *J*=5.79 Hz, 2 H), 7.58 (m, 2 H), 7.67 (dd, *J*=8.79, 2.54 Hz, 1 H), 7.81 (dd, *J*=7.03, 1.17 Hz, 1 H), 7.85 (d, *J*=2.34 Hz, 1 H), 8.00 (m, 1 H), 8.09 (d, *J*=8.20 Hz, 1 H), 8.31 (m, 1 H), 8.50 (d, *J*=8.79 Hz, 1 H), 9.01 (m, 1 H), 9.28 (s, 1 H), 11.74 (s, 1 H). MS (ESI) (*M*+H)⁺ 396.1.

Example 5

N-[4-Chloro-2-[(4-morpholinylamino)carbonyl]phenyl]-1-naphthalenecarboxamide



Following the procedure for Step A in Example 1, using 5-chloro-2-[(1-

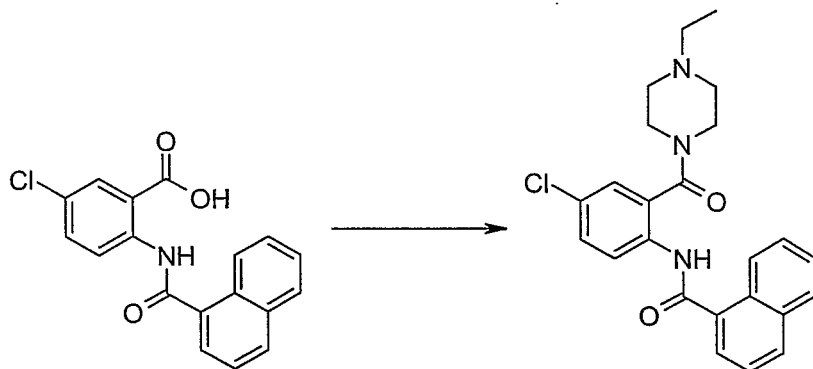
naphthalenylcarbonyl)amino]-benzoic acid (200.0 mg, 0.61 mmol), HATU (257.0 mg, 0.68 mmol) and 4-aminomorpholine (118 μ l, 1.22 mmol) in DMF (5 ml). The product was

purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized to provide the title compound as the corresponding TFA salt (51 mg, 16 %). ¹H NMR (400 MHz, DMSO-D₆) δ 2.78 (m, 4 H), 3.57 (m, 4 H), 7.57 (m, 3 H), 7.70 (m, 1 H), 7.79 (dd,

J=7.03, 1.17 Hz, 1 H), 7.98 (m, 2 H), 8.08 (d, J=8.20 Hz, 1 H), 8.30 (dd, J=6.25, 3.51 Hz, 1 H), 8.36 (d, J=8.98 Hz, 1 H), 9.79 (s, 1 H), 11.42 (s, 1 H). MS (ESI) (M+H)⁺ 410.0.

Example 6

5 *N*-[4-Chloro-2-[(4-ethyl-1-piperazinyl)carbonyl]phenyl]-1-naphthalenecarboxamide

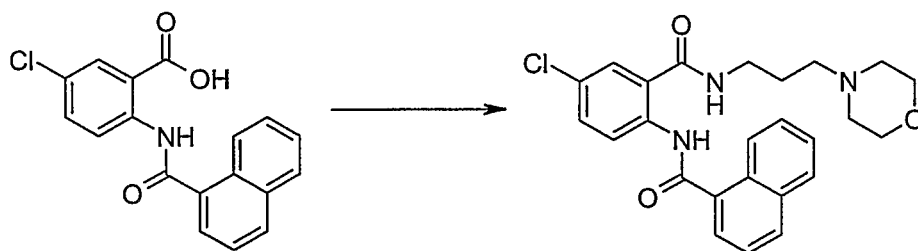


Following the procedure for Step A in Example 1, using 5-chloro-2-[(1-naphthalenylcarbonyl)amino]-benzoic acid (200.0 mg, 0.61 mmol), HATU (257.0 mg, 0.68 mmol) and 1-ethylpiperazine (192 μ l, 1.22 mmol) in DMF (5 ml). The product was purified
10 by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized to provide the title compound as the corresponding TFA salt (64 mg, 20 %). ¹H NMR (400 MHz, DMSO-D₆) δ 1.16 (m, 3 H), 3.08 (m, 2 H), 3.25 (s, 2 H), 3.52 (m, 2 H), 3.84 (m, 2 H), 4.47 (m, 2 H), 7.43 (d, J=8.40 Hz, 1 H), 7.55 (m, 4 H), 7.58 (d, J=8.20 Hz, 1 H), 7.67 (m, 1 H), 7.97 (m, 1 H), 8.04 (d, J=8.20 Hz, 1 H), 8.23 (m, 1 H), 10.68 (s, 1 H). MS (ESI) (M+H)⁺ 422.1.

15

Example 7

N-[4-Chloro-2-[[[3-(4-morpholinyl)propyl]amino]carbonyl]phenyl]-1-naphthalenecarboxamide

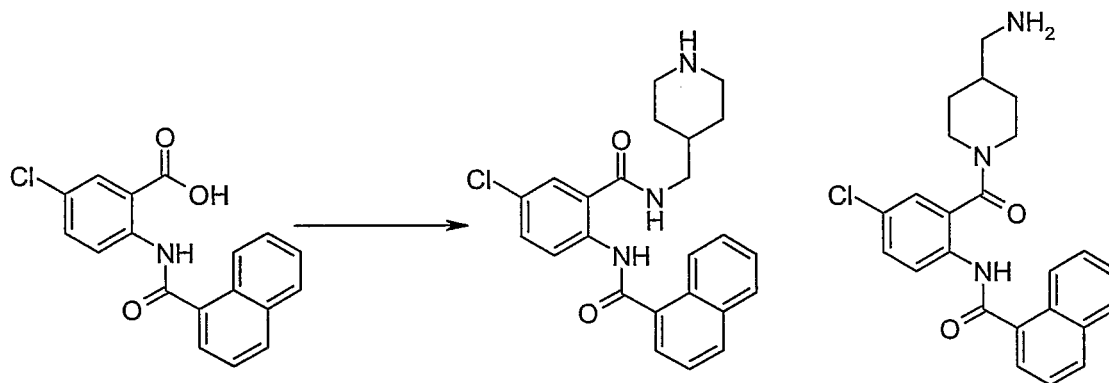


20 Following the procedure for Step A in Example 1, using 5-chloro-2-[(1-naphthalenylcarbonyl)amino]-benzoic acid (200.0 mg, 0.61 mmol), HATU (257.0 mg, 0.68

mmol) and 4-morpholine propanamine (178 μ l, 1.22 mmol) in DMF (5 ml). The product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized to provide the title compound as the corresponding TFA salt (45 mg, 13 %). ¹H NMR (400 MHz, DMSO-D₆) δ 1.80 (m, 2 H), 2.91 (m, 2 H), 3.08 (m, 2 H), 3.23 (m, 4 H), 3.51 (m, 2 H), 3.82 (m, 2 H), 7.57 (m, 2 H), 7.64 (m, 1 H), 7.81 (dd, J=7.42, 1.56 Hz, 2 H), 8.00 (m, 1 H), 8.09 (d, J=8.20 Hz, 1 H), 8.31 (m, 1 H), 8.49 (d, J=8.79 Hz, 1 H), 8.98 (s, 1 H), 9.68 (s, 1 H), 11.84 (s, 1 H). MS (ESI) (M+H)⁺ 452.1.

Examples 8 and 9

N-[4-Chloro-2-[[4-(piperidinylmethyl)amino]carbonyl]phenyl]-1-naphthalenecarboxamide and *N*-[2-[[4-(Aminomethyl)-1-piperidinyl]carbonyl]-4-chlorophenyl]-1-naphthalenecarboxamide



Following the procedure for Step A in Example 1, using 5-chloro-2-[(1-naphthalenyl)carbonyl)amino]-benzoic acid (200.0 mg, 0.61 mmol), HATU (257.0 mg, 0.68 mmol) and 4-(aminomethyl)piperidine (139 mg, 1.22 mmol) in DMF (5 ml). The products were purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized to provide the following two compounds:

a). *N*-[4-chloro-2-[[4-(piperidinylmethyl)amino]carbonyl]phenyl]-1-

naphthalenecarboxamide as the corresponding TFA salt (25 mg, 8 %). ¹H NMR (400 MHz, DMSO-D₆) δ 1.24 (m, 2 H), 1.73 (m, 2 H), 2.74 (d, J=8.40 Hz, 3 H), 3.18 (m, 2 H), 3.30 (m, 2 H), 3.61 (s, 1 H), 7.57 (m, 2 H), 7.65 (dd, J=8.88, 2.44 Hz, 1 H), 7.78 (dd, J=7.03, 1.17 Hz, 1 H), 7.83 (d, J=2.34 Hz, 1 H), 8.00 (dd, J=6.05, 3.32 Hz, 1 H), 8.09 (d, J=8.40 Hz, 1 H), 8.29 (m, 1 H) 8.39 (s, 1 H), 8.56 (m, 1 H), 8.96 (s, 1 H), 11.87 (s, 1 H). MS (ESI)

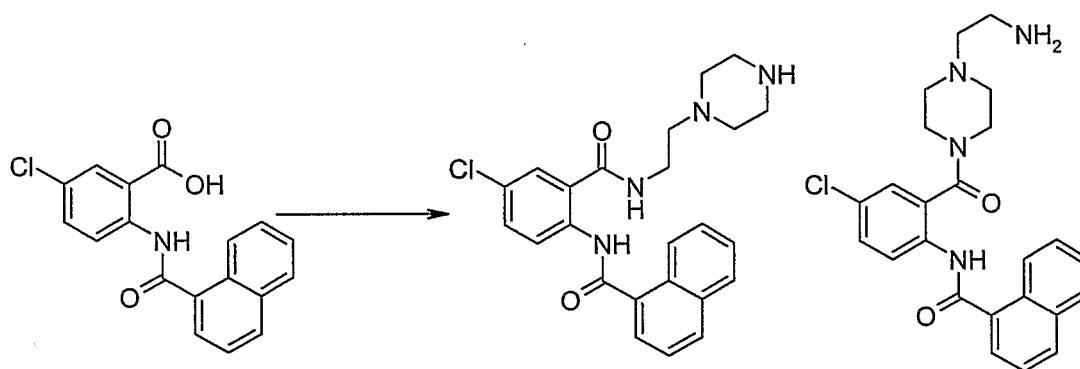
(M+H)⁺ 422.1.

b). *N*-[2-[[4-(aminomethyl)-1-piperidiny]carbonyl]-4-chlorophenyl]-1-naphthalenecarboxamide as the corresponding TFA salt (32 mg, 10 %). ¹H NMR (400 MHz, DMSO-D₆) δ 1.25 (m, 4 H), 1.61 (s, 2 H), 1.74 (m, 3 H), 2.65 (m, 2 H), 4.39 (s, 2 H), 7.38 (d, J=2.54 Hz, 1 H), 7.50 (m, 1 H), 7.54 (m, 3 H), 7.66 (m, 2 H), 7.96 (m, 1 H), 8.02 (m, 1 H), 8.23 (s, 1 H), 10.42 (s, 1 H). MS (ESI) (M+H)⁺ 422.1.

Examples 10 and 11

N-[2-[[4-(2-Aminoethyl)-1-piperaziny]carbonyl]-4-chlorophenyl]-1-naphthalenecarboxamide and *N*-[4-Chloro-2-[[[2-(1-

piperaziny]ethyl]amino]carbonyl]phenyl]-1-naphthalenecarboxamide



Following the procedure for Step A in Example 1, using 5-chloro-2-[(1-naphthalenylcarbonyl)amino]-benzoic acid (200.0 mg, 0.61 mmol), HATU (257.0 mg, 0.68 mmol) and 1-(2-aminoethyl)piperazine (160 µl, 1.22 mmol) in DMF (5 ml). The products were purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized to provide the following two compounds:

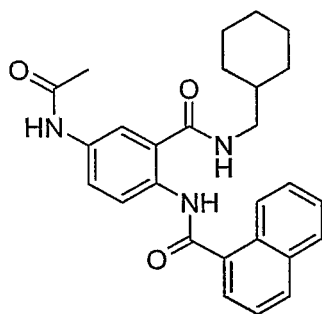
a). *N*-[2-[[4-(2-aminoethyl)-1-piperaziny]carbonyl]-4-chlorophenyl]-1-naphthalenecarboxamide as the corresponding TFA salt (19 mg, 6 %). ¹H NMR (400 MHz, DMSO-D₆) δ 2.45 (m, 2 H), 3.11 (m, 6 H), 3.22 (s, 2 H), 3.63 (m, 2 H), 4.99 (s, 2 H), 7.41 (d, J=8.20 Hz, 1 H), 7.55 (m, 3 H), 7.66 (dd, J=7.03, 0.98 Hz, 1 H), 7.97 (m, 3 H), 8.04 (d, J=8.01 Hz, 1 H), 8.23 (dd, J=6.25, 3.32 Hz, 1 H), 10.64 (s, 1 H). MS (ESI) (M+H)⁺ 437.1.

b) *N*-[4-chloro-2-[[[2-(1-piperaziny)ethyl]amino]carbonyl]phenyl]-1-naphthalenecarboxamide as the corresponding TFA salt (33 mg, 10 %). ¹H NMR (400 MHz, DMSO-D₆) δ 2.44 (m, 2 H), 3.22 (m, 8 H), 3.45 (m, 2 H), 4.86 (s, 1 H), 7.57 (m, 3

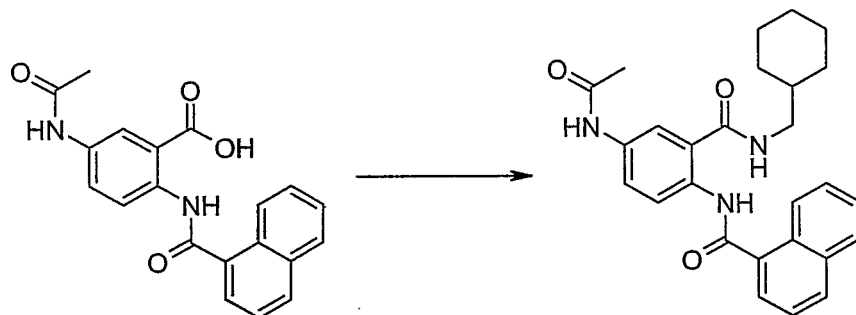
H), 7.82 (m, 2 H), 7.99 (m, 1 H), 8.08 (d, $J=7.81$ Hz, 1 H), 8.31 (s, 1 H), 8.54 (s, 1 H), 8.99 (m, 2 H), 11.81 (s, 1 H). MS (ESI) $(M+H)^+$ 437.1.

Example 12

5 *N*-[4-(Acetylamino)-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-1-naphthalenecarboxamide



Step A. *N*-[4-(Acetylamino)-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-1-naphthalenecarboxamide

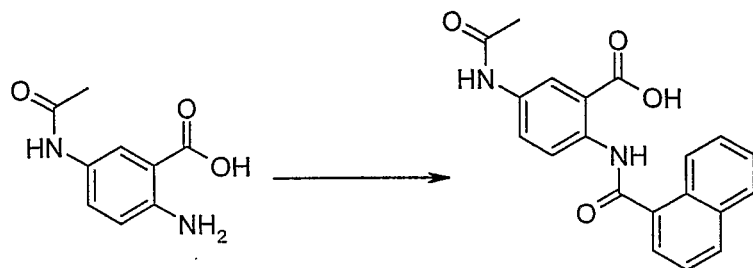


10

Following the procedure for Step A in Example 1, using 5-(acetylamino)-2-[(1-naphthalenylcarbonyl)amino]-benzoic acid (1.55 mmol, see Step B for its preparation), HATU (707.0 mg, 1.86 mmol) and cyclohexylmethylamine (483 μ l, 3.1 mmol) in DMF (5 ml). The product was purified by reversed-phase HPLC using 20-80% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ and
15 then lyophilized to provide the title compound (36 mg, 5 %). ^1H NMR (400 MHz, $\text{DMSO}-\text{D}_6$) δ 0.83 (s, 2 H), 1.07 (s, 2 H), 1.44 (m, 1 H), 1.60 (m, 5 H), 2.02 (s, 3 H), 2.98 (m, 1 H), 7.56 (m, 3 H), 7.72 (m, 2 H), 7.83 (d, $J=2.34$ Hz, 1 H), 7.98 (m, 1 H), 8.06 (d, $J=8.40$ Hz, 1 H), 8.29 (m, 1 H), 8.35 (d, $J=8.79$ Hz, 1 H), 8.67 (t, $J=5.76$ Hz, 1 H), 10.05 (s, 1 H), 11.25 (s, 1 H). MS (ESI) $(M+H)^+$ 444.0.

20

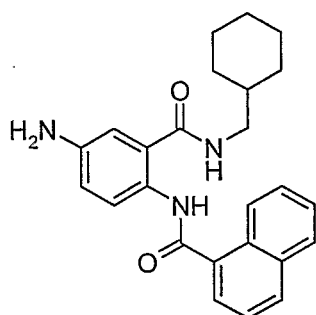
Step B. 5-(Acetylamino)-2-[(1-naphthalenylcarbonyl)amino]-benzoic acid



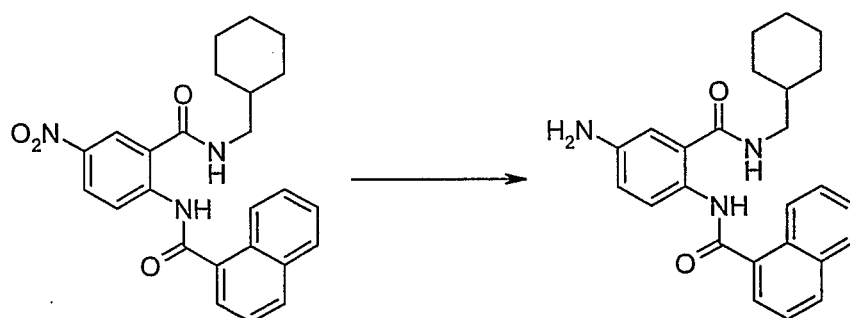
Following the procedure for Step B in Example 1, using 5-(acetylamino)-2-amino-benzoic acid (300 mg, 1.55 mmol), 1-naphthoyl chloride (310 μ l, 1.55 mmol) and triethylamine (216 μ l, 1.55 mmol) in dichloromethane (10 mL). The crude 5-(acetylamino)-2-[(1-naphthalenylcarbonyl)amino]-benzoic acid was used for Step A directly.

Example 13

N-[4-Amino-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-1-naphthalenecarboxamide



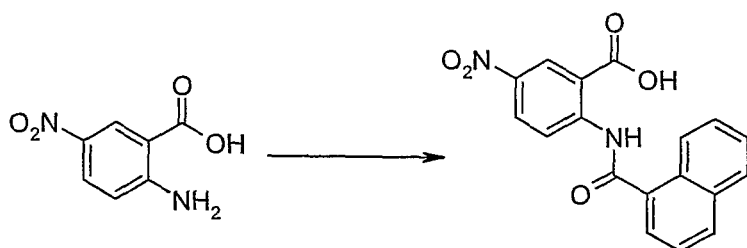
Step A. *N*-[4-Amino-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-1-naphthalenecarboxamide



Palladium on carbon (50 mg, 10% grade) was added to a solution of *N*-[2-[[[(cyclohexylmethyl)amino]carbonyl]-4-nitrophenyl]-1-naphthalenecarboxamide from Step C in ethyl acetate (30 ml). The suspension was placed in a Parr apparatus and shaken for 3 hours under a hydrogen atmosphere (40 psi). The suspension was then brought to normal

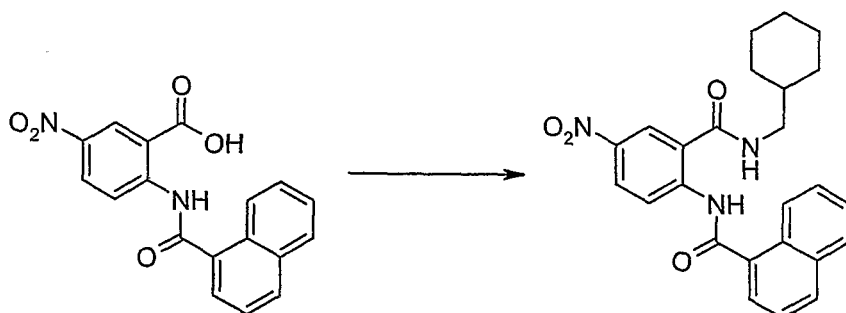
atmosphere and filtered on Celite. The filtrate was concentrated *in vacuo*. The product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized to provide the title compound (36 mg, 1.3 %). ¹H NMR (400 MHz, DMSO-D₆) δ 0.81 (m, 2 H), 1.08 (m, 4 H), 1.42 (m, 1 H), 1.58 (m, 4 H), 2.96 (t, J=6.35 Hz, 2 H), 4.59 (s, 2 H), 7.03 (s, 1 H), 7.15 (s, 1 H), 7.54 (m, 3 H), 7.71 (dd, J=7.03, 0.98 Hz, 1 H), 7.96 (m, 1 H), 8.03 (d, J=8.40 Hz, 1 H), 8.25 (m, 2 H), 8.62 (s, 1 H), 11.19 (s, 1 H). MS (ESI) (M+H)⁺ 402.2.

Step B. 2-[(1-Naphthalenylcarbonyl)amino]-5-nitro-benzoic acid



Following the procedure for Step B in Example 1, using 5-nitro-2-amino-benzoic acid (1.0 mg, 5.49 mmol), 1-naphthoyl chloride (1.1 mL, 5.49 mmol) and triethylamine (765 µl, 5.49 mmol) in dichloromethane (10 mL). The crude 2-[(1-naphthalenylcarbonyl)amino]-5-nitro-benzoic acid was used for Step C directly.

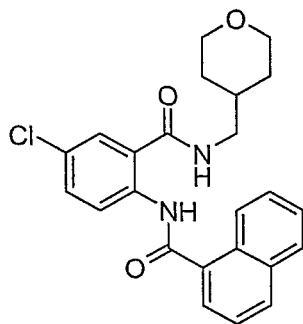
Step C. N-[2-[(1-Naphthalenylcarbonyl)amino]-5-nitro-benzoyl]-cyclohexylmethanamine



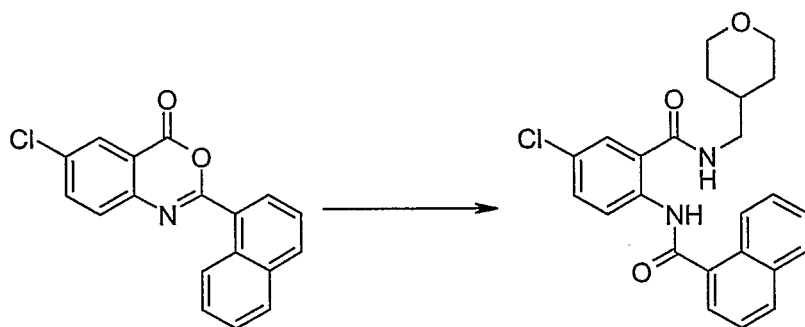
Following the procedure for Step A in Example 1, using 2-[(1-naphthalenylcarbonyl)amino]-5-nitro-benzoic acid (5.49 mmol), HATU (2.3 g, 6.05 mmol) and cyclohexylmethanamine (1.43 mL, 11 mmol) in DMF (5 ml). The product was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then used in Step A directly.

Example 14

N-[4-Chloro-2-[[[(tetrahydro-2*H*-pyran-4-yl)methyl]amino]carbonyl]phenyl]-1-naphthalenecarboxamide

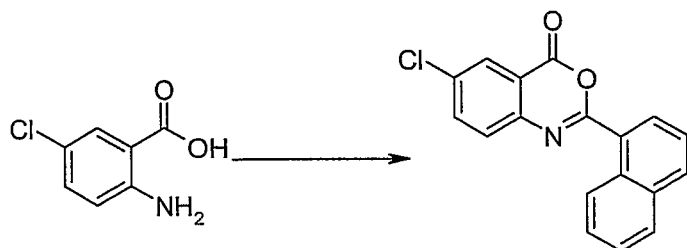


5 Step A. *N*-[4-Chloro-2-[[[(tetrahydro-2*H*-pyran-4-yl)methyl]amino]carbonyl]phenyl]-1-naphthalenecarboxamide



4-Aminomethyltetrahydropyran (75 mg, 0.66 mmol) was added to a solution of 6-chloro-2-(1-naphthalenyl)-4*H*-3,1-benzoxazin-4-one (100 mg, 0.33 mmol, see Step B for its
 10 preparation) and diisopropylethylamine (0.5 mL) in DMF (2 mL) at room temperature. After 2 hr, the reaction mixture was quenched with H₂O (10 mL) and diethyl ether (5 mL). The precipitate was collected and dried *in vacuo* to provide the title compound (130 mg, 93 %).
¹H NMR (400 MHz, CDCl₃) δ 1.16 (m, 2H), 1.62 (m, 2H), 1.82 (m, 1H), 3.29 (m, 2H), 3.36 (m, 2H), 3.98 (m, 2H), 6.30 (brs, 1H), 7.46 (m, 1H), 7.57 (m, 4H), 7.84 (m, 1H), 7.91 (m,
 15 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 8.51 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.87 (dd, *J* = 8.8, 1.2 Hz, 1H), 11.49 (brs, 1H); MS (ESI) (*M*+H)⁺ 423.0.

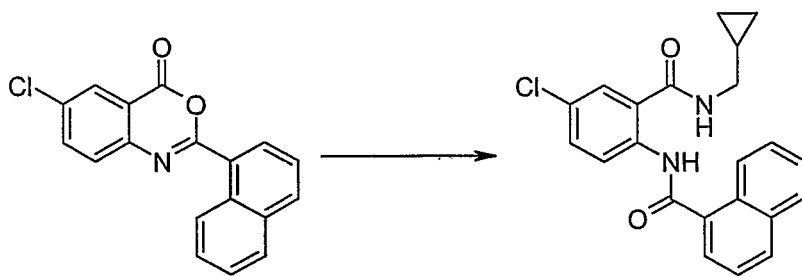
Step B. 6-Chloro-2-(1-naphthalenyl)-4*H*-3,1-benzoxazin-4-one



1-Naphthalenecarbonyl chloride (4.0 g, 21 mmol) in CH_2Cl_2 (2 mL) was added into a solution of 2-amino 5-chlorobenzoic acid (3.43 g, 20.0 mmol) and diisopropylethylamine (3 mL) in dichloromethane (50 mL) at room temperature at 0 °C. The reaction mixture was allowed to stir overnight at room temperature, and then condensed *in vacuo*. The residue was dissolved in anhydrous DMF (30 mL), and followed by addition of diisopropylethylamine (3 mL) and HATU (8.4 g, 22 mmol). After stirring for 1 h at room temperature, the reaction was quenched with cold water (100 mL) at 0 °C. The precipitate was collected and dried *in vacuo* to provide the title compound (6.1 g, 99 %). MS (ESI) $(\text{M}+\text{H})^+$ 308.0.

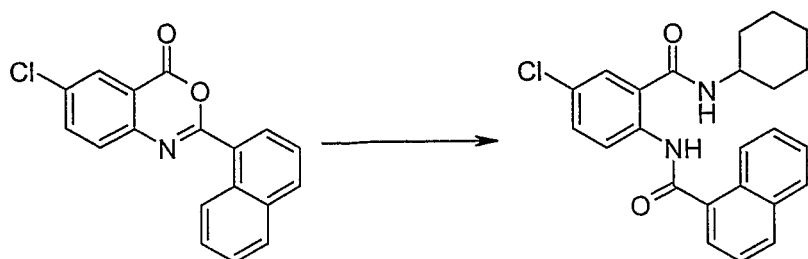
Example 15

N-[4-Chloro-2-[[[(cyclopropylmethyl)amino]carbonyl]phenyl]-1-naphthalenecarboxamide



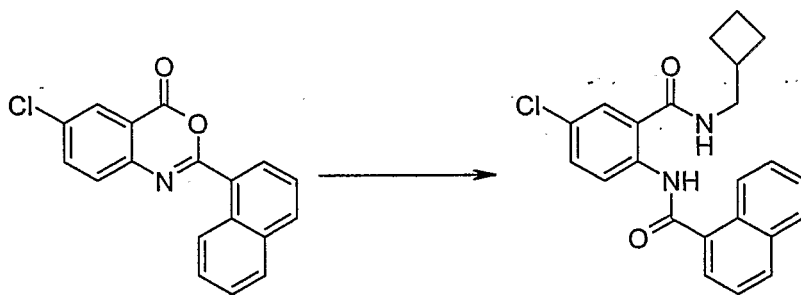
Following the method as the Step A in Example 14, using diisopropylethylamine (0.5 mL), 6-chloro-2-(1-naphthalenyl)-4*H*-3,1-benzoxazin-4-one (100 mg, 0.33 mmol), and cyclopropylmethyl amine (71 mg, 1.0 mmol) provided the title compound (64 mg, 53 %). ^1H NMR (400 MHz, CDCl_3) δ 0.24-0.27 (m, 2 H), 0.55-0.59 (m, 2 H), 0.98-1.08 (m, 1 H), 3.22 (dd, $J=7.23, 5.27$ Hz, 2 H), 6.31-6.36 (br. s., 1 H), 7.51-7.59 (m, 5 H), 7.85 (dd, $J=7.22, 1.17$ Hz, 1 H), 7.89 (m, 1 H), 7.88-7.98 (d, $J=8.20$ Hz, 1 H), 8.52 (m, 1 H), 8.88 (d, $J=8.98$ Hz, 1 H), 11.58 (s, 1 H); MS (ESI) $(\text{M}+\text{H})^+$ 378.9; Anal. Calcd for $\text{C}_{22}\text{H}_{19}\text{ClN}_2\text{O}_2 + 0.1 \text{ H}_2\text{O}$: C, 69.42; H, 5.08; N, 7.36. Found: C, 69.42; H, 5.13; N, 7.36.

