Conformationally constrained, fully synthetic macrocyclic compounds

Macrocyclic natural and synthetic products have played a crucial role in the development of new drugs, especially as anti-infectives (see Review: F. von Nussbaum, M. Brands, B. Hinzen, S. Weigand, D. Häbich, *Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 5072-5129; D. Obrecht, J. A. Robinson, F. Bernardini, C. Bisang, S. J. DeMarco, K. Moehle, F. O. Gombert, *Curr. Med. Chem.* **2009**, *16*, 42-65), as anti-cancer drugs and in other therapeutic areas (C. E. Ballard, H. Yu, B. Wang, *Curr. Med. Chem.* **2002**, 9, 471-498; F. Sarabia, S. Chammaa, A. S. Ruiz, L. M. Ortiz, F. J. Herrera, *Curr. Med. Chem.* **2004**, 11, 1309-1332). They often display remarkable biological activities, and many macrocycles or their derivatives have been successfully developed into drugs (L. A. Wessjohann, E. Ruijter, D. Garcia-Rivera, W. Brandt, *Mol. Divers.* **2005**, *9*, 171-186; D. J. Newman, G. M. Gragg, K. M. Snader, *J. Nat. Prod.* **2003**, *66*, 1022-1037). The chemical diversity of macrocyclic natural products is immense and provides a tremendous source of inspiration for drug design.

Macrocyclic natural and synthetic products generally exhibit semi-rigid backbone conformations placing appended substituents in well-defined positions in space. Certain ring sizes are preferred (L. A. Wessjohann, E. Ruijter, D. Garcia-Rivera, W. Brandt, *Mol. Divers.* **2005**, *9*, 171-186), e.g. 16-membered rings are frequently found in oxygen-containing macrocycles, such as polyketides (M. Q. Zhang, B. Wilkinson, *Curr. Opin. Biotechnol.* **2007**, *18*, 478-488). It is hypothesized that the semi-rigid scaffolds may possess some of the favorable binding properties of rigid molecules (**entropy**), yet still retaining enough flexibility to adapt suitable conformations in the binding event (**induced fit**).

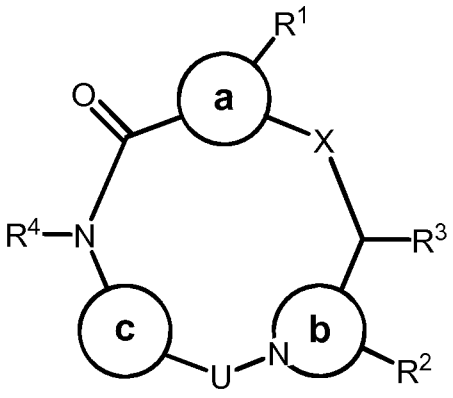
Macrocyclic natural and synthetic products are generally classified according to the chemical nature of the backbone, e.g. cyclic peptides (Y. Hamady, T. Shioiri, *Chem. Rev.* **2005**, *105*, 4441-4482; N.-H. Tan, J. Zhou, *Chem. Rev.* **2006**, *106*, 840-895); cyclic depsipeptides (F. Sarabia, S. Chammaa, A. S. Ruiz, L. M. Ortiz, F. J. Herrera, *Curr. Med. Chem.* **2004**, *11*, 1309-1332); macrocyclic lactones (macrolactones) and macrolides; macrocyclic lactams, macrocyclic amines, macrocyclic ethers, macrocyclic ureas and urethanes, and others. The conformational, physico-chemical, pharmacological and pharmacodynamic properties of macrocyclic natural and synthetic compounds depend largely on the *ring size*, the chemical nature of the *backbone*, and of *appended groups* (L. A. Wessjohann, E. Ruijter, D. Garcia-Rivera, W. Brandt, *Mol. Divers.* **2005**, *9*, 171-186). By modifying these *three parameters* nature has generated a virtually unlimited repertoire of molecular diversity. Despite their undisputed interesting biological properties, natural products show some limitations for drug development, such as:

- High structural complexity
- Metabolic instability
- Low oral bioavailability
- Low membrane permeability; intracellular targets not amenable
- Low tissue penetration
- Short half-life
- Chemical synthesis often very complex and lengthy
- Often accessible only by fermentation or recombinant methods
- High production costs
- Complex QC and development processes.

Broadly speeking, the present invention describes novel, fully synthetic, macrocyclic natural product-like molecules of type **I**, which can be synthesized e.g. by connecting suitably

protected building blocks **A**, **B**, and **C** in a modular fashion to a linear precursor followed by subsequent cyclization (Scheme 1).

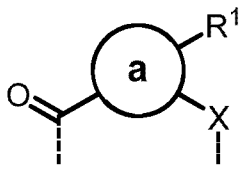
Scheme 1: Summary of the invention



I

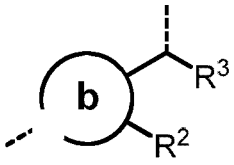
Building Blocks A

"Template"



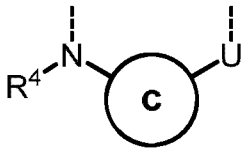
Building Blocks B

"Modulator"



Building Blocks C

"Bridge"

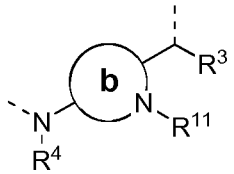


Building blocks **A** serve as conformation-inducing templates and are based on appropriately substituted (R^1) and protected phenolic or thiophenolic aromatic carboxylic acids.

Building blocks **B** are appropriately substituted (R^2, R^3) and protected tertiary amino alcohols, preferably derived from an amino acid such as substituted proline, substituted pipecolic acid or substituted piperazine-2-carboxylic acid. Building blocks **B** are linked to building block **A** via an ether (X=O) or thioether (X=S) bond and to building block **C** via a secondary or

tertiary amide bond. The sulfur atom of a thioether linkage can easily and selectively be oxidized to the corresponding sulfoxide (S=O) or sulfone ($S(=O)_2$) which forms part of the invention. Importantly, the amide bond between modulator **B** and spacer **C** can also be part of an extended connector moiety U. For example in the case of a standard amide bond, U corresponds to a carbonyl group (-C(=O)-). If U is defined as a carbamoyl moiety ($-NR^4-C(=O)-$) the functional connection between **B** and **C** corresponds to a urea moiety. Similarly a carboxyl group (-O-C(=O)-) as U describes a carbamate linkage between **B** and **C**. In addition, U can represent an oxalyl group (-C(=O)-C(=O)-) or the corresponding acetal ($-C(-OR^{20})_2-C(=O)-$).

Importantly, in the case that R^2 of building block **B** constitutes an amine substituent, an alternative incorporation into the macrocyclic ring via the exocyclic amine functionality is possible:

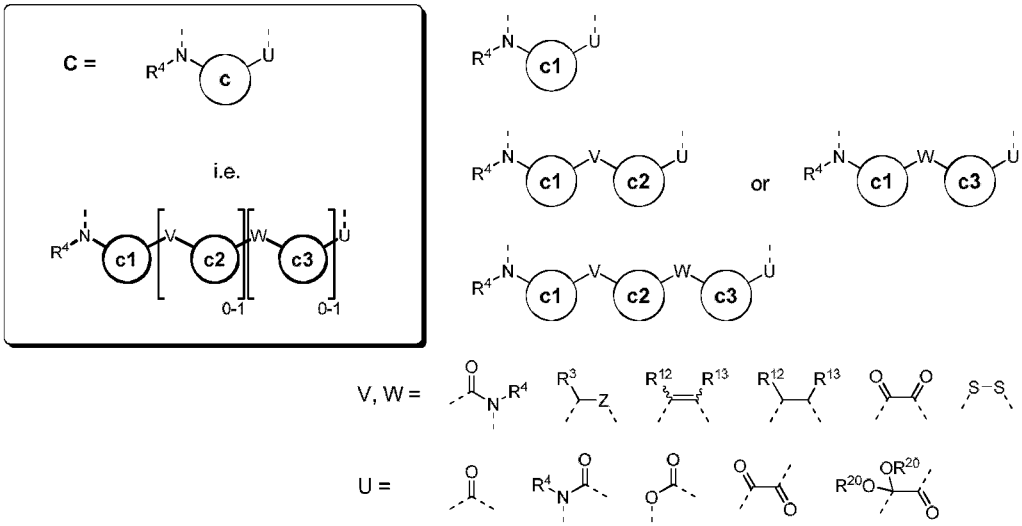


This alternative binding mode is also part of the invention.

Building blocks **B** serve as a conformational modulator by influencing the conformation of the macrocycle through *cis/trans*-isomerization of the amide bond.

In molecules of type **I** the building blocks **A** and **B** are connected via the bridges **C**; the structural element **C** is linked to **A** by a secondary or tertiary amide bond. The bridge **C** can be constituted by one to three appropriately and independently substituted (R^4-R^{10}; R^{14-17}) subunits **c1-c3** derived from suitably substituted and protected precursors, most often from, but not limited to, appropriately substituted and protected amino acid

derivatives or suitably substituted and protected amine derivatives.



These subunits **c1-c3** are in turn independently connected to each other by an amide bond (-C(=O)NR^4-), a methylene-heteroatom linkage (-CHR^3-Z-), an alkene[1,2]diyl moiety (-CHR^{12}=CHR^{13}-), introduced by olefin metathesis, an alkane[1,2]diyl spacer (-CHR^{12}-CHR^{13}-), accessible from the metathesis product by hydrogenation, an oxalyl group (-C(=O)-C(=O)-) or a disulfide bridge (-S-S-).

The spatial orientation of the substituents R^1-R^{13} in compounds of type **I** is modulated by the ring size and the stereochemical connectivity within building blocks **A**, **B** and **C**. Both, the macrocyclic backbone and the substituents R^1-R^{13} can contribute to the biological activity of compounds of type **I**.

The backbone of the compounds of type **I** is composed of an aromatic ether/thioether linkage and one or more tertiary amide bonds; in some cases an aliphatic ether linkage, an ethylidene or an ethylene moiety may also be part of the backbone as defined above. Ether linkages in macrocyclic molecules have been shown to be beneficial by favorably influencing physico-chemical and pharmacological properties, such as e.g.

solubility in water, metabolic stability towards proteolytic degradation, cell permeability and oral absorption (K. X. Chen et al., *J. Med. Chem.* **2006**, *49*, 995-1005). In addition, tertiary amide containing macrocycles show increased proteolytic stability, cell permeability and oral bioavailability compared to the parent molecules with secondary amide bonds (E. Biron, J. Chatterjee, O. Ovadia, D. Langenegger, J. Brueggen, D. Hoyer, H. A. Schmid, R. Jelinek, C. Gilon, A. Hoffmann, H. Kessler, *Angew. Chem. Int. Ed.* **2008**, *47*, 1-6; J. Chatterjee, O. Ovadia, G. Zahn, L. Marinelli, A. Hoffmann, C. Gilon, H. Kessler, *J. Med. Chem.* **2007**, *50*, 5878-5881). For example, the cyclic undecapeptide cyclosporin A (INN: Ciclosporin), which is used as immunosuppressant in organ transplants, contains seven N-methylated amino acids and possesses good oral bioavailability when formulated appropriately (P. R. Beauchesne, N. S. C. Chung, K. M. Wasan, *Drug Develop. Ind. Pharm.* **2007**, *33*, 211-220). Peptidyl *cis/trans* isomerization of proline and pipecolic acid containing polypeptides and proteins is a well known process in protein folding events. *In vivo*, this process can be mediated by peptidyl prolyl *cis/trans* isomerases such as the cyclophilins, the FK506-binding proteins and the parvulins (A. Bell, P. Monaghan, A. P. Page, *Int. J. Parasitol.* **2006**, *36*, 261-276). Besides their role in protein folding and in the immune system, peptidyl prolyl *cis/trans* isomerases have been implicated in cell cycle control (P. E. Shaw, *EMBO Reports* **2002**, *3*, 521-526) and therefore constitute interesting pharmaceutical targets. FK506 and cyclosporin A which bind to the FK506-binding protein and cyclophilins, respectively, are both macrocyclic natural products, with the former one containing a pipecolic acid residue.

For many existing and emerging biological targets it is difficult to find classical small molecule hits as starting points for drug development (J. A. Robinson, S. DeMarco, F. Gombert, K. Moehle, D. Obrecht, *Drug Disc. Today* **2008**, *13*, 944-951). Many of these extra- and intracellular "difficult

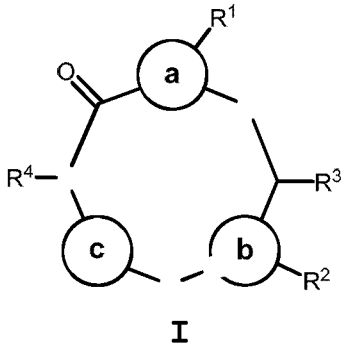
targets" involve protein-protein interactions, such as receptor tyrosine kinases, growth factor receptors, transcriptional activators/transcription factors, chaperones, and others. For several of them macrocyclic natural and synthetic compounds have been described as good starting points for drug discovery programs (e.g. D. Obrecht, J. A. Robinson, F. Bernardini, C. Bisang, S. J. DeMarco, K. Moehle, F. O. Gombert, *Curr. Med. Chem*. **2009**, *16*, 42-65).

The novel and fully synthetic macrocyclic compounds of type **I** described in this invention combine unique features of macrocyclic natural products with beneficial physico-chemical and pharmacological properties of traditional small molecules, like:

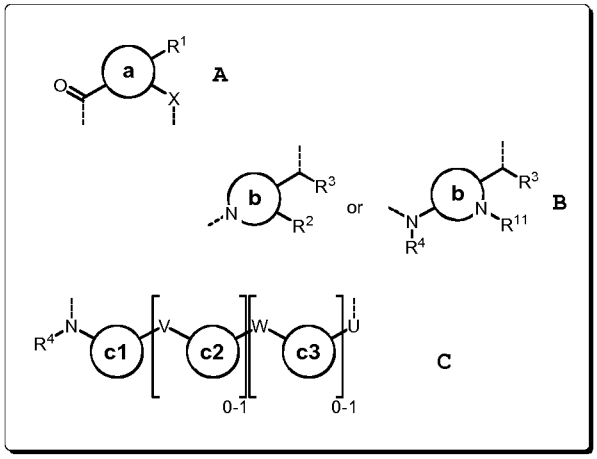
- Natural product-like structural complexity
- Good solubility
- High metabolic stability
- Improved oral bioavailability
- Improved membrane permeability
- Extra- and intracellular targets amenable
- Improved tissue penetration
- Small molecule-like pharmacokinetics
- Modular chemical synthesis
- Synthesis process amenable to parallelization
- Reasonable production costs
- Small molecule-like QC and development processes

More particularly, the present invention provides macrocyclic compounds of the general formula **I** (Figure 2), which are comprised of building blocks of general formulae **A**, **B** and **C** as depicted in Scheme 2 below.

Scheme 2: Compounds of type **I** and building blocks **A**, **B** and **C**

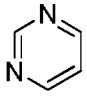
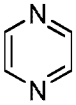


I



With respect to the building blocks **A**, **B** and **C**, the encircled moieties, i.e. **a** in **A**, **b** in **B** and **c1-c3** in **C**, shall represent their most basic skeletons appropriately and independently substituted as is detailed later on. The basic skeletons of **a** and **b** correspond to the ring systems depicted in **Table 1** and **Table 2**.

Table 1: Ring Systems **a1-a25** of Building Blocks **A**

 **a1**	 **a2**	 **a3**	 **a4**
 **a5**	 **a6**	 **a7**	 **a8**

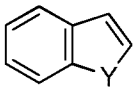
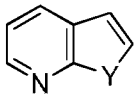
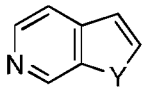
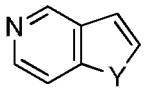
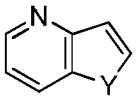
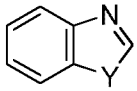
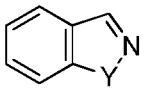
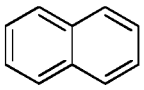
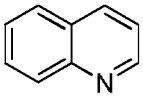
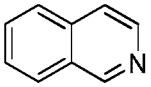
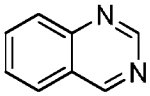
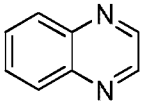
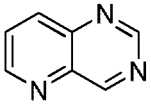
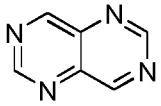
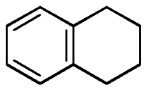
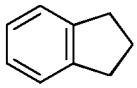
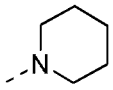
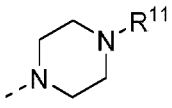
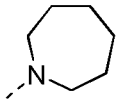
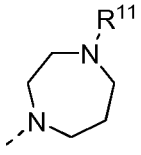
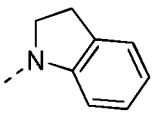
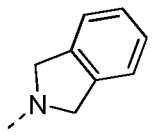
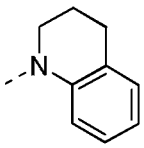
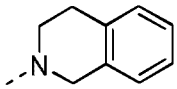
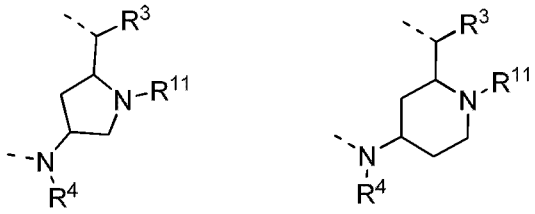
 a9	 a10	 a11	 a12
 a13	 a14	 a15	 a16
 a17	 a18	 a19	 a20
 a21	 a22	 a23	 a24
 a25			

Table 2: Ring Systems **b1-b11** of Building Blocks **B**

 b1	 b2	 b3	 b4
 b5	 b6	 b7	 b8

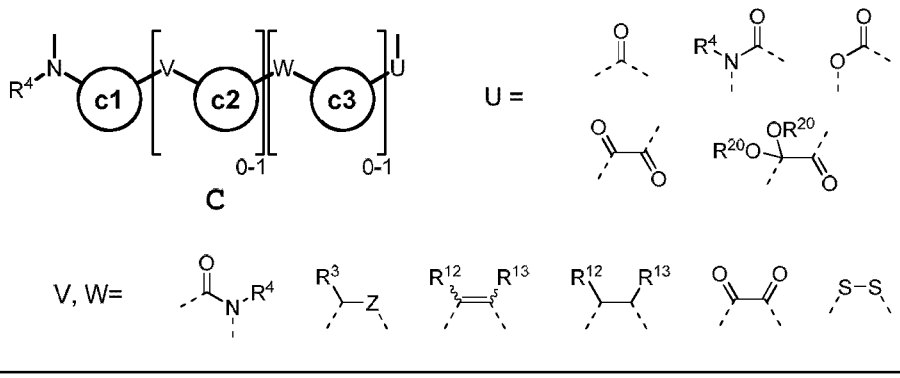
		
b9	**b10**	**b11**

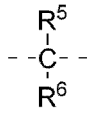
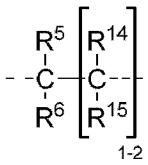
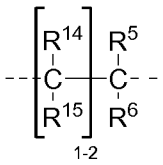
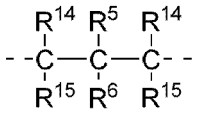
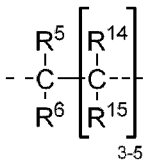
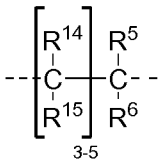
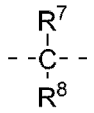
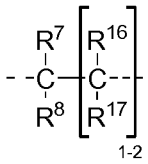
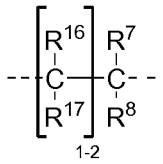
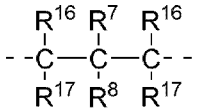
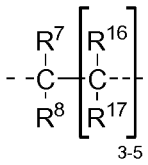
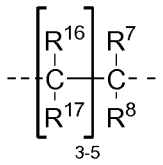
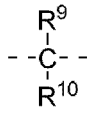
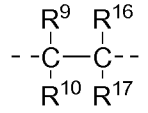
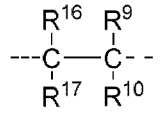
Depending on the substitution pattern of skeletons **b** alternative binding modes are feasible. For skeletons **b3** and **b4** such incorporation via the exocyclic nitrogen atom is represented by the following two structures, which form part of the invention:



The encircled parts of the bridge subunits **c1**-**c3** represent optionally substituted groups. Definitions of **c1**-**c3** are exemplified in **Table 3**, each reading from the *N*-terminus to the *C*-terminus of the linker **C**. In the simplest case the linker **C** is constituted by one subunit **c1**, i.e. **c1-1** to **c1-6**. For the embodiments consisting of two or three subunits all possible combinations of the subunits **c1-c3** and the connectivities U, V and W are part of the invention.

