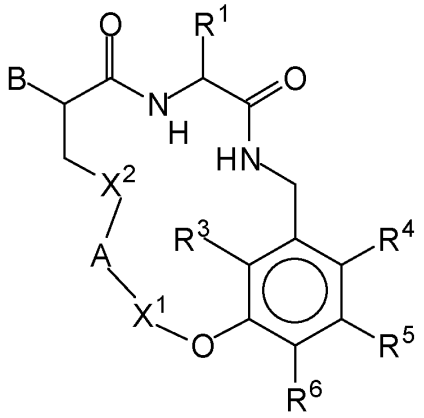
Macrocyclic compounds as proteasome subunit beta type-5 inhibitors

The present invention relates to certain macrocyclic compounds of the formula (I) and pharmaceutically acceptable salts thereof. These compounds are useful in the treatment or prevention of a disease treatable by proteasome inhibition, selected from cancers, infectious diseases, inflammatory dieases, and autoimmune diseases.



(I)

Background of the invention

The proteasome is a multicatalytic proteinase complex with a highly ordered ring-shaped 20S core structure. The core structure is composed of 4 rings of 28 non-identical subunits; 2 rings are composed of 7 alpha subunits and 2 rings are composed of 7 beta subunits. Proteasomes are distributed throughout eukaryotic cells at a high concentration and cleave peptides in an ATP/ubiquitin-dependent process in a non-lysosomal pathway. Two isoforms of the proteasome are the constitutive proteasome and the immunoproteasome which is constitutively expressed in hematopoietic cells and can be induced in non-immune cells by inflammatory cytokines or oxidadtive stress. Both differ from each other in the subunit composition. The constitutive proteasome has three subunits with chymotrypsin-like (beta type-5), caspase-like (beta type-1) and trypsin-like (beta type-2) enzymatic activity. In the immunoproteasome these subunits are replaced by the beta type-5i, beta type-1i and beta type-2i catalytic subunits, which have different substrate preferences and an increased proteolytic activity compared to the corresponding subunits in the constitutive proteasome. An essential function of the immunoproteasome is the processing of class I MHC peptides for antigen presentation.

The proteasomes form a pivotal component for the ubiquitin–proteasome system (UPS) and corresponding cellular Protein Quality Control (PQC). Protein ubiquitination and subsequent proteolysis and degradation by the proteasome are important mechanisms

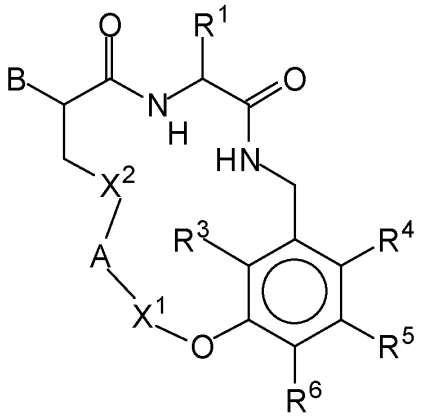
in the regulation of the cell cycle, cell growth and differentiation, gene transcription, signal transduction and apoptosis.

The proteasome plays a central role in the cellular protein degradation pathway. Protein degradation is of particular importance for cancer cells with a high protein turnover, which is usually associated with the formation of misfolded proteins. Inhibition of the proteasome in such cells leads to an accumulation of misfolded proteins activating the caspase cascade and thus contributing to apoptosis. Alternative events induced by proteasome inhibition contributing to induce cell death are: Inhibition of the pro-survival NFkB pathway and induction of pro-apoptotic proteins. Thus proteasome inhibition leads to apoptosis of cells with a high protein turnover such as tumor and myeloma cells. Also plasma cells which have a high protein turnover due to the constant secretion of antibodies show sensitivity to proteasome inhibition. Accordingly proteasome inhibition has been shown to have a signficant effect on autoantibody mediated autoimmune diseases such as systemic lupus erythematosus (SLE) or myasthenia gravis (MG). Since proteasome inhibitors are effective at targeting antibody producing B-cells they are also evaluated as therapies in antibody-mediated allograft rejection. The inhibition of the protozoan proteasome by proteasome inhibitors has been shown to be effective in treating malaria, killing selectively *plasmodium falciparum* while sparing human cells. In addition proteasome inhibitors have shown potential as antibiotics for example against *mycobacterium tuberculosis*.

It is object to the present invention to provide novel compounds as proteasome subunit beta type-5 inhibitors and/or pharmaceutically acceptable salts thereof, which can be used as pharmaceutically active agents, and use thereof especially for prophylaxis and/or treatment of a disease associated with and/or caused by proteasome subunit beta type-5 selected from a cancer, a neurodegenerative disease, an infectious disease, and an inflammatory diease as well as compositions comprising at least one of those compounds and/or pharmaceutically acceptable salts thereof as pharmaceutically active ingredients. The objective of the present invention is solved by the teaching of the independent claims. Further advantageous features, aspects and details of the invention are evident from the dependent claims, the description, and the examples of the present application.

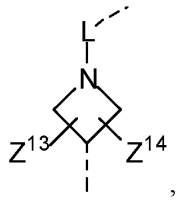
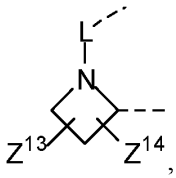
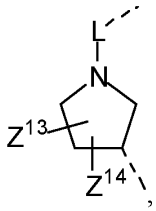
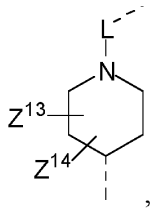
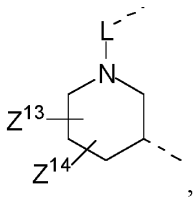
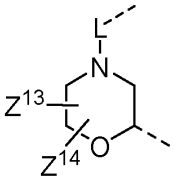
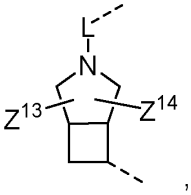
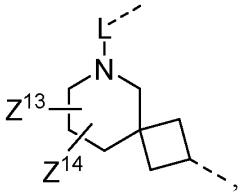
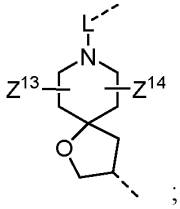
Description of the invention

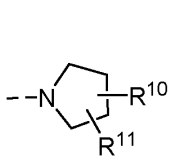
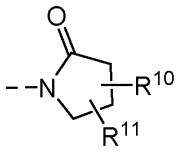
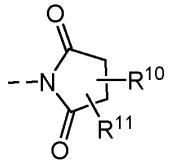
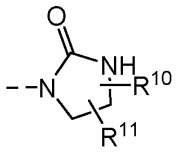
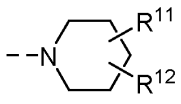
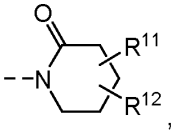
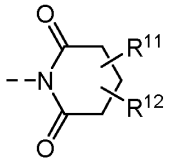
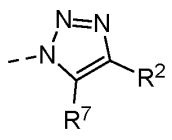
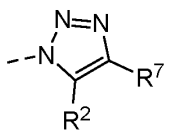
The present invention relates to a compound of the general formula (**I**)



(I)

wherein

A represents –CO–N(**R**^{N6})–,  ,  ,  ,  ,  ,  ,  ,  or  ;

B represents –H, –NH(**R**^{2}), –N(**R**^{2})(**R**^{N5}),  ,  ,  ,  ,  ,  ,  ,  ,  , or ;

L represents –CO–, –CO–NH–, –CO–N(**R**^{N3})–, or –CO–O–;

$\mathbf{R^1}$ represents –H, $-(CH_2)_p-\mathbf{R^7}$, $-(CH_2)_p-NH-\mathbf{R^7}$, $-(CH_2)_p-\mathbf{R^9}$, or $-(CH_2)_p-N\mathbf{R^{N4}}-\mathbf{R^9}$;

$\mathbf{R^2}$ represents –H, $-\mathbf{R^8}$, $-\mathbf{R^{11}}$, $-\mathbf{L^1}-\mathbf{R^{11}}$, $-\mathbf{L^1}-(CH_2)_r-\mathbf{R^8}$, $-\mathbf{L^1}-\mathbf{R^{10}}$, $-\mathbf{L^1}-(C_2H_4O)_s-\mathbf{R^{11}}$, $-\mathbf{L^1}-(CH_2)_t-O-\mathbf{R^{11}}$, $-\mathbf{L^1}-(CH_2)_t-NH-(CH_2)_r-\mathbf{R^8}$, $-\mathbf{L^1}-(CH_2)_t-O-(CH_2)_r-\mathbf{R^8}$, $-\mathbf{L^1}-(CH_2)_t-NH\mathbf{R^8}$, $-\mathbf{L^1}-(CH_2)_t-NH-CO-\mathbf{R^8}$, $-\mathbf{L^1}-(CH_2)_t-NH-SO_2-\mathbf{R^8}$, $-\mathbf{L^1}-(CH_2)_t-N\mathbf{R^{N6}}\mathbf{R^{10}}$, $-\mathbf{L^1}-(CH_2)_t-O-(CH_2)_u-N\mathbf{R^{N6}}\mathbf{R^{10}}$, $-\mathbf{L^1}-(CH_2)_r-\mathbf{R^{14}}$, $-CO-C(\mathbf{R^{12}})(\mathbf{R^{13}})-\mathbf{R^{10}}$, $-CO-C(\mathbf{R^{12}})(\mathbf{R^{13}})-\mathbf{R^8}$, or $-CO-C(\mathbf{R^{12}})(\mathbf{R^{13}})-(CH_2)_u-\mathbf{R^8}$;

$\mathbf{L^1}$ represents a bond, –CO–, $-CO_2-$, –CONH–, or $-SO_2-$;

$\mathbf{R^3}$ – $\mathbf{R^6}$ represent independently of each other –H, $-CH_3$, $-OCH_3$, –F, or –Cl;

or $\mathbf{R^5}$ and $\mathbf{R^6}$ may form together  ;

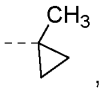
$\mathbf{R^8}$ and $\mathbf{R^9}$ represent independently of each other
C_6–C_{14} aryl, C_1–C_{10} heteroaryl, C_3–C_8 carbocyclyl, C_1–C_9 heterocyclyl, C_4-C_{11} bicyclic carbocyclyl, C_4–C_{11} bridged carbocyclyl, C_1–C_{10} bicyclic heterocyclyl, C_1–C_{10} bridged heterocyclyl, C_7–C_{16}–spiroalkyl, C_5–C_{14}–spiroheterocyclyl,
wherein all afore-mentioned ring systems can be substituted with 1 to 5 substituents selected from Z^1, Z^2, Z^3, Z^4, Z^5, Z^6, Z^7, Z^8, Z^9, Z^{10}, Z^{11}, Z^{12}, R^{N1} and R^{N2}; and
C_1–C_{10} heteroaryl, C_1–C_9 heterocyclyl, C_1–C_{10} bicyclic heterocyclyl, C_1–C_{10} bridged heterocyclyl, C_5–C_{14}–spiroheterocyclyl ring systems contain at least one of heteroatoms N, O, and S;
said C_3–C_8 carbocyclyl, C_1–C_9 heterocyclyl, C_1–C_{10} bicyclic heterocyclyl, C_4–C_{11} bridged carbocyclyl, C_1–C_{10} bicyclic heterocyclyl, C_1–C_{10} bridged heterocyclyl, C_7–C_{16}–spiroalkyl, C_5–C_{14}–spiroheterocyclyl ring systems can be partly saturated or unsaturated;

$\mathbf{R^7}$ and $\mathbf{R^{10}}$ represent independently of each other –H, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CN$, $-C(CH_3)_2-CN$, $-CH_2-C(CH_3)_2-CN$, $-CH_2-CF_3$, $-CH_2-C(CH_3)_2-NH_2$,

, cyclo-C_3H_5, cyclo-C_4H_7, cyclo-C_5H_9, cyclo-C_6H_{11}, cyclo-C_7H_{13},
$-C_4H_9$, $-CH_2-CH(CH_3)_2$, $-CH(CH_3)-C_2H_5$, $-C(CH_3)_3$, $-C_5H_{11}$, $-CH(CH_3)-C_3H_7$, $-CH_2-CH(CH_3)-C_2H_5$, $-CH(CH_3)-CH(CH_3)_2$, $-C(CH_3)_2-C_2H_5$, $-CH_2-C(CH_3)_3$,

–$CH(C_2H_5)_2$, –C_2H_4–$CH(CH_3)_2$, –C_6H_{13}, –C_7H_{15}, –C_8H_{17}, –Ph, –CH_2–Ph, –CH_2–CH_2–Ph, –C_2H_4–$CH=CH_2$, –CH_2–$CH=CH$–CH_3, –CH_2–$C(CH_3)=CH_2$, –$CH(CH_3)$–$CH=CH_2$, –$C(CH_3)=CH$–CH_3, –CH_2–$CH=C(CH_3)_2$, –CO–$CH=C(CH_3)_2$, –CH_2-C≡CH, –C_2H_4–C≡CH, –CH_2–C≡C–CH_3, –CH_2–OCF_3, –C_2H_4–OCF_3, –C_3H_6–OCF_3, –CH_2–$OCHF_2$, –C_2H_4–$OCHF_2$, –C_3H_6–$OCHF_2$, –CH_2–OCH_3, –C_2H_4–OCH_3, –C_3H_6–OCH_3, –CH_2–OC_2H_5, –C_2H_4–OC_2H_5, –C_3H_6–OC_2H_5, –CH_2–OH, –C_2H_4–OH, –C_3H_6–OH, –CH_2–COOH, –C_2H_4–COOH, –C_3H_6–COOH, –$C(CH_3)_2$–CN, –$C(CH_3)_2$–OH, –$C(CH_3)_2$–CH_2–OH, –$C(C_2H_5)_2$–CH_2–OH, –$C(CH_2$–$OH)_2$–CH_3, –$C(CH_2$–$OH)_2$–C_2H_5, –$C(CH_3)_2$–CH_2–SH, –$C(C_2H_5)_2$–CH_2–SH, –$C(CH_2$–$SH)_2$–CH_3, –CO–O–$C(CH_3)_3$, or –$C(CH_2$–$SH)_2$–C_2H_5;

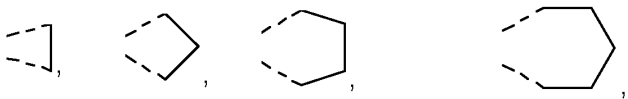
R^{11} represents –H, –CH_3, –C_2H_5, –C_3H_7, –$CH(CH_3)_2$, –CH_2F, –CHF_2, –CF_3, –CH_2CN, –$C(CH_3)_2$–CN, –CH_2–$C(CH_3)_2$–CN, –CH_2–CF_3, –CH_2–$C(CH_3)_2$–NH_2,

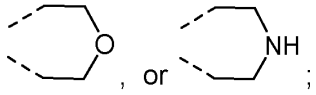


, cyclo-C_3H_5, cyclo-C_4H_7, cyclo-C_5H_9, cyclo-C_6H_{11}, cyclo-C_7H_{13}, –C_4H_9, –CH_2–$CH(CH_3)_2$, –$CH(CH_3)$–C_2H_5, –$C(CH_3)_3$, –C_5H_{11}, –$CH(CH_3)$–C_3H_7, –CH_2–$CH(CH_3)$–C_2H_5, –$CH(CH_3)$–$CH(CH_3)_2$, –$C(CH_3)_2$–C_2H_5, –CH_2–$C(CH_3)_3$, –$CH(C_2H_5)_2$, –C_2H_4–$CH(CH_3)_2$, –C_6H_{13}, –C_7H_{15}, –C_8H_{17}, –Ph, –CH_2–Ph, –CH_2–CH_2–Ph, –$CH=CH_2$, –CH_2–$CH=CH_2$, –$C(CH_3)=CH_2$, –$CH=CH$–CH_3, –$C(CH_3)=CH$–CH_3, –$CH=C(CH_3)_2$, –$C(CH_3)=C(CH_3)_2$, –C_2H_4–$CH=CH_2$, –CH_2–$CH=CH$–CH_3, –CH_2–$C(CH_3)=CH_2$, –$CH(CH_3)$–$CH=CH_2$, –$C(CH_3)=CH$–CH_3, –CH_2–$CH=C(CH_3)_2$, –C≡CH, –CH_2-C≡CH, –C_2H_4–C≡CH, –CH_2–C≡C–CH_3, –C≡C–CH_3, –C≡C–C_2H_5, –CH_2–OCF_3, –C_2H_4–OCF_3, –C_3H_6–OCF_3, –CH_2–$OCHF_2$, –C_2H_4–$OCHF_2$, –C_3H_6–$OCHF_2$, –CH_2–OCH_3, –C_2H_4–OCH_3, –C_3H_6–OCH_3, –CH_2–OC_2H_5, –C_2H_4–OC_2H_5, –C_3H_6–OC_2H_5, –CH_2–OH, –C_2H_4–OH, –C_3H_6–OH, –$C(CH_3)_2$–CH_2–OH, –$C(C_2H_5)_2$–CH_2–OH, –$C(CH_2$–$OH)_2$–CH_3, –$C(CH_2$–$OH)_2$–C_2H_5, –$C(CH_3)_2$–CH_2–SH, –$C(C_2H_5)_2$–CH_2–SH, –$C(CH_2$–$SH)_2$–CH_3, or –$C(CH_2$–$SH)_2$–C_2H_5;

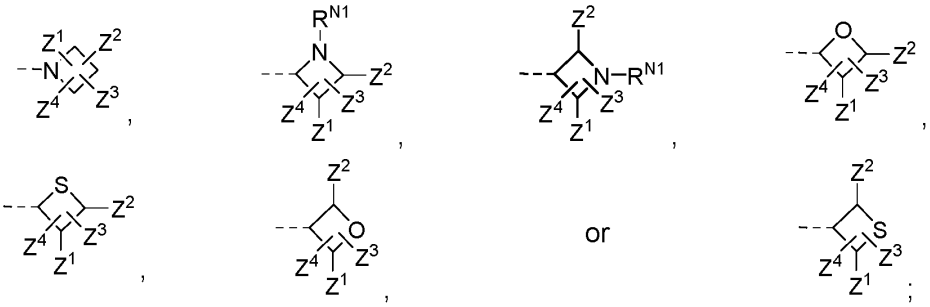
R^{12} and **R^{13}** represent independently of each other –H, –CH_3, –C_2H_5, –C_3H_7, –$CH(CH_3)_2$, –Ph, –CH_2–Ph, –COOH, –NH_2, –$NHCO_2(CCH_3)_3$, –CH_2–NH_2, –CHF_2, –F, –CF_3, –OCF_3, –$OCHF_2$, –OH, –OCH_3, –OC_2H_5, –OC_3H_7, and –$OCH(CH_3)_2$; or

R^{12} and **R^{13}** may form together





R^{14} represents



R^{15} and **R^{16}** represent independently of each other **$-X^3-L^2-R^{17}$**, or $-(OCH_2CH_2)_w-R^{17}$;

L^2 represents $-(CH_2)_v-$, $-(CH_2CH_2-O)_w-CH_2-$, or $-(CH_2CH_2-O)_w-CH_2CH_2-$;

R^{17} represents $-OH$, $-SH$, $-SO_3H$, $-NH_2$, or $-CO_2H$;

R^{N1}, **R^{N2}**, **R^{N3}** and **R^{N4}** represent independently of each other $-H$, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $-CHF_2$, $-CF_3$,



cyclo-C_3H_5, cyclo-C_4H_7, cyclo-C_5H_9, cyclo-C_6H_{11}, cyclo-C_7H_{13}, $-C_4H_9$, $-CH_2-CH(CH_3)_2$, $-CH(CH_3)-C_2H_5$, $-C(CH_3)_3$, $-C_5H_{11}$, $-CH(CH_3)-C_3H_7$, $-CH_2-CH(CH_3)-C_2H_5$, $-CH(CH_3)-CH(CH_3)_2$, $-C(CH_3)_2-C_2H_5$, $-CH_2-C(CH_3)_3$, $-CH(C_2H_5)_2$, $-C_2H_4-CH(CH_3)_2$, $-C_6H_{13}$, $-C_7H_{15}$, $-C_8H_{17}$, $-Ph$, $-CH_2-Ph$, $-CH_2-CH_2-Ph$, $-C_2H_4-CH=CH_2$, $-CH_2-CH=CH-CH_3$, $-CH_2-C(CH_3)=CH_2$, $-CH(CH_3)-CH=CH_2$, $-CH_2-CH=C(CH_3)_2$, $-CH_2-C\equiv CH$, $-C_2H_4-C\equiv CH$, $-CH_2-C\equiv C-CH_3$, $-COCH_3$, $-COC_2H_5$, $-COC_3H_7$, $-CO-$cyclo-C_3H_5, $-COCH(CH_3)_2$, $-COC(CH_3)_3$, $-COOH$, $-COOCH_3$, $-COOC_2H_5$, $-COOC_3H_7$, $-COO-$cyclo-C_3H_5, $-COOCH(CH_3)_2$, $-COOC(CH_3)_3$, $-COOCH_2Ph$, $-CONH_2$, $-CONHCH_3$, $-CONHC_2H_5$, $-CONHC_3H_7$, $-CONH-$cyclo-C_3H_5, $-CONH[CH(CH_3)_2]$, $-CONH[C(CH_3)_3]$, $-CON(CH_3)_2$, $-CON(C_2H_5)_2$, $-CON(C_3H_7)_2$, $-CON($cyclo-$C_3H_5)_2$, $-CON[CH(CH_3)_2]_2$, $-CON[C(CH_3)_3]_2$, $-SO_3H$, or **$-R^{15}$**;

R^{N5} and **R^{N6}** represent independently of each other $-H$, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, cyclo-C_3H_5, $-COOC(CH_3)_3$, or $-COOCH_2Ph$;

X^1 represents $-(CH_2)_m-$;

X^2 represents $-(CH_2)_n-$;

X^3 represents a bond, –O–, –NH–, or –S–;

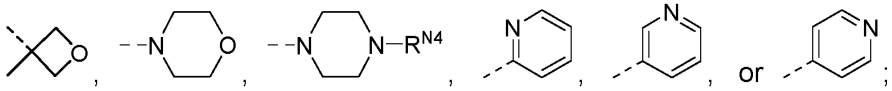
$Z^1 - Z^{14}$ represent independently of each other

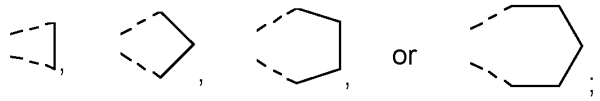


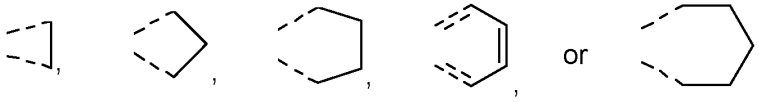
cyclo-C_3H_5, cyclo-C_4H_7, cyclo-C_5H_9, cyclo-C_6H_{11}, cyclo-C_7H_{13}, –R^{16}, –H, –OH, –OCH_3, –OC_2H_5, –OC_3H_7, –O–cyclo-C_3H_5, –$OCH(CH_3)_2$, –$OC(CH_3)_3$, –OC_4H_9, –O–cyclo-C_4H_7, –O–cyclo-C_5H_9, –O–cyclo-C_6H_{11}, –$OCH_2CH(CH_3)_2$, –OCH_2–cyclo-C_3H_5, –OCH_2–cyclo-C_4H_7, –OCH_2–cyclo-C_5H_9, –OCH_2–cyclo-C_6H_{11}, –OPh, –OCH_2–Ph, –$OCPh_3$, –CH_2–OCH_3, –C_2H_4–OCH_3, –C_3H_6–OCH_3, –CH_2–OC_2H_5, –C_2H_4–OC_2H_5, –C_3H_6–OC_2H_5, –CH_2–OC_3H_7, –C_2H_4–OC_3H_7, –C_3H_6–OC_3H_7, –CH_2–O–cyclo-C_3H_5, –C_2H_4–O–cyclo-C_3H_5, –C_3H_6–O–cyclo-C_3H_5, –CH_2–$OCH(CH_3)_2$, –C_2H_4–$OCH(CH_3)_2$, –C_3H_6–$OCH(CH_3)_2$, –CH_2–$OC(CH_3)_3$, –C_2H_4–$OC(CH_3)_3$, –C_3H_6–$OC(CH_3)_3$, –CH_2–OC_4H_9, –C_2H_4–OC_4H_9, –C_3H_6–OC_4H_9, –CH_2–OPh, –C_2H_4–OPh, –C_3H_6–OPh, –CH_2–OCH_2–Ph, –C_2H_4–OCH_2–Ph, –C_3H_6–OCH_2–Ph, –SH, –SCH_3, –SC_2H_5, –SC_3H_7, –S–cyclo-C_3H_5, –$SCH(CH_3)_2$, –$SC(CH_3)_3$, –F, –Cl, –Br, –I, –CN, –$COCH_3$, –COC_2H_5, –COC_3H_7, –CO–cyclo-C_3H_5, –$COCH(CH_3)_2$, –$COC(CH_3)_3$, –COOH, –$COOCH_3$, –$COOC_2H_5$, –$COOC_3H_7$, –COO–cyclo-C_3H_5, –$COOCH(CH_3)_2$, –$COOC(CH_3)_3$, –OOC–CH_3, –OOC–C_2H_5, –OOC–C_3H_7, –OOC–cyclo-C_3H_5, –OOC–$CH(CH_3)_2$, –OOC–$C(CH_3)_3$, –$CONH_2$, –$CONHCH_3$, –$CONHC_2H_5$, –$CONHC_3H_7$, –CONH–cyclo-C_3H_5, –$CONH[CH(CH_3)_2]$, –$CONH[C(CH_3)_3]$, –$CON(CH_3)_2$, –$CON(C_2H_5)_2$, –$CON(C_3H_7)_2$, –CON(cyclo-$C_3H_5)_2$, –$CON[CH(CH_3)_2]_2$, –$CON[C(CH_3)_3]_2$, –$NHCOCH_3$, –$NHCOC_2H_5$, –$NHCOC_3H_7$, –NHCO–cyclo-C_3H_5, –NHCO–$CH(CH_3)_2$, –NHCO–$C(CH_3)_3$, –NHCO–$CH(NH_2)CH_2$–COOH, –NHCO–$CH(NH_2)CH_2CH_2$–COOH, –NHCO–OCH_3, –NHCO–OC_2H_5, –NHCO–OC_3H_7, –NHCO–O–cyclo-C_3H_5, –NHCO–$OCH(CH_3)_2$, –NHCO–$OC(CH_3)_3$, –NH_2, –$NHCH_3$, –NHC_2H_5, –NHC_3H_7, –NH–cyclo-C_3H_5, –$NHCH(CH_3)_2$, –$NHC(CH_3)_3$, –$N(CH_3)_2$, –$N(C_2H_5)_2$, –$N(C_3H_7)_2$, –N(cyclo-$C_3H_5)_2$, –$N[CH(CH_3)_2]_2$, –$N[C(CH_3)_3]_2$, –$SOCH_3$, –SOC_2H_5, –SOC_3H_7, –SO–cyclo-C_3H_5, –$SOCH(CH_3)_2$, –$SOC(CH_3)_3$, –SO_2CH_3, –$SO_2C_2H_5$, –$SO_2C_3H_7$, –SO_2–cyclo-C_3H_5, –$SO_2CH(CH_3)_2$, –$SO_2C(CH_3)_3$, –SO_3H, –SO_3CH_3, –$SO_3C_2H_5$, –$SO_3C_3H_7$, –SO_3–cyclo-C_3H_5, –$SO_3CH(CH_3)_2$, –$SO_3C(CH_3)_3$, –SO_2NH_2, –SO_2NHCH_3, –$SO_2NHC_2H_5$, –$SO_2NHC_3H_7$, –SO_2NH–cyclo-C_3H_5,

$-SO_2NHCH(CH_3)_2$, $-SO_2NHC(CH_3)_3$, $-SO_2N(CH_3)_2$, $-SO_2N(C_2H_5)_2$, $-SO_2N(C_3H_7)_2$, $-SO_2N(\text{cyclo-}C_3H_5)_2$, $-SO_2N[CH(CH_3)_2]_2$, $-SO_2N[C(CH_3)_3]_2$, $-O-S(=O)CH_3$, $-O-S(=O)C_2H_5$, $-O-S(=O)C_3H_7$, $-O-S(=O)-\text{cyclo-}C_3H_5$, $-O-S(=O)CH(CH_3)_2$, $-O-S(=O)C(CH_3)_3$, $-S(=O)(=NH)CH_3$, $-S(=O)(=NH)C_2H_5$, $-S(=O)(=NH)C_3H_7$, $-S(=O)(=NH)-\text{cyclo-}C_3H_5$, $-S(=O)(=NH)CH(CH_3)_2$, $-S(=O)(=NH)C(CH_3)_3$, $-NH-SO_2-CH_3$, $-NH-SO_2-C_2H_5$, $-NH-SO_2-C_3H_7$, $-NH-SO_2-\text{cyclo-}C_3H_5$, $-NH-SO_2-CH(CH_3)_2$, $-NH-SO_2-C(CH_3)_3$, $-O-SO_2-CH_3$, $-O-SO_2-C_2H_5$, $-O-SO_2-C_3H_7$, $-O-SO_2-\text{cyclo-}C_3H_5$, $-O-SO_2-CH(CH_3)_2$, $-O-SO_2-C(CH_3)_3$, $-OCH_2F$, $-OCHF_2$, $-OCF_3$, $-CH_2-OCF_3$, $-C_2H_4-OCF_3$, $-C_3H_6-OCF_3$, $-CH_2-OCHF_2$, $-C_2H_4-OCHF_2$, $-C_3H_6-OCHF_2$, $-OC_2F_5$, $-CH_2-OC_2F_5$, $-C_2H_4-OC_2F_5$, $-C_3H_6-OC_2F_5$, $-O-COOCH_3$, $-O-COOC_2H_5$, $-O-COOC_3H_7$, $-O-COO-\text{cyclo-}C_3H_5$, $-O-COOCH(CH_3)_2$, $-O-COOC(CH_3)_3$, $-NH-CO-NH_2$, $-NH-CO-NHCH_3$, $-NH-CO-NHC_2H_5$, $-NH-CO-NHC_3H_7$, $-NH-C(=NH)-NH_2$, $-NH-CO-N(C_3H_7)_2$, $-NH-CO-NH[CH(CH_3)_2]$, $-NH-CO-NH[C(CH_3)_3]$, $-NH-CO-N(CH_3)_2$, $-NH-CO-N(C_2H_5)_2$, $-NH-CO-NH-\text{cyclo-}C_3H_5$, $-NH-CO-N(\text{cyclo-}C_3H_5)_2$, $-NH-CO-N[CH(CH_3)_2]_2$, $-NH-C(=NH)-NHCH_3$, $-NH-C(=NH)-NHC_2H_5$, $-NH-C(=NH)-NHC_3H_7$, $-O-CO-NH-\text{cyclo-}C_3H_5$, $-NH-C(=NH)-NH-\text{cyclo-}C_3H_5$, $-NH-C(=NH)-NH[CH(CH_3)_2]$, $-O-CO-NH[CH(CH_3)_2]$, $-NH-C(=NH)-NH[C(CH_3)_3]$, $-NH-C(=NH)-N(CH_3)_2$, $-NH-C(=NH)-N(C_2H_5)_2$, $-NH-C(=NH)-N(C_3H_7)_2$, $-NH-C(=NH)-N(\text{cyclo-}C_3H_5)_2$, $-O-CO-NHC_3H_7$, $-NH-C(=NH)-N[CH(CH_3)_2]_2$, $-NH-C(=NH)-N[C(CH_3)_3]_2$, $-O-CO-NH_2$, $-O-CO-NHCH_3$, $-O-CO-NHC_2H_5$, $-O-CO-NH[C(CH_3)_3]$, $-O-CO-N(CH_3)_2$, $-O-CO-N(C_2H_5)_2$, $-O-CO-N(C_3H_7)_2$, $-O-CO-N(\text{cyclo-}C_3H_5)_2$, $-O-CO-N[CH(CH_3)_2]_2$, $-O-CO-N[C(CH_3)_3]_2$, $-O-CO-OCH_3$, $-O-CO-OC_2H_5$, $-O-CO-OC_3H_7$, $-O-CO-O-\text{cyclo-}C_3H_5$, $-O-CO-OCH(CH_3)_2$, $-O-CO-OC(CH_3)_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2-CH_2F$, $-CH_2-CHF_2$, $-CH_2-CF_3$, $\text{cyclo-}C_8H_{15}$, $-Ph$, $-CH_2-Ph$, $-CH_2-CH_2-Ph$, $-CH=CH-Ph$, $-CPh_3$, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $-C_4H_9$, $-CH_2-CH(CH_3)_2$, $-CH(CH_3)-C_2H_5$, $-C(CH_3)_3$, $-C_5H_{11}$, $-CH(CH_3)-C_3H_7$, $-CH_2-CH(CH_3)-C_2H_5$, $-CH(CH_3)-CH(CH_3)_2$, $-C(CH_3)_2-C_2H_5$, $-CH_2-C(CH_3)_3$, $-CH(C_2H_5)_2$, $-C_2H_4-CH(CH_3)_2$, $-C_6H_{13}$, $-C_7H_{15}$, $-C_8H_{17}$, $-C_3H_6-CH(CH_3)_2$, $-C_2H_4-CH(CH_3)-C_2H_5$, $-CH(CH_3)-C_4H_9$, $-CH_2-CH(CH_3)-C_3H_7$, $-CH(CH_3)-CH_2-CH(CH_3)_2$, $-CH(CH_3)-CH(CH_3)-C_2H_5$, $-CH_2-CH(CH_3)-CH(CH_3)_2$, $-CH_2-C(CH_3)_2-C_2H_5$, $-C(CH_3)_2-C_3H_7$, $-C(CH_3)_2-CH(CH_3)_2$, $-C_2H_4-C(CH_3)_3$, $-CH(CH_3)-C(CH_3)_3$, $-CH=CH_2$, $-CH_2-CH=CH_2$, $-C(CH_3)=CH_2$, $-CH=CH-CH_3$, $-C_2H_4-CH=CH_2$, $-CH_2-CH=CH-CH_3$, $-CH=CH-C_2H_5$, $-CH_2-C(CH_3)=CH_2$, $-CH(CH_3)-CH=CH$, $-CH=C(CH_3)_2$, $-C(CH_3)=CH-CH_3$, $-CH=CH-CH=CH_2$, $-C_3H_6-CH=CH_2$, $-C_2H_4-CH=CH-CH_3$, $-CH_2-CH=CH-C_2H_5$, $-CH=CH-C_3H_7$, $-CH=CH-CH=CH-CH_3$, $-C_2H_4-C(CH_3)=CH_2$, $-CH_2-CH(CH_3)-CH=CH_2$,

–CH(CH$_3$)–CH$_2$–CH=CH$_2$, –CH$_2$–CH=C(CH$_3$)$_2$, –CH$_2$–C(CH$_3$)=CH–CH$_3$, –CH(CH$_3$)–CH=CH–CH$_3$, –CH=CH–CH(CH$_3$)$_2$, –CH=C(CH$_3$)–C$_2$H$_5$, –C(CH$_3$)=CH–C$_2$H$_5$, –C(CH$_3$)=C(CH$_3$)$_2$, –C(CH$_3$)$_2$–CH=CH$_2$, –CH(CH$_3$)–C(CH$_3$)=CH$_2$, –C$_4$H$_8$–CH=CH$_2$, –C$_3$H$_6$–CH=CH–CH$_3$, –C$_2$H$_4$–CH=CH–C$_2$H$_5$, –CH$_2$–CH=CH–C$_3$H$_7$, –CH=CH–C$_4$H$_9$, –C$_3$H$_6$–C(CH$_3$)=CH$_2$, –C$_2$H$_4$–CH(CH$_3$)–CH=CH$_2$, –CH$_2$–CH(CH$_3$)–CH$_2$–CH=CH$_2$, –C$_2$H$_4$–CH=C(CH$_3$)$_2$, –CH(CH$_3$)–C$_2$H$_4$–CH=CH$_2$, –C$_2$H$_4$–C(CH$_3$)=CH–CH$_3$, –CH$_2$–CH(CH$_3$)–CH=CH–CH$_3$, –CH(CH$_3$)–CH$_2$–CH=CH–CH$_3$, –CH$_2$–CH=CH–CH(CH$_3$)$_2$, –CH$_2$–CH=C(CH$_3$)–C$_2$H$_5$, –CH$_2$–C(CH$_3$)=CH–C$_2$H$_5$, –CH(CH$_3$)–CH=CH–C$_2$H$_5$, –CH=CH–CH$_2$–CH(CH$_3$)$_2$, –CH=CH–CH(CH$_3$)–C$_2$H$_5$, –CH=C(CH$_3$)–C$_3$H$_7$, –C(CH$_3$)=CH–C$_3$H$_7$, –CH$_2$–CH(CH$_3$)–C(CH$_3$)=CH$_2$, –C[C(CH$_3$)$_3$]=CH$_2$, –CH(CH$_3$)–CH$_2$–C(CH$_3$)=CH$_2$, –CH(CH$_3$)–CH(CH$_3$)–CH=CH$_2$, –CH=CH–C$_2$H$_4$–CH=CH$_2$, –C(CH$_3$)$_2$–CH$_2$–CH=CH$_2$, –CH$_2$–C(CH$_3$)=C(CH$_3$)$_2$, –CH(CH$_3$)–CH=C(CH$_3$)$_2$, –C(CH$_3$)$_2$–CH=CH–CH$_3$, –CH=CH–CH$_2$–CH=CH–CH$_3$, –CH(CH$_3$)–C(CH$_3$)=CH–CH$_3$, –CH=C(CH$_3$)–CH(CH$_3$)$_2$, –C(CH$_3$)=CH–CH(CH$_3$)$_2$, –C(CH$_3$)=C(CH$_3$)–C$_2$H$_5$, –CH=CH–C(CH$_3$)$_3$, –C(CH$_3$)$_2$–C(CH$_3$)=CH$_2$, –CH(C$_2$H$_5$)–C(CH$_3$)=CH$_2$, –C(CH$_3$)(C$_2$H$_5$)–CH=CH$_2$, –CH(CH$_3$)–C(C$_2$H$_5$)=CH$_2$, –CH$_2$–C(C$_3$H$_7$)=CH$_2$, –CH$_2$–C(C$_2$H$_5$)=CH–CH$_3$, –CH(C$_2$H$_5$)–CH=CH–CH$_3$, –C(C$_4$H$_9$)=CH$_2$, –C(C$_3$H$_7$)=CH–CH$_3$, –C(C$_2$H$_5$)=CH–C$_2$H$_5$, –C(C$_2$H$_5$)=C(CH$_3$)$_2$, –C[CH(CH$_3$)(C$_2$H$_5$)]=CH$_2$, –C[CH$_2$–CH(CH$_3$)$_2$]=CH$_2$, –C$_2$H$_4$–CH=CH–CH=CH$_2$, –CH$_2$–CH=CH–CH$_2$–CH=CH$_2$, –C$_3$H$_6$–C≡C–CH$_3$, –CH$_2$–CH=CH–CH=CH–CH$_3$, –CH=CH–CH=CH–C$_2$H$_5$, –CH(CH$_3$)–CH$_2$–C≡CH, –CH(CH$_3$)–C≡C–CH$_3$, –C$_2$H$_4$–CH(CH$_3$)–C≡CH, –CH=CH–CH=C(CH$_3$)$_2$, –CH$_2$–CH(CH$_3$)–CH$_2$–C≡CH, –CH=CH–C(CH$_3$)=CH–CH$_3$, –CH=C(CH$_3$)–CH=CH–CH$_3$, –CH$_2$–CH(CH$_3$)–C≡CH, –C(CH$_3$)=CH–CH=CH–CH$_3$, –C≡CH, –C≡C–CH$_3$, –CH$_2$-C≡CH, –C$_2$H$_4$–C≡CH, –CH$_2$–C≡C–CH$_3$, –C≡C–C$_2$H$_5$, –C$_3$H$_6$–C≡CH, –C$_2$H$_4$–C≡C–CH$_3$, –CH$_2$–C≡C–C$_2$H$_5$, –C≡C–C$_3$H$_7$, –CH(CH$_3$)–C≡CH, –C$_4$H$_8$–C≡CH, –C$_2$H$_4$–C≡C–C$_2$H$_5$, –CH$_2$–C≡C–C$_3$H$_7$, –C≡C–C$_4$H$_9$, –C≡C–CH$_2$–CH(CH$_3$)$_2$, –CH(CH$_3$)–C$_2$H$_4$–C≡CH, –CH$_2$–CH(CH$_3$)–C≡C–CH$_3$, –C(CH$_3$)(C$_2$H$_5$)–C≡CH, –CH(CH$_3$)–CH$_2$–C≡C–CH$_3$, –CH(CH$_3$)–C≡C–C$_2$H$_5$, –CH$_2$–C≡C–CH(CH$_3$)$_2$, –C≡C–CH(CH$_3$)–C$_2$H$_5$, –CH$_2$–C≡C–C≡C–CH$_3$, –CH(C$_2$H$_5$)–C≡C–CH$_3$, –C(CH$_3$)$_2$–C≡C–CH$_3$, –CH(C$_2$H$_5$)–CH$_2$–C≡CH, –CH$_2$–CH(C$_2$H$_5$)–C≡CH, –C(CH$_3$)$_2$–CH$_2$–C≡CH, –CH$_2$–C(CH$_3$)$_2$–C≡CH, –CH(CH$_3$)–CH(CH$_3$)–C≡CH, –CH(C$_3$H$_7$)–C≡CH, –CH$_2$–CH(C≡CH)$_2$, –C≡C–C≡CH, –CH$_2$–C≡C–C≡CH, –C≡C–C≡C–CH$_3$, –CH(C≡CH)$_2$, –C$_2$H$_4$–C≡C–C≡CH, –CH$_2$–C≡C–CH$_2$–C≡CH, –C≡C–C$_2$H$_4$–C≡CH, –C≡C–C(CH$_3$)$_3$, –C≡C–CH$_2$–C≡C–CH$_3$, –C≡C–C≡C–C$_2$H$_5$,



Z^3 and Z^4 may form together 

Z^{13} and Z^{14} may form together 

m is an integer selected from 0, 1, 2, 3, 4, 5, or 6;
n is an integer selected from 0, 1, 2, 3, 4, 5, or 6;
p is an integer selected from 0, 1, 2, 3, 4, 5, or 6;
r is an integer selected from 0, 1, 2, 3, or 4;
s is an integer selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;
t is an integer selected from 1, 2, 3, or 4;
u is an integer selected from 1, 2, 3, or 4;
v is an integer selected from 0, 1, 2, 3, 4, 5, or 6;
w is an integer selected from 0, 1, 2, or 3;

or an enantiomer, a stereoisomeric form, a mixture of enantiomers, a diastereomer, a mixture of diastereomers, a hydrate, a solvate, an acid salt form, a tautomer, a racemate of the above mentioned compounds, or a pharmaceutically acceptable salt thereof.

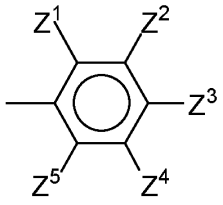
The term “pharmaceutically acceptable salt” refers to a salt of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. The compounds of the present invention may form salts with organic 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 of the compounds of formula (I) with a sufficient amount of

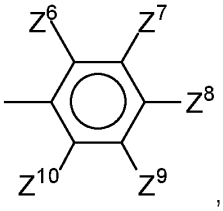
the desired acid to produce a salt in the conventional manner well known to those skilled in the art.

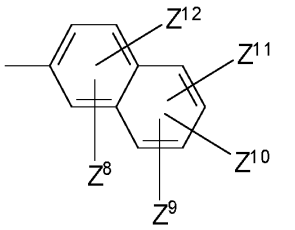
In the case the inventive compounds bear acidic groups, salts could also be formed with inorganic or organic bases. Examples for suitable inorganic or organic bases are, for example, NaOH, KOH, NH_4OH, tetraalkylammonium hydroxide, lysine or arginine and the like. Salts may be prepared in a conventional 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.

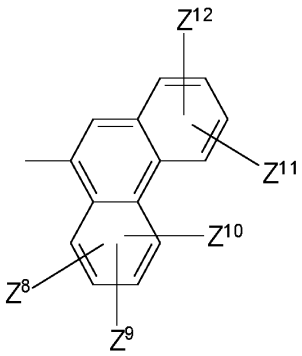
As used herein, the term "**C_6–C_{14}–aryl**" refers to aromatic residues or more specific to aromatic carbocyclic residues with one, two or three aromatic rings and refers preferably to phenyl and naphthyl, wherein these phenyl and naphthyl residues can be substituted with 1 to 5 substituents selected from Z^1 to Z^{12}. However it is clear to a skilled person that the term "can be substituted" refers to the replacement of a hydrogen atom by one of the substituents Z^1 to Z^{12}. The carbon atom number of **C_6–C_{14}** refers only to the carbon atoms of the aromatic ring system (aryl) and does not include the carbon atoms of the substituents Z^1 to Z^{12}.

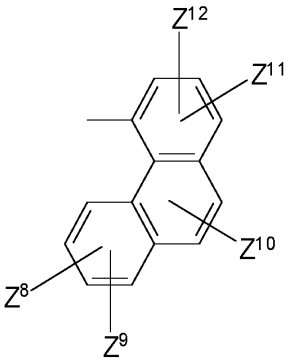
Examples of preferred C_6–C_{14}–aryl groups and substituted C_6–C_{14}–aryl residues are

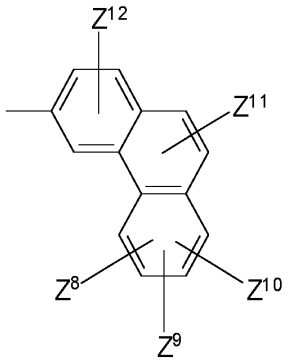


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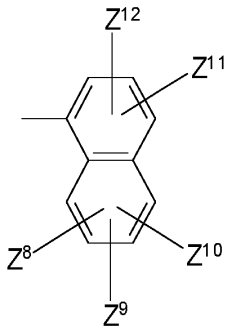
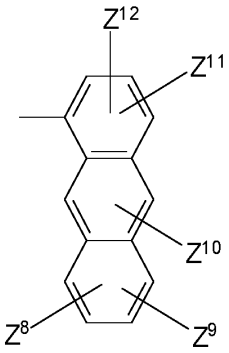
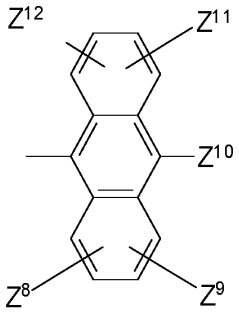
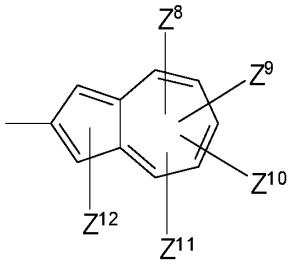
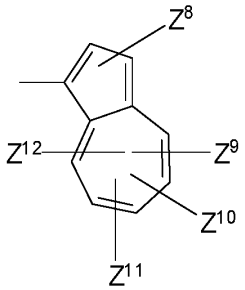
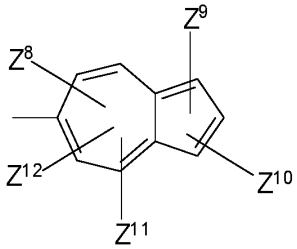
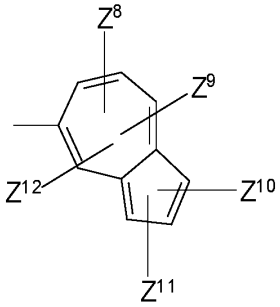
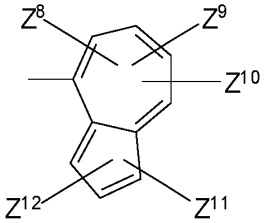
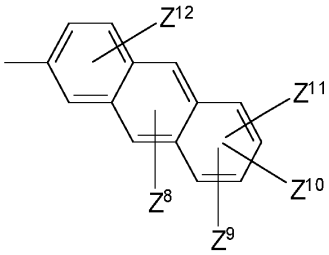
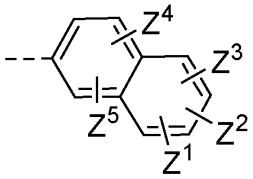
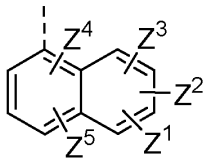
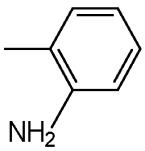
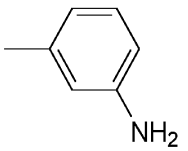
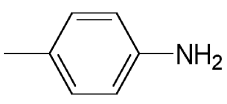
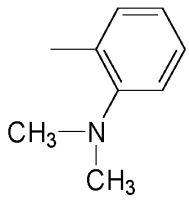
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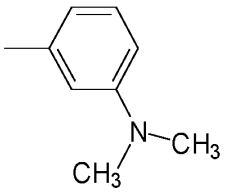
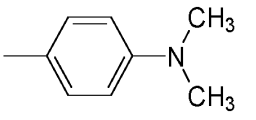
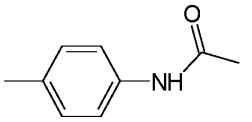
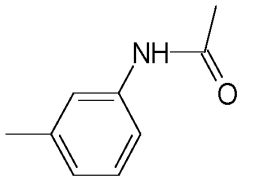
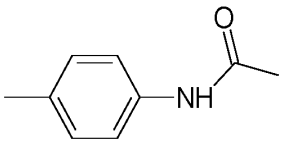
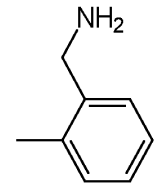
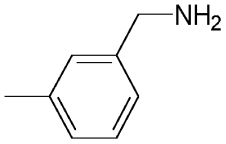
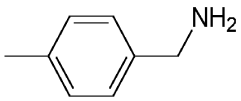
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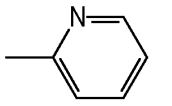
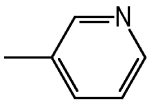
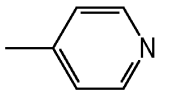
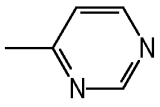
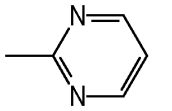
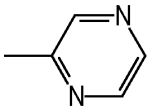
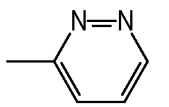
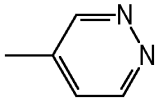
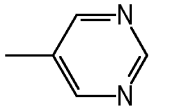
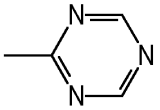
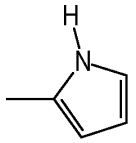
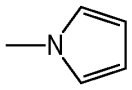
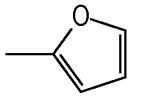
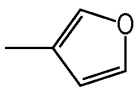
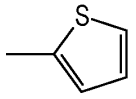
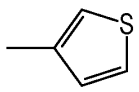
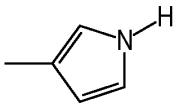
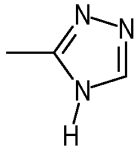
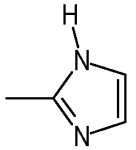
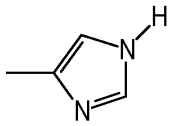
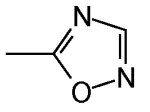
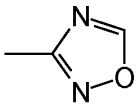
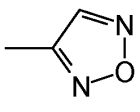
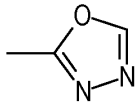
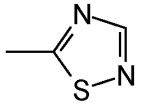
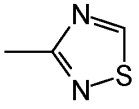
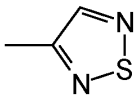
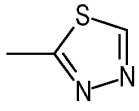
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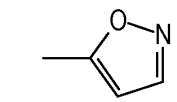
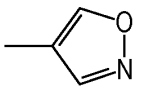
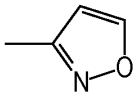
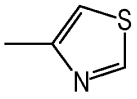
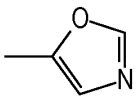
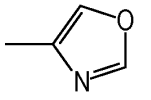
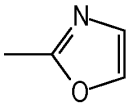
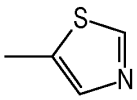
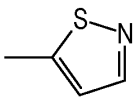
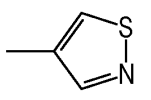
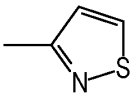
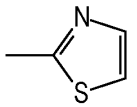
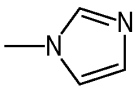
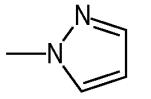
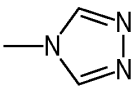
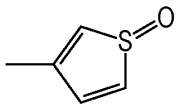
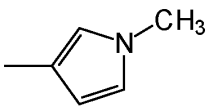
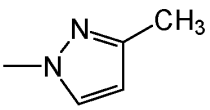
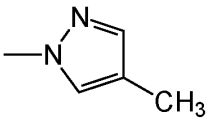
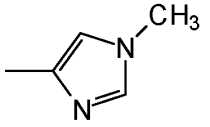
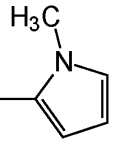
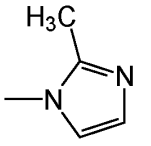
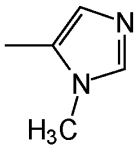
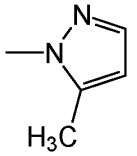
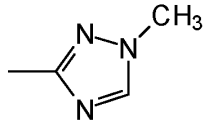
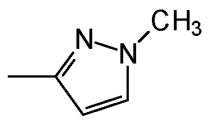
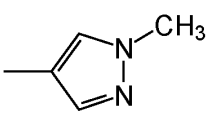
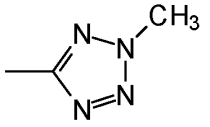
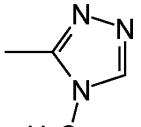
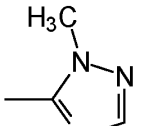
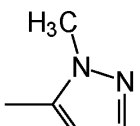
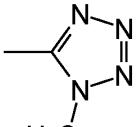
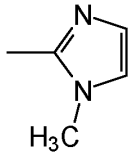
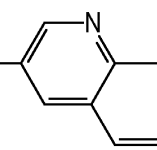
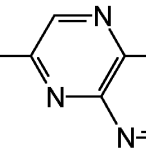
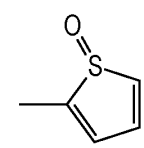
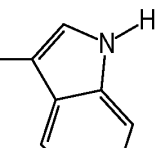
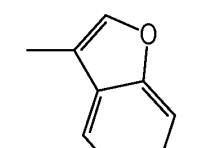
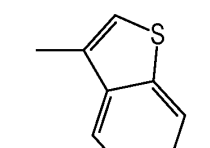
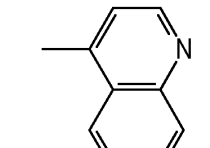
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As used herein, the term "**C_1–C_{10}–heteroaryl**" refers to aromatic residues with one or more heteroatoms such as O, S, N and especially N and refers preferably to

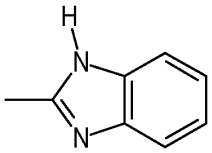
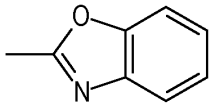
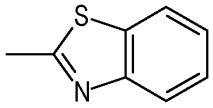
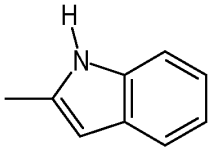
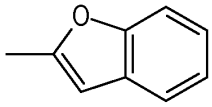
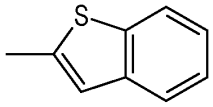
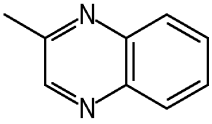
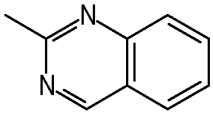
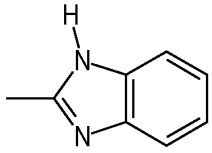
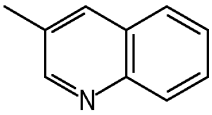
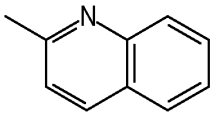
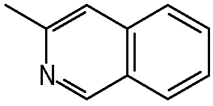
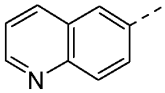
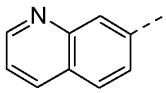
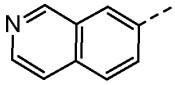
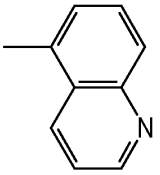
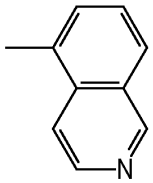
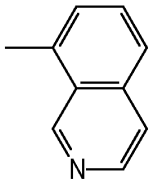
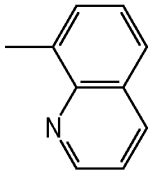
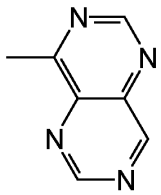
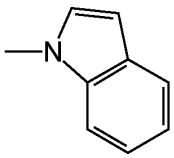
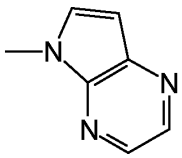
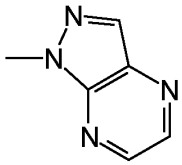
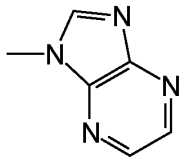
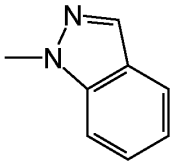
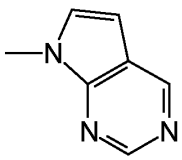
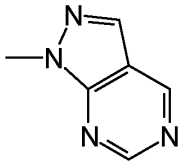
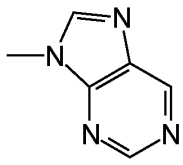
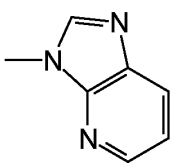
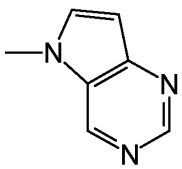
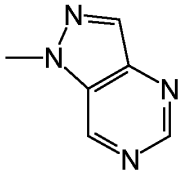
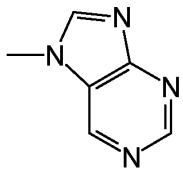

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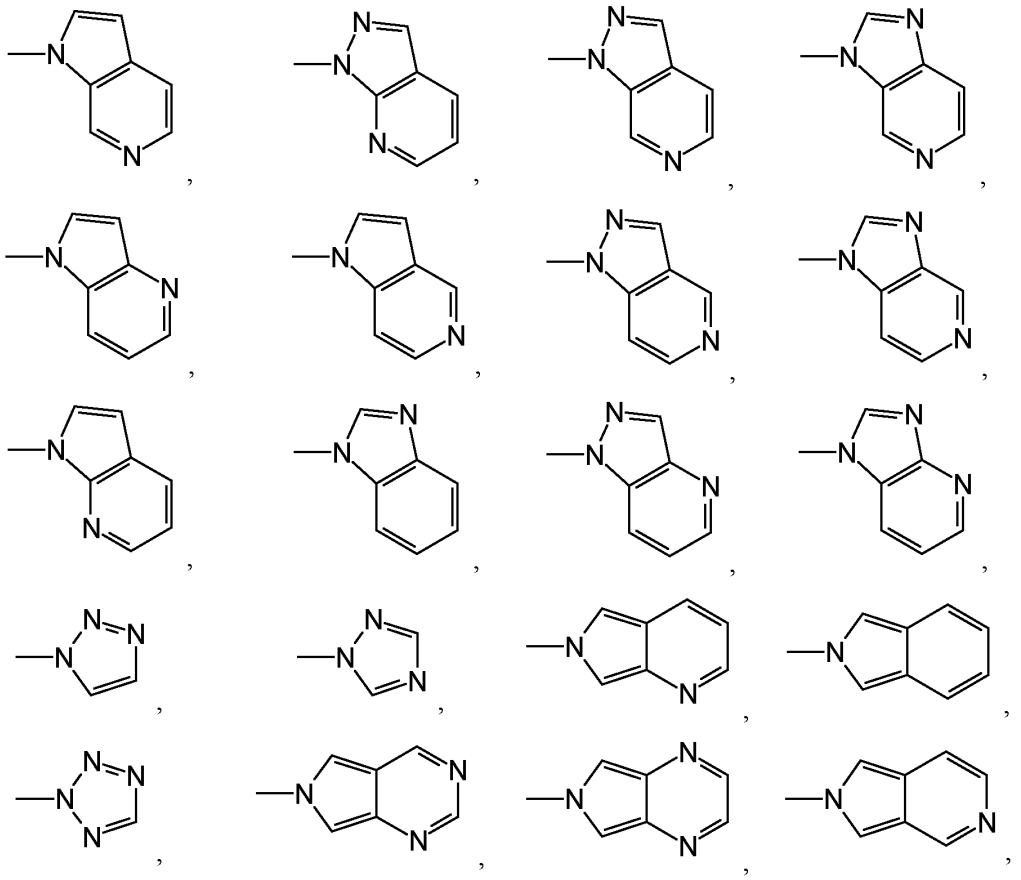
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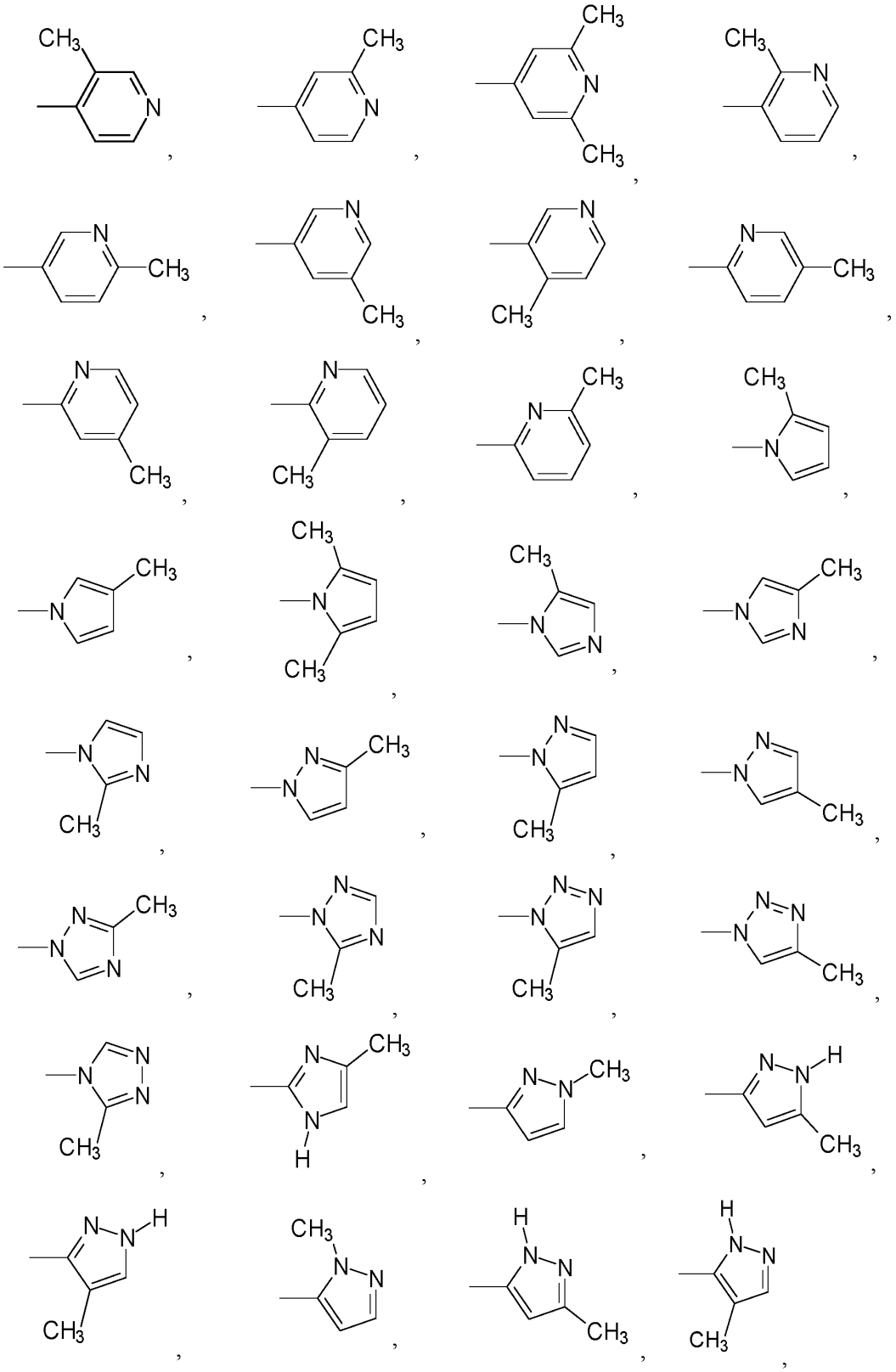
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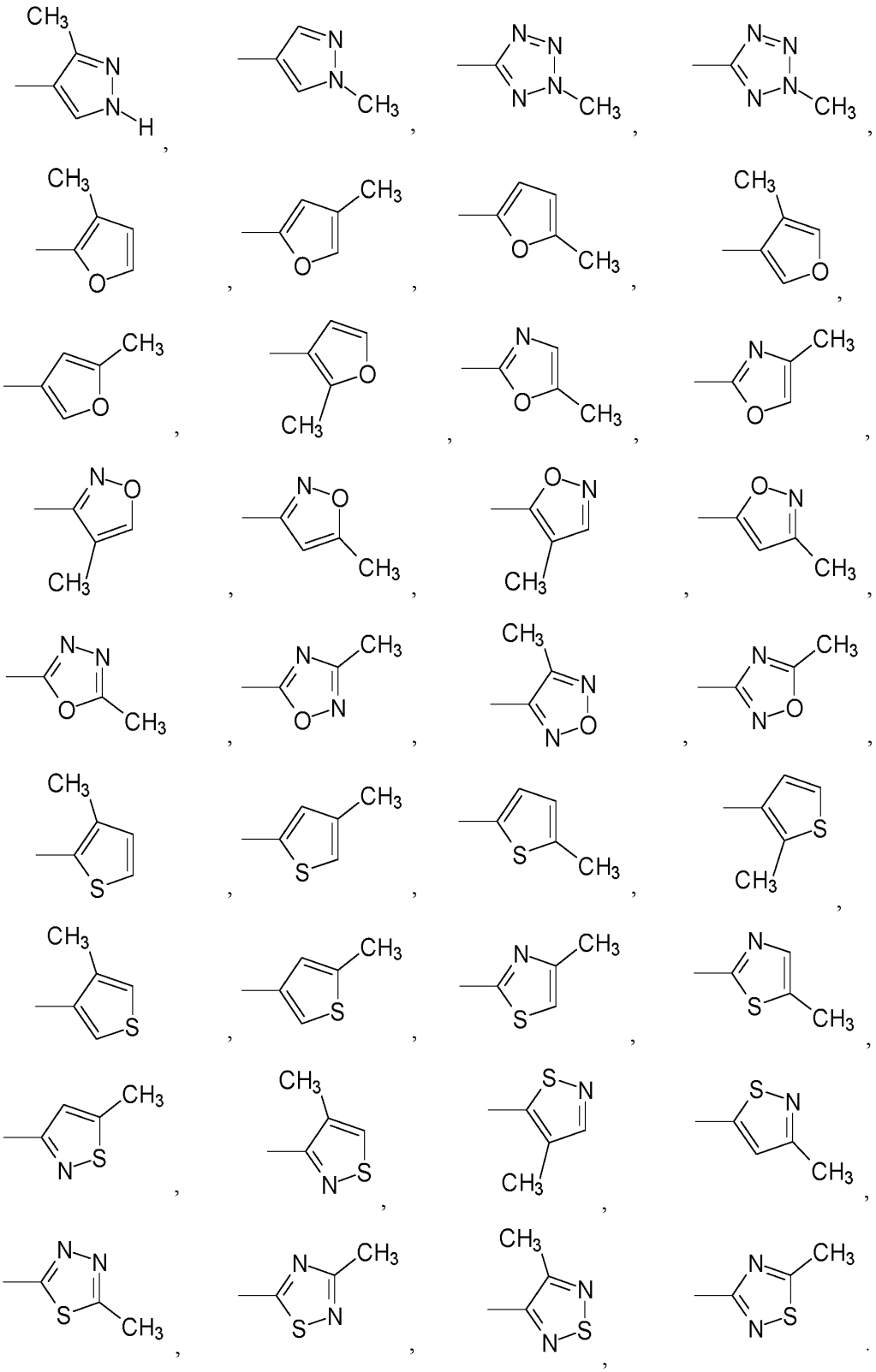

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wherein these residues can be substituted with 1 to 5 substituents selected from R^{N1}, R^{N2}, Z^1 to Z^{12}. However it is clear to a skilled person that the term "can be substituted" refers to the replacement of a hydrogen atom by one of the substituents R^{N1}, R^{N2}, Z^1 to Z^{12}. Moreover it is clear to a skilled person that only these hydrogen atoms which are present in the residue can be replaced by the substituents R^{N1}, R^{N2}, Z^1 to Z^{12}. In case of secondary amine group in these heteroaryl residues, a hydrogen atom of secondary amine group is replaced by the substituent R^{N1} or R^{N2}. Thus, since the oxadiazole group has only one hydrogen atom, only one hydrogen atom can be replaced by one substituent selected from Z^1 to Z^{12}. The carbon atom number of **C_1–C_{10}** refers only to the carbon atoms of the heteroaromatic ring system (heteroaryl) and does not include the carbon atoms of the substituents R^{N1}, R^{N2}, Z^1 to Z^{12}.

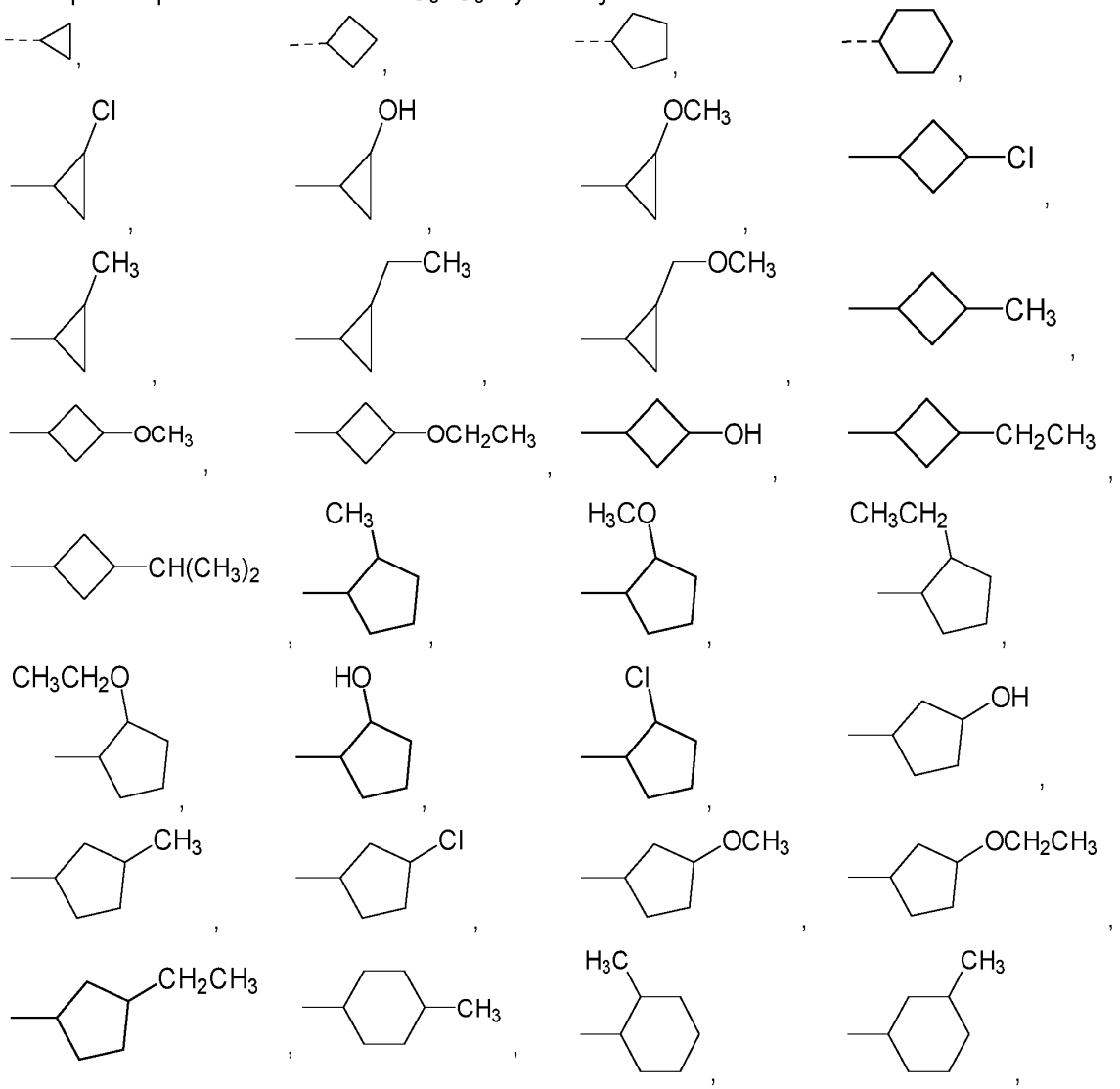
Examples of preferred substituted C_1–C_{10}–heteroaryl residues are

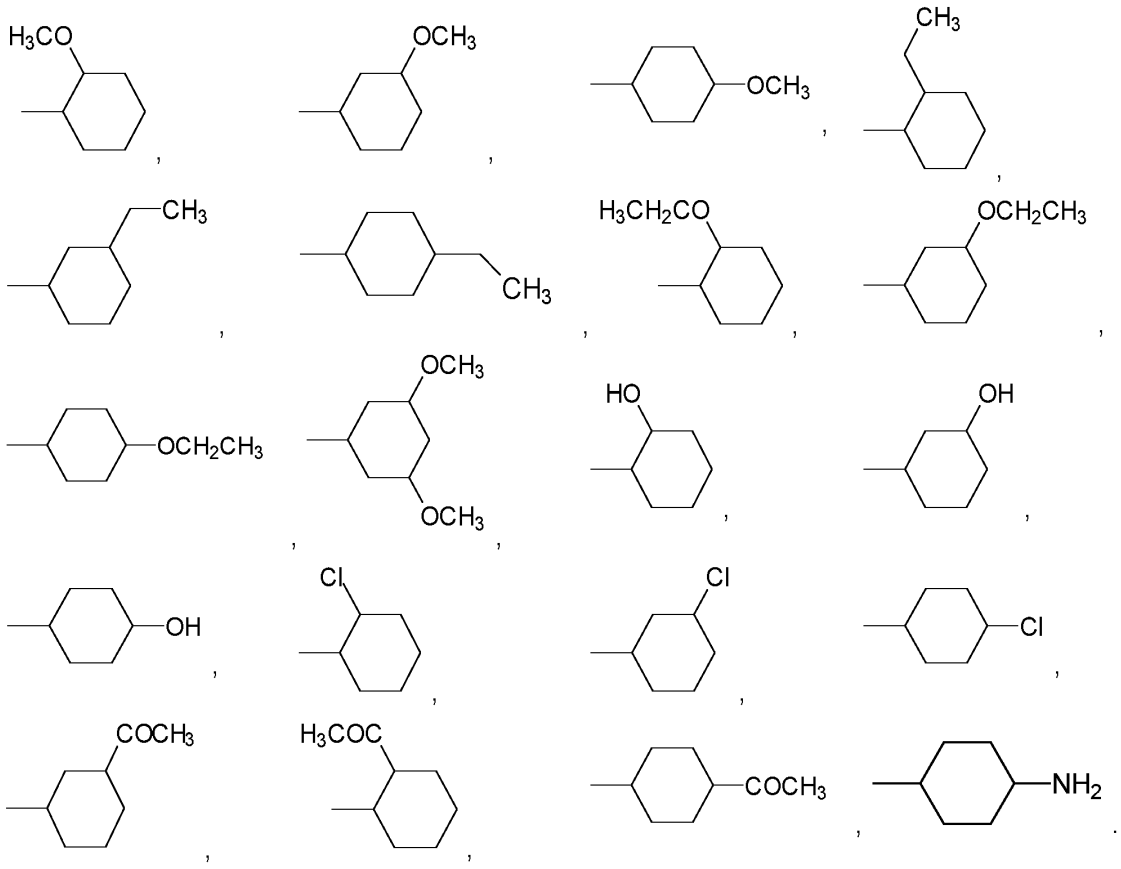




As used herein, **C_3–C_8–carbocyclyl** refers to cyclo-C_3H_5, cyclo-C_4H_7, cyclo-C_5H_9, cyclo-C_6H_{11}, cyclo-C_7H_{13}, and cyclo-C_8H_{15}, wherein these residues can be substituted with 1 to 5 substituents selected from Z^1 to Z^{12}, preferably, Z^1, Z^2, Z^3, Z^4 and Z^5. However it is clear to a skilled person that the term "can be substituted" refers to the replacement of a hydrogen atom by one of the substituents Z^1 to Z^{12}, preferably, Z^1, Z^2, Z^3, Z^4 and Z^5. The carbon atom number of **C_3–C_8** refers only to the carbon atoms of the cycloalkyl residue and does not include the carbon atoms of the substituents Z^1 to Z^{12}.

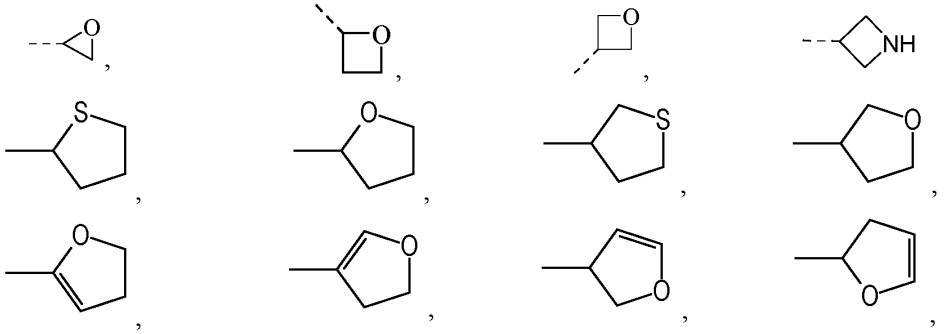
Examples of preferred substituted C_3–C_8–cycloalkyl residues are

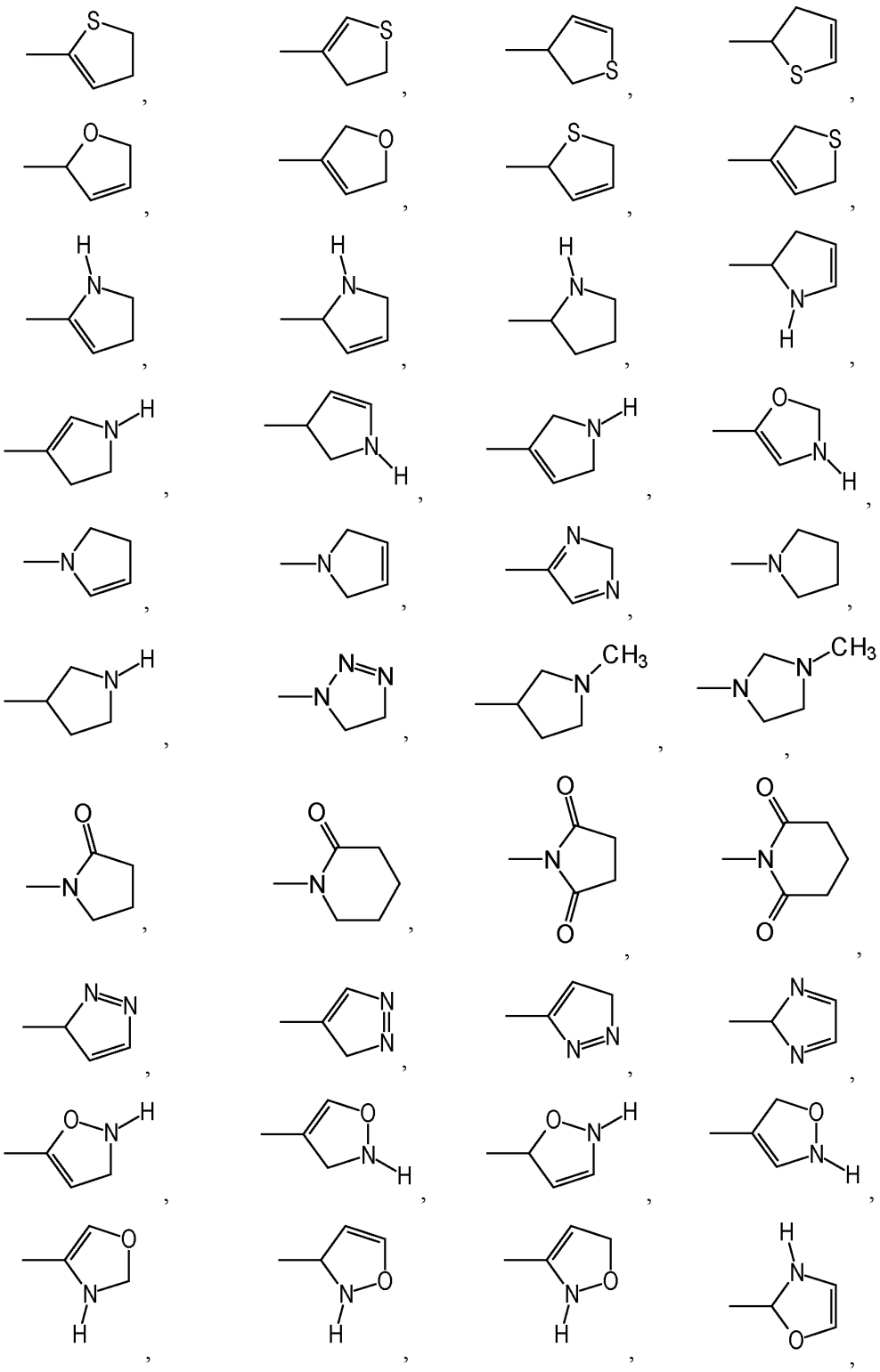


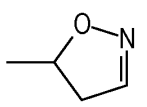
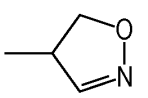
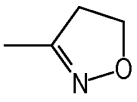
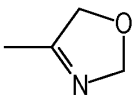
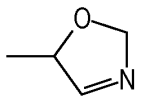
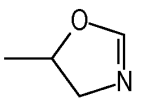
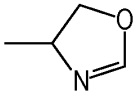
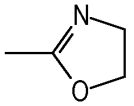
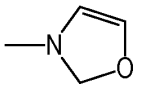
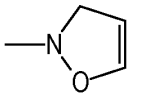
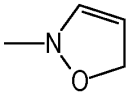
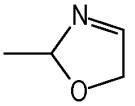
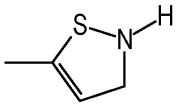
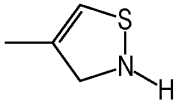
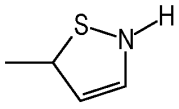
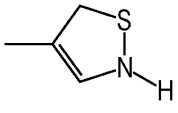
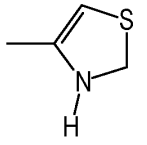
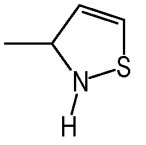
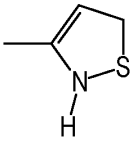
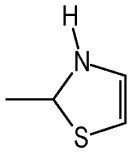
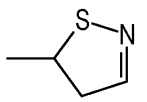
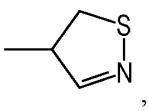
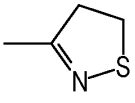
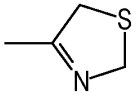
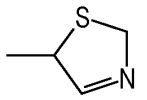
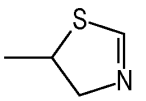
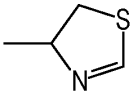
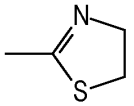
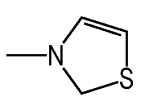
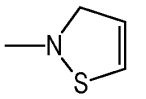
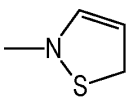
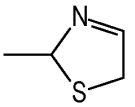
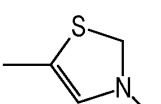
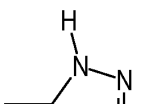
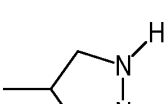
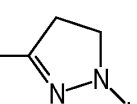
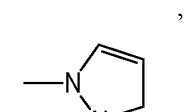
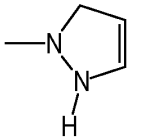
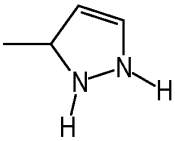
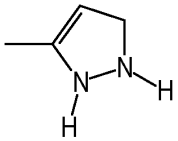
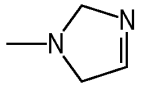
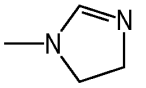
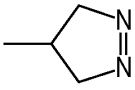
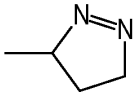


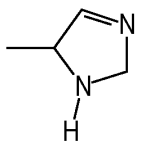
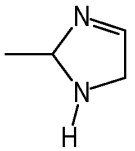
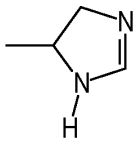
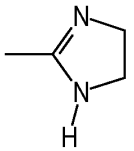
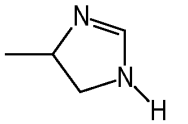
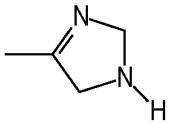
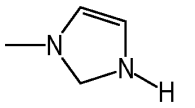
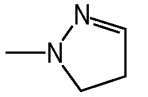
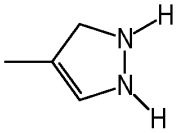
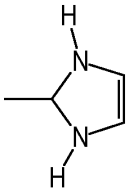
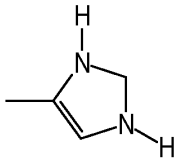
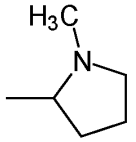
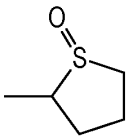
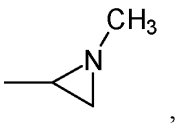
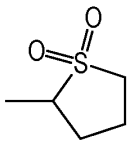
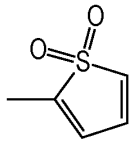
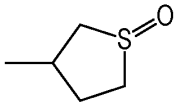
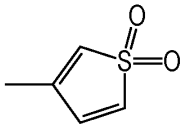
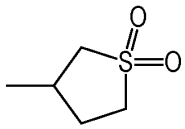
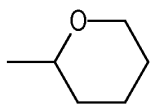
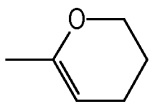
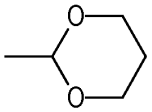
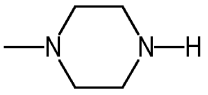
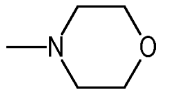
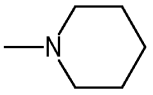
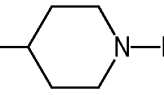
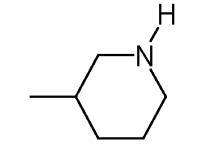
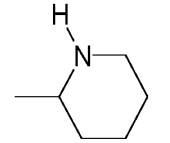
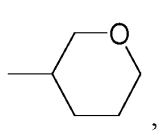
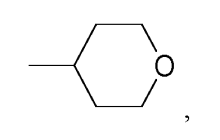
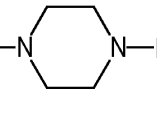
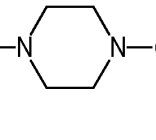
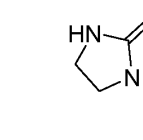
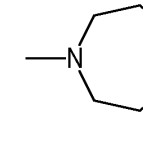
As used herein, the term "**C_1–C_9–heterocyclyl**" covers saturated or partly unsaturated heterocyclic residues with 1 to 9 ring carbon atoms, but not aromatic residues and covers also bicyclic saturated or partly unsaturated residues with 1 to 9 ring carbon atoms, but preferably not fully aromatic residues which are aromatic throughout the bicyclic system but may comprise partly aromatic ring systems, wherein one ring of the bicyclic ring system is aromatic.

Examples of preferred substituted C_1–C_9–heterocyclyl residues are





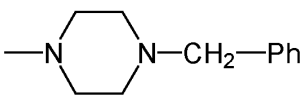
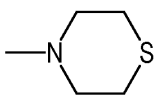
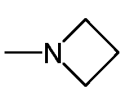
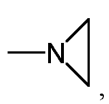
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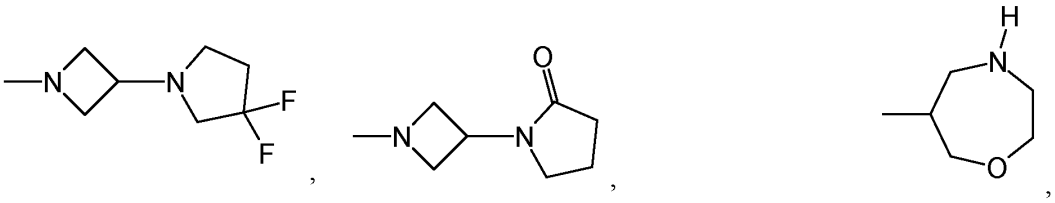

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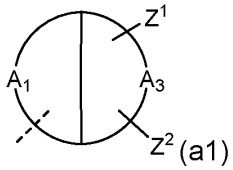
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wherein these residues can be substituted with 1 to 5 substituents selected from R^{N1}, R^{N2}, Z^1 to Z^{12}. However it is clear to a skilled person that the term "can be substituted" refers to the replacement of a hydrogen atom by one of the substituents R^{N1}, R^{N2}, Z^1 to Z^{12}. Moreover it is clear to a skilled person that only these hydrogen atoms which are present in the residue can be replaced by the substituents R^{N1}, R^{N2}, Z^1 to Z^{12}. In case of secondary amine group in these heteroaryl residues, a hydrogen atom of secondary amine group is replaced by the substituent R^{N1} or R^{N2}. Thus, since the oxirane group (also named as ethylene oxide group) has only three hydrogen atoms, only three hydrogen atoms can be replaced by three substituents selected from Z^1 to Z^{12}. The carbon atom number of **C_1–C_9** refers only to the carbon atoms of the heterocyclic ring system (heterocyclyl) and does not include the carbon atoms of the substituents R^{N1}, R^{N2}, Z^1 to Z^{12}.

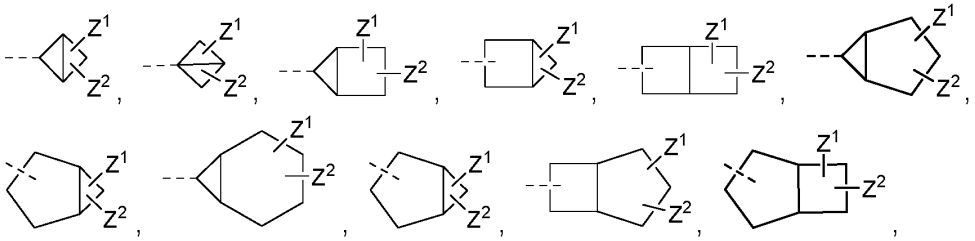
As used herein, **C_4-C_{11} bicyclic carbocyclyl** is represented by generalized formula (**a1**),

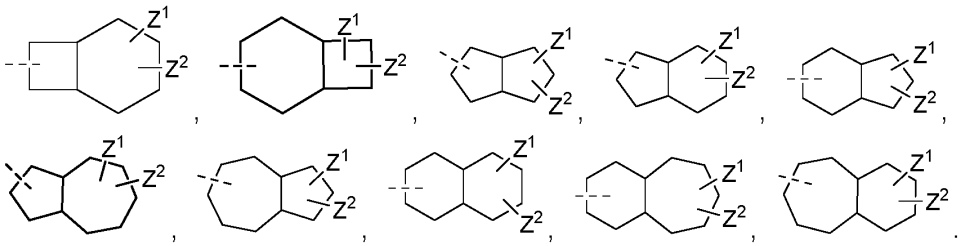


(a1)

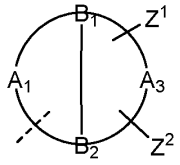
wherein, A_1, and A_3 represent independently C_1-C_7 alkylene; and
C_5-C_{11} bicyclic carbocyclic ring may be optionally substituted with 1 to 5 substituents selected from Z^1 to Z^{12}, preferably substituted by Z^1 and Z^2 and have 0 - 2 double bonds

Examples of preferred C_4-C_{11} bicyclic carbocylcic ring are





As used herein, **C_1–C_{10} bicyclic heterocyclyl** may be represented by generalized formula (**a2**)



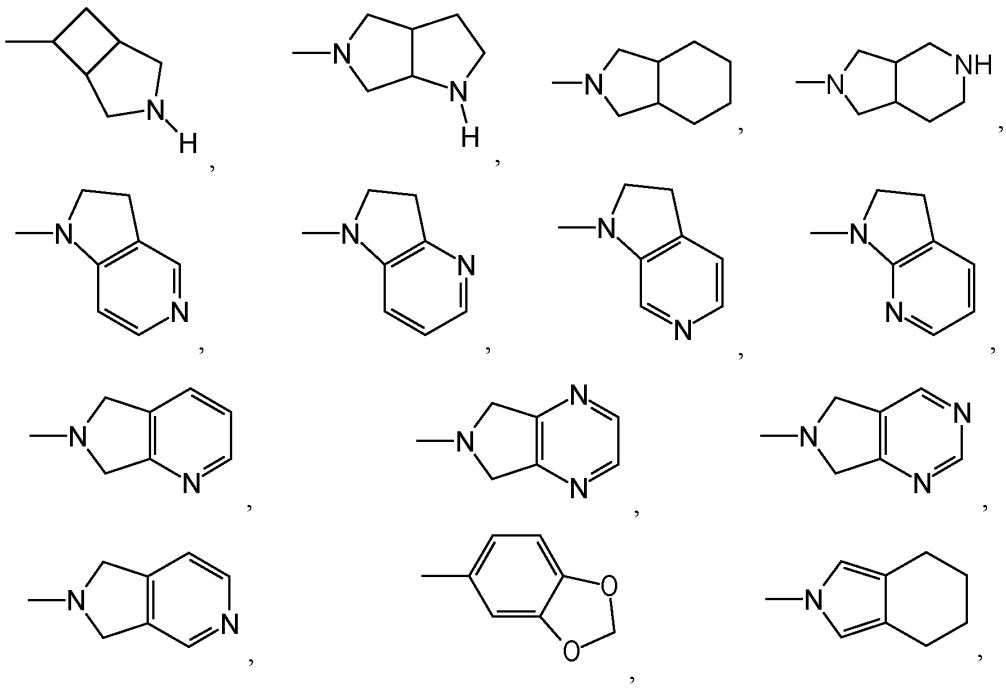
(**a2**)

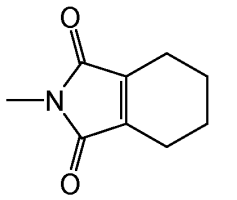
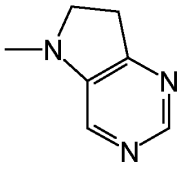
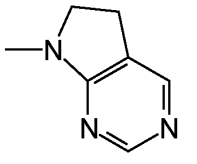
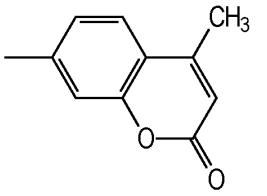
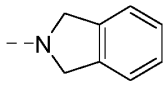
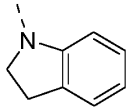
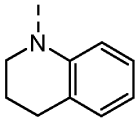
wherein, A_1, and A_3 represent independently C_1-C_5 alkylene and at least one carbon atom of said C_1-C_5 alkylene is replaced with heteroatoms selected from O, N, and S; and

B_1, and B_2 represent independently CH, or N;

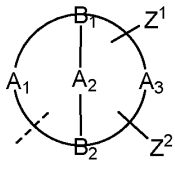
C_5-C_{11} bicyclic heterocylcic ring may be optionally substituted with 1 to 5 substituents selected from Z^1 to Z^{12}, R^{N1} and R^{N2}, preferably substituted by Z^1, Z^2 and R^{N1}, and have 0 – 3 double bonds.

Examples of preferred C_5-C_{11} bicyclic heterocyclic ring are

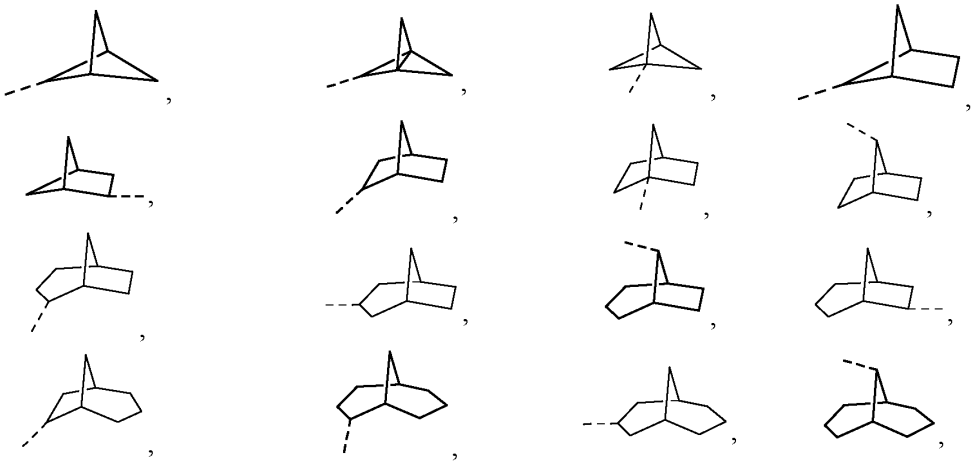


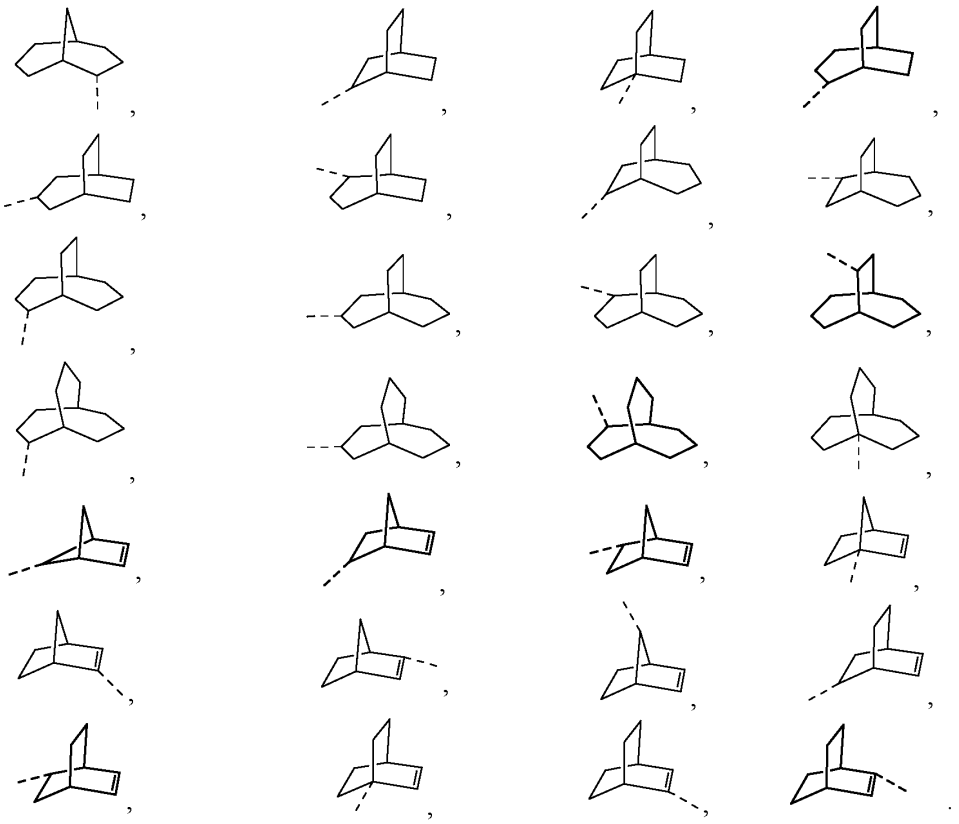

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As used herein, **C_4-C_{11} bridged carbocyclyl** may be represented by generalized formula (**b1**)

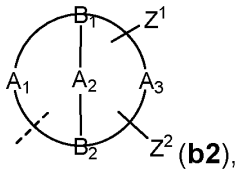

(**b1**),

wherein A_1, A_2, and A_3 represent independently C_1-C_3 alkylene; and
B_1, B_2, represent independently CH, or B_1 and B_2 form a bond;
C_4-C_{11} bridged carbocylcic ring may be optionally substituted with 1 to 5 substituents selected from Z^1 to Z^{12}, preferably substituted by Z^1 and Z^2 and have 0 – 2 double bonds.





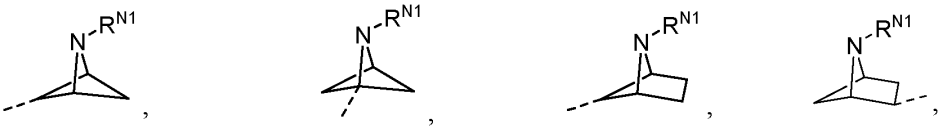
As used herein, **C_1–C_{10} bridged heterocylyl** may be represented by generalized formula (**b2**)

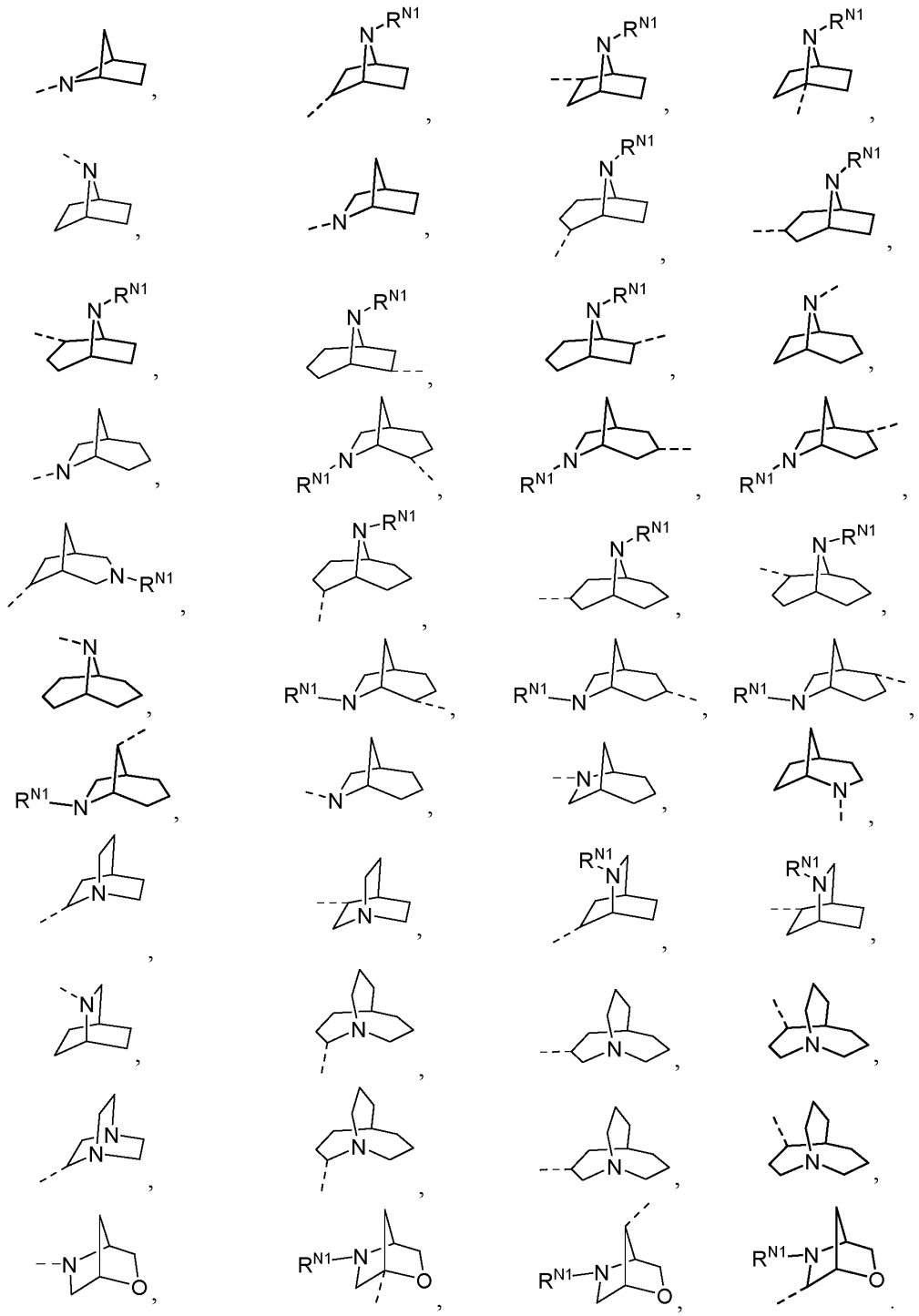


(**b2**),

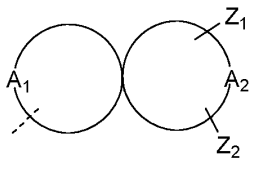
wherein, A_1, A_2, and A_3 represent independently C_1-C_3 alkylene and at least one carbon atom of said C_1-C_3 alkylene is replaced with heteroatoms selected from O, N, and S; and B_1, and B_2, represent independently CH, or N;

C_5-C_{11} bridged heterocyclyl ring may be optionally substituted with 1 to 5 substituents selected from Z^1 to Z^{12}, R^{N1} and R^{N2}, preferably substituted by Z^1, Z^2 and R^{N1}, and have 0 – 2 double bonds.





As used herein, **C_7–C_{16}–spiroalkyl** may be represented by generalized formula (**b3**)

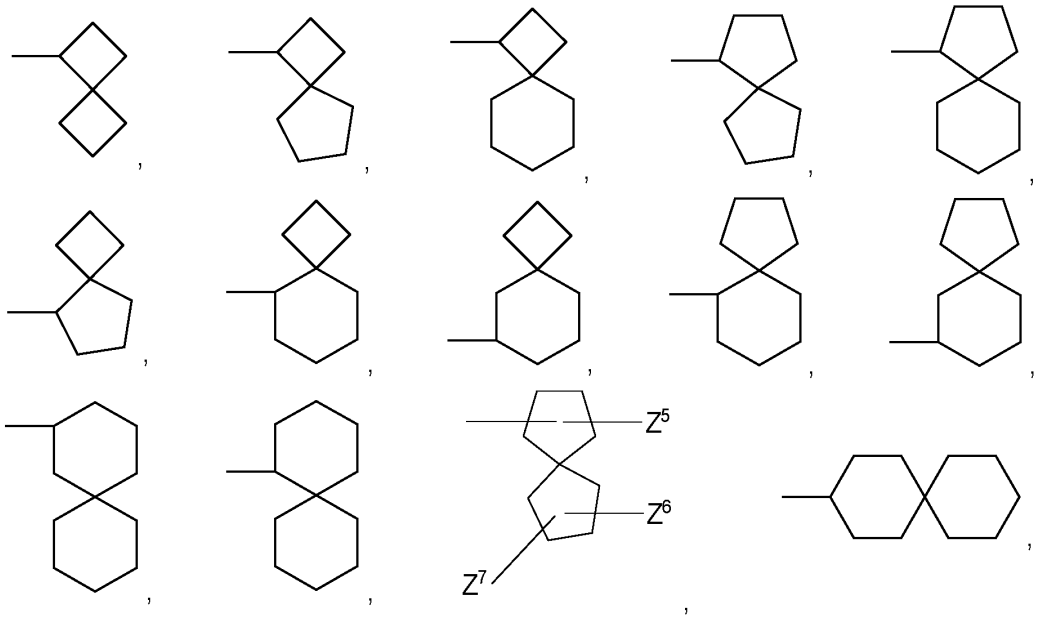


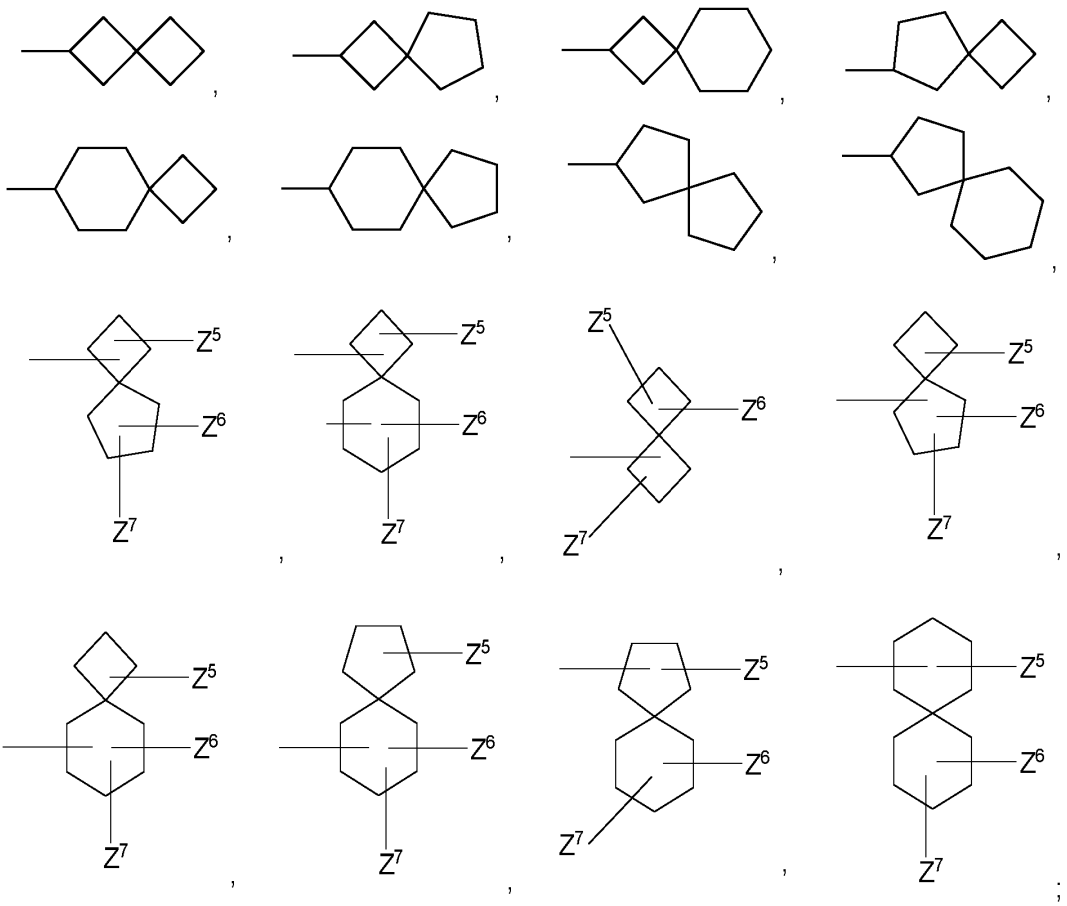
(**b3**)

wherein A_1, and A_2, represent independently C_2-C_7 alkylene; and
C_7-C_{16} spiroaklyl may be optionally substituted with 1 to 5 substituents selected from Z^1 to Z^{12}, preferably substituted by Z^1 – Z^3 , or by Z^5 – Z^7 and have 0 – 2 double bonds.

As used herein, the term "**C_7–C_{16}–spiroalkyl**" refers to spirocarbocyclic residues, wherein these spirocarbocyclic residues can be substituted with 1 to 3 substituents selected from Z^1, Z^2, Z^3, Z^5, Z^6 and Z^7. However it is clear to a skilled person that the term "can be substituted" refers to the replacement of a hydrogen atom by one of the substituents Z^1, Z^2, Z^3, Z^5, Z^6 and Z^7. It is also possible that two of the substituents Z^1, Z^2, Z^3, Z^5, Z^6 and Z^7 represent together an oxygen atom and form together with the carbon atom of the spiroalkyl residue to which they are both attached a carbonyl moiety. The carbon atom number of **C_7–C_{16}** refers only to the carbon atoms of the spiro ring system and does not include the carbon atoms of the substituents. Thus a spiro[4,5]decyl residue is counted as a C_{10}–spiroalkyl regardless if this spiro residue carries five pentyl substituents.

Examples of preferred C_7–C_{16}–spiroalkyl groups and substituted C_7–C_{16}–spiroalkyl groups are

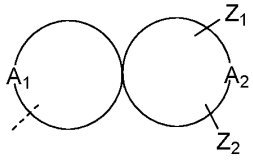




preferred substituents Z^5, Z^6 and Z^7 are –H, $–CH_3$, $–C_2H_5$, $–C_3H_7$, $–CH(CH_3)_2$, –OH, $–OCH_3$, $–OC_2H_5$, $–OC_3H_7$, $–NH_2$, $–N(CH_3)_2$, –F, –Cl, –Br, –I, –CN, $–CH_2F$, $–CHF_2$, $–CF_3$, $–OCHF_2$, $–OCF_3$, more preferably, at least one of Z^5, Z^6 and Z^7 is not –H.

Of course, instead of Z^5 – Z^7 , Z^1 - Z^3 can be substituted and Z^1 - Z^3 have the same meanings of as defined in of Z^5 – Z^7.

As used herein, the term „**C_5–C_{14}–spiroheterocyclyl**" may be represented by generalized formula (**b4**)



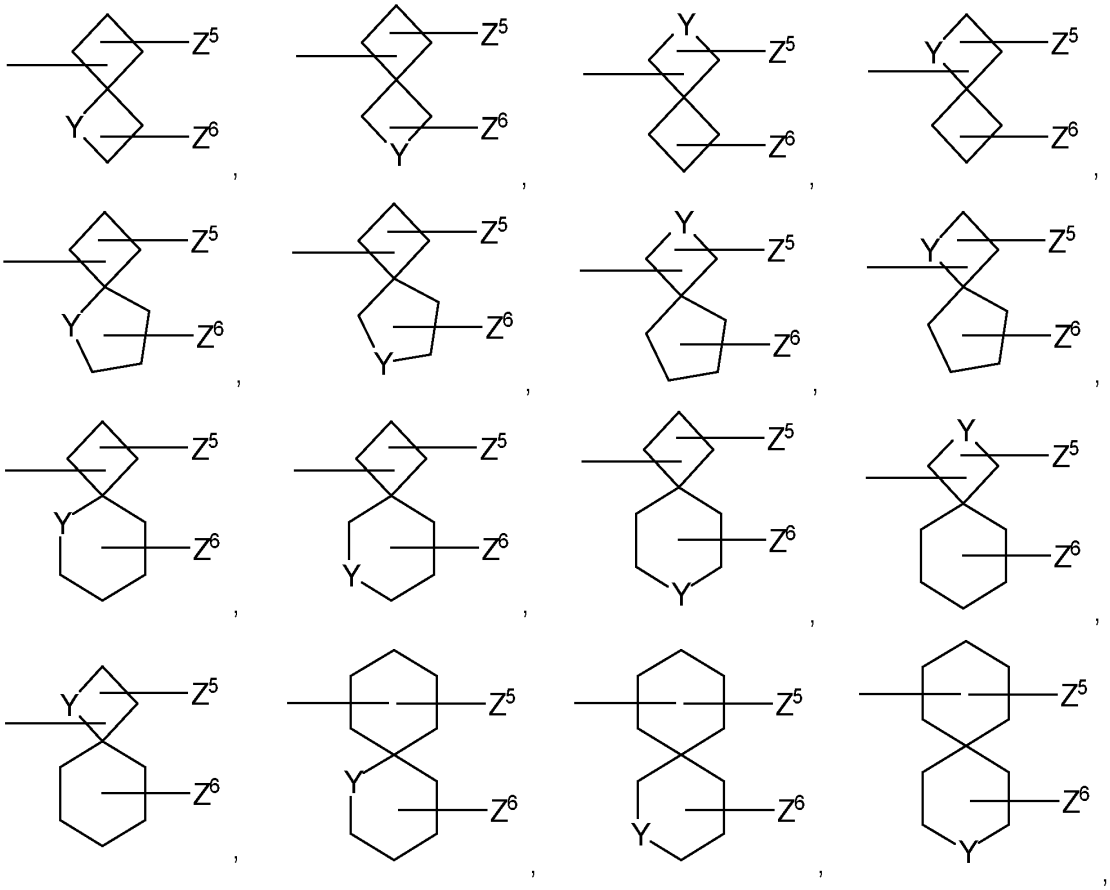
(**b4**)

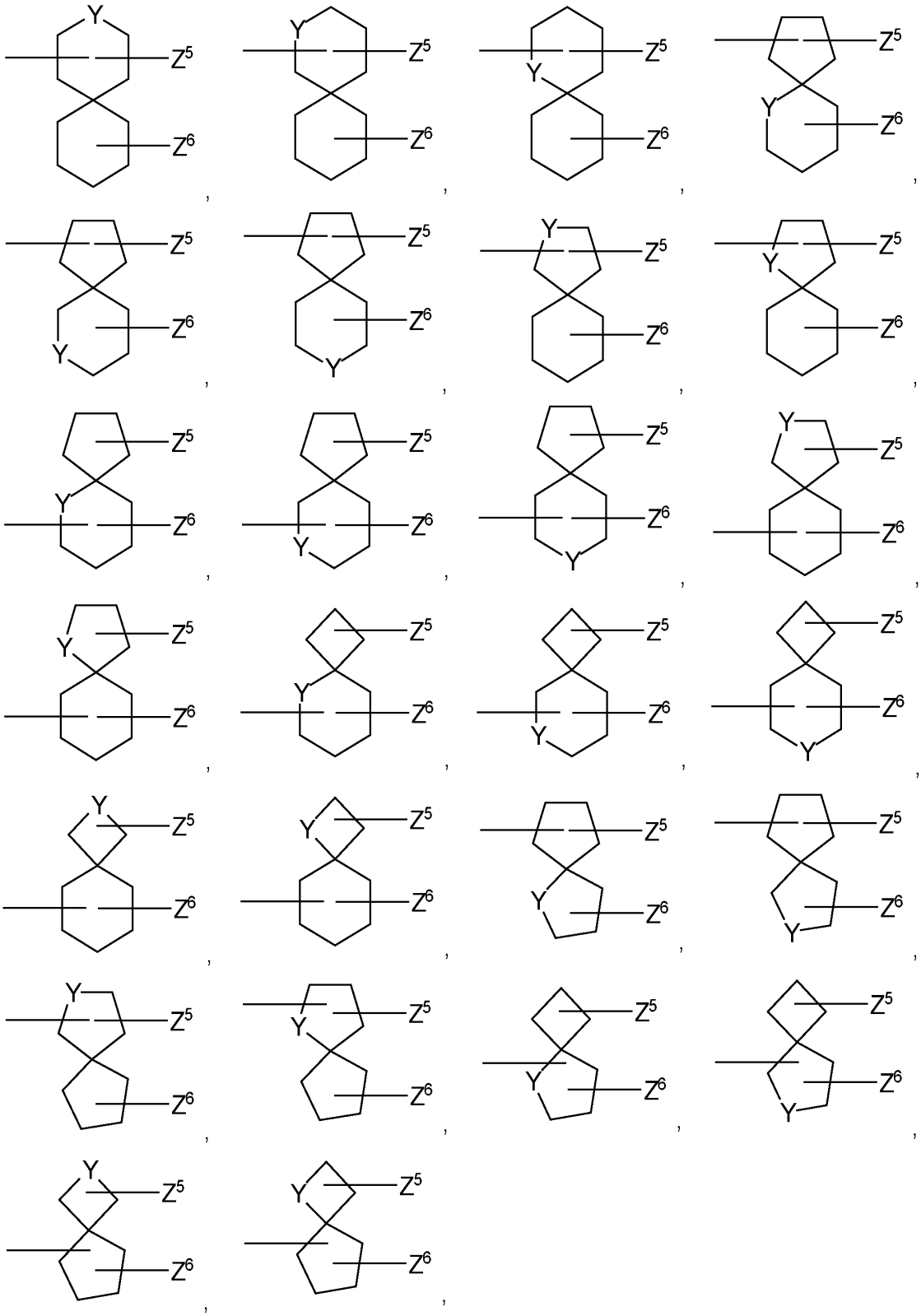
wherein A_1, and A_2, represent independently C_2-C_6 alkylene and at least one carbon atom of said C_2-C_6 alkylene is replaced with heteroatoms selected from O, N, and S; and

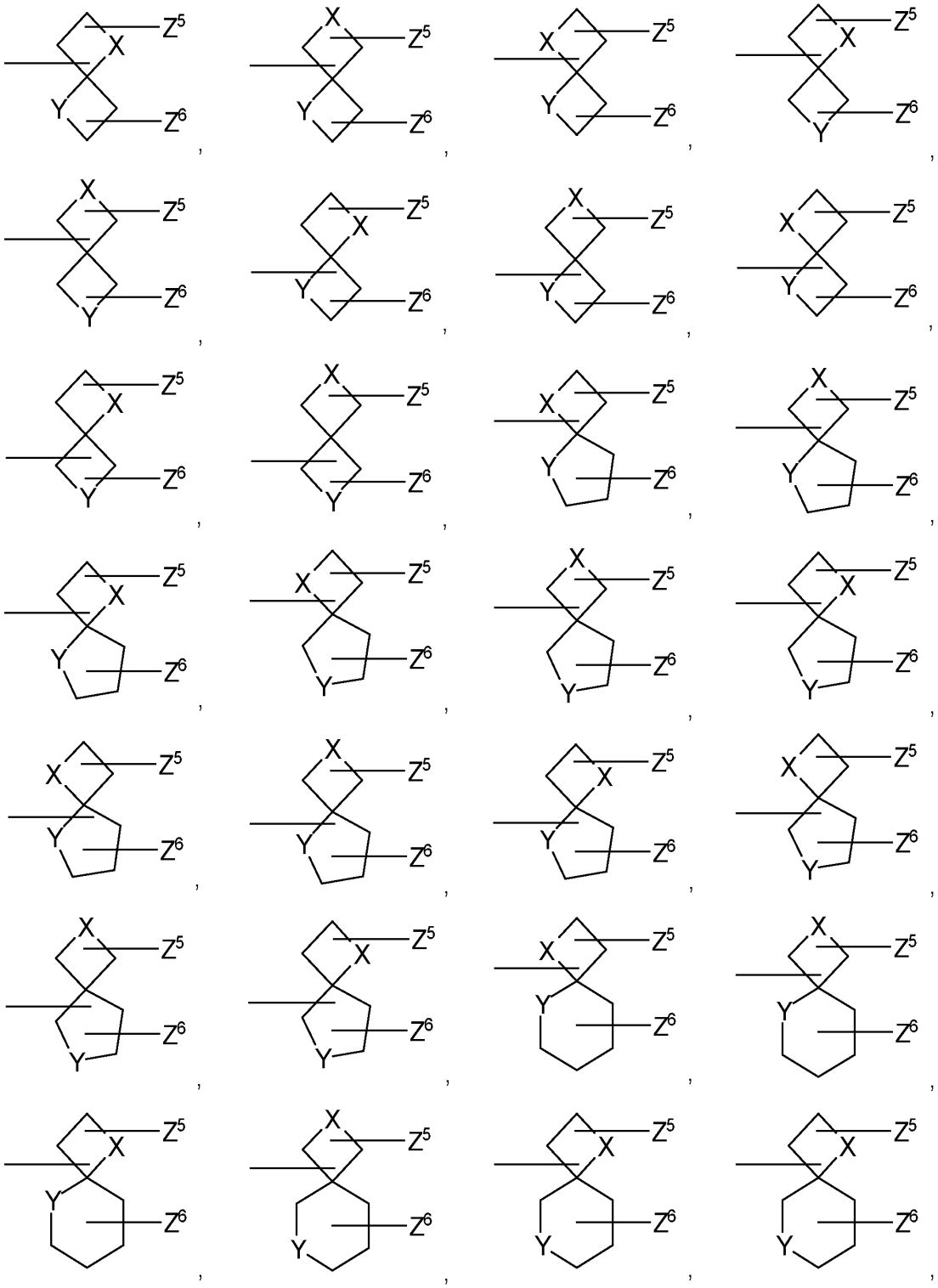
C_5-C_{14} spiroheterocyclyl ring may be optionally substituted with 1 to 5 substituents selected from Z^1 to Z^{12}, R^{N1} and R^{N2}, preferably substituted by R^{N1}, Z_1 and Z^2 and have 0 - 2 double bonds.

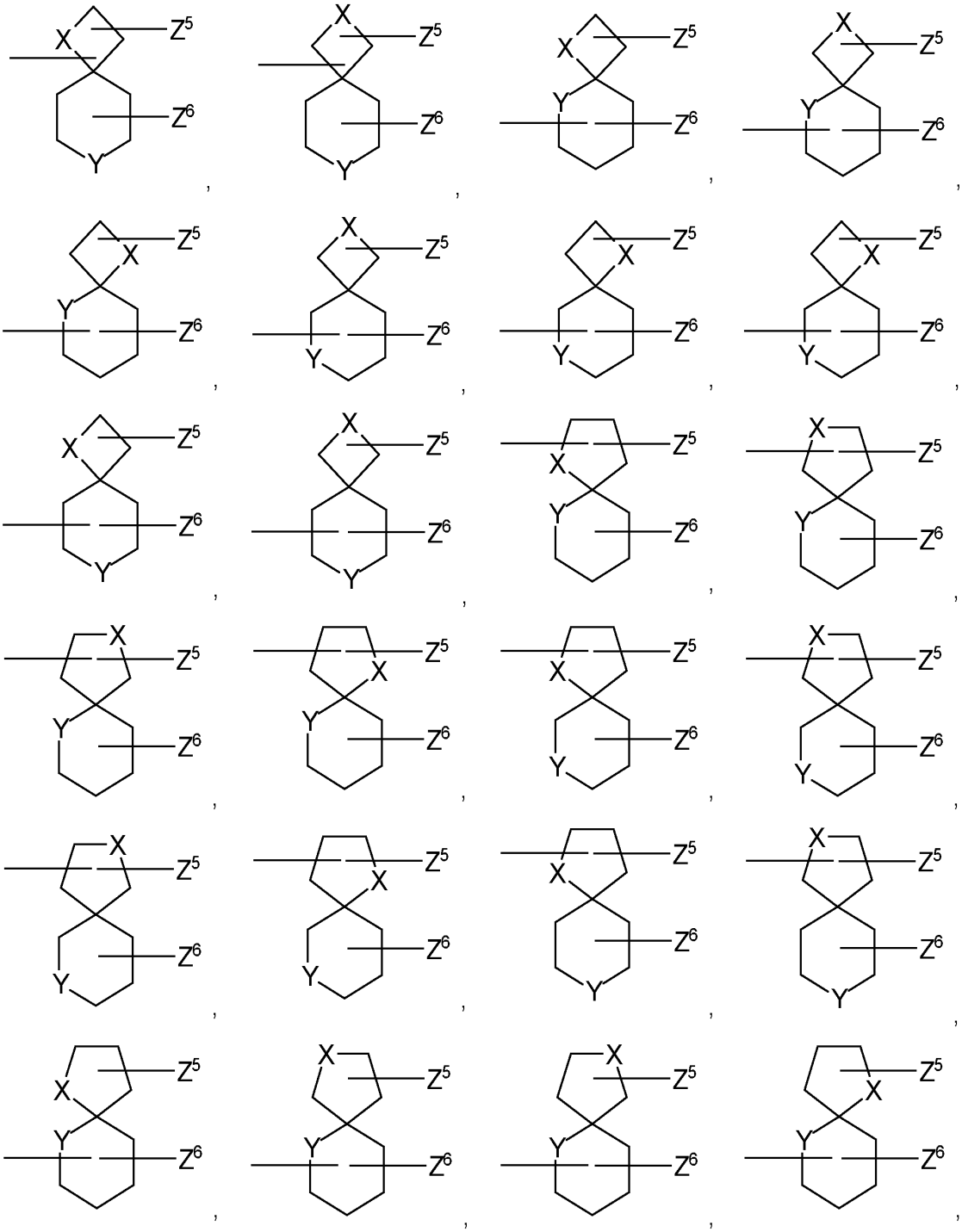
As used herein, the term "**C_5–C_{14}–spiroheterocyclyl**" refers to spiro residues with one, two or three heteroatoms such as O, S, N in the spiro ring system, wherein these spiroheterocyclic residues can be optionally substituted with 1 to 5 substituents selected from Z^1 to Z^{12}, R^{N1} and R^{N2}, preferably substituted with 1 to 3 substituents selected from R^{N1}, Z^1, Z^2, Z^3, Z^5, Z^6 and Z^7. However it is clear to a skilled person that the term "can be substituted" refers to the replacement of a hydrogen atom by one of the substituents R^{N1}, Z^5, Z^6 and Z^7. The carbon atom number of **C_5–C_{14}** refers only to the carbon atoms of the spiro ring system and does not include the carbon atoms of the substituents. Thus, a azaspiro[4,5]decyl residue is counted as a C_9–spiroalkyl regardless if this azaspiro[4,5]decyl residue carries five isopropyl substituents.

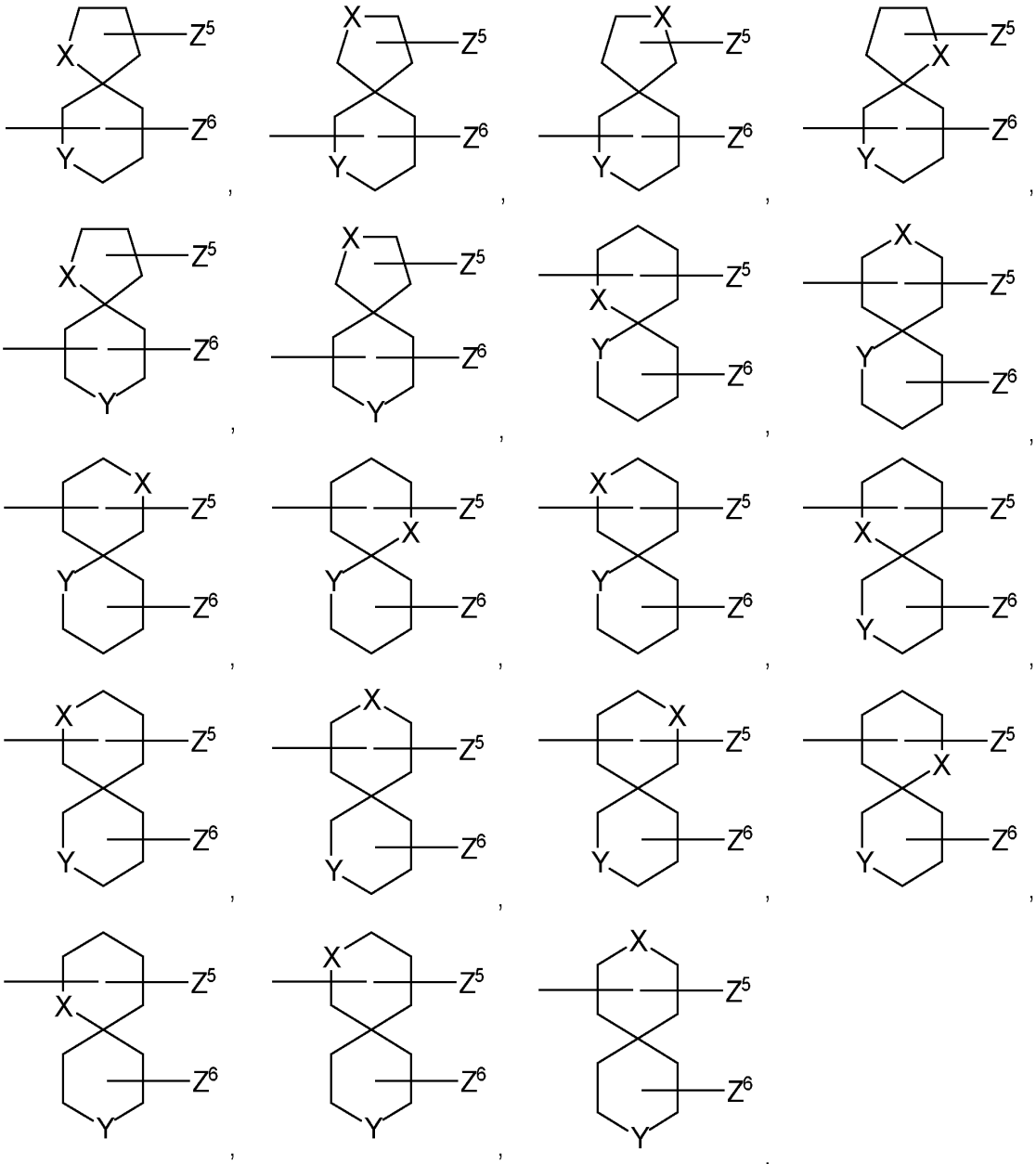
Examples of preferred C_5–C_{14}–spiroheterocyclyl groups and substituted C_5–C_{14}–spiroheterocyclyl groups are




Y
Z5
Z6



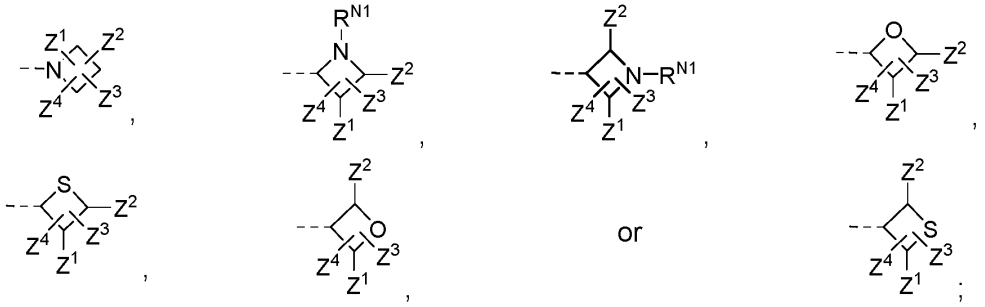




wherein Y and X represent independently of each other –O–, –NH–, –NR^{N1}–, –SO–, or –SO_2–, preferably –NH– or –NR^{N1}–, and Z^5 and Z^6 represent independently of each other –H, –CH_3, –C_2H_5, –C_3H_7, –$CH(CH_3)_2$, –OH, –OCH_3, –OC_2H_5, –OC_3H_7, –NH_2, –$N(CH_3)_2$, –F, –Cl, –Br, –I, –CN, –CH_2F, –CHF_2, –CF_3, –$OCHF_2$, or –OCF_3, more preferably, at least one of Z^5, and Z^6 is not –H.

Of course, instead of Z^5 and Z^6 , Z^1 and Z^2 can be substituted and Z^1 and Z^2 have the same meanings of as defined in of Z^5 and Z^6.

Examples of preferred 4-membered heterocyclic groups and substituted 4-membered heterocyclic groups for **R**[8], **R**[9], and **R**[14] are

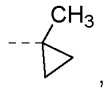


or

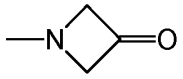
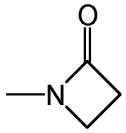
;

Preferably Z^1 to Z^4 represent independently of each other –H, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, –OH, $-OCH_3$, $-OC_2H_5$, $-OC_3H_7$, $-NH_2$, $-N(CH_3)_2$, –F, –Cl, –Br, –I, –CN, $-CH_2F$, $-CHF_2$, $-CF_3$, $-OCHF_2$, or $-OCF_3$, more preferably, at least one of Z^1 to Z^4 is not –H.

Preferred substituents for R^{N1} are -**R**[15], –H, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $-CHF_2$, $-CF_3$,



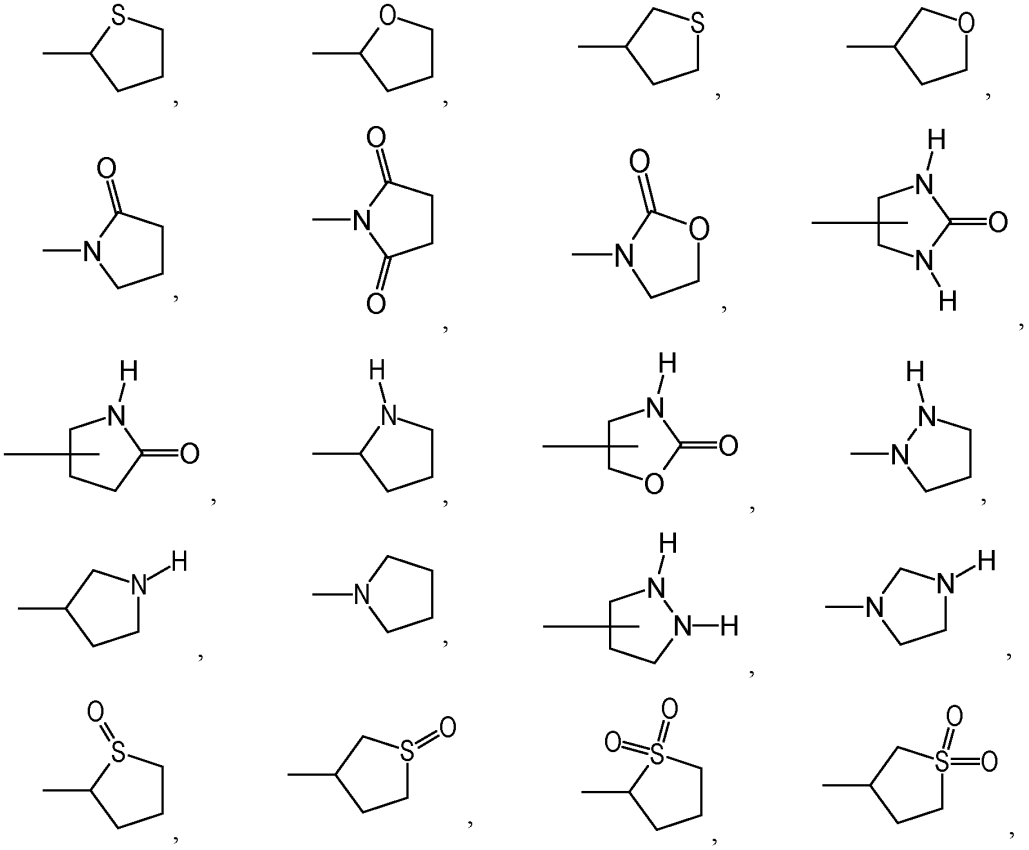
cyclo-C_3H_5, cyclo-C_4H_7, cyclo-C_5H_9, cyclo-C_6H_{11}, cyclo-C_7H_{13}, $-C_4H_9$, $-CH_2-CH(CH_3)_2$, $-CH(CH_3)-C_2H_5$, $-C(CH_3)_3$, $-C_5H_{11}$, $-CH(CH_3)-C_3H_7$, $-CH_2-CH(CH_3)-C_2H_5$, $-CH(CH_3)-CH(CH_3)_2$, $-C(CH_3)_2-C_2H_5$, $-CH_2-C(CH_3)_3$, $-CH(C_2H_5)_2$, $-C_2H_4-CH(CH_3)_2$, $-C_6H_{13}$, $-C_7H_{15}$, $-C_8H_{17}$, –Ph, $-CH_2$–Ph, $-CH_2-CH_2$–Ph, $-C_2H_4-CH=CH_2$, $-CH_2-CH=CH-CH_3$, $-CH_2-C(CH_3)=CH_2$, $-CH(CH_3)-CH=CH_2$, $-CH_2-CH=C(CH_3)_2$, $-CH_2$-C≡CH, $-C_2H_4-C\equiv CH$, $-CH_2-C\equiv C-CH_3$, $-COCH_3$, $-COC_2H_5$, $-COC_3H_7$, –CO–cyclo-C_3H_5, $-COCH(CH_3)_2$, $-COC(CH_3)_3$, –COOH, $-COOCH_3$, $-COOC_2H_5$, $-COOC_3H_7$, –COO–cyclo-C_3H_5, $-COOCH(CH_3)_2$, $-COOC(CH_3)_3$, $-COOCH_2Ph$, $-CONH_2$, $-CONHCH_3$, $-CONHC_2H_5$, $-CONHC_3H_7$, –CONH–cyclo-C_3H_5, $-CONH[CH(CH_3)_2]$, $-CONH[C(CH_3)_3]$, $-CON(CH_3)_2$, $-CON(C_2H_5)_2$, $-CON(C_3H_7)_2$, $-CON(\text{cyclo-}C_3H_5)_2$, $-CON[CH(CH_3)_2]_2$, $-CON[C(CH_3)_3]_2$, or $-SO_3H$.

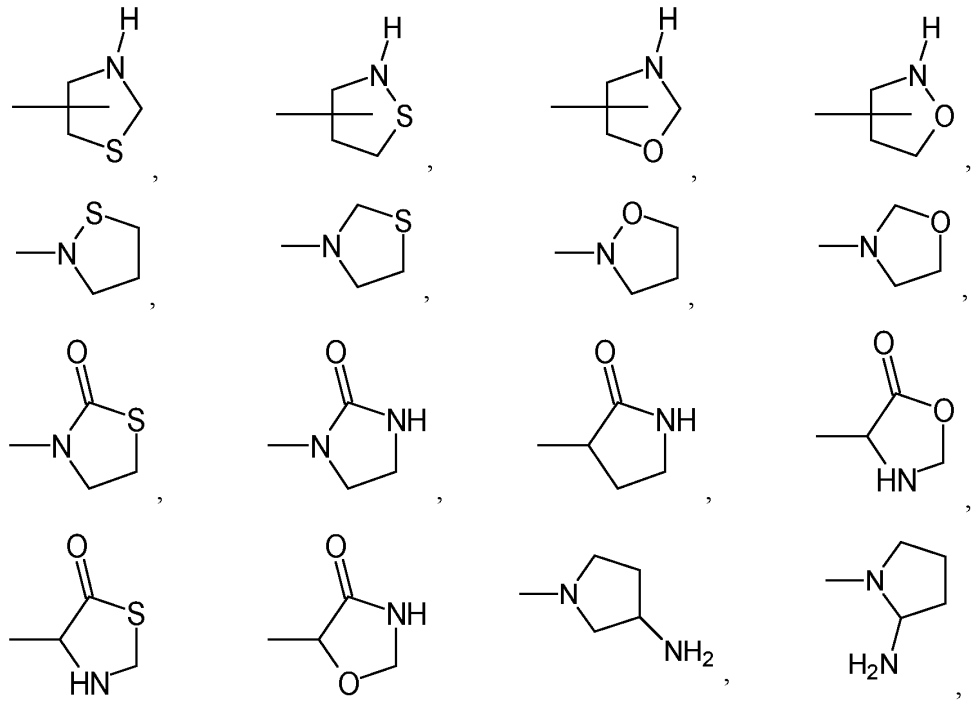
Preferred 4-membered heterocyclyl groups are  and  .

Examples of preferred 5-membered heterocyclyl groups and substituted 5-membered heterocyclyl groups for **R**[8] or **R**[9] are substituted or non substituted ring systems of five atoms including at least one heteroatom such as O, S, SO, SO_2, N, NO, wherein these

5-membered heterocyclic residues can be substituted with 1 to 4 substituents selected from R^{N1}, R^{N2}, Z^1, Z^2, Z^3 and Z^4. It is also possible that two of the substituents Z^1, Z^2, Z^3 and Z^4 represent together an oxygen atom and form together with the ring carbon atom of the heterocyclic ring to which they are both attached a carbonyl moiety or a sulfoxide moiety together with the ring sulphur atom to which they are attached or both Z substituents represent oxygen and form a sulfone moiety together with the ring sulphur atom to which they are attached. If the 5-membered heterocyclic residue contains a nitrogen atom which is substituted by R^{N1}. the first Z substituent represents R^{N1}. If the 5-membered heterocyclic residue contains two nitrogen atoms which are both substituted by one of the substituents R^{N1}, R^{N2}, the first Z substituent represents R^{N1}, and the second Z substituent represents R^{N2}. The same definition applies for the substituent R^9 with the only difference that the optional substituents of the 5-membered heterocyclyl residue are Z^5 to Z^7 instead of Z^1 to Z^4. Thus, for R^9 the optional substituent Z^1 is replaced by Z^5, Z^2 is replaced by Z^6, Z^3 is replaced by Z^7, and Z^4 is hydrogen.

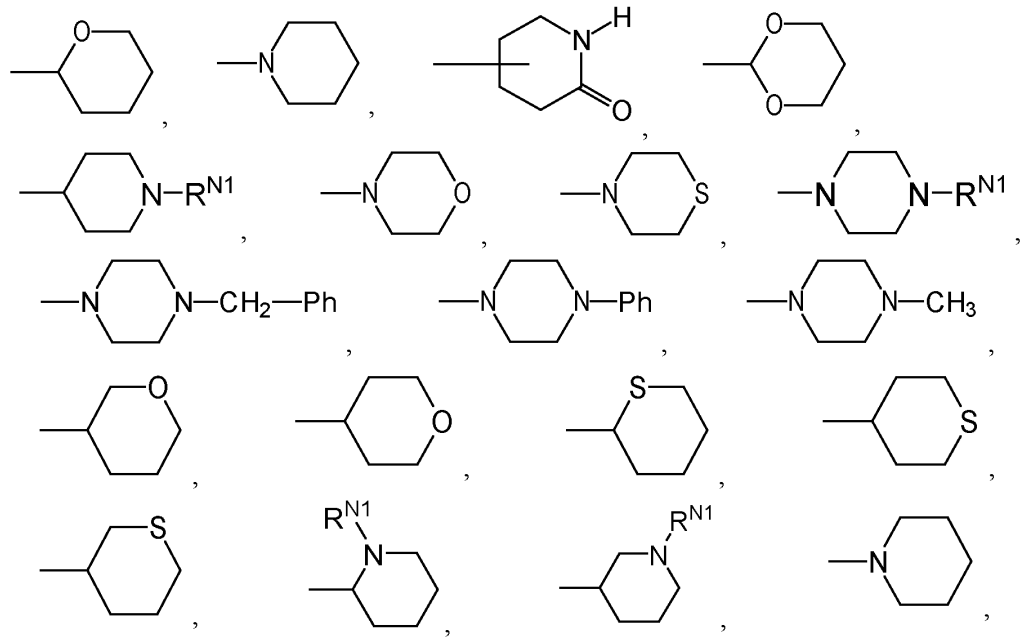
Examples of preferred 5-membered heterocyclic groups and substituted 5-membered heterocyclic groups for R^8 or R^9 are

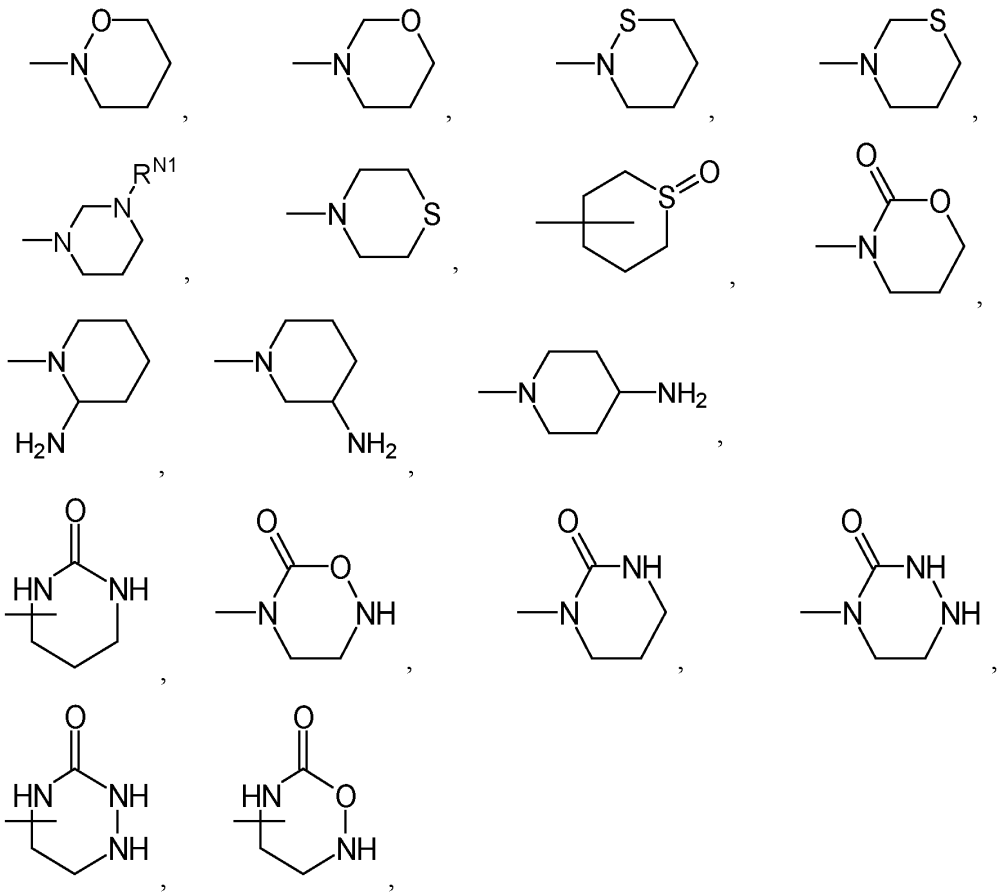




wherein the afore-mentioned 5-membered heterocyclic groups can be substituted with 1 to 4 substituents selected from R^{N1}, Z^1, Z^2, Z^3 and Z^4.

Examples of preferred 6-membered heterocyclic groups and substituted 6-membered heterocyclic groups for R^8 or R^9 are



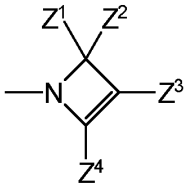
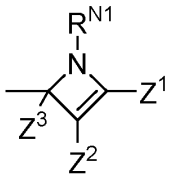
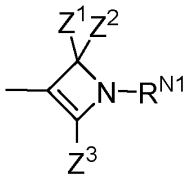
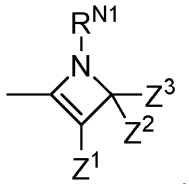
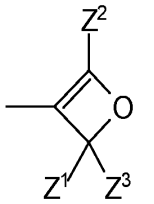
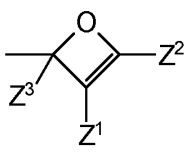
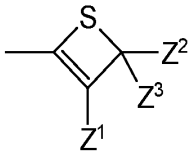
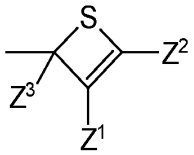
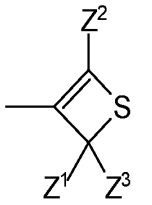


wherein the afore-mentioned 6-membered heterocyclic groups can be substituted with 1 to 4 substituents selected from Z^1, Z^2, Z^3 and Z^4. Preferred residues for the substituents Z^1 to Z^4 are disclosed above.

Examples of preferred "monounsaturated 4-membered heterocyclyl" groups and substituted "monounsaturated 4-membered heterocyclyl" groups for **R^8** or **R^9** are substituted or non substituted ring systems of four atoms including at least one heteroatom such as O, S, SO, SO_2, N, NO, and one double bond, wherein these monounsaturated 4-membered heterocyclic residues can be substituted with 1 to 4 substituents selected from R^{N1}, R^{N2}, Z^1, Z^2, Z^3 and Z^4. However it is clear to a skilled person that the term "can be substituted" refers to the replacement of a hydrogen atom by one of the substituents R^{N1}, R^{N2}, Z^1, Z^2, Z^3 or Z^4. Moreover it is clear to a skilled person that only these hydrogen atoms which are present in the monounsaturated 4-membered heterocyclic residue can be replaced by the substituents R^{N1}, R^{N2}, Z^1, Z^2, Z^3 and Z^4. It is also possible that two of the substituents Z^1, Z^2, Z^3 and Z^4 represent together an oxygen atom and form together with the ring carbon atom of the heterocyclic ring to which they are both attached a carbonyl moiety or a sulfoxide moiety together with the ring sulphur atom

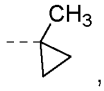
to which they are attached or both Z substituents represent oxygen and form a sulfone moiety together with the ring sulphur atom to which they are attached. If the monounsaturated 4-membered heterocyclic residue contains a nitrogen atom, which is substituted by R^{N1}. the first substituent represents R^{N1}. If the monounsaturated 4-membered heterocyclic residue contains two nitrogen atoms which are both substituted by R^{N1}, R^{N2}, the first substituent represents R^{N1}, and the second substituent represents R^{N2}.

Examples of preferred monounsaturated 4-membered heterocyclic groups and substituted 4-membered heterocyclic groups for R^8 or R^9 are


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Preferably Z^1 to Z^4 represent independently of each other –H, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, –OH, $-OCH_3$, $-OC_2H_5$, $-OC_3H_7$, $-NH_2$, $-N(CH_3)_2$, –F, –Cl, –Br, –I, –CN, $-CH_2F$, $-CHF_2$, $-CF_3$, $-OCHF_2$, or $-OCF_3$.

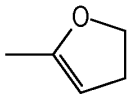
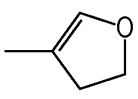
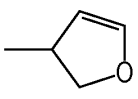
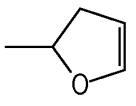
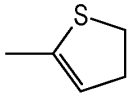
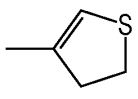
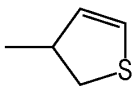
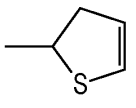
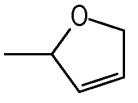
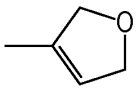
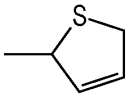
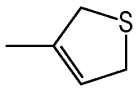
Preferred substituents for R^{N1} are $-\mathbf{R^{15}}$, –H, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $-CHF_2$, $-CF_3$,

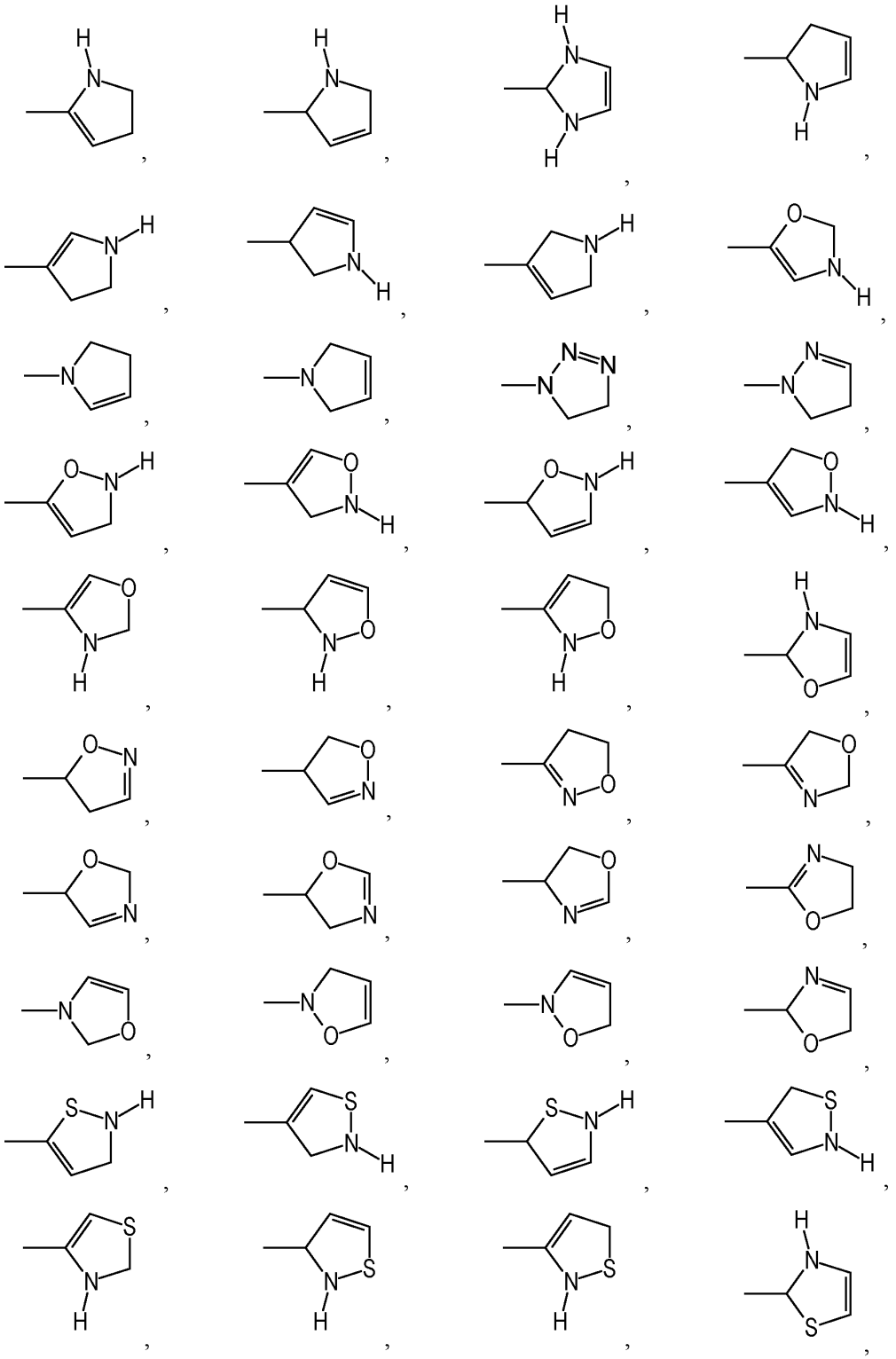

, cyclo-C_3H_5, cyclo-C_4H_7, cyclo-C_5H_9, cyclo-C_6H_{11}, cyclo-C_7H_{13}, $-C_4H_9$, $-CH_2-CH(CH_3)_2$, $-CH(CH_3)-C_2H_5$, $-C(CH_3)_3$, $-C_5H_{11}$, $-CH(CH_3)-C_3H_7$, $-CH_2-CH(CH_3)-C_2H_5$, $-CH(CH_3)-CH(CH_3)_2$, $-C(CH_3)_2-C_2H_5$, $-CH_2-C(CH_3)_3$, $-CH(C_2H_5)_2$, $-C_2H_4-CH(CH_3)_2$, $-C_6H_{13}$, $-C_7H_{15}$, $-C_8H_{17}$, –Ph, $-CH_2$–Ph,

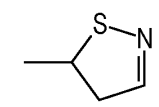
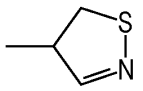
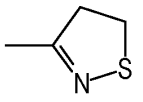
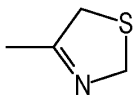
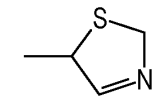
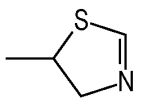
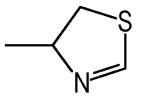
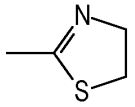
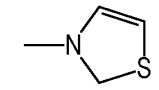
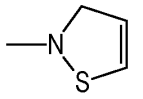
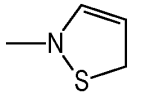
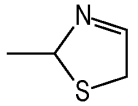
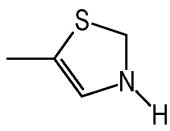
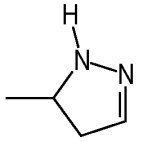
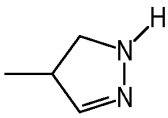
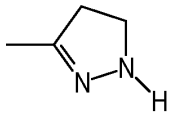
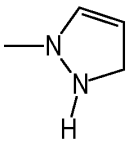
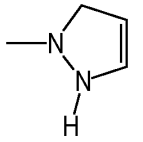
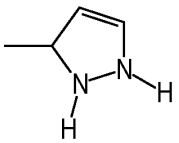
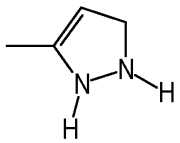
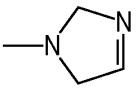
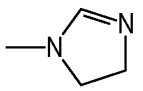
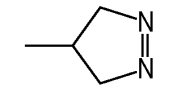
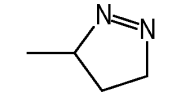
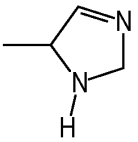
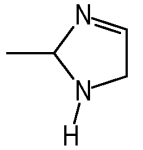
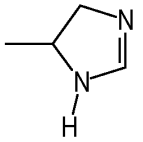
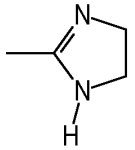
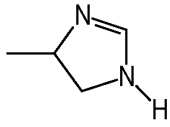
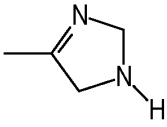
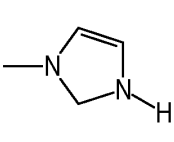
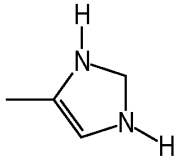
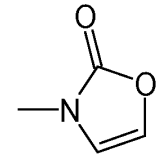
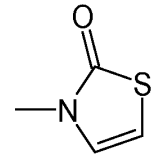
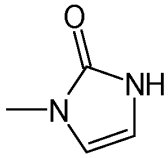
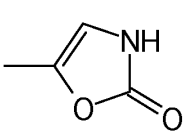
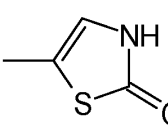
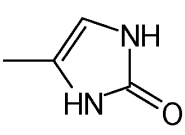
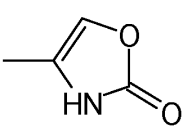
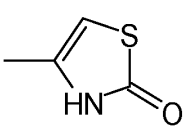
$-CH_2-CH_2-Ph$, $-C_2H_4-CH=CH_2$, $-CH_2-CH=CH-CH_3$, $-CH_2-C(CH_3)=CH_2$, $-CH(CH_3)-CH=CH_2$, $-CH_2-CH=C(CH_3)_2$, $-CH_2-C\equiv CH$, $-C_2H_4-C\equiv CH$, $-CH_2-C\equiv C-CH_3$, $-COCH_3$, $-COC_2H_5$, $-COC_3H_7$, $-CO-cyclo-C_3H_5$, $-COCH(CH_3)_2$, $-COC(CH_3)_3$, $-COOH$, $-COOCH_3$, $-COOC_2H_5$, $-COOC_3H_7$, $-COO-cyclo-C_3H_5$, $-COOCH(CH_3)_2$, $-COOC(CH_3)_3$, $-COOCH_2Ph$, $-CONH_2$, $-CONHCH_3$, $-CONHC_2H_5$, $-CONHC_3H_7$, $-CONH-cyclo-C_3H_5$, $-CONH[CH(CH_3)_2]$, $-CONH[C(CH_3)_3]$, $-CON(CH_3)_2$, $-CON(C_2H_5)_2$, $-CON(C_3H_7)_2$, $-CON(cyclo-C_3H_5)_2$, $-CON[CH(CH_3)_2]_2$, $-CON[C(CH_3)_3]_2$, or $-SO_3H$.

Examples of preferred "monounsaturated 5-membered heterocyclyl" groups and substituted "monounsaturated 5-membered heterocyclyl" groups for **R^8** or **R^9** refers to substituted or non substituted ring systems of five atoms including at least one heteroatom such as O, S, SO, SO_2, N, NO, and one double bond, wherein these monounsaturated 5-membered heterocyclic residues can be substituted with 1 to 4 substituents selected from R^{N1}, R^{N2}, Z^1, Z^2, Z^3 and Z^4. It is also possible that two of the substituents R^{N1}, R^{N2}, Z^1, Z^2, Z^3 and Z^4 represent together an oxygen atom and form together with the ring carbon atom of the heterocyclic ring to which they are both attached a carbonyl moiety or a sulfoxide moiety together with the ring sulphur atom to which they are attached or both Z substituents represent oxygen and form a sulfone moiety together with the ring sulphur atom to which they are attached. If the monounsaturated 5-membered heterocyclic residue contains a nitrogen atom which is substituted by R^{N1}. the first substituent represents R^{N1}. If the monounsaturated 5-membered heterocyclic residue contains two nitrogen atoms which are both substituted by R^{N1}, R^{N2}, the first substituent represents R^{N1} and the second substituent represents R^{N2}.

Examples of preferred monounsaturated 5-membered heterocyclic groups and substituted 5-membered heterocyclic groups for R^3 are

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wherein the afore-mentioned monounsaturated 5-membered heterocyclic groups can be substituted with 1 to 4 substituents selected from R^{N1}, R^{N2}, Z^1, Z^2, Z^3 and Z^4.

R^8, and R^9 represents preferably independently of each other the following spiroheterocyclyl or C_5–C_{14}/N_0–N_2/O_0–O_2/S_0–S_1–spiroheterocyclyl residues: spiro[2,3]heterohexyl, spiro[2,4]heteroheptyl, spiro[2,5]heterooctyl, spiro[2,7]heterononyl, spiro[3,3]heteroheptyl, spiro[3,4]heterooctyl, spiro[3,5]heterononyl, spiro[3,6]heterodecyl, spiro[4,4]heterononyl, spiro[4,5]heterodecyl, spiro[4,6]heteroundecyl, spiro[5,5]heteroundecyl, spiro[5,6]heterododecyl, spiro[6,6]heterotridecyl, wherein the afore-mentioned spiroheterocyclyl or C_5–C_{14}/N_0–N_2/O_0–O_2/S_0–S_1–spiroheterocyclyl residues are linked through a ring carbon atom to the rest of the molecule and wherein the afore-mentioned spiroheterocyclyl or C_5–C_{14}/N_0–N_2/O_0–O_2/S_0–S_1–spiroheterocyclyl residues are optionally substituted with one to three substituents selected from R^{N1}, R^{N2}, Z^1, Z^2, Z^3, Z^5, Z^6 and Z^7. The heteroatom in the afore-mentioned spiroheterocyclyl or C_5–C_{14}/N_0–N_2/O_0–O_2/S_0–S_1–spiroheterocyclyl residues is preferably selected from –O–, –NH–, –NR^{N1}–, –NR^{N2}–, –SO–, and –SO_2–.

More preferably R^8, and R^9 represents independently of each other preferably the following spiroheterocyclyl or C_5–C_{14}/N_0–N_2/O_0–O_2/S_0–S_1–spiroheterocyclyl residues: azaspiro[3,3]heptyl, azaspiro[3,4]octyl, azaspiro[3,5]nonyl, azaspiro[3,6]decyl, azaspiro[4,4]nonyl, azaspiro[4,5]decyl, azaspiro[4,6]undecyl, azaspiro[5,5]undecyl, azaspiro[5,6]dodecyl, azaspiro[6,6]tridecyl, diazaspiro[3,3]heptyl, diazaspiro[3,4]octyl, diazaspiro[3,5]nonyl, diazaspiro[3,6]decyl, diazaspiro[4,4]nonyl, diazaspiro[4,5]decyl, diazaspiro[4,6]undecyl, diazaspiro[5,5]undecyl, diazaspiro[5,6]dodecyl, diazaspiro[6,6]tridecyl, triazaspiro[3,5]nonyl, triazaspiro[3,6]decyl, triazaspiro[4,5]decyl, triazaspiro[4,6]undecyl, triazaspiro[5,5]undecyl, triazaspiro[5,6]dodecyl, triazaspiro[6,6]tridecyl, oxazaspiro[3,3]heptyl, oxazaspiro[3,4]octyl, oxazaspiro[3,5]nonyl, oxazaspiro[3,6]decyl, oxazaspiro[4,4]nonyl, oxazaspiro[4,5]decyl, oxazaspiro[4,6]undecyl, oxazaspiro[5,5]undecyl, oxazaspiro[5,6]dodecyl, oxazaspiro[6,6]tridecyl, oxadiazaspiro[3,5]nonyl, oxadiazaspiro[3,6]decyl, oxadiazaspiro[4,5]decyl, oxadiazaspiro[4,6]undecyl, oxadiazaspiro[5,5]undecyl, oxadiazaspiro[5,6]dodecyl, oxadiazaspiro[6,6]tridecyl, wherein the afore-mentioned spiroheterocyclyl or C_5–C_{14}/N_0–N_2/O_0–O_2/S_0–S_1–spiroheterocyclyl residues are linked through a ring carbon atom to the rest of the molecule and wherein the afore-mentioned spiroheterocyclyl or C_5–C_{14}/N_0–N_2/O_0–O_2/S_0–S_1–spiroheterocyclyl residues are optionally substituted with one to three substituents selected from R^{N1}, R^{N2}, Z^1, Z^2, Z^3, Z^5, Z^6 and Z^7.

Also, R^8 and R^9 represents independently of each other more preferably the following residues: substituted or unsubstituted 4-membered carbocyclyl, substituted or unsubstituted 5-membered carbocyclyl, substituted or unsubstituted 6-membered carbocyclyl, 4-membered heterocyclyl, 5-membered heterocyclyl, 6-membered heterocyclyl, substituted 4-membered heterocyclyl, substituted 5-membered heterocyclyl, substituted 6-membered heterocyclyl, 4-membered nitrogenheterocyclyl, 5-membered nitrogenheterocyclyl, 6-membered nitrogenheterocyclyl, substituted 4-membered nitrogenheterocyclyl, substituted 5-membered nitrogenheterocyclyl, substituted 6-membered nitrogenheterocyclyl, spiro[2,3]heterohexyl, spiro[2,4]heteroheptyl, spiro[2,5]heterooctyl, spiro[2,7]heterononyl, spiro[3,3]heteroheptyl, spiro[3,4]heterooctyl, spiro[3,5]heterononyl, spiro[3,6]heterodecyl, spiro[4,4]heterononyl, spiro[4,5]heterodecyl, spiro[4,6]heteroundecyl, spiro[5,5]heteroundecyl, spiro[5,6]heterododecyl, spiro[6,6]heterotridecyl,

substituted spiro[2,3]heterohexyl, substituted spiro[2,4]heteroheptyl, substituted spiro[2,5]heterooctyl, substituted spiro[2,7]heterononyl, substituted spiro[3,3]heteroheptyl, substituted spiro[3,4]heterooctyl, substituted spiro[3,5]heterononyl, substituted spiro[3,6]heterodecyl, substituted spiro[4,4]heterononyl, substituted spiro[4,5]heterodecyl, substituted spiro[4,6]heteroundecyl, substituted spiro[5,5]heteroundecyl, substituted spiro[5,6]heterododecyl, substituted spiro[6,6]heterotridecyl,

azaspiro[3,3]heptyl, azaspiro[3,4]octyl, azaspiro[3,5]nonyl, azaspiro[3,6]decyl, azaspiro[4,4]nonyl, azaspiro[4,5]decyl, azaspiro[4,6]undecyl, azaspiro[5,5]undecyl, azaspiro[5,6]dodecyl, azaspiro[6,6]tridecyl,

substituted azaspiro[3,3]heptyl, substituted azaspiro[3,4]octyl, substituted azaspiro[3,5]nonyl, substituted azaspiro[3,6]decyl, substituted azaspiro[4,4]nonyl, substituted azaspiro[4,5]decyl, substituted azaspiro[4,6]undecyl, substituted azaspiro[5,5]undecyl, substituted azaspiro[5,6]dodecyl, substituted azaspiro[6,6]tridecyl,

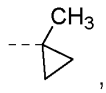
diazaspiro[3,3]heptyl, diazaspiro[3,4]octyl, diazaspiro[3,5]nonyl, diazaspiro[3,6]decyl, diazaspiro[4,4]nonyl, diazaspiro[4,5]decyl, diazaspiro[4,6]undecyl, diazaspiro[5,5]undecyl, diazaspiro[5,6]dodecyl, diazaspiro[6,6]tridecyl,

substituted diazaspiro[3,3]heptyl, substituted diazaspiro[3,4]octyl, substituted diazaspiro[3,5]nonyl, substituted diazaspiro[3,6]decyl, substituted diazaspiro[4,4]nonyl, substituted diazaspiro[4,5]decyl, substituted diazaspiro[4,6]undecyl, substituted diazaspiro[5,5]undecyl, substituted diazaspiro[5,6]dodecyl, substituted diazaspiro[6,6]tridecyl,

triazaspiro[3,5]nonyl, triazaspiro[3,6]decyl, triazaspiro[4,5]decyl, triazaspiro[4,6]undecyl, triazaspiro[5,5]undecyl, triazaspiro[5,6]dodecyl, triazaspiro[6,6]tridecyl,
substituted triazaspiro[3,5]nonyl, substituted triazaspiro[3,6]decyl, substituted triazaspiro[4,5]decyl, substituted triazaspiro[4,6]undecyl, substituted triazaspiro[5,5]undecyl, substituted triazaspiro[5,6]dodecyl, or substituted triazaspiro[6,6]tridecyl,
oxazaspiro[3,3]heptyl, oxazaspiro[3,4]octyl, oxazaspiro[3,5]nonyl, oxazaspiro[3,6]decyl, oxazaspiro[4,4]nonyl, oxazaspiro[4,5]decyl, oxazaspiro[4,6]undecyl, oxazaspiro[5,5]undecyl, oxazaspiro[5,6]dodecyl, oxazaspiro[6,6]tridecyl,
substituted oxazaspiro[3,3]heptyl, substituted oxazaspiro[3,4]octyl, substituted oxazaspiro[3,5]nonyl, substituted oxazaspiro[3,6]decyl, substituted oxazaspiro[4,4]nonyl, substituted oxazaspiro[4,5]decyl, substituted oxazaspiro[4,6]undecyl, substituted oxazaspiro[5,5]undecyl, substituted oxazaspiro[5,6]dodecyl, substituted oxazaspiro[6,6]tridecyl,
oxadiazaspiro[3,5]nonyl, oxadiazaspiro[3,6]decyl, oxadiazaspiro[4,5]decyl, oxadiazaspiro[4,6]undecyl, oxadiazaspiro[5,5]undecyl, oxadiazaspiro[5,6]dodecyl, oxadiazaspiro[6,6]tridecyl,
substituted oxadiazaspiro[3,5]nonyl, substituted oxadiazaspiro[3,6]decyl, substituted oxadiazaspiro[4,5]decyl, substituted oxadiazaspiro[4,6]undecyl, substituted oxadiazaspiro[5,5]undecyl, substituted oxadiazaspiro[5,6]dodecyl, or substituted oxadiazaspiro[6,6]tridecyl,
wherein the afore-mentioned substituted or non-substituted spiroheterocyclyl or C_5–C_{14}/N_0–N_2/O_0–O_2/S_0–S_1–spiroheterocyclyl residues are linked through a ring carbon atom to the rest of the molecule and wherein the afore-mentioned substituted or non-substituted spiroheterocyclyl or C_5–C_{14}/N_0–N_2/O_0–O_2/S_0–S_1–spiroheterocyclyl residues are optionally substituted with one to three substituents selected from Z^1, Z^2, Z^3, Z^5, Z^6 and Z^7. The heteroatom in the afore-mentioned substituted or non-substituted spiroheterocyclyl or C_5–C_{14}/N_0–N_2/O_0–O_2/S_0–S_1–spiroheterocyclyl residues is preferably selected from –O–, –NH–, –NR^{N1}–, –SO–, and –SO_2–.

Preferably Z^5, Z^6 and Z^7 represent independently of each other –H, –CH_3, –C_2H_5, –C_3H_7, –$CH(CH_3)_2$, –OH, –OCH_3, –OC_2H_5, –OC_3H_7, –NH_2, –$N(CH_3)_2$, –F, –Cl, –Br, –I, –CN, –CH_2F, –CHF_2, –CF_3, –$OCHF_2$, or –OCF_3.

If present, $\mathbf{R^{N1}}$ is preferably selected from: –$\mathbf{R^{15}}$, –H, –CH_3, –C_2H_5, –C_3H_7, –$CH(CH_3)_2$, –CHF_2, –CF_3,

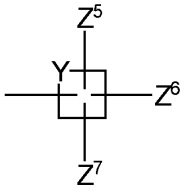
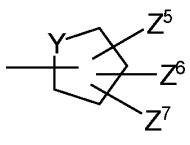
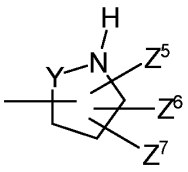
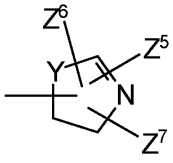
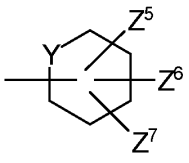

, cyclo-C_3H_5, cyclo-C_4H_7, cyclo-C_5H_9, cyclo-C_6H_{11}, cyclo-C_7H_{13}, $-C_4H_9$, $-CH_2-CH(CH_3)_2$, $-CH(CH_3)-C_2H_5$, $-C(CH_3)_3$, $-C_5H_{11}$, $-CH(CH_3)-C_3H_7$, $-CH_2-CH(CH_3)-C_2H_5$, $-CH(CH_3)-CH(CH_3)_2$, $-C(CH_3)_2-C_2H_5$, $-CH_2-C(CH_3)_3$, $-CH(C_2H_5)_2$, $-C_2H_4-CH(CH_3)_2$, $-C_6H_{13}$, $-C_7H_{15}$, $-C_8H_{17}$, $-Ph$, $-CH_2-Ph$, $-CH_2-CH_2-Ph$, $-C_2H_4-CH=CH_2$, $-CH_2-CH=CH-CH_3$, $-CH_2-C(CH_3)=CH_2$, $-CH(CH_3)-CH=CH_2$, $-CH_2-CH=C(CH_3)_2$, $-CH_2-C\equiv CH$, $-C_2H_4-C\equiv CH$, $-CH_2-C\equiv C-CH_3$, $-COCH_3$, $-COC_2H_5$, $-COC_3H_7$, $-CO$–cyclo-C_3H_5, $-COCH(CH_3)_2$, $-COC(CH_3)_3$, $-COOH$, $-COOCH_3$, $-COOC_2H_5$, $-COOC_3H_7$, $-COO$–cyclo-C_3H_5, $-COOCH(CH_3)_2$, $-COOC(CH_3)_3$, $-COOCH_2Ph$, $-CONH_2$, $-CONHCH_3$, $-CONHC_2H_5$, $-CONHC_3H_7$, $-CONH$–cyclo-C_3H_5, $-CONH[CH(CH_3)_2]$, $-CONH[C(CH_3)_3]$, $-CON(CH_3)_2$, $-CON(C_2H_5)_2$, $-CON(C_3H_7)_2$, $-CON(\text{cyclo-}C_3H_5)_2$, $-CON[CH(CH_3)_2]_2$, $-CON[C(CH_3)_3]_2$, or $-SO_3H$.

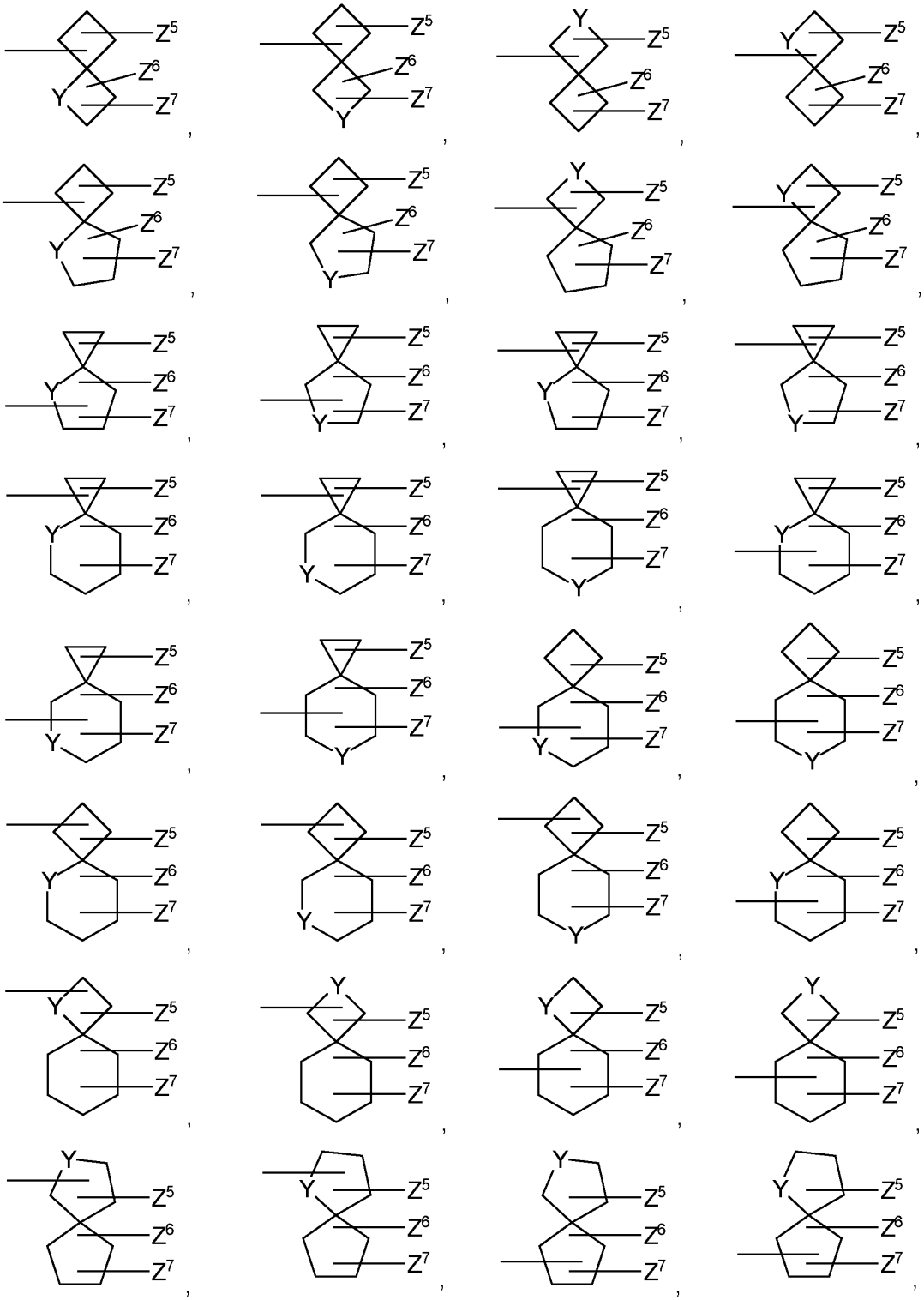
The term "4-membered nitrogenheterocyclyl" refers to the residue "4-membered heterocyclyl" as defined above, wherein at least one heteroatom is a nitrogen atom and the residue is linked through the at least one nitrogen ring atom to the rest of the molecule and wherein Z^1 is replaced by Z^5, Z^2 is replaced by Z^6, Z^3 is replaced by Z^7, and Z^4 is hydrogen.

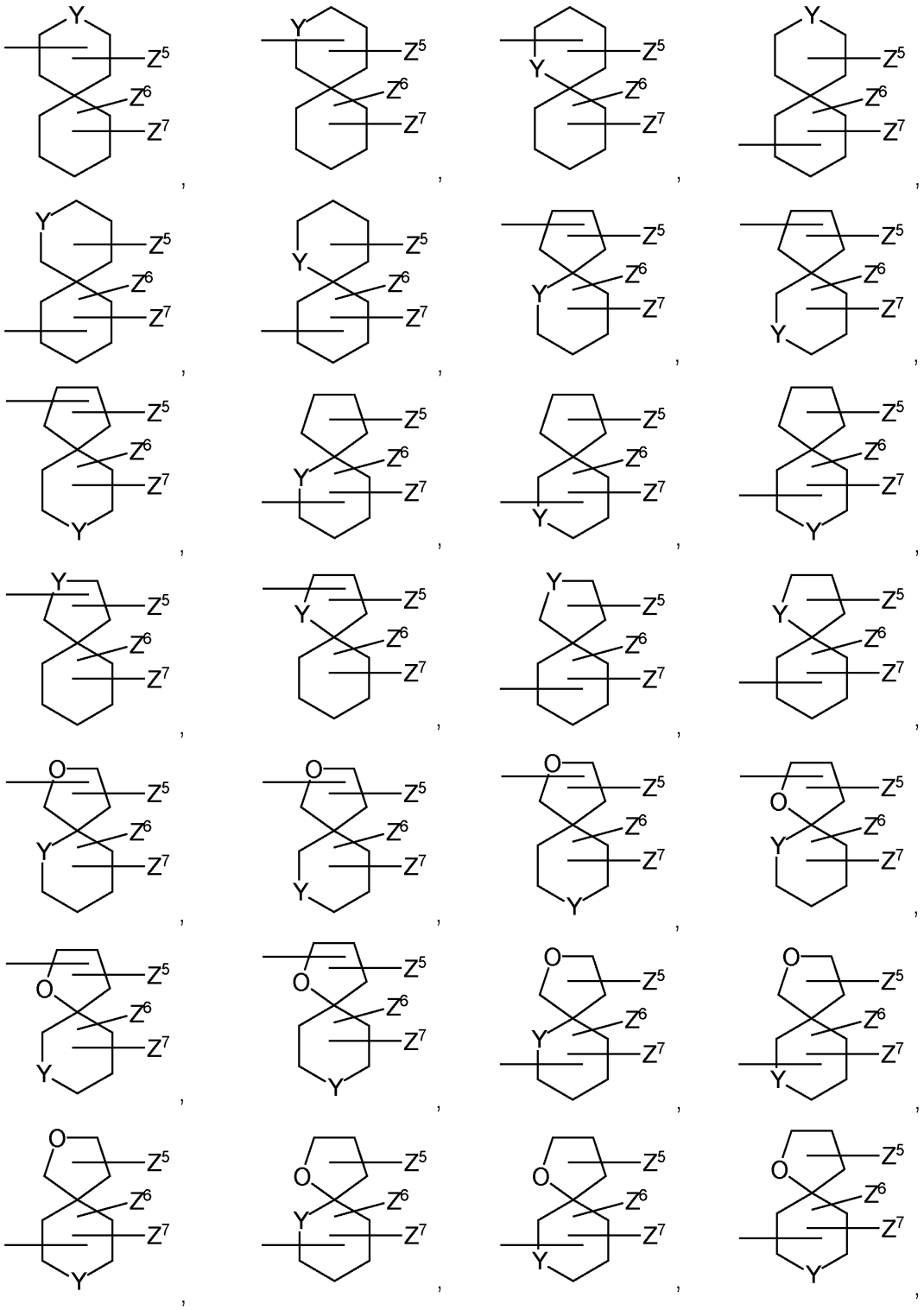
The term "5-membered nitrogenheterocyclyl" refers to the residue "5-membered heterocyclyl" as defined above, wherein at least one heteroatom is a nitrogen atom and the residue is linked through the at least one nitrogen ring atom to the rest of the molecule and wherein Z^1 is replaced by Z^5, Z^2 is replaced by Z^6, Z^3 is replaced by Z^7, and Z^4 is hydrogen.

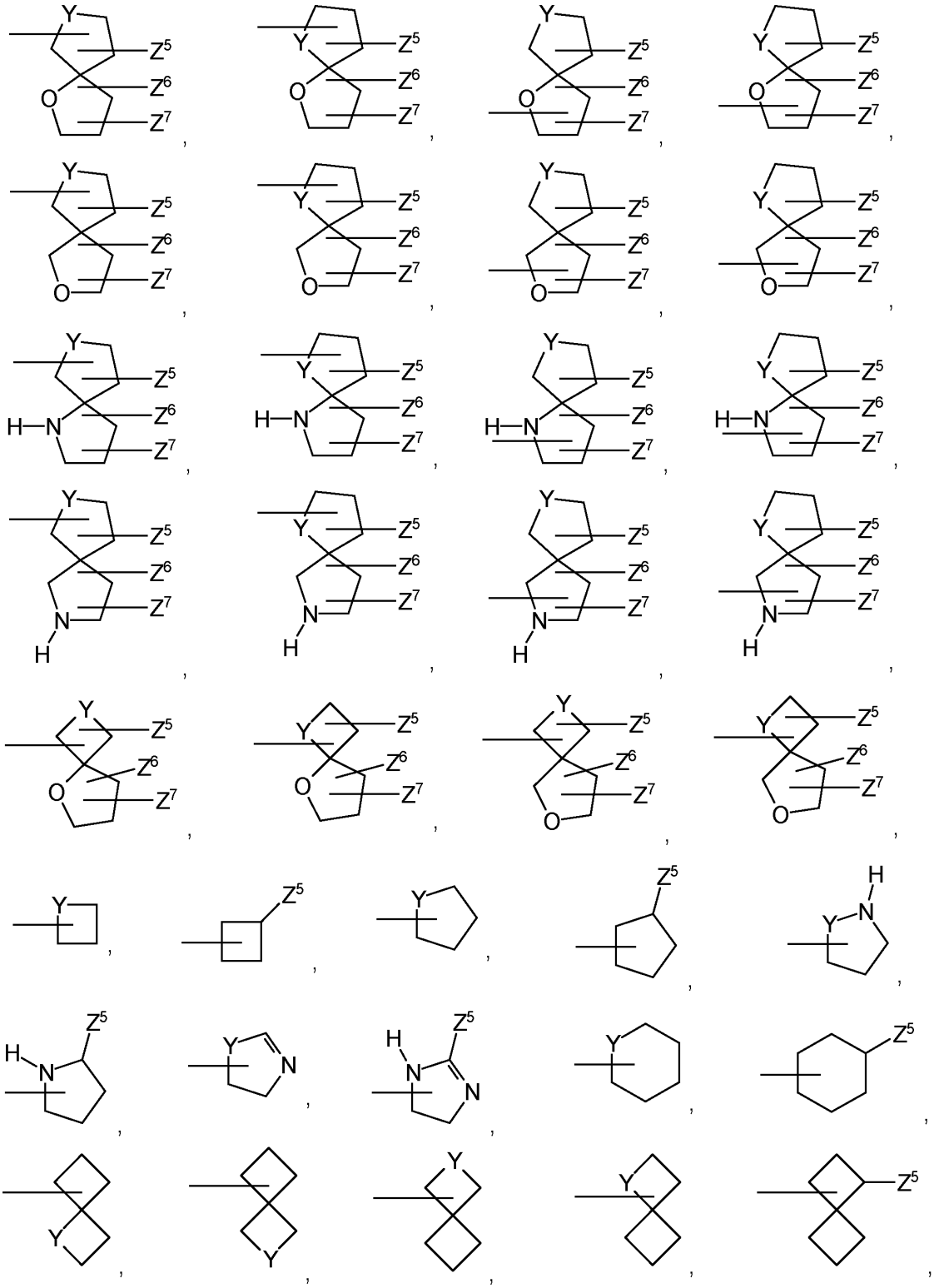
The term "6-membered nitrogenheterocyclyl" refers to the residue "6-membered heterocyclyl" as defined above, wherein at least one heteroatom is a nitrogen atom and the residue is linked through the at least one nitrogen ring atom to the rest of the molecule and wherein Z^1 is replaced by Z^5, Z^2 is replaced by Z^6, Z^3 is replaced by Z^7, and Z^4 is hydrogen.

