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# DESCRIPTION

Description

**[0001]** The invention relates to novel inhibitors of transglutaminases, in particular transglutaminase 2, methods for their synthesis and to their use for the prophylaxis and treatment of diseases associated with transglutaminases, in particular transglutaminase 2. Any references in the description to methods of treatment refer to the compounds or pharmaceutical compositions of the present invention for use in a method for treatment of the human (or animal) body by therapy.

**Background of the invention**

**[0002]** Transglutaminases are part of the class of transferases and according to EC nomenclature they are correctly designated as "protein-glutamine: amine γ-glutamyl transferases" (EC 2.3.2.13). They link the ε-amino group of the amino acid lysine and the γ-glutamyl group of the amino acid glutamine forming an isopeptide bond while ammonia is released. In the absence of suitable amines and/or under certain conditions, deamidation of the glutamine may occur resulting in the corresponding glutamic acid.

**[0003]** Additionally, transglutaminases play an important role in many therapeutic areas such as the cardiovascular diseases (thrombosis and atherosclerosis), autoimmune diseases (celiac disease, Duhring-Brocq-disease, gluten ataxia), neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, Huntington's disease), dermatological diseases (ichthyosis, psoriasis, acne) as well as in wound healing and inflammatory diseases (e.g. tissue fibrosis) (J.M. Wodzinska, Mini-Reviews in medical chemistry, 2005, 5, 279 - 292).

**[0004]** Celiac disease, a gluten intolerance, however, is one of the most important indications.

**[0005]** Celiac disease is characterized by a chronic inflammation of the mucosa of the small intestine. In susceptible patients, the intestinal epithelium is successively destroyed after ingestion of gluten-containing food resulting in reduced absorption of nutrients which again has massive impact on the patients affected and is for example associated with symptoms such as loss of weight, anemia, diarrhea, nausea, vomiting, loss of appetite and fatigue. Due to these findings, there is a large demand for the development of a medicament for the treatment of celiac disease as well as of other diseases associated with tissue transglutaminase (transglutaminase 2, TG2, tTG). The tissue transglutaminase is a central element during pathogenesis. The endogenous enzyme catalyses the deamidation of gluten/gliadin in the small intestinal mucosa and thus triggers the inflammatory response. Therefore inhibitors of tissue transglutaminase are suitable to be used as active agents for medication.

**[0006]** Another very important group of indications for tissue transglutaminase inhibitors are fibrotic disorders. Fibrotic disorders are characterized by the accumulation of crosslinked extracellular matrix proteins. Diabetic nephropathy, cystic fibrosis, idiopathic pulmonary fibrosis, kidney fibrosis as well as liver fibrosis belong to the most important fibrotic disorders to be addressed with the compounds disclosed.

**[0007]** US 9,434,763 B2 discloses pyridinone derivatives having a warhead comprising at least one acceptor-substituted double bond, such as a Michael System, as irreversible transglutaminase inhibitors. Alkylacetamido and arylacetamido pyridinones showed inhibitory activity regarding tissue transglutaminase TG2 in nanomolar range ($IC_{50}$).

**[0008]** Tse et al. (J. Med. Chem. 2020, 63, 11585-11601) report on replacement of phenyl residues by non-classical bioisosteres, such as cubane and bicyclo[1.1.1]pentane (BCP), in anti-malarial triazolopyrazine compounds in order to alter compound solubility and metabolic stability. The authors further evaluated *in vitro* antiplasmodial activity of bioisosteric modified triazolopyrazines against the 3D7 strain of *P. falciparum.* Replacement of phenyl by bioisosteric saturated heterocyclic residues resulted in complete loss of activity. Adamantyl residues as well as other hydrocarbon-caged derivatives led to potency up to 2-9 times lower than the corresponding phenyl triazolopyrazine compounds. In contrast, higher potencies were achieved by replacing phenyl with closo-1,2- and 1,7-carborane isomers. The authors concluded that the effect of non classical bioiostere replacement on biological properties cannot be predicted accurately and that a considerable range of possible bioisosteres has to be tested first in order to identify a suitable replacement leading to the desired properties of a given molecule.

**[0009]** Subbaiah et al. (J. Med. Chem. 2021, 64, 19, 14046-14128) report on bioisosteres of the phenyl ring in lead optimization and drug design. It is noted that bioisosteric phenyl ring replacement with heterocyclic and carbocyclic moieties can lead to enhanced potency, solubility, and metabolic stability while reducing lipophilicity, plasma protein binding, phospholipidosis potential, and inhibition of cytochrome P450 enzymes and the hERG channel. However, this effect depends strongly on the properties of the compound itself and the addressed target.

**[0010]** US 11,072,634 B2 discloses reversible transglutaminase inhibitors comprising an aldehyde, a ketone, an α-ketoaldehyde, an α-ketoketone, an α-ketoacid, an α-ketoester, an α-ketoamide or a halogenmethylketone as warhead. The inhibitors showed inhibitory activity regarding tissue transglutaminase TG2 in nanomolar and micromolar range ($IC_{50}$).

**[0011]** The objective of the present invention is to provide novel, most probably irreversible inhibitors of transglutaminases, in particular transglutaminase 2 and methods for the synthesis of said inhibitors as well as several uses of these inhibitors.

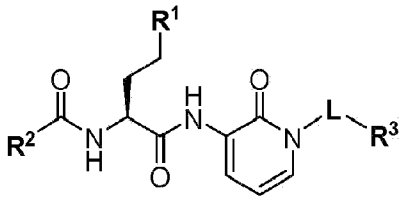
**[0012]** Said objective is solved by the technical teachings of the independent claims. Further

advantageous embodiments, aspects and details of the invention are evident from the dependent claims, the description, and the examples.

**[0013]** Surprisingly, it has been found that irreversible inhibitors having a chemical warhead as disclosed herein inhibit effectively transglutaminases including tissue transglutaminase called transglutaminase 2 or TG2. Herein these terms are used synonymous.

**[0014]** Preferably, such chemical warhead moiety is particularly selected from irreversible warheads such as α,β-unsaturated-ketoester, α,β-unsaturated ketoamide and α,β-unsaturated-sulfone. The compounds of the present invention act as selective inhibitors of transglutaminase 2.

**[0015]** Thus, the present invention relates to compounds of the general formula (**I**):



(I)

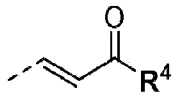
wherein

L represents -$L^1$- or -$L^1$-$L^2$-; preferably -$L^1$-$L^2$-;

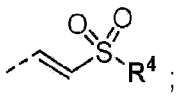
$L^1$ represents -$CH_2$-, -$CH_2CH_2$-, -$CH_2CH_2CH_2$-, -$CH_2CO$-, or -$CH_2CH_2CO$-;

$L^2$ represents a bond, -$NR^{N1}$-, -$NR^{N1}CH_2$-, -$NR^{N1}CH_2CH_2$-, or -$NR^{N1}CH(CH_3)$-,

$R^1$ represents

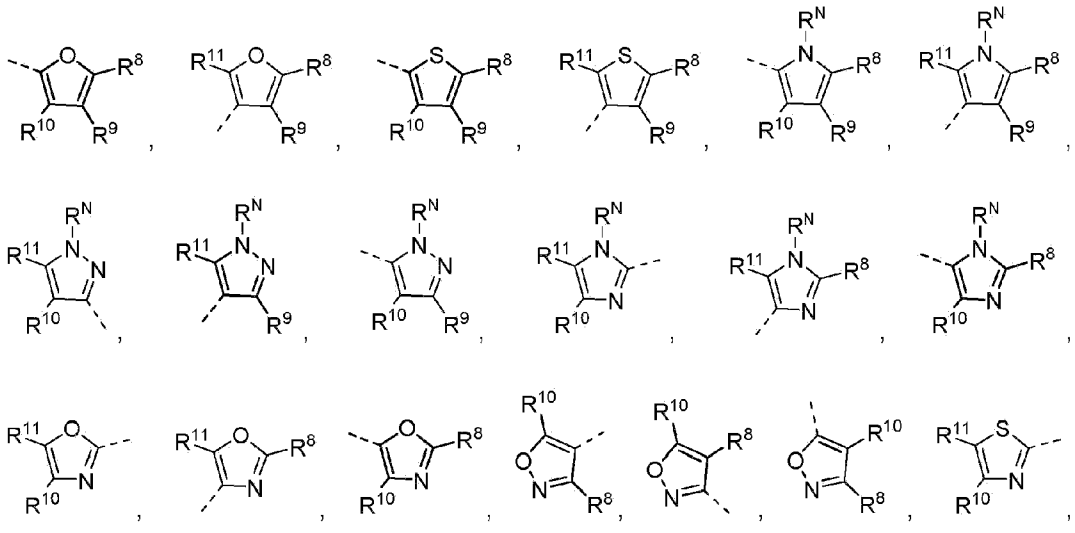


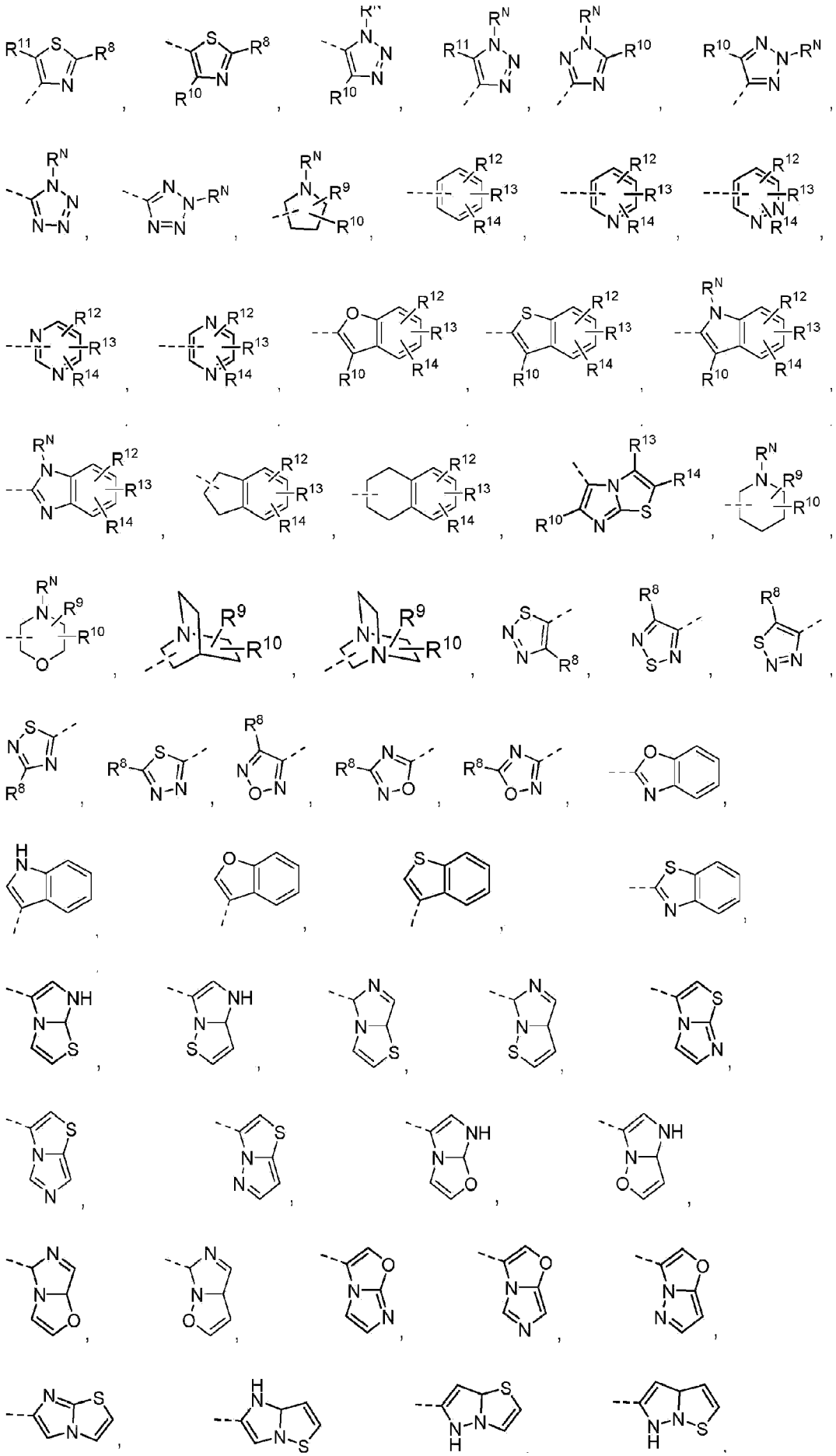
or

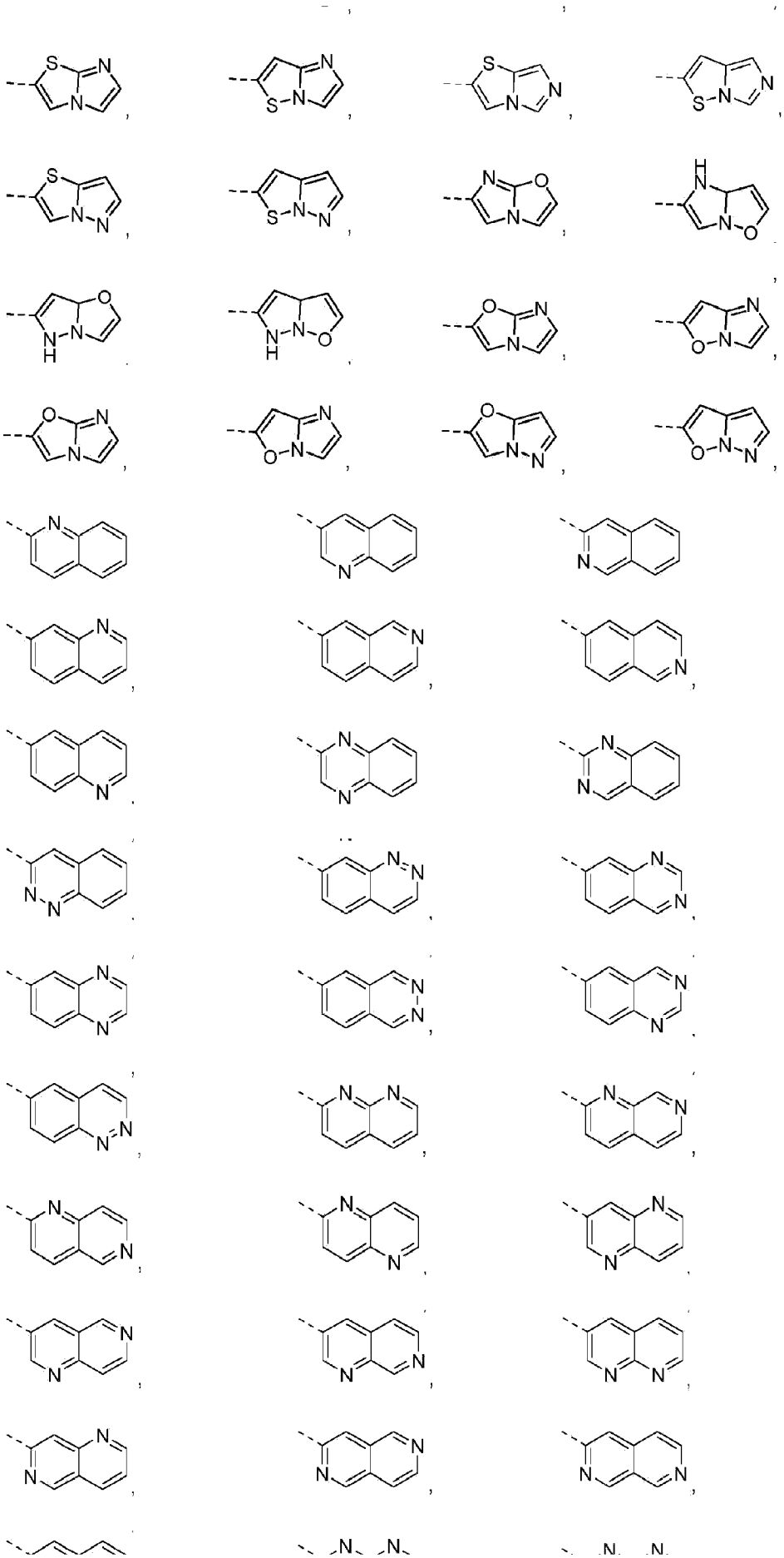


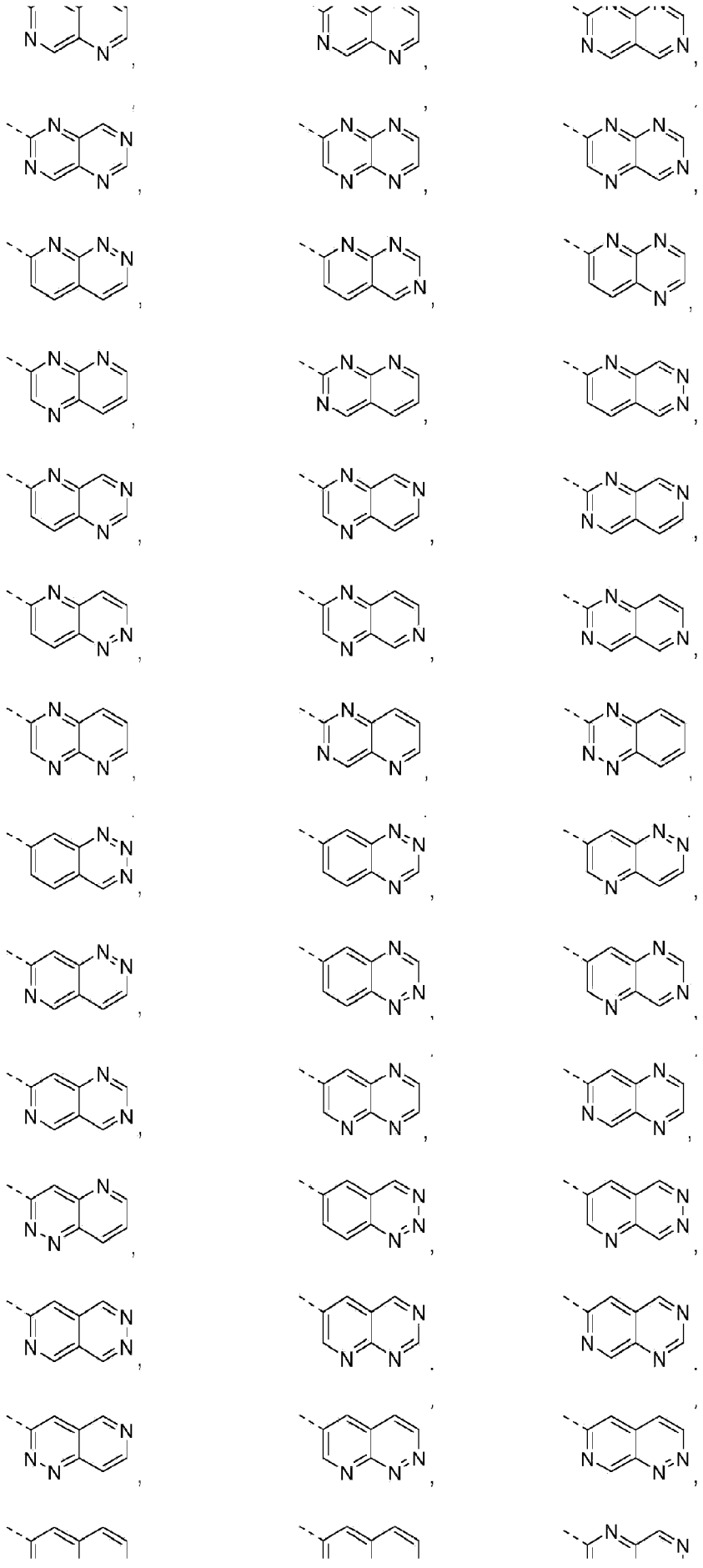
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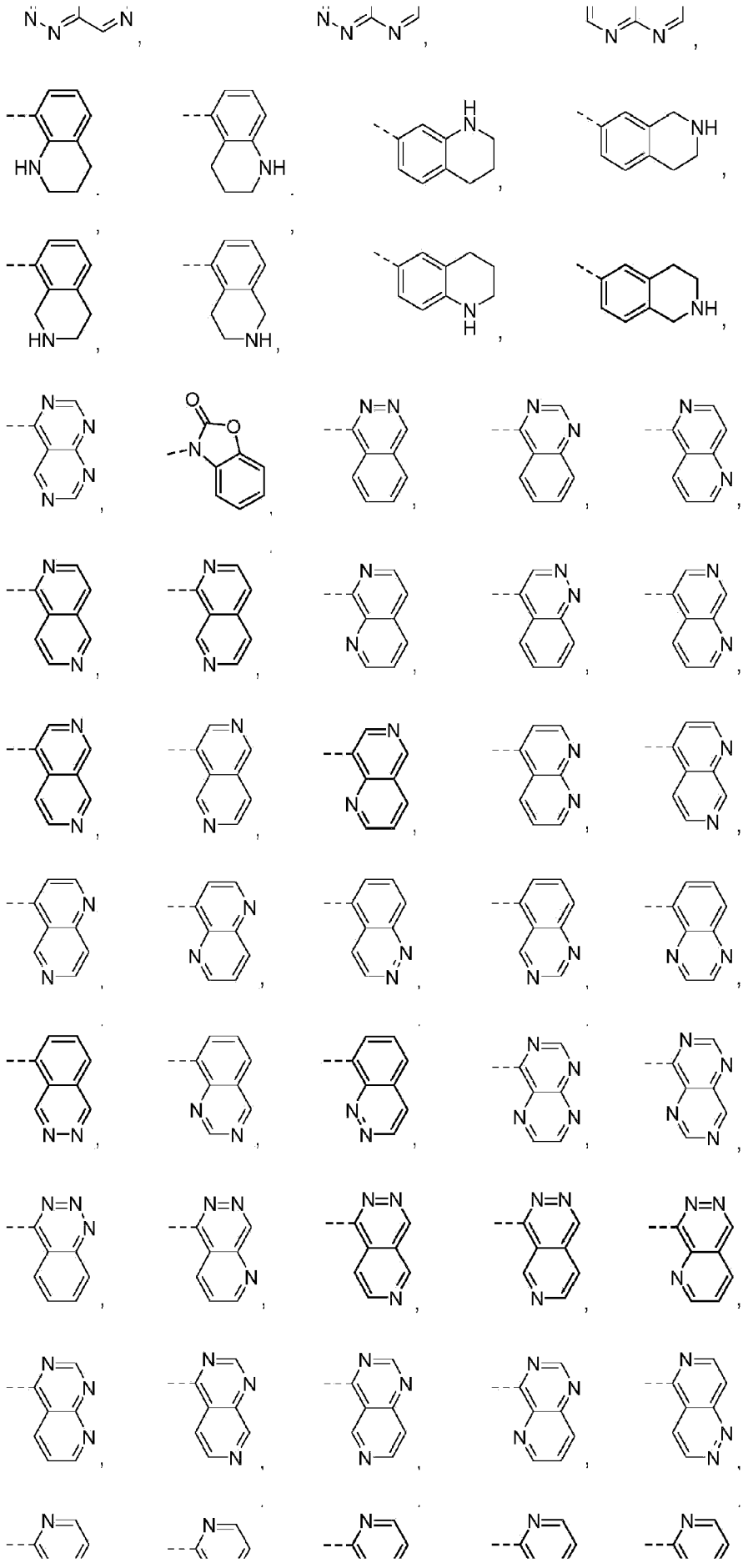
$R^2$ represents

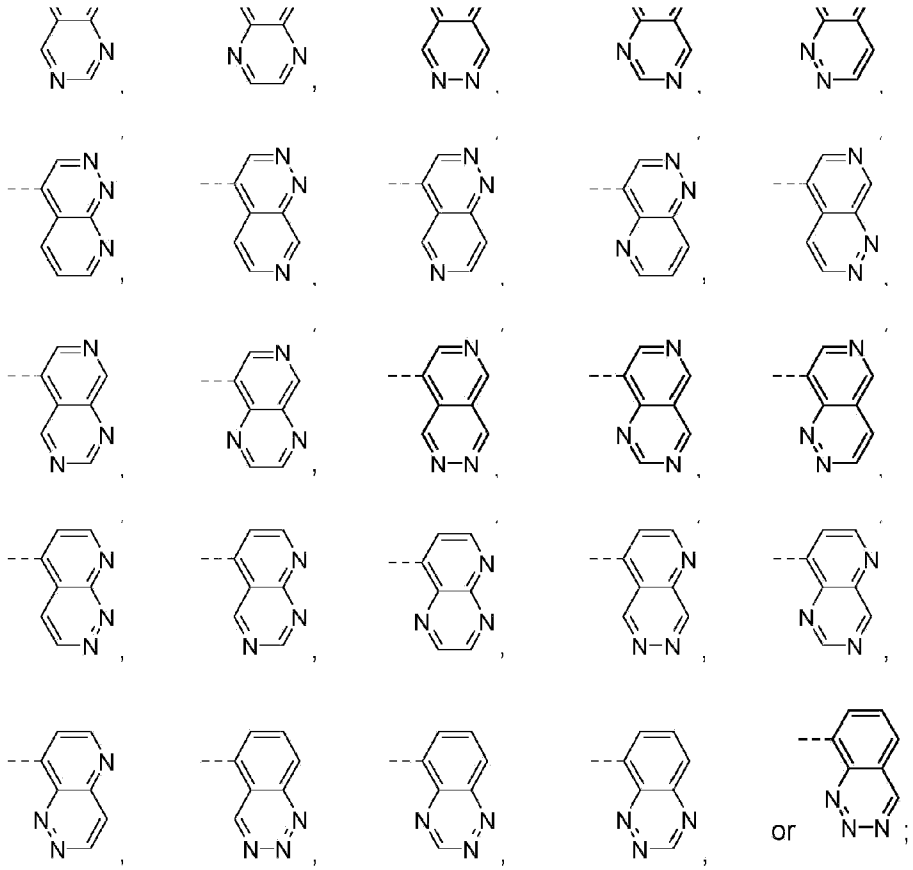












wherein the unsubstituted bicyclic residues can be substituted with 1 to 5 of the substituents **R$^{9}$** -**R$^{14}$**, and **R$^{N}$**; and preferably with 1 to 3 of the substituents **R$^{11}$** - **R$^{13}$**;

**R$^{3}$** represents bicyclo[1.1.1]pentyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.2]decyl, bicyclo[3.3.3]undecyl, 4-homoisotwistyl, adamantyl, diamantyl, or hexamethylenetetraminyl and the afore-mentioned residues optionally contain one or more C=C double bond(s) and/or are optionally substituted by one or more of **R$^{a}$**, **R$^{b}$**, **R$^{c}$**, **R$^{d}$**, and **R$^{e}$**;

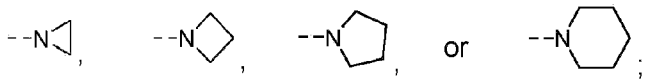
**R$^{a}$**, **R$^{b}$**, **R$^{c}$**, **R$^{d}$**, and **R$^{e}$** represent independently of each other -H, -F, -Cl, -Br, -CN, -OH, -$CH_3$, -$CH_2CH_3$, -$CH_2CH_2CH_3$, -$CH(CH_3)_2$, -$CHF_2$, -$CF_3$, -$CH_2CF_3$, -$COCH_3$, -$COCH_2CH_3$, -$CO_2H$, -$CO_2CH_3$, -$CO_2C_2H_5$, -$CONH_2$, -$CONHCH_3$, -$CON(CH_3)_2$, -$CONHC_2H_5$, -$CH_2CO_2H$, -$CH_2CO_2CH_3$, -$CH_2CO_2C_2H_5$, -$CH_2CONH_2$, -$CH_2CONHCH_3$, -$CH_2CON(CH_3)_2$, -$CH_2CONHC_2H_5$, -$NHCOCH_3$, -$NHCOC_2H_5$, -$NHCOCF_3$, -$NHCOCH_2CF_3$, -$NHSO_2CH_3$, -$NHSO_2C_2H_5$, -$NHSO_2CHF_2$, -$NHSO_2CF_3$, or-$NHSO_2CH_2CF_3$;

**R$^{4}$** represents -**R$^{5}$**, -O**R$^{5}$** or -N**R$^{6}$R$^{7}$**;

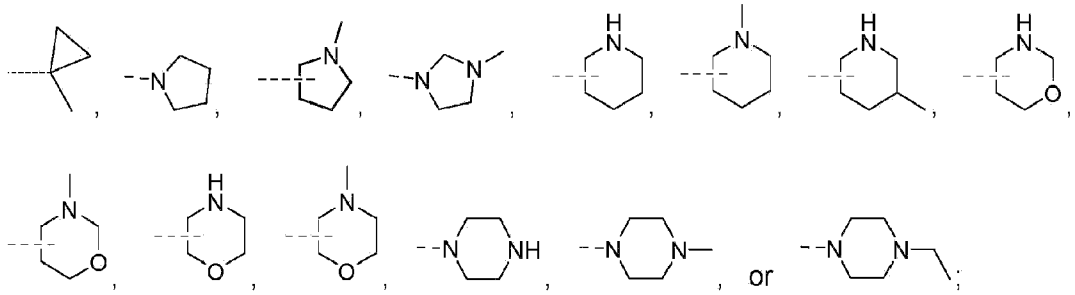
**R$^{5}$** represents -H, -$CH_3$, -$CH_2CH_3$, -$CH_2CH_2CH_3$, -$CH(CH_3)_2$, -$CH_2CH_2CH_2CH_3$, -$CH_2CH(CH_3)_2$, -$C(CH_3)_3$, -$CH_2CH_2CH_2CH_2CH_3$, -$CH_2CH{=}CH_2$, -$CH_2CH{=}CH(CH_3)$, -$CH_2CH{=}C(CH_3)_2$, -$CH_2CH{=}CHCH_2CH_3$, -cyclo-$C_3H_5$, -cyclo-$C_4H_7$, -cyclo-$C_5H_9$, -cyclo-$C_6H_{11}$, -$CH_2$-cyclo-$C_3H_5$, -

$CH_2$-cyclo-$C_4H_7$, -$CH_2$-cyclo-$C_5H_9$, -$CH_2$-cyclo-$C_6H_{11}$, -Ph, -$CH_2$-Ph, -$CH_2OCH_3$, -$CH_2OCH_2CH_3$, -$CH_2CH_2OCH_3$, or -$CH_2CH_2OCH_2CH_3$;

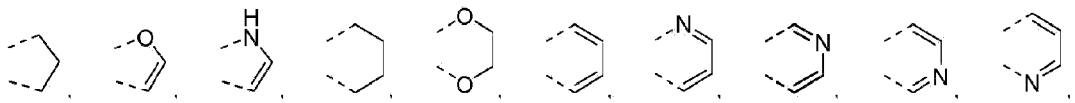
**$R^6$** and **$R^7$** represent independently of each other -H, -$CH_3$, -$CH_2CH_3$, -$CH_2CH_2CH_3$, -$CH(CH_3)_2$, -$CH_2CH_2CH_2CH_3$, -$CH_2CH_2CH_2CH_2CH_3$, -$CH_2CH(CH_3)_2$, -$C(CH_3)_3$, -$CH_2CH{=}CH_2$, -$CH_2CH{=}CH(CH_3)$, -$CH_2CH{=}C(CH_3)_2$, -$CH_2CH{=}CHCH_2CH_3$, -cyclo-$C_3H_5$, -cyclo-$C_4H_7$, -cyclo-$C_5H_9$, -cyclo-$C_6H_{11}$, -$CH_2$-cyclo-$C_3H_5$, -$CH_2$-cyclo-$C_4H_7$, -$CH_2$-cyclo-$C_5H_9$, -$CH_2$-cyclo-$C_6H_{11}$, -Ph, -$CH_2$-Ph, -$CH_2OCH_3$, -$CH_2OCH_2CH_3$, -$CH_2CH_2OCH_3$, -$CH_2CH_2OCH_2CH_3$, -$CH_2CH_2NHCH_3$, -$CH_2CH_2N(CH_3)_2$, or -N**$R^6R^7$** represents

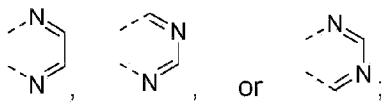


**$R^8$**, **$R^9$**, **$R^{10}$**, **$R^{11}$**, **$R^{12}$**, **$R^{13}$**, and **$R^{14}$** represent independently of each other -H, -F, -Cl, -Br, -I, -OH, -CN, -$NO_2$, -$CH_3$, -$C_2H_5$, -$C_3H_7$, -$CH(CH_3)_2$, -$C_4H_9$, -$CH_2$-$CH(CH_3)_2$, -$CH(CH_3)$-$C_2H_5$, -$C(CH_3)_3$, -cyclo-$C_3H_5$, -$CH_2$-cyclo-$C_3H_5$, -$CH_2OH$, -$CH_2F$, -$CHF_2$, -$CF_3$, -$CH_2Cl$, -$CH_2Br$, -$CH_2I$, -$CH_2$-$CH_2F$, -$CH_2$-$CHF_2$, -$CH_2$-$CF_3$, -$CH_2$-$CH_2Cl$, -$CH_2$-$CH_2Br$, -$CH_2$-$CH_2I$, -$OCH_3$, -$OC_2H_5$, -$OC_3H_7$, -$OCH(CH_3)_2$, -$OC(CH_3)_3$, -$OC_4H_9$, -$OCHF_2$, -$OCF_3$, -$OCH_2CF_3$, -$OC_2F_5$, -$OCH_2OCH_3$, -O-cyclo-$C_3H_5$, -$OCH_2$-cyclo-$C_3H_5$, -O-$C_2H_4$-cyclo-$C_3H_5$, -CHO, -$COCH_3$, -$COCF_3$, -$COC_2H_5$, -$COC_3H_7$, -$COCH(CH_3)_2$, -$COC(CH_3)_3$, -COOH, -$COOCH_3$, -$COOC_2H_5$, -$COOC_3H_7$, -$COOCH(CH_3)_2$, -$COOC(CH_3)_3$, -OOC-$CH_3$, -OOC-$CF_3$, -OOC-$C_2H_5$, -OOC-$C_3H_7$, -OOC-$CH(CH_3)_2$, -OOC-$C(CH_3)_3$, -$NH_2$, -$NHCH_3$, -$NHC_2H_5$, -$NHC_3H_7$, -$NHCH(CH_3)_2$, -$NHC(CH_3)_3$, -$N(CH_3)_2$, -$N(C_2H_5)_2$, -$N(C_3H_7)_2$, -$N[CH(CH_3)_2]_2$, -$N[C(CH_3)_3]_2$, -$NHCOCH_3$, -$NHCOCF_3$, -$NHCOC_2H_5$, -$NHCOC_3H_7$, -$NHCOCH(CH_3)_2$, -$NHCOC(CH_3)_3$, -$CONH_2$, -$CONHCH_3$, -$CONHC_2H_5$, -$CONHC_3H_7$, -$CONHCH(CH_3)_2$, -CONH-cyclo-$C_3H_5$, -$CONHC(CH_3)_3$, -$CON(CH_3)_2$, -$CON(C_2H_5)_2$, -$CON(C_3H_7)_2$, -$CON[CH(CH_3)_2]_2$, -$CON[C(CH_3)_3]_2$, -$SO_2NH_2$, -$SO_2NHCH_3$, -$SO_2NHC_2H_5$, -$SO_2NHC_3H_7$, -$SO_2NHCH(CH_3)_2$, -$SO_2NH$-cyclo-$C_3H_5$, -$SO_2NHC(CH_3)_3$, -$SO_2N(CH_3)_2$, -$SO_2N(C_2H_5)_2$, -$SO_2N(C_3H_7)_2$, -$SO_2N[CH(CH_3)_2]_2$, -$SO_2N[C(CH_3)_3]_2$, -$NHSO_2CH_3$, -$NHSO_2CF_3$, -$NHSO_2C_2H_5$, -$NHSO_2C_3H_7$, -$NHSO_2CH(CH_3)_2$, -$NHSO_2C(CH_3)_3$, -$CH{=}CH_2$, -$CH_2$-$CH{=}CH_2$, -$C(CH_3){=}CH_2$, -CH=CH-$CH_3$, -C≡CH, -C≡C-$CH_3$, -$CH_2$-C≡CH, -Ph, -O-Ph, -O-$CH_2$-Ph,

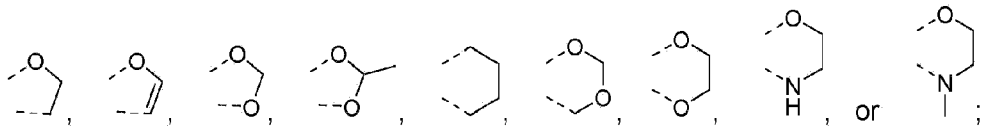


or **$R^8$** and **$R^9$** or **$R^9$** and **$R^{10}$** can form together one of the following five-membered or six-membered rings:





or $R^{12}$ and $R^{13}$ or $R^{13}$ and $R^{14}$ can form together one of the following five-membered or six-membered rings:



$R^N$ represents -H, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $-C_4H_9$, $-CH_2-CH(CH_3)_2$, $-CH(CH_3)-C_2H_5$, $-C(CH_3)_3$, -cyclo-$C_3H_5$, -cyclo-$C_4H_7$, -cyclo-$C_5H_9$, $-CH_2$-cyclo-$C_3H_5$, $-CH_2$-cyclo-$C_4H_7$, $-CH_2$-cyclo-$C_5H_9$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2Cl$, $-CH_2Br$, $-CH_2I$, $-CH_2-CH_2F$, $-CH_2-CHF_2$, $-CH_2-CF_3$, $-CH_2-CH_2Cl$, $-CH_2-CH_2Br$, $-CH_2-CH_2I$, $-CH_2-CH=CH_2$, $-CH_2-C\equiv CH$, -CHO, $-COCH_3$, $-COC_2H_5$, $-COC_3H_7$, $-COCH(CH_3)_2$, $-COC(CH_3)_3$, -CO-cyclo-$C_3H_5$, -CO-cyclo-$C_4H_7$, -CO-cyclo-$C_5H_9$, $-COOCH_3$, $-COOC_2H_5$, $-COOC_3H_7$, $-COOCH(CH_3)_2$, $-COOC(CH_3)_3$, $-COOCH_2Ph$, $-SO_2CH_3$, $-SO_2CF_3$, $-SO_2C_2H_5$, $-SO_2C_3H_7$, $-SO_2CH(CH_3)_2$, $-SO_2$-cyclo-$C_3H_5$, or $-SO_2C(CH_3)_3$;

$R^{N1}$ represent -H, $-CH_3$, or $-CH_2CH_3$;

or a diastereomer, an enantiomer, a mixture of diastereomers, a mixture of enantiomers, a racemate, a solvate, a hydrate, or a pharmaceutically acceptable salt thereof.

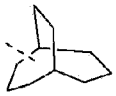
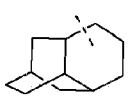
**[0016]** The inventors have found that the reversible inhibitors of formula (**I**) disclosed herein having a bridged bicyclic residue $R^3$ exhibit increased potency over the compounds of the prior art. Particularly, it is demonstrated herein, that the inventive compounds have an improved inhibitory activity compared to the known compounds bearing aromatic moieties $R^3$ instead of bridged bicyclic residues. In order to prove inventiveness of the compounds of the present application, known compounds from US 9,434,763 B2 (Reference 2 (ZED1227), Reference 3 (A8 from US 9,434,763 B2), and Reference 5) were synthesized and tested as reference compounds in comparison to the most similar compounds of the present application. To this extent, inhibition data were determined using the classical fluorescent transamidation assay (dansylcadaverine incorporation into methylated casein, DCC-assay) as described in Büchold et al. [Büchold, C.; Hils, M.; Gerlach, U.; Weber, J.; Pelzer, C.; Heil, A.; Aeschlimann, D.; Pasternack, R. Features of ZED1227: The First-In-Class Tissue Transglutaminase Inhibitor Undergoing Clinical Evaluation for the Treatment of Celiac Disease. Cells 2022, 11, 1667. https:/ldoi.org/10.3390/cells11101667] Casein is one of the best known high molecular weight (24 kDa) protein substrates for transglutaminases. Inhibition data of the inventive compounds was compared with inhibition of compounds disclosed in US 9,434,763 B2, particularly, compound A8, which is denoted herein as Reference 3. It is noteworthy that the $IC_{50}$ values of compounds A8 published in US 9,434,763 B2 cannot be compared to the present data, relying

on a fluorogenic isopeptidase assay. Measured in the DCC-assay, Ref. 2 ($IC_{50}$ = 53 nM) is 80-fold more potent compared to Ref. 3 ($IC_{50}$ = 4,268 nM).

**[0017]** Thus, the inventive compounds of formula (I) rated "A" showed efficacies of about 250-fold higher compared to Ref. 3 (A8). The same argumentation applies to Ref. 5 which is except of the phenylethyl group identical to compound **III-83**. Ref. 5 is more than 25-times less potent in comparison to compound **III-83** as evident from Table 1.

**[0018]** This finding was particularly surprising as a skilled person would not have expected an improved inhibitory activity of the inventive compounds bearing a bridged bicyclic residue over the compounds of the prior art bearing aromatic residues since it is common knowledge that bridged bicyclic groups or bridged cycloalkyl groups are non-classical bioisosters of the phenyl group, such that a skilled person would only expect to obtain a compound having similar physico-chemical and biological properties, including inhibitory activity, when replacing a phenyl group with a bridged bicyclic group. As aromatic moieties showed lower potency, bridged cycloalkyl groups would not be considered improving the physico-chemical and biological properties of the compounds.

**[0019]** The residues bicyclo[1.1.1]pentyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.2]decyl, bicyclo[3.3.3]undecyl, 4-homoisotwistyl, 1-adamantyl, 2-adamantyl, diamantyl, and hexamethylenetetraminyl used herein, have the following parent structures:

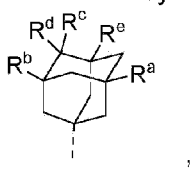
| bicyclo[1.1.1]pentyl | bicyclo[2.1.1]hexyl | bicyclo[2.2.1]heptyl |
|---|---|---|
|  |  |  |
| bicyclor3.1.11heptyl | bicyclo[2.2.2]octyl | bicyclo[3.2.1]octyl |
|  |  |  |
| bicyclo[3.2.2]nonyl | bicyclo[3.3.2]decyl | bicyclo[3.3.3]undecyl |
|  |  |  |
| 4-homoisotwistyl | adamantyl | diamantyl |
|  |  |  |
| hexamethylenetetraminyl | | |
|  | | |



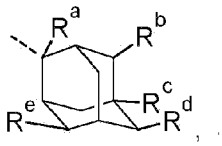
and the afore-mentioned residues optionally contain one or more C=C double bond(s) such as bicyclo[2.2.1]hept-5-enyl (see **III-66**) and/or are optionally substituted with one or more of $R^a$, $R^b$, $R^c$, $R^d$, and $R^e$.

**[0020]** Particularly, the terms "1-adamantyl", "2-adamantyl" and "2-bicyclo[3.1.1]heptyl" have the following structures:

1-adamantyl

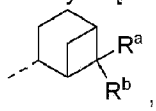


2-adamantyl



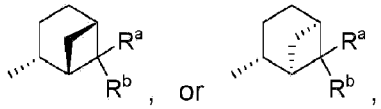
and

2-bicyclo[3.1.1]heptyl



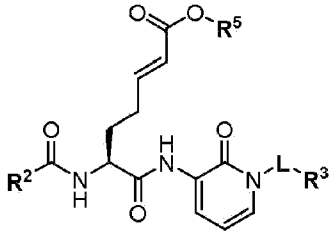
wherein $R^a$, $R^b$, $R^c$, $R^d$ and $R^e$ have the same meanings as defined herein.

**[0021]** Preferably, 2-bicyclo[3.1.1]heptyl has the following structure:



wherein $R^a$ and $R^b$, have the same meanings as defined herein.

**[0022]** Preferred are the compounds of the formula (**Ic**):

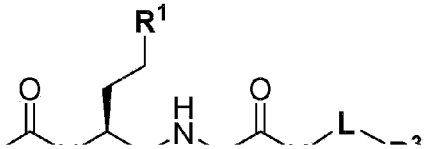


(**Ic**);

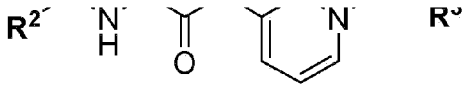
and L, $R^2$, $R^3$, $R^5$, $R^6$, $R^7$ have the same meanings as defined herein for the formula (**I**).

**[0023]** In one aspect of the present invention, the compound of the formula (**I**) has an irreversible warhead, such as α,β-unsaturated-ketoester, α,β-unsaturated ketoamide and α,β-unsaturated-sulfone. The compounds of the present invention act as selective inhibitors of transglutaminase 2.

**[0024]** Thus, in some embodiments the present invention refers to the compounds of the formula (**I**)



(**I**)



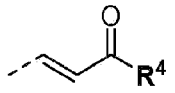
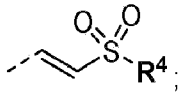
wherein

L represents -$L^1$- or -$L^1$-$L^2$- ; preferably -$L^1$-$L^2$-;

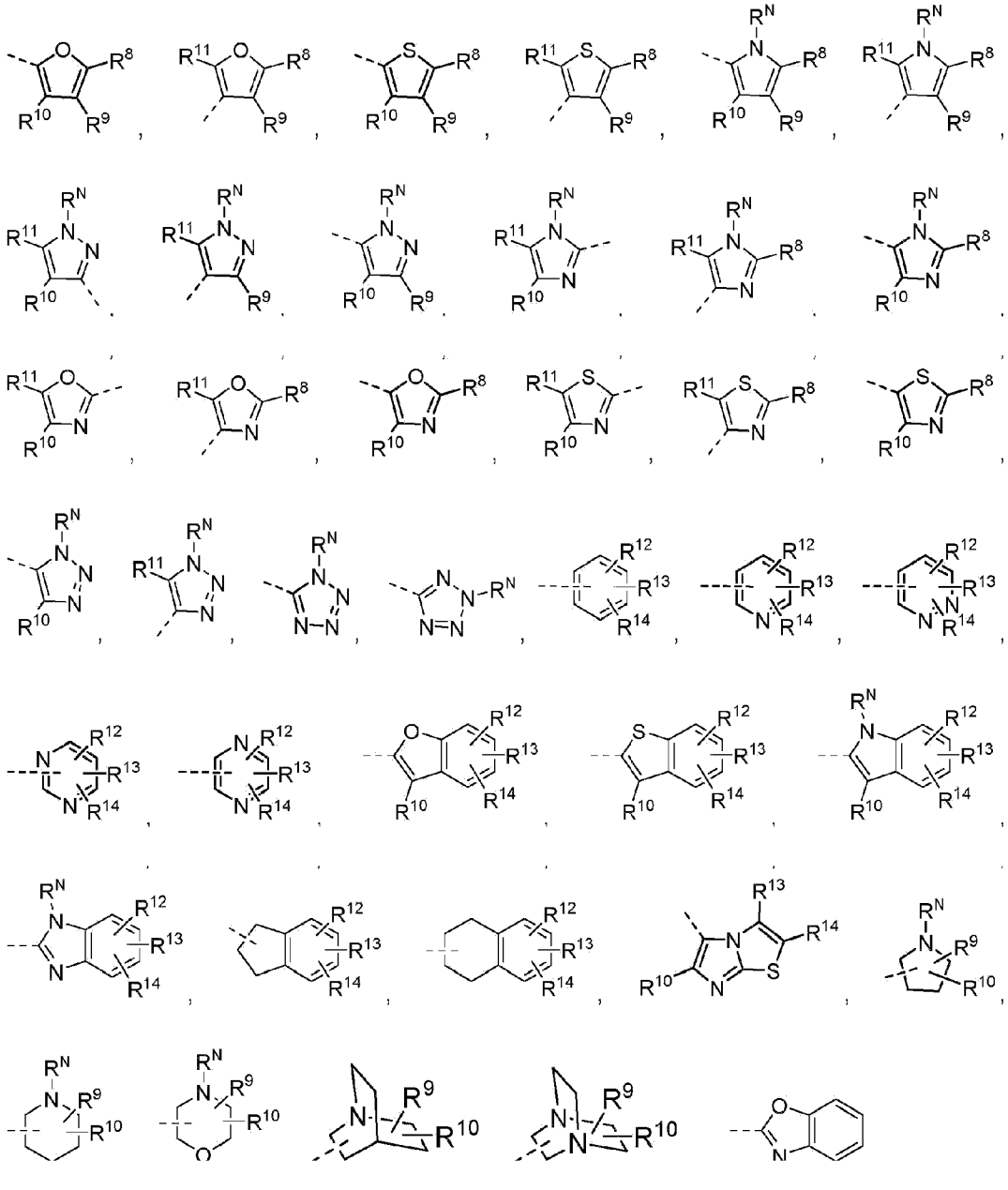
$L^1$ represents -$CH_2$-, -$CH_2CH_2$-, -$CH_2CH_2CH_2$-, -$CH_2CO$-, or -$CH_2CH_2CO$-;

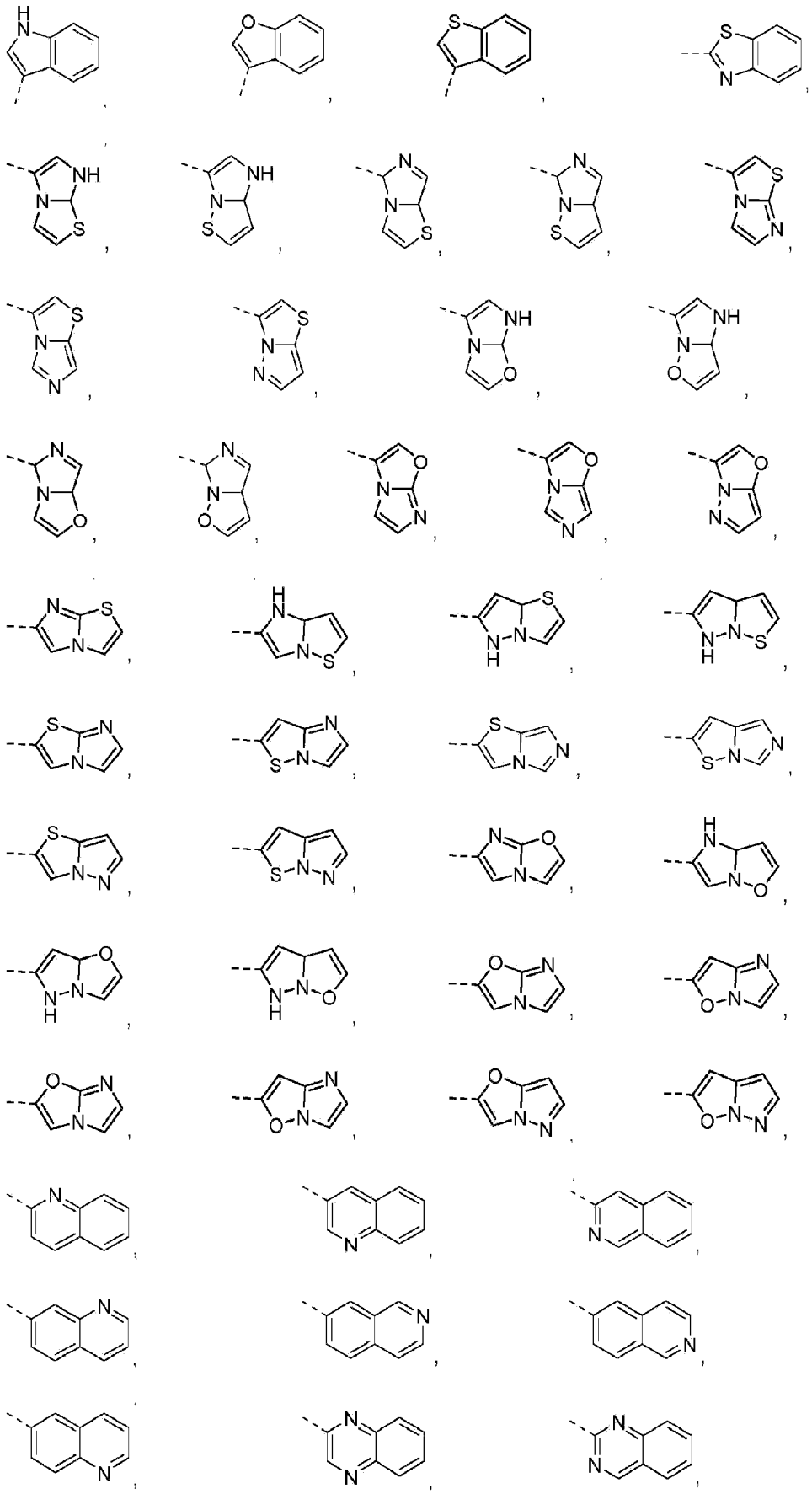
$L^2$ represents a bond, -$NR^{N1}$-, -$NR^{N1}CH_2$-, -$NR^{N1}CH_2CH_2$-, or -$NR^{N1}CH(CH_3)$-;

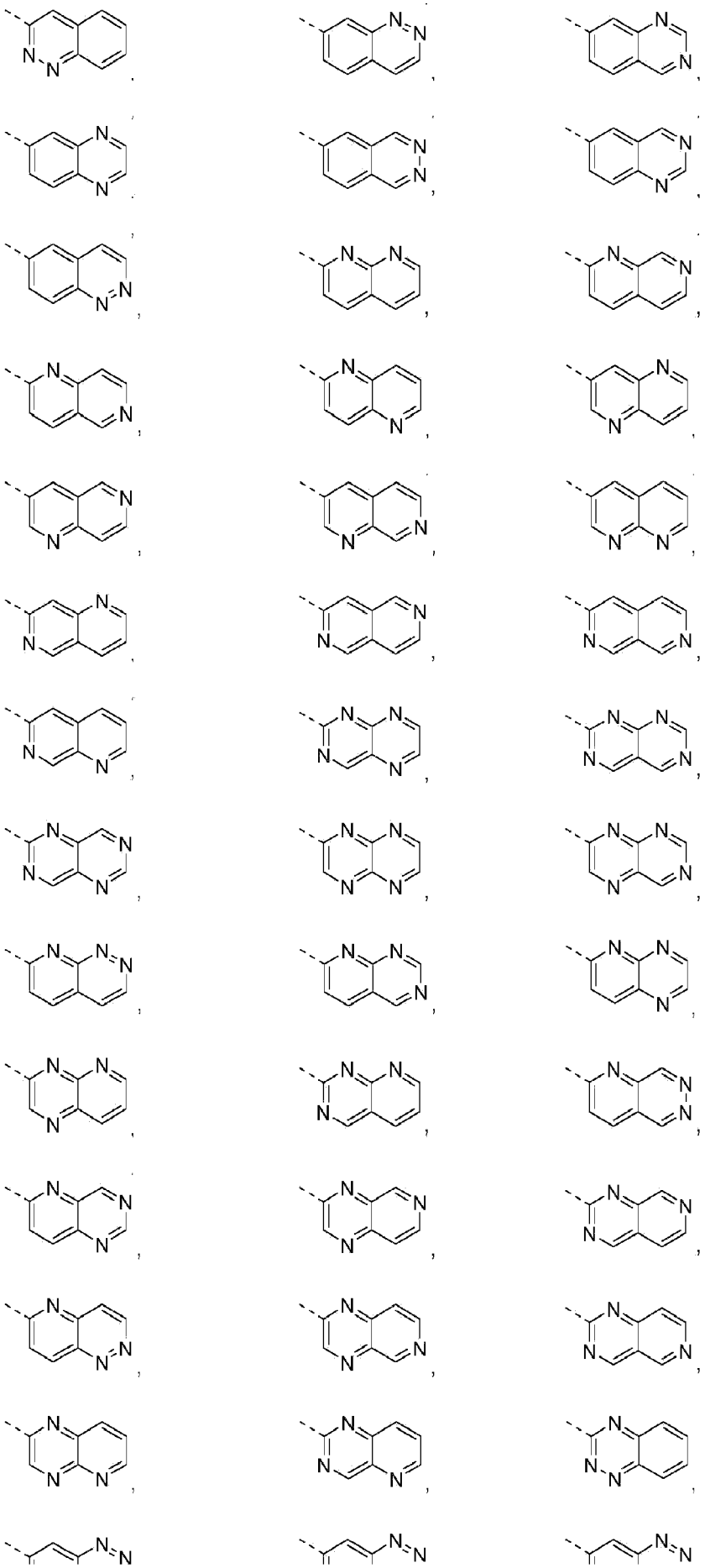
$R^1$ represents

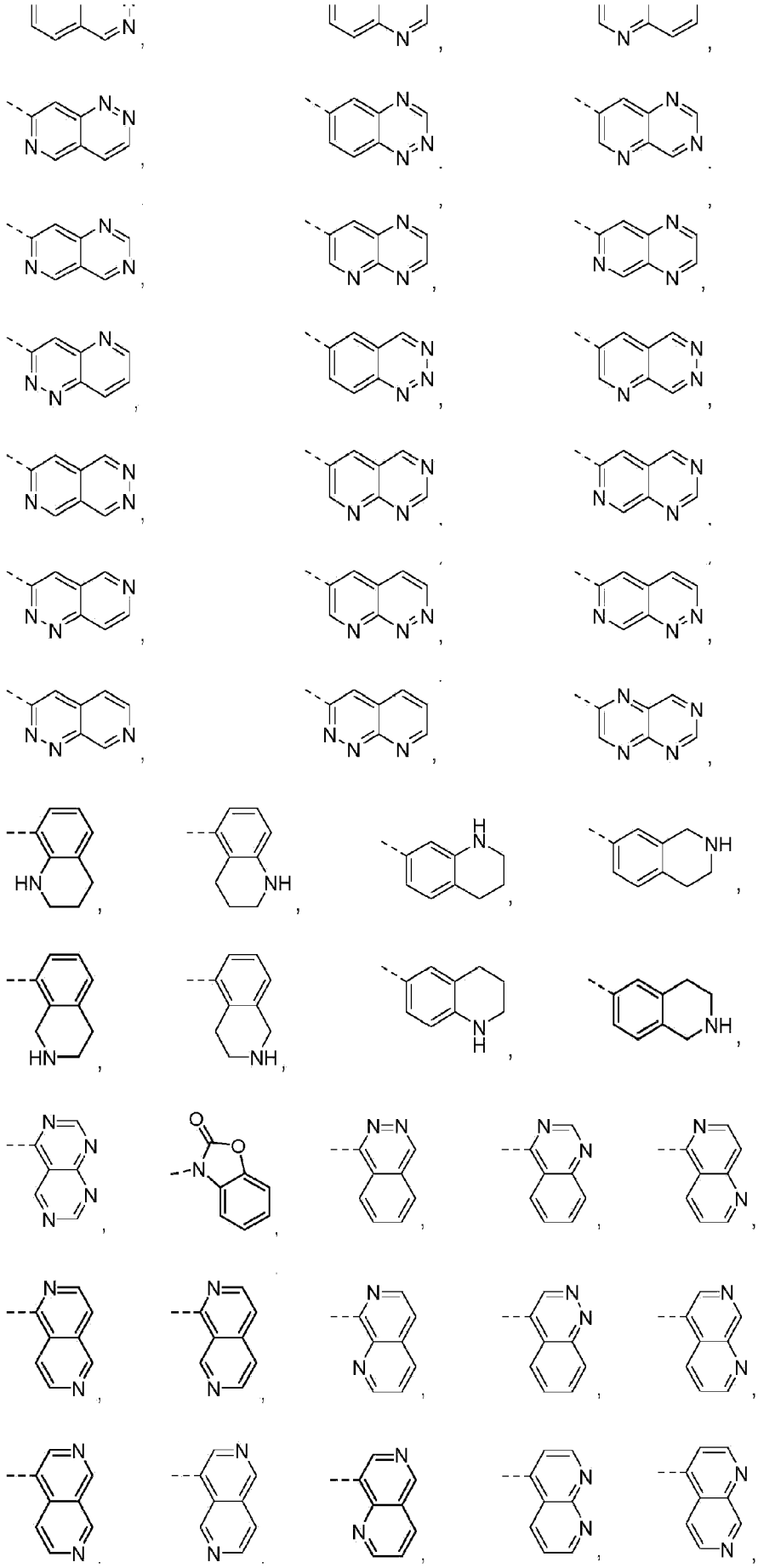

or

;

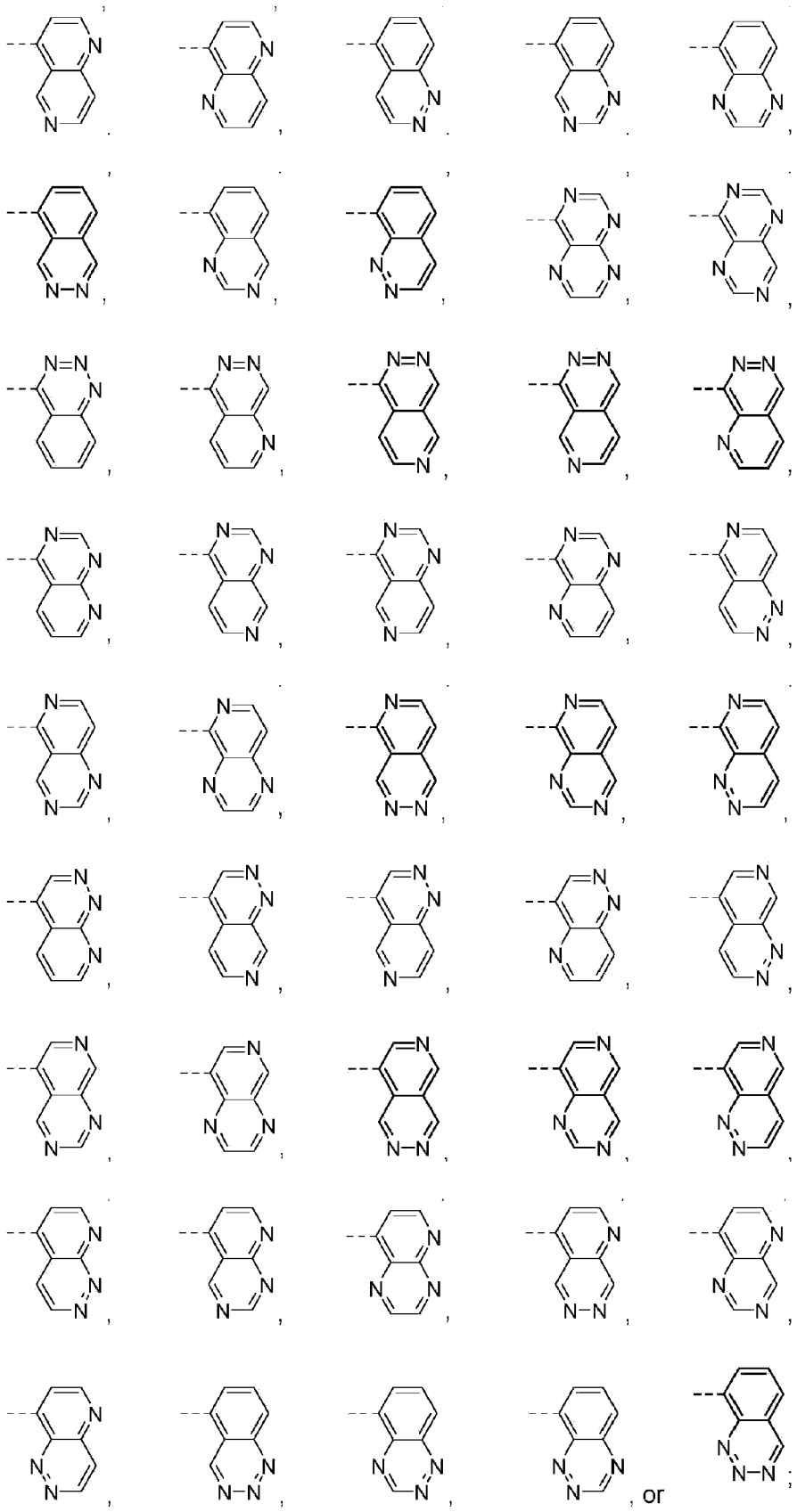
$R^2$ represents











wherein the unsubstituted bicyclic residues can be substituted with 1 to 5 of the substituents $R^9$ -$R^{14}$, and $R^N$; and preferably with 1 to 3 of the substituents $R^{11}$ - $R^{13}$;

$R^3$ represents bicyclo[1.1.1]pentyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.2]decyl, bicyclo[3.3.3]undecyl, 4-homoisotwistyl, adamantyl, diamantyl, or hexamethylenetetraminyl and the afore-mentioned residues optionally contain one or more C=C double bond(s) and/or are substituted by one or more of $R^a$, $R^b$, $R^c$, $R^d$, and $R^e$;

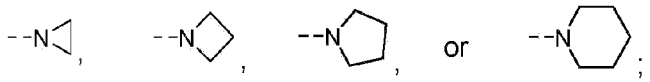
$R^a$, $R^b$, $R^c$, $R^d$, and $R^e$ represent independently of each other -H, -F, -Cl, -Br, -CN, -OH, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CHF_2$, $-CF_3$, $-CH_2CF_3$, $-COCH_3$, $-COCH_2CH_3$, $-CO_2H$, $-CO_2CH_3$, $-CO_2C_2H_5$, $-CONH_2$, $-CONHCH_3$, $-CON(CH_3)_2$, $-CONHC_2H_5$, $-CH_2CO_2H$, $-CH_2CO_2CH_3$, $-CH_2CO_2C_2H_5$, $-CH_2CONH_2$, $-CH_2CONHCH_3$, $-CH_2CON(CH_3)_2$, $-CH_2CONHC_2H_5$, $-NHCOCH_3$, $-NHCOC_2H_5$, $-NHCOCF_3$, $-NHCOCH_2CF_3$, $-NHSO_2CH_3$, $-NHSO_2C_2H_5$, $-NHSO_2CHF_2$, $-NHSO_2CF_3$, or $-NHSO_2CH_2CF_3$;

$R^4$ represents $-R^5$, $-OR^5$ or $-NR^6R^7$;

$R^5$ represents -H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2CH_2CH_2CH_2CH_3$, $-CH_2CH=CH_2$, $-CH_2CH=CH(CH_3)$, $-CH_2CH=C(CH_3)_2$, $-CH_2CH=CHCH_2CH_3$, -cyclo-$C_3H_5$, -cyclo-$C_4H_7$, -cyclo-$C_5H_9$, -cyclo-$C_6H_{11}$, $-CH_2$-cyclo-$C_3H_5$, $-CH_2$-cyclo-$C_4H_7$, $-CH_2$-cyclo-$C_5H_9$, $-CH_2$-cyclo-$C_6H_{11}$, $-CH_2$-Ph, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OCH_3$, or $-CH_2CH_2OCH_2CH_3$;

$R^6$ and $R^7$ represent independently of each other -H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2CH=CH_2$, $-CH_2CH=CH(CH_3)$, $-CH_2CH=C(CH_3)_2$, $-CH_2CH=CHCH_2CH_3$, -cyclo-$C_3H_5$, -cyclo-$C_4H_7$, -cyclo-$C_5H_9$, -cyclo-$C_6H_{11}$, $-CH_2$-cyclo-$C_3H_5$, $-CH_2$-cyclo-$C_4H_7$, $-CH_2$-cyclo-$C_5H_9$, $-CH_2$-cyclo-$C_6H_{11}$, -Ph, $-CH_2$-Ph, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OCH_3$, $-CH_2CH_2OCH_2CH_3$, $-CH_2CH_2NHCH_3$, or $-CH_2CH_2N(CH_3)_2$,

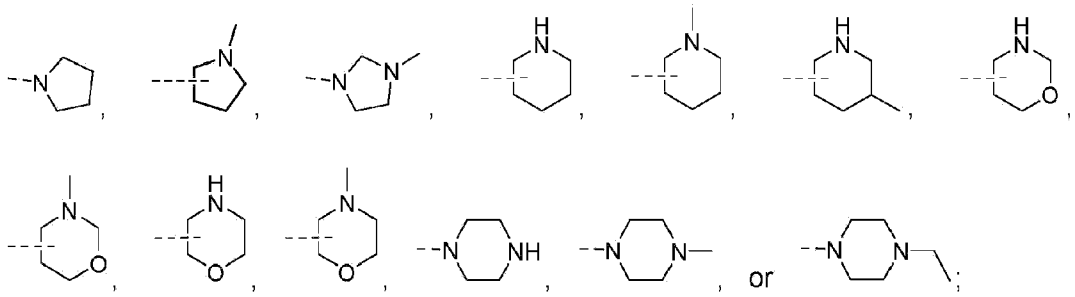
or $-NR^6R^7$ represents



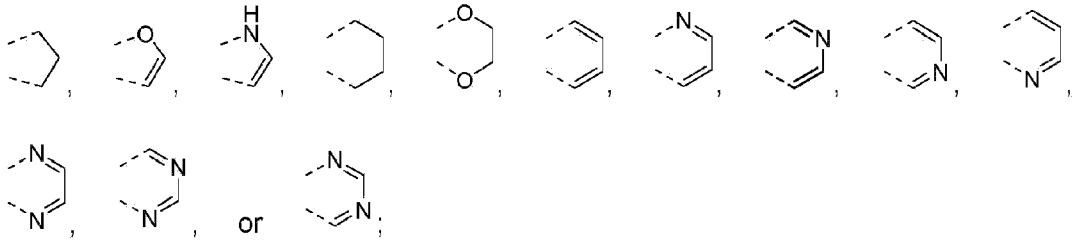
;

$R^8$, $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, $R^{13}$, and $R^{14}$ represent independently of each other -H, -F, -Cl, -Br, -I, -OH, -CN, $-NO_2$, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $-C_4H_9$, $-CH_2$-$CH(CH_3)_2$, $-CH(CH_3)$-$C_2H_5$, $-C(CH_3)_3$, -cyclo-$C_3H_5$, $-CH_2$-cyclo-$C_3H_5$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2Cl$, $-CH_2Br$, $-CH_2I$, $-CH_2$-$CH_2F$, $-CH_2$-$CHF_2$, $-CH_2$-$CF_3$, $-CH_2$-$CH_2Cl$, $-CH_2$-$CH_2Br$, $-CH_2$-$CH_2I$, $-OCH_3$, $-OC_2H_5$, $-OC_3H_7$, $-OCH(CH_3)_2$, $-OC(CH_3)_3$, $-OC_4H_9$, $-OCHF_2$, $-OCF_3$, $-OCH_2CF_3$, $-OC_2F_5$, $-OCH_2OCH_3$, -O-cyclo-$C_3H_5$, $-OCH_2$-cyclo-$C_3H_5$, -O-$C_2H_4$-cyclo-$C_3H_5$, -CHO, $-COCH_3$, $-COCF_3$, $-COC_2H_5$, $-COC_3H_7$, $-COCH(CH_3)_2$, $-COC(CH_3)_3$, -COOH, $-COOCH_3$, $-COOC_2H_5$, $-COOC_3H_7$, $-COOCH(CH_3)_2$, $-COOC(CH_3)_3$, $-OOC$-$CH_3$, $-OOC$-$CF_3$, $-OOC$-$C_2H_5$, $-OOC$-$C_3H_7$, $-OOC$-$CH(CH_3)_2$, $-OOC$-$C(CH_3)_3$, $-NH_2$, $-NHCH_3$, $-NHC_2H_5$, $-NHC_3H_7$, $-NHCH(CH_3)_2$, $-NHC(CH_3)_3$, $-N(CH_3)_2$, $-N(C_2H_5)_2$,

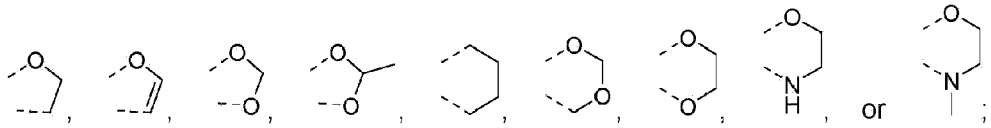
$-N(C_3H_7)_2$, $-N[CH(CH_3)_2]_2$, $-N[C(CH_3)_3]_2$, $-NHCOCH_3$, $-NHCOCF_3$, $-NHCOC_2H_5$, $-NHCOC_3H_7$, $-NHCOCH(CH_3)_2$, $-NHCOC(CH_3)_3$, $-CONH_2$, $-CONHCH_3$, $-CONHC_2H_5$, $-CONHC_3H_7$, $-CONHCH(CH_3)_2$, -CONH-cyclo-$C_3H_5$, $-CONHC(CH_3)_3$, $-CON(CH_3)_2$, $-CON(C_2H_5)_2$, $-CON(C_3H_7)_2$, $-CON[CH(CH_3)_2]_2$, $-CON[C(CH_3)_3]_2$, $-SO_2NH_2$, $-SO_2NHCH_3$, $-SO_2NHC_2H_5$, $-SO_2NHC_3H_7$, $-SO_2NHCH(CH_3)_2$, -$SO_2$NH-cyclo-$C_3H_5$, $-SO_2NHC(CH_3)_3$, $-SO_2N(CH_3)_2$, $-SO_2N(C_2H_5)_2$, $-SO_2N(C_3H_7)_2$, $-SO_2N[CH(CH_3)_2]_2$, $-SO_2N[C(CH_3)_3]_2$, $-NHSO_2CH_3$, $-NHSO_2CF_3$, $-NHSO_2C_2H_5$, $-NHSO_2C_3H_7$, $-NHSO_2CH(CH_3)_2$, $-NHSO_2C(CH_3)_3$, $-CH=CH_2$, $-CH_2-CH=CH_2$, $-C(CH_3)=CH_2$, $-CH=CH-CH_3$, $-C\equiv CH$, $-C\equiv C-CH_3$, $-CH_2-C\equiv CH$, -Ph, -O-Ph, -O-$CH_2$-Ph,



or $R^8$ and $R^9$ or $R^9$ and $R^{10}$ can form together one of the following five-membered or six-membered rings:



or $R^{12}$ and $R^{13}$ or $R^{13}$ and $R^{14}$ can form together one of the following five-membered or six-membered rings:

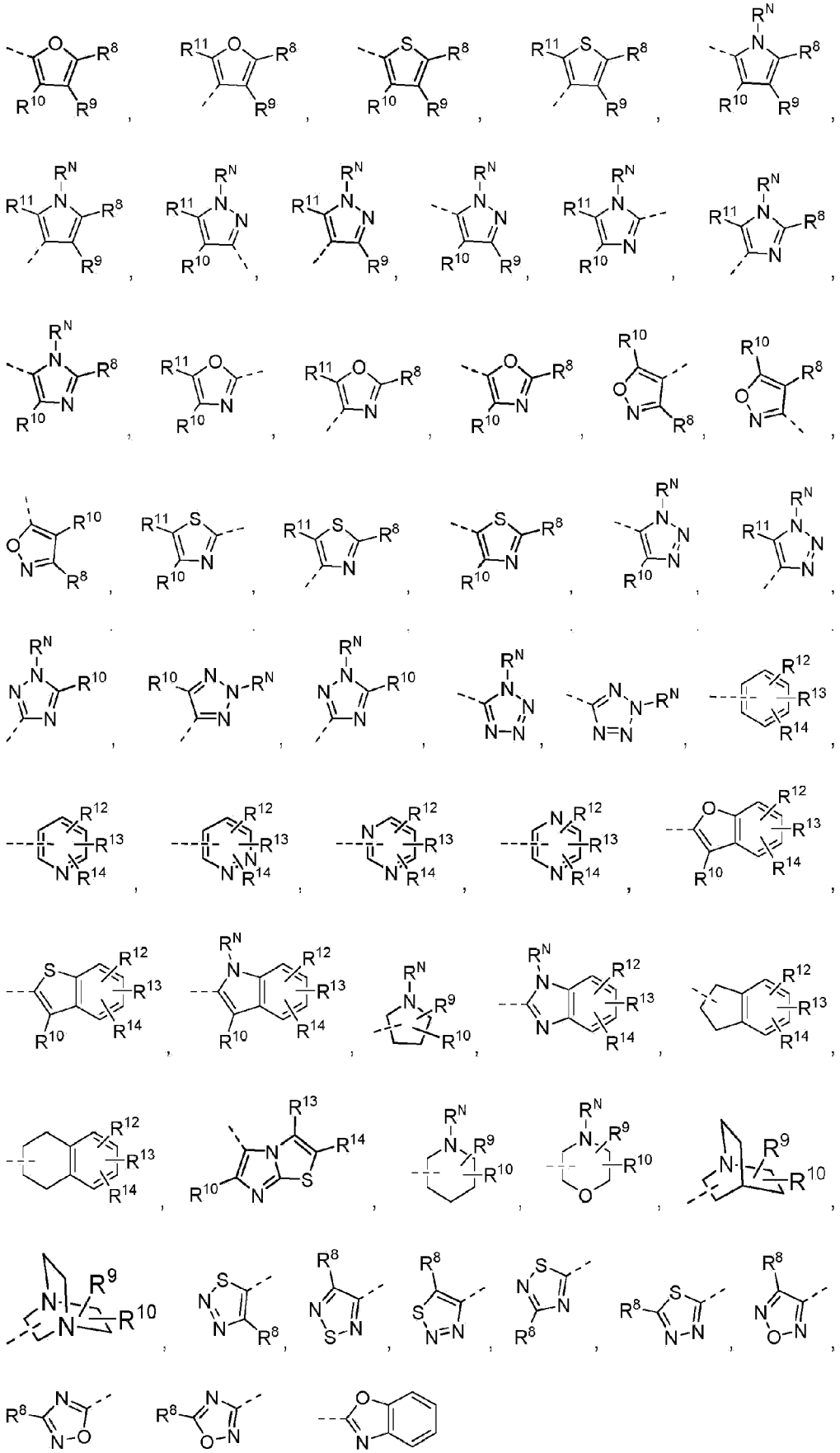


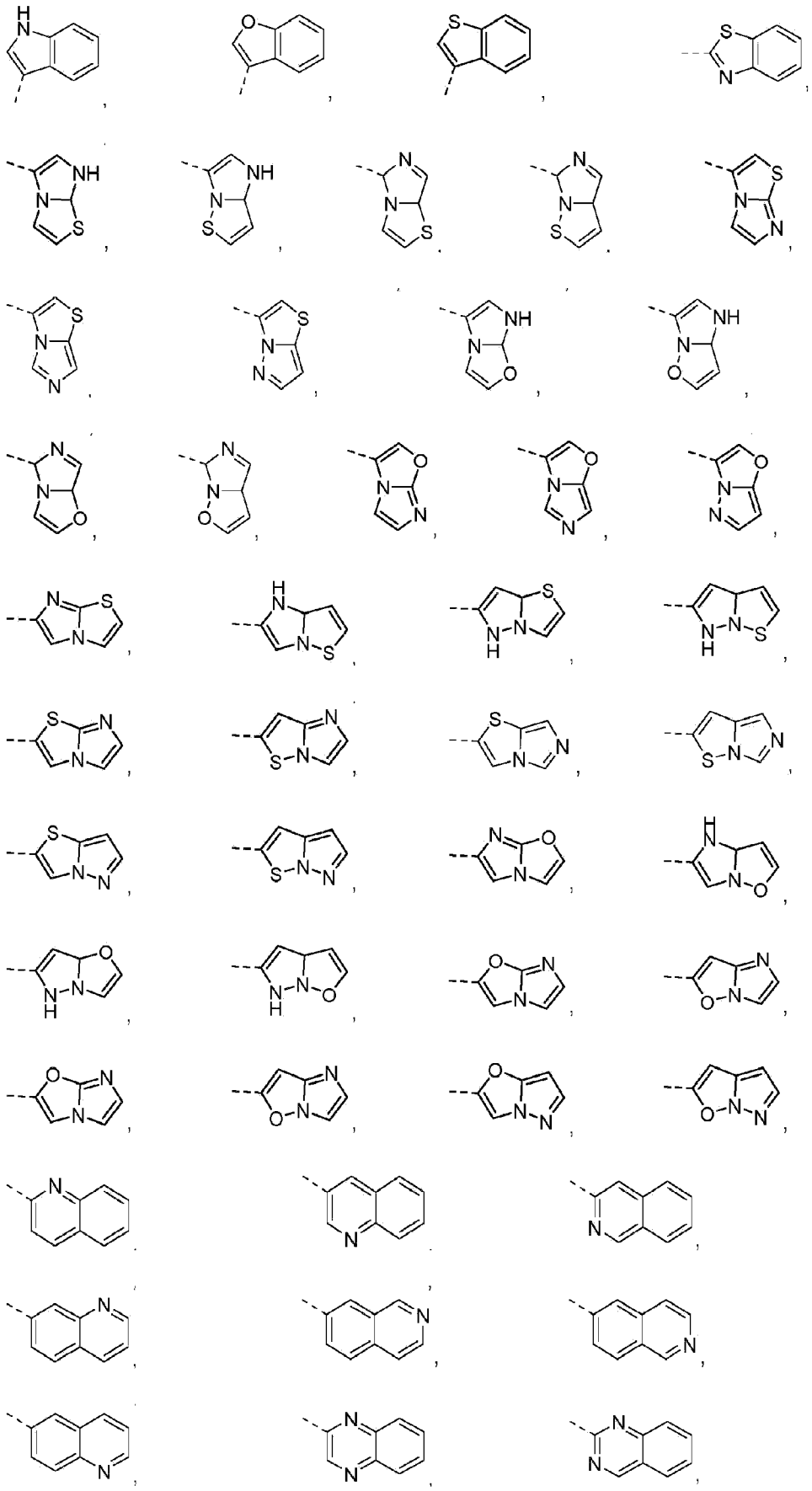
$R^N$ represents -H, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $-C_4H_9$, $-CH_2-CH(CH_3)_2$, $-CH(CH_3)-C_2H_5$, $-C(CH_3)_3$, -cyclo-$C_3H_5$, -cyclo-$C_4H_7$, -cyclo-$C_5H_9$, $-CH_2$-cyclo-$C_3H_5$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2Cl$, $-CH_2Br$, $-CH_2I$, $-CH_2-CH_2F$, $-CH_2-CHF_2$, $-CH_2-CF_3$, $-CH_2-CH_2Cl$, $-CH_2-CH_2Br$, $-CH_2-CH_2I$, $-CH_2-CH=CH_2$, $-CH_2-C\equiv CH$, -CHO, $-COCH_3$, $-COC_2H_5$, $-COC_3H_7$, $-COCH(CH_3)_2$, $-COC(CH_3)_3$, $-COOCH_3$, $-COOC_2H_5$, $-COOC_3H_7$, $-COOCH(CH_3)_2$, $-COOC(CH_3)_3$, $-COOCH_2Ph$, $-SO_2CH_3$, $-SO_2CF_3$, $-SO_2C_2H_5$, $-SO_2C_3H_7$, $-SO_2CH(CH_3)_2$, or $-SO_2C(CH_3)_3$;

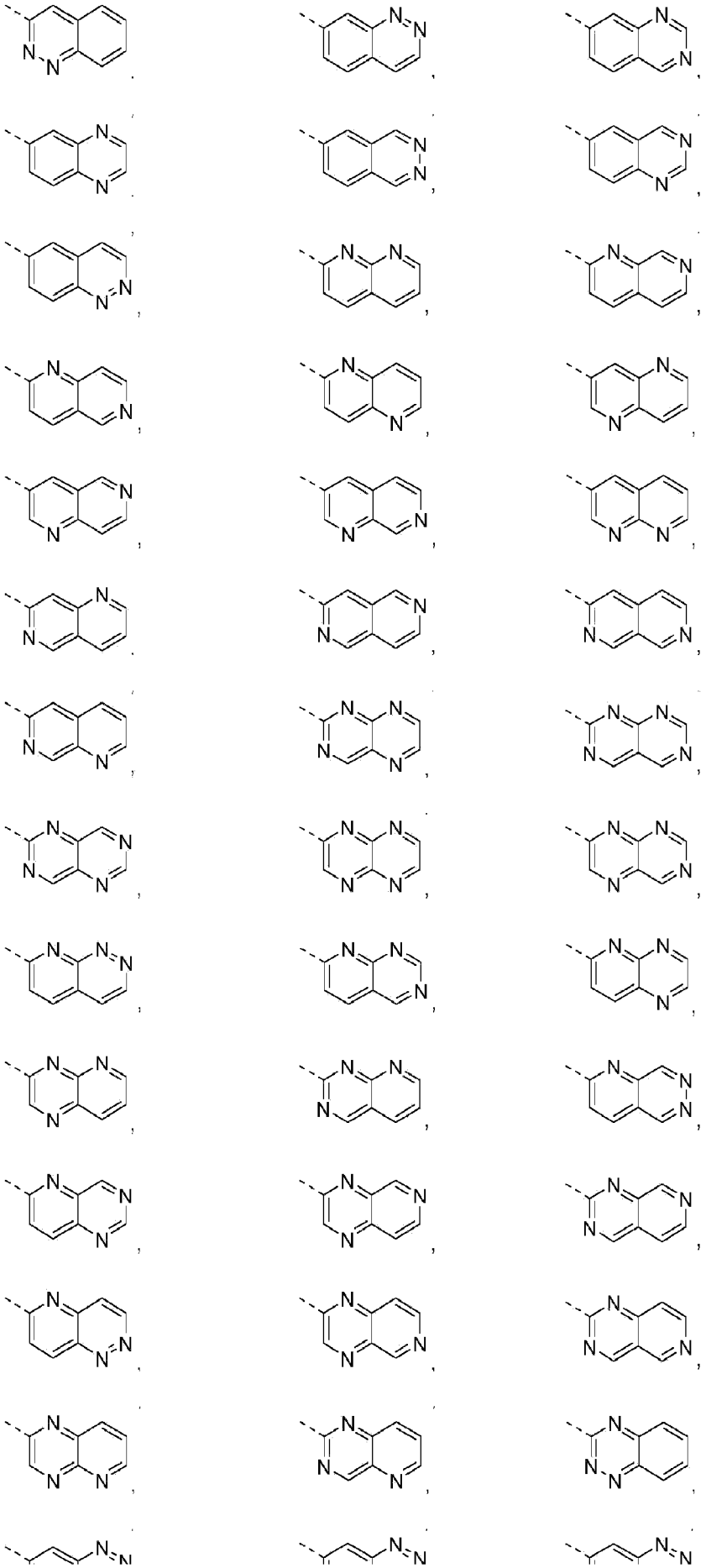
$R^{N1}$ represent -H, $-CH_3$, or $-CH_2CH_3$;

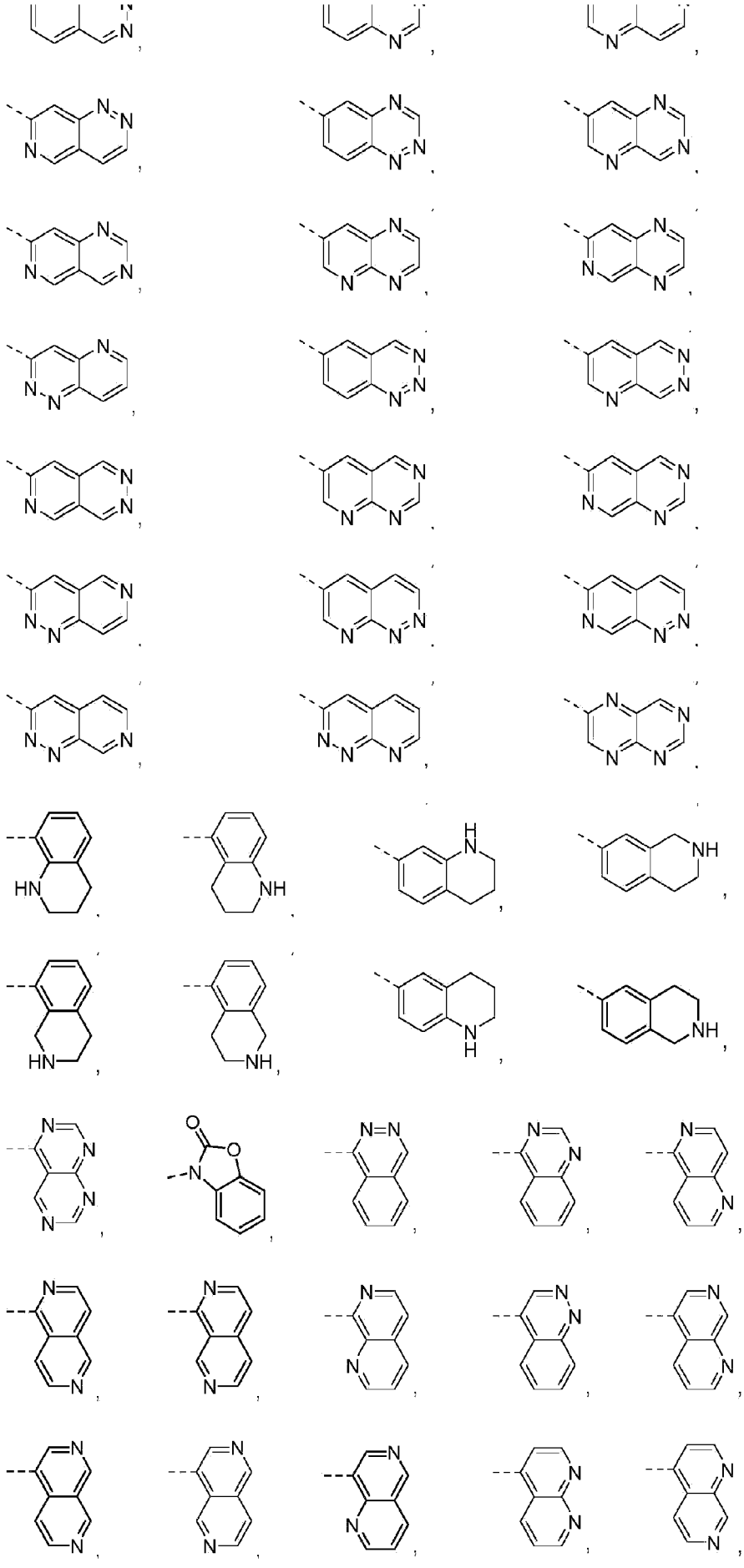
or a diastereomer, an enantiomer, a mixture of diastereomers, a mixture of enantiomers, a racemate, a solvate, a hydrate, or a pharmaceutically acceptable salt thereof.