Table 3: Scope of Subunits **c1-c3** of the Linker Group **C**



c1	 c1-1	 c1-2	 c1-3
	 c1-4	 c1-5	 c1-6
c2	 c2-1	 c2-2	 c2-3
	 c2-4	 c2-5	 c2-6
c3	 c3-1	 c3-2	 c3-3

The substituents directly attached to the basic skeletons containing building block **A**, **B** and **C**, i.e. R^1-R^{17}, are defined as follows:

R^1: H; F; Cl; Br; I; CF_3; OCF_3; $OCHF_2$; NO_2; CN; alkyl; alkenyl; alkynyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{18}R^{19})_qOR^{20}$; $-(CR^{18}R^{19})_qSR^{20}$; $-(CR^{18}R^{19})_qNR^4R^{11}$;

$-(CR^{18}R^{19})_qOCONR^4R^{11}$; $-(CR^{18}R^{19})_qOCOOR^{21}$; $-(CR^{18}R^{19})_qNR^4COOR^{21}$; $-(CR^{18}R^{19})_qNR^4COR^{22}$; $-(CR^{18}R^{19})_qNR^4CONR^4R^{11}$; $-(CR^{18}R^{19})_qNR^4SO_2R^{23}$; $-(CR^{18}R^{19})_qNR^4SO_2NR^4R^{11}$; $-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{11}$; $-(CR^{18}R^{19})_qSO_2NR^4R^{11}$; $-(CR^{18}R^{19})_qPO(OR^{21})_2$; $-(CR^{18}R^{19})_qOPO(OR^{21})_2$; $-(CR^{18}R^{19})_qCOR^{22}$; $-(CR^{18}R^{19})_qSO_2R^{23}$; $-(CR^{18}R^{19})_qOSO_3R^{21}$; $-(CR^{18}R^{19})_qR^{24}$; $-(CR^{18}R^{19})_qR^{25}$; or $-(CR^{18}R^{19})_qR^{26}$.

R^2: H; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{18}R^{19})_qOR^{20}$; $-(CR^{18}R^{19})_qSR^{20}$; $-(CR^{18}R^{19})_qNR^4R^{11}$; $-(CR^{18}R^{19})_qOCONR^4R^{11}$; $-(CR^{18}R^{19})_qOCOOR^{21}$; $-(CR^{18}R^{19})_qNR^4COOR^{21}$; $-(CR^{18}R^{19})_qNR^4COR^{22}$; $-(CR^{18}R^{19})_qNR^4CONR^4R^{11}$; $-(CR^{18}R^{19})_qNR^4SO_2R^{23}$; $-(CR^{18}R^{19})_qNR^4SO_2NR^4R^{11}$; $-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{11}$; $-(CR^{18}R^{19})_qSO_2NR^4R^{11}$; $-(CR^{18}R^{19})_qPO(OR^{21})_2$; $-(CR^{18}R^{19})_qCOR^{22}$; $-(CR^{18}R^{19})_qSO_2R^{23}$; $-(CR^{18}R^{19})_qR^{24}$; $-(CR^{18}R^{19})_qR^{25}$; or $-(CR^{18}R^{19})_qR^{26}$.

R^3: H; CF_3; alkyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl.

R^4: H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; or a suitable *N*-protecting group.

R^5, R^7 and R^9 are independently defined as: H; F; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{18}R^{19})_sOR^{20}$; $-(CR^{18}R^{19})_sSR^{20}$; $-(CR^{18}R^{19})_sNR^4R^{11}$; $-(CR^{18}R^{19})_sOCONR^4R^{11}$; $-(CR^{18}R^{19})_sOCOOR^{21}$; $-(CR^{18}R^{19})_sNR^4COOR^{21}$; $-(CR^{18}R^{19})_sNR^4COR^{22}$; $-(CR^{18}R^{19})_sNR^4CONR^4R^{11}$; $-(CR^{18}R^{19})_sNR^4SO_2R^{23}$; $-(CR^{18}R^{19})_sNR^4SO_2NR^4R^{11}$; $-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{11}$; $-(CR^{18}R^{19})_qSO_2NR^4R^{11}$; $-(CR^{18}R^{19})_qPO(OR^{21})_2$; $-(CR^{18}R^{19})_qCOR^{22}$; $-(CR^{18}R^{19})_qSO_2R^{23}$; $-(CR^{18}R^{19})_qR^{24}$; $-(CR^{18}R^{19})_qR^{25}$; or $-(CR^{18}R^{19})_qR^{26}$.

R^6, R^8 and R^{10} are independently defined as: H; F; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; or heteroarylalkyl.

R^{11}: H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; a suitable protecting group; $-(CR^{18}R^{19})_rOR^{20}$; $-(CR^{18}R^{19})_rSR^{20}$; $-(CR^{18}R^{19})_rNR^4R^{27}$; $-(CR^{18}R^{19})_rOCONR^4R^{27}$; $-(CR^{18}R^{19})_rOCOOR^{21}$; $-(CR^{18}R^{19})_rNR^4COOR^{21}$; $-(CR^{18}R^{19})_rNR^4CONR^4R^{27}$; $-(CR^{18}R^{19})_rNR^4SO_2R^{23}$; $-(CR^{18}R^{19})_rNR^4SO_2NR^4R^{27}$; $-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{27}$; $-(CR^{18}R^{19})_qCOR^{22}$; $-(CR^{18}R^{19})_qSO_2R^{23}$; $-(CR^{18}R^{19})_qSO_2NR^4R^{27}$; $-(CR^{18}R^{19})_qR^{24}$; $-(CR^{18}R^{19})_sR^{25}$; or $-(CR^{18}R^{19})_qR^{26}$.

R^{12} and R^{13} are independently defined as H; or alkyl.

R^{14} and R^{16} are independently defined as: H; F; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{18}R^{19})_sOR^{20}$; $-(CR^{18}R^{19})_sNR^4R^{11}$; $-(CR^{18}R^{19})_sNR^4COOR^{21}$; $-(CR^{18}R^{19})_sNR^4COR^{22}$; $-(CR^{18}R^{19})_sNR^4CONR^4R^{11}$; $-(CR^{18}R^{19})_sNR^4SO_2R^{23}$; $-(CR^{18}R^{19})_sNR^4SO_2NR^4R^{11}$; $-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{11}$; $-(CR^{18}R^{19})_qSO_2NR^4R^{11}$; $-(CR^{18}R^{19})_qCOR^{22}$.

R^{15} and R^{17} are independently defined as: H; F; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; or heteroarylalkyl.

Substituents introduced in the sub-definitions of the radical R^1-R^{17} are:

R^{18}: H; F; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{29}R^{30})_sOR^{31}$; $-(CR^{29}R^{30})_sSR^{31}$; $-(CR^{29}R^{30})_sNR^{28}R^{31}$; $-(CR^{29}R^{30})_sOCONR^{28}R^{31}$; $-(CR^{29}R^{30})_sOCOOR^{21}$; $-(CR^{29}R^{30})_sNR^{28}COOR^{21}$; $-(CR^{29}R^{30})_sNR^{28}COR^{31}$; $-(CR^{29}R^{30})_sNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_sNR^{28}SO_2R^{23}$; $-(CR^{29}R^{30})_sNR^{28}SO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_qSO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qPO(OR^{21})_2$; $-(CR^{29}R^{30})_qCOR^{31}$; $-(CR^{29}R^{30})_qSO_2R^{23}$; $-(CR^{29}R^{30})_qR^{24}$; $-(CR^{29}R^{30})_qR^{25}$; or $-(CR^{29}R^{30})_qR^{26}$.

R^{19}: H; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl.

R^{20}: H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{29}R^{30})_rOR^{31}$; $-(CR^{29}R^{30})_rSR^{31}$; $-(CR^{29}R^{30})_rNR^{28}R^{31}$; $-(CR^{29}R^{30})_rOCONR^{28}R^{31}$; $-(CR^{29}R^{30})_rNR^{28}COOR^{21}$; $-(CR^{29}R^{30})_rNR^{28}COR^{31}$; $-(CR^{29}R^{30})_rNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_rNR^{28}SO_2R^{23}$;$-(CR^{29}R^{30})_rNR^{28}SO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_qSO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOR^{31}$; $-(CR^{29}R^{30})_qSO_2R^{23}$; $-(CR^{29}R^{30})_qR^{24}$; $-(CR^{29}R^{30})_qR^{25}$; or $-(CR^{29}R^{30})_qR^{26}$.

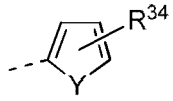
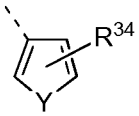
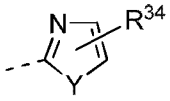
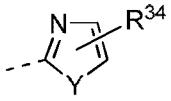
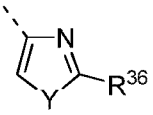
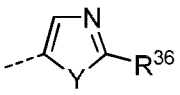
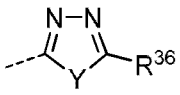
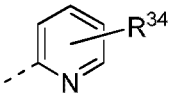
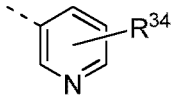
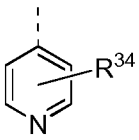
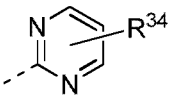
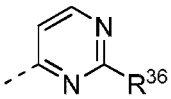
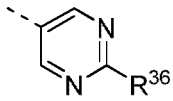
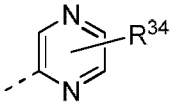
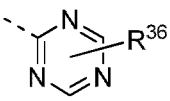
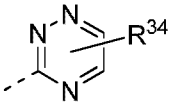
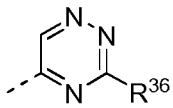
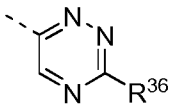
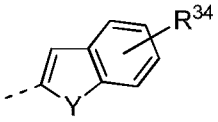
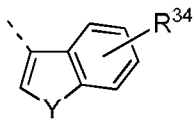
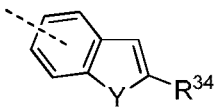
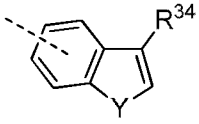
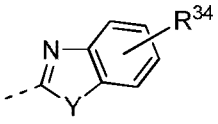
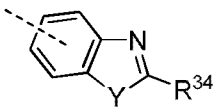
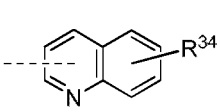
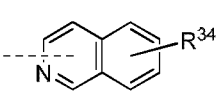
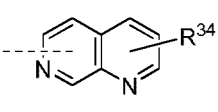
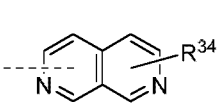
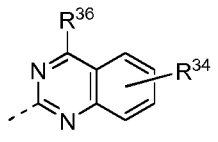
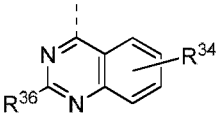
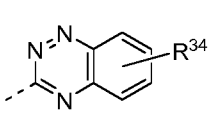
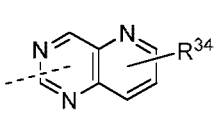
R^{21}: alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; or a suitable *O*-protecting group.

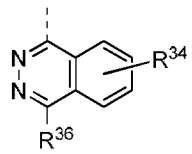
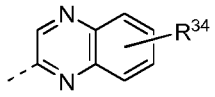
R^{22}: alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{29}R^{30})_sOR^{31}$; $-(CR^{29}R^{30})_sSR^{31}$; $-(CR^{29}R^{30})_sNR^{28}R^{31}$; $-(CR^{29}R^{30})_sOCONR^{28}R^{31}$; $-(CR^{29}R^{30})_sNR^{28}COOR^{21}$; $-(CR^{29}R^{30})_sNR^{28}COR^{31}$; $-(CR^{29}R^{30})_sNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_sNR^{28}SO_2R^{23}$;$-(CR^{29}R^{30})_sNR^{28}SO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_sCOOR^{21}$; $-(CR^{29}R^{30})_sCONR^{28}R^{31}$; $-(CR^{29}R^{30})_sSO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_tCOR^{31}$; $-(CR^{29}R^{30})_sSO_2R^{23}$; $-(CR^{29}R^{30})_tR^{24}$; $-(CR^{29}R^{30})_tR^{25}$; or $-(CR^{29}R^{30})_tR^{26}$.

R^{23}: H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{32}R^{33})_tR^{24}$.

R^{24}: aryl, preferably an optionally substituted phenyl group of type $C_6H_2R^{34}R^{35}R^{31}$; or a heteroaryl group, preferably one of the groups of formulae **H1-H34** (**Table 4**).

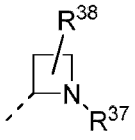
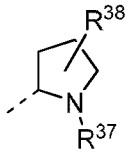
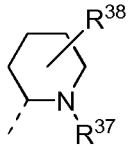
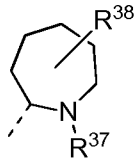
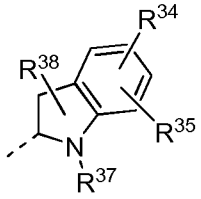
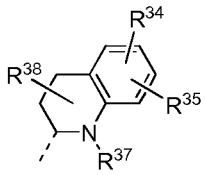
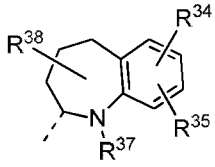
Table 4: Groups of Formulae **H1-H34**

 H1	 H2	 H3	 H4
 H5	 H6	 H7	 H8
 H9	 H10	 H11	 H12
 H13	 H14	 H15	 H16
 H17	 H18	 H19	 H20
 H21	 H22	 H23	 H24
 H25	 H26	 H27	 H28
			

H29	H30	H31	H32
			
H33		H34	

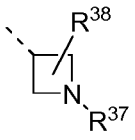
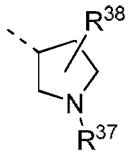
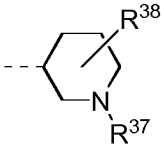
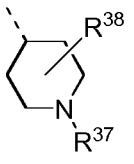
R^{25}: One of the groups of formulae **H35-H41** as shown in **Table 5** below.

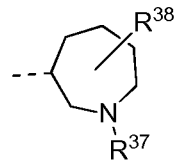
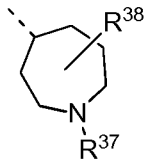
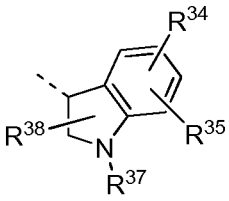
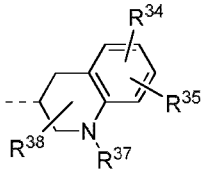
Table 5: Radicals of formulae **H35-H41**

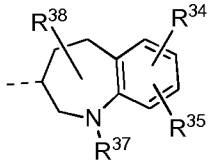
			
H35	H36	H37	H38
			
H39	H40	H41	

R^{26}: One of the groups of formulae **H42-H50** as shown in **Table 6** below.

Table 6: Groups of Formulae **H42-H50**

			
H42	H43	H44	H45

			
H46	**H47**	**H48**	**H49**



H50

R^{27}: H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; a suitable protecting group; or $-(CR^{29}R^{30})_qR^{24}$.

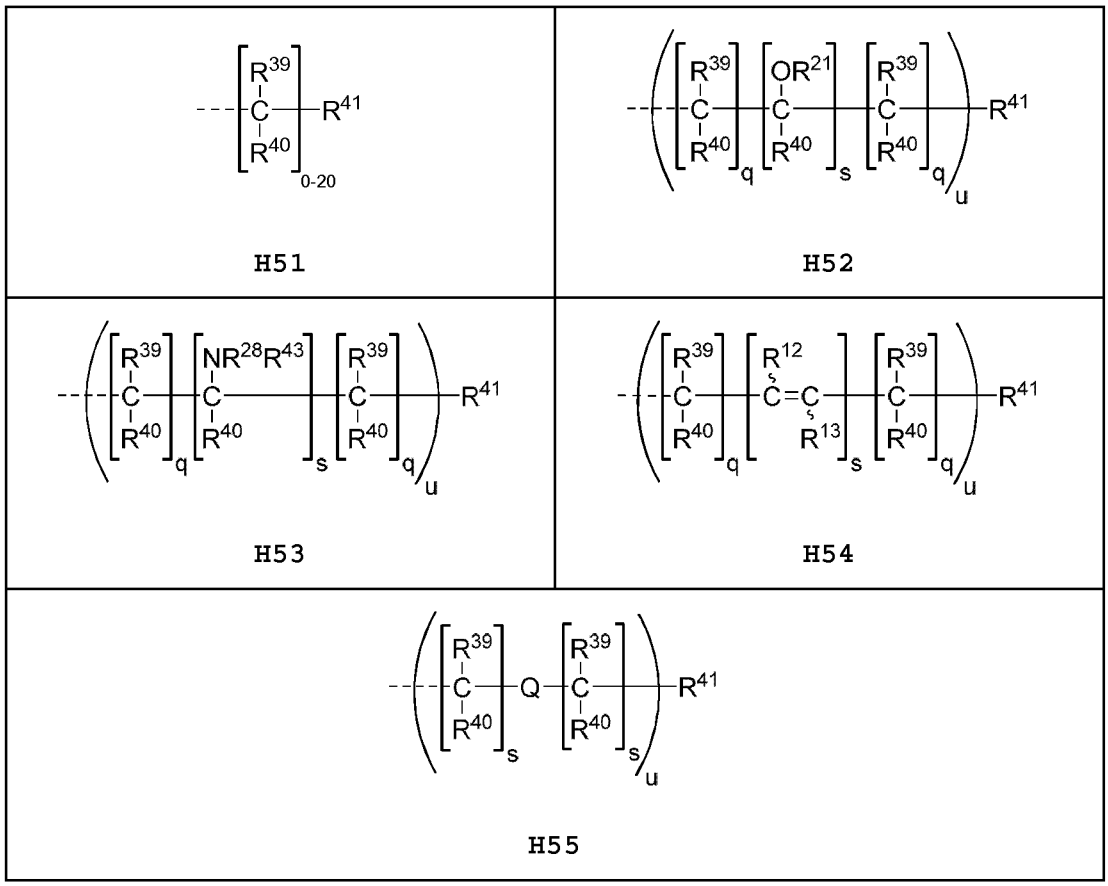
R^{28}: H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; a suitable *N*-protecting group; $-(CR^{32}R^{33})_sOR^{21}$; $-(CR^{32}R^{33})_sNR^{43}R^{42}$; $-(CR^{32}R^{33})_sNR^{42}CONR^{43}R^{42}$; $-(CR^{32}R^{33})_sNR^{42}COR^{21}$; $-(CR^{32}R^{33})_sNR^{42}SO_2NR^{21}$; $-(CR^{32}R^{33})_qCOOR^{21}$; $-(CR^{32}R^{33})_qCOR^{23}$; $-(CR^{32}R^{33})_qSO_2R^{21}$.

R^{29}: H; F; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{32}R^{33})_sOR^{31}$; $-(CR^{32}R^{33})_sSR^{31}$; $-(CR^{32}R^{33})_sNR^{28}R^{31}$; $-(CR^{32}R^{33})_sOCONR^{28}R^{31}$; $-(CR^{32}R^{33})_sOCOOR^{21}$; $-(CR^{32}R^{33})_sNR^{28}COOR^{21}$; $-(CR^{32}R^{33})_sNR^{28}COR^{31}$; $-(CR^{32}R^{33})_sNR^{28}CONR^{28}R^{31}$; $-(CR^{32}R^{33})_sNR^{28}SO_2R^{23}$; $-(CR^{32}R^{33})_sNR^{28}SO_2NR^{28}R^{31}$; $-(CR^{32}R^{33})_qCOOR^{21}$; $-(CR^{32}R^{33})_qCONR^{28}R^{31}$; $-(CR^{32}R^{33})_qSO_2NR^{28}R^{31}$; $-(CR^{32}R^{33})_qPO(OR^{21})_2$; $-(CR^{32}R^{33})_qCOR^{31}$; $-(CR^{32}R^{33})_qSO_2R^{23}$; $-(CR^{32}R^{33})_qR^{31}$.

R^{30}: H; F; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl.

R^{31}: H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; or one of the groups of formulae **H51-H55** as shown in **Table 7** below.

Table 7: Groups of Formulae **H51-H55**



R^{32} and R^{33} are independently defined as H; F; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl.

R^{34} and R^{35} are independently defined as H; F; Cl; CF_3; OCF_3; $OCHF_2$; NO_2; CN; alkyl; alkenyl; alkynyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{29}R^{30})_qOR^{31}$; $-(CR^{29}R^{30})_qSR^{31}$; $-(CR^{29}R^{30})_qNR^{28}R^{31}$; $-(CR^{29}R^{30})_qOCONR^{28}R^{31}$; $-(CR^{29}R^{30})_qNR^{28}COOR^{21}$; $-(CR^{29}R^{30})_qNR^{28}COR^{31}$; $-(CR^{29}R^{30})_qNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_qNR^{28}SO_2R^{23}$; $-(CR^{29}R^{30})_qNR^{28}SO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOOR^{21}$;

$-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_qSO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOR^{31}$; $-(CR^{29}R^{30})_qSO_2R^{23}$; or $-(CR^{29}R^{30})_qR^{31}$.

R^{36}: H; alkyl; alkenyl; alkynyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; or $-NR^{28}R^{31}$.

R^{37}: H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; a suitable *N*-protecting group; $-(CR^{29}R^{30})_rOR^{31}$; $-(CR^{29}R^{30})_rSR^{31}$; $-(CR^{29}R^{30})_rNR^{28}R^{31}$; $-(CR^{29}R^{30})_rOCONR^{28}R^{31}$; $-(CR^{29}R^{30})_rNR^{28}COOR^{21}$; $-(CR^{29}R^{30})_rNR^{28}COR^{31}$; $-(CR^{29}R^{30})_rNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_rNR^{28}SO_2R^{23}$; $-(CR^{29}R^{30})_rNR^{28}SO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_rSO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOR^{31}$; $-(CR^{29}R^{30})_qSO_2R^{23}$; or $-(CR^{29}R^{30})_qR^{31}$.

R^{38}: H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{29}R^{30})_qOR^{31}$; $-(CR^{29}R^{30})_qSR^{31}$; $-(CR^{29}R^{30})_qNR^{28}R^{31}$; $-(CR^{29}R^{30})_qNR^{28}COOR^{21}$; $-(CR^{29}R^{30})_qNR^{28}COR^{31}$; $-(CR^{29}R^{30})_qNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOR^{31}$; or $-(CR^{29}R^{30})_qR^{31}$.