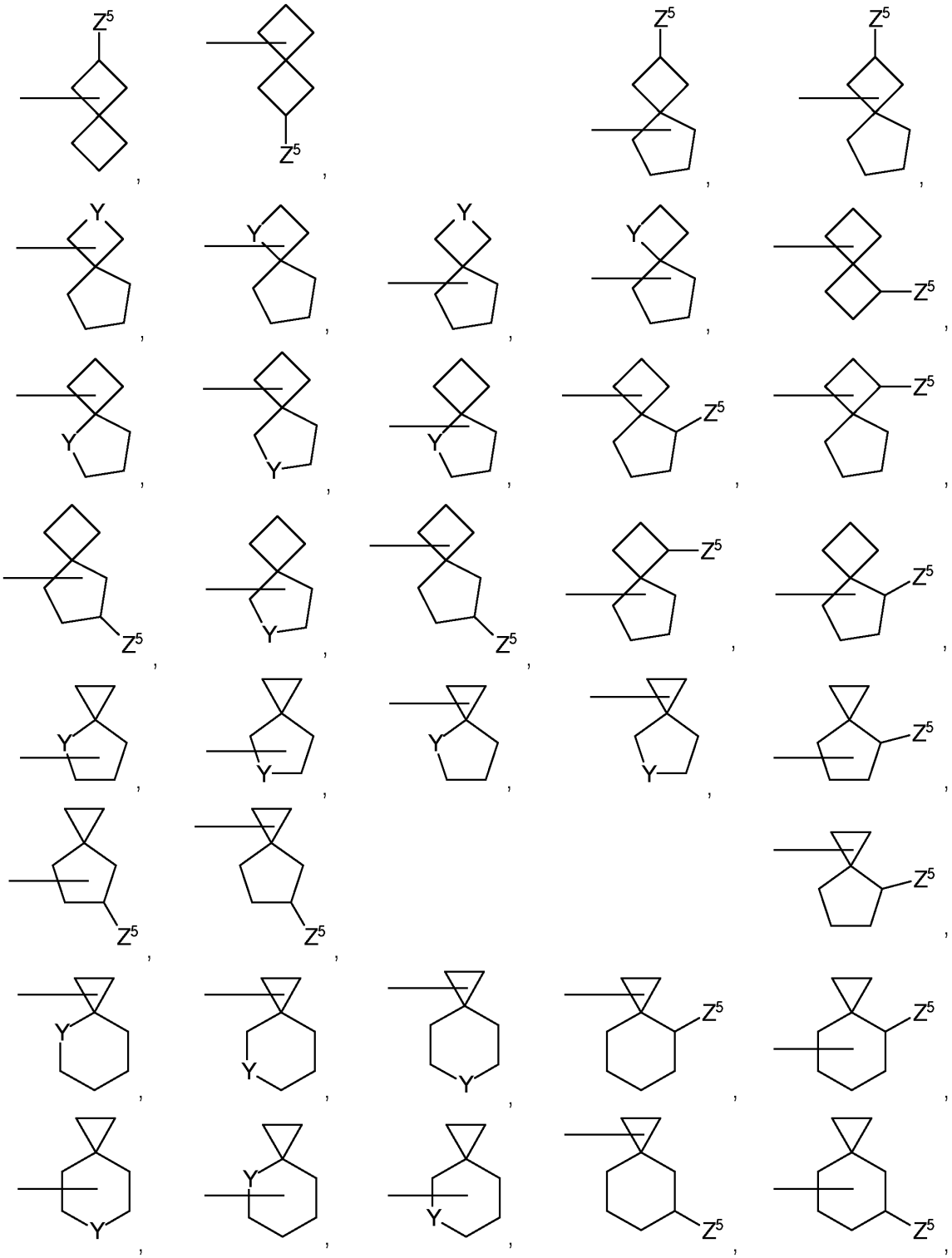
Still more preferably $\mathbf{R^8}$ or $\mathbf{R^9}$ is selected from the following residues:

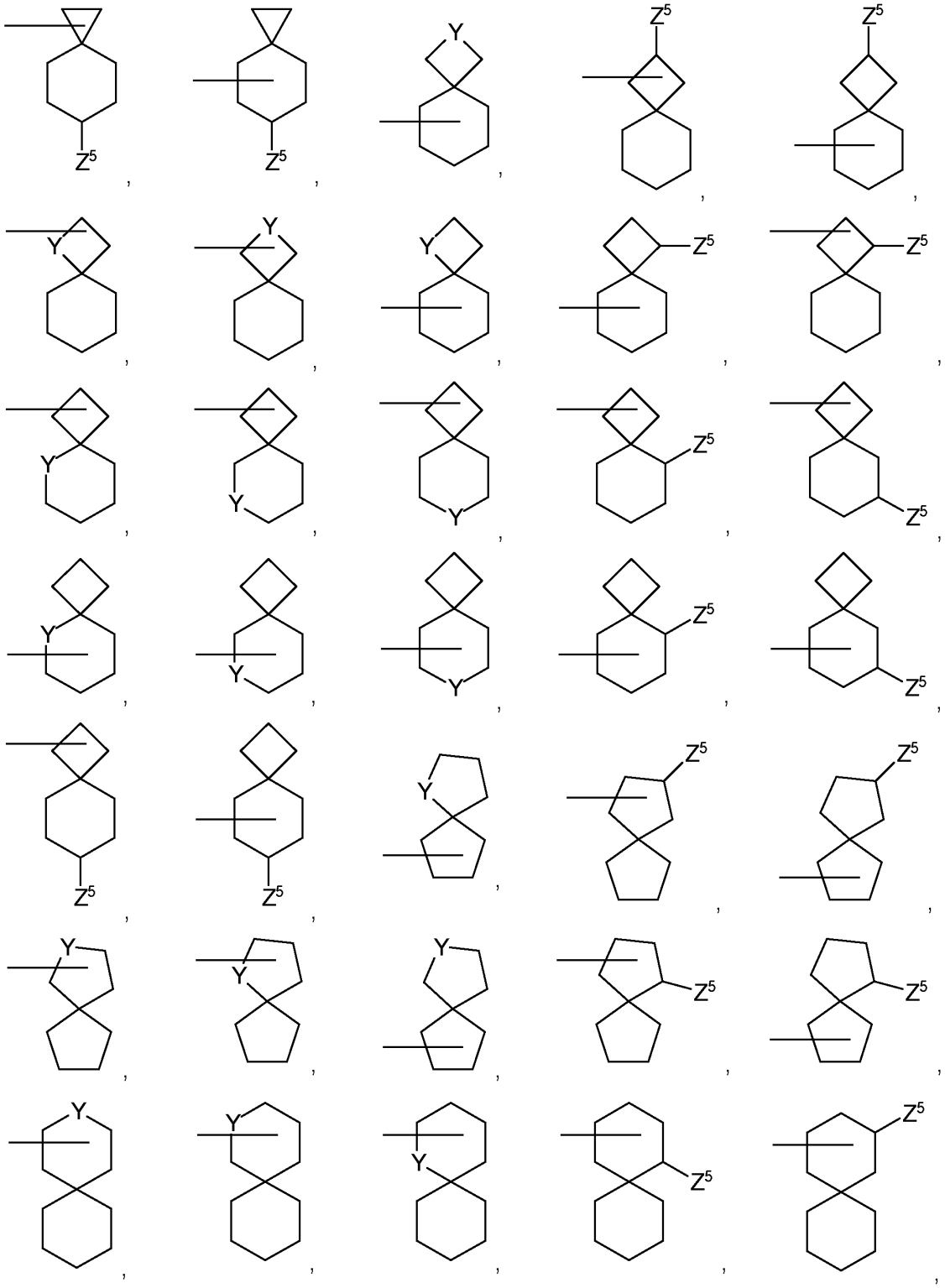

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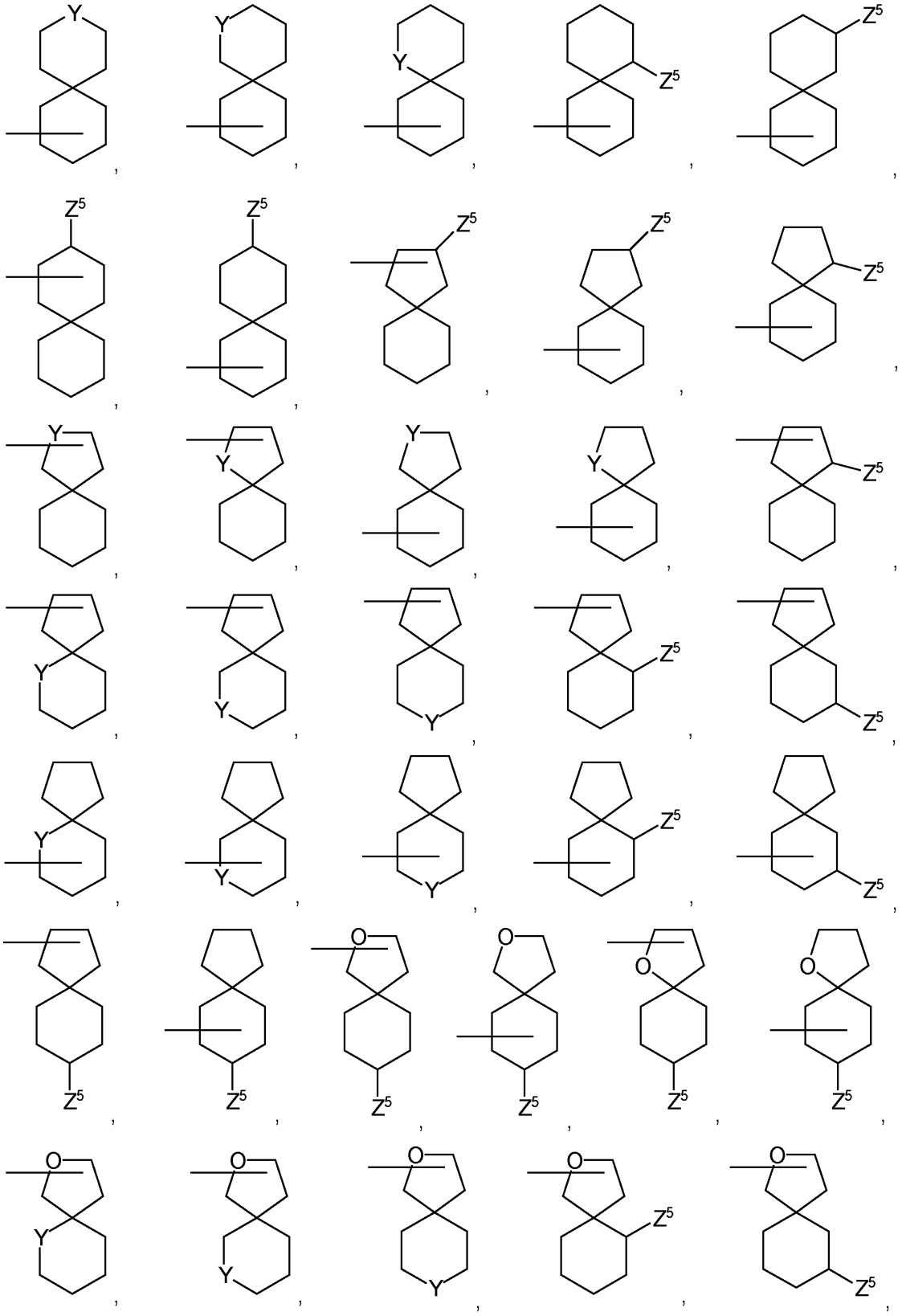


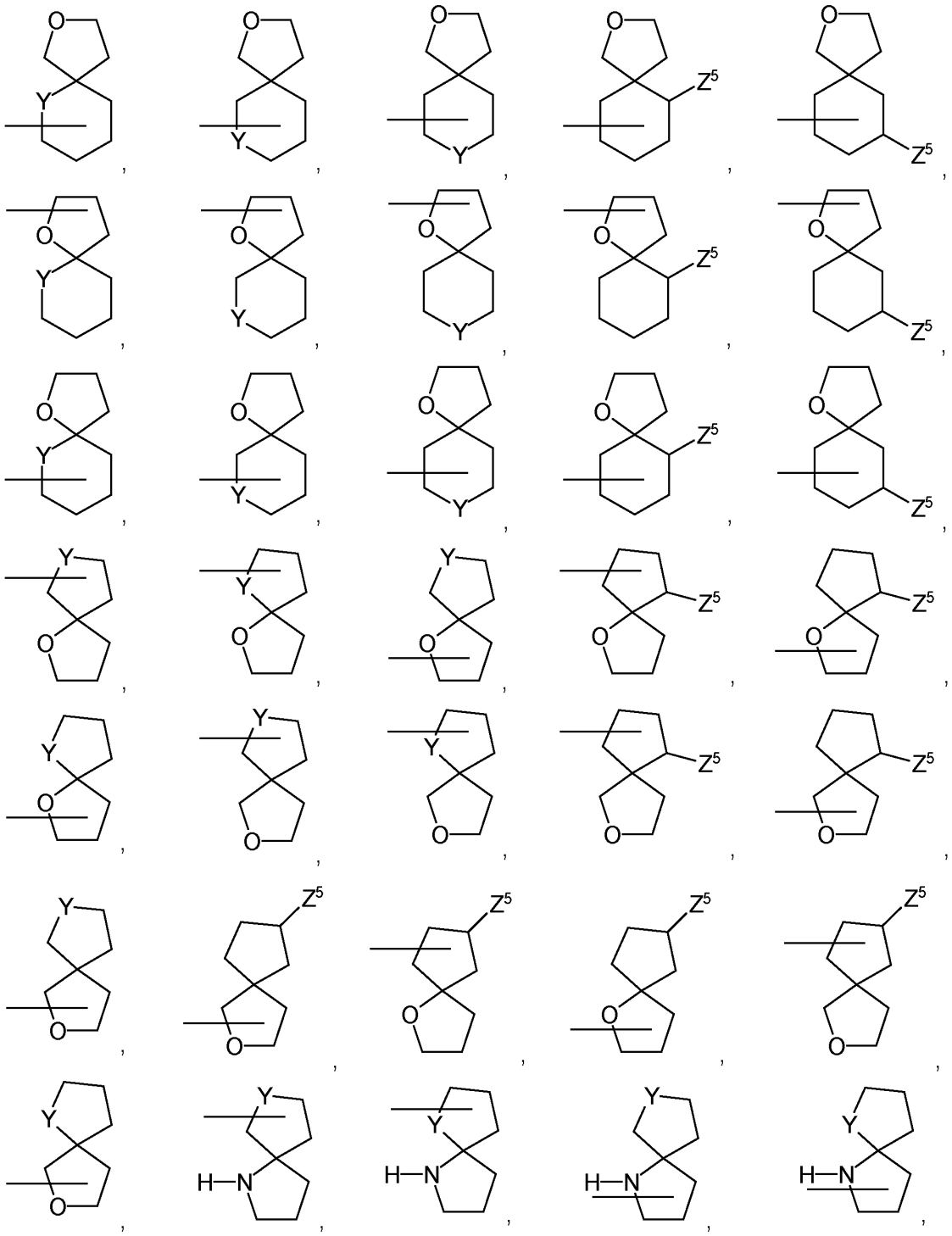


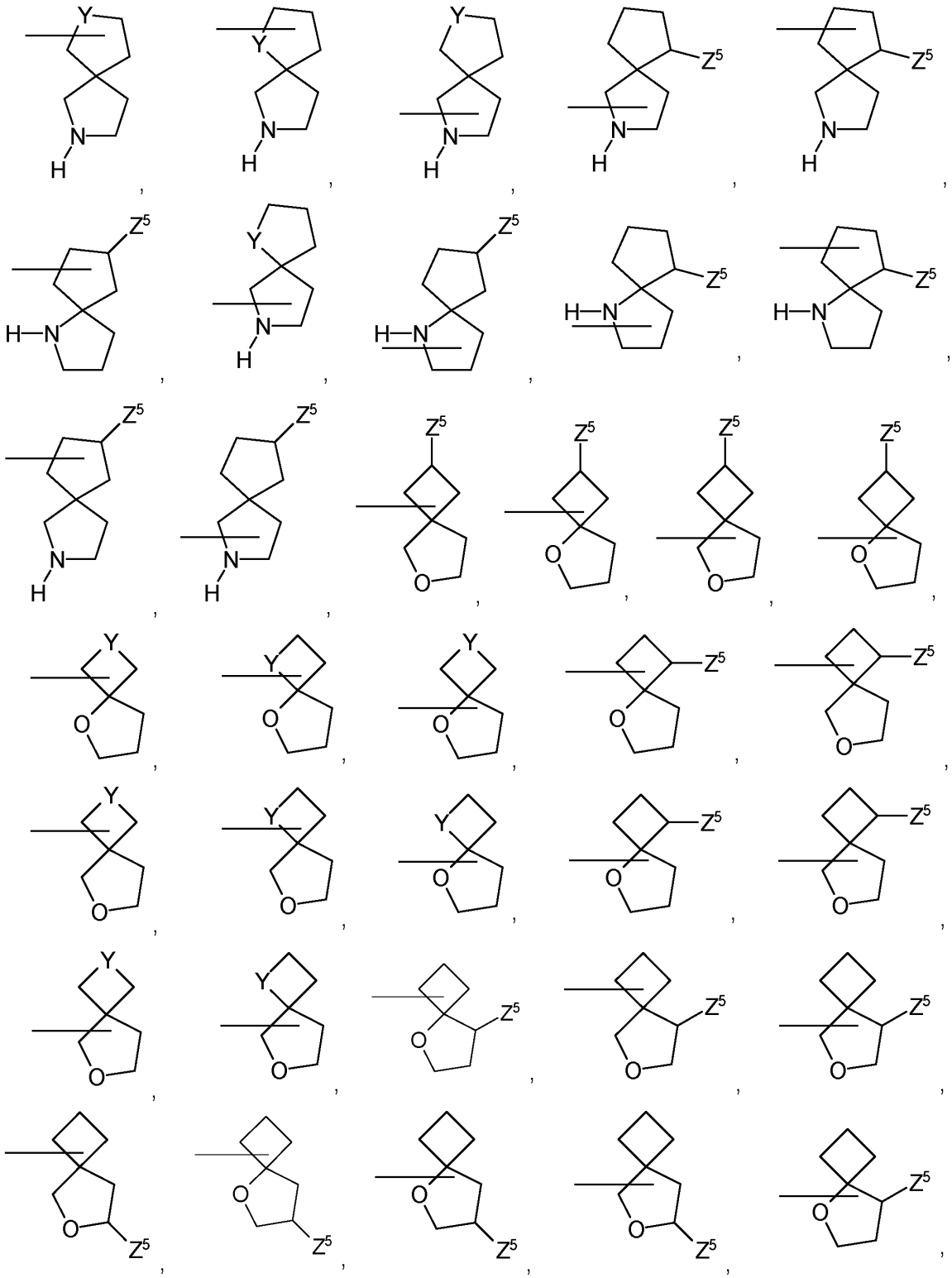



Z5
Y


Z5
Y


Y
Z5
O





wherein Y represents –O–, –NH–, –NR^{N1}–, –NR^{N2}–, –SO–, or –SO_2–, preferably –NH– or –NR^{N1}– and wherein the substituents Z^5, Z^6 and Z^7 have the meanings as

defined herein. Of course, substituents Z^5, Z^6 and Z^7 can be replaced with the substitutents Z^1, Z^2, Z^3, and Z^1, Z^2, Z^3, have the meanings as defined herein.

As used herein, the term "**spironitrogencyclyl**" refers to the **C_5–C_{14}/N_1–N_3–spironitrogencyclyl** residues comprising or including the **C_5–C_{14}–spiroheterocyclyl** residues as disclosed above, wherein the heteroatom is nitrogen, i.e. Y is NH, NR^{N1} or NR^{N2}. The term "C_5–C_{14}/N_1–N_3" means that the spiro ring system consists of 5 to 14 carbon atoms and 1 to 3 nitrogen atoms. Moreover the **spironitrogencyclyl** residues can be substituted with 1 to 3 substituents selected from R^{N1}, R^{N2}, Z^1, Z^2, Z^3 ,Z^5, Z^6 and Z^7. However it is clear to a skilled person that the term "can be substituted" refers to the replacement of a hydrogen atom by one of the substituents R^{N1}, R^{N2}, Z^1, Z^2, Z^3, Z^5, Z^6 or Z^7. It is also possible that two of the substituents Z^5, Z^6 and Z^7 represent together an oxygen atom and form together with the carbon atom of the spironitrogencyclyl residue to which they are both attached a carbonyl moiety. Moreover the **C_5–C_{14}/N_1–N_3–spironitrogencyclyl** residues are characterized in that the spironitrogencyclyl residue is linked through a nitrogen atom of the spiro ring system and not through a carbon atom of the spiro ring system. This means in regard to the above-mentioned C_5–C_{14}–spiroheterocyclyl residue that the heteroatom Y is nitrogen and that this C_5–C_{14}–spiroheterocycly residue is linked to the rest of the molecule through this nitrogen atom (which is Y). If the **C_5–C_{14}/N_1–N_3–spironitrogencyclyl** residue contains a second nitrogen atom, it is substituted by one of the substituents R^{N1}, R^{N2}. Thus the indication "N_2" refers to a first nitrogen atom through which the **spironitrogencyclyl** residue is linked and to the group $\diagup\!\!\diagdown N\!-\!R^{N2}$ of the spiro ring system. If the spironitrogencyclyl residue contains a third nitrogen atom and both nitrogen atoms are substituted by one of the substituents Z^1, Z^2, Z^3, Z^5, Z^6 and Z^7, the first Z substituent on the second nitrogen atom represents R^{N2} and the second Z substituent on the third nitrogen atom represents R^{N1}. Thus, the indication "N_3" refers to a first nitrogen atom through which the **spironitrogencyclyl** residue is linked and to the groups $\diagup\!\!\diagdown N\!-\!R^{N1}$ and $\diagup\!\!\diagdown N\!-\!R^{N2}$ of the spiro ring system. Thus the **C_5–C_{14}/N_1–N_3–spironitrogencyclyl** residue can contain one, two or three nitrogen atoms in the spiro ring system. The numbers of atoms "**C_5–C_{14}/N_1–N_2**" do not include C and N atoms from the substituents Z^1, Z^2, Z^3, Z^5 to Z^7.

As used herein, the term "**nitrogenheterocyclyl**" refers to **C_5–C_{14}/N_1–N_3/O_0–O_2/S_0–S_1–nitrogenheterocyclyl** residues comprising or including the **C_5–C_{14}–spiroheterocyclyl** residues as disclosed above, wherein the heteroatom is nitrogen, i.e. Y is NH, NR^{N1} or NR^{N2}. The term "**C_5–C_{14}/N_1–N_3/O_0–O_2/S_0–S_1**" means that the spiro ring system consists of 5 to 14 carbon atoms and 1 to 3 nitrogen atoms, 0 to 2 oxygen atoms and 0 or 1 sulfur atom. Moreover the **nitrogenheterocyclyl** residues can be substituted with

1 to 3 substituents selected from R^{N1}, R^{N2}, Z^1 to Z^3, Z^5, Z^6 and Z^7. However it is clear to a skilled person that the term "can be substituted" refers to the replacement of a hydrogen atom by one of the substituents Z^1, Z^2, Z^3, Z^5, Z^6 or Z^7. It is also possible that two of the substituents Z^5, Z^6 and Z^7 represent together an oxygen atom and form together with the carbon atom of the **nitrogenheterocyclyl** residue to which they are both attached a carbonyl moiety. Moreover the **C_5–C_{14}/N_1–N_3/O_0–O_2/S_0–S_1–nitrogenheterocyclyl** residues are characterized by that the **nitrogenheterocyclyl** residue is linked through a nitrogen atom of the spiro ring system and not through a carbon atom of the spiro ring system. This means in regard to the above-mentioned C_5–C_{14}–spiroheterocycly residue that the heteroatom Y is nitrogen and that this C_5–C_{14}–spiroheterocycly residue is linked to the rest of the molecule through this nitrogen atom (which is Y). If the C_5–C_{14}/N_1–N_3/O_0–O_2/S_0–S_1–nitrogenheterocyclyl residue contains a second nitrogen atom which is substituted by one of the substituents Z^1, Z^2, Z^3, Z^5, Z^6 and Z^7, said Z substituent represents R^{N2}. Thus, the indication "N_2" refers to a first nitrogen atom through which the nitrogenheterocyclyl residue is linked and to the group $\diagup\!\!\diagdown N\!-\!R^{N2}$ of the spiro ring system. If the **n**itrogenheterocyclyl residue contains a third nitrogen atom and both nitrogen atoms are substituted by one of the substituents Z^5, Z^6 and Z^7, the first Z substituent on the second nitrogen atom represents R^{N2} and the second Z substituent on the third nitrogen atom represents R^{N1}. Thus, the indication "N_3" refers to a first nitrogen atom through which the nitrogenheterocyclyl residue is linked and to the groups $\diagup\!\!\diagdown N\!-\!R^{N1}$ and $\diagup\!\!\diagdown N\!-\!R^{N2}$ of the spiro ring system. The indication "S_1" refers to the group –S– or –SO– or –SO_2– of the spiro ring system. The indication "S_0" means that no sulfur is present in the nitrogenheterocyclyl residue. The indication "O_1" refers to the group –O– and the indication "O_2" to two groups –O– which are not directly linked to each other, while "O_0" indicates that no oxygen is present in the spiro ring system. Thus, the C_5–C_{14}/N_1–N_3/O_0–O_2/S_0–S_1–nitrogenheterocyclyl residue can contain in total 6 hetero atoms while in total not more than 3 hetero atoms should be present in the spiro ring system. Moreover it is preferred that the heteroatoms in the spiro ring system are not directly bound to each other. The numbers of atoms "**C_5–C_{14}/N_1–N_3/O_0–O_2/S_0–S_1**" do not include C, O, S and N atoms from the substituents R^{N1}, R^{N2}, Z^1 to Z^3, Z^5 to Z^7.

Preferred is the presence of one nitrogen atom or two nitrogen atoms or one nitrogen atom and one sulfur atom or one nitrogen atom and one sulfoxide moiety or one nitrogen atom and one sulphone moiety or one nitrogen atom and one oxygen atom or one nitrogen atom and two oxygen atoms or one oxygen atom and two nitrogen atoms in the spiro ring system.

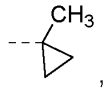
R^8 and **R^9** represents independently of each other preferably the following spironitrogencyclyl, nitrogenheterocyclyl, C_5–C_{14}/N_1–N_3–spironitrogencyclyl or C_5–C_{14}/N_1–N_3/O_0–O_2/S_0–S_1–nitrogenheterocyclyl residues: 4-membered nitrogenheterocyclyl, 5-membered nitrogenheterocyclyl, 6-membered nitrogenheterocyclyl, 5-membered dinitrogenheterocyclyl, 6-membered dinitrogenheterocyclyl, spiro[2,3]heterohexyl, spiro[2,4]heteroheptyl, spiro[2,5]heterooctyl, spiro[2,7]heterononyl, spiro[3,3]heteroheptyl, spiro[3,4]heterooctyl, spiro[3,5]heterononyl, spiro[3,6]heterodecyl, spiro[4,4]heterononyl, spiro[4,5]heterodecyl, spiro[4,6]heteroundecyl, spiro[5,5]heteroundecyl, spiro[5,6]heterododecyl, spiro[6,6]heterotridecyl, wherein the afore-mentioned spironitrogencyclyl, nitrogenheterocyclyl, C_5–C_{14}/N_1–N_3–spironitrogencyclyl or C_5–C_{14}/N_1–N_3/O_0–O_2/S_0–S_1–nitrogenheterocyclyl residues are linked through a ring nitrogen atom to the rest of the molecule and wherein the afore-mentioned spironitrogencyclyl, nitrogenheterocyclyl, C_5–C_{14}/N_1–N_3–spironitrogencyclyl or C_5–C_{14}/N_1–N_3/O_0–O_2/S_0–S_1–nitrogenheterocyclyl residues are optionally substituted with one to three substituents selected from R^{N1}, R^{N2}, Z^1, Z^2, Z^3, Z^5, Z^6 and Z^7.

The term "5-membered dinitrogenheterocyclyl" refers to the residue "5-membered heterocyclyl" as defined above, wherein two heteroatoms are nitrogen atoms and the residue is linked through a nitrogen ring atom to the rest of the molecule and wherein Z^1 is replaced by Z^5, Z^2 is replaced by Z^6, Z^3 is replaced by Z^7, and Z^4 is hydrogen.
The term "6-membered dinitrogenheterocyclyl" refers to the residue "6-membered heterocyclyl" as defined above, wherein two heteroatoms are nitrogen atoms and the residue is linked through a nitrogen ring atom to the rest of the molecule and wherein Z^1 is replaced by Z^5, Z^2 is replaced by Z^6, Z^3 is replaced by Z^7, and Z^4 is hydrogen.

Moreover the afore-mentioned spironitrogencyclyl, nitrogenheterocyclyl, C_5–C_{14}/N_1–N_3–spironitrogencyclyl or C_5–C_{14}/N_1–N_3/O_0–O_2/S_0–S_1–nitrogenheterocyclyl residues contain at least one nitrogen atom through which these residues are linked to the rest of the molecule and may contain one or two further moieties selected from oxygen (–O–), sulfoxide (–SO–), sulfone (–SO_2–), carbonyl (–CO–) and nitrogen (–NR^{N1}–).

Preferable substituents Z^5, Z^6 and Z^7 represent independently of each other –H, –CH_3, –C_2H_5, –C_3H_7, –$CH(CH_3)_2$, –OH, –OCH_3, –OC_2H_5, –OC_3H_7, –NH_2, –$NHCH_3$, –$N(CH_3)_2$, –F, –Cl, –Br, –I, –CN, –CH_2F, –CHF_2, –CF_3, –$OCHF_2$, or –OCF_3.

R^{N1}, and **R^{N2}** are preferably selected independently of each other from: –**R^{15}**, –H, –CH_3, –C_2H_5, –C_3H_7, –$CH(CH_3)_2$, –CHF_2, –CF_3,



cyclo-C_3H_5, cyclo-C_4H_7, cyclo-C_5H_9, cyclo-C_6H_{11}, cyclo-C_7H_{13}, –C_4H_9, –CH_2–$CH(CH_3)_2$, –$CH(CH_3)$–C_2H_5, –$C(CH_3)_3$, –C_5H_{11}, –$CH(CH_3)$–C_3H_7, –CH_2–$CH(CH_3)$–C_2H_5, –$CH(CH_3)$–$CH(CH_3)_2$, –$C(CH_3)_2$–C_2H_5, –CH_2–$C(CH_3)_3$, –$CH(C_2H_5)_2$, –C_2H_4–$CH(CH_3)_2$, –C_6H_{13}, –C_7H_{15}, –C_8H_{17}, –Ph, –CH_2–Ph, –CH_2–CH_2–Ph, –C_2H_4–$CH=CH_2$, –CH_2–$CH=CH$–CH_3, –CH_2–$C(CH_3)=CH_2$, –$CH(CH_3)$–$CH=CH_2$, –CH_2–$CH=C(CH_3)_2$, –CH_2-C≡CH, –C_2H_4–C≡CH, –CH_2–C≡C–CH_3, –$COCH_3$, –COC_2H_5, –COC_3H_7, –CO–cyclo-C_3H_5, –$COCH(CH_3)_2$, –$COC(CH_3)_3$, –COOH, –$COOCH_3$, –$COOC_2H_5$, –$COOC_3H_7$, –COO–cyclo-C_3H_5, –$COOCH(CH_3)_2$, –$COOC(CH_3)_3$, –$COOCH_2Ph$, –$CONH_2$, –$CONHCH_3$, –$CONHC_2H_5$, –$CONHC_3H_7$, –CONH–cyclo-C_3H_5, –$CONH[CH(CH_3)_2]$, –$CONH[C(CH_3)_3]$, –$CON(CH_3)_2$, –$CON(C_2H_5)_2$, –$CON(C_3H_7)_2$, –CON(cyclo-$C_3H_5)_2$, –$CON[CH(CH_3)_2]_2$, –$CON[C(CH_3)_3]_2$, and –SO_3H.

More preferably **R^8** and **R^9** represents independently of each other the following spironitrogencyclyl, nitrogenheterocyclyl, C_5–C_{14}/N_1–N_3–spironitrogencyclyl or C_5–C_{14}/N_1–N_3/O_0–O_2/S_0–S_1–nitrogenheterocyclyl residues: 4-membered nitrogenheterocyclyl linked through the nitrogen atom to the rest of the molecule, 5-membered nitrogenheterocyclyl linked through the nitrogen atom to the rest of the molecule, 6-membered nitrogenheterocyclyl linked through the nitrogen atom, substituted 4-membered nitrogenheterocyclyl linked through the nitrogen atom, substituted 5-membered nitrogenheterocyclyl linked through the nitrogen atom, substituted 6-membered nitrogenheterocyclyl linked through the nitrogen atom, 5-membered dinitrogenheterocyclyl linked through a nitrogen atom, 6-membered dinitrogenheterocyclyl linked through a nitrogen atom, substituted 5-membered dinitrogenheterocyclyl linked through a nitrogen atom, substituted 6-membered dinitrogenheterocyclyl linked through a nitrogen atom to the rest of the molecule, wherein the afore-mentioned spironitrogencyclyl, nitrogenheterocyclyl, C_5–C_{14}/N_1–N_3–spironitrogencyclyl or C_5–C_{14}/N_1–N_3/O_0–O_2/S_0–S_1–nitrogenheterocyclyl residues are optionally substituted with one to three substituents selected from R^{N1}, R^{N2}, Z^1, Z^2, Z^3, Z^5, Z^6 and Z^7.

Still more preferably **R^8** and **R^9** represents independently of each other the following spironitrogencyclyl, nitrogenheterocyclyl, C_5–C_{14}/N_1–N_3–spironitrogencyclyl or C_5–C_{14}/N_1–N_3/O_0–O_2/S_0–S_1–nitrogenheterocyclyl residues:
azaspiro[3,3]heptyl linked through the nitrogen atom, azaspiro[3,4]octyl linked through the nitrogen atom, azaspiro[3,5]nonyl linked through the nitrogen atom, azaspiro[3,6]decyl linked through the nitrogen atom, azaspiro[4,4]nonyl linked through the nitrogen atom, azaspiro[4,5]decyl linked through the nitrogen atom,

azaspiro[4,6]undecyl linked through the nitrogen atom, azaspiro[5,5]undecyl linked through the nitrogen atom, azaspiro[5,6]dodecyl linked through the nitrogen atom, azaspiro[6,6]tridecyl linked through the nitrogen atom,

substituted azaspiro[3,3]heptyl linked through the nitrogen atom, substituted azaspiro[3,4]octyl linked through the nitrogen atom, substituted azaspiro[3,5]nonyl linked through the nitrogen atom, substituted azaspiro[3,6]decyl linked through the nitrogen atom, substituted azaspiro[4,4]nonyl linked through the nitrogen atom, substituted azaspiro[4,5]decyl linked through the nitrogen atom, substituted azaspiro[4,6]undecyl linked through the nitrogen atom, substituted azaspiro[5,5]undecyl linked through the nitrogen atom, substituted azaspiro[5,6]dodecyl linked through the nitrogen atom, substituted azaspiro[6,6]tridecyl linked through the nitrogen atom,

diazaspiro[3,3]heptyl linked through a nitrogen atom, diazaspiro[3,4]octyl linked through a nitrogen atom, diazaspiro[3,5]nonyl linked through a nitrogen atom, diazaspiro[3,6]decyl linked through a nitrogen atom, diazaspiro[4,4]nonyl linked through a nitrogen atom, diazaspiro[4,5]decyl linked through a nitrogen atom, diazaspiro[4,6]undecyl linked through a nitrogen atom, diazaspiro[5,5]undecyl linked through a nitrogen atom, diazaspiro[5,6]dodecyl linked through a nitrogen atom, diazaspiro[6,6]tridecyl linked through a nitrogen atom,

substituted diazaspiro[3,3]heptyl linked through a nitrogen atom, substituted diazaspiro[3,4]octyl linked through a nitrogen atom, substituted diazaspiro[3,5]nonyl linked through a nitrogen atom, substituted diazaspiro[3,6]decyl linked through a nitrogen atom, substituted diazaspiro[4,4]nonyl linked through a nitrogen atom, substituted diazaspiro[4,5]decyl linked through a nitrogen atom, substituted diazaspiro[4,6]undecyl linked through a nitrogen atom, substituted diazaspiro[5,5]undecyl linked through a nitrogen atom, substituted diazaspiro[5,6]dodecyl linked through a nitrogen atom, substituted diazaspiro[6,6]tridecyl linked through a nitrogen atom,

triazaspiro[3,5]nonyl linked through a nitrogen atom, triazaspiro[3,6]decyl linked through a nitrogen atom, triazaspiro[4,5]decyl linked through a nitrogen atom, triazaspiro[4,6]undecyl linked through a nitrogen atom, triazaspiro[5,5]undecyl linked through a nitrogen atom, triazaspiro[5,6]dodecyl linked through a nitrogen atom, triazaspiro[6,6]tridecyl linked through a nitrogen atom,

substituted triazaspiro[3,5]nonyl linked through a nitrogen atom, substituted triazaspiro[3,6]decyl linked through a nitrogen atom, substituted triazaspiro[4,5]decyl linked through a nitrogen atom, substituted triazaspiro[4,6]undecyl linked through a nitrogen atom, substituted triazaspiro[5,5]undecyl linked through a nitrogen atom, substituted triazaspiro[5,6]dodecyl linked through a nitrogen atom, substituted triazaspiro[6,6]tridecyl linked through a nitrogen atom,

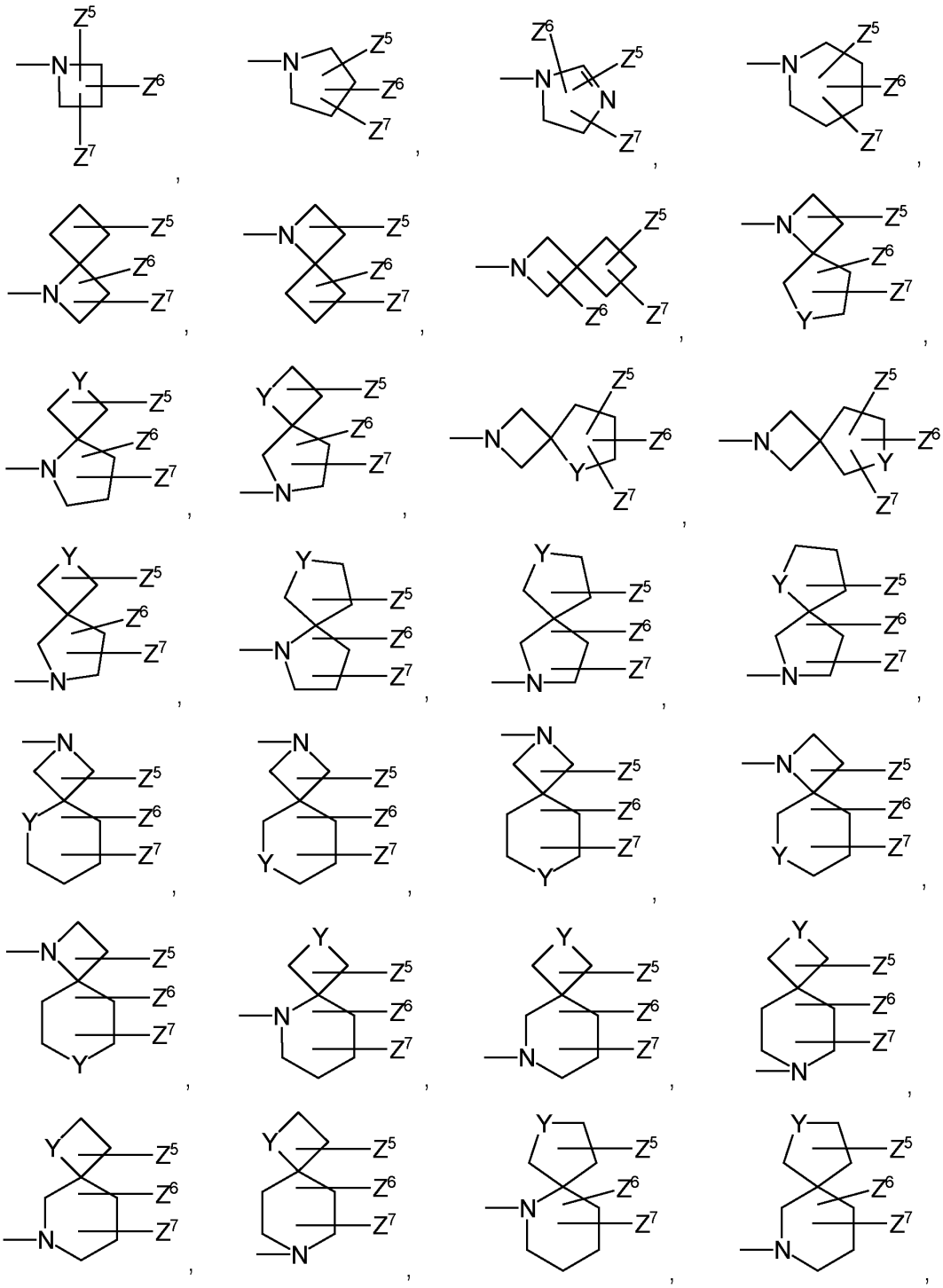
oxazaspiro[3,3]heptyl linked through a nitrogen atom, oxazaspiro[3,4]octyl linked through a nitrogen atom, oxazaspiro[3,5]nonyl linked through a nitrogen atom, oxazaspiro[3,6]decyl linked through a nitrogen atom, oxazaspiro[4,4]nonyl linked through a nitrogen atom, oxazaspiro[4,5]decyl linked through a nitrogen atom, oxazaspiro[4,6]undecyl linked through a nitrogen atom, oxazaspiro[5,5]undecyl linked through a nitrogen atom, oxazaspiro[5,6]dodecyl linked through a nitrogen atom, oxazaspiro[6,6]tridecyl linked through a nitrogen atom,

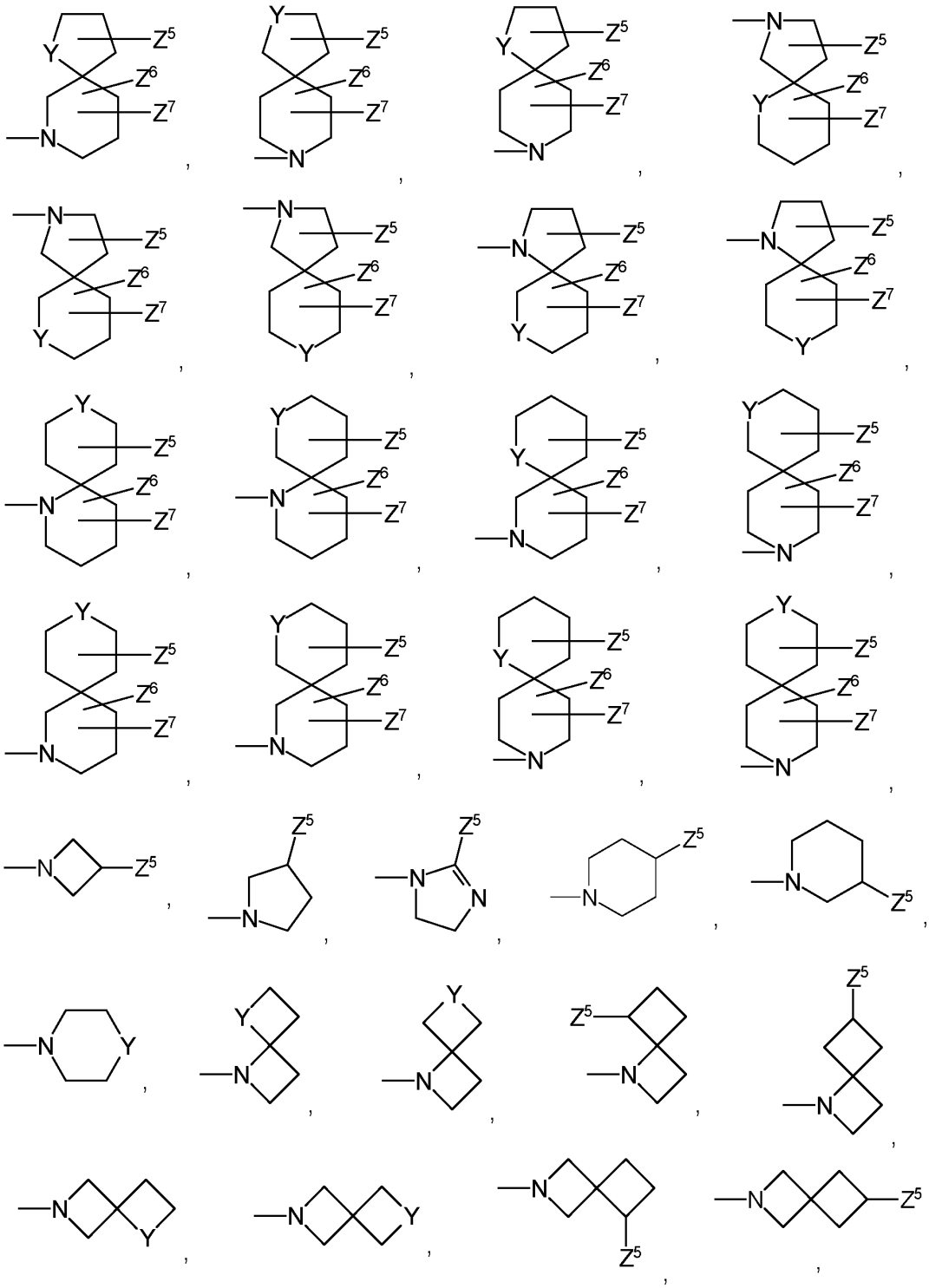
substituted oxazaspiro[3,3]heptyl linked through a nitrogen atom, substituted oxazaspiro[3,4]octyl linked through a nitrogen atom, substituted oxazaspiro[3,5]nonyl linked through a nitrogen atom, substituted oxazaspiro[3,6]decyl linked through a nitrogen atom, substituted oxazaspiro[4,4]nonyl linked through a nitrogen atom, substituted oxazaspiro[4,5]decyl linked through a nitrogen atom, substituted oxazaspiro[4,6]undecyl linked through a nitrogen atom, substituted oxazaspiro[5,5]undecyl linked through a nitrogen atom, substituted oxazaspiro[5,6]dodecyl linked through a nitrogen atom, substituted oxazaspiro[6,6]tridecyl linked through a nitrogen atom,

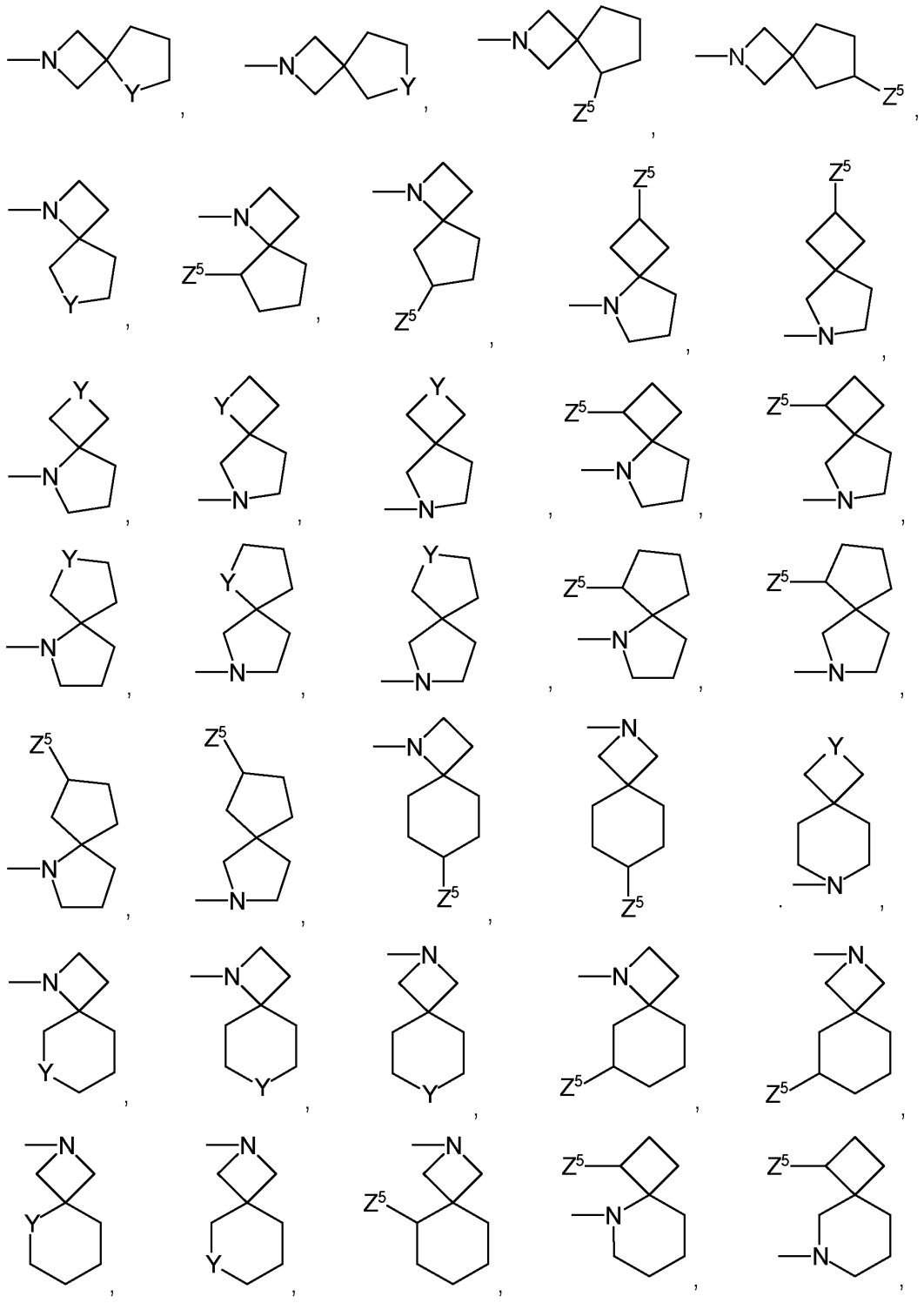
oxadiazaspiro[3,5]nonyl linked through a nitrogen atom, oxadiazaspiro[3,6]decyl linked through a nitrogen atom, oxadiazaspiro[4,5]decyl linked through a nitrogen atom, oxadiazaspiro[4,6]undecyl linked through a nitrogen atom, oxadiazaspiro[5,5]undecyl linked through a nitrogen atom, oxadiazaspiro[5,6]dodecyl linked through a nitrogen atom, oxadiazaspiro[6,6]tridecyl linked through a nitrogen atom,

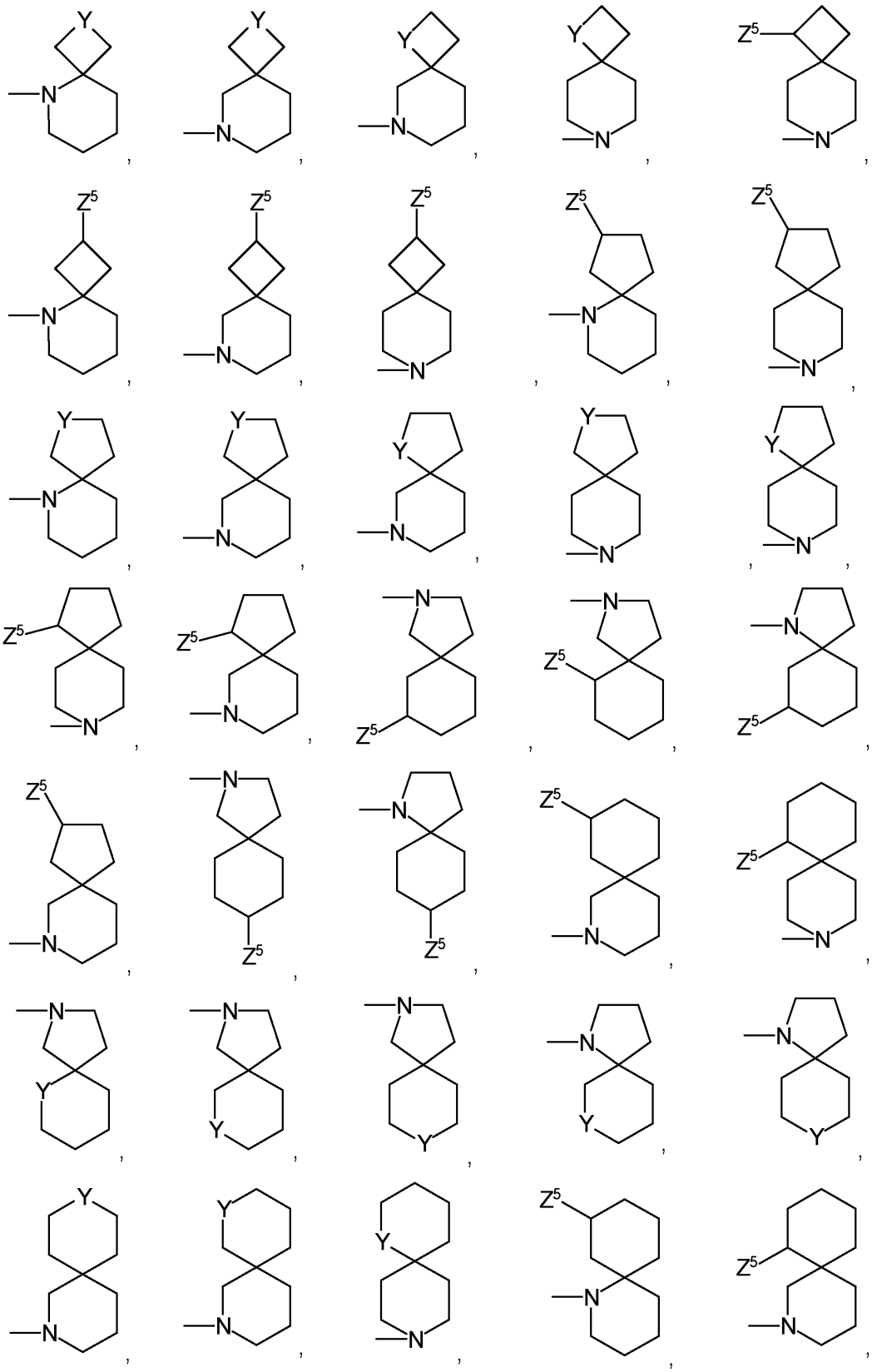
substituted oxadiazaspiro[3,5]nonyl linked through a nitrogen atom, substituted oxadiazaspiro[3,6]decyl linked through a nitrogen atom, substituted oxadiazaspiro[4,5]decyl linked through a nitrogen atom, substituted oxadiazaspiro[4,6]undecyl linked through a nitrogen atom, substituted oxadiazaspiro[5,5]undecyl linked through a nitrogen atom, substituted oxadiazaspiro[5,6]dodecyl linked through a nitrogen atom, substituted oxadiazaspiro[6,6]tridecyl linked through a nitrogen atom, wherein the afore-mentioned substituted spironitrogencyclyl, substituted nitrogenheterocyclyl, substituted C_5–C_{14}/N_1–N_3–spironitrogencyclyl or substituted C_5–C_{14}/N_1–N_3/O_0–O_2/S_0–S_1–nitrogenheterocyclyl residues are optionally substituted with one to three substituents selected from R^{N1}, R^{N2}, Z^5, Z^6 and Z^7. Moreover the afore-mentioned substituted or non-substituted spironitrogencyclyl, substituted or non-substituted nitrogenheterocyclyl, substituted or non-substituted C_5–C_{14}/N_1–N_3–spironitrogencyclyl or substituted or non-substituted C_5–C_{14}/N_1–N_3/O_0–O_2/S_0–S_1–nitrogenheterocyclyl residues contain at least one nitrogen atom through which these residues are linked through the rest of the molecule and may contain one or two further moieties selected from oxygen (–O–), sulfoxide (–SO–), sulfone ($–SO_2–$), carbonyl (–CO–) and nitrogen ($–NR^{N2}–$).

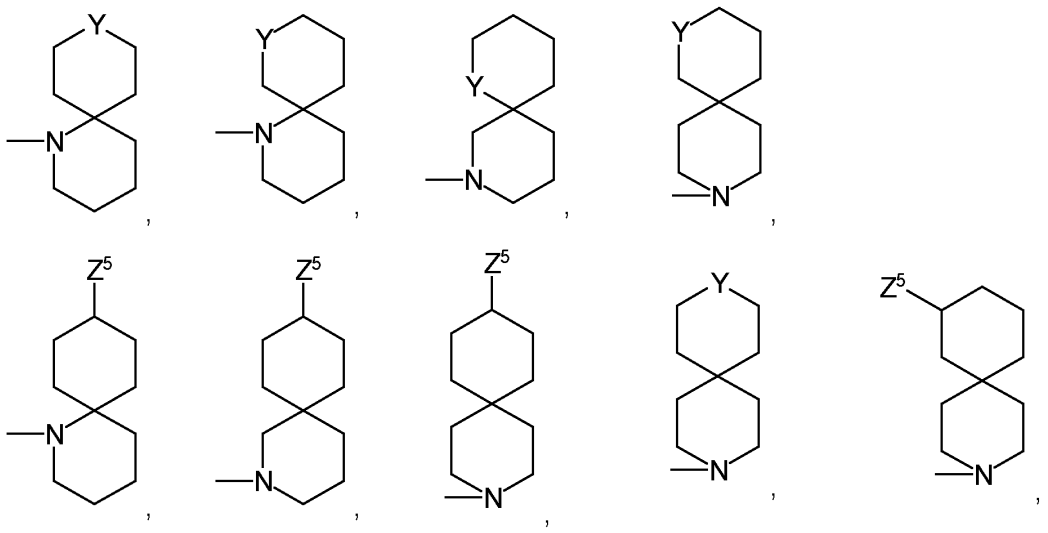
Still more preferably **R**^{8} and **R**^{9} represents independently of each other the following spironitrogencyclyl, nitrogenheterocyclyl, C_5–C_{14}/N_1–N_3–spironitrogencyclyl or C_5–C_{14}/N_1–N_3/O_0–O_2/S_0–S_1–nitrogenheterocyclyl residues:







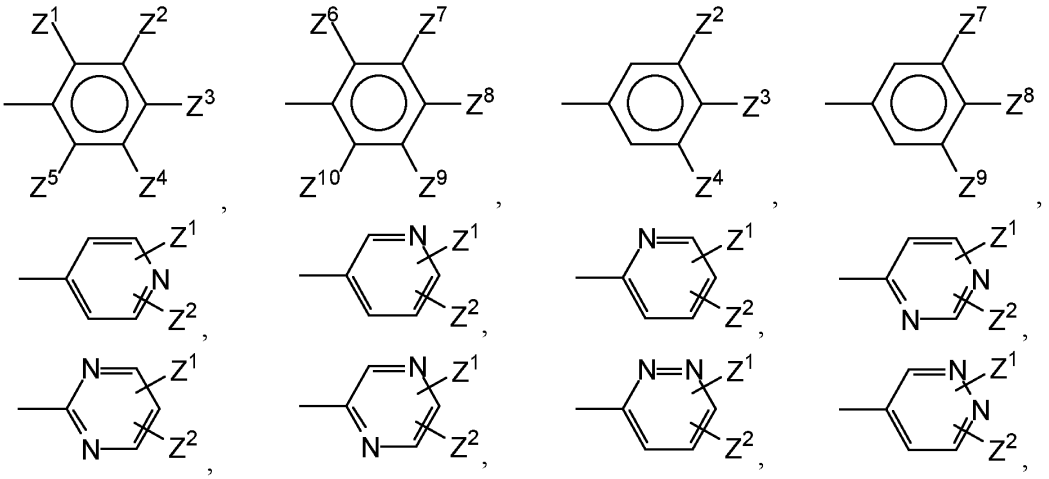


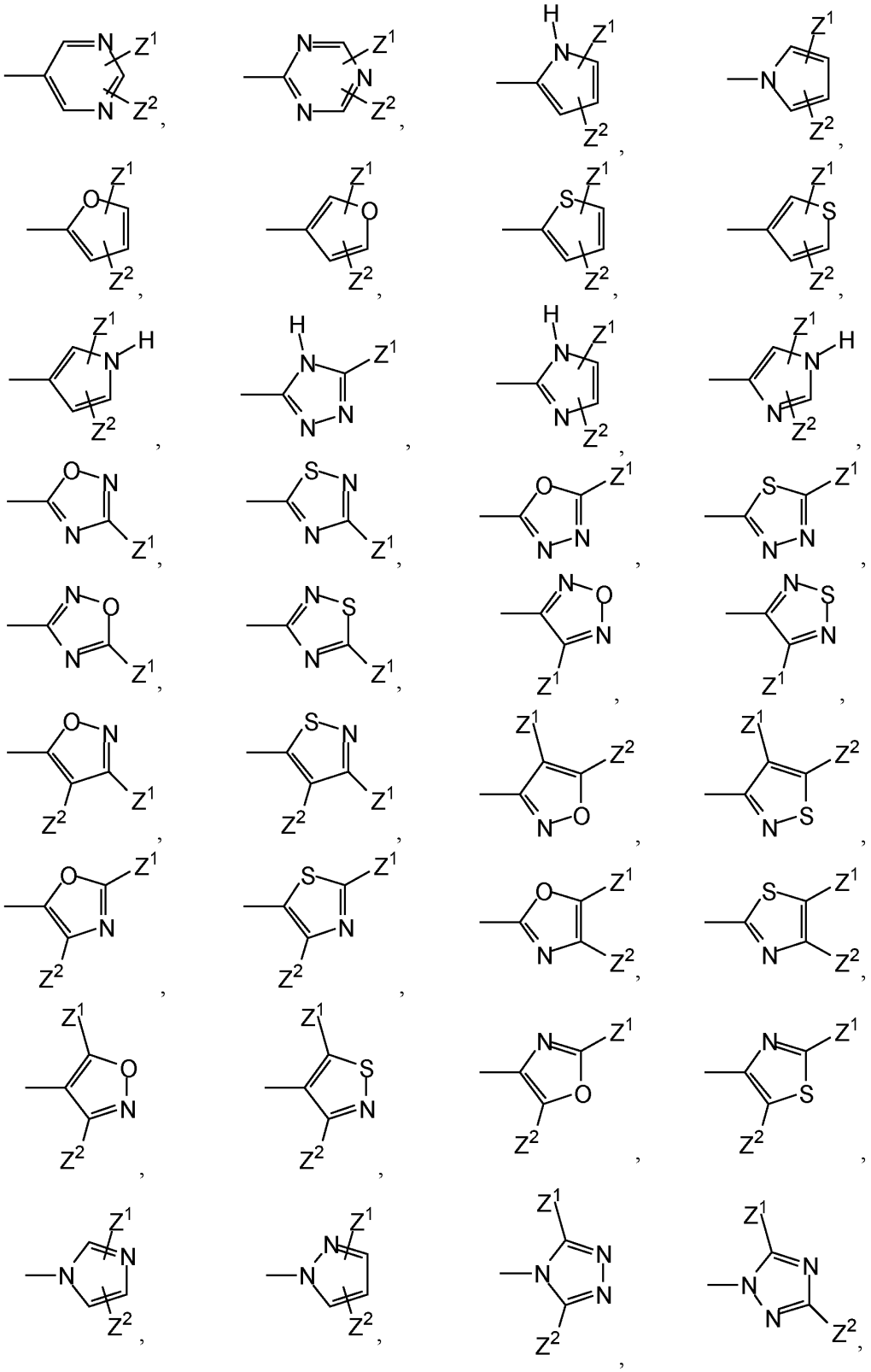


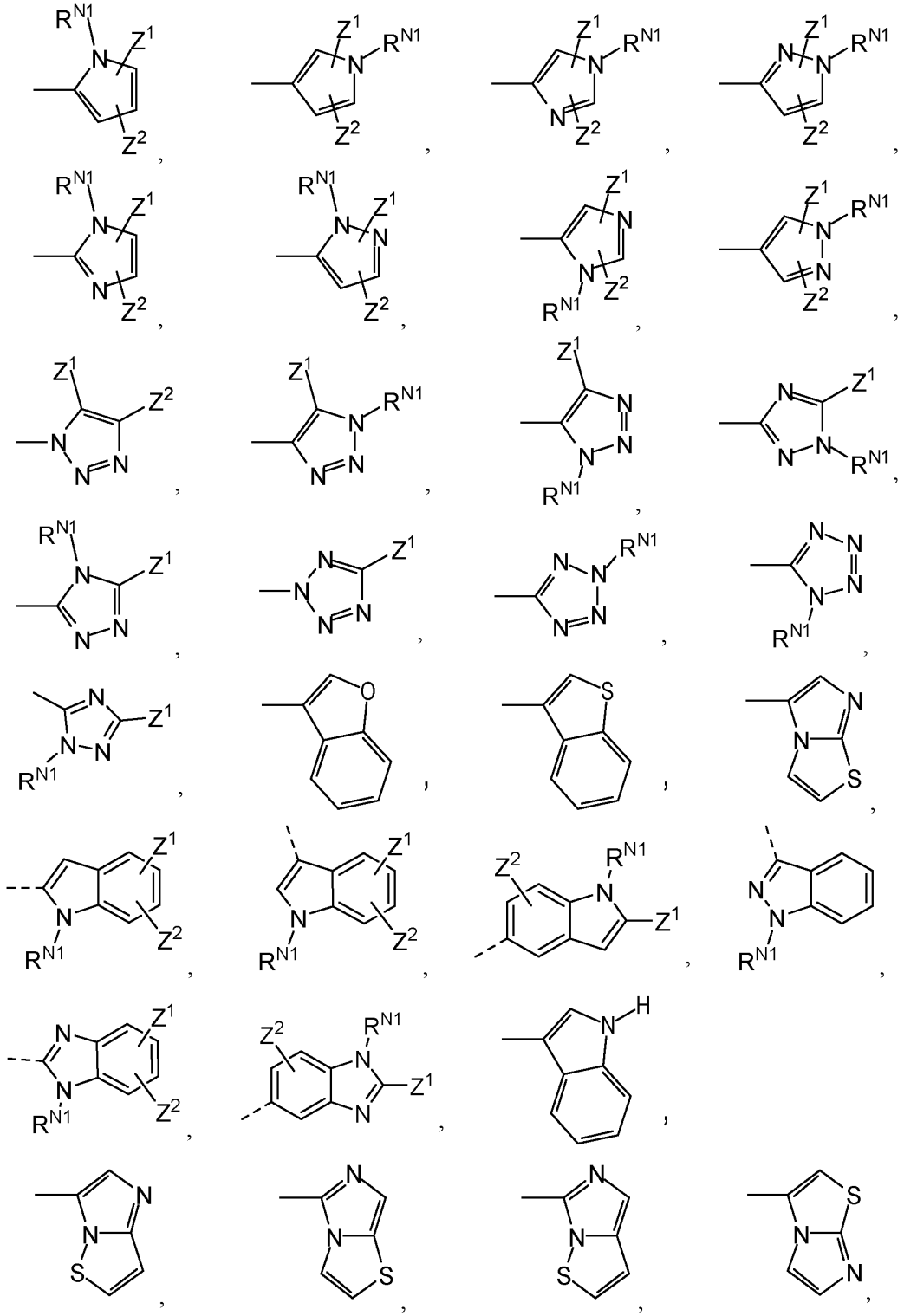
wherein Y represents –O–, –NH–, –NR^{N1}–, –NR^{N2}–, –SO–, or –SO_2–, preferably –NH– or –NR^{N1}– and wherein the substituents Z^5, Z^6 and Z^7 have the meanings as defined herein. the substituents Z^5, Z^6 and Z^7 may be replaced by the substituents Z^1, Z^2 and Z^3.

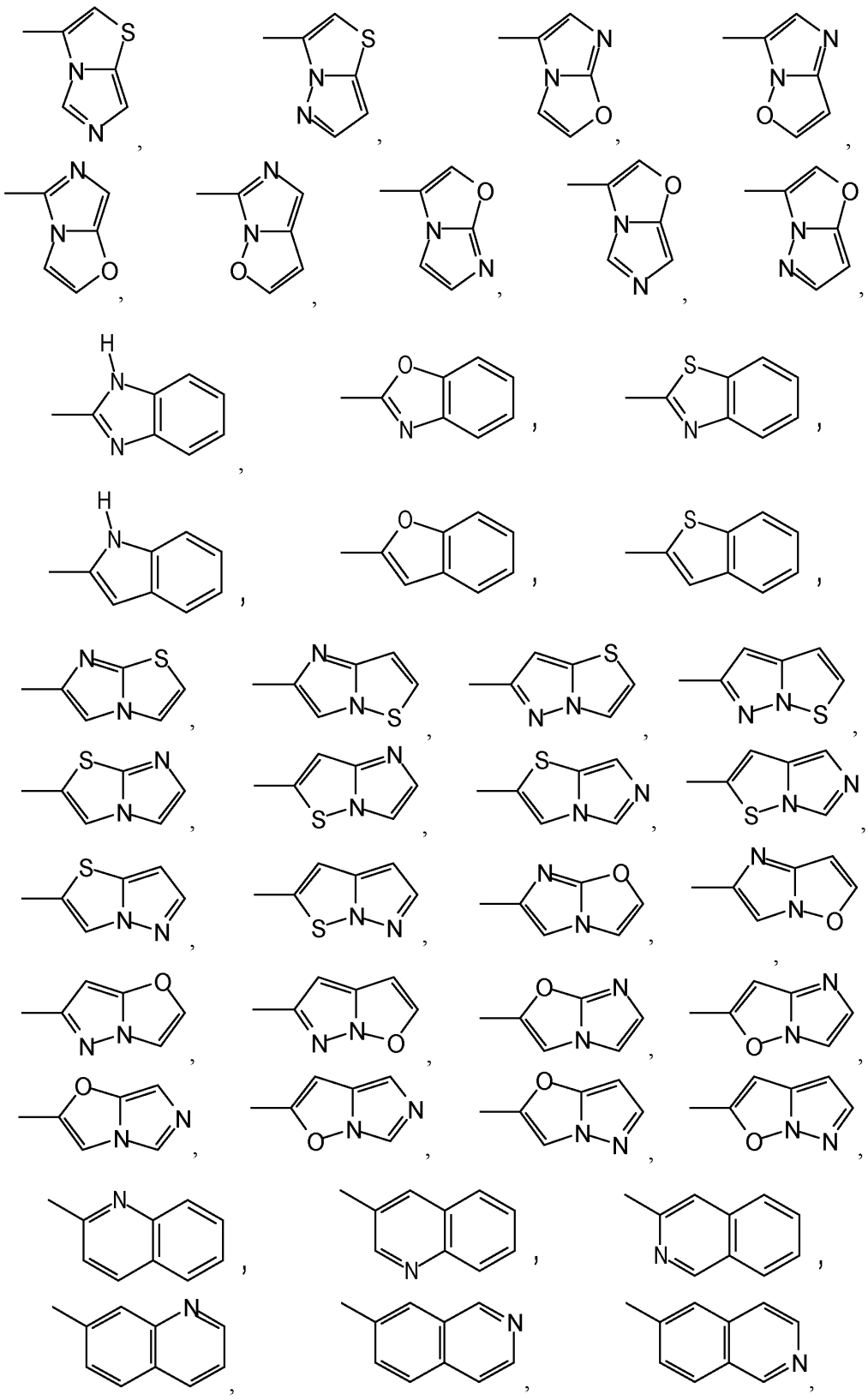
Preferably Z^5, Z^6 and Z^7 represent independently of each other –H, –CH_3, –C_2H_5, –C_3H_7, –$CH(CH_3)_2$, –OH, –OCH_3, –OC_2H_5, –OC_3H_7, –NH_2, –$NH(CH_3)$, –$N(CH_3)_2$, –F, –Cl, –Br, –I, –CN, –CH_2F, –CHF_2, –CF_3, –$OCHF_2$, or –OCF_3, more preferably –NH_2, –$NH(CH_3)$, or –$N(CH_3)_2$.

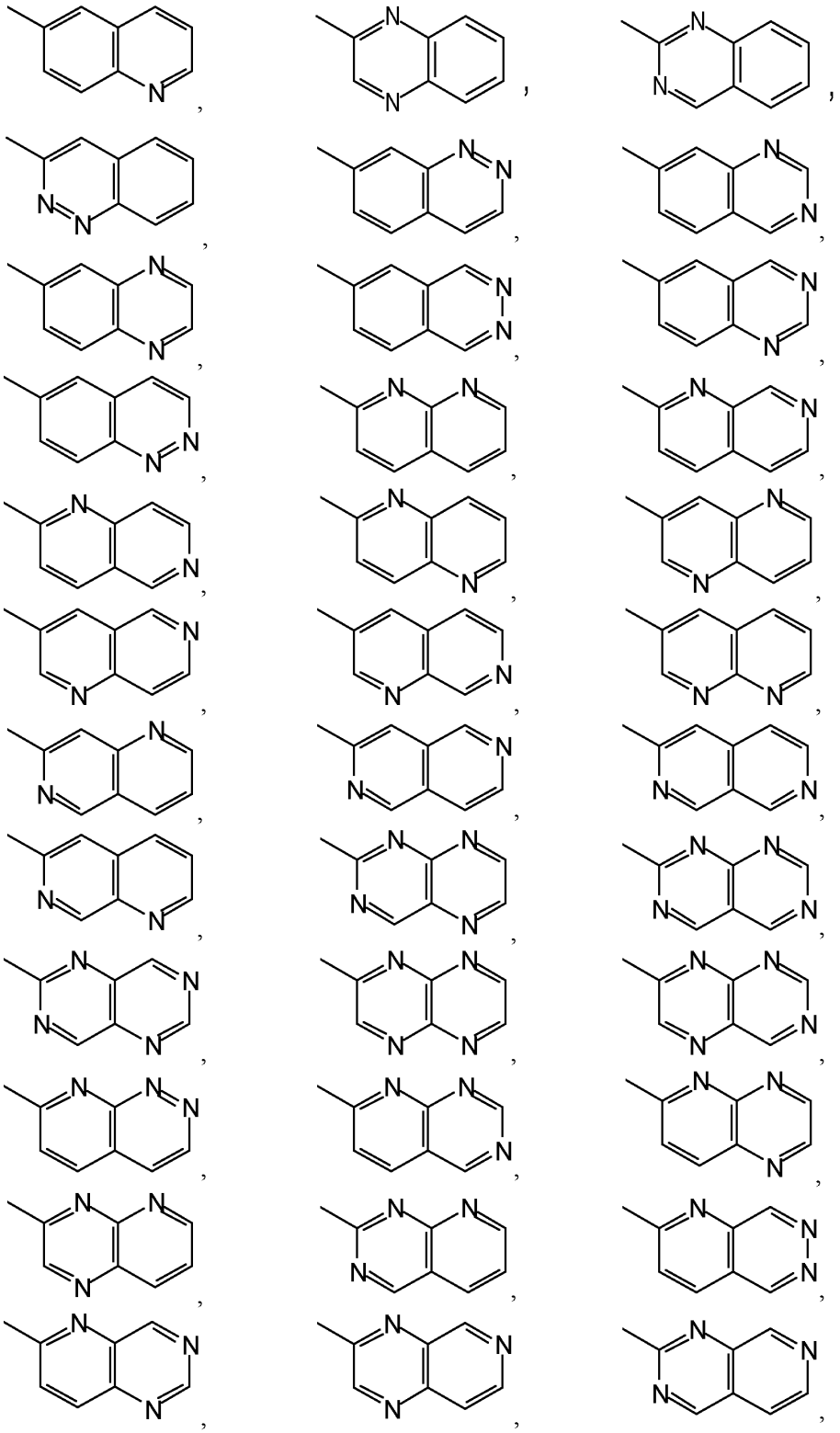
Preferred is the compound of formula (**I**), wherein $\mathbf{R^8}$ and $\mathbf{R^9}$ represent independently of each other:

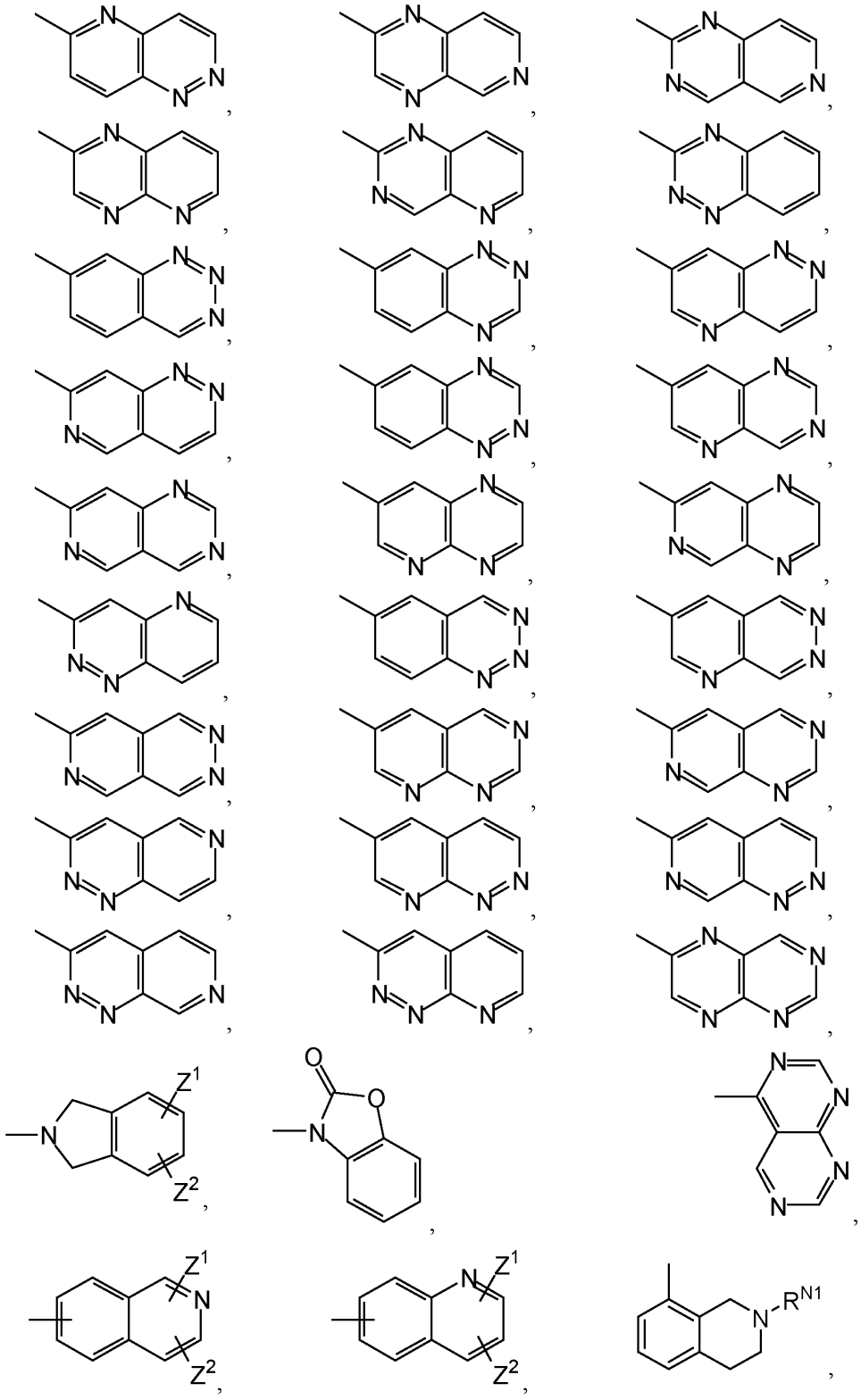


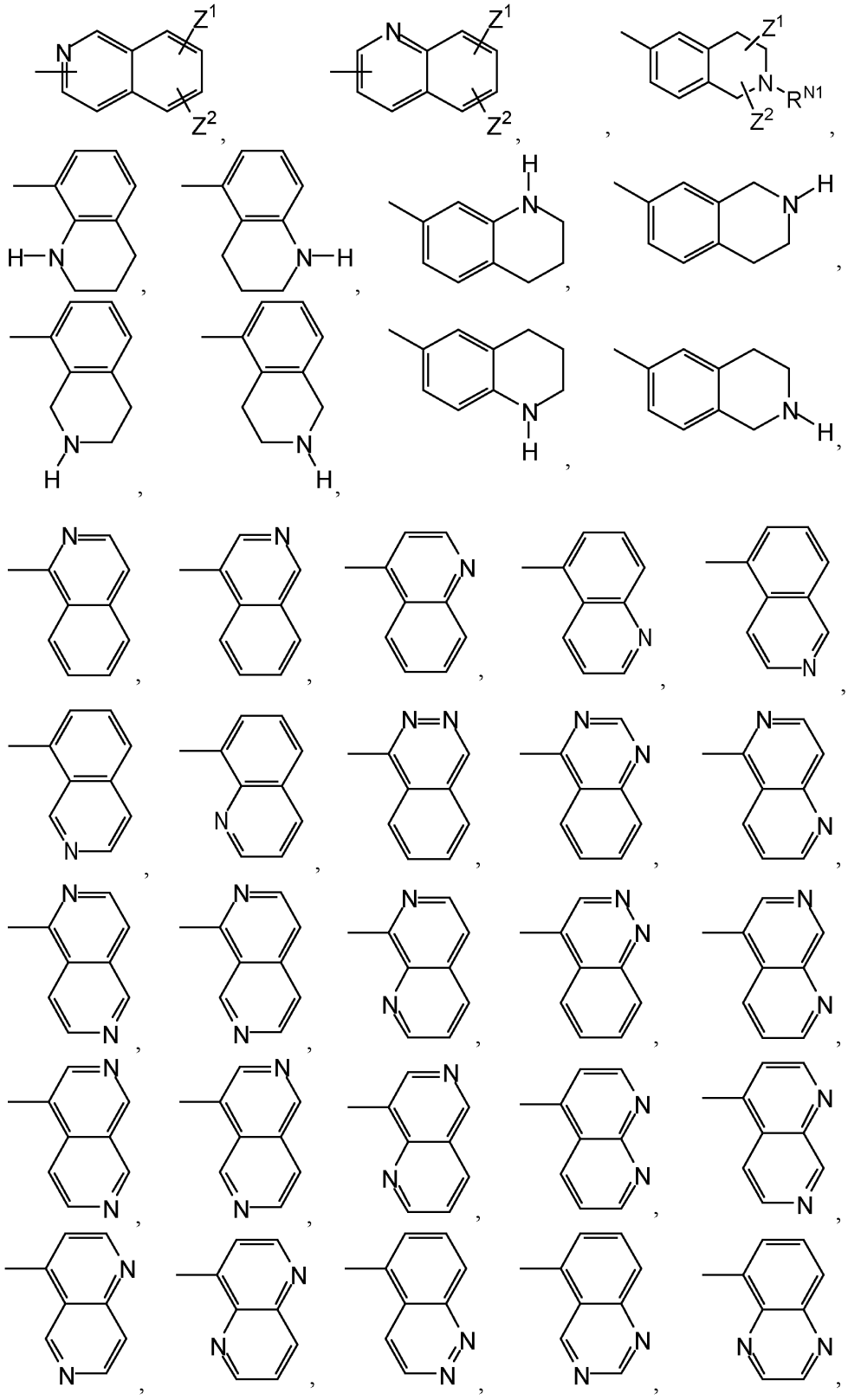


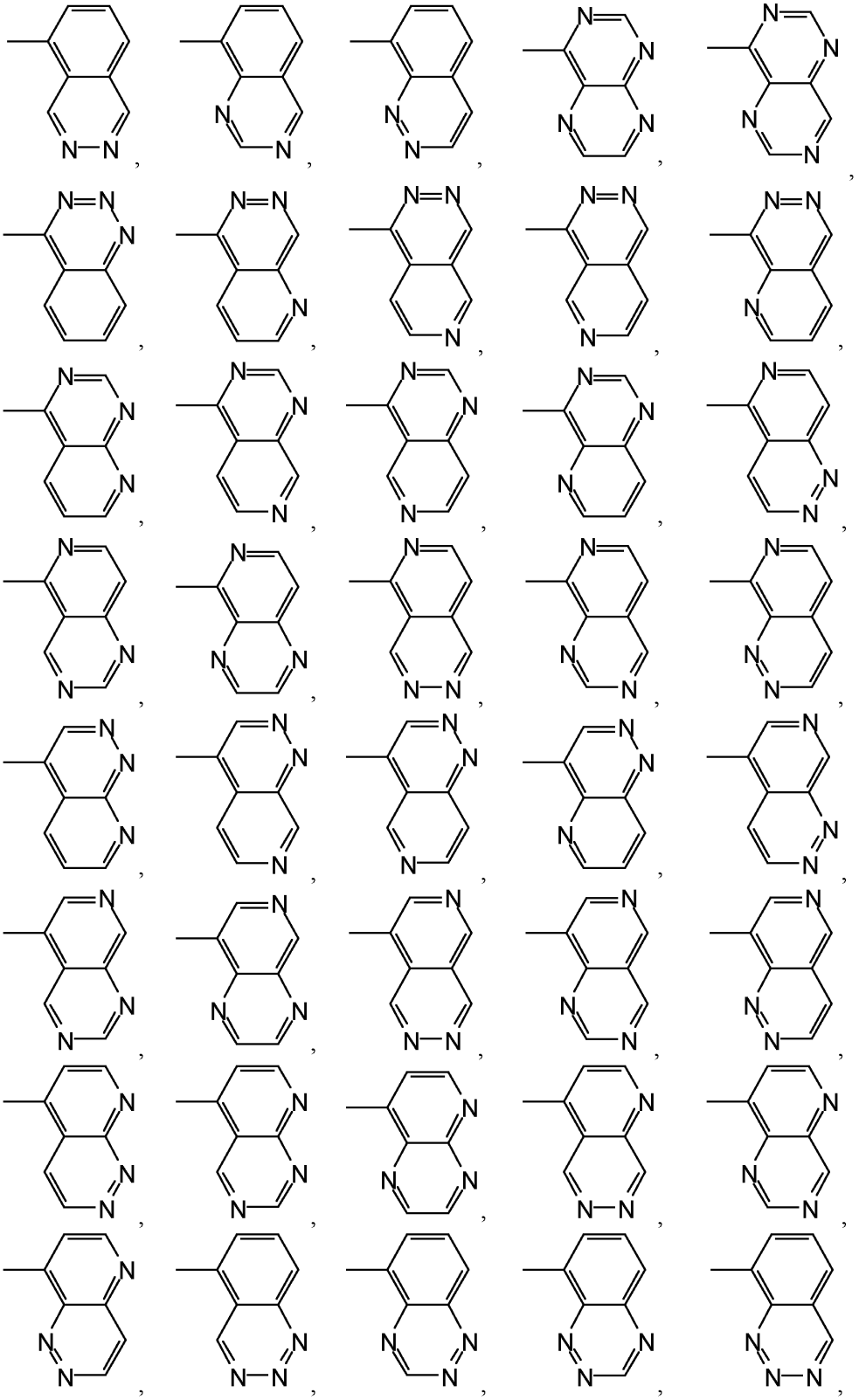


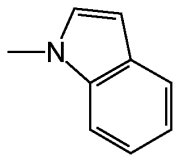
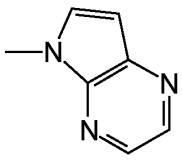
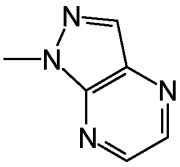
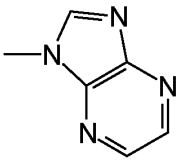
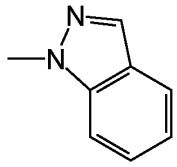
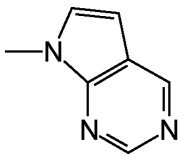
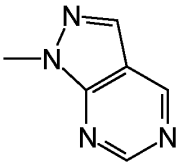
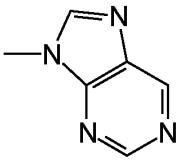
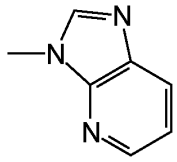
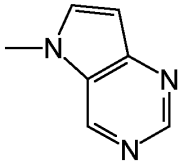
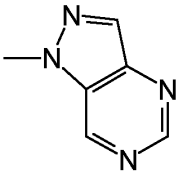
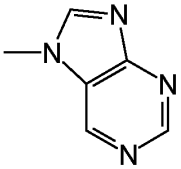
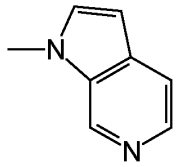
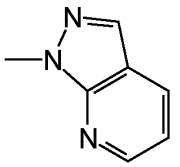
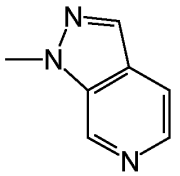
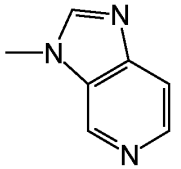
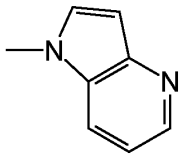
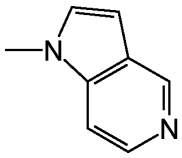
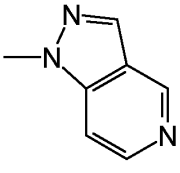
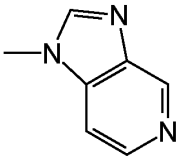
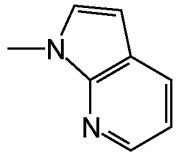
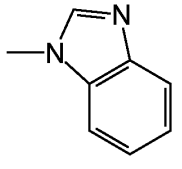
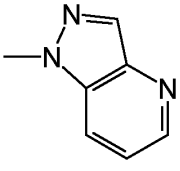
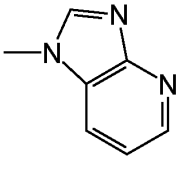
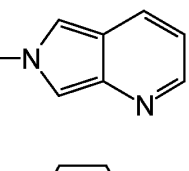
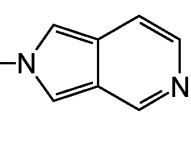
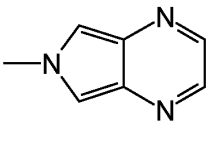
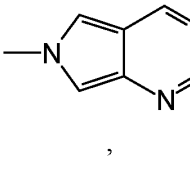
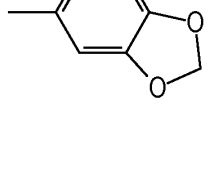
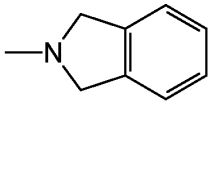
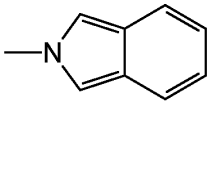


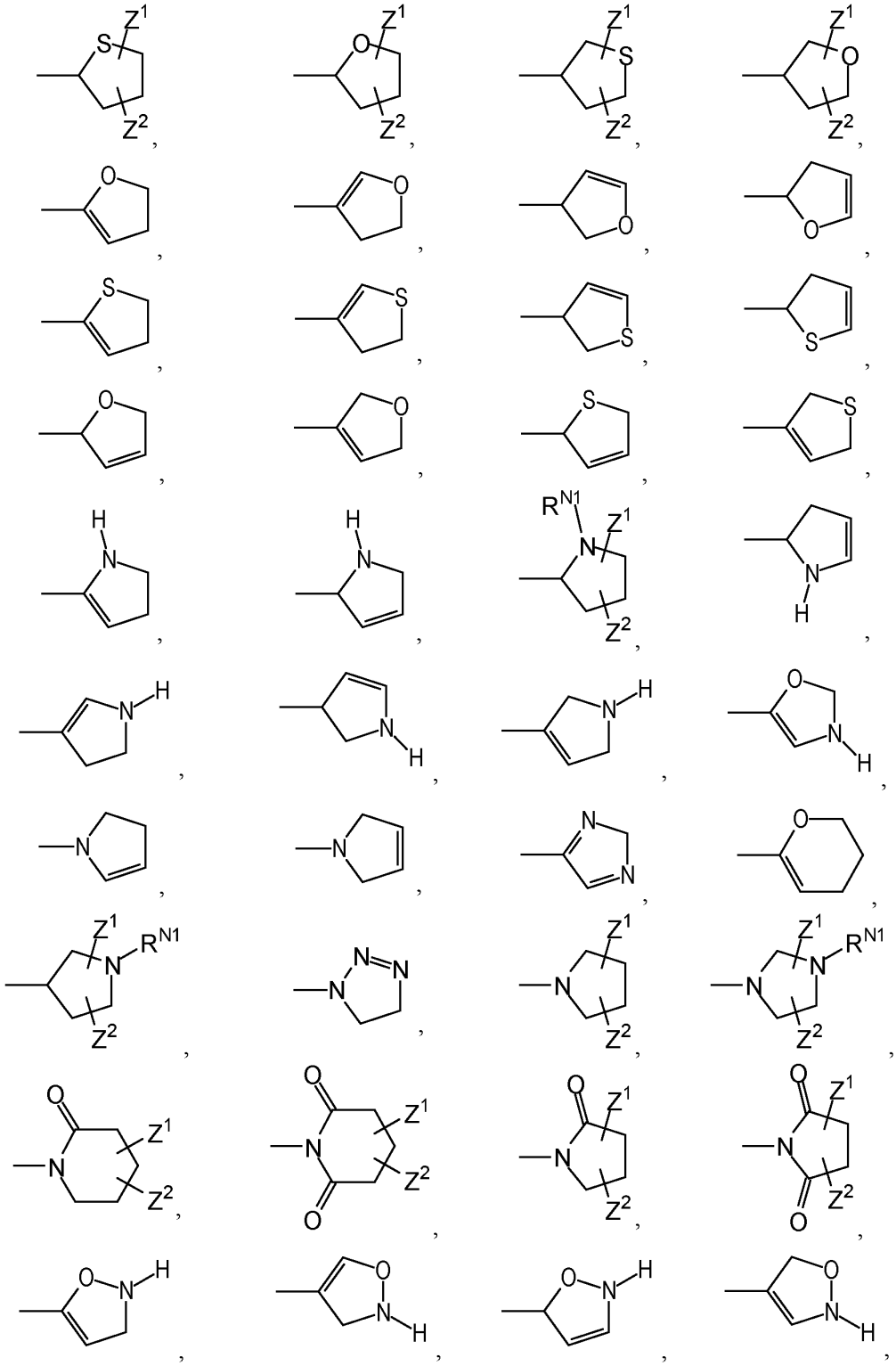


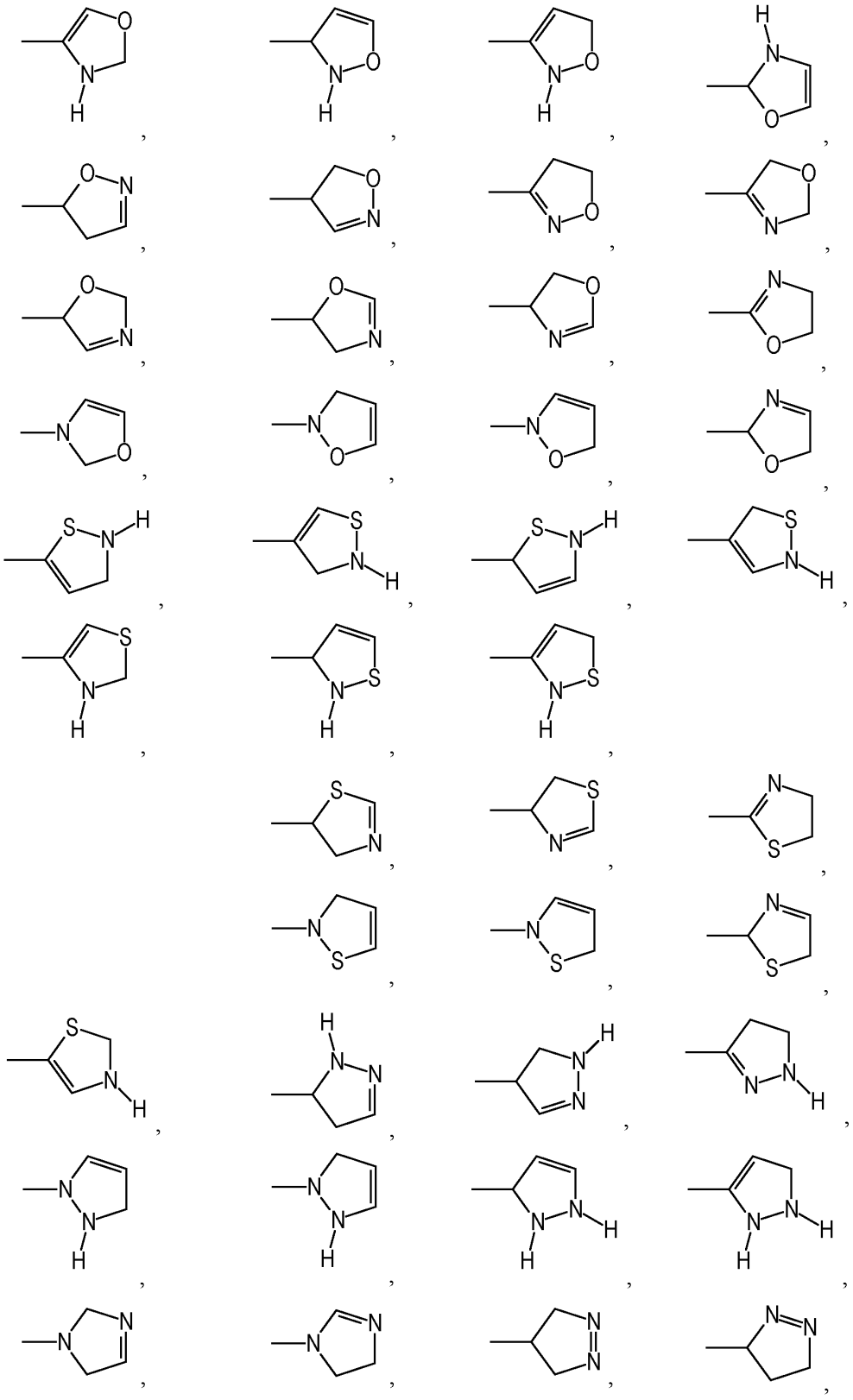


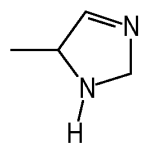
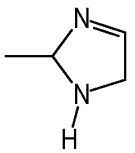
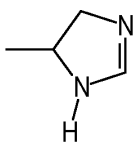
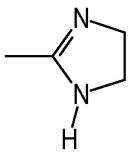
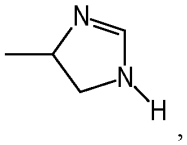
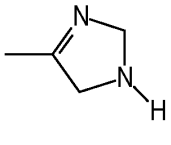
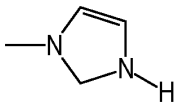
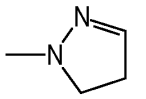
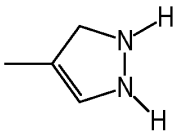
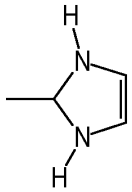
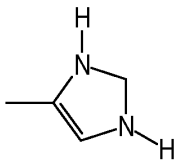
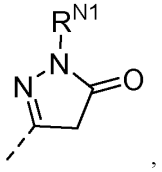
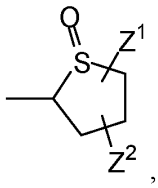
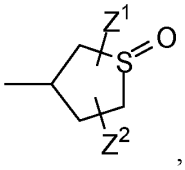
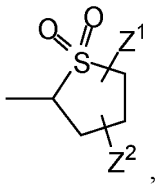
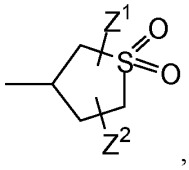
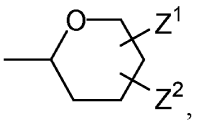
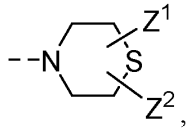
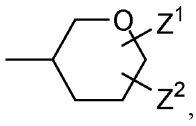
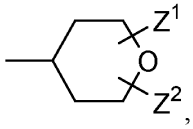
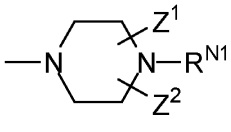
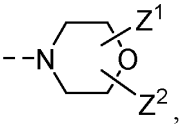
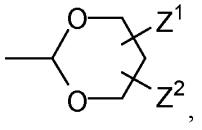
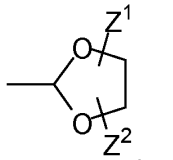
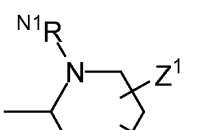
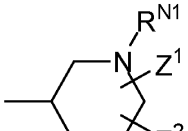
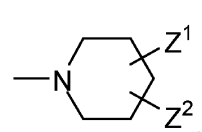
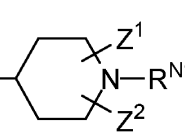
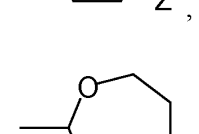
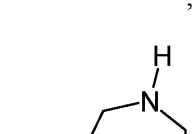
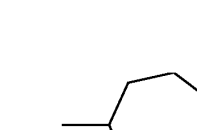
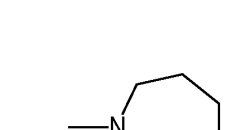
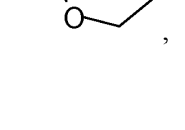
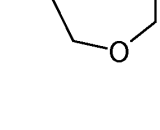
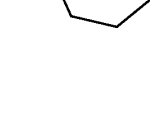
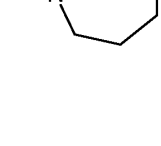


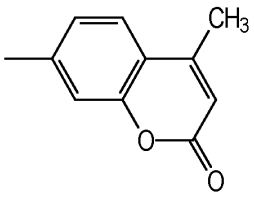
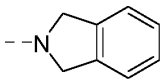
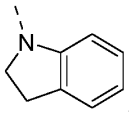
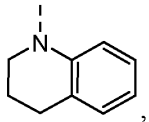


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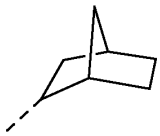


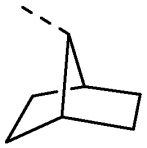
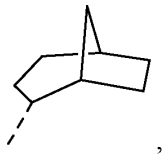
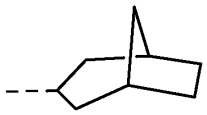

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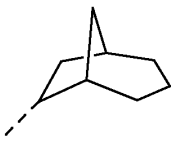
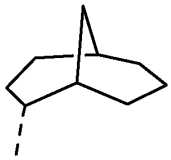
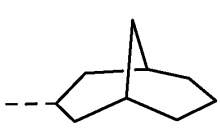
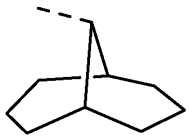
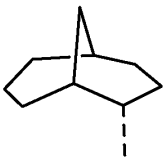
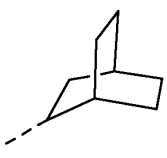
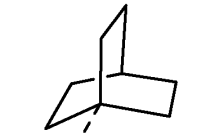
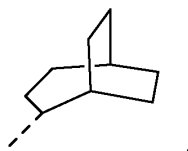
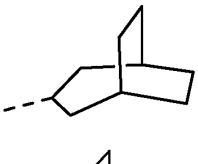
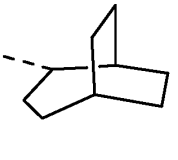
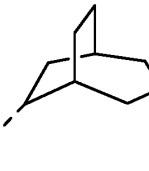
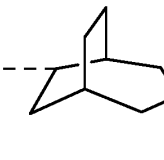
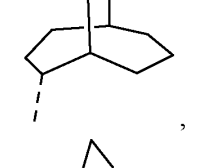
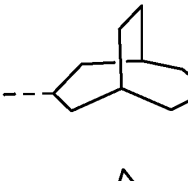
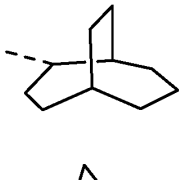
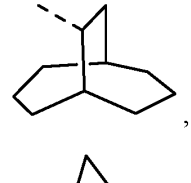
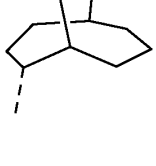
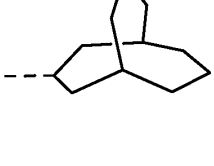
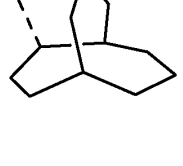
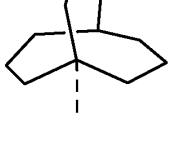





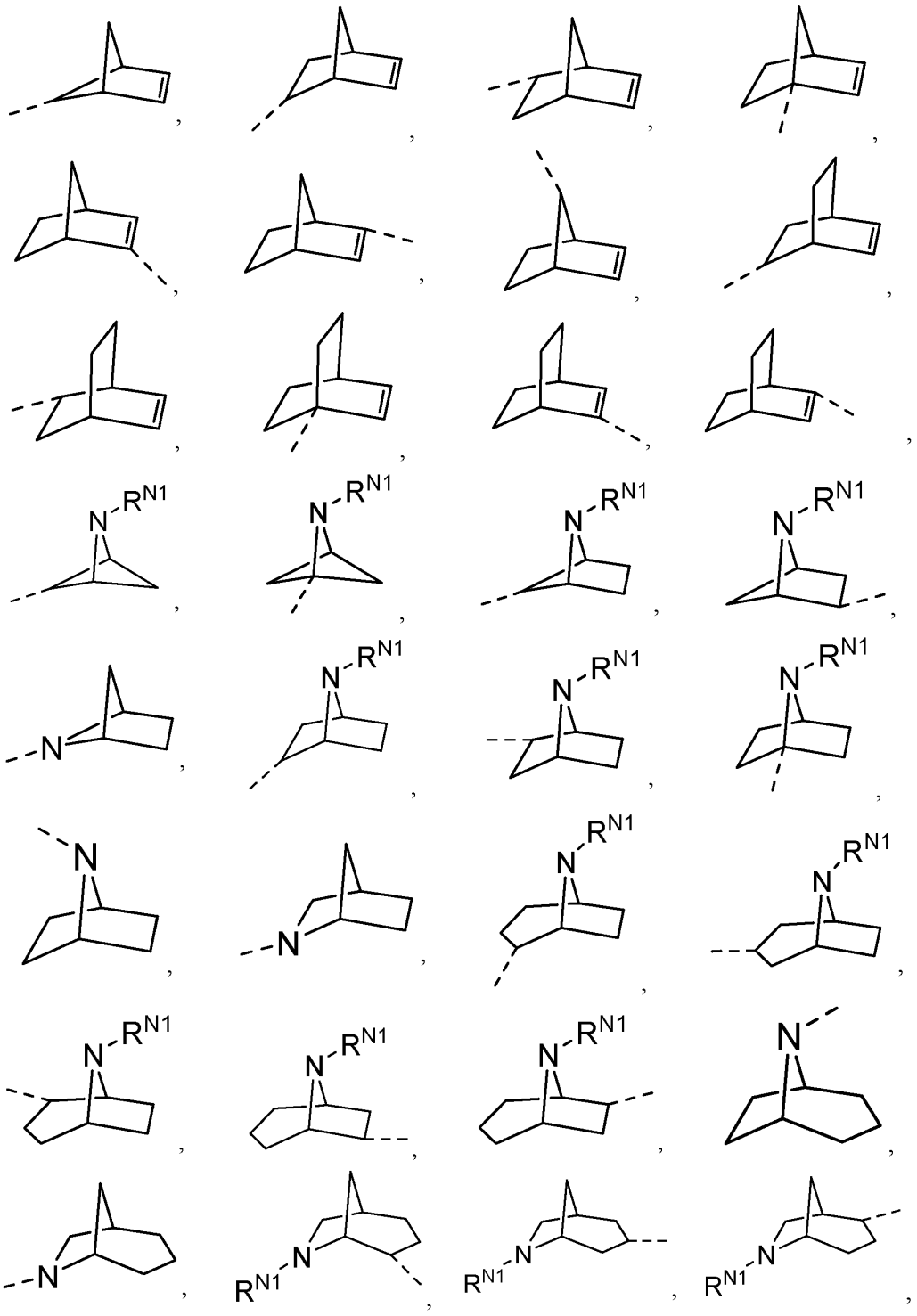


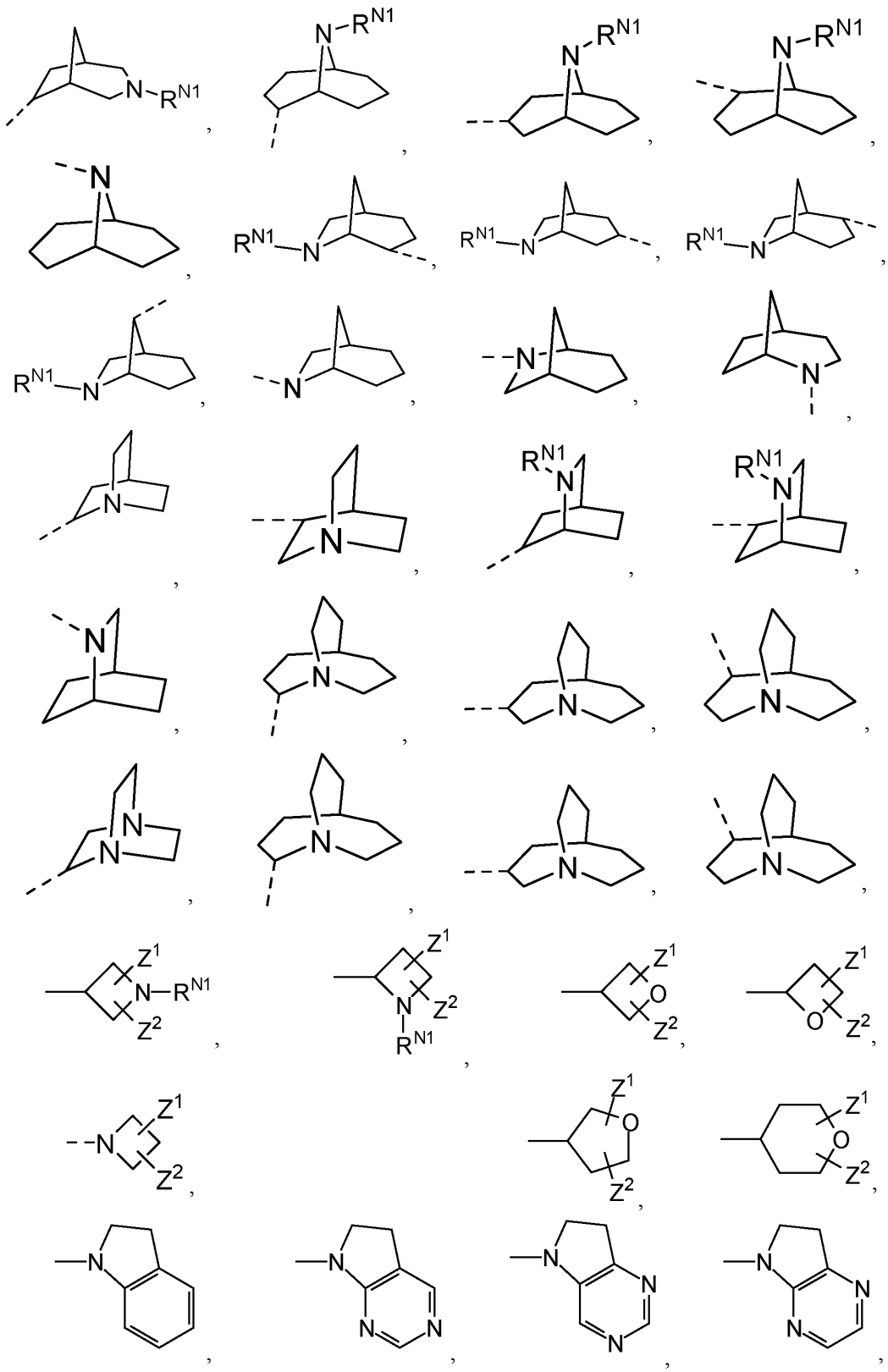


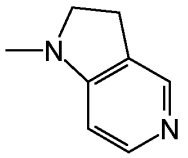
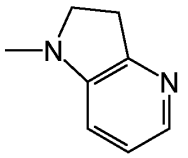
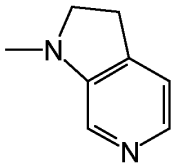
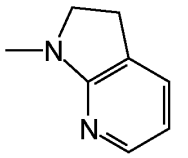
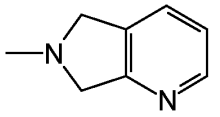
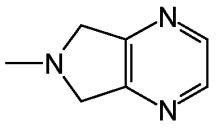
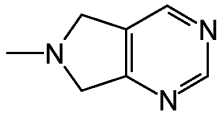
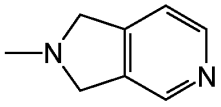
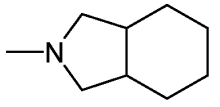
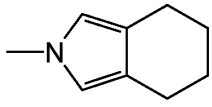
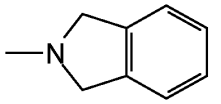
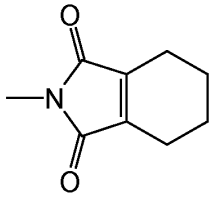
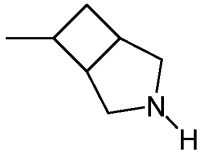
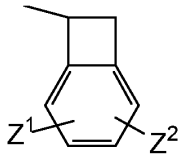
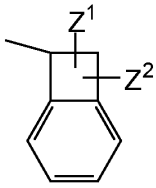
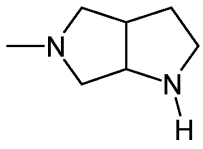
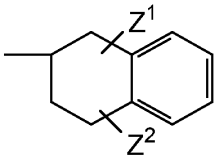
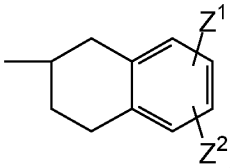
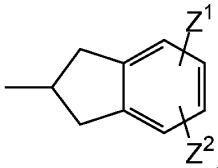
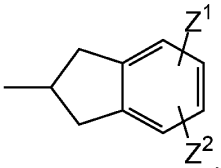
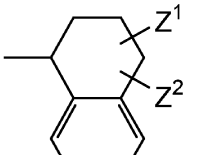
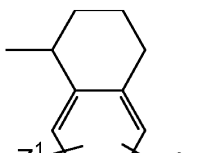
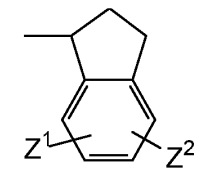
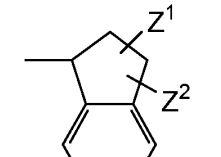
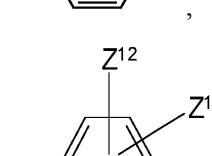
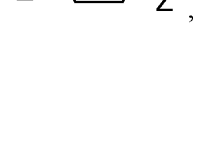


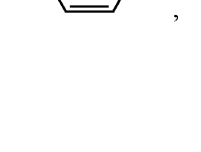
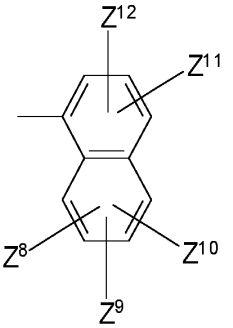
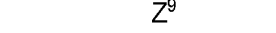




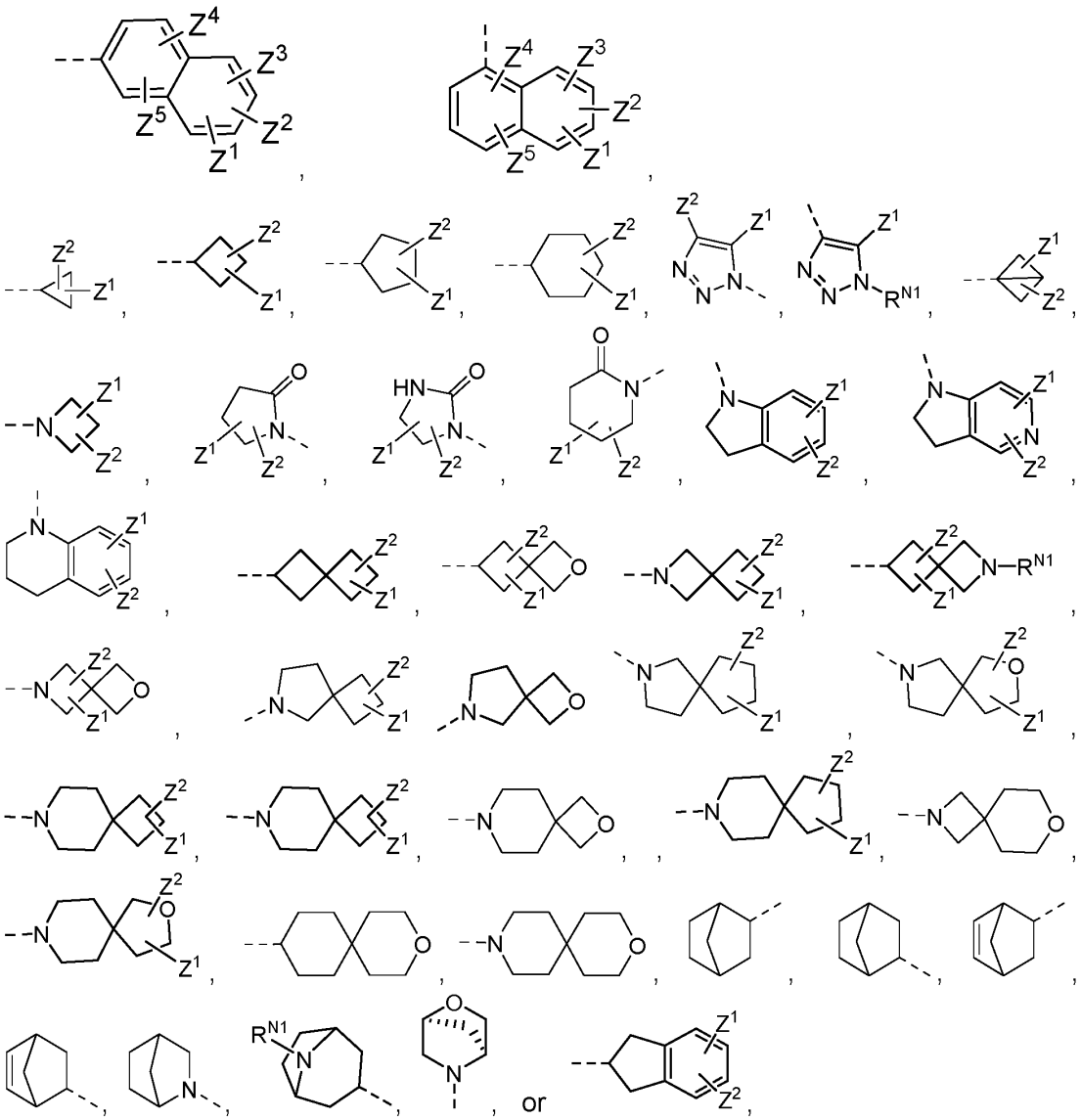























N
RN1



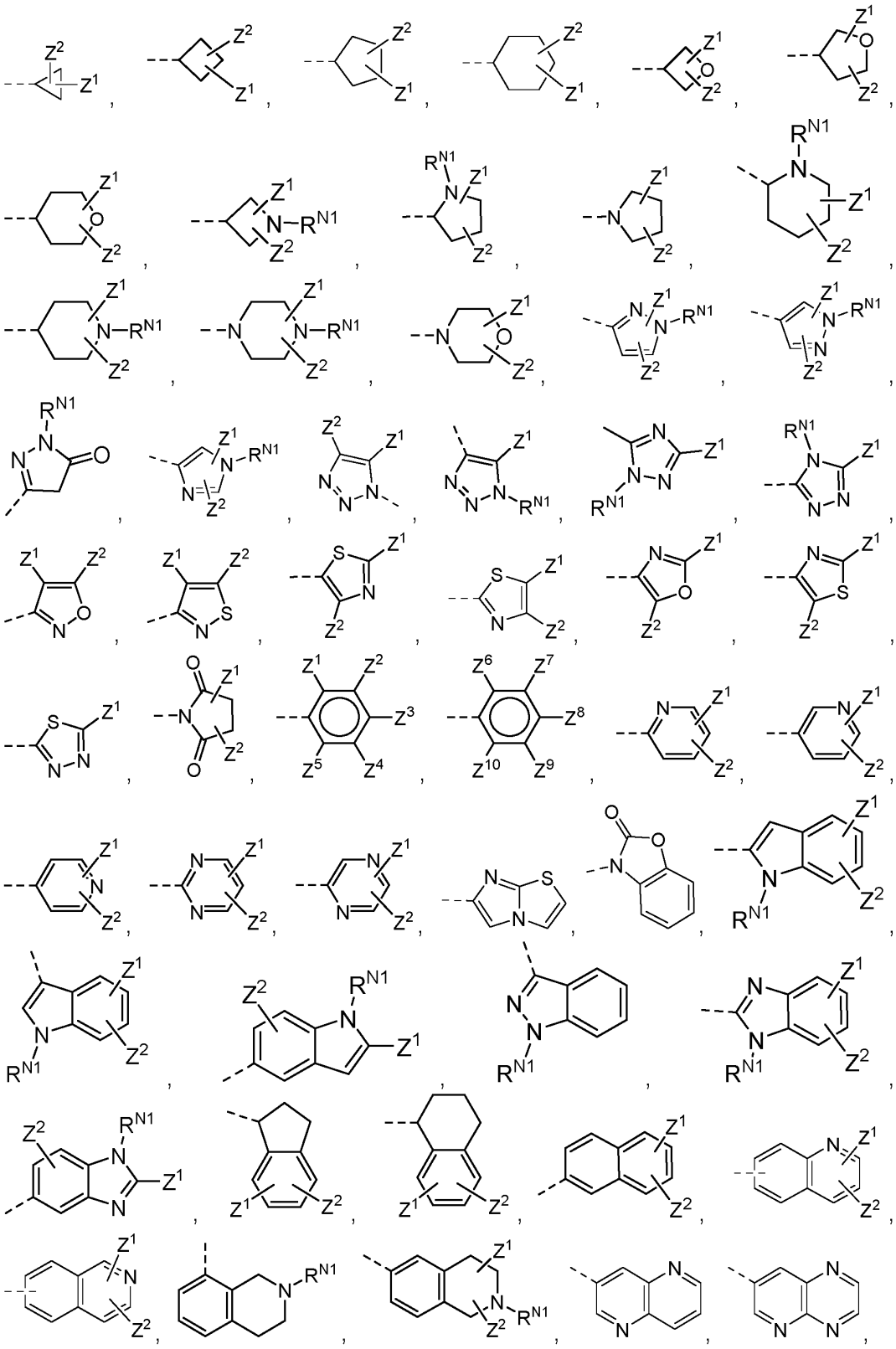

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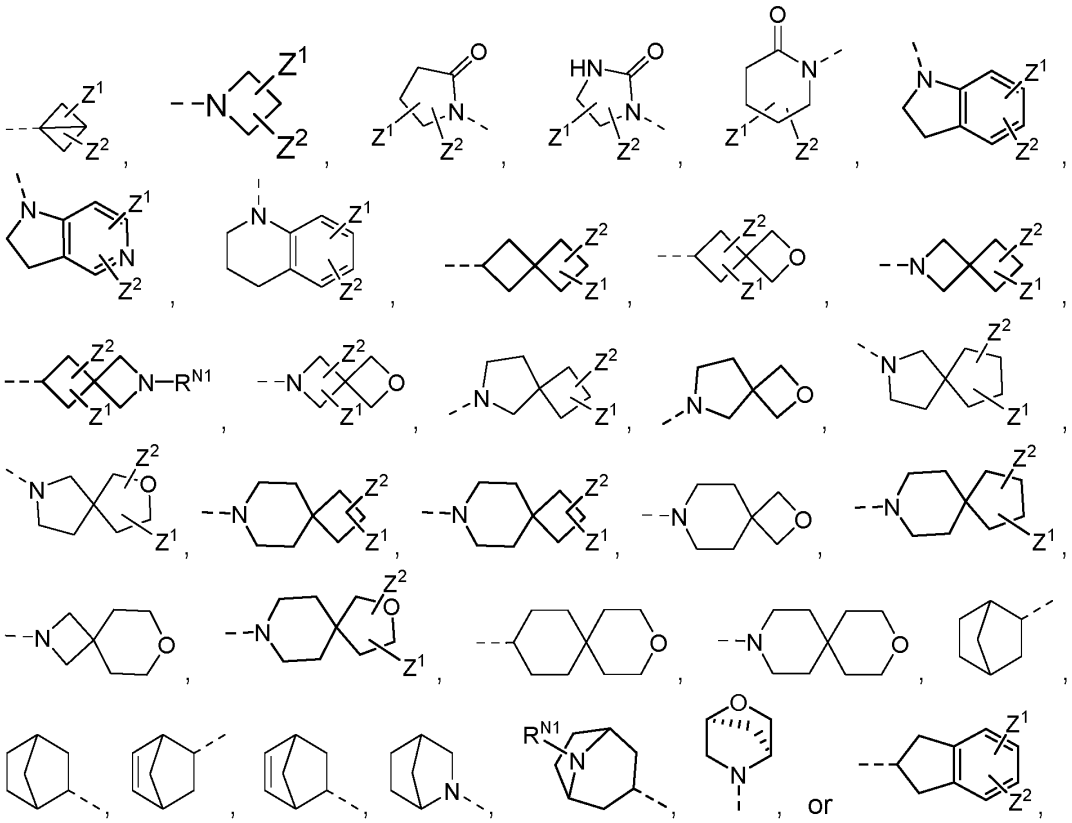
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wherein R^{N1}, Z^1, Z^2, Z^3, Z^4, Z^5, Z^6, Z^7, Z^8, Z^9, Z^{10}, Z^{11}, and Z^{12} have the same meanings as defined in formula (I).

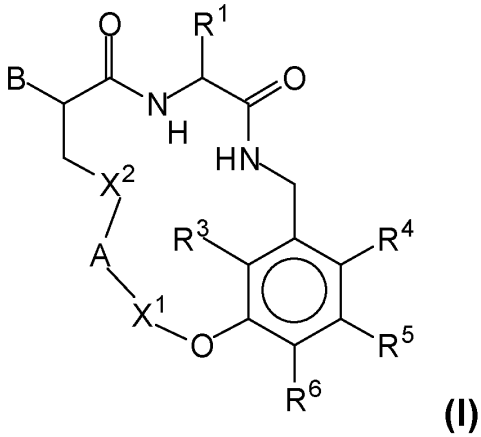
More preferred is the compound of formula (I), wherein R^8 and R^9 represent independently of each other:





wherein R^{N1}, Z^1, Z^2, Z^3, Z^4, Z^5, Z^6, Z^7, Z^8, Z^9, and Z^{10} have the same meanings as defined in formula (I).

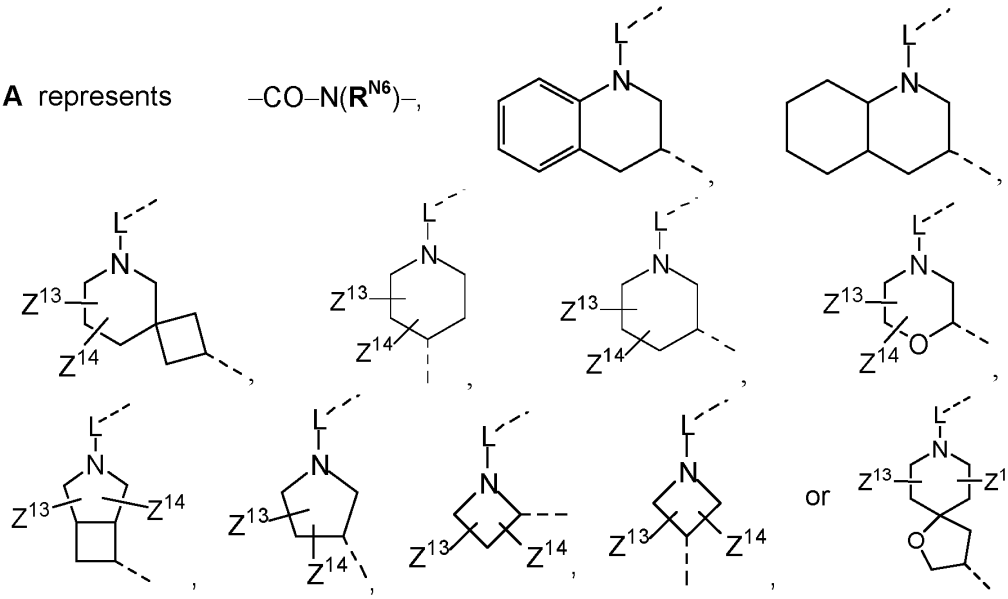
Preferred are the compounds of the general formula (**I**)



(I)

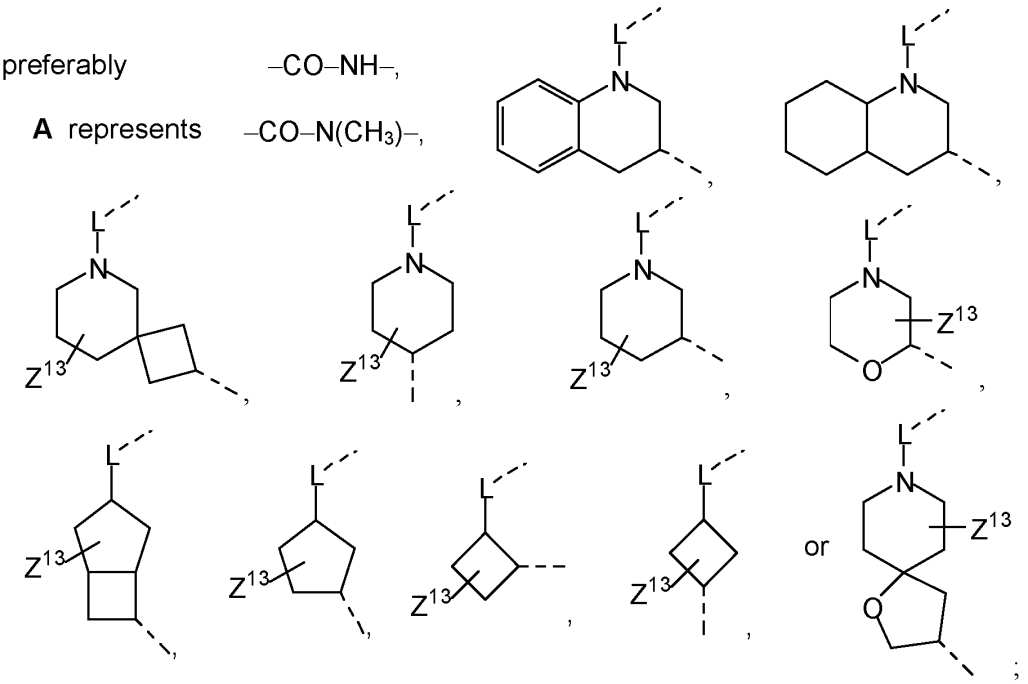
wherein

A represents –CO–N(R^{N6})–,

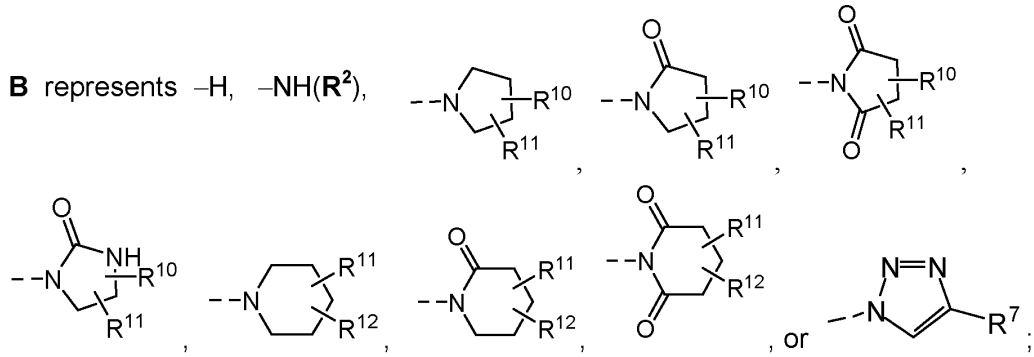


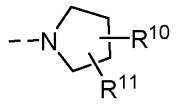
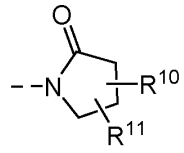
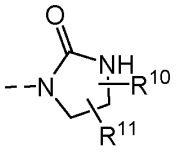
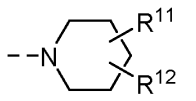
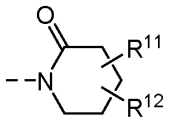
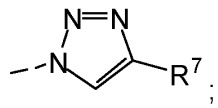
preferably –CO–NH–,

A represents –CO–N(CH_3)–,



B represents –H, –NH(R^2),



preferably **B** represents –H, –NH(**R**^{2}),  ,  ,  ,  ,  , or  ;

L represents –CO–, –CO–NH–, –CO–N(CH$_3$)–, or –CO–O–;

R^{1} represents –H, –(CH$_2$)$_p$–**R**^{7}, –(CH$_2$)$_p$–NH–**R**^{7}, –(CH$_2$)$_p$–**R**^{9}, or –(CH$_2$)$_p$–N(Ph)–**R**^{9}; and preferably –(CH$_2$)$_p$–**R**^{7}, –(CH$_2$)$_p$–**R**^{9}, or –(CH$_2$)$_p$–N(Ph)–**R**^{9};

R^{2} represents –H, –**R**^{8}, –**R**^{11}, –**L**^{1}–**R**^{11}, –**L**^{1}–(CH$_2$)$_r$–**R**^{8}, –**L**^{1}–**R**^{10}, –**L**^{1}–(C$_2$H$_4$O)$_s$–**R**^{11}, –**L**^{1}–(CH$_2$)$_t$–O–**R**^{11}, –**L**^{1}–(CH$_2$)$_t$–NH–(CH$_2$)$_r$–**R**^{8}, –**L**^{1}–(CH$_2$)$_t$–O–(CH$_2$)$_r$–**R**^{8}, –**L**^{1}–(CH$_2$)$_t$–NH**R**^{8}, –**L**^{1}–(CH$_2$)$_t$–NH–CO–**R**^{8}, –**L**^{1}–(CH$_2$)$_t$–NH–SO$_2$–**R**^{8}, –CO–(CH$_2$)$_t$–N(CH$_3$)**R**^{10}, –CO–(CH$_2$)$_t$–O–(CH$_2$)$_u$–N(CH$_3$)**R**^{10}, –**L**^{1}–(CH$_2$)$_r$–**R**^{14}, –CO–C(**R**^{12})(**R**^{13})–**R**^{10}, –CO–C(**R**^{12})(**R**^{13})–**R**^{8}, or –CO–C(**R**^{12})(**R**^{13})–(CH$_2$)$_u$–**R**^{8};

L^{1} represents a bond, –CO–, –CO$_2$–, –CONH–, or –SO$_2$–;

R^{3} represents –H;

R^{4} – **R**^{6} represent independently of each other –H, –CH$_3$, or –OCH$_3$; and more preferably –H or –CH$_3$;

R^{5} and **R**^{6} may form together  ;

R^{8} and **R**^{9} represent independently of each other
C$_6$–C$_{14}$ aryl, C$_1$–C$_{10}$ heteroaryl, C$_3$–C$_8$ carbocyclyl, C$_1$–C$_9$ heterocyclyl, C$_4$-C$_{11}$ bicyclic carbocyclyl, C$_4$–C$_{11}$ bridged carbocyclyl, C$_1$–C$_{10}$ bicyclic heterocyclyl, C$_1$–C$_{10}$ bridged heterocyclyl, C$_7$–C$_{16}$–spiroalkyl, C$_5$–C$_{14}$–spiroheterocyclyl,
wherein all afore-mentioned ring systems can be substituted with 1 to 5 substituents selected from Z^{1}, Z^{2}, Z^{3}, Z^{4}, Z^{5}, Z^{6}, Z^{7}, Z^{8}, Z^{9}, Z^{10}, Z^{11}, Z^{12}, R^{N1} and R^{N2}; and

C_1–C_{10} heteroaryl, C_1–C_9 heterocyclyl, C_1–C_{10} bicyclic heterocyclyl, C_1–C_{10} bridged heterocyclyl, C_5–C_{14}–spiroheterocyclyl ring systems contain at least one of heteroatoms N, O, and S;

said C_3–C_8 carbocyclyl, C_1–C_9 heterocyclyl, C_1–C_{10} bicyclic heterocyclyl, C_4–C_{11} bridged carbocyclyl, C_1–C_{10} bicyclic heterocyclyl, C_1–C_{10} bridged heterocyclyl, C_7–C_{16}–spiroalkyl, C_5–C_{14}–spiroheterocyclyl ring systems can be partly saturated or unsaturated;

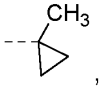
R^7 and **R^{10}** represent independently of each other –H, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CN$, $-C(CH_3)_2-CN$, $-CH_2-C(CH_3)_2-CN$, $-CH_2-CF_3$, $-CH_2-C(CH_3)_2-NH_2$,



cyclo-C_3H_5, cyclo-C_4H_7, cyclo-C_5H_9, cyclo-C_6H_{11},

$-C_4H_9$, $-CH_2-CH(CH_3)_2$, $-CH(CH_3)-C_2H_5$, $-C(CH_3)_3$, $-C_5H_{11}$, $-CH_2-C(CH_3)_3$, $-CH(C_2H_5)_2$, $-C_2H_4-CH(CH_3)_2$, –Ph, $-CH_2$–Ph, $-CH_2-CH_2$–Ph, $-C_2H_4-CH=CH_2$, $-CH_2-CH=CH-CH_3$, $-CH_2-C(CH_3)=CH_2$, $-CH(CH_3)-CH=CH_2$, $-C(CH_3)=CH-CH_3$, $-CH_2-CH=C(CH_3)_2$, $-CO-CH=C(CH_3)_2$, $-CH_2$-C≡CH, $-C_2H_4-C\equiv CH$, $-CH_2-C\equiv C-CH_3$, $-CH_2-OCF_3$, $-C_2H_4-OCF_3$, $-C_3H_6-OCF_3$, $-CH_2-OCHF_2$, $-C_2H_4-OCHF_2$, $-C_3H_6-OCHF_2$, $-CH_2-OCH_3$, $-C_2H_4-OCH_3$, $-C_3H_6-OCH_3$, $-CH_2-OC_2H_5$, $-C_2H_4-OC_2H_5$, $-C_3H_6-OC_2H_5$, $-CH_2-OH$, $-C_2H_4-OH$, $-C_3H_6-OH$, $-CH_2-COOH$, $-C_2H_4-COOH$, $-C_3H_6-COOH$, $-C(CH_3)_2-CN$, $-C(CH_3)_2-OH$, $-C(CH_3)_2-CH_2-OH$, $-C(C_2H_5)_2-CH_2-OH$, $-C(CH_2-OH)_2-CH_3$, $-C(CH_2-OH)_2-C_2H_5$, $-C(CH_3)_2-CH_2-SH$, $-C(C_2H_5)_2-CH_2-SH$, $-C(CH_2-SH)_2-CH_3$, $-CO-O-C(CH_3)_3$, or $-C(CH_2-SH)_2-C_2H_5$;

R^{11} represents –H, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CN$, $-C(CH_3)_2-CN$, $-CH_2-C(CH_3)_2-CN$, $-CH_2-CF_3$, $-CH_2-C(CH_3)_2-NH_2$,

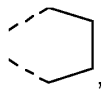
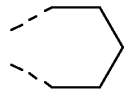
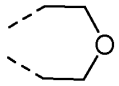
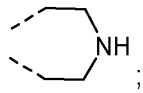


cyclo-C_3H_5, cyclo-C_4H_7, cyclo-C_5H_9, cyclo-C_6H_{11},

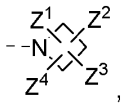
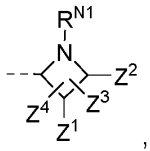
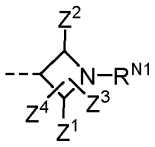
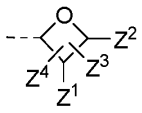
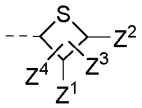
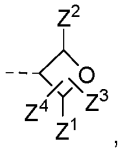
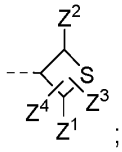
$-C_4H_9$, $-CH_2-CH(CH_3)_2$, $-CH(CH_3)-C_2H_5$, $-C(CH_3)_3$, $-C_5H_{11}$, $-CH_2-C(CH_3)_3$, $-CH(C_2H_5)_2$, –Ph, $-CH_2$–Ph, $-CH_2-CH_2$–Ph, $-CH=CH_2$, $-CH_2-CH=CH_2$, $-C(CH_3)=CH_2$, $-CH=CH-CH_3$, $-C(CH_3)=CH-CH_3$, $-CH=C(CH_3)_2$, $-C(CH_3)=C(CH_3)_2$, $-C_2H_4-CH=CH_2$, $-CH_2-CH=CH-CH_3$, $-CH_2-CH=C(CH_3)_2$, $-C\equiv CH$, $-CH_2$-C≡CH, $-C_2H_4-C\equiv CH$, $-CH_2-C\equiv C-CH_3$, $-C\equiv C-CH_3$, $-C\equiv C-C_2H_5$, $-CH_2-OCF_3$, $-C_2H_4-OCF_3$, $-C_3H_6-OCF_3$, $-CH_2-OCHF_2$, $-C_2H_4-OCHF_2$, $-C_3H_6-OCHF_2$, $-CH_2-OCH_3$, $-C_2H_4-OCH_3$, $-C_3H_6-OCH_3$, $-CH_2-OC_2H_5$, $-C_2H_4-OC_2H_5$, $-C_3H_6-OC_2H_5$, $-CH_2-OH$,

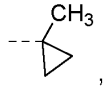
–C_2H_4–OH, –C_3H_6–OH, –$C(CH_3)_2$–CH_2–OH, –$C(C_2H_5)_2$–CH_2–OH, –$C(CH_2$–OH$)_2$–CH_3, –$C(CH_2$–OH$)_2$–C_2H_5, –$C(CH_3)_2$–CH_2–SH, –$C(C_2H_5)_2$–CH_2–SH, –$C(CH_2$–SH$)_2$–CH_3, or –$C(CH_2$–SH$)_2$–C_2H_5;

R^{12} and **R^{13}** represent independently of each other –H, –CH_3, –C_2H_5, –C_3H_7, –Ph, –CH_2–Ph, –NH_2, –$NHCO_2(CCH_3)_3$, –CH_2–NH_2, –CHF_2, –F, –CF_3, –OCF_3, –$OCHF_2$, –OH, –OCH_3, –OC_2H_5, and –OC_3H_7; or

R^{12} and **R^{13}** may form together  ,  ,  ,  ,  , or  ;

R^{14} represents

 ,  ,  ,  ,  ,  , or  ;

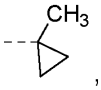
R^{N1}, **R^{N2}**, and **R^{N4}** represent independently of each other –H, –CH_3, –C_2H_5, –C_3H_7, –$CH(CH_3)_2$, –CHF_2, –CF_3,  , cyclo-C_3H_5, cyclo-C_4H_7, cyclo-C_5H_9, cyclo-C_6H_{11}, –C_4H_9, –CH_2–$CH(CH_3)_2$, –$CH(CH_3)$–C_2H_5, –$C(CH_3)_3$, –C_5H_{11}, –$CH(CH_3)$–C_3H_7, –CH_2–$CH(CH_3)$–C_2H_5, –$CH(CH_3)$–$CH(CH_3)_2$, –$C(CH_3)_2$–C_2H_5, –CH_2–$C(CH_3)_3$, –$CH(C_2H_5)_2$, –C_2H_4–$CH(CH_3)_2$, –C_6H_{13}, –C_7H_{15}, –C_8H_{17}, –Ph, –CH_2–Ph, –CH_2–CH_2–Ph, –C_2H_4–CH=CH_2, –CH_2–CH=CH–CH_3, –CH_2–$C(CH_3)$=CH_2, –$CH(CH_3)$–CH=CH_2, –CH_2–CH=$C(CH_3)_2$, –CH_2-C≡CH, –C_2H_4–C≡CH, –CH_2–C≡C–CH_3, –$COCH_3$, –COC_2H_5, –COC_3H_7, –CO–cyclo-C_3H_5, –$COCH(CH_3)_2$, –$COC(CH_3)_3$, –COOH, –$COOCH_3$, –$COOC_2H_5$, –$COOC_3H_7$, –COO–cyclo-C_3H_5, –$COOCH(CH_3)_2$, –$COOC(CH_3)_3$, –$COOCH_2$Ph, –$CONH_2$, –$CONHCH_3$, –$CONHC_2H_5$, –$CONHC_3H_7$, –CONH–cyclo-C_3H_5, –CONH[$CH(CH_3)_2$], –CONH[$C(CH_3)_3$], –$CON(CH_3)_2$, –$CON(C_2H_5)_2$, –$CON(C_3H_7)_2$, –CON(cyclo-$C_3H_5)_2$, –CON[$CH(CH_3)_2]_2$, –CON[$C(CH_3)_3]_2$, –SO_3H, –$(CH_2)_v$–COOH, –$(CH_2)_v$–OH, –$(CH_2)_v$–SH, –$(CH_2)_v$–SO_3H, or –$(CH_2CH_2$–O$)_w$–CH_2CH_2–NH_2 ;

X^1 represents $-(CH_2)_m-$;

X^2 represents $-(CH_2)_n-$;

X^3 represents a bond, –O–, –NH–, or –S–;

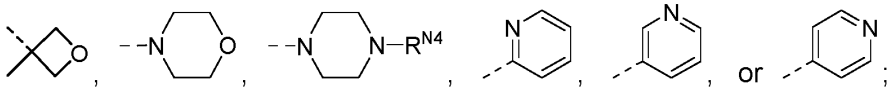
$Z^1 – Z^{14}$ represent independently of each other

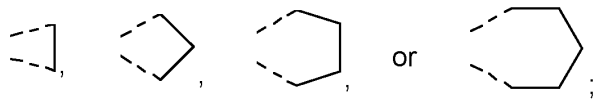


cyclo-C_3H_5, cyclo-C_4H_7, cyclo-C_5H_9, cyclo-C_6H_{11},

–H, –OH, $-OCH_3$, $-OC_2H_5$, $-OC_3H_7$, –O–cyclo-C_3H_5, $-OCH(CH_3)_2$, $-OC(CH_3)_3$, $-OC_4H_9$, –O–cyclo-C_4H_7, –O–cyclo-C_5H_9, –O–cyclo-C_6H_{11}, $-OCH_2CH(CH_3)_2$, $-OCH_2$–cyclo-C_3H_5, $-OCH_2$–cyclo-C_4H_7, $-OCH_2$–cyclo-C_5H_9, $-OCH_2$–cyclo-C_6H_{11}, –OPh, $-OCH_2$–Ph, $-OCPh_3$, $-CH_2-OCH_3$, $-C_2H_4-OCH_3$, $-C_3H_6-OCH_3$, $-CH_2-OC_2H_5$, $-C_2H_4-OC_2H_5$, $-C_3H_6-OC_2H_5$, $-CH_2-OC_3H_7$, $-C_2H_4-OC_3H_7$, $-C_3H_6-OC_3H_7$, $-CH_2$–O–cyclo-C_3H_5, $-C_2H_4$–O–cyclo-C_3H_5, $-C_3H_6$–O–cyclo-C_3H_5, $-CH_2-OCH(CH_3)_2$, $-C_2H_4-OCH(CH_3)_2$, $-C_3H_6-OCH(CH_3)_2$, $-CH_2-OC(CH_3)_3$, $-C_2H_4-OC(CH_3)_3$, $-C_3H_6-OC(CH_3)_3$, $-CH_2-OC_4H_9$, $-C_2H_4-OC_4H_9$, $-C_3H_6-OC_4H_9$, $-CH_2$–OPh, $-C_2H_4$–OPh, $-C_3H_6$–OPh, $-CH_2-OCH_2$–Ph, $-C_2H_4-OCH_2$–Ph, $-C_3H_6-OCH_2$–Ph, –SH, $-SCH_3$, $-SC_2H_5$, $-SC_3H_7$, –S–cyclo-C_3H_5, $-SCH(CH_3)_2$, $-SC(CH_3)_3$, –F, –Cl, –Br, –I, –CN, $-COCH_3$, $-COC_2H_5$, $-COC_3H_7$, –CO–cyclo-C_3H_5, $-COCH(CH_3)_2$, $-COC(CH_3)_3$, –COOH, $-COOCH_3$, $-COOC_2H_5$, $-COOC_3H_7$, –COO–cyclo-C_3H_5, $-COOCH(CH_3)_2$, $-COOC(CH_3)_3$, $-OOC-CH_3$, $-OOC-C_2H_5$, $-OOC-C_3H_7$, –OOC–cyclo-C_3H_5, $-OOC-CH(CH_3)_2$, $-OOC-C(CH_3)_3$, $-CONH_2$, $-CONHCH_3$, $-CONHC_2H_5$, $-CONHC_3H_7$, –CONH–cyclo-C_3H_5, $-CONH[CH(CH_3)_2]$, $-CONH[C(CH_3)_3]$, $-CON(CH_3)_2$, $-CON(C_2H_5)_2$, $-CON(C_3H_7)_2$, $-CON$(cyclo-$C_3H_5)_2$, $-CON[CH(CH_3)_2]_2$, $-CON[C(CH_3)_3]_2$, $-NHCOCH_3$, $-NHCOC_2H_5$, $-NHCOC_3H_7$, –NHCO–cyclo-C_3H_5, $-NHCO-CH(CH_3)_2$, $-NHCO-C(CH_3)_3$, $-NHCO-CH(NH_2)CH_2-COOH$, $-NHCO-CH(NH_2)CH_2CH_2-COOH$, $-NHCO-OCH_3$, $-NHCO-OC_2H_5$, $-NHCO-OC_3H_7$, $-NHCO-O$–cyclo-C_3H_5, $-NHCO-OCH(CH_3)_2$, $-NHCO-OC(CH_3)_3$, $-NH_2$, $-NHCH_3$, $-NHC_2H_5$, $-NHC_3H_7$, –NH–cyclo-C_3H_5, $-NHCH(CH_3)_2$, $-NHC(CH_3)_3$, $-N(CH_3)_2$, $-N(C_2H_5)_2$, $-N(C_3H_7)_2$, $-N$(cyclo-$C_3H_5)_2$, $-N[CH(CH_3)_2]_2$, $-N[C(CH_3)_3]_2$, $-SOCH_3$, $-SOC_2H_5$, $-SOC_3H_7$, –SO–cyclo-C_3H_5, $-SOCH(CH_3)_2$, $-SOC(CH_3)_3$, $-SO_2CH_3$, $-SO_2C_2H_5$, $-SO_2C_3H_7$, $-SO_2$–cyclo-C_3H_5, $-SO_2CH(CH_3)_2$, $-SO_2C(CH_3)_3$, $-SO_3H$, $-SO_3CH_3$, $-SO_3C_2H_5$, $-SO_3C_3H_7$, $-SO_3$–cyclo-C_3H_5, $-SO_3CH(CH_3)_2$, $-SO_3C(CH_3)_3$, $-SO_2NH_2$, $-SO_2NHCH_3$, $-SO_2NHC_2H_5$, $-SO_2NHC_3H_7$, $-SO_2$NH–cyclo-C_3H_5,

–$SO_2NHCH(CH_3)_2$, –$SO_2NHC(CH_3)_3$, –$SO_2N(CH_3)_2$, –$SO_2N(C_2H_5)_2$, –$SO_2N(C_3H_7)_2$, –$SO_2N(cyclo\text{-}C_3H_5)_2$, –$SO_2N[CH(CH_3)_2]_2$, –$SO_2N[C(CH_3)_3]_2$, –O–S(=O)$CH_3$, –O–S(=O)$C_2H_5$, –O–S(=O)$C_3H_7$, –O–S(=O)–cyclo-$C_3H_5$, –O–S(=O)$CH(CH_3)_2$, –O–S(=O)$C(CH_3)_3$, –NH–$SO_2$–$CH_3$, –NH–$SO_2$–$C_2H_5$, –NH–$SO_2$–$C_3H_7$, –NH–$SO_2$–cyclo-$C_3H_5$, –NH–$SO_2$–$CH(CH_3)_2$, –NH–$SO_2$–$C(CH_3)_3$, –O–$SO_2$–$CH_3$, –O–$SO_2$–$C_2H_5$, –O–$SO_2$–$C_3H_7$, –O–$SO_2$–cyclo-$C_3H_5$, –O–$SO_2$–$CH(CH_3)_2$, –O–$SO_2$–$C(CH_3)_3$, –$OCH_2F$, –$OCHF_2$, –$OCF_3$, –$CH_2$–$OCF_3$, –$C_2H_4$–$OCF_3$, –$C_3H_6$–$OCF_3$, –$CH_2$–$OCHF_2$, –$C_2H_4$–$OCHF_2$, –$C_3H_6$–$OCHF_2$, –$OC_2F_5$, –$CH_2$–$OC_2F_5$, –$C_2H_4$–$OC_2F_5$, –$C_3H_6$–$OC_2F_5$, –NH–CO–$NH_2$, –NH–CO–$NHCH_3$, –NH–CO–$NHC_2H_5$, –NH–CO–$NHC_3H_7$, –NH–C(=NH)–$NH_2$, –NH–CO–$N(C_3H_7)_2$, –NH–CO–$NH[CH(CH_3)_2]$, –NH–CO–$NH[C(CH_3)_3]$, –NH–CO–$N(CH_3)_2$, –NH–CO–$N(C_2H_5)_2$, –NH–CO–NH–cyclo-$C_3H_5$, –NH–CO–N(cyclo-$C_3H_5)_2$, –NH–CO–$N[CH(CH_3)_2]_2$, –O–CO–NH–cyclo-$C_3H_5$, –O–CO–$NH[CH(CH_3)_2]$, –NH–C(=NH)–$NH[C(CH_3)_3]$, –O–CO–$NHC_3H_7$, –O–CO–$NH_2$, –O–CO–$NHCH_3$, –O–CO–$NHC_2H_5$, –O–CO–$NH[C(CH_3)_3]$, –O–CO–$N(CH_3)_2$, –O–CO–$N(C_2H_5)_2$, –O–CO–$N(C_3H_7)_2$, –O–CO–N(cyclo-$C_3H_5)_2$, –O–CO–$N[CH(CH_3)_2]_2$, –O–CO–$N[C(CH_3)_3]_2$, –$CH_2F$, –$CHF_2$, –$CF_3$, –$CH_2$–$CH_2F$, –$CH_2$–$CHF_2$, –$CH_2$–$CF_3$, cyclo-$C_8H_{15}$, –Ph, –$CH_2$–Ph, –$CH_2$–$CH_2$–Ph, –CH=CH–Ph, –$CH_3$, –$C_2H_5$, –$C_3H_7$, –$CH(CH_3)_2$, –$C_4H_9$, –$CH_2$–$CH(CH_3)_2$, –$CH_2$–$CH_2$–$CH(CH_3)_2$, –$CH(CH_3)$–$C_2H_5$, –$C(CH_3)_3$, –$C_5H_{11}$, –$C(CH_3)_2$–$C_2H_5$, –$CH_2$–$C(CH_3)_3$, –$CH(C_2H_5)_2$, –$C_6H_{13}$, –$CH=CH_2$, –$CH_2$–$CH=CH_2$, –$C(CH_3)=CH_2$, –CH=CH–$CH_3$, –$C_2H_4$–$CH=CH_2$, –$CH_2$–CH=CH–$CH_3$, –CH=CH–$C_2H_5$, –$CH_2$–$C(CH_3)=CH_2$, –$CH(CH_3)$–CH=CH, –$CH=C(CH_3)_2$, –$C(CH_3)$=CH–$CH_3$, –$C_3H_6$–$CH=CH_2$, –$C_2H_4$–CH=CH–$CH_3$, –C≡CH, –C≡C–$CH_3$, –$CH_2$-C≡CH, –$C_2H_4$–C≡CH, –$CH_2$–C≡C–$CH_3$, –C≡C–$C_2H_5$,



Z^3 and **Z^4** may form together  ;

m is an integer selected from 0, 1, 2, or 3;

n is an integer selected from 0, 1, 2, 3, or 4;

p is an integer selected from 0, 1, or 2;

r is an integer selected from 0, 1, 2, or 3;

s is an integer selected from 1, 2, 3, 4, 5, 6, ot 7;

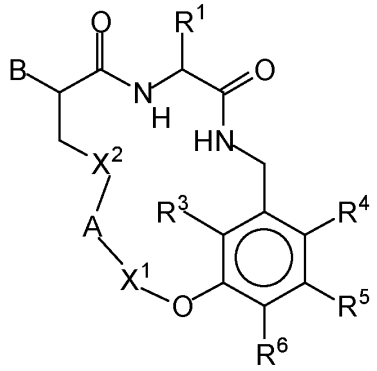
t is an integer selected from 1 or 2;

u is an integer selected from 1 or 2;

v is an integer selected from 1, 2, or 3;
w is an integer selected from 1, 2, or 3;

or an enantiomer, a stereoisomeric form, a mixture of enantiomers, a diastereomer, a mixture of diastereomers, a hydrate, a solvate, an acid salt form, a tautomer, a racemate of the above mentioned compounds, or a pharmaceutically acceptable salt thereof.

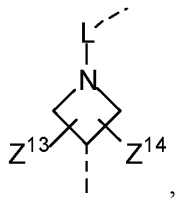
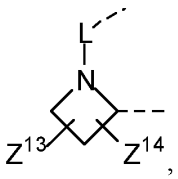
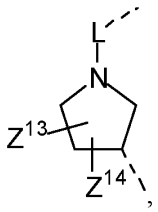
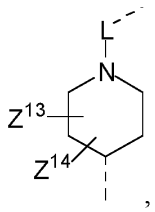
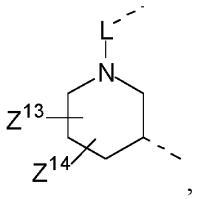
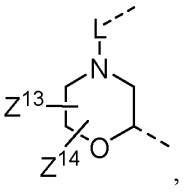
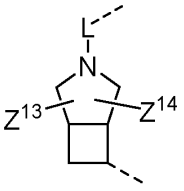
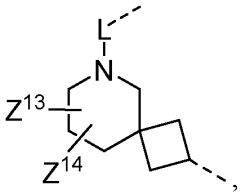
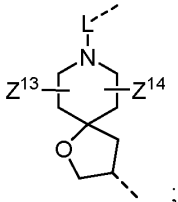
Thus, preferred are the compounds of formula (**I**),



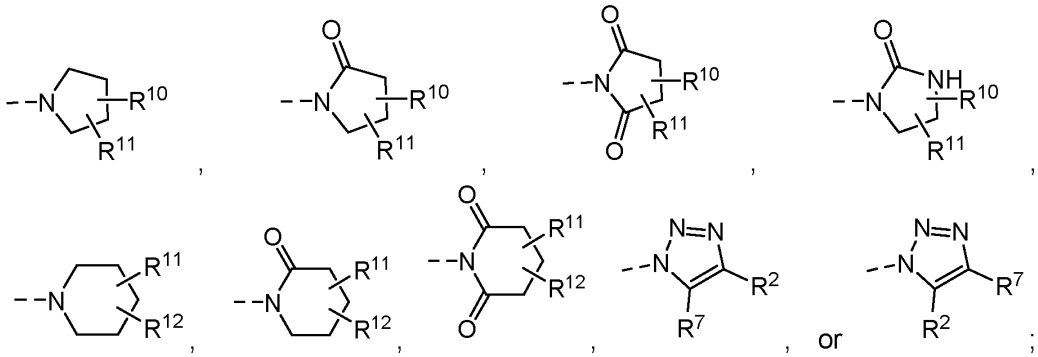
(I)

wherein

A represents –CO–N(**R**^{N6})–,


,

,

,

,

,

,

,

,
or

;

B represents –H, –NH(**R**^{2}), –N(**R**^{2})(**R**^{N5}),



L represents –CO–, –CO–NH–, –CO–N(**R**^{N3})–, or –CO–O–;

R^{1} represents –H, –$(CH_2)_p$–**R**^{7}, –$(CH_2)_p$–NH–**R**^{7}, –$(CH_2)_p$–**R**^{9}, or –$(CH_2)_p$–N**R**^{N4}–**R**^{9};

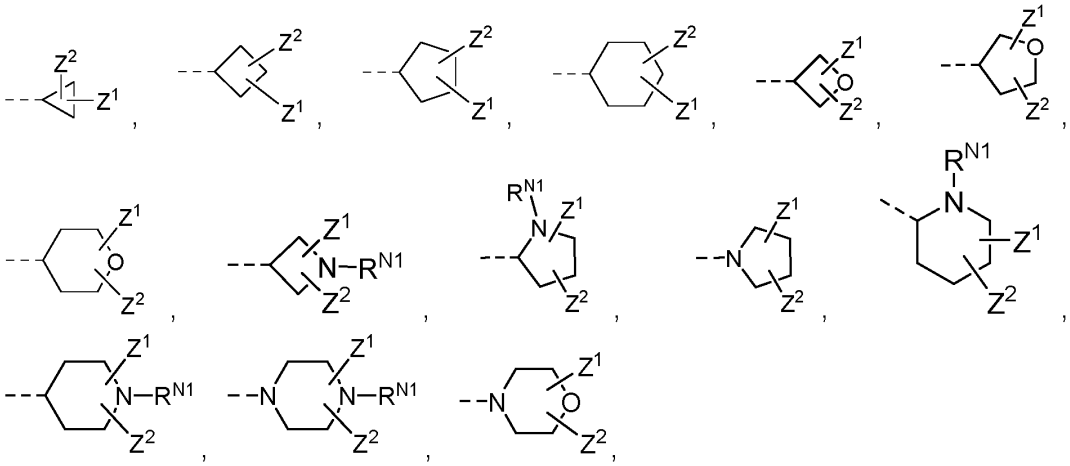
R^{2} represents –H, –**R**^{8}, –**R**^{11}, –**L**^{1}–**R**^{11}, –**L**^{1}–$(CH_2)_r$–**R**^{8}, –**L**^{1}–**R**^{10}, –**L**^{1}–$(C_2H_4O)_s$–**R**^{11}, –**L**^{1}–$(CH_2)_t$–O–**R**^{11}, –**L**^{1}–$(CH_2)_t$–NH–$(CH_2)_r$–**R**^{8}, –**L**^{1}–$(CH_2)_t$–O–$(CH_2)_r$–**R**^{8}, –**L**^{1}–$(CH_2)_t$–NH**R**^{8}, –**L**^{1}–$(CH_2)_t$–NH–CO–**R**^{8}, –**L**^{1}–$(CH_2)_t$–NH–SO_2–**R**^{8}, –**L**^{1}–$(CH_2)_t$–N**R**^{N6}**R**^{10}, –**L**^{1}–$(CH_2)_t$–O–$(CH_2)_u$–N**R**^{N6}**R**^{10}, –**L**^{1}–$(CH_2)_r$–**R**^{14}, –CO–C(**R**^{12})(**R**^{13})–**R**^{10}, –CO–C(**R**^{12})(**R**^{13})–**R**^{8}, or –CO–C(**R**^{12})(**R**^{13})–$(CH_2)_u$–**R**^{8};

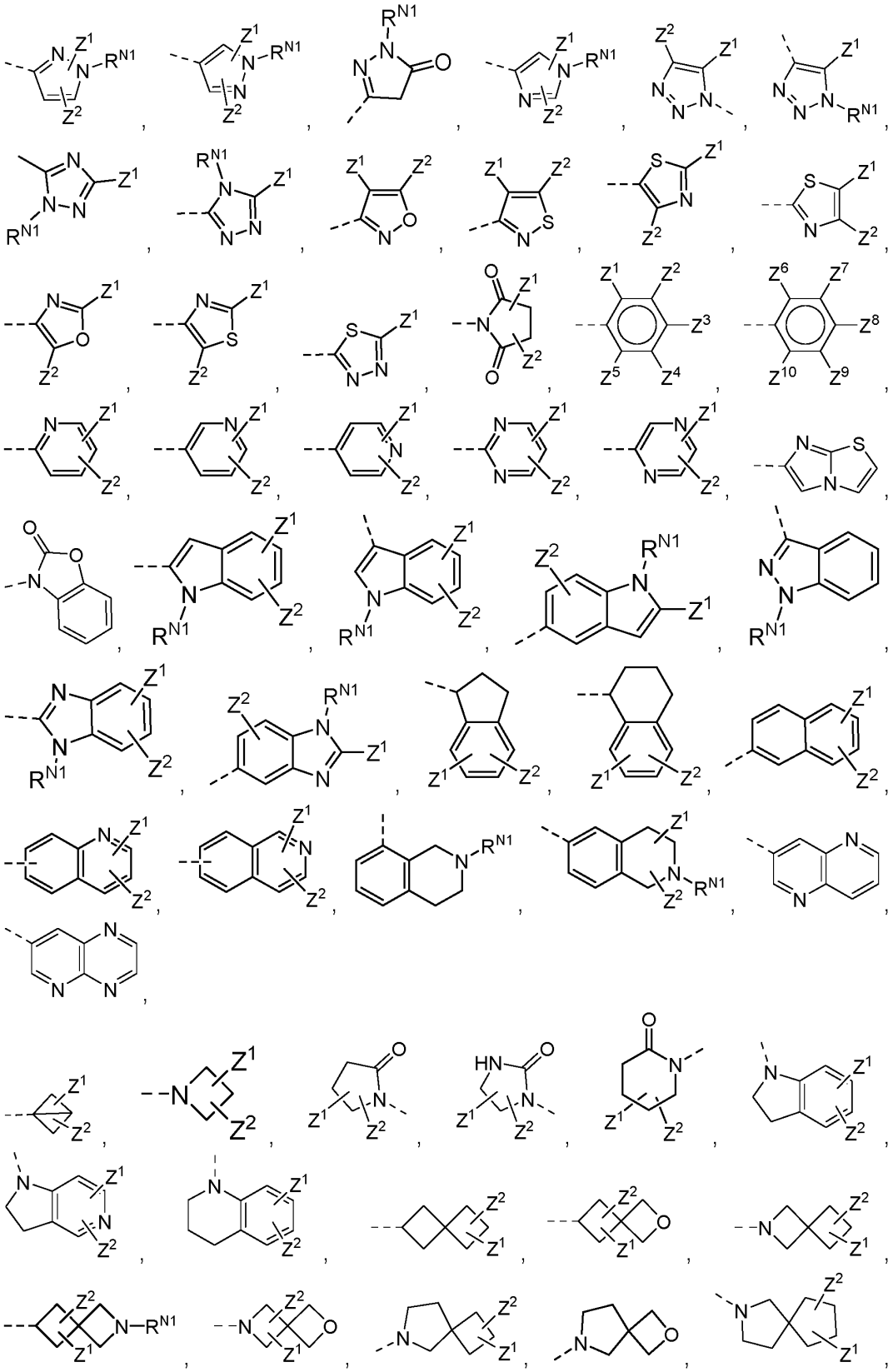
L^{1} represents a bond, –CO–, –CO_2–, –CONH–, or –SO_2–;

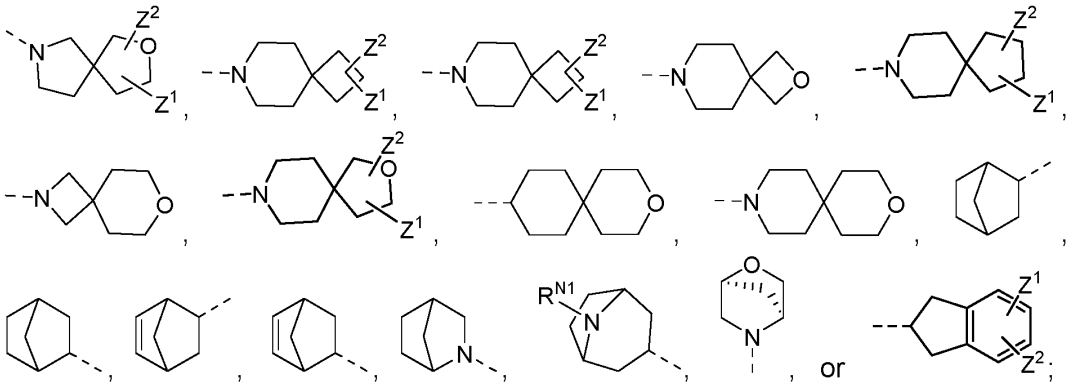
R^{3} – **R**^{6} represent independently of each other –H, –CH_3, –OCH_3, –F, or –Cl;

or **R** ^{5} and **R**^{6} may form together  ;

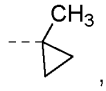
R^{8} and **R**^{9} represent independently of each other





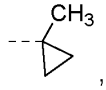


R^{7} and **R^{10}** represent independently of each other –H, –CH_3, –C_2H_5, –C_3H_7, –$CH(CH_3)_2$, –CH_2F, –CHF_2, –CF_3, –CH_2CN, –$C(CH_3)_2$–CN, –CH_2–$C(CH_3)_2$–CN, –CH_2–CF_3, –CH_2–$C(CH_3)_2$–NH_2,



cyclo-C_3H_5, cyclo-C_4H_7, cyclo-C_5H_9, cyclo-C_6H_{11}, cyclo-C_7H_{13}, –C_4H_9, –CH_2–$CH(CH_3)_2$, –$CH(CH_3)$–C_2H_5, –$C(CH_3)_3$, –C_5H_{11}, –$CH(CH_3)$–C_3H_7, –CH_2–$CH(CH_3)$–C_2H_5, –$CH(CH_3)$–$CH(CH_3)_2$, –$C(CH_3)_2$–C_2H_5, –CH_2–$C(CH_3)_3$, –$CH(C_2H_5)_2$, –C_2H_4–$CH(CH_3)_2$, –C_6H_{13}, –C_7H_{15}, –C_8H_{17}, –Ph, –CH_2–Ph, –CH_2–CH_2–Ph, –C_2H_4–$CH=CH_2$, –CH_2–CH=CH–CH_3, –CH_2–$C(CH_3)=CH_2$, –$CH(CH_3)$–$CH=CH_2$, –$C(CH_3)$=CH–CH_3, –CH_2–$CH=C(CH_3)_2$, –CO–$CH=C(CH_3)_2$, –CH_2-C≡CH, –C_2H_4–C≡CH, –CH_2–C≡C–CH_3, –CH_2–OCF_3, –C_2H_4–OCF_3, –C_3H_6–OCF_3, –CH_2–$OCHF_2$, –C_2H_4–$OCHF_2$, –C_3H_6–$OCHF_2$, –CH_2–OCH_3, –C_2H_4–OCH_3, –C_3H_6–OCH_3, –CH_2–OC_2H_5, –C_2H_4–OC_2H_5, –C_3H_6–OC_2H_5, –CH_2–OH, –C_2H_4–OH, –C_3H_6–OH, –CH_2–COOH, –C_2H_4–COOH, –C_3H_6–COOH, –$C(CH_3)_2$–CN, –$C(CH_3)_2$–OH, –$C(CH_3)_2$–CH_2–OH, –$C(C_2H_5)_2$–CH_2–OH, –$C(CH_2$–$OH)_2$–CH_3, –$C(CH_2$–$OH)_2$–C_2H_5, –$C(CH_3)_2$–CH_2–SH, –$C(C_2H_5)_2$–CH_2–SH, –$C(CH_2$–$SH)_2$–CH_3, –CO–O–$C(CH_3)_3$, or –$C(CH_2$–$SH)_2$–C_2H_5;

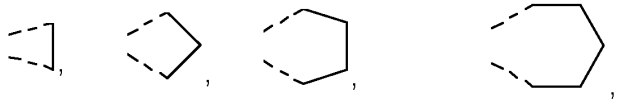
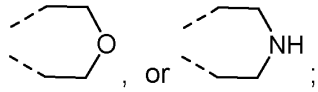
R^{11} represents –H, –CH_3, –C_2H_5, –C_3H_7, –$CH(CH_3)_2$, –CH_2F, –CHF_2, –CF_3, –CH_2CN, –$C(CH_3)_2$–CN, –CH_2–$C(CH_3)_2$–CN, –CH_2–CF_3, –CH_2–$C(CH_3)_2$–NH_2,

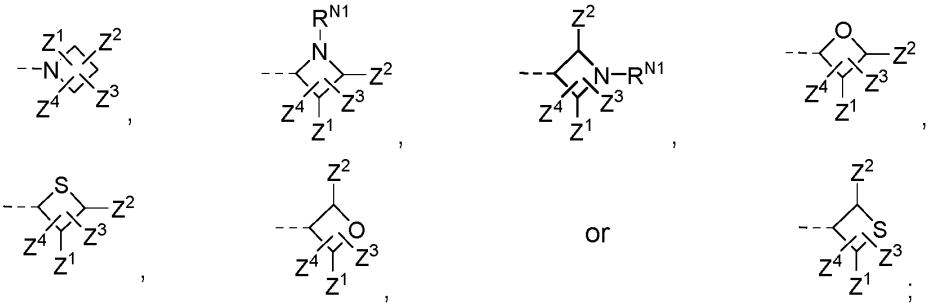


cyclo-C_3H_5, cyclo-C_4H_7, cyclo-C_5H_9, cyclo-C_6H_{11}, cyclo-C_7H_{13}, –C_4H_9, –CH_2–$CH(CH_3)_2$, –$CH(CH_3)$–C_2H_5, –$C(CH_3)_3$, –C_5H_{11}, –$CH(CH_3)$–C_3H_7, –CH_2–$CH(CH_3)$–C_2H_5, –$CH(CH_3)$–$CH(CH_3)_2$, –$C(CH_3)_2$–C_2H_5, –CH_2–$C(CH_3)_3$, –$CH(C_2H_5)_2$, –C_2H_4–$CH(CH_3)_2$, –C_6H_{13}, –C_7H_{15}, –C_8H_{17}, –Ph, –CH_2–Ph, –CH_2–CH_2–Ph, –$CH=CH_2$, –CH_2–$CH=CH_2$, –$C(CH_3)=CH_2$, –CH=CH–CH_3,

–C(CH$_3$)=CH–CH$_3$, –CH=C(CH$_3$)$_2$, –C(CH$_3$)=C(CH$_3$)$_2$, –C$_2$H$_4$–CH=CH$_2$, –CH$_2$–CH=CH–CH$_3$, –CH$_2$–C(CH$_3$)=CH$_2$, –CH(CH$_3$)–CH=CH$_2$, –C(CH$_3$)=CH–CH$_3$, –CH$_2$–CH=C(CH$_3$)$_2$, –C≡CH, –CH$_2$-C≡CH, –C$_2$H$_4$–C≡CH, –CH$_2$–C≡C–CH$_3$, –C≡C–CH$_3$, –C≡C–C$_2$H$_5$, –CH$_2$–OCF$_3$, –C$_2$H$_4$–OCF$_3$, –C$_3$H$_6$–OCF$_3$, –CH$_2$–OCHF$_2$, –C$_2$H$_4$–OCHF$_2$, –C$_3$H$_6$–OCHF$_2$, –CH$_2$–OCH$_3$, –C$_2$H$_4$–OCH$_3$, –C$_3$H$_6$–OCH$_3$, –CH$_2$–OC$_2$H$_5$, –C$_2$H$_4$–OC$_2$H$_5$, –C$_3$H$_6$–OC$_2$H$_5$, –CH$_2$–OH, –C$_2$H$_4$–OH, –C$_3$H$_6$–OH, –C(CH$_3$)$_2$–CH$_2$–OH, –C(C$_2$H$_5$)$_2$–CH$_2$–OH, –C(CH$_2$–OH)$_2$–CH$_3$, –C(CH$_2$–OH)$_2$–C$_2$H$_5$, –C(CH$_3$)$_2$–CH$_2$–SH, –C(C$_2$H$_5$)$_2$–CH$_2$–SH, –C(CH$_2$–SH)$_2$–CH$_3$, or –C(CH$_2$–SH)$_2$–C$_2$H$_5$;

R^{12} and **R^{13}** represent independently of each other –H, –CH$_3$, –C$_2$H$_5$, –C$_3$H$_7$, –CH(CH$_3$)$_2$, –Ph, –CH$_2$–Ph, –COOH, –NH$_2$, –NHCO$_2$(CCH$_3$)$_3$, –CH$_2$–NH$_2$, –CHF$_2$, –CF$_3$, –OCF$_3$, –OCHF$_2$, –OH, –F, –OCH$_3$, –OC$_2$H$_5$, –OC$_3$H$_7$, or –OCH(CH$_3$)$_2$; or

R^{12} and **R^{13}** may form together   ;

R^{14} represents  ;

R^{15} and **R^{16}** represent independently of each other **–X^3–L^2–R^{17}**, or **–(OCH$_2$CH$_2$)$_w$–R^{17}**;

L^2 represents –(CH$_2$)$_v$–, –(CH$_2$CH$_2$–O)$_w$–CH$_2$–, or –(CH$_2$CH$_2$–O)$_w$–CH$_2$CH$_2$–;

R^{17} represents –OH, –SH, –SO$_3$H, –NH$_2$, or –CO$_2$H;

R^{N1}, **R^{N2}**, **R^{N3}**, and **R^{N4}** represent independently of each other **–R^{15}**, –H, –CH$_3$, –C$_2$H$_5$, –C$_3$H$_7$, –CH(CH$_3$)$_2$, –CHF$_2$, –CF$_3$,  , cyclo-C$_3$H$_5$, cyclo-C$_4$H$_7$, cyclo-C$_5$H$_9$, cyclo-C$_6$H$_{11}$, cyclo-C$_7$H$_{13}$,

$-C_4H_9$, $-CH_2-CH(CH_3)_2$, $-CH(CH_3)-C_2H_5$, $-C(CH_3)_3$, $-C_5H_{11}$, $-CH(CH_3)-C_3H_7$, $-CH_2-CH(CH_3)-C_2H_5$, $-CH(CH_3)-CH(CH_3)_2$, $-C(CH_3)_2-C_2H_5$, $-CH_2-C(CH_3)_3$, $-CH(C_2H_5)_2$, $-C_2H_4-CH(CH_3)_2$, $-C_6H_{13}$, $-C_7H_{15}$, $-C_8H_{17}$, $-Ph$, $-CH_2-Ph$, $-CH_2-CH_2-Ph$, $-C_2H_4-CH=CH_2$, $-CH_2-CH=CH-CH_3$, $-CH_2-C(CH_3)=CH_2$, $-CH(CH_3)-CH=CH_2$, $-CH_2-CH=C(CH_3)_2$, $-CH_2-C\equiv CH$, $-C_2H_4-C\equiv CH$, $-CH_2-C\equiv C-CH_3$, $-COCH_3$, $-COC_2H_5$, $-COC_3H_7$, $-CO-cyclo-C_3H_5$, $-COCH(CH_3)_2$, $-COC(CH_3)_3$, $-COOH$, $-COOCH_3$, $-COOC_2H_5$, $-COOC_3H_7$, $-COO-cyclo-C_3H_5$, $-COOCH(CH_3)_2$, $-COOC(CH_3)_3$, $-COOCH_2Ph$, $-CONH_2$, $-CONHCH_3$, $-CONHC_2H_5$, $-CONHC_3H_7$, $-CONH-cyclo-C_3H_5$, $-CONH[CH(CH_3)_2]$, $-CONH[C(CH_3)_3]$, $-CON(CH_3)_2$, $-CON(C_2H_5)_2$, $-CON(C_3H_7)_2$, $-CON(cyclo-C_3H_5)_2$, $-CON[CH(CH_3)_2]_2$, $-CON[C(CH_3)_3]_2$, or $-SO_3H$;

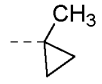
$\mathbf{R^{N5}}$ and $\mathbf{R^{N6}}$ represent independently of each other $-H$, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, cyclo-C_3H_5, $-COOC(CH_3)_3$, or $-COOCH_2Ph$;

$\mathbf{X^1}$ represents $-(CH_2)_m-$;

$\mathbf{X^2}$ represents $-(CH_2)_n-$;

$\mathbf{X^3}$ represents a bond, $-O-$, $-NH-$, or $-S-$;

$\mathbf{Z^1}$ – $\mathbf{Z^{14}}$ represent independently of each other

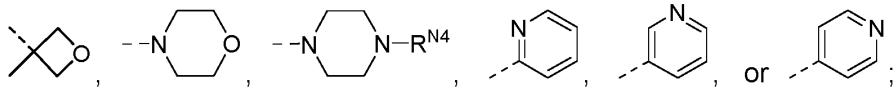


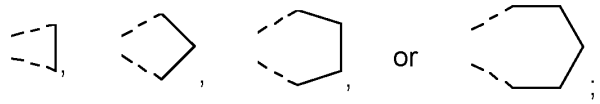
, cyclo-C_3H_5, cyclo-C_4H_7, cyclo-C_5H_9, cyclo-C_6H_{11}, cyclo-C_7H_{13}, $-\mathbf{R^{16}}$, $-H$, $-OH$, $-OCH_3$, $-OC_2H_5$, $-OC_3H_7$, $-O-cyclo-C_3H_5$, $-OCH(CH_3)_2$, $-OC(CH_3)_3$, $-OC_4H_9$, $-O-cyclo-C_4H_7$, $-O-cyclo-C_5H_9$, $-O-cyclo-C_6H_{11}$, $-OCH_2CH(CH_3)_2$, $-OCH_2-cyclo-C_3H_5$, $-OCH_2-cyclo-C_4H_7$, $-OCH_2-cyclo-C_5H_9$, $-OCH_2-cyclo-C_6H_{11}$, $-OPh$, $-OCH_2-Ph$, $-OCPh_3$, $-CH_2-OCH_3$, $-C_2H_4-OCH_3$, $-C_3H_6-OCH_3$, $-CH_2-OC_2H_5$, $-C_2H_4-OC_2H_5$, $-C_3H_6-OC_2H_5$, $-CH_2-OC_3H_7$, $-C_2H_4-OC_3H_7$, $-C_3H_6-OC_3H_7$, $-CH_2-O-cyclo-C_3H_5$, $-C_2H_4-O-cyclo-C_3H_5$, $-C_3H_6-O-cyclo-C_3H_5$, $-CH_2-OCH(CH_3)_2$, $-C_2H_4-OCH(CH_3)_2$, $-C_3H_6-OCH(CH_3)_2$, $-CH_2-OC(CH_3)_3$, $-C_2H_4-OC(CH_3)_3$, $-C_3H_6-OC(CH_3)_3$, $-CH_2-OC_4H_9$, $-C_2H_4-OC_4H_9$, $-C_3H_6-OC_4H_9$, $-CH_2-OPh$, $-C_2H_4-OPh$, $-C_3H_6-OPh$, $-CH_2-OCH_2-Ph$, $-C_2H_4-OCH_2-Ph$, $-C_3H_6-OCH_2-Ph$, $-SH$, $-SCH_3$, $-SC_2H_5$, $-SC_3H_7$, $-S-cyclo-C_3H_5$, $-SCH(CH_3)_2$, $-SC(CH_3)_3$, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-COCH_3$, $-COC_2H_5$, $-COC_3H_7$, $-CO-cyclo-C_3H_5$, $-COCH(CH_3)_2$, $-COC(CH_3)_3$, $-COOH$, $-COOCH_3$, $-COOC_2H_5$, $-COOC_3H_7$, $-COO-cyclo-C_3H_5$, $-COOCH(CH_3)_2$, $-COOC(CH_3)_3$, $-OOC-CH_3$, $-OOC-C_2H_5$, $-OOC-C_3H_7$,

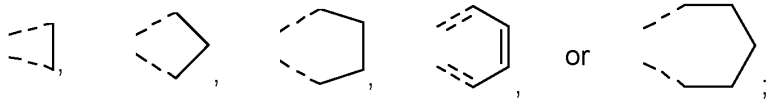
–OOC–cyclo-C_3H_5, –OOC–$CH(CH_3)_2$, –OOC–$C(CH_3)_3$, –$CONH_2$, –$CONHCH_3$, –$CONHC_2H_5$, –$CONHC_3H_7$, –CONH–cyclo-C_3H_5, –$CONH[CH(CH_3)_2]$, –$CONH[C(CH_3)_3]$, –$CON(CH_3)_2$, –$CON(C_2H_5)_2$, –$CON(C_3H_7)_2$, –$CON(cyclo\text{-}C_3H_5)_2$, –$CON[CH(CH_3)_2]_2$, –$CON[C(CH_3)_3]_2$, –$NHCOCH_3$, –$NHCOC_2H_5$, –$NHCOC_3H_7$, –NHCO–cyclo-$C_3H_5$, –NHCO–$CH(CH_3)_2$, –NHCO–$C(CH_3)_3$, –NHCO–$CH(NH_2)CH_2$–COOH, –NHCO–$CH(NH_2)CH_2CH_2$–COOH, –$NHCOOCH_3$, –$NHCOOC_2H_5$, –$NHCOOC_3H_7$, –NHCO–O–cyclo-$C_3H_5$, –NHCO–$OCH(CH_3)_2$, –NHCO–$OC(CH_3)_3$, –$NH_2$, –$NHCH_3$, –$NHC_2H_5$, –$NHC_3H_7$, –NH–cyclo-$C_3H_5$, –$NHCH(CH_3)_2$, –$NHC(CH_3)_3$, –$N(CH_3)_2$, –$N(C_2H_5)_2$, –$N(C_3H_7)_2$, –N(cyclo-$C_3H_5)_2$, –$N[CH(CH_3)_2]_2$, –$N[C(CH_3)_3]_2$, –$SOCH_3$, –$SOC_2H_5$, –$SOC_3H_7$, –SO–cyclo-$C_3H_5$, –$SOCH(CH_3)_2$, –$SOC(CH_3)_3$, –$SO_2CH_3$, –$SO_2C_2H_5$, –$SO_2C_3H_7$, –$SO_2$–cyclo-$C_3H_5$, –$SO_2CH(CH_3)_2$, –$SO_2C(CH_3)_3$, –$SO_3H$, –$SO_3CH_3$, –$SO_3C_2H_5$, –$SO_3C_3H_7$, –$SO_3$–cyclo-$C_3H_5$, –$SO_3CH(CH_3)_2$, –$SO_3C(CH_3)_3$, –$SO_2NH_2$, –$SO_2NHCH_3$, –$SO_2NHC_2H_5$, –$SO_2NHC_3H_7$, –$SO_2$NH–cyclo-$C_3H_5$, –$SO_2NHCH(CH_3)_2$, –$SO_2NHC(CH_3)_3$, –$SO_2N(CH_3)_2$, –$SO_2N(C_2H_5)_2$, –$SO_2N(C_3H_7)_2$, –$SO_2N(cyclo\text{-}C_3H_5)_2$, –$SO_2N[CH(CH_3)_2]_2$, –$SO_2N[C(CH_3)_3]_2$, –O–S(=O)$CH_3$, –O–S(=O)$C_2H_5$, –O–S(=O)$C_3H_7$, –O–S(=O)–cyclo-$C_3H_5$, –O–S(=O)$CH(CH_3)_2$, –O–S(=O)$C(CH_3)_3$, –S(=O)(=NH)$CH_3$, –S(=O)(=NH)$C_2H_5$, –S(=O)(=NH)$C_3H_7$, –S(=O)(=NH)–cyclo-$C_3H_5$, –S(=O)(=NH)$CH(CH_3)_2$, –S(=O)(=NH)$C(CH_3)_3$, –NH–$SO_2$–$CH_3$, –NH–$SO_2$–$C_2H_5$, –NH–$SO_2$–$C_3H_7$, –NH–$SO_2$–cyclo-$C_3H_5$, –NH–$SO_2$–$CH(CH_3)_2$, –NH–$SO_2$–$C(CH_3)_3$, –O–$SO_2$–$CH_3$, –O–$SO_2$–$C_2H_5$, –O–$SO_2$–$C_3H_7$, –O–$SO_2$–cyclo-$C_3H_5$, –O–$SO_2$–$CH(CH_3)_2$, –O–$SO_2$–$C(CH_3)_3$, –$OCH_2F$, –$OCHF_2$, –$OCF_3$, –$CH_2$–$OCF_3$, –$C_2H_4$–$OCF_3$, –$C_3H_6$–$OCF_3$, –$CH_2$–$OCHF_2$, –$C_2H_4$–$OCHF_2$, –$C_3H_6$–$OCHF_2$, –$OC_2F_5$, –$CH_2$–$OC_2F_5$, –$C_2H_4$–$OC_2F_5$, –$C_3H_6$–$OC_2F_5$, –O–$COOCH_3$, –O–$COOC_2H_5$, –O–$COOC_3H_7$, –O–COO–cyclo-$C_3H_5$, –O–$COOCH(CH_3)_2$, –O–$COOC(CH_3)_3$, –NH–CO–$NH_2$, –NH–CO–$NHCH_3$, –NH–CO–$NHC_2H_5$, –NH–CO–$NHC_3H_7$, –NH–C(=NH)–$NH_2$, –NH–CO–$N(C_3H_7)_2$, –NH–CO–$NH[CH(CH_3)_2]$, –NH–CO–$NH[C(CH_3)_3]$, –NH–CO–$N(CH_3)_2$, –NH–CO–$N(C_2H_5)_2$, –NH–CO–NH–cyclo-$C_3H_5$, –NH–CO–N(cyclo-$C_3H_5)_2$, –NH–CO–$N[CH(CH_3)_2]_2$, –NH–C(=NH)–$NHCH_3$, –NH–C(=NH)–$NHC_2H_5$, –NH–C(=NH)–$NHC_3H_7$, –O–CO–NH–cyclo-$C_3H_5$, –NH–C(=NH)–NH–cyclo-$C_3H_5$, –NH–C(=NH)–$NH[CH(CH_3)_2]$, –O–CO–$NH[CH(CH_3)_2]$, –NH–C(=NH)–$NH[C(CH_3)_3]$, –NH–C(=NH)–$N(CH_3)_2$, –NH–C(=NH)–$N(C_2H_5)_2$, –NH–C(=NH)–$N(C_3H_7)_2$, –NH–C(=NH)–N(cyclo-$C_3H_5)_2$, –O–CO–$NHC_3H_7$, –NH–C(=NH)–$N[CH(CH_3)_2]_2$, –NH–C(=NH)–$N[C(CH_3)_3]_2$, –O–CO–$NH_2$, –O–CO–$NHCH_3$, –O–CO–$NHC_2H_5$, –O–CO–$NH[C(CH_3)_3]$, –O–CO–$N(CH_3)_2$, –O–CO–$N(C_2H_5)_2$, –O–CO–$N(C_3H_7)_2$, –O–CO–N(cyclo-$C_3H_5)_2$, –O–CO–$N[CH(CH_3)_2]_2$, –O–CO–$N[C(CH_3)_3]_2$, –O–CO–

OCH_3, –O–CO–OC_2H_5, –O–CO–OC_3H_7, –O–CO–O–cyclo-C_3H_5, –O–CO–$OCH(CH_3)_2$, –O–CO–$OC(CH_3)_3$, –CH_2F, –CHF_2, –CF_3, –CH_2–CH_2F, –CH_2–CHF_2, –CH_2–CF_3, cyclo-C_8H_{15}, –Ph, –CH_2–Ph, –CH_2–CH_2–Ph, –CH=CH–Ph, –CPh_3, –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, –$C(CH_3)_3$, –C_5H_{11}, –$CH(CH_3)$–C_3H_7, –CH_2–$CH(CH_3)$–C_2H_5, –$CH(CH_3)$–$CH(CH_3)_2$, –$C(CH_3)_2$–C_2H_5, –CH_2–$C(CH_3)_3$, –$CH(C_2H_5)_2$, –C_2H_4–$CH(CH_3)_2$, –C_6H_{13}, –C_7H_{15}, –C_8H_{17}, –C_3H_6–$CH(CH_3)_2$, –C_2H_4–$CH(CH_3)$–C_2H_5, –$CH(CH_3)$–C_4H_9, –CH_2–$CH(CH_3)$–C_3H_7, –$CH(CH_3)$–CH_2–$CH(CH_3)_2$, –$CH(CH_3)$–$CH(CH_3)$–C_2H_5, –CH_2–$CH(CH_3)$–$CH(CH_3)_2$, –CH_2–$C(CH_3)_2$–C_2H_5, –$C(CH_3)_2$–C_3H_7, –$C(CH_3)_2$–$CH(CH_3)_2$, –C_2H_4–$C(CH_3)_3$, –$CH(CH_3)$–$C(CH_3)_3$, –$CH=CH_2$, –CH_2–$CH=CH_2$, –$C(CH_3)=CH_2$, –CH=CH–CH_3, –C_2H_4–$CH=CH_2$, –CH_2–CH=CH–CH_3, –CH=CH–C_2H_5, –CH_2–$C(CH_3)=CH_2$, –$CH(CH_3)$–CH=CH, –$CH=C(CH_3)_2$, –$C(CH_3)$=CH–CH_3, –CH=CH–CH=CH_2, –C_3H_6–$CH=CH_2$, –C_2H_4–CH=CH–CH_3, –CH_2–CH=CH–C_2H_5, –CH=CH–C_3H_7, –CH=CH–CH=CH–CH_3, –C_2H_4–$C(CH_3)=CH_2$, –CH_2–$CH(CH_3)$–$CH=CH_2$, –$CH(CH_3)$–CH_2–$CH=CH_2$, –CH_2–CH=$C(CH_3)_2$, –CH_2–$C(CH_3)$=CH–CH_3, –$CH(CH_3)$–CH=CH–CH_3, –CH=CH–$CH(CH_3)_2$, –CH=$C(CH_3)$–C_2H_5, –$C(CH_3)$=CH–C_2H_5, –$C(CH_3)$=$C(CH_3)_2$, –$C(CH_3)_2$–$CH=CH_2$, –$CH(CH_3)$–$C(CH_3)=CH_2$, –C_4H_8–$CH=CH_2$, –C_3H_6–CH=CH–CH_3, –C_2H_4–CH=CH–C_2H_5, –CH_2–CH=CH–C_3H_7, –CH=CH–C_4H_9, –C_3H_6–$C(CH_3)=CH_2$, –C_2H_4–$CH(CH_3)$–$CH=CH_2$, –CH_2–$CH(CH_3)$–CH_2–$CH=CH_2$, –C_2H_4–$CH=C(CH_3)_2$, –$CH(CH_3)$–C_2H_4–$CH=CH_2$, –C_2H_4–$C(CH_3)$=CH–CH_3, –CH_2–$CH(CH_3)$–CH=CH–CH_3, –$CH(CH_3)$–CH_2–CH=CH–CH_3, –CH_2–CH=CH–$CH(CH_3)_2$, –CH_2–CH=$C(CH_3)$–C_2H_5, –CH_2–$C(CH_3)$=CH–C_2H_5, –$CH(CH_3)$–CH=CH–C_2H_5, –CH=CH–CH_2–$CH(CH_3)_2$, –CH=CH–$CH(CH_3)$–C_2H_5, –CH=$C(CH_3)$–C_3H_7, –$C(CH_3)$=CH–C_3H_7, –CH_2–$CH(CH_3)$–$C(CH_3)=CH_2$, –$C[C(CH_3)_3]=CH_2$, –$CH(CH_3)$–CH_2–$C(CH_3)=CH_2$, –$CH(CH_3)$–$CH(CH_3)$–$CH=CH_2$, –CH=CH–C_2H_4–$CH=CH_2$, –$C(CH_3)_2$–CH_2–$CH=CH_2$, –CH_2–$C(CH_3)=C(CH_3)_2$, –$CH(CH_3)$–$CH=C(CH_3)_2$, –$C(CH_3)_2$–CH=CH–CH_3, –CH=CH–CH_2–CH=CH–CH_3, –$CH(CH_3)$–$C(CH_3)$=CH–CH_3, –CH=$C(CH_3)$–$CH(CH_3)_2$, –$C(CH_3)$=CH–$CH(CH_3)_2$, –$C(CH_3)$=$C(CH_3)$–C_2H_5, –CH=CH–$C(CH_3)_3$, –$C(CH_3)_2$–$C(CH_3)=CH_2$, –$CH(C_2H_5)$–$C(CH_3)=CH_2$, –$C(CH_3)(C_2H_5)$–CH=CH_2, –$CH(CH_3)$–$C(C_2H_5)=CH_2$, –CH_2–$C(C_3H_7)=CH_2$, –CH_2–$C(C_2H_5)$=CH–CH_3, –$CH(C_2H_5)$–CH=CH–CH_3, –$C(C_4H_9)=CH_2$, –$C(C_3H_7)$=CH–CH_3, –$C(C_2H_5)$=CH–C_2H_5, –$C(C_2H_5)$=$C(CH_3)_2$, –$C[CH(CH_3)(C_2H_5)]=CH_2$, –$C[CH_2$–$CH(CH_3)_2]=CH_2$, –C_2H_4–CH=CH–CH=CH_2, –CH_2–CH=CH–CH_2–CH=CH_2, –C_3H_6–C≡C–CH_3, –CH_2–CH=CH–CH=CH–CH_3, –CH=CH–CH=CH–C_2H_5, –$CH(CH_3)$–CH_2–C≡CH, –$CH(CH_3)$–C≡C–CH_3, –C_2H_4–$CH(CH_3)$–C≡CH, –CH=CH–CH=$C(CH_3)_2$, –CH_2–$CH(CH_3)$–CH_2–C≡CH, –CH=CH–$C(CH_3)$=CH–CH_3, –CH=$C(CH_3)$–CH=CH–CH_3, –CH_2–$CH(CH_3)$–

C≡CH, –C(CH$_3$)=CH–CH=CH–CH$_3$, –C≡CH, –C≡C–CH$_3$, –CH$_2$-C≡CH, –C$_2$H$_4$–C≡CH, –CH$_2$–C≡C–CH$_3$, –C≡C–C$_2$H$_5$, –C$_3$H$_6$–C≡CH, –C$_2$H$_4$–C≡C–CH$_3$, –CH$_2$–C≡C–C$_2$H$_5$, –C≡C–C$_3$H$_7$, –CH(CH$_3$)–C≡CH, –C$_4$H$_8$–C≡CH, –C$_2$H$_4$–C≡C–C$_2$H$_5$, –CH$_2$–C≡C–C$_3$H$_7$, –C≡C–C$_4$H$_9$, –C≡C–CH$_2$–CH(CH$_3$)$_2$, –CH(CH$_3$)–C$_2$H$_4$–C≡CH, –CH$_2$–CH(CH$_3$)–C≡C–CH$_3$, –C(CH$_3$)(C$_2$H$_5$)–C≡CH, –CH(CH$_3$)–CH$_2$–C≡C–CH$_3$, –CH(CH$_3$)–C≡C–C$_2$H$_5$, –CH$_2$–C≡C–CH(CH$_3$)$_2$, –C≡C–CH(CH$_3$)–C$_2$H$_5$, –CH$_2$–C≡C–C≡C–CH$_3$, –CH(C$_2$H$_5$)–C≡C–CH$_3$, –C(CH$_3$)$_2$–C≡C–CH$_3$, –CH(C$_2$H$_5$)–CH$_2$–C≡CH, –CH$_2$–CH(C$_2$H$_5$)–C≡CH, –C(CH$_3$)$_2$–CH$_2$–C≡CH, –CH$_2$–C(CH$_3$)$_2$–C≡CH, –CH(CH$_3$)–CH(CH$_3$)–C≡CH, –CH(C$_3$H$_7$)–C≡CH, –CH$_2$–CH(C≡CH)$_2$, –C≡C–C≡CH, –CH$_2$–C≡C–C≡CH, –C≡C–C≡C–CH$_3$, –CH(C≡CH)$_2$, –C$_2$H$_4$–C≡C–C≡CH, –CH$_2$–C≡C–CH$_2$–C≡CH, –C≡C–C$_2$H$_4$–C≡CH, –C≡C–C(CH$_3$)$_3$, –C≡C–CH$_2$–C≡C–CH$_3$, –C≡C–C≡C–C$_2$H$_5$,



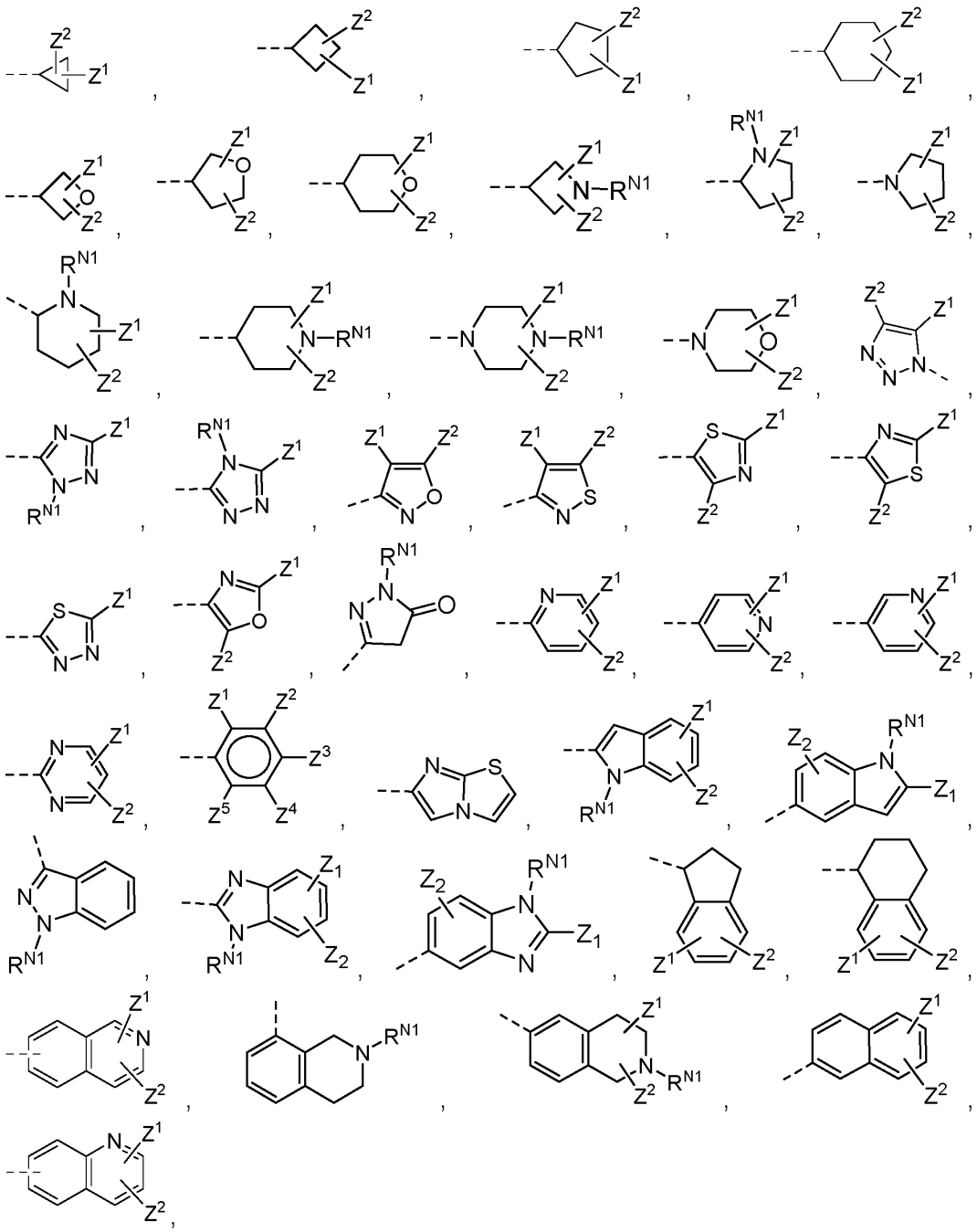
Z^3 and **Z^4** may form together 

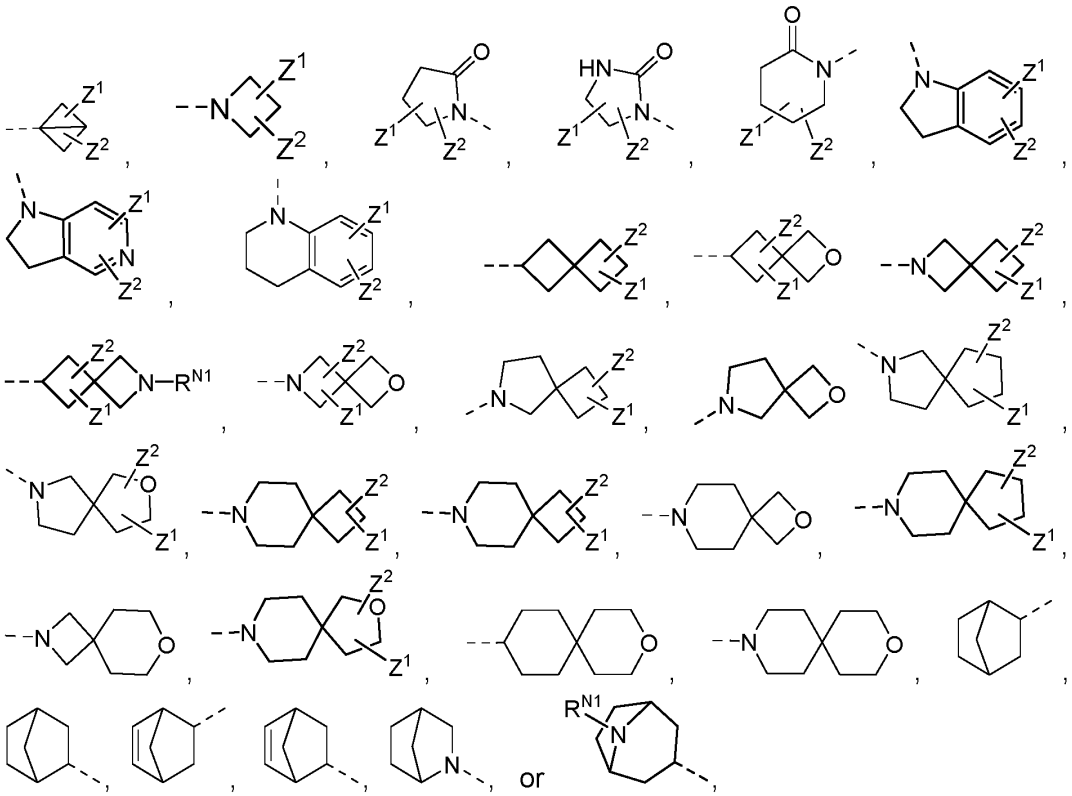
Z^{13} and **Z^{14}** may form together 

m is an integer selected from 0, 1, 2, 3, 4, 5, or 6;
n is an integer selected from 0, 1, 2, 3, 4, 5, or 6;
p is an integer selected from 0, 1, 2, 3, 4, 5, or 6;
r is an integer selected from 0, 1, 2, 3, or 4;
s is an integer selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;
t is an integer selected from 1, 2, 3, or 4;
u is an integer selected from 1, 2, 3, or 4;
v is an integer selected from 0, 1, 2, 3, 4, 5, or 6;
w is an integer selected from 0, 1, 2, 3, 4, 5 or 6;

or an enantiomer, a stereoisomeric form, a mixture of enantiomers, a diastereomer, a mixture of diastereomers, a hydrate, a solvate, an acid salt form, a tautomer, a racemate of the above mentioned compounds, or a pharmaceutically acceptable salt thereof.