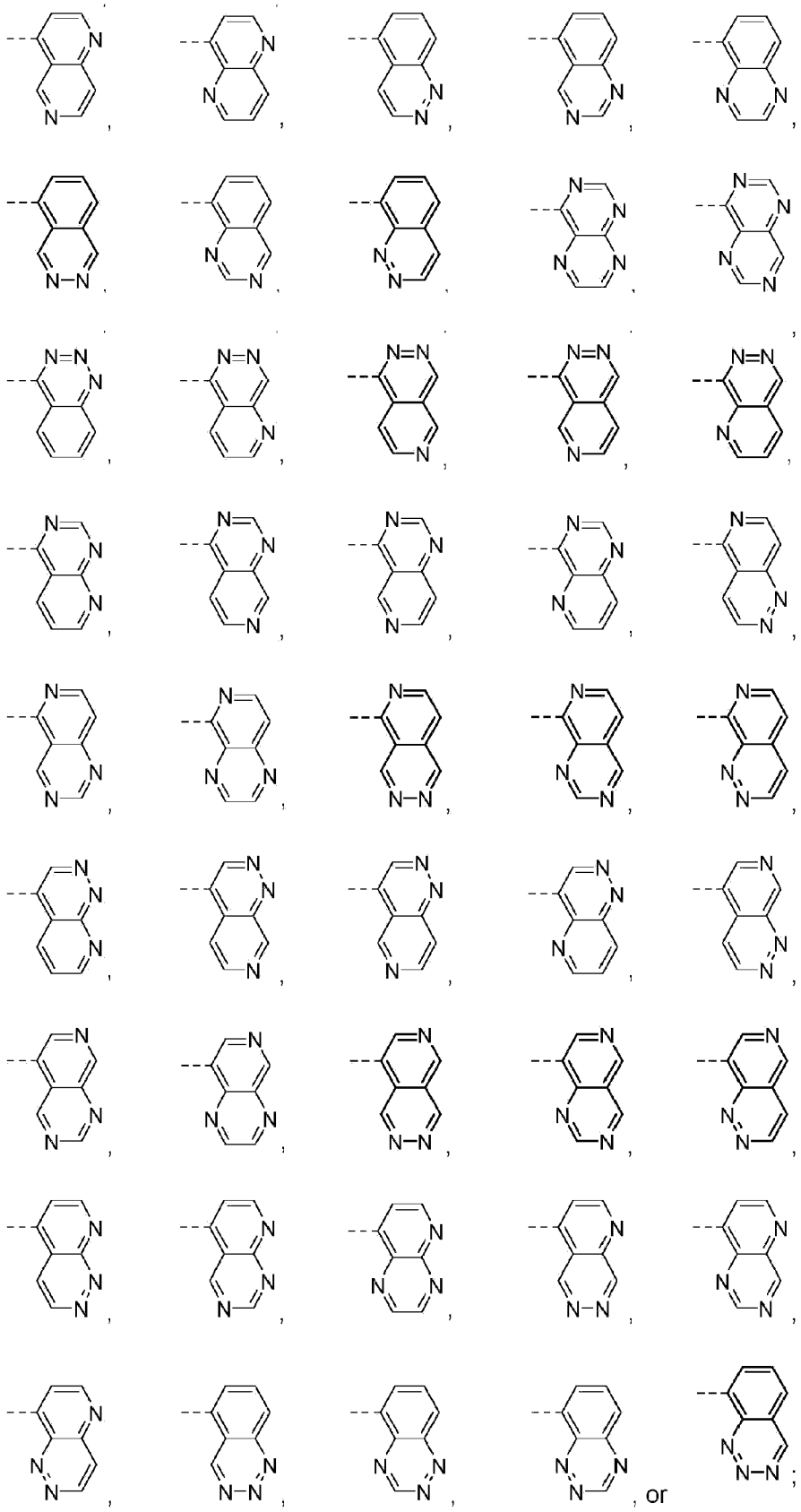
**[0025]** In all general formulae disclosed herein $R^2$ represents preferably







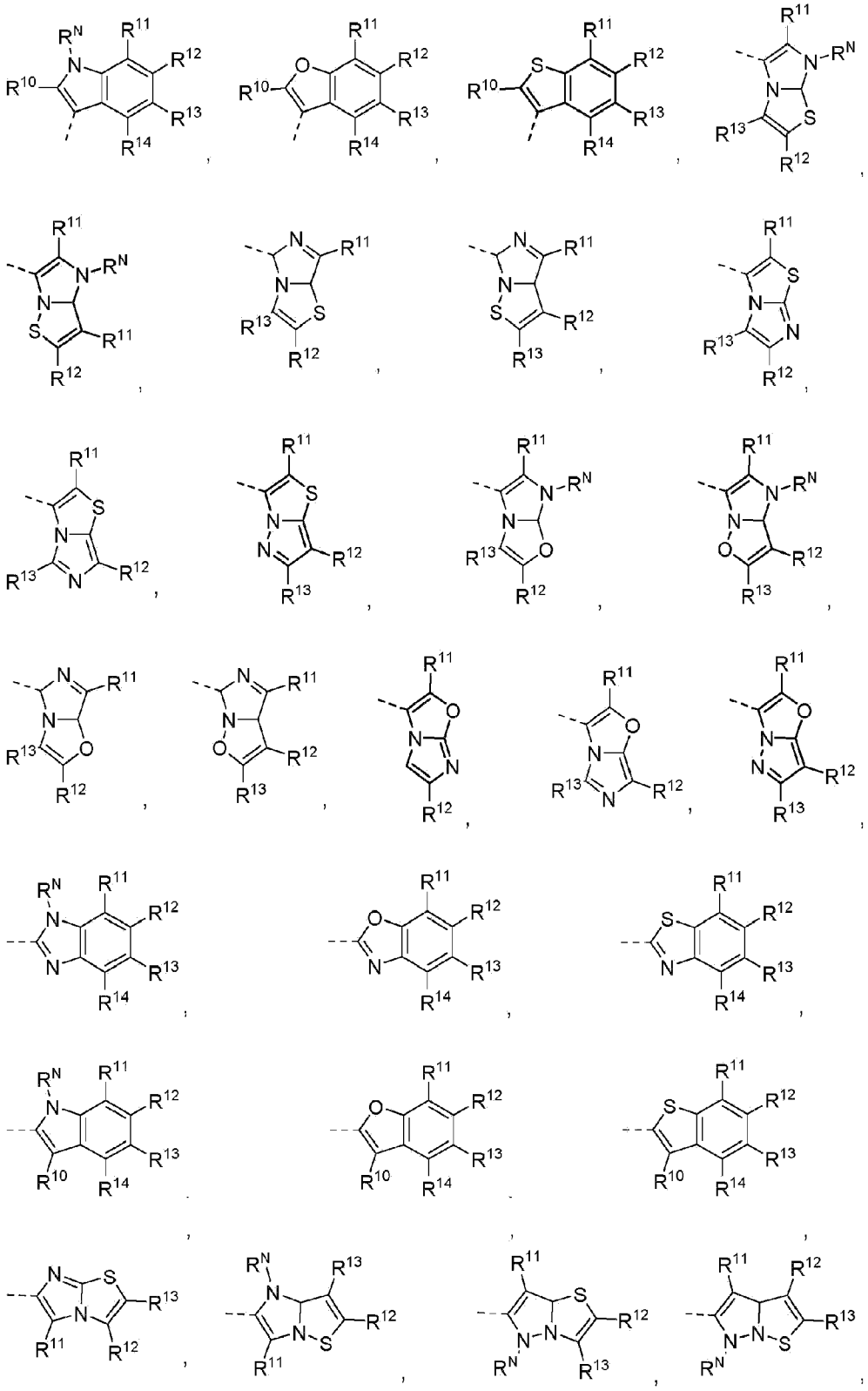


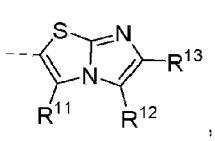
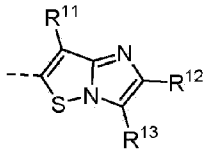
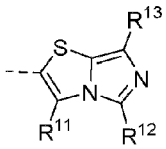
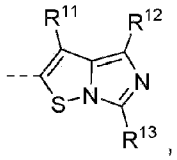
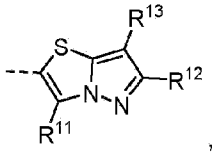
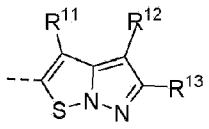
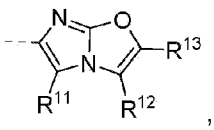
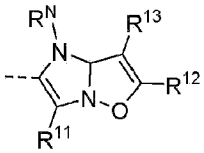
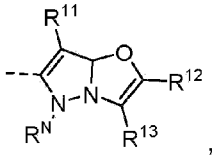
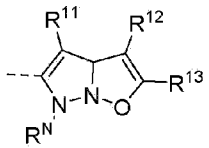
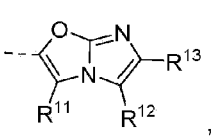
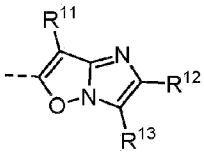
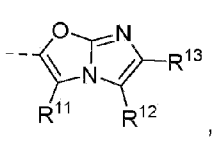
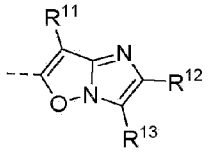
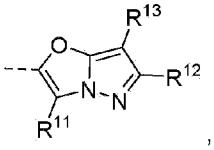
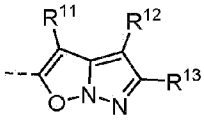
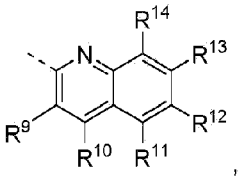
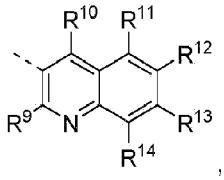
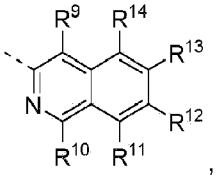
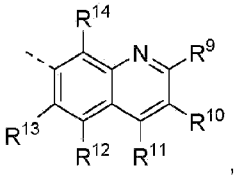
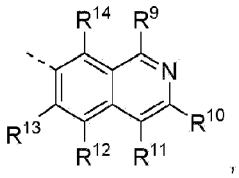
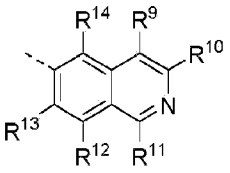
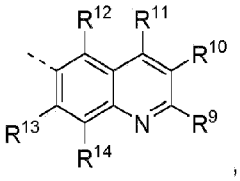
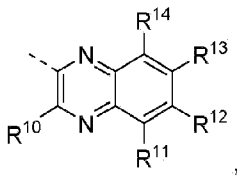
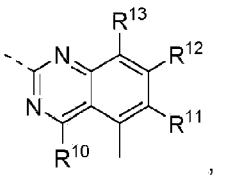
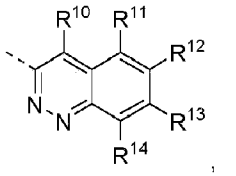
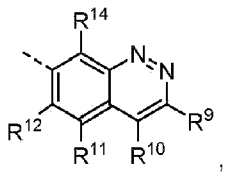
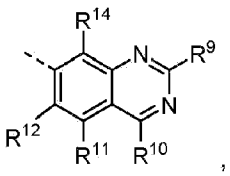
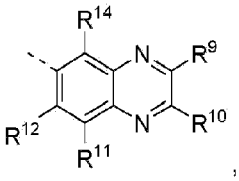
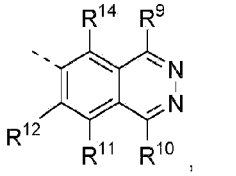
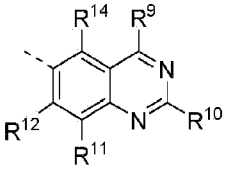


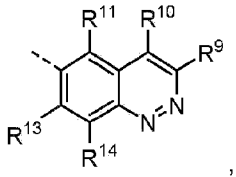
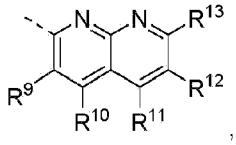
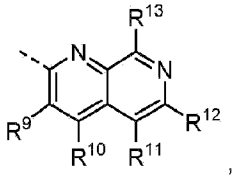
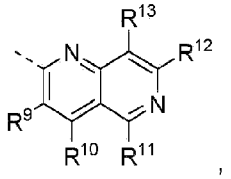
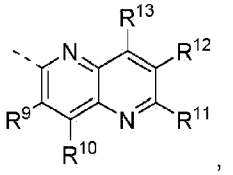
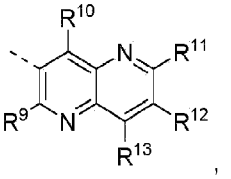
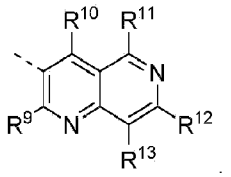
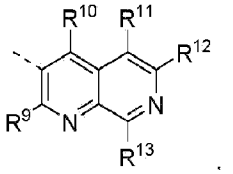
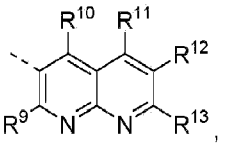
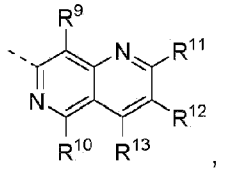
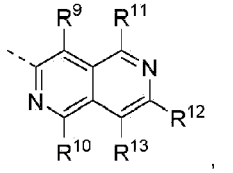
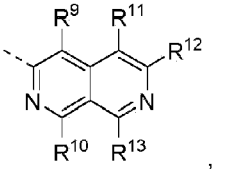
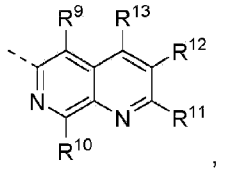
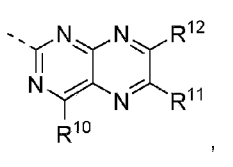
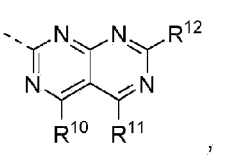
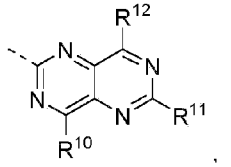
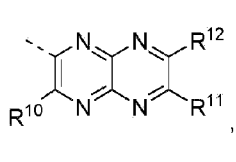
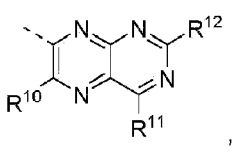
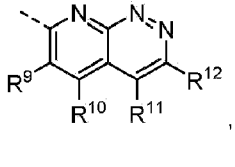
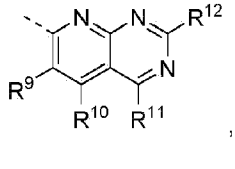
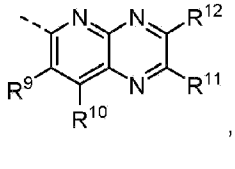
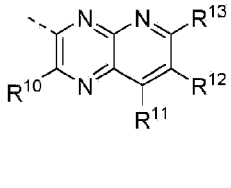
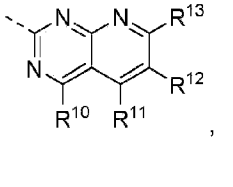
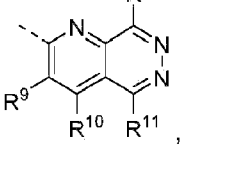
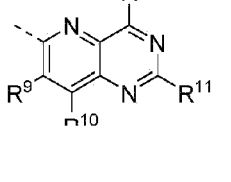
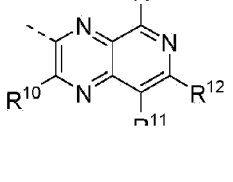
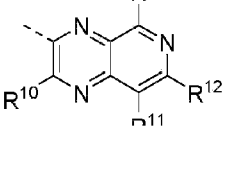
wherein the unsubstituted bicyclic residues can be substituted with 1 to 5 of the substituents $R^9$ -$R^{14}$, and $R^N$ ; and preferably with 1 to 3 of the substituents $R^{11}$ - $R^{13}$ and the substituents $R^9$ -

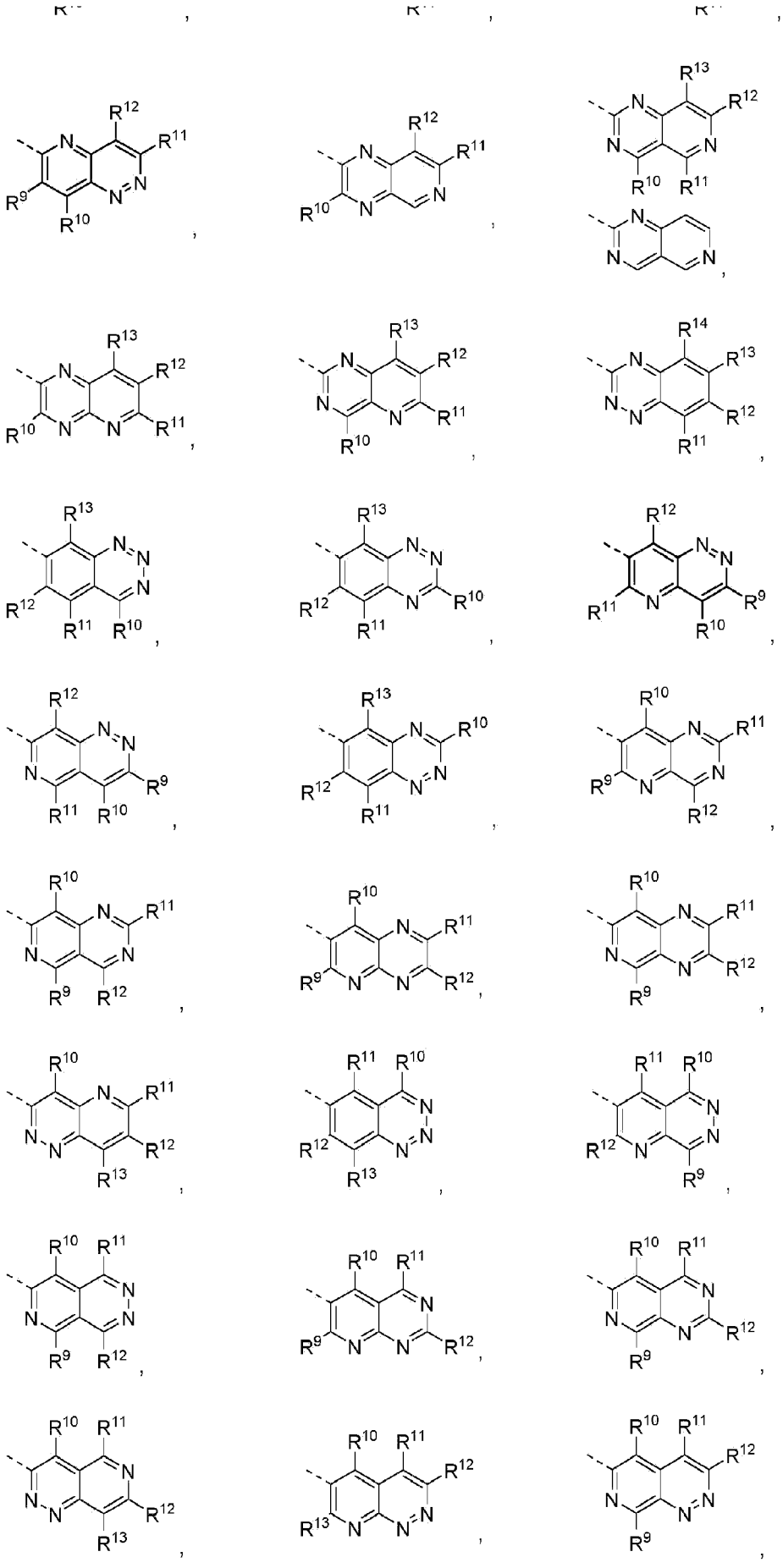
$R^{14}$, and $R^N$ have the meanings as defined herein or as in claim 1.

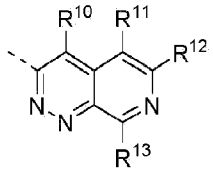
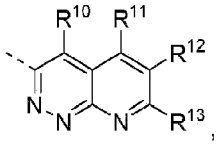
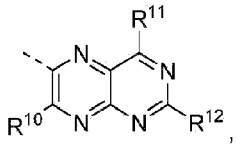
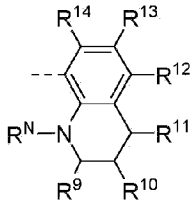
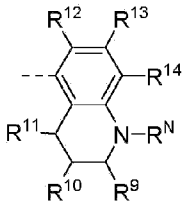
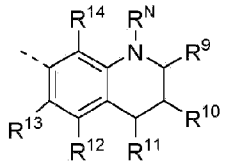
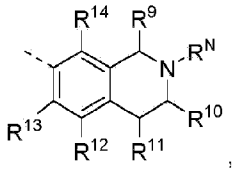
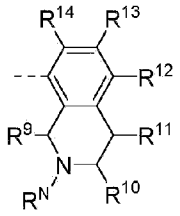
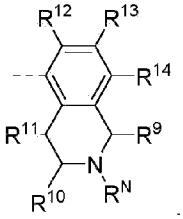
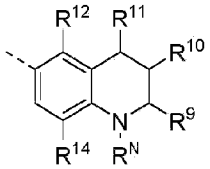
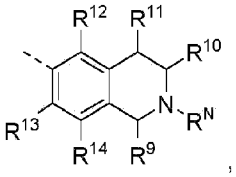
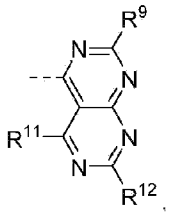
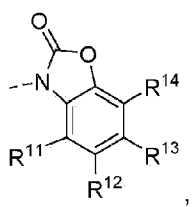
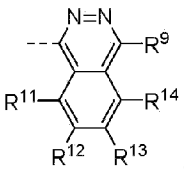
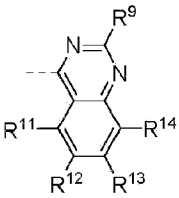
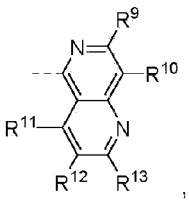
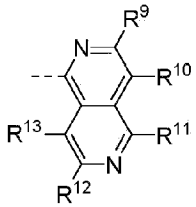
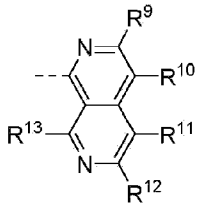
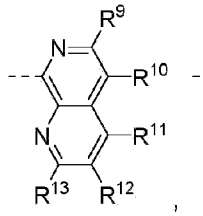
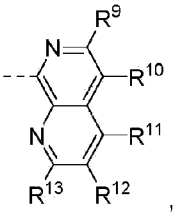
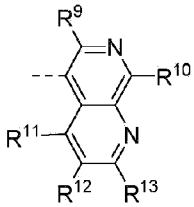
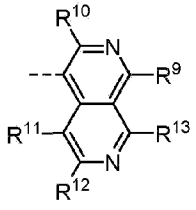
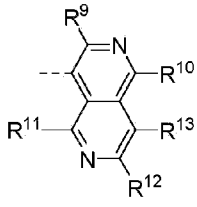
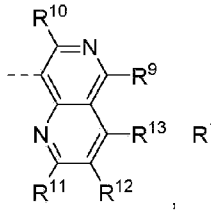
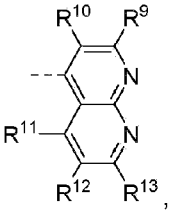
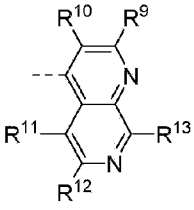
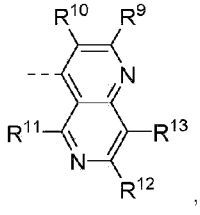
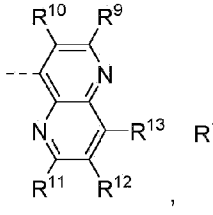
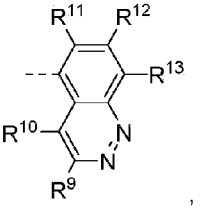
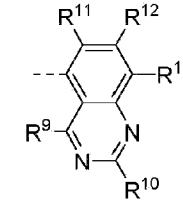
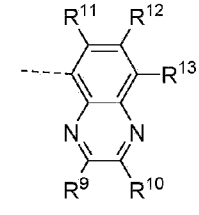
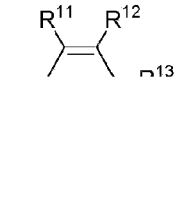
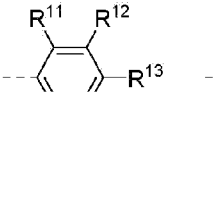
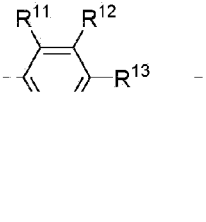
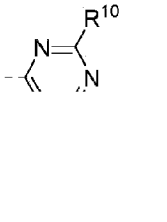
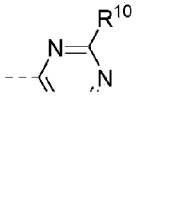
**[0026]** The unsubstituted bicyclic residues which can be substituted with 1 to 5 of the substituents $R^9$ - $R^{14}$ and $R^N$; have the following structure and the substituents $R^9$ -$R^{14}$ and $R^N$ have the meanings as defined herein:

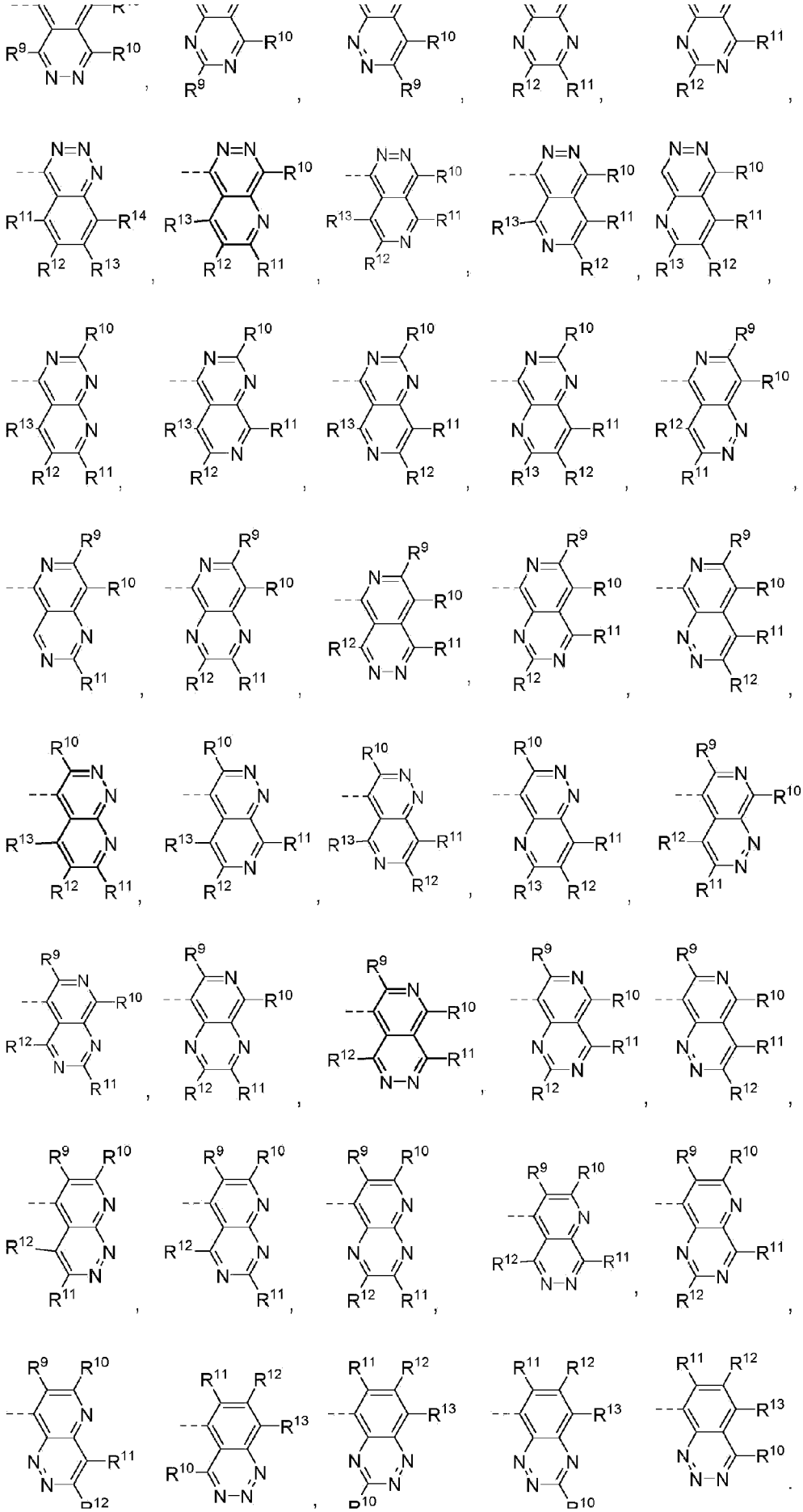



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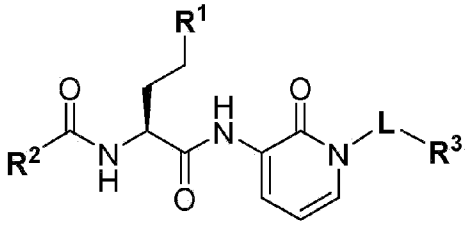



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**[0027]** In one embodiment of the herein disclosed inventive compounds, **L** represents -$CH_2CO$-NH-, -$CH_2CO$-$NCH_3$-, -$CH_2CO$-NH-$CH_2$-, or -$CH_2CO$-NH-$CH(CH_3)$-.

**[0028]** Preferred are the compounds of the formula (**I**),



(I)

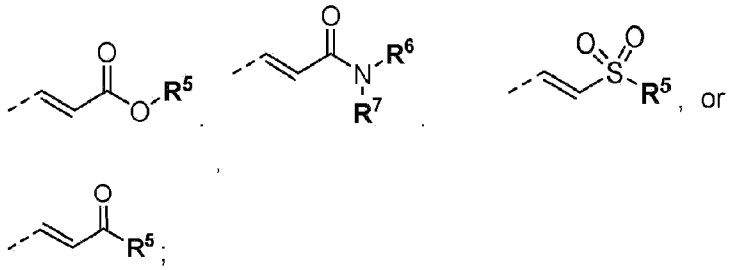
wherein

**L** represents -$L^1$-$L^2$-;

$L^1$ represents -$CH_2$-, -$CH_2CH_2$-, -$CH_2CH_2CH_2$-, -$CH_2CO$-, or -$CH_2CH_2CO$-;

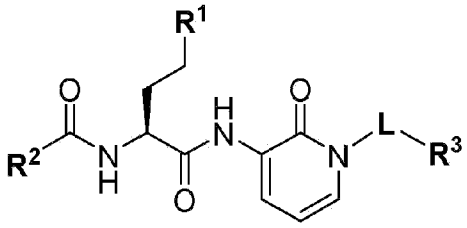
$L^2$ represents a bond, -$NR^{N1}$-, -$NR^{N1}CH_2$-, -$NR^{N1}CH_2CH_2$-, or -$NR^{N1}CH(CH_3)$-;

$R^1$ represents



and $R^2$, $R^3$, $R^5$ - $R^7$, and $R^{N1}$ have the meanings as defined above.

**[0029]** Preferred are the compounds of the formula (**I**),



(I)

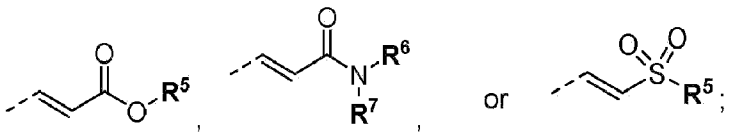
wherein

**L** represents -$L^1$- or -$L^1$-$L^2$-; preferably -$L^1$-$L^2$-;

$L^1$ represents -$CH_2$-, -$CH_2CH_2$-, -$CH_2CH_2CH_2$-, -$CH_2CO$-, or -$CH_2CH_2CO$-;

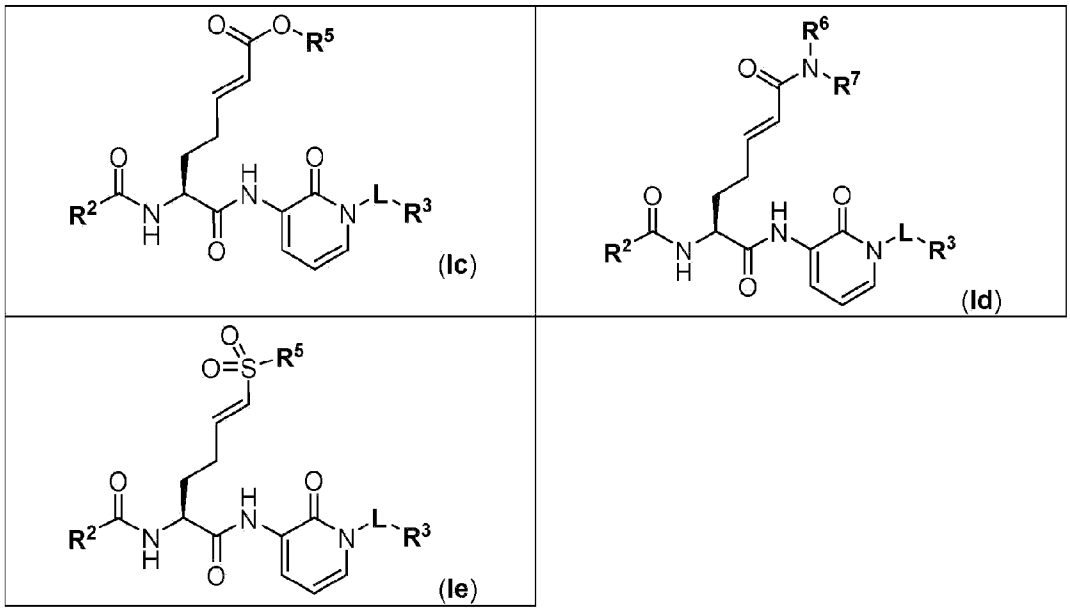
$L^2$ represents a bond, -$NR^{N1}$-, -$NR^{N1}CH_2$-, -$NR^{N1}CH_2CH_2$-, or -$NR^{N1}CH(CH_3)$-;

$R^1$ represents



and $R^2$, $R^3$, $R^5$ - $R^7$, and $R^{N1}$ have the meanings as defined above.

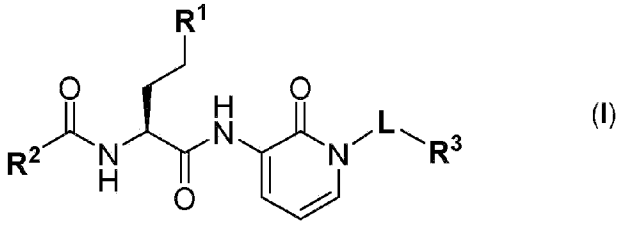
**[0030]** Still more preferred, are the compounds of any one of the formulae **(Ic), (Id),** and **(Ie)**:



wherein

**L** , $R^2$, $R^3$, and $R^5$ - $R^7$ have the meanings as defined above.

**[0031]** Also preferred are the compounds of the formula (**I**)



(**I**)

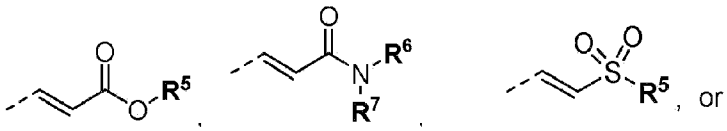
wherein

**L** represents -$L^1$- or -$L^1$-$L^2$-; preferably -$L^1$-$L^2$-;

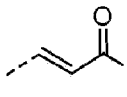
$L^1$ represents -$CH_2$-, -$CH_2CH_2$-, -$CH_2CH_2CH_2$-, -$CH_2CO$-, or -$CH_2CH_2CO$-;

$L^2$ represents a bond, -$NR^{N1}$-, -$NR^{N1}CH_2$-, -$NR^{N1}CH_2CH_2$-, or -$NR^{N1}CH(CH_3)$-;

$R^1$ represents

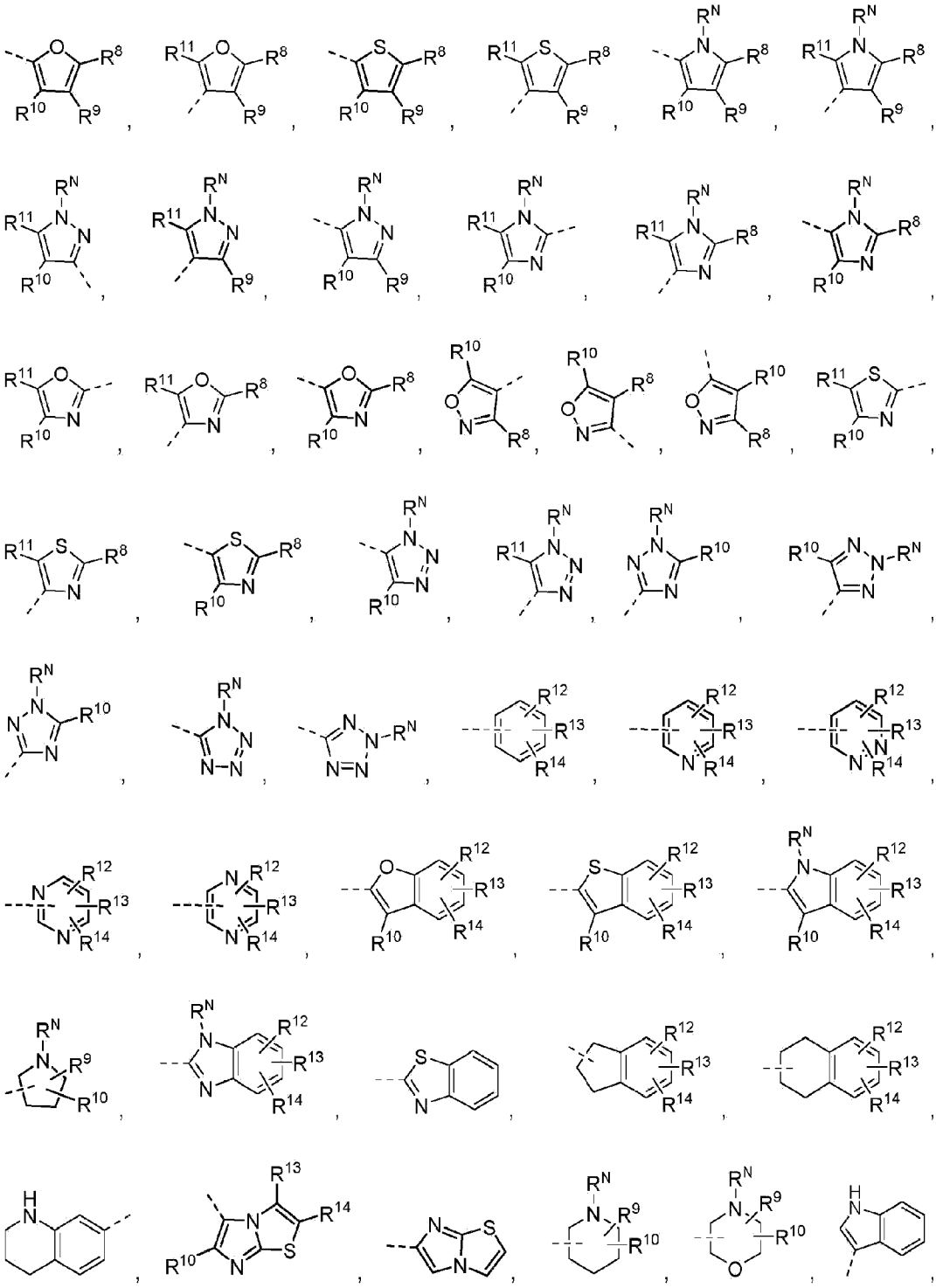


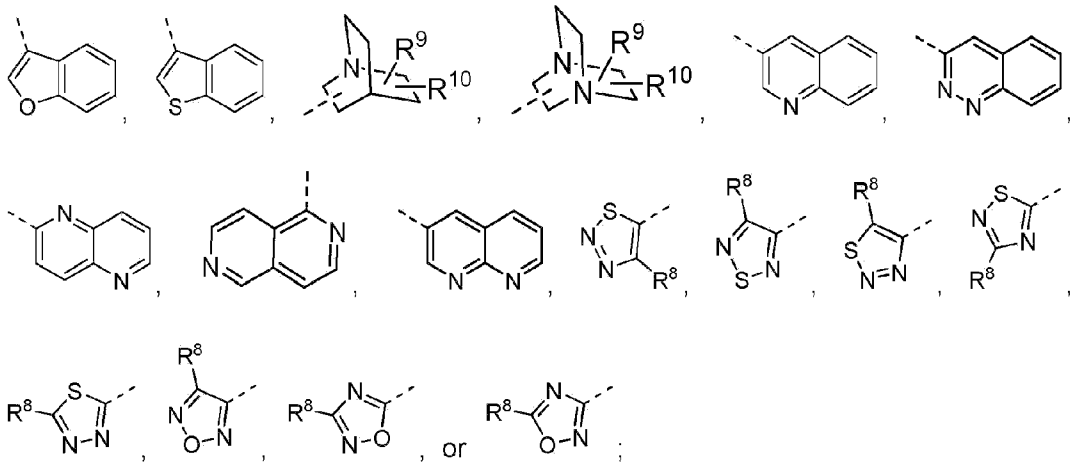
or



;

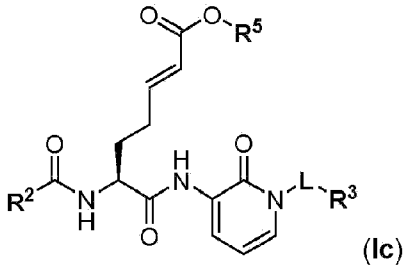
$R^2$ represents



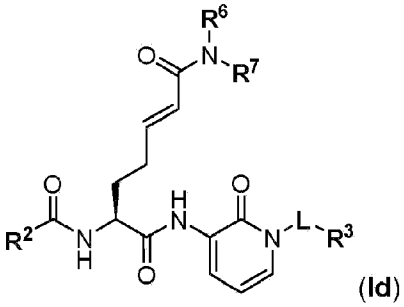


wherein the unsubstituted bicyclic residues can be substituted with 1 to 5 of the substituents **$R^9$ -$R^{14}$**, and **$R^N$**; and preferably with 1 to 3 of the substituents **$R^{11}$ - $R^{13}$**, and **$R^5$ - $R^{14}$, $R^N$** and **$R^{N1}$** have the meanings as defined herein.

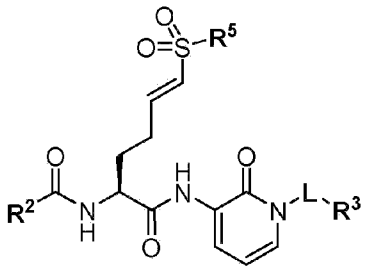
**[0032]** Also preferred are the compounds of any one of the formulae (**Ic**) - **(Ie)**



(**Ic**)



(**Id**)



(**Ie**)

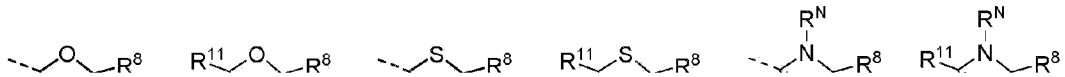
wherein

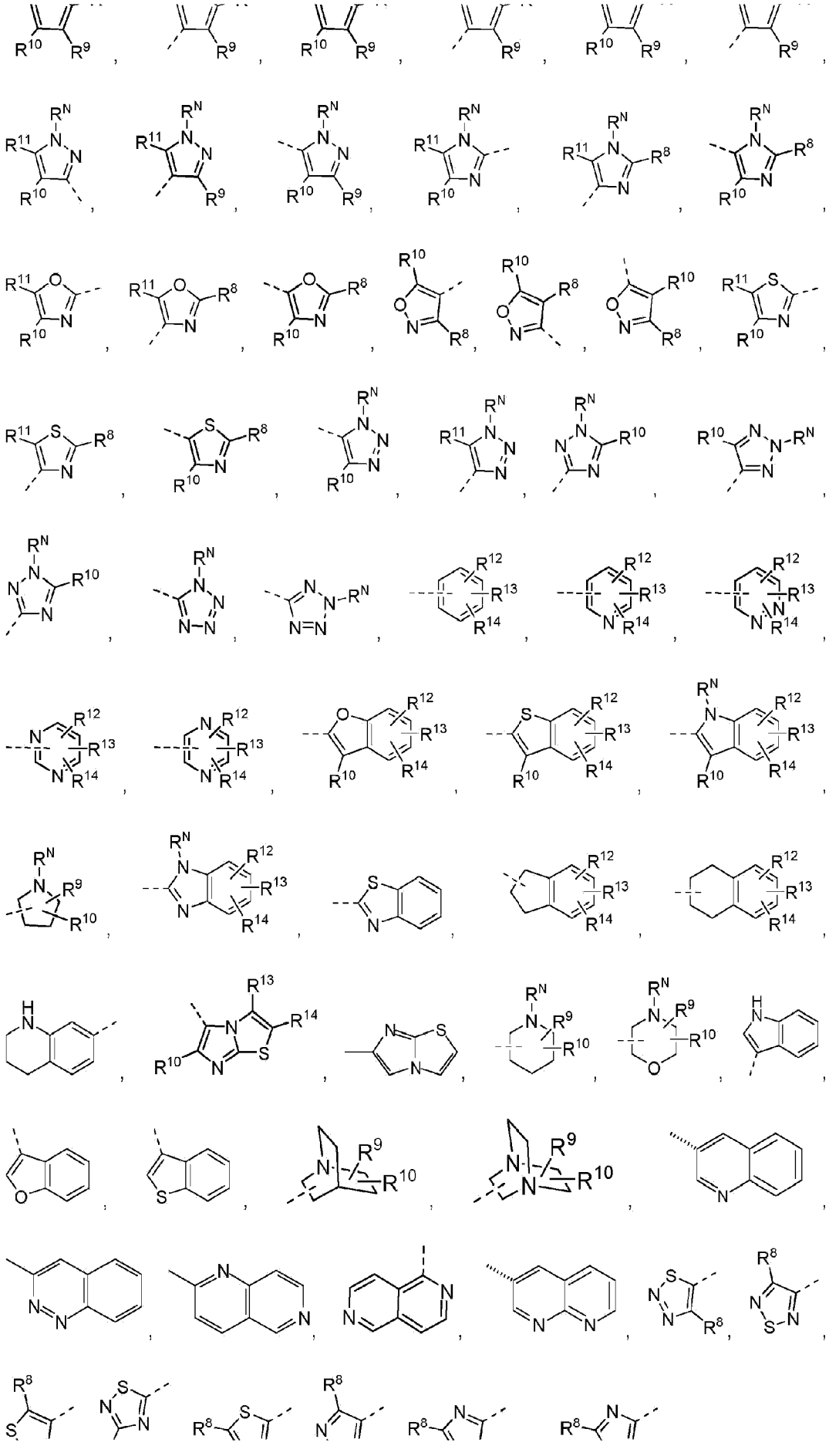
**L** represents **-$L^1$-** or **-$L^1$-$L^2$-**; preferably **-$L^1$-$L^2$-**;

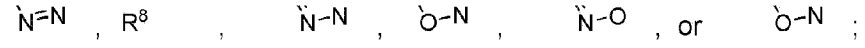
**$L^1$** represents -$CH_2$-, -$CH_2CH_2$-, -$CH_2CH_2CH_2$-, -$CH_2CO$-, or -$CH_2CH_2CO$-;

**$L^2$** represents a bond, **-$NR^{N1}$-**, **-$NR^{N1}CH_2$-**, -$NR^{N1}CH_2CH_2$-, or -$NR^{N1}CH(CH_3)$-;

**$R^2$** represents



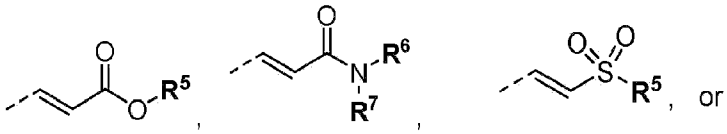


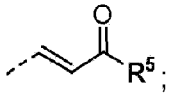


wherein the unsubstituted bicyclic residues can be substituted with 1 to 5 of the substituents $R^9$ -$R^{14}$, and $R^N$ ; and preferably with 1 to 3 of the substituents $R^{11}$ - $R^{13}$, and $R^5$ - $R^{14}$, $R^N$ and $R^{N1}$ have the meanings as defined herein.

**[0033]** More preferred, are the compound of the formula (**I**), wherein

$R^1$ represents





L represents -$L^1$-$L^2$-;

$L^1$ represents -$CH_2$-, or -$CH_2CO$-;

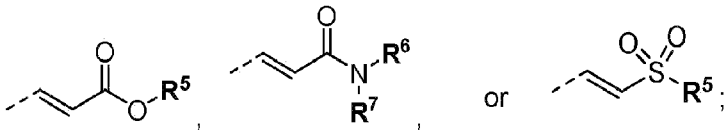
$L^2$ represents a bond, -$NR^{N1}$-, -$NR^{N1}CH_2$-, or -$NR^{N1}CH(CH_3)$-;

$R^3$ represents bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl, 4-homoisotwistyl, adamantyl, or diamantyl and the afore-mentioned residues optionally contain one or more C=C double bond(s) and/or are optionally substituted by one or more of $R^a$, $R^b$, $R^c$, $R^d$, and $R^e$;

and $R^5$, $R^6$, $R^7$, $R^a$, $R^b$, $R^c$, $R^d$, $R^e$ and $R^{N1}$ have the same meanings as defined above.

**[0034]** More preferred, are the compound of the formula (**I**), wherein

$R^1$ represents



L represents -$L^1$- or -$L^1$-$L^2$-; preferably -$L^1$-$L^2$-;

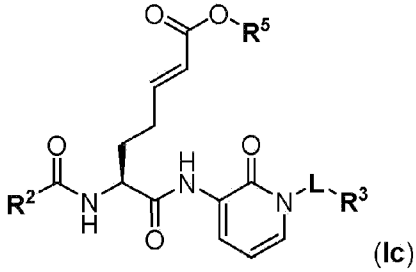
$L^1$ represents -$CH_2$-, or -$CH_2CO$-;

$L^2$ represents a bond, -$NR^{N1}$-, -$NR^{N1}CH_2$-, or -$NR^{N1}CH(CH_3)$-;

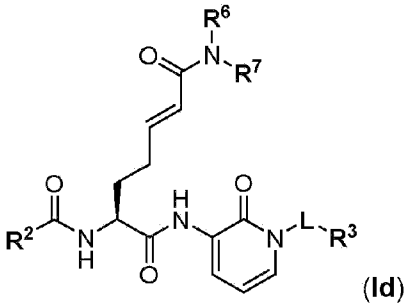
$R^3$ represents bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl, 4-homoisotwistyl, adamantyl, or diamantyl and the afore-mentioned residues optionally contain one or more C=C double bond(s) and/or are optionally substituted by one or more of $R^a$, $R^b$, $R^c$, $R^d$, and $R^e$;

and $R^5$, $R^6$, $R^7$, $R^a$, $R^b$, $R^c$, $R^d$, $R^e$ and $R^{N1}$ have the same meanings as defined above.

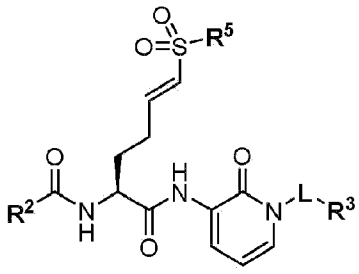
**[0035]** Also preferred are the compound of any one of the formulae (**Ic**) - (**Ie**):



(**Ic**)



(**Id**)



(**Ie**)

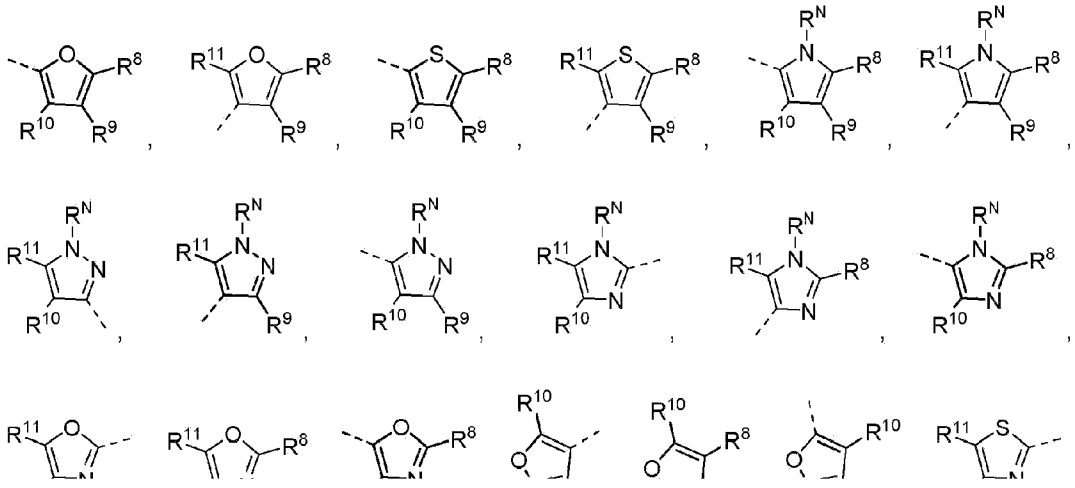
wherein

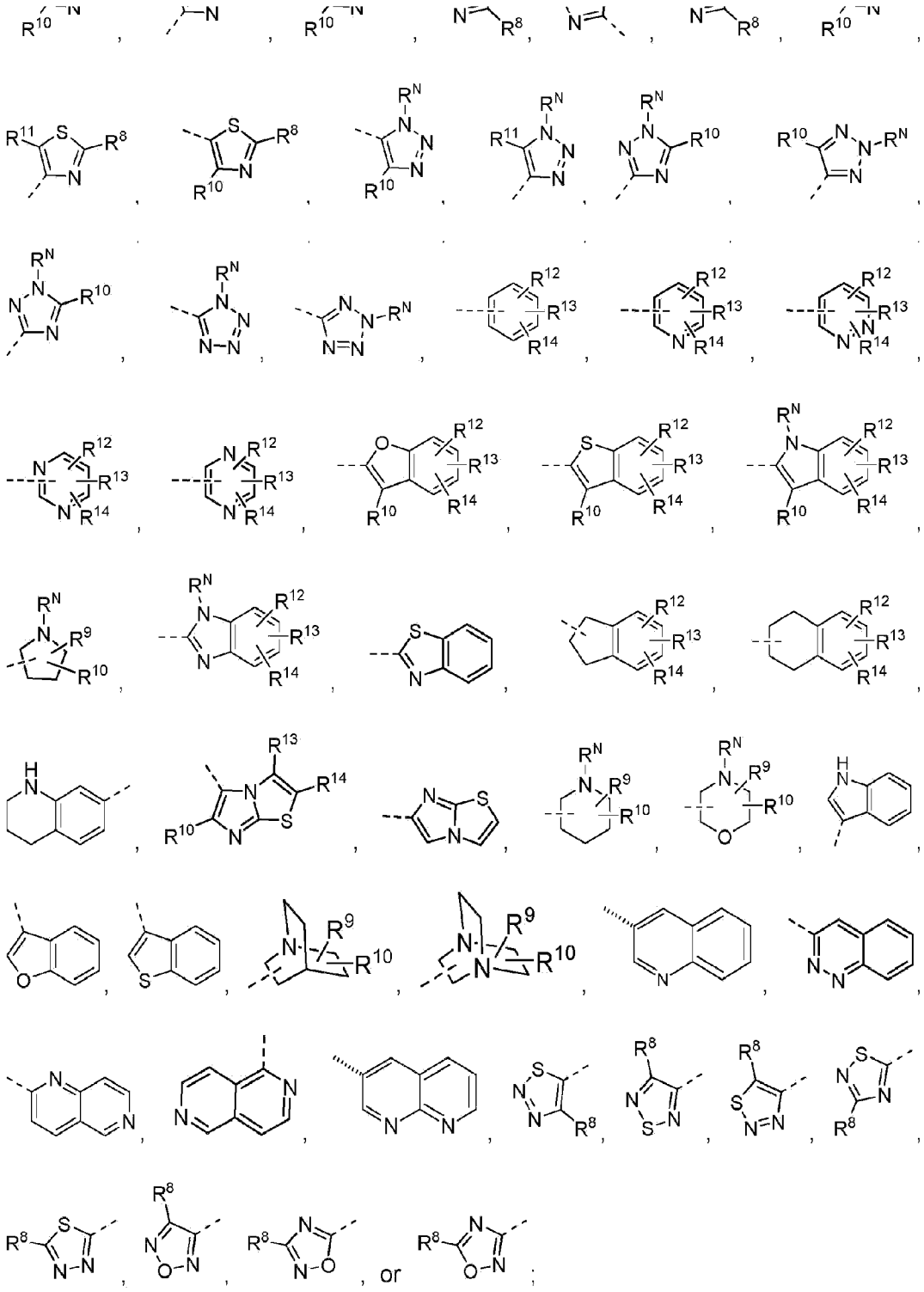
L represents -$L^1$- or -$L^1$-$L^2$-; preferably -$L^1$-$L^2$-;

$L^1$ represents -$CH_2$-, or -$CH_2CO$-;

$L^2$ represents a bond, -$NR^{N1}$-, -$NR^{N1}CH_2$-, or -$NR^{N1}CH(CH_3)$-;

$R^2$ represents

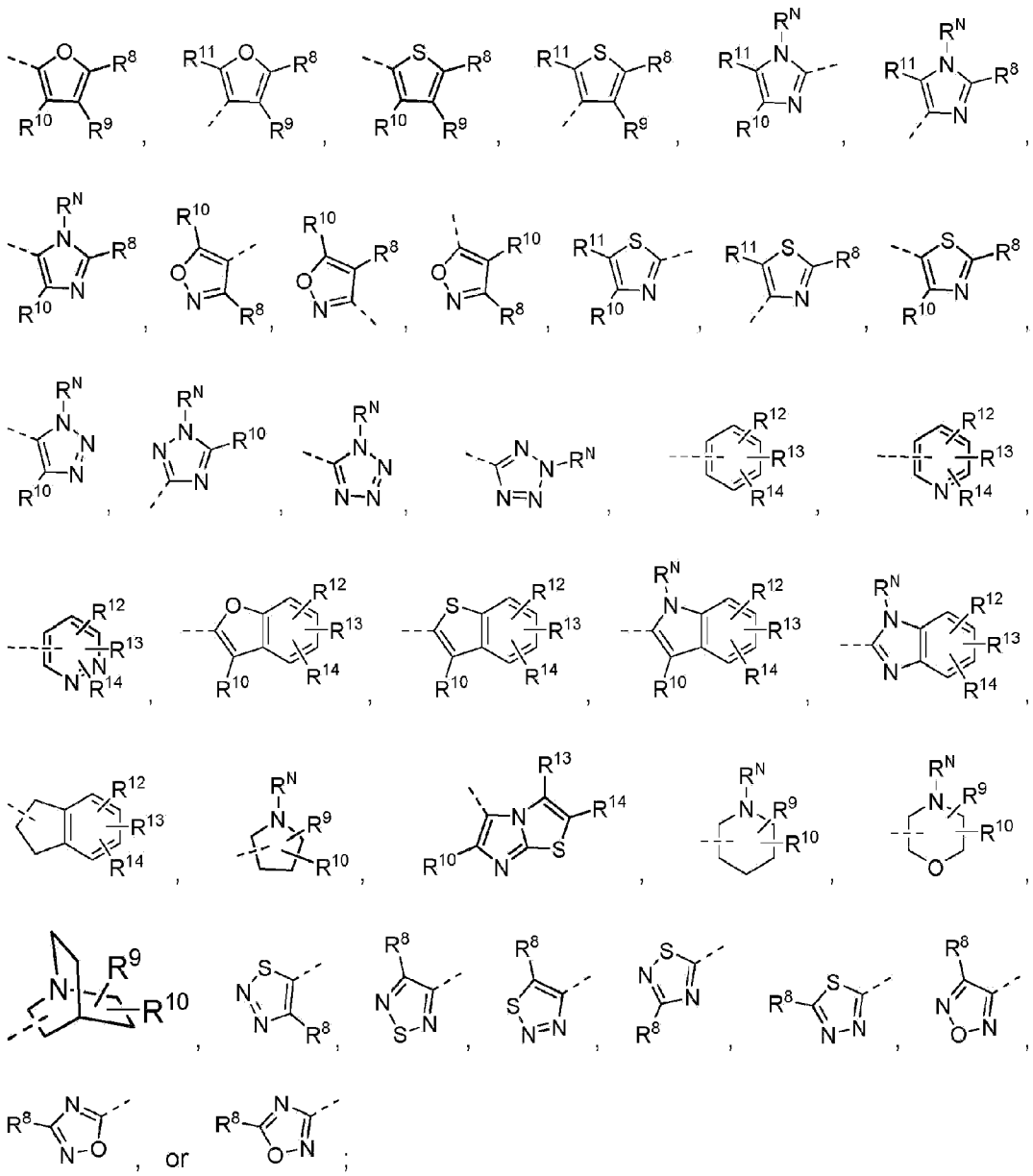




wherein the unsubstituted bicyclic residues can be substituted with 1 to 5 of the substituents **$R^9$ - $R^{14}$, $R^N$**; and preferably with 1 to 3 of the substituents **$R^{11}$ - $R^{13}$**,

and **$R^5$ - $R^{14}$, $R^N$** and **$R^{N1}$** have the meanings as defined herein.

**[0036]** Preferably, **$R^2$** represents

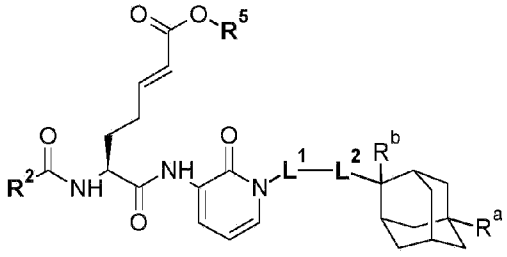


**R$^3$** represents bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl, 4-homoisotwistyl, adamantyl, or diamantyl and the afore-mentioned residues optionally contain one or more C=C double bond(s) and/or are optionally substituted by one or more of **R$^a$**, **R$^b$**, **R$^c$**, **R$^d$**, and **R$^e$**;

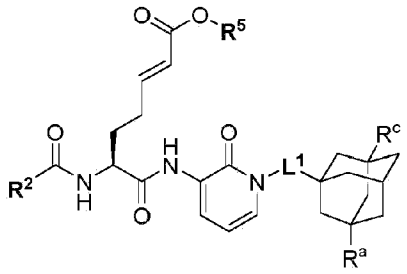
and **R$^5$** - **R$^{14}$** , **R$^a$**, **R$^b$**, **R$^c$**, **R$^d$**, **R$^e$**, **R$^N$** and **R$^{N1}$** have the same meanings as defined above.

**[0037]** In all general formula disclosed herein L represents most preferably -**L$^1$**-**L$^2$**-; wherein **L$^1$** represents preferably -$CH_2CO$- or -$CH_2CH_2CO$-; and more preferably -$CH_2CO$-; and **L$^2$** represents -N**R$^{N1}$**-, -N**R$^{N1}$**$CH_2$-, or -N**R$^{N1}$**$CH(CH_3)$-; more preferably -NH-, -N($CH_3$)-, -NH-$CH_2$-, or -NH-$CH(CH_3)$-; still more preferably -NH-, -NH-$CH_2$-, or -NH-$CH(CH_3)$-; and most preferably -NH-.

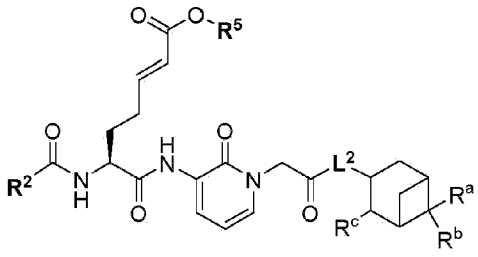
**[0038]** More preferred are compounds of any one the formulae **(VI-a)** - **(VI-l)**, **(VII-a)** - **(VII-l)**, **(VIII-a)** - **(VIII-l)**, **(IX-a)** - **(IX-d)**, **(X-a)** - **(X-d)**, and **(XI-a)** - **(XI-d)**:



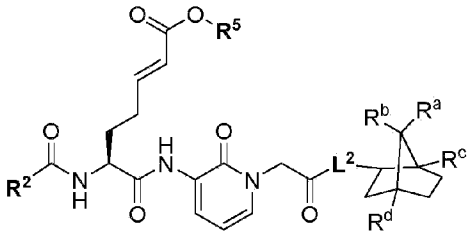
(VI-a)



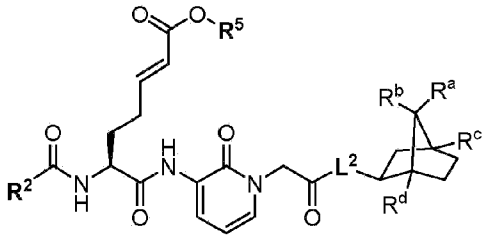
(VI-b)



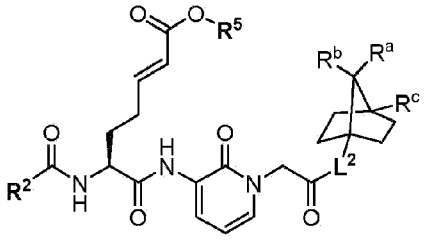
(VI-c)



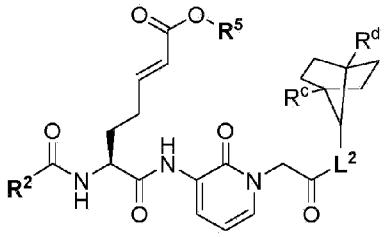
(VI-d)



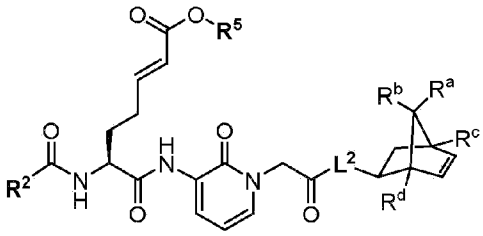
(VI-e)



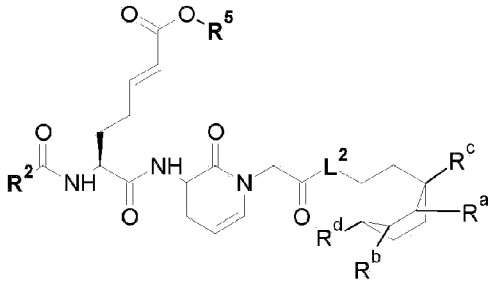
(VI-f)



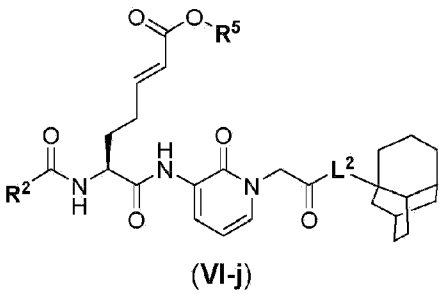
(VI-g)



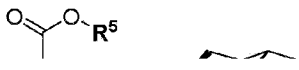
(VI-h)



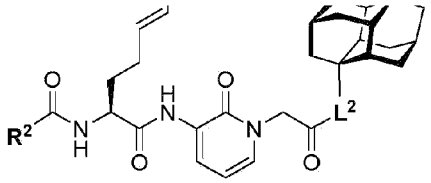
(VI-i)



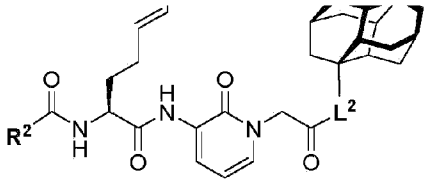
(VI-j)



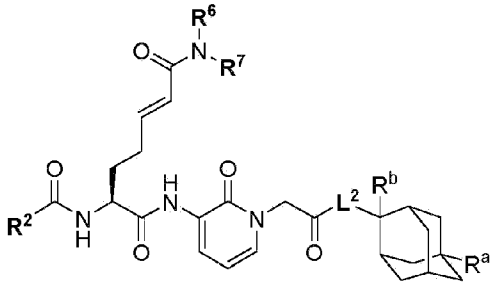




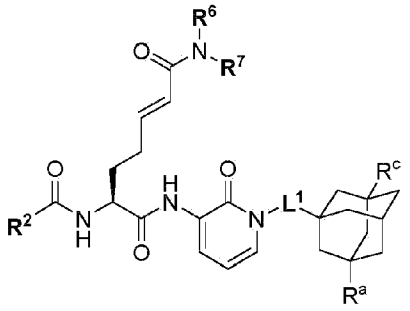
(VI-k)



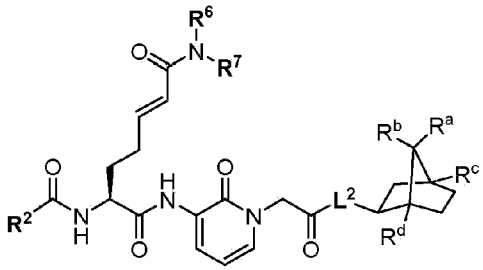
(VI-l)



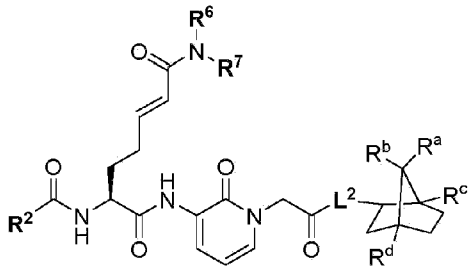
(VII-a)



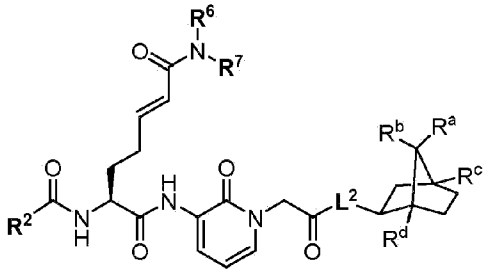
(VII-b)



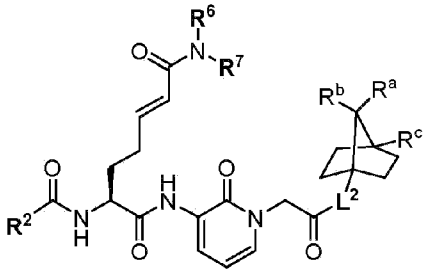
(VII-c)



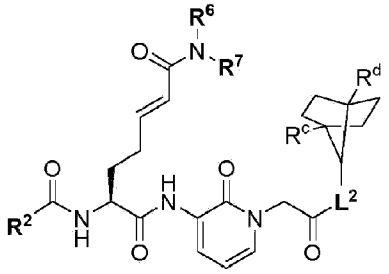
(VII-d)



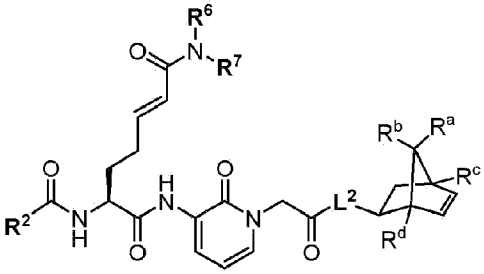
(VII-e)



(VII-f)

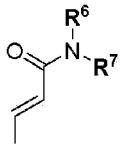


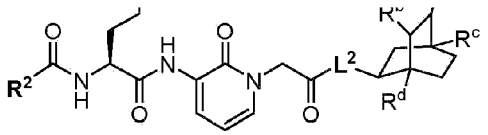
(VII-g)



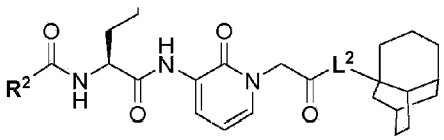
(VII-h)



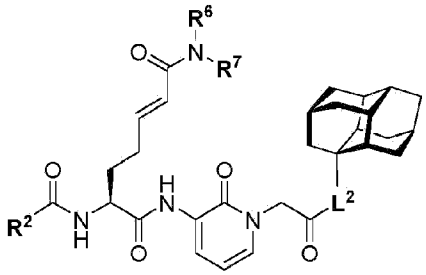




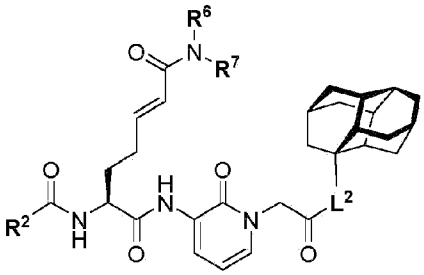
(VII-i)



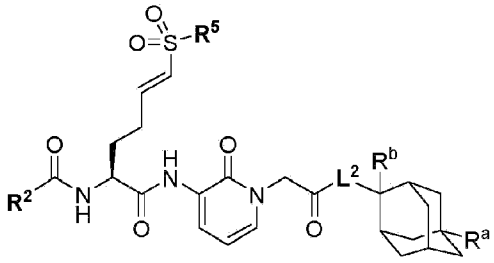
(VII-j)



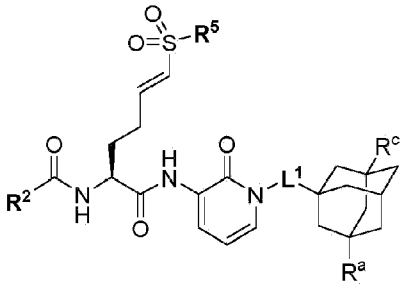
(VII-k)



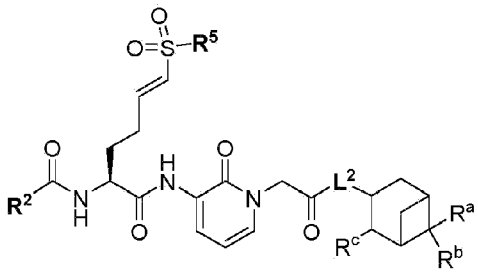
(VII-l)



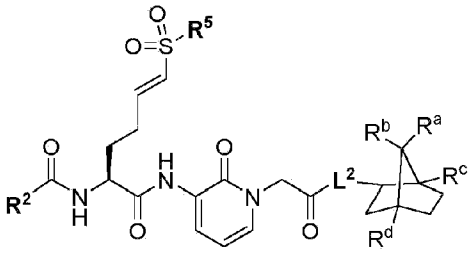
(VIII-a)



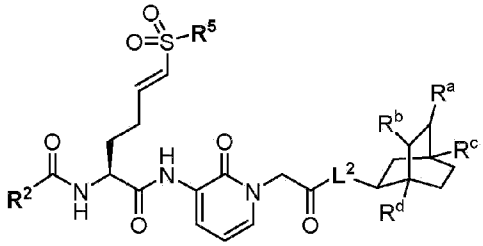
(VIII -b)



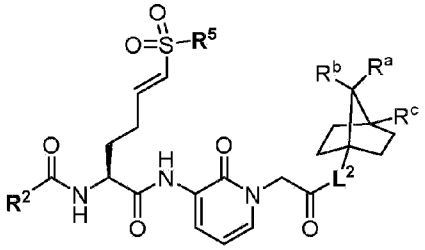
(VIII -c)



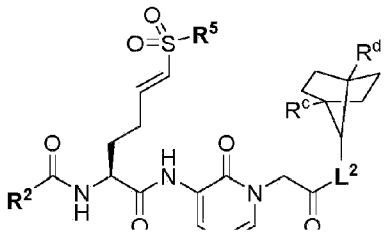
(VIII -d)

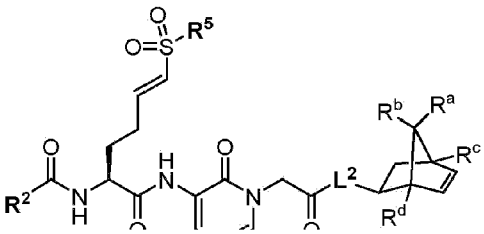


(VIII -e)



(VIII -f)

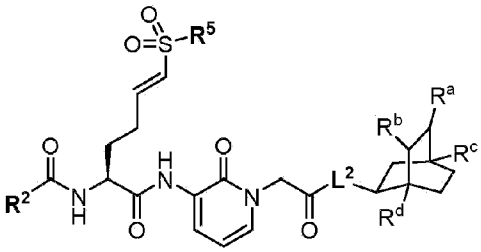




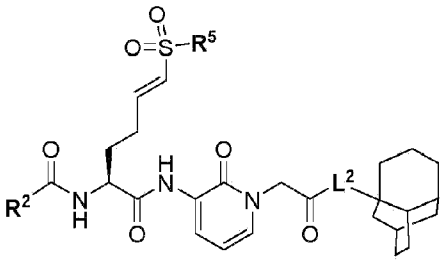
(VIII -g)



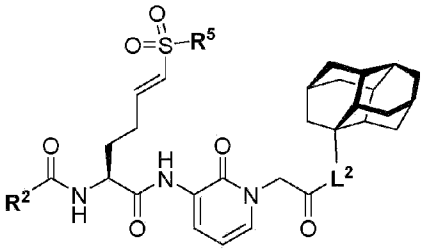
(VIII -h)



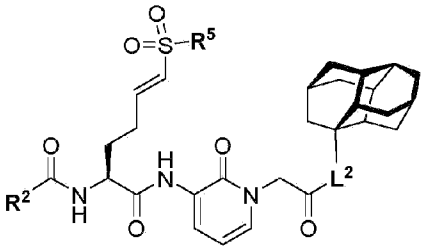
(VIII -i)



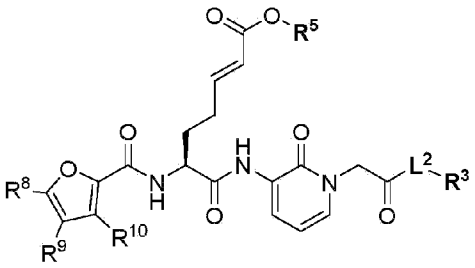
(VIII -j)



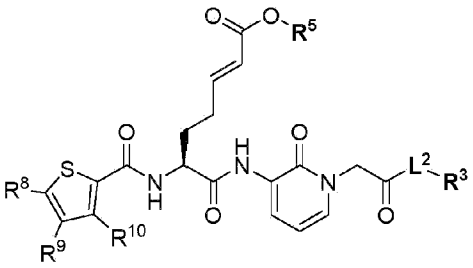
(VIII -k)



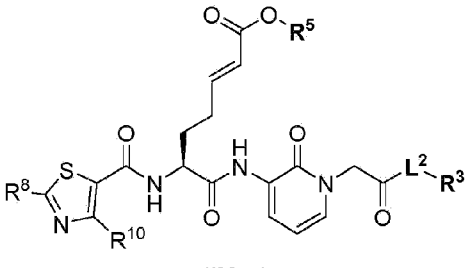
(VIII -l)



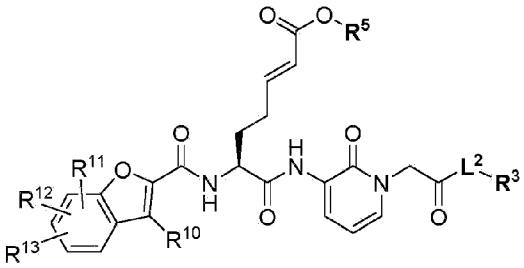
(IX-a)



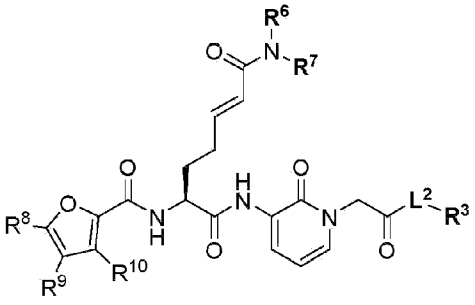
(IX-b)



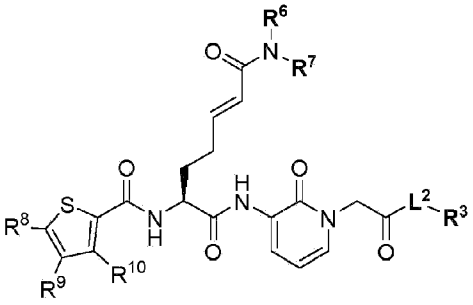
(IX-c)



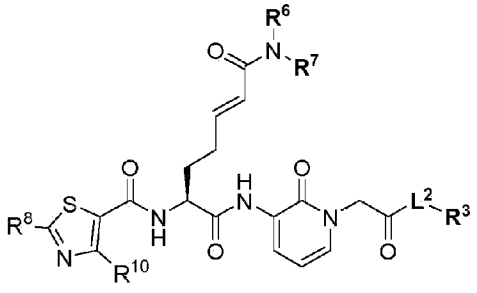
(IX-d)



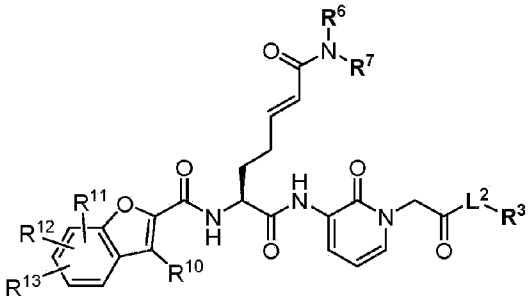
(X-a)



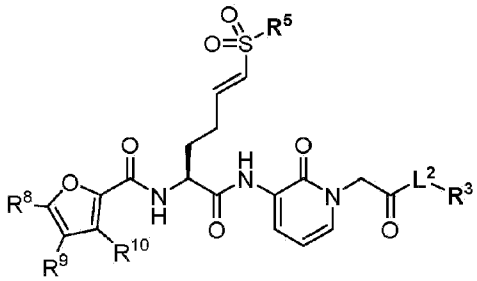
(X-b)



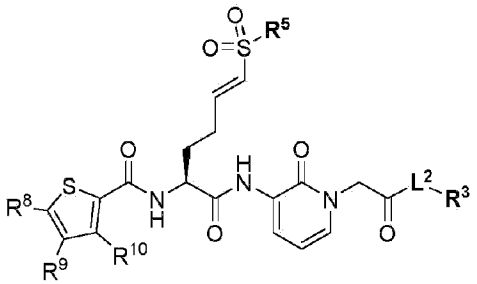
(**X-c**)



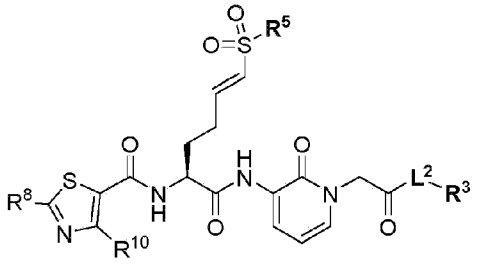
(**X-d**)



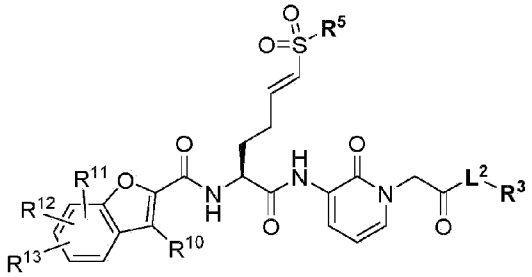
(**XI-a**)



(**XI-b**)



(**XI-c**)

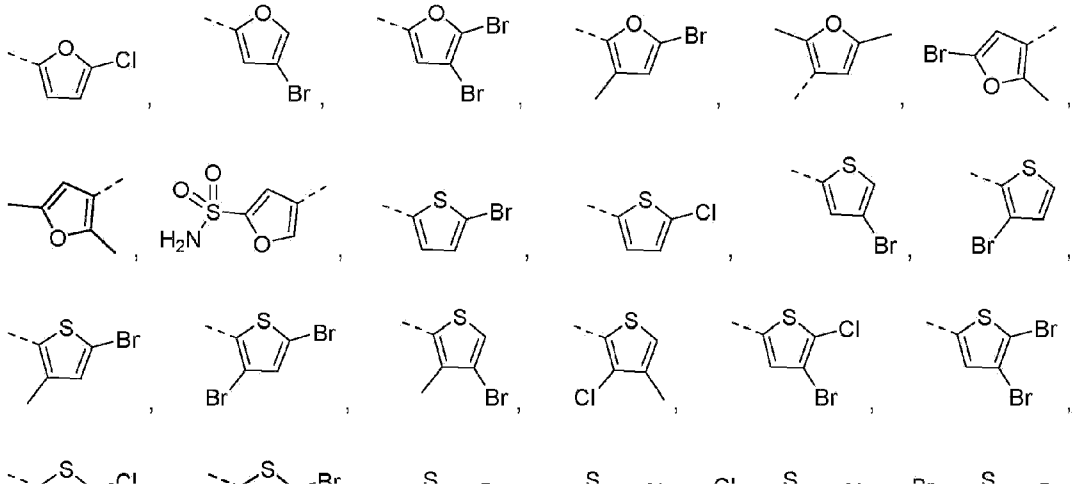


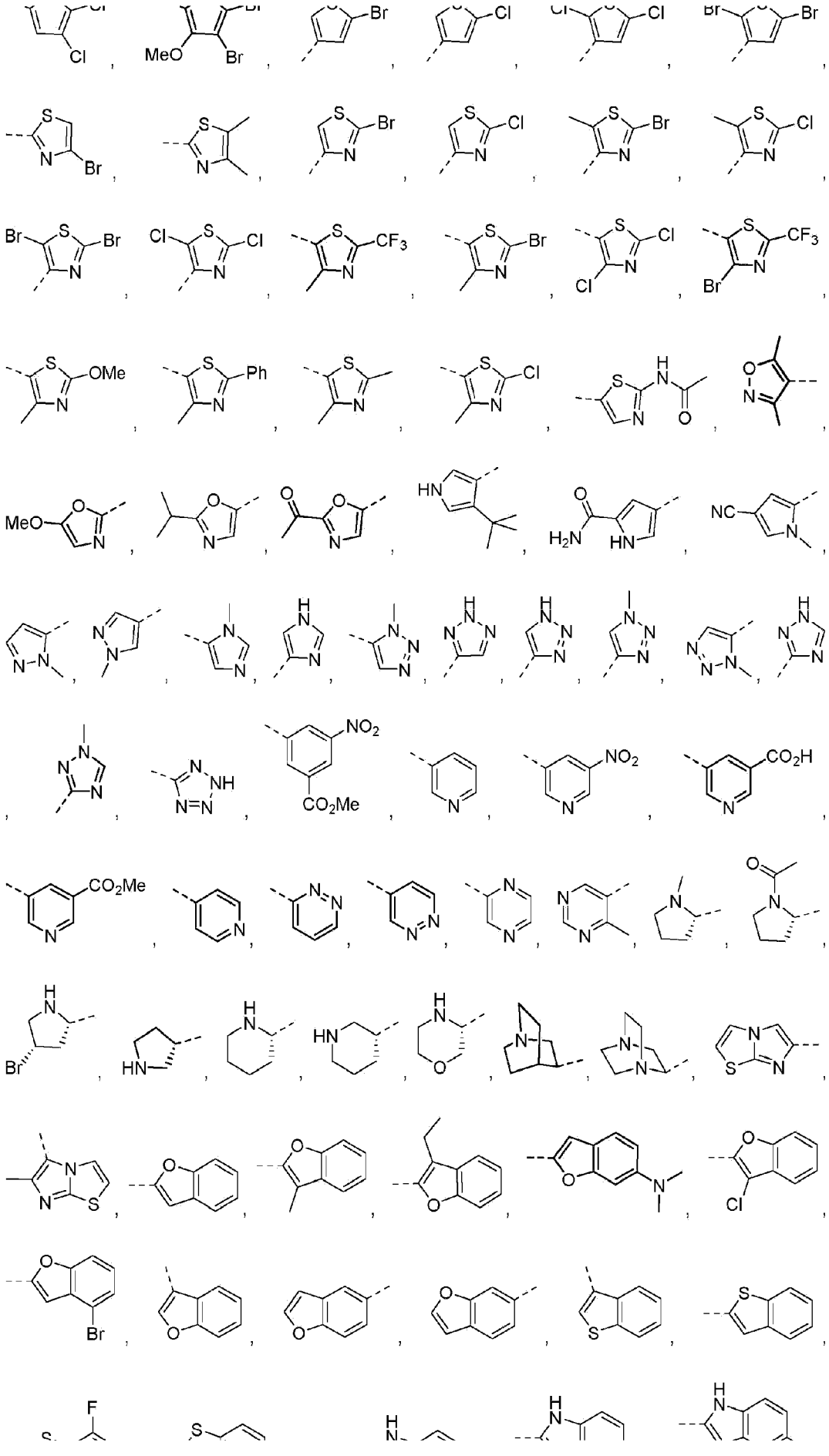
(**XI-d**)

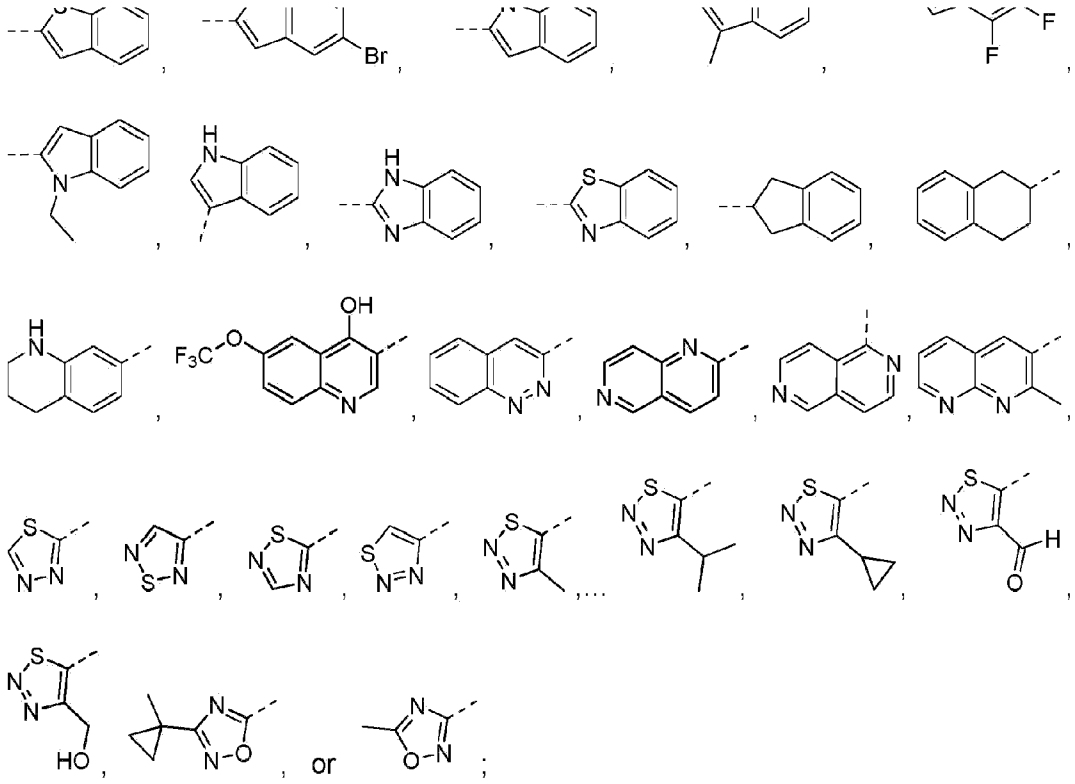
and $R^2$, $R^3$, $R^5$, $R^6$, $R^7$, $R^8$, $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, $R^{13}$, $R^a$, $R^b$, $R^c$, $R^d$ and $L^2$ have the same meanings as defined above

**[0039]** Preferred are the compounds of any one of the formule (**I**), (**Ic**) - **(Ie), (VI-a)** - **(VI-l), (VII-a)** - **(VII-l), (VIII-a)** - **(VIII-l),** wherein

$R^2$ represents







**$R^5$** represents -H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-C(CH_3)_3$, -cyclo-$C_3H_5$, -cyclo-$C_4H_7$, $-CH_2$-cyclo-$C_3H_5$, $-CH_2$-cyclo-$C_4H_7$; $-CH_2Ph$, or -Ph;

**$R^6$** and **$R^7$** represent independently of each other -H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_2CH_3$, -cyclo-$C_3H_5$, -cyclo-$C_5H_9$, -cyclo-$C_6H_{11}$, $-CH_2CH{=}CH_2$, -Ph, or $-CH_2Ph$.

