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(54) Title: NOVEL NPH INSULIN PREPARATIONS

(57) Abstract: This invention relates to NPH-insulin (crystalline preparations) that are prepared in the presence of certain high-affinity ligands for the HisB10 Zn^{2+}-, sites of the R-state insulin hexamer. Preparation of NPH-insulin in the presence of high-affinity ligand results in crystal-line NPH-insulin suspensions that are absorbed more slowly from subcutis than regular NPH-insulin. Hence the resulting action profile is longer and the spike is less pronounced than observed with regular NPH-insulin.

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NOVEL NPH INSULIN PREPARATIONS

FIELD OF THE INVENTION

This invention relates to novel NPH insulin crystalline preparations comprising high-affinity ligands for the HisB10 Zn^{2+}-sites of the R-state insulin hexamer.

BACKGROUND OF THE INVENTION

Diabetes mellitus is a common disorder of glucose metabolism. The disease is characterized by hyperglycemia and may be classified as type 1 diabetes, sometimes termed insulin-dependent diabetes mellitus, or type 2 diabetes, which is sometimes termed non-insulin-dependent. Insulin dependent diabetes mellitus is characterized by severely diminished or absent production of endogenous insulin. This chronic condition must be treated with daily subcutaneous injections of insulin to maintain a reasonably normal blood glucose level. Similar injections are also common in later stage type 2 diabetes. The use of insulin as a therapeutic agent for this treatment is usually considered one of the outstanding successes of modern medicine. However, the therapy has its associated problems mainly because injection of insulin does not lead to normal diurnal concentrations of insulin in the blood.

The kinetics of absorption from the subcutaneous tissue of fast acting human insulin is too slow and lasts too long to precisely mimic the peak of insulin which is normally secreted within minutes in response to carbohydrate ingestion during a meal. More importantly, the action profile of the most commonly used crystalline long-acting basal insulin show a spike, i.e. a high concentration of relatively short duration of insulin in the blood, within a few hours after injection. Also, the total duration of action is somewhat too short for once daily injection, and the absorption times show some fluctuation from day to day leading to poor reproducibility of the basal insulin level.

Long-term studies have shown that the complications of diabetes such as retinopathy and nephropathy can only be prevented or delayed by an intensive treatment regimen aiming at normalization of blood glucose. Consequently, the major challenge of the insulin-replacement therapy consists in reproducing the complex pattern of insulin secretion dynamics in healthy individuals, to achieve constant blood glucose in both basal and meal-related situations.

The most widely used long acting insulin is a neutral crystalline suspension, i.e. NPH insulin, comprising a crystalline complex of human insulin (or an analogue thereof), zinc ion and protamine sulphate together with a suitable preservative such as phenol, m-cresol, or mixtures thereof. In addition, the preparations usually contain a buffering substance such as phosphate and an isotonicity agent such as glycerol, mannitol or sodium chloride.

When the suspension is injected into the subcutaneous tissue, the delayed action is believed to originate from the rate-limiting dissolution of the NPH-insulin crystals in the subcutaneous tissue fluids. Thus the main determinant for the spike in the action profile as well as the total length of duration of action is thought to be the inherent solubility of the NPH-insulin crystal in the subcutis. On the other hand, the poorly reproducible absorption times often encountered with NPH insulin are thought to originate from difficulties in resuspending the vial before injection which may lead to variations in the dose actually delivered from one injection to another. Moreover, the rate of dissolution at the site of injection depends to some extent on the local blood flow which is influenced by e.g. exercise and temperature adding further elements to the poorly reproducible absorption times. Taken together, these factors are considered to limit the inherent quality of the action profile obtained from NPH-insulin.

SUMMARY OF THE INVENTION

It has now surprisingly been found that NPH-insulin (crystalline preparations) may be prepared in the presence of certain high-affinity ligands for the HisB10 Zn^{2+}-sites of the R-state insulin hexamer. Preparation of NPH-insulin in the presence of high-affinity ligand results in crystalline NPH-insulin suspensions that are absorbed more slowly from subcutis than regular NPH-insulin. Hence the resulting action profile is longer and the spike is less pronounced than observed with regular NPH-insulin. The novel NPH-insulin also shows better physical and chemical stability than regular NPH-insulin.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 (example 1011) is a graphic representation of glucose utilization after subcutaneous injection of a NPH preparation showing the effects of stoichiometric and excess concentration of 4-[3-(1H-Tetrazol-5-yl)-carbazol-9-ylmethyl]-benzoic acid compared to Zn^{2+} .

DEFINITIONS

The following is a detailed definition of the terms used to describe the invention:

"Halogen" designates an atom selected from the group consisting of F, Cl, Br and I.

The term "C_1-C_6-alkyl" as used herein represents a saturated, branched or straight hydrocarbon group having from 1 to 6 carbon atoms. Representative examples include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, n-pentyl, isopentyl, neopentyl, *tert*-pentyl, n-hexyl, isohexyl and the like.

The term "C_1-C_6-alkylene" as used herein represents a saturated, branched or straight bivalent hydrocarbon group having from 1 to 6 carbon atoms. Representative examples include, but are not limited to, methylene, 1,2-ethylene, 1,3-propylene, 1,2-propylene, 1,4-butylene, 1,5-pentylene, 1,6-hexylene, and the like.

The term "C_2-C_6-alkenyl" as used herein represents a branched or straight hydrocarbon group having from 2 to 6 carbon atoms and at least one double bond. Examples of such groups include, but are not limited to, vinyl, 1-propenyl, 2-propenyl, iso-propenyl, 1,3-butadienyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl and the like.

The term "C_2-C_6-alkynyl" as used herein represents a branched or straight hydrocarbon group having from 2 to 6 carbon atoms and at least one triple bond. Examples of such groups include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 2,4-hexadiynyl and the like.

The term "C_1-C_6-alkoxy" as used herein refers to the radical -O-C_1-C_6-alkyl, wherein C_1-C_6-alkyl is as defined above. Representative examples are methoxy, ethoxy, n-propoxy, isopropoxy, butoxy, *sec*-butoxy, *tert*-butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy and the like.

The term "C_3-C_8-cycloalkyl" as used herein represents a saturated, carbocyclic group having from 3 to 8 carbon atoms. Representative examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like.

The term "C_{4-8}-cycloalkenyl" as used herein represents a non-aromatic, carbocyclic group having from 4 to 8 carbon atoms containing one or two double bonds. Representative examples are 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 2-cycloheptenyl, 3-cycloheptenyl, 2-cyclooctenyl, 1,4-cyclooctadienyl and the like.

The term "heterocyclyl" as used herein represents a non-aromatic 3 to 10 membered ring containing one or more heteroatoms selected from nitrogen, oxygen and sulphur and optionally

containing one or two double bonds. Representative examples are pyrrolidinyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, aziridinyl, tetrahydrofuranyl and the like.

The term "aryl" as used herein is intended to include carbocyclic, aromatic ring systems such as 6 membered monocyclic and 9 to 14 membered bi- and tricyclic, carbocyclic, aromatic ring systems. Representative examples are phenyl, biphenylyl, naphthyl, anthracenyl, phenanthrenyl, fluorenyl, indenyl, azulenyl and the like. Aryl is also intended to include the partially hydrogenated derivatives of the ring systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 1,2,3,4-tetrahydronaphthyl, 1,4-dihydronaphthyl and the like.

The term "arylene" as used herein is intended to include divalent, carbocyclic, aromatic ring systems such as 6 membered monocyclic and 9 to 14 membered bi- and tricyclic, divalent, carbocyclic, aromatic ring systems. Representative examples are phenylene, biphenylylene, naphthylene, anthracenylene, phenanthrenylene, fluorenylene, indenylene, azulenylene and the like. Arylene is also intended to include the partially hydrogenated derivatives of the ring systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 1,2,3,4-tetrahydronaphthylene, 1,4-dihydronaphthylene and the like.

The term "aryloxy" as used herein denotes a group -O-aryl, wherein aryl is as defined above.

The term "aroyl" as used herein denotes a group -C(O)-aryl, wherein aryl is as defined above.

The term "heteroaryl" as used herein is intended to include aromatic, heterocyclic ring systems containing one or more heteroatoms selected from nitrogen, oxygen and sulphur such as 5 to 7 membered monocyclic and 8 to 14 membered bi- and tricyclic aromatic, heterocyclic ring systems containing one or more heteroatoms selected from nitrogen, oxygen and sulphur. Representative examples are furyl, thienyl, pyrrolyl, pyrazolyl, 3-oxopyrazolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5- triazinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, thiadiazinyl, indolyl, isoindolyl, benzofuryl, benzothienyl, indazolyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, purinyl, quinazolinyl, quinolizinyl, quinolinyl, isoquinolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, azepinyl, diazepinyl, acridinyl, thiazolidinyl, 2-thiooxothiazolidinyl and the like. Heteroaryl is also intended to include the partially hydrogenated derivatives of the ring systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 2,3-dihydrobenzofuranyl, pyrrolinyl, pyrazolinyl, indolinyl, oxazolidinyl, oxazolinyl, oxazepinyl and the like.

The term "heteroarylene" as used herein is intended to include divalent, aromatic, heterocyclic ring systems containing one or more heteroatoms selected from nitrogen, oxygen and sulphur such as 5 to 7 membered monocyclic and 8 to 14 membered bi- and tricyclic aromatic, heterocyclic ring systems containing one or more heteroatoms selected from nitrogen, oxygen and sulphur. Representative examples are furylene, thienylene, pyrrolylene, oxazolylene, thiazolylene, imidazolylene, isoxazolylene, isothiazolylene, 1,2,3-triazolylene, 1,2,4-triazolylene, pyranylene, pyridylene, pyridazinylene, pyrimidinylene, pyrazinylene, 1,2,3-triazinylene, 1,2,4-triazinylene, 1,3,5- triazinylene, 1,2,3-oxadiazolylene, 1,2,4-oxadiazolylene, 1,2,5-oxadiazolylene, 1,3,4-oxadiazolylene, 1,2,3-thiadiazolylene, 1,2,4-thiadiazolylene, 1,2,5-thiadiazolylene, 1,3,4-thiadiazolylene, tetrazolylene, thiadiazinylene, indolylene, isoindolylene, benzofurylene, benzothienylene, indazolylene, benzimidazolylene, benzthiazolylene, benzisothiazolylene, benzoxazolylene, benzisoxazolylene, purinylene, quinazolinylene, quinolizinylene, quinolinylene, isoquinolinylene, quinoxalinylene, naphthyridinylene, pteridinylene, carbazolylene, azepinylene, diazepinylene, acridinylene and the like. Heteroaryl is also intended to include the partially hydrogenated derivatives of the ring systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 2,3-dihydrobenzofuranylene, pyrrolinylene, pyrazolinylene, indolinylene, oxazolidinylene, oxazolinylene, oxazepinylene and the like.

The term "ArG1" as used herein is intended to include an aryl or arylene radical as applicable, where aryl or arylene are as defined above but limited to phenyl, biphenylyl, naphthyl, anthracenyl, phenanthrenyl, fluorenyl, indenyl, and azulenyl as well as the corrresponding divalent radicals.

The term "ArG2" as used herein is intended to include an aryl or arylene radical as applicable, where aryl or arylene are as defined above but limited to phenyl, biphenylyl, naphthyl, fluorenyl, and indenyl, as well as the corrresponding divalent radicals.

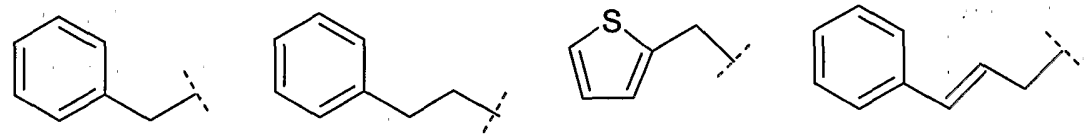
The term "Het1" as used herein is intended to include a heteroaryl or heteroarylene radical as applicable, where heteroaryl or heteroarylene are as defined above but limited to furyl, thienyl, pyrrolyl, pyrazolyl, 3-oxopyrazolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5- triazinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, thiadiazinyl, indolyl, isoindolyl, benzofuryl, benzothienyl, indazolyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, purinyl, quinazolinyl, quinolizinyl, quinolinyl, isoquinolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, azepinyl, di-

azepinyl, acridinyl, thiazolidinyl, 2-thiooxothiazolidinyl, as well as the corrresponding divalent radicals.

The term "Het2" as used herein is intended to include a heteroaryl or heteroarylene radical as applicable, where heteroaryl or heteroarylene are as defined above but limited to furyl, thienyl, pyrrolyl, pyrazolyl, 3-oxopyrazolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5- triazinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, thiadiazinyl, indolyl, isoindolyl, benzofuryl, benzothienyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, quinolinyl, isoquinolinyl, quinoxalinyl, carbazolyl, thiazolidinyl, 2-thiooxothiazolidinyl, as well as the corrresponding divalent radicals.

The term "Het3" as used herein is intended to include a heteroaryl or heteroarylene radical as applicable, where heteroaryl or heteroarylene are as defined above but limited to furyl, thienyl, pyrrolyl, pyrazolyl, 3-oxopyrazolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyridyl, tetrazolyl, indolyl, isoindolyl, benzofuryl, benzothienyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, quinolyl, isoquinolyl, quinoxalinyl, carbazolyl, thiazolidinyl, 2-thiooxothiazolidinyl, as well as the corrresponding divalent radicals.

"Aryl-C_1-C_6-alkyl", "heteroaryl-C_1-C_6-alkyl", "aryl-C_2-C_6-alkenyl" etc. is intended to mean C_1-C_6-alkyl or C_2-C_6-alkenyl as defined above, substituted by an aryl or heteroaryl as defined above, for example:



The term "optionally substituted" as used herein means that the groups in question are either unsubstituted or substituted with one or more of the substituents specified. When the groups in question are substituted with more than one substituent the substituents may be the same or different.

Certain of the above defined terms may occur more than once in the structural formulae, and upon such occurrence each term shall be defined independently of the other.

Furthermore, when using the terms "independently are" and "independently selected from" it should be understood that the groups in question may be the same or different.

The term "protamine" as used herein refers to a mixture of strongly basic proteins usually obtained from fish sperm. "protamine" can refer to a relatively salt-free preparation of the proteins, sometimes termed protamine base. "Protamine" also refers to preparations comprising salts of the proteins. Even though concentrations are commonly given as concentration of protamine sulphate in this application, the person skilled in the art will readily be able to convert this to other protamine preparations.

The terms "treatment" and "treating" as used herein means the management and care of a patient for the purpose of combating a disease, disorder or condition. The term is intended to include the delaying of the progression of the disease, disorder or condition, the alleviation or relief of symptoms and complications, and/or the cure or elimination of the disease, disorder or condition. The patient to be treated is preferably a mammal, in particular a human being.

The term "fragment" as used herein is intended to mean a bivalent chemical group

The term "Neutral amino acid" as used herein is intended to mean any natural (codable) and non-natural amino acid, including α- or β-aminocarboxylic acids, including D-isomers of these (when applicable) without charges at physiologically relevant pH in the side chain, such as glycine, alanine, β-alanine, valine, leucine, isoleucine, phenylalanine, tyrosine, aspargine, glutamine, cysteine, methionine, 3-aminobenzoic acid, 4-aminobenzoic acid or the like.

The term "positively charged group" as used herein is intended to mean any pharmaceutically acceptable group that contains a positive charge at physiologically relevant pH, such as amino (primary, secondary and tertiary), ammonium and guanidino groups.

The term "*α* amino acid" as used herein is intended to mean mean any natural (codable) and non-natural α-aminocarboxylic acid, including D-isomers of these.

The term "*β* amino acid" as used herein is intended to mean any β-aminocarboxylic acid, such as β-alanine, isoserine or the like.

When in the specification or claims mention is made of groups of compounds such as carboxylates, dithiocarboxylates, phenolates, thiophenolates, alkylthiolates, sulfonamides, imidazoles, triazoles, 4-cyano-1,2,3-triazoles, benzimidazoles, benzotriazoles, purines, thiazolidinediones, tetrazoles, 5-mercaptotetrazoles, rhodanines, N-hydroxyazoles, hydantoines, thiohydantoines, naphthoic acids and salicylic acids, these groups of compounds are intended to include also derivatives of the compounds from which the groups take their name.

The term insulin as used herein refers to naturally produced insulin or recombinantly produced insulin. Recombinant insulin may be produced in any suitable host cell, for example the host cells may be bacterial, fungal (including yeast), insect, animal or plant cells.

By "analogue of human insulin" as used herein (and related expressions) is meant human insulin in which one or more amino acids have been deleted and/or replaced by other amino acids, including non-codeable amino acids, or human insulin comprising additional amino acids, i.e. more than 51 amino acids, such that the resulting analogue possesses insulin activity

The expression "insulin derivative" as used herein (and related expressions) refers to human insulin or an analogue thereof in which at least one organic substituent is bound to one or more of the amino acids.

The term "desB30" and the like as used herein is intended to mean meant a natural insulin B chain or an analogue thereof lacking the B30 amino acid residue.

The amino acid residues are indicated in the three letter amino acid code or the one letter amino code.

The terms "B1", "A1" and the like as used herein is intended to mean the amino acid residue in position 1 in the B chain of insulin or analogue thereof (counted from the N-terminal end) and the amino acid residue in position 1 in the A chain of insulin or analogue thereof (counted from the N-terminal end), respectively..

The term "phenolic compound" or similar expressions as used herein refers to a chemical compound in which a hydroxyl group is bound directly to a benzene or substituted benzene ring. Examples of such compounds include, but are not limited to, phenol, o-cresol, m-cresol and p-cresol.

The term "physiologically relevant pH" as used herein is intended to mean a pH of about 7.1 to 7.9.

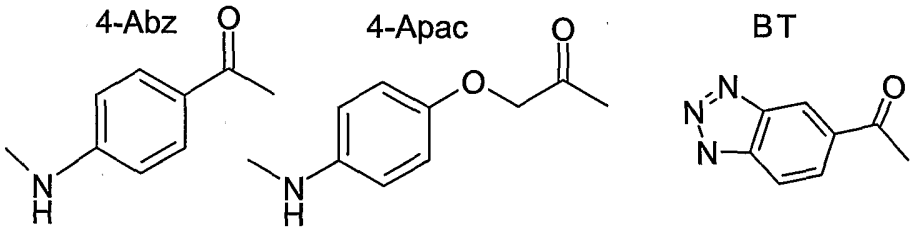
The term "putative insulin hexamer" or similar expressions as used herein is refers to six insulin molecules which may combine to form an insulin hexamer. The chemical environment the insulin is in may determine that the insulin is not always in hexamer form. Thus, a ratio of e.g. 2 moles of Zinc ions per mole putative insulin hexamer corresponds to a ratio of 1 mole per 3 moles insulin monomer regardless of the state of the insulin.

Abbreviations:

4H3N	4-hydroxy-3-nitrobenzoic acid
AcOH	acetic acid

BT	Benzotriazol-5-oyl
DMF	N,N-Dimethylformamide
DMSO	Dimethylsulfoxide
DIC	Diisopropylcarbodiimide
EDAC	1-ethyl-3-(3'-dimethylamino-propyl)carbodiimide, hydrochloride
Fmoc	9*H*-Fluorene-9-ylmethoxycarbonyl
HOAt	1-hydroxy-7-azabenzotriazole
HOBT	1-Hydroxybenzotriazole
NMP	N-methyl-2-pyrrolidone
TFA	Trifluoroacetic acid

Abbreviations for non-natural amino acid residues:



DESCRIPTION OF THE INVENTION

Regular NPH-insulin is a crystalline complex between the R-state insulin hexamer and protamine (usually originating from salmon or herring). The hexamer component of the complex normally has additional small molecules bound to the known binding sites of the R6 insulin, i.e., preservative molecules such as phenol or m-cresol bind to six hydrophobic pockets formed in the dimer-dimer interfaces and anions from added buffers and salts (e.g. chloride) may bind to the two His^{B10} Zn^{2+} sites residing on the 3-fold symmetry axis of the hexamer.

In solution, anions such as chloride bind to the R-state His^{B10} Zn^{2+}-site with modest affinity hence providing little stabilization of the hexamer. However, ligands with substantially higher affinity for the His^{B10} Zn^{2+}-site may be found and characterized by using a fluorescence based competition assay which is based on the displacement of 5-(4-dimethylaminobenzylidene)-thiazolidine-2,4-dione from the R-state His^{B10} Zn^{2+}-site by the incoming ligand in question.

The present invention is based on the discovery that NPH-insulin crystals may be formed in the presence of certain high-affinity ligands for the His^{B10} Zn^{2+} sites of the R-state hexamer. When the ligands are present along with insulin, Zn^{2+}, and optionally phenolic preservative, buffers and isotonicity agents, the NPH-insulin crystals still form upon combination with protamine. Alternatively, regular NPH-insulin crystals without presence of high-affinity ligands for the His^{B10} Zn^{2+} sites of the R-state hexamer may be formed initially and the ligand may then be incorporated by subsequent addition of the ligand to the crystalline suspension. The novel NPH-insulin complex has several advantages over regular NPH-insulin: When the crystalline suspension is injected subcutaneously into pigs, the absorption half-life is significantly increased compared to regular NPH-insulin (see example 1011). Moreover, the action profile of the novel NPH-preparation is longer and smoother than that obtained with regular NPH-insulin. Finally, the physical and chemical stability is significantly enhanced over the reference preparation.

Suitable ligands according to this invention are characterized by a) having high affinity to His^{B10} Zn^{2+} site of the R-state hexamer (e.g. K_d < 10 µM) as measured in the TZD-assay for quantitation of ligands binding to the R-state His^{B10} Zn^{2+} or the 4H3N-assay and b) being capable of forming NPH crystals when included along with the zinc-insulin in the preparation, i.e. the presence of the bound ligand does not impede normal complex formation with protamine (co-crystallization mode). Alternatively, the regular insulin-protamine crystalline complex without presence of high-affinity ligands for the His^{B10} Zn^{2+} sites of the R-state hexamer may be formed initially and the ligand incorporated subsequently by addition of the ligand to the crystalline suspension (soaking mode)

The present invention thus provides in embodiment 1 a pharmaceutical preparation comprising

- Insulin
- Protamine
- Zinc ions
- A ligand that binds reversibly to a His^{B10} Zn^{2+} site of an R-state insulin hexamer, wherein said ligand is selected from the group consisting of carboxylates, dithiocarboxylates, phenolates, thiophenolates, alkylthiolates, sulfonamides, imidazoles, triazoles, 4-cyano-1,2,3-triazoles, benzimidazoles, benzotriazoles, purines, thymines, thiazolidinediones, tetrazoles, 5-mercaptotetrazoles, rhodanines, N-hydroxyazoles, hydantoines, thiohydantoines, naphthoic acids and salicylic acids, or any enantiomer,

diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

Embodiment 2. A pharmaceutical preparation according to embodiment 1 wherein the insulin preparation comprises 60 to 3000 nmol/ml of insulin.

Embodiment 3. A pharmaceutical preparation according to embodiment 2 wherein the insulin preparation comprises 240 to 1200 nmol/ml of insulin.

Embodiment 4. A pharmaceutical preparation according to embodiment 3 wherein the insulin preparation comprises about 600 nmol/ml of insulin.

Embodiment 5. A pharmaceutical preparation according to any one of the embodiments 1 to 4 wherein the insulin is selected from the group consisting of human insulin, an analogue of human insulin, a derivative of human insulin, and combinations of any of these.

Embodiment 6. A pharmaceutical preparation according to embodiment 5 wherein the insulin is an analogue of human insulin selected from the group consisting of

i. An analogue wherein position B28 is Asp, Glu, Lys, Leu, Val, or Ala and position B29 is Lys or Pro;

ii. An analogue wherein position B3 is Lys and position B29 is Glu; and

iii. des(B28-B30), des(B27) or des(B30) human insulin.

Embodiment 7. A pharmaceutical preparation according to embodiment 6, wherein the insulin is an analogue of human insulin wherein position B28 is Asp or Lys, and position B29 is Lys or Pro.

Embodiment 8. A pharmaceutical preparation according to embodiment 6 wherein the insulin is des(B30) human insulin.

Embodiment 9. A pharmaceutical preparation according to embodiment 5 wherein the insulin is a derivative of human insulin having one or more lipophilic substituents.

Embodiment 10. A pharmaceutical preparation according to embodiment 9 wherein the insulin derivative is selected from the group consisting of B29-N$^{\varepsilon}$-myristoyl-des(B30) human insulin, B29-N$^{\varepsilon}$-palmitoyl-des(B30) human insulin, B29-N$^{\varepsilon}$-myristoyl human insulin, B29-N$^{\varepsilon}$-palmitoyl human insulin, B28-N$^{\varepsilon}$-myristoyl Lys^{B28} Pro^{B29} human insulin, B28-N$^{\varepsilon}$-palmitoyl Lys^{B28} Pro^{B29} human insulin, B30-N$^{\varepsilon}$-myristoyl-Thr^{B29}Lys^{B30} human insulin, B30-N$^{\varepsilon}$-palmitoyl-Thr^{B29}Lys^{B30} human insulin, B29-N$^{\varepsilon}$-(N-palmitoyl-γ-glutamyl)-des(B30) human insulin, B29-N$^{\varepsilon}$-(N-lithocholyl-γ-glutamyl)-des(B30) human insulin, B29-N$^{\varepsilon}$-(ω-carboxyheptadecanoyl)-des(B30) human insulin and B29-N$^{\varepsilon}$-(ω-carboxyheptadecanoyl) human insulin.

Embodiment 11. A pharmaceutical preparation according to embodiment 10 wherein the insulin derivative is B29-N$^{\varepsilon}$-myristoyl-des(B30) human insulin.

Embodiment 12. A pharmaceutical preparation according to any one of the embodiments 1 to 11 wherein the protamine is protamine sulphate.

Embodiment 13. A pharmaceutical preparation according to embodiment 13 wherein the concentration of protamine sulphate is from 0.05-3 mg/mL.

Embodiment 14. A pharmaceutical preparation according to embodiment 14 wherein the concentration of protamine sulphate is from 0.1-0.6 mg/mL.

Embodiment 15. A pharmaceutical preparation according to any one of the embodiments 1 to 15 wherein the amount of zinc ions is 2-6 moles per mole putative insulin hexamer.

Embodiment 16. A pharmaceutical preparation according to embodiment 16 wherein the amount of zinc ions is 2 to 3 moles per mole putative insulin hexamer.

Embodiment 17. A pharmaceutical preparation according to any one of the embodiments 1 to 17 wherein the ratio of ligand that binds reversibly to a His^{B10} Zn^{2+} site of an R-state insulin hexamer to zinc ions is 1:3 to 3:1.

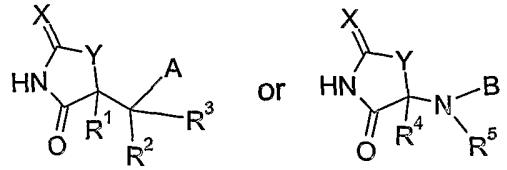
Embodiment 18. A pharmaceutical preparation according to embodiment 18 wherein the ratio of ligand that binds reversibly to a His^{B10} Zn^{2+} site of an R-state insulin hexamer to zinc ions is 1:2 to 2:1.

Embodiment 19. A pharmaceutical preparation according to embodiment 19 wherein the ratio of ligand that binds reversibly to a His^{B10} Zn^{2+} site of an R-state insulin hexamer to zinc ions is 1:.2 to 1.2:1.

Embodiment 20. A pharmaceutical preparation according to any one of the embodiments 1 to 20 wherein the ligand that binds reversibly to a His^{B10} Zn^{2+} site of an R-state insulin hexamer is a chemical structure selected from the group consisting of carboxylates, dithiocarboxylates, phenolates, thiophenolates, alkylthiolates, sulfonamides, imidazoles, triazoles, 4-cyano-1,2,3-triazoles, benzimidazoles, benzotriazoles, purines, thymines, thiazolidinediones, tetrazoles, 5-mercaptotetrazoles, rhodanines, N-hydroxyazoles, hydantoines, thiohydantoines, naphthoic acids and salicylic acids.

Embodiment 21. A pharmaceutical preparation according to embodiment 21 wherein the ligand that binds reversibly to a His^{B10} Zn^{2+} site of an R-state insulin hexamer is a chemical structure selected from the group consisting of benzotriazoles, 3-hydroxy 2-napthoic acids, salicylic acids, tetrazoles or thiazolidinediones.

Embodiment 22. A pharmaceutical composition according to embodiment 1 wherein the ligand that binds reversibly to a HisB10 Zn^{2+} site of an R-state insulin hexamer is



wherein

X is =O, =S or =NH

Y is -S-, -O- or -NH-

R^1 and R^4 are independently selected from hydrogen or C_1-C_6-alkyl,

R^2 is hydrogen or C_1-C_6-alkyl or aryl, R^1 and R^2 may optionally be combined to form a double bond,

R^3 and R^5 are independently selected from hydrogen, halogen, aryl, C_1-C_6-alkyl, or $-C(O)NR^{11}R^{12}$,

A and B are independently selected from C_1-C_6-alkyl, aryl, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl or heteroaryl, wherein the alkyl or alkenyl is optionally substituted with one or more substituents independently selected from R^6 and the aryl or heteroaryl is optionally substituted with up to four substituents R^7, R^8, R^9, and R^{10},

A and R^3 may be connected through one or two valence bonds, B and R^5 may be connected through one or two valence bonds,

R^6 is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, aryl, -COOH and $-NH_2$,

R^7, R^8, R^9 and R^{10} are independently selected from

- hydrogen, halogen, -CN, $-CH_2CN$, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-S(O)_2CF_3$, $-OS(O)_2CF_3$, $-SCF_3$, $-NO_2$, $-OR^{11}$, $-NR^{11}R^{12}$, $-SR^{11}$, $-NR^{11}S(O)_2R^{12}$, $-S(O)_2NR^{11}R^{12}$, $-S(O)NR^{11}R^{12}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-OS(O)_2R^{11}$, $-C(O)NR^{11}R^{12}$, $-OC(O)NR^{11}R^{12}$, $-NR^{11}C(O)R^{12}$, $-CH_2C(O)NR^{11}R^{12}$, $-OC_1$-C_6-alkyl-$C(O)NR^{11}R^{12}$, $-CH_2OR^{11}$, $-CH_2OC(O)R^{11}$, $-CH_2NR^{11}R^{12}$, $-OC(O)R^{11}$, $-OC_1$-C_{15}-alkyl-$C(O)OR^{11}$, $-OC_1$-C_6-alkyl-OR^{11}, $-SC_1$-C_6-alkyl-$C(O)OR^{11}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{11}$, $-NR^{11}$-C(=O)-C_1-C_6-alkyl-$C(=O)OR^{11}$, $-NR^{11}$-C(=O)-C_1-C_6-alkenyl-$C(=O)OR^{11}$, $-C(O)OR^{11}$, $C(O)R^{11}$, or $-C_2$-C_6-alkenyl-$C(=O)R^{11}$, =O, or $-C_2$-C_6-alkenyl-$C(=O)$-$NR^{11}R^{12}$,

  - C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl, each of which may optionally be substituted with one or more substituents independently selected from R^{13},

- aryl, aryloxy, aryloxycarbonyl, aroyl, arylsulfanyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aroyl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl, heteroaryl-C_2-C_6-alkynyl, or C_3-C_6 cycloalkyl,

of which each cyclic moiety may optionally be substituted with one or more substituents independently selected from R^{14},

R^{11} and R^{12} are independently selected from hydrogen, OH, C_1-C_{20}-alkyl, aryl-C_1-C_6-alkyl or aryl, wherein the alkyl groups may optionally be substituted with one or more substituents independently selected from R^{15}, and the aryl groups may optionally be substituted one or more substituents independently selected from R^{16}; R^{11} and R^{12} when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom, the heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

R^{13} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OR^{11}$, $-C(O)OR^{11}$, $-NR^{11}R^{12}$, and $-C(O)NR^{11}R^{12}$,

R^{14} is independently selected from halogen, $-C(O)OR^{11}$, $-CH_2C(O)OR^{11}$, $-CH_2OR^{11}$, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{11}$, $-NR^{11}R^{12}$, $S(O)_2R^{11}$, aryl and C_1-C_6-alkyl,

R^{15} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OC_1$-C_6-alkyl, $-C(O)OC_1$-C_6-alkyl, -COOH and $-NH_2$,

R^{16} is independently selected from halogen, $-C(O)OC_1$-C_6-alkyl, -COOH, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, -OH, $-OC_1$-C_6-alkyl, $-NH_2$, C(=O) or C_1-C_6-alkyl, or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

Embodiment 23. A pharmaceutical composition according to embodiment 23 wherein X is =O or =S.

Embodiment 24. A pharmaceutical composition according to embodiment 24 wherein X is =O.

Embodiment 25. A pharmaceutical composition according to embodiment 24 wherein X is =S.

Embodiment 26. A pharmaceutical composition according to any one of the embodiments 23 to 26 wherein Y is -O- or -S-.

Embodiment 27. A pharmaceutical composition according to embodiment 27 wherein Y is -O-.

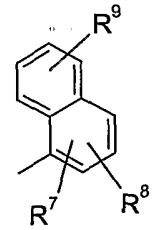
Embodiment 28. A pharmaceutical composition according to embodiment 27 wherein Y is -S-.

Embodiment 29. A pharmaceutical composition according to any one of the embodiments 23 to 30 wherein A is aryl optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different.

Embodiment 30. A pharmaceutical composition according to embodiment 31 wherein A is selected from ArG1 optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different.

Embodiment 31. A pharmaceutical composition according to embodiment 32 wherein A is phenyl or naphtyl optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different.

Embodiment 32. A pharmaceutical composition according to embodiment 33 wherein A is



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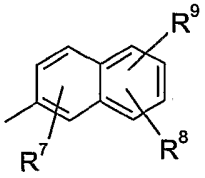


33. A pharmaceutical composition according to embodiment 33 wherein A is phenyl.

Embodiment 34. A pharmaceutical composition according to any one of the embodiments 23 to 30 wherein A is heteroaryl optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different.

Embodiment 35. A pharmaceutical composition according to embodiment 36 wherein A is selected from Het1 optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different.

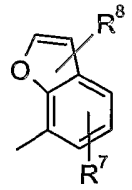
Embodiment 36. A pharmaceutical composition according to embodiment 37 wherein A is selected from Het2 optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different.

Embodiment 37. A pharmaceutical composition according to embodiment 38 wherein A is selected from Het3 optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different.

Embodiment 38. A pharmaceutical composition according to embodiment 39 wherein A is selected from the group consisting of indolyl, benzofuranyl, quinolyl, furyl, thienyl, or pyrrolyl, wherein each heteroaryl may optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different.

Embodiment 39. A pharmaceutical composition according to embodiment 39 wherein A is benzofuranyl optionally substituted with up to four substituents R^7, R^8, R^9, and R^{10} which may be the same or different.

Embodiment 40. A pharmaceutical composition according to embodiment 41 wherein A is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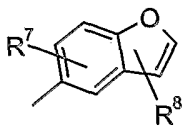
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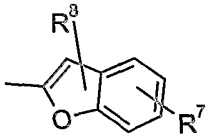
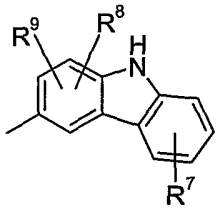


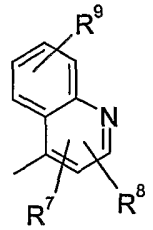
Embodiment 41. A pharmaceutical composition according to embodiment 39 wherein A is carbazolyl optionally substituted with up to four substituents R^7, R^8, R^9, and R^{10} which may be the same or different.

Embodiment 42. A pharmaceutical composition according to embodiment 43 wherein A is



Embodiment 43. A pharmaceutical composition according to embodiment 39 wherein A is quinolyl optionally substituted with up to four substituents R^7, R^8, R^9, and R^{10} which may be the same or different.

Embodiment 44. A pharmaceutical composition according to embodiment 45 wherein A is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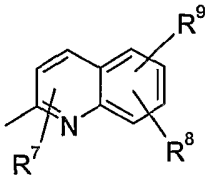
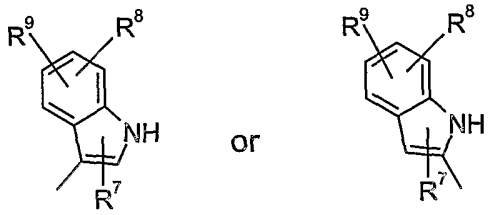


Embodiment 45. A pharmaceutical composition according to embodiment 39 wherein A is indolyl optionally substituted with up to four substituents R^7, R^8, R^9, and R^{10} which may be the same or different.

Embodiment 46. A pharmaceutical composition according to embodiment 47 wherein A is



Embodiment 47. A pharmaceutical composition according to any one of the embodiments 23 to 48 wherein R^1 is hydrogen.

Embodiment 48. A pharmaceutical composition according to any one of the embodiments 23 to 49 wherein R^2 is hydrogen.

Embodiment 49. A pharmaceutical composition according to any one of the embodiments 23 to 48 wherein R^1 and R^2 are combined to form a double bond.

Embodiment 50. A pharmaceutical composition according to any one of the embodiments 23 to 51 wherein R^3 is C_1-C_6-alkyl, halogen, or $C(O)NR^{16}R^{17}$.

Embodiment 51. A pharmaceutical composition according to embodiment 52 wherein R^3 is C_1-C_6-alkyl or $C(O)NR^{16}R^{17}$.

Embodiment 52. A pharmaceutical composition according to embodiment 53 wherein R^3 is methyl.

Embodiment 53. A pharmaceutical composition according to any one of the embodiments 23 to 30 wherein B is phenyl optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different.

Embodiment 54. A pharmaceutical composition according to any one of the embodiments 23 to 30 or 55 wherein R^4 is hydrogen.

Embodiment 55. A pharmaceutical composition according to any one of the embodiments 23 to 30 or 55 to 56 wherein R^5 is hydrogen.

Embodiment 56. A pharmaceutical composition according to any one of the embodiments 23 to 57 wherein R^6 is aryl.

Embodiment 57. A pharmaceutical composition according to embodiment 58 wherein R^6 is phenyl.

Embodiment 58. A pharmaceutical composition according to any one of the embodiments 23 to 59 wherein R^7, R^8, R^9 and R^{10} are independently selected from

- hydrogen, halogen, $-NO_2$, $-OR^{11}$, $-NR^{11}R^{12}$, $-SR^{11}$, $-NR^{11}S(O)_2R^{12}$, $-S(O)_2NR^{11}R^{12}$, $-S(O)NR^{11}R^{12}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-OS(O)_2\ R^{11}$, $-NR^{11}C(O)R^{12}$, $-CH_2OR^{11}$, $-CH_2OC(O)R^{11}$, $-CH_2NR^{11}R^{12}$, $-OC(O)R^{11}$, $-OC_1$-C_6-alkyl-$C(O)OR^{11}$, $-OC_1$-C_6-

alkyl-C(O)$NR^{11}R^{12}$, -OC_1-C_6-alkyl-OR^{11}, -SC_1-C_6-alkyl-$C(O)OR^{11}$, –C_2-C_6-alkenyl-$C(=O)OR^{11}$, -$C(O)OR^{11}$, or –C_2-C_6-alkenyl-$C(=O)R^{11}$,

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl, which may each optionally be substituted with one or more substituents independently selected from R^{13}

- aryl, aryloxy, aroyl, arylsulfanyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aroyl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, wherein each of the cyclic moieties optionally may be substituted with one or more substituents independently selected from R^{14}

Embodiment 59. A pharmaceutical composition according to embodiment 60 wherein R^7, R^8, R^9 and R^{10} are independently selected from

- hydrogen, halogen, -NO_2, -OR^{11}, -$NR^{11}R^{12}$, -SR^{11}, -$S(O)_2R^{11}$, -$OS(O)_2$ R^{11}, -$CH_2OC(O)R^{11}$, -$OC(O)R^{11}$, -OC_1-C_6-alkyl-$C(O)OR^{11}$, -OC_1-C_6-alkyl-OR^{11}, -SC_1-C_6-alkyl-$C(O)OR^{11}$, -$C(O)OR^{11}$, or –C_2-C_6-alkenyl-$C(=O)R^{11}$,

- C_1-C_6-alkyl or C_1-C_6-alkenyl which may each optionally be substituted with one or more substituents independently selected from R^{13}

- aryl, aryloxy, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, heteroaryl,

of which each of the cyclic moieties optionally may be substituted with one or more substituents independently selected from R^{14}

Embodiment 60. A pharmaceutical composition according to embodiment 61 wherein R^7, R^8, R^9 and R^{10} are independently selected from

- hydrogen, halogen, -NO_2, -OR^{11}, -$NR^{11}R^{12}$, -SR^{11}, -$S(O)_2R^{11}$, -$OS(O)_2$ R^{11}, -$CH_2OC(O)R^{11}$, -$OC(O)R^{11}$, -OC_1-C_6-alkyl-$C(O)OR^{11}$, -OC_1-C_6-alkyl-OR^{11}, -SC_1-C_6-alkyl-$C(O)OR^{11}$, -$C(O)OR^{11}$, or –C_2-C_6-alkenyl-$C(=O)R^{11}$,

- C_1-C_6-alkyl or C_1-C_6- which may each optionally be substituted with one or more substituents independently selected from R^{13}

- aryl, aryloxy, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, heteroaryl,

of which each of the cyclic moieties optionally may be substituted with one or more substituents independently selected from R^{14}.

Embodiment 61. A pharmaceutical composition according to embodiment 62 wherein R^7, R^8, R^9 and R^{10} are independently selected from

- hydrogen, halogen, -OR^{11}, -OC_1-C_6-alkyl-C(O)OR^{11}, or -C(O)OR^{11},

- C_1-C_6-alkyl which may each optionally be substituted with one or more substituents independently selected from R^{13}

- aryl, aryloxy, aryl-C_1-C_6-alkoxy,

of which each of the cyclic moieties optionally may be substituted with one or more substituents independently selected from R^{14}.

Embodiment 62. A pharmaceutical composition according to embodiment 63 wherein R^7, R^8, R^9 and R^{10} are independently selected from

- hydrogen, halogen, -OR^{11}, -OC_1-C_6-alkyl-C(O)OR^{11}, or -C(O)OR^{11},

- C_1-C_6-alkyl which may optionally be substituted with one or more substituents independently selected from R^{13}

- phenyl, phenyloxy, phenyl-C_1-C_6-alkoxy, wherein each of the cyclic moieties optionally may be substituted with one or more substituents independently selected from R^{14}.

Embodiment 63. A pharmaceutical composition according to any one of the embodiments 23 to 65 wherein R^{11} and R^{12} are independently selected from hydrogen, C_1-C_{20}-alkyl, aryl or aryl-C_1-C_6-alkyl, wherein the alkyl groups may optionally be substituted with one or more substituents independently selected from R^{15}, and the aryl groups may optionally be substituted one or more substituents independently selected from R^{16}; R^{11} and R^{12} when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom, the heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds.

Embodiment 64. A pharmaceutical composition according to embodiment 66 wherein R^{11} and R^{12} are independently selected from hydrogen, C_1-C_{20}-alkyl, aryl or aryl-C_1-C_6-alkyl, wherein the alkyl groups may optionally be substituted with one or more substituents independently selected from R^{15}, and the aryl groups may optionally be substituted one or more substituents independently selected from R^{16}.

Embodiment 65. A pharmaceutical composition according to embodiment 67 wherein R^{11} and R^{12} are independently selected from phenyl or phenyl-C_1-C_6-alkyl.

Embodiment 66. A pharmaceutical composition according to embodiment 67 wherein one or both of R^{11} and R^{12} are methyl.

Embodiment 67. A pharmaceutical composition according to any one of the embodiments 23 to 69 wherein R^{13} is independently selected from halogen, CF_3, OR^{11} or $NR^{11}R^{12}$.

Embodiment 68. A pharmaceutical composition according to embodiment 70 wherein R^{13} is independently selected from halogen or OR^{11}.

Embodiment 69. A pharmaceutical composition according to embodiment 71 wherein R^{13} is OR^{11}.

Embodiment 70. A pharmaceutical composition according to any one of the embodiments 23 to 72 wherein R^{14} is independently selected from halogen, -C(O)OR^{11}, -CN, -CF_3, -OR^{11}, $S(O)_2R^{11}$, and C_1-C_6-alkyl.

Embodiment 71. A pharmaceutical composition according to embodiment 73 wherein R^{14} is independently selected from halogen, -C(O)OR^{11}, or -OR^{11}.

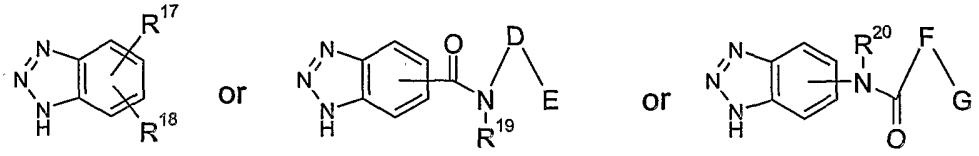
Embodiment 72. A pharmaceutical composition according to any one of the embodiments 23 to 74 wherein R^{15} is independently selected from halogen, -CN, -CF_3, -C(O)OC_1-C_6-alkyl,and –COOH.

Embodiment 73. A pharmaceutical composition according to embodiment 75 wherein R^{15} is independently selected from halogen or -C(O)OC_1-C_6-alkyl.

Embodiment 74. A pharmaceutical composition according to any one of the embodiments 23 to 76 wherein R^{16} is independently selected from halogen, -C(O)OC_1-C_6-alkyl, -COOH, -NO_2, -OC_1-C_6-alkyl, -NH_2, C(=O) or C_1-C_6-alkyl.

Embodiment 75. A pharmaceutical composition according to embodiment 77 wherein R^{16} is independently selected from halogen, -C(O)OC_1-C_6-alkyl, -COOH, -NO_2, or C_1-C_6-alkyl.

Embodiment 76. A pharmaceutical composition according to embodiment 1 wherein the ligand that binds reversibly to a HisB10 Zn^{2+} site of an R-state insulin hexamer is



wherein

R^{19} is hydrogen or C_1-C_6-alkyl,

R^{20} is hydrogen or C_1-C_6-alkyl,

D and F are a valence bond or C_1-C_6-alkylene optionally substituted with one or more substituents independently selected from R^{72},

R^{72} is independently selected from hydroxy, C_1-C_6-alkyl, or aryl,

E is C_1-C_6-alkyl, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with up to three substituents R^{21}, R^{22} and R^{23},

G is C_1-C_6-alkyl, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with up to three substituents R^{24}, R^{25} and R^{26},

R^{17}, R^{18}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25} and R^{26} are independently selected from

- hydrogen, halogen, -CN, -CH_2CN, -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -$S(O)_2CF_3$, -SCF_3, -NO_2, -OR^{27}, -$NR^{27}R^{28}$, -SR^{27}, -$NR^{27}S(O)_2R^{28}$, -$S(O)_2NR^{27}R^{28}$, -$S(O)NR^{27}R^{28}$, -$S(O)R^{27}$, -$S(O)_2R^{27}$, -$C(O)NR^{27}R^{28}$, -$OC(O)NR^{27}R^{28}$, -$NR^{27}C(O)R^{28}$, -$NR^{27}C(O)OR^{28}$, -$CH_2C(O)NR^{27}R^{28}$, -$OCH_2C(O)NR^{27}R^{28}$, -CH_2OR^{27}, -$CH_2NR^{27}R^{28}$, -$OC(O)R^{27}$, -OC_1-C_6-alkyl-$C(O)OR^{27}$, -SC_1-C_6-alkyl-$C(O)OR^{27}$, –C_2-C_6-alkenyl-$C(=O)OR^{27}$, -NR^{27}-$C(=O)$-C_1-C_6-alkyl-$C(=O)OR^{27}$, -NR^{27}-$C(=O)$-C_1-C_6-alkenyl-$C(=O)OR^{27}$, -$C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, -C_1-C_6-alkyl-$C(=O)OR^{27}$,or -$C(O)OR^{27}$,
- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl,

which may optionally be substituted with one or more substituents independently selected from R^{29},

- aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl or heteroaryl-C_2-C_6-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30},

R^{27} and R^{28} are independently selected from hydrogen, C_1-C_6-alkyl, aryl-C_1-C_6-alkyl or aryl, or R^{27} and R^{28} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

R^{29} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OR^{27}$, and $-NR^{27}R^{28}$,

R^{30} is independently selected from halogen, $-C(O)OR^{27}$, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{27}$, $-NR^{27}R^{28}$ and C_1-C_6-alkyl, or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

Embodiment 77. A pharmaceutical composition according to embodiment 79 wherein D is a valence bond.

Embodiment 78. A pharmaceutical composition according to embodiment 79 wherein D is C_1-C_6-alkylene optionally substituted with one or more hydroxy, C_1-C_6-alkyl, or aryl.

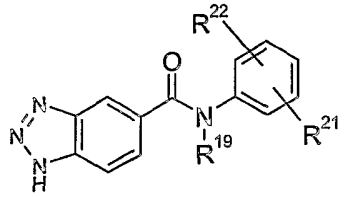
Embodiment 79. A pharmaceutical composition according to any one of the embodiments 79 to 81 wherein E is aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with up to three substituents independently selected from R^{21}, R^{22} and R^{23}.

Embodiment 80. A pharmaceutical composition according to embodiment 82 wherein E is aryl optionally substituted with up to three substituents independently selected from R^{21}, R^{22} and R^{23}.

Embodiment 81. A pharmaceutical composition according to embodiment 83 wherein E is selected from ArG1 and optionally substituted with up to three substituents independently selected from R^{21}, R^{22} and R^{23}.

Embodiment 82. A pharmaceutical composition according to embodiment 84 wherein E is phenyl optionally substituted with up to three substituents independently selected from R^{21}, R^{22} and R^{23}.

Embodiment 83. A pharmaceutical composition according to embodiment 85 wherein the ligand that binds reversibly to a HisB10 Zn^{2+} site of an R-state insulin hexamer is



Embodiment 84. A pharmaceutical composition according to any one of the embodiments 79 to 86 wherein R^{21}, R^{22} and R^{23} are independently selected from

- hydrogen, halogen, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-NO_2$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-C(O)NR^{27}R^{28}$, $-OC(O)NR^{27}R^{28}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-CH_2C(O)NR^{27}R^{28}$, $-OCH_2C(O)NR^{27}R^{28}$, $-CH_2OR^{27}$, $-CH_2NR^{27}R^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{27}$, $-NR^{27}$-$C(=O)$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-NR^{27}$-$C(=O)$-C_1-C_6-alkenyl-$C(=O)OR^{27}$-, $-C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-C_1$-C_6-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl,

which may optionally be substituted with one or more substituents independently selected from R^{29}

- aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl or heteroaryl-C_2-C_6-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

Embodiment 85. A pharmaceutical composition according to embodiment 87 wherein R^{21}, R^{22} and R^{23} are independently selected from

- hydrogen, halogen, $-OCF_3$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-

$C(=O)OR^{27}$, $-C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-C_1$-C_6-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

- C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{29}

- aryl, aryloxy, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, heteroaryl, heteroaryl-C_1-C_6-alkyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

Embodiment 86. A pharmaceutical composition according to embodiment 88 wherein R^{21}, R^{22} and R^{23} are independently selected from

- hydrogen, halogen, $-OCF_3$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{27}$, $-C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-C_1$-C_6-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

- methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R^{29}

- aryl, aryloxy, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, heteroaryl, heteroaryl-C_1-C_6-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

Embodiment 87. A pharmaceutical composition according to embodiment 89 wherein R^{21}, R^{22} and R^{23} are independently selected from

- hydrogen, halogen, $-OCF_3$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{27}$, $-C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-C_1$-C_6-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

- methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R^{29}

  - ArG1, ArG1-O-, ArG1-C(O)-, ArG1-C_1-C_6-alkoxy, ArG1-C_1-C_6-alkyl, Het3, Het3-C_1-C_6-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

Embodiment 88. A pharmaceutical composition according to embodiment 90 wherein R^{21}, R^{22} and R^{23} are independently selected from

  - hydrogen, halogen, $-OCF_3$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{27}$, $-C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-C_1$-C_6-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

- C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{29}

- phenyl, phenyloxy, phenyl-C_1-C_6-alkoxy, phenyl-C_1-C_6-alkyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

Embodiment 89. A pharmaceutical composition according to any one of the embodiments 79 to 91 wherein R^{19} is hydrogen or methyl.

Embodiment 90. A pharmaceutical composition according to embodiment 92 wherein R^{19} is hydrogen.

Embodiment 91. A pharmaceutical composition according to any one of the embodiments 79 to 93 wherein R^{27} is Hydrogen, C_1-C_6-alkyl or aryl.

Embodiment 92. A pharmaceutical composition according to embodiment 94 wherein R^{27} is hydrogen or C_1-C_6-alkyl.

Embodiment 93. A pharmaceutical composition according to any one of the embodiments 79 to 95 wherein R^{28} is hydrogen or C_1-C_6-alkyl.

Embodiment 94. A pharmaceutical composition according to embodiment 79 wherein F is a valence bond.

Embodiment 95. A pharmaceutical composition according to embodiment 79 wherein F is C_1-C_6-alkylene optionally substituted with one or more hydroxy, C_1-C_6-alkyl, or aryl.

Embodiment 96. A pharmaceutical composition according to any one of the embodiments 79 or 97 to 98 wherein G is C_1-C_6-alkyl or aryl, wherein the aryl is optionally substituted with up to three substituents R^{24}, R^{25} and R^{26}.

Embodiment 97. A pharmaceutical composition according to any one of the embodiments 79 or 97 to 98 wherein G is C_1-C_6-alkyl or ArG1, wherein the aryl is optionally substituted with up to three substituents R^{24}, R^{25} and R^{26}.

Embodiment 98. A pharmaceutical composition according to embodiment 99 wherein G is C_1-C_6-alkyl.

Embodiment 99. A pharmaceutical composition according to embodiment 101 wherein G is phenyl optionally substituted with up to three substituents R^{24}, R^{25} and R^{26}.

Embodiment 100. A pharmaceutical composition according to any one of the embodiments 79 to 102 wherein R^{24}, R^{25} and R^{26} are independently selected from

- hydrogen, halogen, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-NO_2$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-C(O)NR^{27}R^{28}$, $-OC(O)NR^{27}R^{28}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-CH_2C(O)NR^{27}R^{28}$, $-OCH_2C(O)NR^{27}R^{28}$, $-CH_2OR^{27}$, $-CH_2NR^{27}R^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{27}$, $-NR^{27}$-$C(=O)$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-NR^{27}$-$C(=O)$-C_1-C_6-alkenyl-$C(=O)OR^{27}$-, $-C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-C_1$-C_6-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl,

which may optionally be substituted with one or more substituents independently selected from R^{29}

- aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl or heteroaryl-C_2-C_6-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

Embodiment 101. A pharmaceutical composition according to embodiment 103 wherein R^{24}, R^{25} and R^{26} are independently selected from

- hydrogen, halogen, $-OCF_3$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{27}$, $-C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-C_1$-C_6-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

  - C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl,

  which may optionally be substituted with one or more substituents independently selected from R^{29}

  - aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl or heteroaryl-C_2-C_6-alkynyl,

  of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

Embodiment 102. A pharmaceutical composition according to embodiment 104 wherein R^{24}, R^{25} and R^{26} are independently selected from

- hydrogen, halogen, $-OCF_3$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{27}$, $-C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-C_1$-C_6-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

- C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{29}

- aryl, aryloxy, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, heteroaryl, heteroaryl-C_1-C_6-alkyl,

  of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

Embodiment 103. A pharmaceutical composition according to embodiment 105 wherein R^{21}, R^{22} and R^{23} are independently selected from

- hydrogen, halogen, $-OCF_3$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{27}$, $-C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-C_1$-C_6-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

  - methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R^{29}

  - ArG1, ArG1-O-, ArG1-C(O)-, ArG1-C_1-C_6-alkoxy, ArG1-C_1-C_6-alkyl, Het3, Het3-C_1-C_6-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

Embodiment 104. A pharmaceutical composition according to embodiment 106 wherein R^{21}, R^{22} and R^{23} are independently selected from

- hydrogen, halogen, $-OCF_3$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{27}$, $-C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-C_1$-C_6-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

- methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R^{29}

- ArG1, ArG1-O-, ArG1-C(O)-, ArG1-C_1-C_6-alkoxy, ArG1-C_1-C_6-alkyl, Het3, Het3-C_1-C_6-alkyl

  of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

Embodiment 105. A pharmaceutical composition according to embodiment 107 wherein R^{21}, R^{22} and R^{23} are independently selected from

  - hydrogen, halogen, $-OCF_3$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{27}$, $-C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-C_1$-C_6-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

- methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R^{29}

  - ArG1, ArG1-O-, ArG1-C_1-C_6-alkoxy, ArG1-C_1-C_6-alkyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

Embodiment 106. A pharmaceutical composition according to any one of the embodiments 79 or 97 to 108 wherein R^{20} is hydrogen or methyl.

Embodiment 107. A pharmaceutical composition according to embodiment 109 wherein R^{20} is hydrogen.

Embodiment 108. A pharmaceutical composition according to any one of the embodiments 79 or 97 to 110 wherein R^{27} is hydrogen, C_1-C_6-alkyl or aryl.

Embodiment 109. A pharmaceutical composition according to embodiment 111 wherein R^{27} is hydrogen or C_1-C_6-alkyl or ArG1.

Embodiment 110. A pharmaceutical composition according to embodiment 112 wherein R^{27} is hydrogen or C_1-C_6-alkyl.

Embodiment 111. A pharmaceutical composition according to any one of the embodiments 79 or 97 to 112 wherein R^{28} is hydrogen or C_1-C_6-alkyl.

Embodiment 112. A pharmaceutical composition according to embodiment 79 wherein R^{17} and R^{18} are independently selected from

- hydrogen, halogen, -CN, -CF_3, -OCF_3, -NO_2, -OR^{27}, -$NR^{27}R^{28}$, -SR^{27}, -$S(O)R^{27}$, -$S(O)_2R^{27}$, -$C(O)NR^{27}R^{28}$, -CH_2OR^{27}, -$OC(O)R^{27}$, -OC_1-C_6-alkyl-$C(O)OR^{27}$, -SC_1-C_6-alkyl-$C(O)OR^{27}$, or -$C(O)OR^{27}$,

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl, optionally substituted with one or more substituents independently selected from R^{29}

- aryl, aryloxy, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, heteroaryl, heteroaryl-C_1-C_6-alkyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

Embodiment 113. A pharmaceutical composition according to embodiment 115 wherein R^{17} and R^{18} are independently selected from

- hydrogen, halogen, -CN, $-CF_3$, $-NO_2$, $-OR^{27}$, $-NR^{27}R^{28}$, or $-C(O)OR^{27}$,

  - C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{29}

  - aryl, aryloxy, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, heteroaryl, heteroaryl-C_1-C_6-alkyl,

  of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

Embodiment 114. A pharmaceutical composition according to embodiment 116 wherein R^{17} and R^{18} are independently selected from

- hydrogen, halogen, -CN, $-CF_3$, $-NO_2$, $-OR^{27}$, $-NR^{27}R^{28}$, or $-C(O)OR^{27}$
- methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R^{29}
- aryl, aryloxy, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, heteroaryl, heteroaryl-C_1-C_6-alkyl

  of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

Embodiment 115. A pharmaceutical composition according to embodiment 117 wherein R^{17} and R^{18} are independently selected from

- hydrogen, halogen, -CN, $-CF_3$, $-NO_2$, $-OR^{27}$, $-NR^{27}R^{28}$, or $-C(O)OR^{27}$
- methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R^{29}
- ArG1, ArG1-O-, ArG1-C(O)-, ArG1-C_1-C_6-alkoxy, ArG1-C_1-C_6-alkyl, Het3, Het3-C_1-C_6-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

Embodiment 116. A pharmaceutical composition according to embodiment 118 wherein R^{17} and R^{18} are independently selected from

- hydrogen, halogen, -CN, $-CF_3$, $-NO_2$, $-OR^{27}$, $-NR^{27}R^{28}$, or $-C(O)OR^{27}$
- C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{29}
- phenyl, phenyloxy, phenyl-C_1-C_6-alkoxy, phenyl-C_1-C_6-alkyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

Embodiment 117. A pharmaceutical composition according to any one of the embodiments 79 to 119 wherein R^{27} is hydrogen or C_1-C_6-alkyl.

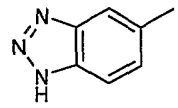
Embodiment 118. A pharmaceutical composition according to embodiment 120 wherein R^{27} is hydrogen, methyl or ethyl.

Embodiment 119. A pharmaceutical composition according to any one of the embodiments 79 to 121 wherein R^{28} is hydrogen or C_1-C_6-alkyl.

Embodiment 120. A pharmaceutical composition according to embodiment 122 wherein R^{28} is hydrogen, methyl or ethyl.

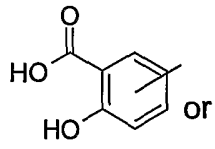
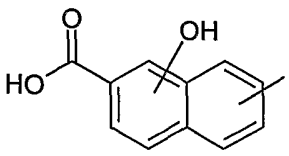
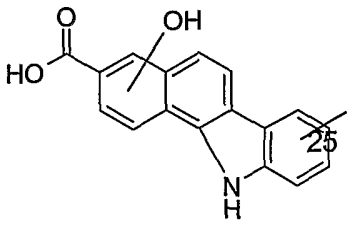
Embodiment 121. A pharmaceutical composition according to any one of the embodiments 79 to 123 wherein R^{72} is –OH or phenyl.

Embodiment 122. A pharmaceutical composition according to embodiment 79 wherein the ligand that binds reversibly to a HisB10 Zn^{2+} site of an R-state insulin hexamer is



Embodiment 123. A pharmaceutical composition according to embodiment 1 wherein the ligand that binds reversibly to a HisB10 Zn^{2+} site of an R-state insulin hexamer is of the form H-I-J

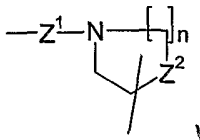
wherein H is

 or  or 

wherein the phenyl, naphthalene or benzocarbazole rings are optionally substituted with one or more substituents independently selected from R^{31}

I is selected from

- a valence bond,
- $–CH_2N(R^{32})-$ or $–SO_2N(R^{33})-$,



- wherein Z^1 is $S(O)_2$ or CH_2, Z^2 is -NH-, -O-or -S-, and n is 1 or 2,

J is

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl, which may each optionally be substituted with one or more substituents selected from R^{34},
- Aryl, aryloxy, aryl-oxycarbonyl-, aroyl, aryl-C_1-C_6-alkoxy-, aryl-C_1-C_6-alkyl-, aryl-C_2-C_6-alkenyl-, aryl-C_2-C_6-alkynyl-, heteroaryl, heteroaryl-C_1-C_6-alkyl-, heteroaryl-C_2-C_6-alkenyl- or heteroaryl-C_2-C_6-alkynyl-, wherein the cyclic moieties are optionally substituted with one or more substituents selected from R^{37},
- Hydrogen,

R^{31} is independently selected from hydrogen, halogen, -CN, $-CH_2CN$, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-S(O)_2CF_3$, $-SCF_3$, $-NO_2$, $-OR^{35}$, $-C(O)R^{35}$, $-NR^{35}R^{36}$, $-SR^{35}$, $-NR^{35}S(O)_2R^{36}$, $-S(O)_2NR^{35}R^{36}$, $-S(O)NR^{35}R^{36}$, $-S(O)R^{35}$, $-S(O)_2R^{35}$, $-C(O)NR^{35}R^{36}$, $-OC(O)NR^{35}R^{36}$, $-NR^{35}C(O)R^{36}$, $-CH_2C(O)NR^{35}R^{36}$, $-OCH_2C(O)NR^{35}R^{36}$, $-CH_2OR^{35}$, $-CH_2NR^{35}R^{36}$, $-OC(O)R^{35}$, $-OC_1$-C_6-alkyl-$C(O)OR^{35}$, $-SC_1$-C_6-alkyl-$C(O)OR^{35}$ $-C_2$-C_6-alkenyl-$C(=O)OR^{35}$, $-NR^{35}$-$C(=O)$-C_1-C_6-alkyl-$C(=O)OR^{35}$, $-NR^{35}$-$C(=O)$-C_1-C_6-alkenyl-$C(=O)OR^{35}$-, C_1-C_6-alkyl, C_1-C_6-alkanoyl or $-C(O)OR^{35}$,

R^{32} and R^{33} are independently selected from hydrogen, C_1-C_6-alkyl or C_1-C_6-alkanoyl,

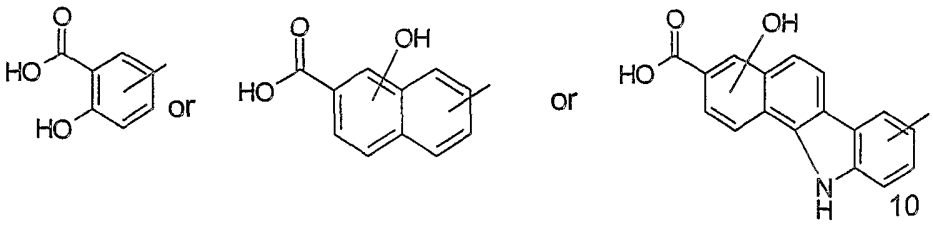
R^{34} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OR^{35}$, and $-NR^{35}R^{36}$,

R^{35} and R^{36} are independently selected from hydrogen, C_1-C_6-alkyl, aryl-C_1-C_6-alkyl or aryl, or R^{35} and R^{36} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

R^{37} is independently selected from halogen, $-C(O)OR^{35}$, -C(O)H, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{35}$, $-NR^{35}R^{36}$, C_1-C_6-alkyl or C_1-C_6-alkanoyl,

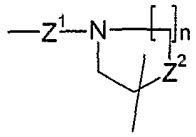
or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

Embodiment 124. A pharmaceutical composition according to embodiment 126 wherein the ligand that binds reversibly to a HisB10 Zn^{2+} site of an R-state insulin hexamer is of the form H-I-J, wherein H is



wherein the phenyl, naphthalene or benzocarbazole rings are optionally substituted with one or more substituents independently selected from R^{31},

I is selected from

- a valence bond,
- $-CH_2N(R^{32})-$ or $-SO_2N(R^{33})-$,
-  wherein Z^1 is $S(O)_2$ or CH_2, Z^2 is N,-O-or -S-, and n is 1 or 2,

J is

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl, which may each optionally be substituted with one or more substituents selected from R^{34},
- Aryl, aryloxy, aryl-oxycarbonyl-, aroyl, aryl-C_1-C_6-alkoxy-, aryl-C_1-C_6-alkyl-, aryl-C_2-C_6-alkenyl-, aryl-C_2-C_6-alkynyl-, heteroaryl, heteroaryl-C_1-C_6-alkyl-, heteroaryl-C_2-C_6-alkenyl- or heteroaryl-C_2-C_6-alkynyl-, wherein the cyclic moieties are optionally substituted with one or more substituents selected from R^{37},
- hydrogen,

R^{31} is independently selected from hydrogen, halogen, -CN, $-CH_2CN$, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-S(O)_2CF_3$, $-SCF_3$, $-NO_2$, $-OR^{35}$, $-C(O)R^{35}$, $-NR^{35}R^{36}$, $-SR^{35}$, $-NR^{35}S(O)_2R^{36}$, $-S(O)_2NR^{35}R^{36}$, $-S(O)NR^{35}R^{36}$, $-S(O)R^{35}$, $-S(O)_2R^{35}$, $-C(O)NR^{35}R^{36}$, $-OC(O)NR^{35}R^{36}$, $-NR^{35}C(O)R^{36}$, $-CH_2C(O)NR^{35}R^{36}$, $-OCH_2C(O)NR^{35}R^{36}$, $-CH_2OR^{35}$,

$-CH_2NR^{35}R^{36}$, $-OC(O)R^{35}$, $-OC_1$-C_6-alkyl-$C(O)OR^{35}$, $-SC_1$-C_6-alkyl-$C(O)OR^{35}$ $-C_2$-C_6-alkenyl-$C(=O)OR^{35}$, $-NR^{35}$-$C(=O)$-C_1-C_6-alkyl-$C(=O)OR^{35}$, $-NR^{35}$-$C(=O)$-C_1-C_6-alkenyl-$C(=O)OR^{35}$-, C_1-C_6-alkyl, C_1-C_6-alkanoyl or $-C(O)OR^{35}$,

R^{32} and R^{33} are independently selected from hydrogen, C_1-C_6-alkyl or C_1-C_6-alkanoyl,

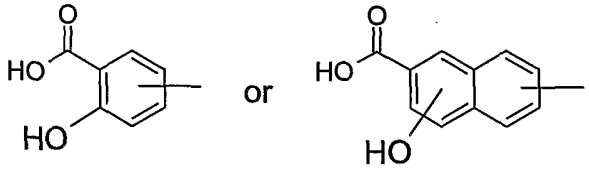
R^{34} is independently selected from halogen, $-CN$, $-CF_3$, $-OCF_3$, $-OR^{35}$, and $-NR^{35}R^{36}$,

R^{35} and R^{36} are independently selected from hydrogen, C_1-C_6-alkyl, aryl-C_1-C_6-alkyl or aryl, or R^{35} and R^{36} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

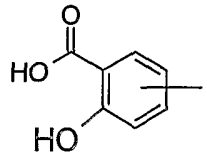
R^{37} is independently selected from halogen, $-C(O)OR^{35}$, $-C(O)H$, $-CN$, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{35}$, $-NR^{35}R^{36}$, C_1-C_6-alkyl or C_1-C_6-alkanoyl,

or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base,
With the proviso that R^{31} and J cannot both be hydrogen.

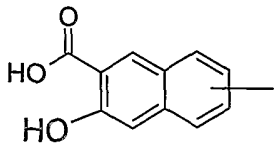
Embodiment 125. A pharmaceutical composition according to any one of the embodiments 126 or 127 wherein H is



Embodiment 126. A pharmaceutical composition according to embodiment 128 wherein H is



Embodiment 127. A pharmaceutical composition according to embodiment 128 wherein H is



Embodiment 128. A pharmaceutical composition according to any one of the embodiments 126 to 130wherein I is a valence bond, $-CH_2N(R^{32})-$, or $-SO_2N(R^{33})-$.

Embodiment 129. A pharmaceutical composition according to embodiment 131 wherein I is a valence bond.

Embodiment 130. A pharmaceutical composition according to any one of the embodiments 126 to 132 wherein J is

- hydrogen,
- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl,

  which may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OR^{35}$, and $-NR^{35}R^{36}$,
- aryl, or heteroaryl, wherein the cyclic moieties are optionally substituted with one or more substituents independently selected from R^{37}.

Embodiment 131. A pharmaceutical composition according to embodiment 133 wherein J is

- hydrogen,
- aryl or heteroaryl, wherein the cyclic moieties are optionally substituted with one or more substituents independently selected from R^{37}.

Embodiment 132. A pharmaceutical composition according to embodiment 133 wherein J is

- hydrogen,
- ArG1 or Het3, wherein the cyclic moieties are optionally substituted with one or more substituents independently selected from R^{37}.

Embodiment 133. A pharmaceutical composition according to embodiment 135 wherein J is

- hydrogen,
- phenyl or naphthyl optionally substituted with one or more substituents independently selected from R^{37}.

Embodiment 134. A pharmaceutical composition according to embodiment 136 wherein J is hydrogen.

Embodiment 135. A pharmaceutical composition according to any one of the embodiments 126 to 137 wherein R^{32} and R^{33} are independently selected from hydrogen or C_1-C_6-alkyl.

Embodiment 136. A pharmaceutical composition according to any one of the embodiments 126 to 138 wherein R^{34} is hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$, $-SCF_3$, $-NO_2$, $-OR^{35}$,

-C(O)R^{35}, -$NR^{35}R^{36}$, -SR^{35}, -C(O)$NR^{35}R^{36}$, -OC(O)$NR^{35}R^{36}$, -NR^{35}C(O)R^{36}, -OC(O)R^{35}, -OC_1-C_6-alkyl-C(O)OR^{35}, -SC_1-C_6-alkyl-C(O)OR^{35} or -C(O)OR^{35}.

Embodiment 137. A pharmaceutical composition according to embodiment 139 wherein R^{34} is hydrogen, halogen, -CF_3, -NO_2, -OR^{35}, -$NR^{35}R^{36}$, -SR^{35}, -NR^{35}C(O)R^{36}, or -C(O)OR^{35}.

Embodiment 138. A pharmaceutical composition according to embodiment 140 wherein R^{34} is hydrogen, halogen, -CF_3, -NO_2, -OR^{35}, -$NR^{35}R^{36}$, or -NR^{35}C(O)R^{36}.

Embodiment 139. A pharmaceutical composition according to embodiment 141 wherein R^{34} is hydrogen, halogen, or -OR^{35}.

Embodiment 140. A pharmaceutical composition according to any one of the embodiments 126 to 142 wherein R^{35} and R^{36} are independently selected from hydrogen, C_1-C_6-alkyl, or aryl.

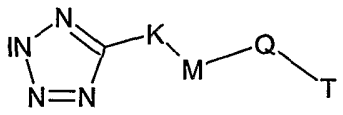
Embodiment 141. A pharmaceutical composition according to embodiment 143 wherein R^{35} and R^{36} are independently selected from hydrogen or C_1-C_6-alkyl.

Embodiment 142. A pharmaceutical composition according to any one of the embodiments 126 to 144 wherein R^{37} is halogen, -C(O)OR^{35}, -CN, -CF_3, -OR^{35}, -$NR^{35}R^{36}$, C_1-C_6-alkyl or C_1-C_6-alkanoyl.

Embodiment 143. A pharmaceutical composition according to embodiment 145 wherein R^{37} is halogen, -C(O)OR^{35}, -OR^{35}, -$NR^{35}R^{36}$, C_1-C_6-alkyl or C_1-C_6-alkanoyl.

Embodiment 144. A pharmaceutical composition according to embodiment 146 wherein R^{37} is halogen, -C(O)OR^{35} or -OR^{35}.

Embodiment 145. A pharmaceutical composition according to embodiment 1 wherein the ligand that binds reversibly to a HisB10 Zn^{2+} site of an R-state insulin hexamer is



wherein K is a valence bond, C_1-C_6-alkylene, -NH-C(=O)-U-, -C_1-C_6-alkyl-S-, -C_1-C_6-alkyl-O-, -C(=O)-, or -C(=O)-NH-, wherein any C_1-C_6-alkyl moiety is optionally substituted with R^{38},

U is a valence bond, C_1-C_6-alkenylene, -C_1-C_6-alkyl-O- or C_1-C_6-alkylene wherein any C_1-C_6-alkyl moiety is optionally substituted with C_1-C_6-alkyl,

R^{38} is C_1-C_6-alkyl, aryl, wherein the alkyl or aryl moieties are optionally substituted with one or more substituents independently selected from R^{39},

R^{39} is independently selected from halogen, cyano, nitro, amino,

M is a valence bond, arylene or heteroarylene, wherein the aryl or heteroaryl moieties are optionally substituted with one or more substituents independently selected from R^{40},

R^{40} is selected from

- hydrogen, halogen, -CN, $-CH_2CN$, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-S(O)_2CF_3$, $-OS(O)_2CF_3$, $-SCF_3$, $-NO_2$, $-OR^{41}$, $-NR^{41}R^{42}$, $-SR^{41}$, $-NR^{41}S(O)_2R^{42}$, $-S(O)_2NR^{41}R^{42}$, $-S(O)NR^{41}R^{42}$, $-S(O)R^{41}$, $-S(O)_2R^{41}$, $-OS(O)_2R^{41}$, $-C(O)NR^{41}R^{42}$, $-OC(O)NR^{41}R^{42}$, $-NR^{41}C(O)R^{42}$, $-CH_2C(O)NR^{41}R^{42}$, $-OC_1$-C_6-alkyl-$C(O)NR^{41}R^{42}$, $-CH_2OR^{41}$, $-CH_2OC(O)R^{41}$, $-CH_2NR^{41}R^{42}$, $-OC(O)R^{41}$, $-OC_1$-C_6-alkyl-$C(O)OR^{41}$, $-OC_1$-C_6-alkyl-OR^{41}, -S-C_1-C_6-alkyl-$C(O)OR^{41}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{41}$, $-NR^{41}$-$C(=O)$-C_1-C_6-alkyl-$C(=O)OR^{41}$, $-NR^{41}$-$C(=O)$-C_1-C_6-alkenyl-$C(=O)OR^{41}$, $-C(O)OR^{41}$, $-C_2$-C_6-alkenyl-$C(=O)R^{41}$, =O, -NH-$C(=O)$-O-C_1-C_6-alkyl, or -NH-$C(=O)$-$C(=O)$-O-C_1-C_6-alkyl,

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl, which may each optionally be substituted with one or more substituents selected from R^{43},

- aryl, aryloxy, aryloxycarbonyl, aroyl, arylsulfanyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aroyl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl or heteroaryl-C_2-C_6-alkynyl, wherein the cyclic moieties optionally may be substituted with one or more substituents selected from R^{44},

R^{41} and R^{42} are independently selected from hydrogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkenyl, aryl-C_1-C_6-alkyl or aryl, wherein the alkyl moieties may optionally be substituted with one or more substituents independently selected from R^{45}, and the aryl moieties may optionally be substituted with one or more substituents independently selected from R^{46}; R^{41} and R^{42} when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom, the heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

R^{43} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OR^{41}$, and $-NR^{41}R^{42}$

R^{44} is independently selected from halogen, $-C(O)OR^{41}$, $-CH_2C(O)OR^{41}$, $-CH_2OR^{41}$, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{41}$, $-NR^{41}R^{42}$ and C_1-C_6-alkyl,
R^{45} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, -O-C_1-C_6-alkyl, -C(O)-O-C_1-C_6-alkyl, -COOH and $-NH_2$,
R^{46} is independently selected from halogen, $-C(O)OC_1$-C_6-alkyl, -COOH, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, -OH, $-OC_1$-C_6-alkyl, $-NH_2$, C(=O) or C_1-C_6-alkyl,

Q is a valence bond, C_1-C_6-alkylene, $-C_1$-C_6-alkyl-O-, $-C_1$-C_6-alkyl-NH-, -NH-C_1-C_6-alkyl, -NH-C(=O)-, -C(=O)-NH-, -O-C_1-C_6-alkyl, -C(=O)-, or $-C_1$-C_6-alkyl-C(=O)-N(R^{47})- wherein the alkyl moieties are optionally substituted with one or more substituents independently selected from R^{48},

R^{47} and R^{48} are independently selected from hydrogen, C_1-C_6-alkyl, aryl optionally substituted with one or more R^{49},

R^{49} is independently selected from halogen and –COOH,

T is

- hydrogen,
- C_1-C_6-alkyl, C_2-C_6-alkenyl , C_2-C_6-alkynyl, C_1-C_6-alkyloxy-carbonyl, wherein the alkyl, alkenyl and alkynyl moieties are optionally substituted with one or more substituents independently selected from R^{50},
- aryl, aryloxy, aryloxy-carbonyl, aryl-C_1-C_6-alkyl, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkyny-, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl, heteroaryl-C_2-C_6-alkynyl,

wherein any alkyl, alkenyl , alkynyl, aryl and heteroaryl moiety is optionally substituted with one or more substituents independently selected from R^{50},

R^{50} is C_1-C_6-alkyl, C_1-C_6-alkoxy, aryl, aryloxy, aryl-C_1-C_6-alkoxy, -C(=O)-NH-C_1-C_6-alkyl-aryl, heteroaryl, heteroaryl-C_1-C_6-alkoxy, -C_1-C_6-alkyl-COOH, -O-C_1-C_6-alkyl-COOH, $-S(O)_2R^{51}$, -C_2-C_6-alkenyl-COOH, $-OR^{51}$, $-NO_2$, halogen, -COOH, $-CF_3$, -CN, =O, $-N(R^{51}R^{52})$, wherein the aryl or heteroaryl moieties are optionally substituted with one or more R^{53},

R^{51} and R^{52} are independently selected from hydrogen and C_1-C_6-alkyl,
R^{53} is independently selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, -C_1-C_6-alkyl-COOH, -C_2-C_6-alkenyl-COOH, -OR^{51}, -NO_2, halogen, -COOH, -CF_3, -CN, or -$N(R^{51}R^{52})$,

or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

Embodiment 146. A pharmaceutical composition according to embodiment 148 wherein K is a valence bond, C_1-C_6-alkylene, -NH-C(=O)-U-, -C_1-C_6-alkyl-S-, -C_1-C_6-alkyl-O-, or -C(=O)-, wherein any C_1-C_6-alkyl moiety is optionally substituted with R^{38}.

Embodiment 147. A pharmaceutical composition according to embodiment 149 wherein K is a valence bond, C_1-C_6-alkylene, -NH-C(=O)-U-, -C_1-C_6-alkyl-S-, or -C_1-C_6-alkyl-O, wherein any C_1-C_6-alkyl moiety is optionally substituted with R^{38}.

Embodiment 148. A pharmaceutical composition according to embodiment 150 wherein K is a valence bond, C_1-C_6-alkylene, or -NH-C(=O)-U, wherein any C_1-C_6-alkyl moiety is optionally substituted with R^{38}.

Embodiment 149. A pharmaceutical composition according to embodiment 151 wherein K is a valence bond or C_1-C_6-alkylene, wherein any C_1-C_6-alkyl moiety is optionally substituted with R^{38}.

Embodiment 150. A pharmaceutical composition according to embodiment 151 wherein K is a valence bond or -NH-C(=O)-U.

Embodiment 151. A pharmaceutical composition according to embodiment 152 wherein K is a valence bond.

Embodiment 152. A pharmaceutical composition according to any one of the embodiments 148 to 154 wherein U is a valence bond or -C_1-C_6-alkyl-O-.

Embodiment 153. A pharmaceutical composition according to embodiment 155 wherein U is a valence bond.

Embodiment 154. A pharmaceutical composition according to any one of the embodiments 148 to 156 wherein M is arylene or heteroarylene, wherein the arylene or heteroarylene moieties are optionally substituted with one or more substituents independently selected from R^{40}.

Embodiment 155. A pharmaceutical composition according to embodiment 157 wherein M is ArG1 or Het1, wherein the arylene or heteroarylene moieties are optionally substituted with one or more substituents independently selected from R^{40}.

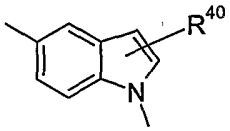
Embodiment 156. A pharmaceutical composition according to embodiment 158 wherein M is ArG1 or Het2, wherein the arylene or heteroarylene moieties are optionally substituted with one or more substituents independently selected from R^{40}.

Embodiment 157. A pharmaceutical composition according to embodiment 159 wherein M is ArG1 or Het3, wherein the arylene or heteroarylene moieties are optionally substituted with one or more substituents independently selected from R^{40}.

Embodiment 158. A pharmaceutical composition according to embodiment 160 wherein M is phenylene optionally substituted with one or more substituents independently selected from R^{40}.

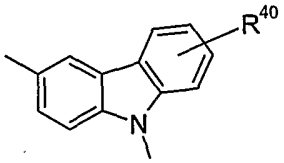
Embodiment 159. A pharmaceutical composition according to embodiment 160 wherein M is indolylene optionally substituted with one or more substituents independently selected from R^{40}.

Embodiment 160. A pharmaceutical composition according to embodiment 162 wherein M is



Embodiment 161. A pharmaceutical composition according to embodiment 160 wherein M is carbazolylene optionally substituted with one or more substituents independently selected from R^{40}.

Embodiment 162. A pharmaceutical composition according to embodiment 164 wherein M is



Embodiment 163. A pharmaceutical composition according to any one of the embodiments 148 to 165 wherein R^{40} is selected from

- hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{41}$, $-NR^{41}R^{42}$, $-SR^{41}$, $-S(O)_2R^{41}$, $-NR^{41}C(O)R^{42}$, $-OC_1$-C_6-alkyl-$C(O)NR^{41}R^{42}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{41}$, $-C(O)OR^{41}$, =O, -NH-C(=O)-O-C_1-C_6-alkyl, or -NH-C(=O)-C(=O)-O-C_1-C_6-alkyl,

C_1-C_6-alkyl or C_2-C_6- alkenyl which may each optionally be substituted with one or more substituents independently selected from R^{43},

- aryl, aryloxy, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, or heteroaryl-C_2-C_6-alkenyl, wherein the cyclic moieties optionally may be substituted with one or more substituents selected from R^{44}.

Embodiment 164. A pharmaceutical composition according to embodiment 166 wherein R^{40} is selected from

- hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{41}$, $-NR^{41}R^{42}$, $-SR^{41}$, $-S(O)_2R^{41}$, $-NR^{41}C(O)R^{42}$, $-OC_1$-C_6-alkyl-$C(O)NR^{41}R^{42}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{41}$, $-C(O)OR^{41}$, =O, -NH-C(=O)-O-C_1-C_6-alkyl, or -NH-C(=O)-C(=O)-O-C_1-C_6-alkyl,

C_1-C_6-alkyl or C_2-C_6- alkenyl which may each optionally be substituted with one or more substituents independently selected from R^{43},

- ArG1, ArG1-O-, ArG1-C_1-C_6-alkoxy, ArG1-C_1-C_6-alkyl, ArG1-C_2-C_6-alkenyl, Het3, Het3-C_1-C_6-alkyl, or Het3-C_2-C_6-alkenyl, wherein the cyclic moieties optionally may be substituted with one or more substituents selected from R^{44}.

Embodiment 165. A pharmaceutical composition according to embodiment 167 wherein R^{40} is selected from

- hydrogen, halogen, $-CF_3$, $-NO_2$, $-OR^{41}$, $-NR^{41}R^{42}$, $-C(O)OR^{41}$, =O, or $-NR^{41}C(O)R^{42}$,
- C_1-C_6-alkyl,
- ArG1.

Embodiment 166. A pharmaceutical composition according to embodiment 168 wherein R^{40} is selected from

- Halogen, $-NO_2$, $-OR^{41}$, $-NR^{41}R^{42}$, $-C(O)OR^{41}$, or $-NR^{41}C(O)R^{42}$,
- Methyl,
- Phenyl.

Embodiment 167. A pharmaceutical composition according to any one of the embodiments 148 to 170 wherein R^{41} and R^{42} are independently selected from hydrogen, C_1-C_6-alkyl, or aryl, wherein the aryl moieties may optionally be substituted with halogen or –COOH.

Embodiment 168. A pharmaceutical composition according to embodiment 171 wherein R^{41} and R^{42} are independently selected from hydrogen, methyl, ethyl, or phenyl, wherein the phenyl moieties may optionally be substituted with halogen or –COOH.

Embodiment 169. A pharmaceutical composition according to any one of the embodiments 148 to 172 wherein Q is a valence bond, C_1-C_6-alkylene, -C_1-C_6-alkyl-O-, -C_1-C_6-alkyl-NH-, -NH-C_1-C_6-alkyl, -NH-C(=O)-, -C(=O)-NH-, -O-C_1-C_6-alkyl, -C(=O)-, or -C_1-

C_6-alkyl-C(=O)-N(R^{47})- wherein the alkyl moieties are optionally substituted with one or more substituents independently selected from R^{48}.

Embodiment 170. A pharmaceutical composition according to embodiment 173 wherein Q is a valence bond, -CH_2-, -CH_2-CH_2-, -CH_2-O-, -CH_2-CH_2-O-, -CH_2-NH-, -CH_2-CH_2-NH-, -NH-CH_2-, -NH-CH_2-CH_2-, -NH-C(=O)-, -C(=O)-NH-, -O-CH_2-, -O-CH_2-CH_2-, or -C(=O)-.

Embodiment 171. A pharmaceutical composition according to any one of the embodiments 148 to 174 wherein R^{47} and R^{48} are independently selected from hydrogen, methyl and phenyl.

Embodiment 172. A pharmaceutical composition according to any one of the embodiments 148 to 178 wherein T is

- Hydrogen,
- C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{50},
- aryl, aryl-C_1-C_6-alkyl, heteroaryl, wherein the alkyl, aryl and heteroaryl moieties are optionally substituted with one or more substituents independently selected from R^{50}.

Embodiment 173. A pharmaceutical composition according to embodiment 179 wherein T is

- hydrogen,
- C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{50},
- ArG1, ArG1-C_1-C_6-alkyl, Het3, wherein the alkyl, aryl and heteroaryl moieties are optionally substituted with one or more substituents independently selected from R^{50}.

Embodiment 174. A pharmaceutical composition according to embodiment 180 wherein T is

- hydrogen,
- C_1-C_6-alkyl, optionally substituted with one or more substituents independently selected from R^{50},
- phenyl, phenyl-C_1-C_6-alkyl, wherein the alkyl and phenyl moieties are optionally substituted with one or more substituents independently selected from R^{50}.

Embodiment 175. A pharmaceutical composition according to any one of the embodiments 148 to 181 wherein R^{50} is C_1-C_6-alkyl, C_1-C_6-alkoxy, aryl, aryloxy, aryl-C_1-C_6-alkoxy, -C(=O)-NH-C_1-C_6-alkyl-aryl, heteroaryl, -C_1-C_6-alkyl-COOH, -O-C_1-C_6-alkyl-COOH, -$S(O)_2R^{51}$, -C_2-C_6-alkenyl-COOH, -OR^{51}, -NO_2, halogen, -COOH, -CF_3, -CN, =O, -N($R^{51}R^{52}$), wherein the aryl or heteroaryl moieties are optionally substituted with one or more R^{53}.

Embodiment 176. A pharmaceutical composition according to embodiment 183 wherein R^{50} is C_1-C_6-alkyl, C_1-C_6-alkoxy, aryl, aryloxy, aryl-C_1-C_6-alkoxy , -OR^{51}, -NO_2, halogen, -COOH, -CF_3, wherein any aryl moiety is optionally substituted with one or more R^{53}.

Embodiment 177. A pharmaceutical composition according to embodiment 184 wherein R^{50} is C_1-C_6-alkyl, aryloxy, aryl-C_1-C_6-alkoxy , -OR^{51}, halogen, -COOH, -CF_3, wherein any aryl moiety is optionally substituted with one or more R^{53}.

Embodiment 178. A pharmaceutical composition according to embodiment 185 wherein R^{50} is C_1-C_6-alkyl, ArG1-O-, ArG1-C_1-C_6-alkoxy , -OR^{51}, halogen, -COOH, -CF_3, wherein any aryl moiety is optionally substituted with one or more R^{53}.

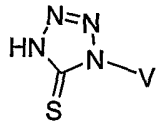
Embodiment 179. A pharmaceutical composition according to embodiment 186 wherein R^{50} is phenyl, methyl or ethyl.

Embodiment 180. A pharmaceutical composition according to embodiment 188 wherein R^{50} is methyl or ethyl.

Embodiment 181. A pharmaceutical composition according to any one of the embodiments 148 to 189 wherein R^{51} is methyl.

Embodiment 182. A pharmaceutical composition according to any one of the embodiments 148 to 192 wherein R^{53} is C_1-C_6-alkyl, C_1-C_6-alkoxy, -OR^{51}, halogen,or -CF_3.

Embodiment 183. A pharmaceutical composition according to embodiment 1 wherein the ligand that binds reversibly to a HisB10 Zn^{2+} site of an R-state insulin hexamer is



wherein V is C_1-C_6-alkyl, aryl, heteroaryl, aryl-C_{1-6}-alkyl- or aryl-C_{2-6}-alkenyl-, wherein the alkyl or alkenyl is optionally substituted with one or more substituents independently selected from R^{54}, and the aryl or heteroaryl is optionally substituted with one or more substituents independently selected from R^{55},

R^{54} is independently selected from halogen, -CN, -CF_3, -OCF_3, aryl, -COOH and –NH_2,

R^{55} is independently selected from

- hydrogen, halogen, -CN, -CH_2CN, -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -$S(O)_2CF_3$, -$OS(O)_2CF_3$, -SCF_3, -NO_2, -OR^{56}, -$NR^{56}R^{57}$, -SR^{56}, -$NR^{56}S(O)_2R^{57}$, -$S(O)_2NR^{56}R^{57}$, -$S(O)NR^{56}R^{57}$, -$S(O)R^{56}$, -$S(O)_2R^{56}$, -$OS(O)_2$ R^{56}, -$C(O)NR^{56}R^{57}$, -$OC(O)NR^{56}R^{57}$, -$NR^{56}C(O)R^{57}$, -$CH_2C(O)NR^{56}R^{57}$, -OC_1-C_6-alkyl-$C(O)NR^{56}R^{57}$, -CH_2OR^{56}, -$CH_2OC(O)R^{56}$, -$CH_2NR^{56}R^{57}$, -$OC(O)R^{56}$, -OC_1-C_8-alkyl-$C(O)OR^{56}$, -OC_1-C_6-alkyl-OR^{56}, -SC_1-C_6-alkyl-$C(O)OR^{56}$, –C_2-C_6-alkenyl-

$C(=O)OR^{56}$, $-NR^{56}-C(=O)-C_1-C_6$-alkyl-$C(=O)OR^{56}$, $-NR^{56}-C(=O)-C_1-C_6$-alkenyl-$C(=O)OR^{56}$, $-C(O)OR^{56}$, or $-C_2-C_6$-alkenyl-$C(=O)R^{56}$,

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl,

which may optionally be substituted with one or more substituents selected from R^{58},

- aryl, aryloxy, aryloxycarbonyl, aroyl, arylsulfanyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aroyl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl or heteroaryl-C_2-C_6-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{59},

R^{56} and R^{57} are independently selected from hydrogen, OH, CF_3, C_1-C_{12}-alkyl, aryl-C_1-C_6-alkyl, $-C(=O)-C_1-C_6$-alkyl or aryl, wherein the alkyl groups may optionally be substituted with one or more substituents independently selected from R^{60}, and the aryl groups may optionally be substituted with one or more substituents independently selected from R^{61}; R^{56} and R^{57} when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom, the heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

R^{58} is independently selected from halogen, $-CN$, $-CF_3$, $-OCF_3$, $-OR^{56}$, and $-NR^{56}R^{57}$,

R^{59} is independently selected from halogen, $-C(O)OR^{56}$, $-CH_2C(O)OR^{56}$, $-CH_2OR^{56}$, $-CN$, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{56}$, $-NR^{56}R^{57}$ and C_1-C_6-alkyl,

R^{60} is independently selected from halogen, $-CN$, $-CF_3$, $-OCF_3$, $-OC_1-C_6$-alkyl, $-C(O)OC_1-C_6$-alkyl, $-C(=O)-R^{62}$, $-COOH$ and $-NH_2$,

R^{61} is independently selected from halogen, $-C(O)OC_1-C_6$-alkyl, $-COOH$, $-CN$, $-CF_3$, $-OCF_3$, $-NO_2$, $-OH$, $-OC_1-C_6$-alkyl, $-NH_2$, $C(=O)$ or C_1-C_6-alkyl,

R^{62} is C_1-C_6-alkyl, aryl optionally substituted with one or more substituents independently selected from halogen, or heteroaryl optionally substituted with one or more C_1-C_6-alkyl independently,

or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

Embodiment 184. A pharmaceutical composition according to embodiment 196 wherein V is aryl, heteroaryl, or aryl-C_{1-6}-alkyl-, wherein the alkyl is optionally substituted with one or more substituents independently selected R^{54}, and the aryl or heteroaryl is optionally substituted with one or more substituents independently selected from R^{55}.