Example 16

N-[4-Chloro-2-[(cyclohexylamino)carbonyl]phenyl]-1-naphthalenecarboxamide

Following the method as the Step A in Example 14, using diisopropylethylamine (0.5 mL), 6-chloro-2-(1-naphthalenyl)-4*H*-3,1-benzoxazin-4-one (100 mg, 0.33 mmol), and
 5 cyclohexylamine (99 mg, 1.0 mmol) provided the title compound (103 mg, 79 %). ¹H NMR (400 MHz, CDCl₃) δ 1.15-1.27 (m, 3 H), 1.31-1.42 (m, 2 H), 1.58-1.67 (m, 1 H), 1.72-1.77 (m, 2 H), 1.95-1.99 (m, 2 H), 3.81-3.90 (m, 1 H), 6.07 (d, *J*=7.42 Hz, 1 H), 7.45 (d, *J*=2.54 Hz, 1 H), 7.50-7.59 (m, 4 H), 7.84 (dd, *J*=7.03, 1.17 Hz, 1 H), 7.88-7.90 (m, 1 H), 7.97 (d, *J*=8.40 Hz, 1 H), 8.51 (dd, *J*=8.01, 1.17 Hz, 1 H), 8.86 (d, *J*=8.79 Hz, 1 H), 11.55-11.59 (br.
 10 s., 1 H); MS (ESI) (*M*+*H*)⁺ 407.0; Anal. Calcd for C₂₄H₂₃ClN₂O₂ + 0.1 H₂O: C, 70.53; H, 5.72; N, 6.85. Found: C, 70.69; H, 5.86; N, 6.79.

Example 17

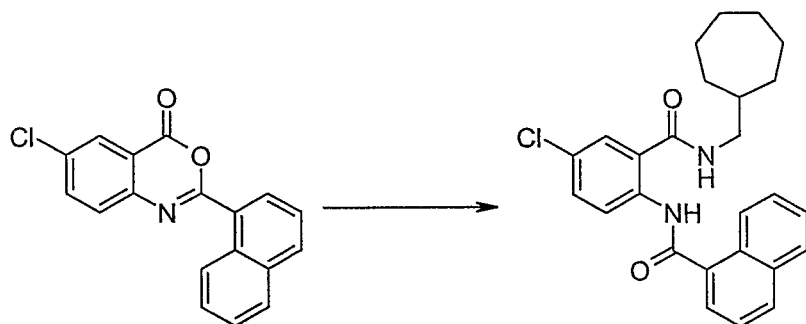
N-[4-Chloro-2-[(cyclobutylmethyl)amino]carbonyl]phenyl]-1-naphthalenecarboxamide

Following the method as the Step A in Example 14, using diisopropylethylamine (0.5 mL), 6-chloro-2-(1-naphthalenyl)-4*H*-3,1-benzoxazin-4-one (100 mg, 0.33 mmol), and
 15 cyclobutylmethyl amine (85 mg, 1.0 mmol) provided the title compound (107 mg, 85 %). ¹H NMR (400 MHz, CDCl₃) δ 1.66-1.76 (m, 2 H), 1.85-1.96 (m, 2 H), 2.05-2.12 (m, 2 H), 2.50-2.58 (m, 1 H), 3.39 (dd, *J*=7.32, 5.76 Hz, 2 H), 6.15-6.22 (m, 1 H), 7.45 (d, *J*=2.54 Hz, 1 H), 7.51-7.59 (m, 4 H), 7.84 (dd, *J*=7.23, 1.17 Hz, 1 H), 7.88-7.90 (m, 1 H), 7.97 (d, *J*=8.40 Hz, 1 H), 8.52 (dd, *J*=8.01, 1.17 Hz, 1 H), 8.87 (d, *J*=8.98 Hz, 1 H), 11.55 (br. s., 1
 20 H).

H); MS (ESI) (M+H)⁺ 393.0; Anal. Calcd for C₂₃H₂₁ClN₂O₂ + 0.1 H₂O: C, 69.99; H, 5.41; N, 7.10. Found: C, 70.09; H, 5.31; N, 7.02.

Example 18

5 *N*-[4-Chloro-2-[[[(cycloheptylmethyl)amino]carbonyl]phenyl]-1-naphthalenecarboxamide

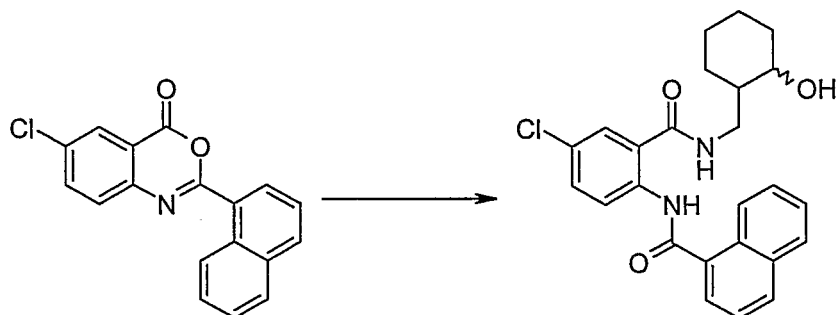


Following the method as the Step A in Example 14, using diisopropylethylamine (0.5 mL), 6-chloro-2-(1-naphthalenyl)-4H-3,1-benzoxazin-4-one (100 mg, 0.33 mmol), and cycloheptanemethanamine (127 mg, 1.0 mmol) provided the title compound (128 mg, 92 %). ¹H NMR (400 MHz, CDCl₃) δ 1.17-1.25 (m, 2 H), 1.38-1.78 (m, 11 H), 3.22 (t, J=6.25 Hz, 2 H), 6.7-6.30 (m, 1 H), 7.46 (d, J=2.54 Hz, 1 H), 7.52-7.59 (m, 4 H), 7.83 (dd, J=7.03, 1.17 Hz, 1 H), 7.88-7.90 (m, 1 H), 7.97 (d, J=8.40 Hz, 1 H), 8.50-8.52 (m, 1 H) 8.87 (d, J=8.98 Hz, 1 H), 11.53 (br. s., 1 H); MS (ESI) (M+H)⁺ 435.0; Anal. Calcd for C₂₆H₂₇ClN₂O₂ + 0.1 H₂O: C, 71.50; H, 6.28; N, 6.41. Found: C, 71.39; H, 6.25; N, 6.36.

15

Example 19

N-[4-Chloro-2-[[[(2-hydroxycyclohexyl)methyl]amino]carbonyl]phenyl]-1-naphthalenecarboxamide

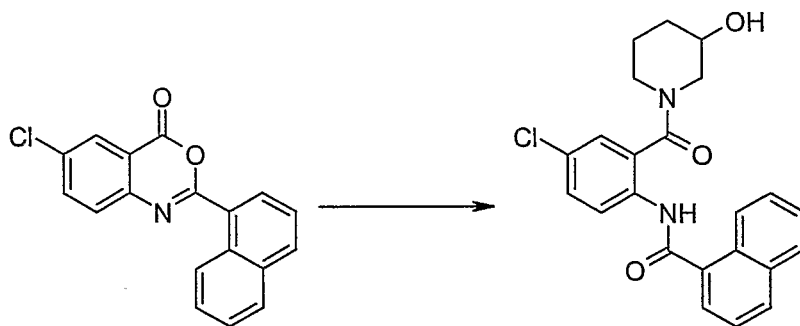


20 Following the method as the Step A in Example 14, using diisopropylethylamine (0.5 mL), 6-chloro-2-(1-naphthalenyl)-4H-3,1-benzoxazin-4-one (100 mg, 0.33 mmol), and 2-

(aminomethyl)-cyclohexanol (129 mg, 1.0 mmol) provided the title compound (80 mg, 57 %). ^1H NMR (400 MHz, CDCl_3) δ 1.27-1.36 (m, 1 H), 1.46-1.67 (m, 8 H), 1.81-1.91 (m, 1 H), 3.39 (d, 5.86 Hz, 2 H), 6.67-6.70 (m, 1 H), 7.51-7.57 (m, 4 H), 7.82 (dd, $J=7.13$, 1.27 Hz, 1 H), 7.87-7.90 (m, 1 H), 7.95-7.98 (m, 1 H), 8.50-8.52 (m, 1 H), 8.86-8.89 (m, 1 H), 11.54-11.58 (br s, 1 H); MS (ESI) $(\text{M}+\text{H})^+$ 473.0; Anal. Calcd for $\text{C}_{25}\text{H}_{25}\text{ClN}_2\text{O}_3 + 0.1 \text{ H}_2\text{O} + 0.1 \text{ CH}_3\text{OH}$: C, 68.22; H, 5.84; N, 6.34. Found: C, 68.28; H, 5.75; N, 6.36.

Example 20

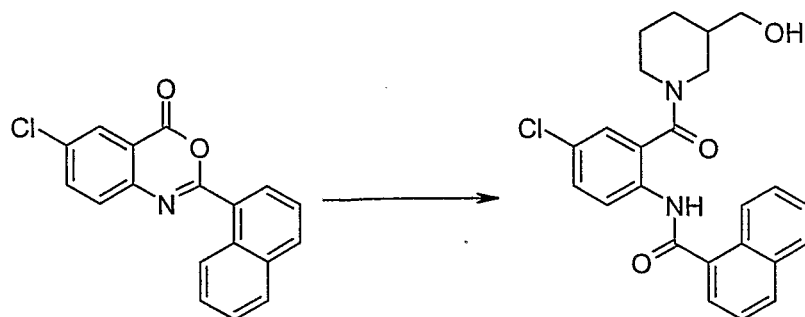
N-[4-Chloro-2-[(3-hydroxy-1-piperidiny)carbonyl]phenyl]-1-naphthalenecarboxamide



Following the method as the Step A in Example 14, using diisopropylethylamine (0.5 mL), 6-chloro-2-(1-naphthalenyl)-4H-3,1-benzoxazin-4-one (100 mg, 0.33 mmol), and 3-hydroxypiperidine (101 mg, 1.0 mmol) provided the title compound (104 mg, 79 %). ^1H NMR (400 MHz, CDCl_3) δ 1.43-1.55 (m, 1 H), 1.63-1.93 (m, 4 H), 1.99-2.15 (m, 1 H), 3.31-3.54 (m, 2 H), 3.76-3.86 (m, 1 H), 7.19-7.25 (m, 1 H), 7.31-7.41 (m, 1 H), 7.45-7.51 (m, 2 H), 7.52-7.58 (m, 3 H), 7.73 (d, $J=6.64$ Hz, 1 H), 7.87-7.89 (m, 1 H), 7.95 (d, $J=8.40$ Hz, 1 H), 8.42 (d, $J=7.62$ Hz, 1 H), 9.29-7.40 (br s., 1 H); MS (ESI) $(\text{M}+\text{H})^+$ 409.0; Anal. Calcd for $\text{C}_{23}\text{H}_{21}\text{ClN}_2\text{O}_3 + 0.1 \text{ H}_2\text{O}$: C, 67.27; H, 5.20; N, 6.82. Found: C, 67.18; H, 5.20; N, 6.75.

Example 21

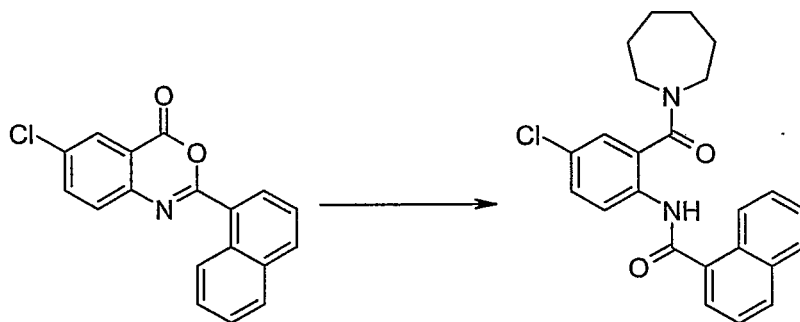
N-[4-Chloro-2-[[3-(hydroxymethyl)-1-piperidiny]carbonyl]phenyl]-1-naphthalenecarboxamide



Following the method as the Step A in Example 14, using diisopropylethylamine (0.5 mL), 6-chloro-2-(1-naphthalenyl)-4H-3,1-benzoxazin-4-one (100 mg, 0.33 mmol), and 3-piperidinemethanol (115 mg, 1.0 mmol) provided the title compound (124 mg, 92 %). ¹H NMR (400 MHz, CDCl₃) δ 1.27-1.87 (m, 8 H), 3.11-3.23 (m, 1 H), 3.44-3.51 (m, 2 H), 7.25 (d, J=2.54 Hz, 1 H), 7.46 (dd, J=8.79, 2.34 Hz, 1 H), 7.44-7.60 (m, 4 H), 7.76 (dd, J=7.13, 0.88 Hz, 1 H), 7.89-7.92 (m, 1 H), 7.98 (d, J=8.20 Hz, 1 H). 8.46-8.48 (br s, 1 H). 9.41 (br s, 1 H); MS (ESI) (M+H)⁺ 423.0; Anal. Calcd for C₂₄H₂₃ClN₂O₃ + 0.1 H₂O: C, 67.87; H, 5.51; N, 6.60. Found: C, 67.85; H, 5.47; N, 6.51.

Example 22

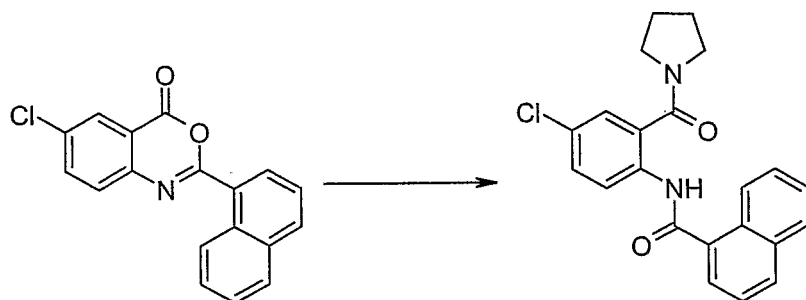
N-[4-Chloro-2-[(hexahydro-1H-azepin-1-yl)carbonyl]phenyl]-1-naphthalenecarboxamide



Following the method as the Step A in Example 14, using diisopropylethylamine (0.5 mL), 6-chloro-2-(1-naphthalenyl)-4H-3,1-benzoxazin-4-one (100 mg, 0.33 mmol), and hexahydro-1H-azepine (99 mg, 1.0 mmol) provided the title compound (61 mg, 47 %). ¹H NMR (400 MHz, CDCl₃) δ 1.54-1.58 (m, 4 H), 1.64-1.78 (m, 4 H), 3.49 (t, J=6.15 Hz, 2 H), 3.59-3.62 (m, 2 H), 7.27 (d, J=2.15 Hz, 1 H), 7.46 (dd, J=8.79, 2.34 Hz, 1 H), 7.45-7.59 (m, 3 H), 7.74 (dd, J=7.13, 1.27 Hz, 1 H), 7.89-7.91 (m, 1 H), 7.98 (d, J=8.20 Hz, 1 H), 8.44-8.48 (m, 2 H), 9.20 (br s, 1 H); MS (ESI) (M+H)⁺ 407.0; Anal. Calcd for C₂₄H₂₃ClN₂O₂ + 0.1 CH₃OH: C, 70.58; H, 5.75; N, 6.83. Found: C, 70.66; H, 5.50; N, 6.74.

Example 23

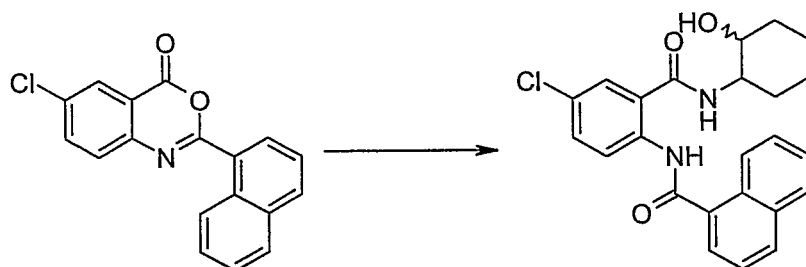
N-[4-Chloro-2-(1-pyrrolidinylcarbonyl)phenyl]-1-naphthalenecarboxamide



- 5 Following the method as the Step A in Example 14, using diisopropylethylamine (0.5 mL), 6-chloro-2-(1-naphthalenyl)-4*H*-3,1-benzoxazin-4-one (100 mg, 0.33 mmol), and pyrrolidine (71 mg, 1.0 mmol) provided the title compound (104 mg, 86 %). ¹H NMR (400 MHz, CDCl₃) δ 1.86-1.99 (m, 4 H), 3.54-3.61 (m, 4 H), 7.40 (d, *J*=2.34 Hz, 1 H), 7.46 (dd, *J*=8.89, 2.44 Hz, 1 H), 7.49-7.59 (m, 3 H), 7.81 (dd, *J*=7.03, 1.17 Hz, 1 H), 7.88-7.91 (m, 1 H), 7.97 (d, *J*=8.40 Hz, 1 H), 8.51-8.53 (m, 1 H), 8.59 (d, *J*=8.98 Hz, 1 H), 10.15-10.22 (br s, 1 H); MS (ESI) (*M*+*H*)⁺ 379.0; Anal. Calcd for C₂₂H₁₉ClN₂O₂ + 0.2 H₂O: C, 69.09; H, 5.11; N, 7.32. Found: C, 69.16; H, 5.02; N, 7.27.

Example 24

- 15 *N*-[4-Chloro-2-[[2-(hydroxycyclohexyl)amino]carbonyl]phenyl]-1-naphthalenecarboxamide

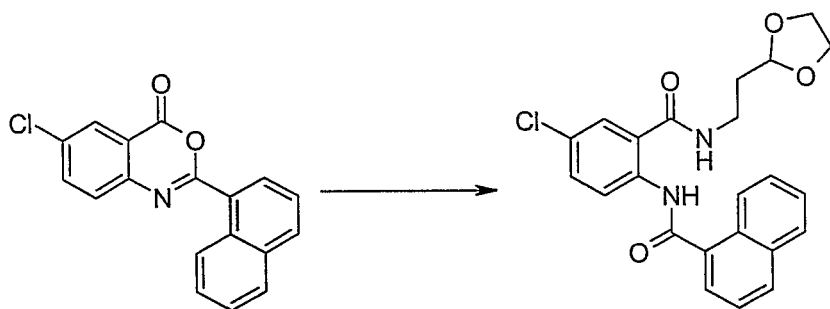


- 20 Following the method as the Step A in Example 14, using diisopropylethylamine (0.5 mL), 6-chloro-2-(1-naphthalenyl)-4*H*-3,1-benzoxazin-4-one (150 mg, 0.49 mmol), and 2-aminocyclohexanol (115 mg, 1.0 mmol) provided the title compound (166 mg, 80 %). ¹H NMR (400 MHz, CDCl₃) δ 1.62 (m, 8H), 4.01 (m, 2H), 6.64 (m, 1H), 7.54 (m, 5H), 7.84

(dd, $J = 7.2, 1.2$ Hz, 1H), 7.89 (d, $J = 8.0$ Hz, 1H), 7.97 (d, $J = 8.4$ Hz, 1H), 8.51 (d, $J = 8.0$ Hz, 1H), 8.87 (d, $J = 8.4$ Hz, 1H), 11.61 (brs, 1H); MS (ESI) $(M+H)^+$ 423.1.

Example 25

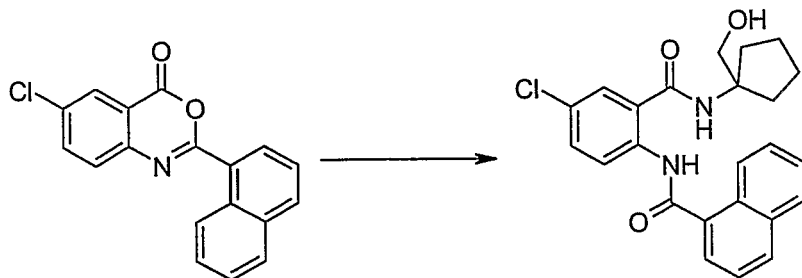
5 *N*-[4-Chloro-2-[[[2-(1,3-dioxolan-2-yl)ethyl]amino]carbonyl]phenyl]-1-naphthalenecarboxamide



Following the method as the Step A in Example 14, using diisopropylethylamine (0.5 mL), 6-chloro-2-(1-naphthalenyl)-4*H*-3,1-benzoxazin-4-one (100 mg, 0.33 mmol), and 2-(2-aminoethyl)-1,3-dioxolane (79 mg, 0.66 mmol) provided the title compound (131 mg, 94 %). ^1H NMR (400 MHz, CDCl_3) δ 2.00 (m, 2H), 3.55 (m, 2H), 3.92 (m, 2H), 4.04 (m, 2H), 5.00 (m, 1H), 7.08 (brs, 1H), 7.47 (m, 1H), 7.53 (m, 4H), 7.88 (m, 2H), 7.97 (d, $J = 8.4$ Hz, 1H), 8.52 (d, $J = 8.0$ Hz, 1H), 8.89 (d, $J = 9.2$ Hz, 1H), 11.72 (brs, 1H); MS (ESI) $(M+H)^+$ 425.1.

Example 26

N-[4-Chloro-2-[[[1-(hydroxymethyl)cyclopentyl]amino]carbonyl]phenyl]-1-naphthalenecarboxamide



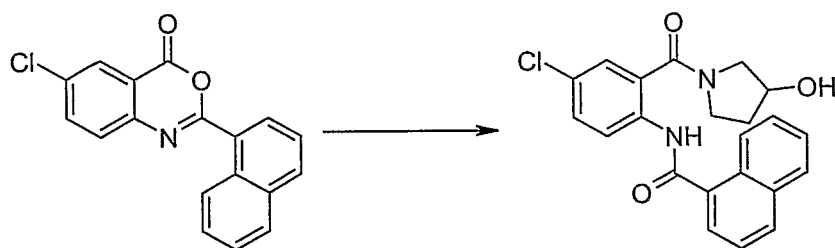
20 Following the method as the Step A in Example 14, using diisopropylethylamine (0.5 mL), 6-chloro-2-(1-naphthalenyl)-4*H*-3,1-benzoxazin-4-one (100 mg, 0.33 mmol), and 1-amino-1-cyclopentanemethanol (78 mg, 0.66 mmol) provided the title compound (75 mg, 54 %).

^1H NMR (400 MHz, CDCl_3) δ 1.65 (m, 2H), 1.78 (m, 2H), 1.88 (m, 4H), 3.37 (t, $J = 5.2$ Hz, 1H), 3.68 (d, $J = 5.2$ Hz, 2H), 6.26 (brs, 1H), 7.41 (m, 1H), 7.50 (m, 4H), 7.78 (dd, $J = 7.2$, 1.2 Hz, 1H), 7.86 (m, 1H), 7.95 (d, $J = 8.4$ Hz, 1H), 8.47 (d, $J = 8.0$ Hz, 1H), 8.78 (d, $J = 9.2$ Hz, 1H), 11.18 (brs, 1H); MS (ESI) $(\text{M}+\text{H})^+$ 423.1.

5

Example 27

N-[4-Chloro-2-[(3-hydroxy-1-pyrrolidinyl)carbonyl]phenyl]-1-naphthalenecarboxamide



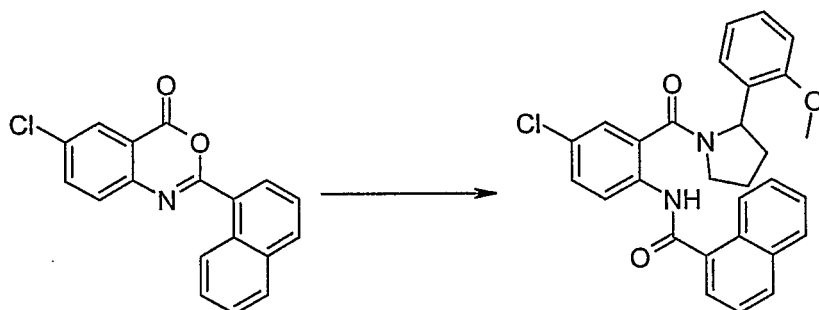
10

Following the method as the Step A in Example 14, using diisopropylethylamine (0.5 mL), 6-chloro-2-(1-naphthalenyl)-4H-3,1-benzoxazin-4-one (100 mg, 0.33 mmol), and 3-pyrrolidinol (53 mg, 0.66 mmol) provided the title compound (45 mg, 35 %). ^1H NMR (400 MHz, CDCl_3) δ 2.00 (m, 2H), 3.65 (m, 4H), 3.84 (m, 1H), 4.46 - 4.56 (m, 1H), 7.50 (m, 5H), 7.78 (m, 1H), 7.895 (d, $J = 7.6$ Hz, 1H), 7.97 (d, $J = 7.6$ Hz, 1H), 8.28 - 8.48 (m, 2H), 9.81 - 10.03 (m, 1H); MS (ESI) $(\text{M}+\text{H})^+$ 395.0.

15

Example 28

N-[4-Chloro-2-[[2-(2-methoxyphenyl)-1-pyrrolidinyl]carbonyl]phenyl]-1-naphthalenecarboxamide



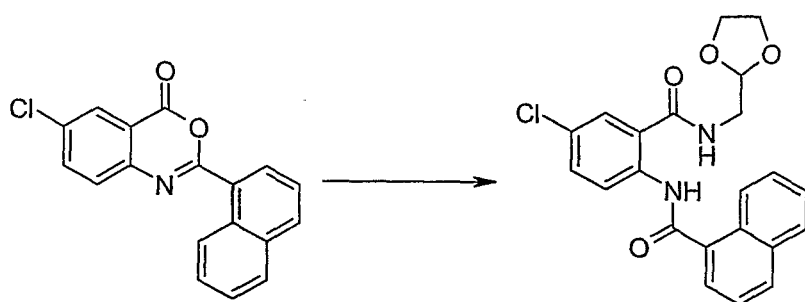
20

Following the method as the Step A in Example 14, using diisopropylethylamine (0.5 mL), 6-chloro-2-(1-naphthalenyl)-4H-3,1-benzoxazin-4-one (100 mg, 0.33 mmol), and 2-(2-methoxyphenyl)-pyrrolidine (117 mg, 0.66 mmol) provided the title compound (52 mg, 33

%). ^1H NMR (400 MHz, CDCl_3) δ 1.87 (m, 3H), 2.24 (m, 1H), 3.00 (m, 1H), 3.66 - 3.83 (m, 3H), 3.83 (m, 1H), 5.30 (m, 1H), 6.67-8.00 (m, 12H), 8.52 (m, 2H), 9.68 - 10.04 (m, 1H); MS (ESI) $(\text{M}+\text{H})^+$ 485.0.

5 Example 29

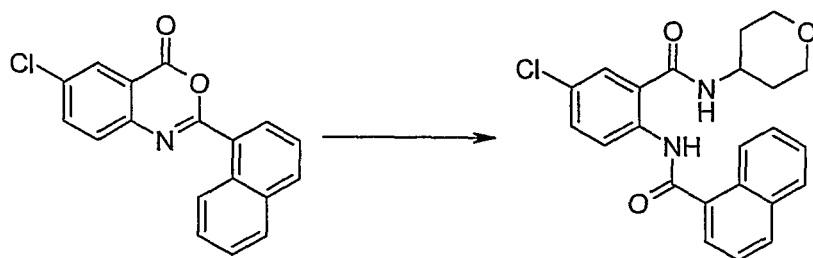
N-[4-Chloro-2-[[[(1,3-dioxolan-2-ylmethyl)amino]carbonyl]phenyl]-1-naphthalenecarboxamide



10 Following the method as the Step A in Example 14, using diisopropylethylamine (0.5 mL), 6-chloro-2-(1-naphthalenyl)-4H-3,1-benzoxazin-4-one (100 mg, 0.33 mmol), and 1,3-dioxolane-2-methanamine (68 mg, 0.66 mmol) provided the title compound (98 mg, 72 %). ^1H NMR (400 MHz, CDCl_3) δ 3.61 (m, 2H), 3.88 (m, 2H), 3.98 (m, 2H), 4.98 (t, $J = 3.6$ Hz, 1H), 6.39 (brs, 1H), 7.46 (s, 1H), 7.50 (m, 4H), 7.83 (dd, $J = 7.2, 1.2$ Hz, 1H), 7.85 (d, $J =$
15 9.2 Hz, 1H), 7.94 (d, $J = 8.4$ Hz, 1H), 8.48 (d, $J = 8.4$ Hz, 1H), 8.86 (d, $J = 8.8$ Hz, 1H), 11.50 (brs, 1H); MS (ESI) $(\text{M}+\text{H})^+$ 411.1.

Example 30

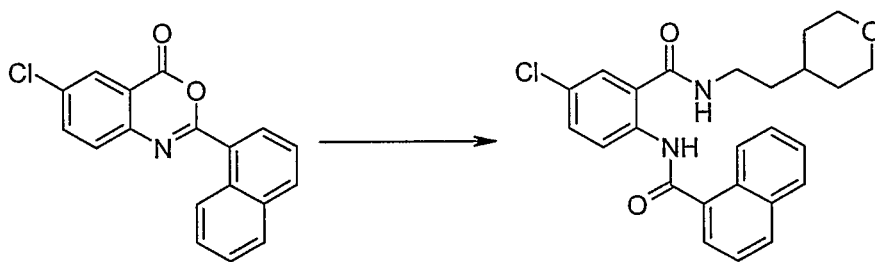
N-[4-Chloro-2-[[[(tetrahydro-2H-pyran-4-yl)amino]carbonyl]phenyl]-1-naphthalenecarboxamide



Following the method as the Step A in Example 14, using diisopropylethylamine (0.5 mL), 6-chloro-2-(1-naphthalenyl)-4*H*-3,1-benzoxazin-4-one (100 mg, 0.33 mmol), and 4-aminotetrahydropyran (67 mg, 0.66 mmol) provided the title compound (116 mg, 86 %). ¹H NMR (400 MHz, CDCl₃) δ 1.59 (m, 2H), 1.94 (m, 2H), 3.47 (dd, J=11.6, 9.6 Hz, 2H), 3.98 (m, 2H), 4.12 (m, 1H), 6.04 (d, J=7.6 Hz, 1H), 7.47 (m, 1H), 7.56 (m, 4H), 7.84 (dd, J = 7.6, 1,2 Hz, 1H), 7.90 (m, 1H), 7.98 (d, J = 8.4 Hz, 1H), 8.51 (d, J = 8.4 Hz, 1H), 8.88 (d, J = 8.8 Hz, 1H), 11.51 (brs, 1H); MS (ESI) (M+H)⁺ 409.0.