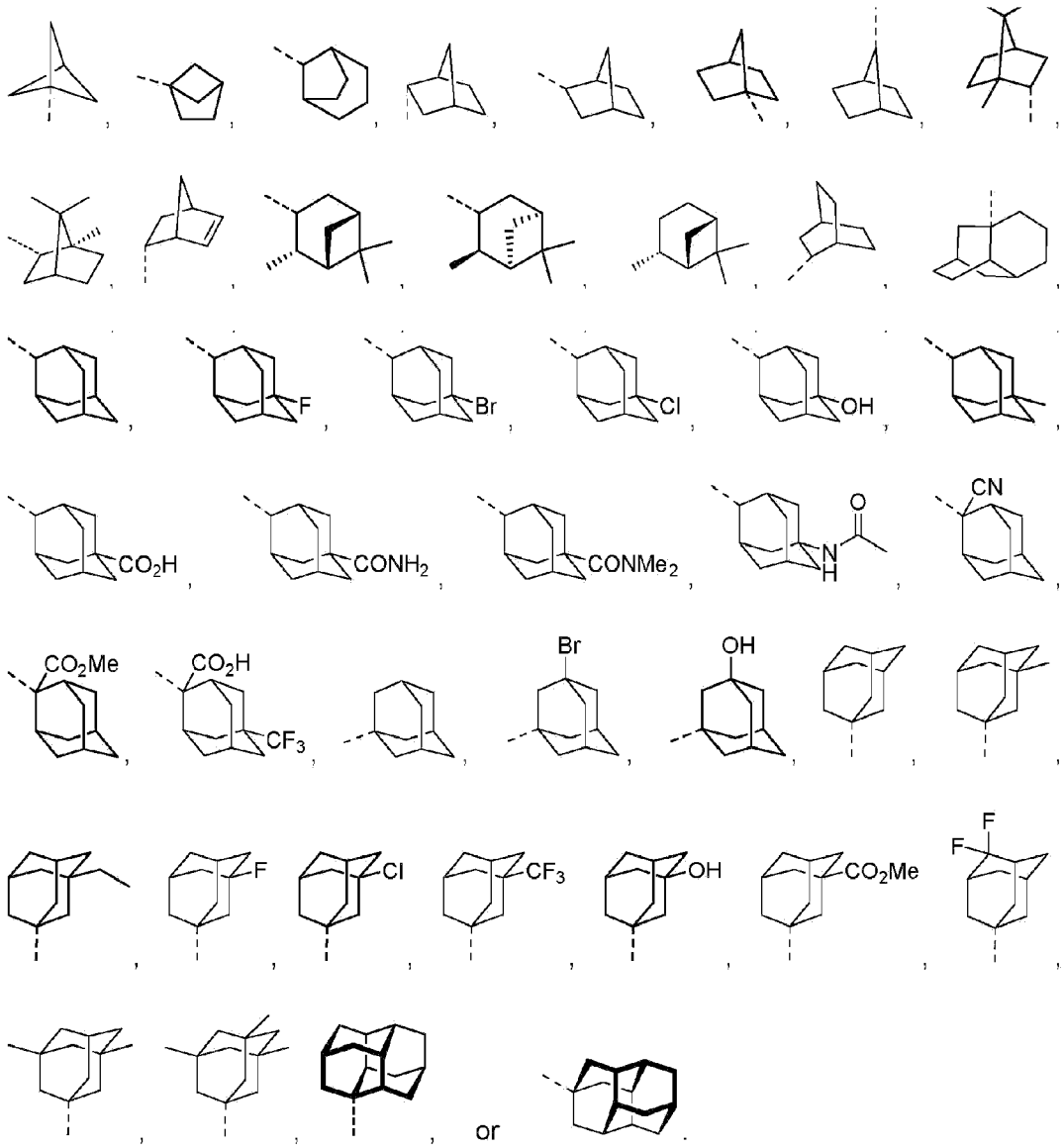
**[0040]** Preferred, are the compounds of any one of the formule **(IX-a)** - **(IX-d), (X-a)** - **(X-d),** and **(XI-a)** - **(XI-d),** wherein

**$R^5$** represents -H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-C(CH_3)_3$, -cyclo-$C_3H_5$, -cyclo-$C_4H_7$, $-CH_2$-cyclo-$C_3H_5$, $-CH_2$-cyclo-$C_4H_7$; $-CH_2Ph$, or -Ph;

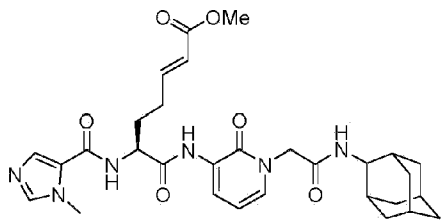
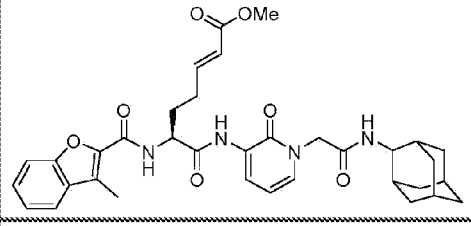
**$R^6$** and **$R^7$** represent independently of each other -H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_2CH_3$, -cyclo-$C_3H_5$, -cyclo-$C_5H_9$, -cyclo-$C_6H_{11}$, $-CH_2CH{=}CH_2$, -Ph, or $-CH_2Ph$.

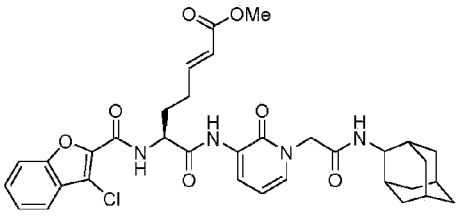
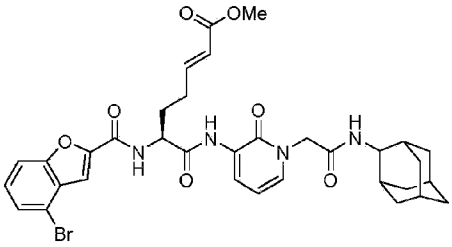
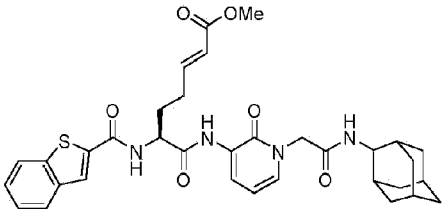
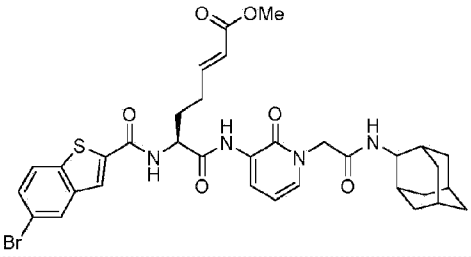
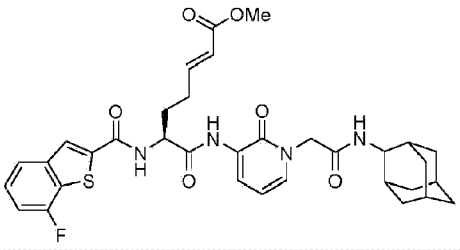
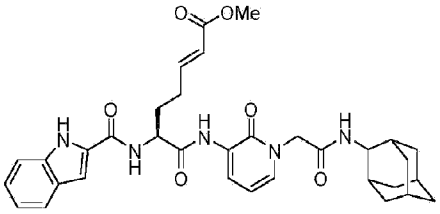
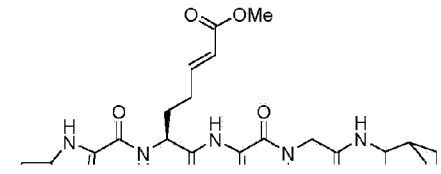
**[0041]** Preferred, are the compound of any of the formulae (I), (**Ic**) - **(Ie), (VI-a)** - (**VI-I**), **(VII-a)** - **(VII-I), (VIII-a)** - **(VIII-I), (IX-a)** - **(IX-d), (X-a)** - **(X-d),** and **(XI-a)** - **(XI-d),** wherein

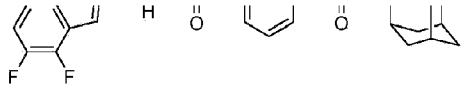
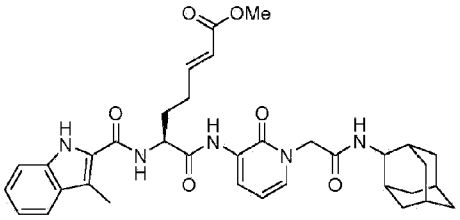
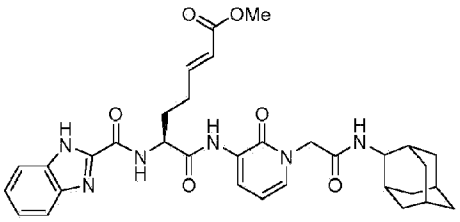
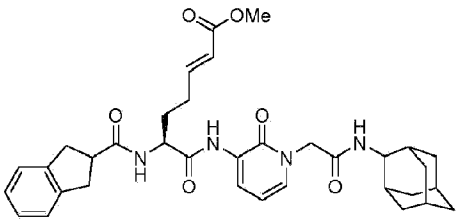
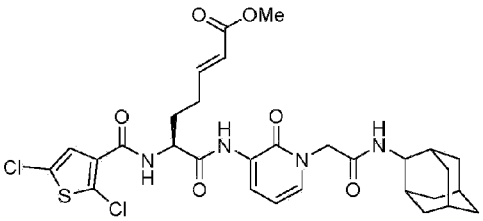
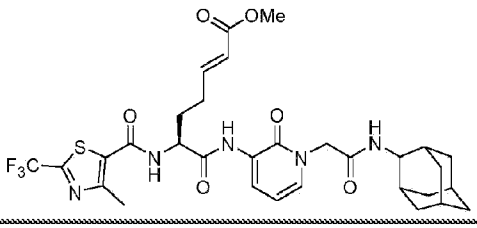
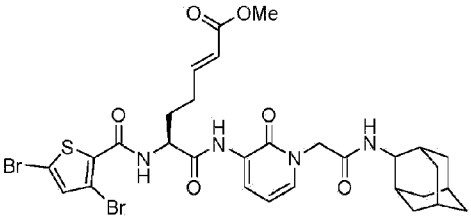
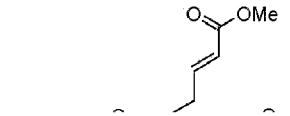
**$R^3$** represents

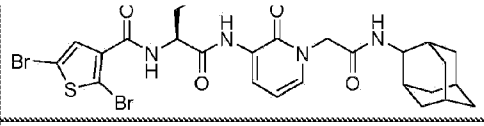
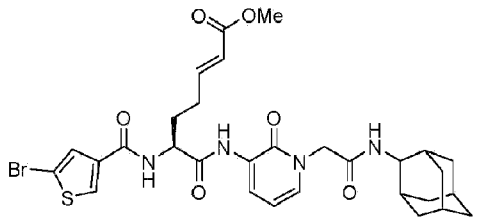
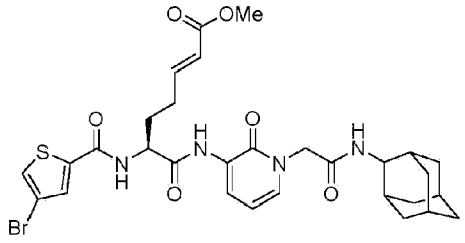
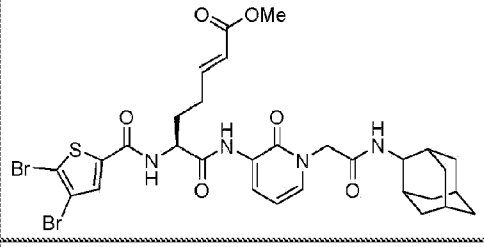
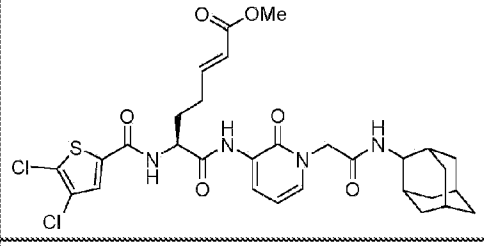
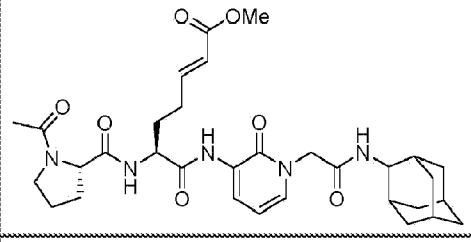
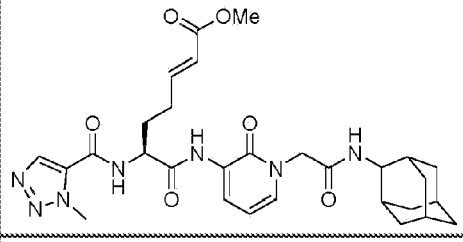


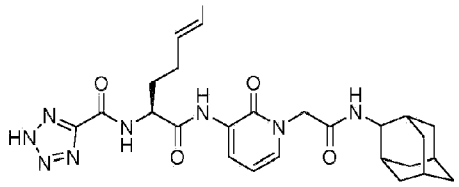
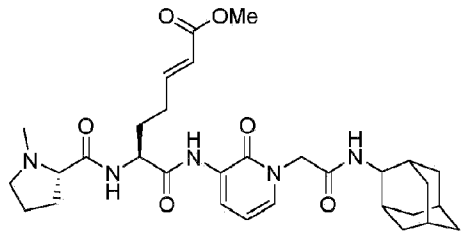
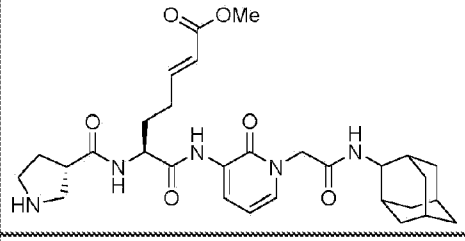
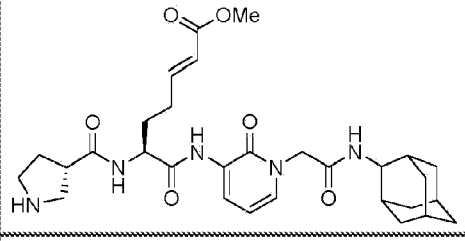
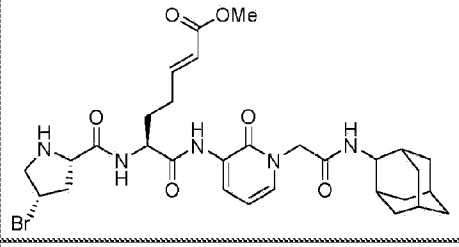
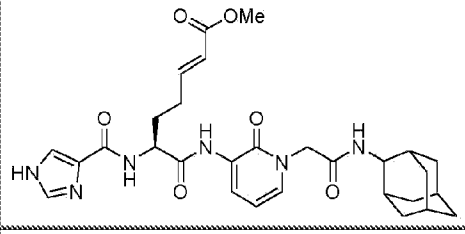
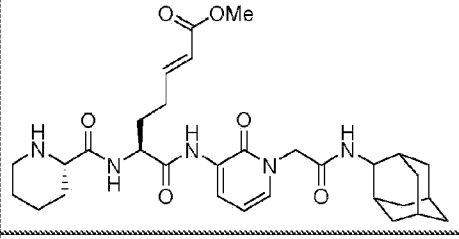

**[0042]** In very preferred embodiment the present invention refers to the compounds selected from the group consisting of:

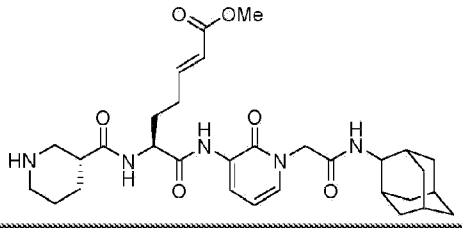
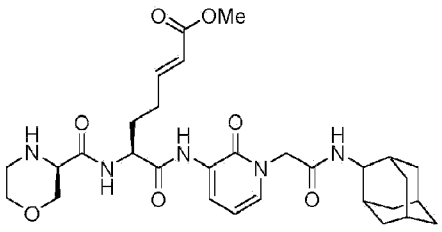
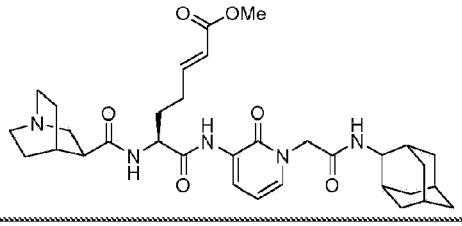
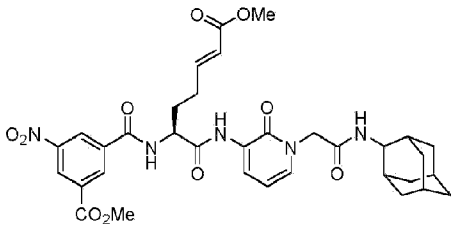
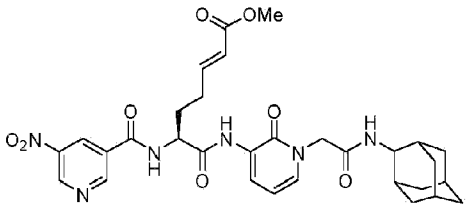
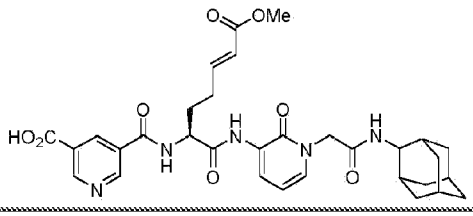
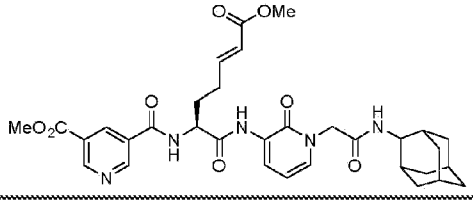
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| **III-1**: |  | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-imidazole-5-carboxamido)-7-oxohept-2-enoate |
| **III-2:** |  | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |

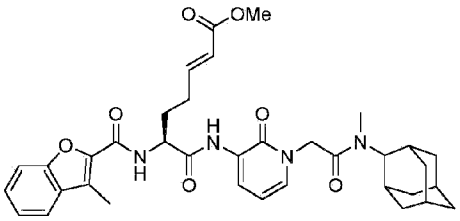
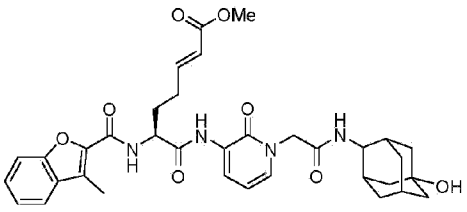
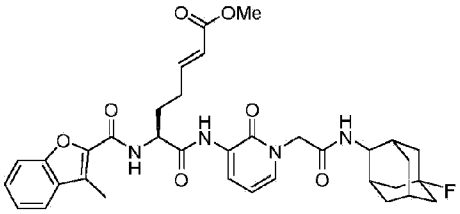
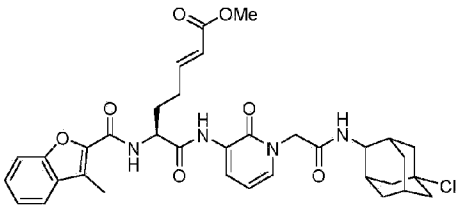
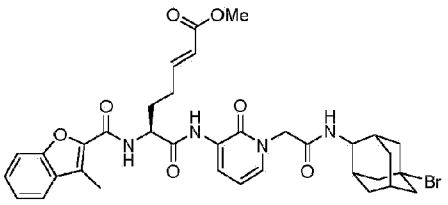
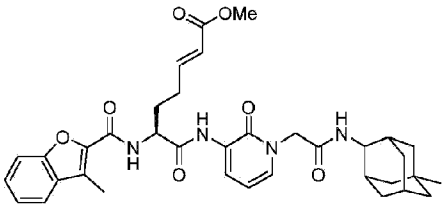
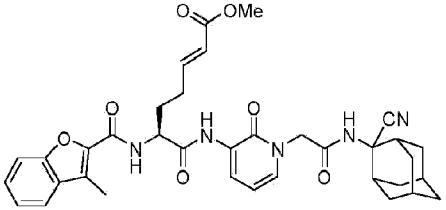
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| **III-3:** |  | (S,E)-methyl 6-(3-chlorobenzofuran-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate |
| **III-4:** |  | (S,E)-methyl 6-(4-bromobenzofuran-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate |
| **III-5:** |  | (S,E)-methyl 6-(benzo[b]thiophene-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate |
| **III-6:** |  | (S,E)-methyl 6-(5-bromobenzo[b]thiophene-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate |
| **III-7:** |  | (S,E)-methyl 6-(7-fluorobenzo[b]thiophene-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate |
| **III-8:** |  | (S,E)-methyl 6-(1H-indole-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate |
| **III-9:** |  | (S,E)-methyl 6-(4,5-difluoro-1H-indole-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate |

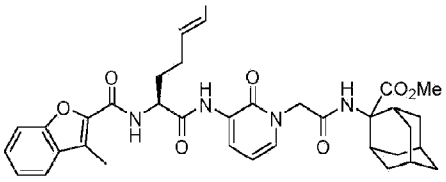
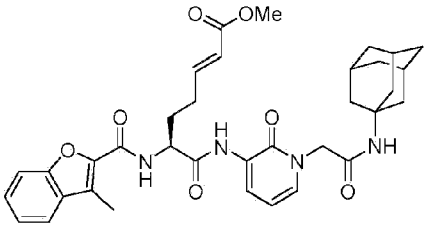
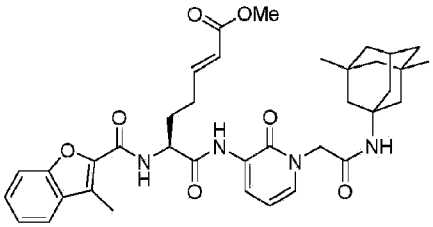
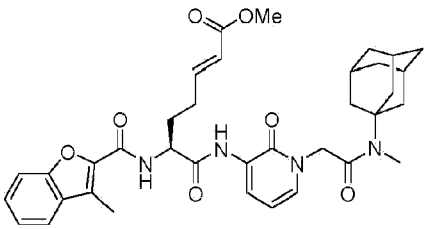
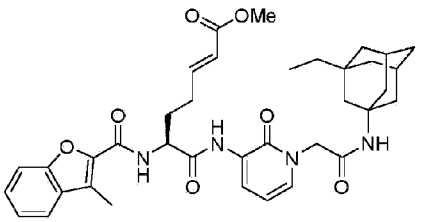
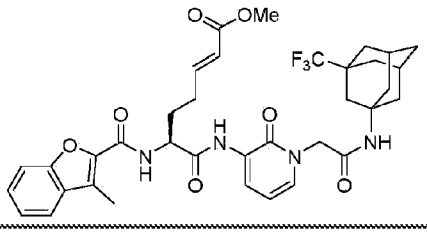
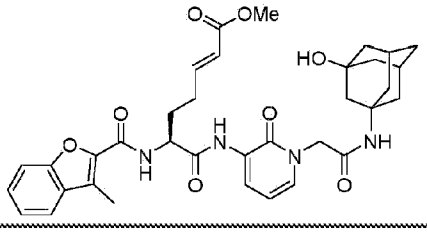
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| III-10: |  | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methyl-1H-indole-2-carboxamido)-7-oxohept-2-enoate |
| III-11: |  | (S,E)-methyl 6-(1H-benzo[d]imidazole-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate |
| III-12: |  | (S,E)-methyl 6-(2,3-dihydro-1H-indene-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate |
| III-13: |  | (S,E)-methyl 6-(2,5-dichlorothiophene-3-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate |
| III-14: |  | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-methyl-2-(trifluoromethyl)thiazole-5-carboxamido)-7-oxohept-2-enoate |
| III-15: |  | (S,E)-methyl 6-(3,5-dibromothiophene-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate |
| III-16: |  | (S,E)-methyl 6-(2,5-dibromothiophene-3-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo- |

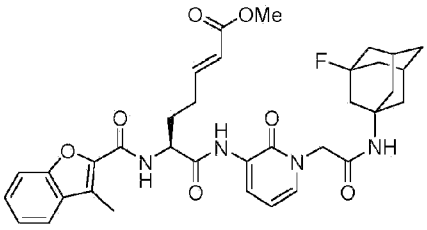
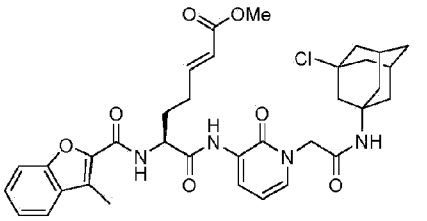
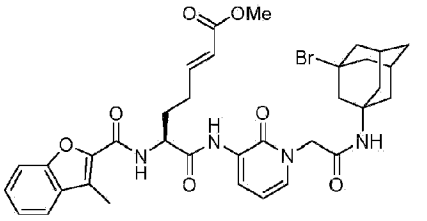
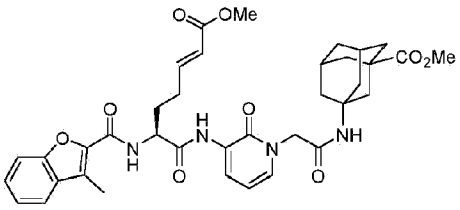
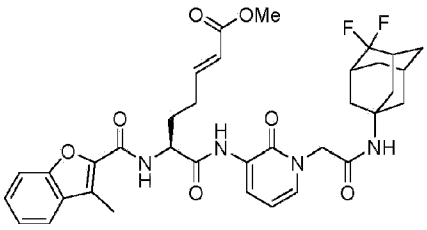
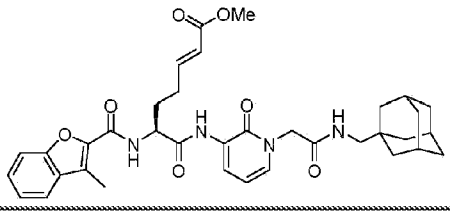
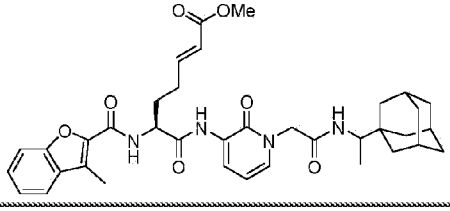
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| |  | 1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate |
| **III-17:** |  | (S,E)-methyl 6-(5-bromothiophene-3-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate |
| **III-18:** |  | (S, E)-methyl 6-(4-bromothiophene-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate |
| **III-19:** |  | (S,E)-methyl 6-(4,5-dibromothiophene-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate |
| **III-20:** |  | (S,E)-methyl 6-(4,5-dichlorothiophene-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate |
| **III-21:** |  | (S,E)-methyl 6-((S)-1-acetylpyrrolidine-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate |
| **III-22:** |  | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-1,2,3-triazole-5-carboxamido)-7-oxohept-2-enoate |
| **III-23:** |  | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo- |

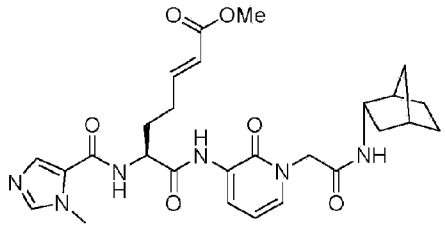
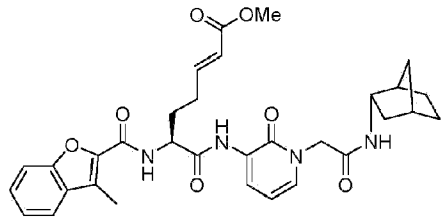
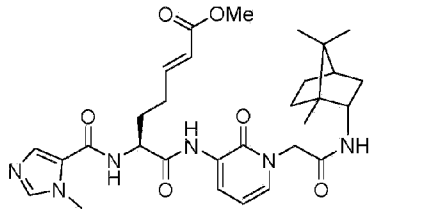
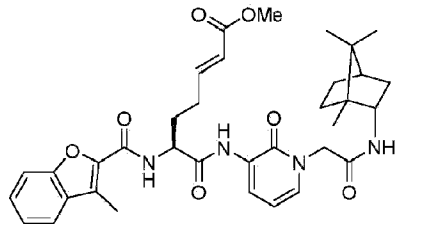
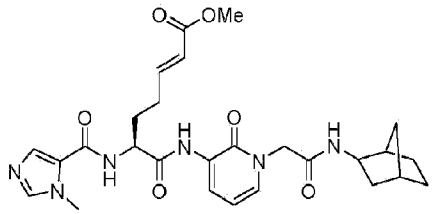
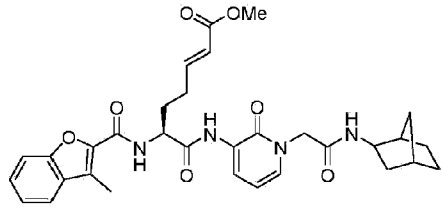
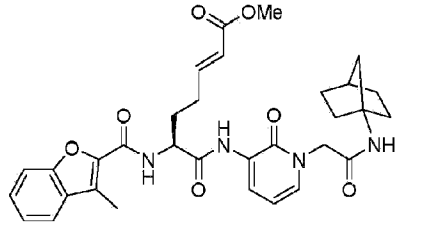
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| |  | 1,2-dihydropyridin-3-ylamino)-7-oxo-6-(2H-tetrazole-5-carboxamido)hept-2-enoate |
| **III-24:** |  | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(pyrazine-2-carboxamido)hept-2-enoate |
| **III-25:** |  | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-((S)-1-methylpyrrolidine-2-carboxamido)-7-oxohept-2-enoate |
| **III-26:** |  | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-((S)-pyrrolidine-3-carboxamido)hept-2-enoate |
| **III-27:** |  | (S,E)-methyl 6-((2S,4S)-4-bromopyrrolidine-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate |
| **III-28:** |  | (S,E)-methyl 6-(1H-imidazole-4-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate |
| **III-29:** |  | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-((S)-piperidine-2-carboxamido)hept-2-enoate |

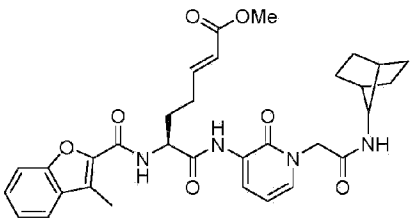
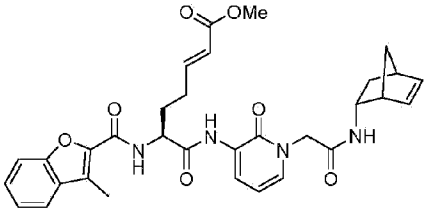
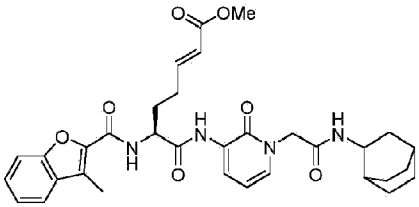
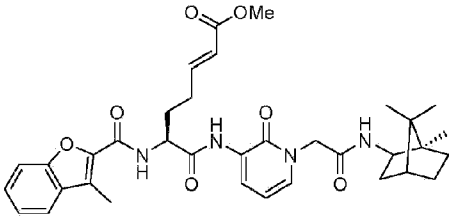
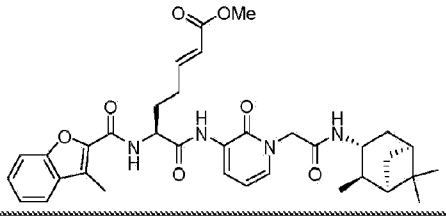
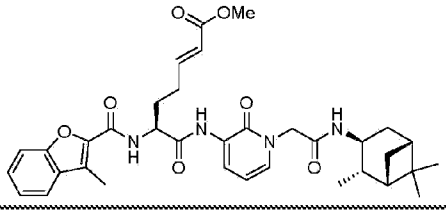
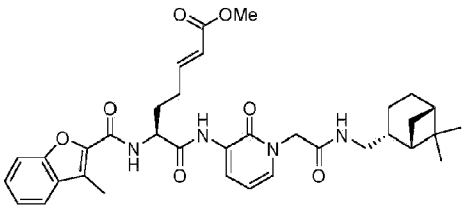
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| **III-30:** |  | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-((R)-piperidine-3-carboxamido)hept-2-enoate |
| **III-31:** |  | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-((R)-morpholine-3-carboxamido)-7-oxohept-2-enoate |
| **III-32:** |  | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(quinuclidine-3-carboxamido)hept-2-enoate |
| **III-33:** |  | (S,E)-methyl 3-(1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-methoxy-1,7-dioxohept-5-en-2-ylcarbamoyl)-5-nitrobenzoate |
| **III-34:** |  | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(5-nitronicotinamido)-7-oxohept-2-enoate |
| **III-35:** |  | (S,E)-5-(1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-methoxy-1,7-dioxohept-5-en-2-ylcarbamoyl)nicotinic acid |
| **III-36:** |  | (S,E)-methyl 5-(1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-methoxy-1,7-dioxohept-5-en-2-ylcarbamoyl)nicotinate |
| **III-** | | (S,E)-methyl 7-(1-(2-(2- |

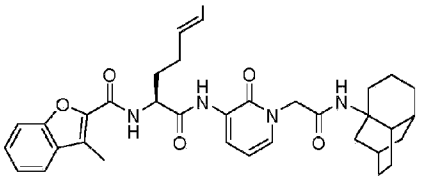
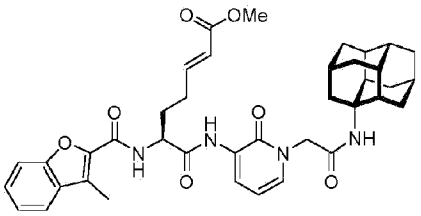
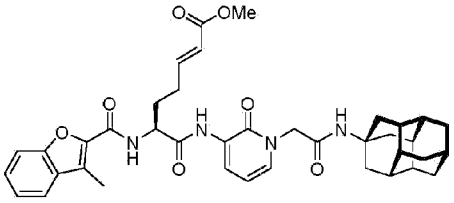
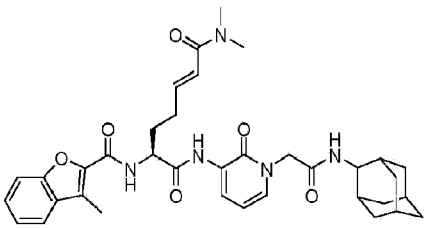
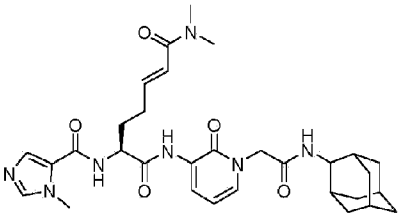
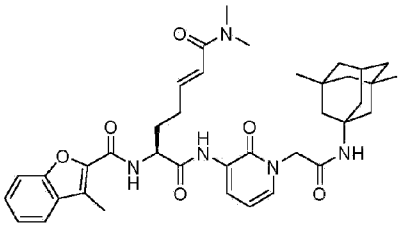
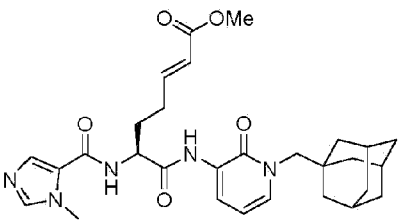
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| **37:** |  | adamantyl(methyl)amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-38:** |  | (S,E)-methyl 7-(1-(2-(5-hydroxyadamantane-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-39:** |  | (S,E)-methyl 7-(1-(2-(5-fluoroadamantane-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-40:** |  | (S,E)-methyl 7-(1-(2-(5-chloroadamantane-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-41:** |  | (S,E)-methyl 7-(1-(2-(5-bromoadamantane-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-42:** |  | (S,E)-methyl 7-(1-(2-(5-methyladamantane-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-43:** |  | (S,E)-methyl 7-(1-(2-(2-carbonitrileadamantane-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-44:** |  | (S,E)-methyl 7-(1-(2-(2-methyl adamantane-2-carboxylate-2- |

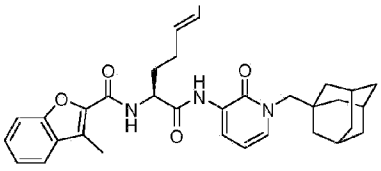
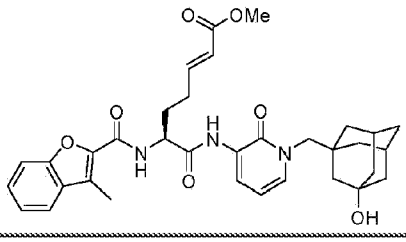
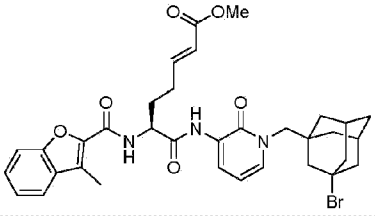
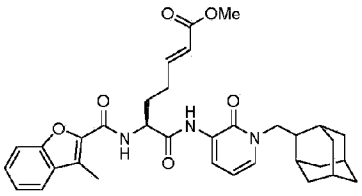
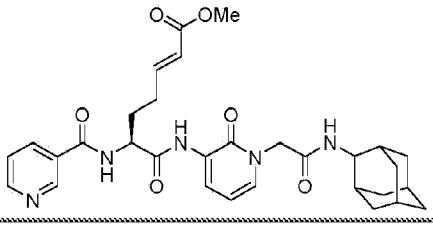
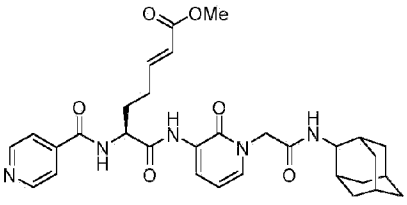
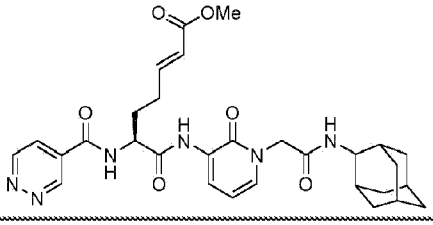
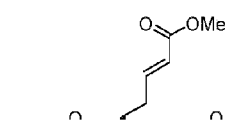
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| |  | amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-45:** |  | (S,E)-methyl 7-(1-(2-(1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-46:** |  | (S,E)-methyl 7-(1-(2-(3,5-dimethyladamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-47:** |  | (S,E)-methyl 7-(1-(2-(1-adamantyl(methyl)amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-48:** |  | (S,E)-methyl 7-(1-(2-(3-ethyladamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-49:** |  | (S,E)-methyl 7-(1-(2-(3-trifluoromethyladamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-50:** |  | (S,E)-methyl 7-(1-(2-(3-hydroxyadamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-** | | (S,E)-methyl 7-(1-(2-(3- |

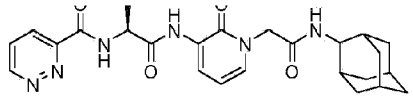
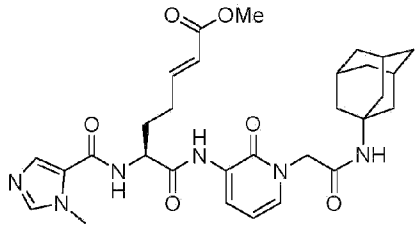
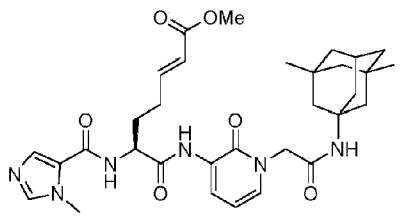
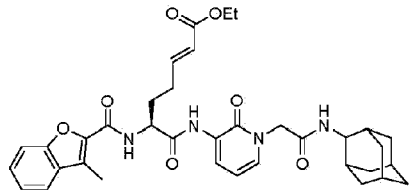
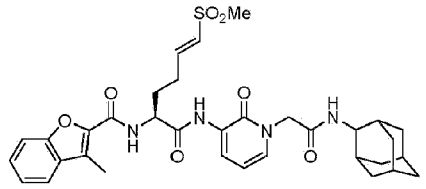
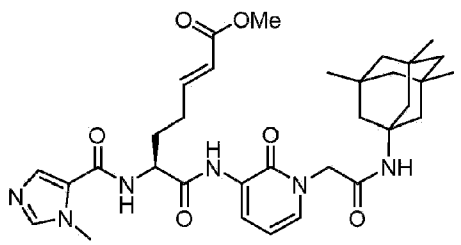
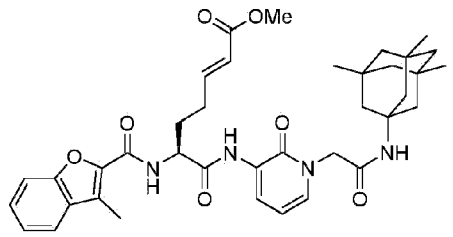
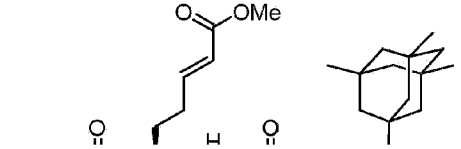
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| **51:** |  | fluoroadamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-52:** |  | (S,E)-methyl 7-(1-(2-(3-chloroadamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-53:** |  | (S,E)-methyl 7-(1-(2-(3-bromoadamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-54:** |  | (S,E)-methyl 7-(1-(2-(3-methyl adamantane-3-carboxylate-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-55:** |  | (S,E)-methyl 7-(1-(2-(4,4-difluoroadamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-56:** |  | (S,E)-methyl 7-(1-(2-(1-adamantylmethylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-57:** |  | (S,E)-methyl 7-(1-(2-(1-(1-adamantyl)ethanamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-** | | (S,E)-methyl7-(1-(2-((1R,2S,4S)- |

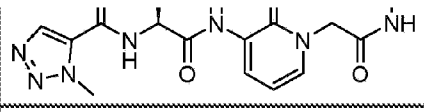
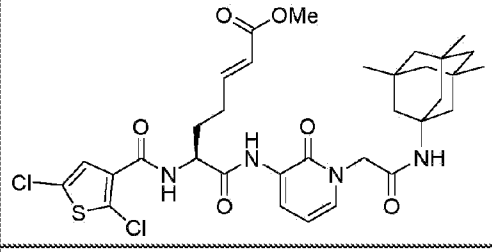
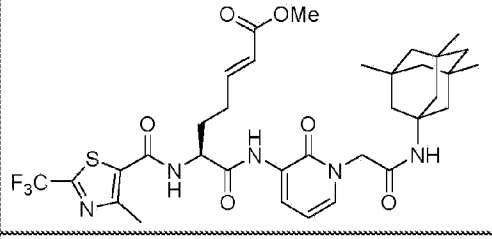
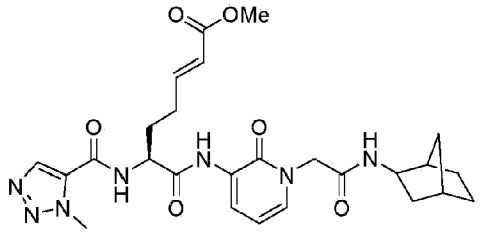
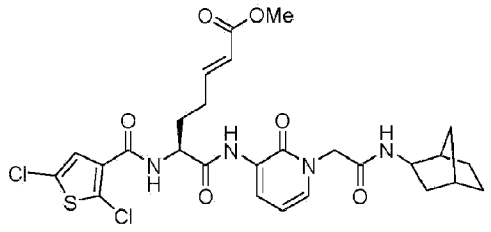
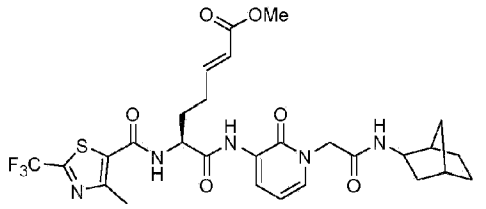
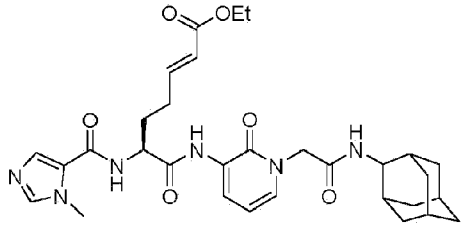
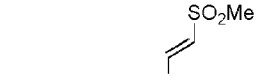
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| **58:** |  | bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-imidazole-5-carboxamido)-7-oxohept-2-enoate |
| **III-59:** |  | (S,E)-methyl 7-(1-(2-((1S,2R,4R)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-60:** |  | (S,E)-methyl 6-(1-methyl-1H-imidazole-5-carboxamido)-7-oxo-7-(2-oxo-1-(2-oxo-2-((1S,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-ylamino)hept-2-enoate |
| **III-61:** |  | (S, E)-methyl 6-(3-methylbenzofuran-2-carboxamido)-7-oxo-7-(2-oxo-1-(2-oxo-2-((1S,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-ylamino)hept-2-enoate |
| **III-62:** |  | (S,E)-methyl 7-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-imidazole-5-carboxamido)-7-oxohept-2-enoate |
| **III-63:** |  | (S,E)-methyl 7-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-64:** |  | (S,E)-methyl 7-(1-(2-(bicyclo[2.2.1]heptan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-** | | (S,E)-methyl 7-(1-(2- |

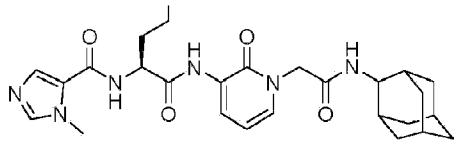
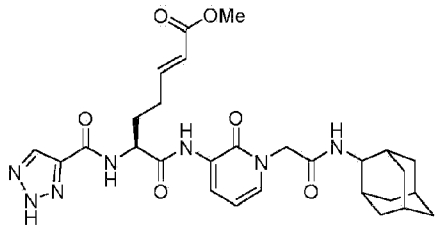
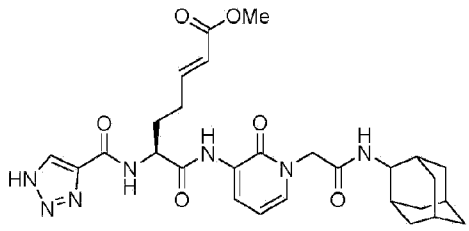
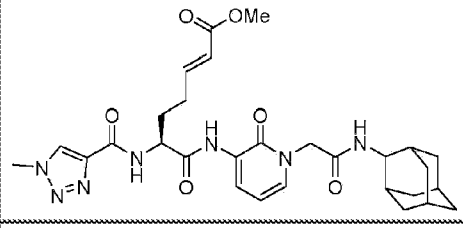
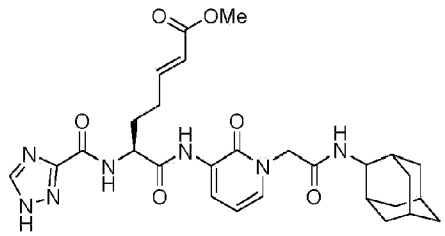
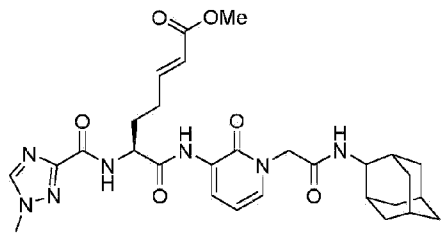
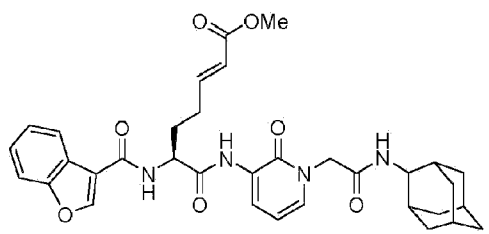
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| **65:** |  | (bicyclo[2.2.1]heptan-7-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-66:** |  | (S,E)-methyl 7-(1-(2-(bicyclo[2.2.1]hept-5-en-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-67:** |  | (6S,E)-methyl 7-(1-(2-(bicyclo[2.2.2]octan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-68:** |  | (S,E)-methyl 6-(3-methylbenzofuran-2-carboxamido)-7-oxo-7-(2-oxo-1-(2-oxo-2-((1R,2R,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-ylamino)hept-2-enoate |
| **III-69:** |  | (S,E)-methyl 6-(3-methylbenzofuran-2-carboxamido)-7-oxo-7-(2-oxo-1-(2-oxo-2-((1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylamino)ethyl)-1,2-dihydropyridin-3-ylamino)hept-2-enoate |
| **III-70:** |  | (S,E)-methyl 6-(3-methylbenzofuran-2-carboxamido)-7-oxo-7-(2-oxo-1-(2-oxo-2-((1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylamino)ethyl)-1,2-dihydropyridin-3-ylamino)hept-2-enoate |
| **III-71:** |  | (S,E)-methyl 7-(1-(2-(((1S,2R,5S)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-72:** |  | (S,E)-methyl 7-(1-(2-(4-homoisotwistane-3-amino)-2- |

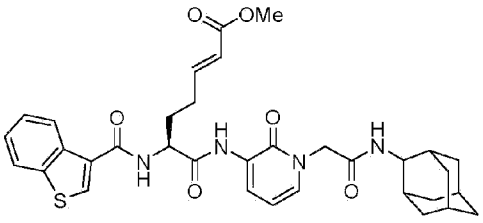
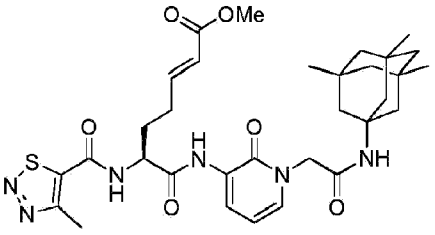
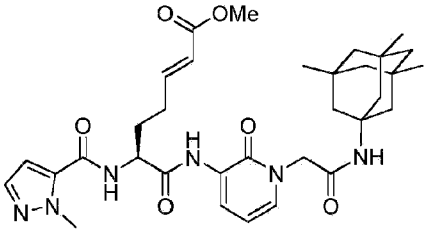
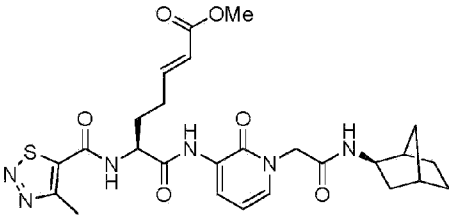
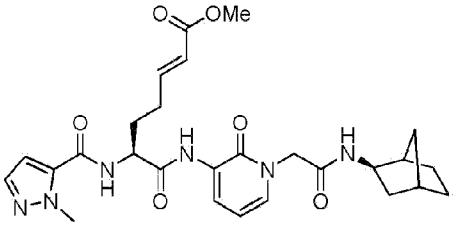
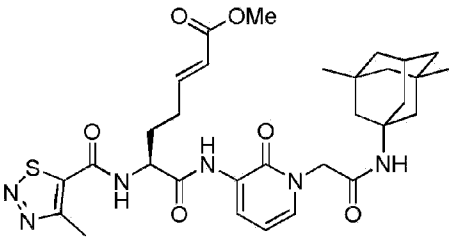
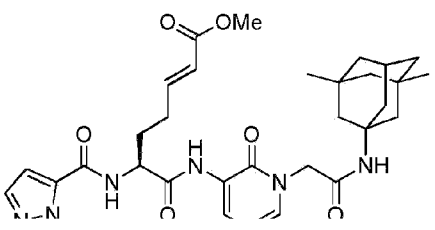
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| |  | oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-73:** |  | (S,E)-methyl 7-(1-(2-(diamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-74:** |  | (S,E)-methyl 7-(1-(2-(diamantane-4-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-75:** |  | (S,E)-N7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N1,N1-dimethyl-6-(3-methylbenzofuran-2-carboxamido)hept-2-enediamide |
| **III-76:** |  | (S,E)-N7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N1,N1-dimethyl-6-(1-methyl-1H-imidazole-5-carboxamido)hept-2-enediamide |
| **III-77:** |  | (S,E)-N7-(1-(2-(3,5-dimethyladamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N1,N1-dimethyl-6-(3-methylbenzofuran-2-carboxamido)hept-2-enediamide |
| **III-78:** |  | (S,E)-methyl 7-(1-(1-adamantylmethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-imidazole-5-carboxamido)-7-oxohept-2-enoate |
| **III-79:** |  | (S,E)-methyl 7-(1-(1-adamantylmethyl)-2-oxo-1,2- |

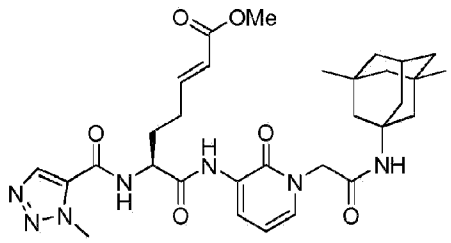
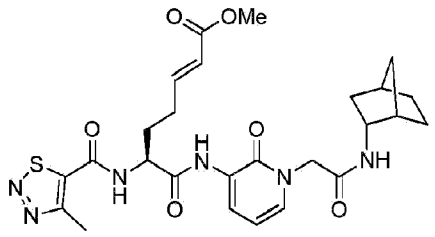
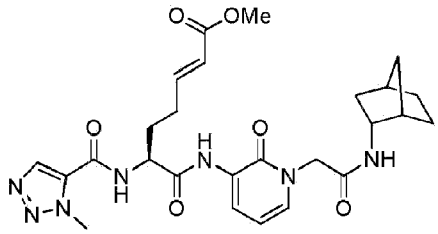
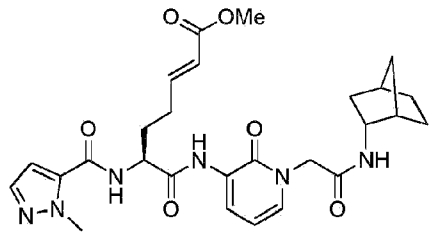
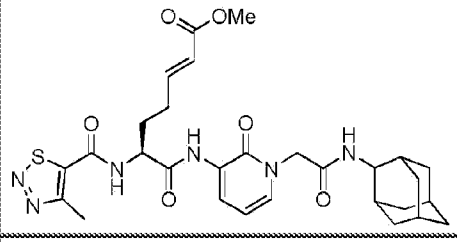
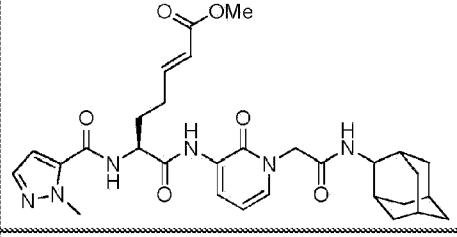
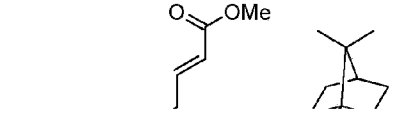
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| |  | dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-80:** |  | (6S,E)-methyl 7-(1-((3-hydroxy-1-adamantyl)methyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-81:** |  | (6S,E)-methyl 7-(1-((3-bromo-1-adamantyl)methyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-82:** |  | (S,E)-methyl 7-(1-(2-adamantylmethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-83:** |  | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(nicotinamido)-7-oxohept-2-enoate |
| **III-84:** |  | (S,E)-methyl 6-(isonicotinamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate |
| **III-85:** |  | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(pyridazine-4-carboxamido)hept-2-enoate |
| **III-86:** |  | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(pyridazine-3-carboxamido)hept-2- |

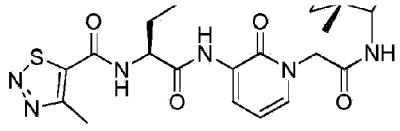
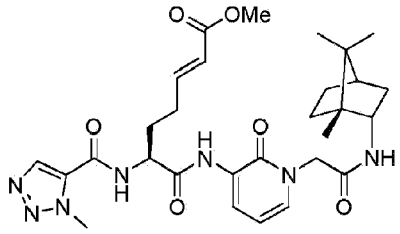
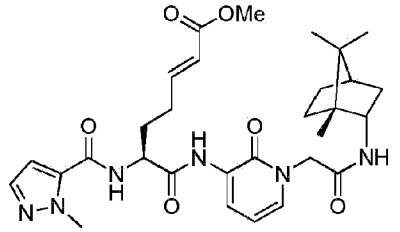
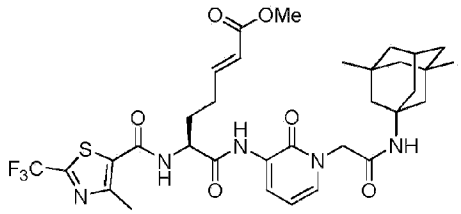
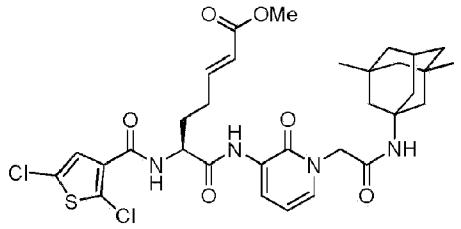
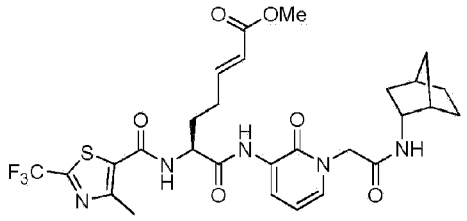
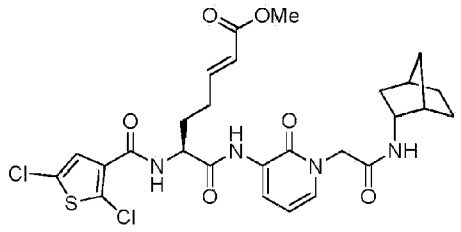
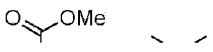
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| |  | enoate |
| **III-87:** |  | (S,E)-methyl 7-(1-(2-(1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-imidazole-2-carboxamido)-7-oxohept-2-enoate |
| **III-88:** |  | (S,E)-methyl 7-(1-(2-(3,5-dimethyladamantane)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-imidazole-5-carboxamido)-7-oxohept-2-enoate |
| **III-89:** |  | (S,E)-ethyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-90:** |  | (S,E)-N-(1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(methylsulfonyl)-1-oxohex-5-en-2-yl)-3-methylbenzofuran-2-carboxamide |
| **III-91**: |  | (S,E)-methyl 7-(1-(2-(3,5,7-trimethyl-1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-imidazole-5-carboxamido)-7-oxohept-2-enoate |
| **III-92** |  | (S,E)-methyl 7-(1-(2-(3,5,7-trimethyl-1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-93** |  | (S,E)-methyl 7-(1-(2-(3,5,7-trimethyl-1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-1,2,3-triazole-5-carboxamido)-7-oxohept-2-enoate |

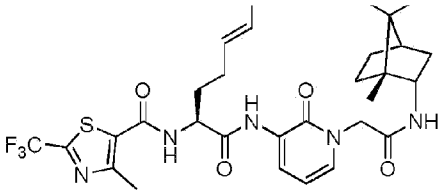
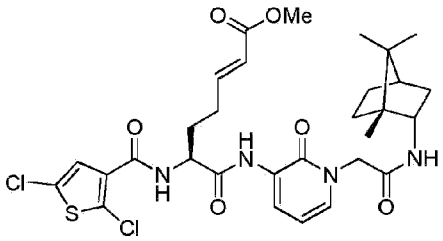
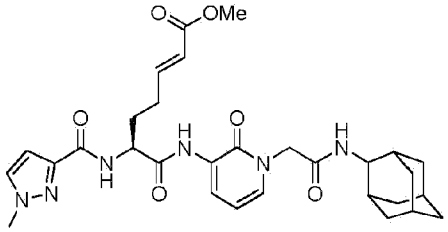
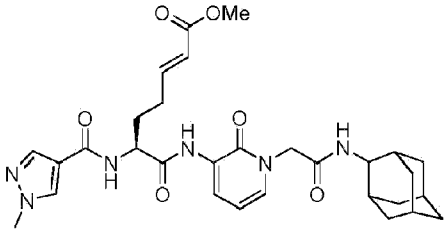
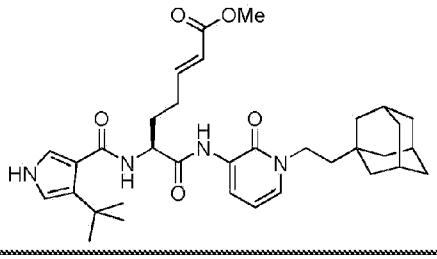
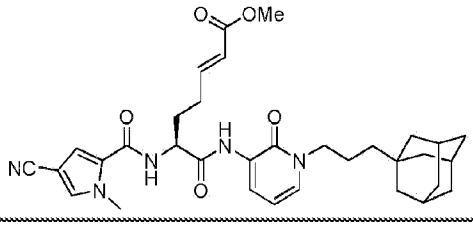
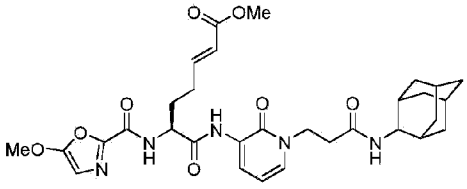
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| III-94 |  | (S,E)-methyl 6-(2,5-dichlorothiophene-3-carboxamido)-7-(1-(2-(3,5,7-trimethyl-1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate |
| III-95 |  | (S,E)-methyl 7-(1-(2-(3,5,7-trimethyl-1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-methyl-2-(trifluoromethyl)thiazole-5-carboxamido)-7-oxohept-2-enoate |
| III-96 |  | (6S, E)-methyl 7-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-1,2,3-triazole-5-carboxamido)-7-oxohept-2-enoate |
| III-97 |  | (6S, E)-methyl 7-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(2,5-dichlorothiophene-3-carboxamido)-7-oxohept-2-enoate |
| III-98 |  | (6S,E)-methyl 7-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-methyl-2-(trifluoromethyl)thiazole-5-carboxamido)-7-oxohept-2-enoate |
| III-99 |  | (S,E)-ethyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-imidazole-5-carboxamido)-7-oxohept-2-enoate |
| III-100 |  | (S,E)-N-(1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6- |

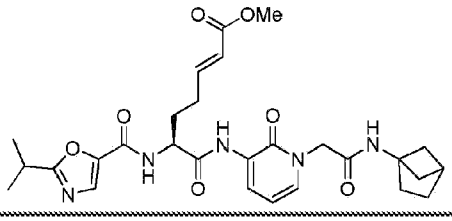
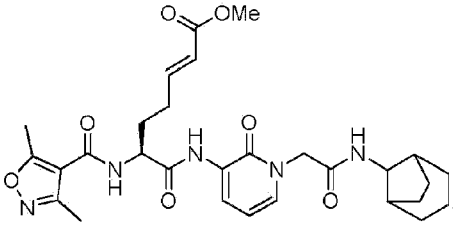
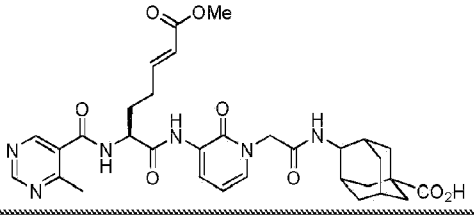
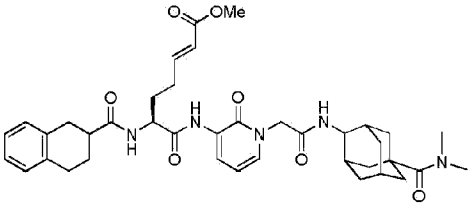
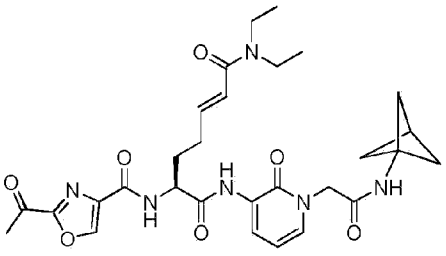
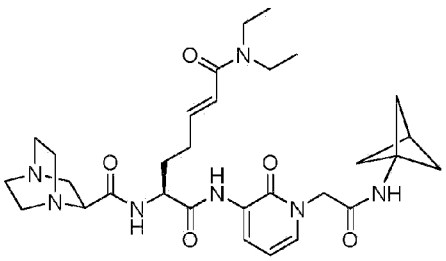
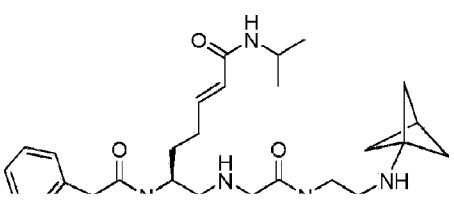
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|---|---|---|
| |  | (methylsulfonyl)-1-oxohex-5-en-2-yl)-1-methyl-1H-imidazole-5-carboxamide |
| **III-101** |  | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(2H-1,2,3-triazole-4-carboxamido)hept-2-enoate |
| **III-102** |  | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(1H-1,2,3-triazole-4-carboxamido)hept-2-enoate |
| **III-103** |  | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-1,2,3-triazole-4-carboxamido)-7-oxohept-2-enoate |
| **III-104** |  | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(1H-1,2,4-triazole-3-carboxamido)hept-2-enoate |
| **III-105** |  | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-1,2,4-triazole-3-carboxamido)-7-oxohept-2-enoate |
| **III-106** |  | (S,E)-methyl 6-(benzofuran-3-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate |
| **III-** | | (S,E)-methyl 6-(benzo[b]thiophene- |

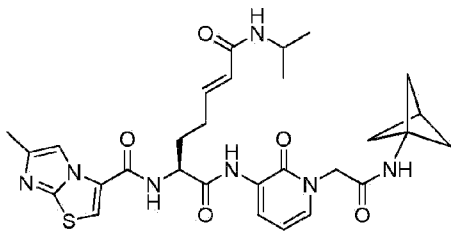
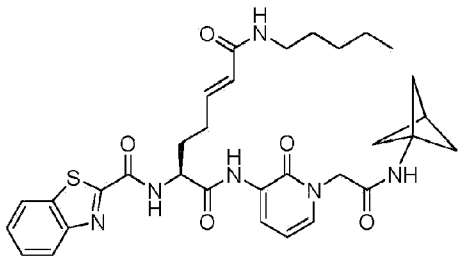
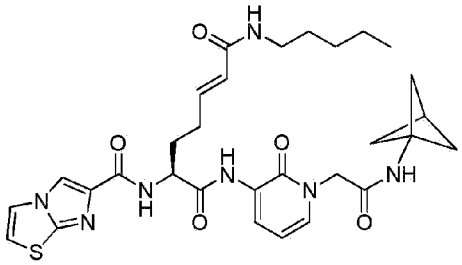
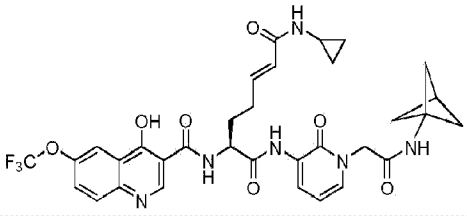
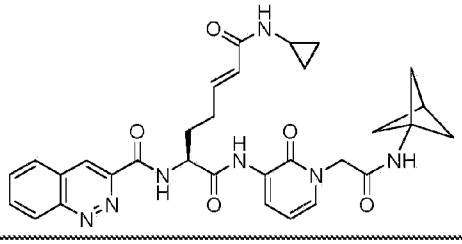
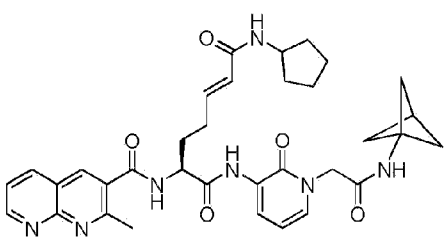
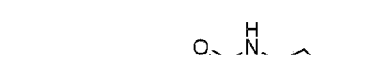
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| **107** |  | 3-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate |
| **III-108** |  | (S,E)-methyl 7-(1-(2-(3,5,7-trimethyl-1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-methyl-1,2,3-thiadiazole-5-carboxamido)-7-oxohept-2-enoate |
| **III-109** |  | (S,E)-methyl 7-(1-(2-(3,5,7-trimethyl-1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-pyrazole-5-carboxamido)-7-oxohept-2-enoate |
| **III-110** |  | (S,E)-methyl 7-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-methyl-1,2,3-thiadiazole-5-carboxamido)-7-oxohept-2-enoate |
| **III-111** |  | (S,E)-methyl 7-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-pyrazole-5-carboxamido)-7-oxohept-2-enoate |
| **III-112** |  | (S,E)-methyl 7-(1-(2-(3,5-dimethyladamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-methyl-1,2,3-thiadiazole-5-carboxamido)-7-oxohept-2-enoate |
| **III-113** |  | (S,E)-methyl 7-(1-(2-(3,5-dimethyladamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-pyrazole-5-carboxamido)-7-oxohept-2-enoate |

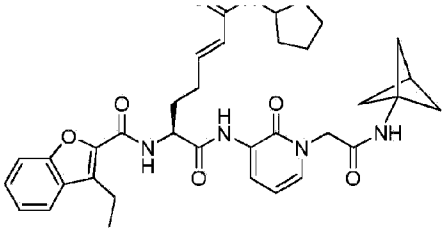
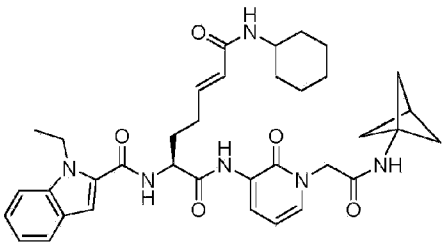
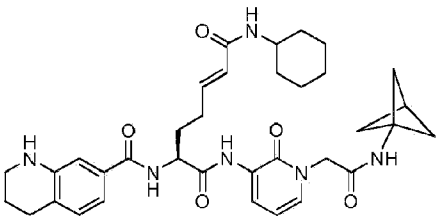
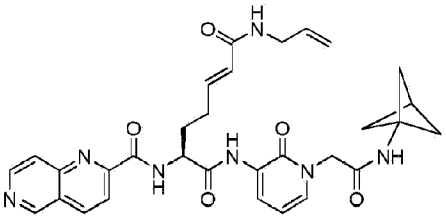
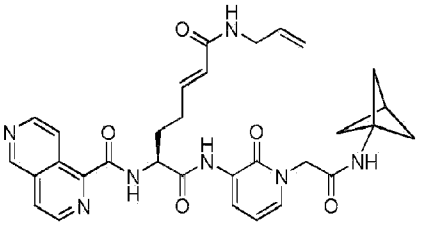
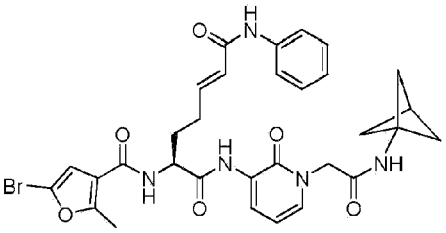
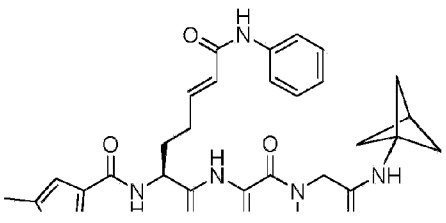
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| III-114 |  | (S,E)-methyl 7-(1-(2-(3,5-dimethyladamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-1,2,3-triazole-5-carboxamido)-7-oxohept-2-enoate |
| III-115 |  | (S,E)-methyl 7-(1-(2-((1S,2R,4R)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-methyl-1,2,3-thiadiazole-5-carboxamido)-7-oxohept-2-enoate |
| III-116 |  | (S,E)-methyl 7-(1-(2-((1S,2R,4R)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-1,2,3-triazole-5-carboxamido)-7-oxohept-2-enoate |
| III-117 |  | (S,E)-methyl 7-(1-(2-((1S,2R,4R)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-pyrazole-5-carboxamido)-7-oxohept-2-enoate |
| III-118 |  | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-methyl-1,2,3-thiadiazole-5-carboxamido)-7-oxohept-2-enoate |
| III-119 |  | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-pyrazole-5-carboxamido)-7-oxohept-2-enoate |
| III-120 |  | (S,E)-methyl 6-(4-methyl-1,2,3-thiadiazole-5-carboxamido)-7-oxo-7-(2-oxo-1-(2-oxo-2-((1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2- |

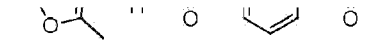
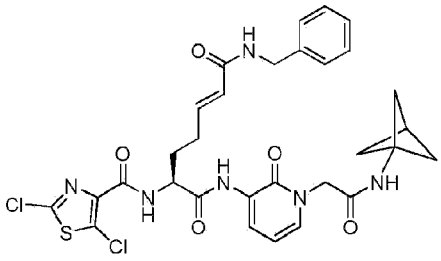
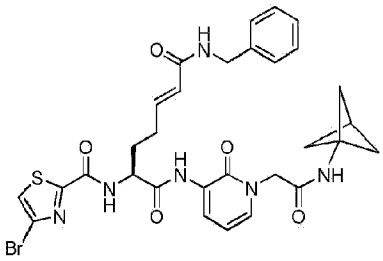
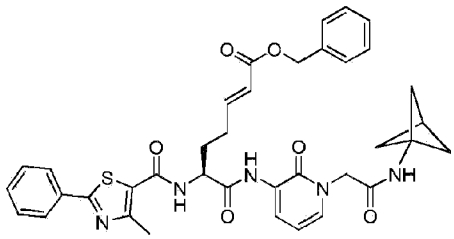
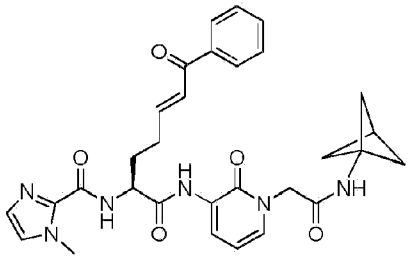
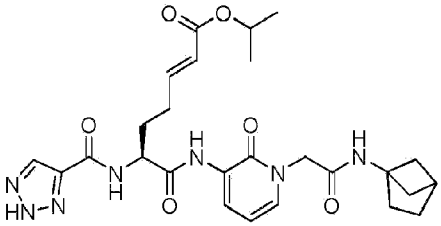
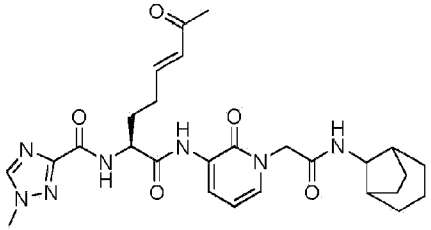
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| |  | ylamino)ethyl)-1,2-dihydropyridin-3-ylamino)hept-2-enoate |
| III-121 |  | (S,E)-methyl 6-(1-methyl-1H-1,2,3-triazole-5-carboxamido)-7-oxo-7-(2-oxo-1-(2-oxo-2-((1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-ylamino)hept-2-enoate |
| III-122 |  | (S,E)-methyl 6-(1-methyl-1H-pyrazole-5-carboxamido)-7-oxo-7-(2-oxo-1-(2-oxo-2-((1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-ylamino)hept-2-enoate |
| III-123 |  | (S,E)-methyl 7-(1-(2-(3,5-dimethyladamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-methyl-2-(trifluoromethyl)thiazole-5-carboxamido)-7-oxohept-2-enoate |
| III-124 |  | (S,E)-methyl 6-(2,5-dichlorothiophene-3-carboxamido)-7-(1-(2-(3,5-dimethyladamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate |
| III-125 |  | (S, E)-methyl 7-(1-(2-((1S,2R,4R)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-methyl-2-(trifluoromethyl)thiazole-5-carboxamido)-7-oxohept-2-enoate |
| III-126 |  | (S,E)-methyl 7-(1-(2-((1S,2R,4R)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(2,5-dichlorothiophene-3-carboxamido)-7-oxohept-2-enoate |
| III-127 |  | (S,E)-methyl 6-(4-methyl-2-(trifluoromethyl)thiazole-5- |

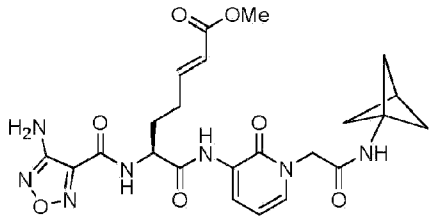
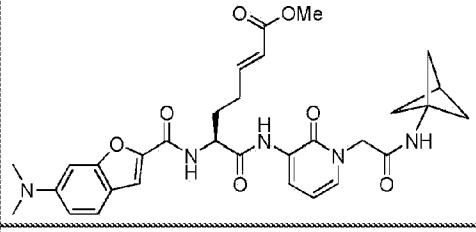
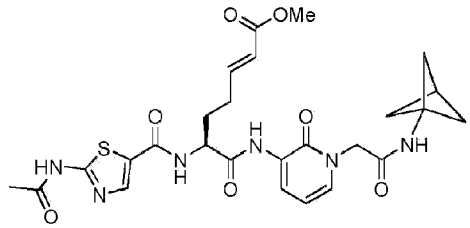
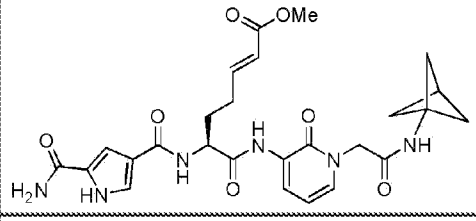
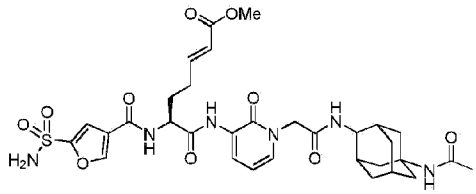
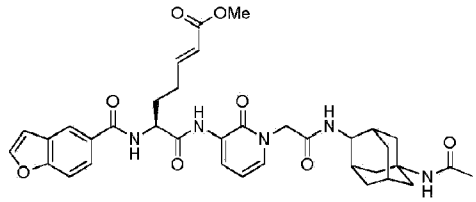
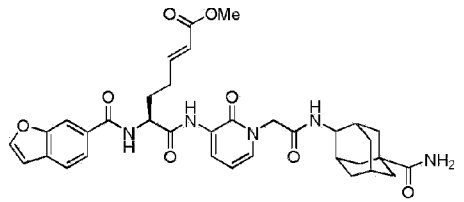
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| |  | carboxamido)-7-oxo-7-(2-oxo-1-(2-oxo-2-((1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-ylamino)hept-2-enoate |
| **III-128** |  | (S,E)-methyl 6-(2,5-dichlorothiophene-3-carboxamido)-7-oxo-7-(2-oxo-1-(2-oxo-2-((1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-ylamino)hept-2-enoate |
| **III-129** |  | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-pyrazole-3-carboxamido)-7-oxohept-2-enoate |
| **III-130** |  | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-pyrazole-4-carboxamido)-7-oxohept-2-enoate |
| **III-131** |  | (S,E)-methyl 6-(4-tert-butyl-1H-pyrrole-3-carboxamido)-7-(1-(2-(1-adamantylamino)ethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate |
| **III-132** |  | (S,E)-methyl 6-(4-cyano-1-methyl-1H-pyrrole-2-carboxamido)-7-(1-(3-(1-adamantylamino)propyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate |
| **III-133** |  | (S,E)-methyl 7-(1-(3-(2-adamantylamino)-3-oxopropyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(5-methoxyoxazole-2-carboxamido)-7-oxohept-2-enoate |

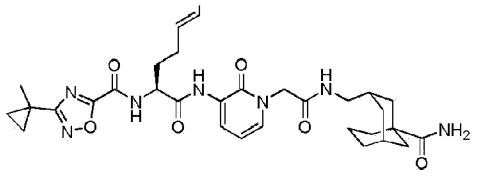
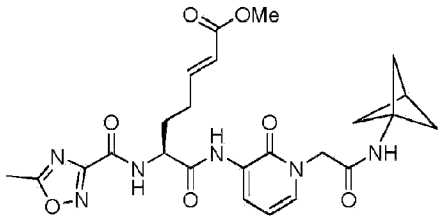
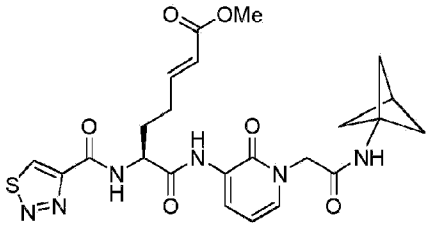
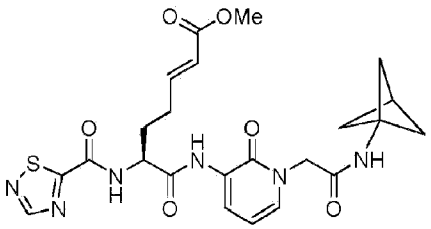
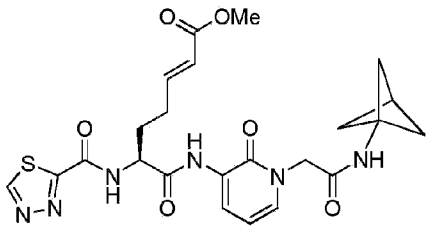
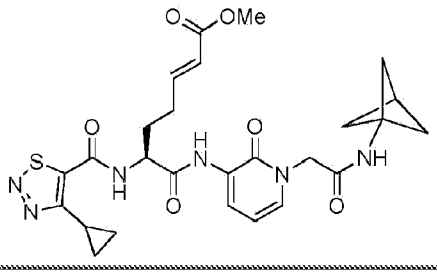
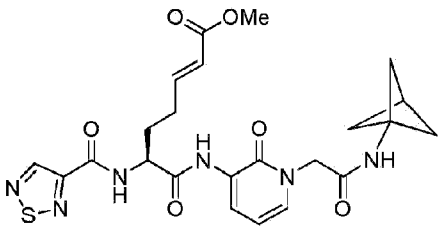
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| III-134 |  | (S,E)-methyl 7-(1-(2-(bicyclo[2.1.1]hexan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(2-isopropyloxazole-5-carboxamido)-7-oxohept-2-enoate |
| III-135 |  | (6S,E)-methyl 7-(1-(2-(bicyclo[3.2.1]octan-8-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3,5-dimethylisoxazole-4-carboxamido)-7-oxohept-2-enoate |
| III-136 |  | (S,E)-methyl 7-(1-(2-(5-carboxy-2-aminoadamantane)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-methylpyrimidine-5-carboxamido)-7-oxohept-2-enoate |
| III-137 |  | (6S,E)-methyl 7-(1-(2-(4-aminoadamantane-N,N-dimethyl-1-carboxamide)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(1,2,3,4-tetrahydronaphthalene-2-carboxamido)hept-2-enoate |
| III-138 |  | (S,E)-6-(2-acetyloxazole-4-carboxamido)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N1,N1-diethylhept-2-enediamide |
| III-139 |  | (S,E)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-6-((S)-1,4-diazabicyclo[2.2.2]octane-2-carboxamido)-N1,N1-diethylhept-2-enediamide |
| III-140 |  | (S,E)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-6-(1H-indole-3-carboxamido)-N1-isopropylhept-2-enediamide |

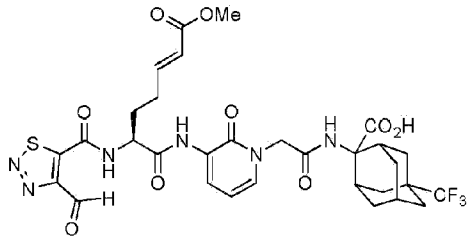
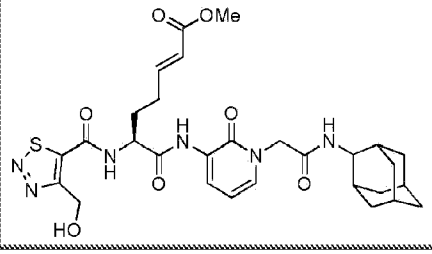
| | | |
|---|---|---|
| |  | |
| III-141 |  | (S,E)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N1-isopropyl-6-(6-methylimidazo[2,1-b]thiazole-3-carboxamido)hept-2-enediamide |
| III-142 |  | (S,E)-6-(benzo[d]thiazole-2-carboxamido)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N1-pentylhept-2-enediamide |
| III-143 |  | (S,E)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-6-(imidazo[2,1-b]th iazole-6-carboxam ido)-N 1-pentylhept-2-enediamide |
| III-144 |  | (S,E)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N1-cyclopropyl-6-(4-hydroxy-6-(trifluoromethoxy)quinoline-3-carboxamido)hept-2-enediamide |
| III-145 |  | (S,E)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-6-(cinnoline-3-carboxamido)-N1 -cyclopropyl hept-2-enediamide |
| III-146 |  | (S,E)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N1-cyclopentyl-6-(2-methyl-1,8-naphthyridine-3-carboxamido)hept-2-enediamide |
| III-147 |  | (S,E)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2- |

| | | |
|---|---|---|
| |  | dihydropyridin-3-yl)-N1-cyclopentyl-6-(3-ethylbenzofuran-2-carboxamido)hept-2-enediamide |
| **III-148** |  | (S,E)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N1-cyclohexyl-6-(1-ethyl-1H-indole-2-carboxamido)hept-2-enediamide |
| **III-149** |  | (S,E)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N1-cyclohexyl-6-(1,2,3,4-tetrahydroquinoline-7-carboxamido)hept-2-enediamide |
| **III-150** |  | (S,E)-N1-allyl-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-6-(1,6-naphthyridine-2-carboxamido)hept-2-enediamide |
| **III-151** |  | (S,E)-N1-allyl-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-6-(2,6-naphthyridine-1-carboxamido)hept-2-enediamide |
| **III-152** |  | (S,E)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-6-(5-bromo-2-methylfuran-3-carboxamido)-N1-phenylhept-2-enediamide |
| **III-153** |  | (S,E)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-6-(2,5-dimethylfuran-3-carboxamido)-N 1-phenylhept-2-enediamide |

| | | |
|---|---|---|
| |  | |
| III-154 |  | (S,E)-N1-benzyl-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-6-(2,5-dichlorothiazole-4-carboxamido)hept-2-enediamide |
| III-155 |  | (S,E)-N1-benzyl-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-6-(4-bromothiazole-2-carboxamido)hept-2-enediamide |
| III-156 |  | (S,E)-benzyl 7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-methyl-2-phenylthiazole-5-carboxamido)-7-oxohept-2-enoate |
| III-157 |  | (S,E)-N-(1-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-1,7-dioxo-7-phenylhept-5-en-2-yl)-1-methyl-1H-imidazole-2-carboxamide |
| III-158 |  | (S,E)-isopropyl 7-(1-(2-(bicyclo[2.1.1]hexan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(2H-1,2,3-triazole-4-carboxamido)hept-2-enoate |
| III-159 |  | N-((2S,E)-1-(1-(2-(bicyclo[3.2.1]octan-8-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-1,7-dioxooct-5-en-2-yl)-1-methyl-1H-1,2,4-triazole-3-carboxamide |
| III- | | (S,E)-methyl 6-(4-amino-1,2,5- |

| | | |
|---|---|---|
| **160** |  | oxadiazole-3-carboxamido)-7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate |
| **III-161** |  | (S,E)-methyl 7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(6-(dimethylamino)benzofuran-2-carboxamido)-7-oxohept-2-enoate |
| **III-162** |  | (S,E)-methyl 6-(2-acetamidothiazole-5-carboxamido)-7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate |
| **III-163** |  | (S,E)-methyl 7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(5-carbamoyl-1H-pyrrole-3-carboxamido)-7-oxohept-2-enoate |
| **III-164** |  | (S,E)-methyl 7-(1-(2-(1-acetylamino-4-aminoadamantane)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(5-sulfamoylfuran-3-carboxamido)hept-2-enoate |
| **III-165** |  | (S,E)-methyl 6-(benzofuran-5-carboxamido)-7-(1-(2-(1-acetylamino-4-aminoadamantane)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate |
| **III-166** |  | (S,E)-methyl 6-(benzofuran-6-carboxamido)-7-(1-(2-(4-aminoadamantane-1-carboxamide)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate |
| **III-167** |  | (S,E)-methyl 7-(1-(2-(4-aminoadamantane-1- |

| | | |
|---|---|---|
| |  | carboxamide)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-(1-methylcyclopropyl)-1,2,4-oxadiazole-5-carboxamido)-7-oxohept-2-enoate |
| **III-168** |  | (S,E)-methyl 7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(5-methyl-1,2,4-oxadiazole-3-carboxamido)-7-oxohept-2-enoate |
| **III-169** |  | (S,E)-methyl 7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(1,2,3-thiadiazole-4-carboxamido)hept-2-enoate |
| **III-170** |  | (S,E)-methyl 7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(1,2,4-thiadiazole-5-carboxamido)hept-2-enoate |
| **III-171** |  | (S,E)-methyl 7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(1,3,4-thiadiazole-2-carboxamido)hept-2-enoate |
| **III-172** |  | (S,E)-methyl 7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-cyclopropyl-1,2,3-thiadiazole-5-carboxamido)-7-oxohept-2-enoate |
| **III-173** |  | (S,E)-methyl 7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(1,2,5-thiadiazole-3-carboxamido)hept-2-enoate |

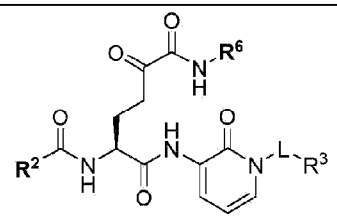
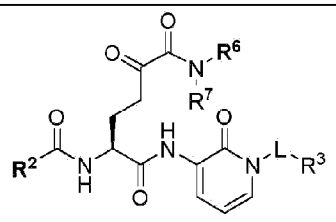
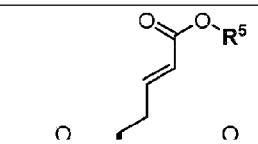
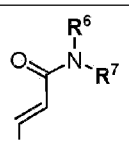
| | | |
|---|---|---|
| **III-174** |  | (S,E)-methyl 6-(4-formyl-1,2,3-thiadiazole-5-carboxamido)-7-(1-(2-(2-carboxy-2-amino-5-(trifluoromethyl)adamantane)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate |
| **III-175** |  | (S,E)-methyl 6-(4-(hydroxymethyl)-1,2,3-thiadiazole-5-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate |

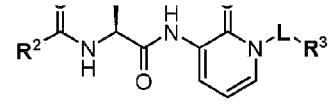
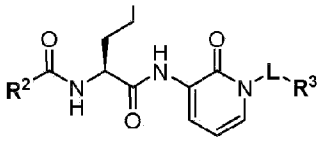
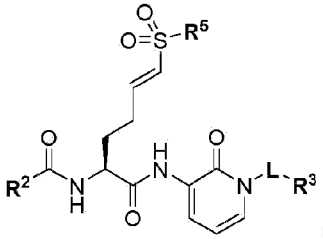
or a pharmaceutically acceptable salt thereof.