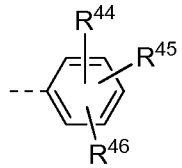
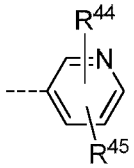
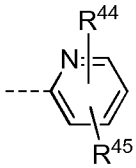
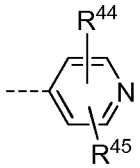
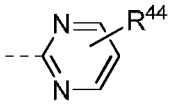
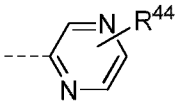
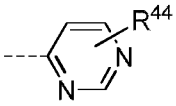
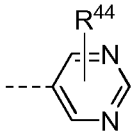
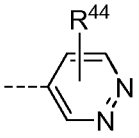
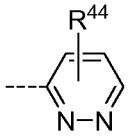
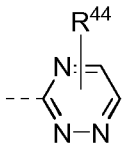
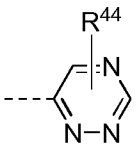
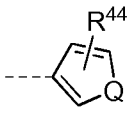
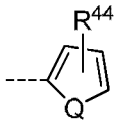
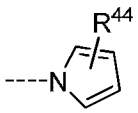
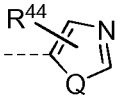
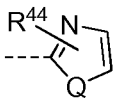
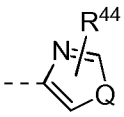
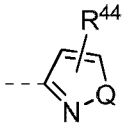
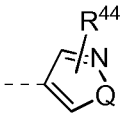
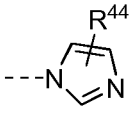
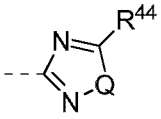
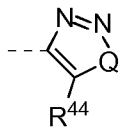
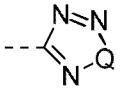
R^{39}: H; F; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{32}R^{33})_uOR^{21}$; $-(CR^{32}R^{33})_uNR^{28}R^{43}$; $-(CR^{32}R^{33})_tCOOR^{21}$; or $-(CR^{32}R^{33})_tCONR^{28}R^{43}$.

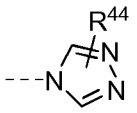
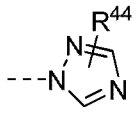
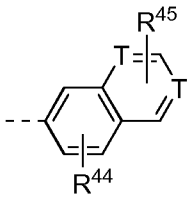
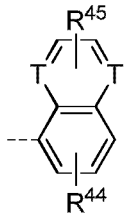
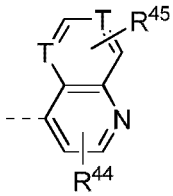
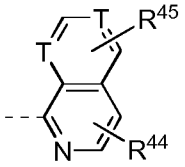
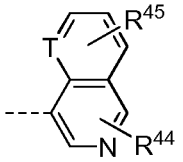
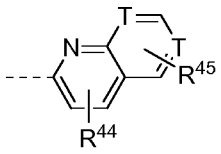
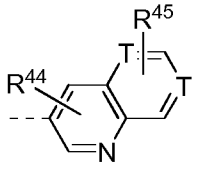
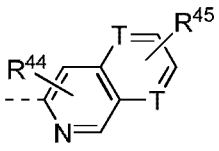
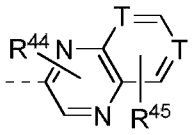
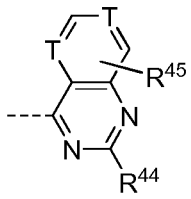
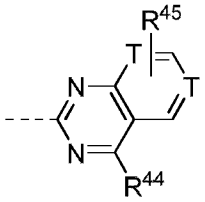
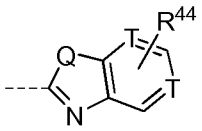
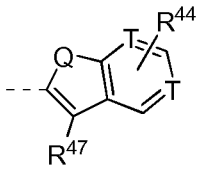
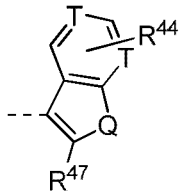
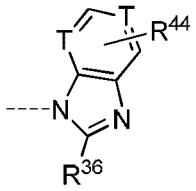
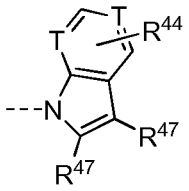
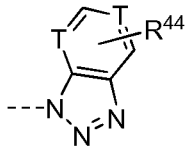
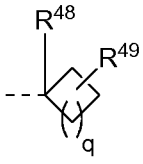
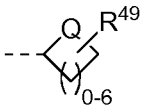
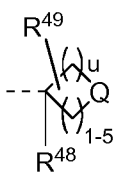
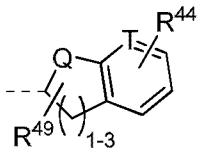
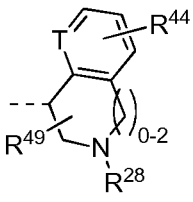
R^{40}: H; F; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{32}R^{33})_uOR^{21}$; $-(CR^{32}R^{33})_uNR^{28}R^{43}$; $-(CR^{32}R^{33})_tCOOR^{21}$; or $-(CR^{32}R^{33})_tCONR^{28}R^{43}$.

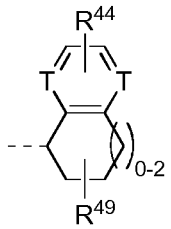
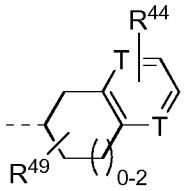
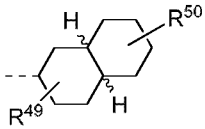
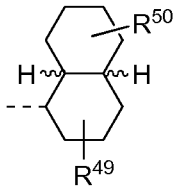
R^{41}: H; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-OR^{21}$; $-NR^{28}R^{43}$; $-NR^{28}COR^{23}$; $-NR^{28}COOR^{21}$;

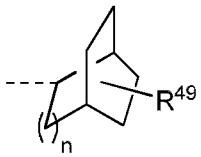
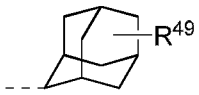
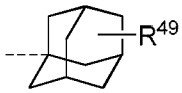
$-NR^{28}SO_2R^{23}$; $-NR^{28}CONR^{28}R^{43}$; $-COOR^{21}$; $-CONR^{28}R^{43}$; $-C(=NR^{43})NR^{28}N^{43}$; $-NR^{28}C(=NR^{43})NR^{28}N^{43}$; or one of the groups of formulae **H56-H110** as shown in **Table 8** below.

Table 8: Groups of Formulae **H56-H110**

 **H56**	 **H57**	 **H58**	 **H59**
 **H60**	 **H61**	 **H62**	 **H63**
 **H64**	 **H65**	 **H66**	 **H67**
 **H68**	 **H69**	 **H70**	 **H71**
 **H72**	 **H73**	 **H74**	 **H75**
 **H76**	 **H77**	 **H78**	 **H79**

 H80	 H81	 H82	 H83
 H84	 H85	 H86	 H87
 H88	 H89	 H90	 H91
 H92	 H93	 H94	 H95
 H96	 H97	 H98	 H99
			

H100	H101	H102	H103
			
H104	H105	H106	H106

H108	H109	H110
		

R^{42}: H; alkyl; alkenyl; cycloalkyl; cycloheteroalkyl; aryl; heteroaryl; -$(CR^{23}R^{33})_sOR^{21}$; -$(CR^{23}R^{33})_sNR^{28}R^{43}$; -$(CR^{23}R^{33})_qCOOR^{21}$; or -$(CR^{23}R^{33})_qCONR^{21}R^{43}$.

R^{43}: H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; or a suitable *N*-protecting group.

R^{44}, R^{45} and R^{46} are independently defined as H; F; CF_3; OCF_3; $OCHF_2$; NO_2; CN; alkyl; alkenyl; alkynyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; -OR^{23}; -$NR^{28}R^{43}$; -$NR^{28}COR^{23}$; -$NR^{28}SO_2R^{23}$; -$NR^{28}CONR^{28}R^{43}$; -COR^{23}; -SO_2R^{23};

R^{47}: H; CF_3; alkyl; alkenyl; alkynyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; -$COOR^{21}$; or -$CONR^{28}R^{43}$.

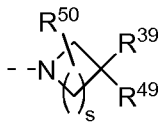
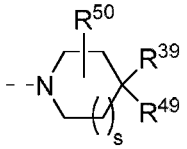
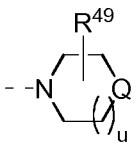
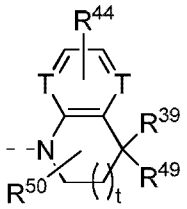
R^{48}: H; F; CF_3; alkyl; alkenyl; cycloalkyl; cycloheteroalkyl; aryl; heteroaryl;

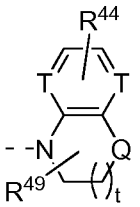
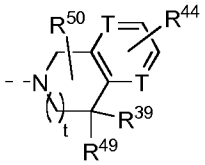
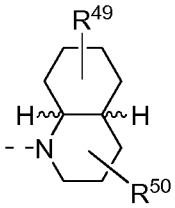
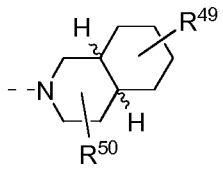
$-(CR^{23}R^{33})_tOR^{21}$; $-(CR^{23}R^{33})_tNR^{28}R^{43}$; $-(CR^{23}R^{33})_tCOOR^{21}$; $-(CR^{23}R^{33})_tCONR^{21}R^{43}$

R^{49} and R^{50} are independently defined as H; F; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{32}R^{33})_qOR^{21}$; $-(CR^{32}R^{33})_qNR^{28}R^{43}$; $-(CR^{32}R^{33})_qCOOR^{21}$; or $-(CR^{32}R^{33})_qCONR^{28}R^{43}$.

Taken together the following pairs of said substituents can define cyclic structural elements:
Taken together (R^4 and R^{11}); (R^4 and R^{27}); (R^5 and R^6); (R^5 and R^7); (R^5 and R^9); (R^5 and R^{14}); (R^5 and R^{16}); (R^7 and R^8); (R^7 and R^9); (R^7 and R^{16}); (R^9 and R^{10}); (R^{14} and R^{15}); (R^{16} and R^{17}); (R^{18} and R^{19}); (R^{27} and R^{28}); (R^{28} and R^{31}); (R^{28} and R^{43}); (R^{29} and R^{30}); (R^{32} and R^{33}); (R^{34} and R^{35}); (R^{37} and R^{38}); (R^{39} and R^{40}); (R^{39} and R^{41}); (R^{39} and R^{49}); (R^{42} and R^{43}); (R^{44} and R^{45}); or (R^{44} and R^{46}) can form optionally substituted cycloalkyl or heterocycloalkyl moieties.
In addition, the structural elements $-NR^4R^{11}$; $-NR^{27}R^{28}$; $-NR^{28}R^{31}$ or $-NR^{28}R^{43}$ can form one of the groups of formulae **H111-H118** as shown in **Table 9** below.

Table 9: Heterocyclic Groups Defined by Linking the Residues of the Disubstituted Amino Groups $-NR^4R^{11}$; $-NR^{27}R^{28}$; $-NR^{28}R^{31}$ or $-NR^{28}R^{43}$.

			
H111	**H112**	**H113**	**H114**

			
H115	**H116**	**H117**	**H118**

Variable heteroatoms and connector groups in the aforementioned structures are

Z: O; S; S(=O); $S(=O)_2$; or NR^{28}.

Y: O; S; or NR^{37}.

X: O; S; S(=O); or $S(=O)_2$.

Q: O; S; or NR^{28}.

U, V and W: As defined in **Table 3**.

T: CR^{46} or N. In case T occurs several times in the same ring structure each T is defined independently of the other.

And indices are defined as: q=0-4; r=2-4; s=1-4; t=0-2; and u=1-2.

Salts are especially the pharmaceutically acceptable salts of compounds of formula **I**.

Such salts are formed, for example, as acid addition salts, preferably with organic or inorganic acids, from compounds of type **I** with a basic nitrogen atom, especially the pharmaceutically acceptable salts. Suitable inorganic acids are, for example, halogen acids, such as hydrochloric acid, sulfuric acid, or phosphoric acid. Suitable organic acids are, for example, carboxylic, phosphonic, sulfonic or sulfamic acids, for example acetic acid, propionic acid, octanoic acid, decanoic acid, dodecanoic acid, glycolic acid, lactic acid, fumaric acid, succinic acid, adipic acid, pimelic acid, suberic acid, azelaic acid, malic acid, tartaric acid, citric acid, amino acids, such as glutamic acid or aspartic acid, maleic acid, hydroxymaleic acid, methylmaleic acid,

cyclohexanecarboxylic acid, adamantanecarboxylic acid, benzoic acid, salicylic acid, 4-aminosalicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid, methane- or ethane-sulfonic acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 1,5-naphthalene-disulfonic acid, 2-, 3- or 4-methylbenzenesulfonic acid, methylsulfuric acid, ethylsulfuric acid, dodecylsulfuric acid, N-cyclohexylsulfamic acid, N-methyl-, N-ethyl- or N-propyl-sulfamic acid, or other organic protonic acids, such as ascorbic acid.

As used in this description, the term "alkyl", taken alone or in combinations (i.a. as part of another group, such as “arylalkyl”) designates saturated, straight-chain or branched hydrocarbon radicals having up to 24, preferably up to 12, carbon atoms. In accordance with a preferred embodiment of the present invention “alkyl” is “lower alkyl” which designated alkyl groups having up to 6 carbon atoms.

The term “alkenyl", taken alone or in combinations, designates straight chain or branched hydrocarbon radicals having up to 24, preferably up to 12, carbon atoms and containing at least one or, depending on the chain length, up to four olefinic double bonds. Such alkenyl moieties can exist as E or Z configurations, both of which are part of the invention.

The term “alkynyl”, taken alone or in combinations, refers to an aliphatic hydrocarbon chain and includes, but is not limited to, straight and branched chains having 2 to 10 carbon atoms (unless explicitly specified otherwise) and containing at least one triple bond.

The term “cycloalkyl", taken alone or in combinations, refers to a saturated alicyclic moiety having from three to ten carbon atoms.

The term "heterocycloalkyl", taken alone or in combinations, describes a saturated or partially unsaturated heterocyclic moiety having from three to seven ring carbon atoms and one or more ring heteroatoms selected from nitrogen, oxygen and sulphur. This term includes, for example, azetidinyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl and the like.

The term "aryl", taken alone or in combinations, designates aromatic carbocyclic hydrocarbon radicals containing one or two six-membered rings, such as phenyl or naphthyl, which may be substituted by up to three substituents such as Br, Cl, F, CF_3, NO_2, lower alkyl or lower alkenyl.

The term "heteroaryl", taken alone or in combinations, designates aromatic heterocyclic radicals containing one or two five- and/or six-membered rings, at least one of them containing up to three heteroatoms selected from the group consisting of O, S and N and whereby the heteroaryl radicals or tautomeric forms thereof may be attached via any suitable atom. Said heteroaryl ring(s) are optionally substituted, e.g. as indicated above for "aryl".

The term "arylalkyl", as used herein, whether used alone or as part of another group, refers to the group $-R^a-R^b$, where R^a is an alkyl group as defined above, substituted by R^b, an aryl group, as defined above. Examples of arylalkyl moieties include, but are not limited to, benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 2-phenylpropyl and the like. Similarly, the term "lower arylalkyl", refers to the above moiety $-R^a-R^b$ but wherein R^a is a "lower alkyl" group.

The term "heteroarylalkyl", whether used alone or as part of another group, refers to the group $-R^a-R^c$, where R^a is an alkyl group as defined above, substituted by R^c, a heteroaryl group,

as defined above. Analogously the term "lower heteroarylalkyl", refers to the above moiety -R^a-R^c but wherein R^a is a "lower alkyl" group.

The terms "alkoxy" and "aryloxy", taken alone or in combinations, refer to the group -O-R^a, wherein R^a, is an alkyl group or an aryl group as defined above.

"Amino" designates primary (i.e. -NH_2), secondary (i.e. -NRH) and tertiary (i.e. -NRR') amines. Particular secondary and tertiary amines are alkylamines, dialkylamines, arylamines, diarylamines, arylalkylamines and diarylamines wherein the alkyl is as herein defined and optionally substituted.

The term "optionally substituted" is intended to mean that a group, such as but not limited to alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, alkoxy and aryloxy may be substituted with one or more substituents independently selected from, e.g., halogen (F, Cl, Br, I), cyano (-CN), nitro (-NO_2), -SR^a, -S(O)R^a, -$S(O)_2R^a$, -R^a, -C(O)R^a,- C(O)OR^a, -C(O)NR^bR^c, -C(=NR^a)N^RbR^c, -OR^a, -OC(O)R^a, -OC(O)OR^a, -OC(O)NR^bR^c, -OS(O)R^a, -$OS(O)_2R^a$, -OS(O)NR^bR^c, -$OS(O)_2NR^bR^c$, -NR^bR^c, -NR^aC(O)R^b, -NR^aC(O)OR^b, -NR^aC(O)NR^bR^c, -NR^aC(=NR^d)NR^bR^c, -NR^aS(O)R^b, -$NR^a$$S(O)_2R^b$, wherein R^a, R^b, R^c, and R^d are each independently, e.g., hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl as described herein; or R^b and R^c may be taken together with the N atom to which they are attached forming heterocycloalkyl or heteroaryl. These groups in turn can be substituted with any described moiety, including, but not limited to, one or more moieties selected from the group consisting of halogen (fluoro, chloro, bromo, or iodo), hydroxyl, amino, alkylamino (e.g., monoalkylamino, dialkylamino, or trialkylamino), arylamino (e.g., monoarylamino, diarylamino, or triarylamino), hydroxy,

carboxy, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate.

Said groups, especially but not limited to hydroxy, amino and carboxyl, may be either unprotected or protected, if necessary, as well-known to those skilled in the art. Examples of suitable protecting groups are as detailed in Peter G. M. Wuts, Theodora W. Greene, *Greene's Protective Groups in Organic Synthesis,* John Wiley and Sons, 4th Edition, **2006.**

As used herein, all groups that can be substituted in one embodiment are indicated to be "optionally substituted," unless otherwise specified.

As mentioned earlier herin, the term "lower" designates radicals and compounds having up to 6 carbon atoms. Thus, for example, the term "lower alkyl" designates saturated, straight-chain, or branched hydrocarbon radicals having up to 6 carbon atoms, such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *s*-butyl, isobutyl, *t*-butyl, and the like. Similarly, the term "lower cycloalkyl" designates saturated cyclic hydrocarbon radicals having up to 6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

The present invention includes within its scope so-called "prodrugs" of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds, which *in vivo* are readily convertible into the required compound. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in Hans Bundgaard, *Design of Prodrugs*, Elsevier, 1985; and in Valentino J. Stella et al., *Prodrugs: Challenges and Rewards*, Springer, 1st ed., 2007.

Some of the aforementioned substituents can occur several times within the same molecular entity, for example, but not limited to R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, and R^{50}. Each of such multiply occurring substituents shall be selected independently from the other radicals of the same type and within the scope of the definition of the respective group.

All possible stereoisomers, explicitly also including rotamers and atropisomers, of macrocycles of type **I** are part of this invention.

The general scope of the current invention is defined by groups of selected building blocks **A**, **B** and **C** and the appending substituents as outlined in this section.

Building blocks **A1-A626** (Table 10) constitute a subset of possible building blocks based on the ring systems **a1-a25** (Table 1). As structural characteristic, groups of type **A** carry one nucleophilic moiety XH (where X is O or S) and one carboxylic acid C(O)OH functionality. The underlying divalent radicals of type -X-**a**-CO- are an integral part of macrocyclic backbones of type **I**, into which they are incorporated by appropriate reactions of the XH and COOH groups of the respective starting materials with suitable reactants.

As mentioned earlier hereinabove, building blocks of type **A** act as templates and exert an important conformational constraint on products of type **I**. The structural effects of building blocks of type **A** depend largely on the relative orientation of the attachment vectors of –X- and –C(O)- and on the spatial distance between these groups. Molecular modeling revealed that the distances (typically between 2.5 and 7.5 Å) and vector arrangements for –X- and –C(O)- in **A1-A626** (Table 10) vary

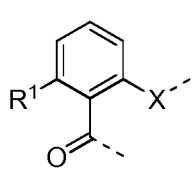
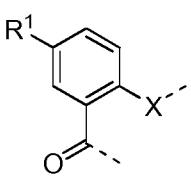
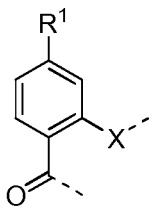
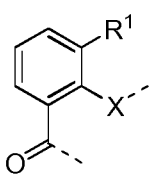
considerably, thus strongly influencing the conformations of macrocycles of type **I**.