Embodiment 185. A pharmaceutical composition according to embodiment 197 wherein V is aryl, Het1, or aryl-C_{1-6}-alkyl-, wherein the alkyl is optionally substituted with one or more substituents independently selected from R^{54}, and the aryl or heteroaryl moiety is optionally substituted with one or more substituents independently selected from R^{55}.

Embodiment 186. A pharmaceutical composition according to embodiment 198 wherein V is aryl, Het2, or aryl-C_{1-6}-alkyl-, wherein the alkyl is optionally substituted with one or more substituents independently selected from R^{54}, and the aryl or heteroaryl moiety is optionally substituted with one or more substituents independently selected from R^{55}.

Embodiment 187. A pharmaceutical composition according to embodiment 199 wherein V is aryl, Het3, or aryl-C_{1-6}-alkyl-, wherein the alkyl is optionally substituted with one or more substituents independently selected from R^{54}, and the aryl or heteroaryl moiety is optionally substituted with one or more substituents independently selected from R^{55}.

Embodiment 188. A pharmaceutical composition according to embodiment 200 wherein V is aryl optionally substituted with one or more substituents independently selected from R^{55}.

Embodiment 189. A pharmaceutical composition according to embodiment 201 wherein V is ArG1 optionally substituted with one or more substituents independently selected from R^{55}.

Embodiment 190. A pharmaceutical composition according to embodiment 202 wherein V is phenyl, naphthyl or anthranyl optionally substituted with one or more substituents independently selected from R^{55}.

Embodiment 191. A pharmaceutical composition according to embodiment 203 wherein V is phenyl optionally substituted with one or more substituents independently selected from R^{55}.

Embodiment 192. A pharmaceutical composition according to any one of the embodiments 196 to 204 wherein R^{55} is independently selected from

- halogen, C_1-C_6-alkyl, -CN, $-OCF_3$,$-CF_3$, $-NO_2$, $-OR^{56}$, $-NR^{56}R^{57}$, $-NR^{56}C(O)R^{57}$ $-SR^{56}$, $-OC_1$-C_8-alkyl-$C(O)OR^{56}$, or $-C(O)OR^{56}$,

- C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{58}
- aryl, aryl-C_1-C_6-alkyl, heteroaryl, or heteroaryl-C_1-C_6-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents independently selected from R^{59}.

Embodiment 193. A pharmaceutical composition according to embodiment 205 wherein R^{55} is independently selected from

- halogen, C_1-C_6-alkyl, -CN, -OCF_3 ,-CF_3, -NO_2, -OR^{56}, -$NR^{56}R^{57}$, -$NR^{56}C(O)R^{57}$ -SR^{56}, -OC_1-C_8-alkyl-$C(O)OR^{56}$, or -$C(O)OR^{56}$
- C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{58}
- ArG1, ArG1-C_1-C_6-alkyl, Het3, or Het3-C_1-C_6-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents independently selected from R^{59}.

Embodiment 194. A pharmaceutical composition according to embodiment 206 wherein R^{55} is independently selected from halogen, -OR^{56}, -$NR^{56}R^{57}$, -$C(O)OR^{56}$, -OC_1-C_8-alkyl-$C(O)OR^{56}$, -$NR^{56}C(O)R^{57}$ or C_1-C_6-alkyl.

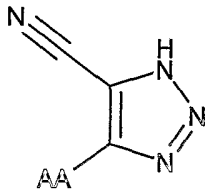
Embodiment 195. A pharmaceutical composition according to embodiment 207 wherein R^{55} is independently selected from halogen, -OR^{56}, -$NR^{56}R^{57}$, -$C(O)OR^{56}$, -OC_1-C_8-alkyl-$C(O)OR^{56}$, -$NR^{56}C(O)R^{57}$, methyl or ethyl.

Embodiment 196. A pharmaceutical composition according to any one of the embodiments 196 to 208 wherein R^{56} and R^{57} are independently selected from hydrogen, CF_3, C_1-C_{12}-alkyl, or -C(=O)-C_1-C_6-alkyl; R^{56} and R^{57} when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom.

Embodiment 197. A pharmaceutical composition according to embodiment 209 wherein R^{56} and R^{57} are independently selected from hydrogen or C_1-C_{12}-alkyl, R^{56} and R^{57} when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom.

Embodiment 198. A pharmaceutical composition according to embodiment 210 wherein R^{56} and R^{57} are independently selected from hydrogen or methyl, ethyl, propyl butyl, R^{56} and R^{57} when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom.

Embodiment 199. A pharmaceutical composition according to embodiment 1 wherein the ligand that binds reversibly to a HisB10 Zn^{2+} site of an R-state insulin hexamer is



wherein AA is C_1-C_6-alkyl, aryl, heteroaryl, aryl-C_{1-6}-alkyl- or aryl-C_{2-6}-alkenyl-, wherein the alkyl or alkenyl is optionally substituted with one or more substituents independently selected from R^{63}, and the aryl or heteroaryl is optionally substituted with one or more substituents independently selected from R^{64},

R^{63} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, aryl, -COOH and $-NH_2$,

R^{64} is independently selected from

- hydrogen, halogen, -CN, $-CH_2CN$, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-S(O)_2CF_3$, $-OS(O)_2CF_3$, $-SCF_3$, $-NO_2$, $-OR^{65}$, $-NR^{65}R^{66}$, $-SR^{65}$, $-NR^{65}S(O)_2R^{66}$, $-S(O)_2NR^{65}R^{66}$, $-S(O)NR^{65}R^{66}$, $-S(O)R^{65}$, $-S(O)_2R^{65}$, $-OS(O)_2\ R^{65}$, $-C(O)NR^{65}R^{66}$, $-OC(O)NR^{65}R^{66}$, $-NR^{65}C(O)R^{66}$, $-CH_2C(O)NR^{65}R^{66}$, $-OC_1$-C_6-alkyl-$C(O)NR^{65}R^{66}$, $-CH_2OR^{65}$, $-CH_2OC(O)R^{65}$, $-CH_2NR^{65}R^{66}$, $-OC(O)R^{65}$, $-OC_1$-C_6-alkyl-$C(O)OR^{65}$, $-OC_1$-C_6-alkyl-OR^{65}, $-SC_1$-C_6-alkyl-$C(O)OR^{65}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{65}$, $-NR^{65}$-$C(=O)$-C_1-C_6-alkyl-$C(=O)OR^{65}$, $-NR^{65}$-$C(=O)$-C_1-C_6-alkenyl-$C(=O)OR^{65}$, $-C(O)OR^{65}$, or $-C_2$-C_6-alkenyl-$C(=O)R^{65}$,

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl, each of which may optionally be substituted with one or more substituents selected from R^{67},

- aryl, aryloxy, aryloxycarbonyl, aroyl, arylsulfanyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aroyl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl or heteroaryl-C_2-C_6-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{68},

R^{65} and R^{66} are independently selected from hydrogen, OH, CF_3, C_1-C_{12}-alkyl, aryl-C_1-C_6-alkyl, $-C(=O)$-R^{69}, aryl or heteroaryl, wherein the alkyl groups may optionally be substituted

with one or more substituents selected from R^{70}, and the aryl and heteroaryl groups may optionally be substituted with one or more substituents independently selected from R^{71}; R^{65} and R^{66} when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom, the heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

R^{67} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OR^{65}$, and $-NR^{65}R^{66}$,

R^{68} is independently selected from halogen, $-C(O)OR^{65}$, $-CH_2C(O)OR^{65}$, $-CH_2OR^{65}$, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{65}$, $-NR^{65}R^{66}$ and C_1-C_6-alkyl,

R^{69} is independently selected from C_1-C_6-alkyl, aryl optionally substituted with one or more halogen, or heteroaryl optionally substituted with one or more C_1-C_6-alkyl,

R^{70} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OC_1$-C_6-alkyl, $-C(O)OC_1$-C_6-alkyl, -COOH and $-NH_2$,

R^{71} is independently selected from halogen, $-C(O)OC_1$-C_6-alkyl, -COOH, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, -OH, $-OC_1$-C_6-alkyl, $-NH_2$, C(=O) or C_1-C_6-alkyl,

or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

Embodiment 200. A pharmaceutical composition according to embodiment 212 wherein AA is aryl, heteroaryl or aryl-C_{1-6}-alkyl-, wherein the alkyl is optionally substituted with one or more R^{63}, and the aryl or heteroaryl is optionally substituted with one or more substituents independently selected from R^{64}.

Embodiment 201. A pharmaceutical composition according to embodiment 213 wherein AA is aryl or heteroaryl optionally substituted with one or more substituents independently selected from R^{64}.

Embodiment 202. A pharmaceutical composition according to embodiment 214 wherein AA is ArG1 or Het1 optionally substituted with one or more substituents independently selected from R^{64}.

Embodiment 203. A pharmaceutical composition according to embodiment 215 wherein AA is ArG1 or Het2 optionally substituted with one or more substituents independently selected from R^{64}.

Embodiment 204. A pharmaceutical composition according to embodiment 216 wherein AA is ArG1 or Het3 optionally substituted with one or more substituents independently selected from R^{64}.

Embodiment 205. A pharmaceutical composition according to embodiment 217 wherein AA is phenyl, naphtyl, anthryl, carbazolyl, thienyl, pyridyl, or benzodioxyl optionally substituted with one or more substituents independently selected from R^{64}.

Embodiment 206. A pharmaceutical composition according to embodiment 218 wherein AA is phenyl or naphtyl optionally substituted with one or more substituents independently selected from R^{64}.

Embodiment 207. A pharmaceutical composition according to any one of the embodiments 212 to 219 wherein R^{64} is independently selected from hydrogen, halogen, $-CF_3$, $-OCF_3$, $-OR^{65}$, $-NR^{65}R^{66}$, C_1-C_6-alkyl , $-OC(O)R^{65}$, $-OC_1$-C_6-alkyl-$C(O)OR^{65}$, aryl-C_2-C_6-alkenyl, aryloxy or aryl, wherein C_1-C_6-alkyl is optionally substituted with one or more substituents independently selected from R^{67}, and the cyclic moieties optionally are substituted with one or more substituents independently selected from R^{68}.

Embodiment 208. A pharmaceutical composition according to embodiment 220 wherein R^{64} is independently selected from halogen, $-CF_3$, $-OCF_3$, $-OR^{65}$, $-NR^{65}R^{66}$, methyl, ethyl, propyl, $-OC(O)R^{65}$, $-OCH_2$-$C(O)OR^{65}$, $-OCH_2$-CH_2-$C(O)OR^{65}$, phenoxy optionally substituted with one or more substituents independently selected from R^{68}.

Embodiment 209. A pharmaceutical composition according to any one of the embodiments 212 to 221 wherein R^{65} and R^{66} are independently selected from hydrogen, CF_3, C_1-C_{12}-alkyl, aryl, or heteroaryl optionally substituted with one or more substituents independently selected from R^{71}.

Embodiment 210. A pharmaceutical composition according to embodiment 222 wherein R^{65} and R^{66} are independently hydrogen, C_1-C_{12}-alkyl, aryl, or heteroaryl optionally substituted with one or more substituents independently selected from R^{71}.

Embodiment 211. A pharmaceutical composition according to embodiment 223 wherein R^{65} and R^{66} are independently hydrogen, methyl, ethyl, propyl, butyl, 2,2-dimethyl-propyl, ArG1 or Het1 optionally substituted with one or more substituents independently selected from R^{71}.

Embodiment 212. A pharmaceutical composition according to embodiment 224 wherein R^{65} and R^{66} are independently hydrogen, methyl, ethyl, propyl, butyl, 2,2-dimethyl-propyl, ArG1 or Het2 optionally substituted with one or more substituents independently selected from R^{71}.

Embodiment 213. A pharmaceutical composition according to embodiment 225 wherein R^{65} and R^{66} are independently hydrogen, methyl, ethyl, propyl, butyl, 2,2-dimethyl-propyl, ArG1 or Het3 optionally substituted with one or more substituents independently selected from R^{71}.

Embodiment 214. A pharmaceutical composition according to embodiment 226 wherein R^{65} and R^{66} are independently hydrogen, methyl, ethyl, propyl, butyl, 2,2-dimethyl-propyl, phenyl, naphtyl, thiadiazolyl optionally substituted with one or more R^{71} independently; or isoxazolyl optionally substituted with one or more substituents independently selected from R^{71}.

Embodiment 215. A pharmaceutical composition according to any one of the embodiments 212 to 227 wherein R^{71} is halogen or C_1-C_6-alkyl.

Embodiment 216. A pharmaceutical composition according to embodiment 228 wherein R^{71} is halogen or methyl.

Embodiment 217. Method of prolonging the action of an insulin preparation comprising insulin, protamine and zinc ions wherein said method comprises adding a zinc-binding ligand according to any of embodiments 21 to 216 to the insulin preparation.

Embodiment 218. A method of treating type 1 or type 2 diabetes comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical preparation according to any one of the embodiments 1 to216.

Embodiment 219. Use of a preparation according to any one of the embodiments 1 to 216for the preparation of a medicament for treatment of type 1 or type 2 diabetes.

Embodiment 220. A method of preparing a pharmaceutical preparation comprising the steps of mixing

- insulin
- a ligand for the His^{B10} Zn^{2+} site of the insulin hexamer according to any of embodiments 21 to 216
- zinc ions
- protamine
- optionally further ingredients selected from the group consisting of phenolic preservative, buffer, isotonicity agent, viscosity increasing agent, and a non-ionic surfactant,

and allowing the mixture to stand until crystals are formed.

Embodiment 221. A method according to embodiment 233 wherein the ligand for the His^{B10} Zn^{2+} site is added to the mixture before crystal growth.

Embodiment 222. A method according to embodiment 233 wherein the ligand for the His^{B10} Zn^{2+} site is added to the mixture after completion of crystal growth.

The novel NPH-insulin preparations disclosed here can be used for parenteral or pulmonal administration.

In another embodiment the NPH preparations of the present invention are used in connection with pen-like injection devices, which may be prefilled and disposable, or the insulin preparations may be supplied from a reservoir which is removable. Non-limiting examples of pen-like injection devices are FlexPen®, InnoLet®, InDuo™, Innovo®.

In a further embodiment NPH preparations of the present invention may be used in connection with devices for pulmonary administration of aqueous insulin preparations. In one embodiment hereof, the NPH preparation of the invention is dried to form a powder. In that embodiment, suitable devices used in pulmonary administration of a NPH preparation according to the present invention may be the dry powder formulation and delivery devices being developed by Inhale Therapeutic Systems, Inc., and the Spiros® dry powder inhaler system being developed by Dura Pharmaceuticals, Inc.

In one aspect of the invention the zinc-binding ligand for the His^{B10} Zn^{2+} site is present in the preparation in a smaller concentration than that of Zn^{2+}. In such an embodiment not all of the insulin hexamers will have zinc-binding ligand for the His^{B10} Zn^{2+} site present, and thus insulin from these hexamers will be released rapidly. Such a preparation will therefore have a dual-release profile after administration, i.e. the administration will result in a both a rapid release of insulin and a protracted release.

PHARMACEUTICAL COMPOSITIONS

Insulin formulations of the invention are usually administered from multi-dose containers where a preservative effect is desired. Since phenolic preservatives also stabilize the R-state hexamer the formulations may contain up to 50 mM of phenolic molecules. The phenolic molecules in the insulin formulation may be selected from the group consisting of phenol, m-cresol, chloro-cresol, thymol, m-chlor-phenol, resorcinole, 7-hydroxyindole or any mixture thereof.

In one embodiment of the invention 0.5 to 5.0 mg/ml of phenolic compound may be employed.

In another embodiment of the invention 0.6 to 5.0 mg/ml of m-cresol may be employed.

In another embodiment of the invention 0.5 to 5.0 mg/ml of phenol may be employed.

In another embodiment of the invention 1.4 to 5.0 mg/ml of phenol may be employed.

In another embodiment of the invention 0.5 to 5.0 mg/ml of a mixture of m-cresol or phenol may be employed.

In another embodiment of the invention 1.4 to 5.0 mg/ml of a mixture of m-cresol or phenol may be employed.

The pharmaceutical preparation may further comprises a buffer substance, such as a TRIS, phosphate, glycine or glycylglycine (or another zwitterionic substance) buffer, an isotonicity agent, such as NaCl, glycerol, mannitol and/or lactose. Chloride would be used at moderate concentrations (e.g. up to 50 mM) to avoid competition with the zinc-site ligands of the present invention.

The action of insulin may further be slowed down in vivo by the addition of physiologically acceptable agents that increase the viscosity of the pharmaceutical preparation. Thus, the pharmaceutical preparation according to the invention may furthermore comprise an agent which increases the viscosity, such as polyethylene glycol, polypropylene glycol, copolymers thereof, dextrans and/or polylactides.

In a particular embodiment the insulin preparation of the invention comprises between 0.001 % by weight and 1 % by weight of a non-ionic surfactant, for example tween 20 or Poloxamer 188.

The insulin preparation of the present invention may have a pH value in the range of 3.5 to 8.5, more preferably 7.1 to 7.9.

COMBINATION TREATMENT

The invention furthermore relates to treatment of a patient in which the pharmaceutical preparation of the invention, i.e. comprising zinc ions, acid-stabilised insulin analogue and a ligand for the R-state His^{B10} Zn^{2+} site, is combined with another form of treatment.

In one aspect of the invention, treatment of a patient with the pharmaceutical preparation of the invention is combined with diet and/or exercise.

In another aspect of the invention the pharmaceutical preparation of the invention is administered in combination with one or more further active substances in any suitable ratios. Such further active substances may e.g. be selected from antiobesity agents, antidiabetics, antihypertensive agents, agents for the treatment of complications resulting from or associated with diabetes and agents for the treatment of complications and disorders resulting from or associated with obesity.

Thus, in a further aspect of the invention the pharmaceutical preparation of the invention may be administered in combination with one or more antiobesity agents or appetite regulating agents.

Such agents may be selected from the group consisting of CART (cocaine amphetamine regulated transcript) agonists, NPY (neuropeptide Y) antagonists, MC4 (melanocortin 4) agonists, MC3 (melanocortin 3) agonists, orexin antagonists, TNF (tumor necrosis factor) agonists, CRF (corticotropin releasing factor) agonists, CRF BP (corticotropin releasing factor binding protein) antagonists, urocortin agonists, β3 adrenergic agonists such as CL-316243, AJ-9677, GW-0604, LY362884, LY377267 or AZ-40140, MSH (melanocyte-stimulating hormone) agonists, MCH (melanocyte-concentrating hormone) antagonists, CCK (cholecystokinin) agonists, serotonin re-uptake inhibitors such as fluoxetine, seroxat or citalopram, serotonin and noradrenaline re-uptake inhibitors, mixed serotonin and noradrenergic compounds, 5HT (serotonin) agonists, bombesin agonists, galanin antagonists, growth hormone, growth factors such as prolactin or placental lactogen, growth hormone releasing compounds, TRH (thyreotropin releasing hormone) agonists, UCP 2 or 3 (uncoupling protein 2 or 3) modulators, leptin agonists, DA agonists (bromocriptin, doprexin), lipase/amylase inhibitors, PPAR (peroxisome proliferator-activated receptor) modulators, RXR (retinoid X receptor) modulators, TR β agonists, AGRP (Agouti related protein) inhibitors, H3 histamine antagonists, opioid antagonists (such as naltrexone), exendin-4, GLP-1 and ciliary neurotrophic factor.

In one embodiment of the invention the antiobesity agent is leptin.

In another embodiment the antiobesity agent is dexamphetamine or amphetamine.

In another embodiment the antiobesity agent is fenfluramine or dexfenfluramine.

In still another embodiment the antiobesity agent is sibutramine.

In a further embodiment the antiobesity agent is orlistat.

In another embodiment the antiobesity agent is mazindol or phentermine.

In still another embodiment the antiobesity agent is phendimetrazine, diethylpropion, fluoxetine, bupropion, topiramate or ecopipam.

The orally active hypoglycemic agents comprise imidazolines, sulphonylureas, biguanides, meglitinides, oxadiazolidinediones, thiazolidinediones, insulin sensitizers, insulin secretagogues such as glimepride, α-glucosidase inhibitors, agents acting on the ATP-dependent potassium channel of the β-cells eg potassium channel openers such as those disclosed in WO 97/26265, WO 99/03861 and WO 00/37474 (Novo Nordisk A/S) which are incorporated herein by reference, or mitiglinide, or a potassium channel blocker, such as

BTS-67582, nateglinide, glucagon antagonists such as those disclosed in WO 99/01423 and WO 00/39088 (Novo Nordisk A/S and Agouron Pharmaceuticals, Inc.), which are incorporated herein by reference, GLP-1 agonists such as those disclosed in WO 00/42026 (Novo Nordisk A/S and Agouron Pharmaceuticals, Inc.), which are incorporated herein by reference, DPP-IV (dipeptidyl peptidase-IV) inhibitors, PTPase (protein tyrosine phosphatase) inhibitors, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis and/or glycogenolysis, glucose uptake modulators, GSK-3 (glycogen synthase kinase-3) inhibitors, compounds modifying the lipid metabolism such as antilipidemic agents, compounds lowering food intake, PPAR (peroxisome proliferator-activated receptor) and RXR (retinoid X receptor) agonists, such as ALRT-268, LG-1268 or LG-1069.

In a further embodiment of the invention the pharmaceutical preparation of the invention is administered in combination with a sulphonylurea e.g. tolbutamide, chlorpropamide, tolazamide, glibenclamide, glipizide, glimepiride, glicazide or glyburide.

In another embodiment of the invention the pharmaceutical preparation of the invention is administered in combination with a biguanide, e.g. metformin.

In yet another embodiment of the invention the pharmaceutical preparation of the invention is administered in combination with a meglitinide eg repaglinide or nateglinide.

In still another embodiment of the invention the pharmaceutical preparation of the invention is administered in combination with a thiazolidinedione insulin sensitizer, e.g. troglitazone, ciglitazone, pioglitazone, rosiglitazone, isaglitazone, darglitazone, englitazone, CS-011/CI-1037 or T 174 or the compounds disclosed in WO 97/41097, WO 97/41119, WO 97/41120, WO 00/41121 and WO 98/45292 (Dr. Reddy's Research Foundation), which are incorporated herein by reference.

In still another embodiment of the invention the pharmaceutical preparation of the invention may be administered in combination with an insulin sensitizer, e.g. such as GI 262570, YM-440, MCC-555, JTT-501, AR-H039242, KRP-297, GW-409544, CRE-16336, AR-H049020, LY510929, MBX-102, CLX-0940, GW-501516 or the compounds disclosed in WO 99/19313, WO 00/50414, WO 00/63191, WO 00/63192, WO 00/63193 (Dr. Reddy's Research Foundation) and WO 00/23425, WO 00/23415, WO 00/23451, WO 00/23445, WO 00/23417, WO 00/23416, WO 00/63153, WO 00/63196, WO 00/63209, WO 00/63190 and WO 00/63189 (Novo Nordisk A/S), which are incorporated herein by reference.

In a further embodiment of the invention the pharmaceutical preparation of the invention is administered in combination with an α-glucosidase inhibitor, e.g. voglibose, emiglitate, miglitol or acarbose.

In another embodiment of the invention the pharmaceutical preparation of the invention is administered in combination with an agent acting on the ATP-dependent potassium channel of the β-cells, e.g. tolbutamide, glibenclamide, glipizide, glicazide, BTS-67582 or repaglinide.

In yet another embodiment of the invention the pharmaceutical preparation of the invention may be administered in combination with nateglinide.

In still another embodiment of the invention the pharmaceutical preparation of the invention is administered in combination with an antilipidemic agent, e.g. cholestyramine, colestipol, clofibrate, gemfibrozil, lovastatin, pravastatin, simvastatin, probucol or dextrothyroxine.

In another aspect of the invention, the pharmaceutical preparation of the invention is administered in combination with more than one of the above-mentioned compounds, e.g. in combination with metformin and a sulphonylurea such as glyburide; a sulphonylurea and acarbose; nateglinide and metformin; acarbose and metformin; a sulphonylurea, metformin and troglitazone; metformin and a sulphonylurea; etc.

Furthermore, the pharmaceutical preparation of the invention may be administered in combination with one or more antihypertensive agents. Examples of antihypertensive agents are β-blockers such as alprenolol, atenolol, timolol, pindolol, propranolol and metoprolol, ACE (angiotensin converting enzyme) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, quinapril and ramipril, calcium channel blockers such as nifedipine, felodipine, nicardipine, isradipine, nimodipine, diltiazem and verapamil, and α-blockers such as doxazosin, urapidil, prazosin and terazosin. The pharmaceutical preparation of the invention may also be combined with NEP inhibitors such as candoxatril.

Further reference can be made to Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

It should be understood that any suitable combination of the compounds according to the invention with diet and/or exercise, one or more of the above-mentioned compounds and optionally one or more other active substances are considered to be within the scope of the present invention.

EXAMPLES

The following examples and general procedures refer to intermediate compounds and final products identified in the specification and in the synthesis schemes. The preparation of the compounds of the present invention is described in detail using the following examples, but the chemical reactions described are disclosed in terms of their general applicability to the

preparation of compounds of the invention. Occasionally, the reaction may not be applicable as described to each compound included within the disclosed scope of the invention. The compounds for which this occurs will be readily recognised by those skilled in the art. In these cases the reactions can be successfully performed by conventional modifications known to those skilled in the art, that is, by appropriate protection of interfering groups, by changing to other conventional reagents, or by routine modification of reaction conditions. Alternatively, other reactions disclosed herein or otherwise conventional will be applicable to the preparation of the corresponding compounds of the invention. In all preparative methods, all starting materials are known or may easily be prepared from known starting materials. All temperatures are set forth in degrees Celsius and unless otherwise indicated, all parts and percentages are by weight when referring to yields and all parts are by volume when referring to solvents and eluents.

HPLC-MS (Method A)

The following instrumentation was used:

- Hewlett Packard series 1100 G1312A Bin Pump
- Hewlett Packard series 1100 Column compartment
- Hewlett Packard series 1100 G13 15A DAD diode array detector
- Hewlett Packard series 1100 MSD

The instrument was controlled by HP Chemstation software.

The HPLC pump was connected to two eluent reservoirs containing:

A: 0.01% TFA in water

B: 0.01% TFA in acetonitrile

The analysis was performed at 40 °C by injecting an appropriate volume of the sample (preferably 1 μL) onto the column, which was eluted with a gradient of acetonitrile.

The HPLC conditions, detector settings and mass spectrometer settings used are given in the following table.

Column	Waters Xterra MS C-18 X 3 mm id
Gradient	10% - 100% acetonitrile lineary during 7.5 min at 1.0 mL/min
Detection	UV: 210 nm (analog output from DAD)
MS	Ionisation mode: API-ES Scan 100-1000 amu step 0.1 amu

HPLC-MS (Method B)

The following instrumentation was used:

Sciex API 100 Single quadropole mass spectrometer

Perkin Elmer Series 200 Quard pump

Perkin Elmer Series 200 autosampler

Applied Biosystems 785A UV detector

Sedex 55 evaporative light scattering detector

A Valco column switch with a Valco actuator controlled by timed events from the pump.

The Sciex Sample control software running on a Macintosh PowerPC 7200 computer was used for the instrument control and data acquisition.

The HPLC pump was connected to four eluent reservoirs containing:

A: Acetonitrile

B: Water

C: 0.5% TFA in water

D: 0.02 M ammonium acetate

The requirements for samples are that they contain approximately 500 µg/mL of the compound to be analysed in an acceptable solvent such as methanol, ethanol, acetonitrile, THF, water and mixtures thereof. (High concentrations of strongly eluting solvents will interfere with the chromatography at low acetonitrile concentrations.)

The analysis was performed at room temperature by injecting 20 µL of the sample solution on the column, which was eluted with a gradient of acetonitrile in either 0.05% TFA or 0.002

M ammonium acetate. Depending on the analysis method varying elution conditions were used.

The eluate from the column was passed through a flow splitting T-connector, which passed approximately 20 µL/min through approx. 1 m. 75 µ fused silica capillary to the API interface of API 100 spectrometer.

The remaining 1.48 mL/min was passed through the UV detector and to the ELS detector.

During the LC-analysis the detection data were acquired concurrently from the mass spectrometer, the UV detector and the ELS detector.

The LC conditions, detector settings and mass spectrometer settings used for the different methods are given in the following table.

Column	YMC ODS-A 120Å s - 5µ 3 mm x 50 mm id	
Gradient	5% - 90% acetonitrile in 0.05% TFA linearly during 7.5 min at 1.5 mL/min	
Detection	UV: 214 nm	ELS: 40 °C
MS	Experiment: Start: 100 amu Stop: 800 amu Step: 0.2 amu Dwell: 0.571 msec Method: Scan 284 times = 9.5 min	

HPLC-MS (Method C) The following instrumentation is used:

- Hewlett Packard series 1100 G1312A Bin Pump
- Hewlett Packard series 1100 Column compartment
- Hewlett Packard series 1100 G1315A DAD diode array detector
- Hewlett Packard series 1100 MSD
- Sedere 75 Evaporative Light Scattering detector

The instrument is controlled by HP Chemstation software.

The HPLC pump is connected to two eluent reservoirs containing:

A **0.01% TFA in water**

B **0.01% TFA in acetonitrile**

The analysis is performed at 40 °C by injecting an appropriate volume of the sample (preferably 1 µl) onto the column which is eluted with a gradient of acetonitrile.
The HPLC conditions, detector settings and mass spectrometer settings used are given in the following table.

Column	**Waters Xterra MS C-18 X 3 mm id 5 µm**
Gradient	**5% - 100% acetonitrile linear during 7.5 min at 1.5 ml/min**
Detection	**210 nm (analogue output from DAD)**
	ELS (analogue output from ELS)
MS	**ionisation mode API-ES**
	Scan 100-1000 amu step 0.1 amu

After the DAD the flow is divided yielding approximately 1 ml/min to the ELS and 0.5 ml/min to the MS.

HPLC-MS (Method D)

The following instrumentation was used:
Sciex API 150 Single Quadropole mass spectrometer
Hewlett Packard Series 1100 G1312A Bin pump
Gilson 215 micro injector
Hewlett Packard Series 1100 G1315A DAD diode array detector
Sedex 55 evaporative light scattering detector
A Valco column switch with a Valco actuator controlled by timed events from the pump.
The Sciex Sample control software running on a Macintosh Power G3 computer was used for the instrument control and data acquisition.
The HPLC pump was connected to two eluent reservoirs containing:

A: Acetonitrile containing 0.05% TFA
B: Water containing 0.05% TFA

The requirements for the samples are that they contain approximately 500 µg/ml of the compound to be analysed in an acceptable solvent such as methanol, ethanol, acetonitrile, THF, water and mixtures thereof. (High concentrations of strongly eluting solvents will interfere with the chromatography at low acetonitrile concentrations.)

The analysis was performed at room temperature by injecting 20 µl of the sample solution on the column, which was eluted with a gradient of acetonitrile in 0.05% TFA

The eluate from the column was passed through a flow splitting T-connector, which passed approximately 20 µl/min through approx. 1 m 75 µ fused silica capillary to the API interface of API 150 spectrometer.

The remaining 1.48 ml/min was passed through the UV detector and to the ELS detector.

During the LC-analysis the detection data were acquired concurrently from the mass spectrometer, the UV detector and the ELS detector.

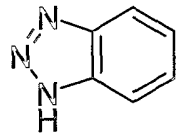
The LC conditions, detector settings and mass spectrometer settings used for the different methods are given in the following table.

Column	Waters X-terra C18 5µ 3 mm x 50 mm id			
Gradient	5% - 90% acetonitrile in 0.05% TFA linearly during 7.5 min at 1.5 ml/min			
Detection	UV: 214 nm		ELS: 40 °C	
MS	Experiment:	Start: 100 amu	Stop: 800 amu	Step: 0.2 amu
	Dwell:	0.571 msec		
	Method:	Scan 284 times = 9.5 min		

EXAMPLES

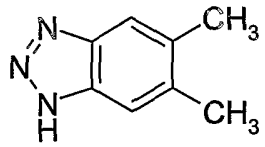
Example 1

1*H*-Benzotriazole



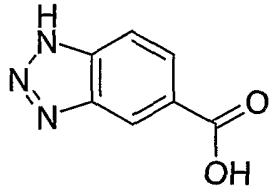
Example 2

5,6-Dimethyl-1*H*-benzotriazole



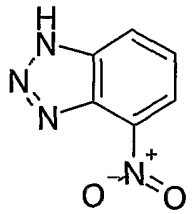
Example 3

1*H*-Benzotriazole-5-carboxylic acid



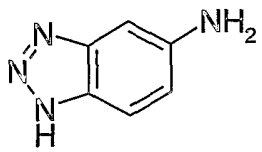
Example 4

4-Nitro-1*H*-benzotriazole



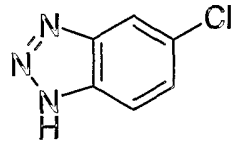
Example 5

5-Amino-1*H*-benzotriazole



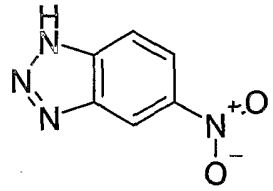
Example 6

5-Chloro-1*H*-benzotriazole



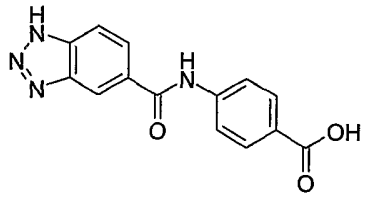
Example 7

5-Nitro-1*H*-benzotriazole



Example 8

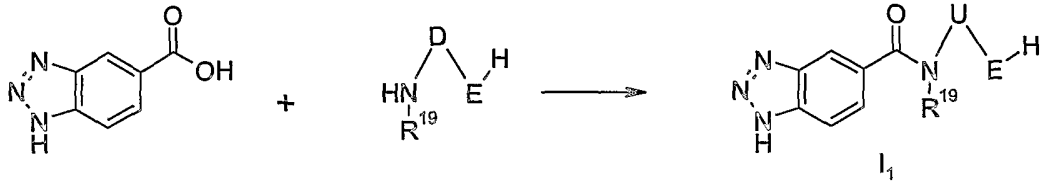
4-[(1*H*-Benzotriazole-5-carbonyl)amino]benzoic acid



4-[(1*H*-Benzotriazole-5-carbonyl)amino]benzoic acid methyl ester (5.2 g, 17.6 mmol) was dissolved in THF (60 mL) and methanol (10 mL) was added followed by 1N sodium hydroxide (35 mL). The mixture was stirred at room temperature for 16 hours and then 1N hydrochloric acid (45 mL) was added. The mixture was added water (200 mL) and extracted with ethyl acetate (2 x 500 mL). The combined organic phases were evaporated *in vacuo* to afford 0.44 g of 4-[(1*H*-benzotriazole-5-carbonyl)amino]benzoic acid. By filtration of the aqueous phase a further crop of 4-[(1*H*-benzotriazole-5-carbonyl)amino]benzoic acid was isolated (0.52 g).

^{1}H-NMR (DMSO-d_6): δ 7.97 (4H, s), 8.03 (2H, m), 8.66 (1H, bs), 10.7 (1H, s), 12.6 (1H, bs); HPLC-MS (Method A): m/z: 283 (M+1); Rt = 1.85 min.

General procedure (A) for preparation of compounds of general formula I_1:



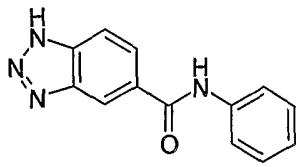
wherein D, E and R^{19} are as defined above, and E is optionally substituted with up to three substituents R^{21}, R^{22} and R^{23} independently as defined above.

The carboxylic acid of 1H-benzotriazole-5-carboxylic acid is activated, ie the OH functionality is converted into a leaving group L (selected from eg fluorine, chlorine, bromine, iodine, 1-imidazolyl, 1,2,4-triazolyl, 1-benzotriazolyloxy, 1-(4-aza benzotriazolyl)oxy, pentafluorophenoxy, N-succinyloxy 3,4-dihydro-4-oxo-3-(1,2,3-benzotriazinyl)oxy, benzotriazole 5-COO, or any other leaving group known to act as a leaving group in acylation reactions. The activated benzotriazole-5-carboxylic acid is then reacted with R^2-$(CH_2)_n$-B' in the presence of a base. The base can be either absent (i.e. R^2-$(CH_2)_n$-B' acts as a base) or triethylamine, N-ethyl-N,N.-diisopropylamine, N-methylmorpholine, 2,6-lutidine, 2,2,6,6-tetramethylpiperidine, potassium carbonate, sodium carbonate, caesium carbonate or any other base known to be useful in acylation reactions. The reaction is performed in a solvent solvent such as THF, dioxane, toluene, dichloromethane, DMF, NMP or a mixture of two or more of these. The reaction is performed between 0 °C and 80 °C, preferably between 20 °C and 40 °C. When the acylation is complete, the product is isolated by extraction, filtration, chromatography or other methods known to those skilled in the art.

The general procedure (A) is further illustrated in the following example:

Example 9 (General Procedure (A))

1*H*-Benzotriazole-5-carboxylic acid phenylamide



Benzotriazole-5-carboxylic acid (856 mg), HOAt (715 mg) and EDAC (1.00 g) were dissolved in DMF (17.5 mL) and the mixture was stirred at room temperature 1 hour. A 0.5 mL aliqot of this mixture was added to aniline (13.7 μL, 0.15 mmol) and the resulting mixture was vigorously shaken at room temperature for 16 hours. 1N hydrochloric acid (2 mL) and ethyl ace-

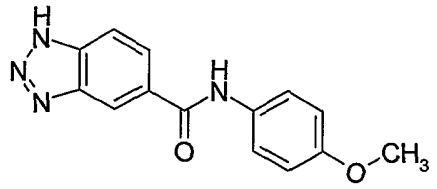
tate (1 mL) were added and the mixture was vigorously shaken at room temperature for 2 hours. The organic phase was isolated and concentrated *in vacuo* to afford the title compound.

HPLC-MS (Method B): m/z: 239 (M+1); Rt = 3.93 min.

The compounds in the following examples were similarly made. Optionally, the compounds may be isolated by filtration or by chromatography.

Example 10 (General Procedure (A))

1*H*-Benzotriazole-5-carboxylic acid (4-methoxyphenyl)amide

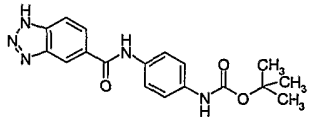


HPLC-MS (Method A): m/z: 269 (M+1) & 291 (M+23); Rt = 2.41 min

HPLC-MS (Method B): m/z: 239 (M+1); Rt = 3.93 min.

Example 11 (General Procedure (A))

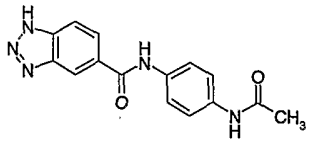
{4-[(1*H*-Benzotriazole-5-carbonyl)amino]phenyl}carbamic acid *tert*-butyl ester



HPLC-MS (Method B): m/z: 354 (M+1); Rt = 4.58 min.

Example 12 (General Procedure (A))

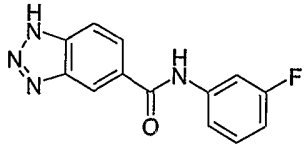
1*H*-Benzotriazole-5-carboxylic acid (4-acetylaminophenyl)amide



HPLC-MS (Method B): m/z: 296 (M+1); Rt = 3.32 min.

Example 13 (General Procedure (A))

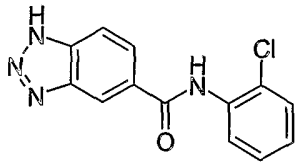
1*H*-Benzotriazole-5-carboxylic acid (3-fluorophenyl)amide



HPLC-MS (Method B): m/z: 257 (M+1); Rt = 4.33 min.

Example 14 (General Procedure (A))

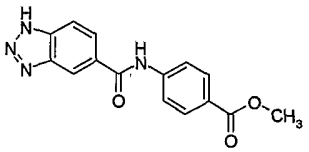
1*H*-Benzotriazole-5-carboxylic acid (2-chlorophenyl)amide



HPLC-MS (Method B): m/z: 273 (M+1); Rt = 4.18 min.

Example 15 (General Procedure (A))

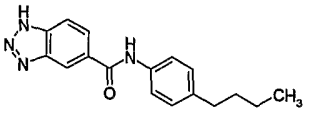
4-[(1*H*-Benzotriazole-5-carbonyl)amino]benzoic acid methyl ester



HPLC-MS (Method A):m/z: 297 (M+1); Rt : 2,60 min. HPLC-MS (Method B): m/z: 297 (M+1); Rt = 4.30 min.

Example 16 (General Procedure (A))

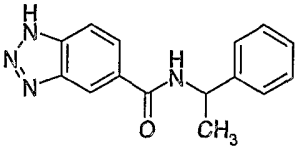
1*H*-Benzotriazole-5-carboxylic acid (4-butylphenyl)amide



HPLC-MS (Method B): m/z: 295 (M+1); Rt = 5.80 min.

Example 17 (General Procedure (A))

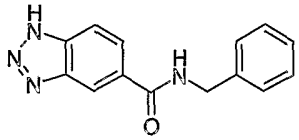
1*H*-Benzotriazole-5-carboxylic acid (1-phenylethyl)amide



HPLC-MS (Method B): m/z: 267 (M+1); Rt = 4.08 min.

Example 18 (General Procedure (A))

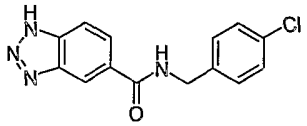
1*H*-Benzotriazole-5-carboxylic acid benzylamide



HPLC-MS (Method B): m/z: 253 (M+1); Rt = 3.88 min.

Example 19 (General Procedure (A))

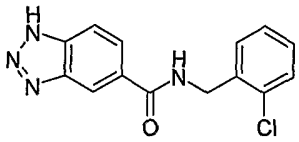
1*H*-Benzotriazole-5-carboxylic acid 4-chlorobenzylamide



HPLC-MS (Method B): m/z: 287 (M+1); Rt = 4.40 min.

Example 20 (General Procedure (A))

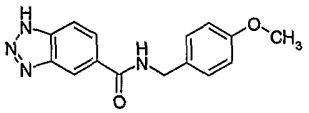
1*H*-Benzotriazole-5-carboxylic acid 2-chlorobenzylamide



HPLC-MS (Method B): m/z: 287 (M+1); Rt = 4.25 min.

Example 21 (General Procedure (A))

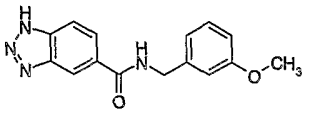
1*H*-Benzotriazole-5-carboxylic acid 4-methoxybenzylamide



HPLC-MS (Method B): m/z: 283 (M+1); Rt = 3.93 min.

Example 22 (General Procedure (A))

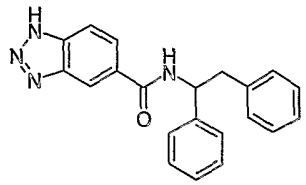
1*H*-Benzotriazole-5-carboxylic acid 3-methoxybenzylamide



HPLC-MS (Method B): m/z: 283 (M+1); Rt = 3.97 min.

Example 23 (General Procedure (A))

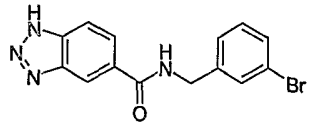
1*H*-Benzotriazole-5-carboxylic acid (1,2-diphenylethyl)amide



HPLC-MS (Method B): m/z: 343 (M+1); Rt = 5.05 min.

Example 24 (General Procedure (A))

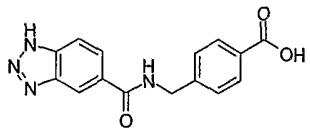
1*H*-Benzotriazole-5-carboxylic acid 3-bromobenzylamide



HPLC-MS (Method B): m/z: 331 (M+1); Rt = 4.45 min.

Example 25 (General Procedure (A))

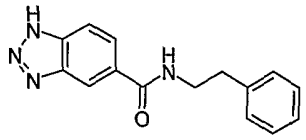
4-{[(1*H*-Benzotriazole-5-carbonyl)amino]methyl}benzoic acid



HPLC-MS (Method B): m/z: 297 (M+1); Rt = 3.35 min.

Example 26 (General Procedure (A))

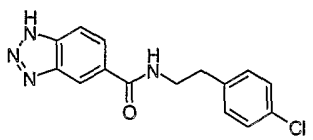
1*H*-Benzotriazole-5-carboxylic acid phenethylamide



HPLC-MS (Method B): m/z: 267 (M+1); Rt = 4.08 min.

Example 27 (General Procedure (A))

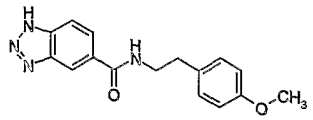
1*H*-Benzotriazole-5-carboxylic acid [2-(4-chlorophenyl)ethyl]amide



HPLC-MS (Method B): m/z: 301 (M+1); Rt = 4.50 min.

Example 28 (General Procedure (A))

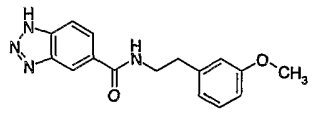
1*H*-Benzotriazole-5-carboxylic acid [2-(4-methoxyphenyl)ethyl]amide



HPLC-MS (Method B): m/z: 297 (M+1); Rt = 4.15 min.

Example 29 (General Procedure (A))

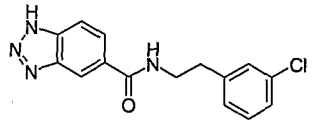
1*H*-Benzotriazole-5-carboxylic acid [2-(3-methoxyphenyl)ethyl]amide



HPLC-MS (Method B): m/z: 297 (M+1); Rt = 4.13 min.

Example 30 (General Procedure (A))

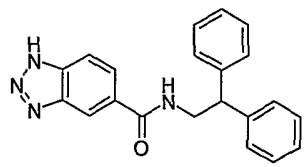
1*H*-Benzotriazole-5-carboxylic acid [2-(3-chlorophenyl)ethyl]amide



HPLC-MS (Method B): m/z: 301 (M+1); Rt = 4.55 min.

Example 31 (General Procedure (A))

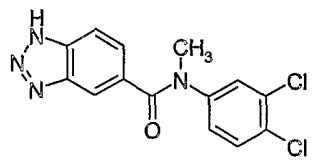
1*H*-Benzotriazole-5-carboxylic acid (2,2-diphenylethyl)amide



HPLC-MS (Method B): m/z: 343 (M+1); Rt = 5.00 min.

Example 32 (General Procedure (A))

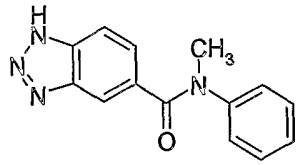
1*H*-Benzotriazole-5-carboxylic acid (3,4-dichlorophenyl)methylamide



HPLC-MS (Method B): m/z: 321 (M+1); Rt = 4.67 min.

Example 33 (General Procedure (A))

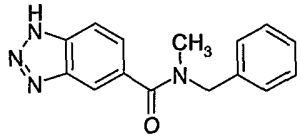
1*H*-Benzotriazole-5-carboxylic acid methylphenylamide



HPLC-MS (Method B): m/z: 253 (M+1); Rt = 3.82 min.

Example 34 (General Procedure (A))

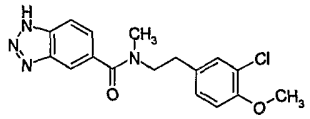
1*H*-Benzotriazole-5-carboxylic acid benzylmethylamide



HPLC-MS (Method B): m/z: 267 (M+1); Rt = 4.05 min.

Example 35 (General Procedure (A))

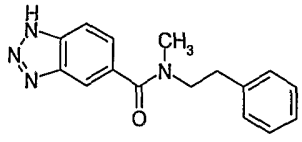
1*H*-Benzotriazole-5-carboxylic acid [2-(3-chloro-4-methoxyphenyl)ethyl]methyl-amide



HPLC-MS (Method B): m/z: 345 (M+1); Rt = 4.37 min.

Example 36 (General Procedure (A))

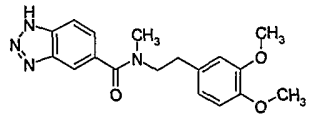
1*H*-Benzotriazole-5-carboxylic acid methylphenethylamide



HPLC-MS (Method B): m/z: 281 (M+1); Rt = 4.15 min.

Example 37 (General Procedure (A))

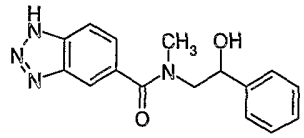
1*H*-Benzotriazole-5-carboxylic acid [2-(3,4-dimethoxyphenyl)ethyl]methylamide



HPLC-MS (Method B): m/z: 341 (M+1); Rt = 3.78 min;

Example 38 (General Procedure (A))

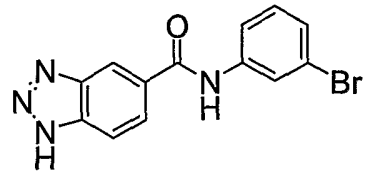
1*H*-Benzotriazole-5-carboxylic acid (2-hydroxy-2-phenylethyl)methylamide



HPLC-MS (Method B): m/z: 297 (M+1); Rt = 3.48 min.

Example 39 (General procedure (A))

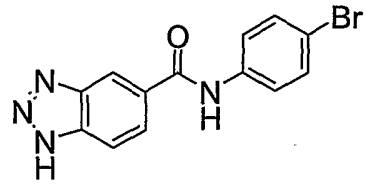
1H-Benzotriazole-5-carboxylic acid (3-bromophenyl)amide



HPLC-MS (Method A): m/z: 317 (M+1); Rt = 3.19 min.

Example 40 (General procedure (A))

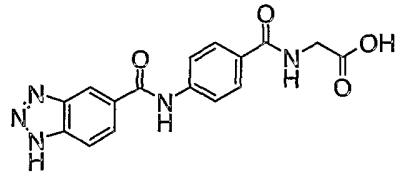
1H-Benzotriazole-5-carboxylic acid (4-bromophenyl)amide



HPLC-MS (Method A): m/z: 317 (M+1); Rt = 3.18 min.

Example 41 (General procedure (A))

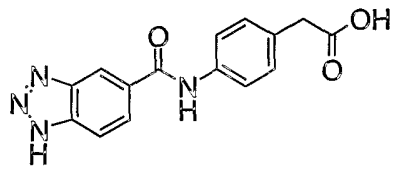
{4-[(1H-Benzotriazole-5-carbonyl)amino]benzoylamino}acetic acid



HPLC-MS (Method A): m/z: 340 (M+1); Rt = 1.71 min.

Example 42 (General procedure (A))

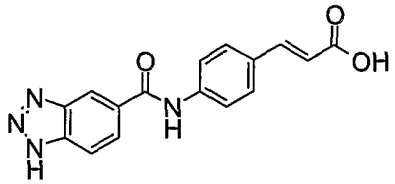
{4-[(1H-Benzotriazole-5-carbonyl)amino]phenyl}acetic acid



HPLC-MS (Method A): m/z: 297 (M+1); Rt = 2.02 min.

Example 43 (General procedure (A))

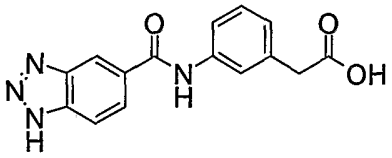
3-{4-[(1H-Benzotriazole-5-carbonyl)amino]phenyl}acrylic acid



HPLC-MS (Method A): m/z: 309 (M+1); Rt = 3.19 min.

Example 44 (General procedure (A))

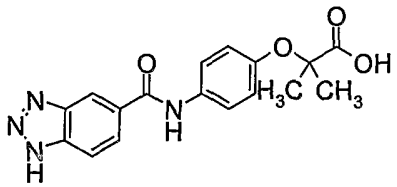
{3-[(1H-Benzotriazole-5-carbonyl)amino]phenyl}acetic acid



HPLC-MS (Method A): m/z: 297 (M+1); Rt = 2.10 min.

Example 45 (General procedure (A))

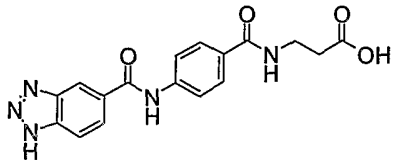
2-{4-[(1H-Benzotriazole-5-carbonyl)amino]phenoxy}-2-methylpropionic acid



HPLC-MS (Method A): m/z: 341 (M+1); Rt = 2.42 min.

Example 46 (General procedure (A))

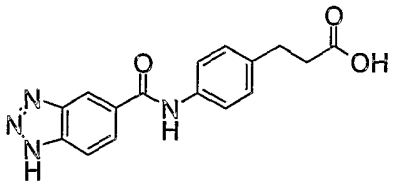
3-{4-[(1H-Benzotriazole-5-carbonyl)amino]benzoylamino}propionic acid



HPLC-MS (Method A): m/z: 354 (M+1); Rt = 1.78 min.

Example 47 (General procedure (A))

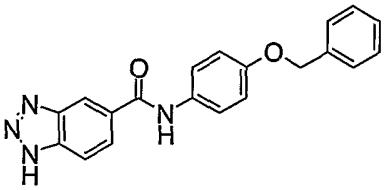
3-{4-[(1H-Benzotriazole-5-carbonyl)amino]phenyl}propionic acid



HPLC-MS (Method A): m/z: 311 (M+1); Rt = 2.20 min.

Example 48 (General procedure (A))

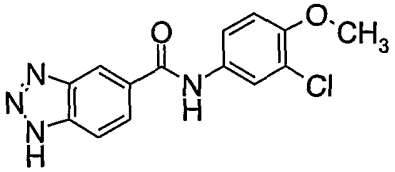
1H-Benzotriazole-5-carboxylic acid (4-benzyloxyphenyl)amide



HPLC-MS (Method A): m/z: 345 (M+1); Rt = 3.60 min.

Example 49 (General procedure (A))

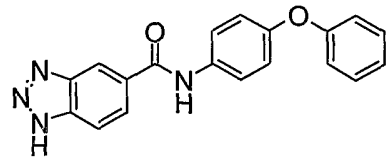
1H-Benzotriazole-5-carboxylic acid (3-chloro-4-methoxyphenyl)amide



HPLC-MS (Method A): m/z: 303 (M+1); Rt = 2.88 min.

Example 50 (General procedure (A))

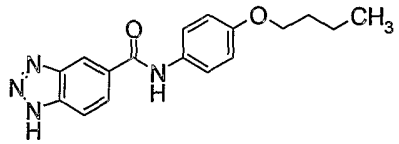
1H-Benzotriazole-5-carboxylic acid (4-phenoxyphenyl)amide



HPLC-MS (Method A): m/z: 331 (M+1); Rt = 3.62 min.

Example 51 (General procedure (A))

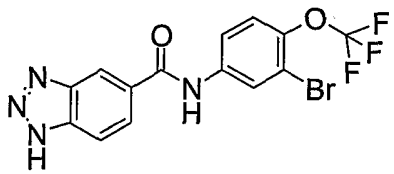
1H-Benzotriazole-5-carboxylic acid (4-butoxyphenyl)amide



HPLC-MS (Method A): m/z: 311 (M+1); Rt = 3.59 min.

Example 52 (General procedure (A))

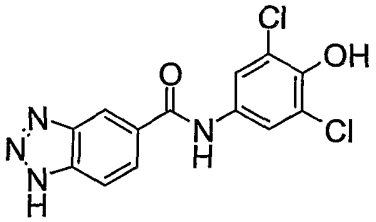
1H-Benzotriazole-5-carboxylic acid (3-bromo-4-trifluoromethoxyphenyl)amide



HPLC-MS (Method A): m/z: 402 (M+1); Rt = 3.93 min.

Example 53 (General procedure (A))

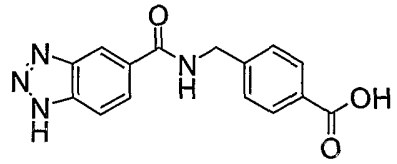
1H-Benzotriazole-5-carboxylic acid (3,5-dichloro-4-hydroxyphenyl)amide



HPLC-MS (Method A): m/z: 323 (M+1); Rt = 2.57 min.

Example 54 (General procedure (A))

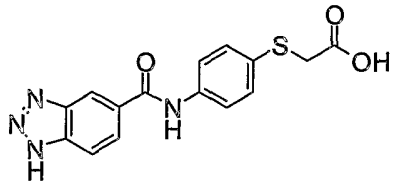
4-{[(1H-Benzotriazole-5-carbonyl)amino]methyl}benzoic acid



HPLC-MS (Method A): m/z: 297 (M+1); Rt = 1.86 min.

Example 55 (General procedure (A))

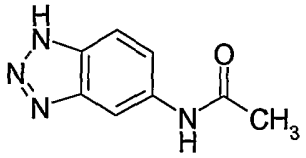
{4-[(1H-Benzotriazole-5-carbonyl)amino]phenylsulfanyl}acetic acid



HPLC-MS (Method A): m/z: 329 (M+1); Rt = 2.34 min.

Example 56

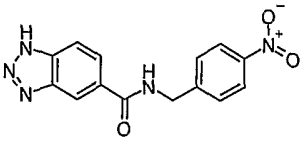
N-(1*H*-Benzotriazol-5-yl)acetamide



HPLC-MS (Method A): m/z: 177 (M+1); Rt = 0.84 min.

Example 57 (General Procedure (A))

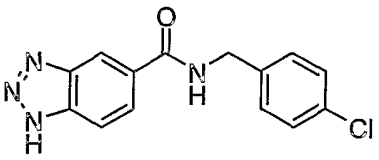
1*H*-Benzotriazole-5-carboxylic acid 4-nitrobenzylamide



The following compound is prepared according to general procedure (N) as described below:

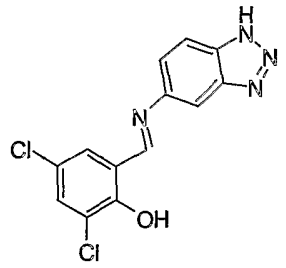
Example 58 (General procedure (N))

1*H*-Benzotriazole-5-carboxylic acid 4-chlorobenzylamide

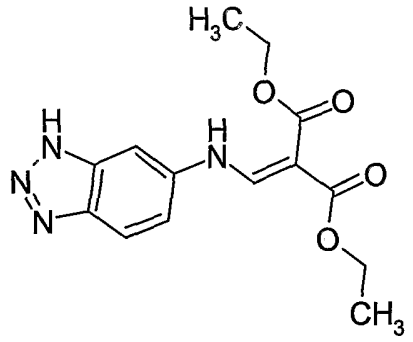


HPLC-MS (Method B): m/z: 287 (M+1); Rt = 4.40 min.

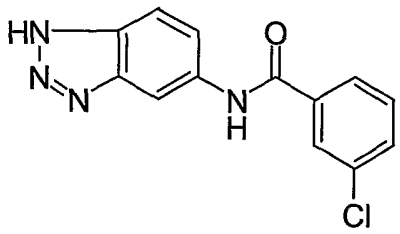
Example 59 2-[(1H-Benzotriazol-5-ylimino)methyl]-4,6-dichlorophenol



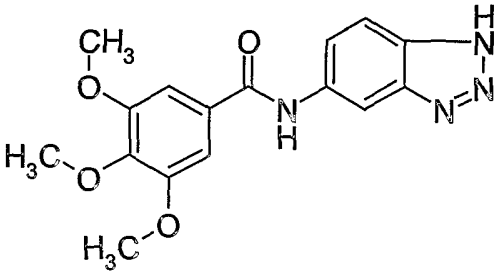
Example 60 Diethyl 2-[(1H-benzotriazol-6-ylamino)methylidene]malonate



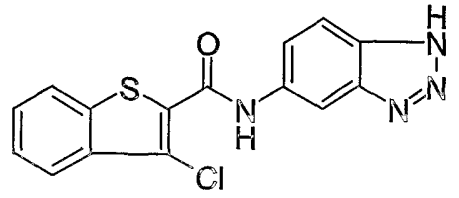
Example 61 N1-(1H-Benzotriazol-5-yl)-3-chlorobenzamide



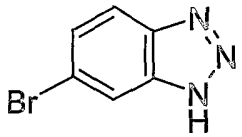
Example 62 N1-(1H-Benzotriazol-5-yl)-3,4,5-trimethoxybenzamide



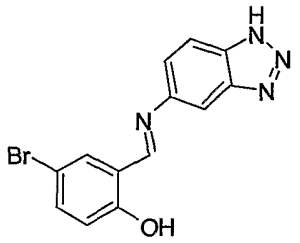
Example 63 N2-(1H-Benzotriazol-5-yl)-3-chlorobenzo[b]thiophene-2-carboxamide



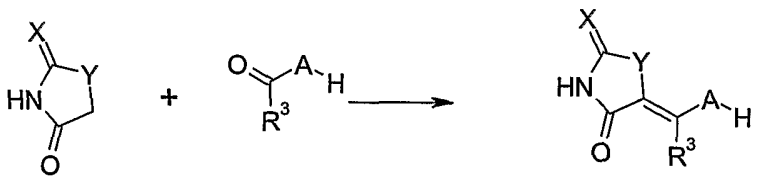
Example 64 6-Bromo-1H-benzotriazole



Example 65 2-[(1H-Benzotriazol-5-ylimino)methyl]-4-bromophenol



General procedure (B) for preparation of compounds of general formula I_2:



I_2

wherein X, Y, A and R^3 are as defined above and A is optionally substituted with up to four substituents R^7, R^8, R^9, and R^{10} as defined above.

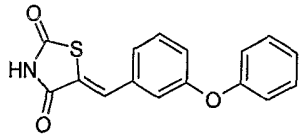
The chemistry is well known (eg Lohray et al., *J. Med. Chem.*, 1999, *42*, 2569-81) and is generally performed by reacting a carbonyl compound (aldehyde or ketone) with the heterocyclic ring (eg thiazolidine-2,4-dione (X = O; Y = S), rhodanine (X = Y = S) and hydantoin (X

= O; Y = NH) in the presence of a base, such as sodium acetate, potassium acetate, ammonium acetate, piperidinium benzoate or an amine (eg piperidine, triethylamine and the like) in a solvent (eg acetic acid, ethanol, methanol, DMSO, DMF, NMP, toluene, benzene) or in a mixture of two or more of these solvents. The reaction is performed at room temperature or at elevated temperature, most often at or near the boiling point of the mixture. Optionally, azeotropic removal of the formed water can be done.

This general procedure (B) is further illustrated in the following example:

Example 66 (General procedure (B))

5-(3-Phenoxybenzylidene)thiazolidine-2,4-dione



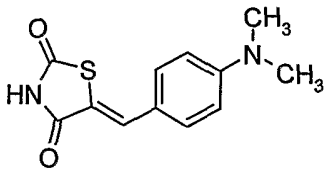
A solution of thiazolidine-2,4-dione (90%, 78 mg, 0.6 mmol) and ammonium acetate (92 mg, 1.2 mmol) in acetic acid (1 mL) was added to 3-phenoxybenzaldehyde (52 µL, 0.6 mmol) and the resulting mixture was shaken at 115 °C for 16 hours. After cooling, the mixture was concentrated *in vacuo* to afford the title compound.

HPLC-MS (Method A): m/z: 298 (M+1); Rt = 4.54 min.

The compounds in the following examples were similarly prepared. Optionally, the compounds can be further purified by filtration and washing with water, ethanol and / or heptane instead of concentration *in vacuo*. Also optionally the compounds can be purified by washing with ethanol, water and/or heptane, or by chromatography, such as preparative HPLC.

Example 67 (General procedure (B))

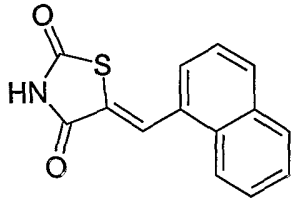
5-(4-Dimethylaminobenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 249 (M+1); Rt = 4.90 min

Example 68 (General procedure (B))

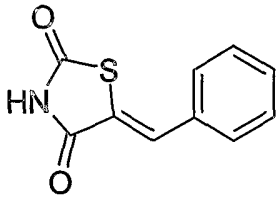
5-Naphthalen-1-ylmethylenethiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 256 (M+1); Rt = 4,16 min.

Example 69 (General procedure (B))

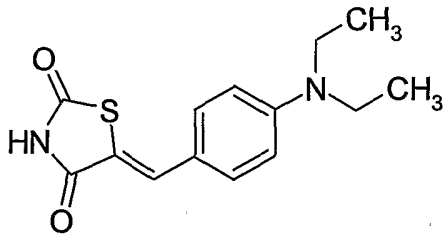
5-Benzylidene-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 206 (M+1); Rt = 4,87 min.

Example 70 (General procedure (B))

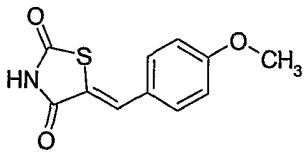
5-(4-Diethylaminobenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 277 (M+1); Rt = 4.73 min.

Example 71 (General procedure (B))

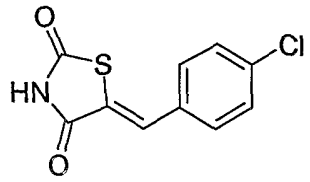
5-(4-Methoxy-benzylidene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 263 (M+1); Rt = 4,90 min.

Example 72 (General procedure (B))

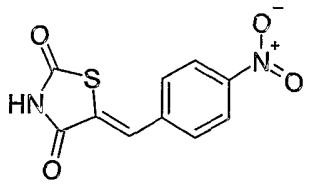
5-(4-Chloro-benzylidene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 240 (M+1); Rt = 5,53 min.

Example 73 (General procedure (B))

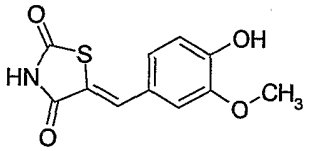
5-(4-Nitro-benzylidene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 251 (M+1); Rt = 4,87 min.

Example 74 (General procedure (B))

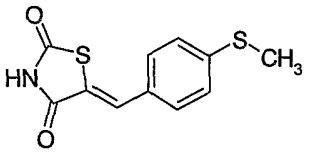
5-(4-Hydroxy-3-methoxy-benzylidene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 252 (M+1); Rt = 4,07 min.

Example 75 (General procedure (B))

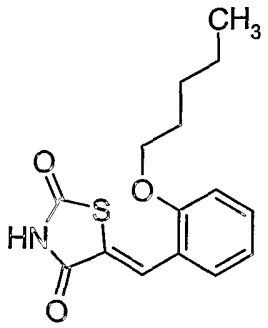
5-(4-Methylsulfanylbenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 252 (M+1); Rt = 5,43 min.

Example 76 (General procedure (B))

5-(2-Pentyloxybenzylidene)thiazolidine-2,4-dione

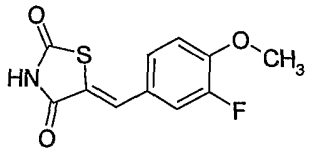


HPLC-MS (Method C): m/z: 292 (M+1); Rt = 4.75 min.

^{1}H NMR (DMSO-d_6): δ = 0.90 (3H, t), 1.39 (4H, m), 1.77 (2H, p), 4.08 (2H, t), 7.08 (1H, t), 7.14 (1H, d), 7.43 (2H, m), 8.03 (1H, s), 12.6 (1H, bs).

Example 77 (General procedure (B))

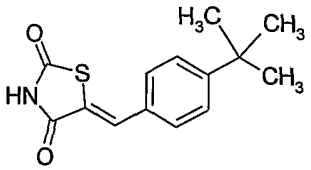
5-(3-Fluoro-4-methoxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 354 (M+1); Rt = 4,97 min.

Example 78 (General procedure (B))

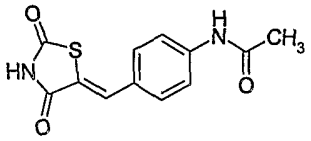
5-(4-tert-Butylbenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 262 (M+1); Rt = 6,70 min.

Example 79 (General procedure (B))

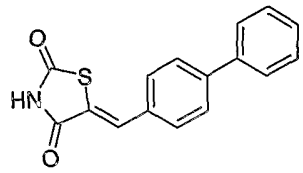
N-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)phenyl]acetamide



HPLC-MS (Method A): m/z: 263 (M+1); Rt = 3,90 min.

Example 80 (General procedure (B))

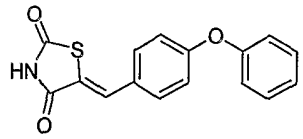
5-Biphenyl-4-ylmethylene-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 282 (M+1); Rt = 4,52 min.

Example 81 (General procedure (B))

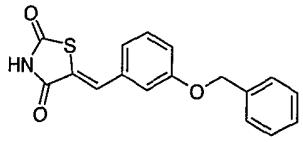
5-(4-Phenoxy-benzylidene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 298 (M+1); Rt = 6,50 min.

Example 82 (General procedure (B))

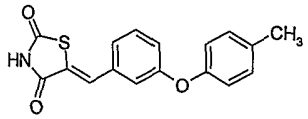
5-(3-Benzyloxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 312 (M+1); Rt = 6,37 min.

Example 83 (General procedure (B))

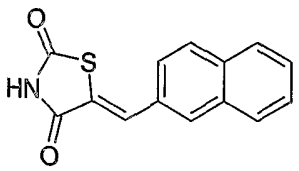
5-(3-p-Tolyloxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 312 (M+1); Rt = 6,87 min.

Example 84 (General procedure (B))

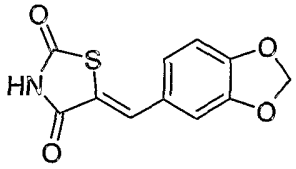
5-Naphthalen-2-ylmethylene-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 256 (M+1); Rt = 4.15 min.

Example 85 (General procedure (B))

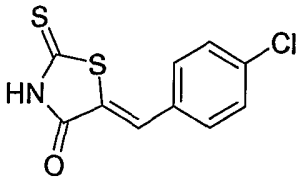
5-Benzo[1,3]dioxol-5-ylmethylenethiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 250 (M+1), Rt = 3.18 min.

Example 86 (General procedure (B))

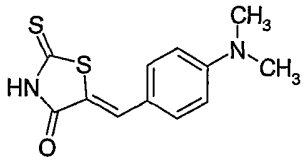
5-(4-Chlorobenzylidene)-2-thioxothiazolidin-4-one



HPLC-MS (Method A): m/z: 256 (M+1); Rt = 4,51 min.

Example 87 (General procedure (B))

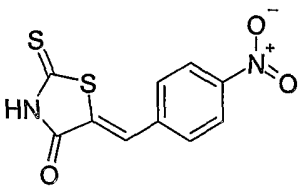
5-(4-Dimethylaminobenzylidene)-2-thioxothiazolidin-4-one



HPLC-MS (Method A): m/z: 265 (M+1); Rt = 5,66 min.

Example 88 (General procedure (B))

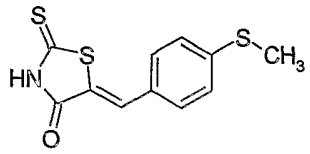
5-(4-Nitrobenzylidene)-2-thioxothiazolidin-4-one



HPLC-MS (Method A): m/z: 267 (M+1); Rt = 3,94 min.

Example 89 (General procedure (B))

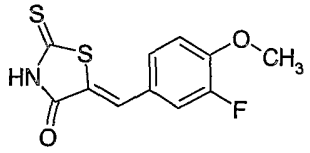
5-(4-Methylsulfanylbenzylidene)-2-thioxothiazolidin-4-one



HPLC-MS (Method A): m/z: 268 (M+1); Rt = 6,39 min.

Example 90 (General procedure (B))

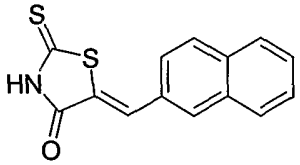
5-(3-Fluoro-4-methoxybenzylidene)-2-thioxothiazolidin-4-one



HPLC-MS (Method A): m/z: 270 (M+1); Rt = 5,52 min.

Example 91 (General procedure (B))

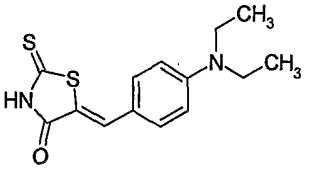
5-Naphthalen-2-ylmethylene-2-thioxothiazolidin-4-one



HPLC-MS (Method A): m/z: 272 (M+1); Rt = 6,75 min.

Example 92 (General procedure (B))

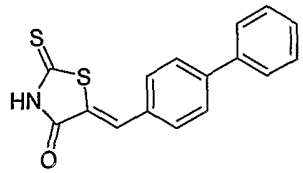
5-(4-Diethylaminobenzylidene)-2-thioxothiazolidin-4-one



HPLC-MS (Method A): m/z: 293 (M+1); Rt = 5,99 min.

Example 93 (General procedure (B))

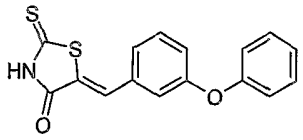
5-Biphenyl-4-ylmethylene-2-thioxothiazolidin-4-one



HPLC-MS (Method A): m/z: 298 (M+1); Rt = 7,03 min.

Example 94 (General procedure (B))

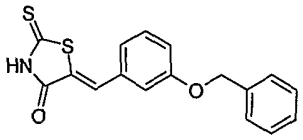
5-(3-Phenoxybenzylidene)-2-thioxothiazolidin-4-one



HPLC-MS (Method A): m/z: 314 (M+1); Rt = 6,89 min.

Example 95 (General procedure (B))

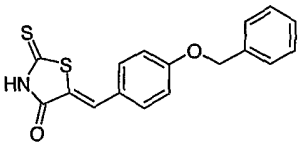
5-(3-Benzyloxybenzylidene)-2-thioxothiazolidin-4-one



HPLC-MS (Method A): m/z: 328 (M+1); Rt = 6,95 min.

Example 96 (General procedure (B))

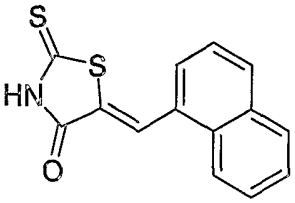
5-(4-Benzyloxybenzylidene)-2-thioxothiazolidin-4-one



HPLC-MS (Method A): m/z: 328 (M+1); RT = 6,89 min.

Example 97 (General procedure (B))

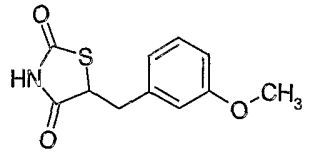
5-Naphthalen-1-ylmethylene-2-thioxothiazolidin-4-one



HPLC-MS (Method A): m/z: 272 (M+1); Rt = 6,43 min.

Example 98 (General procedure (B))

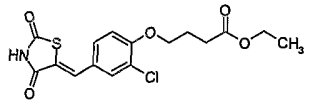
5-(3-Methoxybenzyl)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 236 (M+1); Rt = 3,05 min.

Example 99 (General procedure (D))

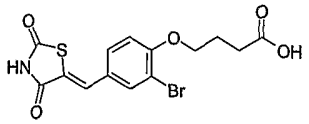
4-[2-Chloro-4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]butyric acid ethyl ester



HPLC-MS (Method A): m/z: 392 (M+23), Rt = 4.32 min.

Example 100 (General procedure (D))

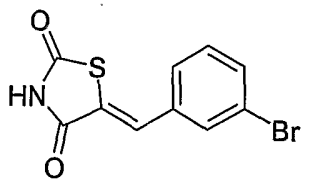
4-[2-Bromo-4-(2,4-dioxothiazolidin-5-ylidenemethyl)-phenoxy]-butyric acid



HPLC-MS (Method A): m/z: 410 (M+23); Rt = 3,35 min.

Example 101 (General procedure (B))

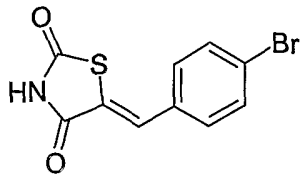
5-(3-Bromobenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 285 (M+1); Rt = 4.01 min.

Example 102 (General procedure (B))

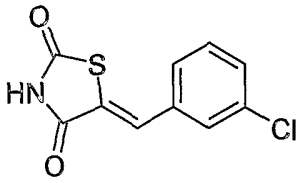
5-(4-Bromobenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 285 (M+1); Rt = 4.05 min.

Example 103 (General procedure (B))

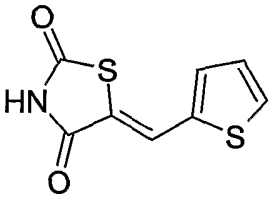
5-(3-Chlorobenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 240 (M+1); Rt = 3.91 min.

Example 104 (General procedure (B))

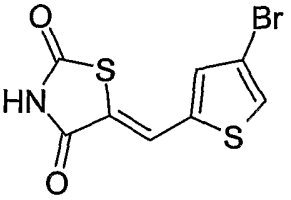
5-Thiophen-2-ylmethylenethiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 212 (M+1); Rt = 3.09 min.

Example 105 (General procedure (B))

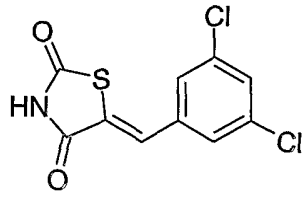
5-(4-Bromothiophen-2-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 291 (M+1); Rt = 3.85 min.

Example 106 (General procedure (B))

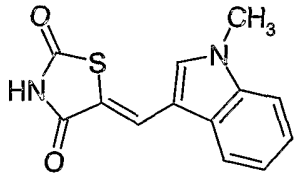
5-(3,5-Dichlorobenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 274 (M+1); Rt = 4.52 min.

Example 107 (General procedure (B))

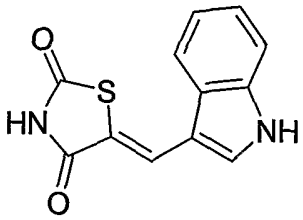
5-(1-Methyl-1H-indol-3-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 259 (M+1); Rt = 3.55 min.

Example 108 (General procedure (B))

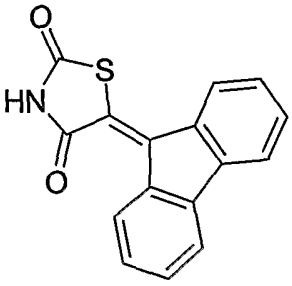
5-(1H-Indol-3-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 245 (M+1); Rt = 2.73 min.

Example 109 (General procedure (B))

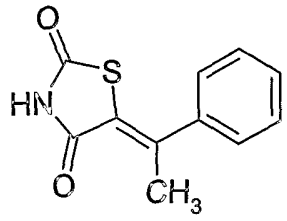
5-Fluoren-9-ylidenethiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 280 (M+1); Rt = 4.34 min.

Example 110 (General procedure (B))

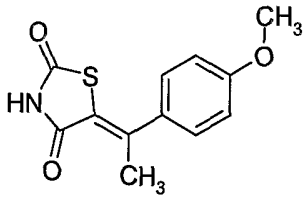
5-(1-Phenylethylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 220 (M+1); Rt = 3,38 min.

Example 111 (General procedure (B))

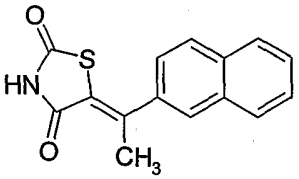
5-[1-(4-Methoxyphenyl)-ethylidene]-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 250 (M+1); Rt = 3.55 min.

Example 112 (General procedure (B))

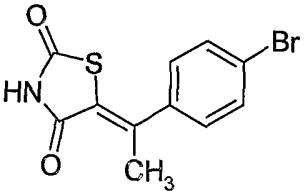
5-(1-Naphthalen-2-yl-ethylidene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 270 (M+1); Rt = 4,30 min.

Example 113 (General procedure (B))

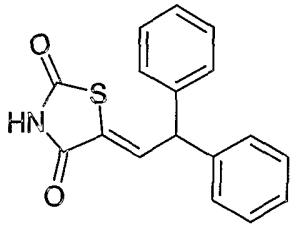
5-[1-(4-Bromophenyl)-ethylidene]-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 300 (M+1); Rt = 4,18 min.

Example 114 (General procedure (B))

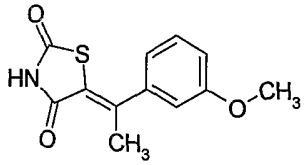
5-(2,2-Diphenylethylidene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 296 (M+1); Rt = 4,49 min.

Example 115 (General procedure (B))

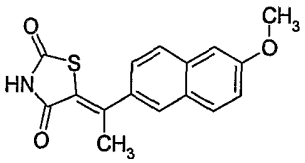
5-[1-(3-Methoxyphenyl)-ethylidene]-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 250 (M+1); Rt = 3,60 min.

Example 116 (General procedure (B))

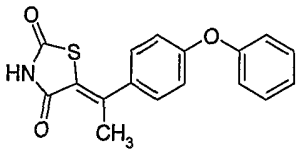
5-[1-(6-Methoxynaphthalen-2-yl)-ethylidene]-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 300 (M+1); Rt = 4,26 min.

Example 117 (General procedure (B))

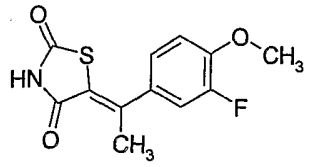
5-[1-(4-Phenoxyphenyl)-ethylidene]-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 312 (M+1); Rt = 4,68 min.

Example 118 (General procedure (B))

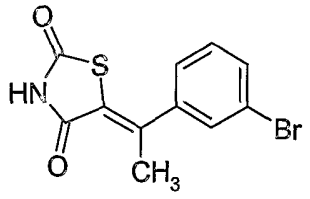
5-[1-(3-Fluoro-4-methoxyphenyl)ethylidene]thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 268 (M+1); Rt = 3,58 min.

Example 119 (General procedure (B))

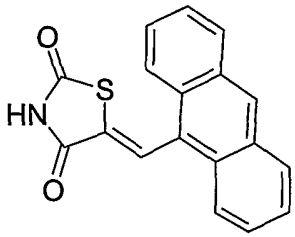
5-[1-(3-Bromophenyl)-ethylidene]-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 300 (M+1); Rt = 4,13 min.

Example 120 (General procedure (B))

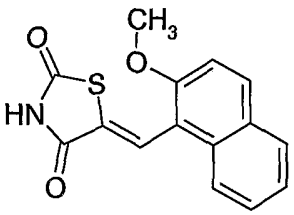
5-Anthracen-9-ylmethylenethiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 306 (M+1); Rt = 4,64 min.

Example 121 (General procedure (B))

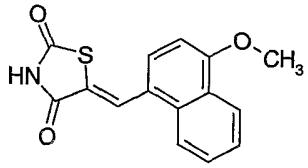
5-(2-Methoxynaphthalen-1-ylmethylene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 286 (M+1); Rt = 4,02 min.

Example 122 (General procedure (B))

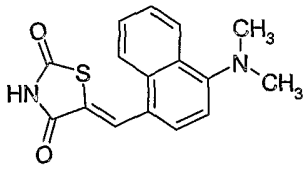
5-(4-Methoxynaphthalen-1-ylmethylene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 286 (M+1); Rt = 4,31 min.

Example 123 (General procedure (B))

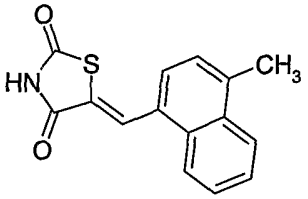
5-(4-Dimethylaminonaphthalen-1-ylmethylene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 299 (M+1); Rt = 4,22 min.

Example 124 (General procedure (B))

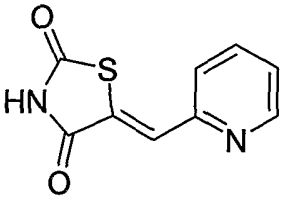
5-(4-Methylnaphthalen-1-ylmethylene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 270 (M+1); Rt = 4,47 min.

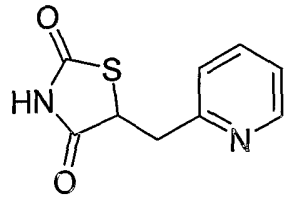
Example 125 (General procedure (B))

5-Pyridin-2-ylmethylene-thiazolidine-2,4-dione



Example 126

5-Pyridin-2-ylmethyl-thiazolidine-2,4-dione

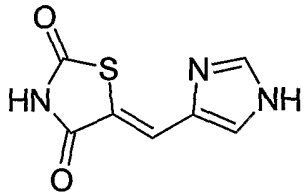


5-Pyridin-2-ylmethylene-thiazolidine-2,4-dione (5 g) in tetrahydrofuran (300 ml) was added 10% Pd/C (1 g) and the mixture was hydrogenated at ambient pressure for 16 hours. More 10% Pd/C (5 g) was added and the mixture was hydrogenated at 50 psi for 16 hours. After filtration and evaporation *in vacuo*, the residue was purified by column chromatography eluting with a mixture of ethyl acetate and heptane (1:1). This afforded the title compound (0.8 g, 16%) as a solid.

TLC: R_f = 0.30 (SiO_2; EtOAc: heptane 1:1)

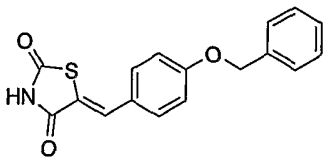
Example 127 (General procedure (B))

5-(1H-Imidazol-4-ylmethylene)-thiazolidine-2,4-dione



Example 128 (General procedure (B))

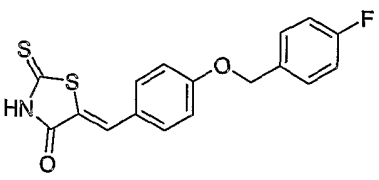
5-(4-Benzyloxy-benzylidene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 6,43 min ; 99 % (2A)

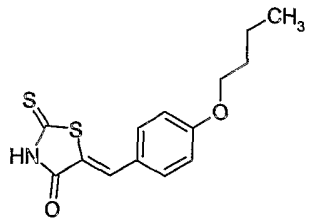
Example 129 (General procedure (B))

5-[4-(4-Fluorobenzyloxy)benzylidene]-2-thioxothiazolidin-4-one



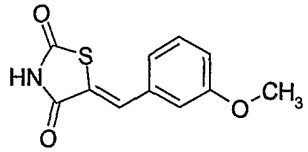
Example 130 (General procedure (B))

5-(4-Butoxybenzylidene)-2-thioxothiazolidin-4-one



Example 131 (General procedure (B))

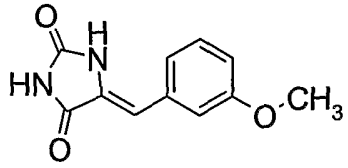
5-(3-Methoxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 236 (M+1); Rt = 4,97 min

Example 132 (General procedure (B))

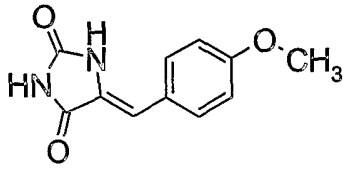
5-(3-Methoxybenzylidene)imidazolidine-2,4-dione



HPLC-MS (Method A): m/z: 219 (M+1); Rt = 2.43 min.

Example 133 (General procedure (B))

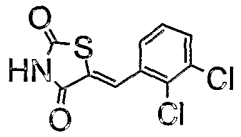
5-(4-Methoxybenzylidene)imidazolidine-2,4-dione



HPLC-MS (Method A): m/z: 219 (M+1); Rt = 2.38 min.

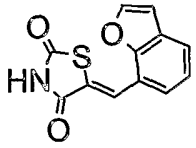
Example 134 (General procedure (B))

5-(2,3-Dichlorobenzylidene)thiazolidine-2,4-dione



Example 135 (General procedure (B))

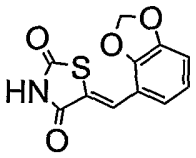
5-Benzofuran-7-ylmethylenethiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 247 (M+1); Rt = 4,57 min.

Example 136 (General procedure (B))

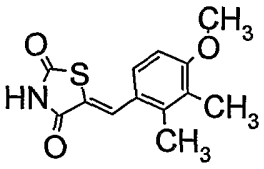
5-Benzo[1,3]dioxol-4-ylmethylenethiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 250 (M+1); Rt = 4,00 min.

Example 137 (General procedure (B))

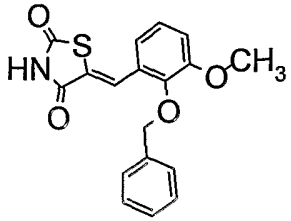
5-(4-Methoxy-2,3-dimethylbenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 264 (M+1); Rt = 5,05 min.

Example 138 (General procedure (B))

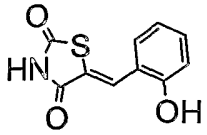
5-(2-Benzyloxy-3-methoxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 342 (M+1); Rt = 5,14 min.

Example 139 (General procedure (B))

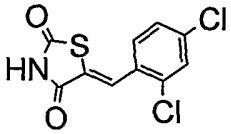
5-(2-Hydroxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 222 (M+1); Rt = 3,67 min.

Example 140 (General procedure (B))

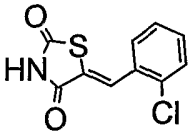
5-(2,4-Dichlorobenzylidene)thiazolidine-2,4-dione



^{1}H-NMR (DMSO-d_6): 7.60 (2H, "s"), 7.78 (1H, s), 7.82 (1H, s).

Example 141 (General procedure (B))

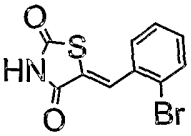
5-(2-Chlorobenzylidene)thiazolidine-2,4-dione



^{1}H-NMR (DMSO-d_6): 7.40 (1H, t), 7.46 (1H, t), 7.57 (1H, d), 7.62 (1H, d), 7.74 (1H, s).

Example 142 (General procedure (B))

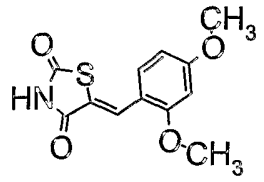
5-(2-Bromobenzylidene)thiazolidine-2,4-dione



^{1}H-NMR (DMSO-d_6): 7.33 (1H, t), 7.52 (1H, t), 7.60 (1H, d), 7.71 (1H, s), 7.77 (1H, d).

Example 143 (General procedure (B))

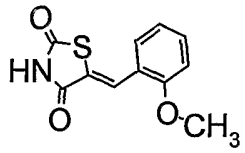
5-(2,4-Dimethoxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 266 (M+1) Rt = 4,40 min.

Example 144 (General procedure (B))

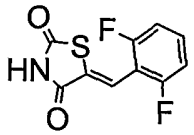
5-(2-Methoxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 236 (M+1); Rt = 4,17 min.

Example 145 (General procedure (B))

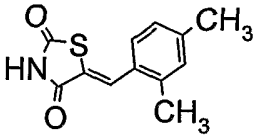
5-(2,6-Difluorobenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 242 (M+1); Rt = 4,30 min.

Example 146 (General procedure (B))

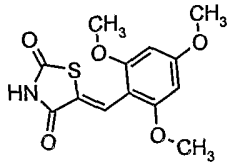
5-(2,4-Dimethylbenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 234 (M+1); Rt = 5,00 min.

Example 147 (General procedure (B))

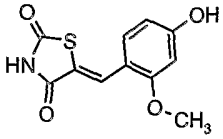
5-(2,4,6-Trimethoxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 296 (M+1); Rt = 4,27 min.

Example 148 (General procedure (B))

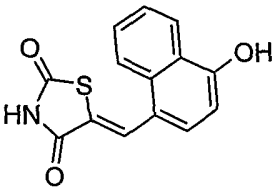
5-(4-Hydroxy-2-methoxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 252 (M+1); Rt = 3,64 min.

Example 149 (General procedure (B))

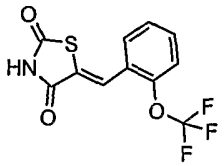
5-(4-Hydroxynaphthalen-1-ylmethylene)thiazolidine-2,4-dione



^{1}H-NMR (DMSO-d_6): δ = 7.04 (1H, d), 7.57 (2H, m), 7.67 (1H, t), 8.11 (1H, d), 8.25 (1H, d), 8.39 (1H, s) 11.1 (1H, s), 12.5 (1H, bs). HPLC-MS (Method C): m/z: 272 (M+1); Rt = 3.44 min.

Example 150 (General procedure (B))

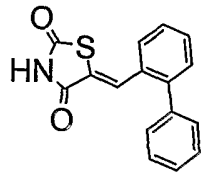
5-(2-Trifluoromethoxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 290 (M+1); Rt = 4,94 min.

Example 151 (General procedure (B))

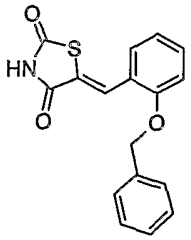
5-Biphenyl-2-ylmethylenethiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 282 (M+1); Rt = 5,17 min.

Example 152 (General procedure (B))

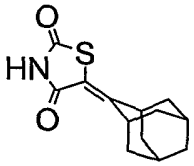
5-(2-Benzyloxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 312 (M+1); Rt = 5,40 min.

Example 153 (General procedure (B))

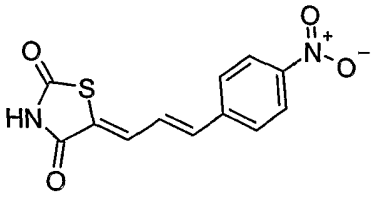
5-Adamantan-2-ylidenethiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 250 (M+1); Rt = 4,30 min.

Example 154 (General Procedure (B))

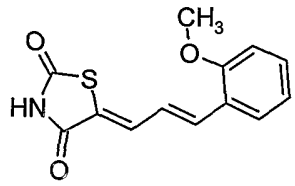
5-[3-(4-Nitrophenyl)allylidene]thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 277 (M+1); Rt = 3.63 min.

Example 155 (General Procedure (B))

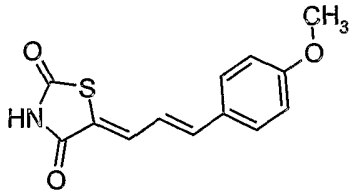
5-[3-(2-Methoxyphenyl)allylidene]thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 262 (M+1); Rt = 3.81 min.

Example 156 (General Procedure (B))

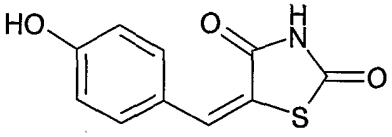
5-[3-(4-Methoxyphenyl)allylidene]thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 262 (M+1); Rt = 3.67 min.