**[0043]** In very preferred embodiment the present invention refers to the compounds selected from the group consisting of: **III-1, III-2, III-3, III-4, III-5, III-6, III-7, III-8, III-9, III-10, III-11, III-12, III-13, III-14, III-15, III-16, III-17, III-18, III-19, III-20, III-21, III-22, III-23, III-24, III-25, III-26, III-27, III-29, III-30, III-31, III-32, III-33, III-34, III-35, III-36, III-37, III-38, III-39, III-40, III-41, III-42, III-43, III-44, III-45, III-46, III-48, III-49, III-50, III-51, III-52, III-53, III-54, III-55, III-56, III-57, III-58, III-59, III-60, III-61, III-62, III-63, III-64, III-65, III-66, III-67, III-68, III-69, III-70, III-71, III-72, III-73, III-74, III-75, III-76, III-77, III-83, III-84, III-85, III-86, III-87, III-88, III-89, III-90, III-91, III-92, III-93, III-94, III-95, III-96, III-97, III-98, III-99, III-100, III-101, III-102, III-103, III-104, III-105, III-106, III-107, III-108, III-109, III-110, III-111, III-112, III-113, III-114, III-115, III-116, III-117, III-118, III-119, III-120, III-121, III-122, III-123, III-124, III-125, III-126, III-127, III-128, III-129, III-130, III-134, III-135, III-140, III-142, III-145, III-147, III-148, III-150, III-152, III-153, III-155, III-165, III-166, III-169, III-170, III-171, III-172,** and **III-173**; or a pharmaceutically acceptable salt thereof.

**Method for production of inventive compounds**

**[0044]** In some embodiments, the present invention relates to a method for the synthesis of a compound of formula (**I**), especially any compound of any one of the formulae (**Ia**) - (**Ie**):

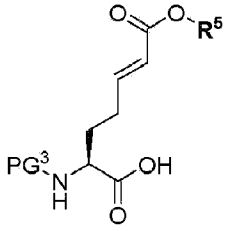
| | |
|---|---|
|  (**Ia**); |  (**Ib**) |
|  |  |

| | |
|---|---|
|  (Ic) |  (Id) |
|  (Ie) | |

**[0045]** A further aspect of the present invention relates to the production of compounds of the formula (**Ic**).

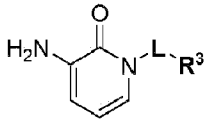
**[0046]** As shown in **Scheme 1**, the method for producing the compound of the formula (**Ic**): comprises the following steps in the following order:

**Step 1C**: providing a compound **4c**



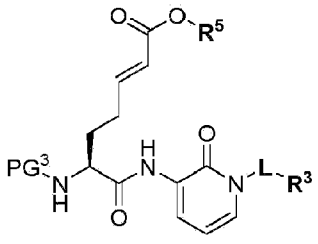
**4c**;

**Step 2C**: performing coupling reaction of the compound **4c** with a compound **5**



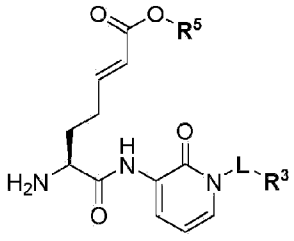
**5**

to obtain a compound 6c



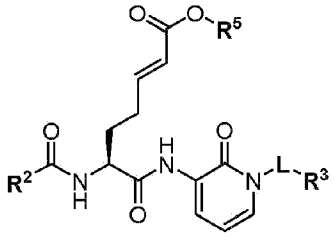
**6c**;

**Step** 3C: deprotecting an amino protecting group $PG^3$ to obtain a compound 7c



**7c**;

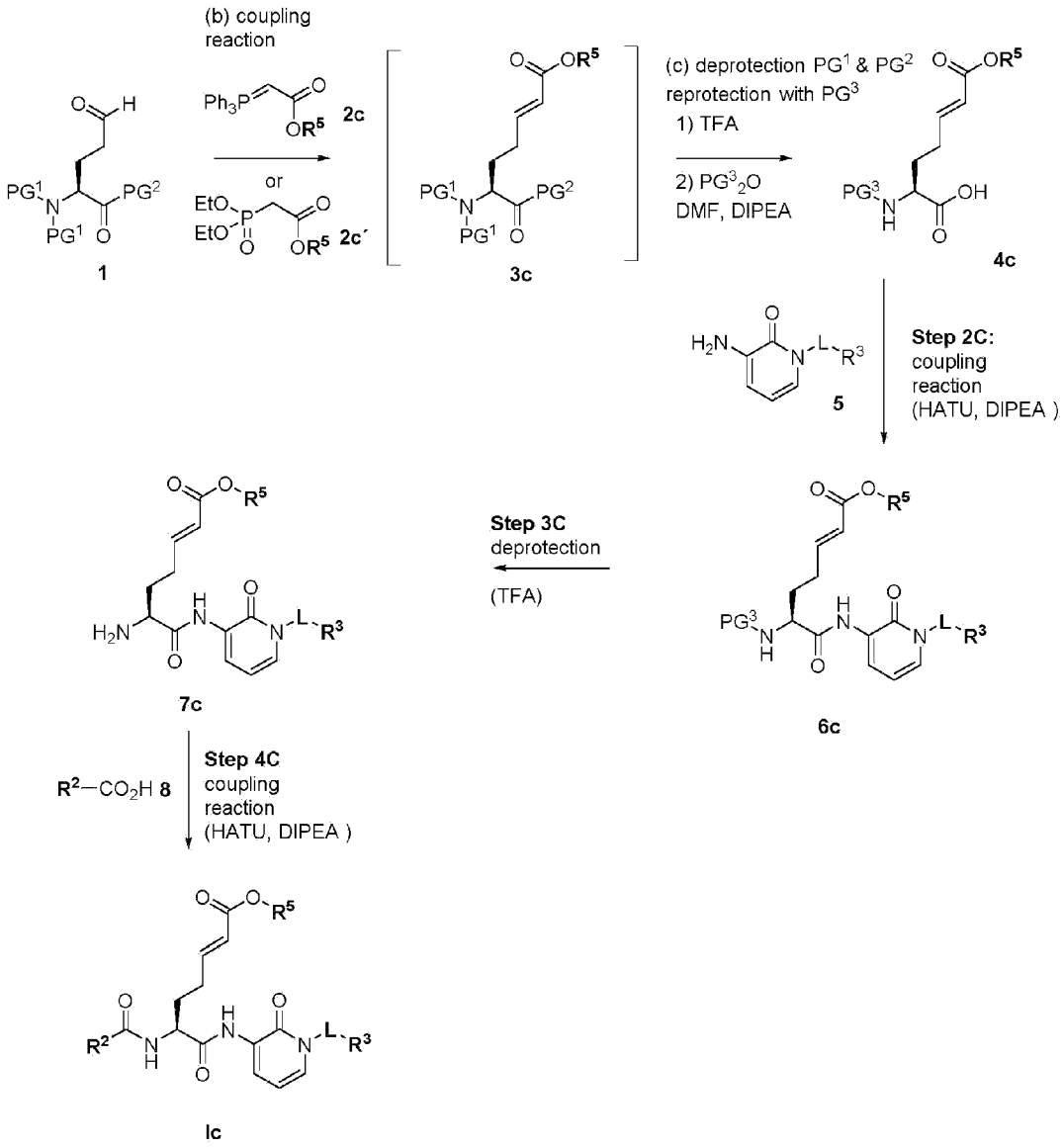
**Step 4C:** performing coupling reaction of the compound **7c** with a carboxylic acid ($R^2$-$CO_2H$ **8**) to produce the compound of the formula (**Ic**)



(**Ic**);

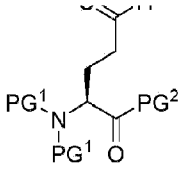
wherein **L**, $R^2$, $R^3$, $R^5$ have the same meanings as defined above above in formula (**Ic**), and $PG^3$ is an amino protecting group.

**Scheme 1**



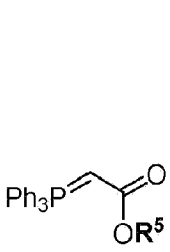

**[0047]** Optionally, Step **1C'** is carried out before the step **1C:**

1. (a) providing a protected aldehyde **1**

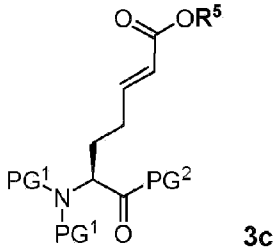


**1** ;

2. (b) performing a coupling reaction of the aldehyde **1** with a triphenyl phosphonium ylide **2c** to obtain an intermediate compound **3c;**



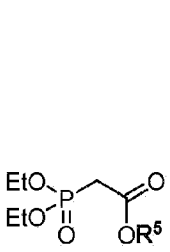
**2c**



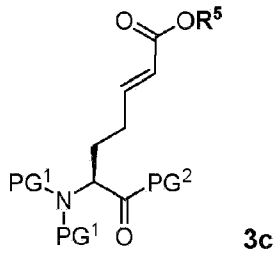
**3c**

or alternatively

(b') performing a coupling reaction of the aldehyde **1** with a phosphonate **2c**' to obtain an intermediate compound **3c;**



**2c´**



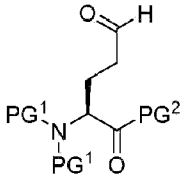
**3c**

3. (c) deprotecting the protecting groups $PG^1$ and $PG^2$ of the compound **3c** and introducing an amino protecting group $PG^3$ to obtain a compound **4c.**

**[0048]** Therefore, the following method for the production of compounds of the formula (**Ic**) is preferred:

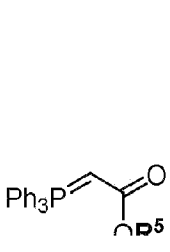
Step **1C':**

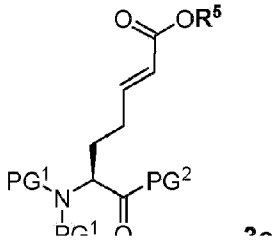
1. (a) providing a protected aldehyde **1**

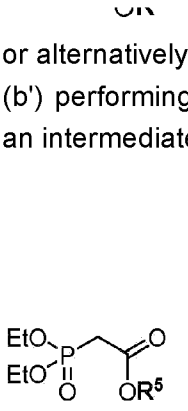


**1**;

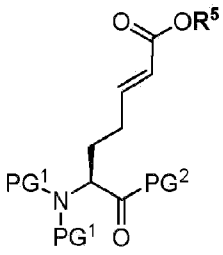
2. (b) performing a coupling reaction of the aldehyde **1** with a triphenyl phosphonium ylide **2c** to obtain an intermediate compound **3c;**








**2c'**

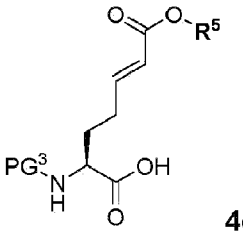



**3c**

or alternatively

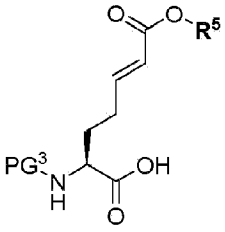
(b') performing a coupling reaction of the aldehyde **1** with a phosphonate **2c'** to obtain an intermediate compound **3c;**

3. (c) deprotecting the protecting groups $PG^1$ and $PG^2$ of the compound **3c** preferably under acidic condition and introducing an amino protecting group $PG^3$ to obtain a compound **4c**



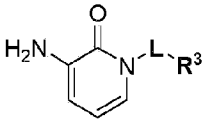

**4c;**

**Step 1C:** providing a compound **4c**



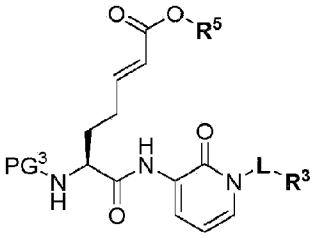

**4c;**

**Step** 2C: performing coupling reaction of the compound **4c** with a compound **5**



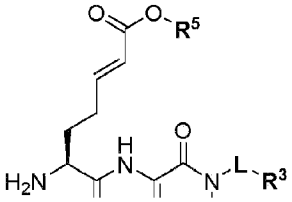

**5**

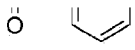
to obtain a compound **6c**




**6c;**

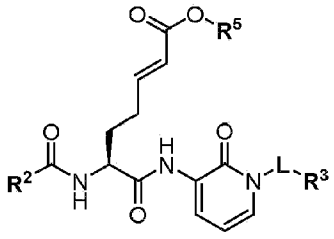
**Step 3C:** deprotecting an amino protecting group $PG^3$ to obtain a compound **7c**





**7c**;

**Step 4C:** performing coupling reaction of the compound **7c** with a carboxylic acid ($R^2$-$CO_2H$ **8**) to produce the compound of the formula **(Ic)**

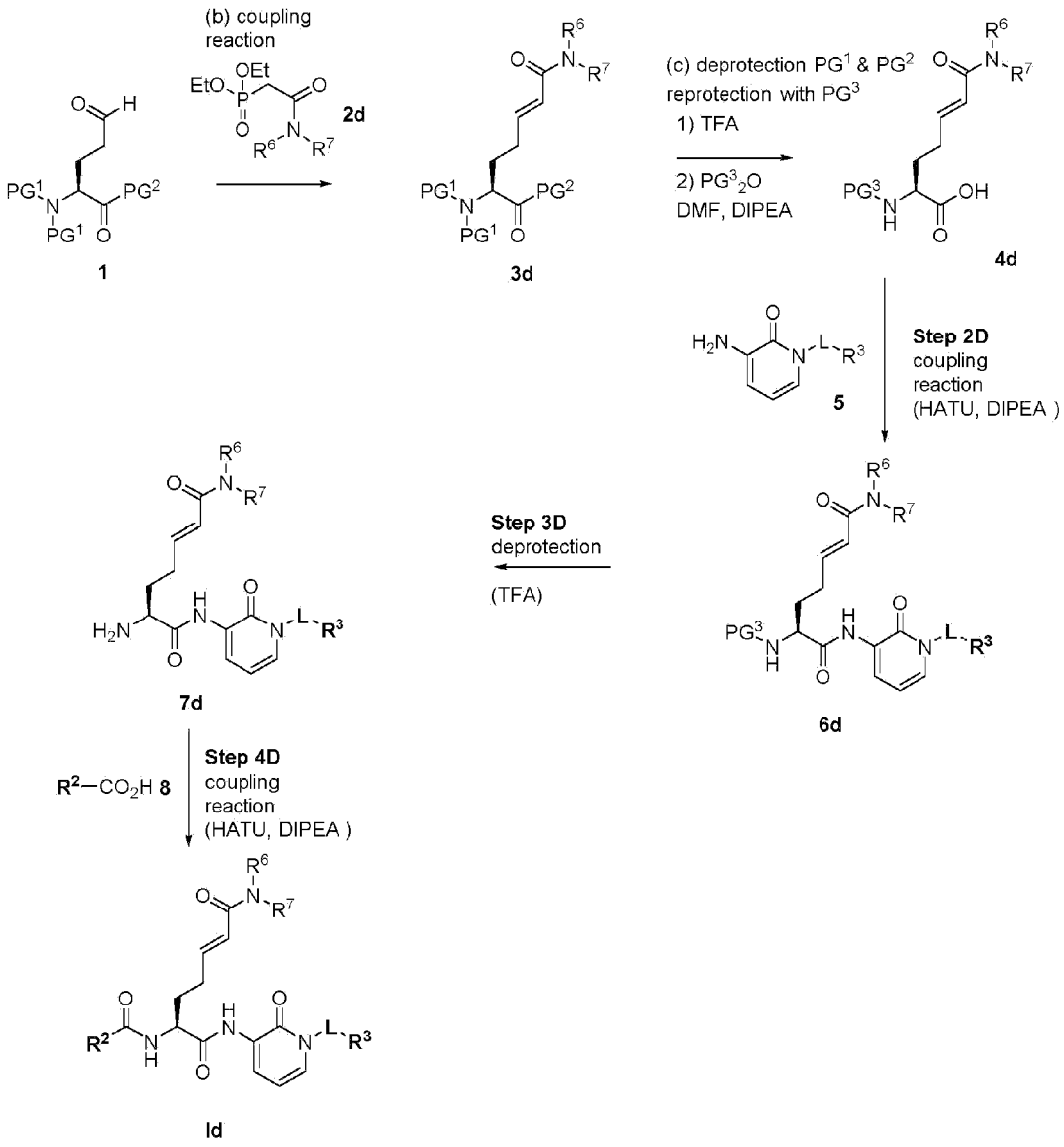


(**Ic**);

wherein **L**, $R^2$, $R^3$, $R^5$ have the same meanings as defined above in formula (**Ic**), and $PG^1$ and $PG^3$ are amino protecting groups,

$PG^2$ is a carboxyl protecting group.

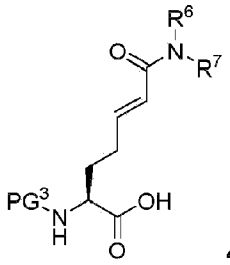
**Scheme 2**



**[0049]** A further aspect of the present invention relates to the production of compounds of the formula (**Id**).

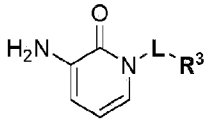
**[0050]** As shown in **Scheme 2,** a method for producing the compound of the formula (**Id**): comprising:

**Step 1D:** providing a compound **4d**



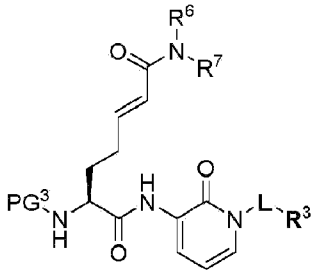
**4d**;

**Step 2D:** performing coupling reaction of the compound **4d** with a compound **5**



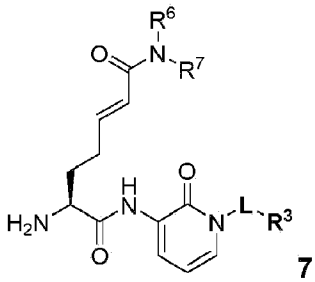
**5**

to obtain a compound **6d**



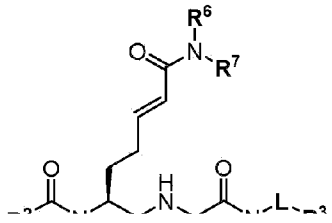
**6d**;

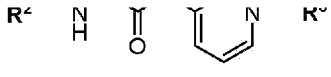
**Step 3D:** deprotecting an amino protecting group $PG^3$ to obtain a compound **7d**



**7d**;

**Step 4D:** performing coupling reaction of the compound **7d** with a carboxylic acid ($R^2$-$CO_2H$ **8**) to produce the compound of the formula (**Id**)

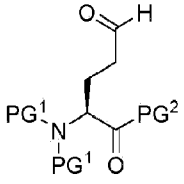



(**Id**) ;

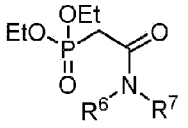
wherein **L**, $R^2$, $R^3$, $R^6$, $R^7$ have the same meanings as defined above in formula (**Id**), and $PG^3$ is an amino protecting group.

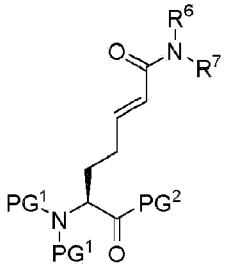
**[0051]** Optionally, Step **1D'** is carried out before the step **1D**:

1. (a) providing a protected aldehyde **1**

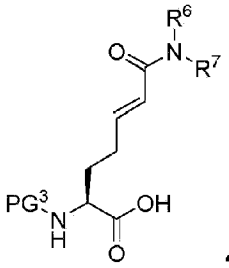

**1** ;

2. (b) performing a coupling reaction of the aldehyde **1** with a phosphonate **2d** to obtain an intermediate compound **3d;**


**2d**


**3d**

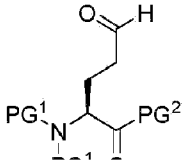
3. (c) deprotecting the protecting groups $PG^1$ and $PG^2$ of the compound **3d** preferably under acidic condition and introducing an amino protecting group $PG^3$ to obtain a compound **4d**


**4d**.

**[0052]** Therefore, the following method for the production of compounds of the formula (**Id**) is preferred:

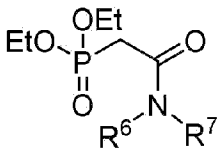
Step **1D'**:

1. (a) providing a protected aldehyde **1**

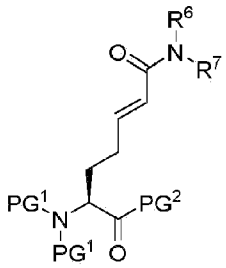


PG' O **1**;

2. (b) performing a coupling reaction of the aldehyde **1** with a phosphonate **2d** to obtain an intermediate compound **3d;**

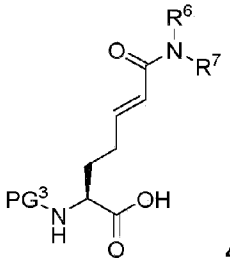


**2d**



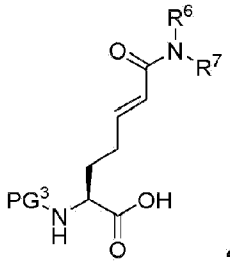
**3d**

3. (c) deprotecting the protecting groups $PG^1$ and $PG^2$ of the compound **3d** preferably under acidic condition and introducing an amino protecting group $PG^3$ to obtain a compound **4d**



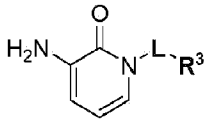
**4d**;

**Step** 1D: providing a compound **4d**



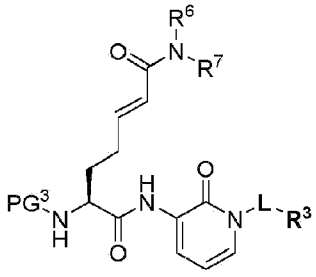
**4d**;

**Step 2D:** performing coupling reaction of the compound **4d** with a compound **5**



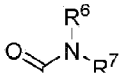
**5**

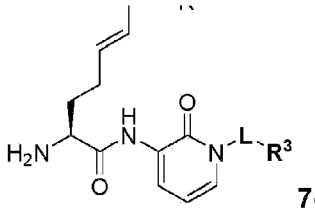
to obtain a compound **6d**



**6d**;

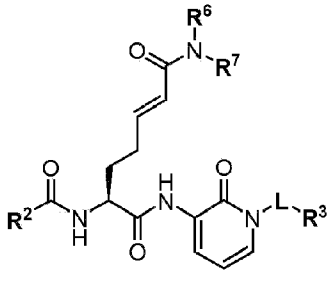
**Step 3D:** deprotecting an amino protecting group $PG^3$ to obtain a compound **7d**





**7d**;

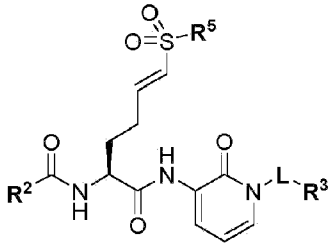
**Step 4D:** performing coupling reaction of the compound **7d** with a carboxylic acid ($R^2$-$CO_2H$ **8**) to produce the compound of the formula (**Id**)



(**Id**) ;

wherein **L**, $R^2$, $R^3$, $R^6$, $R^7$ have the same meanings as defined above in formula (**Id**), and $PG^3$ is an amino protecting group.

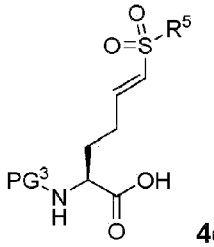
**[0053]** A further aspect of the present invention relates to the production of compounds of the formula (**Ie**).



(**Ie**)

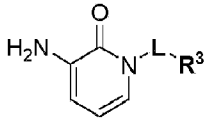
**[0054]** As shown in **Scheme 3,** a method for producing the compound of the formula (**Ie**): comprising:

**Step 1E:** providing a compound **4e**



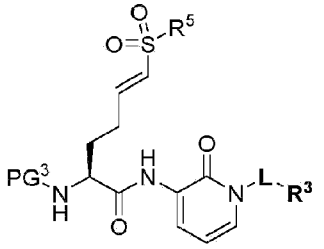
**4e**;

**Step** 2E: performing coupling reaction of the compound **4e** with a compound **5**



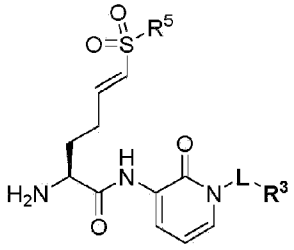
**5**

to obtain a compound 6e



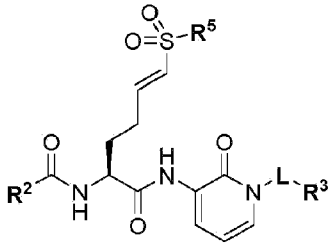
**6e**;

**Step 3E:** deprotecting an amino protecting group $PG^3$ to obtain a compound **7e**



**7e**;

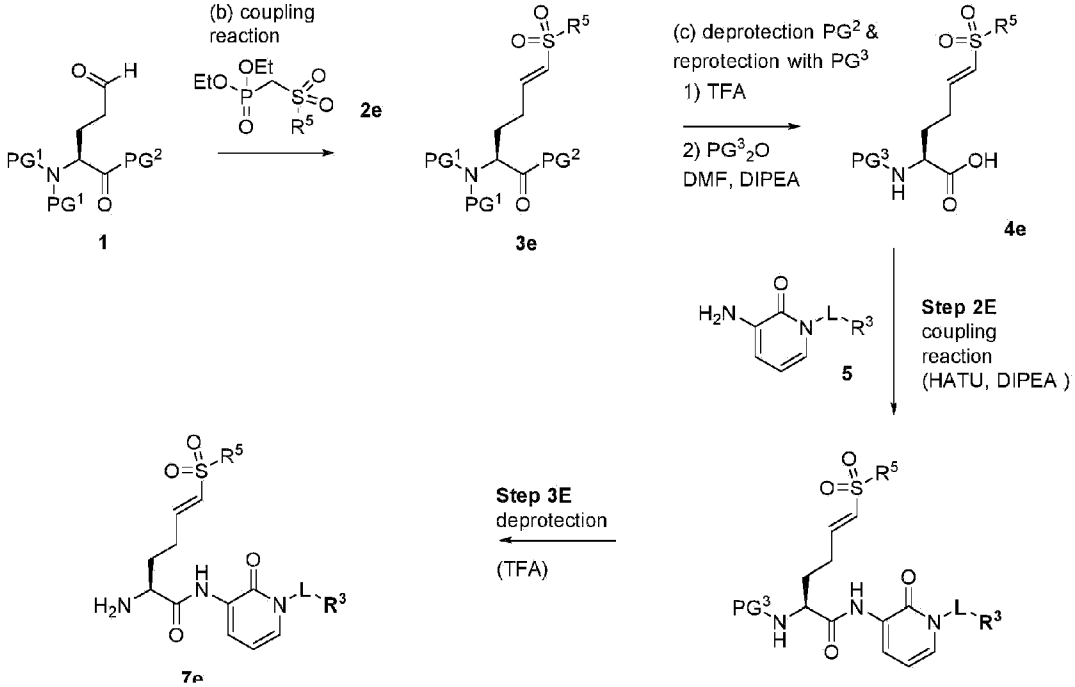
**Step 4E:** performing coupling reaction of the compound **7e** with a carboxylic acid ($R^2$-$CO_2H$ **8**) to produce the compound of the formula (**Ie**)

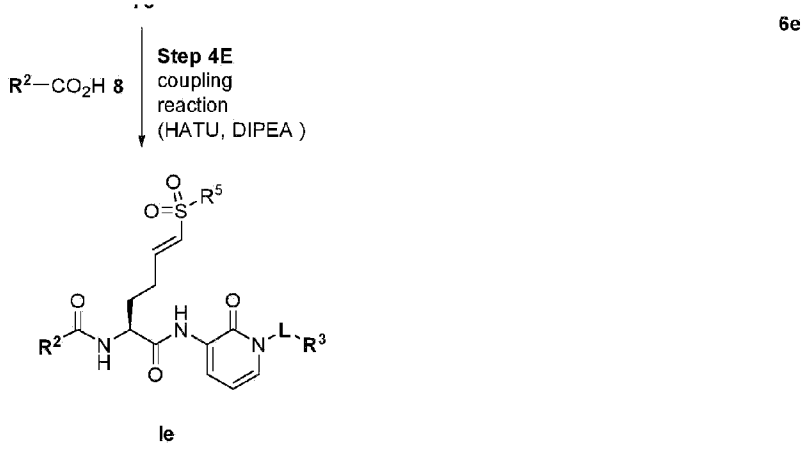


(**Ie**)

wherein **L**, $R^2$, $R^3$, $R^5$ have the same meanings as defined above in formula **(Ie),** and $PG^3$ is an amino protecting group.

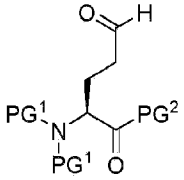
**Scheme 3**





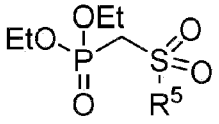

**[0055]** Optionally, Step **1E'** is carried out before the step **1E**:

1. (a) providing a protected aldehyde **1**

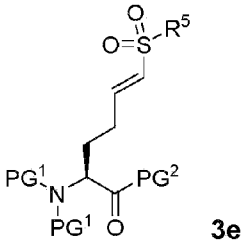



**1** ;

2. (b) performing a coupling reaction of the aldehyde **1** with a sulfonylmethyl phosphonate **2e** to obtain an intermediate compound **3e;**

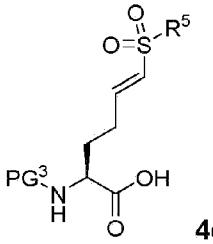



**2e**




**3e**

3. (c) deprotecting the protecting groups $PG^1$ and $PG^2$ of the compound **3e** preferably under acidic condition and introducing an amino protecting group $PG^3$ to obtain a compound **4e**

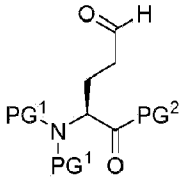



**4e**.

**[0056]** Therefore, the following method for the production of compounds of the formula **(Ie)** is preferred:

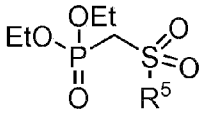
Step **1E'**:

1. (a) providing a protected aldehyde **1**

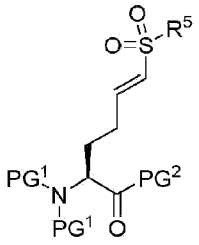


**1** ;

2. (b) performing a coupling reaction of the aldehyde **1** with a sulfonylmethyl phosphonate **2e** to obtain an intermediate compound **3e;**

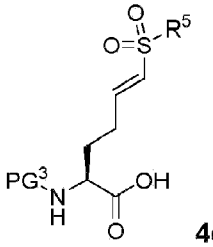


**2e**



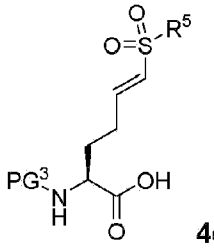
**3e**

3. (c) deprotecting the protecting groups $PG^1$ and $PG^2$ of the compound **3e** preferably under acidic condition and introducing an amino protecting group $PG^3$ to obtain a compound **4e**



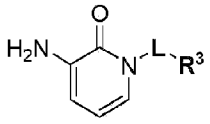
**4e**;

**Step** 1E: providing a compound **4e**



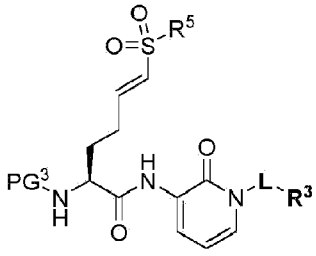
**4e**;

**Step** 2E: performing coupling reaction of the compound **4e** with a compound **5**



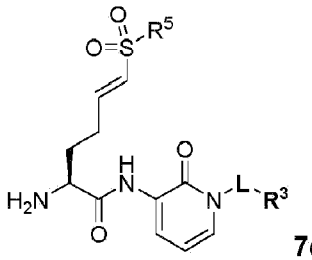
**5**

to obtain a compound 6e



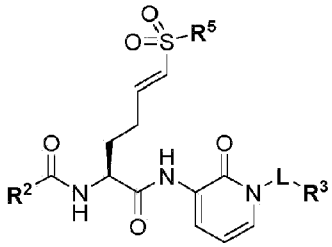
**6e**;

**Step 3E:** deprotecting an amino protecting group $PG^3$ to obtain a compound **7e**



**7e**;

**Step 4E:** performing coupling reaction of the compound **7e** with a carboxylic acid ($\mathbf{R^2}$-$CO_2H$ **8**) to produce the compound of the formula (**Ie**)



(**Ie**)

wherein **L**, $\mathbf{R^2}$, $\mathbf{R^3}$, $\mathbf{R^5}$ have the same meanings as defined above in formula **(Ie),** and $PG^3$ is an amino protecting group.

**[0057]** In an alternative route first all protecting groups $PG^1$ and $PG^2$ are simultaneously removed and the protecting group $PG^3$ is selectively introduced. Preferably, $PG^1$ and $PG^3$ are same.

**[0058]** The term "protecting groups" as used herein refers to commonly used protection groups in organic synthesis, preferably for amino and carboxyl groups. $PG^1$, $PG^3$, and $PG^5$ preferably are suitable protecting groups for amino groups. $PG^2$ and $PG^4$ preferably are suitable protecting groups for carboxyl groups. Preferably, $PG^1$, $PG^3$, and $PG^5$ may be selected from the group consisting of or comprising: acetyl, benzoyl, benzyloxycarbonyl (Cbz), tert-butylcarbonyl, tert-butyloxycarbonyl (Boc), and fluorenylmethylenoxy group (Fmoc). $PG^2$ and $PG^4$ may be selected from the group consisting of or comprising: methoxy, ethoxy, isobutoxy, tert-butoxy, benzyloxy; preferably, tert-butoxy group.

**[0059]** In Steps **2C, 2D, 2E, 4A, 4B, 4C, 4D,** and **4E,** to promote the coupling reaction with amino group of intermediate compound, activating reagents are commonly used to activating carboxylic acid ("Peptide Coupling Reagents, More than a Letter Soup", Ayman El-Faham and Fernando Albericio, Chemical Reviews, 2011, 111(11), p.6557-6602). The activation may be introduced separate reaction or *in situ* reaction. Preferably, any of the following coupling reagent can be used to activate carboxylic acid group: BOP (Benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate), PyBOP (Benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate), AOP (7-(Azabenzotriazol-1-yl)oxy

tris(dimethylamino)phosphonium hexafluorophosphate), PyAOP ((7-Azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate), TBTU (2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate), EEDQ (N-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline), Polyphosphoric Acid (PPA), DPPA (Diphenyl phosphoryl azide), HATU (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate), HBTU (O-Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate), HOBt (1-Hydroxybenzotriazole), HOAt (1-Hydroxy-7-azabenzotriazole), DCC (N,N'-Dicyclohexylcarbodiimide), EDC (or EDAC or EDCI, 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide), BOP-Cl (Bis(2-oxo-3-oxazolidinyl)phosphinic chloride), TFFH (Tetramethylfluoroformamidinium hexafluorophosphate), BroP (Bromo tris(dimethylamino) phosphonium hexafluorophosphate), PyBroP (Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate) and CIP (2-Chloro-1,3-dimethylimidazolidinium hexafluorophosphate), or further, similar acting reagents, providing an activated intermediate, or a mixture thereof.

**Pharmaceutical Composition & Medical Use**

**[0060]** Therefore another aspect of the present invention relates to compounds according to the general formula (**I**) as medicine as well as their use in medicine. Especially preferred is the use as inhibitors of transglutaminases, in particular transglutaminsase 2 (TG2).

**[0061]** Thus the compounds of formula (I) described herein or according to the present invention may be administered themselves or in form of a pharmacologically acceptable salt.

**[0062]** The compounds of the present invention may form of a pharmacologically acceptable salt with organic or inorganic acids or bases. Examples of suitable acids for such acid addition salt formation are hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, acetic acid, citric acid, oxalic acid, malonic acid, salicylic acid, p-aminosalicylic acid, malic acid, fumaric acid, succinic acid, ascorbic acid, maleic acid, sulfonic acid, phosphonic acid, perchloric acid, nitric acid, formic acid, propionic acid, gluconic acid, lactic acid, tartaric acid, hydroxymaleic acid, pyruvic acid, phenylacetic acid, benzoic acid, p-aminobenzoic acid, p-hydroxybenzoic acid, methanesulfonic acid, ethanesulfonic acid, nitrous acid, hydroxyethanesulfonic acid, ethylenesulfonic acid, p-toluenesulfonic acid, naphthylsulfonic acid, sulfanilic acid, camphorsulfonic acid, china acid, mandelic acid, o-methylmandelic acid, hydrogen-benzenesulfonic acid, picric acid, adipic acid, d-o-tolyltartaric acid, tartronic acid, (o, m, p)-toluic acid, naphthylamine sulfonic acid, trifluoroacetic acid, and other mineral or carboxylic acids well known to those skilled in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. Preferred is the mesylate salt, hydrochloride salt and the trifluoroacetate salt and especially preferred is the trifluoroacetate salt and the hydrochloride salt.

**[0063]** In the case the inventive compounds bear acidic groups, salts could also be formed with inorganic or organic bases. Examples for suitable inorganic or organic bases are, for

example, NaOH, KOH, $NH_4OH$, tetraalkylammonium hydroxide, lysine or arginine and the like. Salts may be prepared in a conventional manner using methods well known in the art, for example by treatment of a solution of the compound of the general formula (I) with a solution of an acid, selected out of the group mentioned above.

**Methods of Use**

**[0064]** In a further aspect of the present invention, the novel compounds according to the general formula (I) are used as pharmaceutically active agent, i.e. the compound of the formula (I) is used in medicine.

**[0065]** Furthermore, the present invention relates to a pharmaceutical composition comprising at least one compound according to the general formula (I), as an active ingredient or a pharmacologically acceptable salts thereof as an active ingredient, together with at least one pharmacologically acceptable carrier, excipient and/or diluent.

**[0066]** The compounds according to general formula (I) described herein are especially suitable for the treatment and prophylaxis of diseases associated with and/or caused by transglutaminase 2.

**[0067]** Celiac disease, a gluten intolerance is associated with tissue transglutaminase (TG 2). Another very important group of indications for tissue transglutaminase inhibitors are fibrotic disorders. Fibrotic disorders are characterized by the accumulation of crosslinked extracellular matrix proteins. Diabetic nephropathy, cystic fibrosis, idiopathic pulmonary fibrosis, kidney fibrosis as well as liver fibrosis belong to the most important fibrotic disorders to be addressed with the compounds disclosed.

**[0068]** In the biological example B-1, it is proven that the inventive compounds as reversible and irreversible TG inhibitors effectively inhibit the activity of TGs, especially TG2.

**[0069]** As used herein the term "inhibiting" or "inhibition" refers to the ability of a compound to downregulate, decrease, reduce, suppress, inactivate, or inhibit at least partially the activity of an enzyme, or the expression of an enzyme or protein.

**[0070]** Therefore, another aspect of the present invention is the use of the inventive compounds of the general formula (I), or the pharmaceutical composition thereof as described in the treatment or prophylaxis of autoimmune and inflammatory diseases, vascular diseases, fibrotic diseases, liver diseases, cholestatic liver diseases, cancer, neurodegenerative diseases, ocular diseases, and skin disorders.

**[0071]** Further aspects of the present invention relate to the use of the compounds of general formula (I) for the preparation of a pharmaceutical composition useful for prophylaxis and/or treatment of autoimmune and inflammatory diseases, vascular diseases, fibrotic diseases, liver

diseases, cholestatic liver diseases, cancer, neurodegenerative diseases, ocular diseases, and skin disorders.

**[0072]** In a further aspect of the present invention, a method for preventing and/or treating autoimmune and inflammatory diseases, vascular diseases, fibrotic diseases, liver diseases, cholestatic liver diseases, cancer, neurodegenerative diseases, ocular diseases, and skin disorders, which method comprises administering to a subject, in particular a human, a pharmaceutically effective amount of at least one compound of the general formula (I), to prevent and/or treat said autoimmune and inflammatory diseases, vascular diseases, fibrotic diseases, liver diseases, cholestatic liver diseases, cancer, neurodegenerative diseases, ocular diseases, and skin disorders.

**[0073]** Preferred, the autoimmune and inflammatory diseases comprises multiple sclerosis, celiac disease, Duhring-Brocq-disease (dermatitis herpetiformis), gluten ataxia, gluten neuropathy, diabetes, rheumatoid arthritis, Graves' disease, inflammatory bowel disease, systemic lupus erythematosus psoriasis, and gingivitis;

the vascular diseases comprise atherosclerosis, thrombosis, vascular stiffness;

the fibrotic diseases affecting the lung, the kidney, the liver, the skin or the gut like cystic fibrosis, kidney fibrosis and diabetic nephropathy, intestinal fibrosis, idiopathic lung fibrosis, liver fibrosis;

the liver diseases like alcoholic hepatitis, alcoholic steatohepatitis, nonalcoholic steatohepatitis, non-alcoholic fatty liver disease, liver cirrhosis, autoimmune hepatitis or liver inflammation;

the cholestatic liver diseases comprise primary biliary cholangitis and primary sclerosing cholangitis;

the cancer comprises glioblastoma, melanoma, pancreatic cancer, renal cell carcinoma, meningioma, and breast cancer,

the neurodegenerative diseases comprise Parkinson's disease, Huntington's disease, or Alzheimer's disease,

the ocular diseases comprise glaucoma, cataracts, macular degeneration, or uveitis; the skin disorders comprise acne, psoriasis, scarring, and skin aging.

**[0074]** More preferred, the compound of the formula (**I**), or the pharmaceutical composition thereof is useful in the treatment or prophylaxis of celiac disease.

**[0075]** Furthermore, the compounds of the general formula (**I**), can be administered in form of their pharmaceutically active salts, optionally using essentially non-toxic pharmaceutically acceptable carriers, adjuvants or extenders. Medications are prepared in a known manner in a

conventional solid or fluid carrier or in extenders and a conventional pharmaceutically acceptable adjuvant/expedient in a suitable dose. The preferred preparations are provided in an administrable form suitable for oral application, such as pills, tablets, film tablets, coated tablets, capsules and powders.

**[0076]** Tablets, film tablets, coated tablets, gelatin capsules and opaque capsules are the preferred pharmaceutical formulations. Any pharmaceutical compositions contains at least one compound of the general formula (I), and/or pharmaceutically acceptable salts thereof in an amount of 5 mg to 500 mg, preferably 10 mg to 250 mg and most preferred in an amount of 10 to 100 mg per formulation.

**[0077]** Besides, the object of the present invention also includes pharmaceutical preparations for oral, parenteral, dermal, intradermal, intragastric, intracutaneous, intravascular, intravenous, intramuscular, intraperitoneal, intranasal, intravaginal, intrabuccal, percutaneous, rectal, subcutaneous, sublingual, topic, transdermal or inhalative application, containing, in addition to typical vehicles and extenders, a compound of the general formula (I), and/or a pharmaceutically acceptable salt thereof as active component.

**[0078]** The pharmaceutical compositions of the present invention contain one of the compounds of the formula (I) disclosed herein as active component, typically mixed with suitable carrier materials, selected with respect to the intended form of administration, i.e. tablets to be administered orally, capsules (filled either with a solid, a semi-solid or a liquid), powders, orally administrable gels, elixirs, dispersible granulates, syrups, suspensions and the like in accordance with conventional pharmaceutical practices. For example, the compound of the formula (I) can as active agent component be combined with any oral, non-toxic, pharmaceutically acceptable, inert carrier, such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, talc, mannitol, ethyl alcohol (liquid forms) and the like for the oral administration in form of tablets or capsules. Moreover, suitable binders, lubricants, disintegrants and colorants can be added to the mixture if required. Powders and tablets can consist of said inert carriers to an extent from about 5% per weight to about 95% per weight of the inventive composition.

**[0079]** Suitable binders include starch, gelatin, natural sugars, sweeteners made of corn, natural and synthetic gums, such as acacia gum, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Possible lubricants for the use in said dosage forms include boric acid, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrants include starch, methylcellulose, cyclodextrins, guar gum and the like. If required, sweeteners and flavor additives and preservatives can also be included. Some of the terms used above, namely disintegrants, extenders, lubricants, binders and the like are discussed in greater detail below.

**[0080]** Additionally, the compositions of the present invention can be formulated in a form with sustained release to provide a controlled release rate of any one or more components or active components, in order to optimize the therapeutic effect, i.e. the inhibitory activity and the

like. Suitable dosage forms for sustained release include layered tablets containing layers with varying degradation rates or controlled release polymeric matrices impregnated with the active components and in the form of a tablet or capsule containing such impregnated or encapsulated porous polymeric matrices.

**[0081]** Preparations in fluid form include solutions, suspensions and emulsions. Exemplarily mentioned are water or water propylene glycol solutions for parenteral injections or the addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions.

**[0082]** Aerosol preparations suitable for inhalation may include solutions and solids in the form of powders which can be combined with a pharmaceutically acceptable carrier, such as a compressed inert gas, e.g. nitrogen.

**[0083]** For the preparation of suppositories a low melting wax, such as a mixture of fatty acid glycerides, e.g. cocoa butter, is melted firstly and the active component is homogenously dispersed therein by stirring or similar mixing operations. The melted homogenous mixture is then poured in fitting forms, cooled and thus hardened.

**[0084]** Further preparations in solid form which are to be converted into preparations in fluid form for either oral or parenteral administration shortly before use are included. Such fluid forms include solutions, suspensions and emulsions.

**[0085]** Furthermore, the compounds of the present invention may be administered via transdermal application. The transdermal compositions can have the form of crèmes, lotions, aerosols and/or emulsions.

**[0086]** The term capsule refers to a special container or casing composed of methylcellulose, polyvinyl alcohols or denatured gelatins or starches, in which the active agents can be enclosed. Typically, hard shell capsules are prepared from mixtures of bones and porcine skin gelatins having comparatively high gel strength. The capsule itself can contain small amounts of colorants, opacifiers, softening agents and preservatives.

**[0087]** Tablet means a compressed or cast solid dosage form containing the active components with suitable extenders. The tablet can be produced by compressing mixtures or granulates obtained by wet granulation, dry granulation or compaction, which are known to the one skilled in the art.

**[0088]** Oral gels refer to the active components dispersed or solubilized in a hydrophilic semi-solid matrix.

**[0089]** Powders for compositions refer to powder mixtures containing the active components and suitable extenders which can be suspended in water or juices.

**[0090]** Suitable extenders are substances which usually form the largest part of the

composition or dosage form. Suitable extenders include sugars such as lactose, sucrose, mannitol and sorbitol; starches derived from wheat, corn, rice and potatoes; and celluloses such as microcrystalline cellulose. The amount of extenders in the composition can range from about 5 to about 95% per weight of the total composition, preferably form about 25 to about 75% per weight and further preferred from about 30 to about 60% per weight.

**[0091]** The term disintegrants refers to materials added to the composition in order to support disintegration and release of the medicinal substance. Suitable disintegrants include starches, modified starches which are soluble in cold water, such as sodium carboxymethyl starch; natural and synthetic gums such as locust bean gum, caraya, guar gum, tragacanth and agar; cellulose derivatives such as methylcellulose and sodium carboxymethylcellulose, microcrystalline celluloses and crosslinked microcrystalline celluloses such as croscarmellose sodium; alginates such as alginic acid and sodium alginate; clays such as bentonites and foaming mixtures. The amount of disintegrants used in the composition can range from about 2 to 20% per weight of the composition and further preferred from about 5 to about 10% per weight.

**[0092]** Binders characterize substances binding or "gluing" powders to each other and they consequently serve as "glue" in the formulation. Binders add a cohesion starch which is already available in the extenders or the disintegrant. Suitable binders include sugar, such as sucrose; starches derived from wheat, corn, rice and potatoes; natural gums such as acacia gum, gelatin and tragacanth; derivatives of sea weed such as alginic acid, sodium alginate and ammonium calcium alginate, cellulose materials such as methyl cellulose and sodium carboxymethylcellulose and hydroxypropyl methylcellulose, polyvinylpyrrolidone and inorganic compounds, such as magnesium aluminum silicate. The amount of binders in the composition can range from about 2 to about 20% per weight of the total composition, preferably form about 3 to about 10% per weight and further preferred from about 3 to about 6% per weight.

**[0093]** The term lubricant refers to a substance added to the dosage form in order to allow for the tablet, granulate, etc. to be released from the casting mold or pressing mold, after compression, by reducing the friction. Suitable lubricants include metallic stearates such as magnesium stearate, calcium stearate or potassium stearate; stearic acid; waxes with high melting points and water soluble lubricants such as sodium chloride, sodium benzoate, sodium acetate, sodium oleate, polyethylene glycols and D,L-leucine. Due to the fact that lubricants have to be present on the surface of the granulates as well as between the granulates and parts of the tablet press they are typically added during the last step prior to compression. The amount of lubricants in the composition can range from about 0.2 to about 5% per weight of the total composition, preferably form about 0.5 to about 2% per weight and further preferred from about 0.3 to about 1.5 % per weight.

**[0094]** Lubricants are materials preventing caking and improving the flow characteristics of granulates so that the flow is smooth and uniform. Suitable lubricants include silicon dioxide and talc. The amount of lubricants in the composition can range from about 0.1 to about 5 % per weight of the total composition, preferably form about 0.5 to about 2 % per weight.

**[0095]** Colorants are adjuvants coloring the composition or dosage form. Such adjuvants can include colorants having food quality which are adsorbed on a suitable adsorption means, such as clay or aluminum oxide. The amount of the colorant used can vary from about 0.1 to about 5% per weight of the composition and preferably from about 0.1 to about 1% per weight.

**[0096]** As used herein, a "pharmaceutically effective amount" of a transglutaminase inhibitor is the amount or activity effective for achieving the desired physiological result, either in cells treated *in vitro* or in a patient treated *in vivo.* Specifically, a pharmaceutical effective amount is such an amount which is sufficient for inhibiting, for a certain period of time, one or more of the clinically defined pathological processes associated with transglutaminase 2. The effective amount can vary according to the specific compound of the formula (I) and additionally depends on a plurality of factors and conditions related to the subject to be treated and the severity of the disease. If, for example, an inhibitor is to be administered *in vivo,* factors such as age, weight and health of the patients as well as dose reaction curves and data regarding toxicity obtained from preclinical animal studies are amongst the data to be considered. If the inhibitor in form of the compound of the formula (I) described herein is to be brought in contact with the cells *in vivo,* a plurality of preclinical *in vitro* studies would be designed in order to determine parameters such as absorption, half-life, dose, toxicity, etc. Determining a pharmaceutically effective amount for a given pharmaceutically active ingredient is part of the ordinary skills of the one skilled in the art.

**Examples**

**[0097]** Following abbreviations used in the examples have the following meaning. Boc (tert-butoxycarbonyl), BocOSu (N-tert-butoxycarbonyloxy-succinimide) DCM (dichloromethane), DMAP (4-(Dimethylamino)-pyridine), TEA (triethylamine), DMF (dimethylformamide), DMP (Dess-Martin periodiane), DIPEA (N-Ethyldiisopropylamine), Glu (glutamic acid), EDC (1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide), TFA (trifluoroacetic acid), THF (tetrahydrofuran), EtOAc (ethyl acetate), HATU (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate), HOBt (hydroxybenzotriazole), MTBE (methyl tert-butyl ether), tBu (tert-butyl),

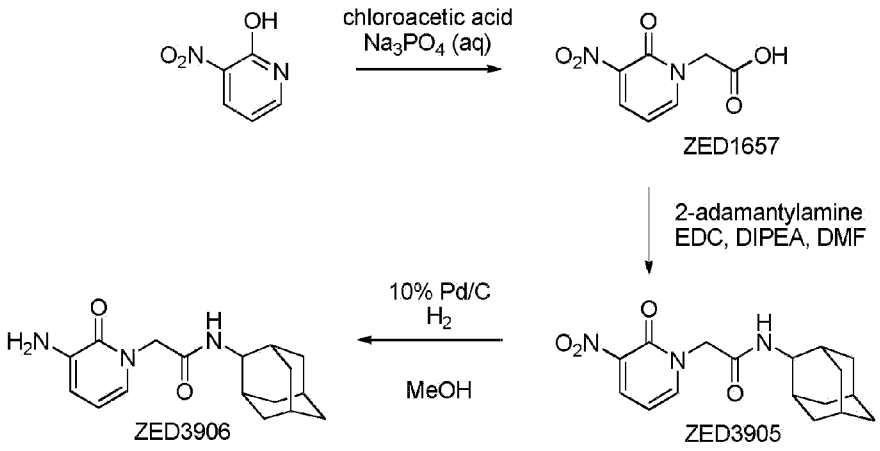
**Chemical Examples**

**[0098]** The following examples are intended to illustrate the invention with selected compounds without limiting the protecting scope of the present intellectual property right on these concrete examples. It is clear for a person skilled in the art that analogous compounds and compounds produced according to analogous synthetic ways fall under the protecting scope of the present intellectual property right.

**Example III. Synthetic method III**

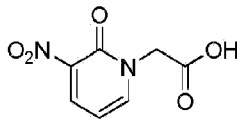
**[0099]**

**Scheme III-1**




**1 Preparation of compound ZED1657**

**[0100]**



2-(3-nitro-2-oxopyridin-1(2*H*)-yl)acetic acid

Chemical Formula: $C_7H_6N_2O_5$

Exact Mass: 198.03

Molecular Weight: 198.13

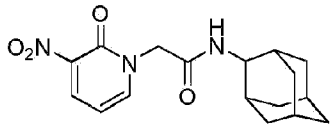
**[0101]** 30.0 g (214 mmol) of 2-hydroxy-3-nitropyridine and 40.5 g (2 eq) of chloroacetic acid were suspended in 600 mL water. At 40°C, 245 g (3 eq) trisodium phosphate dodecahydrate were added, and the reaction was stirred at room temperature overnight. 250 mL HCl (32%) were added, and the suspension was stirred for another night at 4°C. The precipitate was filtered and dried.

Yield: 41.2 g, 97%

ESI-MS: 199.3 $[M+H]^+$

**2 Preparation of compound ZED3905**

**[0102]**



*N*-(2-adamantyl)-2-(3-nitro-2-oxopyridin-1(2*H*)-yl)acetamide

Chemical Formula: $C_{17}H_{21}N_3O_4$

Exact Mass: 331.15

Molecular Weight: 331.37

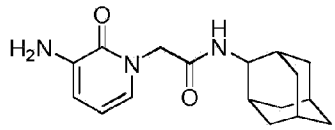
**[0103]** 17.0 g (85.8 mmol) of ZED1657, 16.1 g (1 eq) of 2-adamantanamine hydrochloride and 11.6 g (1 eq) of HOBt were dissolved in 200 mL DMF and 17.9 mL (1.2 eq) DIPEA. 18.1 g (1.1 eq) of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride were added and the reaction was stirred at room temperature overnight. The solvent was evaporated, and the residue was dissolved in 500 mL DCM. The solution was washed with each 200 mL citric acid solution (10%), $NaHCO_3$ solution (10%) and brine. The organic phase was dried over $Na_2SO_4$, filtered and the solvent was evaporated.

Yield: 24.1 g, 85%

ESI-MS: 332.4 $[M+H]^+$

**3 Preparation of compound ZED3906**

**[0104]**



2-(3-amino-2-oxopyridin-1(2H)-yl)-N-(2-adamantyl)acetamide Chemical Formula: $C_{17}H_{23}N_3O_2$

Exact Mass: 301.18

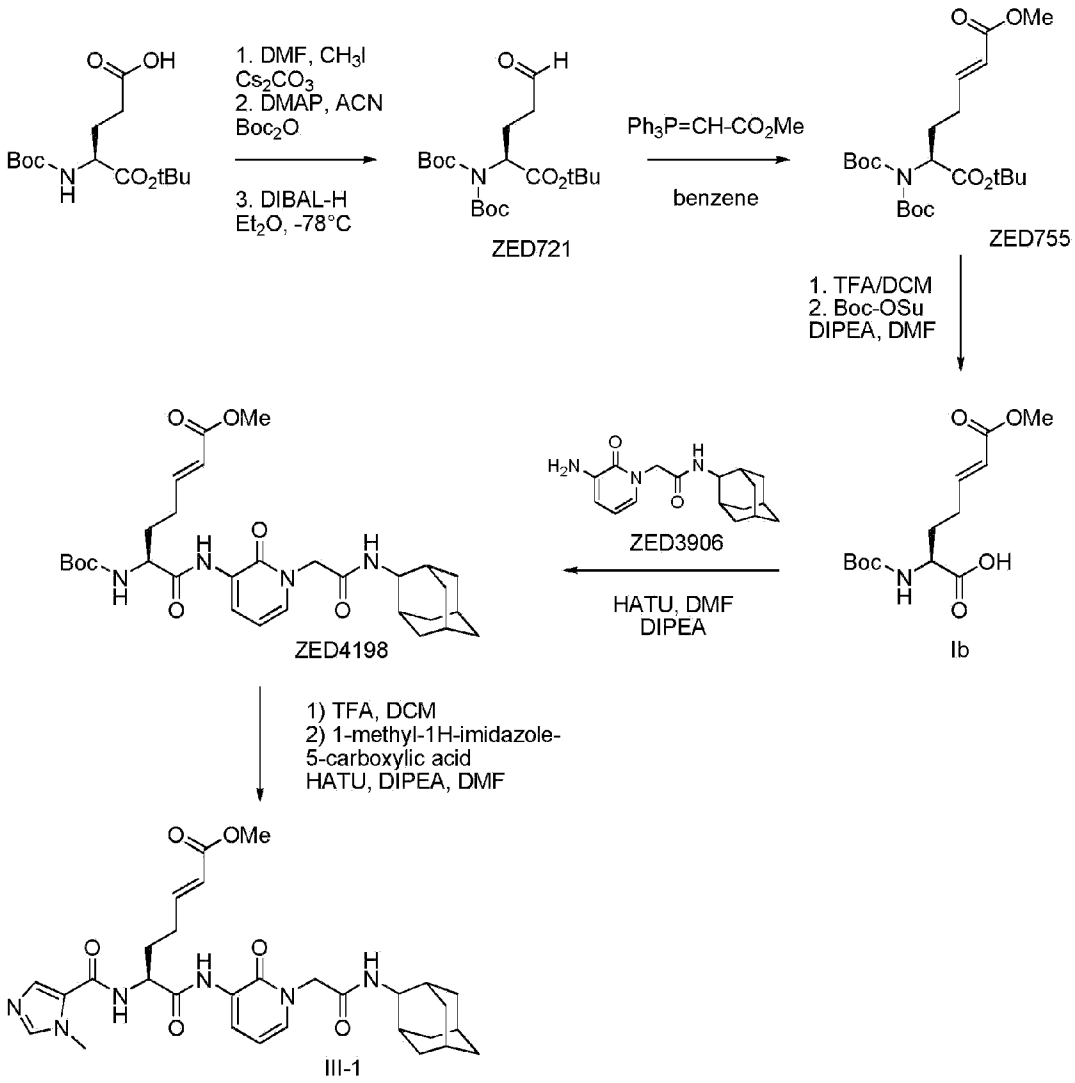
Molecular Weight: 301.38

**[0105]** 24.2 g (73.0 mmol) of ZED3905 were suspended in 600 mL MeOH before 2.42 g of palladium (10%) on activated carbon (unreduced) were added. The suspension was stirred overnight at room temperature under an atmosphere of hydrogen. The catalyst was filtered, and the solvent was evaporated.

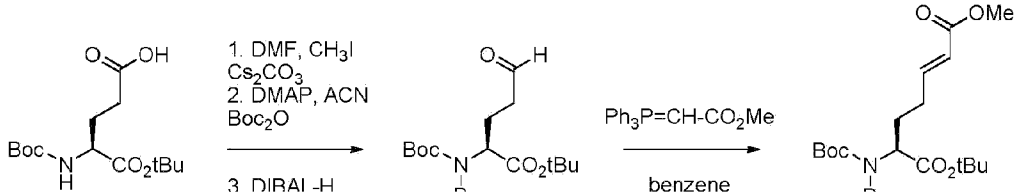
Yield: 15.7 g, 71%

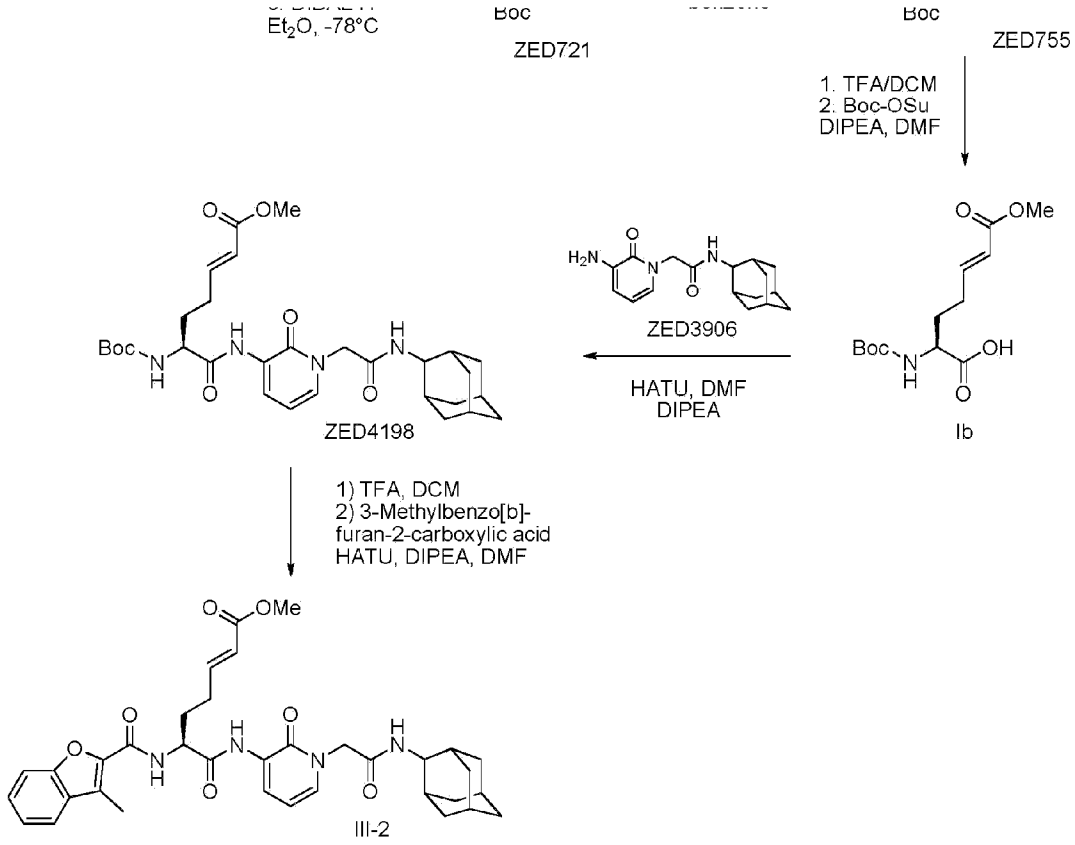
ESI-MS: 302.4 $[M+H]^+$

**Scheme III-2**



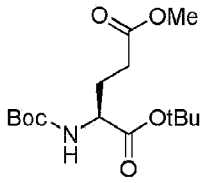

**Scheme III-3**






**Preparation of compound ZED788**

**[0106]**




(*S*)-1-*tert*-butyl 5-methyl 2-(*tert*-butoxycarbonylamino)pentanedioate

Chemical Formula: $C_{15}H_{27}NO_6$

Exact Mass: 317,18

Molecular Weight: 317,38

**[0107]** 12.0 g of Boc-L-Glu-OtBu (39.6 mmol) and 7.09 g of cesium carbonate (21.8 mmol, 0.55 eq) were suspended in 100 ml of DMF and stirred for 1 h at room temperature. 2.47 ml iodomethane (39.6 mmol) we added, and the mixture was stirred at room temperature overnight. The solvent was evaporated, and the residue was dissolved in ethyl acetate and

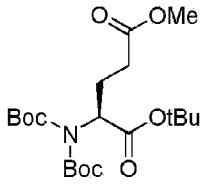
washed twice with each citric acid solution (10%), $NaHCO_3$ solution (10%) and brine. The organic phase was dried over $Na_2SO_4$, filtered and the solvent was evaporated. The raw product was used without further purification.

Yield: 13.4 g, >100%

ESI-MS: 318.3 $[M+H]^+$

**Preparation of compound ZED720**

**[0108]**




(*S*)-1-*tert*-butyl 5-methyl 2-(bis(*tert*-butoxycarbonyl)amino)pentanedioate

Chemical Formula: $C_{20}H_{35}NO_8$

Exact Mass: 417,24

Molecular Weight: 417,49

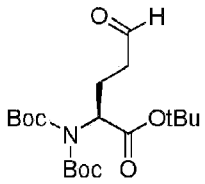
**[0109]** 13.4 g of ZED788 (-39,6 mmol) and 986 mg of N,N-dimethyl-4-aminopyridine (DMAP) were dissolved in 30 ml of acetonitrile. 17.6 g of di-tert-butyl bicarbonate (77.1 mmol) in 100 ml of acetonitrile was added and the solution was stirred at room temperature overnight. The solvent was evaporated, and the residue was dissolved in ethyl acetate and washed twice with each citric acid solution (10%), $NaHCO_3$ solution (10%) and brine. The organic phase was dried over $Na_2SO_4$, filtered and the solvent was evaporated. The raw product was used without further purification.

Yield: 13.7 g, 83%

ESI-MS: 418.3 $[M+H]^+$

**Preparation of compound ZED721**

**[0110]**



(*S*)-*tert*-butyl 2-(bis(*tert*-butoxycarbonyl)amino)-5-oxopentanoate

Chemical Formula: $C_{19}H_{33}NO_7$

Exact Mass: 387,23

Molecular Weight: 387,47

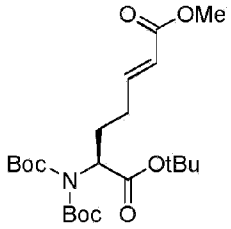
**[0111]** 13.7 g of ZED720 (32.8 mmol) were dissolved in 200 ml of dry diethyl ether and cooled to -78°C under argon atmosphere. 36.1 ml of diisobutylaluminum hydride (1M in hexane) were added dropwise and the solution was stirred for 30 min at -78°C before being quenched with potassium sodium tartrate (Rochelle salt) solution. The organic layer was separated, dried over $Na_2SO_4$, filtered, and concentrated to dryness. The raw product was used without further purification.

Yield: 13.3 g, >100%

ESI-MS: 388.3 $[M+H]^+$

**Preparation of compound ZED755**

**[0112]**



(*S,E*)-7-*tert*-butyl 1-methyl 6-(bis(*tert*-butoxycarbonyl)amino)hept-2-enedioate

Chemical Formula: $C_{22}H_{37}NO_8$

Exact Mass: 443,25

Molecular Weight: 443,53

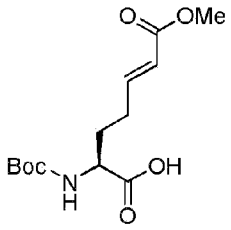
**[0113]** 13.3 g of ZED721 (-32.8 mmol) were dissolved in 60 ml of benzene and 11.2 g of (carbomethoxymethylene)triphenylphosphorane (1 eq) was added portionwise. After stirring overnight, the solvent was evaporated. The residue was purified by flash chromatography.

Yield: 12.0 g, 83%

ESI-MS: 444.3 $[M+H]^+$

**Preparation of compound Ib**

**[0114]**




(*S*,*E*)-2-(*tert*-butoxycarbonylamino)-7-methoxy-7-oxohept-5-enoic acid

Chemical Formula: $C_{13}H_{21}NO_6$

Exact Mass: 287,14

Molecular Weight: 287,31

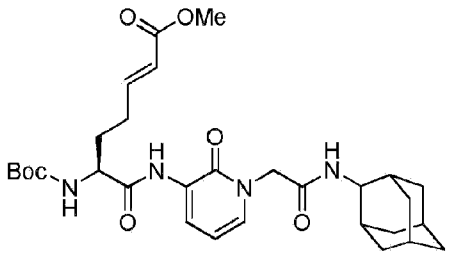
**[0115]** 12.0 g of ZED755 (27.1 mmol) are dissolved in 100 ml DCM/TFA (1:1) and stirred at room temperature for 1 h. The solvent was evaporated, and the residue was dissolved in 100 ml DMF and 9.23 ml DIPEA (2 eq). 7.15 g of N-(tert-butoxycarbonyloxy)succinimide were added and the reaction was stirred at room temperature overnight. The solvent was evaporated, and the residue was dissolved in ethyl acetate and washed twice with each citric acid solution (10%) and brine. The organic phase was dried over $Na_2SO_4$, filtered and the solvent was evaporated. The residue was purified by flash chromatography.

Yield: 5.89 g, 76%

ESI-MS: 288.3 $[M+H]^+$

**4 Preparation of compound ZED4198**

**[0116]**



(*S*)-methyl6-(*tert*-butoxycarbonylamino)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxoheptanoate

Chemical Formula: $C_{30}H_{42}N_4O_7$

Exact Mass: 570.31

Molecular Weight: 570.68

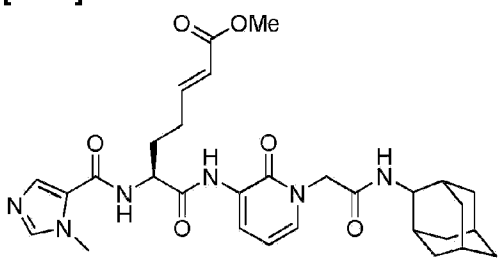
**[0117]** 1.67 g (5.80 mmol) of (S,E)-2-(tert-butoxycarbonylamino)-7-methoxy-7-oxohept-5-enoic acid (Ib), 2.21 g (1 eq) HATU and 1.75 g (1 eq) ZED3906 were dissolved in 25 mL DMF and 1.97 mL DIPEA (2 eq) and stirred at 45°C overnight. The solvent was evaporated; the residue was dissolved in 100 mL EtOAc and washed twice with each 30 mL citric acid solution (10%), $NaHCO_3$ solution (10%) and brine. The organic phase was dried over $Na_2SO_4$, filtered and the solvent was evaporated.

Yield: 1.65 g, 50%

ESI-MS: 571.4 $[M+H]^+$

**5 Preparation of compound III-1**

**[0118]**



(*S*,*E*)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1*H*-imidazole-5-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{30}H_{38}N_6O_6$

Exact Mass: 578.29

Molecular Weight: 578.66

**[0119]** 200 mg (0.35 mmol) of ZED4198 were dissolved in 6 ml DCM/TFA (1:1) and stirred at room temperature for 1 h. The solvent was evaporated, and the residue was dissolved in 9 ml DMF. 44.2 mg (1 eq) 1-methyl-1H-imidazole-5-carboxylic acid, 133 mg (1 eq) HATU and 119 µl (2 eq) DIPEA were added, and the reaction was stirred at room temperature overnight. The solvent was evaporated and the residue was purified by HPLC.

Yield: 165 mg, 81%

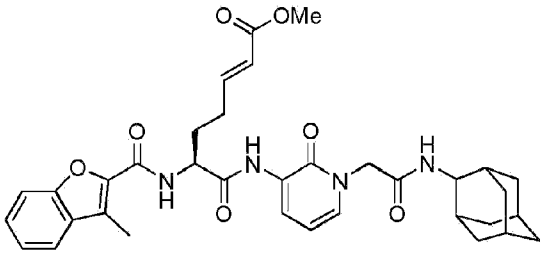
ESI-MS: 579.4 $[M+H]^+$

**[0120]** $^1$H-NMR (DMSO-D6, 500 MHz, δ [ppm]: 1.50 // 2.00 (d // d, 2H // 2H, adamantyl-C4-$H_2$), 1.70 // 1.80 (m, 4H, adamantyl-C4-$H_2$), 1.78 (m, 2H, adamantyl-C1-H), 1.78 (m, 2H, adamantyl-C6-$H_2$), 1.80 (m, 2H, adamantyl-C5-H), 1.90 // 2.03 (m // m, 1H // 1H, β-$CH_2$), 2.32 (m, 2H, γ-$CH_2$), 3.62 (s, 3H, O-$CH_3$), 3.79 (s, 3H, imidazole-N-$CH_3$), 3.83 (m, 1H, adamantyl-C2-H), 4.58 (ddd, 1H, α-$CH_2$), 4.66 (s, 2H, N-$CH_2$), 5.85 (m, 1H, =CH-), 6.25 (t, 1H, pyridinone-C5-H), 6.92 (m, 1H, =CH-), 7.33 (d, 1H, pyridinone-C6-H), 7.72 (s, 1H, imidazole-CH), 7.77 (s, 1H, imidazole-CH), 8.09 (d, 1H, adamantyl-NH), 8.21 (d, 1H, pyridinone-C4-H), 8.61 (d, 1H, α-NH), 9.25 (s, 1H, pyridinone-NH).

**[0121]** $^{13}$C-NMR (DMSO-D6, 500 MHz, δ [ppm]: 26.70 // 26.64 (adamantyl-C5-H), 28.44 (γ -$CH_2$), 29.10 (β-$CH_2$), 30.92 (adamantyl-C4-$H_2$), 31.44 (adamantyl-C1-H), 33.46 (imidazole-N-$CH_3$), 36.74 (adamantyl-C4'-$H_2$), 37.09 (adamantyl-C6-$H_2$), 51.14 (O-$CH_3$), 51.62 (N-$CH_2$), 53.07 (α -$CH_2$), 53.32 (adamantyl-C2-H), 104.59 (pyridinone-C5-H), 121.04 (=CH-), 122.30 (pyridinone-C4-H), 125.06 (imidazole-Cq), 127.90 (pyridinone-N-Cq), 132.78 (imidazole-CH), 133.26 (pyridinone-C6-H), 142.18 (imidazole-CH), 148.54 (=CH-), 156.60 (pyridinone-C=O), 160.24 (imidazole-C=O), 165.71 (C=O-adamantylamide), 165.98 (Cq methyl ester), 170.69 (C=O-NH-pyridinone).

**6 Preparation of compound III-2**

**[0122]**



(*S*,*E*)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{35}H_{40}N_4O_7$

Exact Mass: 628.29

Molecular Weight: 628.71

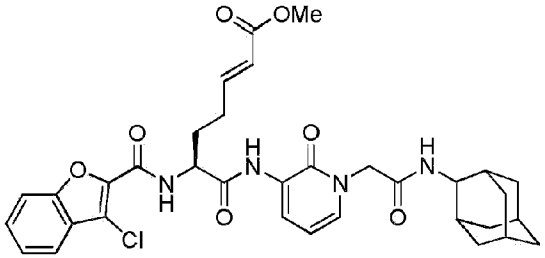
**[0123]** The synthesis of compound **III-2** was performed according to compound **III-1,** using 3-methylbenzo[b]furan-2-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 101 mg, 75% (last step)

ESI-MS: 629.4 $[M+H]^+$

**7 Preparation of compound III-3**

**[0124]**



(*S*,*E*)-methyl 6-(3-chlorobenzofuran-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate

Chemical Formula: $C_{34}H_{37}ClN_4O_7$

Exact Mass: 648.24

Molecular Weight: 649.13

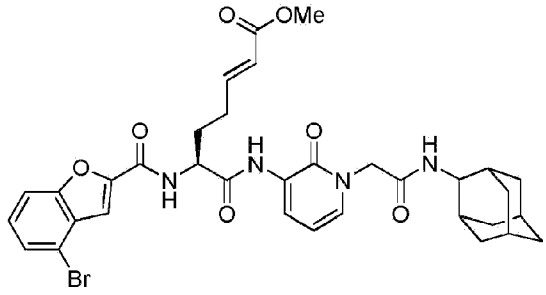
**[0125]** The synthesis of compound **III-3** was performed according to compound **III-1,** using 3-chlorobenzofuran-2-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 214 mg, 82% (last step)

ESI-MS: 649.3 / 651.3 $[M+H]^+$

**8 Preparation of compound III-4**

**[0126]**




(*S*,*E*)-methyl 6-(4-bromobenzofuran-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate

Chemical Formula: $C_{34}H_{37}BrN_4O_7$

Exact Mass: 692.18

Molecular Weight: 693.58

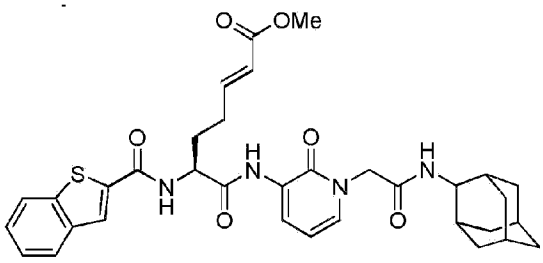
**[0127]** The synthesis of compound **III-4** was performed according to compound **III-1,** using 4-bromo-1-benzofuran-2-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 104 mg, 76% (last step)

ESI-MS: 693.3 / 695.3 $[M+H]^+$

**9 Preparation of compound III-5**

**[0128]**



(*S*,*E*)-methyl 6-(benzo[b]thiophene-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate

Chemical Formula: $C_{34}H_{38}N_4O_6S$

Exact Mass: 630.25

Molecular Weight: 630.75

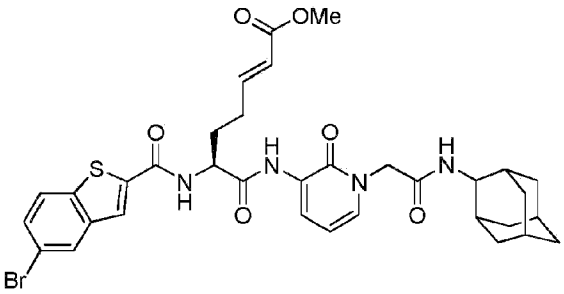
**[0129]** The synthesis of compound **III-5** was performed according to compound **III-1,** using benzo[b]thiophene-2-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 356 mg, 85% (last step)

ESI-MS: 631.3 $[M+H]^+$

**10 Preparation of compound III-6**

**[0130]**



(*S*,*E*)-methyl 6-(5-bromobenzo[b]thiophene-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate

Chemical Formula: $C_{34}H_{37}BrN_4O_6S$

Exact Mass: 708.16

Molecular Weight: 709.65

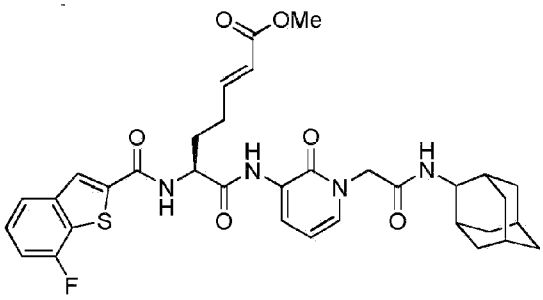
**[0131]** The synthesis of compound **III-6** was performed according to compound **III-1,** using 5-bromobenzo[b]thiophene-2-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 102 mg, 70% (last step)

ESI-MS: 709.2 / 711.2 $[M+H]^+$

**11 Preparation of compound III-7**

**[0132]**




(S,E)-methyl 6-(7-fluorobenzo[b]thiophene-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate

Chemical Formula: $C_{34}H_{37}FN_4O_6S$

Exact Mass: 648.24

Molecular Weight: 648.74

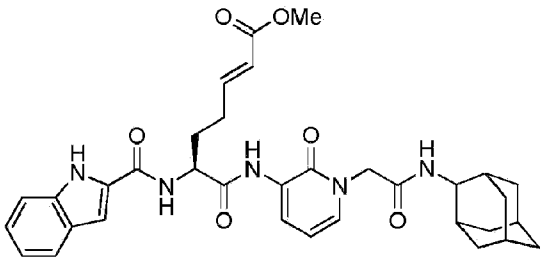
**[0133]** The synthesis of compound **III-7** was performed according to compound **III-1,** using 7-fluorobenzo[b]thiophene-2-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 56 mg, 68% (last step)

ESI-MS: 649.3 $[M+H]^+$

**12 Preparation of compound III-8**

**[0134]**



(S,E)-methyl 6-(1H-indole-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate

Chemical Formula: $C_{34}H_{39}N_5O_6$

Exact Mass: 613.29

Molecular Weight: 613.70

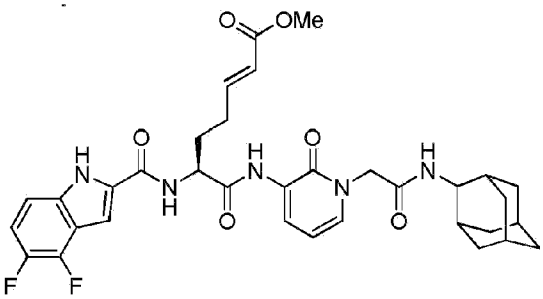
**[0135]** The synthesis of compound **III-8** was performed according to compound **III-1,** using 1H-indole-2-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 79 mg, 76% (last step)

ESI-MS: 614.4 $[M+H]^+$

**13 Preparation of compound III-9**

**[0136]**



(S,E)-methyl 6-(4,5-difluoro-1H-indole-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate

Chemical Formula: $C_{34}H_{37}F_2N_5O_6$

Exact Mass: 649.27

Molecular Weight: 649.68

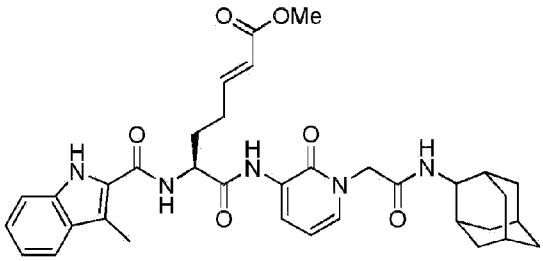
**[0137]** The synthesis of compound **III-9** was performed according to compound **III-1,** using 4,5-difluoro-1H-indole-2-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 43 mg, 76% (last step)

ESI-MS: 650.3 $[M+H]^+$

**14 Preparation of compound III-10**

**[0138]**




(S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methyl-1H-indole-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{35}H_{41}N_5O_6$

Exact Mass: 627.31

Molecular Weight: 627.73

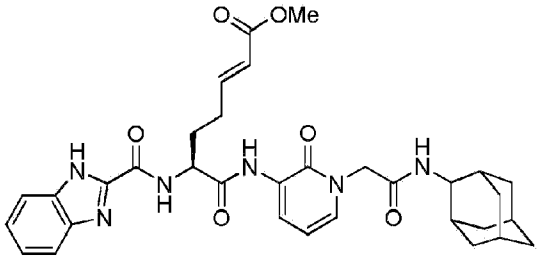
**[0139]** The synthesis of compound **III-10** was performed according to compound **III-1,** using 3-methyl-1H-indole-2-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 73 mg, 82% (last step)

ESI-MS: 628.4 $[M+H]^+$

**15 Preparation of compound III-11**

**[0140]**



(S,E)-methyl 6-(1H-benzo[d]imidazole-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate

Chemical Formula: $C_{33}H_{38}N_6O_6$

Exact Mass: 614.29

Molecular Weight: 614.69

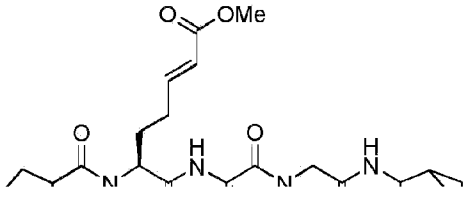
**[0141]** The synthesis of compound **III-11** was performed according to compound **III-1,** using 1H-benzo[d]imidazole-2-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

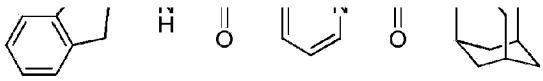
Yield: 22 mg, 41% (last step)

ESI-MS: 615.4 $[M+H]^+$

**16 Preparation of compound III-12**

**[0142]**





(S,E)-methyl 6-(2,3-dihydro-1H-indene-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate

Chemical Formula: $C_{35}H_{42}N_4O_6$

Exact Mass: 614.31

Molecular Weight: 614.73

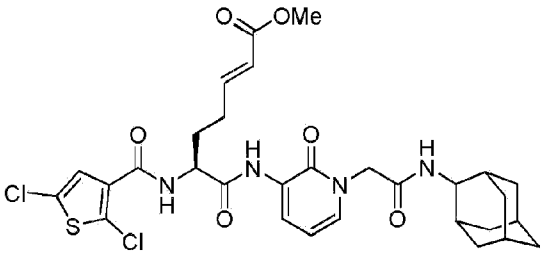
**[0143]** The synthesis of compound **III-12** was performed according to compound **III-1,** using 2,3-dihydro-1H-indene-2-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 51 mg, 75% (last step)

ESI-MS: 615.4 $[M+H]^+$

**17 Preparation of compound III-13**

**[0144]**



(*S*,*E*)-methyl 6-(2,5-dichlorothiophene-3-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate

Chemical Formula: $C_{30}H_{34}Cl_2N_4O_6S$

Exact Mass: 648.16

Molecular Weight: 649.59

**[0145]** The synthesis of compound **III-13** was performed according to compound **III-1,** using 2,5-dichlorothiophene-3-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in

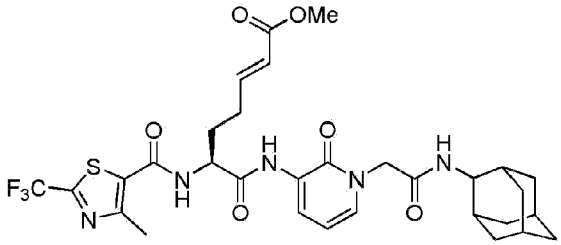
the final step.