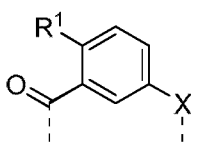
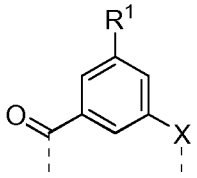
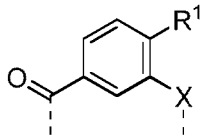
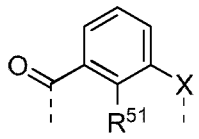
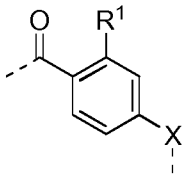
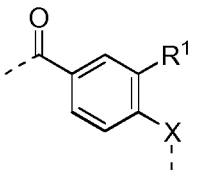
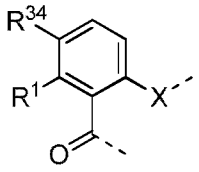
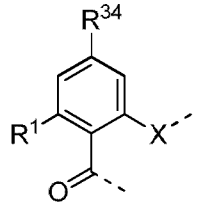
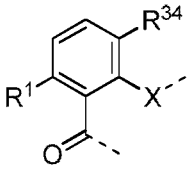
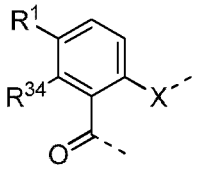
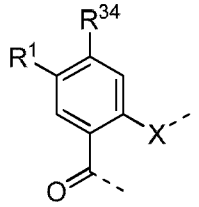
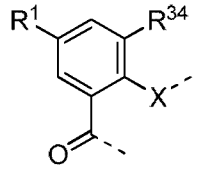
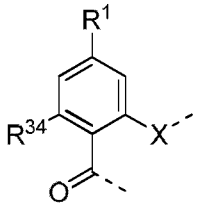
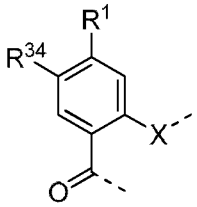
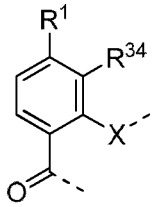
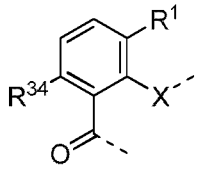
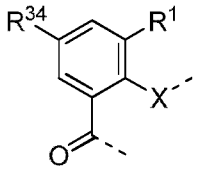
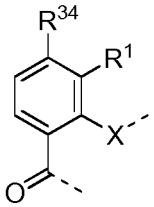
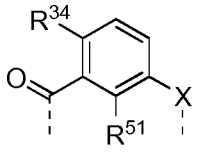
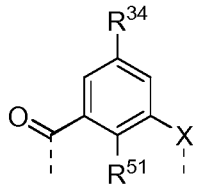
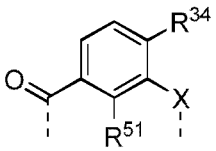
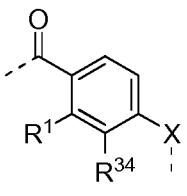
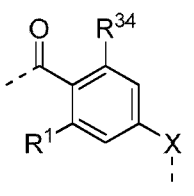
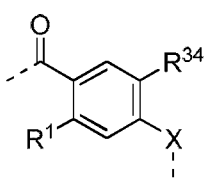
The general scope of the current invention is defined by groups of selected building blocks **A**, **B** and **C** and the appending substituents as outlined in this section.

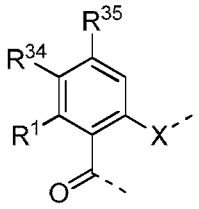
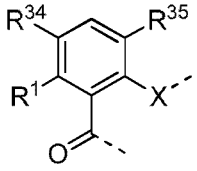
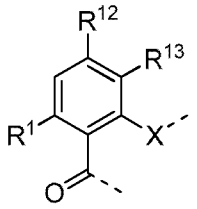
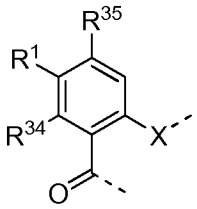
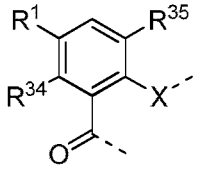
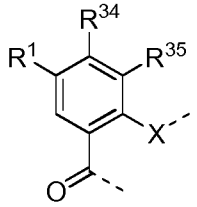
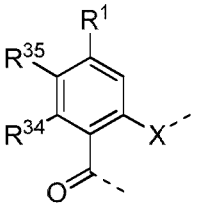
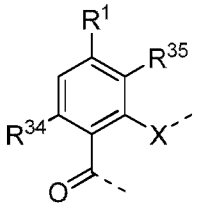
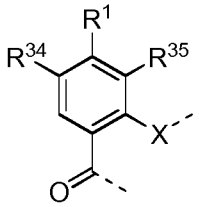
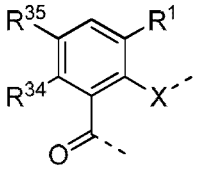
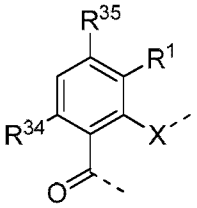
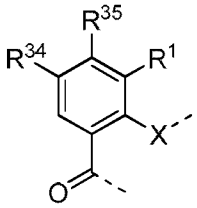
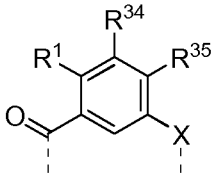
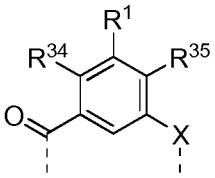
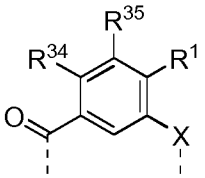
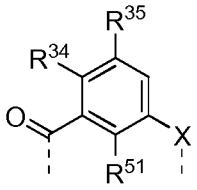
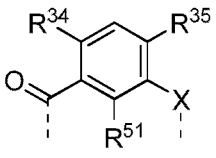
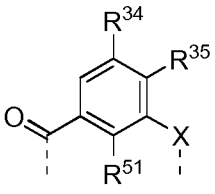
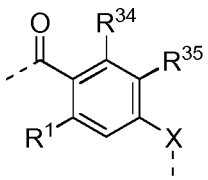
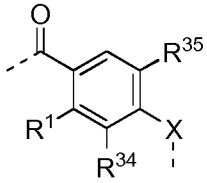
Building blocks **A1-A626** (**Table 10**) constitute a subset of possible building blocks based on the ring systems a1-a25 (**Table 1**). As structural characteristic, groups of type **A** carry one nucleophilic moiety XH (where X is O or S) and one carboxylic acid C(O)OH functionality. The underlying divalent radicals of type -X-a-CO- are an integral part of macrocyclic backbones of type **I**, into which they are incorporated by appropriate reactions of the XH and COOH with suitable reactants.

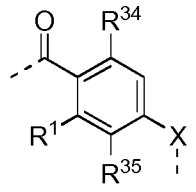
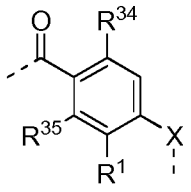
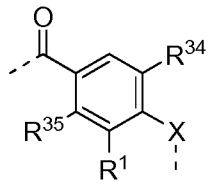
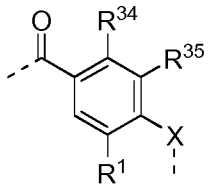
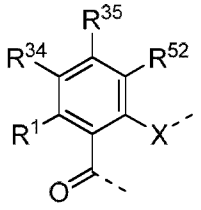
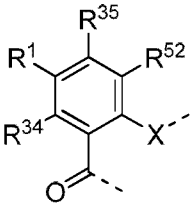
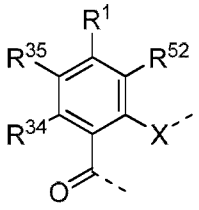
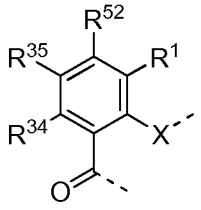
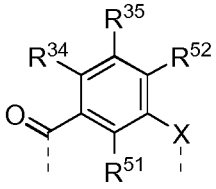
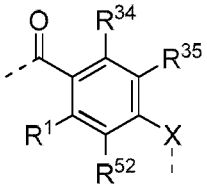
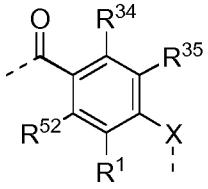
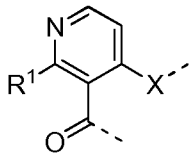
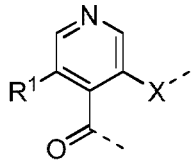
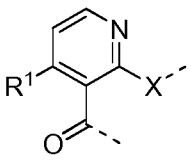
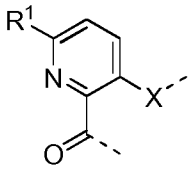
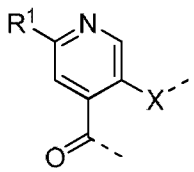
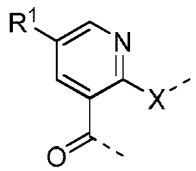
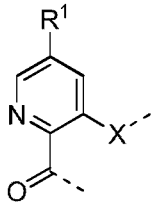
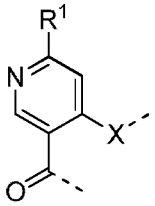
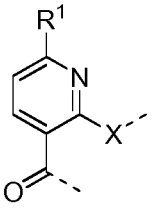
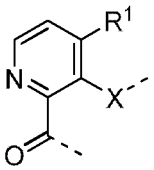
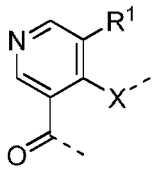
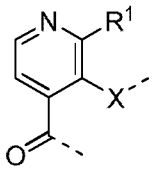
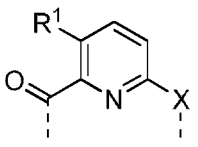
As mentioned earlier hereiabove, building blocks of type **A** act as templates and exert an important conformational constraint on products of type **I**. The structural effects of building blocks of type **A** depends largely on the relative orientation of the attachment vectors of -X- and -C(O)- and on the spatial distance between these groups. Molecular modeling revealed that the distances (typically between 2.5 and 7.5 Å) and vector arrangements for -X- and -C(O)- in **A1-A626** (**Table 10**) vary considerably, thus strongly influencing the conformations of macrocycles of type **I**.

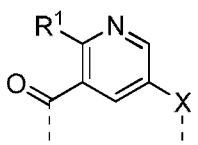
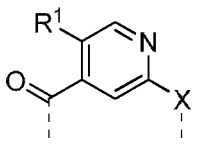
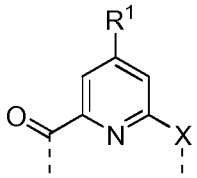
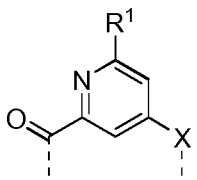
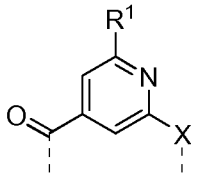
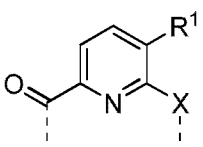
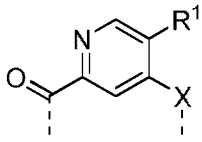
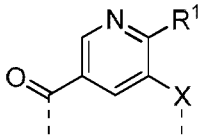
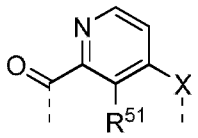
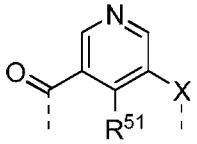
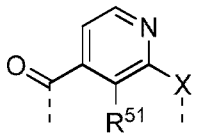
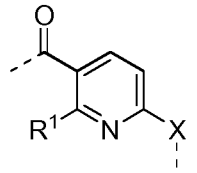
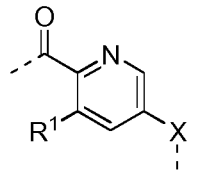
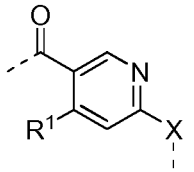
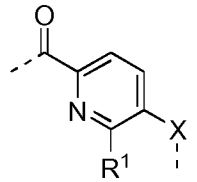
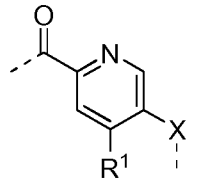
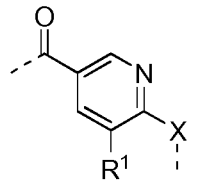
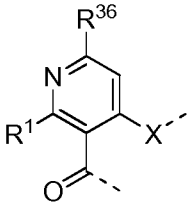
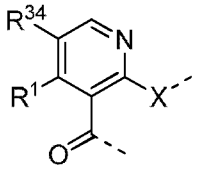
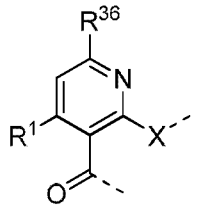
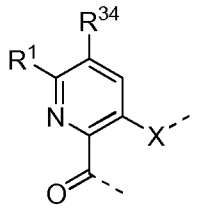
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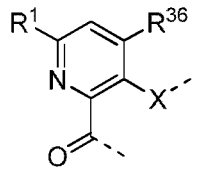
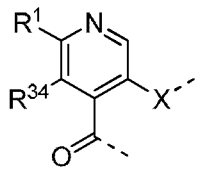
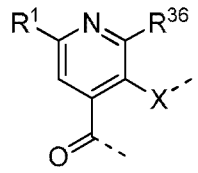
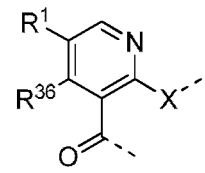
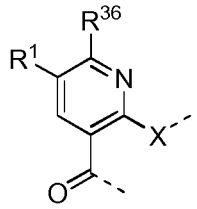
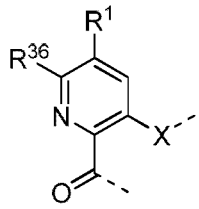
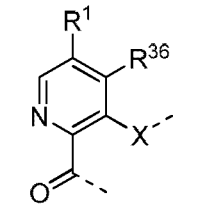
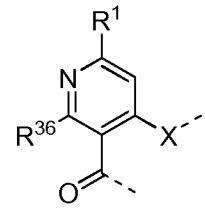
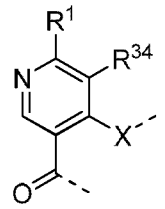
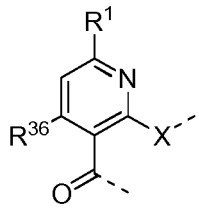
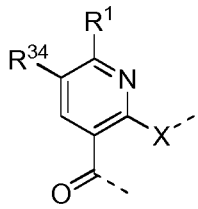
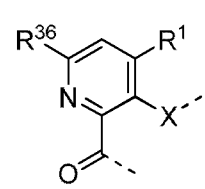
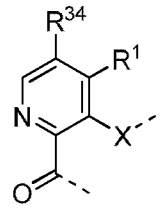
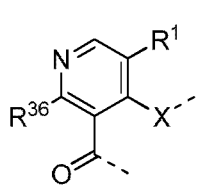
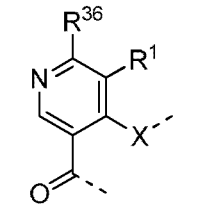
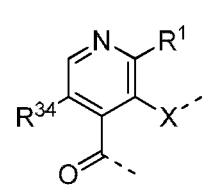
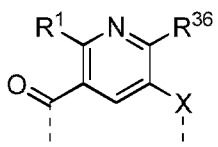
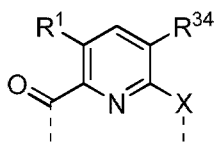
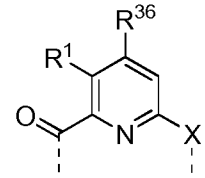
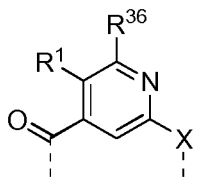
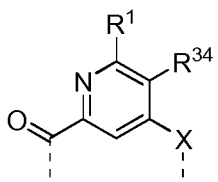
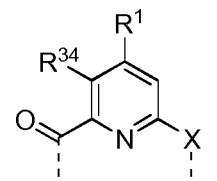
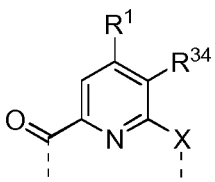
			
A1(a1)	**A2**(a1)	**A3**(a1)	**A4**(a1)