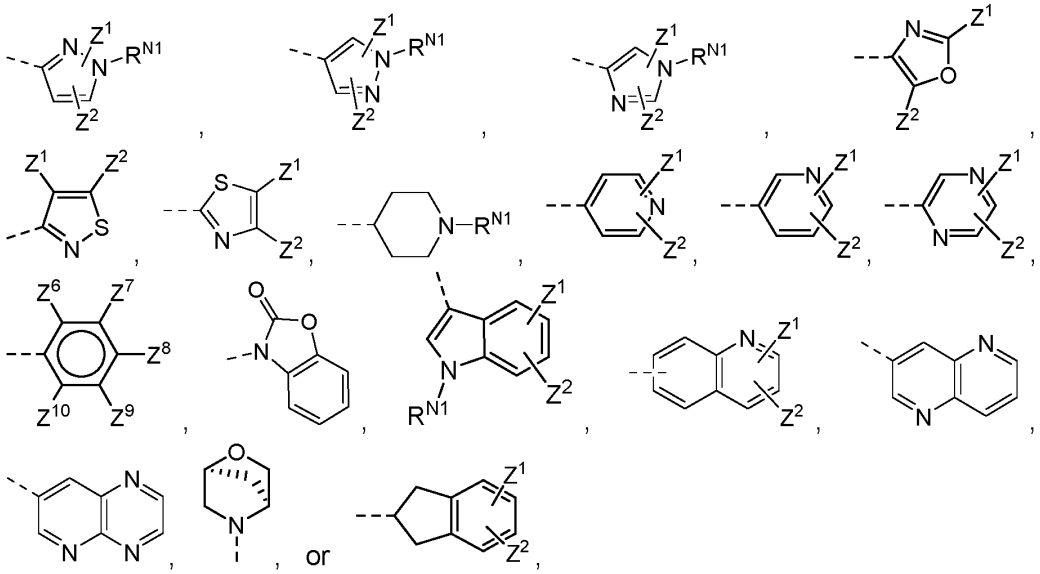
Still more preferred is the compound of formula (**I**), wherein **R^8** represents





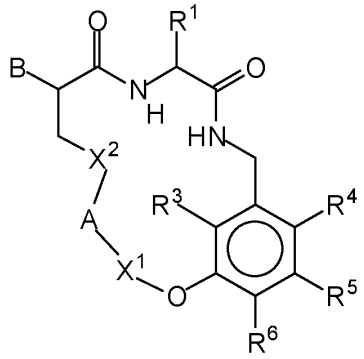
wherein R^{N1}, Z^1, Z^2, Z^3, Z^4, and Z^5 have the same meanings as defined in formula (I).

Still preferred is the compound of the formula (I), wherein R^9 represents



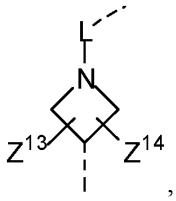
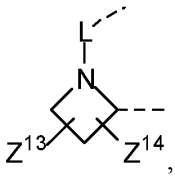
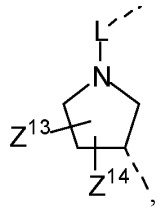
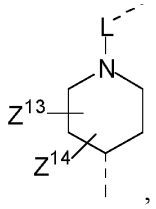
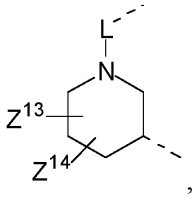
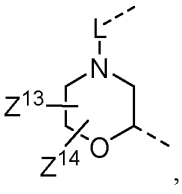
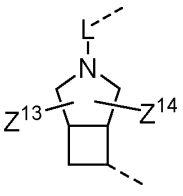
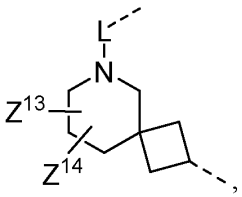
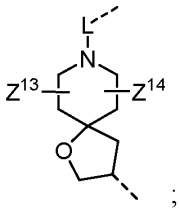
wherein R^{N1}, Z^1, Z^2, Z^6, Z^7, Z^8, Z^9, and Z^{10} have the same meanings as defined in formula (I).

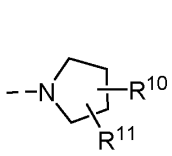
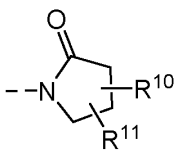
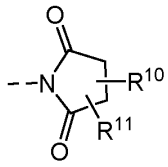
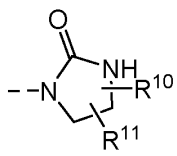
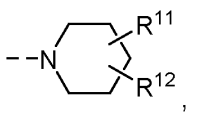
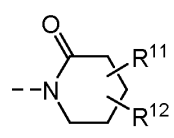
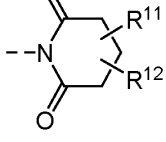
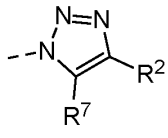
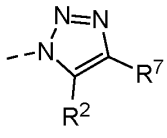
Thus, preferred are the compounds of formula (**I**),



(I)

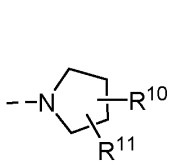
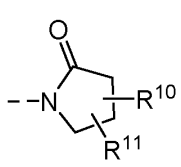
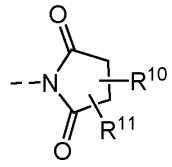
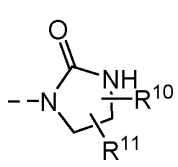
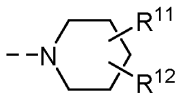
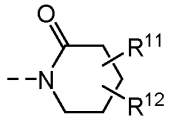
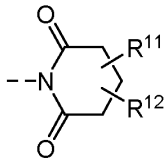
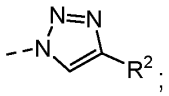
wherein

A represents –CO–N(**R**^{N6})–,  ,  ,  ,  ,  ,  ,  ,  , or  ;

B represents –H, –NH(**R**^{2}), –N(**R**^{2})(**R**^{N5}),  ,  ,  ,  ,  ,  ,  ,  , or  ;

preferably,

B represents –H, –NH(**R**^{2}), –N(**R**^{2})(**R**^{N5}),

L represents –CO–, –CO–NH–, –CO–N(**R**^{N3})–, or –CO–O–;

R^{1} represents –H, –(CH$_2$)$_p$–**R**^{7}, –(CH$_2$)$_p$–NH–**R**^{7}, –(CH$_2$)$_p$–**R**^{9}, or –(CH$_2$)$_p$–N**R**^{N4}–**R**^{9};

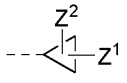
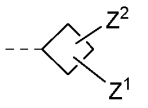
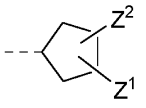
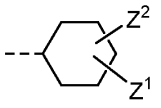
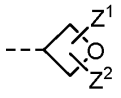
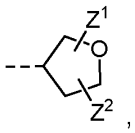
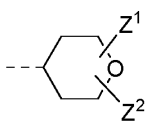
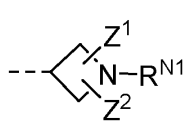
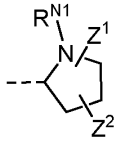
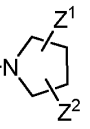
R^{2} represents –H, –**R**^{8}, –**R**^{11}, –**L**^{1}–**R**^{11}, –**L**^{1}–(CH$_2$)$_r$–**R**^{8}, –**L**^{1}–**R**^{10}, –**L**^{1}–(C$_2$H$_4$O)$_s$–**R**^{11}, –**L**^{1}–(CH$_2$)$_t$–O–**R**^{11}, –**L**^{1}–(CH$_2$)$_t$–NH–(CH$_2$)$_r$–**R**^{8}, –**L**^{1}–(CH$_2$)$_t$–O–(CH$_2$)$_r$–**R**^{8}, –**L**^{1}–(CH$_2$)$_t$–NH**R**^{8}, –**L**^{1}–(CH$_2$)$_t$–NH–CO–**R**^{8}, –**L**^{1}–(CH$_2$)$_t$–NH–SO$_2$–**R**^{8}, –**L**^{1}–(CH$_2$)$_t$–N**R**^{N6}**R**^{10}, –**L**^{1}–(CH$_2$)$_t$–O–(CH$_2$)$_u$–N**R**^{N6}**R**^{10}, –**L**^{1}–(CH$_2$)$_r$–**R**^{14}, –CO–C(**R**^{12})(**R**^{13})–**R**^{10}, –CO–C(**R**^{12})(**R**^{13})–**R**^{8}, or –CO–C(**R**^{12})(**R**^{13})–(CH$_2$)$_u$–**R**^{8};

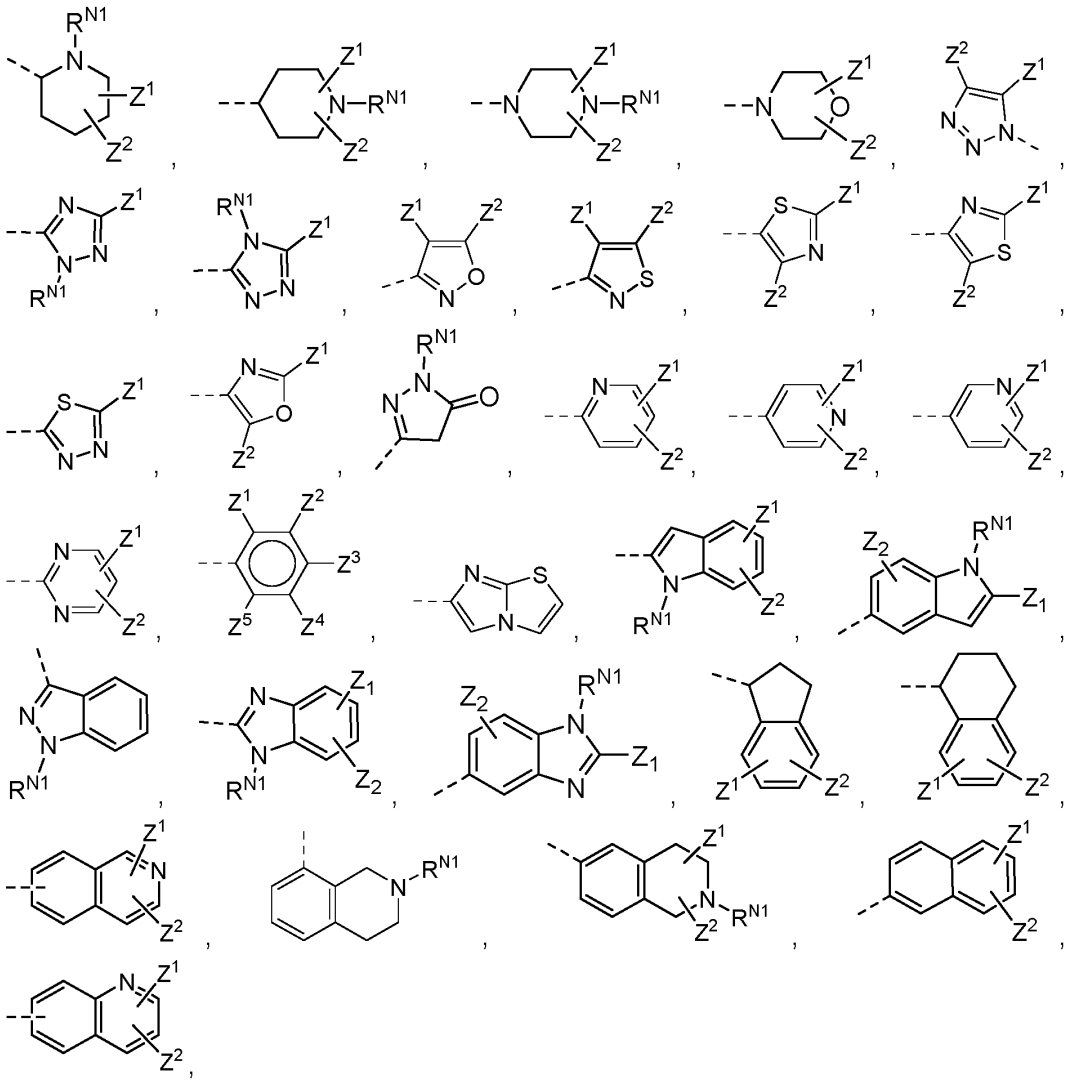
L^{1} represents a bond, –CO–, –CO$_2$–, –CONH–, or –SO$_2$–;

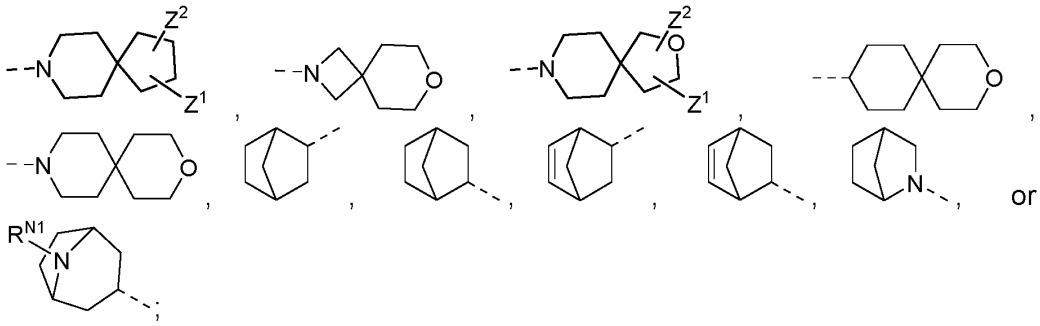
R^{3} – **R**^{6} represent independently of each other –H, –CH$_3$, –OCH$_3$, –F, or –Cl;

or **R** ^{5} and **R**^{6} may form together  ;

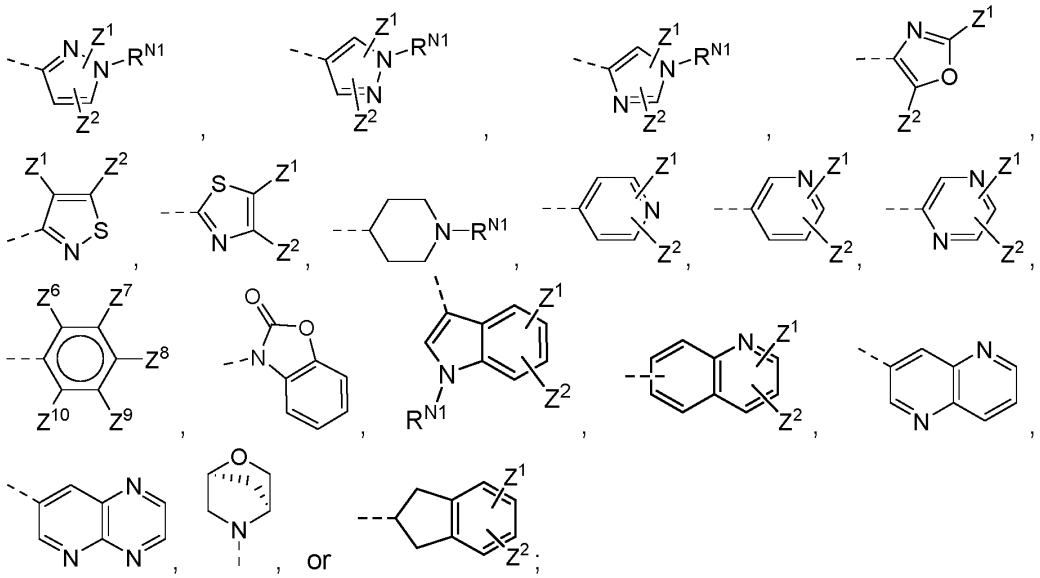
R^{8} represents





R^9 represents



X^1 represents $-(CH_2)_m-$;

X^2 represents $-(CH_2)_n-$;

X^3 represents a bond, –O–, –NH–, or –S–;

and R^{N1}- R^{N6}, R^7, R^{10} - R^{17} , Z^1 - Z^{14}, m, n, o, p, r, s, t, u, v, w have the same meanings as defined above,

or an enantiomer, a stereoisomeric form, a mixture of enantiomers, a diastereomer, a mixture of diastereomers, a hydrate, a solvate, an acid salt form, a tautomer, a racemate of the above mentioned compounds, or a pharmaceutically acceptable salt thereof.

Preferably, R^{15} represents
$-CH_2-OH$, $-CH_2CH_2-OH$, $-CH_2CH_2CH_2-OH$, $-CH_2CH_2CH_2CH_2-OH$, $-CH_2CH_2CH_2CH_2CH_2-OH$, $-CH_2CH_2CH_2CH_2CH_2-OH$, $-CH_2-CO_2H$, $-CH_2CH_2-CO_2H$, $-CH_2CH_2CH_2-CO_2H$, $-CH_2CH_2CH_2CH_2-CO_2H$, $-CH_2CH_2CH_2CH_2CH_2-CO_2H$, $-CH_2CH_2CH_2CH_2CH_2-CO_2H$, $-CH_2-SH$, $-CH_2CH_2-SH$, $-CH_2CH_2CH_2-SH$, $-CH_2CH_2CH_2CH_2-SH$, $-CH_2CH_2CH_2CH_2CH_2-SH$, $-CH_2CH_2CH_2CH_2CH_2-SH$, $-CH_2-SO_3H$, $-CH_2CH_2-SO_3H$, $-CH_2CH_2CH_2-SO_3H$, $-CH_2CH_2CH_2CH_2-SO_3H$, $-CH_2CH_2CH_2CH_2CH_2-SO_3H$, $-CH_2CH_2CH_2CH_2CH_2-SO_3H$, $-CH_2-NH_2$, $-CH_2CH_2-NH_2$, $-CH_2CH_2CH_2-NH_2$, $-CH_2CH_2CH_2CH_2-NH_2$, $-CH_2CH_2CH_2CH_2CH_2-NH_2$, $-CH_2CH_2CH_2CH_2CH_2CH_2-NH_2$, $-CH_2CH_2-O-CH_2-CH_2-OH$, $-(CH_2CH_2-O)_2-CH_2-CH_2-OH$, $-(CH_2CH_2-O)_3-CH_2-CH_2-OH$, $-CH_2CH_2-O-CH_2-CH_2-CO_2H$, $-(CH_2CH_2-O)_2-CH_2-CH_2-CO_2H$, $-(CH_2CH_2-O)_3-CH_2-CH_2-CO_2H$, $-CH_2CH_2-O-CH_2-CH_2-SH$, $-(CH_2CH_2-O)_2-CH_2-CH_2-SH$, $-(CH_2CH_2-O)_3-CH_2-CH_2-SH$, $-CH_2CH_2-O-CH_2-CH_2-SO_3H$, $-(CH_2CH_2-O)_2-CH_2-CH_2-SO_3H$, $-(CH_2CH_2-O)_3-CH_2-CH_2-SO_3H$, $-CH_2CH_2-O-CH_2-CH_2-NH_2$, $-(CH_2CH_2-O)_2-CH_2-CH_2-NH_2$, or $-(CH_2CH_2-O)_3-CH_2-CH_2-NH_2$.

More preferably, R^{15} represents $-CH_2-NH_2$, $-CH_2CH_2-NH_2$, $-CH_2CH_2CH_2-NH_2$, $-CH_2-SO_3H$, $-CH_2CH_2-SO_3H$, $-CH_2CH_2CH_2-SO_3H$, $-CH_2CH_2-O-CH_2-CH_2-NH_2$, $-(CH_2CH_2-O)_2-CH_2-CH_2-NH_2$, or $-(CH_2CH_2-O)_3-CH_2-CH_2-NH_2$.

Preferably, R^{16} represents
$-CH_2-OH$, $-CH_2CH_2-OH$, $-CH_2CH_2CH_2-OH$, $-CH_2CH_2CH_2CH_2-OH$, $-CH_2CH_2CH_2CH_2CH_2-OH$, $-CH_2CH_2CH_2CH_2CH_2-OH$, $-CH_2-CO_2H$, $-CH_2CH_2-CO_2H$, $-CH_2CH_2CH_2-CO_2H$, $-CH_2CH_2CH_2CH_2-CO_2H$, $-CH_2CH_2CH_2CH_2CH_2-CO_2H$, $-CH_2CH_2CH_2CH_2CH_2-CO_2H$, $-CH_2-SH$, $-CH_2CH_2-SH$, $-CH_2CH_2CH_2-SH$, $-CH_2CH_2CH_2CH_2-SH$, $-CH_2CH_2CH_2CH_2CH_2-SH$, $-CH_2CH_2CH_2CH_2CH_2-$ SH, $-CH_2-SO_3H$, $-CH_2CH_2-SO_3H$, $-CH_2CH_2CH_2-SO_3H$, $-CH_2CH_2CH_2CH_2-SO_3H$, $-CH_2CH_2CH_2CH_2CH_2-SO_3H$, $-CH_2CH_2CH_2CH_2CH_2-SO_3H$, $-CH_2-NH_2$, $-CH_2CH_2-NH_2$, $-CH_2CH_2CH_2-NH_2$, $-CH_2CH_2CH_2CH_2-NH_2$, $-CH_2CH_2CH_2CH_2CH_2-NH_2$, $-CH_2CH_2CH_2CH_2CH_2CH_2-NH_2$, $-CH_2CH_2-O-CH_2-CH_2-OH$, $-(CH_2CH_2-O)_2-CH_2-CH_2-OH$, $-(CH_2CH_2-O)_3-CH_2-CH_2-OH$, $-CH_2CH_2-O-CH_2-CH_2-CO_2H$, $-(CH_2CH_2-O)_2-CH_2-CH_2-CO_2H$, $-(CH_2CH_2-O)_3-CH_2-CH_2-CO_2H$, $-CH_2CH_2-O-CH_2-CH_2-SH$, $-(CH_2CH_2-O)_2-CH_2-CH_2-SH$, $-(CH_2CH_2-O)_3-CH_2-CH_2-SH$, $-CH_2CH_2-O-CH_2-CH_2-SO_3H$,

–$(CH_2CH_2$-$O)_2$-CH_2–CH_2–SO_3H, –$(CH_2CH_2$-$O)_3$-CH_2–CH_2–SO_3H, –CH_2CH_2-O-CH_2–CH_2–NH_2, –$(CH_2CH_2$-$O)_2$-CH_2–CH_2–NH_2, –$(CH_2CH_2$-$O)_3$-CH_2–CH_2–NH_2 ,

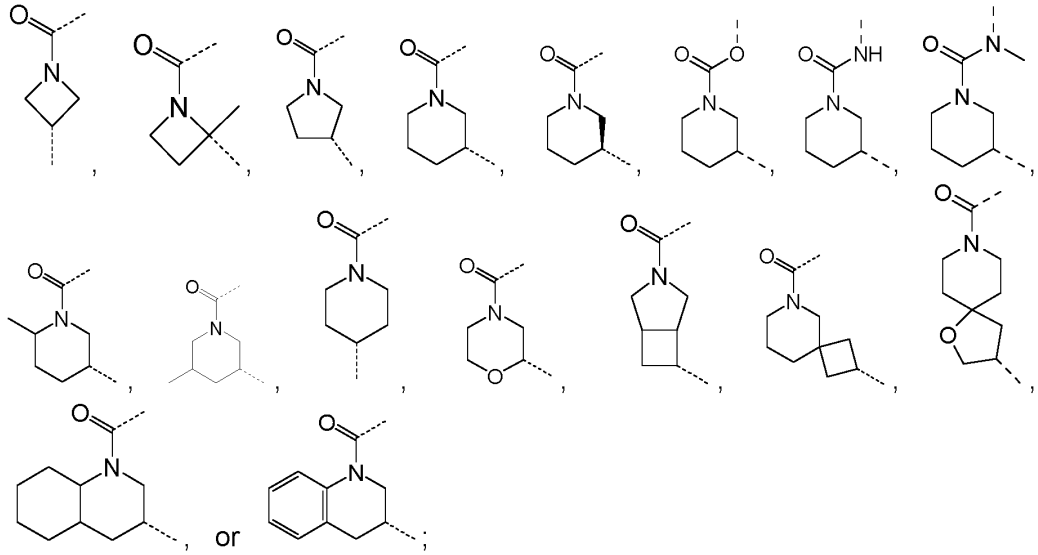
–OCH_2–OH, –OCH_2CH_2–OH, –$OCH_2CH_2CH_2$–OH, –$OCH_2CH_2CH_2CH_2$–OH, –$OCH_2CH_2CH_2CH_2CH_2$–OH, –$OCH_2CH_2CH_2CH_2CH_2$–OH, –OCH_2–CO_2H, –OCH_2CH_2–CO_2H, –$OCH_2CH_2CH_2$–CO_2H, –$OCH_2CH_2CH_2CH_2$–CO_2H, –$OCH_2CH_2CH_2CH_2CH_2$–CO_2H, –$OCH_2CH_2CH_2CH_2CH_2$–CO_2H, –OCH_2–SH, –OCH_2CH_2–SH, –$OCH_2CH_2CH_2$–SH, –$OCH_2CH_2CH_2CH_2$–SH, –$OCH_2CH_2CH_2CH_2CH_2$–SH, –$OCH_2CH_2CH_2CH_2CH_2$–SH, –OCH_2–SO_3H, –OCH_2CH_2–SO_3H, –$OCH_2CH_2CH_2$–SO_3H, –$OCH_2CH_2CH_2CH_2$–SO_3H, –$OCH_2CH_2CH_2CH_2CH_2$–SO_3H, –$OCH_2CH_2CH_2CH_2CH_2$–SO_3H, –OCH_2–NH_2, –OCH_2CH_2–NH_2, –$OCH_2CH_2CH_2$–NH_2, –$OCH_2CH_2CH_2CH_2$–NH_2, –$OCH_2CH_2CH_2CH_2CH_2$–NH_2, –$OCH_2CH_2CH_2CH_2CH_2CH_2$–$NH_2$, –$OCH_2CH_2$-O-$CH_2$–$CH_2$–OH, –$O(CH_2CH_2$-$O)_2$-$CH_2$–$CH_2$–OH, –$O(CH_2CH_2$-$O)_3$-$CH_2$–$CH_2$–OH, –$OCH_2CH_2$-O-$CH_2$–$CH_2$–$CO_2H$, –$O(CH_2CH_2$-$O)_2$-$CH_2$–$CH_2$–$CO_2H$, –$O(CH_2CH_2$-$O)_3$-$CH_2$–$CH_2$–$CO_2H$, –$OCH_2CH_2$-O-$CH_2$–$CH_2$–SH, –$O(CH_2CH_2$-$O)_2$-$CH_2$–$CH_2$–SH, –$O(CH_2CH_2$-$O)_3$-$CH_2$–$CH_2$–SH, –$OCH_2CH_2$-O-$CH_2$–$CH_2$–$SO_3H$, –$O(CH_2CH_2$-$O)_2$-$CH_2$–$CH_2$–$SO_3H$, –$O(CH_2CH_2$-$O)_3$-$CH_2$–$CH_2$–$SO_3H$, –$OCH_2CH_2$-O-$CH_2$–$CH_2$–$NH_2$, –$O(CH_2CH_2$-$O)_2$-$CH_2$–$CH_2$–$NH_2$, –$O(CH_2CH_2$-$O)_3$-$CH_2$–$CH_2$–$NH_2$,

–SCH_2–OH, –SCH_2CH_2–OH, –$SCH_2CH_2CH_2$–OH, –$SCH_2CH_2CH_2CH_2$–OH, –$SCH_2CH_2CH_2CH_2CH_2$–OH, –$SCH_2CH_2CH_2CH_2CH_2$–OH, –SCH_2–CO_2H, –SCH_2CH_2–CO_2H, –$SCH_2CH_2CH_2$–CO_2H, –$SCH_2CH_2CH_2CH_2$–CO_2H, –$SCH_2CH_2CH_2CH_2CH_2$–CO_2H, –$SCH_2CH_2CH_2CH_2CH_2$–CO_2H, –SCH_2–SH, –SCH_2CH_2–SH, –$SCH_2CH_2CH_2$–SH, –$SCH_2CH_2CH_2CH_2$–SH, –$SCH_2CH_2CH_2CH_2CH_2$–SH, –$SCH_2CH_2CH_2CH_2CH_2$–SH, –SCH_2–SO_3H, –SCH_2CH_2–SO_3H, –$SCH_2CH_2CH_2$–SO_3H, –$SCH_2CH_2CH_2CH_2$–SO_3H, –$SCH_2CH_2CH_2CH_2CH_2$–SO_3H, –$SCH_2CH_2CH_2CH_2CH_2$–SO_3H, –SCH_2–NH_2, –SCH_2CH_2–NH_2, –$SCH_2CH_2CH_2$–NH_2, –$SCH_2CH_2CH_2CH_2$–NH_2, –$SCH_2CH_2CH_2CH_2CH_2$–NH_2, –$SCH_2CH_2CH_2CH_2CH_2CH_2$–$NH_2$, –$SCH_2CH_2$-O-$CH_2$–$CH_2$–OH, –$S(CH_2CH_2$-$O)_2$-$CH_2$–$CH_2$–OH, –$S(CH_2CH_2$-$O)_3$-$CH_2$–$CH_2$–OH, –$SCH_2CH_2$-O-$CH_2$–$CH_2$–$CO_2H$, –$S(CH_2CH_2$-$O)_2$-$CH_2$–$CH_2$–$CO_2H$, –$S(CH_2CH_2$-$O)_3$-$CH_2$–$CH_2$–$CO_2H$, –$SCH_2CH_2$-O-$CH_2$–$CH_2$–SH, –$S(CH_2CH_2$-$O)_2$-$CH_2$–$CH_2$–SH, –$S(CH_2CH_2$-$O)_3$-$CH_2$–$CH_2$–SH, –$SCH_2CH_2$-O-$CH_2$–$CH_2$–$SO_3H$, –$S(CH_2CH_2$-$O)_2$-$CH_2$–$CH_2$–$SO_3H$, –$S(CH_2CH_2$-$O)_3$-$CH_2$–$CH_2$–$SO_3H$, –$SCH_2CH_2$-O-$CH_2$–$CH_2$–$NH_2$, –$S(CH_2CH_2$-$O)_2$-$CH_2$–$CH_2$–$NH_2$, –$S(CH_2CH_2$-$O)_3$-$CH_2$–$CH_2$–$NH_2$,

–$NHCH_2$–OH, –$NHCH_2CH_2$–OH, –$NHCH_2CH_2CH_2$–OH, –$NHCH_2CH_2CH_2CH_2$–OH, –$NHCH_2CH_2CH_2CH_2CH_2$–OH, –$NHCH_2CH_2CH_2CH_2CH_2$–OH, –$NHCH_2$–CO_2H, –$NHCH_2CH_2$–CO_2H, –$NHCH_2CH_2CH_2$–CO_2H, –$NHCH_2CH_2CH_2CH_2$–CO_2H, –$NHCH_2CH_2CH_2CH_2CH_2$–CO_2H, –$NHCH_2CH_2CH_2CH_2CH_2$–CO_2H, –$NHCH_2$–SH, –$NHCH_2CH_2$–SH, –$NHCH_2CH_2CH_2$–SH, –$NHCH_2CH_2CH_2CH_2$–SH, –$NHCH_2CH_2CH_2CH_2CH_2$–SH, –$NHCH_2CH_2CH_2CH_2CH_2$–SH, –$NHCH_2$–SO_3H, –$NHCH_2CH_2$–SO_3H, –$NHCH_2CH_2CH_2$–SO_3H, –$NHCH_2CH_2CH_2CH_2$–SO_3H, –$NHCH_2CH_2CH_2CH_2CH_2$–SO_3H, –$NHCH_2CH_2CH_2CH_2CH_2$–SO_3H, –$NHCH_2$–NH_2, –$NHCH_2CH_2$–NH_2, –$NHCH_2CH_2CH_2$–NH_2, –$NHCH_2CH_2CH_2CH_2$–NH_2, –$NHCH_2CH_2CH_2CH_2CH_2$–NH_2, –$NHCH_2CH_2CH_2CH_2CH_2CH_2$–$NH_2$, –$NHCH_2CH_2$-O-$CH_2$–$CH_2$–OH, –$NH(CH_2CH_2$-O$)_2$-$CH_2$–$CH_2$–OH, –$NH(CH_2CH_2$-O$)_3$-$CH_2$–$CH_2$–OH, –$NHCH_2CH_2$-O-$CH_2$–$CH_2$–$CO_2H$, –$NH(CH_2CH_2$-O$)_2$-$CH_2$–$CH_2$–$CO_2H$, –$NH(CH_2CH_2$-O$)_3$-$CH_2$–$CH_2$–$CO_2H$, –$NHCH_2CH_2$-O-$CH_2$–$CH_2$–SH, –$NH(CH_2CH_2$-O$)_2$-$CH_2$–$CH_2$–SH, –$NH(CH_2CH_2$-O$)_3$-$CH_2$–$CH_2$–SH, –$NHCH_2CH_2$-O-$CH_2$–$CH_2$–$SO_3H$, –$NH(CH_2CH_2$-O$)_2$-$CH_2$–$CH_2$–$SO_3H$, –$NH(CH_2CH_2$-O$)_3$-$CH_2$–$CH_2$–$SO_3H$, –$NHCH_2CH_2$-O-$CH_2$–$CH_2$–$NH_2$, –$NH(CH_2CH_2$-O$)_2$-$CH_2$–$CH_2$–$NH_2$, or –$NH(CH_2CH_2$-O$)_3$-$CH_2$–$CH_2$–$NH_2$.

More preferably, $\mathbf{R^{16}}$ represents –CH_2–NH_2, –CH_2CH_2–NH_2, –$CH_2CH_2CH_2$–NH_2, –CH_2–SO_3H, –CH_2CH_2–SO_3H, –$CH_2CH_2CH_2$–SO_3H, –CH_2CH_2-O-CH_2–CH_2–NH_2, –$(CH_2CH_2$-O$)_2$-CH_2–CH_2–NH_2, or –$(CH_2CH_2$-O$)_3$-CH_2–CH_2–NH_2.

Also preferred is the compound of formula (**I**), wherein **A** is –CO–NH–, –CO–NCH_3–,

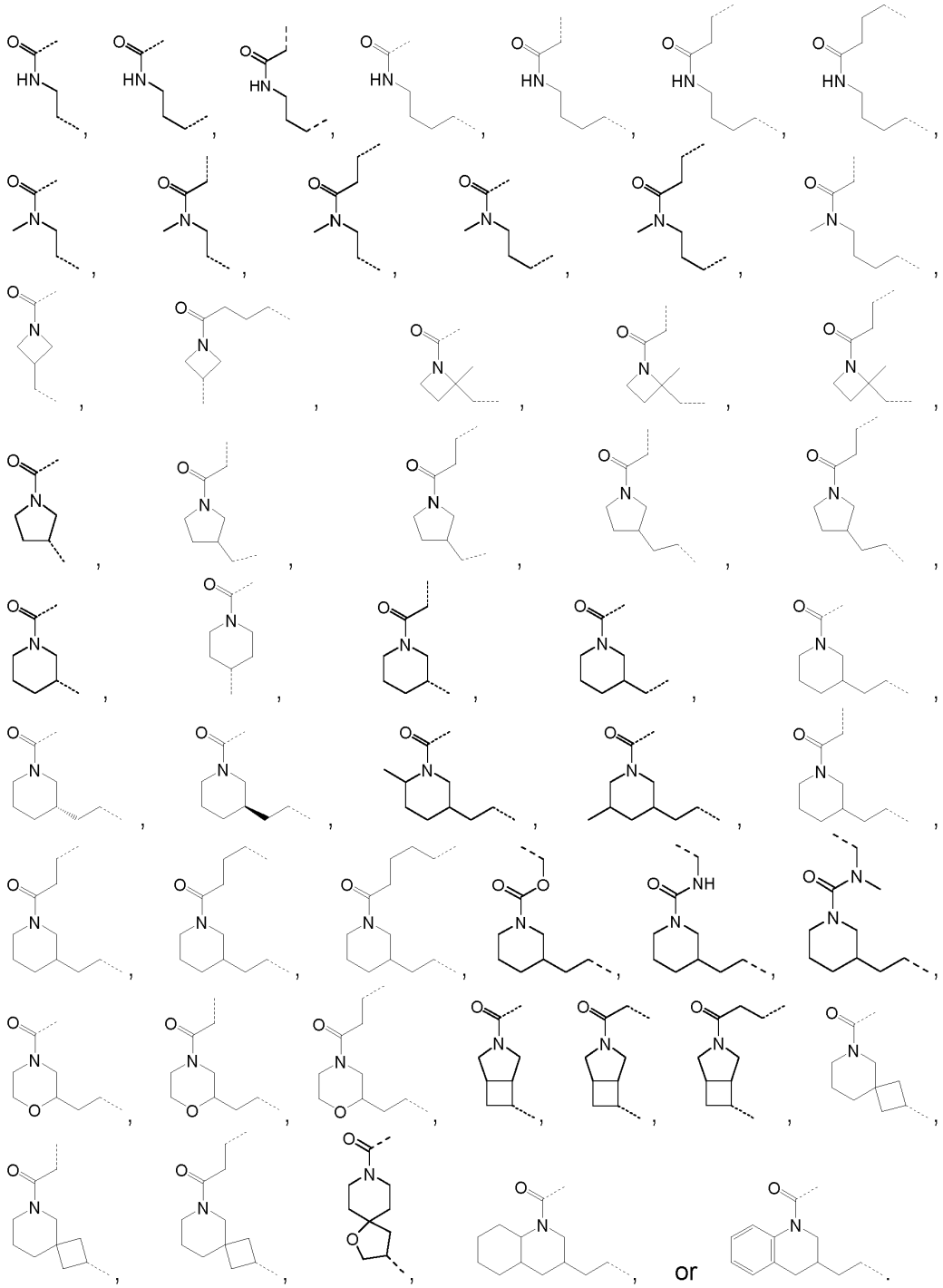


and/or

$\mathbf{X_2}$ represents a bond, $-CH_2-$, $-CH_2CH_2-$, or $-CH_2CH_2CH_2-$; and

$\mathbf{X_1}$ represents a bond, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2-$;

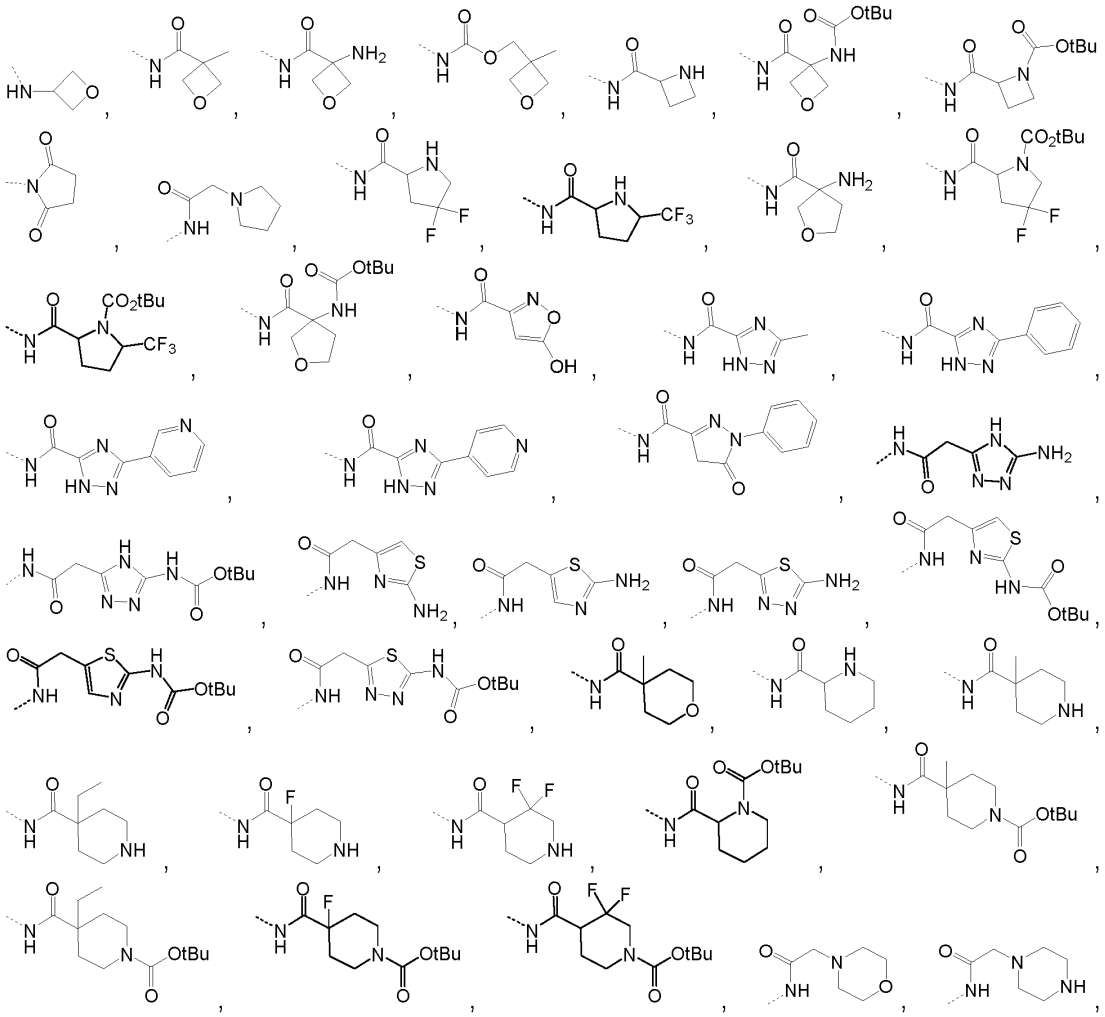
more preferred are compounds wherein $-\mathbf{X_2}\text{-}\mathbf{A}\text{-}\mathbf{X_1}-$ represents

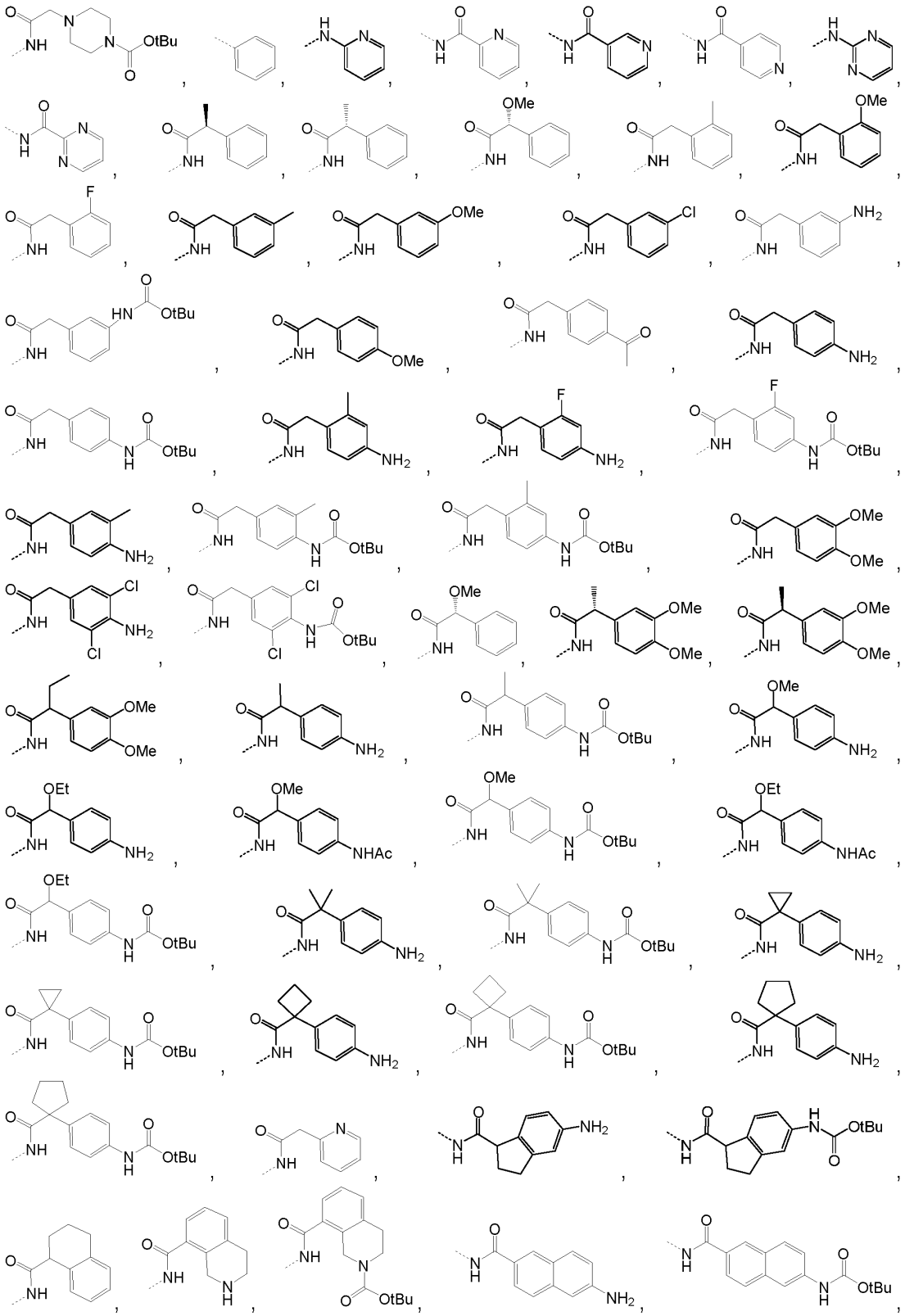


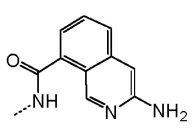
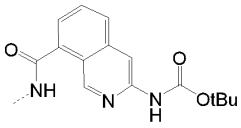
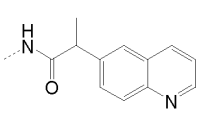
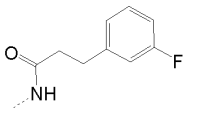
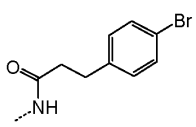
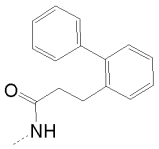
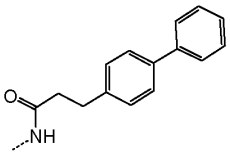
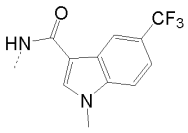
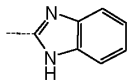
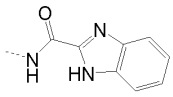
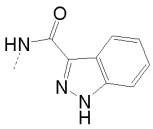
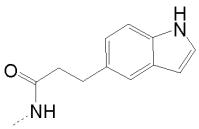
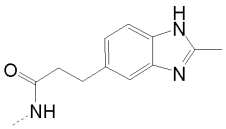
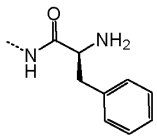
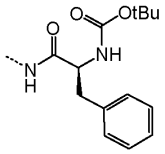
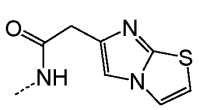
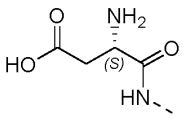
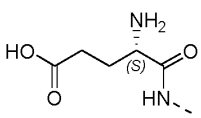
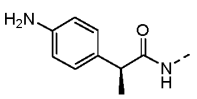
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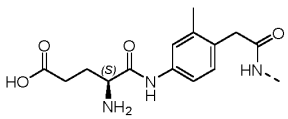
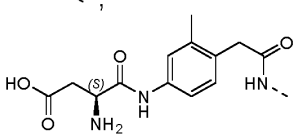
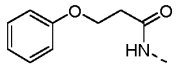
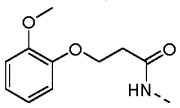
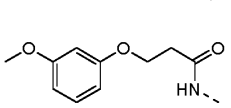
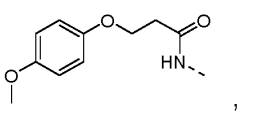
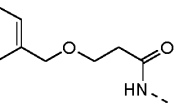
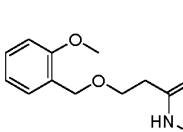
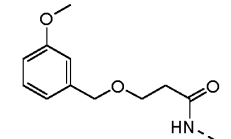
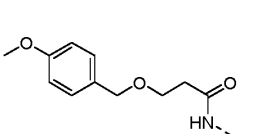
Also preferred is the compound of general formula (**I**), wherein

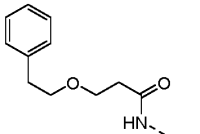
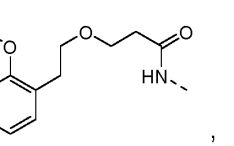
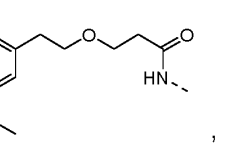
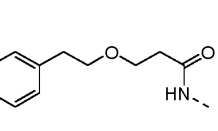
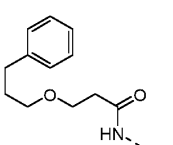
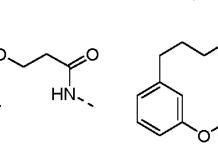
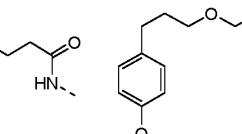
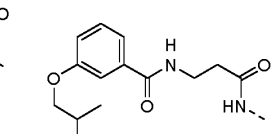
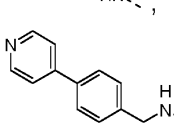
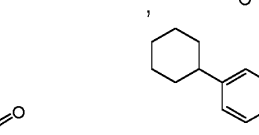
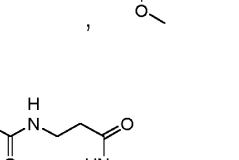
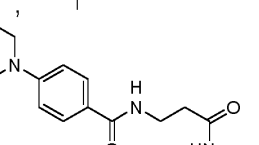
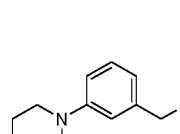
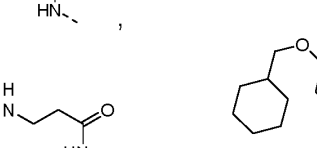
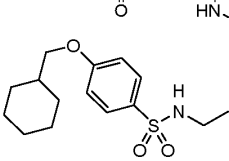
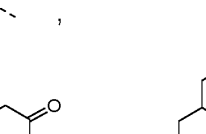
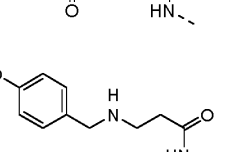
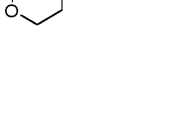
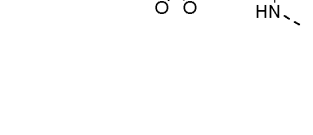
B represents –H, –NH_2, –$NHCOCH_3$, –$NHCOC(CH_3)_3$, –$NHCOC(CN)(CH_3)_2$, –$NHCOCH{=}CH_2$, –$NHCOCH_2C(CH_3)_3$, –NHCOPh, –$NHCOCH_2$Ph, –$NHCOCH_2$–$NH(CH_3)$, –$NHCOCH_2$–$N(CH_3)CO_2tBu$, –$NHCOC(CH_3)_2CH_2OH$, –$NHCOC(CH_3)_2CH_2SH$, –$NHCOC(CH_3)_2CH_2NH_2$, –$NHCOC(CH_3)_2CH_2F$, –$NHCOC(CH_3)_2CF_3$, –$NHCOCF_2CH_2OH$, –$NHCOCF_2CH_2NH_2$, –$NHCOC(CH_2CH_3)_2CH_2OH$, –$NHCOC(CH_3)(CH_2OH)_2$, –$NHCOCH_2OCH_2CH_2$–$NH(CH_3)$, –$NHCOCH_2OCH_2CH_2$–$N(CH_3)CO_2tBu$, –$NHCO(CH_2CH_2O)_2CH_3$, –$NHCO_2CH_2CH_3$, –$NHCO_2(CH_2CH_2O)_3CH_3$, –$NHCO_2(CH_2CH_2O)_5CH_3$, –$NHCO_2(CH_2CH_2O)_7CH_3$, –$NHCO_2CH_2$Ph –$NHCONHCH_2CH_3$, –$NHSO_2CH_3$, –$NHSO_2CH{=}CH_2$, –$NHSO_2CH_2$Ph, –$NHSO_2CH_2CH_2$Ph, –$NHSO_2CH_2CH_2CH_2$Ph, –$NHSO_2CH_2CF_3$, –$NHCH_2CF_3$, –$NHCH_2(CH_3)_2NH_2$, –$NHCH_2(CH_3)_2CH_2OH$,

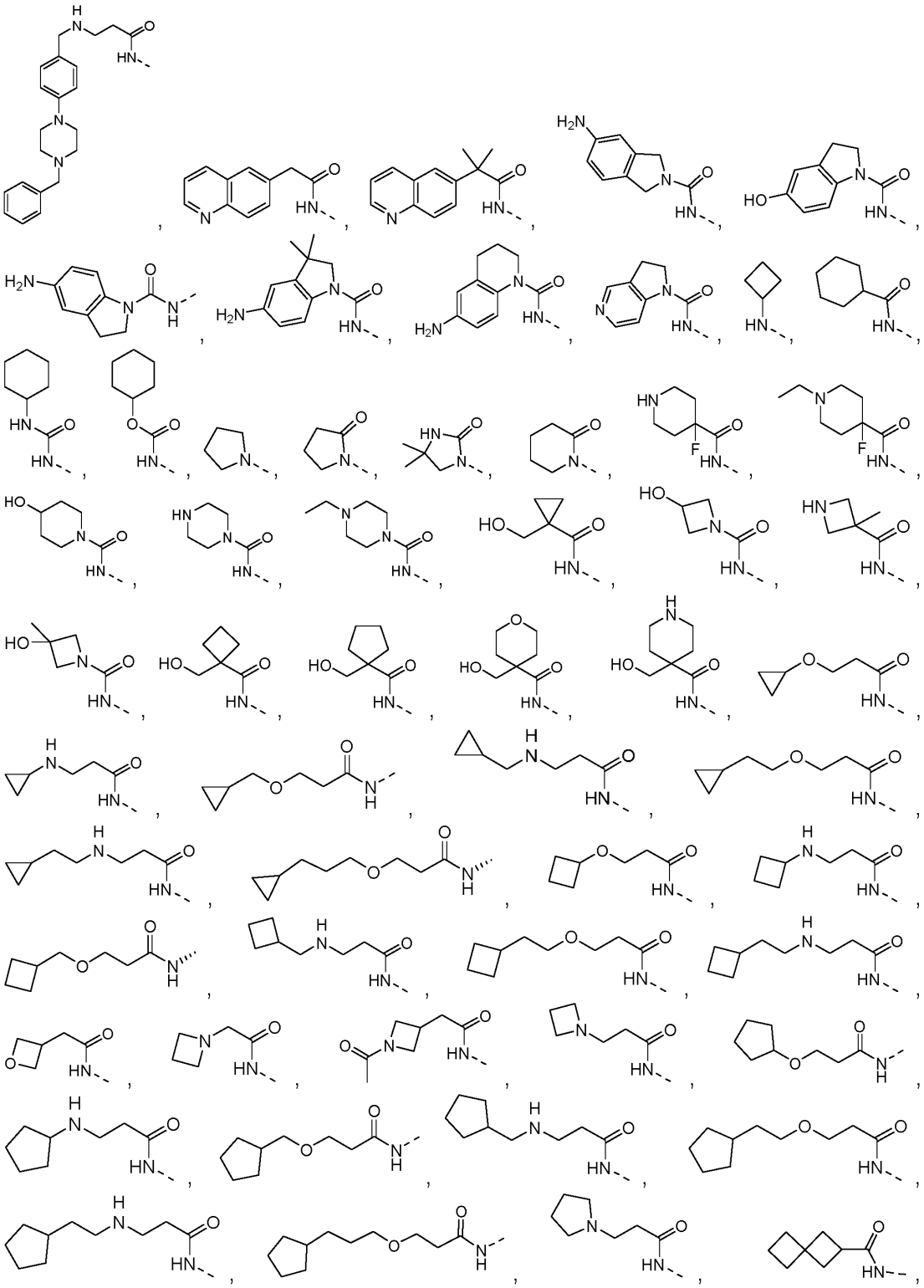


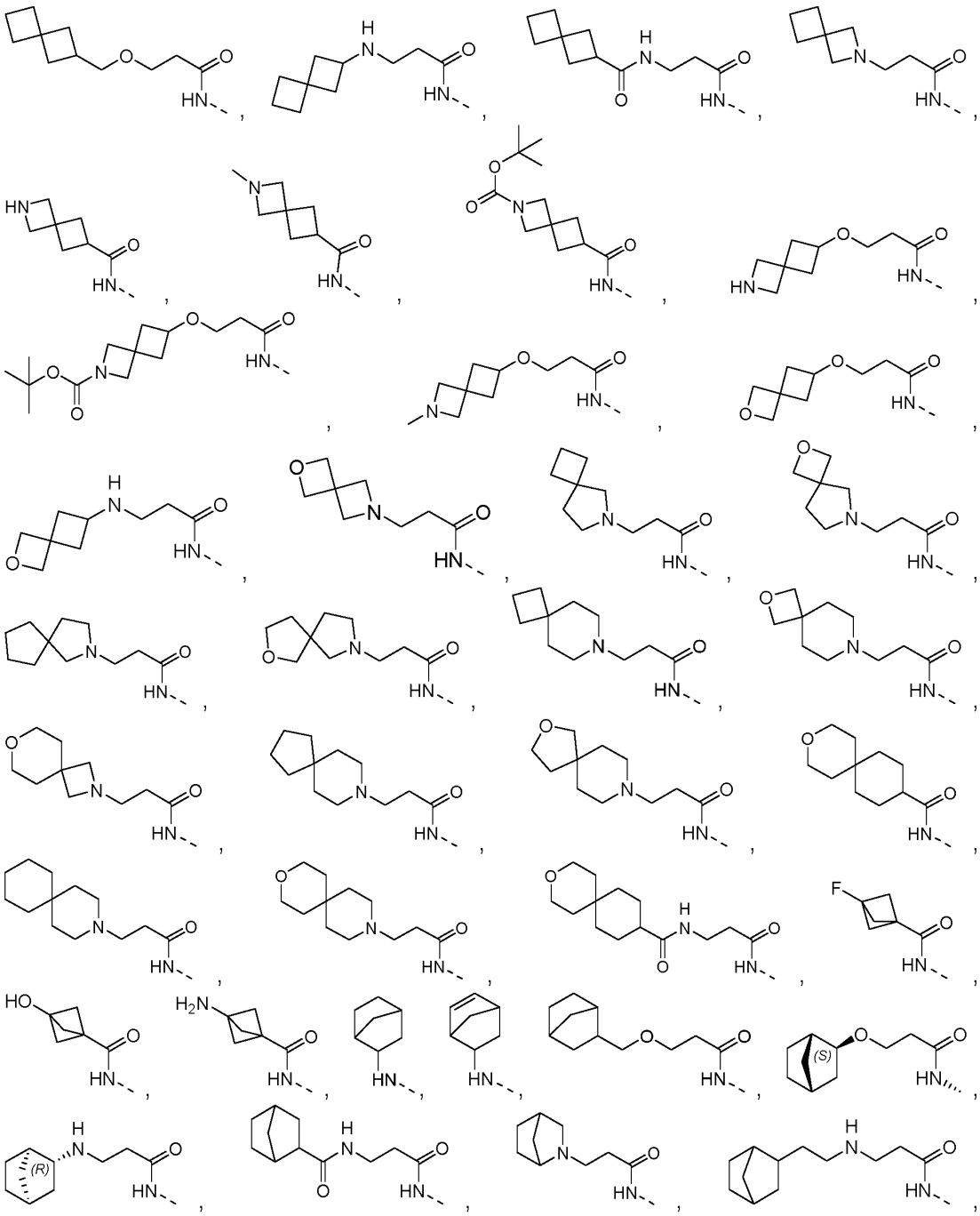


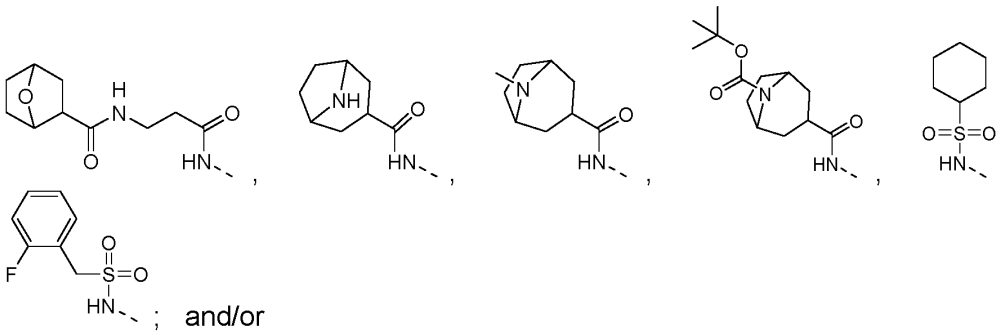




















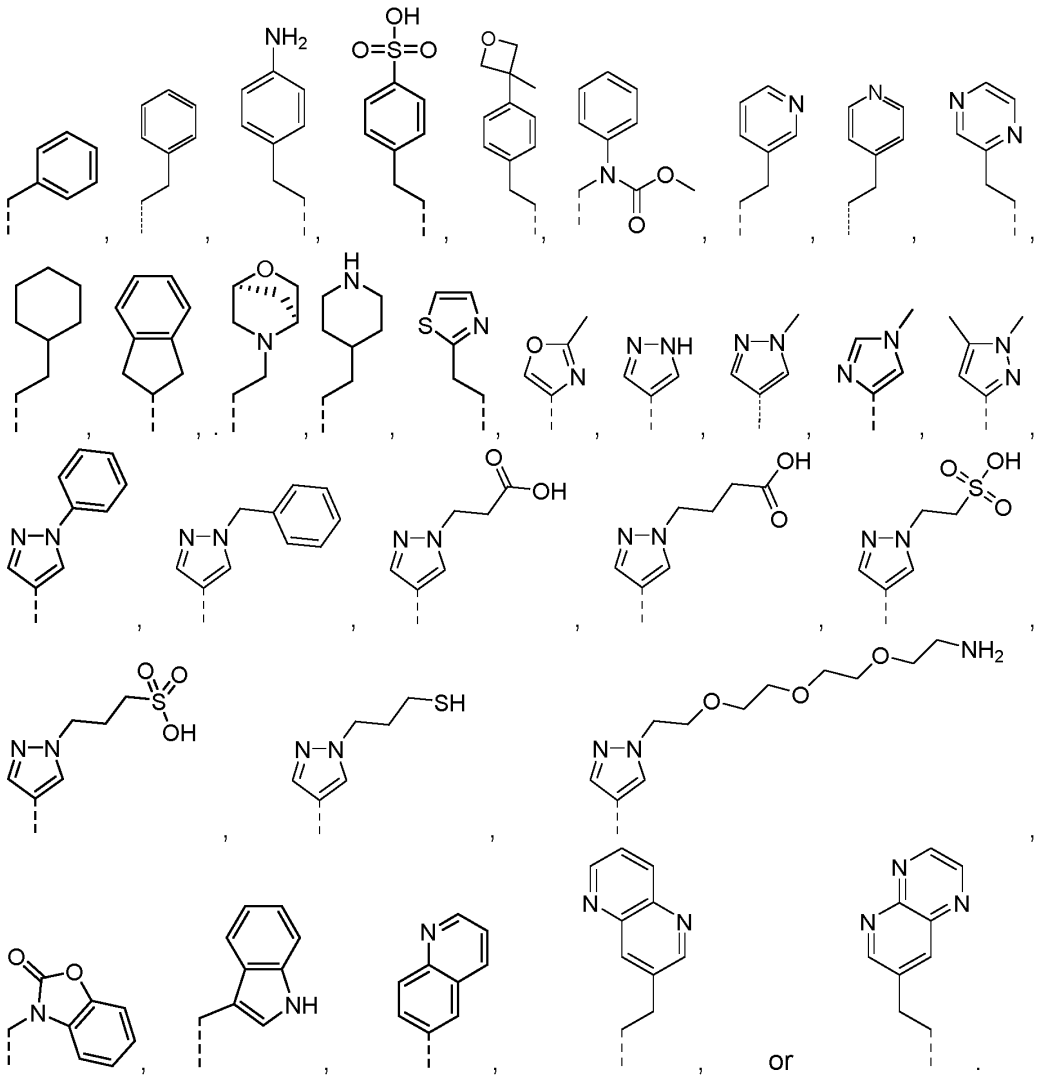







or ; and/or

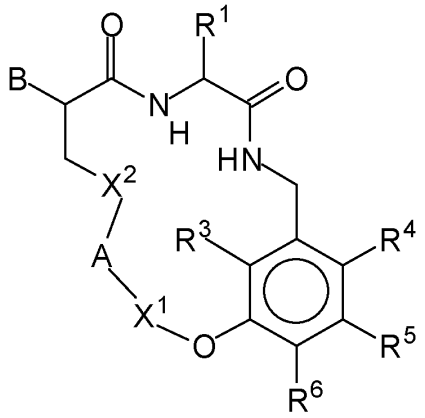
R[1] represents -CH_3, -CH_2CH_2-$CH(CH_3)_2$, -CH_2CH_2-C≡CH,



or .

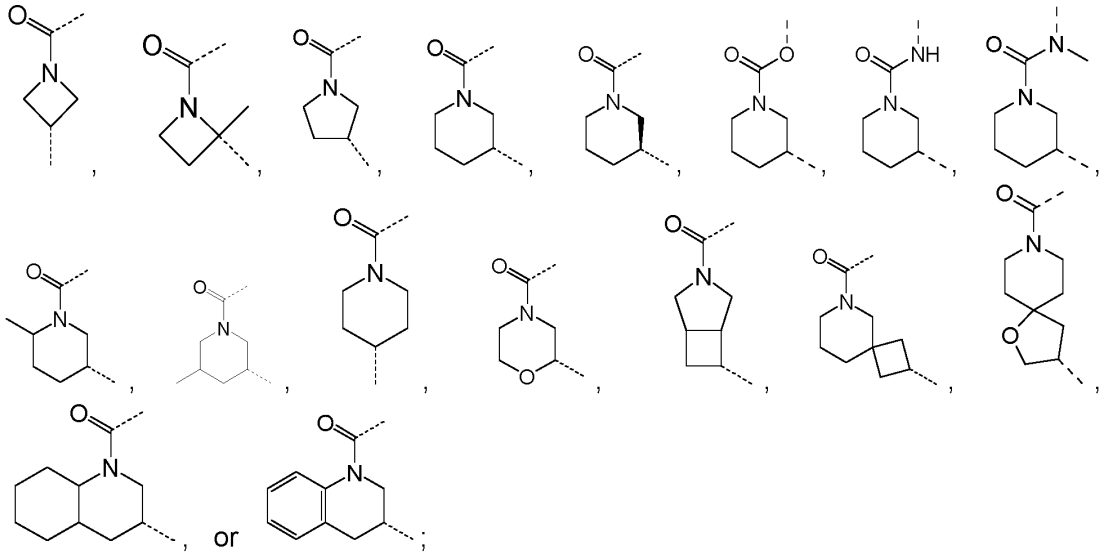
More preferred, the present invention relates to the compound of the formula (I),

(I)



wherein

A represents –CO–NH–, –CO–NCH$_3$–,

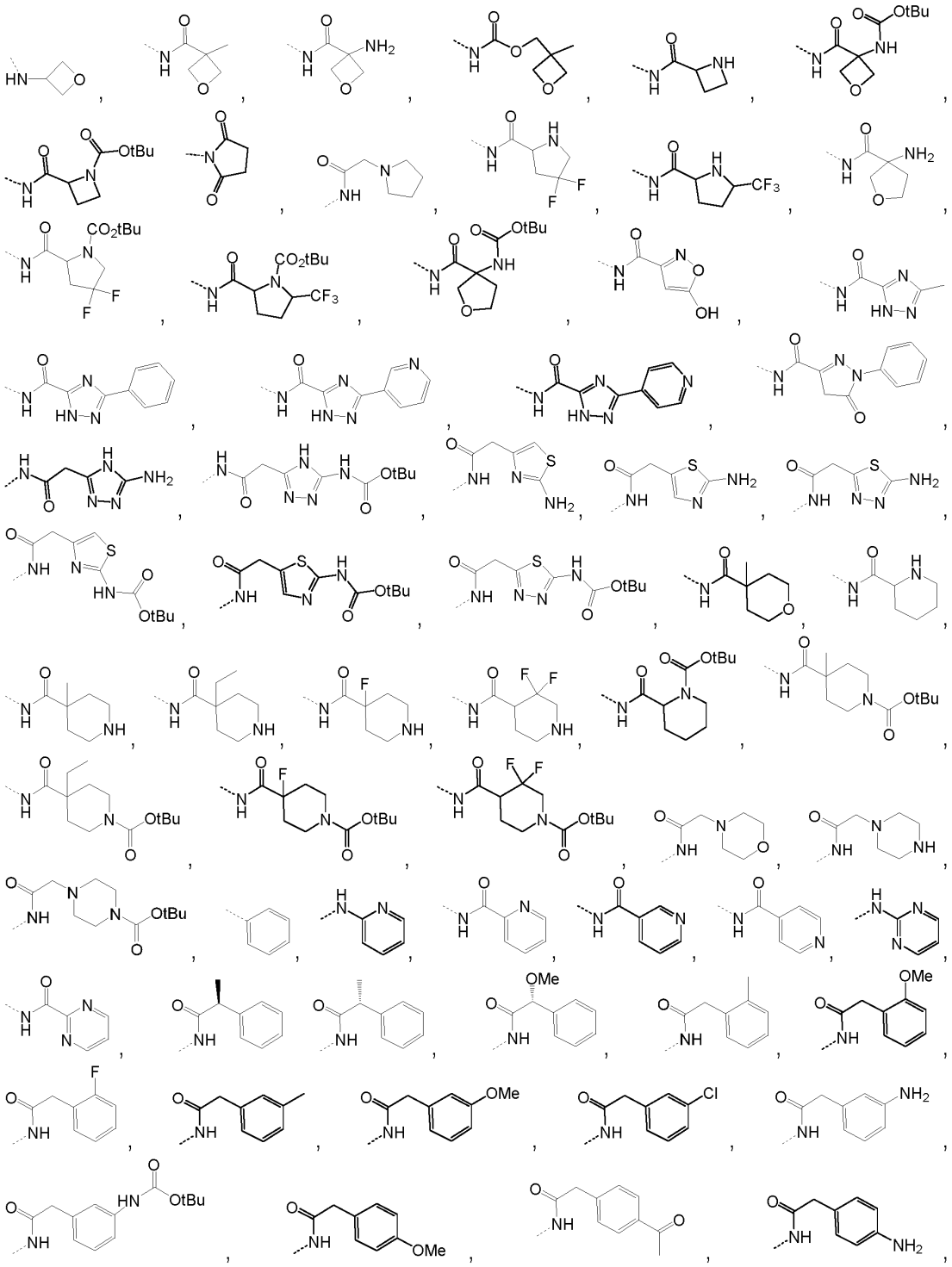


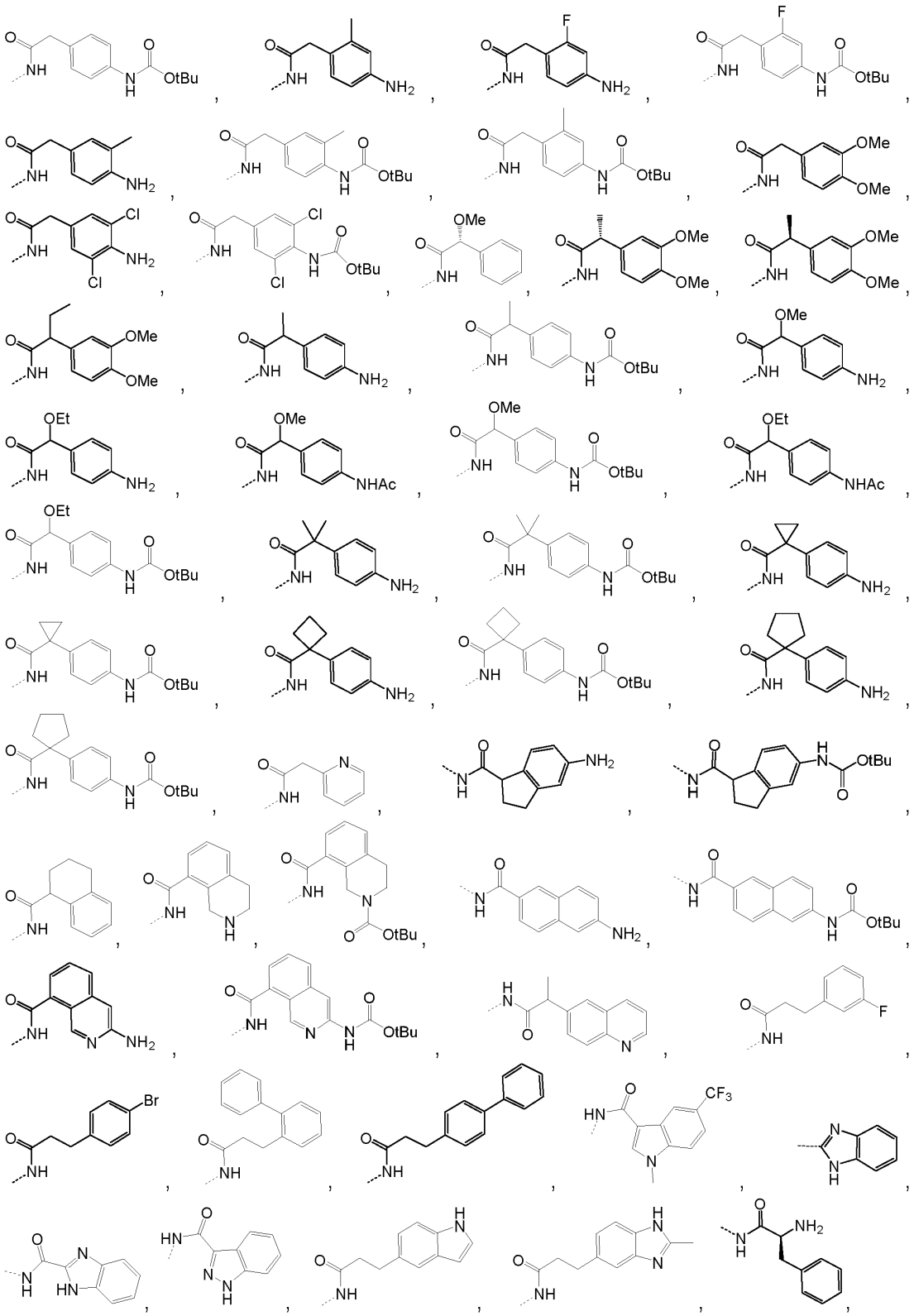
X$_2$ represents a bond, –CH$_2$–, –CH$_2$CH$_2$–, or –CH$_2$CH$_2$CH$_2$–;

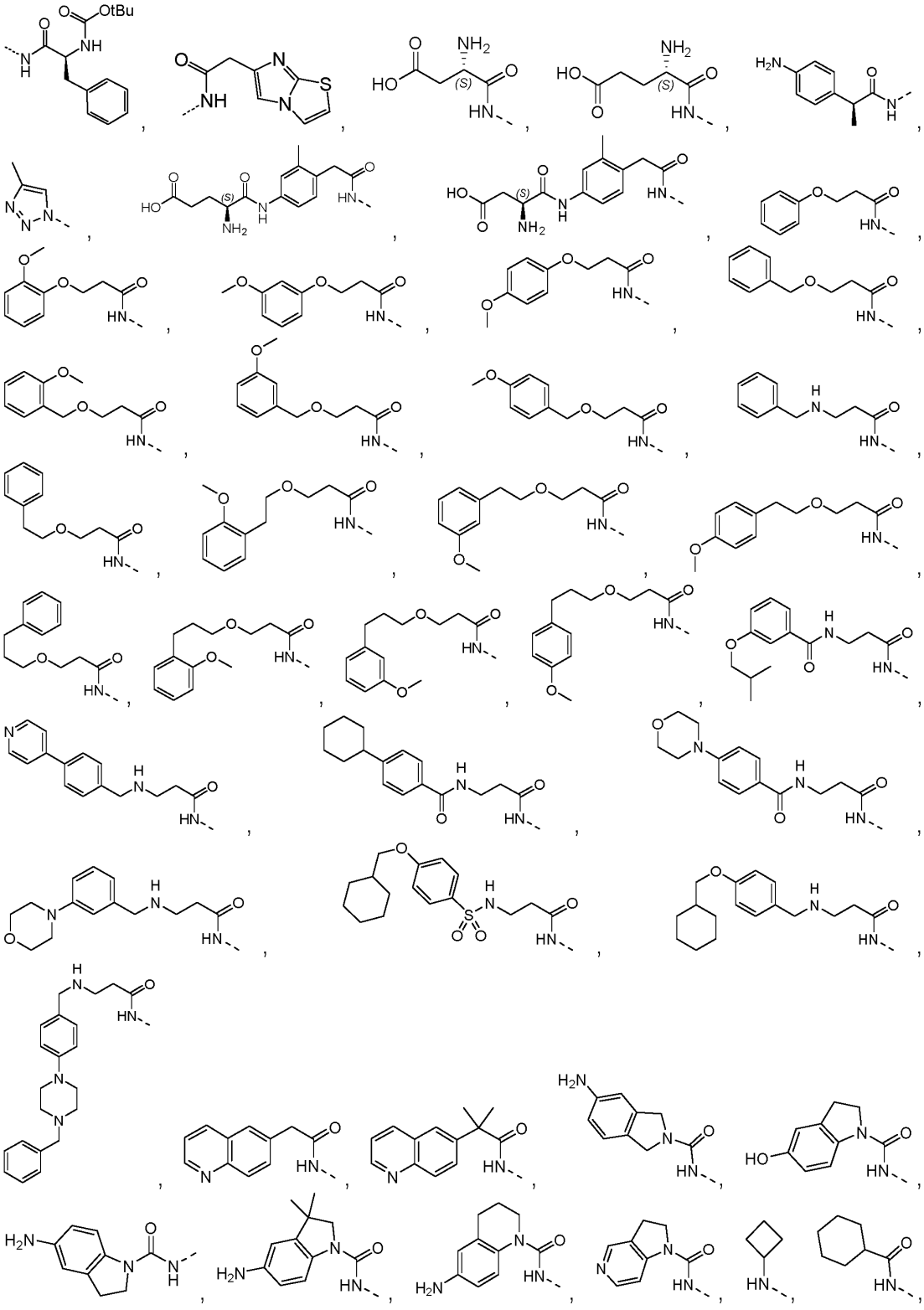
X$_1$ represents a bond, –CH$_2$–, –CH$_2$CH$_2$–, –CH$_2$CH$_2$CH$_2$–, or –CH$_2$CH$_2$CH$_2$CH$_2$–;

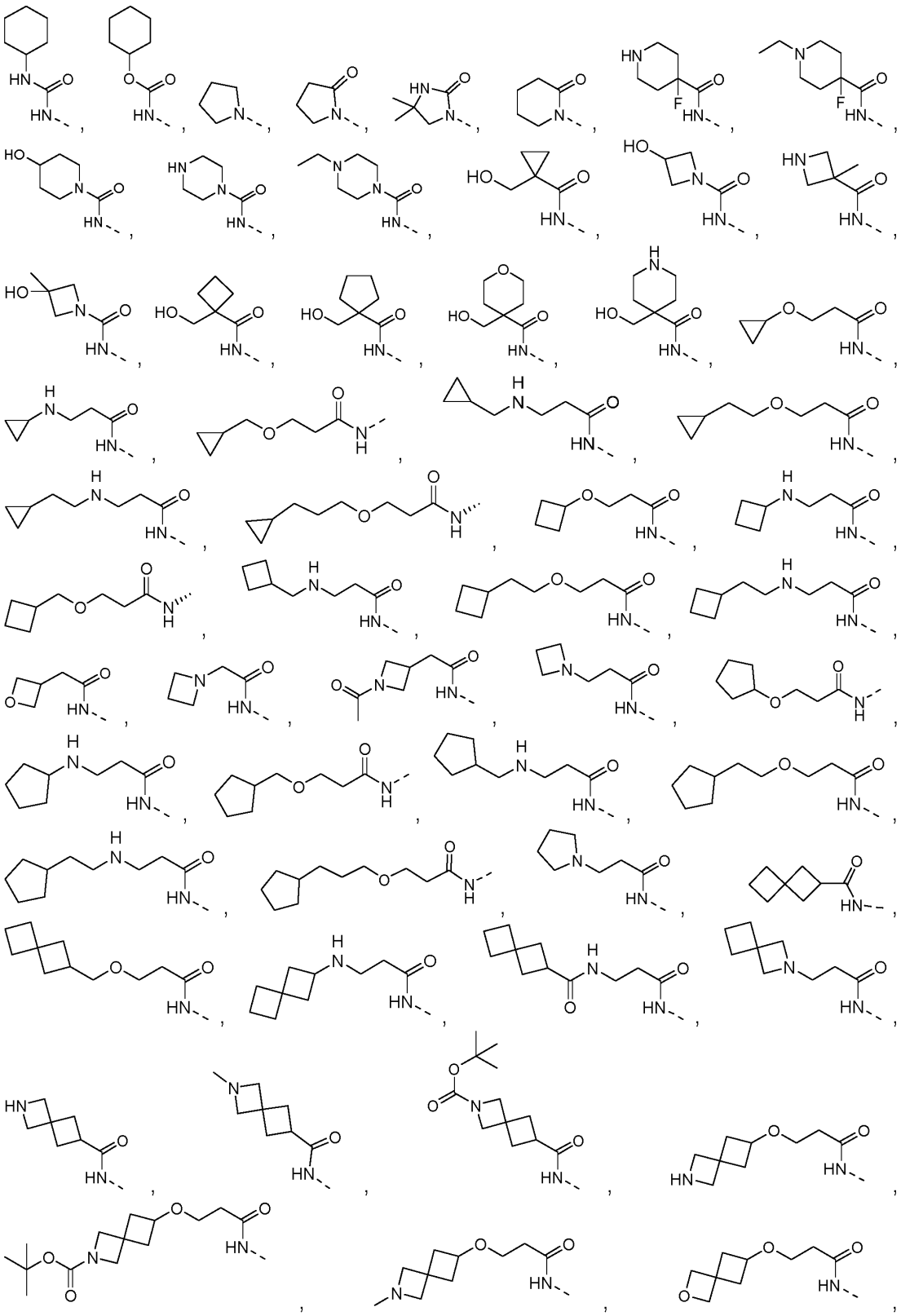
B represents –H, –NH$_2$, –NHCOCH$_3$, –NHCOC(CH$_3$)$_3$, –NHCOC(CN)(CH$_3$)$_2$, –NHCOCH=CH$_2$, –NHCOCH$_2$C(CH$_3$)$_3$, –NHCOPh, –NHCOCH$_2$Ph, –NHCOCH$_2$–NH(CH$_3$), –NHCOCH$_2$–N(CH$_3$)CO$_2$tBu, –NHCOC(CH$_3$)$_2$CH$_2$OH, –NHCOC(CH$_3$)$_2$CH$_2$SH, –NHCOC(CH$_3$)$_2$CH$_2$NH$_2$, –NHCOC(CH$_3$)$_2$CH$_2$F, –NHCOC(CH$_3$)$_2$CF$_3$, –NHCOCF$_2$CH$_2$OH, –NHCOCF$_2$CH$_2$NH$_2$, –NHCOC(CH$_2$CH$_3$)$_2$CH$_2$OH, –NHCO$_2$CH$_2$CH$_3$, –NHCOC(CH$_3$)(CH$_2$OH)$_2$, –NHCOCH$_2$OCH$_2$CH$_2$–NH(CH$_3$), –NHCOCH$_2$OCH$_2$CH$_2$–N(CH$_3$)CO$_2$tBu, –NHCO(CH$_2$CH$_2$O)$_2$CH$_3$, –NHCO$_2$(CH$_2$CH$_2$O)$_3$CH$_3$, –NHCO$_2$(CH$_2$CH$_2$O)$_5$CH$_3$, –NHCO$_2$(CH$_2$CH$_2$O)$_7$CH$_3$, –NHCO$_2$CH$_2$Ph –NHCONHCH$_2$CH$_3$, –NHSO$_2$CH$_3$,

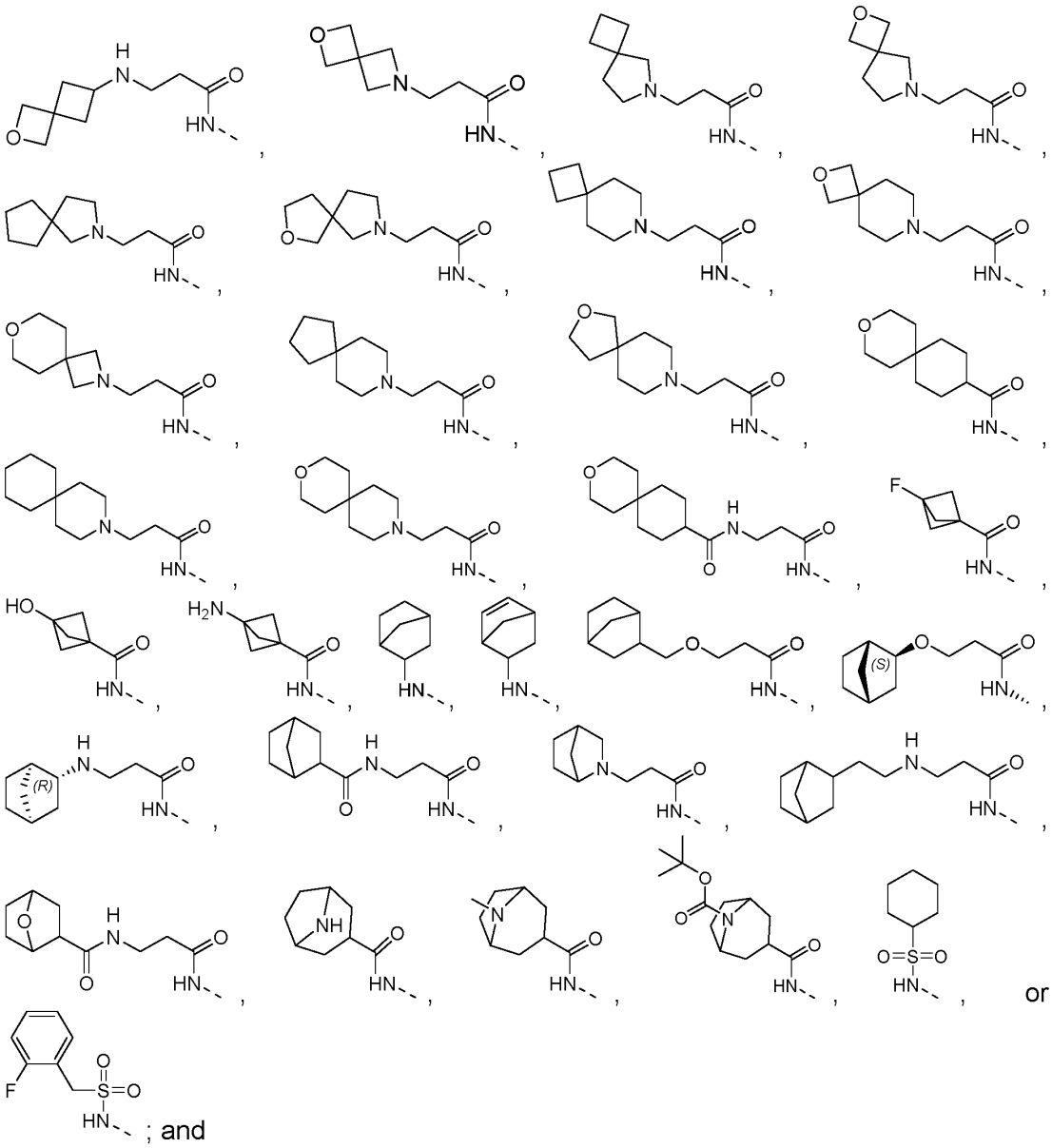
$-NHSO_2CH=CH_2$, $-NHSO_2CH_2Ph$, $-NHSO_2CH_2CH_2Ph$, $-NHSO_2CH_2CH_2CH_2Ph$,
$-NHSO_2CH_2CF_3$, $-NHCH_2CF_3$, $-NHCH_2(CH_3)_2NH_2$, $-NHCH_2(CH_3)_2CH_2OH$,





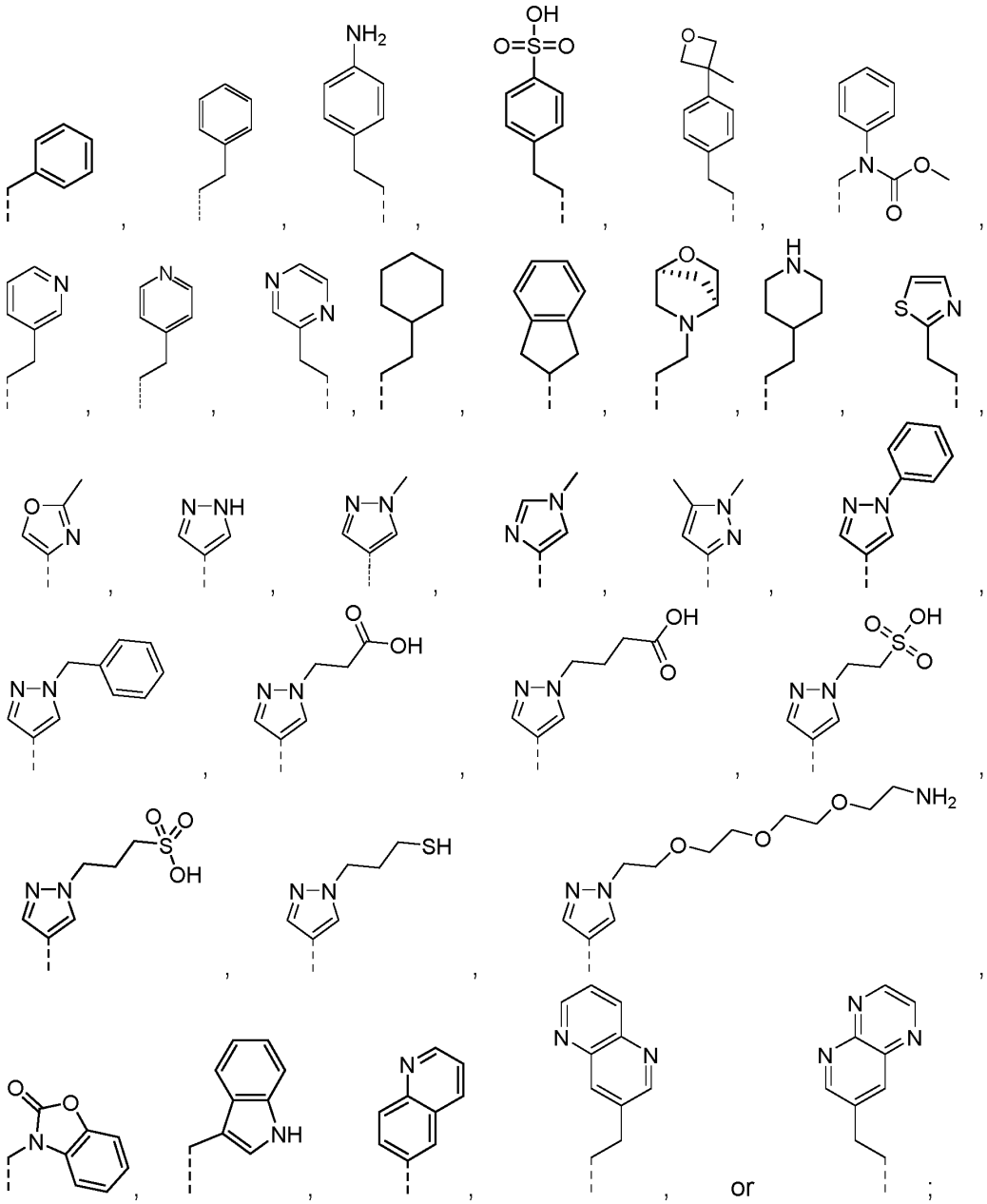






; and

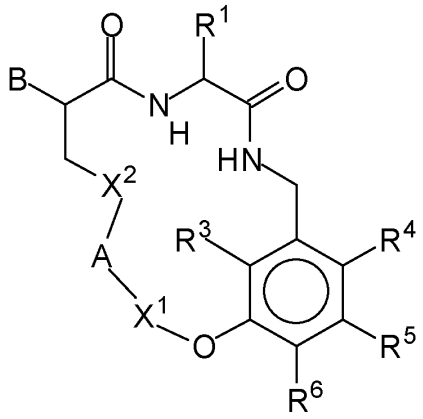
R[1] represents -CH_3, -CH_2CH_2-$CH(CH_3)_2$, -CH_2CH_2-C≡CH,



R^3 – R^6 represent independently of each other –H, –CH_3, –OCH_3, –F, or –Cl;

or **R^5** and **R^6** may form together  .

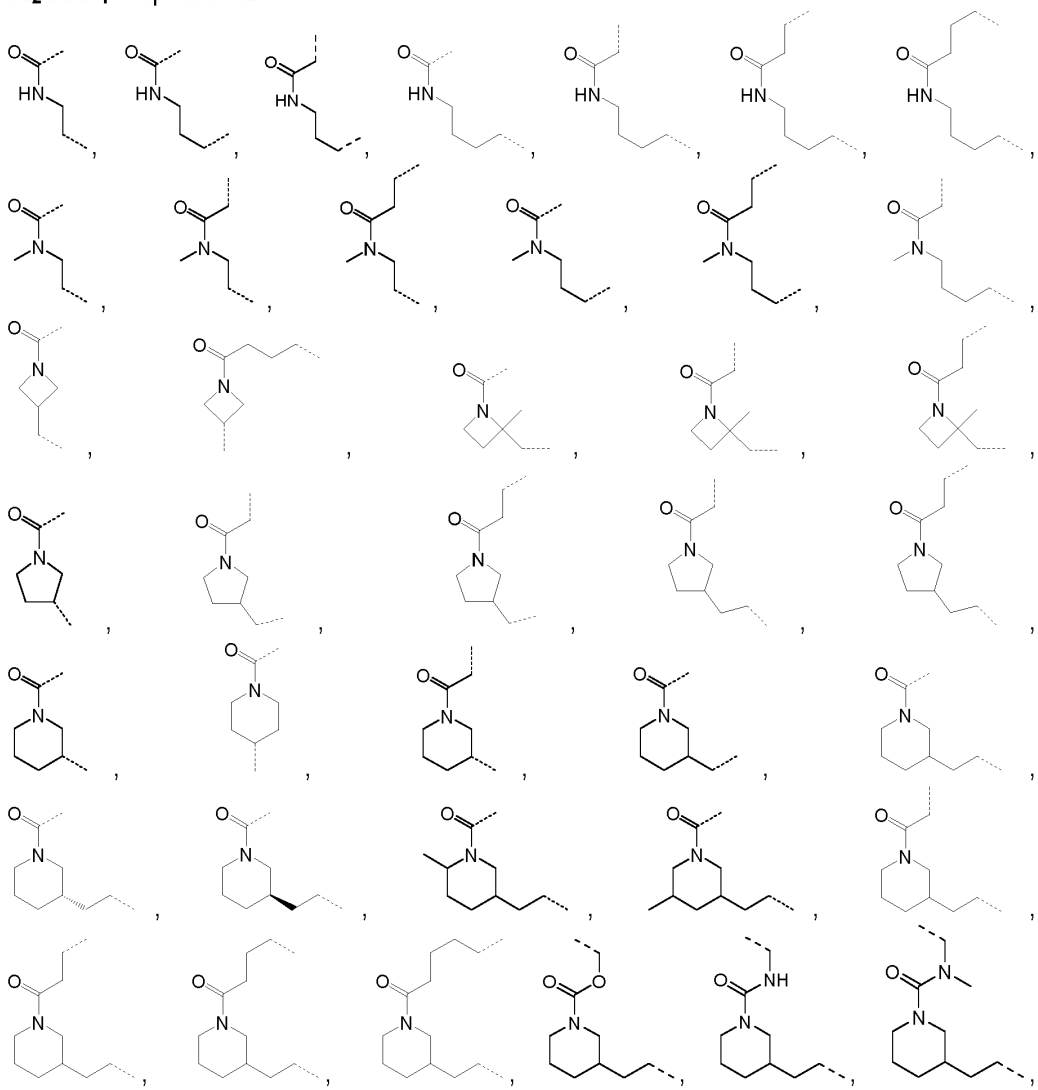
More preferred is the compound of the formula (I)

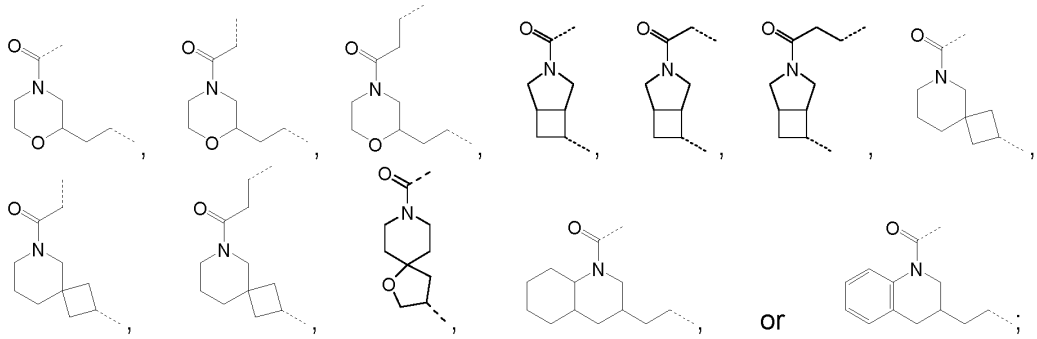


(I)

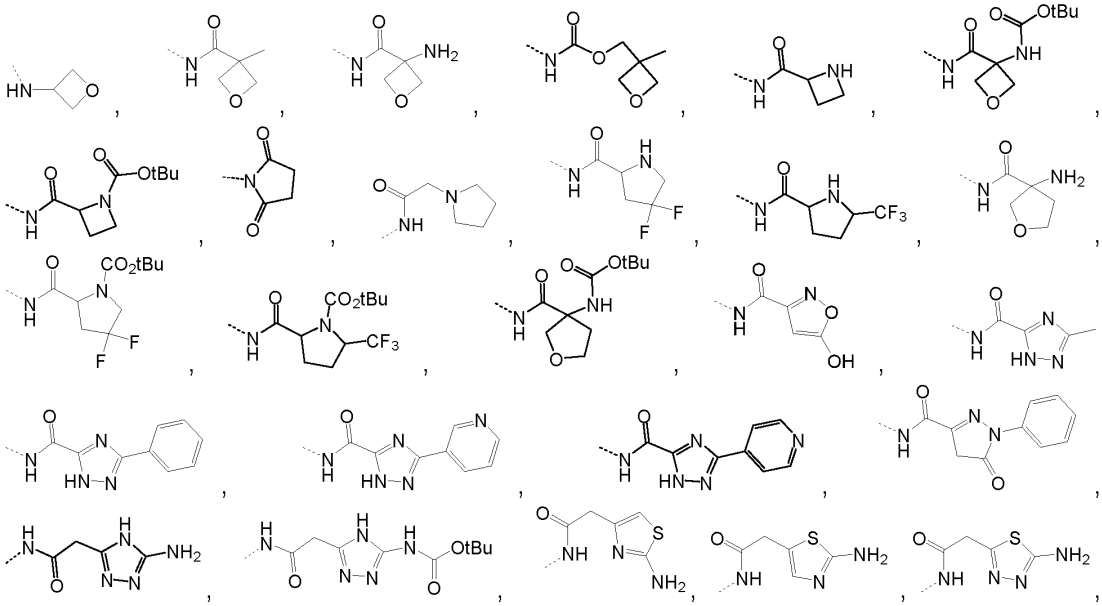
wherein

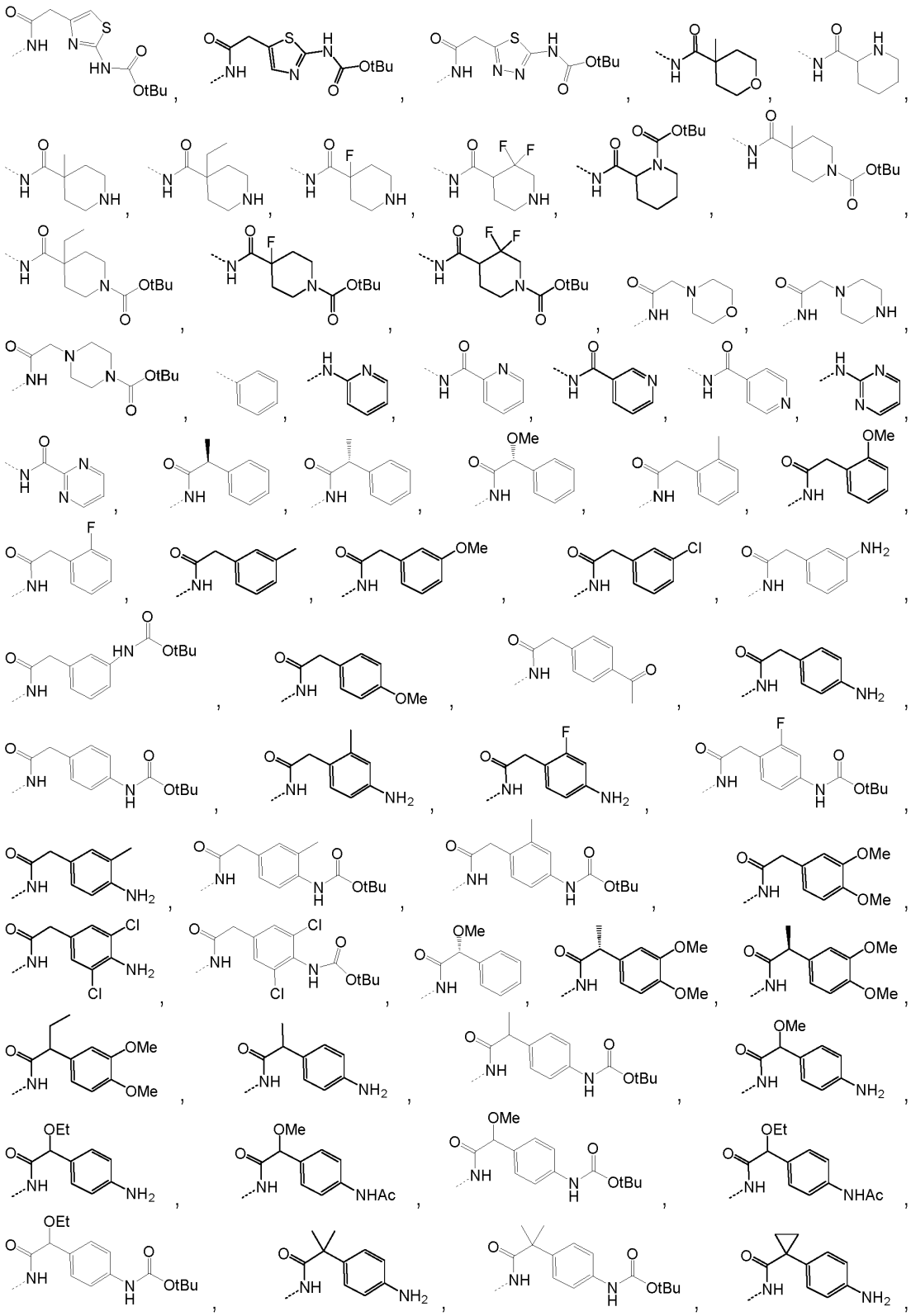
-X_2-A-X_1- represents

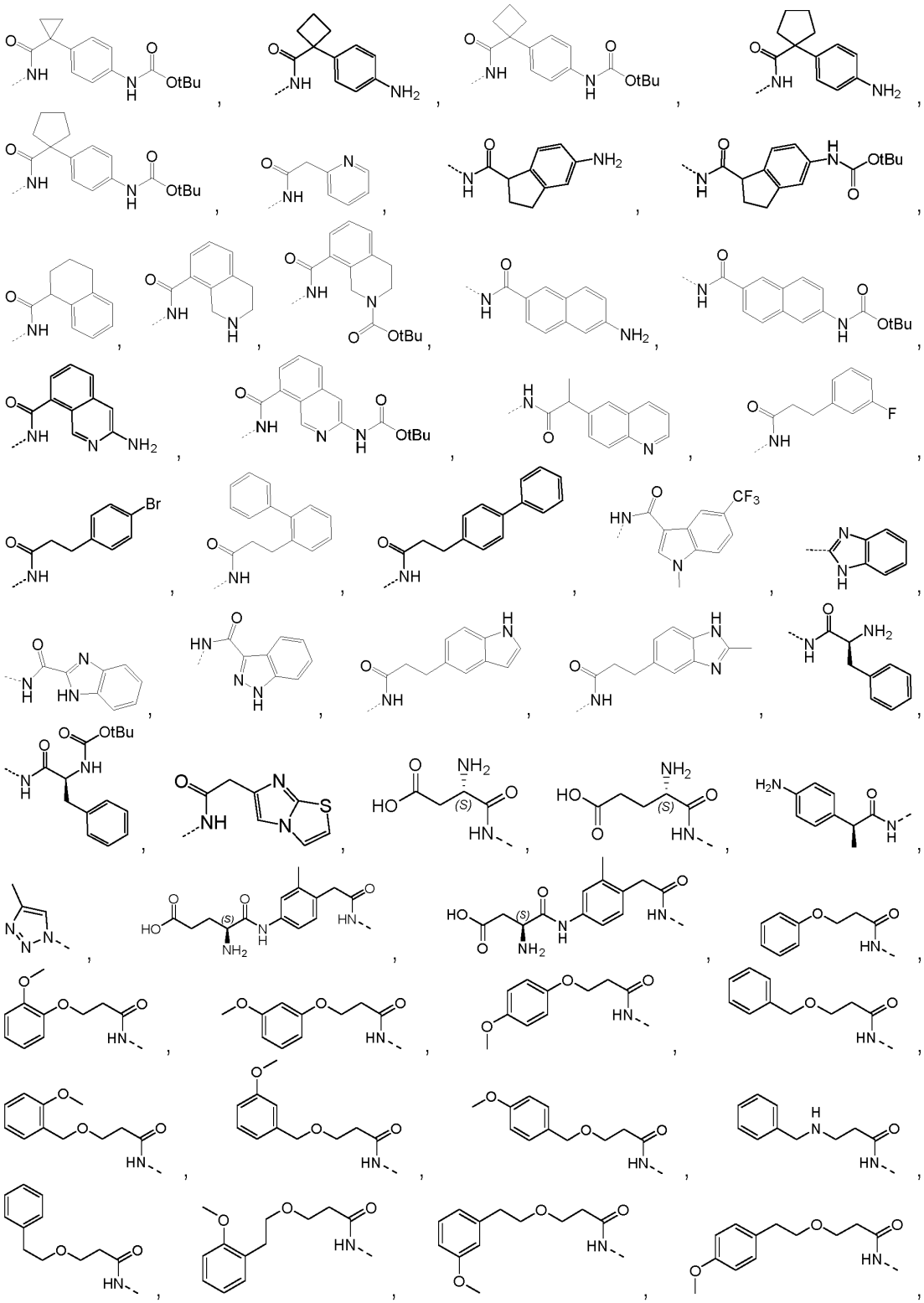


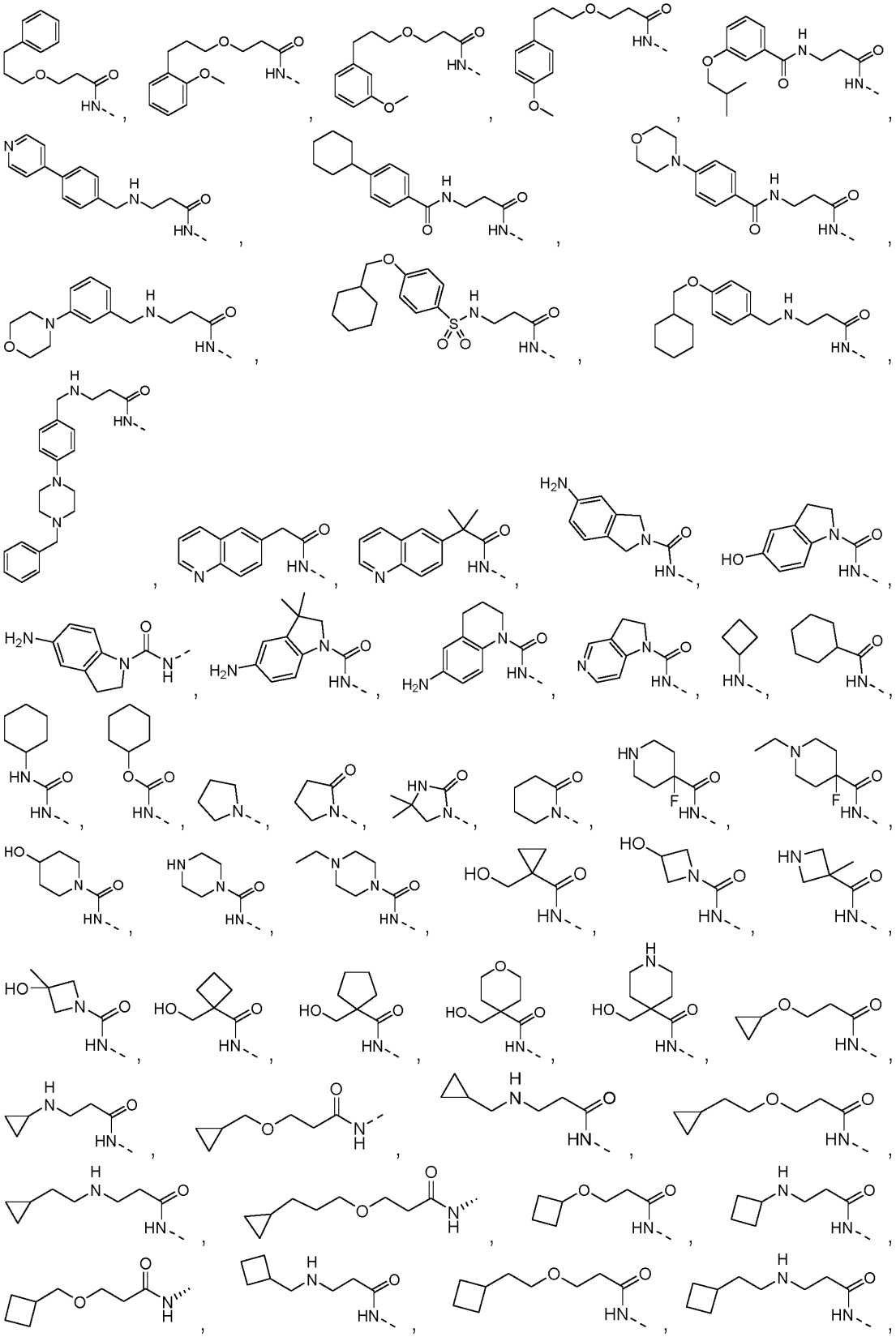


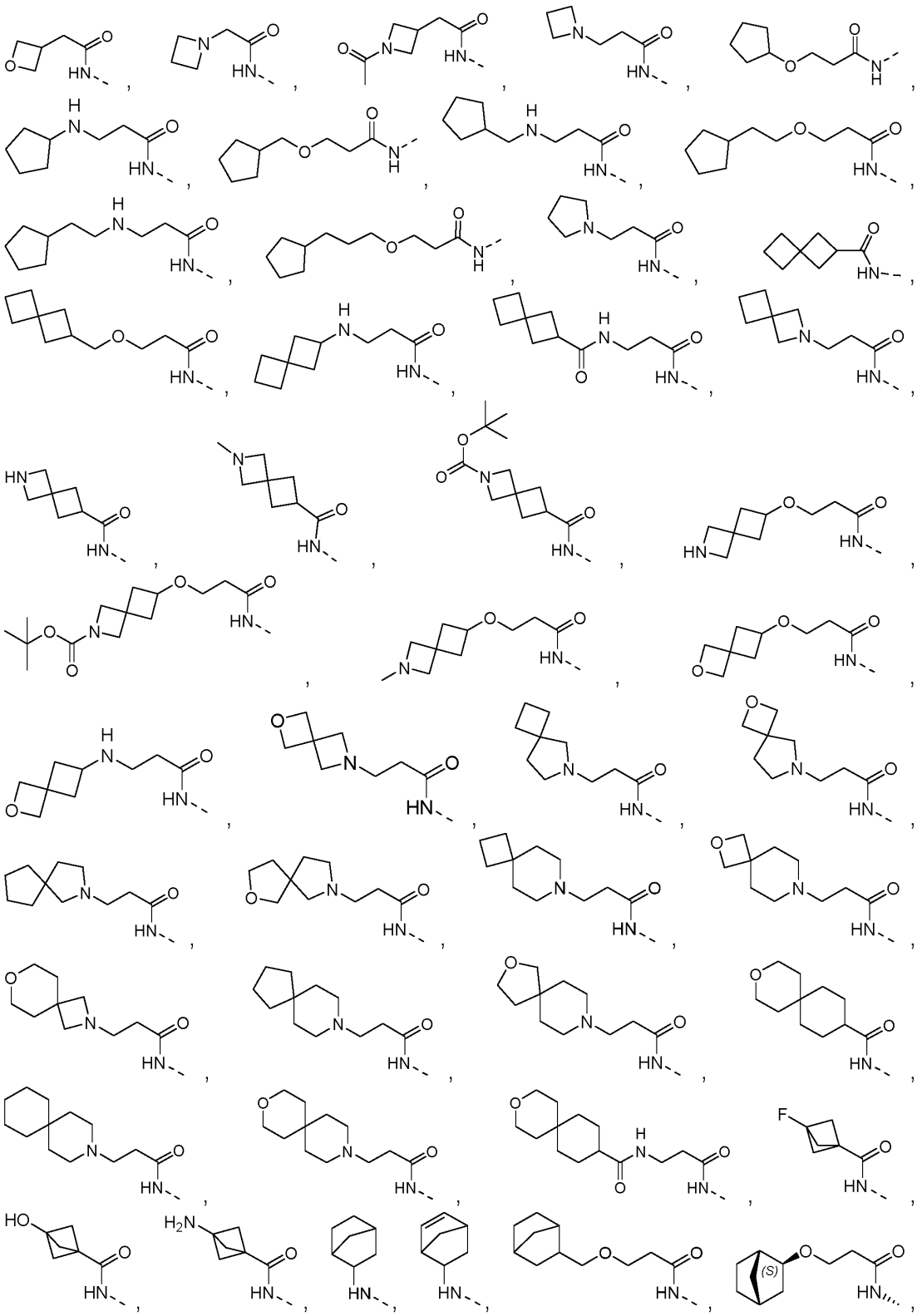
B represents –H, –NH_2, –$NHCOCH_3$, –$NHCOC(CH_3)_3$, –$NHCOC(CN)(CH_3)_2$, –$NHCOCH=CH_2$, –$NHCOCH_2C(CH_3)_3$, –NHCOPh, –$NHCOCH_2Ph$, –$NHCOCH_2$–$NH(CH_3)$, –$NHCOCH_2$–$N(CH_3)CO_2tBu$, –$NHCOC(CH_3)_2CH_2OH$, –$NHCOC(CH_3)_2CH_2SH$, –$NHCOC(CH_3)_2CH_2NH_2$, –$NHCOC(CH_3)_2CH_2F$, –$NHCOC(CH_3)_2CF_3$, –$NHCOCF_2CH_2OH$, –$NHCOCF_2CH_2NH_2$, –$NHCOC(CH_2CH_3)_2CH_2OH$, –$NHCOC(CH_3)(CH_2OH)_2$, –$NHCOCH_2OCH_2CH_2$–$NH(CH_3)$, –$NHCOCH_2OCH_2CH_2$–$N(CH_3)CO_2tBu$, –$NHCO(CH_2CH_2O)_2CH_3$, –$NHCO_2CH_2CH_3$, –$NHCO_2(CH_2CH_2O)_3CH_3$, –$NHCO_2(CH_2CH_2O)_5CH_3$, –$NHCO_2(CH_2CH_2O)_7CH_3$, –$NHCO_2CH_2Ph$ –$NHCONHCH_2CH_3$, –$NHSO_2CH_3$, –$NHSO_2CH=CH_2$, –$NHSO_2CH_2Ph$, –$NHSO_2CH_2CH_2Ph$, –$NHSO_2CH_2CH_2CH_2CH_2Ph$, –$NHSO_2CH_2CF_3$, –$NHCH_2CF_3$, –$NHCH_2(CH_3)_2NH_2$, –$NHCH_2(CH_3)_2CH_2OH$,

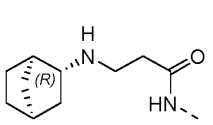
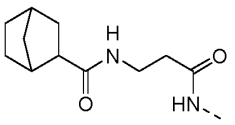
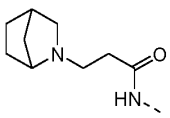
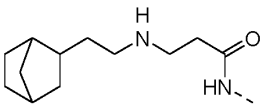
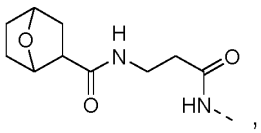
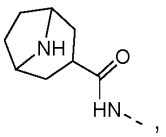
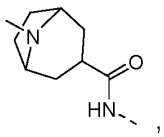
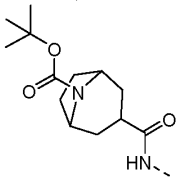
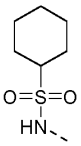






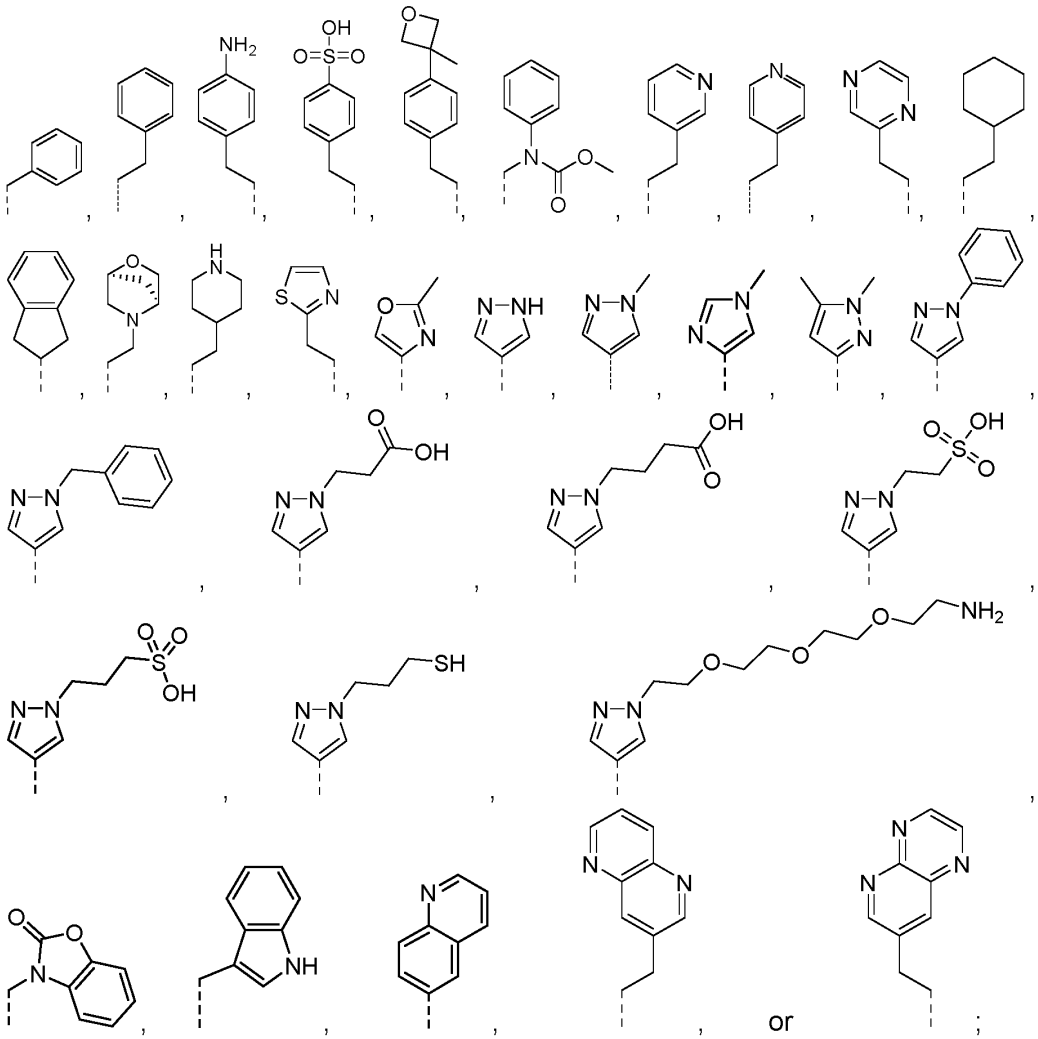





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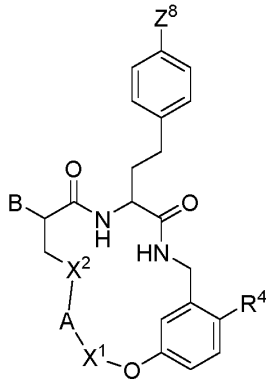
R[1] represents -CH_3, -CH_2CH_2-$CH(CH_3)_2$, -CH_2CH_2-C≡CH,


or ;

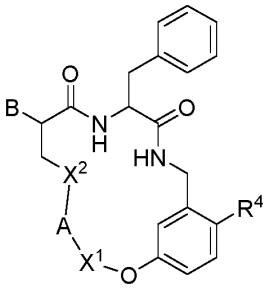
R[3] – **R[6]** represent independently of each other –H, –CH_3, –OCH_3, –F, or –Cl;

or **R** ^{5} and **R**^{6} may form together  .

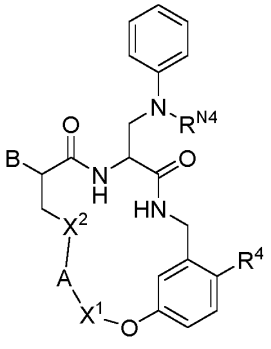
In some embodiments, the present invention relates to the compound having any one of the formulae (**II-1**) – (**II-16**):



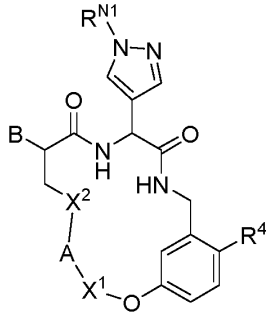
(II-1)



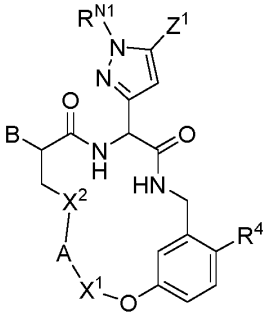
(II-2)



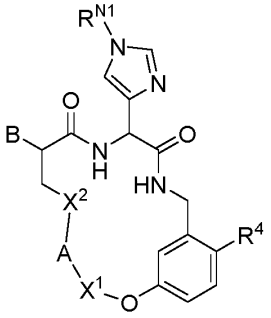
(II-3)



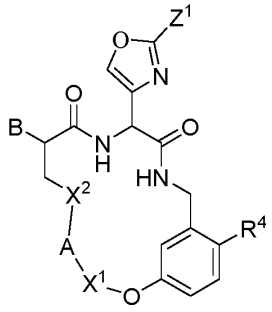
(II-4)



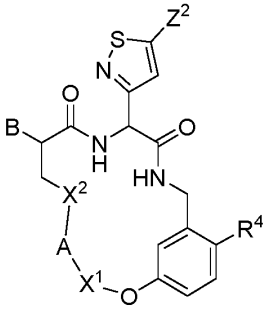
(II-5)



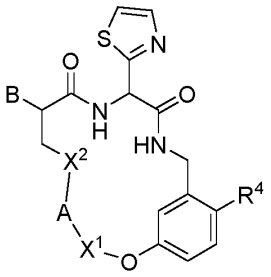
(II-6)



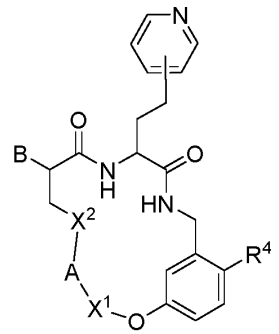
(II-7)



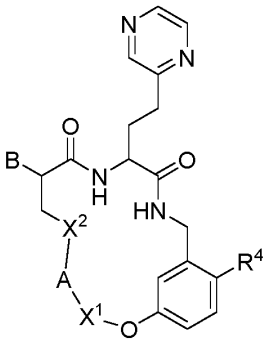
(II-8)



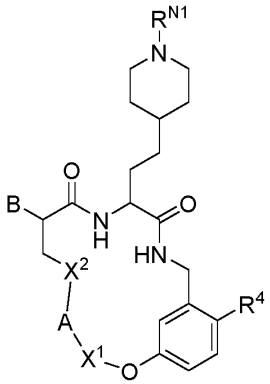
(II-9)



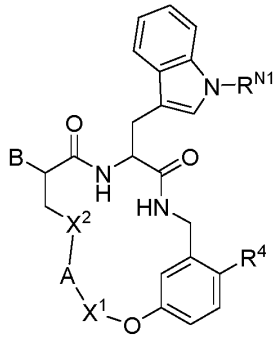
(II-10)



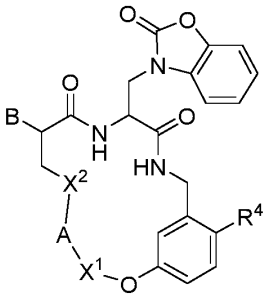
(II-11)



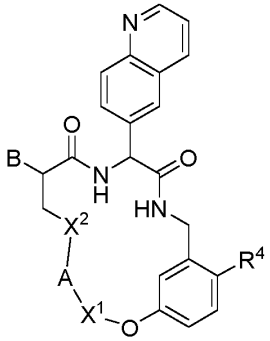
(II-12)



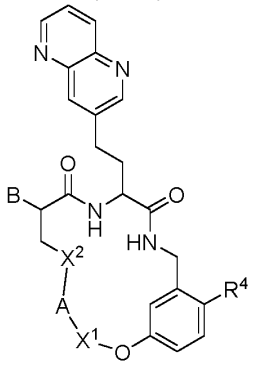
(II-13)



(II-14)



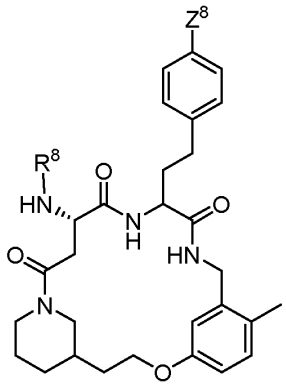
(II-15)



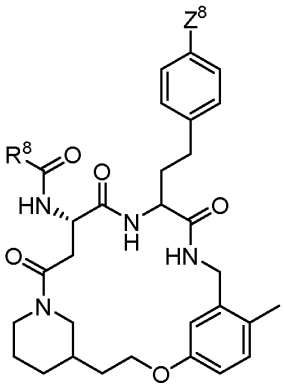
(II-16)

wherein **A**, **B**, R^4, R^{N1}, R^{N4}, X^1, X^2, Z^1, Z^2, and Z^8 have the same meanings as defined above.

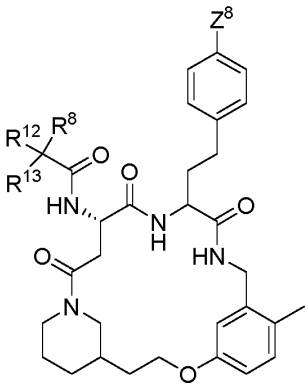
In some embodiments, the present invention relates to the compound having any one of the formulae (**III-1**) – (**III-10**):



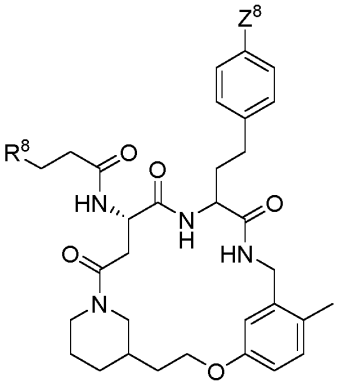
(**III-1**)



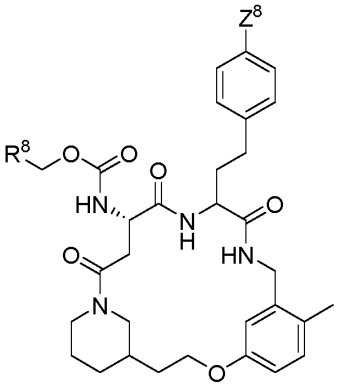
(**III-2**)



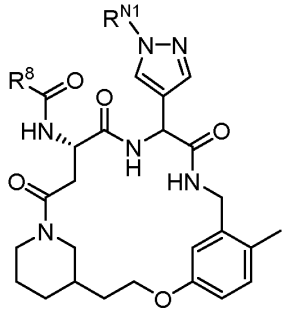
(**III-3**)



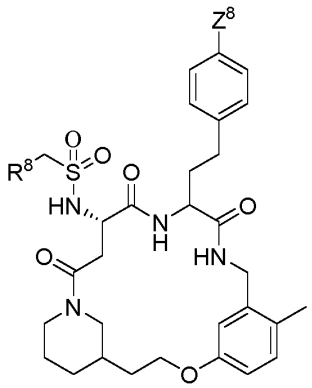
(**III-4**)



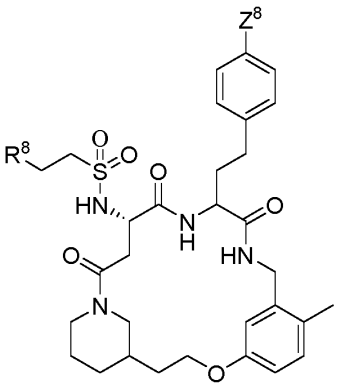
(**III-5**)



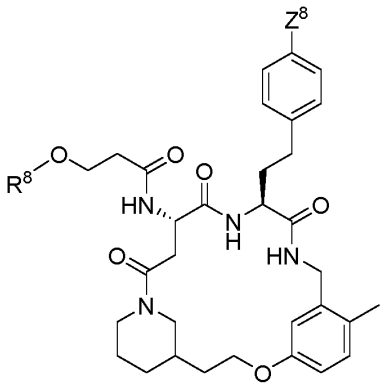
(**III-6**)



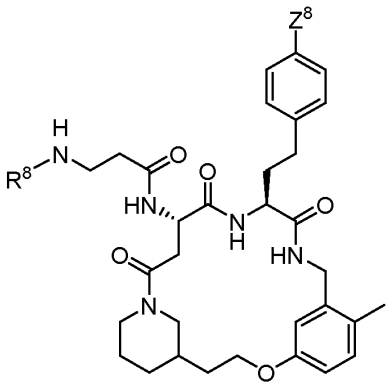
(**III-7**)



(**III-8**)



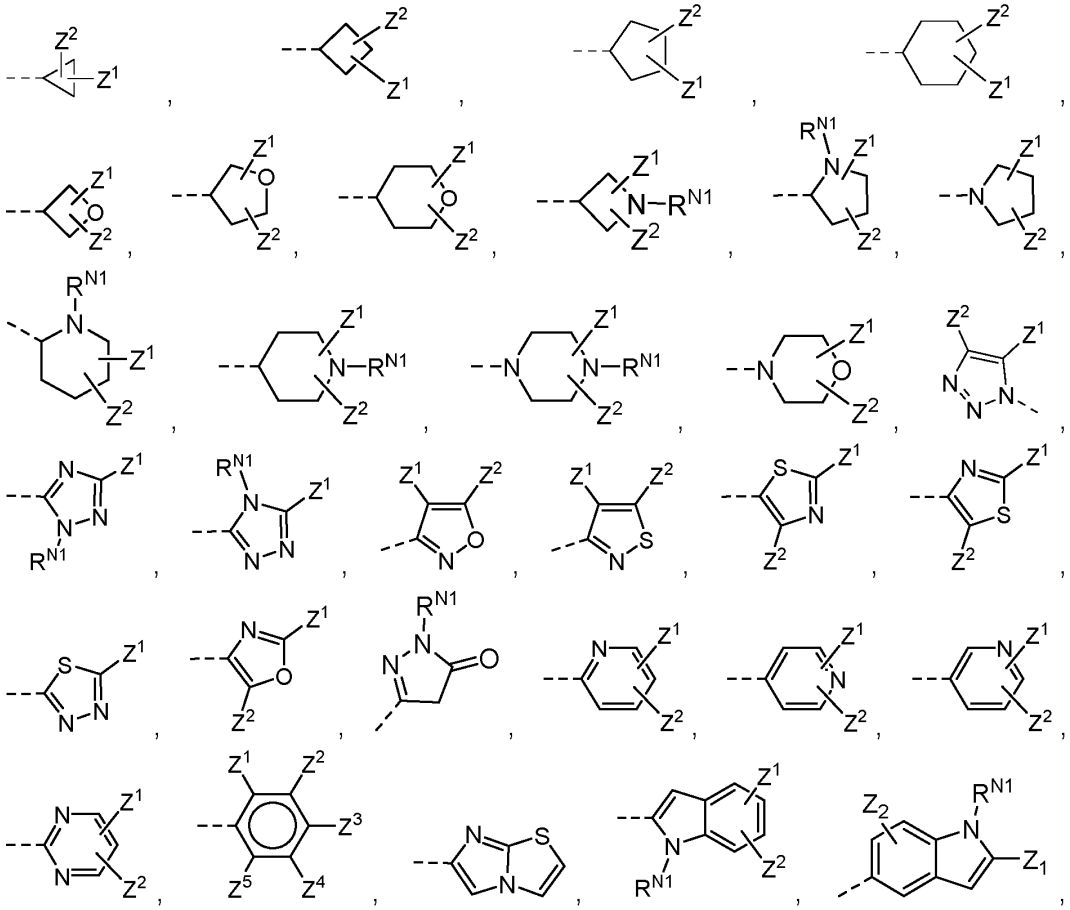
(**III-9**)

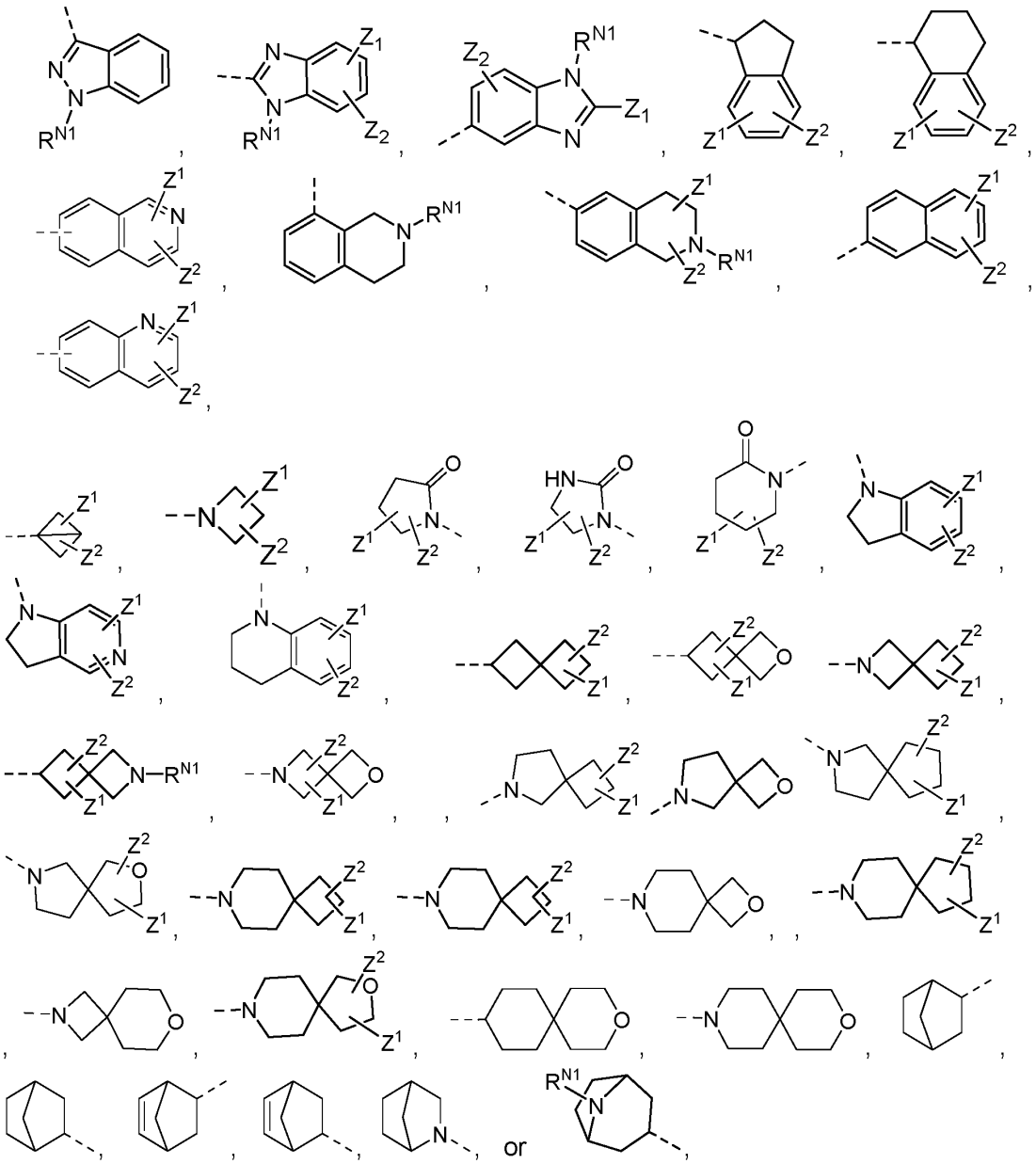


(**III-10**)

wherein R^8, R^{12}, R^{13}, R^{N1}, and Z^8 have the same meanings as defined above.

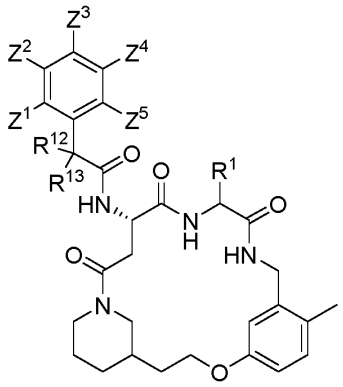
Preferred are the compounds of any one of the formulae (**III-1**) to (**III-10**), wherein R^8 is



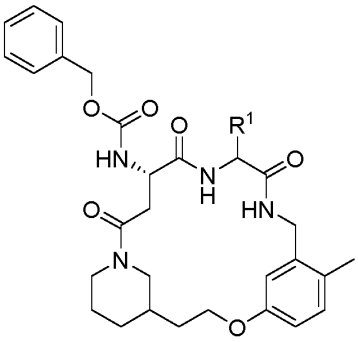


wherein $\mathbf{R^{N1}}$, $\mathbf{Z^1}$, $\mathbf{Z^2}$, $\mathbf{Z^3}$, $\mathbf{Z^4}$, and $\mathbf{Z^5}$, have the same meanings as defined in formula (I).

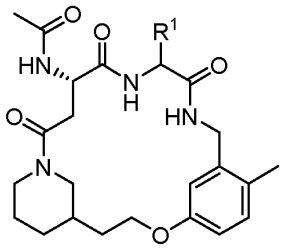
In some embodiments, the present invention relates to the compound having any one of the formulae (**IV-1**) – (**IV-10**):



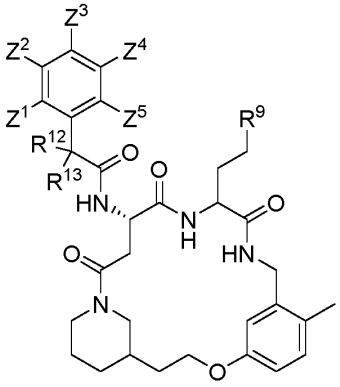
(**IV-1**)



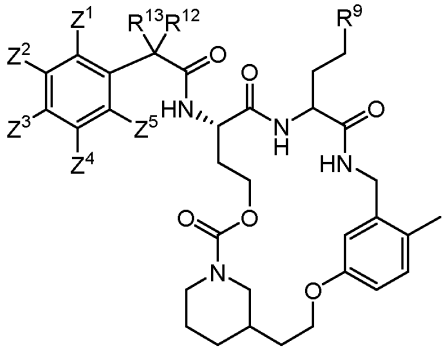
(**IV-2**)



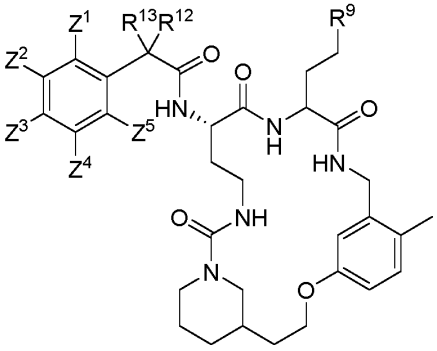
(**IV-3**)



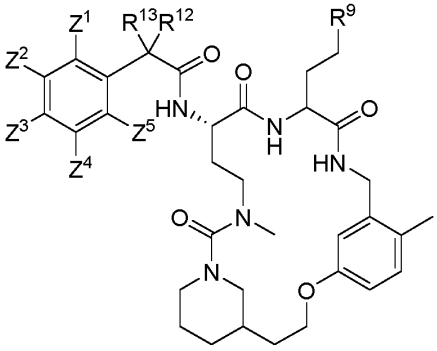
(**IV-4**)



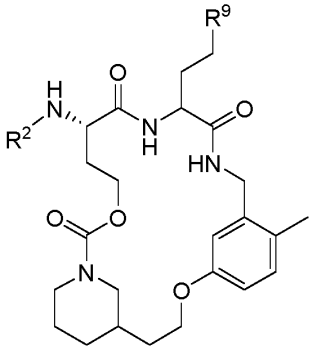
(**IV-5**)



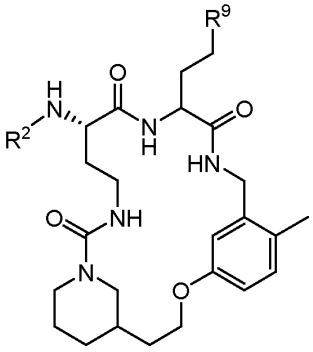
(**IV-6**)



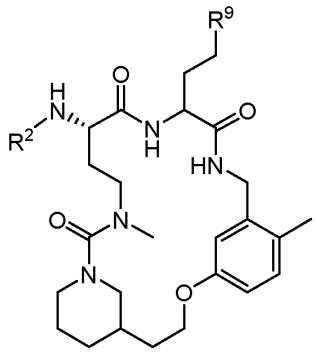
(**IV-7**)



(**IV-8**)



(**IV-9**)



(**IV-10**)

wherein R^1, R^2, R^9, R^{12}, R^{13}, Z^1, Z^2, Z^3, Z^4, and Z^5 have the same meanings as defined above.

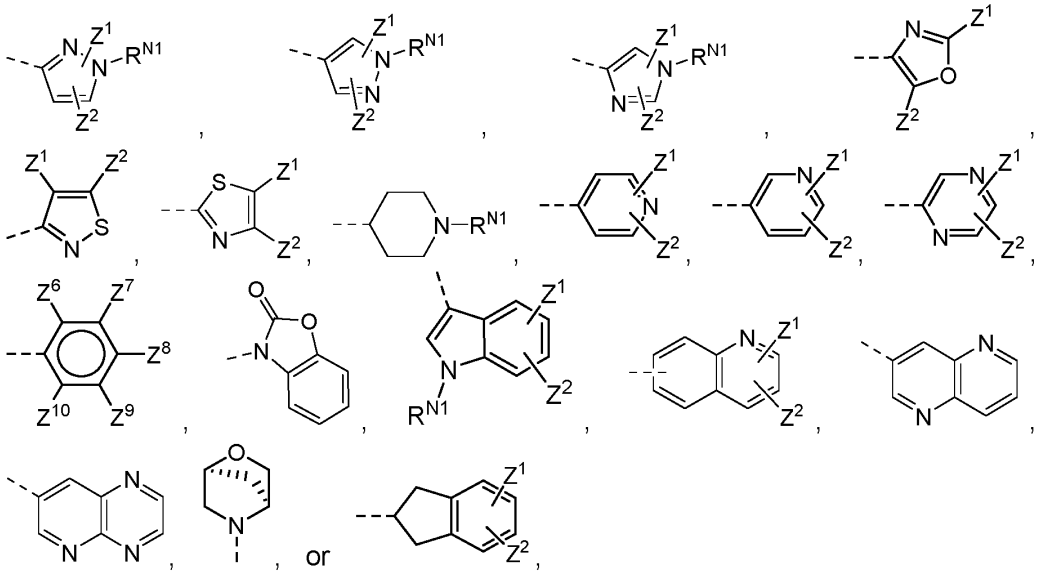
Preferred are the compounds of any one of the formulae (**IV-1**) to (**IV-3**), wherein

$\mathbf{R^1}$ represents $-(CH_2)_p-\mathbf{R^9}$, or $-(CH_2)_p-\mathbf{NR^{N4}}-\mathbf{R^9}$;

p is an integer selected from 0, 1, 2, or 3;

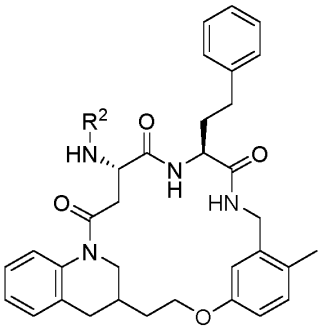
and $\mathbf{R^9}$ and $\mathbf{R^{N4}}$ have the same meaning as defined in the formula (**I**).

More preferred are the compounds of any one of the formulae (**IV-1**) to (**IV-10**), wherein $\mathbf{R^9}$ is

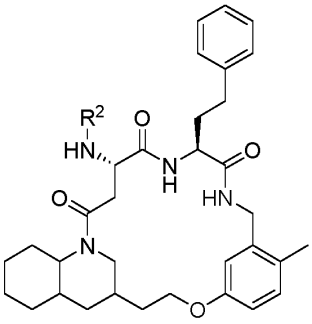


and $\mathbf{Z^1}$, $\mathbf{Z^2}$, $\mathbf{Z^6}$, $\mathbf{Z^7}$, $\mathbf{Z^8}$, $\mathbf{Z^9}$, $\mathbf{Z^{10}}$ and $\mathbf{R^{N1}}$ have the same meaning as defined in the formula (**I**).

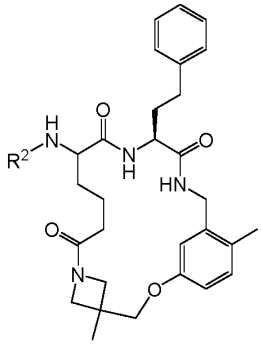
In some embodiments, the present invention relates to the compound having any one of the formulae (**V-1**) – (**V-9**):



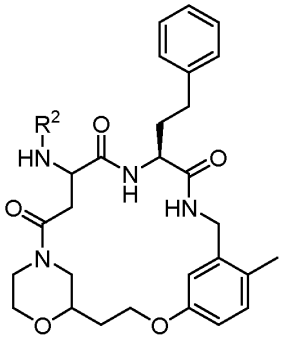
(**V-1**)



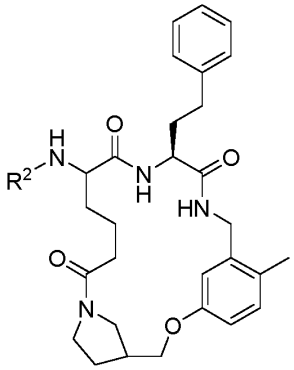
(**V-2**)



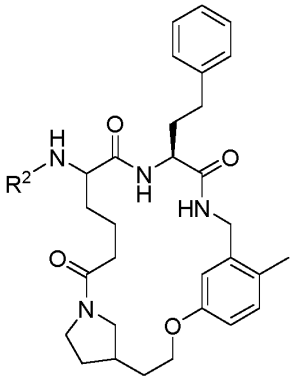
(**V-3**)



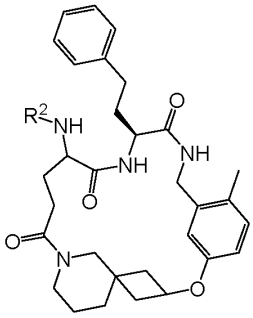
(**V-4**)



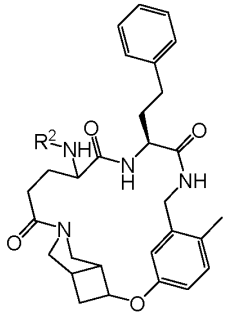
(**V-5**)



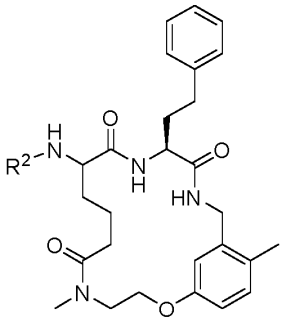
(**V-6**)



(**V-7**)



(**V-8**)



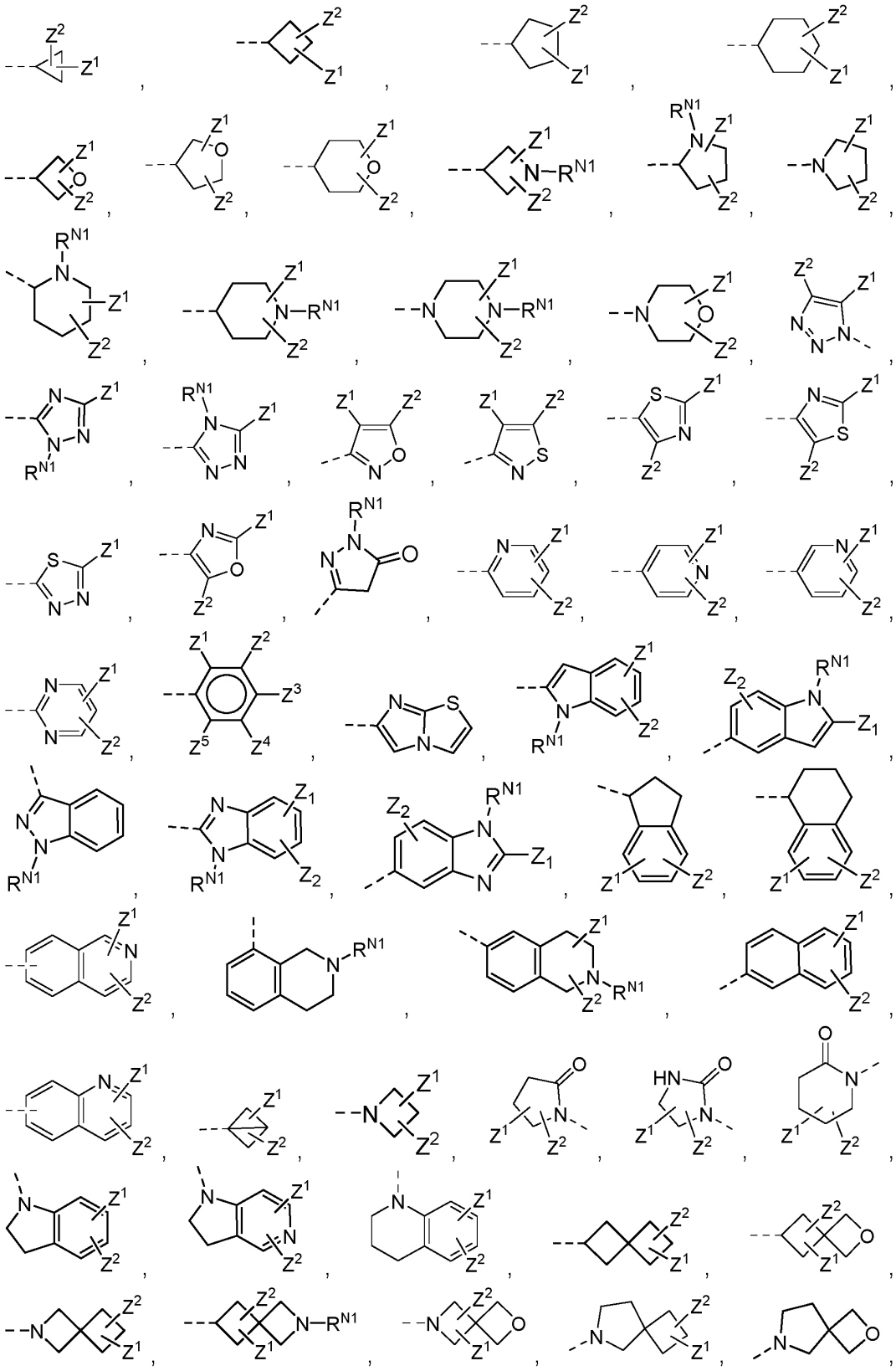
(**V-9**)

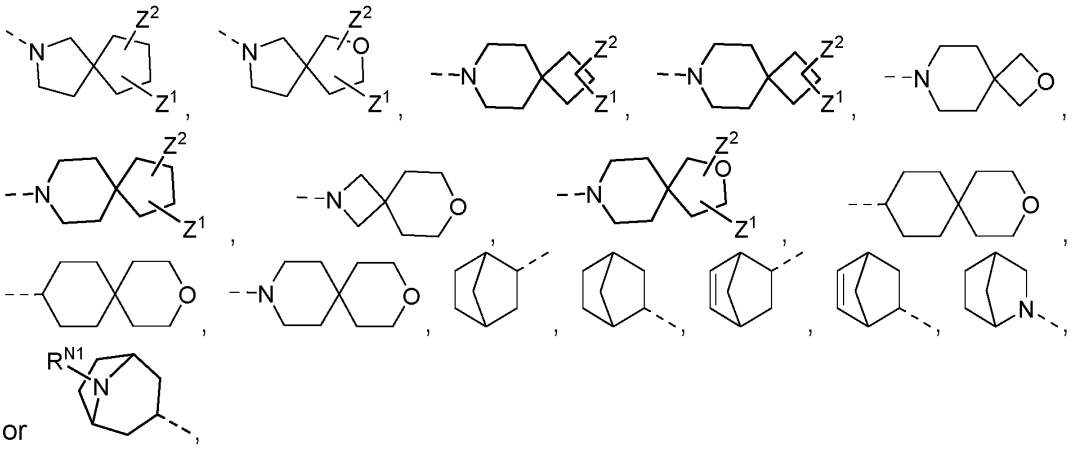
wherein R^2 has the same meaning as defined above.

Preferred are the compounds of any one of the formulae (**V-1**) to (**V-9**), wherein

R^2 represents –H, –**R^8**, –CO–C(**R^{12}**)(**R^{13}**)–**R^8**, –**L^1**–$(CH_2)_t$–NH**R^8**, –**L^1**–$(CH_2)_t$–NH–CO–**R^8**, –**L^1**–$(CH_2)_t$–NH–SO_2–**R^8**, or –CO–C(**R^{12}**)(**R^{13}**)–(CH_2)–**R^8**;

R^8 represents

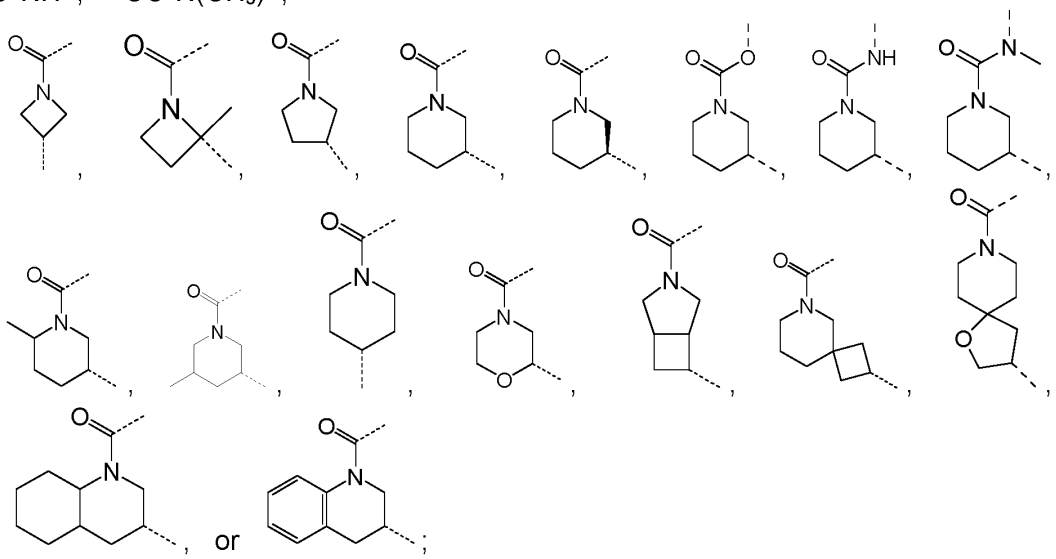




or

wherein R^{12} , R^{13}, R^{N1}, Z^1, Z^2, Z^6, Z^7, Z^8, Z^9, and Z^{10}, have the same meanings as defined as defined above.

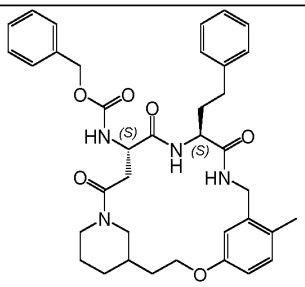
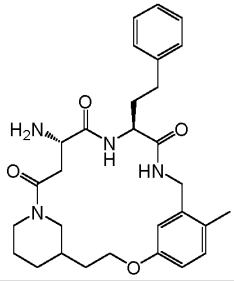
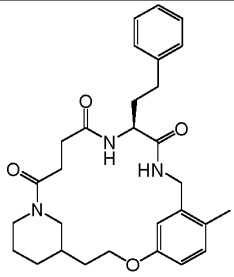
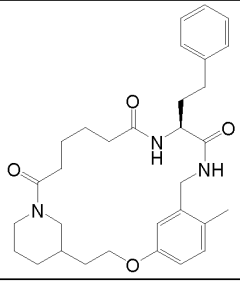
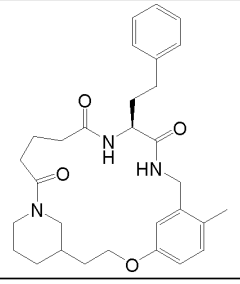
Preferred are the compound of formual (**I**), (**II-1**) – (**II-16**), wherein **A** represents –CO-NH–, –CO-N(CH_3)–,

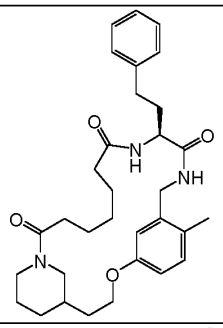
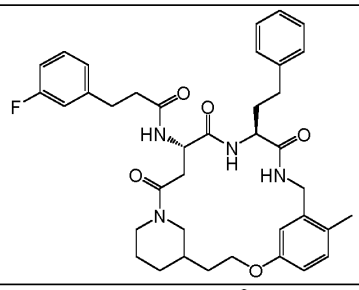
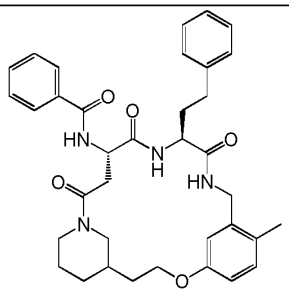
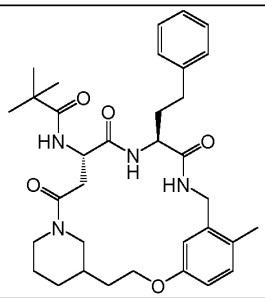
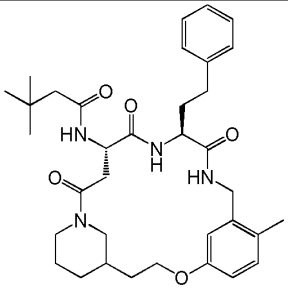


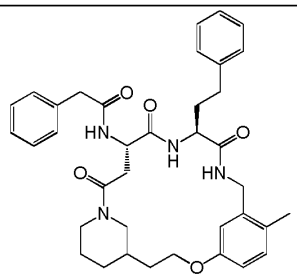
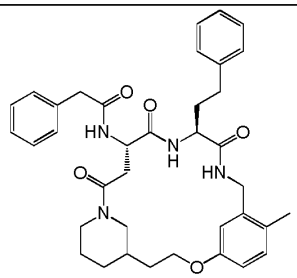
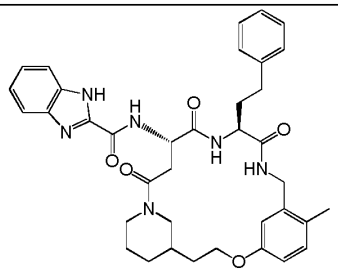
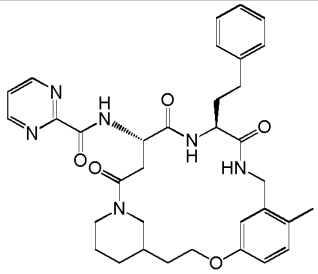
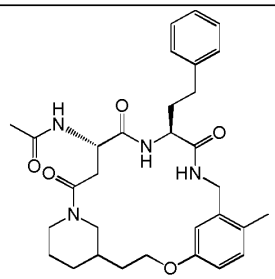
The compounds of any one of the formulae (**III-1**) – (**III-10**), (**IV-1**) – (**IV-10**), and (**V-1**) – (**V-9**) contain also these moieties as **A**.

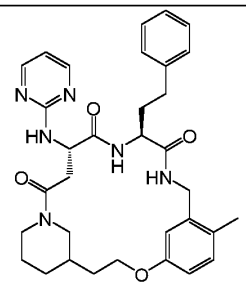
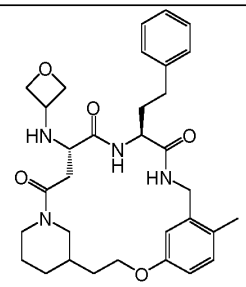
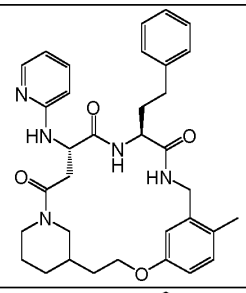
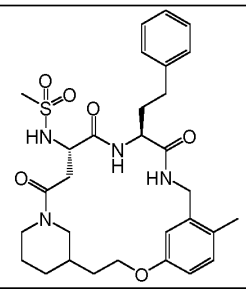
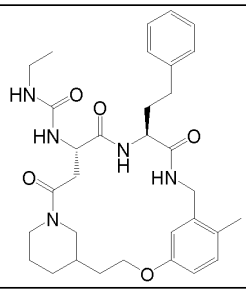
Especially preferred compounds according to the present invention include compounds presented by Table 1.

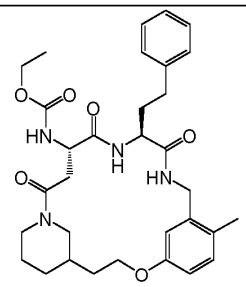
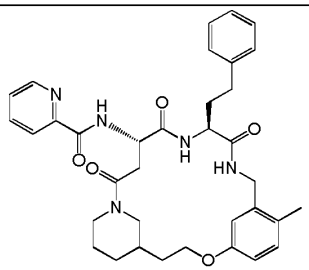
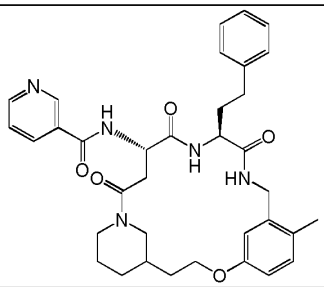
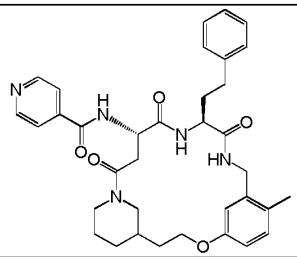
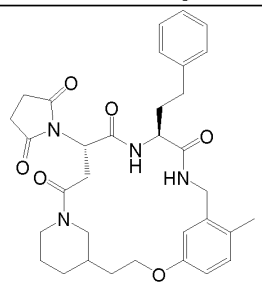
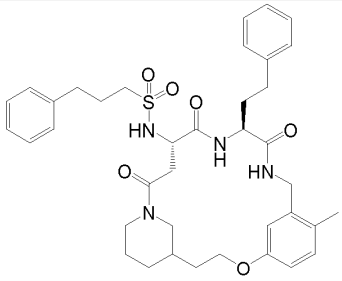
Table 1:

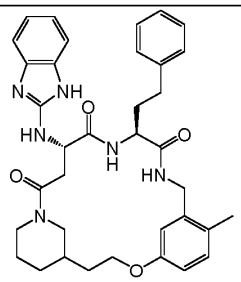
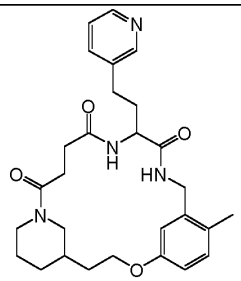
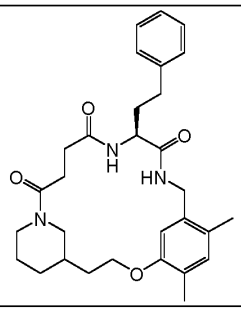
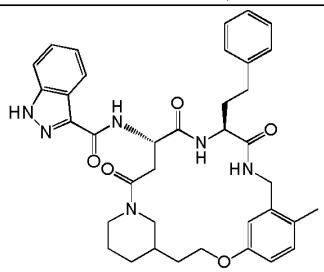
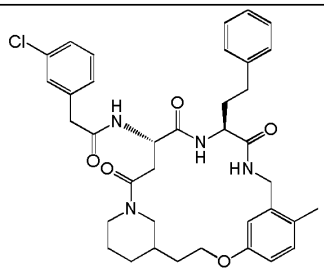
Cpd	structure	IUPAC Name
7		benzyl ((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
8		(9S,12S)-12-amino-5^4-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
13		(9S)-5^4-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
16		(9S)-5^4-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclohexadecaphane-8,11,16-trione
19		(9S)-5^4-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclopentadecaphane-8,11,15-trione

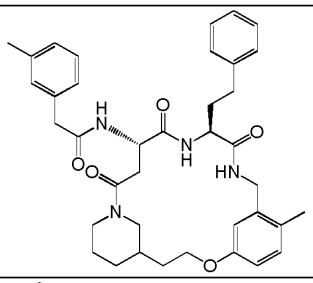
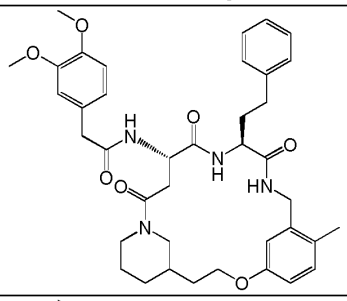
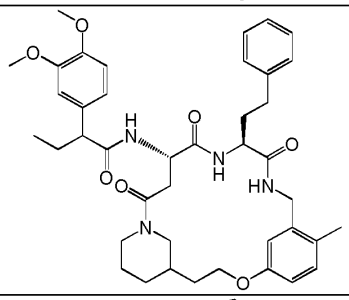
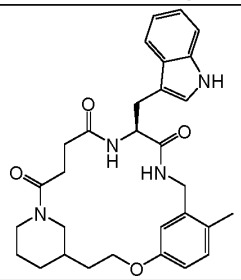
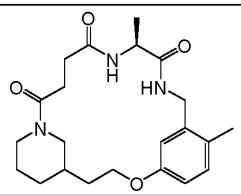
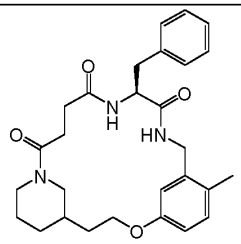
22		(9S)-5^4-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacycloheptadecaphane-8,11,17-trione
25		3-(3-fluorophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
26		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)benzamide
27		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)pivalamide
28		3,3-dimethyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)butanamide

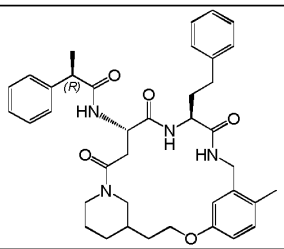
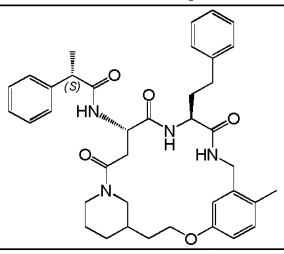
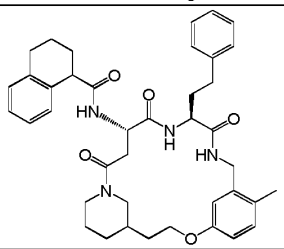
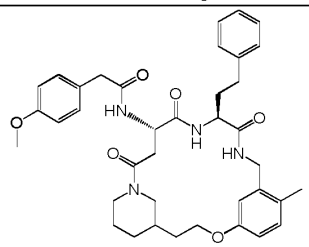
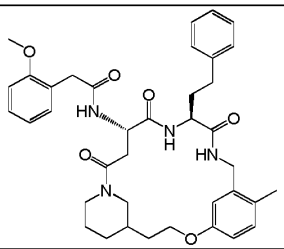
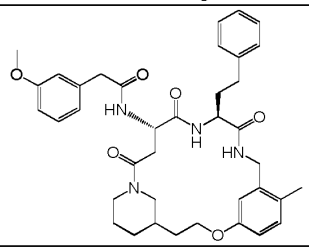
29		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-phenylacetamide
30		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-phenylacetamide
31		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-1H-benzo[d]imidazole-2-carboxamide
32		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)pyrimidine-2-carboxamide
33		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide

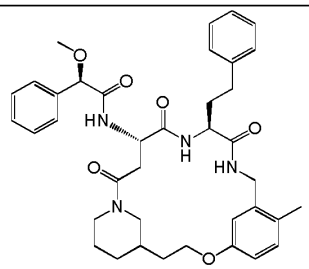
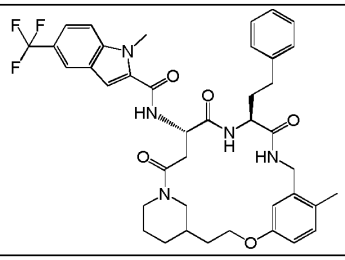
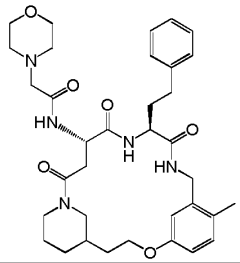
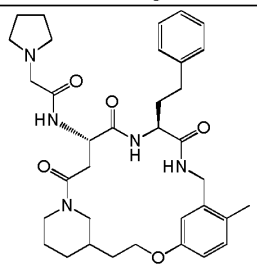
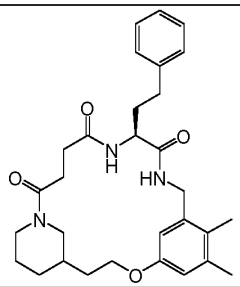
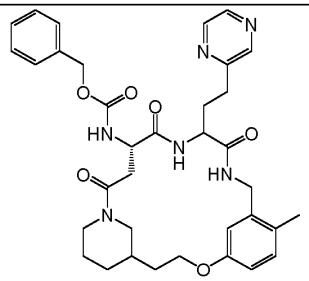
34		(9S,12S)-5^4-methyl-9-phenethyl-12-(pyrimidin-2-ylamino)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
35		(9S,12S)-5^4-methyl-12-(oxetan-3-ylamino)-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
36		(9S,12S)-5^4-methyl-9-phenethyl-12-(pyridin-2-ylamino)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
37		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)methanesulfonamide
38		1-ethyl-3-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)urea

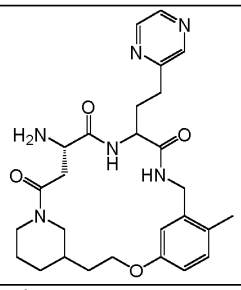
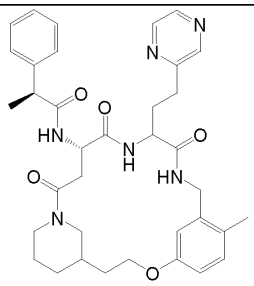
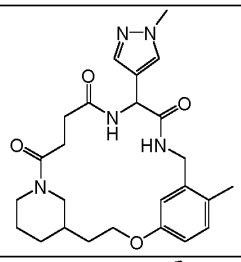
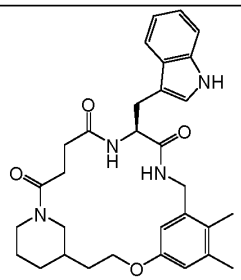
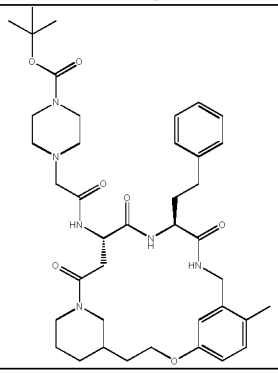
39		ethyl ((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
40		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)picolinamide
41		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)nicotinamide
42		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)isonicotinamide
43		(9S,12S)-12-(2,5-dioxopyrrolidin-1-yl)-5^4-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
44		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-phenylpropane-1-sulfonamide

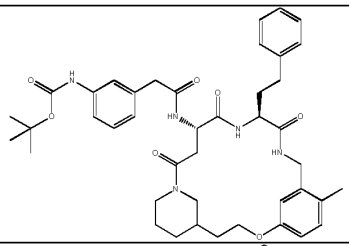
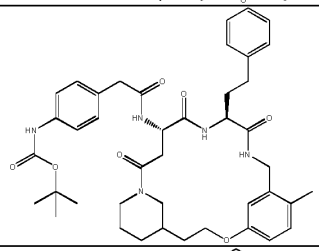
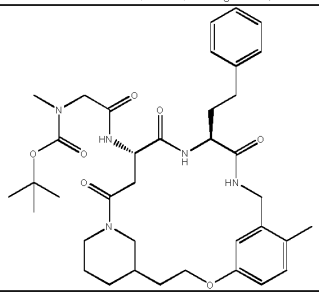
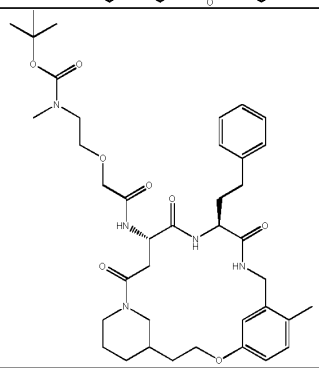
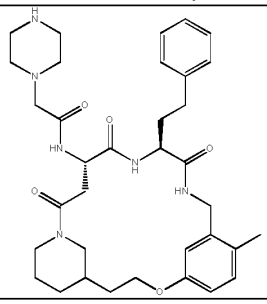
45		(9S,12S)-12-((1H-benzo[d]imidazol-2-yl)amino)-5^4-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
51		5^4-methyl-9-(2-(pyridin-3-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
59		(9R)-5^4,5^6-dimethyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
60		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-1H-indazole-3-carboxamide
61		2-(3-chlorophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide

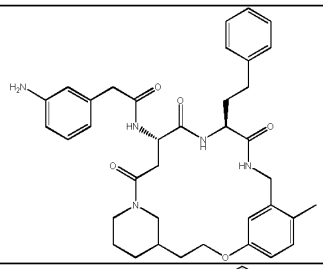
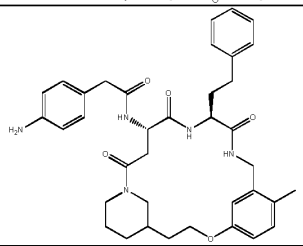
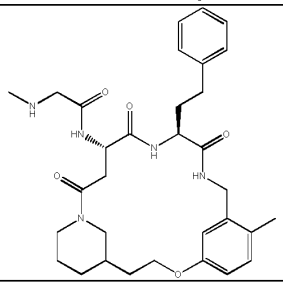
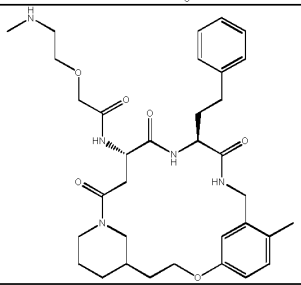
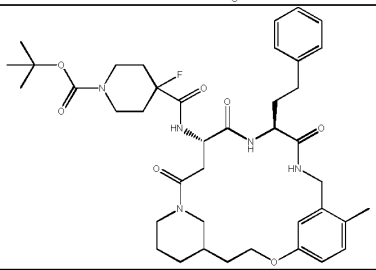
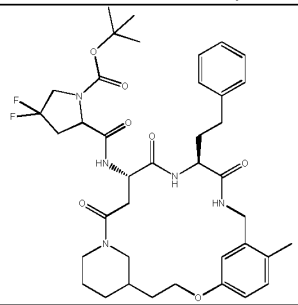
62		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(m-tolyl)acetamide
63		2-(3,4-dimethoxyphenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
64		2-(3,4-dimethoxyphenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)butanamide
77		(9S)-9-((1H-indol-3-yl)methyl)-5^4-methyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
78		(9S)-5^4,9-dimethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
79		(9S)-9-benzyl-5^4-methyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione

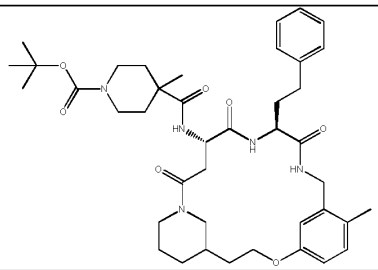
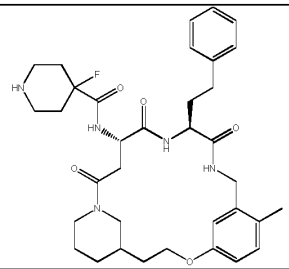
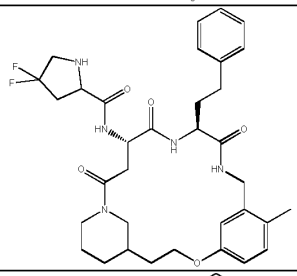
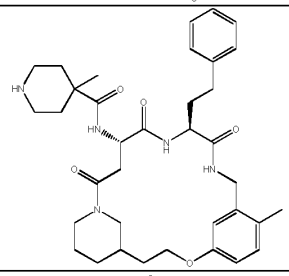
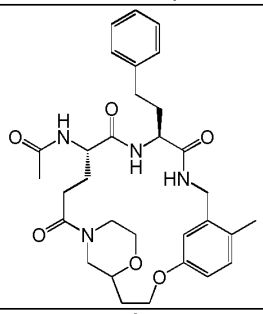
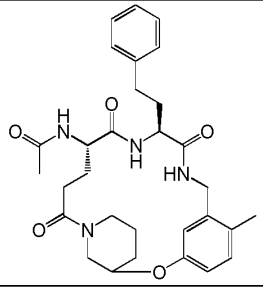
80		(2R)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-phenylpropanamide
81		(2S)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-phenylpropanamide
82		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-1,2,3,4-tetrahydronaphthalene-1-carboxamide
83		2-(4-methoxyphenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
84		2-(2-methoxyphenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
85		2-(3-methoxyphenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide

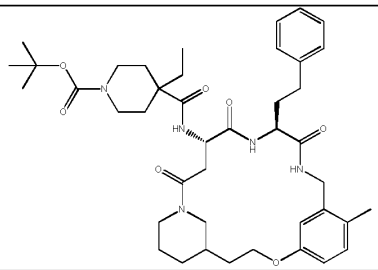
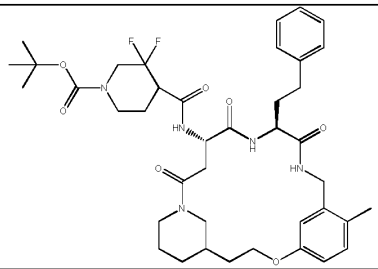
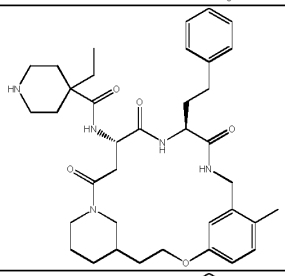
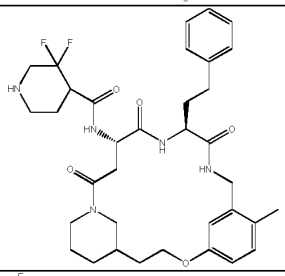
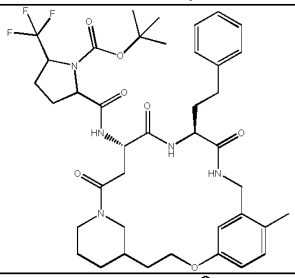
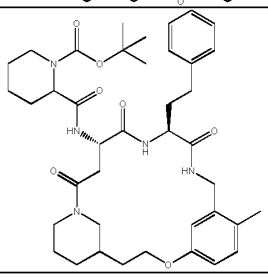
86		(2R)-2-methoxy-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-phenylacetamide
87		1-methyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-5-(trifluoromethyl)-1H-indole-2-carboxamide
88		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-morpholinoacetamide
89		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(pyrrolidin-1-yl)acetamide
95		(9S)-5^4,5^5-dimethyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione (95)
105		benzyl ((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyrazin-2-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate

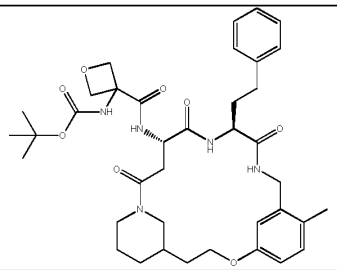
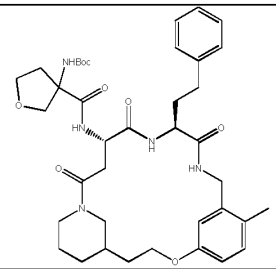
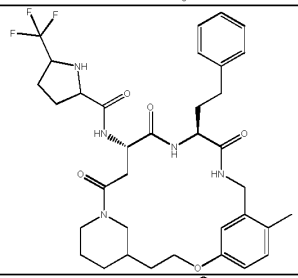
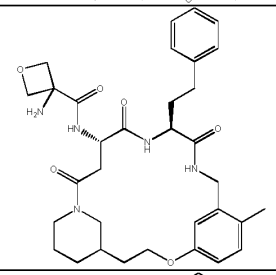
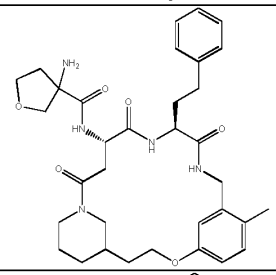
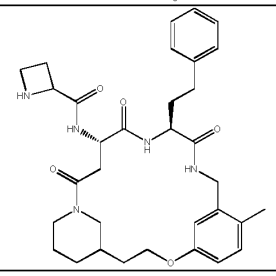
106		(12S)-amino-5^4-methyl-8,11,14-trioxo-9-(2-(pyrazin-2-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane
107		(2S)-N-((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyrazin-2-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-phenylpropanamide
116		5^4-methyl-9-(1-methyl-1H-pyrazol-4-yl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
120		(9S)-9-((1H-indol-3-yl)methyl)-5^4,5^5-dimethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
121		tert-butyl 4-(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)piperazine-1-carboxylate

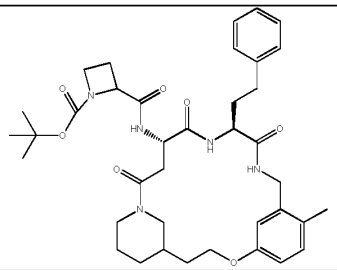
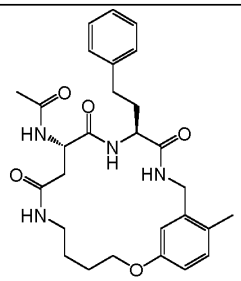
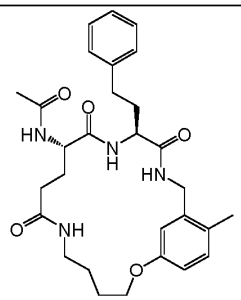
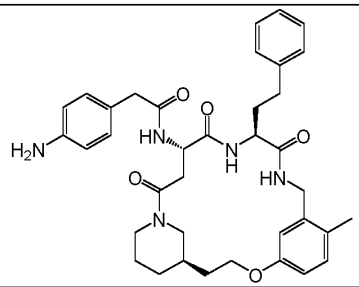
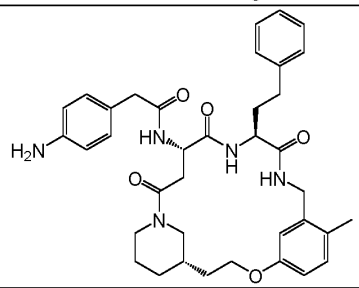
122		tert-butyl (3-(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)phenyl)carbamate
123		tert-butyl (4-(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)phenyl)carbamate
124		tert-butyl methyl(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)carbamate
125		tert-butyl methyl(2-(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethoxy)ethyl)carbamate
126		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(piperazin-1-yl)acetamide

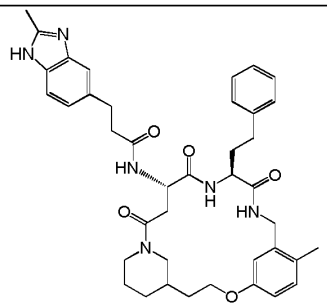
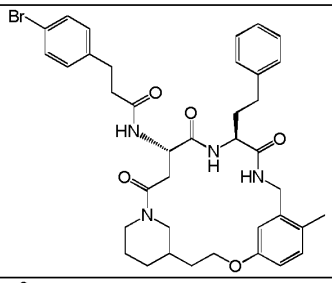
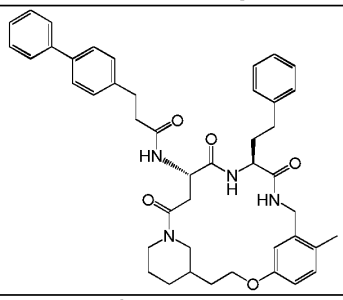
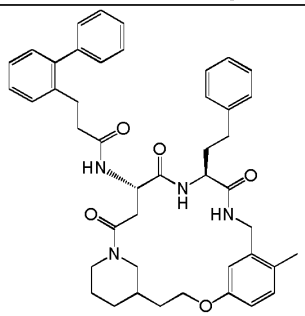
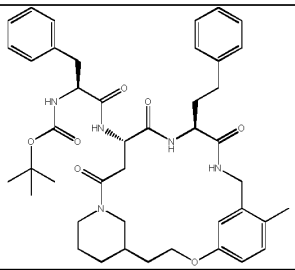
127		2-(3-aminophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
128		2-(4-aminophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
129		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(methylamino)acetamide
130		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(2-(methylamino)ethoxy)acetamide
131		tert-butyl 4-fluoro-4-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)piperidine-1-carboxylate
132		tert-butyl 4,4-difluoro-2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)pyrrolidine-1-carboxylate

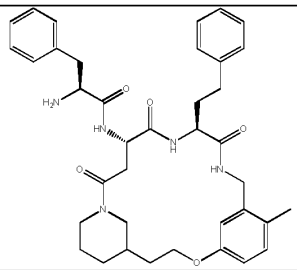
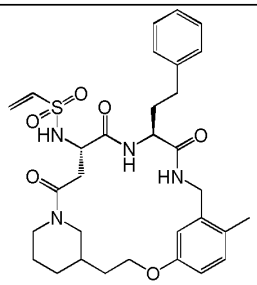
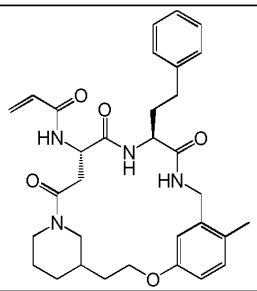
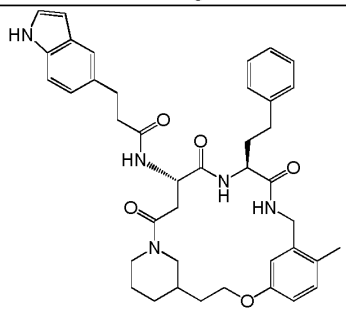
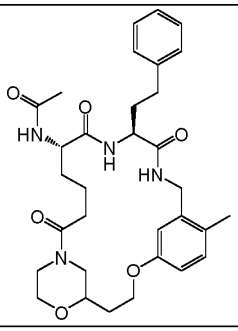
133		tert-butyl 4-methyl-4-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)piperidine-1-carboxylate
134		4-fluoro-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)piperidine-4-carboxamide
135		(2S)-4,4-difluoro-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)pyrrolidine-2-carboxamide
136		4-methyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)piperidine-4-carboxamide
143		N-((9S,12S)-5^4-methyl-8,11,15-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(2,4)-morpholina-5(1,3)-benzenacyclopentadecaphane-12-yl)acetamide
148		N-((7S,10S)-3^4-methyl-6,9,13-trioxo-7-phenethyl-2-oxa-5,8-diaza-1(3,1)-piperidina-3(1,3)-benzenacyclotridecaphane-10-yl)acetamide

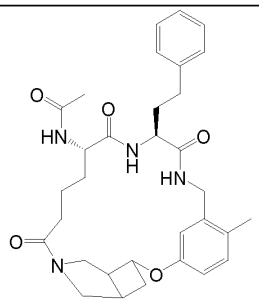
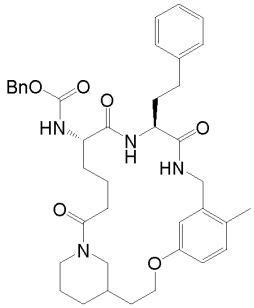
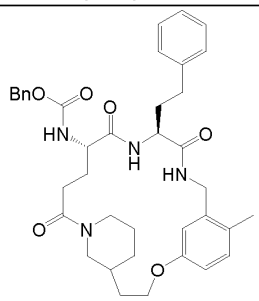
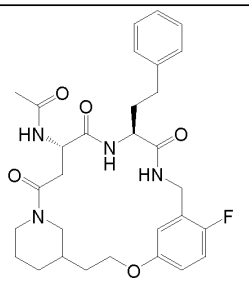
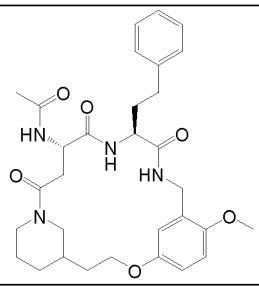
149		tert-butyl 4-ethyl-4-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)piperidine-1-carboxylate
150		tert-butyl 3,3-difluoro-4-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)piperidine-1-carboxylate
151		4-ethyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)piperidine-4-carboxamide
152		3,3-difluoro-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)piperidine-4-carboxamide
153		tert-butyl 2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)-5-(trifluoromethyl)pyrrolidine-1-carboxylate
154		tert-butyl 2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)piperidine-1-carboxylate

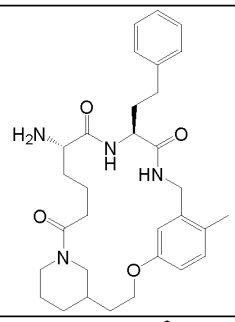
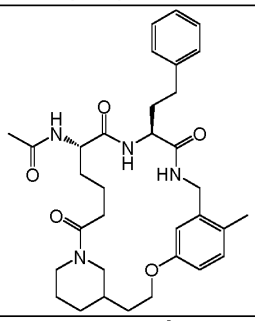
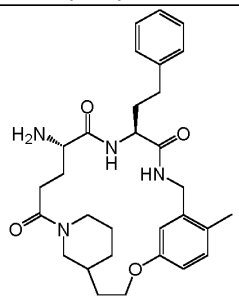
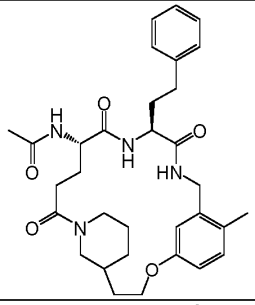
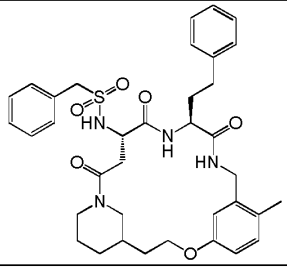
155		tert-butyl (3-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)oxetan-3-yl)carbamate
156		tert-butyl (3-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)tetrahydrofuran-3-yl)carbamate
157		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-5-(trifluoromethyl)pyrrolidine-2-carboxamide
158		3-amino-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)oxetane-3-carboxamide
159		3-amino-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)tetrahydrofuran-3-carboxamide
160		(2R)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)azetidine-2-carboxamide

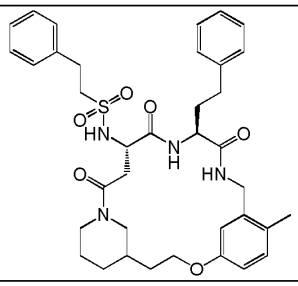
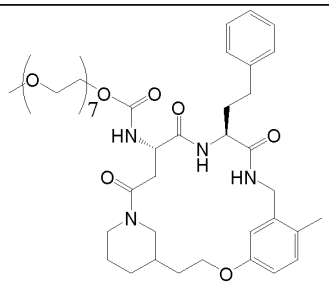
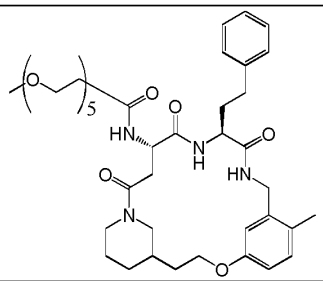
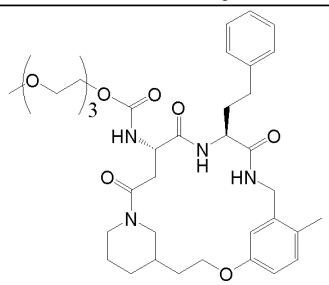
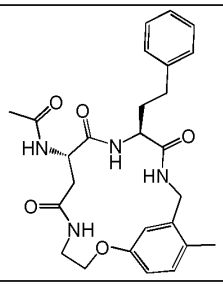
161		tert-butyl 2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)azetidine-1-carboxylate
168		N-((10S,13S)-1^4-methyl-8,11,14-trioxo-13-phenethyl-2-oxa-7,12,15-triaza-1(1,3)-benzenacyclohexadecaphane-10-yl)acetamide
171		N-((11S,14S)-1^4-methyl-8,12,15-trioxo-14-phenethyl-2-oxa-7,13,16-triaza-1(1,3)-benzenacycloheptadecaphane-11-yl)acetamide
172		2-(4-aminophenyl)-N-((13R,9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
173		2-(4-aminophenyl)-N-((13S,9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide

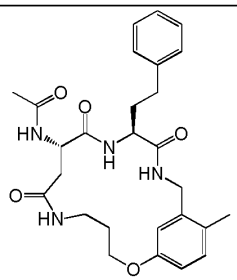
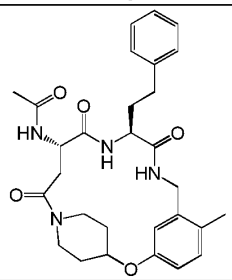
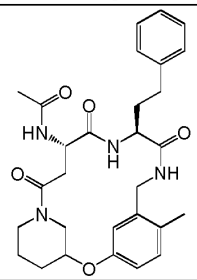
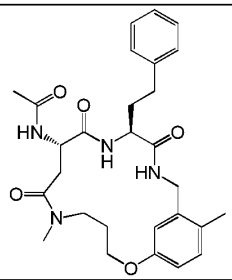
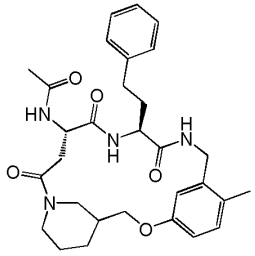
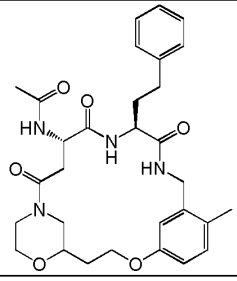
174		3-(2-methyl-1H-benzo[d]imidazol-6-yl)-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
175		3-(4-bromophenyl)-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
176		3-([1,1'-biphenyl]-4-yl)-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
177		N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(2-phenoxyphenyl)propanamide
178		tert-butyl ((2S)-1-(((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate

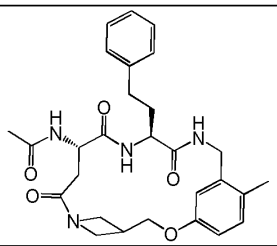
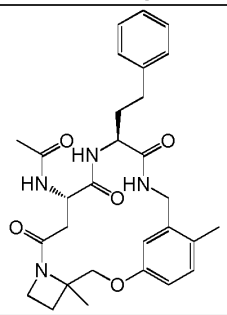
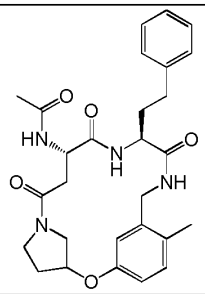
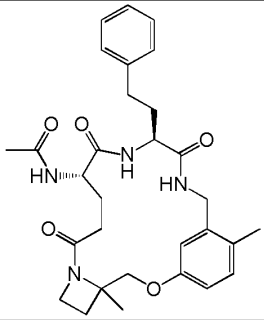
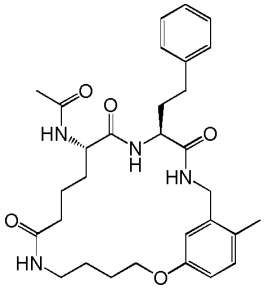
179		(2R)-2-amino-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-phenylpropanamide
180		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)ethenesulfonamide
181		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acrylamide
182		3-(1H-indol-5-yl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
186		N-((9S,12S)-5^4-methyl-8,11,16-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(2,4)-morpholina-5(1,3)-benzenacyclohexadecaphane-12-yl)acetamide

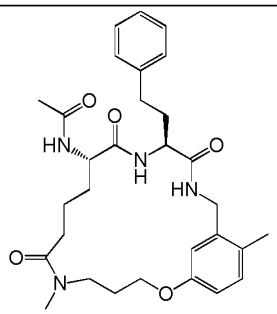
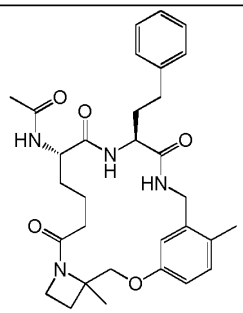
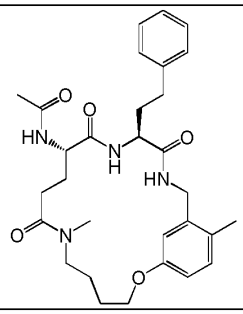
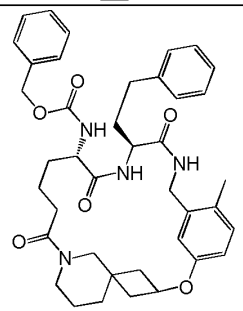
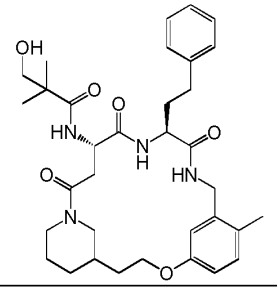
191		N-((11R,15S,7S,10S)-3^4-methyl-6,9,14-trioxo-7-phenethyl-2-oxa-13,5,8-triaza-1(7,3)-bicyclo[3.2.0]heptana-3(1,3)-benzenacyclotetradecaphane-10-yl)acetamide
195		benzyl ((9S,12S)-5^4-methyl-8,11,16-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclohexadecaphane-12-yl)carbamate
199		benzyl ((9S,12S)-5^4-methyl-8,11,15-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclopentadecaphane-12-yl)carbamate
205		N-((9S,12S)-5^4-fluoro-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
211		N-((9S,12S)-5^4-methoxy-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide

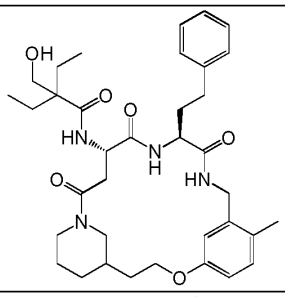
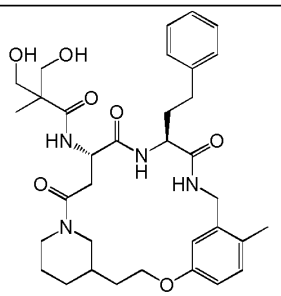
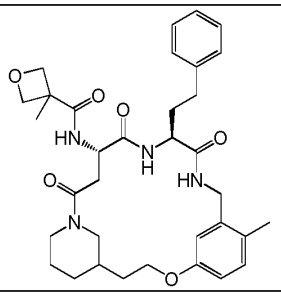
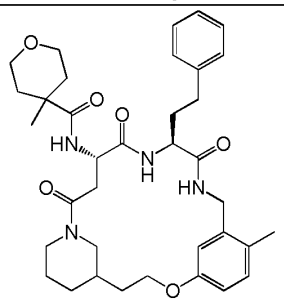
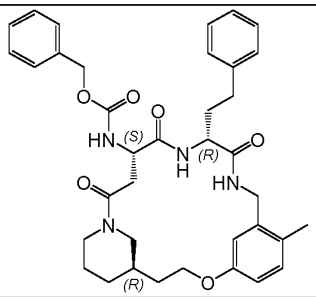
212		(9S,12S)-5^4-methyl-12-amino-8,11,16-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclohexadecaphane
213		N-((9S,12S)-5^4-methyl-8,11,16-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclohexadecaphane-12-yl)acetamide
214		(9S,12S)-12-amino-5^4-methyl-8,11,15-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclopentadecaphane)
215		N-((9S,12S)-5^4-methyl-8,11,15-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclopentadecaphane-12-yl)acetamide
216		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-1-phenylmethanesulfonamide

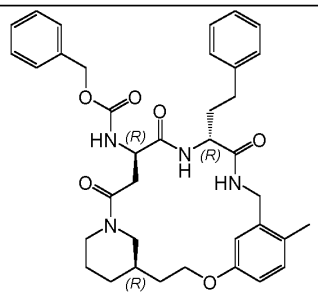
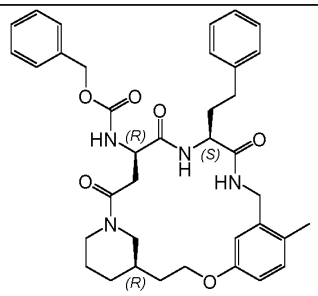
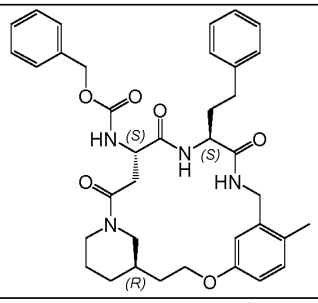
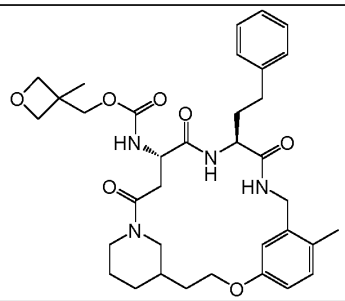
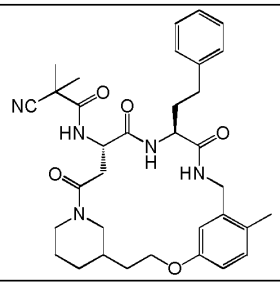
217		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-phenylethane-1-sulfonamide
218		2,5,8,11,14,17,20-heptaoxadocosan-22-yl ((9R,12R)-54-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
219		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2,5,8,11,14-pentaoxaheptadecan-17-amide
220		((9R,12R)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
252		N-((8S,11S)-1^4-methyl-6,9,12-trioxo-11-phenethyl-2-oxa-5,10,13-triaza-1(1,3)-benzenacyclotetradecaphane-8-yl)acetamide

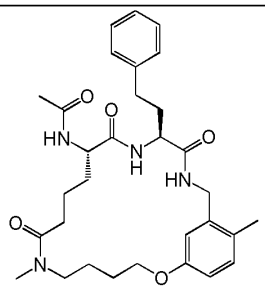
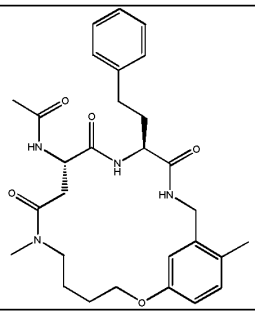
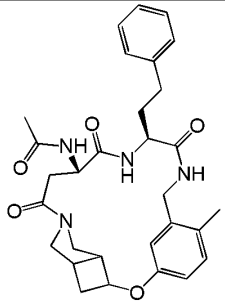
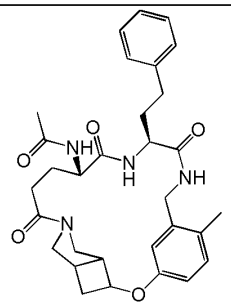
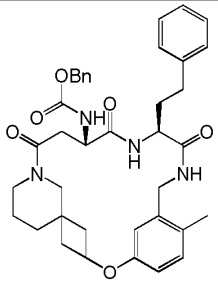
253		N-((9S,12S)-1^4-methyl-7,10,13-trioxo-12-phenethyl-2-oxa-6,11,14-triaza-1(1,3)-benzenacyclopentadecaphane-9-yl)acetamide
254		N-((7S,10S)-3^4-methyl-6,9,12-trioxo-7-phenethyl-2-oxa-5,8-diaza-1(4,1)-piperidina-3(1,3)-benzenacyclododecaphane-10-yl)acetamide
255		N-((7S,10S)-3^4-methyl-6,9,12-trioxo-7-phenethyl-2-oxa-5,8-diaza-1(3,1)-piperidina-3(1,3)-benzenacyclododecaphane-10-yl)acetamide
256		N-((9S,12S)-1^4,6-dimethyl-7,10,13-trioxo-12-phenethyl-2-oxa-6,11,14-triaza-1(1,3)-benzenacyclopentadecaphane-9-yl)acetamide
257		N-((8S,11S)-4^4-methyl-7,10,13-trioxo-8-phenethyl-3-oxa-6,9-diaza-1(3,1)-piperidina-4(1,3)-benzenacyclotridecaphane-11-yl)acetamide
258		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(2,4)-morpholina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide

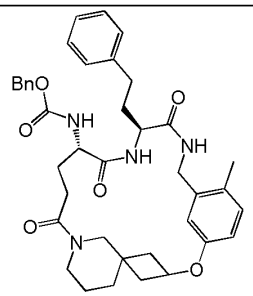
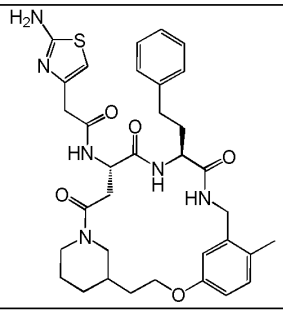
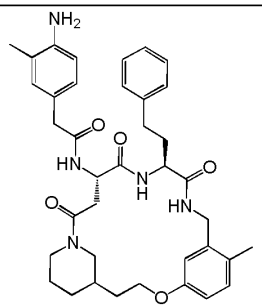
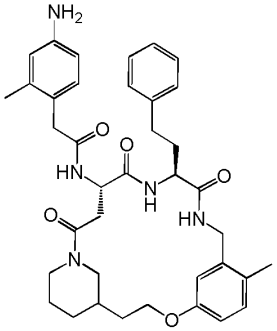
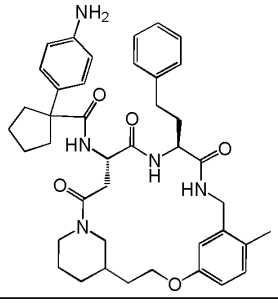
259		N-((8S,11S)-4^4-methyl-7,10,13-trioxo-8-phenethyl-3-oxa-6,9-diaza-1(3,1)-azetidina-4(1,3)-benzenacyclotridecaphane-11-yl)acetamide
260		N-((8S,11S)-1^2,4^4-dimethyl-7,10,13-trioxo-8-phenethyl-3-oxa-6,9-diaza-1(2,1)-azetidina-4(1,3)-benzenacyclotridecaphane-11-yl)acetamide
261		N-((7S,10S)-3^4-methyl-6,9,12-trioxo-7-phenethyl-2-oxa-5,8-diaza-1(3,1)-pyrrolidina-3(1,3)-benzenacyclododecaphane-10-yl)acetamide
265		N-((8S,11S)-1^2,4^4-dimethyl-7,10,14-trioxo-8-phenethyl-3-oxa-6,9-diaza-1(2,1)-azetidina-4(1,3)-benzenacyclotetradecaphane-11-yl)acetamide
269		N-((12S,15S)-1^4-methyl-8,13,16-trioxo-15-phenethyl-2-oxa-7,14,17-triaza-1(1,3)-benzenacyclooctadecaphane-12-yl)acetamide

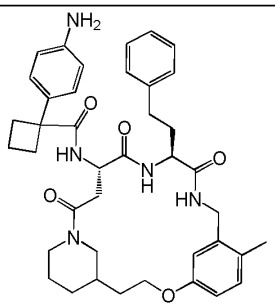
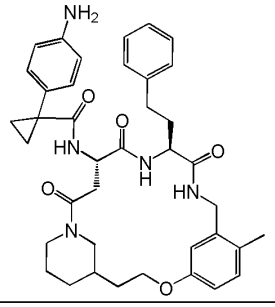
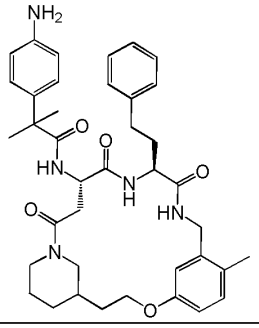
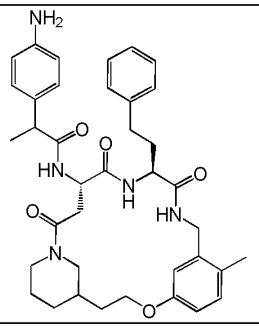
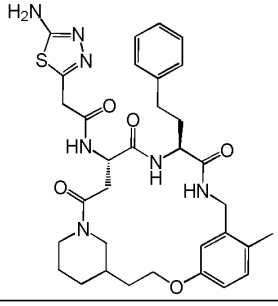
280		N-((11S,14S)-1^4,6-dimethyl-7,12,15-trioxo-14-phenethyl-2-oxa-6,13,16-triaza-1(1,3)-benzenacycloheptadecaphane-11-yl)acetamide
281		N-((8S,11S)-1^2,4^4-dimethyl-7,10,15-trioxo-8-phenethyl-3-oxa-6,9-diaza-1(2,1)-azetidina-4(1,3)-benzenacyclopentadecaphane-11-yl)acetamide
282		N-((11S,14S)-1^4,7-dimethyl-8,12,15-trioxo-14-phenethyl-2-oxa-7,13,16-triaza-1(1,3)-benzenacycloheptadecaphane-11-yl)acetamide
283		benzyl ((7S,10S)-3^4-methyl-6,9,14-trioxo-7-phenethyl-2-oxa-5,8-diaza-15(3,1)-piperidina-3(1,3)-benzena-1(1,3)-cyclobutanapentadecaphane-10-yl)carbamate
284		3-hydroxy-2,2-dimethyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide

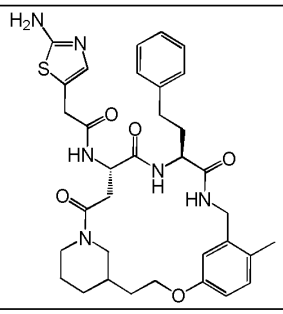
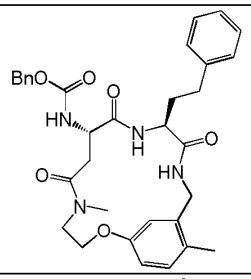
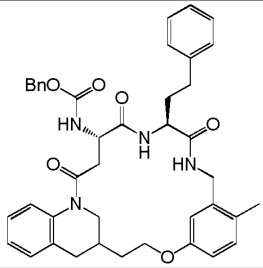
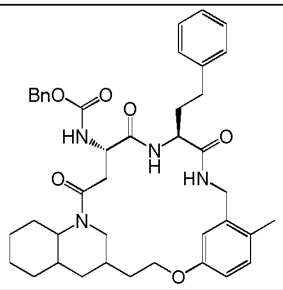
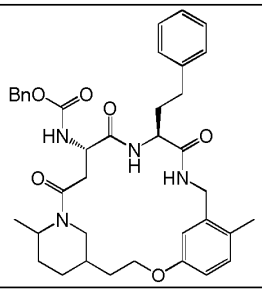
285		2-ethyl-2-(hydroxymethyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)butanamide
286		3-hydroxy-2-(hydroxymethyl)-2-methyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
287		3-methyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)oxetane-3-carboxamide
288		4-methyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)tetrahydro-2H-pyran-4-carboxamide
289		benzyl ((13R,9R,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate

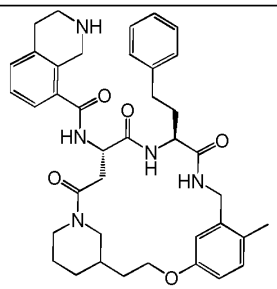
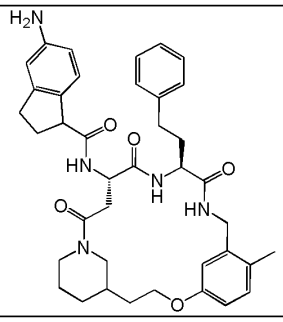
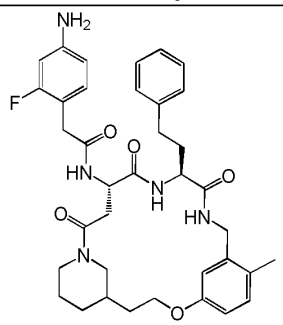
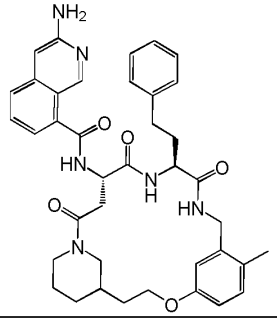
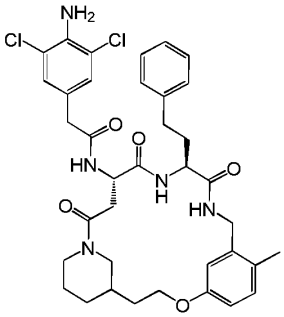
290		benzyl ((13R,9R,12R)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
291		benzyl ((13R,9S,12R)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
292		benzyl ((13R,9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
293		(3-methyloxetan-3-yl)methyl ((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
294		2-cyano-2-methyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide

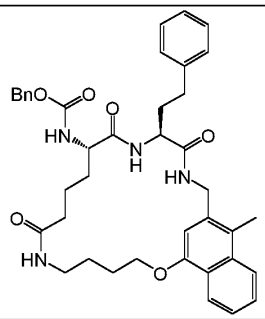
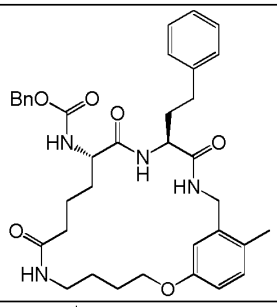
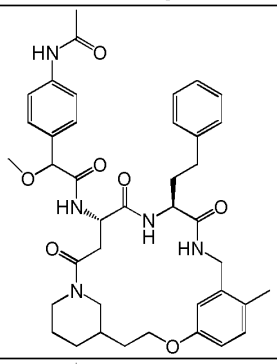
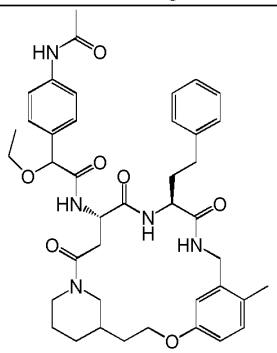
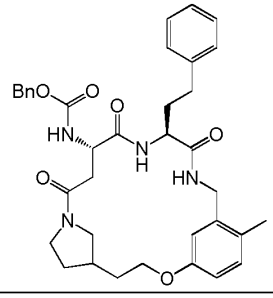
295		N-(1^4,7-dimethyl-8,13,16-trioxo-15-phenethyl-2-oxa-7,14,17-triaza-1(1,3)-benzenacyclooctadecaphane-12-yl)acetamide
296		N-(1^4,7-dimethyl-8,11,14-trioxo-13-phenethyl-2-oxa-7,12,15-triaza-1(1,3)-benzenacyclohexadecaphane-10-yl)acetamide
298		N-(3^4-methyl-6,9,12-trioxo-7-phenethyl-2-oxa-13,5,8-triaza-1(6,3)-bicyclo[3.2.0]heptana-3(1,3)-benzenacyclododecaphane-10-yl)acetamide
299		N-(3^4-methyl-6,9,13-trioxo-7-phenethyl-2-oxa-13,5,8-triaza-1(6,3)-bicyclo[3.2.0]heptana-3(1,3)-benzenacyclotridecaphane-10-yl)acetamide
300		benzyl ((7S,10S)-3^4-methyl-6,9,12-trioxo-7-phenethyl-2-oxa-5,8-diaza-13(3,1)-piperidina-3(1,3)-benzena-1(1,3)-cyclobutanatridecaphane-10-yl)carbamate

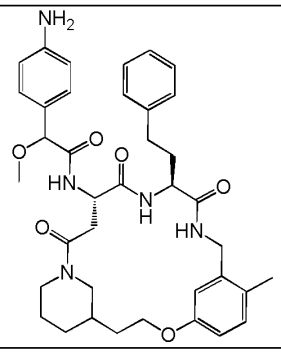
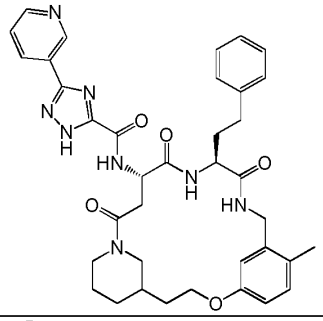
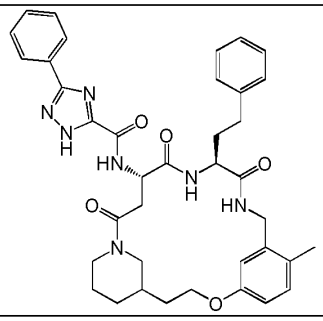
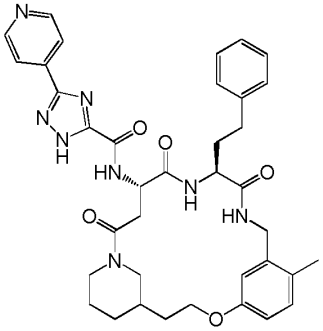
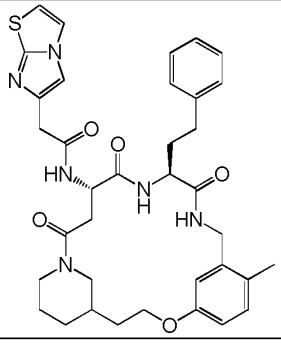
301		benzyl ((7S,10S)-3[4]-methyl-6,9,13-trioxo-7-phenethyl-2-oxa-5,8-diaza-14(3,1)-piperidina-3(1,3)-benzena-1(1,3)-cyclobutanatetradecaphane-10-yl)carbamate
302		2-(2-aminothiazol-4-yl)-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
303		2-(4-amino-3-methylphenyl)-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
304		2-(4-amino-2-methylphenyl)-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
305		1-(4-aminophenyl)-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)cyclopentane-1-carboxamide

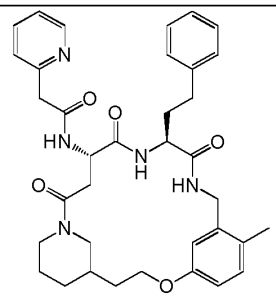
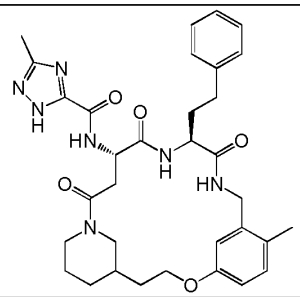
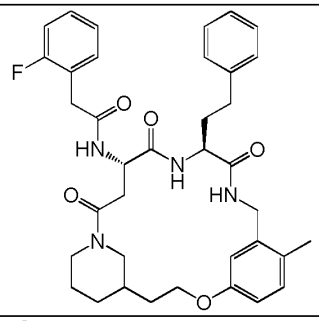
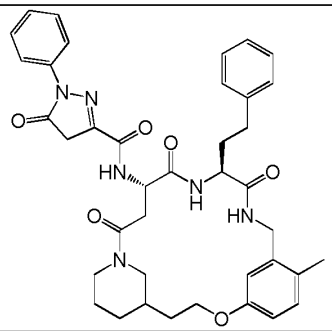
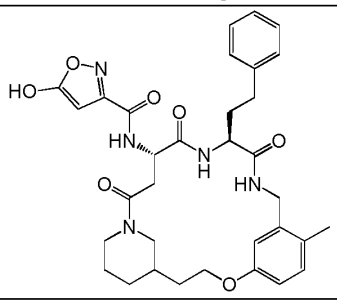
306		1-(4-aminophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)cyclobutane-1-carboxamide
307		1-(4-aminophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)cyclopropane-1-carboxamide
308		2-(4-aminophenyl)-2-methyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
309		2-(4-aminophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
310		2-(5-amino-1,3,4-thiadiazol-2-yl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide

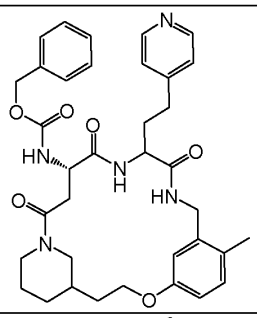
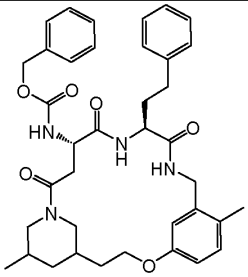
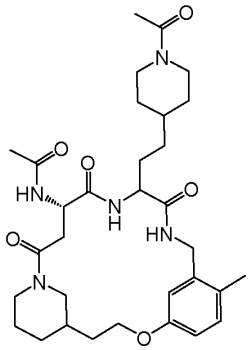
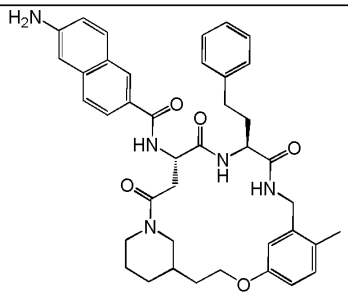
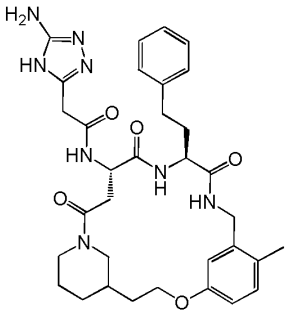
311		2-(2-aminothiazol-5-yl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
312		benzyl ((8S,11S)-1^4,5-dimethyl-6,9,12-trioxo-11-phenethyl-2-oxa-5,10,13-triaza-1(1,3)-benzenacyclotetradecaphane-8-yl)carbamate
313		benzyl ((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-11,12,13,14-tetrahydro-4-oxa-7,10-diaza-1(3,1)-quinolina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
314		benzyl ((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-11,12,13,14,14a,15,16,17,18,18a-decahydro-4-oxa-7,10-diaza-1(3,1)-quinolina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
315		benzyl ((9S,12S)-1^6,5^4-dimethyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate

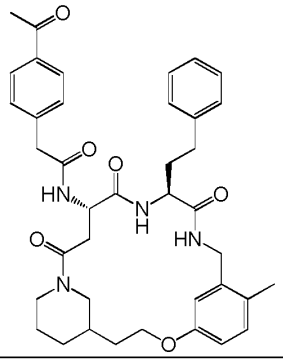
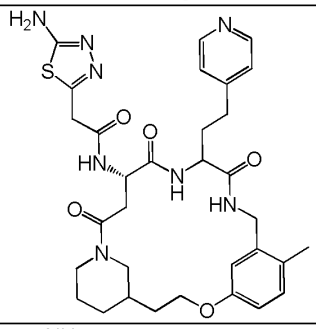
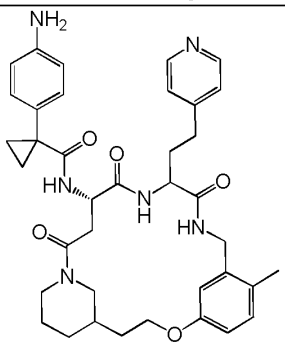
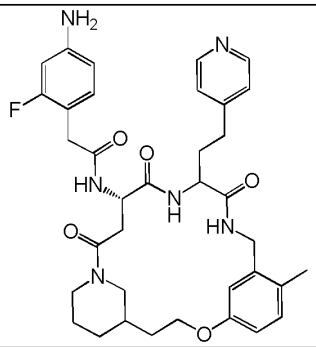
316		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-1,2,3,4-tetrahydroisoquinoline-5-carboxamide
317		5-amino-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2,3-dihydro-1H-indene-1-carboxamide
318		2-(4-amino-2-fluorophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
319		3-amino-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)isoquinoline-8-carboxamide
320		2-(4-amino-3,5-dichlorophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide

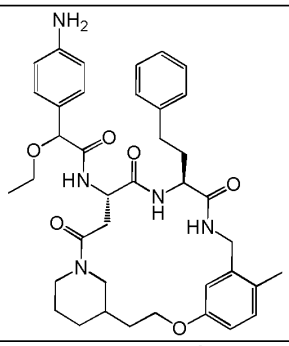
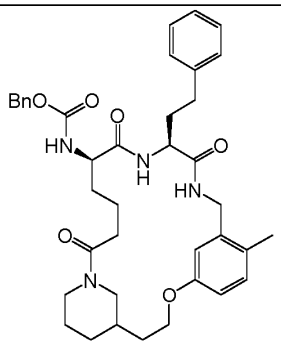
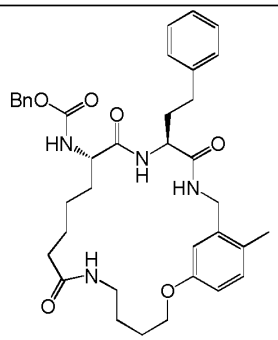
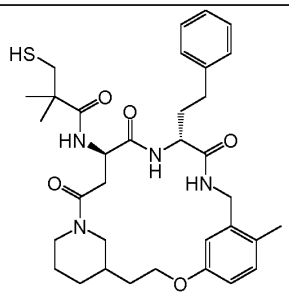
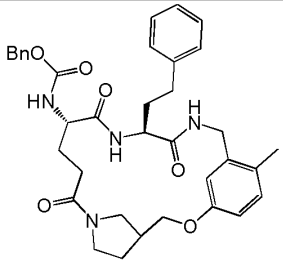
321		benzyl ((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-naphthalenacyclotetradecaphane-12-yl)carbamate
322		benzyl ((12S,15S)-1^4-methyl-8,13,16-trioxo-15-phenethyl-2-oxa-7,14,17-triaza-1(1,3)-benzenacyclooctadecaphane-12-yl)carbamate
323		2-(4-acetamidophenyl)-2-methoxy-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
324		2-(4-acetamidophenyl)-2-ethoxy-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
325		benzyl ((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-pyrrolidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate

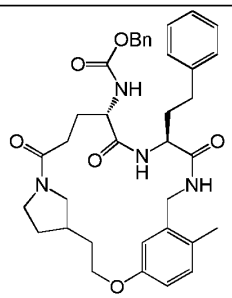
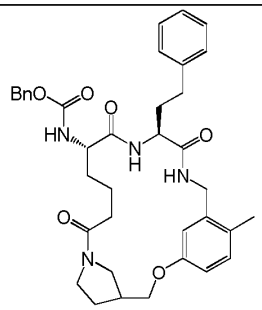
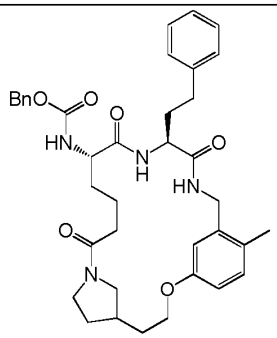
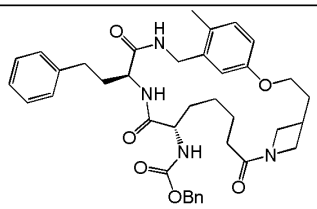
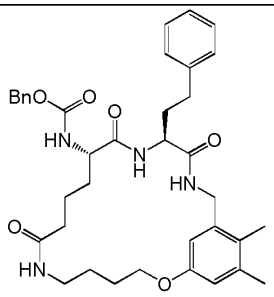
326		2-(4-aminophenyl)-2-methoxy-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
327		N-((9S,12R)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(3-(pyridin-3-yl)-1H-1,2,4-triazol-5-yl)acetamide
328		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(3-phenyl-1H-1,2,4-triazol-5-yl)acetamide
329		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(3-(pyridin-4-yl)-1H-1,2,4-triazol-5-yl)acetamide
330		2-(imidazo[2,1-b]thiazol-6-yl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide

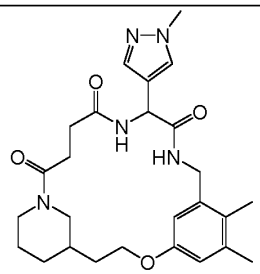
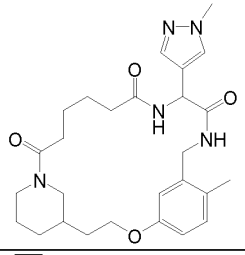
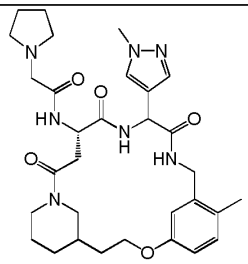
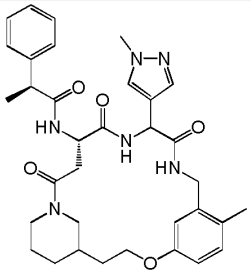
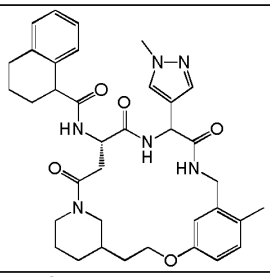
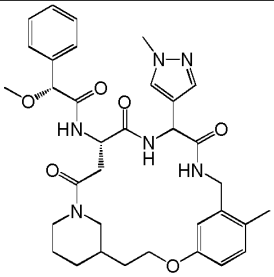
331		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(pyridin-2-yl)acetamide
332		2-(3-methyl-1H-1,2,4-triazol-5-yl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
333		2-(2-fluorophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
334		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)acetamide
335		2-(5-hydroxyisoxazol-3-yl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide

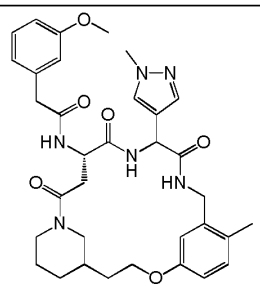
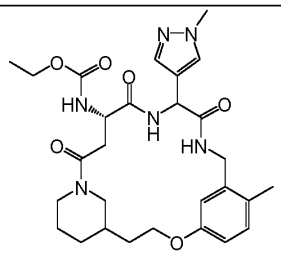
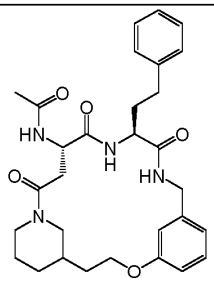
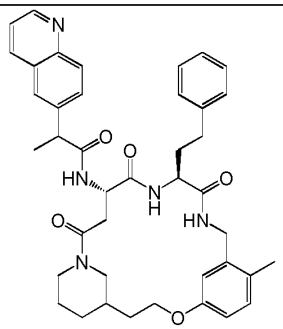
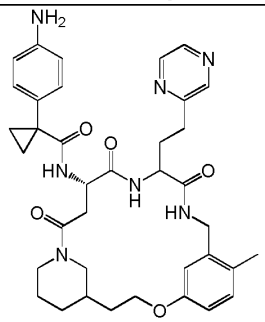
336		benzyl ((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-4-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
337		benzyl ((9S,12S)-1^5,5^4-dimethyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
338		N-((12S)-9-(2-(1-acetylpiperidin-4-yl)ethyl)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
339		6-amino-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-naphthamide
340		2-(5-amino-1H-1,2,4-triazol-3-yl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide

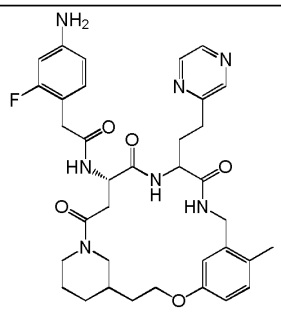
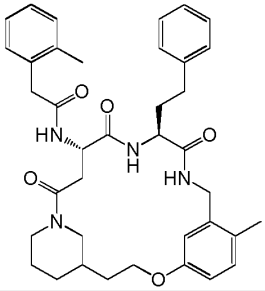
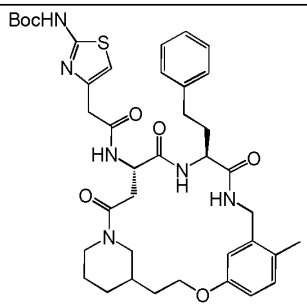
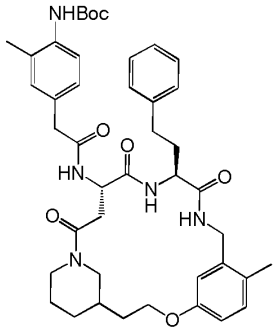
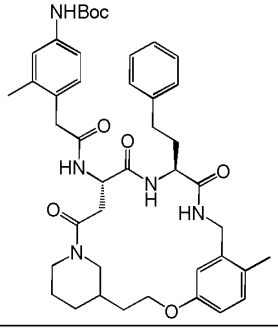
341		2-(4-acetylphenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
342		2-(5-amino-1,3,4-thiadiazol-2-yl)-N-((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-4-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
343		1-(4-aminophenyl)-N-((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-4-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)cyclopropane-1-carboxamide
344		2-(4-amino-2-fluorophenyl)-N-((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-4-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide

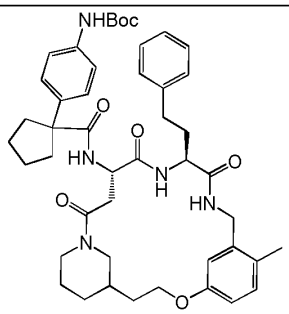
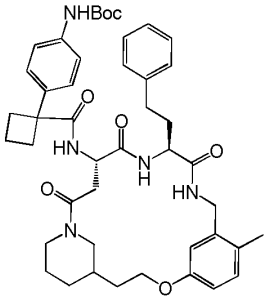
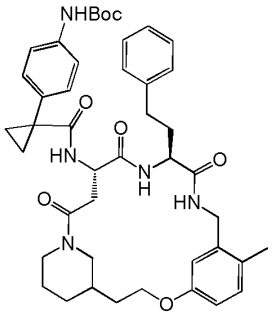
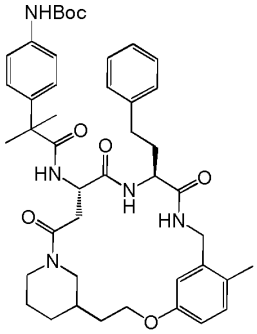
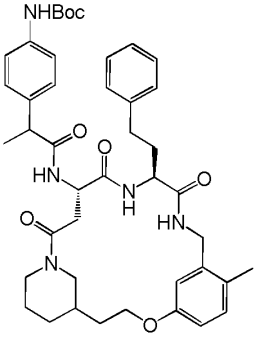
345		2-(4-aminophenyl)-2-ethoxy-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
346		benzyl ((9S,12R)-5^4-methyl-8,11,16-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclohexadecaphane-12-yl)carbamate
347		benzyl ((13S,16S)-1^4-methyl-8,14,17-trioxo-16-phenethyl-2-oxa-7,15,18-triaza-1(1,3)-benzenacyclononadecaphane-13-yl)carbamate
348		3-mercapto-2,2-dimethyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
349		benzyl ((8S,11S)-4^4-methyl-7,10,14-trioxo-8-phenethyl-3-oxa-6,9-diaza-1(3,1)-pyrrolidina-4(1,3)-benzenacyclotetradecaphane-11-yl)carbamate

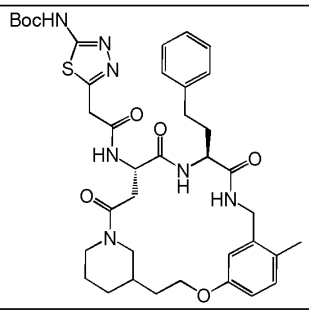
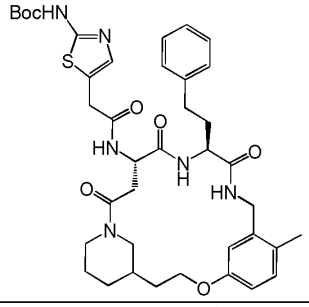
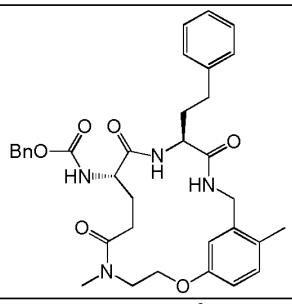
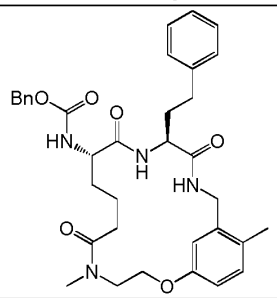
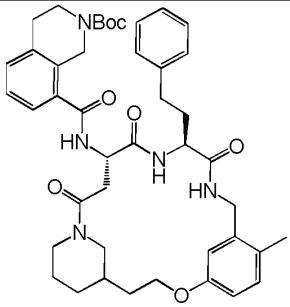
350		benzyl ((9S,12S)-5^4-methyl-8,11,15-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-pyrrolidina-5(1,3)-benzenacyclopentadecaphane-12-yl)carbamate
351		benzyl ((8S,11S)-4^4-methyl-7,10,15-trioxo-8-phenethyl-3-oxa-6,9-diaza-1(3,1)-pyrrolidina-4(1,3)-benzenacyclopentadecaphane-11-yl)carbamate
352		benzyl ((9S,12S)-5^4-methyl-8,11,16-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-pyrrolidina-5(1,3)-benzenacyclohexadecaphane-12-yl)carbamate
353		benzyl ((9S,12S)-5^4-methyl-8,11,17-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-azetidina-5(1,3)-benzenacycloheptadecaphane-12-yl)carbamate
354		benzyl ((12S,15S)-1^4,1^5-dimethyl-8,13,16-trioxo-15-phenethyl-2-oxa-7,14,17-triaza-1(1,3)-benzenacyclooctadecaphane-12-yl)carbamate

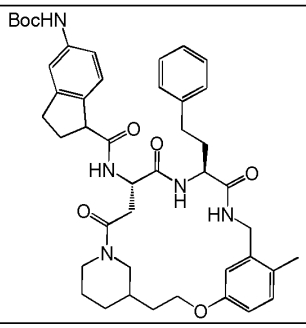
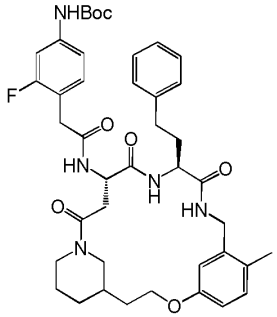
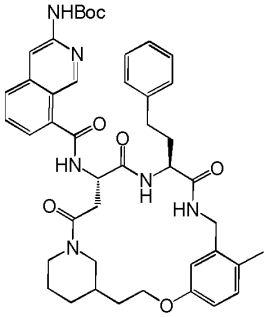
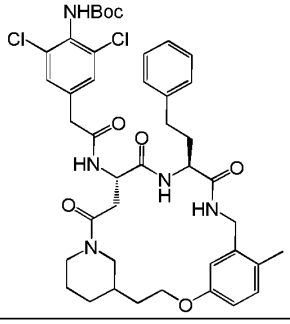
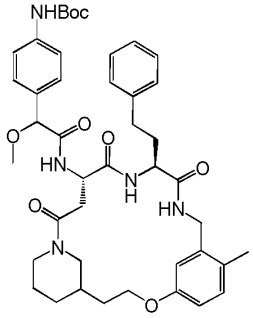
355		$5^4,5^5$-dimethyl-9-(1-methyl-1H-pyrazol-4-yl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
356		5^4-methyl-9-(1-methyl-1H-pyrazol-4-yl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclohexadecaphane-8,11,16-trione
358		N-((12S)-5^4-methyl-9-(1-methyl-1H-pyrazol-4-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(pyrrolidin-1-yl)acetamide
359		(2S)-N-((12S)-5^4-methyl-9-(1-methyl-1H-pyrazol-4-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-phenylpropanamide
360		N-((12S)-5^4-methyl-9-(1-methyl-1H-pyrazol-4-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-1,2,3,4-tetrahydronaphthalene-1-carboxamide
361		(2R)-2-methoxy-N-((12S)-5^4-methyl-9-(1-methyl-1H-pyrazol-4-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-phenylacetamide

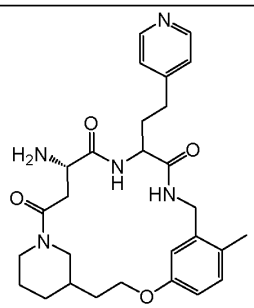
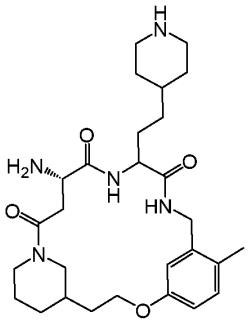
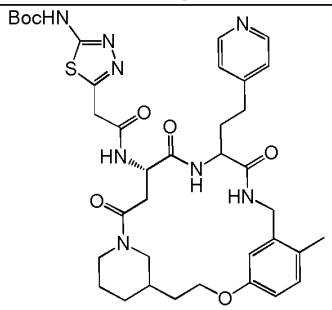
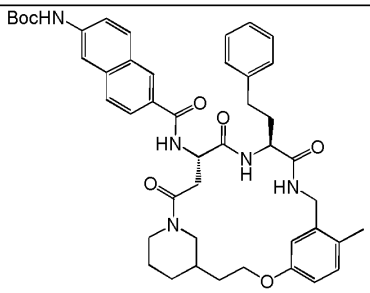
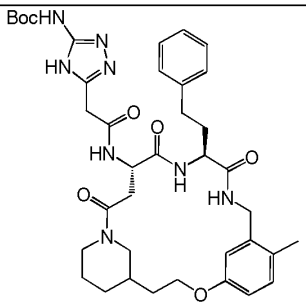
362		2-(3-methoxyphenyl)-N-((12S)-5^4-methyl-9-(1-methyl-1H-pyrazol-4-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
363		Ethyl ((12S)-5^4-methyl-9-(1-methyl-1H-pyrazol-4-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
364		N-((9S,12S)-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
369		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(quinolin-6-yl)propanamide
371		1-(4-aminophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyrazin-2-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)cyclopropane-1-carboxamide

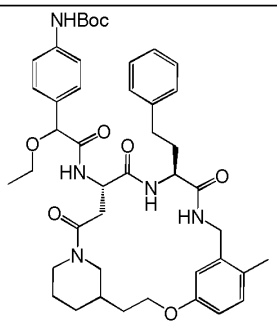
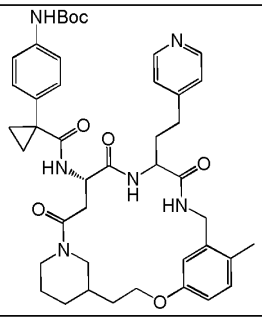
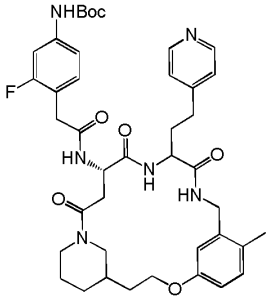
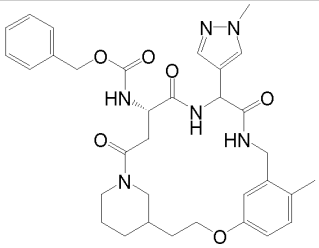
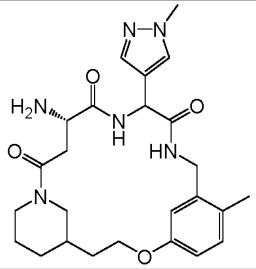
372		2-(4-amino-2-fluorophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyrazin-2-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
373		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(o-tolyl)acetamide
387		tert-butyl (4-(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)thiazol-2-yl)carbamate
388		tert-butyl (2-methyl-4-(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)phenyl)carbamate
389		tert-butyl (3-methyl-4-(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)phenyl)carbamate

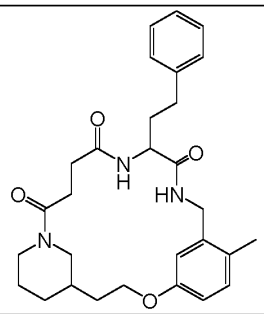
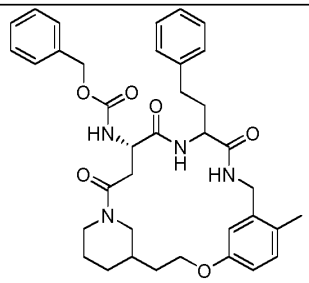
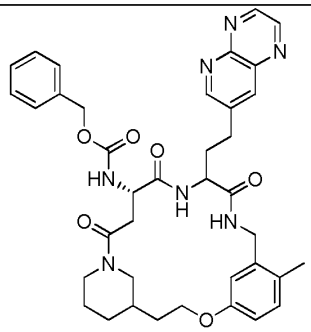
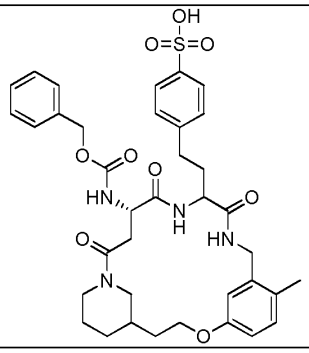
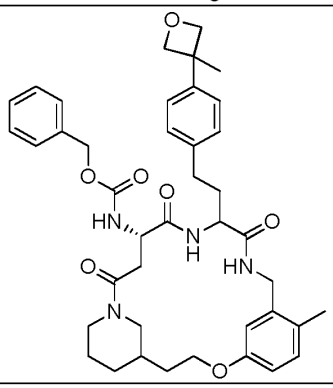
390		tert-butyl (4-(1-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)cyclopentyl)phenyl)carbamate
391		tert-butyl (4-(1-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)cyclobutyl)phenyl)carbamate
392		tert-butyl (4-(1-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)cyclopropyl)phenyl)carbamate
393		tert-butyl (4-(2-methyl-1-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-1-oxopropan-2-yl)phenyl)carbamate
394		2-(4-aminophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide

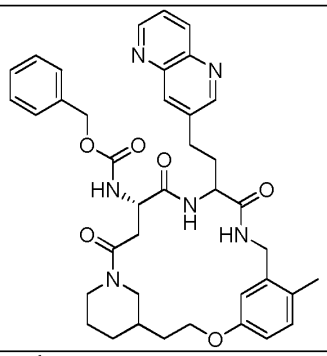
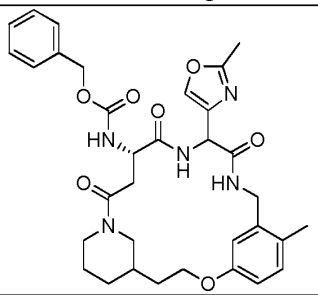
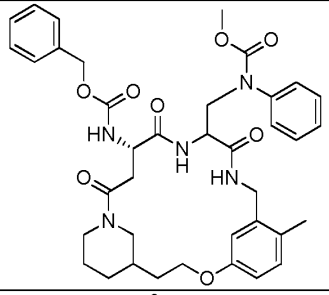
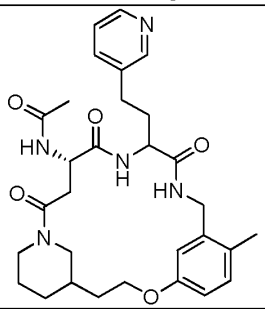
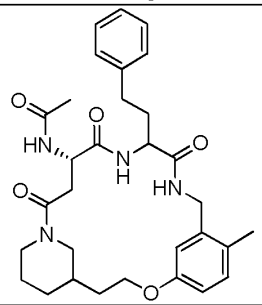
395		tert-butyl (5-(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)-1,3,4-thiadiazol-2-yl)carbamate
396		tert-butyl (5-(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)thiazol-2-yl)carbamate
402		benzyl ((9S,12S)-1^4,5-dimethyl-6,10,13-trioxo-12-phenethyl-2-oxa-5,11,14-triaza-1(1,3)-benzenacyclopentadecaphane-9-yl)carbamate
405		benzyl ((10S,13S)-1^4,5-dimethyl-6,11,14-trioxo-13-phenethyl-2-oxa-5,12,15-triaza-1(1,3)-benzenacyclohexadecaphane-10-yl)carbamate
419		tert-butyl 8-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate

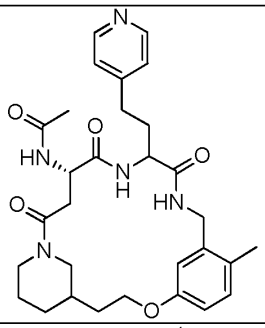
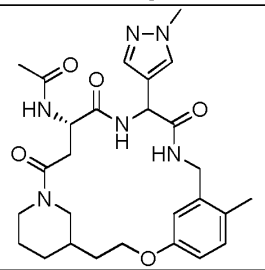
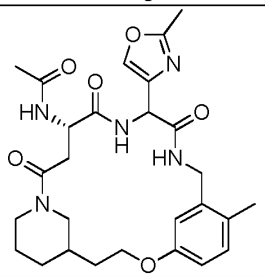
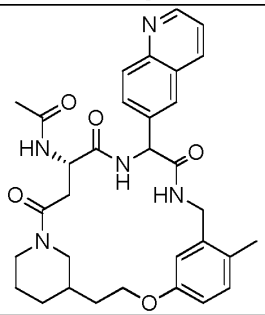
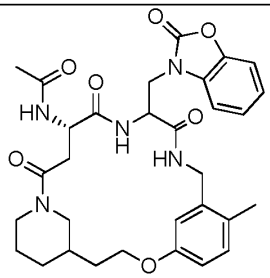
420		tert-butyl (1-(((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)-2,3-dihydro-1H-inden-5-yl)carbamate
421		tert-butyl (3-fluoro-4-(2-(((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)phenyl)carbamate
422		tert-butyl (8-(((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)isoquinolin-3-yl)carbamate
423		tert-butyl (2,6-dichloro-4-(2-(((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)phenyl)carbamate
429		tert-butyl (4-(1-methoxy-2-(((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)phenyl)carbamate

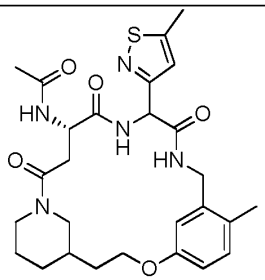
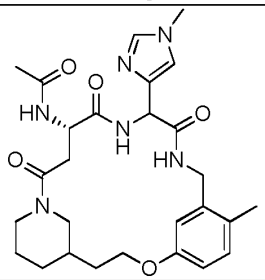
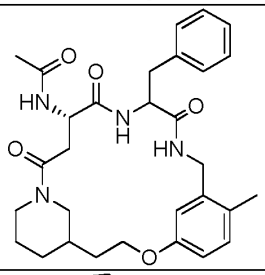
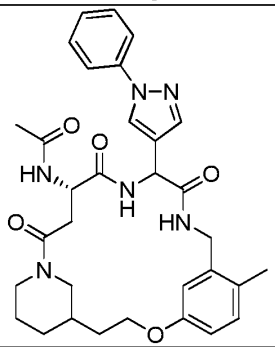
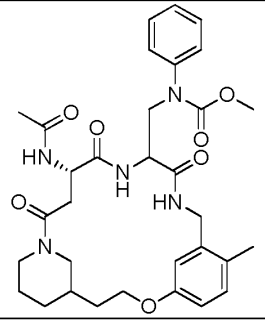
437		((12S)-12-amino-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-4-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-
438		N-((12S)-12-amino-9-(2-(1-acetylpiperidin-4-yl)ethyl)-54-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane
439		tert-butyl (5-(2-(((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-4-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)-1,3,4-thiadiazol-2-yl)carbamate
440		tert-butyl (6-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)naphthalen-2-yl)carbamate
441		tert-butyl (5-(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)-4H-1,2,4-triazol-3-yl)carbamate

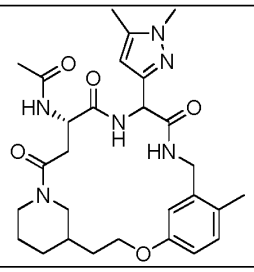
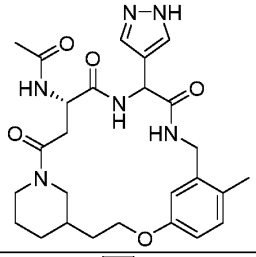
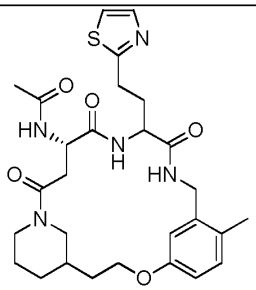
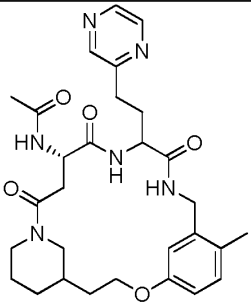
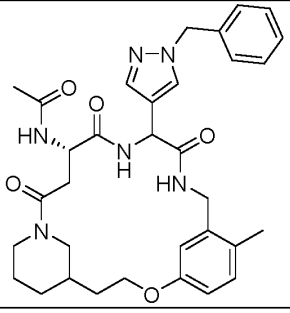
442		tert-butyl (4-(1-ethoxy-2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)phenyl)carbamate
443		tert-butyl (4-(1-(((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-4-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)cyclopropyl)phenyl)carbamate
444		tert-butyl (3-fluoro-4-(2-(((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-4-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)phenyl)carbamate
479		Benzyl ((12S)-5^4-methyl-9-(1-methyl-1H-pyrazol-4-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
480		(12S)-12-amino-5^4-methyl-9-(1-methyl-1H-pyrazol-4-yl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione

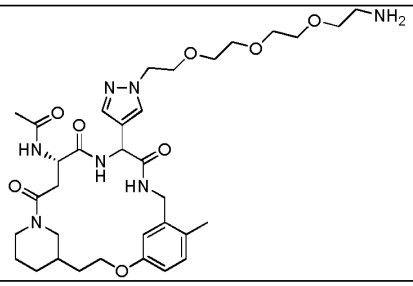
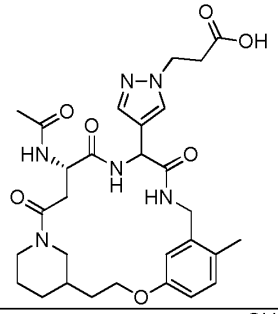
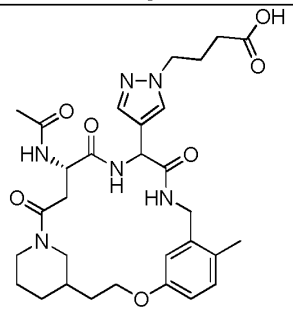
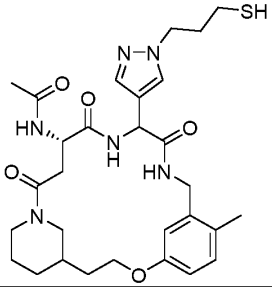
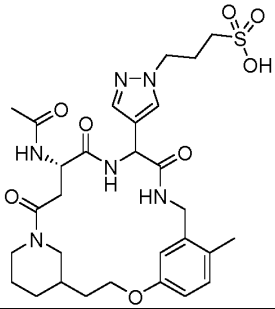
495		5^4-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
503		benzyl ((12S)-9-phenethyl-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
505		benzyl ((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyrido[2,3-b]pyrazin-7-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
509		4-(2-((12S)-12-(((benzyloxy)carbonyl)amino)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-9-yl)ethyl)benzenesulfonic acid
510		benzyl ((12S)-5^4-methyl-9-(4-(3-methyloxetan-3-yl)phenethyl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate

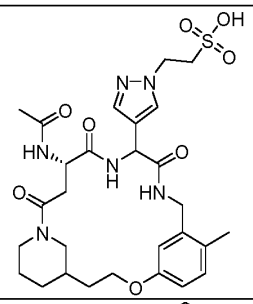
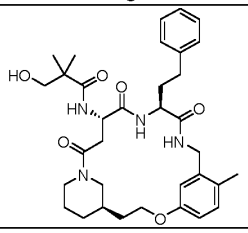
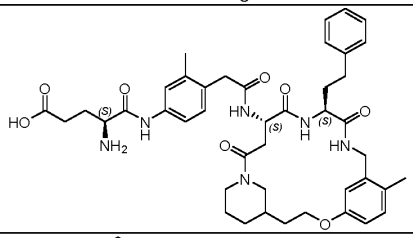
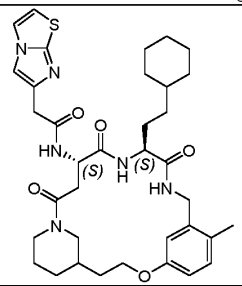
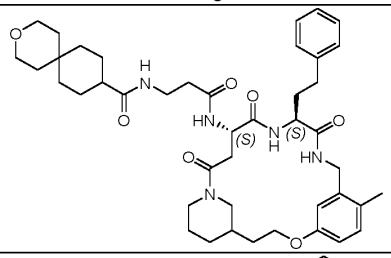
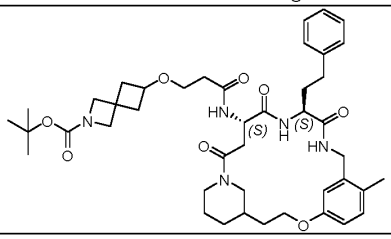
511		benzyl ((12S)-9-(2-(1,5-naphthyridin-3-yl)ethyl)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
512		benzyl ((12S)-5^4-methyl-9-(2-methyloxazol-4-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
513		methyl (((12R)-12-(((benzyloxy)carbonyl)amino)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-9-yl)methyl)(phenyl)carbamate
549		N-((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-3-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
550		N-((12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide

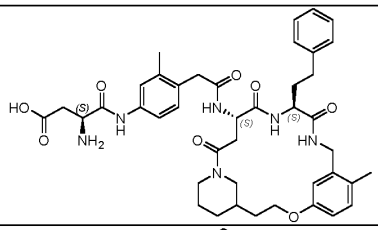
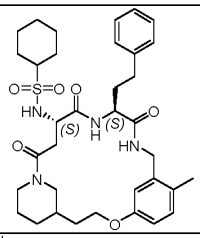
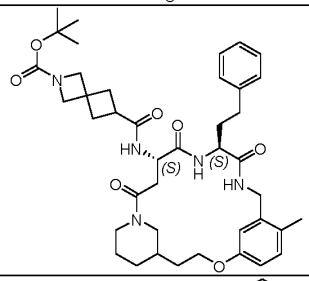
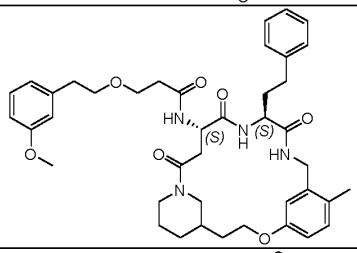
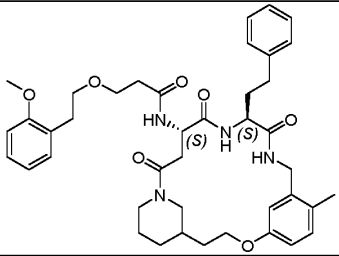
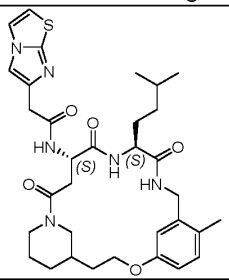
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552		N-((12S)-5^4-methyl-9-(1-methyl-1H-pyrazol-4-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
553		N-((12S)-5^4-methyl-9-(2-methyloxazol-4-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
554		N-((12S)-5^4-methyl-8,11,14-trioxo-9-(quinolin-6-yl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
555		N-((12S)-5^4-methyl-8,11,14-trioxo-9-((2-oxobenzo[d]oxazol-3(2H)-yl)methyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide

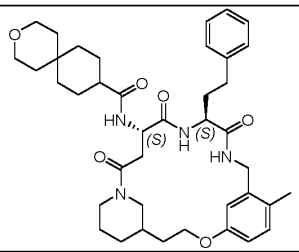
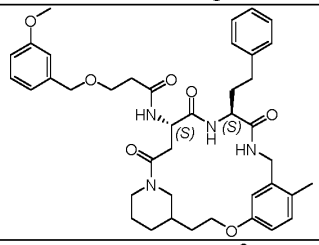
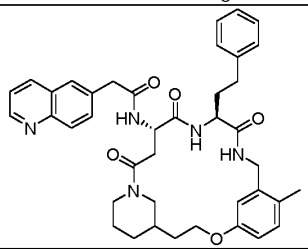
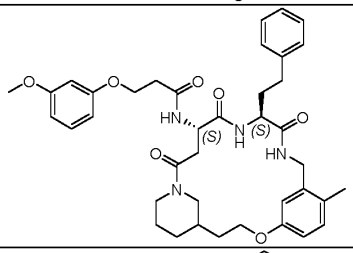
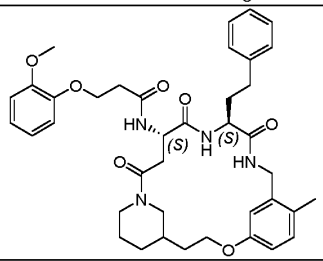
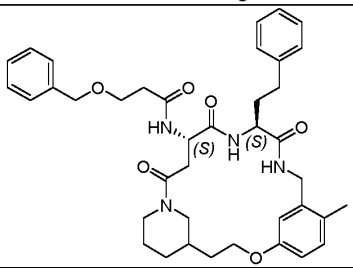
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557		N-((12S)-5^4-methyl-9-(1-methyl-1H-imidazol-4-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
558		N-((12S)-9-benzyl-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
559		N-((12S)-5^4-methyl-8,11,14-trioxo-9-(1-phenyl-1H-pyrazol-4-yl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
560		methyl (((12S)-12-acetamido-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-9-yl)methyl)(phenyl)carbamate

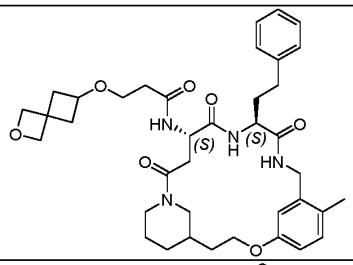
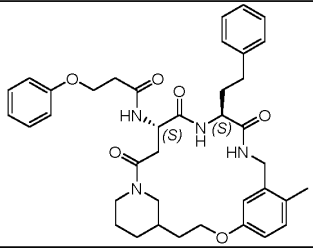
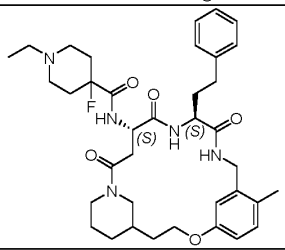
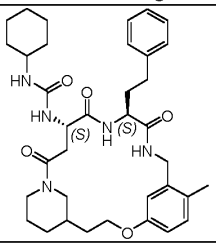
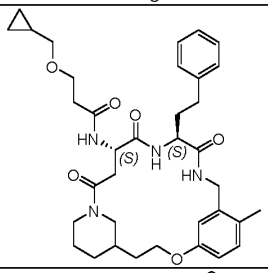
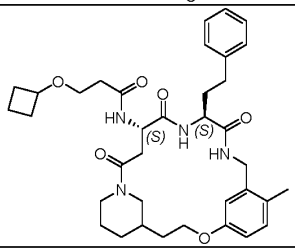
561		N-((12S)-9-(1,5-dimethyl-1H-pyrazol-3-yl)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
562		N-((12S)-5^4-methyl-8,11,14-trioxo-9-(1H-pyrazol-4-yl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
563		N-((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(thiazol-2-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
564		N-((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyrazin-2-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
565		N-((12S)-9-(1-benzyl-1H-pyrazol-4-yl)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide

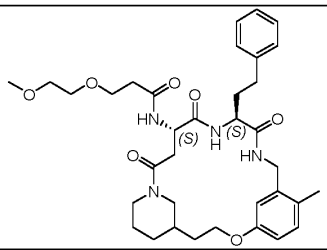
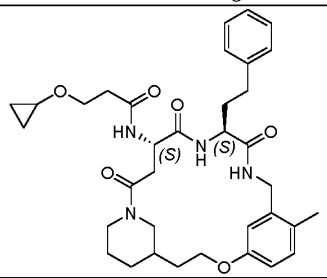
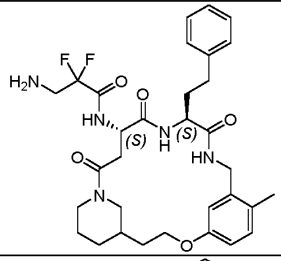
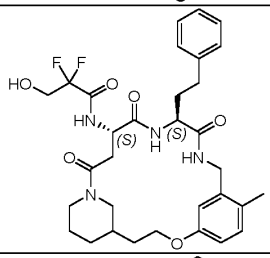
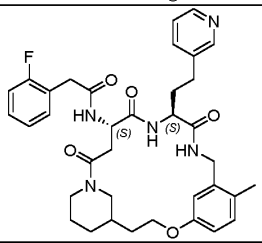
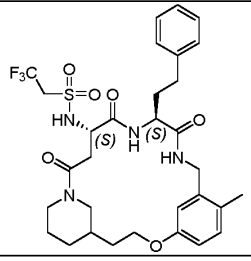
566		N-((12S)-9-(1-(2-(2-(2-(2-aminoethoxy)ethoxy)ethoxy)ethyl)-1H-pyrazol-4-yl)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
567		3-(4-((12S)-12-acetamido-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-9-yl)-1H-pyrazol-1-yl)propanoic acid
568		4-(4-((12S)-12-acetamido-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-9-yl)-1H-pyrazol-1-yl)butanoic acid
570		N-((12S)-9-(1-(3-mercaptopropyl)-1H-pyrazol-4-yl)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
571		3-(4-((12S)-12-acetamido-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-9-yl)-1H-pyrazol-1-yl)propane-1-sulfonic acid

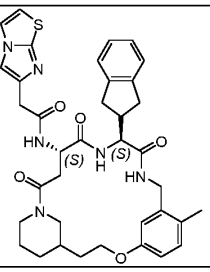
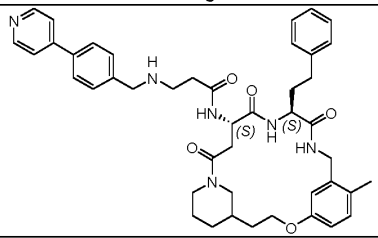
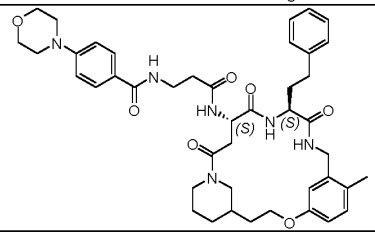
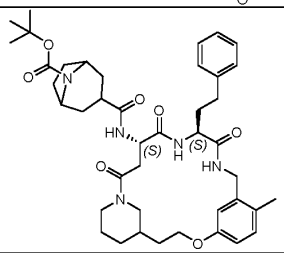
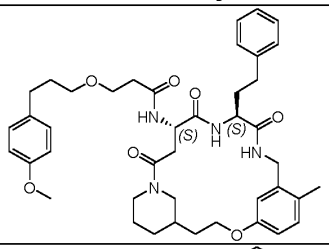
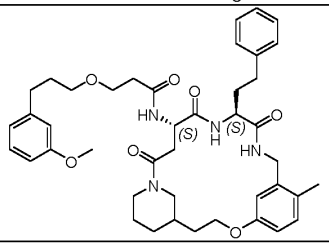
572		N-(4-((12S)-12-acetamido-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-9-yl)-1H-pyrazol-1-yl)ethane-1-sulfonic acid
573		3-hydroxy-2,2-dimethyl-N-((1^{3}R,9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
574		(4S)-4-amino-5-((3-methyl-4-(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)phenyl)amino)-5-oxopentanoic acid
575		N-((9S,12S)-9-(2-cyclohexylethyl)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(imidazo[2,1-b]thiazol-6-yl)acetamide
576		N-(3-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-3-oxopropyl)-3-oxaspiro[5.5]undecane-9-carboxamide
577		tert-butyl 6-(3-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-3-oxopropoxy)-2-azaspiro[3.3]heptane-2-carboxylate

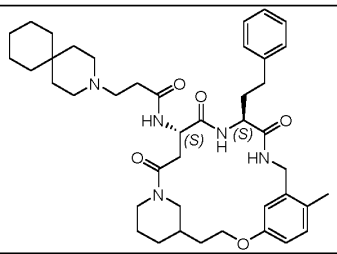
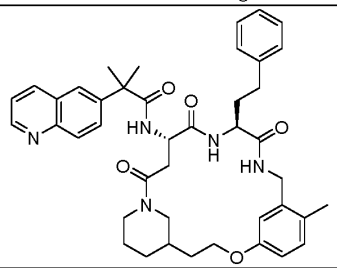
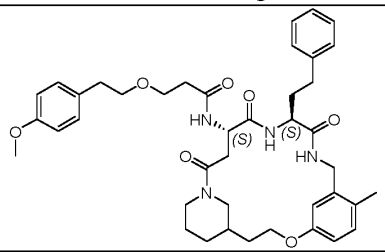
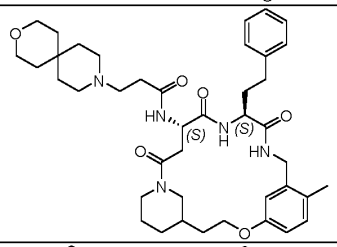
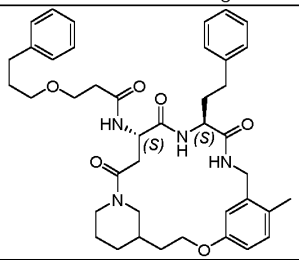
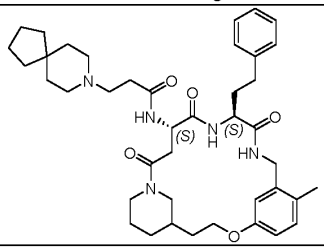
578		(3S)-3-amino-4-((3-methyl-4-(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)phenyl)amino)-4-oxobutanoic acid
579		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)cyclohexanesulfonamide
580		tert-butyl 6-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)-2-azaspiro[3.3]heptane-2-carboxylate
581		3-(3-methoxyphenethoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
582		3-(2-methoxyphenethoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
583		2-(imidazo[2,1-b]thiazol-6-yl)-N-((9S,12S)-9-isopentyl-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide

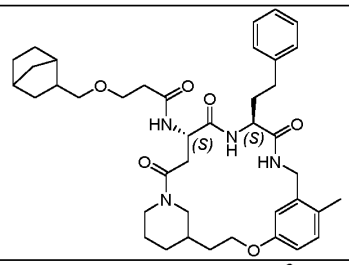
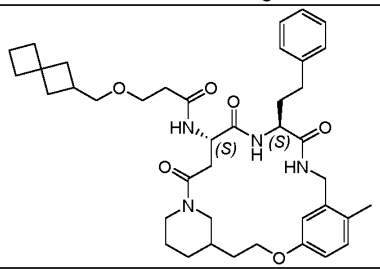
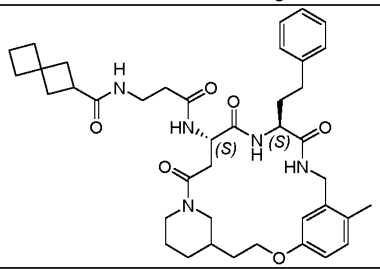
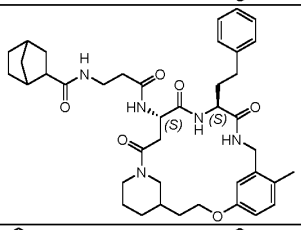
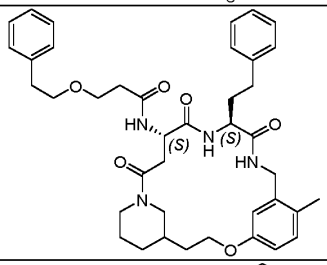
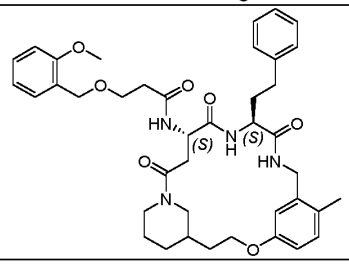
584		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-oxaspiro[5.5]undecane-9-carboxamide
585		3-((3-methoxybenzyl)oxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
586		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(quinolin-6-yl)acetamide
587		3-(3-methoxyphenoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamid
588		3-(2-methoxyphenoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
589		3-(benzyloxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide

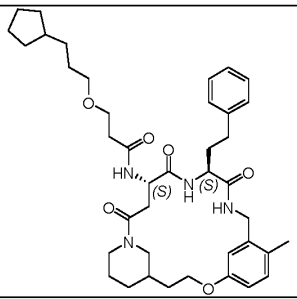
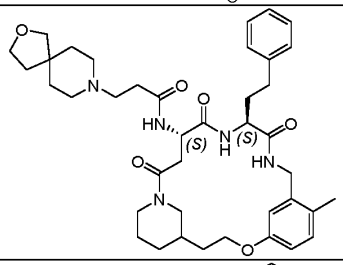
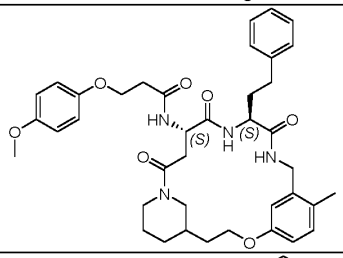
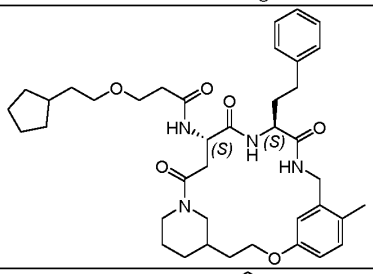
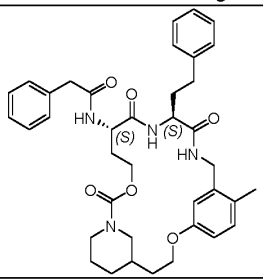
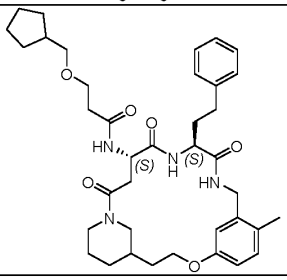
590		3-((2-oxaspiro[3.3]heptan-6-yl)oxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
591		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-phenoxypropanamide
592		1-ethyl-4-fluoro-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)piperidine-4-carboxamide
593		1-cyclohexyl-3-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)urea
594		3-(cyclopropylmethoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
595		3-cyclobutoxy-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide

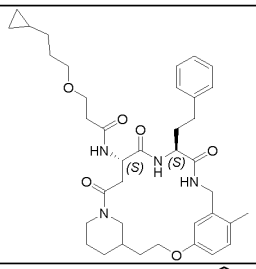
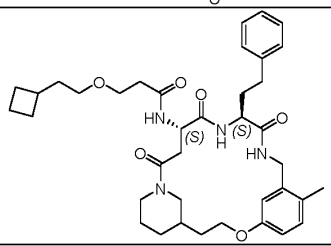
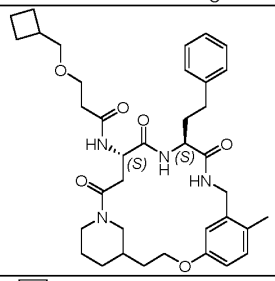
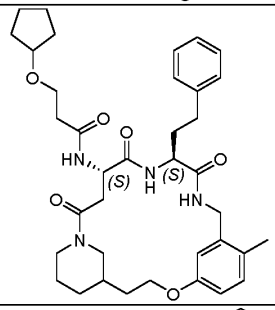
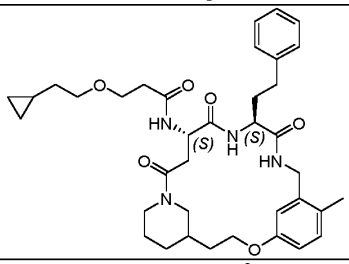
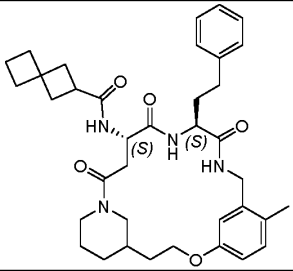
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597		3-cyclopropoxy-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
598		3-amino-2,2-difluoro-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
599		2,2-difluoro-3-hydroxy-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
600		2-(2-fluorophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-3-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
601		2,2,2-trifluoro-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)ethane-1-sulfonamide

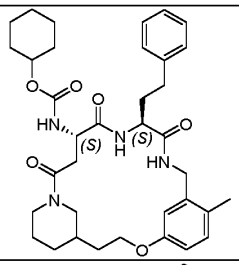
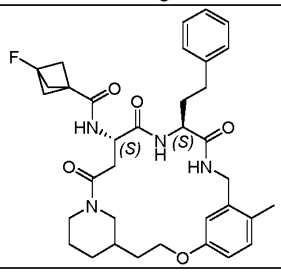
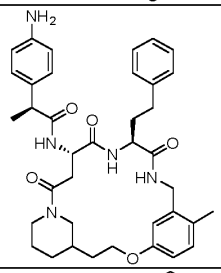
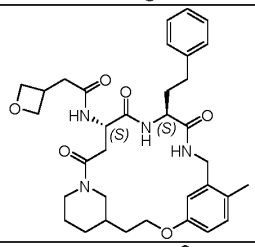
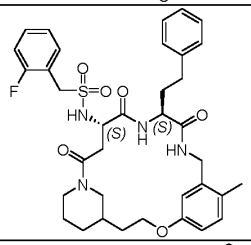
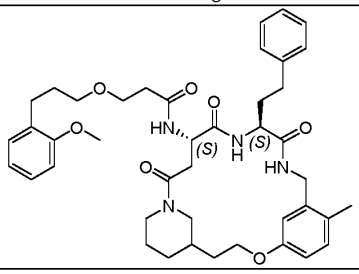
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603		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-((4-(pyridin-4-yl)benzyl)amino)propanamide
604		N-(3-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-3-oxopropyl)-4-morpholinobenzamide
605		tert-butyl 3-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)-8-azabicyclo[3.2.1]octane-8-carboxylate
606		3-(3-(4-methoxyphenyl)propoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
607		3-(3-(3-methoxyphenyl)propoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide

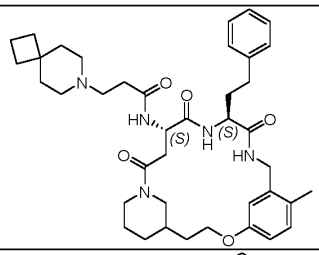
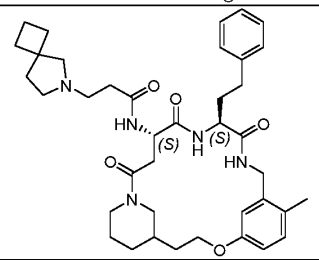
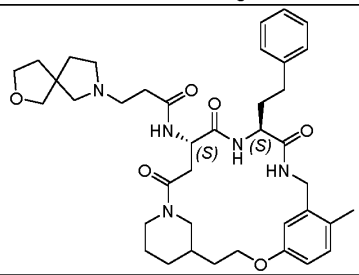
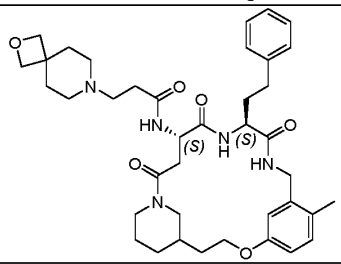
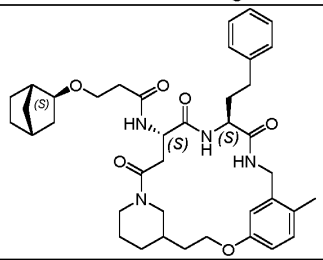
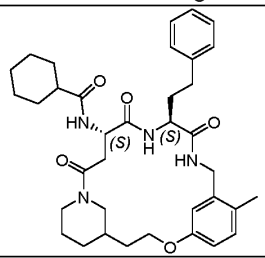
608		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(3-azaspiro[5.5]undecan-3-yl)propanamide
609		2-methyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(quinolin-6-yl)propanamide
610		3-(4-methoxyphenethoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
611		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(3-oxa-9-azaspiro[5.5]undecan-9-yl)propanamide
612		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(3-phenylpropoxy)propanamide
613		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(8-azaspiro[4.5]decan-8-yl)propanamide

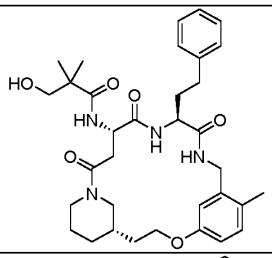
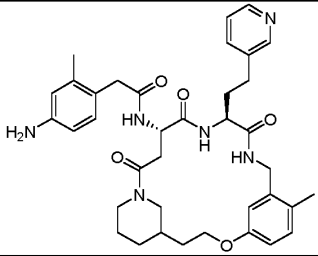
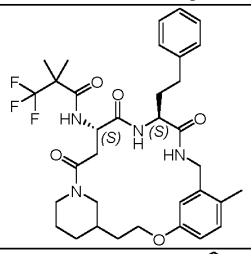
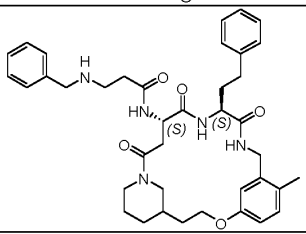
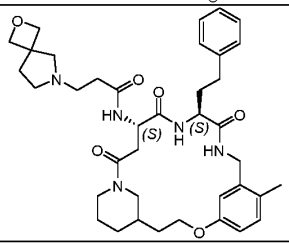
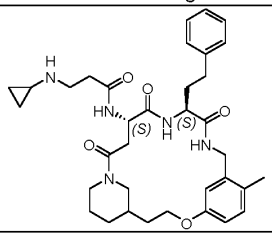
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615		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(spiro[3.3]heptan-2-ylmethoxy)propanamide
616		N-(3-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-3-oxopropyl)spiro[3.3]heptane-2-carboxamide
617		N-(3-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-3-oxopropyl)bicyclo[2.2.1]heptane-2-carboxamide
618		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-phenethoxypropanamide
619		3-((2-methoxybenzyl)oxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide

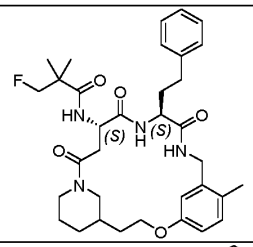
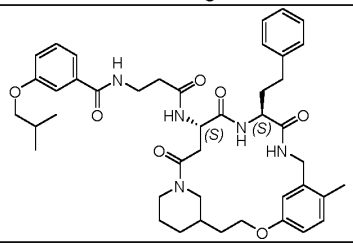
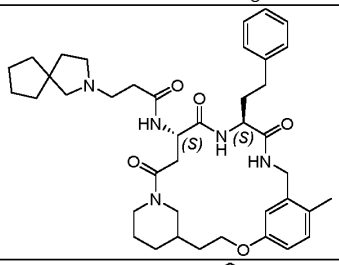
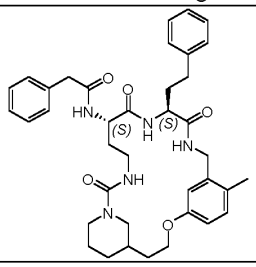
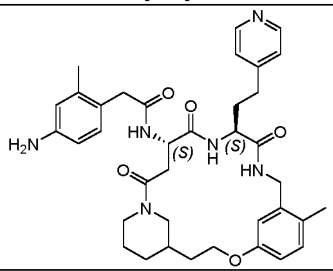
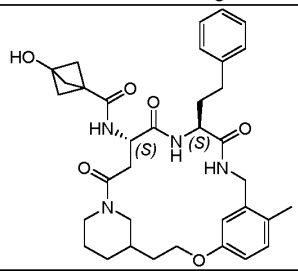
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621		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(2-oxa-8-azaspiro[4.5]decan-8-yl)propanamide
622		3-(4-methoxyphenoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
623		3-(2-cyclopentylethoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
624		N-((9S,12S)-5^4-methyl-8,11,16-trioxo-9-phenethyl-4,15-dioxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclohexadecaphane-12-yl)-2-phenylacetamide
625		3-(cyclopentylmethoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide

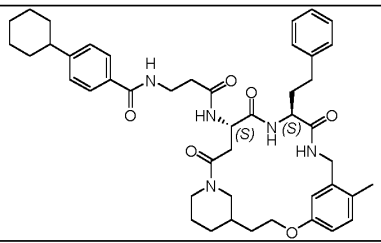
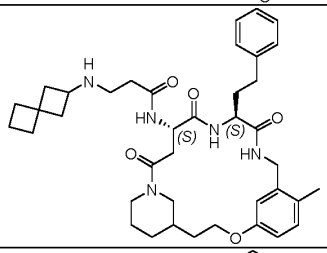
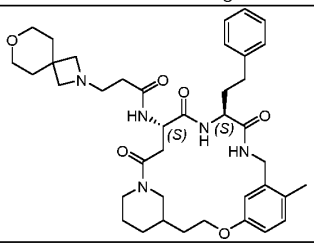
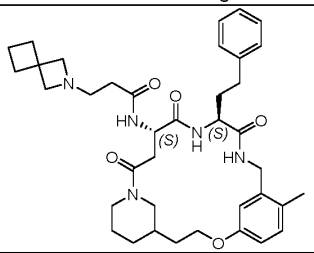
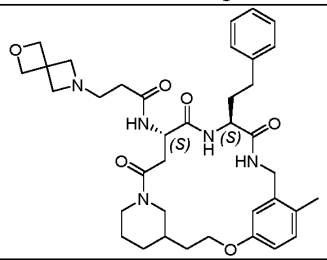
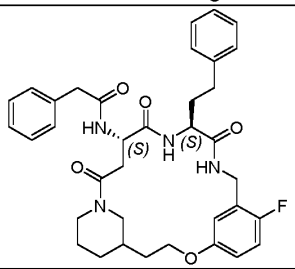
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627		3-(2-cyclobutylethoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
628		3-(cyclobutylmethoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
629		3-(cyclopentyloxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
630		3-(2-cyclopropylethoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
631		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)spiro[3.3]heptane-2-carboxamide

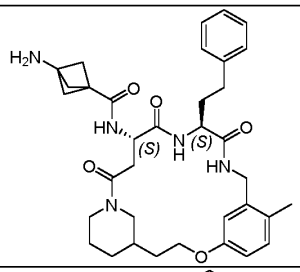
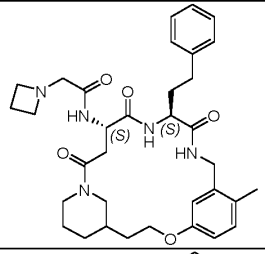
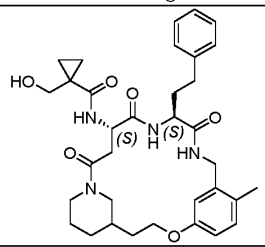
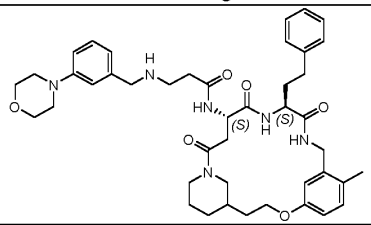
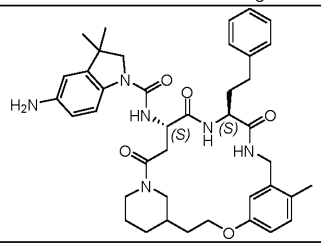
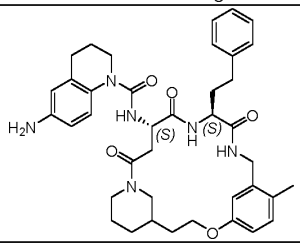
632		cyclohexyl ((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
633		3-fluoro-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)bicyclo[1.1.1]pentane-1-carboxamide
634		(2S)-2-(4-aminophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
635		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(oxetan-3-yl)acetamide
636		1-(2-fluorophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)methanesulfonamide
637		3-(3-(2-methoxyphenyl)propoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide

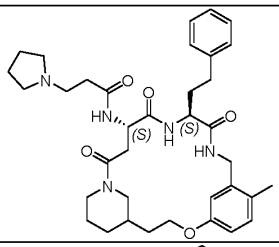
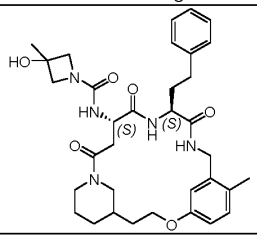
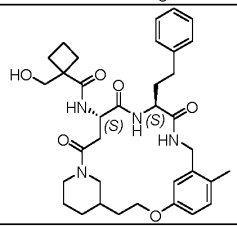
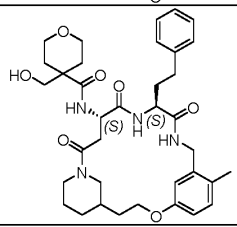
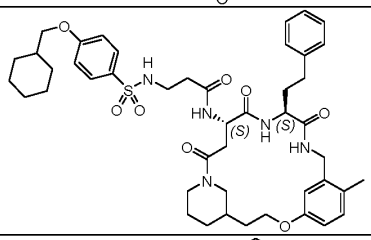
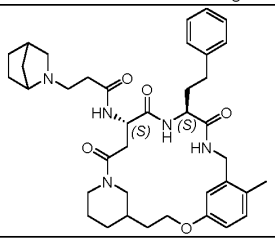
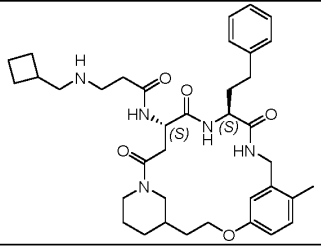
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639		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(6-azaspiro[3.4]octan-6-yl)propanamide
640		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(2-oxa-7-azaspiro[4.4]nonan-7-yl)propanamide
641		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(2-oxa-7-azaspiro[3.5]nonan-7-yl)propanamide
642		3-(((1S,2S,4R)-bicyclo[2.2.1]heptan-2-yl)oxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
643		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)cyclohexanecarboxamide

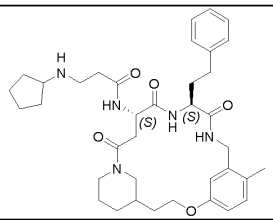
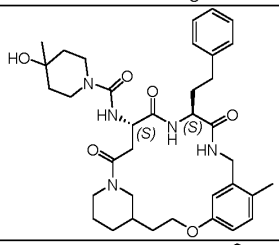
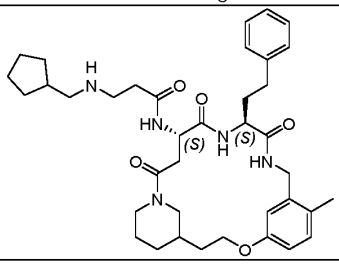
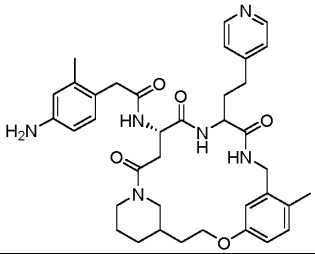
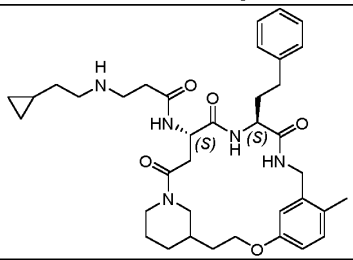
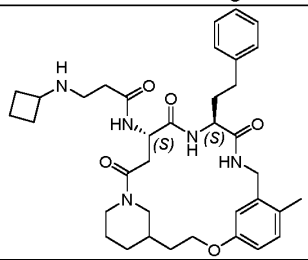
644		3-hydroxy-2,2-dimethyl-N-((1^{3}S,9S,12S)-5^{4}-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
645		2-(4-amino-2-methylphenyl)-N-((9S,12S)-5^{4}-methyl-8,11,14-trioxo-9-(2-(pyridin-3-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
646		3,3,3-trifluoro-2,2-dimethyl-N-((9S,12S)-5^{4}-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
647		3-(benzylamino)-N-((9S,12S)-5^{4}-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
648		N-((9S,12S)-5^{4}-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(2-oxa-6-azaspiro[3.4]octan-6-yl)propanamide
649		3-(cyclopropylamino)-N-((9S,12S)-5^{4}-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide

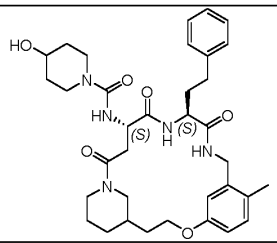
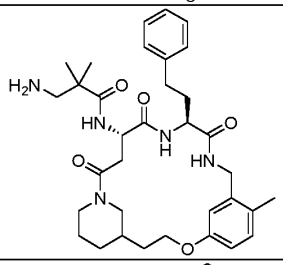
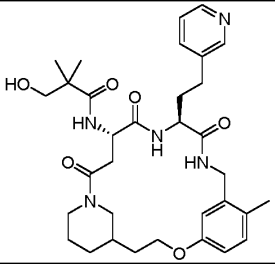
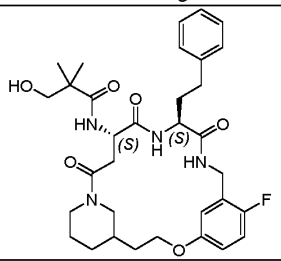
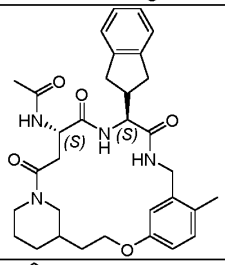
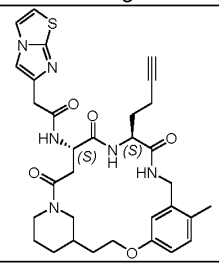
650		3-fluoro-2,2-dimethyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
651		3-isobutoxy-N-(3-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-3-oxopropyl)benzamide
652		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(2-azaspiro[4.4]nonan-2-yl)propanamide
653		N-((9S,12S)-5^4-methyl-8,11,16-trioxo-9-phenethyl-4-oxa-7,10,15-triaza-1(3,1)-piperidina-5(1,3)-benzenacyclohexadecaphane-12-yl)-2-phenylacetamide
654		2-(4-amino-2-methylphenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-4-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
655		3-hydroxy-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)bicyclo[1.1.1]pentane-1-carboxamide

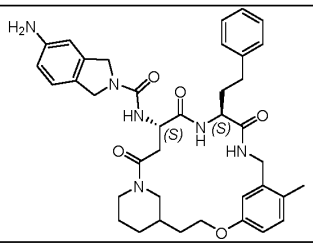
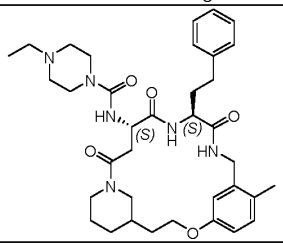
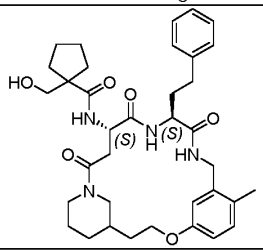
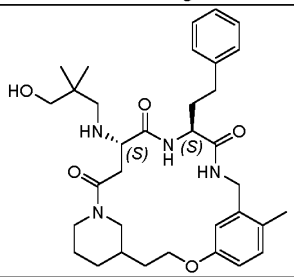
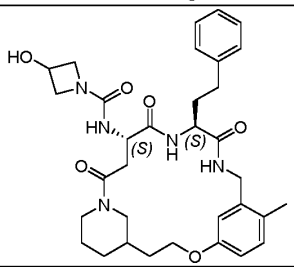
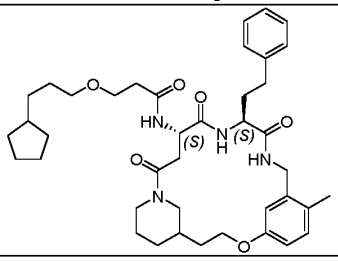
656		4-cyclohexyl-N-(3-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-3-oxopropyl)benzamide
657		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(spiro[3.3]heptan-2-ylamino)propanamide
658		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(7-oxa-2-azaspiro[3.5]nonan-2-yl)propanamide
659		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(2-azaspiro[3.3]heptan-2-yl)propanamide
660		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(2-oxa-6-azaspiro[3.3]heptan-6-yl)propanamide
661		N-((9S,12S)-5^4-fluoro-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-phenylacetamide

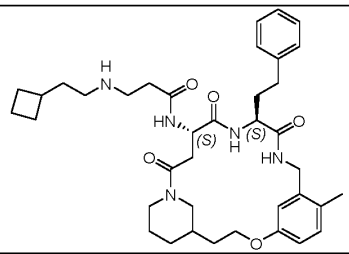
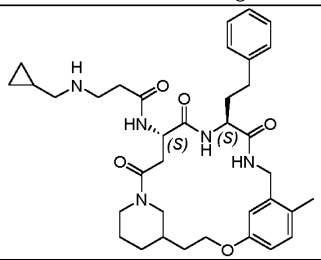
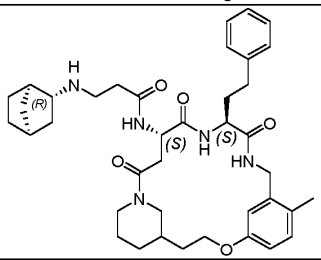
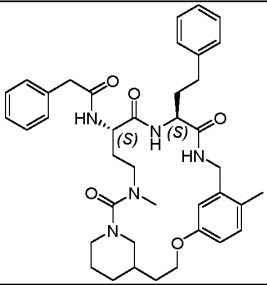
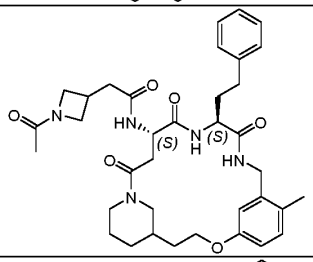
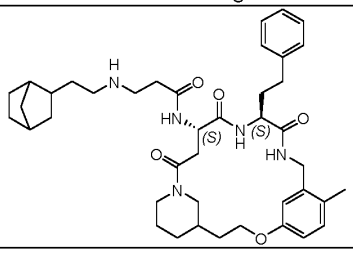
662		3-amino-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)bicyclo[1.1.1]pentane-1-carboxamide
663		2-(azetidin-1-yl)-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
664		1-(hydroxymethyl)-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)cyclopropane-1-carboxamide
665		N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-((3-morpholinobenzyl)amino)propanamide
666		5-amino-3,3-dimethyl-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)indoline-1-carboxamide
667		6-amino-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3,4-dihydroquinoline-1(2H)-carboxamide

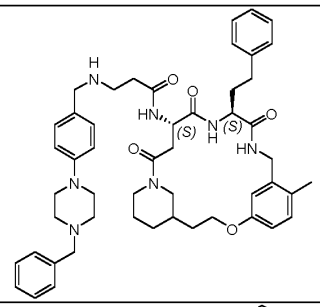
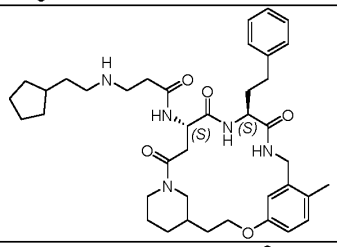
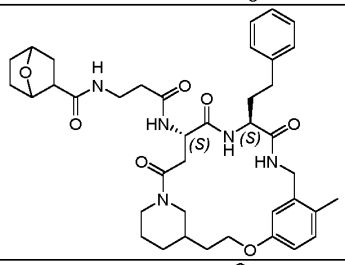
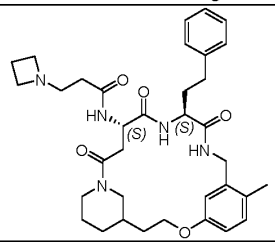
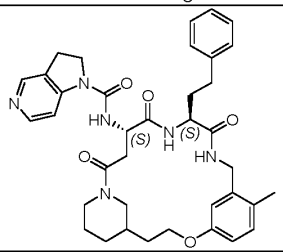
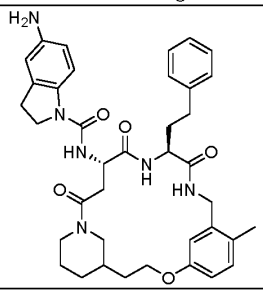
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669		3-hydroxy-3-methyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)azetidine-1-carboxamide
670		1-(hydroxymethyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)cyclobutane-1-carboxamide
671		4-(hydroxymethyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)tetrahydro-2H-pyran-4-carboxamide
672		3-((4-(cyclohexylmethoxy)phenyl)sulfonamido)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
673		3-(2-azabicyclo[2.2.1]heptan-2-yl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
674		3-((cyclobutylmethyl)amino)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide

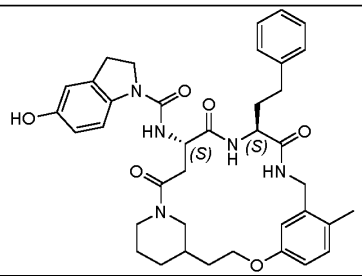
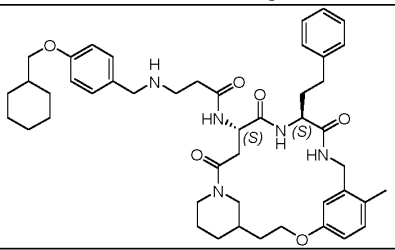
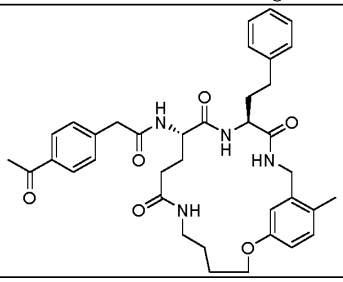
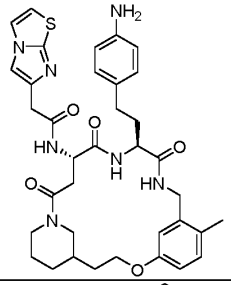
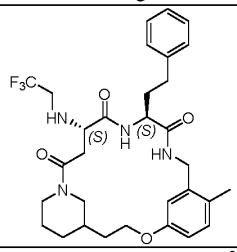
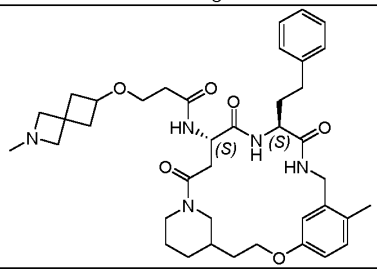
675		3-(cyclopentylamino)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
676		4-hydroxy-4-methyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)piperidine-1-carboxamide
677		3-((cyclopentylmethyl)amino)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
678		2-(4-amino-2-methylphenyl)-N-((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-4-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
679		3-((2-cyclopropylethyl)amino)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
680		3-(cyclobutylamino)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide

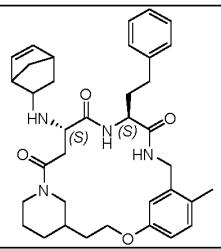
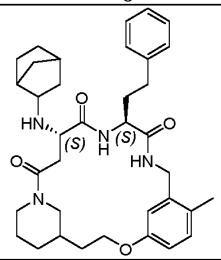
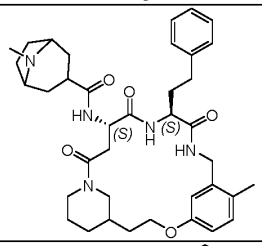
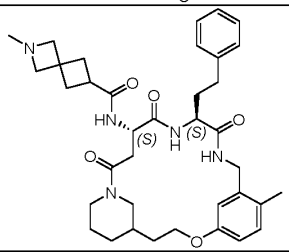
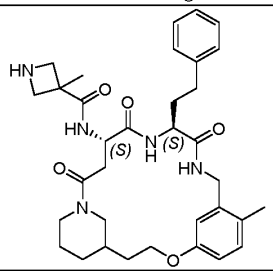
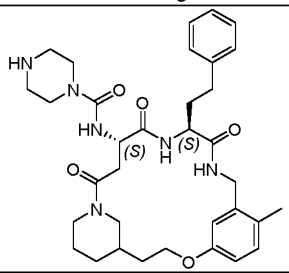
681		4-hydroxy-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)piperidine-1-carboxamide
682		3-amino-2,2-dimethyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
683		3-hydroxy-2,2-dimethyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-3-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
684		N-((9S,12S)-5^4-fluoro-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-hydroxy-2,2-dimethylpropanamide
685		N-((9S,12S)-9-(2,3-dihydro-1H-inden-2-yl)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
686		N-((9S,12S)-9-(but-3-yn-1-yl)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(imidazo[2,1-b]thiazol-6-yl)acetamide

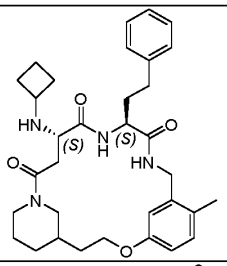
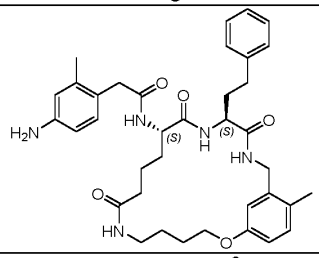
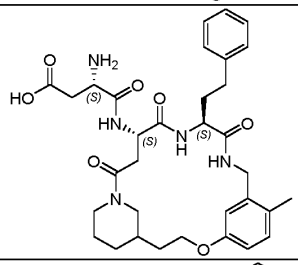
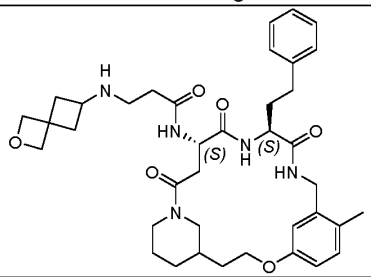
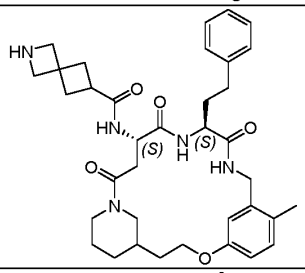
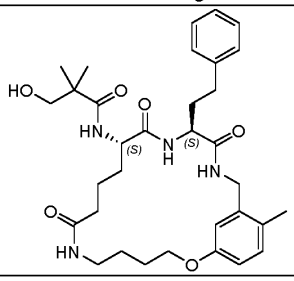
687		5-amino-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)isoindoline-2-carboxamide
688		4-ethyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)piperazine-1-carboxamide
689		1-(hydroxymethyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)cyclopentane-1-carboxamide
690		(9S,12S)-12-((3-hydroxy-2,2-dimethylpropyl)amino)-5^4-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
691		3-hydroxy-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)azetidine-1-carboxamide
692		3-(3-cyclopentylpropoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide

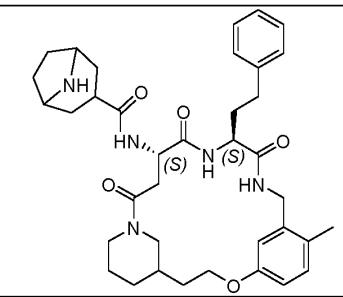
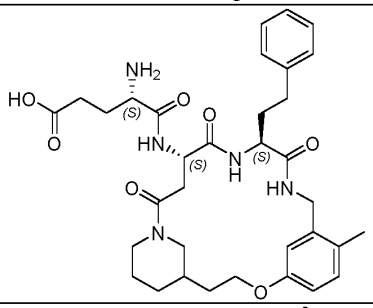
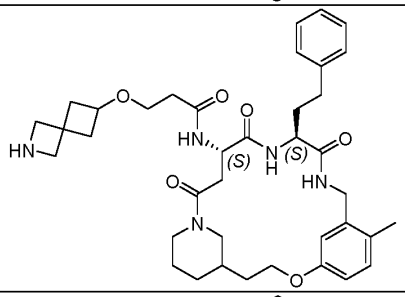
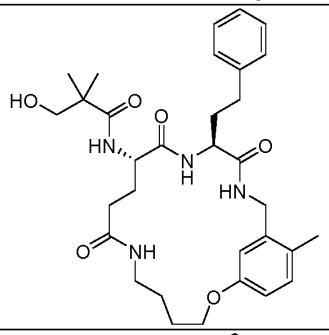
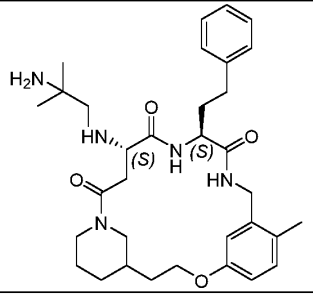
693		3-((2-cyclobutylethyl)amino)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
694		3-((cyclopropylmethyl)amino)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
695		3-(((1R,2R,4S)-bicyclo[2.2.1]heptan-2-yl)amino)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
696		N-((9S,12S)-5^4,15-dimethyl-8,11,16-trioxo-9-phenethyl-4-oxa-7,10,15-triaza-1(3,1)-piperidina-5(1,3)-benzenacyclohexadecaphane-12-yl)-2-phenylacetamide
697		2-(1-acetylazetidin-3-yl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
698		3-((2-(bicyclo[2.2.1]heptan-2-yl)ethyl)amino)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide

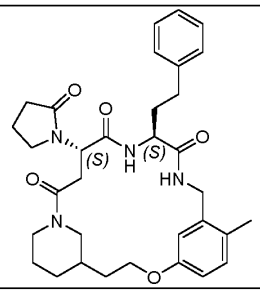
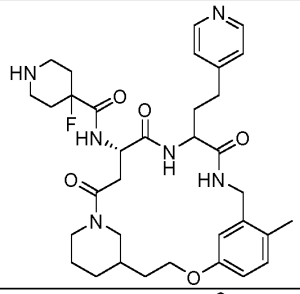
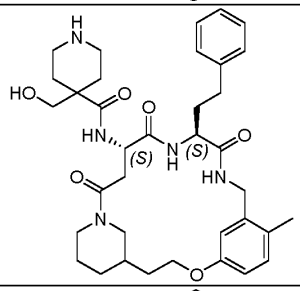
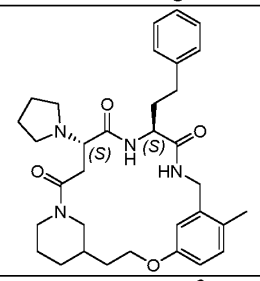
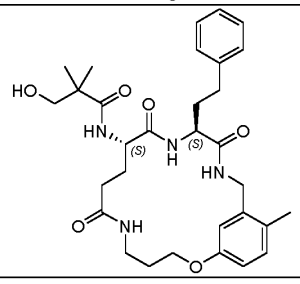
699		3-((4-(4-benzylpiperazin-1-yl)benzyl)amino)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
700		3-((2-cyclopentylethyl)amino)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
701		N-(3-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-3-oxopropyl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide
702		3-(azetidin-1-yl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
703		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2,3-dihydro-1H-pyrrolo[3,2-c]pyridine-1-carboxamide
704		5-amino-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)indoline-1-carboxamide

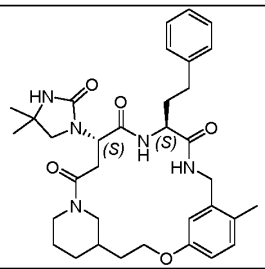
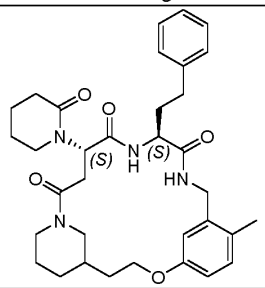
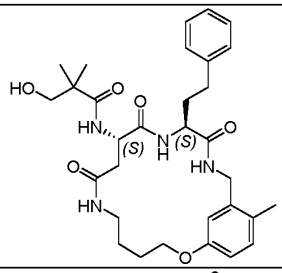
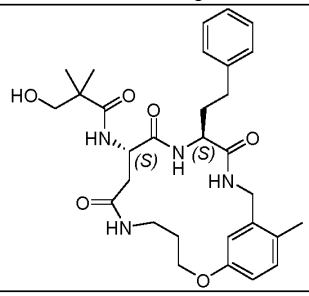
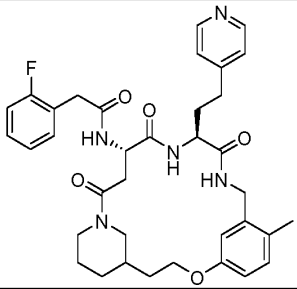
705		5-hydroxy-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)indoline-1-carboxamide
706		3-((4-(cyclohexylmethoxy)benzyl)amino)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
707		2-(4-acetylphenyl)-N-((11S,14S)-14-methyl-8,12,15-trioxo-1^4-phenethyl-2-oxa-7,13,16-triaza-1(1,3)-benzenacycloheptadecaphane-11-yl)acetamide
708		N-((9S,12S)-9-(4-aminophenethyl)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(imidazo[2,1-b]thiazol-6-yl)acetamide
709		(9S,12S)-5^4-methyl-9-phenethyl-12-((2,2,2-trifluoroethyl)amino)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
710		3-((2-methyl-2-azaspiro[3.3]heptan-6-yl)oxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide

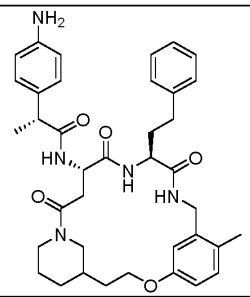
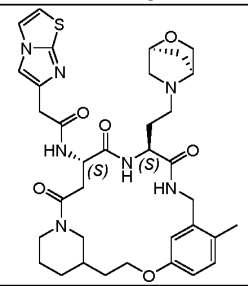
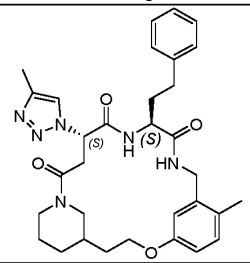
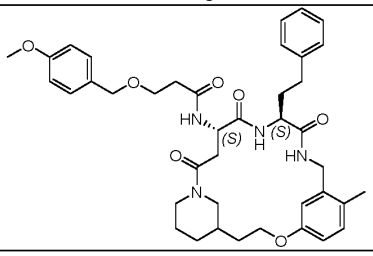
711		(9S,12S)-12-(bicyclo[2.2.1]hept-5-en-2-ylamino)-5^4-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
712		(9S,12S)-12-(bicyclo[2.2.1]heptan-2-ylamino)-5^4-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
713		8-methyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-8-azabicyclo[3.2.1]octane-3-carboxamide
714		2-methyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-azaspiro[3.3]heptane-6-carboxamide
715		3-methyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)azetidine-3-carboxamide
716		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)piperazine-1-carboxamide

717		(9S,12S)-12-(cyclobutylamino)-5^4-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
718		2-(4-amino-2-methylphenyl)-N-((12S,15S)-1^4-methyl-8,13,16-trioxo-15-phenethyl-2-oxa-7,14,17-triaza-1(1,3)-benzenacyclooctadecaphane-12-yl)acetamide
719		(3S)-3-amino-4-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-4-oxobutanoic acid
720		3-((2-oxaspiro[3.3]heptan-6-yl)amino)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
721		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-azaspiro[3.3]heptane-6-carboxamide
722		3-hydroxy-2,2-dimethyl-N-((12S,15S)-1^4-methyl-8,13,16-trioxo-15-phenethyl-2-oxa-7,14,17-triaza-1(1,3)-benzenacyclooctadecaphane-12-yl)propanamide

723		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-8-azabicyclo[3.2.1]octane-3-carboxamide
724		(4S)-4-amino-5-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-5-oxopentanoic acid
725		3-((2-azaspiro[3.3]heptan-6-yl)oxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
726		3-hydroxy-2,2-dimethyl-N-((11S,14S)-1^4-methyl-8,12,15-trioxo-14-phenethyl-2-oxa-7,13,16-triaza-1(1,3)-benzenacycloheptadecaphane-11-yl)propanamide
727		(9S,12S)-12-((2-amino-2-methylpropyl)amino)-5^4-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione

728		(9S,12S)-5^4-methyl-12-(2-oxopyrrolidin-1-yl)-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
729		4-fluoro-N-((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-4-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)piperidine-4-carboxamide
730		4-(hydroxymethyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)piperidine-4-carboxamide
731		(9S,12S)-5^4-methyl-9-phenethyl-12-(pyrrolidin-1-yl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
732		3-hydroxy-2,2-dimethyl-N-((10S,13S)-1^4-methyl-7,11,14-trioxo-13-phenethyl-2-oxa-6,12,15-triaza-1(1,3)-benzenacyclohexadecaphane-10-yl)propanamide

733		(9S,12S)-12-(4,4-dimethyl-2-oxoimidazolidin-1-yl)-5^4-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
734		(9S,12S)-5^4-methyl-12-(2-oxopiperidin-1-yl)-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
735		3-hydroxy-2,2-dimethyl-N-((10S,13S)-1^4-methyl-8,11,14-trioxo-13-phenethyl-2-oxa-7,12,15-triaza-1(1,3)-benzenacyclohexadecaphane-10-yl)propanamide
736		3-hydroxy-2,2-dimethyl-N-((9S,12S)-1^4-methyl-7,10,13-trioxo-12-phenethyl-2-oxa-6,11,14-triaza-1(1,3)-benzenacyclopentadecaphane-9-yl)propanamide
737		2-(2-fluorophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-4-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide

738		(2R)-2-(4-aminophenyl)-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
739		N-((9S,12S)-9-(2-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)ethyl)-5[4]-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(imidazo[2,1-b]thiazol-6-yl)acetamide
740		(9S,12S)-5[4]-methyl-12-(4-methyl-1H-1,2,3-triazol-1-yl)-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
741		3-((4-methoxybenzyl)oxy)-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide

or an enantiomer, a stereoisomeric form, a mixture of enantiomers, a diastereomer, a mixture of diastereomers, a hydrate, a solvate, an acid salt form, a tautomer, a racemate of the above mentioned compounds, or a pharmaceutically acceptable salts thereof.

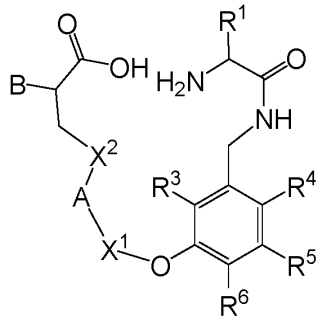
Syntheses of compounds

The compound of formula (**I**) is prepared by reference to the methods illustrated in the following schemes 1-3 by suitable selection of reagents with appropriate substitutions. Solvents, temperatures, pressures, and other reaction conditions may readily be selected

by one of ordinary skill in the art. Starting materials are commercially available or readily prepared by one of ordinary skill in the art.

Another aspect of the present invention is directed to a method for producing the compound of the formula (**I**) comprising:

Step 1A: providing an intermediate compound (**I-1***):

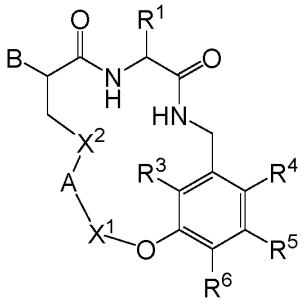


(**I-1***)

wherein

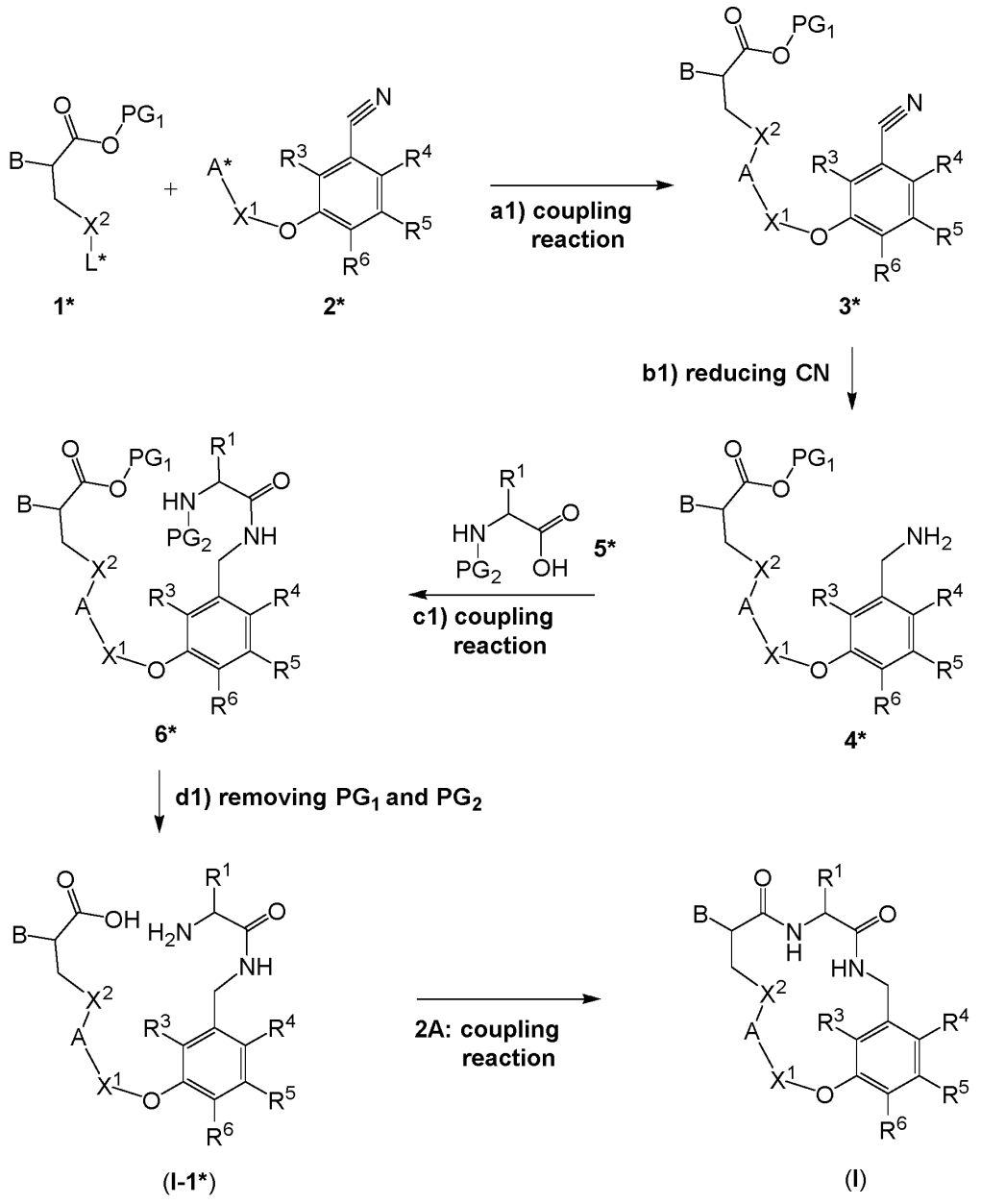
A, **B**, $\mathbf{R^1}$, $\mathbf{R^3}$, $\mathbf{R^4}$, $\mathbf{R^5}$, $\mathbf{R^6}$, $\mathbf{X^1}$, and $\mathbf{X^2}$ have the same meanings as defined in the formula (**I**);

Step 2A: performing an intramolecular amide coupling reaction between a carboxylic acid group and an amine group of the intermediate compound (**I-1***) to obtain the compound of the formula (**I**)



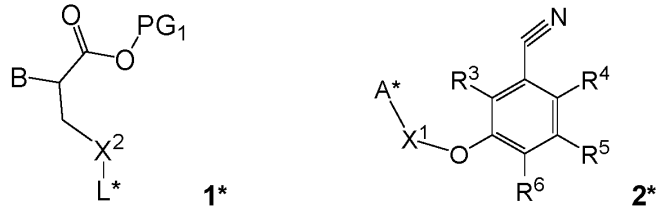
(**I**)

Scheme 1

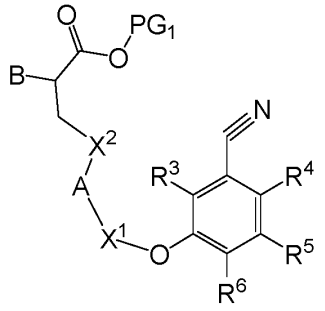


Optionally, the intermediate compound (**I-1***) of **Step 1A** is prepared by **Step 1A´**. **Step1A´** comprises the following steps **a1)** to **d1)**:

a1) performing a coupling reaction between a compound **1*** and a compound **2***

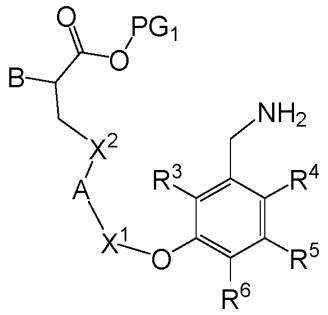


to obtain a compound **3***



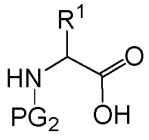
3*

b1) reducing a nitril (-CN) group of the compound **3*** to an aminomethyl ($-CH_2NH_2$) group to obtain a compound **4***



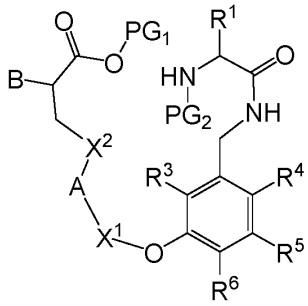
4*

c1) performing a coupling reaction between the compound **4*** and a compound **5***



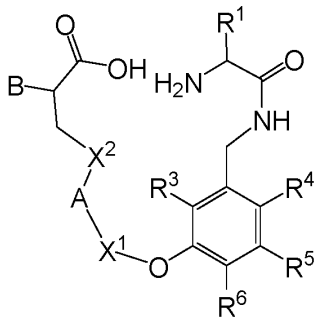
5*

to obtain a compound **6***



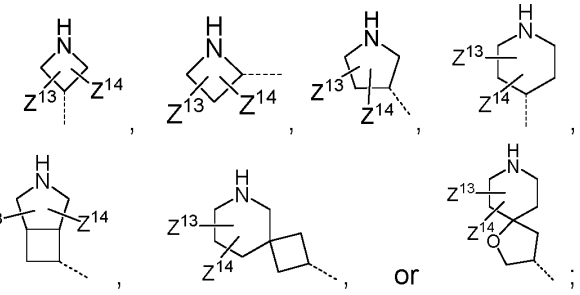
6*

d1) removing a carboxyl protecting group PG_1 and an amine protecting group PG_2 to obtain a compound (**I-1***)



(**I-1***),

wherein

A* represents –NH(**R**^{N6})–, 

or ;

L* represents –CO_2H;

PG$_1$ represents a carboxyl protecting group;

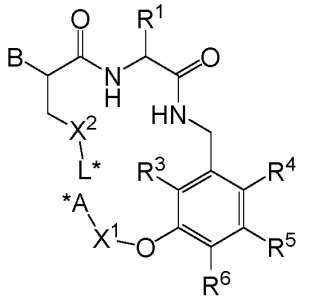
PG$_2$ represents an amine protecting group;

and **A**, **B**, **R^1**, **R^3**, **R^4**, **R^5**, **R^6** , **R^{N6}**, **X^1**, **X^2**, **Z^{13}**, and **Z^{14}** have the same meanings as defined in the formula (**I**).

Thus, the method for producing the compound of the formula (I) may comprise **Step 1A´**, **Step 1A**, and **Step 2A**.

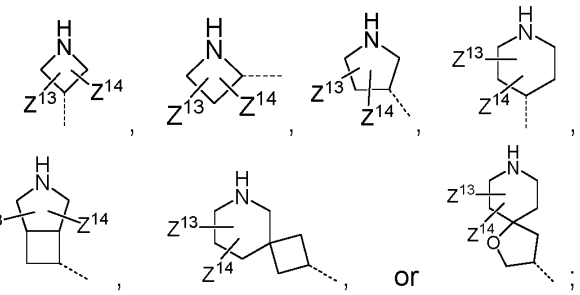
Alternatively, the compound of the formula (I) is produced by the following method and thus the present invention refers to a method for producing the compound of the formula (**I**) comprising:

Step 1B: providing an intermediate compound (**I-2***):



(**I-2***)

wherein

A* represents –NH(R^{N6})–, 

L* represents –CO_2H,

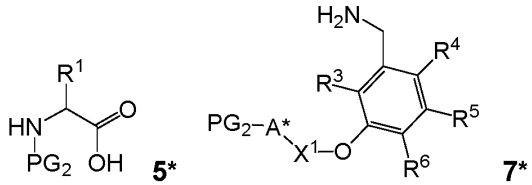
and **B**, R^1, R^3, R^4, R^5, R^6, R^{N6}, X^1, X^2, Z^{13}, and Z^{14} have the same meanings as defined in the formula (**I**);

Step 2B: perform an intramolecular amide coupling reaction between the **L*** and an amino group of **A*** moiety of the intermediated compound (**I-2***) to obtain the compound of the formula (**I**).

Optionally, the intermediate compound (**I-2***) of **Step 1B** is prepared by **Step 1B´**.

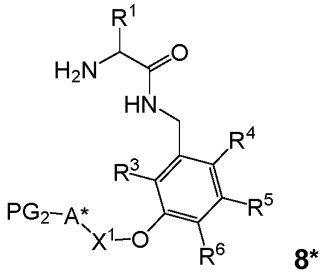
Step1B´ comprises the following steps **a2)** to **c2)**:

a2) performing a coupling reaction between a compound **5*** and a compound **7***



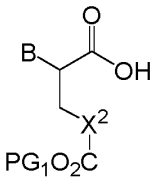
5* **7***

to obtain a compound **8***



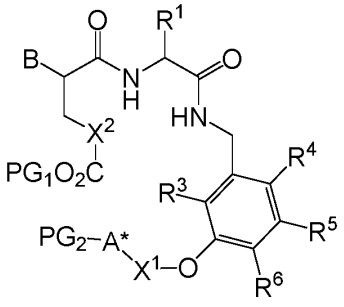
8*

b2) perfoming a coupling reaction between the compound **8*** and a compound **1a***



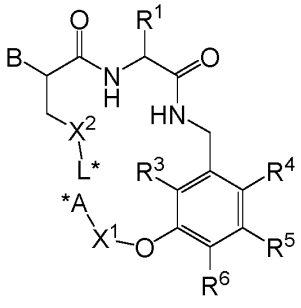
1a*

to obtain a compound **12***



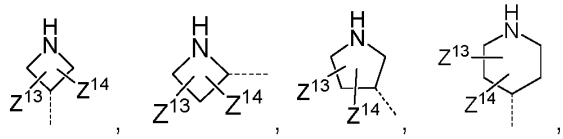
12*

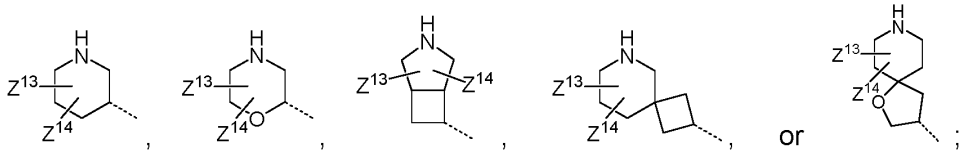
c2) removing a carboxyl protecting group PG_1 and an amine protecting group PG_2 of the compound **12*** to obtain a compound (**I-2***)



(**I-2***),

wherein

A* represents –NH(**R**^{N6})–, 



L* represents $-CO_2H$,

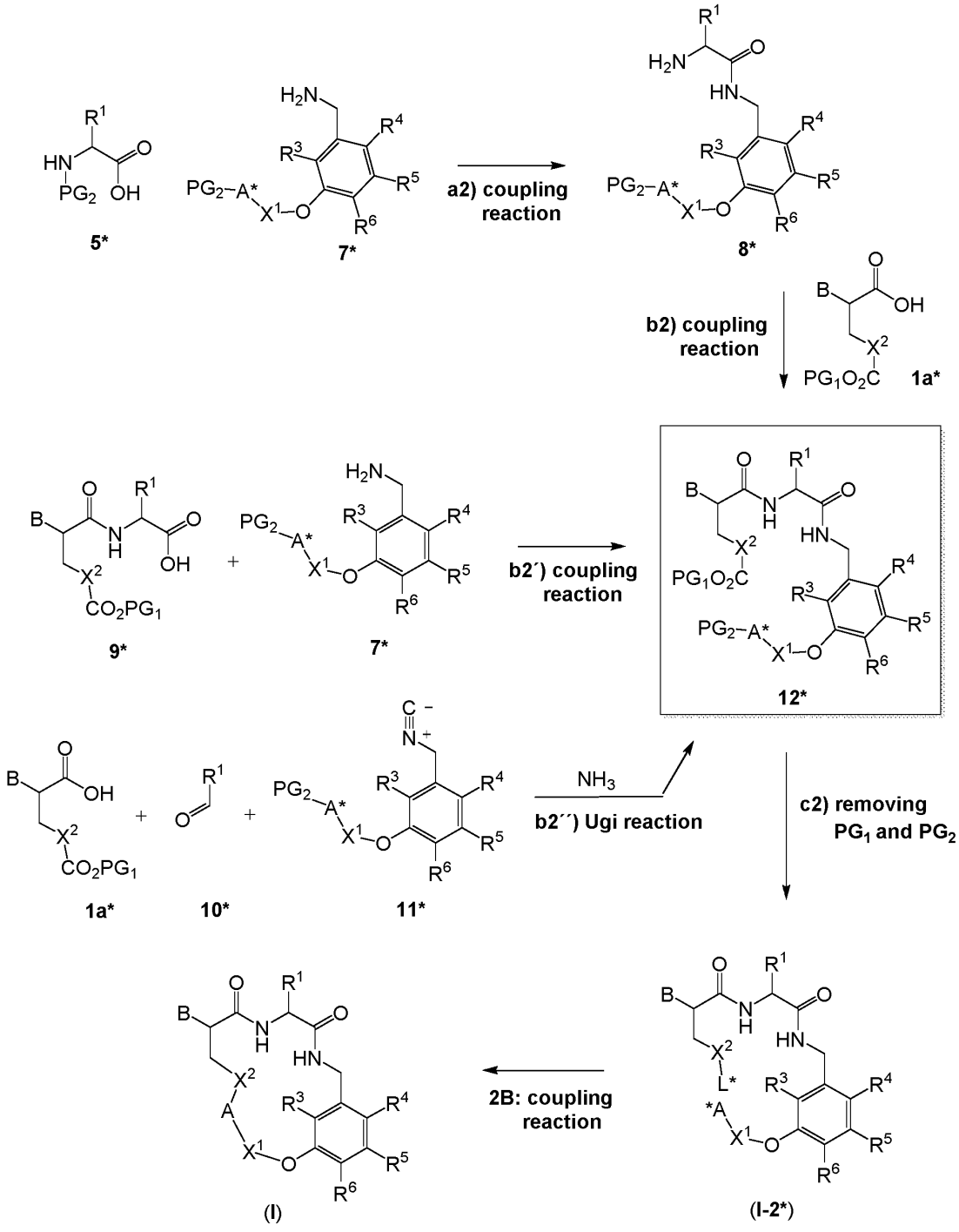
PG$_1$ represents a carboxyl protecting group;

PG$_2$ represents an amine protecting group;

and **B**, **R^1**, **R^2**, **R^3**, **R^4**, **R^5**, **R^6**, **R^{N6}**, **X^1**, **X^2**, **Z^{13}**, and **Z^{14}** have the same meanings as defined in the formula (**I**).

Thus, the method for producing the compound of the formula (**I**) may comprise **Step 1B´**, **Step 1B**, and **Step 2B**.

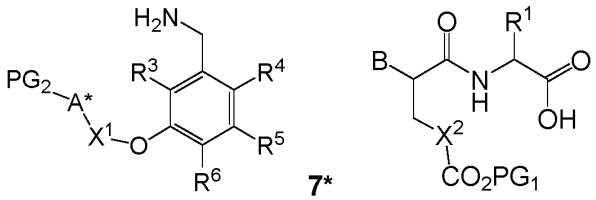
Scheme 2


5*
7*
a2) coupling reaction
8*
b2) coupling reaction
1a*
9*
7*
b2´) coupling reaction
12*
1a*
10*
11*
NH3
b2´´) Ugi reaction
c2) removing PG1 and PG2
(I)
2B: coupling reaction
(I-2*)

5

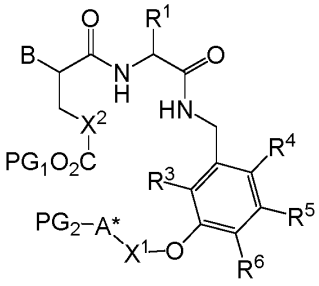
Alternatively, the intermediate compound (**I-2***) of **Step 1B** is prepared by **Step 1B´´**. **Step1B´´**comprises the following steps **b2´)** and **c2)**:

b2´) performing a coupling reaction between the compound **7*** and a compound **9***



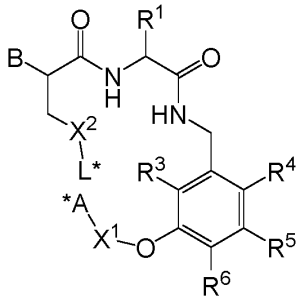
7* **9***

to obtain a compound **12***



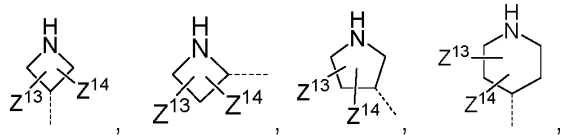
12*

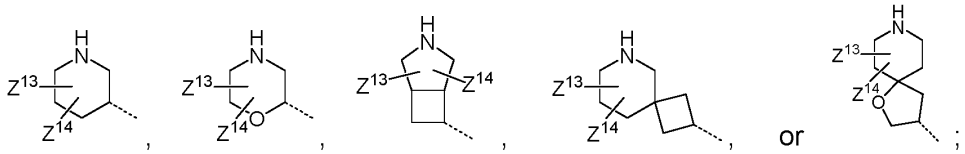
c2) removing a carboxyl protecting group PG_1 and an amine protecting group PG_2 of the compound **12*** to obtain a compound (**I-2***)



(**I-2***),

wherein

A* represents –NH(**R**^{N6})–, 



L* represents –CO_2H,

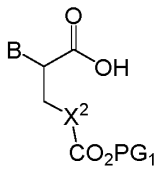
PG_1 represents a carboxyl protecting group;

PG_2 represents an amine protecting group;
and **B**, **R^1**, **R^2**, **R^3**, **R^4**, **R^5**, **R^6**, **R^{N6}**, **X^1**, **X^2**, **Z^{13}**, and **Z^{14}** have the same meanings as defined in the formula (**I**).

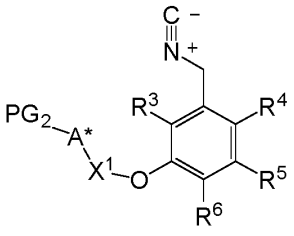
Thus, the method for producing the compound of the formula (**I**) may comprise **Step 1B´´**, **Step 1B**, and **Step 2B**.

Alternatively, the intermediate compound (**I-2***) of **Step 1B** is prepared by **Step 1B´´´**. **Step1B´´´**comprises the following steps **b2´´)** and **c2)**:

b2´´) performing a Ugi reaction of a compound **1a***, a compound **10a*** (R^1-CHO), a compound **11*** and aqueous ammonia (NH_3)

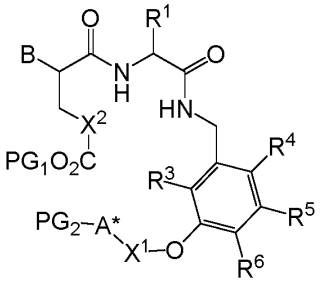


1a*



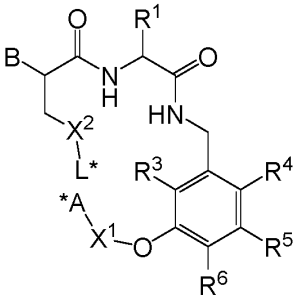
11*

to obtain a compound **12***



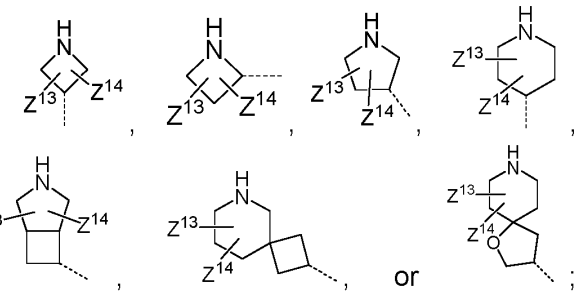
12*

c2) removing a carboxyl protecting group PG_1 and an amine protecting group PG_2 of the compound **12*** to obtain a compound (**I-2***)



(**I-2***),

wherein

A* represents –NH(**R**^{N6})–, 

L* represents –CO_2H,

PG_1 represents a carboxyl protecting group;

PG_2 represents an amine protecting group;

and **B**, **R^1**, **R^2**, **R^3**, **R^4**, **R^5**, **R^6**, **R^{N6}**, **X^1**, **X^2**, **Z^{13}**, and **Z^{14}** have the same meanings as defined in the formula (**I**).

Thus, the method for producing the compound of the formula (**I**) may comprise **Step 1B´´´**, **Step 1B**, and **Step 2B**.

Preferably, the method for producing the compound of the formula (**I**) may comprise **any one of Steps 1B´, 1B´´, and 1B´´´:**

Step 1B´, comprising steps **a2**), **b2**), and **c2**);

Step 1B´´, comprising steps **b2´**) and **c2**);

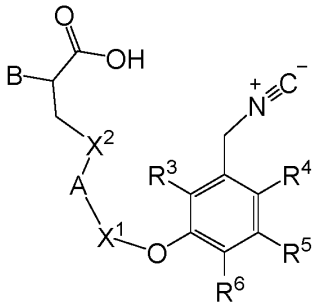
Step 1B´´´, comprising steps **b2´´**) and **c2**);

Step 1B, and

Step 2B.

Alternatively, the compound of the formula (**I**) is produced by the following method and thus the present invention refers to a method for producing the compound of the formula (**I**) comprising:

Step 1C: providing an intermediate compound (**I-3***):



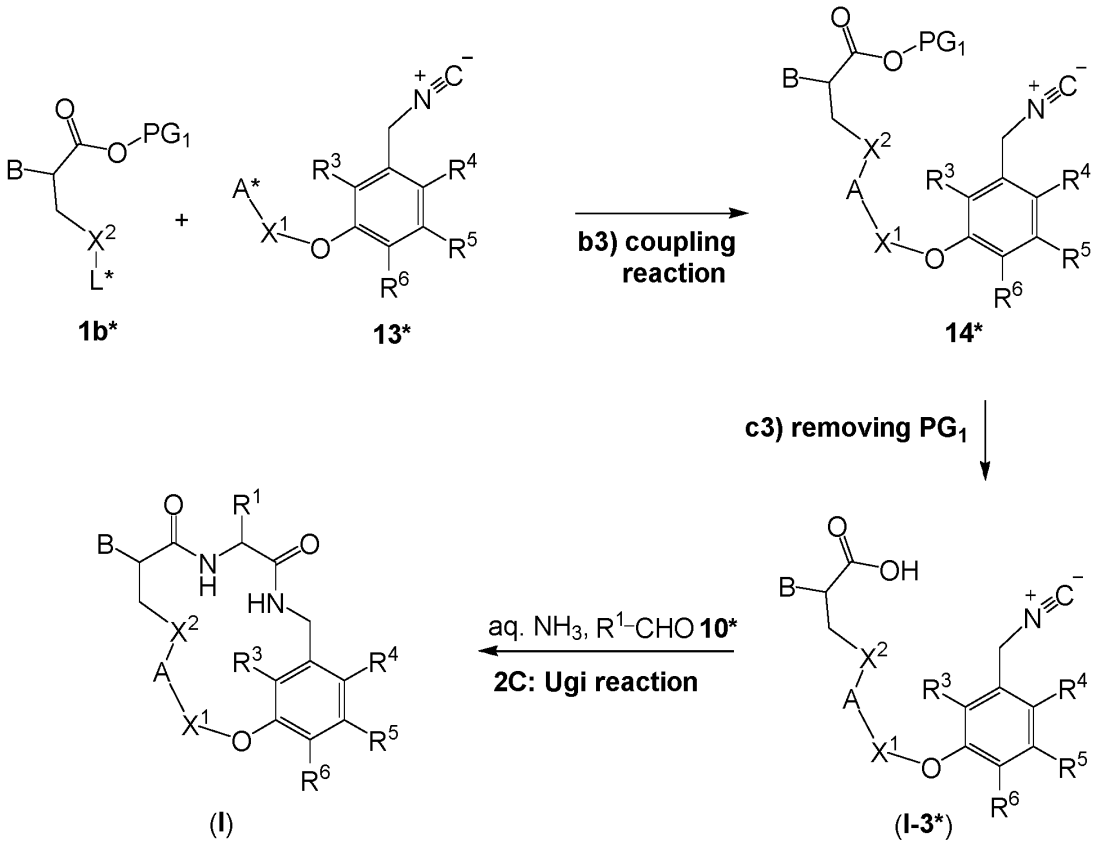
(**I-3***)

wherein

A, **B**, R^1, R^3, R^4, R^5, R^6 , X^1, and X^2 have the same meanings as defined in the formula (**I**);

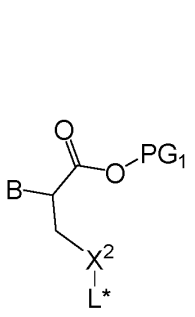
Step 2C: perform an intramolecular Ugi reaction of the intermediate compound (**I-3***) with R^1-CHO **10*** and aqueous ammonia (NH_3) to obtain the compound of the formula (**I**).

Scheme 3

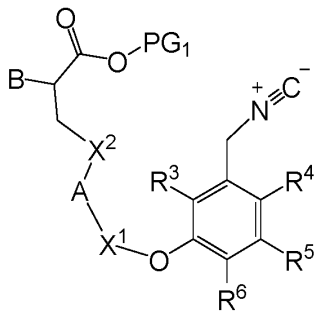


Optionally, the intermediate compound (**I-3***) of **Step 1C** is prepared by **Step 1C´**. **Step1C´**comprises the following steps **b3)** and **c3)**:

b3) performing a coupling reaction between the compound **1b*** and a compound **13***

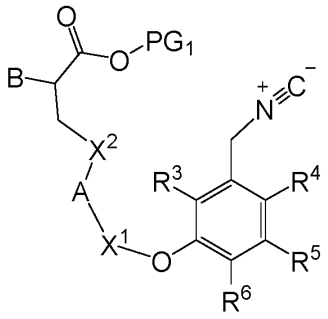


1b*



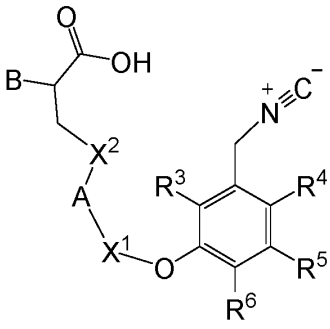
13*

to obtain a compound **14***



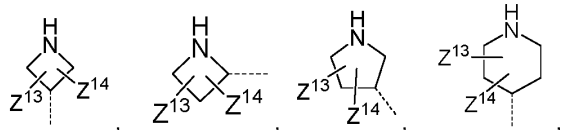
14*

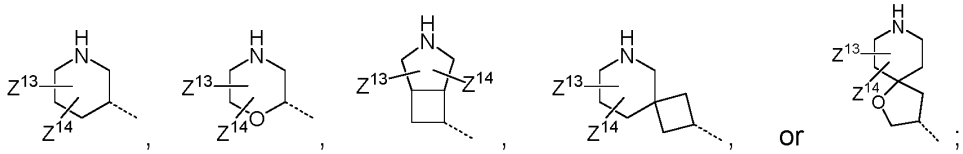
c3) removing a carboxyl protecting group PG_1 of the compound **14*** to obtain a compound (**I-3***)



(**I-3***),

wherein

A* represents –NH(**R^{N6}**)–, 



L* represents –CO_2H,

PG_1 represents a carboxyl protecting group;

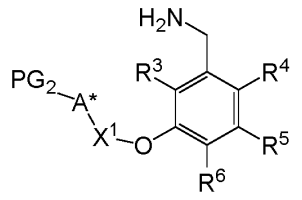
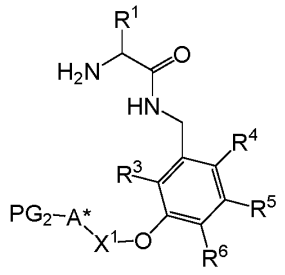
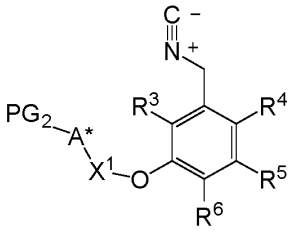
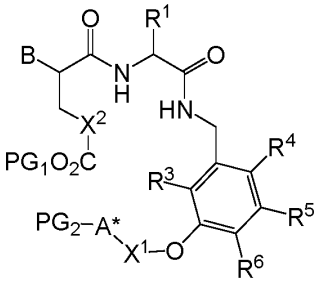
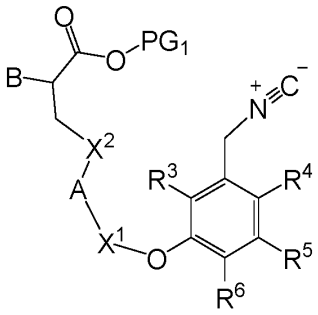
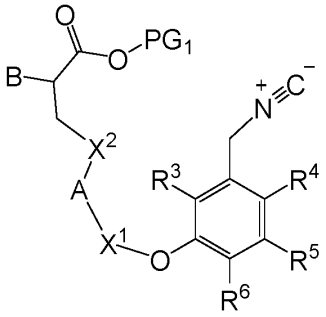
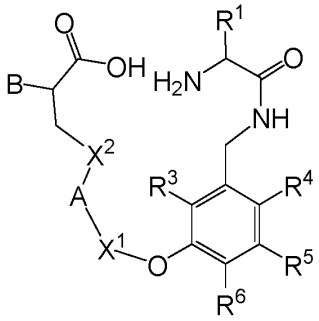
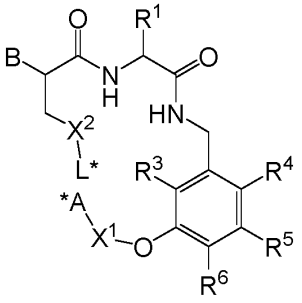
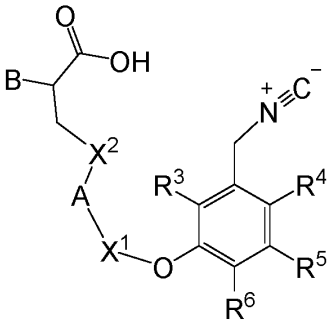
and **B**, R^1, R^3, R^4, R^5, R^6, R^{N6}, X^1, X^2, Z^{13}, and Z^{14} have the same meanings as defined in the formula (**I**).

Thus, the method for producing the compound of the formula (**I**) may comprise **Step 1C´**, **Step 1C**, and **Step 2C**.

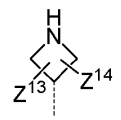
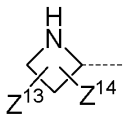
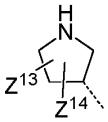
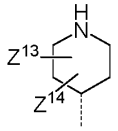
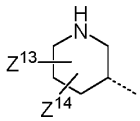
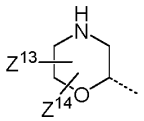
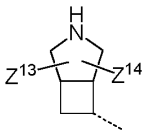
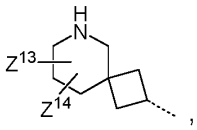
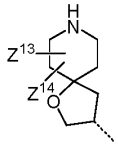
In **Steps 2A**, and **2B** to promote the intramolecular amide coupling reaction between a carboxylic acid group and an amino group of intermediate compound (**I-1***) or (**I-2***), activating reagents are commonly used for activating carboxylic acid. The activation may be introduced separate reaction or *in situ* reaction. Preferably, any of the following coupling reagent can be used to activate carobxylic 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)trispyrrolidinophosphonium 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 (*N*-[(Dimethylamino)-1*H*-1,2,3-triazolo-[4,5-*b*]pyridin-1-ylmethylene]-*N*-methyl methanaminium hexafluorophosphate *N*-oxide), HBTU (*N,N,N′,N′*-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate), HOBt (1-Hydroxybenzotriazole), HOAt (1-Hydroxy-7-azabenzotriazole), DCC (*N,N′*-Dicyclohexylcarbodiimide), EDCI (*N*-Ethyl-*N′*-(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 a mixture thereof.

Preferably, the intramolecular amide coupling reaction between a carboxylic acid group and an amino group of intermediate compound (**I-1***) or (**I-2***) is performed in the presence of HATU as a coupling reagent and DIPEA as a base.

Another aspect of the present invention is directed to the intermediate compounds **7***, **8***, **11***, **12***, **13***, **14***, **I-1***, **I-2***, and **I-3***:

 **7***	 **8***	 **11***
 **12***	 **13***	 **14***
 (**I-1***)	 (**I-2***)	 (**I-3***)

wherein

A* represents –NH(**R**^{N6})–,  ,  ,  ,  ,  ,  ,  ,  , or  ;

L* represents –CO_2H,

PG_1 represents a carboxyl protecting group;

PG_2 represents an amine protecting group;

and **B**, **R^1**, **R^2**, **R^3**, **R^4**, **R^5**, **R^6**, **R^{N6}**, **X^1**, **X^2**, **Z^{13}**, and **Z^{14}** have the same meanings as defined in the formula (**I**).

Indication

In a further aspect of the present invention, the novel compounds according to the general formula (I) are used as pharmaceutically active agent.

Surprisingly it was found that the above-mentioned compounds of general formula (I), as well as the pharmaceutical compositions thereof are acting as proteasome inhibitors, and more specifically as inhibitors of proteasome subunit beta type-5.

In the present application, the inhibitory activity assays were performed to determine IC_{50} values of compounds of general formula (I) against proteasome subunit beta type-5.

Table 2 shows activity data (indicated as IC_{50} values) in the biochemical assays. It is proven that the inventive compounds inhibit proteasome subunit beta type-5 of both the constitutive and immunoproteasome very effectively. In addition it is shown that the inventive compounds also inhibit the subunit beta type-5 of both the constitutive and immunoproteasome in the cell based proteasome glo assays very effectively. Finally it is shown that proteasome inhibition of these compounds translates into inhibition of proliferation of tumor cells (HT29) very effectively.

Tables 3-5 show that the inventive compounds effectively inhibit proliferation of other cancer cells such as A549 (human lung carcinoma *cell* line), A2780 (human ovarian cancer cell line), MDA-MB-468 (breast carcinoma), Hs 746T (human gastric carcinoma cell line), MM1S (B lymphoblast cell line), and RPMI 8226 (B lymphocyte cell line, multiple myeloma).

The pharmaceutical compositions according to the present invention comprise at least one compound according to the present invention as an active ingredient together with at least one pharmaceutically acceptable (i.e. non-toxic) carrier, excipient and/or diluent.

As used herein, proteasome “inhibitor”, especially proteasome subunit beta type-5 "inhibitor" refers to any compound capable of downregulating, decreasing, suppressing or otherwise regulating the amount and/or activity of a proteasome can be achieved by any of a variety of mechanisms known in the art, including, but not limited to binding directly to said proteasome subunit beta type-5.

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.

Proteasome subunit beta type-5 is a protein that in humans is encoded by the *PSMB5* gene in case of the constitutive proteasome and by LMP7 in case of the immunoproteasome. Proteasome subunit beta type-5, along with other beta subunits, assembles into two heptameric rings and subsequently a proteolytic chamber for substrate degradation. This protein contains "chymotrypsin-like" activity and is capable of cleaving after large hydrophobic residues of peptide. The eukaryotic proteasome recognized degradable proteins, including damaged proteins for protein quality control purpose or key regulatory protein components for dynamic biological processes. An essential function of a modified proteasome, the immunoproteasome, is the processing of class I MHC peptides.

Further aspects of the present invention relate to the compound of the general formula (I), or the above-mentioned pharmaceutical composition, for use in prophylaxis and/or treatment of diseases caused by or associated with proteasome, or immunoproteasome, in particular, proteasome subunit beta type-5, selected from a cancer, an infectious disease, an inflammatory disease, autoimmune disease and transplant rejection.

Further aspect of the present invention relates to the use of the compound of general formula (I) for the preparation of a pharmaceutical composition useful for prophylaxis and/or treatment of diseases caused by or associated with proteasome, or immunoproteasome, in particular, proteasome subunit beta type-5, selected from a cancer, an infectious disease, an inflammatory disease, autoimmune disease and transplant rejection.

In a further aspect of the present invention, methods for preventing and/or treating diseases caused by or associated with proteasome, or immunoproteasome, in particular, proteasome subunit beta type-5 in a mammal, especially in a human, are provided, which methods comprise administering to the mammal an amount of at least one compound according to the general formula (I) and/or pharmaceutically acceptable salts thereof, effective to prevent and/or treat the diseases caused by or associated with proteasome, or immunoproteasome, in particular, proteasome subunit beta type-5 selected from a cancer, a neurodegenerative disease, an infectious disease, an inflammatory disease, autoimmune disease and to supress allograft rejection during transplantation.

The term "effective amount" means an amount of compound that, when administered to a patient in need of such treatment, is sufficient to

(i) treat or prevent a particular disease, condition, or disorder which can be treated with a proteasome inhibitor;
(ii) attenuate, ameliorate, or eliminate one or more symptoms of the particular disease, condition, or disorder; or
(iii) prevent or delay the onset of one or more symptoms of the particular disease, condition, or disorder described herein.

The amount of a compound of general formula (I) that will correspond to such an amount will vary depending upon factors such as the particular compound, disease condition and its severity, the identity (e.g., weight) of the patient in need of treatment, but can nevertheless be routinely determined by one skilled in the art.

Cancer

The compounds of the present application or the pharmaceutical composition thereof are useful for the treatment and/or prophylaxis of cancer, wherein the cancer is selected from the group consisting of: adenocarcinoma, choroidal melanoma, acute leukemia, acoustic neurinoma, ampullary carcinoma, anal carcinoma, astrocytoma, basal cell carcinoma, pancreatic cancer, desmoid tumour, bladder cancer, bronchial carcinoma, non-small cell lung cancer (NSCLC), breast cancer, Burkitt's lymphoma, corpus cancer, CUP-syndrome (carcinoma of unknown primary), colorectal cancer, small intestine cancer, small intestinal tumours, ovarian cancer, endometrial carcinoma, ependymoma, epithelial cancer types, Ewing's tumours, gastrointestinal tumours, gastric cancer, gallbladder cancer, gall bladder carcinomas, uterine cancer, cervical cancer, cervix, glioblastomas, gynecologic tumours, ear, nose and throat tumours, hematologic neoplasias, hairy cell leukemia, urethral cancer, skin cancer, skin testis cancer, brain tumours (gliomas), brain metastases, testicle cancer, hypophysis tumour, carcinoids, Kaposi's sarcoma, laryngeal cancer, germ cell tumour, bone cancer, colorectal carcinoma, head and neck tumours (tumours of the ear, nose and throat area), colon carcinoma, craniopharyngiomas, oral cancer (cancer in the mouth area and on lips), cancer of the central nervous system, liver cancer, liver metastases, leukemia, eyelid tumor, lung cancer, lymph node cancer (Hodgkin's/Non-Hodgkin's), lymphomas, stomach cancer, malignant melanoma, malignant neoplasia, malignant tumours gastrointestinal tract, breast carcinoma, rectal cancer, medulloblastomas, melanoma, meningiomas, Hodgkin's disease, mycosis fungoides, nasal cancer, neurinoma, neuroblastoma, kidney cancer, renal cell carcinomas, non-Hodgkin's lymphomas, oligodendroglioma, esophageal carcinoma, osteolytic carcinomas and osteoplastic carcinomas, osteosarcomas, ovarial carcinoma, pancreatic carcinoma, penile cancer, plasmocytoma, squamous cell carcinoma of the head and neck (SCCHN), prostate cancer, pharyngeal cancer, rectal carcinoma, retinoblastoma, vaginal cancer, thyroid

carcinoma, Schneeberger disease, esophageal cancer, spinalioms, T-cell lymphoma (mycosis fungoides), thymoma, tube carcinoma, eye tumours, urethral cancer, urologic tumours, urothelial carcinoma, vulva cancer, wart appearance, soft tissue tumours, soft tissue sarcoma, Wilm's tumour, cervical carcinoma, tongue cancer, astrocytomas, bronchial cancer, laryngeal cancer, malignant melanoma, oesophageal cancer, cholangiocarcinoma, and renal cell cancer.

Preferrably, the present application or the pharmaceutical composition thereof are useful for the treatment and/or prophylaxis of cancer, wherein the cancer is leukemia, multiple myeloma, mantle-cell lymphoma (MCL), breast cancer, colorectal cancer, non-small cell lung cancer or ovarian cancer, more preferably, the cancer is multiple myeloma.

Optionally, the compound of the present invention, or the pharmaceutical composition thereof is used for treatment / prophylaxis of said cancer, in particular, multiple myeloma in combination with a thalidomide or a derivative thereof.

The derivative of thalidomide is selected from lenalidomide, pomalidomide, avadomide, and iberdomide and CC-885. CC-885 is a modulator of the E3 ligase protein cereblon with antiproliferative effects on human myeloid leukemia cell lines. It forms a complex with cereblon and the cell cycle regulator and translation termination factor GSPT1. The antitumour activity of CC-885 relies on cereblon-dependent ubiquitination and degradation of the GSPT1. Formal Name: N-(3-chloro-4-methylphenyl)-N'-[[2-(2,6-dioxo-3-piperidinyl)-2,3-dihydro-1-oxo-1H-isoindol-5-yl]methyl]-urea (CAS Number: 1010100-07-8).

Infectious disease

The compounds of the present application or the pharmaceutical composition thereof are useful for the treatment and/or prophylaxis of the infectious disease, wherein the infectious disease is selected from the group consisting of: HIV, Echinococcosis, Amebiasis (Entamoeba histolytica Infection), Angiostrongylus Infection, Anisakiasis, Anthrax, Babesiosis (Babesia Infection), Balantidium Infection (Balantidiasis), Baylisascaris Infection (Raccoon Roundworm), Bilharzia (Schistosomiasis), Blastocystis hominis Infection (Blastomycosis), Borreliosis, Botulism, Brainerd Diarrhea, Brucellosis, BSE (Bovine Spongiform Encephalopathy), Candidiasis, Capillariasis (Capillaria Infection), CFS (Chronic Fatigue Syndrome), Chagas Disease (American Trypanosomiasis), Chickenpox (Varicella-Zoster virus), Chlamydia pneumoniae Infection, Cholera, CJD (Creutzfeldt-Jakob Disease), Clonorchiasis (Clonorchis Infection), CLM (Cutaneous Larva Migrans, Hookworm Infection), Coccidioidomycosis, Conjunctivitis, Coxsackievirus A16 (Hand, Foot and Mouth

Disease), Cryptococcosis, Cryptosporidium Infection (Cryptosporidiosis), Culex mosquito (Vector of West Nile Virus), Cyclosporiasis (Cyclospora Infection), Cysticercosis (Neurocysticercosis), Cytomegalovirus Infection, Dengue / Dengue Fever, Dipylidium Infection (Dog and Cat Flea Tapeworm), Ebola Virus Hemorrhagic Fever, Echinococcosis (Alveolar Hydatid Disease), Encephalitis, Entamoeba coli Infection, Entamoeba dispar Infection, Entamoeba hartmanni Infection, Entamoeba histolytica Infection (Amebiasis), Entamoeba polecki Infection, Enterobiasis (Pinworm Infection), Enterovirus Infection (non-polio), Epstein-Barr Virus Infection, Escherichia coli Infection, Foodborne Infection, Foot and mouth Disease, Fungal Dermatitis, Gastroenteritis, Group A streptococcal Disease, Group B streptococcal Disease, Hansen's Disease (Leprosy), Hantavirus Pulmonary Syndrome, Head Lice Infestation (Pediculosis), Helicobacter pylori Infection, Hematologic Disease, Hendra Virus Infection, Hepatitis (HCV, HBV), Herpes Zoster (Shingles), Human Ehrlichiosis, Human Parainfluenza Virus Infection, Influenza, Isosporiasis (Isospora Infection), Lassa Fever, Leishmaniasis, Kala-azar (Kala-azar, Leishmania Infection), Leprosy, Lice (Body lice, Head lice, Pubic lice), Lyme Disease, Malaria, Marburg Hemorrhagic Fever, Measles, Meningitis, Mosquito-borne Diseases, Mycobacterium avium Complex (MAC) Infection, Naegleria Infection, Nosocomial Infections, Nonpathogenic Intestinal Amebae Infection, Onchocerciasis (River Blindness), Opisthorciasis (Opisthorcis Infection), Parvovirus Infection, Plague, PCP (Pneumocystis carinii Pneumonia), Polio, Q Fever, Rabies, Respiratory Syncytial Virus (RSV) Infection, Rheumatic Fever, Rift Valley Fever, Rotavirus Infection, Roundworms Infection, Salmonellosis, Salmonella Enteritidis, Scabies, Shigellosis, Shingles, Sleeping Sickness, Smallpox, Streptococcal Infection, Tapeworm Infection (Taenia Infection), Tetanus, Toxic Shock Syndrome, Tuberculosis, Ulcers (Peptic Ulcer Disease), Valley Fever, Vibrio parahaemolyticus Infection, Vibrio vulnificus Infection, Viral Hemorrhagic Fever, Warts, Waterborne infectious Diseases, West Nile Virus Infection (West Nile Encephalitis), Whooping Cough, Yellow Fever.

Inflammatory disease

Inflammatory disease is caused by cytokines, TNF-α, IL-1ß, GM-CSF, IL-6/IL-8, adhesion molecules (ICAM-1, VCAM-1, P-selectin) and prostaglandins and/or nitric oxide (NO).

Autoimmune disease

Furthermore, the compounds of the present application or the pharmaceutical composition thereof are useful for the treatment and/or prophylaxis of autoimmune disease. The autoimmune disease is selected from the group consisting of:

Achalasia, Addison's disease, Adult Still's disease, Agammaglobulinemia, Alopecia areata, Amyloidosis, Ankylosing spondylitis, Anti-GBM/Anti-TBM nephritis, Antiphospholipid syndrome, Autoimmune angioedema, Autoimmune dysautonomia, Autoimmune encephalomyelitis, Autoimmune hepatitis, Autoimmune inner ear disease (AIED), Autoimmune myocarditis, Autoimmune oophoritis, Autoimmune orchitis, Autoimmune pancreatitis, Autoimmune retinopathy, Autoimmune urticaria, Axonal & neuronal neuropathy (AMAN), Baló disease, Behcet's disease, Benign mucosal pemphigoid, Bullous pemphigoid, Castleman disease (CD), Celiac disease, Chagas disease, Chronic inflammatory demyelinating polyneuropathy (CIDP), Chronic recurrent multifocal osteomyelitis (CRMO), Churg-Strauss Syndrome (CSS), Eosinophilic Granulomatosis (EGPA), Cicatricial pemphigoid, Cogan's syndrome, Cold agglutinin disease, Congenital heart block, Coxsackie myocarditis, CREST syndrome, Crohn's disease, Dermatitis herpetiformis, Dermatomyositis, Devic's disease (neuromyelitis optica), Discoid lupus, Dressler's syndrome, Endometriosis, Eosinophilic esophagitis (EoE), Eosinophilic fasciitis, Erythema nodosum, Essential mixed cryoglobulinemia, Evans syndrome, Fibromyalgia, Fibrosing alveolitis, Giant cell arteritis (temporal arteritis), Giant cell myocarditis, Glomerulonephritis, Goodpasture's syndrome, Granulomatosis with Polyangiitis, Graves' disease, Guillain-Barre syndrome, Hashimoto's thyroiditis, Hemolytic anemia, Henoch-Schonlein purpura (HSP), Herpes gestationis or pemphigoid gestationis (PG), Hidradenitis Suppurativa (HS) (Acne Inversa), Hypogammalglobulinemia, IgA Nephropathy, IgG4-related sclerosing disease, Immune thrombocytopenic purpura (ITP), Inclusion body myositis (IBM), Interstitial cystitis (IC), Juvenile arthritis, Juvenile diabetes (Type 1 diabetes), Juvenile myositis (JM), Kawasaki disease, Lambert-Eaton syndrome, Leukocytoclastic vasculitis, Lichen planus, Lichen sclerosus, Ligneous conjunctivitis, Linear IgA disease (LAD), Lupus, Lyme disease chronic, Meniere's disease, Microscopic polyangiitis (MPA), Mixed connective tissue disease (MCTD), Mooren's ulcer, Mucha-Habermann disease, Multifocal Motor Neuropathy (MMN) or MMNCB, Multiple sclerosis, Myasthenia gravis, Myelin Oligodendrocyte Glycoprotein Antibody Disorder, Myositis, Narcolepsy, Neonatal Lupus, Neuromyelitis optica, Neutropenia, Ocular cicatricial pemphigoid, Optic neuritis, Palindromic rheumatism (PR), PANDAS, Paraneoplastic cerebellar degeneration (PCD), Paroxysmal nocturnal hemoglobinuria (PNH), Parry Romberg syndrome, Pars planitis (peripheral uveitis), Parsonage-Turner syndrome, Pemphigus, Peripheral neuropathy, Perivenous encephalomyelitis, Pernicious anemia (PA), POEMS syndrome, Polyarteritis nodosa, Polyglandular syndromes type I, II, III, Polymyalgia rheumatic, Polymyositis, Postmyocardial infarction syndrome, Postpericardiotomy syndrome, Primary Biliary Cholangitis, Primary sclerosing cholangitis, Progesterone dermatitis, Psoriasis, Psoriatic arthritis, Pure red cell aplasia (PRCA), Pyoderma gangrenosum, Raynaud's phenomenon, Reactive Arthritis, Reflex sympathetic dystrophy, Relapsing polychondritis,

Restless legs syndrome (RLS), Retroperitoneal fibrosis, Rheumatic fever, Rheumatoid arthritis, Sarcoidosis, Schmidt syndrome, Scleritis, Scleroderma, Sjögren's syndrome, Sperm & testicular autoimmunity, Stiff person syndrome (SPS), Subacute bacterial endocarditis (SBE), Susac's syndrome, Sympathetic ophthalmia (SO), Takayasu's arteritis, Temporal arteritis/Giant cell arteritis, Thrombocytopenic purpura (TTP), Thyroid eye disease (TED), Tolosa-Hunt syndrome (THS), Transverse myelitis, Type 1 diabetes, Ulcerative colitis (UC), Undifferentiated connective tissue disease (UCTD), Uveitis, Vasculitis, Vitiligo, Vogt-Koyanagi-Harada Disease.

Preferred, the autoimmune disease is selected from Lupus nephritis, lupus, systemic lupus erythematosus, myasthenia gravis, multiple sclerosis, polyarthritis, rheumatoid arthritis, irritant sensitivity, psoriasis, asthma, and colitis, more preferred, the autoimmune disease is myasthenia gravis.

Transplant rejection occurs when transplanted tissue is rejected by the recipient's immune system, which destroys the transplanted tissue. Transplant rejection can be lessened by determining the molecular similitude between donor and recipient and by use of immunosuppressant drugs after transplant. The compound of the present invention may be used as immunosuppressant drugs.

The compounds enlisted explicitly in Table 1 are preferred to be used within the methods or indications disclosed herein.

The pharmaceutical compositions of the present invention can be prepared in a conventional solid or liquid carrier or diluent and a conventional pharmaceutically-made adjuvant at suitable dosage level in a known way. The preferred preparations are adapted for oral application. These administration forms include, for example, pills, tablets, film tablets, coated tablets, capsules, powders and deposits.

Furthermore, the present invention also includes pharmaceutical preparations for parenteral application, including dermal, intradermal, intragastral, intracutan, intravasal, intravenous, intramuscular, intraperitoneal, intranasal, intravaginal, intrabuccal, percutan, rectal, subcutaneous, sublingual, topical, or transdermal application, which preparations in addition to typical vehicles and/or diluents contain at least one compound according to the present invention and/or a pharmaceutical acceptable salt thereof as active ingredient.

The pharmaceutical compositions according to the present invention containing at least one compound according to the present invention and/or a pharmaceutical acceptable

salt thereof as active ingredient will typically be administered together with suitable carrier materials selected with respect to the intended form of administration, i.e. for oral administration in the form of tablets, capsules (either solid filled, semi-solid filled or liquid filled), powders for constitution, gels, elixirs, dispersable granules, syrups, suspensions, and the like, and consistent with conventional pharmaceutical practices. For example, for oral administration in the form of tablets or capsules, the active drug component may be combined with any oral non-toxic pharmaceutically acceptable carrier, preferably with an inert carrier like lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, talc, mannitol, ethyl alcohol (liquid filled capsules) and the like. Moreover, suitable binders, lubricants, disintegrating agents and coloring agents may also be incorporated into the tablet or capsule. Powders and tablets may contain about 5 to about 95-weight % of the compounds of the formula (I) or the respective pharmaceutically active salt as active ingredient.

Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Among suitable lubricants there may be mentioned boric acid, sodium benzoate, sodium acetate, sodium chloride, and the like. Suitable disintegrants include starch, methylcellulose, guar gum, and the like. Sweetening and flavoring agents as well as preservatives may also be included, where appropriate. The disintegrants, diluents, lubricants, binders etc. are discussed in more detail below.

Moreover, the pharmaceutical compositions of the present invention may be formulated in sustained release form to provide the rate controlled release of any one or more of the components or active ingredients to optimise the therapeutic effect(s), e.g. antihistaminic activity and the like. Suitable dosage forms for sustained release include tablets having layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

Liquid form preparations include solutions, suspensions, and emulsions. As an example, there may be mentioned water or water/propylene glycol solutions for parenteral injections or addition of sweeteners and opacifiers for oral solutions, suspensions, and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be present in combination with a pharmaceutically acceptable carrier such as an inert, compressed gas, e.g. nitrogen.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides like cocoa butter is melted first, and the active ingredient is then dispersed homogeneously therein e.g. by stirring. The molten, homogeneous mixture is then poured into conveniently sized moulds, allowed to cool, and thereby solidified.
Also included are solid form preparations, which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions, and emulsions.

The compounds according to the present invention may also be delivered transdermally. The transdermal compositions may have the form of a cream, a lotion, an aerosol and/or an emulsion and may be included in a transdermal patch of the matrix or reservoir type as is known in the art for this purpose.

The term capsule as recited herein refers to a specific container or enclosure made e.g. of methylcellulose, polyvinyl alcohols, or denatured gelatins or starch for holding or containing compositions comprising the active ingredient(s). Capsules with hard shells are typically made of blended of relatively high gel strength gelatins from bones or pork skin. The capsule itself may contain small amounts of dyes, opaquing agents, plasticisers and/or preservatives.

Under tablet a compressed or moulded solid dosage form is understood which comprises the active ingredients with suitable diluents. The tablet may be prepared by compression of mixtures or granulations obtained by wet granulation, dry granulation, or by compaction well known to a person of ordinary skill in the art.
Oral gels refer to the active ingredients dispersed or solubilised in a hydrophilic semi-solid matrix.
Powders for constitution refers to powder blends containing the active ingredients and suitable diluents which can be suspended e.g. in water or in juice.

Suitable diluents are substances that usually make up the major portion of the composition or dosage form. Suitable diluents include sugars such as lactose, sucrose, mannitol, and sorbitol, starches derived from wheat, corn rice, and potato, and celluloses such as microcrystalline cellulose. The amount of diluent in the composition can range from about 5 to about 95 % by weight of the total composition, preferably from about 25 to about 75 weight %, and more preferably from about 30 to about 60 weight %.

The term disintegrants refers to materials added to the composition to support break apart (disintegrate) and release the pharmaceutically active ingredients of a medicament. Suitable disintegrants include starches, “cold water soluble” modified

starches such as sodium carboxymethyl starch, natural and synthetic gums such as locust bean, karaya, guar, tragacanth and agar, cellulose derivatives such as methylcellulose and sodium carboxymethylcellulose, microcrystalline celluloses, and cross-linked microcrystalline celluloses such as sodium croscaramellose, alginates such as alginic acid and sodium alginate, clays such as bentonites, and effervescent mixtures. The amount of disintegrant in the composition may range from about 2 to about 20 weight % of the composition, more preferably from about 5 to ca. 10 weight %.

Binders are substances which bind or “glue” together powder particles and make them cohesive by forming granules, thus serving as the “adhesive” in the formulation. Binders add cohesive strength already available in the diluent or bulking agent. Suitable binders include sugars such as sucrose, starches derived from wheat corn rice and potato, natural gums such as acacia, gelatin and tragacanth, derivatives of seaweed such as alginic acid, sodium alginate and ammonium calcium alginate, cellulose materials such as methylcellulose, sodium carboxymethylcellulose and hydroxypropylmethylcellulose, polyvinylpyrrolidone, and inorganic compounds such as magnesium aluminum silicate. The amount of binder in the composition may range from about 2 to about 20 weight % of the composition, preferably from about 3 to about 10 weight %, and more preferably from about 3 to about 6 weight %.

Lubricants refer to a class of substances which are added to the dosage form to enable the tablet granules etc. after being compressed to release from the mould or die by reducing friction or wear. Suitable lubricants include metallic stearates such as magnesium stearate, calcium stearate, or potassium stearate, stearic acid, high melting point waxes, and other water soluble lubricants such as sodium chloride, sodium benzoate, sodium acetate, sodium oleate, polyethylene glycols and D,L-leucine. Lubricants are usually added at the very last step before compression, since they must be present at the surface of the granules. The amount of lubricant in the composition may range from about 0.2 to about 5 weight % of the composition, preferably from about 0.5 to about 2 weight %, and more preferably from about 0.3 to about 1.5 weight % of the composition.

Glidents are materials that prevent caking of the components of the pharmaceutical composition and improve the flow characteristics of granulate so that flow is smooth and uniform. Suitable glidents include silicon dioxide and talc. The amount of glident in the composition may range from about 0.1 to about 5 weight % of the final composition, preferably from about 0.5 to about 2 weight %.

Coloring agents are excipients that provide coloration to the composition or the dosage form. Such excipients can include food grade dyes adsorbed onto a suitable adsorbent such as clay or aluminum oxide. The amount of the coloring agent may vary from

about 0.1 to about 5 weight % of the composition, preferably from about 0.1 to about 1 weight %.

The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

Further modifications and alternative embodiments of various aspects of the invention will be apparent to those skilled in the art in view of this description. Accordingly, this description is to be construed as illustrative only and is for the purpose of teaching those skilled in the art the general manner of carrying out the invention. It is to be understood that the forms of the invention shown and described herein are to be taken as examples of embodiments. Elements and materials may be substituted for those illustrated and described herein, parts and processes may be reversed, and certain features of the invention may be utilized independently, all as would be apparent to one skilled in the art after having the benefit of this description of the invention. Changes may be made in the elements described herein without departing from the spirit and scope of the invention as described in the following claims.

Examples

Preparation of compounds:

General Information:

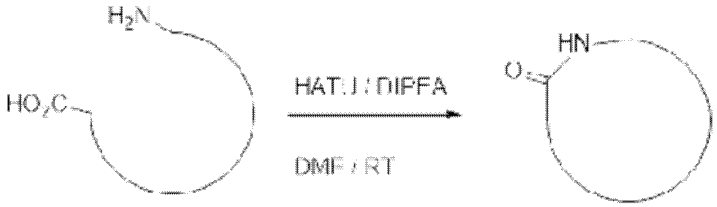
All reactions involving air- or moisture-sensitive reagents or intermediates were carried out in flame-dried glassware under an argon atmosphere. Dry solvents (THF, toluene, MeOH, DMF, DCM) were used as commercially available. ^{1}H-NMR and ^{13}C-NMR were recorded on a Bruker DRX400 (400 MHz). Multiplicities are indicated as: br s (broadened singlet), s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), m (multiplet); and coupling constants (J) are given in Hertz (Hz). HPLC – electrospray mass spectra (HPLC ES-MS) were obtained using Waters Acquity Performance Liquid Chromatography (UPLC) equipped SQ 3100 Mass detector spectrometer. Column: Acquity UPLC BEH C18 1.7um, 2.1x50mm. Flow: 0.5ml/min. Eluents: A: H_2O with 0.05% formic acid and B: ACN with 0.05% TFA. All chemicals and solvents were purchased from commercial sources like Sigma-Aldrich, Fluka, TCI, Acros Organics, ABCR, Alfa Aesar, Enamine, VWR, Combi-Blocks, Apollo Scientific, Aquilla Pharmatech, Ark Pharm, D-L Chiral Chemicals, ChemBridge, Renno Tech, Accela, KeyOrganics, Pharmablock and Chem Impex. Unless otherwise noted, all commercially available compounds were used as received without further purifications.

Abbreviations used in the description of the chemistry and in the Examples that follow are: ACN or MeCN (acetonitrile); Asp (aspartic acid), br (broad); BOC (tert-butyloxycarbonyl), Cbz (benzyloxycarbonyl), $CDCl_3$ (deuterated chloroform); cHex (cyclohexane); CDI (1,1'-Carbonyldiimidazole), DPCP(diphenyl chlorophosphate), DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), DCE (1,2-dichloroethane), DCM (dichloromethane); DIAD (diisopropyl azodicarboxylate); DIEA (N,N-Diisopropylethylamine), DIPEA (di-iso-propylethylamine); DMF (dimethylformamide); DMSO (dimethyl sulfoxide); DPPA (diphenylphosphoryl azide), EA (ethyl acetate), eq. (equivalent); EDCI (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide), ES (electrospray); EtOAc (ethyl acetate); EtOH (ethanol); Glu (glutamic acid), HATU (*O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate); HCl (hydrochloric acid); HOBt (Hydroxybenzotriazole), hPhe (homophenylalanine), MeOH (methanol); MS (mass spectrometry); MTBE (methyl tert-butyl ether), Mwt (molecular weight); NMM (4-methylmorpholine), NMP (*N*-Methyl-2-pyrrolidone), NMR (nuclear magnetic resonance); PE (petroleum ether), RP (reversed-phase); RT/r.t. (room temperature); sat. aq. (saturated aqueous); SiO_2 (silica gel); tBu (tert-butyl), T_3P

(propanephosphonic acid anhydride), TBME (tert-butyl methyl ether), TFA (trifluoroacetic acid); THF (tetrahydrofurane); TIS (triisopropylsilane).

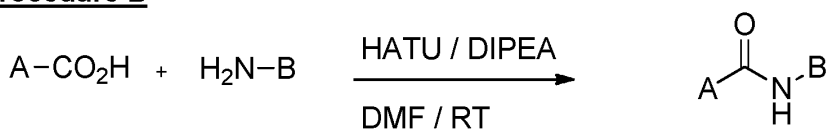
Preparative Examples

General procedure A



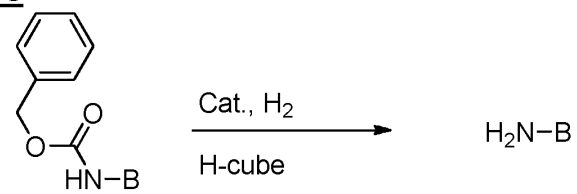
1.2 eq. HATU and 2 eq. DIPEA are dissolved in 1.5 ml/mmol DMF. 1 eq. amino acid in 2 ml/mmol DMF are added dropwise at room temperature or elevated temperature. 1 h after complete addition the reaction mixture was distributed between ethyl acetate and 2 N NaOH solution. The organic phase was separated, washed with brine, dried over sodium sulfate and solvents were evaporated. Depending on scale the raw product was purified by crystallization, flash chromatography or HPLC.

General procedure B



Carboxylic acid (1.5 eq.), HATU (1.1 eq.) and DIPEA (6 eq.) are dissolved in DMF and amine is added. After reaction was completed the reaction mixture can be diluted with ethyl acetate and then washed by sodium hydroxide solution and brine. After drying the organic phase over sodium sulfate and removing the solvents under reduced pressure the raw product was purified by crystallization, flash chromatography or HPLC.

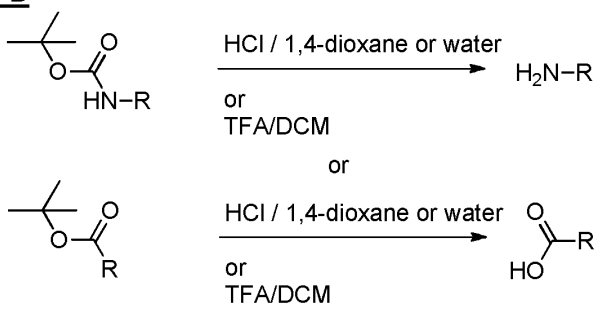
General procedure C



Cbz-protected amine is dissolved in a solvent (e.g. EtOH, ethyl acetate) or solvent mixtures at concentrations of e.g. 10 mg/ml depending on solubility. Hydrogenation by H-Cube® using a Pd/C or Raney-Ni catalyst catridge at 50°C. Typically hydrogen

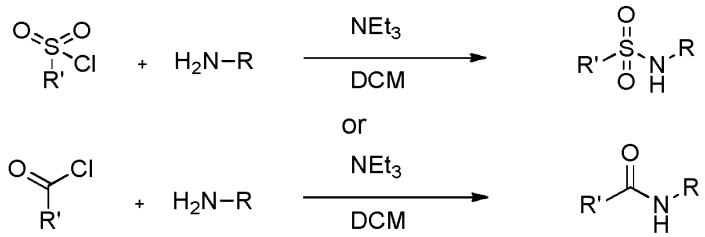
pressure can be set from normal pressure to 50 bar and flow rates of 1 ml/min. If necessary hydrogenation is repeated until complete. Solvent is removed under reduced pressure to give a product usually pure enough to be used in the next reaction. If necessary the product can be purified by normal or revered phase flash chromatography.

General procedure D



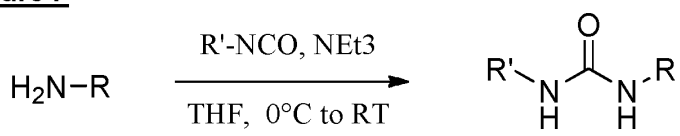
Boc-protected amine or tert-butyl carboxylate is dissolved in e.g. 4 N HCl in 1,4-dioxane, concentrated HCl in water or TFA in DCM (e.g. 20 %) at room temperature or elevated temperature (e.g 60 °C) and stirred at room temperature. After reaction is found to be complete volatiles are removed under reduce pressure. The remaining crude is coevaporated with e.g. acetonitrile or THF to remove excess HCl to give the related ammonium slat or carboxylic acid pure enough to be used in the next reaction.

General procedure E



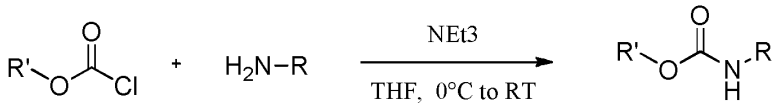
1 eq. amine and triethylamine (3 eq.) are dissolved in DCM (10-15 ml/mmol) and cooled to 0 °C. Sulfonyl chloride or carboxylic acid chloride (1.3 eq.) is added and the mixture is stirred until the reaction was completed. For HPLC purification the reaction mixture was diluted with some methanol. Otherwise the reaction was diluted with ethyl acetate and washed with HCl aq. or Na_2CO_3 aq. and brine. After drying over Na_2SO_4 and removing the solvent under reduced pressure the residue was purified by normal or revered phase flash chromatography.

General procedure F



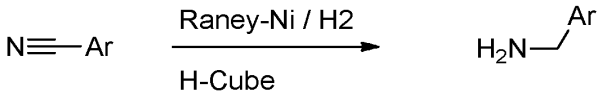
1 eq. amine and triethylamine (3 eq.) are dissolved in THF (10-15 ml/mmol) at RT. The related isocyanate (1.3 eq.) is added and the mixture is stirred until completion. The reaction mixture was diluted with some methanol and directly purified by HPLC.

General procedure G



1 eq. amine and triethylamine (3 eq.) are dissolved in THF (10-15 ml/mmol) at 0°C. The related chloroformate (1.5 eq.) is added and the reaction was allowed to warm to room temperature. After complete reaction the reaction mixture was diluted with some methanol and directly purified by HPLC.

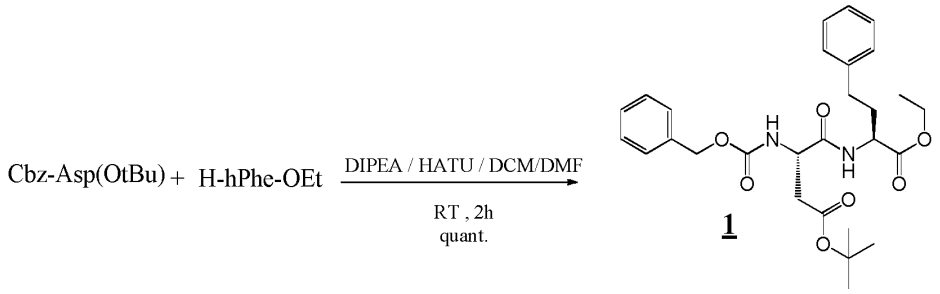
General procedure H



Aromatic nitrile in dissolved in ethanol, 2 M NH_3 in MeOH or other solvents or mixtures at concentrations of e.g. 10 mg/ml depending on solubility. Hydrogenation is achieved by H-Cube® using a Raney-Ni catalyst cartridge at elevated temperatures, e.g. 50-80 °C. Typically hydrogen pressure can be set from 20-50 bar at flow rates of 1 ml/min. If necessary hydrogenation is repeated until complete. Solvent is removed under reduced pressure to give a product usually pure enough to be used in the next reaction. If necessary the product can be purified by normal or revered phase flash chromatography.

Example A-1: Preparation of compound 8

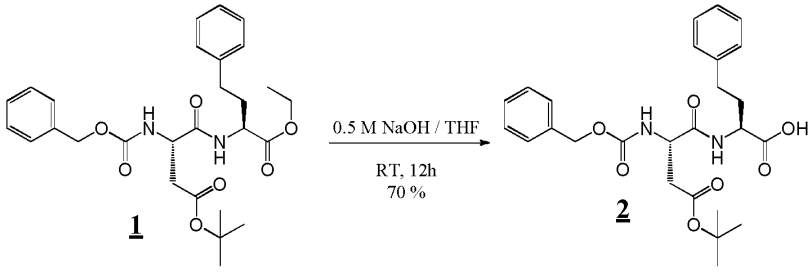
(S)-tert-butyl 3-(((benzyloxy)carbonyl)amino)-4-(((S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoate (**1**)



To a solution of Z-L-aspartic acid tert-butyl ester monohydrate (35 g, 102.5 mmol, 1.0 eq.) in DCM (1.2 L) and dry DMF (0.6 L) was added ethyl (S)-2-amino-4-phenylbutanoate hydrochloride (25 g, 102.5 mmol, 1.0 eq.) and HATU (57.3 g, 150.8 mmol, 1.5 eq.). Once purged under N_2, it was added dropwise and in 10 minutes DIPEA (44.4 g, 56.8 mL, 343.8 mmol, 3.4 equiv., previously filtered through a plug of Alox-basic). After two hours at room temperature, LC-MS monitoring showed none of the starting materials, so, after evaporation of the DCM under reduced pressure, the resulting residue was diluted with EtOAc/TBME 1:1 and then washed two times with saturated $NaHCO_3$ solution, five times with water and once with brine. The organic phase was dried over $MgSO_4$, filtered and the solvents evaporated under reduced pressure to obtain 60.7 g of crude **1**. This crude was used in the next step without purification.

Formula: $C_{28}H_{36}N_2O_7$, exact mass: 512.3, found: 513.4 $[M+H]^+$

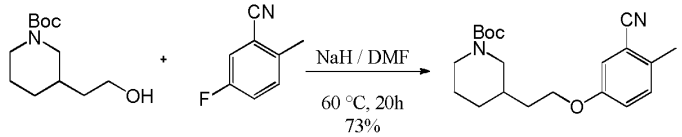
Preparation of (S)-2-((S)-2-(((benzyloxy)carbonyl)amino)-4-(tert-butoxy)-4-oxobutanamido)-4-phenylbutanoic acid (**2**)



To a suspension of **1** (52 g, 101 mmol, 1.0 eq.) in THF (0.7 L) was added NaOH (0.5M, 202 mL, 101 mmol, 1.0 eq.) dropwise. The resulting mixture was stirred at room temperature for 12 hours before evaporation of the THF under reduced pressure. The resulting residue was diluted with water and TBME, and after decantation, the aqueous phase was further extracted two times with TBME. The resulting basic aqueous phase (pH ~8) was acidified to pH 2 by addition of 10% HCl before extraction three times with DCM. The combined organic phase was dried over MgSO4, filtered and evaporated to obtain 37 g of crude. This crude was purified in normal phase using Grace Reveleris and CHCl3/1% AcOH in MeOH as solvents to obtain 34.6 g of expected compound **2**

Formula: $C_{26}H_{32}N_2O_7$, exact mass: 484.2, found: 485.3 $[M+H]^+$

tert-butyl 3-(2-(3-cyano-4-methylphenoxy)ethyl)piperidine-1-carboxylate (**3**)

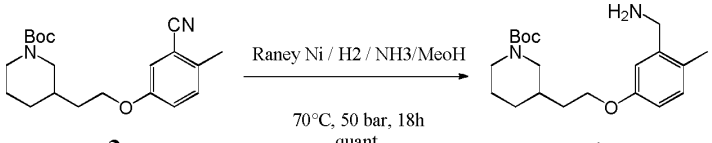


3

To a solution of N-Boc-3-(2-hydroxyethyl)piperidine (21 g, 91.7 mmol, 1.0 eq.) in dry DMF (180 mL) was added NaH (3.7 g, 60%, 91.7 mmol, 1.0 eq.). The resulting mixture was stirred for 30 minutes before the addition dropwise of a solution of 5-Fluoro-2-methylbenzonitrile (12.4 g, 91.7 mmol, 1.0 eq.) in dry DMF (40 mL). Once added, the mixture was heated at 60°C. After 20 hours of heating, LC-MS monitoring showed 78% conversion, so, after cooling to room temperature, additional NaH was added (3.7 g, 60%, 91.7 mmol, 1.0 eq.). The mixture was stirred again at room temperature for 30 minutes before heating at 60°C for 7 hours. Once cooled, the reaction mixture was quenched carefully by addition of saturated NH_4Cl solution, and extracted three times with TBME. The combined organic phase was washed once with saturated NH_4Cl solution, once with saturated $NaHCO_3$ solution, three times with water and once with brine. Once dried over $MgSO_4$ and filtered, the solvent was evaporated under reduced pressure to obtain 33 g of crude. This crude was purified on normal phase using Grace Reveleris and DCM/CyH as solvents to obtain 26.9 g of expected compound **3**.

Formula: $C_{20}H_{28}N_2O_3$, exact mass: 344.2, found: 345.1 $[M+H]^+$

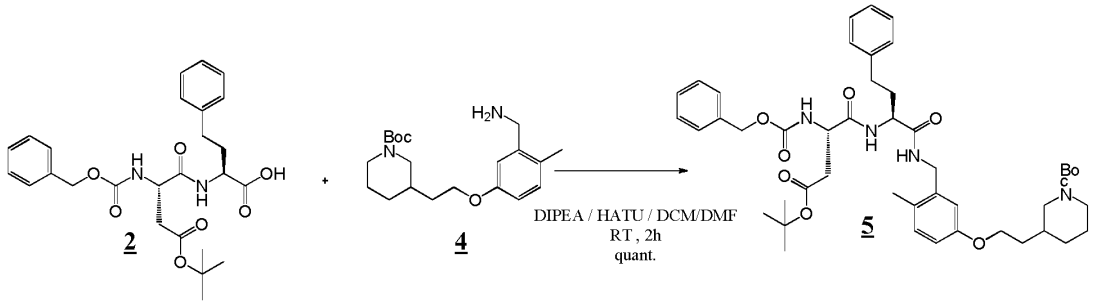
tert-butyl 3-(2-(3-(aminomethyl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate (**4**)



3 **4**

To a solution of **3** (22 g, 63.9 mmol; 1.0 eq.) in 7N ammonia in MeOH (1.2 L) was added Raney-Nickel (22 g, which was washed previously two times with MeOH). The resulting mixture was stirred at 70°C under 50 bar of H_2 for 18 hours. Once cooled, TLC monitoring showed no starting material, so, reaction mixture was filtered and the solid washed with MeOH. The combined filtrate was evaporated under reduced pressure to obtain 25 g of crude **4** as green oil that was used in the next step without purification.

tert-butyl 3-(2-(3-((5S,8S)-5-(2-(tert-butoxy)-2-oxoethyl)-3,6,9-trioxo-8-phenethyl-1-phenyl-2-oxa-4,7,10-triazaundecan-11-yl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate (**5**)

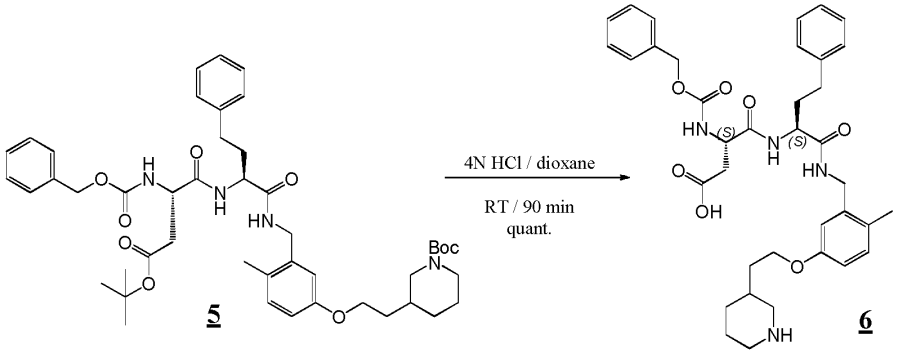


2 4 5

To a solution of **2** (34 g, 70.2 mmol, 1.0 eq.), **4** (24.5 g, 70.2 mmol, 1.0 eq.) and HATU (39.2 g, 103.2 mmol, 1.5 eq.) in DCM (0.86 L) and dry DMF (0.4 L) was added dropwise and in 20 minutes DIPEA (30.4 g, 38.9 mL, 242 mmol, 3.4 eq.). The reaction mixture was stirred at room temperature for 24 hours before evaporation of the DCM under reduced pressure. The resulting solution was added slowly over water (1.2 L) and then stirred at room temperature. The resulted upper layer was decanted and stirred again three times with more water. After final decantation, the slurry was dissolved with ACN and evaporated under reduced pressure. The resulted solid containing water was further co-evaporated three times once dissolved with ACN to obtain 62 g of crude. This crude was purified in normal phase using Grace Reveleris and DCM/CyH as solvents to obtain 43 g of expected compound **5**.