Example 31

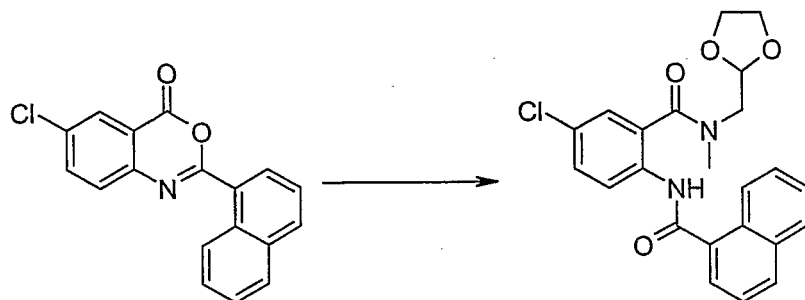
N-[4-Chloro-2-[[[2-(tetrahydro-2*H*-pyran-4-yl)ethyl]amino]carbonyl]phenyl]-1-naphthalenecarboxamide



Following the method as the Step A in Example 14, using diisopropylethylamine (0.5 mL), 6-chloro-2-(1-naphthalenyl)-4*H*-3,1-benzoxazin-4-one (100 mg, 0.33 mmol), and 4-(aminoethyl)tetrahydropyran (86 mg, 0.66 mmol) provided the title compound (119 mg, 83 %). ¹H NMR (400 MHz, CDCl₃) δ 1.38 (m, 2H), 1.59 (m, 5H), 3.31 (m, 2H), 3.43 (m, 2H), 3.92 (m, 2H), 6.15 (m, 1H), 7.51 (m, 1H), 7.57 (m, 4H), 7.84 (dd, J = 7.6, 1,2 Hz, 1H), 7.90 (m, 1H), 7.98 (d, J = 8.4 Hz, 1H), 8.51 (d, J = 8.8 Hz, 1H), 8.88 (d, J = 8.8 Hz, 1H), 11.51 (brs, 1H); MS (ESI) (M+H)⁺ 437.0.

Example 32

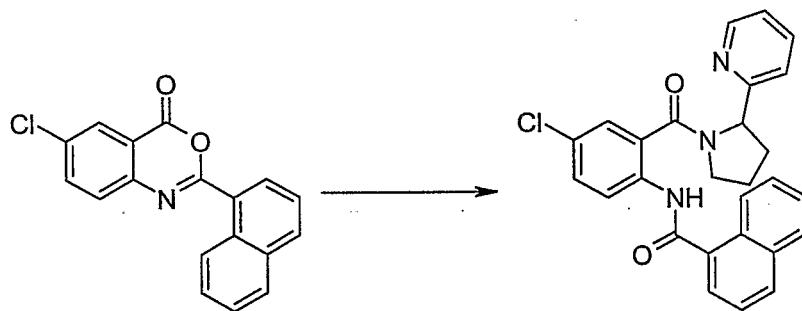
N-[4-Chloro-2-[[[1,3-dioxolan-2-ylmethyl)methylamino]carbonyl]phenyl]-1-naphthalenecarboxamide



Following the method as the Step A in Example 14, using diisopropylethylamine (0.5 mL), 6-chloro-2-(1-naphthalenyl)-4H-3,1-benzoxazin-4-one (100 mg, 0.33 mmol), and *N*-methyl-1,3-dioxolane-2-methanamine (78 mg, 0.66 mmol) provided the title compound (68 mg, 49 %). ¹H NMR (400 MHz, CDCl₃) δ 3.13 (s, 3H), 3.57 (m, 2H), 3.70 (m, 4H), 4.97 (m, 1H), 7.36 (m, 1H), 7.56 (m, 4H), 7.77 (d, J = 7.2 Hz, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 8.43 (m, 2H), 9.15 (m, 1H); MS (ESI) (M+H)⁺ 425.0.

Example 33

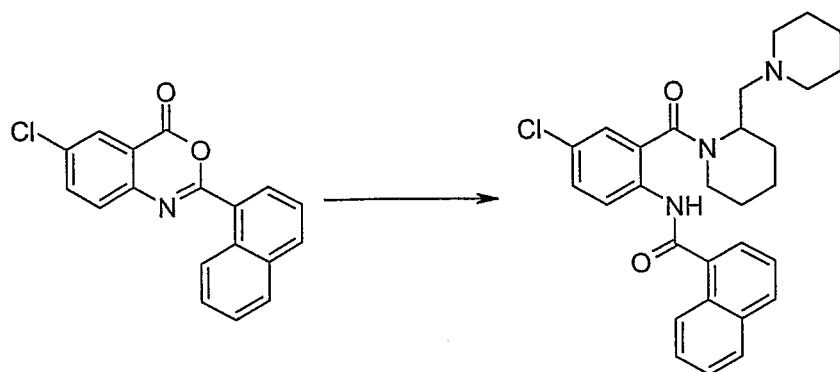
N-[4-Chloro-2-[[2-(2-pyridinyl)-1-pyrrolidinyl]carbonyl]phenyl]-1-naphthalenecarboxamide



Following the method as the Step A in Example 14, using diisopropylethylamine (0.5 mL), 6-chloro-2-(1-naphthalenyl)-4H-3,1-benzoxazin-4-one (100 mg, 0.33 mmol), and 2-(2-pyrrolidinyl)-pyridine (98 mg, 0.66 mmol) provided the title compound (68 mg, 45 %). ¹H NMR (400 MHz, CDCl₃) δ 1.93 (m, 3H), 2.42 (m, 1H), 3.63 (m, 1H), 3.83 (s, 1H), 5.24 (m, 1H), 6.80 (m, 1H), 7.17 (m, 1H), 7.42 (m, 3H), 7.54 (m, 4H), 7.67 (m, 1H), 7.92 (m, 2H), 8.42 (m, 1H), 8.66 (m, 1H), 10.12 (s, 1H); MS (ESI) (M+H)⁺ 456.0.

Example 34

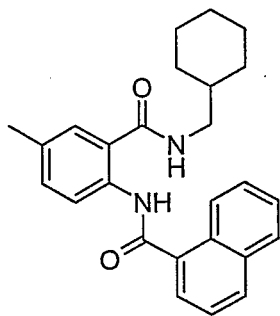
N-[4-Chloro-2-[[2-(1-piperidinylmethyl)-1-piperidinyl]carbonyl]phenyl]-1-naphthalenecarboxamide



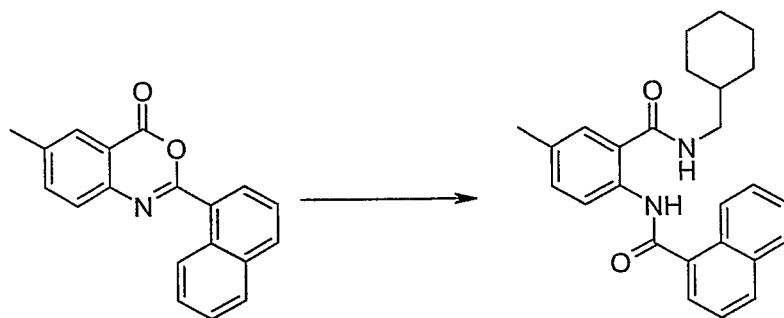
Following the method as the Step A in Example 14, using diisopropylethylamine (0.5 mL), 6-chloro-2-(1-naphthalenyl)-4H-3,1-benzoxazin-4-one (100 mg, 0.33 mmol), and 1-(2-piperidinylmethyl)-piperidine (120 mg, 0.66 mmol) provided the title compound (70 mg, 43 %). ¹H NMR (400 MHz, CDCl₃) δ 1.0-5.0 (m, 21H), 7.38 (brs, 1H), 7.46 (m, 1H), 7.54 (m, 4H), 7.78 (d, J = 6.8 Hz, 1H), 7.89 (m, 1H), 7.97 (d, J = 8.4 Hz, 1H), 8.48 (m, 2H); MS (ESI) (M+H)⁺ 490.0.

Example 35

N-[2-[[[(Cyclohexylmethyl)amino]carbonyl]-4-methylphenyl]-1-naphthalenecarboxamide

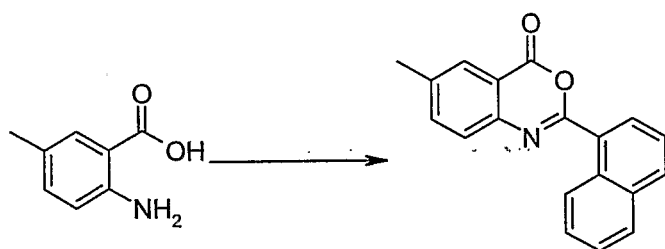


Step A. *N*-[2-[[[(Cyclohexylmethyl)amino]carbonyl]-4-methylphenyl]-1-naphthalenecarboxamide



5 Following the method as the Step A in Example 14, using diisopropylethylamine (0.5 mL), 6-methyl-2-(1-naphthalenyl)-4*H*-3,1-benzoxazin-4-one (80 mg, 0.28 mmol), and cyclohexylmethyl amine (150 mg, 1.3 mmol) provided the title compound (105 mg, 94 %). ¹H NMR (400 MHz, CDCl₃) δ 1.00 (m, 2H), 1.19 (m, 3H), 1.56 (m, 1H), 1.75 (m, 5H), 2.40 (s, 3H), 3.23 (m, 2H), 6.24 (m, 1H), 7.38 (s, 1H), 7.40 (m, 1H), 7.54 (m, 3H), 7.85 (m, 1H),
 10 7.89 (m, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 8.54 (m, 1H), 8.75 (d, *J* = 8.4 Hz, 1H), 11.50 (brs, 1H); MS (ESI) (*M*+*H*)⁺ 401.0.

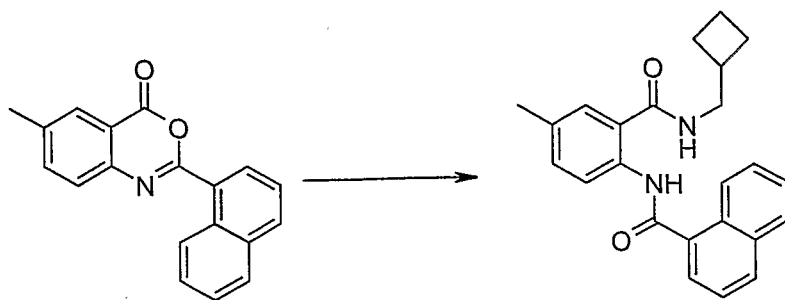
Step B. 6-Methyl-2-(1-naphthalenyl)-4*H*-3,1-benzoxazin-4-one



Following the method as the Step B in Example 14, using diisopropylethylamine (1 mL), 2-amino 5-methylbenzoic acid (760 mg, 5.0 mmol), 1-naphthalenecarbonyl chloride (1.05 g, 5.5 mmol) and HATU (2.1 g, 5.5 mmol) provided the title compound (1.40 g, 98 %). MS (ESI) (*M*+*H*)⁺ 288.1.

Example 36

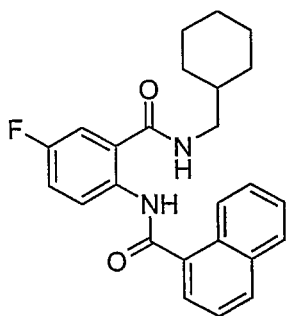
20 *N*-[2-[[[(Cyclobutylmethyl)amino]carbonyl]-4-methylphenyl]-1-naphthalenecarboxamide



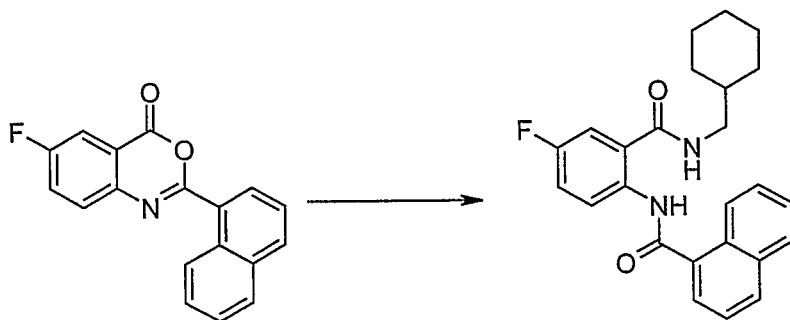
Following the method as the Step A in Example 14, using diisopropylethylamine (0.5 mL), 6-methyl-2-(1-naphthalenyl)-4H-3,1-benzoxazin-4-one (80 mg, 0.28 mmol), and cyclobutylmethyl amine (85 mg, 1.0 mmol) provided the title compound (68 mg, 65 %). ¹H NMR (400 MHz, CDCl₃) δ 1.74 (m, 2H), 1.92 (m, 2H), 2.08 (m, 2H), 2.55 (m, 1H), 2.38 (s, 3H), 3.40 (m, 2H), 6.17 (m, 1H), 7.26 (s, 1H), 7.38 (d, J = 8.8 Hz, 1H), 7.54 (m, 3H), 7.88 (m, 2H), 7.95 (d, J = 8.0 Hz, 1H), 8.54 (d, J = 7.6 Hz, 1H), 8.75 (d, J = 8.4 Hz, 1H), 11.51 (brs, 1H); MS (ESI) (M+H)⁺ 373.0.

Example 37

N-[2-[[[(Cyclohexylmethyl)amino]carbonyl]-4-fluorophenyl]-1-naphthalenecarboxamide

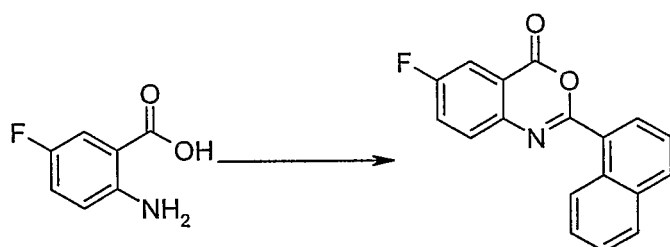


Step A. *N*-[2-[[[(Cyclohexylmethyl)amino]carbonyl]-4-fluorophenyl]-1-naphthalenecarboxamide



Following the method as the Step A in Example 14, using diisopropylethylamine (0.5 mL), 6-fluoro-2-(1-naphthalenyl)-4*H*-3,1-benzoxazin-4-one (80 mg, 0.28 mmol), and cyclohexylmethyl amine (150 mg, 1.3 mmol) provided the title compound (106 mg, 93 %). ¹H NMR (400 MHz, CDCl₃) δ 1.00 (m, 2H), 1.19 (m, 3H), 1.56 (m, 1H), 1.75 (m, 5H), 3.23 (m, 2H), 6.21 (m, 1H), 7.20 (m, 1H), 7.29 (m, 1H), 7.53 (m, 3H), 7.83 (m, 1H), 7.88 (m, 1H), 7.97 (d, J = 8.0 Hz, 1H), 8.52 (m, 1H), 8.87 (dd, J = 9.2, 5.2 Hz, 1H), 11.40 (brs, 1H); MS (ESI) (M+H)⁺ 405.0.

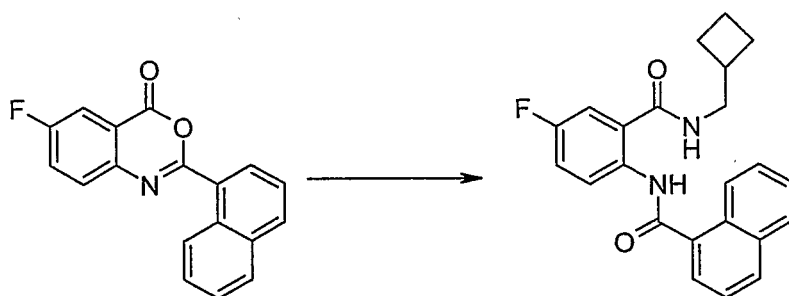
Step B. 6-Fluoro-2-(1-naphthalenyl)-4*H*-3,1-benzoxazin-4-one



Following the method as the Step B in Example 14, using diisopropylethylamine (1 mL), 2-amino 5-fluorobenzoic acid (778 mg, 5.0 mmol), 1-naphthalenecarbonyl chloride (1.05 g, 5.5 mmol) and HATU (2.1 g, 5.5 mmol) provided the title compound (1.44 g, 99 %). MS (ESI) (M+H)⁺ 292.1.

Example 38

N-[2-[[[(Cyclobutylmethyl)amino]carbonyl]-4-fluorophenyl]-1-naphthalenecarboxamide

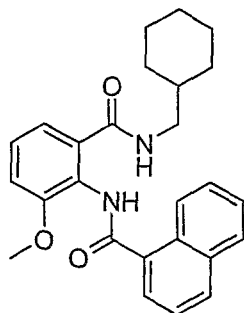


Following the method as the Step A in Example 14, using diisopropylethylamine (0.5 mL), 6-fluoro-2-(1-naphthalenyl)-4*H*-3,1-benzoxazin-4-one (60 mg, 0.206 mmol), and cyclobutylmethyl amine (85 mg, 1.0 mmol) provided the title compound (77 mg, 99 %). ¹H NMR (400 MHz, CDCl₃) δ 1.72 (m, 2H), 1.90 (m, 2H), 2.08 (m, 2H), 2.54 (m, 1H), 3.40 (m, 2H), 6.16 (s, 1H), 7.18 (dd, J = 8.8, 2.8 Hz, 1H), 7.29 (m, 1H), 7.55 (m, 3H), 7.84 (dd, J

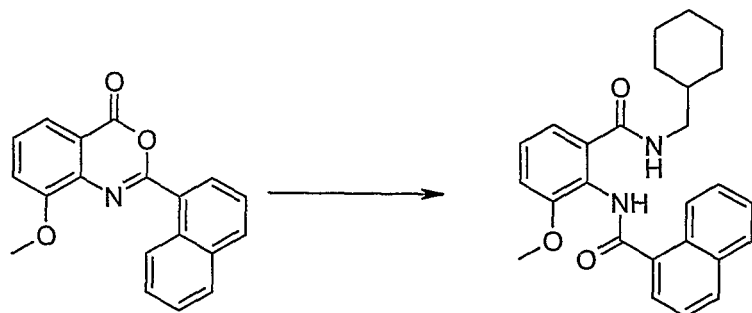
= 7.2, 0.8 Hz, 1H), 7.89 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.97 (d, $J = 8.0$ Hz, 1H), 8.51 (d, $J = 8.4$ Hz, 1H), 8.81 (dd, $J = 9.2, 1.2$ Hz, 1H), 11.41 (brs, 1H); MS (ESI) ($M+H$)⁺ 377.0.

Example 39

5 *N*-[2-[[[(cyclohexylmethyl)amino]carbonyl]-6-methoxyphenyl]-1-naphthalenecarboxamide

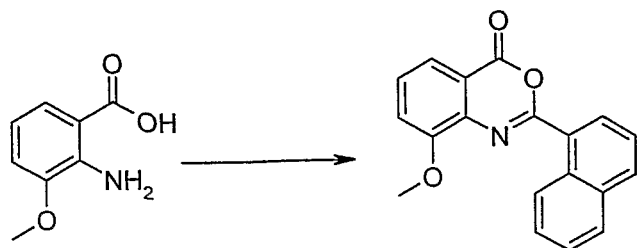


Step A. *N*-[2-[[[(cyclohexylmethyl)amino]carbonyl]-6-methoxyphenyl]-1-naphthalenecarboxamide



10 Following the method as the Step A in Example 14, using diisopropylethylamine (0.5 mL), 8-methoxy-2-(1-naphthalenyl)-4*H*-3,1-benzoxazin-4-one (80 mg, 0.264 mmol), and cyclohexylmethyl amine (150 mg, 1.3 mmol) provided the title compound (92 mg, 84 %).
¹H NMR (400 MHz, CDCl₃) δ 0.98 (m, 2H), 1.16 (m, 3H), 1.65 (m, 4H), 1.78 (m, 2H), 3.26 (m, 2H), 3.92 (s, 3H), 6.43 (m, 1H), 7.09 (dd, $J = 8.4, 1.2$ Hz, 1H), 7.16 (dd, $J = 8.0, 1.2$ Hz, 1H), 7.32 (d, $J = 8.0$ Hz, 1H), 7.55 (m, 3H), 7.88 (m, 2H), 7.97 (d, $J = 8.4$ Hz, 1H), 8.25 (s, 1H), 8.54 (dd, $J = 8.4, 0.8$ Hz, 1H); MS (ESI) ($M+H$)⁺ 417.0.

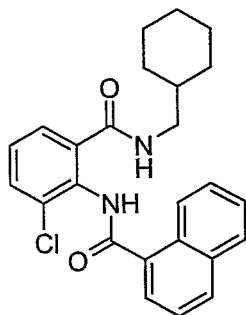
Step B. 8-Methoxy-2-(1-naphthalenyl)-4*H*-3,1-benzoxazin-4-one



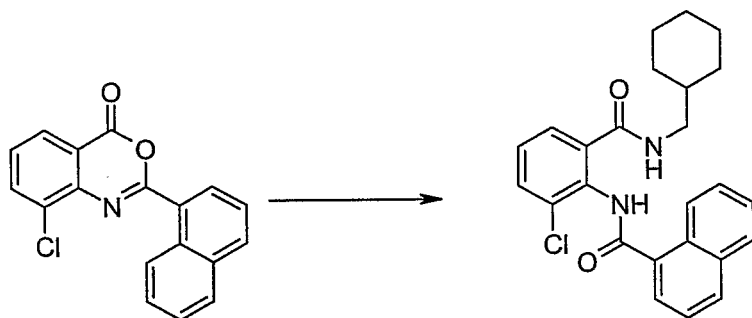
Following the method as the Step B in Example 14, using diisopropylethylamine (1 mL), 2-amino-3-methoxybenzoic acid (835 mg, 5.0 mmol), 1-naphthalenecarbonyl chloride (1.05 g, 5.5 mmol) and HATU (2.1 g, 5.5 mmol) provided the title compound (1.49 g, 98 %). MS (ESI) (M+H)⁺ 304.1.

Example 40

N-[2-Chloro-6-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-1-naphthalenecarboxamide



Step A. *N*-[2-Chloro-6-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-1-naphthalenecarboxamide

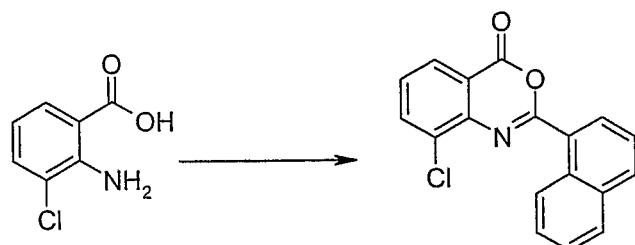


Following the method as the Step A in Example 14, using diisopropylethylamine (0.5 mL), 8-chloro-2-(1-naphthalenyl)-4H-3,1-benzoxazin-4-one (100 mg, 0.33 mmol), and cyclohexylmethyl amine (150 mg, 1.3 mmol) provided the title compound (34 mg, 25 %).

¹H NMR (400 MHz, CDCl₃) δ 0.96 (m, 2H), 1.15 (m, 3H), 1.56 (m, 1H), 1.66 (m, 3H), 1.76 (m, 2H), 3.26 (t, J = 6.4 Hz, 2H), 6.34 (brs, 1H), 7.31 (t, J = 8.0 Hz, 1H), 7.46 (dd, J = 8.0,

1.6 Hz, 1H), 7.58 (m, 4H), 7.91 (d, $J = 7.6$ Hz, 1H), 8.00 (d, $J = 8.4$ Hz, 1H), 8.53 (d, $J = 8.0$ Hz, 1H), 8.59 (s, 1H); MS (ESI) $(M+H)^+$ 421.0.

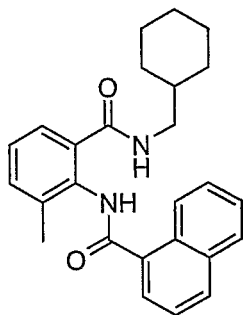
Step B. 8-Chloro-2-(1-naphthalenyl)-4*H*-3,1-benzoxazin-4-one



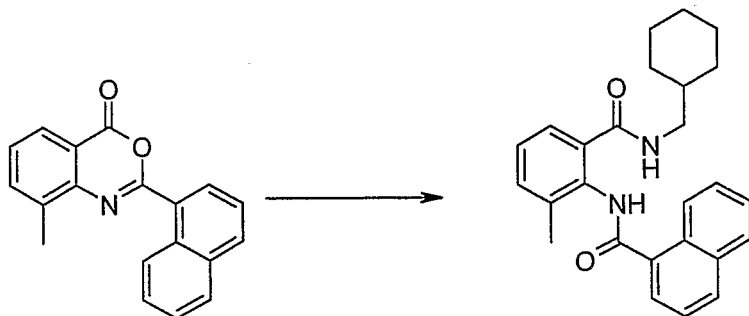
- 5 Following the method as the Step B in Example 14, using diisopropylethylamine (1 mL), 2-amino-3-chlorobenzoic acid (855 mg, 5.0 mmol), 1-naphthalenecarbonyl chloride (1.05 g, 5.5 mmol) and HATU (2.1 g, 5.5 mmol) provided the title compound (1.53 g, 99 %). MS (ESI) $(M+H)^+$ 308.0.

10 Example 41

N-[2-[[[(Cyclohexylmethyl)amino]carbonyl]-6-methylphenyl]-1-naphthalenecarboxamide



Step A. *N*-[2-[[[(Cyclohexylmethyl)amino]carbonyl]-6-methylphenyl]-1-naphthalenecarboxamide



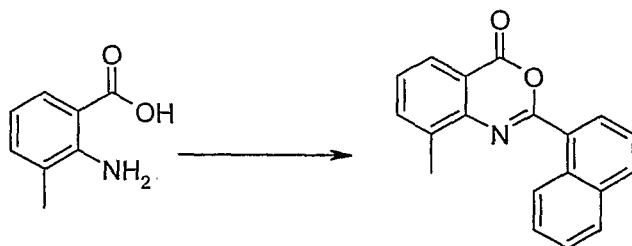
15

Following the method as the Step A in Example 14, using diisopropylethylamine (0.5 mL), 8-methyl-2-(1-naphthalenyl)-4*H*-3,1-benzoxazin-4-one (100 mg, 0.35 mmol), and

cyclohexylmethyl amine (150 mg, 1.3 mmol) provided the title compound (105 mg, 75 %).

^1H NMR (400 MHz, CDCl_3) δ 0.96 (m, 2H), 1.16 (m, 3H), 1.56 (m, 1H), 1.65 (m, 3H), 1.76 (m, 2H), 3.25 (t, $J = 6.4$ Hz, 2H), 6.19 (m, 1H), 7.27 (m, 1H), 7.35 (m, 1H), 7.43 (d, $J = 7.6$ Hz, 1H), 7.55 (m, 3H), 7.90 (m, 2H), 7.98 (d, $J = 8.4$ Hz, 1H), 8.52 (d, $J = 9.2$ Hz, 1H), 9.40 (s, 1H); MS (ESI) $(\text{M}+\text{H})^+$ 401.0.

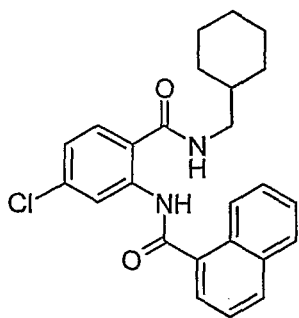
Step B. 8-Methyl-2-(1-naphthalenyl)-4*H*-3,1-benzoxazin-4-one



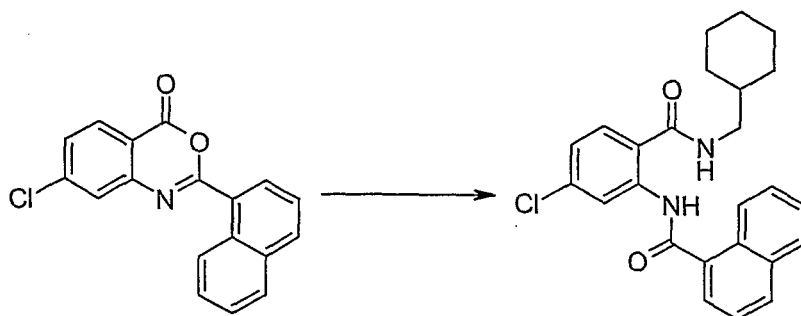
Following the method as the Step B in Example 14, using diisopropylethylamine (1 mL), 2-amino 3-methylbenzoic acid (760 mg, 5.0 mmol), 1-naphthalenecarbonyl chloride (1.05 g, 5.5 mmol) and HATU (2.1 g, 5.5 mmol) provided the title compound (1.39 g, 97 %). MS (ESI) $(\text{M}+\text{H})^+$ 288.1.

Example 42

N-[5-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-1-naphthalenecarboxamide



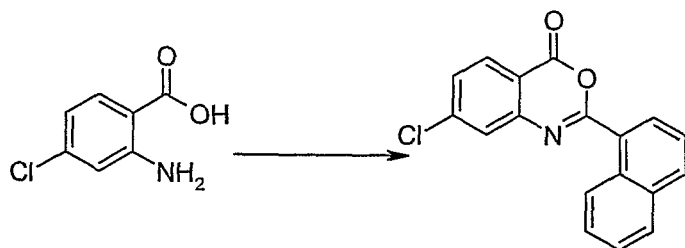
Step A. *N*-[5-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-1-naphthalenecarboxamide



Following the method as the Step A in Example 14, using diisopropylethylamine (0.5 mL), 7-chloro-2-(1-naphthalenyl)-4H-3,1-benzoxazin-4-one (100 mg, 0.33 mmol), and cyclohexylmethyl amine (150 mg, 1.3 mmol) provided the title compound (76 mg, 55 %).

¹H NMR (400 MHz, CDCl₃) δ 0.98 (m, 2H), 1.22 (m, 3H), 1.58 (m, 1H), 1.76 (m, 5H), 3.23 (m, 2H), 6.22 (m, 1H), 7.13 (dd, J=8.4, 2.0 Hz, 1H), 7.43 (d, J=8.4 Hz, 1H), 7.56 (m, 3H), 7.85 (m, 1H), 7.90 (m, 1H), 7.98 (d, J = 8.4 Hz, 1H), 8.53 (dd, J = 8.4, 1.28 Hz, 1H), 9.02 (d, J=2.0 Hz, 1H), 11.81 (brs, 1H); MS (ESI) (M+H)⁺ 421.0.