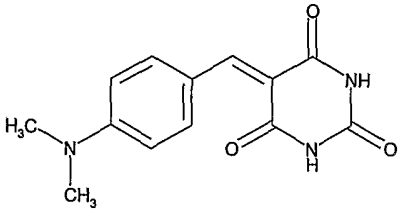
Example 157 (General procedure (B))

5-(4-Hydroxybenzylidene)thiazolidine-2,4-dione



Example 158 (General procedure (B))

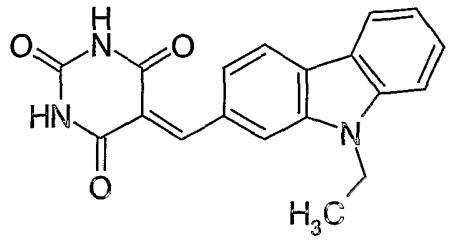
5-(4-Dimethylaminobenzylidene)pyrimidine-2,4,6-trione



HPLC-MS (Method C): m/z = 260 (M+1) Rt = 2,16 min.

Example 159 (General procedure (B))

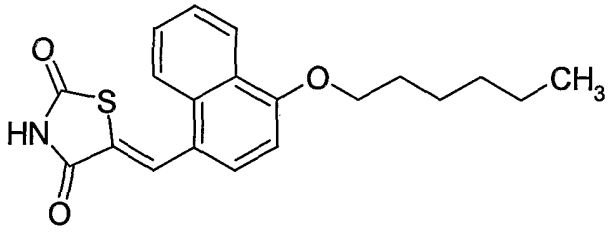
5-(9-Ethyl-9H-carbazol-2-ylmethylene)-pyrimidine-2,4,6-trione



HPLC-MS (Method C): m/z = 334 (M+1); Rt = 3,55 min.

Example 160 (General procedure (B))

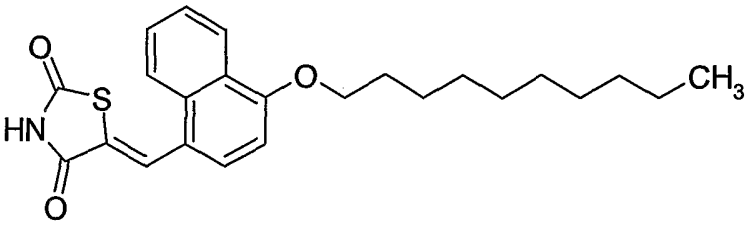
5-(4-Hexyloxynaphthalen-1-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z = 356 (M+1); Rt = 5.75 min.

Example 161 (General procedure (B))

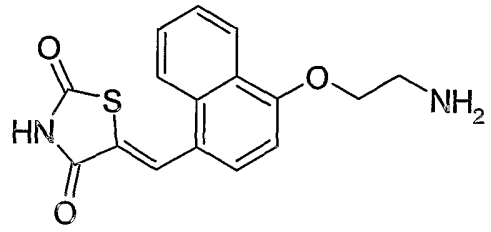
5-(4-Decyloxynaphthalen-1-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z = 412 (M+1); Rt = 6.44 min.

Example 162 (General procedure (B))

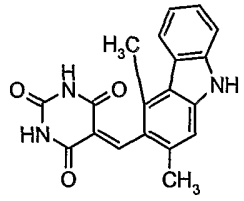
5-[4-(2-Aminoethoxy)-naphthalen-1-ylmethylene]-thiazolidine-2,4-dione



HPLC-MS (Method C): m/z = 315 (M+1); Rt = 3,24 min.

Example 163 (General procedure (B))

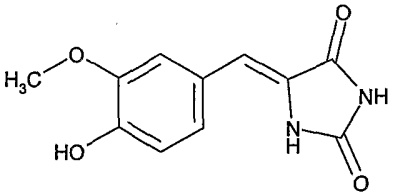
5-(2,4-Dimethyl-9H-carbazol-3-ylmethylene)-pyrimidine-2,4,6-trione



HPLC-MS (Method C): m/z = 334 (M+1); Rt = 3,14 min.

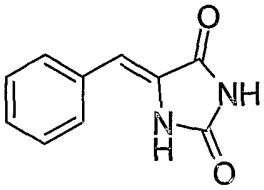
Example 164 (General procedure (B))

4-(4-Hydroxy-3-methoxybenzylidine)hydantoin

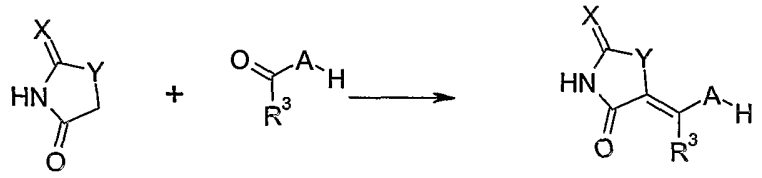


Example 165 (General procedure (B))

5-Benzylidenehydantoin



General procedure (C) for preparation of compounds of general formula I_2:

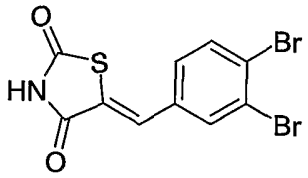


I_2

wherein X, Y, A, and R^3 are as defined above and A is optionally substituted with up to four substituents R^7, R^8, R^9, and R^{10} as defined above.

This general procedure (C) is quite similar to general procedure (B) and is further illustrated in the following example:

Example 166 (General procedure (C))
5-(3,4-Dibromobenzylidene)thiazolidine-2,4-dione

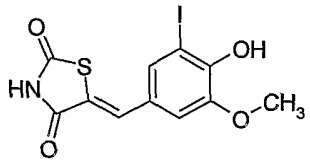


A mixture of thiazolidine-2,4-dione (90%, 65 mg, 0.5 mmol), 3,4-dibromobenzaldehyde (132 mg, 0.5 mmol), and piperidine (247 µL, 2.5 mmol) was shaken in acetic acid (2 mL) at 110 °C for 16 hours. After cooling, the mixture was concentrated to dryness *in vacuo* .
The resulting crude product was shaken with water, centrifuged, and the supernatant was discarded. Subsequently the residue was shaken with ethanol, centrifuged, the supernatant was discarded and the residue was further evaporated to dryness to afford the title compound.

^{1}H NMR (Acetone-d_6): δ_H 7.99 (d,1H), 7.90 (d,1H), 7.70 (s,1H), 7.54 (d,1H); HPLC-MS (Method A): m/z: 364 (M+1); Rt = 4.31 min.

The compounds in the following examples were similarly prepared. Optionally, the compounds can be further purified by filtration and washing with water instead of concentration *in vacuo*. Also optionally the compounds can be purified by washing with ethanol, water and/or heptane, or by preparative HPLC.

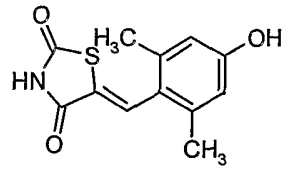
Example 167 (General procedure (C))
5-(4-Hydroxy-3-iodo-5-methoxybenzylidene)thiazolidine-2,4-dione



Mp = 256 °C; ^{1}H NMR (DMSO-d_6) δ = 12.5 (s,broad,1H), 10.5 (s,broad,1H), 7.69 (s,1H), 7.51 (d,1H), 7.19 (d,1H)3.88 (s,3H), ^{13}C NMR (DMSO-d_6) δ_C = 168.0, 167.7 , 149.0, 147.4, 133.0, 131.2, 126.7, 121.2, 113.5, 85.5, 56.5; HPLC-MS (Method A): m/z: 378 (M+1); Rt = 3.21 min.

Example 168 (General procedure (C))

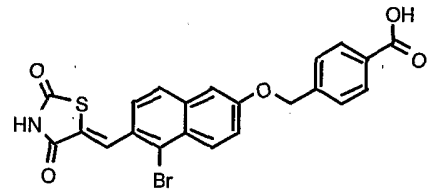
5-(4-Hydroxy-2,6-dimethylbenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 250 (M+1); Rt.= 2.45 min.

Example 169 (General procedure (C))

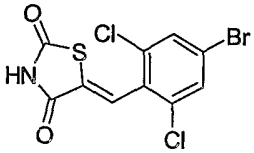
4-[5-Bromo-6-(2,4-dioxothiazolidin-5-ylidenemethyl)-naphthalen-2-yloxymethyl]-benzoic acid



HPLC-MS (Method C): m/z: 506 (M+23); Rt.= 4.27 min.

Example 170 (General procedure (C))

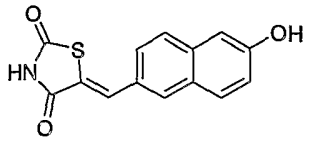
5-(4-Bromo-2,6-dichlorobenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 354 (M+1); Rt.= 4.36 min.

Example 171 (General procedure (C))

5-(6-Hydroxy-2-naphthylmethylene) thiazolidine-2,4-dione



Mp 310-314 °C, ^{1}H NMR (DMSO-d_6): δ_H = 12.5 (s,broad,1H), 8.06(d,1H), 7.90-7.78(m,2H),7.86 (s,1H), 7.58 (dd,1H),7.20 7.12 (m,2H). ^{13}C NMR (DMSO-d_6): δ_C = 166.2, 165.8 , 155.4, 133.3, 130.1, 129.1, 128.6, 125.4, 125.3, 125.1, 124.3, 120.0, 117.8, 106.8; HPLC-MS (Method A): m/z: 272 (M+1); Rt = 3.12 min.

Preparation of the starting material, 6-hydroxy-2-naphtalenecarbaldehyde:

6-Cyano-2-naphthalenecarbaldehyde (1.0 g, 5.9 mmol) was dissolved in dry hexane (15 mL) under nitrogen. The solution was cooled to -60 °C and a solution of diisobutyl aluminium hydride (DIBAH) (15 mL, 1M in hexane) was added dropwise. After the addition, the solution was left at room temperature overnight. Saturated ammonium chloride solution (20 mL) was added and the mixture was stirred at room temperature for 20 min, subsequently aqueous H_2SO_4 (10% solution, 15 mL) was added followed by water until all salt was dissolved. The resulting solution was extracted with ethyl acetate (3x), the combined organic phases were dried with $MgSO_4$, evaporated to dryness to afford 0.89 g of 6-hydroxy-2-naphtalenecarbaldehyde.

Mp.: 153.5-156.5 °C; HPLC-MS (Method A): m/z: 173 (M+1); Rt = 2.67 min; ^{1}H NMR (DMSO-d_6): δ_H = 10.32(s,1H), 8.95 (d,1H), 10.02 (s,1H), 8.42 (s,broad,1H), 8.01 (d,1H), 7.82-7.78 (m,2H), 7.23-7.18 (m,2H).

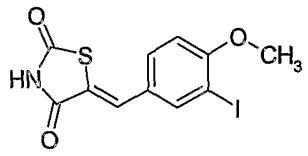
Alternative preparation of 6-hydroxy-2-naphtalenecarbaldehyde:

To a stirred cooled mixture of 6-bromo-2-hydroxynaphthalene (25.3 g, 0.113 mol) in THF (600 mL) at -78 °C was added n-BuLi (2.5 M, 100 mL, 0.250 mol) dropwise. The mixture turned yellow and the temperature rose to –64 °C. After ca 5 min a suspension appeared. After addition, the mixture was maintained at –78 °C. After 20 minutes, a solution of DMF (28.9 mL, 0.373 mol) in THF (100 mL) was added over 20 minutes. After addition, the mixture was allowed to warm slowly to room temperature. After 1 hour, the mixture was poured in ice/water (200 mL). To the mixture citric acid was added to a pH of 5. The mixture was stirred for 0.5 hour. Ethyl acetate (200 mL) was added and the organic layer was separated

and washed with brine (100 mL), dried over Na_2SO_4 and concentrated. To the residue was added heptane with 20% ethyl acetate (ca 50 mL) and the mixture was stirred for 1 hour. The mixture was filtered and the solid was washed with ethyl acetate and dried *in vacuo* to afford 16 g of the title compound.

Example 172 (General procedure (C))

5-(3-Iodo-4-methoxybenzylidene)thiazolidiene-2,4-dione



^{1}H NMR (DMSO-d_6): δ_H 12.55 (s,broad,1H), 8.02 (d,1H), 7.72 (s,1H), 7.61 (d,1H)7.18(d,1H), 3.88 (s,3H); ^{13}C NMR (DMSO-d_6): δ_C 168.1, 167.7 , 159.8, 141.5, 132.0, 130.8, 128.0, 122.1, 112.5, 87.5, 57.3. HPLC-MS (Method A): m/z: 362 (M+1); Rt = 4.08 min.

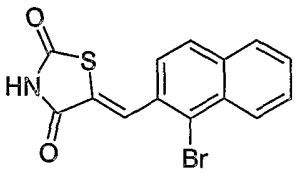
Preparation of the starting material, 3-iodo-4-methoxybenzaldehyde:

4-Methoxybenzaldehyde (0.5 g, 3.67 mmol) and silver trifluoroacetate (0.92 g, 4.19 mmol) were mixed in dichloromethane (25 mL). Iodine (1.19 g, 4.7 mmol) was added in small portions and the mixture was stirred overnight at room temperature under nitrogen. The mixture was subsequently filtered and the residue washed with DCM. The combined filtrates were treated with an acqueous sodium thiosulfate solution (1 M) until the colour disappeared. Subsequent extraction with dichloromethane (3 x 20 mL) followed by drying with $MgSO_4$ and evaporation *in vacuo* afforded 0.94 g of 3-iodo-4-methoxybenzaldehyde.

Mp 104-107 °C; HPLC-MS (Method A): m/z:263 (M+1); Rt = 3.56 min.;^{1}H NMR ($CDCl_3$): δ_H = 8.80 (s,1H), 8.31 (d,1H), 7.85 (dd,1H) 6.92 (d,1H), 3.99 (s, 3H).

Example 173 (General procedure (C))

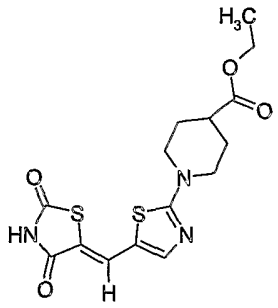
5-(1-Bromonaphthalen-2-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: =336 (M+1); Rt = 4.46 min.

Example 174 (General procedure (C))

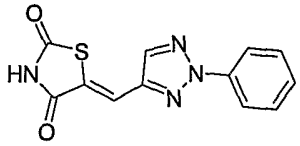
1-[5-(2,4-Dioxothiazolidin-5-ylidenemethyl)thiazol-2-yl]piperidine-4-carboxylic acid ethyl ester



^{1}H NMR (DMSO-d_6): δ_H = 7.88 (s,1H), 7.78 (s,1H), 4.10 (q,2H), 4.0-3.8 (m,2H), 3.40-3.18 (m,2H), 2.75-2.60 (m,1H), 2.04-1.88 (m,2H), 1.73-1.49 (m,2H) , 1.08 (t,3H); HPLC-MS (Method A): m/z: 368 (M+1); Rt = 3.41 min.

Example 175 (General procedure (C))

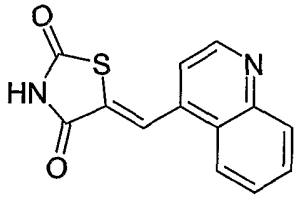
5-(2-Phenyl-[1,2,3]triazol-4-ylmethylene) thiazolidine-2,4-dione



^{1}H NMR (DMSO-d_6): δ_H = 12.6 (s,broad,1H), 8.46 (s,1H), 8.08 (dd,2H), 7.82 (s,1H), 7.70-7.45 (m, 3H). HPLC-MS (Method A): m/z: 273 (M+1); Rt = 3.76 min.

Example 176 (General procedure (C))

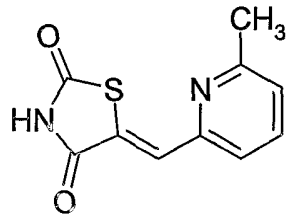
5-(Quinolin-4-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 257 (M+1); Rt = 2.40 min.

Example 177 (General procedure (C))

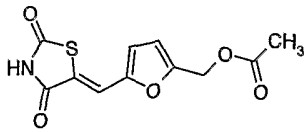
5-(6-Methylpyridin-2-ylmethylene)thiazolidine-2,4-dione



^{1}H NMR (DMSO-d_6): δ_H = 12.35 (s,broad,1H), 7.82 (t,1H), 7.78 (s,1H), 7.65 (d,1H), 7.18 (d,1H), 2.52 (s,3 H); HPLC-MS (Method A): m/z: 221 (M+1); Rt = 3.03 min.

Example 178 (General procedure (C))

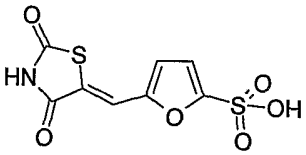
5-(2,4-dioxothiazolidin-5-ylidenemethyl)-furan-2-ylmethylacetate



^{1}H NMR (DMSO-d_6): δ_H = 12.46 (s,broad,1H), 7.58 (s,1H), 7.05 (d,1H), 6.74 (s,1H), 5.13 (s,2H), 2.10 (s,3H). HPLC-MS (Method A): m/z: 208 (M-CH_3COO); Rt = 2.67 min.

Example 179 (General procedure (C))

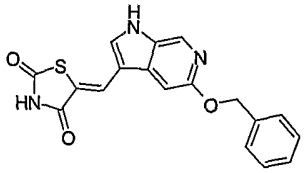
5-(2,4-Dioxothiazolidin-5-ylidenemethyl)furan-2-sulfonic acid



HPLC-MS (Method A): m/z:276 (M+1); Rt = 0.98 min.

Example 180 (General procedure (C))

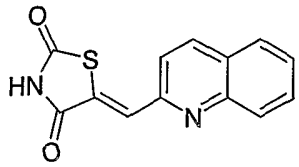
5-(5-Benzyloxy-1H-pyrrolo[2,3-c]pyridin-3-ylmethylene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 352 (M+1); Rt = 3.01 min.

Example 181 (General procedure (C))

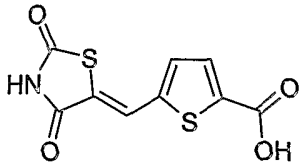
5-(Quinolin-2-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 257 (M+1); Rt = 3.40 min.

Example 182 (General procedure (C))

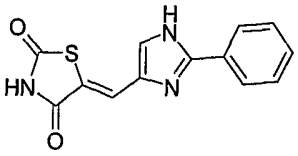
5-(2,4-Dioxothiazolidin-5-ylidenemethyl)thiophene-2-carboxylic acid



HPLC-MS (Method A): m/z: 256 (M+1); Rt = 1.96 min.

Example 183 (General procedure (C))

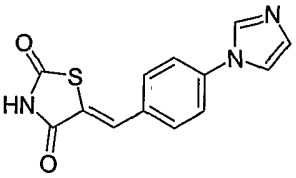
5-(2-Phenyl-1H-imidazol-4-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 272 (M+1); Rt = 2.89 min.

Example 184 (General procedure (C))

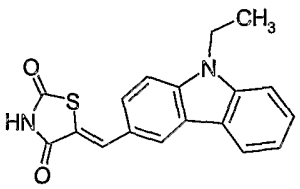
5-(4-Imidazol-1-yl-benzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 272 (M+1); Rt = 1.38 min.

Example 185 (General procedure (C))

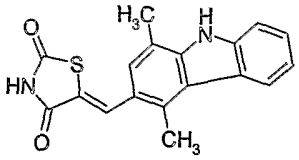
5-(9-Ethyl-9H-carbazol-3-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 323 (M+1); Rt = 4.52 min.

Example 186 (General procedure (C))

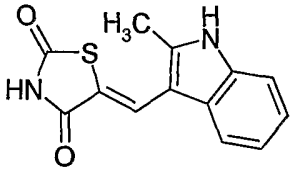
5-(1,4-Dimethyl-9H-carbazol-3-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 323 (M+1); Rt = 4.35 min.

Example 187 (General procedure (C))

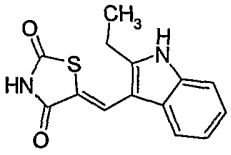
5-(2-Methyl-1H-indol-3-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 259 (M+1); Rt = 3.24 min.

Example 188 (General procedure (C))

5-(2-Ethylindol-3-ylmethylene)thiazolidine-2,4-dione



2-Methylindole (1.0 g, 7.6mmol) dissolved in diethyl ether (100 mL) under nitrogen was treated with n-Butyl lithium (2 M in pentane, 22.8 mmol) and potassium *tert*-butoxide (15.2 mmol) with stirring at RT for 30 min. The temperature was lowered to –70 C and methyl Iodide (15.2 mmol) was added and the resulting mixture was stirred at –70 for 2 h. Then 5 drops of water was added and the mixture allowed to warm up to RT. Subsequently, the mixture was poured into water (300 mL), pH was adjusted to 6 by means of 1N hydrochloric acid and the mixture was extracted with diethyl ether. The organic phase was dried with Na_2SO_4 and evaporated to dryness. The residue was purified by column chromatography on silica gel using heptane/ether(4/1) as eluent. This afforded 720 mg (69 %) of 2-ethylindole.

^{1}H NMR (DMSO-d_6): δ = 10.85 (1H,s); 7.39 (1H,d); 7.25 (1H,d); 6.98(1H,t); 6.90(1H,t); 6.10 (1H,s); 2.71 (2H,q); 1.28 (3H,t).

2-Ethylindole (0.5 g, 3.4mmol) dissolved in DMF (2 mL) was added to a cold (0 °C) premixed (30 minutes) mixture of DMF (1.15 mL) and phosphorous oxychloride (0.64 g, 4.16 mmol). After addition of 2-ethylindole, the mixture was heated to 40 °C for 1 h, water (5 mL) was added and the pH adjusted to 5 by means of 1 N sodium hydroxide.The mixture was subsequently extracted with diethyl ether, the organic phase isolated, dried with $MgSO_4$ and evaporated to dryness affording 2-ethylindole-3-carbaldehyde (300 mg).

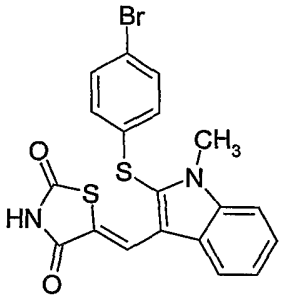
HPLC-MS (Method C): m/z:174 (M+1); Rt. =2.47 min.

2-Ethylindole-3-carbaldehyde (170 mg) was treated with thiazolidine-2,4-dione using the general procedure (C) to afford the title compound (50 mg).

HPLC-MS (Method C):m/z: 273 (M+1); Rt.= 3.26 min.

Example 189 (General procedure (C))

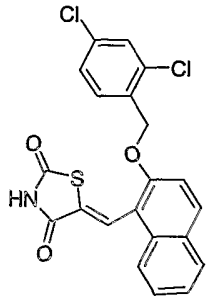
5-[2-(4-Bromophenylsulfanyl)-1-methyl-1H-indol-3-ylmethylene]thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 447 (M+1); Rt = 5.25 min.

Example 190 (General procedure (C))

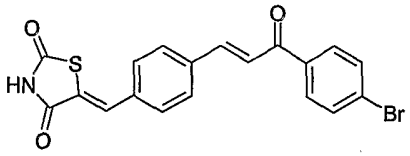
5-[2-(2,4-Dichlorobenzyloxy)-naphthalen-1-ylmethylene]thiazolidine-2,4-dione



HPLC-MS (Method A): (anyone 1) m/z: 430 (M+1); Rt = 5.47 min.

Example 191 (General procedure (C))

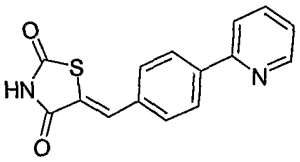
5-{4-[3-(4-Bromophenyl)-3-oxopropenyl]-benzylidene}thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 416 (M+1); Rt = 5.02 min.

Example 192 (General procedure (C))

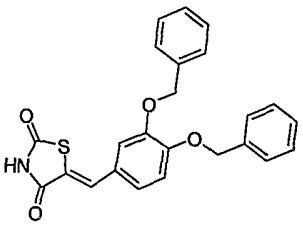
5-(4-Pyridin-2-ylbenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 283 (M+1), Rt = 2.97 min.

Example 193 (General procedure (C))

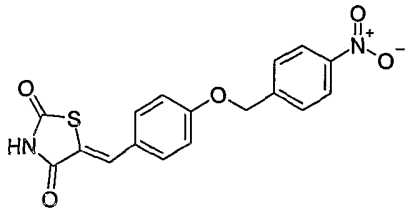
5-(3,4-Bisbenzyloxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 418 (M+1); Rt = 5.13 min.

Example 194 (General procedure (C))

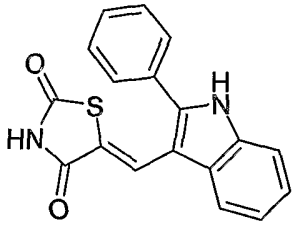
5-[4-(4-Nitrobenzyloxy)-benzylidene]thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 357 (M+1); Rt = 4.45 min.

Example 195 (General procedure (C))

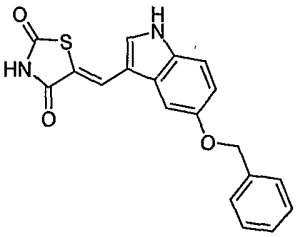
5-(2-Phenyl-1H-indol-3-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 321 (M+1); Rt = 3.93 min.

Example 196 (General procedure (C))

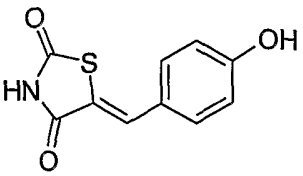
5-(5-Benzyloxy-1H-indol-3-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 351 (M+1); Rt = 4.18 min.

Example 197 (General procedure (C))

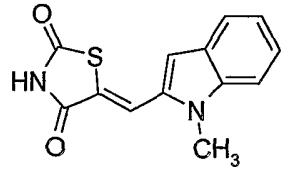
5-(4-Hydroxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 222 (M+1); Rt = 2.42 min.

Example 198 (General procedure (C))

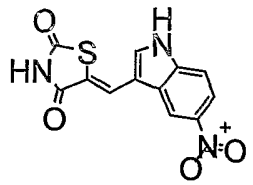
5-(1-Methyl-1H-indol-2-ylmethylene)thiazolidine-2,4-dione



^{1}H NMR (DMSO-d_6): δ_H = 12.60 (s,broad,1H), 7.85 (s,1H), 7.68 (dd,1H), 7.55 (dd,1H), 7.38 (dt,1H), 7.11 (dt,1H) 6.84 (s,1H), 3.88 (s,3H); HPLC-MS (Method A): m/z: 259 (M+1); Rt = 4.00 min.

Example 199 (General procedure (C))

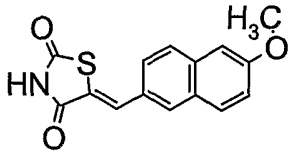
5-(5-Nitro-1H-indol-3-ylmethylene)thiazolidine-2,4-dione



.Mp 330-333 °C, ^{1}H NMR (DMSO-d_6): δ_H = 12.62 (s,broad,1H), 8.95 (d,1H), 8.20 (s,1H), 8.12 (dd,1H), 7.98 (s,broad,1H), 7.68 (d,1H); HPLC-MS (Method A): m/z: 290 (M+1); Rt = 3.18 min.

Example 200 (General procedure (C))

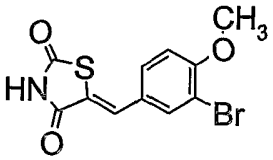
5-(6-Methoxynaphthalen-2-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 286 (M+1); Rt = 4.27 min.

Example 201 (General procedure (C))

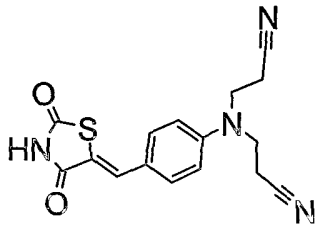
5-(3-Bromo-4-methoxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 314 (M+1), Rt = 3.96 min.

Example 202 (General procedure (C))

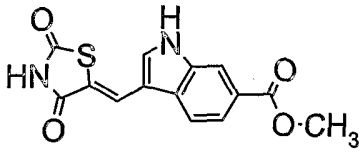
3-{(2-Cyanoethyl)-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenyl]amino}propionitrile



HPLC-MS (Method A): m/z: 327 (M+1); Rt = 2.90 min.

Example 203 (General procedure (C))

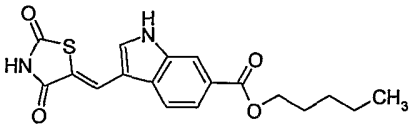
3-(2,4-Dioxothiazolidin-5-ylidenemethyl)indole-6-carboxylic acid methyl ester



HPLC-MS (Method A): m/z: 303 (M+1); Rt = 3.22-3-90 min.

Example 204

3-(2,4-Dioxothiazolidin-5-ylidenemethyl)indole-6-carboxylic acid pentyl ester.

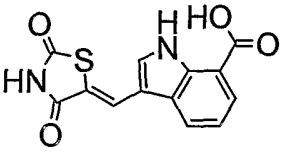


3-(2,4-Dioxothiazolidin-5-ylidenemethyl)indole-6-carboxylic acid methyl ester (example 203, 59 mg; 0.195mmol) was stirred in pentanol (20 mL) at 145 °C for 16 hours. The mixture was evaporated to dryness affording the title compound (69 mg).

HPLC-MS (Method C): m/z: 359 (M+1); Rt.= 4.25 min.

Example 205 (General procedure (C))

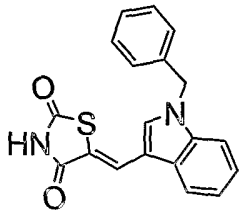
3-(2,4-Dioxothiazolidin-5-ylidenemethyl)indole-7-carboxylic acid



HPLC-MS (Method A): m/z: 289 (M+1); Rt = 2.67 min.

Example 206 (General procedure (C))

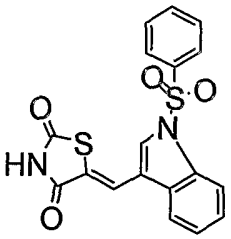
5-(1-Benzylindol-3-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 335 (M+1); Rt = 4.55 min.

Example 207 (General procedure (C))

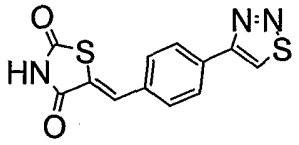
5-(1-Benzenesulfonylindol-3-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: = 385 (M+1); Rt = 4.59 min.

Example 208 (General procedure (C))

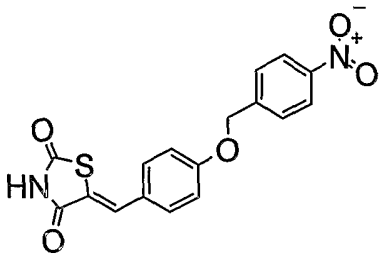
5-(4-[1,2,3]Thiadiazol-4-ylbenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 290 (M+1); Rt = 3.45 min.

Example 209 (General procedure (C))

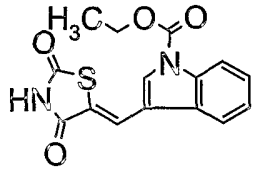
5-[4-(4-Nitrobenzyloxy)-benzylidene]thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 357 (M+1); Rt = 4.42 min.

Example 210 (General procedure (C))

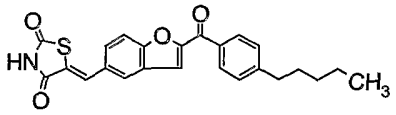
3-(2,4-Dioxothiazolidin-5-ylidenemethyl)indole-1-carboxylic acid ethyl ester



HPLC-MS (Method A): m/z: 317 (M+1); Rt = 4.35 min.

Example 211 (General procedure (C))

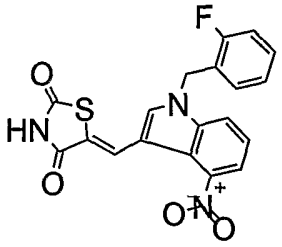
5-[2-(4-Pentylbenzoyl)-benzofuran-5-ylmethylene]thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 420 (M+1); Rt = 5.92 min.

Example 212 (General procedure (C))

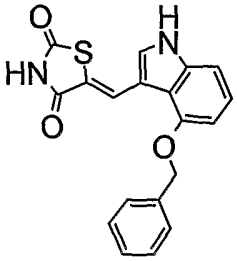
5-[1-(2-Fluorobenzyl)-4-nitroindol-3-ylmethylene]thiazolidine-2,4-dione



HPLC-MS (Method A): (Anyone 1) m/z: 398 (M+1); Rt = 4.42 min.

Example 213 (General procedure (C))

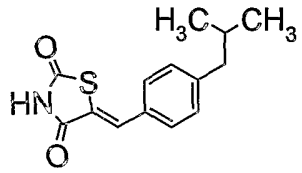
5-(4-Benzyloxyindol-3-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 351 (M+1); Rt = 3.95 min.

Example 214 (General procedure (C))

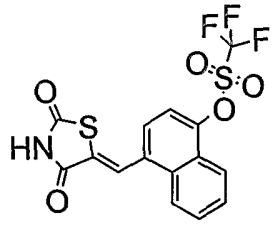
5-(4-Isobutylbenzylidene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 262 (M+1); Rt = 4.97 min.

Example 215 (General procedure (C))

Trifluoromethanesulfonic acid 4-(2,4-dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yl ester



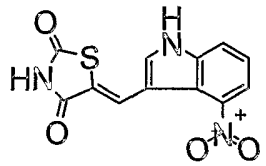
HPLC-MS (Method A): m/z: 404 (M+1); Rt = 4.96 min.

Preparation of starting material:

4-Hydroxy-1-naphthaldehyde (10 g, 58 mmol) was dissolved in pyridin (50 ml) and the mixture was cooled to 0-5 °C. With stirring, trifluoromethanesulfonic acid anhydride (11.7 ml, 70 mmol) was added drop-wise. After addition was complete, the mixture was allowed to warm up to room temperature, and diethyl ether (200 ml) was added. The mixture was washed with water (2 x 250 ml), hydrochloric acid (3N, 200 ml), and saturated aqueous sodium chloride (100 ml). After drying (MgSO4), filtration and concentration in vacuo, the residue was purified by column chromatography on silica gel eluting with a mixture of ethyl acetate and heptane (1:4). This afforded 8.35 g (47%) trifluoromethanesulfonic acid 4-formylnaphthalen-1-yl ester, mp 44-46.6 °C.

Example 216 (General procedure (C))

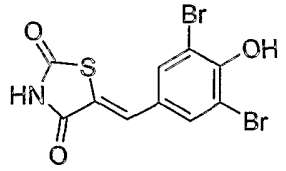
5-(4-Nitroindol-3-ylmethylene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 290 (M+1); Rt = 3.14 min.

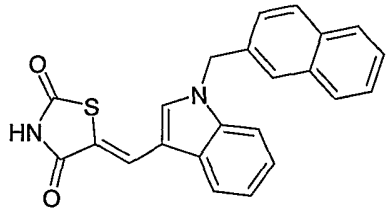
Example 217 (General procedure (C))

5-(3,5-Dibromo-4-hydroxy-benzylidene)thiazolidine-2,4-dione



^{1}H NMR (DMSO-d_6): δ_H = 12.65 (broad,1H), 10.85 (broad,1H), 7.78 (s,2H), 7.70 (s,1H); HPLC-MS (Method A): m/z: 380 (M+1); Rt = 3.56 min.

Example 218 (General procedure (C))



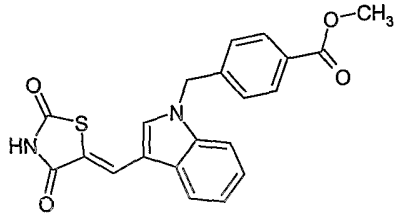
HPLC-MS (Method A): m/z: 385 (M+1); Rt = 5.08 min.

General procedure for preparation of starting materials for examples 218 - 221:
Indole-3-carbaldehyde (3.8 g, 26 mmol) was stirred with potassium hydroxide (1.7 g) in acetone (200 mL) at RT until a solution was obtained indicating full conversion to the indole potassium salt. Subsequently the solution was evaporated to dryness *in vacuo*. The residue was dissolved in acetone to give a solution containing 2.6 mmol/20 mL.

20 mL portions of this solution were mixed with equimolar amounts of arylmethylbromides in acetone (10 mL). The mixtures were stirred at RT for 4 days and subsequently evaporated to dryness and checked by HPLC-MS. The crude products, 1-benzylated indole-3-carbaldehydes, were used for the reaction with thiazolidine-2,4-dione using the general procedure C.

Example 219 (General procedure (C))

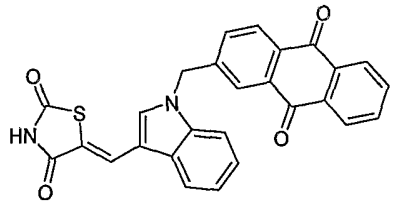
4-[3-(2,4-Dioxothiazolidin-5-ylidenemethyl)indol-1-ylmethyl]benzoic acid methyl ester



HPLC-MS (Method A): m/z: 393 (M+1); Rt = 4.60 min.

Example 220 (General procedure (C))

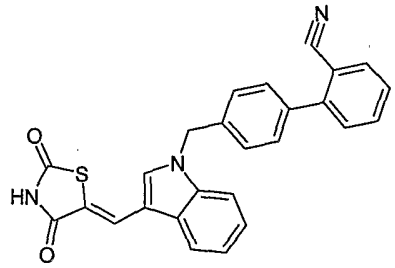
5-[1-(9,10-Dioxo-9,10-dihydroanthracen-2-ylmethyl)-1*H*-indol-3-ylmethylene]thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 465 (M+1); Rt = 5.02 min.

Example 221 (General procedure (C))

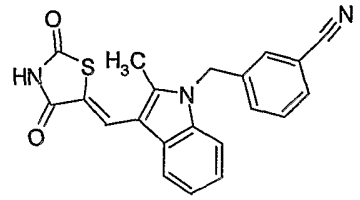
4'-[3-(2,4-Dioxothiazolidin-5-ylidenemethyl)indol-1-ylmethyl]biphenyl-2-carbonitrile



HPLC-MS (Method A): m/z: 458 (M+23); Rt = 4.81 min.

Example 222 (General procedure (C))

3-[3-(2,4-Dioxothiazolidin-5-ylidenemethyl)-2-methylindol-1-ylmethyl]benzonitrile.

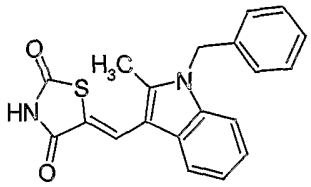


2-Methylindole-3-carbaldehyde (200 mg, 1.26 mmol) was added to a slurry of 3-bromomethylbenzenecarbonitrile (1.26 mmol) followed by sodium hydride, 60%, (1.26 mmol) in DMF (2 mL). The mixture was shaken for 16 hours, evaporated to dryness and washed

with water and ethanol. The residue was treated with thiazolidine-2,4-dione following the general procedure C to afford the title compound (100 mg).

HPLC-MS (Method C): m/z: 374 (M+1); Rt. = 3.95 min.

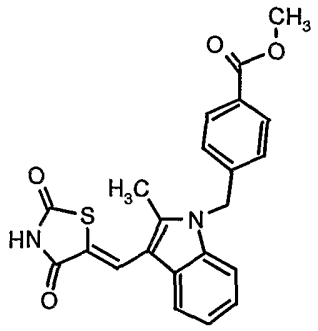
Example 223 (General procedure (C))
5-(1-Benzyl-2-methylindol-3-ylmethylene)thiazolidine-2,4-dione.



This compound was prepared in analogy with the compound described in example 222 from benzyl bromide and 2-methylindole-3-carbaldehyde, followed by reaction with thiazolidine-2,4-dione resulting in 50 mg of the title compound.

HPLC-MS (Method C): m/z: 349 (M+1); Rt. = 4.19 min.

Example 224
4-[3-(2,4-Dioxothiazolidin-5-ylidenemethyl)-2-methylindol-1-ylmethyl]benzoic acid methyl ester

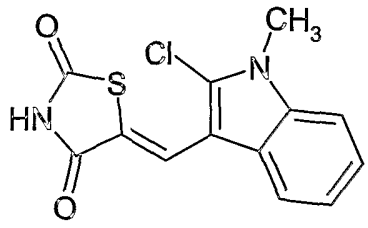


This compound was prepared in analogy with the compound described in example 222 from 4-(bromomethyl)benzoic acid methyl ester and 2-methylindole-3-carbaldehyde, followed by reaction with thiazolidine-2,4-dione.

HPLC-MS (Method C): m/z: 407 (M+1); Rt.= 4.19 min.

Example 225 (General procedure (C))

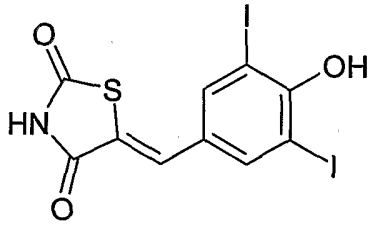
5-(2-Chloro-1-methyl-1H-indol-3-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 293 (M+1); Rt = 4.10 min.

Example 226 (General procedure (C))

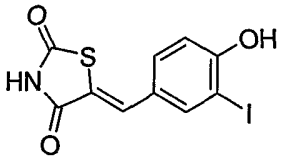
5-(4-Hydroxy-3,5-diiodo-benzylidene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 474 (M+1); Rt = 6.61 min.

Example 227 (General procedure (C))

5-(4-Hydroxy-3-iodobenzylidene)thiazolidine-2,4-dione

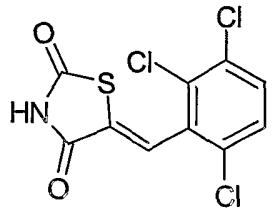


HPLC-MS (Method C): m/z: 348 (M+1); Rt. = 3.13 min

^{1}H-NMR: (DMSO-d_6): 11.5 (1H,broad); 7.95(1H,d); 7.65(1H,s); 7.45 (1H,dd); 7.01(1H,dd); 3.4 (1H,broad).

Example 228 (General procedure (C))

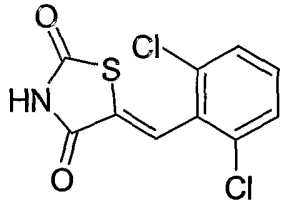
5-(2,3,6-Trichlorobenzylidene)thiazolidine-2,4-dione



H PLC-MS (Method C): m/z: 309 (M+1); Rt.= 4.07 min

Example 229 (General procedure (C))

5-(2,6-Dichlorobenzylidene)thiazolidine-2,4-dione



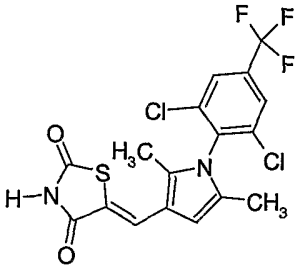
Mp. 152-154°C.

HPLC-MS (Method C): m/z: 274 (M+1), Rt.= 3.70 min

^{1}H-NMR: (DMSO-d_6): 12.8 (1H, broad); 7.72 (1H,s); 7.60 (2H,d); 7.50 (1H,t).

Example 230 (General procedure (C))

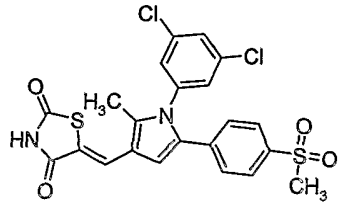
5-[1-(2,6-Dichloro-4-trifluoromethylphenyl)-2,5-dimethyl-1*H*-pyrrol-3-ylmethylene]thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 436 (M+1); Rt. 4.81 min

Example 231 (General procedure (C))

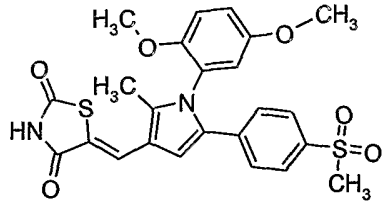
5-[1-(3,5-Dichlorophenyl)-5-(4-methanesulfonylphenyl)-2-methyl-1*H*-pyrrol-3-ylmethylene]-thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 508 (M+1); Rt. = 4.31 min

Example 232 (General procedure (C))

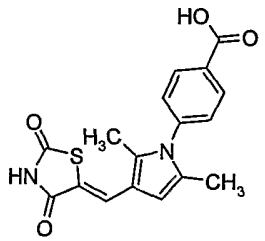
5-[1-(2,5-Dimethoxyphenyl)-5-(4-methanesulfonylphenyl)-2-methyl-1*H*-pyrrol-3-ylmethylene]-thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 499 (M+1); Rt. = 3.70 min

Example 233 (General procedure (C))

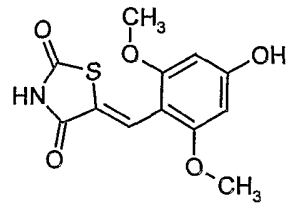
4-[3-(2,4-Dioxothiazolidin-5-ylidenemethyl)-2,5-dimethylpyrrol-1-yl]benzoic acid



HPLC-MS (Method C): m/z:342 (M+1); Rt.= 3.19 min

Example 234 (General procedure (C))

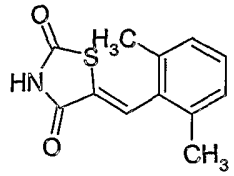
5-(4-Hydroxy-2,6-dimethoxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z:282(M+1); Rt.= 2.56, mp=331-333 °C

Example 235 (General procedure (C))

5-(2,6-Dimethylbenzylidene)thiazolidine-2,4-dione

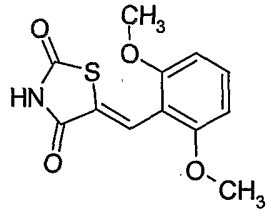


M.p: 104-105 °C

HPLC-MS (Method C): m/z: 234 (M+1); Rt.= 3.58 min,

Example 236 (General procedure (C))

5-(2,6-Dimethoxybenzylidene)thiazolidine-2,4-dione

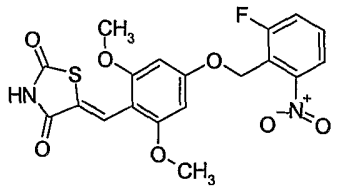


Mp: 241-242 °C

HPLC-MS (Method C): m/z: 266 (M+1); Rt.= 3.25 min;

Example 237 (General procedure (C))

5-[4-(2-Fluoro-6-nitrobenzyloxy)-2,6-dimethoxybenzylidene]thiazolidine-2,4-dione

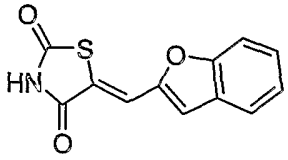


Mp: 255-256 °C

HPLC-MS (Method C): m/z: 435 (M+1), Rt 4.13 min,

Example 238 (General procedure (C))

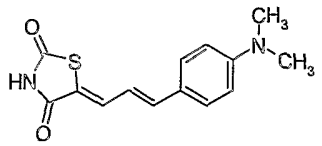
5-Benzofuran-2-ylmethylenethiazolidine-2,4-dione



HPLC-MS (Method C): m/z:246 (M+1); Rt.= 3.65 min, mp = 265-266 °C .

Example 239 (General procedure (C))

5-[3-(4-Dimethylaminophenyl)allylidene]thiazolidine-2,4-dione

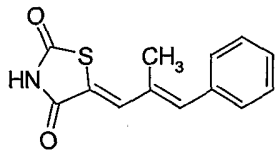


HPLC-MS (Method C): m/z:276(M+1); Rt.= 3.63, mp = 259-263 °C

^{1}H-NMR: (DMSO-d_6) δ= 12.3 (1H,broad); 7.46 (2H,d); 7.39 (1H,d); 7.11 (1H,d); 6.69 (2H,d); 6.59 (1H, dd); 2.98 (3H,s).

Example 240 (General procedure (C))

5-(2-Methyl-3-phenylallylidene)thiazolidine-2,4-dione

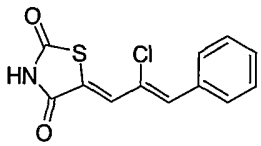


Mp: 203-210 °C

HPLC-MS (Method C): m/z: 246 (M+1); Rt = 3.79 min.

Example 241 (General procedure (C))

5-(2-Chloro-3-phenylallylidene)thiazolidine-2,4-dione

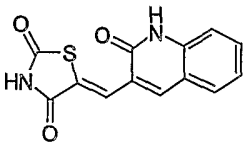


Mp: 251-254 °C

HPLC-MS (Method C): m/z: 266 (M+1; Rt = 3.90 min

Example 242 (General procedure (C))

5-(2-Oxo-1,2-dihydroquinolin-3-ylmethylene)thiazolidine-2,4-dione

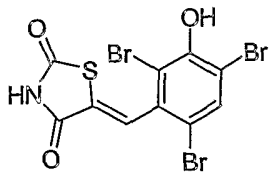


Mp: 338-347 °C

HPLC-MS (Method C): m/z: 273 (M+1); Rt. = 2.59 min.

Example 243 (General procedure (C))

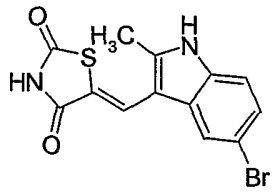
5-(2,4,6-Tribromo-3-hydroxybenzylidene)thiazolidine-2,4-dione.



HPLC-MS (Method C): m/z: 459 (M+1);Rt.= 3.65 min.

Example 244 (General procedure (C))

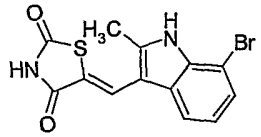
5-(5-Bromo-2-methylindol-3-ylmethylene)thiazolidine-2,4-dione.



HPLC-MS (Method C): m/z: 339 (M+1); Rt = 3.37min.

Example 245 (General procedure (C))

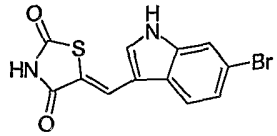
5-(7-Bromo-2-methylindol-3-ylmethylene)thiazolidine-2,4-dione.



HPLC-MS (Method C): m/z: 319 (M+1); Rt = 3.48min.

Example 246 (General procedure (C))

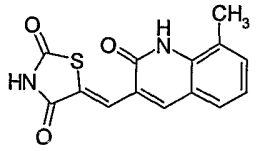
5-(6-Bromoindol-3-ylmethylene)thiazolidine-2,4-dione.



HPLC-MS (Method C): m/z: 325 (M+1); Rt = 3.54 min.

Example 247 (General procedure (C))

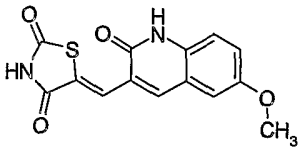
5-(8-Methyl-2-oxo-1,2-dihydroquinolin-3-ylmethylene)thiazolidine-2,4-dione.



HPLC-MS (Method C): m/z: 287 (M+1); Rt = 2.86 min.

Example 248 (General procedure (C))

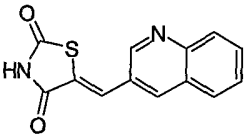
5-(6-Methoxy-2-oxo-1,2-dihydroquinolin-3-ylmethylene)thiazolidine-2,4-dione.



HPLC-MS (Method C): m/z: 303 (M+1); Rt = 2.65 min.

Example 249 (General procedure (C))

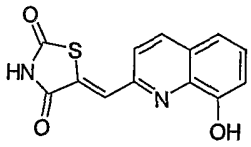
5-Quinolin-3-ylmethylenethiazolidine-2,4-dione.



HPLC-MS (Method C): m/z: 257 (M+1); Rt = 2.77 min.

Example 250 (General procedure (C))

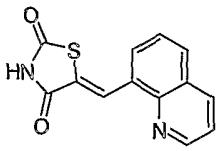
5-(8-Hydroxyquinolin-2-ylmethylene)thiazolidine-2,4-dione.



HPLC-MS (Method C): m/z: 273 (M+1); Rt = 3.44 min.

Example 251 (General procedure (C))

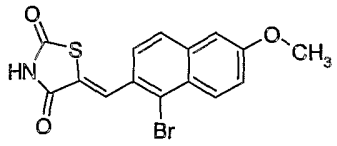
5-Quinolin-8-ylmethylenethiazolidine-2,4-dione.



HPLC-MS (Method C): m/z: 257 (M+1); Rt = 3.15 min.

Example 252 (General procedure (C))

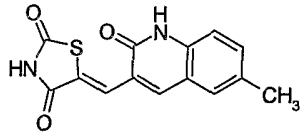
5-(1-Bromo-6-methoxynaphthalen-2-ylmethylene)thiazolidine-2,4-dione.



HPLC-MS (Method C): m/z: 366 (M+1); Rt = 4.44 min.

Example 253 (General procedure (C))

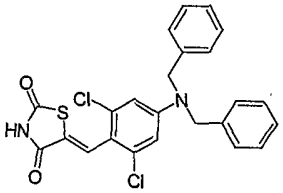
5-(6-Methyl-2-oxo-1,2-dihydroquinolin-3-ylmethylene)thiazolidine-2,4-dione.



HPLC-MS (Method C): m/z: 287 (M+1); Rt. = 2.89 min.

Example 254 (General procedure (D))

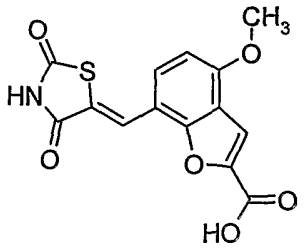
5-(2,6-Dichloro-4-dibenzylaminobenzylidene)thiazolidine-2,4-dione.



HPLC-MS (Method C): m/z: 469 (M+1); Rt = 5.35 min.

Example 255 (General Procedure (C))

7-(2,4-Dioxothiazolidin-5-ylidenemethyl)-4-methoxybenzofuran-2-carboxylic acid



HPLC-MS (Method C): m/z: 320 (M+1); Rt = 2.71 mln.

Preparation of the intermediate, 7-formyl-4-methoxybenzofuran-2-carboxylic acid:

A mixture of 2-hydroxy-6-methoxybenzaldehyde (6.4 g, 42 mmol), ethyl bromoacetate (14.2 mL, 128 mmol) and potassium carbonate (26 g, 185 mmol) was heated to 130 ^{0}C. After 3 h the mixture was cooled to room temperature and acetone (100 mL) was added, the mixture was subsequently filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with a mixture of ethyl acetate and heptane (1:4). This afforded 7.5 g (55%) of ethyl 4-methoxybenzofuran-2-carboxylate.

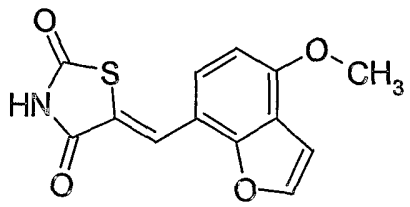
A solution of ethyl 4-methoxybenzofuran-2-carboxylate (6.9 g, 31.3 mmol) in dichloromethane (70 ml) was cooled to 0 ^{0}C and a solution of titanium tetrachloride (13.08 g, 69 mmol) was added drop wise. After 10 minutes dichloromethoxymethane (3.958 g, 34 mmol) was added over 10 minutes. After addition, the mixture was warmed to room temperature for 18 hours and the mixture poured into hydrochloric acid (2N, 100 mL). The mixture was stirred for 0.5 hour and then extracted with a mixture of ethyl acetate and toluene (1:1). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with a mixture of ethyl acetate and heptane (1:4). This afforded 5.8 g (80%) of ethyl 7-formyl-4-methoxybenzofuran-2-carboxylate.

7-formyl-4-methoxybenzofuran-2-carboxylate (5.0 g, 21.5 mmol) and sodium carbonate (43 mmol) in water (100 mL) was refluxed until a clear solution appeared (about 0.5 hour). The solution was filtered and acidified to pH =1 with hydrochloric acid (2 N), the resulting product was filtered off and washed with ethyl acetate and ethanol and dried to afford 3.5 g (74%) of 7-formyl-4-methoxybenzofuran-2-carboxylic acid as a solid.

^{1}H NMR (DMSO-d_6): δ = 10.20 (s, 1H) ; 8.07 (d, 1H) ; 7.70 (s, 1H) ; 7.17 (d, 1H) ; 4.08 (s, 3H).

Example 256 (General Procedure (C))

5-(4-Methoxybenzofuran-7-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 267 (M+1); Rt = 3.30 min.

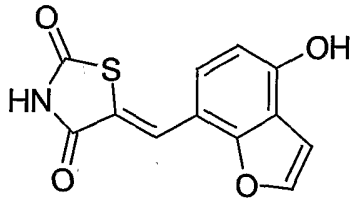
Preparation of the intermediate, 4-methoxybenzofuran-7-carbaldehyde:

A mixture of 7-formyl-4-methoxybenzofuran-2-carboxylic acid (3.0 g, 13.6 mmol) and Cu (0.6 g, 9.44 mmol) in quinoline (6 mL) was refluxed. After 0.5 h the mixture was cooled to room temperature and water (100 mL) and hydrochloric acid (10 N, 20 mL) were added. The mixture was extracted with a mixture of ethyl acetate and toluene (1:1), filtered through celite and the organic layer separated and washed with a sodium carbonate solution, dried over Na_2SO_4 and concentrated *in vacuo* to afford 1.5 g crude product. Column chromatography SiO_2, EtOAc/heptanes=1/4 gave 1.1 g (46%) of 4-methoxybenzofuran-7-carbaldehyde as a solid.

^{1}H NMR ($CDCl_3$): δ: 10.30 (s,1H) ; 7.85 (d,1H) ; 7.75 (d,1H) ; 6.98 (d,1H) ; 6.87 (d,1H) ; 4.10 (s,3H). HPLC-MS (Method C) :m/z: 177 (M+1); Rt. = 7.65 min.

Example 257 (General Procedure (C))

5-(4-Hydroxybenzofuran-7-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: = 262 (M+1); Rt 2.45 min.

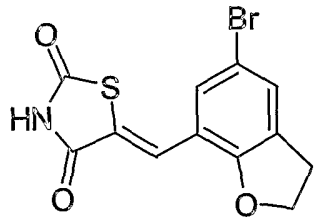
Preparation of the intermediate, 4-hydroxybenzofuran-7-carbaldehyde

A mixture of 4-methoxybenzofuran-7-carbaldehyde (1.6 g, 9.1 mmol) and pyridine hydrochloride (4.8 g, 41.7mmol) in quinoline (8 mL) was refluxed. After 8 h the mixture was cooled to room temperature and poured into water (100 mL) and hydrochloric acid (2 N) was added to pH = 2. The mixture was extracted with a mixture of ethyl acetate and toluene (1:1), washed with a sodium carbonate solution, dried with Na_2SO_4 and concentrated *in vacuo* to afford 0.8 g crude product. This was purified by column chromatography on silica gel, eluting with a mixture of ethyl acetate and heptane (1:3). This afforded 250 mg of 4-hydroxybenzofuran-7-carbaldehyde as a solid.

^{1}H NMR (DMSO-d_6): δ = 11.35 (s, broad,1H) ; 10.15 (s, 1H) ; 8.05 (d, 1H) ; 7.75 (d, 1H) ; 7.10 (d, 1H); 6.83 (d, 1H). HPLC-MS (Method C): m/z: 163 (M+1); Rt. = 6.36 min.

Example 258 (General Procedure (C))

5-(5-Bromo-2,3-dihydrobenzofuran-7-ylmethylene)thiazolidine-2,4-dione



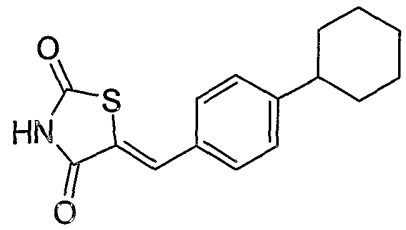
HPLC-MS (Method C): m/z: 328 (M+1); Rt = 3.66 min.

Preparation of the intermediate, 5-bromo-2,3-dihydrobenzofuran-7-carbaldehyde:
To a cooled (15 ^{0}C) stirred mixture dihydrobenzofuran (50.9 g, 0.424 mol) in acetic acid (500 mL), *a solution of bromine (65.5 mL, 1.27 mol) in acetic acid (200 mL) was added drop wise* over 1 hour. After stirring for 18 hours, a mixture of $Na_2S_2O_5$ (150 g) in water (250 mL) was added carefully, and the mixture was concentrated *in vacuo.* Water (200 mL) was added and the mixture was extracted with ethyl acetate containing 10% heptane, dried over Na_2SO_4 and concentrated *in vacuo* to give crude 5,7-dibromo-2,3-dihydrobenzofuran which was used as such for the following reaction steps. To a cooled solution (-78 ^{0}C) of crude 5,7-dibromo-2,3-dihydrobenzofuran (50.7 g, 0.182 mol) in THF (375 mL) a solution of n-BuLi (2.5 M, 80 mL, 0.200 mol) in hexane was added. After addition, the mixture was stirred for 20 min. DMF (16 mL) was then added drop wise at -78 ^{0}C. After addition, the mixture was stirred at room temperature for 3 h and then the mixture was poured into a mixture of ice water, (500 mL) and hydrochloric acid (10 N, 40 mL) and extracted with toluene, dried over Na_2SO_4 and concentrated *in vacuo.* Column chromatography on silica gel eluting with a mixture of ethyl acetate and heptane (1:4) afforede 23 g of 5-bromo-2,3-dihydrobenzofuran-7-carbaldehyde as a solid.

^{1}H NMR ($CDCl_3$): δ:10.18 (s,1H) ; 7.75 (d,1H) ;7.55 (d,1H) ; 4.80 (t,2H) ; 3.28 (t,2H).

Example 259 (General Procedure (C))

5-(4-Cyclohexylbenzylidene)thiazolidine-2,4-dione



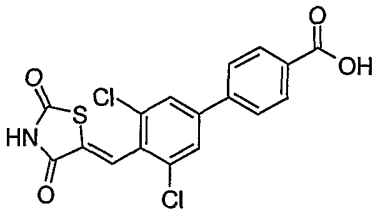
HPLC-MS (Method C): m/z: 288 (M+1); Rt = 5.03 min.

Preparation of the intermediate, 4-cyclohexylbenzaldehyde:

This compound was synthesized according to a modified literature procedure (*J. Org. Chem.*, 37, No.24, (1972), 3972-3973).
Cyclohexylbenzene (112.5 g, 0.702 mol) and hexamethylenetetramine (99.3 g, 0.708 mol) were mixed in TFA (375 mL). The mixture was stirred under nitrogen at 90 °C for 3 days. After cooling to room temperature the red-brown mixture was poured into ice-water (3600 ml) and stirred for 1 hour. The solution was neutralized with Na_2CO_3 (2 M solution in water) and extracted with dichloromethane (2.5 L). The organic phase was dried (Na_2SO_4) and the solvent was removed *in vacuo*. The remaining red-brown oil was purified by fractional distillation to afford the title compound (51 g, 39%).
^{1}H NMR ($CDCl_3$): δ 9.96 (s, 1H), 7.80 (d, 2H), 7.35 (d, 2H), 2.58 (m, 1H), 1.94-1.70 (m, 5 H), 1.51-1.17 (m, 5H)

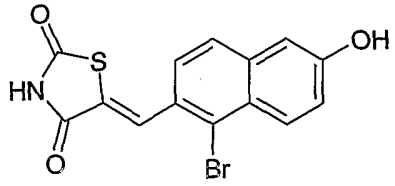
Other ligands of the invention include

3',5'-Dichloro-4'-(2,4-dioxothiazolidin-5-ylidenemethyl)biphenyl-4-carboxylic acid:



Example 260 (General procedure (C))

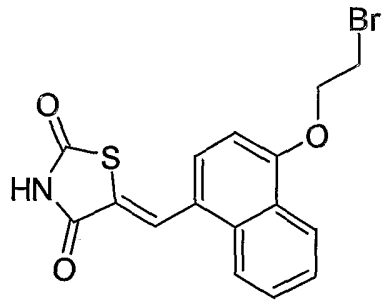
5-(1-Bromo-6-hydroxynaphthalen-2-ylmethylene)-thiazolidine-2,4-dione



HPLC-MS (Method C): m/z = 350 (M+1); Rt. = 3.45 min.

Example 261 (General procedure (C))

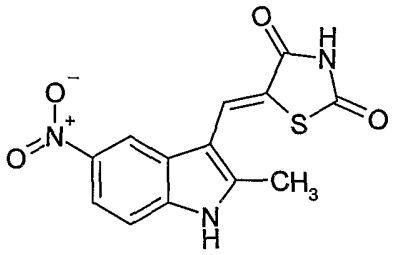
5-[4-(2-Bromoethoxy)-naphthalen-1-ylmethylene]-thiazolidine-2,4-dione



HPLC-MS (Method C): m/z = 380 (M+1); Rt = 3.52 min.

Example 262 (General procedure (C))

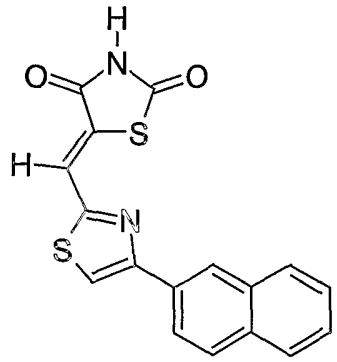
5-(2-Methyl-5-nitro-1H-indol-3-ylmethylene)-thiazolidine-2,4-dione



HPLC-MS (Method C): m/z = 304 (M+1); Rt = 2.95 min.

Example 263 (General procedure (C))

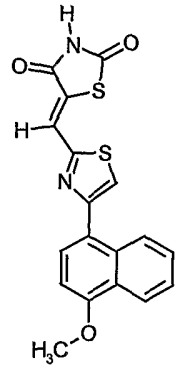
5-(4-Naphthalen-2-yl-thiazol-2-ylmethylene)-thiazolidine-2,4-dione



HPLC-MS (Method C): m/z = 339 (M+1); Rt.= 4.498 min.

Example 264 (General procedure (C))

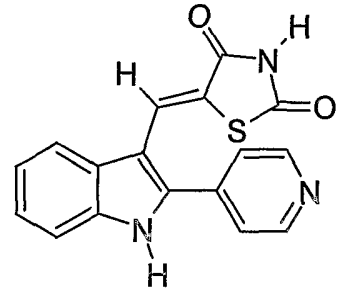
5-[4-(4-Methoxy-naphthalen-1-yl)-thiazol-2-ylmethylene]-thiazolidine-2,4-dione



HPLC-MS (Method C): m/z = 369 (M+1); Rt.= 4.456 min.

Example 265 (General procedure (C))

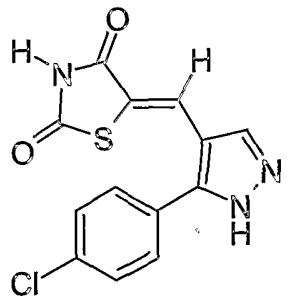
5-(2-Pyridin-4-yl-1H-indol-3-ylmethylene)-thiazolidine-2,4-dione



HPLC-MS (Method C): m/z = 322 (M+1); Rt. = 2.307 min.

Example 266 (General procedure (C))

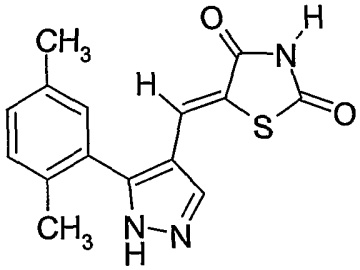
5-[5-(4-Chlorophenyl)-1H-pyrazol-4-ylmethylene]-thiazolidine-2,4-dione



HPLC-MS (Method C): m/z = 306 (M+1); Rt.= 3.60 min.

Example 267 (General procedure (C))

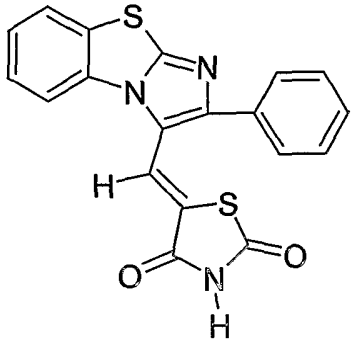
5-[5-(2,5-Dimethylphenyl)-1H-pyrazol-4-ylmethylene]-thiazolidine-2,4-dione



HPLC-MS (Method C): m/z = 300 (M+1); Rt. = 3.063 min.

Example 268 (General procedure (C))

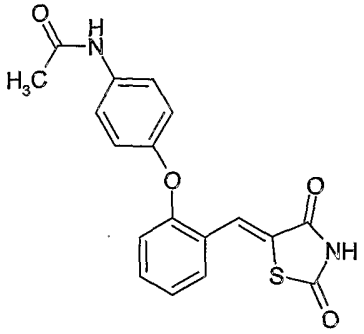
5-(2-Phenyl-benzo[d]imidazo[2,1-b]thiazol-3-ylmethylene)-thiazolidine-2,4-dione



HPLC-MS (Method C): m/z = 378 (M+1); Rt = 3.90 min.

Example 269 (General procedure (C))

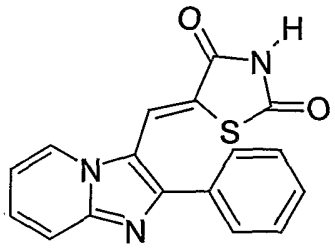
N-{4-[2-(2,4-Dioxothiazolidin-5-ylidenemethyl)-phenoxy]-phenyl}-acetamide



HPLC-MS (Method C): m/z = 355 (M+1); Rt 3.33 min.

Example 270 (General procedure (C))

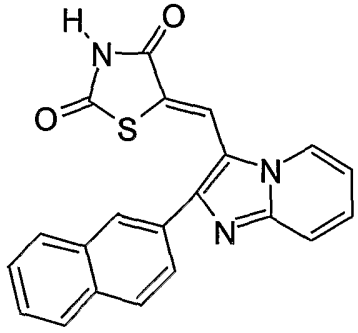
5-(2-Phenyl-imidazo[1,2-a]pyridin-3-ylmethylene)-thiazolidine-2,4-dione



HPLC-MS (Method C): m/z = 322 (M+1); Rt. = 2.78 min.

Example 271 (General procedure (C))

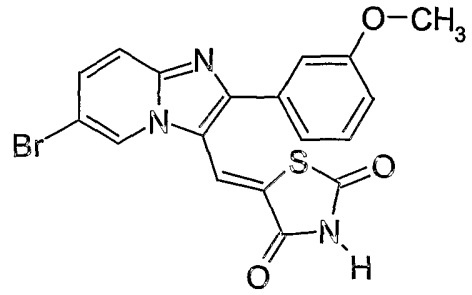
5-(2-Naphthalen-2-yl-imidazo[1,2-a]pyridin-3-ylmethylene)-thiazolidine-2,4-dione



HPLC-MS (Method C): m/z = 372 (M+1); Rt. = 2.78 min.

Example 272 (General procedure (C))

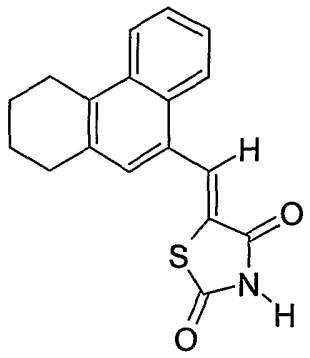
5-[6-Bromo-2-(3-methoxyphenyl)-imidazo[1,2-a]pyridin-3-ylmethylene]-thiazolidine-2,4-dione



HPLC-MS (Method C): m/z = 431 (M+1); Rt.= 3.30 min.

Example 273 (General procedure (C))

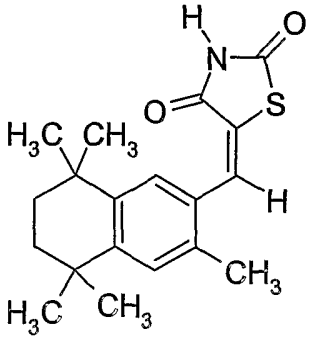
5-(1,2,3,4-Tetrahydrophenanthren-9-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z = 310 (M+1); Rt.= 4.97 min.

Example 274 (General procedure (C))

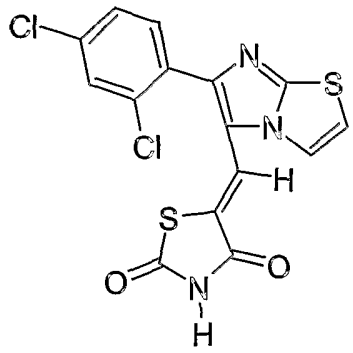
5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z = 330 (M+1); Rt.= 5.33 min.

Example 275 (General procedure (C))

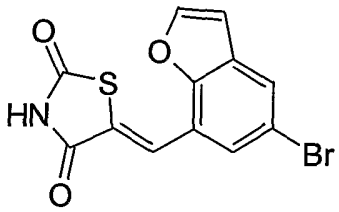
5-[6-(2,4-Dichloro-phenyl)-imidazo[2,1-b]thiazol-5-ylmethylene]-thiazolidine-2,4-dione



HPLC-MS (Method C): m/z = 396 (M+1); Rt. = 3.82 min.

Example 276 (General procedure (C))

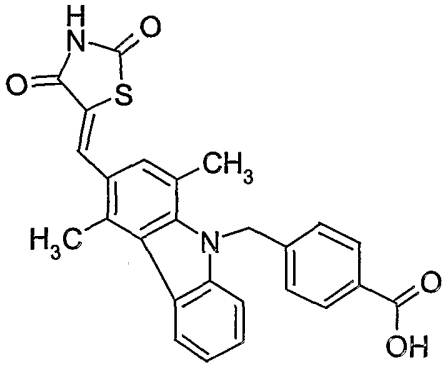
5-(5-Bromobenzofuran-7-ylmethylene)-thiazolidine-2,4-dione



HPLC-MS (Method C): m/z = 324 (M+1); Rt. = 3.82 min.

Example 277 (General procedure (C))

4-[3-(2,4-Dioxothiazolidin-5-ylidenemethyl)-1,4-dimethylcarbazol-9-ylmethyl]-benzoic acid



HPLC-MS (Method C): m/z = 457 (M+1); Rt = 4,23 min.

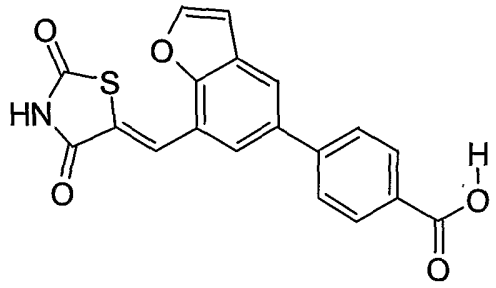
Preparation of intermediary aldehyde:

1,4 Dimethylcarbazol-3-carbaldehyde (0.68 g, 3.08 mmol) was dissolved in dry DMF (15 mL), NaH (diethyl ether washed) (0.162 g, 6.7 mol) was slowly added under nitrogen and the mixture was stirred for 1 hour at room temperature. 4-Bromomethylbenzoic acid (0.73 g, 3.4 mmol) was slowly added and the resulting slurry was heated to 40 °C for 16 hours. Water (5 mL) and hydrochloric acid (6N, 3 mL) were added. After stirring for 20 min at room temperature, the precipitate was filtered off and washed twice with acetone to afford after drying 0.38 g (34%) of 4-(3-formyl-1,4-dimethylcarbazol-9-ylmethyl)benzoic acid.

HPLC-MS (Method C) : m/z = 358 (M+1), RT. = 4.15 min.

Example 278 (General procedure (C))

4-[7-(2,4-Dioxothiazolidin-5-ylidenemethyl)-benzofuran-5-yl]-benzoic acid

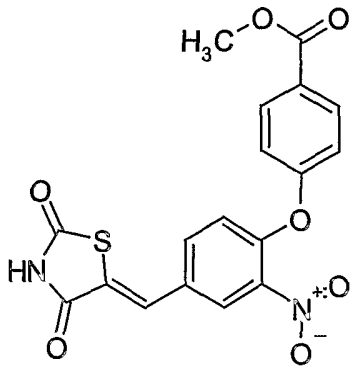


Starting aldehyde commercially available (Syncom BV, NL)

HPLC-MS (Method C): m/z = 366 (M+1); Rt. = 3.37 min.

Example 279 (General procedure (C))

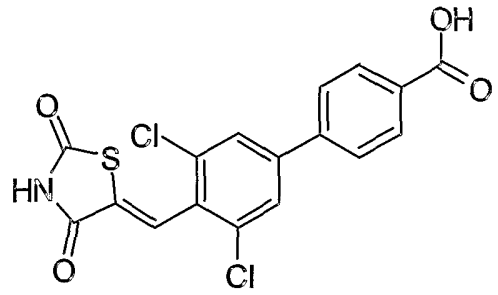
4-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)-2-nitrophenoxy]-benzoic acid methyl ester



HPLC-MS (Method C): m/z = 401 (M+1); Rt. = 4.08 min.

Example 280 (General procedure (C))

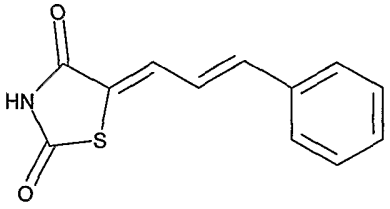
3',5'-Dichloro-4'-(2,4-dioxothiazolidin-5-ylidenemethyl)-biphenyl-4-carboxylic acid



Starting aldehyde commercially available (Syncom BV, NL)

HPLC-MS (Method C): m/z = 394 (M+1); Rt. = 3.71 min.

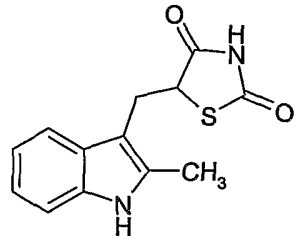
Example 281 (General procedure (C))



HPLC-MS (Method C): m/z = 232(M+1); Rt.= 3.6 min.

Example 282

5-(2-Methyl-1H-indol-3-ylmethyl)-thiazolidine-2,4-dione



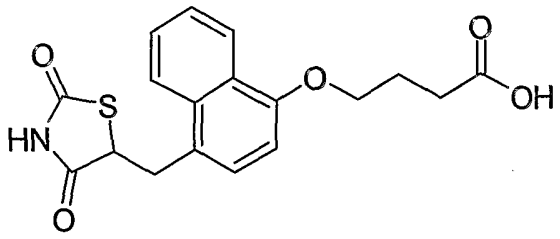
5-(2-Methyl-1H-indol-3-ylmethylene)thiazolidine-2,4-dione (prepared as described in example 187, 1.5 g, 5.8 mmol) was dissolved in pyridine (20 mL) and THF (50 mL), $LiBH_4$ (2 M in THF, 23.2 mmol) was slowly added with a syringe under cooling on ice. The mixture was heated to 85 °C for 2 days. After cooling, the mixture was acidified with concentrated hydro-

chloric acid to pH 1. The aquous layer was extracted 3 times with ethyl acetate, dried with $MgSO_4$ treated with activated carbon, filtered and the resulting filtrate was evaporated *in vacuo* to give 1.3 g (88%) of the title compound.

HPLC-MS (Method C): m/z = 261 (M+1); Rt. = 3.00 min.

Example 283

4-[4-(2,4-Dioxothiazolidin-5-ylmethyl)naphthalen-1-yloxy]butyric acid

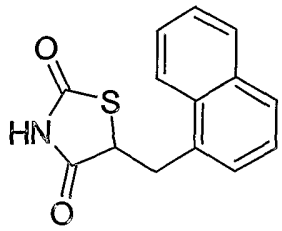


4-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]butyric acid (4.98 g, 13.9 mmol, prepared as described in example 469) was dissolved in dry THF (50 mL) and added dry pyridine (50 mL) and, in portions, lithium borohydride (2.0 M, in THF, 14 mL). The resulting slurry was refluxed under nitrogen for 16 hours, added (after cooling) more lithium borohydride (2.0 M, in THF, 7 mL). The resulting mixture was refluxed under nitrogen for 16 hours. The mixture was cooled and added more lithium borohydride (2.0 M, in THF, 5 mL). The resulting mixture was refluxed under nitrogen for 16 hours. After cooling to 5 °C, the mixture was added water (300 mL) and hydrochloric acid (150 mL). The solid was isolated by filtration, washed with water (3 x 500 mL) and dried. Recrystallization from acetonitrile (500 mL) afforded2.5 g of the title compound.

^{1}H-NMR (DMSO-d_6, selected peaks): δ = 3.42 (1H, dd), 3.90 (1H, dd), 4.16 (2H, "t"), 4.95 (1H, dd), 6.92 (1H, d), 7.31 (1H, d), 7.54 (1H, t), 7.62 (1H, t), 8.02 (1H, d), 8.23 (1H, d), 12.1 (1H, bs), 12.2 (1H, bs).
HPLC-MS (Method C): m/z = 382 (M+23); Rt = 3,23 min.

Example 284

5-Naphthalen-1-ylmethylthiazolidine-2,4-dione

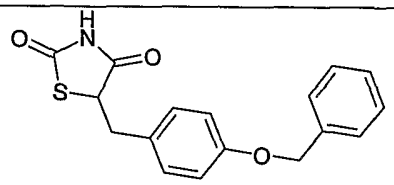
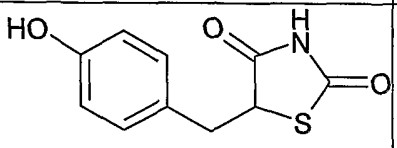
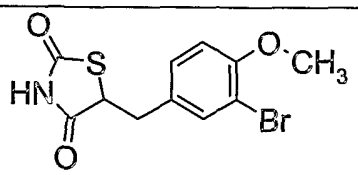


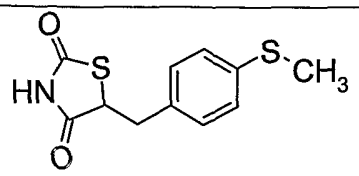
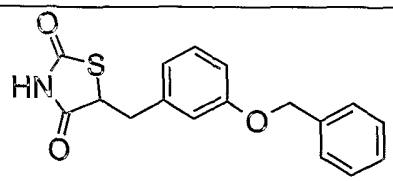
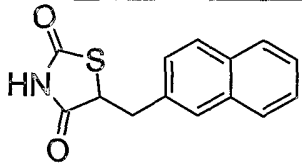
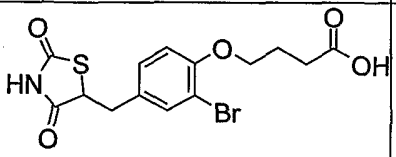
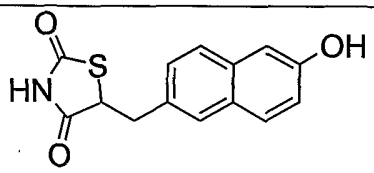
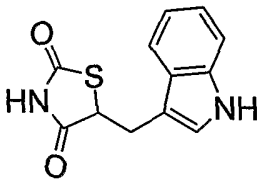
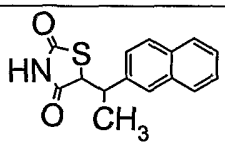
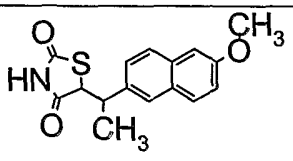
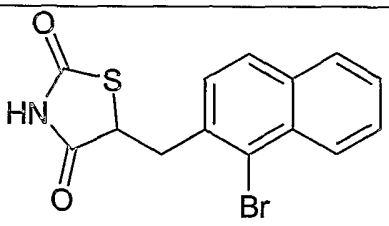
5-Naphthalen-1-ylmethylenethiazolidine-2,4-dione (1.08 g, 4.2 mmol, prepared as described in example 68) was dissolved in dry THF (15 mL) and added dry pyridine (15 mL) and, in portions, lithium borohydride (2.0 M, in THF, 4.6 mL). The resulting mixture was refluxed under nitrogen for 16 hours. After cooling to 5 °C, the mixture was added water (100 mL), and, in portions, concentrated hydrochloric acid (40 mL). More water (100 mL) was added, and the mixture was extracted with ethyl acetate (200 mL). The organic phase was washed with water (3 x 100 mL), dried and concentrated *in vacuo*. The residue was dissolved in ethyl acetate (50 mL) added activated carbon, filtered and concentrated in vacuo and dried to afford 0.82 g (75%) of the title compound.

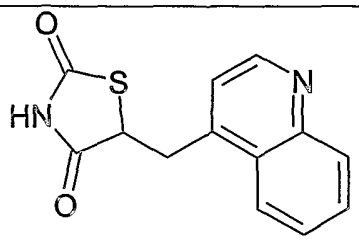
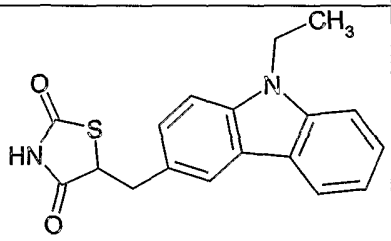
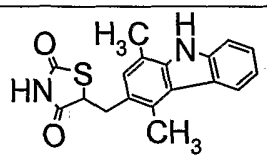
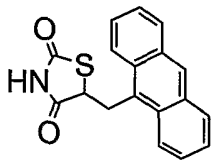
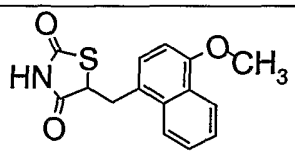
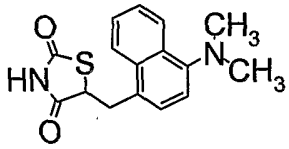
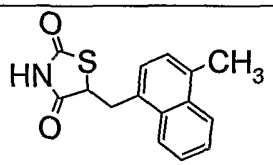
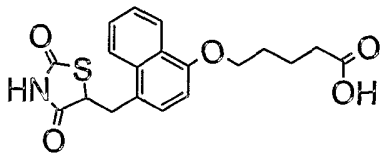
^{1}H-NMR (DMSO-d_6): δ = 3.54 (1H, dd), 3.98 (1H, dd), 5.00 (1H, dd), 7.4-7.6 (4H, m), 7.87 (1H, d), 7.96 (1H, d), 8.11 (1H, d), 12.2 (1H, bs).

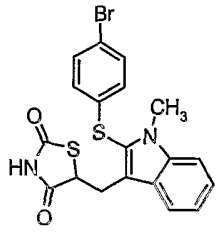
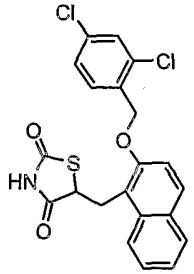
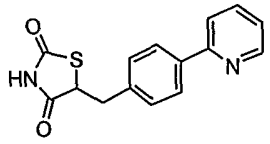
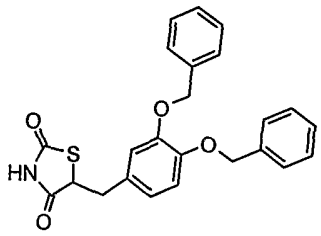
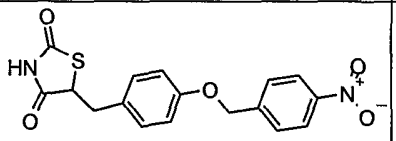
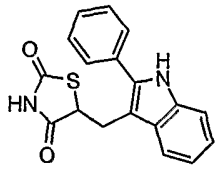
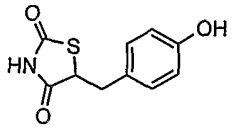
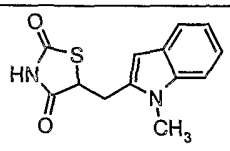
HPLC-MS (Method C): m/z = 258 (M+1); Rt = 3,638 min.