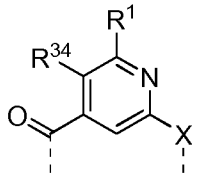
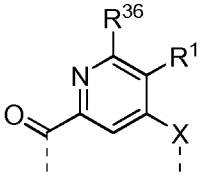
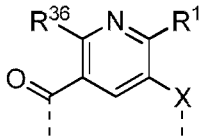
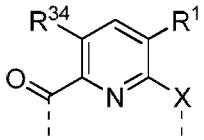
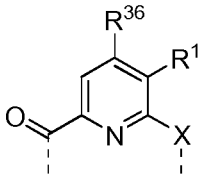
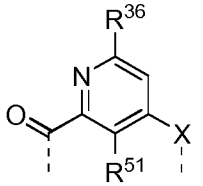
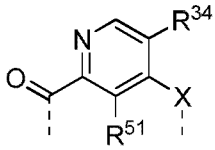
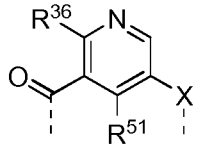
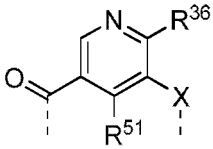
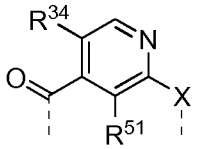
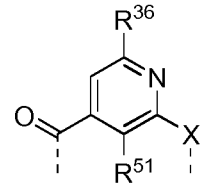
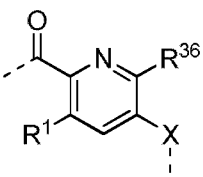
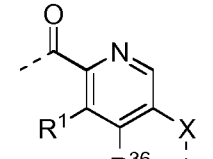
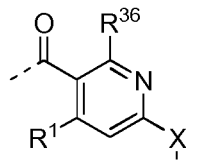
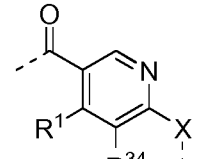
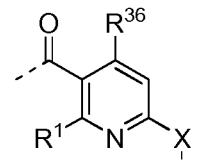
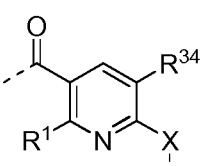
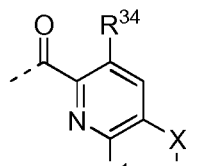
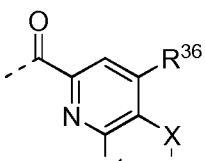
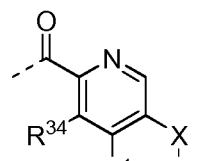
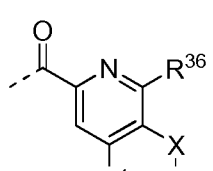
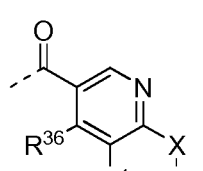
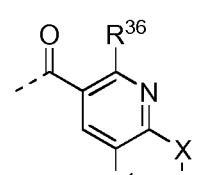
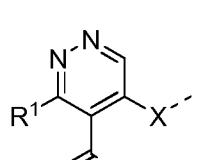
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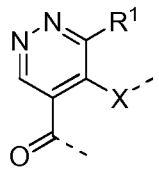
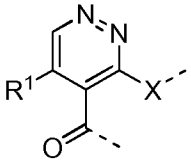
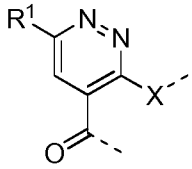
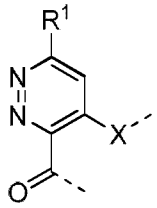
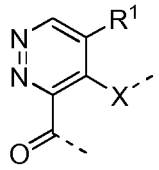
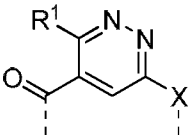
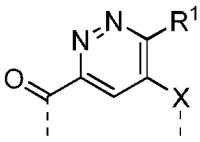
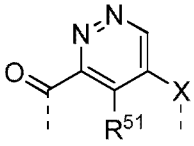
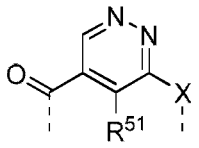
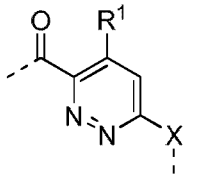
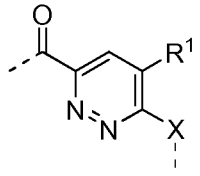
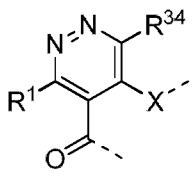
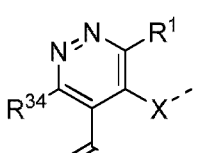
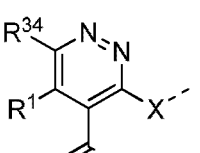
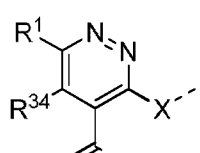
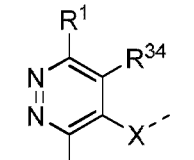
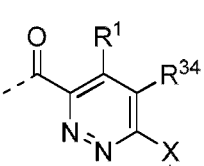
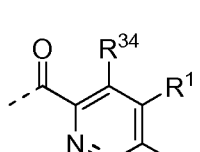
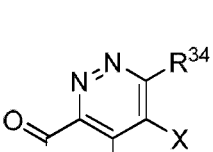
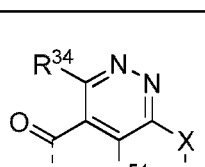
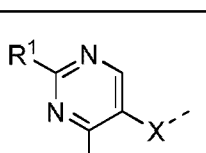
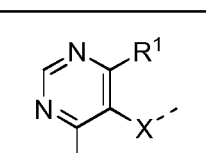
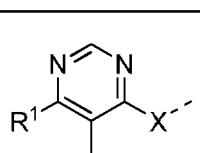
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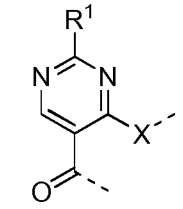
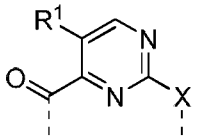
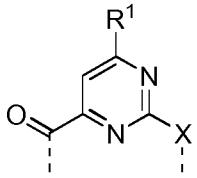
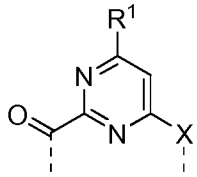
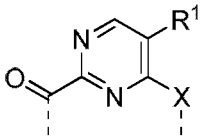
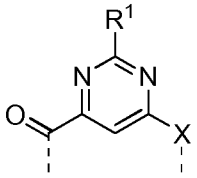
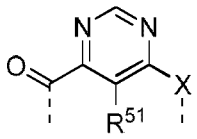
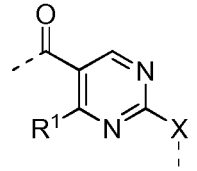
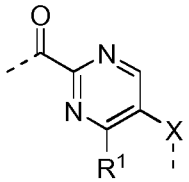
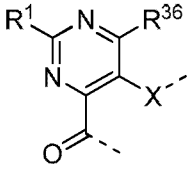
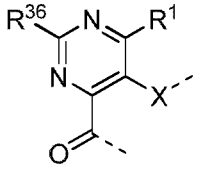
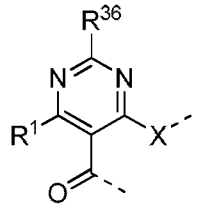
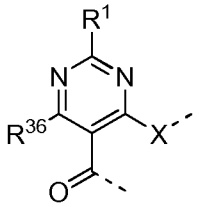
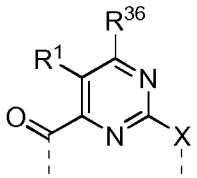
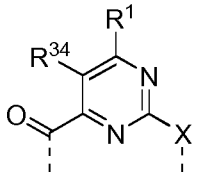
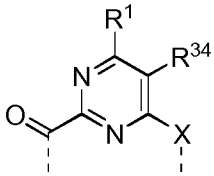
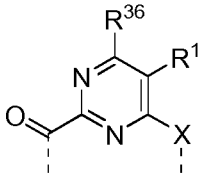
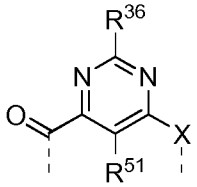
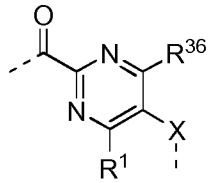
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 **A53** (a1)	 **A54** (a1)	 **A55** (a1)	 **A56** (a1)
 **A57** (a1)	 **A58** (a1)	 **A59** (a1)	 **A60** (a2)
 **A61** (a2)	 **A62** (a2)	 **A63** (a2)	 **A64** (a2)
 **A65** (a2)	 **A66** (a2)	 **A67** (a2)	 **A68** (a2)
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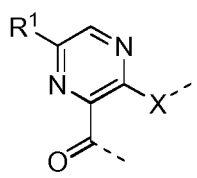
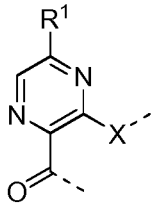
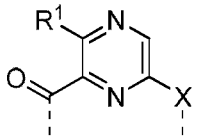
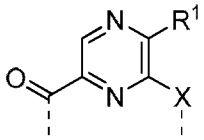
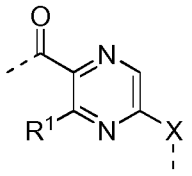
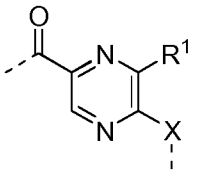
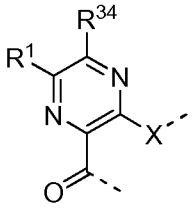
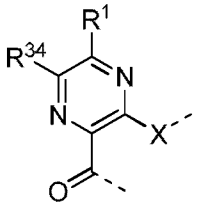
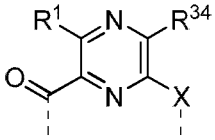
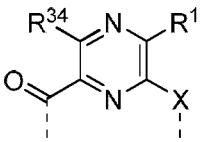
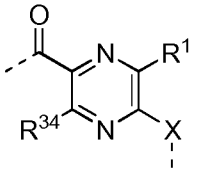
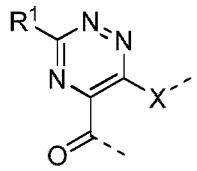
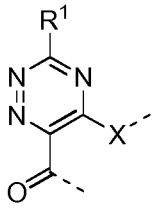
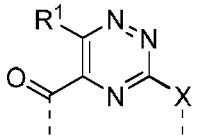
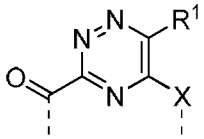
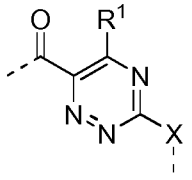
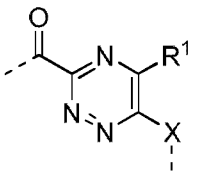
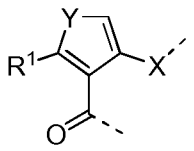
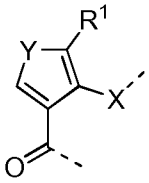
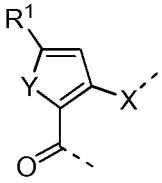
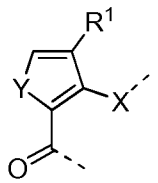
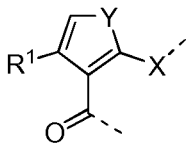
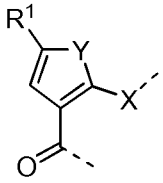
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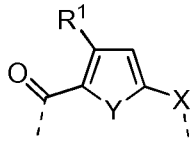
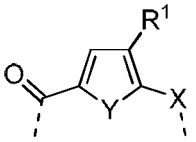
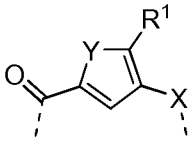
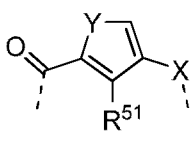
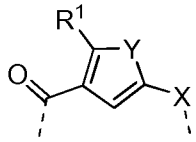
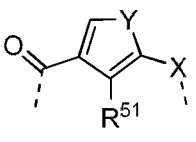
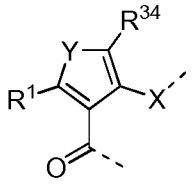
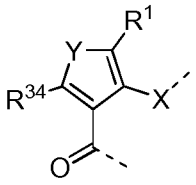
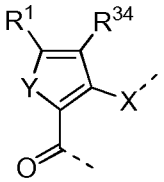
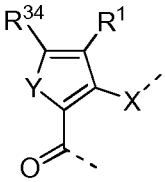
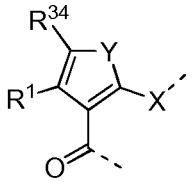
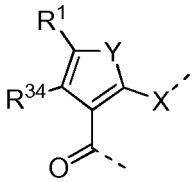
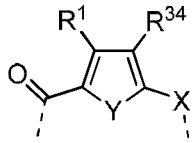
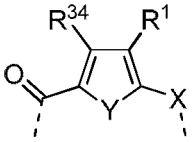
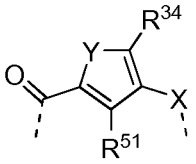
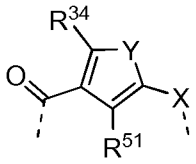
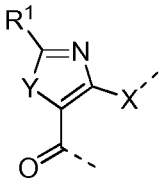
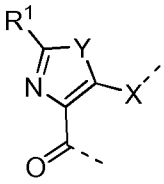
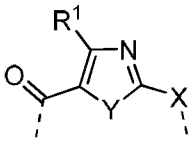
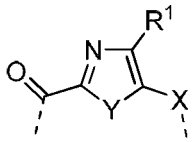
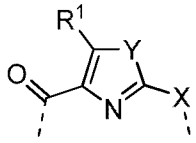
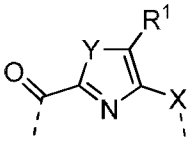
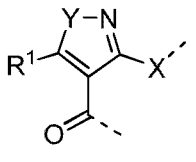
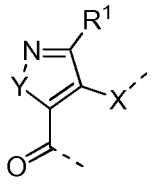
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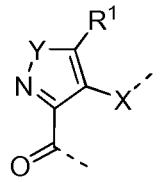
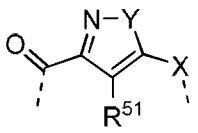
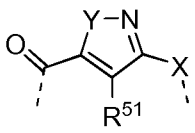
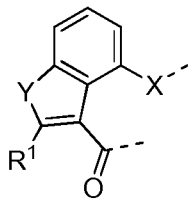
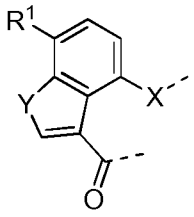
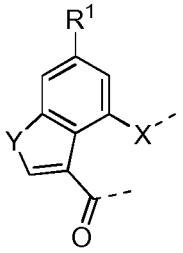
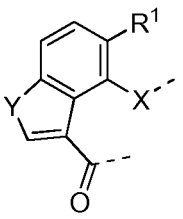
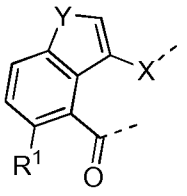
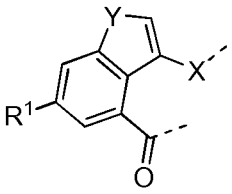
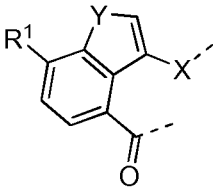
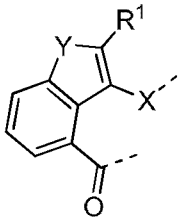
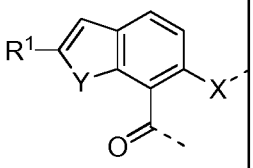
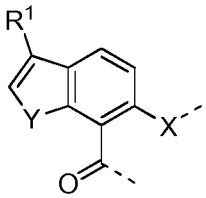
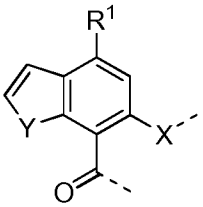
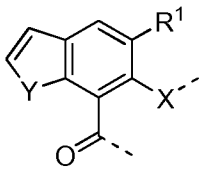
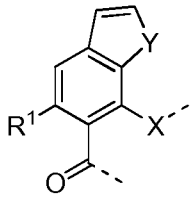
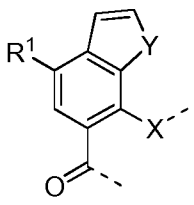
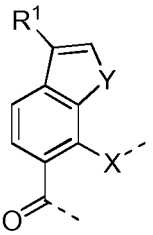
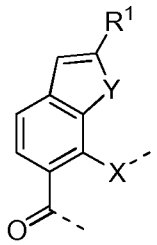
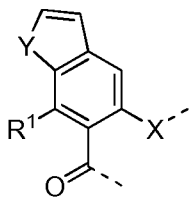
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A121 (a2)	A122 (a2)	A123 (a2)	A124 (a2)
			
A125 (a2)	A126 (a2)	A127 (a2)	A128 (a2)
			
A129 (a2)	A130 (a2)	A131 (a2)	A132 (a2)
			
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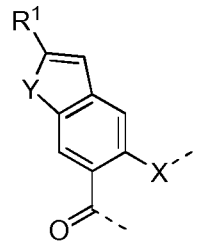
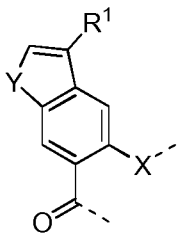
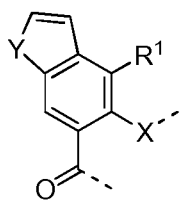
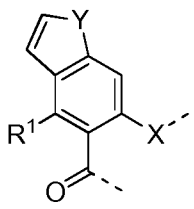
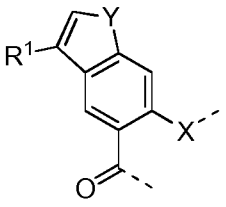
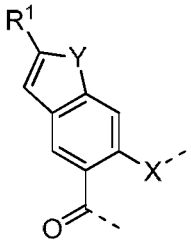
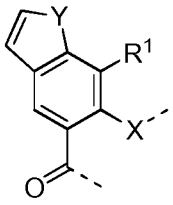
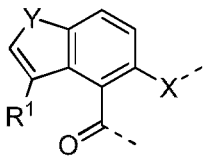
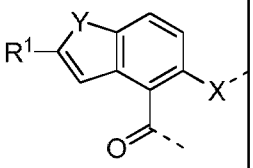
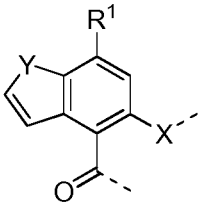
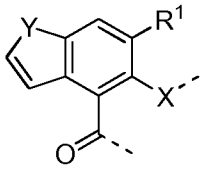
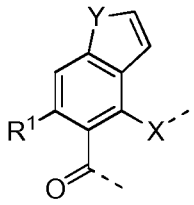
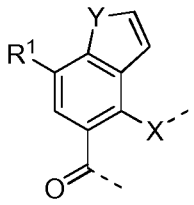
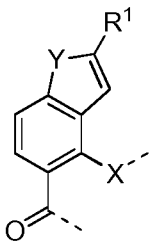
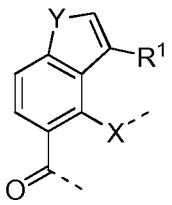
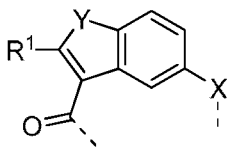
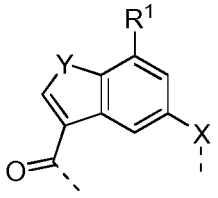
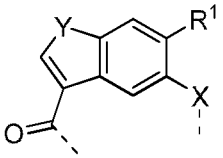
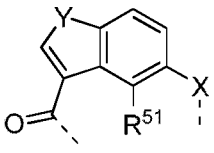
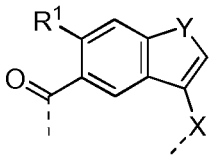
A141 (a2)	**A142** (a2)	**A143** (a2)	**A144** (a3)
			
A145 (a3)	**A146** (a3)	**A147** (a3)	**A148** (a3)
			
A149 (a3)	**A150** (a3)	**A151** (a3)	**A152** (a3)
			
A153 (a3)	**A154** (a3)	**A155** (a3)	**A156** (a3)
			
A157 (a3)	**A158** (a3)	**A159** (a3)	**A160** (a3)
			
A161 (a3)	**A162** (a3)	**A163** (a3)	**A164** (a3)
			