Formula: $C_{46}H_{62}N_4O_9$, exact mass: 814.5, found: 815.6 $[M+H]^+$

(3S)-3-(((benzyloxy)carbonyl)amino)-4-(((2S)-1-((2-methyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoic acid (**6**)

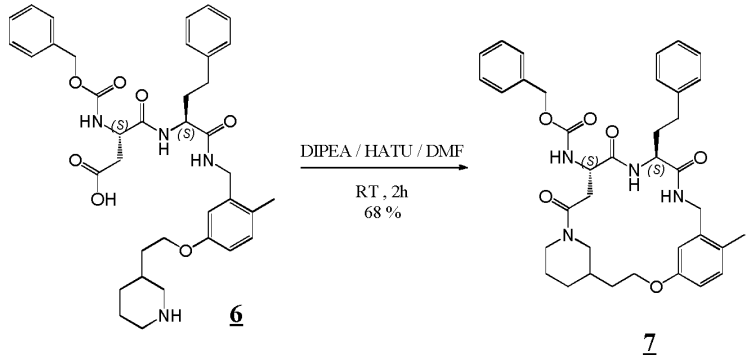


5 6

39.84 g (48.9 mmol) starting material **5** were dissolved in 40 ml 4 M HCl in dioxane and stirred at room temperature for 90 min. The solution was concentrated and stirred with additional 20 ml of 4 M HCl in dioxane at 60 °C for 1 h. Volatiles were removed under reduced pressure. Coevaporation with acetonitrile. Crude product **6** was used in the next step without further purification.

Formula: $C_{37}H_{46}N_4O_7$, exact mass: 658.3, found: 659.6 $[M+H]^+$

benzyl ((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate (**7**)



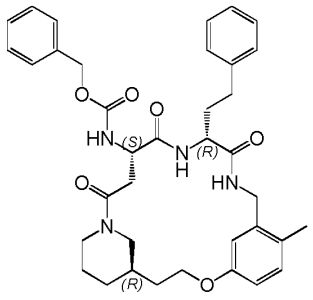
6 **7**

22.3 g (59 mmol) HATU were dissolved in 80 ml DMF. 48.9 mmol amino acid **6** in 114 ml DMF and 51.2 ml DIPEA were added dropwise at room temperature. The reaction mixture was distributed between ethyl acetate and 2 N NaOH solution. Some product precipitated and was collected and washed with MeOH. The organic phase was dried and evaporated. The remaining was triturated with methanol. Combined products summed up to 21.6 g of **7**.

Formula: $C_{37}H_{44}N_4O_6$, exact mass: 640.3, found:641.4 $[M+H]^+$

In analogy to compound **7** the following diastereomers **289**, **290**, **291** and **292** were synthesized utilizing enantiomerically pure and commercially available building blocks as depicted in the related structures:

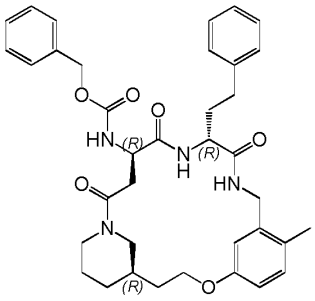
benzyl ((13R,9R,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate (**289**)



289

Formula: $C_{37}H_{44}N_4O_6$, exact mass: 640.3, found: 641.5 $[M+H]^+$

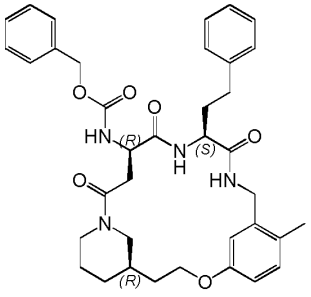
benzyl ((13R,9R,12R)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate (**290**)



290

Formula: $C_{37}H_{44}N_4O_6$, exact mass: 640.3, found: 641.5 $[M+H]^+$

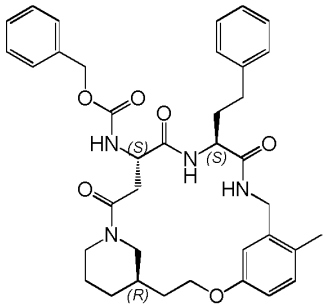
benzyl ((13R,9S,12R)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate (**291**)



291

Formula: $C_{37}H_{44}N_4O_6$, exact mass: 640.3, found: 641.5 $[M+H]^+$

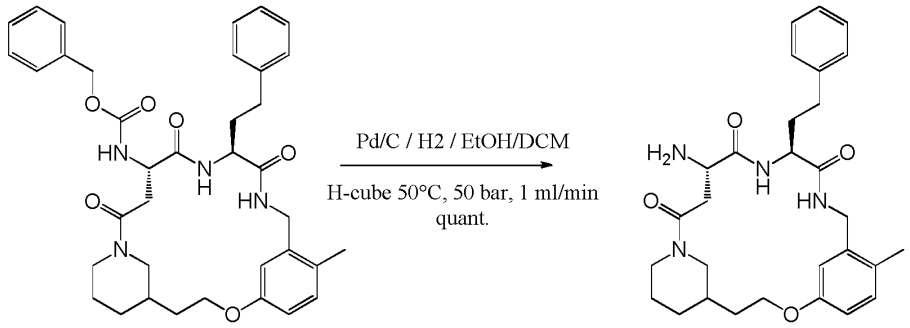
benzyl ((13R,9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate (**292**)



292

Formula: $C_{37}H_{44}N_4O_6$, exact mass: 640.3, found: 641.4 $[M+H]^+$

(9S,12S)-12-amino-5[4]-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione (**8**)

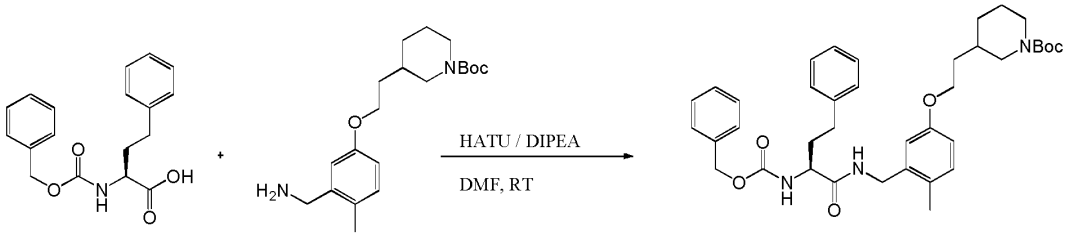


7 **8**

6.8 g benzyl carbamate **7** were dissolved EtOH/DCM (5:1) and hydrogenated with an H-cube (ThalesNano), 10 % Pd/C at 50°C under 50 bar H2 and a flow rate of 1 ml/min. 4 cycles were necessary to completely remove the protecting group. Quantitative yield after evaporation. Formula: $C_{29}H_{38}N_4O_4$, exact mass: 506.3, found: 507.3 $[M+H]^+$

Example A-2: Preparation of macrocyclic compounds 13, 16, 19 and 22

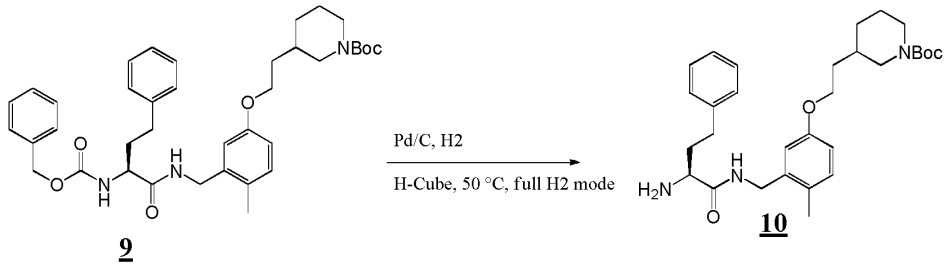
tert-butyl 3-(2-(3-(((S)-2-(((benzyloxy)carbonyl)amino)-4-phenylbutanamido)methyl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate (**9**)



4 **9**

Synthesis according to general procedure B with 473 mg amine **4** and 350 mg Cbz-hPhe. Purification was achieved by normal phase flash chromatography.
Formula: $C_{38}H_{49}N_3O_6$, exact mass: 643.4, found: 644.4 $[M+H]^+$

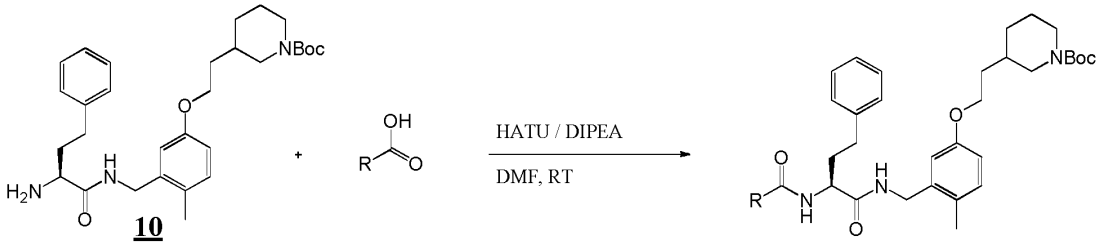
tert-butyl 3-(2-(3-(((S)-2-amino-4-phenylbutanamido)methyl)-4-methylphenoxy)ethyl) piperidine-1-carboxylate (**10**)



9 **10**

Following general procedure C using 260 mg Cbz-protected amine dissolved in 100 ml ethyl acetate / ethanol (1:1). H-Cube conditions: 1 ml/min, 50°C, full H2 mode. After removing of volatiles under reduced pressure the product was used without further purification.

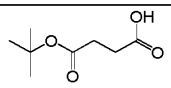
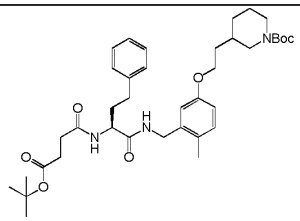
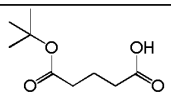
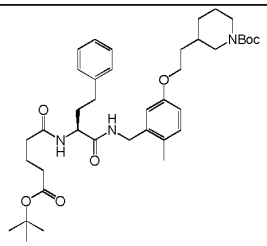
Amide derivatives of amine **10**

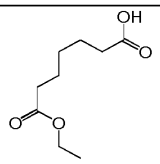
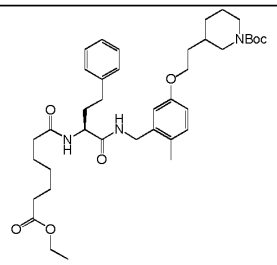
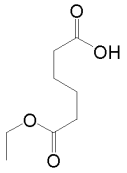
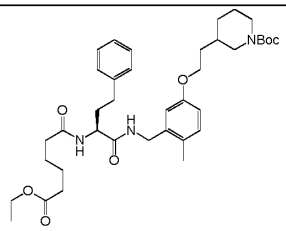


10

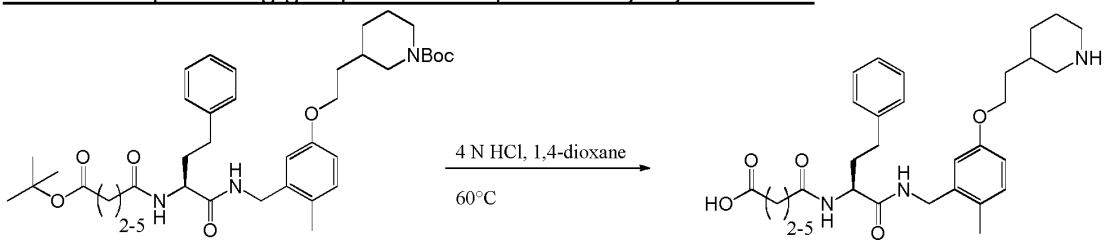
According to general procedure B with 75 mg amine **10**. Purification was achieved by normal phase flash chromatography

Table A-1

Cpd No	Carboxylic acid	structure	name	exact mass	$[M+H]^+$ found
11			tert-butyl 3-(2-(3-(((S)-2-(4-(tert-butoxy)-4-oxobutanamido)-4-phenylbutanamido)methyl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate	665.4 $C_{38}H_{55}N_3O_7$	666.6
17			tert-butyl 3-(2-(3-(((S)-2-(5-(tert-butoxy)-5-oxopentanamido)-4-phenylbutanamido)methyl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate	679.4 $C_{39}H_{57}N_3O_7$	680.6

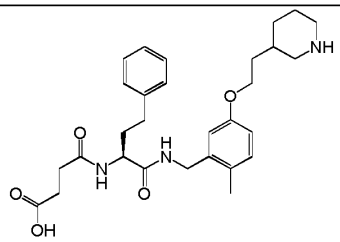
20			tert-butyl 3-(2-(3-(((S)-2-(7-ethoxy-7-oxoheptanamido)-4-phenylbutanamido)methyl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate	679.4 $C_{39}H_{57}N_3O_7$	680.7
14			tert-butyl 3-(2-(3-(((S)-2-(6-ethoxy-6-oxohexanamido)-4-phenylbutanamido)methyl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate	665.4 $C_{38}H_{55}N_3O_7$	666.8

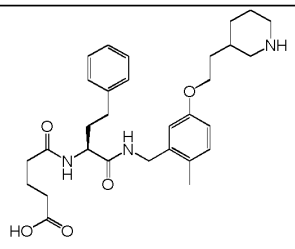
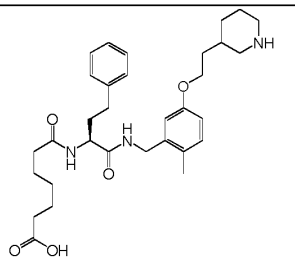
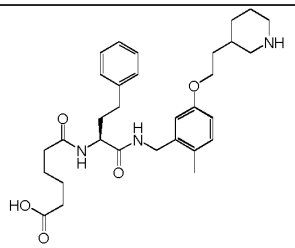
Removal of protecting groups from compounds **11, 14, 17** and **20**



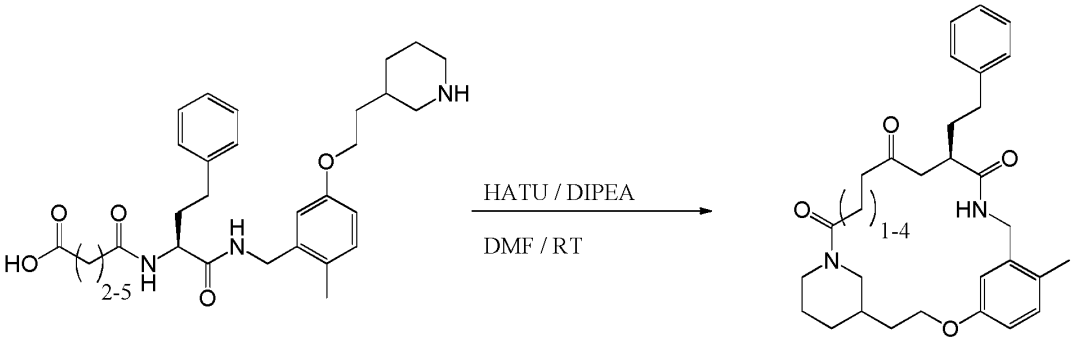
Protecting groups were cleaved according to general procedure D stirring compounds in 4 N HCl / 1,4-dioxane at 60 °C for about 30 min.

Table A-2

Cpd no	starting material	product structure	name	exact mass	$[M+H]^+$ found
12	**11**		4-(((2S)-1-((2-methyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoic acid	509.3 $C_{29}H_{39}N_3O_5$	510.2

18	**17**		5-(((2S)-1-((2-methyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-5-oxopentanoic acid	523.3 $C_{30}H_{41}N_3O_5$	524.3
21	**20**		7-(((2S)-1-((2-methyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-7-oxoheptanoic acid	551.3 $C_{32}H_{45}N_3O_5$	552.3
15	**14**		6-(((2S)-1-((2-methyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-6-oxohexanoic acid	537.3 $C_{31}H_{43}N_3O_5$	538.7

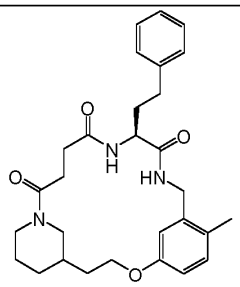
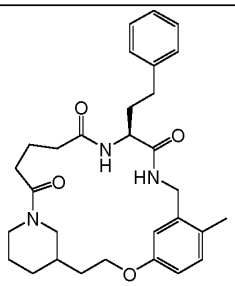
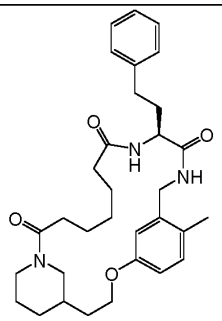
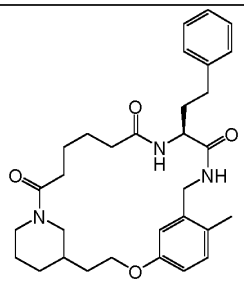
Macrocyclization of amino acids **12, 15, 18** and **21**



Macrocyclizations according to general procedure A. reaction mixtures were diluted with some methanol and purified via HPLC.

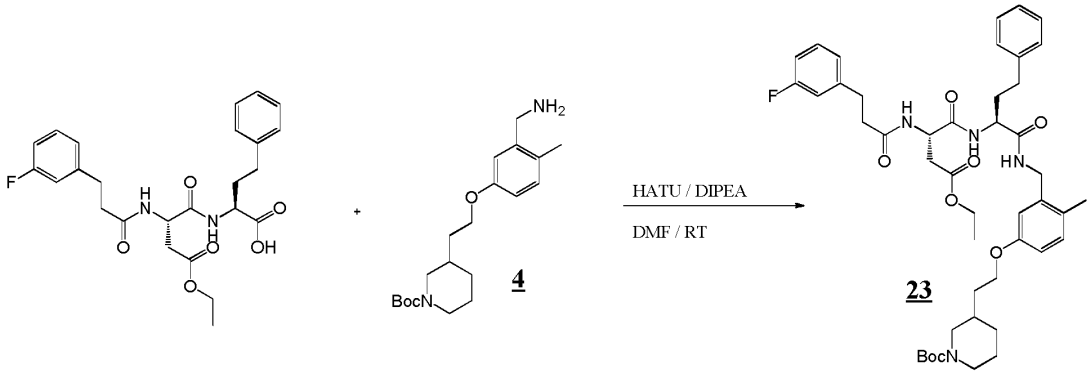
Table A-3

Startingmaterial		Product				
Cpd	Amount [mmol]	structure	name	**Cpd no**	exact mass	$[M+H]^+$ found

12	0.09		(9S)-5^4-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione	**13**	491.3 $C_{29}H_{37}N_3O_4$	492.5
18	0.171		(9S)-5^4-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclopentadecaphane-8,11,15-trione	**19**	505.3 $C_{30}H_{39}N_3O_4$	506.5
21	0.196		(9S)-5^4-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacycloheptadecaphane-8,11,17-trione	**22**	533.3 $C_{32}H_{43}N_3O_4$	534.5
15	0.138		(9S)-5^4-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclohexadecaphane-8,11,16-trione	**16**	519.3 $C_{31}H_{41}N_3O_4$	520.5

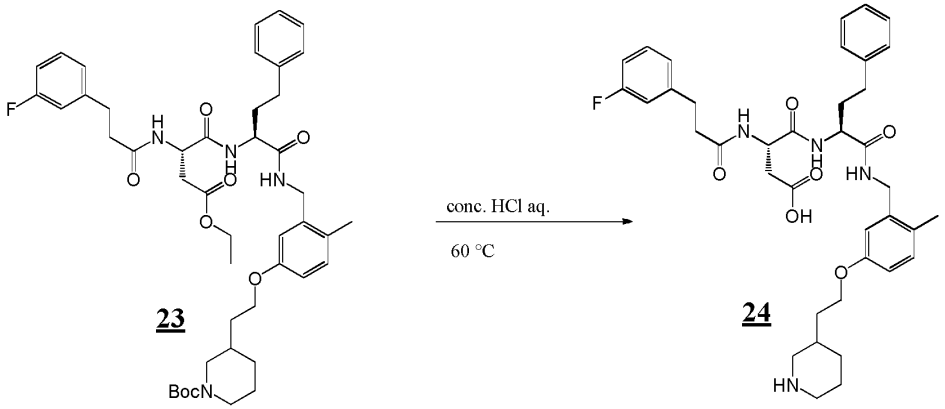
Example A-3: Preparation of Macrocyclic compounds 25, 26, 27, 28, 29, 30, 31, 32, 33, 40, 41, 42, 60, 61, 62, 63, 64, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 174, 175, 176, 177, 182, 219, 284, 285, 286, 287, 288, 323, 324, 327, 328, 329, 330, 331, 332, 333, 334, 335, 341, 369, 373,

tert-butyl 3-(2-(3-(((S)-2-((S)-4-ethoxy-2-(3-(3-fluorophenyl)propanamido)-4-oxobutanamido)-4-phenylbutanamido)methyl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate (**23**)



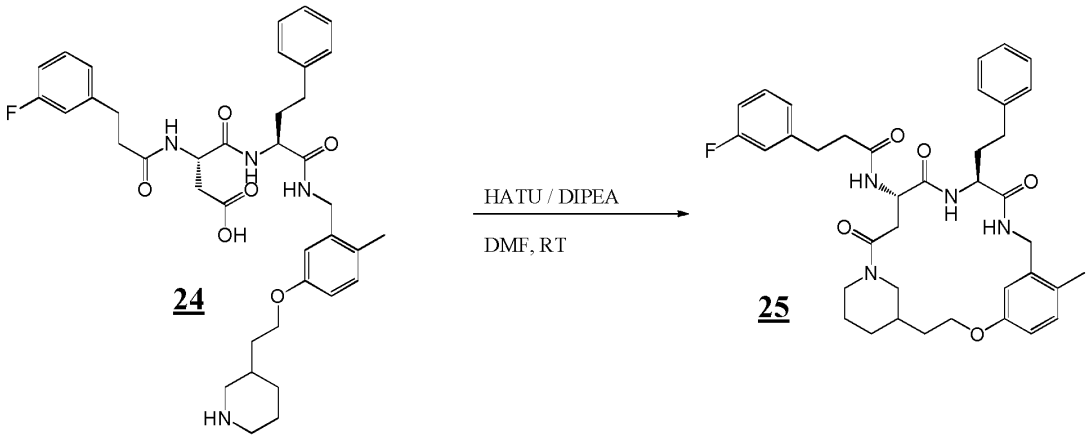
Amide coupling according to general procedure B with 113 mg carboxylic acid (prepared in analogy to compound **2**) and 108 mg benzyl amine **4**. Purification was achieved by normal phase flash chromatography applying a cyclohexane/ ethyl acetate gradient.
Formula: $C_{45}H_{59}FN_4O_8$, exact mass: 802.4, found: 703.6 [M+H-Boc]+

(3S)-3-(3-(3-fluorophenyl)propanamido)-4-(((2S)-1-((2-methyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoic acid (**24**)



Both protecting groups were cleaved according to general procedure D in concentrated HCl in water at 60 °C for 90 min.
Formula: $C_{38}H_{47}FN_4O_6$, exact mass: 674.3, found: 675.2 [M+H]+

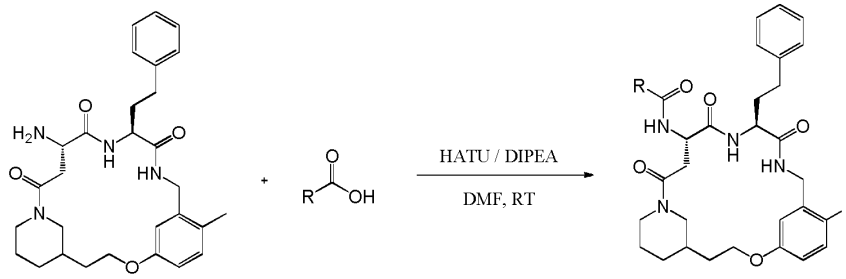
3-(3-fluorophenyl)-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide (**25**)



24 25

0.146 mmol amino acid **24** were cyclized according to general procedure A. Purification via RP18 flash chromatography.
Formula: $C_{38}H_{45}FN_4O_5$, exact mass: 656.3, found: 657.3 [M+H]+

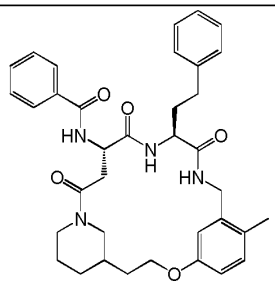
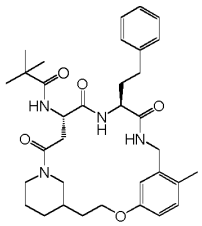
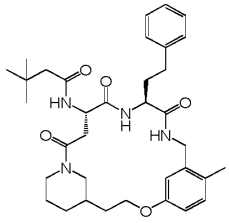
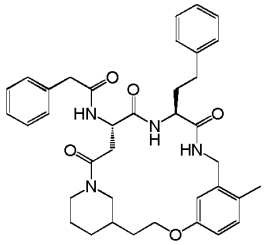
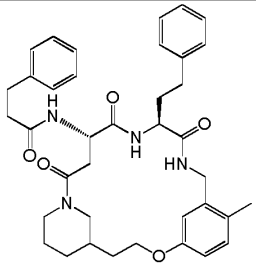
Amide derivatizations of compound **8** according to general procedure B

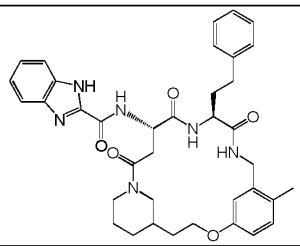
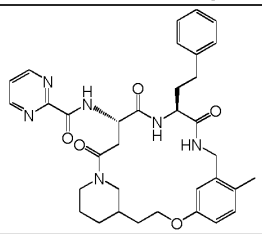
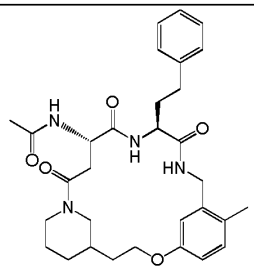
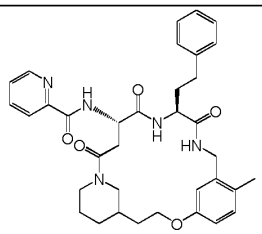
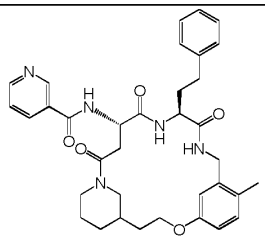
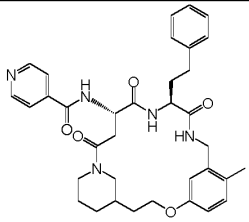
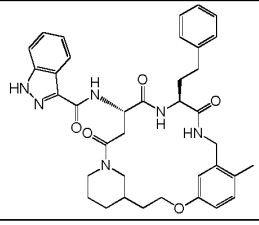


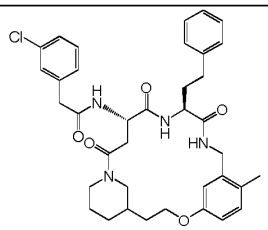
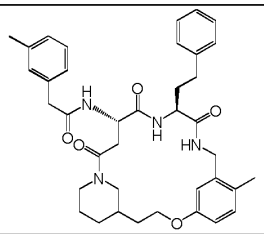
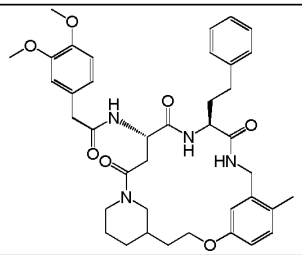
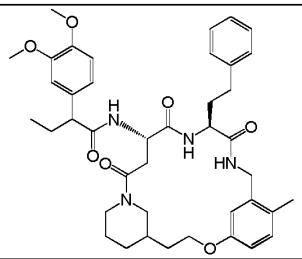
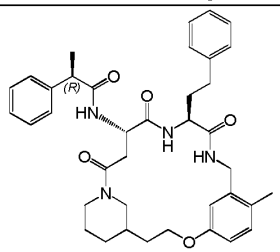
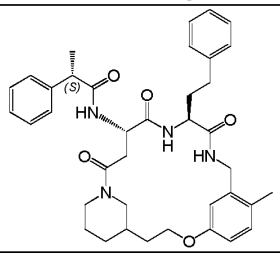
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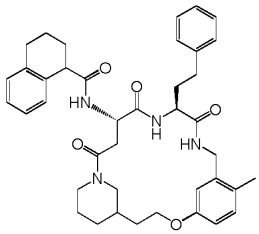
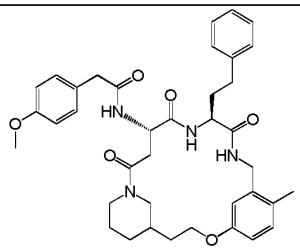
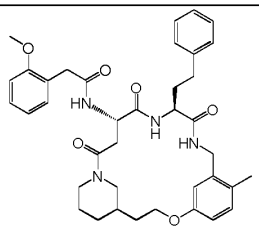
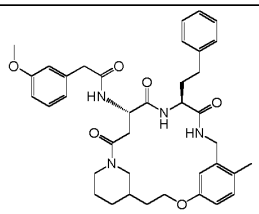
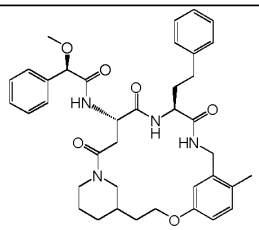
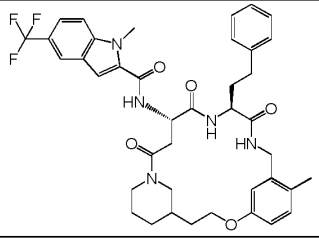
Amine **8** (e.g. 20 mg) was coupled with carboxylic acids according to general procedure B to give amides disclosed in table below. Purifications were achieved by HPLC or reversed phase flash chromatography.

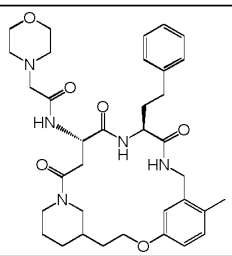
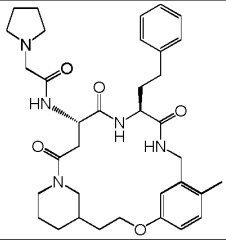
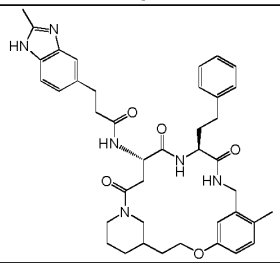
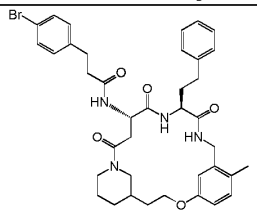
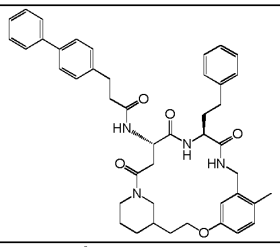
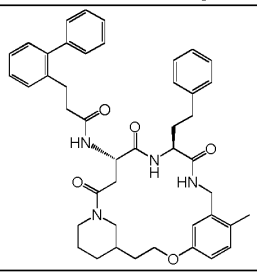
Table A-4

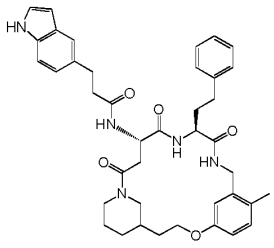
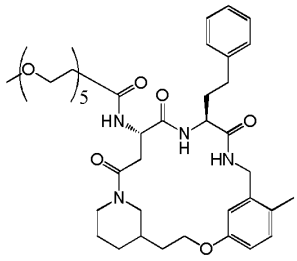
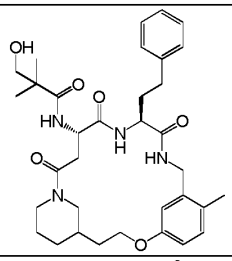
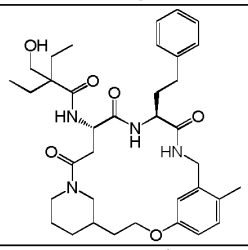
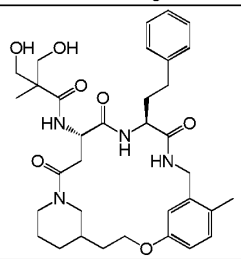
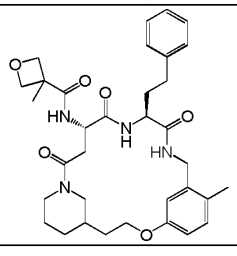
Cpd No	structure	name	Exact mass	$[M+H]^+$ found
26		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)benzamide	610.3 $C_{36}H_{42}N_4O_5$	611.4
27		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)pivalamide	590.3 $C_{34}H_{46}N_4O_5$	591.4
28		3,3-dimethyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)butanamide	604.4 $C_{35}H_{48}N_4O_5$	605.4
29		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-phenylacetamide	624.3 $C_{37}H_{44}N_4O_5$	625.5
30		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-phenylpropanamide	638.3 $C_{38}H_{46}N_4O_5$	639.5

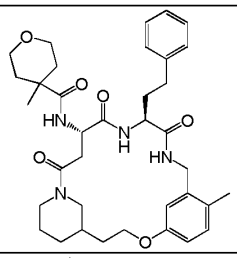
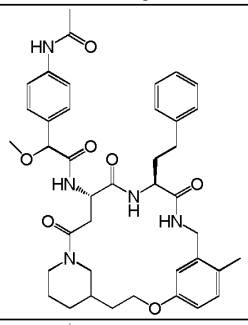
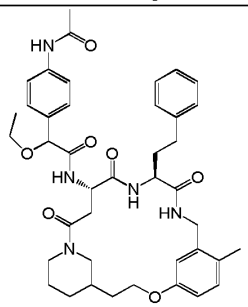
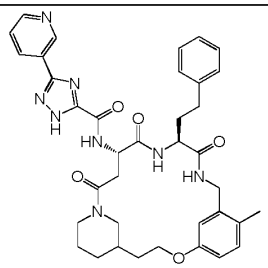
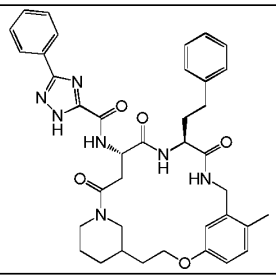
31		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-1H-benzo[d]imidazole-2-carboxamide	650.3 $C_{37}H_{42}N_6O_5$	651.1
32		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)pyrimidine-2-carboxamide	612.3 $C_{34}H_{40}N_6O_5$	613.4
33		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	548.3 $C_{31}H_{40}N_4O_5$	549.3
40		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)picolinamide	611.3 $C_{35}H_{41}N_5O_5$	612.4
41		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)nicotinamide	611.3 $C_{35}H_{41}N_5O_5$	612.4
42		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)isonicotinamide	611.3 $C_{35}H_{41}N_5O_5$	612.3
60		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-1H-indazole-3-carboxamide	650.3 $C_{37}H_{42}N_6O_5$	651.5

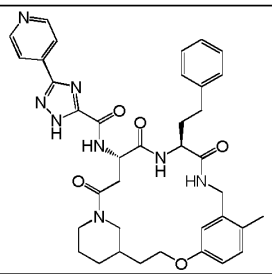
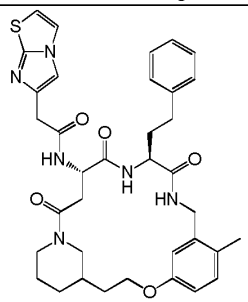
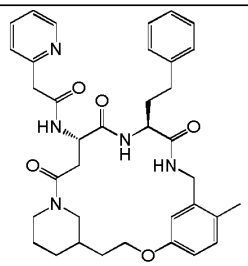
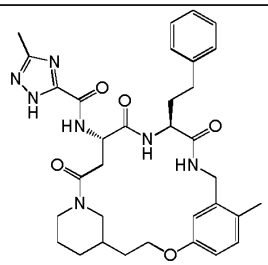
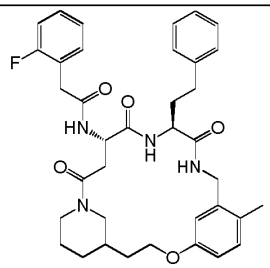
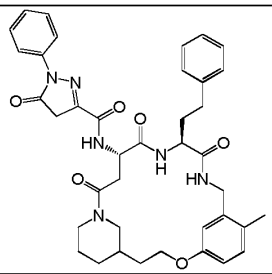
61		2-(3-chlorophenyl)-N-((9S,12S)-54-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	658.3 $C_{37}H_{43}ClN_4O_5$	659.3
62		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(m-tolyl)acetamide	638.3 $C_{38}H_{46}N_4O_5$	639.4
63		2-(3,4-dimethoxyphenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	684.4 $C_{39}H_{48}N_4O_7$	685.4
64		2-(3,4-dimethoxyphenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)butanamide	712.4 $C_{41}H_{52}N_4O_7$	713.4
80		(2R)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-phenylpropanamide	638.3 $C_{38}H_{46}N_4O_5$	639.4
81		(2S)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-phenylpropanamide	638.3 $C_{38}H_{46}N_4O_5$	639.4

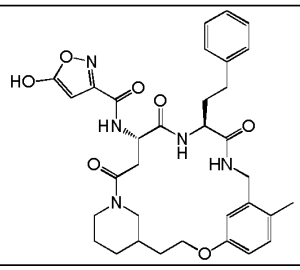
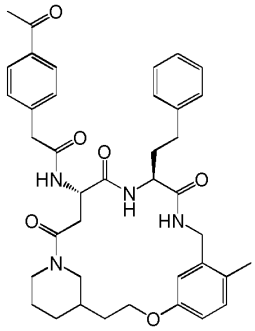
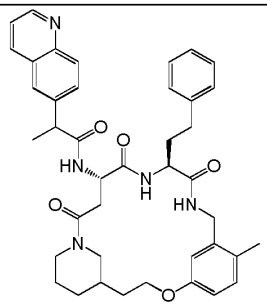
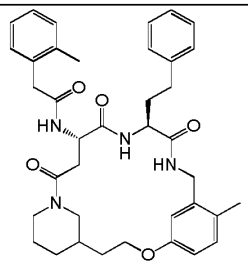
82		N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-1,2,3,4-tetrahydronaphthalene-1-carboxamide	664.4 $C_{40}H_{48}N_4O_5$	665.4
83		2-(4-methoxyphenyl)-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	654.3 $C_{38}H_{46}N_4O_6$	655.4
84		2-(2-methoxyphenyl)-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	654.3 $C_{38}H_{46}N_4O_6$	655.3
85		2-(3-methoxyphenyl)-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	654.3 $C_{38}H_{46}N_4O_6$	655.4
86		(2R)-2-methoxy-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-phenylacetamide	654.3 $C_{38}H_{46}N_4O_6$	655.4
87		1-methyl-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-5-(trifluoromethyl)-1H-indole-2-carboxamide	731.3 $C_{40}H_{44}F_3N_5O_5$	732.4

88		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-morpholinoacetamide	633.4 $C_{35}H_{47}N_5O_6$	634.4
89		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(pyrrolidin-1-yl)acetamide	617.4 $C_{35}H_{47}N_5O_5$	618.4
174		3-(2-methyl-1H-benzo[d]imidazol-6-yl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide	692.4 $C_{40}H_{48}N_6O_5$	693.4
175		3-(4-bromophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide	716.3 $C_{38}H_{45}BrN_4O_5$	717.3
176		3-([1,1'-biphenyl]-4-yl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide	714.4 $C_{44}H_{50}N_4O_5$	715.4
177		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(2-phenoxyphenyl)propanamide	714.4 $C_{44}H_{50}N_4O_5$	715.4

182		3-(1H-indol-5-yl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide	677.4 $C_{40}H_{47}N_5O_5$	678.5
219		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2,5,8,11,14-pentaoxaheptadecan-17-amide	768.4 $C_{41}H_{60}N_4O_{10}$	769.6
284		3-hydroxy-2,2-dimethyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide	606.3 $C_{34}H_{46}N_4O_6$	607.5
285		2-ethyl-2-(hydroxymethyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)butanamide	634.4 $C_{36}H_{50}N_4O_6$	635.5
286		3-hydroxy-2-(hydroxymethyl)-2-methyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide	622.3 $C_{34}H_{46}N_4O_7$	623.5
287		3-methyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)oxetane-3-carboxamide	604.3 $C_{34}H_{44}N_4O_6$	605.7

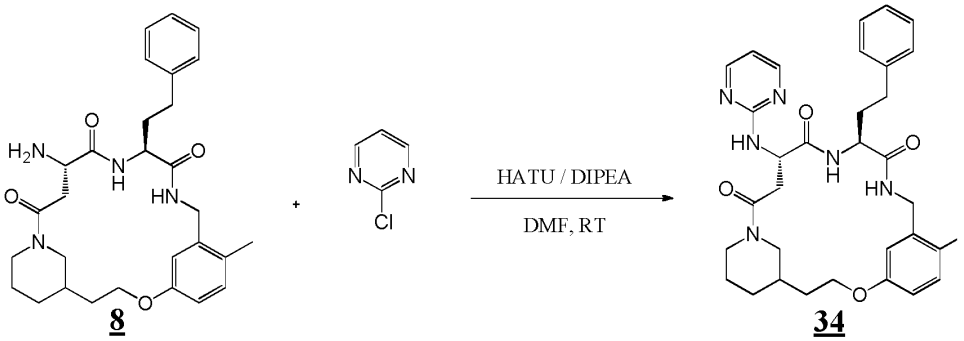
288		4-methyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)tetrahydro-2H-pyran-4-carboxamide	632.4 $C_{36}H_{48}N_4O_6$	633.5
323		2-(4-acetamidophenyl)-2-methoxy-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	711.4 $C_{40}H_{49}N_5O_7$	712.4
324		2-(4-acetamidophenyl)-2-ethoxy-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	725.4 $C_{41}H_{51}N_5O_7$	726.4
327		N-((9S,12R)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(3-(pyridin-3-yl)-1H-1,2,4-triazol-5-yl)acetamide	692.3 $C_{38}H_{44}N_8O_5$	693.4
328		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(3-phenyl-1H-1,2,4-triazol-5-yl)acetamide	691.3 $C_{39}H_{45}N_7O_5$	692.4

329		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(3-(pyridin-4-yl)-1H-1,2,4-triazol-5-yl)acetamide	692.3 $C_{38}H_{44}N_8O_5$	693.3
330		2-(imidazo[2,1-b]thiazol-6-yl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	670.3 $C_{36}H_{42}N_6O_5S$	671.3
331		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(pyridin-2-yl)acetamide	625.3 $C_{36}H_{43}N_5O_5$	507.4
332		2-(3-methyl-1H-1,2,4-triazol-5-yl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	629.3 $C_{34}H_{43}N_7O_5$	630.4
333		2-(2-fluorophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	642.3 $C_{37}H_{43}FN_4O_5$	643.4
334		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)acetamide	706.3 $C_{40}H_{46}N_6O_6$	707.4

335		2-(5-hydroxyisoxazol-3-yl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	631.3 $C_{34}H_{41}N_5O_7$	632.4
341		2-(4-acetylphenyl)-N-((9S,12S)-54-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	666.3 $C_{39}H_{46}N_4O_6$	667.4
369		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(quinolin-6-yl)propanamide	689.4 $C_{41}H_{47}N_5O_5$	690.4
373		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(o-tolyl)acetamide	638.3 $C_{38}H_{46}N_4O_5$	639.4

Example A-4: Preparation of macrocyclic compounds 34, 35, 36, 37, 38, 39, 43, 44, 45, and 364

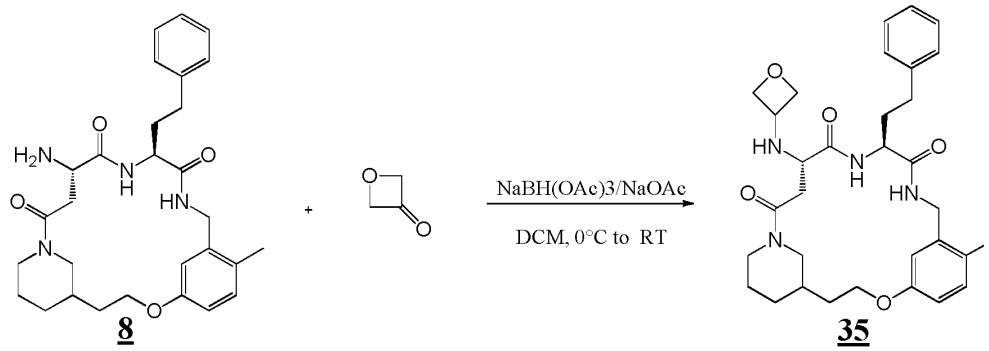
(9S,12S)-5^4-methyl-9-phenethyl-12-(pyrimidin-2-ylamino)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione (**34**)



8 **34**

20 mg amine **8**, 9 mg 2-chloropyrimidine and 25 mg K_3PO_4 in 0.5 ml DMF were heated to 100 °C over night. Diluted with some methanol, filtered and purified via HPLC.
Formula: $C_{33}H_{40}N_6O_4$, exact mass: 584.3, found: 585.3 $[M+H]^+$

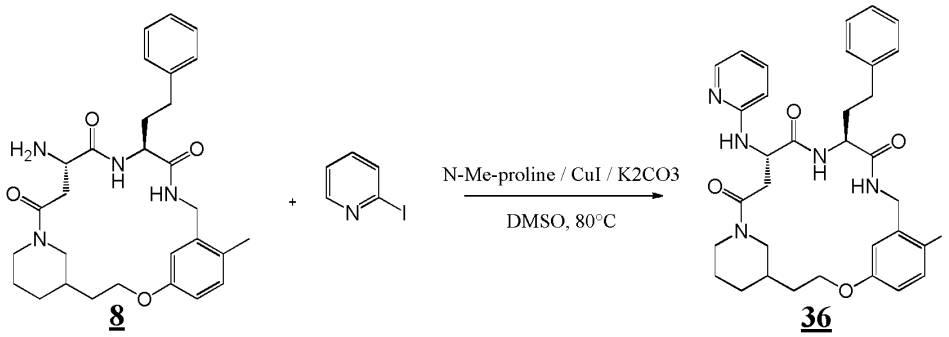
(9S,12S)-5^4-methyl-12-(oxetan-3-ylamino)-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione (**35**)



8 **35**

20 mg amine **8** and 4 mg 3-oxetanone in DCM were cooled in an ice bath. Sodium acetate (0.5 eq.) and 3 eq. sodium triacetoxyborohydride were added and the reaction mixture was allowed to warm to room temperature overnight. Additional 4.3 mg ketone and 17 mg borohydride were added and stirring was continued for another 3h when some methanol was added and the reaction mixture was purified via HPLC.
Formula: $C_{32}H_{42}N_4O_5$, exact mass: 562.3, found: 563.5 $[M+H]^+$

(9S,12S)-5^4-methyl-9-phenethyl-12-(pyridin-2-ylamino)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione (**36**)

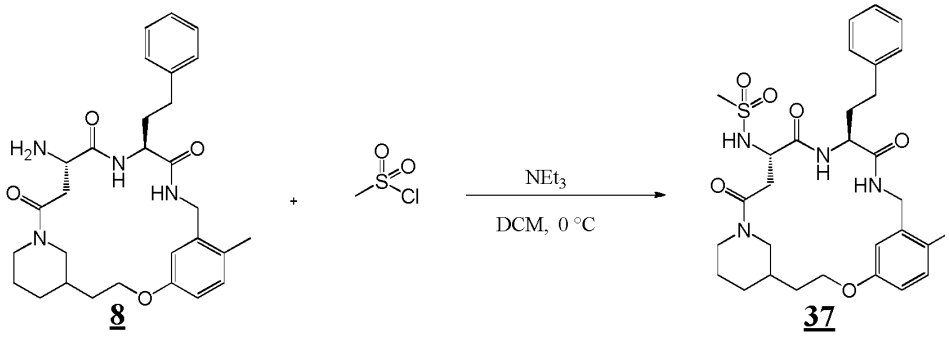


8 36

20 mg amine **8**, 6.4 mg 2-iodopyridine, 5.2 mg N-Me-proline, 3.8 mg CuI and 11.1 mg K_2CO_3 in 500 µl DMSO were heated to 80 °C for 24 h. The mixture was diluted with some methanol, filtered and purified via HPLC.

Formula: $C_{34}H_{41}N_5O_4$, exact mass: 583.3, found: 584.3 $[M+H]^+$

N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)methanesulfonamide (**37**)

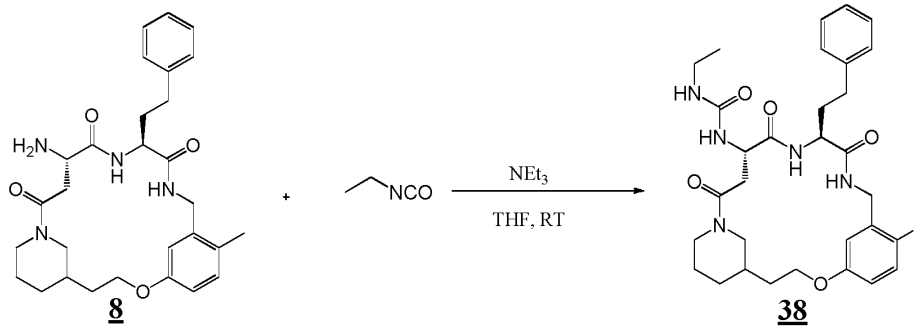


8 37

Compound **37** was synthesized according to general procedure E with 20 mg amine 8. Product was purified by HPLC.

Formula: $C_{30}H_{40}N_4O_6S$, exact mass: 584.3, found: 585.4 $[M+H]^+$

1-ethyl-3-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)urea (**38**)

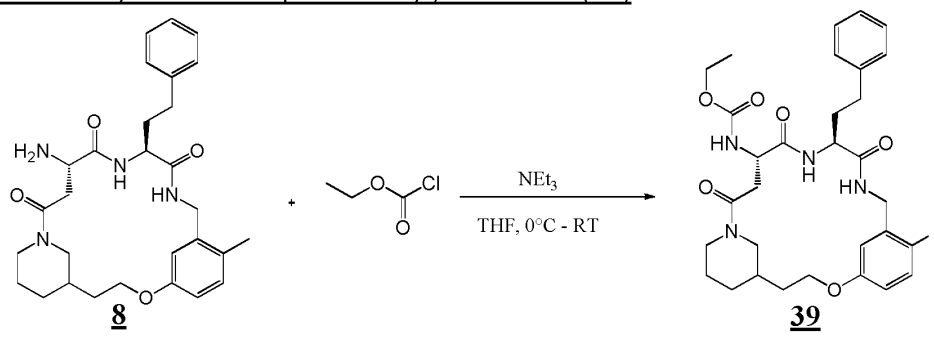


8 38

Compound **38** was synthesized according to general procedure F with 20 mg amine 8 in 0.5 ml THF.

Formula: $C_{32}H_{43}N_5O_5$, exact mass: 577.3, found: 578.4 $[M+H]^+$

ethyl ((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate (**39**)

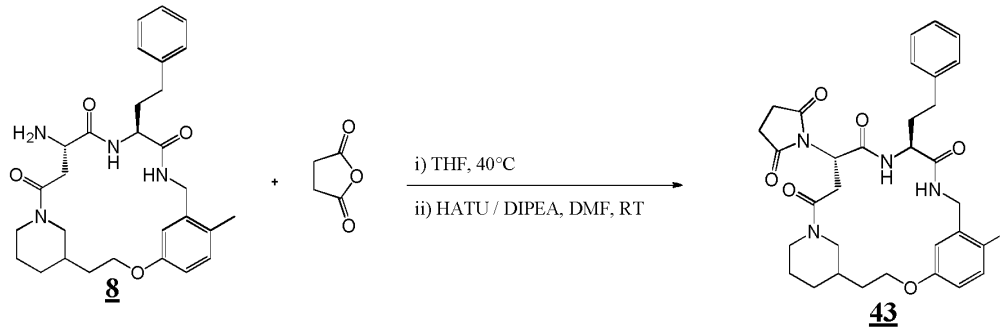


8 **39**

Compound **39** was synthesized according to general procedure G with 20 mg amine 8 in 0.5 ml THF.

Formula: $C_{32}H_{42}N_4O_6$, exact mass: 578.3, found: 579.4 $[M+H]^+$

(9S,12S)-12-(2,5-dioxopyrrolidin-1-yl)-5[4]-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione (**43**)

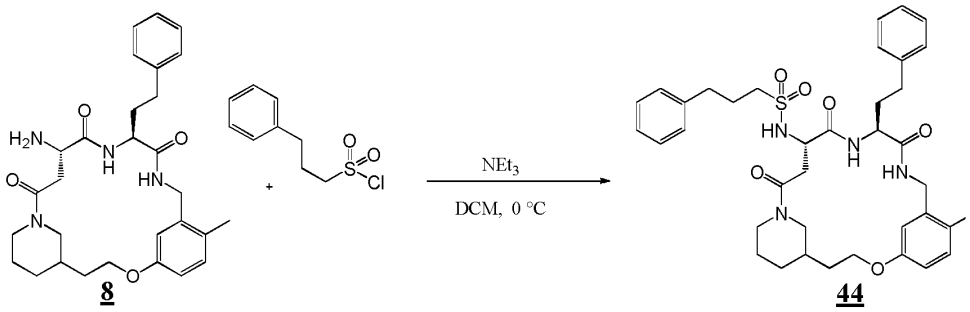


8 **43**

10 mg amine **8** and 2.0 mg succinic anhydride in 0.3 ml THF were stirred at 40 °C overnight. Volatiles were removed under reduced pressure and the residue dissolved in 300 µl DMF. 8.4 mg HATU and 20.9 µl DIPEA in additional 300 µl DMF were added at RT. After complete reaction some methanol was added and purification was achieved by HPLC.

Formula: $C_{33}H_{40}N_4O_6$, exact mass: 588.3, found: 589.4 $[M+H]^+$

N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-phenylpropane-1-sulfonamide (**44**)

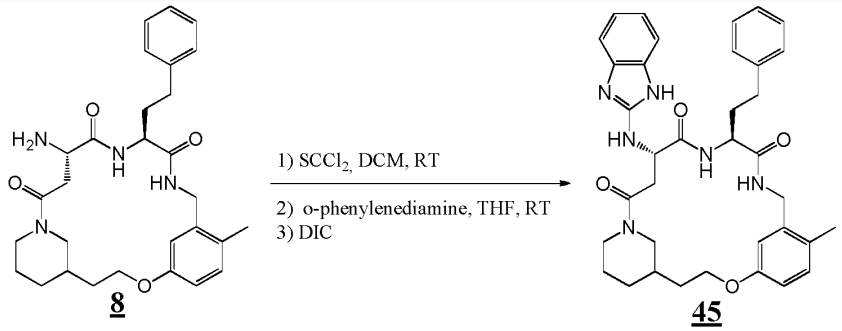


8 44

Compound **44** was synthesized according to general procedure E with 20 mg amine 8. Product was purified by HPLC.

Formula: $C_{38}H_{48}N_4O_6S$, exact mass: 688.3, found: 689.5 $[M+H]^+$

(9S,12S)-12-((1H-benzo[d]imidazol-2-yl)amino)-5[4]-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione (**45**)

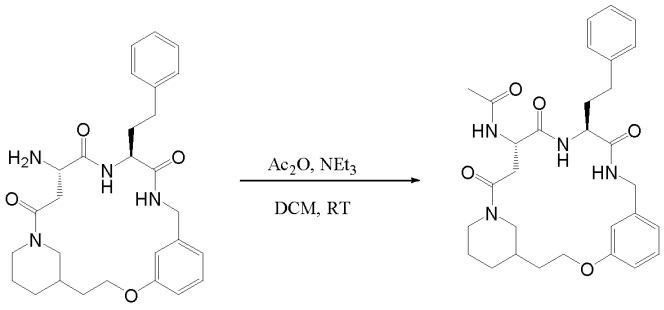


8 45

To 20 mg amine **8** in 1 ml DCM 30.5 µl thiophosgene were added. 1 ml saturated $NaHCO_3$ solution was added and the mixture was stirred for until starting material was consumed. The organic phase was separated, dried and volatiles were removed under reduced pressure. The residue and 5.2 mg o-phenylenediamine were dissolved in 0.5 ml THF and stirred overnight to give the intermediate thiourea. 5.6 mg *N,N'*-diisopropylcarbodiimid were added and the mixture was kept at 55 °C until reaction was almost complete. The mixture was diluted with some methanol and purified by HPLC.

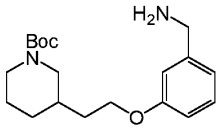
Formula: $C_{36}H_{42}N_6O_4$, exact mass: 622.3, found: 623.5 $[M+H]^+$

N-((9S,12S)-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide (**364**)



580 **364**

Compound **580** was made in analogy to compound **8** utilizing tert-butyl-3-(2-(3-aminomethyl(phenoxy)ethyl)piperidine-1-carboxylate **579** instead of amine **4**.

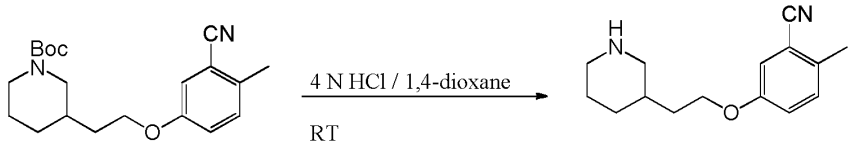


579

Formula: $C_{30}H_{38}N_4O_5$, exact mass: 534.3, found: 535.5 $[M+H]^+$

Example A-5: Preparation of macrocyclic compound 51

2-methyl-5-(2-(piperidin-3-yl)ethoxy)benzonitrile (**46**)

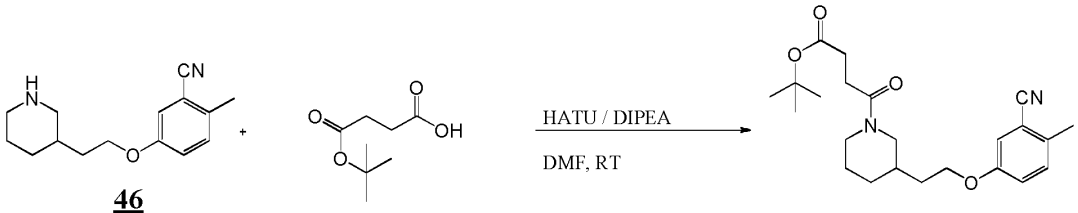


3 **46**

Compound **46** was prepared from 390 mg Boc-protected amine **3** according to general procedure D with 4 N HCl in 1,4-dioxane at RT. Raw product was coevaporated twice with methanol and use without further purification.

Formula: $C_{15}H_{20}N_2O$, exact mass: 244.2, found: 245.2 $[M+H]^+$

tert-butyl 4-(3-(2-(3-cyano-4-methylphenoxy)ethyl)piperidin-1-yl)-4-oxobutanoate (**47**)

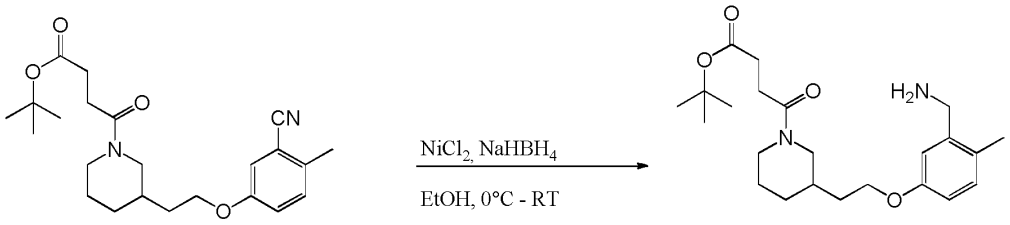


46 **47**

Synthesis according to general procedure B with 1.13 mmol amine **4** and 296 mg mono-tert.-butyl succinate. Purification was achieved by normal phase flash chromatography.

Formula: $C_{23}H_{32}N_2O_4$, exact mass: 400.2, found: 401.4 $[M+H]^+$

tert-butyl 4-(3-(2-(3-(aminomethyl)-4-methylphenoxy)ethyl)piperidin-1-yl)-4-oxobutanoate (**48**)

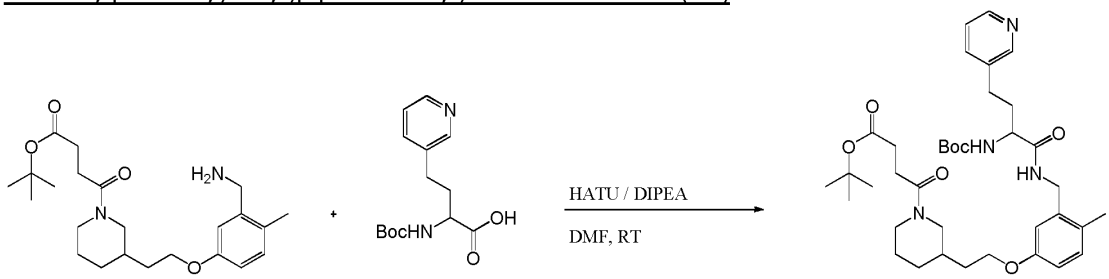


47 **48**

142 mg nitrile **47** and 91 mg $NiCl_2$ were stirred in 7 ml ethanol at 0 °C. 54 mg $NaBH_4$ were added and the mixture was allowed to come to room temperature. After 1h each same amounts as before of $NaBH_4$ and $NiCl_2$ were added. After 1h the mixture was filtered over Celite. Filtrate was concentrated under reduced pressure, distributed between water and ethyl acetate. The organic phase was sepatrated and the aqueous phase extracted several times with ethyl acetat. Combined organic phases were dried over $MgSO_4$ and solvent was removed under reduce pressure. The crude was used without further purification.

Formula: $C_{23}H_{36}N_2O_4$, exact mass: 404.3, found: 405.1 $[M+H]^+$

tert-butyl 4-(3-(2-(3-((2-((tert-butoxycarbonyl)amino)-4-(pyridin-3-yl)butanamido)methyl)-4-methylphenoxy)ethyl)piperidin-1-yl)-4-oxobutanoate (**49**)

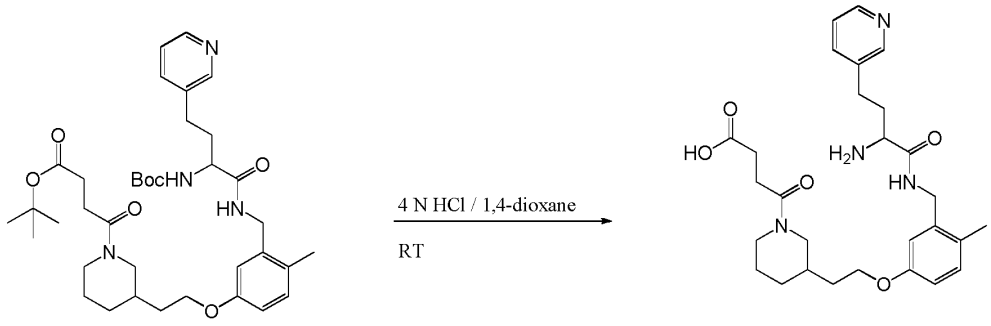


48 **49**

Synthesis according to general procedure B with 94 mg amine **48** and 50 mg 2-((tert-butoxycarbonyl)amino)-4-(pyridin-3-yl)butanoic acid. Purification was achieved by normal phase flash chromatography

Formula: $C_{37}H_{54}N_4O_7$, exact mass: 666.4, found: 667.4 $[M+H]^+$

4-(3-(2-(3-((2-amino-4-(pyridin-3-yl)butanamido)methyl)-4-methylphenoxy)ethyl) piperidin-1-yl)-4-oxobutanoic acid (**50**)

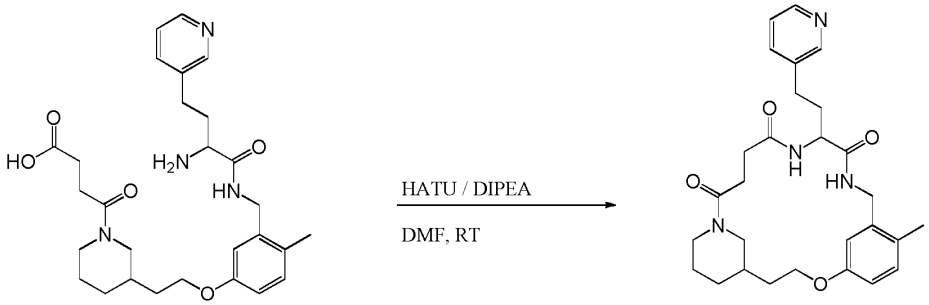


49 **50**

Protecting groups were cleaved according to general procedure D stirring compounds in 4 N HCl / 1,4-dioxane at room temperature. After deprotection was complete solvent was removed and the crude dissolved in acetonitrile and concentrated twice. Product used without further purification.

Formula: $C_{28}H_{38}N_4O_5$, exact mass: 510.3, found: 511.3 $[M+H]^+$

5[4]-methyl-9-(2-(pyridin-3-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione (**51**)



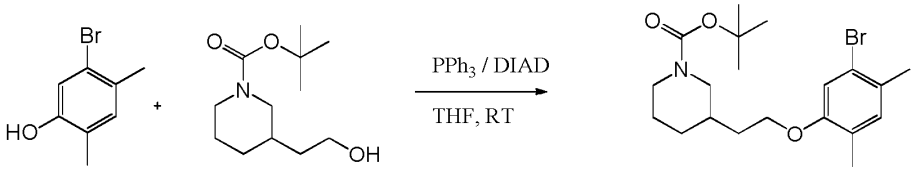
50 **51**

Macrocyclization was achieved according to general procedure A with 0.179 mmol amino acid **50**. Reaction mixtures were diluted with some methanol and purified via HPLC.

Formula: $C_{28}H_{36}N_4O_4$, exact mass: 492.3, found: 493.3 $[M+H]^+$

Example A-6: Preparation of macrocyclic compound 59

tert-butyl 3-(2-(5-bromo-2,4-dimethylphenoxy)ethyl)piperidine-1-carboxylate (**52**)

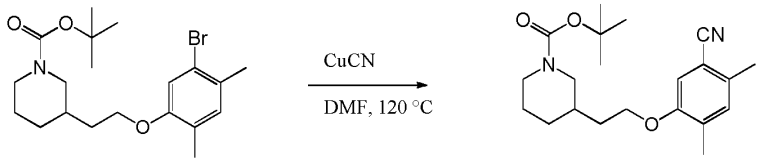


52

855 mg tert-butyl 3-(2-hydroxyethyl)piperidine-1-carboxylate, 500 mg 5-bromo-2,4-dimethylphenol and 978 mg PPh_3 were dissolved in 12 ml THF. 734 µl diisopropyl azodicarboxylate in 3 ml THF were added dropwise and the reaction was stirred for 2h at room temperature. The reaction was diluted with ethyl acetate and washed with saturated $NaHCO_3$ solution and brine. After drying the organic phase over $MgSO_4$ and removing volatiles under reduced pressure the crude was purified by normal phase flash chromatography.

Formula: $C_{20}H_{30}BrNO_3$, exact mass: 411.1, found: 414.1 $[M+H]^+$

tert-butyl 3-(2-(5-cyano-2,4-dimethylphenoxy)ethyl)piperidine-1-carboxylate (**53**)

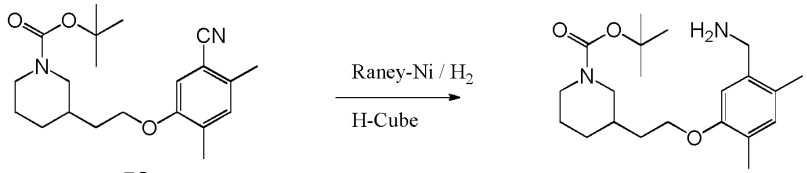


52 **53**

Bromide **52** (780 mg) and 340 mg CuCN in DMF were stirred at 120 °C for 4d. The mixture was diluted with ethyl acetate, washed with saturated $NaHCO_3$ solution and brine and dried over $MgSO_4$. Solvent was removed under reduced pressure and the residue was purified by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient).

Formula: $C_{21}H_{30}N_2O_3$, exact mass: 358.2, found: 358.3 $[M+H]^+$

tert-butyl 3-(2-(5-(aminomethyl)-2,4-dimethylphenoxy)ethyl)piperidine-1-carboxylate (**54**)

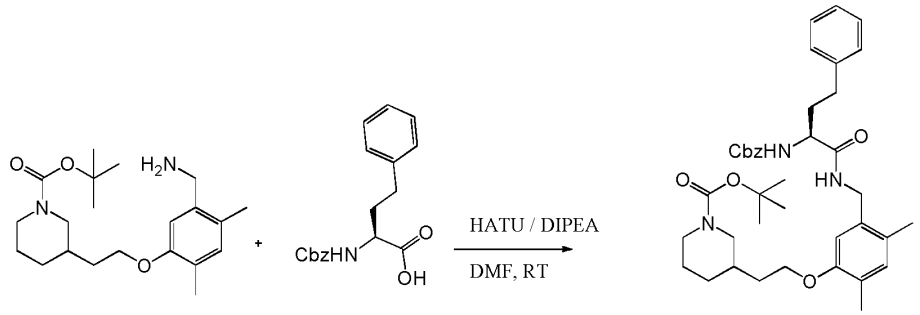


53 **54**

Nitrile **53** (432 mg) in 40 ml EtOH were reduced according to general procedure H in 4 cycles at 50 bar, 70 °C and 0.5 ml/min. After removing volatiles the residue was used without further purification.

Formula: $C_{21}H_{34}N_2O_3$, exact mass: 362.3, found: 363.3 $[M+H]^+$

tert-butyl 3-(2-(5-(((S)-2-(((benzyloxy)carbonyl)amino)-4-phenylbutanamido)methyl)-2,4-dimethylphenoxy)ethyl)piperidine-1-carboxylate (**55**)

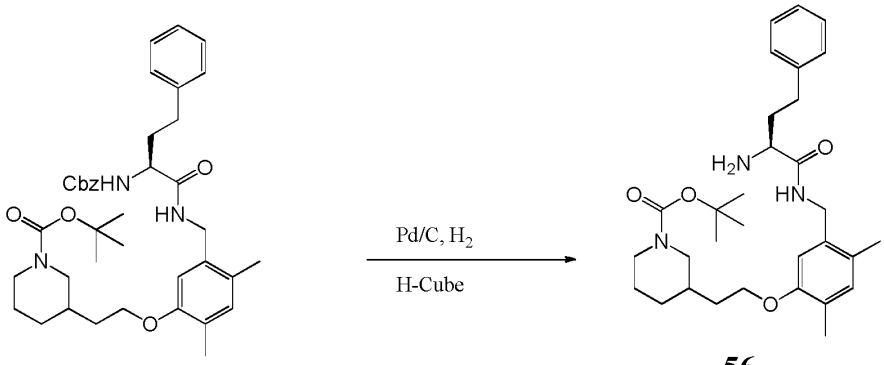


54 **55**

Synthesis according to general procedure B with 1.21 mmol amine **54** and 493 mg (S)-2-(((benzyloxy)carbonyl)amino)-4-phenylbutanoic acid. Purification was achieved by normal phase flash chromatography.

Formula: $C_{39}H_{51}N_3O_6$, exact mass: 657.4, found: 658.3 $[M+H]^+$

tert-butyl 3-(2-(5-(((S)-2-amino-4-phenylbutanamido)methyl)-2,4-dimethylphenoxy)ethyl)piperidine-1-carboxylate (**56**)

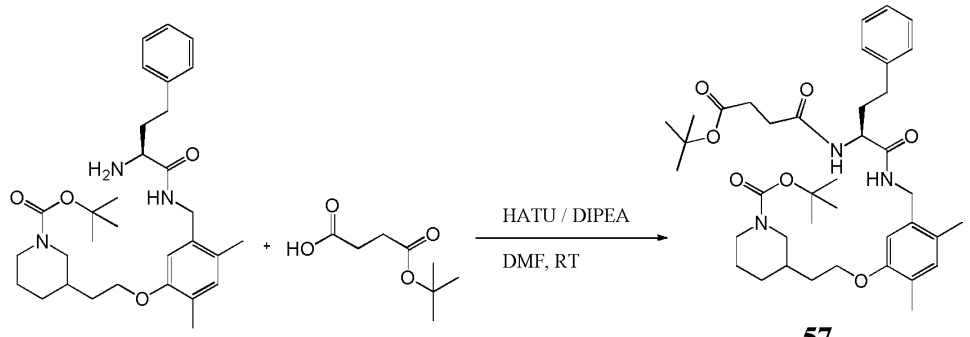


55 **56**

Synthesis according general procedure C with 695 mg protected amine in 80 ml ethanol / ethyl acetate (1:1) with 20 bar, 50°C and 0.5 ml/min. After removing volatiles the crude was used for the next step.

Formula: $C_{31}H_{45}N_3O_4$, exact mass: 523.3, found: 524.4 $[M+H]^+$

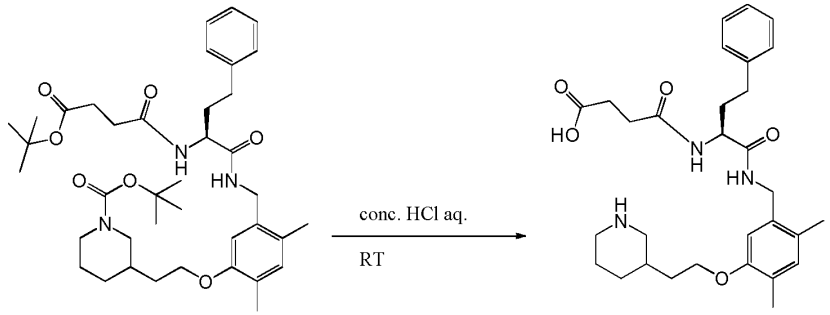
tert-butyl 3-(2-(5-(((S)-2-(4-(tert-butoxy)-4-oxobutanamido)-4-phenylbutanamido)methyl)-2,4-dimethylphenoxy)ethyl)piperidine-1-carboxylate (**57**)



56 **57**

Synthesis according to general procedure B with 200 mg amine **56** and 100 mg mono-tert.-butyl succinate. Purification was achieved by normal phase flash chromatography.
Formula: $C_{39}H_{57}N_3O_7$, exact mass: 679.4, found: 680.4 $[M+H]^+$

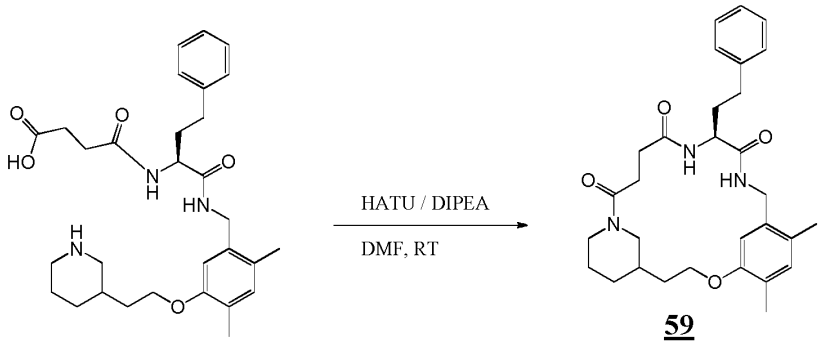
4-(((2S)-1-((2,4-dimethyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoic acid (**58**)



57 **58**

Both protecting groups were cleaved according to general procedure D in concentrated HCl in water at RT for 2h. Crude was coevaporated twice with acetonitrile and used without further purification.
Formula: $C_{30}H_{41}N_3O_5$, exact mass: 523.3, found: - $[M+H]^+$

(9R)-5^4,5^6-dimethyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione (**59**)



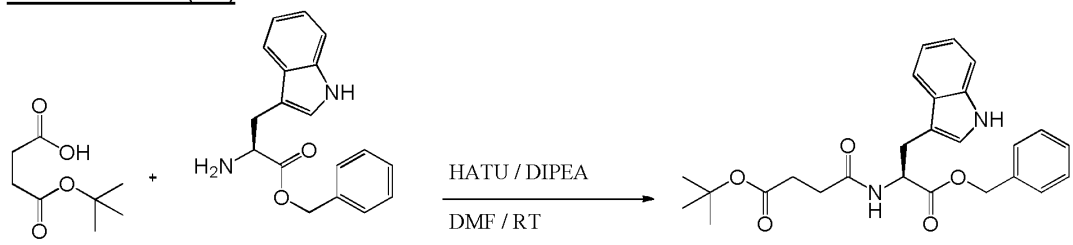
58 **59**

Macrocyclization was achieved according to general procedure A with 0.447 mmol amino acid **58**. Reaction mixtures were diluted with some methanol and purified via HPLC.

Formula: $C_{30}H_{39}N_3O_4$, exact mass: 505.3, found: 506.3 $[M+H]^+$

Example A-7: Preparation of macrocyclic compounds 77, 78, and 79

(S)-tert-butyl 4-((1-(benzyloxy)-3-(1H-indol-3-yl)-1-oxopropan-2-yl)amino)-4-oxobutanoate (**65**)



65

The amide bond was formed according to general procedure B with 1.02 g (S)-benzyl 2-amino-3-(1H-indol-3-yl)propanoate and 400 mg mono-tert.-butyl succinate. Purification was achieved by RP18 reversed phase flash chromatography.

Formula: $C_{26}H_{30}N_2O_5$, exact mass: 450.2, found: 451.3 $[M+H]^+$

(S)-tert-butyl 4-((1-(benzyloxy)-1-oxopropan-2-yl)amino)-4-oxobutanoate (**66**)



66

The amide bond was formed according to general procedure B with 744 g (S)-benzyl 2-aminopropanoate and 400 mg mono-tert.-butyl succinate. Purification was achieved by RP18 reversed phase flash chromatography.

Formula: $C_{18}H_{25}NO_5$, exact mass: 360.2, found: 361.2 $[M+H]^+$

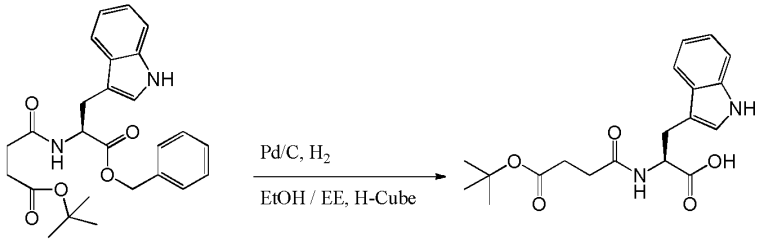
(S)-tert-butyl 4-((1-(benzyloxy)-1-oxo-3-phenylpropan-2-yl)amino)-4-oxobutanoate (**67**)



67

The amide bond was formed according to general procedure B with 1.01 g (S)-benzyl 2-amino-3-phenylpropanoate and 400 mg mono-tert.-butyl succinate. Purification was achieved by RP18 reversed phase flash chromatography.
Formula: $C_{24}H_{29}NO_5$, exact mass: 411.2, found: 412.3 $[M+H]^+$

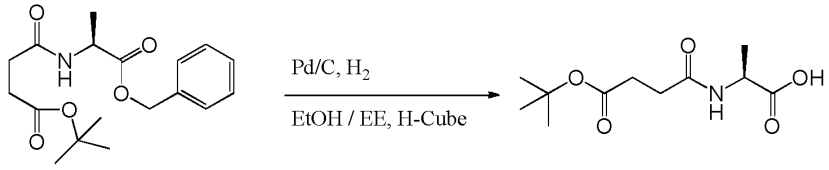
(S)-2-(4-(tert-butoxy)-4-oxobutanamido)-3-(1H-indol-3-yl)propanoic acid (**68**)



65 **68**

Benzyl ester was cleaved according to general procedure C using Raney-Ni catalyst cartridge, 20 bar at 50 °C in a solvent mixture of ethanol / ethyl acetate (3:1). Product was purified by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient). Formula: $C_{19}H_{24}N_2O_5$, exact mass: 360.2, found: 361.2 $[M+H]^+$

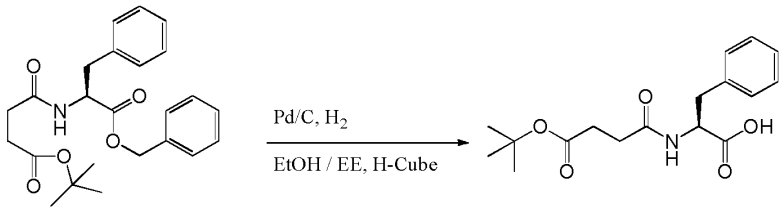
(S)-2-(4-(tert-butoxy)-4-oxobutanamido)propanoic acid (**69**)



66 **69**

Benzyl ester was cleaved according to general procedure C using Raney-Ni catalyst cartridge, 20 bar at 50 °C in a solvent mixture of ethanol / ethyl acetate (3:1). Product was purified by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient). Formula: $C_{11}H_{19}NO_5$, exact mass: 245.1, found: 246.2 $[M+H]^+$

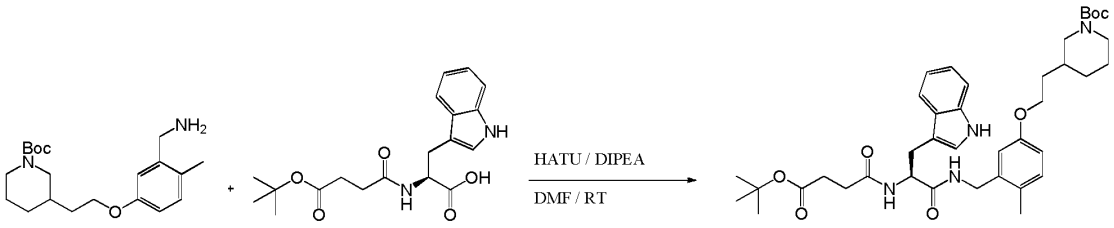
(S)-2-(4-(tert-butoxy)-4-oxobutanamido)-3-phenylpropanoic acid (**70**)



67 **70**

Benzyl ester was cleaved according to general procedure C using Raney-Ni catalyst cartridge, 20 bar at 50 °C in a solvent mixture of ethanol / ethyl acetate (3:1). Product was purified by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient). Formula: $C_{17}H_{23}NO_5$, exact mass: 321.2, found: 322.2 $[M+H]^+$

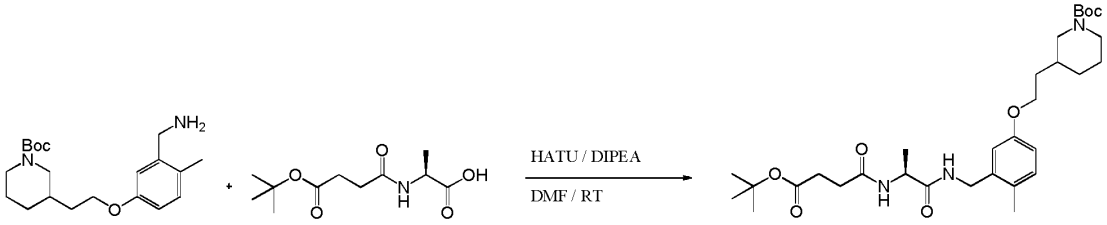
tert-butyl 3-(2-(3-(((S)-2-(4-(tert-butoxy)-4-oxobutanamido)-3-(1H-indol-3-yl)propanamido)methyl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate (**71**)



4 **68** **71**

The amide bond was formed according to general procedure B with 100 mg amine **4** and 134 mg carboxylic acid **68**. Purification was achieved by RP18 reversed phase flash chromatography. Formula: $C_{39}H_{54}N_4O_7$, exact mass: 690.4, found: 691.6 $[M+H]^+$

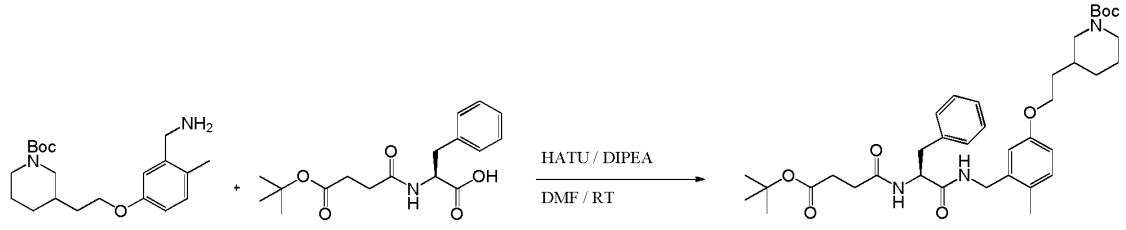
tert-butyl 3-(2-(3-(((S)-2-(4-(tert-butoxy)-4-oxobutanamido)propanamido)methyl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate (**72**)



4 **69** **72**

The amide bond was formed according to general procedure B with 100 mg amine **4** and 91 mg carboxylic acid 69. Purification was achieved by RP18 reversed phase flash chromatography. Formula: $C_{31}H_{49}N_3O_7$, exact mass: 575.4, found: 576.4 $[M+H]^+$

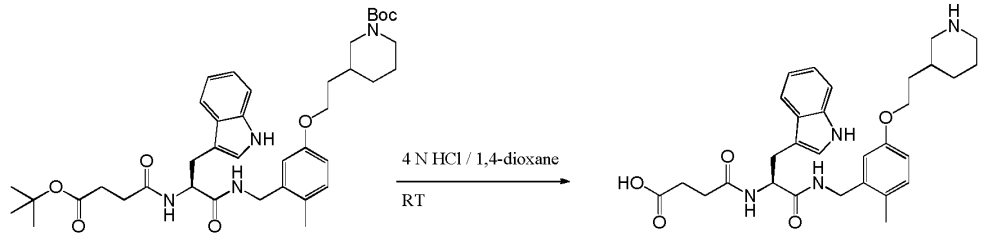
tert-butyl 3-(2-(3-(((S)-2-(4-(tert-butoxy)-4-oxobutanamido)-3-phenylpropanamido)methyl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate (**73**)



4 70 73

The amide bond was formed according to general procedure B with 100 mg amine **4** and 120 mg carboxylic acid **70**. Purification was achieved by RP18 reversed phase flash chromatography. Formula: $C_{37}H_{53}N_3O_7$, exact mass: 651.4, found: 652.4 $[M+H]^+$

4-(((2S)-3-(1H-indol-3-yl)-1-((2-methyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-1-oxopropan-2-yl)amino)-4-oxobutanoic acid (**74**)

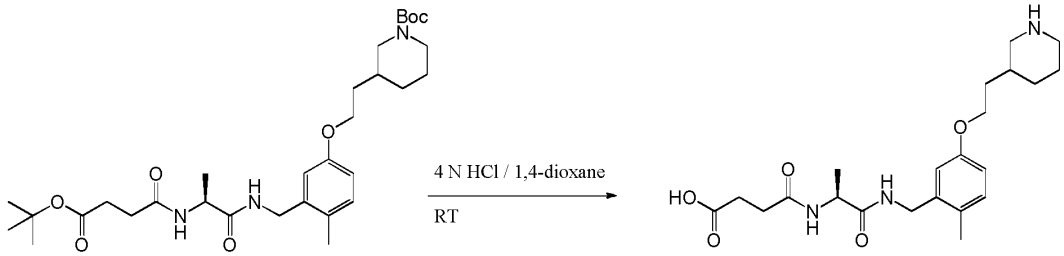


71 74

Protecting groups were cleaved according to general procedure D stirring compounds in 4 N HCl / 1,4-dioxane at room temperature. After deprotection was complete solvent was removed and the crude dissolved in acetonitrile and concentrated twice. Product used without further purification.

Formula: $C_{30}H_{38}N_4O_5$, exact mass: 534.3, found: 536.3 $[M+H]^+$

4-(((2S)-1-((2-methyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-1-oxopropan-2-yl)amino)-4-oxobutanoic acid (**75**)

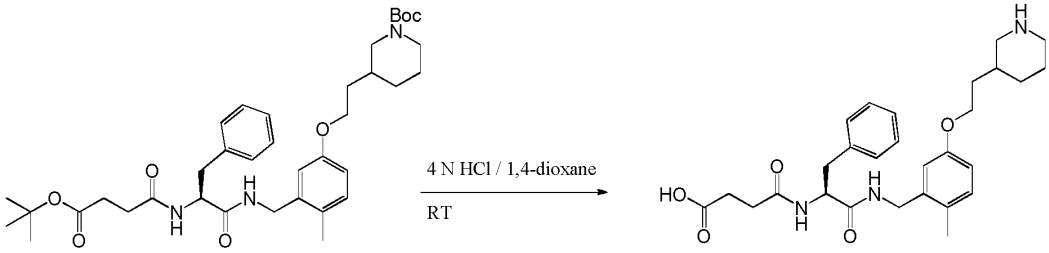


72 75

Protecting groups were cleaved according to general procedure D stirring compounds in 4 N HCl / 1,4-dioxane at room temperature. After deprotection was complete solvent

was removed and the crude dissolved in acetonitrile and concentrated twice. Product used without further purification.
Formula: $C_{22}H_{33}N_3O_5$, exact mass: 419.2, found: 420.1 $[M+H]^+$

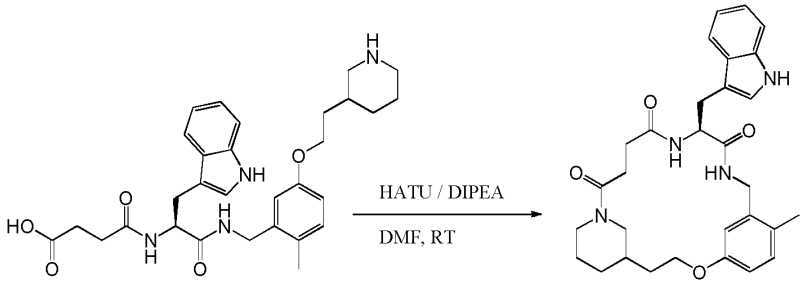
4-(((2S)-1-((2-methyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-1-oxo-3-phenylpropan-2-yl)amino)-4-oxobutanoic acid (**76**)



73 **76**

Protecting groups were cleaved according to general procedure D stirring compounds in 4 N HCl / 1,4-dioxane at room temperature. After deprotection was complete solvent was removed and the crude dissolved in acetonitrile and concentrated twice. Product used without further purification.
Formula: $C_{28}H_{37}N_3O_5$, exact mass: 495.3, found: 496.3 $[M+H]^+$

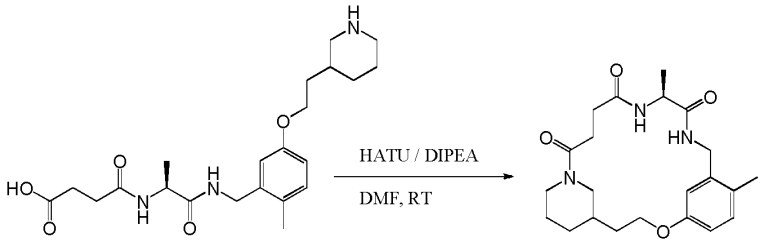
(9S)-9-((1H-indol-3-yl)methyl)-5^4-methyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione (**77**)



74 **77**

Macrocyclization was achieved according to general procedure A with 0.287 mmol amino acid **74** Reaction mixtures were diluted with some methanol and purified via HPLC. Formula: $C_{30}H_{36}N_4O_4$, exact mass: 516.3, found: 517.3 $[M+H]^+$

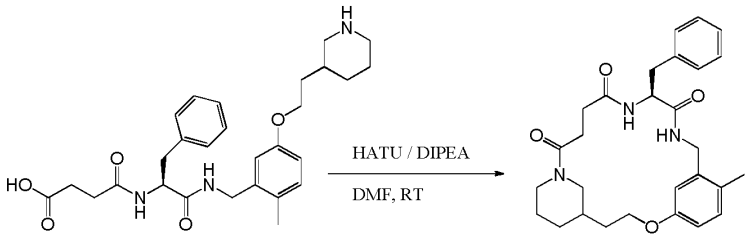
(9S)-5^4,9-dimethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione (**78**)



75 78

Macrocyclization was achieved according to general procedure A with 0.224 mmol amino acid **75** Reaction mixtures were diluted with some methanol and purified via HPLC. Formula: $C_{22}H_{31}N_3O_4$, exact mass: 401.2, found: 402.3 $[M+H]^+$

(9S)-9-benzyl-5^4-methyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione (**79**)

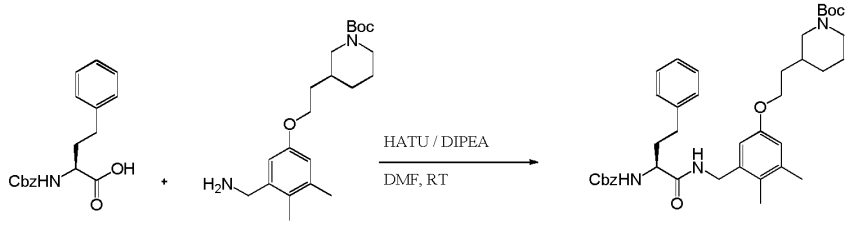


76 79

Macrocyclization was achieved according to general procedure A with 0.215 mmol amino acid **76** Reaction mixtures were diluted with some methanol and purified via HPLC. Formula: $C_{28}H_{35}N_3O_4$, exact mass: 477.3, found: 478.3 $[M+H]^+$

Example A-8: Preparation of macrocyclic compound 95

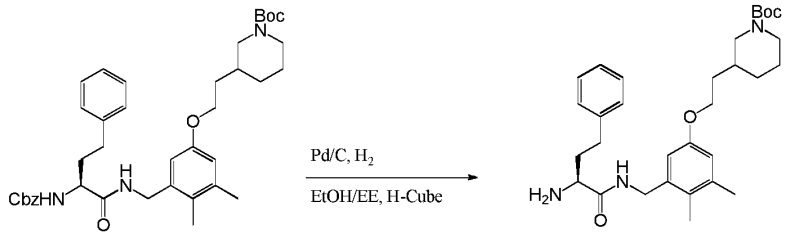
tert-butyl 3-(2-(3-(((S)-2-(((benzyloxy)carbonyl)amino)-4-phenylbutanamido)methyl)-4,5-dimethylphenoxy)ethyl)piperidine-1-carboxylate (**91**)



90 91

The amide bond was formed according to general procedure B. Purification was achieved normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient). Formula: $C_{39}H_{51}N_3O_6$, exact mass: 657.4, found: 658.6 $[M+H]^+$

tert-butyl 3-(2-(3-(((S)-2-amino-4-phenylbutanamido)methyl)-4,5-dimethylphenoxy)ethyl)-piperidine-1-carboxylate (**92**)

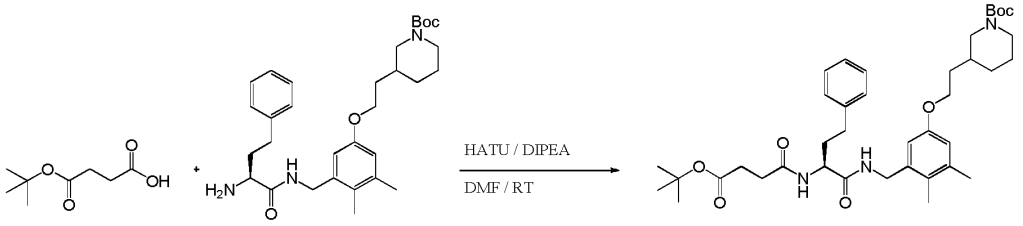


91 **92**

Benzyl carbamate was cleaved according to general procedure C using 10% Pd/C catalyst cartridge, 20 bar at 50 °C in a solvent mixture of ethanol / ethyl acetate (1:1). Dried product was used without further purification.

Formula: $C_{31}H_{45}N_3O_4$, exact mass: 523.3, found: 524.6 $[M+H]^+$

tert-butyl 3-(2-(3-(((S)-2-(4-(tert-butoxy)-4-oxobutanamido)-4-phenylbutanamido)methyl)-4,5-dimethylphenoxy)ethyl)piperidine-1-carboxylate (**93**)

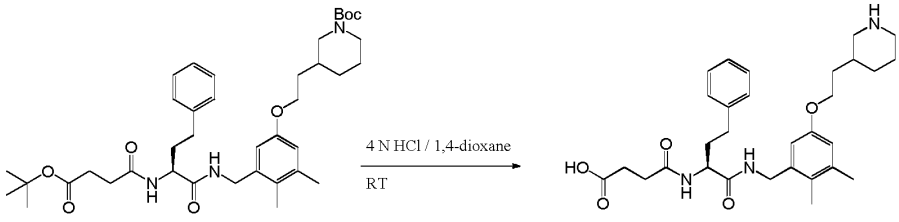


92 **93**

The amide bond was formed according to general procedure B with about 0.181 mmol amine **92** and 47 mg carboxylic acid. Purification was achieved by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient).

Formula: $C_{39}H_{57}N_3O_7$, exact mass: 679.4, found: 680.7 $[M+H]^+$

4-(((2S)-1-((2,3-dimethyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoic acid (**94**)

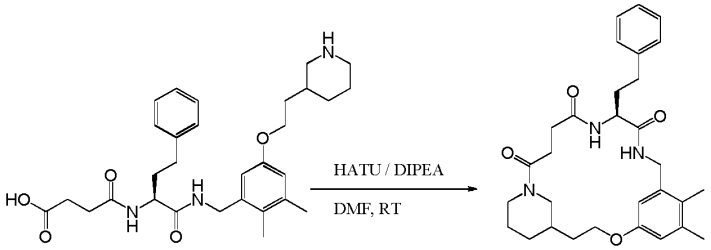


93 **94**

Protecting groups were cleaved according to general procedure D stirring compounds in 4 N HCl / 1,4-dioxane at room temperature. After deprotection was complete solvent was removed and the crude dissolved in acetonitrile and concentrated twice. Product used without further purification.

Formula: $C_{30}H_{41}N_3O_5$, exact mass: 523.3, found: 524.5 $[M+H]^+$

(9S)-5^4,5^5-dimethyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione (**95**)

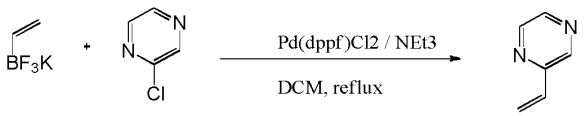


94 **95**

Macrocyclization was achieved according to general procedure A with about 0.125 mmol amino acid **94**. Reaction mixture was diluted with some methanol and purified via HPLC. Formula: $C_{30}H_{39}N_3O_4$, exact mass: 505.3, found: 506.4 $[M+H]^+$

Example A-9: Preparation of macrocyclic compounds 105, 106, 107, 371, and 372

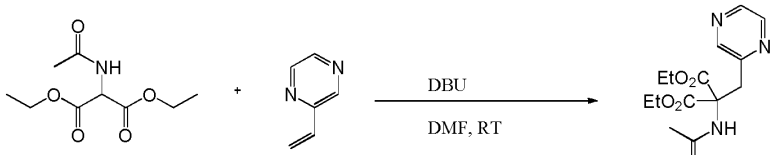
2-vinylpyrazine (**96**)



96

To a solution of 2-chloropyrazine (78 g, 681 mmol) in THF (800 mL) under argon atm. was added potassium vinyltrifluoroborate (137 g, 1022 mmol), triethylamine (247 mL, 2020 mmol), and $Pd(dppf)Cl_2$ in dichloromethane (5.6 g, 6.9 mmol). The reaction mass was refluxed for 24 h, cooled to r.t., diluted with MTBE (800 mL), and filtered through a pad of Na_2SO_4. The filtrate was evaporated under reduced pressure to obtain crude 2-vinylpyrazine (60 g, 565.5 mmol) which was used in the next step without further purification.

diethyl 2-acetamido-2-(pyrazin-2-ylmethyl)malonate (**97**)

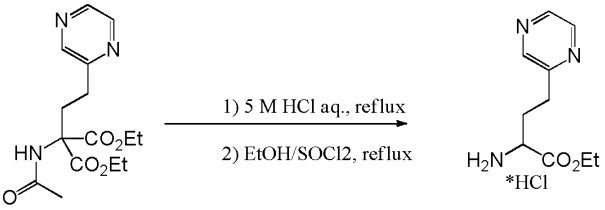


97

Diethyl acetamidomalonate (184.6 g, 850 mmol) and DBU (127 mL, 850 mmol) were dissolved in DMF (800 mL) and it was stirred 15 min at r.t. After that 2-vinylpyrazine (60 g, 565.5 mmol) was slowly added dropwise into reaction mixture and stirred for 24 h at r.t. Then it was concentrated under reduced pressure diluted with water (800 mL), and extracted with ethyl acetate (2×800 mL). Combined organic layers were washed with brine (3×800 mL), dried over Na_2SO_4, and concentrated to obtained 120 g of diethyl

2-acetamido-2-(pyrazin-2-ylmethyl)malonate (371 mmol, 65.6% yield) which was used in the next step without further purification.

ethyl 2-amino-4-(pyrazin-2-yl)butanoate (**98**)



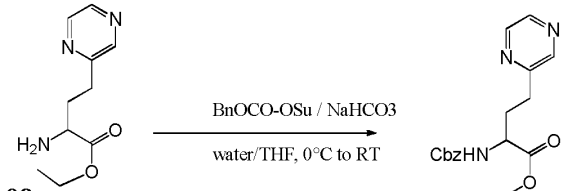
98

The diethyl 2-acetamido-2-(pyrazin-2-ylmethyl)malonate (120 g, 371 mmol) was dissolved in 5M hydrochloric acid (1000 mL) and refluxed for 14 h. Then the solvent was evaporated under reduced pressure to give 96 g of crude intermediate (441 mmol, 19% yield) which was used in the next step without further purification.

To cooled (5-10°C) solution of crude from step before (441 mmol) in absolute ethanol (500 mL) was slowly added dropwise $SOCl_2$ (14.5 mL, 199 mmol) and stirred for 30 min. Then it was refluxed for 12 h without air access. Then the reaction mixture was concentrated under reduced pressure, and the obtained ethyl 2-amino-4-(pyrazin-2-yl)butanoate (100 g, 407 mmol) was used in the next step without further purification.

Formula: $C_{10}H_{15}N_3O_2$, exact mass: 209.1, found: 210.2 $[M+H]^+$

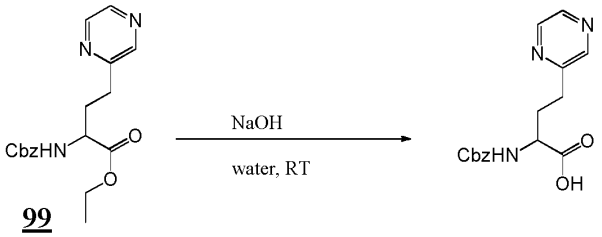
ethyl 2-(((benzyloxy)carbonyl)amino)-4-(pyrazin-2-yl)butanoate (**99**)



98 **99**

5.0 g amino ester **98** were dissolved in 25 ml water and 68 ml THF and cooled to 0°C. 5.07 g N-(benzyloxycarbonyloxy)succinimide and 8.24 g trimethylamine were added and the mixture was allow to warm to room temperature. After complete consumption of starting material the mixture was distributed between saturated $NaHCO_3$ solution and ethyl acetate. The organic phase was dried over $MgSO_4$ and volatiles were removed under reduced pressure. The crude was used without further purification.

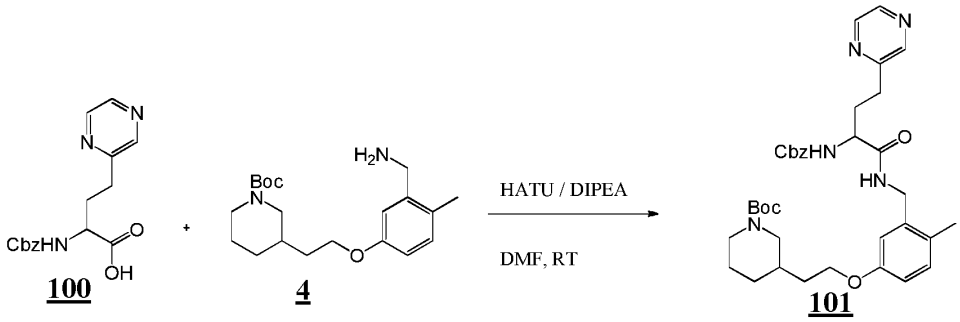
2-(((benzyloxy)carbonyl)amino)-4-(pyrazin-2-yl)butanoic acid (**100**)



99 100

6.45 g ester **99** were dissolved in 47 ml 1,4-dioxane and 20 mL 1 M NaOH solution in water at room temperature. After 3h the mixture was brought to pH 3 with 1 M HCl solution in water. The mixture was extracted with ethyl acetate twice and combined organic phases were dried over $MgSO_4$. Volatiles were removed under reduced pressure. The crude was pure enough to be used in the following reactions.
Formula: $C_{16}H_{17}N_3O_4$, exact mass: 315.1, found: 316.1 $[M+H]^+$

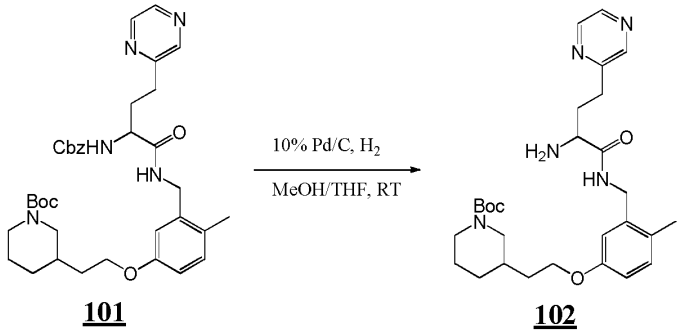
tert-butyl 3-(2-(3-((2-(((benzyloxy)carbonyl)amino)-4-(pyrazin-2-yl)butanamido)methyl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate (**101**)



100 4 101

600 mg carboxylic acid **100** was coupled with 663 mg amine **4** according to general procedure B. Purification was achieved by reversed phase column chromatography (RP18, water/acetonitrile gradient).

tert-butyl 3-(2-(3-((2-amino-4-(pyrazin-2-yl)butanamido)methyl)-4-methylphenoxy)ethyl) piperidine-1-carboxylate (**102**)

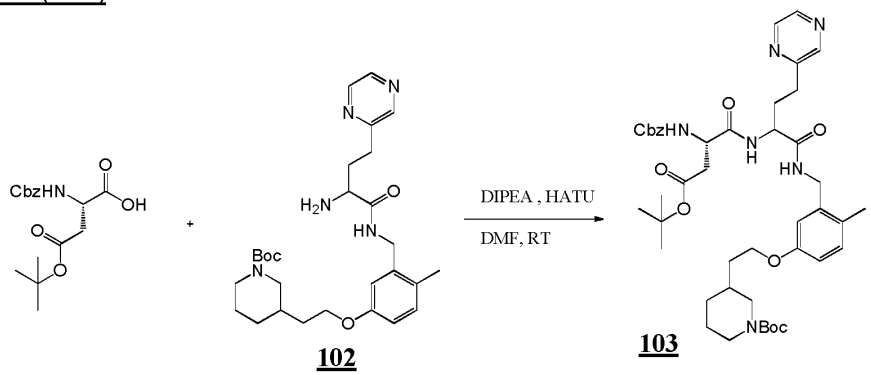


101 102

660 mg compound **101** and 70 mg 10% Pd/C in 8 ml methanol and 1.5 ml THF were hydrogenated at room temperature under normal pressure. After complete reaction the

mixture was filtrated and volatiles were removed. Purification was achieved by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient).
Formula: $C_{28}H_{41}N_5O_4$, exact mass: 511.3, found: 512.3 $[M+H]^+$

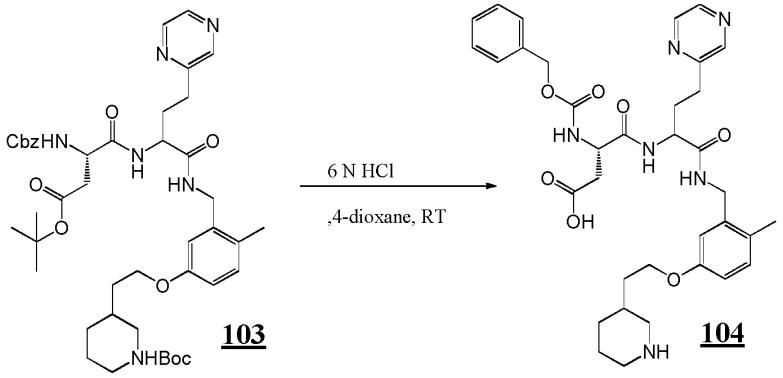
tert-butyl 3-(2-(3-((5S)-5-(2-(tert-butoxy)-2-oxoethyl)-3,6,9-trioxo-1-phenyl-8-(2-(pyrazin-2-yl)ethyl)-2-oxa-4,7,10-triazaundecan-11-yl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate (**103**)



102 **103**

The amide bond was formed according to general procedure B with 243 mg amine **102** and 230 mg Cbz-Asp(OtBu)-OH. Purification was achieved by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient).
Formula: $C_{44}H_{60}N_6O_9$, exact mass: 816.4, found: 717.6 $[M+H\text{-}Boc]^+$

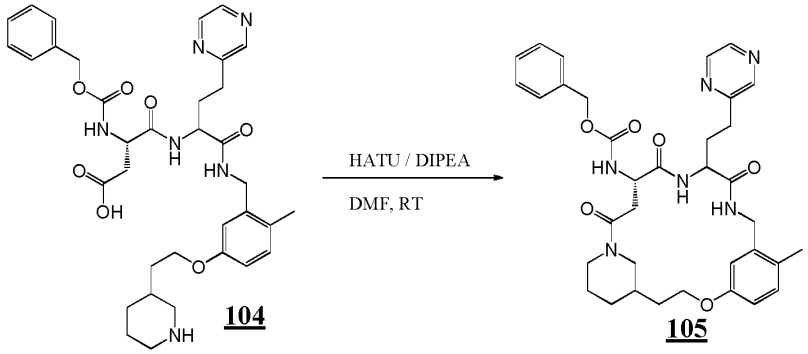
(3S)-3-(((benzyloxy)carbonyl)amino)-4-((1-((2-methyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-1-oxo-4-(pyrazin-2-yl)butan-2-yl)amino)-4-oxobutanoic acid (**104**)



103 **104**

Protecting groups were cleaved from 280 mg compound **103** according to general procedure D stirring compounds in 10 ml 6 N HCl / 1,4-dioxane at room temperature. After deprotection was complete solvent was removed and the crude dissolved in acetonitrile and concentrated twice. Product used without further purification.
Formula: $C_{35}H_{44}N_6O_7$, exact mass: 660.3, found: 662.3 $[M+H]^+$

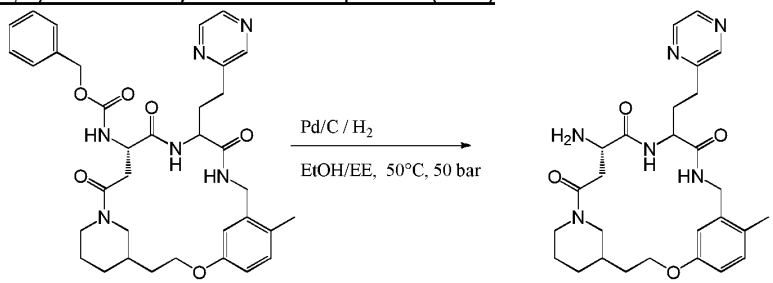
benzyl ((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyrazin-2-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate (**105**)



104 **105**

Macrocyclization was achieved according to general procedure A with 0.343 mmol amino acid **58**. Reaction mixtures were diluted with some methanol and purified by reversed phase column chromatography (RP18, water/methanol gradient).
Formula: $C_{35}H_{42}N_6O_6$, exact mass: 642.3, found: 643.5 $[M+H]^+$

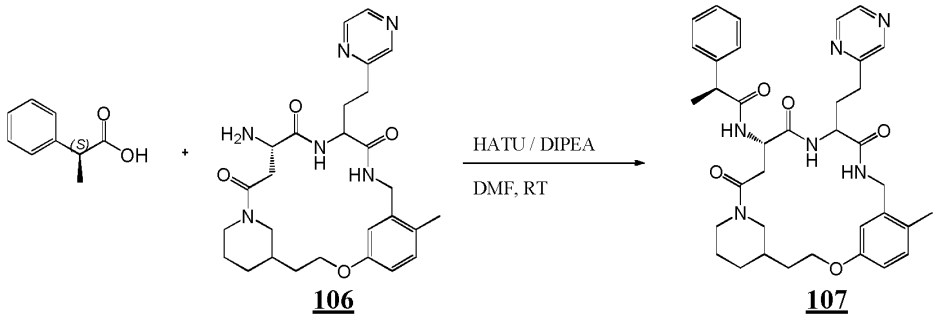
(12S)-amino-5^4-methyl-8,11,14-trioxo-9-(2-(pyrazin-2-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane (**106**)



105 **106**

Benzyl carbamate was cleaved according to general procedure C using 10% Pd/C catalyst cartridge, 20 bar at 50 °C in a solvent mixture of ethanol / ethyl acetate (3:1). After removing of volatiles the residue was directly used in the next step.
Formula: $C_{27}H_{36}N_6O_4$, exact mass: 508.3, found: - $[M+H]^+$

(2S)-N-((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyrazin-2-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-phenylpropanamide (**107**)

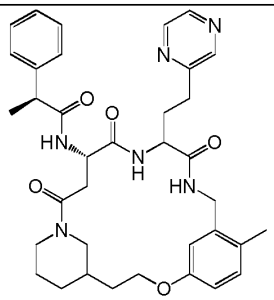
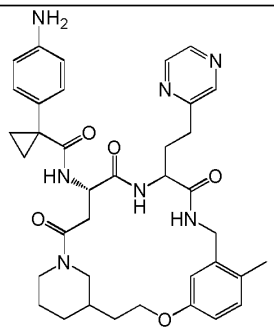


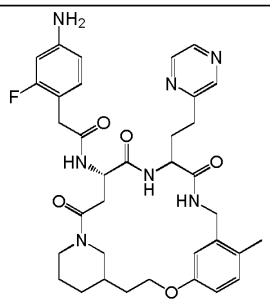
106 **107**

The amide bond was formed according to general procedure B with e.g. 25 mg amine **106** and 11 mg carboxylic acid. Purification was achieved by revered phase HPLC.
Formula: $C_{36}H_{44}N_6O_5$, exact mass: 640.3, found: 641.4 $[M+H]^+$

Additional examples as exemplified by compound **107** are disclosed in the table below. In the cases of compounds **371** and **372** Boc groups were cleaved from the related Boc-protected intermediates with 40% TFA in DCM before final purification via HPLC.

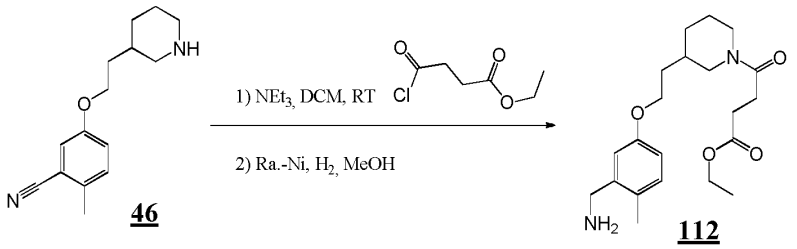
Table A-5

Cpd no	structure	name	Exact mass	$[M+H]^+$ found
107		(2S)-N-((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyrazin-2-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-phenylpropanamide	640.3 $C_{36}H_{44}N_6O_5$	641.4
371		1-(4-aminophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyrazin-2-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)cyclopropane-1-carboxamide	667.3 $C_{37}H_{45}N_7O_5$	668.5

372		2-(4-amino-2-fluorophenyl)-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-(2-(pyrazin-2-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	659.3 $C_{35}H_{42}FN_7O_5$	660.4

Example A-10: Preparation of compound (116)

ethyl 4-(3-(2-(3-(aminomethyl)-4-methylphenoxy)ethyl)piperidin-1-yl)-4-oxobutanoate (**112**)



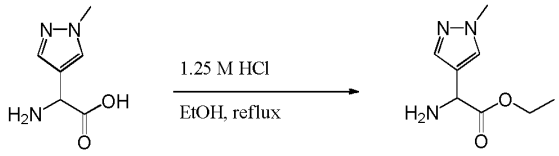
46 **112**

2.48 g amine **46** and 5.64 ml NEt_3 were dissolved in 60 ml DCM and cooled to 0°C. 1.86 g ethyl 4-chloro-4-oxobutanoate were added dropwise and the mixture was allowed to come to room temperature. After complete consumption of the starting amine saturated $NaHCO_3$ solution was added and the mixture was extracted with DCM. The organic phase was dried and concentrated under reduced pressure. Purification of the residue was achieved by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient).

2.0 g of the intermediate ester were dissolved in 135 ml methanol and hydrogenated with 7.0 Raney nickel under 50 bar at 70 °C. The mixture was filtered and concentrated under reduced pressure. The residue was pure enough to be used in the following reactions (mixture of methyl and ethyl ester).

Formula: $C_{21}H_{32}N_2O_4$, exact mass: 376.2, found: 377.3 $[M+H]^+$

ethyl 2-amino-2-(1-methyl-1H-pyrazol-4-yl)acetate (**109**)

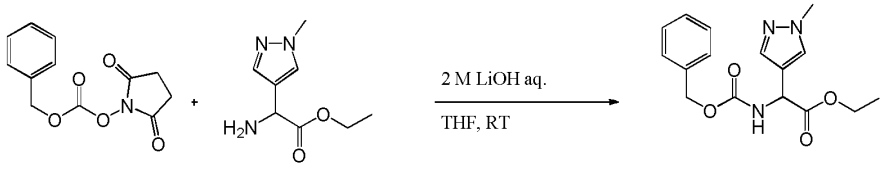


108 **109**

3.75 g 2-amino-2-(1-methyl-1H-pyrazol-4-yl)acetic acid are refluxed in 60 ml 1.25 M HCl in ethanol until esterification was found to be complete. Volatiles were removed under

reduced pressure and the residue was coevaporated with acetonitrile twice. The crude was used without further purification.
Formula: $C_8H_{13}N_3O_2$, exact mass: 183.1, found: 184.3 $[M+H]^+$

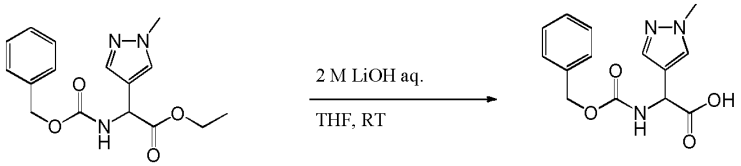
ethyl 2-(((benzyloxy)carbonyl)amino)-2-(1-methyl-1H-pyrazol-4-yl)acetate (**110**)



109 **110**

24 mmol amino ester **109** was dissolved in THF/water (3:1) at 0°C. 6.0 g CbzOSu and 13.1 ml NEt_3 were added and the mixtures was allowed to come to room temperature. The mixture was distributed between ethyl acetate and saturated $NaHCO_3$ solution. The organic phase was washed with 2 N HCl, dried over Na_2SO_4 and concentrated. The crude was purified by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient) to give 3.54 g ester **110**.
Formula: $C_{16}H_{19}N_3O_4$, exact mass: 317.1, found: 318.3 $[M+H]^+$

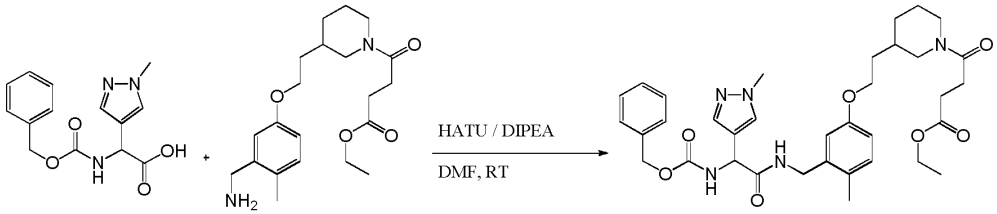
2-(((benzyloxy)carbonyl)amino)-2-(1-methyl-1H-pyrazol-4-yl)acetic acid (**111**)



110 **111**

3.4 g ester **110** were dissolved in 12 ml THF and 4 ml 2 M LiOH aq. were added. Some additional water was added to obtain only one phase. After completion of reaction the mixture was washed with ethyl acetate and the aqueous phase was acified to pH 2. Extraction with ethyl acetate and removing the solvent under reduced pressure afforded 2.1 g Cbz protected amino acid **111**.
Formula: $C_{14}H_{15}N_3O_4$, exact mass: 289.1, found: 290.3 $[M+H]^+$

ethyl 4-(3-(2-(3-((2-(((benzyloxy)carbonyl)amino)-2-(1-methyl-1H-pyrazol-4-yl)acetamido)methyl) -4-methylphenoxy)ethyl)piperidin-1-yl)-4-oxobutanoate (**113**)

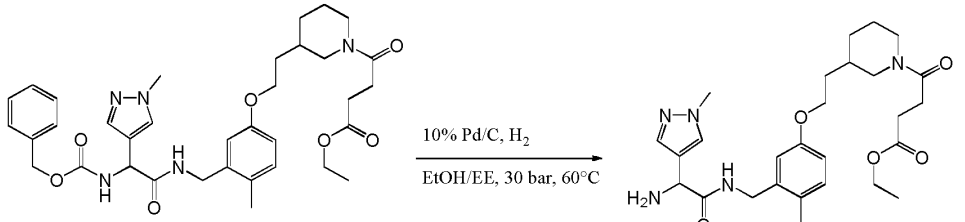


111 112 113

Peptide coupling was done according to general procedure B with 468 mg amine **112** and 300 mg amino acid **111**. Purification was achieved by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient).

Formula: $C_{35}H_{45}N_5O_7$, exact mass: 647.3, found: 648.3 $[M+H]^+$

ethyl 4-(3-(2-(3-((2-amino-2-(1-methyl-1H-pyrazol-4-yl)acetamido)methyl)-4-methylphenoxy) ethyl)piperidin-1-yl)-4-oxobutanoate (**114**)

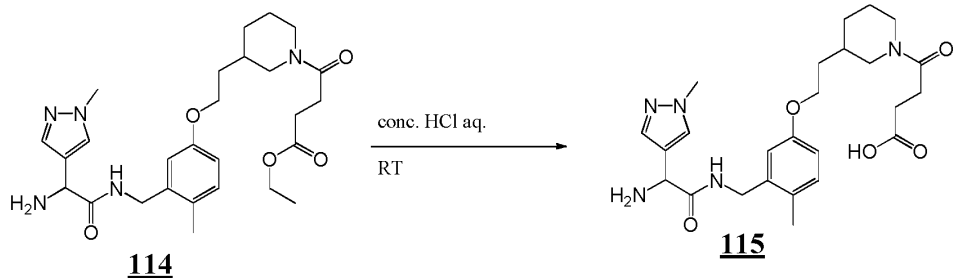


113 114

From 647 mg compound **113** the benzyl carbamate was cleaved according to general procedure C using 10% Pd/C catalyst cartridge, 30 bar at 60 °C in a solvent mixture of ethanol / ethyl acetate (1:1). Product was used without further purification after removing the volatiles.

Formula: $C_{27}H_{39}N_5O_5$, exact mass: 513.3, found: 514.3 $[M+H]^+$

4-(3-(2-(3-((2-amino-2-(1-methyl-1H-pyrazol-4-yl)acetamido)methyl)-4-methylphenoxy)ethyl)piperidin-1-yl)-4-oxobutanoic acid (**115**)

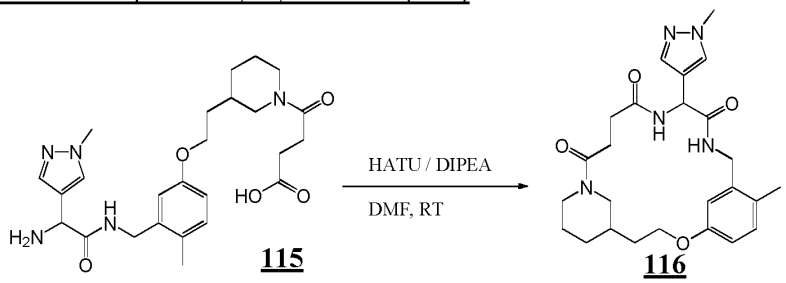


114 115

1.04 mmol ester **114** were dissolved in 20 ml concentrated aqueous HCl solution at room temperature. After complete reaction volatiles were removed under reduced pressure and the crude was directly used in the next step.

Formula: $C_{22}H_{35}N_5O_5$, exact mass: 485.3, found: 486.2 $[M+H]^+$

5[4]-methyl-9-(1-methyl-1H-pyrazol-4-yl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione (**116**)

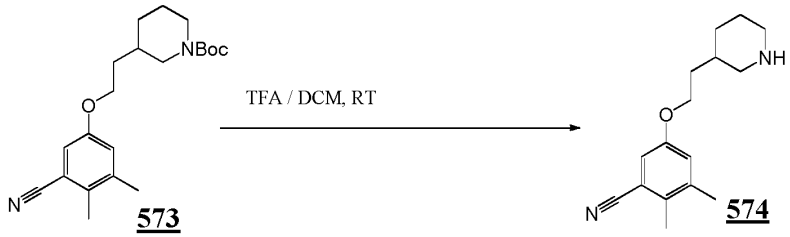


115 **116**

Macrocyclization was achieved according to general procedure A with 1.04 mmol amino acid **115**. Reaction mixtures were diluted with some methanol and purified via HPLC. Formula: $C_{25}H_{33}N_5O_4$, exact mass: 467.3, found: 468.3 $[M+H]^+$

Example A-11: Preparation of compound (120)

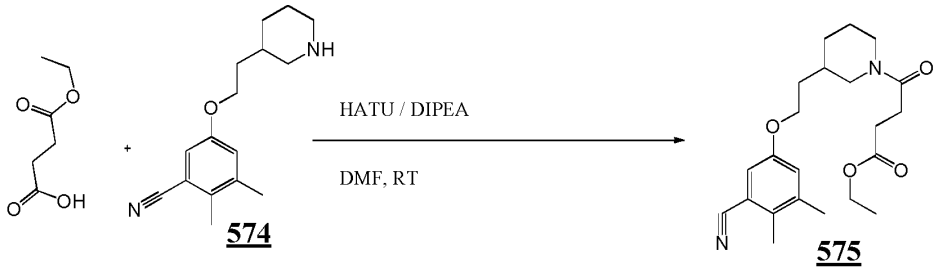
2,3-dimethyl-5-(2-(piperidin-3-yl)ethoxy)benzonitrile (**574**)



573 **574**

Boc group was removed from 1.77 g of compound **573** according general procedure D using 2.8 g TFA in 49 ml DCM. Volatiles were removed, the residue was dissolved in DCM and washed with 5 % aqueous NaOH solution. The organic phase was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude was used without further purification.

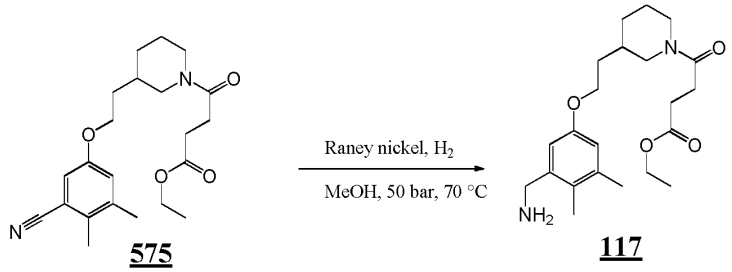
ethyl 4-(3-(2-(3-cyano-4,5-dimethylphenoxy)ethyl)piperidin-1-yl)-4-oxobutanoate (**575**)



574 **575**

The amide bond was formed according to general procedure B with amine **574.** Purification was achieved by normal phase flash chromatography.

ethyl 4-(3-(2-(3-(aminomethyl)-4,5-dimethylphenoxy)ethyl)piperidin-1-yl)-4-oxobutanoate (**117**)

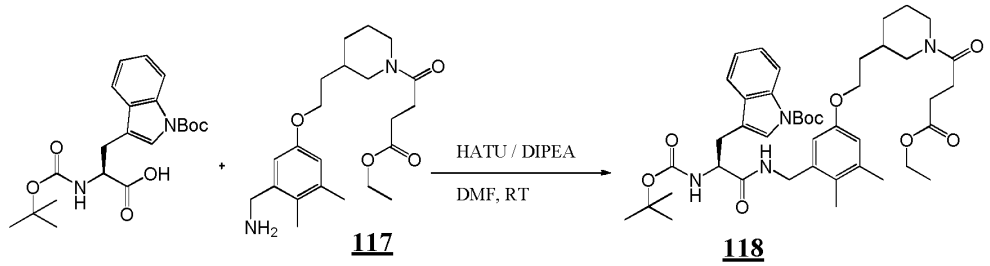


575 **117**

536 mg of the intermediate nitrile **575** were dissolved in 36 ml methanol and hydrogenated with 1.9 g Raney nickel at 70 °C and 50 bar. The mixture was filtered and concentrated under reduced pressure. The residue was pure enough to be used in the following reactions (mixture of methyl and ethyl ester).

Formula: $C_{22}H_{34}N_2O_4$, exact mass: 390.3, found: 391.3 $[M+H]^+$

tert-butyl 3-((2S)-2-((tert-butoxycarbonyl)amino)-3-((5-(2-(1-(4-ethoxy-4-oxobutanoyl)piperidin-3-yl)ethoxy)-2,3-dimethylbenzyl)amino)-3-oxopropyl)-1H-indole-1-carboxylate (**118**)

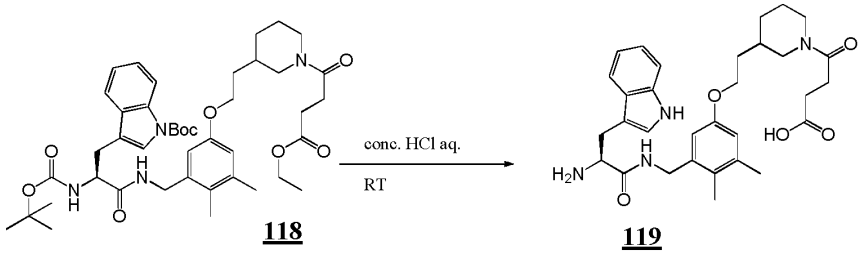


117 **118**

Condensation was achieved according to general procedure B with 232 mg amine **117** and 312 mg Boc protected amino acid. Purification was achieved by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient).

Formula: $C_{43}H_{60}N_4O_9$, exact mass: 776.4, found: 777.5 $[M+H]^+$

4-(3-(2-(3-(((S)-2-amino-3-(1H-indol-3-yl)propanamido)methyl)-4,5-dimethylphenoxy)ethyl)piperidin-1-yl)-4-oxobutanoic acid (**119**)



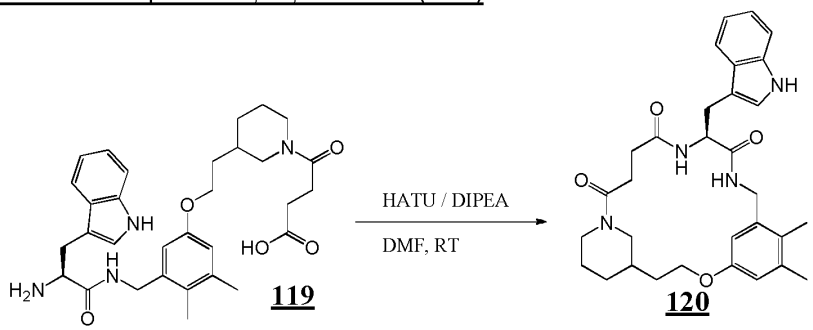
118 **119**

Protecting groups were cleaved from 240 mg compound **118** according to general procedure D stirring compounds in 10 ml concentrated aqueous HCl solution at room

temperature. After deprotection was complete solvent was removed and the crude dissolved in acetonitrile and concentrated twice. Product used without further purification.

Formula: $C_{31}H_{40}N_4O_5$, exact mass: 548.3, found: 549.4 $[M+H]^+$

(9S)-9-((1H-indol-3-yl)methyl)-5^4,5^5-dimethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione (**120**)

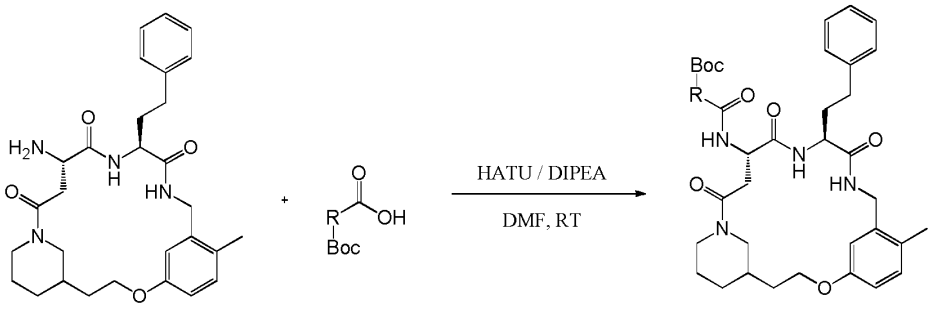


119 **120**

Macrocyclization was achieved according to general procedure A with 0.309 mmol amino acid **119**. Reaction mixture was diluted with some methanol and purified via HPLC.

Formula: $C_{31}H_{38}N_4O_4$, exact mass: 530.3, found: 531.4 $[M+H]^+$

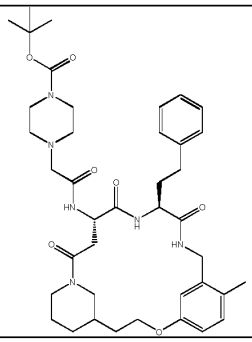
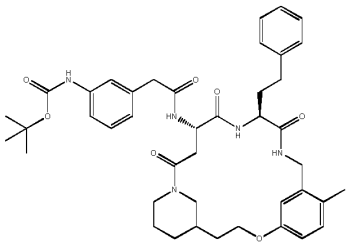
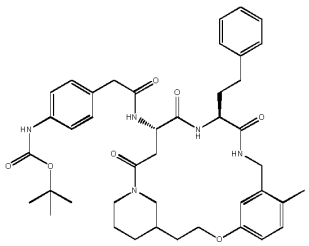
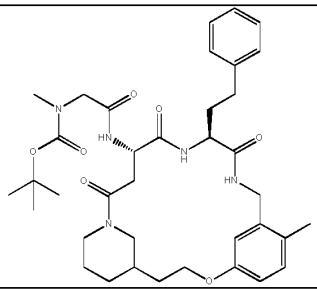
Example A-12: Derivatizations of compound 8 with Boc-protected amino acids

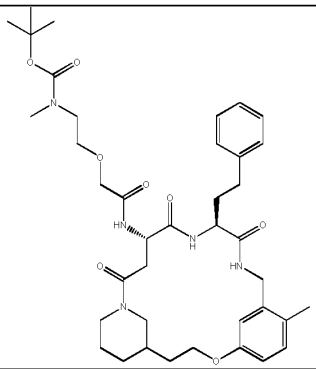
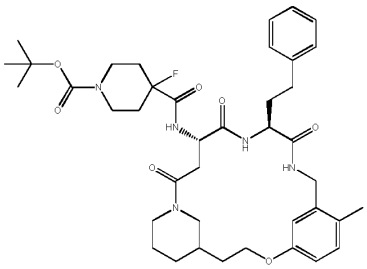
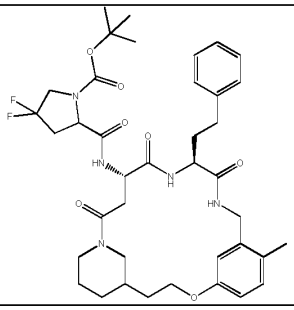
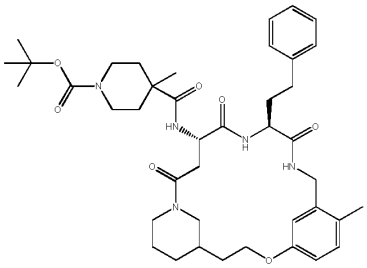
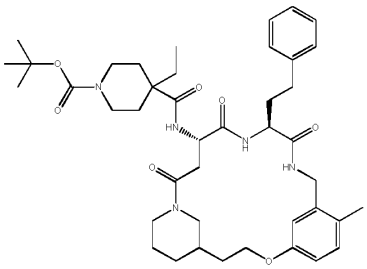


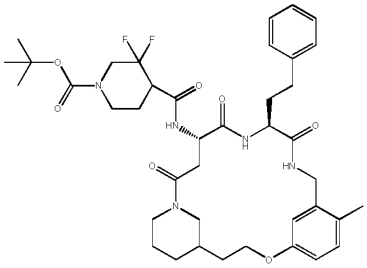
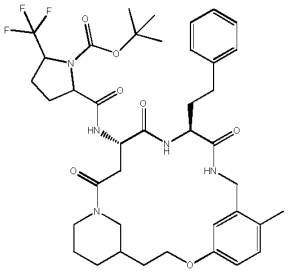
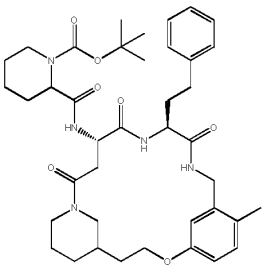
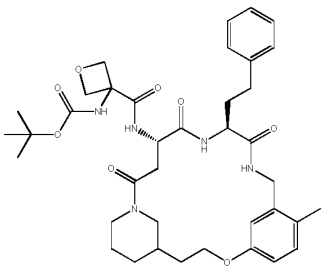
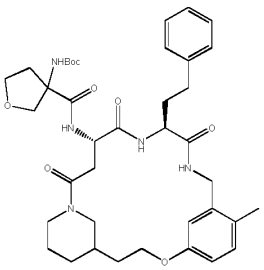
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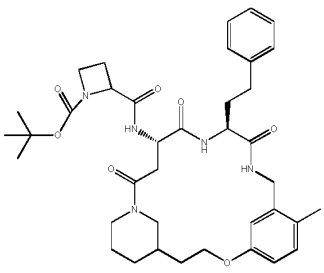
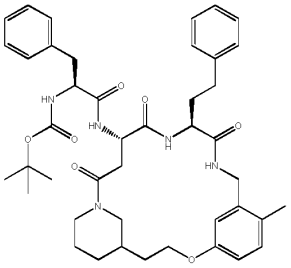
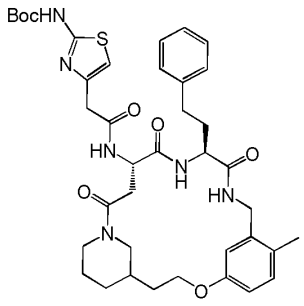
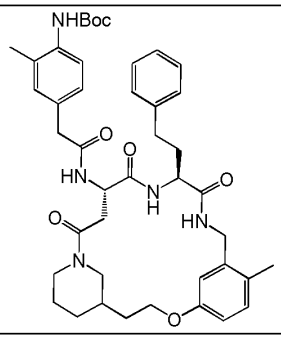
Amine **8** (e.g. 20 to 100 mg) was coupled with carboxylic acids according to general procedure B to give amides disclosed in table below. Purifications were achieved by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient).

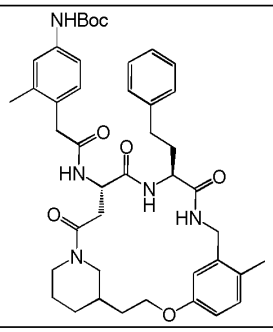
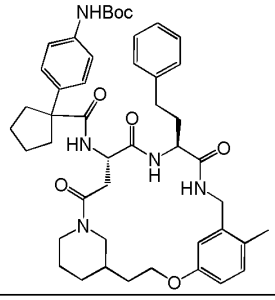
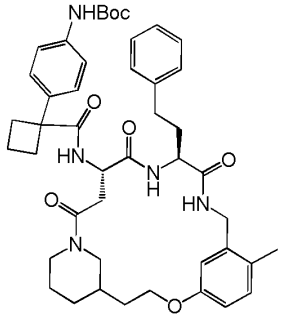
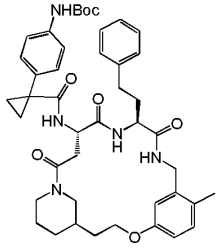
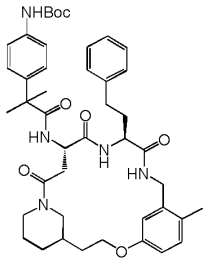
Table A-6

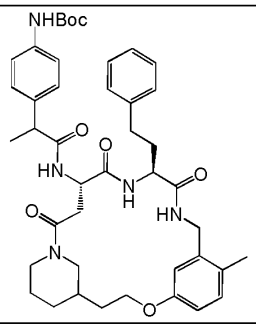
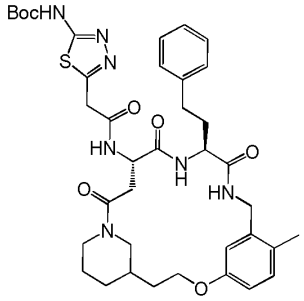
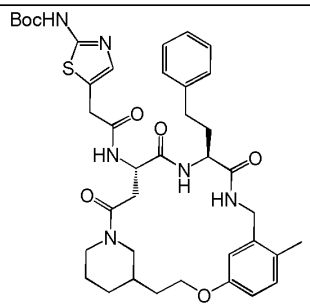
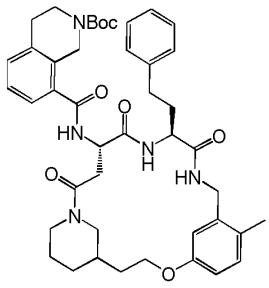
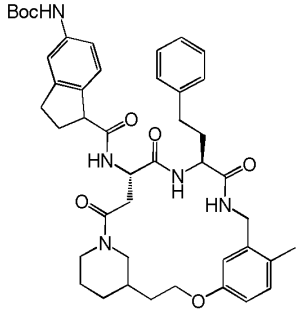
Cpd no	structure	name	Exact mass	$[M+H]^+$ found
121		tert-butyl 4-(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)piperazine-1-carboxylate	732.4 $C_{40}H_{56}N_6O_7$	733.5
122		tert-butyl (3-(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)phenyl)carbamate	739.4 $C_{42}H_{53}N_5O_7$	740.6
123		tert-butyl (4-(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)phenyl)carbamate	739.4 $C_{42}H_{53}N_5O_7$	740.7
124		tert-butyl methyl(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)carbamate	677.4 $C_{37}H_{51}N_5O_7$	678.5

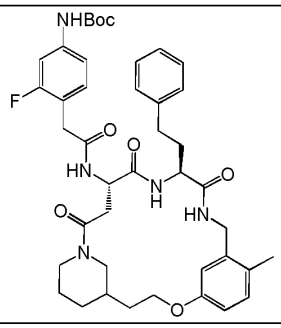
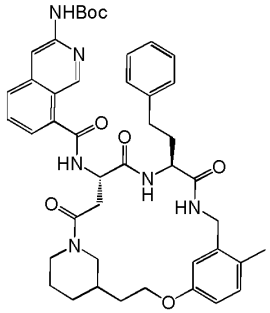
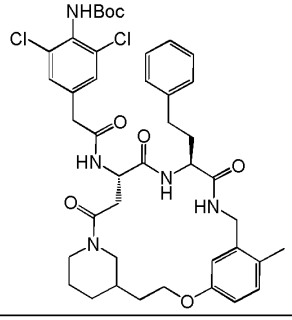
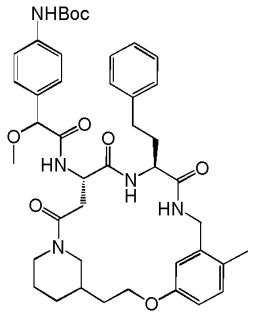
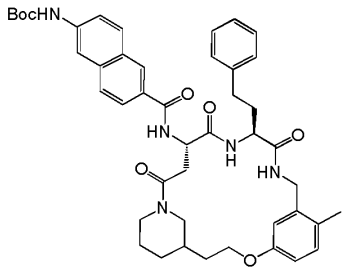
125		tert-butyl methyl(2-(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethoxy)ethyl)carbamate	721.4 $C_{39}H_{55}N_5O_8$	722.6
131		tert-butyl 4-fluoro-4-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)piperidine-1-carboxylate	735.4 $C_{40}H_{54}FN_5O_7$	736.7
132		tert-butyl 4,4-difluoro-2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)pyrrolidine-1-carboxylate	739.4 $C_{39}H_{51}F_2N_5O_7$	740.6
133		tert-butyl 4-methyl-4-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)piperidine-1-carboxylate	731.4 $C_{41}H_{57}N_5O_7$	732.8
149		tert-butyl 4-ethyl-4-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)piperidine-1-carboxylate	745.4 $C_{42}H_{59}N_5O_7$	746.7

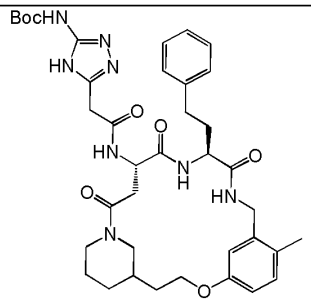
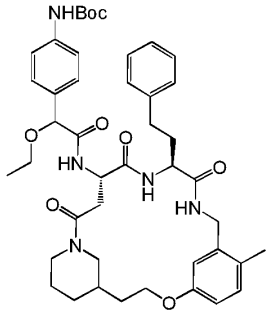
150		tert-butyl 3,3-difluoro-4-(((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)piperidine-1-carboxylate	753.4 $C_{40}H_{53}F_2N_5O_7$	754.6
153		tert-butyl 2-(((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)-5-(trifluoromethyl)pyrrolidine-1-carboxylate	771.4 $C_{40}H_{52}F_3N_5O_7$	772.5
154		tert-butyl 2-(((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)piperidine-1-carboxylate	717.4 $C_{40}H_{55}N_5O_7$	718.5
155		tert-butyl (3-(((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)oxetan-3-yl)carbamate	705.4 $C_{38}H_{51}N_5O_8$	706.4
156		tert-butyl (3-(((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)tetrahydrofuran-3-yl)carbamate	719.4 $C_{39}H_{53}N_5O_8$	720.5

161		tert-butyl 2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)azetidine-1-carboxylate	689.4 $C_{38}H_{51}N_5O_7$	690.6
178		tert-butyl ((2S)-1-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate	753.4 $C_{43}H_{55}N_5O_7$	654.4 [M+H-Boc]+
387		tert-butyl (4-(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)thiazol-2-yl)carbamate	746.3 $C_{39}H_{50}N_6O_7S$	747.1
388		tert-butyl (2-methyl-4-(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)phenyl)carbamate	753.4 $C_{43}H_{55}N_5O_7$	754.4

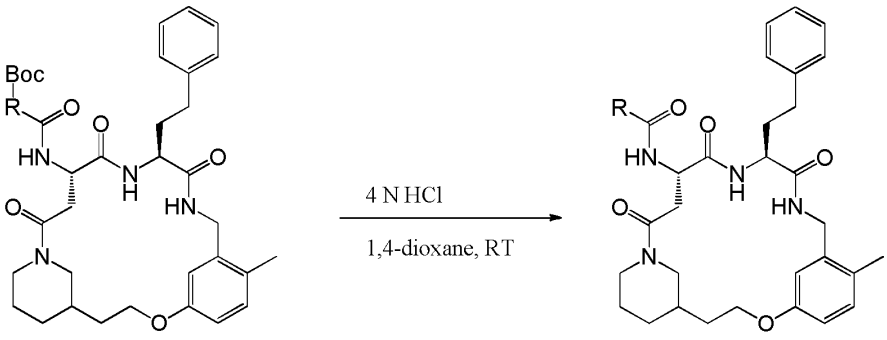
389		tert-butyl (3-methyl-4-(2-(((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)phenyl)carbamate	753.4 $C_{43}H_{55}N_5O_7$	754.4
390		tert-butyl (4-(1-(((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)cyclopentyl)phenyl)carbamate	793.4 $C_{46}H_{59}N_5O_7$	794.4
391		tert-butyl (4-(1-(((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)cyclobutyl)phenyl)carbamate	779.4 $C_{45}H_{57}N_5O_7$	780.4
392		tert-butyl (4-(1-(((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)cyclopropyl)phenyl)carbamate	765.4 $C_{44}H_{55}N_5O_7$	766.4
393		tert-butyl (4-(2-methyl-1-(((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-1-oxopropan-2-yl)phenyl)carbamate	767.4 $C_{44}H_{57}N_5O_7$	768.4

394		2-(4-aminophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide	653.4 $C_{38}H_{47}N_5O_5$	654.4
395		tert-butyl (5-(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)-1,3,4-thiadiazol-2-yl)carbamate	747.3 $C_{38}H_{49}N_7O_7S$	748.4
396		tert-butyl (5-(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)thiazol-2-yl)carbamate	746.3 $C_{39}H_{50}N_6O_7S$	747.4
419		tert-butyl 8-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate	765.4 $C_{44}H_{55}N_5O_7$	766.4
420		tert-butyl (1-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)-2,3-dihydro-1H-inden-5-yl)carbamate	765.4 $C_{44}H_{55}N_5O_7$	766.3

421		tert-butyl (3-fluoro-4-(2-(((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)phenyl)carbamate	757.4 $C_{42}H_{52}FN_5O_7$	758.3
422		tert-butyl (8-(((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)isoquinolin-3-yl)carbamate	776.4 $C_{44}H_{52}N_6O_7$	777.3
423		tert-butyl (2,6-dichloro-4-(2-(((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)phenyl)carbamate	807.3 $C_{42}H_{51}Cl_2N_5O_7$	708.3 [M+H-Boc]+
429		tert-butyl (4-(1-methoxy-2-(((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)phenyl)carbamate	769.4 $C_{43}H_{55}N_5O_8$	770.4
440		tert-butyl (6-(((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)naphthalen-2-yl)carbamate	775.4 $C_{45}H_{53}N_5O_7$	775.4

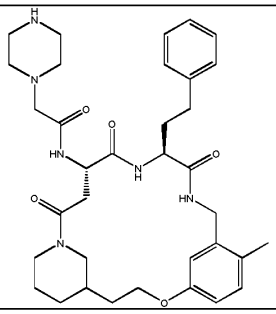
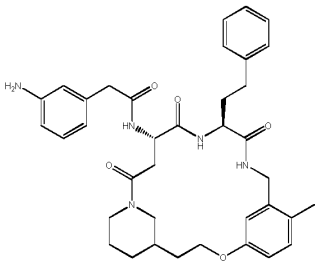
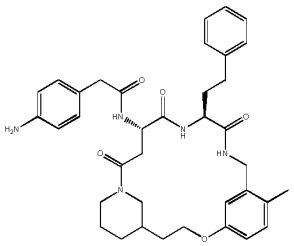
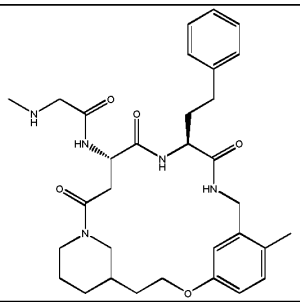
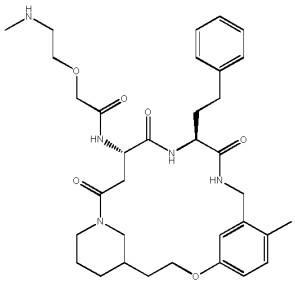
441		tert-butyl (5-(2-(((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)-4H-1,2,4-triazol-3-yl)carbamate	730.4 $C_{38}H_{50}N_8O_7$	731.4
442		tert-butyl (4-(1-ethoxy-2-(((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)phenyl)carbamate	783.4 $C_{44}H_{57}N_5O_8$	784.5

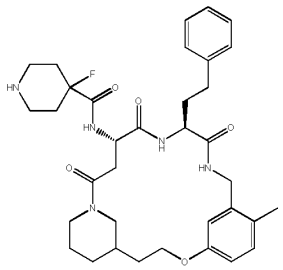
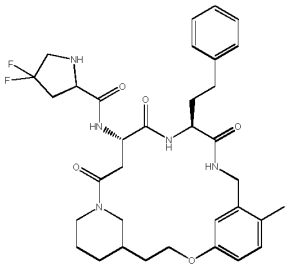
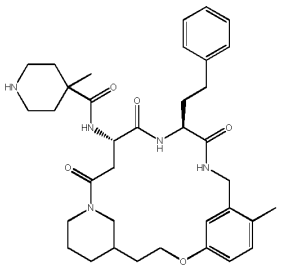
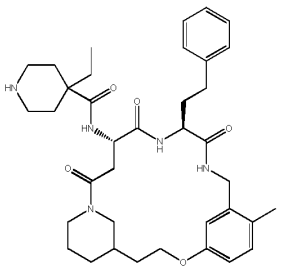
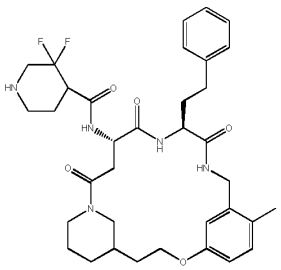
Example A-13: Removal of Boc-protecting groups to give basic macrocycles

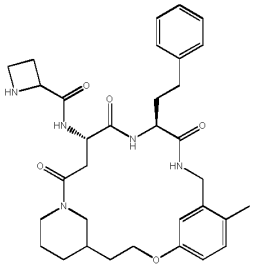
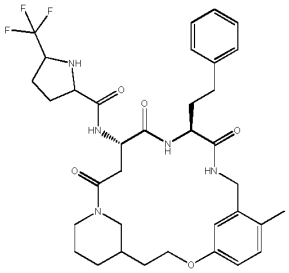
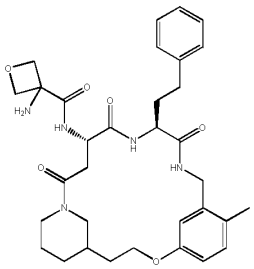
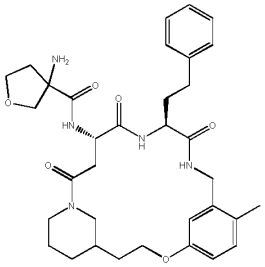
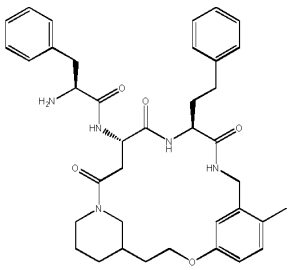


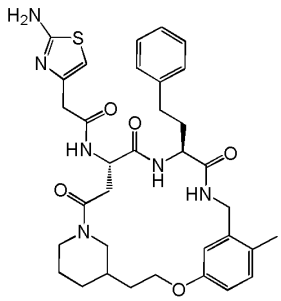
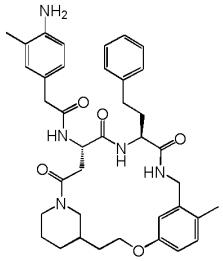
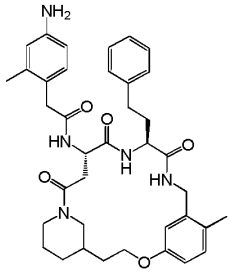
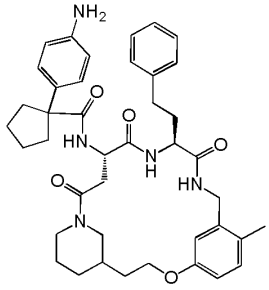
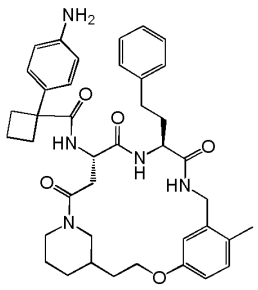
Boc protecting groups were cleaved from the compound according to general procedure D stirring compounds in 4-10 ml 4 N HCl / 1,4-dioxane at room temperature. After deprotection was complete solvent was removed and the crude product was purified by reversed phase HPLC.

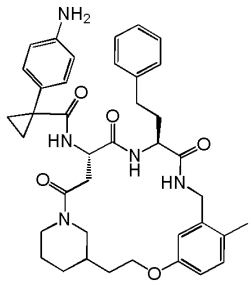
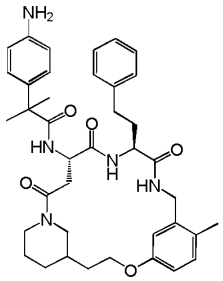
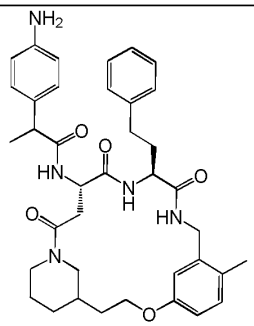
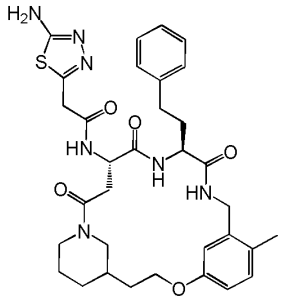
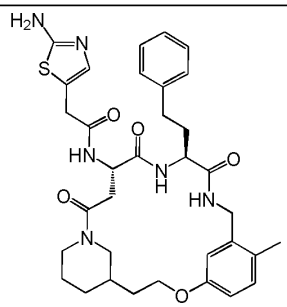
Table A-7

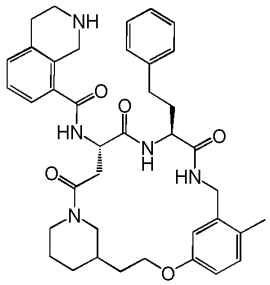
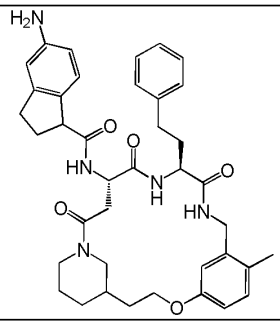
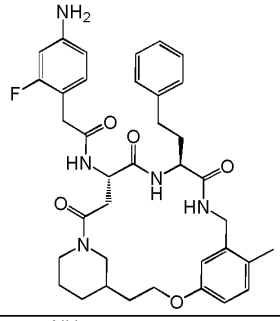
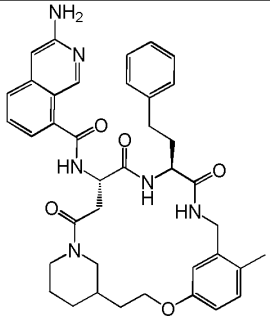
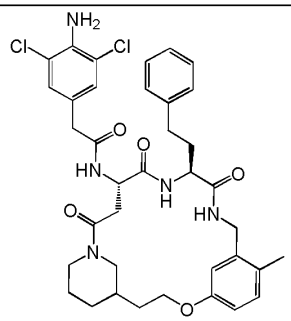
Cpd no	From cpd	structure	name	Exact mass	$[M+H]^+$ found
126	**121**		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(piperazin-1-yl)acetamide	632.4 $C_{35}H_{48}N_6O_5$	633.5
127	**122**		2-(3-aminophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	639.3 $C_{37}H_{45}N_5O_5$	640.5
128	**123**		2-(4-aminophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	639.3 $C_{37}H_{45}N_5O_5$	640.5
129	**124**		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(methylamino)acetamide	577.3 $C_{32}H_{43}N_5O_5$	578.5
130	**125**		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(2-(methyl amino)ethoxy)acetamide	621.4 $C_{34}H_{47}N_5O_6$	622.6

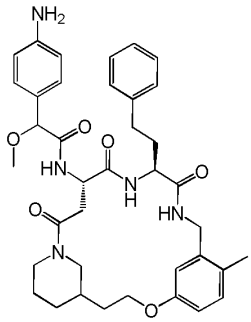
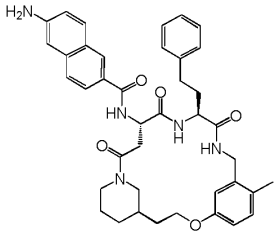
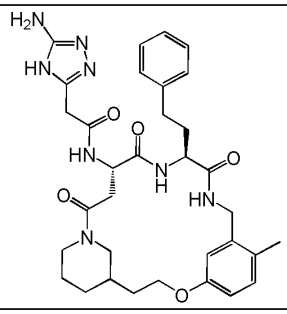
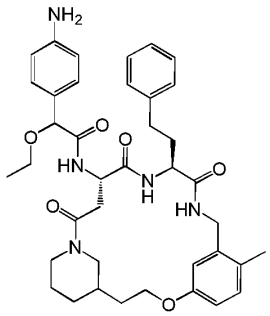
134	**131**		4-fluoro-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)piperidine-4-carboxamide	635.3 $C_{35}H_{46}FN_5O_5$	636.5
135	**132**		(2S)-4,4-difluoro-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)pyrrolidine-2-carboxamide	639.3 $C_{34}H_{43}F_2N_5O_5$	640.4
136	**133**		4-methyl-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)piperidine-4-carboxamide	631.4 $C_{36}H_{49}N_5O_5$	632.5
151	**149**		4-ethyl-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)piperidine-4-carboxamide	645.4 $C_{37}H_{51}N_5O_5$	646.5
152	**150**		3,3-difluoro-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)piperidine-4-carboxamide	653.3 $C_{35}H_{45}F_2N_5O_5$	654.4

160	**161**		(2R)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)azetidine-2-carboxamide	589.74 $C_{33}H_{43}N_5O_5$	-
157	**153**		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-5-(trifluoromethyl)pyrrolidine-2-carboxamide	671.3 $C_{35}H_{44}F_3N_5O_5$	672.5
158	**154**		3-amino-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)oxetane-3-carboxamide	605.3 $C_{33}H_{43}N_5O_6$	606.5
159	**155**		3-amino-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)tetrahydrofuran-3-carboxamide	619.3 $C_{34}H_{45}N_5O_6$	620.5
179	**178**		(2R)-2-amino-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-phenylpropanamide	653.4 $C_{38}H_{47}N_5O_5$	654.4

302	**387**		2-(2-aminothiazol-4-yl)-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	646.3 $C_{34}H_{42}N_6O_5S$	647.7
303	**388**		2-(4-amino-3-methylphenyl)-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	653.4 $C_{38}H_{47}N_5O_5$	654.6
304	**389**		2-(4-amino-2-methylphenyl)-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	653.4 $C_{38}H_{47}N_5O_5$	654.4
305	**390**		1-(4-aminophenyl)-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)cyclopentane-1-carboxamide	693.4 $C_{41}H_{51}N_5O_5$	694.5
306	**391**		1-(4-aminophenyl)-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)cyclobutane-1-carboxamide	679.4 $C_{40}H_{49}N_5O_5$	680.4

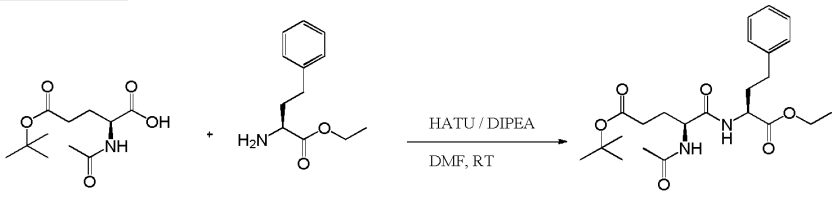
307	**392**		1-(4-aminophenyl)-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)cyclopropane-1-carboxamide	665.4 $C_{39}H_{47}N_5O_5$	666.4
308	**393**		2-(4-aminophenyl)-2-methyl-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide	667.4 $C_{39}H_{49}N_5O_5$	668.5
309	**394**		2-(4-aminophenyl)-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide	653.4 $C_{38}H_{47}N_5O_5$	654.4
310	**395**		2-(5-amino-1,3,4-thiadiazol-2-yl)-N-((9S,12S)-54-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	647.3 $C_{33}H_{41}N_7O_5S$	648.3
311	**396**		2-(2-aminothiazol-5-yl)-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	646.3 $C_{34}H_{42}N_6O_5S$	647.4

316	**419**		N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-1,2,3,4-tetrahydroisoquinoline-5-carboxamide	665.4 $C_{39}H_{47}N_5O_5$	666.4
317	**420**		5-amino-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2,3-dihydro-1H-indene-1-carboxamide	665.4 $C_{39}H_{47}N_5O_5$	666.5
318	**421**		2-(4-amino-2-fluorophenyl)-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	657.3 $C_{37}H_{44}FN_5O_5$	658.4
319	**422**		3-amino-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)isoquinoline-8-carboxamide	676.3 $C_{39}H_{44}N_6O_5$	677.4
320	**423**		2-(4-amino-3,5-dichlorophenyl)-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	707.3 $C_{37}H_{43}Cl_2N_5O_5$	708.3

326	**429**		2-(4-aminophenyl)-2-methoxy-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	669.4 $C_{38}H_{47}N_5O_6$	670.4
339	**440**		6-amino-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-naphthamide	675.3 $C_{40}H_{45}N_5O_5$	676.4
340	**441**		2-(5-amino-1H-1,2,4-triazol-3-yl)-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	630.3 $C_{33}H_{42}N_8O_5$	631.4
345	**442**		2-(4-aminophenyl)-2-ethoxy-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	683.4 $C_{39}H_{49}N_5O_6$	684.4

Example A-14: Preparation of intermediate compounds

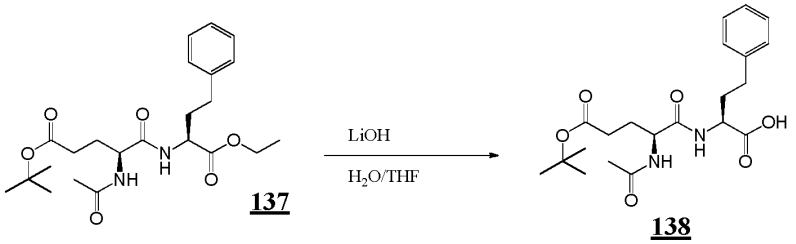
(S)-tert-butyl 4-acetamido-5-(((S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl)amino)-5-oxopentanoate (**137**)



137

The amide bond can be formed according to general procedure B with Ac-Glu(OtBu)-OH and H-hPhe-OEt. Purification can be achieved by normal phase flash chromatography.
Formula: $C_{23}H_{34}N_2O_6$, exact mass: 434.2, found: 435.3 $[M+H]^+$

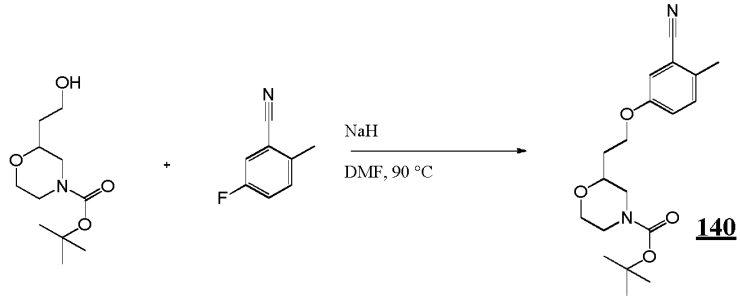
(S)-2-((S)-2-acetamido-5-(tert-butoxy)-5-oxopentanamido)-4-phenylbutanoic acid (**138**)



137 **138**

Ester **137** was dissolved in 3 ml THF. 0.5 ml water and 0.5 2 M LiOH aq. were added at room temperature. After complete saponification the mixture was acidified to pH 2 and extracted with ethyl acetate. The organic phase was dried over $MgSO_4$ and solvents were removed under reduced pressure. The residue was used in the next step without further purification.
Formula: $C_{21}H_{30}N_2O_6$, exact mass: 406.2, found: 407.5 $[M+H]^+$

tert-butyl 2-(2-(3-cyano-4-methylphenoxy)ethyl)morpholine-4-carboxylate (**140**)

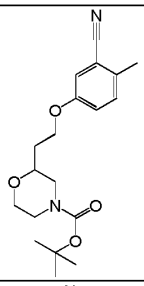
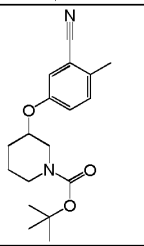
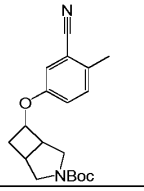
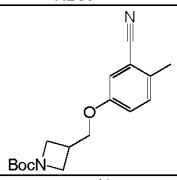
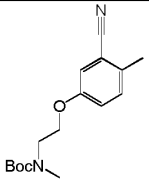
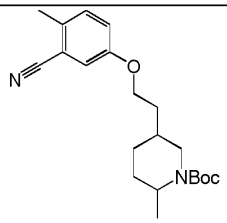
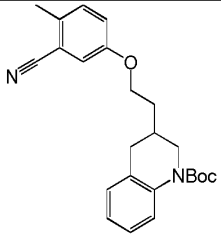


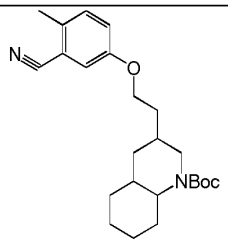
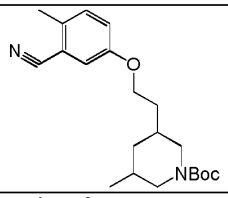
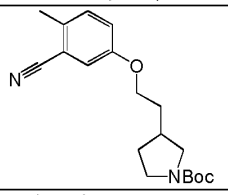
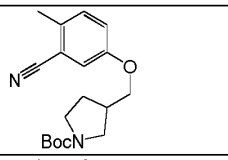
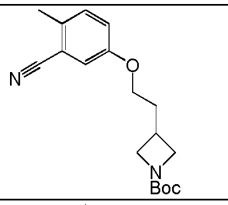
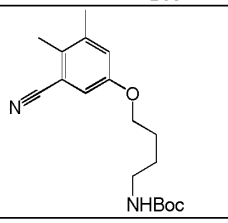
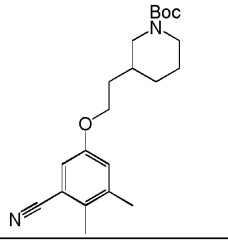
140

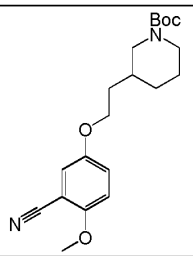
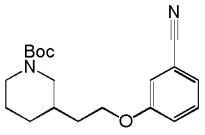
924 mg alcohol was deprotonated in DMF with 153 mg NaH at room temperature. 450 mg 5-fluoro-2-methylbenzonitrile were added and the mixture was heated to 90 °C until reaction was complete. Reaction mixture was diluted with ethyl acetate and washed with saturated $NaHCO_3$ solution and brine. After drying over $MgSO_4$ and removing the solvent under reduced pressure the residue was purified by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient).
Formula: $C_{19}H_{26}N_2O_4$, exact mass: 346.2, found: 247.3 $[M+H]^+$

Building blocks in the following table were synthesized as exemplified by compound **140** utilizing appropriately substituted 3-fluorobenzonitriles and related boc-protected aminoalcoholes.

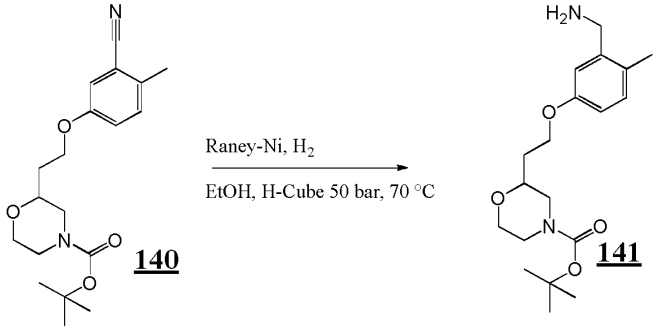
Table A-8

Cpd no	structure	name	Exact mass	$[M+H]^+$ found
140		tert-butyl 2-(2-(3-cyano-4-methylphenoxy)ethyl)morpholine-4-carboxylate	346.2 $C_{19}H_{26}N_2O_4$	247.3 [M+H-Boc]+
144		ert-butyl 3-(3-cyano-4-methylphenoxy)piperidine-1-carboxylate	316.2 $C_{18}H_{24}N_2O_3$	217.1 [M+H-Boc]+
187		tert-butyl 6-(3-cyano-4-methylphenoxy)-3-azabicyclo[3.2.0]heptane-3-carboxylate	328.2 $C_{19}H_{24}N_2O_3$	229.3 [M+H-Boc]+
229		tert-butyl 3-((3-cyano-4-methylphenoxy)methyl)azetidine-1-carboxylate	302.2 $C_{17}H_{22}N_2O_3$	
413		tert-butyl (2-(3-cyano-4-methylphenoxy)ethyl)(methyl)carbamate	290.2 $C_{16}H_{22}N_2O_3$	
412		tert-butyl 5-(2-(3-cyano-4-methylphenoxy)ethyl)-2-methylpiperidine-1-carboxylate	358.2 $C_{21}H_{30}N_2O_3$	
414		tert-butyl 3-(2-(3-cyano-4-methylphenoxy)ethyl)-3,4-dihydroquinoline-1(2H)-carboxylate	392.2 $C_{24}H_{28}N_2O_3$	

415		tert-butyl 3-(2-(3-cyano-4-methylphenoxy)ethyl)octahydroquinoline-1(2H)-carboxylate	398.3 $C_{24}H_{34}N_2O_3$	
431		tert-butyl 3-(2-(3-cyano-4-methylphenoxy)ethyl)-5-methylpiperidine-1-carboxylate	358.2 $C_{21}H_{30}N_2O_3$	359.3
454		tert-butyl 3-(2-(3-cyano-4-methylphenoxy)ethyl)pyrrolidine-1-carboxylate	330.2 $C_{19}H_{26}N_2O_3$	331.4
453		tert-butyl 3-((3-cyano-4-methylphenoxy)methyl)pyrrolidine-1-carboxylate	316.2 $C_{18}H_{24}N_2O_3$	317.4
462		tert-butyl 3-(2-(3-cyano-4-methylphenoxy)ethyl)azetidine-1-carboxylate	316.2 $C_{18}H_{24}N_2O_3$	317.3
466		tert-butyl (4-(3-cyano-4,5-dimethylphenoxy)butyl)carbamate	318.2 $C_{18}H_{26}N_2O_3$	319.4
573		tert-butyl 3-(2-(3-cyano-4,5-dimethylphenoxy)ethyl)piperidine-1-carboxylate	358.2 $C_{21}H_{30}N_2O_3$	

577		tert-butyl 3-(2-(3-cyano-4-methoxyphenoxy)ethyl)piperidine-1-carboxylate	360.2 $C_{20}H_{28}N_2O_4$	
578		tert-butyl 3-(2-(3-cyanophenoxy)ethyl)piperidine-1-carboxylate	330.2 $C_{19}H_{26}N_2O_3$	331.3

tert-butyl 2-(2-(3-(aminomethyl)-4-methylphenoxy)ethyl)morpholine-4-carboxylate (**141**)

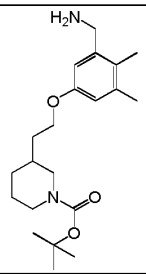


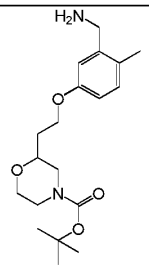
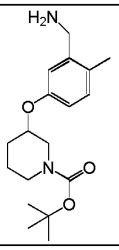
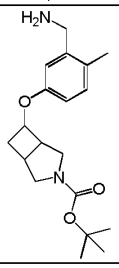
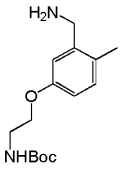
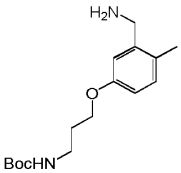
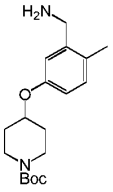
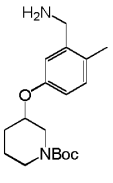
140 **141**

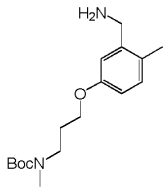
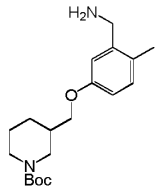
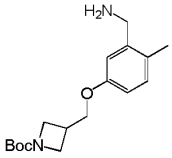
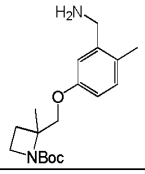
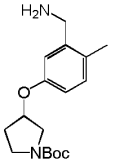
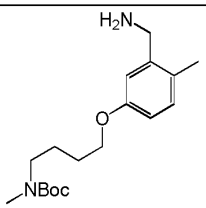
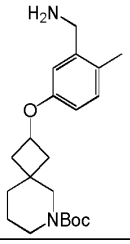
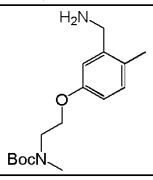
1.15 g nitrile 140 were reduced was cleaved according to general procedure H using Raney-Ni catalyst cartridge, 50 bar at 70 °C in 70 ml ethanol. Volatiles were removed under reduced pressure and the residue was purified by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient). Building blocks in the following table were synthesized as exemplified by compound **141**.

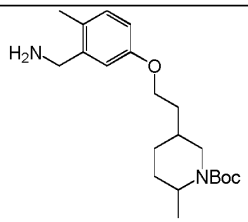
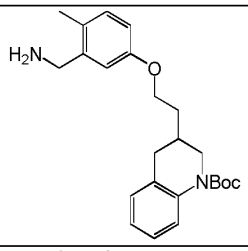
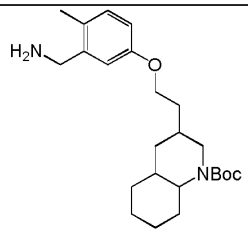
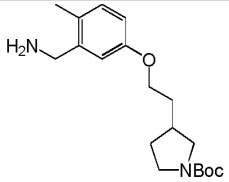
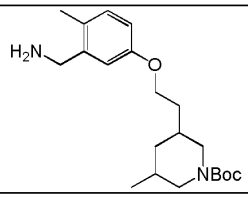
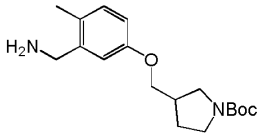
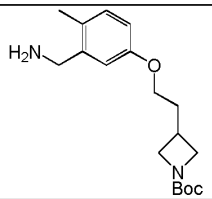
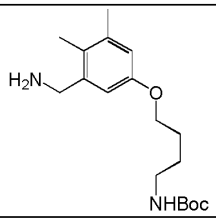
Formula: $C_{19}H_{30}N_2O_4$, exact mass: 350.2, found: 351.3 $[M+H]^+$

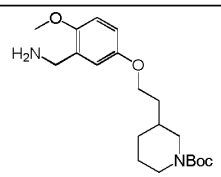
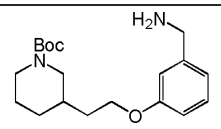
Table A-9

Cpd no	From cpd	structure	name	Exact mass	$[M+H]^+$ found
90	**573**		tert-butyl 3-(2-(3-(aminomethyl)-4,5-dimethylphenoxy)ethyl)piperidine-1-carboxylate	362.3 $C_{21}H_{34}N_2O_3$	363.3

141	**140**		tert-butyl 2-(2-(3-(aminomethyl)-4-methylphenoxy)ethyl)morpholine-4-carboxylate	350.2 $C_{19}H_{30}N_2O_4$	351.3
145	**144**		tert-butyl 3-(3-(aminomethyl)-4-methylphenoxy)piperidine-1-carboxylate	320.2 $C_{18}H_{28}N_2O_3$	321.3
188	**187**		tert-butyl 6-(3-(aminomethyl)-4-methylphenoxy)-3-azabicyclo[3.2.0]heptane-3-carboxylate	332.2 $C_{19}H_{28}N_2O_3$	333.3
222			tert-butyl (2-(3-(aminomethyl)-4-methylphenoxy)ethyl)carbamate	280.2 $C_{15}H_{24}N_2O_3$	281.2
224			tert-butyl (3-(3-(aminomethyl)-4-methylphenoxy)propyl)carbamate	294.2 $C_{16}H_{26}N_2O_3$	295.2
225			tert-butyl 4-(3-(aminomethyl)-4-methylphenoxy)piperidine-1-carboxylate	320.2 $C_{18}H_{28}N_2O_3$	321.5
226			tert-butyl 3-(3-(aminomethyl)-4-methylphenoxy)piperidine-1-carboxylate	320.2 $C_{18}H_{28}N_2O_3$	321.3

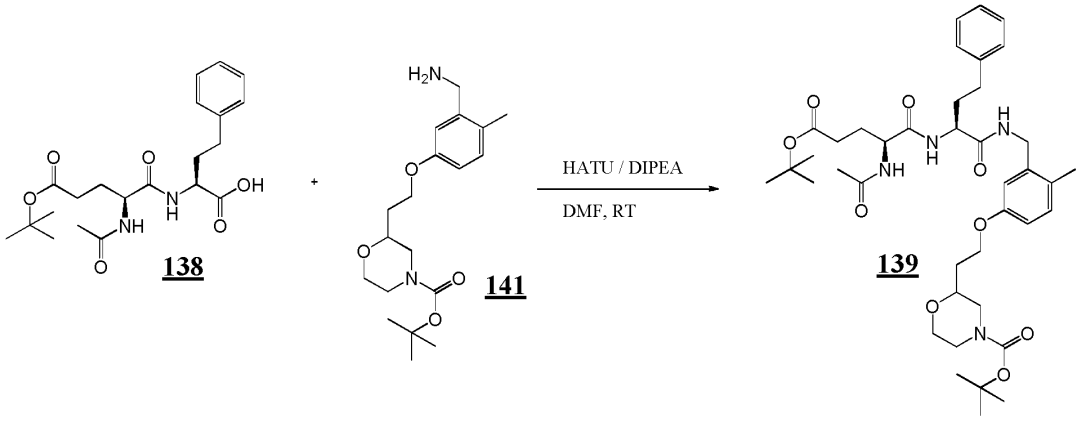
227			tert-butyl (3-(3-(aminomethyl)-4-methylphenoxy)propyl)(methyl)carbamate	308.2 $C_{17}H_{28}N_2O_3$	309.1
228			tert-butyl 3-((3-(aminomethyl)-4-methylphenoxy)methyl)piperidine-1-carboxylate	334.2 $C_{19}H_{30}N_2O_3$	335.3
230	**229**		tert-butyl 3-((3-(aminomethyl)-4-methylphenoxy)methyl)azetidine-1-carboxylate	306.2 $C_{17}H_{26}N_2O_3$	307.3
231			tert-butyl 2-((3-(aminomethyl)-4-methylphenoxy)methyl)-2-methylazetidine-1-carboxylate	320.2 $C_{18}H_{28}N_2O_3$	321.2
232			tert-butyl 3-(3-(aminomethyl)-4-methylphenoxy)pyrrolidine-1-carboxylate	306.2 $C_{17}H_{26}N_2O_3$	307.2
270			tert-butyl (4-(3-(aminomethyl)-4-methylphenoxy)butyl)(methyl)carbamate	322.2 $C_{18}H_{30}N_2O_3$	323.2
271			tert-butyl 2-(3-(aminomethyl)-4-methylphenoxy)-6-azaspiro[3.5]nonane-6-carboxylate	360.2 $C_{21}H_{32}N_2O_3$	361.1
399	**413**		tert-butyl (2-(3-(aminomethyl)-4-methylphenoxy)ethyl)(methyl)carbamate	294.2 $C_{16}H_{26}N_2O_3$	-

411	**412**		tert-butyl 5-(2-(3-(aminomethyl)-4-methylphenoxy)ethyl)-2-methylpiperidine-1-carboxylate	362.3 $C_{21}H_{34}N_2O_3$	363.3
416	**414**		tert-butyl 3-(2-(3-(aminomethyl)-4-methylphenoxy)ethyl)-3,4-dihydroquinoline-1(2H)-carboxylate	396.2 $C_{24}H_{32}N_2O_3$	397.3
417	**415**		tert-butyl 3-(2-(3-(aminomethyl)-4-methylphenoxy)ethyl)octahydroquinoline-1(2H)-carboxylate	402.3 $C_{24}H_{38}N_2O_3$	403.4
426	**454**		tert-butyl 3-(2-(3-(aminomethyl)-4-methylphenoxy)ethyl)pyrrolidine-1-carboxylate	334.2 $C_{19}H_{30}N_2O_3$	335.4
430	**431**		tert-butyl 3-(2-(3-(aminomethyl)-4-methylphenoxy)ethyl)-5-methylpiperidine-1-carboxylate	362.3 $C_{21}H_{34}N_2O_3$	363.4
455	**453**		tert-butyl 3-((3-(aminomethyl)-4-methylphenoxy)methyl)pyrrolidine-1-carboxylate	320.2 $C_{18}H_{28}N_2O_3$	321.3
463	**462**		tert-butyl 3-(2-(3-(aminomethyl)-4-methylphenoxy)ethyl)azetidine-1-carboxylate	320.2 $C_{18}H_{28}N_2O_3$	321.3
468	**466**		tert-butyl (4-(3-(aminomethyl)-4,5-dimethylphenoxy)butyl)carbamate	322.2 $C_{18}H_{30}N_2O_3$	323.3

206	**577**		tert-butyl 3-(2-(3-(aminomethyl)-4-methoxyphenoxy)ethyl)piperidine-1-carboxylate	364.2 $C_{20}H_{32}N_2O_4$	365.0
579	**578**		tert-butyl 3-(2-(3-(aminomethyl)phenoxy)ethyl)piperidine-1-carboxylate	334.2 $C_{19}H_{30}N_2O_3$	335.3

Example A-15: Preparation of macrocyclic compounds 143, and 148

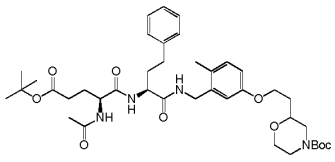
tert-butyl 2-(2-(3-(((S)-2-((S)-2-acetamido-5-(tert-butoxy)-5-oxopentanamido)-4-phenylbutanamido)methyl)-4-methylphenoxy)ethyl)morpholine-4-carboxylate (**139**)

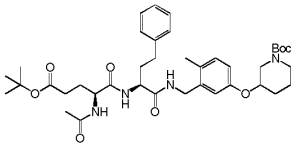


138 **141** **139**

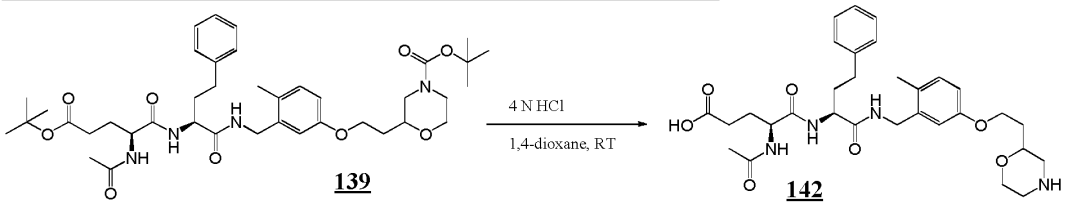
The amide bond was formed according to general procedure B with 96 mg amine **141** and 94 mg protected amino acid **138**. Purification was achieved by normal phase flash chromatography. Building blocks in the following table were synthesized as exemplified by compound **139**.

Table A-10

Cpd no	From cpd	structure	name	Exact mass	$[M+H]^+$ found
139	**141**		tert-butyl 2-(2-(3-(((S)-2-((S)-2-acetamido-5-(tert-butoxy)-5-oxopentanamido)-4-phenylbutanamido)methyl)-4-methylphenoxy)ethyl)morpholine-4-carboxylate	738.4 $C_{40}H_{58}N_4O_9$	739.5

146	**145**		tert-butyl 3-(3-(((S)-2-((S)-2-acetamido-5-(tert-butoxy)-5-oxopentanamido)-4-phenylbutanamido)methyl)-4-methylphenoxy)piperidine-1-carboxylate	708.4 $C_{39}H_{56}N_4O_8$	709.6

(4S)-4-acetamido-5-(((2S)-1-((2-methyl-5-(2-(morpholin-2-yl)ethoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-5-oxopentanoic acid (**142**)

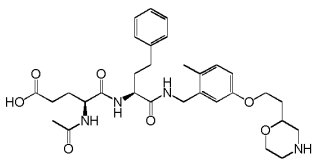
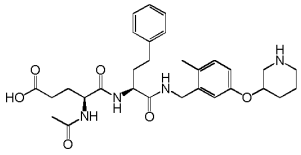


139 **142**

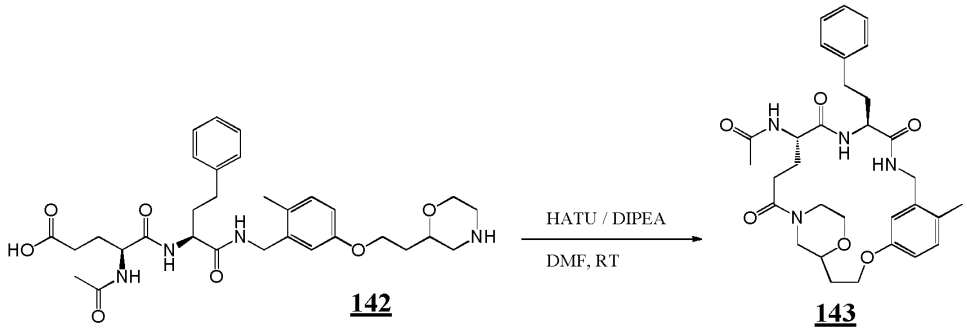
Protecting groups were cleaved from compound **139** according to general procedure D stirring compounds in 10 ml 4 N HCl / 1,4-dioxane at room temperature. After deprotection was complete solvent was removed and the crude dissolved in acetonitrile and concentrated twice. Product used without further purification.

Building blocks in the following table were synthesized as exemplified by compound **142**.

Table A-11

Cpd no	From cpd	structure	name	$[M+H]^+$ calc.	$[M+H]^+$ found
142	**139**		(4S)-4-acetamido-5-(((2S)-1-((2-methyl-5-(2-(morpholin-2-yl)ethoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-5-oxopentanoic acid	582.3 $C_{31}H_{42}N_4O_7$	583.6
147	**146**		(4S)-4-acetamido-5-(((2S)-1-((2-methyl-5-(piperidin-3-yloxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-5-oxopentanoic acid	552.3 $C_{30}H_{40}N_4O_6$	553.4

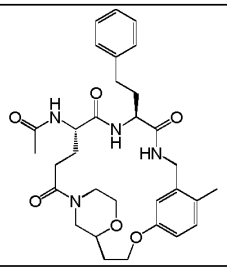
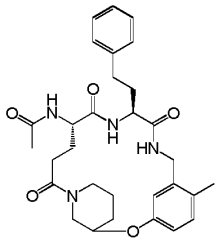
N-((9S,12S)-5^4-methyl-8,11,15-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(2,4)-morpholina-5(1,3)-benzenacyclopentadecaphane-12-yl)acetamide (**143**)



142 **143**

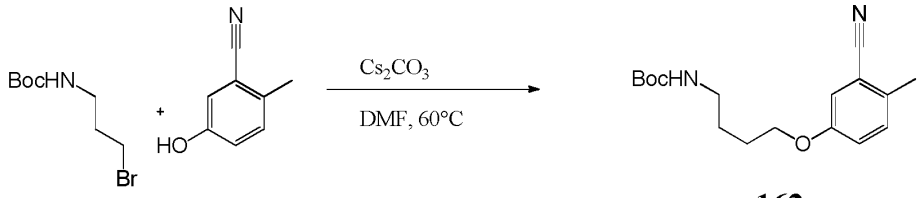
Macrocyclization was achieved according to general procedure A with 0.20 mmol amino acid **142**. Reaction mixture was diluted with some methanol and purified via HPLC. Compounds in the following table were synthesized as exemplified by compound **143**.

Table A-12

Cpd no	From cpd	Scale [nmol]	structure	name	Exact mass	$[M+H]^+$ found
143	**142**	200		N-((9S,12S)-5^4-methyl-8,11,15-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(2,4)-morpholina-5(1,3)-benzenacyclopentadecaphane-12-yl)acetamide	564.3 $C_{31}H_{40}N_4O_6$	565.4
148	**147**	230		N-((7S,10S)-3^4-methyl-6,9,13-trioxo-7-phenethyl-2-oxa-5,8-diaza-1(3,1)-piperidina-3(1,3)-benzenacyclotridecaphane-10-yl)acetamide	534.3 $C_{30}H_{38}N_4O_5$	535.4

Example A-16: Preparation of macrocyclic compound 168

tert-butyl (4-(3-cyano-4-methylphenoxy)butyl)carbamate (**162**)

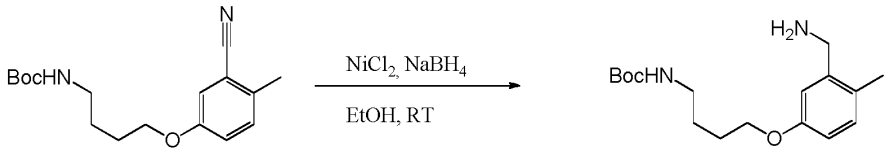


162

978 mg phenol, 2.5 g bromide and 6.46 g Cs_2CO_3 were stirred in 10 ml DMF at 60 °C until the phenol was consumed. The reaction mixture was diluted with DCM and washed

with brine. Solvent was removed and the residue was purified by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient).
Formula: $C_{17}H_{24}N_2O_3$, exact mass: 304.2, found: 304 (GC), 205.2 $[M+H\text{-}Boc]^+$

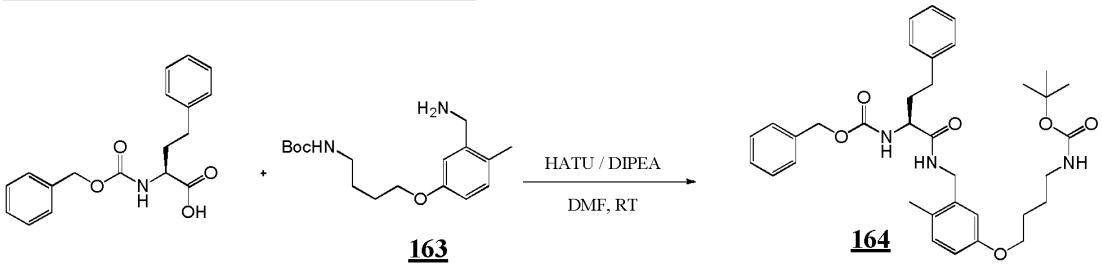
tert-butyl (4-(3-(aminomethyl)-4-methylphenoxy)butyl)carbamate (**163**)



162 **163**

To 1.55 g nitrile **162** an 660 mg $NiCl_2$ in ethanol 680 mg $NaBH_4$ were added in portions at room temperature. After complete reaction the mixture was filtered over a pad of Celite. Crude was purified by normal phase column chromatography (silica, DCM/methanol gradient).
Formula: $C_{17}H_{28}N_2O_3$, exact mass: 308.2, found: 309.2 $[M+H]^+$

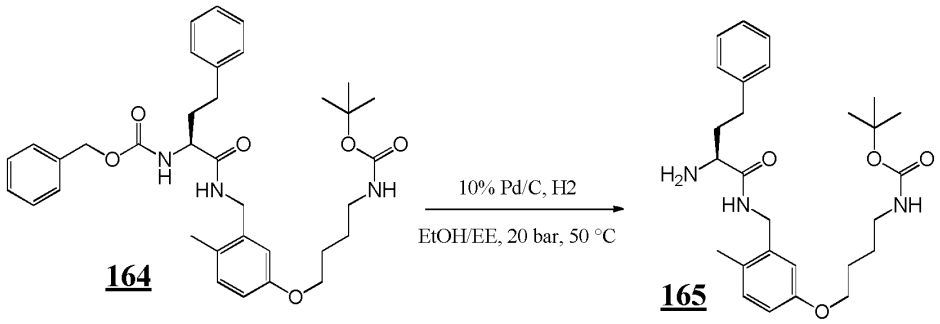
(S)-tert-butyl-(4-(3-((2-(((benzyloxy)carbonyl)amino)-4-phenylbutanamido)methyl)-4-methylphenoxy)butyl)carbamate (**164**)



163 **164**

The amide bond was formed according to general procedure B with 346 mg amine **163** and 421 mg Cbz-hPhe-OH. Purification was achieved by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient).
Formula: $C_{35}H_{45}N_3O_6$, exact mass: 603.3, found: 604.4 $[M+H]^+$

(S)-tert-butyl (4-(3-((2-amino-4-phenylbutanamido)methyl)-4-methylphenoxy)butyl) carbamate (**165**)

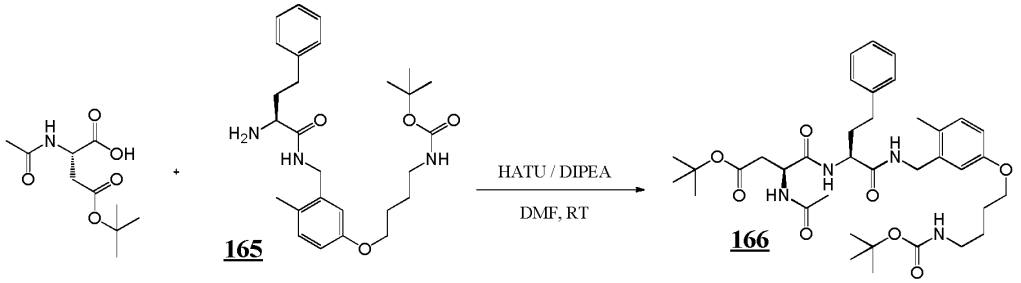


164 165

Benzyl ester was cleaved according to general procedure C using 10 % Pd/C catalyst cartridge, 20 bar at 50 °C in a solvent mixture of ethanol / ethyl acetate. Product was directly used after removing of volatiles.