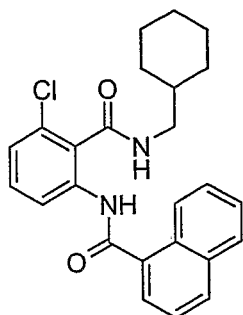
Step B. 7-Chloro-2-(1-naphthalenyl)-4H-3,1-benzoxazin-4-one



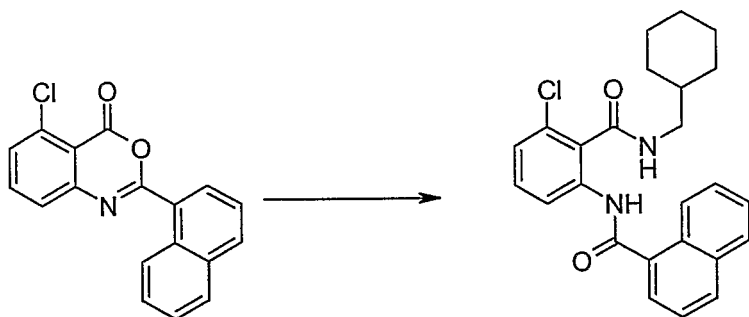
Following the method as the Step B in Example 14, using diisopropylethylamine (1 mL), 2-amino-4-chlorobenzoic acid (855 mg, 5.0 mmol), 1-naphthalenecarbonyl chloride (1.05 g, 5.5 mmol) and HATU (2.1 g, 5.5 mmol) provided the title compound (1.45 g, 94 %). MS (ESI) (M+H)⁺ 308.0.

Example 43

N-[3-Chloro-2-[(cyclohexylmethyl)amino]carbonyl]phenyl]-1-naphthalenecarboxamide

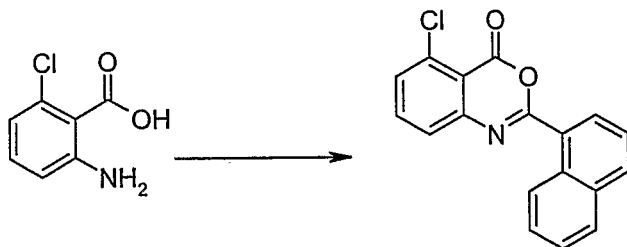


Step A. *N*-[3-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-1-naphthalenecarboxamide



- 5 Following the method as the Step A in Example 14, using diisopropylethylamine (0.5 mL), 5-chloro-2-(1-naphthalenyl)-4*H*-3,1-benzoxazin-4-one (100 mg, 0.33 mmol), and cyclohexylmethyl amine (150 mg, 1.3 mmol) provided the title compound (128 mg, 92 %). ¹H NMR (400 MHz, CDCl₃) δ 0.98 (m, 2H), 1.18 (m, 3H), 1.58 (m, 1H), 1.64 (m, 3H), 1.74 (m, 2H), 3.28 (m, 2H), 6.25 (m, 1H), 7.23 (dd, *J*=8.0, 0.8 Hz, 1H), 7.43 (m, 1H), 7.54 (m, 3H), 7.77 (dd, *J*=6.8, 1.2 Hz, 1H), 7.89 (m, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 8.48 (m, 2H), 9.73 (brs, 1H); MS (ESI) (*M*+*H*)⁺ 421.0.
- 10

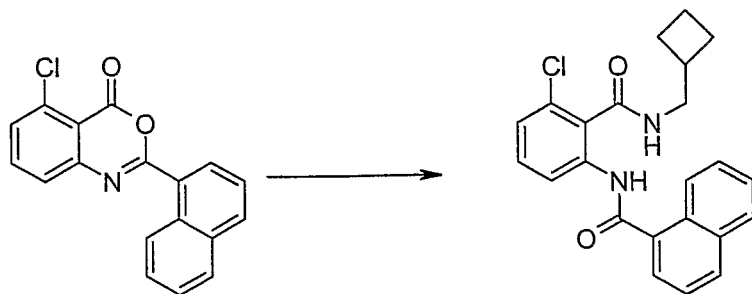
Step B. 5-Chloro-2-(1-naphthalenyl)-4*H*-3,1-benzoxazin-4-one



- Following the method as the Step B in Example 14, using diisopropylethylamine (1 mL), 2-amino-6-chlorobenzoic acid (855 mg, 5.0 mmol), 1-naphthalenecarbonyl chloride (1.05 g, 5.5 mmol) and HATU (2.1 g, 5.5 mmol) provided the title compound (1.50 g, 98 %). MS (ESI) (*M*+*H*)⁺ 308.0.
- 15

Example 44

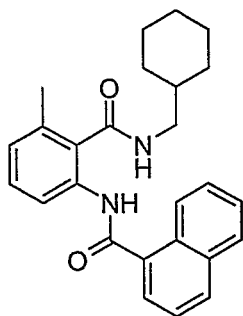
N-[3-Chloro-2-[[[(cyclobutylmethyl)amino]carbonyl]phenyl]-1-naphthalenecarboxamide



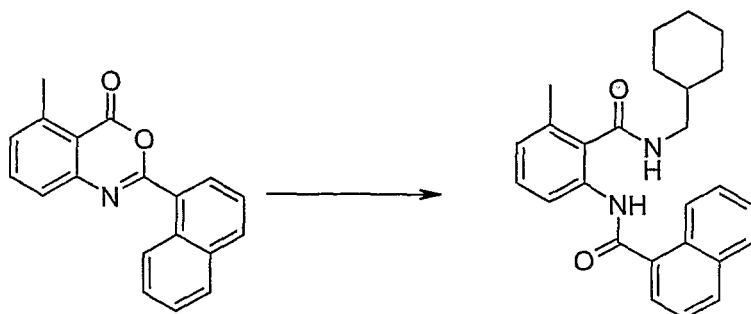
- 5 Following the method as the Step A in Example 14, using 5-chloro-2-(1-naphthalenyl)-4*H*-3,1-benzoxazin-4-one (716 mg, 2.33 mmol), and cyclobutylmethyl amine (5.3 M in MeOH, 0.88 mL, 4.66 mmol) provided the title compound (849 mg, 93 %). ¹H NMR (400 MHz, CDCl₃) δ 1.73 (m, 2 H) 1.86 (m, 2 H) 2.05 (m, 2 H) 2.56 (m, 1 H) 3.45 (dd, *J*=7.23, 5.86 Hz, 2 H) 6.20 (m, 1 H) 7.22 (dd, *J*=8.01, 0.98 Hz, 1 H) 7.43 (t, *J*=8.30 Hz, 1 H) 7.55 (m, 3 H) 7.78 (dd, *J*=7.03, 1.17 Hz, 1 H) 7.90 (m, 1 H) 7.98 (d, *J*=8.40 Hz, 1 H) 8.48 (m, 2 H) 9.75 (s, 1 H); MS (ESI) (*M*+*H*)⁺ 393.0; Anal. Calcd for C₂₃H₂₁ClN₂O₂: C, 70.31; H, 5.39; N, 7.13. Found: C, 70.54; H, 5.62; N, 7.05.

Example 45

- 15 *N*-[2-[[[(Cyclohexylmethyl)amino]carbonyl]-3-methylphenyl]-1-naphthalenecarboxamide



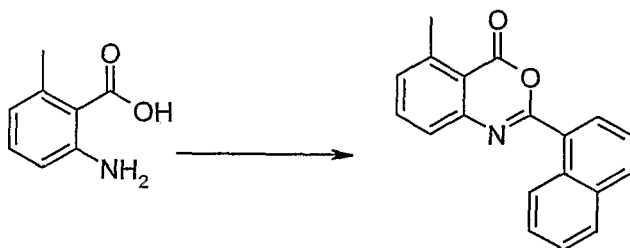
Step A. *N*-[2-[[[(Cyclohexylmethyl)amino]carbonyl]-3-methylphenyl]-1-naphthalenecarboxamide



Following the method as the Step A in Example 14, using diisopropylethylamine (0.5 mL), 5-methyl-2-(1-naphthalenyl)-4H-3,1-benzoxazin-4-one (100 mg, 0.35 mmol), and cyclohexylmethyl amine (150 mg, 1.3 mmol) provided the title compound (102 mg, 73 %).

¹H NMR (400 MHz, CDCl₃) δ 0.91 (m, 2H), 1.07 (m, 3H), 1.54 (m, 1H), 1.59 (m, 3H), 1.68 (m, 2H), 2.43 (s, 3H), 3.25 (t, J = 6.4 Hz, 2H), 5.97 (brs, 1H), 7.06 (d, J = 7.6 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.53 (m, 3H), 7.74 (dd, J = 7.2, 1.2 Hz, 1H), 7.88 (m, 1H), 7.97 (d, J = 7.6 Hz, 1H), 8.17 (d, J = 8.4 Hz, 1H), 8.45 (m, 1H), 8.93 (s, 1H); MS (ESI) (M+H)⁺ 401.0.

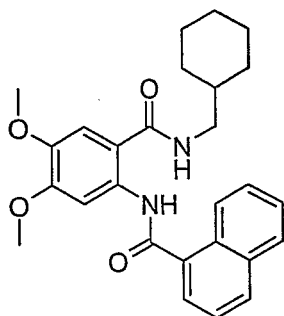
Step B. 5-Methyl-2-(1-naphthalenyl)-4H-3,1-benzoxazin-4-one



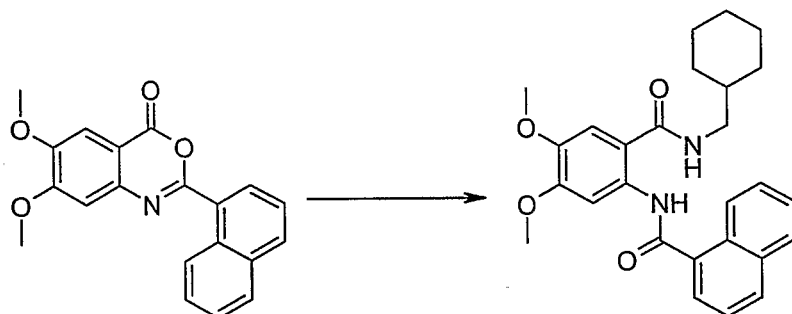
Following the method as the Step B in Example 14, using diisopropylethylamine (1 mL), 2-amino 6-methylbenzoic acid (760 mg, 5.0 mmol), 1-naphthalenecarbonyl chloride (1.05 g, 5.5 mmol) and HATU (2.1 g, 5.5 mmol) provided the title compound (1.30 g, 91 %). MS (ESI) (M+H)⁺ 288.1.

Example 46

N-[2-[[[(Cyclohexylmethyl)amino]carbonyl]-4,5-dimethoxyphenyl]-1-naphthalenecarboxamide

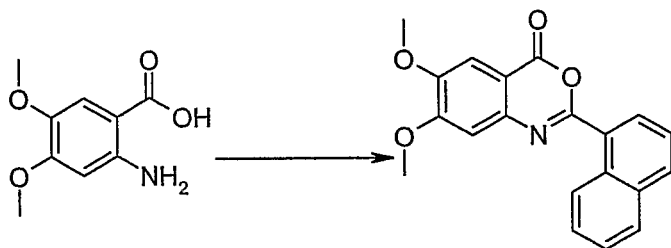


Step A. *N*-[2-[[[(Cyclohexylmethyl)amino]carbonyl]-4,5-dimethoxyphenyl]-1-naphthalenecarboxamide



- 5 Following the method as the Step A in Example 14, using diisopropylethylamine (0.5 mL), 6,7-dimethoxy-2-(1-naphthalenyl)-4*H*-3,1-benzoxazin-4-one (100 mg, 0.30 mmol), and cyclohexylmethyl amine (150 mg, 1.3 mmol) provided the title compound (119 mg, 89 %). ¹H NMR (400 MHz, CDCl₃) δ 0.98 (m, 2H), 1.22 (m, 3H), 1.56 (m, 1H), 1.74 (m, 5H), 3.23 (t, *J* = 6.4 Hz, 2H), 3.94 (s, 3H), 4.05 (s, 3H), 6.09 (brs, 1H), 6.93 (s, 1H), 7.53 (m, 3H),
 10 7.86 (dd, *J* = 6.8, 1.2 Hz, 1H), 7.89 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 8.54 (d, *J* = 9.2 Hz, 1H), 8.68 (s, 1H), 11.88 (s, 1H); MS (ESI) (*M*+*H*)⁺ 447.0.

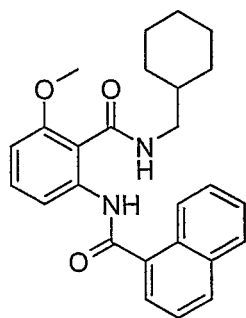
Step B. 6,7-Dimethoxy-2-(1-naphthalenyl)-4*H*-3,1-benzoxazin-4-one



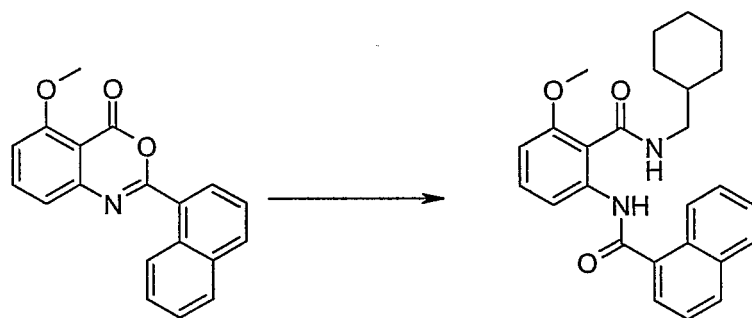
- 15 Following the method as the Step B in Example 14, using diisopropylethylamine (1 mL), 2-amino 4,5-dimethoxy-benzoic acid (990 mg, 5.0 mmol), 1-naphthalenecarbonyl chloride (1.05 g, 5.5 mmol) and HATU (2.1 g, 5.5 mmol) provided the title compound (1.28 g, 77 %). MS (ESI) (*M*+*H*)⁺ 334.1.

Example 47

N-[2-[[[(Cyclohexylmethyl)amino]carbonyl]-3-methoxyphenyl]-1-naphthalenecarboxamide

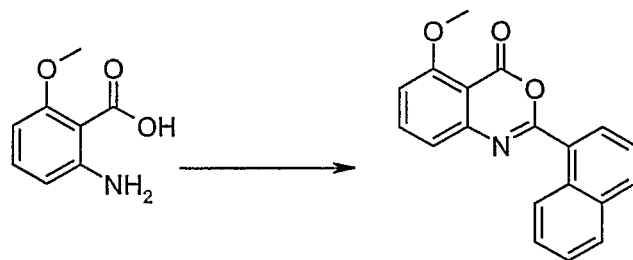


Step A. *N*-[2-[[[(Cyclohexylmethyl)amino]carbonyl]-3-methoxyphenyl]-1-naphthalenecarboxamide



Following the method as the Step A in Example 14, using diisopropylethylamine (0.5 mL), 5-methoxy-2-(1-naphthalenyl)-4*H*-3,1-benzoxazin-4-one (303 mg, 1.0 mmol), and cyclohexylmethyl amine (300 mg, 2.6 mmol) provided the title compound (350 mg, 84 %). ¹H NMR (400 MHz, CDCl₃) δ 0.99 (m, 2H), 1.22 (m, 3H), 1.56 (m, 1H), 1.74 (m, 5H), 3.23 (m, 2H), 3.89 (s, 3H), 6.78 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.52 (m, 4H), 7.80 (s, 1H), 7.86 (m, 2H), 7.95 (d, *J* = 8.0 Hz, 1H), 8.53 (d, *J* = 7.6 Hz, 1H), 8.58 (dd, *J* = 8.4, 0.8 Hz, 1H), 12.52 (s, 1H); MS (ESI) (*M*+*H*)⁺ 417.0.

Step B. 5-Methoxy-2-(1-naphthalenyl)-4*H*-3,1-benzoxazin-4-one

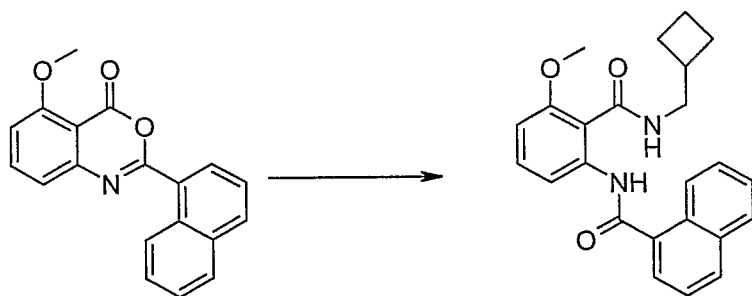


Following the method as the Step B in Example 14, using diisopropylethylamine (1 mL), 2-amino-6-methoxy-benzoic acid (840 mg, 5.0 mmol), 1-naphthalenecarbonyl chloride (1.05 g, 5.5 mmol) and HATU (2.1 g, 5.5 mmol) provided the title compound (1.33 g, 88 %). MS (ESI) (M+H)⁺ 304.1.

5

Example 48

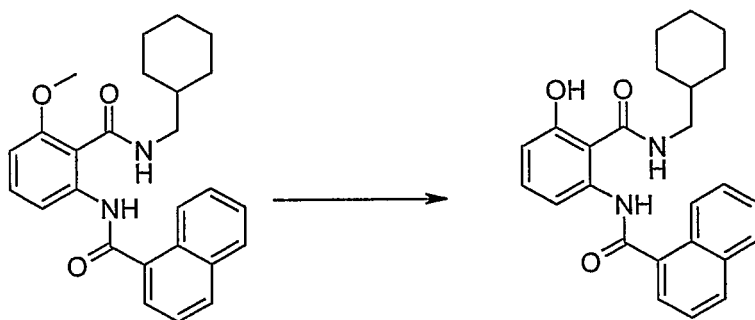
N-[2-[[[(Cyclobutylmethyl)amino]carbonyl]-3-methoxyphenyl]-1-naphthalenecarboxamide



Following the method as the Step A in Example 14, using diisopropylethylamine (0.5 mL),
 10 5-methoxy-2-(1-naphthalenyl)-4*H*-3,1-benzoxazin-4-one (61 mg, 0.2 mmol), and
 cyclobutylmethyl amine (85 mg, 1.0 mmol) provided the title compound (35 mg, 45 %). ¹H
 NMR (400 MHz, CDCl₃) δ 1.74 (m, 2H), 1.92 (m, 2H), 2.08 (m, 2H), 2.55 (m, 1H), 3.23
 (m, 2H), 3.89 (s, 3H), 6.78 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.52 (m, 4H), 7.80 (s, 1H), 7.86 (m,
 2H), 7.95 (d, *J* = 8.0 Hz, 1H), 8.53 (d, *J* = 7.6 Hz, 1H), 8.58 (dd, *J* = 8.4, 0.8 Hz, 1H), 12.52
 15 (s, 1H); MS (ESI) (M+H)⁺ 389.0.

Example 49

N-[2-[[[(Cyclohexylmethyl)amino]carbonyl]-3-hydroxyphenyl]-1-naphthalenecarboxamide

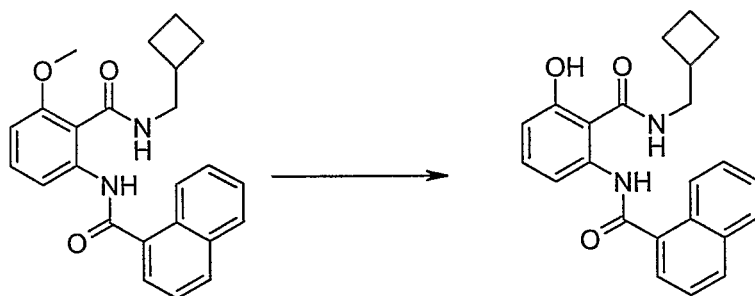


20 BBr₃ (1 mL) was added to a CH₂Cl₂ (15 ml) solution of *N*-[2-
 [[[(cyclohexylmethyl)amino]carbonyl]-3-methoxyphenyl]-1-naphthalenecarboxamide

(300.0 mg, 0.72 mmol) at 0 °C. The reaction mixture was stirred overnight at room temperature, and was then concentrated *in vacuo*. The crude product was dissolved in EtOAc and washed with 1M NH₄OH aqueous solution, brine and dried over anhydrous MgSO₄. After removal of solvents, the residue was purified by reversed-phase HPLC using 20-80% CH₃CN/H₂O and then lyophilized to provide the title compound (59 mg, 20 %). ¹H NMR (400 MHz, CDCl₃) δ 0.89 (m, 2H), 1.12 (m, 3H), 1.44 (m, 1H), 1.64 (m, 5H), 3.17 (m, 2H), 6.66 (brs, 1H), 7.28 (m, 1H), 7.54 (m, 3H), 7.83 (d, J = 7.2 Hz, 2H), 7.88 (m, 1H), 7.96 (d, J = 8.0 Hz, 2H), 8.26 (m, 1H), 8.48 (d, J = 8.8 Hz, 1H), 12.08 (s, 1H); MS (ESI) (M+H)⁺ 403.0.

Example 50

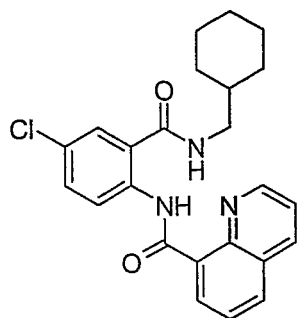
N-[2-[[[(cyclobutylmethyl)amino]carbonyl]-3-hydroxyphenyl]-1-naphthalenecarboxamide



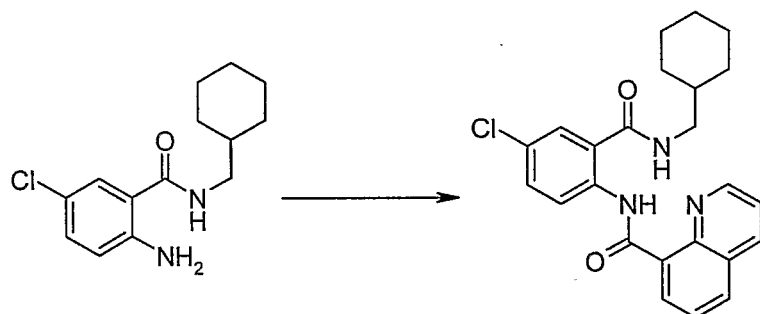
Following the method as the Example 49, using *N*-[2-[[[(cyclobutylmethyl)amino]carbonyl]-3-methoxyphenyl]-1-naphthalenecarboxamide (100.0 mg, 0.26 mmol) and BBr₃ (1 mL) provided the title compound (22 mg, 23 %). ¹H NMR (400 MHz, CDCl₃) δ 1.62 (m, 2H), 1.81 (m, 2H), 1.98 (m, 2H), 2.44 (m, 1H), 3.32 (m, 2H), 6.67 (d, J = 8.0 Hz, 1H), 7.21 (m, 1H), 7.50 (m, 3H), 7.81 (d, J = 6.8 Hz, 1H), 7.87 (m, 1H), 7.95 (d, J = 8.0 Hz, 1H), 8.06 (s, 1H), 8.26 (m, 1H), 8.40 (d, J = 8.0 Hz, 1H), 12.38 (s, 1H); MS (ESI) (M+H)⁺ 375.2.

Example 51

N-[4-chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-8-quinolinecarboxamide

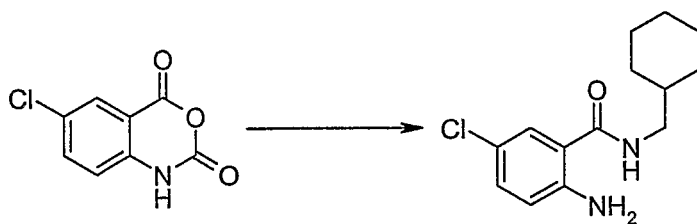


Step A. *N*-[4-chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]- 8-quinolinecarboxamide



- Diisopropylethylamine (127 mg, 1.0 mmol) was added into a solution of 2-amino-5-chloro-*N*-(cyclohexylmethyl)-benzamide (134 mg, 0.5 mmol, see Step B for its preparation), and 8-quinolinecarboxylic acid (130 mg, 0.75 mmol) in DMF (10 mL) at 0 °C. After stirring for 20 min. HATU (570 mg, 1.5 mmol) was added. The reaction mixture was stirred for 24 h at room temperature, and was then quenched with H₂O (50 mL). The precipitate was collected and dried *in vacuo* to provide the title compound (88 mg, 42 %). ¹H NMR (400 MHz, CDCl₃) δ 0.95 (m, 2H), 1.01 (m, 3H), 1.45 (m, 1H), 1.56 (m, 3H), 1.64 (m, 2H), 3.25 (d, J = 6.4 Hz, 2H), 6.19 (brs, 1H), 7.45 (m, 2H), 7.56 (m, 1H), 7.72 (d, J = 7.6 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 8.31 (d, J = 8.4 Hz, 1H), 8.41 (d, J = 8.8 Hz, 1H), 8.87 (d, J = 7.6 Hz, 1H), 9.11 (d, J = 4.4 Hz, 1H), 13.98 (brs, 1H); MS (ESI) (M+H)⁺ 421.9.

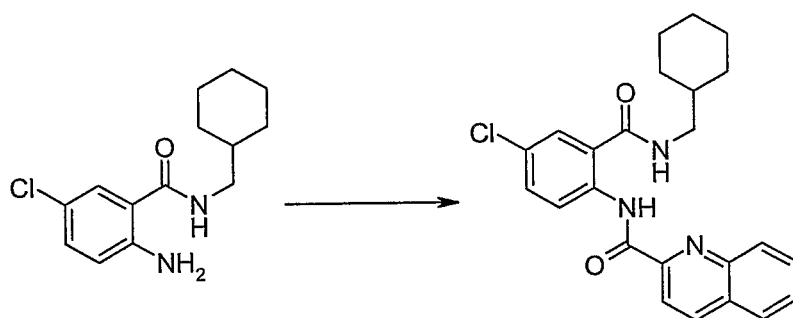
- Step B. 2-Amino-5-chloro-*N*-(cyclohexylmethyl)-benzamide



Cyclohexylmethylamine (6.8 g, 60 mmol) was added to a solution of 5-chloroisatonic anhydride (6.0 g, 30 mmol) and diisopropylethylamine (3.8 g, 30 mmol) in DMF (50 ml) at room temperature. After 2 hr, the reaction mixture was quenched with H₂O (100 mL) and diethyl ether (50 mL). The precipitate was collected and dried *in vacuo* to provide the title compound (7.0 g, 87 %). MS (ESI) (M+H)⁺ 267.1.

Example 52

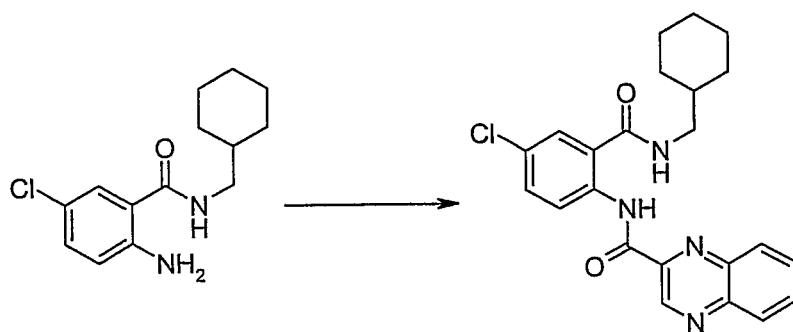
N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-2-quinolinecarboxamide



Following the method as the Step A in Example 51, using diisopropylethylamine (381 mg, 3.0 mmol), 2-amino-5-chloro-*N*-(cyclohexylmethyl)-benzamide (400 mg, 1.5 mmol), quinaldic acid (346 mg, 2.0 mmol) and HATU (760 mg, 2.0 mmol) provided the title compound (380 mg, 60 %). ¹H NMR (400 MHz, CDCl₃) δ 1.02 (m, 2H), 1.17 (m, 3H), 1.61 (m, 2H), 1.68 (m, 2H), 1.77 (m, 2H), 3.35 (d, J = 6.4 Hz, 2H), 6.13 (brs, 1H), 7.47 (m, 2H), 7.62 (m, 1H), 7.78 (dt, J = 8.4, 1.6 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 8.30 (m, 3H), 8.80 (d, J = 9.6 Hz, 1H), 12.75 (brs, 1H); MS (ESI) (M+H)⁺ 422.1.

Example 53

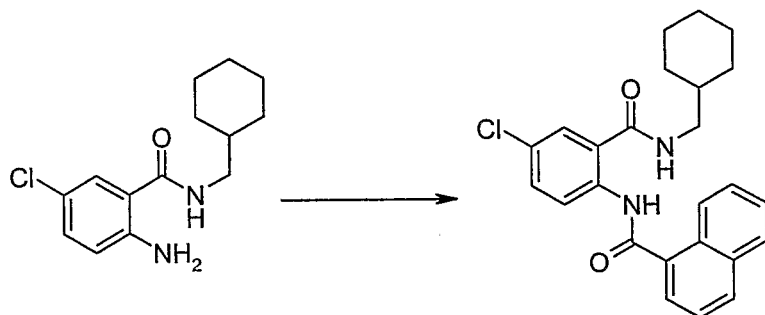
N-[4-chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-2-quinoxalinecarboxamide



A solution of 2-quinoxaloyl chloride (148 mg, 0.75 mmol) in CH_2Cl_2 (0.5 mL) was added to a mixture of diisopropylethylamine (127 mg, 1.0 mmol), 2-amino-5-chloro-*N*-(cyclohexylmethyl)-benzamide (134 mg, 0.5 mmol) in DMF (5 mL) at 0 °C. The reaction mixture was then stirred for 2h at room temperature, and was then quenched with H_2O (20 mL). The precipitate was collected and dried *in vacuo* to provide the title compound (106 mg, 50 %). ^1H NMR (400 MHz, CDCl_3) δ 1.03 (m, 2H), 1.19 (m, 3H), 1.61 (m, 2H), 1.69 (m, 2H), 1.77 (m, 2H), 3.34 (d, J = 6.4 Hz, 2H), 6.16 (brs, 1H), 7.50 (m, 2H), 7.87 (m, 2H), 8.17 (m, 1H), 8.31 (m, 1H), 8.81 (d, J = 9.2 Hz, 1H), 9.69 (s, 1H), 12.74 (brs, 1H); MS (ESI) $(\text{M}+\text{H})^+$ 423.1.