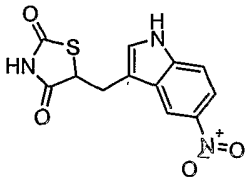
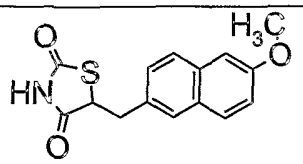
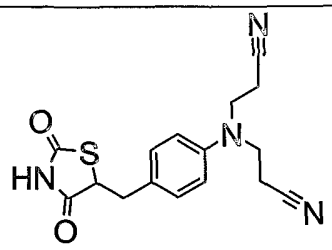
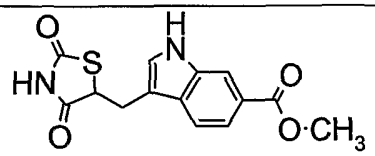
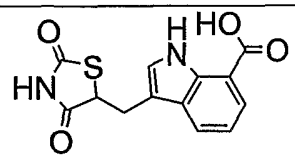
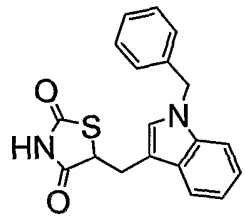
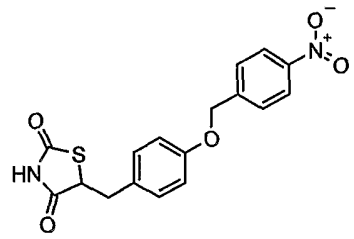
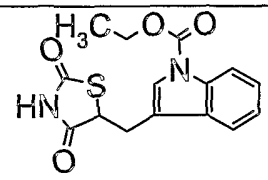
The following preferred compounds of the invention may be prepared according to procedures similar to those described in the three examples above:

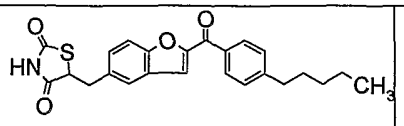
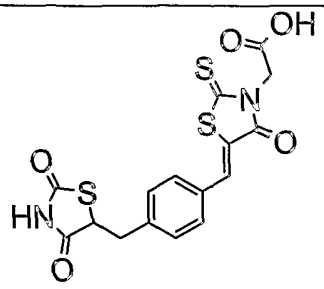
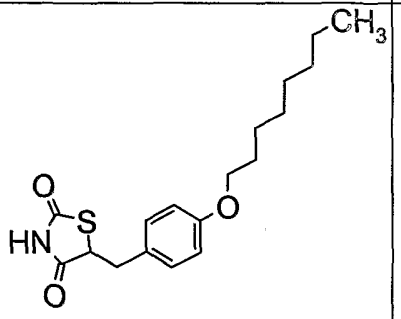
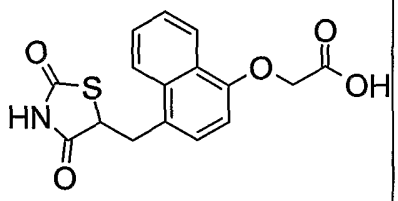
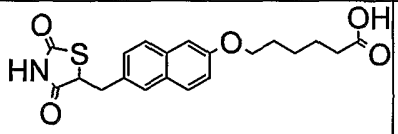
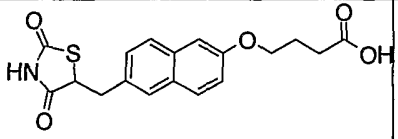
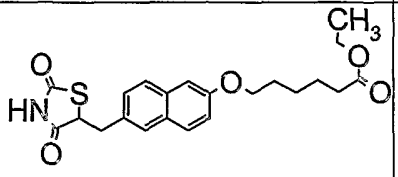
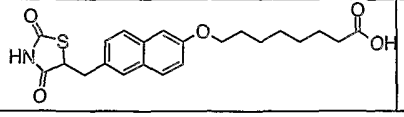
Example 285		
Example 286		
Example 287		

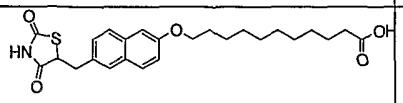
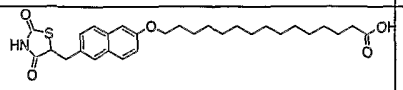
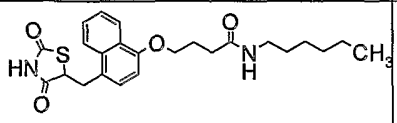
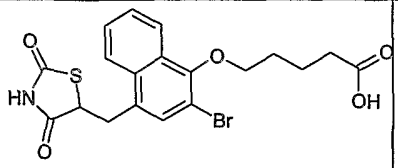
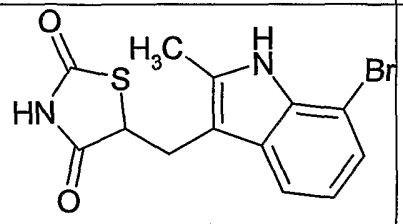
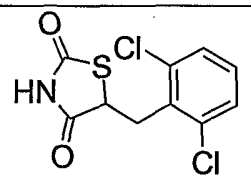
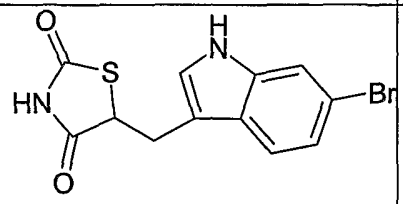
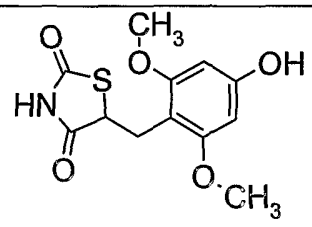
Example 288		
Example 289		
Example 290		
Example 291		
Example 292		
Example 293		
Example 294		
Example 295		
Example 296		

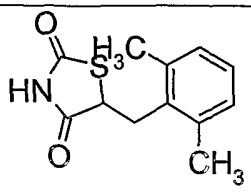
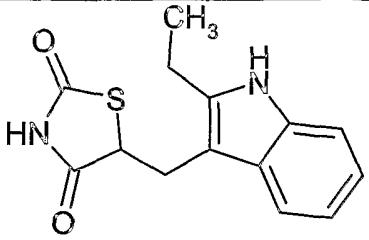
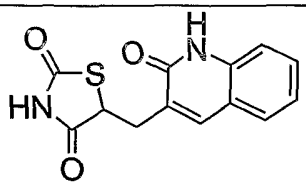
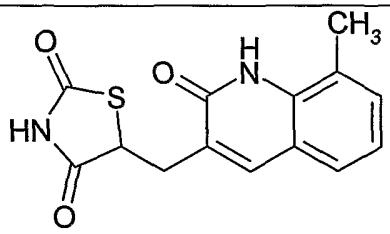
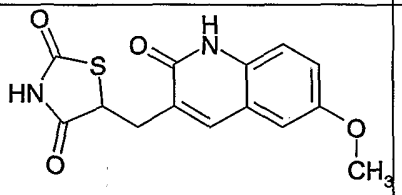
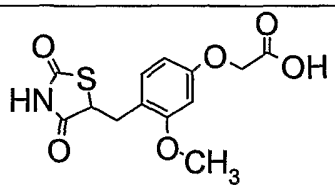
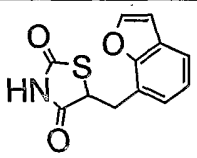
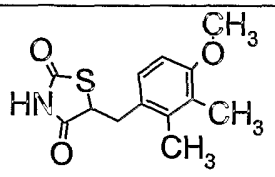
Example 297		
Example 298		
Example 299		
Example 300		
Example 301		
Example 302		
Example 303		
Example 304		

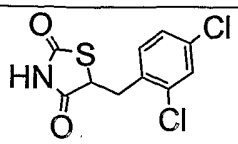
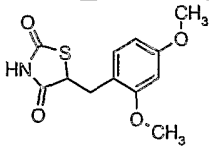
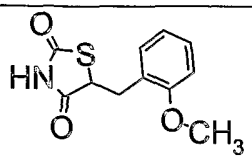
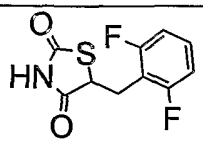
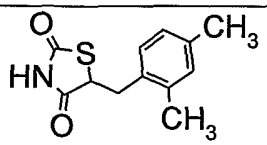
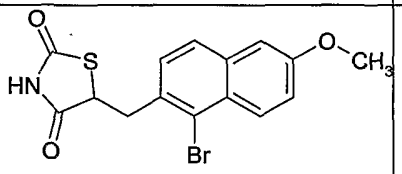
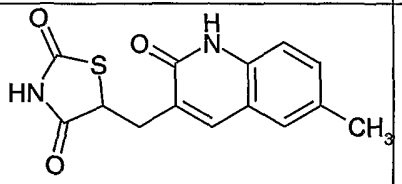
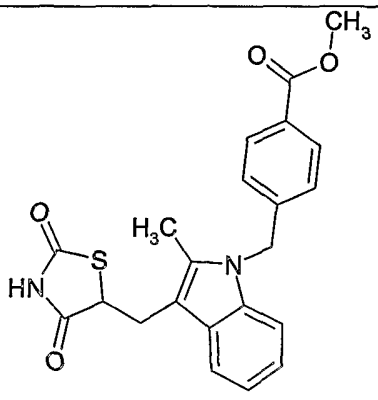
Example 305		
Example 306		
Example 307		
Example 308		
Example 309		
Example 310		
Example 311		
Example 312		

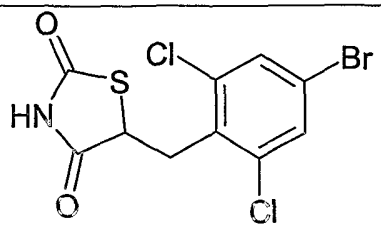
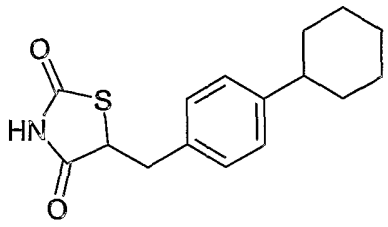
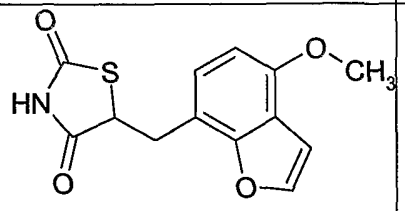
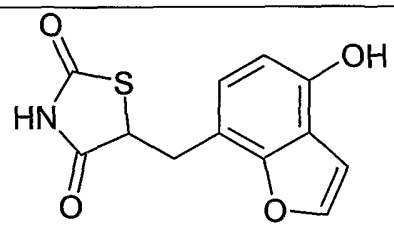
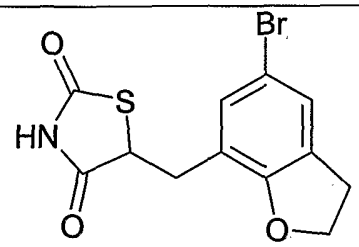
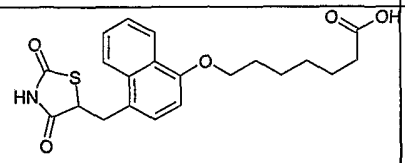
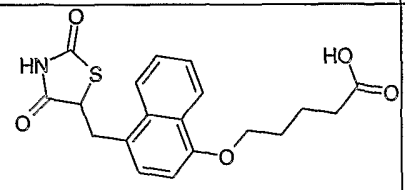
Example 313		
Example 314		
Example 315		
Example 316		
Example 317		
Example 318		
Example 319		
Example 320		

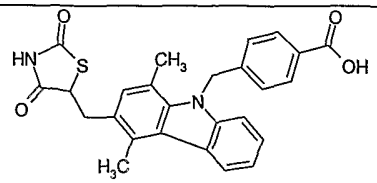
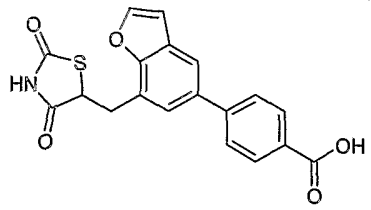
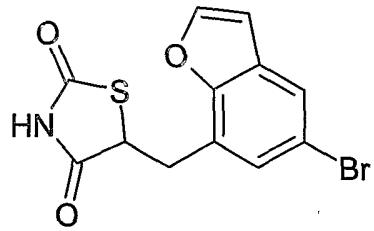
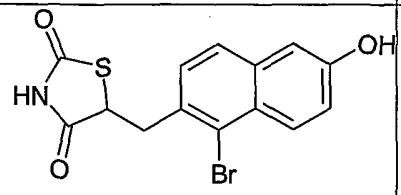
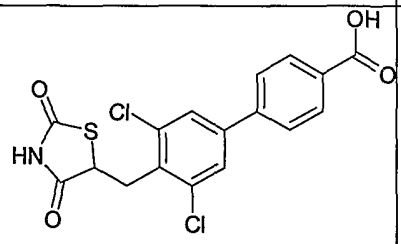
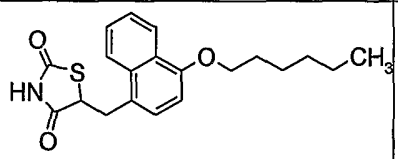
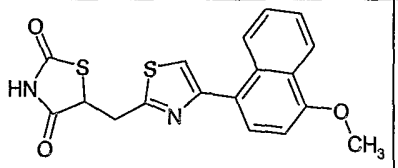
Example 321		
Example 322		
Example 323		
Example 324		
Example 325		
Example 326		
Example 327		
Example 328		

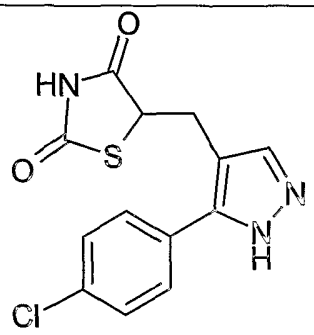
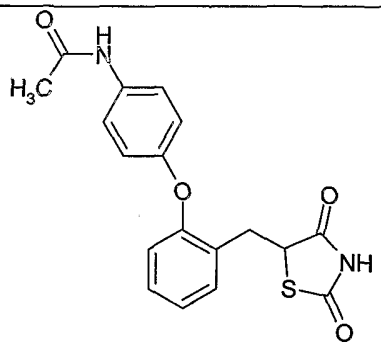
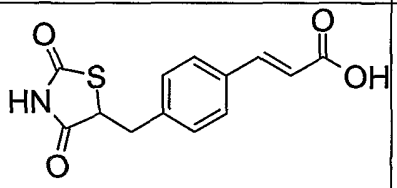
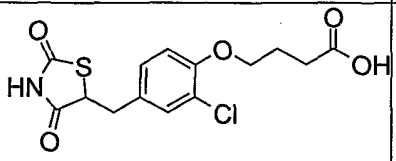
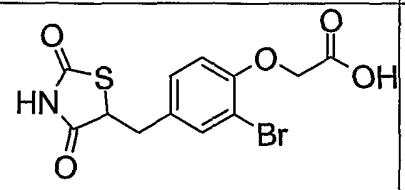
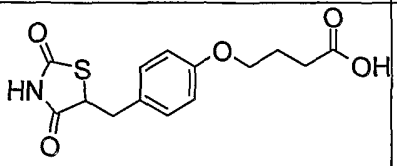
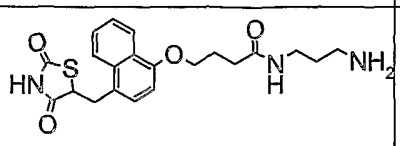
Example 329		
Example 330		
Example 331		
Example 332		
Example 333		
Example 334		
Example 335		
Example 336		

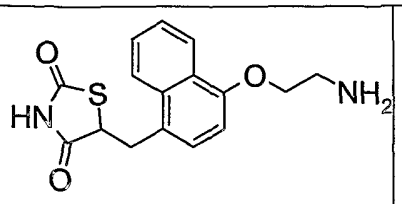
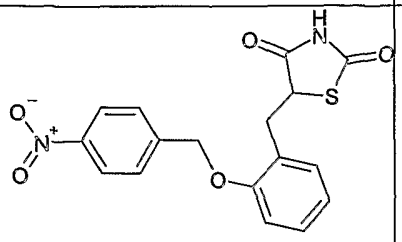
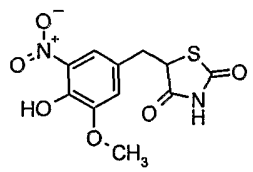
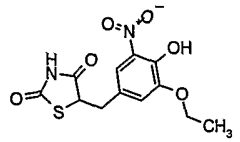
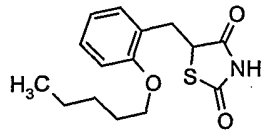
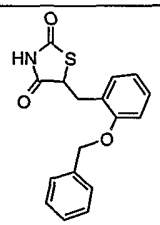
Example 337		
Example 338		
Example 339		
Example 340		
Example 341		
Example 342		
Example 343		
Example 344		

Example 345		
Example 346		
Example 347		
Example 348		
Example 349		
Example 350		
Example 351		
Example 352		

Example 353		
Example 354		
Example 355		
Example 356		
Example 357		
Example 358		
Example 359		

Example 360		
Example 361		
Example 362		
Example 363		
Example 364		
Example 365		
Example 366		

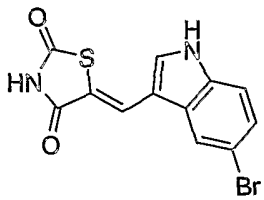
Example 367		
Example 368		
Example 369		
Example 370		
Example 371		
Example 372		
Example 373		

Example 374		
Example 375		
Example 376		
Example 377		
Example 378		
Example 379		

The following compounds are commercially available and may be prepared using general procedures (B) and / or (C).

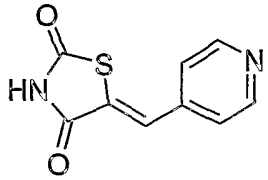
Example 380

5-(5-Bromo-1H-indol-3-ylmethylene)thiazolidine-2,4-dione



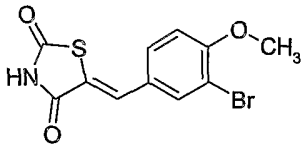
Example 381

5-Pyridin-4-ylmethylenethiazolidine-2,4-dione



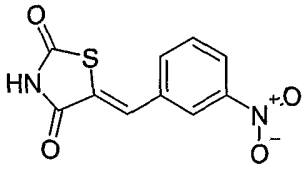
Example 382

5-(3-Bromo-4-methoxybenzylidene)thiazolidine-2,4-dione



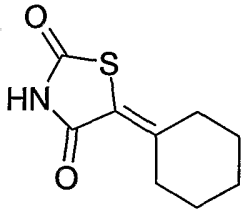
Example 383

5-(3-Nitrobenzylidene)thiazolidine-2,4-dione



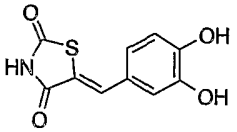
Example 384

5-Cyclohexylidene-1,3-thiazolidine-2,4-dione



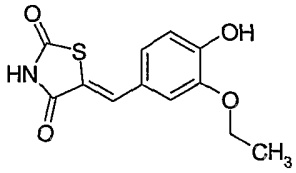
Example 385

5-(3,4-Dihydroxybenzylidene)thiazolidine-2,4-dione



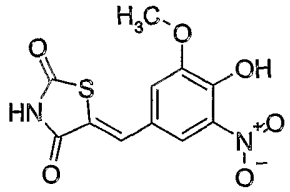
Example 386

5-(3-Ethoxy-4-hydroxybenzylidene)thiazolidine-2,4-dione



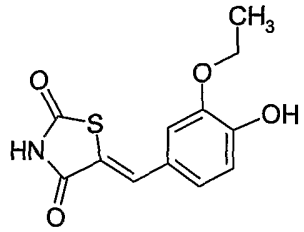
Example 387

5-(4-Hydroxy-3-methoxy-5-nitrobenzylidene)thiazolidine-2,4-dione



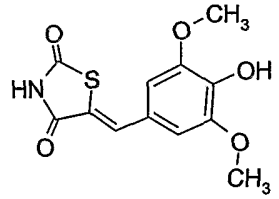
Example 388

5-(3-Ethoxy-4-hydroxybenzylidene)thiazolidine-2,4-dione



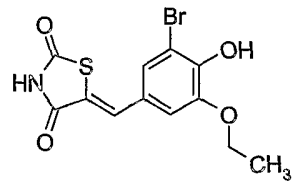
Example 389

5-(4-Hydroxy-3,5-dimethoxybenzylidene)thiazolidine-2,4-dione



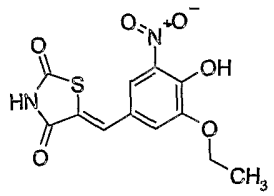
Example 390

5-(3-Bromo-5-ethoxy-4-hydroxybenzylidene)thiazolidine-2,4-dione

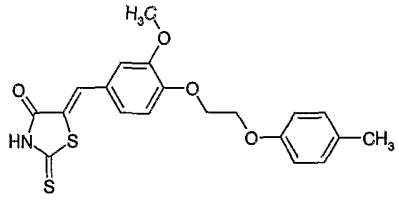


Example 391

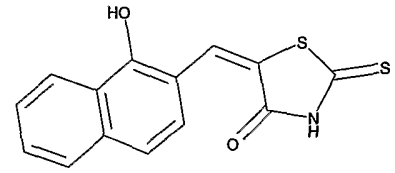
5-(3-Ethoxy-4-hydroxy-5-nitrobenzylidene)thiazolidine-2,4-dione



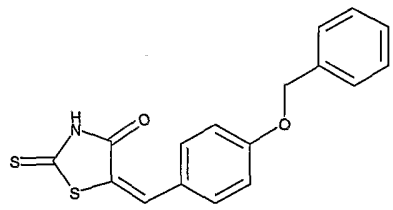
Example 392



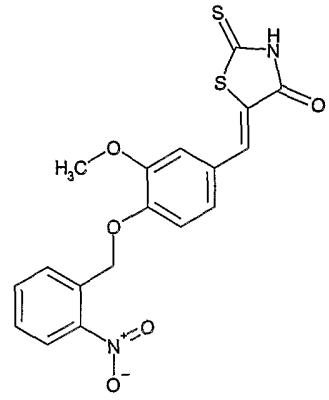
Example 393



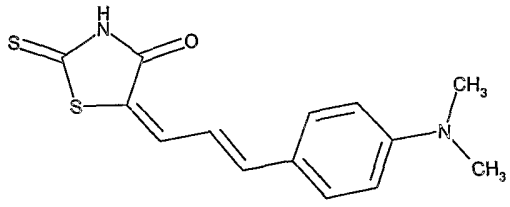
Example 394



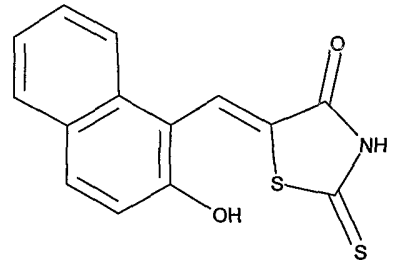
Example 395



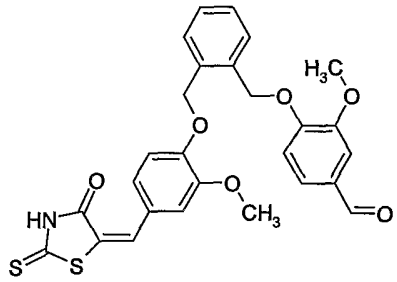
Example 396



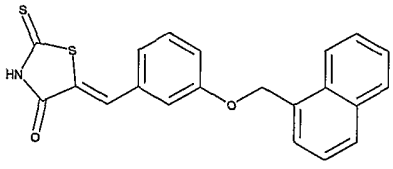
Example 397



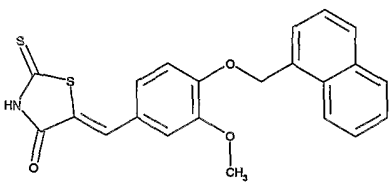
Example 398



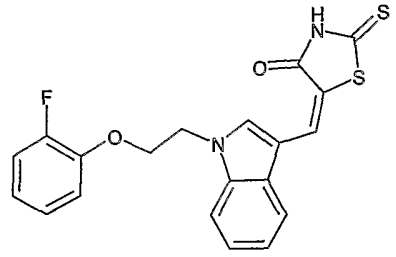
Example 399



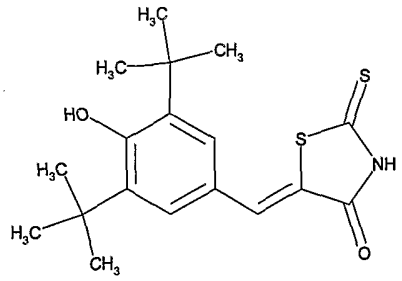
Example 400



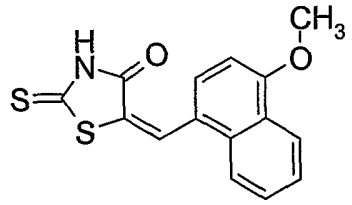
Example 401



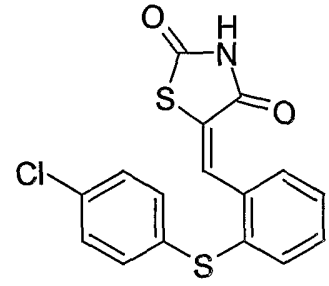
Example 402



Example 403

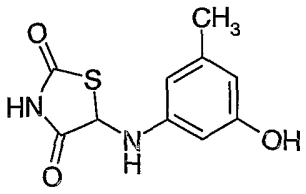


Example 404

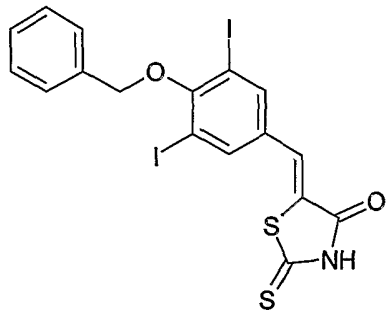


Example 405

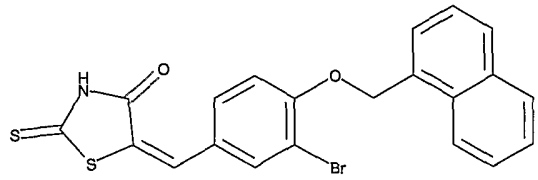
5-(3-Hydroxy-5-methyl-phenylamino)-thiazolidine-2,4-dione



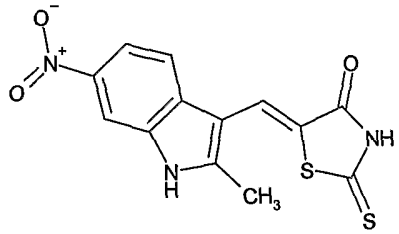
Example 406



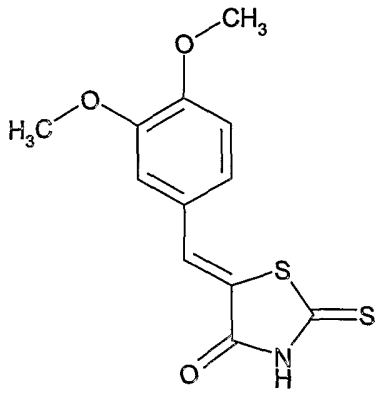
Example 407



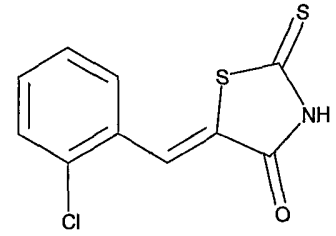
Example 408



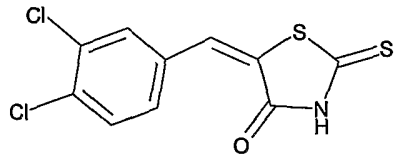
Example 409



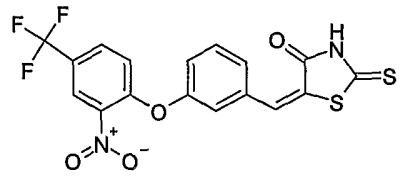
Example 410



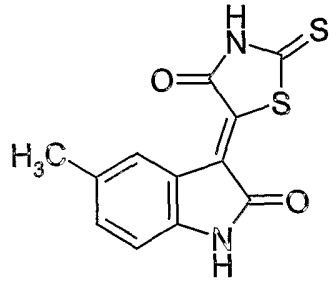
Example 411



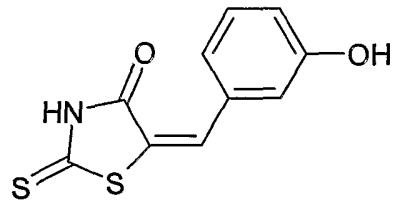
Example 412



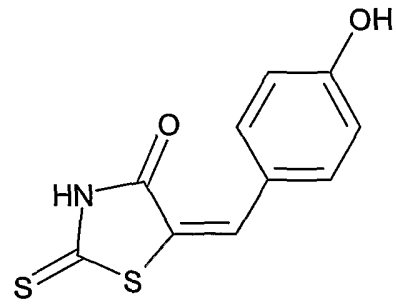
Example 413



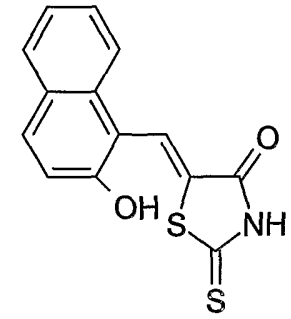
Example 414



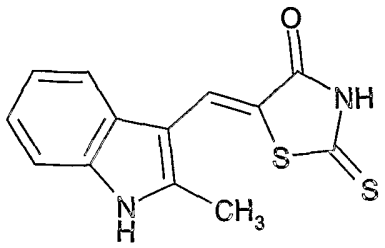
Example 415



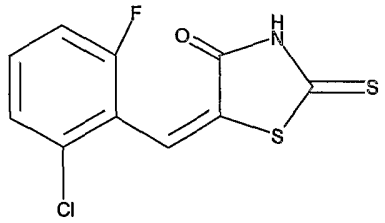
Example 416



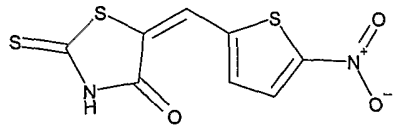
Example 417



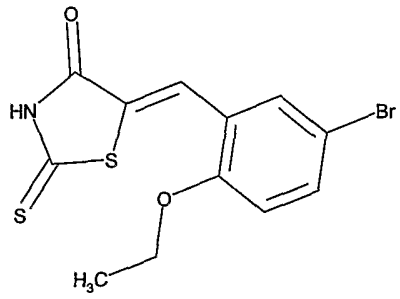
Example 418



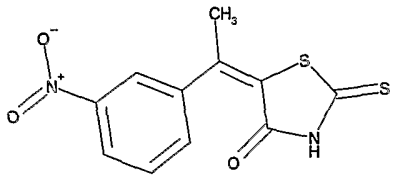
Example 419



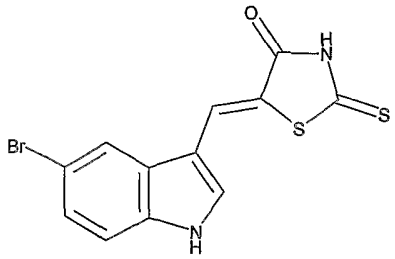
Example 420



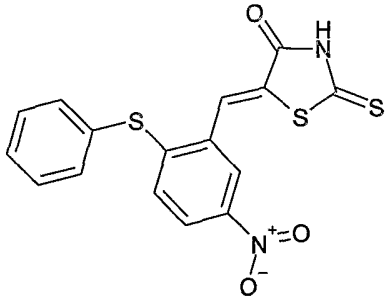
Example 421



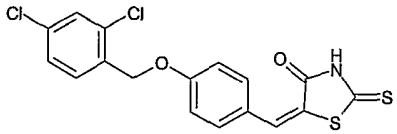
Example 422



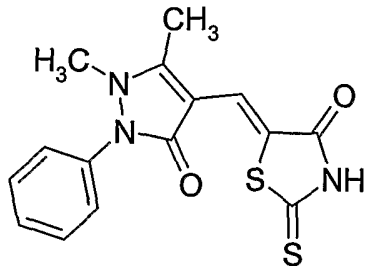
Example 423



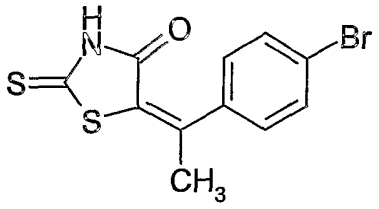
Example 424



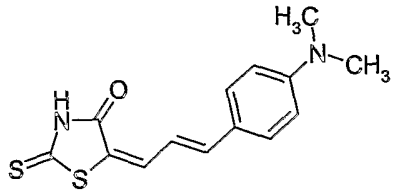
Example 425



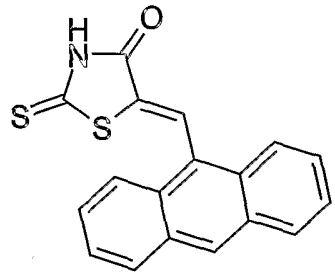
Example 426



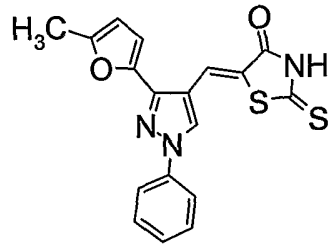
Example 427



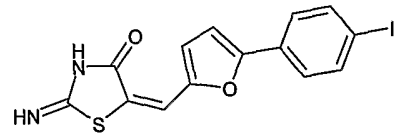
Example 428



Example 429

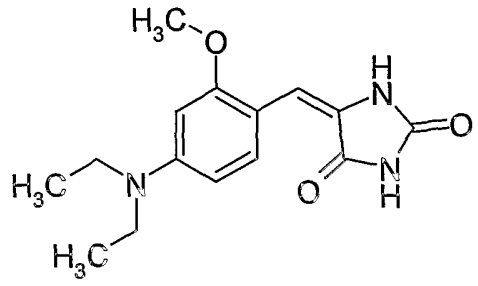


Example 430

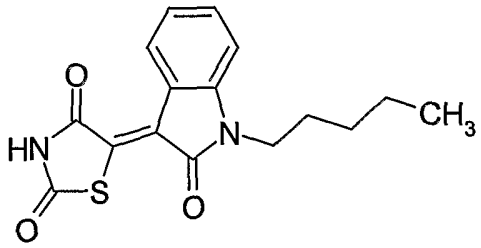


Example 431

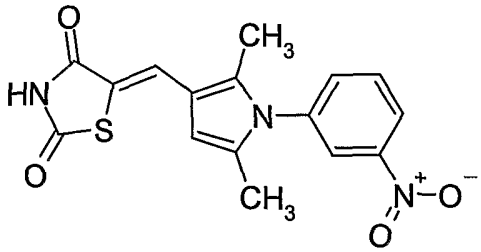
5-(4-Diethylamino-2-methoxy-benzylidene)-imidazolidine-2,4-dione



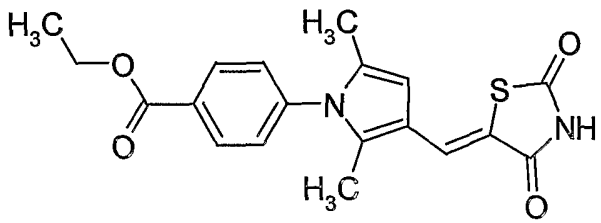
Example 432



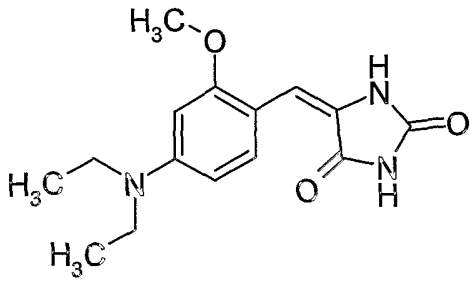
Example 433



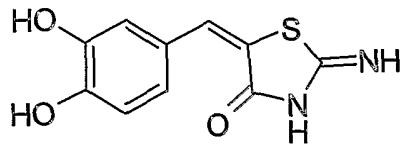
Example 434



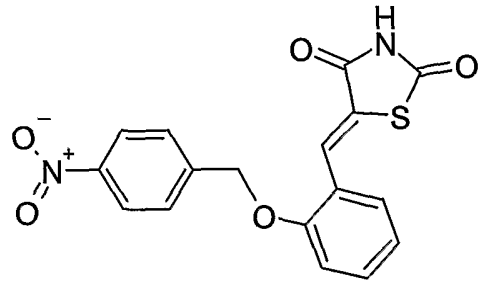
Example 435



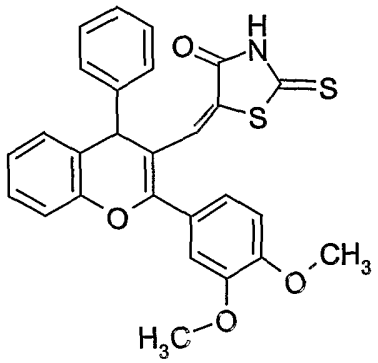
Example 436



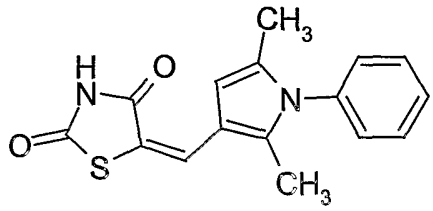
Example 437



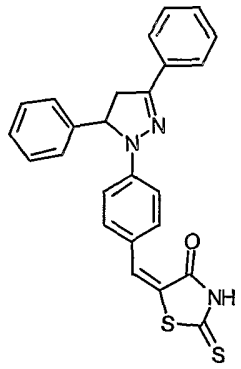
Example 438



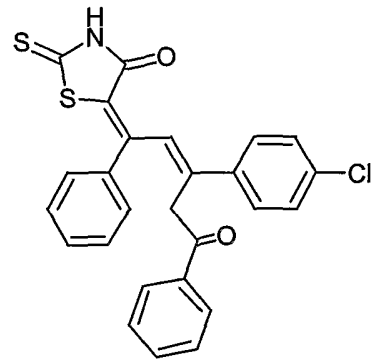
Example 439



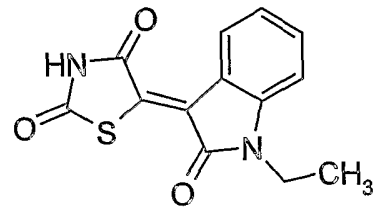
Example 440



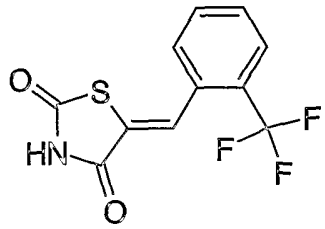
Example 441



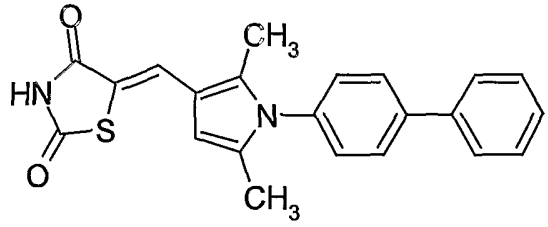
Example 442



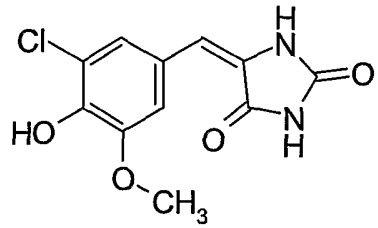
Example 443



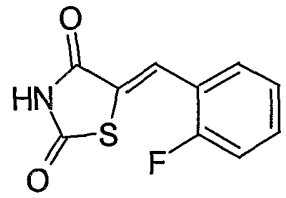
Example 444



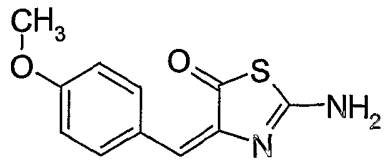
Example 445



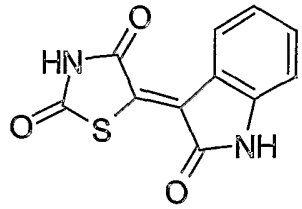
Example 446



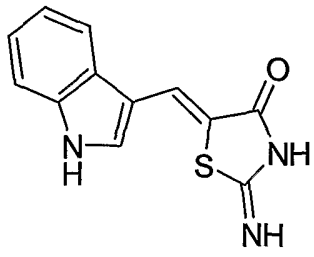
Example 447



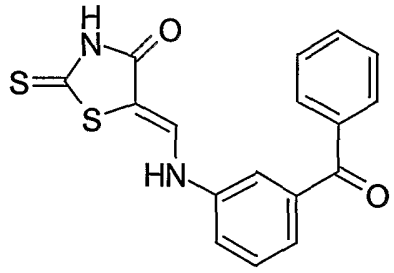
Example 448



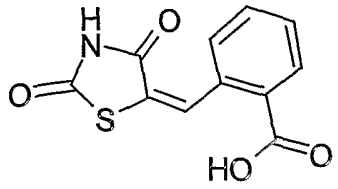
Example 449



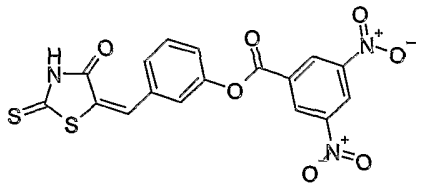
Example 450



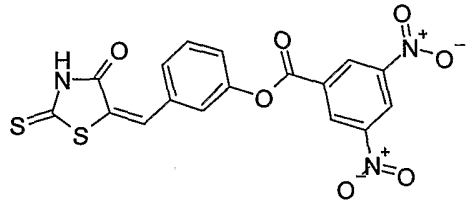
Example 451



Example 452

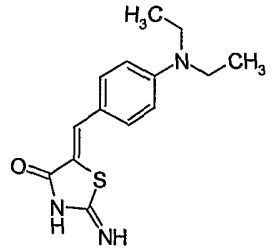


Example 453

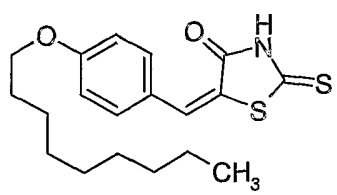


Example 454

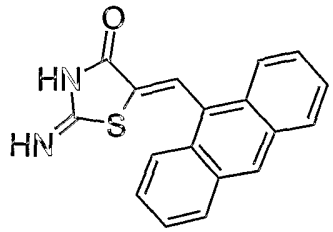
5-(4-Diethylamino-benzylidene)-2-imino-thiazolidin-4-one



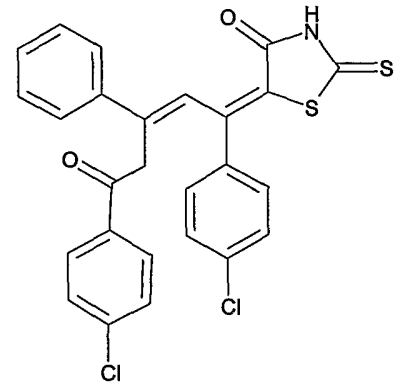
Example 455



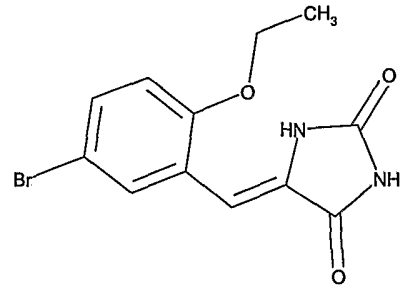
Example 456



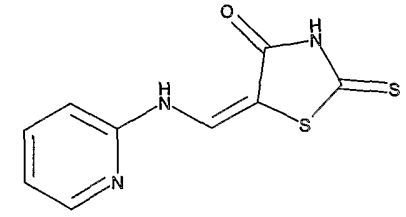
Example 457



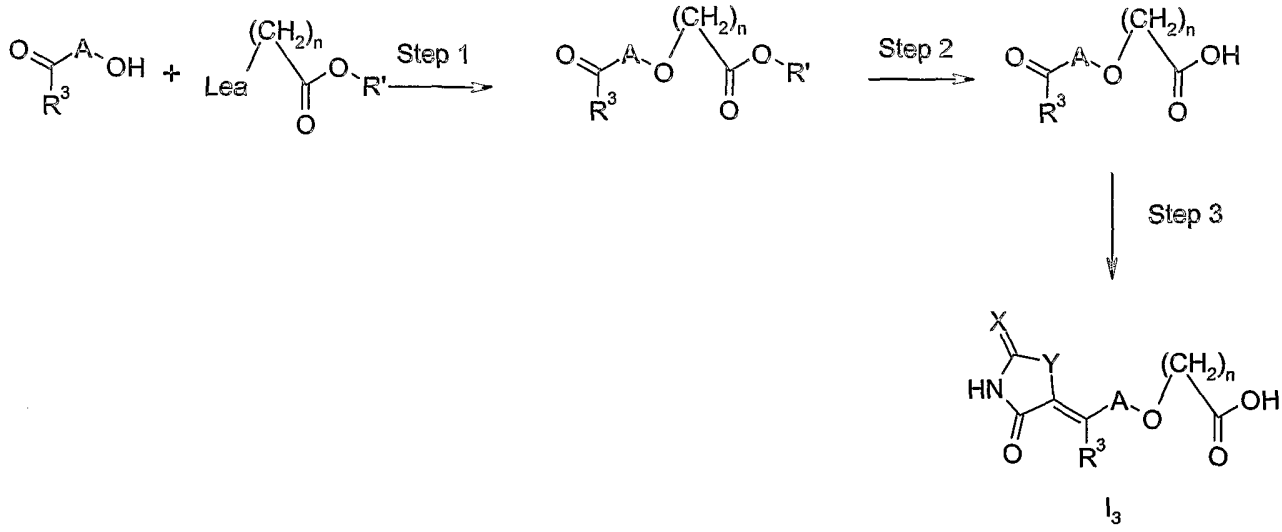
Example 458



Example 459



General procedure (D) for preparation of compounds of general formula I_3:



wherein X, Y, and R^3 are as defined above,

n is 1 or 3-20,

E is arylene or heterarylene (including up to four optional substituents, R^{13}, R^{14}, R^{15}, and R^{15A} as defined above),

R' is a standard carboxylic acid protecting group, such as C_1-C_6-alkyl or benzyl and Lea is a leaving group, such as chloro, bromo, iodo, methanesulfonyloxy, toluenesulfonyloxy or the like.

Step 1 is an alkylation of a phenol moiety. The reaction is preformed by reacting R^{10}-C(=O)-E-OH with an ω-bromo-alkane-carboxylic acid ester (or a synthetic equivalent) in the presence of a base such as sodium or potassium carbonate, sodium or potassium hydroxide, sodium hydride, sodium or potassium alkoxide in a solvent, such as DMF, NMP, DMSO, acetone, acetonitrile, ethyl acetate or isopropyl acetate. The reaction is performed at 20 – 160 °C, usually at room temperature, but when the phenol moiety has one or more substituents heating to 50 °C or more can be beneficial, especially when the substituents are in the ortho position relatively to the phenol. This will readily be recognised by those skilled in the art.

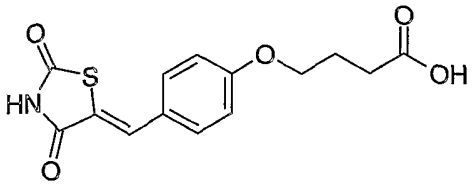
Step 2 is a hydrolysis of the product from step 1.

Step 3 is similar to general procedure (B) and (C).

This general procedure (D) is further illustrated in the following examples:

Example 460 (General procedure (D))

4-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)phenoxy]butyric acid



Step 1:

A mixture of 4-hydroxybenzaldehyde (9.21 g, 75 mmol), potassium carbonate (56 g, 410 mmol) and 4-bromobutyric acid ethyl ester (12.9 mL, 90 mmol) in *N,N*-dimethylformamide (250 mL) was stirred vigorously for 16 hours at room temperature. The mixture was filtered and concentrated *in vacuo* to afford 19.6 g (100%) of 4-(4-formylphenoxy)butyric acid ethyl ester as an oil. ^{1}H-NMR (DMSO-d_6): δ 1.21 (3H, t), 2.05 (2H, p), 2.49 (2H, t), 4.12 (4H, m), 7.13 (2H, d), 7.87 (2H, d), 9.90 (1H, s). HPLC-MS (Method A): m/z = 237 (M+1); R_t = 3.46 min.

Step 2:

4-(4-Formylphenoxy)butyric acid ethyl ester (19.6 g, 75 mmol) was dissolved in methanol (250 mL) and 1N sodium hydroxide (100 mL) was added and the resulting mixture was stirred at room temperature for 16 hours. The organic solvent was evaporated *in vacuo* (40 °C, 120 mBar) and the residue was acidified with 1N hydrochloric acid (110 mL). The mixture was filtered and washed with water and dried in vacuo to afford 14.3 g (91%) 4-(4-formylphenoxy)butyric acid as a solid. ^{1}H-NMR (DMSO-d_6): δ 1.99 (2H, p), 2.42 (2H, t), 4.13 (2H, t), 7.14 (2H, d), 7.88 (2H, d), 9.90 (1H, s), 12.2 (1H, bs). HPLC-MS (Method A): m/z = 209 (M+1); R_t = 2.19 min.

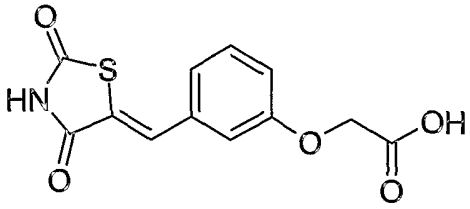
Step 3:

Thiazolidine-2,4-dione (3.55 g, 27.6 mmol), 4-(4-formylphenoxy)butyric acid (5.74 g, 27.6 mmol), anhydrous sodium acetate (11.3 g, 138 mmol) and acetic acid (100 mL) was refluxed for 16 h. After cooling, the mixture was filtered and washed with acetic acid and water. Drying in vacuo afforded 2.74 g (32%) of 4-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]butyric acid as a solid.

^{1}H-NMR (DMSO-d_6): δ 1.97 (2H, p), 2.40 (2H, t), 4.07 (2H, t), 7.08 (2H, d), 7.56 (2H, d), 7.77 (1H, s), 12.2 (1H, bs), 12.5 (1H, bs); HPLC-MS (Method A): m/z: 308 (M+1); Rt = 2.89 min.

Example 461 (General procedure (D))

[3-(2,4-Dioxothiazolidin-5-ylidenemethyl)phenoxy]acetic acid



Step 3:

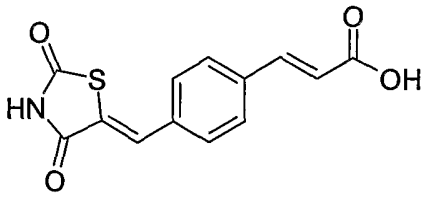
Thiazolidine-2,4-dione (3.9 g, 33 mmol), 3-formylphenoxyacetic acid (6.0 g, 33 mmol), anhydrous sodium acetate (13.6 g, 165 mmol) and acetic acid (100 mL) was refluxed for 16 h. After cooling, the mixture was filtered and washed with acetic acid and water. Drying in vacuo afforded 5.13 g (56%) of [3-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]acetic acid as a solid.

^{1}H-NMR (DMSO-d_6): δ 4.69 (2H, s), 6.95 (1H, dd), 7.09 (1H, t), 7.15 (1H, d), 7.39 (1H, t),7.53 (1H, s); HPLC-MS (Method A): m/z = 280 (M+1) (poor ionisation); R_t = 2.49 min.

The compounds in the following examples were similarly prepared.

Example 462 (General procedure (D))

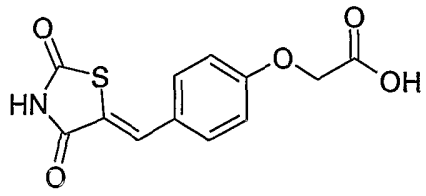
3-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)phenyl]acrylic acid



^{1}H-NMR (DMSO-d_6): δ 6.63 (1H, d), 7.59-7.64 (3H, m), 7.77 (1H, s), 7.83 (2H, m).

Example 463 (General procedure (D))

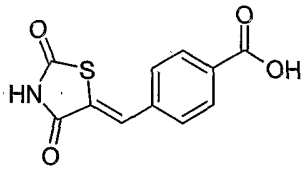
[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)phenoxy]acetic acid



Triethylamine salt: ^{1}H-NMR (DMSO-d_6): δ 4.27 (2H, s), 6.90 (2H, d), 7.26 (1H, s), 7.40 (2H, d).

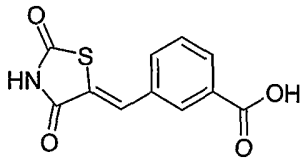
Example 464 (General procedure (D))

4-(2,4-Dioxothiazolidin-5-ylidenemethyl)benzoic acid



Example 465 (General procedure (D))

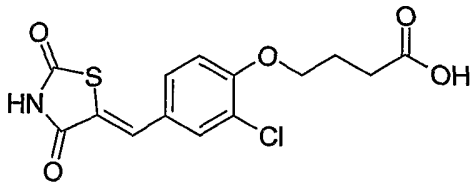
3-(2,4-Dioxothiazolidin-5-ylidenemethyl)benzoic acid



^{1}H-NMR (DMSO-d_6): δ 7.57 (1H, s), 7.60 (1H, t), 7.79 (1H, dt), 7.92 (1H, dt), 8.14 (1H, t).

Example 466 (General procedure (D))

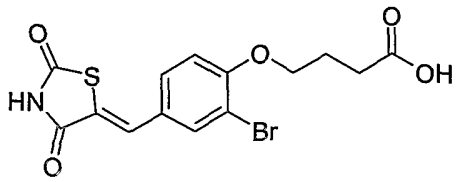
4-[2-Chloro-4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]butyric acid



^{1}H-NMR (DMSO-d_6): δ 2.00 (2H, p), 2.45 (2H, t), 4.17 (2H, t), 7.31 (1H, d), 7.54 (1H, dd), 7.69 (1H, d), 7.74 (1H, s), 12.2 (1H, bs), 12.6 (1H, bs). HPLC-MS (Method A): m/z: 364 (M+23); Rt = 3.19 min.

Example 467 (General procedure (D))

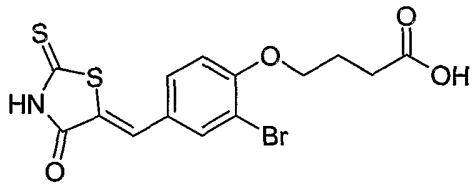
4-[2-Bromo-4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]butyric acid



^{1}H-NMR (DMSO-d_6): δ 1.99 (2H, p), 2.46 (2H, t), 4.17 (2H, t), 7.28 (1H, d), 7.57 (1H, dd), 7.25 (1H, s), 7.85 (1H, d), 12.2 (1H, bs), 12.6 (1H, bs). HPLC-MS (Method A): m/z: 410 (M+23); Rt = 3.35 min.

Example 468 (General procedure (D))

4-[2-Bromo-4-(4-oxo-2-thioxothiazolidin-5-ylidenemethyl)phenoxy]butyric acid

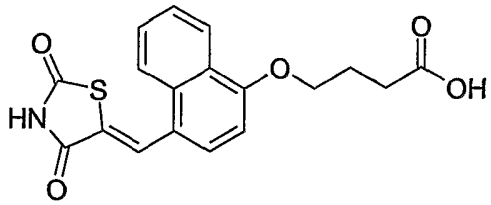


^{1}H-NMR (DMSO-d_6): δ 1.99 (2H, p), 2.45 (2H, t), 4.18 (2H, t), 7.28 (1H, d), 7.55 (1H, dd), 7.60 (1H, s), 7.86 (1H, d), 12.2 (1H, bs), 13.8 (1H, bs). HPLC-MS (Method A): m/z: 424 (M+23); Rt = 3.84 min.

HPLC-MS (Method A): m/z: 424 (M+23); Rt = 3,84 min

Example 469 (General procedure (D))

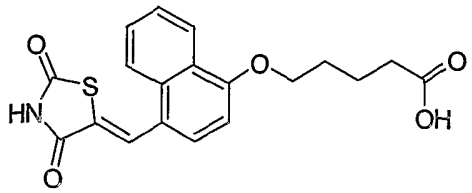
4-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]butyric acid



^{1}H-NMR (DMSO-d_6): δ 2.12 (2H, p), 2.5 (below DMSO), 4.28 (2H, t), 7.12 (1H, d), 7.6-7.7 (3H, m), 8.12 (1H, d), 8.31 (1H, d), 8.39 (1H, s), 12.2 (1H, bs), 12.6 (1H, bs). HPLC-MS (Method A): m/z: 380 (M+23); Rt = 3.76 min.

Example 470 (General procedure (D))

5-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]pentanoic acid

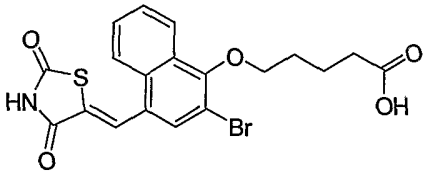


HPLC-MS (Method A): m/z: 394 (M+23); Rt = 3.62 min.

^{1}H-NMR (DMSO-d_6): δ 1.78 (2H, m), 1.90 (2H, m), 2.38 (2H, t), 4.27 (2H, t), 7.16 (1H, d), 7.6-7.75 (3H, m), 8.13 (1H, d), 8.28 (1H, d), 8.39 (1H, s), 12.1 (1H, bs), 12.6 (1H, bs).

Example 471

5-[2-Bromo-4-(2,4-dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]pentanoic acid.

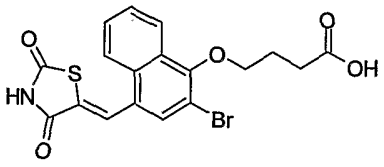


5-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)-naphthalen-1-yloxy]pentanoic acid (example 470, 185 mg, 0.5 mmol) was treated with an equimolar amount of bromine in acetic acid (10 mL). Stirring at RT for 14 days followed by evaporation to dryness afforded a mixture of the brominated compound and unchanged starting material. Purification by preparative HPLC on a C18 column using acetonitrile and water as eluent afforded 8 mg of the title compound.

HPLC-MS (Method C): m/z: 473 (M+23), Rt. = 3.77 min

Example 472

4-[2-Bromo-4-(2,4-dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]butyric acid.

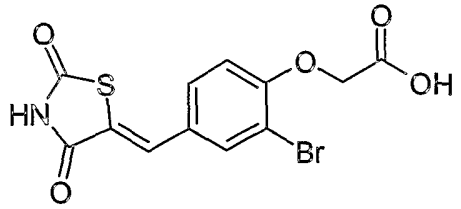


Starting with 4-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)-naphthalen-1-yloxy]-butyric acid (example 469, 0.5 mmol) using the same method as in example 471 afforded 66 mg of the title compound.

HPLC-MS (Method C): m/z: 459 (M+23) ; Rt. = 3.59 min.

Example 473 (General procedure (D))

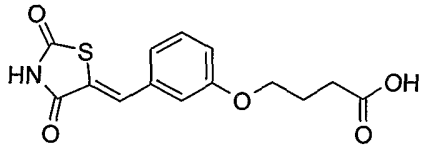
[2-Bromo-4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]acetic acid



^{1}H-NMR (DMSO-d_6): δ 4.90 (2H, s), 7.12 (1H, d), 7.52 (1H, dd), 7.65 (1H, s) 7.84 (1H, d).HPLC-MS (Method A): m/z: not observed; Rt = 2.89 min.

Example 474 (General procedure (D))

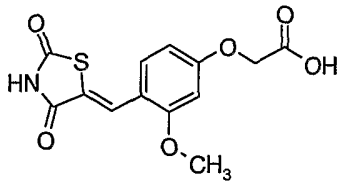
4-[3-(2,4-Dioxothiazolidin-5-ylidenemethyl)phenoxy]butyric acid



^{1}H-NMR (DMSO-d_6): δ 1.98 (2H, p), 2.42 (2H, t), 4.04 (2H, t), 7.05 (1H, dd), 7.15 (2H, m), 7.45 (1H, t), 7.77 (1H, s), 12.1 (1H, bs), 12.6 (1H, bs). HPLC-MS (Method A): m/z: 330 (M+23); Rt = 3.05 min.

Example 475 (General procedure (D))

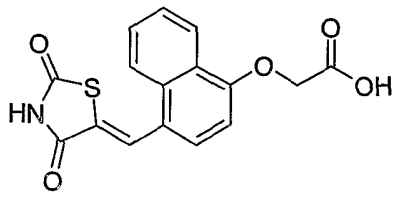
[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)-3-methoxyphenoxy]acetic acid



HPLC-MS (Method B): m/z: 310 (M+1); Rt = 3,43 min.

Example 476 (General procedure (D))

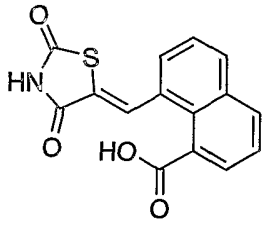
[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]acetic acid



HPLC-MS (Method A): m/z: 330 (M+1); Rt = 3.25 min.

Example 477 (General procedure (D))

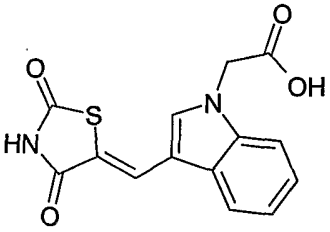
8-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalene-1-carboxylic acid



HPLC-MS (Method A): m/z: 299 (M+1); Rt = 2,49 min.

Example 478 (General procedure (D))

[3-(2,4-Dioxothiazolidin-5-ylidenemethyl)indol-1-yl]acetic acid



HPLC-MS (Method A): m/z: 303 (M+1); Rt = 2.90 min.

Preparation of starting material:

3-Formylindol (10 g, 69 mmol) was dissolved in *N,N*-dimethylformamide (100 mL) and under an atmosphere of nitrogenand with external cooling, keeping the temperature below 15 °C, sodium hydride (60% in mineral oil, 3.0 g, 76 mmol) was added in portions. Then a solution of ethyl bromoacetate (8.4 mL, 76 mmol) in *N,N*-dimethylformamide (15 mL) was added dropwise over 30 minutes and the resulting mixture was stirred at room temperature for 16 hours. The mixture was concentrated *in vacuo* and the residue was partitioned between water (300 mL) and ethyl acetate (2 x 150 mL). The combined organic extracts were washed with a saturated aqueous solution of ammonium chloride (100 mL), dried ($MgSO_4$) and con-

centrated in vacuo to afford 15.9 g (quant.) of (3-formylindol-1-yl)acetic acid ethyl ester as an oil.

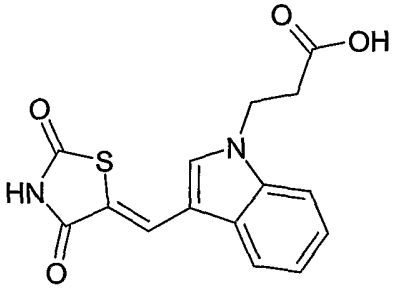
^{1}H-NMR ($CDCl_3$): δ_H = 1.30 (3H, t), 4.23 (2H, q), 4.90 (2H, s), 7.3 (3H, m), 7.77 (1H, s), 8.32 (1H, d), 10.0 (1H, s).

(3-Formylindol-1-yl)acetic acid ethyl ester (15.9 g 69 mmol) was dissolved in 1,4-dioxane (100 mL) and 1N sodium hydroxide (10 mL) was added and the resulting mixture was stirred at room temperature for 4 days. Water (500 mL) was added and the mixture was washed with diethyl ether (150 mL). The aqueous phase was acidified with 5N hydrochloric acid and extracted with ethyl acetate (250 + 150 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to afford 10.3 g (73%) of (3-formylindol-1-yl)acetic acid as a solid.

^{1}H-NMR (DMSO-d_6): δ_H = 5.20 (2H, s), 7.3 (2H, m), 7.55 (1H, d), 8.12 (1H, d), 8.30 (1H, s), 9.95 (1H, s), 13.3 (1H, bs).

Example 479 (General procedure (D))

3-[3-(2,4-Dioxothiazolidin-5-ylidenemethyl)indol-1-yl]propionic acid



HPLC-MS (Method A): m/z: 317 (M+1); Rt = 3.08 min.

Preparation of starting material:

A mixture of 3-formylindol (10 g, 69 mmol), ethyl 3-bromopropionate (10.5 mL, 83 mmol) and potassium carbonate (28.5 g, 207 mmol) and acetonitrile (100 mL) was stirred vigorously at refux temperature for 2 days. After cooling, the mixture was filtered and the filtrate was concentrated *in vacuo* to afford 17.5 g (quant.) of 3-(3-formylindol-1-yl)propionic acid ethyl ester as a solid.

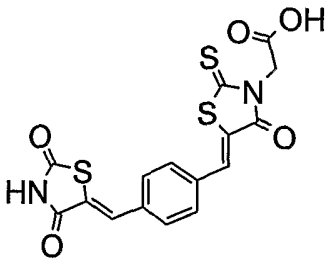
^{1}H-NMR (DMSO-d_6): δ_H = 1.10 (3H, t), 2.94 (2H, t), 4.02 (2H, q), 4.55 (2H, t), 7.3 (2H, m), 7.67 (1H, d), 8.12 (1H, d), 8.30 (1H, s), 9.90 (1H, s).

3-(3-Formylindol-1-yl)propionic acid ethyl ester (17.5 g 69 mmol) was hydrolysed as described above to afford 12.5 g (83%) of 3-(3-formylindol-1-yl)propionic acid as a solid.

^{1}H-NMR (DMSO-d_6): δ_H = 2.87 (2H, t), 4.50 (2H, t), 7.3 (2H, m), 7.68 (1H, d), 8.12 (1H, d), 8.31 (1H, s), 9.95 (1H, s), 12.5 (1H, bs).

Example 480 (General procedure (D))

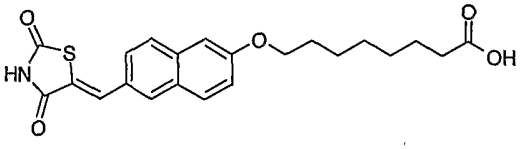
{5-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)benzylidene]-4-oxo-2-thioxothiazolidin-3-yl}acetic acid



HPLC-MS (Method A): m/z: 429 (M+23); Rt = 3.89 min.

Example 481 (General procedure (D))

6-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-2-yloxyoctanoic acid



HPLC-MS (Method C): m/z: 436 (M+23); Rt.= 4.36 min

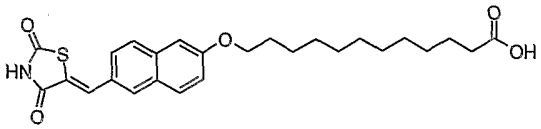
The intermediate aldehyde for this compound was prepared by a slightly modified procedure: 6-Hydroxynaphthalene-2-carbaldehyde (1.0 g, 5.8 mmol) was dissolved in DMF (10 mL) and sodium hydride 60% (278 mg) was added and the mixture stirred at RT for 15 min. 8-Bromooctanoic acid (0.37 g, 1.7 mmol) was converted to the sodium salt by addition of sodium hydride 60% and added to an aliquot (2.5 mL) of the above naphtholate solution and the resulting mixture was stirred at RT for 16 hours. Aqueous acetic acid (10 %) was added and the mixture was extracted 3 times with diethyl ether. The combined organic phases were

dried with $MgSO_4$ and evaporated to dryness affording 300 mg of 8-(6-formylnaphthalen-2-yloxy)octanoic acid.

HPLC-MS (Method C): m/z 315 (M+1); Rt. = 4.24 min.

Example 482 (General procedure (D))

12-[6-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-2-yloxy]dodecanoic acid.

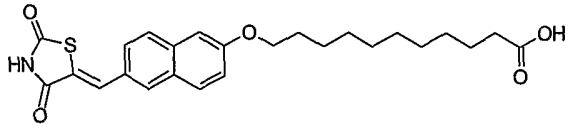


HPLC-MS (Method C): m/z: 492 (M+23); Rt.= 5.3 min.

The intermediate aldehyde was prepared similarly as described in example 481.

Example 483 (General procedure (D))

11-[6-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-2-yloxy]undecanoic acid.

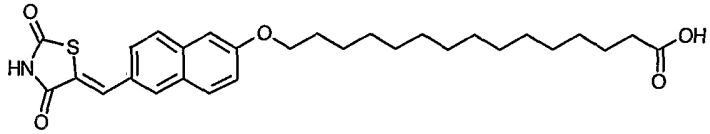


HPLC-MS (Method C): m/z:478 (M+23); Rt.= 5.17 min.

The intermediate aldehyde was prepared similarly as described in example 481.

Example 484 (General procedure (D))

15-[6-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-2-yloxy]pentadecanoic acid.

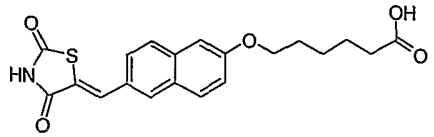


HPLC-MS (Method C): m/z: 534 (M+23); Rt.= 6.07 min.

The intermediate aldehyde was prepared similarly as described in example 481.

Example 485 (General procedure (D))

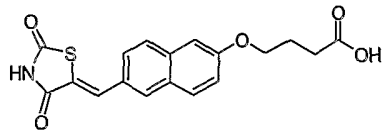
6-[6-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-2-yloxy]hexanoic acid.



HPLC-MS (Method C): m/z: 408 (M+23); Rt.= 3.71 min.

Example 486 (General procedure (D))

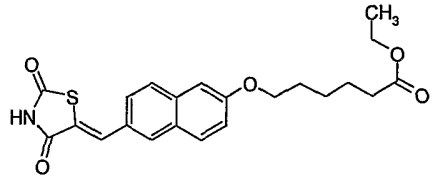
4-[6-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-2-yloxy]butyric acid.



HPLC-MS (Method C): m/z: 380 (M+23); Rt.= 3.23 min.

Example 487 (General procedure (D))

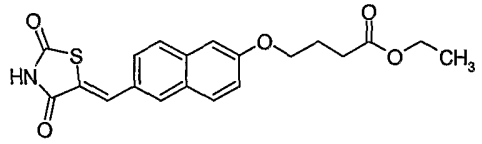
6-[6-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-2-yloxy]hexanoic acid ethyl ester.



HPLC-MS (Method C): m/z: 436 (M+23); Rt.= 4.64 min.

Example 488 (General procedure (D))

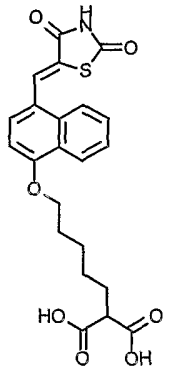
4-[6-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-2-yloxy]butyric acid ethyl ester.



HPLC-MS (Method C): m/z: 408 (M+23); Rt.= 4.28 min.

Example 489 (General procedure (D))

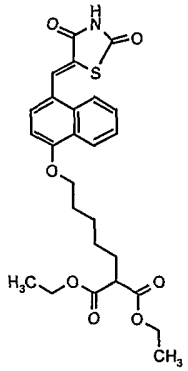
2-{5-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]pentyl}malonic acid



HPLC-MS (Method C): m/z = 444 (M+1); Rt = 3,84 min.

Example 490 (General procedure (D)

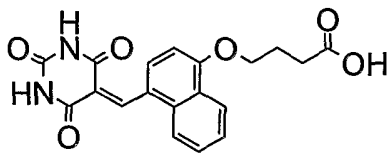
2-{5-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]pentyl}malonic acid diethyl ester



HPLC-MS (Method C): m/z = 500 (M+1); Rt = 5.18 min.

Example 491 (General procedure (D))

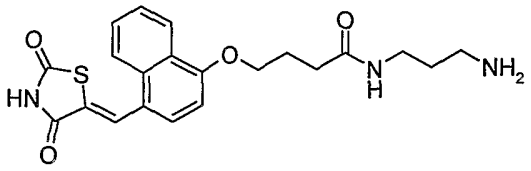
4-[4-(2,4,6-Trioxotetrahydropyrimidin-5-ylidenemethyl)naphthalen-1-yloxy]butyric acid



HPLC-MS (Method C): m/z = 369 (M+1); Rt = 2,68 min.

Example 492

N-(3-Aminopropyl)-4-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)-naphthalen-1-yloxy]-butyramide



To a mixture of 4-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]butyric acid (example 469, 5.9 g, 16.5 mmol) and 1-hydroxybenzotriazole (3.35 g, 24.8 mmol) in DMF (60 mL) was added 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (4.75 g, 24.8 mmol) and the resulting mixture was stirred at room temperature for 2 hours. *N*-(3-amino-propylcarbamic acid *tert*-butyl ester (3.45 g, 19.8 mmol) was added and the resulting mixture was stirred at room temperature for 16 hours. The mixture was concentrated *in vacuo* and ethyl acetate and dichloromethane were added to the residue. The mixture was filtered, washed with water and dried *in vacuo* to afford 4.98 g (59%) of (3-{4-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]butyrylamino}propyl)carbamic acid tert-butyl ester.

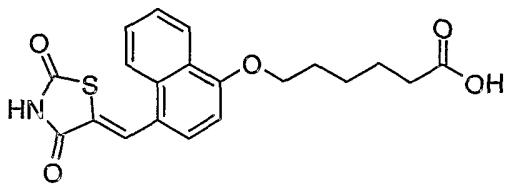
HPLC-MS (Method C): m/z: 515 (M+1); Rt = 3.79 min.

(3-{4-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]butyrylamino}-propyl)carbamic acid tert-butyl ester (4.9 g, 9.5 mmol) was added dichloromethane (50 mL) and trifluoroacetic acid (50 mL) and the resulting mixture was stirred at room temperature for 45 minutes. The mixture was concentrated *in vacuo* and co-evaporated with toluene. To the residue was added ethyl acetate (100 mL) and the mixture was filtered and dried *in vacuo* to afford the title compound as the trifluoroacetic acid salt.

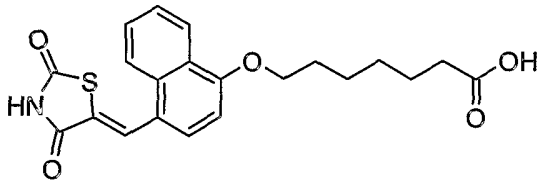
HPLC-MS (Method C): m/z: 414 (M+1); Rt = 2,27 min.

Compounds of the invention includes:

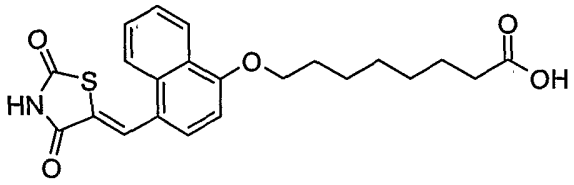
Example 493



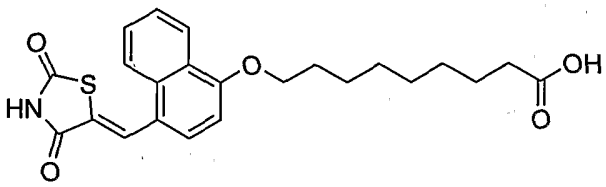
Example 494



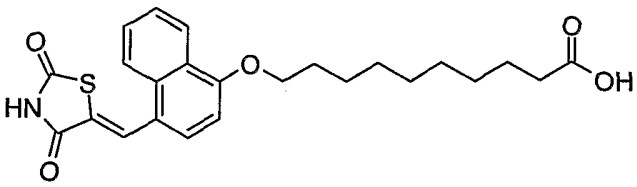
Example 495



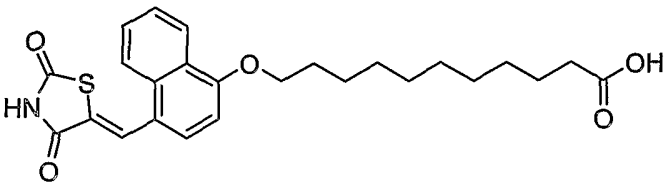
Example 496



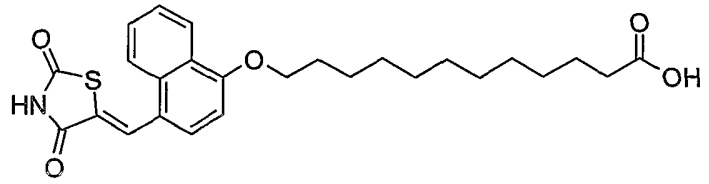
Example 497



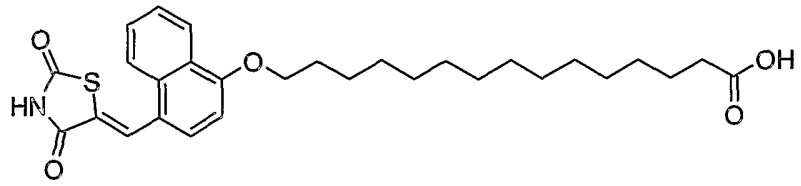
Example 498



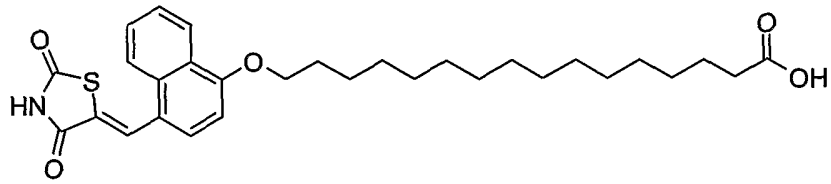
Example 499



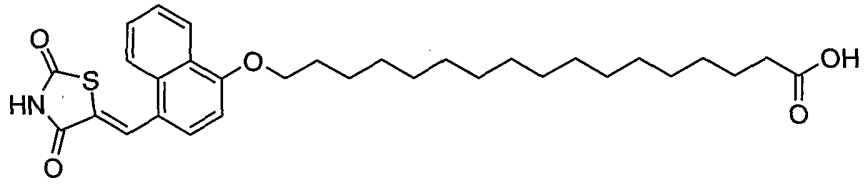
Example 500



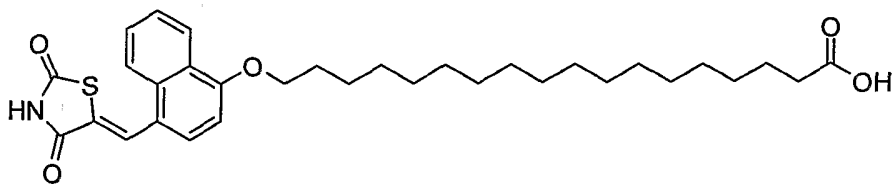
Example 501



Example 502

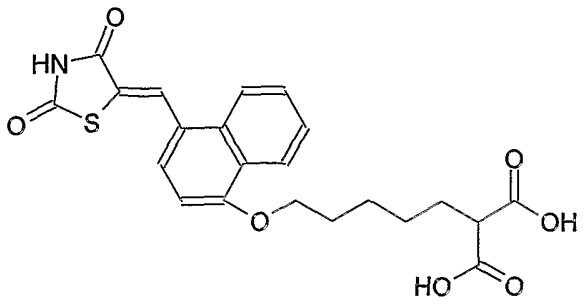


Example 503



Example 504 (Prepared analogously to General Procedure (D))

2-{5-[4-(2,4-Thiazolidindion-5-ylidenemethyl)naphthalen-1-yloxy]pentyl}malonic acid



A solution of 4-hydroxy-1-naphtaldehyde (1.0 g, 5.81 mmol), 2-(5-bromopentyl)malonic acid diethyl ester (2.07 g, 6.68 mmol) and potassium carbonate (4.01 g, 29 mmol) in DMF (50 mL) was stirred at 100° C for 3 hours. The mixture was cooled and the salt was filtered off. The solvent was then removed under reduced pressure to afford 2.9 g of crude 2-[5-(4-formylnaphtalen-1-yloxy)pentyl]malonic acid diethyl ester which was used for the next reaction without further purification.

HPLC-MS (Method C): m/z: 401 (M+1); Rt = 5.16 min. ^{1}H-NMR (DMSO-*d*6): δ = 1.18 (t, 6 H), 1,39 (m, 2 H), 1.55 (m, 2 H), 1.87 (m, 4 H), 3.48 (t, 1 H), 4.13 (m, 4 H), 4.27 (t, 2 H), 7.17 (d, 1 H), 7.64(t, 1 H), 7.75 (t, 1 H), 8.13 (d, 1 H), 8.29 (d, 1 H), 9.24 (d, 1 H), 10.19 (s, 1 H).

1.4 g (3.5 mmol) of crude 2-[5-(4-formylnaphtalen-1-yloxy)pentyl]malonic acid diethyl ester was treated with aqueous sodium hydroxide (1N, 8.75 mL, 8.75 mmol) and methanol (50 mL). The solution was stirred at 70° C for 5 hours and the mixture was concentrated under reduced pressure. Hydrochloric acid (6 N) was added until pH <2. The resulting slurry was stirred untill it solidified. The crystals were filtered off, washed with water and then dried *in vacuo* to afford 1.1 g (92%) of 2-[5-(4-formylnaphtalen-1-yloxy)pentyl]malonic acid. The product was used in the next step without further purification.

HPLC-MS (Method C): m/z: 345 (M+1); Rt = 3.52 min. ^{1}H-NMR(DMSO-*d*6): δ = 1,40 (m, 2 H), 1.55 (m, 2 H), 1.80 (m, 2 H), 1.90 (m, 2 H), 3.24 (t, 1 H), 4.29 (t, 2 H), 7.19 (d, 1 H), 7.64(t, 1 H), 7.75 (t, 1 H), 8.14 (d, 1 H), 8.30 (d, 1 H), 9.23 (d, 1 H), 10.18 (s, 1 H), 12.69 (s, 2 H).

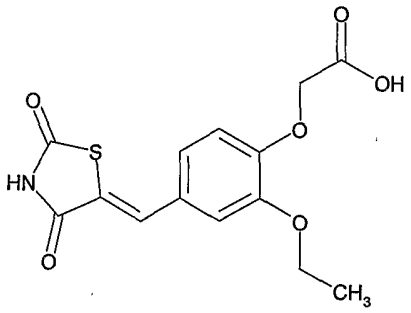
To a solution of 2-[5-(4-formylnaphtalen-1-yloxy) pentyl]malonic acid (0.36 g, 1.05 mmol) in acetic acid (10 mL) was added 2,4-thiazolidindione (0.16 g,1.36 mmol) and piperidine (0.52 mL, 5.25 mmol). The solution was heated to 105 °C for 24 hours. After cooling to room temperature, the solvents were removed *in vacuo*. Water was added to the residue. The precipi-

tate was filtered off and washed with water. Recrystalisation from acetonitrile afforded 200 mg (43%) of the title compound as a solid.

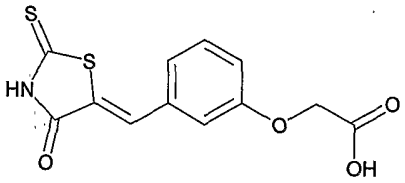
HPLC-MS (Method C): m/z: 422 (M-CO_2+Na); Rt = 4.08 min. ^{1}H-NMR(DMSO-d_6): δ = 1,41 (m, 2 H), 1.55 (m, 4 H), 1.88 (m, 2 H), 2.23 (t, 1 H), 4.24 (t, 2 H), 7.61-7.74 (m, 3 H), 8.12 (d, 1 H), 8.28 (d, 1 H), 8.38 (s, 1 H), 12.00 (s, 1 H), 12.59 (s, 2 H).

The following compounds are commercially available and may be prepared according to general procedure (D):

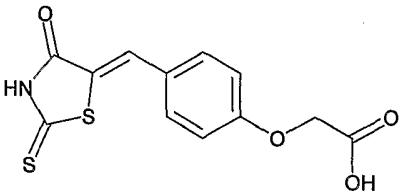
Example 505



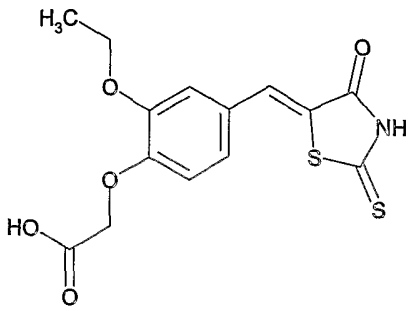
Example 506



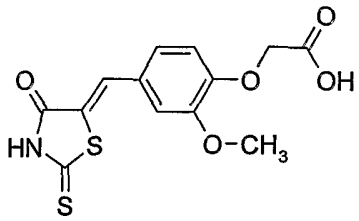
Example 507



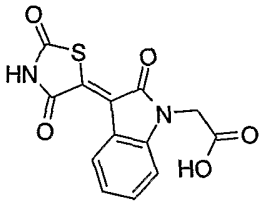
Example 508



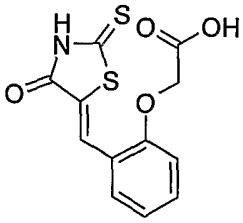
Example 509



Example 510



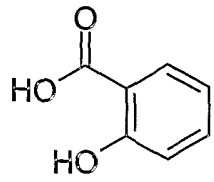
Example 511



The following salicylic acid derivatives do all bind to the His B10 Zn^{2+} site of the insulin hexamer:

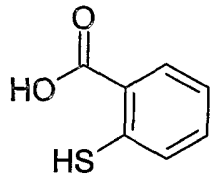
Example 512

Salicylic acid



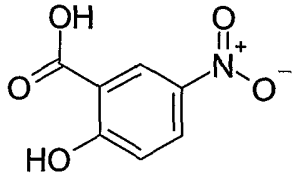
Example 513

Thiosalicylic acid (or: 2-Mercaptobenzoic acid)



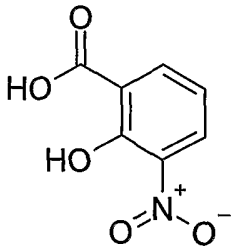
Example 514

2-Hydroxy-5-nitrobenzoic acid



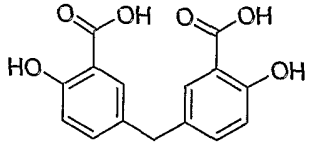
Example 515

3-Nitrosalicyclic acid



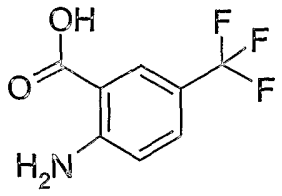
Example 516

5,5'-Methylenedisalicylic acid



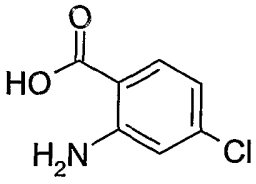
Example 517

2-Amino-5-trifluoromethylbenzoesyre



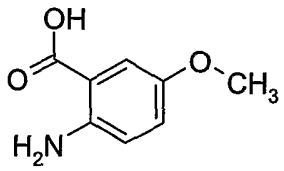
Example 518

2-Amino-4-chlorobenzoic acid

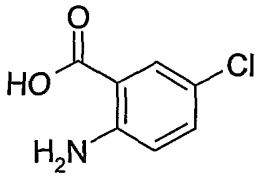


Example 519

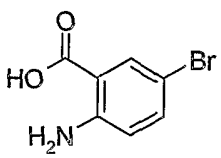
2-Amino-5-methoxybenzoesyre



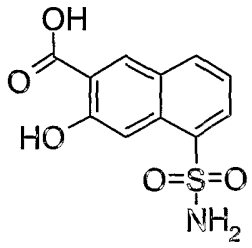
Example 520



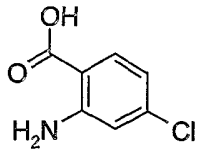
Example 521



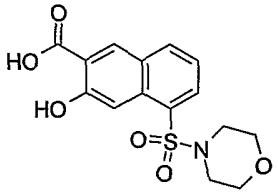
Example 522



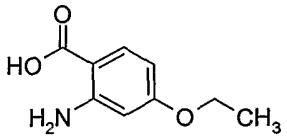
Example 523



Example 524

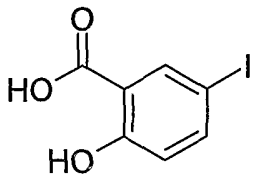


Example 525



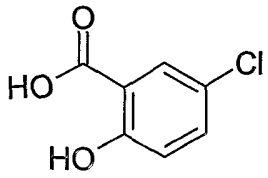
Example 526

5-Iodosalicylic acid



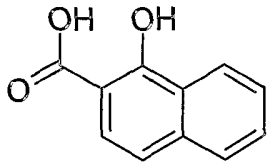
Example 527

5-Chlorosalicylic acid



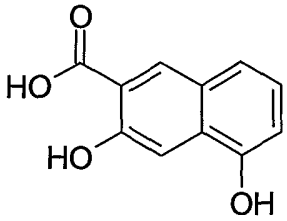
Example 528

1-Hydroxy-2-naphthoic acid



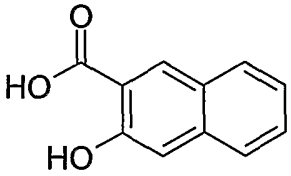
Example 529

3,5-Dihydroxy-2-naphthoic acid



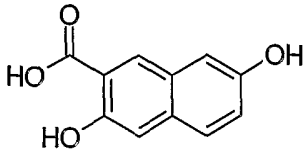
Example 530

3-Hydroxy-2-naphthoic acid



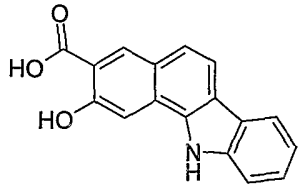
Example 531

3,7-Dihydroxy-2-naphthoic acid



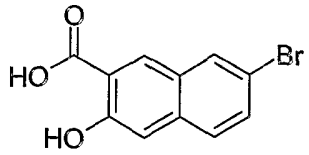
Example 532

2-Hydroxybenzo[a]carbazole-3-carboxylic acid



Example 533

7-Bromo-3-hydroxy-2-naphthoic acid

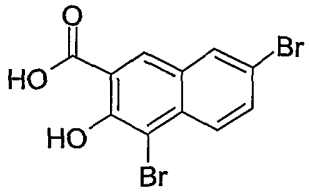


This compound was prepared according to Murphy *et al.*, *J. Med. Chem.* **1990**, *33*, 171-8.

HPLC-MS (Method A): m/z: 267 (M+1); Rt: = 3.78 min.

Example 534

1,6-Dibromo-2-hydroxynaphthalene-3-carboxylic acid

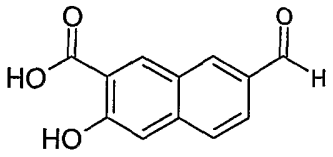


This compound was prepared according to Murphy *et al.*, *J. Med. Chem.* **1990**, *33*, 171-8.

HPLC-MS (Method A): m/z: 346 (M+1); Rt: = 4,19 min.

Example 535

7-Formyl-3-hydroxynaphthalene-2-carboxylic Acid



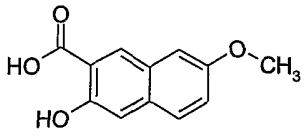
A solution of 7-bromo-3-hydroxynaphthalene-2-carboxylic acid (15.0 g, 56.2 mmol) (example 533) in tetrahydrofuran (100 mL) was added to a solution of lithium hydride (893 mg, 112 mmol) in tetrahydrofuran (350 mL). After 30 minutes stirring at room temperature, the resulting solution was heated to 50 °C for 2 minutes and then allowed to cool to ambient temperature over a period of 30 minutes. The mixture was cooled to -78 °C, and butyllithium (1.6 M in hexanes, 53 mL, 85 mmol) was added over a period of 15 minutes. *N*,*N*-Dimethylformamide

(8.7 mL, 8.2 g, 112 mmol) was added after 90 minutes additional stirring. The cooling was discontinued, and the reaction mixture was stirred at room temperature for 17 hours before it was poured into 1 N hydrochloric acid (aq.) (750 mL). The organic solvents were evaporated in vacuo, and the resulting precipitate was filtered off and rinsed with water (3 x 100 mL) to yield the crude product (16.2 g). Purification on silica gel (dichloromethane / methanol / acetic acid = 90:9:1) furnished the title compound as a solid.

^{1}H-NMR (DMSO-d_6): δ 11.95 (1H, bs), 10.02 (1H, s), 8.61 (1H, s), 8.54 (1H, s), 7.80 (2H, bs), 7.24 (1H, s); HPLC-MS (Method (A)): m/z: 217 (M+1); Rt = 2.49 min.

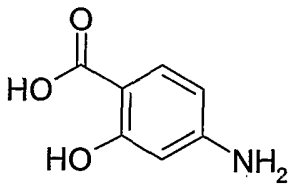
Example 536

3-Hydroxy-7-methoxy-2-naphthoic acid



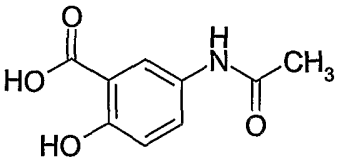
Example 537

4-Amino-2-hydroxybenzoic acid



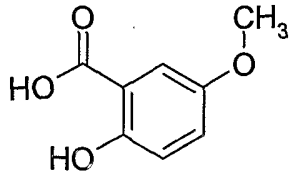
Example 538

5-Acetylamino-2-hydroxybenzoic acid



Example 539

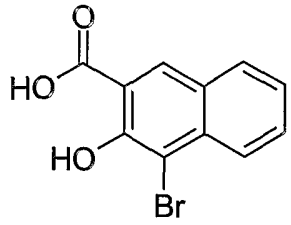
2-Hydroxy-5-methoxybenzoic acid



The following compounds were prepared as described below:

Example 540

4-Bromo-3-hydroxynaphthalene-2-carboxylic acid

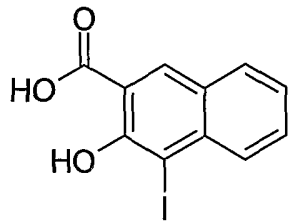


3-Hydroxynaphthalene-2-carboxylic acid (3.0 g, 15.9 mmol) was suspended in acetic acid (40 mL) and with vigorous stirring a solution of bromine (817 µL, 15.9 mmol) in acetic acid (10 mL) was added drop wise during 30 minutes. The suspension was stirred at room temperature for 1 hour, filtered and washed with water. Drying in vacuo afforded 3.74 g (88%) of 4-bromo-3-hydroxynaphthalene-2-carboxylic acid as a solid.

^{1}H-NMR (DMSO-d_6): δ 7.49 (1H, t), 7.75 (1H, t), 8.07 (2H, "t"), 8.64 (1H, s). The substitution pattern was confirmed by a COSY experiment, showing connectivities between the 3 (4 hydrogen) "triplets". HPLC-MS (Method A): m/z: 267 (M+1); Rt = 3.73 min.

Example 541

3-Hydroxy-4-iodonaphthalene-2-carboxylic acid

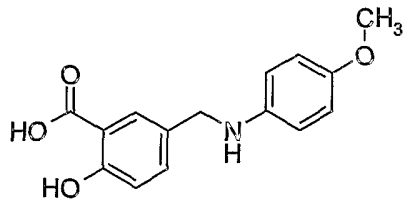


3-Hydroxynaphthalene-2-carboxylic acid (0.5 g, 2.7 mmol) was suspended in acetic acid (5 mL) and with stirring iodine monochloride (135 µL, 2.7 mml) was added. The suspension was stirred at room temperature for 1 hour, filtered and washed with water. Drying afforded 0.72 g (85%) of 4-iodo-3-hydroxynaphthalene-2-carboxylic acid as a solid.

^{1}H-NMR (DMSO-d_6): δ 7.47 (1H, t), 7.73 (1H, t), 7.98 (1H, d), 8.05 (1H, d), 8.66 (1H, s). HPLC-MS (Method A): m/z: 315 (M+1); Rt = 3.94 min.

Example 542

2-Hydroxy-5-[(4-methoxyphenylamino)methyl]benzoic acid



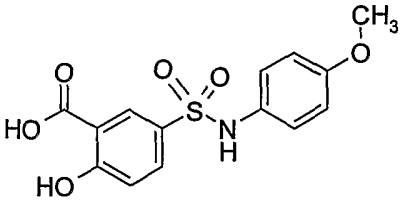
p-Anisidine (1.3 g, 10.6 mmol) was dissolved in methanol (20 mL) and 5-formylsalicylic acid (1.75 g, 10.6 mmol)was added and the resulting mixture was stirred at room temperature for 16 hours. The solid formed was isolated by filtration, re-dissolved in N-methyl pyrrolidone (20 mL) and methanol (2 mL). To the mixture was added sodium cyanoborohydride (1.2 g) and the mixture was heated to 70 °C for 3 hours. To the cooled mixture was added ethyl acetate (100 mL) and the mixture was extracted with water (100 mL) and saturated aqueous ammonium chloride (100 mL). The combined aqueous phases were concentrated *in vacuo* and a 2 g aliquot was purified by SepPac chromatography eluting with mixtures of aetonitrile and water containing 0.1% trifluoroacetic acid to afford the title compound.

HPLC-MS (Method A): m/z: 274 (M+1); Rt = 1.77 min.

^{1}H-NMR (methanol-d_4): δ 3.82 (3H, s), 4.45 (2H, s), 6.96 (1H, d), 7.03 (2H, d), 7.23 (2H, d), 7.45 (1H, dd), 7.92 (1H, d).

Example 543

2-Hydroxy-5-(4-methoxyphenylsulfamoyl)benzoic acid

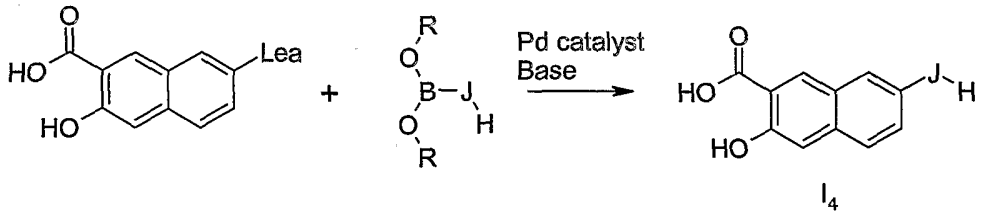


A solution of 5-chlrosulfonylsalicylic acid (0.96 g, 4.1 mmol) in dichloromethane (20 mL) and triethylamine (1.69 mL, 12.2 mmol) was added p-anisidine (0.49 g, 4.1 mmol) and the resulting mixture was stirred at room temperature for 16 hours. The mixture was added dichloromethane (50 mL) and was washed with water (2 x 100 mL). Drying ($MgSO_4$) of the organic phase and concentration *in vacuo* afforded 0.57 g crude product. Purification by column

chromatography on silica gel eluting first with ethyl acetate:heptane (1:1) then with methanol afforded 0.1 g of *the title compound*.

HPLC-MS (Method A): m/z: 346 (M+23); Rt = 2.89 min.
^{1}H-NMR (DMSO-d_6): δ 3.67 (3H, s), 6.62 (1H, d), 6.77 (2H, d), 6.96 (2H, d), 7.40 (1H, dd), 8.05 (1H, d), 9.6 (1H, bs).

General procedure (E) for preparation of compounds of general formula I_4:

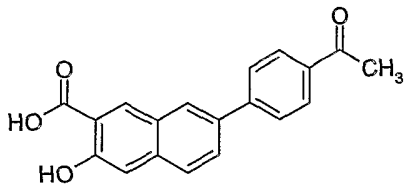


I_4

wherein Lea is a leaving group such as Cl, Br, I or OSO_2CF_3, R is hydrogen or C_1-C_6-alkyl, optionally the two R-groups may together form a 5-8 membered ring, a cyclic boronic acid ester, and J is as defined above.

An analogous chemical transformation has previously been described in the literature (Bumagin et al., *Tetrahedron*, **1997**, *53*, 14437-14450). The reaction is generally known as the Suzuki coupling reaction and is generally performed by reacting an aryl halide or triflate with an arylboronic acid or a heteroarylboronic acid in the presence of a palladium catalyst and a base such as sodium acetate, sodium carbonate or sodium hydroxide. The solvent can be water, acetone, DMF, NMP, HMPA, methanol, ethanol toluene or a mixture of two or more of these solvents. The reaction is performed at room temperature or at elevated temperature.

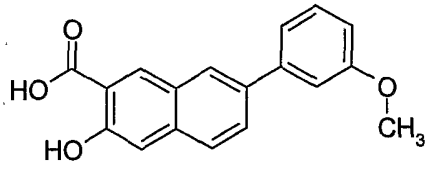
The general procedure (E) is further illustrated in the following example:
Example 544 (General Procedure (E))
7-(4-Acetylphenyl)-3-hydroxynaphthalene-2-carboxylic Acid



To 7-bromo-3-hydroxynaphthalene-2-carboxylic acid (100 mg, 0.37 mmol) (example 533) was added a solution of 4-acetylphenylboronic acid (92 mg, 0.56 mmol) in acetone (2.2 mL) followed by a solution of sodium carbonate (198 mg, 1.87 mmol) in water (3.3 mL). A suspension of palladium(II) acetate (4 mg, 0.02 mmol) in acetone (0.5 mL) was filtered and added to the above solution. The mixture was purged with N_2 and stirred vigorously for 24 hours at room temperature. The reaction mixture was poured into 1 N hydrochloric acid (aq.) (60 mL) and the precipitate was filtered off and rinsed with water (3 x 40 mL). The crude product was dissolved in acetone (25 mL) and dried with magnesium sulfate (1 h). Filtration followed by concentration furnished the title compound as a solid (92 mg).
^{1}H-NMR (DMSO-d_6): δ 12.60 (1H, bs), 8.64 (1H, s), 8.42 (1H, s), 8.08 (2H, d), 7.97 (2H, d), 7.92 (2H, m), 7.33 (1H, s), 2.63 (3H, s); HPLC-MS (Method (A): m/z: 307 (M+1); Rt = 3.84 min.

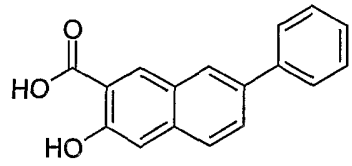
The compounds in the following examples were prepared in a similar fashion. Optionally, the compounds can be further purified by recrystallization from e.g. ethanol or by chromatography.

Example 545 (General Procedure (E))
3-Hydroxy-7-(3-methoxyphenyl)naphthalene-2-carboxylic acid



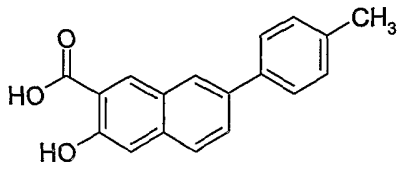
HPLC-MS (Method (A)): m/z: 295 (M+1); Rt = 4.60 min.