Yield: 78 mg, 71% (last step)

ESI-MS: 649.3 / 651.3 $[M+H]^+$

**18 Preparation of compound III-14**

**[0146]**



(*S,E*)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-methyl-2-(trifluoromethyl)thiazole-5-carboxamido)-7-oxohept-2-enoate Chemical Formula: $C_{31}H_{36}F_3N_5O_6S$

Exact Mass: 663.23

Molecular Weight: 663.71

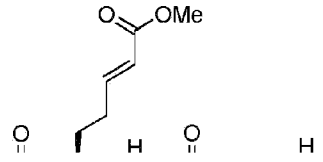
**[0147]** The synthesis of compound **III-14** was performed according to compound **III-1,** using 4-methyl-2-(trifluoromethyl)thiazole-5-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

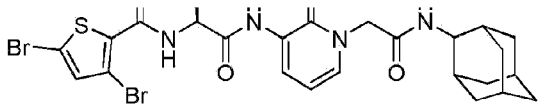
Yield: 52 mg, 67% (last step)

ESI-MS: 664.4 $[M+H]^+$

**19 Preparation of compound III-15**

**[0148]**





(S,E)-methyl 6-(3,5-dibromothiophene-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate

Chemical Formula: $C_{30}H_{34}Br_2N_4O_6S$

Exact Mass: 736.06

Molecular Weight: 738.49

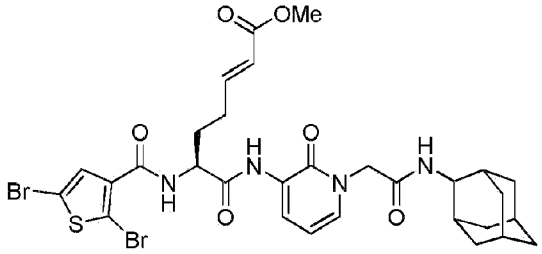
**[0149]** The synthesis of compound **III-15** was performed according to compound **III-1,** using 3,5-dibromothiophene-2-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 143 mg, 86% (last step)

ESI-MS: 737.2 / 739.2 / 741.2 $[M+H]^+$

**20 Preparation of compound III-16**

**[0150]**



(S,E)-methyl 6-(2,5-dibromothiophene-3-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate

Chemical Formula: $C_{30}H_{34}Br_2N_4O_6S$

Exact Mass: 736.06

Molecular Weight: 738.49

**[0151]** The synthesis of compound **III-16** was performed according to compound **III-1,** using

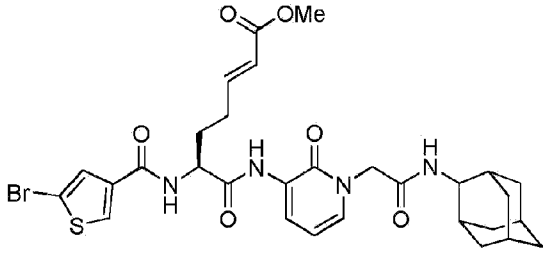
2,5-dibromothiophene-3-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 107 mg, 65% (last step)

ESI-MS: 737.2 / 739.2 / 741.2 $[M+H]^+$

**21 Preparation of compound III-17**

**[0152]**




(*S*,*E*)-methyl 6-(5-bromothiophene-3-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate

Chemical Formula: $C_{30}H_{35}BrN_4O_6S$

Exact Mass: 658.15

Molecular Weight: 659.59

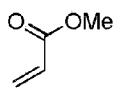
**[0153]** The synthesis of compound **III-17** was performed according to compound **III-1,** using 5-bromothiophene-3-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

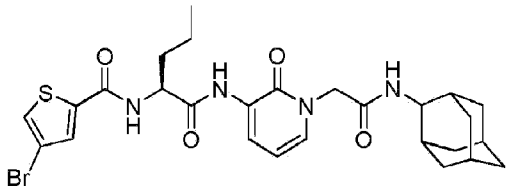
Yield: 89 mg, 80% (last step)

ESI-MS: 659.2 / 661.2 $[M+H]^+$

**22 Preparation of compound III-18**

**[0154]**





(*S*,*E*)-methyl 6-(4-bromothiophene-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate

Chemical Formula: $C_{30}H_{35}BrN_4O_6S$

Exact Mass: 658.15

Molecular Weight: 659.59

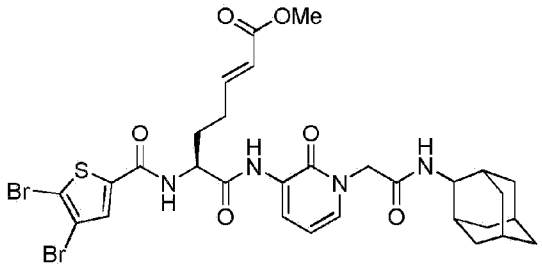
**[0155]** The synthesis of compound **III-18** was performed according to compound **III-1,** using 4-bromothiophene-2-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 143 mg, 76% (last step)

ESI-MS: 659.2 / 661.2 $[M+H]^+$

**23 Preparation of compound III-19**

**[0156]**



(S,E)-methyl 6-(4,5-dibromothiophene-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate

Chemical Formula: $C_{30}H_{34}Br_2N_4O_6S$

Exact Mass: 736.06

Molecular Weight: 738.49

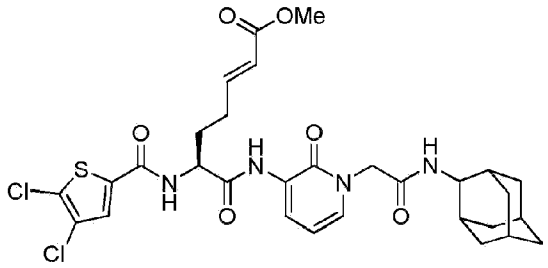
**[0157]** The synthesis of compound **III-19** was performed according to compound **III-1,** using 4,5-dibromothiophene-2-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 57 mg, 64% (last step)

ESI-MS: 737.2 / 739.2 / 741.2 $[M+H]^+$

**24 Preparation of compound III-20**

**[0158]**



(*S*,*E*)-methyl 6-(4,5-dichlorothiophene-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate

Chemical Formula: $C_{30}H_{34}Cl_2N_4O_6S$

Exact Mass: 648.16

Molecular Weight: 649.59

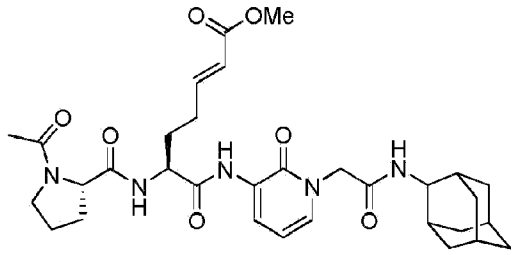
**[0159]** The synthesis of compound **III-20** was performed according to compound **III-1,** using 4,5-dichlorothiophene-2-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 78 mg, 73% (last step)

ESI-MS: 649.3 / 651.3 $[M+H]^+$

**25 Preparation of compound III-21**

**[0160]**



(S,E)-methyl6-((S)-1-acetylpyrrolidine-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate

Chemical Formula: $C_{32}H_{43}N_5O_7$

Exact Mass: 609.32

Molecular Weight: 609.71

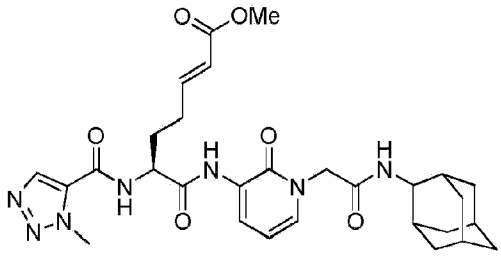
**[0161]** The synthesis of compound **III-21** was performed according to compound **III-1,** using (S)-1-acetylpyrrolidine-2-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 114 mg, 86% (last step)

ESI-MS: 610.4 $[M+H]^+$

**26 Preparation of compound III-22**

**[0162]**



(S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-1,2,3-triazole-5-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{29}H_{37}N_7O_6$

Exact Mass: 579.28

Molecular Weight: 579.65

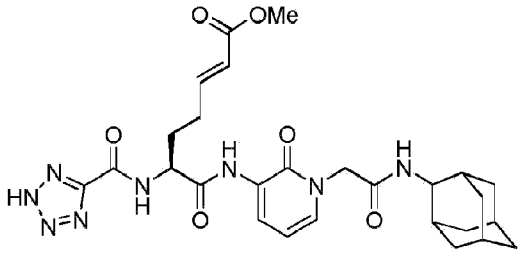
**[0163]** The synthesis of compound **III-22** was performed according to compound **III-1,** using 1-methyl-1H-1,2,3-triazole-5-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 45 mg, 59% (last step)

ESI-MS: 580.4 $[M+H]^+$

**27 Preparation of compound III-23**

**[0164]**



(S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(2H-tetrazole-5-carboxamido)hept-2-enoate

Chemical Formula: $C_{27}H_{34}N_8O_6$

Exact Mass: 566.26

Molecular Weight: 566.61

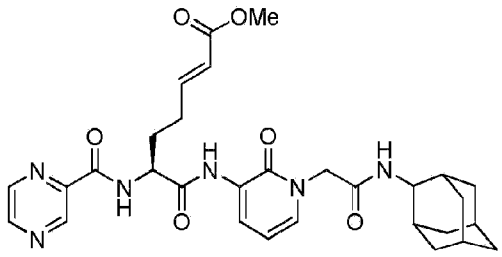
**[0165]** The synthesis of compound **III-23** was performed according to compound **III-1,** using 2H-tetrazole-5-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 42 mg, 57% (last step)

ESI-MS: 567.4 $[M+H]^+$

**28 Preparation of compound III-24**

**[0166]**



(S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(pyrazine-2-carboxamido)hept-2-enoate

Chemical Formula: $C_{30}H_{36}N_6O_6$

Exact Mass: 576.27

Molecular Weight: 576.64

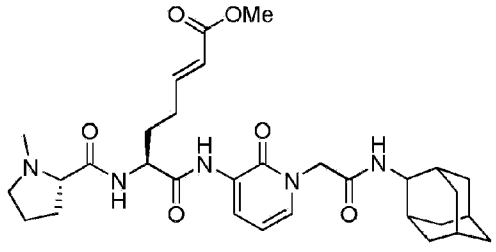
**[0167]** The synthesis of compound **III-24** was performed according to compound **III-1,** using pyrazine-2-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 54 mg, 68% (last step)

ESI-MS: 577.3 $[M+H]^+$

**29 Preparation of compound III-25**

**[0168]**



(S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-((S)-1-methylpyrrolidine-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{31}H_{43}N_5O_6$

Exact Mass: 581.32

Molecular Weight: 581.70

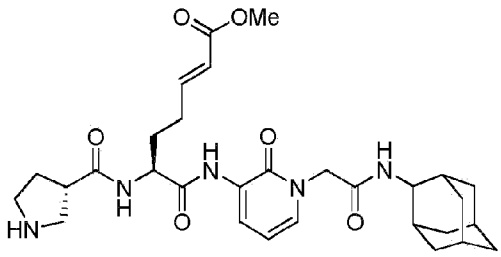
**[0169]** The synthesis of compound **III-25** was performed according to compound **III-1,** using (S)-1-methylpyrrolidine-2-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 85 mg, 79% (last step)

ESI-MS: 582.4 $[M+H]^+$

**30 Preparation of compound III-26**

**[0170]**




(S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-((S)-pyrrolidine-3-carboxamido)hept-2-enoate

Chemical Formula: $C_{30}H_{41}N_5O_6$

Exact Mass: 567.31

Molecular Weight: 567.68

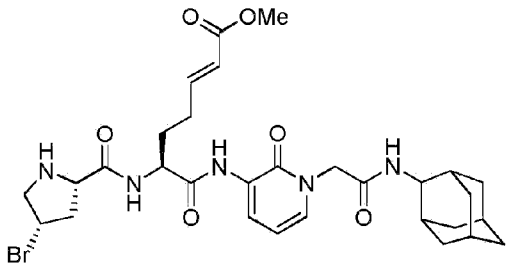
**[0171]** The synthesis of compound **III-26** was performed according to compound **III-1,** using (S)-1-Boc-pyrrolidine-3-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid. The final product was obtained by deprotection (DCM/TFA) as described above and purified by HPLC.

Yield: 78 mg, 93% (last step)

ESI-MS: 568.4 $[M+H]^+$

**31 Preparation of compound III-27**

**[0172]**



(S,E)-methyl 6-((2S,4S)-4-bromopyrrolidine-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate

Chemical Formula: $C_{30}H_{40}BrN_5O_6$

Exact Mass: 645.22

Molecular Weight: 646.57

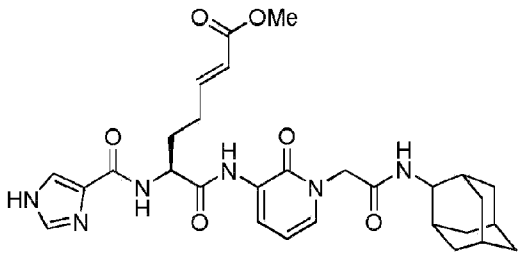
**[0173]** The synthesis of compound **III-27** was performed according to compound **III-1,** using (2S,4S)-1-Boc-4-bromopyrrolidine-2-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid. The final product was obtained by deprotection (DCM/TFA) as described above and purified by HPLC.

Yield: 56 mg, 89% (last step)

ESI-MS: 646.3 / 648.3 $[M+H]^+$

**32 Preparation of compound III-28**

**[0174]**



(S,E)-methyl 6-(1H-imidazole-4-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate

Chemical Formula: $C_{29}H_{36}N_6O_6$

Exact Mass: 564.27

Molecular Weight: 564.63

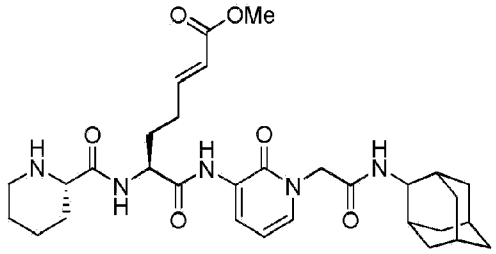
**[0175]** The synthesis of compound **III-28** was performed according to compound **III-1,** using 1-Boc-imidazole-4-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid. The final product was obtained by deprotection (DCM/TFA) as described above and purified by HPLC.

Yield: 45 mg, 86% (last step)

ESI-MS: 565.3 $[M+H]^+$

**33 Preparation of compound III-29**

**[0176]**



(S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-((S)-piperidine-2-carboxamido)hept-2-enoate

Chemical Formula: $C_{31}H_{43}N_5O_6$

Exact Mass: 581.32

Molecular Weight: 581.70

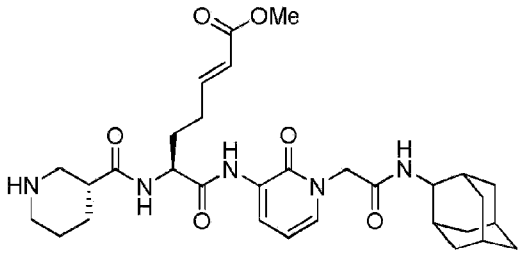
**[0177]** The synthesis of compound **III-29** was performed according to compound **III-1,** using (S)-1-Boc-piperidine-2-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid. The final product was obtained by deprotection (DCM/TFA) as described above and purified by HPLC.

Yield: 108 mg, 94% (last step)

ESI-MS: 582.4 $[M+H]^+$

**34 Preparation of compound III-30**

**[0178]**



(S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-((R)-piperidine-3-carboxamido)hept-2-enoate

Chemical Formula: $C_{31}H_{43}N_5O_6$

Exact Mass: 581.32

Molecular Weight: 581.70

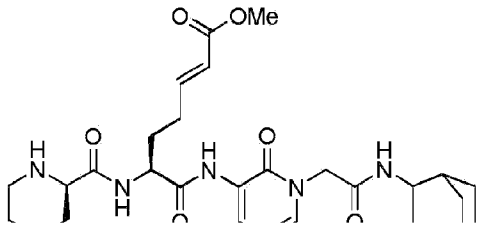
**[0179]** The synthesis of compound **III-30** was performed according to compound **III-1,** using (R)-1-Boc-piperidine-3-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid. The final product was obtained by deprotection (DCM/TFA) as described above and purified by HPLC.

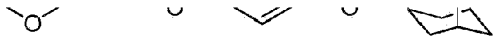
Yield: 68 mg, 87% (last step)

ESI-MS: 582.4 $[M+H]^+$

**35 Preparation of compound III-31**

**[0180]**





(S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-((R)-morpholine-3-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{30}H_{41}N_5O_7$

Exact Mass: 583.30

Molecular Weight: 583.68

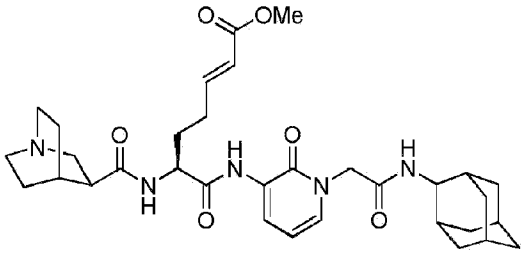
**[0181]** The synthesis of compound **III-31** was performed according to compound **III-1,** using (R)-4-Boc-morpholine-3-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid. The final product was obtained by deprotection (DCM/TFA) as described above and purified by HPLC.

Yield: 73 mg, 90% (last step)

ESI-MS: 584.4 $[M+H]^+$

**36 Preparation of compound III-32**

**[0182]**



(S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(quinuclidine-3-carboxamido)hept-2-enoate

Chemical Formula: $C_{33}H_{45}N_5O_6$

Exact Mass: 607.34

Molecular Weight: 607.74

**[0183]** The synthesis of compound **III-32** was performed according to compound **III-1,** using quinuclidine-3-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final

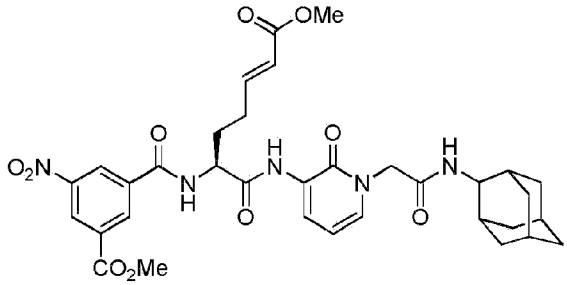
step.

Yield: 23 mg, 71% (last step)

ESI-MS: 608.4 $[M+H]^+$

**37 Preparation of compound III-33**

**[0184]**



(S,E)-methyl 3-(1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-methoxy-1,7-dioxohept-5-en-2-ylcarbamoyl)-5-nitrobenzoate

Chemical Formula: $C_{34}H_{39}N_5O_{10}$

Exact Mass: 677.27

Molecular Weight: 677.70

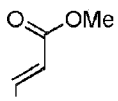
**[0185]** The synthesis of compound **III-33** was performed according to compound **III-1,** using mono-methyl 5-nitroisophthalate instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

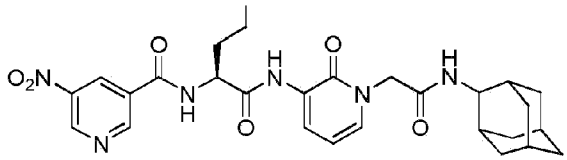
Yield: 68 mg, 86% (last step)

ESI-MS: 678.3 $[M+H]^+$

**38 Preparation of compound III-34**

**[0186]**





(*S*,*E*)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(5-nitronicotinamido)-7-oxohept-2-enoate

Chemical Formula: $C_{31}H_{36}N_6O_8$

Exact Mass: 620.26

Molecular Weight: 620.65

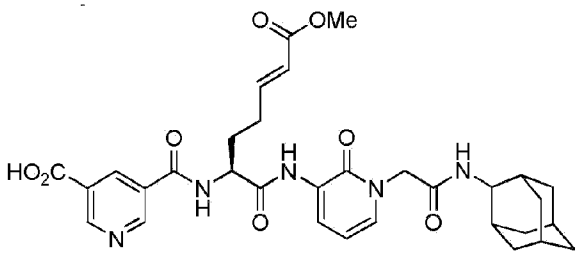
**[0187]** The synthesis of compound **III-34** was performed according to compound **III-1,** using 5-nitronicotinic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 54 mg, 75% (last step)

ESI-MS: 621.3 $[M+H]^+$

**39 Preparation of compound III-35**

**[0188]**



(S,E)-5-(1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-methoxy-1,7-dioxohept-5-en-2-ylcarbamoyl)nicotinic acid

Chemical Formula: $C_{32}H_{37}N_5O_8$

Exact Mass: 619.26

Molecular Weight: 619.66

**[0189]** The synthesis of compound **III-35** was performed according to compound **III-1,** using

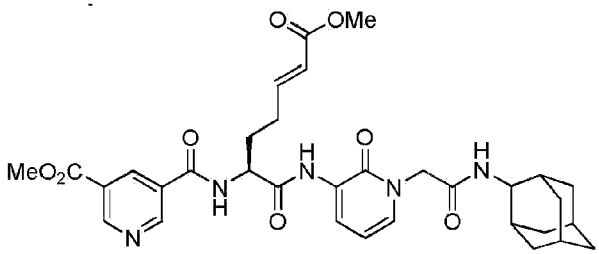
3,5-pyridinedicarboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 28 mg, 63% (last step)

ESI-MS: 620.3 $[M+H]^+$

**40 Preparation of compound III-36**

**[0190]**



(S,E)-methyl 5-(1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-methoxy-1,7-dioxohept-5-en-2-ylcarbamoyl)nicotinate

Chemical Formula: $C_{33}H_{39}N_5O_8$

Exact Mass: 633.28

Molecular Weight: 633.69

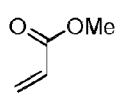
**[0191]** The synthesis of compound **III-36** was performed according to compound **III-1,** using 5-(methoxycarbonyl)nicotinic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

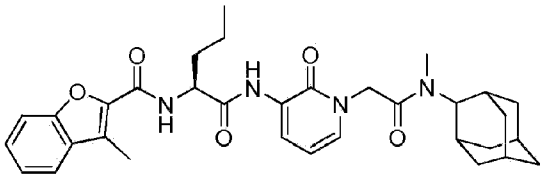
Yield: 48 mg, 77% (last step)

ESI-MS: 634.3 $[M+H]^+$

**41 Preparation of compound III-37**

**[0192]**





(*S*,*E*)-methyl 7-(1-(2-(2-adamantyl(methyl)amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{36}H_{42}N_4O_7$

Exact Mass: 642.31

Molecular Weight: 642.74

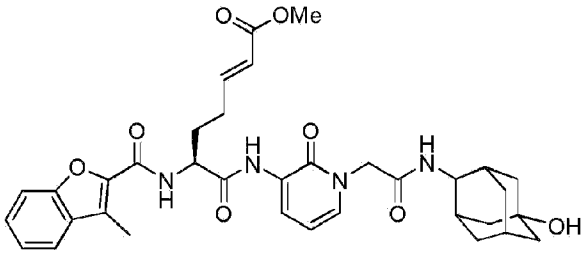
**[0193]** The synthesis of compound **III-37** was performed according to compound **III-2,** using N-methyl-2-adamantanamine instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 42 mg, 47% (last step)

ESI-MS: 643.4 $[M+H]^+$

**42 Preparation of compound III-38**

**[0194]**



(*S*,*E*)-methyl 7-(1-(2-(5-hydroxyadamantan-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{35}H_{40}N_4O_8$

Exact Mass: 644.28

Molecular Weight: 644.71

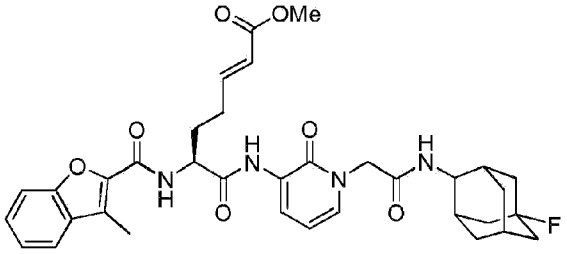
**[0195]** The synthesis of compound **III-38** was performed according to compound **III-2,** using 5-hydroxy-2-adamantanamine instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 35 mg, 24% (last step)

ESI-MS: 645.4 $[M+H]^+$

**43 Preparation of compound III-39**

**[0196]**



(*S*,*E*)-methyl 7-(1-(2-(5-fluoroadamantan-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{35}H_{39}FN_4O_7$

Exact Mass: 646.28

Molecular Weight: 646.71

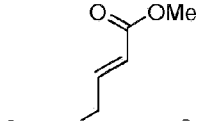
**[0197]** The synthesis of compound **IIII-39** was performed according to compound **IIII-2,** using 5-fluoro-2-adamantanamine instead of 2-adamantanamine in step 2 (according to ZED3905).

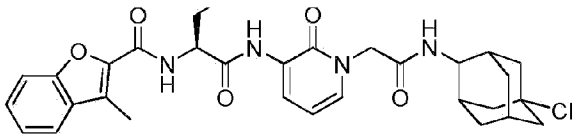
Yield: 64 mg, 68% (last step)

ESI-MS: 647.4 $[M+H]^+$

**44 Preparation of compound III-40**

**[0198]**





(*S*,*E*)-methyl 7-(1-(2-(5-chloroadamantan-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{35}H_{39}ClN_4O_7$

Exact Mass: 662.25

Molecular Weight: 663.16

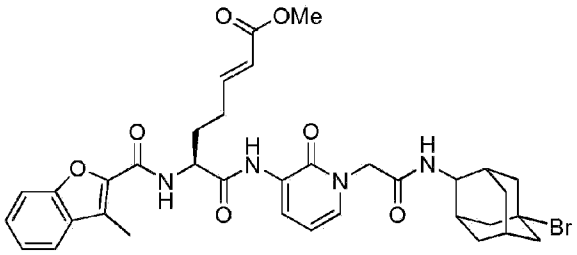
**[0199]** The synthesis of compound **III-40** was performed according to compound **III-2,** using 5-chloro-2-adamantanamine instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 32 mg, 27% (last step)

ESI-MS: 663.3 / 665.3 $[M+H]^+$

**45 Preparation of compound III-41**

**[0200]**



(*S*,*E*)-methyl 7-(1-(2-(5-bromoadamantan-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{35}H_{39}BrN_4O_7$

Exact Mass: 706.20

Molecular Weight: 707.61

**[0201]** The synthesis of compound **III-41** was performed according to compound **III-2,** using 5-

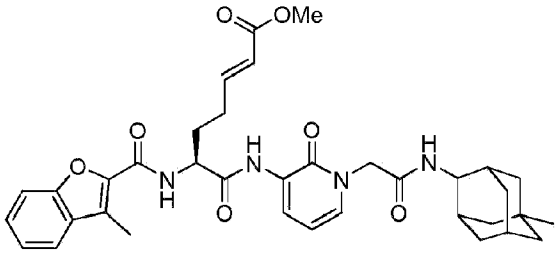
bromo-2-adamantanamine instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 41 mg, 57% (last step)

ESI-MS: 707.3 / 709.3 $[M+H]^+$

**46 Preparation of compound III-42**

**[0202]**



(*S*,*E*)-methyl 7-(1-(2-(5-methyladamantan-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{36}H_{42}N_4O_7$

Exact Mass: 642.31

Molecular Weight: 642.74

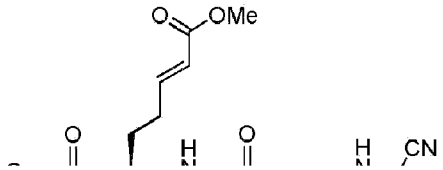
**[0203]** The synthesis of compound **III-42** was performed according to compound **III-2,** using 5-methyl-2-adamantanamine instead of 2-adamantanamine in step 2 (according to ZED3905).

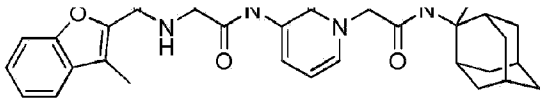
Yield: 51 mg, 47% (last step)

ESI-MS: 643.4 $[M+H]^+$

**47 Preparation of compound III-43**

**[0204]**





(S,E)-methyl 7-(1-(2-(2-carbonitrileadamantane-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{36}H_{39}N_5O_7$

Exact Mass: 653.28

Molecular Weight: 653.72

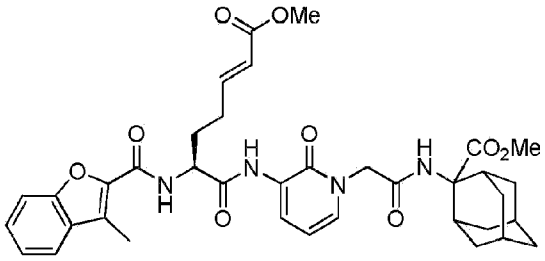
**[0205]** The synthesis of compound **III-43** was performed according to compound **III-2,** using 2-aminoadamantane-2-carbonitrile instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 36 mg, 52% (last step)

ESI-MS: 654.4 $[M+H]^+$

**48 Preparation of compound III-44**

**[0206]**



(S,E)-methyl 7-(1-(2-(2-methyl adamantane-2-carboxylate-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{37}H_{42}N_4O_9$

Exact Mass: 686.30

Molecular Weight: 686.75

**[0207]** The synthesis of compound **III-44** was performed according to compound **III-2,** using 2-

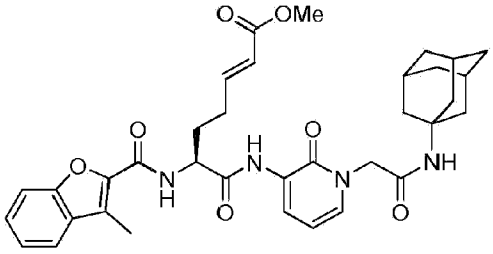
methyl 2-aminoadamantane-2-carboxylate instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 49 mg, 68% (last step)

ESI-MS: 687.4 $[M+H]^+$

**49 Preparation of compound III-45**

**[0208]**



(*S*,*E*)-methyl 7-(1-(2-(1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{35}H_{40}N_4O_7$

Exact Mass: 628.29

Molecular Weight: 628.71

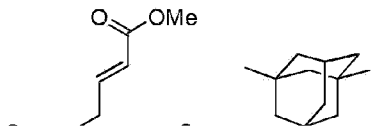
**[0209]** The synthesis of compound **III-45** was performed according to compound **III-2,** using 1-adamantanamine instead of 2-adamantanamine in step 2 (according to ZED3905).

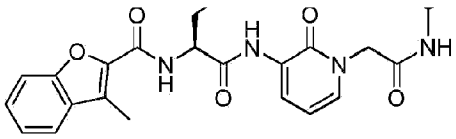
Yield: 214 mg, 77% (last step)

ESI-MS: 629.4 $[M+H]^+$

**50 Preparation of compound III-46**

**[0210]**





(*S*,*E*)-methyl 7-(1-(2-(3,5-dimethyladamantan-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{37}H_{44}N_4O_7$

Exact Mass: 656.32

Molecular Weight: 656.77

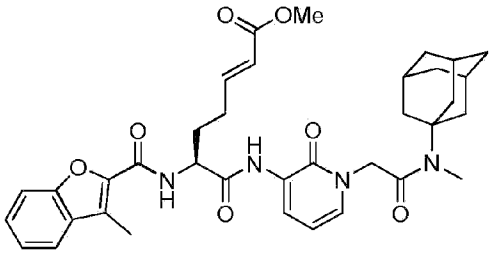
**[0211]** The synthesis of compound **III-46** was performed according to compound **III-2,** using 3,5-dimethyl-1-adamantanamine instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 67 mg, 77% (last step)

ESI-MS: 657.4 $[M+H]^+$

**51 Preparation of compound III-47**

**[0212]**



(S,E)-methyl 7-(1-(2-(1-adamantyl(methyl)amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{36}H_{42}N_4O_7$

Exact Mass: 642.31

Molecular Weight: 642.74

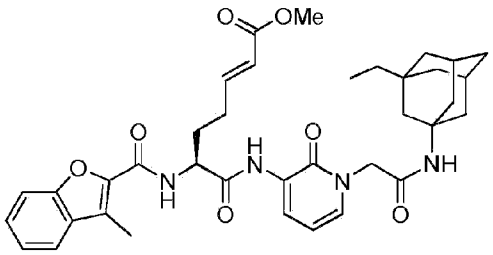
**[0213]** The synthesis of compound **III-47** was performed according to compound **III-2,** using N-methyl-1-adamantanamine instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 36 mg, 41% (last step)

ESI-MS: 643.4 $[M+H]^+$

**52 Preparation of compound III-48**

**[0214]**



(*S*,*E*)-methyl 7-(1-(2-(3-ethyladamantan-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{37}H_{44}N_4O_7$

Exact Mass: 656.32

Molecular Weight: 656.77

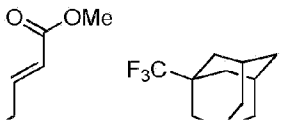
**[0215]** The synthesis of compound **III-48** was performed according to compound **III-2,** using 3-ethyl-1-adamantanamine instead of 2-adamantanamine in step 2 (according to ZED3905).

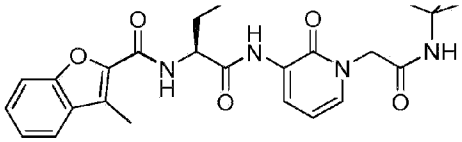
Yield: 78 mg, 54% (last step)

ESI-MS: 657.4 $[M+H]^+$

**53 Preparation of compound III-49**

**[0216]**





(*S*,*E*)-methyl 7-(1-(2-(3-trifluoromethyladamantan-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{36}H_{39}F_3N_4O_7$

Exact Mass: 696.28

Molecular Weight: 696.71

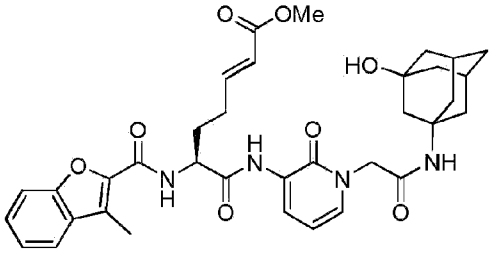
**[0217]** The synthesis of compound **III-49** was performed according to compound **III-2,** using 3-trifluoromethyl-1-adamantanamine instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 29 mg, 45% (last step)

ESI-MS: 697.4 $[M+H]^+$

**54 Preparation of compound III-50**

**[0218]**



(*S*,*E*)-methyl 7-(1-(2-(3-hydroxyadamantan-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{35}H_{40}N_4O_8$

Exact Mass: 644.28

Molecular Weight: 644.71

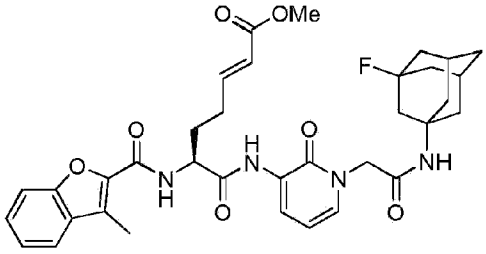
**[0219]** The synthesis of compound **III-50** was performed according to compound **III-2,** using 3-hydroxy-1-adamantanamine instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 23 mg, 37% (last step)

ESI-MS: 645.4 $[M+H]^+$

**55 Preparation of compound III-51**

**[0220]**




(*S*,*E*)-methyl 7-(1-(2-(3-fluoroadamantan-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{35}H_{39}FN_4O_7$

Exact Mass: 646.28

Molecular Weight: 646.71

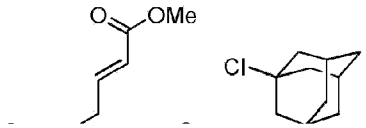
**[0221]** The synthesis of compound **III-51** was performed according to compound **III-2,** using 3-fluoro-1-adamantanamine instead of 2-adamantanamine in step 2 (according to ZED3905).

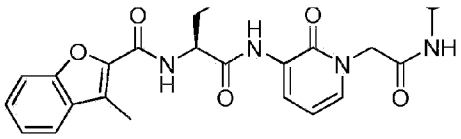
Yield: 56 mg, 62% (last step)

ESI-MS: 647.4 $[M+H]^+$

**56 Preparation of compound III-52**

**[0222]**





(*S*,*E*)-methyl 7-(1-(2-(3-chloroadamantan-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{35}H_{39}ClN_4O_7$

Exact Mass: 662.25

Molecular Weight: 663.16

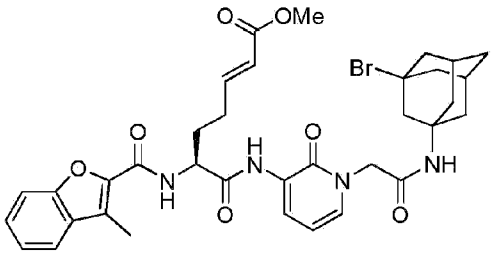
**[0223]** The synthesis of compound **III-52** was performed according to compound **III-2,** using 3-chloro-1-adamantanamine instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 24 mg, 32% (last step)

ESI-MS: 663.3 / 665.3 $[M+H]^+$

**57 Preparation of compound III-53**

**[0224]**



(*S*,*E*)-methyl 7-(1-(2-(3-bromoadamantan-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{35}H_{39}BrN_4O_7$

Exact Mass: 706.20

Molecular Weight: 707.61

**[0225]** The synthesis of compound **III-53** was performed according to compound **III-2,** using 3-

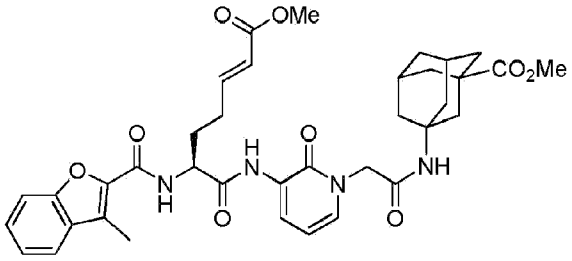
bromo-1-adamantanamine instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 25 mg, 42% (last step)

ESI-MS: 707.3 / 709.3 $[M+H]^+$

**58 Preparation of compound III-54**

**[0226]**



(S,E)-methyl 7-(1-(2-(3-methyl adamantane-3-carboxylate-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{37}H_{42}N_4O_9$

Exact Mass: 686.30

Molecular Weight: 686.75

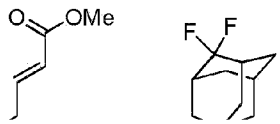
**[0227]** The synthesis of compound **III-54** was performed according to compound **III-2,** using methyl 3-aminoadamantane-1-carboxylate instead of 2-adamantanamine in step 2 (according to ZED3905).

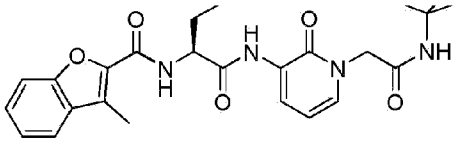
Yield: 38 mg, 52% (last step)

ESI-MS: 687.4 $[M+H]^+$

**59 Preparation of compound III-55**

**[0228]**





(*S*,*E*)-methyl 7-(1-(2-(4,4-difluoroadamantan-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{35}H_{38}F_2N_4O_7$

Exact Mass: 664.27

Molecular Weight: 664.70

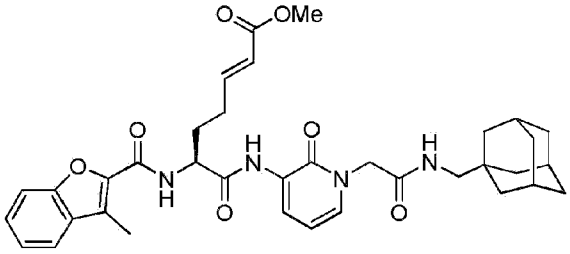
**[0229]** The synthesis of compound **III-55** was performed according to compound **III-2,** using 4,4-difluoro-1-adamantanamine instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 11 mg, 36% (last step)

ESI-MS: 665.4 $[M+H]^+$

**60 Preparation of compound III-56**

**[0230]**



(S,E)-methyl 7-(1-(2-(1-adamantylmethylamino)-2-oxoethyl)-2-oxo-1 ,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{36}H_{42}N_4O_7$

Exact Mass: 642.31

Molecular Weight: 642.74

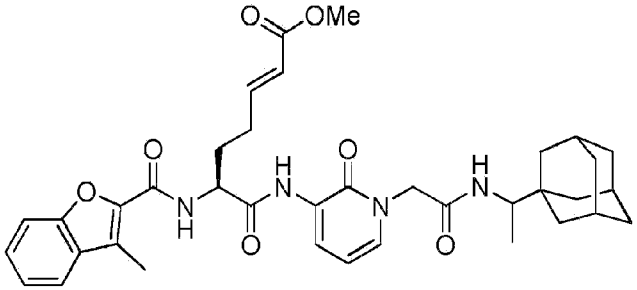
**[0231]** The synthesis of compound **III-56** was performed according to compound **III-2,** using 1-adamantanemethylamine instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 47 mg, 68% (last step)

ESI-MS: 643.4 $[M+H]^+$

**61 Preparation of compound III-57**

**[0232]**



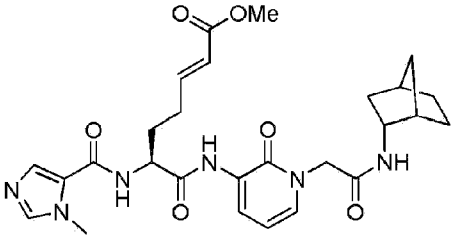
**[0233]** The synthesis of compound **III-57** was performed according to compound **III-2,** using 1-rimantadine instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 23 mg, 35% (last step)

ESI-MS: 657.5 $[M+H]^+$

**62 Preparation of compound III-58**

**[0234]**



(S,E)-methyl 7-(1-(2-((1S,2R,4R)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-imidazole-5-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{27}H_{34}N_6O_6$

Exact Mass: 538.25

Molecular Weight: 538.60

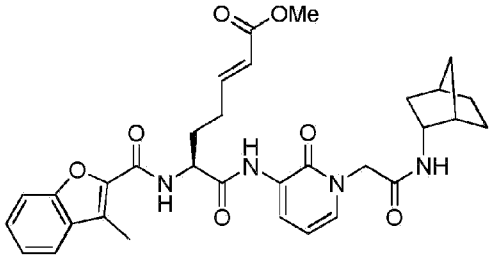
**[0235]** The synthesis of compound **III-58** was performed according to compound **III-1,** using (±)-endo-2-norbornylamine instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 36 mg, 53% (last step)

ESI-MS: 539.4 $[M+H]^+$

**63 Preparation of compound III-59**

**[0236]**



(*S,E*)-methyl 7-(1-(2-((1*S*,2*R*,4*R*)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{32}H_{36}N_4O_7$

Exact Mass: 588.26

Molecular Weight: 588.65

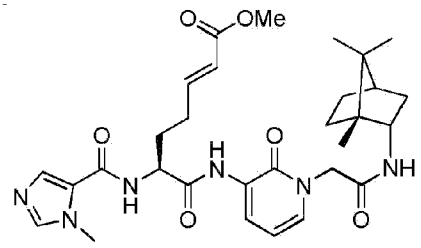
**[0237]** The synthesis of compound **III-59** was performed according to compound **III-2,** using (±)-endo-2-norbornylamine instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 56 mg, 69% (last step)

ESI-MS: 589.4 $[M+H]^+$

**64 Preparation of compound III-60**

**[0238]**



(S,E)-methyl 6-(1-methyl-1H-imidazole-5-carboxamido)-7-oxo-7-(2-oxo-1-(2-oxo-2-((1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-ylamino)hept-2-enoate

Chemical Formula: $C_{30}H_{40}N_6O_6$

Exact Mass: 580.30

Molecular Weight: 580.68

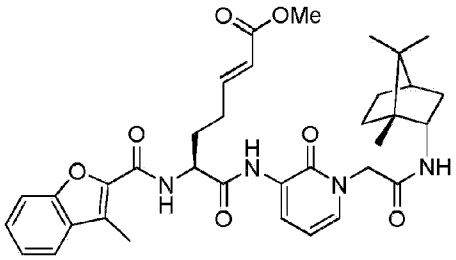
**[0239]** The synthesis of compound **III-60** was performed according to compound **III-1,** using (R)-(+)-bornylamine instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 25 mg, 49% (last step)

ESI-MS: 581.5 $[M+H]^+$

**65 Preparation of compound III-61**

**[0240]**



(S,E)-methyl 6-(3-methylbenzofuran-2-carboxamido)-7-oxo-7-(2-oxo-1-(2-oxo-2-((1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-ylamino)hept-2-enoate

Chemical Formula: $C_{35}H_{42}N_4O_7$

Exact Mass: 630.31

Molecular Weight: 630.73

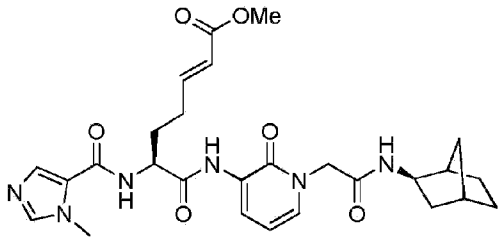
**[0241]** The synthesis of compound **III-61** was performed according to compound **III-2,** using (R)-(+)-bornylamine instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 42 mg, 63% (last step)

ESI-MS: 631.5 $[M+H]^+$

**66 Preparation of compound III-62**

**[0242]**



(S,E)-methyl 7-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-imidazole-5-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{27}H_{34}N_6O_6$

Exact Mass: 538.25

Molecular Weight: 538.60

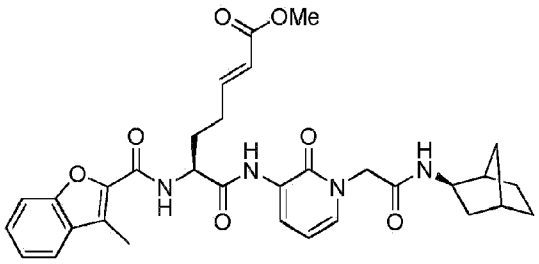
**[0243]** The synthesis of compound **III-62** was performed according to compound **III-1,** using exo-2-aminonorbornane instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 56 mg, 64% (last step)

ESI-MS: 539.4 $[M+H]^+$

**67 Preparation of compound III-63**

**[0244]**



(S,E)-methyl 7-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{27}H_{34}N_6O_6$

Exact Mass: 538.25

Molecular Weight: 538.60

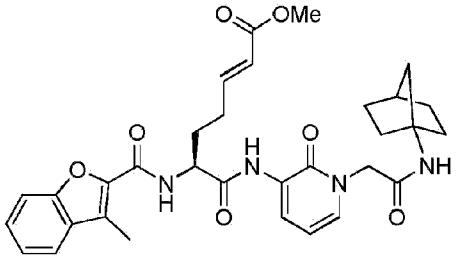
**[0245]** The synthesis of compound **III-63** was performed according to compound **III-2,** using exo-2-aminonorbornane instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 78 mg, 71% (last step)

ESI-MS: 589.4 $[M+H]^+$

**68 Preparation of compound III-64**

**[0246]**



(S,E)-methyl 7-(1-(2-(bicyclo[2.2.1]heptan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{32}H_{36}N_4O_7$

Exact Mass: 588.26

Molecular Weight: 588.65

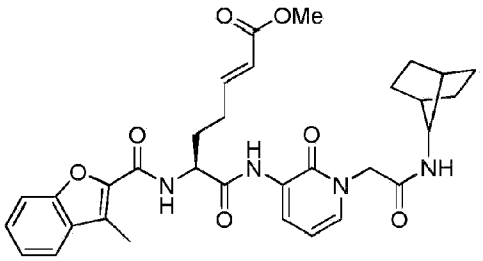
**[0247]** The synthesis of compound **III-64** was performed according to compound **III-2,** using bicyclo[2.2.1]heptan-1-ylamine instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 27 mg, 52% (last step)

ESI-MS: 589.4 $[M+H]^+$

**69 Preparation of compound III-65**

**[0248]**



(S,E)-methyl 7-(1-(2-(bicyclo[2.2.1]heptan-7-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{32}H_{36}N_4O_7$

Exact Mass: 588.26

Molecular Weight: 588.65

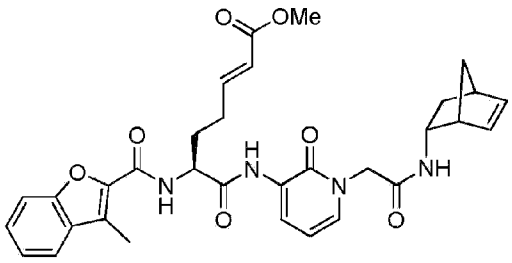
**[0249]** The synthesis of compound **III-65** was performed according to compound **III-2,** using bicyclo[2.2.1]heptan-7-ylamine instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 52 mg, 75% (last step)

ESI-MS: 589.4 $[M+H]^+$

**70 Preparation of compound III-66**

**[0250]**



(S,E)-methyl 7-(1-(2-(bicyclo[2.2.1]hept-5-en-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{32}H_{34}N_4O_7$

Exact Mass: 586.24

Molecular Weight: 586.63

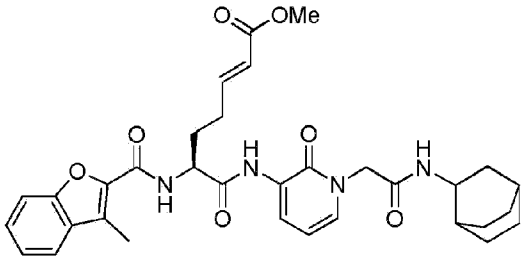
**[0251]** The synthesis of compound **III-66** was performed according to compound **III-2,** using bicyclo[2.2.1]hept-5-en-2-amine instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 36 mg, 54% (last step)

ESI-MS: 587.4 $[M+H]^+$

**71 Preparation of compound III-67**

**[0252]**



(6S,E)-methyl 7-(1-(2-(bicyclo[2.2.2]octan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{33}H_{38}N_4O_7$

Exact Mass: 602.27

Molecular Weight: 602.68

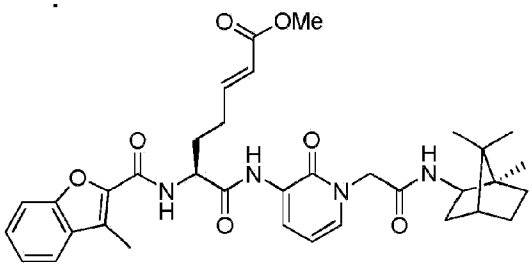
**[0253]** The synthesis of compound **III-67** was performed according to compound **III-2,** using bicyclo[2.2.2]oct-2-ylamine instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 42 mg, 51% (last step)

ESI-MS: 603.4 $[M+H]^+$

**72 Preparation of compound III-68**

**[0254]**



(S,E)-methyl 6-(3-methylbenzofuran-2-carboxamido)-7-oxo-7-(2-oxo-1-(2-oxo-2-((1R,2R,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-ylamino)hept-2-enoate

Chemical Formula: $C_{35}H_{42}N_4O_7$

Exact Mass: 630.31

Molecular Weight: 630.73

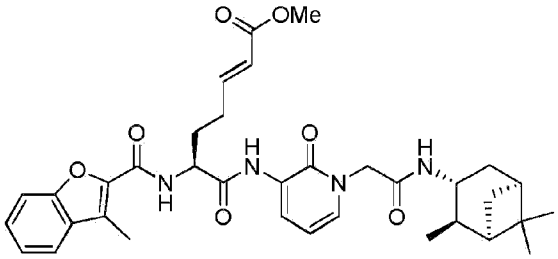
**[0255]** The synthesis of compound **III-68** was performed according to compound **III-2,** using (R)-(-)-isobornylamine instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 26 mg, 56% (last step)

ESI-MS: 631.5 $[M+H]^+$

**73 Preparation of compound III-69**

**[0256]**



(S,E)-methyl 6-(3-methylbenzofuran-2-carboxamido)-7-oxo-7-(2-oxo-1-(2-oxo-2-((1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylamino)ethyl)-1,2-dihydropyridin-3-ylamino)hept-2-enoate

Chemical Formula: $C_{35}H_{42}N_4O_7$

Exact Mass: 630.31

Molecular Weight: 630.73

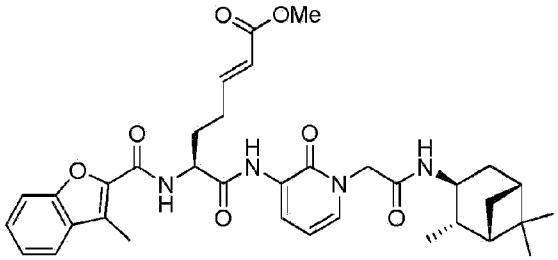
**[0257]** The synthesis of compound **III-69** was performed according to compound **III-2,** using (1R,2R,3R,5S)-(-)-isopinocampheylamine instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 15 mg, 48% (last step)

ESI-MS: 631.5 $[M+H]^+$

**74 Preparation of compound III-70**

**[0258]**



(S,E)-methyl 6-(3-methylbenzofuran-2-carboxamido)-7-oxo-7-(2-oxo-1-(2-oxo-2-((1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylamino)ethyl)-1,2-dihydropyridin-3-

ylamino)hept-2-enoate

Chemical Formula: $C_{35}H_{42}N_4O_7$

Exact Mass: 630.31

Molecular Weight: 630.73

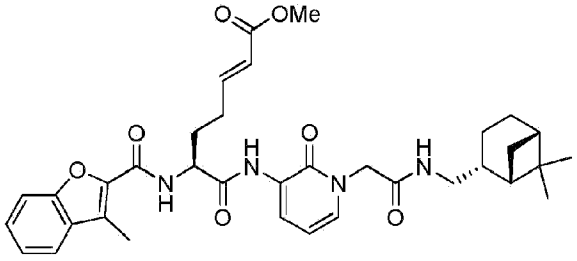
**[0259]** The synthesis of compound **III-70** was performed according to compound **III-2,** using (1S,2S,3S,5R)-(+)-isopinocampheylamine instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 21 mg, 58% (last step)

ESI-MS: 631.5 $[M+H]^+$

**75 Preparation of compound III-71**

**[0260]**



(S,E)-methyl 7-(1-(2-(((1S,2R,5S)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{35}H_{42}N_4O_7$

Exact Mass: 630.31

Molecular Weight: 630.73

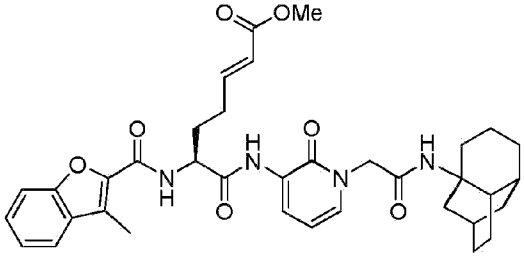
**[0261]** The synthesis of compound **III-71** was performed according to compound **III-2,** using (-)-cis-myrtanylamine instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 12 mg, 45% (last step)

ESI-MS: 631.5 $[M+H]^+$

**76 Preparation of compound III-72**

**[0262]**



(S,E)-methyl 7-(1-(2-(4-homoisotwistane-3-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{36}H_{42}N_4O_7$

Exact Mass: 642.31

Molecular Weight: 642.74

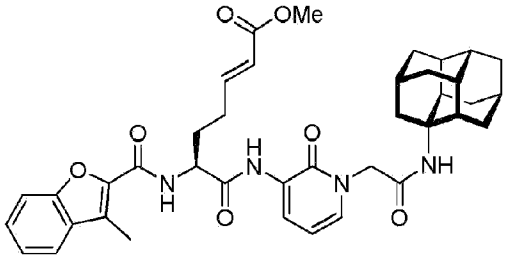
**[0263]** The synthesis of compound **III-72** was performed according to compound **III-2,** using 3-amino-4-homoisotwistane instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 23 mg, 59% (last step)

ESI-MS: 643.5 $[M+H]^+$

**77 Preparation of compound III-73**

**[0264]**



(S,E)-methyl 7-(1-(2-(diamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{39}H_{44}N_4O_7$

Exact Mass: 680.32

Molecular Weight: 680.79

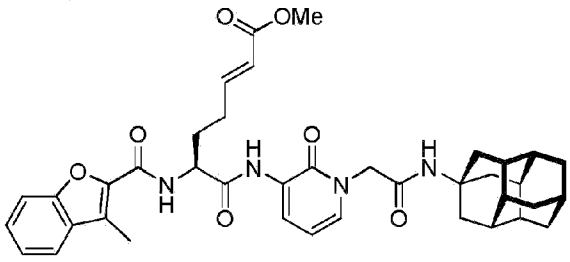
**[0265]** The synthesis of compound **III-73** was performed according to compound **III-2,** using 1-aminodiamantane instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 26 mg, 62% (last step)

ESI-MS: 681.5 $[M+H]^+$

**78 Preparation of compound III-74**

**[0266]**



(S,E)-methyl 7-(1-(2-(diamantane-4-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{39}H_{44}N_4O_7$

Exact Mass: 680.32

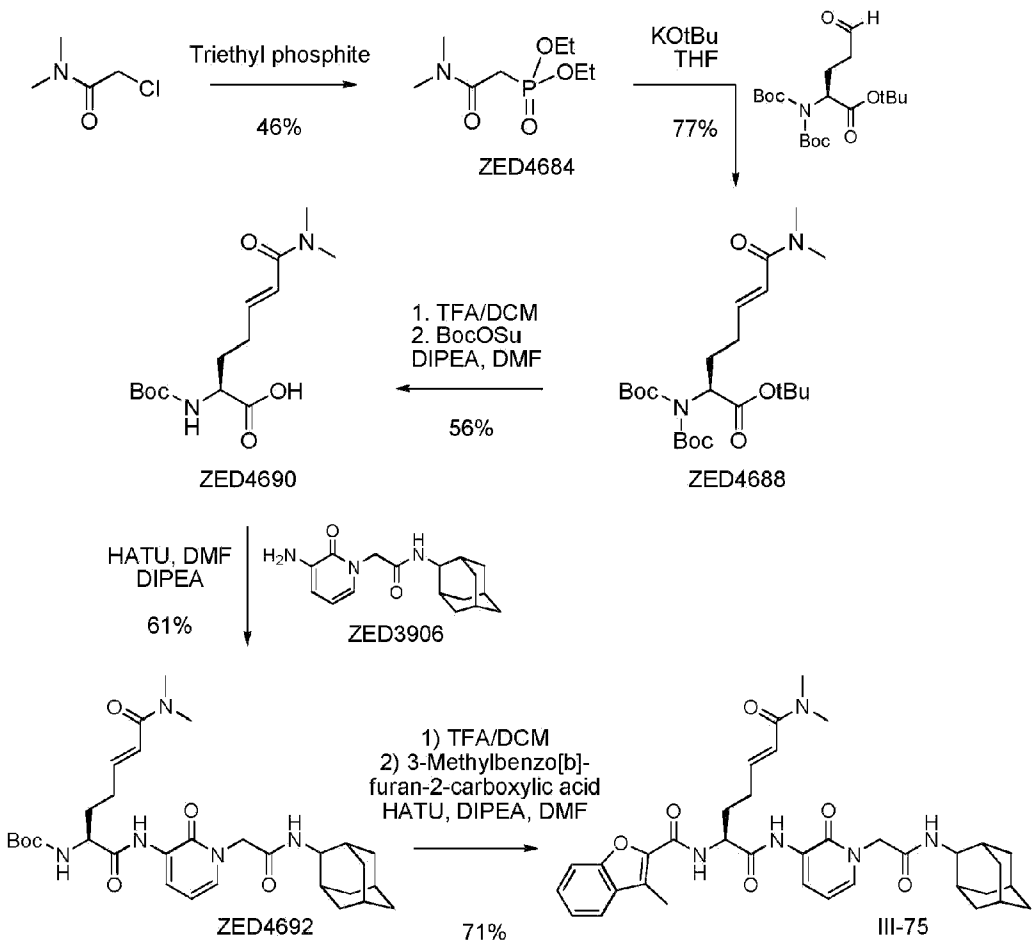
Molecular Weight: 680.79

**[0267]** The synthesis of compound **III-74** was performed according to compound **III-2,** using 4-aminodiamantane instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 17 mg, 53% (last step)

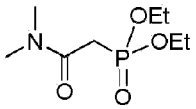
ESI-MS: 681.5 $[M+H]^+$

**Scheme III-4**




**79 Preparation of ZED4684**

**[0268]**



diethyl 2-(dimethylamino)-2-oxoethylphosphonate

Chemical Formula: $C_8H_{18}NO_4P$

Exact Mass: 223.10

Molecular Weight: 223.21

**[0269]** 2.5 mL (24.3 mmol) of 2-chloro-N,N-dimethylacetamide and 4.2 mL (1 eq) of triethyl

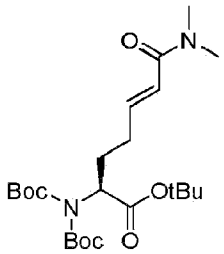
phosphite were stirred at 160°C for 8 h. The mixture was purified by HPLC.

Yield: 2.50 g, 46%

ESI-MS: 224.4 $[M+H]^+$

**80 Preparation of ZED4688**

**[0270]**




(*S,E*)-*tert*-butyl 2-(bis(*tert*-butoxycarbonyl)amino)-7-(dimethylamino)-7-oxohept-5-enoate
Chemical Formula: $C_{23}H_{40}N_2O_7$

Exact Mass: 456.28

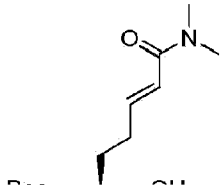
Molecular Weight: 456.57

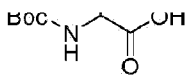
**[0271]** 500 mg (2.24 mmol) of **ZED4684** were dissolved in 16 mL THF. At 0°C, 251 mg (2.24 mmol) of potassium tert-butoxide were added. After 30 min, 723 mg (1.87 mmol) of the aldehyde (S)-tert-butyl 2-(bis(tert-butoxycarbonyl)amino)-5-oxopentanoate **(ZED721)** in 16 mL THF were added and the mixture was stirred at 0°C for 1.5 h before being quenched with water (16 mL, 0°C). After extraction with EtOAc (2 x 32 mL), the combined organic phases were washed with brine (15 mL), dried over $Na_2SO_4$, filtered and the solvent was evaporated. The residue was purified by HPLC.

Yield: 659 mg, 77% ESI-MS: 457.5 $[M+H]^+$

**81 Preparation of ZED4690**

**[0272]**





(*S,E*)-2-(*tert*-butoxycarbonylamino)-7-(dimethylamino)-7-oxohept-5-enoic acid

Chemical Formula: $C_{14}H_{24}N_2O_5$

Exact Mass: 300.17

Molecular Weight: 300.35

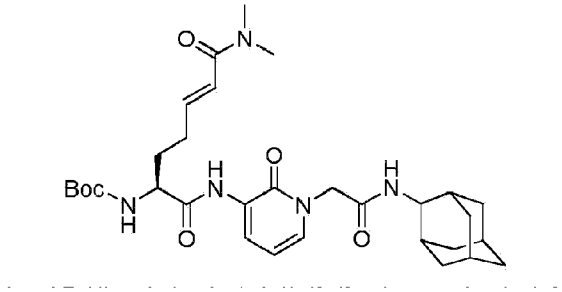
**[0273]** 659 mg of **ZED4688** (1.44 mmol) were dissolved in 20 ml DCM/TFA (1:1) and stirred at room temperature for 1 h. The solvent was evaporated, and the residue was dissolved in 10 ml DMF and 245 µl DIPEA (2 eq). 310 mg (1 eq) of N-(tert-butoxycarbonyloxy)succinimide were added and the reaction was stirred at room temperature overnight. The solvent was evaporated and the residue was dissolved in ethyl acetate and washed twice with each citric acid solution (10%) and brine. The organic phase was dried over $Na_2SO_4$, filtered and the solvent was evaporated. The residue was purified by HPLC.

Yield: 242 mg, 56%

ESI-MS: 301.5 $[M+H]^+$

**82 Preparation of ZED4692**

**[0274]**



(*S,E*)-*tert*-butyl 7-(dimethylamino)-1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-1,7-dioxohept-5-en-2-ylcarbamate

Chemical Formula: $C_{31}H_{45}N_5O_6$

Exact Mass: 583.34

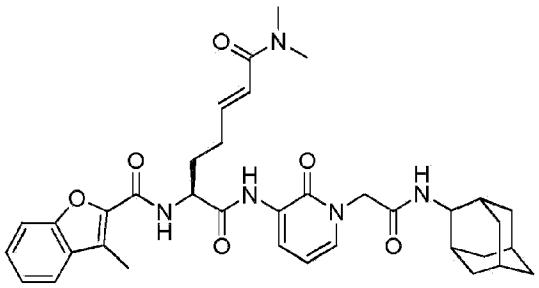
Molecular Weight: 583.72

**[0275]** 242 mg (0.81 mmol) of **ZED4688,** 308 mg (1 eq) HATU and 244 mg (1 eq) ZED3906 were dissolved in 10 mL DMF and 276 µL DIPEA (2 eq) and stirred at 45°C overnight. The solvent was evaporated; the residue was dissolved in 50 mL EtOAc and washed twice with each 15 mL citric acid solution (10%), $NaHCO_3$ solution (10%) and brine. The organic phase was dried over $Na_2SO_4$, filtered and the solvent was evaporated. The residue was purified by HPLC.

Yield: 288 mg, 61% ESI-MS: 584.4 $[M+H]^+$

**83 Preparation of compound III-75**

**[0276]**



(*S,E*)-$N^7$-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-$N^1$,$N^1$-dimethyl-6-(3-methylbenzofuran-2-carboxamido)hept-2-enediamide

Chemical Formula: $C_{36}H_{43}N_5O_6$

Exact Mass: 641.32

Molecular Weight: 641.76

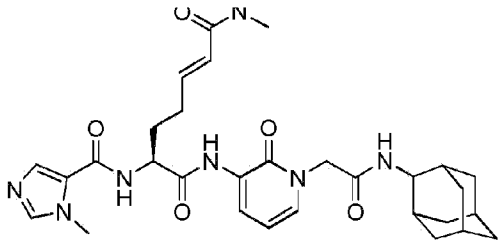
**[0277]** 100 mg (0.17 mmol) of **ZED4692** were dissolved in 6 ml DCM/TFA (1:1) and stirred at room temperature for 1 h. The solvent was evaporated, and the residue was dissolved in 15 ml DMF and 58 µl DIPEA (2 eq). 30 mg (1 eq) of 3-methylbenzo[b]furan-2-carboxylic acid and 65 mg (1 eq) of HATU were added, and the reaction was stirred at room temperature overnight. The solvent was evaporated; the residue was purified by HPLC.

Yield: 78 mg, 71% ESI-MS: 642.5 $[M+H]^+$

**84 Preparation of compound III-76**

**[0278]**





(*S*,*E*)-$N^7$-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-$N^1$,$N^1$-dimethyl-6-(1-methyl-1*H*-imidazole-5-carboxamido)hept-2-enediamide

Chemical Formula: $C_{31}H_{41}N_7O_5$

Exact Mass: 591.32

Molecular Weight: 591.70

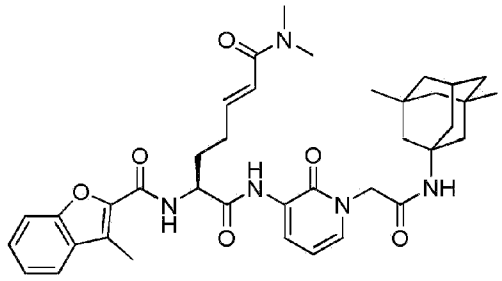
**[0279]** The synthesis of compound **III-76** was performed according to compound **III-75,** using 1-methyl-1H-imidazole-5-carboxylic acid instead of 3-methylbenzo[b]furan-2-carboxylic acid in the final step.

Yield: 70 mg, 69% (last step)

ESI-MS: 592.5 $[M+H]^+$

**85 Preparation of compound III-77**

**[0280]**



(*S*,*E*)-$N^7$-(1-(2-(3,5-dimethyladamantan-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-$N^1$,$N^1$-dimethyl-6-(3-methylbenzofuran-2-carboxamido)hept-2-enediamide

Chemical Formula: $C_{38}H_{47}N_5O_6$

Exact Mass: 669.35

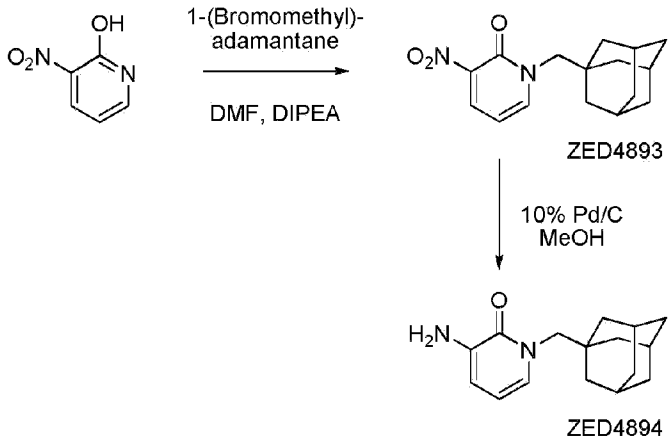
Molecular Weight: 669.81

**[0281]** The synthesis of compound **III-77** was performed according to compound **III-75,** using 3,5-dimethyl-1-adamantanamine instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 45 mg, 57% (last step)

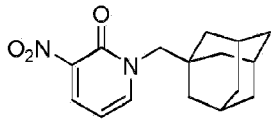
ESI-MS: 670.5 $[M+H]^+$

**Scheme III-5 New Building Block**




**86 Preparation of compound ZED4893**

**[0282]**




1-(1-adamantylmethyl)-3-nitropyridin-2(1H)-one

Chemical Formula: $C_{16}H_{20}N_2O_3$

Exact Mass: 288.15

Molecular Weight: 288.34

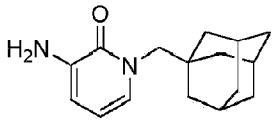
**[0283]** 500 mg (3.57 mmol) of 2-hydroxy-3-nitropyridine and 818 mg (1 eq) of 1-(bromomethyl)adamantane were dissolved in 10 mL DMF and 1.24 mL DIPEA (2 eq) and stirred at room temperature overnight. The solvent was evaporated; the residue was dissolved

in 30 mL EtOAc and washed twice with each 10 mL citric acid solution (10%), $NaHCO_3$ solution (10%) and brine. The organic phase was dried over $Na_2SO_4$, filtered and the solvent was evaporated. The residue was purified by HPLC.

Yield: 484 mg, 47% ESI-MS: 289.3 $[M+H]^+$

**87 Preparation of compound ZED4894**

**[0284]**



3-amino-1-(1-adamantylmethyl)pyridin-2(1H)-one

Chemical Formula: $C_{16}H_{22}N_2O$

Exact Mass: 258.17

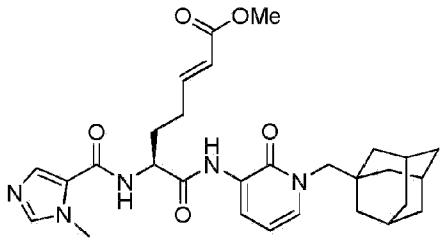
Molecular Weight: 258.36

**[0285]** 484 mg (1.68 mmol) of ZED4893 were suspended in 30 mL MeOH before 50 mg of palladium (10%) on activated carbon (unreduced) were added. The suspension was stirred for 3 h at room temperature under an atmosphere of hydrogen. The catalyst was filtered, and the solvent was evaporated.

Yield: 339 mg, 78% ESI-MS: 259.4 $[M+H]^+$

**88 Preparation of compound III-78**

**[0286]**



(S,E)-methyl 7-(1-(1-adamantylmethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-imidazole-5-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{29}H_{37}N_5O_5$

Exact Mass: 535.28

Molecular Weight: 535.63

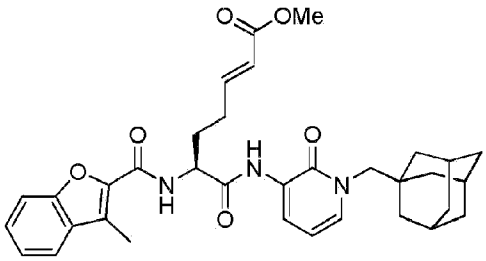
**[0287]** The synthesis of compound **III-78** was performed according to compound **III-1,** using **ZED4894** instead of **ZED3906** in step 5 (according to ZED3907).

Yield: 43 mg, 59% (last step)

ESI-MS: 536.4 $[M+H]^+$

**89 Preparation of compound III-79**

**[0288]**




(S,E)-methyl 7-(1-(1-adamantylmethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{34}H_{39}N_3O_6$

Exact Mass: 585.28

Molecular Weight: 585.69

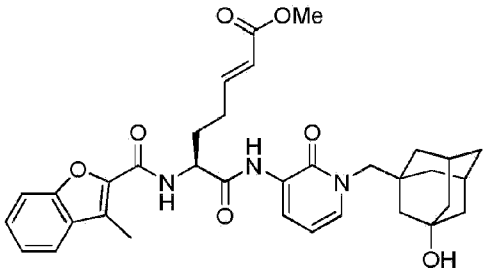
**[0289]** The synthesis of compound **III-79** was performed according to compound **III-2,** using **ZED4894** instead of **ZED3906** in step 5 (according to ZED3907).

Yield: 56 mg, 69% (last step)

ESI-MS: 586.4 $[M+H]^+$

**90 Preparation of compound III-80**

**[0290]**




(6S,E)-methyl 7-(1-((3-hydroxy-1-adamantyl)methyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{34}H_{39}N_3O_7$

Exact Mass: 601.28

Molecular Weight: 601.69

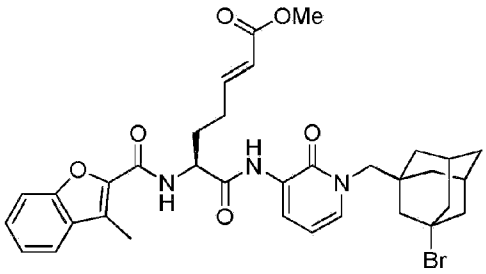
**[0291]** The synthesis of compound **III-80** was performed according to compound **III-79,** using 3-(bromomethyl)-1-adamantanol instead of 1-(bromomethyl)adamantane (according to ZED4893).

Yield: 29 mg, 51% (last step)

ESI-MS: 602.4 $[M+H]^+$

**91 Preparation of compound III-81**

**[0292]**




(6S,E)-methyl 7-(1-((3-bromo-1-adamantyl)methyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{34}H_{38}BrN_3O_6$

Exact Mass: 663.19

Molecular Weight: 664.59

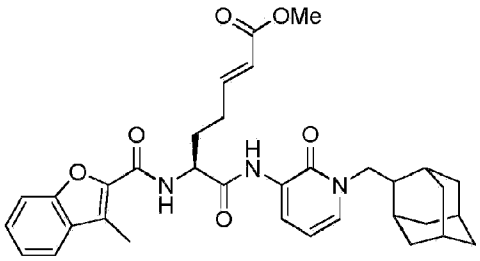
**[0293]** The synthesis of compound **III-81** was performed according to compound **III-79,** using 1-bromo-3-(bromomethyl)adamantane instead of 1-(bromomethyl)adamantane (according to ZED4893).

Yield: 37 mg, 61% (last step)

ESI-MS: 664.3 / 666.3 $[M+H]^+$

**92 Preparation of compound III-82**

**[0294]**




(S,E)-methyl 7-(1-(2-adamantylmethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{34}H_{39}N_3O_6$

Exact Mass: 585.28

Molecular Weight: 585.69

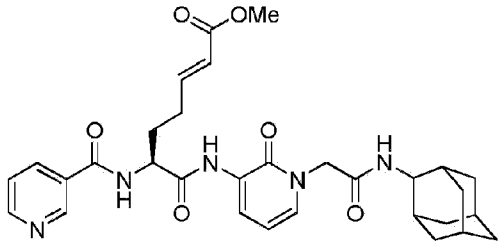
**[0295]** The synthesis of compound **III-82** was performed according to compound **III-79,** using 2-(bromomethyl)adamantane instead of 1-(bromomethyl)adamantane (according to ZED4893).

Yield: 58 mg, 77% (last step)

ESI-MS: 586.4 $[M+H]^+$

**93 Preparation of compound III-83**

**[0296]**



(S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(nicotinamido)-7-oxohept-2-enoate

Chemical Formula: $C_{31}H_{37}N_5O_6$

Exact Mass: 575.27

Molecular Weight: 575.66

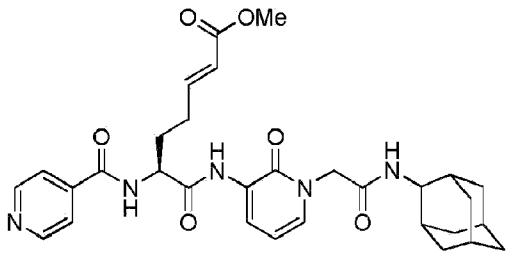
**[0297]** The synthesis of compound **III-83** was performed according to compound **III-1,** using nicotinic acid instead of 3-methylbenzo[b]furan-2-carboxylic acid in the final step.

Yield: 59 mg, 79% (last step)

ESI-MS: 576.4 $[M+H]^+$

**94 Preparation of compound III-84**

**[0298]**



(S,E)-methyl 6-(isonicotinamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate

Chemical Formula: $C_{31}H_{37}N_5O_6$

Exact Mass: 575.27

Molecular Weight: 575.66

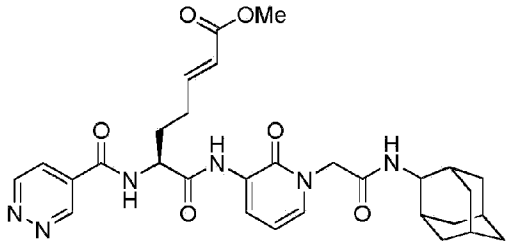
**[0299]** The synthesis of compound **III-84** was performed according to compound **III-1,** using isonicotinic acid instead of 3-methylbenzo[b]furan-2-carboxylic acid in the final step.

Yield: 73 mg, 85% (last step)

ESI-MS: 576.4 $[M+H]^+$

**95 Preparation of compound III-85**

**[0300]**



(S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(pyridazine-4-carboxamido)hept-2-enoate

Chemical Formula: $C_{30}H_{36}N_6O_6$

Exact Mass: 576.27

Molecular Weight: 576.64

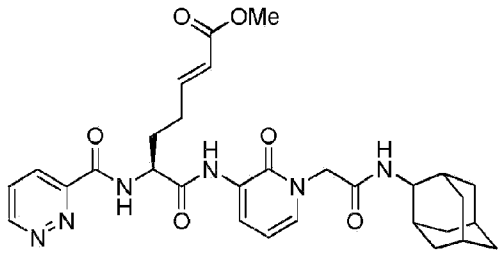
**[0301]** The synthesis of compound **III-85** was performed according to compound **III-1,** using pyridazine-4-carboxylic acid instead of 3-methylbenzo[b]furan-2-carboxylic acid in the final step.

Yield: 54 mg, 78% (last step)

ESI-MS: 577.4 $[M+H]^+$

**96 Preparation of compound III-86**

**[0302]**



(S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(pyridazine-3-carboxamido)hept-2-enoate

Chemical Formula: $C_{30}H_{36}N_6O_6$

Exact Mass: 576.27

Molecular Weight: 576.64

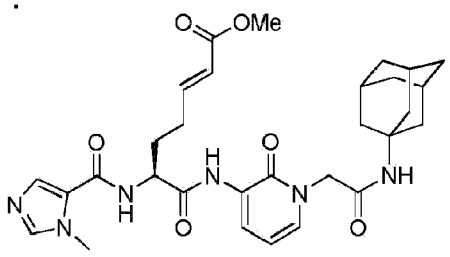
**[0303]** The synthesis of compound **III-86** was performed according to compound **III-1,** using pyridazine-3-carboxylic acid instead of 3-methylbenzo[b]furan-2-carboxylic acid in the final step.

Yield: 47 mg, 82% (last step)

ESI-MS: 577.4 $[M+H]^+$

**97 Preparation of compound III-87**

**[0304]**



(S,E)-methyl 7-(1-(2-(1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-imidazole-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{30}H_{38}N_6O_6$

Exact Mass: 578.29

Molecular Weight: 578.66

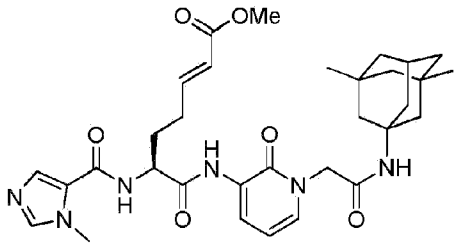
**[0305]** The synthesis of compound **III-87** was performed according to compound **III-1,** using 1-adamantanamine instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 117 mg, 78% (last step)

ESI-MS: 579.5 $[M+H]^+$

**98 Preparation of compound III-88**

**[0306]**




(S,E)-methyl 7-(1-(2-(3,5-dimethyladamantane)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-imidazole-5-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{32}H_{42}N_6O_6$

Exact Mass: 606.32

Molecular Weight: 606.71

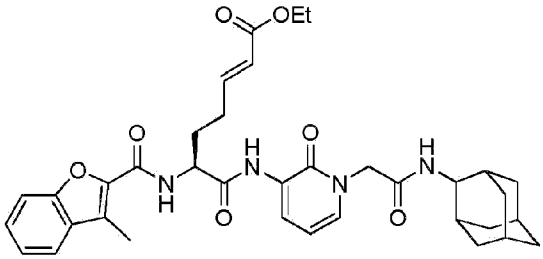
**[0307]** The synthesis of compound **III-88** was performed according to compound **III-1**, using 3,5-dimethyl-1-adamantanamine instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 132 mg, 83% (last step)

ESI-MS: 607.5 $[M+H]^+$

**99 Preparation of compound III-89**

**[0308]**



(S,E)-ethyl 7 -(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{36}H_{42}N_4O_7$

Exact Mass: 642.31

Molecular Weight: 642.74

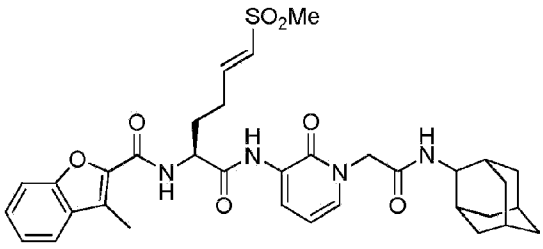
**[0309]** The synthesis of compound **III-89** was performed according to compound **III-2**, using (carbethoxyethylidene)triphenylphosphorane instead of (carbomethoxymethylene)triphenylphosphorane (according to ZED755).

Yield: 57 mg, 85% (last step)

ESI-MS: 643.5 $[M+H]^+$

**100 Preparation of compound III-90**

**[0310]**



(S,E)-N-(1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(methylsulfonyl)-1-oxohex-5-en-2-yl)-3-methylbenzofuran-2-carboxamide

Chemical Formula: $C_{34}H_{40}N_4O_7S$

Exact Mass: 648.26

Molecular Weight: 648.77

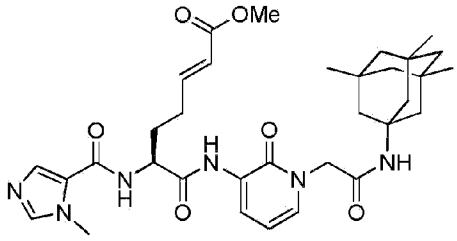
**[0311]** The synthesis of compound **III-90** was performed according to compound **III-2**, using diethyl (methanesulfonylmethyl)phosphonate instead of (carbomethoxymethylene)triphenylphosphorane (according to ZED755).

Yield: 79 mg, 72% (last step)

ESI-MS: 649.4 $[M+H]^+$

**101 Preparation of compound III-91**

**[0312]**



Chemical Formula: $C_{33}H_{44}N_6O_6$

Exact Mass: 620.33

Molecular Weight: 620.74

(S,E)-methyl 7-(1-(2-(3,5,7-trimethyl-1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-imidazole-5-carboxamido)-7-oxohept-2-enoate

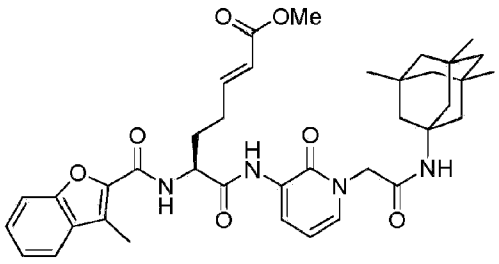
**[0313]** The synthesis of compound **III-91** was performed according to compound **III-1**, using 3,5,7-trimethyl-1-adamantanamine instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 41 mg, 69% (last step)

ESI-MS: 621.5 $[M+H]^+$

**102 Preparation of compound III-92**

**[0314]**



Chemical Formula: $C_{38}H_{46}N_4O_7$

Exact Mass: 670.34

Molecular Weight: 670.79

(S,E)-methyl 7-(1-(2-(3,5,7-trimethyl-1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoate

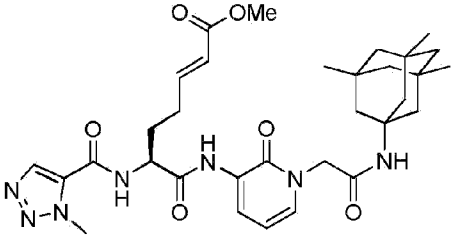
**[0315]** The synthesis of compound **III-92** was performed according to compound **III-2**, using 3,5,7-trimethyl-1-adamantanamine instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 67 mg, 75% (last step)

ESI-MS: 671.5 $[M+H]^+$

**103 Preparation of compound III-93**

**[0316]**



Chemical Formula: $C_{32}H_{43}N_7O_6$

Exact Mass: 621.33

Molecular Weight: 621.73

(S,E)-methyl 7-(1-(2-(3,5,7-trimethyl-1-adamantylamino)-2-oxoethyl)-2-oxo-1 ,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-1,2,3-triazole-5-carboxamido)-7-oxohept-2-enoate

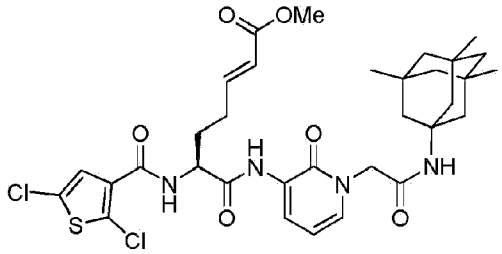
**[0317]** The synthesis of compound **III-93** was performed according to compound **III-22**, using 3,5,7-trimethyl-1-adamantanamine instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 34 mg, 68% (last step)

ESI-MS: 622.5 $[M+H]^+$

**104 Preparation of compound III-94**

**[0318]**




Chemical Formula: $C_{33}H_{40}Cl_2N_4O_6S$

Exact Mass: 690.20

Molecular Weight: 691.66

(S,E)-methyl 6-(2,5-dichlorothiophene-3-carboxamido)-7-(1-(2-(3,5,7-trimethyl-1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate

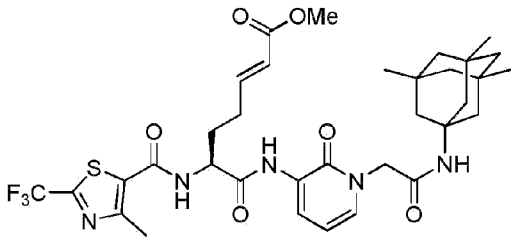
**[0319]** The synthesis of compound **III-94** was performed according to compound **III-13,** using 3,5,7-trimethyl-1-adamantanamine instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 69 mg, 88% (last step)

ESI-MS: 691.3 / 693.3 $[M+H]^+$

**105 Preparation of compound III-95**

**[0320]**



Chemical Formula: $C_{34}H_{42}F_3N_5O_6S$

Exact Mass: 705.28

Molecular Weight: 705.79

(S,E)-methyl 7-(1-(2-(3,5,7-trimethyl-1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-methyl-2-(trifluoromethyl)thiazole-5-carboxamido)-7-oxohept-2-enoate

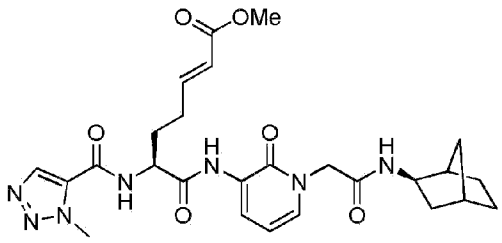
**[0321]** The synthesis of compound **III-95** was performed according to compound **III-14,** using 3,5,7-trimethyl-1-adamantanamine instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 35 mg, 64% (last step)

ESI-MS: 706.4 $[M+H]^+$

**106 Preparation of compound III-96**

**[0322]**



(S,E)-methyl 7-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-

dihydropyridin-3-ylamino)-6-(1-methyl-1H-1,2,3-triazole-5-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{26}H_{33}N_7O_6$

Exact Mass: 539.25

Molecular Weight: 539.58

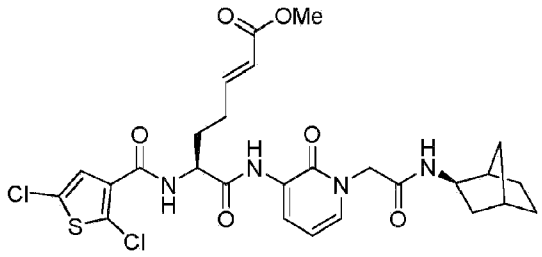
**[0323]** The synthesis of compound **III-96** was performed according to compound **III-22**, using exo-2-aminonorbornane instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 24 mg, 64% (last step)

ESI-MS: 540.4 $[M+H]^+$

**107 Preparation of compound III-97**

**[0324]**




(S,E)-methyl 7-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(2,5-dichlorothiophene-3-carboxamido)-7-oxohept-2-enoate
Chemical Formula: $C_{27}H_{30}Cl_2N_4O_6S$

Exact Mass: 608.13

Molecular Weight: 609.52

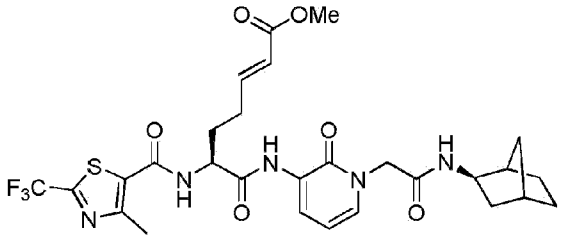
**[0325]** The synthesis of compound **III-97** was performed according to compound **III-13**, using exo-2-aminonorbornane instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 78 mg, 84% (last step)

ESI-MS: 609.3 / 611.3 $[M+H]^+$

**108 Preparation of compound III-98**

**[0326]**



(S,E)-methyl 7-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1 ,2-dihydropyridin-3-ylamino)-6-(4-methyl-2-(trifluoromethyl)thiazole-5-carboxamido)-7-oxohept-2-enoate Chemical Formula: $C_{28}H_{32}F_3N_5O_6S$

Exact Mass: 623.20

Molecular Weight: 623.64

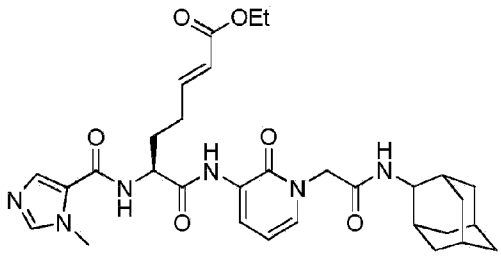
**[0327]** The synthesis of compound **III-98** was performed according to compound **III-14,** using exo-2-aminonorbornane instead of 2-adamantanamine in step 2 (according to ZED3905).

Yield: 48 mg, 68% (last step)

ESI-MS: 624.3 $[M+H]^+$

**109 Preparation of compound III-99**

**[0328]**



Chemical Formula: $C_{31}H_{40}N_6O_6$

Exact Mass: 592.30

Molecular Weight: 592.69

(S,E)-ethyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-imidazole-5-carboxamido)-7-oxohept-2-enoate

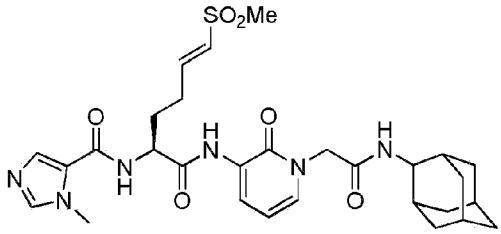
**[0329]** The synthesis of compound **III-99** was performed according to compound **III-89**, using 1-methyl-1H-imidazole-5-carboxylic acid instead of 3-methylbenzo[b]furan-2-carboxylic acid in the final step.

Yield: 68 mg, 79% (last step)

ESI-MS: 593.5 $[M+H]^+$

**110 Preparation of compound III-100**

**[0330]**




Chemical Formula: $C_{29}H_{38}N_6O_6S$

Exact Mass: 598.26

Molecular Weight: 598.71

(S,E)-N-(1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(methylsulfonyl)-1-oxohex-5-en-2-yl)-1-methyl-1H-imidazole-5-carboxamide

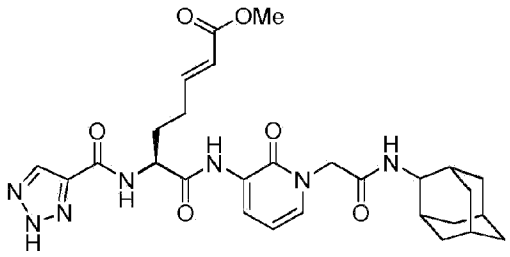
**[0331]** The synthesis of compound **III-100** was performed according to compound **III-90**, using 1-methyl-1H-imidazole-5-carboxylic acid instead of 3-methylbenzo[b]furan-2-carboxylic acid in the final step.