Formula: $C_{27}H_{39}N_3O_4$, exact mass: 469.3, found: 470.4 $[M+H]^+$

(S)-tert-butyl 3-acetamido-4-(((S)-1-((5-(4-((tert-butoxycarbonyl)amino)butoxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoate (**166**)

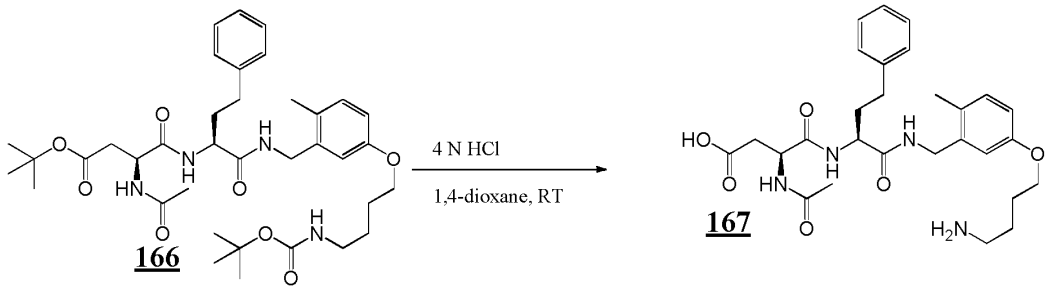


165 166

The amide bond was formed according to general procedure B with 190 mg amine **165** and 112 mg Ac-Asp(OtBu)-OH. Purification was achieved by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient).

Formula: $C_{37}H_{54}N_4O_8$, exact mass: 682.4, found: 683.4 $[M+H]^+$

(S)-3-acetamido-4-(((S)-1-((5-(4-aminobutoxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoic acid (**167**)

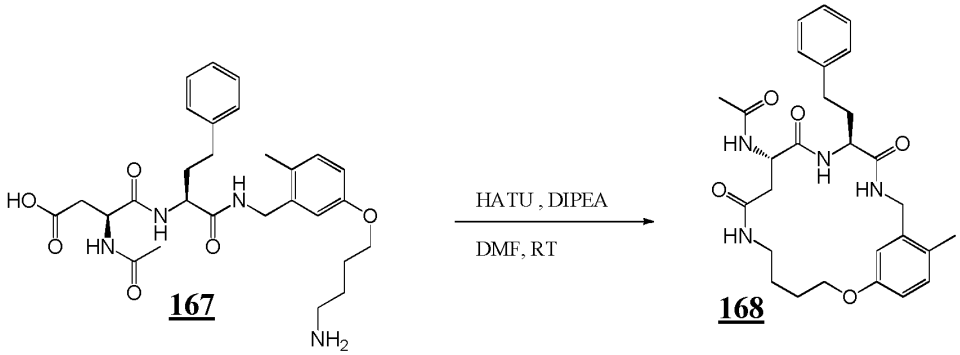


166 167

Protecting groups were cleaved from 276 mg compound **166** according to general procedure D stirring compounds in 6 ml 4 N HCl / 1,4-dioxane at room temperature.

After deprotection was complete solvent was removed and the crude dissolved in acetonitrile and concentrated twice. Product used without further purification.
Formula: $C_{28}H_{38}N_4O_6$, exact mass: 526.3, found: 527.3 $[M+H]^+$

N-((10S,13S)-1^4-methyl-8,11,14-trioxo-13-phenethyl-2-oxa-7,12,15-triaza-1(1,3)-benzenacyclohexadecaphane-10-yl)acetamide (**168**)

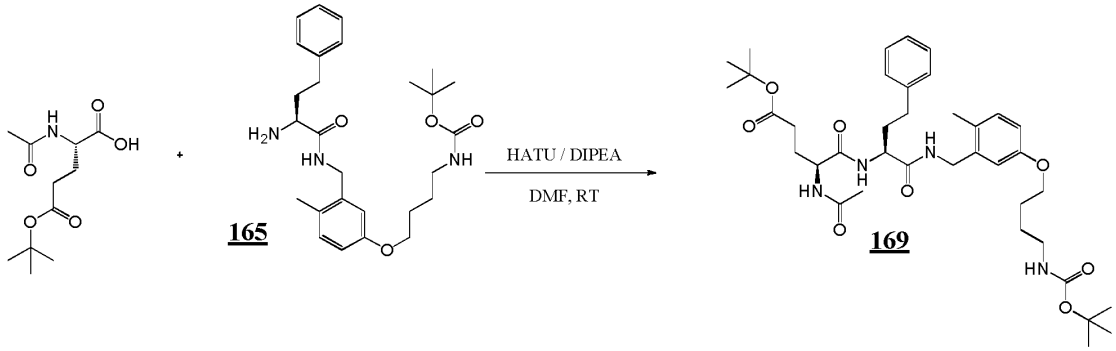


167 **168**

Macrocyclization was achieved according to general procedure A with 0.40 mmol amino acid **167**. Reaction mixtures were diluted with some methanol and purified via HPLC.
Formula: $C_{28}H_{36}N_4O_5$, exact mass: 508.3, found: 509.3 $[M+H]^+$

Example A-17: Preparation of macrocyclic compounds 171-173

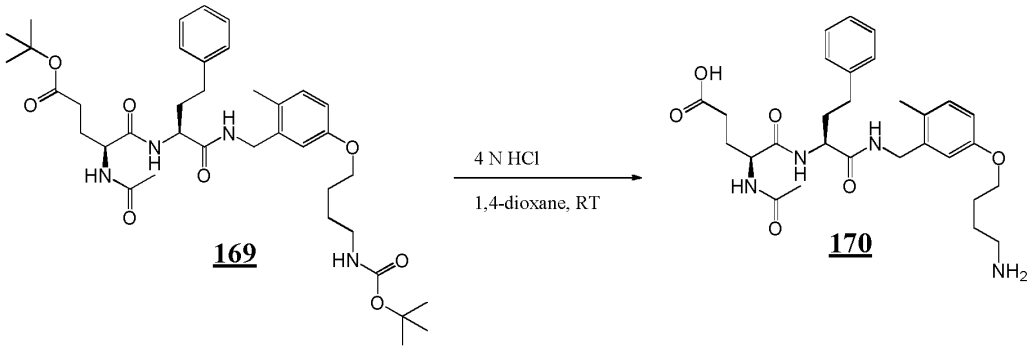
(S)-tert-butyl 4-acetamido-5-(((S)-1-((5-(4-((tert-butoxycarbonyl)amino)butoxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-5-oxopentanoate (**169**)



165 **169**

The amide bond was formed according to general procedure B with 190 mg amine **165** and 119 mg Ac-Glut(OtBu)-OH. Purification was achieved by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient).
Formula: $C_{38}H_{56}N_4O_8$, exact mass: 696.4, found: 697.5 $[M+H]^+$

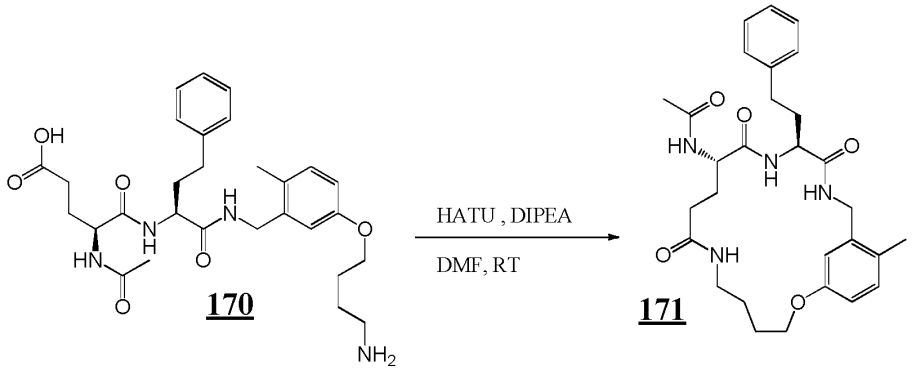
(S)-4-acetamido-5-(((S)-1-((5-(4-aminobutoxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-5-oxopentanoic acid (**170**)



169 **170**

Protecting groups were cleaved from 282 mg compound **169** according to general procedure D stirring compounds in 6 ml 4 N HCl / 1,4-dioxane at room temperature. After deprotection was complete solvent was removed and the crude dissolved in acetonitrile and concentrated twice. Product used without further purification.
Formula: $C_{29}H_{40}N_4O_6$, exact mass: 540.3, found: 541.3 $[M+H]^+$

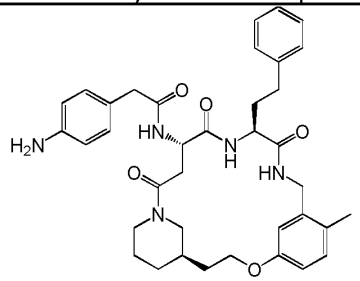
N-((11S,14S)-1^4-methyl-8,12,15-trioxo-14-phenethyl-2-oxa-7,13,16-triaza-1(1,3)-benzenacycloheptadecaphane-11-yl)acetamide (**171**)



170 **171**

Macrocyclization was achieved according to general procedure A with 0.40 mmol amino acid **170**. Reaction mixtures were diluted with some methanol and purified via HPLC.
Formula: $C_{29}H_{38}N_4O_6$, exact mass: 522.3, found: 523.3 $[M+H]^+$

2-(4-aminophenyl)-N-((13R,9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide (**172**)

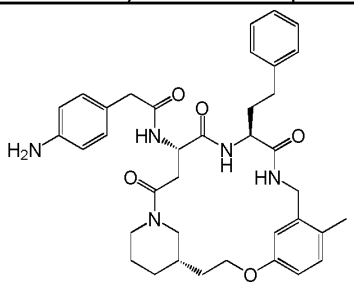


172

Compound **172** was prepared in analogy to compound 128 with the exception that (R)-tert-butyl 3-(2-hydroxyethyl)piperidine-1-carboxylate was used to synthesize a enantiomerically pure derivative of tert-butyl 3-(2-(3-cyano-4-methylphenoxy)ethyl)piperidine-1-carboxylate **3**.

Formula: $C_{37}H_{45}N_5O_5$, exact mass: 639.3, found: 640.4 $[M+H]^+$

2-(4-aminophenyl)-N-((13S,9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide (**173**)



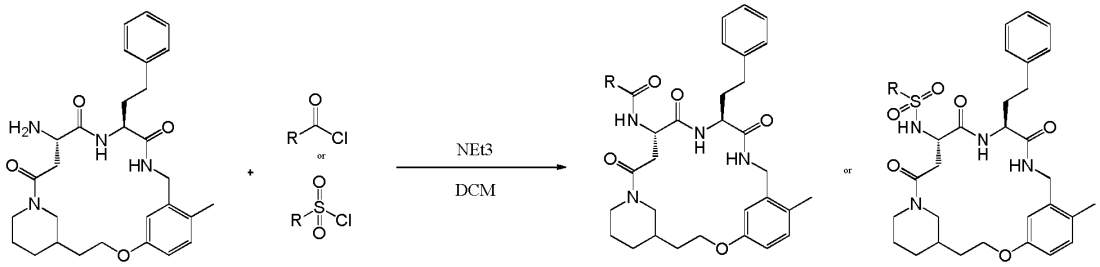
173

Compound **172** was prepared in analogy to compound **128** with the exception that (S)-tert-butyl 3-(2-hydroxyethyl)piperidine-1-carboxylate was used to synthesize a enantiomerically pure derivative of tert-butyl 3-(2-(3-cyano-4-methylphenoxy)ethyl)piperidine-1-carboxylate **3**.

Formula: $C_{37}H_{45}N_5O_5$, exact mass: 639.3, found: 640.4 $[M+H]^+$

Example A-18: Preparation of macrocyclic compounds 180, 181, 216, 217, and 294

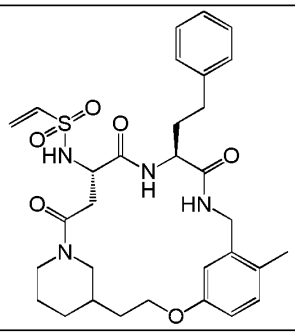
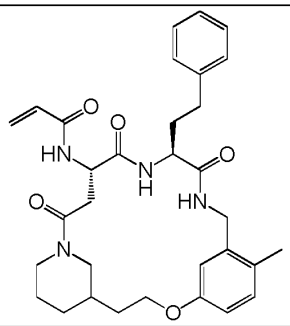
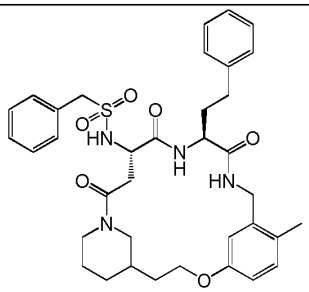
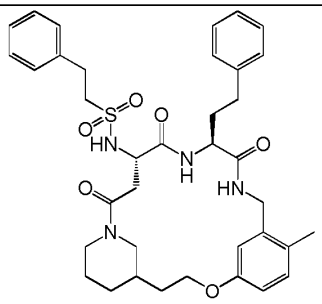
Amide derivatizations of compound **8** according to general procedure E

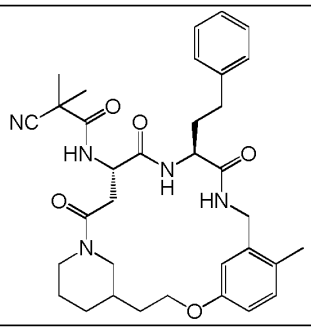


8

Compounds were synthesized according to general procedure E with e.g. 20 to 100 mg amine **8** and carboxylic acid chlorides or sulfonyl chlorides to give amides or sulfonamides as disclosed in table below. Purifications were achieved by HPLC or reversed phase flash chromatography.

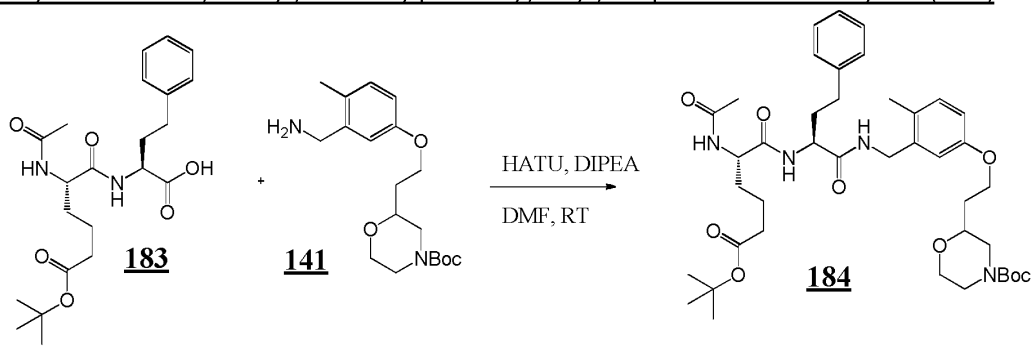
Table A-13

Cpd no	structure	name	Exact mass	$[M+H]^+$ found
180		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)ethenesulfonamide	596.3 $C_{31}H_{40}N_4O_6S$	597.4
181		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acrylamide	560.3 $C_{32}H_{40}N_4O_5$	561.4
216		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-1-phenylmethanesulfonamide	660.3 $C_{36}H_{44}N_4O_6S$	661.7
217		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-phenylethane-1-sulfonamide	674.3 $C_{37}H_{46}N_4O_6S$	675.7

294		2-cyano-2-methyl-N-((9S,12S)-54-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide	601.3 $C_{34}H_{43}N_5O_5$	602.5

Example A-19: Preparation of macrocyclic compound 186

tert-butyl 2-(2-(3-(((S)-2-((S)-2-acetamido-6-(tert-butoxy)-6-oxohexanamido)-4-phenylbutanamido)methyl)-4-methylphenoxy)ethyl)morpholine-4-carboxylate (**184**)

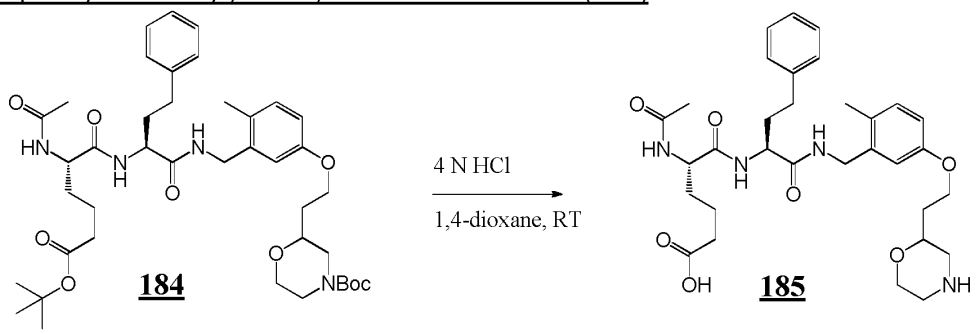


183 **141** **184**

The amide bond was formed according to general procedure B with 140 mg amine **141** and 268 mg acid **183**. Purification was achieved by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient).

Formula: $C_{41}H_{60}N_4O_9$, exact mass: 752.4, found: 753.7 $[M+H]^+$

(5S)-5-acetamido-6-(((2S)-1-((2-methyl-5-(2-(morpholin-2-yl)ethoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-6-oxohexanoic acid (**185**)

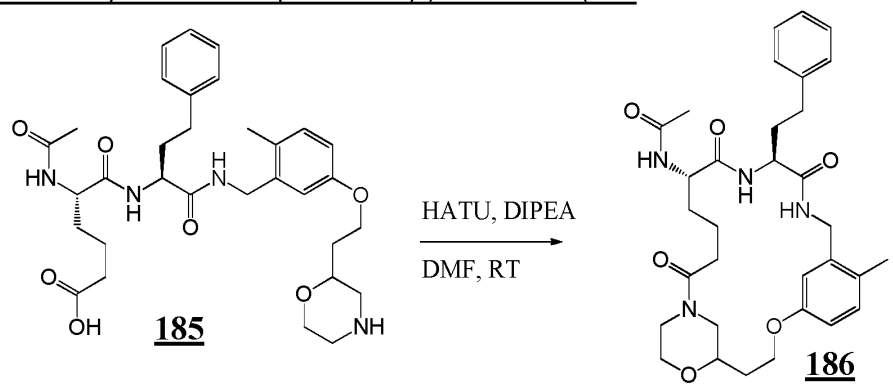


184 **185**

Protecting groups were cleaved from 99 mg compound **184** according to general procedure D stirring compounds in 10 ml 4 N HCl / 1,4-dioxane at room temperature. After deprotection was complete solvent was removed and the crude dissolved in acetonitrile and concentrated twice. Product used without further purification

Formula: $C_{32}H_{44}N_4O_7$, exact mass: 596.3, found: 597.3 $[M+H]^+$

N-((9S,12S)-5[4]-methyl-8,11,16-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(2,4)-morpholina-5(1,3)-benzenacyclohexadecaphane-12-yl)acetamide (**186**

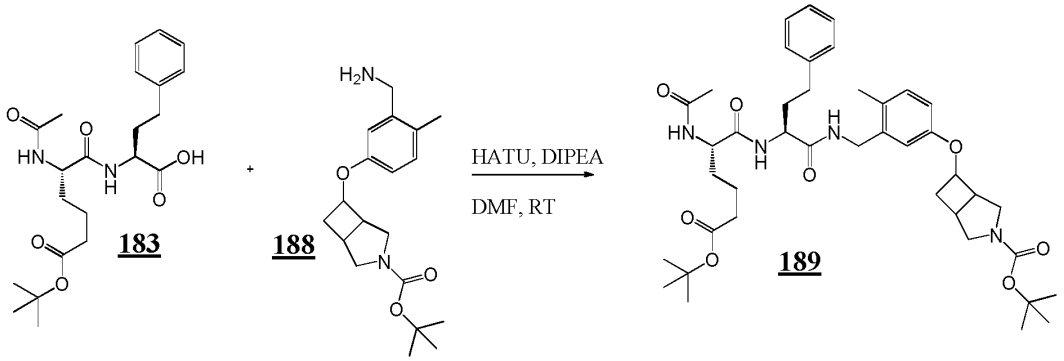


185 **186**

Macrocyclization was achieved according to general procedure A with 0.166 mmol amino acid **185**. Reaction mixtures were diluted with some methanol and purified via HPLC. Formula: $C_{32}H_{42}N_4O_6$, exact mass: 578.3, found: 579.6 $[M+H]^+$

Example A-20: Preparation of macrocyclic compound 191

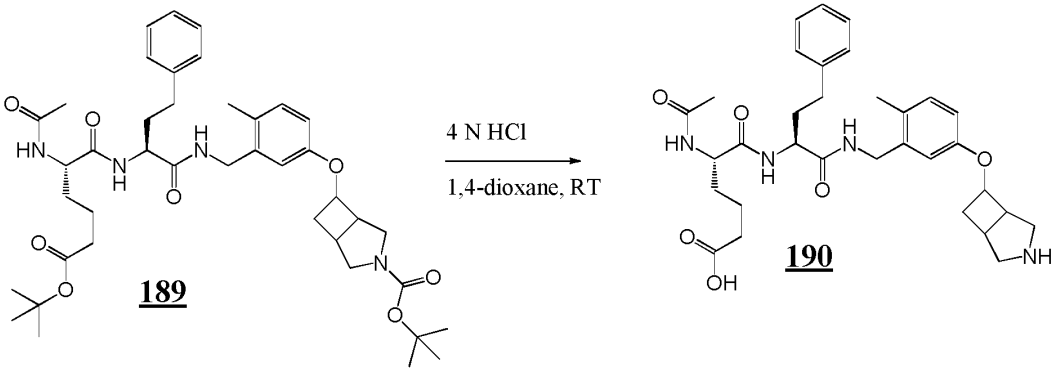
tert-butyl 6-(3-(((S)-2-((S)-2-acetamido-6-(tert-butoxy)-6-oxohexanamido)-4-phenylbutanamido)methyl)-4-methylphenoxy)-3-azabicyclo[3.2.0]heptane-3-carboxylate (**189**)



183 **188** **189**

The amide bond was formed according to general procedure B with 134 mg amine **188** and 113 mg acid **183**. Purification was achieved by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient).
Formula: $C_{41}H_{58}N_4O_8$, exact mass: 734.4, found: 735.7 $[M+H]^+$

(5S)-6-(((2S)-1-((5-(3-azabicyclo[3.2.0]heptan-6-yloxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-5-acetamido-6-oxohexanoic acid (**190**)

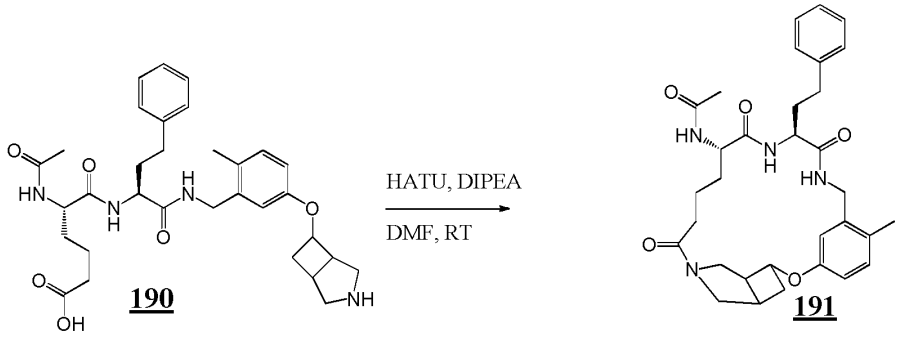


189 190

Protecting groups were cleaved from 168 mg compound **189** according to general procedure D stirring compounds in 10 ml 4 N HCl / 1,4-dioxane at room temperature. After deprotection was complete solvent was removed and the crude dissolved in acetonitrile and concentrated twice. Product used without further purification

Formula: $C_{32}H_{42}N_4O_6$, exact mass: 578.3, found: 579.3 $[M+H]^+$

N-((11R,15S,7S,10S)-3[4]-methyl-6,9,14-trioxo-7-phenethyl-2-oxa-13,5,8-triaza-1(7,3)-bicyclo[3.2.0]heptana-3(1,3)-benzenacyclotetradecaphane-10-yl)acetamide (**191**)



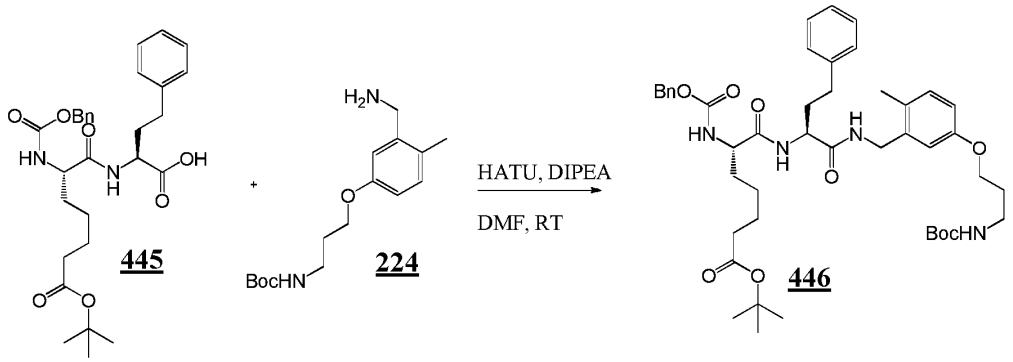
190 191

Macrocyclization was achieved according to general procedure A with 0.166 mmol amino acid **190**. Reaction mixtures were diluted with some methanol and purified via HPLC.

Formula: $C_{32}H_{40}N_4O_5$, exact mass: 560.3, found: 561.5 $[M+H]^+$

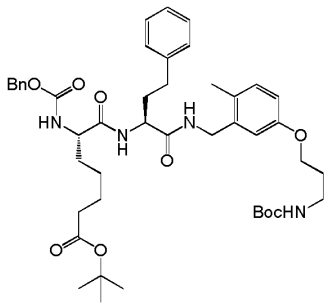
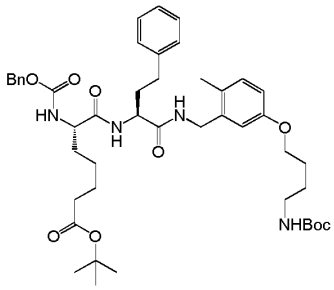
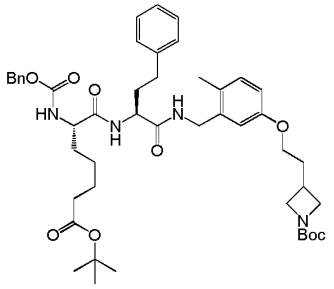
Example A-21: Preparation of macrocyclic compounds 347 and 353

(S)-tert-butyl 6-(((benzyloxy)carbonyl)amino)-7-(((S)-1-((5-(3-((tert-butoxycarbonyl)amino)propoxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-7-oxoheptanoate (**446**)

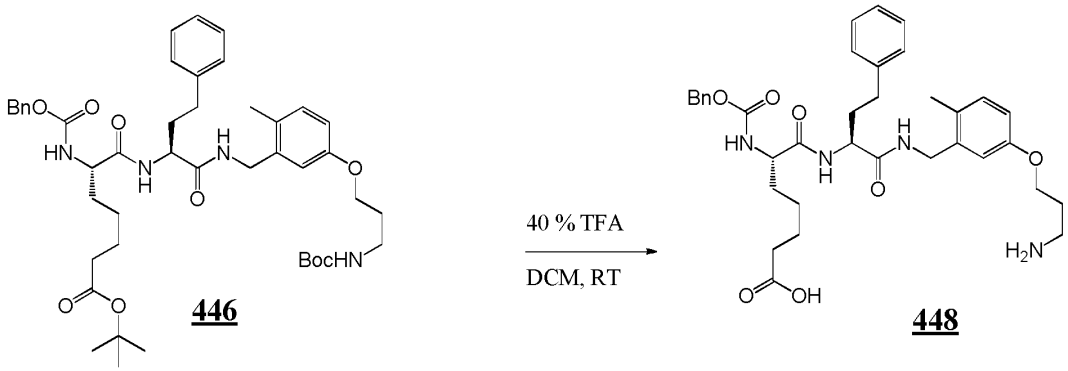


The amide bond was formed according to general procedure B with 187 mg amine **224** and 222 mg acid **445**. Purification was achieved by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient). Additional examples utilizing other amines than amine 4 are disclosed in the following table.

Table A-14

Cpd no	From amine	structure	name	Exact mass	$[M+H]^+$ found
446	**224**		(S)-tert-butyl 6-(((benzyloxy)carbonyl)amino)-7-(((S)-1-((5-(3-((tert-butoxycarbonyl)amino)propoxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-7-oxoheptanoate	802.5 $C_{45}H_{62}N_4O_9$	703.4
447	**163**		(S)-tert-butyl 6-(((benzyloxy)carbonyl)amino)-7-(((S)-1-((5-(4-((tert-butoxycarbonyl)amino)butoxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-7-oxoheptanoate	816.5 $C_{46}H_{64}N_4O_9$	717.5 [M+H-Boc]+
464			tert-butyl 3-(2-(3-((5S,8S)-5-(5-(tert-butoxy)-5-oxopentyl)-3,6,9-trioxo-8-phenethyl-1-phenyl-2-oxa-4,7,10-triazaundecan-11-yl)-4-methylphenoxy)ethyl) azetidine-1-carboxylate	828.5 $C_{47}H_{64}N_4O_9$	829.7

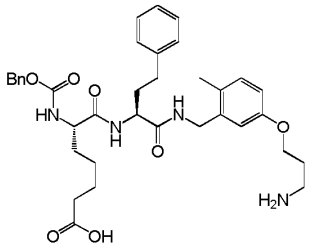
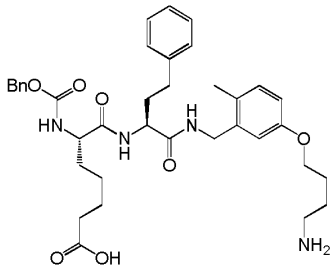
(S)-7-(((S)-1-((5-(3-aminopropoxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-6-(((benzyloxy)carbonyl)amino)-7-oxoheptanoic acid (**448**)

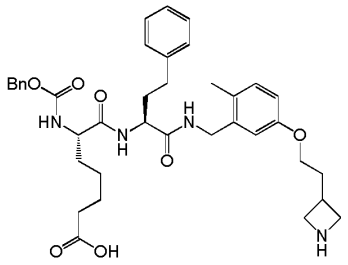


446 **448**

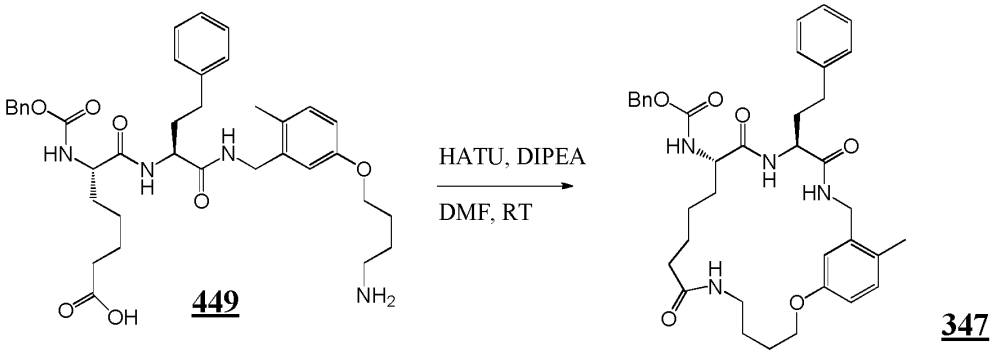
Protecting groups were cleaved from 244 mg compound **446** according to general procedure D stirring compounds in 5 ml 40 % TFA in DCM at room temperature. After deprotection was complete solvent was removed and the crude dissolved in acetonitrile and concentrated twice. Product used without further purification. Additional examples are disclosed in the following table.

Table A-15

Cpd no	From cpd	structure	name	Exact mass	$[M+H]^+$ found
448	**446**		(S)-7-(((S)-1-((5-(3-aminopropoxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-6-(((benzyloxy)carbonyl)amino)-7-oxoheptanoic acid	646.3 $C_{36}H_{46}N_4O_7$	647.4
449	**447**		(S)-7-(((S)-1-((5-(4-aminobutoxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-6-(((benzyloxy)carbonyl)amino)-7-oxoheptanoic acid	660.4 $C_{37}H_{48}N_4O_7$	661.4

465	**464**		(S)-7-(((S)-1-((5-(2-(azetidin-3-yl)ethoxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-6-(((benzyloxy)carbonyl)amino)-7-oxoheptanoic acid	672.4 $C_{38}H_{48}N_4O_7$	673.4

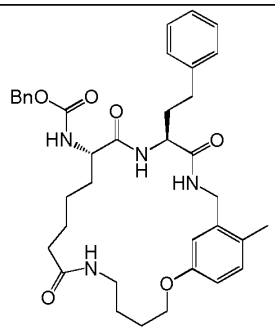
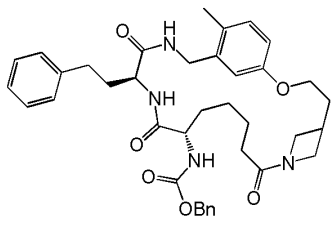
benzyl ((13S,16S)-1^4-methyl-8,14,17-trioxo-16-phenethyl-2-oxa-7,15,18-triaza-1(1,3)-benzenacyclononadecaphane-13-yl)carbamate (**347**)



449 **347**

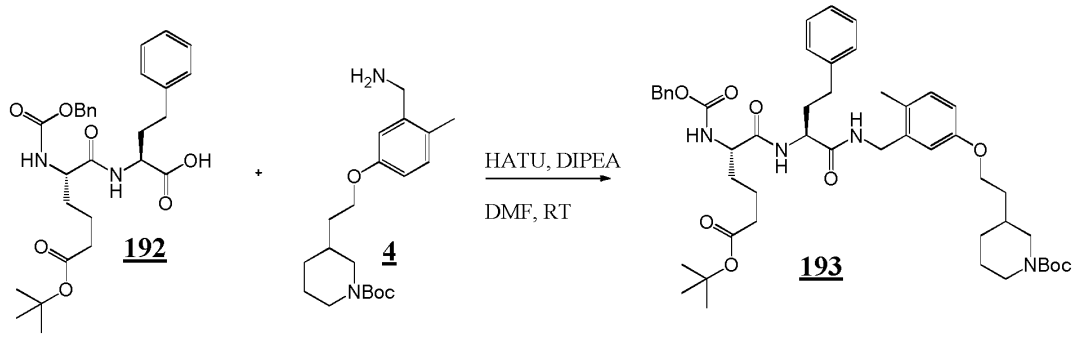
Macrocyclization was achieved according to general procedure A with 0.3 mmol amino acid **449**. Reaction mixtures were diluted with some methanol and purified via HPLC. Additional examples are disclosed in the following table.

Table A-16

Cpd no	From cpd	structure	name	Exact mass	$[M+H]^+$ found
347	**449**		benzyl ((13S,16S)-1^4-methyl-8,14,17-trioxo-16-phenethyl-2-oxa-7,15,18-triaza-1(1,3)-benzenacyclononadecaphane-13-yl)carbamate	642.3 $C_{37}H_{46}N_4O_6$	643.4
353	**465**		benzyl ((9S,12S)-5^4-methyl-8,11,17-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-azetidina-5(1,3)-benzenacyclohepta decaphane-12-yl)carbamate	654.3 $C_{38}H_{46}N_4O_6$	655.5

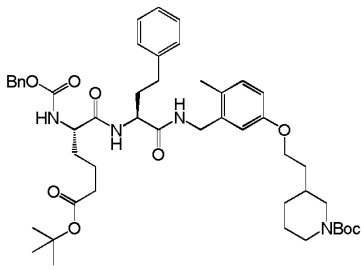
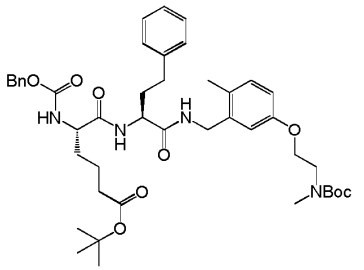
Example A-22: Preparation of macrocyclic compounds 195, 283, 322, 351, 352, 354, and 405

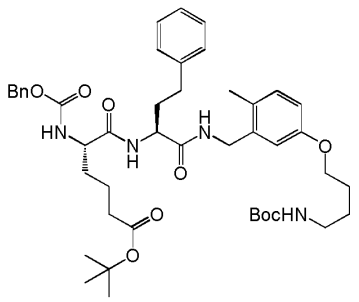
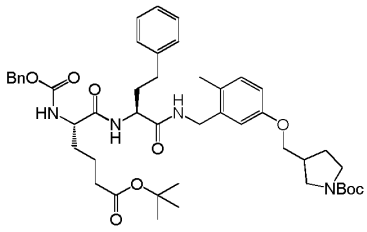
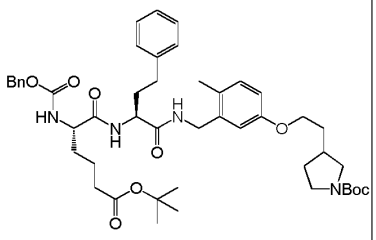
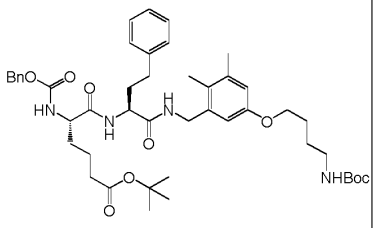
tert-butyl 3-(2-(3-((5S,8S)-5-(4-(tert-butoxy)-4-oxobutyl)-3,6,9-trioxo-8-phenethyl-1-phenyl-2-oxa-4,7,10-triazaundecan-11-yl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate (**193**)

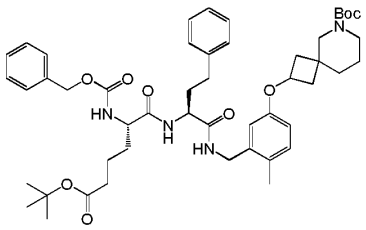


The amide bond was formed according to general procedure B with 615 mg amine **4** and 711 mg acid **192**. Purification was achieved by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient). Additional examples utilizing other amines than amine 4 are disclosed in the following table.

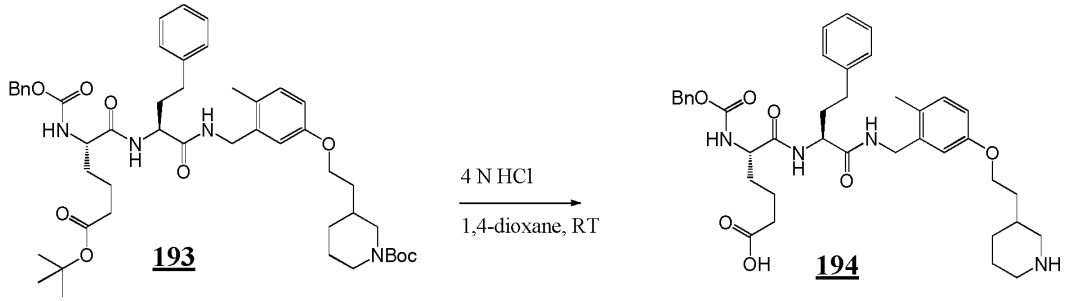
Table A-17

Cpd no	From amine	structure	name	Exact mass	$[M+H]^+$ found
193	**4**		tert-butyl 3-(2-(3-((5S,8S)-5-(4-(tert-butoxy)-4-oxobutyl)-3,6,9-trioxo-8-phenethyl-1-phenyl-2-oxa-4,7,10-triazaundecan-11-yl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate	842.5 $C_{48}H_{66}N_4O_9$	843.8
403	**399**		(S)-tert-butyl 5-(((benzyloxy)carbonyl)amino)-6-(((S)-1-((5-(2-((tert-butoxycarbonyl)(methyl)amino)ethoxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-6-oxohexanoate	788.4 $C_{44}H_{60}N_4O_9$	789.4

424	**224**		(S)-tert-butyl 5-(((benzyloxy)carbonyl)amino)-6-(((S)-1-((5-(4-((tert-butoxycarbonyl)amino)butoxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-6-oxohexanoate	802.5 $C_{45}H_{62}N_4O_9$	703.4
458	**426**		tert-butyl 3-((3-((5S,8S)-5-(4-(tert-butoxy)-4-oxobutyl)-3,6,9-trioxo-8-phenethyl-1-phenyl-2-oxa-4,7,10-triazaundecan-11-yl)-4-methylphenoxy)methyl)pyrrolidine-1-carboxylate	814.5 $C_{46}H_{62}N_4O_9$	815.7
459	**455**		tert-butyl 3-(2-(3-((5S,8S)-5-(4-(tert-butoxy)-4-oxobutyl)-3,6,9-trioxo-8-phenethyl-1-phenyl-2-oxa-4,7,10-triazaundecan-11-yl)-4-methylphenoxy)ethyl)pyrrolidine-1-carboxylate	828.4 $C_{47}H_{64}N_4O_9$	829.4
467	**468**		(S)-tert-butyl 5-(((benzyloxy)carbonyl)amino)-6-(((S)-1-((5-(4-((tert-butoxycarbonyl)amino)butoxy)-2,3-dimethylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-6-oxohexanoate	816.5 $C_{46}H_{64}N_4O_9$	817.4

275	**271**		tert-butyl 2-(3-((5S,8S)-5-(4-(tert-butoxy)-4-oxobutyl)-3,6,9-trioxo-8-phenethyl-1-phenyl-2-oxa-4,7,10-triazaundecan-11-yl)-4-methylphenoxy)-6-azaspiro[3.5]nonane-6-carboxylate	854.5 $C_{49}H_{66}N_4O_9$	855.3

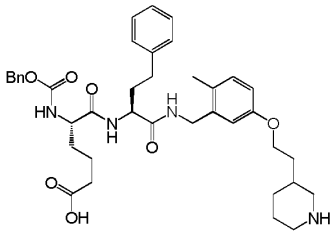
(5S)-5-(((benzyloxy)carbonyl)amino)-6-(((2S)-1-((2-methyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-6-oxohexanoic acid (194)

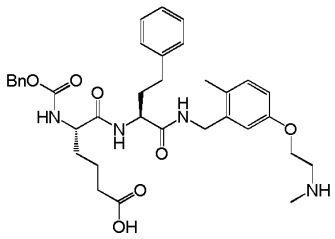
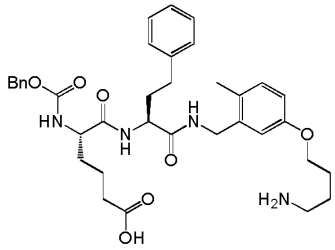
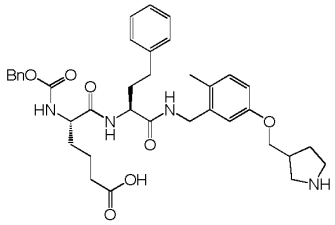
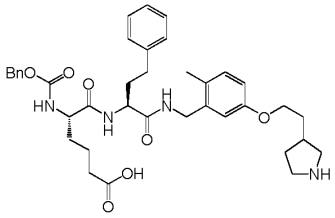
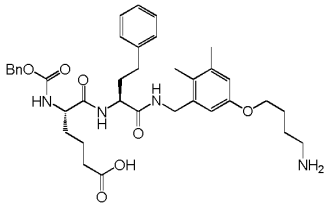


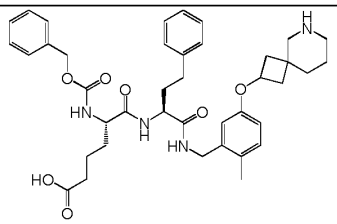
193 **194**

Protecting groups were cleaved from 900 mg compound **193** according to general procedure D stirring compounds in 10 ml 4 N HCl / 1,4-dioxane at room temperature. After deprotection was complete solvent was removed and the crude dissolved in acetonitrile and concentrated twice. Product used without further purification. Additional examples are disclosed in the following table.

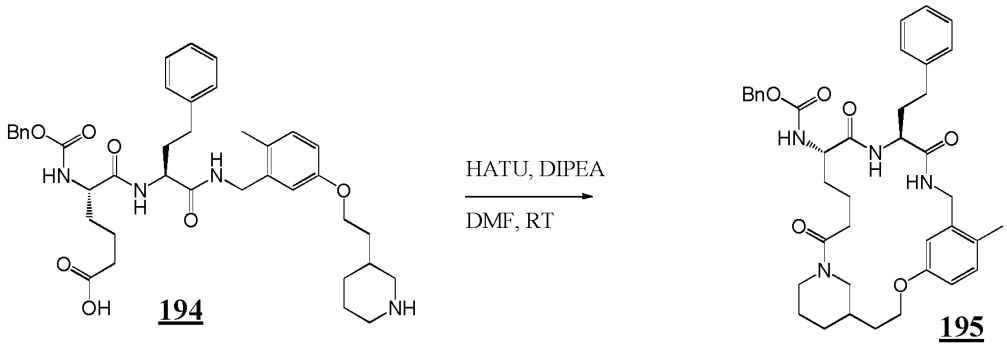
Table A-18

Cpd no	From cpd	structure	name	Exact mass	$[M+H]^+$ found
194	**193**		(5S)-5-(((benzyloxy)carbonyl)amino)-6-(((2S)-1-((2-methyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-6-oxohexanoic acid	686.4 $C_{39}H_{50}N_4O_7$	687.4

404	**403**		(S)-5-(((benzyloxy)carbonyl)amino)-6-(((S)-1-((2-methyl-5-(2-(methylamino)ethoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-6-oxohexanoic acid	632.3 $C_{35}H_{44}N_4O_7$	-
425	**424**		(S)-6-(((S)-1-((5-(4-aminobutoxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-5-(((benzyloxy)carbonyl)amino)-6-oxohexanoic acid	646.3 $C_{36}H_{46}N_4O_7$	647.3
460	**458**		(5S)-5-(((benzyloxy)carbonyl)amino)-6-(((2S)-1-((2-methyl-5-(pyrrolidin-3-ylmethoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-6-oxohexanoic acid	658.3 $C_{37}H_{46}N_4O_7$	659.6
461	**459**		(5S)-5-(((benzyloxy)carbonyl)amino)-6-(((2S)-1-((2-methyl-5-(2-(pyrrolidin-3-yl)ethoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-6-oxohexanoic acid	672.4 $C_{38}H_{48}N_4O_7$	673.4
469	**467**		(S)-6-(((S)-1-((5-(4-aminobutoxy)-2,3-dimethylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-5-(((benzyloxy)carbonyl)amino)-6-oxohexanoic acid	660.4 $C_{37}H_{48}N_4O_7$	661.5

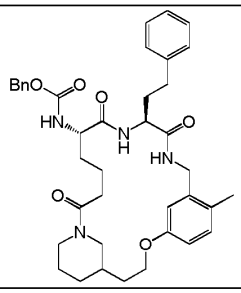
279	**275**		(S)-6-(((S)-1-((5-(6-azaspiro[3.5]nonan-2-yloxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-5-(((benzyloxy)carbonyl)amino)-6-oxohexanoic acid	698.4 $C_{40}H_{50}N_4O_7$	699.4

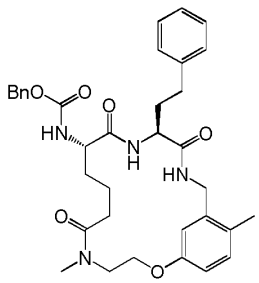
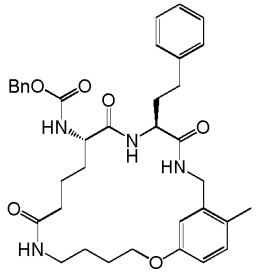
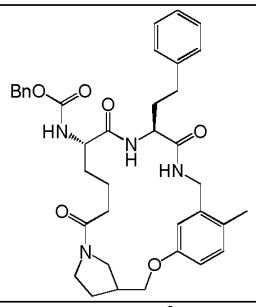
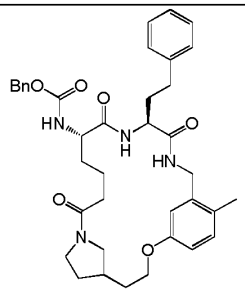
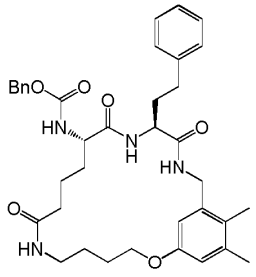
benzyl ((9S,12S)-5[4]-methyl-8,11,16-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclohexadecaphane-12-yl)carbamate (**195**)

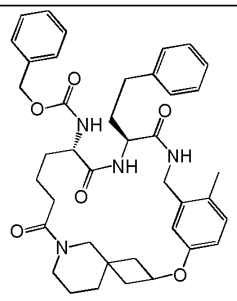


Macrocyclization was achieved according to general procedure A with 1.07 mmol amino acid **194**. Reaction mixtures were diluted with some methanol and purified via HPLC. Additional examples are disclosed in the following table.

Table A-19

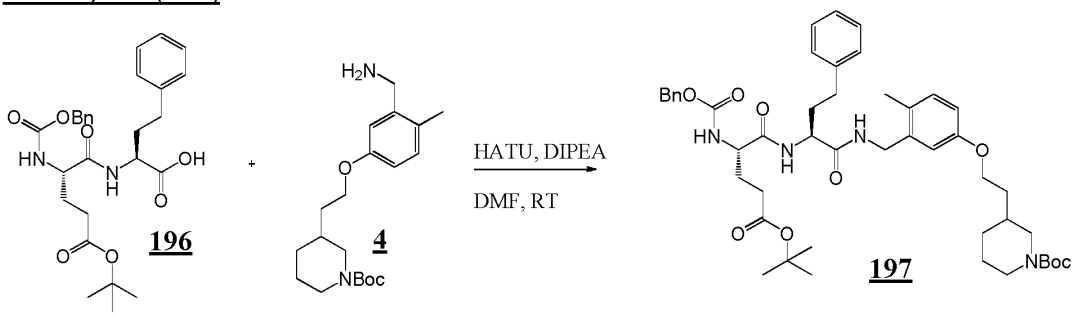
Cpd no	From cpd	structure	name	Exact mass	$[M+H]^+$ found
195	**194**		benzyl ((9S,12S)-5[4]-methyl-8,11,16-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclohexadecaphane-12-yl)carbamate	668.4 $C_{39}H_{48}N_4O_6$	669.7

405	**404**		benzyl ((10S,13S)-1^4,5-dimethyl-6,11,14-trioxo-13-phenethyl-2-oxa-5,12,15-triaza-1(1,3)-benzenacyclohexadecaphane-10-yl)carbamate	614.3 $C_{35}H_{42}N_4O_6$	615.3
322	**425**		benzyl ((12S,15S)-1^4-methyl-8,13,16-trioxo-15-phenethyl-2-oxa-7,14,17-triaza-1(1,3)-benzenacyclooctadecaphane-12-yl)carbamate	628.3 $C_{36}H_{44}N_4O_6$	629.4
351	**460**		benzyl ((8S,11S)-4^4-methyl-7,10,15-trioxo-8-phenethyl-3-oxa-6,9-diaza-1(3,1)-pyrrolidina-4(1,3)-benzenacyclopentadecaphane-11-yl)carbamate	640.3 $C_{37}H_{44}N_4O_6$	641.5
352	**461**		benzyl ((9S,12S)-5^4-methyl-8,11,16-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-pyrrolidina-5(1,3)-benzenacyclohexadecaphane-12-yl)carbamate	654.3 $C_{38}H_{46}N_4O_6$	655.6
354	**469**		benzyl ((12S,15S)-14,15-dimethyl-8,13,16-trioxo-15-phenethyl-2-oxa-7,14,17-triaza-1(1,3)-benzenacyclooctadecaphane-12-yl)carbamate	642.3 $C_{37}H_{46}N_4O_6$	643.5

283	**279**		benzyl ((7S,10S)-34-methyl-6,9,14-trioxo-7-phenethyl-2-oxa-5,8-diaza-15(3,1)-piperidina-3(1,3)-benzena-1(1,3)-cyclobutanapentadecaphane-10-yl)carbamate	680.4 $C_{40}H_{48}N_4O_6$	681.5

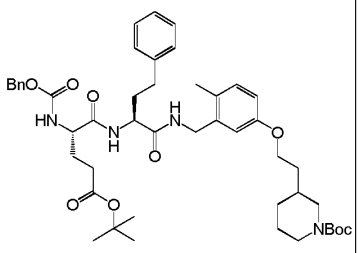
Example A-23: Preparation of macrocyclic compounds 199, 301, 349, 350 and 402

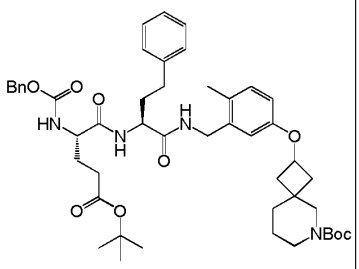
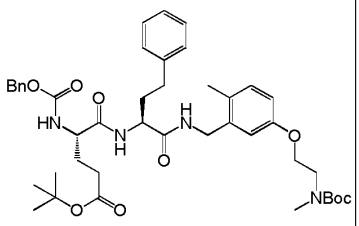
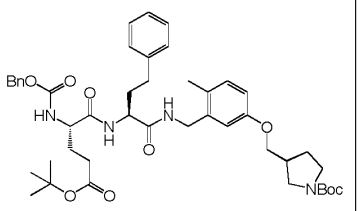
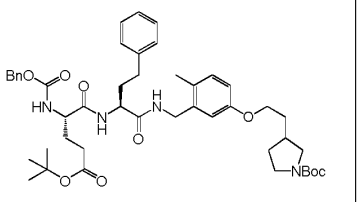
tert-butyl 3-(2-(3-((5S,8S)-5-(3-(tert-butoxy)-3-oxopropyl)-3,6,9-trioxo-8-phenethyl-1-phenyl-2-oxa-4,7,10-triazaundecan-11-yl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate (**197**)



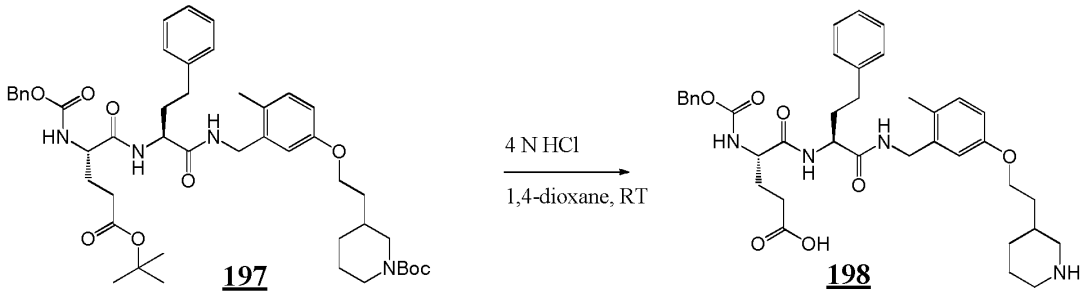
The amide bond was formed according to general procedure B with 615 mg amine **4** and 808 mg acid **196**. Purification was achieved by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient). Additional examples utilizing other amines than amine 4 are disclosed in the following table.

Table A-20

Cpd no	From amine	structure	name	Exact mass	$[M+H]^+$ found
197	**4**		tert-butyl 3-(2-(3-((5S,8S)-5-(3-(tert-butoxy)-3-oxopropyl)-3,6,9-trioxo-8-phenethyl-1-phenyl-2-oxa-4,7,10-triazaundecan-11-yl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate	828.5 $C_{47}H_{64}N_4O_9$	830.6

385	**271**		tert-butyl 2-(3-((5S,8S)-5-(3-(tert-butoxy)-3-oxopropyl)-3,6,9-trioxo-8-phenethyl-1-phenyl-2-oxa-4,7,10-triazaundecan-11-yl)-4-methylphenoxy)-6-azaspiro[3.5]nonane-6-carboxylate	840.5 $C_{48}H_{64}N_4O_9$	841.6
400	**399**		(S)-tert-butyl 4-(((benzyloxy)carbonyl)amino)-5-(((S)-1-((5-(2-((tert-butoxycarbonyl)(methyl)amino)ethoxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-5-oxopentanoate	774.4 $C_{43}H_{58}N_4O_9$	-
451	**426**		tert-butyl 3-((3-((5S,8S)-5-(3-(tert-butoxy)-3-oxopropyl)-3,6,9-trioxo-8-phenethyl-1-phenyl-2-oxa-4,7,10-triazaundecan-11-yl)-4-methylphenoxy)methyl)pyrrolidine-1-carboxylate	800.4 $C_{45}H_{60}N_4O_9$	801.4
452	**455**		tert-butyl 3-(2-(3-((5S,8S)-5-(3-(tert-butoxy)-3-oxopropyl)-3,6,9-trioxo-8-phenethyl-1-phenyl-2-oxa-4,7,10-triazaundecan-11-yl)-4-methylphenoxy)ethyl)pyrrolidine-1-carboxylate	814.5 $C_{46}H_{62}N_4O_9$	815.4

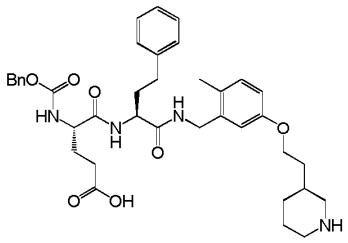
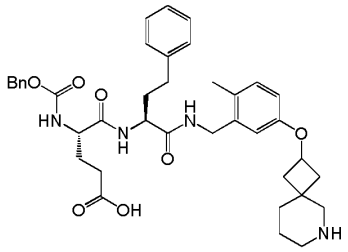
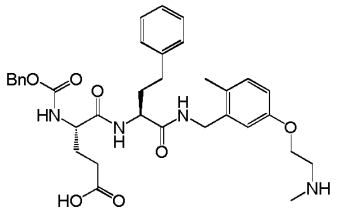
(4S)-4-(((benzyloxy)carbonyl)amino)-5-(((2S)-1-((2-methyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-5-oxopentanoic acid (**198**)

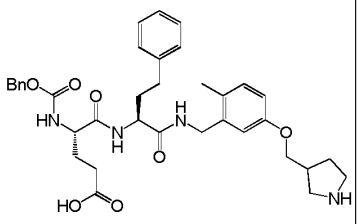
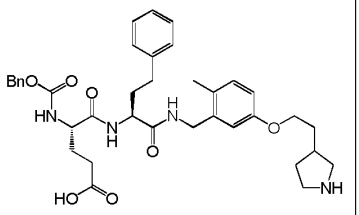


197 198

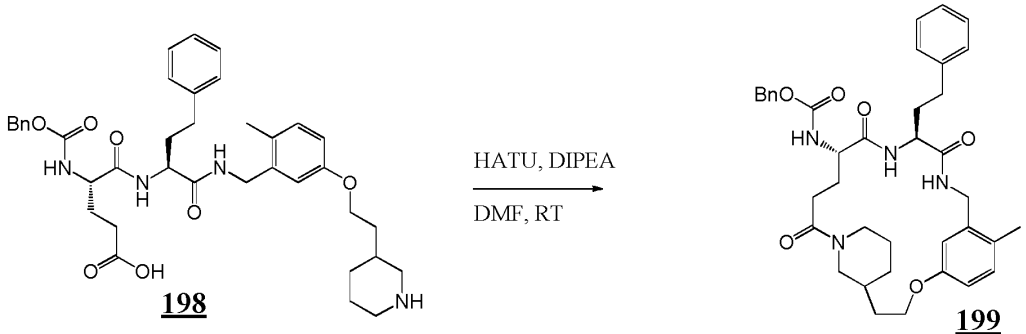
Protecting groups were cleaved from 850 mg compound **197** according to general procedure D stirring compounds in 10 ml 4 N HCl / 1,4-dioxane at room temperature. After deprotection was complete solvent was removed and the crude dissolved in acetonitrile and concentrated twice. Product used without further purification. Additional examples are disclosed in the following table.

Table A-21

Cpd no	From cpd	structure	name	Exact mass	$[M+H]^+$ found
198	**197**		(4S)-4-(((benzyloxy)carbonyl)amino)-5-(((2S)-1-((2-methyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-5-oxopentanoic acid	672.4 $C_{38}H_{48}N_4O_7$	673.7
386	**385**		(S)-5-(((S)-1-((5-(6-azaspiro[3.5]nonan-2-yloxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-(((benzyloxy)carbonyl)amino)-5-oxopentanoic acid	684.4 $C_{39}H_{48}N_4O_7$	685.4
401	**400**		(S)-4-(((benzyloxy)carbonyl)amino)-5-(((S)-1-((2-methyl-5-(2-(methylamino)ethoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-5-oxopentanoic acid	618.3 $C_{34}H_{42}N_4O_7$	-

456	**451**		(4S)-4-(((benzyloxy)carbonyl)amino)-5-(((2S)-1-((2-methyl-5-(pyrrolidin-3-ylmethoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-5-oxopentanoic acid	644.3 $C_{36}H_{44}N_4O_7$	645.5
457	**452**		(4S)-4-(((benzyloxy)carbonyl)amino)-5-(((2S)-1-((2-methyl-5-(2-(pyrrolidin-3-yl)ethoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-5-oxopentanoic acid	658.3 $C_{37}H_{46}N_4O_7$	629.5

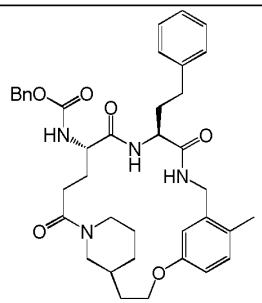
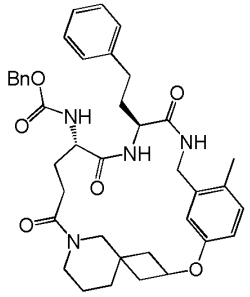
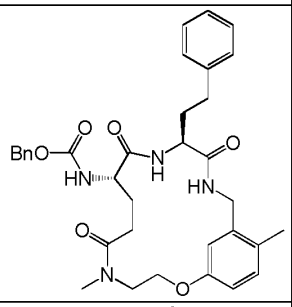
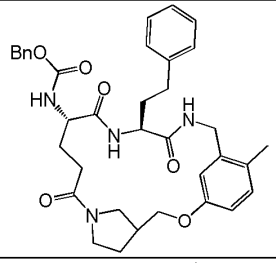
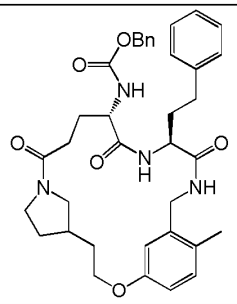
benzyl ((9S,12S)-5[4]-methyl-8,11,15-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclopentadecaphane-12-yl)carbamate (**199**)



198 **199**

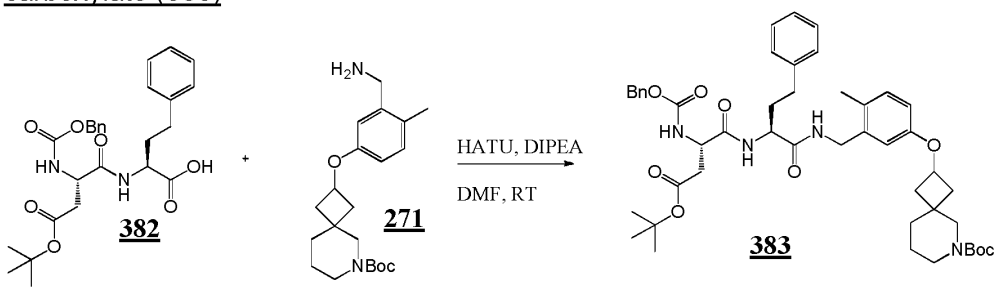
Macrocyclization was achieved according to general procedure A with 1.03 mmol amino acid **198**. Reaction mixtures were diluted with some methanol and purified via HPLC. Additional examples are disclosed in the following table.

Table A-22

Cpd no	From cpd	structure	name	Exact mass	$[M+H]^+$ found
199	**198**		benzyl ((9S,12S)-5^4-methyl-8,11,15-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclopentadecaphane-12-yl)carbamate	654.3 $C_{38}H_{46}N_4O_6$	655.6
301	**386**		benzyl ((7S,10S)-3^4-methyl-6,9,13-trioxo-7-phenethyl-2-oxa-5,8-diaza-14(3,1)-piperidina-3(1,3)-benzena-1(1,3)-cyclobutanatetradecaphane-10-yl)carbamate	666.3 $C_{39}H_{46}N_4O_6$	667.4
402	**401**		benzyl ((9S,12S)-1^4,5-dimethyl-6,10,13-trioxo-12-phenethyl-2-oxa-5,11,14-triaza-1(1,3)-benzenacyclopentadecaphane-9-yl)carbamate	600.3 $C_{34}H_{40}N_4O_6$	601.3
349	**456**		benzyl ((8S,11S)-4^4-methyl-7,10,14-trioxo-8-phenethyl-3-oxa-6,9-diaza-1(3,1)-pyrrolidina-4(1,3)-benzenacyclotetradecaphane-11-yl)carbamate	626.3 $C_{36}H_{42}N_4O_6$	627.4
350	**457**		benzyl ((9S,12S)-5^4-methyl-8,11,15-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-pyrrolidina-5(1,3)-benzenacyclopentadecaphane-12-yl)carbamate	640.3 $C_{37}H_{44}N_4O_6$	640.5

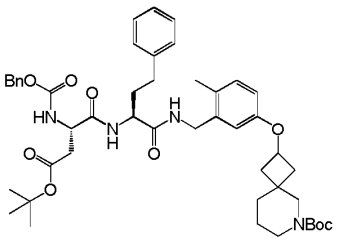
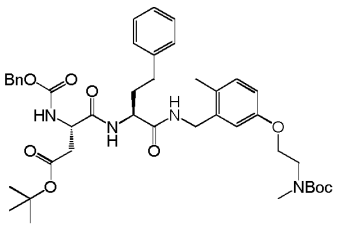
Example A-24: Preparation of macrocyclic compounds 300, 312, 313, 314, 315, 325, and 337

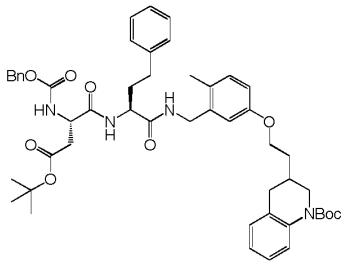
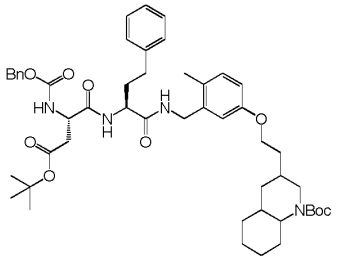
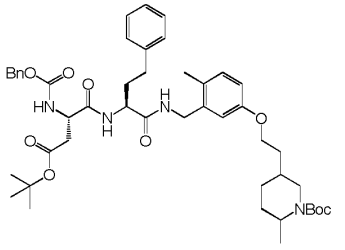
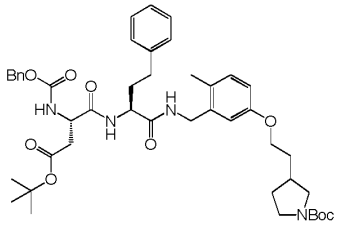
tert-butyl 2-(3-((5S,8S)-5-(2-(tert-butoxy)-2-oxoethyl)-3,6,9-trioxo-8-phenethyl-1-phenyl-2-oxa-4,7,10-triazaundecan-11-yl)-4-methylphenoxy)-6-azaspiro[3.5]nonane-6-carboxylate (**383**)

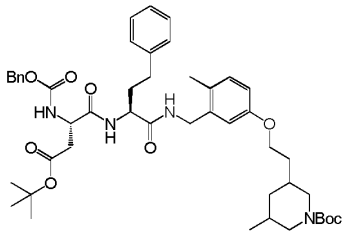


The amide bond was formed according to general procedure B with 100 mg amine **271** and 336 mg acid **382**. Purification was achieved by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient). Additional examples utilizing other amines than amine **271** are disclosed in the following table.

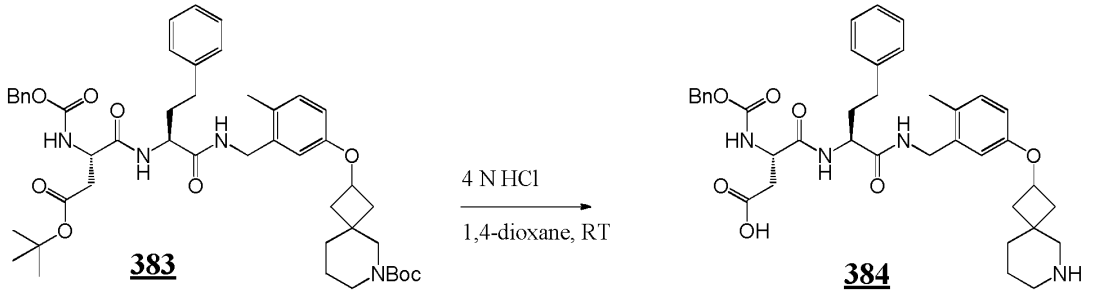
Table A-23

Cpd no	From amine	structure	name	Exact mass	$[M+H]^+$ found
383	**271**		tert-butyl 2-(3-((5S,8S)-5-(2-(tert-butoxy)-2-oxoethyl)-3,6,9-trioxo-8-phenethyl-1-phenyl-2-oxa-4,7,10-triazaundecan-11-yl)-4-methylphenoxy)-6-azaspiro[3.5]nonane-6-carboxylate	814.5	717.5 [M+H-Boc]+
397	**399**		(S)-tert-butyl 3-(((benzyloxy)carbonyl)amino)-4-(((S)-1-((5-(2-((tert-butoxycarbonyl)(methyl)amino)ethoxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoate	826.5	727.5 [M+H-Boc]+

406	**416**		tert-butyl 3-(2-(3-((5S,8S)-5-(2-(tert-butoxy)-2-oxoethyl)-3,6,9-trioxo-8-phenethyl-1-phenyl-2-oxa-4,7,10-triazaundecan-11-yl)-4-methylphenoxy)ethyl)-3,4-dihydroquinoline-1(2H)-carboxylate	862.5	863.3
407	**417**		tert-butyl 3-(2-(3-((5S,8S)-5-(2-(tert-butoxy)-2-oxoethyl)-3,6,9-trioxo-8-phenethyl-1-phenyl-2-oxa-4,7,10-triazaundecan-11-yl)-4-methylphenoxy)ethyl)octahydroquinoline-1(2H)-carboxylate	868.5	869.3
410	**411**		tert-butyl 5-(2-(3-((5S,8S)-5-(2-(tert-butoxy)-2-oxoethyl)-3,6,9-trioxo-8-phenethyl-1-phenyl-2-oxa-4,7,10-triazaundecan-11-yl)-4-methylphenoxy)ethyl)-2-methylpiperidine-1-carboxylate	828.5	729.6 [M+H-Boc]+
427	**426**		tert-butyl 3-(2-(3-((5S,8S)-5-(2-(tert-butoxy)-2-oxoethyl)-3,6,9-trioxo-8-phenethyl-1-phenyl-2-oxa-4,7,10-triazaundecan-11-yl)-4-methylphenoxy)ethyl)pyrrolidine-1-carboxylate	800.4	701.4 [M+H-Boc]+

432	**430**		tert-butyl 3-(2-(3-((5S,8S)-5-(2-(tert-butoxy)-2-oxoethyl)-3,6,9-trioxo-8-phenethyl-1-phenyl-2-oxa-4,7,10-triazaundecan-11-yl)-4-methylphenoxy)ethyl)-5-methylpiperidine-1-carboxylate	828.5	829.4

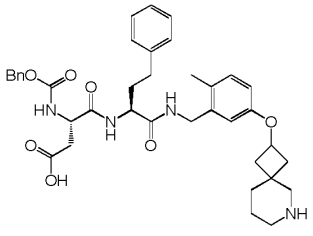
(S)-4-(((S)-1-((5-(6-azaspiro[3.5]nonan-2-yloxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-3-(((benzyloxy)carbonyl)amino)-4-oxobutanoic acid (**384**)

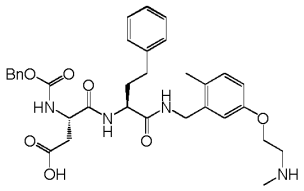
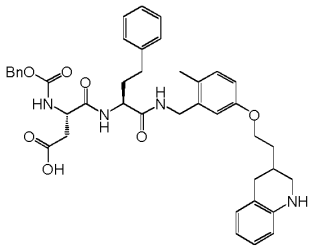
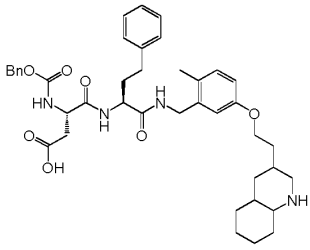
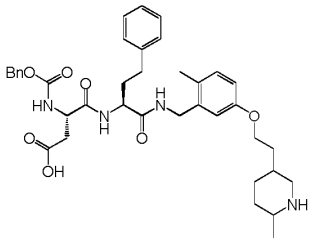
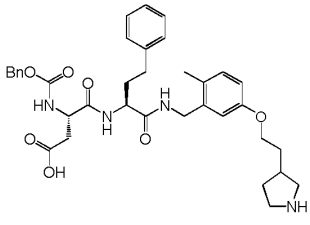


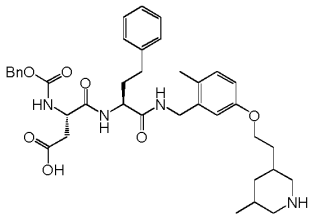
383 **384**

Protecting groups were cleaved from 900 mg compound **383** according to general procedure D stirring compounds in 10 ml 4 N HCl / 1,4-dioxane at room temperature. After deprotection was complete solvent was removed and the crude dissolved in acetonitrile and concentrated twice. Product used without further purification. Additional examples are disclosed in the following table.

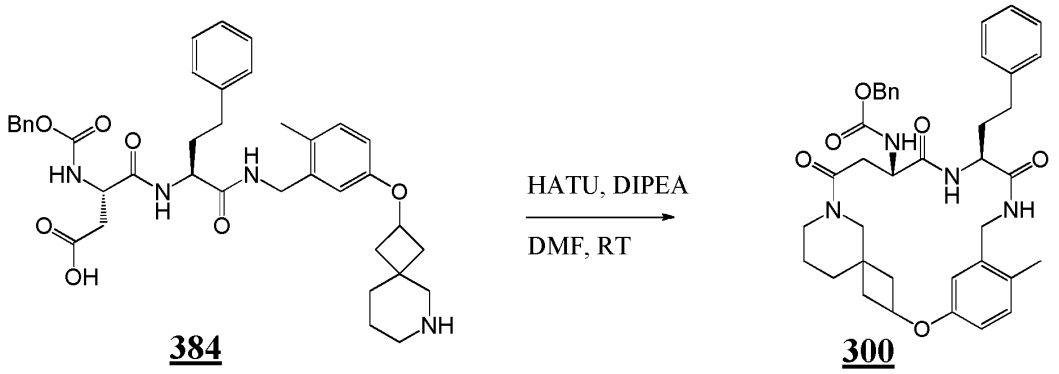
Table A-24

Cpd no	From cpd	structure	name	Exact mass	$[M+H]^+$ found
384	**383**		(S)-4-(((S)-1-((5-(6-azaspiro[3.5]nonan-2-yloxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-3-(((benzyloxy)carbonyl)amino)-4-oxobutanoic acid	670.3	671.4

398	**397**		(S)-3-(((benzyloxy)carbonyl)amino)-4-(((S)-1-((2-methyl-5-(2-(methylamino)ethoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoic acid	604.3	
408	**406**		(3S)-3-(((benzyloxy)carbonyl)amino)-4-(((2S)-1-((2-methyl-5-(2-(1,2,3,4-tetrahydroquinolin-3-yl)ethoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoic acid	706.3	707.3
409	**407**		(3S)-3-(((benzyloxy)carbonyl)amino)-4-(((2S)-1-((5-(2-(decahydroquinolin-3-yl)ethoxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoic acid	712.4	713.3
418	**410**		(3S)-3-(((benzyloxy)carbonyl)amino)-4-(((2S)-1-((2-methyl-5-(2-(6-methylpiperidin-3-yl)ethoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoic acid	672.4	673.3
428	**427**		(3S)-3-(((benzyloxy)carbonyl)amino)-4-(((2S)-1-((2-methyl-5-(2-(pyrrolidin-3-yl)ethoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoic acid	644.3	645.2

433	**432**		(3S)-3-(((benzyloxy)carbonyl)amino)-4-(((2S)-1-((2-methyl-5-(2-(5-methylpiperidin-3-yl)ethoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoic acid	672.4	673.4

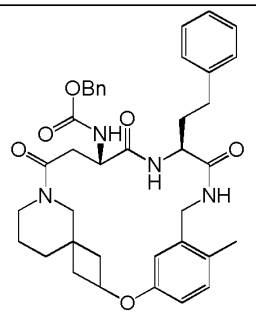
benzyl ((7S,10S)-3^4-methyl-6,9,12-trioxo-7-phenethyl-2-oxa-5,8-diaza-13(3,1)-piperidina-3(1,3)-benzena-1(1,3)-cyclobutanatridecaphane-10-yl)carbamate (**300**)

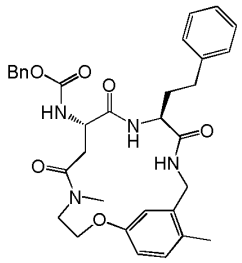
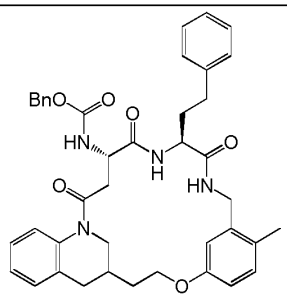
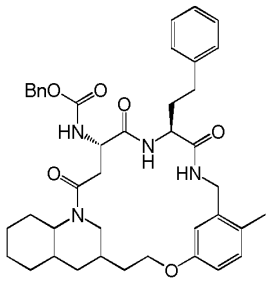
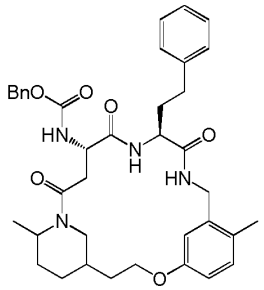
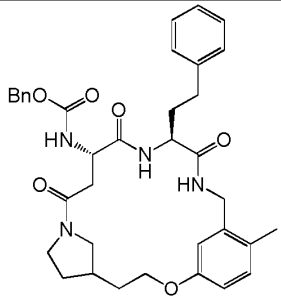


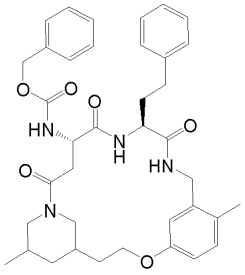
384 **300**

Macrocyclization was achieved according to general procedure A with 93 mg amino acid **384**. Reaction mixtures were diluted with some methanol and purified via HPLC. Additional examples are disclosed in the following table.

Table A-25

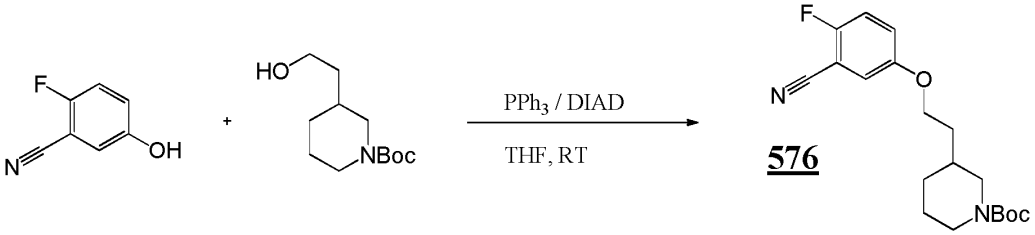
Cpd no	From cpd	structure	name	Exact mass	$[M+H]^+$ found
300	384		benzyl ((7S,10S)-3^4-methyl-6,9,12-trioxo-7-phenethyl-2-oxa-5,8-diaza-13(3,1)-piperidina-3(1,3)-benzena-1(1,3)-cyclobutanatridecaphane-10-yl)carbamate	652.3	653.4

312	398		benzyl ((8S,11S)-1^4,5-dimethyl-6,9,12-trioxo-11-phenethyl-2-oxa-5,10,13-triaza-1(1,3)-benzenacyclotetradecaphane-8-yl)carbamate	586.3	587.3
313	408		benzyl ((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-11,12,13,14-tetrahydro-4-oxa-7,10-diaza-1(3,1)-quinolina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate	688.3	689.4
314	409		benzyl ((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-11,12,13,14,14a,15,16,17,18,18a-decahydro-4-oxa-7,10-diaza-1(3,1)-quinolina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate	694.4	965.4
315	418		benzyl ((9S,12S)-1^6,5^4-dimethyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate	654.3	655.4
325	428		benzyl ((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-pyrrolidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate	626.3	627.3

337	433		benzyl ((9S,12S)-1^5,5^4-dimethyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate	654.3	655.4

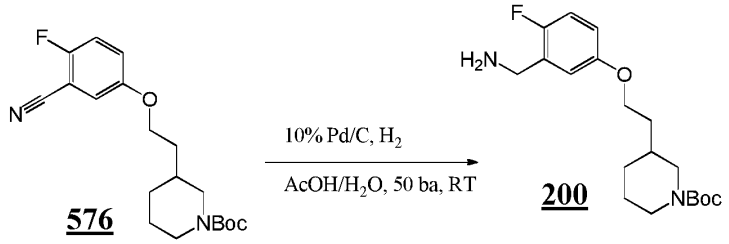
Example A-25: Preparation of macrocyclic compound 211

tert-butyl 3-(2-(3-cyano-4-fluorophenoxy)ethyl)piperidine-1-carboxylate (**576**)



1.03 g tert-butyl 3-(2-hydroxyethyl)piperidine-1-carboxylate, 500mg 2-fluoro-5-hydroxybenzonitrile and 1.17 g PPh_3 were dissolved in THF. 879 µl DIAD in 5 ml THF were added and the mixture was stirred at room temperature for 2h. Saturated $NaHCO_3$ solution was added and the mixture was extracted with DCM. The organic phase was dried over $MgSO_4$ and volatiles were removed. Purification was achieved by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient).

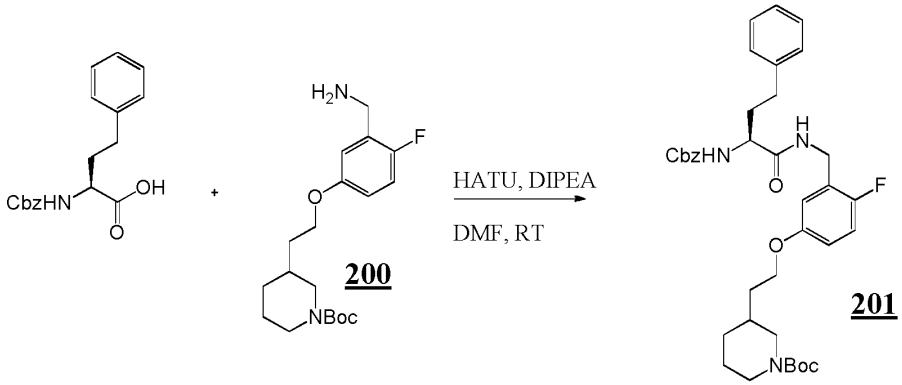
tert-butyl 3-(2-(3-(aminomethyl)-4-fluorophenoxy)ethyl)piperidine-1-carboxylate (**200**)



1.02 g nitrile were dissolved in 36 ml acetic acid and 5 ml water. Hydrogenation to amine **200** was achieved with 706 mg 10 % Pd/C under 50 bar hydrogen at room temperature. The mixture was filtered over a pad of celite and washed with MeOH. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with $NaHCO_3$-solution (3x). Combined organic layers were dried over $MgSO_4$, filtered off, and concentrated under reduced pressure. The residue was pure enough for the next reactions.

Formula: $C_{19}H_{29}FN_2O_3$, exact mass: 352.2.3, found: 353.0 $[M+H]^+$

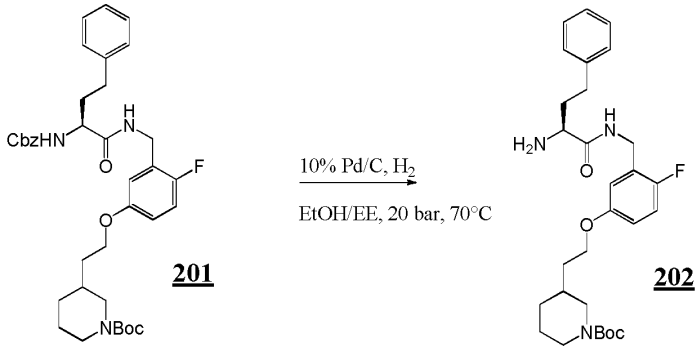
tert-butyl 3-(2-(3-(((S)-2-(((benzyloxy)carbonyl)amino)-4-phenylbutanamido)methyl)-4-fluorophenoxy)ethyl)piperidine-1-carboxylate (**201**)



The amide bond was formed according to general procedure B with 615 mg amine **200** and 820 mg Cbz-hPhe-OH. Purification was achieved by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient).

Formula: $C_{37}H_{46}FN_3O_6$, exact mass: 647.3, found: 648.6 $[M+H]^+$

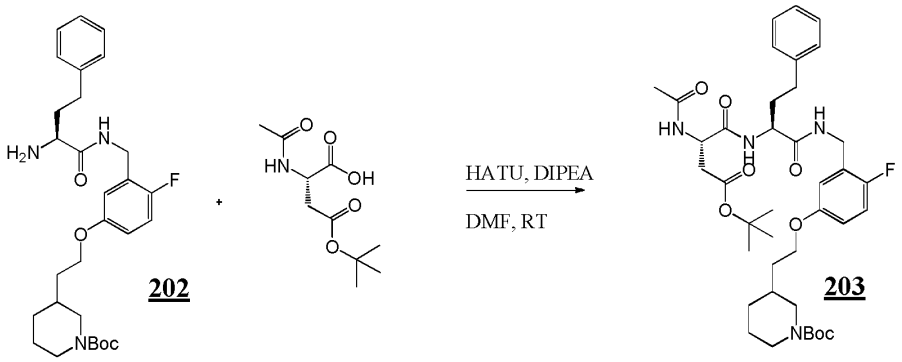
tert-butyl 3-(2-(3-(((S)-2-amino-4-phenylbutanamido)methyl)-4-fluorophenoxy)ethyl)piperidine-1-carboxylate (**202**)



Benzyl carbamate was cleaved according to general procedure C using 10% Pd/C catalyst cartridge, 20 bar at 70 °C in a solvent mixture of ethanol / ethyl acetate. Product was purified by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient).

Formula: $C_{29}H_{40}FN_3O_4$, exact mass: 513.3, found: 514.3 $[M+H]^+$

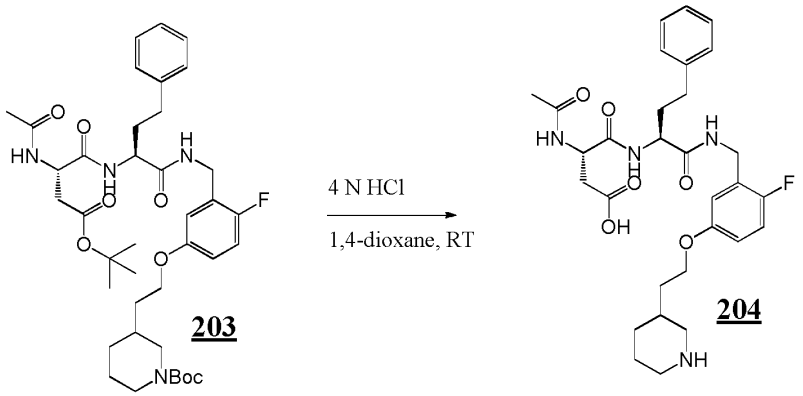
tert-butyl 3-(2-(3-(((S)-2-((S)-2-acetamido-4-(tert-butoxy)-4-oxobutanamido)-4-phenylbutanamido)methyl)-4-fluorophenoxy)ethyl)piperidine-1-carboxylate (**203**)



The amide bond was formed according to general procedure B with 150 mg amine **202** and 88 mg Ac-Asp(OtBu)-OH. Purification was achieved by normal phase flash chromatography.

Formula: $C_{39}H_{55}FN_4O_8$, exact mass: 726.4, found: 727.7 $[M+H]^+$

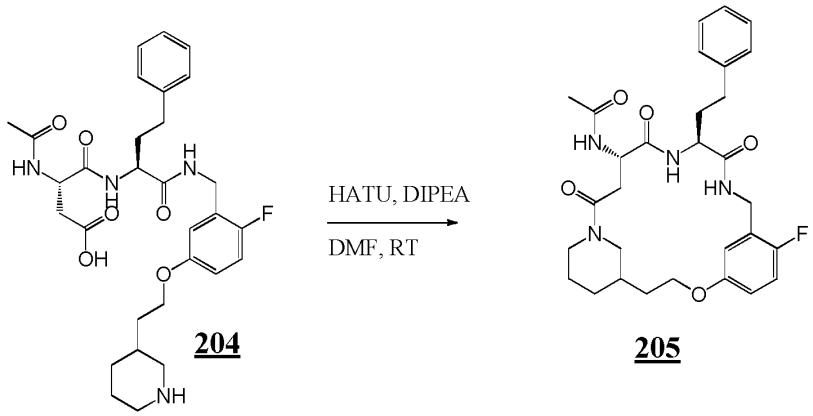
(3S)-3-acetamido-4-(((2S)-1-((2-fluoro-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoic acid (**204**)



Protecting groups were cleaved from 101 mg compound **203** according to general procedure D stirring compounds in 10 ml 4 N HCl / 1,4-dioxane at room temperature. After deprotection was complete solvent was removed and the crude dissolved in acetonitrile and concentrated twice. Product used without further purification

Formula: $C_{30}H_{39}FN_4O_6$, exact mass: 570.3, found: 571.4 $[M+H]^+$

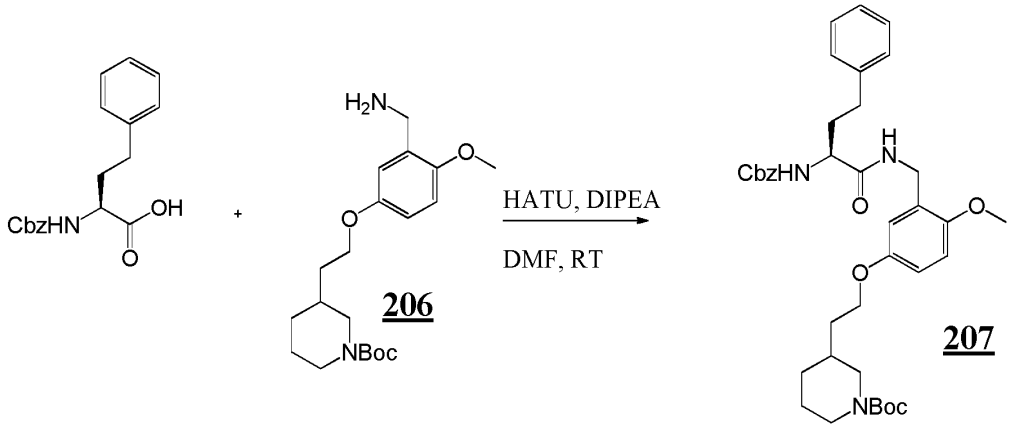
N-((9S,12S)-5^4-fluoro-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide (**205**)



204 **205**

Macrocyclization was achieved according to general procedure A with 1.03 mmol amino acid **204**. Reaction mixtures were diluted with some methanol and purified via HPLC.
Formula: $C_{30}H_{37}FN_4O_5$, exact mass: 552.3, found: 553.6 $[M+H]^+$

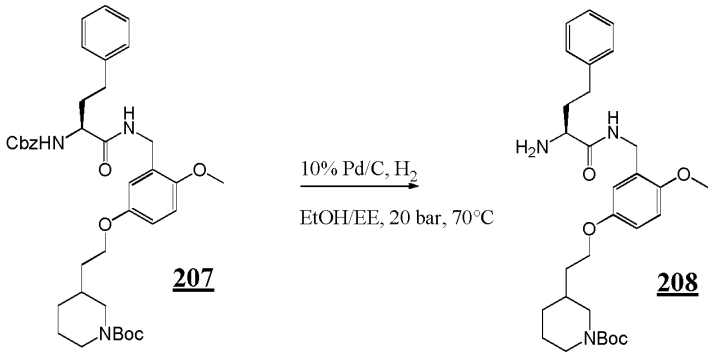
tert-butyl 3-(2-(3-(((S)-2-(((benzyloxy)carbonyl)amino)-4-phenylbutanamido)methyl)-4-methoxyphenoxy)ethyl)piperidine-1-carboxylate (**207**)



206 **207**

The amide bond was formed according to general procedure B with 648 mg amine **206** and 836 mg Cbz-hPhe-OH. Purification was achieved by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient).
Formula: $C_{38}H_{49}N_3O_7$, exact mass: 659.4, found: 660.7 $[M+H]^+$

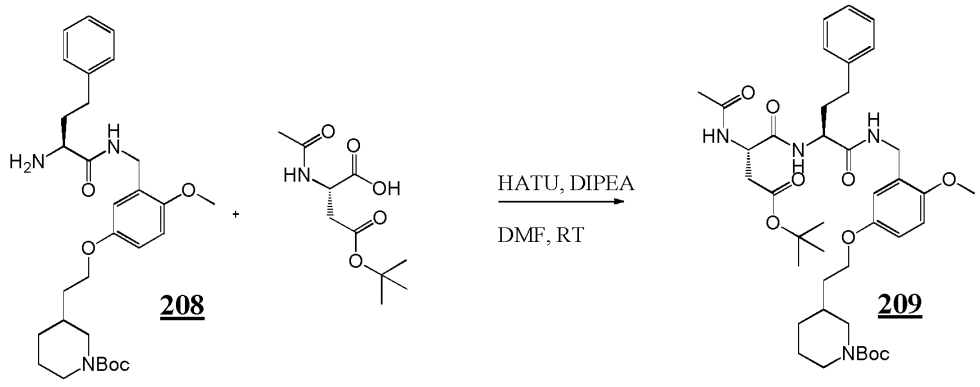
tert-butyl 3-(2-(3-(((S)-2-amino-4-phenylbutanamido)methyl)-4-methoxyphenoxy)ethyl) piperidine-1-carboxylate (**208**)



Benzyl carbamate was cleaved according to general procedure C using 10% Pd/C catalyst cartridge, 20 bar at 70 °C in a solvent mixture of ethanol / ethyl acetate. Product was purified by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient).

Formula: $C_{30}H_{43}N_3O_5$, exact mass: 525.3, found: 526.5 $[M+H]^+$

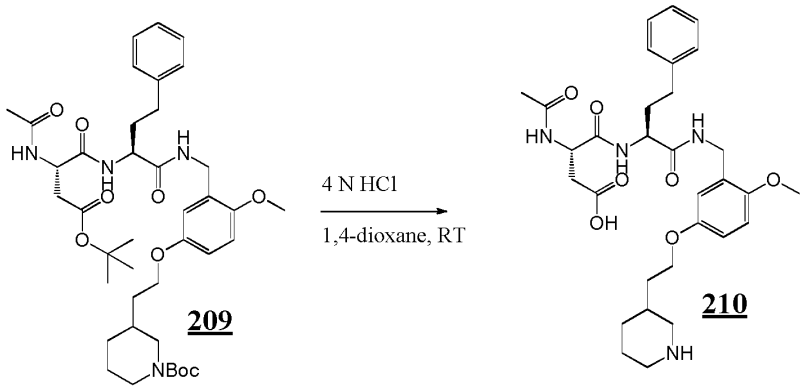
tert tert-butyl 3-(2-(3-(((S)-2-((S)-2-acetamido-4-(tert-butoxy)-4-oxobutanamido)-4-phenylbutanamido)methyl)-4-methoxyphenoxy)ethyl)piperidine-1-carboxylate (**209**)



The amide bond was formed according to general procedure B with 150 mg amine **208** and 86 mg Ac-Asp(OtBu)-OH. Purification was achieved by normal phase flash chromatography.

Formula: $C_{40}H_{58}N_4O_9$, exact mass: 738.4, found: 739.7 $[M+H]^+$

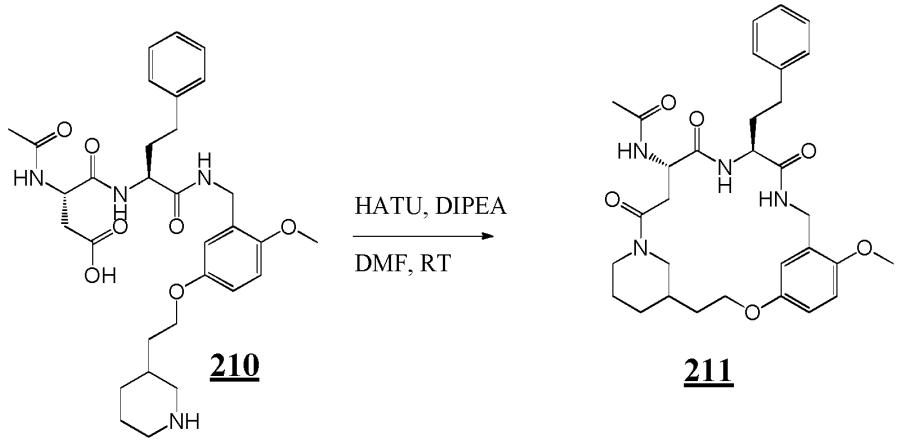
(3S)-3-acetamido-4-(((2S)-1-((2-methoxy-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoic acid (**210**)



Protecting groups were cleaved from 188 mg compound **209** according to general procedure D stirring compounds in 10 ml 4 N HCl / 1,4-dioxane at room temperature. After deprotection was complete solvent was removed and the crude dissolved in acetonitrile and concentrated twice. Product used without further purification

Formula: $C_{31}H_{42}N_4O_7$, exact mass: 582.3, found: 583.4 $[M+H]^+$

N-((9S,12S)-5^4-methoxy-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide (**211**)

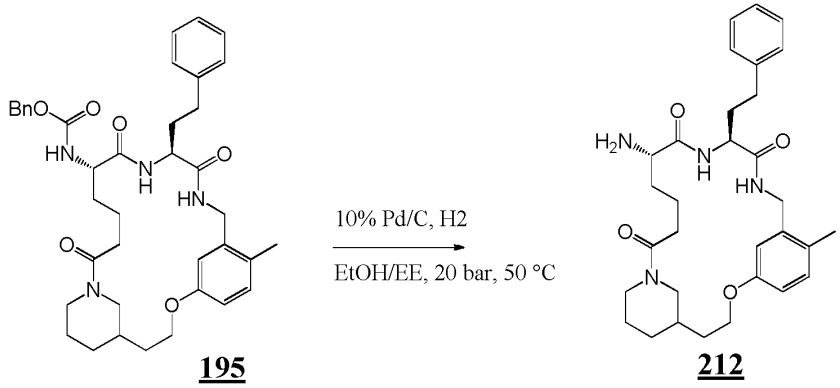


Macrocyclization was achieved according to general procedure A with 0.289 mmol amino acid **210**. Reaction mixtures were diluted with some methanol and purified via HPLC.

Formula: $C_{31}H_{40}N_4O_6$, exact mass: 564.3, found: 565.5 $[M+H]^+$

Example A-26: Preparation of macrocyclic compound 212, 213, 214, and 215

(9S,12S)-5^4-methyl-12-amino-8,11,16-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclohexadecaphane (**212**)

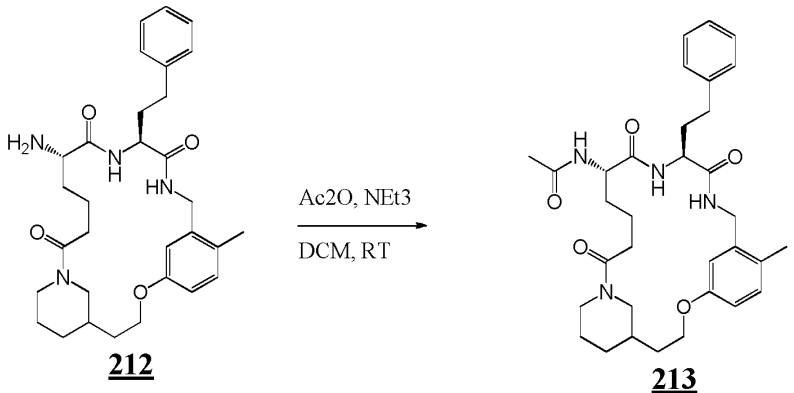


195 **212**

Benzyl carbamate was cleaved according to general procedure C using 10% Pd/C catalyst cartridge, 20 bar at 70 °C in a solvent mixture of ethanol / ethyl acetate. Product was purified by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient).

Formula: $C_{31}H_{42}N_4O_4$, exact mass: 534.3, found: 535.6 $[M+H]^+$

N-((9S,12S)-5^4-methyl-8,11,16-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclohexadecaphane-12-yl)acetamide (**213**)

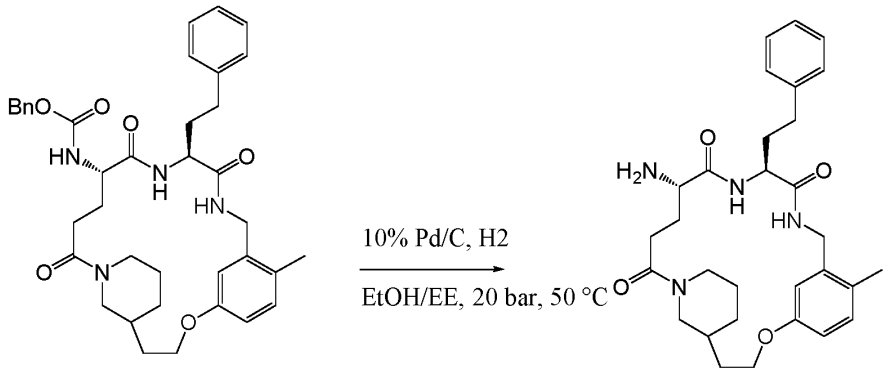


212 **213**

50 mg amine **212** and 54 µL NEt_3 were dissolved DCM and 14 µl acetic anhydride were added. After complete reaction solvent was removed and the residue dissolved in some methanol. Purification via HPLC.

Formula: $C_{33}H_{44}N_4O_5$, exact mass: 576.3, found: 577.6 $[M+H]^+$

(9S,12S)-12-amino-5^4-methyl-8,11,15-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclopentadecaphane) (**214**)

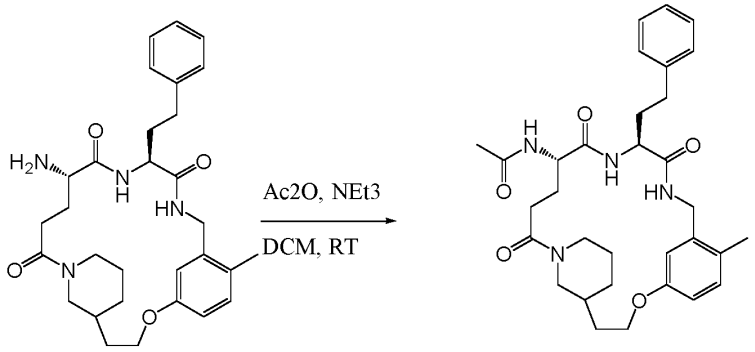


199 **214**

Benzyl carbamate was cleaved from compound **199** according to general procedure C using 10% Pd/C catalyst cartridge, 20 bar at 70 °C in a solvent mixture of ethanol / ethyl acetate. Product was purified by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient).

Formula: $C_{30}H_{40}N_4O_4$, exact mass: 520.3, found: 521.5 $[M+H]^+$

N-((9S,12S)-5[4]-methyl-8,11,15-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclopentadecaphane-12-yl)acetamide (**215**)



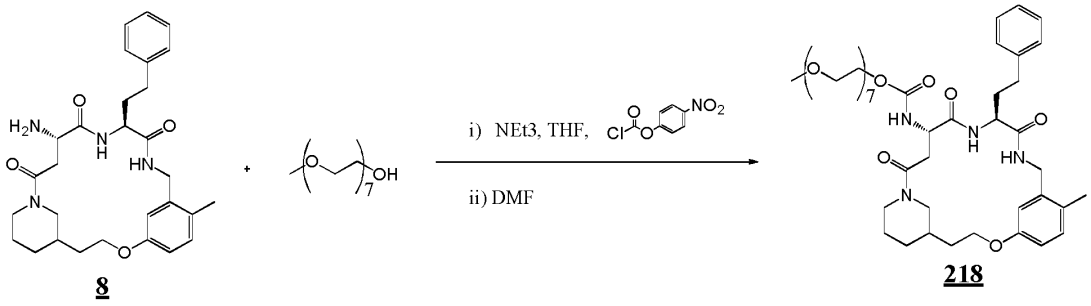
213 **215**

50 mg amine **213** and 54 µL NEt_3 were dissolved DCM and 14 µl acetic anhydride were added. After complete reaction solvent was removed and the residue dissolved in some methanol. Purification via HPLC.

Formula: $C_{32}H_{42}N_4O_5$, exact mass: 562.3, found: 563.5 $[M+H]^+$

Example A-27: Preparation of macrocyclic compounds 218, 220, and 293

2,5,8,11,14,17,20-heptaoxadocosan-22-yl ((9R,12R)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate (**218**)

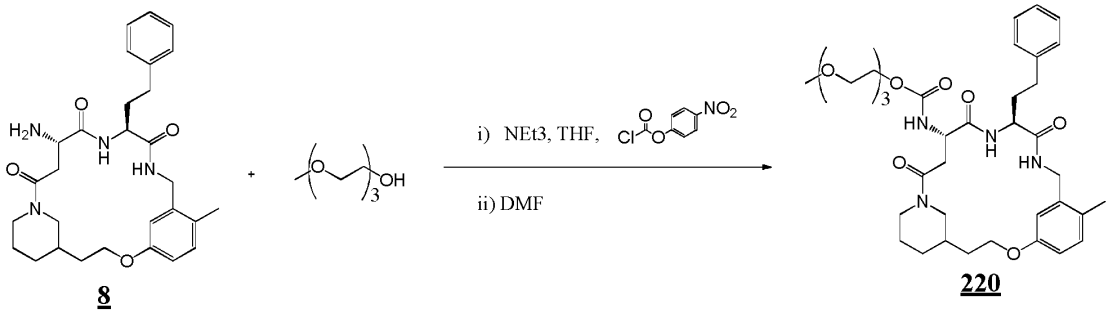


8 218

20 mg 2,5,8,11,14,17,20-heptaoxadocosan-22-ol and 24.7 µl trimethylamine in THF were cooled to 0°C. 4-Nitrophenyl chloroformate (14.2 mg) were added and the mixture was allowed to warm to room temperature. Volatiles were removed under reduced pressure and the residue dissolved in 1 ml DMF. 30 mg amine 8 were added together with 62 µl DIPEA at room temperature. After consumption of compound 8 the reaction mixture was purified by reversed phase HPLC.

Formula: $C_{45}H_{68}N_4O_{13}$, exact mass: 872.5, found: 873.9 $[M+H]^+$

2-(2-(2-methoxyethoxy)ethoxy)ethyl ((9R,12R)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate (**220**)

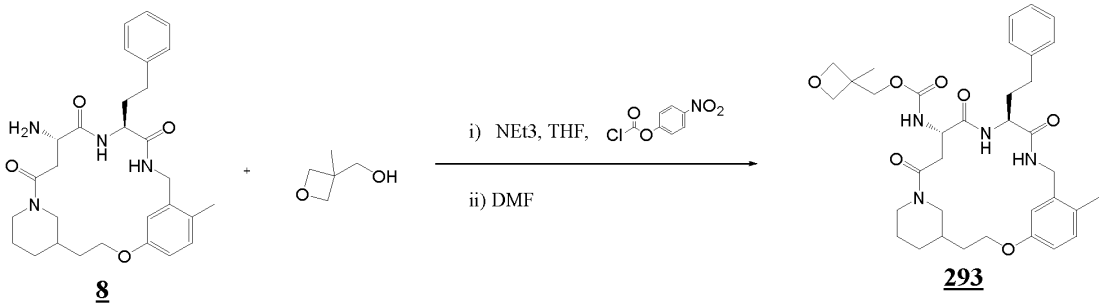


8 220

50 mg 2-(2-(2-methoxyethoxy)ethoxy)ethanol and 213 µl trimethylamine in THF were cooled to 0°C. 4-Nitrophenyl chloroformate (92 mg) were added and the mixture was allowed to warm to room temperature. Volatiles were removed under reduced pressure and the residue dissolved in 1 ml DMF. 103 mg amine **8** were added together with 212 µl DIPEA at room temperature. After consumption of compound **8** the reaction mixture was purified by reversed phase HPLC.

Formula: $C_{37}H_{52}N_4O_9$, exact mass: 696.4, found: 697.5 $[M+H]^+$

(3-methyloxetan-3-yl)methyl ((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate (**293**)



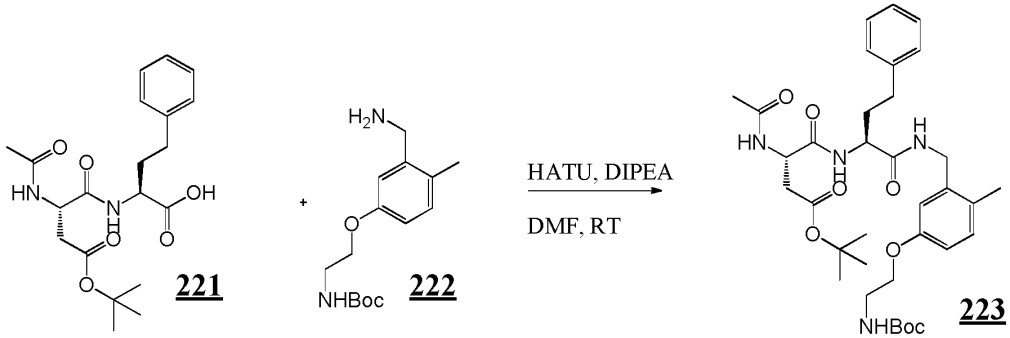
8 293

50 (3-methyloxetan-3-yl)methanol and 341 µl trimethylamine in THF were cooled to 0°C. 4-Nitrophenyl chloroformate (148 mg) were added and the mixture was allowed to warm to room temperature. Volatiles were removed under reduced pressure and the residue dissolved in 1 ml DMF. 124 mg amine **8** were added together with 742 µl DIPEA at room temperature. After consumption of compound **8** the reaction mixture was purified by reversed phase HPLC.

Formula: $C_{35}H_{46}N_4O_7$, exact mass: 634.3, found: 635.4 $[M+H]^+$

Example A-28: Preparation of macrocyclic compounds 252 -261, 296 and 298

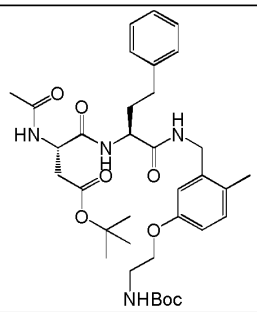
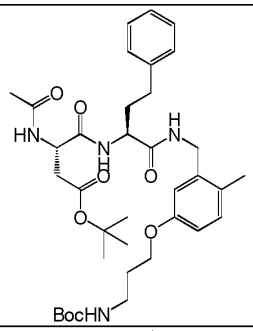
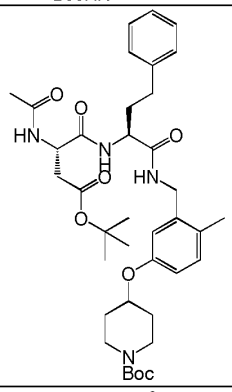
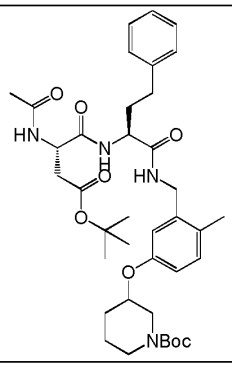
(S)-tert-butyl 3-acetamido-4-(((S)-1-((5-(2-((tert-butoxycarbonyl)amino)ethoxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoate (**223**)

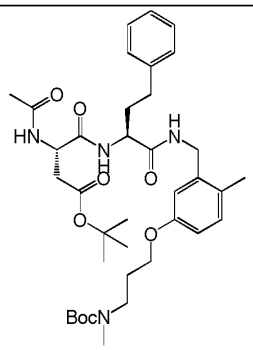
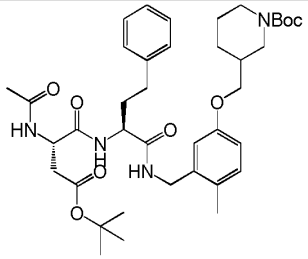
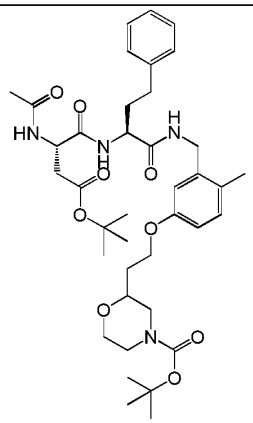
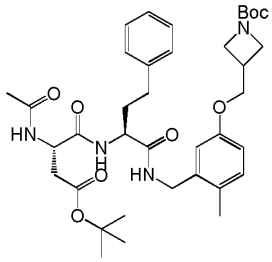
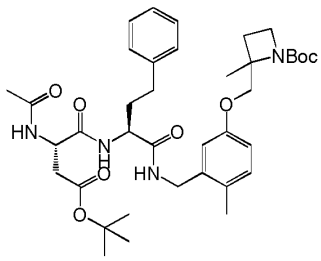


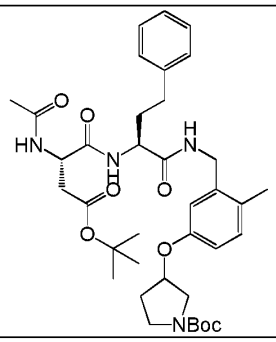
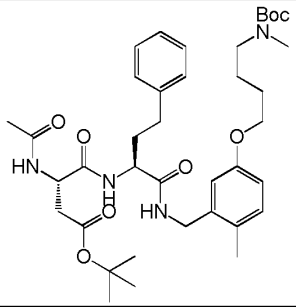
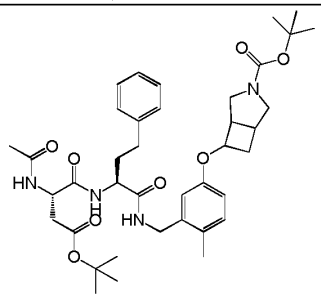
221 222 223

Amide couplings between benzylamine derivatives and dipeptide **221** were accomplished according to general procedure B, typically using 100 mg dipeptide **221**. As an example compound **223** was synthesized from 100 mg dipeptide **221**, 93 mg amine **222**, 116 mg HATU and 266 µl DIPEA in DMF at room temperature. Purification was achieved by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient). Additional examples are disclosed in the following table.

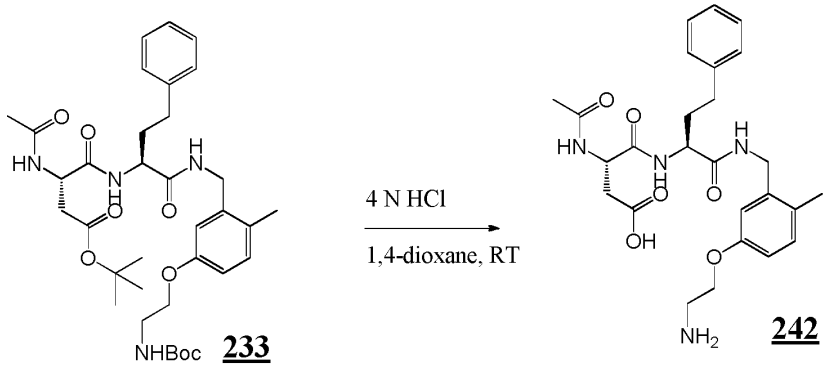
Table A-26

Cpd no	From amine	structure	name	Exact mass	$[M+H]^+$ found
223	**222**		(S)-tert-butyl 3-acetamido-4-(((S)-1-((5-(2-((tert-butoxycarbonyl)amino)ethoxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoate	654.4	655.7
233	**224**		(S)-tert-butyl 3-acetamido-4-(((S)-1-((5-(3-((tert-butoxycarbonyl)amino)propoxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoate	668.4	669.7
234	**225**		tert-butyl 4-(3-(((S)-2-((S)-2-acetamido-4-(tert-butoxy)-4-oxobutanamido)-4-phenylbutanamido)methyl)-4-methylphenoxy)piperidine-1-carboxylate	694.4	695.7
235	**226**		tert-butyl 3-(3-(((S)-2-((S)-2-acetamido-4-(tert-butoxy)-4-oxobutanamido)-4-phenylbutanamido)methyl)-4-methylphenoxy)piperidine-1-carboxylate	694.4	695.7

236	227		(S)-tert-butyl 3-acetamido-4-(((S)-1-((5-(3-((tert-butoxycarbonyl)(methyl)amino)propoxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoate	682.4	683.5
237	228		tert-butyl 3-((3-(((S)-2-((S)-2-acetamido-4-(tert-butoxy)-4-oxobutanamido)-4-phenylbutanamido)methyl)-4-methylphenoxy)methyl)piperidine-1-carboxylate	708.4	709.7
238	141		tert-butyl 2-(2-(3-(((S)-2-((S)-2-acetamido-4-(tert-butoxy)-4-oxobutanamido)-4-phenylbutanamido)methyl)-4-methylphenoxy)ethyl)morpholine-4-carboxylate	724.4	725.7
239	230		tert-butyl 3-((3-(((S)-2-((S)-2-acetamido-4-(tert-butoxy)-4-oxobutanamido)-4-phenylbutanamido)methyl)-4-methylphenoxy)methyl)azetidine-1-carboxylate	680.4	681.7
240	231		tert-butyl 2-((3-(((S)-2-((S)-2-acetamido-4-(tert-butoxy)-4-oxobutanamido)-4-phenylbutanamido)methyl)-4-methylphenoxy)methyl)-2-methylazetidine-1-carboxylate	694.4	695.7

241	**232**		tert-butyl 3-(3-(((S)-2-((S)-2-acetamido-4-(tert-butoxy)-4-oxobutanamido)-4-phenylbutanamido)methyl)-4-methylphenoxy)pyrrolidine-1-carboxylate	680.4	681.7
376	**270**		(S)-tert-butyl 3-acetamido-4-(((S)-1-((5-(4-((tert-butoxycarbonyl)(methyl)amino)butoxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoate	568.3	569.4
378	**188**		tert-butyl 6-(3-(((S)-2-((S)-2-acetamido-4-(tert-butoxy)-4-oxobutanamido)-4-phenylbutanamido)methyl)-4-methylphenoxy)-3-azabicyclo[3.2.0]heptane-3-carboxylate	540.3	541.3

(S)-3-acetamido-4-(((S)-1-((5-(2-aminoethoxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoic acid (**242**)

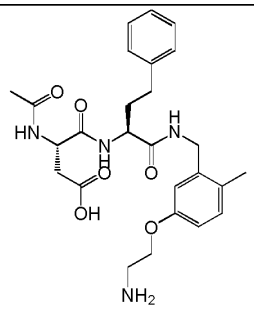
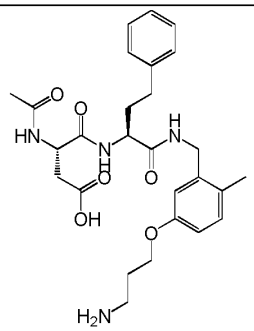
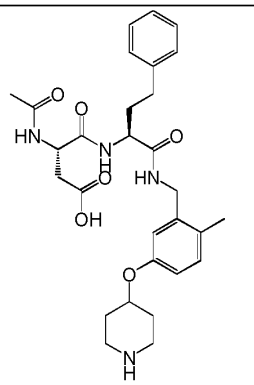
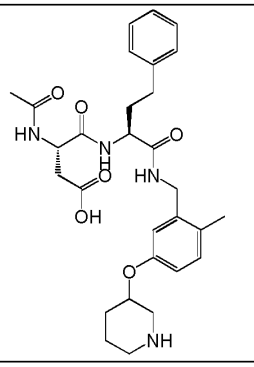


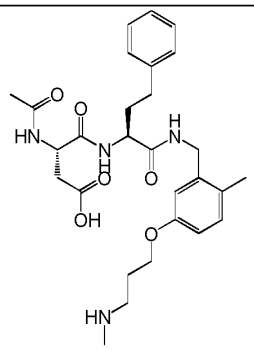
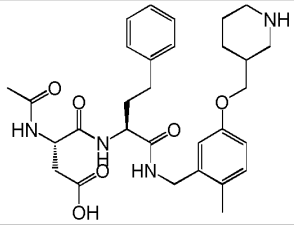
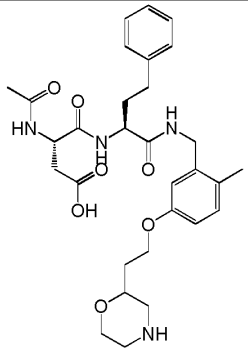
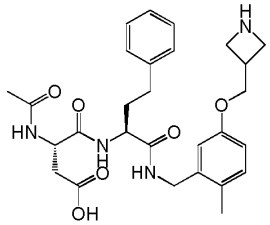
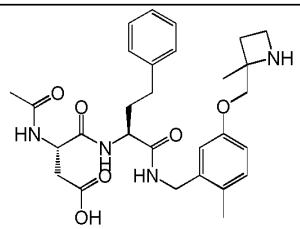
233 **242**

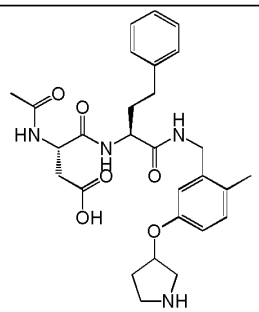
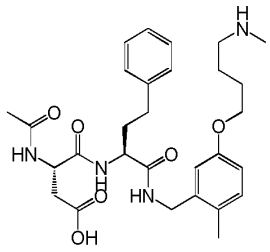
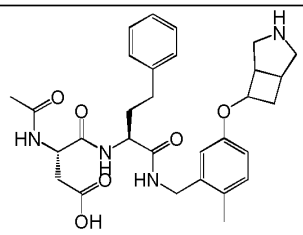
Protecting groups were cleaved from 65 mg compound **233** according to general procedure D stirring compounds in 10 ml 4 N HCl / 1,4-dioxane at room temperature. After deprotection was complete solvent was removed and the crude dissolved in acetonitrile and concentrated twice. Product used without further purification.

As exemplified by compound 242 additional examples disclosed in the following table were prepared.

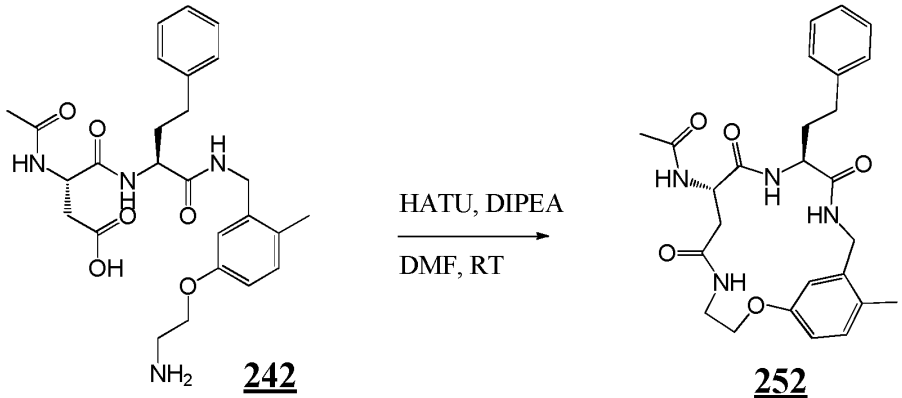
Table A-27

Cpd no	From cpd	structure	name	Exact mass	$[M+H]^+$ found
242	**223**		(S)-3-acetamido-4-(((S)-1-((5-(2-aminoethoxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoic acid	498.2	499.2
243	**233**		(S)-3-acetamido-4-(((S)-1-((5-(3-aminopropoxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoic acid	512.3	513.4
244	**234**		(S)-3-acetamido-4-(((S)-1-((2-methyl-5-(piperidin-4-yloxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoic acid	538.3	539.3
245	**235**		(3S)-3-acetamido-4-(((2S)-1-((2-methyl-5-(piperidin-3-yloxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoic acid	538.3	539.4

246	**236**		(S)-3-acetamido-4-(((S)-1-((2-methyl-5-(3-(methylamino)propoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoic acid	526.3	527.4
247	**237**		(3S)-3-acetamido-4-(((2S)-1-((2-methyl-5-(piperidin-3-ylmethoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoic acid	552.3	553.5
248	**238**		(3S)-3-acetamido-4-(((2S)-1-((2-methyl-5-(2-(morpholin-2-yl)ethoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoic acid	568.3	569.7
249	**239**		(S)-3-acetamido-4-(((S)-1-((5-(azetidin-3-ylmethoxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoic acid	524.3	525.5
250	**240**		(3S)-3-acetamido-4-(((2S)-1-((2-methyl-5-((2-methylazetidin-2-yl)methoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoic acid	538.3	539.5

251	**241**		(3S)-3-acetamido-4-(((2S)-1-((2-methyl-5-(pyrrolidin-3-yloxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoic acid	524.3	525.3
377	**376**		(S)-3-acetamido-4-(((S)-1-((2-methyl-5-(4-(methylamino)butoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoic acid	540.3	541.3
379	**378**		(3S)-4-(((2S)-1-((5-(3-azabicyclo[3.2.0]heptan-6-yloxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-3-acetamido-4-oxobutanoic acid	550.3	-

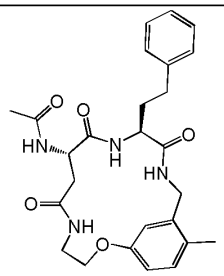
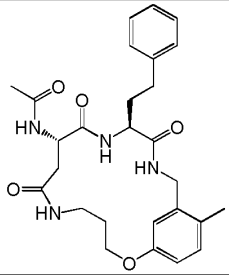
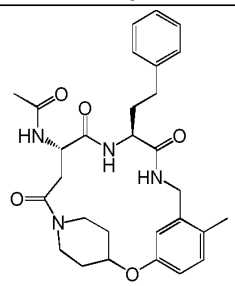
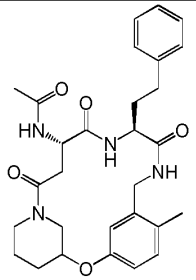
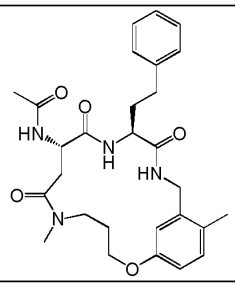
N-((8S,11S)-1^4-methyl-6,9,12-trioxo-11-phenethyl-2-oxa-5,10,13-triaza-1(1,3)-benzenacyclotetradecaphane-8-yl)acetamide (**252**)

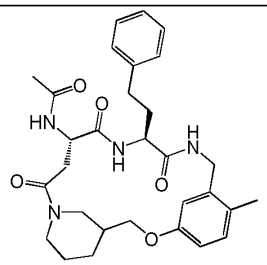
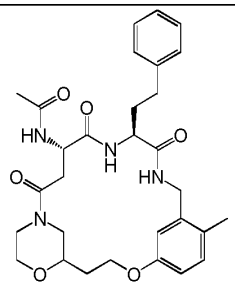
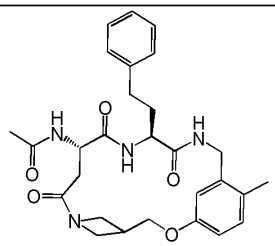
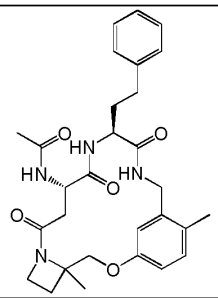
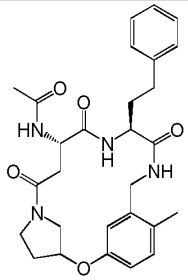
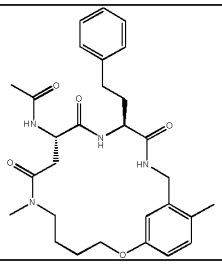


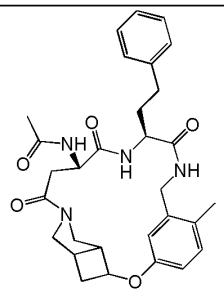
242 **252**

Macrocyclization was achieved according to general procedure A with 0.248 mmol amino acid **242**. Reaction mixtures were diluted with some methanol and purified via HPLC. As exemplified by compound **252** additional examples disclosed in the following table were prepared.

Table A-28

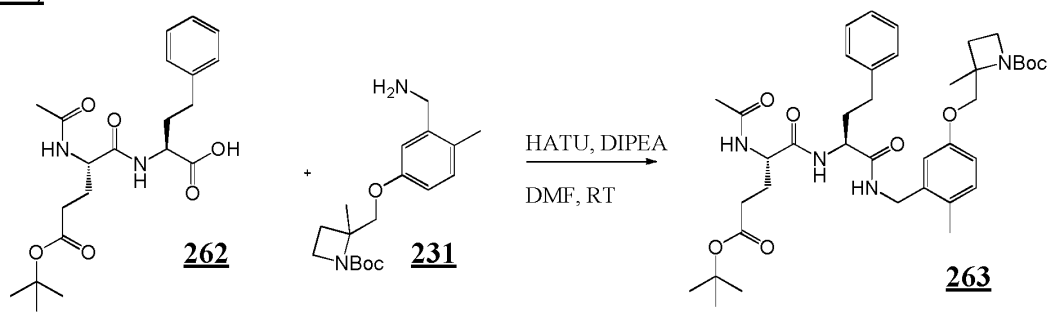
Cpd no	From cpd	structure	name	Exact mass	$[M+H]^+$ found
252	242		N-((8S,11S)-1^4-methyl-6,9,12-trioxo-11-phenethyl-2-oxa-5,10,13-triaza-1(1,3)-benzenacyclotetradecaphane-8-yl)acetamide	480.2 $C_{26}H_{32}N_4O_5$	481.4
253	243		N-((9S,12S)-1^4-methyl-7,10,13-trioxo-12-phenethyl-2-oxa-6,11,14-triaza-1(1,3)-benzenacyclopentadecaphane-9-yl)acetamide	494.3 $C_{27}H_{34}N_4O_5$	495.4
254	244		N-((7S,10S)-3^4-methyl-6,9,12-trioxo-7-phenethyl-2-oxa-5,8-diaza-1(4,1)-piperidina-3(1,3)-benzenacyclododecaphane-10-yl)acetamide	520.3 $C_{29}H_{36}N_4O_5$	521.4
255	245		N-((7S,10S)-3^4-methyl-6,9,12-trioxo-7-phenethyl-2-oxa-5,8-diaza-1(3,1)-piperidina-3(1,3)-benzenacyclododecaphane-10-yl)acetamide	520.3 $C_{29}H_{36}N_4O_5$	521.4
256	246		N-((9S,12S)-1^4,6-dimethyl-7,10,13-trioxo-12-phenethyl-2-oxa-6,11,14-triaza-1(1,3)-benzenacyclopentadecaphane-9-yl)acetamide	508.3 $C_{28}H_{36}N_4O_5$	509.4

257	247		N-((8S,11S)-4^4-methyl-7,10,13-trioxo-8-phenethyl-3-oxa-6,9-diaza-1(3,1)-piperidina-4(1,3)-benzenacyclotridecaphane-11-yl)acetamide	534.3 $C_{30}H_{38}N_4O_5$	535.4
258	248		N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(2,4)-morpholina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	550.3 $C_{30}H_{38}N_4O_6$	551.4
259	249		N-((8S,11S)-4^4-methyl-7,10,13-trioxo-8-phenethyl-3-oxa-6,9-diaza-1(3,1)-azetidina-4(1,3)-benzenacyclotridecaphane-11-yl)acetamide	506.3 $C_{28}H_{34}N_4O_5$	507.4
260	250		N-((8S,11S)-1^2,4^4-dimethyl-7,10,13-trioxo-8-phenethyl-3-oxa-6,9-diaza-1(2,1)-azetidina-4(1,3)-benzenacyclotridecaphane-11-yl)acetamide	520.3 $C_{29}H_{36}N_4O_5$	521.4
261	251		N-((7S,10S)-3^4-methyl-6,9,12-trioxo-7-phenethyl-2-oxa-5,8-diaza-1(3,1)-pyrrolidina-3(1,3)-benzenacyclododecaphane-10-yl)acetamide	506.3 $C_{28}H_{34}N_4O_5$	507.4
296	377		N-(1^4,7-dimethyl-8,11,14-trioxo-13-phenethyl-2-oxa-7,12,15-triaza-1(1,3)-benzenacyclohexadecaphane-10-yl)acetamide	522.3 $C_{29}H_{38}N_4O_5$	523.4

298	379		N-(3^4-methyl-6,9,12-trioxo-7-phenethyl-2-oxa-13,5,8-triaza-1(6,3)-bicyclo[3.2.0]heptana-3(1,3)-benzenacyclododecaphane-10-yl)acetamide	532.3 $C_{30}H_{36}N_4O_5$	533.3

Example A-29: Preparation of macrocyclic compounds 265, 282 and 299

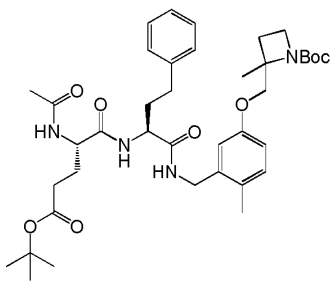
tert-butyl 2-((3-(((S)-2-((S)-2-acetamido-5-(tert-butoxy)-5-oxopentanamido)-4-phenylbutanamido)methyl)-4-methylphenoxy)methyl)-2-methylazetidine-1-carboxylate (**263**)

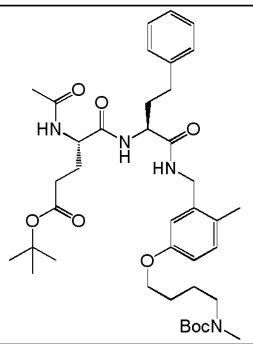
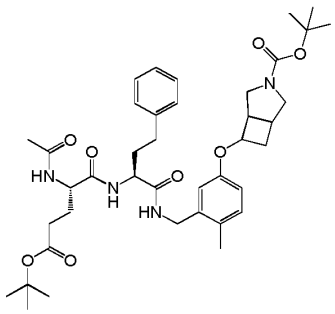


262 **231** **263**

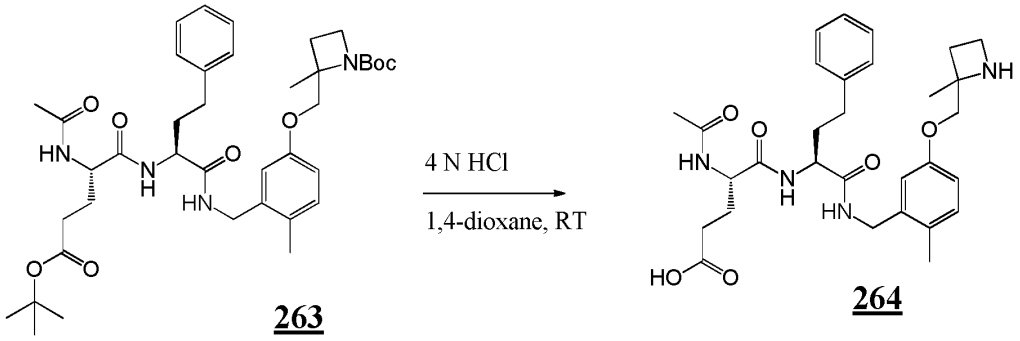
Amide couplings between benzylamine derivatives and dipeptide **262** were accomplished according to general procedure B, typically using 100 mg dipeptide **262**. As an example compound **263** was synthesized from 112 mg dipeptide **262**, 115 mg amine **231**, 125 mg HATU and 214 µl DIPEA in DMF at room temperature. Purification was achieved by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient). Additional examples are disclosed in the following table.

Table A-29

Cpd no	From amine	structure	name	Exactm mass.	$[M+H]^+$ found
263	**231**		tert-butyl 2-((3-(((S)-2-((S)-2-acetamido-5-(tert-butoxy)-5-oxopentanamido)-4-phenylbutanamido)methyl)-4-methylphenoxy)methyl)-2-methylazetidine-1-carboxylate	708.4	709.7

274	**270**		(S)-tert-butyl 4-acetamido-5-(((S)-1-((5-(4-((tert-butoxycarbonyl)(methyl)amino)butoxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-5-oxopentanoate	710.4	711.5
380	**188**		tert-butyl 6-(3-(((S)-2-((S)-2-acetamido-5-(tert-butoxy)-5-oxopentanamido)-4-phenylbutanamido)methyl)-4-methylphenoxy)-3-azabicyclo[3.2.0]heptane-3-carboxylate	720.4	721.5

(4S)-4-acetamido-5-(((2S)-1-((2-methyl-5-((2-methylazetidin-2-yl)methoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-5-oxopentanoic acid (**264**)

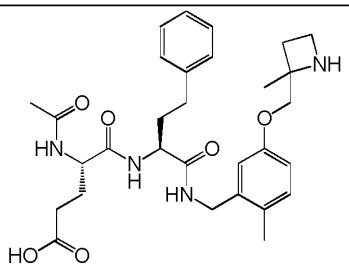
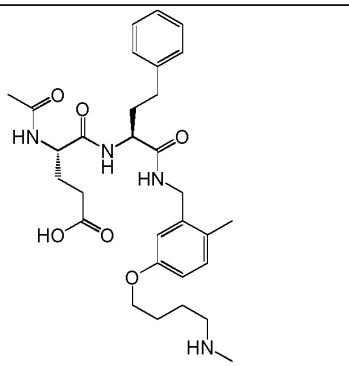
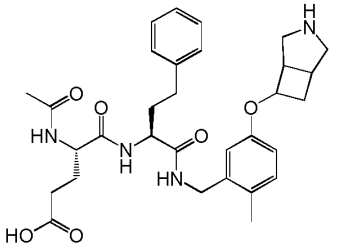


263 **264**

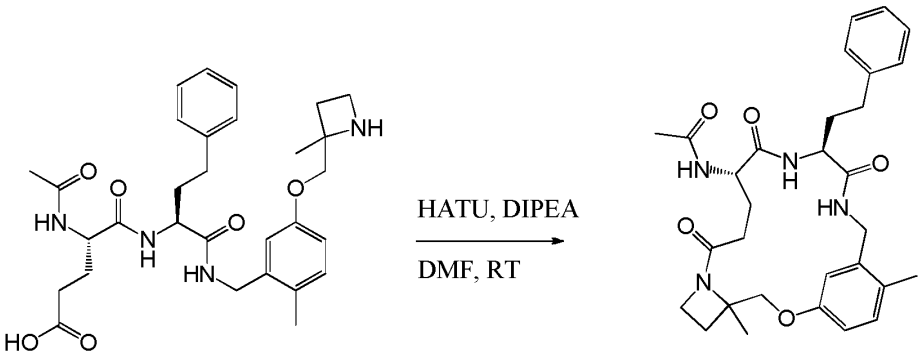
Protecting groups were cleaved from 117 mg compound **263** according to general procedure D stirring compounds in 10 ml 4 N HCl / 1,4-dioxane at room temperature. After deprotection was complete solvent was removed and the crude dissolved in acetonitrile and concentrated twice. Product used without further purification.

As exemplified by compound 264 additional examples disclosed in the following table were prepared.

Table A-30

Cpd no	From cpd	structure	name	Exact mass	$[M+H]^+$ found
264	**263**		(4S)-4-acetamido-5-(((2S)-1-((2-methyl-5-((2-methylazetidin-2-yl)methoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-5-oxopentanoic acid	552.3	553.4
278	**274**		(S)-4-acetamido-5-(((S)-1-((2-methyl-5-(4-(methylamino)butoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-5-oxopentanoic acid	554.3	555.4
381	**380**		(4S)-5-(((2S)-1-((5-(3-azabicyclo[3.2.0]heptan-6-yloxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-acetamido-5-oxopentanoic acid	564.3	565.4

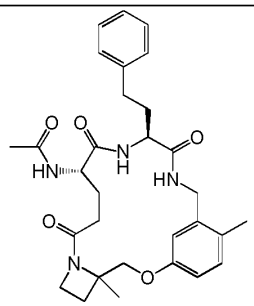
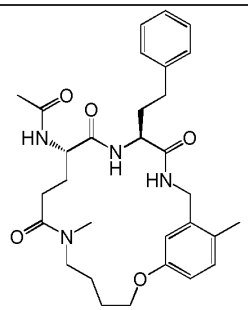
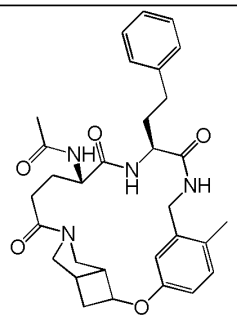
N-((8S,11S)-1^2,4^4-dimethyl-7,10,14-trioxo-8-phenethyl-3-oxa-6,9-diaza-1(2,1)-azetidina-4(1,3)-benzenacyclotetradecaphane-11-yl)acetamide (**265**)



264 **265**

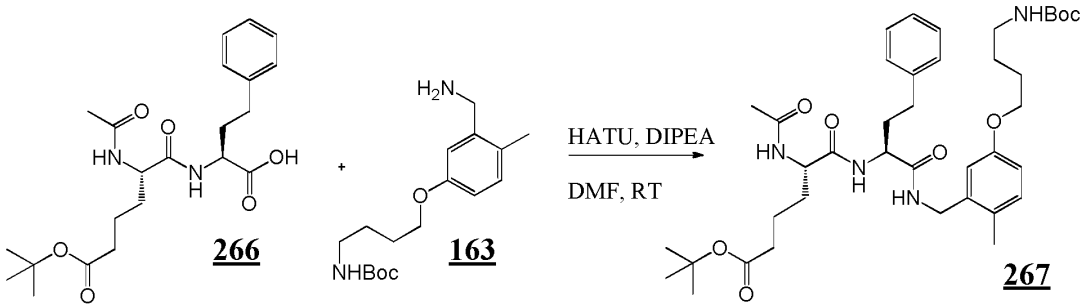
Macrocyclization was achieved according to general procedure A with 0.165 mmol amino acid **264**. Reaction mixtures were diluted with some methanol and purified via HPLC. As exemplified by compound **265** additional examples disclosed in the following table were prepared.

Table A-31

Cpd no	From cpd	structure	name	Exact mass	$[M+H]^+$ found
265	**264**		N-((8S,11S)-1^2,4^4-dimethyl-7,10,14-trioxo-8-phenethyl-3-oxa-6,9-diaza-1(2,1)-azetidina-4(1,3)-benzenacyclotetradecaphane-11-yl)acetamide	534.3 $C_{30}H_{38}N_4O_5$	535.4
282	**278**		N-((11S,14S)-1^4,7-dimethyl-8,12,15-trioxo-14-phenethyl-2-oxa-7,13,16-triaza-1(1,3)-benzenacycloheptadecaphane-11-yl)acetamide	536.3 $C_{30}H_{40}N_4O_5$	537.3
299	**381**		N-(3^4-methyl-6,9,13-trioxo-7-phenethyl-2-oxa-13,5,8-triaza-1(6,3)-bicyclo[3.2.0]heptana-3(1,3)-benzenacyclotridecaphane-10-yl)acetamide	546.3 $C_{31}H_{38}N_4O_5$	547.3

Example A-30: Preparation of macrocyclic compounds 269, 280, 281 and 29

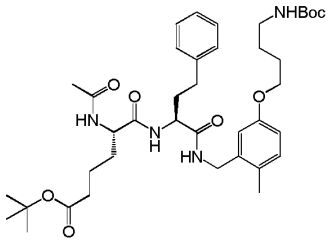
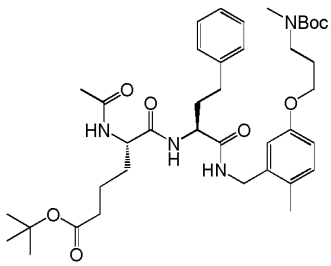
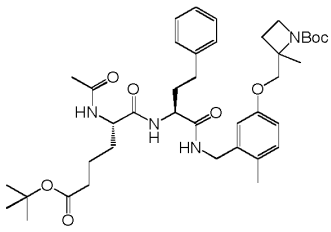
(S)-tert-butyl 5-acetamido-6-(((S)-1-((5-(4-((tert-butoxycarbonyl)amino)butoxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-6-oxohexanoate (**267**)

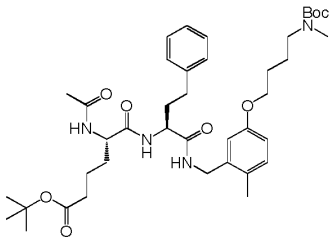


266 163 267

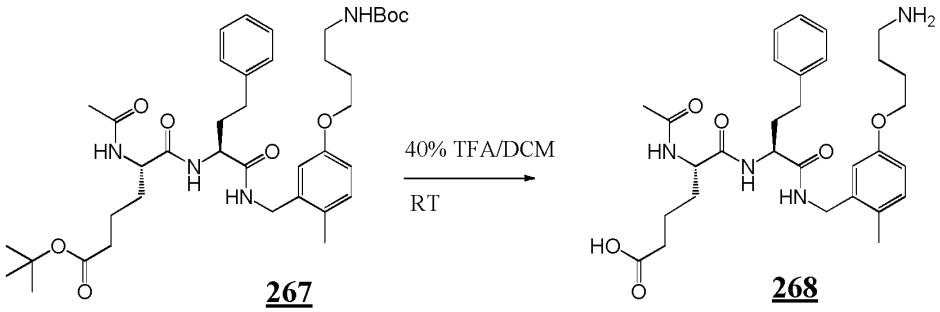
Amide couplings between benzylamine derivatives and dipeptide **266** were accomplished according to general procedure B, typically using 100 mg dipeptide **262**. As an example compound **263** was synthesized from 113 mg dipeptide **266**, 107 mg amine **163**, 122 mg HATU and 280 µl DIPEA in DMF at room temperature. Purification was achieved by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient). Additional examples are disclosed in the following table.

Table A-32

Cpd no	From amine	structure	name	Exact mass	$[M+H]^+$ found
267	**163**		(S)-tert-butyl 5-acetamido-6-(((S)-1-((5-(4-((tert-butoxycarbonyl)amino)butoxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-6-oxohexanoate	710.4	710.7
272	**227**		(S)-tert-butyl 5-acetamido-6-(((S)-1-((5-(3-((tert-butoxycarbonyl)(methyl)amino)propoxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-6-oxohexanoate	722.4	723.8
273	**232**		tert-butyl 2-((3-(((S)-2-((S)-2-acetamido-6-(tert-butoxy)-6-oxohexanamido)-4-phenylbutanamido)methyl)-4-methylphenoxy)methyl)-2-methylazetidine-1-carboxylate	710.4	711.5

374	**270**		(S)-tert-butyl 5-acetamido-6-(((S)-1-((5-(4-((tert-butoxycarbonyl)(methyl)amino)butoxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-6-oxohexanoate	724.4	725.6

(S)-5-acetamido-6-(((S)-1-((5-(4-aminobutoxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-6-oxohexanoic acid (**268**)

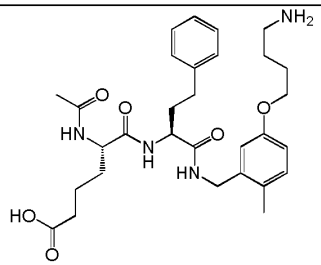


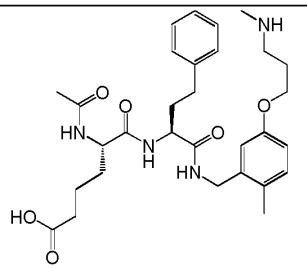
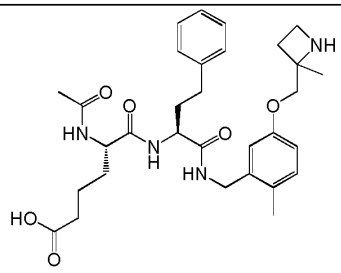
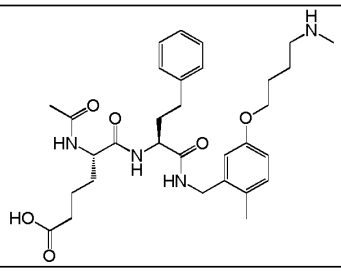
267 **268**

Protecting groups were cleaved from 78 mg compound **267** according to general procedure D stirring compounds in 5 ml 40% TFA/DCM at room temperature. After deprotection was complete solvent was removed and the crude dissolved in acetonitrile and concentrated twice. Product used without further purification.

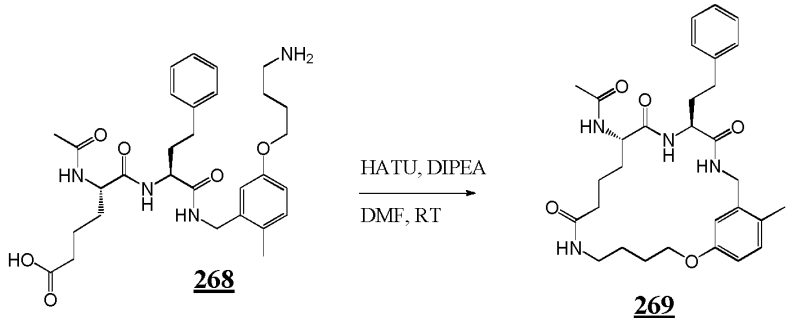
As exemplified by compound **268** additional examples disclosed in the following table were prepared.

Table A-33

Cpd no	From cpd	structure	name	Exact mass	$[M+H]^+$ found
268	**267**		(S)-5-acetamido-6-(((S)-1-((5-(4-aminobutoxy)-2-methylbenzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-6-oxohexanoic acid	554.3	555.4

276	**272**		(S)-5-acetamido-6-(((S)-1-((2-methyl-5-(3-(methylamino)propoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-6-oxohexanoic acid	554.3	555.4
277	**273**		(5S)-5-acetamido-6-(((2S)-1-((2-methyl-5-((2-methylazetidin-2-yl)methoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-6-oxohexanoic acid	566.3	567.4
375	**374**		(S)-5-acetamido-6-(((S)-1-((2-methyl-5-(4-(methylamino)butoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-6-oxohexanoic acid	568.3	569.4

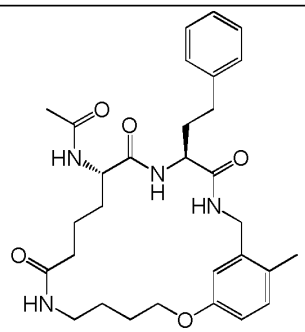
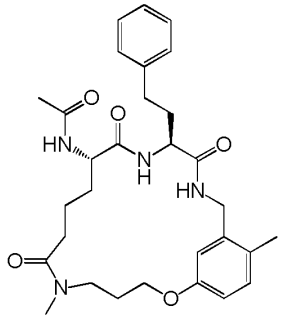
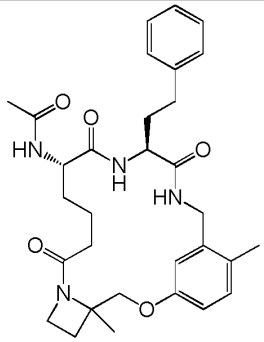
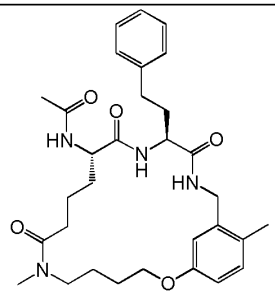
N-((12S,15S)-1[4]-methyl-8,13,16-trioxo-15-phenethyl-2-oxa-7,14,17-triaza-1(1,3)-benzenacyclooctadecaphane-12-yl)acetamide (**269**)



268 **269**

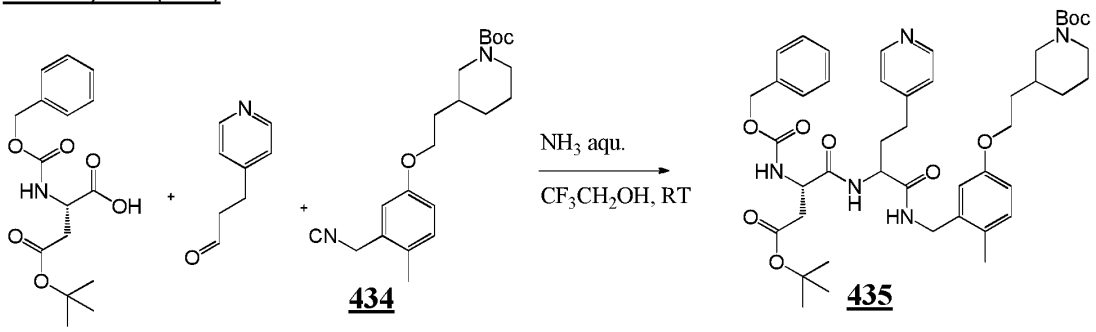
Macrocyclization was achieved according to general procedure A with 0.120 mmol amino acid **268**. Reaction mixtures were diluted with some methanol and purified via HPLC. As exemplified by compound **269** additional examples disclosed in the following table were prepared.

Table A-34

Cpd no	From cpd	structure	name	$[M+H]^+$ calc.	$[M+H]^+$ found
269	**268**		N-((12S,15S)-1^4-methyl-8,13,16-trioxo-15-phenethyl-2-oxa-7,14,17-triaza-1(1,3)-benzenacyclooctadecaphane-12-yl)acetamide	536.3 $C_{30}H_{40}N_4O_5$	537.4
280	**276**		N-((11S,14S)-1^4,6-dimethyl-7,12,15-trioxo-14-phenethyl-2-oxa-6,13,16-triaza-1(1,3)-benzenacycloheptadecaphane-11-yl)acetamide	536.3 $C_{30}H_{40}N_4O_5$	537.4
281	277		N-((8S,11S)-1^2,4^4-dimethyl-7,10,15-trioxo-8-phenethyl-3-oxa-6,9-diaza-1(2,1)-azetidina-4(1,3)-benzenacyclopentadecaphane-11-yl)acetamide	548.3 $C_{31}H_{42}N_4O_6$	549.5
295	375		N-(1^4,7-dimethyl-8,13,16-trioxo-15-phenethyl-2-oxa-7,14,17-triaza-1(1,3)-benzenacyclooctadecaphane-12-yl)acetamide	550.3 $C_{31}H_{42}N_4O_5$	551.4

Example A-31: Preparation of macrocyclic compounds 336, and 549 - 564

tert-butyl 3-(2-(3-((5S)-5-(2-(tert-butoxy)-2-oxoethyl)-3,6,9-trioxo-1-phenyl-8-(2-(pyridin-4-yl)ethyl)-2-oxa-4,7,10-triazaundecan-11-yl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate (**435**)

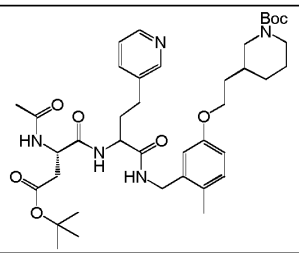


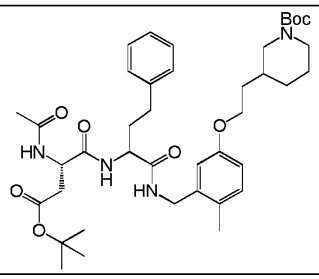
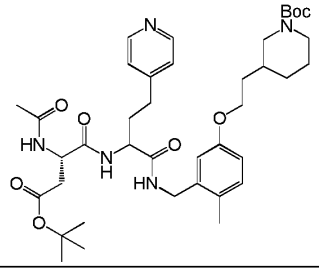
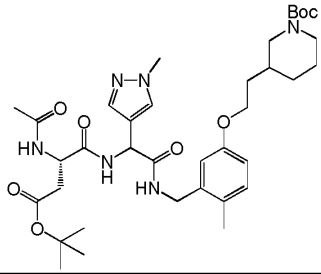
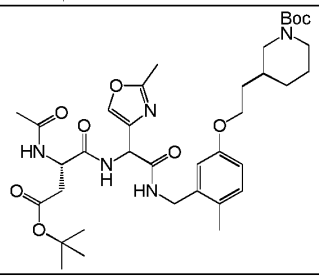
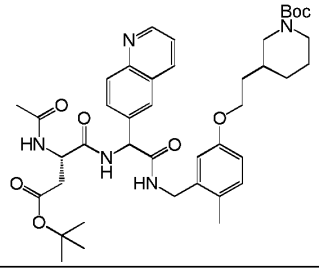
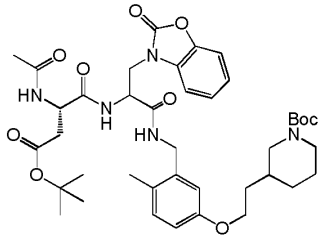
434 435

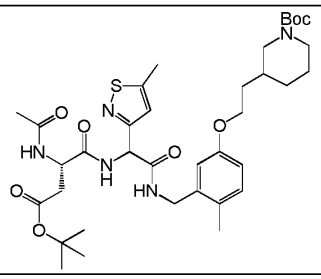
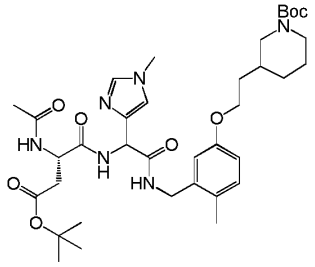
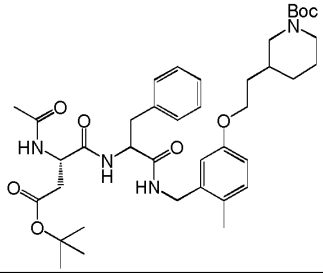
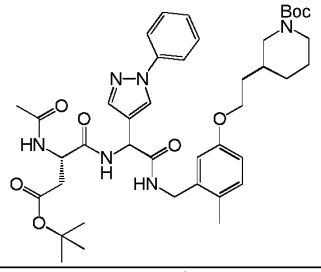
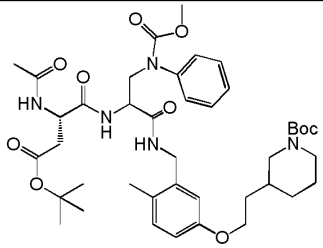
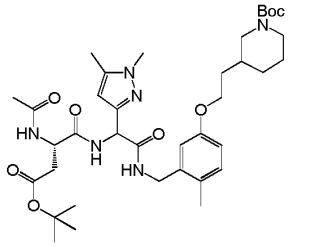
For this Ugi reaction with 400 mg 3-(pyridin-4-yl)propanal and 960 mg Cbz-Asp(OtBu)-OH were dissolved in 3.5 ml 2,2,2-trifluoroethanol. 700 µl ammonia solution (30%, aqueous) and 715 mg isonitrile **434** were added and the mixture was stirred at room temperature overnight. Additional ammonia solution (350 µl) and 250 mg aldehyde in 3.5 ml 2,2,2-trifluoroethanol were added and stirring at room temperature was continued for another day. Saturated $NaHCO_3$ solution was added and the mixture was extracted with ethyl acetate. After drying the combined organic phases over $MgSO_4$ and removing volatiles under reduced pressure the product was obtained after normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient).
Formula: $C_{45}H_{61}N_5O_9$, exact mass: 815.4, found: 716.4 $[M+H]^+$

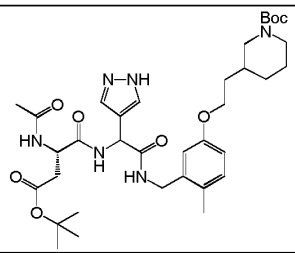
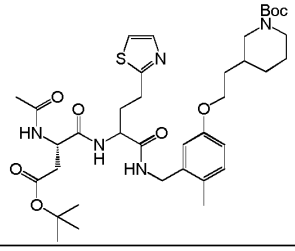
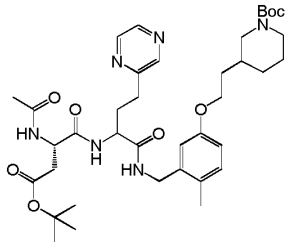
The examples in the following table were prepared according to the procedure described for compound **435** but utilizing Ac-Asp(OtBu)-OH instead of Cbz-Asp(OtBu)-OH and related aldehydes:

Table A-35

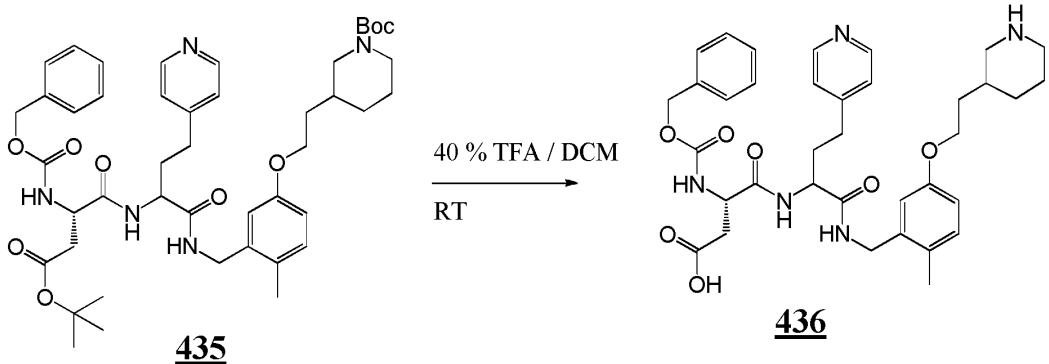
Cpd no	structure	name	Exact mass	$[M+H]^+$ found
541		tert-butyl 3-(2-(3-((2-((S)-2-acetamido-4-(tert-butoxy)-4-oxobutanamido)-4-(pyridin-3-yl)butanamido)methyl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate	723.4	724.8

542		tert-butyl 3-(2-(3-((2-((S)-2-acetamido-4-(tert-butoxy)-4-oxobutanamido)-4-phenylbutanamido)methyl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate	722.4	723.7
543		tert-butyl 3-(2-(3-((2-((S)-2-acetamido-4-(tert-butoxy)-4-oxobutanamido)-4-(pyridin-4-yl)butanamido)methyl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate	723.4	724.5
544		tert-butyl 3-(2-(3-((2-((S)-2-acetamido-4-(tert-butoxy)-4-oxobutanamido)-2-(1-methyl-1H-pyrazol-4-yl)acetamido)methyl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate	698.4	699.6
517		tert-butyl 3-(2-(3-((2-((S)-2-acetamido-4-(tert-butoxy)-4-oxobutanamido)-2-(2-methyloxazol-4-yl)acetamido)methyl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate	699.4	700.6
518		tert-butyl 3-(2-(3-((2-((S)-2-acetamido-4-(tert-butoxy)-4-oxobutanamido)-2-(quinolin-6-yl)acetamido)methyl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate	745.4	746.7
519		tert-butyl 3-(2-(3-((2-((S)-2-acetamido-4-(tert-butoxy)-4-oxobutanamido)-3-(2-oxobenzo[d]oxazol-3(2H)-yl)propanamido)methyl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate	765.4	766.7

520		tert-butyl 3-(2-(3-((2-((S)-2-acetamido-4-(tert-butoxy)-4-oxobutanamido)-2-(5-methylisothiazol-3-yl)acetamido)methyl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate	715.4	716.8
521		tert-butyl 3-(2-(3-((2-((S)-2-acetamido-4-(tert-butoxy)-4-oxobutanamido)-2-(1-methyl-1H-imidazol-4-yl)acetamido)methyl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate	698.4	699.7
522		tert-butyl 3-(2-(3-((2-((S)-2-acetamido-4-(tert-butoxy)-4-oxobutanamido)-3-phenylpropanamido)methyl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate	708.4	709.8
523		tert-butyl 3-(2-(3-((2-((S)-2-acetamido-4-(tert-butoxy)-4-oxobutanamido)-2-(1-phenyl-1H-pyrazol-4-yl)acetamido)methyl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate	760.4	761.5
524		tert-butyl 3-(2-(3-((2-((S)-2-acetamido-4-(tert-butoxy)-4-oxobutanamido)-3-((methoxycarbonyl)(phenyl)amino)propanamido)methyl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate	781.4	782.8
525		tert-butyl 3-(2-(3-((2-((S)-2-acetamido-4-(tert-butoxy)-4-oxobutanamido)-2-(1,5-dimethyl-1H-pyrazol-3-yl)acetamido)methyl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate	712.4	713.8

526		tert-butyl 3-(2-(3-((2-((S)-2-acetamido-4-(tert-butoxy)-4-oxobutanamido)-2-(1H-pyrazol-3-yl)acetamido)methyl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate	684.4	685.7
527		tert-butyl 3-(2-(3-((2-((S)-2-acetamido-4-(tert-butoxy)-4-oxobutanamido)-4-(thiazol-2-yl)butanamido)methyl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate	729.4	730.7
528		tert-butyl 3-(2-(3-((2-((S)-2-acetamido-4-(tert-butoxy)-4-oxobutanamido)-4-(pyrazin-2-yl)butanamido)methyl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate	724.4	725.8

(3S)-3-(((benzyloxy)carbonyl)amino)-4-((1-((2-methyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-1-oxo-4-(pyridin-4-yl)butan-2-yl)amino)-4-oxobutanoic acid (**436**)

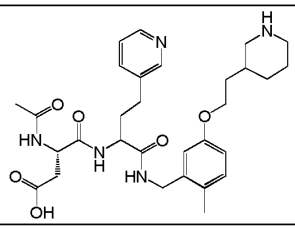
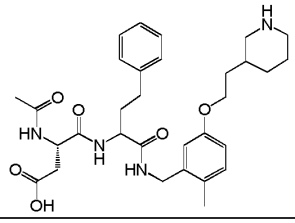
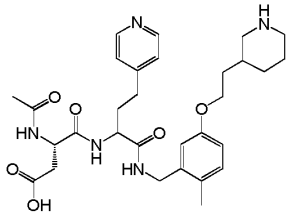
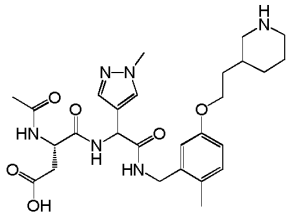
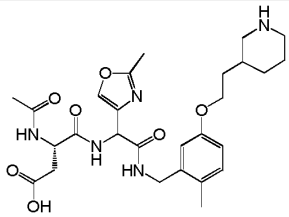
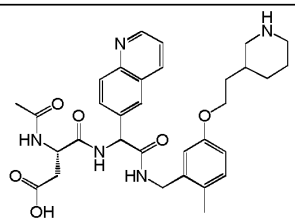


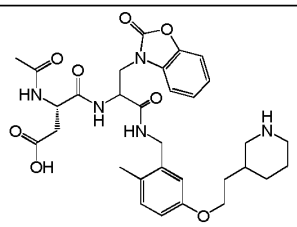
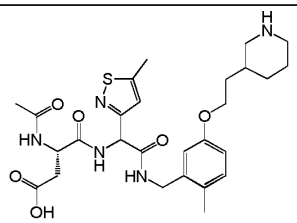
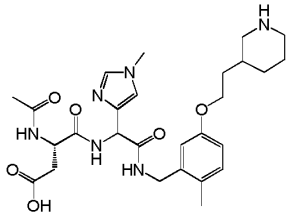
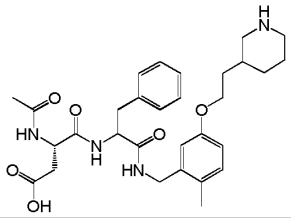
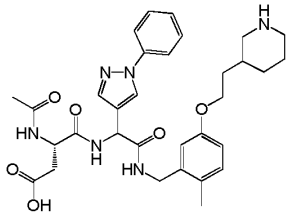
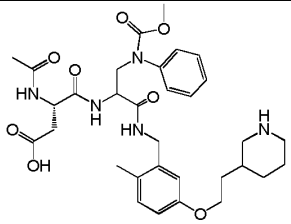
435 **436**

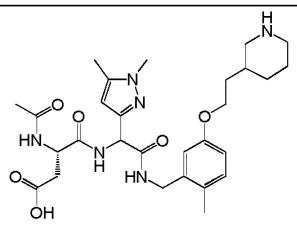
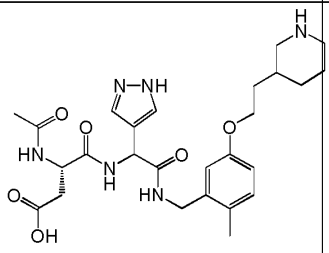
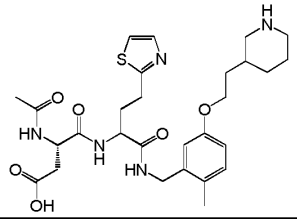
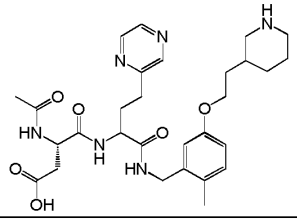
Protecting groups were cleaved from 750 mg compound **435** according to general procedure D stirring compounds in 5 ml 40% TFA/DCM at room temperature. After deprotection was complete solvent was removed and the crude dissolved in acetonitrile and concentrated twice. Product used without further purification.
Formula: $C_{35}H_{45}N_5O_7$, exact mass: 659.3, found: 660.3 $[M+H]^+$

The examples in the following table were prepared similar to the procedure described for compound **436**:

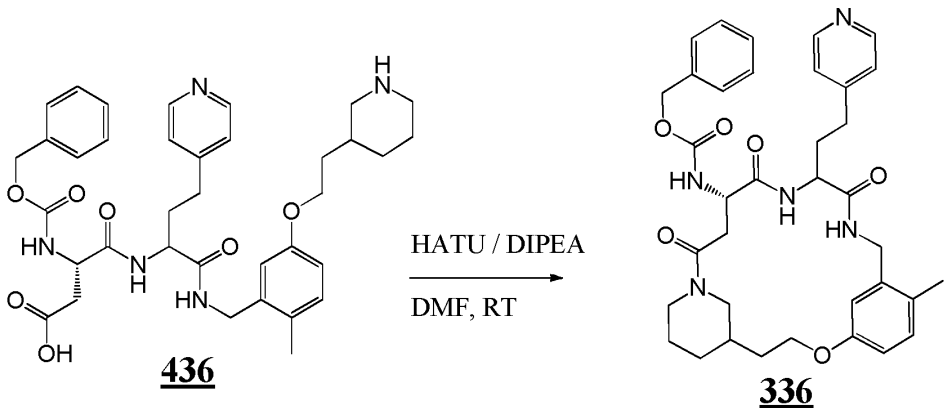
Table A-36

Cpd no	From Cpd	structure	name	Exact mass	$[M+H]^+$ found
545	**541**		(3S)-3-acetamido-4-((1-((2-methyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-1-oxo-4-(pyridin-3-yl)butan-2-yl)amino)-4-oxobutanoic acid	567.3	568.4
546	**542**		(3S)-3-acetamido-4-((1-((2-methyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-1-oxo-4-phenylbutan-2-yl)amino)-4-oxobutanoic acid	566.3	567.4
547	**543**		(3S)-3-acetamido-4-((1-((2-methyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-1-oxo-4-(pyridin-4-yl)butan-2-yl)amino)-4-oxobutanoic acid	567.3	568.4
548	**544**		(3S)-3-acetamido-4-((1-(1-methyl-1H-pyrazol-4-yl)-2-((2-methyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-2-oxoethyl)amino)-4-oxobutanoic acid	542.3	543.3
529	**517**		(3S)-3-acetamido-4-((2-((2-methyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-1-(2-methyloxazol-4-yl)-2-oxoethyl)amino)-4-oxobutanoic acid	543.3	544.3
530	**518**		(3S)-3-acetamido-4-((2-((2-methyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-2-oxo-1-(quinolin-6-yl)ethyl)amino)-4-oxobutanoic acid	589.3	590.6

531	**519**		(3S)-3-acetamido-4-((1-((2-methyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-1-oxo-3-(2-oxobenzo[d]oxazol-3(2H)-yl)propan-2-yl)amino)-4-oxobutanoic acid	609.3	610.4
532	**520**		(3S)-3-acetamido-4-((2-((2-methyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-1-(5-methylisothiazol-3-yl)-2-oxoethyl)amino)-4-oxobutanoic acid	559.2	560.4
533	**521**		(3S)-3-acetamido-4-((1-(1-methyl-1H-imidazol-4-yl)-2-((2-methyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-2-oxoethyl)amino)-4-oxobutanoic acid	542.3	543.4
534	**522**		(3S)-3-acetamido-4-((1-((2-methyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-1-oxo-3-phenylpropan-2-yl)amino)-4-oxobutanoic acid	552.3	553.4
535	**523**		(3S)-3-acetamido-4-((2-((2-methyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-2-oxo-1-(1-phenyl-1H-pyrazol-4-yl)ethyl)amino)-4-oxobutanoic acid	604.3	605.6
536	**524**		(3S)-3-acetamido-4-((3-((methoxycarbonyl)(phenyl)amino)-1-((2-methyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-1-oxopropan-2-yl)amino)-4-oxobutanoic acid	625.3	626.6

537	**525**		(3S)-3-acetamido-4-((1-(1,5-dimethyl-1H-pyrazol-3-yl)-2-((2-methyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-2-oxoethyl)amino)-4-oxobutanoic acid	556.3	557.4
538	**526**		(3S)-3-acetamido-4-((2-((2-methyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-2-oxo-1-(1H-pyrazol-4-yl)ethyl)amino)-4-oxobutanoic acid	528.3	529.4
539	**527**		(3S)-3-acetamido-4-((1-((2-methyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-1-oxo-4-(thiazol-2-yl)butan-2-yl)amino)-4-oxobutanoic acid	573.3	574.6
540	**528**		(3S)-3-acetamido-4-((1-((2-methyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-1-oxo-4-(pyrazin-2-yl)butan-2-yl)amino)-4-oxobutanoic acid	568.3	569.3

benzyl ((12S)-5[4]-methyl-8,11,14-trioxo-9-(2-(pyridin-4-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate (**336**)

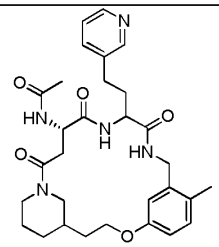
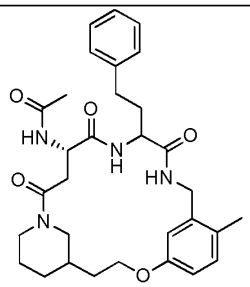
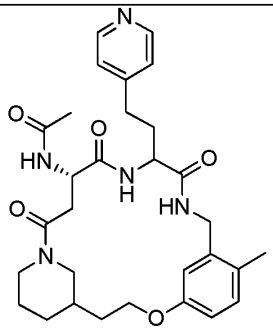
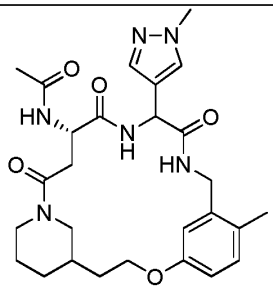


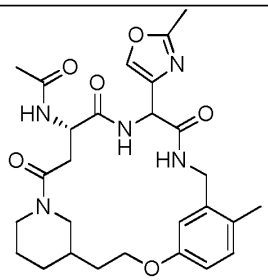
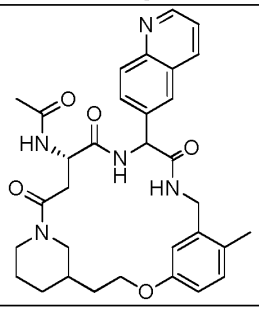
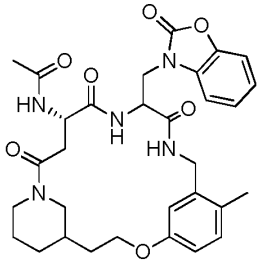
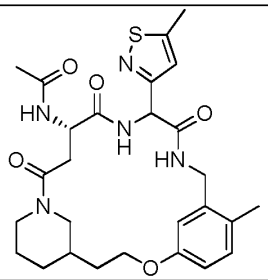
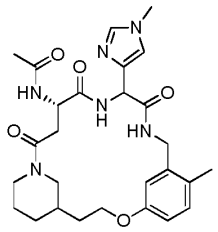
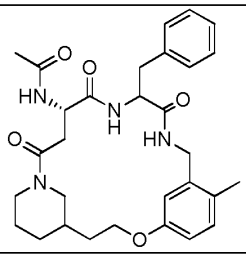
436 **336**

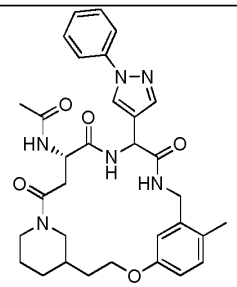
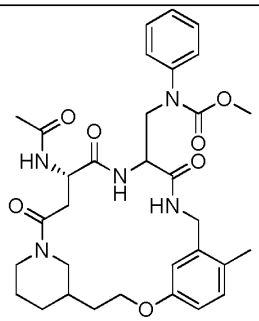
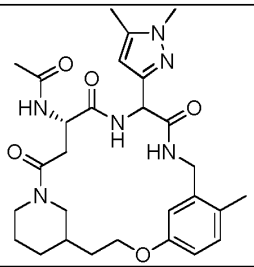
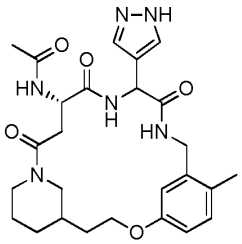
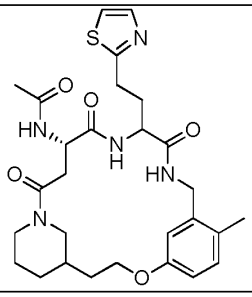
Macrocyclization was achieved according to general procedure A with 606 mg amino acid **436**. Reaction mixtures were diluted with some methanol and purified via reversed phase column chromatography (RP18, water/acetonitrile gradient) and HPLC.
Formula: $C_{36}H_{43}N_5O_6$, exact mass: 641.3, found: 642.3 [M+H]+

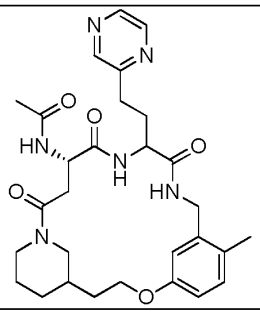
The examples in the following table were prepared similar to the procedure described for compound **336**:

Table A-37

Cpd no	From Cpd	structure	name	Exact mass	$[M+H]^+$ found
549	**545**		N-((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-3-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	549	550
550	**546**		N-((12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	548	549
551	**547**		N-((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-4-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	549	550
552	**548**		N-((12S)-5^4-methyl-9-(1-methyl-1H-pyrazol-4-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	524	525

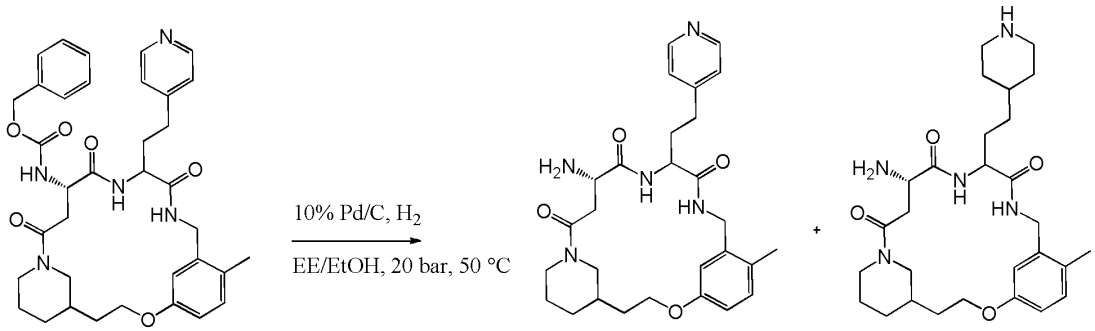
553	**529**		N-((12S)-5^4-methyl-9-(2-methyloxazol-4-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	525	526
554	**530**		N-((12S)-5^4-methyl-8,11,14-trioxo-9-(quinolin-6-yl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	571	572
555	**531**		N-((12S)-5^4-methyl-8,11,14-trioxo-9-((2-oxobenzo[d]oxazol-3(2H)-yl)methyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	591	592
556	**532**		N-((12S)-5^4-methyl-9-(5-methylisothiazol-3-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	541	542
557	**533**		N-((12S)-5^4-methyl-9-(1-methyl-1H-imidazol-4-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	524	525
558	**534**		N-((12S)-9-benzyl-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	534	535

559	**535**		N-((12S)-5^4-methyl-8,11,14-trioxo-9-(1-phenyl-1H-pyrazol-4-yl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	586	587
560	**536**		methyl (((12S)-12-acetamido-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-9-yl)methyl)(phenyl)carbamate	607	608
561	**537**		N-((12S)-9-(1,5-dimethyl-1H-pyrazol-3-yl)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	538	539
562	**538**		N-((12S)-5^4-methyl-8,11,14-trioxo-9-(1H-pyrazol-4-yl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	510	511
563	**539**		N-((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(thiazol-2-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	555	556

564	**540**		N-((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyrazin-2-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	550	551

Example A-32: Preparation of macrocyclic compounds 338, 342- 344, 437 439, 443 and 444

((12S)-12-amino-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-4-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl) (**437**)



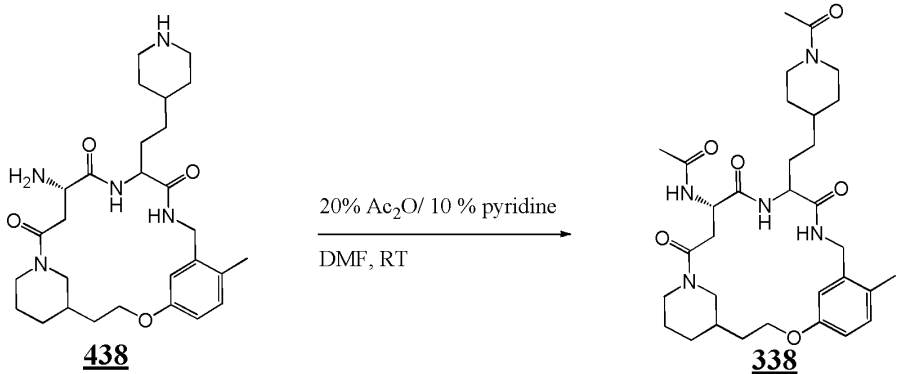
336 **437** **438**

Following general procedure C using 190 mg Cbz-protected amine **336** were dissolved ethyl acetate / ethanol (1:1). H-Cube conditions: 1 ml/min, 50°C, 20 bar H_2. After removing of volatiles under reduced pressure the product was used without further purification. Some piperidyl side product **438** was removed after the following step.

437- Formula: $C_{28}H_{37}N_5O_4$, exact mass: 507.3, found: 508.3 $[M+H]^+$

438- Formula: $C_{28}H_{43}N_5O_4$, exact mass: 513.3, found: 514.3 $[M+H]^+$

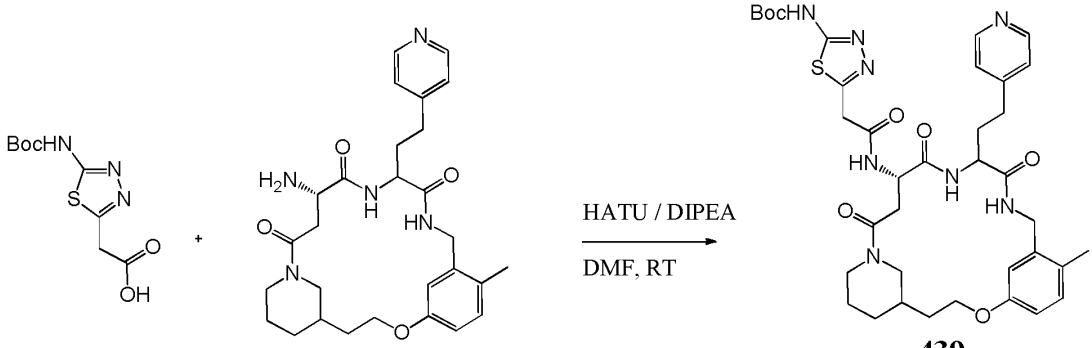
N-((12S)-9-(2-(1-acetylpiperidin-4-yl)ethyl)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide (**338**)



438 **338**

Both free amines in compound **438** were acetylated by dissolving amine 438 in Ac_2O/pyridine/DMF (20/10/70) at room temperature. Purification of the reaction mixture was achieved by HPLC to give compound **338**.
Formula: $C_{32}H_{47}N_5O_6$, exact mass: 597.4, found: 598.4 $[M+H]^+$

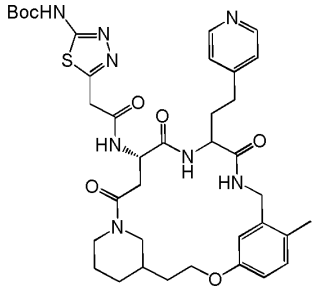
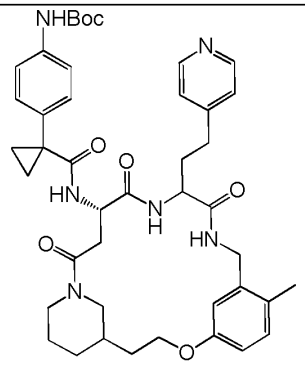
Amide derivatizations of compound **437** according to general procedure B

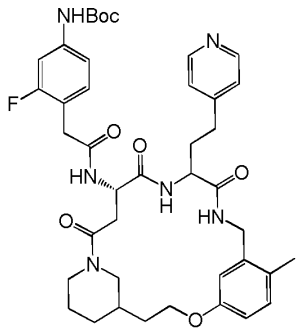


437 **439**

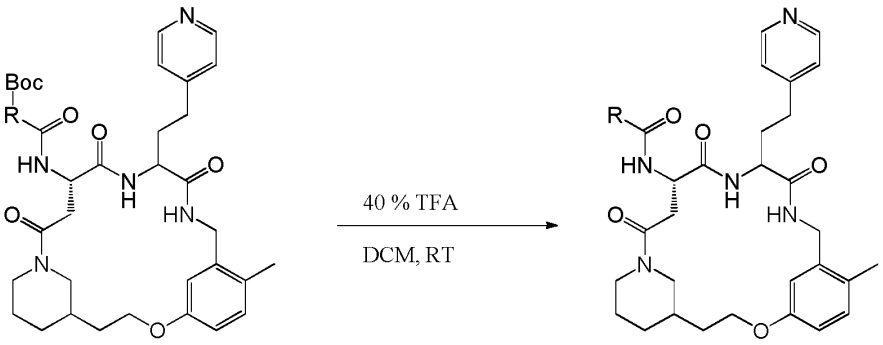
Amine **437** (32 mg) was coupled with carboxylic acids according to general procedure B to give amides disclosed in table below as exemplified for derivative **439**. Purifications were achieved by HPLC or reversed phase flash chromatography.

Table A-38

Cpd no	structure	name	Exact mass	$[M+H]^+$ found
439		tert-butyl (5-(2-(((12S)-5⁴-methyl-8,11,14-trioxo-9-(2-(pyridin-4-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)-1,3,4-thiadiazol-2-yl)carbamate	748.3 $C_{37}H_{48}N_8O_7S$	749.3
443		tert-butyl (4-(1-(((12S)-5⁴-methyl-8,11,14-trioxo-9-(2-(pyridin-4-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)cyclopropyl)phenyl)carbamate	766.4 $C_{43}H_{54}N_6O_7$	767.4

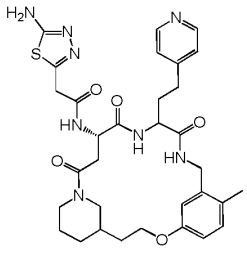
444		tert-butyl (3-fluoro-4-(2-(((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-4-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)phenyl)carbamate	758.4 $C_{41}H_{51}FN_6O_7$	759.4

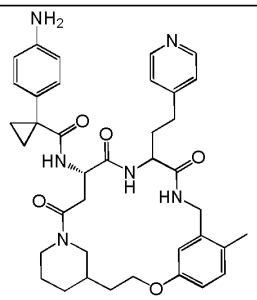
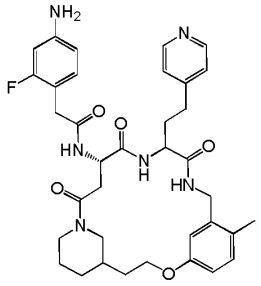
Removal of Boc-protecting groups



Boc protecting groups were cleaved from the compound according to general procedure D stirring compounds in 5 ml 40% TFA in DCM at room temperature. After deprotection was complete solvent was removed and the crude product was purified by reversed phase HPLC.

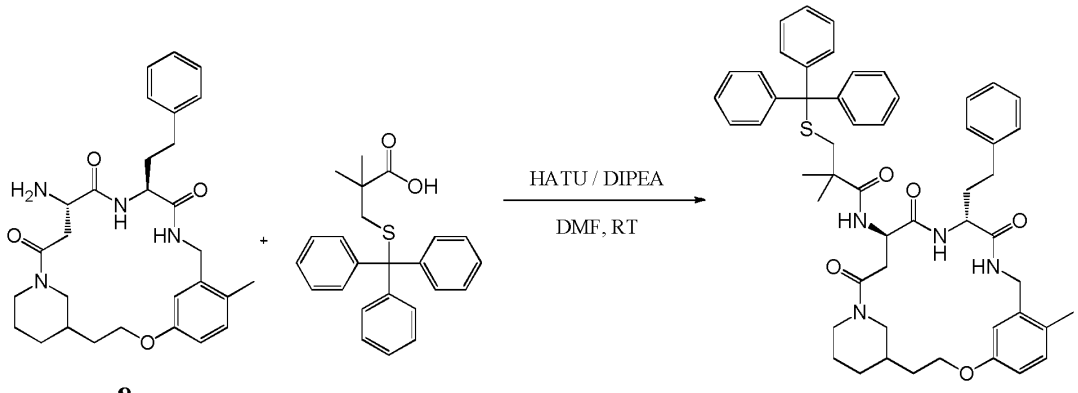
Table A-39

Cpd no	From cpd	structure	name	Exact mass	$[M+H]^+$ found
342	**439**		2-(5-amino-1,3,4-thiadiazol-2-yl)-N-((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-4-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	648.3 $C_{32}H_{40}N_8O_5S$	649.3

343	**443**		1-(4-aminophenyl)-N-((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-4-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)cyclopropane-1-carboxamide	666.4 $C_{38}H_{46}N_6O_5$	667.4
344	**444**		2-(4-amino-2-fluorophenyl)-N-((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-4-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	658.3 $C_{36}H_{43}FN_6O_5$	659.4

Example A-33: Preparation of macrocyclic compound 348

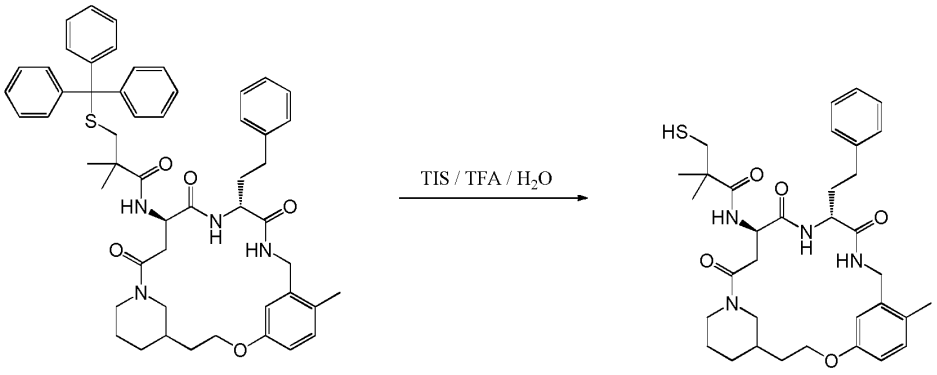
2,2-dimethyl-N-((9R,12R)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(tritylthio)propanamide (**450**)



8 **450**

Amine **8** (100 mg) was coupled with the carboxylic acid according to general procedure B to give protected thiol **450**. Purification was achieved by reversed phase HPLC. Formula: $C_{32}H_{47}N_5O_6$, exact mass: 597.4, found: 598.4 $[M+H]^+$

3-mercapto-2,2-dimethyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide (**348**)



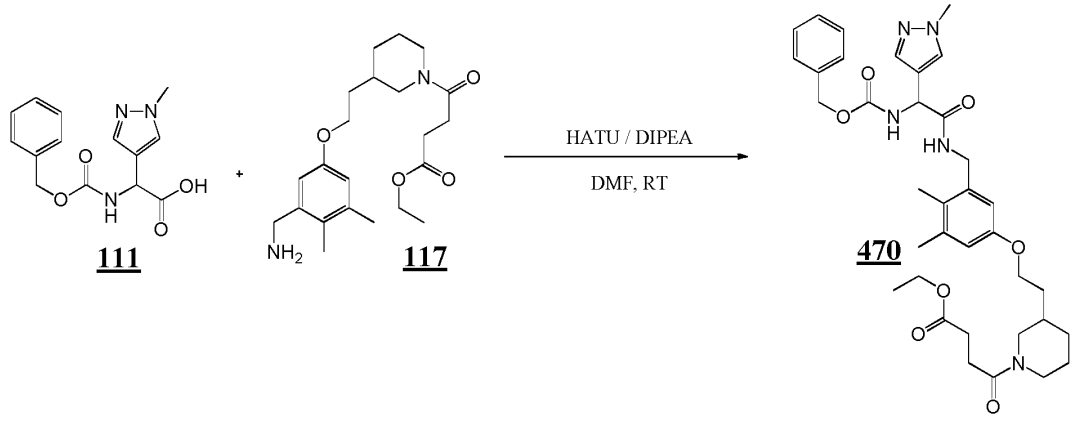
450 348

Compound **450** (140 mg) was dissolved in 1 ml TIS/TFA/H_2O (10/2/2) at room temperature and stirred for 1h. Purification by reversed phase column chromatography (RP18, water/acetonitrile gradient).

Formula: $C_{34}H_{46}N_4O_6$, exact mass: 622.3, found: 623.5 $[M+H]^+$

Example A-34: Preparation of macrocyclic compound 355

ethyl 4-(3-(2-(3-((2-(((benzyloxy)carbonyl)amino)-2-(1-methyl-1H-pyrazol-4-yl)acetamido)methyl)-4,5-dimethylphenoxy)ethyl)piperidin-1-yl)-4-oxobutanoate (**470**)

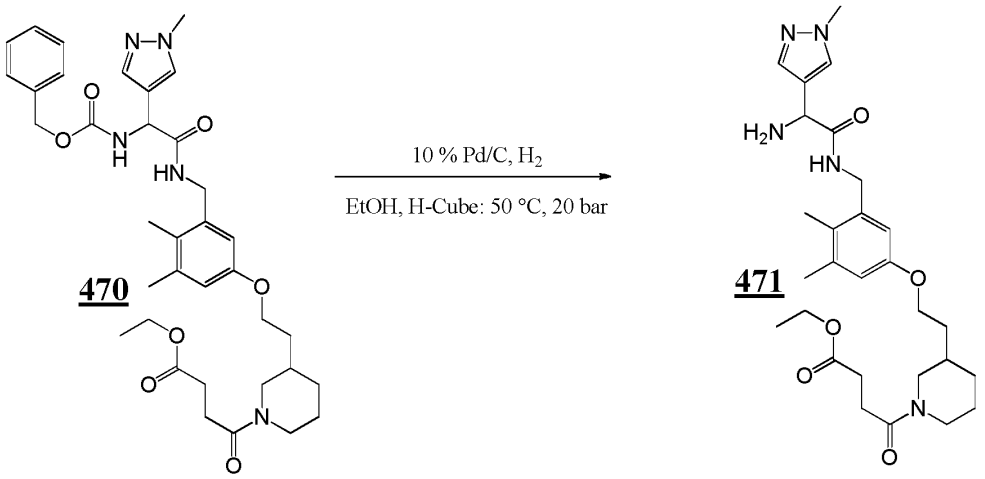


111 117 470

162 mg amine **117** and 100 mg carboxylic acid **111** were coupled according to general procedure B to give compound **470**. Purification was achieved by reversed phase column chromatography (RP18, water/acetonitrile gradient).

Formula: $C_{36}H_{47}N_5O_7$, exact mass: 661.3, found: 662.5 $[M+H]^+$

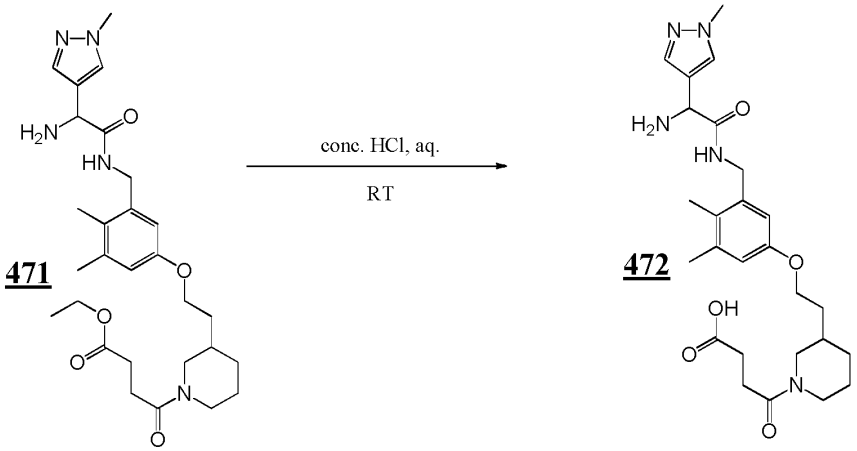
ethyl 4-(3-(2-(3-((2-amino-2-(1-methyl-1H-pyrazol-4-yl)acetamido)methyl)-4,5-dimethylphenoxy)ethyl)piperidin-1-yl)-4-oxobutanoate (**471**)



Cbz-protection group was removed according to general procedure C in EtOH at 50 °C and 20 bar H_2 pressure. Solvent was removed under reduced pressure to give a product pure enough to be used in the next reaction.

Formula: $C_{28}H_{41}N_5O_5$, exact mass: 527.3, found: 528.4 $[M+H]^+$

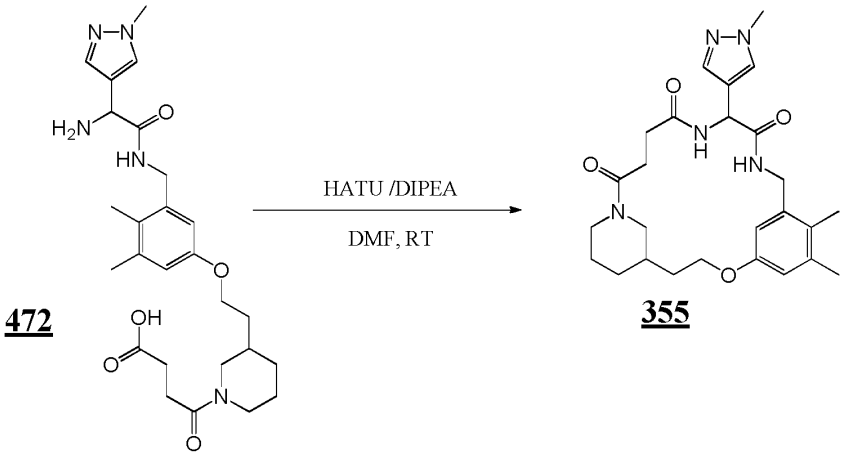
4-(3-(2-(3-((2-amino-2-(1-methyl-1H-pyrazol-4-yl)acetamido)methyl)-4,5-dimethylphenoxy)ethyl) piperidin-1-yl)-4-oxobutanoic acid (**472**)



The crude ester **471** was dissolved in concentrated aqueous HCl solution at room temperature. The solution was stirred until the reaction was complete. Volatiles were removed and dissolved in acetonitrile. After drying the crude was used in the following cyclization.