Example 54

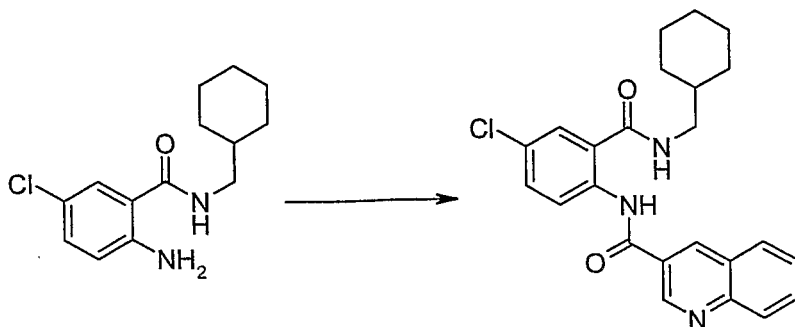
N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-1-naphthalenecarboxamide



Following the method as the Example 53, using diisopropylethylamine (190 mg, 1.5 mmol), 2-amino-5-chloro-*N*-(cyclohexylmethyl)-benzamide (267 mg, 1.0 mmol), and 1-naphthoyl chloride (296 mg, 1.5 mmol) provided the title compound (178 mg, 43 %). ^1H NMR (400 MHz, CDCl_3) δ 0.99 (m, 2H), 1.22 (m, 3H), 1.56 (m, 1H), 1.75 (m, 5H), 3.23 (d, J = 6.4 Hz, 2H), 6.21 (brs, 1H), 7.46 (m, 1H), 7.53 (m, 4H), 7.84 (dd, J = 7.2, 1.2 Hz, 1H), 7.89 (m, 1H), 7.97 (d, J = 8.0 Hz, 1H), 8.52 (m, 1H), 8.88 (d, J = 9.2 Hz, 1H), 11.53 (brs, 1H); MS (ESI) $(\text{M}+\text{H})^+$ 420.9.

Example 55

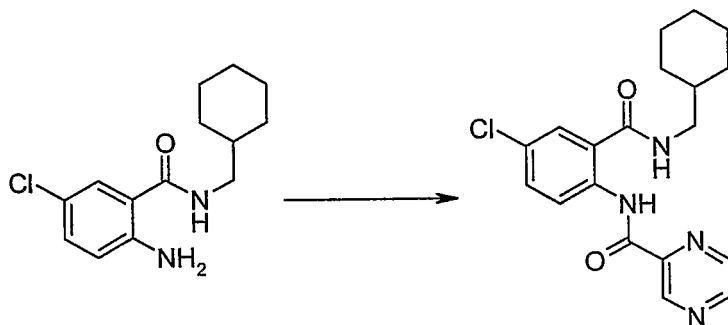
N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-3-quinolinecarboxamide



Following the method as the Step A in Example 51, using diisopropylethylamine (190 mg, 1.5 mmol), 2-amino-5-chloro-*N*-(cyclohexylmethyl)-benzamide (187 mg, 0.7 mmol), 3-quinolinecarboxylic acid (173 mg, 1.0 mmol) and HATU (380 mg, 1.0 mmol) provided the title compound (25 mg, 8.5 %). ^1H NMR (400 MHz, CDCl_3) δ 1.00 (m, 2H), 1.22 (m, 3H), 1.56 (m, 1H), 1.75 (m, 5H), 3.30 (d, $J = 6.4$ Hz, 2H), 6.26 (brs, 1H), 7.48 (m, 1H), 7.51 (m, 1H), 7.62 (m, 1H), 7.81 (m, 1H), 7.99 (d, $J = 7.2$ Hz, 1H), 8.15 (d, $J = 8.0$ Hz, 1H), 8.74 (s, 1H), 8.80 (d, $J = 9.2$ Hz, 1H), 9.50 (s, 1H), 12.38 (brs, 1H); MS (ESI) $(\text{M}+\text{H})^+$ 422.1.

Example 56

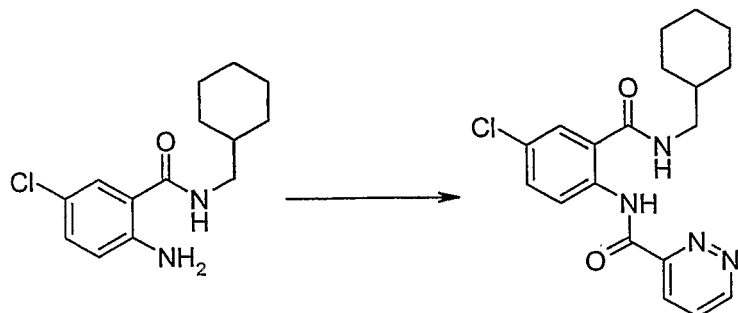
N-[4-Chloro-2-[(cyclohexylmethyl)amino]carbonyl]phenyl]-2-pyrazinecarboxamide



Following the method as the Step A in Example 51, using diisopropylethylamine (190 mg, 1.5 mmol), 2-amino-5-chloro-*N*-(cyclohexylmethyl)-benzamide (134 mg, 0.5 mmol), 2-pyrazinecarboxylic acid (186 mg, 1.5 mmol) and HATU (570 mg, 1.5 mmol) provided the title compound (103 mg, 55 %). ^1H NMR (400 MHz, CDCl_3) δ 1.04 (m, 2H), 1.24 (m, 3H), 1.57 (m, 1H), 1.74 (m, 5H), 3.34 (t, $J = 6.4$ Hz, 2H), 6.22 (brs, 1H), 7.49 (m, 2H), 8.73 (s, 1H), 8.79 (m, 2H), 9.47 (s, 1H), 12.65 (brs, 1H); MS (ESI) $(\text{M}+\text{H})^+$ 373.1.

Example 57

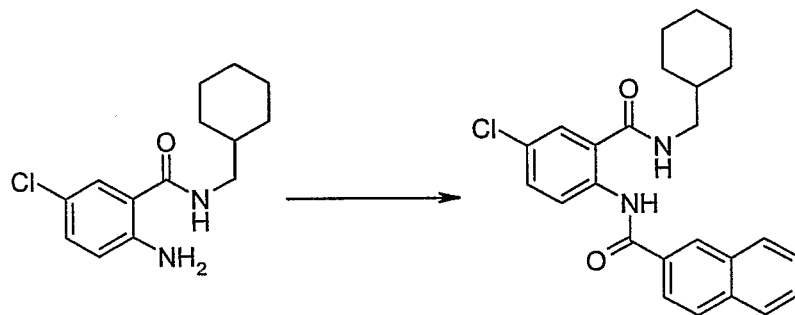
N-[4-Chloro-2-[(cyclohexylmethyl)amino]carbonyl]phenyl]-3-pyridazinecarboxamide



Following the method as the Step A in Example 51, using diisopropylethylamine (190 mg, 1.5 mmol), 2-amino-5-chloro-*N*-(cyclohexylmethyl)-benzamide (134 mg, 0.5 mmol), 3-pyridazinecarboxylic acid (186 mg, 1.5 mmol) and HATU (570 mg, 1.5 mmol) provided the title compound (105 mg, 56 %). ^1H NMR (400 MHz, CDCl_3) δ 1.02 (m, 2H), 1.24 (m, 3H), 1.74 (m, 6H), 3.35 (t, $J = 6.4$ Hz, 2H), 6.20 (brs, 1H), 7.51 (m, 2H), 7.69 (m, 1H), 8.36 (d, $J = 10.0$ Hz, 1H), 8.81 (d, $J = 10.0$ Hz, 1H), 9.34 (s, 1H), 13.06 (brs, 1H); MS (ESI) $(\text{M}+\text{H})^+$ 373.1.

Example 58

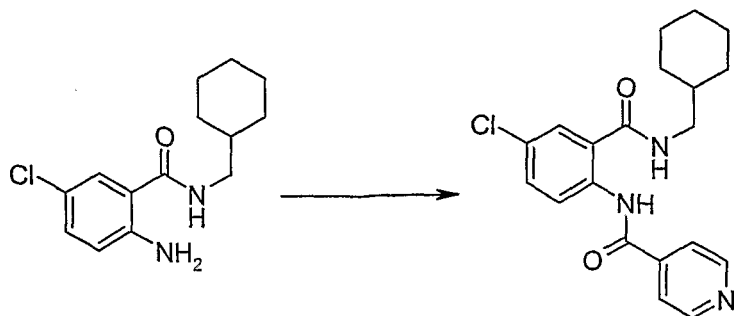
N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-2-naphthalenecarboxamide



Following the method as the Example 53, using diisopropylethylamine (190 mg, 1.5 mmol), 2-amino-5-chloro-*N*-(cyclohexylmethyl)-benzamide (134 mg, 0.5 mmol), and 2-naphthoyl chloride (148 mg, 0.75 mmol) provided the title compound (109 mg, 52 %). ^1H NMR (400 MHz, CDCl_3) δ 1.04 (m, 2H), 1.23 (m, 3H), 1.79 (m, 6H), 3.34 (t, $J = 6.4$ Hz, 2H), 6.32 (brs, 1H), 7.49 (m, 2H), 7.58 (m, 2H), 8.04 (m, 4H), 8.55 (s, 1H), 8.84 (d, $J = 8.8$ Hz, 1H), 12.15 (brs, 1H); MS (ESI) $(\text{M}+\text{H})^+$ 421.1.

Example 59

N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-4-pyridinecarboxamide

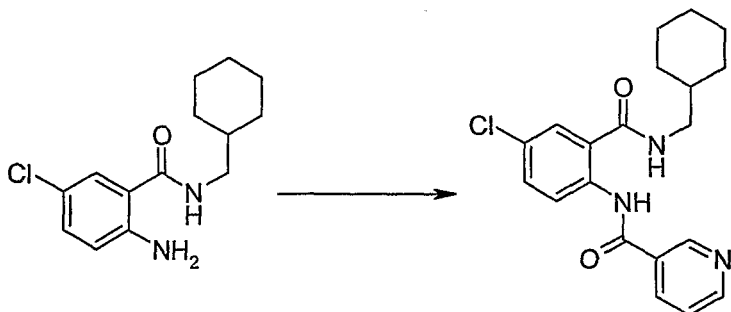


Following the method as the Example 53, using diisopropylethylamine (190 mg, 1.5 mmol), 2-amino-5-chloro-N-(cyclohexylmethyl)-benzamide (134 mg, 0.5 mmol), and isonicotinoyl chloride hydrochloride (135 mg, 0.75 mmol) provided the title compound (27 mg, 14 %).

¹H NMR (400 MHz, CDCl₃) δ 1.02 (m, 2H), 1.24 (m, 3H), 1.74 (m, 6H), 3.29 (t, J = 6.4 Hz, 2H), 6.28 (brs, 1H), 7.45 (m, 1H), 7.47 (m, 1H), 7.81 (dd, J = 4.4, 1.6 Hz, 2H), 8.79 (m, 3H), 12.30 (brs, 1H); MS (ESI) (M+H)⁺ 372.1.

Example 60

10 *N*-[4-Chloro-2-[(cyclohexylmethyl)amino]carbonyl]phenyl]- 3-pyridinecarboxamide

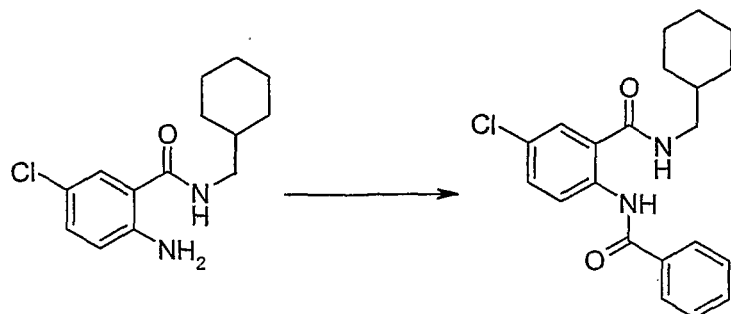


Following the method as the Example 53, using diisopropylethylamine (190 mg, 1.5 mmol), 2-amino-5-chloro-N-(cyclohexylmethyl)-benzamide (134 mg, 0.5 mmol), and nicotinoyl chloride hydrochloride (135 mg, 0.75 mmol) provided the title compound (24 mg, 13 %).

15 ¹H NMR (400 MHz, CDCl₃) δ 1.04 (m, 2H), 1.23 (m, 3H), 1.79 (m, 6H), 3.32 (t, J = 6.4 Hz, 2H), 6.29 (brs, 1H), 7.48 (m, 3H), 8.28 (m, 1H), 8.79 (m, 2H), 9.27 (s, 1H), 12.25 (brs, 1H); MS (ESI) (M+H)⁺ 372.1.

Example 61

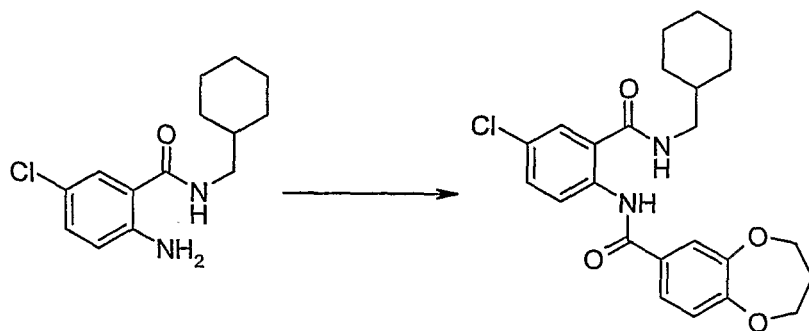
20 2-(Benzoylamino)-5-chloro-N-(cyclohexylmethyl)- benzamide



Following the method as the Example 53, using diisopropylethylamine (190 mg, 1.5 mmol), 2-amino-5-chloro-*N*-(cyclohexylmethyl)-benzamide (134 mg, 0.5 mmol), and benzoyl chloride (105 mg, 0.75 mmol) provided the title compound (75 mg, 41 %). ¹H NMR (400 MHz, CDCl₃) δ 1.04 (m, 2H), 1.25 (m, 3H), 1.59 (m, 1H), 1.78 (m, 5H), 3.32 (d, J = 6.4 Hz, 2H), 6.25 (brs, 1H), 7.50 (m, 5H), 8.02 (dd, J = 6.8, 1.2 Hz, 2H), 8.81 (d, J = 8.8 Hz, 1H), 11.96 (brs, 1H); MS (ESI) (M+H)⁺ 371.1.

Example 62

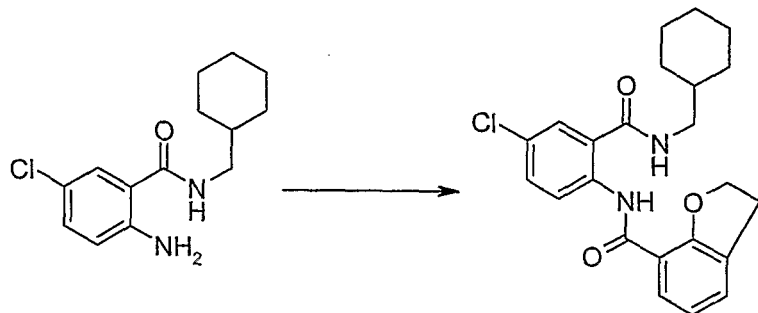
N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-3,4-dihydro-2*H*-1,5-benzodioxepin-7-carboxamide



Following the method as the Example 53, using diisopropylethylamine (190 mg, 1.5 mmol), 2-amino-5-chloro-*N*-(cyclohexylmethyl)-benzamide (134 mg, 0.5 mmol), and 3,4-dihydro-2*H*-1,5-benzodioxepine-7-carbonyl chloride (160 mg, 0.75 mmol) provided the title compound (36 mg, 16 %). ¹H NMR (400 MHz, CDCl₃) δ 0.98 (m, 2H), 1.17 (m, 3H), 1.59 (m, 1H), 1.73 (m, 5H), 2.19 (m, 2H), 3.25 (d, J = 6.4 Hz, 2H), 4.25 (m, 4H), 6.55 (m, 1H), 7.00 (d, J = 8.4 Hz, 1H), 7.39 (m, 1H), 7.49 (dd, J = 8.4, 2.4 Hz, 1H), 7.57 (d, J = 2.4 Hz, 1H), 8.61 (d, J = 8.8 Hz, 1H), 11.74 (brs, 1H); MS (ESI) (M+H)⁺ 443.1.

Example 63

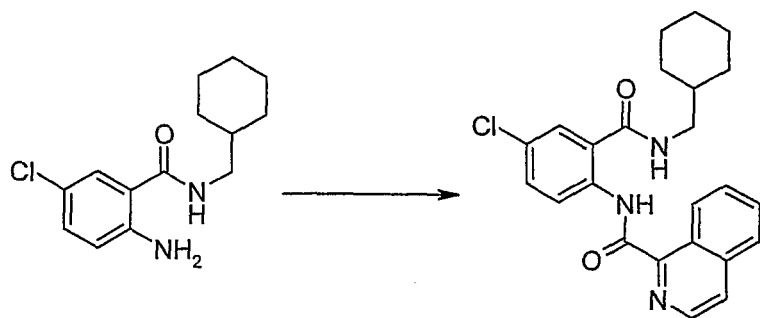
N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-2,3-dihydro-7-benzofurancarboxamide



Following the method as the Step A in Example 51, using diisopropylethylamine (127 mg, 1.0 mmol), 2-amino-5-chloro-*N*-(cyclohexylmethyl)-benzamide (134 mg, 0.5 mmol), 2,3-dihydrobenzofuran-7-carboxylic acid (99 mg, 0.6 mmol) and HATU (380 mg, 1.0 mmol) provided the title compound (15 mg, 7 %) after purification by reversed-phase HPLC. ¹H NMR (400 MHz, CDCl₃) δ 0.96 (m, 2H), 1.17 (m, 3H), 1.56 (m, 1H), 1.71 (m, 5H), 3.22 (m, 4H), 4.78 (t, J = 8.4 Hz, 2H), 6.13 (brs, 1H), 6.93 (t, J = 7.6 Hz, 1H), 7.31 (dd, J = 7.2, 1.2 Hz, 1H), 7.37 (m, 1H), 7.84 (d, J = 7.6 Hz, 1H), 8.45 (d, J = 9.2 Hz, 1H), 11.01 (brs, 1H); MS (ESI) (M+H)⁺ 413.1.

Example 64

N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-1-isoquinolinecarboxamide

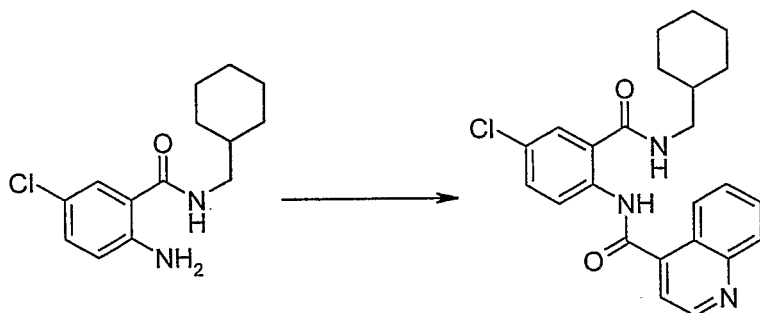


Following the method as the Step A in Example 51, using diisopropylethylamine (127 mg, 1.0 mmol), 2-amino-5-chloro-*N*-(cyclohexylmethyl)-benzamide (134 mg, 0.5 mmol), 1-isoquinolinecarboxylic acid (173 mg, 1.0 mmol) and HATU (380 mg, 1.0 mmol) provided the title compound (28 mg, 13 %) after purification by reversed-phase HPLC. ¹H NMR (400 MHz, CDCl₃) δ 0.99 (m, 2H), 1.17 (m, 3H), 1.56 (m, 1H), 1.72 (m, 5H), 3.30 (t, J = 6.4 Hz, 2H), 6.14 (brs, 1H), 7.46 (m, 2H), 7.67 (m, 2H), 7.84 (m, 2H), 8.63 (d, J = 5.6 Hz,

1H), 8.81 (d, J = 8.8 Hz, 1H), 9.49 (d, J = 9.2 Hz, 1H), 12.60 (brs, 1H); MS (ESI) (M+H)⁺ 422.1.

Example 65

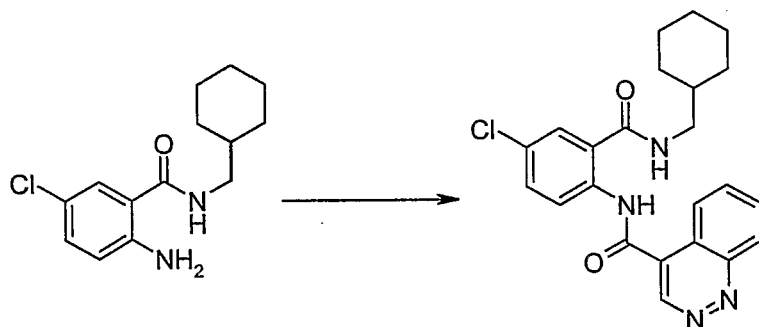
5 *N*-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-4-quinolinecarboxamide



Following the method as the Step A in Example 51, using diisopropylethylamine (127 mg, 1.0 mmol), 2-amino-5-chloro-*N*-(cyclohexylmethyl)-benzamide (134 mg, 0.5 mmol), 4-quinolinecarboxylic acid (173 mg, 1.0 mmol) and HATU (380 mg, 1.0 mmol) provided the
 10 title compound (20 mg, 10 %) after purification by reversed-phase HPLC. ¹H NMR (400 MHz, CD₃OD) δ 0.91 (m, 2H), 1.17 (m, 3H), 1.68 (m, 6H), 3.10 (d, J = 6.8 Hz, 2H), 7.56 (dd, J = 8.8, 2.4 Hz, 1H), 7.74 (m, 1H), 7.84 (m, 1H), 8.01 (m, 2H), 8.18 (d, J = 8.8 Hz, 1H), 8.48 (m, 2H), 9.16 (d, J = 4.8 Hz, 1H); MS (ESI) (M+H)⁺ 422.1.

Example 66

15 *N*-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-4-cinnolinecarboxamide

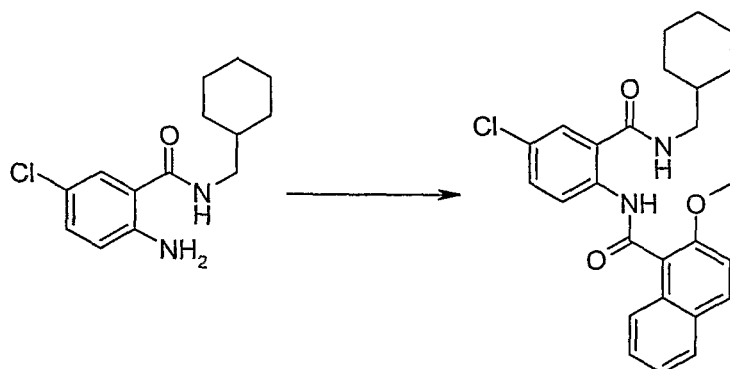


Following the method as the Step A in Example 51, using diisopropylethylamine (127 mg, 1.0 mmol), 2-amino-5-chloro-*N*-(cyclohexylmethyl)-benzamide (134 mg, 0.5 mmol), cinnoline-4-carboxylic acid (174 mg, 1.0 mmol) and HATU (380 mg, 1.0 mmol) provided
 20 the title compound (25 mg, 12 %) after purification by reversed-phase HPLC. ¹H NMR (400 MHz, CD₃OD) δ 0.94 (m, 2H), 1.17 (m, 3H), 1.66 (m, 6H), 3.14 (d, J = 6.8 Hz, 2H),

7.58 (dd, $J = 8.8, 2.4$ Hz, 1H), 7.75 (d, $J = 2.4$ Hz, 1H), 7.96 (m, 1H), 8.03 (m, 1H), 8.51 (m, 3H), 9.52 (s, 1H); MS (ESI) $(M+H)^+$ 423.1.

Example 67

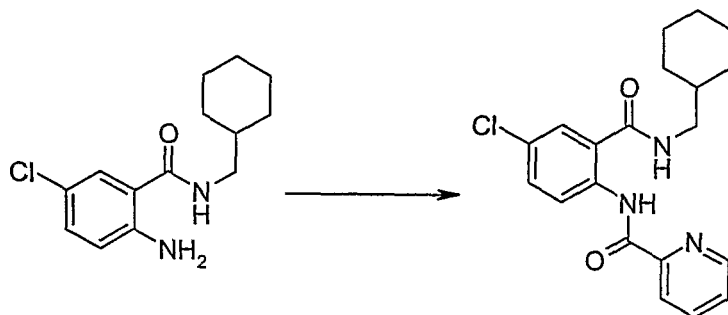
- 5 *N*-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-2-methoxy-1-naphthalenecarboxamide



Following the method as the Step A in Example 51, using diisopropylethylamine (127 mg, 1.0 mmol), 2-amino-5-chloro-*N*-(cyclohexylmethyl)-benzamide (134 mg, 0.5 mmol), 2-methoxy-1-naphthoic acid (203 mg, 1.0 mmol) and HATU (380 mg, 1.0 mmol) provided the title compound (12 mg, 5 %) after purification by reversed-phase HPLC. ^1H NMR (400 MHz, CD_3OD) δ 0.89 (m, 2H), 1.17 (m, 3H), 1.56 (m, 1H), 1.69 (m, 5H), 3.06 (d, $J = 6.4$ Hz, 2H), 3.96 (s, 3H), 7.36 (m, 1H), 7.47 (m, 2H), 7.55 (dd, $J = 9.2, 2.4$ Hz, 1H), 7.67 (d, $J = 2.4$ Hz, 1H), 7.84 (m, 2H), 7.98 (d, $J = 9.2$ Hz, 1H), 8.65 (d, $J = 8.8$ Hz, 1H), 8.69 (m, 1H); MS (ESI) $(M+H)^+$ 451.1.

Example 68

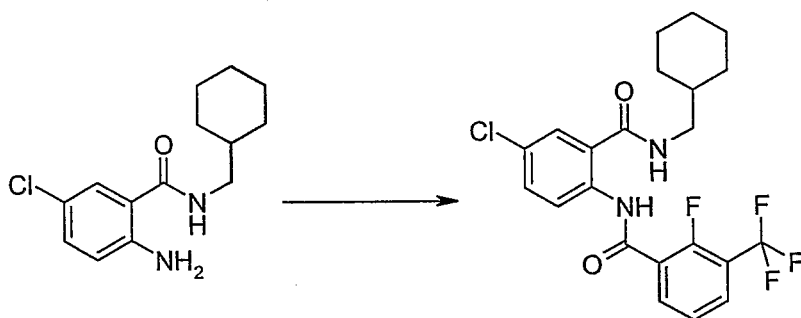
N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-2-pyridinecarboxamide



Following the method as the Example 53, using diisopropylethylamine (190 mg, 1.5 mmol), 2-amino-5-chloro-*N*-(cyclohexylmethyl)-benzamide (134 mg, 0.5 mmol), and 2-pyridinecarbonyl chloride hydrochloride (135 mg, 0.75 mmol) provided the title compound (78 mg, 42 %). ¹H NMR (400 MHz, CDCl₃) δ 1.00 (m, 2H), 1.21 (m, 3H), 1.56 (m, 1H), 1.74 (m, 5H), 3.30 (m, 2H), 6.13 (brs, 1H), 7.44 (m, 3H), 7.86 (m, 1H), 8.22 (dd, J = 8.0, 1.2 Hz, 1H), 8.73 (m, 1H), 8.78 (d, J = 9.2 Hz, 1H), 12.57 (brs, 1H); MS (ESI) (M+H)⁺ 372.1.

Example 69

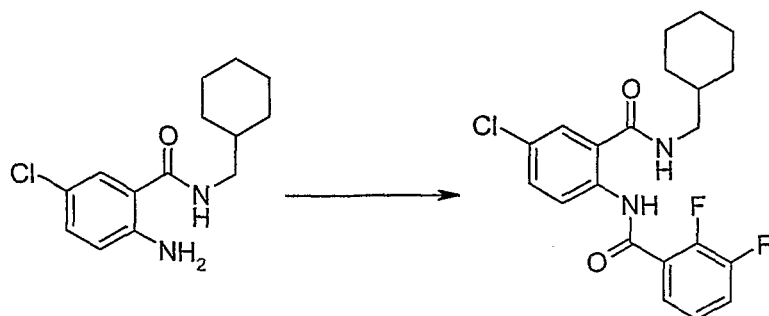
N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-2-fluoro-3-(trifluoromethyl)-benzamide



Following the method as the Example 53, using diisopropylethylamine (190 mg, 1.5 mmol), 2-amino-5-chloro-*N*-(cyclohexylmethyl)-benzamide (134 mg, 0.5 mmol), and 2-fluoro-3-(trifluoromethyl)benzoyl chloride (177 mg, 0.75 mmol) provided the title compound (84 mg, 37 %). ¹H NMR (400 MHz, CDCl₃) δ 1.02 (m, 2H), 1.22 (m, 3H), 1.58 (m, 1H), 1.77 (m, 5H), 3.30 (m, 2H), 6.19 (brs, 1H), 7.39 (t, J = 8.0 Hz, 1H), 7.45 (s, 1H), 7.49 (d, J = 9.2 Hz, 1H), 7.78 (m, 1H), 8.18 (m, 1H), 8.69 (d, J = 9.2 Hz, 1H), 11.64 (brs, 1H); MS (ESI) (M+H)⁺ 457.0.

Example 70

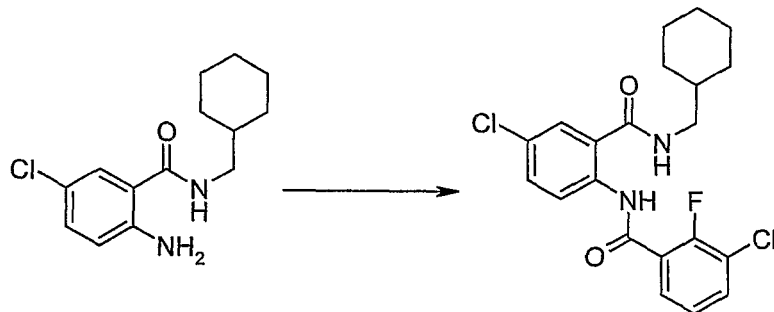
N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-2,3-difluoro-benzamide



Following the method as the Example 53, using diisopropylethylamine (190 mg, 1.5 mmol), 2-amino-5-chloro-*N*-(cyclohexylmethyl)-benzamide (134 mg, 0.5 mmol), and 2,3-difluorobenzoyl chloride (132 mg, 0.75 mmol) provided the title compound (17 mg, 8 %). ¹H NMR (400 MHz, CDCl₃) δ 1.02 (m, 2H), 1.22 (m, 3H), 1.58 (m, 1H), 1.78 (m, 5H), 3.30 (m, 2H), 6.19 (brs, 1H), 7.21 (m, 1H), 7.34 (m, 1H), 7.45 (s, 1H), 7.48 (m, 1H), 7.74 (m, 1H), 8.71 (d, *J* = 8.8 Hz, 1H), 11.64 (brs, 1H); MS (ESI) (*M*+*H*)⁺ 407.0.