Yield: 46 mg, 73% (last step)

ESI-MS: 599.4 $[M+H]^+$

**111 Preparation of compound III-101**

**[0332]**



Chemical Formula: $C_{28}H_{35}N_7O_6$

Exact Mass: 565.26

Molecular Weight: 565.62

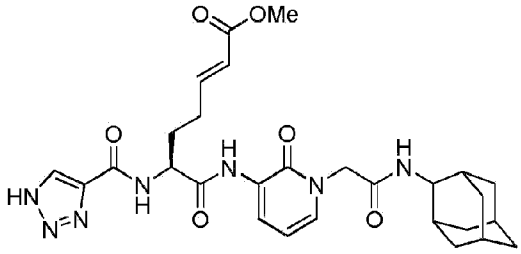
(S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(2H-1,2,3-triazole-4-carboxamido)hept-2-enoate

**[0333]** The synthesis of compound **III-101** was performed according to compound **III-1**, using 2H-1,2,3-triazole-4-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 28 mg, 63% (last step)

ESI-MS: 566.4 $[M+H]^+$

**[0334] 112 Preparation of compound III-102**



Chemical Formula: $C_{28}H_{35}N_7O_6$

Exact Mass: 565.26

Molecular Weight: 565.62

(S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-

oxo-6-(1H-1,2,3-triazole-4-carboxamido)hept-2-enoate

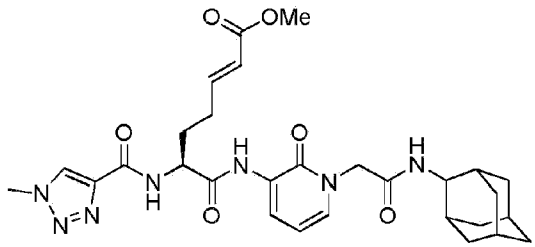
**[0335]** The synthesis of compound **III-102** was performed according to compound **III-1**, using 1H-1,2,3-triazole-4-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 37 mg, 70% (last step)

ESI-MS: 566.4 $[M+H]^+$

**113 Preparation of compound III-103**

**[0336]**



Chemical Formula: $C_{29}H_{37}N_7O_6$

Exact Mass: 579.28

Molecular Weight: 579.65

(S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-1,2,3-triazole-4-carboxamido)-7-oxohept-2-enoate

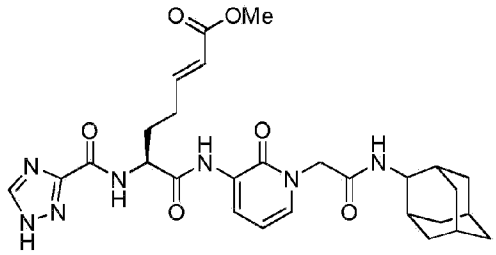
**[0337]** The synthesis of compound **III-103** was performed according to compound **III-1**, using 1-methyl-1H-1,2,3-triazole-4-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 52 mg, 76% (last step)

ESI-MS: 580.4 $[M+H]^+$

**114 Preparation of compound III-104**

**[0338]**



Chemical Formula: $C_{28}H_{35}N_7O_6$

Exact Mass: 565.26

Molecular Weight: 565.62

(S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(1H-1,2,4-triazole-3-carboxamido)hept-2-enoate

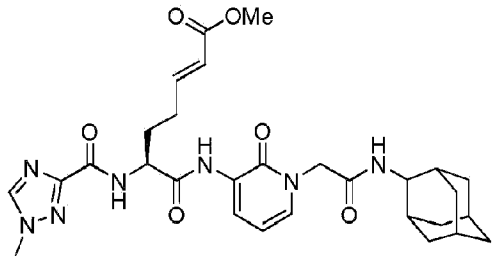
**[0339]** The synthesis of compound **III-104** was performed according to compound **III-1**, using 1H-1,2,4-triazole-3-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 31 mg, 59% (last step)

ESI-MS: 566.4 $[M+H]^+$

**115 Preparation of compound III-105**

**[0340]**



Chemical Formula: $C_{29}H_{37}N_7O_6$

Exact Mass: 579.28

Molecular Weight: 579.65

(S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-1,2,4-triazole-3-carboxamido)-7-oxohept-2-enoate

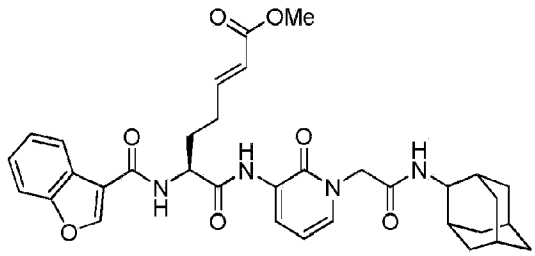
**[0341]** The synthesis of compound **III-105** was performed according to compound **III-1**, using 1-methyl-1H-1,2,4-triazole-3-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 42 mg, 72% (last step)

ESI-MS: 580.4 $[M+H]^+$

**116 Preparation of compound III-106**

**[0342]**



Chemical Formula: $C_{34}H_{38}N_4O_7$

Exact Mass: 614.27

Molecular Weight: 614.69

(S,E)-methyl 6-(benzofuran-3-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate

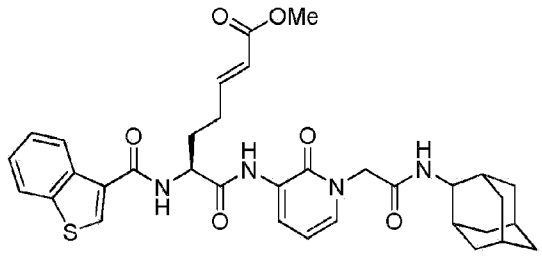
**[0343]** The synthesis of compound **III-106** was performed according to compound **III-1**, using benzofuran-3-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 56 mg, 77% (last step)

ESI-MS: 615.4 $[M+H]^+$

**117 Preparation of compound III-107**

**[0344]**



Chemical Formula: $C_{34}H_{38}N_4O_6S$

Exact Mass: 630.25

Molecular Weight: 630.75

(S,E)-methyl 6-(benzo[b]thiophene-3-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate

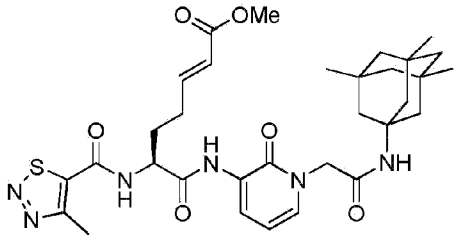
**[0345]** The synthesis of compound **III-107** was performed according to compound **III-1,** using benzo[b]thiophene-3-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 61 mg, 82% (last step)

ESI-MS: 631.4 $[M+H]^+$

**118 Preparation of compound III-108**

**[0346]**



(S,E)-methyl 7-(1-(2-(3,5,7-trimethyl-1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-methyl-1,2,3-thiadiazole-5-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{32}H_{42}N_6O_6S$

Exact Mass: 638.29

Molecular Weight: 638.78

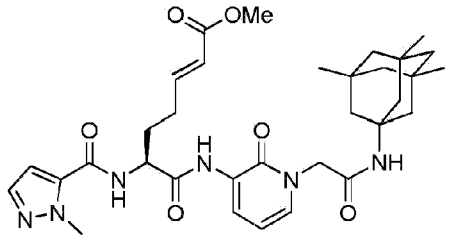
**[0347]** The synthesis of compound **III-108** was performed according to compound **III-91**, using 4-methyl-1,2,3-thiadiazole-5-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 25 mg, 43% (last step)

ESI-MS: 639.4 $[M+H]^+$

**119 Preparation of compound III-109**

**[0348]**




(S,E)-methyl 7-(1-(2-(3,5,7-trimethyl-1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-pyrazole-5-carboxamido)-7-oxohept-2-enoate Chemical Formula: $C_{33}H_{44}N_6O_6$

Exact Mass: 620.33

Molecular Weight: 620.74

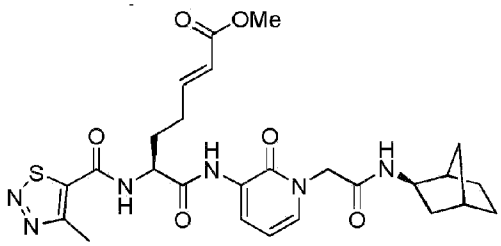
**[0349]** The synthesis of compound **III-109** was performed according to compound **III-91**, using 1-methyl-1H-pyrazole-5-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 39 mg, 62% (last step)

ESI-MS: 621.5 $[M+H]^+$

**120 Preparation of compound III-110**

**[0350]**



(S,E)-methyl 7-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-methyl-1,2,3-thiadiazole-5-carboxamido)-7-oxohept-2-enoate
Chemical Formula: $C_{26}H_{32}N_6O_6S$

Exact Mass: 556.21

Molecular Weight: 556.63

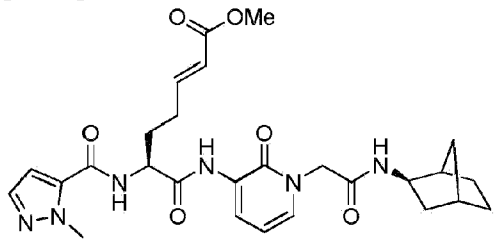
**[0351]** The synthesis of compound **III-110** was performed according to compound **III-62**, using 4-methyl-1,2,3-thiadiazole-5-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 19 mg, 36% (last step)

ESI-MS: 557.4 $[M+H]^+$

**121 Preparation of compound III-111**

**[0352]**



(S,E)-methyl 7-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-pyrazole-5-carboxamido)-7-oxohept-2-enoate
Chemical Formula: $C_{27}H_{34}N_6O_6$

Exact Mass: 538.25

Molecular Weight: 538.60

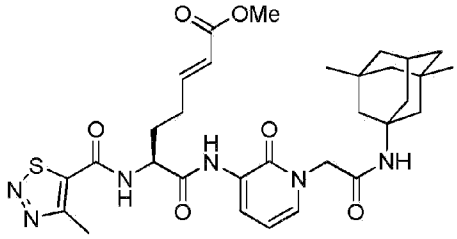
**[0353]** The synthesis of compound **III-111** was performed according to compound **III-62**, using 1-methyl-1H-pyrazole-5-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 32 mg, 69% (last step)

ESI-MS: 539.4 $[M+H]^+$

**122 Preparation of compound III-112**

**[0354]**



(S,E)-methyl 7-(1-(2-(3,5-dimethyladamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-methyl-1,2,3-thiadiazole-5-carboxamido)-7-oxohept-2-enoate Chemical Formula: $C_{31}H_{40}N_6O_6S$

Exact Mass: 624.27

Molecular Weight: 624.75

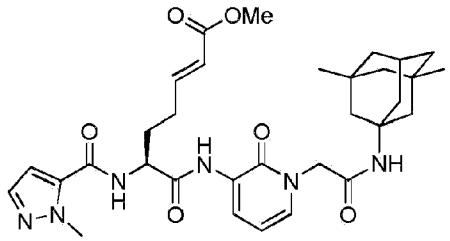
**[0355]** The synthesis of compound **III-112** was performed according to compound **III-46,** using 4-methyl-1,2,3-thiadiazole-5-carboxylic acid instead of 3-methylbenzo[b]furan-2-carboxylic acid in the final step.

Yield: 24 mg, 43% (last step)

ESI-MS: 625.4 $[M+H]^+$

**123 Preparation of compound III-113**

**[0356]**



(S,E)-methyl 7-(1-(2-(3,5-dimethyladamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-pyrazole-5-carboxamido)-7-oxohept-2-enoate Chemical Formula: $C_{32}H_{42}N_6O_6$

Exact Mass: 606.32

Molecular Weight: 606.71

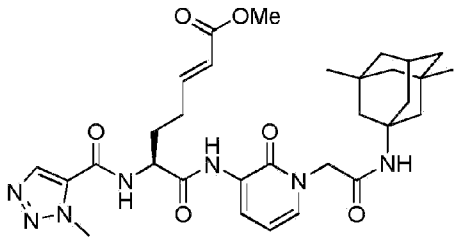
**[0357]** The synthesis of compound **III-113** was performed according to compound **III-46,** using 1-methyl-1H-pyrazole-5-carboxylic acid instead of 3-methylbenzo[b]furan-2-carboxylic acid in the final step.

Yield: 31 mg, 56% (last step)

ESI-MS: 607.5 $[M+H]^+$

**124 Preparation of compound III-114**

**[0358]**



(S,E)-methyl 7-(1-(2-(3,5-dimethyladamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-1,2,3-triazole-5-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{31}H_{41}N_7O_6$

Exact Mass: 607.31

Molecular Weight: 607.70

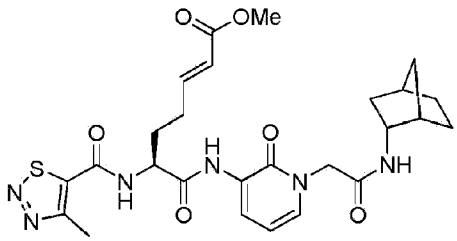
**[0359]** The synthesis of compound **III-114** was performed according to compound **III-46,** using 1-methyl-1H-1,2,3-triazole-5-carboxylic acid instead of 3-methylbenzo[b]furan-2-carboxylic acid in the final step.

Yield: 14 mg, 42% (last step)

ESI-MS: 608.5 $[M+H]^+$

**125 Preparation of compound III-115**

**[0360]**




(S,E)-methyl 7-(1-(2-((1S,2R,4R)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-methyl-1,2,3-thiadiazole-5-carboxamido)-7-oxohept-2-enoate
Chemical Formula: $C_{26}H_{32}N_6O_6S$

Exact Mass: 556.21

Molecular Weight: 556.63

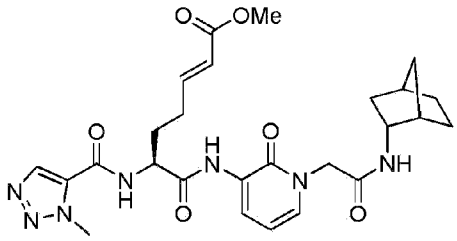
**[0361]** The synthesis of compound **III-115** was performed according to compound **III-58**, using 4-methyl-1,2,3-thiadiazole-5-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 26 mg, 48% (last step)

ESI-MS: 557.4 $[M+H]^+$

**126 Preparation of compound III-116**

**[0362]**



(S,E)-methyl 7-(1-(2-((1S,2R,4R)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-1,2,3-triazole-5-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{26}H_{33}N_7O_6$

Exact Mass: 539.25

Molecular Weight: 539.58

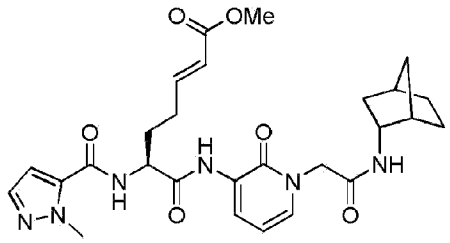
**[0363]** The synthesis of compound **III-116** was performed according to compound **III-58**, using 1-methyl-1H-1,2,3-triazole-5-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 20 mg, 39% (last step)

ESI-MS: 540.4 $[M+H]^+$

**127 Preparation of compound III-117**

**[0364]**



(S,E)-methyl 7-(1-(2-((1S,2R,4R)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-pyrazole-5-carboxamido)-7-oxohept-2-enoate
Chemical Formula: $C_{27}H_{34}N_6O_6$

Exact Mass: 538.25

Molecular Weight: 538.60

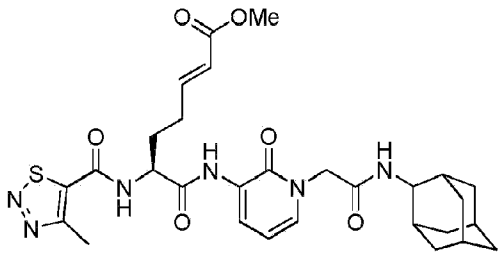
**[0365]** The synthesis of compound **III-117** was performed according to compound **III-58**, using 1-methyl-1H-pyrazole-5-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 23 mg, 53% (last step)

ESI-MS: 539.4 $[M+H]^+$

**128 Preparation of compound III-118**

**[0366]**



(S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1 ,2-dihydropyridin-3-ylamino)-6-(4-methyl-1,2,3-thiadiazole-5-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{29}H_{36}N_6O_6S$

Exact Mass: 596.24

Molecular Weight: 596.70

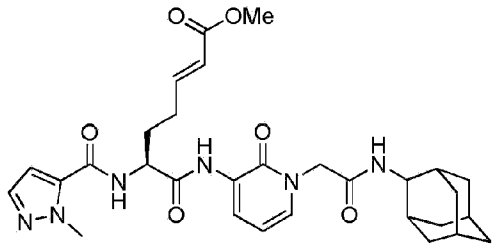
**[0367]** The synthesis of compound **III-118** was performed according to compound **III-1**, using 4-methyl-1,2,3-thiadiazole-5-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 31 mg, 49% (last step)

ESI-MS: 597.4 $[M+H]^+$

**129 Preparation of compound III-119**

**[0368]**



(S,E)-methyl 7 -(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-pyrazole-5-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{30}H_{38}N_6O_6$

Exact Mass: 578.29

Molecular Weight: 578.66

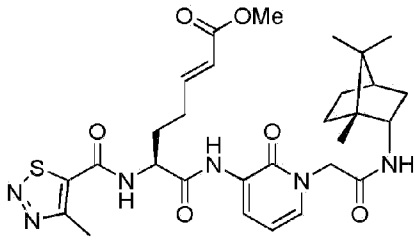
**[0369]** The synthesis of compound **III-119** was performed according to compound **III-1**, using 1-methyl-1H-pyrazole-5-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 39 mg, 62% (last step)

ESI-MS: 579.4 $[M+H]^+$

**130 Preparation of compound III-120**

**[0370]**



(S,E)-methyl 6-(4-methyl-1,2,3-thiadiazole-5-carboxamido)-7-oxo-7-(2-oxo-1-(2-oxo-2-((1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-ylamino)hept-2-enoate Chemical Formula: $C_{35}H_{42}N_4O_7$

Exact Mass: 630.31

Molecular Weight: 630.73

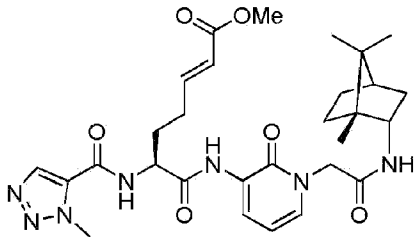
**[0371]** The synthesis of compound **III-120** was performed according to compound **III-60**, using 4-methyl-1,2,3-thiadiazole-5-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 12 mg, 33% (last step)

ESI-MS: 631.4 $[M+H]^+$

**131 Preparation of compound III-121**

**[0372]**



(S,E)-methyl 6-(1-methyl-1H-1,2,3-triazole-5-carboxamido)-7-oxo-7-(2-oxo-1-(2-oxo-2-((1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-ylamino)hept-2-enoate Chemical Formula: $C_{29}H_{39}N_7O_6$

Exact Mass: 581.30

Molecular Weight: 581.66

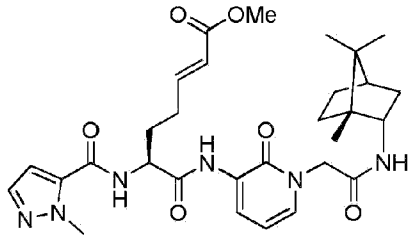
**[0373]** The synthesis of compound **III-121** was performed according to compound **III-60**, using 1-methyl-1H-1,2,3-triazole-5-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 15 mg, 29% (last step)

ESI-MS: 582.5 $[M+H]^+$

**132 Preparation of compound III-122**

**[0374]**



(S,E)-methyl 6-(1-methyl-1H-pyrazole-5-carboxamido)-7-oxo-7-(2-oxo-1-(2-oxo-2-((1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-ylamino)hept-2-enoate Chemical Formula: $C_{30}H_{40}N_6O_6$

Exact Mass: 580.30

Molecular Weight: 580.68

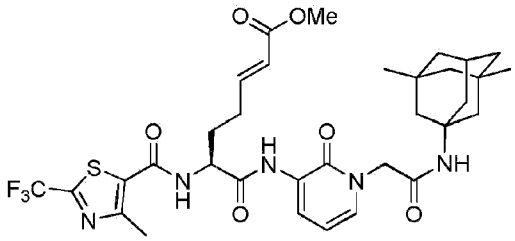
**[0375]** The synthesis of compound **III-122** was performed according to compound **III-60**, using 1-methyl-1H-pyrazole-5-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 23 mg, 46% (last step)

ESI-MS: 581.5 $[M+H]^+$

**133 Preparation of compound III-123**

**[0376]**



(S,E)-methyl 7-(1-(2-(3,5-dimethyladamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-methyl-2-(trifluoromethyl)thiazole-5-carboxamido)-7-oxohept-2-enoate Chemical Formula: $C_{33}H_{40}F_3N_5O_6S$

Exact Mass: 691.27

Molecular Weight: 691.76

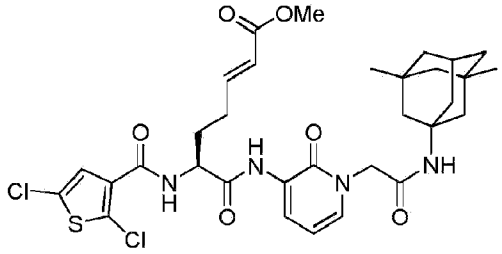
**[0377]** The synthesis of compound **III-123** was performed according to compound **III-46**, using 4-methyl-2-(trifluoromethyl)thiazole-5-carboxylic acid instead of 3-methylbenzo[b]furan-2-carboxylic acid in the final step.

Yield: 35 mg, 71% (last step)

ESI-MS: 692.4 $[M+H]^+$

**134 Preparation of compound III-124**

**[0378]**




(S,E)-methyl 6-(2,5-dichlorothiophene-3-carboxamido)-7-(1-(2-(3,5-dimethyladamantane-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate

Chemical Formula: $C_{32}H_{38}Cl_2N_4O_6S$

Exact Mass: 676.19

Molecular Weight: 677.64

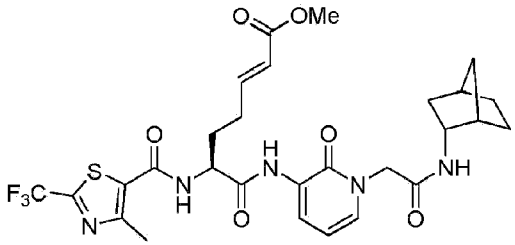
**[0379]** The synthesis of compound **III-124** was performed according to compound **III-46,** using 2,5-dichlorothiophene-3-carboxylic acid instead of 3-methylbenzo[b]furan-2-carboxylic acid in the final step.

Yield: 52 mg, 78% (last step)

ESI-MS: 677.4 / 679.4 $[M+H]^+$

**135 Preparation of compound III-125**

**[0380]**



(S,E)-methyl 7-(1-(2-((1S,2R,4R)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-methyl-2-(trifluoromethyl)thiazole-5-carboxamido)-7-oxohept-2-enoate Chemical Formula: $C_{28}H_{32}F_3N_5O_6S$

Exact Mass: 623.20

Molecular Weight: 623.64

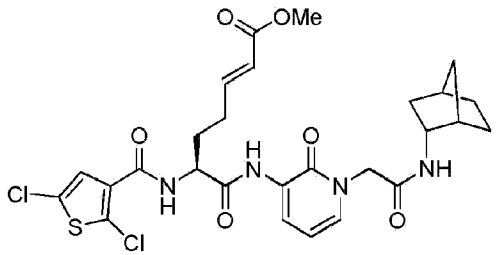
**[0381]** The synthesis of compound **III-125** was performed according to compound **III-58**, using 4-methyl-2-(trifluoromethyl)thiazole-5-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 34 mg, 67% (last step)

ESI-MS: 624.4 $[M+H]^+$

**136 Preparation of compound III-126**

**[0382]**



(S,E)-methyl 7-(1-(2-((1S,2R,4R)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(2,5-dichlorothiophene-3-carboxamido)-7-oxohept-2-enoate Chemical Formula: $C_{27}H_{30}Cl_2N_4O_6S$

Exact Mass: 608.13

Molecular Weight: 609.52

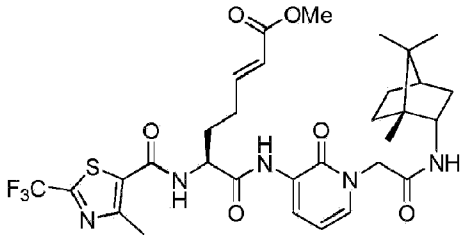
**[0383]** The synthesis of compound **III-126** was performed according to compound **III-58**, using 2,5-dichlorothiophene-3-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 56 mg, 74% (last step)

ESI-MS: 609.3 / 611.3 $[M+H]^+$

**137 Preparation of compound III-127**

**[0384]**



(S,E)-methyl 6-(4-methyl-2-(trifluoromethyl)thiazole-5-carboxamido)-7-oxo-7-(2-oxo-1-(2-oxo-2-((1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-ylamino)hept-2-enoate Chemical Formula: $C_{31}H_{38}F_3N_5O_6S$

Exact Mass: 665.25

Molecular Weight: 665.72

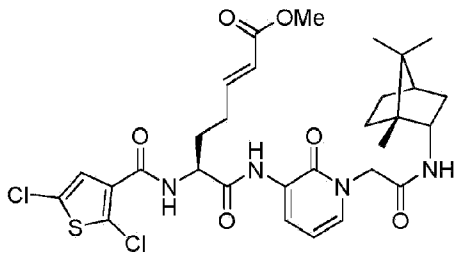
**[0385]** The synthesis of compound **III-127** was performed according to compound **III-60**, using 4-methyl-2-(trifluoromethyl)thiazole-5-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 27 mg, 46% (last step)

ESI-MS: 666.4 $[M+H]^+$

**138 Preparation of compound III-128**

**[0386]**



(S,E)-methyl 6-(2,5-dichlorothiophene-3-carboxamido)-7-oxo-7-(2-oxo-1-(2-oxo-2-((1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-ylamino)hept-2-enoate Chemical Formula: $C_{30}H_{36}Cl_2N_4O_6S$

Exact Mass: 650.17

Molecular Weight: 651.60

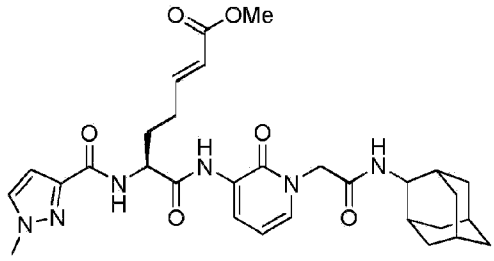
**[0387]** The synthesis of compound **III-128** was performed according to compound **III-60**, using 2,5-dichlorothiophene-3-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 76 mg, 70% (last step)

ESI-MS: 651.3 / 653.3 $[M+H]^+$

**139 Preparation of compound III-129**

**[0388]**



(S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-pyrazole-3-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{30}H_{38}N_6O_6$

Exact Mass: 578.29

Molecular Weight: 578.66

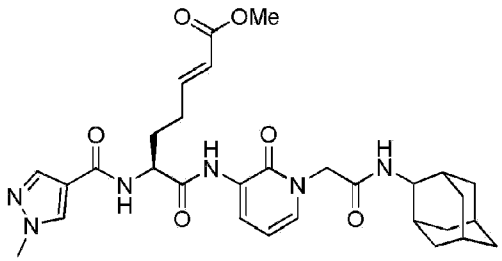
**[0389]** The synthesis of compound **III-129** was performed according to compound **III-1**, using 1-methyl-1H-pyrazole-3-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 56 mg, 75% (last step)

ESI-MS: 579.4 $[M+H]^+$

**140 Preparation of compound III-130**

**[0390]**



(S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1 H-pyrazole-4-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{30}H_{38}N_6O_6$

Exact Mass: 578.29

Molecular Weight: 578.66

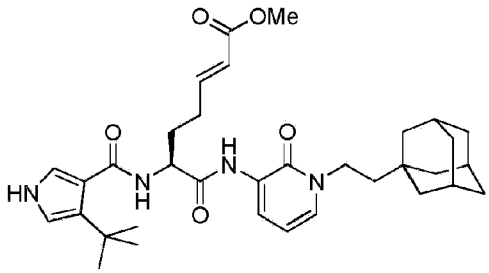
**[0391]** The synthesis of compound **III-130** was performed according to compound **III-1,** using 1-methyl-1H-pyrazole-4-carboxylic acid instead of 1-methyl-1H-imidazole-5-carboxylic acid in the final step.

Yield: 73 mg, 78% (last step)

ESI-MS: 579.4 $[M+H]^+$

**141 Preparation of compound III-131**

**[0392]**



(S,E)-methyl 6-(4-tert-butyl-1H-pyrrole-3-carboxamido)-7-(1-(2-(1-adamantylamino)ethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate

Chemical Formula: $C_{34}H_{46}N_4O_5$

Exact Mass: 590.35

Molecular Weight: 590.75

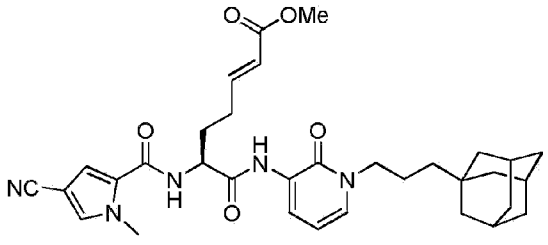
**[0393]** The synthesis of compound **III-131** was performed according to compound **III-79**, using 1-(2-bromoethyl)adamantane instead of 1-(bromomethyl)adamantane (according to ZED4893) and 5-tert-butyl-1H-pyrrole-3-carboxylic acid instead of 3-methyl-benzo[b]furan-2-carboxylic acid in the final step.

Yield: 18 mg, 42% (last step)

ESI-MS: 591.5 $[M+H]^+$

**142 Preparation of compound III-132**

**[0394]**



(S,E)-methyl 6-(4-cyano-1-methyl-1H-pyrrole-2-carboxamido)-7-(1-(3-(1-adamantylamino)propyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate

Chemical Formula: $C_{33}H_{41}N_5O_5$

Exact Mass: 587.31

Molecular Weight: 587.71

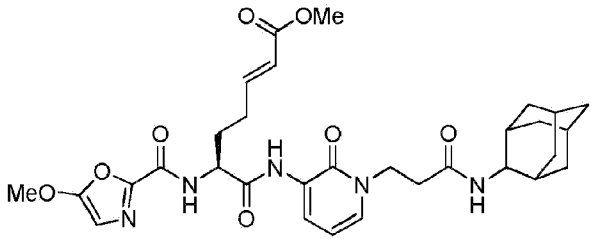
**[0395]** The synthesis of compound **III-132** was performed according to compound **III-79**, using 1-(3-bromopropyl)adamantane instead of 1-(bromomethyl)adamantane (according to ZED4893) and 4-cyano-1-methyl-1H-pyrrole-2-carboxylic acid instead of 3-methyl-benzo[b]furan-2-carboxylic acid in the final step.

Yield: 13 mg, 36% (last step)

ESI-MS: 588.5 $[M+H]^+$

**143 Preparation of compound III-133**

**[0396]**




(S,E)-methyl 7-(1-(3-(2-adamantylamino)-3-oxopropyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(5-methoxyoxazole-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{31}H_{39}N_5O_8$

Exact Mass: 609.28

Molecular Weight: 609.67

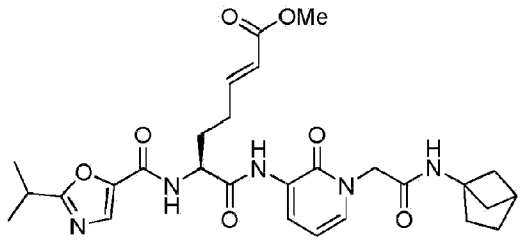
**[0397]** The synthesis of compound **III-133** was performed according to compound **III-2**, using 3-chloropropionic acid instead of chloroacetic acid (according to ZED1657) and 5-methoxyoxazole-2-carboxylic acid instead of 3-methylbenzo[b]furan-2-carboxylic acid in the final step.

Yield: 46 mg, 72% (last step)

ESI-MS: 610.4 $[M+H]^+$

**144 Preparation of compound III-134**

**[0398]**



(S,E)-methyl 7-(1-(2-(bicyclo[2.1.1]hexan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(2-isopropyloxazole-5-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{28}H_{35}N_5O_7$

Exact Mass: 553.25

Molecular Weight: 553.61

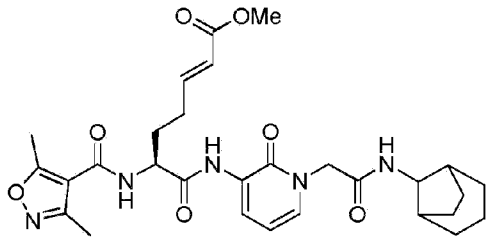
**[0399]** The synthesis of compound **III-134** was performed according to compound **III-2**, using bicyclo[2.1.1]hexan-1-amine instead of 2-adamantanamine in step 2 (according to ZED3905) and 2-isopropyloxazole-5-carboxylic acid instead of 3-methylbenzo[b]furan-2-carboxylic acid in the final step.

Yield: 52 mg, 70% (last step)

ESI-MS: 554.4 $[M+H]^+$

**145 Preparation of compound III-135**

**[0400]**



(6S,E)-methyl 7-(1-(2-(bicyclo[3.2.1]octan-8-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3,5-dimethylisoxazole-4-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{29}H_{37}N_5O_7$

Exact Mass: 567.27

Molecular Weight: 567.63

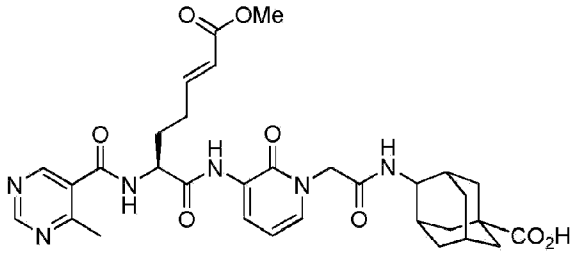
**[0401]** The synthesis of compound **III-135** was performed according to compound **III-2**, using bicyclo[3.2.1]octan-8-amine instead of 2-adamantanamine in step 2 (according to ZED3905) and 3,5-dimethylisoxazole-4-carboxylic acid instead of 3-methyl-benzo[b]furan-2-carboxylic acid in the final step.

Yield: 41 mg, 68% (last step)

ESI-MS: 568.4 $[M+H]^+$

**146 Preparation of compound III-136**

**[0402]**




(S,E)-methyl 7-(1-(2-(5-carboxy-2-aminoadamantane)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-methylpyrimidine-5-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{32}H_{38}N_6O_8$

Exact Mass: 634.28

Molecular Weight: 634.68

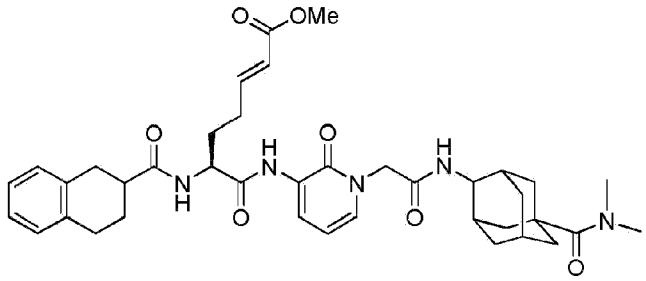
**[0403]** The synthesis of compound **III-136** was performed according to compound **III-2**, using 4-aminoadamantane-1-carboxylic acid instead of 2-adamantanamine in step 2 (according to ZED3905) and 4-methylpyrimidine-5-carboxylic acid instead of 3-methyl-benzo[b]furan-2-carboxylic acid in the final step.

Yield: 16 mg, 34% (last step)

ESI-MS: 635.4 $[M+H]^+$

**147 Preparation of compound III-137**

**[0404]**



(6S,E)-methyl 7-(1-(2-(4-aminoadamantane-N,N-dimethyl-1-carboxamide)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(1,2,3,4-tetrahydronaphthalene-2-carboxamido)hept-2-enoate Chemical Formula: $C_{35}H_{43}N_5O_7$

Exact Mass: 645.32

Molecular Weight: 645.75

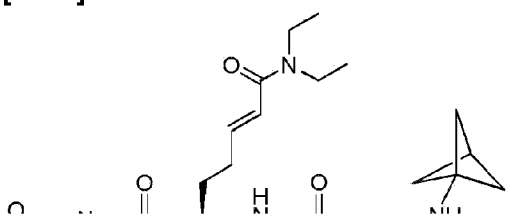
**[0405]** The synthesis of compound **III-137** was performed according to compound **III-2**, using 4-aminoadamantane-N,N-dimethyl-1-carboxamide instead of 2-adamantanamine in step 2 (according to ZED3905) and 1,2,3,4-tetrahydronaphthalene-2-carboxylic acid instead of 3-methylbenzo[b]furan-2-carboxylic acid in the final step.

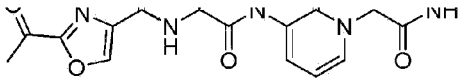
Yield: 38 mg, 53% (last step)

ESI-MS: 646.5 $[M+H]^+$

**148 Preparation of compound III-138**

**[0406]**





(S,E)-6-(2-acetyloxazole-4-carboxamido)-N7-(1-(2-(bicyclo[1.1,1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N1 ,N1-diethylhept-2-enediamide

Chemical Formula: $C_{29}H_{36}N_6O_7$

Exact Mass: 580.26

Molecular Weight: 580.63

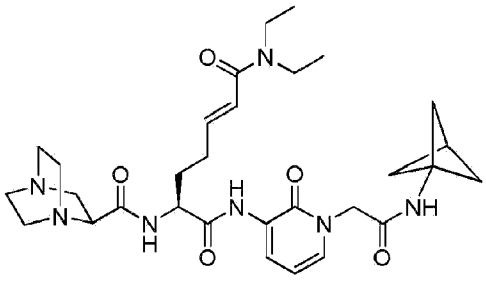
**[0407]** The synthesis of compound **III-138** was performed according to compound **III-75**, using N,N-diethylchloroacetamide instead of 2-chloro-N,N-dimethylacetamide (according to ZED4684) and 1-bicyclo[1.1.1]pentylamine instead of 2-adamantanamine in step 2 (according to ZED3905) and 2-acetyloxazole-4-carboxylic acid instead of 3-methyl-benzo[b]furan-2-carboxylic acid in the final step.

Yield: 25 mg, 63% (last step)

ESI-MS: 581.4 $[M+H]^+$

**149 Preparation of compound III-139**

**[0408]**



(S,E)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-6-((S)-1,4-diazabicyclo[2.2.2]octane-2-carboxamido)-N1,N1-diethylhept-2-enediamide Chemical Formula: $C_{30}H_{43}N_7O_5$

Exact Mass: 581.33

Molecular Weight: 581.71

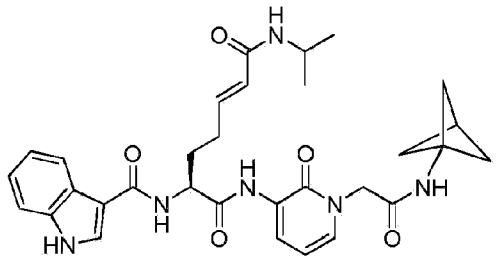
**[0409]** The synthesis of compound **III-139** was performed according to compound **III-138**, using 1,4-diazabicyclo[2.2.2]octane-2-carboxylic acid instead of 2-acetyloxazole-4-carboxylic acid in the final step.

Yield: 16 mg, 54% (last step)

ESI-MS: 582.5 $[M+H]^+$

**150 Preparation of compound III-140**

**[0410]**



(S,E)-N7-(1-(2-(bicyclo[1.1,1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-6-(1H-indole-3-carboxamido)-N1-isopropylhept-2-enediamide

Chemical Formula: $C_{31}H_{36}N_6O_5$

Exact Mass: 572.27

Molecular Weight: 572.65

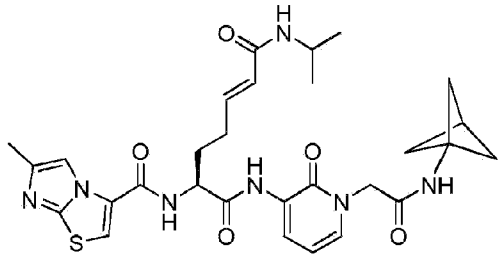
**[0411]** The synthesis of compound **III-140** was performed according to compound **III-75,** using 2-chloro-N-isopropylacetamide instead of 2-chloro-N,N-dimethylacetamide (according to ZED4684) and 1-bicyclo[1.1.1]pentylamine instead of 2-adamantanamine in step 2 (according to ZED3905) and 1H-indole-3-carboxylic acid instead of 3-methyl-benzo[b]furan-2-carboxylic acid in the final step.

Yield: 36 mg, 68% (last step)

ESI-MS: 573.4 $[M+H]^+$

**151 Preparation of compound III-141**

**[0412]**



(S,E)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N1-isopropyl-6-(6-methylimidazo[2,1-b]thiazole-3-carboxamido)hept-2-enediamide

Chemical Formula: $C_{29}H_{35}N_7O_5S$

Exact Mass: 593.24

Molecular Weight: 593.70

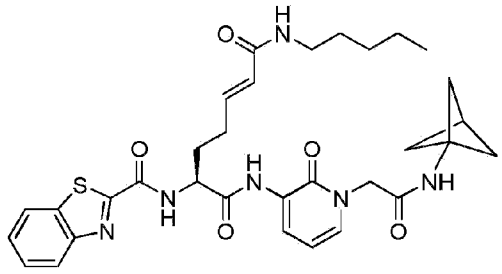
**[0413]** The synthesis of compound **III-141** was performed according to compound **III-140**, using 6-methylimidazo[2,1-b][1,3]thiazole-3-carboxylic acid instead of 1H-Indole-3-carboxylic acid in the final step.

Yield: 29 mg, 54% (last step)

ESI-MS: 594.4 $[M+H]^+$

**152 Preparation of compound III-142**

**[0414]**



(S,E)-6-(benzo[d]thiazole-2-carboxamido)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N1-pentylhept-2-enediamide

Chemical Formula: $C_{32}H_{38}N_6O_5S$

Exact Mass: 618.26

Molecular Weight: 618.75

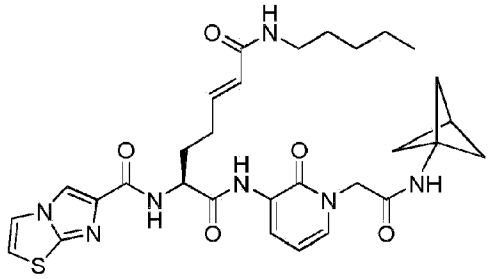
**[0415]** The synthesis of compound **III-142** was performed according to compound **III-75,** using 2-chloro-N-pentylacetamide instead of 2-chloro-N,N-dimethylacetamide (according to ZED4684) and 1-bicyclo[1.1.1]pentylamine instead of 2-adamantanamine in step 2 (according to ZED3905) and 1,3-benzothiazole-2-carboxylic acid instead of 3-methyl-benzo[b]furan-2-carboxylic acid in the final step.

Yield: 42 mg, 65% (last step)

ESI-MS: 619.4 $[M+H]^+$

**153 Preparation of compound III-143**

**[0416]**



(S,E)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-6-(imidazo[2,1-b]thiazole-6-carboxamido)-N1-pentylhept-2-enediamide

Chemical Formula: $C_{30}H_{37}N_7O_5S$

Exact Mass: 607.26

Molecular Weight: 607.72

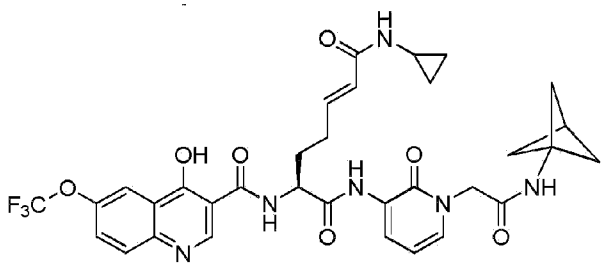
**[0417]** The synthesis of compound **III-143** was performed according to compound **III-142**, using imidazo[2,1-b][1,3]thiazole-6-carboxylic acid instead of 1,3-benzothiazole-2-carboxylic acid in the final step.

Yield: 23 mg, 59% (last step)

ESI-MS: 608.4 $[M+H]^+$

**154 Preparation of compound III-144**

**[0418]**



(S,E)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N1-cyclopropyl-6-(4-hydroxy-6-(trifluoromethoxy)quinoline-3-carboxamido)hept-2-enediamide
Chemical Formula: $C_{33}H_{33}F_3N_6O_7$

Exact Mass: 682.24

Molecular Weight: 682.65

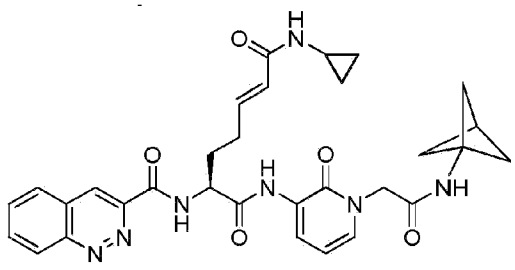
**[0419]** The synthesis of compound **III-144** was performed according to compound **III-75,** using 2-chloro-N-cyclopropylacetamide instead of 2-chloro-N,N-dimethylacetamide (according to ZED4684) and 1-bicyclo[1.1.1]pentylamine instead of 2-adamantanamine in step 2 (according to ZED3905) and 4-hydroxy-6-(trifluoromethoxy)quinoline-3-carboxylic acid instead of 3-methylbenzo[b]furan-2-carboxylic acid in the final step.

Yield: 12 mg, 36% (last step)

ESI-MS: 683.4 $[M+H]^+$

**155 Preparation of compound III-145**

**[0420]**



(S,E)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-6-(cinnoline-3-carboxamido)-N1-cyclopropylhept-2-enediamide

Chemical Formula: $C_{31}H_{33}N_7O_5$

Exact Mass: 583.25

Molecular Weight: 583.64

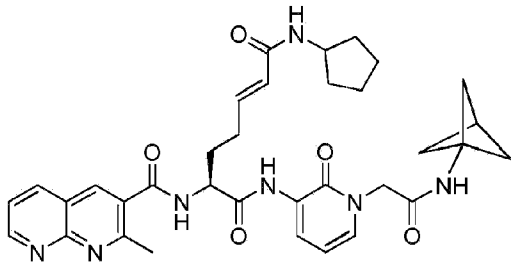
**[0421]** The synthesis of compound **III-145** was performed according to compound **III-144**, using 3-cinnolinecarboxylic acid instead of 4-hydroxy-6-(trifluoromethoxy)quinoline-3-carboxylic acid in the final step.

Yield: 32 mg, 66% (last step)

ESI-MS: 584.4 $[M+H]^+$

**156 Preparation of compound III-146**

**[0422]**



(S,E)-N7-(1-(2-(bicyclo[1.1,1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N1-cyclopentyl-6-(2-methyl-1,8-naphthyridine-3-carboxamido)hept-2-enediamide

Chemical Formula: $C_{34}H_{39}N_7O_5$

Exact Mass: 625.30

Molecular Weight: 625.72

**[0423]** The synthesis of compound **III-146** was performed according to compound **III-75,** using 2-chloro-N-cyclopentylacetamide instead of 2-chloro-N,N-dimethylacetamide (according to ZED4684) and 1-bicyclo[1.1.1]pentylamine instead of 2-adamantanamine in step 2 (according to ZED3905) and 2-methyl-1,8-naphthyridine-3-carboxylic acid instead of 3-

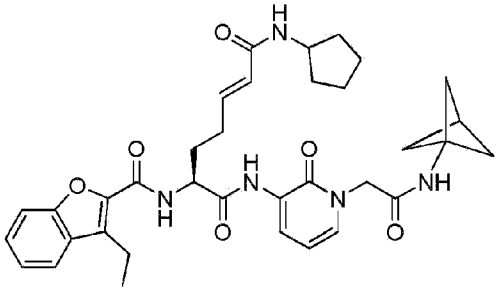
methylbenzo[b]furan-2-carboxylic acid in the final step.

Yield: 28 mg, 68% (last step)

ESI-MS: 626.5 $[M+H]^+$

**157 Preparation of compound III-147**

**[0424]**



(S,E)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N1-cyclopentyl-6-(3-ethylbenzofuran-2-carboxamido)hept-2-enediamide

Chemical Formula: $C_{35}H_{41}N_5O_6$

Exact Mass: 627.31

Molecular Weight: 627.73

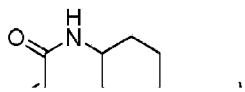
**[0425]** The synthesis of compound **III-147** was performed according to compound **III-146**, using 3-ethyl-1-benzofuran-2-carboxylic acid instead of 2-methyl-1,8-naphthyridine-3-carboxylic acid in the final step.

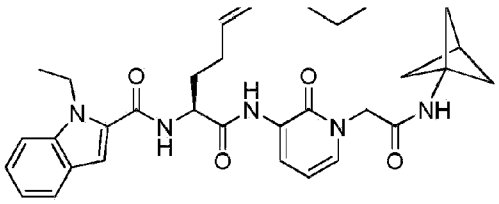
Yield: 54 mg, 72% (last step)

ESI-MS: 628.5 $[M+H]^+$

**158 Preparation of compound III-148**

**[0426]**





(S,E)-N7-(1-(2-(bicyclo[1.1,1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N1-cyclohexyl-6-(1-ethyl-1H-indole-2-carboxamido)hept-2-enediamide

Chemical Formula: $C_{36}H_{44}N_6O_5$

Exact Mass: 640.34

Molecular Weight: 640.77

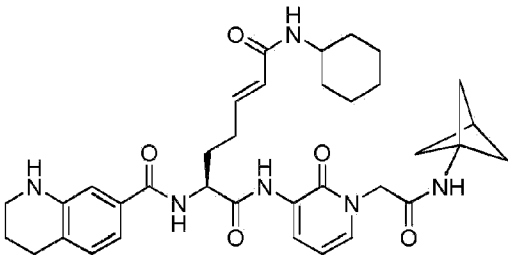
**[0427]** The synthesis of compound **III-148** was performed according to compound **III-75**, using 2-chloro-N-cyclohexylacetamide instead of 2-chloro-N,N-dimethylacetamide (according to ZED4684) and 1-bicyclo[1.1.1]pentylamine instead of 2-adamantanamine in step 2 (according to ZED3905) and 1-ethyl-1H-indole-2-carboxylic acid instead of 3-methyl-benzo[b]furan-2-carboxylic acid in the final step.

Yield: 62 mg, 67% (last step)

ESI-MS: 641.5 $[M+H]^+$

**159 Preparation of compound III-149**

**[0428]**



(S,E)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N1-cyclohexyl-6-(1,2,3,4-tetrahydroquinoline-7-carboxamido)hept-2-enediamide

Chemical Formula: $C_{35}H_{44}N_6O_5$

Exact Mass: 628.34

Molecular Weight: 628.76

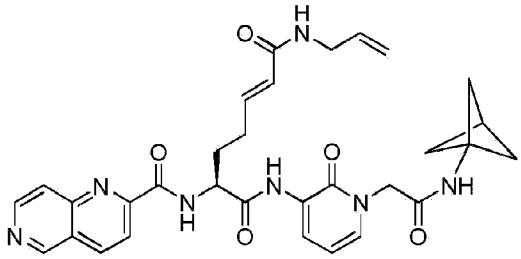
**[0429]** The synthesis of compound **III-149** was performed according to compound **III-148**, using N-Boc-1,2,3,4-tetrahydroquinoline-7-carboxylic acid instead of 1-ethyl-1H-indole-2-carboxylic acid in the final step. The final product was obtained by deprotection (DCM/TFA) as described above and purified by HPLC.

Yield: 24 mg, 53% (last step)

ESI-MS: 629.5 $[M+H]^+$

**160 Preparation of compound III-150**

**[0430]**



(S,E)-N1-allyl-N7-(1-(2-(bicyclo[1.1,1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-6-(1,6-naphthyridine-2-carboxamido)hept-2-enediamide

Chemical Formula: $C_{31}H_{33}N_7O_5$

Exact Mass: 583.25

Molecular Weight: 583.64

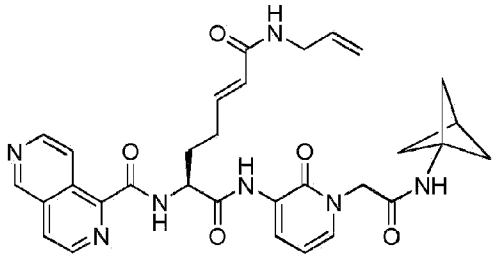
**[0431]** The synthesis of compound **III-150** was performed according to compound **III-75**, using N-allyl-2-chloroacetamide instead of 2-chloro-N,N-dimethylacetamide (according to ZED4684) and 1-bicyclo[1.1.1]pentylamine instead of 2-adamantanamine in step 2 (according to ZED3905) and 1,6-naphthyridine-2-carboxylic acid instead of 3-methyl-benzo[b]furan-2-carboxylic acid in the final step.

Yield: 26 mg, 52% (last step)

ESI-MS: 584.4 $[M+H]^+$

**161 Preparation of compound III-151**

**[0432]**



(S,E)-N1-allyl-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-6-(2,6-naphthyridine-1-carboxamido)hept-2-enediamide

Chemical Formula: $C_{31}H_{33}N_7O_5$

Exact Mass: 583.25

Molecular Weight: 583.64

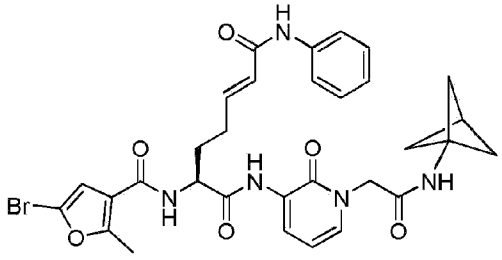
**[0433]** The synthesis of compound **III-151** was performed according to compound **III-150b,** using 2,6-naphthyridine-1-carboxylic acid instead of 1,6-naphthyridine-2-carboxylic acid in the final step.

Yield: 29 mg, 55% (last step)

ESI-MS: 584.4 $[M+H]^+$

**162 Preparation of compound III-152**

**[0434]**



(S,E)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-6-

(5-bromo-2-methylfuran-3-carboxamido)-N1-phenylhept-2-enediamide

Chemical Formula: $C_{31}H_{32}BrN_5O_6$

Exact Mass: 649.15

Molecular Weight: 650.52

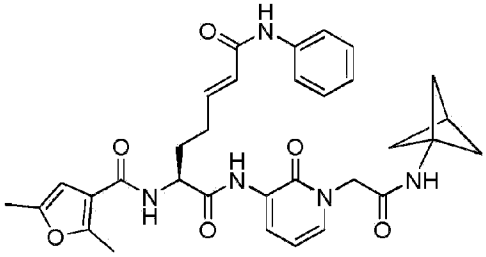
**[0435]** The synthesis of compound **III-152** was performed according to compound **III-75**, using 2-chloro-N-phenylacetamide instead of 2-chloro-N,N-dimethylacetamide (according to ZED4684) and 1-bicyclo[1.1.1]pentylamine instead of 2-adamantanamine in step 2 (according to ZED3905) and 5-Bromo-2-methylfuran-3-carboxylic acid instead of 3-methylbenzo[b]furan-2-carboxylic acid in the final step.

Yield: 43 mg, 75% (last step)

ESI-MS: 650.3 / 652.3 $[M+H]^+$

**163 Preparation of compound III-153**

**[0436]**



(S,E)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-6-(2,5-dimethylfuran-3-carboxamido)-N1-phenylhept-2-enediamide

Chemical Formula: $C_{32}H_{35}N_5O_6$

Exact Mass: 585.26

Molecular Weight: 585.65

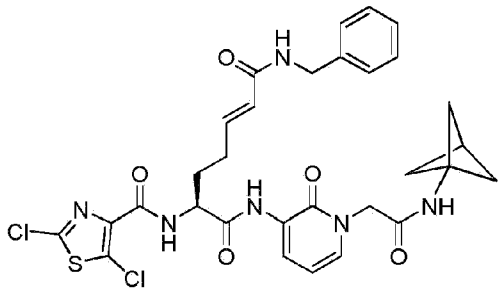
**[0437]** The synthesis of compound **III-153** was performed according to compound **III-152**, using 2,5-dimethylfuran-3-carboxylic acid instead of 5-Bromo-2-methylfuran-3-carboxylic acid in the final step.

Yield: 57 mg, 82% (last step)

ESI-MS: 586.4 $[M+H]^+$

**164 Preparation of compound III-154**

**[0438]**



(S,E)-N1-benzyl-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-6-(2,5-dichlorothiazole-4-carboxamido)hept-2-enediamide

Chemical Formula: $C_{30}H_{30}Cl_2N_6O_5S$

Exact Mass: 656.14

Molecular Weight: 657.57

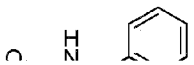
**[0439]** The synthesis of compound **III-154** was performed according to compound **III-75,** using N-benzyl-2-chloroacetamide instead of 2-chloro-N,N-dimethylacetamide (according to ZED4684) and 1-bicyclo[1.1.1]pentylamine instead of 2-adamantanamine in step 2 (according to ZED3905) and 2,5-dichlorothiazole-4-carboxylic acid instead of 3-methyl-benzo[b]furan-2-carboxylic acid in the final step.

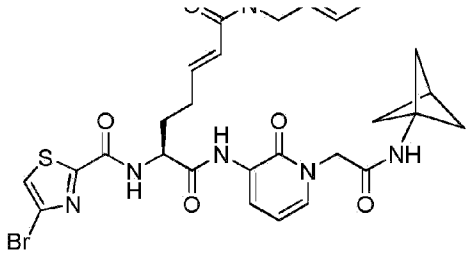
Yield: 22 mg, 46% (last step)

ESI-MS: 657.2 / 659.2 $[M+H]^+$

**165 Preparation of compound III-155**

**[0440]**





(S,E)-N1-benzyl-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-6-(4-bromothiazole-2-carboxamido)hept-2-enediamide

Chemical Formula: $C_{30}H_{31}BrN_6O_5S$

Exact Mass: 666.13

Molecular Weight: 667.57

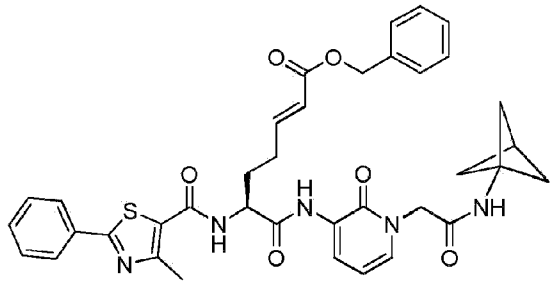
**[0441]** The synthesis of compound **III-155** was performed according to compound **III-154**, using 4-bromothiazole-2-carboxylic acid instead of 2,5-dichlorothiazole-4-carboxylic acid in the final step.

Yield: 42 mg, 73% (last step)

ESI-MS: 667.2 / 669.2 $[M+H]^+$

**166 Preparation of compound III-156**

**[0442]**



(S,E)-benzyl 7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-methyl-2-phenylthiazole-5-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{37}H_{37}N_5O_6S$

Exact Mass: 679.25

Molecular Weight: 679.78

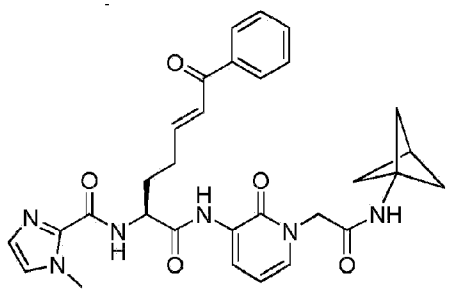
**[0443]** The synthesis of compound **III-156** was performed according to compound **III-2**, using (benzyloxycarbonylmethylene)triphenylphosphorane instead of (carbomethoxy-methylene)triphenylphosphorane (according to ZED755) and 1-bicyclo[1.1.1]-pentylamine instead of 2-adamantanamine in step 2 (according to ZED3905) and 4-methyl-2-phenylthiazole-5-carboxylic acid instead of 3-methylbenzo[b]furan-2-carboxylic acid in the final step.

Yield: 26 mg, 72% (last step)

ESI-MS: 680.4 $[M+H]^+$

**167 Preparation of compound III-157**

**[0444]**



(S,E)-N-(1-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-1,7-dioxo-7-phenylhept-5-en-2-yl)-1-methyl-1H-imidazole-2-carboxamide

Chemical Formula: $C_{30}H_{32}N_6O_5$

Exact Mass: 556.24

Molecular Weight: 556.61

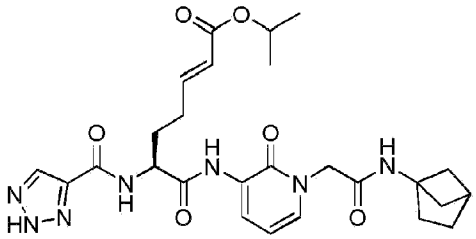
**[0445]** The synthesis of compound **III-157** was performed according to compound **III-2**, using (benzoylmethylene)triphenylphosphorane instead of (carbomethoxymethylene)triphenylphosphorane (according to ZED755) and 1-bicyclo[1.1.1]pentylamine instead of 2-adamantanamine in step 2 (according to ZED3905) and 1-methyl-1H-imidazole-2-carboxylic acid instead of 3-methylbenzo[b]furan-2-carboxylic acid in the final step.

Yield: 39 mg, 68% (last step)

ESI-MS: 557.4 $[M+H]^+$

**168 Preparation of compound III-158**

**[0446]**



(S,E)-isopropyl 7-(1-(2-(bicyclo[2.1.1]hexan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(2H-1,2,3-triazole-4-carboxamido)hept-2-enoate

Chemical Formula: $C_{26}H_{33}N_7O_6$

Exact Mass: 539.25

Molecular Weight: 539.58

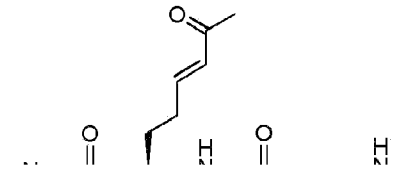
**[0447]** The synthesis of compound **III-158** was performed according to compound **III-2**, using (isopropyloxycarbonylmethylene)triphenylphosphorane instead of (carbomethoxy-methylene)triphenylphosphorane (according to ZED755) and bicyclo[2.1.1]hexan-1-amine instead of 2-adamantanamine in step 2 (according to ZED3905) and 2H-1,2,3-triazole-4-carboxylic acid instead of 3-methylbenzo[b]furan-2-carboxylic acid in the final step.

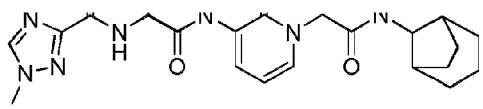
Yield: 11 mg, 44% (last step)

ESI-MS: 540.4 $[M+H]^+$

**169 Preparation of compound III-159**

**[0448]**





N-((2S,E)-1-(1-(2-(bicyclo[3.2.1]octan-8-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-1,7-dioxooct-5-en-2-yl)-1-methyl-1H-1,2,4-triazole-3-carboxamide

Chemical Formula: $C_{27}H_{35}N_7O_5$

Exact Mass: 537.27

Molecular Weight: 537.61

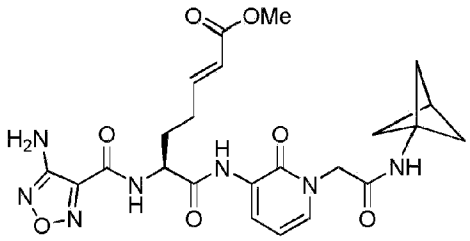
**[0449]** The synthesis of compound **III-159** was performed according to compound **III-2**, using (acetylmethylene)triphenylphosphorane instead of (carbomethoxymethylene)triphenylphosphorane (according to ZED755) and bicyclo[3.2.1]octan-8-amine in step 2 (according to ZED3905) and 1-methyl-1H-1,2,4-triazole-3-carboxylic acid instead of 3-methylbenzo[b]furan-2-carboxylic acid in the final step.

Yield: 26 mg, 53% (last step)

ESI-MS: 538.4 $[M+H]^+$

**170 Preparation of compound III-160**

**[0450]**



(S,E)-methyl 6-(4-amino-1,2,5-oxadiazole-3-carboxamido)-7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate

Chemical Formula: $C_{23}H_{27}N_7O_7$

Exact Mass: 513.20

Molecular Weight: 513.50

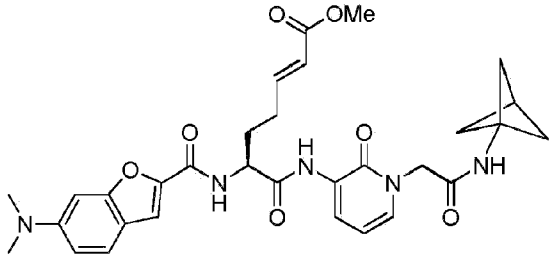
**[0451]** The synthesis of compound **III-160** was performed according to compound **III-2**, using 1-bicyclo[1.1.1]pentylamine in step 2 (according to ZED3905) and 4-Boc-amino-1,2,5-oxadiazole-3-carboxylic acid instead of 3-methylbenzo[b]furan-2-carboxylic acid in the final step before being deprotected by TFA.

Yield: 42 mg, 61% (last step)

ESI-MS: 514.4 $[M+H]^+$

**171 Preparation of compound III-161**

**[0452]**



(S,E)-methyl 7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(6-(dimethylamino)benzofuran-2-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{31}H_{35}N_5O_7$

Exact Mass: 589.25

Molecular Weight: 589.64

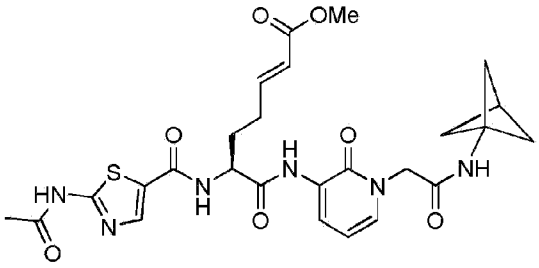
**[0453]** The synthesis of compound **III-161** was performed according to compound **III-160**, using 6-(dimethylamino)benzofuran-2-carboxylic acid instead of 4-Boc-amino-1,2,5-oxadiazole-3-carboxylic acid in the final step.

Yield: 24 mg, 58% (last step)

ESI-MS: 590.4 $[M+H]^+$

**172 Preparation of compound III-162**

**[0454]**



(S,E)-methyl6-(2-acetamidothiazole-5-carboxamido)-7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate

Chemical Formula: $C_{26}H_{30}N_6O_7S$

Exact Mass: 570.19

Molecular Weight: 570.62

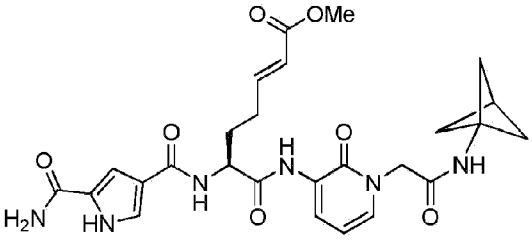
**[0455]** The synthesis of compound **III-162** was performed according to compound **III-160**, using 2-acetylamino-5-thiazolecarboxylic acid instead of 4-Boc-amino-1,2,5-oxadiazole-3-carboxylic acid in the final step.

Yield: 33 mg, 68% (last step)

ESI-MS: 571.3 $[M+H]^+$

**173 Preparation of compound III-163**

**[0456]**



(S,E)-methyl 7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(5-carbamoyl-1H-pyrrole-3-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{26}H_{30}N_6O_7$

Exact Mass: 538.22

Molecular Weight: 538.55

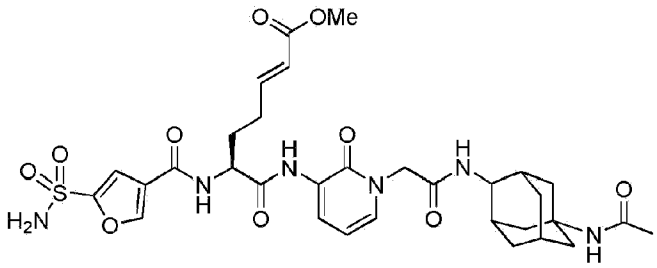
**[0457]** The synthesis of compound **III-163** was performed according to compound **III-160**, using 5-carbamoyl-1H-pyrrole-3-carboxylic acid instead of 4-Boc-amino-1,2,5-oxadiazole-3-carboxylic acid in the final step.

Yield: 41 mg, 62% (last step)

ESI-MS: 539.4 $[M+H]^+$

**174 Preparation of compound III-164**

**[0458]**



(S,E)-methyl 7-(1-(2-(1-acetylamino-4-aminoadamantane)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(5-sulfamoylfuran-3-carboxamido)hept-2-enoate

Chemical Formula: $C_{32}H_{40}N_6O_{10}S$

Exact Mass: 700.25

Molecular Weight: 700.76

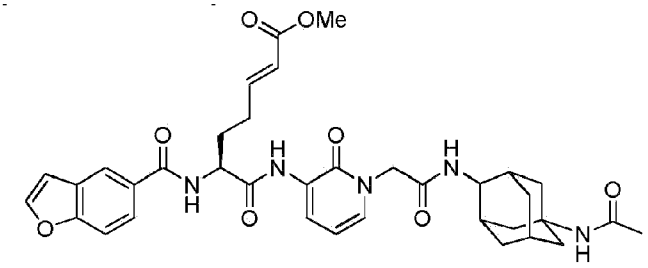
**[0459]** The synthesis of compound **III-164** was performed according to compound **III-2**, using 1-acetylamino-4-aminoadamantane in step 2 (according to ZED3905) and 5-sulfamoyl-furan-3-carboxylic acid instead of 3-methylbenzo[b]furan-2-carboxylic acid in the final step.

Yield: 35 mg, 58% (last step)

ESI-MS: 701.4 $[M+H]^+$

**175 Preparation of compound III-165**

**[0460]**



(S,E)-methyl 6-(benzofuran-5-carboxamido)-7-(1-(2-(1-acetylamino-4-aminoadamantane)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate

Chemical Formula: $C_{36}H_{41}N_5O_8$

Exact Mass: 671.30

Molecular Weight: 671.74

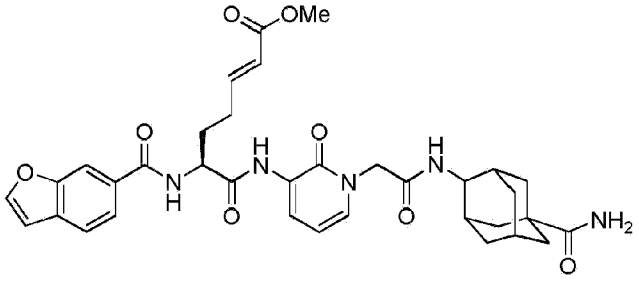
**[0461]** The synthesis of compound **III-165** was performed according to compound **III-164**, using benzofuran-5-carboxylic acid instead of 5-sulfamoylfuran-3-carboxylic acid in the final step.

Yield: 53 mg, 61% (last step)

ESI-MS: 672.5 $[M+H]^+$

**176 Preparation of compound III-166**

**[0462]**



(S,E)-methyl 6-(benzofuran-6-carboxamido)-7-(1-(2-(4-aminoadamantane-1-carboxamide)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate

Chemical Formula: $C_{35}H_{39}N_5O_8$

Exact Mass: 657.28

Molecular Weight: 657.71

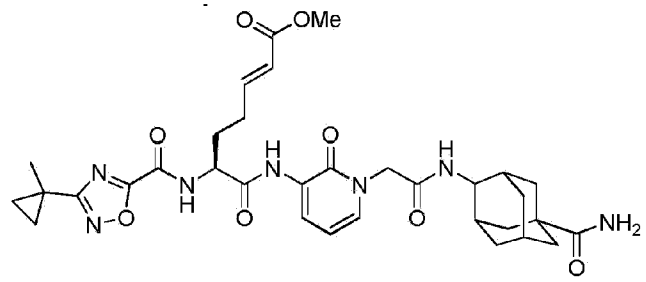
**[0463]** The synthesis of compound **III-166** was performed according to compound **III-2**, using 4-aminoadamantane-1-carboxamide in step 2 (according to ZED3905) and benzofuran-6-carboxylic acid instead of 3-methylbenzo[b]furan-2-carboxylic acid in the final step.

Yield: 43 mg, 66% (last step)

ESI-MS: 658.4 $[M+H]^+$

**177 Preparation of compound III-167**

**[0464]**



(S,E)-methyl 7-(1-(2-(4-aminoadamantane-1-carboxamide)-2-oxoethyl)-2-oxo-1 ,2-dihydropyridin-3-ylamino)-6-(3-(1-methylcyclopropyl)-1,2,4-oxadiazole-5-carboxamido)-7-oxohept-2-enoate Chemical Formula: $C_{33}H_{41}N_7O_8$

Exact Mass: 663.30

Molecular Weight: 663.72

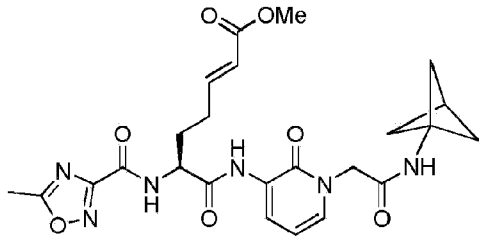
**[0465]** The synthesis of compound **III-167** was performed according to compound **III-166**, using 3-(1-methylcyclopropyl)-1,2,4-oxadiazole-5-carboxylic acid instead of benzofuran-6-carboxylic acid in the final step.

Yield: 28 mg, 49% (last step)

ESI-MS: 664.5 $[M+H]^+$

**178 Preparation of compound III-168**

**[0466]**



(S,E)-methyl 7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(5-methyl-1,2,4-oxadiazole-3-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{24}H_{28}N_6O_7$

Exact Mass: 512.20

Molecular Weight: 512.52

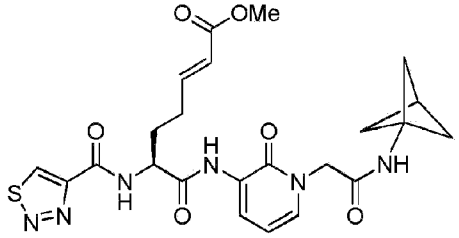
**[0467]** The synthesis of compound **III-168** was performed according to compound **III-160**, using 5-methyl-1,2,4-oxadiazole-3-carboxylic acid instead of 4-Boc-amino-1,2,5-oxadiazole-3-carboxylic acid in the final step.

Yield: 55 mg, 68% (last step)

ESI-MS: 513.4 $[M+H]^+$

**179 Preparation of compound III-169**

**[0468]**



(S,E)-methyl 7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(1,2,3-thiadiazole-4-carboxamido)hept-2-enoate

Chemical Formula: $C_{23}H_{26}N_6O_6S$

Exact Mass: 514.16

Molecular Weight: 514.55

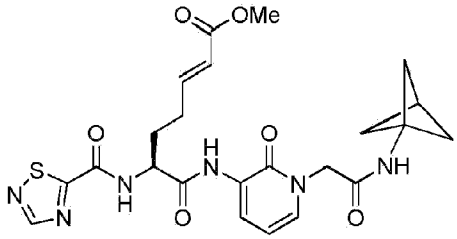
**[0469]** The synthesis of compound **III-169** was performed according to compound **III-160**, using 1,2,3-thiadiazole-4-carboxylic acid instead of 4-Boc-amino-1,2,5-oxadiazole-3-carboxylic acid in the final step.

Yield: 38 mg, 53% (last step)

ESI-MS: 515.3 $[M+H]^+$

**180 Preparation of compound III-170**

**[0470]**




(S,E)-methyl 7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(1,2,4-thiadiazole-5-carboxamido)hept-2-enoate

Chemical Formula: $C_{23}H_{26}N_6O_6S$

Exact Mass: 514.16

Molecular Weight: 514.55

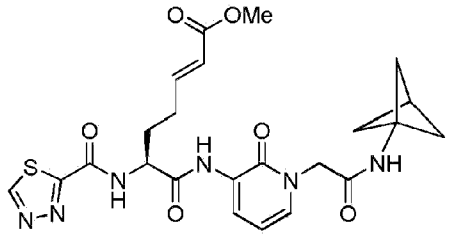
**[0471]** The synthesis of compound **III-170** was performed according to compound **III-160**, using 1,2,4-thiadiazole-5-carboxylic acid instead of 4-Boc-amino-1,2,5-oxadiazole-3-carboxylic acid in the final step.

Yield: 25 mg, 46% (last step)

ESI-MS: 515.3 $[M+H]^+$

**181 Preparation of compound III-171**

**[0472]**



(S,E)-methyl 7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(1,3,4-thiadiazole-2-carboxamido)hept-2-enoate

Chemical Formula: $C_{23}H_{26}N_6O_6S$

Exact Mass: 514.16

Molecular Weight: 514.55

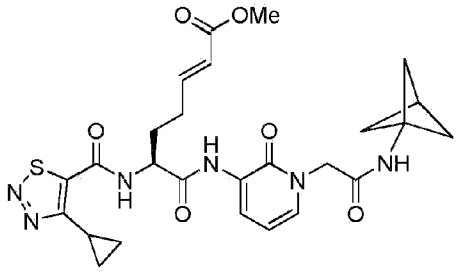
**[0473]** The synthesis of compound **III-171** was performed according to compound **III-160**, using 1,3,4-thiadiazole-2-carboxylic acid instead of 4-Boc-amino-1,2,5-oxadiazole-3-carboxylic acid in the final step.

Yield: 36 mg, 57% (last step)

ESI-MS: 515.3 $[M+H]^+$

**182 Preparation of compound III-172**

**[0474]**



(S,E)-methyl 7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-cyclopropyl-1,2,3-thiadiazole-5-carboxamido)-7-oxohept-2-enoate

Chemical Formula: $C_{26}H_{30}N_6O_6S$

Exact Mass: 554.19

Molecular Weight: 554.62

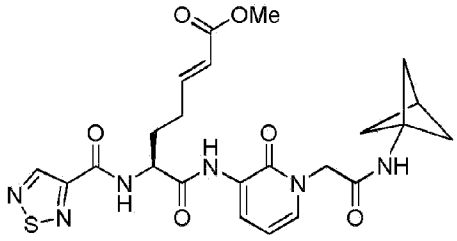
**[0475]** The synthesis of compound **III-172** was performed according to compound **III-160**, using 4-cyclopropyl-[1,2,3]thiadiazole-5-carboxylic acid instead of 4-Boc-amino-1,2,5-oxadiazole-3-carboxylic acid in the final step.

Yield: 57 mg, 71% (last step)

ESI-MS: 555.3 $[M+H]^+$

**183 Preparation of compound III-173**

**[0476]**




(S,E)-methyl 7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(1,2,5-thiadiazole-3-carboxamido)hept-2-enoate

Chemical Formula: $C_{23}H_{26}N_6O_6S$

Exact Mass: 514.16

Molecular Weight: 514.55

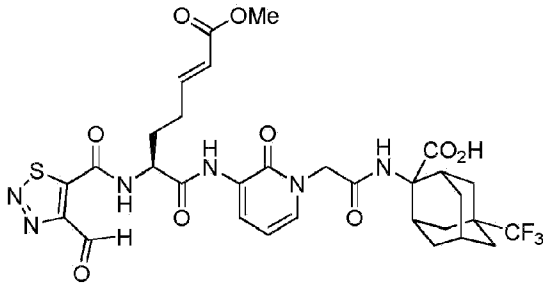
**[0477]** The synthesis of compound **III-173** was performed according to compound **III-160**, using 1,2,5-thiadiazole-3-carboxylic acid instead of 4-Boc-amino-1,2,5-oxadiazole-3-carboxylic acid in the final step.

Yield: 23 mg, 42% (last step)

ESI-MS: 515.3 $[M+H]^+$

**184 Preparation of compound III-174**

**[0478]**



(S,E)-methyl 6-(4-formyl-1,2,3-thiadiazole-5-carboxamido)-7-(1-(2-(2-carboxy-2-amino-5-(trifluoromethyl)adamantane)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate Chemical Formula: $C_{31}H_{33}F_3N_6O_9S$

Exact Mass: 722.20

Molecular Weight: 722.69

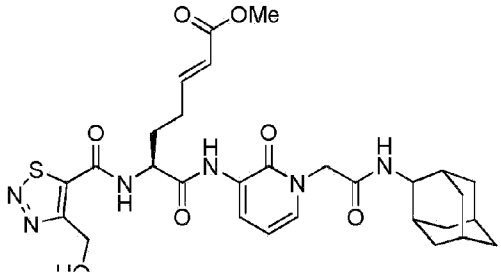
**[0479]** The synthesis of compound **III-174** was performed according to compound **III-2**, using 1-acetylamino-4-aminoadamantane in step 2 (according to ZED3905) and 4-(hydroxymethyl)-1,2,3-thiadiazole-5-carboxylic acid instead of 3-methylbenzo[b]furan-2-carboxylic acid in the final step.

Yield: 15 mg, 34% (last step)

ESI-MS: 723.4 $[M+H]^+$

**185 Preparation of compound III-175**

**[0480]**



HO

(S,E)-methyl 6-(4-(hydroxymethyl)-1,2,3-thiadiazole-5-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoate
Chemical Formula: $C_{29}H_{36}N_6O_7S$

Exact Mass: 612.24

Molecular Weight: 612.70

**[0481]** The synthesis of compound **III-175** was performed according to compound **III-2**, using 4-((tetrahydro-2H-pyran-2-yloxy)methyl)-1,2,3-thiadiazole-5-carboxylic acid in the final step before the tetrahydropyranyl (Thp) protecting group was cleaved by TFA.

Yield: 23 mg, 42% (last step)

ESI-MS: 613.4 $[M+H]^+$

**Biological Examples**

**Example B-1. inhibitory effect of the compounds according to the invention**

**Transglutaminase assay**

**[0482]** For the determination of potency of inhibitors against tissue transglutaminase, the incorporation of dansylcadaverine into dimethylcasein (Zedira product T036, Lorand et al., Anal Biochem, 1971, 44:221-31) was measured using recombinant human transglutaminase 2 (Zedira Product T022).

**[0483]** The tissue transglutaminase is diluted in buffer (50 mM Tris-HCl, 7.5 mM $CaCl_2$, 150 mM NaCl, pH = 7.4). The final concentration of TG2 in the assay is 10 nM.

**[0484]** A 10 mM inhibitor stock solution is prepared in DMSO, and from this a serial 1:2-fold dilution series is prepared also in DMSO. Each of the initial dilutions is subsequently diluted 1:50-fold with buffer (50 mM Tris-HCl, 7.5 mM $CaCl_2$, 150 mM NaCl, pH = 7.4) to yield the final working dilutions containing 2% (v/v) DMSO. 15 µl of inhibitor working dilution are added per well of a 96 well microtiter plate. As control, 15 µl of a 2% (v/v) DMSO solution prepared using the buffer mentioned above are added per well.

**[0485]** Immediately before starting the assay, 600 µl transglutaminase working solution are added to 11.4 ml assay buffer (50 mM Tris-HCl, 10 mM $CaCl_2$, 10 mM glutathione, 2.5% glycerol, 16.7 µM dansylcadaverine, 4 µM N,N-dimethylcasein, 200 mM NaCl, pH = 8.0). 285 µl of this reaction mix are added per well containing the inhibitor.

**[0486]** Increase in fluorescence is measured using $\lambda_{ex}$ = 330 nm and $\lambda_{em}$ = 500 nm at 37°C for 30 min. A slope of the increase in fluorescence between 20 and 30 min is calculated for determination of the $IC_{50}$ value (inhibitor concentration at which 50% of the initial activity is blocked).

**[0487]** Analysis of enzymatic activity is performed by calculation of the slope of an increase in fluorescence intensity. $IC_{50}$ values are calculated by plotting the enzymatic activity (as percentage from control containing 2% DMSO instead of inhibitor) against the inhibitor concentration. $IC_{50}$ is defined as the inhibitor concentration blocking 50 % of initial enzyme activity.

**[0488]** The inhibitory activity of the inventive compounds in regard to tissue transglutaminase (TG2) is shown in the following table 1 using $IC_{50}$-values.

**Table 1. efficacy of irreversible TG2 inhibitors**

| **A:** $IC_{50}$ < 25 nM, **B:** 25 nM < $IC_{50}$ < 250 nM, **C:** 250 nM ≤ $IC_{50}$ < 1,500 nM, | | | |
|---|---|---|---|
| **D:** 1,500 nM ≤ $IC_{50}$ < 10,000 nM | | | |
| Compound | $IC_{50}$ TG2 [nM] | Compound | $IC_{50}$ TG2 [nM] |
| **III-1** | A | **III-89** | A |
| **III-2** | A | **III-90** | A |
| **III-3** | A | **III-91** | A |
| **III-4** | A | **III-92** | A |
| **III-5** | A | **III-93** | A |
| **III-6** | A | **III-94** | A |
| **III-7** | A | **III-95** | A |
| **III-8** | A | **III-96** | A |
| **III-9** | A | **III-97** | A |
| **III-10** | A | **III-98** | A |
| **III-11** | B | **III-99** | B |
| **III-12** | A | **III-100** | B |
| **III-13** | A | **III-101** | B |
| **III-14** | A | **III-102** | B |
| **III-15** | A | **III-103** | B |
| **III-16** | A | **III-104** | B |

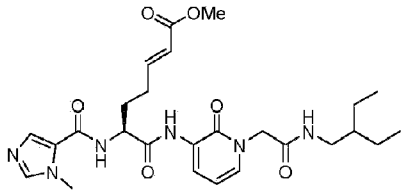
| **A:** $IC_{50}$ < 25 nM, **B:** 25 nM < $IC_{50}$ < 250 nM, **C:** 250 nM ≤ $IC_{50}$ < 1,500 nM, | | | |
|---|---|---|---|
| **D:** 1,500 nM ≤ $IC_{50}$ < 10,000 nM | | | |
| Compound | $IC_{50}$ TG2 [nM] | Compound | $IC_{50}$ TG2 [nM] |
| **III-17** | A | **III-105** | B |
| **III-18** | A | **III-106** | B |
| **III-19** | A | **III-107** | B |
| **III-20** | A | **III-108** | A |
| **III-21** | A | **III-109** | A |
| **III-22** | A | **III-110** | A |
| **III-23** | B | **III-111** | A |
| **III-24** | B | **III-112** | A |
| **III-25** | B | **III-113** | A |
| **III-26** | B | **III-114** | A |
| **III-27** | B | **III-115** | A |
| **III-28** | C | **III-116** | A |
| **III-29** | B | **III-117** | A |
| **III-30** | B | **III-118** | A |
| **III-31** | B | **III-119** | A |
| **III-32** | B | **III-120** | A |
| **III-33** | A | **III-121** | A |
| **III-34** | A | **III-122** | B |
| **III-35** | A | **III-123** | A |
| **III-36** | B | **III-124** | A |
| **III-37** | B | **III-125** | A |
| **III-38** | B | **III-126** | A |
| **III-39** | A | **III-127** | A |
| **III-40** | A | **III-128** | A |
| **III-41** | A | **III-129** | B |
| **III-42** | A | **III-130** | B |
| **III-43** | B | **III-131** | C |
| **III-44** | B | **III-132** | C |
| **III-45** | B | **III-133** | C |
| **III-46** | A | **III-134** | B |
| **III-47** | C | **III-135** | B |
| **III-48** | B | **III-136** | C |

| **A:** $IC_{50}$ < 25 nM, **B:** 25 nM < $IC_{50}$ < 250 nM, **C:** 250 nM ≤ $IC_{50}$ < 1,500 nM, | | | |
|---|---|---|---|
| **D:** 1,500 nM ≤ $IC_{50}$ < 10,000 nM | | | |
| Compound | $IC_{50}$ TG2 [nM] | Compound | $IC_{50}$ TG2 [nM] |
| **III-49** | B | **III-137** | C |
| **III-50** | B | **III-138** | C |
| **III-51** | A | **III-139** | C |
| **III-52** | A | **III-140** | B |
| **III-53** | A | **III-141** | C |
| **III-54** | B | **III-142** | B |
| **III-55** | B | **III-143** | C |
| **III-56** | B | **III-144** | C |
| **III-57** | B | **III-145** | B |
| **III-58** | A | **III-146** | C |
| **III-59** | A | **III-147** | B |
| **III-60** | A | **III-148** | B |
| **III-61** | B | **III-149** | C |
| **III-62** | A | **III-150** | B |
| **III-63** | A | **III-151** | C |
| **III-64** | A | **III-152** | B |
| **III-65** | A | **III-153** | B |
| **III-66** | B | **III-154** | C |
| **III-67** | A | **III-155** | B |
| **III-68** | A | **III-156** | C |
| **III-69** | A | **III-157** | C |
| **III-70** | A | **III-158** | C |
| **III-71** | B | **III-159** | C |
| **III-72** | B | **III-160** | C |
| **III-73** | A | **III-161** | C |
| **III-74** | A | **III-162** | C |
| **III-75** | B | **III-163** | C |
| **III-76** | B | **III-164** | C |
| **III-77** | B | **III-165** | B |
| **III-78** | C | **III-166** | B |
| **III-79** | C | **III-167** | C |
| **III-80** | C | **III-168** | C |

| **A:** $IC_{50}$ < 25 nM, **B:** 25 nM < $IC_{50}$ < 250 nM, **C:** 250 nM ≤ $IC_{50}$ < 1,500 nM, | | | |
|---|---|---|---|
| **D:** 1,500 nM ≤ $IC_{50}$ < 10,000 nM | | | |
| Compound | $IC_{50}$ TG2 [nM] | Compound | $IC_{50}$ TG2 [nM] |
| **III-81** | C | **III-169** | B |
| **III-82** | C | **III-170** | B |
| **III-83** | A | **III-171** | B |
| **III-84** | A | **III-172** | B |
| **III-85** | A | **III-173** | B |
| **III-86** | A | **III-174** | C |
| **III-87** | B | **III-175** | C |
| **III-88** | A | **Ref. 2** | B |
| | | **Ref. 3** | D |
| | | **Ref. 5** | C |

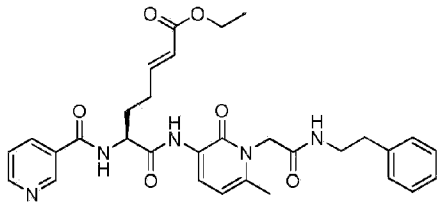
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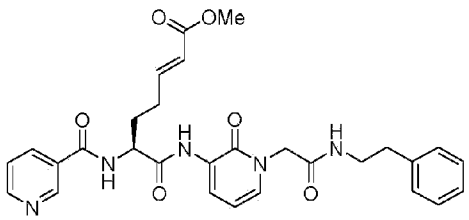
**[0489]**



**Ref. 3 (A8, ZED1047) Ref. 5**

**[0490]**





**Example B-2. logD values of the inventive compounds**

**[0491]** In order to classify the inventive compounds according to their lipophilicity, LogD values (distribution coefficient) were determined by means of the well-established shake flask method, measuring the partition of a compound between an octanol and phosphate-buffered saline (PBS, pH 7.4) by HPLC.

**[0492]** The LogD is pH dependent and is a "predictor" for in-vivo properties. LogD combines lipophilicity (intrinsic structural property of the molecule, logP) and ionizability (pKa).

**[0493]** Compounds with a moderate lipophilicity (LogD values from 0 to 3) are usually advantaged for oral absorption, being in balance between solubility and permeability. However, sophisticated formulation of a compound might improve oral bioavailability for highly lipophilic compounds.