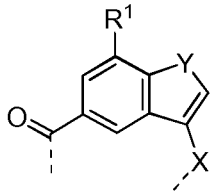
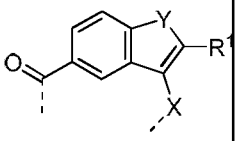
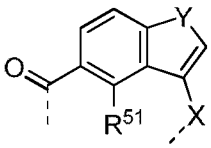
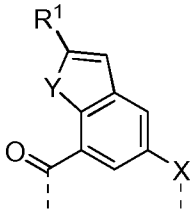
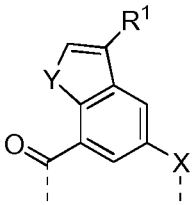
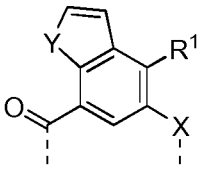
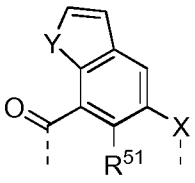
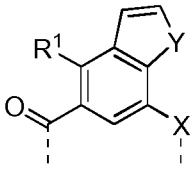
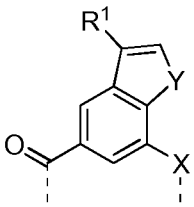
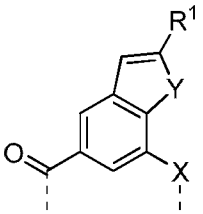
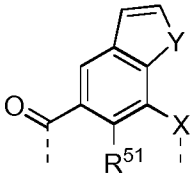
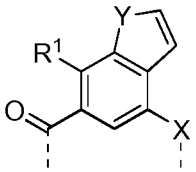
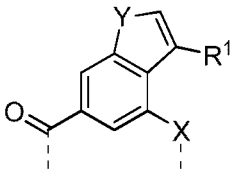
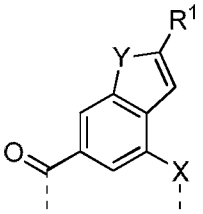
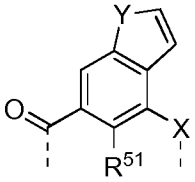
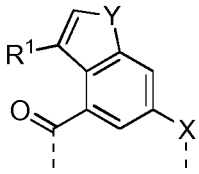
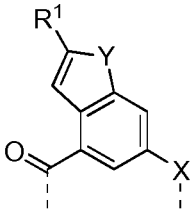
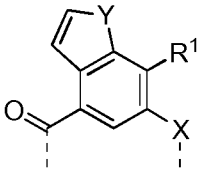
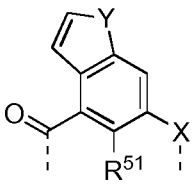
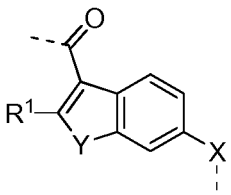
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 **A169** (a4)	 **A170** (a4)	 **A171** (a4)	 **A172** (a4)
 **A173** (a4)	 **A174** (a4)	 **A175** (a4)	 **A176** (a4)
 **A177** (a4)	 **A178** (a4)	 **A179** (a4)	 **A180** (a4)
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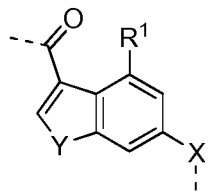
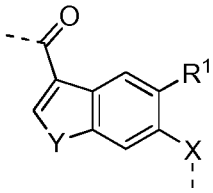
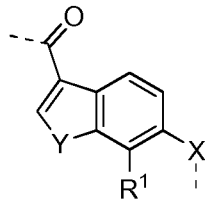
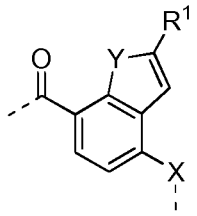
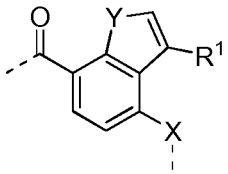
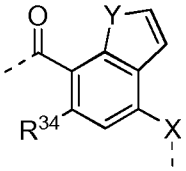
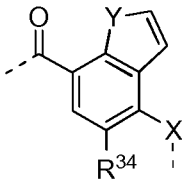
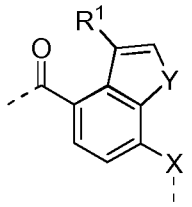
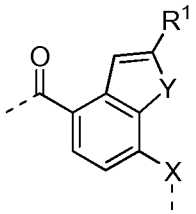
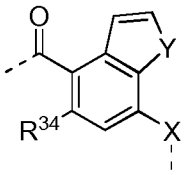
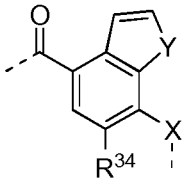
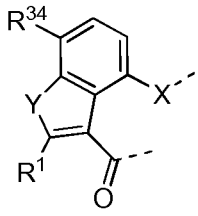
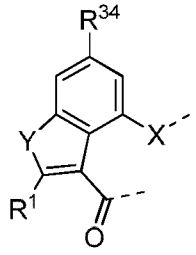
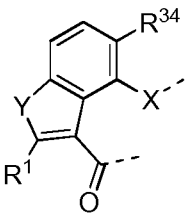
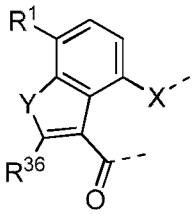
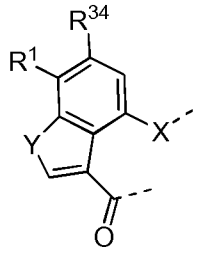
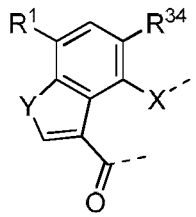
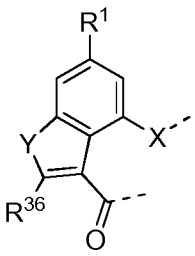
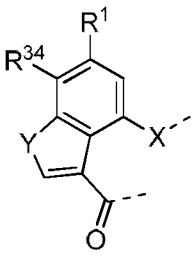
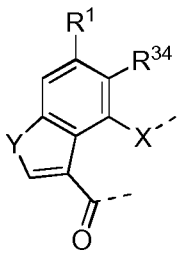
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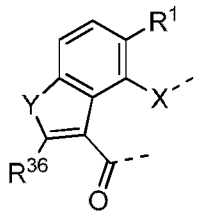
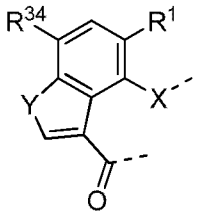
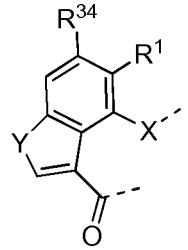
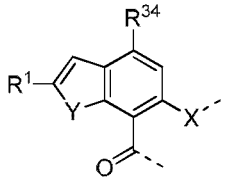
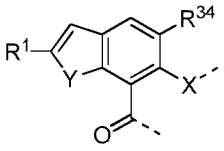
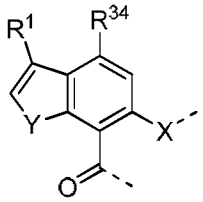
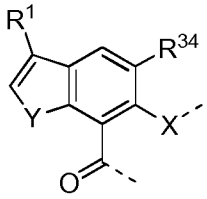
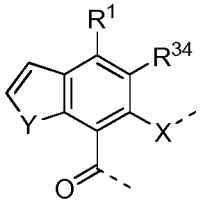
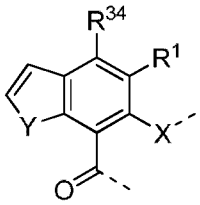
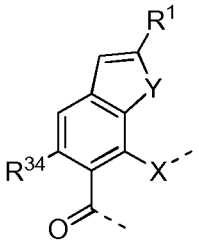
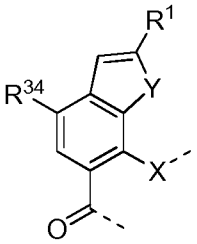
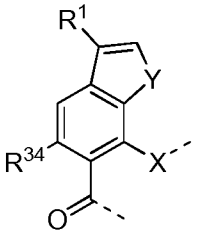
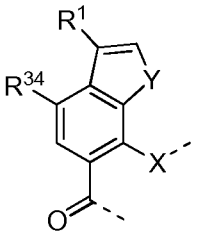
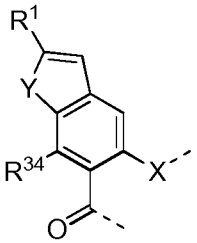
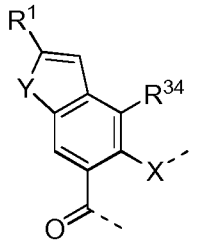
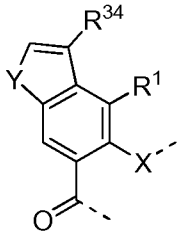
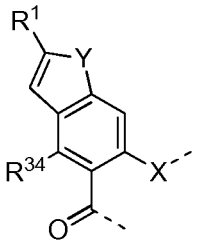
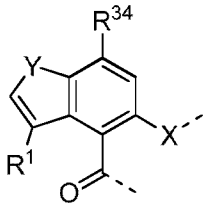
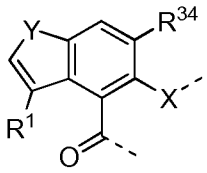
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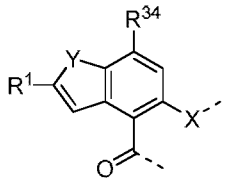
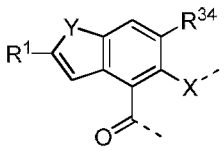
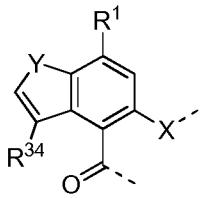
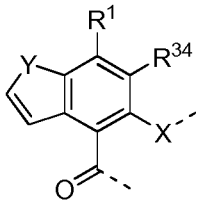
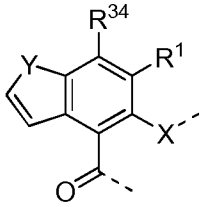
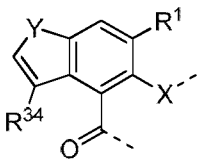
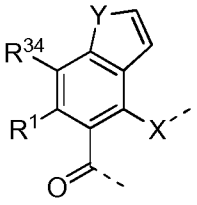
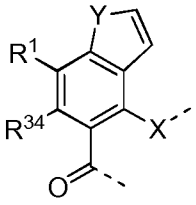
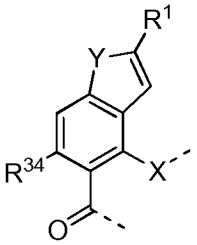
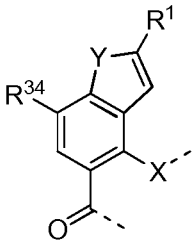
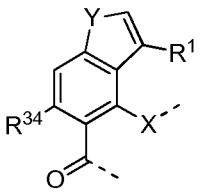
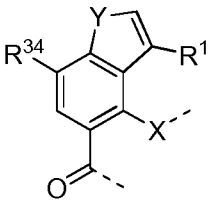
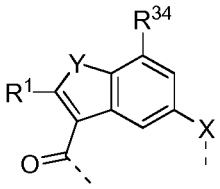
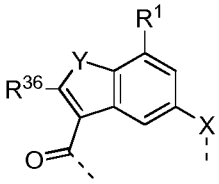
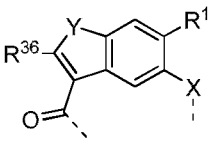
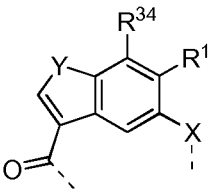
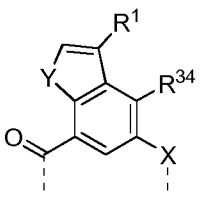
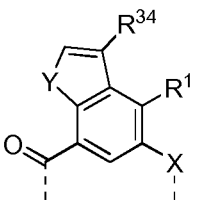
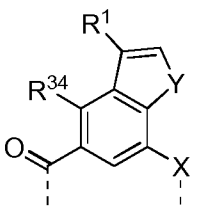
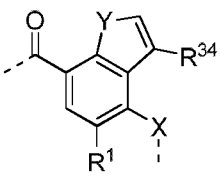
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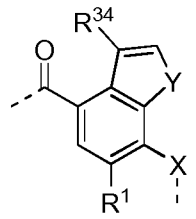
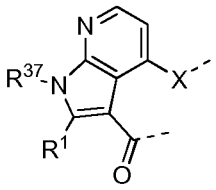
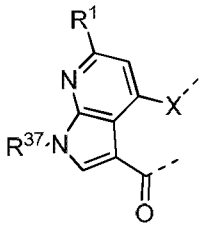
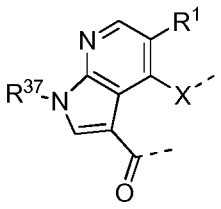
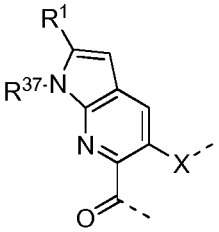
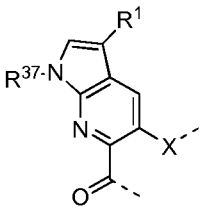
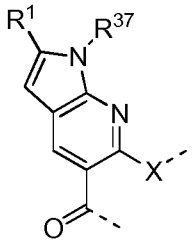
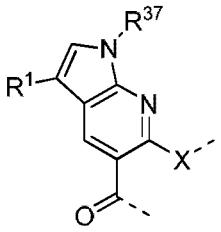
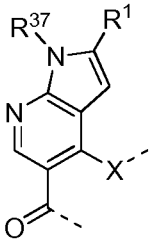
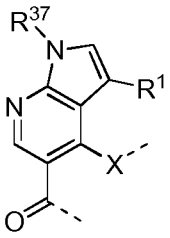
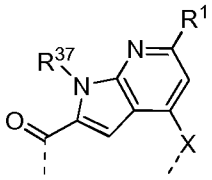
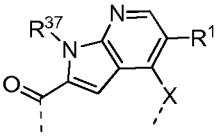
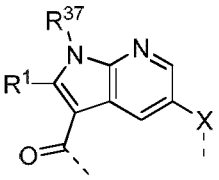
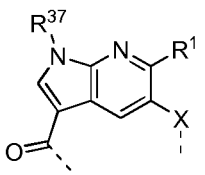
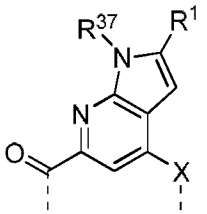
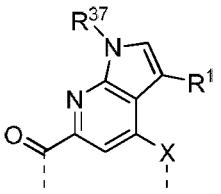
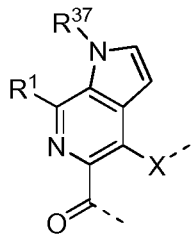
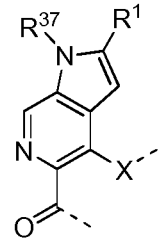
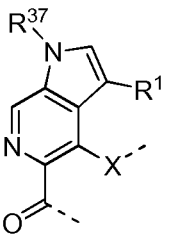
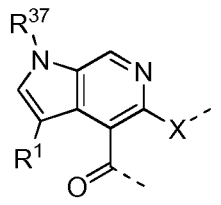
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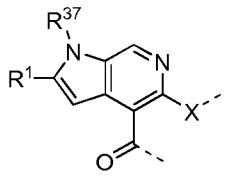
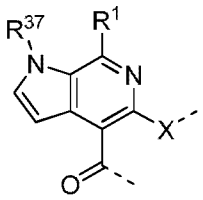
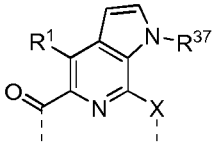
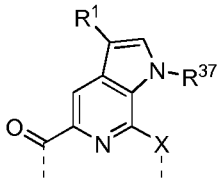
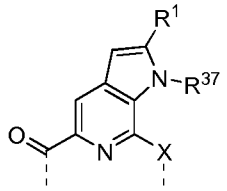
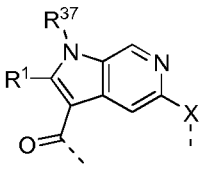
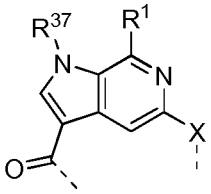
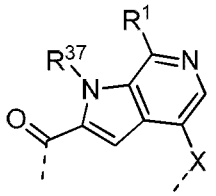
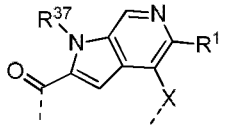
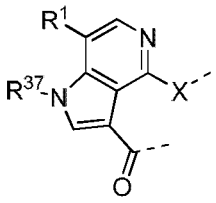
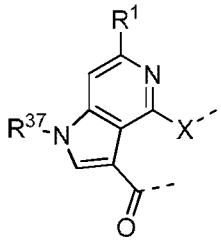
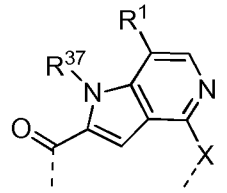
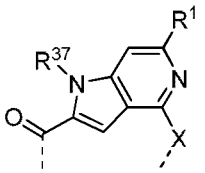
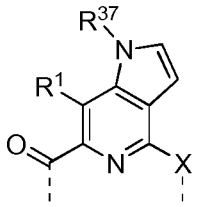
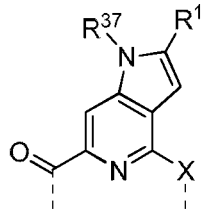
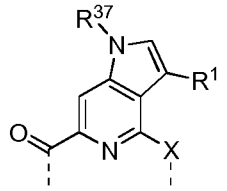
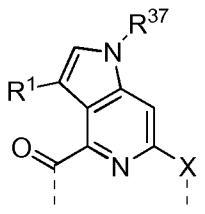
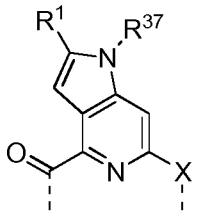
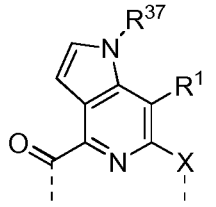
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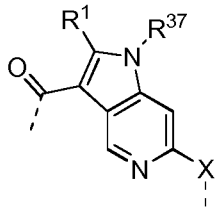
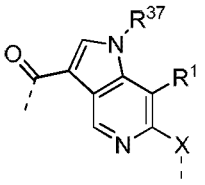
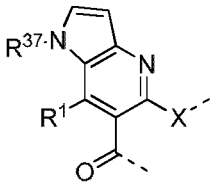
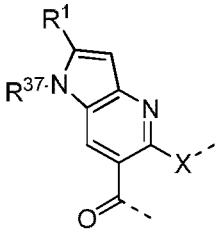
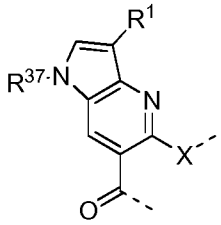
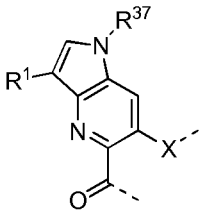
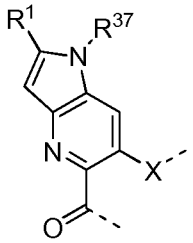
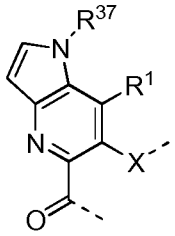
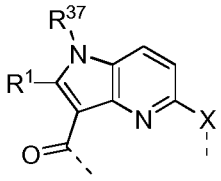
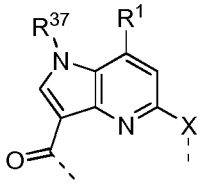
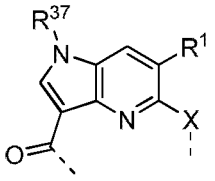
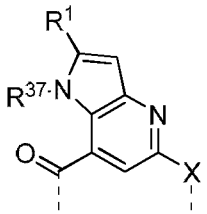
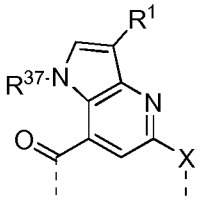
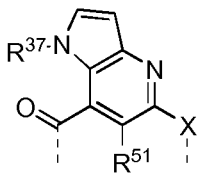
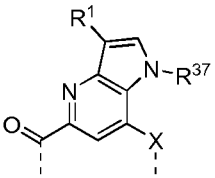
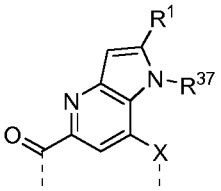
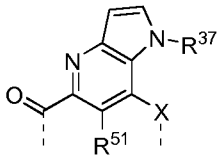
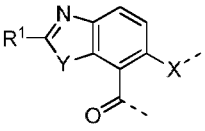
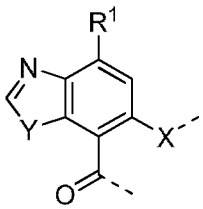
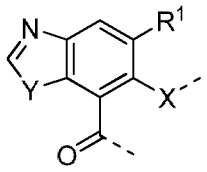
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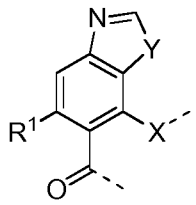
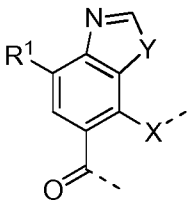
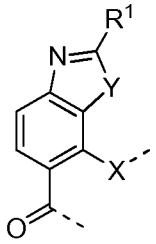
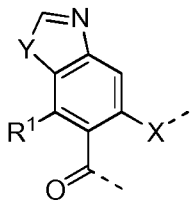
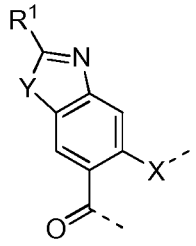
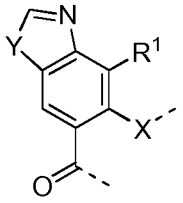
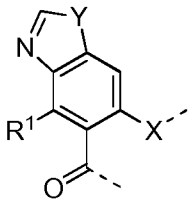
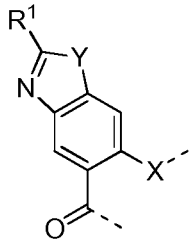
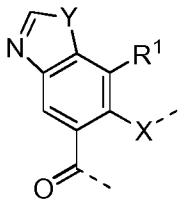
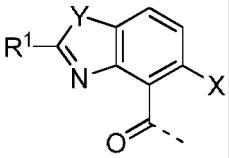
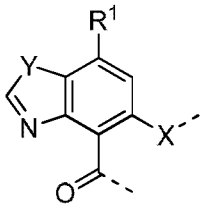
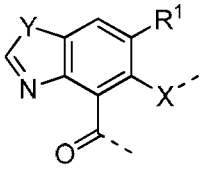
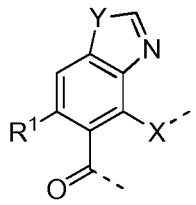
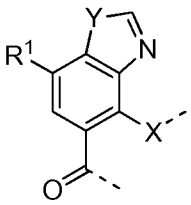
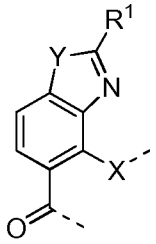
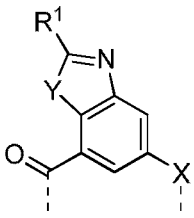
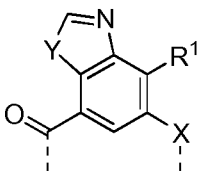
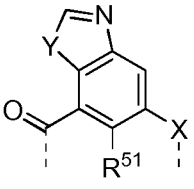
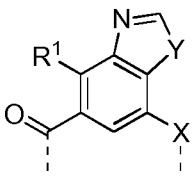
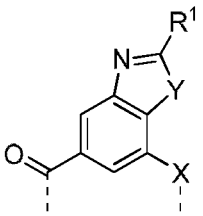
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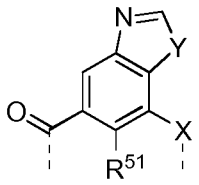
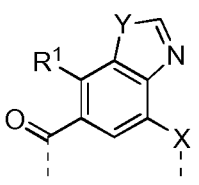
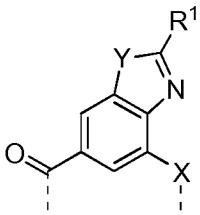
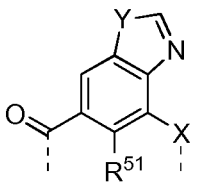
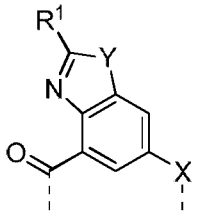
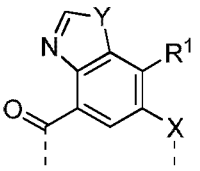
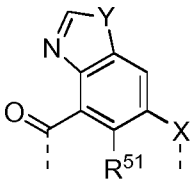
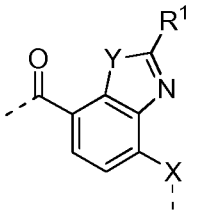
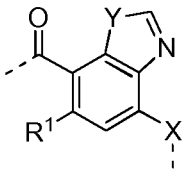
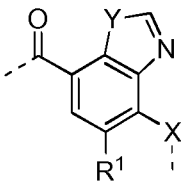
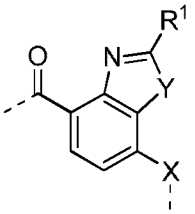
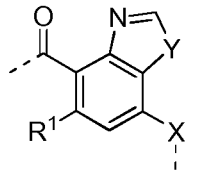
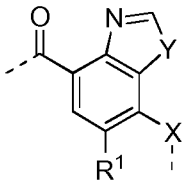
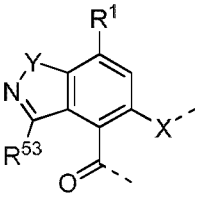
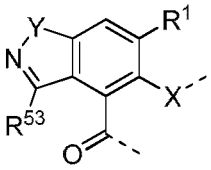
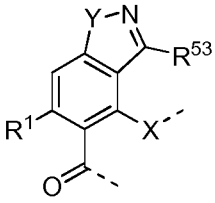
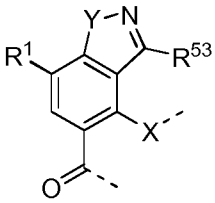
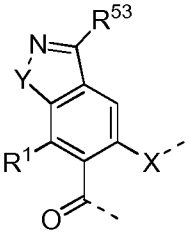
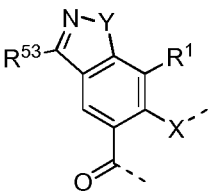
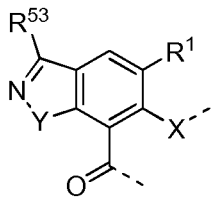
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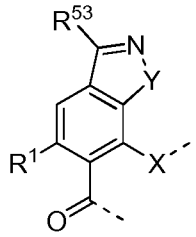
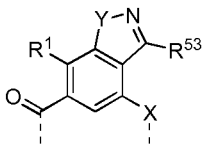
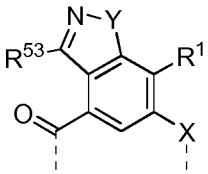
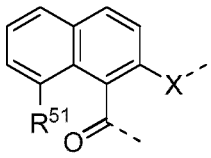
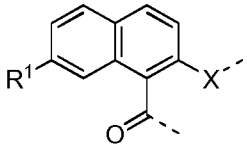
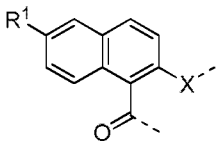
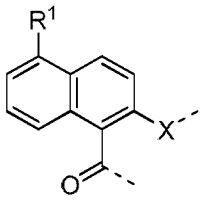
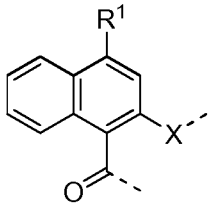
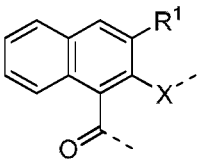
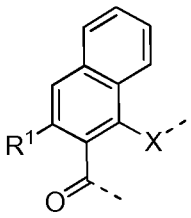
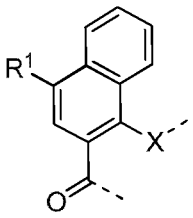
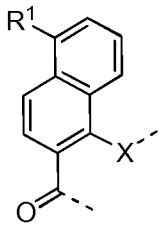
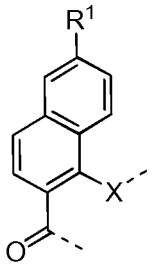
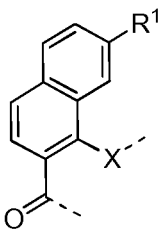
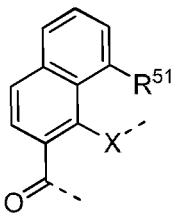
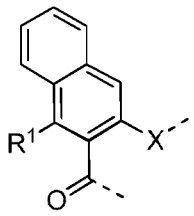
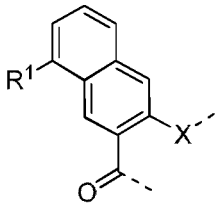
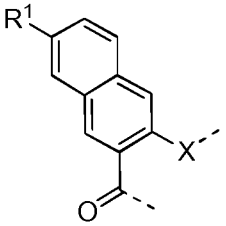
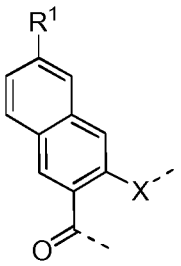
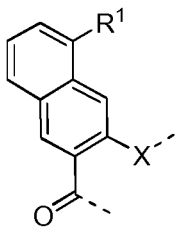
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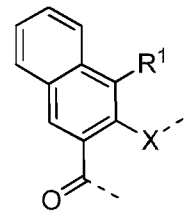
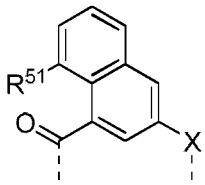
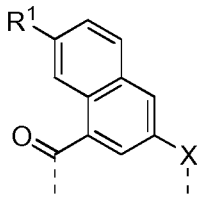
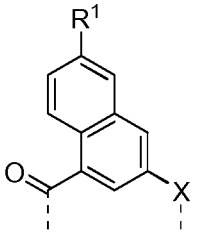
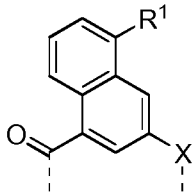
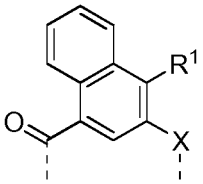
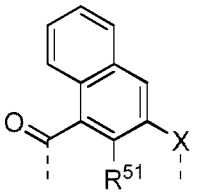
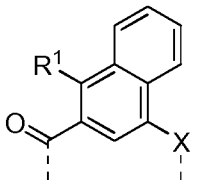
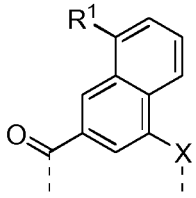
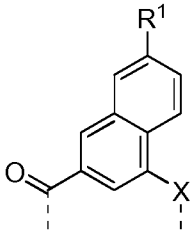
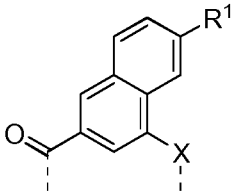
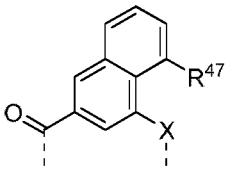
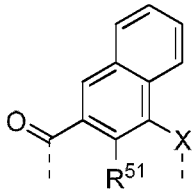
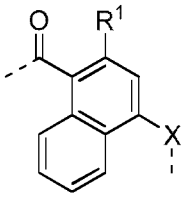
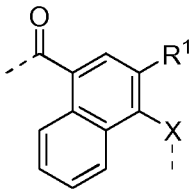
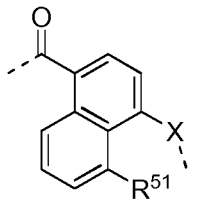
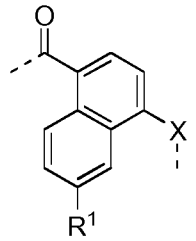
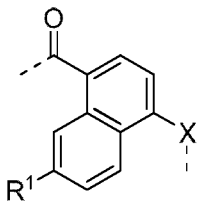
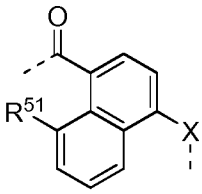
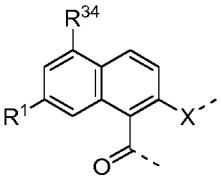
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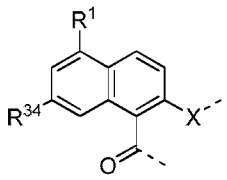
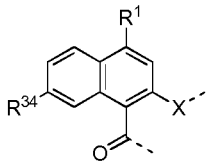
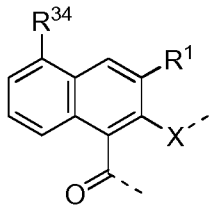
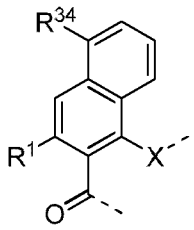
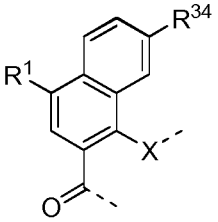
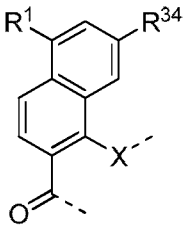
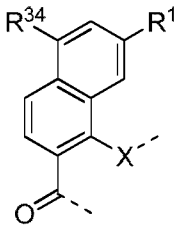
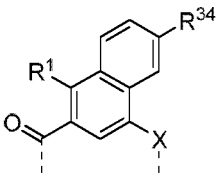
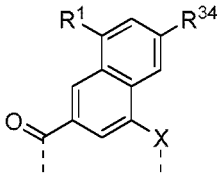
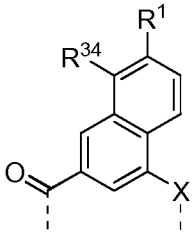
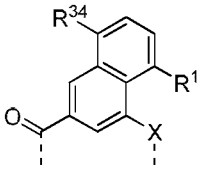
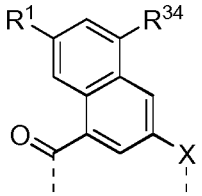
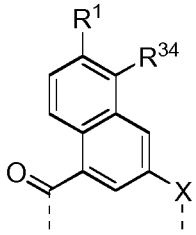
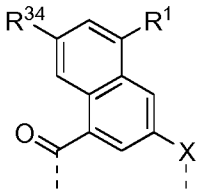
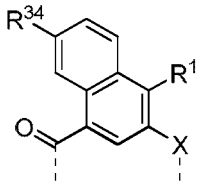
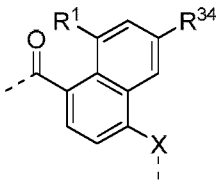
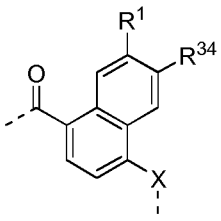
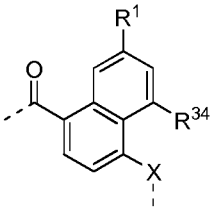
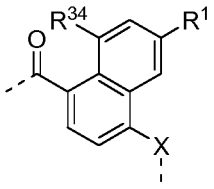
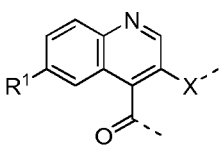
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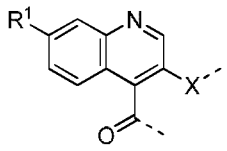
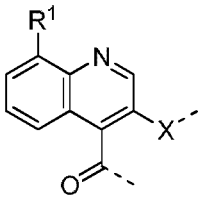
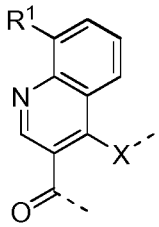
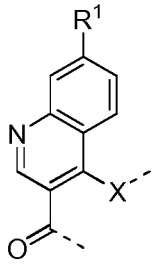
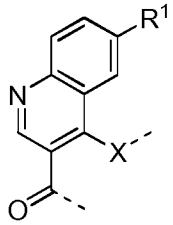
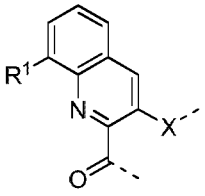
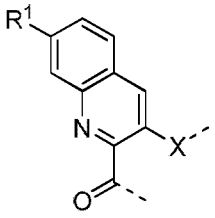
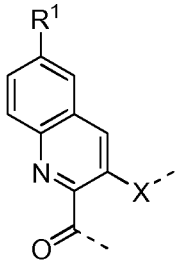
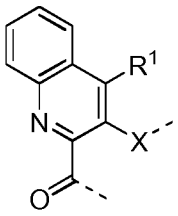
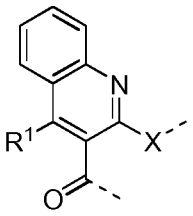
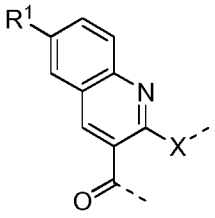
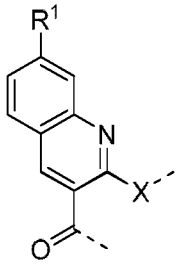
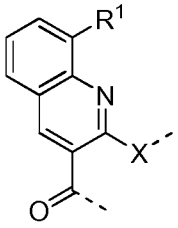
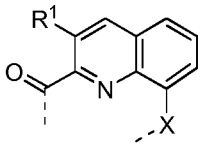
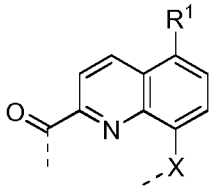
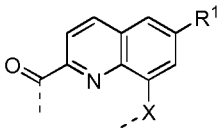
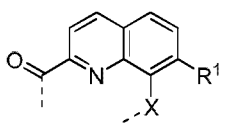
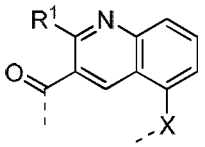
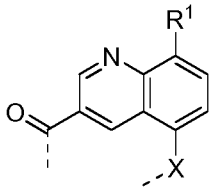
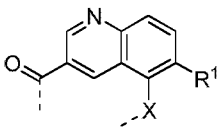
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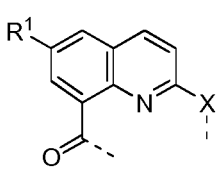
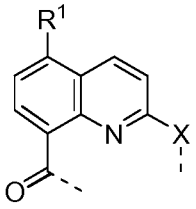
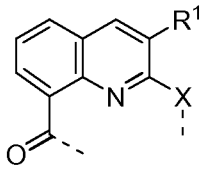
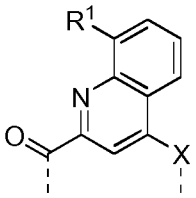
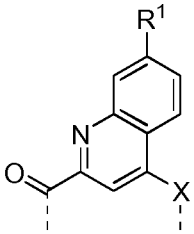
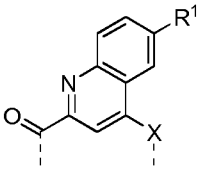
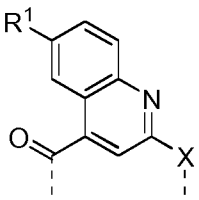
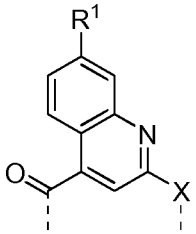
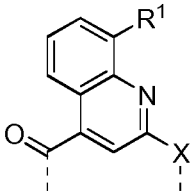
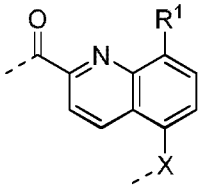
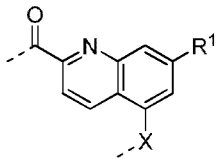
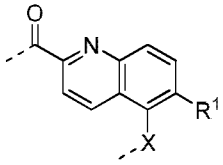
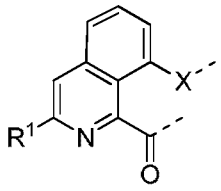
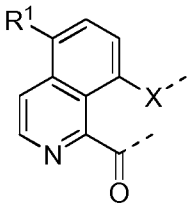
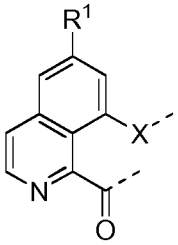
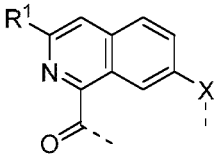
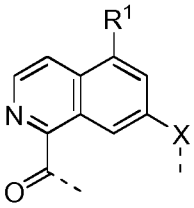
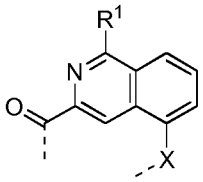
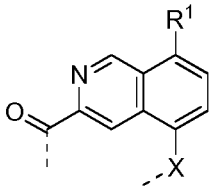
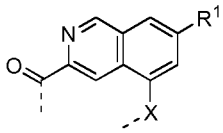
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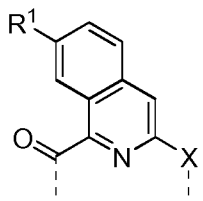
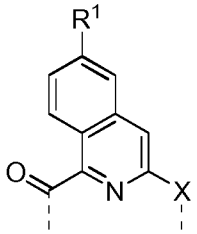
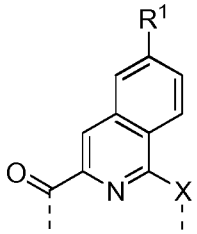
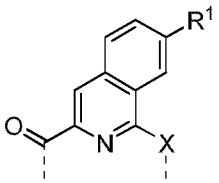
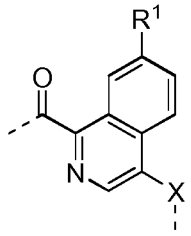
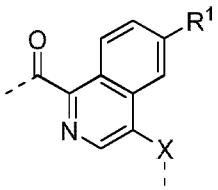
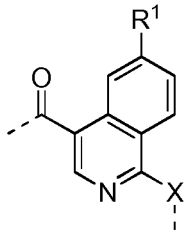
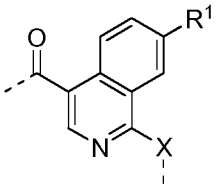
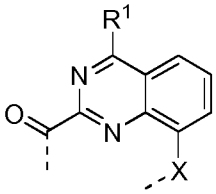
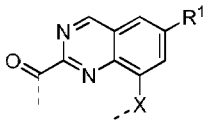
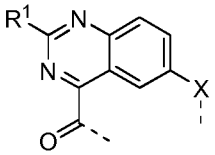
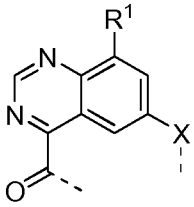
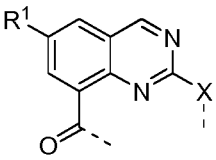
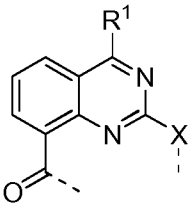
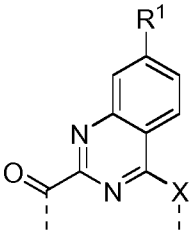
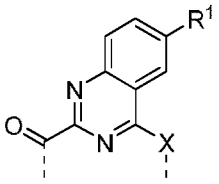
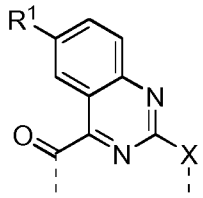
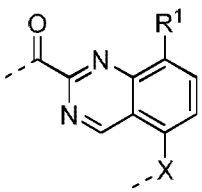
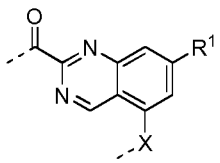
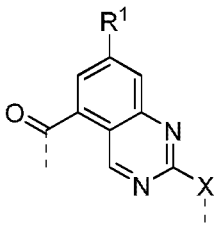
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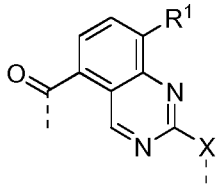
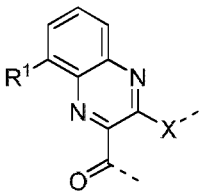
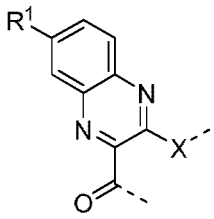
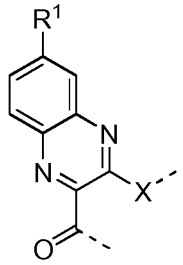
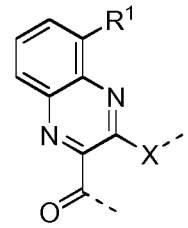
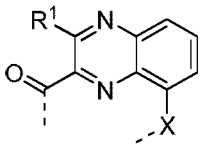
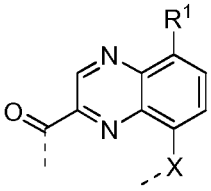
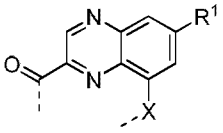
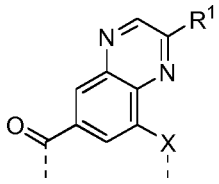
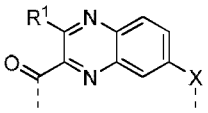
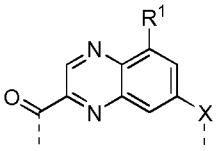
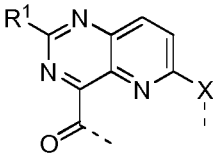
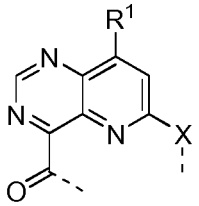
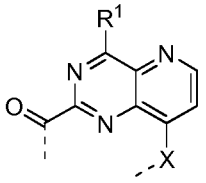
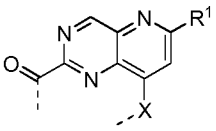
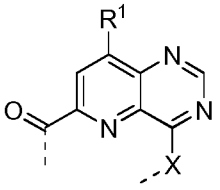
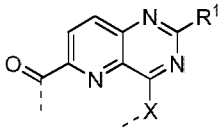
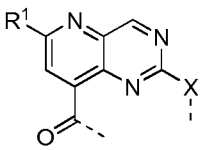
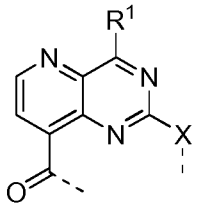
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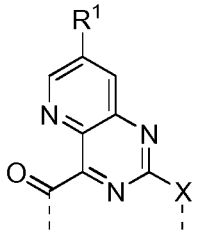
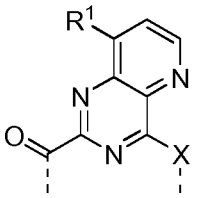
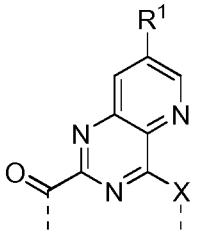
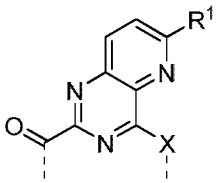
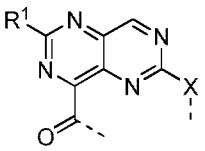
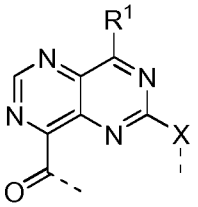
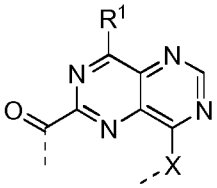
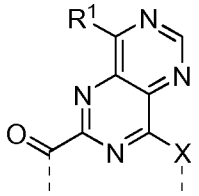
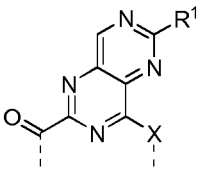
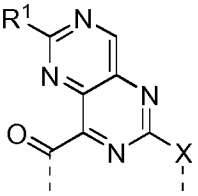
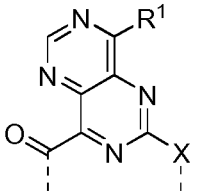
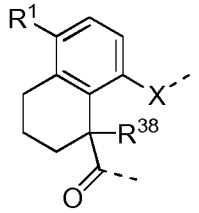
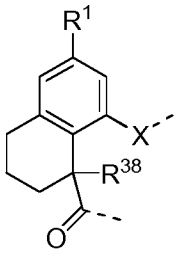
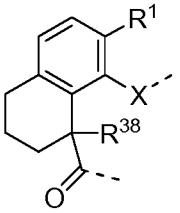
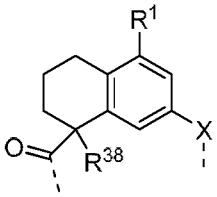
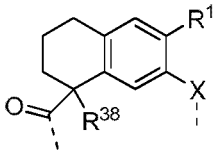
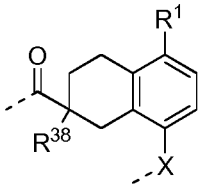
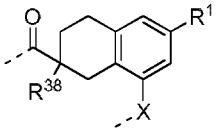
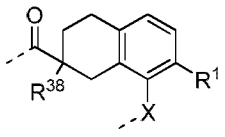
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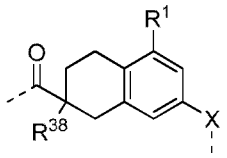
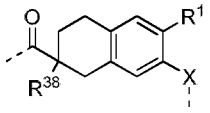
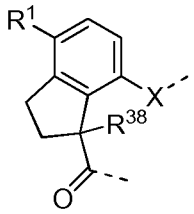
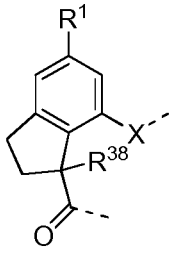
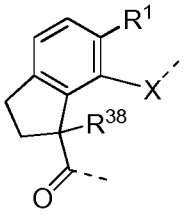
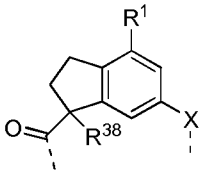
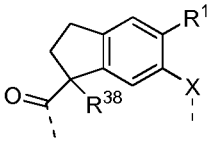
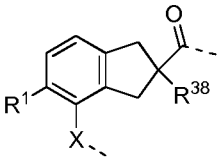
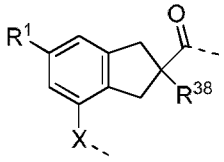
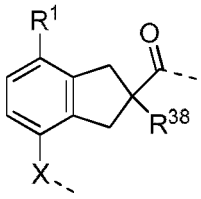
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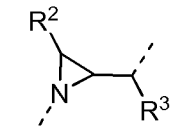
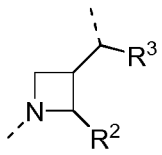
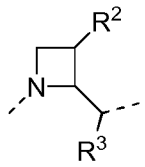
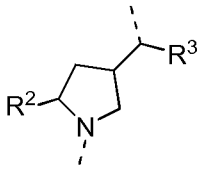
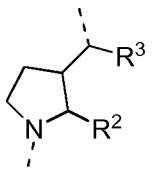
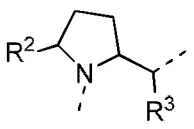
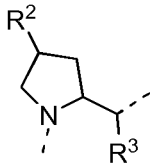
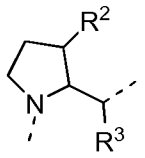
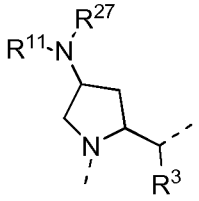
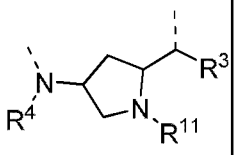
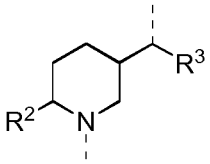
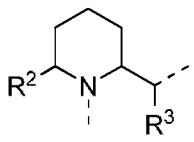
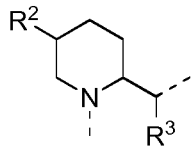
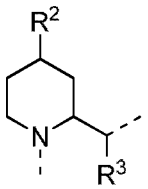
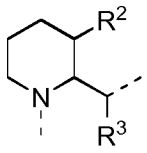
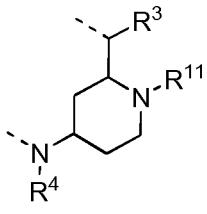
 **A617** (a24)	 **A618** (a24)	 **A619** (a25)	 **A620** (a25)
 **A621** (a25)	 **A622** (a25)	 **A623** (a25)	 **A624** (a25)
 **A625** (a25)		 **A626** (a25)	