Formula: $C_{26}H_{37}N_5O_5$, exact mass: 499.3, found: 500.2 $[M+H]^+$

$5^4,5^5$-dimethyl-9-(1-methyl-1H-pyrazol-4-yl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione (**355**)



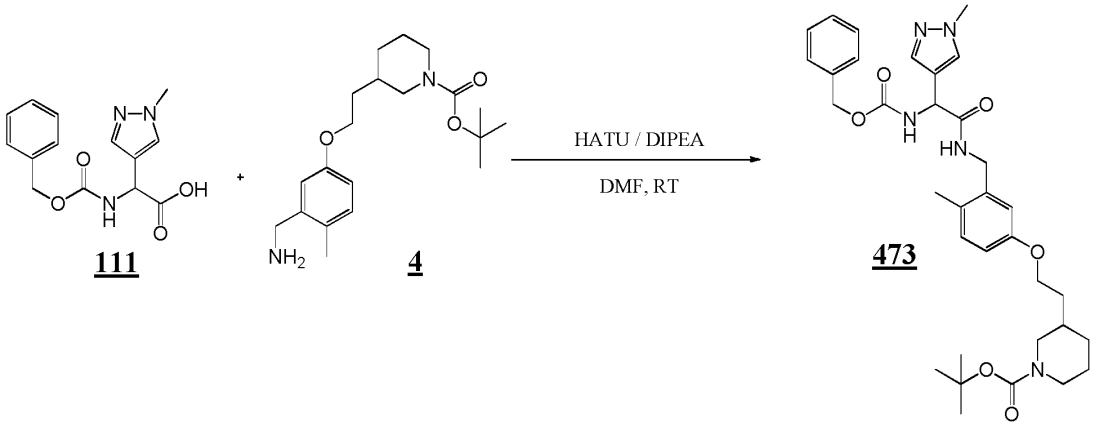
472 355

Macrocyclization was achieved according to general procedure A with 75 mg amino acid **472**. Reaction mixtures were diluted with some methanol and purified via reversed phase column chromatography (RP18, water/acetonitrile gradient) and HPLC.

Formula: $C_{26}H_{35}N_5O_4$, exact mass: 481.3, found: 482.3 $[M+H]^+$

Example A-35: Preparation of macrocyclic compound 356

tert-butyl 3-(2-(3-((2-(((benzyloxy)carbonyl)amino)-2-(1-methyl-1H-pyrazol-4-yl)acetamido)methyl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate (**473**)

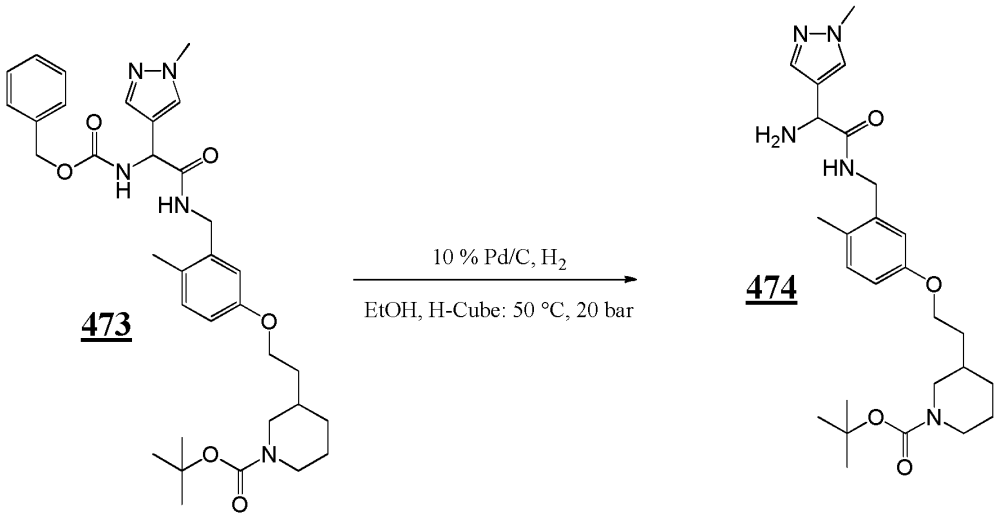


111 4 473

452 mg amine **4** and 341 mg carboxylic acid **111** were coupled according to general procedure B to give compound **473**. Purification was achieved by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient).

Formula: $C_{34}H_{45}N_5O_6$, exact mass: 619.3, found: 620.3 $[M+H]^+$

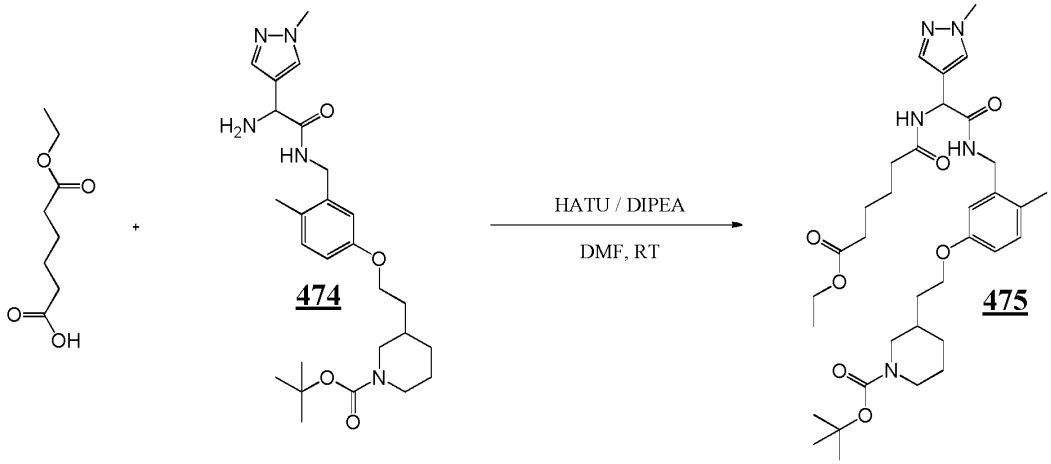
tert-butyl 3-(2-(3-((2-amino-2-(1-methyl-1H-pyrazol-4-yl)acetamido)methyl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate (**474**)



Cbz-protection group was removed according to general procedure C in EtOH at 50 °C and 20 bar H_2 pressure. Solvent was removed under reduced pressure to give a product pure enough to be used in the next reaction.

Formula: $C_{26}H_{39}N_5O_4$, exact mass: 485.3, found: 486.3 $[M+H]^+$

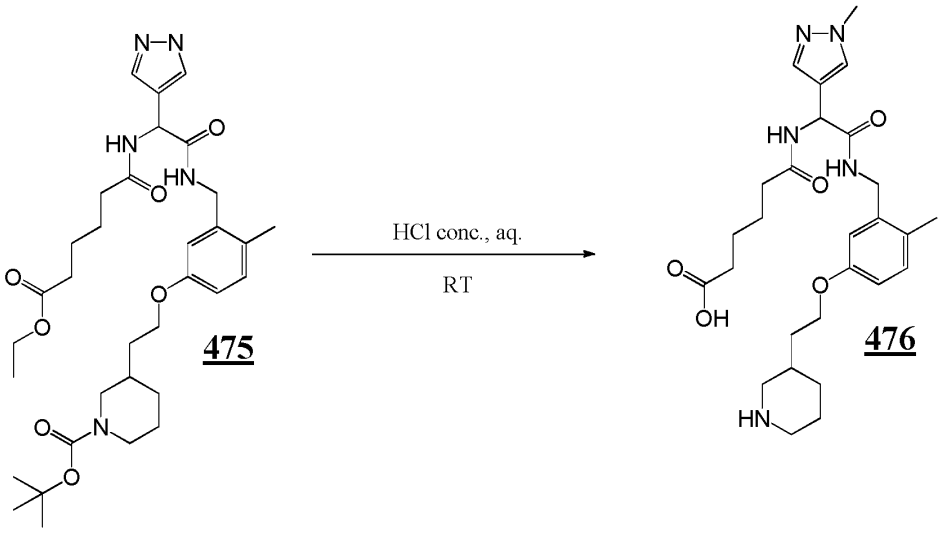
tert-butyl 3-(2-(3-((2-(6-ethoxy-6-oxohexanamido)-2-(1-methyl-1H-pyrazol-4-yl)acetamido)methyl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate (**475**)



100 mg amine **474** and 43 mg 6-ethoxy-6-oxohexanoic acid were coupled according to general procedure B to give compound **475**. Purification was achieved by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient).

Formula: $C_{34}H_{51}N_5O_7$, exact mass: 641.4, found: 642.4 $[M+H]^+$

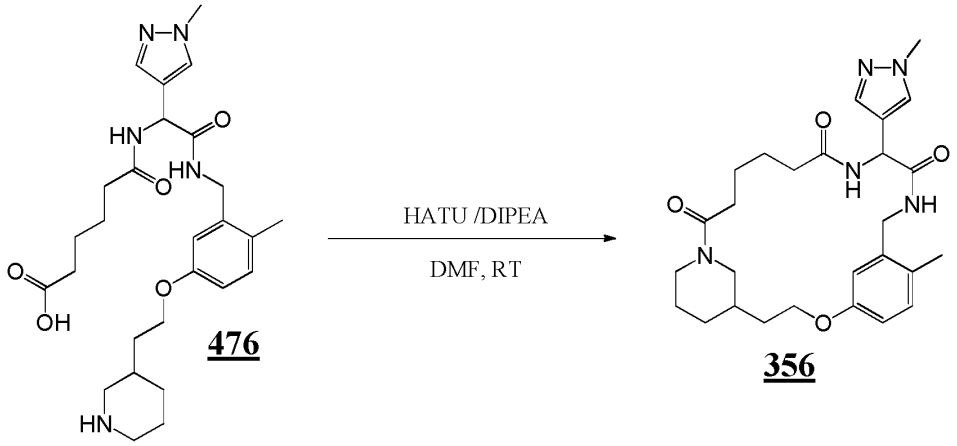
6-((1-(1-methyl-1H-pyrazol-4-yl)-2-((2-methyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-2-oxoethyl)amino)-6-oxohexanoic acid (**476**)



Ester **475** was dissolved in concentrated aqueous HCl solution at room temperature. The solution was stirred until the reaction was complete. Volatiles were removed and dissolved in acetonitrile. After drying the crude was used in the following cyclization.

Formula: $C_{27}H_{39}N_5O_5$, exact mass: 513.3, found: 514.3 $[M+H]^+$

5^4-methyl-9-(1-methyl-1H-pyrazol-4-yl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclohexadecaphane-8,11,16-trione (**356**)

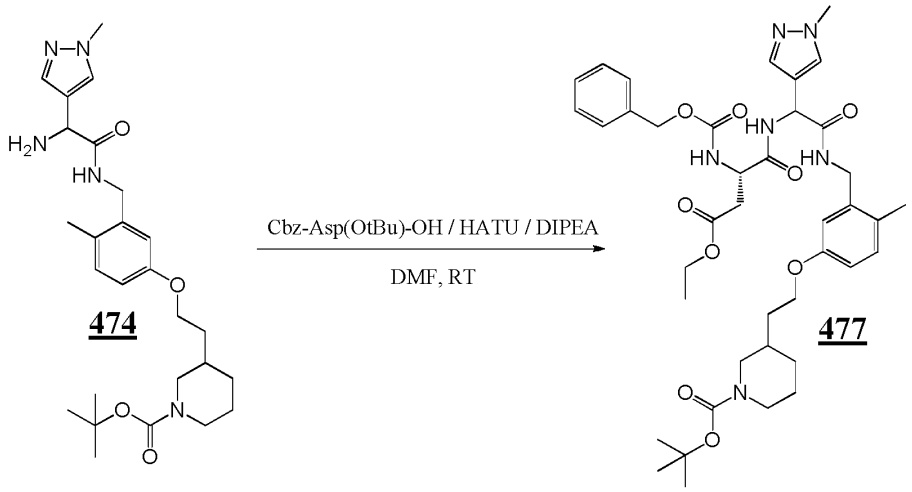


Macrocyclization was achieved according to general procedure A with 0.11 amino acid **476**. Reaction mixtures were diluted with some methanol and purified via HPLC.

Formula: $C_{27}H_{37}N_5O_4$, exact mass: 495.3, found: 496.3 $[M+H]^+$

Example A-36: Preparation of macrocyclic compounds 358-363, 479, 480, and 552

tert-butyl 3-(2-(3-((5S)-5-(2-ethoxy-2-oxoethyl)-8-(1-methyl-1H-pyrazol-4-yl)-3,6,9-trioxo-1-phenyl-2-oxa-4,7,10-triazaundecan-11-yl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate (**477**)

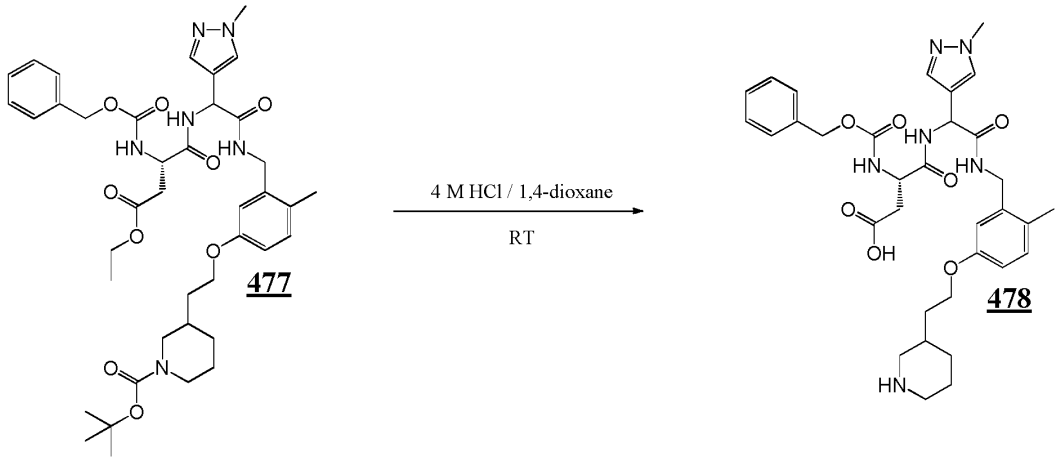


474 477

3 g amine **474** and 3 g Cbz-Asp(OtBu)-OH were coupled according to general procedure B to give compound **477**. Purification was achieved by normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient).

Formula: $C_{40}H_{54}N_6O_9$, exact mass: 762.4, found: 763.5 $[M+H]^+$

(3S)-3-(((benzyloxy)carbonyl)amino)-4-((1-(1-methyl-1H-pyrazol-4-yl)-2-((2-methyl-5-(2-(piperidin-3-yl)ethoxy)benzyl)amino)-2-oxoethyl)amino)-4-oxobutanoic acid (**478**)

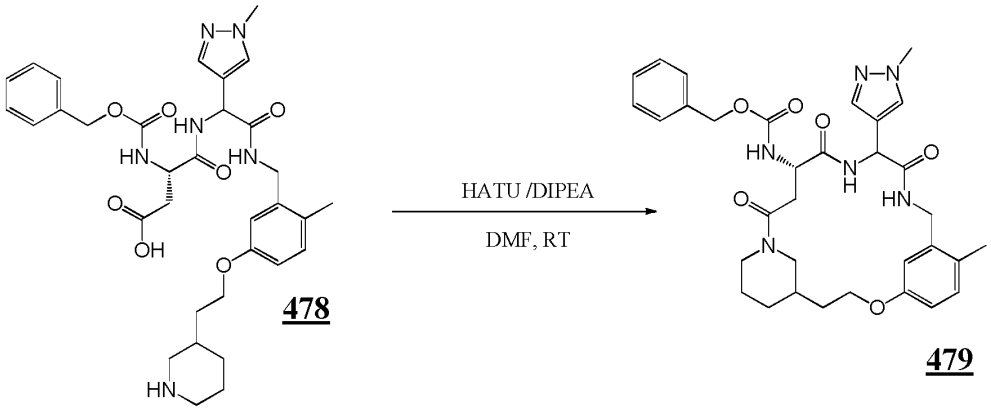


477 478

4.2 g ester **477** was dissolved in 40 ml 4 M HCl solution in 1,4-dioxane at room temperature. The solution was stirred until the reaction was complete. Volatiles were removed and dissolved in acetonitrile. After drying the crude was used in the following cyclization.

Formula: $C_{33}H_{42}N_6O_7$, exact mass: 634.3, found: 635.3 $[M+H]^+$

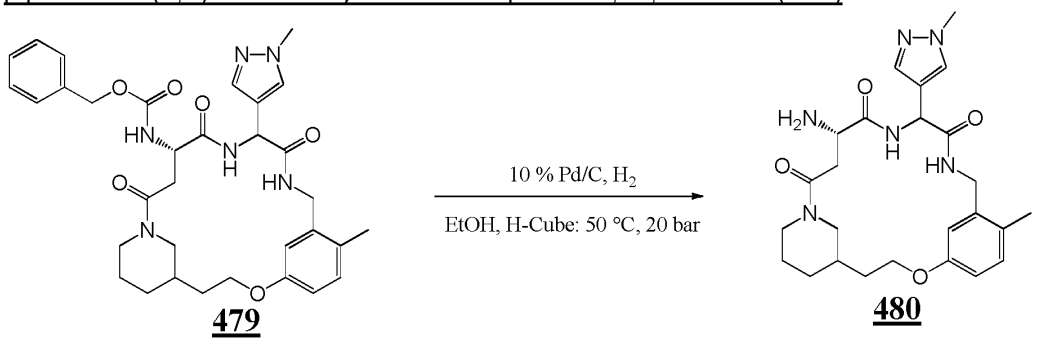
benzyl ((12S)-5[4]-methyl-9-(1-methyl-1H-pyrazol-4-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate(**479**)



478 479

Macrocyclization was achieved according to general procedure A with 2.42 g amino acid **478**. Saturated $NaHCO_3$ solution was added to the reaction mixture and this was extracted with ethyl acetate. Organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification was achieved via normal phase column chromatography (silica, cyclohexane/ethyl acetate gradient).
Formula: $C_{33}H_{40}N_6O_6$, exact mass: 616.3, found: 617.3 $[M+H]^+$

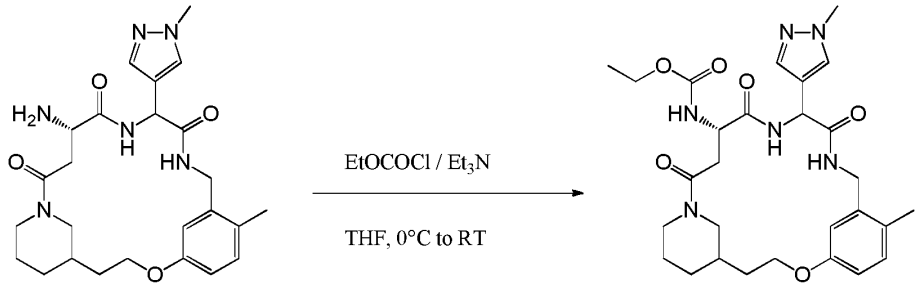
(12S)-12-amino-5^4-methyl-9-(1-methyl-1H-pyrazol-4-yl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione (**480**)



479 480

Cbz-group was removed according to general procedure C in EtOH at 50 °C and 20 bar H_2 pressure. Solvent was removed under reduced pressure to give a product pure enough to be used in the next reaction.
Formula: $C_{25}H_{34}N_6O_4$, exact mass: 482.3

ethyl ((12S)-5^4-methyl-9-(1-methyl-1H-pyrazol-4-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate (**363**)

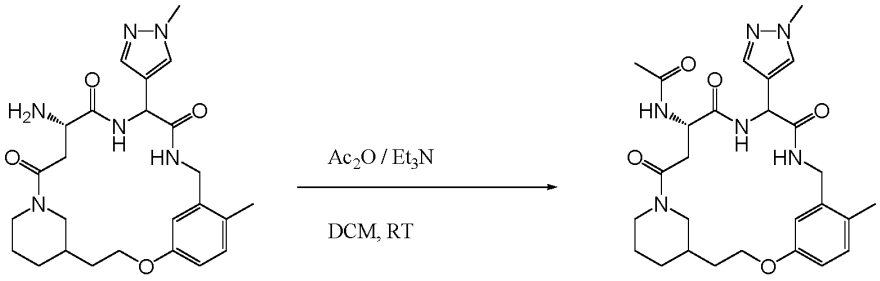


480 **363**

Compound **363** was synthesized according to general procedure G from 75 mg amine **480**. Final purification was achieved by HPLC.

Formula: $C_{28}H_{38}N_6O_6$, exact mass: 554.3, found: 555.3 $[M+H]^+$

N-((12S)-5^4-methyl-9-(1-methyl-1H-pyrazol-4-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide (**552**)

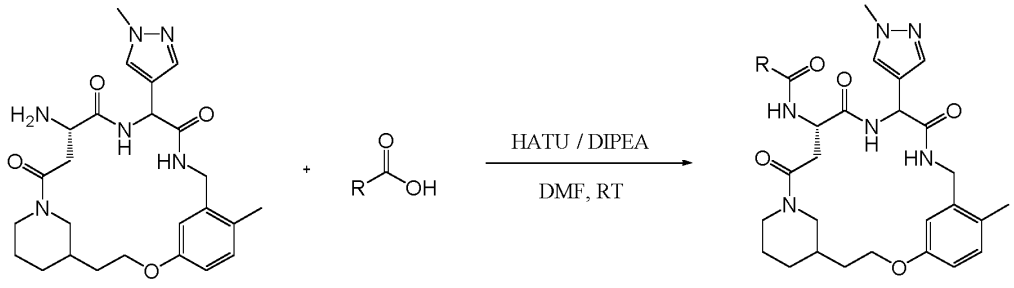


480 **552**

Compound **552** was synthesized from 75 mg amine **480**. Final purification was achieved by HPLC.

Formula: $C_{27}H_{36}N_6O_5$, exact mass: 524.3, found: 525.4 $[M+H]^+$

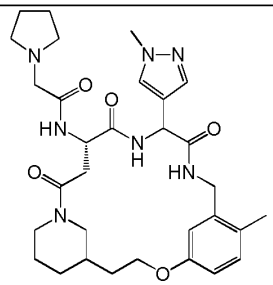
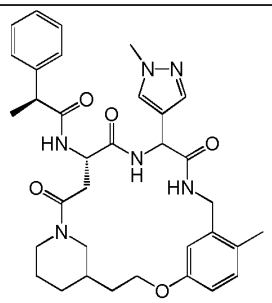
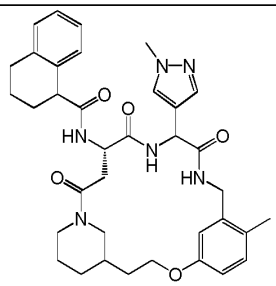
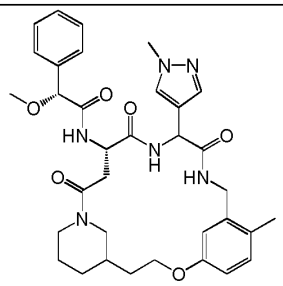
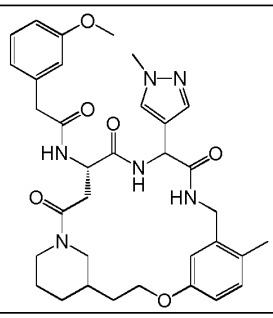
Amide derivatizations of compound **480** according to general procedure B



480

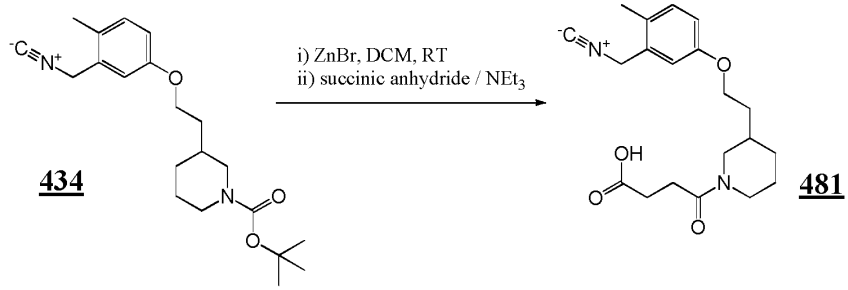
Amine **480** (e.g. 75 mg) was coupled with carboxylic acids according to general procedure B to give amides disclosed in table below. Purifications were achieved by HPLC.

Table A-40

Cpd no	structure	name	Exact mass	$[M+H]^+$ found
358		N-((12S)-5^4-methyl-9-(1-methyl-1H-pyrazol-4-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(pyrrolidin-1-yl)acetamide	593.3	594.4
359		(2S)-N-((12S)-5^4-methyl-9-(1-methyl-1H-pyrazol-4-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-phenylpropanamide	614.3	615.4
360		N-((12S)-5^4-methyl-9-(1-methyl-1H-pyrazol-4-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-1,2,3,4-tetrahydronaphthalene-1-carboxamide	640.3	641.4
361		(2R)-2-methoxy-N-((12S)-5^4-methyl-9-(1-methyl-1H-pyrazol-4-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-phenylacetamide	630.3	631.4
362		2-(3-methoxyphenyl)-N-((12S)-5^4-methyl-9-(1-methyl-1H-pyrazol-4-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	630.3	631.3

Example A-37: Preparation of macrocyclic compound 495

4-(3-(2-(3-(isocyanomethyl)-4-methylphenoxy)ethyl)piperidin-1-yl)-4-oxobutanoic (**481**)



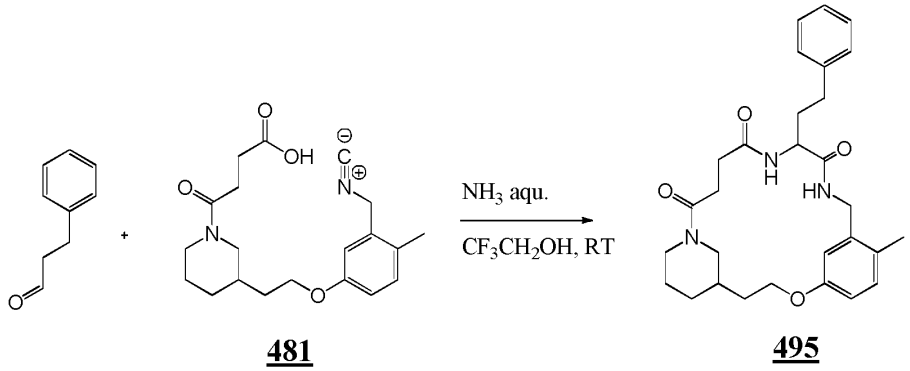
tert-butyl 3-(2-(3-(isocyanomethyl)-4-methylphenoxy)ethyl)piperidine-1-carboxylate (307 mg, 0.86 mmol, 1.0 eq.) was dissolved in DCM (10 mL) and zinc bromide (385 mg, 1.7 mmol, 2 eq.) was added to the solution. The reaction mixture was stirred for 72h to provide the free piperidine derivation in situ. MS (ES) $C_{16}H_{22}N_2O$ requires: 258, found: 259 (M+H)+.

To the reaction mixture was added Et_3N (343 mg, 3.4 mmol, 4 eq.) and succinic anhydride (120 mg, 1.2 mmol, 1.4 eq.) and the reaction mixture was stirred for 2h. The reaction mixture was diluted with DCM and H_2O. The aqueous layer was adjusted to pH 2-4 using a 0.1 M HCl solution before it was extracted 3X with DCM. The combined organic layers were dried over $MgSO_4$ and the solvents were removed under reduced pressure.

The crude product was purified by flash chromatography on silica gel (0-100 % EtOAc/cHex, 0-100 % MeOH/DCM) to yield the title compound **481** (50 mg, 0.14 mmol, 16%). Compound **481** is very unstable and hydrolyses easily to the corresponding formamide.

MS (ES) $C_{20}H_{26}N_2O_4$ requires: 358 ,found: 359 $(M+H)^+$.

5^4-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione (**495**)



4-(3-(2-(3-(isocyanomethyl)-4-methylphenoxy)ethyl)piperidin-1-yl)-4-oxobutanoic acid (50 mg, 0.14 mmol, 1.0 eq.) was dissolved in 2,2,2-trifluoroethanol (1 mL), a solution of

3-phenylpropanal (52 mg, 0.40 mmol, 2.8 eq.) in 2,2,2-trifluoroethanol (1 mL), and aq. NH_3 (32%) (153 mg, 1.4 mmol, 10.0 eq.) were added to the solution. The reaction mixture was stirred for 10min at RT.

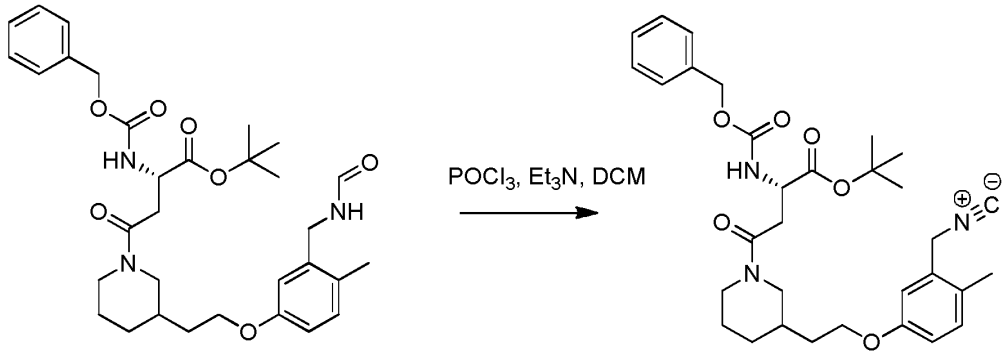
The reaction mixture was diluted with DCM and $NaHCO_3$ and the aqueous layer was extracted 3X with DCM before the combined organic layers were dried over $MgSO_4$ and the solvents were removed *in vacuo*.

The crude product was purified by flash chromatography on silica gel (0-100 % EtOAc/cHex, 0-100 % MeOH/DCM) and by a subsequent reversed-phase RP-HPLC (column: C18), using H_2O (0.1 %TFA) and ACN (0.1 %TFA) as eluents. The desired fractions were lyophilized to yield the compound **495** (30 mg, 0.06 mmol, 44%) as a white solid. MS (ES) $C_{29}H_{37}N_3O_4$ requires: 491, found: 492 $(M+H)^+$.

^1H NMR (400MHz, d_6-DMSO, 300K) δ 8.42-7.70 (m, 2H), 7.33-7.24 (m, 2H), 7.24-7.13 (m, 3H), 7.06-7.00 (m, 1H), 6.99-6.66 (m, 2H), 4.77-3.72 (m, 6H), 3.10-2.54 (m, 4H), 2.54-2.26 (m, 3H), 2.20-2.12 (m, 3H), 2.10-0.97 (m, 11H).

Example A-38: Preparation of macrocyclic compounds 503, 505, and 509 -513

tert-butyl (2S)-2-(((benzyloxy)carbonyl)amino)-4-(3-(2-(3-(isocyanomethyl)-4-methylphenoxy)ethyl)piperidin-1-yl)-4-oxobutanoate (**515**)



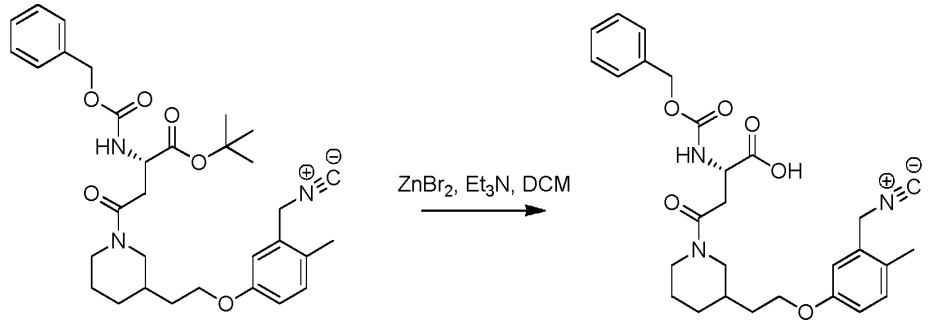
514 **515**

tert-butyl (2S)-2-(((benzyloxy)carbonyl)amino)-4-(3-(2-(3-(formamidomethyl)-4-methylphenoxy)ethyl)piperidin-1-yl)-4-oxobutanoate (100 mg, 0.172 mmol, 1.0 eq.) was dissolved in DCM (10 mL) and Et_3N (104 mg, 1.0 mmol, 6 eq.) was added to the solution. A solution of $POCl_3$ (53 mg, 0.34 mmol, 2 eq.) in DCM (1 mL) was added dropwise to the reaction mixture at 0°C. After 1h still 20 % of starting material was observed. An additional solution of $POCl_3$ (26 mg, 0.172 mmol, 1 eq.) in DCM (0.5 mL) was added dropwise to the reaction mixture at 0°C. The reaction was kept for further 30min.

The reaction mixture was diluted with DCM and $NaHCO_3$ and the aqueous layer was extracted 3X with DCM. The combined organic layers were dried over $MgSO_4$ and the solvents were removed under reduced pressure.

The crude product was purified by flash chromatography on silica gel (0-100 % EtOAc/cHex) to yield the title compound **515** (95 mg, 0.168 mmol, 98%). MS (ES) $C_{32}H_{41}N_3O_6$ requires: 563, found: 564 $(M+H)^+$.

(2S)-2-(((benzyloxy)carbonyl)amino)-4-(3-(2-(3-(isocyanomethyl)-4-methylphenoxy)ethyl)piperidin-1-yl)-4-oxobutanoic acid (**516**)

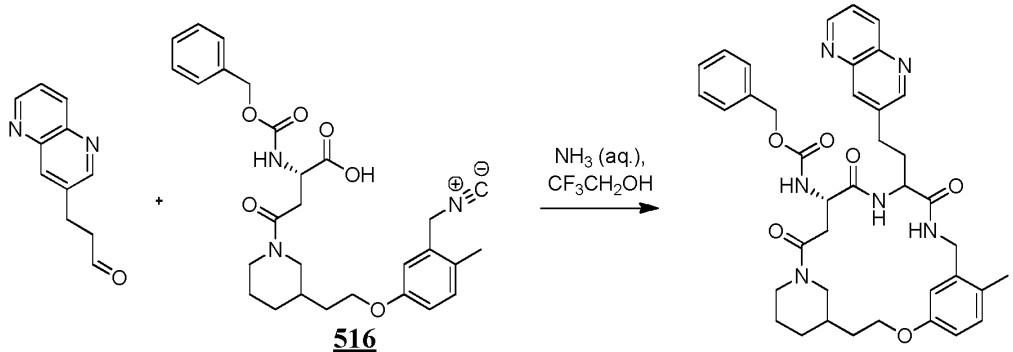


515 **516**

To a solution of tert-butyl (2S)-2-(((benzyloxy)carbonyl)amino)-4-(3-(2-(3-(isocyanomethyl)-4-methylphenoxy)ethyl)piperidin-1-yl)-4-oxobutanoate (1 g, 1.77 mmol, 1.0 eq.) in DCM (40 mL) was added Et_3N (358 mg, 3.54 mmol, 2 eq.) and zinc bromide (2 g, 8.9 mmol, 5 eq.). The reaction mixture was stirred for 16 h.

The reaction mixture was purified by reversed-phase chromatography (column: C18), using H_2O and ACN as eluents. The desired fractions were directly lyophilized to yield title compound **516** (672 mg, 1.32 mmol, 75%) as a white solid. MS (ES) $C_{28}H_{33}N_3O_6$ requires: 507, found: 508 $(M+H)^+$.

benzyl ((12S)-9-(2-(1,5-naphthyridin-3-yl)ethyl)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate (**511**)



516 **511**

(2S)-2-(((benzyloxy)carbonyl)amino)-4-(3-(2-(3-(isocyanomethyl)-4-methylphenoxy)ethyl)piperidin-1-yl)-4-oxobutanoic acid (77 mg, 0.15 mmol, 1.0 eq.) was dissolved in 2,2,2-trifluoroethanol (4 mL), 3-(1,5-naphthyridin-3-yl)propanal (39 mg, 0.21

mmol, 1.4 eq.) and aq. NH_3 (32%) (550 mg, 0.46 mmol, 3.0 eq.) were added to the solution. The reaction mixture was stirred for 12 h at RT.

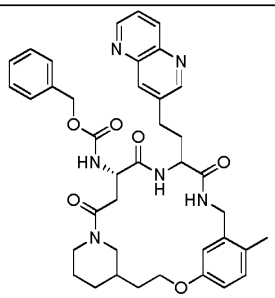
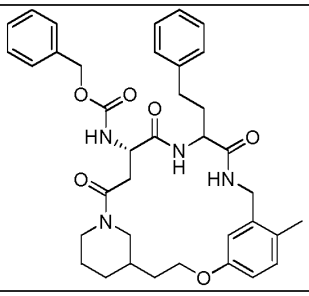
The reaction mixture was diluted with DCM and $NaHCO_3$ and the aqueous layer was extracted 3X with DCM before the combined organic layers were dried over $MgSO_4$ and the solvents were removed in vacuo.

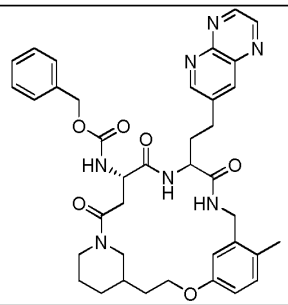
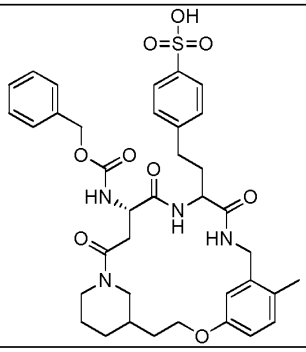
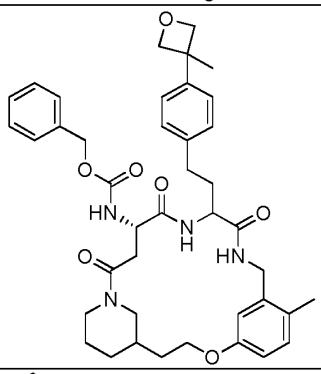
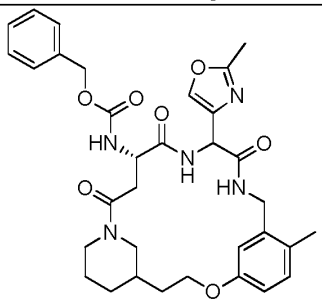
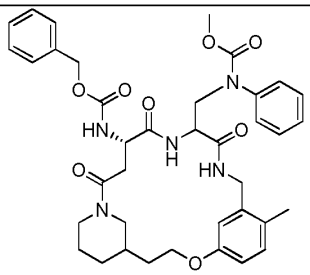
The crude product was purified by flash chromatography on silica gel (0-100 % EtOAc/cHex, 0-100 % MeOH/DCM) and by a subsequent reversed-phase RP-HPLC (column: C18), using H_2O (0.1 %TFA) and ACN (0.1 %TFA) as eluents to yield the title compound **511** (35 mg, 0.04 mmol, 29%) as a yellowish solid (TFA salt). MS (ES) $C_{39}H_{44}N_6O_6$ requires: 692, found: 693 $(M+H)^+$.

^1H NMR (400MHz, d_6-DMSO, 300K) δ 9.14-8.71 (m, 2H), 8.63-7.56 (m, 5H), 7.52-6.96 (m, 7H), 6.98-6.54 (m, 2H), 5.22-4.87 (m, 2H), 4.68-3.62 (8H), 3.13-2.58 (m, 6H), 2.22-1.88 (m, 4H), 1.81-1.02 (m, 8H).

The examples in the following table were prepared according to the procedure described for compound **511**.

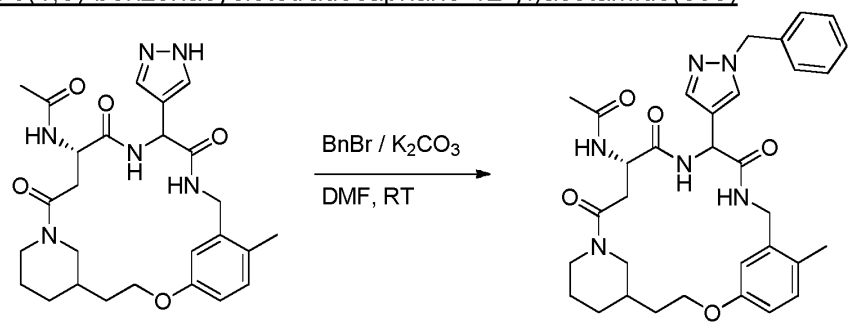
Table A-41

Cpd no	structure	name	Exact mass	$[M+H]^+$ found
511		benzyl ((12S)-9-(2-(1,5-naphthyridin-3-yl)ethyl)-5[4]-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate	692	693
503		benzyl ((12S)-9-phenethyl-5[4]-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate	640	641

505		benzyl ((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyrido[2,3-b]pyrazin-7-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate	693	694
509		4-(2-((12S)-12-(((benzyloxy)carbonyl)amino)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-9-yl)ethyl)benzenesulfonic acid	720	721
510		benzyl ((12S)-5^4-methyl-9-(4-(3-methyloxetan-3-yl)phenethyl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate	710	711
512		benzyl ((12S)-5^4-methyl-9-(2-methyloxazol-4-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate	617	618
513		methyl (((12R)-12-(((benzyloxy)carbonyl)amino)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-9-yl)methyl)(phenyl)carbamate	699	700

Example A-39: Preparation of macrocyclic compounds 565 -568

N-((12S)-9-(1-benzyl-1H-pyrazol-4-yl)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide(**565**)



562 **565**

N-((12S)-5^4-methyl-8,11,14-trioxo-9-(1H-pyrazol-4-yl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide **562** (50 mg, 0.098 mmol, 1.0 eq.) was dissolved in DMF (2 ml), potassium carbonate (41 mg, 0.29 mmol, 3.0 eq.), and benzyl bromide (21 mg, 0.12 mmol, 1.2 eq.) were added to the solution at RT and the reaction mixture was stirred for 12h.

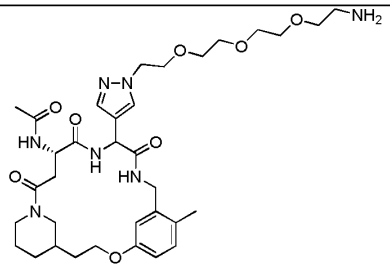
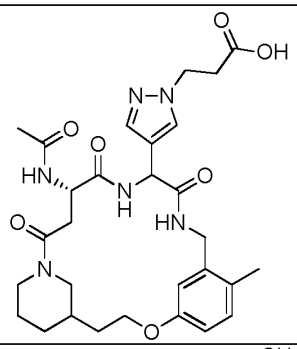
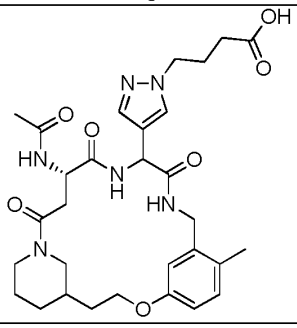
The reaction mixture was diluted with EtOAc and $NaHCO_3$ and the aqueous layer was extracted 3X with EtOAc. The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo*.

The crude product was purified by flash chromatography on silica gel (0-100 % EtOAc/ cHex, 0-100% MeOH/DCM) and by a subsequent reversed-phase RP-HPLC (column: C18), using H_2O (0.1 %TFA) and ACN (0.1 %TFA) as eluents. The desired fractions were lyophilized to yield title compound **565** (23.4 mg, 0.033 mmol, 34%) as a white solid (TFA salt). MS (ES) $C_{33}H_{40}N_6O_5$ requires: 600, found: 601 $(M+H)^+$.

^{1}H NMR (400MHz, d_6-DMSO, 300K) δ 8.69-8.34 (m, 1H), 8.27-7.65 (m, 3H), 7.54-7.20 (m, 6H), 7.09-7.02 (m, 1H), 6.97-6.66 (m, 2H), 5.57-5.21 (m, 3H), 4.77-4.04 (m, 6H), 3.21-2.53 (m, 3H), 2.22-2.02 (m, 4H), 1.95-1.16 (m, 11H).

Examples in the following table were prepared similar to the procedure described for **565**.

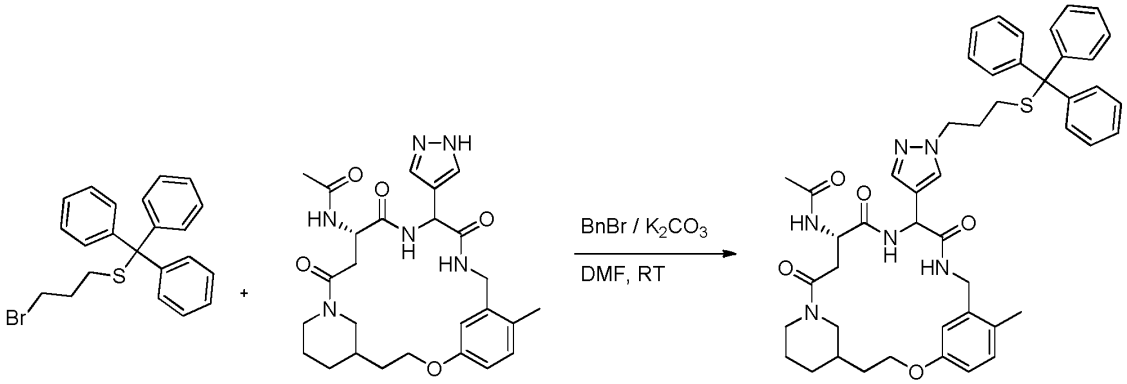
Table A-42

Cpd No	Structure	name	M	$[M+H]^+$
566		N-((12S)-9-(1-(2-(2-(2-(2-aminoethoxy)ethoxy)ethoxy)ethyl)-1H-pyrazol-4-yl)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide	685	686
567		3-(4-((12S)-12-acetamido-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-9-yl)-1H-pyrazol-1-yl)propanoic acid	582	583
568		4-(4-((12S)-12-acetamido-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-9-yl)-1H-pyrazol-1-yl)butanoic acid	596	597

In order to obtain the examples **566**, **567** and **568** subsequent standard acidic BOC (or tert-butyl)-deprotection according to general procedure D was performed.

Example A-40: Preparation of macrocyclic compounds 570 -572

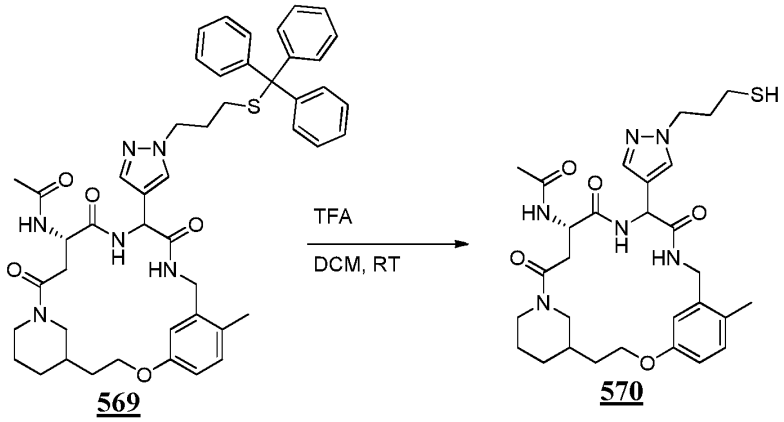
N-((12S)-5^4-methyl-8,11,14-trioxo-9-(1-(3-(tritylthio)propyl)-1H-pyrazol-4-yl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide (**569**)



562 569

N-((12S)-5^4-methyl-8,11,14-trioxo-9-(1H-pyrazol-4-yl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide **562** (100 mg, 0.20 mmol, 1.0 eq.) was dissolved in DMF (5 mL), potassium carbonate (81 mg, 0.59 mmol, 3.0 eq.), and (3-bromopropyl)(trityl)sulfane (187 mg, 0.47 mmol, 2.4 eq.) were added to the solution at RT and the reaction mixture was heated to 80°C and stirred for 18h.
The reaction mixture was diluted with DCM and $NaHCO_3$ and the aqueous layer was extracted 3X with DCM. The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. The crude product was purified by flash chromatography on silica gel (0-100 % EtOAc/ cHex, 0-100% MeOH/DCM) and led to the desired title compound **569** (35.2 mg, 0.043 mmol, 22%). MS (ES) $C_{48}H_{54}N_6O_5S$ requires: 826, found: 827 $(M+H)^+$.

N-((12S)-9-(1-(3-mercaptopropyl)-1H-pyrazol-4-yl)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide (**570**)

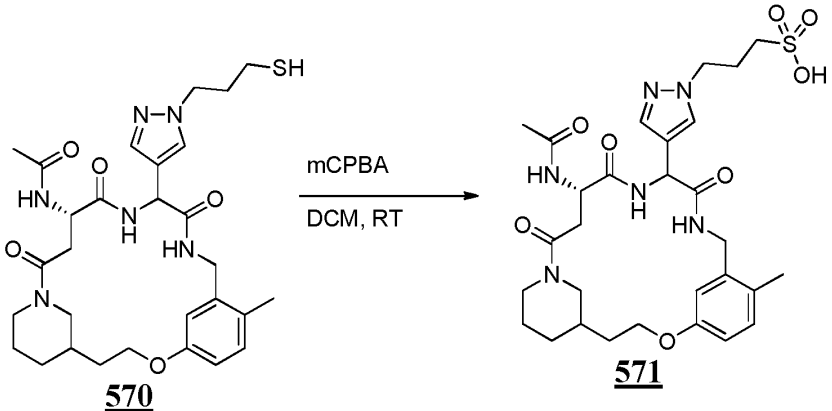


569 570

N-((12S)-5^4-methyl-8,11,14-trioxo-9-(1-(3-(tritylthio)propyl)-1H-pyrazol-4-yl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide (35.2 mg, 0.043 mmol, 1.0 eq.) was dissolved in 25 % TFA/DCM (3 mL) and stirred for 30min at

RT. Removing the solvents under reduced pressure led to the title compound **570** (30 mg, 0.043 mmol, quant.) as TFA salt. MS (ES) $C_{29}H_{40}N_6O_5S$ requires: 584, found: 585 $(M+H)^+$.

3-(4-((12S)-12-acetamido-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-9-yl)-1H-pyrazol-1-yl)propane-1-sulfonic acid (**571**)

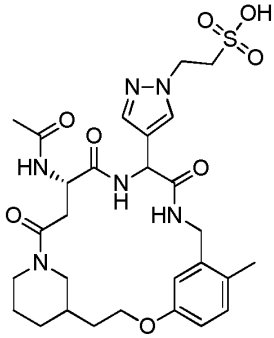


570 **571**

N-((12S)-9-(1-(3-mercaptopropyl)-1H-pyrazol-4-yl)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide **570** (25 mg, 0.043 mmol, 1.0 eq.) was dissolved in DCM (5 mL) and 3-chlorobenzoperoxoic acid (45 mg, 0.26 mmol, 6.0 eq.) was added to the solution at 0°C and the reaction mixture was stirred for 12h at RT. Drops of H_2O were added to the reaction and the solvents were removed in vacuo.

The crude product was purified by reversed-phase RP-HPLC (column: C18), using H_2O (0.1 %TFA) and ACN (0.1 %TFA) as eluents. The desired fractions were lyophilized to yield the title compound **571** (7 mg, 0.009 mmol, 22%) as a yellowish solid (TFA salt). MS (ES) $C_{29}H_{40}N_6O_8S$ requires: 632, found: 633 $(M+H)^+$.

N-(4-((12S)-12-acetamido-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-9-yl)-1H-pyrazol-1-yl)ethane-1-sulfonic acid (**572**)



572

Compound 2-(4-((12S)-12-acetamido-5[4]-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-9-yl)-1H-pyrazol-1-yl)ethane-1-sulfonic acid **571** was prepared in analogy to compound **570**. MS (ES) $C_{29}H_{40}N_6O_8S$ requires: 618, found: 619 $(M+H)^+$.

Preparation of macrocyclic compounds 573 - 741

General Methods

^1H NMR spectra were recorded on Bruker 400 MHz and TMS was used as an internal standard.

LCMS was taken on a quadrupole Mass Spectrometer on Shimadzu LCMS 2010 (Shim-pack XR-ODS 3.0*30 mm 2.2 µm) operating in ES (+) ionization mode. Flow Rate: 0.8 mL/min, Acquire Time: 3 min, Wavelength: UV220, Oven Temp.: 50°C.

Prep-HPLC was performed at conditions: Column: YMC Triart (30*150mm*7um); Wavelength 220 nm; Mobile phase A: water ($NH_3H_2O+NH_4HCO_3$); B acetonitrile; Flow rate: 25 mL /min; Injection volume: 2 mL; Run time: 10 min; Equilibration: 9.0 min.

General Methods

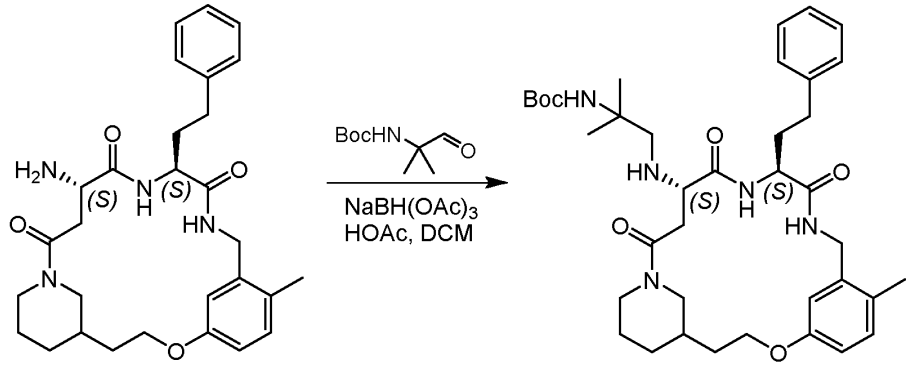
^1H NMR spectra were recorded on Bruker 400 MHz and TMS was used as an internal standard.

LCMS was taken on a quadrupole Mass Spectrometer on Shimadzu LCMS 2010 (Shim-pack XR-ODS 3.0*30 mm 2.2 µm) operating in ES (+) ionization mode. Flow Rate: 0.8 mL/min, Acquire Time: 3 min, Wavelength: UV220, Oven Temp.: 50°C.

Prep-HPLC was performed at conditions: Column: YMC Triart (30*150mm*7um); Wavelength 220 nm; Mobile phase A: water ($NH_3H_2O+NH_4HCO_3$); B acetonitrile; Flow rate: 25 mL /min; Injection volume: 2 mL; Run time: 10 min; Equilibration: 9.0 min.

Example A-41 : Preparation of macrocyclic compound 733

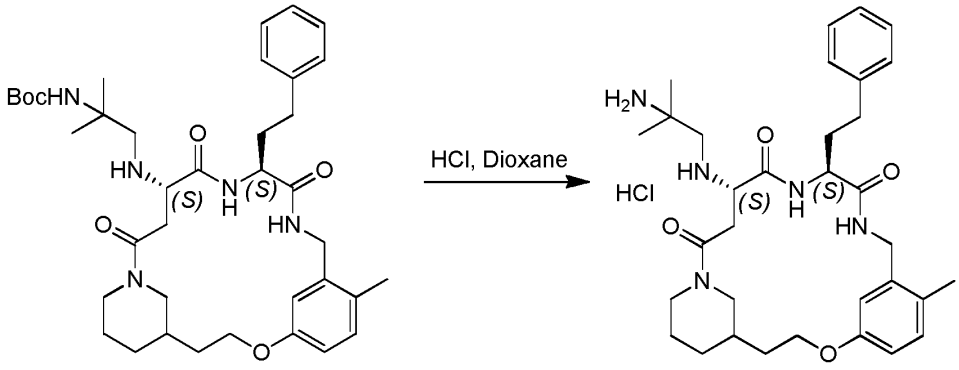
1. Preparation of compound **A41-2**:



8 **A41-2**

To a solution of **8** (300 mg, 0.552 mmol, 1 *eq*, HCl) in DCM (18 mL) was added DIEA (142.78 mg, 1.10 mmol, 0.192 mL, 2 *eq*), tert-butyl N-(1,1-dimethyl-2-oxo-ethyl)carbamate (310.28 mg, 1.66 mmol, 3 *eq*) and AcOH (66.34 mg, 1.10 mmol, 0.063 mL, 2 *eq*) , the reaction was stirred at 20 °C for 2 hr to give a white mixture. Then added $NaBH(OAc)_3$ (234.15 mg, 1.10 mmol, 2 *eq*) to the mixture and it was stirred at 20 °C for 17 hr to give a white mixture. LCMS showed a desired mass. The reaction mixture was diluted with H_2O (50 mL) and extracted with EA (40 mL x 2). The combined organic layers were washed with brine (80 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The **A41-2** (900 mg, crude) as yellow oil was used to the next step without purification.

2. Preparation of compound **A41-3**:

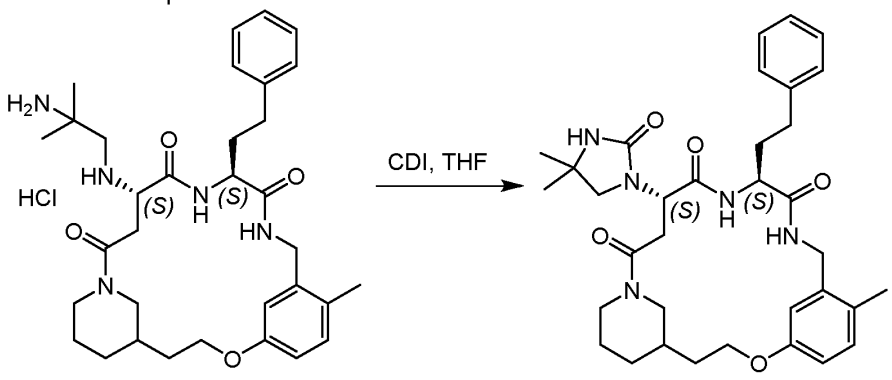


A41-2 **A41-3**

To a solution of **A41-2** (900 mg, 1.33 mmol, 1 *eq*) in dioxane (5 mL) was added HCl/Dioxane (4 M, 3.32 mL, 10 *eq*). The mixture was stirred at 20 °C for 1 hr to give a light yellow solution. LCMS showed **A41-2** was remained. Added 3 mL HCl/dioxane to the reaction and it was stirred for 1 hr to give a light yellow solution. LCMS showed **A41-2** was consumed up. The reaction solution

was concentrated under reduced pressure to give a residue. The **A41-3** (800 mg, 1.30 mmol, 98.10% yield, HCl) as yellow gum was used to the next step without purification.

3. Preparation of compound**733**:



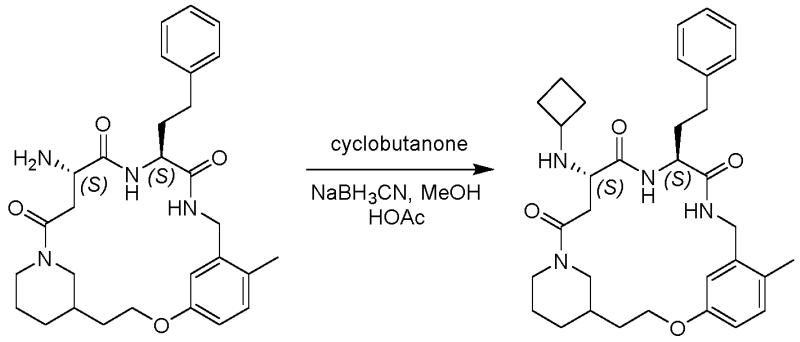
A41-3 **733**

To a solution of **A41-3** (700 mg, 1.14 mmol, 1 *eq*, HCl) in THF (15 mL) was added CDI (1.11 g, 6.84 mmol, 6 *eq*). The mixture was stirred at 70 °C for 6 hr to give a yellow solution. LCMS showed **A41-3** was consumed up. The reaction mixture was diluted with H_2O (50 mL) and extracted with EA (40 mL x 3). The combined organic layers were washed with brine (80 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (basic condition, column: YMC Triart 30*150mm*7um; mobile phase: [water (NH_3H_2O+NH_4HCO_3)-ACN]; B%: 43%-63%, 9 min) to give **733** (154.1 mg, 0.255 mmol, 22.40% yield) as white solid.

^{1}H NMR (DMSO-d_6, 400MHz): δ = 7.59-8.55 (m, 2H), 7.08-7.34 (m, 5H), 6.83-7.06 (m, 2H), 6.55 (br s, 1H), 6.42-6.77 (m, 1H), 4.47-4.74 (m, 2H), 3.60-4.44 (m, 7H), 2.79-3.31 (m, 4H), 2.59-2.73 (m, 2H), 2.29-2.47 (m, 1H), 2.07-2.22 (m, 3H), 1.88-2.02 (m, 1H), 1.27-1.81 (m, 7H), 1.10-1.20 (m, 1H), 1.10-1.20 (m, 1H), 1.06-1.23 ppm (m, 6H).

LCMS: 100.00 %, MS (ESI): m/z 604.3 $[M + H]^+$.

Example A-42 : Preparation of macrocyclic compound 717



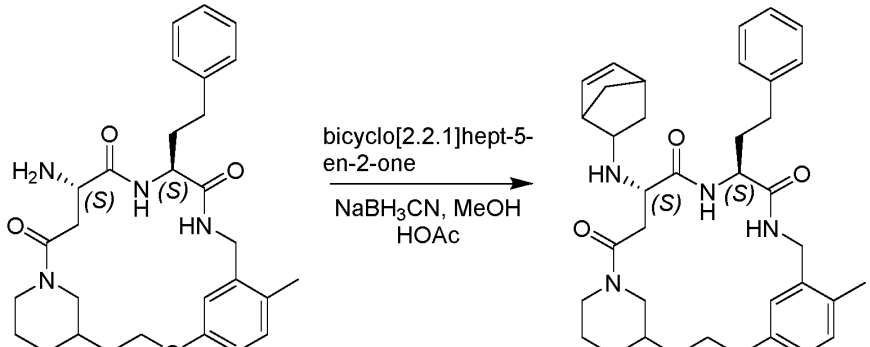
8 717

To a solution of **8** (0.15 g, 0.276 mmol, 1 *eq*, HCl), DIEA (71 mg, 0.552 mmol, 2 *eq*) in DCM (6 mL) was added cyclobutanone (39 mg, 0.552 mmol, 2 *eq*), AcOH (33 mg, 0.552 mmol, 2 *eq*). The reaction was stirred at 20°C for 1.5 h to give a yellow mixture. $NaBH(OAc)_3$ (117 mg, 0.552 mmol, 2 *eq*) was added. The reaction was stirred at 20°C for 17 h to give a yellow mixture. LCMS showed the reaction was completed. The mixture was partitioned between EA (60 mL) and H_2O (40 mL). The organic layer was washed with H_2O (40 mL), brine (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a white powder. The crude product was purified by prep-HPLC(column: 2_Phenomenex Gemini C18 75*40mm*3um;mobile phase: [water(NH_3H_2O+NH_4HCO_3)-ACN];B%: 46%-76%,7.8min). The eluent was lyophilized to give **717** (32.9 mg, 21% yield, 100% purity) as a white powder.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.16-2.36 (m, 20H), 2.58-3.00 (m, 4H), 3.09-3.29 (m, 2H), 3.49-4.76 (m, 8H), 6.60-7.08 (m, 3H), 7.12-7.36 (m, 5H), 7.84-8.43 (m, 2H)

LCMS: 100%, MS (ESI): m/z 561.3 $[M + H]^+$.

Example A-43 : Preparation of macrocyclic compound 711



8 711

To a solution of **8** (0.15 g, 0.276 mmol, 1 *eq*, HCl), DIEA (71 mg, 0.552 mmol, 2 *eq*) in DCM (6 mL) was added bicyclo[2.2.1]hept-5-en-2-one (60 mg, 0.552 mmol, 2 *eq*), AcOH (33 mg, 0.552 mmol, 2 *eq*). The reaction was stirred at 20°C for 1.5 h to

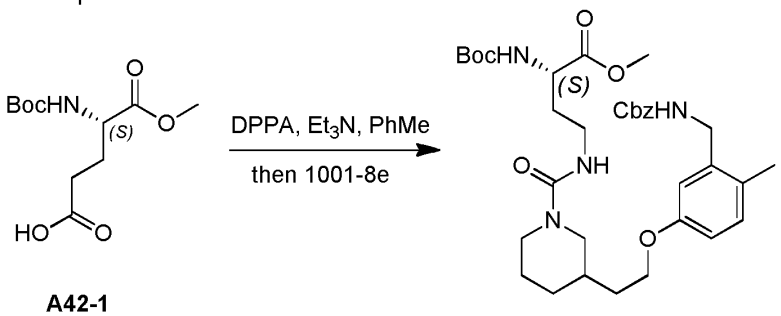
give a yellow mixture. $NaBH(OAc)_3$ (117 mg, 0.552 mmol, 2 *eq*) was added. The reaction was stirred at 20°C for 17 h to give a yellow mixture. LCMS showed the starting material was not consumed completely. $NaBH(OAc)_3$ (117 mg, 0.552 mmol, 2 *eq*) was added. The reaction was stirred at 20°C for 8 h to give a yellow mixture. LCMS showed the starting material was consumed completely. The mixture was partitioned between EA (60 mL) and H_2O (40 mL). The organic layer was washed with H_2O (40 mL), brine (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a white powder. The crude product was triturated with EtOH (2 mL). After filtration, the filter cake was dried under reduced pressure to give a white solid. MeCN (2 mL) and H_2O (2 mL) were added. The mixture was lyophilized to give **711** (78.1 mg, 47% yield) as a white powder.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.96-2.37 (m, 18H), 2.55-3.31 (m, 8H), 3.59-4.81 (m, 8H), 5.78-6.28 (m, 2H), 6.54-7.38 (m, 8H), 7.84-8.65 (m, 2H)

LCMS: 100%, MS (ESI): m/z 599.3 $[M + H]^+$.

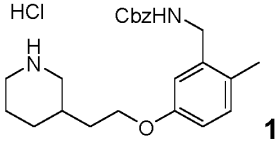
Example A-44 : Preparation of macrocyclic compound 653

1. Preparation of **A42-2**:



A42-1 **A42-2**

To a solution of **A42-1** (0.3 g, 1.15 mmol, 1 *eq*), DPPA (diphenylphosphoryl azide) (443 mg, 1.61 mmol, 1.4 *eq*) in toluene (11 mL) was Et_3N (233 mg, 2.30 mmol, 2 *eq*). The reaction was stirred at 80°C for 1 h to give a colorless solution. **1001-8e** (578 mg, 1.38 mmol, 1.2 *eq*, HCl), Et_3N (233 mg, 2.30 mmol, 2 *eq*) was added.

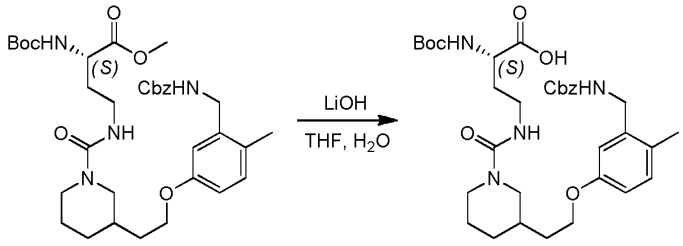


1001-8e

The reaction was stirred at 20°C for 17 h to give a yellow mixture. LCMS showed desired MS was detected. The solution was partitioned between EA (60 mL) and H_2O (20 mL). The organic layer was washed with sat. $NaHCO_3$ (20 mL x 2), brine (20 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give a yellow

oil. The yellow oil was purified by combi flash (EA/PE = 0/1 to 1/1) to give **A42-2** (0.41 g, 55% yield) as yellow oil.

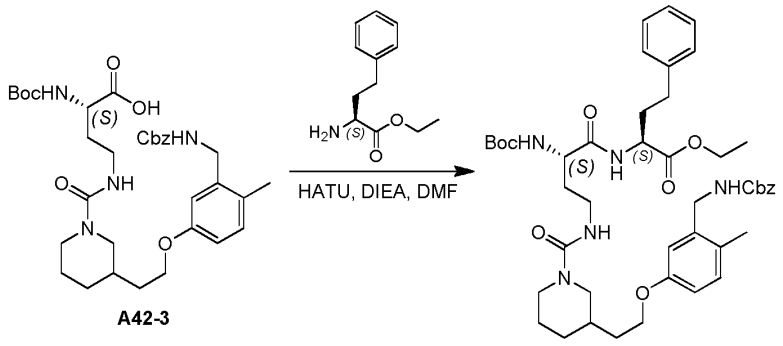
2. Preparation of **A42-3**:



A42-2 **A42-3**

To a solution of **A42-2** (0.41 g, 0.640 mmol, 1 *eq*) in THF (5 mL) was added LiOH.H_2O (31 mg, 0.736 mmol, 1.15 *eq*) in H_2O (1 mL). The reaction was stirred at 20°C for 1 h to give a yellow mixture. LCMS showed the starting material was not consumed completely. A solution of LiOH H_2O (30 mg) in H_2O (1 mL) was added. The reaction was stirred at 20°C for 1 h to give a yellow mixture. LCMS showed the reaction was completed. H_2O (15 mL) was added. Then the aqueous layer was acidified to pH = 4 by addition of 1 M HCl. The aqueous layer was extracted with DCM (20 mL x 2). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give **A42-3** (0.352 g, 88% yield) as yellow gum.

3. Preparation of **A42-4**:

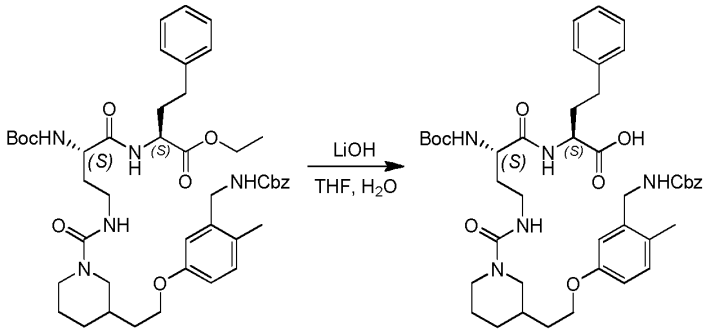


A42-3 **A42-4**

To a solution of ethyl (2S)-2-amino-4-phenyl-butanoate (0.13 g, 0.533 mmol, 1 *eq*, HCl), **A42-3** (351 mg, 0.560 mmol, 1.05 *eq*), DIEA (276 mg, 2.13 mmol, 4 *eq*) in DMF (1 mL) and DCM (4 mL) was added HATU (223 mg, 0.587 mmol, 1.1 *eq*) at 0°C. The reaction was stirred at 0-10°C for 1 h to give a yellow mixture. LCMS showed the reaction was completed. H_2O (10 mL) was added. The mixture was concentrated under reduced pressure to give a residue. The residue was partitioned between EA (60 mL) and H_2O (20 mL). The organic layer was washed with H_2O (20 mL x 2), brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give

yellow oil. The crude product was purified by combi flash (EA/PE = 0/1 to 1/1) to give **A42-4** (0.5 g, 100% yield, 87% purity) as yellow oil.

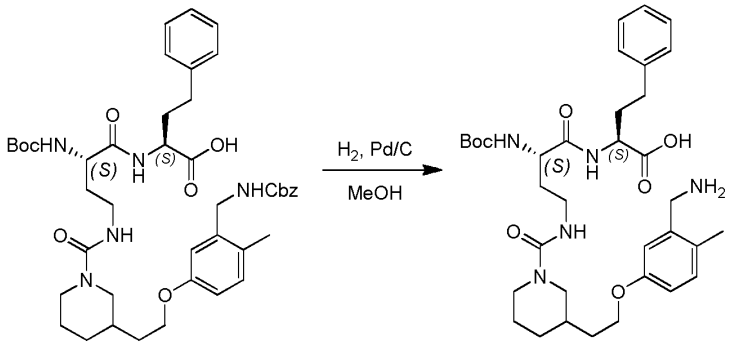
4. Preparation of **A42-5**:



A42-4 **A42-5**

To a solution of **A42-4** (0.5 g, 0.613 mmol, 1 *eq*) in THF (5 mL) was added LiOH.H_2O (30 mg, 0.705 mmol, 1.15 *eq*) in H_2O (1 mL). The reaction was stirred at 20°C for 1 h to give a yellow mixture. LCMS showed the starting material was not consumed completely. A solution of LiOH H_2O (20 mg) in H_2O (1 mL) was added. The reaction was stirred at 20°C for 0.5 h to give a yellow mixture. LCMS showed the reaction was completed. H_2O (15 mL) was added. Then the aqueous layer was acidified to pH = 4 by addition of 1 M HCl. The aqueous layer was extracted with DCM (20 mL x 2). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give **A42-5** (0.42 g, 87% yield) as yellow oil. ,

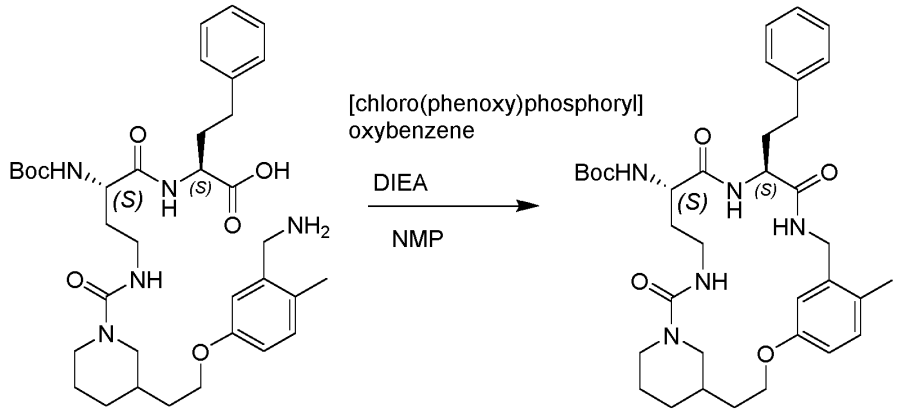
5. Preparation of **A42-6**:



A42-5 **A42-6**

To a solution of **A42-5** (0.42 g, 0.533 mmol, 1 *eq*) in EtOH (6 mL) and DCM (6 mL) was added Pd/C (0.15 g, 10% purity). The reaction suspension was stirred at 20°C under 15 psi of H_2 for 17 h to give a black suspension. LCMS showed the starting material was consumed completely. The reaction mixture was filtered through a pad of celite cake. The filtrate was concentrated in vacuum to give **A42-6** (0.28 g, 80% yield) as white gum.

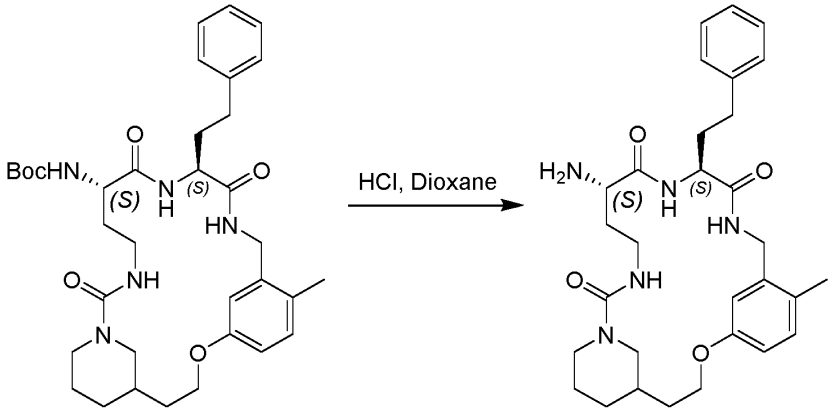
6. Preparation of **A42-7**:



A42-6 **A42-7**

To a solution of ethyl (2E)-2-cyano-2-hydroxyimino-acetate (122 mg, 0.856 mmol, 2 *eq*), 4-methylmorpholine (260 mg, 2.57 mmol, 6 *eq*), [chloro(phenoxy)phosphoryl] oxybenzene (230 mg, 0.857 mmol, 2 *eq*) in NMP (2 mL) and DCM (5 mL) was added **A42-6** (0.28 g, 0.428 mmol, 1 *eq*) and the reaction was stirred at 20°C for 1.5 h to give a yellow solution. LCMS showed the starting material was consumed completely. H_2O (15 mL) was added. The resultant solution was concentrated to remove DCM. The residue was partitioned between EA (80 mL) and H_2O (80 mL). The organic layer was washed with water (80 mL*2), brine (80 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give a yellow oil. The mother liquid was purified by combi flash (EA/PE = 0/1 to 3/1) to give **A42-7** (0.15 g, 44% yield, 80% purity) as white solid.

7. Preparation of **8**:

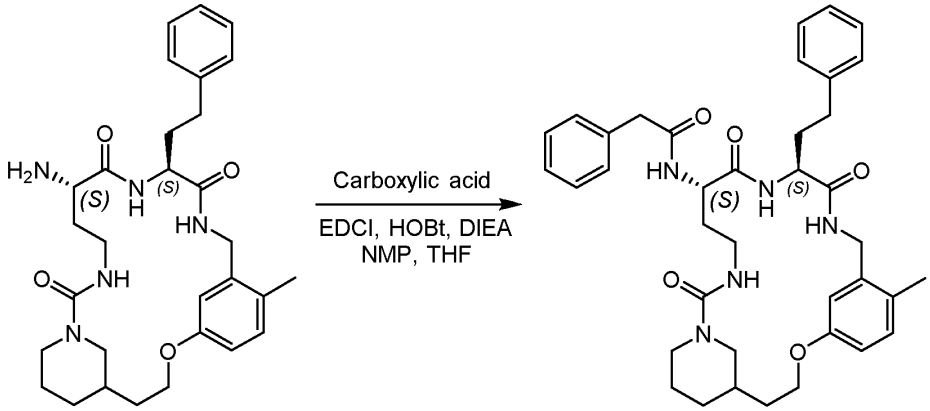


A42-7 **8**

To a solution of **A42-7** (150 mg, 0.236 mmol, 1 *eq*) in dioxane (1 mL) was added HCl/dioxane (4 M, 1.18 mL, 20 *eq*). The reaction was stirred at 20°C for 30 min to give a yellow solution. LCMS showed the starting material was consumed completely.

HCl/dioxane (4 M, 0.5 mL) was added. The reaction was stirred at 20°C for 30 min to give a yellow solution. LCMS showed the starting material was consumed completely. The solution was concentrated under reduced pressure to give **8** (141 mg, crude, HCl) as a white solid.

8. Preparation of **653**:



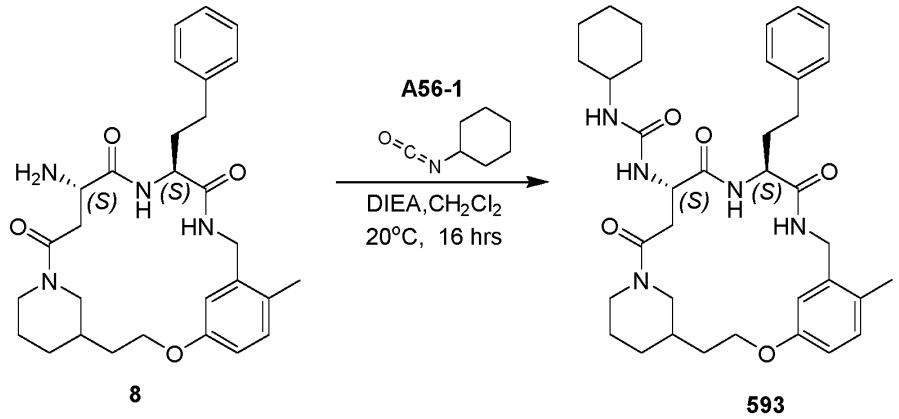
8 **653**

A solution of **8** (0.13 g, 0.227 mmol, 1 *eq*, HCl), 2-phenylacetic acid (40 mg, 0.295 mmol, 1.3 *eq*), 1-hydroxybenzotriazole (43 mg, 0.318 mmol, 1.4 *eq*), DIEA (88 mg, 0.682 mmol, 3 *eq*) in DCM (3 mL) and THF (3 mL) was stirred at 20°C for 15 min to give a yellow mixture. 3-(ethyliminomethyleneamino)-N,N-dimethyl-propan-1-amine;hydrochloride (61 mg, 0.318 mmol, 1.4 *eq*) were added. The reaction was stirred at 20°C for 1 h to give a yellow mixture. LCMS showed the starting material was consumed completely. The solution was partitioned between EA (100 mL) and H_2O (20 mL). The organic layer was washed with 0.2 M HCl (40 mL), sat. $NaHCO_3$ (30 mL, brine (30 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give yellow oil. The yellow oil was purified by prep-HPLC(column: 2_Phenomenex Gemini C18 75*40mm*3um;mobile phase: [water(NH_3H_2O+NH_4HCO_3) -ACN];B%: 50%-80%,7.8min). The eluent was lyophilized to give **653** (99.4 mg, 67% yield, 100 % purity) as a white powder.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.12-2.04 (m, 11H), 2.15 (s, 3H), 2.60-3.24 (m, 5H), 3.52 (s, 2H), 3.57-4.39 (m, 9H), 6.30-7.04 (m, 3H), 7.00 (d, *J*=8 Hz, 1H), 7.09-7.35 (m, 10H), 8.06-8.50 (m, 3H)

LCMS: 100%, MS (ESI): m/z 654.3 $[M + H]^+$.

Example A-45 : Preparation of macrocyclic compound 593



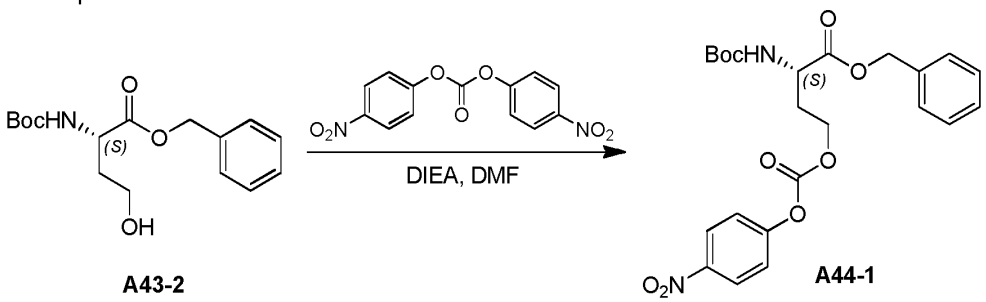
8 **593**

To a solution of **8** (100 mg, 184.13 umol, 1 eq, HCl) in DCM (5 mL) was added DIEA (71.39 mg, 552.39 umol, 96.22 uL, 3 eq) and **A56-1** (34.57 mg, 276.19 umol, 35.28 uL, 1.5 eq). The mixture was stirred at 20°C for 16 hrs to give a yellow solution. The reaction mixture was filtered. The filter cake was washed with DCM (10mL) dired in concentrated. The crude product was by trituration with DCM:EtOAc (5:1, 6ml) to afford **593** (66.13 mg, 104.67 umol, 56.85% yield, 100% purity) as white solid.

^{1}H NMR (400MHz, DMSO-d_6) δ = 8.34 - 7.88 (m, 2H), 7.30 - 7.13 (m, 5H), 7.03 (dd, *J*=3.8, 8.3 Hz, 1H), 6.97 - 6.64 (m, 2H), 6.12 - 5.97 (m, 2H), 4.64 - 3.70 (m, 8H), 3.03 - 2.59 (m, 5H), 2.34 - 2.11 (m, 4H), 2.00 - 0.97 (m, 20H)
LCMS: 100%, MS (ESI): m/z 632.3 $[M + H]^+$.

Example A-46 : Preparation of macrocyclic compound 624

1. Preparation of **A44-1**:

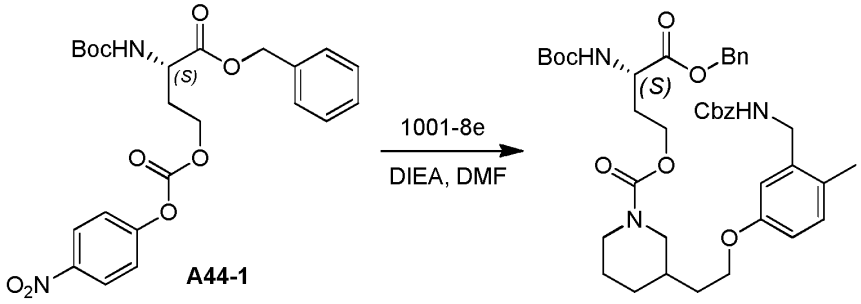


A43-2 **A44-1**

To a solution of **A43-2** (508 mg, 1.64 mmol, 1 *eq*), bis(4-nitrophenyl) carbonate (0.5 g, 1.64 mmol, 1 *eq*) in DMF (8 mL) was added DIEA (637 mg, 4.93 mmol, 3 *eq*). The reaction was stirred at 20°C for 17 h to give a yellow mixture. LCMS showed desired MS value was detected. The mixture was partitioned between EA (60 mL) and H_2O (40 mL). The organic layer was washed with H_2O (40 mL), brine (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give yellow oil. The yellow

oil was purified by combi flash (EA/PE = 0/1 to 1/9) to give **A44-1** (0.72 g, 89% yield, 97% purity) as yellow oil.

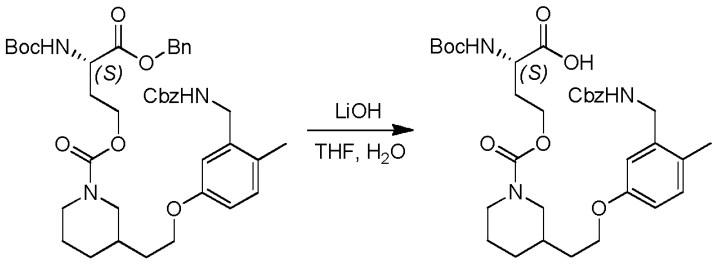
2. Preparation of **A44-2**:



A44-1 A44-2

To a solution of **A44-1** (0.6 g, 1.26 mmol, 1 *eq*), **1001-8e** (657 mg, 1.39 mmol, 1.1 *eq*, oxalic acid) in DMF (12 mL) was added DIEA (490 mg, 3.79 mmol, 3 *eq*). The reaction was stirred at 20°C for 17 h to give a yellow mixture. LCMS showed desired MS value was detected. The mixture was partitioned between EA (100 mL) and H_2O (60 mL). The organic layer was washed with H_2O (60 mL), brine (60 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give yellow oil. The yellow oil was purified by combi flash (EA/PE = 0/1 to 1/3) to give **A44-2** (0.88 g, 94% yield, 97% purity) as colorless oil.

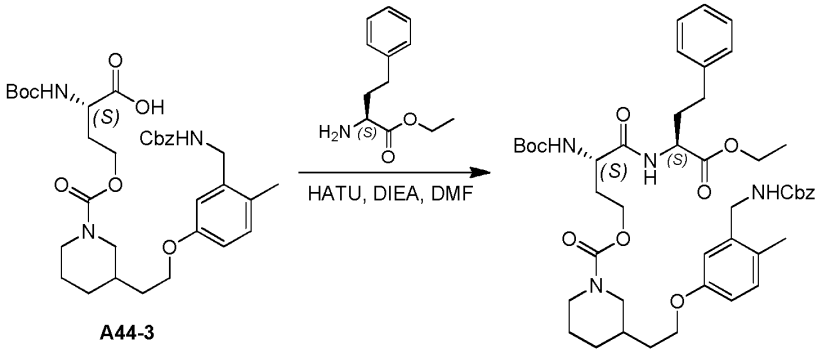
3. Preparation of **A44-3**:



A44-2 A44-3

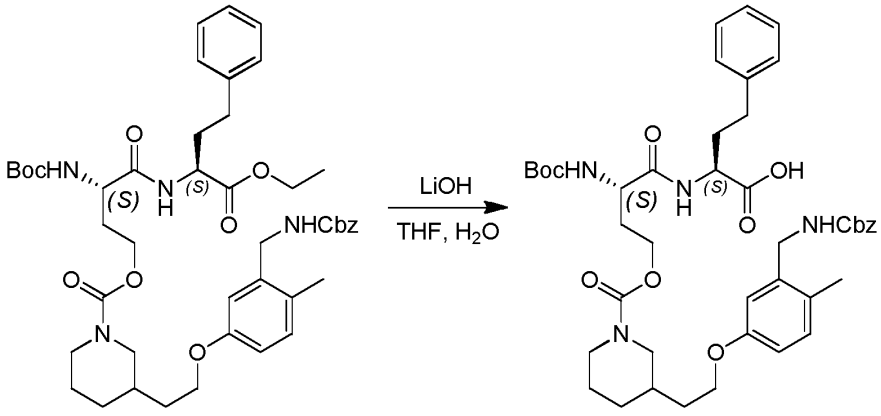
To a solution of **A44-2** (0.88 g, 1.23 mmol, 1 *eq*) in THF (10 mL) was added LiOH.H_2O (59 mg, 1.41 mmol, 1.15 *eq*) in H_2O (2 mL). The reaction was stirred at 20°C for 2.5 h to give a yellow mixture. LCMS showed the reaction was completed. H_2O (15 mL) was added. Then the aqueous layer was acidified to pH = 4 by addition of 1 M HCl. The aqueous layer was extracted with EA (40 mL x 2). The combined organic layer was washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give **A44-3** (0.8 g, crude) as yellow oil.

4. Preparation of **A44-4**:



To a solution of ethyl (2S)-2-amino-4-phenyl-butanoate (0.38 g, 1.56 mmol, 1 *eq*, HCl), **A44-3** (1.03 g, 1.64 mmol, 1.05 *eq*), DIEA (806 mg, 6.24 mmol, 4 *eq*) in DMF (4 mL) and DCM (16 mL) was added HATU (652 mg, 1.72 mmol, 1.1 *eq*) at 0°C. The reaction was stirred at 0-10°C for 1 h to give a yellow mixture. LCMS showed the reaction was completed. H_2O (10 mL) was added. The mixture was concentrated under reduced pressure to give a residue. The residue was partitioned between EA (60 mL) and H_2O (20 mL). The organic layer was washed with H_2O (20 mL x 2), brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give yellow oil. The crude product was purified by combi flash (EA/PE = 0/1 to 2/5) to give **A44-4** (1.16 g, 91% yield) as colorless oil.

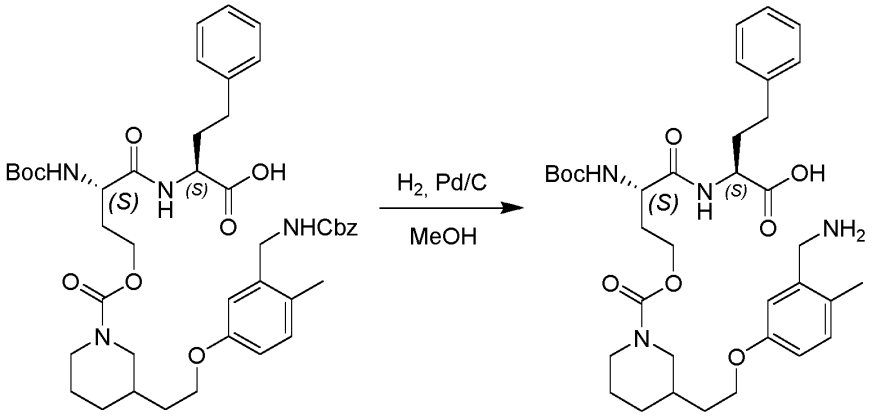
5. Preparation of **A44-5**:



To a solution of **A44-4** (1.16 g, 1.42 mmol, 1 *eq*) in THF (12 mL) was added $LiOH.H_2O$ (68 mg, 1.63 mmol, 1.15 *eq*) in H_2O (3 mL). The reaction was stirred at 20°C for 3 h to give a yellow mixture. LCMS showed the starting material was not consumed completely. A solution of LiOH H_2O (30 mg) in H_2O (1 mL) was added. The reaction was stirred at 20°C for 1 h to give a yellow mixture. LCMS showed the reaction was

completed. H_2O (15 mL) was added. Then the aqueous layer was acidified to pH = 4 by addition of 1 M HCl. The aqueous layer was extracted with EA (30 mL x 2). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give **A44-5** (1.14 g, crude) as yellow oil.

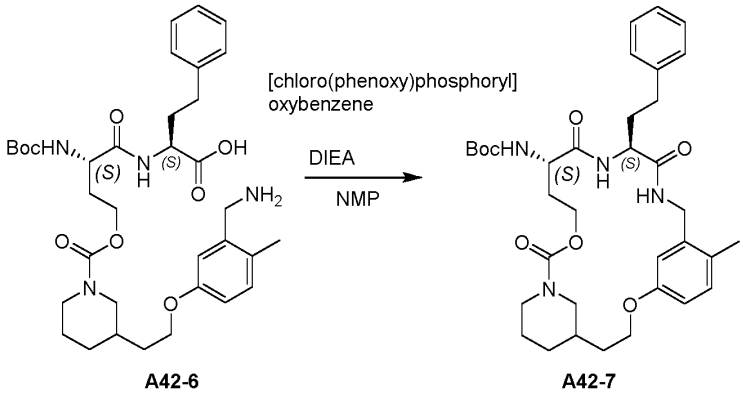
6. Preparation of **A42-6**:



A44-5 **A42-6**

To a solution of **A44-5** (1.12 g, 1.42 mmol, 1 *eq*) in EtOH (20 mL) and DCM (20 mL) was added Pd/C (0.4 g, 10% purity). The reaction suspension was stirred at 20°C under 15 psi of H_2 for 17 h to give a black suspension. LCMS showed the starting material was consumed completely. The reaction mixture was filtered through a pad of celite cake. The filtrate was concentrated in vacuum to give **A42-6** (0.91 g, 97% yield) as white gum.

7. Preparation of **A42-7**:

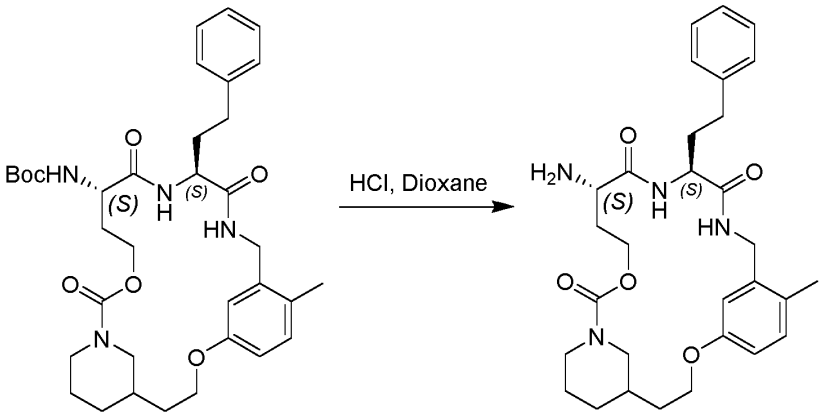


A42-6 **A42-7**

To a solution of ethyl (2E)-2-cyano-2-hydroxyimino-acetate (395 mg, 2.78 mmol, 2 *eq*), 4-methylmorpholine (843 mg, 8.34 mmol, 6 *eq*), [chloro(phenoxy)phosphoryl]oxybenzene (747 mg, 2.78 mmol, 2 *eq*) in NMP (4 mL) and DCM (12 mL) was added **A42-6** (910 mg, 1.39 mmol, 1 *eq*) and the reaction was stirred at 20°C for 1.5 h to give a yellow solution. LCMS showed the starting

material was consumed completely. H_2O (15 mL) was added. The resultant solution was concentrated to remove DCM. The residue was partitioned between EA (80 mL) and H_2O (80 mL). The organic layer was washed with water (80 mL*2), brine (80 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give a yellow oil. The mother liquid was purified by combi flash (EA/PE = 0/1 to 2/3) to give **A42-7** (230 mg, 23% yield, 89% purity) as white solid.

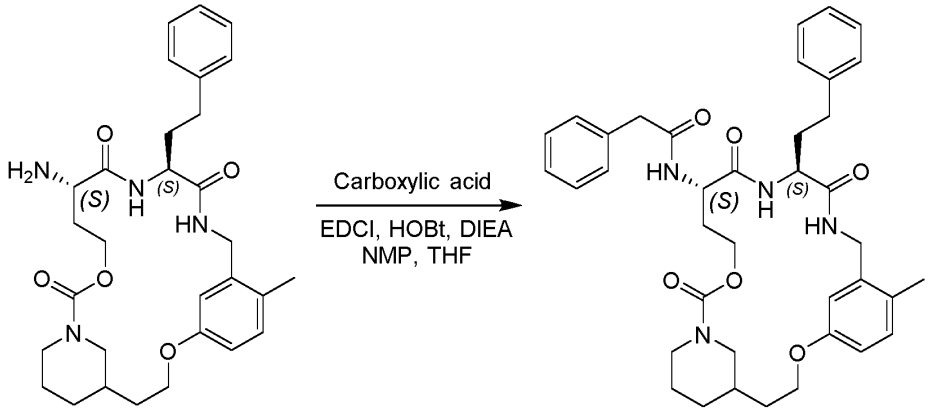
8. Preparation of compound **8**:



A42-7 **8**

To a solution of **A42-7** (230 mg, 0.361 mmol, 1 *eq*) in dioxane (1 mL) was added HCl/dioxane (4 M, 1.81 mL, 20 *eq*). The reaction was stirred at 20°C for 1 h to give a yellow solution. LCMS showed the starting material was consumed completely. The solution was concentrated under reduced pressure to give **8** (0.2 g, 96% yield, HCl) as a white solid.

9. Preparation of compound **624**:



8 **624**

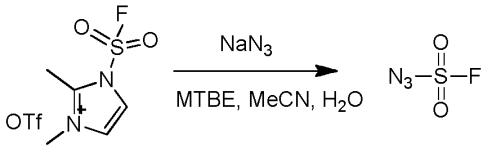
A solution of **8** (100 mg, 0.174 mmol, 1 *eq*, HCl), 2-phenylacetic acid (31 mg, 0.227 mmol, 1.3 *eq*), 1-hydroxybenzotriazole (33 mg, 0.244 mmol, 1.4 *eq*), DIEA (68 mg, 0.523 mmol, 3 *eq*) in DCM (3 mL) and THF (3 mL) was stirred at 20°C for 15 min to give a yellow mixture. 3-(ethyliminomethyleneamino)-N,N-dimethyl-propan-1-amine;hydrochloride (47 mg, 0.244 mmol, 1.4 *eq*) were added. The reaction was stirred at 20°C for 1 h to give a yellow mixture. LCMS showed the starting material was consumed completely. The solution was partitioned between EA (60 mL) and H_2O (20 mL). The organic layer was washed with 0.2 M HCl (40 mL), sat. $NaHCO_3$ (30 mL), brine (30 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give yellow oil. The yellow oil was purified by prep-HPLC (column: 2_Phenomenex Gemini C18 75*40mm*3um;mobile phase: [water(NH_3H_2O+NH_4HCO_3)-ACN];B%: 52%-82%,7.8min). The eluent was lyophilized to give **624** (65.9 mg, 57% yield, 100% purity) as a white powder.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.12-2.09 (m, 11H), 2.16 (s, 3H), 2.56-3.05 (m, 4H), 3.49-4.44 (m, 12H), 6.58-7.09 (m, 3H), 7.09-7.39 (m, 10H), 7.89-8.58 (m, 3H)

LCMS: 100%, MS (ESI): m/z 655.3 $[M + H]^+$.

Example A-47 : Preparation of macrocyclic compound 740

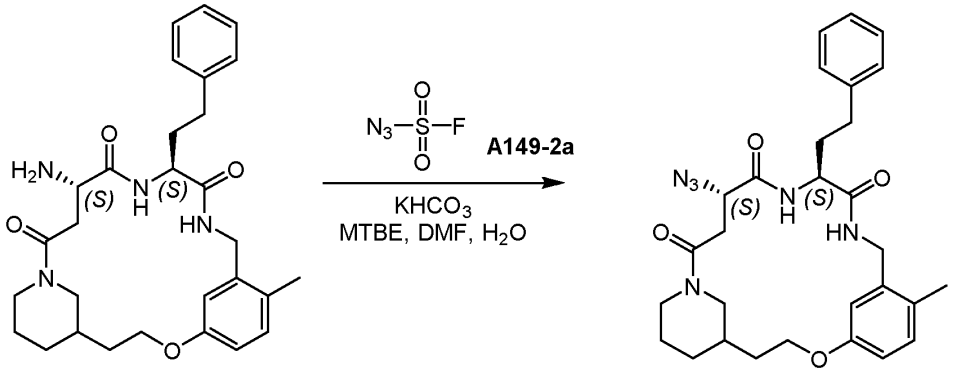
1. Preparation of **A149-2a**:



A149-1a **A149-2a**

To a mixture of NaN_3 (103.97 mg, 1.60 mmol, 1.05 eq) in H_2O (4 mL) and MTBE (4 mL) was added **A149-1a** (500 mg, 1.52 mmol, 1 eq) in MeCN (0.5 mL) at 0°C, and then the resulting mixture was stirred at 0-5°C for 30 min to give a colorless mixture. The mixture was partitioned between MTBE (4 mL) and water (4 mL). The organic layer was monitored by ^{19}F-NMR. Obtained **A149-2a** (180 mg, crude) in MTBE (4 mL), which was used directly.

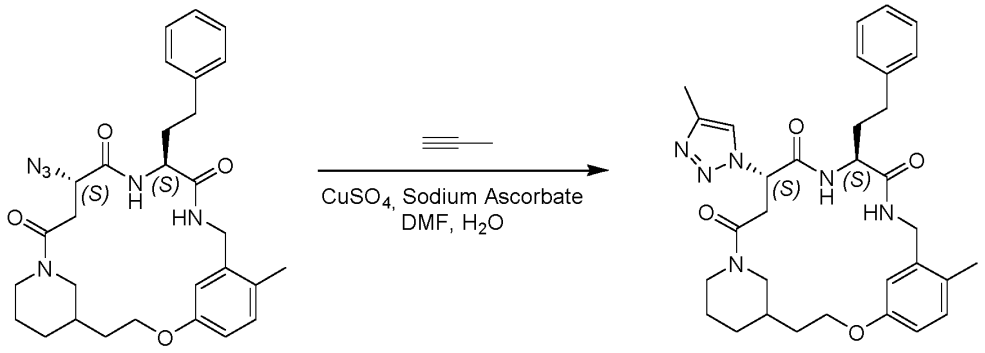
2. Preparation of **A149-1**:



8 A149-1

To a mixture of **8** (150 mg, 0.296 mmol, 1 eq) and **A149-2a** in MTBE (4 mL) and DMF (1 mL) was added $KHCO_3$ (59.28 mg, 0.592 mmol, 2 eq) in H_2O (1 mL). The resulting mixture was stirred at 20-25°C for 20 h to give a colorless mixture. TLC showed the reaction was completed. The mixture was diluted with H_2O (20 mL), extracted with EA (20 mLx2), washed with water (20 mLx3). The combined organic layer was concentrated to dryness. The residue was purified by flash column (THF/PE=40-60%, SiO_2) to afford **A149-1** (50 mg, 0.093 mmol, 31.71% yield) as a white solid.

3. Preparation of compound **740**:



A149-1 740

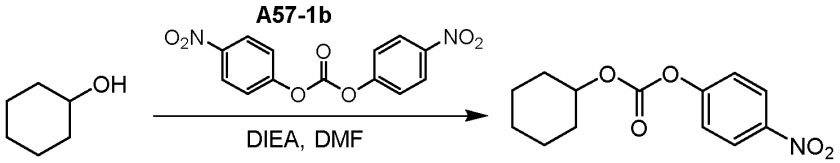
A mixture of **A149-1** (50 mg, 0.65 mmol, 1 eq), prop-1-yne (1 M, 0.394 mL, 6 eq), $CuSO_4$ (2.10 mg, 0.013 mmol, 0.002 mL, 0.2 eq) and Sodium Ascorbate (6.51 mg, 0.032 mmol, 0.5 eq) in DMF (0.5 mL) and H_2O (0.3 mL) was stirred at 45°C for 2 h under N_2 to give a yellow mixture. TLC showed new spot. The mixture was added 10 mL EA, filtered by a pad of celite. Then the mixture was diluted with H_2O (10 mL), extracted with EA (10 mLx2), washed with water (10 mLx2). The combined organic layer was concentrated to dryness. The residue was purified by flash column (EA in PE = 40-100%, SiO_2) to afford **740** (15.1 mg, 0.026 mmol, 40.12% yield) as a white powder.

^1H NMR (400 MHz, DMSO-d_6): δ= 8.93-8.94 (m, 1H), 7.89-8.45 (m, 2H), 7.19-7.30 (m, 3H), 6.98-7.13 (m, 1H), 6.82-6.93 (m, 1H), 6.65-6.80 (m, 1H), 5.50-5.80 (m, 1H), 4.17-

4.26 (m, 6H), 3.50-3.90 (m, 2H), 2.60-3.30 (m, 4H), 1.76-2.20 (m, 12H), 1.23-1.75 (m, 6H).
HPLC: 96.67%, MS (ESI): m/z 573.3 $[M + H]^+$.

Example A-48 : Preparation of macrocyclic compound 632

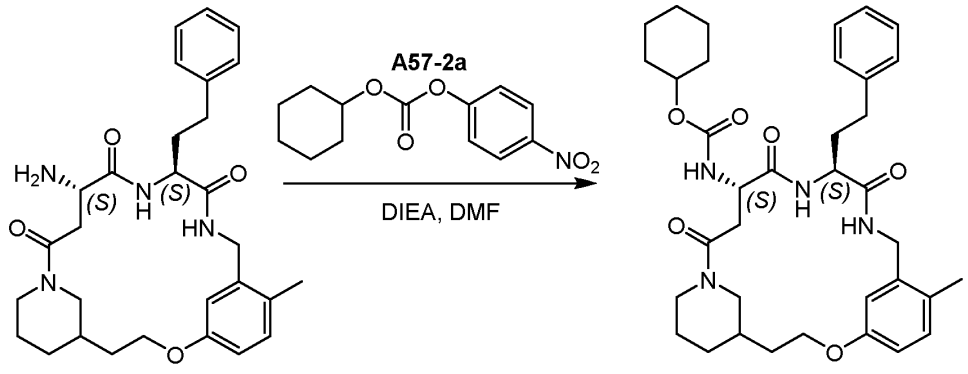
1. Preparation of **A57-2a**:



A57-1a **A57-2a**

To a solution of **A57-1a** (127 mg, 1.27 mmol, 132.29 uL, 1 eq) and **A57-1b** (1.16 g, 3.80 mmol, 3eq.) in DMF (3 mL) was added DIEA (491.64 mg, 3.80 mmol, 662.58 uL, 3 eq). The mixture was stirred at 25°C for 3h. The solution was partitioned between EA (20 mL) and H_2O (10 mL). The organic layer was washed with H_2O (10 mL x 3), brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by column chromatography (SiO_2, PE/EA =80/20) to afford (306 mg, 1.15 mmol, 90.98% yield) as yellow solid.

2. Preparation of compound **632**:



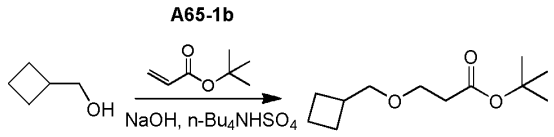
8 **632**

To a solution of **A57-2a** (306 mg, 1.15 mmol, 1 eq) and **8** (584.44 mg, 1.15 mmol, 1 eq) in DMF (5 mL) was added DIEA (447.28 mg, 3.46 mmol, 602.80 uL, 3 eq). The mixture was stirred at 25°C for 3h as colorless solution. The solution was partitioned between EA (20 mL) and H_2O (10 mL). The organic layer was washed with H_2O (10 mL x 3), brine (1 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by pre-HPLC (column: ACE 5 C18-AR

150*30mm*5μm; mobile phase: [water (HCl)-ACN]; B%: 55%-85%, 8min) to afford **632** (318 mg, 502.54 umol, 43.56% yield) as white solid.
1H NMR (400 MHz, DMSO-d6) δ = 8.46 - 7.77 (m, 2H), 7.52 - 7.10 (m, 6H), 7.03 - 6.58 (m, 3H), 4.57 - 3.79 (m, 9H), 2.80 - 2.53 (m, 5H), 2.20 - 2.13 (m, 3H), 1.99 - 1.11 (m, 20H)
LCMS: 96.1%, MS (ESI): m/z 633.7 $[M+H]^+$

Example A-49 : Preparation of macrocyclic compound 628

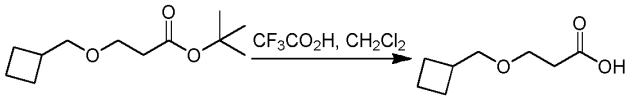
1. Preparation of **A69-2a**:



A69-1a **A69-2a**

To a solution of **A65-1b** (1.34 g, 10.45 mmol, 1.52 mL, 3 *eq*), NaOH (5 M, 696.61 uL, 1 *eq*) n-BuNHSO$_4$ (295.65 mg, 870.76 umol, 0.25 *eq*) in DCM (3 mL) was added **A69-1a** (300 mg,
3.48 mmol, 0.328 mL, 1 *eq*) at 0ºC , the resulting mixture was stirred at 20ºC for 14 hours to give white solution. The reaction mixture was poured into water (5 mL) and extracted with EtOAc (5 mL x 4). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column (SiO_2, PE to 10% EtOAc in PE) to afford **A69-2a** (500 mg, 2.33 mmol, 66.99% yield) was obtained as white oil.

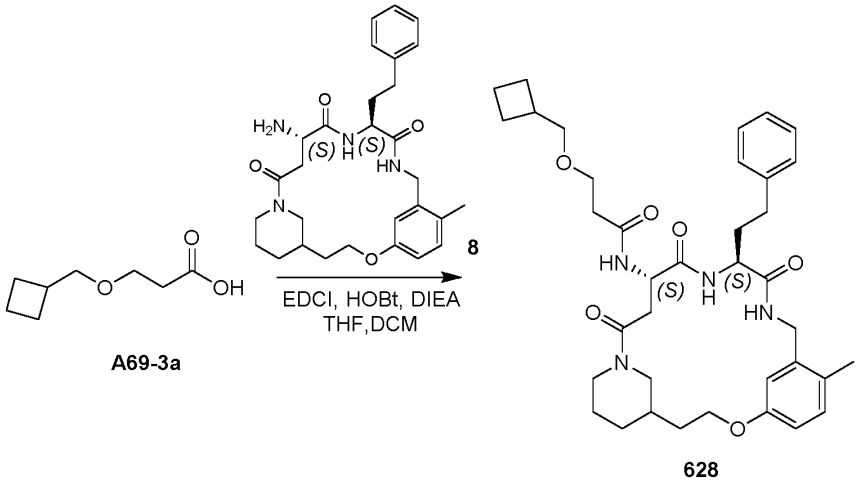
2. Preparation of **A69-3a**:



A69-2a **A69-3a**

To a solution of **A69-2a** (500 mg, 2.33 mmol, 1 *eq*) in DCM (3 mL) was added CF_3COOH CF_3COOH (1.54 g, 13.51 mmol, 1 mL, 5.79 *eq*) at 0ºC, the resulting mixture was stirred at 20ºC for 4 hours to give white solution. The reaction mixture was concentrated directly to afford **A69-3a** (360 mg, crude) was obtained as yellow oil.

3, Preparation of compound **628**:



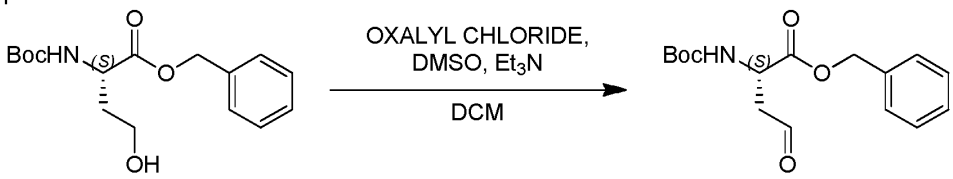
To a solution of **8** (130 mg, 0.239 mmol, 1 *eq*, HCl), **A69-3a** (49.23 mg, 0.311 mmol, 1.3 *eq*), HOBt (45.28 mg, 0.335 mmol, 1.4 *eq*), DIEA (92.81 mg, 0.718 mmol, 0.125 mL, 3 *eq*) in THF (2 mL) and DCM (2 mL) was stirred at 20ºC for 15 min to give a yellow mixture. Then EDCI (64.24 mg, 0.335 mmol, 1.4 *eq*) were added. The reaction was stirred at 20°C for 1 h to give a yellow mixture. The reaction mixture was poured into water (10 mL) and extracted with EtOAc (10 mL x 4). The organic layer was washed with 0.2 M HCl (20 mL), sat.$NaHCO_3$ (30 mL), brine (30 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give yellow oil. The residue was purified by prep-HPLC (basic, column: 2_Phenomenex Gemini C18 75*40mm*3um; mobile phase: [water (NH_3H_2O+NH_4HCO_3)-ACN]; B%: 54%-84%, 7.8min). The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to afford **628** (53.09 mg, 0.082 mmol, 34.29% yield, 100% purity) was obtained as white solid.

^{1}H NMR (400MHz, DMSO-d_6) δ = 8.40 - 7.77 (m, 3H), 7.29 - 6.63 (m, 9H), 4.75 - 3.49 (m, 11H), 3.04 - 2.54 (m, 6H), 2.41 - 2.28 (m, 3H), 2.20 - 2.11 (m, 4H), 2.00 - 1.15 (m, 16H)

LCMS: 100%, Time t1=4.151 min, MS (ESI): m/z 647.3 $[M + H]^+$.

Example A-50 : Preparation of macrocyclic compound 739

1. Preparation of **A61-2a**:

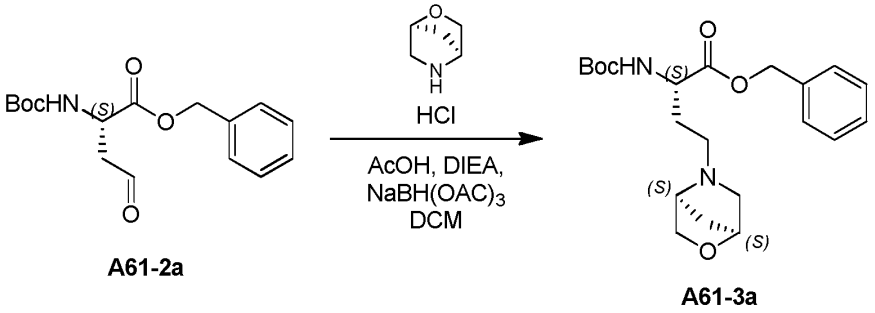


To a solution of oxalyl chloride (923.15 mg, 7.27 mmol, 636.66 uL, 1.5 eq) in DCM (15 mL) at -78 °C was added DMSO (947.13 mg, 12.12 mmol, 947.13 uL, 2.5 eq) in DCM (5 mL). After 20 min, **A61-1a** (1.5 g, 4.85 mmol, 1 eq) in DCM (5 mL) was added and the

reaction stirred for 45 min at -78 °C. Then Et_3N (2.45 g, 24.24 mmol, 3.37 mL, 5 eq) was added and the mixture was stirred at 25 °C for 1 h. LCMS showed a desired mass. The reaction mixture was diluted with $NaHCO_3$ (60 mL), and extracted with EA (70 mL x 2). The organic layer was washed with H_2O (50 mL x 2), brine (60 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give **A61-2a** (1.39 g, crude) as yellow oil.

LCMS: 72.57%, MS (ESI): m/z 252.0 $[M - 56 + H]^+$.

2. Preparation of **A61-3a**:

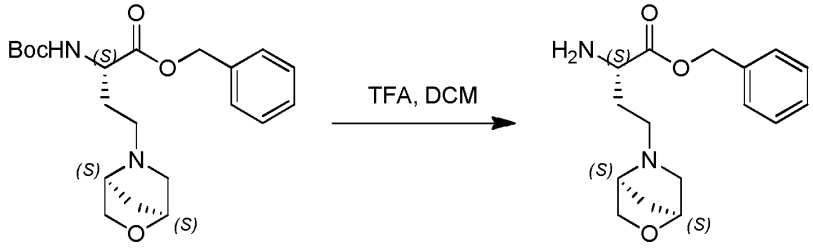


A61-2a **A61-3a**

To a solution of **A61-2a** (500 mg, 1.63 mmol, 1 eq) and DIEA (420.52 mg, 3.25 mmol, 0.566 mL, 2 eq) in DCM (15 mL) was added (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane;hydrochloride (441.18 mg, 3.25 mmol, 2 eq) and AcOH (195.39 mg, 3.25 mmol, 0.186 mL, 2 eq) . The reaction stirred at 25 °C for 1.5 h. Then $NaBH(OAc)_3$ (689.60 mg, 3.25 mmol, 2 eq) was added and the mixture was stirred at 25 °C for 17 h. LCMS showed a desired mass. The reaction mixture was diluted with H_2O (10 mL) and extracted with EA (20 mL x 2). The organic later was washed with H2O (20 mL x 2), brine (20 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give **A61-3a** (690 mg, crude) as colorless oil.

LCMS: 80.19%, MS (ESI): m/z 391.1 $[M + H]^+$.

3. Preparation of **A61-4a**:

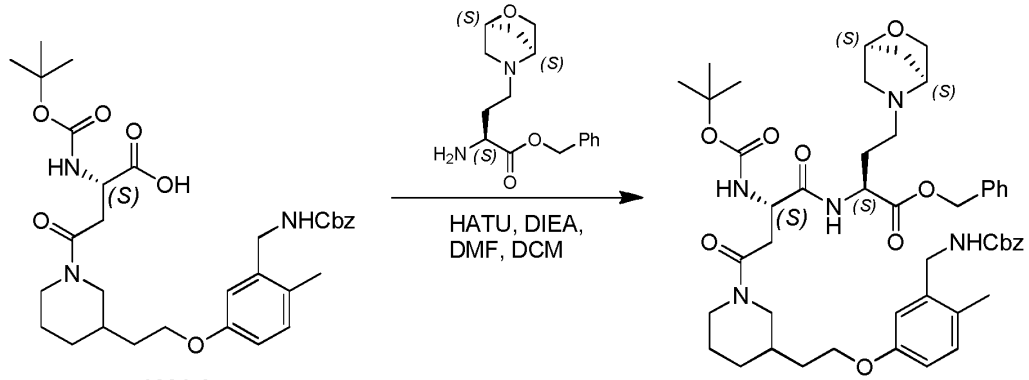


A61-3a **A61-4a**

To a solution of **A61-3a** (640 mg, 1.64 mmol, 1 eq) in DCM (6 mL) was added TFA (2.46 g, 21.61 mmol, 1.6 mL, 13.18 eq). The reaction was stirred at 20 °C for 2 h to give a

yellow solution. LCMS showed the reaction was completed. The solution was concentrated under reduced pressure to give **A61-4a** (830 mg, crude) as yellow oil.
LCMS: 73.53%, MS (ESI): m/z 291.1 $[M + H]^+$.

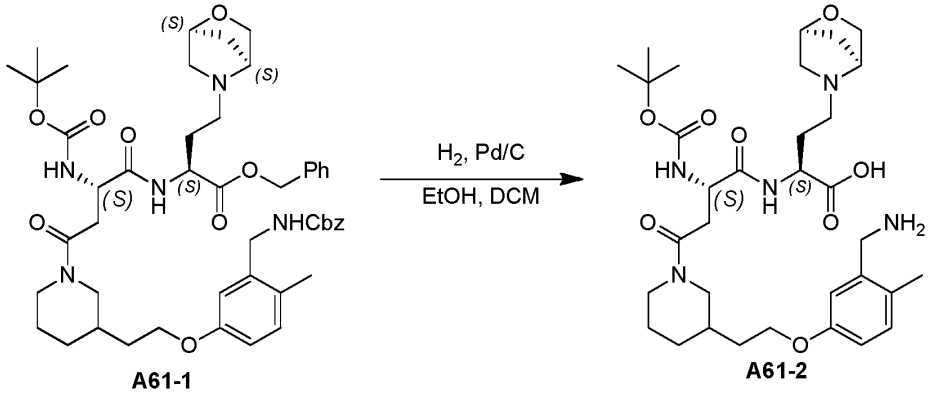
4. Preparation of **A61-1**:



1001-3e **A61-1**

To a solution of **1001-3e** (1 g, 1.67 mmol, 1 eq) and **A61-4a** (763.39 mg, 1.84 mmol, 70% purity, 1.1 eq) in DMF (6 mL) and DCM (8 mL) was added HATU (954.24 mg, 2.51 mmol, 1.5 eq) and DIEA (864.94 mg, 6.69 mmol, 1.17 mL, 4 eq). The mixture was stirred at 20 °C for1 h to give a yellow solution. LCMS showed a desired mass. The reaction mixture was diluted with H_2O (60 mL) and extracted with EA (70 mL x 2). The combined organic layers were washed with H_2O (60 mL x 8) and with brine (60 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by combi flash (SiO2， PE:EA=0% to 65%） to give **A61-1** (670 mg, crude) as colorless oil.
LCMS: 71.88%, MS (ESI): m/z 870.3 $[M + H]^+$.

5. Preparation of **A61-2**:

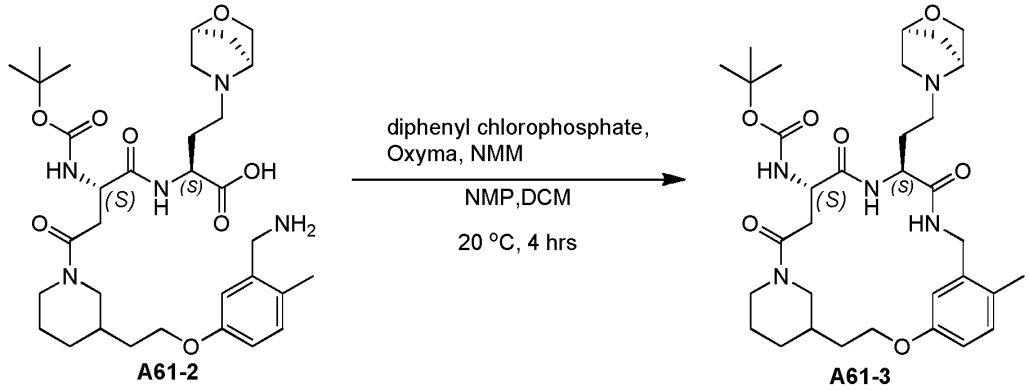


A61-1 **A61-2**

To a solution of **A61-1** (430 mg, 0.494 mmol, 1 eq) in EtOH (4 mL) and DCM (4 mL) was added Pd/C (0.4 g, 10% purity). The reaction suspension was stirred at 20 °C under

15psi of H_2 for 16 h to give a black suspension. LCMS showed the starting material was consumed completely. The reaction mixture was filtered through a pad of celite cake. The filtrate was concentrated in vacuum to give **A61-2** (320 mg, crude) as colorless oil.
LCMS: 69.13%, MS (ESI): m/z 646.4 $[M + H]^+$.

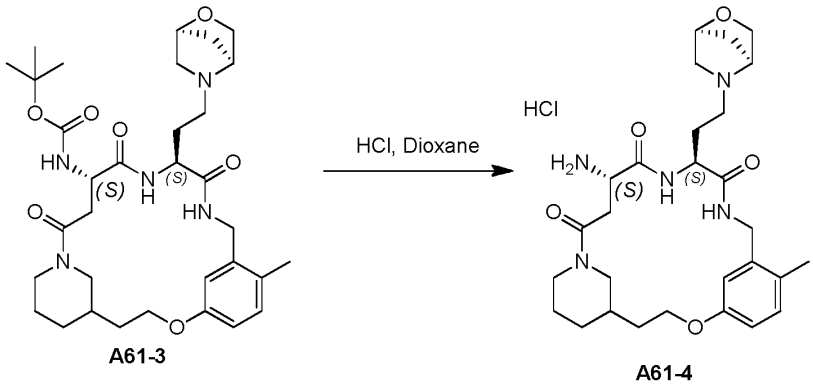
6. Preparation of **A61-3**:



A61-2 **A61-3**

To a solution of ethyl (2E)-2-cyano-2-hydroxyimino-acetate (140.84 mg, 0.991 mmol, 2 eq), 4-methylmorpholine (300.73 mg, 2.97 mmol, 0.326 mL, 6 eq), [chloro(phenoxy)phosphoryl]oxybenzene (266.22 mg, 0.991 mmol, 0.204 mL, 2 eq) in NMP (2 mL) and DCM (5 mL) was added **A61-2** (320 mg, 0.495 mmol, 1 eq) and the reaction was stirred at 20 °C for 1.5 h to give a yellow solution. LCMS showed the starting material was consumed completely. H_2O (20 mL) was added. The resultant solution was concentrated to remove DCM. The residue was partitioned between EA (80 mL) and H_2O (80 mL). The organic layer was washed with water (80 mL x 2) and brine (80 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give a yellow oil. The mother liquid was purified by combi flash (SiO2, MeOH/DCM=0:1 to 1:9) to give **A61-3** (100 mg, crude) as yellow oil.
LCMS: 93.86%, MS (ESI): m/z 628.3 $[M + H]^+$.

7. Preparation of **A61-4**:

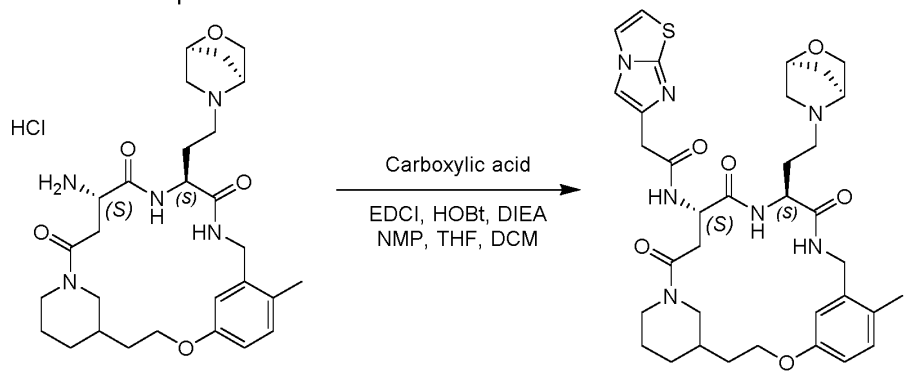


A61-3 **A61-4**

To a solution of **A61-3** (100 mg, 0.159 mmol, 1 eq) in dioxane (2 mL) was added HCl/dioxane (4 M, 2 mL, 50.22 eq). The reaction was stirred at 20 °C for 2 h to give a yellow solution. LCMS showed the reaction was completed. The solution was concentrated under reduced pressure to give **A61-4** (130 mg, crude, HCl) as a yellow solid.

LCMS: 84.18%, MS (ESI): m/z 528.2 $[M + H]^+$.

8. Preparation of compound **739**:



A61-4 **739**

To a solution of **A61-4** (130 mg, 0.230 mmol, 1 eq, HCl), 2-imidazo[2,1-b]thiazol-6-ylacetic acid (54.58 mg, 0.299 mmol, 1.3 eq), 1-hydroxybenzotriazole (43.59 mg, 0.322 mmol, 1.4 eq), DIEA (131.05 mg, 1.01 mmol, 0.176 mL, 4.4 eq) in DCM (3 mL) and THF (3 mL) was stirred at 20 °C for 15 min to give a yellow mixture. EDCI (61.85 mg, 0.322 mmol, 1.4 eq) were added. The reaction was stirred at 20 °C for 1.5 h to give a yellow mixture. LCMS showed the starting material was consumed completely. The solution was partitioned between EA (100 mL) and H_2O (20 mL). The organic layer was washed with 0.2 M HCl (20 mL), sat. $NaHCO_3$ (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give yellow oil. The residue was purified by prep-HPLC (HCl).

Prep-HPLC was performed at conditions: Column: Phenomenex Gemini 21.2*100*5um); Wavelength 220 nm; Mobile phase A: water (10 mM TFA); B acetonitrile; Flow rate: 25 mL /min; Injection volume: 2 mL; Run time: 10 min; Equilibration: 3 min.

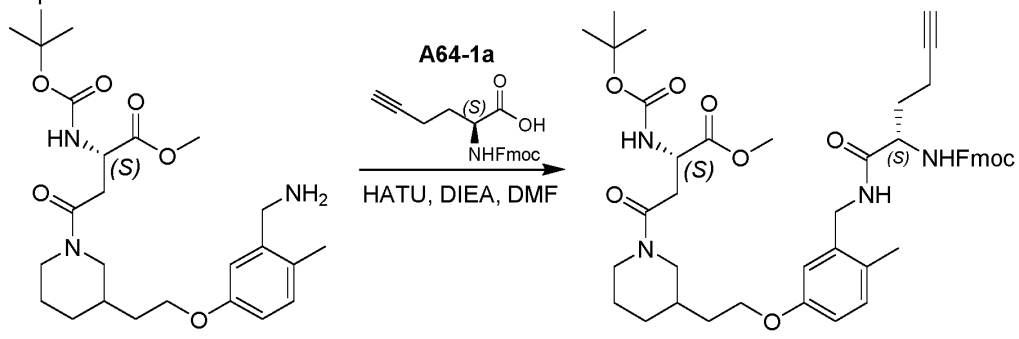
The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized. Compound **739** (10 mg, 0.013 mmol, 6.03% yield, 96.21% purity) was obtained as yellow solid.

^1H NMR (400MHz, DMSO-d_6) δ = 8.81 - 7.85 (m, 5H), 7.70 - 7.55 (m, 1H), 7.12 - 6.60 (m, 3H), 4.71 - 3.86 (m, 14H), 3.14 - 2.64 (m, 7H), 2.38 - 1.90 (m, 7H), 1.86 - 1.08 (m, 8H)

LCMS: 96.21 %, MS (ESI): m/z 692.6 $[M + H]^+$.

Example A-51 : Preparation of macrocyclic compound 686

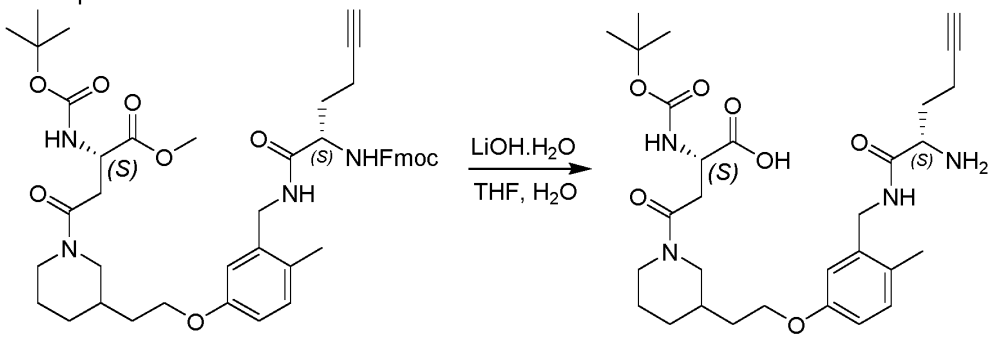
1. Preparation of **A64-2**:



A64-1 **A64-2**

To a solution of **A 64-1** (300 mg, 628.15 umol, 1 eq) and **A64-1a** (219.46 mg, 628.15 umol, 1 eq) in DMF (6 mL) was added DIEA (324.74 mg, 2.51 mmol, 437.65 uL, 4 eq) and HATU (358.26 mg, 942.23 umol, 1.5 eq) at 0°C**.** The mixture was stirred at 25°C for 2h to give a colorless solution. The mixture was diluted with EA (5mL) andwashed with H_2O (5ML*3), brine (5mL*2), then dried and concentrated under reduced pressure. The crude product was purified by flash column (SiO_2, PE/EA=10/90) to afford **A64-2** (400 mg, 494.46 umol, 78.72% yield) as yellow oil.

2. Preparation of **A64-3**:

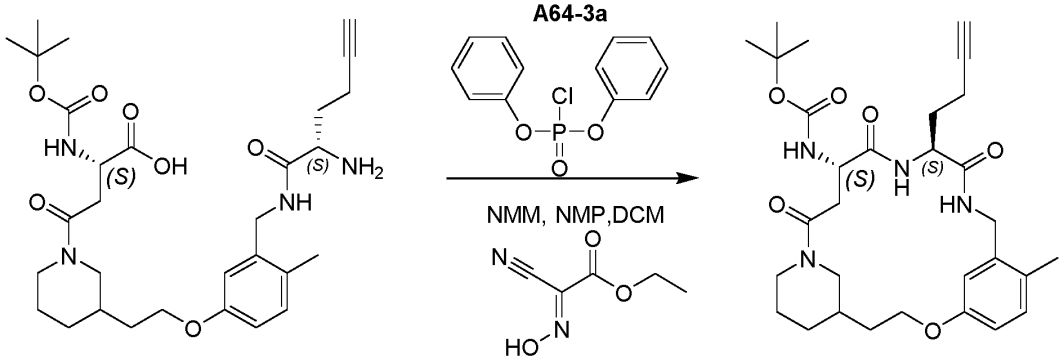


A64-2 **A64-3**

To a solution of **A64-2** (400 mg, 494.46 umol, 1 eq) in THF (6 mL) and H_2O (1.5 mL) was added LiOH.H_2O (103.74 mg, 2.47 mmol, 5 eq). The mixture was stirred at 25 °C for 5h.

The mixture was acidized with HCl(1M) to pH=6, and extracted with EA (300 mL *2) . The organic layer was concentrated under reduced pressure. **A64-3** (0.92 g, crude) was obtained as light yellow oil without purification.

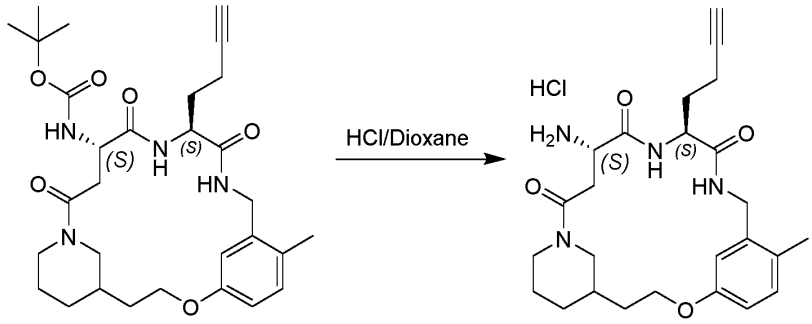
3. Preparation of **A64-4**:



A64-3 **A64-4**

To a solution of **A64-3a** (70.97 mg, 499.40 umol, 2 eq), NMM (151.54 mg, 1.50 mmol, 164.71 uL, 6 eq), **A64-3b** (134.15 mg, 499.40 umol, 103.20 uL, 2 eq) in NMP (3 mL) and DCM (6 mL) was added **A64-3** (143 mg, 249.70 umol, 1 eq). The mixture was stirred at 20°C for 1.5 h to give a yellow solution. The mixture was partitioned between DCM (30 mL) and water (10 mL). The organic layer was washed with water (10mL*5) and saturated brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by pre-TLC (SiO_2, PE/EA=1:1) to afford **A64-4** (99 mg, crude) as yellow oil.

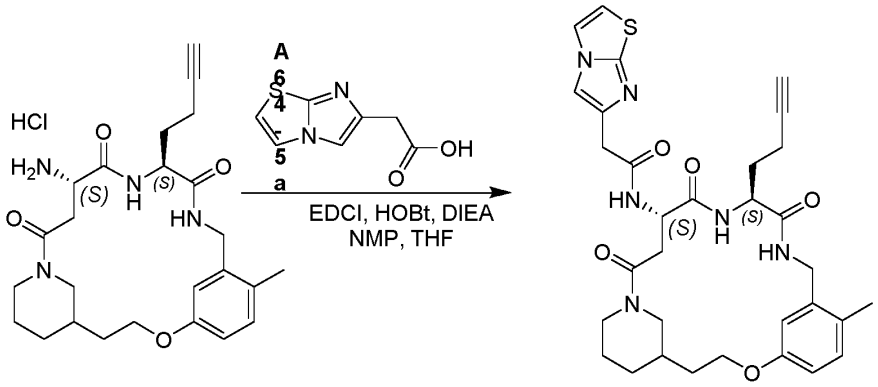
4. Preparation of **A64-5**:



A64-4 **A64-5**

To a solution of **A64-4** (99 mg, umol, 1eq.) in dioxane (20 mL) was added HCl/dioxane (4 M, 20mL). The mixture was stirred at 20 °C for 2hr under N_2 to give a colorless solution. The reaction was concentrated under reduced pressure. **A64-5** (95 mg, 193.47 umol, 1 eq, HCl) was obtained as colorless oil.

5. Preparation of compound **686**:



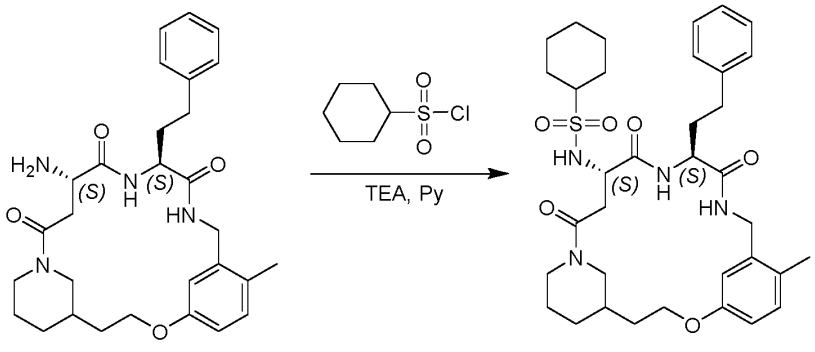
A64-5 686

To a solution of **A64-5** (95 mg, 193.47 umol, 1 eq, HCl) ,HOBt (36.60 mg, 270.86 umol, 1.4 eq), **A64-5a** (45.83 mg, 251.52 umol, 1.3 eq) and DIEA (75.02 mg, 580.42 umol, 101.10 uL, 3 eq) in DCM (2.5 mL) and THF (2.5 mL) was stirred 15 min and then EDCI (51.93 mg, 270.86 umol, 1.4 eq) was added. The mixture was stirred at 20°C for 1h. The mixture was partitioned between EA (100 mL) and H_2O(20 mL). The organic layer was washed with 0.2 MHCl (40 mL), sat. $NaHCO_3$ (30 mL) , brine (30 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The crude was purified by prep- HPLC (column: Welch Xtimate C18 100*40mm*3um;mobile phase: [water(HCl)-ACN];B%: 15%-45%,10min) to afford **686** (6.3 mg, 10.18 umol, 5.26% yield) as gray powder.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.53 - 7.71 (m, 1H), 8.55 - 7.70 (m, 4H), 7.48 - 7.38 (m, 1H), 7.07 - 6.61 (m, 3H), 4.74 - 4.49 (m, 1H), 4.36 - 4.16 (m, 3H), 4.13 - 3.84 (m, 4H), 3.64 - 3.57 (m, 3H), 2.82 - 2.72 (m, 2H), 2.19 - 2.13 (m, 5H), 1.81 - 1.50 (m, 7H), 1.30 - 1.14 (m, 4H)

LCMS: 100.0%, MS (ESI): m/z 619.2 $[M+H]^+$

Example A-52 : Preparation of macrocyclic compound 579



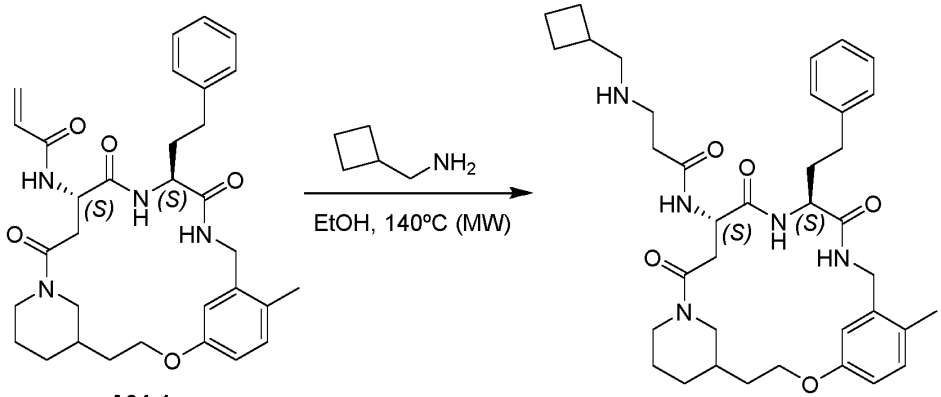
8 579

To a solution of **8** (400 mg, 789.52 mmol, 1 *eq*) in pyridine (Py, 10 mL) was added TEA (239.67 mg, 2.37 mmol, 329.67 mL, 3 *eq*) and cyclohexane sulfonyl chloride (288.44 mg, 1.58 mmol, 2 *eq*) , the resulting mixture was stirred at 40 °C for 16 hr hours to give yellow solution. LCMS showed the reaction was completed. The resultant solution was partitioned between EA (100 mL) and H_2O (80 mL). The organic layer was washed with water (90 mL X 2), brine (90 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a yellow oil. The residue was purified by prep-HPLC (basic condition, column: 2_Phenomenex Gemini C18 75*40mm*3um; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 55 %-85 %, 7.8 min). The afforded flows were combined, concentrated to remove most of CH_3CN, and lyophilized to give **579** (30.3 mg, 46.41 mmol, 50.50% yield) as white solid.

^{1}H NMR (DMSO-d_6, 400MHz): δ = 7.68-8.68 (m, 2H), 7.16-7.30 (m, 6H), 7.00-7.07 (m, 1H), 6.53-6.99 (m, 2H), 3.56-4.67 (m, 10H), 2.58-3.03 (m, 6H), 2.11-2.21 (m, 4H), 1.05-2.10 ppm (m, 25H).

LCMS: 96.71 %, MS (ESI): m/z 651.2 $[M + H]^+$.

Example A-53 : Preparation of macrocyclic compound 674



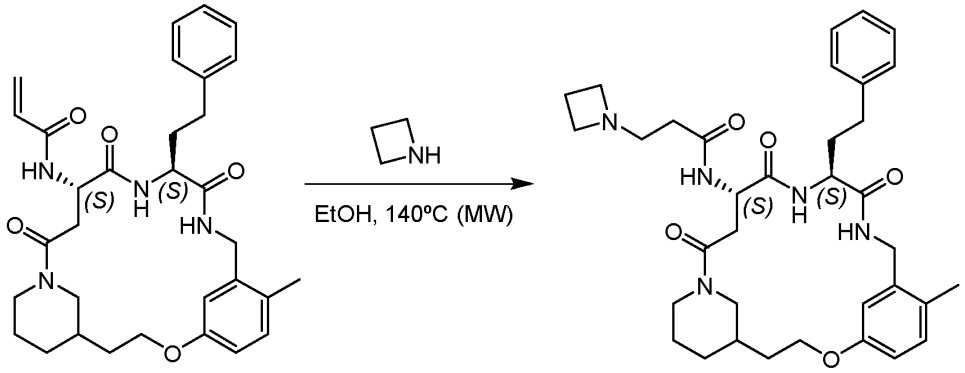
A84-1 **674**

To a solution of **A84-1** (80 mg, 0.142 mmol, 1 *eq*) and cyclobutylmethanamine (121.49 mg, 1.43 mmol, 10 *eq*) in EtOH (3 mL) in a sealed tube and heated to 140 °C with microwave equipment for 30 min to give a yellow solution. LCMS showed a main peak. The reaction solution was purified directly. The residue was purified by prep-HPLC (formic acid(FA) condition, column: Welch Xtimate C18 100*25mm*3um;mobile phase: [water(FA)-ACN]; B%: 15%-45%, 8 min) to give **674** (65.1 mg, 0.094 mmol, 65.95% yield, FA) as white solid.

^{1}H NMR (DMSO-d_6, 400MHz): δ = 7.81-8.60 (m, 4H), 7.14-7.33 (m, 5H), 6.82-7.08 (m, 1H), 6.54-6.81 (m, 2H), 4.41-4.76 (m, 2H), 3.84-4.37 (m, 10H), 2.54-3.03 (m, 10H), 2.06-2.24 (m, 4H), 1.10-2.00 ppm (m, 16H).

LCMS: 95.75 %, MS (ESI): m/z 646.4 $[M + H]^+$.

Example A-54 : Preparation of macrocyclic compound 702



A84-1 **702**

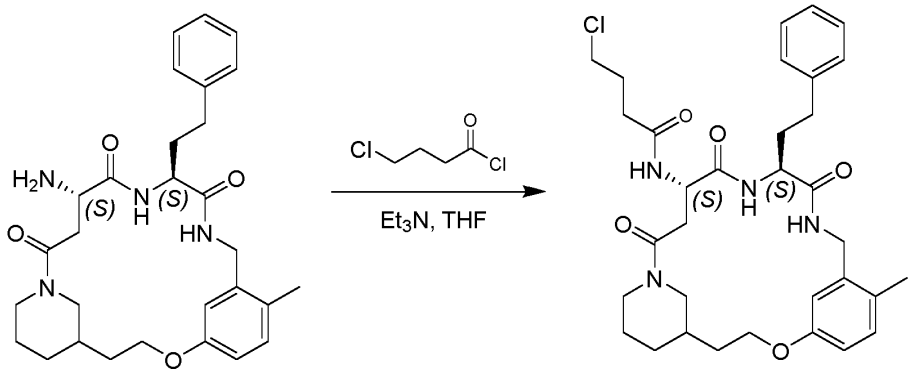
To a solution of **A84-1** (100 mg, 0.178 mmol, 1 *eq*) and azetidine (101.83 mg, 1.78 mmol, 0.120 mL, 10 *eq*) in EtOH (3 mL) in a sealed tube and heated to 140 °C with microwave equipment for 30 min to give a yellow solution. LCMS showed a desired mass. The reaction solution was purified directly. The residue was purified by prep-HPLC (formic acid (FA) condition, column: Welch Xtimate C18 100*25mm*3um; mobile phase: [water (FA)-ACN]; B%: 15%-45%, 8 min). The afforded flows were combined, concentrated to remove most of CH_3CN, and lyophilized to **702** (61.2 mg, 0.092 mmol, 51.69% yield, FA) as white solid.

^1H NMR (DMSO-d_6, 400MHz): δ = 8.15-8.45 (m, 3H), 7.11-7.32 (m, 5H), 6.99-7.07 (m, 1H), 6.52-6.96 (m, 2H), 3.80-4.68 (m, 13H), 3.07-3.31 (m, 3H), 2.57-2.87 (m, 6H), 2.04-2.24 (m, 6H), 1.13-2.00 ppm (m, 9H).

LCMS: 98.22 %, MS (ESI): m/z 618.2 $[M + H]^+$.

Example A-55 : Preparation of macrocyclic compound 728

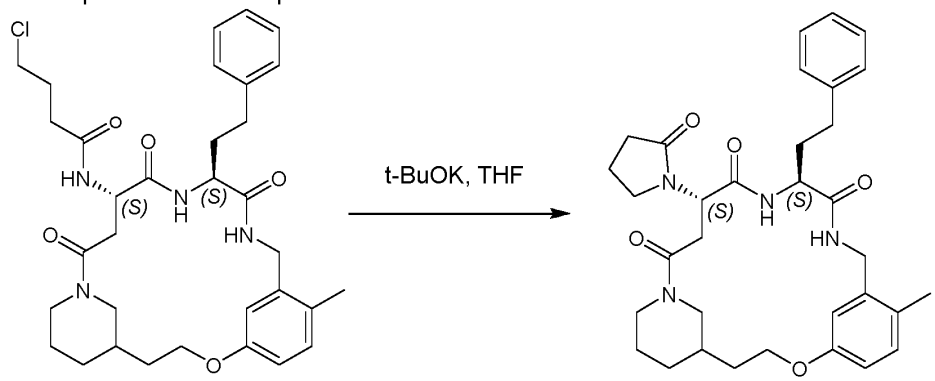
1. Preparation of **A152-1:**



8 **A152-1**

To a solution of **8** (100 mg, 0.184 mmol, 1 eq, HCl) and Et3N (37.26 mg, 0.368 mmol, 0.051 mL, 2 eq) in THF (5 mL) was added 4-chlorobutanoyl chloride (31.15 mg, 0.220 mmol, 0.024 mL, 1.2 eq) at 0°C. The mixture was stirred at 25°C for 2 h. The mixture was poured into H_2O (5 mL) and extracted with EA (5 mL x 2). The organic was dried with Na_2SO_4 and concentrated under reduced pressure. **A152-1** (175.9 mg, crude) was obtained without purification as colorless oil.

2. Preparation of compound **728:**



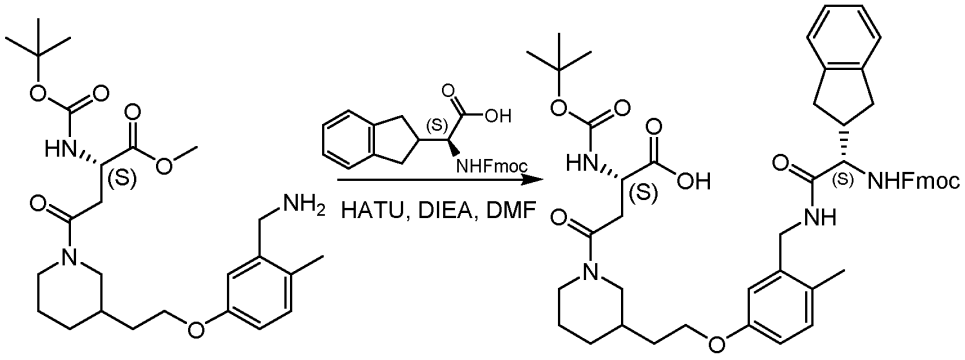
A152-1 **728**

To a solution of **A152-1** (112.5 mg, 0.184 mmol, 1 eq) in THF (7 mL) was added t-BuOK (103.28 mg, 0.920 mmol, 5 eq).The mixture was stirred at 20°C for 2 h. The mixture was concentrated under reduced pressure. The crude product was purified by prep-HPLC (column: 2_Phenomenex Gemini C18 75*40mm*3um; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 45%-75%, 7.8 min) to afford **728** (27.52 mg, 0.047 mmol, 26.01% yield) as white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.43 - 7.71 (m, 3H), 7.31 - 7.02 (m, 6H), 6.95 - 6.72 (m, 2H), 5.16 - 4.53 (m, 2H), 4.48 - 4.34 (m, 1H), 4.31 - 3.96 (m, 5H), 3.91 - 3.59 (m, 1H), 3.46 - 3.35 (m, 3H), 3.06 - 2.57 (m, 5H), 2.18 - 1.86 (m, 2H), 1.82 - 1.53 (m, 5H), 1.36 - 1.18 (m, 2H), 1.10 - 0.98 (m, 6H)
LCMS: 100.0%, MS (ESI): m/z 575.2 $[M + H]^+$

Example A-56 : Preparation of macrocyclic compound 602

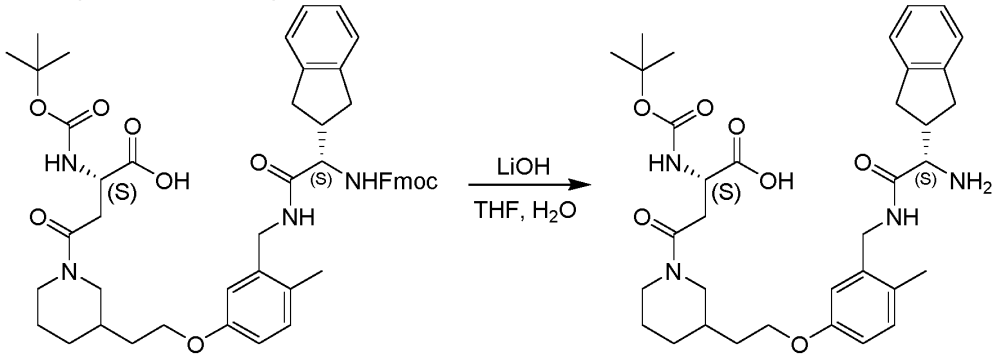
1. Preparation of compound **A63-2:**



A63-1 A63-2

To a solution of **A63-1** (500 mg, 836.54 umol, 1 eq), (2S)-2-(9H-fluoren-9-ylmethoxycarbony
-lamino)-2-indan-2-yl-acetic acid (345.88 mg, 836.54 umol, 1 eq), HATU (381.69 mg, 1.00 mmol, 1.2 eq) in DCM (4 mL) and DMF (4 mL) was added DIEA (432.46 mg, 3.35 mmol, 582.83 uL, 4 eq) at 0°C.The reaction was stirred at 0-10°C for 30 min to give a yellow mixture. LCMS showed that the starting material was consumed completely. H_2O (10 mL) was added. The mixture was concentrated under reduced pressure to give a residue. The solution was partitioned between EA (30 mL) and H_2O (10 mL). The organic layer was washed with 4% lithium chloride solution (30 mL x 2), brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give yellow oil. The crude product was was purified by silica gel chromatography eluted (EA: PE=0:1 to 2:3) to give **A63-2** (457.17 mg, 513.18 umol, 61.35% yield, 98% purity) as yellow oil.

2. Preparation of compound **A63-3:**

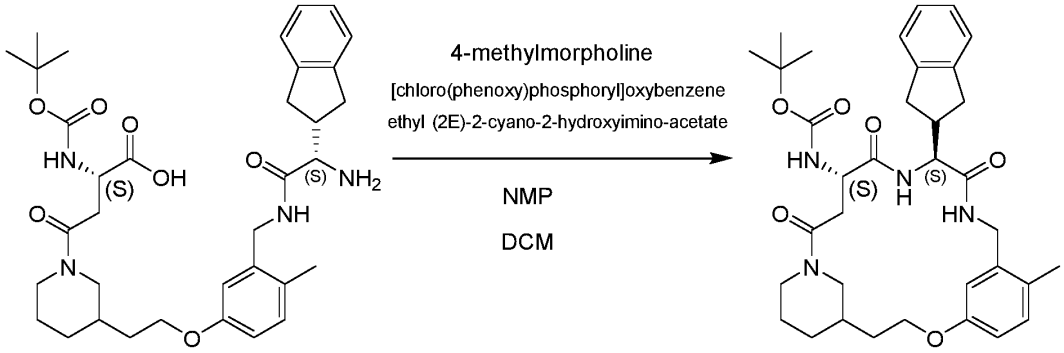


A63-2 A63-3

to a solution of **A63-2** (417.7 mg, 478.44 umol, 1 eq) in $LiOH.H_2O$ (60.23 mg, 1.44 mmol, 3 eq)was added H_2O (1 mL) in THF (4 mL) .The reaction was stirred at 20°C for 1 h to give a yellow mixture. LCMS showed the starting material was consumed

completely. H_2O (60 mL) was added. Then the aqueous layer was acidified to pH = 4 by addition of 1 M HCl. The aqueous layer was extracted with EA (60 mL x 2). The combined organic layer was washed with brine (60 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give **A63-3** (290 mg, 455.42 umol, 95.19% yield) as yellow oil. The crude product was used for the next step without purification.

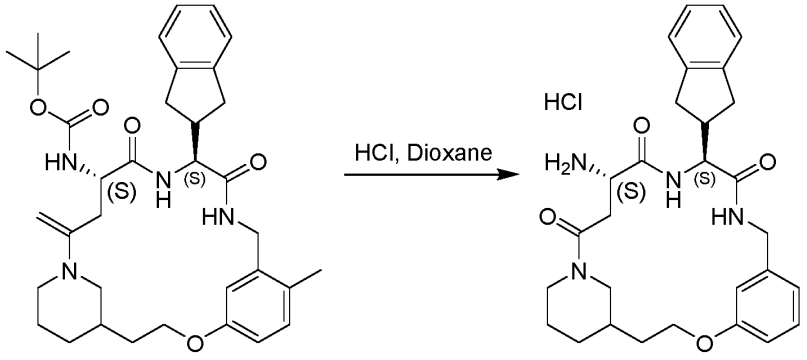
3. Preparation of compound **A63-4:**



A63-3 **A63-4**

To a solution of ethyl (2E)-2-cyano-2-hydroxyimino-acetate (129.44 mg, 910.84 umol, 2 eq), [chloro(phenoxy)phosphoryl]oxybenzene (244.68 mg, 910.84 umol, 188.21 uL, 2 eq), NMM (276.39 mg, 2.73 mmol, 300.43 uL, 6 eq) in NMP (2 mL) and DCM (4 mL) was **A63-3** (290 mg, 455.42 umol, 1 eq). The reaction was stirred at 20°C for 1.5 h to give a yellow solution. LCMS showed that the reaction was completed. The resultant solution was partitioned between H_2O (100 mL) and EA (120 mLx 2). The organic layer was washed with water (200 mLx 3), brine (60 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give a yellow oil. The crude product was purified by silica gel chromatography eluted (EA: PE=0:1 to 2:3) to give **A63-4** (126.3 mg, 204.12 umol, 44.82% yield) as yellow oil.

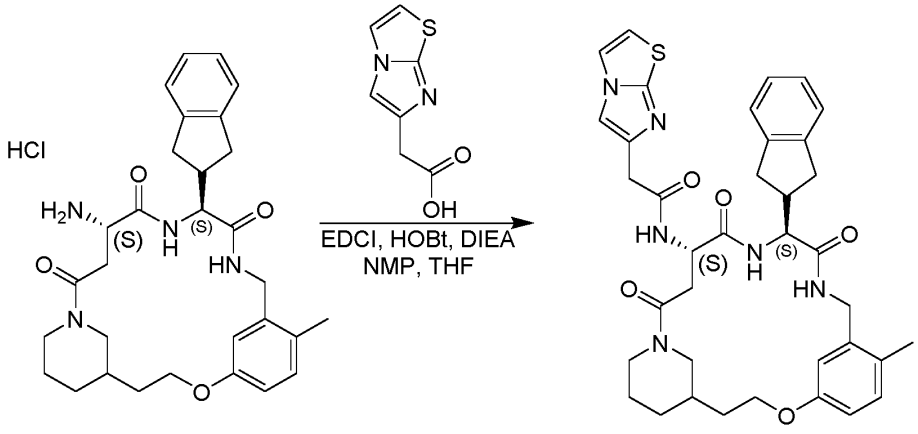
4. Preparation of compound **A63-5:**



A63-4 **A63-5**

To a solution of **A63-4** (126.3 mg, 204.12 umol, 1 eq) in dioxane (2 mL)was added HCl/dioxane (4 M, 153.09 uL, 3 eq)The reaction was stirred at 20°C for 30 min to give a yellow solution. LCMS showed the starting material was consumed completely. The solution was concentrated under reduced pressure to give **A63-5** (94 mg, crude, HCl) as yellow oil. The crude product was used for the next step without purification.

5. Preparation of compound **602:**



A63-5 **602**

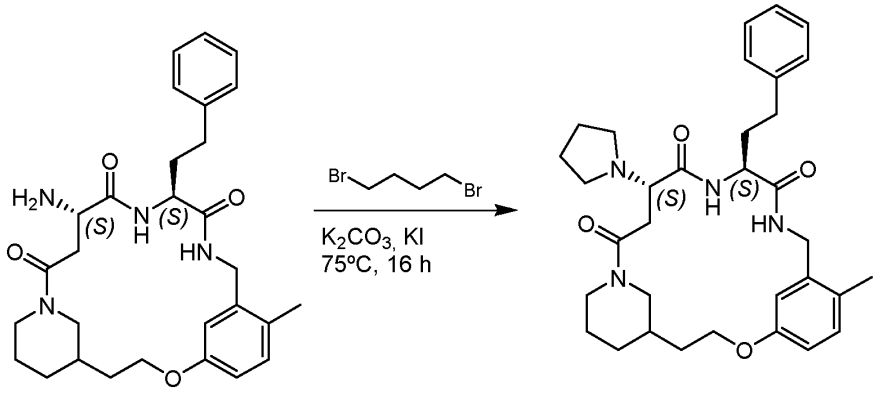
A solution of **A63-5** (60 mg, 108.09 umol, 1 eq, HCl), 2-imidazo[2,1-b]thiazol-6-ylacetic acid (19.69 mg, 108.09 umol, 1 eq), DIEA (41.91 mg, 324.26 umol, 56.48 uL, 3 eq), HOBt (18.99 mg, 140.51 umol, 1.3 eq) in THF (2 mL) and DCM (2 mL) was stirred at 20°C for 15 min to give a yellow mixture. EDCI (24.86 mg, 129.70 umol, 1.2 eq) were added. The reaction was stirred at 20°C for 1 h to give a yellow mixture. LCMS showed the starting material was consumed not completely. 2-imidazo[2,1-b]thiazol-6-ylacetic acid (19.69 mg, 108.09 umol, 1 eq), DIEA (41.91 mg, 324.26 umol, 56.48 uL, 3 eq), EDCI (24.86 mg, 129.70 umol, 1.2 eq), HOBt (18.99 mg, 140.51 umol, 1.3 eq) was added. The reaction was stirred at 20°C for 1 h to give a yellow mixture. LCMS showed the starting material was consumed completely. The solution was partitioned between

EA (30 mL) and H_2O (15 mL). The organic layer was washed with 0.2 M HCl (30 mL), sat. $NaHCO_3$ (30 mL), brine (30 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give yellow oil. The crude product was purified by prep-HPLC (column: 2_Phenomenex Gemini C18 75*40mm*3um; mobile phase: [water(NH_4HCO_3)-ACN];B%: 38%-68%,9.5min). The eluent was lyophilized to give **602** (2 mg, 2.78 umol, 2.57% yield, 95% purity) as off-white powder.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.53 - 8.58 (m, 4 H) 7.26 - 7.27 (m, 1 H) 6.58 - 7.30 (m, 6 H) 3.57 - 4.75 (m, 9 H) 2.70 - 3.21 (m, 8 H) 1.08 - 2.13 (m, 12 H)

LCMS: 95.17%, MS (ESI): m/z 683.2 [M + H] $^+$.

Example A-57 : Preparation of macrocyclic compound 731



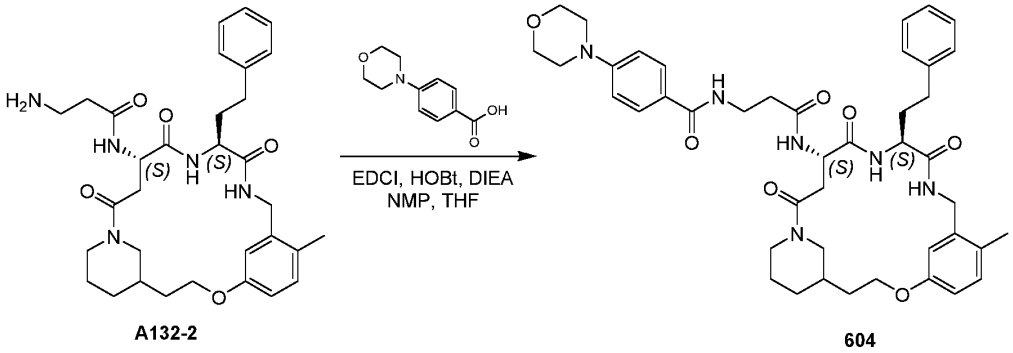
8 **731**

To a solution of **8** (80 mg, 0.157 mmol, 1 *eq*) in AcCN (5 mL) was added K_2CO_3 (21.82 mg, 0.157 mmol, 1 *eq*) and KI (1.31 mg, 0.0079 mmol, 0.05 *eq*), then the mixture was combined with 1, 4-dibromobutane (34.09 mg, 0.157 mmol, 0.019 mL, 1 *eq*) and stirred at 75°C for 14 h to give a yellow solution. The reaction was diluted with water (10 ml) and extracted with EtOAc (20 ml x 2). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by Prep-HPLC (NH_4Cl) to obtained **731** (11.67 mg, 0.020 mmol, 13.18% yield) as white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.05 - 1.85 (m, 13 H) 1.97 - 2.36 (m, 5 H) 2.53 - 2.59 (m, 3 H) 2.60 - 2.89 (m, 6 H) 3.36 - 3.50 (m, 1 H) 3.77 - 4.59 (m, 7 H) 6.69 - 7.31 (m, 8 H) 7.69 - 8.50 (m, 2 H)

LCMS: 100.00%, ESI-MS (m/z): m/z 561.2 [M + H$^+$]

Example A-58 : Preparation of macrocyclic compound 604



A132-2 604

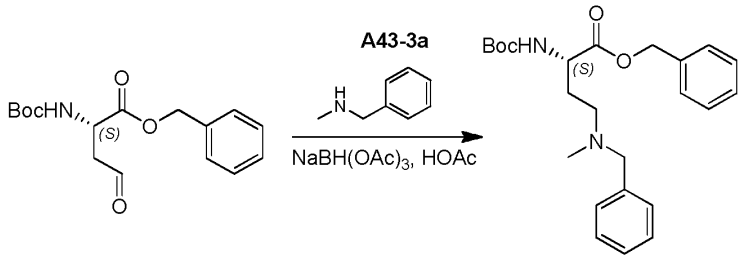
To a solution of **A132-2** (120 mg, 0.195 mmol, 1 eq, HCl) and 4-morpholinobenzoic acid (60.73 mg, 0.293 mmol, 1.5 eq) in NMP (1 mL) and THF (4 mL) was added HOBt (39.60 mg, 0.293 mmol, 1.5 eq) and DIEA (101.01 mg, 0.781 mmol, 0.136 mL, 4 eq) stirred for 20 min. Added EDCI (56.18 mg, 0.293 mmol, 1.5 eq) to the reaction. The mixture was stirred at 20 °C for 1 hr to give a colorless solution. LCMS showed the starting material was consumed completely. The reaction mixture was diluted with H_2O (20 mL) and extracted with EA (15 mL x3). The combined organic layers were washed with brine (30mL x2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: 2_Phenomenex Gemini C18 75*40mm*3um;mobile phase: [water(NH4HCO3)-ACN];B%: 43%-73%,7.8min) afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to give **604** (25.9 mg, 0.033 mmol, 17.28% yield, 100% purity) as white powder.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.11 - 8.53 (3 H, m) 7.69 - 7.91 (2 H, m) 7.10 - 7.29 (5 H, m) 6.86 - 7.05 (3 H, m) 6.64 - 6.77 (1 H, m) 3.70 - 4.78 (13 H, m) 3.17 (3 H, br d, *J*=4.17 Hz) 2.54 - 2.99 (7 H, m) 2.29 - 2.48 (3 H, m) 2.09 - 2.19 (3 H, m) 1.14 - 2.01 (9 H, m)

LCMS: 100%, MS (ESI): m/z 767.6 $[M + H]^+$

Example A-59 : Preparation of macrocyclic compound 696

1. Preparation of **A43-4**:

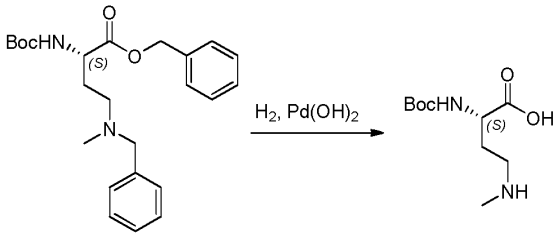


A43-3 A43-4

To a solution of **A43-3** (1 g, 3.25 mmol, 1 *eq*) in DCM (10 mL) was added **A43-3a** (788.57 mg, 6.51 mmol, 839.79 uL, 2 *eq*), HOAc (acetic acid, 39.08 mg, 650.74 umol, 37.22 uL, 0.2 *eq*). Then 30min after was added $NaBH(OAc)_3$ (1.38 g, 6.51 mmol, 2 *eq*).

The mixture was stirred at 20 °C for 16 hrs to give a yellow solution. The reaction mixture was poured into 0.2M HCl (10ml) and extracted with EtOAc (10 mL x 4).The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column (SiO_2, PE to 50% EtOAc in PE) to afford **A43-4** (620 mg, 1.11 mmol, 34.09% yield, 73.8% purity) was obtained as yellow oil.

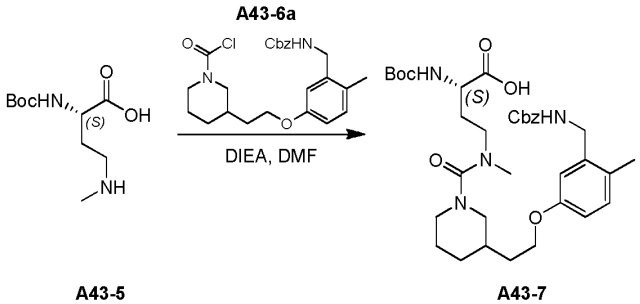
2. Preparation of **A43-5**:



A43-4 **A43-5**

To a solution of **A43-5** (620 mg, 1.50 mmol, 1 *eq*) in MeOH (10 mL) was added $Pd(OH)_2$ (1.06 g, 1.50 mmol, 20% purity, 1 *eq*) under H_2 (15 Psi) , the resulting mixture was stirred at 20°C for 14 hours to give yellow solution. The reaction mixture was removed by filtration and the filtrate was concentrated under vacuum to afford **A43-5** (349 mg, crude) was obtained as white oil.

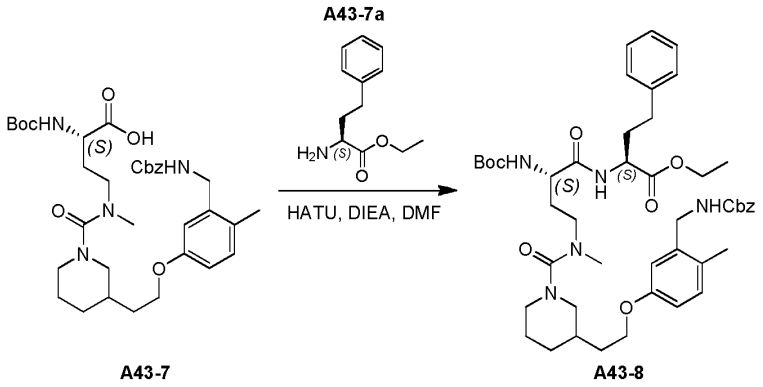
3. Preparation of **A43-7**:



A43-5 **A43-7**

To a solution of **A43-5** (340 mg, 1.46 mmol, 1 *eq*), **A43-6a** (651.31 mg, 1.46 mmol, 1 *eq*), DIEA (103.79 mg, 803.08 umol, 139.88 uL, 1.2 eq) in NMP (3 mL) was added DIEA (567.55 mg, 4.39 mmol, 764.89 mL, 3 *eq*). The mixture was stirred at 20 °C for 2 hr to give a yellow solution. The reaction mixture was poured into 1M HCl(10 mL) and water (50 mL) and extracted with EtOAc (30 mL x 4).The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford **A43-7** (1.1 g, crude) was obtained as white oil.

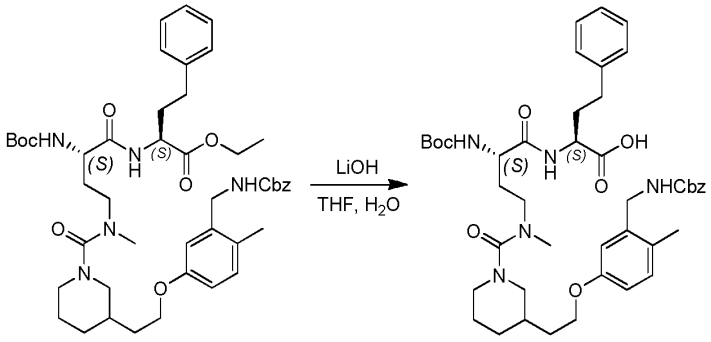
4. Preparation of **A43-8**:



A43-7 A43-8

To a solution of **A43-7** (1.1 g, 0.546 mmol, 31.5% purity, 1 *eq*), **A43-7a** (131.80 mg, 0.546 mmol, 1 *eq*, HCl), DIEA (209.67 mg, 1.62 mmol, 0.282 mL, 3 *eq*) in DMF (2 mL) and DCM (4 mL) was added HATU (411.23 mg, 1.08 mmol, 2 *eq*) at 0°C . The reaction was stirred at 0-10°C for 2 h to give a yellow solution. The reaction mixture was concentrated directly. The reaction mixture was poured into water (10 mL) and extracted with EtOAc (10 mL x 4).The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column (SiO_2, PE to 50% EtOAc in PE) to afford **A43-8** (240 mg, 0.289 mmol, 53.47% yield, 100% purity) was obtained as white solid.

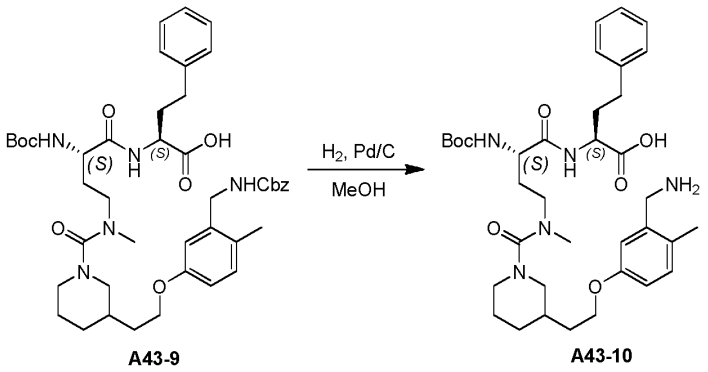
5. Preparation of **A43-9**:



A43-8 A43-9

To a solution of **A43-8** (240 mg, 0.289 mmol, 1 *eq*) in H_2O (1 mL) and THF (4 mL) was added $LiOH{\cdot}H_2O$ (24.27 mg, 0.578 mmol, 2 *eq*), the resulting mixture was stirred at 20ºC for 4 hours to give yellow solution. The reaction mixture was concentrated directly. The reaction was poured into H_2O (4 mL). The afforded water layer was acidified with 1 N HCl aq. to pH=3, extracted with DCM (100 mL x 3).The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure.to afford **A43-9** (180 mg, crude) was obtained as white solid.

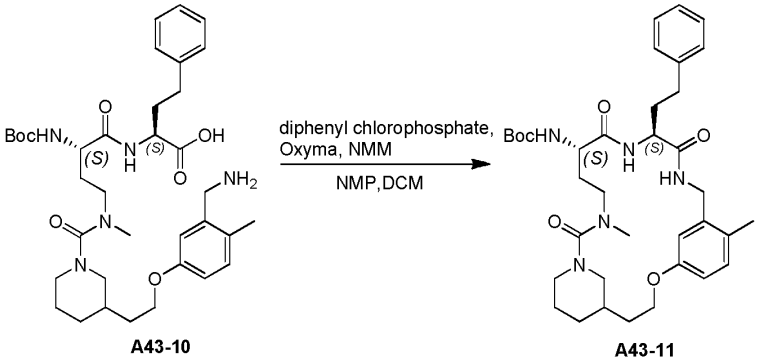
6. Preparation of **A43-10**:



A43-9 A43-10

To a solution of **A43-10** (180 mg, 0.224 mmol, 1 *eq*) in MeOH (5 mL) was added Pd/C (50 mg, 0.224 mmol, 10% purity, 1 *eq*) under H_2 (15Psi) , the resulting mixture was stirred at 20°C for 14 hours to give yellow solution. The reaction mixture was removed by filtration and the filtrate was concentrated under vacuum to afford **A43-10** (149 mg, crude) was obtained as yellow oil.

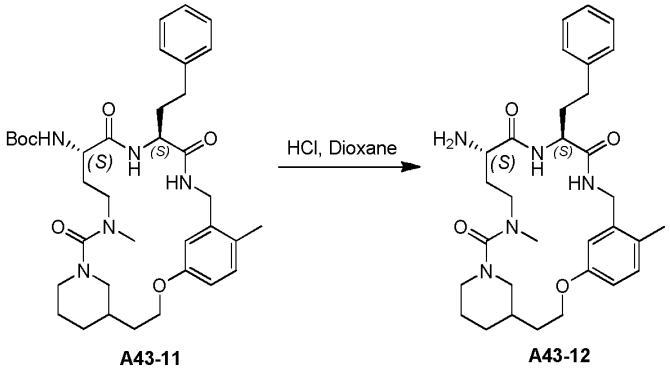
7. Preparation of **A43-11**:



A43-10 A43-11

To a solution of Oxyma (63.41 mg, 0.446 mmol, 2 *eq*), DPCP(diphenyl chlorophosphate) (119.87 mg, 0.446 mmol, 92.21 uL, 2 *eq*), NMM(N-methylmorpholine) (135.40 mg, 1.34 mmol, 147.18 uL, 6 *eq*) in NMP(N-methylpyrrolidone) (2 mL) and DCM (5 mL) was added **A43-10** (149 mg, 0.223 mmol, 1 *eq*) and the reaction was stirred at 20ºC for 2 h to give a yellow solution. The resultant solution was concentrated to remove DCM. The reaction mixture was poured into water (10 mL) and extracted with EtOAc (10 mL x 4). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column (SiO_2, PE to 90% EtOAc in PE) to afford **A43-11** (70 mg, 0.107 mmol, 48.28% yield) was obtained as yellow oil.

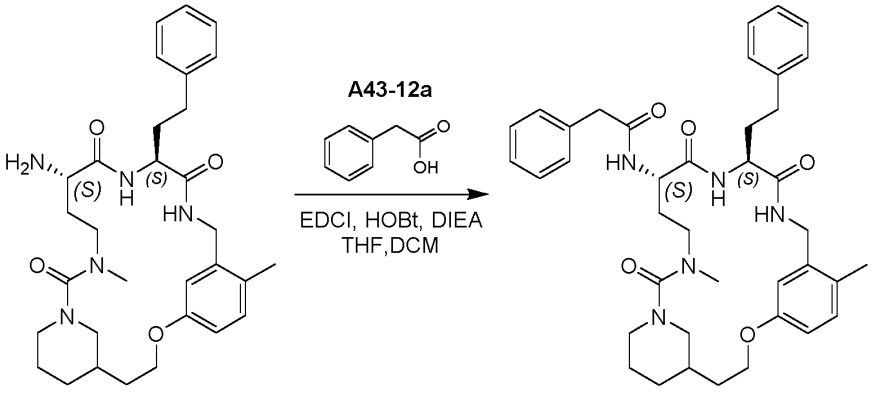
8. Preparation of **A43-12**:



A43-11 A43-12

To a solution of **A43-12** (70 mg, 0.107 mmol, 1 *eq*) in HCl/dioxane (1 mL), the resulting mixture was stirred at 0ºC for 4 hours to give yellow mixture. The reaction mixture was concentrated directly to afford **A43-12** (63 mg, crude, HCl) was obtained as yellow oil.

9. Preparation of compound **696**:



A43-12 696

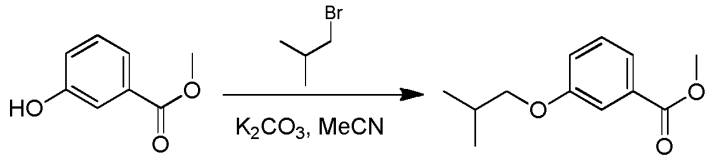
To a solution of **A43-5** (50 mg, 0.091 mmol, 1 *eq*, HCl), **A43-5a** (21.57 mg, 0.118 mmol, 1.3 *eq*), HOBt (17.22 mg, 0.127 mmol, 1.4 *eq*) ,DIEA (35.30 mg, 0.273 mmol, 0.047 mL, 3*eq*) in THF (2 mL) and DCM (2 mL) was stirred at 20°C for 15 min to give a yellow mixture. EDC HCl (24.44 mg, 0.127 mmol, 1.4 *eq*) were added. the reaction was stirred at 20°C for 1 h to give a yellow mixture. The reaction mixture was poured into water (10 mL) and extracted with EtOAc (10 mL x 4). The organic layer was washed with 0.2 M HCl (20 mL), sat. $NaHCO_3$ (30 mL), brine (30 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give yellow oil. The residue was purified by prep-HPLC (neutral, column: 2_Phenomenex Gemini C18 75*40mm*3um; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 52%-82%, 7.8min). The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to afford **696** (12.40 mg, 0.018 mmol, 18.14% yield, 100% purity) was obtained as white solid.

^1H NMR (400MHz, DMSO-d_6) δ = 8.46 - 8.00 (m, 3H), 7.34 - 6.59 (m, 14H), 4.33 - 3.43 (m, 4H), 3.28 - 2.55 (m, 1H), 2.16 (d, *J*=3.0 Hz, 3H), 2.07 - 1.07 (m, 13H)

LCMS: 100%, MS (ESI): m/z 668.3 [M + H]+.

Example A-60 : Preparation of macrocyclic compound 651

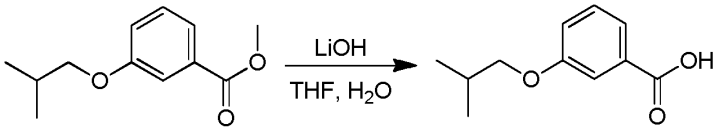
1. Preparation of **A141-2a**:



A141-1a **A141-2a**

To a solution of **A141-1a** (300 mg, 1.97 mmol, 1 eq) in DMF (3.5 mL) was added 1-bromo-2-methyl-propane (405.25 mg, 2.96 mmol, 0.321 m, 1.5 eq) and K_2CO_3 (817.53 mg, 5.92 mmol, 3 eq), the mixture stirred at 80°C for 3h to give a brown mixture. TLC showed the starting material was consumed completely. The mixture was partitioned between EA (10 mL x 2) and H_2O (10 mL). The organic layer was washed with H_2O (10 mL x3), brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by flash column (SiO_2, 100% PE) to give **A141-2a** (340 mg, crude) as brown oil.

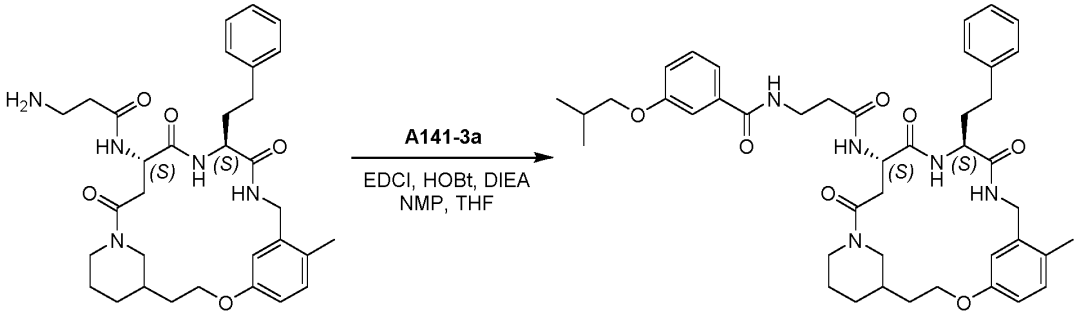
2. Preparation of **A141-3a**:



A141-2a **A141-3a**

To a solution of **A141-2a** (260 mg, 1.25 mmol, 1 eq) in THF (3 mL) and H_2O (0.5 mL) was added LiOH.H2O (157.17 mg, 3.75 mmol, 3 eq) at 0 °C. The mixture was stirred at 20°C for 3 h to give yellow mixture. TLC showed the starting material was consumed completely. The reaction was diluted with EA (10 mL) and neutralized with 1N HCl. The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give **A141-3a** (150 mg, crude) was obtained as colorless oil.

3. Preparation of compound **651**:



A132-2 651

To a solution of **A132-2** (100 mg, 0.162 mmol, 1 eq, HCl) and **A141-3a** (47.44 mg, 0.244 mmol, 1.5 eq) in NMP (0.8 mL) and THF (3 mL) was added HOBt (33.00 mg, 0.244 mmol, 1.5 eq) and DIEA (84.17 mg, 0.651 mmol, 0.113 mL, 4 eq) stirred for 20 min. Added EDCI (46.82 mg, 0.244 mmol, 1.5 eq) to the reaction. The mixture was stirred at 20 °C for 1 hr to give a colorless solution. LCMS showed the starting material was consumed completely. The reaction mixture was diluted with H_2O (20 mL) and extracted with EA (15 mL x 3). The combined organic layers were washed with brine (30mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: 2_Phenomenex Gemini C18 75*40mm*3um;mobile phase: [water(NH_4HCO_3)-ACN];B%: 55%-85%,7.8min). The afforded flows were combined, concentrated to remove most of CH_3CN and lyophilized to give **651** (28.08 mg, 0.037 mmol, 22.87% yield, 100% purity) as white powder

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.78 - 8.51 (4 H, m) 7.10 - 7.43 (8 H, m) 6.60 - 7.08 (2 H, m) 3.41 - 4.81 (12 H, m) 2.65 - 2.96 (3 H, m) 2.28 - 2.40 (3 H, m) 2.12 - 2.18 (3 H, m) 1.08 - 2.08 (12 H, m) 0.97 (6 H, br d, *J*=6.27 Hz)

LCMS: 100%, MS (ESI): m/z 754.2 $[M + H]^+$

Example A-61 : The following compounds have been synthesized according to the above-described methods.

LCMS was taken on a quadrupole Mass Spectrometer on Shimadzu LCMS 2010 (Shim-pack XR-ODS 3.0*30 mm 2.2 μm) operating in ES (+) ionization mode. Flow Rate: 0.8 mL/min, Acquire Time: 3 min, Wavelength: UV220, Oven Temp.: 50°C.

Table A-43

Cpd No.	Chemical Formula	Exact mass	$[M+H]^+$ found	Purity (%)
573	C34H46N4O6	606.3	607.6	100
574	C43H54N6O8	782.4	783.8	96.9
575	C36H48N6O5S	676.3	677.2	100
576	C43H59N5O7	757.4	758.3	100.0
577	C43H59N5O8	773.4	774.9	99.8
578	C42H52N6O8	768.4	769.4	98.1
580	C41H55N5O7	729.4	730.2	100
581	C41H52N4O7	712.4	713.3	97.7
582	C41H52N4O7	712.4	713.3	99.2
583	C33H44N6O5S	636.3	637.3	99.8
584	C40H54N4O6	686.4	687.3	100
585	C40H50N4O7	698.4	699.3	100.0
586	C40H45N5O5	675.3	676.4	100
587	C39H48N4O7	684.4	685.3	100.0
588	C39H48N4O7	684.4	685.2	98.4
589	C39H48N4O6	668.4	669.3	97.8
590	C38H50N4O7	674.4	675.2	100.0
591	C38H46N4O6	654.3	655.2	100.0
592	C37H50FN5O5	663.4	664.4	100
594	C36H48N4O6	632.4	633.3	100.0
595	C36H48N4O6	632.4	633.3	100.0
596	C35H48N4O7	636.4	637.3	100.0
597	C35H46N4O6	618.3	619.2	100.0

598	C32H41F2N5O5	613.3	614.3	90
599	C32H40F2N4O6	614.3	615.5	100
600	C36H42FN5O5	643.3	644.4	100
601	C31H39F3N4O6S	652.3	653.2	100
603	C44H52N6O5	744.4	745.3	98.5
605	C42H57N5O7	743.4	744.3	100
606	C42H54N4O7	726.4	727.3	100
607	C42H54N4O7	726.4	727.3	98.7
608	C42H59N5O5	713.5	714.3	100
609	C42H49N5O5	703.4	704.5	100
610	C41H52N4O7	712.4	713.3	99.8
611	C41H57N5O6	715.4	716.3	100
612	C41H52N4O6	696.4	697.3	100
613	C41H57N5O5	699.4	700.4	99.6
614	C40H54N4O6	686.4	687.3	98.4
615	C40H54N4O6	686.4	687.3	100
616	C40H53N5O6	699.4	700.3	100
617	C40H53N5O6	699.4	700.3	99.2
618	C40H50N4O6	682.4	683.3	100
619	C40H50N4O7	698.4	699.2	100
620	C40H56N4O6	688.4	689.8	99.4
621	C40H55N5O6	701.4	702.3	97.3
622	C39H48N4O7	684.4	685.2	100
623	C39H54N4O6	674.4	675.3	100
625	C38H52N4O6	660.4	661.3	100
626	C38H52N4O6	660.4	661.5	99.1

627	C38H52N4O6	660.4	661.3	100
629	C37H50N4O6	646.4	647.3	94.8
630	C37H50N4O6	646.4	647.3	97.0
631	C37H48N4O5	628.4	629.3	100
633	C35H43FN4O5	618.3	619.3	100
634	C38H47N5O5	653.4	654.4	100
635	C34H44N4O6	604.3	605.2	100
636	C36H43FN4O6S	678.3	679.3	96.5
637	C42H54N4O7	726.4	727.2	100
638	C40H55N5O5	685.4	686.4	99.7
639	C39H53N5O5	671.4	672.3	100
640	C39H53N5O6	687.4	688.3	97.8
641	C39H53N5O6	687.4	688.3	100
642	C39H52N4O6	672.4	673.3	98.6
643	C36H48N4O5	616.4	617.3	100
644	C34H46N4O6	606.3	607.5	100
645	C37H46N6O5	654.4	655.6	100
646	C34H43F3N4O5	644.3	645.3	98.1
647	C39H49N5O5	667.4	668.3	99.6
648	C38H51N5O6	673.4	674.3	100
649	C35H47N5O5	617.4	618.5	98.0
650	C34H45FN4O5	608.3	609.4	100
652	C40H55N5O5	685.4	686.3	95.8
654	C37H46N6O5	654.4	655.2	100
655	C35H44N4O6	616.3	617.2	94.5
656	C45H57N5O6	763.4	764.3	94.8

657	C39H53N5O5	671.4	672.3	100
658	C39H53N5O6	687.4	688.3	99.0
659	C38H51N5O5	657.4	658.3	100
660	C37H49N5O6	659.4	660.5	100
661	C36H41FN4O5	628.3	629.2	98.0
662	C35H45N5O5	615.3	616.5	97.4
663	C34H45N5O5	603.3	604.3	100
664	C34H44N4O6	604.3	605.4	95.6
665	C43H56N6O6	752.4	753.3	100
666	C40H50N6O5	694.4	695.2	98.6
667	C39H48N6O5	680.4	681.6	96.1
668	C36H49N5O5	631.4	632.5	100
669	C34H45N5O6	619.3	620.3	100
670	C35H46N4O6	618.3	619.5	100
671	C36H48N4O7	648.4	649.5	100
672	C45H59N5O8S	829.4	830.3	100
673	C38H51N5O5	657.4	658.3	96.1
675	C37H51N5O5	645.4	646.4	99.8
676	C36H49N5O6	647.4	648.3	100
677	C38H53N5O5	659.4	660.3	99.9
678	C37H46N6O5	654.4	655.4	100
679	C37H51N5O5	645.4	646.5	93.9
680	C36H49N5O5	631.4	632.3	100
681	C35H47N5O6	633.4	634.3	95.2
682	C34H47N5O5	605.4	606.4	97.4
683	C33H45N5O6	607.3	608.5	100

684	C33H43FN4O6	610.3	611.3	100
685	C32H40N4O5	560.3	561.2	100
687	C38H46N6O5	666.4	667.3	96.8
688	C36H50N6O5	646.4	647.3	98.3
689	C36H48N4O6	632.4	633.5	100
690	C34H48N4O5	592.4	593.3	100
691	C33H43N5O6	605.3	606.2	100
692	C40H56N4O6	688.4	688.6	99.0
693	C38H53N5O5	659.4	660.5	99.1
694	C36H49N5O5	631.4	632.3	100
695	C39H53N5O5	671.4	672.3	100
697	C36H47N5O6	645.4	646.2	100
698	C41H57N5O5	699.4	700.7	94.1
699	C50H63N7O5	841.5	842.3	99.7
700	C39H55N5O5	673.4	674.7	94.8
701	C39H51N5O7	701.4	702.2	100
703	C37H44N6O5	652.3	653.3	97.9
704	C38H46N6O5	666.4	667.4	97.4
705	C38H45N5O6	667.3	668.5	96.3
706	C46H61N5O6	779.5	780.8	97.2
707	C37H44N4O6	640.3	641.4	98.5
708	C36H43N7O5S	685.3	686.4	95.9
709	C31H39F3N4O4	588.3	589.3	100
710	C39H53N5O6	687.4	688.6	98.0
712	C36H48N4O4	600.4	601.3	100
713	C38H51N5O5	657.4	658.6	96.5

714	C37H49N5O5	643.4	644.5	96.7
715	C34H45N5O5	603.3	604.4	94.6
716	C34H46N6O5	618.4	619.3	100
718	C37H47N5O5	641.4	642.4	100
719	C33H43N5O7	621.3	622.6	100
720	C38H51N5O6	673.4	674.5	87.7
721	C36H47N5O5	629.4	630.5	96.7
722	C33H46N4O6	594.3	595.3	100
723	C37H49N5O5	643.4	644.6	99
724	C34H45N5O7	635.3	636.6	99
725	C38H51N5O6	673.4	674.7	99.7
726	C32H44N4O6	580.3	581.3	97.6
727	C33H47N5O4	577.4	578.7	97.9
729	C34H45FN6O5	636.3	637.4	100
730	C36H49N5O6	647.4	648.5	100
732	C31H42N4O6	566.3	567.5	100
734	C34H44N4O5	588.3	589.2	100
735	C31H42N4O6	566.3	567.5	100
736	C30H40N4O6	552.3	553.5	100
737	C36H42FN5O5	643.3	644.4	100
738	C38H47N5O5	653.4	654.5	100
741	C40H50N4O7	698.4	699.5	99.4

Biological Assays

Example B-1 : ß5 Inhibition Assay for the human constitutibe proeasome and the human immunoproteasome

Assay Description constitutive proteasome and immunoproteasome

The enzymatic activity of the ß5 subunit of the human constitutive proteasome (CPS) is analyzed. In another assay, which differs from the assay of the human constitutive proteasome only in using the human immunoproteasome (IPS) the enzymatic activity of the ß5 subunit of the human immunoproteasome (IPS) is analyzed.

Incubation of the enzyme with its fluorogenic substrate Suc-LLVY-AMC leads to liberation of the fluorescent dye AMC which can be measured with a suitable plate reader.

Reagents / Materials

Human cPS	E-360	Boston Biochem or
Human IPS	E-370	Boston Biochem
Suc-LLVY-AMC	I-1955	Bachem
Bortezomib	349320:01	Proteros
Assay plate	4514	Corning

Assay Buffer

- 100mM HEPES pH7,5
- 50mM NaCl
- 0,02% SDS
- 1mM DTT (add fresh)

Microplate reader settings

Victor X5 (Perkin Elmer)
Label: Umbeliferone (0,1s)
Excitation wavelength: 355nm
Emission wavelength: 460nm

Assay procedure (384 well plate)

- 4µl human cPS or IPS enzyme in assay buffer (final assay concentration 1nM) or 4µl assay buffer for negative controls
- Compound addition via acoustic dispenser (Echo 520, Labcyte)
- Mix and incubate @ RT for 10min

- 4µl Suc-LLVY-AMC substrate (final assay concentration 22.6µM)
- Mix and incubate @ RT for 4 h (dark)
- Stop reaction with 4µl Bortezomib (final assay concentration 1µM)
- 15min @ RT
- Measure (Excitation 355nm; Emission 460nm)

Table 2 shows activity data in the Human cPS ß5 Inhibition Assay. Inhibition is indicated as IC_{50} [nM] ("–" = not measured). Compounds having an activity designated as "A" provided an $IC_{50} \leq 100$ nM; compounds having an activity designated as "B" provided an 100 nM < $IC_{50} \leq 500$ nM; compounds having an activity designated as "C" provided an 500 nM < $IC_{50} \leq 1000$ nM; compounds having an activity designated as "D" provided an 1000nM < $IC_{50} \leq 5000$ nM; compounds having an activity designated as "E" provided an an $IC_{50} > 5000$nM.

Table 2:

Cpd	IPS [nM]	CPS [nM]
7	A	A
13	A	A
19	A	A
16	A	A
25	A	A
26	A	A
27	A	A
28	A	A
29	A	A
30	A	A
31	A	A
32	A	A
33	A	A
34	A	A
35	A	A
36	A	A
37	A	A
39	A	A
40	A	A
42	A	A
43	A	A
45	A	A

51	A	A
8	A	A
60	A	A
63	A	A
64	A	-
77	A	A
78	B	D
79	A	B
80	A	A
81	A	A
82	A	A
83	A	A
84	A	A
85	A	A
86	A	A
87	A	A
88	A	A
89	A	A
95	A	A
116	B	E
120	A	A
126	A	A
127	A	A
128	A	A
129	A	A
130	A	A
134	A	A
135	A	A
136	A	A
143	A	A
148	A	D
152	A	A
160	A	A
157	A	A
158	A	A
159	A	A
168	D	E
171	A	B

174	A	A
175	A	A
176	A	A
177	A	A
179	A	A
180	A	A
181	A	A
182	A	A
186	A	A
191	A	C
195	A	A
199	A	A
205	A	A
211	A	B
213	A	A
215	A	A
216	A	A
217	A	A
219	A	A
220	A	A
258	A	B
265	B	-
269	A	D
281	D	D
284	A	A
285	A	A
286	A	A
287	A	A
288	A	A
289	B	B
290	C	D
291	A	-
293	A	-
294	A	A
292	A	-
282	C	E
295	A	A
296	B	C

299	C	E
300	A	B
301	C	D
283	A	C
302	A	A
303	A	A
304	A	A
305	A	A
306	A	A
307	A	A
308	A	A
309	A	A
310	A	A
311	A	A
312	B	E
313	C	E
314	A	A
315	A	A
316	A	A
317	A	A
318	A	A
319	A	A
320	A	A
322	A	A
323	A	A
324	A	A
325	A	A
326	A	A
327	A	A
328	A	A
329	A	A
330	A	A
331	A	A
332	A	A
333	A	A
334	A	A
335	A	A
336	A	A

337	A	A
338	A	A
339	A	A
340	A	A
341	A	A
342	A	A
343	A	A
344	A	A
345	A	A
347	A	A
348	A	A
349	A	A
350	A	A
352	A	A
353	A	A
355	A	D
356	A	C
358	A	B
359	A	A
360	A	A
361	A	A
362	A	A
363	A	A
364	A	A
369	A	A
371	A	A
372	A	A
373	A	A
503	A	A
505	A	A
509	A	A
510	A	A
511	A	A
512	A	A
513	A	A
549	A	A
551	A	A
552	A	A

553	A	A
554	A	A
555	A	A
556	A	A
557	A	A
558	A	A
559	A	A
560	A	A
561	A	A
562	A	A
563	A	A
564	A	-
565	A	-
566	A	A
567	A	A
568	A	A
571	A	A
573	A	A
574	A	A
575	A	A
576	A	A
577	A	A
578	A	A
579	A	A
580	A	A
581	A	A
582	A	A
583	A	A
584	A	A
585	A	A
586	A	A
587	A	A
588	A	A
589	A	A
590	A	A
591	A	A
592	A	A
593	A	A

594	A	A
595	A	A
596	A	A
597	A	A
598	A	A
599	A	A
600	A	A
601	A	A
602	A	A
603	A	A
604	A	A
605	A	A
606	A	A
607	A	A
608	A	A
609	A	A
610	A	A
611	A	A
612	A	A
613	A	A
614	A	A
615	A	A
616	A	A
617	A	A
618	A	A
619	A	A
620	A	A
621	A	A
622	A	A
623	A	A
624	A	A
625	A	A
626	A	A
627	A	A
628	A	A
629	A	A
630	A	A
631	A	A

632	A	A
633	A	A
634	A	A
635	A	A
636	A	A
637	A	A
638	A	A
639	A	A
640	A	A
641	A	A
642	A	A
643	A	A
644	A	A
645	A	A
646	A	A
647	A	A
648	A	A
649	A	A
650	A	A
651	A	A
652	A	A
653	A	A
654	A	A
655	A	A
656	A	A
657	A	A
658	A	A
659	A	A
660	A	A
661	A	A
662	A	A
663	A	A
664	A	A
665	A	A
666	A	A
667	A	A
668	A	A
669	A	A

670	A	A
671	A	A
672	A	A
673	A	A
674	A	A
675	A	A
676	A	A
677	A	A
678	A	A
679	A	A
680	A	A
681	A	A
682	A	A
683	A	A
684	A	A
685	A	A
686	A	A
687	A	A
688	A	A
689	A	A
690	A	A
691	A	A
692	A	A
693	A	A
694	A	A
695	A	A
696	A	A
697	A	A
698	A	A
699	A	A
700	A	A
701	A	A
702	A	A
703	A	A
704	A	A
705	A	A
706	A	A
707	A	A

708	A	A
709	A	A
710	A	A
711	A	A
712	A	A
713	A	A
714	A	A
715	A	A
716	A	A
717	A	A
718	A	A
719	A	A
720	A	A
721	A	A
722	A	A
723	A	A
724	A	A
725	A	A
726	A	A
727	A	A
728	B	B
729	A	A
730	A	A
731	A	B
732	A	A
733	B	D
734	B	D
735	A	B
736	D	D
737	A	A
738	A	A
739	A	A
740	A	A
741	-	-

Example B-2 : CellTiter-Glo Luminescent Cell Viability Assay

Cell Titer Glo Viability Assay with HT-29 cells (72h incubation)

The CellTiter-Glo Luminescent Cell Viability Assay (Promega) is a homogeneous method of determining the number of viable cells in culture. It is based on quantification of ATP, indicating the presence of metabolically active cells.