**Table 2. logD values of irreversible TG2 inhibitors**

| **A:** logD < 1, **B:** 1 ≤ logO < 3, **C:** 3 ≤ logO < 5 | | | |
|---|---|---|---|
| Compound | logD | Compound | logD |
| **III-1** | B | **III-89** | C |
| **III-2** | C | **III-90** | B |
| **III-3** | C | **III-91** | C |
| **III-4** | C | **III-92** | C |
| **III-5** | C | **III-93** | B |
| **III-6** | C | **III-94** | C |
| **III-7** | C | **III-95** | C |
| **III-8** | C | **III-96** | A |
| **III-9** | C | **III-97** | C |
| **III-10** | C | **III-98** | B |
| **III-11** | C | **III-99** | C |
| **III-12** | C | **III-100** | B |
| **III-13** | C | **III-101** | B |
| **III-14** | C | **III-102** | B |
| **III-15** | C | **III-103** | B |
| **III-16** | C | **III-104** | B |
| **III-17** | C | **III-105** | B |
| **III-18** | C | **III-106** | C |
| **III-19** | C | **III-107** | C |
| **III-20** | C | **III-108** | C |
| **III-21** | B | **III-109** | C |
| **III-22** | B | **III-110** | B |
| **III-23** | B | **III-111** | B |

| **A:** logD < 1, **B:** 1 ≤ logO < 3, **C:** 3 ≤ logO < 5 | | | |
|---|---|---|---|
| Compound | logD | Compound | logD |
| **III-24** | B | **III-112** | B |
| **III-25** | C | **III-113** | B |
| **III-26** | B | **III-114** | B |
| **III-27** | C | **III-115** | B |
| **III-28** | C | **III-116** | A |
| **III-29** | C | **III-117** | B |
| **III-30** | C | **III-118** | B |
| **III-31** | B | **III-119** | A |
| **III-32** | C | **III-120** | B |
| **III-33** | C | **III-121** | B |
| **III-34** | C | **III-122** | B |
| **III-35** | C | **III-123** | C |
| **III-36** | C | **III-124** | C |
| **III-37** | C | **III-125** | B |
| **III-38** | B | **III-126** | C |
| **III-39** | C | **III-127** | C |
| **III-40** | C | **III-128** | C |
| **III-41** | C | **III-129** | B |
| **III-42** | C | **III-130** | B |
| **III-43** | C | **III-131** | C |
| **III-44** | C | **III-132** | C |
| **III-45** | C | **III-133** | C |
| **III-46** | C | **III-134** | B |
| **III-47** | C | **III-135** | B |
| **III-48** | C | **III-136** | A |
| **III-49** | C | **III-137** | B |
| **III-50** | B | **III-138** | A |
| **III-51** | C | **III-139** | A |
| **III-52** | C | **III-140** | A |
| **III-53** | C | **III-141** | A |
| **III-54** | C | **III-142** | B |
| **III-55** | C | **III-143** | B |
| **III-56** | C | **III-144** | C |
| **III-57** | C | **III-145** | A |

| **A:** logD < 1, **B:** 1 ≤ logO < 3, **C:** 3 ≤ logO < 5 | | | |
|---|---|---|---|
| Compound | logD | Compound | logD |
| **III-58** | B | **III-146** | A |
| **III-59** | C | **III-147** | B |
| **III-60** | C | **III-148** | C |
| **III-61** | C | **III-149** | B |
| **III-62** | B | **III-150** | A |
| **III-63** | C | **III-151** | A |
| **III-64** | B | **III-152** | B |
| **III-65** | C | **III-153** | B |
| **III-66** | B | **III-154** | B |
| **III-67** | C | **III-155** | B |
| **III-68** | C | **III-156** | C |
| **III-69** | C | **III-157** | B |
| **III-70** | C | **III-158** | A |
| **III-71** | C | **III-159** | A |
| **III-72** | C | **III-160** | A |
| **III-73** | C | **III-161** | B |
| **III-74** | C | **III-162** | A |
| **III-75** | C | **III-163** | A |
| **III-76** | B | **III-164** | A |
| **III-77** | C | **III-165** | B |
| **III-78** | C | **III-166** | B |
| **III-79** | C | **III-167** | A |
| **III-80** | B | **III-168** | A |
| **III-81** | C | **III-169** | A |
| **III-82** | C | **III-170** | A |
| **III-83** | C | **III-171** | A |
| **III-84** | C | **III-172** | A |
| **III-85** | B | **III-173** | A |
| **III-86** | B | **III-174** | B |
| **III-87** | B | **III-175** | B |
| **III-88** | B | **Ref. 2** | B |
| | | **Ref. 3** | B |
| | | **Ref. 5** | B |

**Example B-3. Caco-2 permeability assay of the inventive compounds**

**[0494]** Permeability coefficients ($P_{app}$ values) were obtained from Caco-2 barrier studies predicting oral/intestinal bioavailability of the tested compounds. The assays were performed by using CacoReady™ ready-to-use kits from ReadyCell according to the manufacturers protocol.

**[0495]** It is considered that compounds bearing $P_{app}$ values above $1\times10^{-6}$ cm/s are classified as permeable whereas compounds bearing $P_{app}$ values below $1\times10^{-6}$ cm/s are classified as not permeable.

**Table 3. Caco2 permeability assay of irreversible TG2 inhibitors**

| **A:** $P_{app} < 1\times10^{-6}$ cm/s, **B:** $1\times10^{-6}$ cm/s $\leq P_{app} < 10\times10^{-6}$ cm/s | | | |
|---|---|---|---|
| Compound | $P_{app}$ [cm/s] $\times10^{-6}$ | Compound | $P_{app}$ [cm/s] $\times10^{-6}$ |
| **III-1** | A | **III-89** | B |
| **III-2** | B | **III-90** | B |
| **III-3** | B | **III-91** | B |
| **III-4** | B | **III-92** | B |
| **III-5** | B | **III-93** | B |
| **III-6** | B | **III-94** | B |
| **III-7** | B | **III-95** | B |
| **III-8** | A | **III-96** | B |
| **III-9** | A | **III-97** | B |
| **III-10** | B | **III-98** | B |
| **III-11** | A | **III-99** | A |
| **III-12** | B | **III-100** | A |
| **III-13** | B | **III-101** | A |
| **III-14** | B | **III-102** | A |
| **III-15** | B | **III-103** | B |
| **III-16** | B | **III-104** | A |
| **III-17** | A | **III-105** | B |
| **III-18** | A | **III-106** | B |
| **III-19** | B | **III-107** | B |
| **III-20** | B | **III-108** | A |
| **III-21** | A | **III-109** | A |

| **A:** $P_{app}$ < $1\times10^{-6}$ cm/s, **B:** $1\times10^{-6}$ cm/s ≤ $P_{app}$ < $10\times10^{-6}$ cm/s | | | |
|---|---|---|---|
| Compound | $P_{app}$ [cm/s] $\times10^{-6}$ | Compound | $P_{app}$ [cm/s] $\times10^{-6}$ |
| **III-22** | B | **III-110** | A |
| **III-23** | B | **III-111** | A |
| **III-24** | A | **III-112** | A |
| **III-25** | A | **III-113** | A |
| **III-26** | B | **III-114** | A |
| **III-27** | A | **III-115** | A |
| **III-28** | A | **III-116** | A |
| **III-29** | A | **III-117** | A |
| **III-30** | A | **III-118** | A |
| **III-31** | A | **III-119** | A |
| **III-32** | A | **III-120** | A |
| **III-33** | A | **III-121** | A |
| **III-34** | A | **III-122** | A |
| **III-35** | A | **III-123** | B |
| **III-36** | A | **III-124** | B |
| **III-37** | B | **III-125** | B |
| **III-38** | A | **III-126** | B |
| **III-39** | B | **III-127** | B |
| **III-40** | B | **III-128** | B |
| **III-41** | B | **III-129** | A |
| **III-42** | B | **III-130** | A |
| **III-43** | A | **III-131** | B |
| **III-44** | A | **III-132** | B |
| **III-45** | B | **III-133** | A |
| **III-46** | B | **III-134** | B |
| **III-47** | B | **III-135** | B |
| **III-48** | B | **III-136** | A |
| **III-49** | B | **III-137** | A |
| **III-50** | A | **III-138** | A |
| **III-51** | B | **III-139** | A |
| **III-52** | B | **III-140** | B |
| **III-53** | B | **III-141** | B |
| **III-54** | A | **III-142** | B |

| **A:** $P_{app}$ < $1\times10^{-6}$ cm/s, **B:** $1\times10^{-6}$ cm/s ≤ $P_{app}$ < $10\times10^{-6}$ cm/s | | | |
|---|---|---|---|
| Compound | $P_{app}$ [cm/s] $\times10^{-6}$ | Compound | $P_{app}$ [cm/s] $\times10^{-6}$ |
| **III-55** | B | **III-143** | B |
| **III-56** | B | **III-144** | A |
| **III-57** | B | **III-145** | A |
| **III-58** | A | **III-146** | A |
| **III-59** | B | **III-147** | B |
| **III-60** | A | **III-148** | B |
| **III-61** | B | **III-149** | A |
| **III-62** | A | **III-150** | A |
| **III-63** | B | **III-151** | A |
| **III-64** | B | **III-152** | B |
| **III-65** | B | **III-153** | B |
| **III-66** | B | **III-154** | B |
| **III-67** | B | **III-155** | B |
| **III-68** | B | **III-156** | B |
| **III-69** | B | **III-157** | A |
| **III-70** | B | **III-158** | A |
| **III-71** | B | **III-159** | A |
| **III-72** | B | **III-160** | A |
| **III-73** | B | **III-161** | A |
| **III-74** | B | **III-162** | A |
| **III-75** | B | **III-163** | A |
| **III-76** | A | **III-164** | A |
| **III-77** | B | **III-165** | A |
| **III-78** | A | **III-166** | A |
| **III-79** | B | **III-167** | A |
| **III-80** | A | **III-168** | A |
| **III-81** | B | **III-169** | A |
| **III-82** | B | **III-170** | A |
| **III-83** | A | **III-171** | A |
| **III-84** | A | **III-172** | A |
| **III-85** | A | **III-173** | A |
| **III-86** | A | **III-174** | A |
| **III-87** | A | **III-175** | A |

| **A:** $P_{app}$ < 1×10$^{-6}$ cm/s, **B:** 1×10$^{-6}$ cm/s ≤ $P_{app}$ < 10×10$^{-6}$ cm/s | | | |
|---|---|---|---|
| Compound | $P_{app}$ [cm/s] ×10$^{-6}$ | Compound | $P_{app}$ [cm/s] ×10$^{-6}$ |
| **III-88** | A | **Ref. 2** | A |
| | | **Ref. 3** | A |
| | | **Ref. 5** | A |

# REFERENCES CITED IN THE DESCRIPTION

Cited references

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

**Patent documents cited in the description**

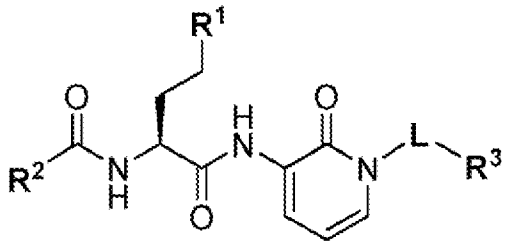
- US9434763B2 [0007] [0016] [0016] [0016] [0016]
- US11072634B2 [0010]

**Non-patent literature cited in the description**

- **J.M. WODZINSKA**Mini-Reviews in medical chemistry, 2005, vol. 5, 279-292 [0003]
- **TSE et al.**J. Med. Chem., 2020, vol. 63, 11585-11601 [0008]
- **SUBBAIAH et al.**J. Med. Chem., 2021, vol. 64, 1914046-14128 [0009]
- **BÜCHOLD, CHILS, MGERLACH, UWEBER, JPELZER, CHEIL, AAESCHLIMANN, D.PASTERNACK, R**Features of ZED1227: The First-In-Class Tissue Transglutaminase Inhibitor Undergoing Clinical Evaluation for the Treatment of Celiac DiseaseCells, 2022, vol. 11, 1667- [0016]
- **AYMAN EL-FAHAMFERNANDO ALBERICIO**Peptide Coupling Reagents, More than a Letter SoupChemical Reviews, 2011, vol. 111, 116557-6602 [0059]
- **LORAND et al.**Anal Biochem, 1971, vol. 44, 221-31 [0482]

## Patentkrav

**1.** Forbindelse med den almene formel (**I**):



(I)

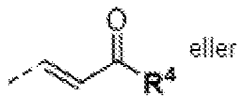
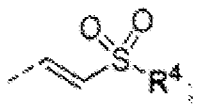
hvor

**L** repræsenterer -**L**$^{1}$- eller -**L**$^{1}$-**L**$^{2}$-; og fortrinsvis -**L**$^{1}$-**L**$^{2}$-;

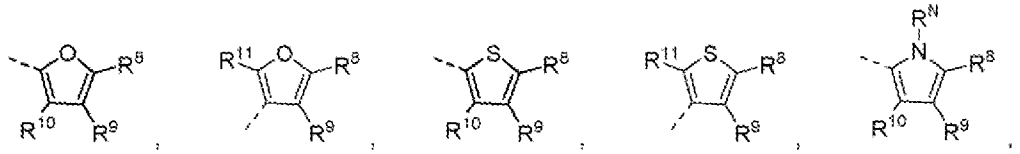
**L**$^{1}$ repræsenterer -$CH_2$-, -$CH_2CH_2$-, -$CH_2CH_2CH_2$-, -$CH_2CO$- eller -$CH_2CH_2CO$-;

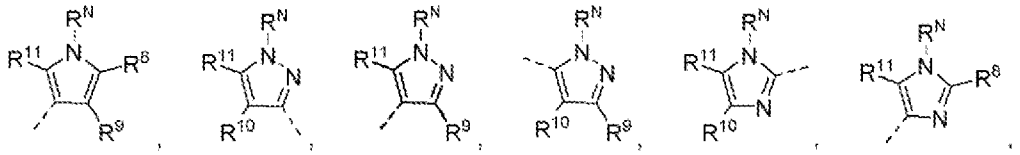
**L**$^{2}$ repræsenterer en binding, -N**R**$^{N1}$-, -N**R**$^{N1}CH_2$-, -N**R**$^{N1}CH_2CH_2$- eller -$NR^{N1}CH(CH_3)$-;

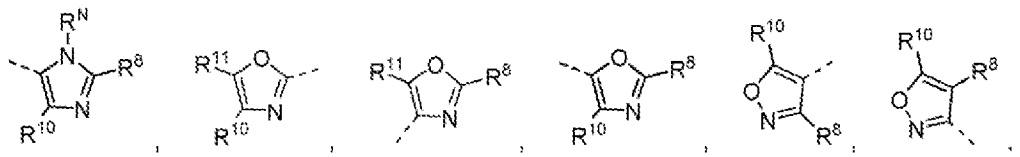
**R**$^{1}$ repræsenterer

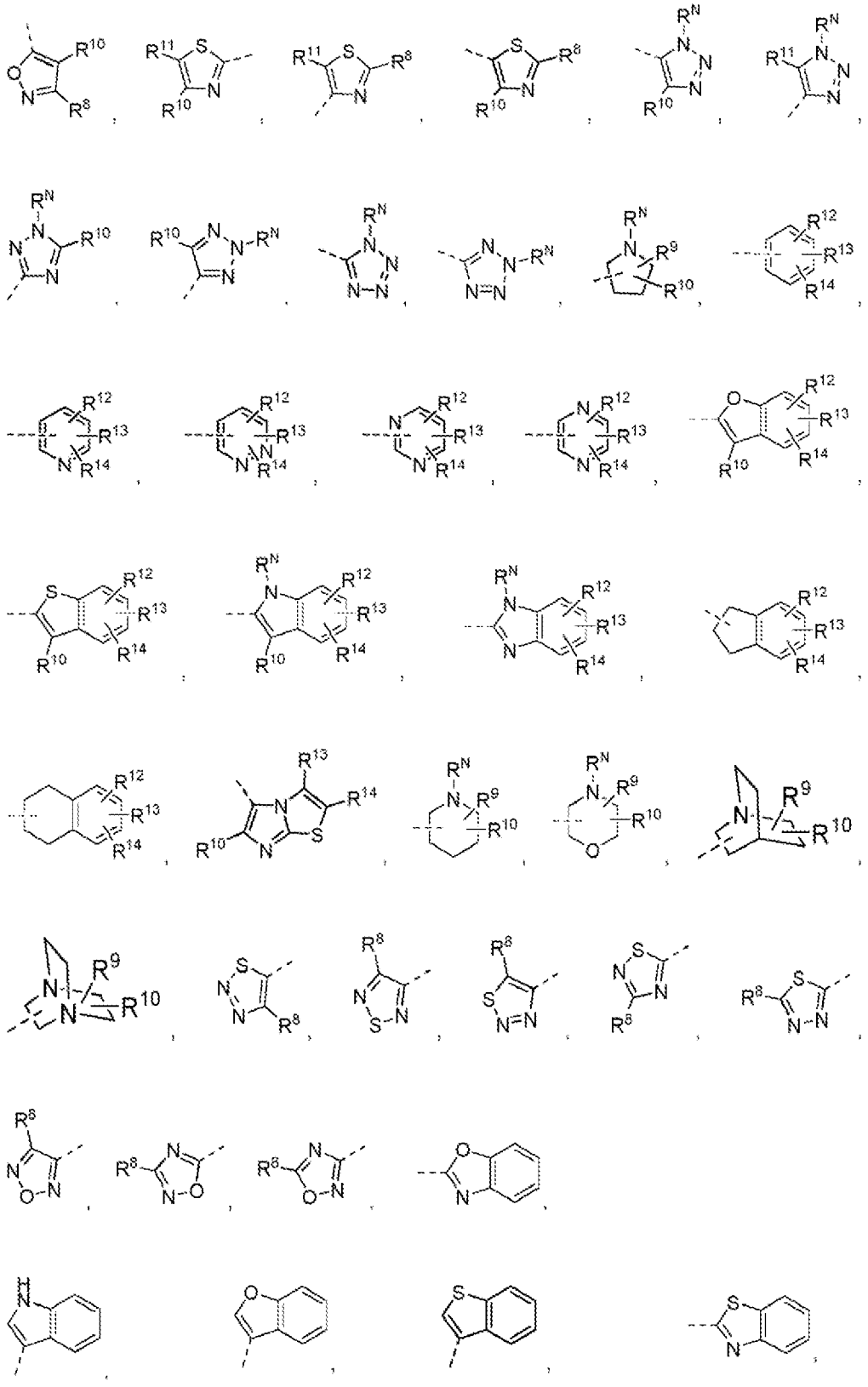

eller


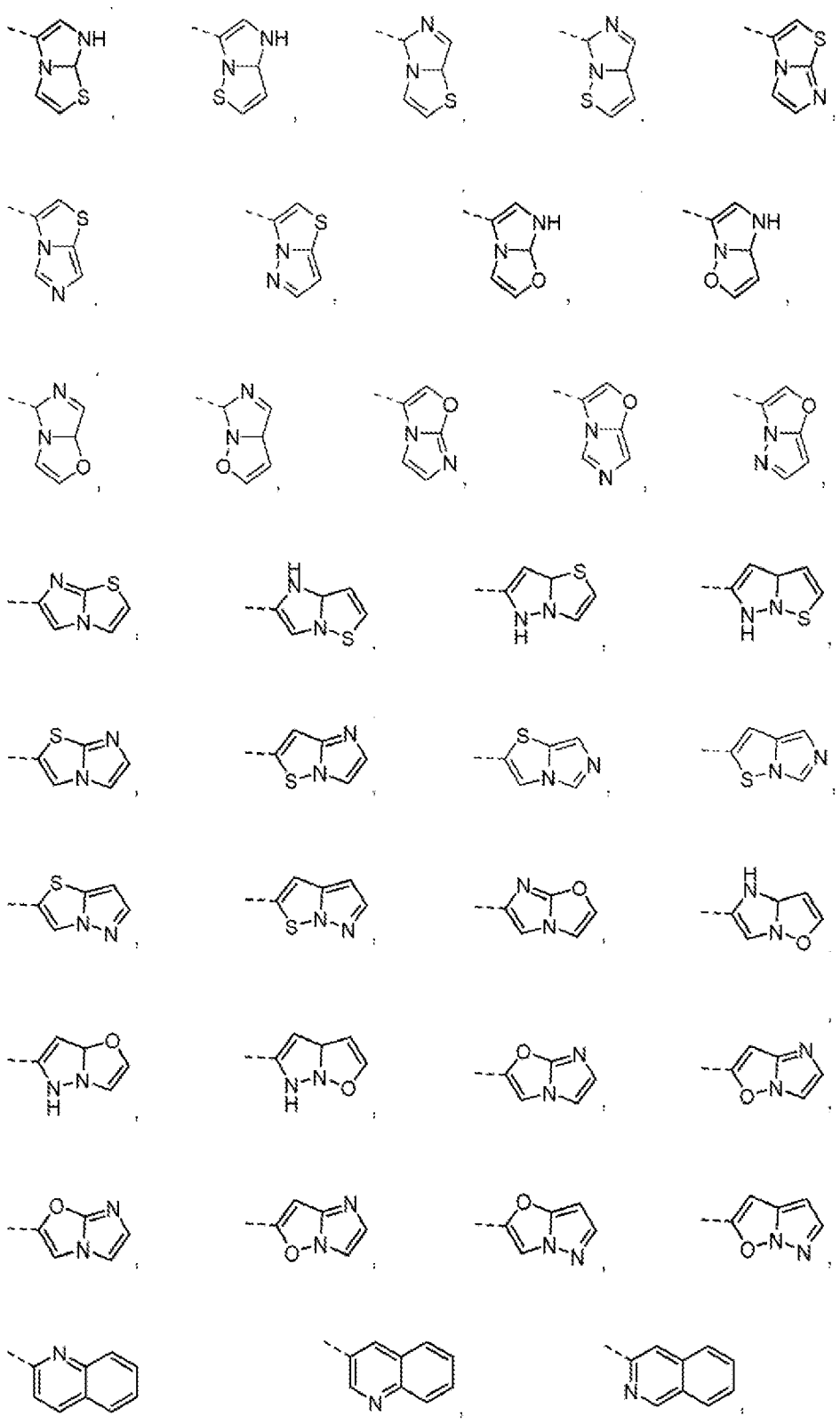
**R**$^{2}$ repræsenterer

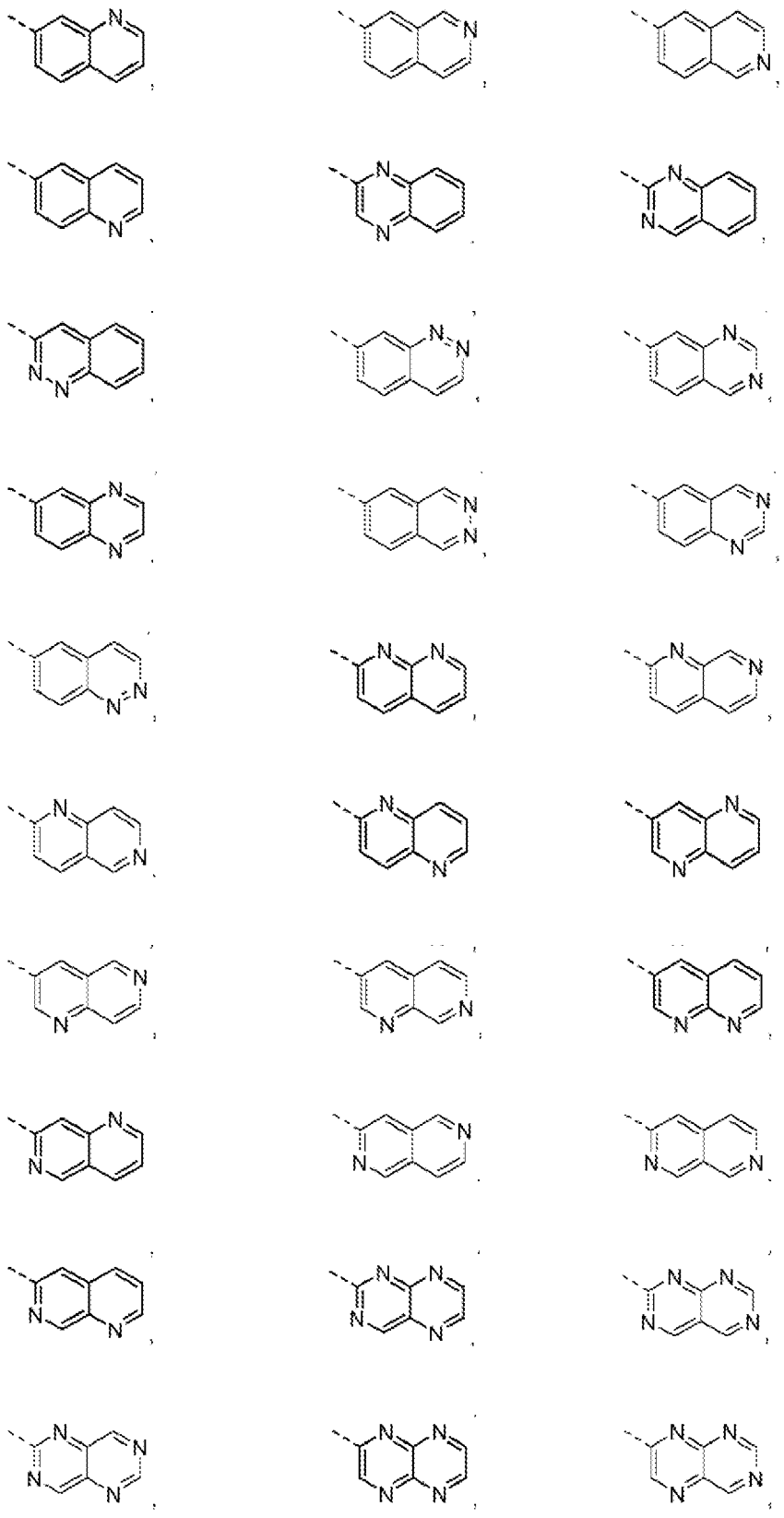


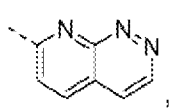
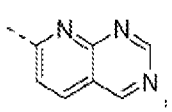
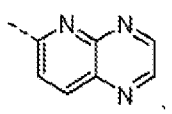
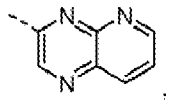
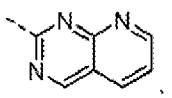
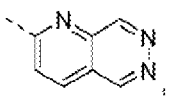
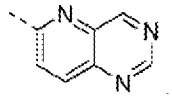
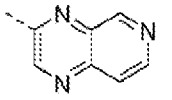
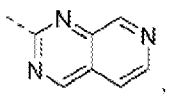
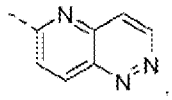
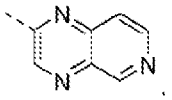
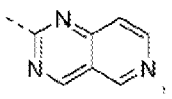
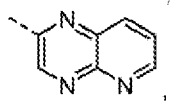
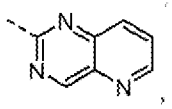
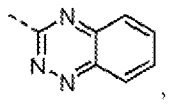
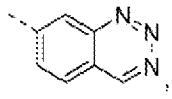
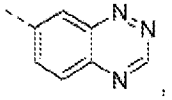
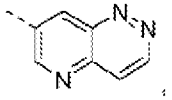
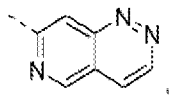
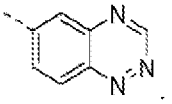
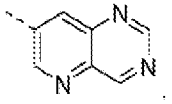
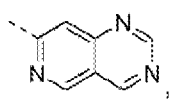
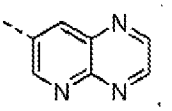
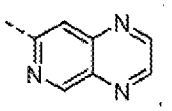
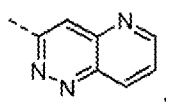
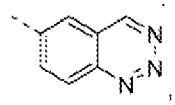
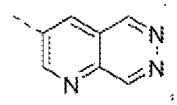
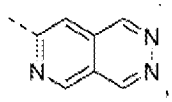
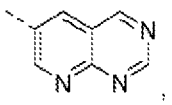
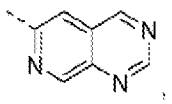


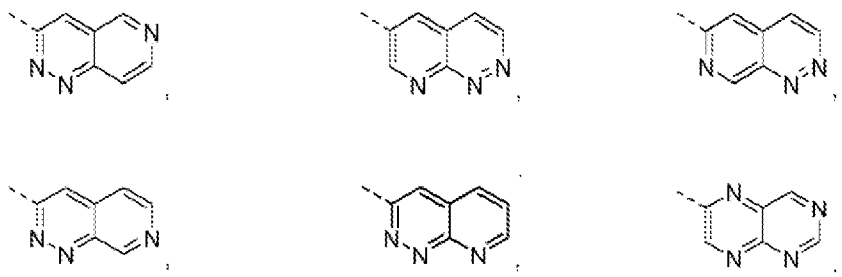


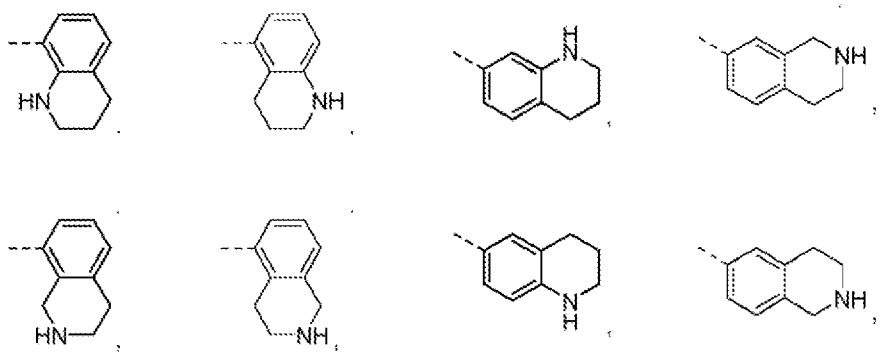


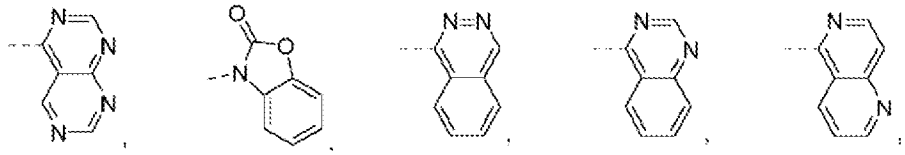


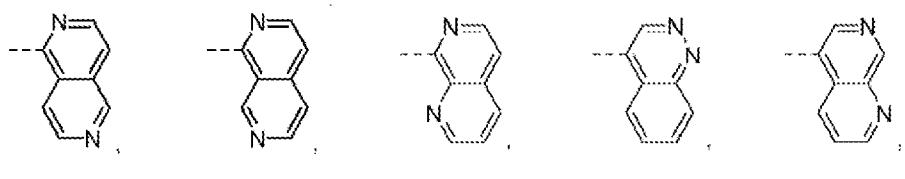


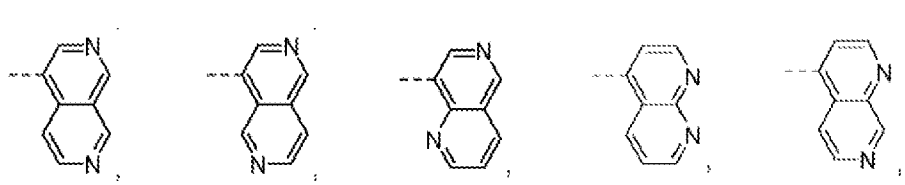































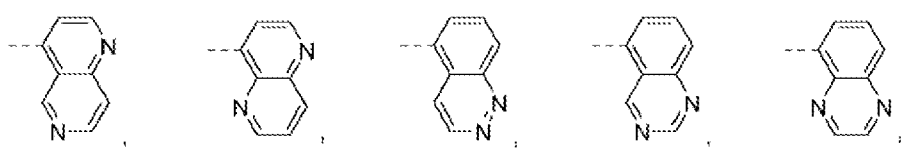


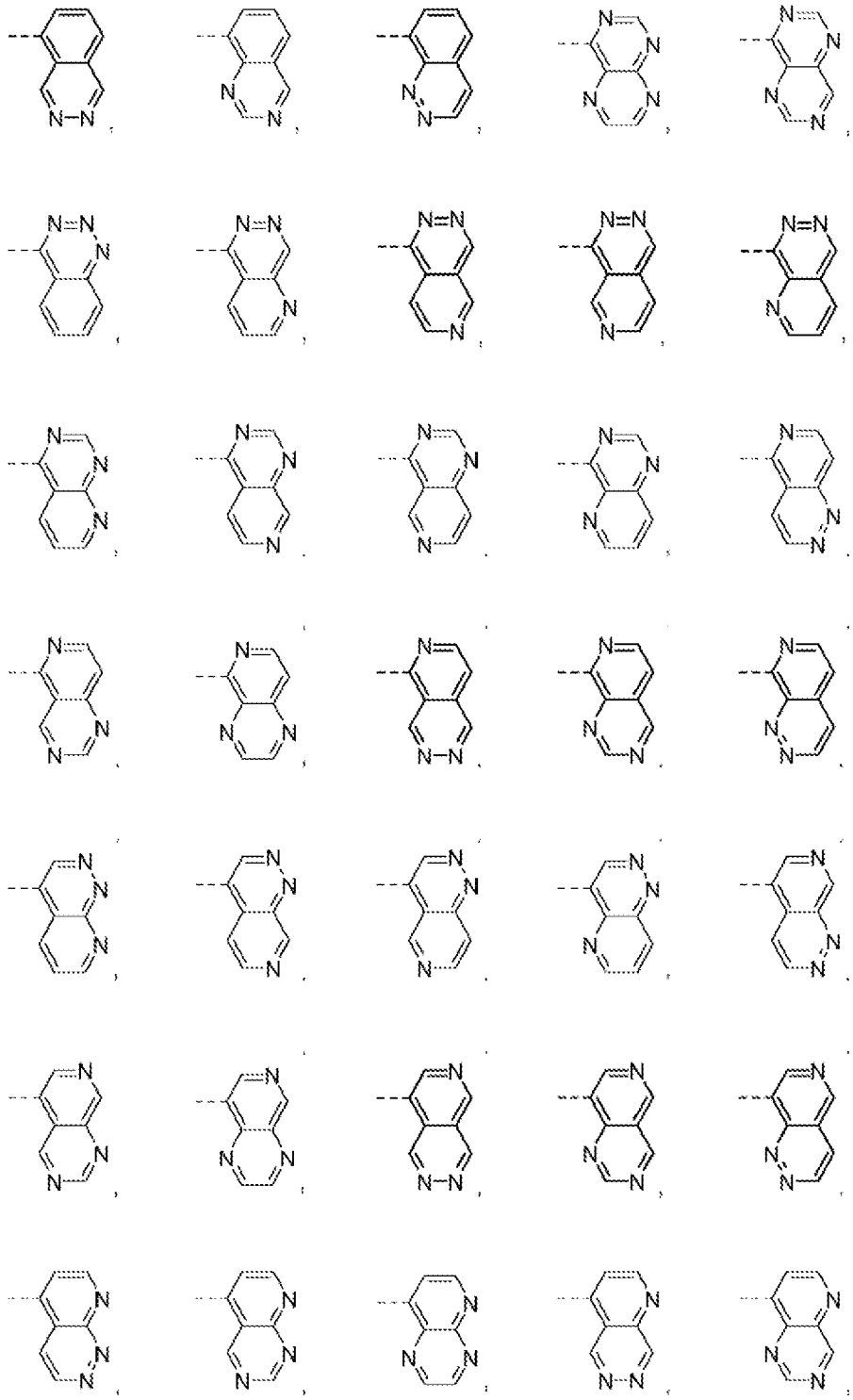


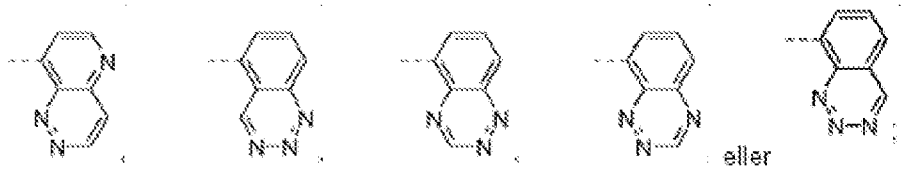













hvor de usubstituerede bicykliske rester kan være substitueret med 1 til 5 af substituenterne **$R^9$ -$R^{14}$, $R^N$**; og fortrinsvis med 1 til 3 af substituenterne **$R^{11}$ - $R^{13}$**;

**$R^3$** betegner bicyclo[1.1.1]pentyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.2]decyl, bicyclo[3.3.3]undecyl, 4-homoisotwistyl, adamantyl, diamantyl, hexamethylentetraminyl og de førnævnte rester indeholder eventuelt en eller flere C=C dobbeltbinding( s) og/eller er substitueret med en eller flere af **$R^a$, $R^b$, $R^c$, $R^d$** og **$R^e$**;

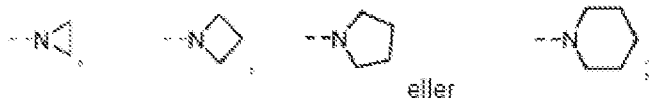
**$R^a$, $R^b$, $R^c$, $R^d$** og **$R^e$** repræsenterer uafhængigt af hinanden -H, -F, -Cl, -Br, -CN, -OH, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CHF_2$, $-CF_3$, $-CH_2CF_3$, $-COCH_3$, $-COCH_2CH_3$, $-CO_2H$, $-CO_2CH_3$, $-CO_2C_2H_5$, $-CONH_2$, $-CONHCH_3$, $-CON(CH_3)_2$, $-CONHC_2H_5$, $-CH_2CO_2H$, $-CH_2CO_2CH_3$, $-CH_2CO_2C_2H_5$, $-CH_2CONH_2$, $-CH_2CONHCH_3$, $-CH_2CON(CH_3)_2$, $-CH_2CONHC_2H_5$, $-NHCOCH_3$, $-NHCOC_2H_5$, $-NHCOCF_3$, $-NHCOCH_2CF_3$, $-NHSO_2CH_3$, $-NHSO_2C_2H_5$, $-NHSO_2CHF_2$, $-NHSO_2CF_3$ eller $-NHSO_2CH_2CF_3$;

**$R^4$** repræsenterer **-$R^5$**, -O**$R^5$** eller -N**$R^6R^7$**;

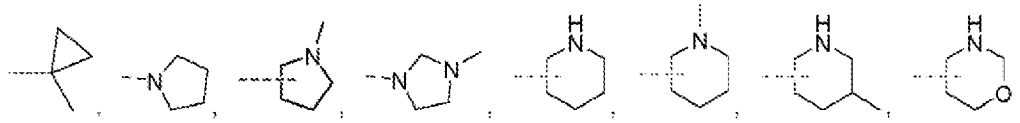
**$R^5$** repræsenterer -H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2CH_2CH_2CH_2CH_3$, $-CH_2CH=CH_2$, $-CH_2CH=CH(CH_3)$, $-CH_2CH=C(CH_3)_2$, $-CH_2CH=CHCH_2CH_3$, -cyclo-$C_3H_5$, -cyclo-$C_4H_7$, -cyclo-$C_5H_9$, -cyclo-$C_6H_{11}$, $-CH_2$-cyclo-$C_3H_5$, $-CH_2$-cyclo-$C_4H_7$, $-CH_2$-cyclo-$C_5H_9$, $-CH_2$-cyclo-$C_6H_{11}$, -Ph, $-CH_2$-Ph, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OCH_3$ eller $-CH_2CH_2OCH_2CH_3$;

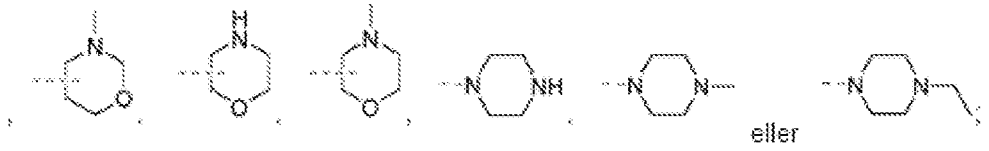
**$R^6$** og **$R^7$** repræsenterer uafhængigt af hinanden -H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2CH=CH_2$, $-CH_2CH=CH(CH_3)$, $-CH_2CH=C(CH_3)_2$,

$-CH_2CH=CHCH_2CH_3$, -cyclo-$C_3H_5$, -cyclo-$C_4H_7$, -cyclo-$C_5H_9$, -cyclo-$C_6H_{11}$, -$CH_2$-cyclo-$C_3H_5$, -$CH_2$-cyclo-$C_4H_7$, -$CH_2$-cyclo-$C_5H_9$, -$CH_2$-cyclo-$C_6H_{11}$, -Ph, -$CH_2$-Ph, -$CH_2OCH_3$, -$CH_2OCH_2CH_3$, -$CH_2CH_2OCH_3$, -$CH_2CH_2OCH_2CH_3$, -$CH_2CH_2NHCH_3$ eller -$CH_2CH_2N(CH_3)_2$ eller -$NR^6R^7$ repræsenterer

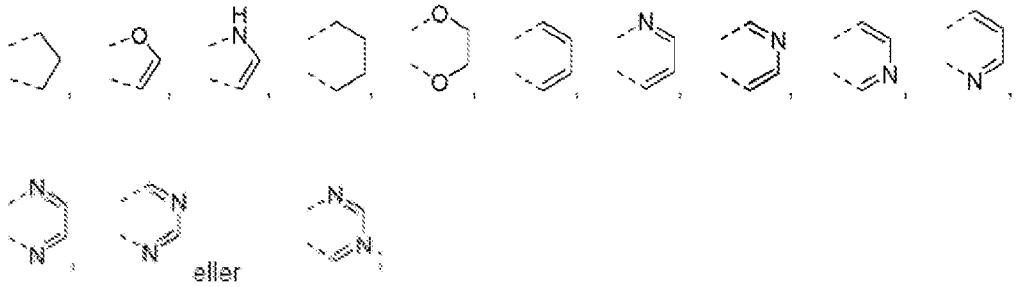



**$R^8$**, **$R^9$**, **$R^{10}$**, **$R^{11}$**, **$R^{12}$**, **$R^{13}$** eller **$R^{14}$** repræsenterer uafhængigt af hinanden -H, -F, -Cl, -Br, -I, -OH, -CN, -$NO_2$, -$CH_3$, -$C_2H_5$, -$C_3H_7$, -$CH(CH_3)_2$, -$C_4H_9$, -$CH_2$-$CH(CH_3)_2$, -$CH(CH_3)$-$C_2H_5$, -$C(CH_3)_3$, -cyclo-$C_3H_5$, -$CH_2$-cyclo-$C_3H_5$, -$CH_2OH$, -$CH_2F$, -$CHF_2$, -$CF_3$, -$CH_2Cl$, -$CH_2Br$, -$CH_2I$, -$CH_2$-$CH_2F$, -$CH_2$-$CHF_2$, -$CH_2$-$CF_3$, -$CH_2$-$CH_2Cl$, -$CH_2$-$CH_2Br$, -$CH_2$-$CH_2I$, -$OCH_3$, -$OC_2H_5$, -$OC_3H_7$, -$OCH(CH_3)_2$, -$OC(CH_3)_3$, -$OC_4H_9$, -$OCHF_2$, -$OCF_3$, -$OCH_2CF_3$, -$OC_2F_5$, -$OCH_2OCH_3$, -O-cyclo-$C_3H_5$, -$OCH_2$-cyclo-$C_3H_5$, -O-$C_2H_4$-cyclo-$C_3H_5$, -CHO, -$COCH_3$, -$COCF_3$, -$COC_2H_5$, -$COC_3H_7$, -$COCH(CH_3)_2$, -$COC(CH_3)_3$, -COOH, -$COOCH_3$, -$COOC_2H_5$, -$COOC_3H_7$, -$COOCH(CH_3)_2$, -$COOC(CH_3)_3$, -OOC-$CH_3$, -OOC-$CF_3$, -OOC-$C_2H_5$, -OOC-$C_3H_7$, -OOC-$CH(CH_3)_2$, -OOC-$C(CH_3)_3$, -$NH_2$, -$NHCH_3$, -$NHC_2H_5$, -$NHC_3H_7$, -$NHCH(CH_3)_2$, -$NHC(CH_3)_3$, -$N(CH_3)_2$, -$N(C_2H_5)_2$, -$N(C_3H_7)_2$, -$N[CH(CH_3)_2]_2$, -$N[C(CH_3)_3]_2$, -$NHCOCH_3$, -$NHCOCF_3$, -$NHCOC_2H_5$, -$NHCOC_3H_7$, -$NHCOCH(CH_3)_2$, -$NHCOC(CH_3)_3$, -$CONH_2$, -$CONHCH_3$, -$CONHC_2H_5$, -$CONHC_3H_7$, -$CONHCH(CH_3)_2$, -CONH-cyclo-$C_3H_5$, -$CONHC(CH_3)_3$, -$CON(CH_3)_2$, -$CON(C_2H_5)_2$, -$CON(C_3H_7)_2$, -$CON[CH(CH_3)_2]_2$, -$CON[C(CH_3)_3]_2$, -$SO_2NH_2$, -$SO_2NHCH_3$, -$SO_2NHC_2H_5$, -$SO_2NHC_3H_7$, -$SO_2NHCH(CH_3)_2$, -$SO_2NH$-cyclo-$C_3H_5$, -$SO_2NHC(CH_3)_3$, -$SO_2N(CH_3)_2$, -$SO_2N(C_2H_5)_2$, -$SO_2N(C_3H_7)_2$, -$SO_2N[CH(CH_3)_2]_2$, -$SO_2N[C(CH_3)_3]_2$, -$NHSO_2CH_3$, -$NHSO_2CF_3$, -$NHSO_2C_2H_5$, -$NHSO_2C_3H_7$, -$NHSO_2CH(CH_3)_2$, -$NHSO_2C(CH_3)_3$, -$CH=CH_2$, -$CH_2$-$CH=CH_2$, -$C(CH_3)=CH_2$, -$CH=CH$-$CH_3$, -$C\equiv CH$, -$C\equiv C$-$CH_3$, -$CH_2$-$C\equiv CH$, -Ph, -O-Ph, -O-$CH_2$-Ph,

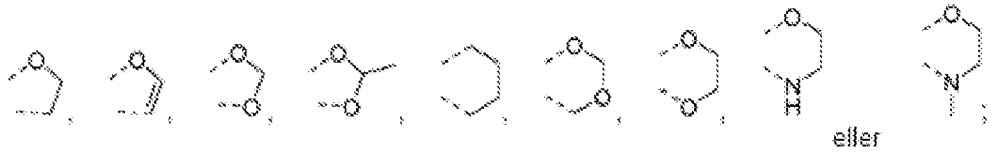





eller **R**$^{8}$ og **R**$^{9}$ eller **R**$^{9}$ og **R**$^{10}$ kan sammen danne en af følgende fem- eller seksleddede ringe:




eller **R**$^{12}$ og **R**$^{13}$ eller **R**$^{13}$ og **R**$^{14}$ kan sammen danne en af følgende fem- eller seksleddede ringe:

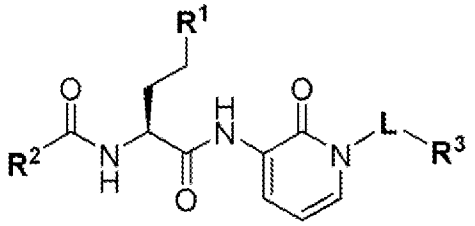



**R**$^{N}$ repræsenterer -H, -$CH_3$, -$C_2H_5$, -$C_3H_7$, -$CH(CH_3)_2$, -$C_4H_9$, -$CH_2$-$CH(CH_3)_2$, -$CH(CH_3)$-$C_2H_5$, -$C(CH_3)_3$, -cyclo-$C_3H_5$, -cyclo-$C_4H_7$, -cyclo-$C_5H_9$, -$CH_2$-cyclo-$C_3H_5$, -$CH_2$-cyclo-$C_4H_7$, -$CH_2$-cyclo-$C_5H_9$, -$CH_2F$, -$CHF_2$, -$CF_3$, -$CH_2Cl$, -$CH_2Br$, -$CH_2I$, -$CH_2$-$CH_2F$, -$CH_2$-$CHF_2$, -$CH_2$-$CF_3$, -$CH_2$-$CH_2Cl$, -$CH_2$-$CH_2Br$, -$CH_2$-$CH_2I$, -$CH_2$-CH=$CH_2$, -$CH_2$-C≡CH, -CHO, -$COCH_3$, -$COC_2H_5$, -$COC_3H_7$, -$COCH(CH_3)_2$, -$COC(CH_3)_3$, -CO-cyclo-$C_3H_5$, -CO-cyclo-$C_4H_7$, -CO-cyclo-$C_5H_9$, -$COOCH_3$, -$COOC_2H_5$, -$COOC_3H_7$, -$COOCH(CH_3)_2$, -$COOC(CH_3)_3$, -$COOCH_2Ph$, -$SO_2CH_3$, -$SO_2CF_3$, -$SO_2C_2H_5$, -$SO_2C_3H_7$, -$SO_2CH(CH_3)_2$, -$SO_2$-cyclo-$C_3H_5$ eller -$SO_2C(CH_3)_3$,

**R**$^{N1}$ repræsenterer -H, -$CH_3$ eller -$CH_2CH_3$;

eller en diastereomer, en enantiomer, en blanding af diastereomerer, en blanding af enantiomerer, et racemat, et solvat, et hydrat eller et farmaceutisk acceptabelt salt deraf.

**2.** Forbindelse ifølge krav 1, hvor forbindelsen har formlen (**I**):



(I)

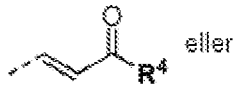
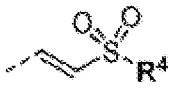
hvor

**L** repræsenterer -**L**$^{1}$- eller -**L**$^{1}$-**L**$^{2}$-; og fortrinsvis -**L**$^{1}$-**L**$^{2}$-;

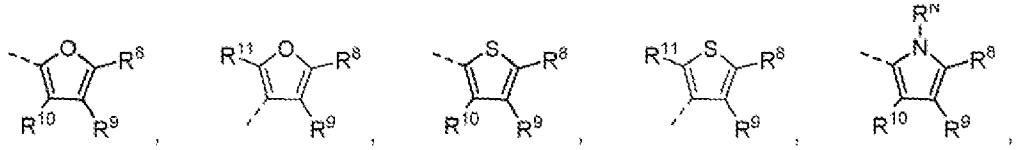
**L**$^{1}$ repræsenterer -$CH_2$-, -$CH_2CH_2$-, -$CH_2CH_2CH_2$-, -$CH_2CO$- eller -$CH_2CH_2CO$-;

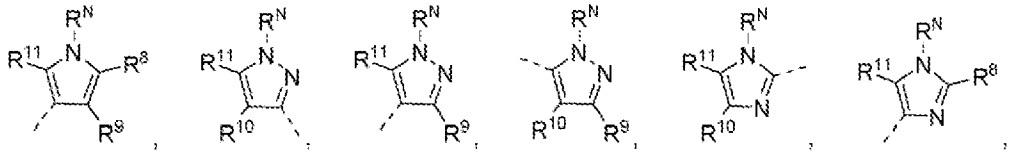
**L**$^{2}$ repræsenterer en binding, -N**R**$^{N1}$-, -N**R**$^{N1}$$CH_2$-, -N**R**$^{N1}$$CH_2CH_2$- eller -$NR^{N1}CH(CH_3)$-;

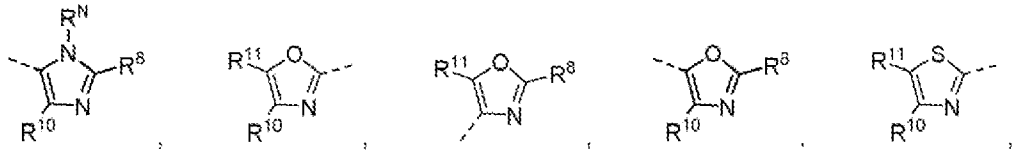
**R**$^{1}$ repræsenterer

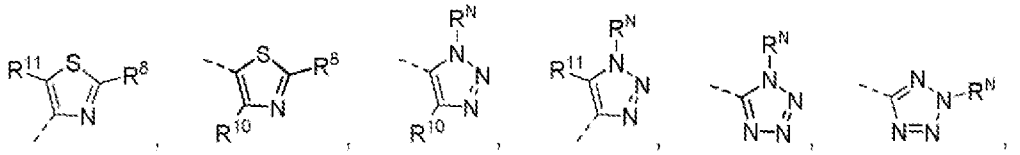

eller

;

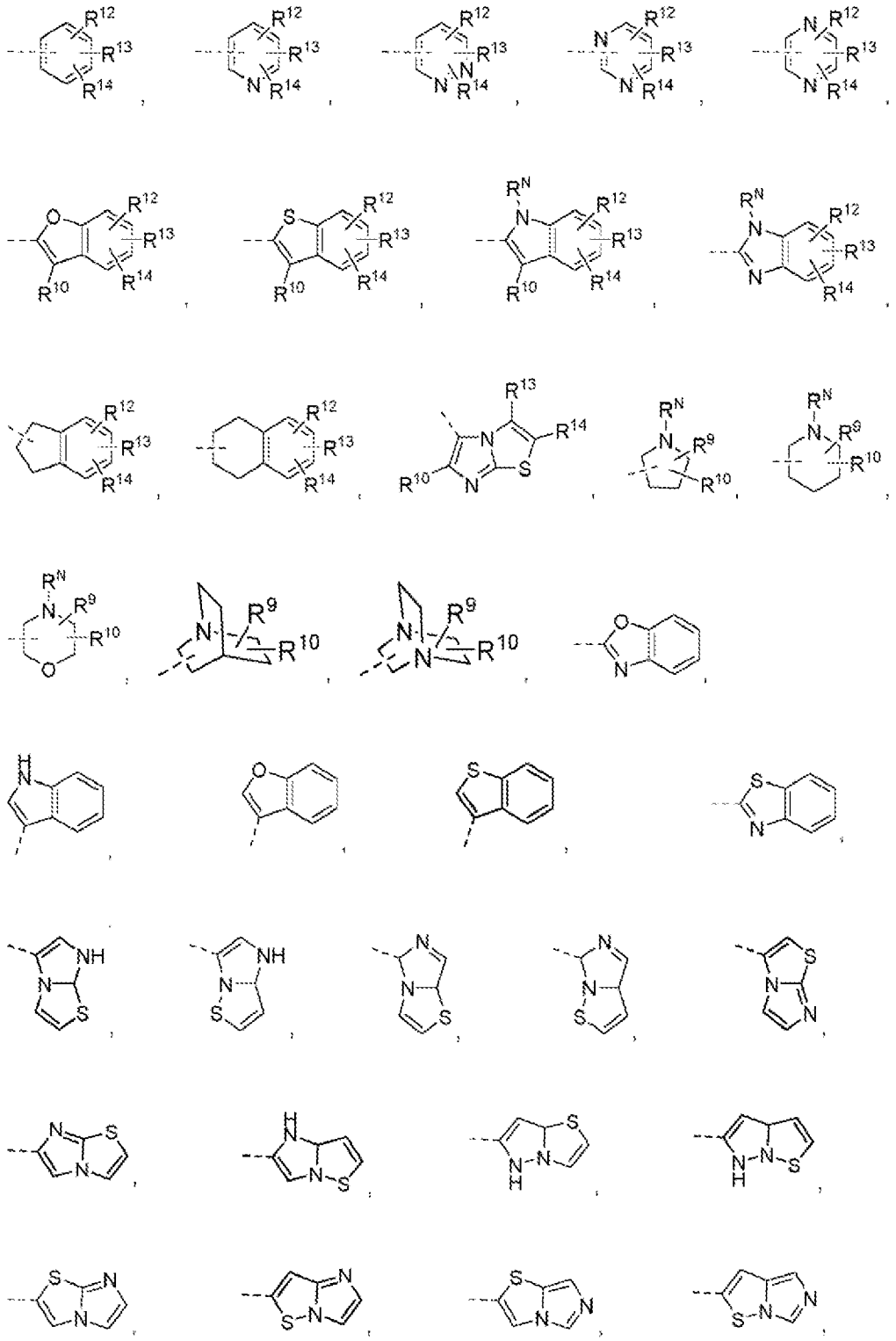
**R**$^{2}$ repræsenterer

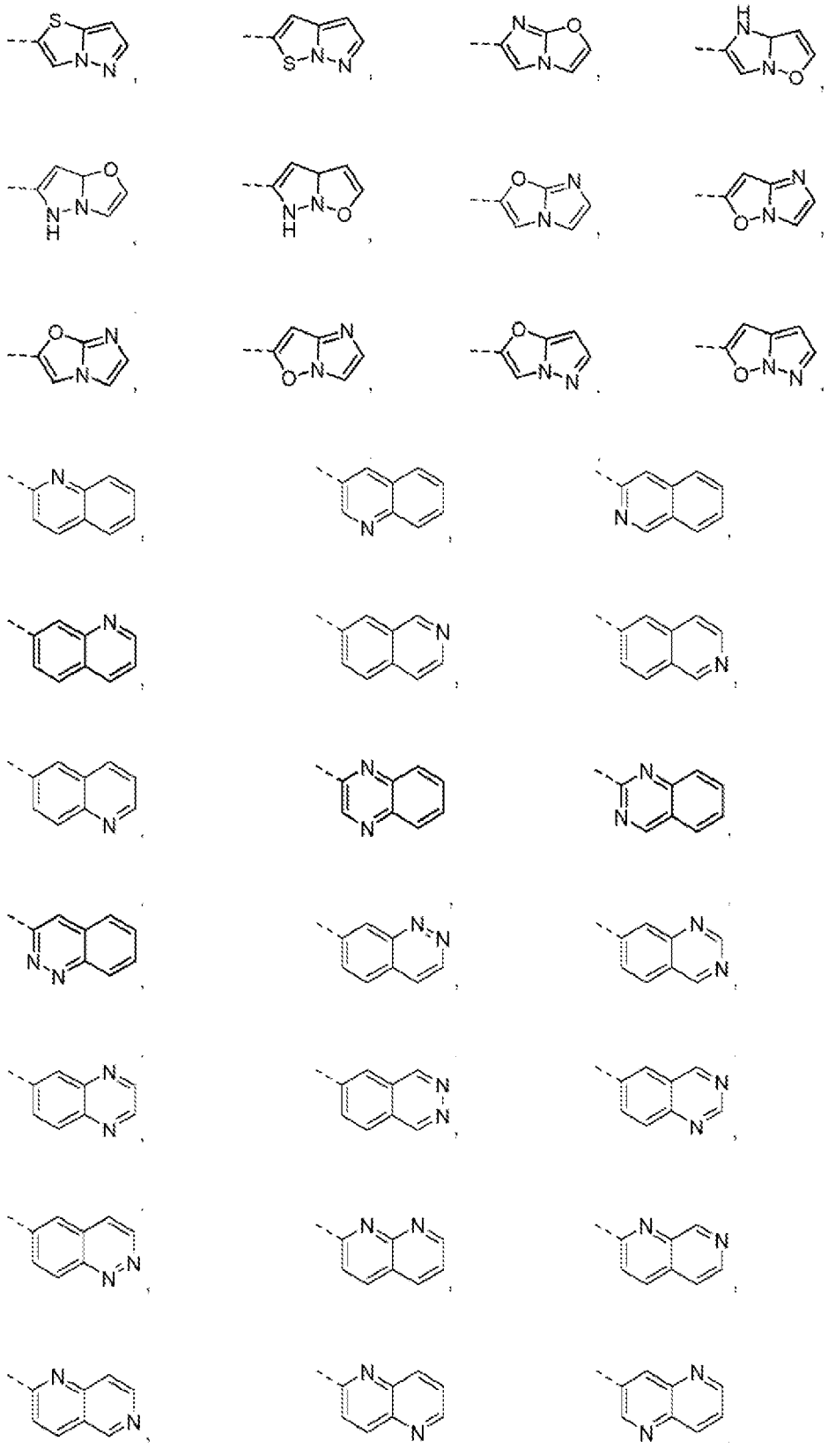


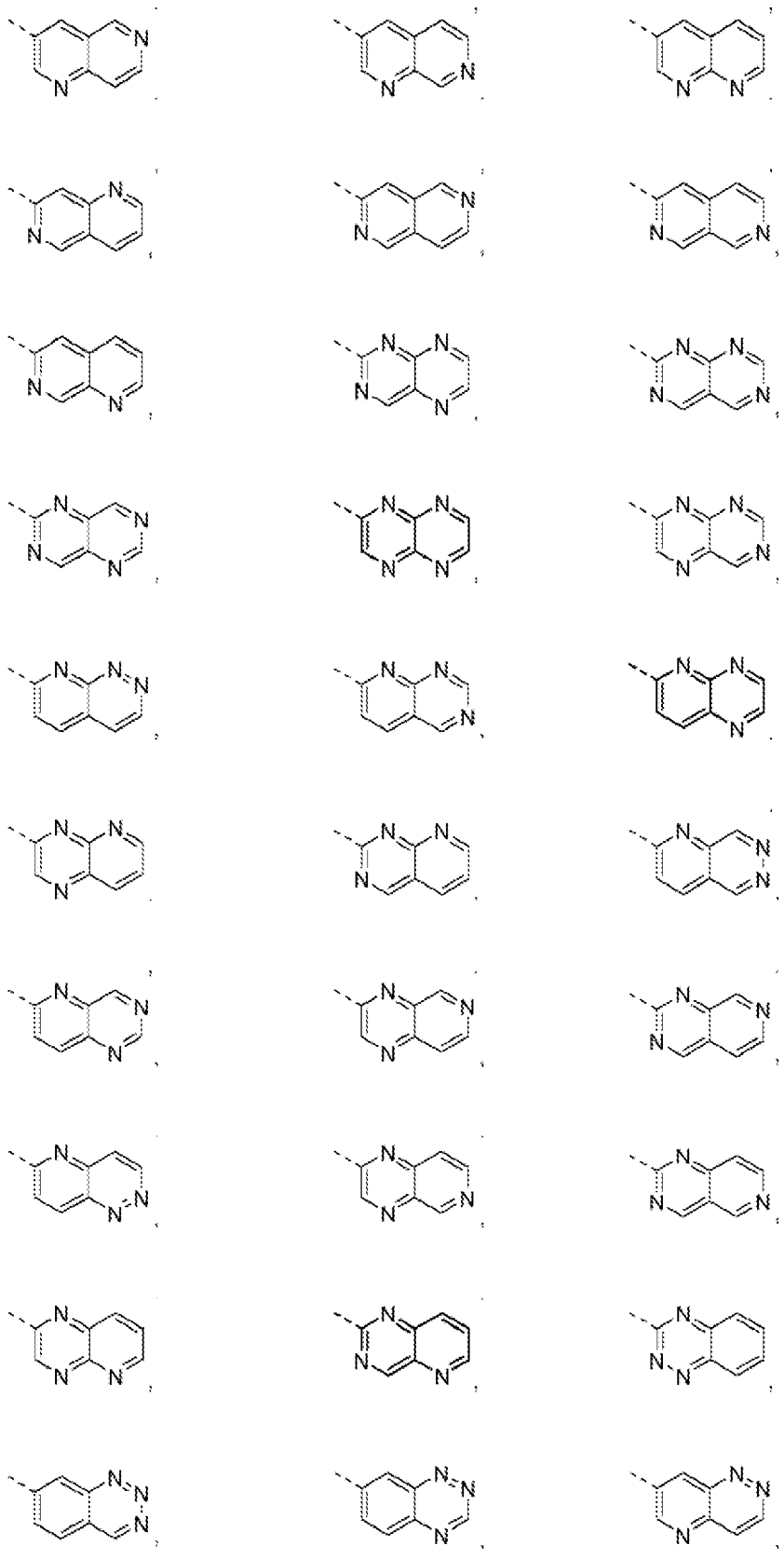


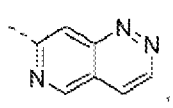
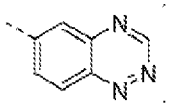
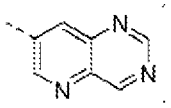
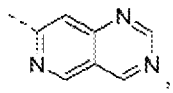
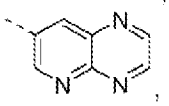
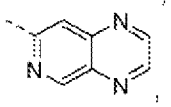
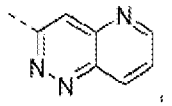
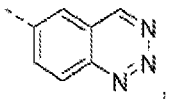
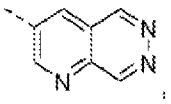
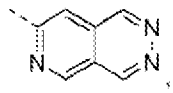
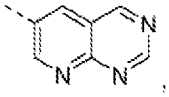
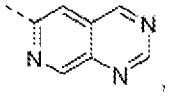
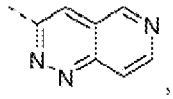
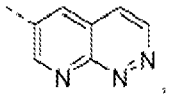
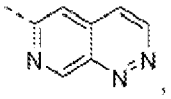
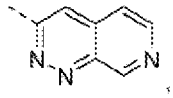
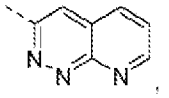
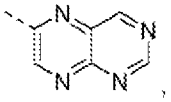
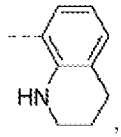
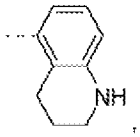
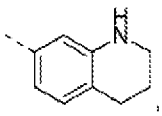
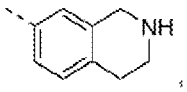
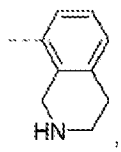
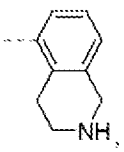
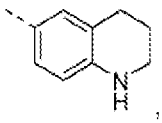
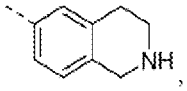
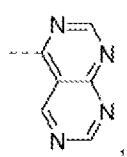
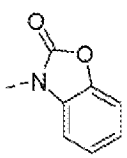
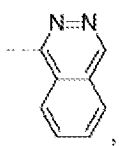
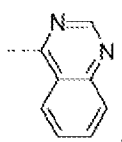
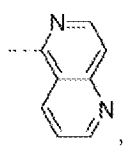


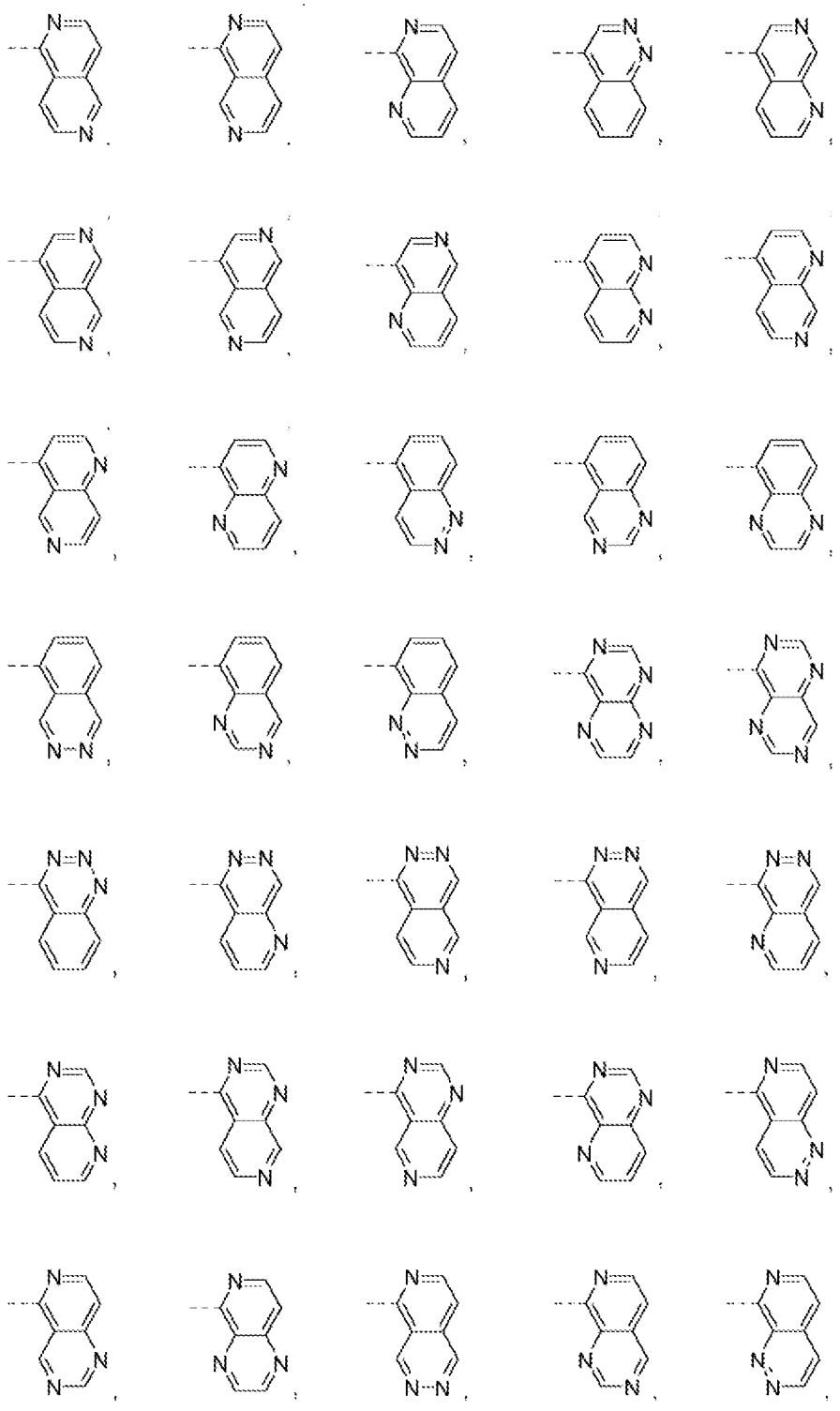


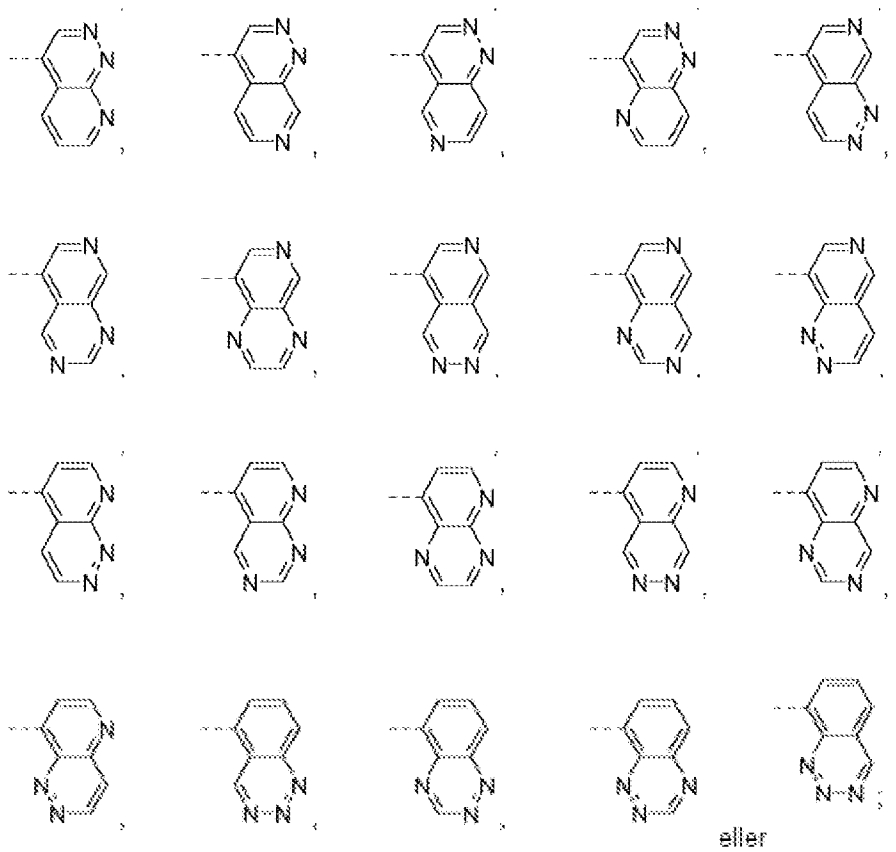










eller

**R$^3$** betegner bicyclo[1.1.1]pentyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.2]decyl, bicyclo[3.3.3]undecyl, 4-homoisotwistyl, adamantyl, diamantyl eller hexamethylentetraminyl og de førnævnte rester indeholder eventuelt en eller flere C=C-dobbeltbindinger og/eller er eventuelt substitueret med en eller flere af **R$^a$, R$^b$, R$^c$, R$^d$** og **R$^e$**;

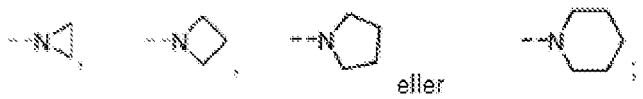
**R$^a$, R$^b$, R$^c$, R$^d$** og **R$^e$** repræsenterer uafhængigt af hinanden -H, -F, -Cl, -Br, -CN, -OH, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CHF_2$, $-CF_3$, $-CH_2CF_3$, $-COCH_3$, $-COCH_2CH_3$, $-CO_2H$, $-CO_2CH_3$, $-CO_2C_2H_5$, $-CONH_2$, $-CONHCH_3$, $-CON(CH_3)_2$, $-CONHC_2H_5$, $-CH_2CO_2H$, $-CH_2CO_2CH_3$, $-CH_2CO_2C_2H_5$, $-CH_2CONH_2$, $-CH_2CONHCH_3$, $-CH_2CON(CH_3)_2$, $-CH_2CONHC_2H_5$, $-NHCOCH_3$, $-NHCOC_2H_5$, $-NHCOCF_3$, $-NHCOCH_2CF_3$, $-NHSO_2CH_3$, $-NHSO_2C_2H_5$, $-NHSO_2CHF_2$, $-NHSO_2CF_3$ eller $-NHSO_2CH_2CF_3$;

**R$^4$** repræsenterer **-R$^5$**, -O**R$^5$** eller -N**R$^6$R$^7$**;

**R$^5$** repræsenterer -H, -$CH_3$, -$CH_2CH_3$, -$CH_2CH_2CH_3$, -$CH(CH_3)_2$, -$CH_2CH_2CH_2CH_3$, -$CH_2CH(CH_3)_2$, -$C(CH_3)_3$, -$CH_2CH_2CH_2CH_2CH_3$, -$CH_2CH=CH_2$, -$CH_2CH=CH(CH_3)$, -$CH_2CH=C(CH_3)_2$, -$CH_2CH=CHCH_2CH_3$, -cyclo-$C_3H_5$, -cyclo-$C_4H_7$, -cyclo-$C_5H_9$, -cyclo-$C_6H_{11}$, -$CH_2$-cyclo-$C_3H_5$, -$CH_2$-cyclo-$C_4H_7$, -$CH_2$-cyclo-$C_5H_9$, -$CH_2$-cyclo-$C_6H_{11}$, -$CH_2$-Ph, -$CH_2OCH_3$, -$CH_2OCH_2CH_3$, -$CH_2CH_2OCH_3$ eller -$CH_2CH_2OCH_2CH_3$;

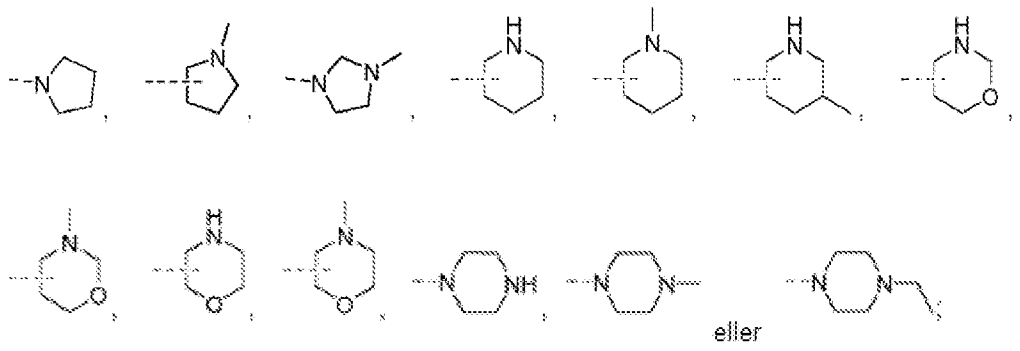
**R$^6$** og **R$^7$** repræsenterer uafhængigt af hinanden -H, -$CH_3$, -$CH_2CH_3$, -$CH_2CH_2CH_3$, -$CH(CH_3)_2$, -$CH_2CH_2CH_2CH_3$, -$CH_2CH_2CH_2CH_2CH_3$, -$CH_2CH(CH_3)_2$, -$C(CH_3)_3$, -$CH_2CH=CH_2$, -$CH_2CH=CH(CH_3)$, -$CH_2CH=C(CH_3)_2$, -$CH_2CH=CHCH_2CH_3$, -cyclo-$C_3H_5$, -cyclo-$C_4H_7$, -cyclo-$C_5H_9$, -cyclo-$C_6H_{11}$, -$CH_2$-cyclo-$C_3H_5$, -$CH_2$-cyclo-$C_4H_7$, -$CH_2$-cyclo-$C_5H_9$, -$CH_2$-cyclo-$C_6H_{11}$, -Ph, -$CH_2$-Ph, -$CH_2OCH_3$, -$CH_2OCH_2CH_3$, -$CH_2CH_2OCH_3$, -$CH_2CH_2OCH_2CH_3$, -$CH_2CH_2NHCH_3$, or -$CH_2CH_2N(CH_3)_2$

eller -N**R$^6$R$^7$** repræsenterer

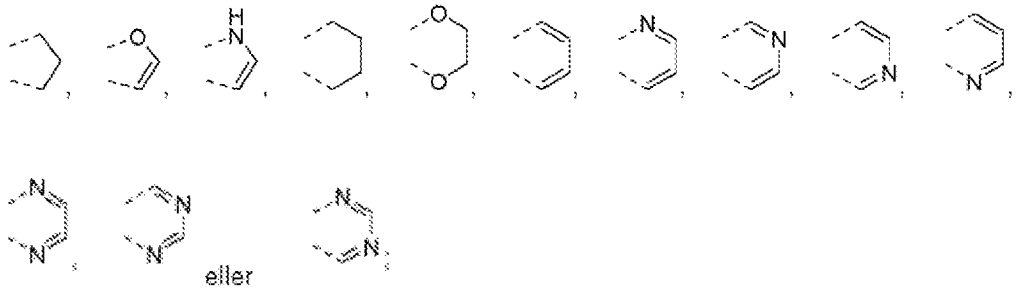



**R$^8$, R$^9$, R$^{10}$, R$^{11}$, R$^{12}$, R$^{13}$** og **R$^{14}$** repræsenterer uafhængigt af hinanden -H, -F, -Cl, -Br, -I, -OH, -CN, -$NO_2$, -$CH_3$, -$C_2H_5$, -$C_3H_7$, -$CH(CH_3)_2$, -$C_4H_9$, -$CH_2$-$CH(CH_3)_2$, -$CH(CH_3)$-$C_2H_5$, -$C(CH_3)_3$, -cyclo-$C_3H_5$, -$CH_2$-cyclo-$C_3H_5$, -$CH_2F$, -$CHF_2$, -$CF_3$, -$CH_2Cl$, -$CH_2Br$, -$CH_2I$, -$CH_2$-$CH_2F$, -$CH_2$-$CHF_2$, -$CH_2$-$CF_3$, -$CH_2$-$CH_2Cl$, -$CH_2$-$CH_2Br$, -$CH_2$-$CH_2I$, -$OCH_3$, -$OC_2H_5$, -$OC_3H_7$, -$OCH(CH_3)_2$, -$OC(CH_3)_3$, -$OC_4H_9$, -$OCHF_2$, -$OCF_3$, -$OCH_2CF_3$, -$OC_2F_5$, -$OCH_2OCH_3$, -O-cyclo-$C_3H_5$, -$OCH_2$-cyclo-$C_3H_5$, -O-$C_2H_4$-cyclo-$C_3H_5$, -CHO, -$COCH_3$, -$COCF_3$, -$COC_2H_5$, -$COC_3H_7$, -$COCH(CH_3)_2$, -$COC(CH_3)_3$, -COOH, -$COOCH_3$, -$COOC_2H_5$, -$COOC_3H_7$, -$COOCH(CH_3)_2$, -$COOC(CH_3)_3$, -OOC-$CH_3$, -OOC-$CF_3$, -OOC-$C_2H_5$, -OOC-$C_3H_7$, -OOC-$CH(CH_3)_2$, -OOC-$C(CH_3)_3$, -$NH_2$, -$NHCH_3$, -$NHC_2H_5$, -$NHC_3H_7$, -$NHCH(CH_3)_2$, -$NHC(CH_3)_3$, -$N(CH_3)_2$, -$N(C_2H_5)_2$, -$N(C_3H_7)_2$, -$N[CH(CH_3)_2]_2$, -$N[C(CH_3)_3]_2$, -$NHCOCH_3$, -$NHCOCF_3$, -$NHCOC_2H_5$, -$NHCOC_3H_7$, -$NHCOCH(CH_3)_2$, -$NHCOC(CH_3)_3$, -$CONH_2$, -$CONHCH_3$, -$CONHC_2H_5$, -$CONHC_3H_7$, -$CONHCH(CH_3)_2$, -CONH-cyclo-$C_3H_5$, -

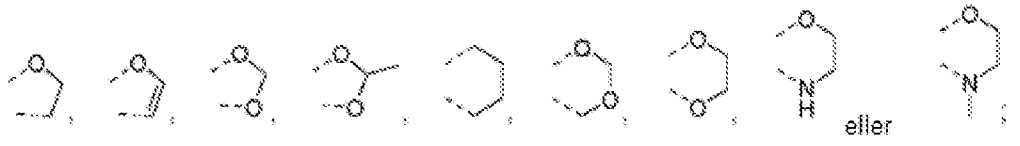
$CONHC(CH_3)_3$, $-CON(CH_3)_2$, $-CON(C_2H_5)_2$, $-CON(C_3H_7)_2$, $-CON[CH(CH_3)_2]_2$, $-CON[C(CH_3)_3]_2$, $-SO_2NH_2$, $-SO_2NHCH_3$, $-SO_2NHC_2H_5$, $-SO_2NHC_3H_7$, $-SO_2NHCH(CH_3)_2$, $-SO_2NH$-cyclo-$C_3H_5$, $-SO_2NHC(CH_3)_3$, $-SO_2N(CH_3)_2$, $-SO_2N(C_2H_5)_2$, $-SO_2N(C_3H_7)_2$, $-SO_2N[CH(CH_3)_2]_2$, $-SO_2N[C(CH_3)_3]_2$, $-NHSO_2CH_3$, $-NHSO_2CF_3$, $-NHSO_2C_2H_5$, $-NHSO_2C_3H_7$, $-NHSO_2CH(CH_3)_2$, $-NHSO_2C(CH_3)_3$, $-CH=CH_2$, $-CH_2-CH=CH_2$, $-C(CH_3)=CH_2$, $-CH=CH-CH_3$, $-C\equiv CH$, $-C\equiv C-CH_3$, $-CH_2-C\equiv CH$, -Ph, -O-Ph, $-O-CH_2$-Ph,




eller $\mathbf{R^8}$ og $\mathbf{R^9}$ eller $\mathbf{R^9}$ and $\mathbf{R^{10}}$ kan sammen danne en af følgende fem- eller seksledde ringe:




eller $\mathbf{R^{12}}$ og $\mathbf{R^{13}}$ eller $\mathbf{R^{13}}$ og $\mathbf{R^{14}}$ kan sammen danne en af følgende fem- eller seksledde ringe:




$\mathbf{R^N}$ repræsenterer -H, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $-C_4H_9$, $-CH_2-CH(CH_3)_2$, $-CH(CH_3)-C_2H_5$, $-C(CH_3)_3$, -cyclo-$C_3H_5$, -cyclo-$C_4H_7$, -cyclo-$C_5H_9$, $-CH_2$-cyclo-$C_3H_5$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2Cl$, $-CH_2Br$, $-CH_2I$, $-CH_2-CH_2F$, $-CH_2-CHF_2$, -

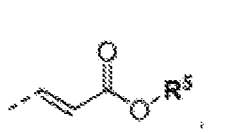
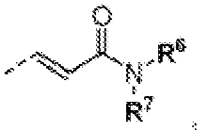
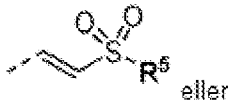
$CH_2$-$CF_3$, -$CH_2$-$CH_2Cl$, -$CH_2$-$CH_2Br$, -$CH_2$-$CH_2I$, -$CH_2$-CH=$CH_2$, -$CH_2$-C≡CH, -CHO, -$COCH_3$, -$COC_2H_5$, -$COC_3H_7$, -$COCH(CH_3)_2$, -$COC(CH_3)_3$, -$COOCH_3$, -$COOC_2H_5$, -$COOC_3H_7$, -$COOCH(CH_3)_2$, -$COOC(CH_3)_3$, -$COOCH_2Ph$, -$SO_2CH_3$, -$SO_2CF_3$, -$SO_2C_2H_5$, -$SO_2C_3H_7$, -$SO_2CH(CH_3)_2$ eller -$SO_2C(CH_3)_3$;

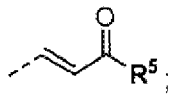
$\mathbf{R}^{N1}$ repræsenterer -H, -$CH_3$ eller -$CH_2CH_3$;

eller en diastereomer, en enantiomer, en blanding af diastereomerer, en blanding af enantiomer, et racemat, et solvat, et hydrat eller et farmaceutisk acceptabelt salt deraf.