Example 546 (General Procedure (E))
3-Hydroxy-7-phenylnaphthalene-2-carboxylic acid



HPLC-MS (Method (A)): m/z: 265 (M+1); Rt = 4.6 min.

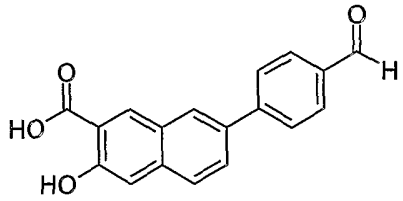
Example 547 (General Procedure (E))
3-Hydroxy-7-p-tolylnaphthalene-2-carboxylic acid



HPLC-MS (Method (A)): m/z: 279 (M+1); Rt = 4.95 min.

Example 548 (General Procedure (E))

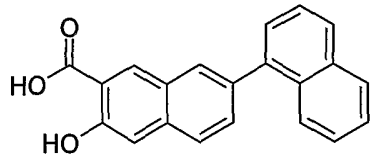
7-(4-Formylphenyl)-3-hydroxynaphthalene-2-carboxylic acid



HPLC-MS (Method (A)): m/z: 293 (M+1); Rt = 4.4 min.

Example 549 (General Procedure (E))

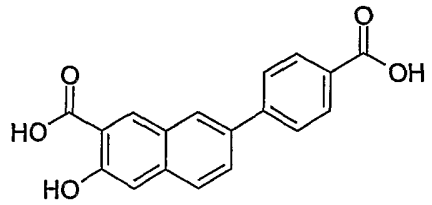
6-Hydroxy-[1,2]binaphthalenyl-7-carboxylic acid



HPLC-MS (Method (A)): m/z: 315 (M+1); Rt = 5.17 min.

Example 550 (General Procedure (E))

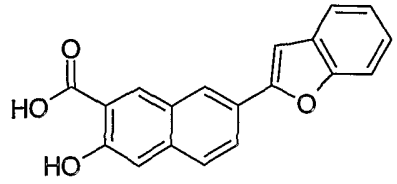
7-(4-Carboxy-phenyl)-3-hydroxynaphthalene-2-carboxylic acid



HPLC-MS (Method (A)): m/z: 309 (M+1); Rt = 3.60 min.

Example 551 (General Procedure (E))

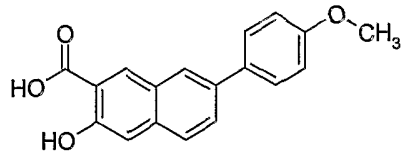
7-Benzofuran-2-yl-3-hydroxynaphthalene-2-carboxylic acid



HPLC-MS (Method (A)): m/z: 305 (M+1); Rt = 4.97 min.

Example 552 (General Procedure (E))

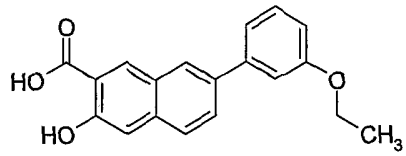
3-Hydroxy-7-(4-methoxyphenyl)-naphthalene-2-carboxylic acid



HPLC-MS (Method (A)): m/z: 295 (M+1); Rt = 4.68 min.

Example 553 (General Procedure (E))

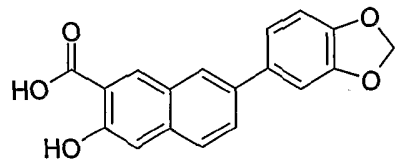
7-(3-Ethoxyphenyl)-3-hydroxynaphthalene-2-carboxylic acid



HPLC-MS (Method (A)): m/z: 309 (M+1); Rt = 4.89 min.

Example 554 (General Procedure (E))

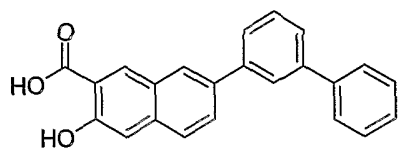
7-Benzo[1,3]dioxol-5-yl-3-hydroxynaphthalene-2-carboxylic acid



HPLC-MS (Method (A)): m/z: 309 (M+1); Rt = 5.61 min.

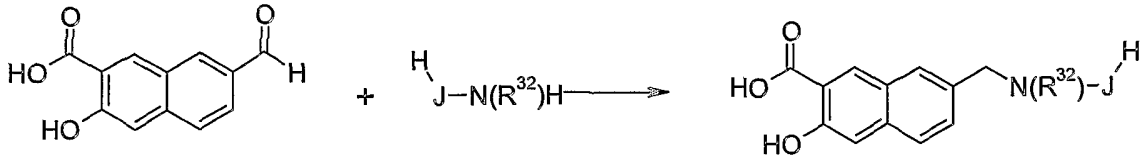
Example 555 (General Procedure (E))

7-Biphenyl-3-yl-3-hydroxynaphthalene-2-carboxylic acid



HPLC-MS (Method (A)): m/z: 341 (M+1); Rt = 5.45 min.

General procedure (F) for preparation of compounds of general formula I_5:



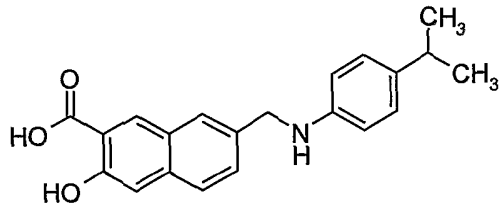
I_5

wherein R^{30} is hydrogen or C_1-C_6-alkyl and T is as defined above

This general procedure (F) is further illustrated in the following example:

Example 556 (General procedure (F))

3-Hydroxy-7-[(4-(2-propyl)phenylamino)methyl]naphthalene-2-carboxylic Acid



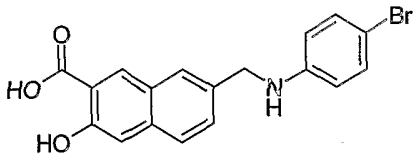
7-Formyl-3-hydroxynaphthalene-2-carboxylic acid (40 mg, 0.19 mmol) (example 535) was suspended in methanol (300 µL). Acetic acid (16 µL, 17 mg, 0.28 mmol) and 4-(2-propyl)aniline (40 µL, 40 mg, 0.30 mmol) were added consecutively, and the resulting mixture was stirred vigorously at room temperature for 2 hours. Sodium cyanoborohydride (1.0 *M in tetrahydrofuran*, 300 µL, 0.3 mmol) was added, and the stirring was continued for another 17 hours. The reaction mixture was poured into 6 N hydrochloric acid (aq.) (6 mL), and the precipitate was filtered off and rinsed with water (3 x 2 mL) to yield the title compound (40 *mg) as its hydrochloride salt. No further purification was necessary.*

^{1}H-NMR (DMSO-d_6): δ 10.95 (1H, bs), 8.45 (1H, s), 7.96 (1H, s), 7.78 (1H, d), 7.62 (1H, d), 7.32 (1H, s), 7.13 (2H, bd), 6.98 (2H, bd), 4.48 (2H, s), 2.79 (1H, sept), 1.14 (6H, d); HPLC-MS (Method (A)): m/z: 336 (M+1); Rt = 3.92 min.

The compounds in the following examples were made using this general procedure (F).

Example 557 (General procedure (F))

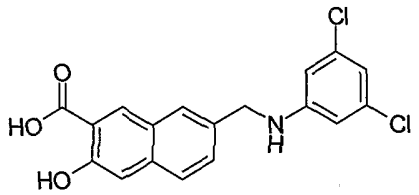
7-{[(4-Bromophenyl)amino]methyl}-3-hydroxynaphthalene-2-carboxylic Acid



HPLC-MS (Method C): m/z: 372 (M+1); Rt = 4.31min.

Example 558 (General procedure (F))

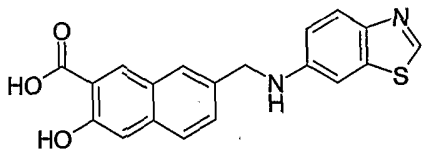
7-{[(3,5-Dichlorophenyl)amino]methyl}-3-hydroxynaphthalene-2-carboxylic Acid



HPLC-MS (Method C): m/z: 362 (M+1); Rt = 4.75 min.

Example 559 (General procedure (F))

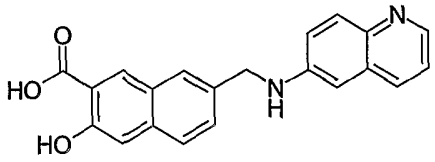
7-{[(Benzothiazol-6-yl)amino]methyl}-3-hydroxynaphthalene-2-carboxylic Acid



HPLC-MS (Method C): m/z: 351 (M+1); Rt = 3.43 min.

Example 560 (General procedure (F))

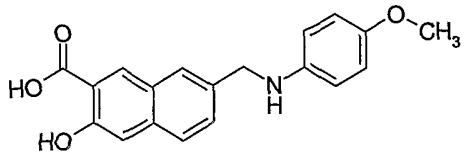
3-Hydroxy-7-{[(quinolin-6-yl)amino]methyl}naphthalene-2-carboxylic Acid



HPLC-MS (Method C): m/z: 345 (M+1); Rt = 2.26 min.

Example 561 (General procedure (F))

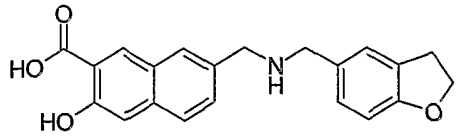
3-Hydroxy-7-{[(4-methoxyphenyl)amino]methyl}naphthalene-2-carboxylic Acid



HPLC-MS (Method C): m/z: 324 (M+1); Rt = 2.57min.

Example 562 (General procedure (F))

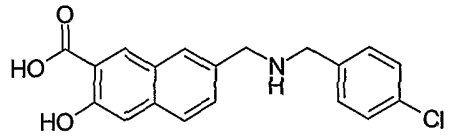
7-{[(2,3-Dihydrobenzofuran-5-ylmethyl)amino]methyl}-3-hydroxynaphthalene-2-carboxylic Acid



HPLC-MS (Method C): m/z: 350 (M+1); Rt = 2.22 min.

Example 563 (General procedure (F))

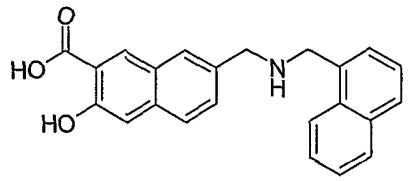
7-{[(4-Chlorobenzyl)amino]methyl}-3-hydroxynaphthalene-2-carboxylic Acid



HPLC-MS (Method C): m/z: 342 (M+1); Rt = 2.45 min.

Example 564 (General procedure (F))

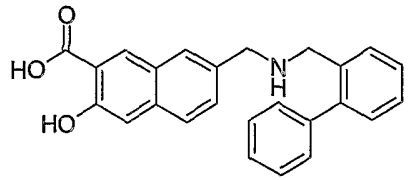
3-Hydroxy-7-{[(naphthalen-1-ylmethyl)amino]methyl}naphthalene-2-carboxylic Acid



HPLC-MS (Method C): m/z: 357 (M+1); Rt = 2.63 min.

Example 565 (General procedure (F))

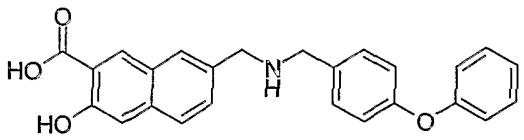
7-{[(Biphenyl-2-ylmethyl)amino]methyl}-3-hydroxynaphthalene-2-carboxylic Acid



HPLC-MS (Method C): m/z: 384 (M+1); Rt = 2.90 min.

Example 566 (General procedure (F))

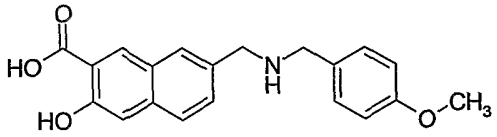
3-Hydroxy-7-{[(4-phenoxybenzyl)amino]methyl}naphthalene-2-carboxylic Acid



HPLC-MS (Method C): m/z: 400 (M+1); Rt = 3.15 min.

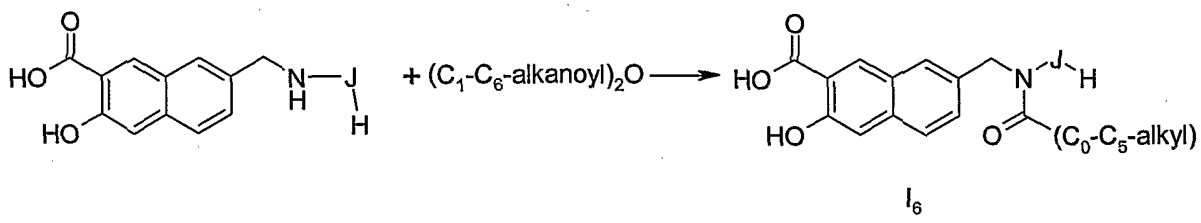
Example 567 (General procedure (F))

3-Hydroxy-7-{[(4-methoxybenzyl)amino]methyl}naphthalene-2-carboxylic Acid



HPLC-MS (Method C): m/z: 338 (M+1); Rt = 2.32 min.

General procedure (G) for preparation of compounds of general formula I_6:



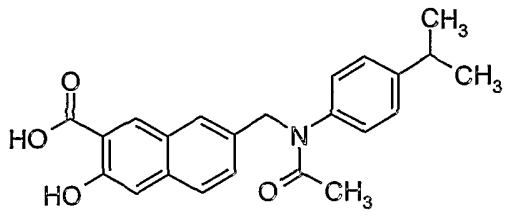
I_6

wherein J is as defined above and the moiety $(C_1\text{-}C_6\text{-alkanoyl})_2O$ is an anhydride.

The general procedure (G) is illustrated by the following example:

Example 568 (General procedure (G))

N-Acetyl-3-hydroxy-7-[(4-(2-propyl)phenylamino)methyl]naphthalene-2-carboxylic Acid



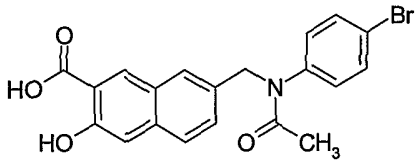
3-Hydroxy-7-[(4-(2-propyl)phenylamino)methyl]naphthalene-2-carboxylic acid (25 mg, 0.07 mmol) (example 556) was suspended in tetrahydrofuran (200 µL). A solution of sodium hydrogencarbonate (23 mg, 0.27 mmol) in water (200 µL) was added followed by acetic anhydride (14 µL, 15 mg, 0.15 mmol). The reaction mixture was stirred vigorously for 65 hours at room temperature before 6 N hydrochloric acid (4 mL) was added. The precipitate was filtered off and rinsed with water (3 x 1 mL) to yield the title compound (21 mg). No further purification was necessary.

^{1}H-NMR (*DMSO-d_6*): δ 10.96 (1H, bs), 8.48 (1H, s), 7.73 (1H, s), 7.72 (1H, d), 7.41 (1H, dd), 7.28 (1H, s), 7.23 (2H, d), 7.18 (2H, d), 4.96 (2H, s), 2.85 (1H, sept), 1.86 (3H, s), 1.15 (6H, d); HPLC-MS (Method (A)): m/z: 378 (M+1); Rt = 3.90 min.

The compounds in the following examples were prepared in a similar fashion.

Example 569 (General procedure (G))

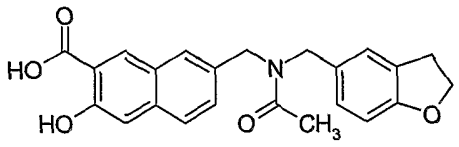
N-Acetyl-7-{[(4-bromophenyl)amino]methyl}-3-hydroxynaphthalene-2-carboxylic Acid



HPLC-MS (Method C): m/z: 414 (M+1); Rt = 3.76 min.

Example 570 (General procedure (G))

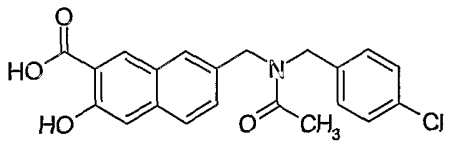
N-Acetyl-7-{[(2,3-dihydrobenzofuran-5-ylmethyl)amino]methyl}-3-hydroxynaphthalene-2-carboxylic Acid



HPLC-MS (Method C): m/z: 392 (M+1); Rt = 3.26 min.

Example 571 (General procedure (G))

N-Acetyl-7-{[(4-chlorobenzyl)amino]methyl}-3-hydroxynaphthalene-2-carboxylic Acid

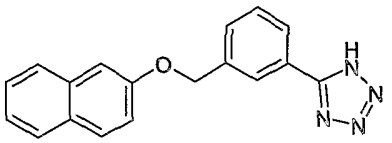


HPLC-MS (Method C): m/z: 384 (M+1); Rt = 3.67 min.

Compounds of the invention may also include tetrazoles:

Example 572

5-(3-(Naphthalen-2-yloxymethyl)-phenyl)-1*H*-tetrazole



To a mixture of 2-naphthol (10 g, 0.07 mol) and potassium carbonate (10 g, 0.073 mol) in acetone (150 mL), alpha-bromo-m-tolunitril (13.6 g, 0.07 mol) was added in portions. The reaction mixture was stirred at reflux temperature for 2.5 hours. The cooled reaction mixture was filtered and evaporated in vacuo affording an oily residue (19 g) which was dissolved in diethyl ether (150 mL) and stirred with a mixture of active carbon and $MgSO_4$ for 16 hours. The mixture was filtered and evaporated in vacuo affording crude 18.0 g (100 %) of 3-(naphthalen-2-yloxymethyl)-benzonitrile as a solid.

12 g of the above benzonitrile was recrystallised from ethanol (150 mL) affording 8.3 g (69 %) of 3-(naphthalen-2-yloxymethyl)-benzonitrile as a solid.

M.p. 60 - 61 °C.

Calculated for $C_{18}H_{13}NO$:

C, 83.37 %; H, 5.05 %; N, 5.40 %; Found

C, 83.51 %; H, 5.03 %; N, 5.38 %.

To a mixture of sodium azide (1.46 g, 22.5 mmol) and ammonium chloride (1.28 g, 24.0 mmol) in dry dimethylformamide (20 mL) under an atmosphere of nitrogen, 3-(naphthalen-2-yloxymethyl)-benzonitrile (3.9 g, 15 mmol) was added and the reaction mixture was stirred at 125 °C for 4 hours. The cooled reaction mixture was poured on to ice water (300 mL) and acidified to pH = 1 with 1 N hydrochloric acid. The precipitate was filtered off and washed with water, dried at 100 °C for 4 hours affording 4.2 g (93 %) of the title compound.

M.p. 200 - 202 °C.

Calculated for $C_{18}H_{14}N_4O$:

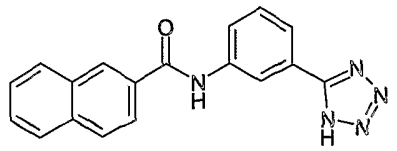
C, 71.51 %; H, 4.67 %; N, 18.54 %; Found

C, 72.11 %; H, 4.65 %; N, 17.43 %.

^{1}H NMR (400 MHz, DMSO-d_6) δ_H 5.36 (s, 2H), 7.29 (dd, 1H), 7.36 (dt, 1H), 7.47 (m, 2H), 7.66 (t, 1H), 7.74 (d, 1H), 7.84 (m, 3H), 8.02 (d, 1H), 8.22 (s, 1H).

Example 573

N-(3-(Tetrazol-5-yl)phenyl)-2-naphtoic acid amide



2-Naphtoic acid (10 g, 58 mmol) was dissolved in dichloromethane (100 mL) and N,N-dimethylformamide (0.2 mL) was added followed by thionyl chloride (5.1 ml, 70 mmol). The mixture was heated at reflux temperature for 2 hours. After cooling to room temperature, the mixture was added dropwise to a mixture of 3-aminobenzonitril (6.90 g, 58 mmol) and triethyl amine (10 mL) in dichloromethane (75 mL). The resulting mixture was stirred at room temperature for 30 minutes. Water (50 mL) was added and the volatiles was exaporated in vacuo. The resulting mixture was filtered and the filter cake was washed with water followed by heptane (2 x 25 mL). Drying in vacuo at 50 °C for 16 hours afforded 15.0 g (95 %) of N-(3-cyanophenyl)-2-naphtoic acid amide.

M.p. 138-140 °C

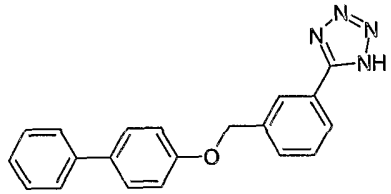
The above naphthoic acid amide (10 g, 37 mmol) was dissolved in N,N-dimethylformamide (200 mL) and sodium azide (2.63 g, 40 mmol) and ammonium chloride (2.16 g, 40 mmol) were added and the mixture heated at 125 °C for 6 hours. Sodium azide (1.2 g) and ammonium chloride (0.98 g) were added and the mixture heated at 125 °C for 16 hours. After cooling, the mixture was poured into water (1.5 l) and stirred at room temperature for 30 minutes. The solid formed was filtered off, washed with water and dried in vacuo at 50 °C for 3 days affording 9.69 g (84 %) of the title compound as a solid which could be further purified by treatment with ethanol at reflux temperature.

^{1}H NMR (200 MHz, DMSO-d_6): δ_H 7.58-7.70 (m, 3H), 7.77 (d, 1H), 8.04-8.13 (m, 5H), 8.65 (d, 1H), 10.7 (s, 1H).

Calculated for $C_{18}H_{13}N_5O$, 0.75 H_2O:
C, 65.74 %; H, 4.44 %; N, 21.30 %. Found:
C, 65.58 %; H, 4.50 %; N, 21.05 %.

Example 574

5-[3-(Biphenyl-4-yloxymethyl)phenyl]-1*H*-tetrazole



To a solution of 4-phenylphenol (10.0 g, 59 mmol) in dry N,N-dimethyl-formamide (45 mL) kept under an atmosphere of nitrogen, sodium hydride (2.82 g, 71 mmol, 60 % dispersion in oil) was added in portions and the reaction mixture was stirred until gas evolution ceased. A solution of m-cyanobenzyl bromide (13 g, 65 mmol) in dry N,N-dimethylformamide (45 mL) was added dropwise and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was poured on to ice water (150 mL). The precipitate was filtered of and washed with 50 % ethanol
(3 x 50 mL), ethanol (2 x 50 mL), diethyl ether (80 mL), and dried in vacuo at
50 °C for 18 hours affording crude 17.39 g of 3-(biphenyl-4-yloxymethyl)-benzonitrile as a solid.

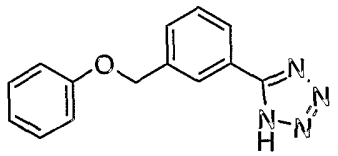
^{1}H NMR (200 MHz, $CDCl_3$) δ_H 5.14 (s, 2H), 7.05 (m, 2H), 7.30 - 7.78 (m, 11H).

To a mixture of sodium azide (2.96 g, 45.6 mmol) and ammonium chloride (2.44 g, 45.6 mmol) in dry N,N-dimethylformamide (100 mL) under an atmosphere of nitrogen, 3-(biphenyl-4-yloxymethyl)-benzonitrile (10.0 g, 35.0 mmol) was added and the reaction mixture was stirred at 125 °C for 18 hours. The cooled reaction mixture was poured on to a mixture of 1N hydrochloric acid (60 mL) and ice water (500 mL). The precipitate was filtered off and *washed with water (3 x 100 mL), 50 % ethanol (3 x 100 mL), ethanol (50 mL), diethyl ether* (50 mL), ethanol (80 mL), and dried in vacuo at 50 °C for 18 hours affording 8.02 g (70 %) of the title compound.

^{1}H NMR (200 MHz, DMSO-d_6) δ_H 5.31 (s, 2H), 7.19 (m, 2H), 7.34 (m, 1H), 7.47 (m, 2H), 7.69 (m, 6H), 8.05 (dt, 1H), 8.24 (s, 1H).

Example 575

5-(3-Phenoxymethyl)-phenyl)-tetrazole



3-Bromomethylbenzonitrile (5.00 g, 25.5 mmol) was dissolved in N,N-dimethylformamide (50 mL), phenol (2.40 g, 25.5 mmol) and potassium carbonate (10.6 g, 77 mmol) were added. The mixture was stirred at room temperature for 16 hours. The mixture was poured into water (400 mL) and extracted with ethyl acetate (2 x 200 mL). The combined organic extracts were washed with water (2 x 100 mL), dried ($MgSO_4$) and evaporated in vacuo to afford 5.19 g (97 %) 3-(phenoxymethyl)benzonitrile as an oil.

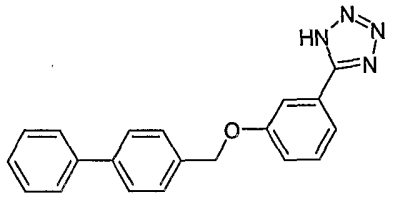
TLC: R_f = 0.38 (Ethyl acetate/heptane = 1:4)

The above benzonitrile (5.19 g, 24.8 mmol) was dissolved in N,N-dimethylformamide (100 mL) and sodium azide (1.93 g, 30 mmol) and ammonium chloride (1.59 g, 30 mmol) were added and the mixture was heated at 140 °C for 16 hours. After cooling, the mixture was poured into water (800 mL). The aqeous mixture was washed with ethyl acetate (200 mL). The pH of the aqueous phase was adjusted to 1 with 5 N hydrochloric acid and stirred at room temperature for 30 minutes. Filtration, washing with water and drying in vacuo at 50 °C afforded 2.06 g (33 %) of the title compound as a solid.

^1H NMR (200 MHz, $CDCl_3$ + DMSO-d_6) δ_H 5.05 (s, 2H), 6.88 (m, 3H), 7.21 (m, 2H), 7.51 (m, 2H), 7.96 (dt, 1H), 8.14 (s, 1H).

Example 576

5-[3-(Biphenyl-4-ylmethoxy)phenyl]-1H-tetrazole



To a solution of 3-cyanophenol (5.0 g, 40.72 mmol) in dry N,N-dimethylformamide (100 mL) kept under an atmosphere of nitrogen, sodium hydride (2 g, 48.86 mmol, 60 % dispersion in oil) was added in portions and the reaction mixture was stirred until gas evolution ceased. p-

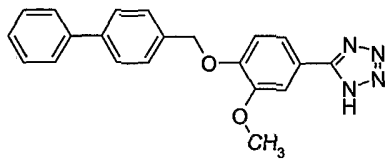
Phenylbenzyl chloride (9.26 g, 44.79 mmol) and potassium iodide (0.2 g, 1.21 mmol) were added and the reaction mixture was stirred at room temperature for 60 hours. The reaction mixture was poured on to a mixture of saturated sodium carbonate (100 mL) and ice water (300 mL). The precipitate was filtered of and washed with water (3 x 100 mL), n-hexane (2 x 80 mL) and dried in vacuo at 50 °C for 18 hours affording 11.34 g (98 %) of 3-(biphenyl-4-ylmethoxy)-benzonitrile as a solid.

To a mixture of sodium azide (2.37 g, 36.45 mmol) and ammonium chloride (1.95 g, 36.45 mmol) in dry N,N-dimethylformamide (100 mL) under an atmosphere of nitrogen, 3-(biphenyl-4-ylmethoxy)-benzonitrile (8.0 g, 28.04 mmol) was added and the reaction mixture was stirred at
125 °C for 18 hours. To the cooled reaction mixture water (100 mL) was added and the reaction mixture stirred for 0.75 hour. The precipitate was filtered off and washed with water, 96 % ethanol (2 x 50 mL), and dried in vacuo at 50°C for 18 hours affording 5.13 g (56 %) of the title compound.

^{1}H NMR (200 MHz, DMSO-d_6) δ_H 5.29 (s, 2H), 7.31 (dd, 1H), 7.37 - 7.77 (m, 12H).

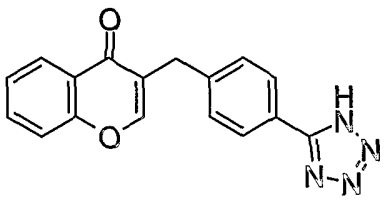
Example 577

5-[4-(Biphenyl-4-ylmethoxy)-3-methoxyphenyl]-1H-tetrazol



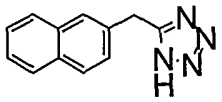
This compound was made similarly as described in example 576.

Example 578



Example 579

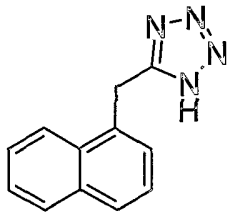
5-(2-Naphtylmethyl)-1H-tetrazole



This compound was prepared similarly as described in example 572, step 2.

Example 580

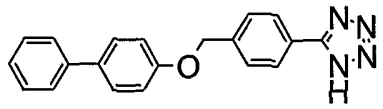
5-(1-Naphtylmethyl)-1H-tetrazole



This compound was prepared similarly as described in example 572, step 2.

Example 581

5-[4-(Biphenyl-4-yloxymethyl)phenyl]-1H-tetrazole



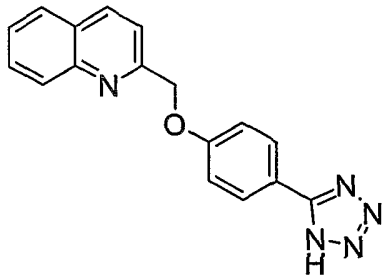
A solution of alpha-bromo-p-tolunitrile (5.00 g, 25.5 mmol), 4-phenylphenol (4.56 g, 26.8 mmol), and potassium carbonate (10.6 g, 76.5 mmol) in N,N-dimethylformamide (75 mL) was stirred vigorously for 16 hours at room temperature. Water (75 mL) was added and the mixture was stirred at room temperature for 1 hour. The precipitate was filtered off and washed with thoroughly with water. Drying in vacuo over night at 50 °C afforded 7.09 g (97 %) of 4-(biphenyl-4-yloxymethyl)benzonitrile as a solid.

The above benzonitrile (3.00 g, 10.5 mmol) was dissolved in N,N-dimethylformamide (50 mL), and sodium azide (1.03 g, 15.8 mmol) and ammonium chloride (0.84 g, 15.8 mmol) were added and the mixture was stirred 16 hours at 125 °C. The mixture was cooled to room temperature and water (50 mL) was added. The suspension was stirred overnight, filtered, washed with water and dried in vacuo at 50 °C for 3 days to give crude 3.07 g (89 %) of the title compound. From the mother liquor crystals were colected and washed with water, dried by suction to give 0.18 g
(5 %) of the title compound as a solid.

^{1}H NMR (200 MHz, DMSO-d_6): δ_H 5.21 (s, 2H), 7.12 (d, 2H), 7.30 (t, 1H), 7.42 (t, 2H), 7.56-7.63 (m, 6H), 8.03 (d, 2H).

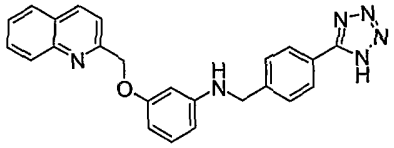
Calculated for $C_{20}H_{16}N_4O$, $2H_2O$:
C, 65.92 %; H, 5.53 %; N, 15.37 %. Found:
C, 65.65 %; H, 5.01 %; N, 14.92 %.

Example 582

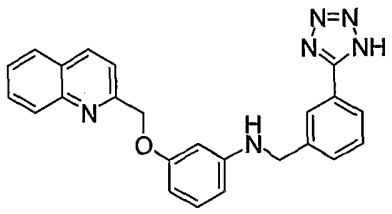


This compound was prepared similarly as described in example 576.

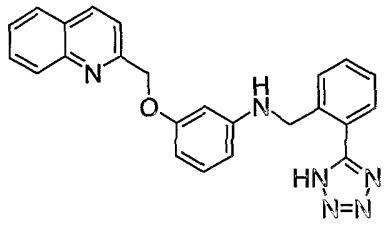
Example 583



Example 584

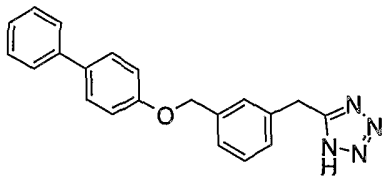


Example 585



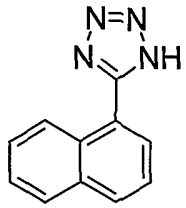
Example 586

5-(3-(Biphenyl-4-yloxymethyl)-benzyl)-1*H*-tetrazole



Example 587

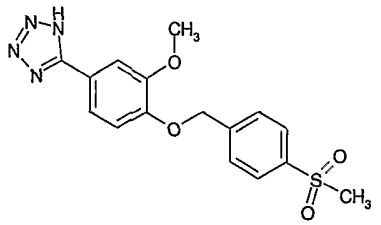
5-(1-Naphthyl)-1H-tetrazole



This compound was prepared similarly as described in example 572, step 2.

Example 588

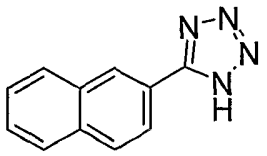
5-[3-Methoxy-4-(4-methylsulfonylbenzyloxy)phenyl]-1*H*-tetrazole



This compound was made similarly as described in example 576.

Example 589

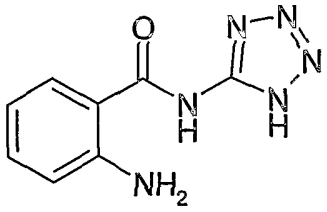
5-(2-Naphthyl)-1*H*-tetrazole



This compound was prepared similarly as described in example 572, step 2.

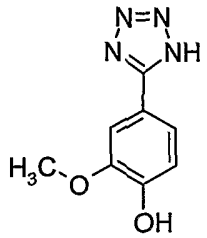
Example 590

2-Amino-N-(1*H*-tetrazol-5-yl)-benzamide



Example 591

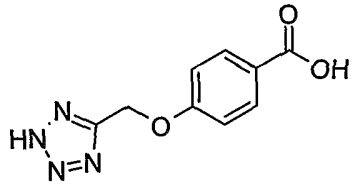
5-(4-Hydroxy-3-methoxyphenyl)-1*H*-tetrazole



This compound was prepared similarly as described in example 572, step 2.

Example 592

4-(2H-Tetrazol-5-ylmethoxy)benzoic acid



To a mixture of methyl 4-hydroxybenzoate (30.0 g, 0.20 mol), sodium iodide (30.0 g, 0.20 mol) and potassium carbonate (27.6 g, 0.20 mol) in acetone (2000 mL) was added chloroacetonitrile (14.9 g , 0.20 mol). The mixture was stirred at RT for 3 days. Water was added and the mixture was acidified with 1N hydrochloric acid and the mixture was extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in acetone and chloroacetonitrile (6.04 g,0.08 mol), so-

dium iodide (12.0 g, 0.08 mol) and potassium carbonate (11.1 g, 0.08 mol) were added and the mixture was stirred for 16 hours at RT and at 60 °C. More chloroacetonitrile was added until the conversion was 97%. Water was added and the mixture was acidified with 1N hydrochloric acid and the mixture was extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford methyl 4-cyanomethyloxybenzoate in quantitative yield. This compound was used without further purification in the following step.

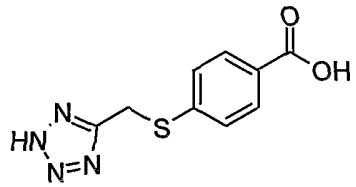
A mixture of methyl 4-cyanomethyloxybenzoate (53.5 g,0.20 mol), sodium azide (16.9 g, 0.26 mol) and ammonium chloride (13.9 g, 0.26 mol) in DMF 1000 (mL) was refluxed overnight under N_2. After cooling, the mixture was concentrated *in vacuo*. The residue was suspended in cold water and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo,* to afford methyl 4-(2*H*-tetrazol-5-ylmethoxy)benzoate. This compound was used as such in the following step.

Methyl 4-(2H-Tetrazol-5-ylmethoxy)-benzoate was refluxed in 3N sodium hydroxide. The reaction was followed by TLC (DCM:MeOH = 9:1). The reaction mixture was cooled, acidified and the product filtered off. The impure product was washed with DCM, dissolved in MeOH, filtered and purified by column chromatography on silica gel (DCM:MeOH = 9:1).The resulting product was recrystallised from DCM:MeOH=95:5. This was repeated until the product was pure. This afforded 13.82 g (30 %) of the title compound.

^{1}H-NMR (DMSO-d_6): 4.70 (2H, s), 7.48 (2H, d), 7.73 (2H, d), 13 (1H, bs).

Example 593

4-(2H-Tetrazol-5-ylmethylsulfanyl)benzoic acid



To a solution of sodium hydroxide (10.4 g, 0.26 mol) in degassed water (600 mL) was added 4-mercaptobenzoic acid (20.0 g, 0.13 mol). This solution was stirred for 30 minutes. To a solution of potassium carbonate (9.0 g, 65 mmol) in degassed water (400 mL) was added chloroacetonitrile (9.8 g, (0.13 mol) portion-wise. These two solutions were mixed and stirred for 48 hours at RT under N_2. The mixture was filtered and washed with heptane. The aque-

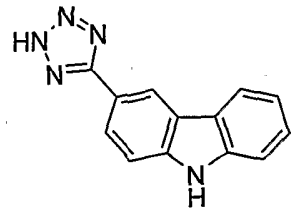
ous phase was acidified with 3N hydrochloric acid and the product was filtered off, washed with water and dried, affording 4-cyanomethylsulfanylbenzoic acid (27.2 g, 88%). This compound was used without further purification in the following step.

A mixture of 4-cyanomethylsulfanylbenzoic acid (27.2 g, 0.14 mol), sodium azide (11.8 g, 0,18 mol) and ammonium chloride (9.7 g, 0.18 mol) in DMF (1000 mL) was refluxed overnight under N_2. The mixture was concentrated *in vacuo*. The residue was suspended in cold water and extracted with diethyl ether. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Water was added and the precipitate was filtered off. The aqueous layer was concentrated *in vacuo*, water was added and the precipitate filtered off. The combined impure products were purified by column chromatography *using DCM:MeOH = 9:1 as eluent, affording the title compound (5.2 g, 16%).*

^{1}H-NMR (DMSO-d_6): 5.58 (2H, s), 7.15 (2H, d), 7.93 (2H, d), 12.7 (1H, bs).

Example 594

3-(2*H*-Tetrazol-5-yl)-9*H*-carbazole



3-Bromo-9*H*-carbazole was prepared as described by Smith *et al.* in *Tetrahedron* **1992**, *48, 7479-7488.*

A solution of 3-bromo-9*H*-carbazole (23.08 g, 0.094 mol) and cuprous cyanide (9.33 g, 0.103 mol) in *N*-methyl-pyrrolidone (300 ml) was heated at 200 °C for 5 h. The cooled reaction mixture was poured on to water (600 ml) and the precipitate was filtered off and washed with ethyl acetate (3 x 50 ml). The filtrate was extracted with ethyl acetate (3 x 250 ml) and the combined ethyl acetate extracts were washed with water (150 ml), brine (150 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was crystallised from heptanes and recrystallised from acetonitrile (70 ml) affording 7.16 g (40 %) of 3-cyano-9*H*-carbazole as a solid. M.p. 180 - 181 °C.

3-Cyano-9*H*-carbazole (5.77 g, 30 mmol) was dissolved in *N*,*N*-dimethylformamide (150 ml), and sodium azide (9.85 g, 152 mmol), ammonium chloride (8.04 g, 150 mmol) and lithium

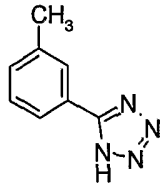
chloride (1.93 g, 46 mmol) were added and the mixture was stirred for 20 h at 125 °C. To the reaction mixture was added an additional portion of sodium azide (9.85 g, 152 mmol) and ammonium chloride (8.04 g, 150 mmol) and the reaction mixture was stirred for an additional 24 h at 125 °C. The cooled reaction mixture was poured on to water (500 ml). The suspension was stirred for 0.5 h, and the precipitate was filtered off and washed with water (3 x 200 ml) and dried *in vacuo* at 50 °C. The dried crude product was suspended in diethyl ether (500 ml) and stirred for 2 h, filtered off and washed with diethyl ether (2 x 200 ml) and dried *in vacuo* at 50 °C affording 5.79 g (82 %) of the title compound as a solid.

^{1}H-NMR (DMSO-d_6): δ 11.78 (1H, bs), 8.93 (1H, d), 8.23 (1H, d), 8.14 (1H, dd), 7.72 (1H, d), 7.60 (1H, d), 7.49 (1H, t), 7.28 (1H, t); HPLC-MS (Method C): m/z: 236 (M+1); Rt = 2.77 min.

The following commercially available tetrazoles do all bind to the His B10 Zn^{2+} site of the insulin hexamer:

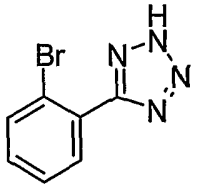
Example 595

5-(3-Tolyl)-1*H*-tetrazole



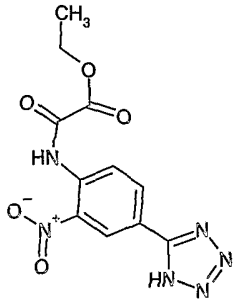
Example 596

5-(2-Bromophenyl)tetrazole

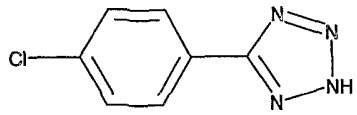


Example 597

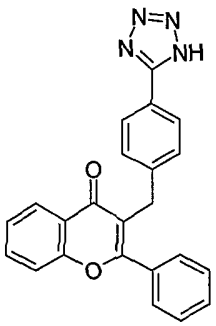
5-(4-Ethoxalylamino-3-nitrophenyl)tetrazole



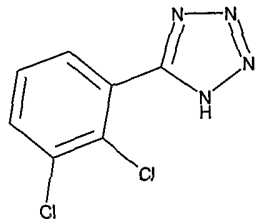
Example 598



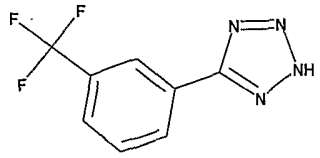
Example 599



Example 600

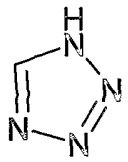


Example 601



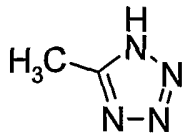
Example 602

Tetrazole



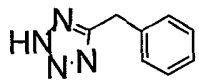
Example 603

5-Methyltetrazole



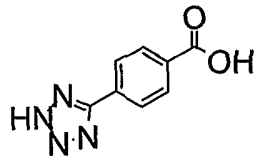
Example 604

5-Benzyl-2H-tetrazole



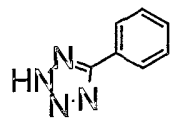
Example 605

4-(2H-Tetrazol-5-yl)benzoic acid



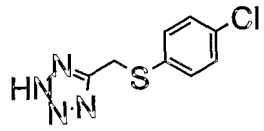
Example 606

5-Phenyl-2H-tetrazole



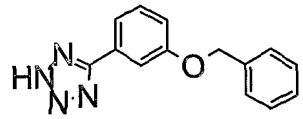
Example 607

5-(4-Chlorophenylsulfanylmethyl)-2H-tetrazole



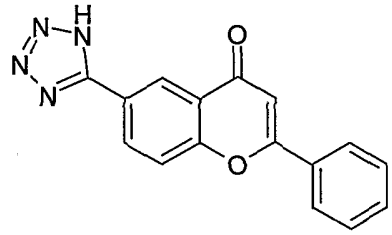
Example 608

5-(3-Benzyloxyphenyl)-2H-tetrazole

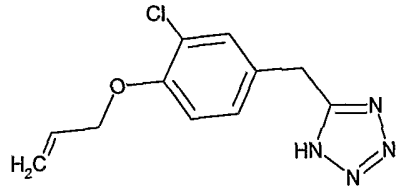


Example 609

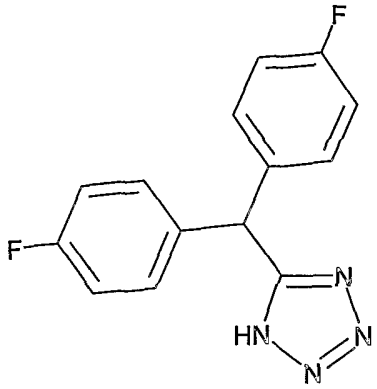
2-Phenyl-6-(1H-tetrazol-5-yl)-chromen-4-one



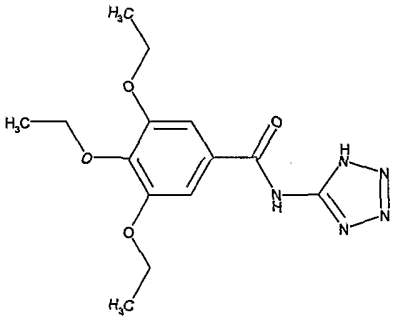
Example 610



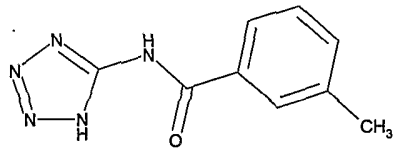
Example 611



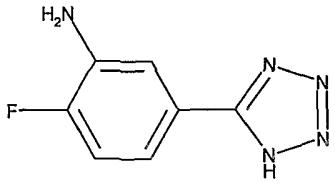
Example 612



Example 613

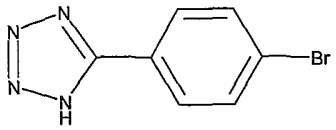


Example 614

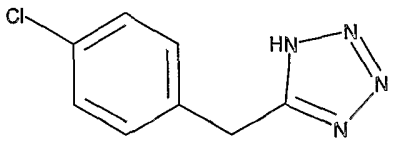


Example 615

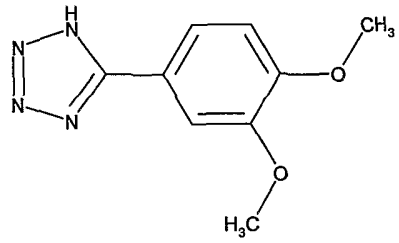
5-(4-Bromo-phenyl)-1H-tetrazole



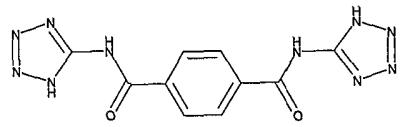
Example 616



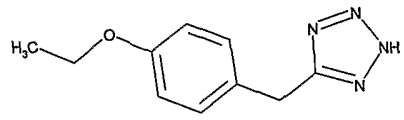
Example 617



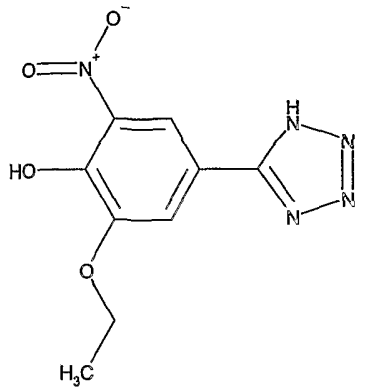
Example 618



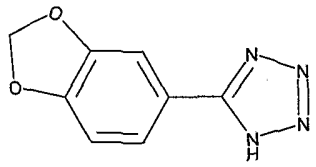
Example 619



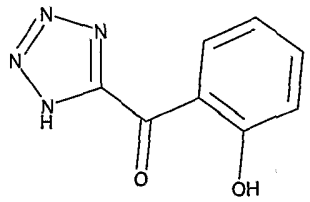
Example 620



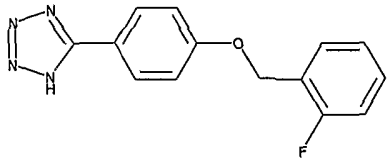
Example 621



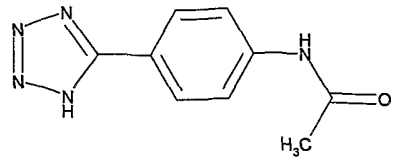
Example 622



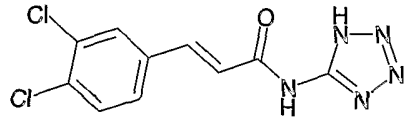
Example 623



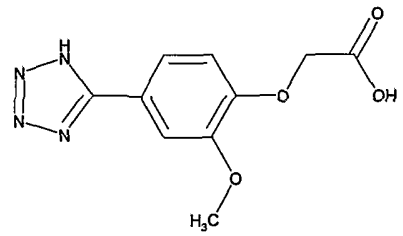
Example 624



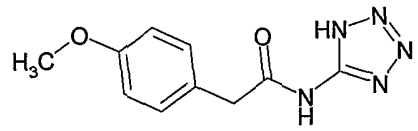
Example 625



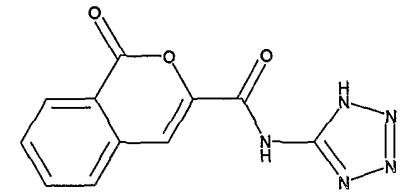
Example 626



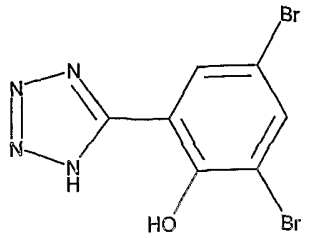
Example 627



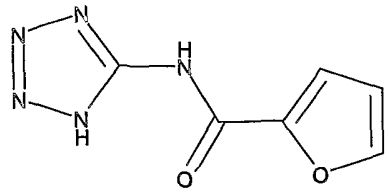
Example 628



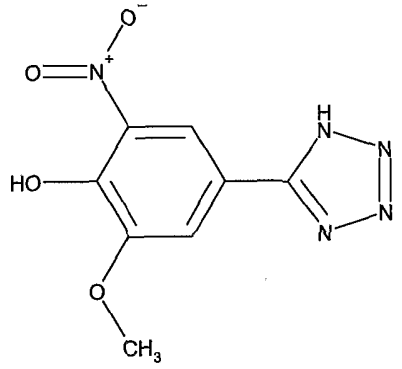
Example 629



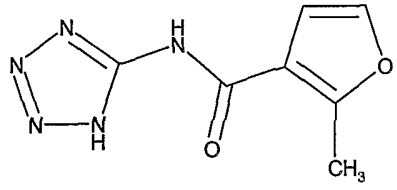
Example 630



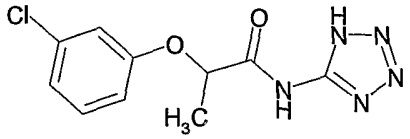
Example 631



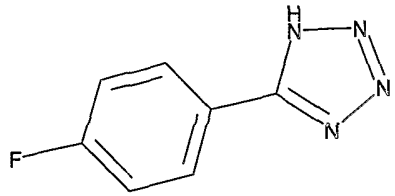
Example 632



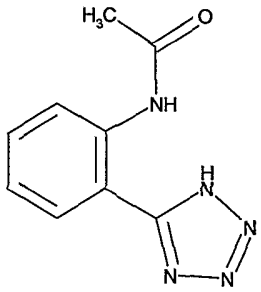
Example 633



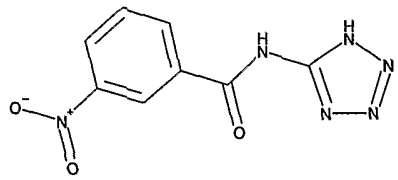
Example 634



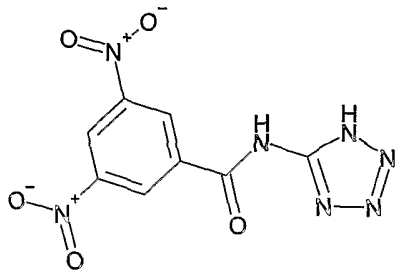
Example 635



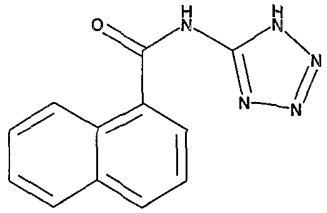
Example 636



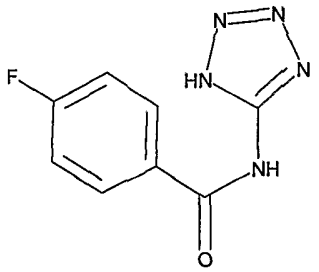
Example 637



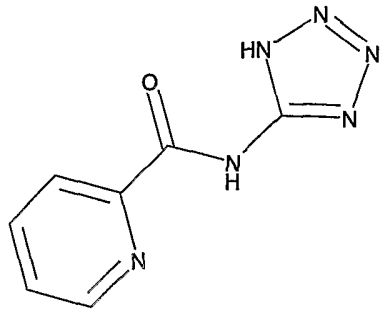
Example 638



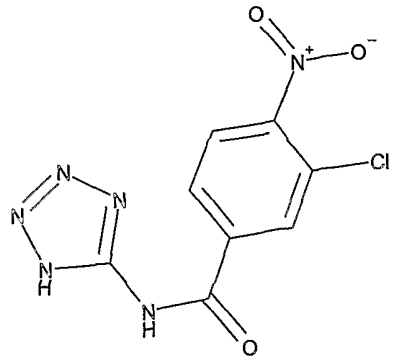
Example 639



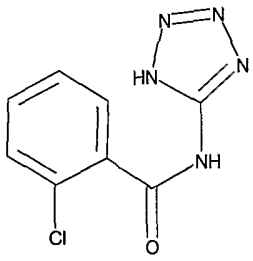
Example 640



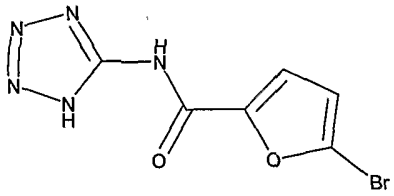
Example 641



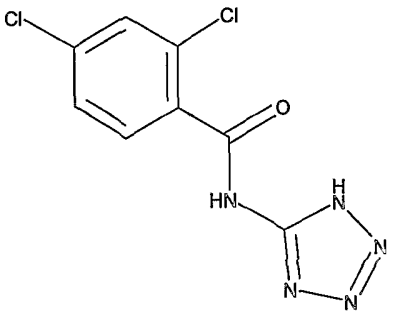
Example 642



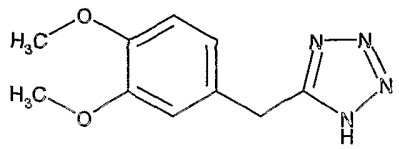
Example 643



Example 644

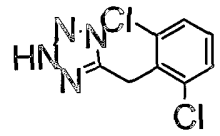


Example 645

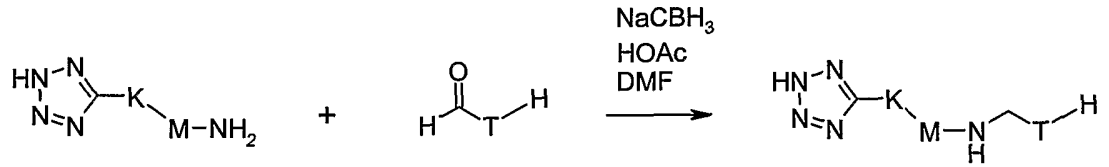


Example 646

5-(2,6-Dichlorobenzyl)-2*H*-tetrazole



General procedure (H) for preparation of compounds of general formula I_7:



I_7

wherein K, M, and T are as defined above.

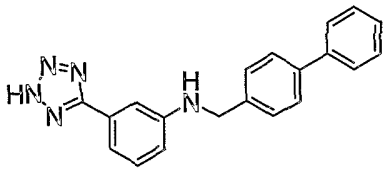
The reaction is generally known as a reductive alkylation reaction and is generally performed *by stirring an aldehyde with an amine at low pH (by addition of an acid, such as acetic acid or* formic acid) in a solvent such as THF, DMF, NMP, methanol, ethanol, DMSO, dichloromethane, 1,2-dichloroethane, trimethyl orthoformate, triethyl orthoformate, or a mixture of two or more of these. *As reducing agent sodium cyano borohydride or sodium triacetoxy* borohydride may be used. The reaction is performed between 20°C and 120°C, preferably at room temperature.

When the reductive alkylation is complete, the product is isolated by extraction, filtration, chromatography or other methods known to those skilled in the art.

The general procedure (H) is further illustrated in the following example 647:

Example 647 (General procedure (H))

Biphenyl-4-ylmethyl-[3-(2*H*-tetrazol-5-yl)phenyl]amine

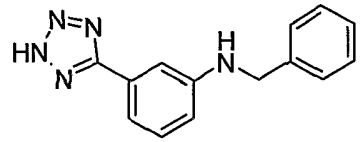


A solution of 5-(3-aminophenyl)-2*H*-tetrazole (example 873, 48 mg, 0.3 mmol) in DMF (250 µL) was mixed with a solution of 4-biphenylylcarbaldehyde (54 mg, 0.3 mmol) in DMF (250 µL) and acetic acid glacial (250 µL) was added to the mixture followed by a solution of sodium cyano borohydride (15 mg, 0.24 mmol) in methanol (250 µL). The resulting mixture was shaken at room temperature for 2 hours. Water (2 mL) was added to the mixture and the resulting mixture was shaken at room temperature for 16 hours. The mixture was centrifugated (6000 rpm, 10 minutes) and the supernatant was removed by a pipette. The residue was washed with water (3 mL), centrifugated (6000 rpm, 10 minutes) and the supernatant was removed by a pipette. The residue was dried *in vacuo* at 40 °C for 16 hours to afford the title compound as a solid.

HPLC-MS (Method C): m/z: 328 (M+1), 350 (M+23); Rt = 4.09 min.

Example 648 (General procedure (H))

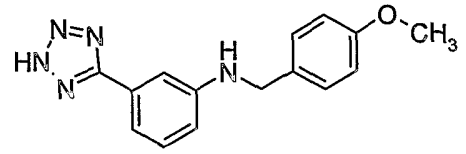
Benzyl-[3-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 252 (M+1); Rt = 3,74 min.

Example 649 (General procedure (H))

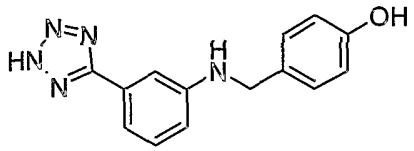
(4-Methoxybenzyl)-[3-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 282,2 (M+1); Rt = 3,57min.

Example 650 (General procedure (H))

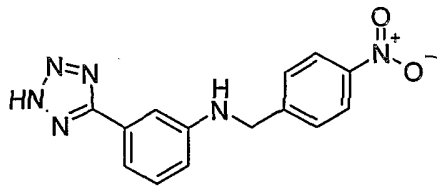
4-{[3-(2*H*-Tetrazol-5-yl)phenylamino]methyl}phenol



HPLC-MS (Method D): m/z: 268,4 (M+1); Rt = 2,64 min.

Example 651 (General procedure (H))

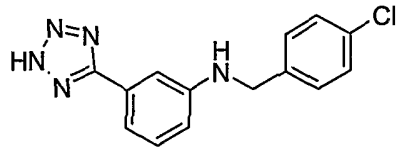
(4-Nitrobenzyl)-[3-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 297,4 (M+1); Rt = 3,94 min.

Example 652 (General procedure (H))

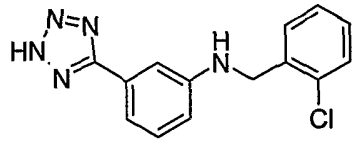
(4-Chlorobenzyl)-[3-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 287,2 (M+1); Rt = 4,30 min.

Example 653 (General procedure (H))

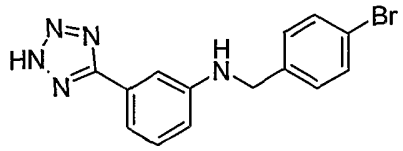
(2-Chlorobenzyl)-[3-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 286 (M+1); Rt = 4,40 min.

Example 654 (General procedure (H))

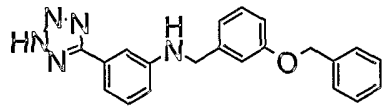
(4-Bromobenzyl)-[3-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z:332 (M+1); Rt = 4,50 min.

Example 655 (General procedure (H))

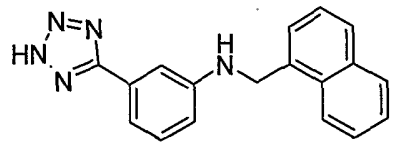
(3-Benzyloxybenzyl)-[3-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 358 (M+1); Rt = 4,94 min.

Example 656 (General procedure (H))

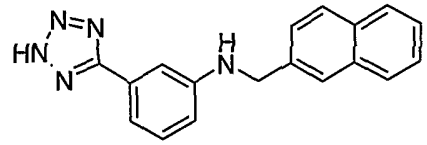
Naphthalen-1-ylmethyl-[3-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 302 (M+1); Rt = 4,70 min.

Example 657 (General procedure (H))

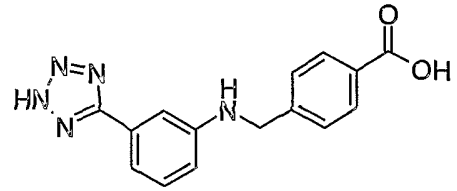
Naphthalen-2-ylmethyl-[3-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 302 (M+1); Rt = 4,60 min.

Example 658 (General procedure (H))

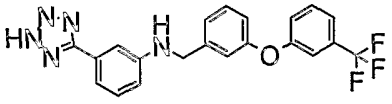
4-{[3-(2*H*-Tetrazol-5-yl)phenylamino]methyl}benzoic acid



HPLC-MS (Method D): m/z: 296 (M+1); Rt = 3,24 min.

Example 659 (General procedure (H))

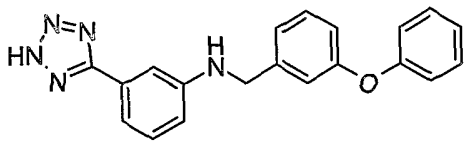
[3-(2*H*-Tetrazol-5-yl)-phenyl]-[3-(3-trifluoromethyl-phenoxy)benzyl]amine



HPLC-MS (Method D): m/z: 412 (M+1); Rt = 5,54 min.

Example 660 (General procedure (H))

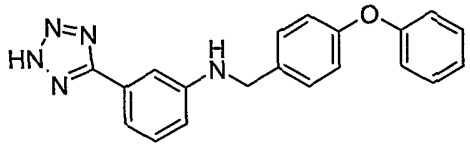
(3-Phenoxybenzyl)-[3-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 344 (M+1); Rt = 5,04 min.

Example 661 (General procedure (H))

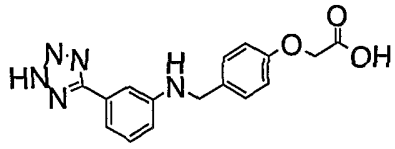
(4-Phenoxy-benzyl)-[3-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 344 (M+1); Rt = 5,00 min.

Example 662 (General procedure (H))

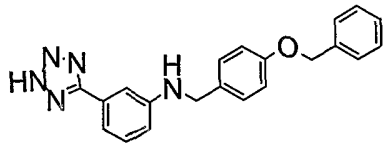
(4-{[3-(2*H*-Tetrazol-5-yl)phenylamino]methyl}phenoxy)acetic acid



HPLC-MS (Method D): m/z: 326 (M+1); Rt = 3,10 min.

Example 663 (General procedure (H))

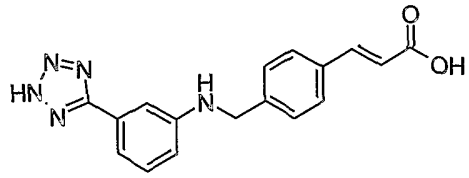
(4-Benzyloxybenzyl)-[3-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 358 (M+1); Rt = 4,97 min.

Example 664 (General procedure (H))

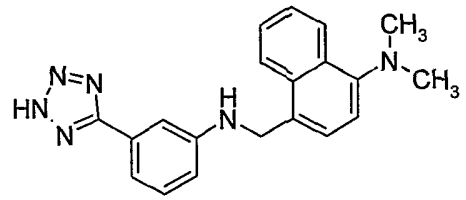
3-(4-{[3-(2*H*-Tetrazol-5-yl)phenylamino]methyl}phenyl)acrylic acid



HPLC-MS (Method D): m/z: 322 (M+1); Rt = 3,60 min.

Example 665 (General procedure (H))

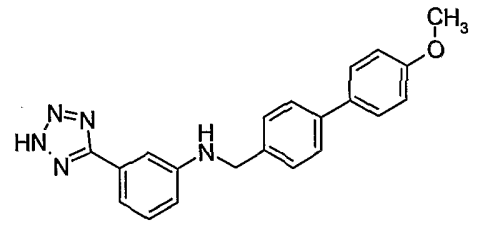
Dimethyl-(4-{[3-(2*H*-tetrazol-5-yl)phenylamino]methyl}naphthalen-1-yl)amine



HPLC-MS (Method D): m/z: 345 (M+1); Rt = 3,07 min.

Example 666 (General procedure (H))

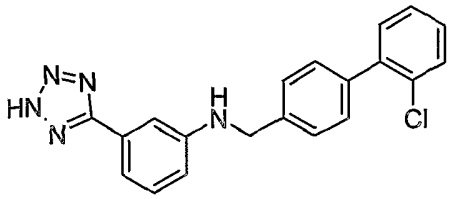
(4'-Methoxybiphenyl-4-ylmethyl)-[3-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 358 (M+1); Rt = 4,97 min.

Example 667 (General procedure (H))

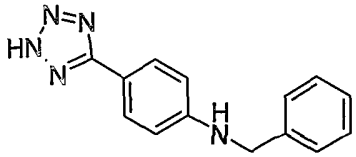
(2'-Chlorobiphenyl-4-ylmethyl)-[3-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 362 (M+1); Rt = 5,27 min.

Example 668 (General procedure (H))

Benzyl-[4-(2*H*-tetrazol-5-yl)phenyl]amine

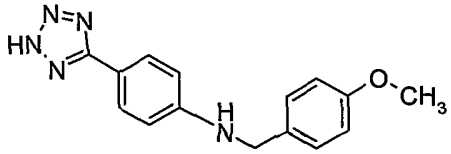


For preparation of starting material, see example 874.

HPLC-MS (Method D): m/z: 252 (M+1); Rt = 3,97 min.

Example 669 (General procedure (H))

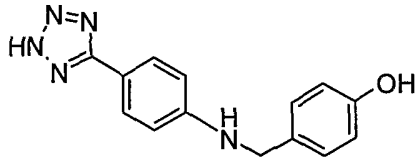
(4-Methoxybenzyl)-[4-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 282 (M+1); Rt = 3,94 min.

Example 670 (General procedure (H))

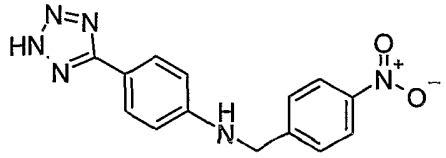
4-{[4-(2*H*-Tetrazol-5-yl)phenylamino]methyl}phenol



HPLC-MS (Method D): m/z: 268 (M+1); Rt = 3,14 min.

Example 671 (General procedure (H))

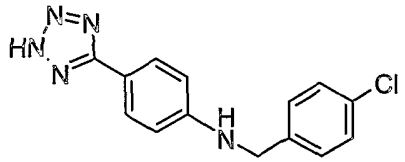
(4-Nitrobenzyl)-[4-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: (M+1); Rt = 3,94 min.

Example 672 (General procedure (H))

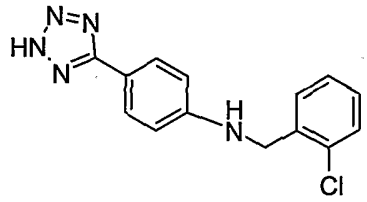
(4-Chlorobenzyl)-[4-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: (M+1); Rt = 4,47 min.

Example 673 (General procedure (H))

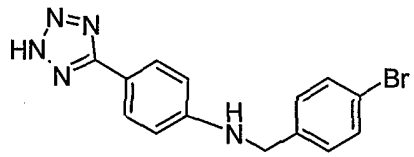
(2-Chlorobenzyl)-[4-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 286 (M+1); Rt = 4,37 min.

Example 674 (General procedure (H))

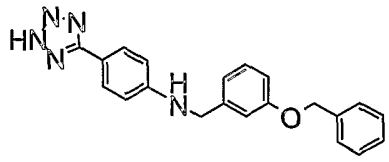
(4-Bromobenzyl)-[4-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 331 (M+1); Rt = 4,57 min.

Example 675 (General procedure (H))

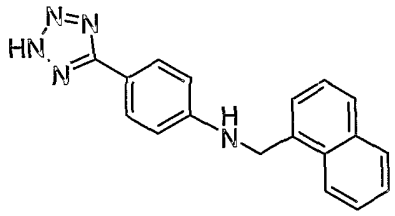
(3-Benzyloxybenzyl)-[4-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 358 (M+1); Rt = 5,07min.

Example 676 (General procedure (H))

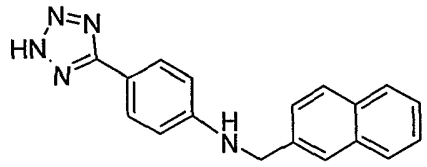
Naphthalen-1-ylmethyl-[4-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 302 (M+1); Rt = 4,70 min.

Example 677 (General procedure (H))

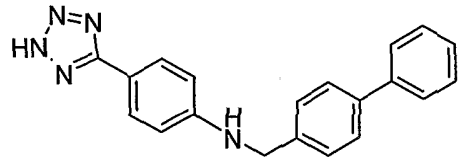
Naphthalen-2-ylmethyl-[4-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 302 (M+1); Rt = 4,70 min.

Example 678 (General procedure (H))

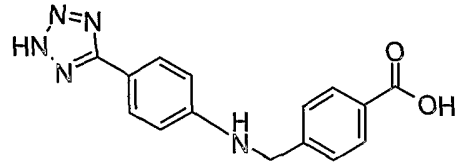
Biphenyl-4-ylmethyl-[4-(2H-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 328 (M+1); Rt = 5,07 min.

Example 679 (General procedure (H))

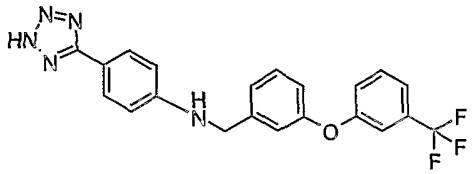
4-{[4-(2*H*-Tetrazol-5-yl)phenylamino]methyl}benzoic acid



HPLC-MS (Method D): m/z: 296 (M+1); Rt = 3,34 min.

Example 680 (General procedure (H))

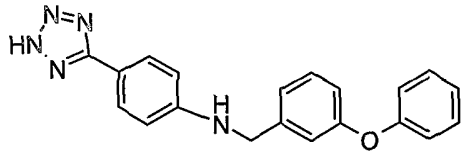
[4-(2*H*-Tetrazol-5-yl)phenyl]-[3-(3-trifluoromethylphenoxy)benzyl]amine



HPLC-MS (Method D): m/z: 412 (M+1); Rt = 5,54 min.

Example 681 (General procedure (H))

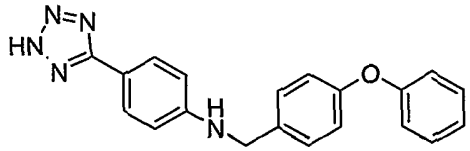
(3-Phenoxybenzyl)-[4-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 344 (M+1); Rt = 5,07 min.

Example 682 (General procedure (H))

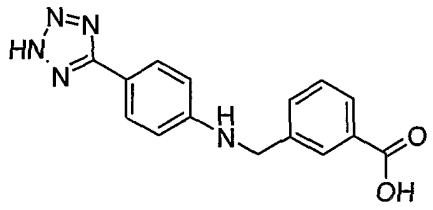
(4-Phenoxybenzyl)-[4-(2*H*-tetrazol-5-yl)-phenyl]-amine



HPLC-MS (Method D): m/z: 344 (M+1); Rt = 5,03 min.

Example 683 (General procedure (H))

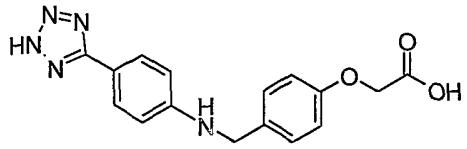
3-{[4-(2*H*-Tetrazol-5-yl)phenylamino]methyl}benzoic acid



HPLC-MS (Method D): m/z: 286 (M+1); Rt = 3,47 min.

Example 684 (General procedure (H))

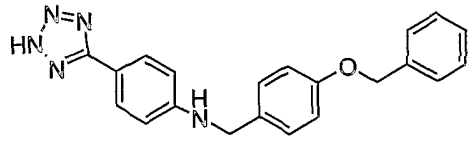
(4-{[4-(2*H*-Tetrazol-5-yl)phenylamino]methyl}phenoxy)acetic acid



HPLC-MS (Method D): m/z: 326 (M+1); Rt = 3,40 min.

Example 685 (General procedure (*H*))

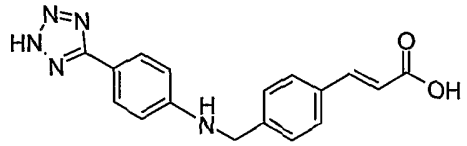
(4-Benzyloxybenzyl)-[4-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 358 (M+1); Rt = 5,14 min.

Example 686 (General procedure (H))

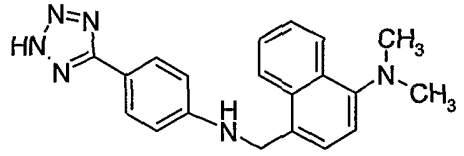
3-(4-{[4-(2*H*-Tetrazol-5-yl)phenylamino]methyl}phenyl)acrylic acid



HPLC-MS (Method D): m/z: 322 (M+1); Rt = 3,66 min.

Example 687 (General procedure (H))

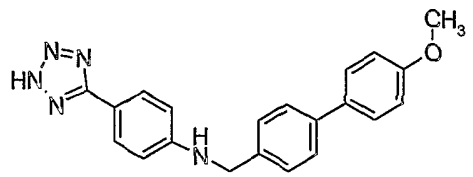
Dimethyl-(4-{[4-(2*H*-tetrazol-5-yl)phenylamino]methyl}naphthalen-1-yl)amine



HPLC-MS (Method D): m/z: 345 (M+1); Rt = 3,10 min.

Example 688 (General procedure (H))

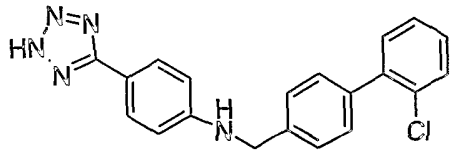
(4'-Methoxybiphenyl-4-ylmethyl)-[4-(2H-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 358 (M+1); Rt = 5,04 min.

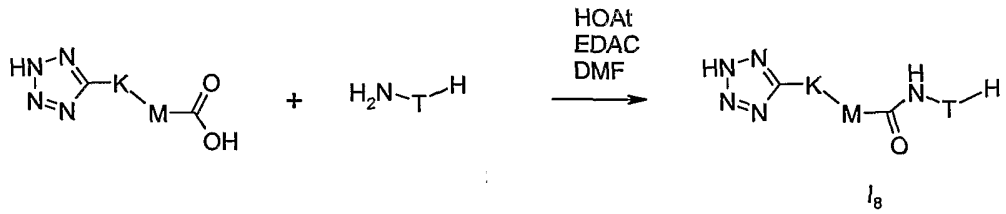
Example 689 (General procedure (H))

(2'-Chlorobiphenyl-4-ylmethyl)-[4-(2*H*-tetrazol-5-yl)-phenyl]-amine



HPLC-MS (Method D): m/z: 362 (M+1); Rt = 5,30 min.

General procedure (I) for preparation of compounds of general formula I_8:



I_8

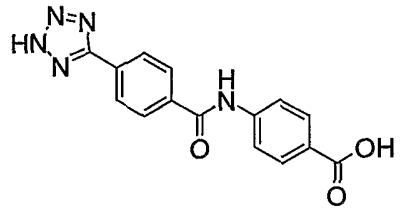
wherein K, M and T are as defined above.

This procedure is very similar to general procedure (A), the only difference being the carboxylic acid is containing a tetrazole moiety. When the acylation is complete, the product is isolated by extraction, filtration, chromatography or other methods known to those skilled in the art.

The general procedure (I) is further illustrated in the following example 690:

Example 690 (General procedure (I))

4-[4-(2*H*-Tetrazol-5-yl)benzoylamino]benzoic acid



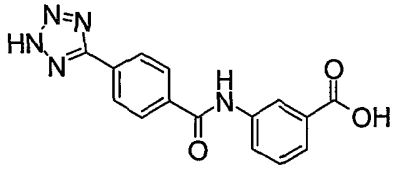
To a solution of 4-(2H-tetrazol-5-yl)benzoic acid (example 605, 4 mmol) and HOAt (4.2 mmol) in DMF (6 mL) was added 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (4.2 mmol) and the resulting mixture was stirred at room temperature for 1 hour. An alquot of this HOAt-ester solution (0.45 mL) was mixed with 0.25 mL of a solution of 4-aminobenzoic acid (1.2 mmol in 1 mL DMF). (Anilines as hydrochlorides can also be utilised,

a slight excess of triethylamine was added to the hydrochloride suspension in DMF prior to mixing with the HOAt-ester.) The resulting mixture was shaken for 3 days at room temperature. 1N hydrochloric acid (2 mL) was added and the mixture was shaken for 16 hours at room temperature. The solid was isolated by centrifugation (alternatively by filtration or extraction) and was washed with water (3 mL). Drying *in vacuo* at 40 °C for 2 days afforded the title compound.

HPLC-MS (Method D): m/z: 310 (M+1); Rt = 2.83 min.

Example 691 (General procedure (I))

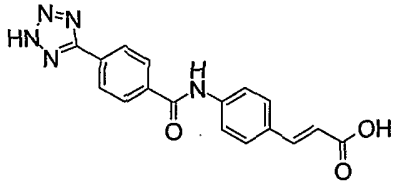
3-[4-(2*H*-Tetrazol-5-yl)benzoylamino]benzoic acid



HPLC-MS (Method D): m/z: 310 (M+1); Rt = 2.89 min.

Example 692 (General procedure (I))

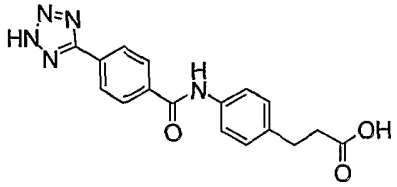
3-{4-[4-(2*H*-Tetrazol-5-yl)benzoylamino]phenyl}acrylic acid



HPLC-MS (Method D): m/z: 336 (M+1); Rt = 3.10 min.

Example 693 (General procedure (I))

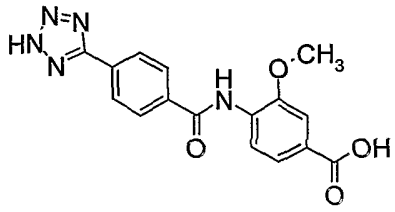
3-{4-[4-(2*H*-Tetrazol-5-yl)benzoylamino]phenyl}propionic acid



HPLC-MS (Method D): m/z: 338 (M+1); Rt = 2.97 min.

Example 694 (General procedure (I))

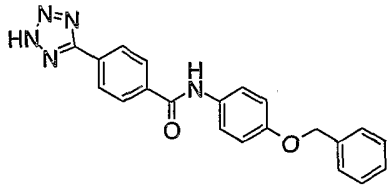
3-Methoxy-4-[4-(2*H*-tetrazol-5-yl)benzoylamino]benzoic acid



HPLC-MS (Method D): m/z: 340 (M+1); Rt = 3.03 min.

Example 695 (General procedure (I))

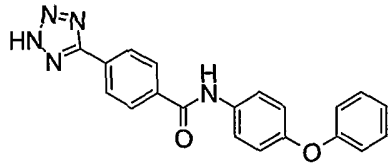
N-(4-Benzyloxyphenyl)-4-(2*H*-tetrazol-5-yl)benzamide



HPLC-MS (Method D): m/z: 372 (M+1); Rt = 4.47 min.

Example 696 (General procedure (I))

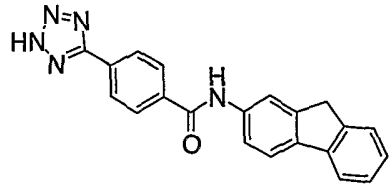
N-(4-Phenoxyphenyl)-4-(2*H*-tetrazol-5-yl)benzamide



HPLC-MS (Method D): m/z: 358 (M+1); Rt = 4.50 min.

Example 697 (General procedure (I))

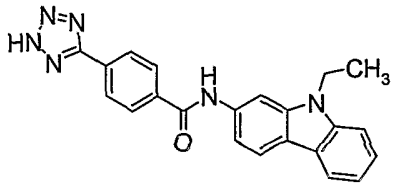
N-(9*H*-Fluoren-2-yl)-4-(2*H*-tetrazol-5-yl)benzamide



HPLC-MS (Method D): m/z: 354 (M+1); Rt = 4.60 min.

Example 698 (General procedure (I))

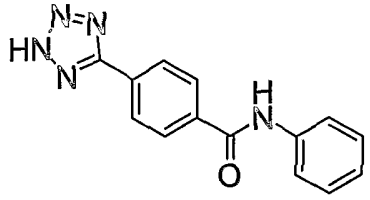
N-(9-Ethyl-9*H*-carbazol-2-yl)-4-(2*H*-tetrazol-5-yl)benzamide



HPLC-MS (Method D): m/z: 383 (M+1); Rt = 4.60 min.

Example 699 (General procedure (I))

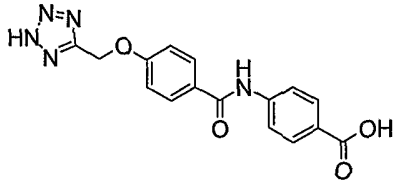
N-Phenyl-4-(2*H*-tetrazol-5-yl)benzamide



HPLC-MS (Method D): m/z: 266 (M+1); Rt = 3.23 min.

Example 700 (General procedure (I))

4-[4-(2*H*-Tetrazol-5-ylmethoxy)benzoylamino]benzoic acid

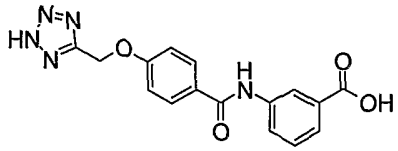


The starting material was prepared as described in example 592.

HPLC-MS (Method D): m/z: 340 (M+1); Rt = 2.83 min.

Example 701 (General procedure (I))

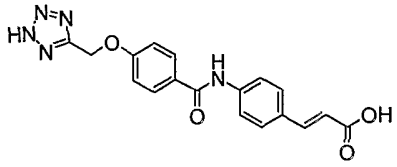
3-[4-(2*H*-Tetrazol-5-ylmethoxy)benzoylamino]benzoic acid



HPLC-MS (Method D): m/z: 340 (M+1); Rt = 2.90 min.

Example 702 (General procedure (I))

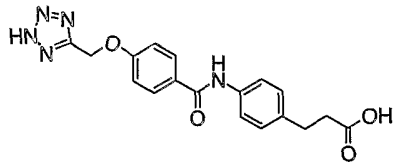
3-{4-[4-(2*H*-Tetrazol-5-ylmethoxy)benzoylamino]phenyl}acrylic acid



HPLC-MS (Method D): m/z: 366 (M+1); Rt = 3.07 min.

Example 703 (General procedure (I))

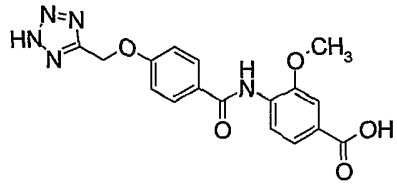
3-{4-[4-(2*H*-Tetrazol-5-ylmethoxy)benzoylamino]phenyl}propionic acid



HPLC-MS (Method D): m/z: 368 (M+1); Rt = 2.97 min.

Example 704 (General procedure (I))

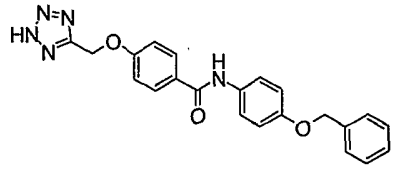
3-Methoxy-4-[4-(2*H*-tetrazol-5-ylmethoxy)benzoylamino]benzoic acid



HPLC-MS (Method D): m/z: 370 (M+1); Rt = 3.07 min.

Example 705 (General procedure (I))

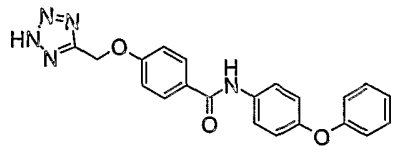
N-(4-Benzyloxyphenyl)-4-(2*H*-tetrazol-5-ylmethoxy)benzamide



HPLC-MS (Method D): m/z: 402 (M+1); Rt = 4.43 min.

Example 706 (General procedure (I))

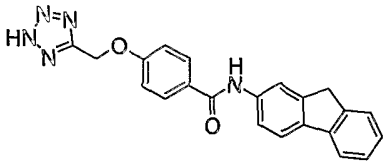
N-(4-Phenoxyphenyl)-4-(2*H*-tetrazol-5-ylmethoxy)benzamide



HPLC-MS (Method D): m/z: 388 (M+1); Rt = 4.50 min.

Example 707 (General procedure (I))

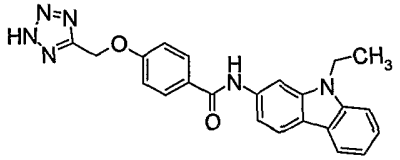
N-(9H-Fluoren-2-yl)-4-(2*H*-tetrazol-5-ylmethoxy)benzamide



HPLC-MS (Method D): m/z: 384 (M+1); Rt = 4.57 min.

Example 708 (General procedure (I))

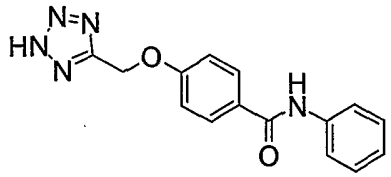
N-(9-Ethyl-9H-carbazol-2-yl)-4-(2*H*-tetrazol-5-ylmethoxy)benzamide



HPLC-MS (Method D): m/z: 413 (M+1); Rt = 4.57 min.

Example 709 (General procedure (I))

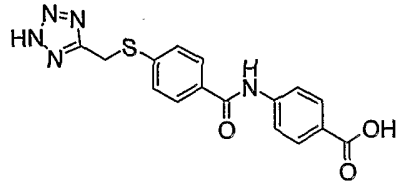
N-Phenyl-4-(2*H*-tetrazol-5-ylmethoxy)benzamide



HPLC-MS (Method D): m/z: 296 (M+1); Rt = 3.23 min.

Example 710 (General procedure (I))

4-[4-(2*H*-Tetrazol-5-ylmethylsulfanyl)benzoylamino]benzoic acid

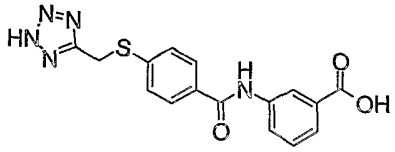


The starting material was prepared as described in example 593.

HPLC-MS (Method D): m/z: 356 (M+1); Rt = 2.93 min.

Example 711 (General procedure (I))

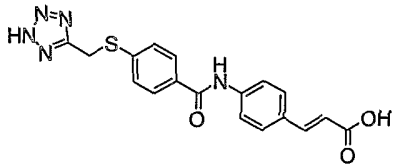
3-[4-(2*H*-Tetrazol-5-ylmethylsulfanyl)benzoylamino]benzoic acid



HPLC-MS (Method D): m/z: 356 (M+1); Rt = 3.00 min.

Example 712 (General procedure (I))

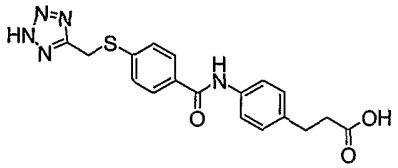
3-{4-[4-(2*H*-Tetrazol-5-ylmethylsulfanyl)benzoylamino]phenyl}acrylic acid



HPLC-MS (Method D): m/z: 382 (M+1); Rt = 3.26 min.

Example 713 (General procedure (I))

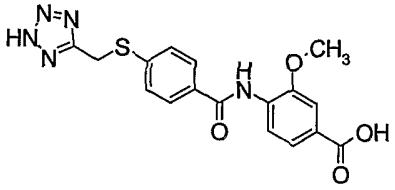
3-{4-[4-(2*H*-Tetrazol-5-ylmethylsulfanyl)benzoylamino]phenyl}propionic acid



HPLC-MS (Method D): m/z: 384 (M+1); Rt = 3.10 min.

Example 714 (General procedure (I))

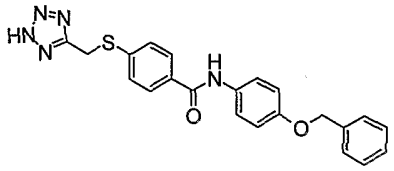
3-Methoxy-4-[4-(2*H*-tetrazol-5-ylmethylsulfanyl)benzoylamino]benzoic acid



HPLC-MS (Method D): m/z: 386 (M+1); Rt = 3.20 min.

Example 715 (General procedure (I))

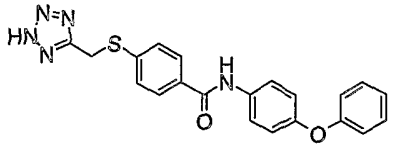
N-(4-Benzyloxyphenyl)-4-(2*H*-tetrazol-5-ylmethylsulfanyl)benzamide



HPLC-MS (Method D): m/z: 418 (M+1); Rt = 4.57 min.

Example 716 (General procedure (I))

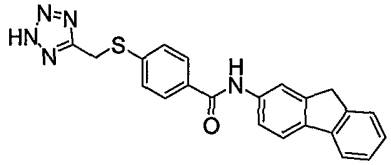
N-(4-Phenoxyphenyl)-4-(2*H*-tetrazol-5-ylmethylsulfanyl)benzamide



HPLC-MS (Method D): m/z: 404 (M+1); Rt = 4.60 min.

Example 717 (General procedure (I))

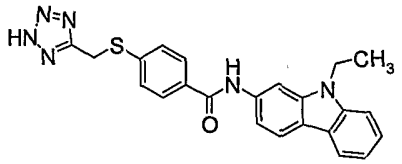
N-(9*H*-Fluoren-2-yl)-4-(2*H*-tetrazol-5-ylmethylsulfanyl)benzamide



HPLC-MS (Method D): m/z: 400 (M+1); Rt = 4.67 min.

Example 718 (General procedure (I))

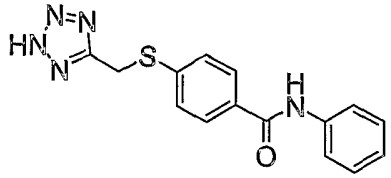
N-(9-Ethyl-9*H*-carbazol-2-yl)-4-(2*H*-tetrazol-5-ylmethylsulfanyl)benzamide



HPLC-MS (Method D): m/z: 429 (M+1); Rt = 4.67 min.

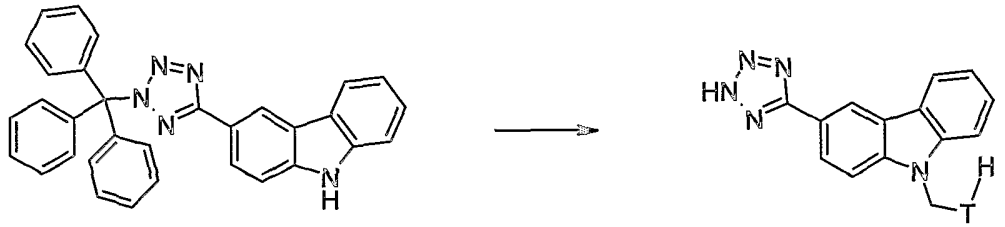
Example 719 (General procedure (I))

N-Phenyl-4-(2*H*-tetrazol-5-ylmethylsulfanyl)benzamide



HPLC-MS (Method D): m/z: 312 (M+1); Rt = 3.40 min.

General procedure (J) for solution phase preparation of amides of general formula I_9:



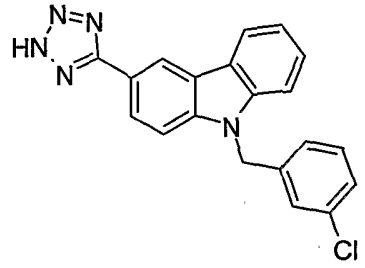
I_9

wherein *T is as defined above.*

This general procedure (J) is further illustrated in the following example.

Example 720 (General procedure (J)).

9-(3-Chlorobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



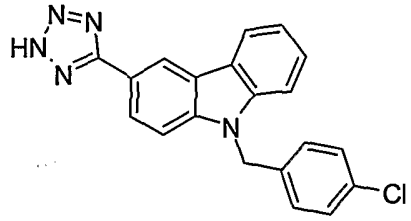
3-(2*H*-Tetrazol-5-yl)-9*H*-carbazole (example 594, 17 g, 72.26 mmol) was dissolved in *N,N*-dimethylformamide (150 mL). Triphenylmethyl chloride (21.153 g, 75.88 mmol) and triethylamine (20.14 mL, 14.62 g, 144.50 mmol) were added consecutively. The reaction mixture was stirred for 18 hours at room temperature, poured into water (1.5 L) and stirred for an additional 1 hour. The crude product was filtered off and dissolved in dichloromethane (500 mL). The organic phase was washed with water (2 x 250 mL) and dried with magnesium sulfate (1 h). Filtration followed by concentration yielded a solid which was triturated in heptanes (200 mL). Filtration furnished 3-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]-9*H*-carbazole (31.5 g) which was used without further purification.

^{1}H-NMR ($CDCl_3$): δ 8.87 (1H, d), 8.28 (1H, bs), 8.22 (1H, dd), 8.13 (1H, d), 7.49 (1H, d), 7.47-7.19 (18H, m); HPLC-MS (Method C): m/z: 243 (triphenylmethyl); Rt = 5.72 min.

3-[2-(Triphenylmethyl)-2*H*-tetrazol-5-yl]-9*H*-carbazole (200 mg, 0.42 mmol) was dissolved in methyl sulfoxide (1.5 mL). Sodium hydride (34 mg, 60 %, 0.85 mmol) was added, and the resulting suspension was stirred for 30 min at room temperature. 3-Chlorobenzyl chloride (85 µL, 108 mg, 0.67 mmol) was added, and the stirring was continued at 40 °C for 18 hours. The reaction mixture was cooled to ambient temperature and poured into 0.1 N hydrochloric acid (aq.) (15 mL). The precipitated solid was filtered off and washed with water (3 x 10 mL) to furnish 9-(3-chlorobenzyl)-3-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]-9*H*-carbazole, which was dissolved in a mixture of tetrahydrofuran and 6 N hydrochloric acid (aq.) (9:1) (10 mL) and stirred at room temperature for 18 hours. The reaction mixture was poured into water (100 mL). The solid was filtered off and rinsed with water (3 x 10 mL) and dichloromethane (3 x 10 mL) to yield the title compound (127 mg). No further purification was necessary. ^{1}*H-NMR (DMSO-d$_6$)*: δ *8.89 (1H, d), 8.29 (1H, d), 8.12 (1H, dd),* 7.90 (1H, d), 7.72 (1H, d), 7.53 (1H, t), 7.36-7.27 (4H, m), 7.08 (1H, bt), 5.78 (2H, s); HPLC-MS (Method B): m/z: 360 (M+1); Rt = 5.07 min.