Example 71

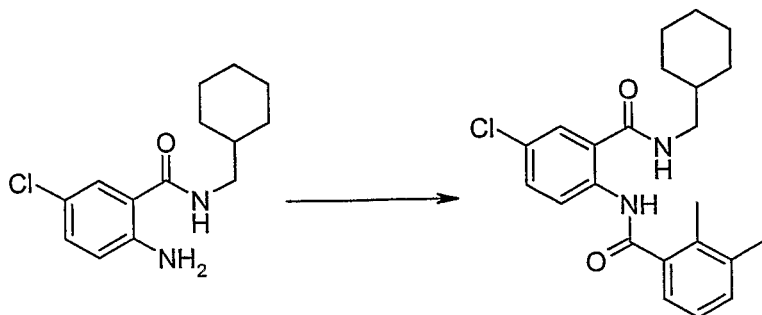
3-Chloro-*N*-[4-chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-2-fluoro-benzamide



Following the method as the Example 53, using diisopropylethylamine (127 mg, 1.0 mmol), 2-amino-5-chloro-*N*-(cyclohexylmethyl)-benzamide (50 mg, 0.19 mmol), and 2-fluoro-3-chloro-benzoyl chloride (58 mg, 0.3 mmol) provided the title compound (14 mg, 18 %). ¹H NMR (400 MHz, CDCl₃) δ 1.02 (m, 2H), 1.23 (m, 3H), 1.56 (m, 1H), 1.75 (m, 5H), 3.30 (m, 2H), 6.19 (brs, 1H), 7.22 (m, 2H), 7.46 (s, 2H), 7.87 (m, 1H), 8.69 (d, *J* = 8.8 Hz, 1H), 11.59 (brs, 1H); MS (ESI) (*M*+*H*)⁺ 423.0.

Example 72

N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-2,3-dimethyl-benzamide

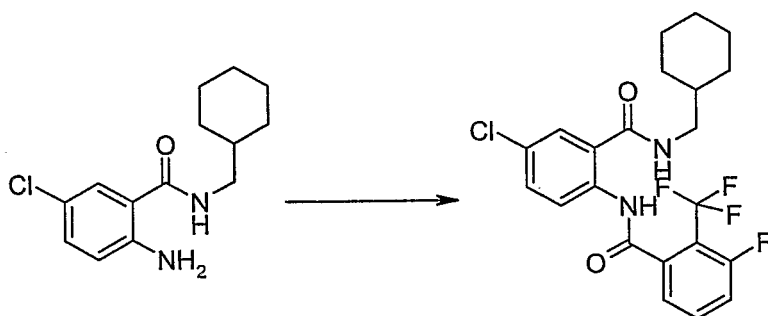


Following the method as the Example 53, using diisopropylethylamine (127 mg, 1.0 mmol), 2-amino-5-chloro-*N*-(cyclohexylmethyl)-benzamide (50 mg, 0.19 mmol), and 2,3-

¹H NMR (400 MHz, CDCl₃) δ 0.96 (m, 2H), 1.21 (m, 3H), 1.56 (m, 1H), 1.75 (m, 5H), 2.32 (s, 3H), 2.39 (s, 3H), 3.24 (m, 2H), 6.20 (brs, 1H), 7.16 (m, 1H), 7.24 (m, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.43 (s, 1H), 7.48 (d, J = 8.8 Hz, 1H), 8.78 (d, J = 8.8 Hz, 1H), 11.14 (brs, 1H); MS (ESI) (M+H)⁺ 399.0.

Example 73

N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-3-fluoro-2-(trifluoromethyl)-benzamide

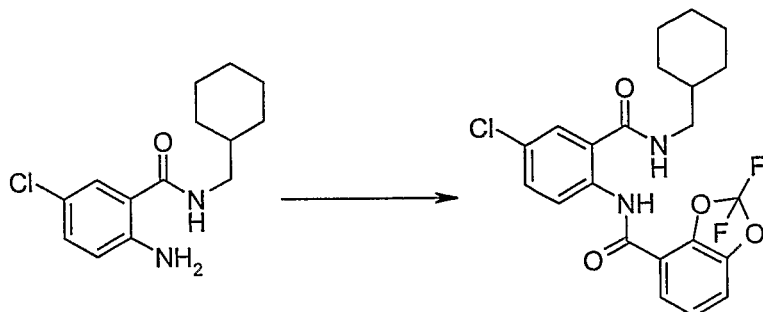


Following the method as the Example 53, using diisopropylethylamine (127 mg, 1.0 mmol),

2-amino-5-chloro-*N*-(cyclohexylmethyl)-benzamide (50 mg, 0.19 mmol), and 3-fluoro-2-(trifluoromethyl)benzoyl chloride (68 mg, 0.3 mmol) provided the title compound (20 mg, 15 %). ¹H NMR (400 MHz, CDCl₃) δ 0.99 (m, 2H), 1.24 (m, 3H), 1.56 (m, 1H), 1.75 (m, 5H), 3.24 (m, 2H), 6.22 (brs, 1H), 7.30 (m, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.45 (s, 1H), 7.50 (dd, J = 9.2, 2.4 Hz, 1H), 7.60 (m, 1H), 8.67 (d, J = 9.2 Hz, 1H), 11.31 (brs, 1H); MS (ESI) (M+H)⁺ 457.0.

Example 74

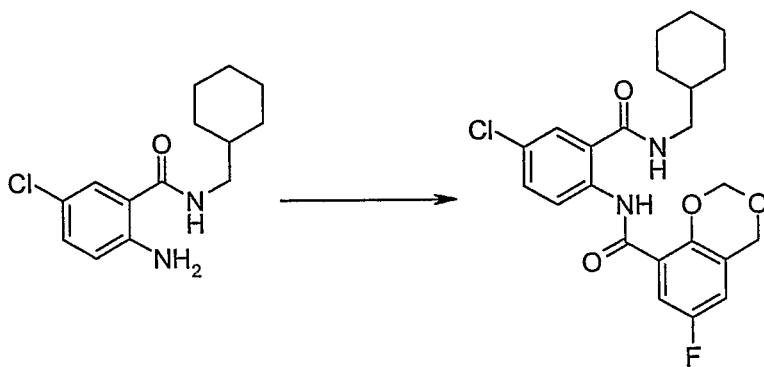
N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-2,2-difluoro-1,3-benzodioxole-4-carboxamide



Following the method as the Example 53, using diisopropylethylamine (127 mg, 1.0 mmol),
 5 2-amino-5-chloro-*N*-(cyclohexylmethyl)-benzamide (50 mg, 0.19 mmol), and 2,2-difluoro-1,3-benzodioxole-4-carbonyl chloride (66 mg, 0.3 mmol) provided the title compound (13 mg, 10 %). ¹H NMR (400 MHz, CDCl₃) δ 1.02 (m, 2H), 1.23 (m, 3H), 1.56 (m, 1H), 1.75 (m, 5H), 3.30 (m, 2H), 6.18 (brs, 1H), 7.22 (m, 2H), 7.47 (s, 2H), 7.68 (dd, *J* = 6.8, 2.4 Hz, 1H), 8.71 (d, *J* = 8.8 Hz, 1H), 11.66 (brs, 1H); MS (ESI) (*M*+*H*)⁺ 451.0.

10 Example 75

N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-6-fluoro-4*H*-1,3-benzodioxin-8-carboxamide

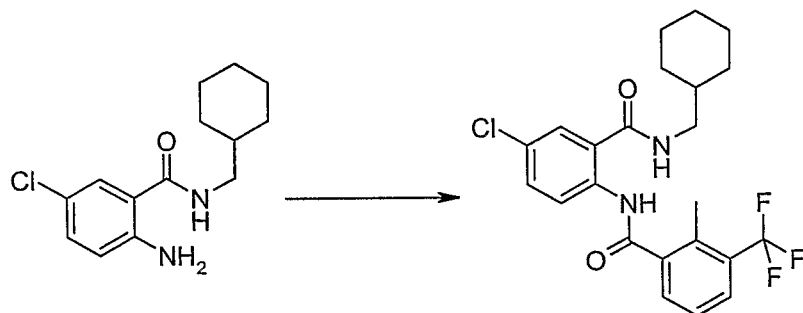


Following the method as the Step A in Example 51, using diisopropylethylamine (51 mg, 0.4 mmol), 2-amino-5-chloro-*N*-(cyclohexylmethyl)-benzamide (50 mg, 0.19 mmol), 6-fluoro-4*H*-1,3-benzodioxine-8-carboxylic acid (60 mg, 0.3 mmol) and HATU (152 mg, 0.4 mmol) provided the title compound (39 mg, 47 %) after purification by reversed-phase HPLC. ¹H NMR (400 MHz, CDCl₃) δ 1.01 (m, 2H), 1.23 (m, 3H), 1.56 (m, 1H), 1.76 (m, 5H), 3.26 (m, 2H), 4.97 (s, 2H), 5.50 (s, 2H), 6.06 (brs, 1H), 6.86 (m, 1H), 7.40 (s, 1H),

7.44 (dd, $J = 7.6, 1.2$ Hz, 1H), 7.78 (dd, $J = 7.6, 1.2$ Hz, 1H), 8.66 (d, $J = 9.2$ Hz, 1H), 11.61 (brs, 1H); MS (ESI) $(M+H)^+$ 447.0.

Example 76

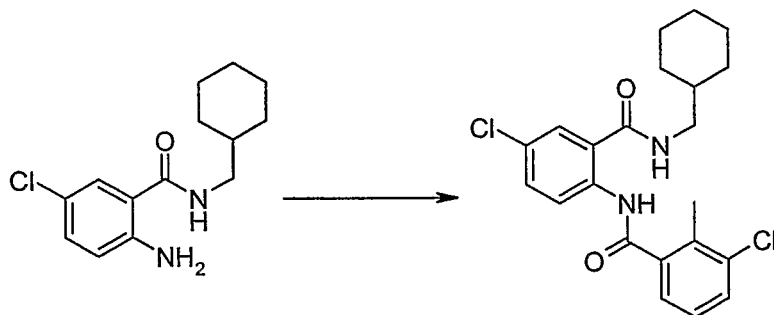
N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-2-methyl-3-(trifluoromethyl)-benzamide



Following the method as the Step A in Example 51, using diisopropylethylamine (51 mg, 0.4 mmol), 2-amino-5-chloro-*N*-(cyclohexylmethyl)-benzamide (50 mg, 0.19 mmol), 2-methyl-3-(trifluoromethyl)-benzoic acid (61 mg, 0.3 mmol) and HATU (152 mg, 0.4 mmol) provided the title compound (20 mg, 23 %) after purification by reversed-phase HPLC. ^1H NMR (400 MHz, CDCl_3) δ 0.99 (m, 2H), 1.22 (m, 3H), 1.56 (m, 1H), 1.74 (m, 5H), 2.59 (s, 3H), 3.25 (m, 2H), 6.25 (brs, 1H), 7.40 (m, 1H), 7.45 (s, 1H), 7.51 (dd, $J = 8.8, 2.4$ Hz, 1H), 7.67 (d, $J = 7.6$ Hz, 1H), 7.73 (d, $J = 7.6$ Hz, 1H), 8.77 (d, $J = 7.6$ Hz, 1H), 11.36 (brs, 1H); MS (ESI) $(M+H)^+$ 453.0.

Example 77

3-Chloro-*N*-[4-chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-2-methyl- benzamide

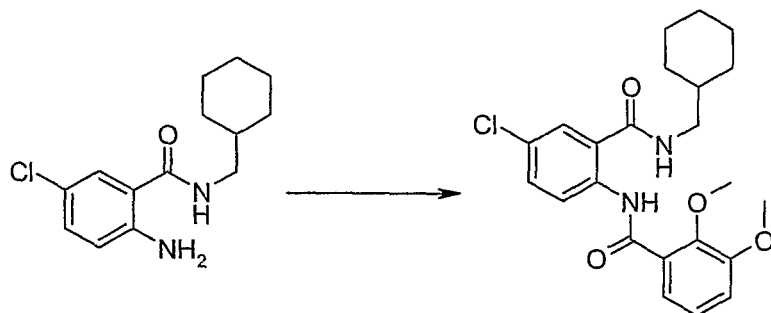


Following the method as the Step A in Example 51, using diisopropylethylamine (51 mg, 0.4 mmol), 2-amino-5-chloro-*N*-(cyclohexylmethyl)-benzamide (50 mg, 0.19 mmol), 2-methyl-3-chloro-benzoic acid (51 mg, 0.3 mmol) and HATU (152 mg, 0.4 mmol) provided the title compound (10 mg, 13 %) after purification by reversed-phase HPLC. ^1H NMR

(400 MHz, CDCl_3) δ 0.97 (m, 2H), 1.21 (m, 3H), 1.56 (m, 1H), 1.72 (m, 5H), 2.50 (s, 3H), 3.22 (m, 2H), 6.22 (brs, 1H), 7.20 (m, 2H), 7.42 (m, 3H), 8.73 (d, $J = 8.8$ Hz, 1H), 11.29 (brs, 1H); MS (ESI) $(M+H)^+$ 419.0.

Example 78

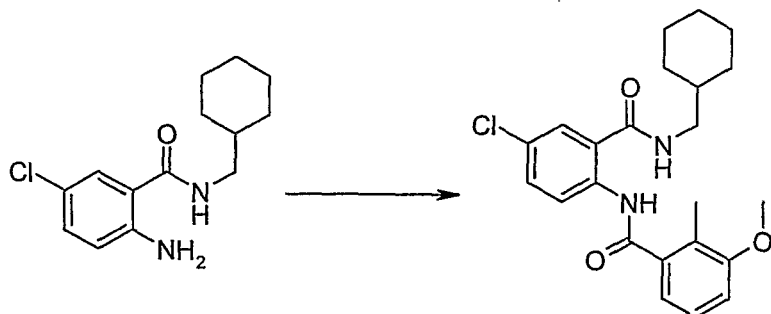
5 *N*-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-2,3-dimethoxy- benzamide



Following the method as the Step A in Example 51, using diisopropylethylamine (51 mg, 0.4 mmol), 2-amino-5-chloro-*N*-(cyclohexylmethyl)-benzamide (50 mg, 0.19 mmol), 2,3-dimethoxybenzoic acid (55 mg, 0.3 mmol) and HATU (152 mg, 0.4 mmol) provided the
 10 title compound (20 mg, 25 %) after purification by reversed-phase HPLC. ^1H NMR (400 MHz, CDCl_3) δ 0.99 (m, 2H), 1.22 (m, 3H), 1.56 (m, 1H), 1.74 (m, 5H), 3.27 (m, 2H), 3.91 (s, 3H), 4.02 (s, 3H), 6.12 (brs, 1H), 7.06 (d, $J = 8.0$ Hz, 1H), 7.13 (m, 1H), 7.40 (s, 1H), 7.44 (dd, $J = 9.2, 2.4$ Hz, 1H), 7.65 (dd, $J = 8.0, 1.6$ Hz, 1H), 8.61 (d, $J = 8.8$ Hz, 1H), 11.54 (brs, 1H); MS (ESI) $(M+H)^+$ 431.0.

15 Example 79

N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-3-methoxy-2-methyl- benzamide

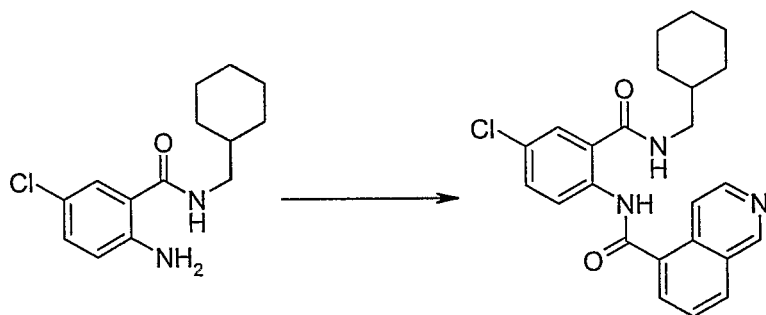


Following the method as the Step A in Example 51, using diisopropylethylamine (51 mg, 0.4 mmol), 2-amino-5-chloro-*N*-(cyclohexylmethyl)-benzamide (50 mg, 0.19 mmol), 2-methyl-3-methoxybenzoic acid (50 mg, 0.3 mmol) and HATU (152 mg, 0.4 mmol)
 20

provided the title compound (15 mg, 19 %) after purification by reversed-phase HPLC. ^1H NMR (400 MHz, CDCl_3) δ 0.99 (m, 2H), 1.24 (m, 3H), 1.56 (m, 1H), 1.77 (m, 5H), 2.36 (s, 3H), 3.24 (m, 2H), 3.86 (s, 3H), 6.22 (brs, 1H), 6.93 (d, $J = 8.0$ Hz, 1H), 7.14 (d, $J = 7.2$ Hz, 1H), 7.23 (d, $J = 8.0$ Hz, 1H), 7.43 (s, 1H), 7.48 (dd, $J = 9.2, 2.4$ Hz, 1H), 8.77 (d, $J = 9.2$ Hz, 1H), 11.16 (brs, 1H); MS (ESI) $(\text{M}+\text{H})^+$ 415.0.

Example 80

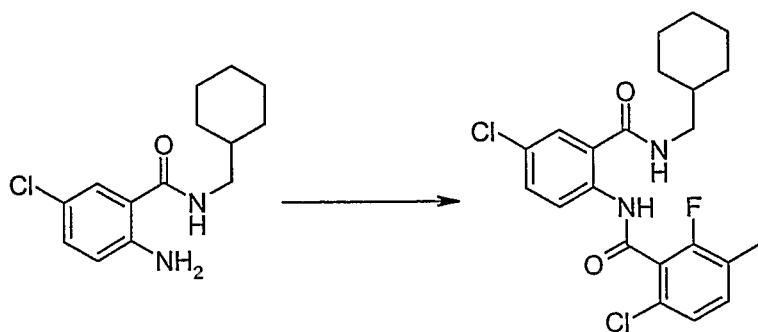
N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-5-isoquinolinecarboxamide



Following the method as the Step A in Example 51, using diisopropylethylamine (51 mg, 0.4 mmol), 2-amino-5-chloro-*N*-(cyclohexylmethyl)-benzamide (50 mg, 0.19 mmol), isoquinoline-5-carboxylic acid (52 mg, 0.3 mmol) and HATU (152 mg, 0.4 mmol) provided the title compound (18 mg, 23 %) after purification by reversed-phase HPLC. ^1H NMR (400 MHz, CDCl_3) δ 0.99 (m, 2H), 1.22 (m, 3H), 1.56 (m, 1H), 1.74 (m, 5H), 3.25 (m, 2H), 6.25 (brs, 1H), 7.46 (s, 1H), 7.54 (m, 1H), 7.68 (m, 1H), 8.12 (m, 2H), 8.40 (m, 1H), 8.62 (d, $J = 8.0$ Hz, 1H), 8.86 (d, $J = 8.0$ Hz, 1H), 9.32 (s, 1H), 11.76 (brs, 1H); MS (ESI) $(\text{M}+\text{H})^+$ 422.0.

Example 81

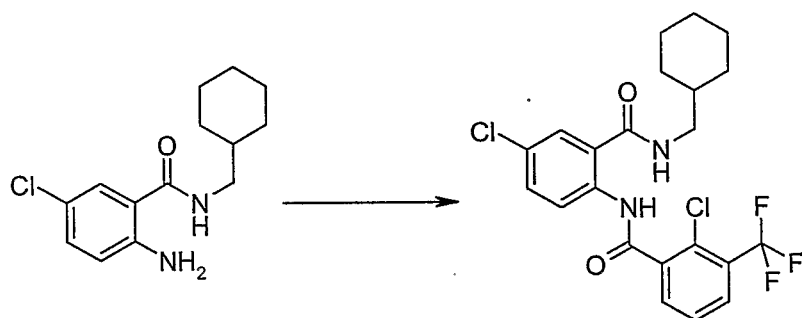
6-Chloro-*N*-[4-chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-2-fluoro-3-methylbenzamide



Following the method as the Example 53, using diisopropylethylamine (127 mg, 1.0 mmol), 2-amino-5-chloro-*N*-(cyclohexylmethyl)-benzamide (50 mg, 0.19 mmol), and 2-fluoro-6-chloro-3-methyl-benzoyl chloride (62 mg, 0.3 mmol) provided the title compound (43 mg, 53 %). ¹H NMR (400 MHz, CDCl₃) δ 0.99 (m, 2H), 1.21 (m, 3H), 1.56 (m, 1H), 1.76 (m, 5H), 2.27 (s, 3H), 3.24 (m, 2H), 6.22 (brs, 1H), 7.15 (m, 2H), 7.44 (s, 1H), 7.50 (dd, J = 8.8, 2.0 Hz, 1H), 8.75 (d, J = 9.2 Hz, 1H), 11.20 (brs, 1H); MS (ESI) (M+H)⁺ 437.0.

Example 82

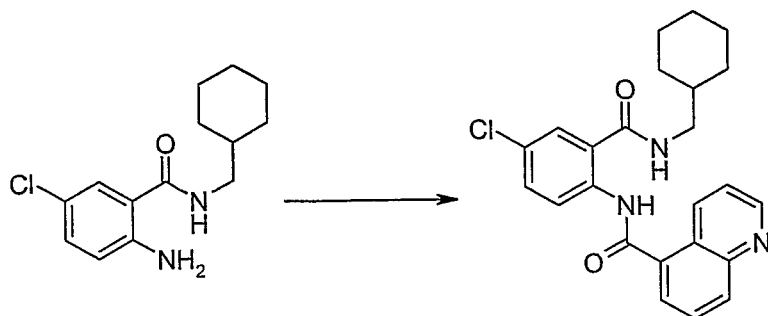
2-Chloro-*N*-[4-chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-3-(trifluoromethyl)-benzamide



Following the method as the Step A in Example 51, using diisopropylethylamine (51 mg, 0.4 mmol), 2-amino-5-chloro-*N*-(cyclohexylmethyl)-benzamide (50 mg, 0.19 mmol), 2-chloro-3-(trifluoromethyl)-benzoic acid (69 mg, 0.3 mmol) and HATU (152 mg, 0.4 mmol) provided the title compound (12 mg, 14 %) after purification by reversed-phase HPLC. ¹H NMR (400 MHz, CDCl₃) δ 0.99 (m, 2H), 1.22 (m, 3H), 1.56 (m, 1H), 1.74 (m, 5H), 3.25 (m, 2H), 6.25 (brs, 1H), 7.53 (m, 3H), 7.74 (d, J = 7.6 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 8.75 (d, J = 9.2 Hz, 1H), 11.42 (brs, 1H); MS (ESI) (M+H)⁺ 473.0.

Example 83

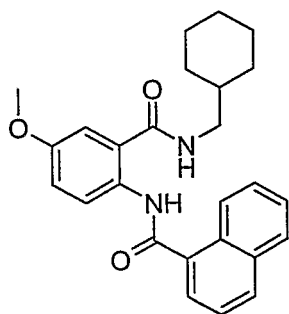
N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-5-quinolinecarboxamide



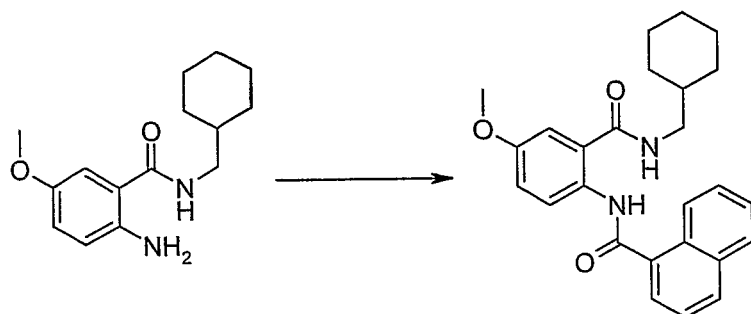
Following the method as the Step A in Example 51, using diisopropylethylamine (51 mg, 0.4 mmol), 2-amino-5-chloro-*N*-(cyclohexylmethyl)-benzamide (50 mg, 0.19 mmol), quinoline-5-carboxylic acid (52 mg, 0.3 mmol) and HATU (152 mg, 0.4 mmol) provided the title compound (23 mg, 29 %) after purification by reversed-phase HPLC. ¹H NMR (400 MHz, CD₃OD) δ .98 (m, 2H), 1.22 (m, 3H), 1.74 (m, 6H), 3.17 (d, J = 6.8 Hz, 2H), 7.60 (d, J = 6.8 Hz, 1H), 7.78 (s, 1H), 7.90 (m, 1H), 8.10 (m, 1H), 8.19 (d, J = 6.80 Hz, 1H), 8.31 (d, J = 8.4 Hz, 1H), 8.60 (d, J = 8.8 Hz, 1H), 9.11 (s, 1H), 9.37 (d, J = 8.8 Hz, 1H); MS (ESI) (M+H)⁺ 422.0.

Example 84

N-[2-[[[(Cyclohexylmethyl)amino]carbonyl]-4-methoxyphenyl]-1-naphthalenecarboxamide

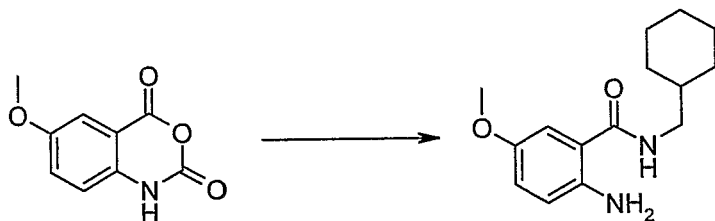


Step A. *N*-[2-[[[(Cyclohexylmethyl)amino]carbonyl]-4-methoxyphenyl]-1-naphthalenecarboxamide



Following the method as the Example 53, using diisopropylethylamine (1 mL), 2-amino-5-methoxy-*N*-(cyclohexylmethyl)-benzamide (5.17 mmol, see Step B for its preparation), and 1-naphthoyl chloride (1.14 mL, 5.68 mmol) provided the title compound (72 mg, 4 %). ¹H NMR (400 MHz, DMSO-*D*₆) δ 0.81 (d, *J*=11.72 Hz, 2 H) 1.06 (m, 3 H) 1.58 (m, 6 H) 3.00 (t, *J*=6.35 Hz, 2 H) 3.78 (s, 3 H) 7.15 (dd, *J*=8.98, 2.93 Hz, 1 H) 7.29 (d, *J*=2.93 Hz, 1 H) 7.56 (m, 3 H) 7.75 (dd, *J*=7.03, 0.98 Hz, 1 H) 7.97 (dd, *J*=6.15, 3.42 Hz, 1 H) 8.05 (d, *J*=8.20 Hz, 1 H) 8.30 (dd, *J*=6.35, 3.61 Hz, 1 H) 8.46 (d, *J*=8.98 Hz, 1 H) 8.73 (s, 1 H) 11.64 (s, 1 H). MS (ESI) (*M*+*H*)⁺ 417.1.

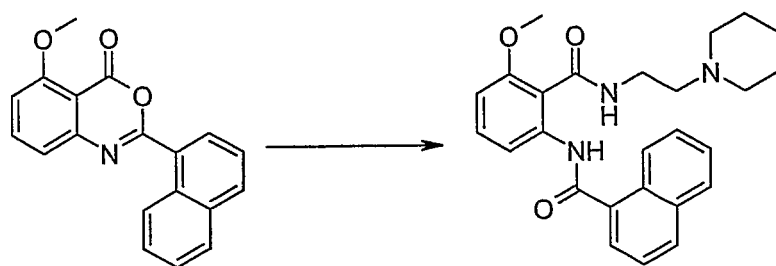
Step B. 2-Amino-5-methoxy-*N*-(cyclohexylmethyl)-benzamide



Following the method as the Step B in Example 51, using diisopropylethylamine (1 mL), 5-methoxy-isatonic anhydride (1.0 g, 5.17 mmol), cyclohexylmethylamine (673 μL, 5.17 mmol) provided the title compound, which was used directly in the Step A.

Example 85

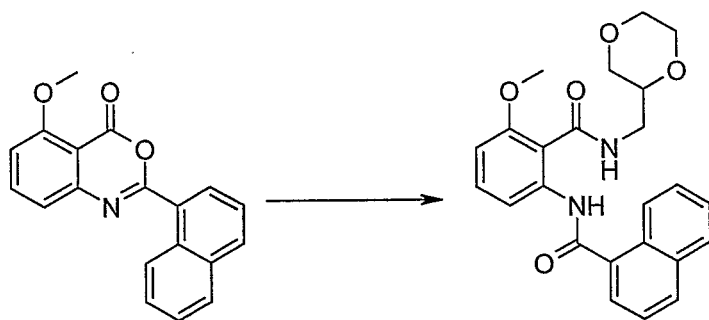
N-(3-Methoxy-2-[[[(2-piperidin-1-ylethyl)amino]carbonyl}phenyl]-1-naphthamide



Following the method as the Step A in Example 14, using 5-methoxy-2-(1-naphthalenyl)-4*H*-3,1-benzoxazin-4-one (100 mg, 0.33 mmol), and (2-piperidin-1-ylethyl)amine (128 mg, 1.0 mmol) provided the title compound (79 mg, 56 %). ¹H NMR (400 MHz, CDCl₃) δ 1.47 (m, 2H), 1.58 (m, 4H), 2.41 (m, 4H), 2.48 (m, 2H), 3.44 (m, 2H), 3.98 (s, 3H), 6.77 (dd, J= 8.4, 1.2 Hz, 1H), 7.53 (m, 4H), 7.87 (dd, J= 7.2, 1.2 Hz, 2H), 7.94 (d, J = 8.4 Hz, 1H), 8.50 (brs, 1H), 8.54 (d, J = 8.0 Hz, 1H), 8.61 (dd, J= 8.4, 1.2 Hz, 1H), 12.79 (brs, 1H); MS (ESI) (M+H)⁺ 432.0.