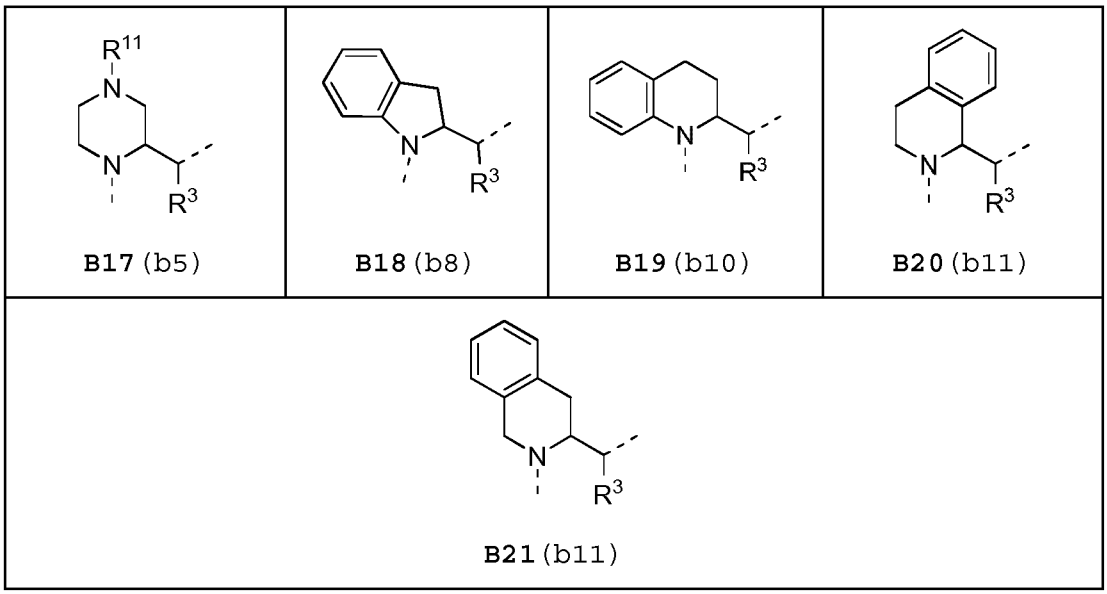
Divalent building blocks **B1-B21** (Table 11, hereinbelow) constitute a subset of possible building blocks based on the ring systems **b1-b11** (Table 2, above). They are based on optionally substituted cyclic secondary amines carrying a moiety of type $-CHR^3-LG$, wherein LG is a suitable leaving group (e.g., but not limited to, -OH forming a suitable LG *in situ* during Mitsunobu reactions, or halogens like –Br or –I amenable to S_N reactions) that can be replaced by the nucleophilic groups of building blocks **A** thus forming an ether (-O-) or a thioether (-S-) linkage between building blocks of type **A** and **B**. In most products of type **I**, the secondary amine nitrogen of building block **B** forms a tertiary amide linkage with the carboxyl group of building blocks of type **C**. In case a suitable exocyclic amine functionality is present, it can be, instead of the ring-nitrogen, involved in the formation of a secondary or