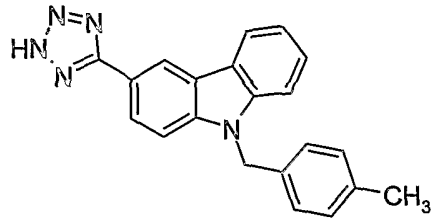
The compounds in the following examples were prepared in a similar fashion. Optionally, the compounds can be further purified by recrystallization from e.g. aqueous sodium hydroxide (1 N) or by chromatography.

Example 721 (General Procedure (J)).
9-(4-Chlorobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 360 (M+1); Rt = 4.31 min.

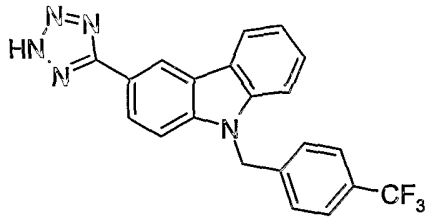
Example 722 (General Procedure (J)).
9-(4-Methylbenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 340 (M+1); Rt = 4.26 min.

Example 723 (General Procedure (J)).

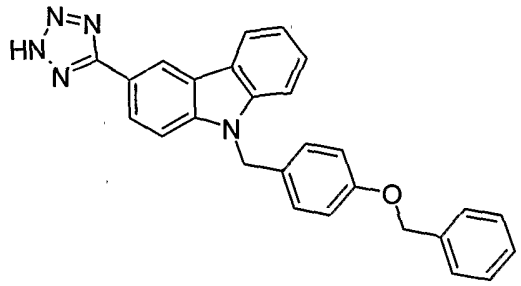
3-(2*H*-Tetrazol-5-yl)-9-(4-trifluoromethylbenzyl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 394 (M+1); Rt = 4.40 min.

Example 724 (General Procedure (J)).

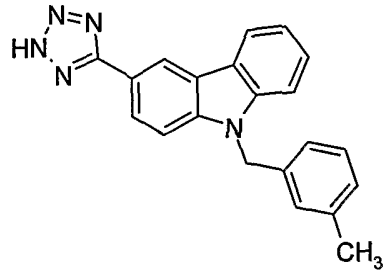
9-(4-Benzyloxybenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 432 (M+1); Rt = 4.70 min.

Example 725 (General Procedure (J)).

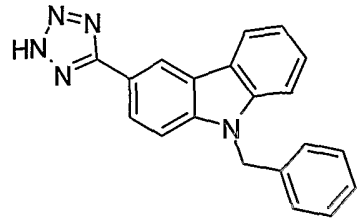
9-(3-Methylbenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 340 (M+1); Rt = 4.25 min.

Example 726 (General Procedure (J)).

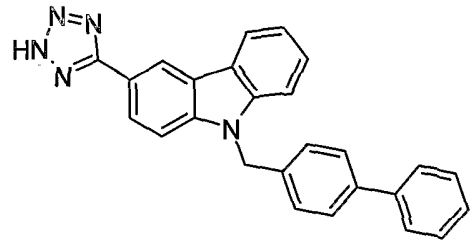
9-Benzyl-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



^{1}H-NMR (DMSO-d_6): δ 8.91 (1H, dd), 8.30 (1H, d), 8.13 (1H, dd), 7.90 (1H, d), 7.73 (1H, d), 7.53 (1H, t), 7.36-7.20 (6H, m), 5.77 (2H, s).

Example 727 (General Procedure (J)).

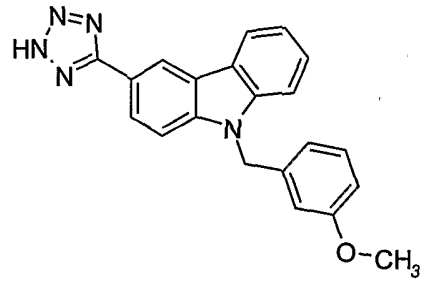
9-(4-Phenylbenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



^{1}H-NMR (DMSO-d_6): δ 8.94 (1H, s), 8.33 (1H, d), 8.17 (1H, dd), 7.95 (1H, d), 7.77 (1H, d), 7.61-7.27 (11H, m), 5.82 (2H, s).

Example 728 (General Procedure (J)).

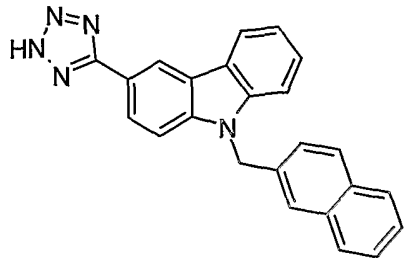
9-(3-Methoxybenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 356 (M+1); Rt = 3.99 min.

Example 729 (General Procedure (J)).

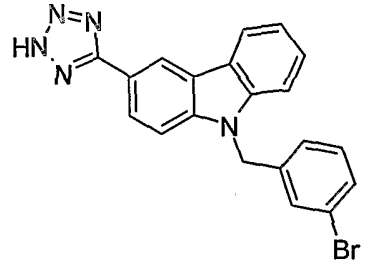
9-(Naphthalen-2-ylmethyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 376 (M+1); Rt = 4.48 min.

Example 730 (General Procedure (J)).

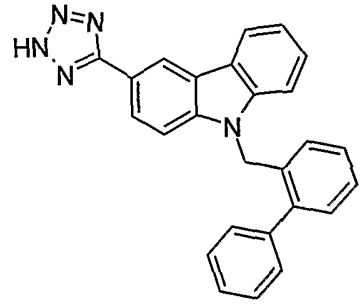
9-(3-Bromobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 404 (M+1); Rt = 4.33 min.

Example 731 (General Procedure (J)).

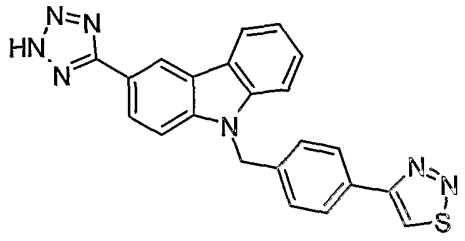
9-(Biphenyl-2-ylmethyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 402 (M+1); Rt = 4.80 min.

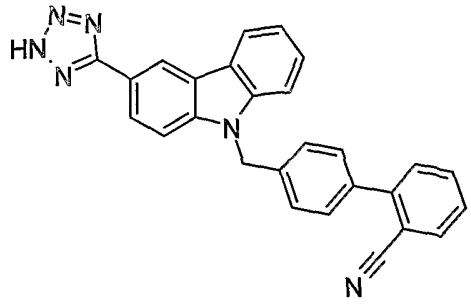
Example 732 (General Procedure (J)).

3-(2*H*-Tetrazol-5-yl)-9-[4-(1,2,3-thiadiazol-4-yl)benzyl]-9*H*-carbazole



Example 733 (General Procedure (J)).

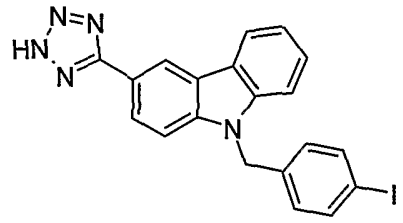
9-(2'-Cyanobiphenyl-4-ylmethyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



^{1}H-NMR (DMSO-d_6): δ 8.91 (1H, d), 8.31 (1H, d), 8.13 (1H, dd), 7.95 (1H, d), 7.92 (1H, d), 7.78 (1H, d), 7.75 (1H, dt), 7.60-7.47 (5H, m), 7.38-7.28 (3H, m), 5.86 (2H, s); HPLC-MS (*Method C*): *m/z: 427 (M+1)*; Rt = *4.38 min.*

Example 734 (General Procedure (J)).

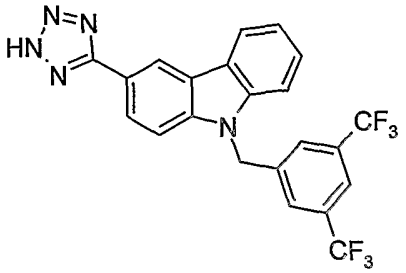
9-(4-Iodobenzyl)-3-(2H-tetrazol-5-yl)-9H-carbazole



HPLC-MS (Method C): m/z: 452 (M+1); Rt = 4.37 min.

Example 735 (General Procedure (J)).

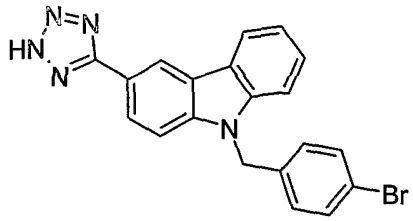
9-(3,5-Bis(trifluoromethyl)benzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 462 (M+1); Rt = 4.70 min.

Example 736 (General Procedure (J)).

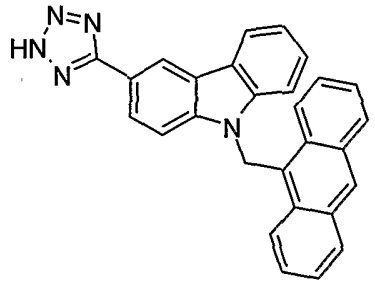
9-(4-Bromobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



^{1}H-NMR (DMSO-d_6): δ 8.89 (1H, d), 8.29 (1H, d), 8.11 (1H, dd), 7.88 (1H, d), 7.70 (1H, d), 7.52 (1H, t), 7.49 (2H, d), 7.31 (1H, t), 7.14 (2H, d), 5.74 (2H, s); HPLC-MS (Method C): m/z: 404 (M+1); Rt = 4.40 min.

Example 737 (General Procedure (J)).

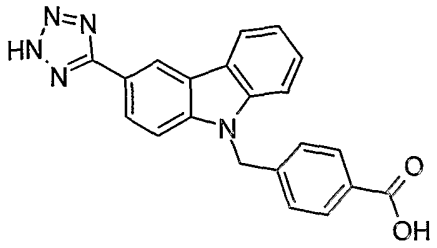
9-(Anthracen-9-ylmethyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 426 (M+1); Rt = 4.78 min.

Example 738 (General Procedure (J)).

9-(4-Carboxybenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole

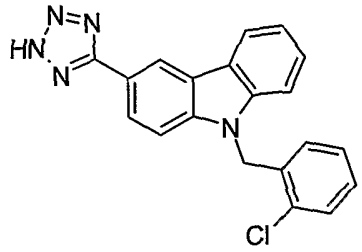


3.6 fold excess sodium hydride was used.

^{1}H-NMR (DMSO-d_6): δ 12.89 (1H, bs), 8.89 (1H, d), 8.30 (1H, d), 8.10 (1H, dd), 7.87 (1H, d), 7.86 (2H, d), 7.68 (1H, d), 7.51 (1H, t), 7.32 (1H, t), 7.27 (2H, d), 5.84 (2H, s); HPLC-MS (Method C): m/z: 370 (M+1); Rt = 3.37 min.

Example 739 (General Procedure (J)).

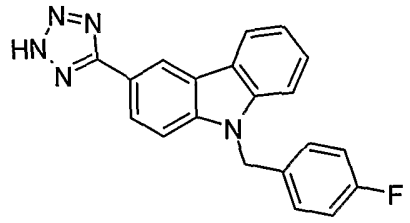
9-(2-Chlorobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method B): m/z: 360 (M+1); Rt = 5.30 min.

Example 740 (General Procedure (J)).

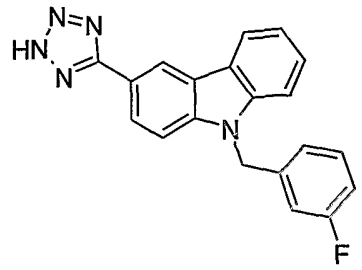
9-(4-Fluorobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



^{1}H-NMR (DMSO-d_6): δ 8.88 (1H, d), 8.28 (1H, d), 8.10 (1H, dd), 7.89 (1H, d), 7.72 (1H, d), 7.52 (1H, t), 7.31 (1H, t), 7.31-7.08 (4H, m), 5.74 (2H, s); HPLC-MS (Method C): m/z: 344 (M+1); Rt = 4.10 min.

Example 741 (General Procedure (J)).

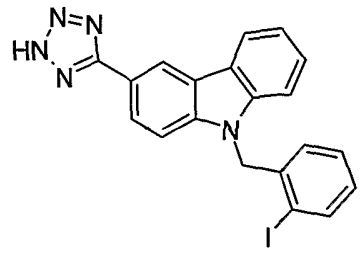
9-(3-Fluorobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



^{1}H-NMR (DMSO-d_6): δ 8.89 (1H, d), 8.29 (1H, d), 8.12 (1H, dd), 7.90 (1H, d), 7.72 (1H, d), 7.53 (1H, t), 7.37-7.27 (2H, m), 7.12-7.02 (2H, m), 6.97 (1H, d), 5.78 (2H, s); HPLC-MS (Method C): m/z: 344 (M+1); Rt = 4.10 min.

Example 742 (General Procedure (J)).

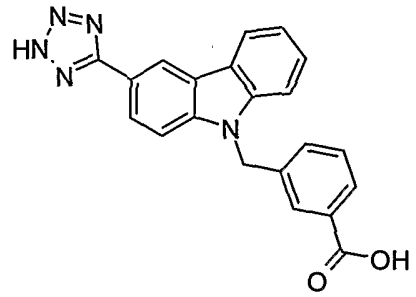
9-(2-Iodobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 452 (M+1); Rt = 4.58 min.

Example 743 (General Procedure (J)).

9-(3-Carboxybenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole

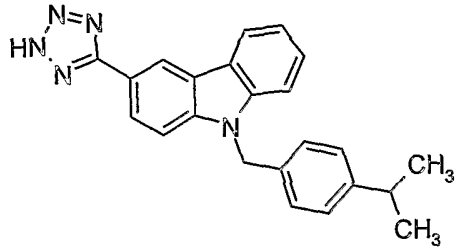


3.6 fold excess sodium hydride was used.

^{1}H-NMR (DMSO-d_6): δ 12.97 (1H, bs), 8.90 (1H, bs), 8.30 (1H, d), 8.12 (1H, bd), 7.89 (1H, d), 7.82 (1H, m), 7.77 (1H, bs), 7.71 (1H, d), 7.53 (1H, t), 7.46-7.41 (2H, m), 7.32 (1H, t), 5.84 (2H, s); HPLC-MS (Method C): m/z: 370 (M+1); Rt = 3.35 min.

Example 744 (General Procedure (J)).

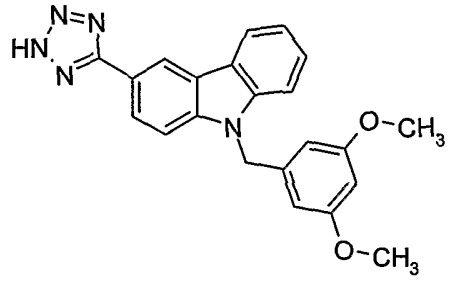
9-[4-(2-Propyl)benzyl]-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



^{1}H-NMR (DMSO-d_6): δ 8.87 (1H, d), 8.27 (1H, d), 8.10 (1H, dd), 7.87 (1H, d), 7.71 (1H, d), 7.51 (1H, t), 7.31 (1H, t), 7.15 (2H, d), 7.12 (2H, d), 5.69 (2H, s), 2.80 (1H, sept), 1.12 (6H, d); HPLC-MS (Method C): m/z: 368 (M+1); Rt = 4.73 min.

Example 745 (General Procedure (J)).

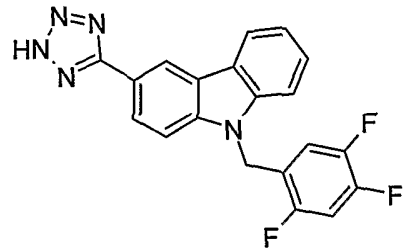
9-(3,5-Dimethoxybenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 386 (M+1); Rt = 4.03 min.

Example 746 (General Procedure (J)).

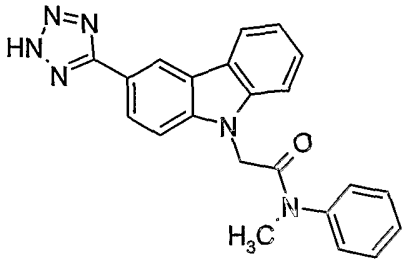
3-(2*H*-Tetrazol-5-yl)-9-(2,4,5-trifluorobenzyl)-9*H*-carbazole



HPLC-MS (Method B): m/z: 380 (M+1); Rt = 5.00 min.

Example 747 (General Procedure (J)).

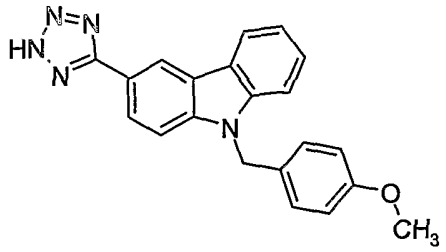
N-Methyl-*N*-phenyl-2-[3-(2*H*-tetrazol-5-yl)carbazol-9-yl]acetamide



HPLC-MS (Method B): m/z: 383 (M+1); Rt = 4.30 min.

Example 748 (General Procedure (J)).

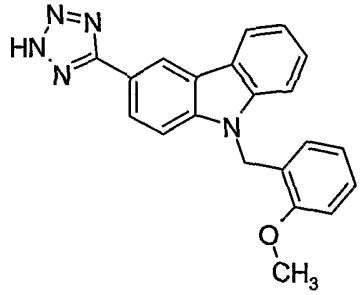
9-(4-Methoxybenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



^{1}H-NMR (DMSO-d_6): δ 8.86 (1H, d), 8.26 (1H, d), 8.10 (1H, dd), 7.90 (1H, d), 7.73 (1H, d), 7.51 (1H, t), 7.30 (1H, t), 7.18 (2H, d), 6.84 (2H, d), 5.66 (2H, s), 3.67 (3H, s); HPLC-MS (Method B): m/z: 356 (M+1); Rt = 4.73 min.

Example 749 (General Procedure (J)).

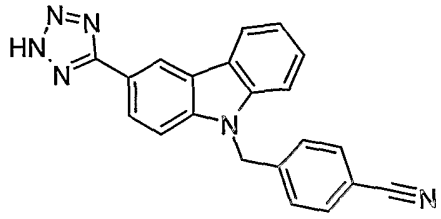
9-(2-Methoxybenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



^{1}H-NMR (DMSO-d_6): δ 8.87 (1H, d), 8.27 (1H, d), 8.09 (1H, dd), 7.77 (1H, d), 7.60 (1H, d), 7.49 (1H, t), 7.29 (1H, t), 7.23 (1H, bt), 7.07 (1H, bd), 6.74 (1H, bt), 6.61 (1H, bd), 5.65 (2H, s), 3.88 (3H, s); HPLC-MS (Method B): m/z: 356 (M+1); Rt = 4.97 min.

Example 750 (General Procedure (J)).

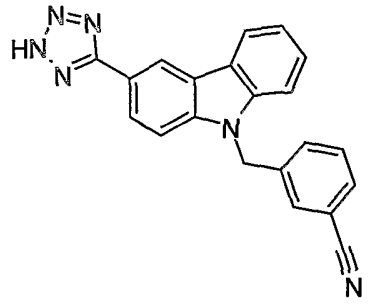
9-(4-Cyanobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 351 (M+1); Rt = 3.74 min.

Example 751 (General Procedure (J)).

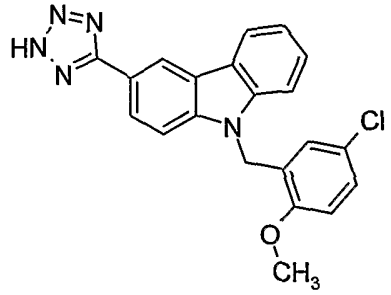
9-(3-Cyanobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 351 (M+1); Rt = 3.73 min.

Example 752 (General Procedure (J)).

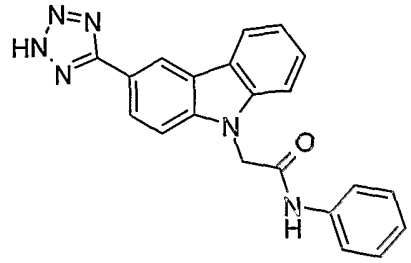
9-(5-Chloro-2-methoxybenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



^{1}H-NMR (DMSO-d_6): δ 8.87 (1H, d), 8.35 (1H, d), 8.10 (1H, dd), 7.73 (1H, d), 7.59 (1H, d), 7.49 (1H, t), 7.29 (1H, t), 7.27 (1H, dd), 7.11 (1H, d), 6.51 (1H, d), 5.63 (2H, s), 3.88 (3H, s); HPLC-MS (Method C): m/z: 390 (M+1); Rt = 4.37 min.

Example 753 (General Procedure (J)).

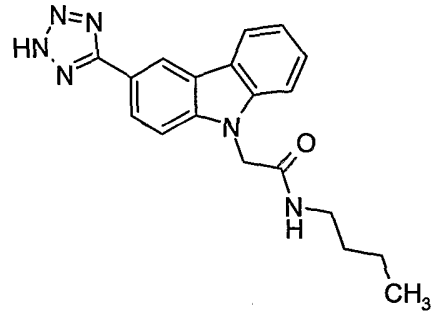
N-Phenyl-2-[3-(2*H*-tetrazol-5-yl)carbazol-9-yl]acetamide



^{1}H-NMR (DMSO-d_6): δ 10.54 (1H, s), 8.87 (1H, bs), 8.27 (1H, d), 8.12 (1H, bd), 7.83 (1H, d), 7.66 (1H, d), 7.61 (2H, d), 7.53 (1H,t), 7.32 (1H, t), 7.32 (2H, t), 7.07 (1H, t), 5.36 (2H, s); HPLC-MS (Method C): m/z: 369 (M+1); Rt = 3.44 min.

Example 754 (General Procedure (J)).

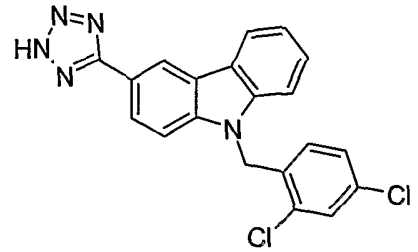
N-Butyl-2-[3-(2*H*-tetrazol-5-yl)carbazol-9-yl]acetamide



^{1}H-NMR (DMSO-d_6): δ 8.85 (1H, d), 8.31 (1H, t), 8.25 (1H, d), 8.10 (1H, dd), 7.75 (1H, d), 7.58 (1H, d), 7.52 (1H, t), 7.30 (1H, t), 5.09 (2H, s), 3.11 (2H, q), 1.42 (2H, quint), 1.30 (2H, sext), 0.87 (3H, t); HPLC-MS (Method C): m/z: 349 (M+1); Rt = 3.20 min.

Example 755 (General Procedure (J)).

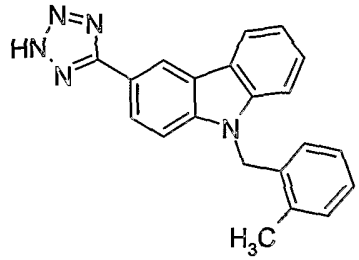
9-(2,4-Dichlorobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



^{1}H-NMR (DMSO-d_6): δ 8.92 (1H, d), 8.32 (1H, d), 8.09 (1H, dd), 7.76 (1H, d), 7.74 (1H, d), 7.58 (1H, d), 7.51 (1H, t), 7.33 (1H, t), 7.23 (1H, dd), 6.42 (1H, d), 5.80 (2H, s); HPLC-MS (Method B): m/z: 394 (M+1); Rt = 5.87 min.

Example 756 (General Procedure (J)).

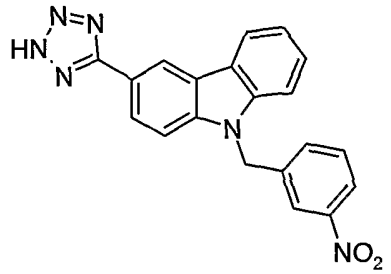
9-(2-Methylbenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



^{1}H-NMR (DMSO-d_6): δ 8.92 (1H, d), 8.32 (1H, d), 8.08 (1H, dd), 7.72 (1H, d), 7.55 (1H, d), 7.48 (1H, t), 7.32 (1H, t), 7.26 (1H, d), 7.12 (1H, t), 6.92 (1H, t), 6.17 (1H, d), 5.73 (2H, s), 2.46 (3H, s); HPLC-MS (Method B): m/z: 340 (M+1); Rt = 5.30 min.

Example 757 (General Procedure (J)).

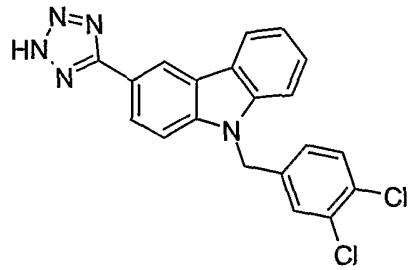
9-(3-Nitrobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 371 (M+1); Rt = 3.78 min.

Example 758 (General Procedure (J)).

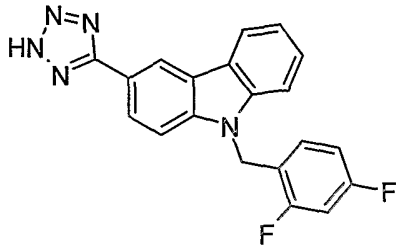
9-(3,4-Dichlorobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method B): m/z: 394 (M+1); Rt = 5.62 min.

Example 759 (General Procedure (J)).

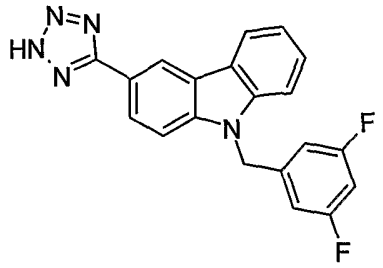
9-(2,4-Difluorobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



^{1}H-NMR (DMSO-d_6): δ 8.89 (1H, d), 8.29 (1H, d), 8.11 (1H, dd), 7.88 (1H, d), 7.69 (1H, d), 7.52 (1H, t), 7.36-7.24 (2H, m), 7.06-6.91 (2H, m), 5.78 (2H, s); HPLC-MS (Method B): m/z: 362 (M+1); Rt = 5.17 min.

Example 760 (General Procedure (J)).

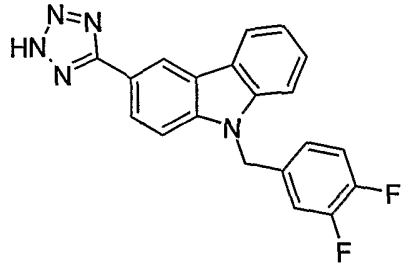
9-(3,5-Difluorobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



^{1}H-NMR (DMSO-d_6): δ 8.90 (1H, bs), 8.31 (1H, d), 8.13 (1H, bd), 7.90 (1H, d), 7.73 (1H, d), 7.54 (1H, t), 7.34 (1H, t), 7.14 (1H, t), 6.87 (2H, bd), 5.80 (2H, s); HPLC-MS (Method B): m/z: 362 (M+1); Rt = 5.17 min.

Example 761 (General Procedure (J)).

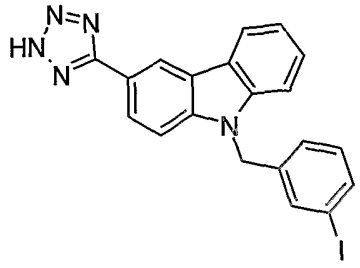
9-(3,4-Difluorobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



^{1}H-NMR (DMSO-d_6): δ 8.89 (1H, bs), 8.29 (1H, d), 8.12 (1H, bd), 7.92 (1H, d), 7.74 (1H, d), 7.54 (1H, t), 7.42-7.25 (3H, m), 6.97 (1H, bm), 5.75 (2H, s); HPLC-MS (Method B): m/z: 362 (M+1); Rt = 5.17 min.

Example 762 (General Procedure (J)).

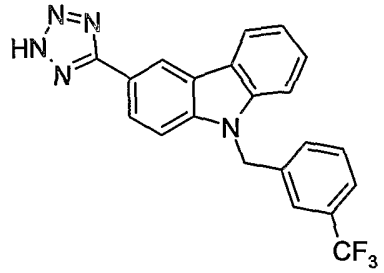
9-(3-Iodobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method B): m/z: 452 (M+1); Rt = 5.50 min.

Example 763 (General Procedure (J)).

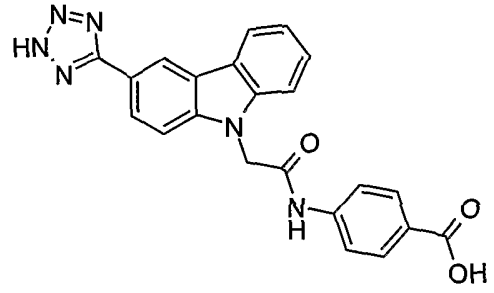
3-(2*H*-Tetrazol-5-yl)-9-[3-(trifluoromethyl)benzyl]-9*H*-carbazole



^{1}H-NMR (DMSO-d_6): δ 8.89 (1H, d), 8.30 (1H, d), 8.11 (1H, dd), 7.90 (1H, d), 7.72 (1H, d), 7.67 (1H, bs), 7.62 (1H, bd), 7.53 (1H, t), 7.50 (1H, bt), 7.33 (1H, bd), 7.32 (1H, t), 5.87 (2H, s); HPLC-MS (Method B): m/z: 394 (M+1); Rt = 5.40 min.

Example 764 (General Procedure (J)).

N-(4-Carboxyphenyl)-2-[3-(2*H*-tetrazol-5-yl)carbazol-9-yl]acetamide

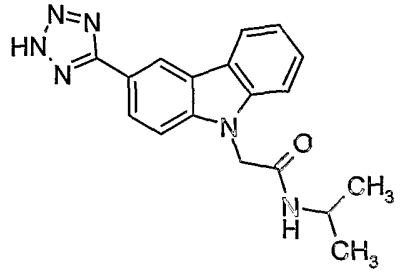


3.6 fold excess sodium hydride was used.

HPLC-MS (Method B): m/z: 413 (M+1); Rt = 3.92 min.

Example 765 (General Procedure (J)).

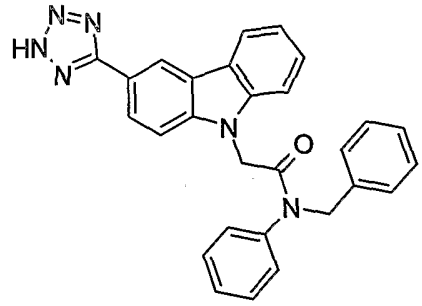
N-(2-Propyl)-2-[3-(2*H*-tetrazol-5-yl)carbazol-9-yl]acetamide



HPLC-MS (Method B): m/z: 335 (M+1); Rt = 3.70 min.

Example 766 (General Procedure (J)).

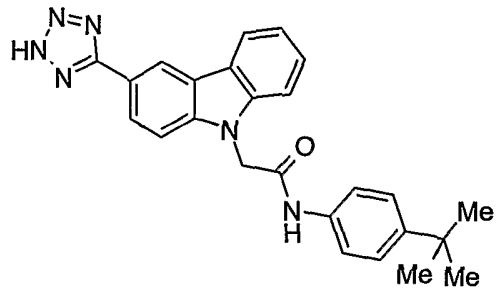
N-Benzyl-*N*-phenyl-2-[3-(2*H*-tetrazol-5-yl)carbazol-9-yl]acetamide



HPLC-MS (Method B): m/z: 459 (M+1); Rt = 5.37 min.

Example 767 (General Procedure (J)).

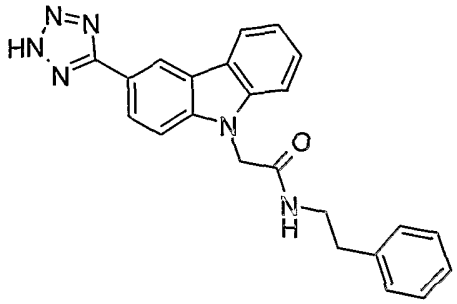
N-[4-(2-Methyl-2-propyl)phenyl]-2-[3-(2*H*-tetrazol-5-yl)carbazol-9-yl]acetamide



HPLC-MS (Method B): m/z: 425 (M+1); Rt = 5.35 min.

Example 768 (General Procedure (J)).

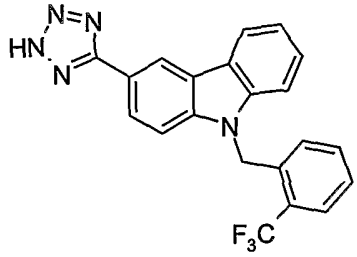
N-Phenethyl-2-[3-(2*H*-tetrazol-5-yl)carbazol-9-yl]acetamide



HPLC-MS (Method C): m/z: 397 (M+1); Rt = 3.43 min.

Example 769 (General Procedure (J)).

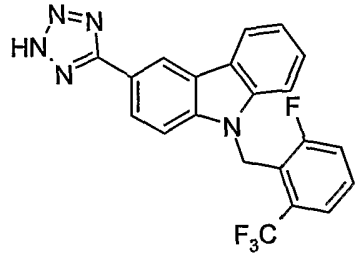
3-(2*H*-Tetrazol-5-yl)-9-[2-(trifluoromethyl)benzyl]-9*H*-carbazole



HPLC-MS (Method C): m/z: 394 (M+1); Rt = 4.44 min.

Example 770 (General Procedure (J)).

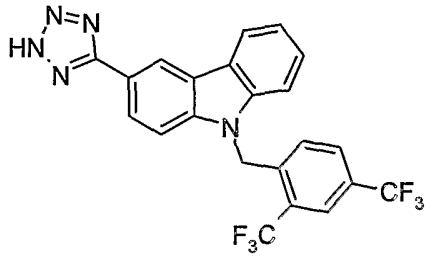
9-[2-Fluoro-6-(trifluoromethyl)benzyl]-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 412 (M+1); Rt = 4.21 min.

Example 771 (General Procedure (J)).

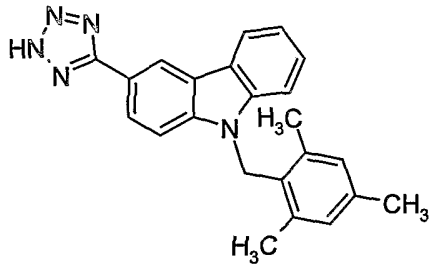
9-[2,4-Bis(trifluoromethyl)benzyl)]-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 462 (M+1); Rt = 4.82 min.

Example 772 (General Procedure (J)).

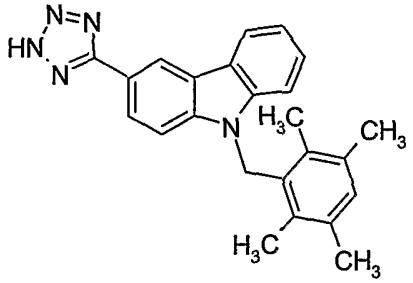
3-(2*H*-Tetrazol-5-yl)-9-(2,4,6-trimethylbenzyl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 368 (M+1); Rt = 4.59 min.

Example 773 (General Procedure (J)).

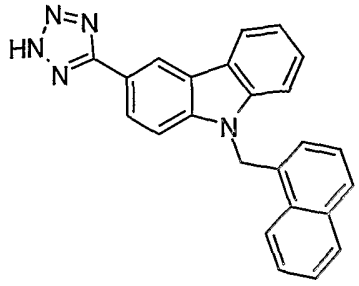
9-(2,3,5,6-Tetramethylbenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 382 (M+1); Rt = 4.47 min.

Example 774 (General Procedure (J)).

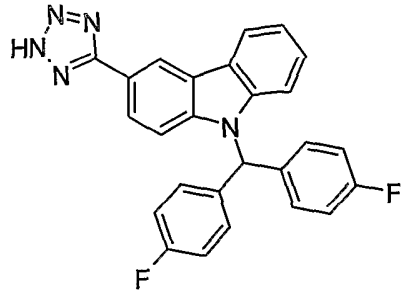
9-[(Naphthalen-1-yl)methyl]-3-(2H-tetrazol-5-yl)-9H-carbazole



HPLC-MS (Method C): m/z: 376 (M+1); Rt = 4.43 min.

Example 775 (General Procedure (J)).

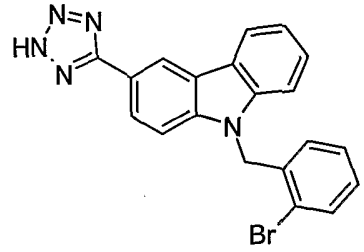
9-[Bis(4-fluorophenyl)methyl]-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 438 (M+1); Rt = 4.60 min.

Example 776 (General Procedure (J)).

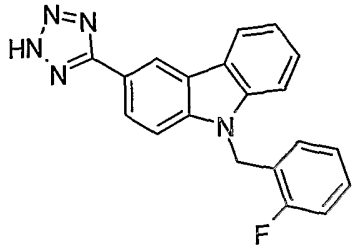
9-(2-Bromobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 404 (M+1); Rt = 4.50 min.

Example 777 (General Procedure (J)).

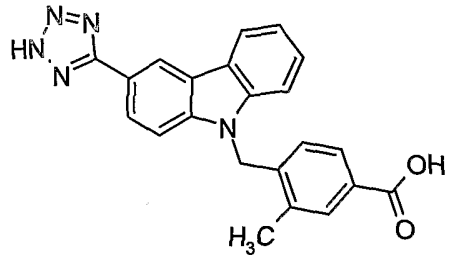
9-(2-Fluorobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 344 (M+1); Rt = 4.09 min.

Example 778 (General Procedure (J)).

9-(4-Carboxy-2-methylbenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole

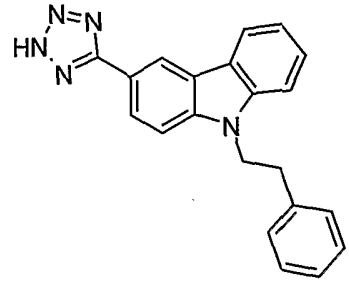


In this preparation, a 3.6-fold excess of sodium hydride was used.

HPLC-MS (Method C): m/z: 384 (M+1); Rt = 3.56 min.

Example 779 (General Procedure (J)).

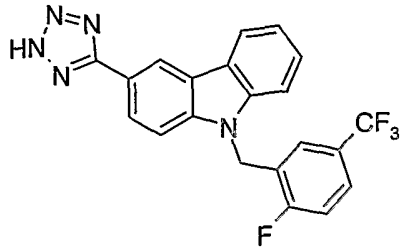
9-(2-Phenylethyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 340 (M+1); Rt = 4.08 min.

Example 780 (General Procedure (J)).

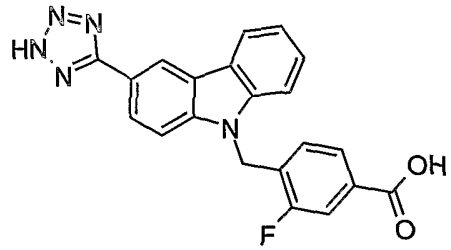
9-[2-Fluoro-5-(trifluoromethyl)benzyl]-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 412 (M+1); Rt = 4.34 min.

Example 781 (General Procedure (J)).

9-(4-Carboxy-2-fluorobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



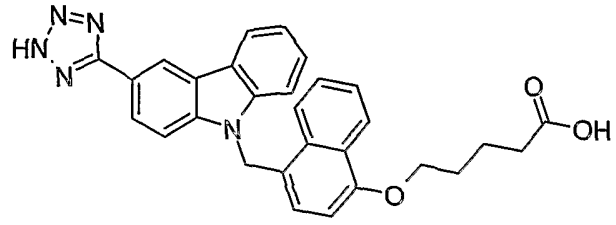
3-Fluoro-4-methylbenzoic acid (3.0 g, 19.5 mmol) and benzoyl peroxide (0.18 g, 0.74 mmol) were suspended in benzene. The mixture was purged with N_2 and heated to reflux. *N*-Bromosuccinimide (3.47 g, 19.5 mmol) was added portionwise, and reflux was maintained for 18 hours. The reaction mixture was concentrated, and the residue was washed with water (20 mL) at 70 °C for 1 hour. The crude product was isolated by filtration and washed with additional water (2 x 10 mL). The dry product was recrystallized from heptanes. Filtration furnished 4-bromomethyl-3-fluorobenzoic acid (1.92 g) which was used in the following step according to General Procedure (J).

In this preparation, a 3.6-fold excess of sodium hydride was used.

HPLC-MS (Method C): m/z: 388 (M+1); Rt = 3.49 min.

Example 782 (General Procedure (J)).

5-{4-[[(3-(2*H*-Tetrazol-5-yl)carbazol-9-yl)methyl]naphthalen-1-yl]oxy}pentanoic Acid



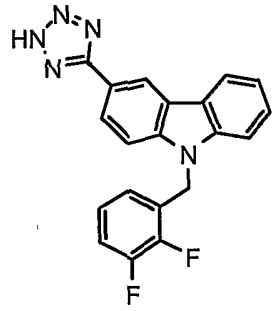
5-[(4-Formylnaphthalen-1-yl)oxy]pentanoic acid intermediate obtained in example 470(3.0 g, 11.0 mmol) was dissolved in a mixture of methanol and tetrahydrofuran (9:1) (100 mL), and

sodium borohydride (1.67 g, 44.1 mmol) was added portionwise at ambient temperature. After 30 minutes, the reaction mixture was concentrated to 50 mL and added to hydrochloric acid (0.1 N, 500 mL). Additional hydrochloric acid (1 N, 40 mL) was added, and 5-[(4-hydroxymethyl-naphthalen-1-yl)oxy]pentanoic acid (2.90 g) was collected by filtration. To the crude product was added concentrated hydrochloric acid (100 mL), and the suspension was stirred vigorously for 48 hours at room temperature. The crude product was filtered off and washed with water, until the pH was essentially neutral. The material was washed with heptanes to furnish 5-[(4-chloromethylnaphthalen-1-yl)oxy]pentanoic acid (3.0 g) which was used in the following step according to General Procedure (J).

In this preparation, a 3.6-fold excess of sodium hydride was used.
HPLC-MS (Method C): m/z: 492 (M+1); Rt = 4.27 min.

Example 783 (General procedure (J))

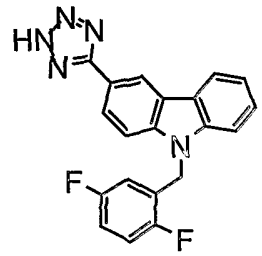
9-(2,3-Difluorobenzyl)-3-(2H-tetrazol-5-yl)-9H-carbazole



HPLC-MS (Method C): m/z= 362 (M+1); Rt = 4.13 min.

Example 784 (General procedure (J))

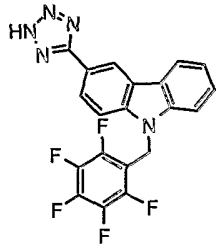
9-(2,5-Difluorobenzyl)-3-(2H-tetrazol-5-yl)-9H-carbazole



HPLC-MS (Method C): m/z = 362 (M+1); Rt = 4.08 min.

Example 785 (General procedure (J))

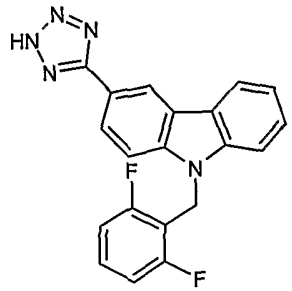
9-Pentafluorophenylmethyl-3-(2H-tetrazol-5-yl)-9H-carbazole



HPLC-MS (Method C): m/z = 416 (M+1); Rt = 4.32 min.

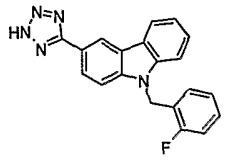
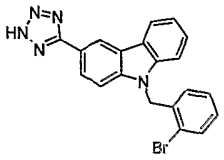
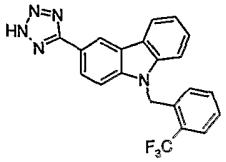
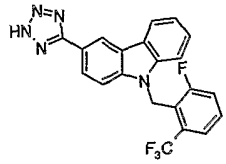
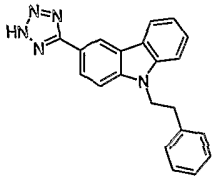
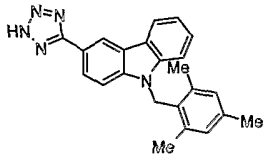
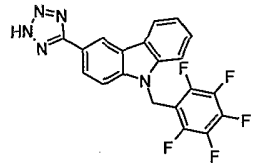
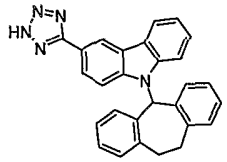
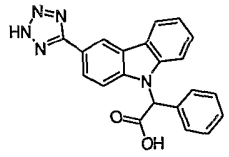
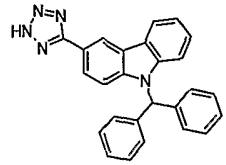
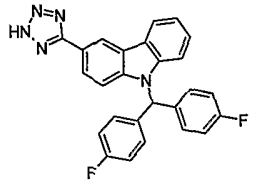
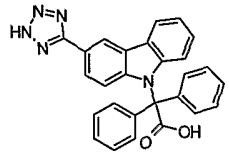
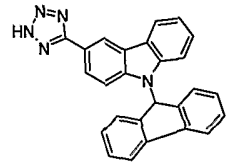
Example 786 (General procedure (J))

9-(2,6-Difluorobenzyl)-3-(2H-tetrazol-5-yl)-9H-carbazole

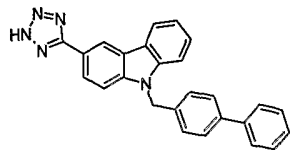
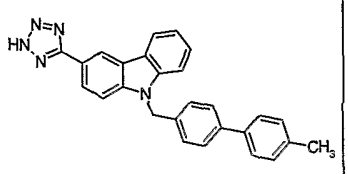
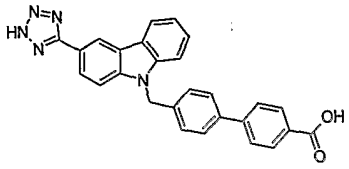
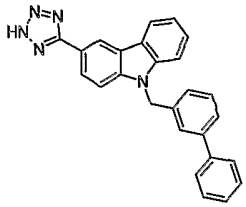
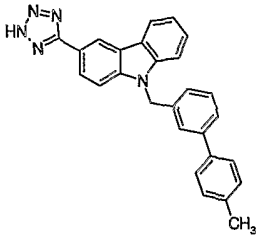
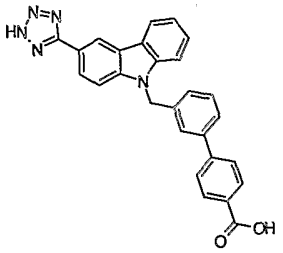


HPLC-MS (Method C): m/z = 362 (M+1); Rt = 3.77 min.

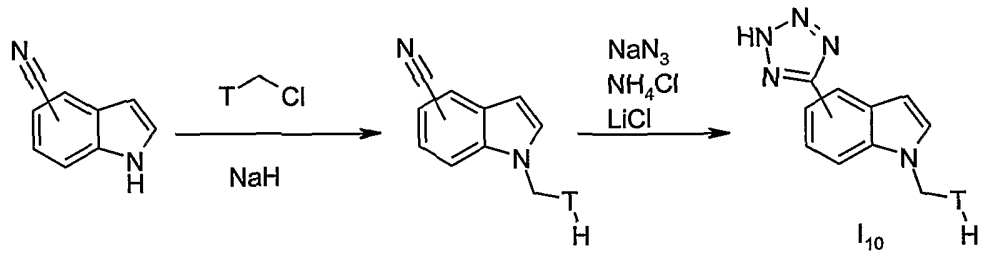
Further compounds of the invention that may be prepared according to general procedure (J), and includes:

Example 787 	Example 788 	Example 789 
Example 790 	Example 791 	Example 792 
Example 793 	Example 794 	Example 795 
Example 796 	Example 797 	Example 798 
Example 799 		

The following compounds of the invention may be prepared eg. from 9-(4-bromobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole (example 736) or from 9-(3-bromobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole (example 730) and aryl boronic acids *via* the Suzuki coupling reaction eg as described in Littke, Dai & Fu *J. Am. Chem. Soc.*, **2000**, *122*, 4020-8 (or references cited therein), or using the methodology described in general procedure (E), optionally changing the palladium catalyst to bis(tri-*tert*-butylphosphine)palladium (0).

Example 800 	Example 801 	Example 802 
Example 803 	Example 804 	Example 805 

General procedure (K) for preparation of compounds of general formula I_{10}:

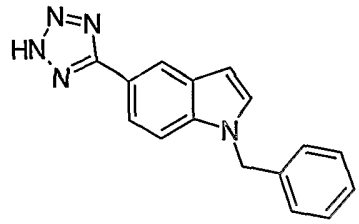


wherein T is as defined above.

The general procedure (K) is further illustrated by the following example:

Example 806 (General procedure (K)).

1-Benzyl-5-(2*H*-tetrazol-5-yl)-1*H*-indole



5-Cyanoindole (1.0 g, 7.0 mmol) was dissolved in *N*,*N*-dimethylformamide (14 mL) and cooled in an ice-water bath. Sodium hydride (0.31 g, 60 %, 7.8 mmol) was added, and the resulting suspension was stirred for 30 min. Benzyl chloride (0.85 mL, 0.94 g, 7.4 mmol) was

added, and the cooling was discontinued. The stirring was continued for 65 hours at room temperature. Water (150 mL) was added, and the mixture was extracted with ethyl acetate (3 x 25 mL). The combined organic phases were washed with brine (30 mL) and dried with sodium sulfate (1 hour). Filtration and concentration yielded the crude material. Purification by flash chromatography on silica gel eluting with ethyl acetate/heptanes = 1:3 afforded 1.60 g 1-benzyl-1*H*-indole-5-carbonitrile.

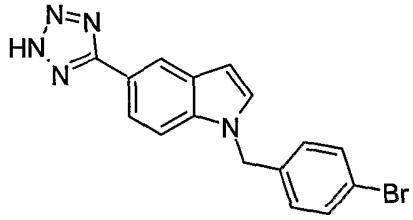
HPLC-MS (Method C): m/z: 233 (M+1); Rt = 4.17 min.

1-Benzyl-1*H*-indole-5-carbonitrile was transformed into 1-benzyl-5-(2*H*-tetrazol-5-yl)-1*H*-indole by the method described in general procedure (J) and in example 594. Purification was done by flash chromatography on silica gel eluting with dichloromethane/methanol = 9:1.

HPLC-MS (Method C): m/z: 276 (M+1); Rt = 3.35 min.

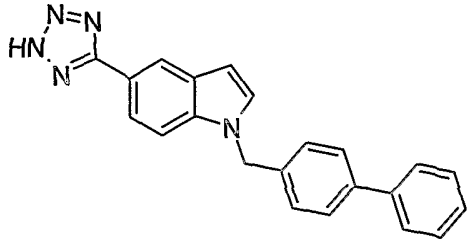
The compounds in the following examples were prepared by the same procedure.

Example 807 (General procedure (K)).
1-(4-Bromobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



HPLC-MS (Method C): m/z: 354 (M+1); Rt = 3.80 min.

Example 808 (General procedure (K)).
1-(4-Phenylbenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole

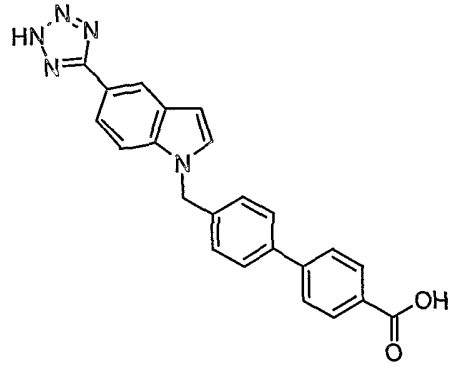


^{1}H-NMR (200 MHz, DMSO-d_6): δ = 5.52 (2H, s), 6.70 (1H, d), 7.3-7.45 (6H, m), 7.6 (4H, m), 7.7-7.8 (2H, m), 7.85(1H, dd), 8.35 (1H, d).

Calculated for $C_{22}H_{17}N_5$, H_2O:
73.32% C; 5.03% H; 19.43% N. Found:
73.81% C; 4.90% H; 19.31% N.

Example 809

4'-[5-(2H-Tetrazol-5-yl)indol-1-ylmethyl]biphenyl-4-carboxylic acid



5-(2H-Tetrazol-5-yl)-1H-indole (Syncom BV, Groningen, NL) (1.66g, 8.9 mmol) was treated with trityl chloride (2.5 g, 8.9 mmol) and triethyl amine (2.5 mL, 17.9 mmol) in DMF(25 mL) by stirring at RT overnight. The resulting mixture was treated with water. The gel was isolated, dissolved in methanol, treated with activated carbon; filtered and evaporated to dryness *in vacuo*. This afforded 3.6 g (94%) of crude 5-(2-trityl-2*H*-tetrazol-5-yl)-1*H*-indole.

HPLC-MS (Method C): m/z = 450 (M+23); Rt. = 5.32 min.

4-Methylphenylbenzoic acid (5 g, 23.5 mmol) was mixed with CCl_4 (100 mL) and under an atmosphere of nitrogen, the slurry was added *N*-Bromosuccinimide (4.19 g, 23.55 mmol) and dibenzoyl peroxide (0.228 g, 0.94 mmol). The mixture was subsequently heated to reflux for 0.5 hour. After cooling, DCM and water (each 30 mL) were added. The resulting precipitate was isolated, washed with water and a small amount of methanol. The solid was dried *in vacuo* to afford 5.27 g (77%) of 4'-bromomethylbiphenyl-4-carboxylic acid.

HPLC-MS (Method C): m/z = 291 (M+1); Rt. = 3.96 min.

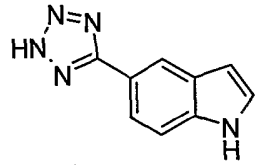
5-(2-Trityl-2*H*-tetrazol-5-yl)-1*H*-indole (3.6 g, 8.4 mmol) was dissolved in DMF (100 mL). Under nitrogen, NaH (60 % suspension in mineral oil, 34 mmol) was added slowly. 4'-Bromomethylbiphenyl-4-carboxylic acid (2.7 g, 9.2 mmol) was added over 5 minutes and the

resulting slurry was heated at 40 °C for 16 hours. The mixture was poured into water (100mL) and the precipitate was isolated by filtration and treated with THF/6N HCl (9/1) (70 mL) at room temperature for 16 hours. The mixture was subsequently evaporated to dryness *in vacuo*, the residue was treated with water and the solid was isolated by filtration and washed thoroughly 3 times with DCM. The solid was dissolved in hot THF (400 mL) treated with activated carbon and filtered. The filtrate was evaporated *in vacuo* to dryness. This afforded 1.6 g (50%) of the title compound.

HPLC-MS (Method C): m/z = 396 (M+1); Rt. = 3.51 min.

Example 810 (General procedure (K)).

5-(2*H*-Tetrazol-5-yl)-1*H*-indole

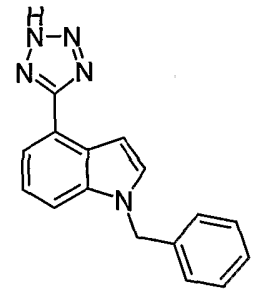


5-(2*H*-Tetrazol-5-yl)-1*H*-indole was prepared from 5-cyanoindole according to the method described in example 594.

HPLC-MS (Method C): m/z: 186 (M+1); Rt = 1.68 min.

Example 811 (General procedure (K)).

1-Benzyl-4-(2*H*-tetrazol-5-yl)-1*H*-indole



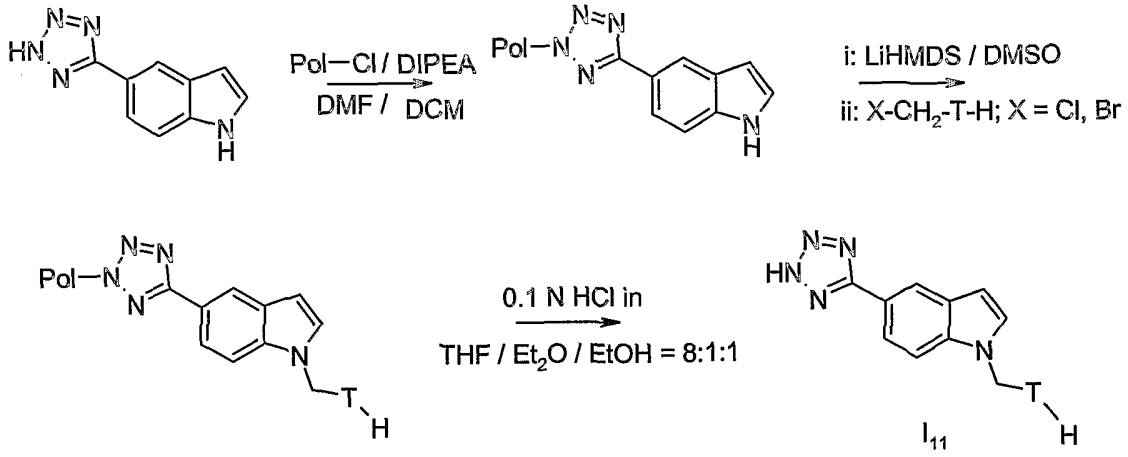
1-Benzyl-1*H*-indole-4-carbonitrile was prepared from 4-cyanoindole according to the method described in example 806.

HPLC-MS (Method C): m/z: 233 (M+1); Rt = 4.24 min.

1-Benzyl-4-(2*H*-tetrazol-5-yl)-1*H*-indole was prepared from 1-benzyl-1*H*-indole-4-carbonitrile according to the method described in example 594.

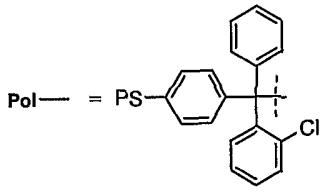
HPLC-MS (Method C): m/z: 276 (M+1); Rt = 3.44 min.

General procedure (L) for preparation of compounds of general formula I_{11}:



wherein T is as defined above and

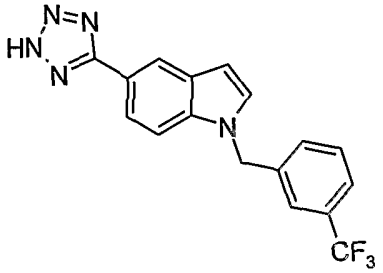
Pol- is a polystyrene resin loaded with a 2-chlorotrityl linker, graphically shown below:



This general procedure (L) is further illustrated by the following example:

Example 812 (General procedure (L)).

5-(2*H*-Tetrazol-5-yl)-1-[3-(trifluoromethyl)benzyl]-1*H*-indole



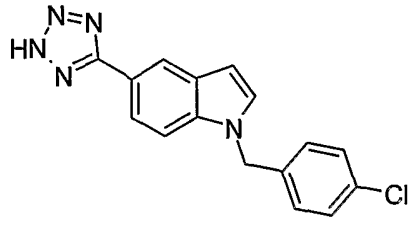
2-Chlorotritylchloride resin (100 mg, 0.114 mmol active chloride) was swelled in dichloromethane (2 mL) for 30 min. The solvent was drained, and a solution of 5-(2*H*-tetrazol-5-yl)-

1*H*-indole (example 810) (63 mg, 0.34 mmol) in a mixture of *N,N*-dimethylformamide, dichloromethane and *N,N*-di(2-propyl)ethylamine (DIPEA) (5:5:2) (1.1 mL) was added. The reaction mixture was shaken at room temperature for 20 hours. The solvent was removed by filtration, and the resin was washed consecutively with *N,N*-dimethylformamide (2 x 4 mL), dichloromethane (6 x 4 mL) and methyl sulfoxide (2 x 4 mL). Methyl sulfoxide (1 mL) was added, followed by the addition of a solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (1.0 M, 0.57 mL, 0.57 mmol). The mixture was shaken for 30 min at room temperature, before 3-(trifluoromethyl)benzyl bromide (273 mg, 1.14 mmol) was added as a solution in methyl sulfoxide (0.2 mL). The reaction mixture was shaken for 20 hours at room temperature. The drained resin was washed consecutively with methyl sulfoxide (2 x 4 mL), dichloromethane (2 x 4 mL), methanol (2 x 4 mL), dichloromethane (2 x 4 mL) and tetrahydrofuran (4 mL). The resin was treated with a solution of hydrogen chloride in tetrahydrofuran, ethyl ether and ethanol = 8:1:1 (0.1 M, 3 mL) for 6 hours at room temperature. The resin was drained and the filtrate was concentrated *in vacuo*. The crude product was re-suspended in dichloromethane (1.5 mL) and concentrated three times to afford the title compound (35 mg). No further purification was necessary.

HPLC-MS (Method B): m/z: 344 (M+1); Rt = 4.35 min.
^{1}H-NMR (DMSO-d_6): δ 8.29 (1H, s), 7.80 (1H, dd), 7.72 (2H, m), 7.64 (2H, bs), 7.56 (1H, t), 7.48 (1H, d), 6.70 (1H, d), 5.62 (2H, s).

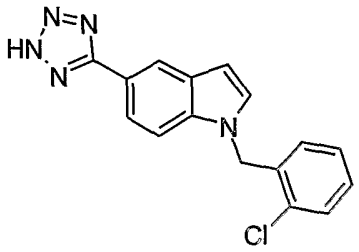
The compounds in the following examples were prepared in a similar fashion. Optionally, the compounds can be further purified by recrystallization or by chromatography.

Example 813 (General procedure (L)).
1-(4-Chlorobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



HPLC-MS (Method B): m/z: 310 (M+1); Rt = 4.11 min.

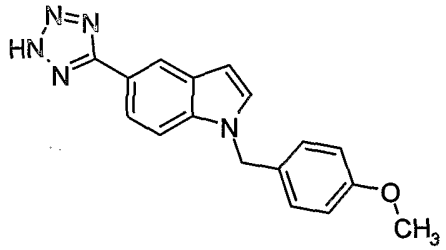
Example 814 (General procedure (L)).
1-(2-Chlorobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



HPLC-MS (Method B): m/z: 310 (M+1); Rt = 4.05 min.

Example 815 (General procedure (L)).

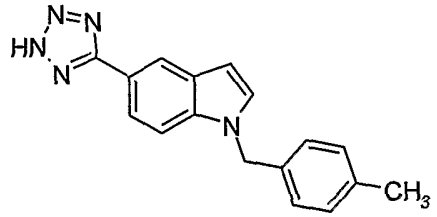
1-(4-Methoxybenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



HPLC-MS (Method B): m/z: 306 (M+1); Rt = 3.68 min.

Example 816 (General procedure (L)).

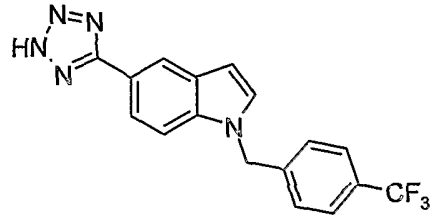
1-(4-Methylbenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



HPLC-MS (Method B): m/z: 290 (M+1); Rt = 3.98 min.

Example 817 (General procedure (L)).

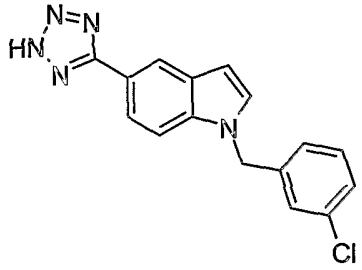
5-(2*H*-Tetrazol-5-yl)-1-[4-(trifluoromethyl)benzyl]-1*H*-indole



HPLC-MS (Method B): m/z: 344 (M+1); Rt = 4.18 min.

Example 818 (General procedure (L)).

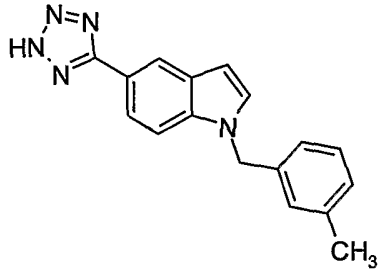
1-(3-Chlorobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



HPLC-MS (Method B): m/z: 310 (M+1); Rt = 4.01 min.

Example 819 (General procedure (L)).

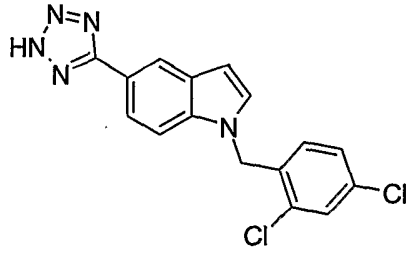
1-(3-Methylbenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



HPLC-MS (Method B): m/z: 290 (M+1); Rt = 3.98 min.

Example 820 (General procedure (L)).

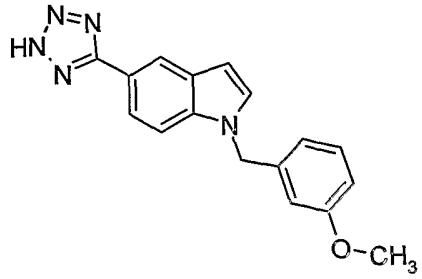
1-(2,4-Dichlorobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



HPLC-MS (Method B): m/z: 344 (M+1); Rt = 4.41 min.

Example 821 (General procedure (L)).

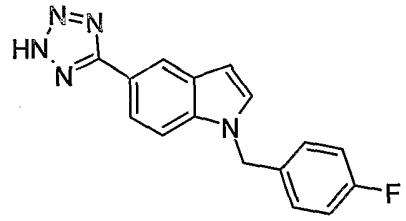
1-(3-Methoxybenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



HPLC-MS (Method B): m/z: 306 (M+1); Rt = 3.64 min.

Example 822 (General procedure (L)).

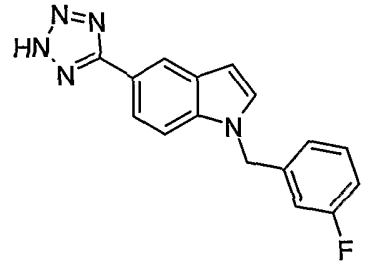
1-(4-Fluorobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



HPLC-MS (Method B): m/z: 294 (M+1); Rt = 3.71 min.

Example 823 (General procedure (L)).

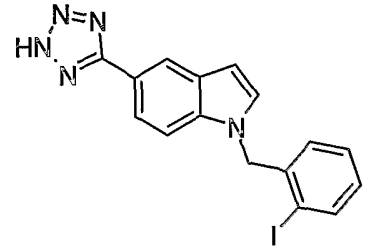
1-(3-Fluorobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



HPLC-MS (Method B): m/z: 294 (M+1); Rt = 3.68 min.

Example 824 (General procedure (L)).

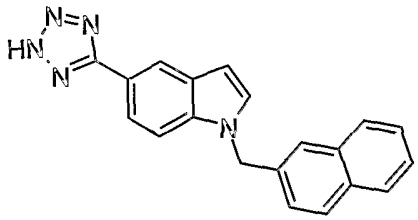
1-(2-Iodobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



HPLC-MS (Method B): m/z: 402 (M+1); Rt = 4.11 min.

Example 825 (General procedure (L)).

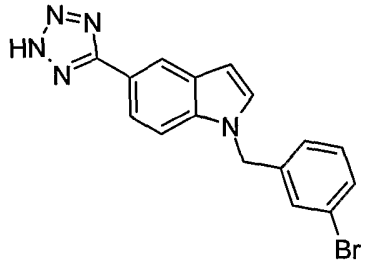
1-[(Naphthalen-2-yl)methyl]-5-(2*H*-tetrazol-5-yl)-1*H*-indole



HPLC-MS (Method B): m/z: 326 (M+1); Rt = 4.18 min.

Example 826 (General procedure (L)).

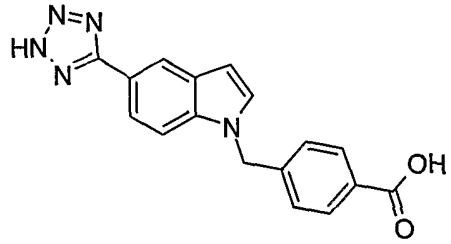
1-(3-Bromobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



HPLC-MS (Method B): m/z: 354 (M+1); Rt = 4.08 min.

Example 827 (General procedure (L)).

1-(4-Carboxybenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole

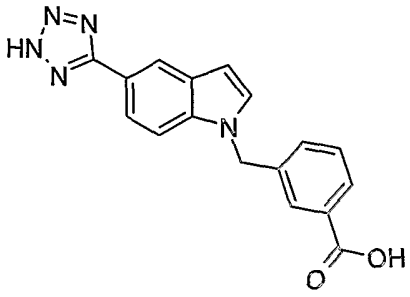


In this preparation, a larger excess of lithium bis(trimethylsilyl)amide in tetrahydrofuran (1.0 M, 1.7 mL, 1.7 mmol) was used.

HPLC-MS (Method B): m/z: 320 (M+1); Rt = 2.84 min.

Example 828 (General procedure (L)).

1-(3-Carboxybenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole

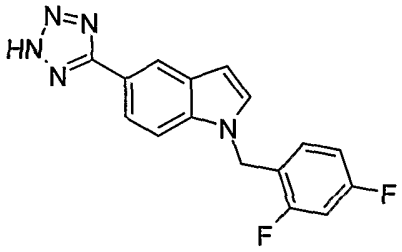


In this preparation, a larger excess of lithium bis(trimethylsilyl)amide in tetrahydrofuran (1.0 M, 1.7 mL, 1.7 mmol) was used.

HPLC-MS (Method B): m/z: 320 (M+1); Rt = 2.91 min.

Example 829 (General procedure (L)).

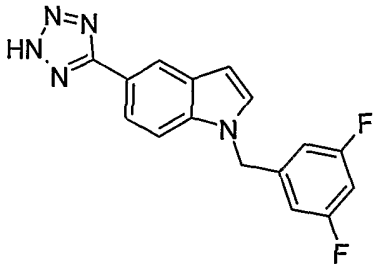
1-(2,4-Difluorobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



HPLC-MS (Method B): m/z: 312 (M+1); Rt = 3.78 min.

Example 830 (General procedure (L)).

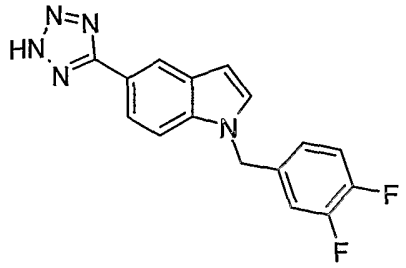
1-(3,5-Difluorobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



HPLC-MS (Method B): m/z: 312 (M+1); Rt = 3.78 min.

Example 831 (General procedure (L)).

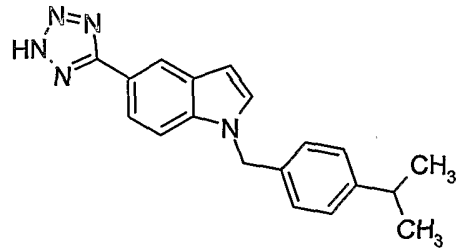
1-(3,4-Difluorobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



HPLC-MS (Method B): m/z: 312 (M+1); Rt = 3.81 min.

Example 832 (General procedure (L)).

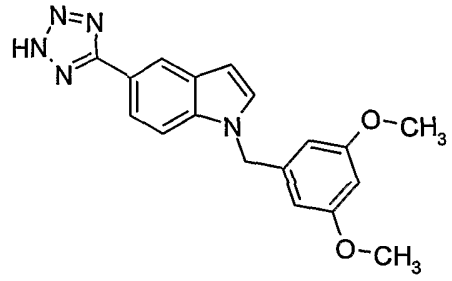
1-[4-(2-Propyl)benzyl]-5-(2*H*-tetrazol-5-yl)-1*H*-indole



HPLC-MS (Method B): m/z: 318 (M+1); Rt = 4.61 min.

Example 833 (General procedure (L)).

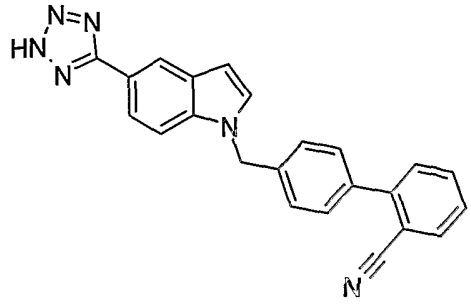
1-(3,5-Dimethoxybenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



HPLC-MS (Method B): m/z: 336 (M+1); Rt = 3.68 min.

Example 834 (General procedure (L)).

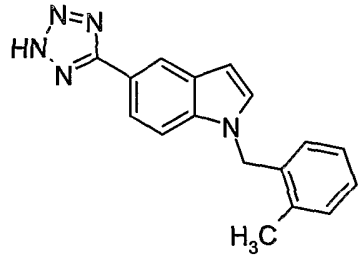
1-(2'-Cyanobiphenyl-4-ylmethyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



HPLC-MS (Method B): m/z: 377 (M+1); Rt = 4.11 min.

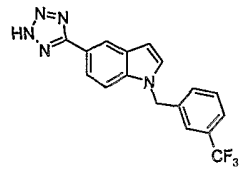
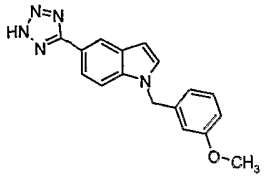
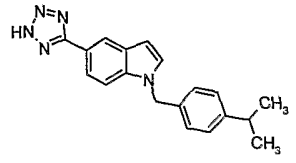
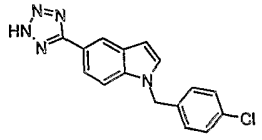
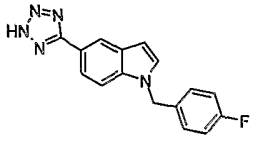
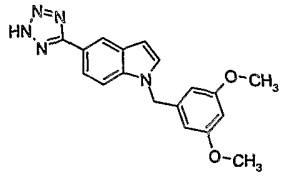
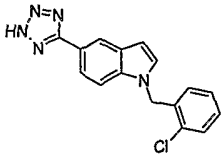
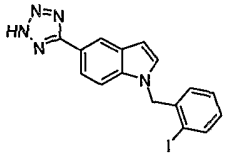
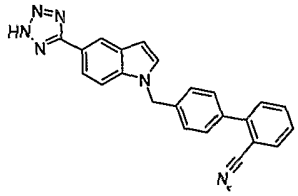
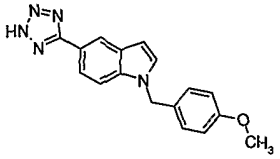
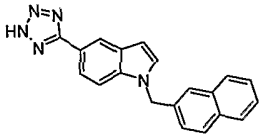
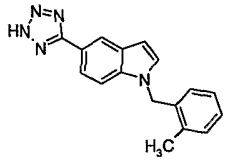
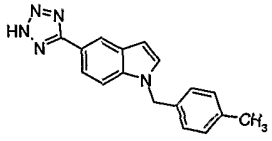
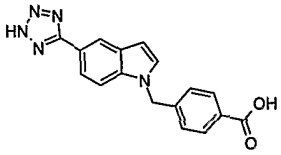
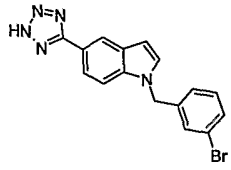
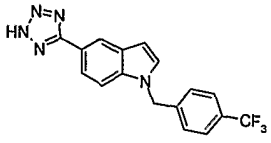
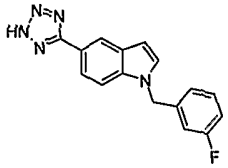
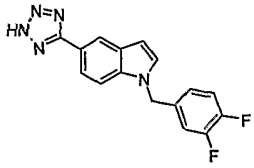
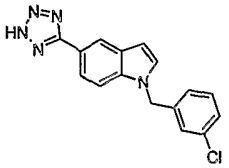
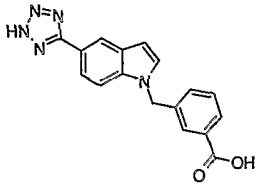
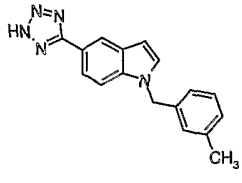
Example 835 (General procedure (L)).

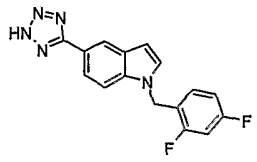
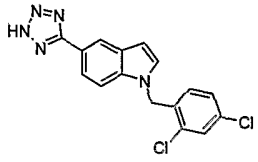
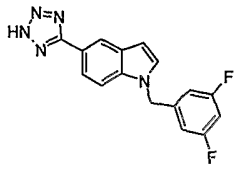
1-(2-Methylbenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



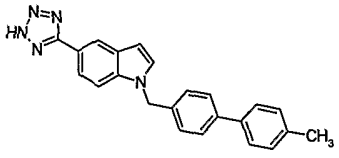
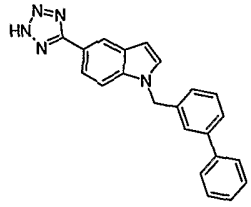
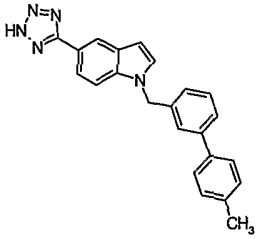
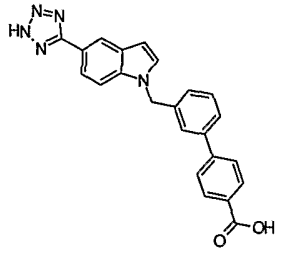
HPLC-MS (Method B): m/z: 290 (M+1); Rt = 3.98 min.

Further compounds of the invention that may be prepared according to general procedure (K) and/or (L) includes:

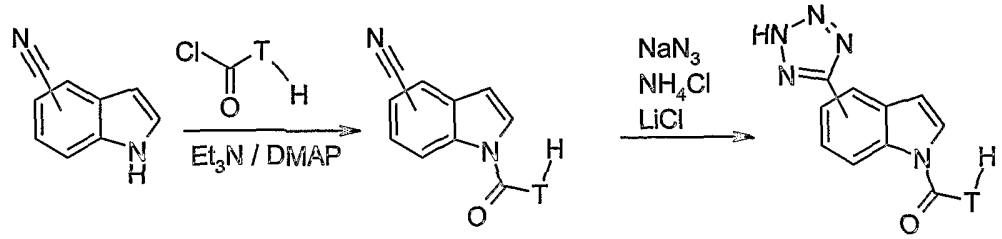
Example 836 	Example 837 	Example 838 
Example 839 	Example 840 	Example 841 
Example 842 	Example 843 	Example 844 
Example 845 	Example 846 	Example 847 
Example 848 	Example 849 	Example 850 
Example 851 	Example 852 	Example 853 
Example 854 	Example 855 	Example 856 

Example 857	Example 858	Example 859
		

The following compounds of the invention may be prepared eg. from 1-(4-bromobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole (example 807) or from the analogue 1-(3-bromobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole and aryl boronic acids *via* the Suzuki coupling reaction eg as described in Littke, Dai & Fu *J. Am. Chem. Soc.*, **2000**, *122*, 4020-8 (or references cited therein), or using the methodology described in general procedure (E), optionally changing the palladium catalyst to bis(tri-*tert*-butylphosphine)palladium (0).

	Example 860	
		
Example 861	Example 862	Example 863
		

General procedure (M) for preparation of compounds of general formula I_{12}:



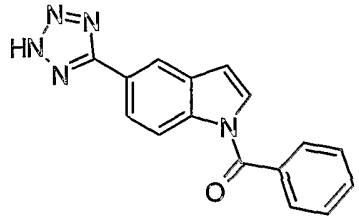
I_{12}

wherein T is as defined above.

The general procedure (M) is further illustrated by the following example:

Example 864 (General procedure (M)).

1-Benzoyl-5-(2*H*-tetrazol-5-yl)-1*H*-indole



To a solution of 5-cyanoindole (1.0 g, 7.0 mmol) in dichloromethane (8 mL) was added 4-(dimethylamino)pyridine (0.171 g, 1.4 mmol), triethylamine (1.96 mL, 1.42 g, 14 mmol) and benzoyl chloride (0.89 mL, 1.08 g, 7.7 mmol). The resulting mixture was stirred for 18 hours at room temperature. The mixture was diluted with dichloromethane (80 mL) and washed consecutively with a saturated solution of sodium hydrogencarbonate (40 mL) and brine (40 mL). The organic phase was dried with magnesium sulfate (1 hour). Filtration and concentration furnished the crude material which was purified by flash chromatography on silica gel, eluting with ethyl acetate/heptanes = 2:3. 1-Benzoyl-1*H*-indole-5-carbonitrile was obtained as a solid.

HPLC-MS (Method C): m/z: 247 (M+1); Rt = 4.07 min.

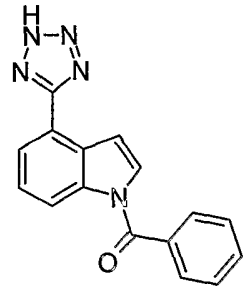
1-Benzoyl-1*H*-indole-5-carbonitrile was transformed into 1-benzoyl-5-(2*H*-tetrazol-5-yl)-1*H*-indole by the method described in example 594.

HPLC (Method C): Rt = 1.68 min.

The compound in the following example was prepared by the same procedure.

Example 865 (General procedure (M)).

1-Benzoyl-4-(2*H*-tetrazol-5-yl)-1*H*-indole



1-Benzoyl-1*H*-indole-4-carbonitrile was prepared from 4-cyanoindole according to the method described in example 864.

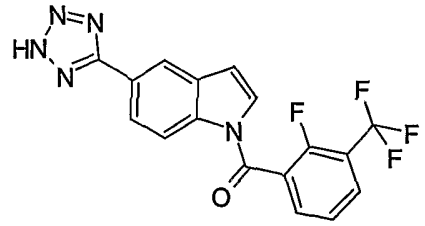
HPLC-MS (Method C): m/z: 247 (M+1); Rt = 4.24 min.

1-Benzoyl-4-(2*H*-tetrazol-5-yl)-1*H*-indole was prepared from 1-benzoyl-1*H*-indole-4-carbonitrile according to the method described in example 594.

HPLC (Method C): Rt = 1.56 min.

Example 866 (General procedure (M))

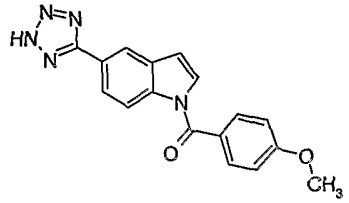
(2-Fluoro-3-trifluoromethylphenyl)-[5-(2H-tetrazol-5-yl)-indol-1-yl]-methanone



HPLC-MS (Method B): m/z = 376 (M+1); Rt = 4.32 min.

Example 867 (General procedure (M))

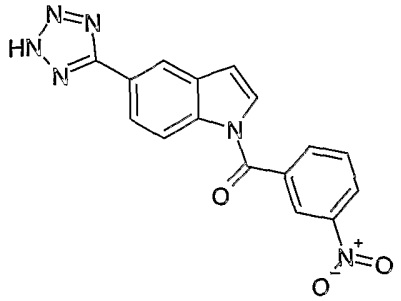
(4-Methoxyphenyl)-[5-(2H-tetrazol-5-yl)-indol-1-yl]-methanone



HPLC-MS (Method B): m/z = 320 (M+1); Rt = 3.70 min.

Example 868 (General procedure (M))

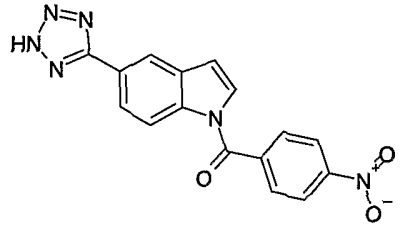
(3-Nitrophenyl)-[5-(2H-tetrazol-5-yl)-indol-1-yl]-methanone



HPLC-MS (Method B): m/z = 335 (M+1); Rt = 3.72 min.

Example 869 (General procedure (M))

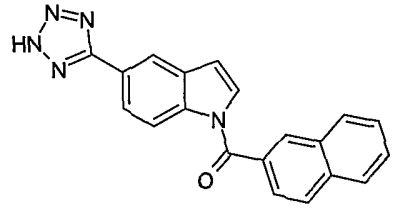
(4-Nitrophenyl)-[5-(2H-tetrazol-5-yl)-indol-1-yl]-methanone



HPLC-MS (Method B): m/z = 335 (M+1); Rt = 3.71 min.

Example 870 (General procedure (M))

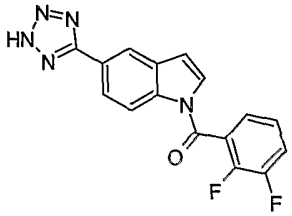
Naphthalen-2-yl-[5-(2H-tetrazol-5-yl)-indol-1-yl]-methanone



HPLC-MS (Method C): m/z = 340 (M+1); Rt = 4.25 min.

Example 871 (General procedure (M))

(2,3-Difluorophenyl)-[5-(2H-tetrazol-5-yl)-indol-1-yl]-methanone

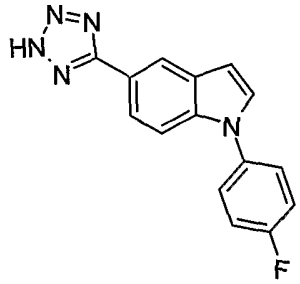


HPLC-MS (Method B: m/z = 326 (M+1); Rt = 3.85 min.

The following known and commercially available compounds do all bind to the His B10 Zn^{2+} site of the insulin hexamer:

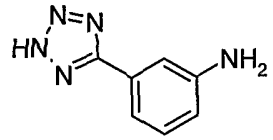
Example 872

1-(4-Fluorophenyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



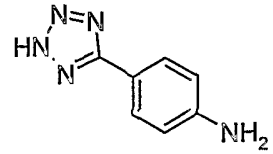
Example 873

1-Amino-3-(2*H*-tetrazol-5-yl)benzene



Example 874

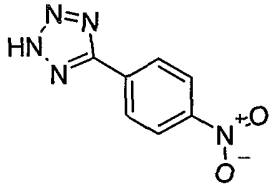
1-Amino-4-(2*H*-tetrazol-5-yl)benzene



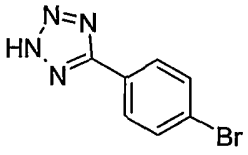
A mixture of 4-aminobenzonitrile (10 g, 84.6 mmol), sodium azide (16.5 g, 254 mmol) and ammonium chloride (13.6 g, 254 mmol) in DMF was heated at 125 °C for 16 hours. The cooled mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was added water (200 mL) and diethyl ether (200 mL) which resulted in crystallisation. The mixture was filtered and the solid was dried *in vacuo* at 40 °C for 16 hours to afford 5-(4-aminophenyl)-2*H*-tetrazole.

^{1}H NMR DMSO-d_6): δ = 5.7 (3H, bs), 6.69 (2H, d), 7.69 (2H, d).
HPLC-MS (Method C): m/z: 162 (M+1); Rt = 0,55 min.

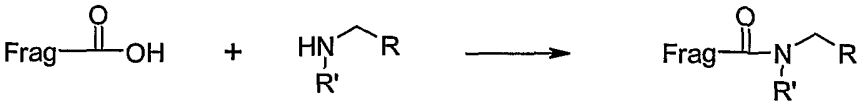
Example 8751-Nitro-4-(2*H*-tetrazol-5-yl)benzene



Example 8761-Bromo-4-(2*H*-tetrazol-5-yl)benzene



General procedure (N) for solution phase preparation of amides of general formula I_{13}:



I_{13}

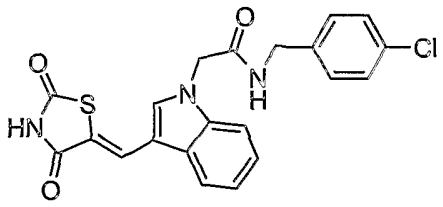
wherein Frag is any fragment carrying a carboxylic acid group, **R** is hydrogen, optionally substituted aryl or C_{1-8}-alkyl and **R'** is hydrogen or C_{1-4}-alkyl.

Frag-CO_2H may be prepared eg by general procedure (D) or by other similar procedures described herein, or may be commercially available.

The procedure is further illustrated in the following example 877:

Example 877 (General procedure (N))

N-(4-Chlorobenzyl)-2-[3-(2,4-dioxothiazolidin-5-ylidenemethyl)-1*H*-indol-1-yl]acetamide

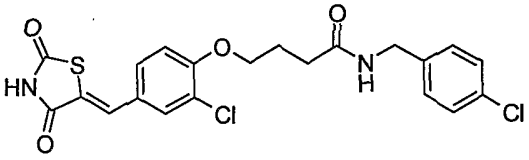


[3-(2,4-Dioxothiazolidin-5-ylidenemethyl)indol-1-yl]acetic acid (example 478, 90.7 mg, 0.3 mmol) was dissolved in NMP (1 mL) and added to a mixture of 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide, hydrochloride (86.4 mg, 0.45 mmol) and 1-hydroxybenzotriazol (68.8 mg, 0.45 mmol) in NMP (1 mL). The resulting mixture was shaken at RT for 2 h. 4-Chlorobenzylamine (51 mg, 0.36 mmol) and DIPEA (46.4 mg, 0.36 mmol) in NMP (1 mL) were added to the mixture and the resulting mixture shaken at RT for 2 days. Subsequently ethyl acetate (10 mL) was added and the resulting mixture washed with 2x10 mL water followed by saturated ammonium chloride (5 mL). The organic phase was evaporated to dryness giving 75 mg (57%) of the title compound.

HPLC-MS (Method C): m/z: 426 (M+1); Rt. = 3.79 min.

Example 878 (General procedure (N))

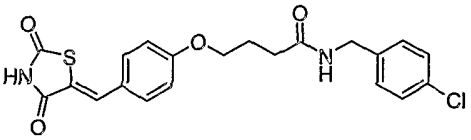
N-(4-Chlorobenzyl)-4-[2-chloro-4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]butyramide



HPLC-MS (Method A): m/z: 465 (M+1); Rt = 4.35 min.

Example 879 (General procedure (N))

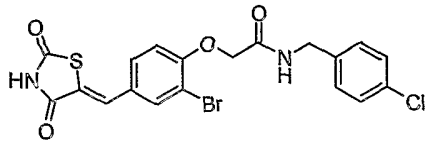
N-(4-Chlorobenzyl)-4-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]butyramide



HPLC-MS (Method A): m/z: 431 (M+1); Rt = 3.68 min.

Example 880 (General procedure (N))

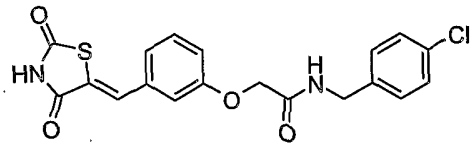
2-[2-Bromo-4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]-*N*-(4-chlorobenzyl)acetamide



HPLC-MS (Method A): m/z: 483 (M+1); Rt = 4.06 min.

Example 881 (General procedure (N))

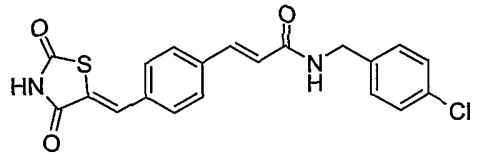
N-(4-Chlorobenzyl)-2-[3-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]acetamide



HPLC-MS (Method A): m/z: 403 (M+1); Rt = 4.03 min.

Example 882 (General procedure (N))

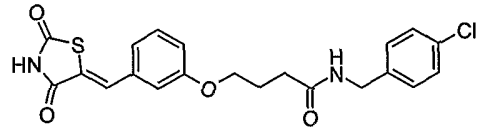
N-(4-Chlorobenzyl)-3-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenyl]acrylamide



HPLC-MS (Method A): m/z: 399 (M+1); Rt = 3.82.

Example 883 (General procedure (N))

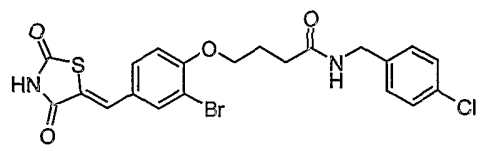
N-(4-Chlorobenzyl)-4-[3-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]butyramide



HPLC-MS (Method A): m/z: 431 (M+1); Rt = 3.84 min.

Example 884 (General procedure (N))

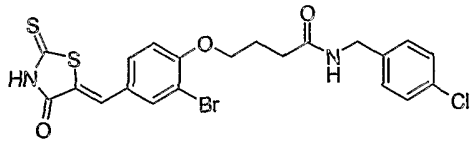
4-[2-Bromo-4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]-*N*-(4-chlorobenzyl)butyramide



HPLC-MS (Method A): m/z: 511 (M+1); Rt = 4.05 min.

Example 885 (General procedure (N))

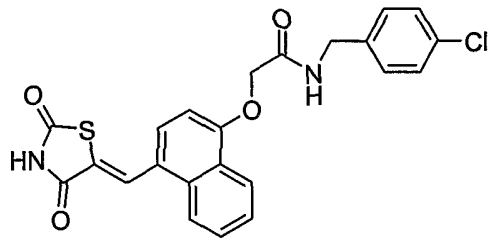
4-[2-Bromo-4-(4-oxo-2-thioxothiazolidin-5-ylidenemethyl)-phenoxy]-*N*-(4-chlorobenzyl)-butyramide



HPLC-MS (Method A): m/z: 527 (M+1); Rt = 4.77 min.

Example 886 (General procedure (N))

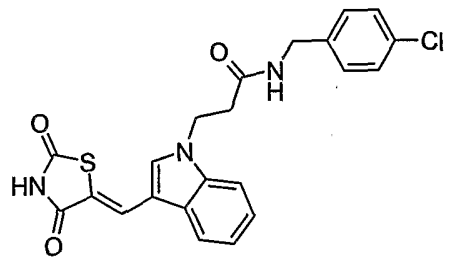
N-(4-Chlorobenzyl)-2-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]acetamide



HPLC-MS (Method C): m/z: 431 (M+1); Rt. = 4.03 min.

Example 887 (General procedure (N))

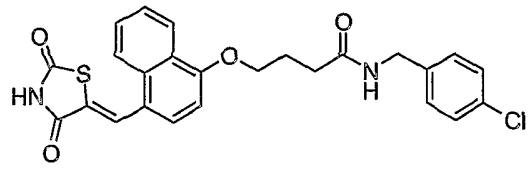
N-(4-Chlorobenzyl)-3-[3-(2,4-dioxothiazolidin-5-ylidenemethyl)-1*H*-indol-1-yl]propionamide



HPLC-MS (Method C): m/z: 440 (M+1); Rt. = 3.57 min.