Example 86

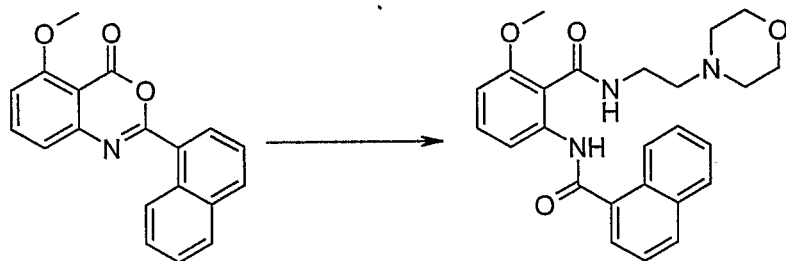
N-(2-[[[(1,4-Dioxan-2-ylmethyl)amino]carbonyl]-3-methoxyphenyl]-1-naphthamide



Following the method as the Step A in Example 14, using 5-methoxy-2-(1-naphthalenyl)-4*H*-3,1-benzoxazin-4-one (100 mg, 0.33 mmol), and (1,4-dioxan-2-ylmethyl)amine (117 mg, 1.0 mmol) provided the title compound (94 mg, 68 %). ¹H NMR (400 MHz, CDCl₃) δ 3.37 (m, 2H), 3.59 (m, 2H), 3.78 (m, 5H), 3.97 (s, 3H), 6.79 (d, J= 8.4 Hz, 1H), 7.53 (m, 4H), 7.86 (m, 2H), 7.95 (d, J = 8.4 Hz, 1H), 8.20 (brs, 1H), 8.53 (d, J = 8.0 Hz, 1H), 8.61 (dd, J= 8.4, 0.8 Hz, 1H), 12.56 (brs, 1H); MS (ESI) (M+H)⁺ 421.0.

Example 87

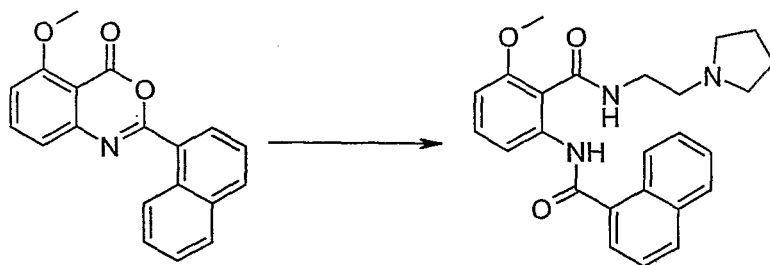
N-(3-Methoxy-2-[[[(2-morpholin-4-ylethyl)amino]carbonyl]phenyl]-1-naphthamide



Following the method as the Step A in Example 14, using 5-methoxy-2-(1-naphthalenyl)-4*H*-3,1-benzoxazin-4-one (100 mg, 0.33 mmol), and (2-morpholin-4-ylethyl)amine (130 mg, 1.0 mmol) provided the title compound (112 mg, 78 %). ¹H NMR (400 MHz, CDCl₃) δ 2.50 (m, 4H), 2.56 (m, 2H), 3.49 (m, 2H), 3.72 (m, 4H), 3.99 (s, 3H), 6.78 (dd, J= 8.4, 1.2 Hz, 1H), 7.53 (m, 4H), 7.87 (m, 2H), 7.95 (d, J = 8.4 Hz, 1H), 8.41 (brs, 1H), 8.53 (d, J = 7.6 Hz, 1H), 8.61 (dd, J= 8.4, 0.8 Hz, 1H), 12.72 (brs, 1H); MS (ESI) (M+H)⁺ 434.0.

Example 88

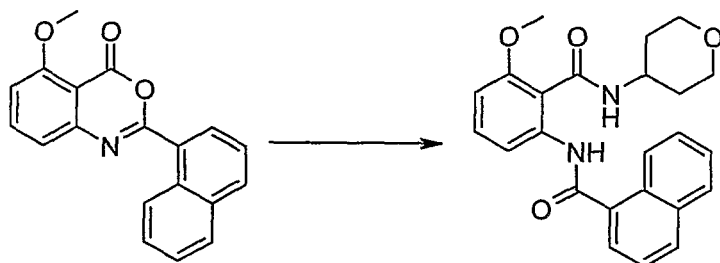
N-(3-Methoxy-2-[(2-pyrrolidin-1-ylethyl)amino]carbonyl}phenyl)-1-naphthamide



Following the method as the Step A in Example 14, using 5-methoxy-2-(1-naphthalenyl)-4*H*-3,1-benzoxazin-4-one (100 mg, 0.33 mmol), and (2-pyrrolidin-1-ylethyl)amine (114 mg, 1.0 mmol) provided the title compound (108 mg, 78 %). ¹H NMR (400 MHz, CDCl₃) δ 1.80 (m, 4H), 2.54 (m, 4H), 2.65 (m, 2H), 3.47 (m, 2H), 3.92 (s, 3H), 6.76 (d, J= 8.0 Hz, 1H), 7.52 (m, 4H), 7.87 (d, J= 8.0 Hz, 2H), 7.94 (d, J = 8.4 Hz, 1H), 8.46 (brs, 1H), 8.54 (d, J = 8.0 Hz, 1H), 8.60 (d, J= 8.0 Hz, 1H), 12.71 (brs, 1H); MS (ESI) (M+H)⁺ 418.0.

Example 89

N-{3-Methoxy-2-[(tetrahydro-2*H*-pyran-4-ylamino)carbonyl]phenyl}-1-naphthamide

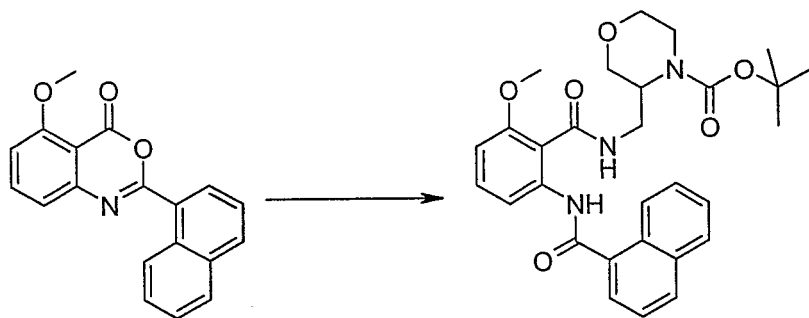


Following the method as the Step A in Example 14, using 5-methoxy-2-(1-naphthalenyl)-4*H*-3,1-benzoxazin-4-one (100 mg, 0.33 mmol), and tetrahydro-2*H*-pyran-4-amine (101 mg, 1.0 mmol) provided the title compound (98 mg, 74 %). ¹H NMR (400 MHz, CDCl₃) δ

1.56 (m, 2H), 1.95 (m, 2H), 3.50 (m, 2H), 3.92 (m, 2H), 3.96 (s, 3H), 4.16 (m, 1H), 6.78 (d, $J = 7.6$ Hz, 1H), 7.53 (m, 4H), 7.78 (m, 1H), 7.87 (m, 2H), 7.95 (d, $J = 8.4$ Hz, 1H), 8.53 (d, $J = 8.0$ Hz, 1H), 8.60 (d, $J = 8.0$ Hz, 1H), 12.50 (brs, 1H); MS (ESI) $(M+H)^+$ 405.0.

5 Example 90

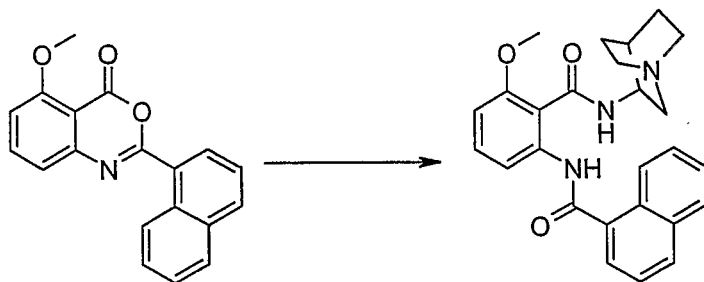
tert-Butyl 3-({[2-methoxy-6-(1-naphthoylamino)benzoyl]amino}methyl)morpholine-4-carboxylate



Following the method as the Step A in Example 14, using 5-methoxy-2-(1-naphthalenyl)-
 10 4H-3,1-benzoxazin-4-one (100 mg, 0.33 mmol), and *tert*-butyl 3-(aminomethyl)morpholine-4-carboxylate (216 mg, 1.0 mmol) provided the title compound (120 mg, 70 %). ^1H NMR (400 MHz, CDCl_3) δ 1.30 (s, 9H), 3.19 (m, 1H), 3.44 (m, 1H), 3.59 (m, 1H), 3.80 (m, 5H), 3.95 (s, 3H), 4.22 (m, 1H), 6.75 (d, $J = 8.0$ Hz, 1H), 7.50 (m, 4H), 7.88 (m, 2H), 7.95 (d, $J = 8.4$ Hz, 1H), 8.18 (brs, 1H), 8.54 (d, $J = 8.0$ Hz, 1H), 8.64 (d,
 15 $J = 8.4$ Hz, 1H), 12.80 (brs, 1H); MS (ESI) $(M+H)^+$ 520.0.

Example 91

N-{2-[(1-Azabicyclo[2.2.2]oct-3-ylamino)carbonyl]-3-methoxyphenyl}-1-naphthamide

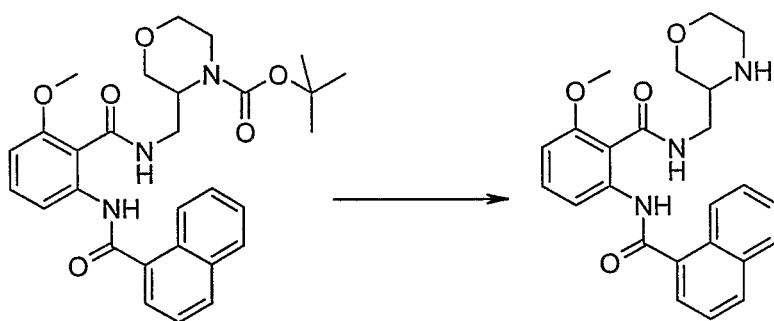


Following the method as the Step A in Example 14, using 5-methoxy-2-(1-naphthalenyl)-
 20 4H-3,1-benzoxazin-4-one (100 mg, 0.33 mmol), and quinuclidin-3-amine (126 mg, 1.0

mmol) provided the title compound (55 mg, 39 %). ^1H NMR (400 MHz, CD_3OD) δ 1.86 (m, 1H), 2.01 (m, 2H), 2.24 (m, 1H), 2.30 (m, 1H), 3.18 (m, 1H), 3.31 (m, 4H), 3.72 (m, 1H), 3.94 (s, 3H), 4.40 (m, 1H), 7.04 (d, $J = 8.4$ Hz, 1H), 7.53 (m, 1H), 7.56 (m, 4H), 7.79 (d, $J = 6.8$ Hz, 1H), 7.95 (m, 1H), 8.04 (d, $J = 8.4$ Hz, 1H), 8.34 (m, 1H); MS (ESI) $(\text{M}+\text{H})^+$ 430.2.

Example 92

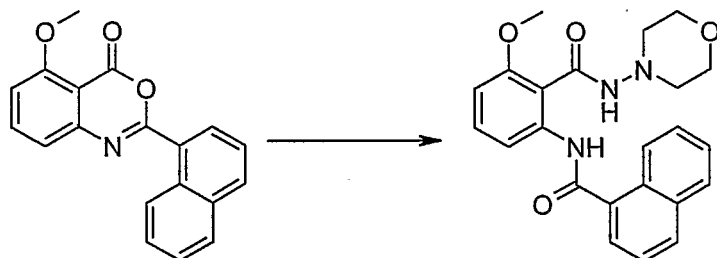
N-(3-Methoxy-2-[[[(morpholin-3-ylmethyl)amino]carbonyl]phenyl]-1-naphthamide



tert-Butyl 3-([2-methoxy-6-(1-naphthoylamino)benzoyl]amino)methyl)morpholine-4-carboxylate (100 mg) was treated with 4 N HCl in dioxane for 2 hr at r.t. Removal of solvents provided the title compound as its HCl salt in quantitative yield. ^1H NMR (400 MHz, CD_3OD) δ 2.85 (m, 2H), 3.42 (m, 1H), 3.60 (m, 4H), 3.75 (m, 1H), 3.95 (s, 3H), 3.98 (m, 1H), 7.04 (dd, $J = 8.0, 1.2$ Hz, 1H), 7.58 (m, 5H), 7.87 (dd, $J = 7.2, 1.2$ Hz, 1H), 7.97 (d, $J = 8.4$ Hz, 1H), 8.06 (d, $J = 8.4$ Hz, 1H), 8.38 (d, $J = 8.0$ Hz, 1H); MS (ESI) $(\text{M}+\text{H})^+$ 420.2.

Example 93

N-{3-Methoxy-2-[(morpholin-4-ylamino)carbonyl]phenyl}-1-naphthamide

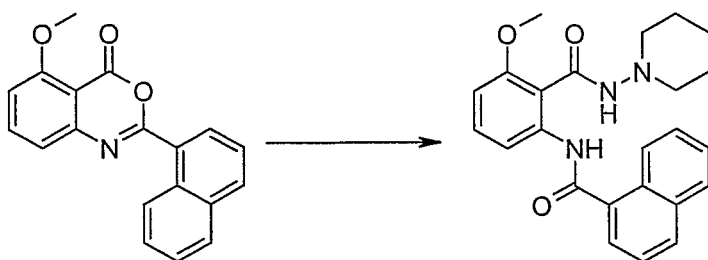


Following the method as the Step A in Example 14, using 5-methoxy-2-(1-naphthalenyl)-4H-3,1-benzoxazin-4-one (100 mg, 0.33 mmol), and morpholin-4-amine (102 mg, 1.0 mmol) provided the title compound as its TFA salt (35 mg, 20 %). ^1H NMR (400 MHz,

CD₃OD) δ 2.87 (m, 4H), 3.73 (m, 4H), 3.90 (s, 3H), 6.99 (d, J = 8.4 Hz, 1H), 7.57 (m, 4H), 7.72 (m, 1H), 7.78 (d, J = 7.2 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 8.33 (d, J = 8.0 Hz, 1H); MS (ESI) (M+H)⁺ 406.2.

5 Example 94

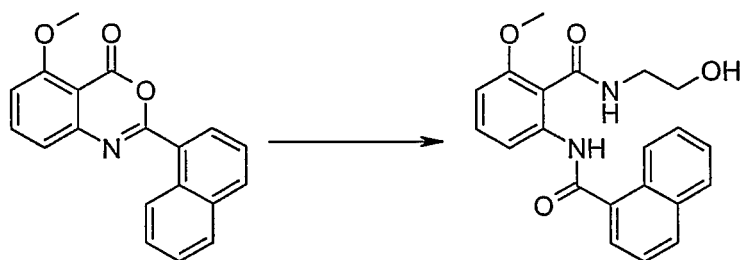
N-{3-Methoxy-2-[(piperidin-1-ylamino)carbonyl]phenyl}-1-naphthamide



Following the method as the Step A in Example 14, using 5-methoxy-2-(1-naphthalenyl)-4H-3,1-benzoxazin-4-one (100 mg, 0.33 mmol), and piperidin-1-amine (100 mg, 1.0 mmol) provided the title compound as its TFA salt (24 mg, 14 %). ¹H NMR (400 MHz, CD₃OD) δ 1.56 (m, 2H), 1.83 (m, 4H), 3.30 (m, 4H), 3.92 (s, 3H), 7.04 (d, J = 8.4 Hz, 1H), 7.56 (m, 5H), 7.79 (d, J = 6.0 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 8.33 (d, J = 9.2 Hz, 1H); MS (ESI) (M+H)⁺ 404.2.

15 Example 95

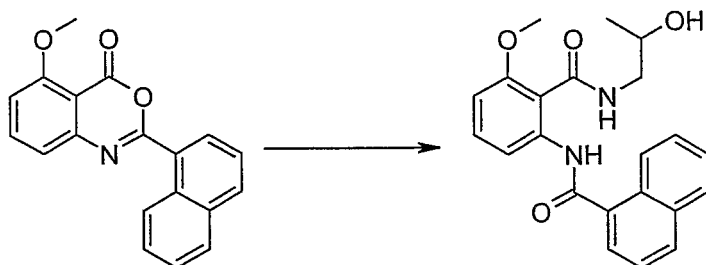
N-(2-{[(2-Hydroxyethyl)amino]carbonyl}-3-methoxyphenyl)-1-naphthamide



Following the method as the Step A in Example 14, using 5-methoxy-2-(1-naphthalenyl)-4H-3,1-benzoxazin-4-one (100 mg, 0.33 mmol), and 2-aminoethanol (61 mg, 1.0 mmol) provided the title compound (72 mg, 60 %). ¹H NMR (400 MHz, CDCl₃) δ 2.30 (m, 1H), 3.57 (m, 2H), 3.78 (m, 2H), 3.97 (s, 3H), 6.78 (d, J = 8.4 Hz, 1H), 7.54 (m, 4H), 7.85 (m, 2H), 7.95 (d, J = 8.2 Hz, 1H), 8.27 (s, 1H), 8.53 (d, J = 8.0 Hz, 1H), 8.61 (d, J = 8.4 Hz, 1H), 12.55 (s, 1H); MS (ESI) (M+H)⁺ 365.2.

Example 96

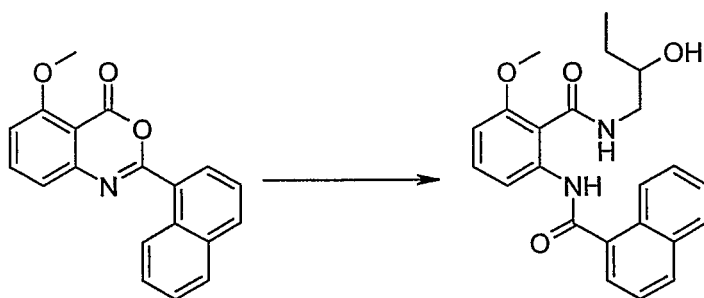
N-(2-{[(2-Hydroxypropyl)amino]carbonyl}-3-methoxyphenyl)-1-naphthamide



- 5 Following the method as the Step A in Example 14, using 5-methoxy-2-(1-naphthalenyl)-4H-3,1-benzoxazin-4-one (100 mg, 0.33 mmol), and 1-aminopropan-2-ol (75 mg, 1.0 mmol) provided the title compound (65 mg, 52 %). ¹H NMR (400 MHz, CDCl₃) δ 1.21 (d, J=6.4 Hz, 3H), 2.34 (m, 1H), 3.27 (m, 1H), 3.55 (m, 1H), 3.96 (s, 3H), 4.00 (m, 1H), 6.78 (d, J=8.4 Hz, 1H), 7.54 (m, 4H), 7.86 (m, 2H), , 7.95 (d, J= 8.2 Hz, 1H), 8.21 (s, 1H), ,
10 8.53 (d, J=8.0 Hz, 1H), 8.60 (d, J=8.4 Hz, 1H), 12.49 (s, 1H); MS (ESI) (M+H)⁺ 379.2.

Example 97

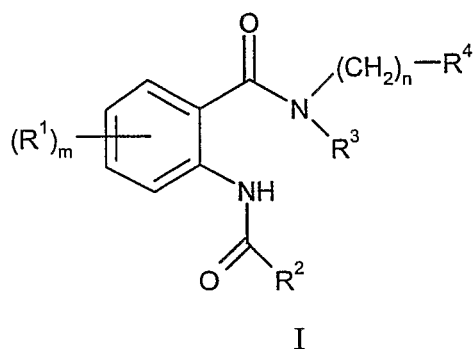
N-(2-{[(2-Hydroxybutyl)amino]carbonyl}-3-methoxyphenyl)-1-naphthamide



- 15 Following the method as the Step A in Example 14, using 5-methoxy-2-(1-naphthalenyl)-4H-3,1-benzoxazin-4-one (100 mg, 0.33 mmol), and 1-aminobutan-2-ol (89 mg, 1.0 mmol) provided the title compound. MS (ESI) (M+H)⁺ 393.2.

What is claimed is:

1. A compound of formula I or a pharmaceutically acceptable salt, diastereomers, enantiomers, or mixtures thereof:



wherein:

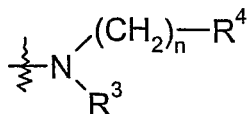
m is selected from 0, 1 and 2;

n is selected from 0, 1, 2, 3, 4 and 5;

10 R^1 is independently selected from halogen, cyano, amino, nitro, C_{1-6} alkylamino, di C_{1-6} alkylamino, acetylamino, hydroxyl, C_{1-6} alkoxy, C_{1-6} alkyl, halogenated C_{1-6} alkoxy, C_{1-6} alkenyl, and halogenated C_{1-6} alkyl;

R^2 is selected from C_{6-10} aryl and C_{2-10} heterocyclyl; wherein said C_{6-10} aryl and C_{2-10} heterocyclyl used in defining R^2 is optionally substituted by one or more groups selected
15 from halogen, halogenated C_{1-6} alkyl, C_{1-6} alkyl, cyano, nitro, C_{1-6} alkoxy, halogenated C_{1-6} alkoxy, hydroxy, hydroxy- C_{1-6} alkyl, amino, C_{1-6} alkoxy- C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylamino, di C_{1-6} alkyl-amino, amino- C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} heteroaryl, heteroaryl- C_{1-6} alkyl, C_{6-10} aryl, and C_{6-10} aryl- C_{1-6} alkyl; and

R^3 is selected from hydrogen and C_{1-6} alkyl; R^4 is selected from C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, C_{6-10} aryl, C_{2-6} heterocyclyl-amino, C_{2-6} heterocycloxy-amino and C_{2-6} heterocyclyl; wherein said C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, C_{6-10} aryl, C_{2-6} heterocyclyl-amino, C_{2-6} heterocycloxy-amino and C_{2-6} heterocyclyl used in defining R^4 is optionally substituted by one or more groups selected from halogen, halogenated C_{1-6} alkyl, C_{1-6} alkyl, cyano, nitro, C_{1-6} alkoxy, halogenated C_{1-6} alkoxy, hydroxy, hydroxy- C_{1-6} alkyl, amino, C_{1-6} alkoxy- C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylamino, di C_{1-6} alkyl-amino, amino- C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} heteroaryl, heteroaryl- C_{1-6} alkyl, C_{6-10} aryl, and C_{6-10} aryl- C_{1-6} alkyl; and
25



10 aryl, and C₆₋₁₀aryl-C₁₋₆alkyl; or is C₂₋₁₀heterocyclyl, which is optionally substituted by one or more groups selected from halogen, halogen substituted C₁₋₆alkyl, C₁₋₆alkyl, cyano, nitro, C₁₋₆alkoxy, halogenated C₁₋₆alkoxy, hydroxy, hydroxy-C₁₋₆alkyl, amino, C₁₋₆alkoxy-C₁₋₆alkyl, C₁₋₆alkylcarbonyl, C₁₋₆alkoxycarbonyl, C₁₋₆alkylamino, diC₁₋₆alkyl-amino, amino-C₁₋₆alkyl, C₃₋₆cycloalkyl, C₂₋₆heteroaryl, heteroaryl-C₁₋₆alkyl, C₆₋₁₀aryl, and C₆₋₁₀aryl-C₁₋₆alkyl.

2. A compound as claimed in claim 1, wherein

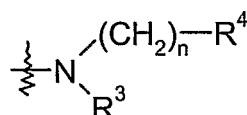
m is selected from 0, 1 and 2;

10 n is selected from 0, 1, 2, 3 and 4;

R¹ is independently selected from halogen, cyano, amino, nitro, acetylamino, hydroxyl, C₁₋₃alkoxy, C₁₋₃alkyl, halogenated C₁₋₃alkoxy, and halogenated C₁₋₃alkyl;

R² is selected from C₆₋₁₀aryl and C₂₋₁₀heterocyclyl, wherein said C₆₋₁₀aryl and C₂₋₁₀heterocyclyl used in defining R² is optionally substituted by one or more groups selected from halogen, halogenated C₁₋₃alkyl, C₁₋₃alkyl, nitro, C₁₋₃alkoxy, halogenated C₁₋₃alkoxy, hydroxy, hydroxy-C₁₋₃alkyl, amino, C₁₋₃alkoxy-C₁₋₃alkyl, C₂₋₅heterocyclyl-C₁₋₃alkyl, C₁₋₆alkoxycarbonyl, C₁₋₃alkylamino, diC₁₋₃alkyl-amino, and amino-C₁₋₃alkyl; and

R³ is selected from hydrogen and C₁₋₆alkyl; R⁴ is selected from C₁₋₆alkyl, C₃₋₇cycloalkyl, C₂₋₆heterocyclyl-amino, C₂₋₆heterocycliloxy-amino, and C₂₋₆heterocyclyl; wherein said C₁₋₆alkyl, C₃₋₇cycloalkyl, C₂₋₆heterocyclyl-amino, C₂₋₆heterocycliloxy-amino, and C₂₋₆heterocyclyl used in defining R⁴ is optionally substituted by one or more groups selected from halogen, halogenated C₁₋₃alkyl, C₁₋₃alkyl, nitro, C₁₋₃alkoxy, halogenated C₁₋₃alkoxy, hydroxy, hydroxy-C₁₋₃alkyl, amino, C₁₋₃alkoxy-C₁₋₃alkyl, C₁₋₆alkoxycarbonyl, C₁₋



3alkylamino, diC₁₋₃alkyl-amino, and amino-C₁₋₃alkyl; or is selected

25 from azepanyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, isoxazolidinyl, triazolyl, morpholinyl, piperidinyl, thiomorpholinyl, pyridazinyl, piperazinyl, triazinyl or 1,4-dioxo-8-azaspiro[4.5]decan-8-yl; wherein said azepanyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolidinyl,

pyrazolyl, pyrazolinyl, pyrazolidinyl, isoxazolidinyl, trazolyl, morpholinyl, piperidinyl, thiomorpholinyl, piperazinyl, triazinyl and 1,4-dioxo-8-azaspiro[4.5]decan-8-yl are optionally substituted by one or more groups selected from halogen, halogenated C₁₋₃alkyl, C₁₋₃alkyl, nitro, C₁₋₃alkoxy, halogenated C₁₋₃alkoxy, hydroxy, hydroxy-C₁₋₃alkyl, amino, C₁₋₃alkoxy-C₁₋₃alkyl, C₁₋₆alkoxycarbonyl, C₁₋₃alkylamino, diC₁₋₃alkyl-amino, and amino-C₁₋₃alkyl.

3. A compound as claimed in claim 1, wherein

m is selected from 0 and 1;

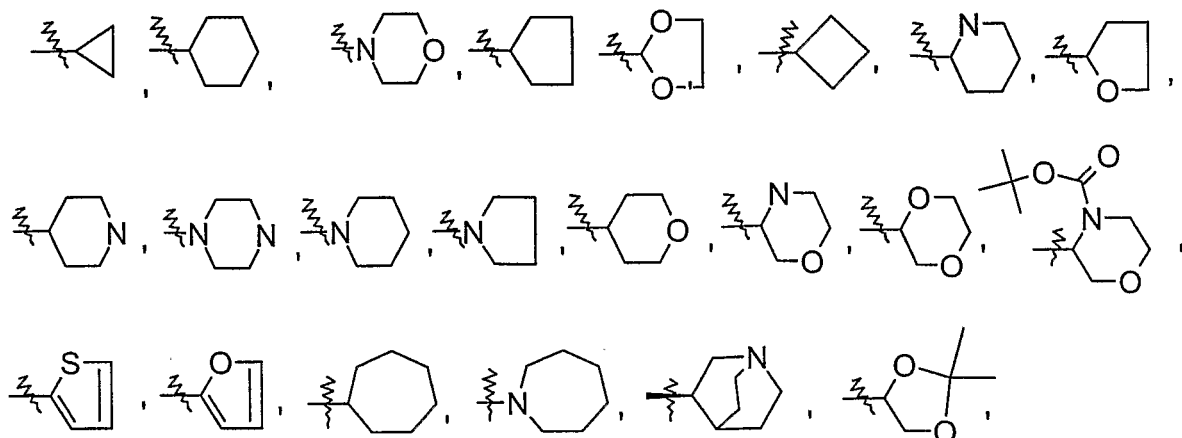
n is selected from 0, 1, 2, 3 and 4;

R¹ is independently selected from halogen, amino, nitro, acetylamino, hydroxyl, C₁₋₃alkoxy, C₁₋₃alkyl, halogenated C₁₋₃alkoxy, and halogenated C₁₋₃alkyl;

R² is selected from phenyl, naphthyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4-oxadiazolyl, indolyl, indolinyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, 1,4-benzodioxanyl, coumarin, dihydrocoumarinyl, 2,3-dihydrobenzofuranyl, 1,2-benzisoxazolyl, 1,3-benzodioxolyl, 2,3-dihydro-1,4-benzodioxinyl, 3,4-dihydro-2H-1,5-benzodioxepinyl, 4H-1,3-benzodioxinyl, benzofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benzimidazolyl, benztriazolyl, thioxanthinyl, carbazolyl, carbolinyl, acridinyl, pyrrolizidinyl, and quinolizidinyl that are optionally substituted by one or more groups selected from halogen, hydroxy, methyl, methoxy, amino, trifluoromethyl, trifluoromethoxy, methoxymethyl, 1*H*-1,2,3-triazolylmethyl and 1*H*-pyrazolylmethyl;

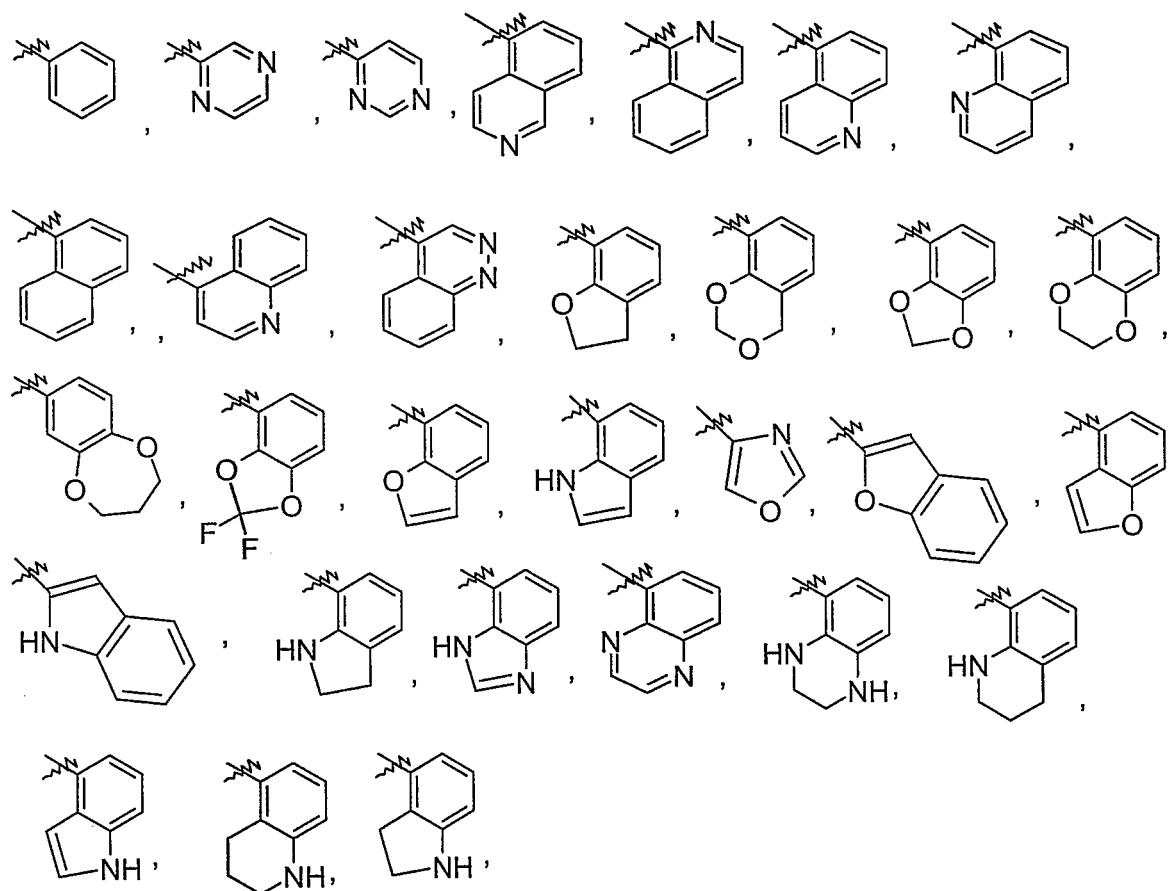
R³ is selected from hydrogen and C₁₋₆ alkyl; and

R⁴ is selected from



pyrrolidin-1-amino, piperidin-1-amino, O-cyclohexylhydroxyamino, O-cyclopentylhydroxyamino, O-cyclobutylhydroxyamino, O-cyclopropylhydroxyamino, and C₁₋₃alkyl that are optionally substituted by one or more groups selected from halogen, amino, aminomethyl, 2-aminoethyl, hydroxy, hydroxymethyl, methyl and ethyl.