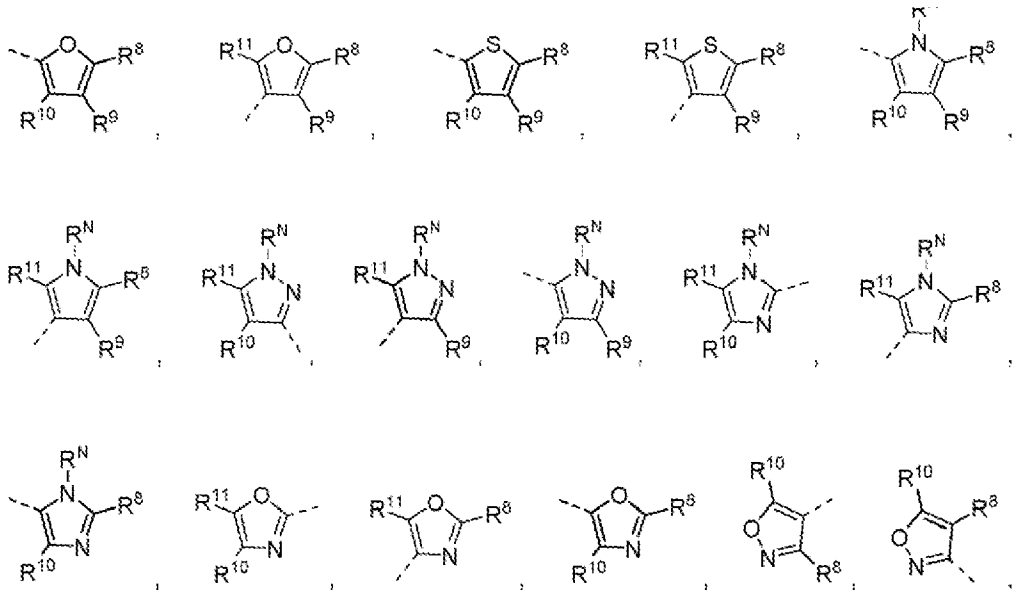
**3.** Forbindelse ifølge krav 1, hvor

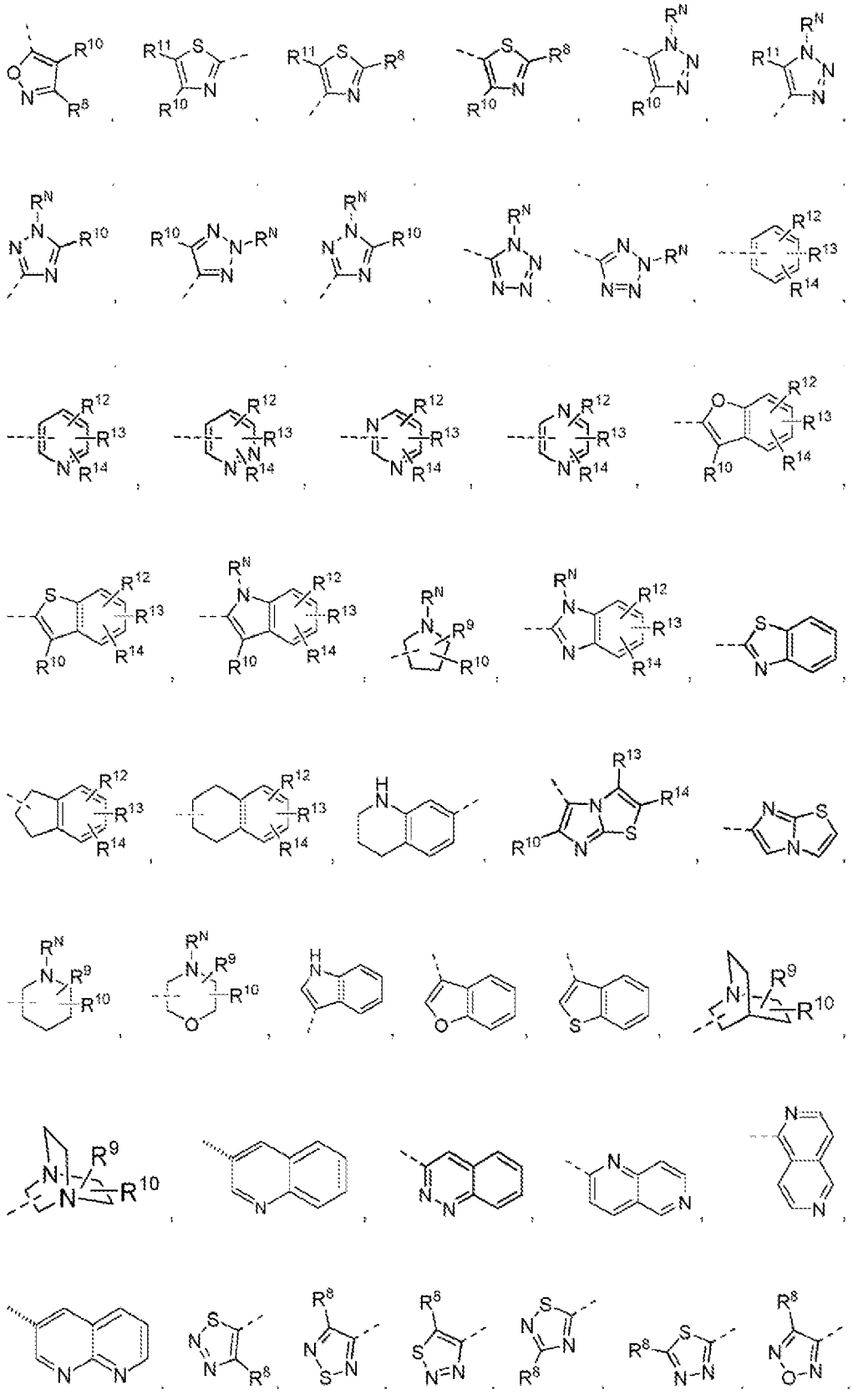
$\mathbf{R}^1$ repræsenterer

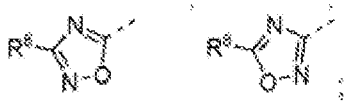



eller



$\mathbf{R}^2$ repræsenterer



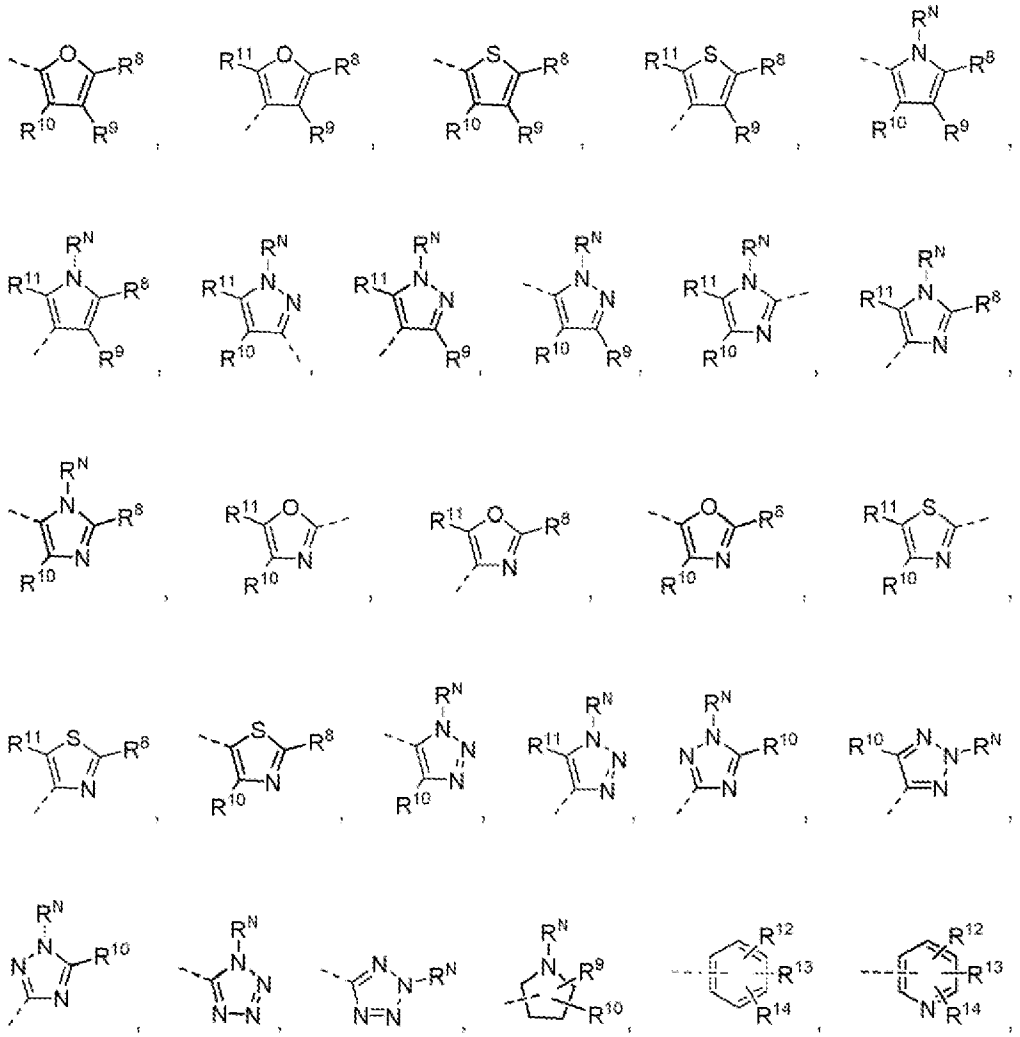


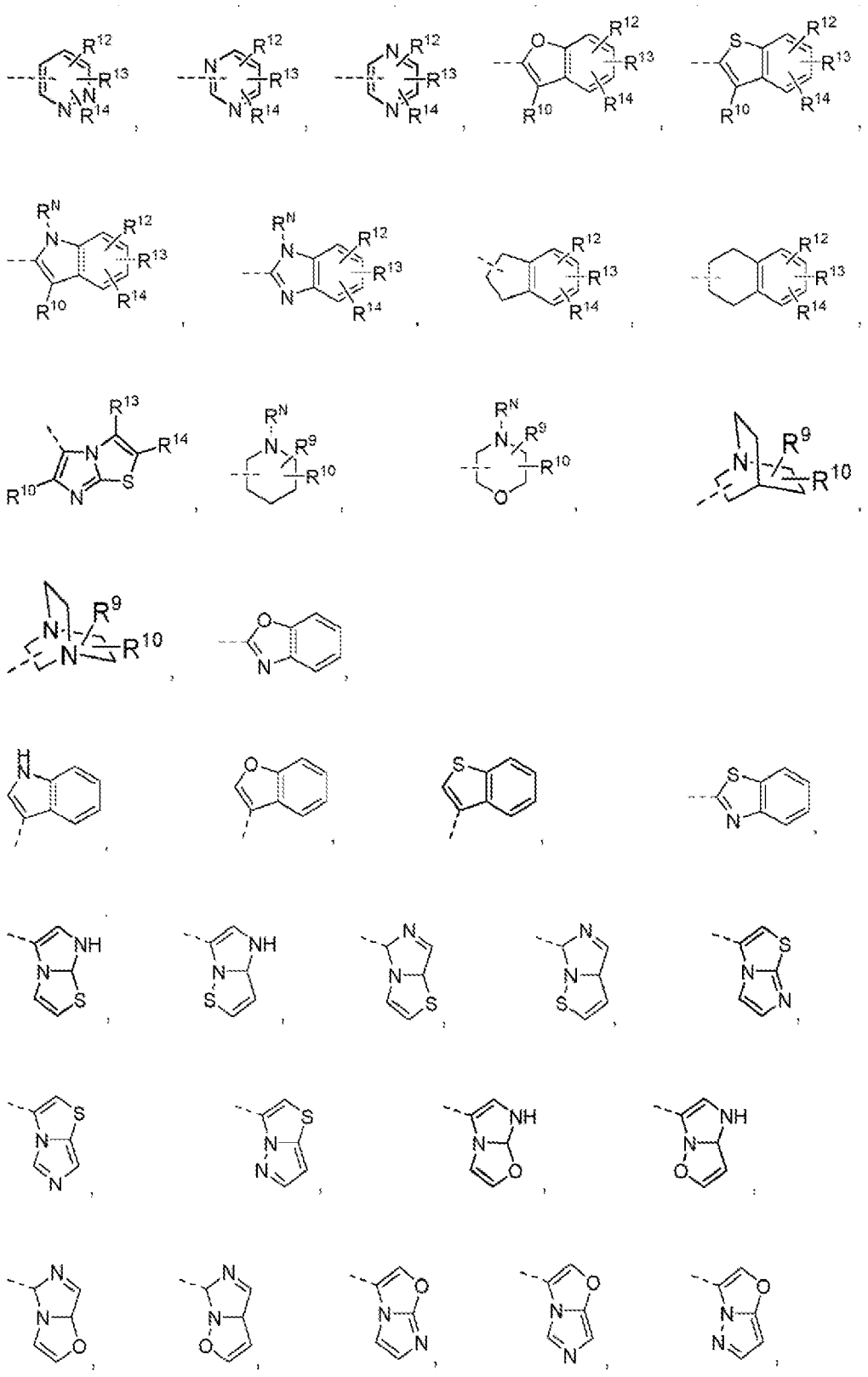


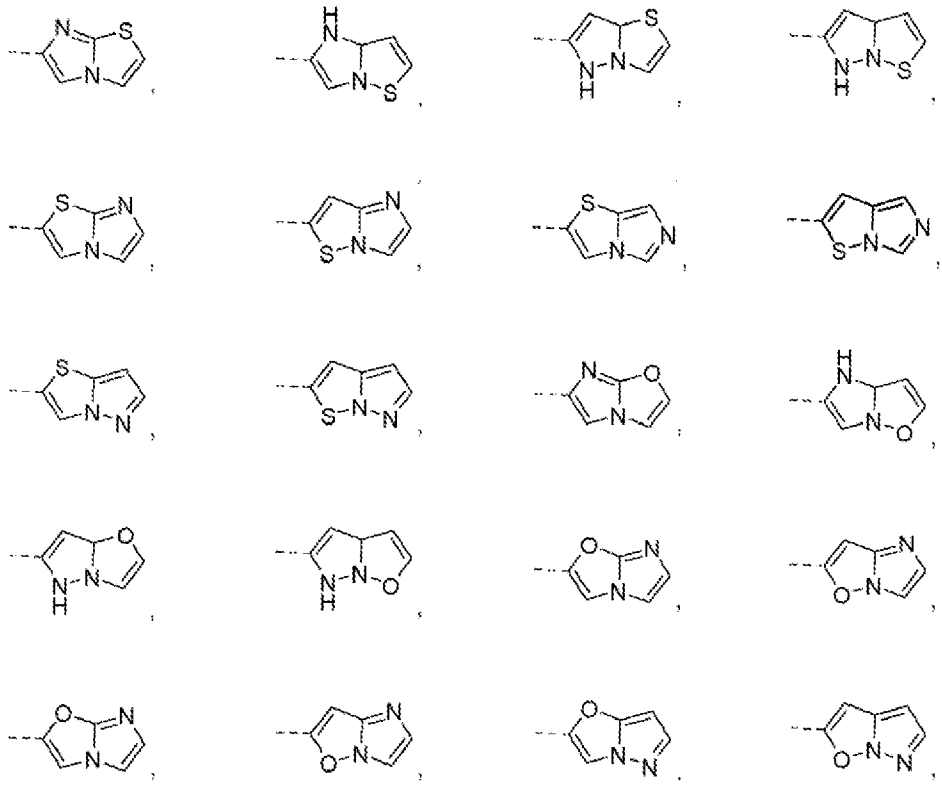
eller

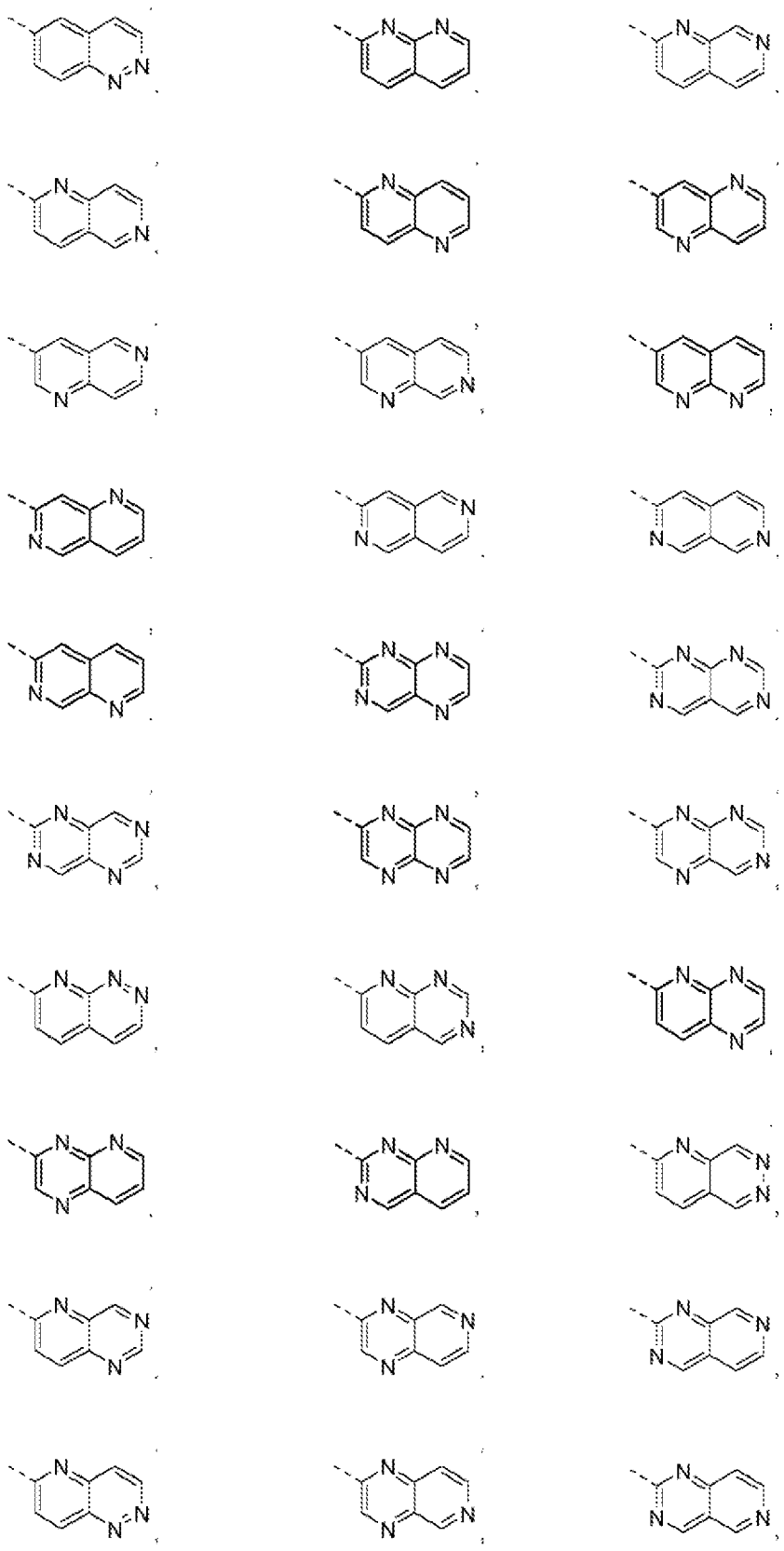
hvor de usubstituerede bicykliske rester kan være substitueret med 1 til 5 af substituenterne **R$^{9}$ -R$^{14}$** og **R$^{N}$**; og fortrinsvis med 1 til 3 af substituenterne **R$^{11}$ - R$^{13}$**, og **R$^{5}$ - R$^{14}$** og **R$^{N}$** har betydningerne som defineret i krav 1.

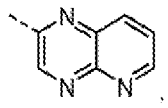
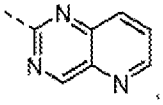
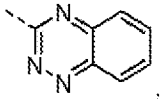
**4.** Forbindelse ifølge krav 1, hvor **R$^{2}$** repræsenterer

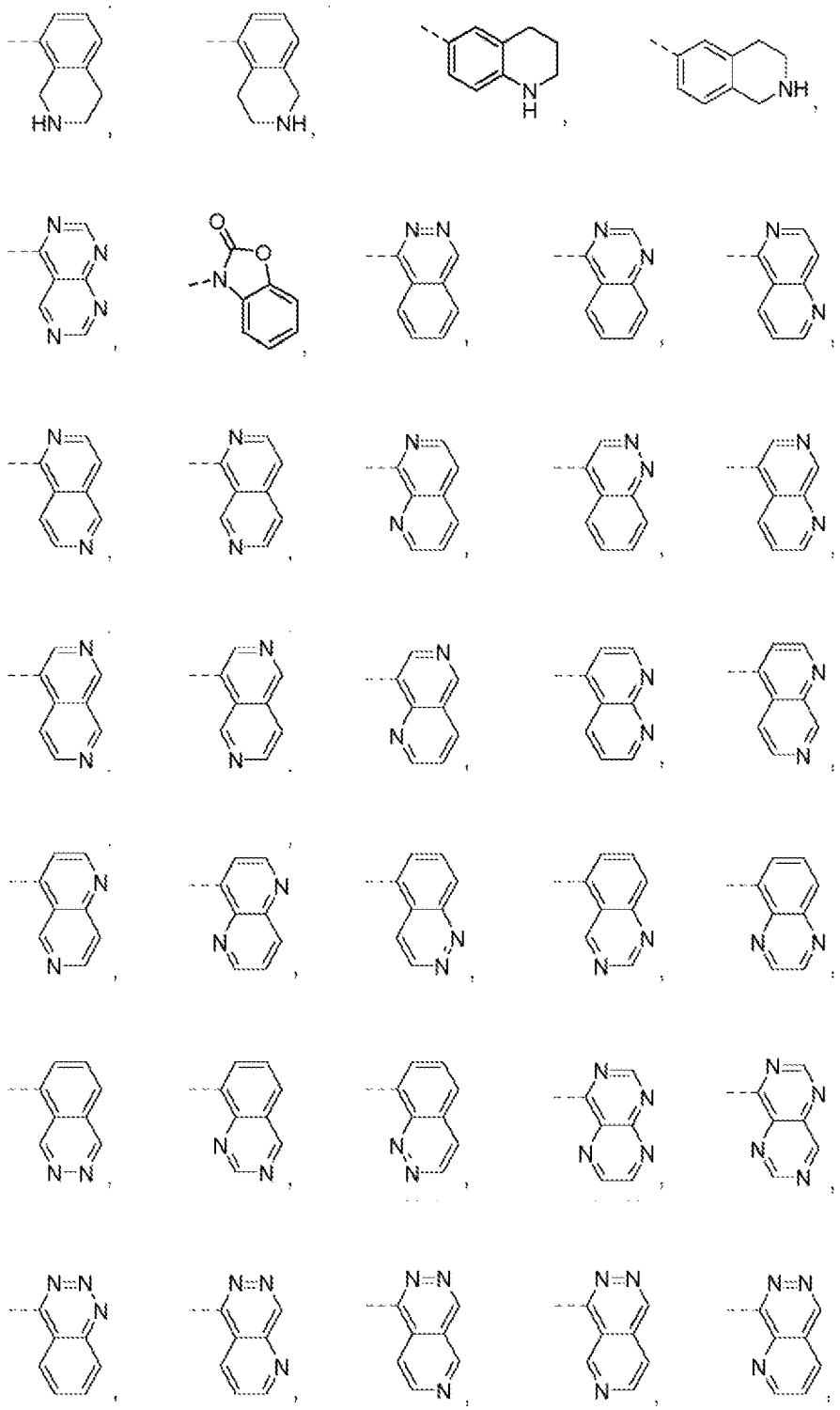


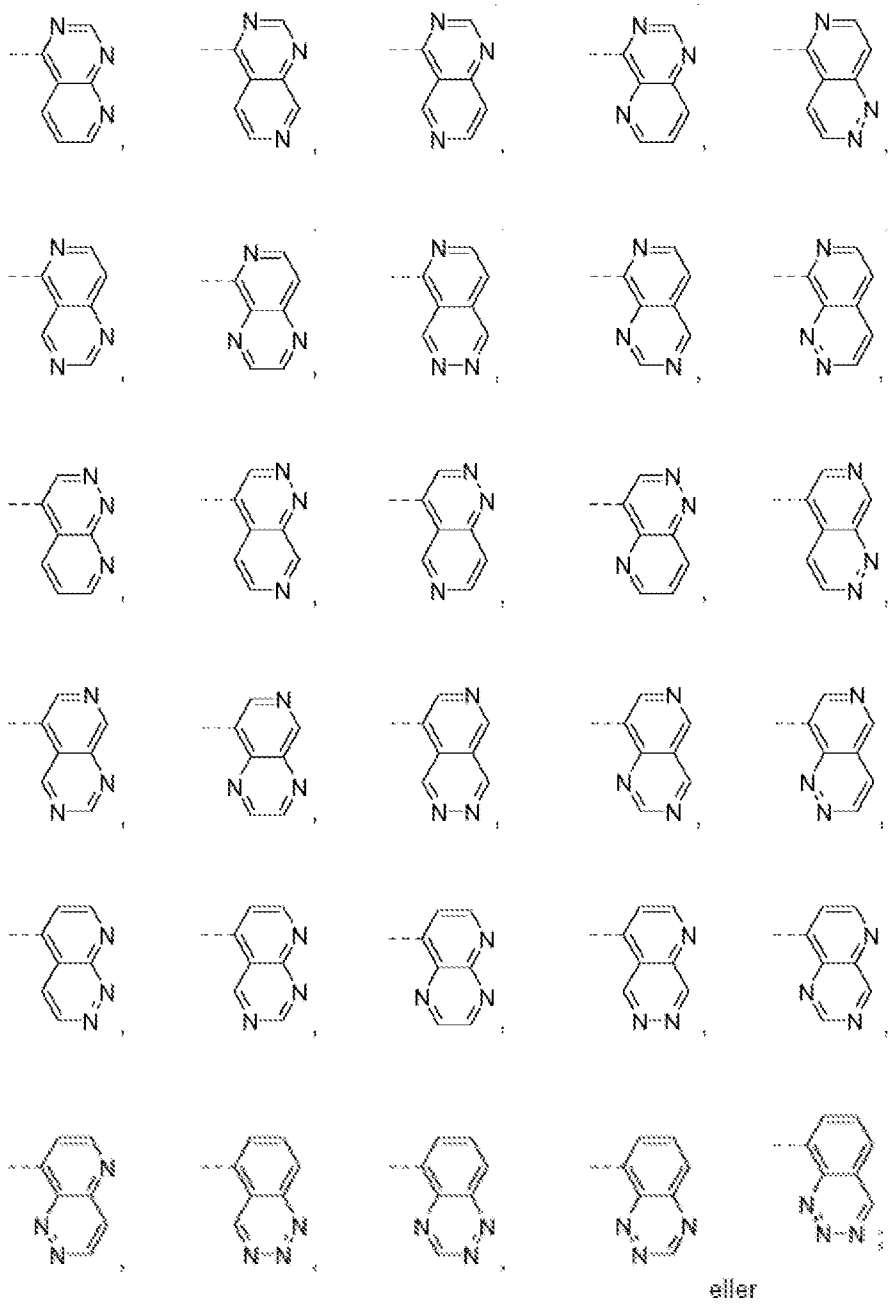








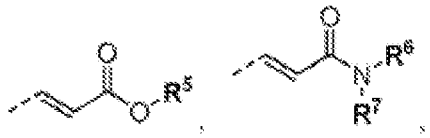


eller

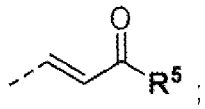
hvor de usubstituerede bicykliske rester kan være substitueret med 1 til 5 af substituenterne **$R^9$** - **$R^{14}$**, **$R^N$**; og fortrinsvis med 1 til 3 af substituenterne **$R^{11}$** - **$R^{13}$** og substituenterne **$R^9$** -**$R^{14}$**, og **$R^N$** har betydningerne som defineret i krav 1.

**5.** Forbindelse ifølge et hvilket som helst af kravene 1, 3 og 4, hvor

**$R^1$** repræsenterer



eller



;

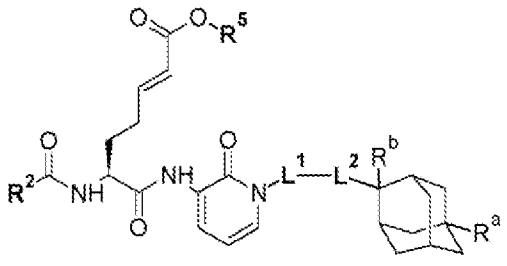
**$L^1$** repræsenterer $-CH_2-$ eller $-CH_2CO-$;

**$L^2$** repræsenterer en binding, $-NR^{N1}-$, $-NR^{N1}CH_2-$ eller $-NR^{N1}CH(CH_3)-$;

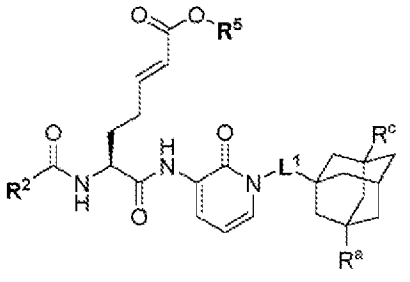
**$R^3$** repræsenterer bicyclo[1.1.1]pentyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, 4-homoisotwistyl, adamantyl eller diamantyl, og de førnævnte rester indeholder eventuelt en eller flere C=C-dobbeltbinding(er) og/eller er substitueret med en eller flere af **$R^a$**, **$R^b$**, **$R^c$**, **$R^d$** og **$R^e$**;

og **$R^5$**, **$R^6$**, **$R^7$**, **$R^a$**, **$R^b$**, **$R^c$**, **$R^d$**, **$R^e$** og **$R^{N1}$** har de samme betydninger som defineret i krav 1.

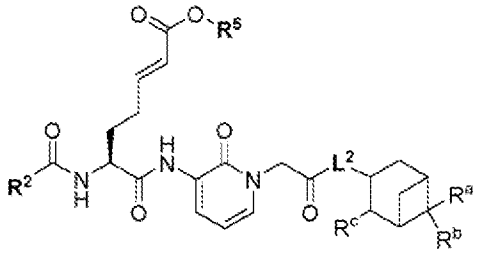
**6.** Forbindelse ifølge et hvilket som helst af kravene 1 og 3-5, hvor forbindelsen har en hvilken som helst af formlerne **(VI-a)** - **(VI-l)**, **(VII-a)** - **(VII-l)**, **(VIII-a)** - **(VIII-l)**, **(IX-a)** - **(IX-d)**, **(X-a)** - **(X-d)** og **(XI-a)** - **(XI-d)**:



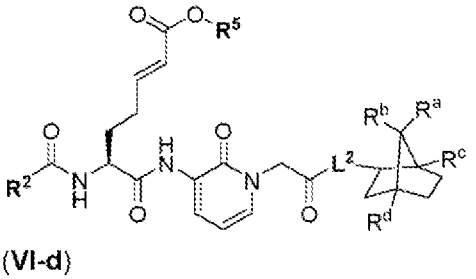
**(VI-a)**



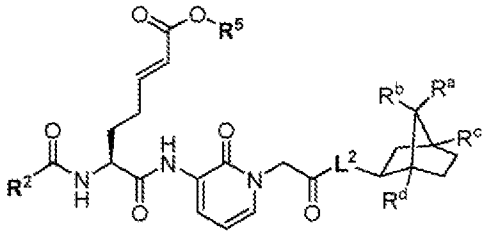
**(VI-b)**



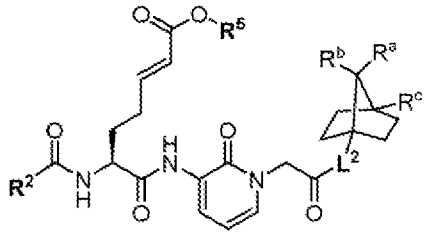
(VI-c)



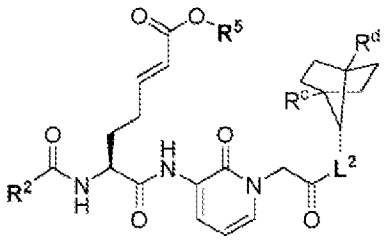
(VI-d)



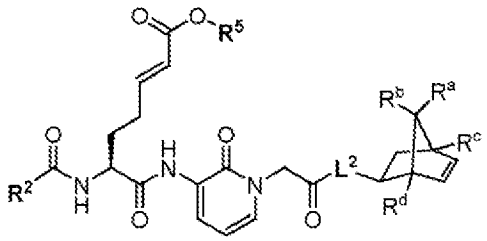
(VI-e)



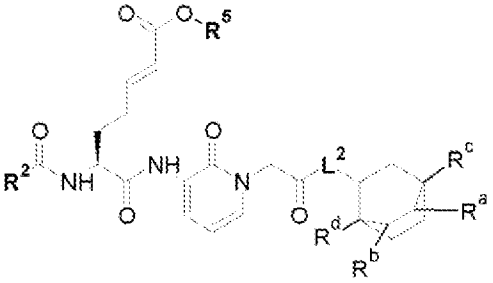
(VI-f)



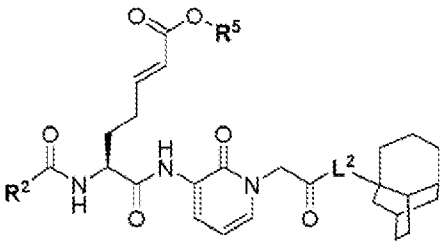
(VI-g)



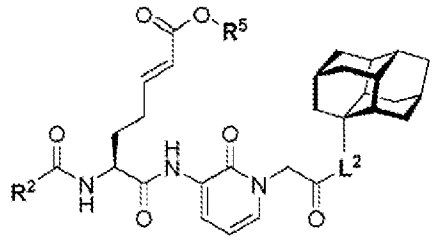
(VI-h)



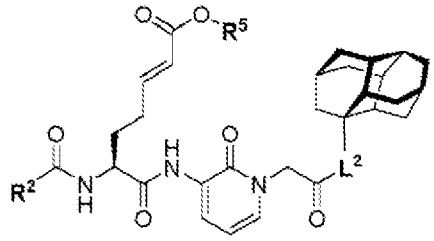
(VI-i)



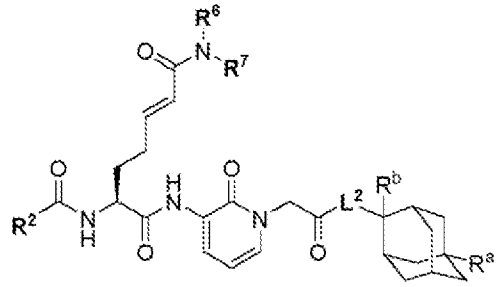
(VI-j)



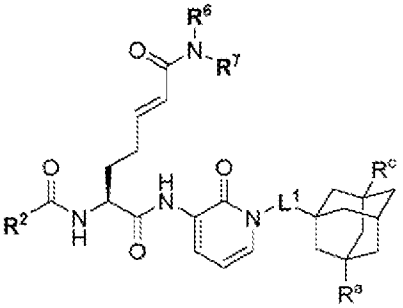
(VI-k)



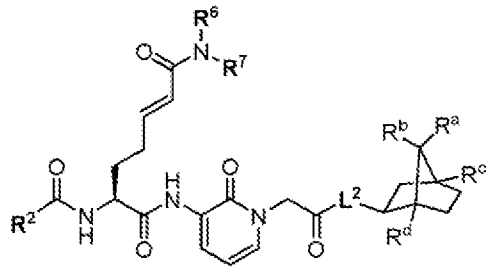
(VI-l)



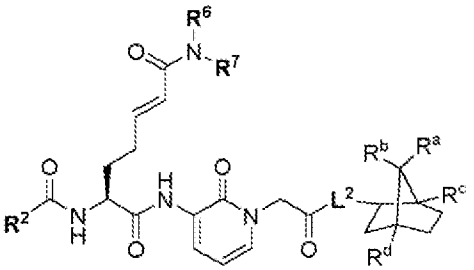
(VII-a)



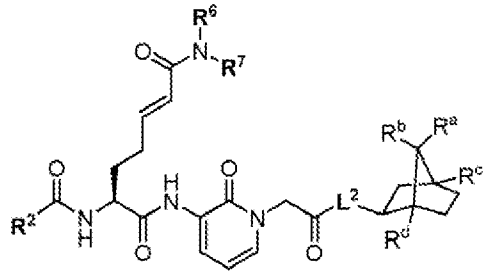
(VII-b)



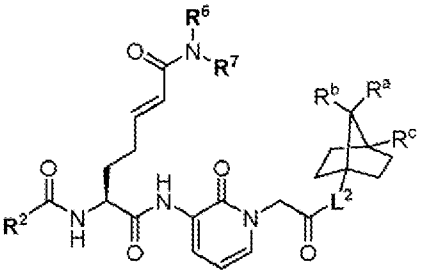
(VII-c)



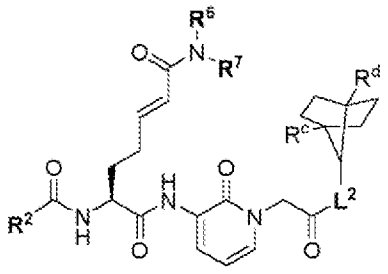
(VII-d)



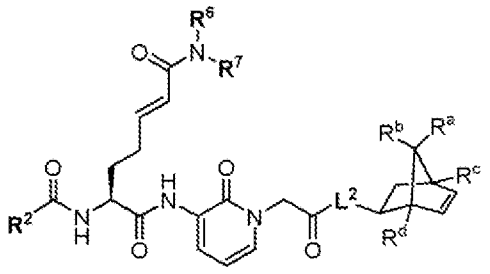
(VII-e)



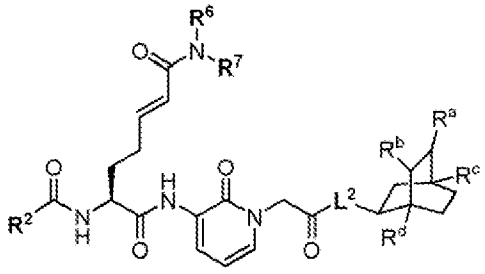
(VII-f)



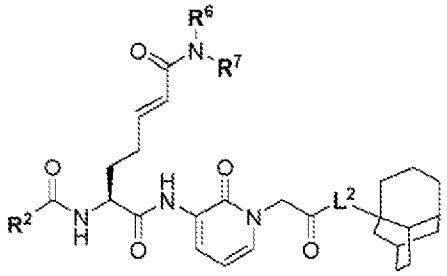
(VII-g)



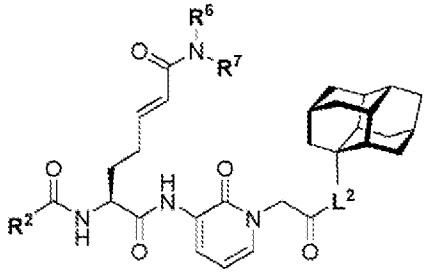
(VII-h)



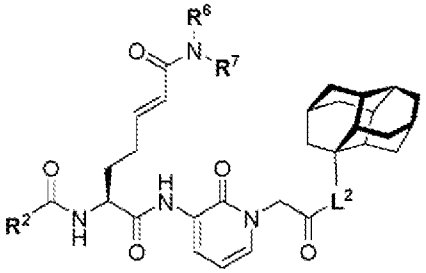
(VII-i)



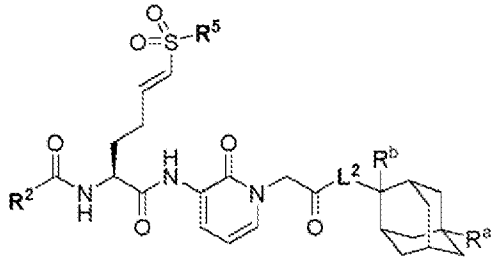
(VII-j)



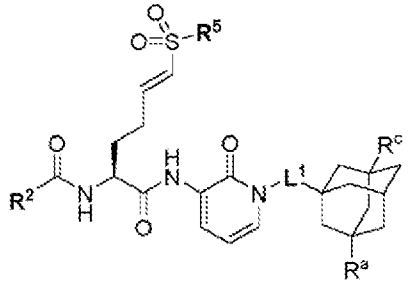
(VII-k)



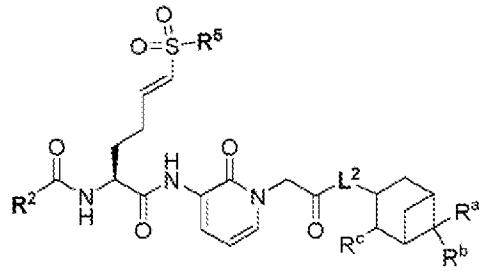
(VII-l)



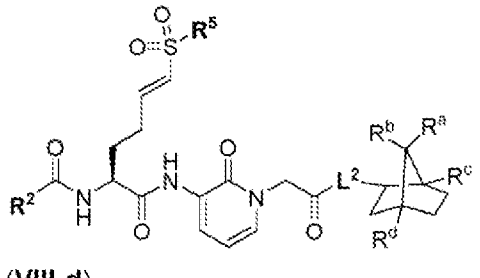
(VIII-a)



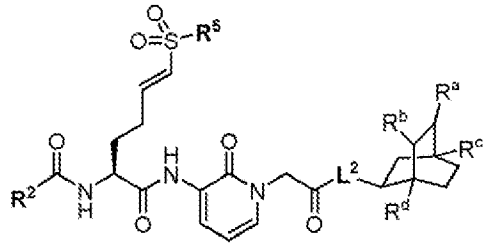
(VIII-b)



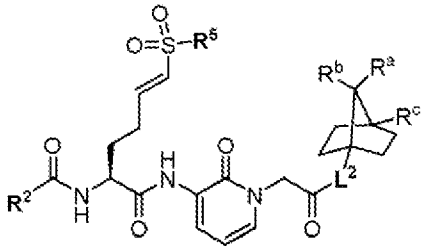
(VIII-c)



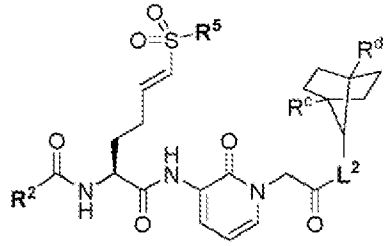
(VIII-d)



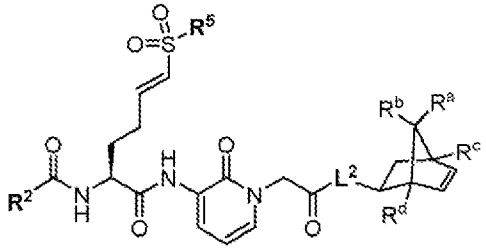
(VIII-e)



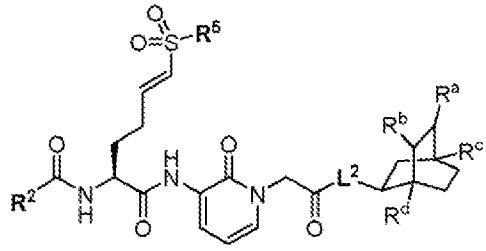
(VIII-f)



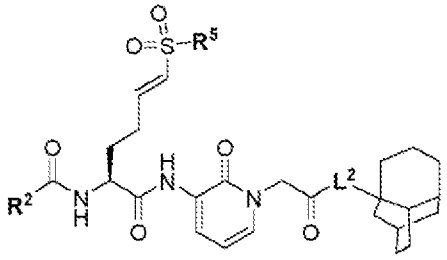
(VIII-g)



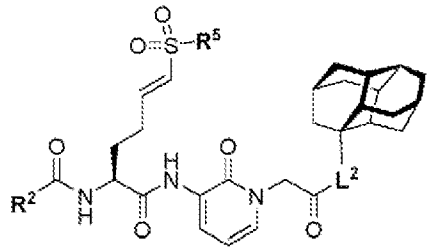
(VIII-h)



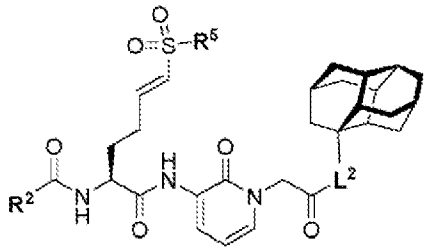
(VIII-i)



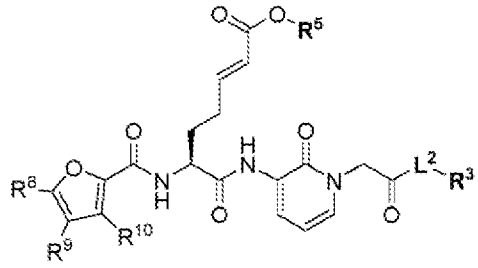
(VIII-j)



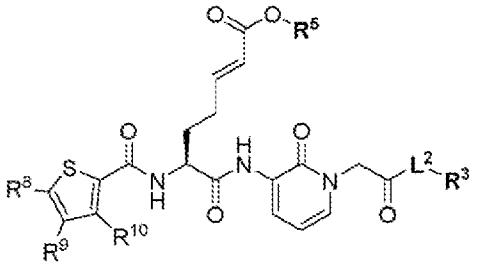
(VIII-k)



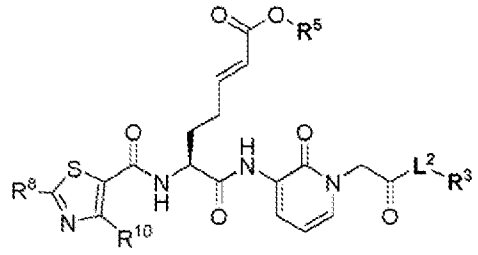
(VIII-l)



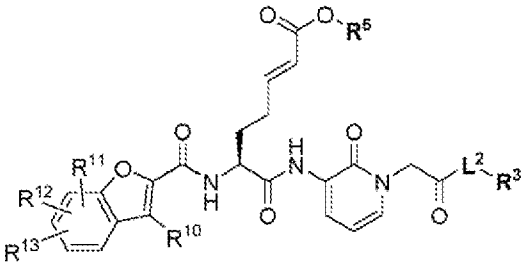
(IX-a)



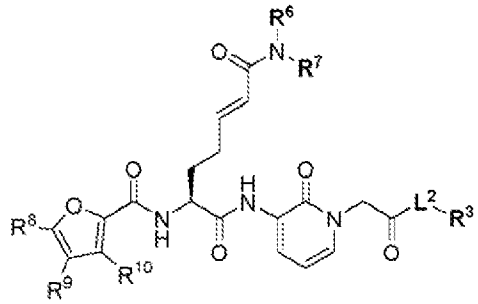
(IX-b)



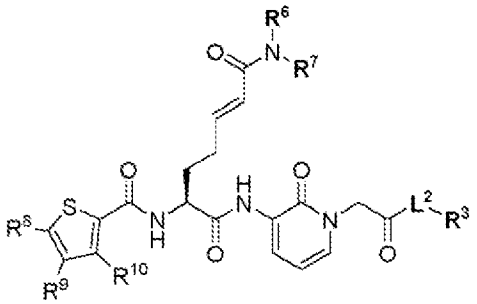
(IX-c)



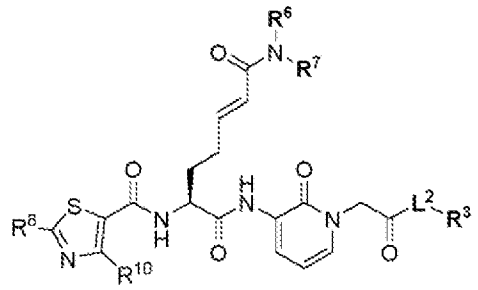
(IX-d)



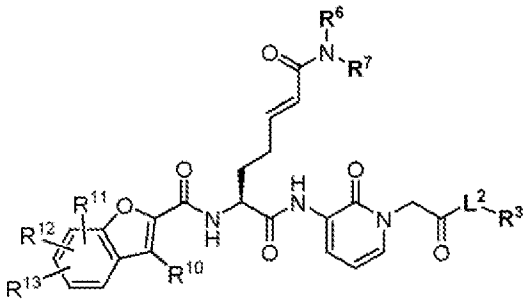
(X-a)



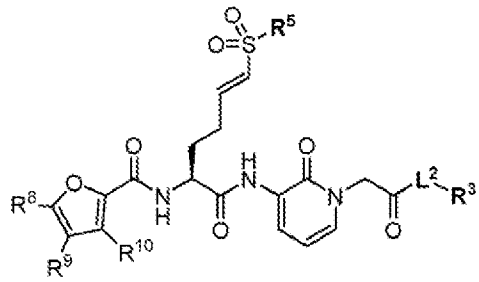
(X-b)



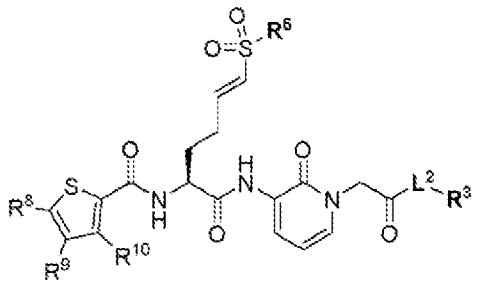
(**X-c**)



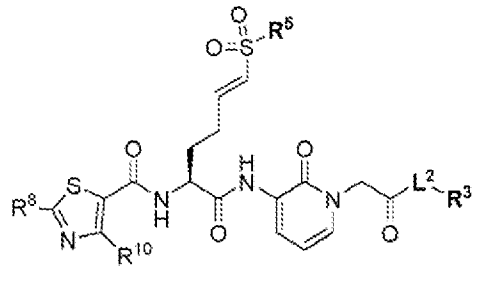
(**X-d**)



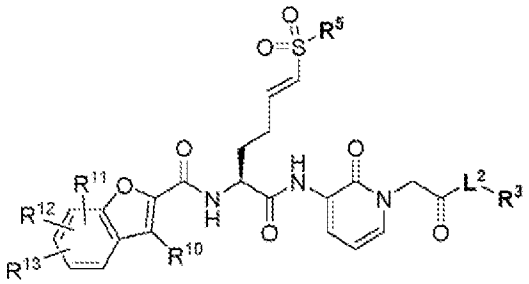
(**XI-a**)



(**XI-b**)



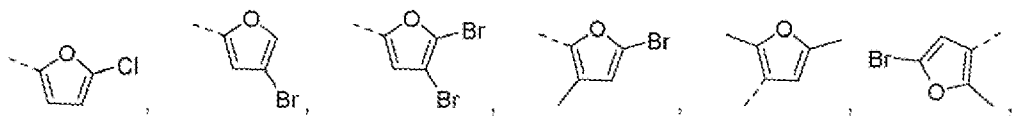
(**XI-c**)

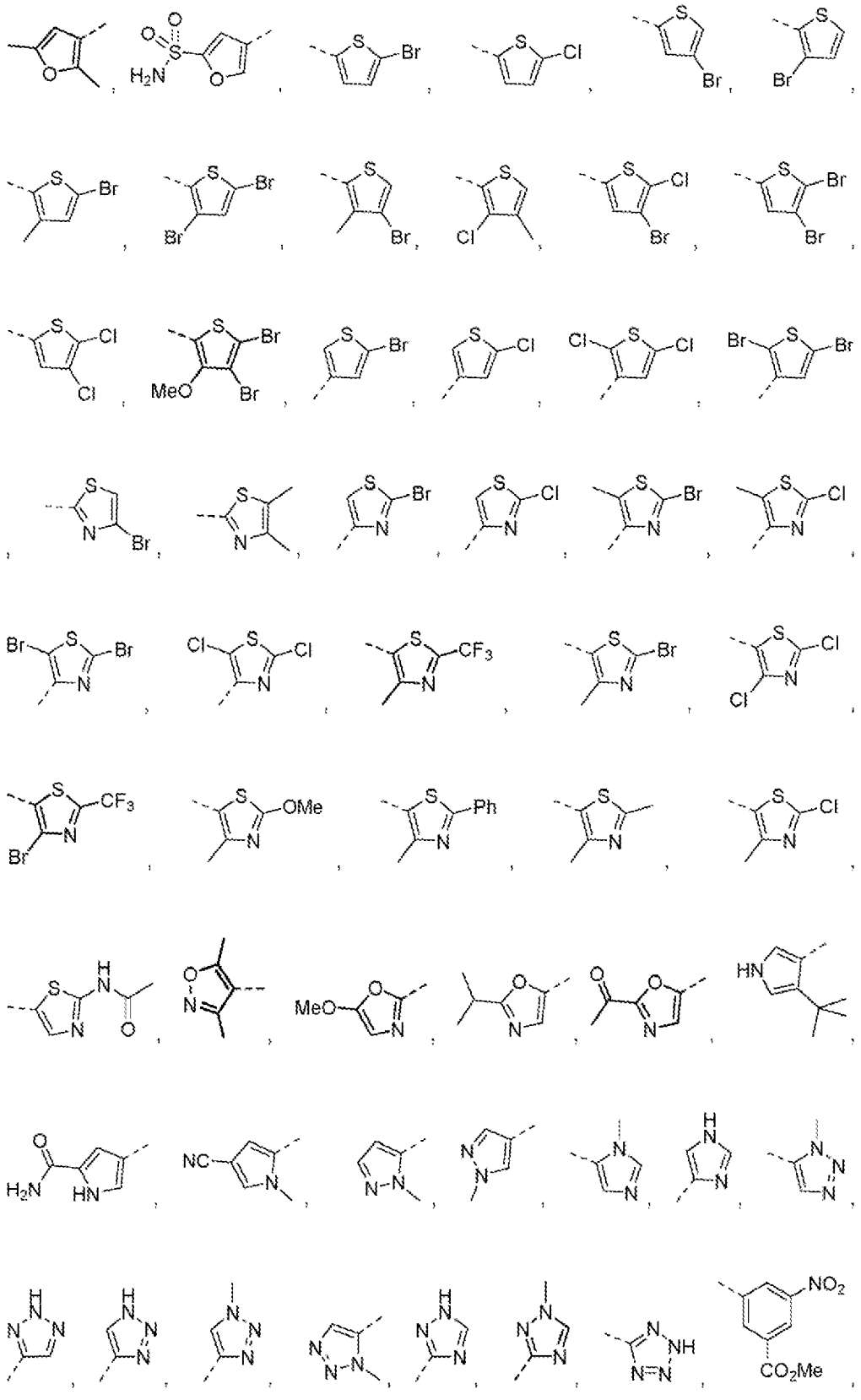


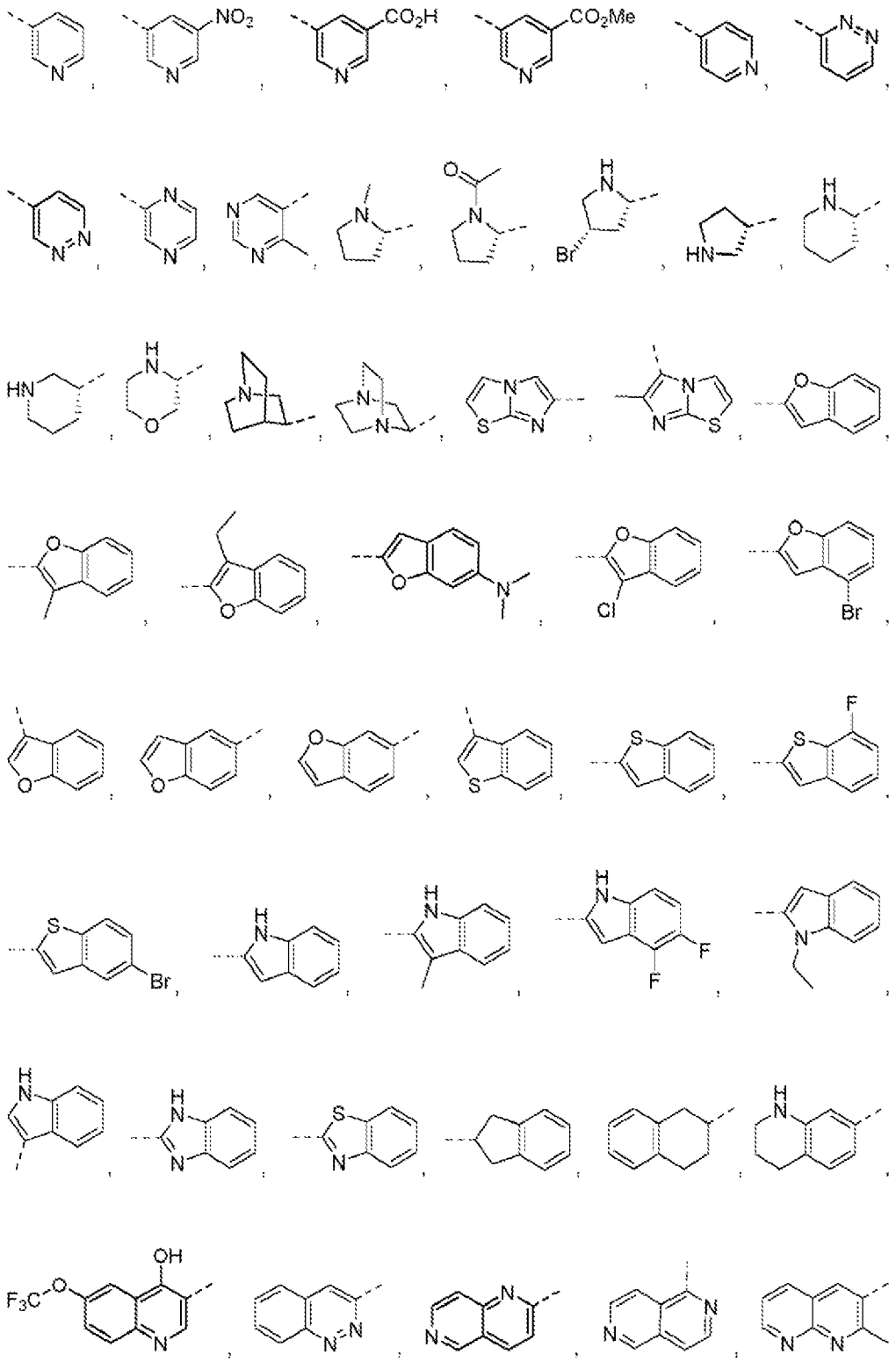
(**XI-d**)

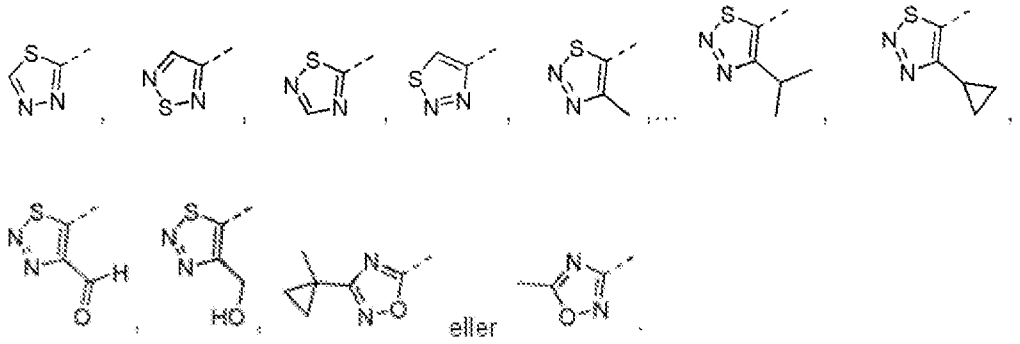
og $R^2$ $R^3$, $R^5$, $R^6$, $R^7$, $R^8$, $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, $R^{13}$, $R^a$, $R^b$, $R^c$, $R^d$ og $L^2$ har de samme betydninger som defineret i krav 1.

**7.** Forbindelse ifølge et hvilket som helst af kravene 1 og 3-6, hvor $R^2$ repræsenterer

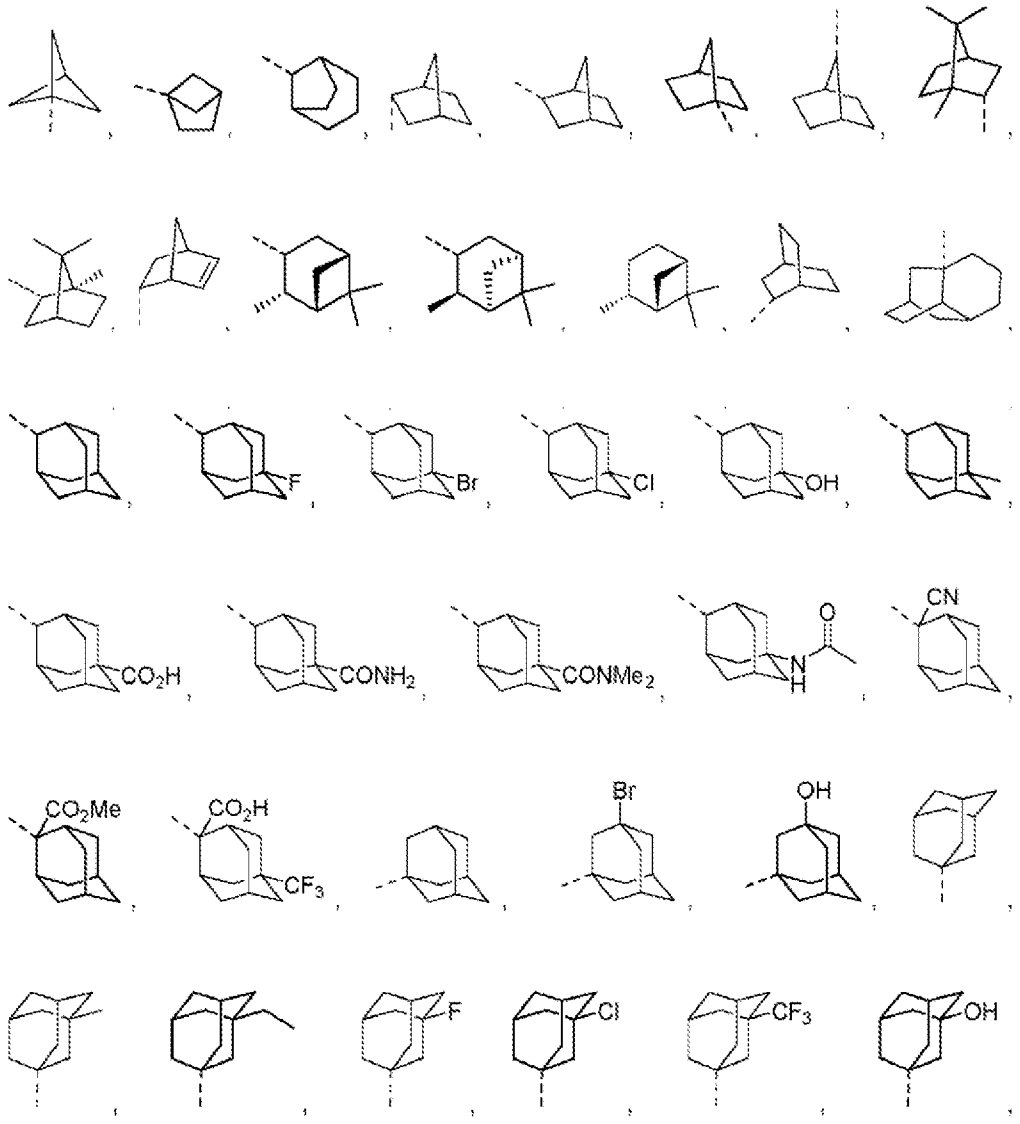


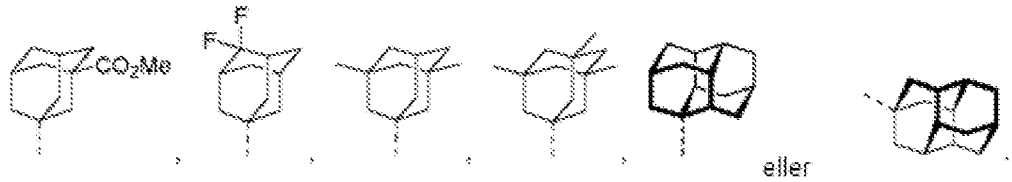







**8.** Forbindelse ifølge et hvilket som helst af kravene 1 og 3-7, hvor **R**$^{3}$ repræsenterer






**9.** Forbindelse ifølge krav 1 valgt fra gruppen bestående af:

| Forbindelse | Navn |
|---|---|
| **III-1:** | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-imidazol-5-carboxamido)-7-oxohept-2-enoat |
| **III-2:** | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-3:** | (S,E)-methyl 6-(3-chlorbenzofuran-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoat |
| **III-4**: | (S,E)-methyl 6-(4-bromobenzofuran-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoat |
| **III-5:** | (S,E)-methyl 6-(benzo[b]thiophen-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoat |
| **III-6:** | (S,E)-methyl 6-(5-bromobenzo[b]thiophen-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoat |
| **III-7:** | (S,E)-methyl 6-(7-fluorbenzo[b]thiophen-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoat |
| **III-8:** | (S,E)-methyl 6-(1H-indol-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoat |
| **III-9:** | (S,E)-methyl 6-(4,5-difluor-1H-indol-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoat |

| Forbin-delse | Navn |
|---|---|
| **III-10:** | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methyl-1H-indol-2-carboxamido)-7-oxohept-2-enoat |
| **III-11:** | (S,E)-methyl 6-(1H-benzo[d]imidazol-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoat |
| **III-12:** | (S,E)-methyl 6-(2,3-dihydro-1H-inden-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoat |
| **III-13:** | (S,E)-methyl 6-(2,5-dichlorthiophen-3-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoat |
| **III-14:** | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-methyl-2-(trifluormethyl)thiazol-5-carboxamido)-7-oxohept-2-enoat |
| **III-15:** | (S,E)-methyl 6-(3,5-dibromothiophen-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoat |
| **III-16:** | (S,E)-methyl 6-(2,5-dibromothiophen-3-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoat |
| **III-17:** | (S,E)-methyl 6-(5-bromothiophen-3-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoat |
| **III-18:** | (S,E)-methyl 6-(4-bromothiophen-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoat |
| **III-19:** | (S,E)-methyl 6-(4,5-dibromothiophen-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoat |
| **III-20:** | (S,E)-methyl 6-(4,5-dichlorthiophen-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoat |
| **III-21:** | (S,E)-methyl 6-((S)-1-acetylpyrrolidin-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoat |

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| **III-22:** | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-1,2,3-triazol-5-carboxamido)-7-oxohept-2-enoat |
| **III-23:** | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(2H-tetrazol-5-carboxamido)hept-2-enoat |
| **III-24:** | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(pyrazin-2-carboxamido)hept-2-enoat |
| **III-25:** | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-((S)-1-methylpyrrolidin-2-carboxamido)-7-oxohept-2-enoat |
| **III-26:** | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-((S)-pyrrolidin-3-carboxamido)hept-2-enoat |
| **III-27:** | (S,E)-methyl 6-((2S,4S)-4-bromopyrrolidin-2-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoat |
| **III-28:** | (S,E)-methyl 6-(1H-imidazol-4-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoat |
| **III-29:** | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-((S)-piperidin-2-carboxamido)hept-2-enoat |
| **III-30:** | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-((R)-piperidin-3-carboxamido)hept-2-enoat |
| **III-31**: | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-((R)-morpholin-3-carboxamido)-7-oxohept-2-enoat |
| **III-32:** | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(quinuclidin-3-carboxamido)hept-2-enoat |
| **III-33:** | (S,E)-methyl 3-(1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-methoxy-1,7-dioxohept-5-en-2-ylcarbamoyl)-5-nitrobenzoat |

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| **III-34:** | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(5-nitronicotinamido)-7-oxohept-2-enoat |
| **III-35:** | (S,E)-5-(1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-methoxy-1,7-dioxohept-5-en-2-ylcarbamoyl)nicotinsyre |
| **III-36:** | (S,E)-methyl 5-(1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-methoxy-1,7-dioxohept-5-en-2-ylcarbamoyl)nicotinat |
| **III-37:** | (S,E)-methyl 7-(1-(2-(2-adamantyl(methyl)amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-38:** | (S,E)-methyl 7-(1-(2-(5-hydroxyadamantan-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-39:** | (S,E)-methyl 7-(1-(2-(5-fluoradamantan-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-40:** | (S,E)-methyl 7-(1-(2-(5-chloradamantan-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-41:** | (S,E)-methyl 7-(1-(2-(5-bromoadamantan-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-42:** | (S,E)-methyl 7-(1-(2-(5-methyladamantan-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-43:** | (S,E)-methyl 7-(1-(2-(2-carbonitrileadamantan-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-44**: | (S,E)-methyl 7-(1-(2-(2-methyl adamantan-2-carboxylat-2-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-45:** | (S,E)-methyl 7-(1-(2-(1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |

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| **III-46:** | (S,E)-methyl 7-(1-(2-(3,5-dimethyladamantan-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-47:** | (S,E)-methyl 7-(1-(2-(1-adamantyl(methyl)amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-48:** | (S,E)-methyl 7-(1-(2-(3-ethyladamantan-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-49:** | (S,E)-methyl 7-(1-(2-(3-trifluormethyladamantan-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-50:** | (S,E)-methyl 7-(1-(2-(3-hydroxyadamantan-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-51**: | (S,E)-methyl 7-(1-(2-(3-fluoradamantan-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-52:** | (S,E)-methyl 7-(1-(2-(3-chloradamantan-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-53:** | (S,E)-methyl 7-(1-(2-(3-bromoadamantan-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-54:** | (S,E)-methyl 7-(1-(2-(3-methyl adamantan-3-carboxylat-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-55:** | (S,E)-methyl 7-(1-(2-(4,4-difluoradamantan-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-56:** | (S,E)-methyl 7-(1-(2-(1-adamantylmethylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-57:** | (S,E)-methyl 7-(1-(2-(1-(1-adamantyl)ethanamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |

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| **III-58:** | (S,E)-methyl 7-(1-(2-((1R,2S,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-imidazol-5-carboxamido)-7-oxohept-2-enoat |
| **III-59:** | (S,E)-methyl 7-(1-(2-((1S,2R,4R)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-60:** | (S,E)-methyl 6-(1-methyl-1H-imidazol-5-carboxamido)-7-oxo-7-(2-oxo-1-(2-oxo-2-((1S,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-ylamino)hept-2-enoat |
| **III-61**: | (S,E)-methyl 6-(3-methylbenzofuran-2-carboxamido)-7-oxo-7-(2-oxo-1-(2-oxo-2-((1S,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-ylamino)hept-2-enoat |
| **III-62:** | (S,E)-methyl 7-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-imidazol-5-carboxamido)-7-oxohept-2-enoat |
| **III-63:** | (S,E)-methyl 7-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-64:** | (S,E)-methyl 7-(1-(2-(bicyclo[2.2.1]heptan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-65:** | (S,E)-methyl 7-(1-(2-(bicyclo[2.2.1]heptan-7-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-66:** | (S,E)-methyl 7-(1-(2-(bicyclo[2.2.1]hept-5-en-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-67:** | (6S,E)-methyl 7-(1-(2-(bicyclo[2.2.2]octan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-68:** | (S,E)-methyl 6-(3-methylbenzofuran-2-carboxamido)-7-oxo-7-(2-oxo-1-(2-oxo-2-((1R,2R,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-ylamino)hept-2-enoat |

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| **III-69:** | (S,E)-methyl 6-(3-methylbenzofuran-2-carboxamido)-7-oxo-7-(2-oxo-1-(2-oxo-2-((1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylamino)ethyl)-1,2-dihydropyridin-3-ylamino)hept-2-enoat |
| **III-70:** | (S,E)-methyl 6-(3-methylbenzofuran-2-carboxamido)-7-oxo-7-(2-oxo-1-(2-oxo-2-((1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylamino)ethyl)-1,2-dihydropyridin-3-ylamino)hept-2-enoat |
| **III-71:** | (S,E)-methyl 7-(1-(2-(((1S,2R,5S)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-72:** | (S,E)-methyl 7-(1-(2-(4-homoisotwistan-3-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-73:** | (S,E)-methyl 7-(1-(2-(diamantan-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-74:** | (S,E)-methyl 7-(1-(2-(diamantan-4-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-75:** | (S,E)-N7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N1,N1-dimethyl-6-(3-methylbenzofuran-2-carboxamido)hept-2-enediamid |
| **III-76:** | (S,E)-N7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N1,N1-dimethyl-6-(1-methyl-1H-imidazol-5-carboxamido)hept-2-enediamid |
| **III-77:** | (S,E)-N7-(1-(2-(3,5-dimethyladamantan-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N1,N1-dimethyl-6-(3-methylbenzofuran-2-carboxamido)hept-2-enediamid |
| **III-78:** | (S,E)-methyl 7-(1-(1-adamantylmethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-imidazol-5-carboxamido)-7-oxohept-2-enoat |
| **III-79:** | (S,E)-methyl 7-(1-(1-adamantylmethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |

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| **III-80:** | (6S,E)-methyl 7-(1-((3-hydroxy-1-adamantyl)methyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-81:** | (6S,E)-methyl 7-(1-((3-bromo-1-adamantyl)methyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-82:** | (S,E)-methyl 7-(1-(2-adamantylmethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-83:** | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(nicotinamido)-7-oxohept-2-enoat |
| **III-84:** | (S,E)-methyl 6-(isonicotinamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoat |
| **III-85:** | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(pyridazine-4-carboxamido)hept-2-enoat |
| **III-86:** | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(pyridazine-3-carboxamido)hept-2-enoat |
| **III-87:** | (S,E)-methyl 7-(1-(2-(1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1 H-imidazol-2-carboxamido)-7-oxohept-2-enoat |
| **III-88:** | (S,E)-methyl 7-(1-(2-(3,5-dimethyladamantan)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-imidazol-5-carboxamido)-7-oxohept-2-enoat |
| **III-89:** | (S,E)-ethyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-90:** | (S,E)-N-(1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(methylsulfonyl)-1-oxohex-5-en-2-yl)-3-methylbenzofuran-2-carboxamid |
| **III-91**: | (S,E)-methyl 7-(1-(2-(3,5,7-trimethyl-1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-imidazol-5-carboxamido)-7-oxohept-2-enoat |

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| **III-92:** | (S,E)-methyl 7-(1-(2-(3,5,7-trimethyl-1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydro-pyridin-3-ylamino)-6-(3-methylbenzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-93:** | (S,E)-methyl 7-(1-(2-(3,5,7-trimethyl-1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydro-pyridin-3-ylamino)-6-(1-methyl-1H-1,2,3-triazol-5-carboxamido)-7-oxohept-2-enoat |
| **III-94:** | (S,E)-methyl 6-(2,5-dichlorthiophen-3-carboxamido)-7-(1-(2-(3,5,7-trimethyl-1-adaman-tylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoat |
| **III-95:** | (S,E)-methyl 7-(1-(2-(3,5,7-trimethyl-1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydro-pyridin-3-ylamino)-6-(4-methyl-2-(trifluormethyl)thiazol-5-carboxamido)-7-oxohept-2-enoat |
| **III-96:** | (6S,E)-methyl 7-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-1,2,3-triazol-5-carboxamido)-7-oxohept-2-enoat |
| **III-97:** | (6S,E)-methyl 7-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(2,5-dichlorthiophen-3-carboxamido)-7-oxohept-2-enoat |
| **III-98:** | (6S,E)-methyl 7-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-methyl-2-(trifluormethyl)thiazol-5-carboxamido)-7-oxohept-2-enoat |
| **III-99:** | (S,E)-ethyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-imidazol-5-carboxamido)-7-oxohept-2-enoat |
| **III-100:** | (S,E)-N-(1-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(methylsulfonyl)-1-oxohex-5-en-2-yl)-1-methyl-1H-imidazol-5-carboxamid |
| **III-101**: | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yla-mino)-7-oxo-6-(2H-1,2,3-triazol-4-carboxamido)hept-2-enoat |
| **III-102:** | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yla-mino)-7-oxo-6-(1H-1,2,3-triazol-4-carboxamido)hept-2-enoat |

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| **III-103:** | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-1,2,3-triazol-4-carboxamido)-7-oxohept-2-enoat |
| **III-104:** | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(1H-1,2,4-triazol-3-carboxamido)hept-2-enoat |
| **III-105:** | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-1,2,4-triazol-3-carboxamido)-7-oxohept-2-enoat |
| **III-106:** | (S,E)-methyl 6-(benzofuran-3-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoat |
| **III-107:** | (S,E)-methyl 6-(benzo[b]thiophen-3-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoat |
| **III-108** | (S,E)-methyl 7-(1-(2-(3,5,7-trimethyl-1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-methyl-1,2,3-thiadiazol-5-carboxamido)-7-oxohept-2-enoat |
| **III-109** | (S,E)-methyl 7-(1-(2-(3,5,7-trimethyl-1-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-pyrazol-5-carboxamido)-7-oxohept-2-enoat |
| **III-110** | (S,E)-methyl 7-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-methyl-1,2,3-thiadiazol-5-carboxamido)-7-oxohept-2-enoat |
| **III-111** | (S,E)-methyl 7-(1-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-pyrazol-5-carboxamido)-7-oxohept-2-enoat |
| **III-112** | (S,E)-methyl 7-(1-(2-(3,5-dimethyladamantan-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-methyl-1,2,3-thiadiazol-5-carboxamido)-7-oxohept-2-enoat |
| **III-113** | (S,E)-methyl 7-(1-(2-(3,5-dimethyladamantan-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-pyrazol-5-carboxamido)-7-oxohept-2-enoat |
| **III-114** | (S,E)-methyl 7-(1-(2-(3,5-dimethyladamantan-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-1,2,3-triazol-5-carboxamido)-7-oxohept-2-enoat |

| Forbin-delse | Navn |
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| **III-115** | (S,E)-methyl 7-(1-(2-((1S,2R,4R)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-methyl-1,2,3-thiadiazol-5-carboxamido)-7-oxohept-2-enoat |
| **III-116** | (S,E)-methyl 7-(1-(2-((1S,2R,4R)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-1,2,3-triazol-5-carboxamido)-7-oxohept-2-enoat |
| **III-117** | (S,E)-methyl 7-(1-(2-((1S,2R,4R)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-pyrazol-5-carboxamido)-7-oxohept-2-enoat |
| **III-118** | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-methyl-1,2,3-thiadiazol-5-carboxamido)-7-oxohept-2-enoat |
| **III-119** | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-pyrazol-5-carboxamido)-7-oxohept-2-enoat |
| **III-120** | (S,E)-methyl 6-(4-methyl-1,2,3-thiadiazol-5-carboxamido)-7-oxo-7-(2-oxo-1-(2-oxo-2-((1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-ylamino)hept-2-enoat |
| **III-121** | (S,E)-methyl 6-(1-methyl-1H-1,2,3-triazol-5-carboxamido)-7-oxo-7-(2-oxo-1-(2-oxo-2-((1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-ylamino)hept-2-enoat |
| **III-122** | (S,E)-methyl 6-(1-methyl-1H-pyrazol-5-carboxamido)-7-oxo-7-(2-oxo-1-(2-oxo-2-((1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-ylamino)hept-2-enoat |
| **III-123** | (S,E)-methyl 7-(1-(2-(3,5-dimethyladamantan-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-methyl-2-(trifluormethyl)thiazol-5-carboxamido)-7-oxohept-2-enoat |
| **III-124** | (S,E)-methyl 6-(2,5-dichlorthiophen-3-carboxamido)-7-(1-(2-(3, 5-dimethyladamantan-1-amino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoat |

| Forbin-delse | Navn |
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| **III-125** | (S,E)-methyl 7-(1-(2-((1S,2R,4R)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-methyl-2-(trifluormethyl)thiazol-5-carboxamido)-7-oxohept-2-enoat |
| **III-126** | (S,E)-methyl 7-(1-(2-((1S,2R,4R)-bicyclo[2.2.1]heptan-2-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(2,5-dichlorthiophen-3-carboxamido)-7-oxohept-2-enoat |
| **III-127** | (S,E)-methyl 6-(4-methyl-2-(trifluormethyl)thiazol-5-carboxamido)-7-oxo-7-(2-oxo-1-(2-oxo-2-((1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-ylamino)hept-2-enoat |
| **III-128** | (S,E)-methyl 6-(2,5-dichlorthiophen-3-carboxamido)-7-oxo-7-(2-oxo-1-(2-oxo-2-((1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)ethyl)-1,2-dihydropyridin-3-ylamino)hept-2-enoat |
| **III-129** | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1-methyl-1H-pyrazol-3-carboxamido)-7-oxohept-2-enoat |
| **III-130** | (S,E)-methyl 7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(1 -methyl-1H-pyrazol-4-carboxamido)-7-oxohept-2-enoat |
| **III-131** | (S,E)-methyl 6-(4-tert-butyl-1H-pyrrole-3-carboxamido)-7-(1-(2-(1-adamantylamino)ethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoat |
| **III-132** | (S,E)-methyl 6-(4-cyano-1-methyl-1H-pyrrole-2-carboxamido)-7-(1-(3-(1-adamantylamino)propyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoat |
| **III-133** | (S,E)-methyl 7-(1-(3-(2-adamantylamino)-3-oxopropyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(5-methoxyoxazol-2-carboxamido)-7-oxohept-2-enoat |
| **III-134** | (S,E)-methyl 7-(1-(2-(bicyclo[2.1.1]hexan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(2-isopropyloxazol-5-carboxamido)-7-oxohept-2-enoat |
| **III-135** | (6S,E)-methyl 7-(1-(2-(bicyclo[3.2.1]octan-8-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3,5-dimethylisoxazol-4-carboxamido)-7-oxohept-2-enoat |

| Forbin-delse | Navn |
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| **III-136** | (S, E)-m ethyl 7-(1-(2-(5-carboxy-2-am inoadamantan)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-methylpyrimidin-5-carboxamido)-7-oxohept-2-enoat |
| **III-137** | (6S,E)-methyl 7-(1-(2-(4-aminoadamantan-N,N-dimethyl-1-carboxamid)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(1,2,3,4-tetrahydronaphthalen-2-carboxamido)hept-2-enoat |
| **III-138** | (S,E)-6-(2-acetyloxazol-4-carboxamido)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N1,N1-diethylhept-2-enediamid |
| **III-139** | (S,E)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-6-((S)-1,4-diazabicyclo[2.2.2]octan-2-carboxamido)-N1,N1-diethylhept-2-enediamid |
| **III-140** | (S,E)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-6-(1H-indol-3-carboxamido)-N1-isopropylhept-2-enediamid |
| **III-141** | (S,E)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N1-isopropyl-6-(6-methylimidazo[2,1-b]thiazol-3-carboxamido)hept-2-enediamid |
| **III-142** | (S,E)-6-(benzo[d]thiazol-2-carboxamido)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N1-pentylhept-2-enediamid |
| **III-143** | (S,E)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-6-(imidazo[2,1-b]thiazol-6-carboxamido)-N1-pentylhept-2-enediamid |
| **III-144** | (S,E)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N1-cyclopropyl-6-(4-hydroxy-6-(trifluormethoxy)quinolin-3-carboxamido)hept-2-enediamid |
| **III-145** | (S,E)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-6-(cinnolin-3-carboxamido)-N1-cyclopropylhept-2-enediamid |
| **III-146** | (S,E)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N1-cyclopentyl-6-(2-methyl-1,8-naphthyridin-3-carboxamido)hept-2-enediamid |

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| **III-147** | (S,E)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N1-cyclopentyl-6-(3-ethylbenzofuran-2-carboxamido)hept-2-enediamid |
| **III-148** | (S,E)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N1-cyclohexyl-6-(1-ethyl-1H-indol-2-carboxamido)hept-2-enediamid |
| **III-149** | (S,E)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-N1-cyclohexyl-6-(1,2,3,4-tetrahydroquinolin-7-carboxamido)hept-2-enediamid |
| **III-150** | (S,E)-N1-allyl-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-6-(1,6-naphthyridin-2-carboxamido)hept-2-enediamid |
| **III-151** | (S,E)-N1-allyl-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-6-(2,6-naphthyridin-1-carboxamido)hept-2-enediamid |
| **III-152** | (S,E)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-6-(5-bromo-2-methylfuran-3-carboxamido)-N1-phenylhept-2-enediamid |
| **III-153** | (S,E)-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-6-(2,5-dimethylfuran-3-carboxamido)-N1-phenylhept-2-enediamid |
| **III-154** | (S,E)-N1-benzyl-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-6-(2,5-dichlorthiazol-4-carboxamido)hept-2-enediamid |
| **III-155** | (S,E)-N1-benzyl-N7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-yl)-6-(4-bromothiazol-2-carboxamido)hept-2-enediamid |
| **III-156** | (S,E)-benzyl 7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-methyl-2-phenylthiazol-5-carboxamido)-7-oxohept-2-enoat |
| **III-157** | (S,E)-N-(1-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-1,7-dioxo-7-phenylhept-5-en-2-yl)-1-methyl-1H-imidazol-2-carboxamid |
| **III-158** | (S,E)-isopropyl 7-(1-(2-(bicyclo[2.1.1]hexan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(2H-1,2,3-triazol-4-carboxamido)hept-2-enoat |

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| **III-159** | N-((2S,E)-1-(1-(2-(bicyclo[3.2.1]octan-8-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-1,7-dioxooct-5-en-2-yl)-1-methyl-1H-1,2,4-triazol-3-carboxamid |
| **III-160** | (S,E)-methyl 6-(4-amino-1,2,5-oxad iazol-3-carboxamido)-7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoat |
| **III-161** | (S,E)-methyl 7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(6-(dimethylamino)benzofuran-2-carboxamido)-7-oxohept-2-enoat |
| **III-162** | (S,E)-methyl 6-(2-acetamidothiazol-5-carboxamido)-7-(1-(2-(bicyclo[1.1,1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoat |
| **III-163** | (S,E)-methyl 7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(5-carbamoyl-1H-pyrrole-3-carboxamido)-7-oxohept-2-enoat |
| **III-164** | (S,E)-methyl 7-(1-(2-(1-acetylamino-4-aminoadamantan)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(5-sulfamoylfuran-3-carboxamido)hept-2-enoat |
| **III-165** | (S,E)-m ethyl 6-(benzofuran-5-carboxamido)-7-(1-(2-(1-acetylam ino-4-aminoadamantan)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoat |
| **III-166** | (S,E)-methyl 6-(benzofuran-6-carboxamido)-7-(1-(2-(4-aminoadamantan-1-carboxamid)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoat |
| **III-167** | (S,E)-methyl 7-(1-(2-(4-aminoadamantan-1-carboxamid)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(3-(1- methylcyclopropyl)-1,2,4-oxadiazol-5-carboxamido)-7-oxohept-2-enoat |
| **III-168** | (S,E)-methyl 7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(5-methyl-1,2,4-oxadiazol-3-carboxamido)-7-oxohept-2-enoat |
| **III-169** | (S,E)-methyl 7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(1,2,3-thiadiazol-4-carboxamido)hept-2-enoat |
| **III-170** | (S,E)-methyl 7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(1,2,4-thiadiazol-5-carboxamido)hept-2-enoat |

| Forbin-delse | Navn |
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| **III-171** | (S,E)-methyl 7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(1,3,4-thiadiazol-2-carboxamido)hept-2-enoat |
| **III-172** | (S,E)-methyl 7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-6-(4-cyclopropyl-1,2,3-thiadiazol-5-carboxamido)-7-oxohept-2-enoat |
| **III-173** | (S,E)-methyl 7-(1-(2-(bicyclo[1.1.1]pentan-1-ylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxo-6-(1,2,5-thiadiazol-3-carboxamido)hept-2-enoat |
| **III-174** | (S,E)-methyl 6-(4-formyl-1,2,3-thiadiazol-5-carboxamido)-7-(1-(2-(2-carboxy-2-amino-5-(trifluormethyl)adamantan)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoat |
| **III-175** | (S,E)-methyl 6-(4-(hydroxymethyl)-1,2,3-thiadiazol-5-carboxamido)-7-(1-(2-(2-adamantylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-3-ylamino)-7-oxohept-2-enoat |

eller et farmaceutisk acceptabelt salt deraf.

**10.** Farmaceutisk sammensætning omfattende en forbindelse ifølge et hvilket som helst af kravene 1-9 som en aktiv bestanddel sammen med mindst én farmaceutisk acceptabel bærer, excipiens og/eller fortyndingsmiddel.

**11.** Forbindelse ifølge et hvilket som helst af kravene 1-9 til anvendelse i medicin.

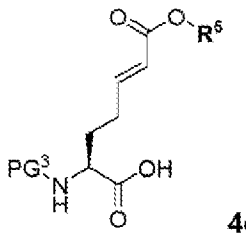
**12.** Forbindelse ifølge et hvilket som helst af kravene 1-9 eller den farmaceutiske sammensætning ifølge krav 10 til anvendelse i behandling eller profylakse af autoimmune og inflammatoriske sygdomme, vaskulære sygdomme, fibrotiske sygdomme, leversygdomme, kolestatiske leversygdomme, cancer, neurodegenerative sygdomme, øjensygdomme og hudlidelser.

**13.** Forbindelse til anvendelse eller den farmaceutiske sammensætning til anvendelse ifølge krav 12, hvor de autoimmune og inflammatoriske sygdomme omfatter multipel sklerose, cøliaki, Duhring-Brocq-sygdom (dermatitis herpetiformis), glutenataksi, glutenneuropati, diabetes, reumatoid arthritis, Graves sygdom, inflammatorisk tarmsygdom, systemisk lupus erythematosus psoriasis og gingivitis; hvor de vaskulære sygdomme omfatter aterosklerose, trombose, vaskulær stivhed; hvor de fibrotiske sygdomme påvirker lungen, nyren, leveren, huden eller tarmen som cystisk fibrose, nyrefibrose og diabetisk nefropati, tarmfibrose, idiopatisk lungefibrose, leverfibrose; hvor leversygdomme omfatter alkoholisk hepatitis, alkoholisk steatohepatitis, ikke-alkoholisk steatohepatitis, ikke-alkoholisk fedtleversygdom, levercirrhose, autoimmun hepatitis eller leverbetændelse; hvor de kolestatiske leversygdomme omfatter primær biliær cholangitis og primær skleroserende cholangitis; hvor canceren omfatter glioblastom, melanom, bugspytkirtelcancer, nyrecellecarcinom, meningiom og brystcancer, hvor de neurodegenerative sygdomme omfatter Parkinsons sygdom, Huntingtons sygdom eller Alzheimers sygdom, hvor øjensygdommene omfatter glaukom, grå stær, makuladegeneration eller uveitis ; og hvor hudlidelserne omfatter acne, psoriasis, ardannelse og hudældning.

**14.** Forbindelse til anvendelse eller den farmaceutiske sammensætning til anvendelse ifølge et hvilket som helst af kravene 12 og 13 til behandling eller profylakse af cøliaki.

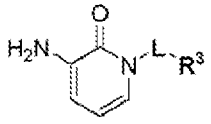
**15.** Fremgangsmåde til fremstilling af forbindelsen med formlen (**Ic**) ifølge krav 1, omfattende:

**Trin 1C**: tilvejebringelse af en forbindelse **4c**



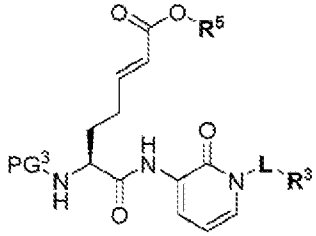
**4c**;

**Trin** 2C: udførelse af koblingsreaktion af forbindelsen **4c** med en forbindelse **5**



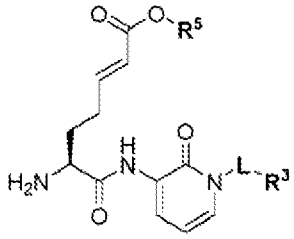
**5**

for at opnå en forbindelse 6c



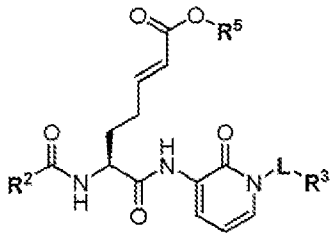
**6c**;

**Trin** 3C: afbeskyttelse af en aminobeskyttelsesgruppe $PG^3$ for at opnå en forbindelse 7c



**7c**;

**Trin** 4C: udførelse af koblingsreaktion af forbindelsen **7c** med en carboxylsyre (**$R^2$**-$CO_2H$ **8**) til fremstilling af forbindelsen med formlen (**Ic**)



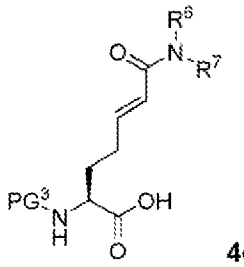
(**Ic**);

hvor **L, $R^2$**, **$R^3$**, **$R^5$** har samme betydninger som defineret i krav 1, og $PG^3$ er en aminobeskyttelsesgruppe;

eller

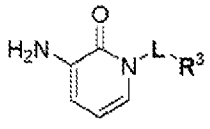
en fremgangsmåde til fremstilling af forbindelsen med formlen (**Id**) ifølge krav 1 omfattende:

**Trin** 1D: tilvejebringelse af en forbindelse **4d**



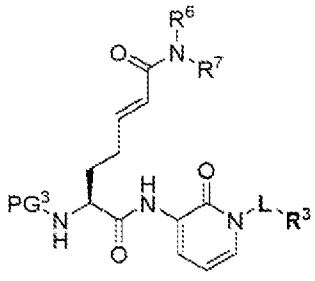
**4d**;

**Trin** 2D: udførelse af koblingsreaktion af forbindelsen **4d** med en forbindelse **5**



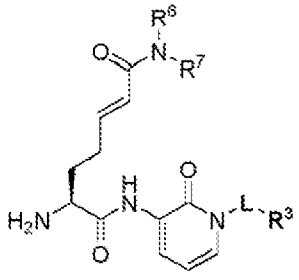
**5**

for at opnå en forbindelse **6d**



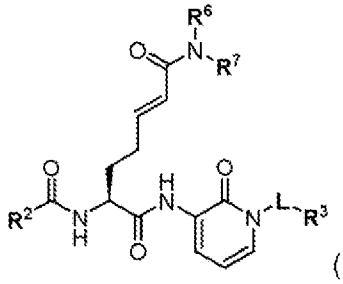
**6d**;

**Trin** 3D: afbeskyttelse af en aminobeskyttelsesgruppe $PG^3$ for at opnå en forbindelse **7d**



**7d**;

**Trin** 4D: udførelse af koblingsreaktion af forbindelsen **7d** med en carboxylsyre ($\mathbf{R^2}$-$CO_2H$ **8)** for at fremstille forbindelsen med formlen (**Id**)



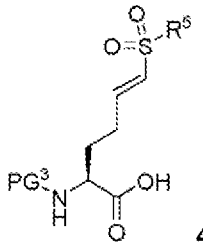
(**Id**) ;

hvor **L, $R^2$**, **$R^3$**, **$R^6$**, **$R^7$** har samme betydninger som defineret ovenfor i formlen (**Id**), og $PG^3$ er en aminobeskyttelsesgruppe;

eller

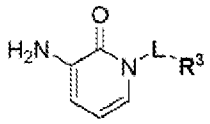
en fremgangsmåde til fremstilling af forbindelsen med formlen (**Ie**) ifølge krav 1 omfattende:

**Trin 1E**: tilvejebringelse af en forbindelse **4e**



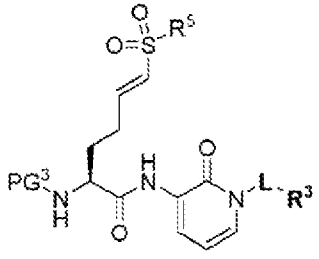
**4e**;

**Trin 2E**: udførelse af koblingsreaktion af forbindelsen **4e** med en forbindelse **5**



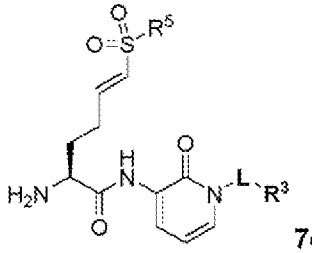
**5**

for at opnå en forbindelse **6e**



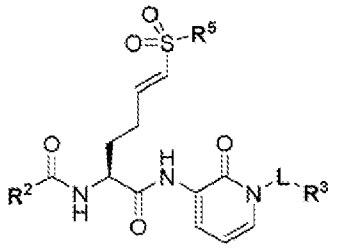
**6e**;

**Trin 3E**: afbeskyttelse af en aminobeskyttelsesgruppe $PG^3$ for at opnå en forbindelse **7e**



**7e**;

**Trin 4E**: udførelse af koblingsreaktion af forbindelsen **7e** med en carboxylsyre (**$R^2$-$CO_2H$ 8)** for at fremstille forbindelsen med formlen (**Ie**)



(Ie)

hvor **L, R2, R3, R5** har de samme betydninger som defineret ovenfor i formlen (**Ie**), og $PG^3$ er en aminobeskyttelsesgruppe.