Example 888 (General procedure (N))

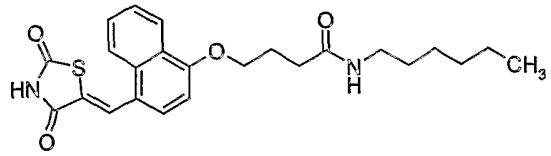
N-(4-Chlorobenzyl)-4-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]butyramide



HPLC-MS (Method C): m/z: 481 (M+1); Rt = 4.08 min.

Example 889 (General procedure (N))

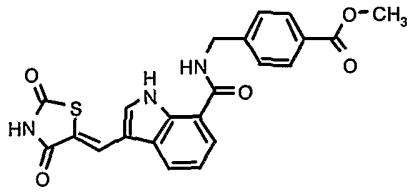
4-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)-naphthalen-1-yloxy]-*N*-hexylbutyramide



HPLC-MS (Method C): m/z: 441 (M+1); Rt = 4.31 min.

Example 890 (General Procedure (N))

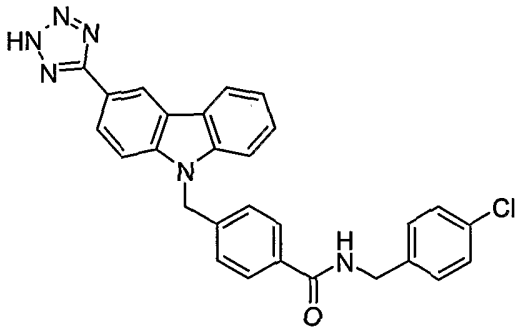
4-({[3-(2,4-Dioxothiazolidin-5-ylidenemethyl)indole-7-carbonyl]amino}methyl)benzoic acid methyl ester



HPLC-MS (Method C): m/z: 436 (M+1); Rt.= 3.55 min.

Example 891 (General procedure (N))

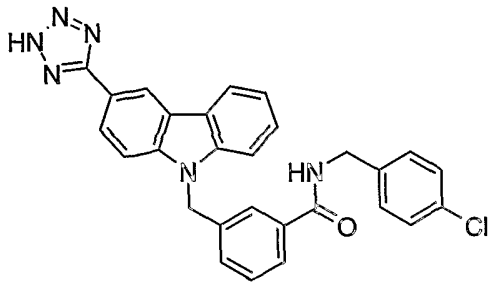
N-(4-Chlorobenzyl)-4-[3-(2*H*-tetrazol-5-yl)carbazol-9-ylmethyl]benzamide



HPLC-MS (Method C): m/z:493 (M+1); Rt = 4.19 min.

Example 892 (General procedure (N))

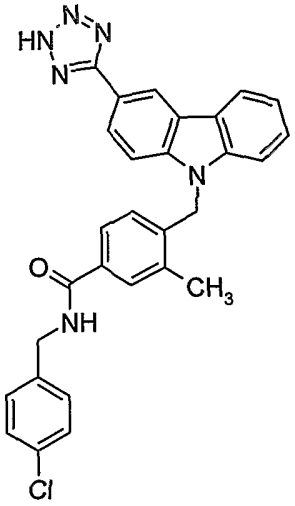
N-(4-Chlorobenzyl)-3-[3-(2*H*-tetrazol-5-yl)carbazol-9-ylmethyl]benzamide



HPLC-MS (Method C): m/z: 493 (M+1); Rt = 4.20 min.

Example 893 (General Procedure (N))

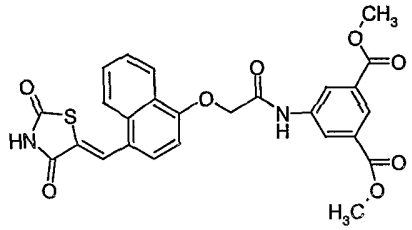
N-(4-Chlorobenzyl)-3-methyl-4-[3-(2*H*-tetrazol-5-yl)-carbazol-9-ylmethyl]benzamide



HPLC-MS (Method C): m/z: 507 (M+1); Rt = 4.37min.

Example 894 (General procedure (N))

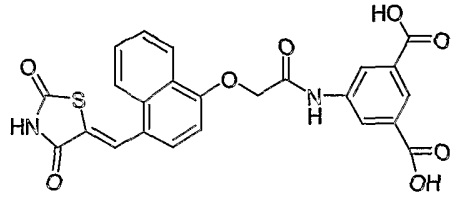
5-{2-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)-naphthalen-1-yloxy]-acetylamino}-isophthalic acid dimethyl ester



HPLC-MS (Method C): m/z = 521 (M+1); Rt. = 4.57 min.

Example 895 (General procedure (N))

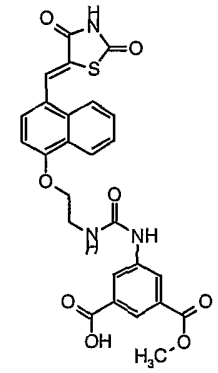
5-{2-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)-naphthalen-1-yloxy]-acetylamino}-isophthalic acid



HPLC-MS (Method C): m/z = 515 (M+23); Rt. = 3.09 min.

Example 896 (General procedure (N))

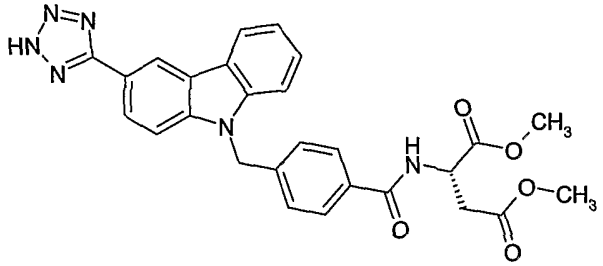
5-(3-{2-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)-naphthalen-1-yloxy]-ethyl}-ureido)-isophthalic acid monomethyl ester



HPLC-MS (Method C): m/z = 536 (M+1); Rt = 3,58 min.

Example 897 (General Procedure (N)).

2-{4-[3-(2H-Tetrazol-5-yl)carbazol-9-ylmethyl]benzoylamino}succinic acid dimethyl ester



4-[3-(1H-Tetrazol-5-yl)carbazol-9-ylmethyl]benzoic acid (2.00 g, 5.41 mmol), 1-hydroxybenzotriazole (1.46 g, 10.8 mmol) and N,N-di(2-propyl)ethylamine (4.72 mL, 3.50 g, 27.1 mmol) were dissolved in dry N,N-dimethylformamide (60 mL). The mixture was cooled in an ice-water bath, and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.45 g, 7.56 mmol) and (S)-aminosuccinic acid dimethyl ester hydrochloride (1.28 g, 6.48

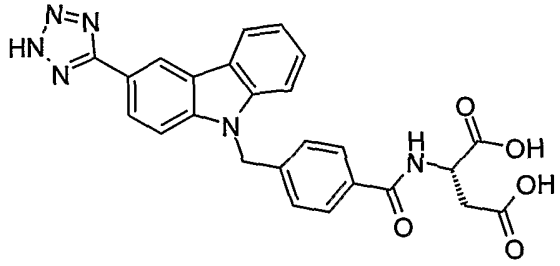
mmol) were added. The cooling was discontinued, and the reaction mixture was stirred at room temperature for 18 hours before it was poured into hydrochloric acid (0.1 N, 600 mL). The solid was collected by filtration and washed with water (2 X 25 mL) to furnish the title compound.

HPLC-MS (Method C): m/z: 513 (M+1); Rt = 3.65 min.

^{1}H-NMR (DMSO-d_6): δ 8.90 (1H, d), 8.86 (1H, d), 8.29 (1H, d), 8.11 (1H, dd), 7.87 (1H, d), 7.75 (2H, d), 7.69 (1H, d), 7.51 (1H, t), 7.32 (1H, t), 7.28 (2H, d), 5.82 (2H, s), 4.79 (1H, m), 3.61 (3H, s), 3.58 (3H, s), 2.92 (1H, dd), 2.78 (1H, dd).

Example 898 (General Procedure (N)).

2-{4-[3-(2H-Tetrazol-5-yl)carbazol-9-ylmethyl]benzoylamino}succinic acid



2-{4-[3-(2H-Tetrazol-5-yl)carbazol-9-ylmethyl]benzoylamino}*succinic acid dimethyl ester* (1.20 g, 2.34 mmol) was dissolved in tetrahydrofuran (30 mL). Aqueous sodium hydroxide (1 N, 14 mL) was added, and the resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was poured into hydrochloric acid (0.1 N, 500 mL). The solid was collected by filtration and washed with water (2 X 25 mL) and diethyl ether (2 X 25 mL) to furnish the title compound.

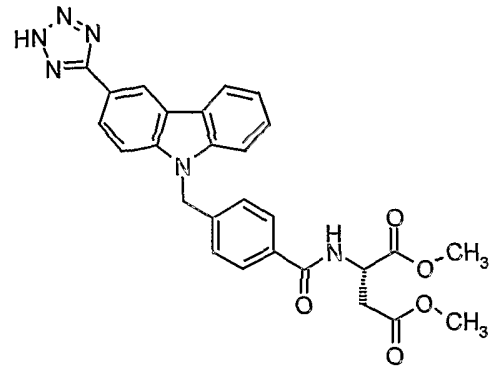
HPLC-MS (Method C): m/z: 485 (M+1); Rt = 2.94 min.

^{1}H-NMR (DMSO-d_6): δ 12.44 (2H, s (br)), 8.90 (1H, d), 8.68 (1H, d), 8.29 (1H, d), 8.11 (1H, dd), 7.87 (1H, d), 7.75 (2H, d), 7.68 (1H, d), 7.52 (1H, t), 7.32 (1H, t), 7.27 (2H, d), 5.82 (2H, s), 4.70 (1H, m), 2.81 (1H, dd), 2.65 (1H, dd).

The compounds in the following examples were prepared in a similar fashion.

Example 899 (General procedure (N))

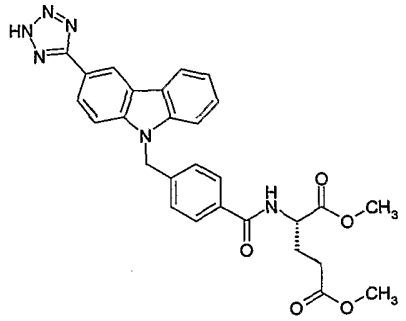
2-{4-[3-(2H-Tetrazol-5-yl)-carbazol-9-ylmethyl]-benzoylamino}-succinic acid dimethyl ester



HPLC-MS (Method C): m/z = 513 (M+1); Rt = 3.65min.

Example 900 (General procedure (N))

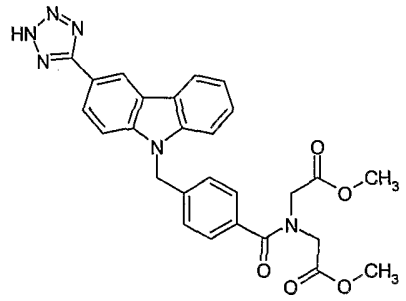
2-{4-[3-(2H-Tetrazol-5-yl)carbazol-9-ylmethyl]benzoylamino}pentanedioic acid dimethyl ester



HPLC-MS (Method C): m/z = 527 (M+1); Rt = 3.57min.

Example 901 (General procedure (N))

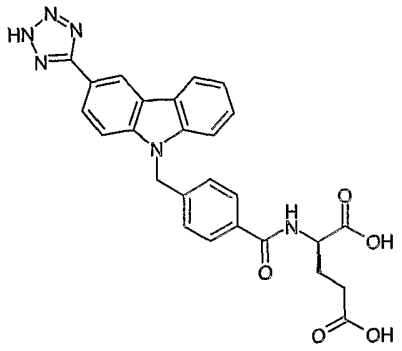
(Methoxycarbonylmethyl-{4-[3-(2H-tetrazol-5-yl)-carbazol-9-ylmethyl]-benzoyl}-amino)-acetic acid methyl ester



HPLC-MS (Method C): m/z = 513 (M+1); Rt = 3,55min.

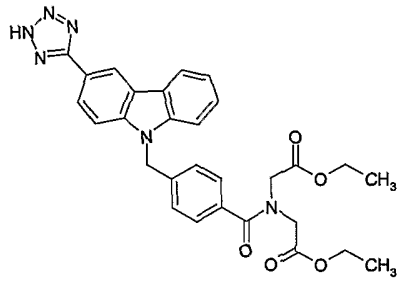
Example 902 (General procedure (N))

2-{4-[3-(2H-Tetrazol-5-yl)carbazol-9-ylmethyl]benzoylamino}pentanedioic acid



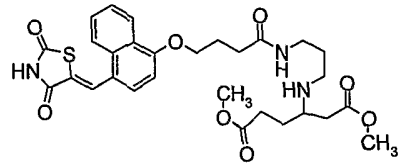
HPLC-MS (Method C): m/z = 499 (M+1); Rt = 2.87min.

Example 903 (General procedure (N))
(Ethoxycarbonylmethyl-{4-[3-(2H-tetrazol-5-yl)-carbazol-9-ylmethyl]-benzoyl}-amino)-acetic acid ethyl ester



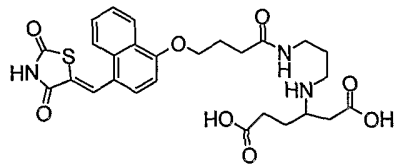
HPLC-MS (Method C): m/z = 541 (M+1); Rt = 3.91min.

Example 904 (General procedure (N))
3-(3-{4-[4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-naphthalen-1-yloxy]-butyrylamino}-propylamino)-hexanedioic acid dimethyl ester



HPLC-MS (Method C: m/z = 585 (M+1); Rt = 2,81 min.

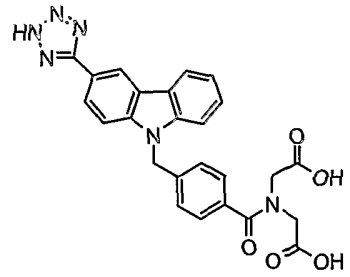
Example 905 (General procedure (N))
3-(3-{4-[4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-naphthalen-1-yloxy]-butyrylamino}-propylamino)-hexanedioic acid



HPLC-MS (Method C): m/z = 554 (M-3); Rt = 3,19 min.

Example 906 (General procedure (N))

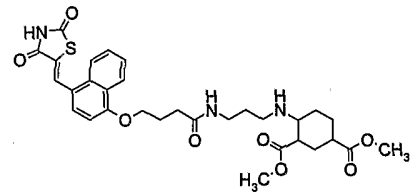
(Carboxymethyl-{4-[3-(2H-tetrazol-5-yl)-carbazol-9-ylmethyl]-benzoyl}-amino)-acetic acid



HPLC-MS (Method C): m/z = 485 (M+1); Rt = 3.04 min.

Example 907 (General procedure (N))

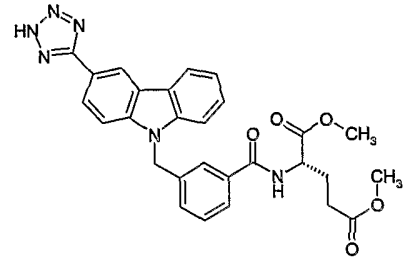
4-(3-{4-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)-naphthalen-1-yloxy]-butyrylamino}-propylamino)-cyclohexane-1,3-dicarboxylic acid dimethyl ester



HPLC-MS (Method C): m/z = 612 (M+1); Rt = 3,24 min.

Example 908 (General procedure (N))

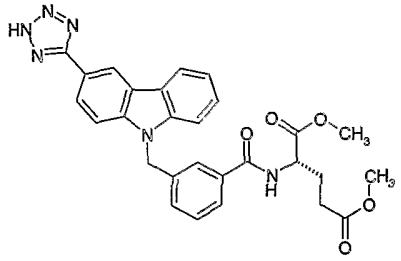
2-{3-[3-(2H-Tetrazol-5-yl)carbazol-9-ylmethyl]benzoylamino}pentanedioic acid dimethyl ester



HPLC-MS (Method C): m/z = 527 (M+1); Rt = 3.65min.

Example 909 (General procedure (N))

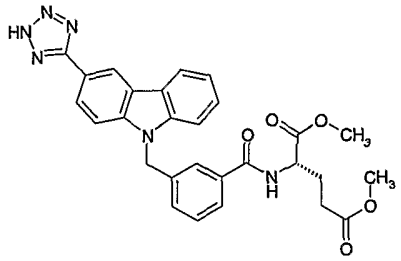
2-{3-[3-(2H-Tetrazol-5-yl)carbazol-9-ylmethyl]benzoylamino}pentanedioic acid dimethyl ester



HPLC-MS (Method C): m/z = 527 (M+1); Rt = 3.65min.

Example 910 (General procedure (N))

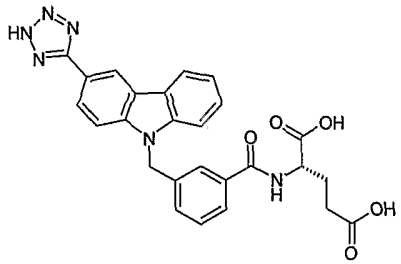
2-{3-[3-(2H-Tetrazol-5-yl)carbazol-9-ylmethyl]benzoylamino}pentanedioic acid dimethyl ester



HPLC-MS (Method C): m/z = 527 (M+1); Rt = 3.65min.

Example 911 (General procedure (N))

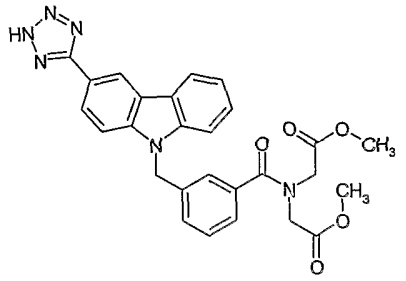
2-{3-[3-(2H-Tetrazol-5-yl)carbazol-9-ylmethyl]benzoylamino}pentanedioic acid



HPLC-MS (Method C): m/z = 499 (M+1); Rt = 3.00 min.

Example 912 (General procedure (N))

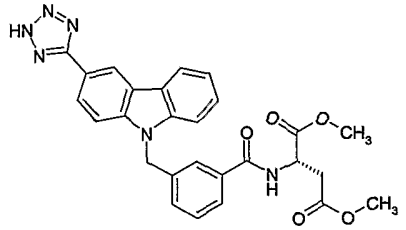
(Methoxycarbonylmethyl-{3-[3-(2H-tetrazol-5-yl)carbazol-9-ylmethyl]benzoyl}amino)acetic acid methyl ester



^{1}H-NMR (DMSO-d_6): δ 8.88 (1H, d), 8.29 (1H, d), 8.10 (1H, dd), 7.85 (1H, d), 7.67 (1H, d), 7.52 (1H, t), 7.39 (1H, t), 7.30 (2H, m), 7.17 (2H, m), 5.79 (2H, s), 4.17 (2H, s), 4.02 (2H, s), 3.62 (3H, s), 3.49 (3H, s).

Example 913 (General procedure (N))

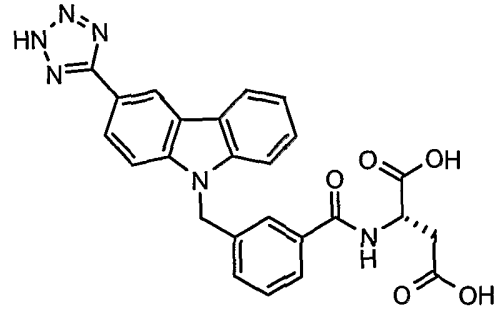
2-{3-[3-(2H-Tetrazol-5-yl)carbazol-9-ylmethyl]benzoylamino}succinic acid dimethyl ester



HPLC-MS (Method C): m/z = 513 (M+1); Rt = 3.70 min.

Example 914 (General procedure (N))

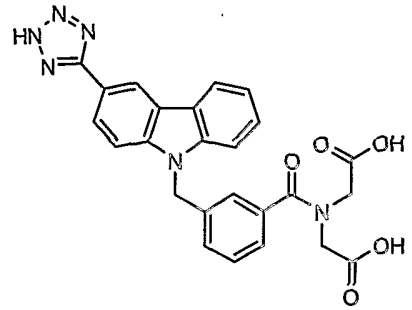
2-{3-[3-(2H-Tetrazol-5-yl)-carbazol-9-ylmethyl]-benzoylamino}-succinic acid



HPLC-MS (Method C): m/z = 485 (M+1); Rt = 2.96 min.

Example 915 (General procedure (N))

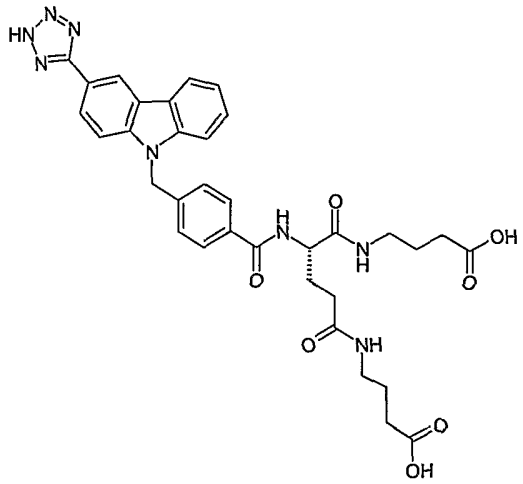
(Carboxymethyl-{3-[3-(2H-tetrazol-5-yl)carbazol-9-ylmethyl]benzoyl}amino)acetic acid



HPLC-MS (Method C): m/z = 485 (M+1); Rt = 2.87 min.

Example 916 (General procedure (N))

4-(4-(3-Carboxy-propylcarbamoyl)4-{4-[3-(2H-tetrazol-5-yl)carbazol-9-ylmethyl]-benzoylamino}-butyrylamino)-butyric acid

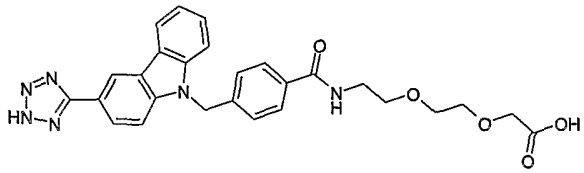


The title compound was prepared by coupling of (S)-2-{4-[3-(2H-tetrazol-5-yl)carbazol-9-ylmethyl]*benzoylamino*}*pentanedioic acid bis-*(2,5-*dioxopyrrolidin*-1-yl) *ester* (prepared from (S)-2-{4-[3-(2H-tetrazol-5-yl)carbazol-9-ylmethyl]benzoylamino}pentanedioic acid by essentially the same procedure as described for the synthesis of 4-[3-(2H-tetrazol-5-yl)carbazol-9-ylmethyl]*benzoic acid* 2,5-dioxopyrrolidin-1-yl ester) *with* 4-*aminobutyric acid according to the* procedure described for the preparation of 4-{4-[3-(2H-tetrazol-5-yl)carbazol-9-ylmethyl]-benzoylamino}butyric acid .

HPLC-MS (Method C): m/z: 669 (M+1); Rt = 2.84 min.

Example 917 (General procedure (N))

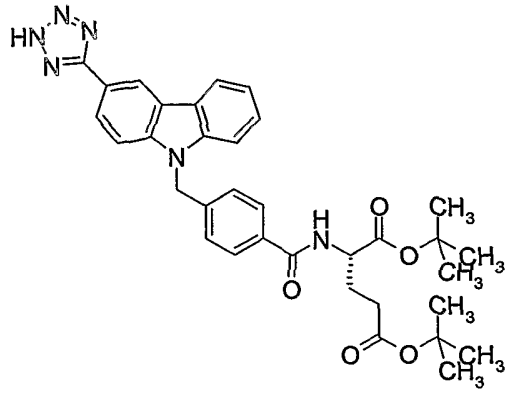
[2-(2-{4-[3-(2H-Tetrazol-5-yl)-carbazol-9-ylmethyl]benzoylamino}ethoxy)ethoxy]acetic acid



HPLC-MS (Method C): m/z: 515 (M+1); Rt = 3.10 min.

Example 918 (General procedure (N))

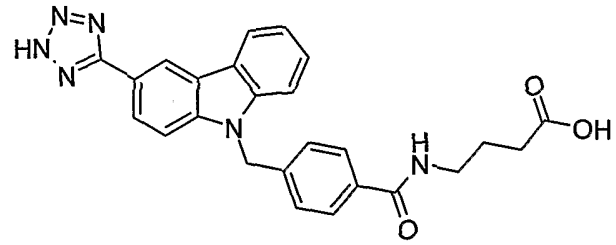
2-{4-[3-(2H-Tetrazol-5-yl)-carbazol-9-ylmethyl]-benzoylamino}-pentanedioic acid di-tert-butyl ester



HPLC-MS (Method C): m/z = 611 (M+1); Rt = 4.64 min.

Example 919 (General Procedure (N)).

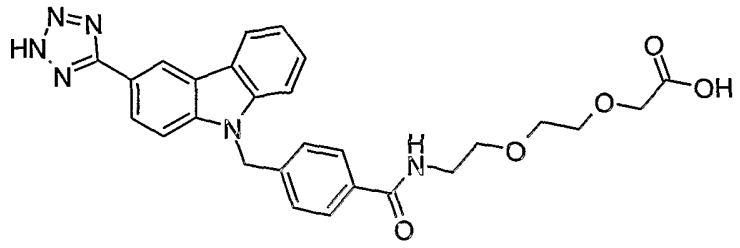
4-{4-[3-(2H-Tetrazol-5-yl)carbazol-9-ylmethyl]benzoylamino}butyric Acid



HPLC-MS (Method C): m/z: 455 (M+1); Rt = 3.13 min.

Example 920 (General Procedure (N)).

[2-(2-{4-[3-(2H-Tetrazol-5-yl)carbazol-9-ylmethyl]benzoylamino}ethoxy)ethoxy]acetic acid



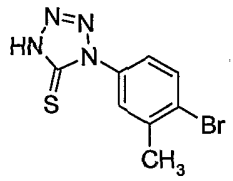
The title compound was prepared by coupling of 4-[3-(2H-tetrazol-5-yl)carbazol-9-ylmethyl]benzoic acid 2,5-dioxopyrrolidin-1-yl ester with [2-(2-aminoethoxy)ethoxy]acetic acid (prepared from [2-[2-(Fmoc-amino)ethoxy]ethoxy]acetic acid by treatment with PS-Trisamine resin in DMF).

HPLC-MS (Method C): m/z: 515 (M+1); Rt = 3.10 min.

The commercially available compounds in the following examples do all bind to the HisB10 Zn^{2+}site:

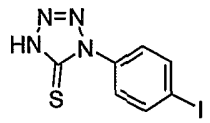
Example 921

1-(4-Bromo-3-methylphenyl)-1,4-dihydrotetrazole-5-thione



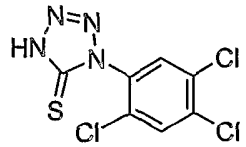
Example 922

1-(4-Iodophenyl)-1,4-dihydrotetrazole-5-thione



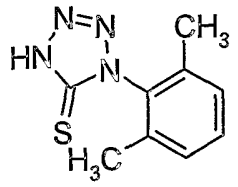
Example 923

1-(2,4,5-Trichlorophenyl)-1*H*-tetrazole-5-thiol



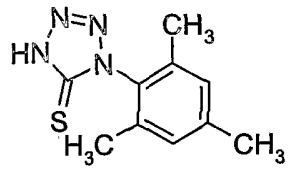
Example 924

1-(2,6-Dimethylphenyl)-1,4-dihydrotetrazole-5-thione



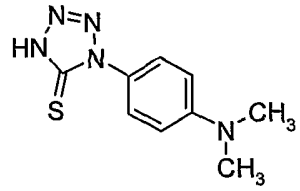
Example 925

1-(2,4,6-Trimethylphenyl)-1,4-dihydrotetrazole-5-thione



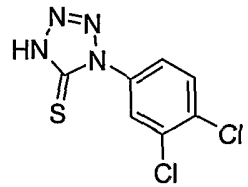
Example 926

1-(4-Dimethylaminophenyl)-1*H*-tetrazole-5-thiol



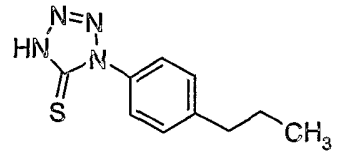
Example 927

1-(3,4-Dichlorophenyl)-1,4-dihydro-1*H*-tetrazole-5-thione



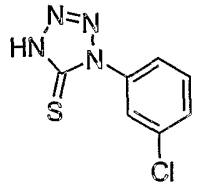
Example 928

1-(4-Propylphenyl)-1,4-dihydro-1H-tetrazole-5-thione



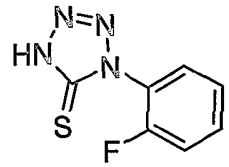
Example 929

1-(3-Chlorophenyl)-1,4-dihydro-1*H*-tetrazole-5-thione



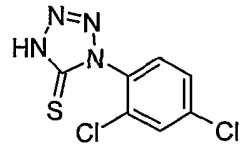
Example 930

1-(2-Fluorophenyl)-1,4-dihydro-1H-tetrazole-5-thione



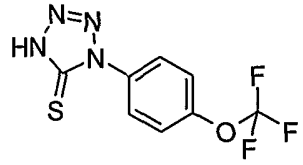
Example 931

1-(2,4-Dichlorophenyl)-1,4-dihydro-1*H*-tetrazole-5-thione



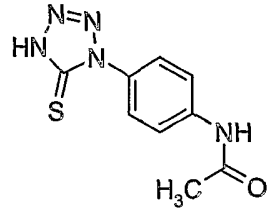
Example 932

1-(4-Trifluoromethoxyphenyl)-1,4-dihydro-1*H*-tetrazole-5-thione



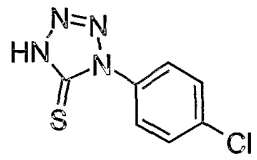
Example 933

N-[4-(5-Mercaptotetrazol-1-yl)-phenyl]-acetamide



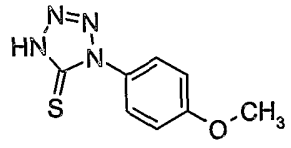
Example 934

1-(4-Chlorophenyl)-1,4-dihydrotetrazole-5-thione



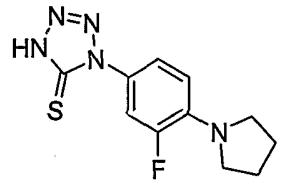
Example 935

1-(4-Methoxyphenyl)-1,4-dihydrotetrazole-5-thione



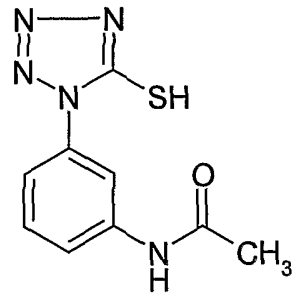
Example 936

1-(3-Fluoro-4-pyrrolidin-1-ylphenyl)-1,4-dihydrotetrazole-5-thione



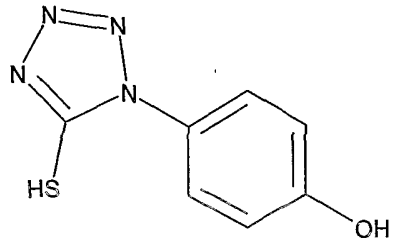
Example 937

N-[3-(5-Mercaptotetrazol-1-yl)phenyl]acetamide

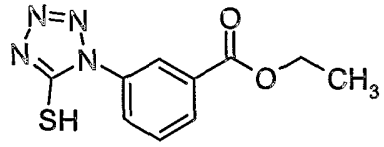


Example 938

1-(4-Hydroxyphenyl)-5-mercaptotetrazole

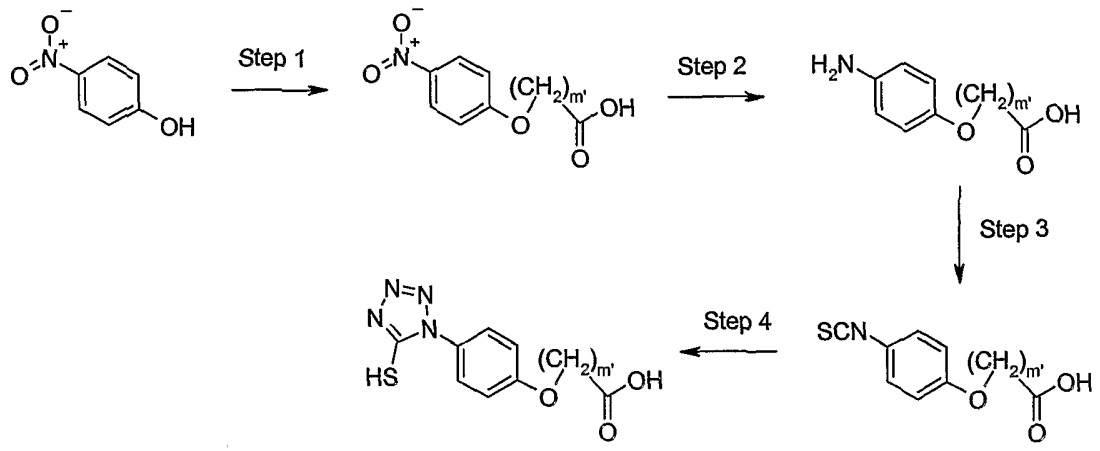


Example 939



Preparation of 1-aryl-1,4-dihydrotetrazole-5-thiones (or the tautomeric 1-aryltetrazole-5-thiols) is described in the literature (eg. by Kauer & Sheppard, *J. Org. Chem.*, **32**, 3580-92 (1967)) and is generally performed eg. by reaction of aryl-isothiocyanates with sodium azide followed by acidification

1-Aryl-1,4-dihydrotetrazole-5-thiones with a carboxylic acid tethered to the aryl group may be prepared as shown in the following scheme:



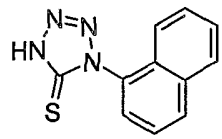
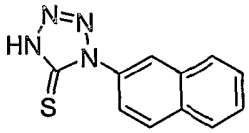
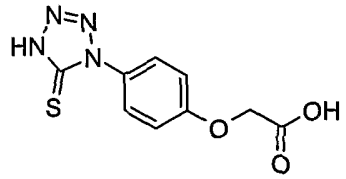
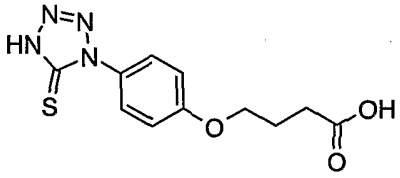
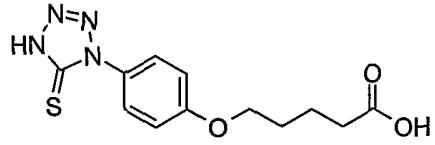
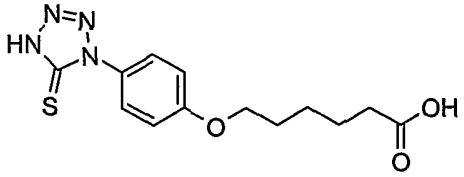
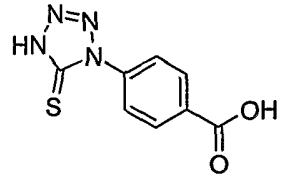
Step 1 is a phenol alkylation and is very similar to steps 1 and 2 of general procedure (D) and may also be prepared similarly as described in example 481.

Step 2 is a reduction of the nitro group. $SnCl_2$, H_2 over Pd/C and many other procedures known to those skilled in the art may be utilised.

Step 3 is formation of an arylisothiocyanate from the corresponding aniline. As reagents CS_2, $CSCl_2$, or other reagents known to those skilled in the art, may be utilised.

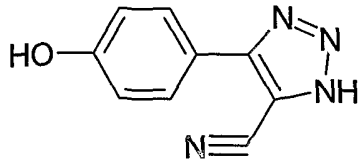
Step 4 is a conversion to mercaptotetrazole as described above.

Compounds of the invention include:

Example 940 	Example 941 
Example 942 	Example 943 
Example 944 	Example 945 
Example 946 	

Example 947

4-(4-Hydroxyphenyl)-1*H*-[1,2,3]triazole-5-carbonitrile

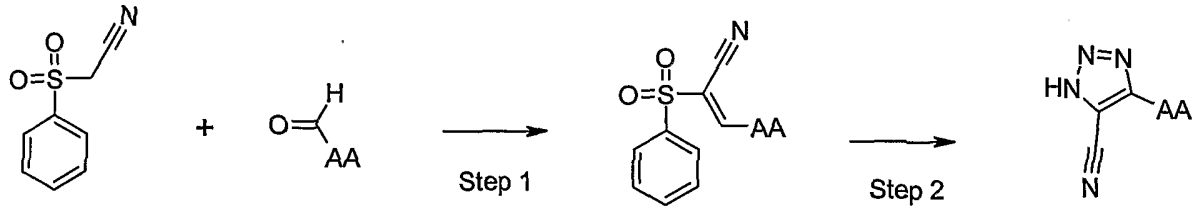


Phenylsulphonyl acetonitrile (2.0 g, 11.04 mmol) was mixed with 4-hydroxybenzaldehyde (1.35 g, 11.04 mmol) in DMF (10 mL) and toluene (20 mL). The mixture was refluxed for 3 hours and subsequently evaporated to dryness *in vacuo*. The residue was treated with diethyl ether and toluene. The solid formed was filtered to afford 2.08 g (66%) of 2-benzenesulfonyl-3-(4-hydroxyphenyl)acrylonitrile.
HPLC-MS (Method C): m/z: 286 (M+1); Rt. = 3.56 min.

A mixture of 2-benzenesulfonyl-3-(4-hydroxyphenyl)acrylonitrile (2.08 g, 7.3 mmol) and sodium azide (0.47g,7.3 mmol) in DMF (50 mL) was heated at reflux temperature 2 hours. After cooling, the mixture was poured on ice. The mixture was evaporated in vacuo to almost dryness and toluene was added. After filtration, the organic phase was evaporated *in vacuo.* The residue was purified by silicagel chromatography eluting with a mixture of ethyl acetate and heptane (1:2). This afforded 1.2 g (76%) of the title compound.

1H NMR (DMSO-d_6): 10.2 (broad,1H); 7.74 (d,2H); 6.99 (d,2H); 3.6-3.2 (broad,1H).
HPLC-MS (Method C) m/z: = 187 (M+1); Rt. = 1.93 min

General procedure (O) for preparation of compounds of general formula I_{14}:



I_{14}

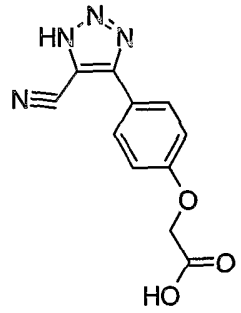
wherein
AA is as defined above,

Steps 1 and 2 are described in the literature (eg Beck & Gûnther, *Chem. Ber.*, 106, 2758-66 (1973))

Step 1 is a Knoevenagel condensation of the aldehyde AA-CHO with phenylsulfonyl-acetonitrile and step 2 is a reaction of the vinylsulfonyl compound obtained in step 1 with sodium azide. This reaction is usually performed in DMF at 90 – 110 °C.

This general procedure is further illustrated in the following example 948:

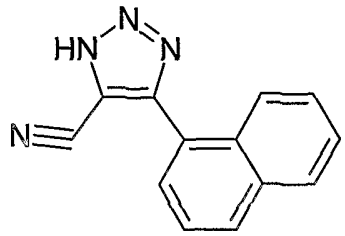
Example 948 (General Procedure (O))
[4-(5-Cyano-1*H*-[1,2,3]triazol-4-yl)phenoxy]acetic acid



Phenylsulphonylacetonitrile (0.1 g, 0.55 mmol) was mixed with 4-formylphenoxyactic acid (0.099 g, 0.55 mmol) in DMF (3 mL) and heated to 110 °C for 3 h and subsequently cooled to RT. Sodium azide (0.036 g, 0.55 mmol) was added and the resulting mixture was heated to 110 °C for 3 h and cooled to RT. The mixture was poured into water (20 mL) and centrifuged. The supernatant was discarded, ethanol (5 mL) was added and the mixture was centrifuged again. After discarding the supernatant, the residue was dried *in vacuo* to afford 50 mg (37%) of [4-(5-Cyano-1*H*-[1,2,3]triazol-4-yl)phenoxy]acetic acid.

HPLC-MS (Method C): m/z: 245 (M+1) Rt. 2.19 min.

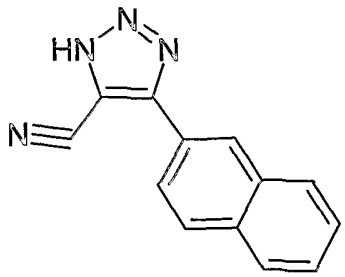
Example 949 (General Procedure (O))
5-(Naphthalen-1-yl)-3*H*-[1,2,3]triazole-4-carbonitrile



HPLC-MS (Method C): m/z: 221 (M+1); Rt. 3.43 min.

Example 950 (General Procedure (O))

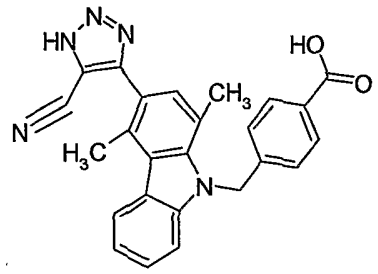
5-(Naphthalen-2-yl)-3*H*-[1,2,3]triazole-4-carbonitrile



HPLC-MS (Method C): m/z: 221 (M+1); Rt = 3.66 min.

Example 951 (General procedure (O))

4-[3-(5-Cyano-[1,2,3]triazol-4-yl)-1,4-dimethylcarbazol-9-ylmethyl]-benzoic acid



HPLC-MS (Method C): m/z = 422 (M+1); Rt = 3.85 min.

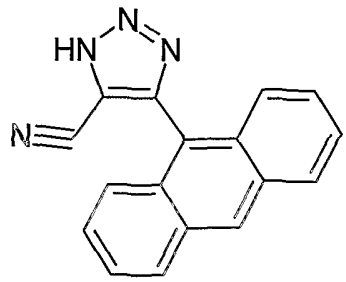
Preparation of intermediary aldehyde:

1,4 Dimethylcarbazol-3-carbaldehyde (0.68 g, 3.08 mmol) was dissolved in dry DMF (15 mL), NaH (diethyl ether washed) (0.162 g, 6.7 mol) was slowly added under nitrogen and the mixture was stirred for 1 hour at room temperature. 4-Bromomethylbenzoic acid (0.73 g, 3.4 mmol) was slowly added and the resulting slurry was heated to 40 °C for 16 hours. Water (5 mL) and hydrochloric acid (6N, 3 mL) were added. After stirring for 20 min at room temperature, the precipitate was filtered off and washed twice with acetone to afford after drying 0.38 g (34%) of 4-(3-formyl-1,4-dimethylcarbazol-9-ylmethyl)benzoic acid.

HPLC-MS (Method C) : m/z = 358 (M+1), RT. = 4.15 min.

Example 952 (General Procedure (O))

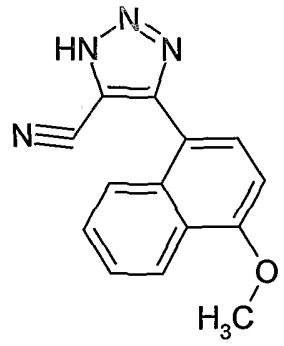
5-(Anthracen-9-yl)-3*H*-[1,2,3]triazole-4-carbonitrile



HPLC-MS (Method C): m/z: 271 (M+1); Rt = 3.87 min.

Example 953 (General Procedure (O))

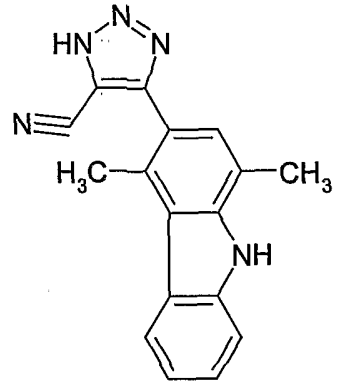
5-(4-Methoxynaphthalen-1-yl)-3*H*-[1,2,3]triazole-4-carbonitrile



HPLC-MS (Method C): m/z: 251 (M+1); Rt = 3.57 min.

Example 954 (General Procedure (O))

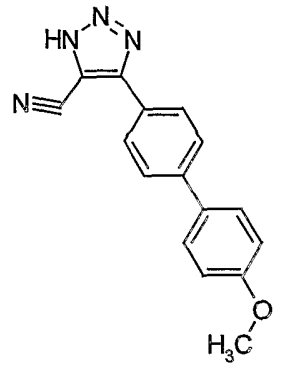
5-(1,4-Dimethyl-9*H*-carbazol-3-yl)-3*H*-[1,2,3]triazole-4-carbonitrile



HPLC-MS (Method C): m/z: 288 (M+1); Rt = 3.67 min.

Example 955 (General procedure (O))

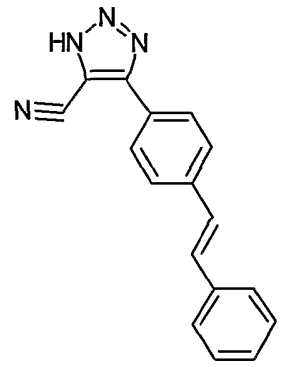
5-(4'-Methoxybiphenyl-4-yl)-3H-[1,2,3]triazole-4-carbonitrile



HPLC-MS (Method C): m/z = 277 (M+1); Rt = 3.60 min.

Example 956 (General procedure (O))

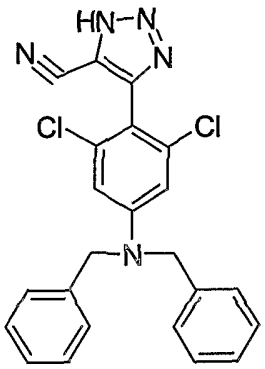
5-(4-Styrylphenyl)-3H-[1,2,3]triazole-4-carbonitrile



HPLC-MS (Method C): m/z = 273 (M+1); Rt = 4.12 min.

Example 957 (General procedure (O))

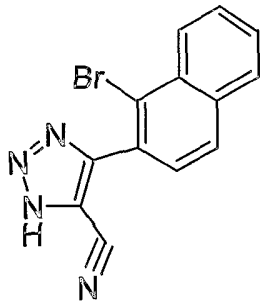
5-(2,6-Dichloro-4-dibenzylaminophenyl)-3H-[1,2,3]triazole-4-carbonitrile



HPLC-MS (Method C): m/z = 434 (M+1); Rt = 4.64 min.

Example 958 (General procedure (O))

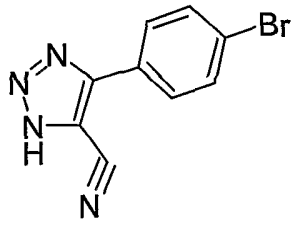
5-(1-Bromonaphthalen-2-yl)-3H-[1,2,3]triazole-4-carbonitrile



HPLC-MS (Method C: m/z = 300 (M+1); Rt. = 3.79 min.

Example 959

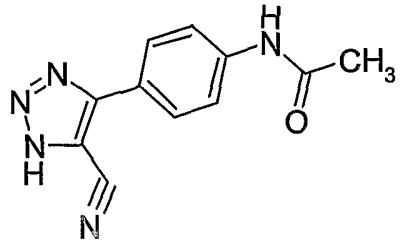
4-(4-Bromophenyl)-1H-[1,2,3]triazole-5-carbonitrile



This compound is commercially available (MENAI).

Example 960

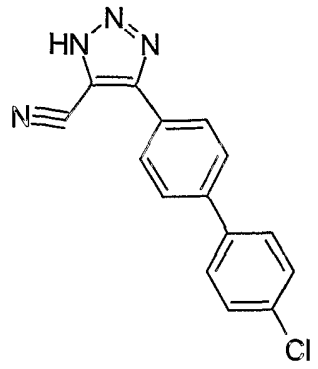
N-[4-(5-Cyano-1H-[1,2,3]triazol-4-yl)-phenyl]-acetamide



This compound is commercially available (MENAI).

Example 961 (General procedure (O))

5-(4'-Chlorobiphenyl-4-yl)-3H-[1,2,3]triazole-4-carbonitrile

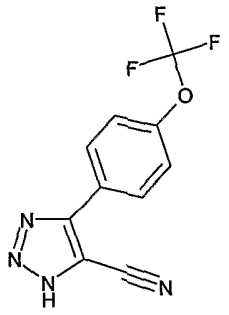


HPLC-MS (Method C): m/z = 281 (M+1); Rt = 4.22 min.

The compounds in the following examples are commercially available and may be prepared using a similar methodology:

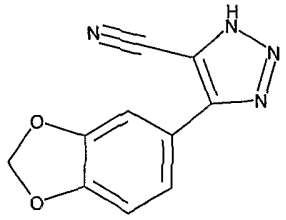
Example 962

4-(4-Trifluoromethoxyphenyl)-1*H*-[1,2,3]triazole-5-carbonitrile



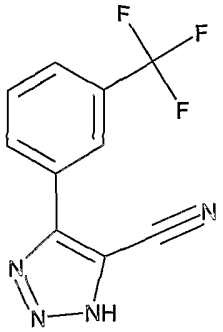
Example 963

4-Benzo[1,3]dioxol-5-yl-1*H*-[1,2,3]triazole-5-carbonitrile



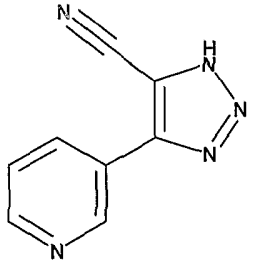
Example 964

4-(3-Trifluoromethylphenyl)-1*H*-[1,2,3]triazole-5-carbonitrile



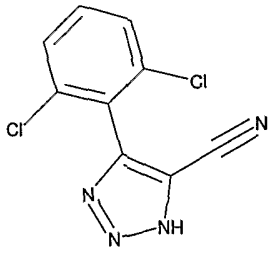
Example 965

4-Pyridin-3-yl-1*H*-[1,2,3]triazole-5-carbonitrile



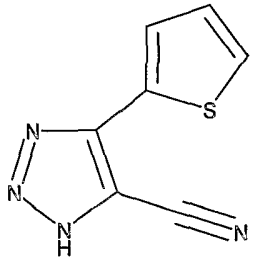
Example 966

4-(2,6-Dichlorophenyl)-1*H*-[1,2,3]triazole-5-carbonitrile



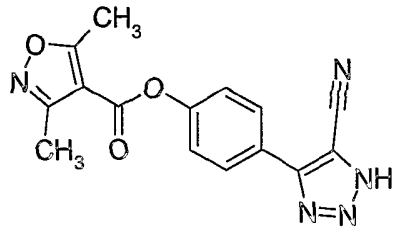
Example 967

4-Thiophen-2-yl-1*H*-[1,2,3]triazole-5-carbonitrile



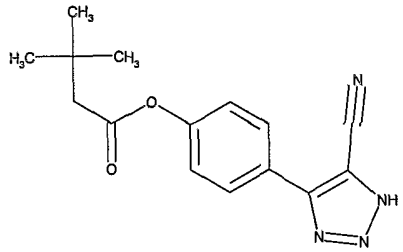
Example 968

3,5-Dimethylisoxazole-4-carboxylic acid 4-(5-cyano-1*H*-[1,2,3]triazol-4-yl)phenyl ester



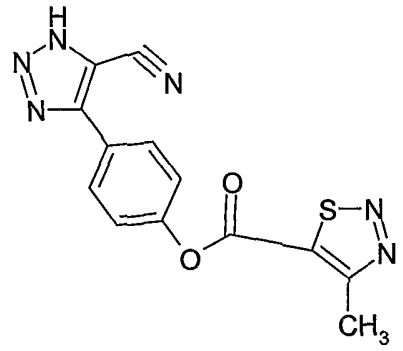
Example 969

3,3-Dimethyl-butyric acid 4-(5-cyano-1*H*-[1,2,3]triazol-4-yl)phenyl ester



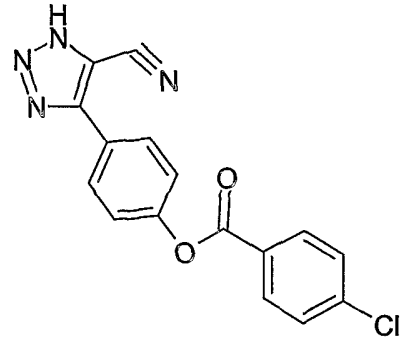
Example 970

4-Methyl-[1,2,3]thiadiazole-5-carboxylic acid 4-(5-cyano-1*H*-[1,2,3]triazol-4-yl)phenyl ester



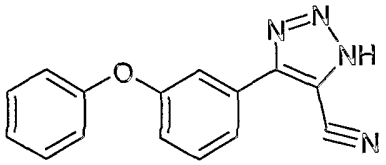
Example 971

4-Chlorobenzoic acid 4-(5-cyano-1*H*-[1,2,3]triazol-4-yl)phenyl ester



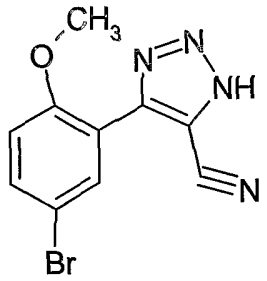
Example 972

4-(3-Phenoxyphenyl)-1*H*-[1,2,3]triazole-5-carbonitrile



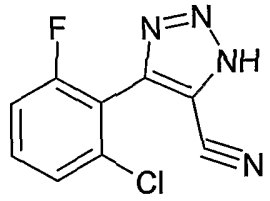
Example 973

4-(5-Bromo-2-methoxyphenyl)-1*H*-[1,2,3]triazole-5-carbonitrile



Example 974

4-(2-Chloro-6-fluorophenyl)-1*H*-[1,2,3]triazole-5-carbonitrile



The following cyanotriazoles are also compounds of the invention:

4-(2-Chloro-6-fluorophenyl)-1*H*-[1,2,3]triazole-5-carbonitrile.

Terephthalic acid mono[4-(5-cyano-1*H*-[1,2,3]triazol-4-yl)phenyl] ester.

N- [4-(5-cyano-1*H*-[1,2,3]triazol-4-yl)-phenyl]terephthalamic acid

4-(4-Octyloxyphenyl)-1*H*-[1,2,3]triazole-5-carbonitrile

4-(4-Styrylphenyl)-1*H*-[1,2,3]triazole-5-carbonitrile.

4-(4'-Trifluoromethylbiphenyl-4-yl)-1*H*-[1,2,3]triazole-5-carbonitrile.

4-(4'-Chlorobiphenyl-4-yl)-1*H*-[1,2,3]triazole-5-carbonitrile.

4-(4'-Methoxybiphenyl-4-yl)-1*H*-[1,2,3]triazole-5-carbonitrile.

4-(1-Naphthyl)-1*H*-[1,2,3]triazole-5-carbonitrile.

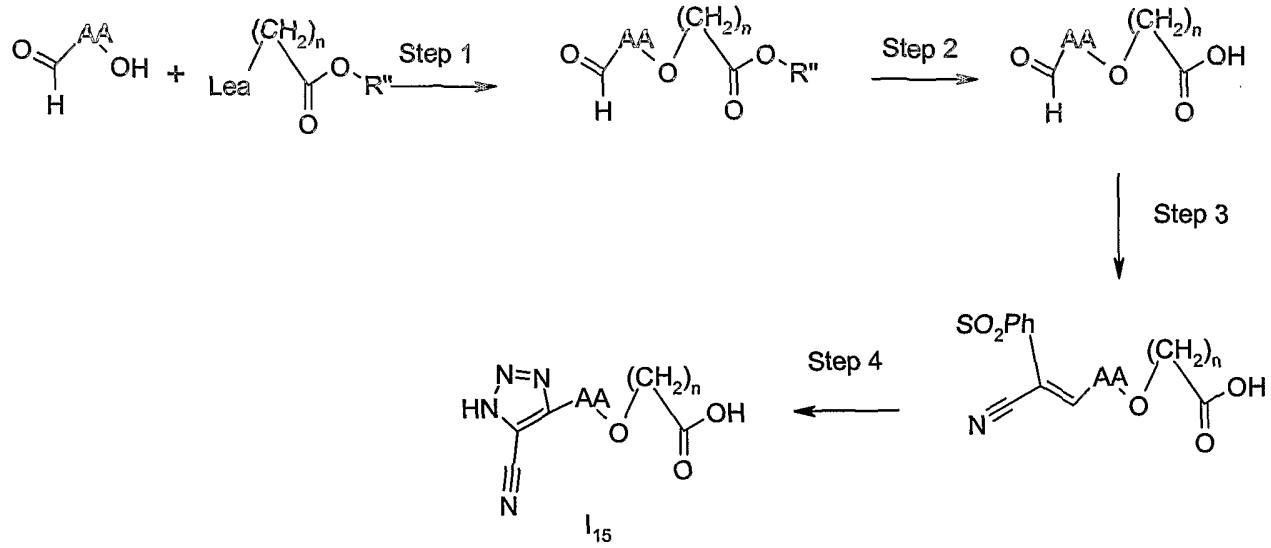
4-(9-Anthranyl)-1*H*-[1,2,3]triazole-5-carbonitrile.

4-(4-Methoxy-1-naphthyl)-1*H*-[1,2,3]triazole-5-carbonitrile.

4-(4-Aminophenyl)-1*H*-[1,2,3]triazole-5-carbonitrile.

4-(2-Naphthyl)-1*H*-[1,2,3]triazole-5-carbonitrile.

General procedure (P) for preparation of compounds of general formula I_{15}:



wherein

n is 1 or 3-20,

AA is as defined above,

R" is a standard carboxylic acid protecting group, such as C_1-C_6-alkyl or benzyl and Lea is a leaving group, such as chloro, bromo, iodo, methanesulfonyloxy, toluenesulfonyloxy or the like.

This procedure is very similar to general procedure (D), steps 1 and 2 are identical.

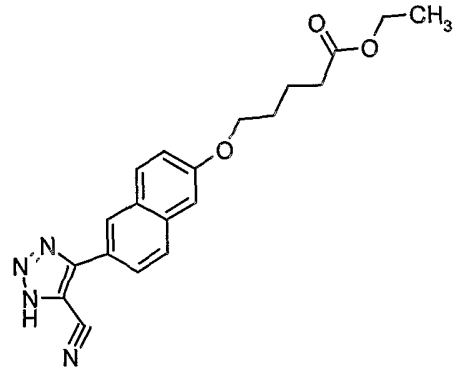
Steps 3 and 4 are described in the literature (eg Beck & Gûnther, *Chem. Ber.*, **106**, 2758-66 (1973))

Step 3 is a Knoevenagel condensation of the aldehyde obtained in step 2 with phenylsulfonylacetonitrile and step 4 is a reaction of the vinylsulfonyl compound obtained in step 3 with sodium azide. This reaction is usually performed in DMF at 90 – 110 °C.

This General procedure (P) is further illustrated in the following two examples

Example 975 (General procedure (P))

5-[6-(5-Cyano-1H-[1,2,3]triazol-4-yl)-naphthalen-2-yloxy]-pentanoic acid ethyl ester



6-Hydroxynaphthalene-2-carbaldehyde (Syncom BV. NL, 15.5 g, 90 mmol) and K_2CO_3 (62.2 g, 450 mmol) were mixed in DMF (300mL) and stirred at room temperature for 1hour. Ethyl 5-bromovalerate (21.65 g, 103.5 mmol) was added and the mixture was stirred at room temperature for 16 hours. Activated carbon was added and the mixture was filtered. The filtrate was evaporated to dryness *in vacuo* to afford 28.4 g of crude 5-(6-formylnaphthalen-2-yloxy)pentanoic acid ethyl ester, which was used without further purification.

HPLC-MS (Method C): m/z = 301 (M+1); Rt. = 4.39 min.

5-(6-Formylnaphthalen-2-yloxy)pentanoic acid ethyl ester (28.4 g, 94.5 mmol), phenylsulfonylacetonitrile (20.6 g, 113.5 mmol), and piperidine (0.94 mL) were dissolved in DMF (200 mL) and the mixture was heated at 50 °C for 16 hours. The resulting mixture was evaporated to dryness *in vacuo* and the residue was dried for 16 hours at 40 °C *in vacuo*. The solid was recrystallised from 2-propanol (800 mL) and dried again as described above. This afforded 35 g (80%) of 5-[6-(2-benzenesulfonyl-2-cyanovinyl)naphthalen-2-yloxy]pentanoic acid ethyl ester.

HPLC-MS (Method C): m/z = 486 (M+23); Rt. = 5.09 min.

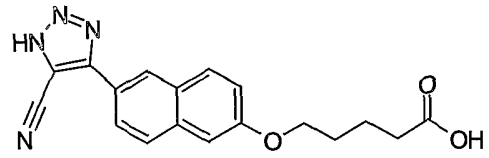
5-[6-(2-Benzenesulfonyl-2-cyanovinyl)naphthalen-2-yloxy]pentanoic acid ethyl ester (35 g, 74.6 mmol) and sodium azide (4.9 g, 75.6 mmol) were dissolved in DMF (100 mL) and stirred

for 16 hours at 50 °C. The mixture was evaporated to dryness *in vacuo*, redissolved in THF / ethanol and a small amount of precipitate was filtered off. The resulting filtrate was poured into water (2.5 L). Filtration afforded after drying 24.5 g (88%) of 5-[6-(5-cyano-1*H*-[1,2,3]triazol-4-yl)naphthalen-2-yloxy]pentanoic acid ethyl ester (24.5 g, 88%).

HPLC-MS (Method C): m/z = 365 (M+1); Rt. = 4.36 min.

Example 976 (General procedure (B))

5-[6-(5-Cyano-1H-[1,2,3]triazol-4-yl)-naphthalen-2-yloxy]-pentanoic acid

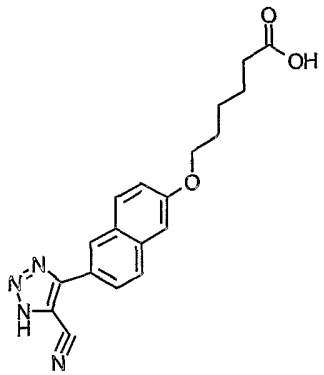


5-[6-(5-Cyano-1*H*-[1,2,3]triazol-4-yl)naphthalen-2-yloxy]pentanoicacid ethyl ester (24.5 g, 67.4 mmol) was dissolved in THF (150 mL) and mixed with sodium hydroxide (8.1 g, 202 mmol) dissolved in water (50 mL). The mixture was stirred for 2 days and the volatiles were evaporated *in vacuo*. The resulting aqueous solution was poured into a mixture of water (1 L) and hydrochloric acid (1N, 250 mL). The solid was isolated by filtration, dissolved in sodium hydroxide (1N, 200 mL), and the solution was washed with DCM and then ethyl acetate, the aquous layer was acidified with hydrochloric acid (12N). The precipitate was isolated by filtration, dissolved in THF / diethyl ether, the solution was treated with $MgSO_4$ and activated carbon, filtrated and evaporated *in vacuo* to almost dryness followed by precipitation by addition of pentane (1L). This afforded after drying *in vacuo* 17.2 g (76%) of the title compound.

HPLC-MS (Method C): m/z = 337 (M+1); Rt. = 3.49 min.

Example 977 (General procedure (P))

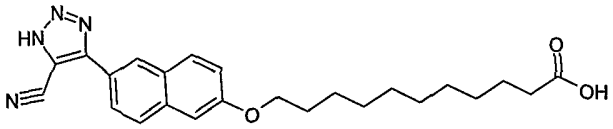
6-[6-(5-Cyano-1H-[1,2,3]triazol-4-yl)naphthalen-2-yloxy]hexanoic acid



HPLC-MS (Method C): m/z = 351 (M+1); Rt = 3.68 min.

Example 978 (General procedure (P))

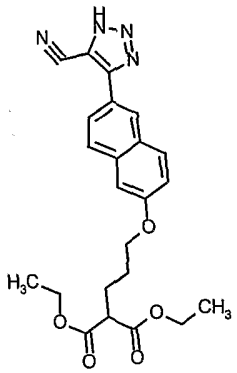
11-[6-(5-Cyano-1H-[1,2,3]triazol-4-yl)-naphthalen-2-yloxy]-undecanoic acid



HPLC-MS (Method C): m/z = 443 (M+23); Rt = 4.92 min.

Example 979 (General procedure (P))

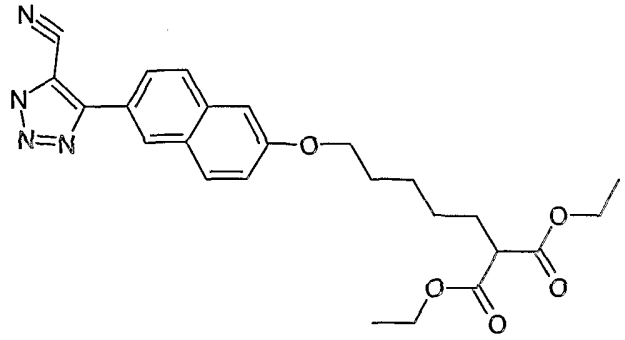
2-{3-[6-(5-Cyano-1H-[1,2,3]triazol-4-yl)-naphthalen-2-yloxy]-propyl}-malonic acid diethyl ester



HPLC-MS (Method C): m/z = 465 (M+1); Rt. = 4.95 min.

Example 980 (General procedure (P))

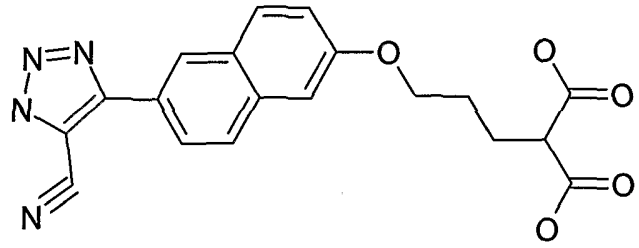
2-{5-[6-(5-Cyano-1H-[1,2,3]triazol-4-yl)-naphthalen-2-yloxy]-pentyl}-malonic acid diethyl ester



HPLC-MS (Method C): m/z = 465 (M+1); Rt. = 4.95 min.

Example 981 (General procedure (P))

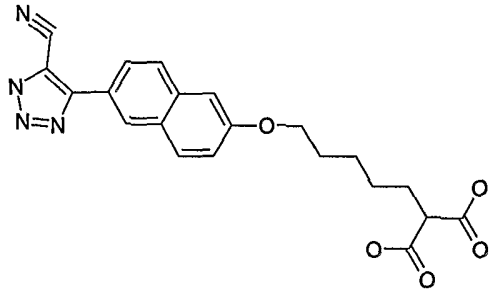
2-{3-[6-(5-Cyano-1H-[1,2,3]triazol-4-yl)-naphthalen-2-yloxy]-propyl}-malonic acid



HPLC-MS (Method C): m/z = 381 (M+1); Rt. = 3.12 min.

Example 982 (General procedure (P))

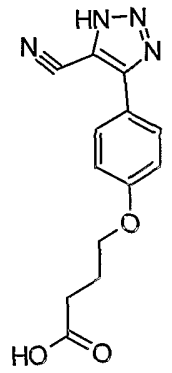
2-{5-[6-(5-Cyano-1H-[1,2,3]triazol-4-yl)-naphthalen-2-yloxy]-pentyl}-malonic acid



HPLC-MS (Method C): m/z 0 409 (M+1); Rt. = 3.51 min.

Example 983 (General procedure (P))

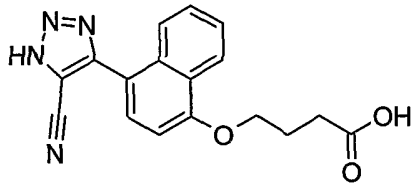
4-[4-(5-Cyano-1H-[1,2,3]triazol-4-yl)-phenoxy]butyric acid

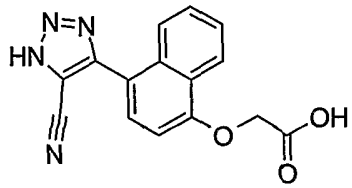


HPLC-MS (Method C): m/z = 273 (M+1); Rt = 2.44 min.

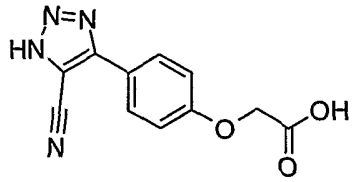
The following compounds may be prepared according to this general procedure (P):

4-(4-(5-Cyano-1*H*-[1,2,3]triazol-4-yl)phenoxy)butyric acid:





2-(4-(5-Cyano-1*H*-[1,2,3]triazol-4-yl)phenoxy)acetic acid:



4-(4-(5-Cyano-1*H*-[1,2,3]triazol-4-yl)phenoxy)butyric acid ethyl ester

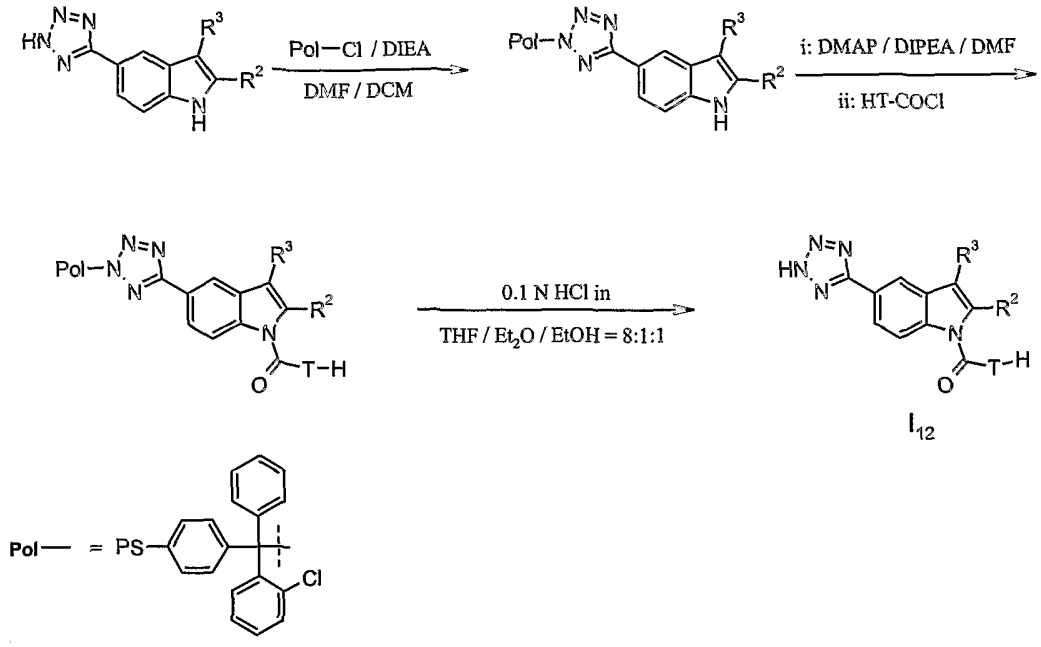
5-(4-(5-Cyano-1*H*-[1,2,3]triazol-4-yl)phenoxy)pentanoic acid

8-(4-(5-Cyano-1*H*-[1,2,3]triazol-4-yl)phenoxy)octanoic acid

10-(4-(5-Cyano-1*H*-[1,2,3]triazol-4-yl)phenoxy)decanoic acid

12-(4-(5-Cyano-1*H*-[1,2,3]triazol-4-yl)phenoxy)dodecanoic acid

General procedure (R) for preparation of compounds of general formula I_{12}:

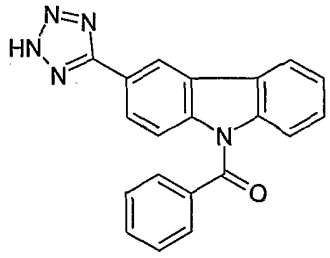


wherein T is as defined above and R^2 and R^3 are hydrogen, aryl or lower alkyl, both optionally substituted.

The general procedure (R) is further illustrated by the following example:

Example 984 (General procedure (R))

Phenyl-[3-(2H-tetrazol-5-yl)-carbazol-9-yl]-methanone



2-Chlorotritylchloride resin (100 mg, 0.114 mmol active chloride) was swelled in dichloromethane (4 mL) for 30 minutes. The solvent was drained, and a solution of 3-(2H-tetrazol-5-yl)-9H-carbazole (80 mg, 0.34 mmol) in a mixture of N,N-dimethylformamide / dichloromethane / N,N-di(2-propyl)ethylamine (5:5:1) (3 mL) was added. The reaction mixture was shaken at room temperature for 20 hours. The solvent was removed by filtration, and the resin was washed thoroughly with N,N-dimethylformamide (2 x 4 mL) and dichloromethane

(6 x 4 mL). A solution of 4-(dimethylamino)pyridine (14 mg, 0.11 mmol) and N,N-di(2-propyl)ethylamine (0.23 mL, 171 mg, 1.32 mmol) in N,N-dimethylformamide (2 mL) was added followed by benzoyl chloride (0.13 mL, 157 mg, 1.12 mmol). The mixture was shaken for 48 hours at room temperature. The drained resin was washed consecutively with dichloromethane (2 x 4 mL), methanol (2 x 4 mL) and tetrahydrofuran (4 mL). The resin was treated for 2 hours at room temperature with a solution of dry hydrogen chloride in tetrahydrofuran / ethyl ether / ethanol = 8:1:1 (0.1 M, 3 mL). The reaction mixture was drained and concentrated. The crude product was stripped with dichloromethane (1.5 mL) three times to yield the title compound.

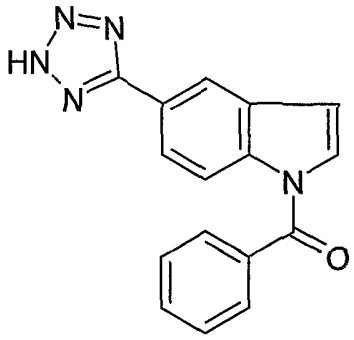
HPLC-MS (Method C): m/z: 340 (M+1); Rt = 3.68 min.

^{1}H-NMR (DMSO-d_6): δ 8.91 (1H, s), 8.34 (1H, d), 8.05 (1H, d), 7.78 (3H, m), 7.63 (3H, m), 7.46 (2H, m), 7.33 (1H, dd).

The compounds in the following examples were prepared in a similar fashion.

Example 985 (General procedure (R))

Phenyl-[5-(2H-tetrazol-5-yl)-indol-1-yl]-methanone

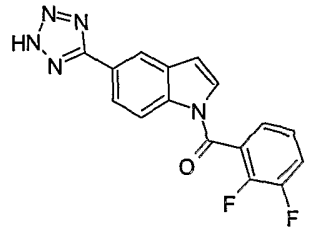


HPLC-MS (Method C): m/z: 290 (M+1); Rt = 3.04 min.

^{1}H-NMR (DMSO-d_6): δ 8.46 (1H, d), 8.42 (1H, d), 8.08 (1H, dd), 7.82 (2H, d), 7.74 (1H, t), 7.64 (2H, t), 7.55 (1H, d), 6.93 (1H, d).

Example 986 (General procedure (R))

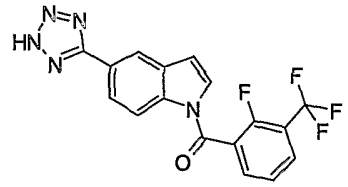
(2,3-Difluorophenyl)-[5-(2H-tetrazol-5-yl)-indol-1-yl]-methanone



HPLC-MS (Method B): m/z = 326 (M+1); Rt = 3.85 min.

Example 987 (General procedure (R))

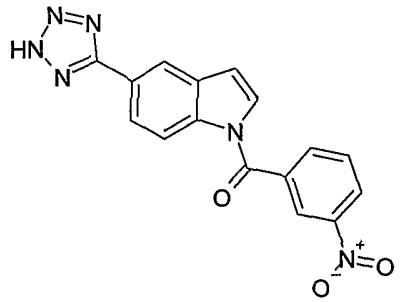
(2-Fluoro-3-trifluoromethylphenyl)-[5-(2H-tetrazol-5-yl)-indol-1-yl]-methanone



HPLC-MS (Method B): m/z = 376 (M+1); Rt = 4.32 min.

Example 988 (General procedure (R))

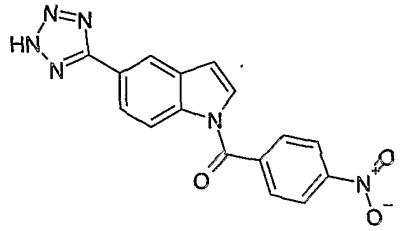
(3-Nitrophenyl)-[5-(2H-tetrazol-5-yl)-indol-1-yl]-methanone



HPLC-MS (Method B): m/z = 335 (M+1); Rt = 3.72 min.

Example 989 (General procedure (R))

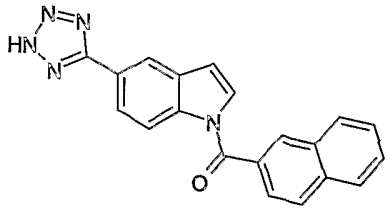
(4-Nitrophenyl)-[5-(2H-tetrazol-5-yl)-indol-1-yl]-methanone



HPLC-MS (Method B): m/z = 335 (M+1); Rt = 3.71 min.

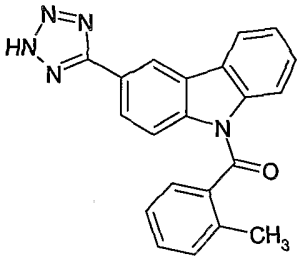
Example 990 (General procedure (R))

Naphthalen-2-yl-[5-(2H-tetrazol-5-yl)-indol-1-yl]-methanone



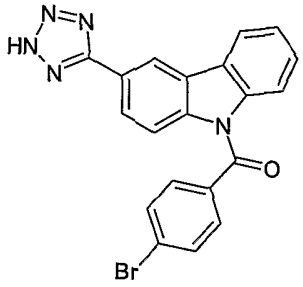
HPLC-MS (Method C): m/z = 340 (M+1); Rt = 4.25 min.

Example 991 (General procedure (R))



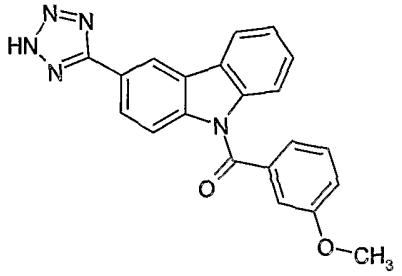
HPLC-MS (Method C): m/z: 354 (M+1); Rt = 3.91 min.

Example 992 (General procedure (R))



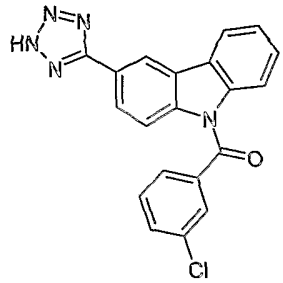
HPLC-MS (Method C): m/z: 418 (M+1); Rt = 4.39 min.

Example 993 (General procedure (R))



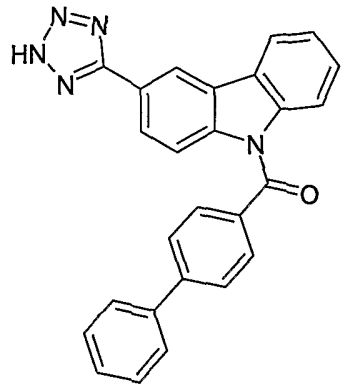
HPLC-MS (Method C): m/z: 370 (M+1); Rt = 4.01 min.

Example 994 (General procedure (R))



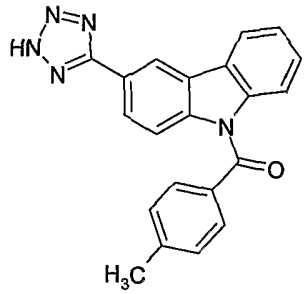
HPLC-MS (Method C): m/z: 374 (M+1); Rt = 4.28 min.

Example 995 (General procedure (R))



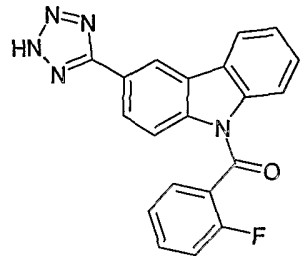
HPLC-MS (Method C): m/z: 416 (M+1); Rt = 4.55 min.

Example 996 (General procedure (R))



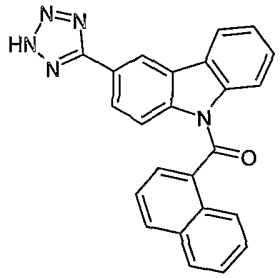
HPLC-MS (Method C): m/z: 354 (M+1); Rt = 4.22 min.

Example 997 (General procedure (R))



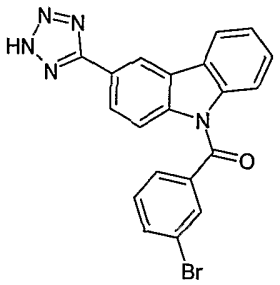
HPLC-MS (Method C): m/z: 358 (M+1); Rt = 3.91 min.

Example 998 (General procedure (R))



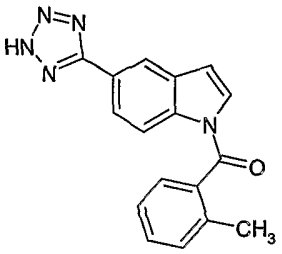
HPLC-MS (Method C): m/z: 390 (M+1); Rt = 4.38 min.

Example 999 (General procedure (R))



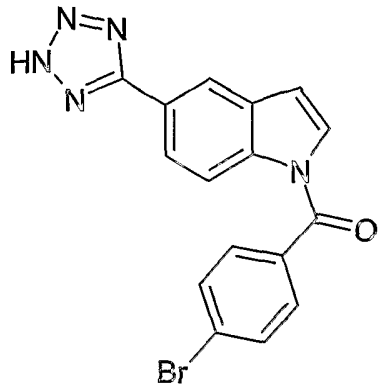
HPLC-MS (Method C): m/z: 418 (M+1); Rt = 4.36 min.

Example 1000 (General procedure (R))



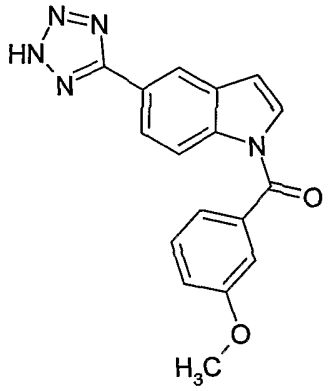
HPLC-MS (Method C): m/z: 304 (M+1); Rt = 3.32 min.

Example 1001 (General procedure (R))



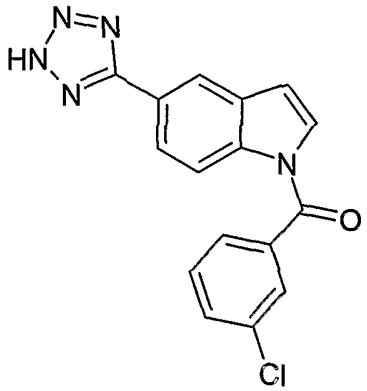
HPLC-MS (Method C): m/z: 368 (M+1); Rt = 3.84 min.

Example 1002 (General procedure (R))



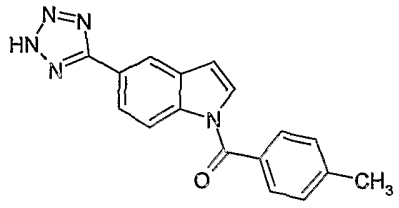
HPLC-MS (Method C): m/z: 320 (M+1); Rt = 3.44 min.

Example 1003 (General procedure (R))



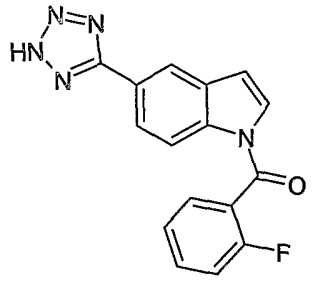
HPLC-MS (Method C): m/z: 324 (M+1); Rt = 3.73 min.

Example 1004 (General procedure (R))



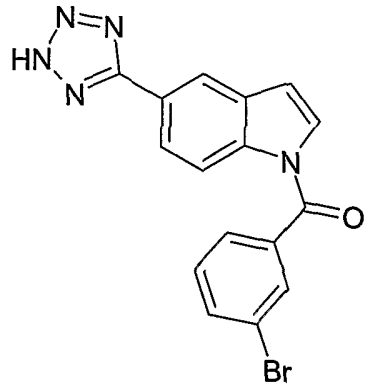
HPLC-MS (Method C): m/z: 304 (M+1); Rt = 3.64 min.

Example 1005 (General procedure (R))



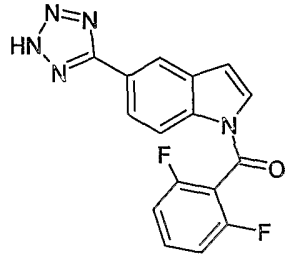
HPLC-MS (Method A): m/z: 308 (M+1); Rt = 3.61 min.

Example 1006 (General procedure (R))



HPLC-MS (Method C): m/z: 368 (M+1); Rt = 3.77 min.

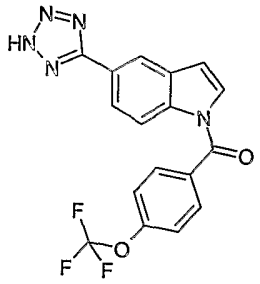
Example 1007 (General procedure (R))



HPLC-MS (Method A): (sciex) m/z: 326 (M+1); Rt = 3.73 min.

HPLC-MS (Method C): m/z: 326 (M+1); Rt = 3.37 min.

Example 1008 (General procedure (R))

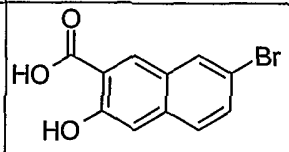
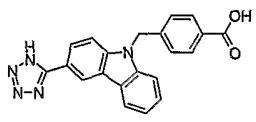


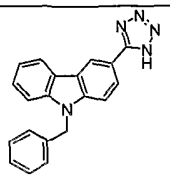
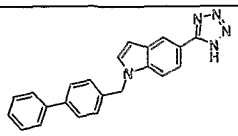
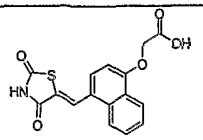
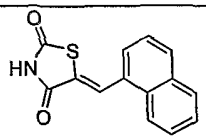
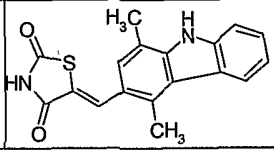
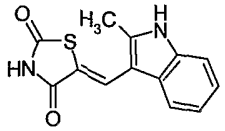
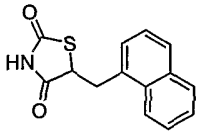
HPLC-MS (Method C): m/z: 374 (M+1); Rt = 4.03 min.

Example 1009

Preparation of NPH-insulin in the presence of ligands for the His^{B10} Zn^{2+}-site of the R-state insulin hexamer.

Preparations are prepared by mixing equal volumes of the following two solutions: a) 1.2 mM human insulin, 0.46 mM Zn^{2+}, 28 mM phosphate, 1.6 % glycerol, 0.15 % m-cresol, 0.065 % phenol, and 0.46 mM ligand for the His^{B10} Zn^{2+}-site (see below), optionally the ligand was added as a 9.2 mM DMSO solution, pH 7.5; and b) 0.636 mg/mL protamine sulphate 1.6 % glycerol, 0.15 % m-cresol, 0.065 % phenol, pH 6. The NPH-crystals grow overnight from the resulting suspension, pH 7.3.

Ligand for the His^{B10} Zn^{2+}-site	Formula	K_d as observed in the 5-(4-imethylaminobenzylidene)-thiazolidine-2,4-dione assay	NPH-insulin crystal size
7-Bromo-3-hydroxy-2-napthoic acid		264 nM	5-20 µ
4-[3-(1H-Tetrazol-5-yl)-carbazol-9-ylmethyl]-benzoic acid		174 nM	< 2 µ

9-Benzyl-3-(1H-tetrazol-5-yl)-9H-carbazole		68 nM	1-3 µ
1-(4-Phenylbenzyl)-5-(1H-tetrazol-5-yl)-1H-indole		38 nM	< 2 µ
[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)-naphthalen-1-yloxy]-acetic acid		11 nM	2-10 µ
5-Napthalen-1-ylmethylene-thiazolidine-2,4-dione		21 nM	4-10 µ
5-(1,4-Dimethyl-9H-carbazol-3-ylmethylene)-thiazolidine-2,4-dione		< 10 nM	<2 µ
5-(2-methyl-1H-indol-3-ylmethylene)thiazolidine –2,4-dione		< 10 nM	2-6 µ
5-Napthalen-1-ylmethyl-thiazolidine-2,4-dione		99 nM	2 µ

Example 1010

Formulation of ligand-incorporated NPH-insulin preparation by addition of ligand for the His^{B10} Zn^{2+}-site of the R-state insulin hexamer to pre-crystallized NPH-insulin.

The following four solutions are prepared:

A. 2.4 mM Human Insulin
0.92 mM Zn^{2+}
12.8 mM Hydrochloric acid
1.29 mg/ml Protamine sulphate
16 mg/ml Glycerol
1.5 mg/ml m-Cresol
0.65 mg/ml Phenol

B. 28 mM Disodium hydrogen phosphate
1.2 mM Sodium hydroxide
16 mg/ml Glycerol
1.5 mg/ml m-Cresol
0.65 mg/ml Phenol

C. 0.92 mM 4-[3-(1H-Tetrazol-5-yl)-carbazol-9-ylmethyl]-benzoic acid
(added as a 9.2 mM solution in DMSO)
14 mM Disodium hydrogen phosphate
16 mg/ml Glycerol
1.5 mg/ml m-Cresol
0.65 mg/ml Phenol
pH adjusted to 7.3 with Hydrochloric acid.

D. 0.21 mg/ml Protamine sulphate
14 mM Disodium hydrogen phosphate
16 mg/ml Glycerol
1.5 mg/ml m-Cresol
0.65 mg/ml Phenol
pH adjusted to 7.3 with Hydrochloric acid.

The ligand-incorporated NPH-insulin preparation is prepared by mixing equal volumes of the four solutions in the following manner:

Solutions A and B are mixed and the resulting suspension is adjusted to pH 7.3 and left overnight at 20-23°C for crystallisation. Solution C is then added with gentle agitation and after 30 minutes standing solution D is admixed.

Example 1011

The glucose utilization effect following a subcutaneous injection of the NPH-insulin preparations of the present invention were characterized using a pig clamp model as described in Kurtzhals & Ribel, Diabetes 44, 1381-1385, 1995.

Figure 1 compares a regular NPH preparation to two NPH preparations formulated with different (stoichiometric/excess) concentrations compared to Zn^{2+} of 4-[3-(1H-Tetrazol-5-yl)-carbazol-9-ylmethyl]-benzoic acid as described in the table below.

	Prep a)	Prep. b)	Prep. c)
Insulin (mM)	*0.6 human insulin*	*0.6 human insulin*	0.6 human insulin
Zn^{2+} (mM)	0.224	0.224	0.224
Protamine sulphate	0.318 mg/mL	0.376 mg/ml	0.485 mg/ml
Phenolic ligand	0.15 % m-cresol, 0.065 % phenol	0.15 % m-cresol, 0.065 % phenol	0.15 % m-cresol, 0.065 % phenol
Zn^{2+} ligand, 4-[3-(1H-Tetrazol-5-yl)-carbazol-9-ylmethyl]-benzoic acid		0.224 mM	0.460mM
Glycerol (%)	1.6	1.6	1.6
Phosphate buffer (mM)	14	14	14

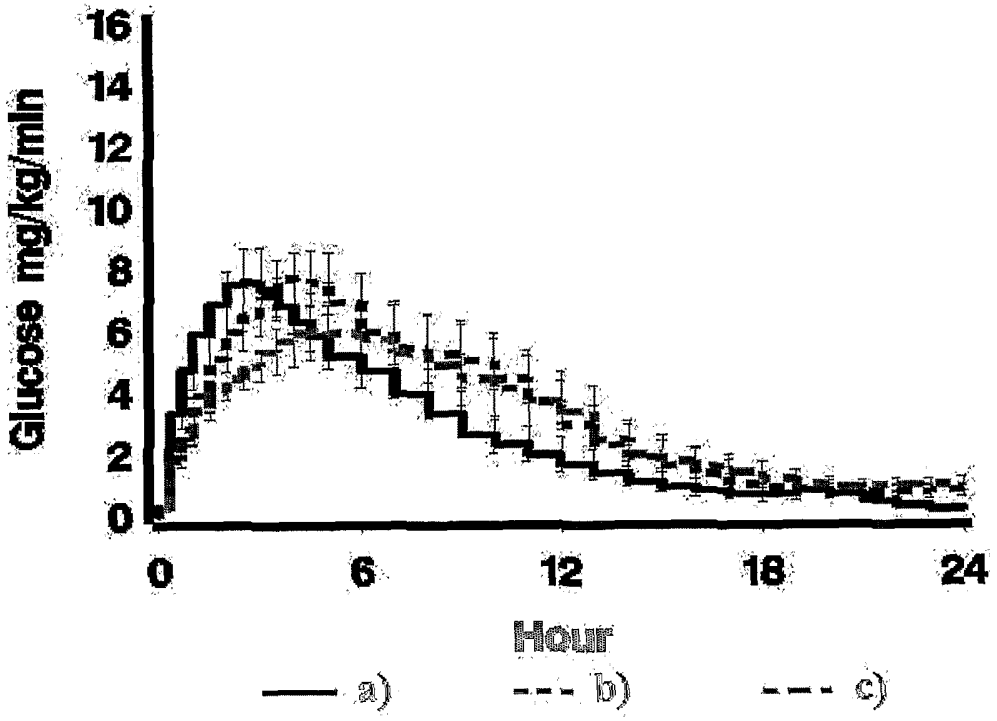


Figure 1: Glucose utilization after subcutaneous injection of a) 144nmol NPH (7 pigs), b) 144 nmol of *NPH preparation with stoichiometric concentration of 4-[3-(1H-Tetrazol-5-yl)-*

carbazol-9-ylmethyl]-benzoic acid compared to Zn^{2+} (8 pigs) and c) 144nmol of NPH preparation with excess concentration of 4-[3-(1H-Tetrazol-5-yl)-carbazol-9-ylmethyl]-benzoic acid compared to Zn^{2+} (8 pigs). The results are expressed as means ± SE.

ANALYTICAL METHODS

TZD-assay for quantitation of ligands binding to the R-state $His^{B10}Zn^{2+}$:

The binding affinity of ligands to the metal site of insulin R_6 hexamers are measured in a fluorescense based displacement assay. The fluorescence of 5-(4-dimethylaminobenzylidene)thiazolidine-2,4-dione (TZD) which is a ligand for the metal site of insulin R_6 is quenched upon displacement from the metal site to the solution. Titration of a ligand to a stock solution of insulin R_6 hexamers with this compound mounted in the metal site allows the binding affinity of these ligands to be determined measuring the fluorescence at 455nm upon excitation at 410nm.