4. A compound as claimed in claim 3, wherein R^2 is selected from



that are optionally substituted with one or more groups selected from halogen, methyl, methoxy, hydroxyl, methoxymethyl, 1*H*-1,2,3-triazolylmethyl and 1*H*-1,2-diazolylmethyl.

5

5. A compound as claimed in claim 1, wherein *m* is 1;

n is selected from 0, 1, 2, and 3;

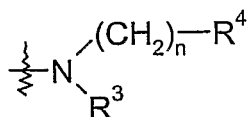
*R*¹ is independently selected from halogen, amino, nitro, acetylamino, hydroxyl, C₁₋₃alkoxy, C₁₋₃alkyl, halogenated C₁₋₃alkoxy, and halogenated C₁₋₃alkyl;

10

*R*² is selected from phenyl, naphthyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4-oxadiazolyl, indolyl, indolinyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, 1,4-benzodioxanyl, coumarin, dihydrocoumarinyl, 2,3-dihydrobenzofuranyl, 1,2-benzisoxazolyl, 1,3-benzodioxolyl, 2,3-dihydro-1,4-benzodioxinyl, 3,4-dihydro-2*H*-1,5-

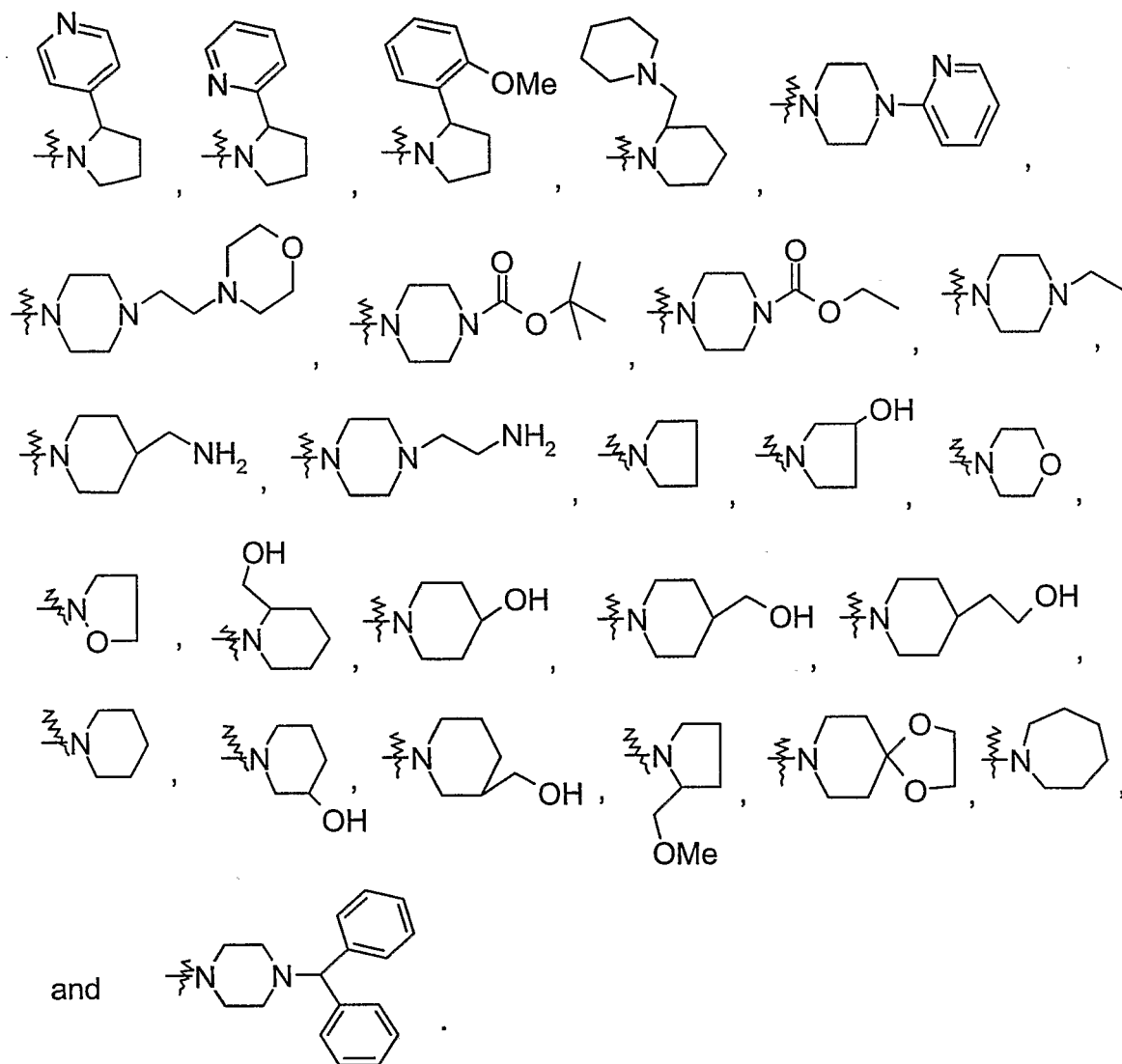
15

benzodioxepinyl, 4H-1,3-benzodioxinyl, benzofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benzimidazolyl, benztriazolyl, thioxanthinyl, carbazolyl, carbolinyl, acridinyl, pyrrolizidinyl, and quinolizidinyl that are optionally substituted by one or more groups selected from halogen, hydroxy, methyl, methoxy, amino, trifluoromethyl, trifluoromethoxy, methoxymethyl, 1*H*-1,2,3-triazolylmethyl, 1*H*-pyrazolylmethyl; and

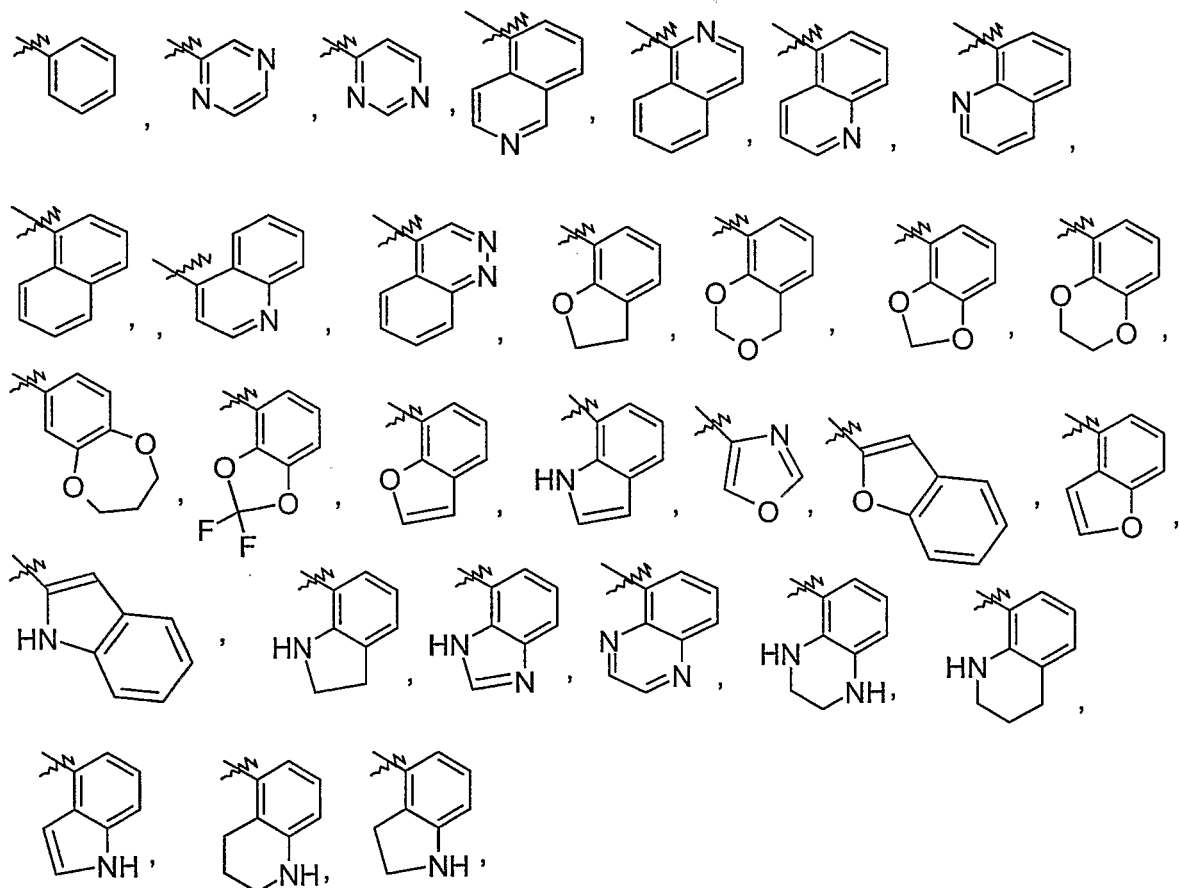


is selected from azetidiny, azepanyl, isoxazolidinyl, morpholinyl, piperazinyl, piperidinyl, pyrrolidinyl, and 1,4-dioxa-8-azaspiro[4.5]decan-8-yl that were optionally substituted with one or more groups selected from halogen, cyano, nitro, methyl, ethyl, hydroxy, hydroxy-methyl, hydroxy-ethyl, amino-methyl, amino-ethyl, methoxy-methyl, methoxy-phenyl, ethoxycarbonyl, tert-butoxycarbonyl, diphenyl-methyl, morpholinyl-eth-2-yl, piperidinyl-methyl and pyridinyl.

6. A compound as claimed in claim 5, $\begin{array}{c} \text{---}(\text{CH}_2)_n\text{---R}^4 \\ \diagup \\ \text{N} \\ \diagdown \\ \text{R}^3 \end{array}$ is selected from



7. A compound as claimed in claim 5 or 6, R^2 is selected from

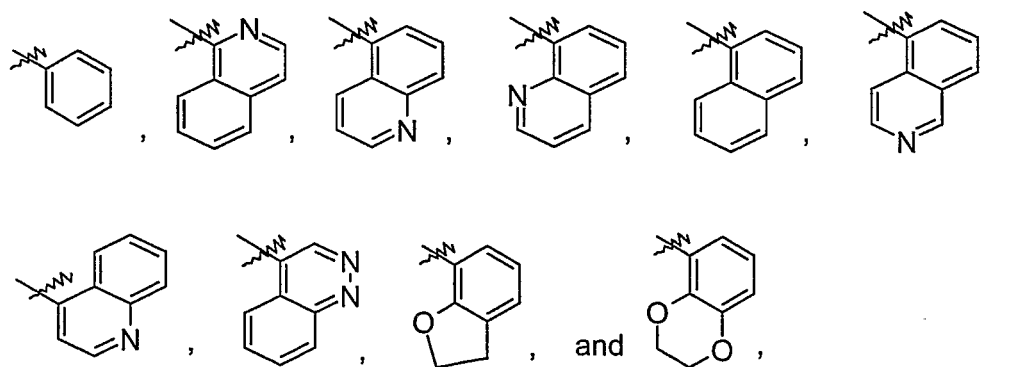


that are optionally substituted with one or more groups selected from halogen, methyl, methoxy, hydroxyl, methoxymethyl, 1*H*-1,2,3-triazolylmethyl and 1*H*-pyrazolylmethyl.

5

8. A compound as claimed in any one of claims 1-7, wherein

R^2 is selected from



that are

optionally substituted with one or more groups selected from halogen, methyl, methoxy, hydroxyl, methoxymethyl, 1*H*-1,2,3-triazolylmethyl and 1*H*-pyrazolylmethyl.

10

9. A compound selected from:

N-[4-Chloro-2-[[[(1-ethyl-2-pyrrolidinyl)methyl]amino]carbonyl]phenyl]-1-naphthalenecarboxamide;

5 *N*-[4-Chloro-2-[[[2-(4-morpholinyl)ethyl]amino]carbonyl]phenyl]-1-naphthalenecarboxamide;

N-[4-Chloro-2-[[4-[2-(4-morpholinyl)ethyl]-1-piperazinyl]carbonyl]phenyl]-1-naphthalenecarboxamide;

10 *N*-[4-Chloro-2-[[[2-(dimethylamino)ethyl]amino]carbonyl]phenyl]-1-naphthalenecarboxamide;

N-[4-Chloro-2-[(4-morpholinylamino)carbonyl]phenyl]-1-naphthalenecarboxamide;

N-[4-Chloro-2-[(4-ethyl-1-piperazinyl)carbonyl]phenyl]-1-naphthalenecarboxamide;

N-[4-Chloro-2-[[[3-(4-morpholinyl)propyl]amino]carbonyl]phenyl]-1-naphthalenecarboxamide;

15 *N*-[4-Chloro-2-[[[4-(piperidinylmethyl)amino]carbonyl]phenyl]-1-naphthalenecarboxamide;

N-[2-[[4-(Aminomethyl)-1-piperidinyl]carbonyl]-4-chlorophenyl]-1-naphthalenecarboxamide;

N-[2-[[4-(2-Aminoethyl)-1-piperazinyl]carbonyl]-4-chlorophenyl]-1-naphthalenecarboxamide;

20 *N*-[4-Chloro-2-[[[2-(1-piperazinyl)ethyl]amino]carbonyl]phenyl]-1-naphthalenecarboxamide;

N-[4-(Acetylamino)-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-1-naphthalenecarboxamide;

N-[4-Amino-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-1-naphthalenecarboxamide;

25 *N*-[4-Chloro-2-[[[(tetrahydro-2*H*-pyran-4-yl)methyl]amino]carbonyl]phenyl]-1-naphthalenecarboxamide;

N-[4-Chloro-2-[[[(cyclopropylmethyl)amino]carbonyl]phenyl]-1-naphthalenecarboxamide;

N-[4-Chloro-2-[(cyclohexylamino)carbonyl]phenyl]-1-naphthalenecarboxamide;

N-[4-Chloro-2-[[[(cyclobutylmethyl)amino]carbonyl]phenyl]-1-naphthalenecarboxamide;

30 *N*-[4-Chloro-2-[[[(cycloheptylmethyl)amino]carbonyl]phenyl]-1-naphthalenecarboxamide;

N-[4-Chloro-2-[[[(2-hydroxycyclohexyl)methyl]amino]carbonyl]phenyl]-1-naphthalenecarboxamide;

- N*-[4-Chloro-2-[(3-hydroxy-1-piperidiny)carbonyl]phenyl]-1-naphthalenecarboxamide;
N-[4-Chloro-2-[[3-(hydroxymethyl)-1-piperidiny]carbonyl]phenyl]-1-naphthalenecarboxamide;
N-[4-Chloro-2-[(hexahydro-1*H*-azepin-1-yl)carbonyl]phenyl]-1-naphthalenecarboxamide;
5 *N*-[4-Chloro-2-(1-pyrrolidinylcarbonyl)phenyl]-1-naphthalenecarboxamide;
N-[4-Chloro-2-[(2-hydroxycyclohexyl)amino]carbonyl]phenyl]-1-naphthalenecarboxamide;
N-[4-Chloro-2-[[[2-(1,3-dioxolan-2-yl)ethyl]amino]carbonyl]phenyl]-1-naphthalenecarboxamide;
10 *N*-[4-Chloro-2-[[[1-(hydroxymethyl)cyclopentyl]amino]carbonyl]phenyl]-1-naphthalenecarboxamide;
N-[4-Chloro-2-[(3-hydroxy-1-pyrrolidinyl)carbonyl]phenyl]-1-naphthalenecarboxamide;
N-[4-Chloro-2-[[2-(2-methoxyphenyl)-1-pyrrolidinyl]carbonyl]phenyl]-1-naphthalenecarboxamide;
15 *N*-[4-Chloro-2-[[[1,3-dioxolan-2-ylmethyl]amino]carbonyl]phenyl]-1-naphthalenecarboxamide;
N-[4-Chloro-2-[[[tetrahydro-2*H*-pyran-4-yl]amino]carbonyl]phenyl]-1-naphthalenecarboxamide;
N-[4-Chloro-2-[[[2-(tetrahydro-2*H*-pyran-4-yl)ethyl]amino]carbonyl]phenyl]-1-naphthalenecarboxamide;
20 *N*-[4-Chloro-2-[[[1,3-dioxolan-2-ylmethyl]methylamino]carbonyl]phenyl]-1-naphthalenecarboxamide;
N-[4-Chloro-2-[[2-(2-pyridinyl)-1-pyrrolidinyl]carbonyl]phenyl]-1-naphthalenecarboxamide;
25 *N*-[4-Chloro-2-[[2-(1-piperidinylmethyl)-1-piperidinyl]carbonyl]phenyl]-1-naphthalenecarboxamide;
N-[2-[[[Cyclohexylmethyl]amino]carbonyl]-4-methylphenyl]-1-naphthalenecarboxamide;
N-[2-[[[Cyclobutylmethyl]amino]carbonyl]-4-methylphenyl]-1-naphthalenecarboxamide;
N-[2-[[[Cyclohexylmethyl]amino]carbonyl]-4-fluorophenyl]-1-naphthalenecarboxamide;
30 *N*-[2-[[[Cyclobutylmethyl]amino]carbonyl]-4-fluorophenyl]-1-naphthalenecarboxamide;
N-[2-[[[cyclohexylmethyl]amino]carbonyl]-6-methoxyphenyl]-1-naphthalenecarboxamide;
N-[2-Chloro-6-[[[cyclohexylmethyl]amino]carbonyl]phenyl]-1-naphthalenecarboxamide;

- N*-[2-[[[(Cyclohexylmethyl)amino]carbonyl]-6-methylphenyl]-1-naphthalenecarboxamide;
N-[5-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-1-naphthalenecarboxamide;
N-[3-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-1-naphthalenecarboxamide;
N-[3-Chloro-2-[[[(cyclobutylmethyl)amino]carbonyl]phenyl]-1-naphthalenecarboxamide;
5 *N*-[2-[[[(Cyclohexylmethyl)amino]carbonyl]-3-methylphenyl]-1-naphthalenecarboxamide;
N-[2-[[[(Cyclohexylmethyl)amino]carbonyl]-4,5-dimethoxyphenyl]-1-naphthalenecarboxamide;
N-[2-[[[(Cyclohexylmethyl)amino]carbonyl]-3-methoxyphenyl]-1-naphthalenecarboxamide;
N-[2-[[[(Cyclobutylmethyl)amino]carbonyl]-3-methoxyphenyl]-1-naphthalenecarboxamide;
10 *N*-[2-[[[(Cyclohexylmethyl)amino]carbonyl]-3-hydroxyphenyl]-1-naphthalenecarboxamide;
N-[2-[[[(cyclobutylmethyl)amino]carbonyl]-3-hydroxyphenyl]-1-naphthalenecarboxamide;
N-[4-chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-8-quinolinecarboxamide;
N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-2-quinolinecarboxamide;
N-[4-chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-2-quinoxalinecarboxamide;
15 *N*-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-1-naphthalenecarboxamide;
N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-3-quinolinecarboxamide;
N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-2-pyrazinecarboxamide;
N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-3-pyridazinecarboxamide;
N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-2-naphthalenecarboxamide;
20 *N*-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-4-pyridinecarboxamide;
N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-3-pyridinecarboxamide;
2-(Benzoylamino)-5-chloro-*N*-(cyclohexylmethyl)-benzamide;
N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-3,4-dihydro-2*H*-1,5-benzodioxepin-7-carboxamide;
25 *N*-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-2,3-dihydro-7-benzofurancarboxamide;
N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-1-isoquinolinecarboxamide;
N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-4-quinolinecarboxamide;
N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-4-cinnolinecarboxamide;
30 *N*-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-2-methoxy-1-naphthalenecarboxamide;
N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-2-pyridinecarboxamide;

N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-2-fluoro-3-(trifluoromethyl)-benzamide;

N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-2,3-difluoro- benzamide;

3-Chloro-*N*-[4-chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-2-fluoro- benzamide;

5 *N*-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-2,3-dimethyl- benzamide;

N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-3-fluoro-2-(trifluoromethyl)-benzamide;

N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-2,2-difluoro-1,3-benzodioxole-4-carboxamide;

10 *N*-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-6-fluoro-4*H*-1,3-benzodioxin-8-carboxamide;

N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-2-methyl-3-(trifluoromethyl)-benzamide;

15 3-Chloro-*N*-[4-chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-2-methyl-benzamide;

N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-2,3-dimethoxy- benzamide;

N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-3-methoxy-2-methyl-benzamide;

N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]- 5-isoquinolinecarboxamide;

20 6-Chloro-*N*-[4-chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-2-fluoro-3-methyl-benzamide;

2-Chloro-*N*-[4-chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]-3-(trifluoromethyl)-benzamide;

N-[4-Chloro-2-[[[(cyclohexylmethyl)amino]carbonyl]phenyl]- 5-quinolinecarboxamide;

25 *N*-[2-[[[(Cyclohexylmethyl)amino]carbonyl]-4-methoxyphenyl]-1-naphthalenecarboxamide;

N-(3-Methoxy-2-{{(2-piperidin-1-ylethyl)amino}carbonyl}phenyl)-1-naphthamide;

N-(2-{{(1,4-Dioxan-2-ylmethyl)amino}carbonyl}-3-methoxyphenyl)-1-naphthamide;

N-(3-Methoxy-2-{{(2-morpholin-4-ylethyl)amino}carbonyl}phenyl)-1-naphthamide;

N-(3-Methoxy-2-{{(2-pyrrolidin-1-ylethyl)amino}carbonyl}phenyl)-1-naphthamide;

30 *N*-{3-Methoxy-2-[(tetrahydro-2*H*-pyran-4-ylamino)carbonyl]phenyl}-1-naphthamide;

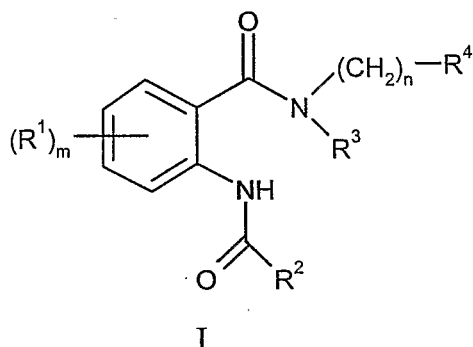
tert-Butyl 3-({[2-methoxy-6-(1-naphthoylamino)benzoyl]amino}methyl)morpholine-4-carboxylate;

N-{2-[(1-Azabicyclo[2.2.2]oct-3-ylamino)carbonyl]-3-methoxyphenyl}-1-naphthamide;
N-(3-Methoxy-2-[(morpholin-3-ylmethyl)amino]carbonyl]phenyl)-1-naphthamide;
N-(3-Methoxy-2-[(morpholin-4-ylamino)carbonyl]phenyl)-1-naphthamide;
N-(3-Methoxy-2-[(piperidin-1-ylamino)carbonyl]phenyl)-1-naphthamide;
5 *N*-(2-[(2-Hydroxyethyl)amino]carbonyl)-3-methoxyphenyl)-1-naphthamide;
N-(2-[(2-Hydroxypropyl)amino]carbonyl)-3-methoxyphenyl)-1-naphthamide;
N-(2-[(2-Hydroxybutyl)amino]carbonyl)-3-methoxyphenyl)-1-naphthamide;
and pharmaceutically acceptable salts thereof.

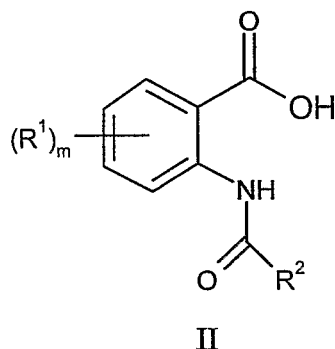
- 10 10. A compound according to any one of claims 1-9 for use as a medicament.
11. The use of a compound according to any one of claims 1-9 in the manufacture of a medicament for the therapy of pain.
- 15 12. The use of a compound according to any one of claims 1-9 in the manufacture of a medicament for the therapy of functional gastrointestinal disorders.
13. The use of a compound according to any one of claims 1-9 in the manufacture of a medicament for the treatment of irritable bowel syndrome.
- 20 14. The use of a compound according to any one of claims 1-9 in the manufacture of a medicament for the treatment of anxiety, cancer, multiple sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's disease, and cardiovascular disorders.
- 25 15. A pharmaceutical composition comprising a compound according to any one of claims 1-9 and a pharmaceutically acceptable carrier.
16. A method for the therapy of functional gastrointestinal disorders in a warm-blooded animal, comprising the step of administering to said animal in need of such therapy a
30 therapeutically effective amount of a compound according to any one of claims 1-9.

17. A method for the therapy of irritable bowel syndrome in a warm-blooded animal, comprising the step of administering to said animal in need of such therapy a therapeutically effective amount of a compound according to any one of claims 1-9.

18. A method for preparing a compound of formula I,



comprising the step of reacting a compound of formula II,



with a compound of $R^3(CH_2)_nR^4NH$, in the presence of a base, such as an DIPEA, a solvent such as DMF, and optionally a coupling reagent, such as HATU, wherein:

m is selected from 0, 1 and 2;

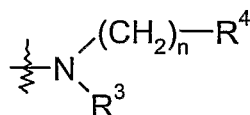
n is selected from 0, 1, 2, 3, 4 and 5;

R^1 is independently selected from halogen, cyano, amino, nitro, C_{1-6} alkylamino, di C_{1-6} alkylamino, acetylamino, hydroxyl, C_{1-6} alkoxy, C_{1-6} alkyl, halogenated C_{1-6} alkoxy, C_{1-6} alkenyl, and halogenated C_{1-6} alkyl;

R^2 is selected from C_{6-10} aryl and C_{2-10} heterocyclyl; wherein said C_{6-10} aryl and C_{2-10} heterocyclyl used in defining R^2 is optionally substituted by one or more groups selected from halogen, halogenated C_{1-6} alkyl, C_{1-6} alkyl, cyano, nitro, C_{1-6} alkoxy, halogenated C_{1-6} alkoxy, hydroxy, hydroxy- C_{1-6} alkyl, amino, C_{1-6} alkoxy- C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkyl,

alkoxycarbonyl, C₁₋₆alkylamino, diC₁₋₆alkyl-amino, amino-C₁₋₆alkyl, C₂₋₅heterocyclyl-C₁₋₃alkyl, C₃₋₆cycloalkyl, C₂₋₆heteroaryl, heteroaryl-C₁₋₆alkyl, C₆₋₁₀aryl, and C₆₋₁₀aryl-C₁₋₆alkyl; and

R³ is selected from hydrogen and C₁₋₆alkyl; R⁴ is selected from C₁₋₆alkyl, C₃₋₇cycloalkyl, C₄₋₇cycloalkenyl, C₆₋₁₀aryl, C₂₋₆heterocyclyl-amino, C₂₋₆heterocyclyloxy-amino, and C₂₋₆heterocyclyl; wherein said C₁₋₆alkyl, C₃₋₇cycloalkyl, C₄₋₇cycloalkenyl, C₆₋₁₀aryl, C₂₋₆heterocyclyl-amino, C₂₋₆heterocyclyloxy-amino, and C₂₋₆heterocyclyl used in defining R⁴ is optionally substituted by one or more groups selected from halogen, halogenated C₁₋₆alkyl, C₁₋₆alkyl, cyano, nitro, C₁₋₆alkoxy, halogenated C₁₋₆alkoxy, hydroxy, hydroxy-C₁₋₆alkyl, amino, C₁₋₆alkoxy-C₁₋₆alkyl, C₁₋₆alkylcarbonyl, C₁₋₆alkoxycarbonyl, C₁₋₆alkylamino, diC₁₋₆alkyl-amino, amino-C₁₋₆alkyl, C₃₋₆cycloalkyl, C₂₋₆heteroaryl, heteroaryl-



C₁₋₆alkyl, C₆₋₁₀aryl, and C₆₋₁₀aryl-C₁₋₆alkyl; or is selected from a C₂₋₁₀heterocyclyl, which is optionally substituted by one or more groups selected from halogen, halogen substituted C₁₋₆alkyl, C₁₋₆alkyl, cyano, nitro, C₁₋₆alkoxy, halogenated C₁₋₆alkoxy, hydroxy, hydroxy-C₁₋₆alkyl, amino, C₁₋₆alkoxy-C₁₋₆alkyl, C₁₋₆alkylcarbonyl, C₁₋₆alkoxycarbonyl, C₁₋₆alkylamino, diC₁₋₆alkyl-amino, amino-C₁₋₆alkyl, C₃₋₆cycloalkyl, C₂₋₆heteroaryl, heteroaryl-C₁₋₆alkyl, C₆₋₁₀aryl, and C₆₋₁₀aryl-C₁₋₆alkyl.