On day 1 400 HT-29 cells per well are seeded in white 384well plates (Greiner, # 781080) in 25µl cell culture medium (DMEM (PAN-Biotech # P04-03590) + 10% FCS + glutamine). After incubation for 24h at 37°C/5% CO_2 compounds or DMSO are added at different concentrations by Echo Liquid Handling Technology. Cells are further incubated in humidified chambers for 72 h at 37°C and 5% CO_2. Cells treated with the compound vehicle DMSO are used as positive controls and cells treated with 10 µM Staurosporine serve as negative controls.

At day 5 – 72h after compound addition - the CellTiter Glo Reagent is prepared according to the instructions of the kit (Promega Inc.): Reagent is mixed 1:1 with cell culture medium. Thereon, mixture and assay plates are equilibrated at room temperature for 20 min. Equal volumes of the reagent-medium-mixture is added to the volume of culture medium present in each well. The plates are mixed at ~300 rpm for 2 minutes on an orbital shaker. The microplates are then incubated at room temperature for 10 minutes for stabilization of the luminescent signal. Following incubation the luminescence is recorded on a Victor microplate reader (Perkin Elmer) using a 200 ms integration time. The data is then analyzed with Excel using the XLFIT Plugin (dose response Fit 205) for IC_{50}-determination.

As quality control the Z´-factor is calculated from 16 positive and negative control values. Only assay results showing a Z´-factor ≥ 0.5 are used for further analysis.

Table 3 shows activity data in the biochemical Glo cell viability assays of A549 (human lung carcinoma *cell* line) and Karpas and CTG assay of HT29 (human colone cancer cell line) cell. Inhibition is indicated as IC_{50} [nM] ("–" = not measured). Compounds having an activity designated as "A" provided an $IC_{50} \leq 100$ nM; compounds having an activity designated as "B" provided an 100 nM < $IC_{50} \leq 500$ nM; compounds having an activity designated as "C" provided an 500 nM < $IC_{50} \leq 1000$ nM; compounds having an activity designated as "D" provided an 1000nM < $IC_{50} \leq 5000$ nM; compounds having an activity designated as "E" provided an an $IC_{50} > 5000$nM.

Table 3:

Cpd No.	PGLo A549 [nM]	Pglo Karpas [nM]	CTG HT29 [nM]
7	A		A
8	C	A	B
13	C		C
19	D	C	D
16	C		B
22	-		D
25	A		A
26	A		A
27	A		A
28	A	A	A
29	A		A
30	A		A
31	A		A
32	A		A
33	A		A
34	A		A
35	B		B
36	B		B
37	A		A
38			A
39	A		A
40	A		A
41			A
42	A		A
43	B		A
44			A
45	B		B
51	B		D
59	ND		D
60	B	B	A
61			A
62			A
63	A	A	A
64	A	A	A
77	C	B	D

78	E	B	
79	D	C	D
80	A	A	A
81	A	A	A
82	A	A	A
83	A	A	A
84	A	A	A
85	A	A	A
86	A	A	A
87	A	A	A
88	A	A	A
89	A	A	A
95	D		C
107	-		A
116	E		B
120	D		B
126	A		B
127	A		A
128	A		A
129	A		A
130	B		B
134	A		A
135	A		A
136	A		B
143	B		B
148	E		B
151			A
152	A		A
160	B		A
157	B		A
158	A		A
159	B		A
168	-		B
171	C		B
172	-		A
173	-		B
174	A		A
175	A		A

176	A		A
177	A		A
179	A		A
180	A		A
181	A		A
182	A		A
186	B		B
191	D		D
195	B		A
199	A		A
205	A		A
211	C		B
213	B		A
215	B		A
216	B		A
217	A		A
218			A
219	A		A
220	A		A
252			B
253			B
254			B
255	E		B
256			B
257			B
258	C		B
259			B
260			B
261			B
265	E		B
269	D		D
281	D		B
284	B		A
285	B		A
286	B		A
287	A		A
288	B		A
289	C		B

290	E		B
291	D		A
293	A		A
294	A		A
292	A		A
282	E		B
295	B		A
296	C		B
298			B
299	E		B
300	D		B
301	D		B
283	D		B
302	A		A
303			A
304			A
305			A
306			A
307			A
308			A
309	A		A
310	A		A
311	A		A
312			B
313			B
314	A		A
315			A
316			A
317			A
318			A
319			A
320	A		A
322	D		B
323	A		A
324	A		A
325	A		A
326	A		A
327	B		A

328	B		A
329	B		A
330	A		A
331	A		A
332	A		A
333	A		A
334	B		A
335	A		A
336	A		A
337	B		A
338	B		A
339	B		A
340	A		B
341	A		A
342	A		A
343	A		A
344	A		A
345	B		A
347	B		A
348	A		A
349	B		B
350	A		A
351	B		B
352	A		A
353	A		A
354			B
355	E		D
356	C		C
358	A		B
359	A		A
360	A		A
361	B		A
362	A		A
363	A		A
364	A		A
369	A		A
371	A		A
372	A		A

373	A	A	
495			B
503	B		A
571	A		C
505	A		A
572			B
509	A		B
510	A		A
511	A		A
512	A		A
513	A		A
549	B		A
550			A
551	A		A
552	B		A
553	B		A
554	B		A
555	A		A
556	A		A
557	A		B
558	B		A
559	B		A
560	B		A
561	A		A
562	B		B
563	A		A
564	A		A
565	A		A
566	A		B
567	A		B
568	A		B
573	A		
574	A		
575	A		
576	A		
577	A		
578	A		
579	A		

580	A		
581	A		
582	A		
583	A		
584	A		
585	A		
586	A		
587	A		
588	A		
589	A		
590	A		
591	A		
592	A		
593	A		
594	A		
595	A		
596	A		
597	A		
598	A		
599	A		
600	-		
601	A		
602	A		
603	A		
604	A		
605	A		
606	A		
607	A		
608	A		
609	A		
610	A		
611	A		
612	A		
613	A		
614	A		
615	A		
616	A		
617	A		

618	A		
619	A		
620	A		
621	A		
622	A		
623	A		
624	A		
625	A		
626	A		
627	A		
628	A		
629	A		
630	A		
631	A		
632	A		
633	A		
634	A		
635	A		
636	A		
637	A		
638	A		
639	A		
640	A		
641	A		
642	A		
643	A		
644	A		
645	A		
646	A		
647	A		
648	A		
649	A		
650	A		
651	A		
652	A		
653	A		
654	A		
655	A		

656	A		
657	A		
658	A		
659	A		
660	A		
661	A		
662	A		
663	A		
664	A		
665	A		
666	A		
667	A		
668	A		
669	A		
670	A		
671	A		
672	A		
673	A		
674	A		
675	A		
676	A		
677	B		
678	A		
679	A		
680	A		
681	A		
682	A		
683	A		
684	A		
685	A		
686	A		
687	A		
688	A		
689	A		
690	A		
691	A		
692	A		
693	A		

694	A		
695	A		
696	A		
697	A		
698	A		
699	A		
700	A		
701	A		
702	A		
703	A		
704	A		
705	A		
706	A		
707	A		
708	A		
709	A		
710	A		
711	B		
712	A		
713	A		
714	A		
715	A		
716	A		
717	A		
718	A		
719	A		
720	A		
721	B		
722	B		
723	A		
724	A		
725	A		
726	B		
727	B		
728	C		
729	A		
730	B		
731	D		

732	D		
733	D		
734	D		
735	E		
736	E		
737	A		
738	A		
739	A		
740	B		
741	-		

Example B-3 : Chymotrypsin-like ProteasomeGlo assay

Chymotrypsin-like ProteasomeGlo assay in the B-cells isolated from PBMC's following compound addition (IC_{50}).

1. PBMC's will be isolated from human blood followed by B-cell isolation from the PBMC's using the Miltenyi Isolation Kit.
2. This experiment will use the Chymotrypsin-like ProteasomeGlo read-out to generate IC50's folowing compound treatment.
3. Dilute all compounds 1:100 for the assay.
4. Do not make a staurosporine transfer for lane 12! Repeat the DMSO transfer with lane 12.
5. Lane 12 should not be seeded with any cells. Only medium!
6. For all steps, make sure the samples and reagents remain cool!
7. While dealing with the buffy coats, be careful to not let any exposed skin to be in direct contact with the blood.

Reagents

Separating medium

Lymphocyte Separating Medium (Pancoll) (PAN Biotech; P04-60125)

RBC Lysis Buffer (10x) (BioLegend; 420301)

Prepare 1x RBC Lysis Buffer by diluting 10x RBC Lysis Buffer to 1x with ddH_2O.

PBMC cell medium

Component	Manufacturer information	Concentration	Volume (ml)	Final concentration
RPMI 1640	PAN Biotech; P04-22100		500	

HyClone Heat inactivated FCS	Thermo Scientific; SV30180.03 (Lot No.: TXK40002)	100 %	50	10 %
L-Glutamine	PAN Biotech; P04-80100	100x	5	1X

Cultivation medium for B-cells

Component	Manufacturer information	Concentration	Volume (ml)	Final concentration
DMEM	Gibco; 41965039		500	
Heat inactivated FCS	Capricon; FBS-11A	100%	50	10%
L-Glutamine	PAN Biotech; P04-80100	100x	5	1X

Wash buffer

Component	Manufacturer information	Concentration	Volume (ml)	Final concentration
DPBS	Gibco; 14190136		178	89 %
DMEM	Gibco; 41965039		20	10 %
Heat inactivated FCS	Capricon; FBS-11A	100 %	2	1 %

B cell isolation buffer

Component	Manufacturer information	Concentration	Final concentration	Amount	Unit
DPBS	Gibco; 14190136			300	ml
Bovine Serum albumin (BSA)			0.50%	1.5	g
EDTA Solution	Self-made	250 mM	2 mM	2.4	ml

Chymotrypsin-Like Cell-Based Proteasome-Glo™ Assay (Promega; G8661)
Cell culture 384-well plates (Greiner BioOne; 781080)
Dispensing cassette, MultiDrop Standard tube dispensing cassette (Thermo Scientific; 24072670)
DPBS (Pan BioTech; P04-36500)
Cell culture 384-well plates (Greiner BioOne; 781080)
CPD source plate: diamond-shape plate (Labcyte; LP-0200)

Intermediate plate (Labcyte; P-05525)

Day 1	Seed A549 cells
Day 2	Seed Karpas cells and ProteasomeGlo assay

B cell Isolation Kit II, human (Miltenyi Biotec; 130-091-151)

includes,

1. QuadroMACS™ Starting Kit (LS) (#130-091-051)

QuadroMACS™ Separator ((#130-090-976)
MACS MultiStand ((#130-042-303)
LS Columns (#130-042-401)
MACS® 15 mL Tube Rack (#130-091-052)
One unit of MACS Microbeads, or one MACS Microbead Kit, or one MACS Cell Isolation Kit.

2. B cell Isolation Kit II

Components:	- 1mLB Cell Biotin-Antibody Cocktail, human: Cocktail of biotin-conjugated monoclonal antibodies against CD2, CD14, CD16, CD36, Cd43, and CD235a (Glycophorin A)- - 2 mL Anti-Biotin Microbeads: Microbeas conjugated to monoclonla anti-biotin antibodies (isotype: mouse IgG1).
Capacity	For 10^9 total cells
Product format	All components are supplied in buffer containing stabilizer and 0.05 % sodium azide.
Storage	Store protected from light at 2-8 °C. Do not freeze. The expiration date is indicated on the vial labels.

Components of the Miltenyi Biotec Starting and B cell Isolation Kit

- MACS® MultiStand
- LS Columns
- QuadroMACS™ Separator

Method

Day 1: PBMC isolation followed by B-cell isolation using the Miltenyi Kit
Day 2: B-cell plating, ECHO transfer and ProteasomeGlo assay

Day 1

1. Prepare the wash buffer and cultivation medium for the assay.

a. Cultivation medium: Prepare and store at 4°C. The cultivation medium will be used at the end of B-cell isolation for overnight incubation of the B-cells and subsequent experiment.
b. Wash buffer: Prepare fresh before each assay taking into care to be exact with the volumes prepared.
~ 200ml of the wash buffer is required per B-cell isolation from PBMCs.
c. Buffer for B cell isolation: Prepare the buffer fresh before each assay as it contains BSA which is unstable in a solution for long term storage. Cool the buffer own on ice before use!
d. PBMC cell medium: Prepare and store at 4°C. The medium is to be pre-warmed before starting the PBMC isolation from the buffy coats.

2. Assemble the components of the Miltenyi Separator + MACS MultiStand as follows:

a. Attach the QuadroMACS Separator to the MACS MultiStand by placing the separator adjacent to the MultiStand and slowly sliding the separator onto the stand. not to trap your fingers while attaching the two components together.
b. Check that the ejection blocks in the gap pf the magnet (separator) are attached before placing the MACS LS columns into the magnetic field of the separator.
c. Place the LS Columns with the column wings to the front into the slots of the separator.

3. PBMC isolation from buffy coats

For the initial steps and to make processing the buffy coats easier, separately process the buffy coats.

a. Cut the tube attached to the buffy coats carefully using a clean, sterile and fresh scalpel.
b. Transfer the blood into 2 individual 50ml falcons.
c. Add an equal volume of DPBS to the blood in the falcons.
d. Add ~20ml of lymphocyte separating medium to two 50ml falcons.
e. Carefully pour 15-20ml of the blood + DPBS mix from step c. onto the lymphocyte separating medium from step d.

f. Centrifuge the falcons with the lymphocyte separating medium + blood mix at 800xg for 15minutes using a swing-out rotor.
g. Following centrifugation, carefully remove the falcons from the centrifuge.
h. The following layers will be observed:
i. Aspirate the plasma layer off carefully without disturbing the different layers.
j. Remove the cell pellet using a pipette into two fresh 50ml falcons.
k. Fill the falcons with the cells upto 50ml with DPBS.
l. Centrifuge the falcons at 250xg for 10minutes using a swing-out rotor (Brake-off).
m. Aspirate the complete DPBS off the cells without disturbing the cell pellet at the bottom of the falcon.
n. Re-suspend the cell pellet in 10ml of 1x RBC lysis buffer.
o. Incubate the falcons at room temperature in the dark for 10minutes.
p. After RBC lysis, centrifuge the tubes at 250xg for 10minutes using a swing-out rotor (brake-off).
(***Note:** If the cell pellet is still red or light red, repeat steps n. to p.!)
q. Re-suspend the cell pellet in DPBS up to 50ml in the falcon.
r. Centrifuge the falcons at 250xg for 10minutes using a swing-out rotor (Brake-off).
s. Aspirate the DPBS off the cells without disturbing the cell pellet at the bottom of the falcon.
t. Repeat the wash step as described in steps q. to s. 2x times more (total number of washes is 3x).
u. Aspirate the DPBS completely off the cell pellet after the last wash without disturbing the cell pellet.
v. Re-suspend the cell pellet in 20ml of PBMC cell medium.
w. Proceed to counting of cells and B-cell isolation from PBMCs.
(***Note:** Keep the cells isolated from the two donors or more always separate and do not pool the cells from multiple donors at any step!(

4. B cell isolation from PBMCs

a. Collect the PBMCs and re-suspend the entire amount of cells into 30ml of wash buffer in a 50ml falcon.
b. Count the PBMCs using the CEDEX.

	Patient 1 (719)	Patient 2 (724)
Number of PBMC/ml	17774000	13101000
Total volume of suspension	40 ml	40 ml
Total number of PBMCs	710960000	524040000

c. Leave the cell suspension at room temperature for 30mins.
d. Centrifuge the cell suspension at the end of 30 minutes for 10mins at 1500rpm.

e. Aspirate the wash buffer carefully from the cells without disturbing the pellet at the bottom of the falcon.

f. Re-suspend the pellet in volume of the B-cell isolation buffer calculated as follows:

Volume of B-cell isolation buffer per 10^7 total cells	40 µl	40 µl
Total number of cells	710960000	524040000
Total volume of B-cell isolation buffer needed for re-suspension	2843.84 µl	2096.16 µl

g. Add the calculated volume of Biotin-Antibody Cocktail as follows:

Volume of Biotin-Antibody cocktail per 10^7 total cells	10 µl	10 µl
Total number of cells	710960000	524040000
Total volume of Biotin-Antibody cocktail to be added	710.96 µl	524.04 µl

h. Mix well using a 1ml pipette and incubate on ice for 10mins.

i. Add more B-cell isolation buffer to the cell + antibody suspension as follows:

Volume of B-cell isolation buffer per 10^7 total cells	30 µl	30 µl
Total number of cells	710960000	524040000
Total volume of B-cell isolation buffer to be added	2132.88 µl	1572.12 µl

j. Add the calculated volume of anti-Biotin Microbeads to the cell + antibody mix as follows:

Volume of anti-Biotin microbeads per 10^7 total cells	20 µl	20 µl
Total number of cells	710960000	524040000
Total volume of Biotin-Antibody cocktail to be added	1421.92 µl	1048.08 µl

k. Mix well using a 1ml pipette and incubate the mix on ice for 20mins.

l. In the meantime, equilibrate one LS Column as follows:

1. Insert one LS Column into one slot of the separator as depicted in the pictures above.
2. Place a 50ml falcon at the bottom of the LS column to collect the wash flow-through.
3. Add 3ml of the B-cell isolation buffer into the column.
4. Allow the buffer to flow-through making sure that the entire volume passes the column and that the column reservior is empty before the addition of the cells.
5. Remove the falcon with the flow-through and discard.

m. Place a fresh 50ml falcon under the LS Column to collect the untouched B-cells isolated from the PBMCs.

n. Apply the entire volume of the cell + antibody + microbeads mix to the LS Column.

o. Collect the flow-through from each application of the mix into the same 50ml falcon under the LS Column.

p. Once the complete volume of the cell + antibody + microbead mix has been passed through, proceed to washing of the column.

q. Add 3ml of the B-cell isolation buffer to the LS Column and allow the buffer to flow-through. Collect the flow-through and repeat the wash 2x times more (in total 3x washes).

r. Centrifuge the B-cells isolated in the collection falkan at 1500rpm and 4°C for 15mins.

s. Aspirate the B-cell isolation buffer off the pellet keeping in mind the relatively low attachment of the B-cells to tubes and that the B-cells are not aspirated off.

t. Re-suspend the B-cell pellet in 1000 µl of fresh B-cell isolation buffer.

u. Collect 50µl of the B-cell suspension into a fresh, labelled eppi and add 25 µl of 3x Laemmli buffer to the cell suspension (Sample)

v. Make up the volume of the B-cell suspension to 10ml with B-cell cultivation medium and store the suspension overnight at 4°C.

w. Place a fresh 2ml eppendorf under the LS Column. Remove the column from the separator and carefully depress the plunger through the column, collecting the unwanted cells removed from the B-cells (Pass).

x. Add 100 µl of 3x Laemmli buffer to the Pass from step u and 25 µl of 3x Laemmli buffer to the Input collected in step f.

y. Boil all three samples (Input, Sample and Pass) at 98°C for 15mins.

z. Proceed to western blotting from the samples prepared.

a1. For the B-cell suspension stored overnight, proceed to B-cell counting and plating for cell number titration on Day 2.

Day 2

Proceed directly with the cell suspension from Day 1 for cell counting.

1. Count the cells using the CEDEX

Cell number required per well	10.000	/25µl
Number of cells/ml	400.000	
Number of wells	384	
Total number of plates	3	
Volume of cell suspension to be seeded per well	25	µl
Total volume of cell suspension required	28800	µl
Total Volume of cells required	20000000	

	B-cells		**B-cells**
Number of cell/ml	21777000		14331000
Number of cells/ml			

Total volume of cells suspension	0.91840015 ml		1.39557602 ml
Volume of medium required	49.0815999 ml		48.604424 ml

2. Using a multi-channel pipette, pipette 25 µl of the cell suspensions

3. Place the cells **for 3hrs** in the high humidity incubator at 37°C and 5% CO_2.

ECHO Compound transfer

Destination plate refers to the plates onto which the compounds will be transferred (meaning the plates with the cells already plated).

1. Compound plate from compound management:

a. Pipette 2x 8µl of the compounds (10mM or 1mM stock solutions) into rows A1-P1, A2-P2 and A3-L3 of a diamond shaped plate.

b. Once pipetted, seal the compound plate with an aluminum foil seal and spin down briefly. Place the plate in the dark till further use.

2. DMSO intermediate plate:

a. Pipette 25µl of DMSO into columns 1-12 of an intermediate plate.

b. Seal the lanes 1-12 using an aluminum foil seal.

c. Spin the plate down briefly and store till further use.

4. ECHO transfer

a. Remove the plates with cells from the incubator.

b. Take all the plates including the compound plate, intermediate plate and Staurosporine plate to the ECHO.

c. Click on "Open" in the ECHO software and select the protocol "QLI5_25ul_30uM-Grenier".

d. Follow the on-screen prompts and instructions once you click "Start" to insert the compound plate, intermediate plate and destination plates.

e. Change the final number of destination plates on the program.

f. Follow the on-screen prompts and instructions once you click "Start" to load the Staurosporine and destination plates.

g. Once all the compounds, DMSO and Staurosporine have been transferred, place the destination plates in a wet tissue box.

h. Place the destination plates back into the incubator and incubate at 37°C, 5% CO_2 for 105 minutes.

i. Re-seal all the compound + Stauro diamond and intermediate plates and store in the dark.

Chymotrypsin like ProteasomeGlo Assay

1. Thaw the components of the ProteasomeGlo assay at room temperature including the ProteasomeGlo Buffer, the lyophilized Luciferin Detection Reagent and the Suc-LLVY-Glo Substrate.
2. Reconstitute the Luciferin Detection Reagent in the amber coloured bottle by adding 50ml of the ProteasomeGlo Buffer.
3. Vortex the Suc-LLVY-Glo Substrate briefly to reconstitute the Substrate well.
4. Spin down the Substrate and add 250µl of the Substrate to the reconstituted Luciferin Detection Reagent from step 2.
5. Briefly vortex the amber bottle with the mix to prepare a homogenous solution.
6. Place the mix prepared in step 5 to sit at room temperature for 60 minutes.
7. After 60minutes, pipette 25µl of the mix from step 5 into all wells with the cells.
8. Shake the plates for 2-5minutes to ensure the complete mixing of the ProteasomeGlo reagent with the cells.
9. Leave the plates in the dark for 10-15minutes.
10. Measure the luminescence read-out using the Viktor and the protocol "Luminescence_384Well_0.2sec".

(**Note:** The Protoeasome-Glo™ Reagent (combined Proteasome-Glo™ Substrate, Proteasome-Glo™ Buffer and Luciferin Detection Reagent) can be stored at 4°C or –20°C for 1 month with minimal loss of activity.)

Table 4 shows activity data in the Chymotrypsin-like ProteasomeGlo assay of B-cell and hPMBC. Inhibition is indicated as IC_{50} [nM] ("–" = not measured). Compounds having an activity designated as "A" provided an $IC_{50} \leq 100$ nM; compounds having an activity designated as "B" provided an 100 nM < $IC_{50} \leq 500$ nM; compounds having an activity designated as "C" provided an 500 nM < $IC_{50} \leq 1000$ nM; compounds having an activity designated as "D" provided an 1000nM < $IC_{50} \leq 5000$ nM; compounds having an activity designated as "E" provided an an $IC_{50} > 5000$nM.

Table 4:

Cpd No.	Pglo B-Cell [nM]	Pglo hPBMC [nM]	B cell diff. [nM]	PBMC IL17 stim. [nM]
7		A		
8	A	B		
13	A		B	
16	A		A	A
22				
25	A			

26	A			
27	A		A	A
28		B		
29	A		A	A
30	A		A	
31	A			
32	A			
33	A		A	
34	A		A	
35	A		A	
36	B		A	
37	A		A	
39	A			
40	A			
42	A		A	
43	A		A	
44				
45	B		A	
51	A			
59	B			
60	B	B		
63	A	A		A
64	A	A		
77	B	B		
78	B	C		
79	C			
80	A	A		
81	A	A		
82	A	A		
83	A	A		
84		A		
85		A		
86		A		
87		A		
88	A	A		
89		A		
116		C		
120		B		

126		A		
127		A		
128		A		
129		A		
130		A		
134		A		
135		A		
136		A		
143		A		
148		C		
151				
152		A		
160		A		
157		A		
158		A		
159		A		
168		D		
171		A		
174		A		
175		A		
176		A		
177		A		
179		A		
180		A		
181		A		
182		A		
186		B		
191		B		
195		A		
199		A		
205		A		
211		B		
213		A		
215		A		
216		A		
217		A		
219		A		
220		A		

253		E		
255		E		
256		E		
257		D		
258		B		
259		E		
260		E		
281		D		
284		A		
285		A		
286		A		
287		A		
288		A		
289		C		
290		E		
291		D		
293		A		
294		A		
292		A		
282		C		
295		B		
296		B		
299		D		
300		C		
301		D		
283		C		
302		A		
309		A		
310		A		
311		A		
314		A		
320		A		
322		C		
326		A		
329		B		
332		A		
333		A		
334		B		

335		A		
336		A		
337		A		
338		A		
339		B		
340		A		
341		A		
342		A		
343		A		
344		A		
345		A		
347		A		
348		A		
349		A		
350		A		
351		A		
352		B		
353		A		
354		A		
355		A		
356		A		
358		A		
359		A		
360		A		
361		A		
362		A		
363		A		
364		A		
371		A		
372		A		
373	A	A		
503		B		
505		B		
509		B		
510		A		
511		A		
512		A		
513		A		

549		A		
550				
551		A		
552		A		
553		A		
554		B		
555		A		
556		A		
557		A		
558		A		
559		A		
560		A		
561		A		
562		A		
563		A		
564		A		
565		B		
566		B		
567		A		
568		A		
571		A		

Example B-4 : CTG assays

A viability assay was conducted for 48 hours to evaluate the inhibition of cancer cell growth by proteasome inhibitors. Briefly, the candidate cell line was plated with a 96-well plate following density of cells, respectively. 6 x 10^3 Cells/well for A2780 (human ovarian cancer cell line) and MDA-MB-468 (breast carcinoma), 8 x 10^3 Cells/well for Hs746T (human gastric carcinoma cell line), 1.1 x 10^4 Cells/well for MM1S and RPMI 8226 (multiple myeloma). After 24 hours, the cells were treated with various concentrations of the compound (ranging from 0.0015 uM to 10 uM). DMSO solvent without compound served as control and the final DMSO concentration was less than 0.1%. After 48 hours of incubation at 37 ℃, 5% CO_2 incubator, cells were analyzed for viability using the CellTiter-Glo Luminescent Cell Viability assay (Promega, Cat# G7570). All viability assays were performed in duplicate and Luminescence was read using an Envision (Perkin Elmer, USA). Data were analyzed using XLfit software.

Table 5 shows activity data in the 48 hr CTG assays of A2780 (human ovarian cancer cell line), MDA-MB-468 (breast carcinoma), Hs 746T (human gastric carcinoma cell

line), MM1S (B lymphoblast cell line), and RPMI 8226 (B lymphocyte cell line, multiple myeloma). Inhibition is indicated as IC_{50} [nM] ("–" = not measured). Compounds having an activity designated as "A" provided an $IC_{50} \leq 100$ nM; compounds having an activity designated as "B" provided an 100 nM < $IC_{50} \leq 500$ nM; compounds having an activity designated as "C" provided an 500 nM < $IC_{50} \leq 1000$ nM; compounds having an activity designated as "D" provided an 1000nM < $IC_{50} \leq 5000$ nM; compounds having an activity designated as "E" provided an an $IC_{50} > 5000$nM.

Table 5

Cpd	A2780 IC_{50} [nM]	MDA-MB-468 IC_{50} [nM]	Hs 746T IC_{50} [nM]	MM1S IC_{50} [nM]	RPMI-8226 IC_{50} [nM]
573				A	A
574		A	A	A	A
575			A	A	A
576			A	A	A
577			A	A	A
578			A	A	A
579			A	A	A
580			A	A	A
581			A	A	A
582			A	A	A
583			A	A	A
584			A	A	A
585			A	A	A
586			A	A	A
587			A	A	A
588			A	A	A
589			A	A	A
590			A	A	A
591			A	A	A
592			A	A	A
593			A	A	A
594			A	A	A
595			A	A	A
596			A	A	A
597			A	A	A
598			A	A	A

599		A	A	A	A
600				A	A
601			A	A	A
602			A	A	A
603			A	A	A
604			A	A	A
605			B	A	A
606			A	A	A
607			A	A	A
608			A	A	A
609			A	A	A
610			A	A	A
611			A	A	A
612			A	A	A
613			A	A	A
614			A	A	A
615			A	A	A
616			A	A	A
617			A	A	A
618			A	A	A
619			A	A	A
620			A	A	A
621			A	A	A
622			A	A	A
623			A	A	A
624			A	A	A
625			A	A	A
626			A	A	A
627			A	A	A
628			A	A	A
629			A	A	A
630			A	A	A
631			A	A	A
632			A	A	A
633			A	A	A
634	A	A	A	A	A
635			A	A	A
636			A	A	A

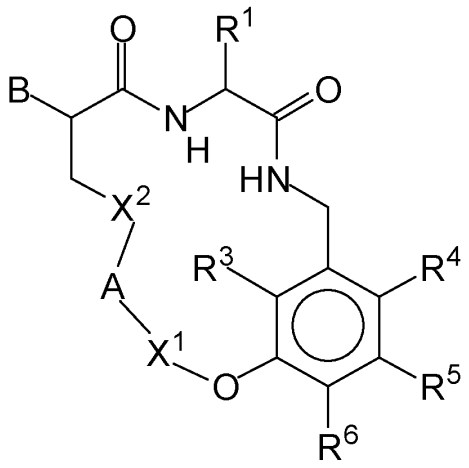
637			A	A	A
638			A	A	A
639			A	A	A
640			A	A	A
641			A	A	A
642			A	A	A
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644				A	A
645			A	A	A
646			A	A	A
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648			A	A	A
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657			A	A	A
658			A	A	A
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662			A	A	A
663			A	A	A
664		A	A	A	A
665			A	A	A
666			A	A	A
667			A	A	A
668			A	A	A
669			A	A	A
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671		A	A	A	A
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673			A	A	A
674			A	A	A

675			A	A	A
676			A	A	A
677			A	A	A
678			A	A	A
679			A	A	A
680			A	A	A
681			A	A	A
682				A	A
683		A	A	A	A
684			A	A	A
685			A	A	A
686			A	A	A
687			A	A	A
688			A	A	A
689				A	A
690			A	A	A
691			A	A	A
692			A	A	A
693			A	A	A
694			A	A	A
695			A	A	A
696			A	A	A
697			A	A	A
698			A	A	A
699			A	A	A
700			A	A	A
701			A	A	A
702			A	A	A
703			A	A	A
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706			A	A	A
707			A	A	A
708			A	A	A
709			B	A	A
710			A	A	A
711			B	A	A
712			B	A	A

713			B	A	A
714			B	B	A
715			B	A	A
716			B	A	A
717			B	B	B
718			B	A	B
719			C	B	B
720			C	B	B
721			A	A	B
722			C	B	B
723			B	B	B
724			C	B	B
725			B	B	B
726			C	B	B
727			D	C	B
728			D	B	B
729			B	B	B
730		D	C	B	C
731			D	B	C
732		D	E	D	C
733				B	D
734			E	D	D
735		E	E	D	D
736			E	D	D
737			A	A	A
738	A	A	A	A	A
739			B	A	A
740			D	B	B
741					

Claims

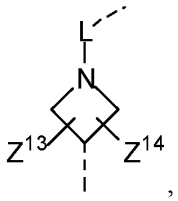
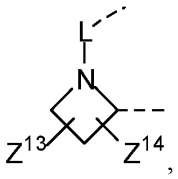
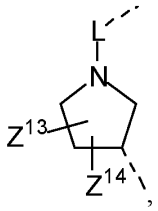
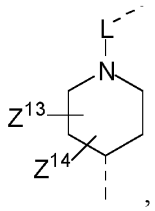
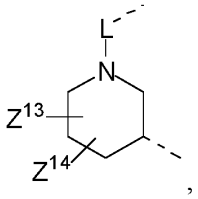
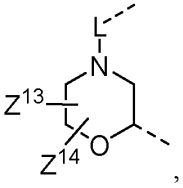
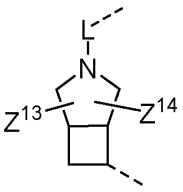
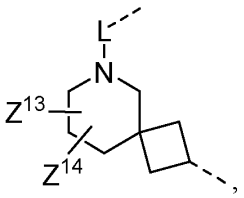
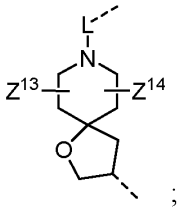
1. Compound of the general formula (I)



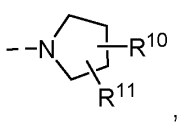
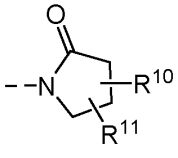
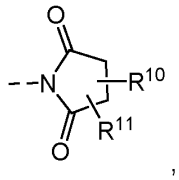
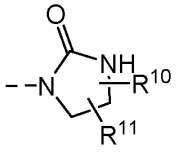
(I)

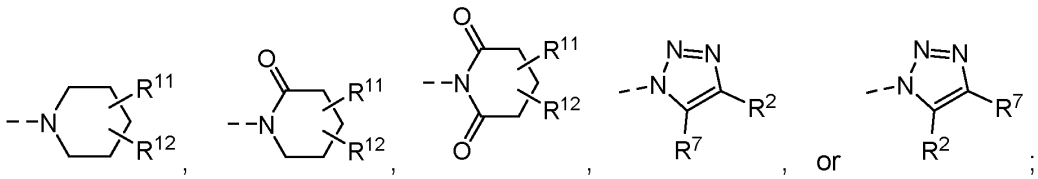
wherein

A represents –CO–N($\mathbf{R}^{N6}$)–,


,

,

,

,

,

,

,

,
or

;

B represents –H, –NH($\mathbf{R}^{2}$), –N($\mathbf{R}^{2}$)($\mathbf{R}^{N5}$),


,

,

,

,



L represents –CO–, –CO–NH–, –CO–N($\mathbf{R^{N3}}$)–, or –CO–O–;

$\mathbf{R^1}$ represents –H, –$(CH_2)_p$–$\mathbf{R^7}$, –$(CH_2)_p$–NH–$\mathbf{R^7}$, –$(CH_2)_p$–$\mathbf{R^9}$, or –$(CH_2)_p$–NR^{N4}–$\mathbf{R^9}$;

$\mathbf{R^2}$ represents –H, –$\mathbf{R^8}$, –$\mathbf{R^{11}}$, –$\mathbf{L^1}$–$\mathbf{R^{11}}$, –$\mathbf{L^1}$–$(CH_2)_r$–$\mathbf{R^8}$, –$\mathbf{L^1}$–$\mathbf{R^{10}}$, –$\mathbf{L^1}$–$(C_2H_4O)_s$–$\mathbf{R^{11}}$, –$\mathbf{L^1}$–$(CH_2)_t$–O–$\mathbf{R^{11}}$, –$\mathbf{L^1}$–$(CH_2)_t$–NH–$(CH_2)_r$–$\mathbf{R^8}$, –$\mathbf{L^1}$–$(CH_2)_t$–O–$(CH_2)_r$–$\mathbf{R^8}$, –$\mathbf{L^1}$–$(CH_2)_t$–NH$\mathbf{R^8}$, –$\mathbf{L^1}$–$(CH_2)_t$–NH–CO–$\mathbf{R^8}$, –$\mathbf{L^1}$–$(CH_2)_t$–NH–SO_2–$\mathbf{R^8}$, –$\mathbf{L^1}$–$(CH_2)_t$–$NR^{N6}\mathbf{R^{10}}$, –$\mathbf{L^1}$–$(CH_2)_t$–O–$(CH_2)_u$–$NR^{N6}\mathbf{R^{10}}$, –$\mathbf{L^1}$–$(CH_2)_r$–$\mathbf{R^{14}}$, –CO–C($\mathbf{R^{12}}$)($\mathbf{R^{13}}$)–$\mathbf{R^{10}}$, –CO–C($\mathbf{R^{12}}$)($\mathbf{R^{13}}$)–$\mathbf{R^8}$, or –CO–C($\mathbf{R^{12}}$)($\mathbf{R^{13}}$)–$(CH_2)_u$–$\mathbf{R^8}$;

$\mathbf{L^1}$ represents a bond, –CO–, –CO_2–, –CONH–, or –SO_2–;

$\mathbf{R^3}$ – $\mathbf{R^6}$ represent independently of each other –H, –CH_3, –OCH_3, –F, or –Cl;

or $\mathbf{R^5}$ and $\mathbf{R^6}$ form  ;

$\mathbf{R^8}$ and $\mathbf{R^9}$ represent independently of each other

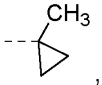
C_6–C_{14} aryl, C_1–C_{10} heteroaryl, C_3–C_8 carbocyclyl, C_1–C_9 heterocyclyl, C_4-C_{11} bicyclic carbocyclyl, C_4–C_{11} bridged carbocyclyl, C_1–C_{10} bicyclic heterocyclyl, C_1–C_{10} bridged heterocyclyl, C_7–C_{16}–spiroalkyl, C_5–C_{14}–spiroheterocyclyl,

wherein all afore-mentioned ring systems can be substituted with 1 to 5 substituents selected from Z^1, Z^2, Z^3, Z^4, Z^5, Z^6, Z^7, Z^8, Z^9, Z^{10}, Z^{11}, Z^{12}, $R^{N1}$and R^{N2}; and

C_1–C_{10} heteroaryl, C_1–C_9 heterocyclyl, C_1–C_{10} bicyclic heterocyclyl, C_1–C_{10} bridged heterocyclyl, C_5–C_{14}–spiroheterocyclyl ring systems contain at least one of heteroatoms N, O, and S;

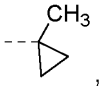
said C_3–C_8 carbocyclyl, C_1–C_9 heterocyclyl, C_1–C_{10} bicyclic heterocyclyl, C_4–C_{11} bridged carbocyclyl, C_1–C_{10} bicyclic heterocyclyl, C_1–C_{10} bridged heterocyclyl, C_7–C_{16}–spiroalkyl, C_5–C_{14}–spiroheterocyclyl ring systems can be partly saturated or unsaturated;

R^7 and R^{10} represent independently of each other –H, $–CH_3$, $–C_2H_5$, $–C_3H_7$, $–CH(CH_3)_2$, $–CH_2F$, $–CHF_2$, $–CF_3$, $–CH_2CN$, $–C(CH_3)_2–CN$, $–CH_2–C(CH_3)_2–CN$, $–CH_2–CF_3$, $–CH_2–C(CH_3)_2–NH_2$,



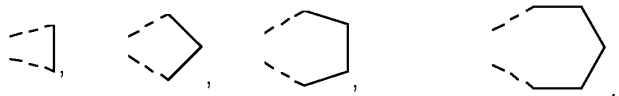
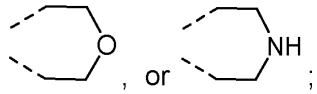
, cyclo-C_3H_5, cyclo-C_4H_7, cyclo-C_5H_9, cyclo-C_6H_{11}, cyclo-C_7H_{13}, $–C_4H_9$, $–CH_2–CH(CH_3)_2$, $–CH(CH_3)–C_2H_5$, $–C(CH_3)_3$, $–C_5H_{11}$, $–CH(CH_3)–C_3H_7$, $–CH_2–CH(CH_3)–C_2H_5$, $–CH(CH_3)–CH(CH_3)_2$, $–C(CH_3)_2–C_2H_5$, $–CH_2–C(CH_3)_3$, $–CH(C_2H_5)_2$, $–C_2H_4–CH(CH_3)_2$, $–C_6H_{13}$, $–C_7H_{15}$, $–C_8H_{17}$, –Ph, $–CH_2–Ph$, $–CH_2–CH_2–Ph$, $–C_2H_4–CH=CH_2$, $–CH_2–CH=CH–CH_3$, $–CH_2–C(CH_3)=CH_2$, $–CH(CH_3)–CH=CH_2$, $–C(CH_3)=CH–CH_3$, $–CH_2–CH=C(CH_3)_2$, $–CO–CH=C(CH_3)_2$, $–CH_2–C≡CH$, $–C_2H_4–C≡CH$, $–CH_2–C≡C–CH_3$, $–CH_2–OCF_3$, $–C_2H_4–OCF_3$, $–C_3H_6–OCF_3$, $–CH_2–OCHF_2$, $–C_2H_4–OCHF_2$, $–C_3H_6–OCHF_2$, $–CH_2–OCH_3$, $–C_2H_4–OCH_3$, $–C_3H_6–OCH_3$, $–CH_2–OC_2H_5$, $–C_2H_4–OC_2H_5$, $–C_3H_6–OC_2H_5$, $–CH_2–OH$, $–C_2H_4–OH$, $–C_3H_6–OH$, $–CH_2–COOH$, $–C_2H_4–COOH$, $–C_3H_6–COOH$, $–C(CH_3)_2–CN$, $–C(CH_3)_2–OH$, $–C(CH_3)_2–CH_2–OH$, $–C(C_2H_5)_2–CH_2–OH$, $–C(CH_2–OH)_2–CH_3$, $–C(CH_2–OH)_2–C_2H_5$, $–C(CH_3)_2–CH_2–SH$, $–C(C_2H_5)_2–CH_2–SH$, $–C(CH_2–SH)_2–CH_3$, $–CO–O–C(CH_3)_3$, or $–C(CH_2–SH)_2–C_2H_5$;

R^{11} represents –H, $–CH_3$, $–C_2H_5$, $–C_3H_7$, $–CH(CH_3)_2$, $–CH_2F$, $–CHF_2$, $–CF_3$, $–CH_2CN$, $–C(CH_3)_2–CN$, $–CH_2–C(CH_3)_2–CN$, $–CH_2–CF_3$, $–CH_2–C(CH_3)_2–NH_2$,

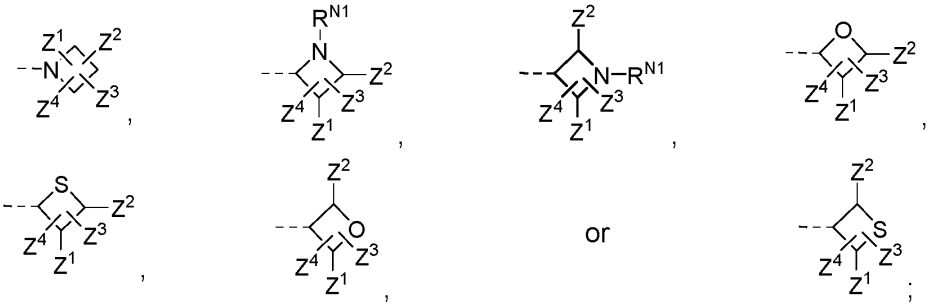


, cyclo-C_3H_5, cyclo-C_4H_7, cyclo-C_5H_9, cyclo-C_6H_{11}, cyclo-C_7H_{13}, $–C_4H_9$, $–CH_2–CH(CH_3)_2$, $–CH(CH_3)–C_2H_5$, $–C(CH_3)_3$, $–C_5H_{11}$, $–CH(CH_3)–C_3H_7$, $–CH_2–CH(CH_3)–C_2H_5$, $–CH(CH_3)–CH(CH_3)_2$, $–C(CH_3)_2–C_2H_5$, $–CH_2–C(CH_3)_3$, $–CH(C_2H_5)_2$, $–C_2H_4–CH(CH_3)_2$, $–C_6H_{13}$, $–C_7H_{15}$, $–C_8H_{17}$, –Ph, $–CH_2–Ph$, $–CH_2–CH_2–Ph$, $–CH=CH_2$, $–CH_2–CH=CH_2$, $–C(CH_3)=CH_2$, $–CH=CH–CH_3$, $–C(CH_3)=CH–CH_3$, $–CH=C(CH_3)_2$, $–C(CH_3)=C(CH_3)_2$, $–C_2H_4–CH=CH_2$, $–CH_2–CH=CH–CH_3$, $–CH_2–C(CH_3)=CH_2$, $–CH(CH_3)–CH=CH_2$, $–C(CH_3)=CH–CH_3$, $–CH_2–CH=C(CH_3)_2$, $–C≡CH$, $–CH_2–C≡CH$, $–C_2H_4–C≡CH$, $–CH_2–C≡C–CH_3$, $–C≡C–CH_3$, $–C≡C–C_2H_5$, $–CH_2–OCF_3$, $–C_2H_4–OCF_3$, $–C_3H_6–OCF_3$, $–CH_2–OCHF_2$, $–C_2H_4–OCHF_2$, $–C_3H_6–OCHF_2$, $–CH_2–OCH_3$, $–C_2H_4–OCH_3$, $–C_3H_6–OCH_3$, $–CH_2–OC_2H_5$, $–C_2H_4–OC_2H_5$, $–C_3H_6–OC_2H_5$, $–CH_2–OH$, $–C_2H_4–OH$, $–C_3H_6–OH$, $–C(CH_3)_2–CH_2–OH$, $–C(C_2H_5)_2–CH_2–OH$, $–C(CH_2–OH)_2–CH_3$, $–C(CH_2–OH)_2–C_2H_5$, $–C(CH_3)_2–CH_2–SH$, $–C(C_2H_5)_2–CH_2–SH$, $–C(CH_2–SH)_2–CH_3$, or $–C(CH_2–SH)_2–C_2H_5$;

R^{12} and **R^{13}** represent independently of each other –H, –CH_3, –C_2H_5, –C_3H_7, –$CH(CH_3)_2$, –Ph, –CH_2–Ph, –COOH, –NH_2, –$NHCO_2(CCH_3)_3$, –CH_2–NH_2, –CHF_2, –CF_3, –F, –OCF_3, –$OCHF_2$, –OH, –OCH_3, –OC_2H_5, –OC_3H_7, or –$OCH(CH_3)_2$; or

R^{12} and **R^{13}** form together  ,  , or ;

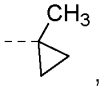
R^{14} represents



R^{15} and **R^{16}** represent independently of each other **–X^3–L^2–R^{17}**, or –$(OCH_2CH_2)_w$–**R^{17}**;

L^2 represents –$(CH_2)_v$–, –$(CH_2CH_2$–O$)_w$–CH_2–, or –$(CH_2CH_2$–O$)_w$–CH_2CH_2–;

R^{17} represents –OH, –SH, –SO_3H, –NH_2, or –CO_2H;

R^{N1}, **R^{N2}**, **R^{N3}**, and **R^{N4}** represent independently of each other **–R^{15}**, –H, –CH_3, –C_2H_5, –C_3H_7, –$CH(CH_3)_2$, –CHF_2, –CF_3,  , cyclo-C_3H_5, cyclo-C_4H_7, cyclo-C_5H_9, cyclo-C_6H_{11}, cyclo-C_7H_{13}, –C_4H_9, –CH_2–$CH(CH_3)_2$, –$CH(CH_3)$–C_2H_5, –$C(CH_3)_3$, –C_5H_{11}, –$CH(CH_3)$–C_3H_7, –CH_2–$CH(CH_3)$–C_2H_5, –$CH(CH_3)$–$CH(CH_3)_2$, –$C(CH_3)_2$–C_2H_5, –CH_2–$C(CH_3)_3$, –$CH(C_2H_5)_2$, –C_2H_4–$CH(CH_3)_2$, –C_6H_{13}, –C_7H_{15}, –C_8H_{17}, –Ph, –CH_2–Ph, –CH_2–CH_2–Ph, –C_2H_4–CH=CH_2, –CH_2–CH=CH–CH_3, –CH_2–$C(CH_3)$=CH_2, –$CH(CH_3)$–CH=CH_2, –CH_2–CH=$C(CH_3)_2$, –CH_2-C≡CH, –C_2H_4–C≡CH, –CH_2–C≡C–CH_3, –$COCH_3$, –COC_2H_5, –COC_3H_7, –CO–cyclo-C_3H_5, –$COCH(CH_3)_2$, –$COC(CH_3)_3$, –COOH, –$COOCH_3$, –$COOC_2H_5$, –$COOC_3H_7$, –COO–cyclo-C_3H_5, –$COOCH(CH_3)_2$, –$COOC(CH_3)_3$, –$COOCH_2$Ph, –$CONH_2$, –$CONHCH_3$, –$CONHC_2H_5$, –$CONHC_3H_7$, –CONH–cyclo-C_3H_5, –$CONH[CH(CH_3)_2]$, –$CONH[C(CH_3)_3]$, –$CON(CH_3)_2$, –$CON(C_2H_5)_2$,

$-CON(C_3H_7)_2$, $-CON(cyclo\text{-}C_3H_5)_2$, $-CON[CH(CH_3)_2]_2$, $-CON[C(CH_3)_3]_2$, or $-SO_3H$;

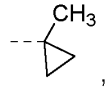
$\mathbf{R^{N5}}$ and $\mathbf{R^{N6}}$ represent independently of each other –H, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $cyclo\text{-}C_3H_5$, $-COOC(CH_3)_3$, or $-COOCH_2Ph$;

$\mathbf{X^1}$ represents $-(CH_2)_m-$;

$\mathbf{X^2}$ represents $-(CH_2)_n-$;

$\mathbf{X^3}$ represents a bond, –O–, –NH–, or –S–;

$\mathbf{Z^1 - Z^{14}}$ represent independently of each other

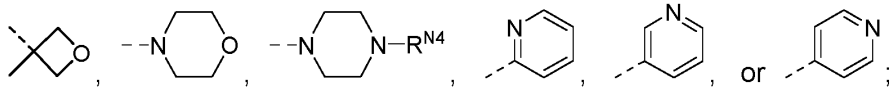


$cyclo\text{-}C_3H_5$, $cyclo\text{-}C_4H_7$, $cyclo\text{-}C_5H_9$, $cyclo\text{-}C_6H_{11}$, $cyclo\text{-}C_7H_{13}$, $-\mathbf{R^{16}}$, –H, –OH, $-OCH_3$, $-OC_2H_5$, $-OC_3H_7$, $-O\text{–}cyclo\text{-}C_3H_5$, $-OCH(CH_3)_2$, $-OC(CH_3)_3$, $-OC_4H_9$, $-O\text{–}cyclo\text{-}C_4H_7$, $-O\text{–}cyclo\text{-}C_5H_9$, $-O\text{–}cyclo\text{-}C_6H_{11}$, $-OCH_2CH(CH_3)_2$, $-OCH_2\text{–}cyclo\text{-}C_3H_5$, $-OCH_2\text{–}cyclo\text{-}C_4H_7$, $-OCH_2\text{–}cyclo\text{-}C_5H_9$, $-OCH_2\text{–}cyclo\text{-}C_6H_{11}$, –OPh, $-OCH_2$–Ph, $-OCPh_3$, $-CH_2-OCH_3$, $-C_2H_4-OCH_3$, $-C_3H_6-OCH_3$, $-CH_2-OC_2H_5$, $-C_2H_4-OC_2H_5$, $-C_3H_6-OC_2H_5$, $-CH_2-OC_3H_7$, $-C_2H_4-OC_3H_7$, $-C_3H_6-OC_3H_7$, $-CH_2-O\text{–}cyclo\text{-}C_3H_5$, $-C_2H_4-O\text{–}cyclo\text{-}C_3H_5$, $-C_3H_6-O\text{–}cyclo\text{-}C_3H_5$, $-CH_2-OCH(CH_3)_2$, $-C_2H_4-OCH(CH_3)_2$, $-C_3H_6-OCH(CH_3)_2$, $-CH_2-OC(CH_3)_3$, $-C_2H_4-OC(CH_3)_3$, $-C_3H_6-OC(CH_3)_3$, $-CH_2-OC_4H_9$, $-C_2H_4-OC_4H_9$, $-C_3H_6-OC_4H_9$, $-CH_2$–OPh, $-C_2H_4$–OPh, $-C_3H_6$–OPh, $-CH_2-OCH_2$–Ph, $-C_2H_4-OCH_2$–Ph, $-C_3H_6-OCH_2$–Ph, –SH, $-SCH_3$, $-SC_2H_5$, $-SC_3H_7$, $-S\text{–}cyclo\text{-}C_3H_5$, $-SCH(CH_3)_2$, $-SC(CH_3)_3$, –F, –Cl, –Br, –I, –CN, $-COCH_3$, $-COC_2H_5$, $-COC_3H_7$, $-CO\text{–}cyclo\text{-}C_3H_5$, $-COCH(CH_3)_2$, $-COC(CH_3)_3$, –COOH, $-COOCH_3$, $-COOC_2H_5$, $-COOC_3H_7$, $-COO\text{–}cyclo\text{-}C_3H_5$, $-COOCH(CH_3)_2$, $-COOC(CH_3)_3$, $-OOC-CH_3$, $-OOC-C_2H_5$, $-OOC-C_3H_7$, $-OOC\text{–}cyclo\text{-}C_3H_5$, $-OOC-CH(CH_3)_2$, $-OOC-C(CH_3)_3$, $-CONH_2$, $-CONHCH_3$, $-CONHC_2H_5$, $-CONHC_3H_7$, $-CONH\text{–}cyclo\text{-}C_3H_5$, $-CONH[CH(CH_3)_2]$, $-CONH[C(CH_3)_3]$, $-CON(CH_3)_2$, $-CON(C_2H_5)_2$, $-CON(C_3H_7)_2$, $-CON(cyclo\text{-}C_3H_5)_2$, $-CON[CH(CH_3)_2]_2$, $-CON[C(CH_3)_3]_2$, $-NHCOCH_3$, $-NHCOC_2H_5$, $-NHCOC_3H_7$, $-NHCO\text{–}cyclo\text{-}C_3H_5$, $-NHCO-CH(CH_3)_2$, $-NHCO-C(CH_3)_3$, $-NHCO-CH(NH_2)CH_2-COOH$, $-NHCO-CH(NH_2)CH_2CH_2-COOH$, $-NHCO-OCH_3$, $-NHCO-OC_2H_5$, $-NHCO-OC_3H_7$, $-NHCO-O\text{–}cyclo\text{-}C_3H_5$, $-NHCO-OCH(CH_3)_2$, $-NHCO-OC(CH_3)_3$, $-NH_2$, $-NHCH_3$, $-NHC_2H_5$, $-NHC_3H_7$, $-NH\text{–}cyclo\text{-}C_3H_5$, $-NHCH(CH_3)_2$, $-NHC(CH_3)_3$, $-N(CH_3)_2$, $-N(C_2H_5)_2$, $-N(C_3H_7)_2$, $-N(cyclo\text{-}C_3H_5)_2$,

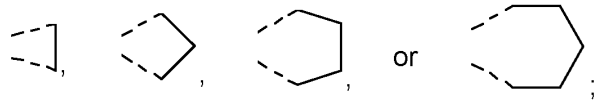
–N[CH(CH$_3$)$_2$]$_2$, –N[C(CH$_3$)$_3$]$_2$, –SOCH$_3$, –SOC$_2$H$_5$, –SOC$_3$H$_7$, –SO–cyclo-C$_3$H$_5$, –SOCH(CH$_3$)$_2$, –SOC(CH$_3$)$_3$, –SO$_2$CH$_3$, –SO$_2$C$_2$H$_5$, –SO$_2$C$_3$H$_7$, –SO$_2$–cyclo-C$_3$H$_5$, –SO$_2$CH(CH$_3$)$_2$, –SO$_2$C(CH$_3$)$_3$, –SO$_3$H, –SO$_3$CH$_3$, –SO$_3$C$_2$H$_5$, –SO$_3$C$_3$H$_7$, –SO$_3$–cyclo-C$_3$H$_5$, –SO$_3$CH(CH$_3$)$_2$, –SO$_3$C(CH$_3$)$_3$, –SO$_2$NH$_2$, –SO$_2$NHCH$_3$, –SO$_2$NHC$_2$H$_5$, –SO$_2$NHC$_3$H$_7$, –SO$_2$NH–cyclo-C$_3$H$_5$, –SO$_2$NHCH(CH$_3$)$_2$, –SO$_2$NHC(CH$_3$)$_3$, –SO$_2$N(CH$_3$)$_2$, –SO$_2$N(C$_2$H$_5$)$_2$, –SO$_2$N(C$_3$H$_7$)$_2$, –SO$_2$N(cyclo-C$_3$H$_5$)$_2$, –SO$_2$N[CH(CH$_3$)$_2$]$_2$, –SO$_2$N[C(CH$_3$)$_3$]$_2$, –O–S(=O)CH$_3$, –O–S(=O)C$_2$H$_5$, –O–S(=O)C$_3$H$_7$, –O–S(=O)–cyclo-C$_3$H$_5$, –O–S(=O)CH(CH$_3$)$_2$, –O–S(=O)C(CH$_3$)$_3$, –S(=O)(=NH)CH$_3$, –S(=O)(=NH)C$_2$H$_5$, –S(=O)(=NH)C$_3$H$_7$, –S(=O)(=NH)–cyclo-C$_3$H$_5$, –S(=O)(=NH)CH(CH$_3$)$_2$, –S(=O)(=NH)C(CH$_3$)$_3$, –NH–SO$_2$–CH$_3$, –NH–SO$_2$–C$_2$H$_5$, –NH–SO$_2$–C$_3$H$_7$, –NH–SO$_2$–cyclo-C$_3$H$_5$, –NH–SO$_2$–CH(CH$_3$)$_2$, –NH–SO$_2$–C(CH$_3$)$_3$, –O–SO$_2$–CH$_3$, –O–SO$_2$–C$_2$H$_5$, –O–SO$_2$–C$_3$H$_7$, –O–SO$_2$–cyclo-C$_3$H$_5$, –O–SO$_2$–CH(CH$_3$)$_2$, –O–SO$_2$–C(CH$_3$)$_3$, –OCH$_2$F, –OCHF$_2$, –OCF$_3$, –CH$_2$–OCF$_3$, –C$_2$H$_4$–OCF$_3$, –C$_3$H$_6$–OCF$_3$, –CH$_2$–OCHF$_2$, –C$_2$H$_4$–OCHF$_2$, –C$_3$H$_6$–OCHF$_2$, –OC$_2$F$_5$, –CH$_2$–OC$_2$F$_5$, –C$_2$H$_4$–OC$_2$F$_5$, –C$_3$H$_6$–OC$_2$F$_5$, –O–COOCH$_3$, –O–COOC$_2$H$_5$, –O–COOC$_3$H$_7$, –O–COO–cyclo-C$_3$H$_5$, –O–COOCH(CH$_3$)$_2$, –O–COOC(CH$_3$)$_3$, –NH–CO–NH$_2$, –NH–CO–NHCH$_3$, –NH–CO–NHC$_2$H$_5$, –NH–CO–NHC$_3$H$_7$, –NH–C(=NH)–NH$_2$, –NH–CO–N(C$_3$H$_7$)$_2$, –NH–CO–NH[CH(CH$_3$)$_2$], –NH–CO–NH[C(CH$_3$)$_3$], –NH–CO–N(CH$_3$)$_2$, –NH–CO–N(C$_2$H$_5$)$_2$, –NH–CO–NH–cyclo-C$_3$H$_5$, –NH–CO–N(cyclo-C$_3$H$_5$)$_2$, –NH–CO–N[CH(CH$_3$)$_2$]$_2$, –NH–C(=NH)–NHCH$_3$, –NH–C(=NH)–NHC$_2$H$_5$, –NH–C(=NH)–NHC$_3$H$_7$, –O–CO–NH–cyclo-C$_3$H$_5$, –NH–C(=NH)–NH–cyclo-C$_3$H$_5$, –NH–C(=NH)–NH[CH(CH$_3$)$_2$], –O–CO–NH[CH(CH$_3$)$_2$], –NH–C(=NH)–NH[C(CH$_3$)$_3$], –NH–C(=NH)–N(CH$_3$)$_2$, –NH–C(=NH)–N(C$_2$H$_5$)$_2$, –NH–C(=NH)–N(C$_3$H$_7$)$_2$, –NH–C(=NH)–N(cyclo-C$_3$H$_5$)$_2$, –O–CO–NHC$_3$H$_7$, –NH–C(=NH)–N[CH(CH$_3$)$_2$]$_2$, –NH–C(=NH)–N[C(CH$_3$)$_3$]$_2$, –O–CO–NH$_2$, –O–CO–NHCH$_3$, –O–CO–NHC$_2$H$_5$, –O–CO–NH[C(CH$_3$)$_3$], –O–CO–N(CH$_3$)$_2$, –O–CO–N(C$_2$H$_5$)$_2$, –O–CO–N(C$_3$H$_7$)$_2$, –O–CO–N(cyclo-C$_3$H$_5$)$_2$, –O–CO–N[CH(CH$_3$)$_2$]$_2$, –O–CO–N[C(CH$_3$)$_3$]$_2$, –O–CO–OCH$_3$, –O–CO–OC$_2$H$_5$, –O–CO–OC$_3$H$_7$, –O–CO–O–cyclo-C$_3$H$_5$, –O–CO–OCH(CH$_3$)$_2$, –O–CO–OC(CH$_3$)$_3$, –CH$_2$F, –CHF$_2$, –CF$_3$, –CH$_2$–CH$_2$F, –CH$_2$–CHF$_2$, –CH$_2$–CF$_3$, cyclo-C$_8$H$_{15}$, –Ph, –CH$_2$–Ph, –CH$_2$–CH$_2$–Ph, –CH=CH–Ph, –CPh$_3$, –CH$_3$, –C$_2$H$_5$, –C$_3$H$_7$, –CH(CH$_3$)$_2$, –C$_4$H$_9$, –CH$_2$–CH(CH$_3$)$_2$, –CH(CH$_3$)–C$_2$H$_5$, –C(CH$_3$)$_3$, –C$_5$H$_{11}$, –CH(CH$_3$)–C$_3$H$_7$, –CH$_2$–CH(CH$_3$)–C$_2$H$_5$, –CH(CH$_3$)–CH(CH$_3$)$_2$, –C(CH$_3$)$_2$–C$_2$H$_5$, –CH$_2$–C(CH$_3$)$_3$, –CH(C$_2$H$_5$)$_2$, –C$_2$H$_4$–CH(CH$_3$)$_2$, –C$_6$H$_{13}$, –C$_7$H$_{15}$, –C$_8$H$_{17}$, –C$_3$H$_6$–CH(CH$_3$)$_2$, –C$_2$H$_4$–CH(CH$_3$)–C$_2$H$_5$, –CH(CH$_3$)–C$_4$H$_9$, –CH$_2$–CH(CH$_3$)–C$_3$H$_7$, –CH(CH$_3$)–CH$_2$–CH(CH$_3$)$_2$, –CH(CH$_3$)–CH(CH$_3$)–C$_2$H$_5$, –CH$_2$–CH(CH$_3$)–CH(CH$_3$)$_2$, –CH$_2$–C(CH$_3$)$_2$–C$_2$H$_5$, –C(CH$_3$)$_2$–C$_3$H$_7$, –C(CH$_3$)$_2$–CH(CH$_3$)$_2$, –C$_2$H$_4$–C(CH$_3$)$_3$, –CH(CH$_3$)–C(CH$_3$)$_3$,

–CH=CH_2, –CH_2–CH=CH_2, –C(CH_3)=CH_2, –CH=CH–CH_3, –C_2H_4–CH=CH_2, –CH_2–CH=CH–CH_3, –CH=CH–C_2H_5, –CH_2–C(CH_3)=CH_2, –CH(CH_3)–CH=CH, –CH=C(CH_3)$_2$, –C(CH_3)=CH–CH_3, –CH=CH–CH=CH_2, –C_3H_6–CH=CH_2, –C_2H_4–CH=CH–CH_3, –CH_2–CH=CH–C_2H_5, –CH=CH–C_3H_7, –CH=CH–CH=CH–CH_3, –C_2H_4–C(CH_3)=CH_2, –CH_2–CH(CH_3)–CH=CH_2, –CH(CH_3)–CH_2–CH=CH_2, –CH_2–CH=C(CH_3)$_2$, –CH_2–C(CH_3)=CH–CH_3, –CH(CH_3)–CH=CH–CH_3, –CH=CH–CH(CH_3)$_2$, –CH=C(CH_3)–C_2H_5, –C(CH_3)=CH–C_2H_5, –C(CH_3)=C(CH_3)$_2$, –C(CH_3)$_2$–CH=CH_2, –CH(CH_3)–C(CH_3)=CH_2, –C_4H_8–CH=CH_2, –C_3H_6–CH=CH–CH_3, –C_2H_4–CH=CH–C_2H_5, –CH_2–CH=CH–C_3H_7, –CH=CH–C_4H_9, –C_3H_6–C(CH_3)=CH_2, –C_2H_4–CH(CH_3)–CH=CH_2, –CH_2–CH(CH_3)–CH_2–CH=CH_2, –C_2H_4–CH=C(CH_3)$_2$, –CH(CH_3)–C_2H_4–CH=CH_2, –C_2H_4–C(CH_3)=CH–CH_3, –CH_2–CH(CH_3)–CH=CH–CH_3, –CH(CH_3)–CH_2–CH=CH–CH_3, –CH_2–CH=CH–CH(CH_3)$_2$, –CH_2–CH=C(CH_3)–C_2H_5, –CH_2–C(CH_3)=CH–C_2H_5, –CH(CH_3)–CH=CH–C_2H_5, –CH=CH–CH_2–CH(CH_3)$_2$, –CH=CH–CH(CH_3)–C_2H_5, –CH=C(CH_3)–C_3H_7, –C(CH_3)=CH–C_3H_7, –CH_2–CH(CH_3)–C(CH_3)=CH_2, –C[C(CH_3)$_3$]=CH_2, –CH(CH_3)–CH_2–C(CH_3)=CH_2, –CH(CH_3)–CH(CH_3)–CH=CH_2, –CH=CH–C_2H_4–CH=CH_2, –C(CH_3)$_2$–CH_2–CH=CH_2, –CH_2–C(CH_3)=C(CH_3)$_2$, –CH(CH_3)–CH=C(CH_3)$_2$, –C(CH_3)$_2$–CH=CH–CH_3, –CH=CH–CH_2–CH=CH–CH_3, –CH(CH_3)–C(CH_3)=CH–CH_3, –CH=C(CH_3)–CH(CH_3)$_2$, –C(CH_3)=CH–CH(CH_3)$_2$, –C(CH_3)=C(CH_3)–C_2H_5, –CH=CH–C(CH_3)$_3$, –C(CH_3)$_2$–C(CH_3)=CH_2, –CH(C_2H_5)–C(CH_3)=CH_2, –C(CH_3)(C_2H_5)–CH=CH_2, –CH(CH_3)–C(C_2H_5)=CH_2, –CH_2–C(C_3H_7)=CH_2, –CH_2–C(C_2H_5)=CH–CH_3, –CH(C_2H_5)–CH=CH–CH_3, –C(C_4H_9)=CH_2, –C(C_3H_7)=CH–CH_3, –C(C_2H_5)=CH–C_2H_5, –C(C_2H_5)=C(CH_3)$_2$, –C[CH(CH_3)(C_2H_5)]=CH_2, –C[CH_2–CH(CH_3)$_2$]=CH_2, –C_2H_4–CH=CH–CH=CH_2, –CH_2–CH=CH–CH_2–CH=CH_2, –C_3H_6–C≡C–CH_3, –CH_2–CH=CH–CH=CH–CH_3, –CH=CH–CH=CH–C_2H_5, –CH(CH_3)–CH_2–C≡CH, –CH(CH_3)–C≡C–CH_3, –C_2H_4–CH(CH_3)–C≡CH, –CH=CH–CH=C(CH_3)$_2$, –CH_2–CH(CH_3)–CH_2–C≡CH, –CH=CH–C(CH_3)=CH–CH_3, –CH=C(CH_3)–CH=CH–CH_3, –CH_2–CH(CH_3)–C≡CH, –C(CH_3)=CH–CH=CH–CH_3, –C≡CH, –C≡C–CH_3, –CH_2-C≡CH, –C_2H_4–C≡CH, –CH_2–C≡C–CH_3, –C≡C–C_2H_5, –C_3H_6–C≡CH, –C_2H_4–C≡C–CH_3, –CH_2–C≡C–C_2H_5, –C≡C–C_3H_7, –CH(CH_3)–C≡CH, –C_4H_8–C≡CH, –C_2H_4–C≡C–C_2H_5, –CH_2–C≡C–C_3H_7, –C≡C–C_4H_9, –C≡C–CH_2–CH(CH_3)$_2$, –CH(CH_3)–C_2H_4–C≡CH, –CH_2–CH(CH_3)–C≡C–CH_3, –C(CH_3)(C_2H_5)–C≡CH, –CH(CH_3)–CH_2–C≡C–CH_3, –CH(CH_3)–C≡C–C_2H_5, –CH_2–C≡C–CH(CH_3)$_2$, –C≡C–CH(CH_3)–C_2H_5, –CH_2–C≡C–C≡C–CH_3, –CH(C_2H_5)–C≡C–CH_3, –C(CH_3)$_2$–C≡C–CH_3, –CH(C_2H_5)–CH_2–C≡CH, –CH_2–CH(C_2H_5)–C≡CH, –C(CH_3)$_2$–CH_2–C≡CH, –CH_2–C(CH_3)$_2$–C≡CH, –CH(CH_3)–CH(CH_3)–C≡CH, –CH(C_3H_7)–C≡CH, –CH_2–CH(C≡CH)$_2$, –C≡C–C≡CH, –CH_2–C≡C–C≡CH,

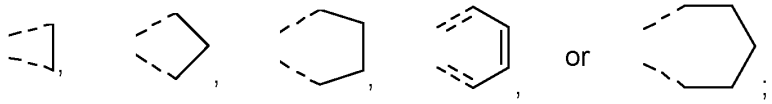
$-C\equiv C-C\equiv C-CH_3$, $-CH(C\equiv CH)_2$, $-C_2H_4-C\equiv C-C\equiv CH$, $-CH_2-C\equiv C-CH_2-C\equiv CH$, $-C\equiv C-C_2H_4-C\equiv CH$, $-C\equiv C-C(CH_3)_3$, $-C\equiv C-CH_2-C\equiv C-CH_3$, $-C\equiv C-C\equiv C-C_2H_5$,



Z^3 and Z^4 may form together



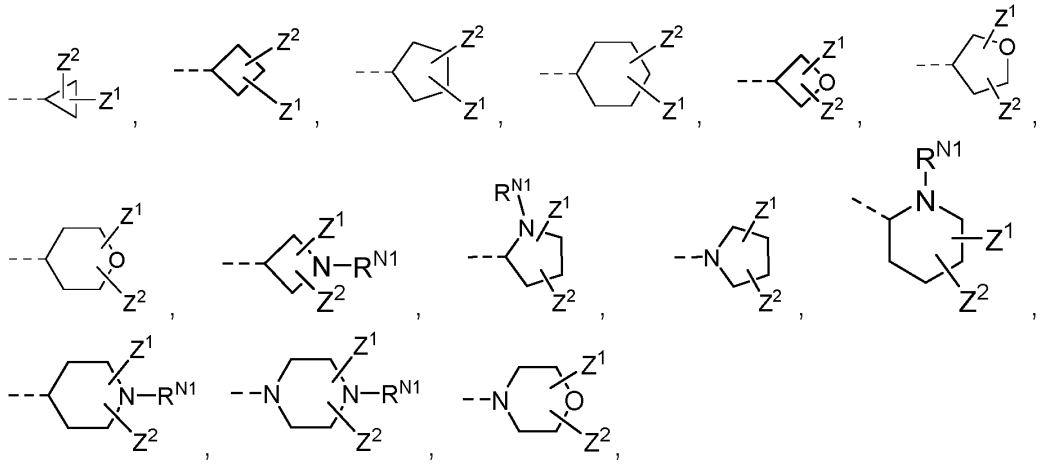
Z^{13} and Z^{14} may form together

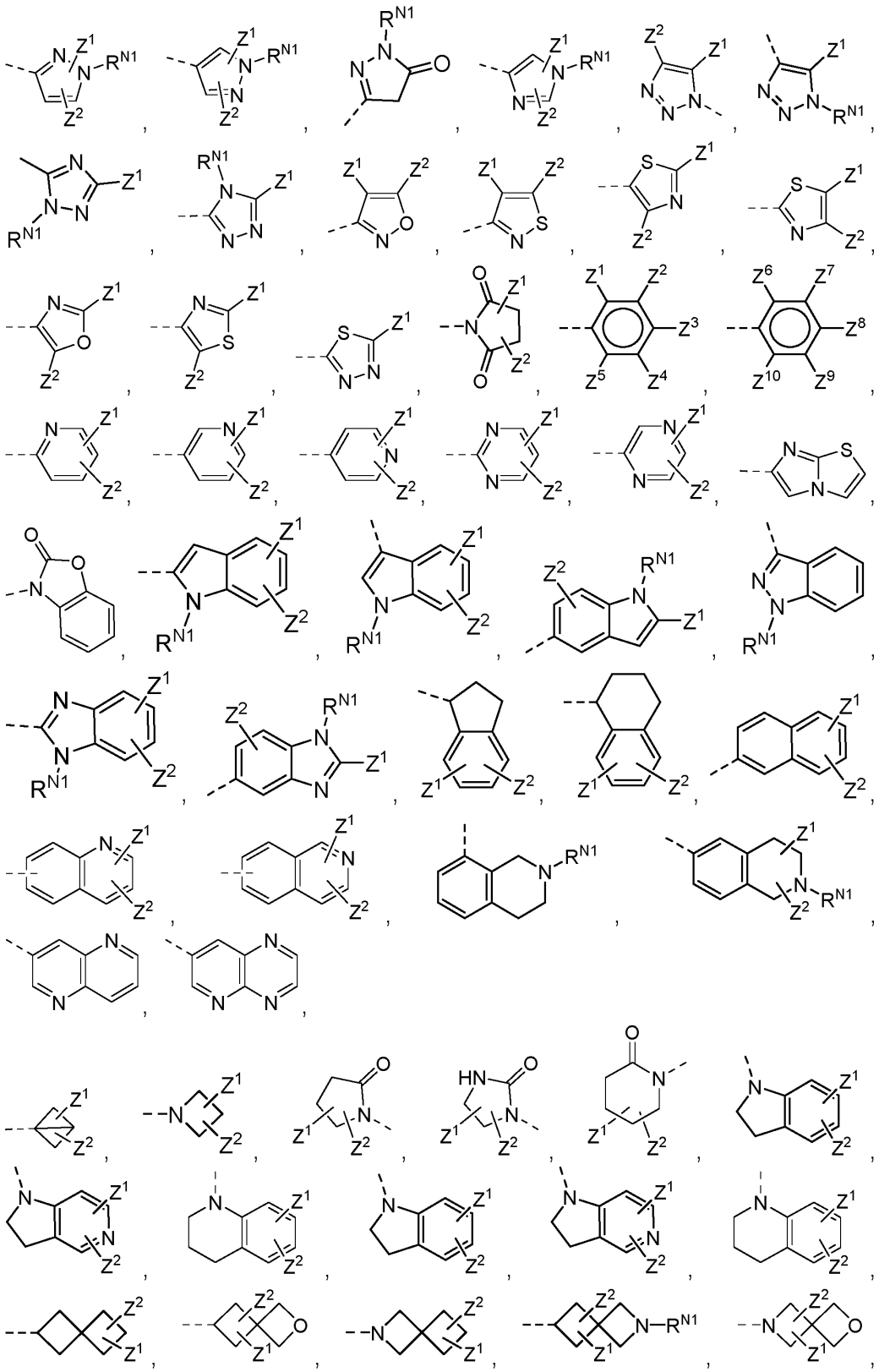


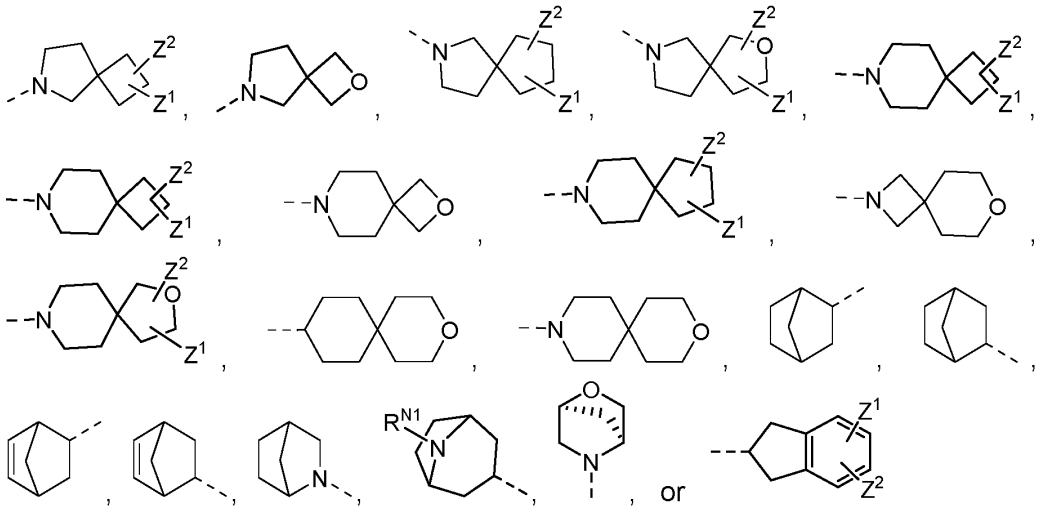
m is an integer selected from 0, 1, 2, 3, 4, 5, or 6;
n is an integer selected from 0, 1, 2, 3, 4, 5, or 6;
p is an integer selected from 0, 1, 2, 3, 4, 5, or 6;
r is an integer selected from 0, 1, 2, 3, or 4;
s is an integer selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;
t is an integer selected from 1, 2, 3, or 4;
u is an integer selected from 1, 2, 3, or 4;
v is an integer selected from 0, 1, 2, 3, 4, 5, or 6;
w is an integer selected from 0, 1, 2, 3, 4, 5 or 6;

or an enantiomer, a stereoisomeric form, a mixture of enantiomers, a diastereomer, a mixture of diastereomers, a hydrate, a solvate, an acid salt form, a tautomer, a racemate of the above mentioned compounds, or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, wherein R^8 and R^9 represent independently of each other:

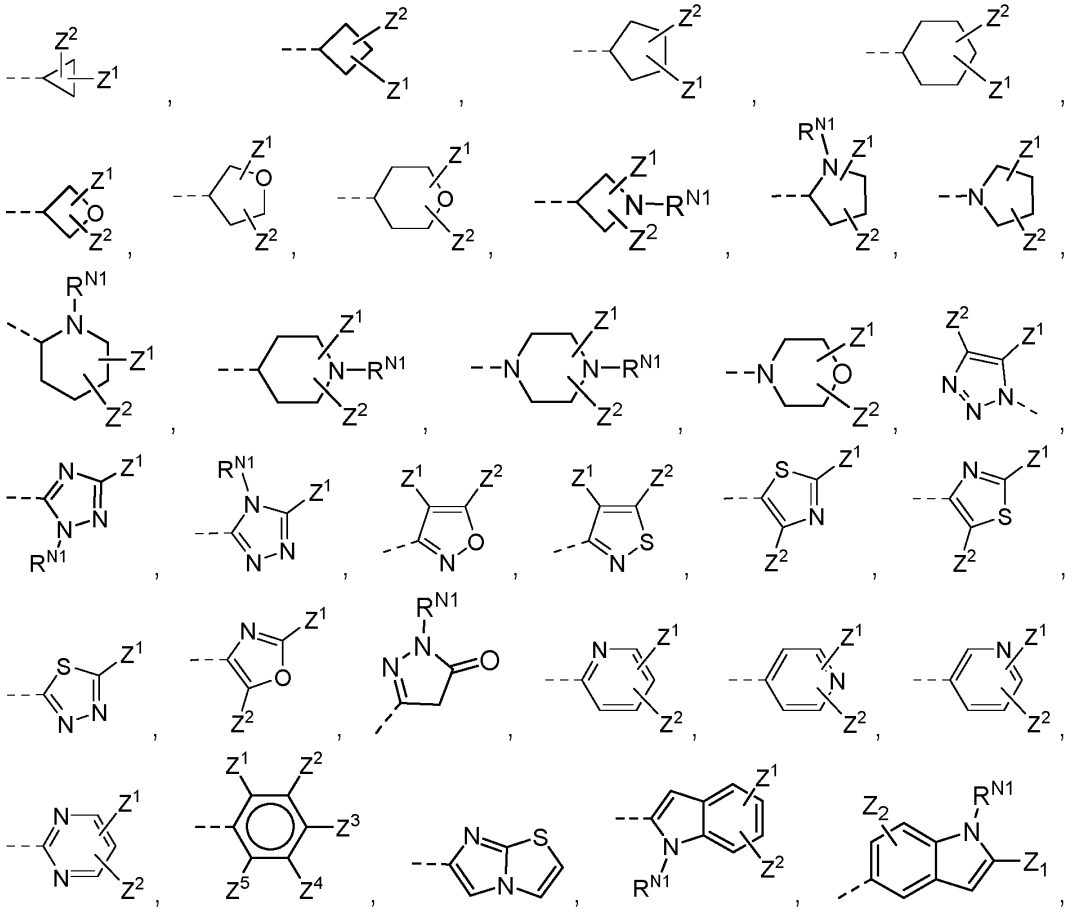


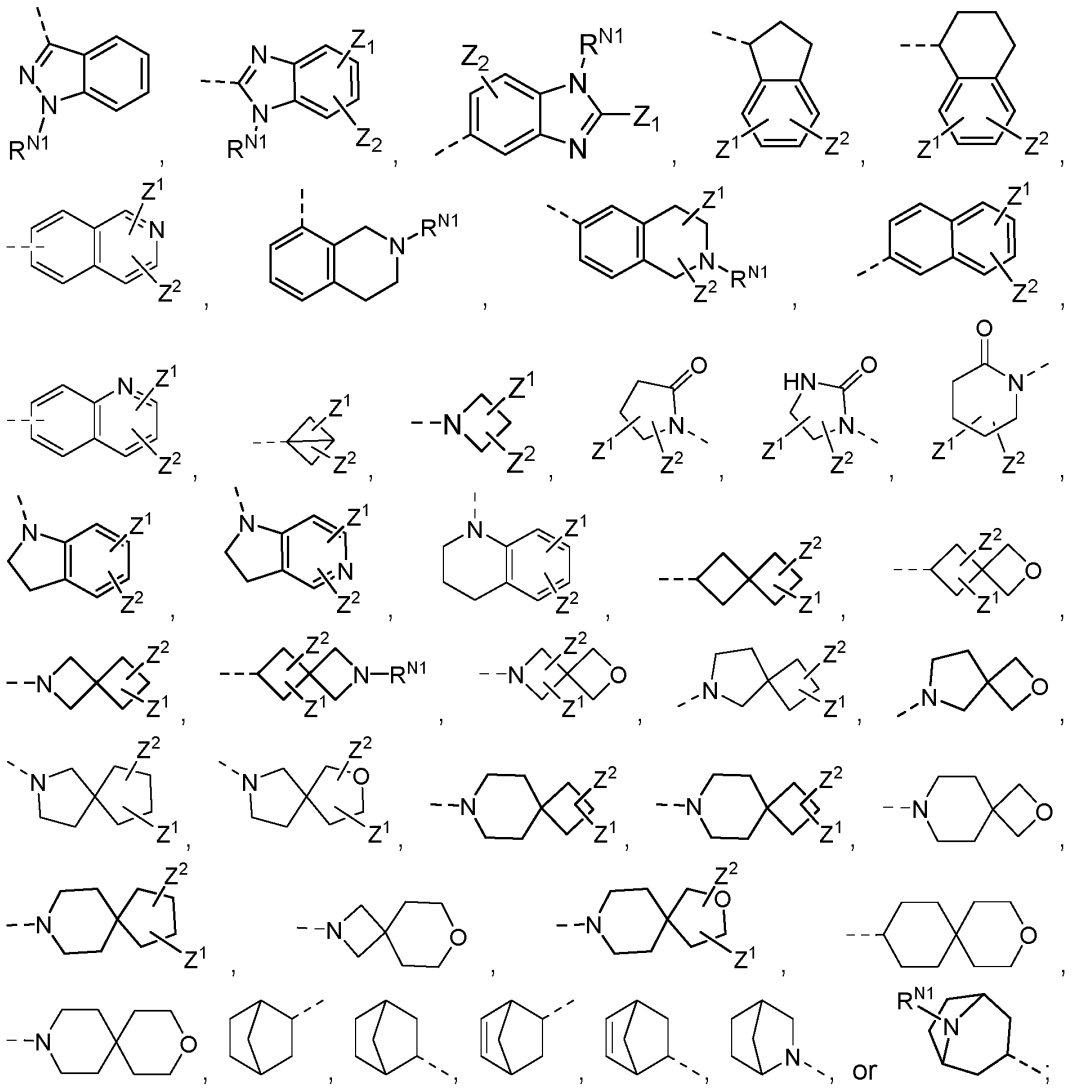




wherein R^{N1}, Z^1, Z^2, Z^3, Z^4, Z^5, Z^6, Z^7, Z^8, Z^9, and Z^{10} have the same meanings as defined in claim 1.

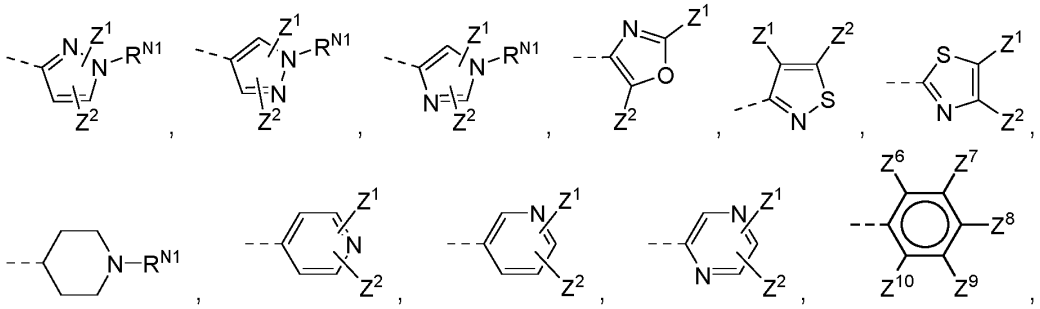
3. The compound according to claim 1 or 2, wherein R^8 represents

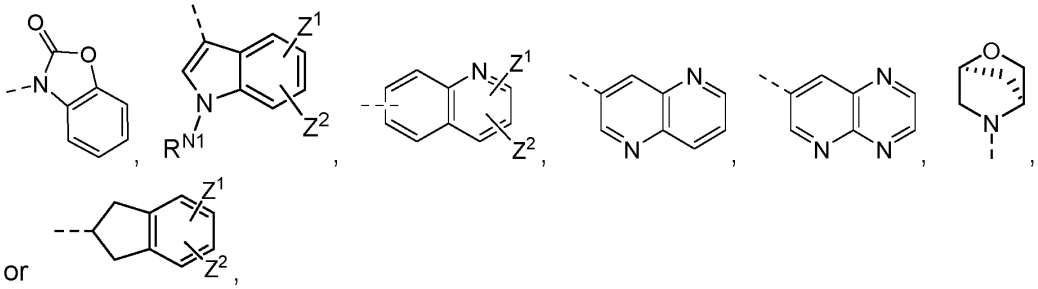




wherein R^{N1}, Z^1, Z^2, Z^6, Z^7, Z^8, Z^9, and Z^{10} have the same meanings as defined in claim 1.

4. The compound according to any one of the claims 1 – 3, wherein R^9 represents

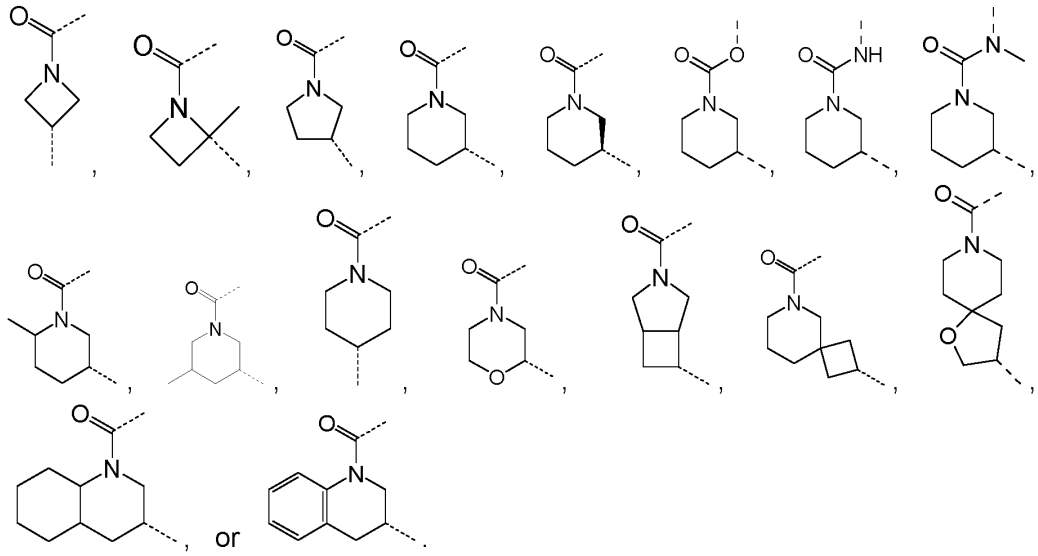




or

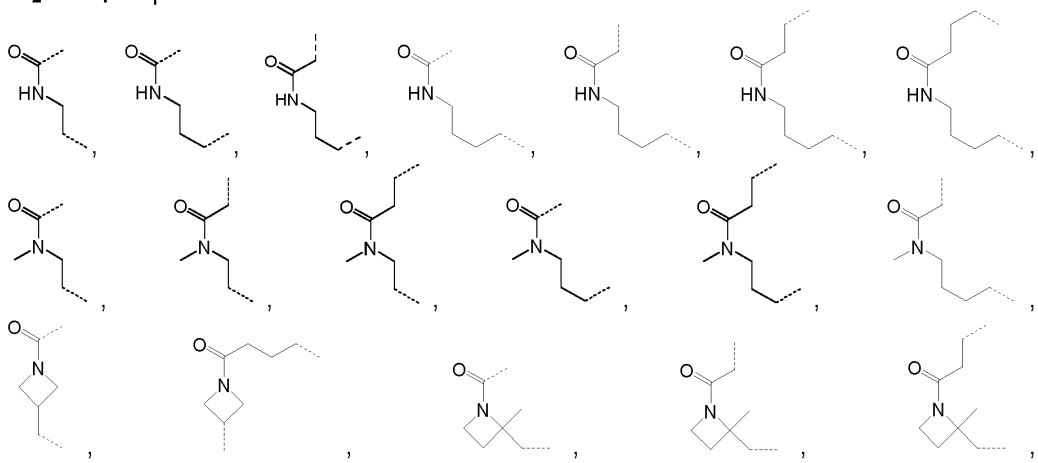
wherein R^{N1}, Z^1, Z^2, Z^6, Z^7, Z^8, Z^9, and Z^{10} have the same meanings as defined in claim 1.

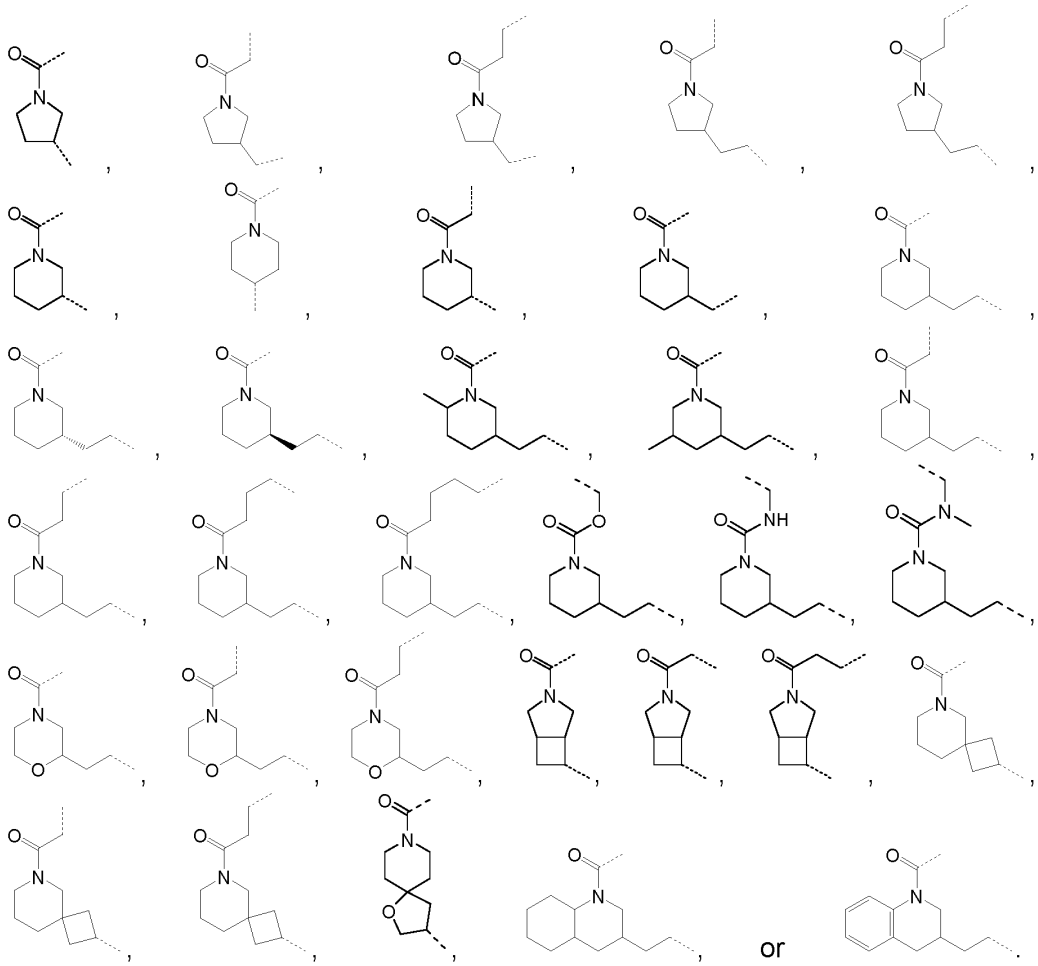
5. The compound according to any one of the claims 1 – 4, wherein **A** represents –CO-NH–, –CO-N(CH_3)–,



or

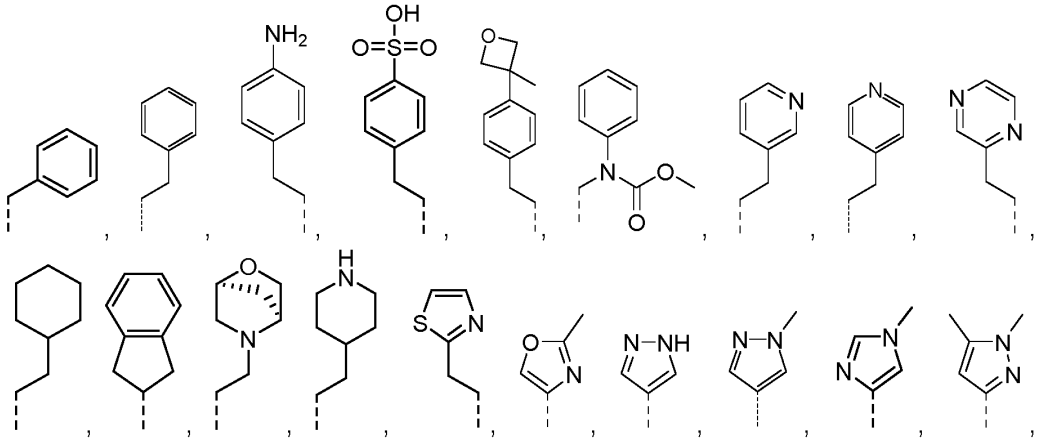
6. The compound according to any one of the claims 1 – 5, wherein -X_2-A-X_1- represents

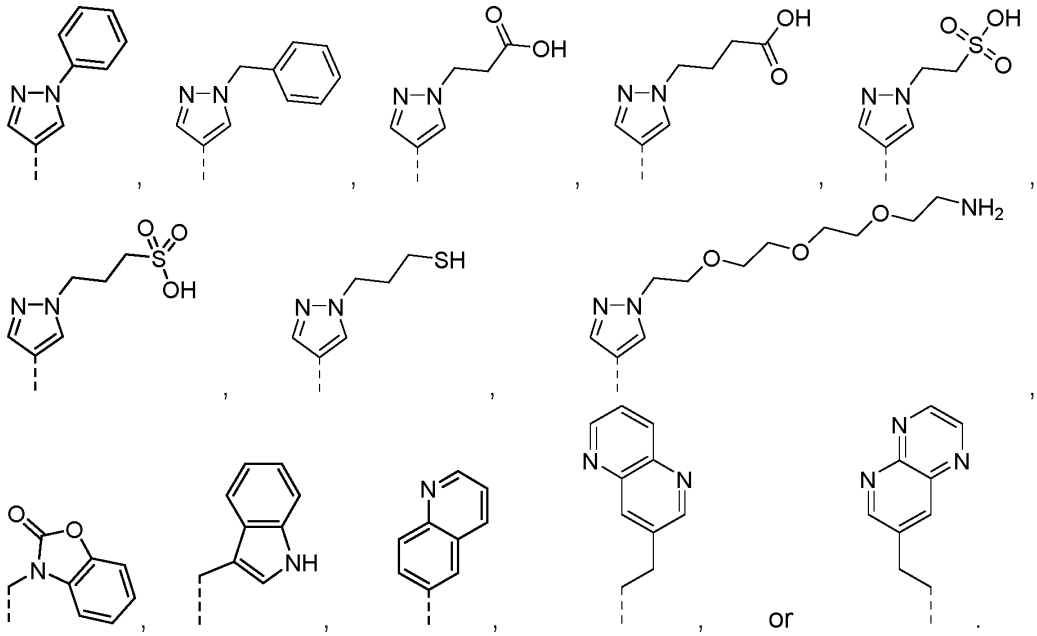




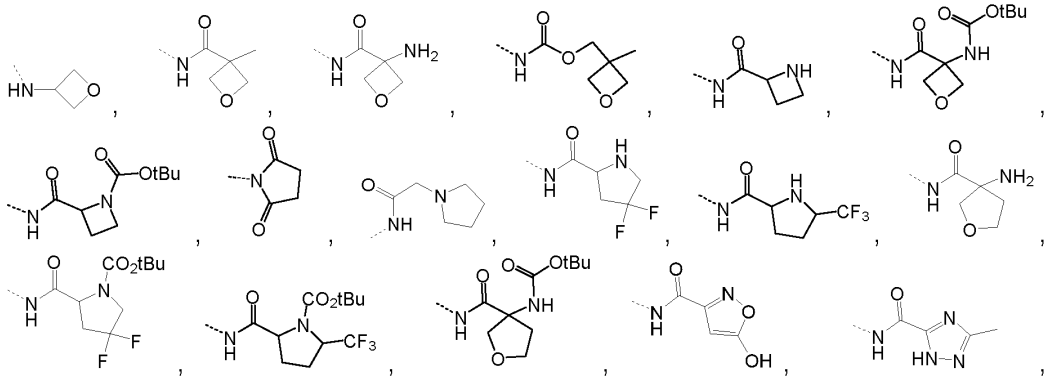
or

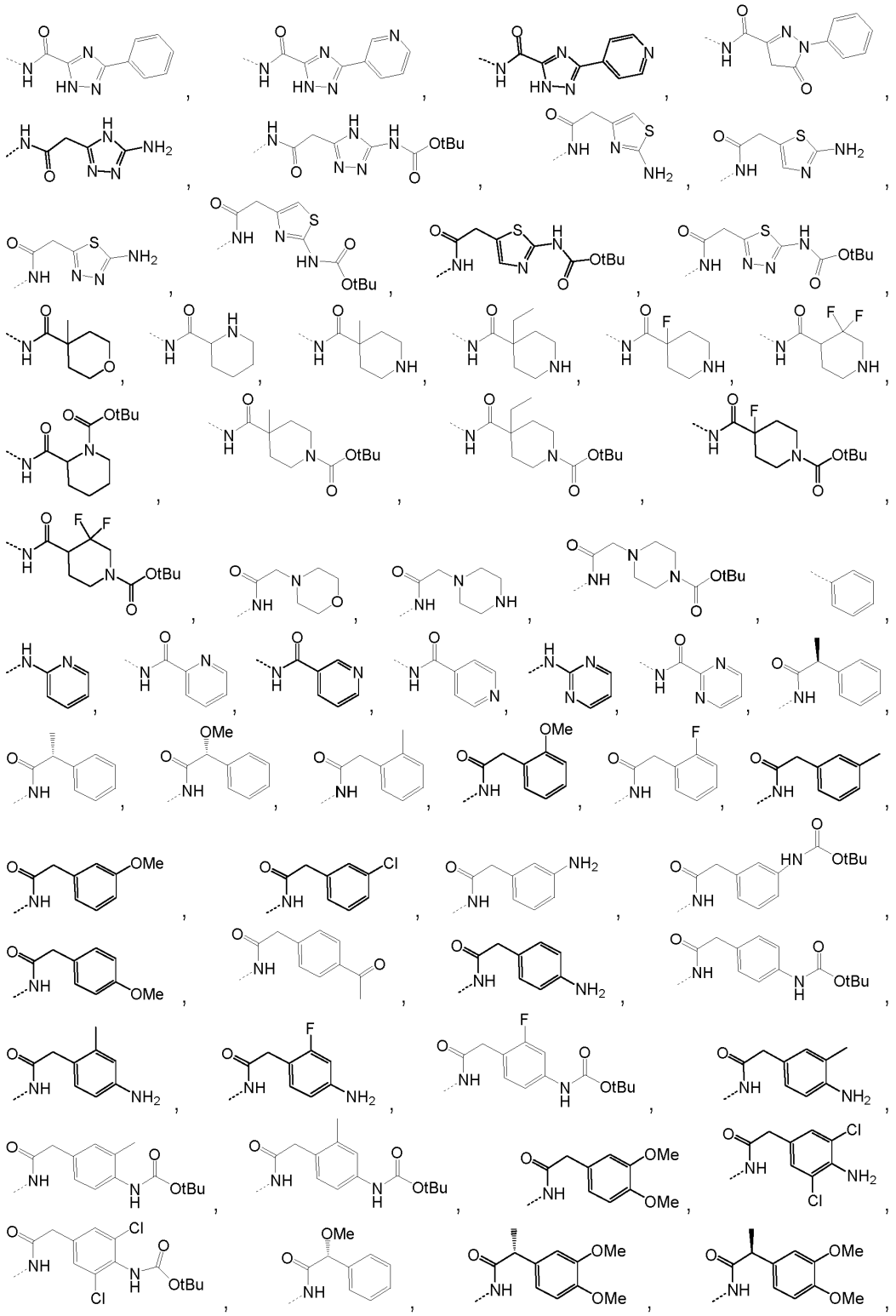
7. The compound according to any one of the claims 1 – 6, wherein **R**[1] represents -CH_3, –CH_2CH_2-$CH(CH_3)_2$, –CH_2CH_2-C≡CH,

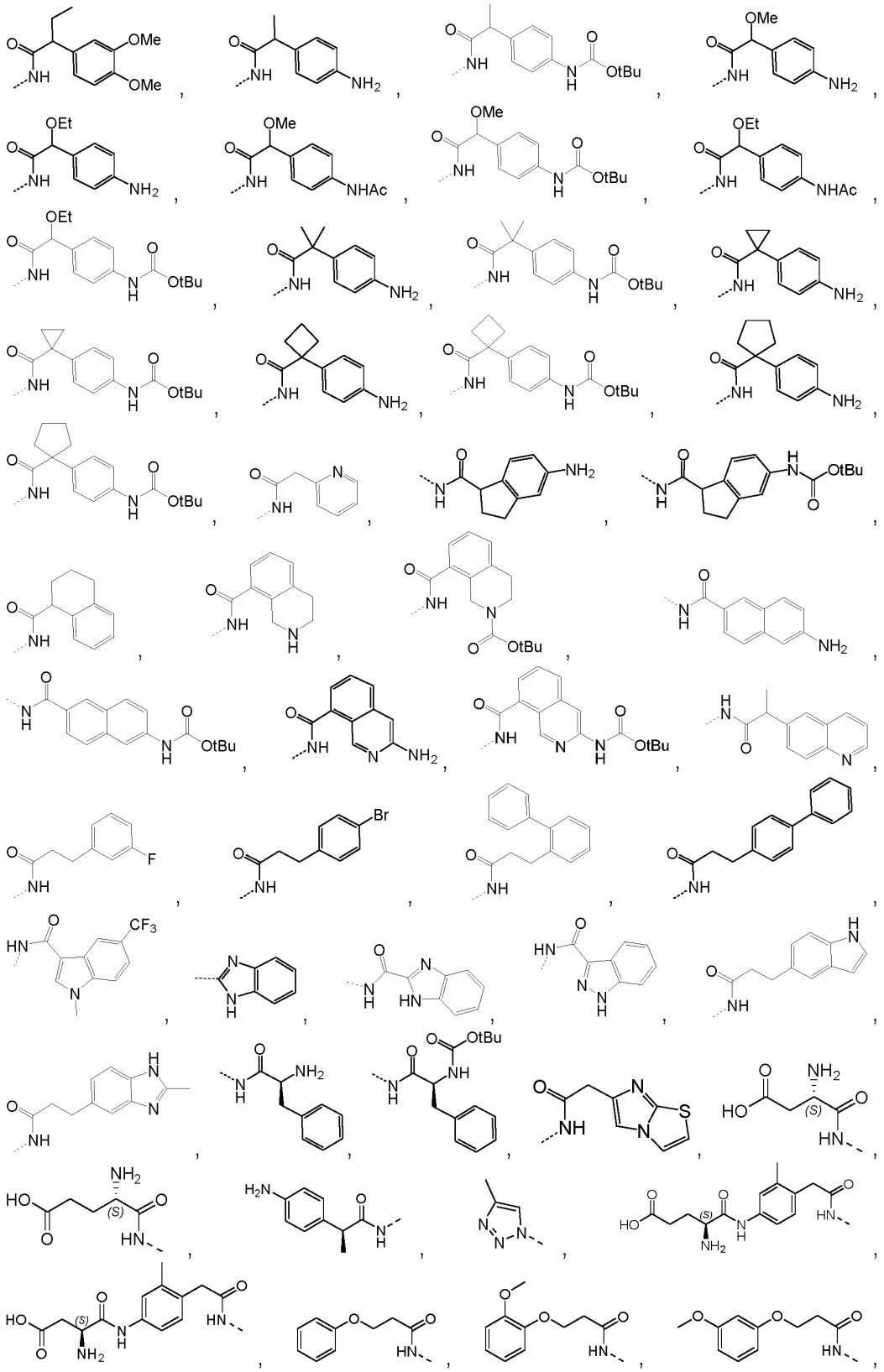


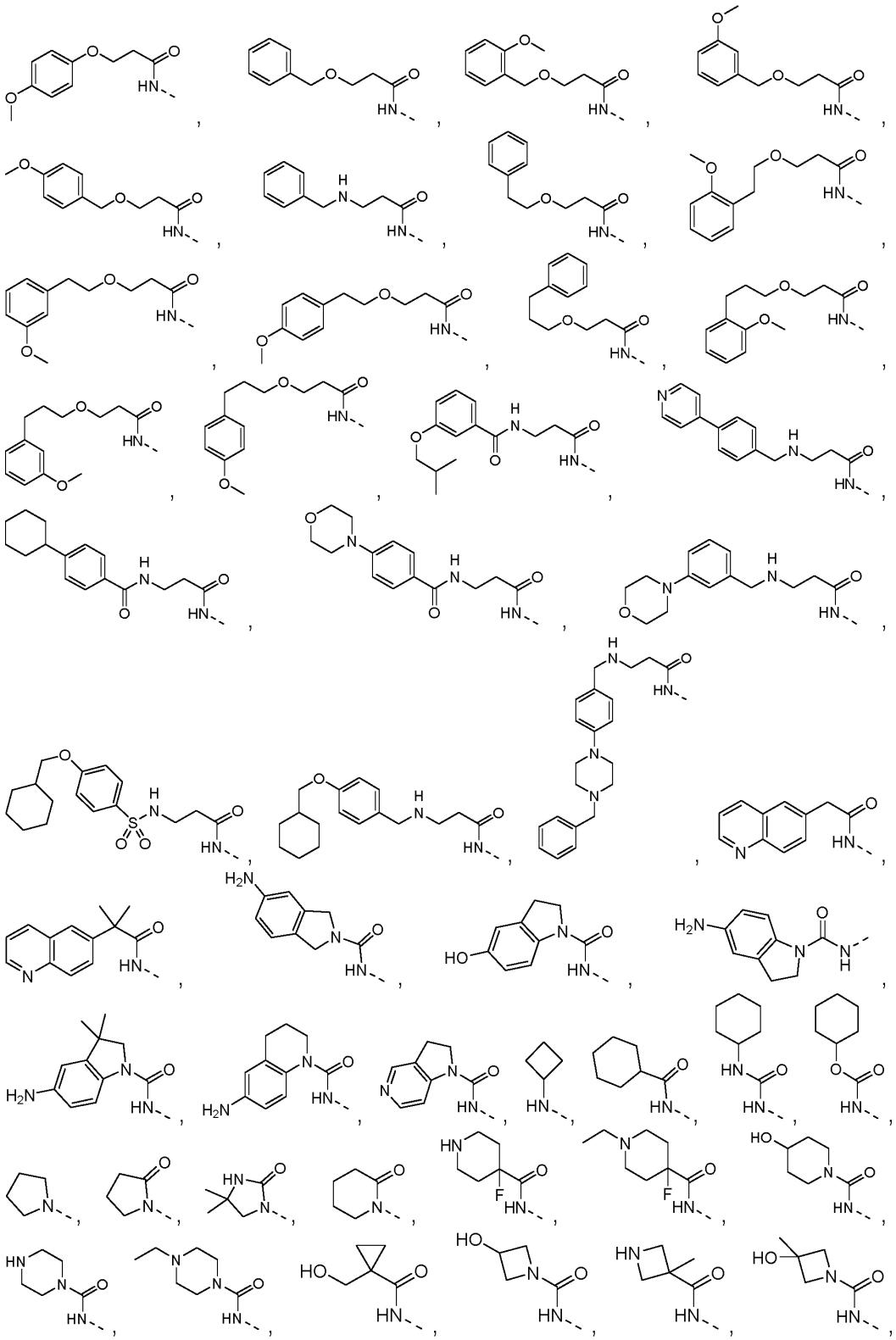


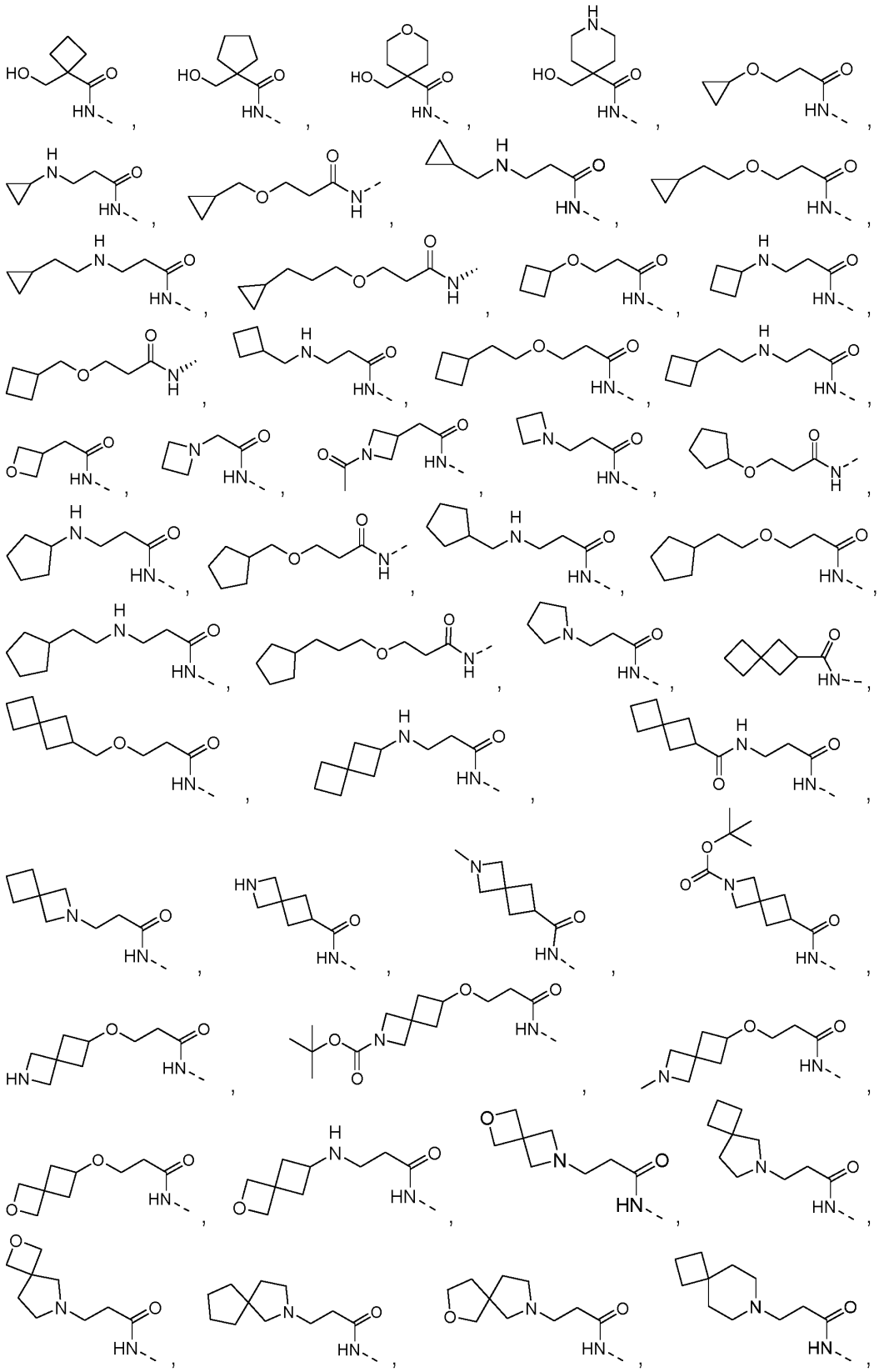
8. The compound according to any one of the claims 1 – 7, wherein **B** represents –H, $–NH_2$, $–NHCOCH_3$, $–NHCOC(CH_3)_3$, $–NHCOC(CN)(CH_3)_2$, $–NHCOCH=CH_2$, $–NHCOCH_2C(CH_3)_3$, –NHCOPh, $–NHCOCH_2Ph$, $–NHCOCH_2–NH(CH_3)$, $–NHCOCH_2–N(CH_3)CO_2tBu$, $–NHCOC(CH_3)_2CH_2OH$, $–NHCOC(CH_3)_2CH_2SH$, $–NHCOC(CH_3)_2CH_2NH_2$, $–NHCOC(CH_3)_2CH_2F$, $–NHCOC(CH_3)_2CF_3$, $–NHCOCF_2CH_2OH$, $–NHCOCF_2CH_2NH_2$, $–NHCOC(CH_2CH_3)_2CH_2OH$, $–NHCOC(CH_3)(CH_2OH)_2$, $–NHCOCH_2OCH_2CH_2–NH(CH_3)$, $–NHCOCH_2OCH_2CH_2–N(CH_3)CO_2tBu$, $–NHCO(CH_2CH_2O)_2CH_3$, $–NHCO_2CH_2CH_3$, $–NHCO_2(CH_2CH_2O)_3CH_3$, $–NHCO_2(CH_2CH_2O)_5CH_3$, $–NHCO_2(CH_2CH_2O)_7CH_3$, $–NHCO_2CH_2Ph$ $–NHCONHCH_2CH_3$, $–NHSO_2CH_3$, $–NHSO_2CH=CH_2$, $–NHSO_2CH_2Ph$, $–NHSO_2CH_2CH_2Ph$, $–NHSO_2CH_2CH_2CH_2Ph$, $–NHSO_2CH_2CF_3$, $–NHCH_2CF_3$, $–NHCH_2(CH_3)_2NH_2$, $–NHCH_2(CH_3)_2CH_2OH$,

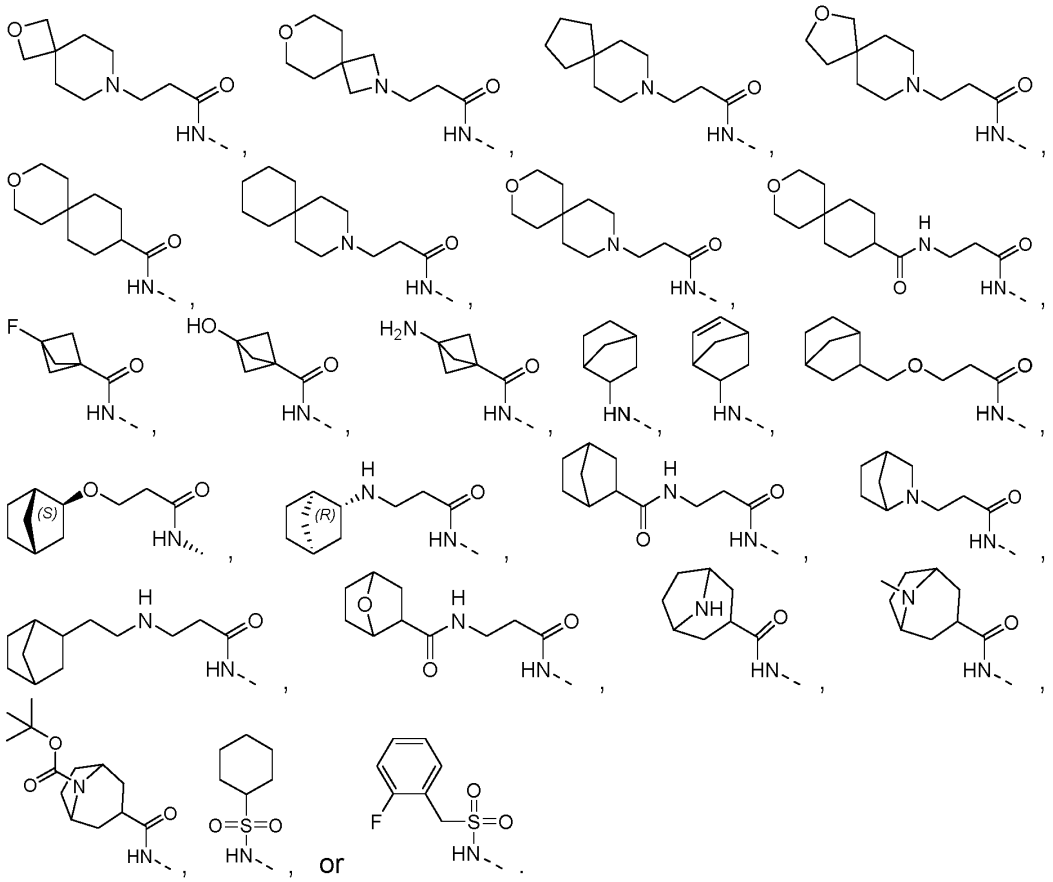




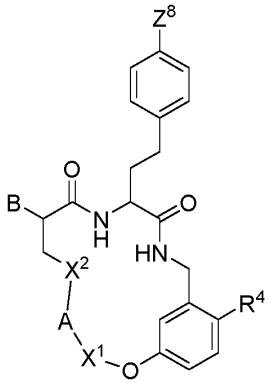




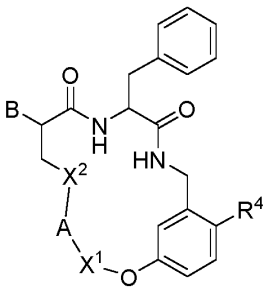




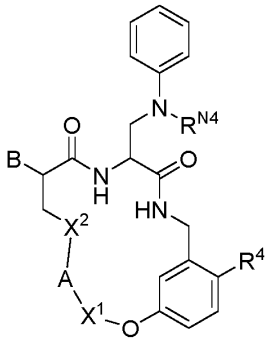
9. The compound according to any one of the claims 1 – 8, wherein the compound has any one of the formulae (**II-1**) – (**II-16**), (**III-1**) – (**III-10**), (**IV-1**) – (**IV-10**), and (**V-1**) – (**V-9**)



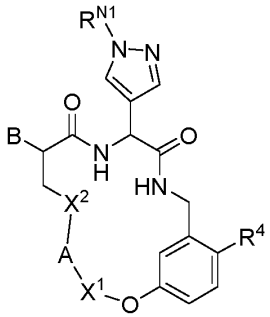
(**II-1**)



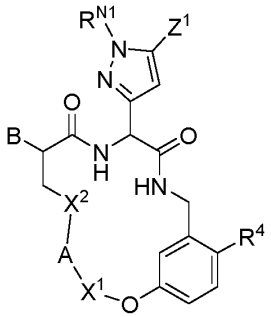
(**II-2**)



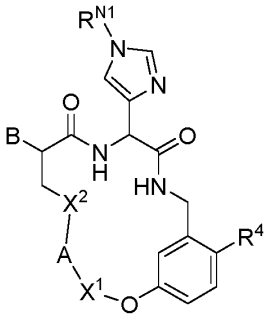
(**II-3**)



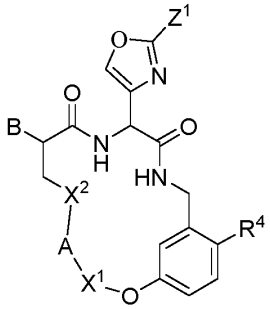
(**II-4**)



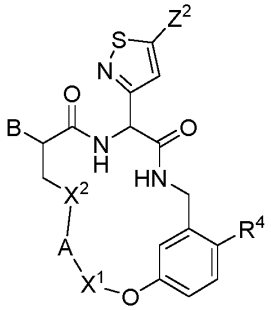
(**II-5**)



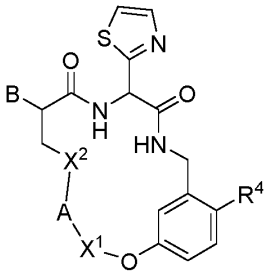
(**II-6**)



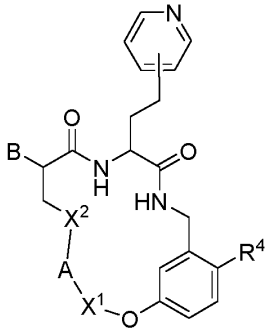
(**II-7**)



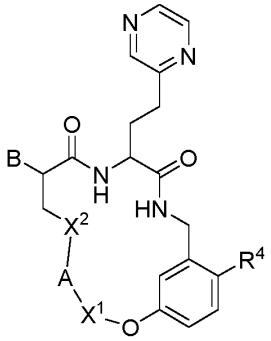
(**II-8**)



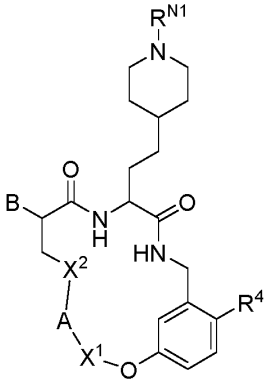
(**II-9**)



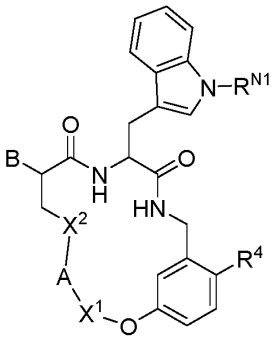
(**II-10**)



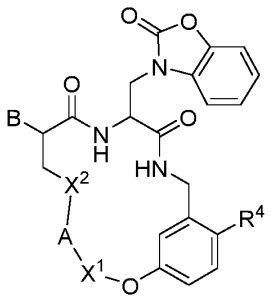
(**II-11**)



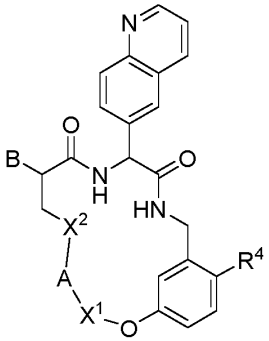
(**II-12**)



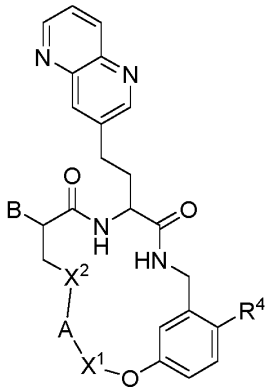
(**II-13**)



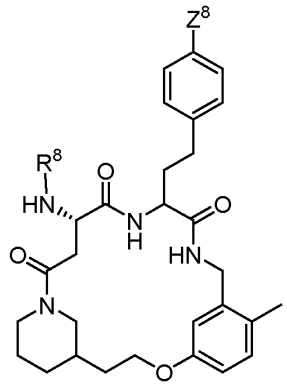
(**II-14**)



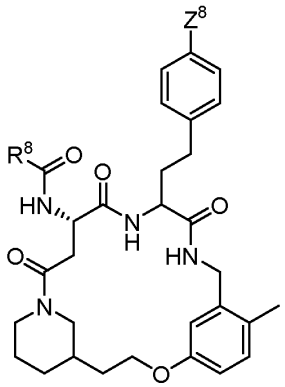
(**II-15**)



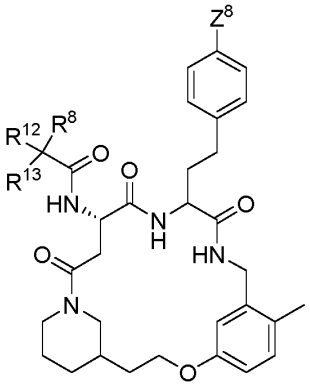
(**II-16**)



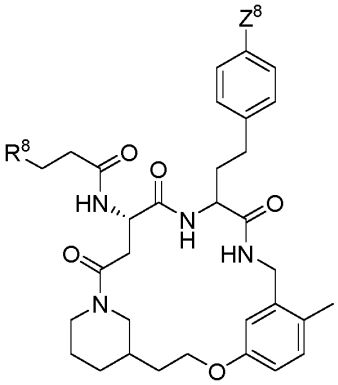
(**III-1**)



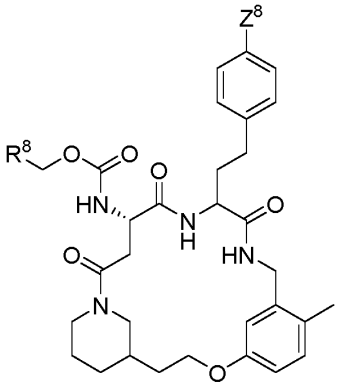
(**III-2**)



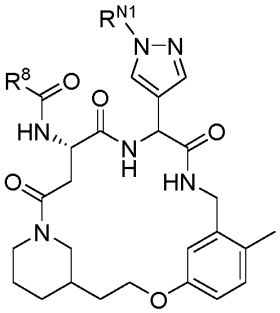
(**III-3**)



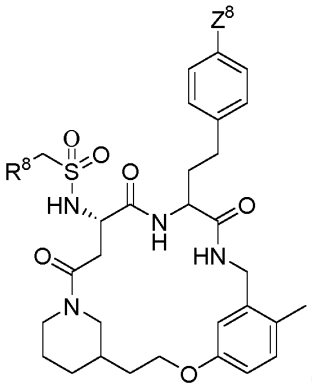
(**III-4**)



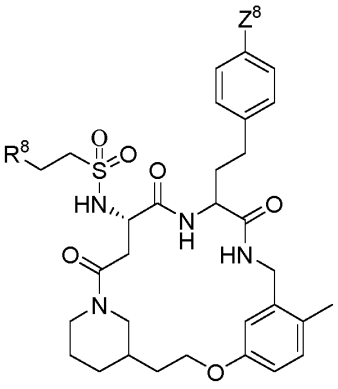
(**III-5**)



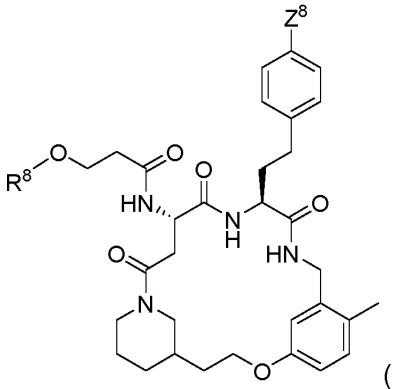
(**III-6**)



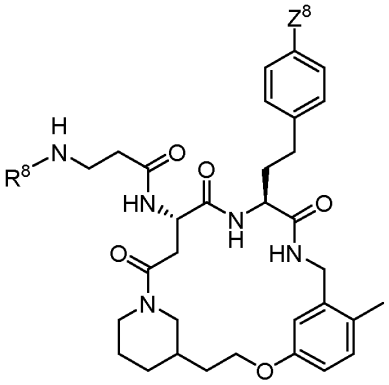
(**III-7**)



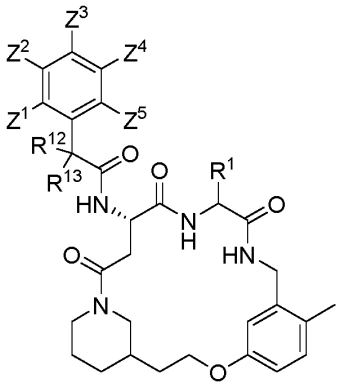
(**III-8**)



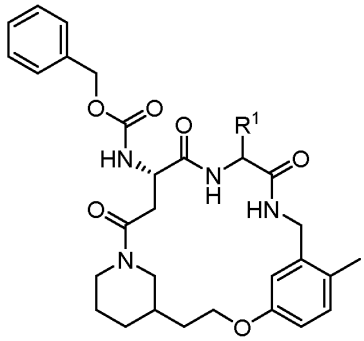
(**III-9**)



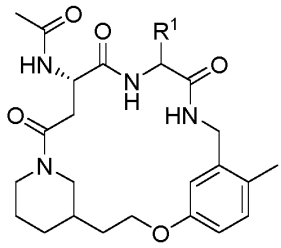
(**III-10**)



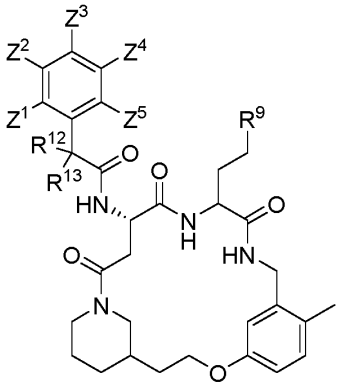
(**IV-1**)



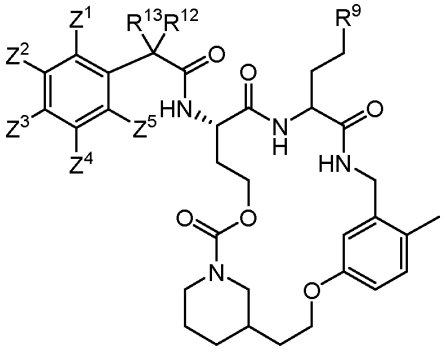
(**IV-2**)



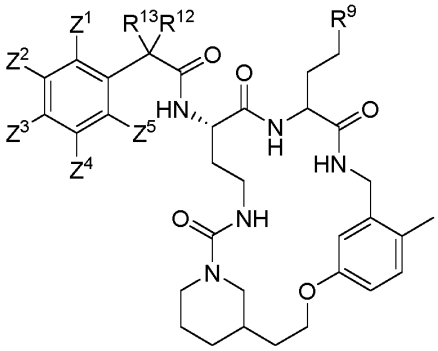
(**IV-3**)



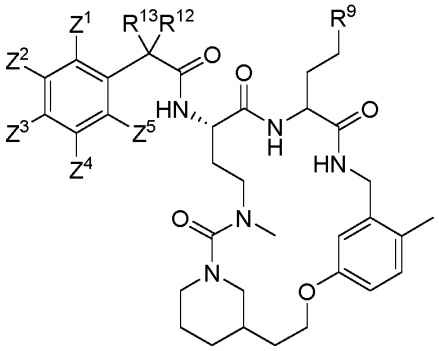
(**IV-4**)



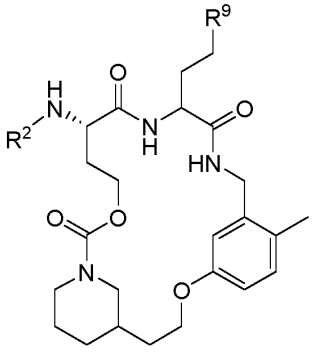
(**IV-5**)



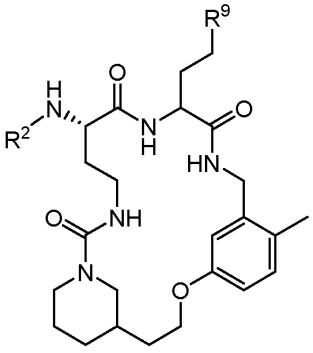
(**IV-6**)



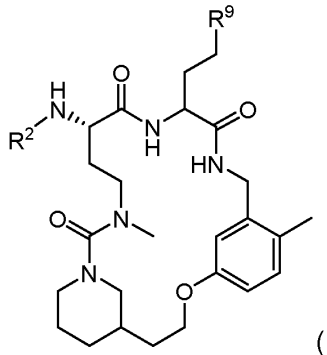
(**IV-7**)



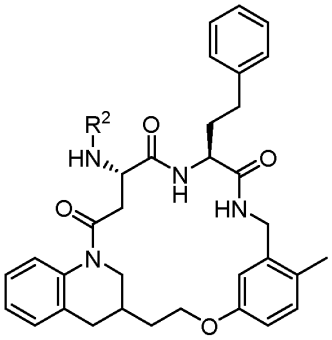
(**IV-8**)



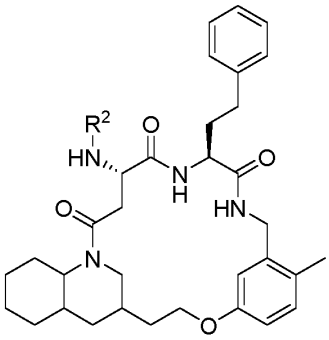
(**IV-9**)



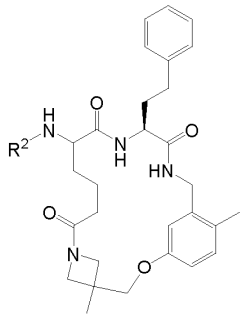
(**IV-10**)



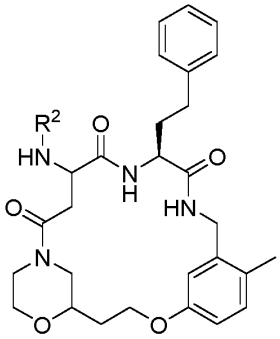
(**V-1**)



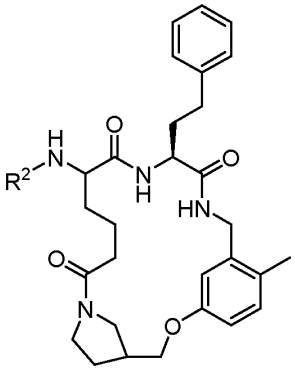
(**V-2**)



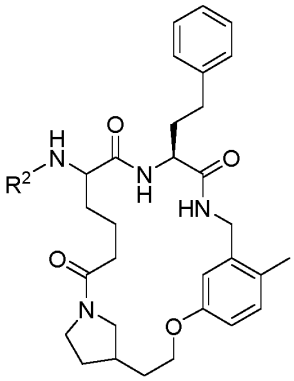
(**V-3**)



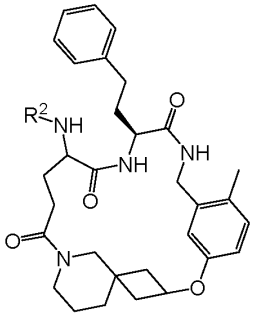
(**V-4**)



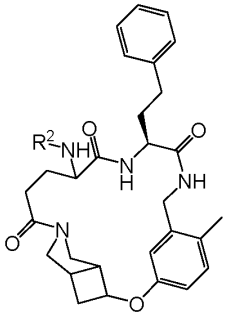
(**V-5**)



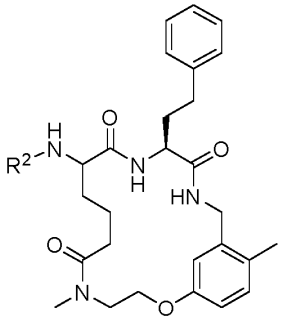
(**V-6**)



(**V-7**)



(**V-8**)



(**V-9**)

wherein A, B, R^1, R^2, R^4, R^8, R^9, R^{12}, R^{13}, R^{N1}, R^{N4}, X^1, X^2, Z^1 , Z^2 , Z^3 , Z^4 , Z^5 and Z^8 have the same meanings as defined in any one of claims 1 - 8.

10. The compound according to claim 1 selected from the group consisting of:

Com-pound	IUPAC Name
7	benzyl ((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
8	(9S,12S)-12-amino-5^4-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
13	(9S)-5^4-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
16	(9S)-5^4-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclohexadecaphane-8,11,16-trione
19	(9S)-5^4-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclopentadecaphane-8,11,15-trione
22	(9S)-5^4-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacycloheptadecaphane-8,11,17-trione
25	3-(3-fluorophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
26	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)benzamide
27	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)pivalamide
28	3,3-dimethyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)butanamide
29	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-phenylacetamide
30	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-phenylacetamide
31	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-

	1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-1H-benzo[d]imidazole-2-carboxamide
32	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)pyrimidine-2-carboxamide
33	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
34	(9S,12S)-5^4-methyl-9-phenethyl-12-(pyrimidin-2-ylamino)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
35	(9S,12S)-5^4-methyl-12-(oxetan-3-ylamino)-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
36	(9S,12S)-5^4-methyl-9-phenethyl-12-(pyridin-2-ylamino)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
37	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)methanesulfonamide
38	1-ethyl-3-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)urea
39	ethyl ((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
40	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)picolinamide
41	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)nicotinamide
42	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)isonicotinamide
43	(9S,12S)-12-(2,5-dioxopyrrolidin-1-yl)-5^4-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
44	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-phenylpropane-1-sulfonamide
45	(9S,12S)-12-((1H-benzo[d]imidazol-2-yl)amino)-5^4-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-

	8,11,14-trione
51	5^4-methyl-9-(2-(pyridin-3-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
59	(9R)-5^4,5^6-dimethyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
60	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-1H-indazole-3-carboxamide
61	2-(3-chlorophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
62	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(m-tolyl)acetamide
63	2-(3,4-dimethoxyphenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
64	2-(3,4-dimethoxyphenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)butanamide
77	(9S)-9-((1H-indol-3-yl)methyl)-5^4-methyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
78	(9S)-5^4,9-dimethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
79	(9S)-9-benzyl-5^4-methyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
80	(2R)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-phenylpropanamide
81	(2S)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-phenylpropanamide
82	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-1,2,3,4-

	tetrahydronaphthalene-1-carboxamide
83	2-(4-methoxyphenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
84	2-(2-methoxyphenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
85	2-(3-methoxyphenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
86	(2R)-2-methoxy-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-phenylacetamide
87	1-methyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-5-(trifluoromethyl)-1H-indole-2-carboxamide
88	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-morpholinoacetamide
89	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(pyrrolidin-1-yl)acetamide
95	(9S)-5^4,5^5-dimethyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione (95)
105	benzyl ((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyrazin-2-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
106	(12S)-amino-5^4-methyl-8,11,14-trioxo-9-(2-(pyrazin-2-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane
107	(2S)-N-((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyrazin-2-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-phenylpropanamide
116	5^4-methyl-9-(1-methyl-1H-pyrazol-4-yl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione

120	(9S)-9-((1H-indol-3-yl)methyl)-5^4,5^5-dimethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
121	tert-butyl 4-(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)piperazine-1-carboxylate
122	tert-butyl (3-(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)phenyl)carbamate
123	tert-butyl (4-(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)phenyl)carbamate
124	tert-butyl methyl(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)carbamate
125	tert-butyl methyl(2-(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethoxy)ethyl)carbamate
126	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(piperazin-1-yl)acetamide
127	2-(3-aminophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
128	2-(4-aminophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
129	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(methylamino)acetamide
130	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(2-(methylamino)ethoxy)acetamide
131	tert-butyl 4-fluoro-4-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-

	yl)carbamoyl)piperidine-1-carboxylate
132	tert-butyl 4,4-difluoro-2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)pyrrolidine-1-carboxylate
133	tert-butyl 4-methyl-4-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)piperidine-1-carboxylate
134	4-fluoro-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)piperidine-4-carboxamide
135	(2S)-4,4-difluoro-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)pyrrolidine-2-carboxamide
136	4-methyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)piperidine-4-carboxamide
143	N-((9S,12S)-5^4-methyl-8,11,15-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(2,4)-morpholina-5(1,3)-benzenacyclopentadecaphane-12-yl)acetamide
148	N-((7S,10S)-3^4-methyl-6,9,13-trioxo-7-phenethyl-2-oxa-5,8-diaza-1(3,1)-piperidina-3(1,3)-benzenacyclotridecaphane-10-yl)acetamide
149	tert-butyl 4-ethyl-4-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)piperidine-1-carboxylate
150	tert-butyl 3,3-difluoro-4-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)piperidine-1-carboxylate
151	4-ethyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)piperidine-4-carboxamide
152	3,3-difluoro-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)piperidine-4-carboxamide
153	tert-butyl 2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-

	yl)carbamoyl)-5-(trifluoromethyl)pyrrolidine-1-carboxylate
154	tert-butyl 2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)piperidine-1-carboxylate
155	tert-butyl (3-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)oxetan-3-yl)carbamate
156	tert-butyl (3-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)tetrahydrofuran-3-yl)carbamate
157	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-5-(trifluoromethyl)pyrrolidine-2-carboxamide
158	3-amino-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)oxetane-3-carboxamide
159	3-amino-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)tetrahydrofuran-3-carboxamide
160	(2R)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)azetidine-2-carboxamide
161	tert-butyl 2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)azetidine-1-carboxylate
168	N-((10S,13S)-1^4-methyl-8,11,14-trioxo-13-phenethyl-2-oxa-7,12,15-triaza-1(1,3)-benzenacyclohexadecaphane-10-yl)acetamide
171	N-((11S,14S)-1^4-methyl-8,12,15-trioxo-14-phenethyl-2-oxa-7,13,16-triaza-1(1,3)-benzenacycloheptadecaphane-11-yl)acetamide
172	2-(4-aminophenyl)-N-((13R,9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
173	2-(4-aminophenyl)-N-((13S,9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-

	12-yl)acetamide
174	3-(2-methyl-1H-benzo[d]imidazol-6-yl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
175	3-(4-bromophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
176	3-([1,1'-biphenyl]-4-yl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
177	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(2-phenoxyphenyl)propanamide
178	tert-butyl ((2S)-1-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate
179	(2R)-2-amino-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-phenylpropanamide
180	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)ethenesulfonamide
181	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acrylamide
182	3-(1H-indol-5-yl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
186	N-((9S,12S)-5^4-methyl-8,11,16-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(2,4)-morpholina-5(1,3)-benzenacyclohexadecaphane-12-yl)acetamide
191	N-((11R,15S,7S,10S)-3^4-methyl-6,9,14-trioxo-7-phenethyl-2-oxa-13,5,8-triaza-1(7,3)-bicyclo[3.2.0]heptana-3(1,3)-benzenacyclotetradecaphane-10-yl)acetamide
195	benzyl ((9S,12S)-5^4-methyl-8,11,16-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclohexadecaphane-12-yl)carbamate

199	benzyl ((9S,12S)-5^4-methyl-8,11,15-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclopentadecaphane-12-yl)carbamate
205	N-((9S,12S)-5^4-fluoro-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
211	N-((9S,12S)-5^4-methoxy-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
212	(9S,12S)-5^4-methyl-12-amino-8,11,16-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclohexadecaphane
213	N-((9S,12S)-5^4-methyl-8,11,16-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclohexadecaphane-12-yl)acetamide
214	(9S,12S)-12-amino-5^4-methyl-8,11,15-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclopentadecaphane)
215	N-((9S,12S)-5^4-methyl-8,11,15-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclopentadecaphane-12-yl)acetamide
216	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-1-phenylmethanesulfonamide
217	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-phenylethane-1-sulfonamide
218	2,5,8,11,14,17,20-heptaoxadocosan-22-yl ((9R,12R)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
219	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2,5,8,11,14-pentaoxaheptadecan-17-amide
220	((9R,12R)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
252	N-((8S,11S)-1^4-methyl-6,9,12-trioxo-11-phenethyl-2-oxa-5,10,13-triaza-1(1,3)-benzenacyclotetradecaphane-8-yl)acetamide
253	N-((9S,12S)-1^4-methyl-7,10,13-trioxo-12-phenethyl-2-oxa-6,11,14-triaza-1(1,3)-benzenacyclopentadecaphane-9-yl)acetamide
254	N-((7S,10S)-3^4-methyl-6,9,12-trioxo-7-phenethyl-2-oxa-5,8-diaza-1(4,1)-

	piperidina-3(1,3)-benzenacyclododecaphane-10-yl)acetamide
255	N-((7S,10S)-3^4-methyl-6,9,12-trioxo-7-phenethyl-2-oxa-5,8-diaza-1(3,1)-piperidina-3(1,3)-benzenacyclododecaphane-10-yl)acetamide
256	N-((9S,12S)-14,6-dimethyl-7,10,13-trioxo-12-phenethyl-2-oxa-6,11,14-triaza-1(1,3)-benzenacyclopentadecaphane-9-yl)acetamide
257	N-((8S,11S)-4^4-methyl-7,10,13-trioxo-8-phenethyl-3-oxa-6,9-diaza-1(3,1)-piperidina-4(1,3)-benzenacyclotridecaphane-11-yl)acetamide
258	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(2,4)-morpholina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
259	N-((8S,11S)-4^4-methyl-7,10,13-trioxo-8-phenethyl-3-oxa-6,9-diaza-1(3,1)-azetidina-4(1,3)-benzenacyclotridecaphane-11-yl)acetamide
260	N-((8S,11S)-1^2,4^4-dimethyl-7,10,13-trioxo-8-phenethyl-3-oxa-6,9-diaza-1(2,1)-azetidina-4(1,3)-benzenacyclotridecaphane-11-yl)acetamide
261	N-((7S,10S)-3^4-methyl-6,9,12-trioxo-7-phenethyl-2-oxa-5,8-diaza-1(3,1)-pyrrolidina-3(1,3)-benzenacyclododecaphane-10-yl)acetamide
265	N-((8S,11S)-1^2,4^4-dimethyl-7,10,14-trioxo-8-phenethyl-3-oxa-6,9-diaza-1(2,1)-azetidina-4(1,3)-benzenacyclotetradecaphane-11-yl)acetamide
269	N-((8S,11S)-1^2,4^4-dimethyl-7,10,14-trioxo-8-phenethyl-3-oxa-6,9-diaza-1(2,1)-azetidina-4(1,3)-benzenacyclotetradecaphane-11-yl)acetamide
280	N-((11S,14S)-1^4,6-dimethyl-7,12,15-trioxo-14-phenethyl-2-oxa-6,13,16-triaza-1(1,3)-benzenacycloheptadecaphane-11-yl)acetamide
281	N-((8S,11S)-1^2,4^4-dimethyl-7,10,15-trioxo-8-phenethyl-3-oxa-6,9-diaza-1(2,1)-azetidina-4(1,3)-benzenacyclopentadecaphane-11-yl)acetamide
282	N-((11S,14S)-1^4,7-dimethyl-8,12,15-trioxo-14-phenethyl-2-oxa-7,13,16-triaza-1(1,3)-benzenacycloheptadecaphane-11-yl)acetamide
283	benzyl ((7S,10S)-3^4-methyl-6,9,14-trioxo-7-phenethyl-2-oxa-5,8-diaza-15(3,1)-piperidina-3(1,3)-benzena-1(1,3)-cyclobutanapentadecaphane-10-yl)carbamate
284	3-hydroxy-2,2-dimethyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
285	2-ethyl-2-(hydroxymethyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-

	benzenacyclotetradecaphane-12-yl)butanamide
286	3-hydroxy-2-(hydroxymethyl)-2-methyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
287	3-methyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)oxetane-3-carboxamide
288	4-methyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)tetrahydro-2H-pyran-4-carboxamide
289	benzyl ((13R,9R,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
290	benzyl ((13R,9R,12R)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
291	benzyl ((13R,9S,12R)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
292	benzyl ((13R,9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
293	(3-methyloxetan-3-yl)methyl ((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
294	2-cyano-2-methyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
295	N-(1^4,7-dimethyl-8,13,16-trioxo-15-phenethyl-2-oxa-7,14,17-triaza-1(1,3)-benzenacyclooctadecaphane-12-yl)acetamide
296	N-(1^4,7-dimethyl-8,11,14-trioxo-13-phenethyl-2-oxa-7,12,15-triaza-1(1,3)-benzenacyclohexadecaphane-10-yl)acetamide
298	N-(3^4-methyl-6,9,12-trioxo-7-phenethyl-2-oxa-13,5,8-triaza-1(6,3)-bicyclo[3.2.0]heptana-3(1,3)-benzenacyclododecaphane-10-yl)acetamide

299	N-(3^4-methyl-6,9,13-trioxo-7-phenethyl-2-oxa-13,5,8-triaza-1(6,3)-bicyclo[3.2.0]heptana-3(1,3)-benzenacyclotridecaphane-10-yl)acetamide
300	benzyl ((7S,10S)-3^4-methyl-6,9,12-trioxo-7-phenethyl-2-oxa-5,8-diaza-13(3,1)-piperidina-3(1,3)-benzena-1(1,3)-cyclobutanatridecaphane-10-yl)carbamate
301	benzyl ((7S,10S)-3^4-methyl-6,9,13-trioxo-7-phenethyl-2-oxa-5,8-diaza-14(3,1)-piperidina-3(1,3)-benzena-1(1,3)-cyclobutanatetradecaphane-10-yl)carbamate
302	2-(2-aminothiazol-4-yl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
303	2-(4-amino-3-methylphenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
304	2-(4-amino-2-methylphenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
305	1-(4-aminophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)cyclopentane-1-carboxamide
306	1-(4-aminophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)cyclobutane-1-carboxamide
307	1-(4-aminophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)cyclopropane-1-carboxamide
308	2-(4-aminophenyl)-2-methyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
309	2-(4-aminophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
310	2-(5-amino-1,3,4-thiadiazol-2-yl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-

	benzenacyclotetradecaphane-12-yl)acetamide
311	2-(2-aminothiazol-5-yl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
312	benzyl ((8S,11S)-1^4,5-dimethyl-6,9,12-trioxo-11-phenethyl-2-oxa-5,10,13-triaza-1(1,3)-benzenacyclotetradecaphane-8-yl)carbamate
313	benzyl ((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-11,12,13,14-tetrahydro-4-oxa-7,10-diaza-1(3,1)-quinolina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
314	benzyl ((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-11,12,13,14,14a,15,16,17,18,18a-decahydro-4-oxa-7,10-diaza-1(3,1)-quinolina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
315	benzyl ((9S,12S)-1^6,5^4-dimethyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
316	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-1,2,3,4-tetrahydroisoquinoline-5-carboxamide
317	5-amino-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2,3-dihydro-1H-indene-1-carboxamide
318	2-(4-amino-2-fluorophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
319	3-amino-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)isoquinoline-8-carboxamide
320	2-(4-amino-3,5-dichlorophenyl)-N-((9S,12S)-54-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
321	benzyl ((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-naphthalenacyclotetradecaphane-12-yl)carbamate
322	benzyl ((12S,15S)-1^4-methyl-8,13,16-trioxo-15-phenethyl-2-oxa-7,14,17-triaza-1(1,3)-benzenacyclooctadecaphane-12-yl)carbamate

323	2-(4-acetamidophenyl)-2-methoxy-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
324	2-(4-acetamidophenyl)-2-ethoxy-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
325	benzyl ((9S,12S)-54-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-pyrrolidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
326	2-(4-aminophenyl)-2-methoxy-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
327	N-((9S,12R)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(3-(pyridin-3-yl)-1H-1,2,4-triazol-5-yl)acetamide
328	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(3-phenyl-1H-1,2,4-triazol-5-yl)acetamide
329	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(3-(pyridin-4-yl)-1H-1,2,4-triazol-5-yl)acetamide
330	2-(imidazo[2,1-b]thiazol-6-yl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
331	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(pyridin-2-yl)acetamide
332	2-(3-methyl-1H-1,2,4-triazol-5-yl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
333	2-(2-fluorophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
334	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(5-oxo-1-

	phenyl-4,5-dihydro-1H-pyrazol-3-yl)acetamide
335	2-(5-hydroxyisoxazol-3-yl)-N-((9S,12S)-54-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
336	benzyl ((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-4-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
337	benzyl ((9S,12S)-1^5,5^4-dimethyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
338	N-((12S)-9-(2-(1-acetylpiperidin-4-yl)ethyl)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
339	6-amino-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-naphthamide
340	2-(5-amino-1H-1,2,4-triazol-3-yl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
341	2-(4-acetylphenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
342	2-(5-amino-1,3,4-thiadiazol-2-yl)-N-((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-4-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
343	1-(4-aminophenyl)-N-((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-4-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)cyclopropane-1-carboxamide
344	2-(4-amino-2-fluorophenyl)-N-((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-4-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
345	2-(4-aminophenyl)-2-ethoxy-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide

347	benzyl ((13S,16S)-1^4-methyl-8,14,17-trioxo-16-phenethyl-2-oxa-7,15,18-triaza-1(1,3)-benzenacyclononadecaphane-13-yl)carbamate
348	3-mercapto-2,2-dimethyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
349	benzyl ((8S,11S)-4^4-methyl-7,10,14-trioxo-8-phenethyl-3-oxa-6,9-diaza-1(3,1)-pyrrolidina-4(1,3)-benzenacyclotetradecaphane-11-yl)carbamate
350	benzyl ((9S,12S)-5^4-methyl-8,11,15-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-pyrrolidina-5(1,3)-benzenacyclopentadecaphane-12-yl)carbamate
351	benzyl ((8S,11S)-4^4-methyl-7,10,15-trioxo-8-phenethyl-3-oxa-6,9-diaza-1(3,1)-pyrrolidina-4(1,3)-benzenacyclopentadecaphane-11-yl)carbamate
352	benzyl ((9S,12S)-5^4-methyl-8,11,16-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-pyrrolidina-5(1,3)-benzenacyclohexadecaphane-12-yl)carbamate
353	benzyl ((9S,12S)-5^4-methyl-8,11,17-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-azetidina-5(1,3)-benzenacycloheptadecaphane-12-yl)carbamate
354	benzyl ((12S,15S)-1^4,1^5-dimethyl-8,13,16-trioxo-15-phenethyl-2-oxa-7,14,17-triaza-1(1,3)-benzenacyclooctadecaphane-12-yl)carbamate
355	5^4,5^5-dimethyl-9-(1-methyl-1H-pyrazol-4-yl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
356	5^4-methyl-9-(1-methyl-1H-pyrazol-4-yl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclohexadecaphane-8,11,16-trione
358	N-((12S)-5^4-methyl-9-(1-methyl-1H-pyrazol-4-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(pyrrolidin-1-yl)acetamide
359	(2S)-N-((12S)-5^4-methyl-9-(1-methyl-1H-pyrazol-4-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-phenylpropanamide
360	N-((12S)-5^4-methyl-9-(1-methyl-1H-pyrazol-4-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-1,2,3,4-tetrahydronaphthalene-1-carboxamide
361	(2R)-2-methoxy-N-((12S)-5^4-methyl-9-(1-methyl-1H-pyrazol-4-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-phenylacetamide

362	2-(3-methoxyphenyl)-N-((12S)-5^4-methyl-9-(1-methyl-1H-pyrazol-4-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
363	Ethyl ((12S)-5^4-methyl-9-(1-methyl-1H-pyrazol-4-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
364	N-((12S,15S)-1^4-methyl-8,13,16-trioxo-15-phenethyl-2-oxa-7,14,17-triaza-1(1,3)-benzenacyclooctadecaphane-12-yl)acetamide
369	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(quinolin-6-yl)propanamide
371	1-(4-aminophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyrazin-2-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)cyclopropane-1-carboxamide
372	2-(4-amino-2-fluorophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyrazin-2-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
373	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(o-tolyl)acetamide
387	tert-butyl (4-(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)thiazol-2-yl)carbamate
388	tert-butyl (2-methyl-4-(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)phenyl)carbamate
389	tert-butyl (3-methyl-4-(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)phenyl)carbamate
390	tert-butyl (4-(1-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)cyclopentyl)phenyl)carbamate
391	tert-butyl (4-(1-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-

	yl)carbamoyl)cyclobutyl)phenyl)carbamate
392	tert-butyl (4-(1-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)cyclopropyl)phenyl)carbamate
393	tert-butyl (4-(2-methyl-1-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-1-oxopropan-2-yl)phenyl)carbamate
394	2-(4-aminophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
395	tert-butyl (5-(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)-1,3,4-thiadiazol-2-yl)carbamate
396	tert-butyl (5-(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)thiazol-2-yl)carbamate
402	benzyl ((9S,12S)-1^4,5-dimethyl-6,10,13-trioxo-12-phenethyl-2-oxa-5,11,14-triaza-1(1,3)-benzenacyclopentadecaphane-9-yl)carbamate
405	benzyl ((10S,13S)-1^4,5-dimethyl-6,11,14-trioxo-13-phenethyl-2-oxa-5,12,15-triaza-1(1,3)-benzenacyclohexadecaphane-10-yl)carbamate
419	tert-butyl 8-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate
420	tert-butyl (1-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)-2,3-dihydro-1H-inden-5-yl)carbamate
421	tert-butyl (3-fluoro-4-(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)phenyl)carbamate
422	tert-butyl (8-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)isoquinolin-3-yl)carbamate
423	tert-butyl (2,6-dichloro-4-(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-

	benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)phenyl)carbamate
429	tert-butyl (4-(1-methoxy-2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)phenyl)carbamate
437	((12S)-12-amino-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-4-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane
438	N-((12S)-12-amino-9-(2-(1-acetylpiperidin-4-yl)ethyl)-54-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane
439	tert-butyl (5-(2-(((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-4-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)-1,3,4-thiadiazol-2-yl)carbamate
440	tert-butyl (6-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)naphthalen-2-yl)carbamate
441	tert-butyl (5-(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)-4H-1,2,4-triazol-3-yl)carbamate
442	tert-butyl (4-(1-ethoxy-2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)phenyl)carbamate
443	tert-butyl (4-(1-(((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-4-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)cyclopropyl)phenyl)carbamate
444	tert-butyl (3-fluoro-4-(2-(((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-4-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)phenyl)carbamate
479	benzyl ((12S)-5^4-methyl-9-(1-methyl-1H-pyrazol-4-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
480	(12S)-12-amino-5^4-methyl-9-(1-methyl-1H-pyrazol-4-yl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
495	5^4-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione

511	benzyl ((12S)-9-(2-(1,5-naphthyridin-3-yl)ethyl)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
503	benzyl ((12S)-9-phenethyl-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
505	benzyl ((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyrido[2,3-b]pyrazin-7-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
509	4-(2-((12S)-12-(((benzyloxy)carbonyl)amino)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-9-yl)ethyl)benzenesulfonic acid
510	benzyl ((12S)-5^4-methyl-9-(4-(3-methyloxetan-3-yl)phenethyl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
512	benzyl ((12S)-5^4-methyl-9-(2-methyloxazol-4-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
513	methyl (((12R)-12-(((benzyloxy)carbonyl)amino)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-9-yl)methyl)(phenyl)carbamate
549	N-((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-3-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
550	N-((12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
551	N-((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-4-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
552	N-((12S)-5^4-methyl-9-(1-methyl-1H-pyrazol-4-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
553	N-((12S)-5^4-methyl-9-(2-methyloxazol-4-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide

554	N-((12S)-5^4-methyl-8,11,14-trioxo-9-(quinolin-6-yl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
555	N-((12S)-5^4-methyl-8,11,14-trioxo-9-((2-oxobenzo[d]oxazol-3(2H)-yl)methyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
556	N-((12S)-5^4-methyl-9-(5-methylisothiazol-3-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
557	N-((12S)-5^4-methyl-9-(1-methyl-1H-imidazol-4-yl)-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
558	N-((12S)-9-benzyl-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
559	N-((12S)-5^4-methyl-8,11,14-trioxo-9-(1-phenyl-1H-pyrazol-4-yl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
560	methyl (((12S)-12-acetamido-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-9-yl)methyl)(phenyl)carbamate
561	N-((12S)-9-(1,5-dimethyl-1H-pyrazol-3-yl)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
562	N-((12S)-5^4-methyl-8,11,14-trioxo-9-(1H-pyrazol-4-yl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
563	N-((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(thiazol-2-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
564	N-((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyrazin-2-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
565	N-((12S)-9-(1-benzyl-1H-pyrazol-4-yl)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
566	N-((12S)-9-(1-(2-(2-(2-(2-aminoethoxy)ethoxy)ethoxy)ethyl)-1H-pyrazol-4-

	yl)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
567	3-(4-((12S)-12-acetamido-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-9-yl)-1H-pyrazol-1-yl)propanoic acid
568	4-(4-((12S)-12-acetamido-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-9-yl)-1H-pyrazol-1-yl)butanoic acid
570	N-((12S)-9-(1-(3-mercaptopropyl)-1H-pyrazol-4-yl)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
571	3-(4-((12S)-12-acetamido-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-9-yl)-1H-pyrazol-1-yl)propane-1-sulfonic acid
572	N-(4-((12S)-12-acetamido-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-9-yl)-1H-pyrazol-1-yl)ethane-1-sulfonic acid
573	3-hydroxy-2,2-dimethyl-N-((1^{3}R,9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
574	(4S)-4-amino-5-((3-methyl-4-(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)phenyl)amino)-5-oxopentanoic acid
575	N-((9S,12S)-9-(2-cyclohexylethyl)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(imidazo[2,1-b]thiazol-6-yl)acetamide
576	N-(3-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-3-oxopropyl)-3-oxaspiro[5.5]undecane-9-carboxamide
577	tert-butyl 6-(3-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-3-oxopropoxy)-2-azaspiro[3.3]heptane-2-carboxylate
578	(3S)-3-amino-4-((3-methyl-4-(2-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-

	benzenacyclotetradecaphane-12-yl)amino)-2-oxoethyl)phenyl)amino)-4-oxobutanoic acid
579	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)cyclohexanesulfonamide
580	tert-butyl 6-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)-2-azaspiro[3.3]heptane-2-carboxylate
581	3-(3-methoxyphenethoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
582	3-(2-methoxyphenethoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
583	2-(imidazo[2,1-b]thiazol-6-yl)-N-((9S,12S)-9-isopentyl-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
584	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-oxaspiro[5.5]undecane-9-carboxamide
585	3-((3-methoxybenzyl)oxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
586	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(quinolin-6-yl)acetamide
587	3-(3-methoxyphenoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamid
588	3-(2-methoxyphenoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
589	3-(benzyloxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
590	3-((2-oxaspiro[3.3]heptan-6-yl)oxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-

	9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
591	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-phenoxypropanamide
592	1-ethyl-4-fluoro-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)piperidine-4-carboxamide
593	1-cyclohexyl-3-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)urea
594	3-(cyclopropylmethoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
595	3-cyclobutoxy-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
596	3-(2-methoxyethoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
597	3-cyclopropoxy-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
598	3-amino-2,2-difluoro-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
599	2,2-difluoro-3-hydroxy-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
600	2-(2-fluorophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-3-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
601	2,2,2-trifluoro-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)ethane-1-sulfonamide
602	N-((9S,12S)-9-(2,3-dihydro-1H-inden-2-yl)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(imidazo[2,1-b]thiazol-6-yl)acetamide

603	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-((4-(pyridin-4-yl)benzyl)amino)propanamide
604	N-(3-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-3-oxopropyl)-4-morpholinobenzamide
605	tert-butyl 3-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamoyl)-8-azabicyclo[3.2.1]octane-8-carboxylate
606	3-(3-(4-methoxyphenyl)propoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
607	3-(3-(3-methoxyphenyl)propoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
608	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(3-azaspiro[5.5]undecan-3-yl)propanamide
609	2-methyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(quinolin-6-yl)propanamide
610	3-(4-methoxyphenethoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
611	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(3-oxa-9-azaspiro[5.5]undecan-9-yl)propanamide
612	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(3-phenylpropoxy)propanamide
613	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(8-azaspiro[4.5]decan-8-yl)propanamide
614	3-(bicyclo[2.2.1]heptan-2-ylmethoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
615	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-

	(spiro[3.3]heptan-2-ylmethoxy)propanamide
616	N-(3-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-3-oxopropyl)spiro[3.3]heptane-2-carboxamide
617	N-(3-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-3-oxopropyl)bicyclo[2.2.1]heptane-2-carboxamide
618	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-phenethoxypropanamide
619	3-((2-methoxybenzyl)oxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
620	3-(3-cyclopentylpropoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
621	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(2-oxa-8-azaspiro[4.5]decan-8-yl)propanamide
622	3-(4-methoxyphenoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
623	3-(2-cyclopentylethoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
624	N-((9S,12S)-5^4-methyl-8,11,16-trioxo-9-phenethyl-4,15-dioxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclohexadecaphane-12-yl)-2-phenylacetamide
625	3-(cyclopentylmethoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
626	3-(3-cyclopropylpropoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
627	3-(2-cyclobutylethoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
628	3-(cyclobutylmethoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-

	4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
629	3-(cyclopentyloxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
630	3-(2-cyclopropylethoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
631	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)spiro[3.3]heptane-2-carboxamide
632	cyclohexyl ((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)carbamate
633	3-fluoro-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)bicyclo[1.1.1]pentane-1-carboxamide
634	(2S)-2-(4-aminophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
635	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(oxetan-3-yl)acetamide
636	1-(2-fluorophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)methanesulfonamide
637	3-(3-(2-methoxyphenyl)propoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
638	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(7-azaspiro[3.5]nonan-7-yl)propanamide
639	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(6-azaspiro[3.4]octan-6-yl)propanamide
640	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(2-oxa-7-azaspiro[4.4]nonan-7-yl)propanamide

641	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(2-oxa-7-azaspiro[3.5]nonan-7-yl)propanamide
642	3-(((1S,2S,4R)-bicyclo[2.2.1]heptan-2-yl)oxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
643	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)cyclohexanecarboxamide
644	3-hydroxy-2,2-dimethyl-N-((1^{3}S,9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
645	2-(4-amino-2-methylphenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-3-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
646	3,3,3-trifluoro-2,2-dimethyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
647	3-(benzylamino)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
648	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(2-oxa-6-azaspiro[3.4]octan-6-yl)propanamide
649	3-(cyclopropylamino)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
650	3-fluoro-2,2-dimethyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
651	3-isobutoxy-N-(3-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-3-oxopropyl)benzamide
652	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(2-azaspiro[4.4]nonan-2-yl)propanamide
653	N-((9S,12S)-5^4-methyl-8,11,16-trioxo-9-phenethyl-4-oxa-7,10,15-triaza-1(3,1)-piperidina-5(1,3)-benzenacyclohexadecaphane-12-yl)-2-

	phenylacetamide
654	2-(4-amino-2-methylphenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-4-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
655	3-hydroxy-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)bicyclo[1.1.1]pentane-1-carboxamide
656	4-cyclohexyl-N-(3-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-3-oxopropyl)benzamide
657	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(spiro[3.3]heptan-2-ylamino)propanamide
658	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(7-oxa-2-azaspiro[3.5]nonan-2-yl)propanamide
659	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(2-azaspiro[3.3]heptan-2-yl)propanamide
660	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(2-oxa-6-azaspiro[3.3]heptan-6-yl)propanamide
661	N-((9S,12S)-5^4-fluoro-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-phenylacetamide
662	3-amino-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)bicyclo[1.1.1]pentane-1-carboxamide
663	2-(azetidin-1-yl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
664	1-(hydroxymethyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)cyclopropane-1-carboxamide
665	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-((3-morpholinobenzyl)amino)propanamide
666	5-amino-3,3-dimethyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-

	yl)indoline-1-carboxamide
667	6-amino-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3,4-dihydroquinoline-1(2H)-carboxamide
668	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-(pyrrolidin-1-yl)propanamide
669	3-hydroxy-3-methyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)azetidine-1-carboxamide
670	1-(hydroxymethyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)cyclobutane-1-carboxamide
671	4-(hydroxymethyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)tetrahydro-2H-pyran-4-carboxamide
672	3-((4-(cyclohexylmethoxy)phenyl)sulfonamido)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
673	3-(2-azabicyclo[2.2.1]heptan-2-yl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
674	3-((cyclobutylmethyl)amino)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
675	3-(cyclopentylamino)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
676	4-hydroxy-4-methyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)piperidine-1-carboxamide
677	3-((cyclopentylmethyl)amino)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
678	2-(4-amino-2-methylphenyl)-N-((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-4-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide

679	3-((2-cyclopropylethyl)amino)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
680	3-(cyclobutylamino)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
681	4-hydroxy-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)piperidine-1-carboxamide
682	3-amino-2,2-dimethyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
683	3-hydroxy-2,2-dimethyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-3-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
684	N-((9S,12S)-5^4-fluoro-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-3-hydroxy-2,2-dimethylpropanamide
685	N-((9S,12S)-9-(2,3-dihydro-1H-inden-2-yl)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
686	N-((9S,12S)-9-(but-3-yn-1-yl)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(imidazo[2,1-b]thiazol-6-yl)acetamide
687	5-amino-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)isoindoline-2-carboxamide
688	4-ethyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)piperazine-1-carboxamide
689	1-(hydroxymethyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)cyclopentane-1-carboxamide
690	(9S,12S)-12-((3-hydroxy-2,2-dimethylpropyl)amino)-5^4-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-

	benzenacyclotetradecaphane-8,11,14-trione
691	3-hydroxy-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)azetidine-1-carboxamide
692	3-(3-cyclopentylpropoxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
693	3-((2-cyclobutylethyl)amino)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
694	3-((cyclopropylmethyl)amino)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
695	3-(((1R,2R,4S)-bicyclo[2.2.1]heptan-2-yl)amino)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
696	N-((9S,12S)-5^4,15-dimethyl-8,11,16-trioxo-9-phenethyl-4-oxa-7,10,15-triaza-1(3,1)-piperidina-5(1,3)-benzenacyclohexadecaphane-12-yl)-2-phenylacetamide
697	2-(1-acetylazetidin-3-yl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
698	3-((2-(bicyclo[2.2.1]heptan-2-yl)ethyl)amino)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
699	3-((4-(4-benzylpiperazin-1-yl)benzyl)amino)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
700	3-((2-cyclopentylethyl)amino)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
701	N-(3-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-3-oxopropyl)-7-oxabicyclo[2.2.1]heptane-2-carboxamide
702	3-(azetidin-1-yl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
703	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-

	1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2,3-dihydro-1H-pyrrolo[3,2-c]pyridine-1-carboxamide
704	5-amino-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)indoline-1-carboxamide
705	5-hydroxy-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)indoline-1-carboxamide
706	3-((4-(cyclohexylmethoxy)benzyl)amino)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
707	2-(4-acetylphenyl)-N-((11S,14S)-14-methyl-8,12,15-trioxo-1^4-phenethyl-2-oxa-7,13,16-triaza-1(1,3)-benzenacycloheptadecaphane-11-yl)acetamide
708	N-((9S,12S)-9-(4-aminophenethyl)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(imidazo[2,1-b]thiazol-6-yl)acetamide
709	(9S,12S)-5^4-methyl-9-phenethyl-12-((2,2,2-trifluoroethyl)amino)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
710	3-((2-methyl-2-azaspiro[3.3]heptan-6-yl)oxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
711	(9S,12S)-12-(bicyclo[2.2.1]hept-5-en-2-ylamino)-5^4-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
712	(9S,12S)-12-(bicyclo[2.2.1]heptan-2-ylamino)-5^4-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
713	8-methyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-8-azabicyclo[3.2.1]octane-3-carboxamide
714	2-methyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-azaspiro[3.3]heptane-6-carboxamide
715	3-methyl-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)azetidine-3-carboxamide

716	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)piperazine-1-carboxamide
717	(9S,12S)-12-(cyclobutylamino)-5^4-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
718	2-(4-amino-2-methylphenyl)-N-((12S,15S)-1^4-methyl-8,13,16-trioxo-15-phenethyl-2-oxa-7,14,17-triaza-1(1,3)-benzenacyclooctadecaphane-12-yl)acetamide
719	(3S)-3-amino-4-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-4-oxobutanoic acid
720	3-((2-oxaspiro[3.3]heptan-6-yl)amino)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
721	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-azaspiro[3.3]heptane-6-carboxamide
722	3-hydroxy-2,2-dimethyl-N-((12S,15S)-1^4-methyl-8,13,16-trioxo-15-phenethyl-2-oxa-7,14,17-triaza-1(1,3)-benzenacyclooctadecaphane-12-yl)propanamide
723	N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-8-azabicyclo[3.2.1]octane-3-carboxamide
724	(4S)-4-amino-5-(((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)amino)-5-oxopentanoic acid
725	3-((2-azaspiro[3.3]heptan-6-yl)oxy)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
726	3-hydroxy-2,2-dimethyl-N-((11S,14S)-1^4-methyl-8,12,15-trioxo-14-phenethyl-2-oxa-7,13,16-triaza-1(1,3)-benzenacycloheptadecaphane-11-yl)propanamide
727	(9S,12S)-12-((2-amino-2-methylpropyl)amino)-5^4-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-

	8,11,14-trione
728	(9S,12S)-5^4-methyl-12-(2-oxopyrrolidin-1-yl)-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
729	4-fluoro-N-((12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-4-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)piperidine-4-carboxamide
730	4-(hydroxymethyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)piperidine-4-carboxamide
731	(9S,12S)-5^4-methyl-9-phenethyl-12-(pyrrolidin-1-yl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
732	3-hydroxy-2,2-dimethyl-N-((10S,13S)-1^4-methyl-7,11,14-trioxo-13-phenethyl-2-oxa-6,12,15-triaza-1(1,3)-benzenacyclohexadecaphane-10-yl)propanamide
733	(9S,12S)-12-(4,4-dimethyl-2-oxoimidazolidin-1-yl)-5^4-methyl-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
734	(9S,12S)-5^4-methyl-12-(2-oxopiperidin-1-yl)-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-trione
735	3-hydroxy-2,2-dimethyl-N-((10S,13S)-1^4-methyl-8,11,14-trioxo-13-phenethyl-2-oxa-7,12,15-triaza-1(1,3)-benzenacyclohexadecaphane-10-yl)propanamide
736	3-hydroxy-2,2-dimethyl-N-((9S,12S)-1^4-methyl-7,10,13-trioxo-12-phenethyl-2-oxa-6,11,14-triaza-1(1,3)-benzenacyclopentadecaphane-9-yl)propanamide
737	2-(2-fluorophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-(2-(pyridin-4-yl)ethyl)-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)acetamide
738	(2R)-2-(4-aminophenyl)-N-((9S,12S)-5^4-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide
739	N-((9S,12S)-9-(2-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)ethyl)-5^4-methyl-8,11,14-trioxo-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)-2-(imidazo[2,1-b]thiazol-6-yl)acetamide
740	(9S,12S)-5^4-methyl-12-(4-methyl-1H-1,2,3-triazol-1-yl)-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-8,11,14-

	trione
741	3-((4-methoxybenzyl)oxy)-N-((9S,12S)-5[4]-methyl-8,11,14-trioxo-9-phenethyl-4-oxa-7,10-diaza-1(3,1)-piperidina-5(1,3)-benzenacyclotetradecaphane-12-yl)propanamide

or an enantiomer, a stereoisomeric form, a mixture of enantiomers, a diastereomer, a mixture of diastereomers, a hydrate, a solvate, an acid salt form, a tautomer, a racemate of the above mentioned compounds, or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition comprising at least one compound according to any one of the claims 1 – 10 as an active ingredient, together with at least one pharmaceutically acceptable carrier, excipient and/or diluent.

12. A compound according to any one of the claims 1 -- 10 for use as a medicament.

13. A compound according to any one of the claims 1 – 10, or a pharmaceutical composition according to claim 11, for use in the prophylaxis and/or treatment of a disease associated with and/or caused by proteasome or immunoproteasome, selected from a cancer, an infectious disease, an inflammatory disease, autoimmune disease, and transplant rejection.

14. The compound for use or the pharmaceutical composition for use according to claim 13, wherein the cancer is selected from the group consisting of: adenocarcinoma, choroidal melanoma, acute leukemia, acoustic neurinoma, ampullary carcinoma, anal carcinoma, astrocytoma, basal cell carcinoma, pancreatic cancer, desmoid tumour, bladder cancer, bronchial carcinoma, non-small cell lung cancer (NSCLC), breast cancer, Burkitt's lymphoma, corpus cancer, CUP-syndrome (carcinoma of unknown primary), colorectal cancer, small intestine cancer, small intestinal tumours, ovarian cancer, endometrial carcinoma, ependymoma, epithelial cancer types, Ewing's tumours, gastrointestinal tumours, gastric cancer, gallbladder cancer, gall bladder carcinomas, uterine cancer, cervical cancer, glioblastomas, gynecologic tumours, ear, nose and throat tumours, hematologic neoplasias, hairy cell leukemia, urethral cancer, skin cancer, skin testis cancer, brain tumours (gliomas), brain metastases, testicle cancer, hypophysis tumour, carcinoids, Kaposi's sarcoma, laryngeal cancer, germ cell tumour, bone cancer, colorectal carcinoma, head and neck tumours (tumours of the ear, nose and throat area), colon carcinoma, craniopharyngiomas, oral cancer (cancer in the mouth area and on lips), cancer of the central nervous system, liver cancer, liver metastases, leukemia, eyelid tumor, lung cancer, lymph node cancer

(Hodgkin's/Non-Hodgkin's), lymphomas, stomach cancer, malignant melanoma, malignant neoplasia, malignant tumours gastrointestinal tract, breast carcinoma, rectal cancer, medulloblastomas, melanoma, meningiomas, Hodgkin's disease, mycosis fungoides, nasal cancer, neurinoma, neuroblastoma, kidney cancer, renal cell carcinomas, non-Hodgkin's lymphomas, oligodendroglioma, esophageal carcinoma, osteolytic carcinomas and osteoplastic carcinomas, osteosarcomas, ovarial carcinoma, pancreatic carcinoma, penile cancer, plasmocytoma, squamous cell carcinoma of the head and neck (SCCHN), prostate cancer, pharyngeal cancer, rectal carcinoma, retinoblastoma, vaginal cancer, thyroid carcinoma, Schneeberger disease, esophageal cancer, spinalioms, T-cell lymphoma (mycosis fungoides), thymoma, tube carcinoma, eye tumours, urethral cancer, urologic tumours, urothelial carcinoma, vulva cancer, wart appearance, soft tissue tumours, soft tissue sarcoma, Wilm's tumour, cervical carcinoma, tongue cancer, astrocytomas, bronchial cancer, laryngeal cancer, malignant melanoma, oesophageal cancer, cholangiocarcinoma, and renal cell cancer.

15. The compound for use or the pharmaceutical composition for use according to claim 13 or 14, wherein the cancer is leukemia, multiple myeloma, mantle-cell lymphoma (MCL), breast cancer, colorectal cancer, non-small cell lung cancer, or ovarian cancer.

16. The compound for use or the pharmaceutical composition for use according to claim 14 or 15, wherein the cancer is multiple myeloma.

17. The compound for use or the pharmaceutical composition for use according to claim 16, in combination with a thalidomide or a derivative thereof.

18. The compound for use or the pharmaceutical composition for use according to claim 17, wherein the derivative of thalidomide is selected from lenalidomide, pomalidomide, avadomide, iberdomide, and CC-885.

19. The compound for use or the pharmaceutical composition for use according to claim 13, wherein the infectious disease is selected from the group consisting of: HIV, Echinococcosis, Amebiasis (Entamoeba histolytica Infection), Angiostrongylus Infection, Anisakiasis, Anthrax, Babesiosis (Babesia Infection), Balantidium Infection (Balantidiasis), Baylisascaris Infection (Raccoon Roundworm), Bilharzia (Schistosomiasis), Blastocystis hominis Infection (Blastomycosis), Borreliosis, Botulism, Brainerd Diarrhea, Brucellosis, BSE (Bovine Spongiform Encephalopathy), Candidiasis, Capillariasis (Capillaria

Infection), CFS (Chronic Fatigue Syndrome), Chagas Disease (American Trypanosomiasis), Chickenpox (Varicella-Zoster virus), Chlamydia pneumoniae Infection, Cholera, CJD (Creutzfeldt-Jakob Disease), Clonorchiasis (Clonorchis Infection), CLM (Cutaneous Larva Migrans, Hookworm Infection), Coccidioidomycosis, Conjunctivitis, Coxsackievirus A16 (Hand, Foot and Mouth Disease), Cryptococcosis, Cryptosporidium Infection (Cryptosporidiosis), Culex mosquito (Vector of West Nile Virus), Cyclosporiasis (Cyclospora Infection), Cysticercosis (Neurocysticercosis), Cytomegalovirus Infection, Dengue / Dengue Fever, Dipylidium Infection (Dog and Cat Flea Tapeworm), Ebola Virus Hemorrhagic Fever, Echinococcosis (Alveolar Hydatid Disease), Encephalitis, Entamoeba coli Infection, Entamoeba dispar Infection, Entamoeba hartmanni Infection, Entamoeba histolytica Infection (Amebiasis), Entamoeba polecki Infection, Enterobiasis (Pinworm Infection), Enterovirus Infection (non-polio), Epstein-Barr Virus Infection, Escherichia coli Infection, Foodborne Infection, Foot and mouth Disease, Fungal Dermatitis, Gastroenteritis, Group A streptococcal Disease, Group B streptococcal Disease, Hansen's Disease (Leprosy), Hantavirus Pulmonary Syndrome, Head Lice Infestation (Pediculosis), Helicobacter pylori Infection, Hematologic Disease, Hendra Virus Infection, Hepatitis (HCV, HBV), Herpes Zoster (Shingles), Human Ehrlichiosis, Human Parainfluenza Virus Infection, Influenza, Isosporiasis (Isospora Infection), Lassa Fever, Leishmaniasis, Kala-azar (Kala-azar, Leishmania Infection), Leprosy, Lice (Body lice, Head lice, Pubic lice), Lyme Disease, Malaria, Marburg Hemorrhagic Fever, Measles, Meningitis, Mosquito-borne Diseases, Mycobacterium avium Complex (MAC) Infection, Naegleria Infection, Nosocomial Infections, Nonpathogenic Intestinal Amebae Infection, Onchocerciasis (River Blindness), Opisthorciasis (Opisthorcis Infection), Parvovirus Infection, Plague, PCP (Pneumocystis carinii Pneumonia), Polio, Q Fever, Rabies, Respiratory Syncytial Virus (RSV) Infection, Rheumatic Fever, Rift Valley Fever, Rotavirus Infection, Roundworms Infection, Salmonellosis, Salmonella Enteritidis, Scabies, Shigellosis, Shingles, Sleeping Sickness, Smallpox, Streptococcal Infection, Tapeworm Infection (Taenia Infection), Tetanus, Toxic Shock Syndrome, Tuberculosis, Ulcers (Peptic Ulcer Disease), Valley Fever, Vibrio parahaemolyticus Infection, Vibrio vulnificus Infection, Viral Hemorrhagic Fever, Warts, Waterborne infectious Diseases, West Nile Virus Infection (West Nile Encephalitis), Whooping Cough, and Yellow Fever.

20. The compound for use or the pharmaceutical composition for use according to claim 13, wherein the autoimmune disease is selected from the group consisting of:

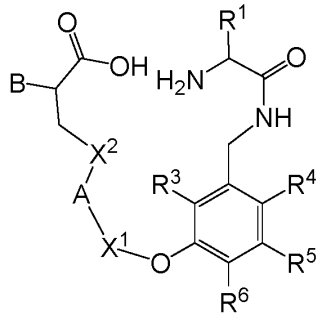
Achalasia, Addison's disease, Adult Still's disease, Agammaglobulinemia, Alopecia areata, Amyloidosis, Ankylosing spondylitis, Anti-GBM/Anti-TBM nephritis, Antiphospholipid syndrome, Autoimmune angioedema, Autoimmune dysautonomia, Autoimmune encephalomyelitis, Autoimmune hepatitis, Autoimmune inner ear disease (AIED), Autoimmune myocarditis, Autoimmune oophoritis, Autoimmune orchitis, Autoimmune pancreatitis, Autoimmune retinopathy, Autoimmune urticaria, Axonal & neuronal neuropathy (AMAN), Baló disease, Behcet's disease, Benign mucosal pemphigoid, Bullous pemphigoid, Castleman disease (CD), Celiac disease, Chagas disease, Chronic inflammatory demyelinating polyneuropathy (CIDP), Chronic recurrent multifocal osteomyelitis (CRMO), Churg-Strauss Syndrome (CSS), Eosinophilic Granulomatosis (EGPA), Cicatricial pemphigoid, Cogan's syndrome, Cold agglutinin disease, Congenital heart block, Coxsackie myocarditis, CREST syndrome, Crohn's disease, Dermatitis herpetiformis, Dermatomyositis, Devic's disease (neuromyelitis optica), Discoid lupus, Dressler's syndrome, Endometriosis, Eosinophilic esophagitis (EoE), Eosinophilic fasciitis, Erythema nodosum, Essential mixed cryoglobulinemia, Evans syndrome, Fibromyalgia, Fibrosing alveolitis, Giant cell arteritis (temporal arteritis), Giant cell myocarditis, Glomerulonephritis, Goodpasture's syndrome, Granulomatosis with Polyangiitis, Graves' disease, Guillain-Barre syndrome, Hashimoto's thyroiditis, Hemolytic anemia, Henoch-Schonlein purpura (HSP), Herpes gestationis or pemphigoid gestationis (PG), Hidradenitis Suppurativa (HS) (Acne Inversa), Hypogammalglobulinemia, IgA Nephropathy, IgG4-related sclerosing disease, Immune thrombocytopenic purpura (ITP), Inclusion body myositis (IBM), Interstitial cystitis (IC), Juvenile arthritis, Juvenile diabetes (Type 1 diabetes), Juvenile myositis (JM), Kawasaki disease, Lambert-Eaton syndrome, Leukocytoclastic vasculitis, Lichen planus, Lichen sclerosus, Ligneous conjunctivitis, Linear IgA disease (LAD), Lupus, Lyme disease chronic, Meniere's disease, Microscopic polyangiitis (MPA), Mixed connective tissue disease (MCTD), Mooren's ulcer, Mucha-Habermann disease, Multifocal Motor Neuropathy (MMN) or MMNCB, Multiple sclerosis, Myasthenia gravis, Myelin Oligodendrocyte Glycoprotein Antibody Disorder, Myositis, Narcolepsy, Neonatal Lupus, Neuromyelitis optica, Neutropenia, Ocular cicatricial pemphigoid, Optic neuritis, Palindromic rheumatism (PR), PANDAS, Paraneoplastic cerebellar degeneration (PCD), Paroxysmal nocturnal hemoglobinuria (PNH), Parry Romberg syndrome, Pars planitis (peripheral uveitis), Parsonage-Turner syndrome, Pemphigus, Peripheral neuropathy, Perivenous encephalomyelitis, Pernicious anemia (PA), POEMS syndrome, Polyarteritis nodosa, Polyglandular syndromes type I, II, III, Polymyalgia rheumatic, Polymyositis, Postmyocardial infarction syndrome, Postpericardiotomy syndrome, Primary Biliary Cholangitis, Primary

sclerosing cholangitis, Progesterone dermatitis, Psoriasis, Psoriatic arthritis, Pure red cell aplasia (PRCA), Pyoderma gangrenosum, Raynaud's phenomenon, Reactive Arthritis, Reflex sympathetic dystrophy, Relapsing polychondritis, Restless legs syndrome (RLS), Retroperitoneal fibrosis, Rheumatic fever, Rheumatoid arthritis, Sarcoidosis, Schmidt syndrome, Scleritis, Scleroderma, Sjögren's syndrome, Sperm & testicular autoimmunity, Stiff person syndrome (SPS), Subacute bacterial endocarditis (SBE), Susac's syndrome, Sympathetic ophthalmia (SO), Takayasu's arteritis, Temporal arteritis/Giant cell arteritis, Thrombocytopenic purpura (TTP), Thyroid eye disease (TED), Tolosa-Hunt syndrome (THS), Transverse myelitis, Type 1 diabetes, Ulcerative colitis (UC), Undifferentiated connective tissue disease (UCTD), Uveitis, Vasculitis, Vitiligo, and Vogt-Koyanagi-Harada Disease.

21. The compound for use or the pharmaceutical composition for use according to claim 20, wherein the autoimmune disease is selected from Lupus nephritis, lupus, systemic lupus erythematosus, myasthenia gravis, multiple sclerosis, polyarthritis, rheumatoid arthritis, irritant sensitivity, psoriasis, asthma, and colitis.

22. The compound for use or the pharmaceutical composition for use according to claim 21, wherein the autoimmune disease is myasthenia gravis.

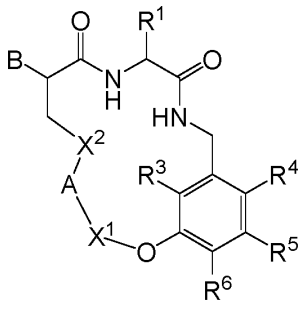
23. A method for producing a compound of the formula (**I**) comprising:
Step 1A: providing an intermediate compound (**I-1***):



(**I-1***)

wherein **A**, **B**, $\mathbf{R^1}$, $\mathbf{R^3}$, $\mathbf{R^4}$, $\mathbf{R^5}$, $\mathbf{R^6}$, $\mathbf{X^1}$, and $\mathbf{X^2}$ have the same meanings as defined in the formula (**I**) according to claim 1;

Step 2A: perform an intramolecular amide coupling reaction between a carboxylic acid group and an amine group of the intermediate compound (**I-1***) to obtain the compound of the formula (**I**)

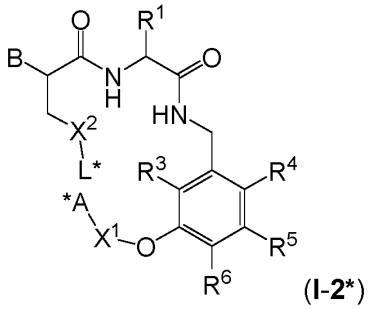


(**I**);

or

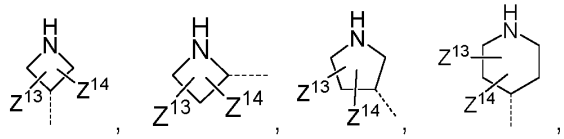
a method for producing the compound of the formula (**I**) comprising:

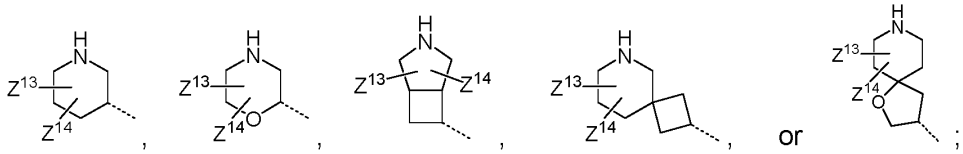
Step 1B: providing an intermediate compound (**I-2***):



(**I-2***)

wherein

A* represents –NH(**R**^{N6})–, 



or ;

L* represents –CO_2H,

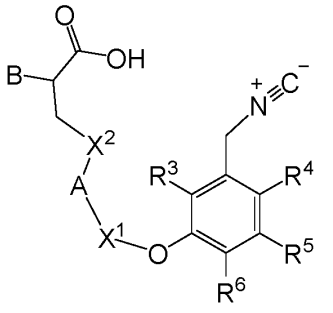
and **B**, **R**^{1}, **R**^{3}, **R**^{4}, **R**^{5}, **R**^{6}, **R**^{N6}, **X**^{1}, **X**^{2}, **Z**^{13}, and **Z**^{14} have the same meanings as defined in the formula (**I**) according to claim 1;

Step 2B: perform an intramolecular amide coupling reaction between the **L*** and an amino group of **A*** moiety of the intermediate compound (**I-2***) to obtain the compound of the formula (**I**);

or

a method for producing the compound of the formula (**I**) comprising:

Step 1C: providing an intermediate compound (**I-3***):



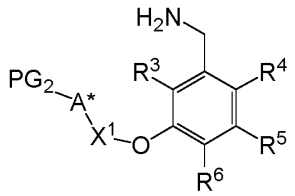
(**I-3***)

wherein

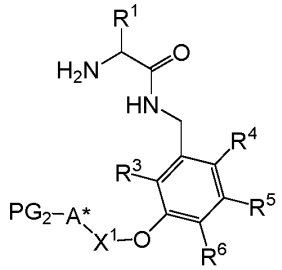
A, **B**, R^1, R^3, R^4, R^5, R^6 , X^1, and X^2 have the same meanings as defined in the formula (**I**) according to claim 1;

Step 2C: perform an intramolecular Ugi reaction of the intermediate compound (**I-3***) with R^1-CHO and aqueous ammonia (NH_3) to obtain the compound of the formula (**I**).

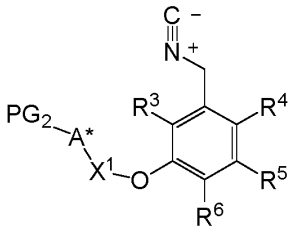
24. An intermediate compound selected from the compounds **7***, **8***, **11***, **12***, **13***, **14***, **I-1***, **I-2***, and **I-3***:



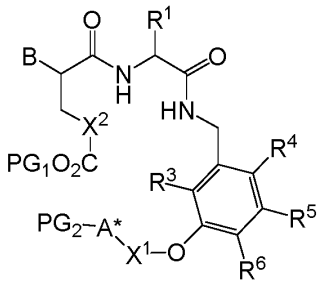
7*



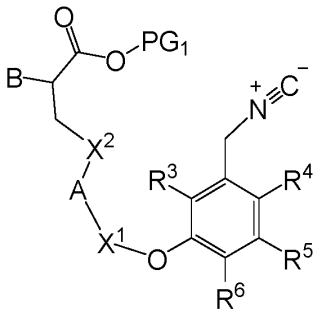
8*



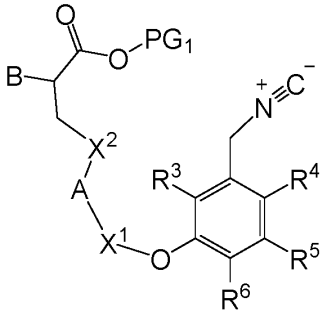
11*



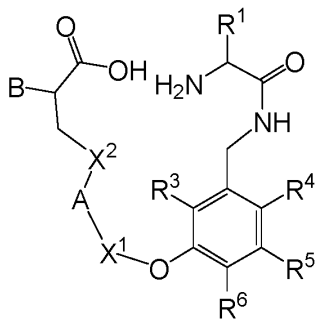
12*



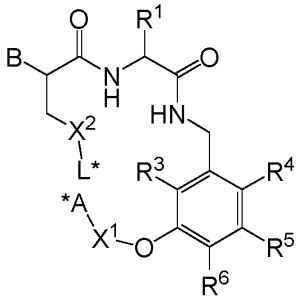
13*



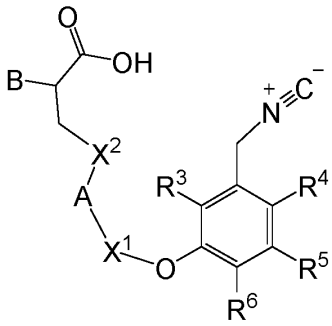
14*



I-1*

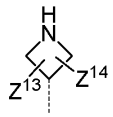
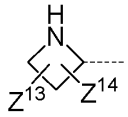
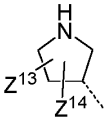
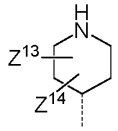
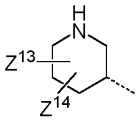
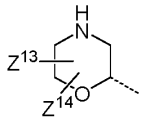
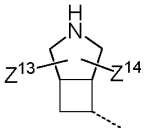
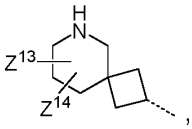
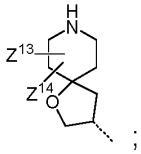


I-2*



I-3*

wherein

A* represents –NH(**R**^{N6})–,  ,  ,  ,  ,  ,  ,  ,  , or  ;

L* represents –CO_2H;

PG_1 represents a carboxyl protecting group;

PG_2 represents an amine protecting group;

and **A**, **B**, **R^1**, **R^3**, **R^4**, **R^5**, **R^6**, **R^{N6}**, **X^1**, **X^2**, **Z^{13}**, and **Z^{14}** have the same meanings as defined in the formula (**I**) according to claim 1.