Preparation

Stock solution: 0.02 mM human insulin, 0.007 mM Zn-acetate, 40 mM phenol, 0.01 mM TZD in 50mM tris buffer adjusted to pH=8.0 with NaOH/ClO_4^-.

The ligand is dissolved in DMSO to a concentration of 5 mM and added in aliquots to the stock solution to final concentrations of 0-250 µM.

Measurements

Fluorescence measurements were carried out on a Perkin Elmer Spectrofluorometer LS50B.The main absorption band was excited at 410 nm and emission was detected at 455 nm. The resolution was 10 nm and 2.5 nm for excitation and emission, respectively.

Data analysis

This equation is fitted to the datapoints

$\Delta F(455nm)) = \Delta F_{max} * [ligand]_{free}/(K_D(app) * (1+[TZD]/K_{TZD})+ [ligand]_{free})$

$K_D(app)$ is the apparent dissociation constant and F_{max} is the fluorescence at maximal ligand concentration. The value of K_{TZD} is measured separately to 230 nM

Two different fitting-procedures can be used. One in which both parameters, K_D(app) and F_{max}, are adjusted to best fit the data and a second in which the value of F_{max} is fixed (F_{max}=1) and only K_D(app) is adjusted. The given data are from the second fitting procedure. The Solver module of Microsoft Excel can be used to generate the fits from the datapoints.

4H3N-assay:

The binding affinity of ligands to the metal site of insulin R_6 hexamers are measured in a UV/vis based displacement assay. The UV/vis spectrum of 3-hydroxy-4-nitro benzoic acid (4H3N) which is a known ligand for the metal site of insulin R_6 shows a shift in absorption maximum upon displacement from the metal site to the solution (Huang et al., 1997, Biochemistry 36, 9878-9888). Titration of a ligand to a solution of insulin R_6 hexamers with 4H3N mounted in the metal site allows the binding affinity of these ligands to be determined following the reduction of absorption at 444 nm.

A stock solution with the following composition 0.2 mM human insulin, 0.067 mM Zn-acetate, 40 mM phenol, 0.101 mM 4H3N is prepared in a 10mL quantum as described below. Buffer is always 50mM tris buffer adjusted to pH=8.0 with NaOH/ClO_4^-.

1000 µL of 2.0mM human insulin in buffer

66.7 µL of 10mM Zn-acetate in buffer

800 µL of 500mM phenol in H_2O

201 µL of 4H3N in H_2O

7.93 ml buffer

The ligand is dissolved in DMSO to a concentration of 20 mM.

The ligand solution is titrated to a cuvette containing 2 mL stock solution and after each addition the UV/vis spectrum is measured. The titration points are listed in Table 3 below.

Table 3

ligand addition (µl)	ligand conc. (mM)	dilution factor
1	0.010	1.0005
1	0.020	1.0010
1	0.030	1.0015
2	0.050	1.0025
5	0.100	1.0050
10	0.198	1.0100
20	0.392	1.0200
20	0.583	1.0300
20	0.769	1.0400
20	0.952	1.0500

The UV/vis spectra resulting from a titration of the compound 3-hydroxy-2-naphthoic acid is shown in Figure 5. Inserted in the upper right corner is the absorbance at 444nm vs. the concentration of ligand.

The following equation is fitted to these datapoints to determine the two parameters K_D(obs), the observed dissociation constant, and abs_{max} the absorbance at maximal ligand concentration.

$$abs([ligand]_{free}) = (abs_{max} * [ligand]_{free}) / (K_D(obs) + [ligand]_{free})$$

The observed dissociation constant is recalculated to obtain the apparent dissociation constant

$$K_D(app) = K_D(obs) / (1+[4H3N]/K_{4H3N})$$

The value of K_{4H3N}=50 μM is taken from Huang et al., 1997, Biochemistry 36, 9878-9888.

CLAIMS

1. Pharmaceutical preparation comprising

- Insulin
- Protamine
- Zinc ions
- A ligand that binds reversibly to a His^{B10} Zn^{2+} site of an R-state insulin hexamer, wherein said ligand is selected from the group consisting of carboxylates, dithiocarboxylates, phenolates, thiophenolates, alkylthiolates, sulfonamides, imidazoles, triazoles, 4-cyano-1,2,3-triazoles, benzimidazoles, benzotriazoles, purines, thymines, thiazolidinediones, tetrazoles, 5-mercaptotetrazoles, rhodanines, N-hydroxyazoles, hydantoines, thiohydantoines, naphthoic acids and salicylic acids, or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

2. A pharmaceutical preparation according to claim 1 wherein the insulin preparation comprises 60 to 3000 nmol/ml of insulin.

3. A pharmaceutical preparation according to claim 2 wherein the insulin preparation comprises 240 to 1200 nmol/ml of insulin.

4. A pharmaceutical preparation according to claim 3 wherein the insulin preparation comprises about 600 nmol/ml of insulin.

5. A pharmaceutical preparation according to any one of the claims 1 to 4 wherein the insulin is selected from the group consisting of human insulin, an analogue of human insulin, a derivative of human insulin, and combinations of any of these

6. A pharmaceutical preparation according to claim 5 wherein the insulin is an analogue of human insulin selected from the group consisting of

i. An analogue wherein position B28 is Asp, Glu, Lys, Leu, Val, or Ala and position B29 is Lys or Pro;
ii. An analogue wherein position B3 is Lys and position B29 is Glu; and
iii. des(B28-B30), des(B27) or des(B30) human insulin.

7. A pharmaceutical preparation according to claim 6, wherein the insulin is an analogue of human insulin wherein position B28 is Asp or Lys, and position B29 is Lys or Pro.

8. A pharmaceutical preparation according to claim 6 wherein the insulin is des(B30) human insulin.

9. A pharmaceutical preparation according to claim 5 wherein the insulin is a derivative of human insulin having one or more lipophilic substituents.

10. A pharmaceutical preparation according to claim 9 wherein the insulin derivative is selected from the group consisting of B29-N$^{\varepsilon}$-myristoyl-des(B30) human insulin, B29-N$^{\varepsilon}$-palmitoyl-des(B30) human insulin, B29-N$^{\varepsilon}$-myristoyl human insulin, B29-N$^{\varepsilon}$-palmitoyl human insulin, B28-N$^{\varepsilon}$-myristoyl Lys^{B28} Pro^{B29} human insulin, B28-N$^{\varepsilon}$-palmitoyl Lys^{B28} Pro^{B29} human insulin, B30-N$^{\varepsilon}$-myristoyl-Thr^{B29}Lys^{B30} human insulin, B30-N$^{\varepsilon}$-palmitoyl-Thr^{B29}Lys^{B30} human insulin, B29-N$^{\varepsilon}$-(N-palmitoyl-γ-glutamyl)-des(B30) human insulin, B29-N$^{\varepsilon}$-(N-lithocholyl-γ-glutamyl)-des(B30) human insulin, B29-N$^{\varepsilon}$-(ω-carboxyheptadecanoyl)-des(B30) human insulin and B29-N$^{\varepsilon}$-(ω-carboxyheptadecanoyl) human insulin.

11. A pharmaceutical preparation according to claim 10 wherein the insulin derivative is B29-N$^{\varepsilon}$-myristoyl-des(B30) human insulin.

12. A pharmaceutical preparation according to claim 10 wherein the insulin derivative is B29-N$^{\varepsilon}$-(N-lithocholyl-γ-glutamyl)-des(B30) human insulin

13. A pharmaceutical preparation according to any one of the claims 1 to 12 wherein the protamine is protamine sulphate.

14. A pharmaceutical preparation according to claim 13 wherein the concentration of protamine sulphate is from 0.05-3 mg/mL.

15. A pharmaceutical preparation according to claim 14 wherein the concentration of protamine sulphate is from 0.1-0.6 mg/mL.

16. A pharmaceutical preparation according to any one of the claims 1 to 15 wherein the amount of zinc ions is 2-6 moles per mole putative insulin hexamer.

17. A pharmaceutical preparation according to claim 16 wherein the amount of zinc ions is 2 to 3 moles per mole putative insulin hexamer.

18. A pharmaceutical preparation according to any one of the claims 1 to 17 wherein the ratio of ligand that binds reversibly to a His^{B10} Zn^{2+} site of an R-state insulin hexamer to zinc ions is 1:3 to 3:1.

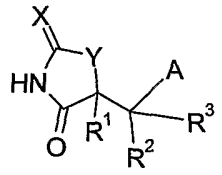
19. A pharmaceutical preparation according to claim 18 wherein the ratio of ligand that binds reversibly to a His^{B10} Zn^{2+} site of an R-state insulin hexamer to zinc ions is 1:2 to 2:1.

20. A pharmaceutical preparation according to claim 19 wherein the ratio of ligand that binds reversibly to a His^{B10} Zn^{2+} site of an R-state insulin hexamer to zinc ions is 1:.2 to 1.2:1.

21. A pharmaceutical preparation according to any one of the claims 1 to 20 wherein the ligand that binds reversibly to a His^{B10} Zn^{2+} site of an R-state insulin hexamer is a chemical structure selected from the group consisting of carboxylates, dithiocarboxylates, phenolates, thiophenolates, alkylthiolates, sulfonamides, imidazoles, triazoles, 4-cyano-1,2,3-triazoles, benzimidazoles, benzotriazoles, purines, thymines, thiazolidinediones, tetrazoles, 5-mercaptotetrazoles, rhodanines, N-hydroxyazoles, hydantoines, thiohydantoines, naphthoic acids and salicylic acids.

22. A pharmaceutical preparation according to claim 21 wherein the ligand that binds reversibly to a His^{B10} Zn^{2+} site of an R-state insulin hexamer is a chemical structure selected from the group consisting of benzotriazoles, 3-hydroxy 2-napthoic acids, salicylic acids, tetrazoles or thiazolidinediones

23. A pharmaceutical preparation according to claim 22 wherein the zinc-binding ligand is



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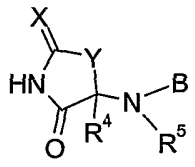

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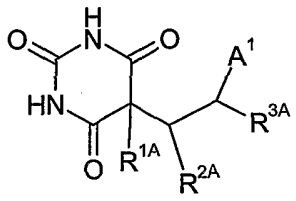


wherein

X is =O, =S or =NH

Y is -S-, -O- or -NH-

R^1, R^{1A} and R^4 are independently selected from hydrogen or C_1-C_6-alkyl,

R^2 and R^{2A} are hydrogen or C_1-C_6-alkyl or aryl, R^1 and R^2 may optionally be combined to form a double bond, R^{1A} and R^{2A} may optionally be combined to form a double bond,

R^3, R^{3A} and R^5 are independently selected from hydrogen, halogen, aryl optionally substituted with one or more substituents independently selected from R^{16}, C_1-C_6-alkyl, or -C(O)$NR^{11}R^{12}$,

A, A^1 and B are independently selected from C_1-C_6-alkyl, aryl, aryl-C_1-C_6-alkyl, -NR^{11}-aryl, aryl-C_2-C_6-alkenyl or heteroaryl, wherein the alkyl or alkenyl is optionally substituted with one or more substituents independently selected from R^6 and the aryl or heteroaryl is optionally substituted with up to four substituents R^7, R^8, R^9, and R^{10},

A and R^3 may be connected through one or two valence bonds, B and R^5 may be connected through one or two valence bonds,

R^6 is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, aryl, -COOH and $-NH_2$,

R^7, R^8, R^9 and R^{10} are independently selected from

- hydrogen, halogen, -CN, $-CH_2CN$, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-S(O)_2CF_3$, $-OS(O)_2CF_3$, $-SCF_3$, $-NO_2$, $-OR^{11}$, $-NR^{11}R^{12}$, $-SR^{11}$, $-NR^{11}S(O)_2R^{12}$, $-S(O)_2NR^{11}R^{12}$, $-S(O)NR^{11}R^{12}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-OS(O)_2R^{11}$, $-C(O)NR^{11}R^{12}$, $-OC(O)NR^{11}R^{12}$, $-NR^{11}C(O)R^{12}$, $-CH_2C(O)NR^{11}R^{12}$, $-OC_1$-C_6-alkyl-$C(O)NR^{11}R^{12}$, $-CH_2OR^{11}$, $-CH_2OC(O)R^{11}$, $-CH_2NR^{11}R^{12}$, $-OC(O)R^{11}$, $-OC_1$-C_{15}-alkyl-$C(O)OR^{11}$, $-OC_1$-C_6-alkyl-OR^{11}, $-SC_1$-C_6-alkyl-$C(O)OR^{11}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{11}$, $-NR^{11}$-$C(=O)$-C_1-C_6-alkyl-$C(=O)OR^{11}$, $-NR^{11}$-$C(=O)$-C_1-C_6-alkenyl-$C(=O)OR^{11}$, $-C(O)OR^{11}$, $C(O)R^{11}$, or $-C_2$-C_6-alkenyl-$C(=O)R^{11}$, =O, or $-C_2$-C_6-alkenyl-$C(=O)$-$NR^{11}R^{12}$,

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl, each of which may optionally be substituted with one or more substituents independently selected from R^{13},

- aryl, aryloxy, aryloxycarbonyl, aroyl, arylsulfanyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aroyl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl, heteroaryl-C_2-C_6-alkynyl, or C_3-C_6 cycloalkyl,

of which each cyclic moiety may optionally be substituted with one or more substituents independently selected from R^{14},

R^{11} and R^{12} are independently selected from hydrogen, OH, C_1-C_{20}-alkyl, aryl-C_1-C_6-alkyl or aryl, wherein the alkyl groups may optionally be substituted with one or more substituents independently selected from R^{15}, and the aryl groups may optionally be substituted one or more substituents independently selected from R^{16}; R^{11} and R^{12} when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom, the heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

R^{13} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OR^{11}$, $-C(O)OR^{11}$, $-NR^{11}R^{12}$, and $-C(O)NR^{11}R^{12}$,

R^{14} is independently selected from halogen, $-C(O)OR^{11}$, $-CH_2C(O)OR^{11}$, $-CH_2OR^{11}$, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{11}$, $-NR^{11}R^{12}$, $-NR^{11}C(O)R^{11}$, $-S(O)_2R^{11}$, aryl and C_1-C_6-alkyl,

R^{15} is independently selected from halogen, -CN, $-CF_3$, =O, $-OCF_3$, $-OC_1$-C_6-alkyl, $-C(O)OC_1$-C_6-alkyl, -COOH and $-NH_2$,

R^{16} is independently selected from halogen, $-C(O)OC_1$-C_6-alkyl, -COOH, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, -OH, $-OC_1$-C_6-alkyl, $-NH_2$, C(=O) or C_1-C_6-alkyl, or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

24. A pharmaceutical preparation according to claim 23 wherein X is =O or =S.

25. A pharmaceutical preparation according to claim 24 wherein X is =O.

26. A pharmaceutical preparation according to claim 24 wherein X is =S.

27. A pharmaceutical preparation according to any one of the claims 23 to 26 wherein Y is -O- or -S-.

28. A pharmaceutical preparation according to claim 27 wherein Y is -O-.

29. A pharmaceutical preparation according to claim 27 wherein Y is -NH-.

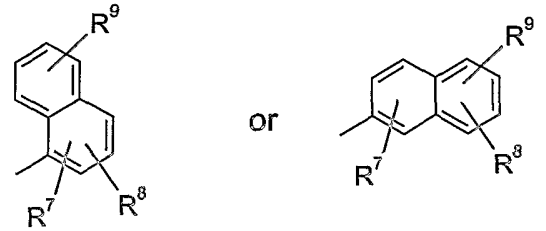
30. A pharmaceutical preparation according to claim 27 wherein Y is -S-.

31. A pharmaceutical preparation according to any one of the claims 23 to 30 wherein A is aryl optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different.

32. A pharmaceutical preparation according to claim 31 wherein A is selected from ArG1 optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different.

33. A pharmaceutical preparation according to claim 32 wherein A is phenyl or naphtyl optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different.

34. A pharmaceutical preparation according to claim 33 wherein A is



35. A pharmaceutical preparation according to claim 33 wherein A is phenyl.

36. A pharmaceutical preparation according to any one of the claims 23 to 30 wherein A is heteroaryl optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different.

37. A pharmaceutical preparation according to claim 36 wherein A is selected from Het1 optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different, and wherein Het1 is furyl, thienyl, pyrrolyl, pyrazolyl, 3-oxopyrazolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5- triazinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, thiadiazinyl, indolyl, isoindolyl, benzofuryl, benzothienyl, indazolyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, purinyl, quinazolinyl, quinolizinyl, quinolinyl, isoquinolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, azepinyl, diazepinyl, acridinyl, thiazolidinyl, or 2-thiooxothiazolidinyl.

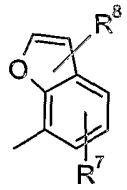
38. A pharmaceutical preparation according to claim 37 wherein A is selected from Het2 optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different, and wherein Het2 is furyl, thienyl, pyrrolyl, pyrazolyl, 3-oxopyrazolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5- triazinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, thiadiazinyl, indolyl, isoindolyl, benzofuryl, benzothienyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, quinolinyl, isoquinolinyl, quinoxalinyl, carbazolyl, thiazolidinyl, or 2-thiooxothiazolidinyl.

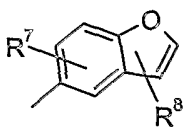
39. A pharmaceutical preparation according to claim 38 wherein A is selected from Het3 optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different, and wherein Het3 is furyl, thienyl, pyrrolyl, pyrazolyl, 3-oxopyrazolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyridyl, tetrazolyl, indolyl, isoindolyl, benzofuryl, benzothienyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, quinolyl, isoquinolyl, quinoxalinyl, carbazolyl, thiazolidinyl, or 2-thiooxothiazolidinyl.

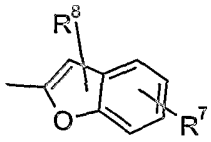
40. A pharmaceutical preparation according to claim 39 wherein A is selected from the group consisting of indolyl, benzofuranyl, quinolyl, furyl, thienyl, or pyrrolyl, wherein each heteroaryl may optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different.

41. A pharmaceutical preparation according to claim 39 wherein A is benzofuranyl optionally substituted with up to four substituents R^7, R^8, R^9, and R^{10} which may be the same or different.

42. A pharmaceutical preparation according to claim 41 wherein A is

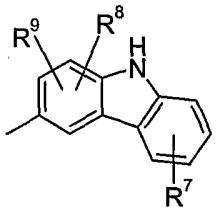


or


or


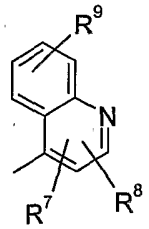
43. A pharmaceutical preparation according to claim 39 wherein A is carbazolyl optionally substituted with up to four substituents R^7, R^8, R^9, and R^{10} which may be the same or different.

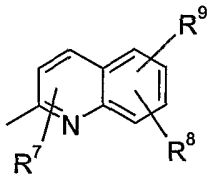
44. A pharmaceutical preparation according to claim 43 wherein A is



45. A pharmaceutical preparation according to claim 39 wherein A is quinolyl optionally substituted with up to four substituents R^7, R^8, R^9, and R^{10} which may be the same or different.

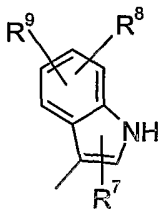
46. A pharmaceutical preparation according to claim 45 wherein A is

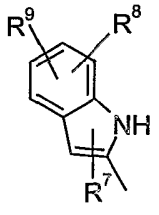


or


47. A pharmaceutical preparation according to claim 39 wherein A is indolyl optionally substituted with up to four substituents R^7, R^8, R^9, and R^{10} which may be the same or different.

48. A pharmaceutical preparation according to claim 47 wherein A is



or


49. A pharmaceutical preparation according to any one of the claims 23 to 48 wherein R^1 is hydrogen.

50. A pharmaceutical preparation according to any one of the claims 23 to 49 wherein R^2 is hydrogen.

51. A pharmaceutical preparation according to any one of the claims 23 to 48 wherein R^1 and R^2 are combined to form a double bond.

52. A pharmaceutical preparation according to any one of the claims 23 to 51 wherein R^3 is C_1-C_6-alkyl, halogen, or $C(O)NR^{16}R^{17}$.

53. A pharmaceutical preparation according to claim 52 wherein R^3 is C_1-C_6-alkyl or $C(O)NR^{16}R^{17}$.

54. A pharmaceutical preparation according to claim 53 wherein R^3 is methyl.

55. A pharmaceutical preparation according to any one of the claims 23 to 30 wherein B is phenyl optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different.

56. A pharmaceutical preparation according to any one of the claims 23 to 30 or 55 wherein R^4 is hydrogen.

57. A pharmaceutical preparation according to any one of the claims 23 to 30 or 55 to 56 wherein R^5 is hydrogen.

58. A pharmaceutical preparation according to any one of the claims 23 to 57 wherein R^6 is aryl.

59. A pharmaceutical preparation according to claim 58 wherein R^6 is phenyl.

60. A pharmaceutical preparation according to any one of the claims 23 to 59 wherein R^7, R^8, R^9 and R^{10} are independently selected from

- hydrogen, halogen, $-NO_2$, $-OR^{11}$, $-NR^{11}R^{12}$, $-SR^{11}$, $-NR^{11}S(O)_2R^{12}$, $-S(O)_2NR^{11}R^{12}$, $-S(O)NR^{11}R^{12}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-OS(O)_2\ R^{11}$, $-NR^{11}C(O)R^{12}$, $-CH_2OR^{11}$, $-CH_2OC(O)R^{11}$, $-CH_2NR^{11}R^{12}$, $-OC(O)R^{11}$, $-OC_1$-C_6-alkyl-$C(O)OR^{11}$, $-OC_1$-C_6-alkyl-$C(O)NR^{11}R^{12}$, $-OC_1$-C_6-alkyl-OR^{11}, $-SC_1$-C_6-alkyl-$C(O)OR^{11}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{11}$, $-C(O)OR^{11}$, or $-C_2$-C_6-alkenyl-$C(=O)R^{11}$,

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl, which may each optionally be substituted with one or more substituents independently selected from R^{13}

  - aryl, aryloxy, aroyl, arylsulfanyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aroyl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, wherein each of the cyclic moieties optionally may be substituted with one or more substituents independently selected from R^{14}

61. A pharmaceutical preparation according to claim 60 wherein R^7, R^8, R^9 and R^{10} are independently selected from

- hydrogen, halogen, $-NO_2$, $-OR^{11}$, $-NR^{11}R^{12}$, $-SR^{11}$, $-S(O)_2R^{11}$, $-OS(O)_2\ R^{11}$, $-CH_2OC(O)R^{11}$, $-OC(O)R^{11}$, $-OC_1$-C_6-alkyl-$C(O)OR^{11}$, $-OC_1$-C_6-alkyl-OR^{11}, $-SC_1$-C_6-alkyl-$C(O)OR^{11}$, $-C(O)OR^{11}$, or $-C_2$-C_6-alkenyl-$C(=O)R^{11}$,

- C_1-C_6-alkyl or C_1-C_6-alkenyl which may each optionally be substituted with one or more substituents independently selected from R^{13}

- aryl, aryloxy, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, heteroaryl,

of which each of the cyclic moieties optionally may be substituted with one or more substituents independently selected from R^{14}

62. A pharmaceutical preparation according to claim 61 wherein R^7, R^8, R^9 and R^{10} are independently selected from

- hydrogen, halogen, $-NO_2$, $-OR^{11}$, $-NR^{11}R^{12}$, $-SR^{11}$, $-S(O)_2R^{11}$, $-OS(O)_2\ R^{11}$, $-CH_2OC(O)R^{11}$, $-OC(O)R^{11}$, $-OC_1$-C_6-alkyl-$C(O)OR^{11}$, $-OC_1$-C_6-alkyl-OR^{11}, $-SC_1$-C_6-alkyl-$C(O)OR^{11}$, $-C(O)OR^{11}$, or $-C_2$-C_6-alkenyl-$C(=O)R^{11}$,

- C_1-C_6-alkyl or C_1-C_6- which may each optionally be substituted with one or more substituents independently selected from R^{13}

- aryl, aryloxy, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, heteroaryl,

of which each of the cyclic moieties optionally may be substituted with one or more substituents independently selected from R^{14}.

63. A pharmaceutical preparation according to claim 62 wherein R^7, R^8, R^9 and R^{10} are independently selected from

- hydrogen, halogen, $-OR^{11}$, $-OC_1$-C_6-alkyl-$C(O)OR^{11}$, or $-C(O)OR^{11}$,

- C_1-C_6-alkyl which may each optionally be substituted with one or more substituents independently selected from R^{13}

- aryl, aryloxy, aryl-C_1-C_6-alkoxy,

of which each of the cyclic moieties optionally may be substituted with one or more substituents independently selected from R^{14}.

64. A pharmaceutical preparation according to claim 63 wherein R^7, R^8, R^9 and R^{10} are independently selected from

- hydrogen, halogen, $-OR^{11}$, $-OC_1$-C_6-alkyl-$C(O)OR^{11}$, or $-C(O)OR^{11}$,

- C_1-C_6-alkyl which may each optionally be substituted with one or more substituents independently selected from R^{13}

- ArG1, ArG1oxy, ArG1-C_1-C_6-alkoxy,

of which each of the cyclic moieties optionally may be substituted with one or more substituents independently selected from R^{14}.

65. A pharmaceutical preparation according to claim 64 wherein R^7, R^8, R^9 and R^{10} are independently selected from

- hydrogen, halogen, $-OR^{11}$, $-OC_1$-C_6-alkyl-$C(O)OR^{11}$, or $-C(O)OR^{11}$,

- C_1-C_6-alkyl which may optionally be substituted with one or more substituents independently selected from R^{13}

- phenyl, phenyloxy, phenyl-C_1-C_6-alkoxy, wherein each of the cyclic moieties optionally may be substituted with one or more substituents independently selected from R^{14}.

66. A pharmaceutical preparation according to any one of the claims 23 to 65 wherein R^{11} and R^{12} are independently selected from hydrogen, C_1-C_{20}-alkyl, aryl or aryl-C_1-C_6-alkyl, wherein the alkyl groups may optionally be substituted with one or more substituents independently selected from R^{15}, and the aryl groups may optionally be substituted one or more substituents independently selected from R^{16}; R^{11} and R^{12} when attached to the same nitro-

gen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom, the heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds.

67. A pharmaceutical preparation according to claim 66 wherein R^{11} and R^{12} are independently selected from hydrogen, C_1-C_{20}-alkyl, aryl or aryl-C_1-C_6-alkyl, wherein the alkyl groups may optionally be substituted with one or more substituents independently selected from R^{15}, and the aryl groups may optionally be substituted one or more substituents independently selected from R^{16}.

68. A pharmaceutical preparation according to claim 67 wherein R^{11} and R^{12} are independently selected from phenyl or phenyl-C_1-C_6-alkyl.

69. A pharmaceutical preparation according to claim 67 wherein one or both of R^{11} and R^{12} are methyl.

70. A pharmaceutical preparation according to any one of the claims 23 to 69 wherein R^{13} is independently selected from halogen, CF_3, OR^{11} or $NR^{11}R^{12}$.

71. A pharmaceutical preparation according to claim 70 wherein R^{13} is independently selected from halogen or OR^{11}.

72. A pharmaceutical preparation according to claim 71 wherein R^{13} is OR^{11}.

73. A pharmaceutical preparation according to any one of the claims 23 to 72 wherein R^{14} is independently selected from halogen, -C(O)OR^{11}, -CN, -CF_3, -OR^{11}, $S(O)_2R^{11}$, and C_1-C_6-alkyl.

74. A pharmaceutical preparation according to claim 73 wherein R^{14} is independently selected from halogen, -C(O)OR^{11}, or -OR^{11}.

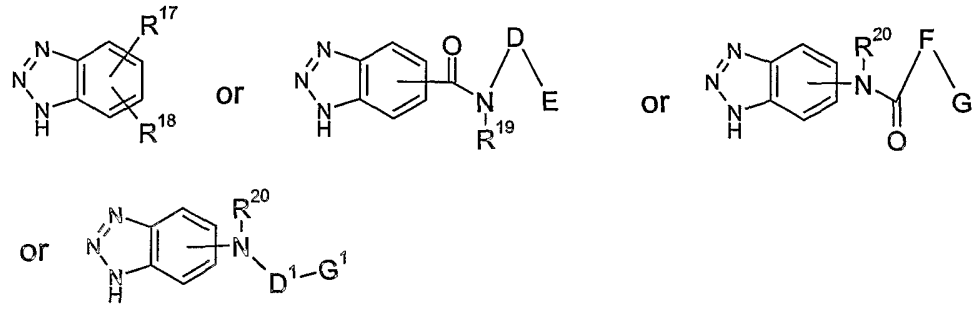
75. A pharmaceutical preparation according to any one of the claims 23 to 74 wherein R^{15} is independently selected from halogen, -CN, -CF_3, -C(O)OC_1-C_6-alkyl, and –COOH.

76. A pharmaceutical preparation according to claim 75 wherein R^{15} is independently selected from halogen or -C(O)OC_1-C_6-alkyl.

77. A pharmaceutical preparation according to any one of the claims 23 to 76 wherein R^{16} is independently selected from halogen, -C(O)OC_1-C_6-alkyl, -COOH, -NO_2, -OC_1-C_6-alkyl, -NH_2, C(=O) or C_1-C_6-alkyl.

78. A pharmaceutical preparation according to claim 77 wherein R^{16} is independently selected from halogen, -C(O)OC_1-C_6-alkyl, -COOH, -NO_2, or C_1-C_6-alkyl.

79. A pharmaceutical preparation according to claim 22 wherein the zinc-binding ligand is



wherein

R^{19} is hydrogen or C_1-C_6-alkyl,

R^{20} is hydrogen or C_1-C_6-alkyl,

D, D^1 and F are a valence bond, C_1-C_6-alkylene or C_1-C_6-alkenylene optionally substituted with one or more substituents independently selected from R^{72},

R^{72} is independently selected from hydroxy, C_1-C_6-alkyl, or aryl,

E is C_1-C_6-alkyl, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with up to three substituents R^{21}, R^{22} and R^{23},

G and G^1 are C_1-C_6-alkyl, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with up to three substituents R^{24}, R^{25} and R^{26},

R^{17}, R^{18}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25} and R^{26} are independently selected from

- hydrogen, halogen, -CN, $-CH_2CN$, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-S(O)_2CF_3$, $-SCF_3$, $-NO_2$, =O, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-NR^{27}S(O)_2R^{28}$, $-S(O)_2NR^{27}R^{28}$, $-S(O)NR^{27}R^{28}$, $-S(O)R^{27}$, $-S(O)_2R^{27}$, $-C(O)NR^{27}R^{28}$, $-OC(O)NR^{27}R^{28}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-CH_2C(O)NR^{27}R^{28}$, $-OCH_2C(O)NR^{27}R^{28}$, $-CH_2OR^{27}$, $-CH_2NR^{27}R^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{27}$, $-NR^{27}$-$C(=O)$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-NR^{27}$-$C(=O)$-C_1-C_6-alkenyl-$C(=O)OR^{27}$, $-C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-C_1$-C_6-alkyl-$C(=O)OR^{27}$,or $-C(O)OR^{27}$,

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl,

which may optionally be substituted with one or more substituents independently selected from R^{29},

- aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl or heteroaryl-C_2-C_6-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30},

R^{27} and R^{28} are independently selected from hydrogen, C_1-C_6-alkyl, aryl-C_1-C_6-alkyl or aryl, or R^{27} and R^{28} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

R^{29} is independently selected from halogen, -CN, -CF_3, -OCF_3, -OR^{27}, and -$NR^{27}R^{28}$,

R^{30} is independently selected from halogen, -$C(O)OR^{27}$, -CN, -CF_3, -OCF_3, -NO_2, -OR^{27}, -$NR^{27}R^{28}$ and C_1-C_6-alkyl, or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

80. A pharmaceutical preparation according to claim 79 wherein D is a valence bond.

81. A pharmaceutical preparation according to claim 79 wherein D is C_1-C_6-alkylene optionally substituted with one or more hydroxy, C_1-C_6-alkyl, or aryl.

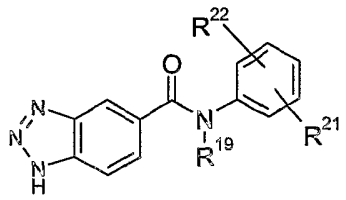
82. A pharmaceutical preparation according to any one of the claims 79 to 81 wherein E is aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with up to three substituents independently selected from R^{21}, R^{22} and R^{23}.

83. A pharmaceutical preparation according to claim 82 wherein E is aryl optionally substituted with up to three substituents independently selected from R^{21}, R^{22} and R^{23}.

84. A pharmaceutical preparation according to claim 83 wherein E is selected from ArG1 and optionally substituted with up to three substituents independently selected from R^{21}, R^{22} and R^{23}.

85. A pharmaceutical preparation according to claim 84 wherein E is phenyl optionally substituted with up to three substituents independently selected from R^{21}, R^{22} and R^{23}.

86. A pharmaceutical preparation according to claim 85 wherein the zinc-binding ligand is



87. A pharmaceutical preparation according to any one of the claims 79 to 86 wherein R^{21}, R^{22} and R^{23} are independently selected from

- hydrogen, halogen, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-NO_2$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-C(O)NR^{27}R^{28}$, $-OC(O)NR^{27}R^{28}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-CH_2C(O)NR^{27}R^{28}$, $-OCH_2C(O)NR^{27}R^{28}$, $-CH_2OR^{27}$, $-CH_2NR^{27}R^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{27}$, $-NR^{27}$-$C(=O)$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-NR^{27}$-$C(=O)$-C_1-C_6-alkenyl-$C(=O)OR^{27}$-, $-C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-C_1$-C_6-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl,

which may optionally be substituted with one or more substituents independently selected from R^{29}

- aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl or heteroaryl-C_2-C_6-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

88. A pharmaceutical preparation according to claim 87 wherein R^{21}, R^{22} and R^{23} are independently selected from

- hydrogen, halogen, $-OCF_3$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-

$C(=O)OR^{27}$, $-C(=O)NR^{27}-C_1-C_6$-alkyl-$C(=O)OR^{27}$, $-C_1-C_6$-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

- C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{29}

- aryl, aryloxy, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, heteroaryl, heteroaryl-C_1-C_6-alkyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

89. A pharmaceutical preparation according to claim 88 wherein R^{21}, R^{22} and R^{23} are independently selected from

- hydrogen, halogen, $-OCF_3$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-OC(O)R^{27}$, $-OC_1-C_6$-alkyl-$C(O)OR^{27}$, $-SC_1-C_6$-alkyl-$C(O)OR^{27}$, $-C_2-C_6$-alkenyl-$C(=O)OR^{27}$, $-C(=O)NR^{27}-C_1-C_6$-alkyl-$C(=O)OR^{27}$, $-C_1-C_6$-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

- methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R^{29}

- aryl, aryloxy, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, heteroaryl, heteroaryl-C_1-C_6-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

90. A pharmaceutical preparation according to claim 89 wherein R^{21}, R^{22} and R^{23} are independently selected from

- hydrogen, halogen, $-OCF_3$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-OC(O)R^{27}$, $-OC_1-C_6$-alkyl-$C(O)OR^{27}$, $-SC_1-C_6$-alkyl-$C(O)OR^{27}$, $-C_2-C_6$-alkenyl-$C(=O)OR^{27}$, $-C(=O)NR^{27}-C_1-C_6$-alkyl-$C(=O)OR^{27}$, $-C_1-C_6$-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

- methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R^{29}

- ArG1, ArG1-O-, ArG1-C(O)-, ArG1-C_1-C_6-alkoxy, ArG1-C_1-C_6-alkyl, Het3, Het3-C_1-C_6-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

91. A pharmaceutical preparation according to claim 90 wherein R^{21}, R^{22} and R^{23} are independently selected from

- hydrogen, halogen, $-OCF_3$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{27}$, $-C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-C_1$-C_6-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

- C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{29}

- phenyl, phenyloxy, phenyl-C_1-C_6-alkoxy, phenyl-C_1-C_6-alkyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

92. A pharmaceutical preparation according to any one of the claims 79 to 91 wherein R^{19} is hydrogen or methyl.

93. A pharmaceutical preparation according to claim 92 wherein R^{19} is hydrogen.

94. A pharmaceutical preparation according to any one of the claims 79 to 93 wherein R^{27} is Hydrogen, C_1-C_6-alkyl or aryl.

95. A pharmaceutical preparation according to claim 94 wherein R^{27} is hydrogen or C_1-C_6-alkyl.

96. A pharmaceutical preparation according to any one of the claims 79 to 95 wherein R^{28} is hydrogen or C_1-C_6-alkyl.

97. A pharmaceutical preparation according to claim 79 wherein F is a valence bond.

98. A pharmaceutical preparation according to claim 79 wherein F is C_1-C_6-alkylene optionally substituted with one or more hydroxy, C_1-C_6-alkyl, or aryl.

99. A pharmaceutical preparation according to any one of the claims 79 or 97 to 98 wherein G is C_1-C_6-alkyl or aryl, wherein the aryl is optionally substituted with up to three substituents R^{24}, R^{25} and R^{26}.

100. A pharmaceutical preparation according to any one of the claims 79 or 97 to 98 wherein G is C_1-C_6-alkyl or ArG1, wherein the aryl is optionally substituted with up to three substituents R^{24}, R^{25} and R^{26}.

101. A pharmaceutical preparation according to claim 99 wherein G is C_1-C_6-alkyl.

102. A pharmaceutical preparation according to claim 101 wherein G is phenyl optionally substituted with up to three substituents R^{24}, R^{25} and R^{26}.

103. A pharmaceutical preparation according to any one of the claims 79 to 102 wherein R^{24}, R^{25} and R^{26} are independently selected from

- hydrogen, halogen, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-NO_2$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-C(O)NR^{27}R^{28}$, $-OC(O)NR^{27}R^{28}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-CH_2C(O)NR^{27}R^{28}$, $-OCH_2C(O)NR^{27}R^{28}$, $-CH_2OR^{27}$, $-CH_2NR^{27}R^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{27}$, $-NR^{27}$-$C(=O)$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-NR^{27}$-$C(=O)$-C_1-C_6-alkenyl-$C(=O)OR^{27}$-, $-C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-C_1$-C_6-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl,

which may optionally be substituted with one or more substituents independently selected from R^{29}

- aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl or heteroaryl-C_2-C_6-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

104. A pharmaceutical preparation according to claim 103 wherein R^{24}, R^{25} and R^{26} are independently selected from

- hydrogen, halogen, $-OCF_3$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{27}$, $-C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-C_1$-C_6-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

  - C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl,

  which may optionally be substituted with one or more substituents independently selected from R^{29}

  - aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl or heteroaryl-C_2-C_6-alkynyl,

  of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

105. A pharmaceutical preparation according to claim 104 wherein R^{24}, R^{25} and R^{26} are independently selected from

- hydrogen, halogen, $-OCF_3$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{27}$, $-C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-C_1$-C_6-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

- C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{29}

- aryl, aryloxy, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, heteroaryl, heteroaryl-C_1-C_6-alkyl,

  of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

106. A pharmaceutical preparation according to claim 105 wherein R^{21}, R^{22} and R^{23} are independently selected from

- hydrogen, halogen, $-OCF_3$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{27}$, $-C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-C_1$-C_6-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

- methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R^{29}

- ArG1, ArG1-O-, ArG1-C(O)-, ArG1-C_1-C_6-alkoxy, ArG1-C_1-C_6-alkyl, Het3, Het3-C_1-C_6-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

107. A pharmaceutical preparation according to claim 106 wherein R^{21}, R^{22} and R^{23} are independently selected from

- hydrogen, halogen, $-OCF_3$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{27}$, $-C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-C_1$-C_6-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

- methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R^{29}

- ArG1, ArG1-O-, ArG1-C(O)-, ArG1-C_1-C_6-alkoxy, ArG1-C_1-C_6-alkyl, Het3, Het3-C_1-C_6-alkyl

  of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

108. A pharmaceutical preparation according to claim 107 wherein R^{21}, R^{22} and R^{23} are independently selected from

- hydrogen, halogen, $-OCF_3$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-

$C(=O)OR^{27}$, $-C(=O)NR^{27}-C_1-C_6$-alkyl-$C(=O)OR^{27}$, $-C_1-C_6$-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

- methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R^{29}

  - ArG1, ArG1-O-, ArG1-C_1-C_6-alkoxy, ArG1-C_1-C_6-alkyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

109. A pharmaceutical preparation according to any one of the claims 79 or 97 to 108 wherein R^{20} is hydrogen or methyl.

110. A pharmaceutical preparation according to claim 109 wherein R^{20} is hydrogen.

111. A pharmaceutical preparation according to any one of the claims 79 or 97 to 110 wherein R^{27} is hydrogen, C_1-C_6-alkyl or aryl.

112. A pharmaceutical preparation according to claim 111 wherein R^{27} is hydrogen or C_1-C_6-alkyl or ArG1.

113. A pharmaceutical preparation according to claim 112 wherein R^{27} is hydrogen or C_1-C_6-alkyl.

114. A pharmaceutical preparation according to any one of the claims 79 or 97 to 112 wherein R^{28} is hydrogen or C_1-C_6-alkyl.

115. A pharmaceutical preparation according to claim 79 wherein R^{17} and R^{18} are independently selected from

- hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-S(O)R^{27}$, $-S(O)_2R^{27}$, $-C(O)NR^{27}R^{28}$, $-CH_2OR^{27}$, $-OC(O)R^{27}$, $-OC_1-C_6$-alkyl-$C(O)OR^{27}$, $-SC_1-C_6$-alkyl-$C(O)OR^{27}$, or $-C(O)OR^{27}$,

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl, optionally substituted with one or more substituents independently selected from R^{29}

- aryl, aryloxy, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, heteroaryl, heteroaryl-C_1-C_6-alkyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

116. A pharmaceutical preparation according to claim 115 wherein R^{17} and R^{18} are independently selected from

- hydrogen, halogen, -CN, $-CF_3$, $-NO_2$, $-OR^{27}$, $-NR^{27}R^{28}$, or $-C(O)OR^{27}$,
- C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{29}
- aryl, aryloxy, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, heteroaryl, heteroaryl-C_1-C_6-alkyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

117. A pharmaceutical preparation according to claim 116 wherein R^{17} and R^{18} are independently selected from

- hydrogen, halogen, -CN, $-CF_3$, $-NO_2$, $-OR^{27}$, $-NR^{27}R^{28}$, or $-C(O)OR^{27}$
- methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R^{29}
- aryl, aryloxy, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, heteroaryl, heteroaryl-C_1-C_6-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

118. A pharmaceutical preparation according to claim 117 wherein R^{17} and R^{18} are independently selected from

- hydrogen, halogen, -CN, $-CF_3$, $-NO_2$, $-OR^{27}$, $-NR^{27}R^{28}$, or $-C(O)OR^{27}$
- methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R^{29}
- ArG1, ArG1-O-, ArG1-C(O)-, ArG1-C_1-C_6-alkoxy, ArG1-C_1-C_6-alkyl, Het3, Het3-C_1-C_6-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

119. A pharmaceutical preparation according to claim 118 wherein R^{17} and R^{18} are independently selected from

- hydrogen, halogen, -CN, $-CF_3$, $-NO_2$, $-OR^{27}$, $-NR^{27}R^{28}$, or $-C(O)OR^{27}$

- C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{29}
- phenyl, phenyloxy, phenyl-C_1-C_6-alkoxy, phenyl-C_1-C_6-alkyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

120. A pharmaceutical preparation according to any one of the claims 79 to 119 wherein R^{27} is hydrogen or C_1-C_6-alkyl.

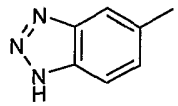
121. A pharmaceutical preparation according to claim 120 wherein R^{27} is hydrogen, methyl or ethyl.

122. A pharmaceutical preparation according to any one of the claims 79 to 121 wherein R^{28} is hydrogen or C_1-C_6-alkyl.

123. A pharmaceutical preparation according to claim 122 wherein R^{28} is hydrogen, methyl or ethyl.

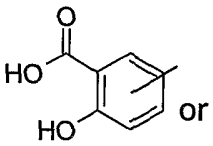
124. A pharmaceutical preparation according to any one of the claims 79 to 123 wherein R^{72} is –OH or phenyl.

125. A pharmaceutical preparation according to claim 79 wherein the zinc-binding ligand is

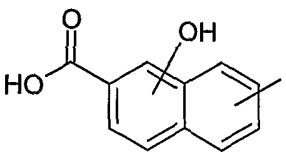


126. A pharmaceutical preparation according to claim 22 wherein the zinc-binding ligand is of the form H-I-J

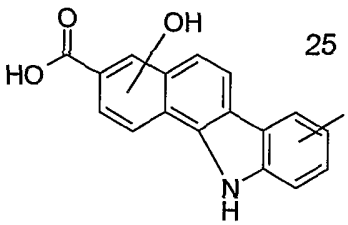
wherein H is



or

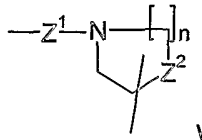


or



wherein the phenyl, naphthalene or benzocarbazole rings are optionally substituted with one or more substituents independently selected from R^{31}

I is selected from

- a valence bond,
- $-CH_2N(R^{32})-$ or $-SO_2N(R^{33})-$,
- 
  wherein Z^1 is $S(O)_2$ or CH_2, Z^2 is -NH-, -O-or -S-, and n is 1 or 2,

J is

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl, which may each optionally be substituted with one or more substituents selected from R^{34},
- Aryl, aryloxy, aryl-oxycarbonyl-, aroyl, aryl-C_1-C_6-alkoxy-, aryl-C_1-C_6-alkyl-, aryl-C_2-C_6-alkenyl-, aryl-C_2-C_6-alkynyl-, heteroaryl, heteroaryl-C_1-C_6-alkyl-, heteroaryl-C_2-C_6-alkenyl- or heteroaryl-C_2-C_6-alkynyl-, wherein the cyclic moieties are optionally substituted with one or more substituents selected from R^{37},
- Hydrogen,

R^{31} is independently selected from hydrogen, halogen, -CN, $-CH_2CN$, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-S(O)_2CF_3$, $-SCF_3$, $-NO_2$, $-OR^{35}$, $-C(O)R^{35}$, $-NR^{35}R^{36}$, $-SR^{35}$, $-NR^{35}S(O)_2R^{36}$, $-S(O)_2NR^{35}R^{36}$, $-S(O)NR^{35}R^{36}$, $-S(O)R^{35}$, $-S(O)_2R^{35}$, $-C(O)NR^{35}R^{36}$, $-OC(O)NR^{35}R^{36}$, $-NR^{35}C(O)R^{36}$, $-CH_2C(O)NR^{35}R^{36}$, $-OCH_2C(O)NR^{35}R^{36}$, $-CH_2OR^{35}$, $-CH_2NR^{35}R^{36}$, $-OC(O)R^{35}$, $-OC_1$-C_6-alkyl-$C(O)OR^{35}$, $-SC_1$-C_6-alkyl-$C(O)OR^{35}$ $-C_2$-C_6-alkenyl-$C(=O)OR^{35}$, $-NR^{35}$-$C(=O)$-C_1-C_6-alkyl-$C(=O)OR^{35}$, $-NR^{35}$-$C(=O)$-C_1-C_6-alkenyl-$C(=O)OR^{35}$-, C_1-C_6-alkyl, C_1-C_6-alkanoyl or $-C(O)OR^{35}$,

R^{32} and R^{33} are independently selected from hydrogen, C_1-C_6-alkyl or C_1-C_6-alkanoyl,

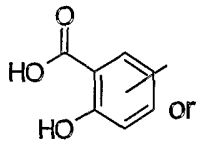
R^{34} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OR^{35}$, and $-NR^{35}R^{36}$,

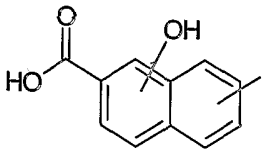
R^{35} and R^{36} are independently selected from hydrogen, C_1-C_6-alkyl, aryl-C_1-C_6-alkyl or aryl, or R^{35} and R^{36} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

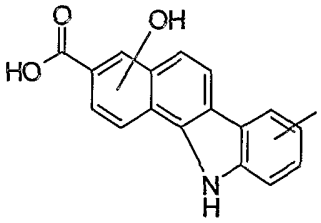
R^{37} is independently selected from halogen, -C(O)OR^{35}, -C(O)H, -CN, -CF_3, -OCF_3, -NO_2, -OR^{35}, -$NR^{35}R^{36}$, C_1-C_6-alkyl or C_1-C_6-alkanoyl,

or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

127. A pharmaceutical preparation according to claim 126 wherein the zinc-binding ligand is of the form H-I-J, wherein H is

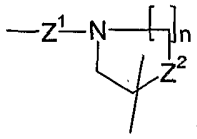


or


or


wherein the phenyl, naphthalene or benzocarbazole rings are optionally substituted with one or more substituents independently selected from R^{31},

I is selected from

- a valence bond,
- –$CH_2N(R^{32})$- or –$SO_2N(R^{33})$-,
-  wherein Z^1 is $S(O)_2$ or CH_2, Z^2 is N,-O-or -S-, and n is 1 or 2,

J is

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl, which may each optionally be substituted with one or more substituents selected from R^{34},
- Aryl, aryloxy, aryl-oxycarbonyl-, aroyl, aryl-C_1-C_6-alkoxy-, aryl-C_1-C_6-alkyl-, aryl-C_2-C_6-alkenyl-, aryl-C_2-C_6-alkynyl-, heteroaryl, heteroaryl-C_1-C_6-alkyl-, heteroaryl-C_2-C_6-alkenyl- or heteroaryl-C_2-C_6-alkynyl-, wherein the cyclic moieties are optionally substituted with one or more substituents selected from R^{37},
  - hydrogen,

R^{31} is independently selected from hydrogen, halogen, -CN, -CH_2CN, -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -$S(O)_2CF_3$, -SCF_3, -NO_2, -OR^{35}, -C(O)R^{35}, -$NR^{35}R^{36}$, -SR^{35},

$-NR^{35}S(O)_2R^{36}$, $-S(O)_2NR^{35}R^{36}$, $-S(O)NR^{35}R^{36}$, $-S(O)R^{35}$, $-S(O)_2R^{35}$, $-C(O)NR^{35}R^{36}$, $-OC(O)NR^{35}R^{36}$, $-NR^{35}C(O)R^{36}$, $-CH_2C(O)NR^{35}R^{36}$, $-OCH_2C(O)NR^{35}R^{36}$, $-CH_2OR^{35}$, $-CH_2NR^{35}R^{36}$, $-OC(O)R^{35}$, $-OC_1$-C_6-alkyl-$C(O)OR^{35}$, $-SC_1$-C_6-alkyl-$C(O)OR^{35}$ $-C_2$-C_6-alkenyl-$C(=O)OR^{35}$, $-NR^{35}$-$C(=O)$-C_1-C_6-alkyl-$C(=O)OR^{35}$, $-NR^{35}$-$C(=O)$-C_1-C_6-alkenyl-$C(=O)OR^{35}$-, C_1-C_6-alkyl, C_1-C_6-alkanoyl or $-C(O)OR^{35}$,

R^{32} and R^{33} are independently selected from hydrogen, C_1-C_6-alkyl or C_1-C_6-alkanoyl,

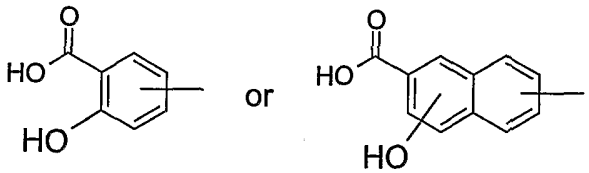
R^{34} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OR^{35}$, and $-NR^{35}R^{36}$,

R^{35} and R^{36} are independently selected from hydrogen, C_1-C_6-alkyl, aryl-C_1-C_6-alkyl or aryl, or R^{35} and R^{36} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

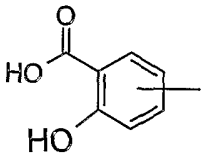
R^{37} is independently selected from halogen, $-C(O)OR^{35}$, -C(O)H, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{35}$, $-NR^{35}R^{36}$, C_1-C_6-alkyl or C_1-C_6-alkanoyl,

or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base,
With the proviso that R^{31} and J cannot both be hydrogen.

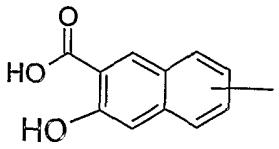
128. A pharmaceutical preparation according to any one of the claims 126 or 127 wherein H is



129. A pharmaceutical preparation according to claim 128 wherein H is



130. A pharmaceutical preparation according to claim 128 wherein H is



131. A pharmaceutical preparation according to any one of the claims 126 to 130wherein I is a valence bond, $-CH_2N(R^{32})-$, or $-SO_2N(R^{33})-$.

132. A pharmaceutical preparation according to claim 131 wherein I is a valence bond.

133. A pharmaceutical preparation according to any one of the claims 126 to 132 wherein J is

- hydrogen,
- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl,

  which may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OR^{35}$, and $-NR^{35}R^{36}$,
- aryl, or heteroaryl, wherein the cyclic moieties are optionally substituted with one or more substituents independently selected from R^{37}.

134. A pharmaceutical preparation according to claim 133 wherein J is

- hydrogen,
- aryl or heteroaryl, wherein the cyclic moieties are optionally substituted with one or more substituents independently selected from R^{37}.

135. A pharmaceutical preparation according to claim 133 wherein J is

- hydrogen,
- ArG1 or Het3, wherein the cyclic moieties are optionally substituted with one or more substituents independently selected from R^{37}.

136. A pharmaceutical preparation according to claim 135 wherein J is

- hydrogen,
- phenyl or naphthyl optionally substituted with one or more substituents independently selected from R^{37}.

137. A pharmaceutical preparation according to claim 136 wherein J is hydrogen.

138. A pharmaceutical preparation according to any one of the claims 126 to 137 wherein R^{32} and R^{33} are independently selected from hydrogen or C_1-C_6-alkyl.

139. A pharmaceutical preparation according to any one of the claims 126 to 138 wherein R^{34} is hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$, $-SCF_3$, $-NO_2$, $-OR^{35}$, $-C(O)R^{35}$, $-NR^{35}R^{36}$, $-SR^{35}$, $-C(O)NR^{35}R^{36}$, $-OC(O)NR^{35}R^{36}$, $-NR^{35}C(O)R^{36}$, $-OC(O)R^{35}$, $-OC_1$-C_6-alkyl-$C(O)OR^{35}$, $-SC_1$-C_6-alkyl-$C(O)OR^{35}$ or $-C(O)OR^{35}$.

140. A pharmaceutical preparation according to claim 139 wherein R^{34} is hydrogen, halogen, $-CF_3$, $-NO_2$, $-OR^{35}$, $-NR^{35}R^{36}$, $-SR^{35}$, $-NR^{35}C(O)R^{36}$, or $-C(O)OR^{35}$.

141. A pharmaceutical preparation according to claim 140 wherein R^{34} is hydrogen, halogen, $-CF_3$, $-NO_2$, $-OR^{35}$, $-NR^{35}R^{36}$, or $-NR^{35}C(O)R^{36}$.

142. A pharmaceutical preparation according to claim 141 wherein R^{34} is hydrogen, halogen, or $-OR^{35}$.

143. A pharmaceutical preparation according to any one of the claims 126 to 142 wherein R^{35} and R^{36} are independently selected from hydrogen, C_1-C_6-alkyl, or aryl.

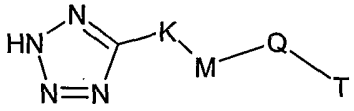
144. A pharmaceutical preparation according to claim 143 wherein R^{35} and R^{36} are independently selected from hydrogen or C_1-C_6-alkyl.

145. A pharmaceutical preparation according to any one of the claims 126 to 144 wherein R^{37} is halogen, $-C(O)OR^{35}$, -CN, $-CF_3$, $-OR^{35}$, $-NR^{35}R^{36}$, C_1-C_6-alkyl or C_1-C_6-alkanoyl.

146. A pharmaceutical preparation according to claim 145 wherein R^{37} is halogen, $-C(O)OR^{35}$, $-OR^{35}$, $-NR^{35}R^{36}$, C_1-C_6-alkyl or C_1-C_6-alkanoyl.

147. A pharmaceutical preparation according to claim 146 wherein R^{37} is halogen, $-C(O)OR^{35}$ or $-OR^{35}$.

148. A pharmaceutical preparation according to claim 22 wherein the zinc-binding ligand is



wherein K is a valence bond, C_1-C_6-alkylene, -NH-C(=O)-U-, $-C_1$-C_6-alkyl-S-, $-C_1$-C_6-alkyl-O-, -C(=O)-, or -C(=O)-NH-, wherein any C_1-C_6-alkyl moiety is optionally substituted with R^{38},

U is a valence bond, C_1-C_6-alkenylene, $-C_1$-C_6-alkyl-O- or C_1-C_6-alkylene wherein any C_1-C_6-alkyl moiety is optionally substituted with C_1-C_6-alkyl,

R^{38} is C_1-C_6-alkyl, aryl, wherein the alkyl or aryl moieties are optionally substituted with one or more substituents independently selected from R^{39},

R^{39} is independently selected from halogen, cyano, nitro, amino,

M is a valence bond, arylene or heteroarylene, wherein the aryl or heteroaryl moieties are optionally substituted with one or more substituents independently selected from R^{40},

R^{40} is selected from

- hydrogen, halogen, -CN, -CH_2CN, -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -$S(O)_2CF_3$, -$OS(O)_2CF_3$, -SCF_3, -NO_2, -OR^{41}, -$NR^{41}R^{42}$, -SR^{41}, -$NR^{41}S(O)_2R^{42}$, -$S(O)_2NR^{41}R^{42}$, -$S(O)NR^{41}R^{42}$, -$S(O)R^{41}$, -$S(O)_2R^{41}$, -$OS(O)_2$ R^{41}, -$C(O)NR^{41}R^{42}$, -$OC(O)NR^{41}R^{42}$, -$NR^{41}C(O)R^{42}$, -$CH_2C(O)NR^{41}R^{42}$, -OC_1-C_6-alkyl-$C(O)NR^{41}R^{42}$, -CH_2OR^{41}, -$CH_2OC(O)R^{41}$, -$CH_2NR^{41}R^{42}$, -$OC(O)R^{41}$, -OC_1-C_6-alkyl-$C(O)OR^{41}$, -OC_1-C_6-alkyl-OR^{41}, -S-C_1-C_6-alkyl-$C(O)OR^{41}$, –C_2-C_6-alkenyl-$C(=O)OR^{41}$, -NR^{41}-$C(=O)$-C_1-C_6-alkyl-$C(=O)OR^{41}$, -NR^{41}-$C(=O)$-C_1-C_6-alkenyl-$C(=O)OR^{41}$, -$C(O)OR^{41}$, –C_2-C_6-alkenyl-$C(=O)R^{41}$, =O, -NH-$C(=O)$-O-C_1-C_6-alkyl, or -NH-$C(=O)$-$C(=O)$-O-C_1-C_6-alkyl,

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl, which may each optionally be substituted with one or more substituents selected from R^{43},

- aryl, aryloxy, aryloxycarbonyl, aroyl, arylsulfanyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aroyl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl or heteroaryl-C_2-C_6-alkynyl, wherein the cyclic moieties optionally may be substituted with one or more substituents selected from R^{44},

R^{41} and R^{42} are independently selected from hydrogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkenyl, aryl-C_1-C_6-alkyl or aryl, wherein the alkyl moieties may optionally be substituted with one or more substituents independently selected from R^{45}, and the aryl moieties may optionally be substituted with one or more substituents independently selected from R^{46}; R^{41} and R^{42} when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom, the heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

R^{43} is independently selected from halogen, -CN, -CF_3, -OCF_3, -OR^{41}, and -$NR^{41}R^{42}$

R^{44} is independently selected from halogen, -$C(O)OR^{41}$, -$CH_2C(O)OR^{41}$, -CH_2OR^{41}, -CN, -CF_3, -OCF_3, -NO_2, -OR^{41}, -$NR^{41}R^{42}$ and C_1-C_6-alkyl,

R^{45} is independently selected from halogen, -CN, -CF_3, -OCF_3, -O-C_1-C_6-alkyl, -C(O)-O-C_1-C_6-alkyl, -COOH and –NH_2,

R^{46} is independently selected from halogen, -C(O)OC_1-C_6-alkyl, -COOH, -CN, -CF_3, -OCF_3, -NO_2, -OH, -OC_1-C_6-alkyl, -NH_2, C(=O) or C_1-C_6-alkyl,

Q is a valence bond, C_1-C_6-alkylene, -C_1-C_6-alkyl-O-, -C_1-C_6-alkyl-NH-, -NH-C_1-C_6-alkyl, -NH-C(=O)-, -C(=O)-NH-, -O-C_1-C_6-alkyl, -C(=O)-, or -C_1-C_6-alkyl-C(=O)-N(R^{47})- wherein the alkyl moieties are optionally substituted with one or more substituents independently selected from R^{48},

R^{47} and R^{48} are independently selected from hydrogen, C_1-C_6-alkyl, aryl optionally substituted with one or more R^{49},

R^{49} is independently selected from halogen and –COOH,

T is

- hydrogen,
- C_1-C_6-alkyl, C_2-C_6-alkenyl , C_2-C_6-alkynyl, C_1-C_6-alkyloxy-carbonyl, wherein the alkyl, alkenyl and alkynyl moieties are optionally substituted with one or more substituents independently selected from R^{50},
- aryl, aryloxy, aryloxy-carbonyl, aryl-C_1-C_6-alkyl, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkyny-, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl, heteroaryl-C_2-C_6-alkynyl,

wherein any alkyl, alkenyl , alkynyl, aryl and heteroaryl moiety is optionally substituted with one or more substituents independently selected from R^{50},

R^{50} is C_1-C_6-alkyl, C_1-C_6-alkoxy, aryl, aryloxy, aryl-C_1-C_6-alkoxy, -C(=O)-NH-C_1-C_6-alkyl-aryl, -C(=O)-NR^{50A}-C_1-C_6-alkyl, -C(=O)-NH-$(CH_2CH_2O)_m$$C_1$-$C_6$-alkyl-COOH, heteroaryl, heteroaryl-C_1-C_6-alkoxy, -C_1-C_6-alkyl-COOH, -O-C_1-C_6-alkyl-COOH, -$S(O)_2R^{51}$, -C_2-C_6-alkenyl-COOH, -OR^{51}, -NO_2, halogen, -COOH, -CF_3, -CN, =O, -N($R^{51}R^{52}$), wherein m is 1, 2, 3 or 4, and wherein the aryl or heteroaryl moieties are optionally substituted with one or more R^{53}, and the alkyl moieties are optionally substituted with one or more R^{50B}.

R^{50A} and R^{50B} are independently selected from -C(O)OC_1-C_6-alkyl, -COOH, -C_1-C_6-alkyl-C(O)OC_1-C_6-alkyl, -C_1-C_6-alkyl-COOH, or C_1-C_6-alkyl,

R^{51} and R^{52} are independently selected from hydrogen and C_1-C_6-alkyl,

R^{53} is independently selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, -C_1-C_6-alkyl-COOH, -C_2-C_6-alkenyl-COOH, -OR^{51}, -NO_2, halogen, -COOH, -CF_3, -CN, or -$N(R^{51}R^{52})$,

or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

149. A pharmaceutical preparation according to claim 148 wherein K is a valence bond, C_1-C_6-alkylene, -NH-C(=O)-U-, -C_1-C_6-alkyl-S-, -C_1-C_6-alkyl-O-, or -C(=O)-, wherein any C_1-C_6-alkyl moiety is optionally substituted with R^{38}.

150. A pharmaceutical preparation according to claim 149 wherein K is a valence bond, C_1-C_6-alkylene, -NH-C(=O)-U-, -C_1-C_6-alkyl-S-, or -C_1-C_6-alkyl-O, wherein any C_1-C_6-alkyl moiety is optionally substituted with R^{38}.

151. A pharmaceutical preparation according to claim 150 wherein K is a valence bond, C_1-C_6-alkylene, or -NH-C(=O)-U, wherein any C_1-C_6-alkyl moiety is optionally substituted with R^{38}.

152. A pharmaceutical preparation according to claim 151 wherein K is a valence bond or C_1-C_6-alkylene, wherein any C_1-C_6-alkyl moiety is optionally substituted with R^{38}.

153. A pharmaceutical preparation according to claim 151 wherein K is a valence bond or -NH-C(=O)-U.

154. A pharmaceutical preparation according to claim 152 wherein K is a valence bond.

155. A pharmaceutical preparation according to any one of the claims 148 to 154 wherein U is a valence bond or -C_1-C_6-alkyl-O-.

156. A pharmaceutical preparation according to claim 155 wherein U is a valence bond

157. A pharmaceutical preparation according to any one of the claims 148 to 156 wherein M is arylene or heteroarylene, wherein the arylene or heteroarylene moieties are optionally substituted with one or more substituents independently selected from R^{40}.

158. A pharmaceutical preparation according to claim 157 wherein M is ArG1 or Het1, wherein the arylene or heteroarylene moieties are optionally substituted with one or more substituents independently selected from R^{40}.

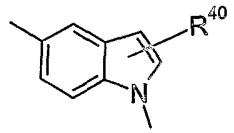
159. A pharmaceutical preparation according to claim 158 wherein M is ArG1 or Het2, wherein the arylene or heteroarylene moieties are optionally substituted with one or more substituents independently selected from R^{40}.

160. A pharmaceutical preparation according to claim 159 wherein M is ArG1 or Het3, wherein the arylene or heteroarylene moieties are optionally substituted with one or more substituents independently selected from R^{40}.

161. A pharmaceutical preparation according to claim 160 wherein M is phenylene optionally substituted with one or more substituents independently selected from R^{40}.

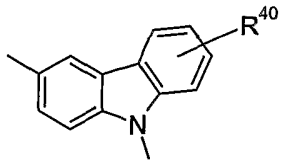
162. A pharmaceutical preparation according to claim 160 wherein M is indolylene optionally substituted with one or more substituents independently selected from R^{40}.

163. A pharmaceutical preparation according to claim 162 wherein M is



164. A pharmaceutical preparation according to claim 160 wherein M is carbazolylene optionally substituted with one or more substituents independently selected from R^{40}.

165. A pharmaceutical preparation according to claim 164 wherein M is



166. A pharmaceutical preparation according to any one of the claims 148 to 165 wherein R^{40} is selected from

- hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{41}$, $-NR^{41}R^{42}$, $-SR^{41}$, $-S(O)_2R^{41}$, $-NR^{41}C(O)R^{42}$, $-OC_1$-C_6-alkyl-$C(O)NR^{41}R^{42}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{41}$, $-C(O)OR^{41}$, =O, -NH-C(=O)-O-C_1-C_6-alkyl, or -NH-C(=O)-C(=O)-O-C_1-C_6-alkyl,

  C_1-C_6-alkyl or C_2-C_6- alkenyl which may each optionally be substituted with one or more substituents independently selected from R^{43},

- aryl, aryloxy, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, or heteroaryl-C_2-C_6-alkenyl, wherein the cyclic moieties optionally may be substituted with one or more substituents selected from R^{44}.

167. A pharmaceutical preparation according to claim 166 wherein R^{40} is selected from

- hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{41}$, $-NR^{41}R^{42}$, $-SR^{41}$, $-S(O)_2R^{41}$, $-NR^{41}C(O)R^{42}$, $-OC_1$-C_6-alkyl-$C(O)NR^{41}R^{42}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{41}$, $-C(O)OR^{41}$, =O, -NH-C(=O)-O-C_1-C_6-alkyl, or -NH-C(=O)-C(=O)-O-C_1-C_6-alkyl,

  C_1-C_6-alkyl or C_2-C_6- alkenyl which may each optionally be substituted with one or more substituents independently selected from R^{43},

- ArG1, ArG1-O-, ArG1-C_1-C_6-alkoxy, ArG1-C_1-C_6-alkyl, ArG1-C_2-C_6-alkenyl, Het3, Het3-C_1-C_6-alkyl, or Het3-C_2-C_6-alkenyl, wherein the cyclic moieties optionally may be substituted with one or more substituents selected from R^{44}.

168. A pharmaceutical preparation according to claim 167 wherein R^{40} is selected from

- hydrogen, halogen, $-CF_3$, $-NO_2$, $-OR^{41}$, $-NR^{41}R^{42}$, $-C(O)OR^{41}$, =O, or $-NR^{41}C(O)R^{42}$,
- C_1-C_6-alkyl,
- ArG1.

169. A pharmaceutical preparation according to claim 168 wherein R^{40} is hydrogen.

170. A pharmaceutical preparation according to claim 168 wherein R^{40} is selected from

- Halogen, $-NO_2$, $-OR^{41}$, $-NR^{41}R^{42}$, $-C(O)OR^{41}$, or $-NR^{41}C(O)R^{42}$,
- Methyl,
- Phenyl.

171. A pharmaceutical preparation according to any one of the claims 148 to 170 wherein R^{41} and R^{42} are independently selected from hydrogen, C_1-C_6-alkyl, or aryl, wherein the aryl moieties may optionally be substituted with halogen or –COOH.

172. A pharmaceutical preparation according to claim 171 wherein R^{41} and R^{42} are independently selected from hydrogen, methyl, ethyl, or phenyl, wherein the phenyl moieties may optionally be substituted with halogen or –COOH.

173. A pharmaceutical preparation according to any one of the claims 148 to 172 wherein Q is a valence bond, C_1-C_6-alkylene, -C_1-C_6-alkyl-O-, -C_1-C_6-alkyl-NH-, -NH-C_1-C_6-alkyl, -NH-C(=O)-, -C(=O)-NH-, -O-C_1-C_6-alkyl, -C(=O)-, or -C_1-C_6-alkyl-C(=O)-N(R^{47})- wherein the alkyl moieties are optionally substituted with one or more substituents independently selected from R^{48}.

174. A pharmaceutical preparation according to claim 173 wherein Q is a valence bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-CH_2-CH_2-O-$, $-CH_2-NH-$, $-CH_2-CH_2-NH-$, $-NH-CH_2-$, $-NH-CH_2-CH_2-$, -NH-C(=O)-, -C(=O)-NH-, $-O-CH_2-$, $-O-CH_2-CH_2-$, or -C(=O)-.

175. A pharmaceutical preparation according to claim 174 wherein Q is a valence bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$,or $-CH_2-CH_2-O-$.

176. A pharmaceutical preparation according to claim 175 wherein Q is a valence bond, $-CH_2-$, or $-CH_2-CH_2-$.

177. A pharmaceutical preparation according to claim 176 wherein Q is $-CH_2-$.

178. A pharmaceutical preparation according to any one of the claims 148 to 177 wherein R^{47} and R^{48} are independently selected from hydrogen, methyl and phenyl.

179. A pharmaceutical preparation according to any one of the claims 148 to 178 wherein T is

- hydrogen,
- C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{50},
- aryl, aryl-C_1-C_6-alkyl, heteroaryl, wherein the alkyl, aryl and heteroaryl moieties are optionally substituted with one or more substituents independently selected from R^{50}.

180. A pharmaceutical preparation according to claim 179 wherein T is

- hydrogen,
- C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{50},
- ArG1, ArG1-C_1-C_6-alkyl, Het3, wherein the alkyl, aryl and heteroaryl moieties are optionally substituted with one or more substituents independently selected from R^{50}.

181. A pharmaceutical preparation according to claim 180 wherein T is

- hydrogen,
- C_1-C_6-alkyl, optionally substituted with one or more substituents independently selected from R^{50},
- phenyl, phenyl-C_1-C_6-alkyl, wherein the alkyl and phenyl moieties are optionally substituted with one or more substituents independently selected from R^{50}.

182. A pharmaceutical preparation according to claim 181 wherein T is phenyl substituted with R^{50}.

183. A pharmaceutical preparation according to any one of the claims 148 to 182 wherein R^{50} is C_1-C_6-alkyl, C_1-C_6-alkoxy, aryl, aryloxy, aryl-C_1-C_6-alkoxy, -C(=O)-NH-C_1-C_6-alkyl-aryl, -C(=O)-NR^{50A}-C_1-C_6-alkyl, -C(=O)-NH-$(CH_2CH_2O)_mC_1$-C_6-alkyl-COOH, heteroaryl, -C_1-C_6-alkyl-COOH, -O-C_1-C_6-alkyl-COOH, -$S(O)_2R^{51}$, -C_2-C_6-alkenyl-COOH, -OR^{51}, -NO_2, halogen, -COOH, -CF_3, -CN, =O, -$N(R^{51}R^{52})$, wherein the aryl or heteroaryl moieties are optionally substituted with one or more R^{53}.

184. A pharmaceutical preparation according to claim 183 wherein R^{50} is C_1-C_6-alkyl, C_1-C_6-alkoxy, aryl, aryloxy, -C(=O)-NR^{50A}-C_1-C_6-alkyl, -C(=O)-NH-$(CH_2CH_2O)_mC_1$-C_6-alkyl-COOH, aryl-C_1-C_6-alkoxy , -OR^{51}, -NO_2, halogen, -COOH, -CF_3, wherein any aryl moiety is optionally substituted with one or more R^{53}.

185. A pharmaceutical preparation according to claim 184 wherein R^{50} is C_1-C_6-alkyl, aryloxy, -C(=O)-NR^{50A}-C_1-C_6-alkyl, -C(=O)-NH-$(CH_2CH_2O)_mC_1$-C_6-alkyl-COOH, aryl-C_1-C_6-alkoxy ,

-OR^{51}, halogen, -COOH, -CF_3, wherein any aryl moiety is optionally substituted with one or more R^{53}.

186. A pharmaceutical preparation according to claim 185 wherein R^{50} is C_1-C_6-alkyl, ArG1-O-, -C(=O)-NR^{50A}-C_1-C_6-alkyl, -C(=O)-NH-$(CH_2CH_2O)_mC_1$-C_6-alkyl-COOH, ArG1-C_1-C_6-alkoxy , -OR^{51}, halogen, -COOH, -CF_3, wherein any aryl moiety is optionally substituted with one or more R^{53}.

187. A pharmaceutical preparation according to claim 186 wherein R^{50} is -C(=O)-$NR^{50A}CH_2$, -C(=O)-NH-$(CH_2CH_2O)_2CH_2$I-COOH, or -C(=O)-$NR^{50A}CH_2CH_2$

188. A pharmaceutical preparation according to claim 186 wherein R^{50} is phenyl, methyl, ethyl, halogen, or -COOH.

189. A pharmaceutical preparation according to claim 188 wherein R^{50} is methyl or ethyl.

190. A pharmaceutical preparation according to claim 188 wherein R^{50} is COOH.

191. A pharmaceutical preparation according to any one of the claims 148 to 190 wherein m is 1 or 2.

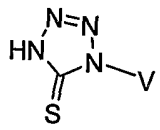
192. A pharmaceutical preparation according to any one of the claims 148 to 191 wherein R^{51} is methyl.

193. A pharmaceutical preparation according to any one of the claims 148 to 192 wherein R^{53} is C_1-C_6-alkyl, C_1-C_6-alkoxy, -OR^{51}, halogen,or -CF_3.

194. A pharmaceutical preparation according to any one of the claims 148 to 193 wherein R^{50A} is -$C(O)OCH_3$, -$C(O)OCH_2CH_3$ -COOH, -$CH_2C(O)OCH_3$, -$CH_2C(O)OCH_2CH_3$, -$CH_2CH_2C(O)OCH_3$, -$CH_2CH_2C(O)OCH_2CH_3$, -CH_2COOH, methyl, or ethyl.

195. A pharmaceutical preparation according to any one of the claims 148 to 194 wherein R^{50B} is -$C(O)OCH_3$, -$C(O)OCH_2CH_3$ -COOH, -$CH_2C(O)OCH_3$, -$CH_2C(O)OCH_2CH_3$, -$CH_2CH_2C(O)OCH_3$, -$CH_2CH_2C(O)OCH_2CH_3$, -CH_2COOH, methyl, or ethyl.

196. A pharmaceutical preparation according to claim 22 wherein the zinc-binding ligand is



wherein V is C_1-C_6-alkyl, aryl, heteroaryl, aryl-C_{1-6}-alkyl- or aryl-C_{2-6}-alkenyl-, wherein the alkyl or alkenyl is optionally substituted with one or more substituents independently selected from R^{54}, and the aryl or heteroaryl is optionally substituted with one or more substituents independently selected from R^{55},

R^{54} is independently selected from halogen, -CN, -CF_3, -OCF_3, aryl, -COOH and –NH_2,

R^{55} is independently selected from

- hydrogen, halogen, -CN, -CH_2CN, -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -$S(O)_2CF_3$, -$OS(O)_2CF_3$, -SCF_3, -NO_2, -OR^{56}, -$NR^{56}R^{57}$, -SR^{56}, -$NR^{56}S(O)_2R^{57}$, -$S(O)_2NR^{56}R^{57}$, -$S(O)NR^{56}R^{57}$, -$S(O)R^{56}$, -$S(O)_2R^{56}$, -$OS(O)_2$ R^{56}, -$C(O)NR^{56}R^{57}$, -$OC(O)NR^{56}R^{57}$, -$NR^{56}C(O)R^{57}$, -$CH_2C(O)NR^{56}R^{57}$, -OC_1-C_6-alkyl-$C(O)NR^{56}R^{57}$, -CH_2OR^{56}, -$CH_2OC(O)R^{56}$, -$CH_2NR^{56}R^{57}$, -$OC(O)R^{56}$, -OC_1-C_8-alkyl-$C(O)OR^{56}$, -OC_1-C_6-alkyl-OR^{56}, -SC_1-C_6-alkyl-$C(O)OR^{56}$, –C_2-C_6-alkenyl-$C(=O)OR^{56}$, -NR^{56}-C(=O)-C_1-C_6-alkyl-$C(=O)OR^{56}$, -NR^{56}-C(=O)-C_1-C_6-alkenyl-$C(=O)OR^{56}$, -$C(O)OR^{56}$, or –C_2-C_6-alkenyl-$C(=O)R^{56}$,

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl,

which may optionally be substituted with one or more substituents selected from R^{58},

- aryl, aryloxy, aryloxycarbonyl, aroyl, arylsulfanyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aroyl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl or heteroaryl-C_2-C_6-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{59},

R^{56} and R^{57} are independently selected from hydrogen, OH, CF_3, C_1-C_{12}-alkyl, aryl-C_1-C_6-alkyl, -C(=O)-C_1-C_6-alkyl or aryl, wherein the alkyl groups may optionally be substituted with one or more substituents independently selected from R^{60}, and the aryl groups may optionally be substituted with one or more substituents independently selected from R^{61}; R^{56} and R^{57} when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom, the heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

R^{58} is independently selected from halogen, -CN, -CF_3, -OCF_3, -OR^{56}, and –$NR^{56}R^{57}$,

R^{59} is independently selected from halogen, -$C(O)OR^{56}$, -$CH_2C(O)OR^{56}$, -CH_2OR^{56}, -CN, -CF_3, -OCF_3, -NO_2, -OR^{56}, -$NR^{56}R^{57}$ and C_1-C_6-alkyl,

R^{60} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OC_1$-C_6-alkyl, $-C(O)OC_1$-C_6-alkyl, $-C(=O)-R^{62}$, -COOH and $-NH_2$,

R^{61} is independently selected from halogen, $-C(O)OC_1$-C_6-alkyl, -COOH, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, -OH, $-OC_1$-C_6-alkyl, $-NH_2$, C(=O) or C_1-C_6-alkyl,

R^{62} is C_1-C_6-alkyl, aryl optionally substituted with one or more substituents independently selected from halogen, or heteroaryl optionally substituted with one or more C_1-C_6-alkyl independently,
or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

197. A pharmaceutical preparation according to claim 196 wherein V is aryl, heteroaryl, or aryl-C_{1-6}-alkyl-, wherein the alkyl is optionally substituted with one or more substituents independently selected R^{54}, and the aryl or heteroaryl is optionally substituted with one or more substituents independently selected from R^{55}.
198. A pharmaceutical preparation according to claim 197 wherein V is aryl, Het1, or aryl-C_{1-6}-alkyl-, wherein the alkyl is optionally substituted with one or more substituents independently selected from R^{54}, and the aryl or heteroaryl moiety is optionally substituted with one or more substituents independently selected from R^{55}.
199. A pharmaceutical preparation according to claim 198 wherein V is aryl, Het2, or aryl-C_{1-6}-alkyl-, wherein the alkyl is optionally substituted with one or more substituents independently selected from R^{54}, and the aryl or heteroaryl moiety is optionally substituted with one or more substituents independently selected from R^{55}.
200. A pharmaceutical preparation according to claim 199 wherein V is aryl, Het3, or aryl-C_{1-6}-alkyl-, wherein the alkyl is optionally substituted with one or more substituents independently selected from R^{54}, and the aryl or heteroaryl moiety is optionally substituted with one or more substituents independently selected from R^{55}.
201. A pharmaceutical preparation according to claim 200 wherein V is aryl optionally substituted with one or more substituents independently selected from R^{55}.
202. A pharmaceutical preparation according to claim 201 wherein V is ArG1 optionally substituted with one or more substituents independently selected from R^{55}.

203. A pharmaceutical preparation according to claim 202 wherein V is phenyl, naphthyl or anthranyl optionally substituted with one or more substituents independently selected from R^{55}.

204. A pharmaceutical preparation according to claim 203 wherein V is phenyl optionally substituted with one or more substituents independently selected from R^{55}.

205. A pharmaceutical preparation according to any one of the claims 196 to 204 wherein R^{55} is independently selected from

- halogen, C_1-C_6-alkyl, -CN, -OCF_3 ,-CF_3, -NO_2, -OR^{56}, -$NR^{56}R^{57}$, -$NR^{56}C(O)R^{57}$ -SR^{56}, -OC_1-C_8-alkyl-$C(O)OR^{56}$, or -$C(O)OR^{56}$,
- C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{58}
- aryl, aryl-C_1-C_6-alkyl, heteroaryl, or heteroaryl-C_1-C_6-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents independently selected from R^{59}.

206. A pharmaceutical preparation according to claim 205 wherein R^{55} is independently selected from

- halogen, C_1-C_6-alkyl, -CN, -OCF_3 ,-CF_3, -NO_2, -OR^{56}, -$NR^{56}R^{57}$, -$NR^{56}C(O)R^{57}$ -SR^{56}, -OC_1-C_8-alkyl-$C(O)OR^{56}$, or -$C(O)OR^{56}$
- C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{58}
- ArG1, ArG1-C_1-C_6-alkyl, Het3, or Het3-C_1-C_6-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents independently selected from R^{59}.

207. A pharmaceutical preparation according to claim 206 wherein R^{55} is independently selected from halogen, -OR^{56}, -$NR^{56}R^{57}$, -$C(O)OR^{56}$, -OC_1-C_8-alkyl-$C(O)OR^{56}$, -$NR^{56}C(O)R^{57}$ or C_1-C_6-alkyl.

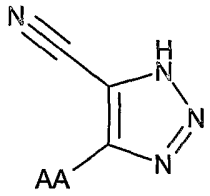
208. A pharmaceutical preparation according to claim 207 wherein R^{55} is independently selected from halogen, -OR^{56}, -$NR^{56}R^{57}$, -$C(O)OR^{56}$, -OC_1-C_8-alkyl-$C(O)OR^{56}$, -$NR^{56}C(O)R^{57}$, methyl or ethyl.

209. A pharmaceutical preparation according to any one of the claims 196 to 208 wherein R^{56} and R^{57} are independently selected from hydrogen, CF_3, C_1-C_{12}-alkyl, or -C(=O)-C_1-C_6-alkyl; R^{56} and R^{57} when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom.

210. A pharmaceutical preparation according to claim 209 wherein R^{56} and R^{57} are independently selected from hydrogen or C_1-C_{12}-alkyl, R^{56} and R^{57} when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom.

211. A pharmaceutical preparation according to claim 210 wherein R^{56} and R^{57} are independently selected from hydrogen or methyl, ethyl, propyl butyl, R^{56} and R^{57} when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom.

212. A pharmaceutical preparation according to claim 22 wherein the zinc-binding ligand is



wherein AA is C_1-C_6-alkyl, aryl, heteroaryl, aryl-C_{1-6}-alkyl- or aryl-C_{2-6}-alkenyl-, wherein the alkyl or alkenyl is optionally substituted with one or more substituents independently selected from R^{63}, and the aryl or heteroaryl is optionally substituted with one or more substituents independently selected from R^{64},

R^{63} is independently selected from halogen, -CN, -CF_3, -OCF_3, aryl, -COOH and –NH_2,

R^{64} is independently selected from

- hydrogen, halogen, -CN, -CH_2CN, -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -$S(O)_2CF_3$, -$OS(O)_2CF_3$, -SCF_3, -NO_2, -OR^{65}, -$NR^{65}R^{66}$, -SR^{65}, -$NR^{65}S(O)_2R^{66}$, -$S(O)_2NR^{65}R^{66}$, -$S(O)NR^{65}R^{66}$, -$S(O)R^{65}$, -$S(O)_2R^{65}$, -$OS(O)_2$ R^{65}, -$C(O)NR^{65}R^{66}$, -$OC(O)NR^{65}R^{66}$, -$NR^{65}C(O)R^{66}$, -$CH_2C(O)NR^{65}R^{66}$, -OC_1-C_6-alkyl-$C(O)NR^{65}R^{66}$, -CH_2OR^{65}, -$CH_2OC(O)R^{65}$, -$CH_2NR^{65}R^{66}$, -$OC(O)R^{65}$, -OC_1-C_6-alkyl-$C(O)OR^{65}$, -OC_1-C_6-alkyl-OR^{65}, -SC_1-C_6-alkyl-$C(O)OR^{65}$, –C_2-C_6-alkenyl-$C(=O)OR^{65}$, -NR^{65}-$C(=O)$-C_1-C_6-alkyl-$C(=O)OR^{65}$, -NR^{65}-$C(=O)$-C_1-C_6-alkenyl-$C(=O)OR^{65}$, -$C(O)OR^{65}$, or –C_2-C_6-alkenyl-$C(=O)R^{65}$,

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl, each of which may optionally be substituted with one or more substituents selected from R^{67},

- aryl, aryloxy, aryloxycarbonyl, aroyl, arylsulfanyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aroyl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl or heteroaryl-C_2-C_6-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{68},

R^{65} and R^{66} are independently selected from hydrogen, OH, CF_3, C_1-C_{12}-alkyl, aryl-C_1-C_6-alkyl, -C(=O)-R^{69}, aryl or heteroaryl, wherein the alkyl groups may optionally be substituted with one or more substituents selected from R^{70}, and the aryl and heteroaryl groups may optionally be substituted with one or more substituents independently selected from R^{71}; R^{65} and R^{66} when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom, the heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

R^{67} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OR^{65}$, and $-NR^{65}R^{66}$,

R^{68} is independently selected from halogen, $-C(O)OR^{65}$, $-CH_2C(O)OR^{65}$, $-CH_2OR^{65}$, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{65}$, $-NR^{65}R^{66}$ and C_1-C_6-alkyl,

R^{69} is independently selected from C_1-C_6-alkyl, aryl optionally substituted with one or more halogen, or heteroaryl optionally substituted with one or more C_1-C_6-alkyl,

R^{70} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OC_1$-C_6-alkyl, $-C(O)OC_1$-C_6-alkyl, -COOH and $-NH_2$,

R^{71} is independently selected from halogen, $-C(O)OC_1$-C_6-alkyl, -COOH, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, -OH, $-OC_1$-C_6-alkyl, $-NH_2$, C(=O) or C_1-C_6-alkyl,

or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

213. A pharmaceutical preparation according to claim 212 wherein AA is aryl, heteroaryl or aryl-C_{1-6}-alkyl-, wherein the alkyl is optionally substituted with one or more R^{63}, and the aryl

or heteroaryl is optionally substituted with one or more substituents independently selected from R^{64}.

214. A pharmaceutical preparation according to claim 213 wherein AA is aryl or heteroaryl optionally substituted with one or more substituents independently selected from R^{64}.

215. A pharmaceutical preparation according to claim 214 wherein AA is ArG1 or Het1 optionally substituted with one or more substituents independently selected from R^{64}.

216. A pharmaceutical preparation according to claim 215 wherein AA is ArG1 or Het2 optionally substituted with one or more substituents independently selected from R^{64}.

217. A pharmaceutical preparation according to claim 216 wherein AA is ArG1 or Het3 optionally substituted with one or more substituents independently selected from R^{64}.

218. A pharmaceutical preparation according to claim 217 wherein AA is phenyl, naphtyl, anthryl, carbazolyl, thienyl, pyridyl, or benzodioxyl optionally substituted with one or more substituents independently selected from R^{64}.

219. A pharmaceutical preparation according to claim 218 wherein AA is phenyl or naphtyl optionally substituted with one or more substituents independently selected from R^{64}.

220. A pharmaceutical preparation according to any one of the claims 212 to 219 wherein R^{64} is independently selected from hydrogen, halogen, $-CF_3$, $-OCF_3$, $-OR^{65}$, $-NR^{65}R^{66}$, C_1-C_6-alkyl, $-OC(O)R^{65}$, $-OC_1$-C_6-alkyl-$C(O)OR^{65}$, aryl-C_2-C_6-alkenyl, aryloxy or aryl, wherein C_1-C_6-alkyl is optionally substituted with one or more substituents independently selected from R^{67}, and the cyclic moieties optionally are substituted with one or more substituents independently selected from R^{68}.

221. A pharmaceutical preparation according to claim 220 wherein R^{64} is independently selected from halogen, $-CF_3$, $-OCF_3$, $-OR^{65}$, $-NR^{65}R^{66}$, methyl, ethyl, propyl, $-OC(O)R^{65}$, $-OCH_2$-$C(O)OR^{65}$, $-OCH_2$-CH_2-$C(O)OR^{65}$, phenoxy optionally substituted with one or more substituents independently selected from R^{68}.

222. A pharmaceutical preparation according to any one of the claims 212 to 221 wherein R^{65} and R^{66} are independently selected from hydrogen, CF_3, C_1-C_{12}-alkyl, aryl, or heteroaryl optionally substituted with one or more substituents independently selected from R^{71}.

223. A pharmaceutical preparation according to claim 222 wherein R^{65} and R^{66} are independently hydrogen, C_1-C_{12}-alkyl, aryl, or heteroaryl optionally substituted with one or more substituents independently selected from R^{71}.

224. A pharmaceutical preparation according to claim 223 wherein R^{65} and R^{66} are independently hydrogen, methyl, ethyl, propyl, butyl, 2,2-dimethyl-propyl, ArG1 or Het1 optionally substituted with one or more substituents independently selected from R^{71}.

225. A pharmaceutical preparation according to claim 224 wherein R^{65} and R^{66} are independently hydrogen, methyl, ethyl, propyl, butyl, 2,2-dimethyl-propyl, ArG1 or Het2 optionally substituted with one or more substituents independently selected from R^{71}.

226. A pharmaceutical preparation according to claim 225 wherein R^{65} and R^{66} are independently hydrogen, methyl, ethyl, propyl, butyl, 2,2-dimethyl-propyl, ArG1 or Het3 optionally substituted with one or more substituents independently selected from R^{71}.

227. A pharmaceutical preparation according to claim 226 wherein R^{65} and R^{66} are independently hydrogen, methyl, ethyl, propyl, butyl, 2,2-dimethyl-propyl, phenyl, naphtyl, thiadiazolyl optionally substituted with one or more R^{71} independently; or isoxazolyl optionally substituted with one or more substituents independently selected from R^{71}.

228. A pharmaceutical preparation according to any one of the claims 212 to 227 wherein R^{71} is halogen or C_1-C_6-alkyl.

229. A pharmaceutical preparation according to claim 228 wherein R^{71} is halogen or methyl.

230. Method of prolonging the action of an insulin preparation comprising insulin, protamine and zinc ions wherein said method comprises adding a zinc-binding ligand according to any of claims 21 to 229 to the insulin preparation.

231. A method of treating type 1 or type 2 diabetes comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical preparation according to any one of the claims 1 to 229.

232. Use of a preparation according to any one of the claims 1 to 229 for the preparation of a medicament for treatment of type 1 or type 2 diabetes.

233. A method of preparing a pharmaceutical preparation comprising the steps of mixing

- insulin
- a ligand for the His^{B10} Zn^{2+} site of the insulin hexamer according to any of claims 21 to 229
- zinc ions
- protamine
- optionally further ingredients selected from the group consisting of phenolic preservative, buffer, isotonicity agent, viscosity increasing agent, and a non-ionic surfactant,

and allowing the mixture to stand until crystals are formed.

234. A method according to claim 233 wherein the ligand for the His^{B10} Zn^{2+} site is added to the mixture before crystal growth.

235. A method according to claim 233 wherein the ligand for the His^{B10} Zn^{2+} site is added to the mixture after completion of crystal growth.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK2004/000160

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/28 A61K47/10 A61K47/22

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 925 792 A (LILLY CO ELI) 30 June 1999 (1999-06-30) page 9, line 36 - line 55	1, 230-233
X	US 3 060 093 A (ERIK POULSEN JAKOB ET AL) 23 October 1962 (1962-10-23) examples	1, 230-233
P,X	EP 1 396 272 A (LILLY CO ELI) 10 March 2004 (2004-03-10) page 9, line 31 - line 50	1, 230-233
X	US 2001/036916 A1 (BRADER MARK LAURENCE) 1 November 2001 (2001-11-01) column 5, paragraph 51	1, 230-233

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

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

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

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

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

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 July 2004	27/07/2004

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

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK2004/000160

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 03/053460 A (MYERS SHARON RUTH ; LILLY CO ELI (US); BRADER MARK LAURENCE (US); SUKU) 3 July 2003 (2003-07-03) page 2, line 29 - line 30 page 14, line 23 - page 15, line 2	1, 230-233
X	US 2002/082199 A1 (BRADER MARK LAURENCE) 27 June 2002 (2002-06-27) column 5, paragraph 51	1, 230-233
A	US 5 830 999 A (DUNN MICHAEL F) 3 November 1998 (1998-11-03) column 6; table 1	1, 230-233
A	WO 00/29013 A (NOVONORDISK AS) 25 May 2000 (2000-05-25) claims; examples	1, 230-233
A	SHENG TUNG HUANG ET AL: "Carboxylate Ions Are Strong Allosteric Ligands for the HisB10 sites of the R-State Insulin Hexamer" BIOCHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, PA, US, vol. 36, 1997, pages 9878-9888, XP002234225 ISSN: 0006-2960 page 9882	1, 230-233
A	BRANGE J ET AL: "CHEMICAL STABILITY OF INSULIN 3. INFLUENCE OF EXCIPIENTS, FORMULATION, AND PH" ACTA PHARMACEUTICA NORDICA, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 4, no. 3, 1992, pages 149-158, XP000990198 ISSN: 1100-1801 page 150 - page 151	1, 230-233

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK2004/000160

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 230 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK2004/000160

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