preferably tertiary amide bond to **C**. Such an alternative binding mode is realized with, but not limited to **B10**.

By virtue of inducing peptidyl *cis-trans* isomerization or stabilizing *cis* amide bonds, building blocks of type **B** can function as conformational modulators in products of type **I**.

Table 11: Radicals **B1-B21**

 **B1** (b1)	 **B2** (b2)	 **B3** (b2)	 **B4** (b3)
 **B5** (b3)	 **B6** (b3)	 **B7** (b3)	 **B8** (b3)
 **B9** (b3)	 **B10** (b3)	 **B11** (b4)	 **B12** (b4)
 **B13** (b4)	 **B14** (b4)	 **B15** (b4)	 **B16** (b4)

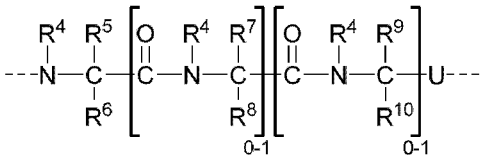
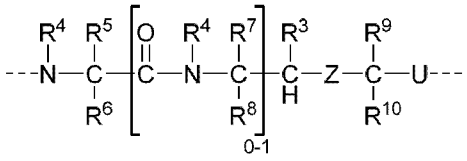
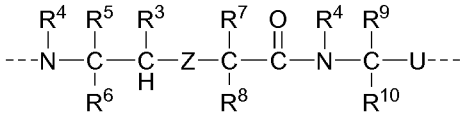
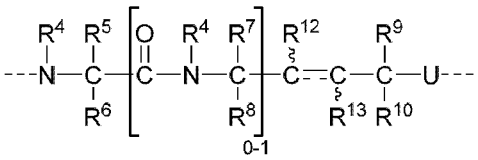
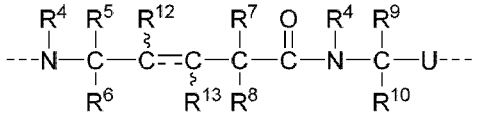
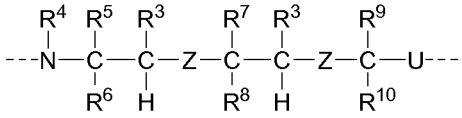
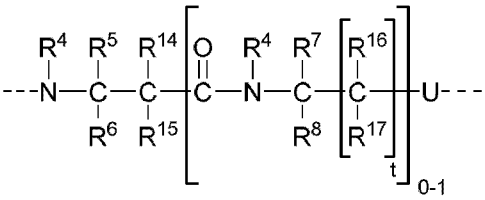
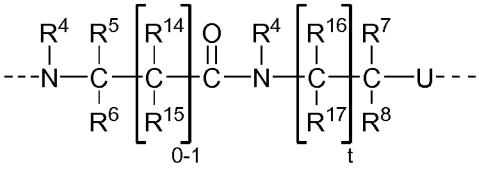
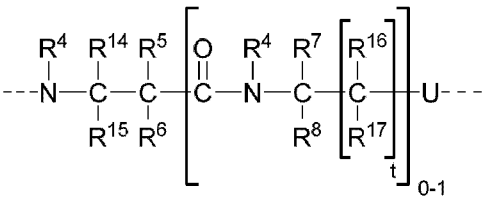
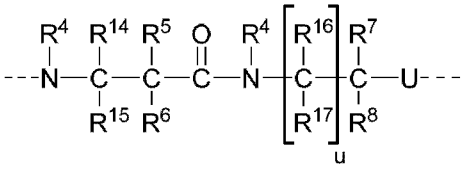


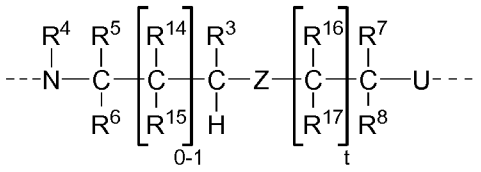
The divalent moiety **C** may consist of an ensemble of one to three subunits **c1-c3**, each derived from suitably protected and functionalized amine or amino acid derivatives. As a consequence the **C** moiety directly influences the ring size of the resulting macrocycle and can be regarded as spacer or linker. This linker ensemble **C** is joined to building block **A** via its N-terminus and to building block **B** via its C-terminus to form a macrocyclic ring of type **I**. According to its definition the connections within the linker ensemble, i.e. V or W, can be accomplished by amide bonds ($-NR^4-C(=O)-$), an alkene[1,2]diyl ($-CHR^{12}=CHR^{13}-$), an alkane[1,2]diyl ($-CHR^{12}-CHR^{13}-$), or methylene-heteroatom moiety ($-CHR^3-Z-$), an oxalyl unit ($-C(=O)-C(=O)-$) or a disulfide bridge (-S-S-). With respect to the macrocyclic backbone of **I** it follows that the linker **C** contributes at least one amide bonds.

Suitable linker **C** can be represented by, but are not limited to, the moieties shown in **Table 12**. For example **C1** represents a linker moiety constituted of one to three α-amino acid derivatives connected along their main chains, while **C7-C10** are equivalent to dipeptide moieties of β– amino acids. Te simplest embodiments in which at least one connection between the subunits is realized by a non-amidic group are **C2-C5**. Finally

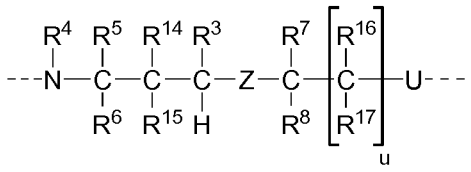
C58-C101 shall depict situations in which a longer (> 3 C-atoms) side chain connection of a suitable diamine or diacid is involved in an amide bond.

Table 12: Representative Embodiments of Linker **C**

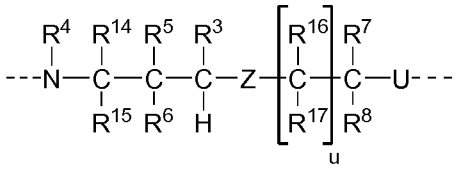
 C1	 C2
 C3	 C4
 C5	 C6
 C7	 C8
 C9	 C10



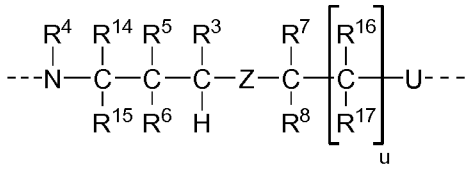
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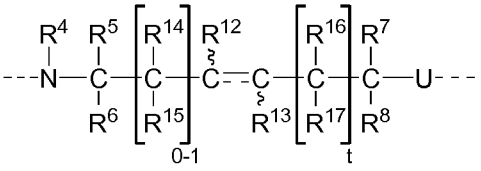
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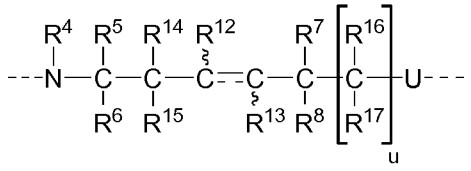
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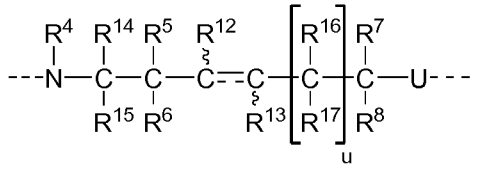
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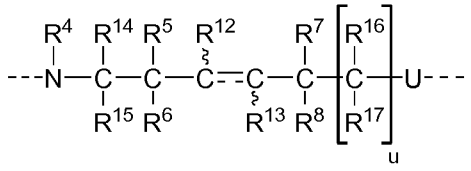
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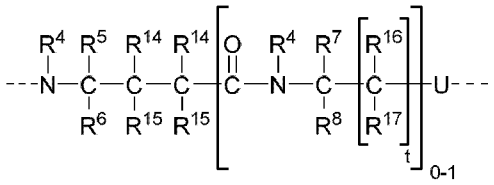
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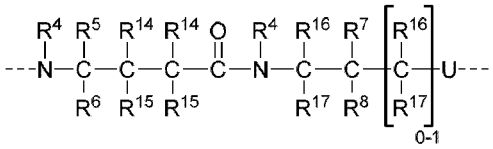
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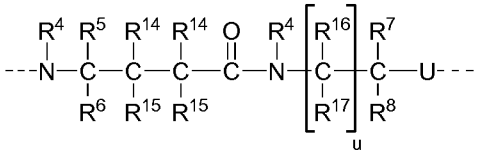
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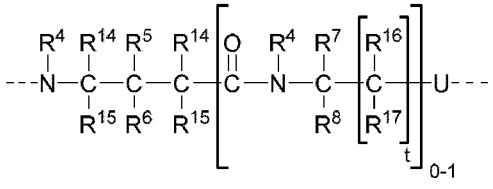
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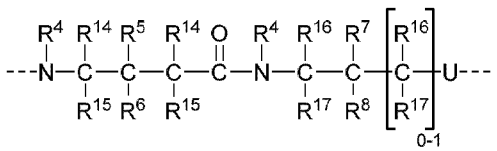
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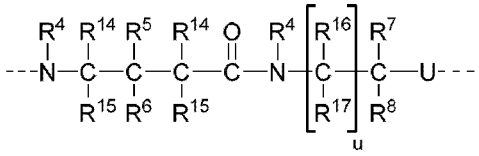
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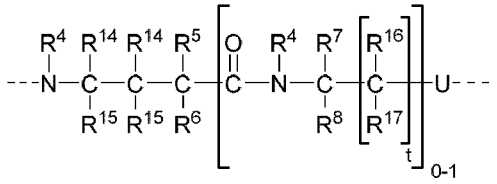
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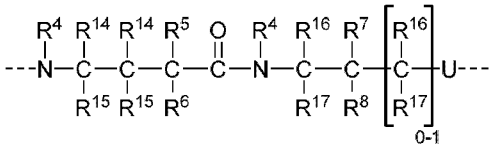
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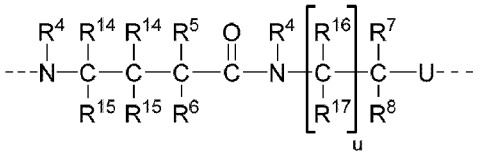
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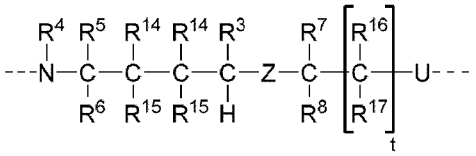
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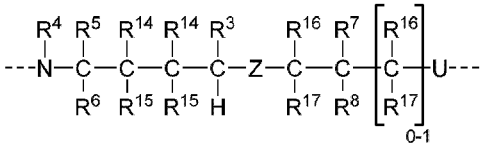
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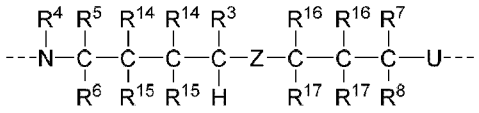
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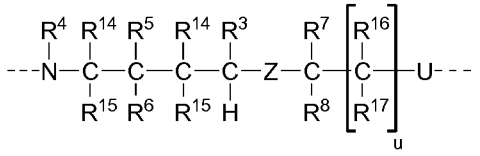
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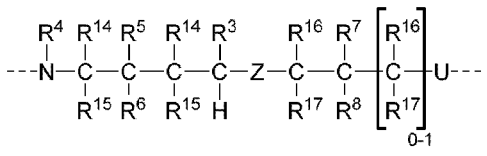
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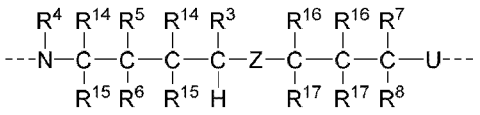
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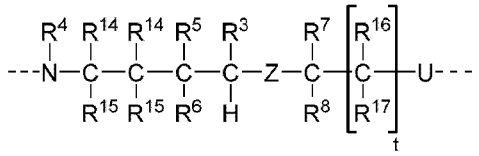
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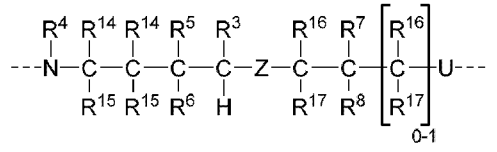
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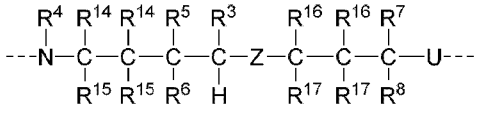


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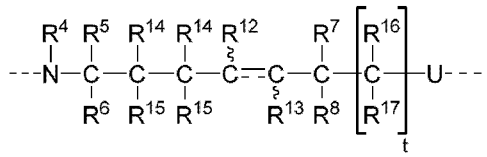


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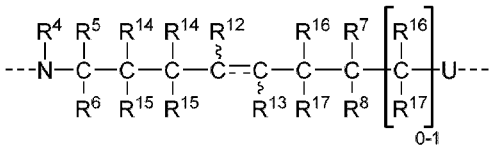




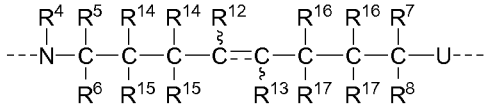
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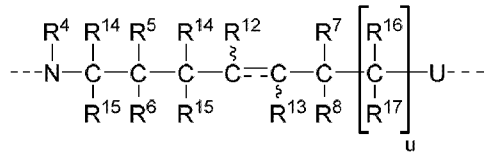
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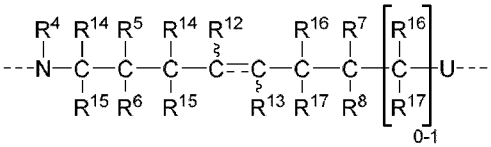
C37



C38



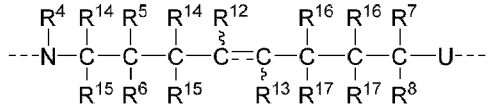
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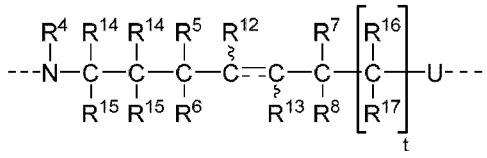
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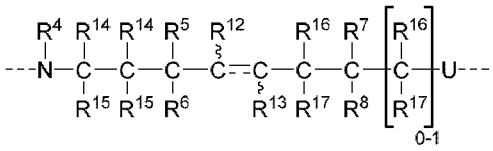
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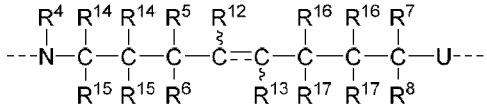
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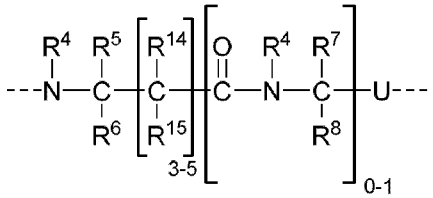
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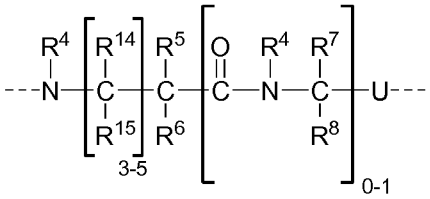
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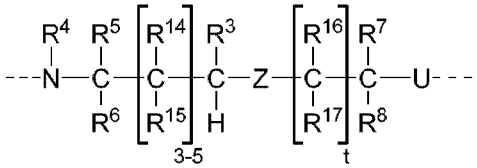
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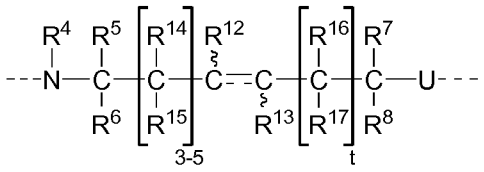


C47

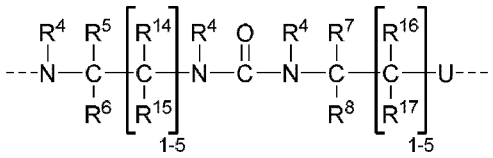


C48

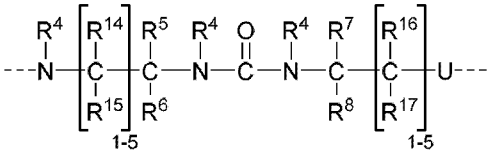




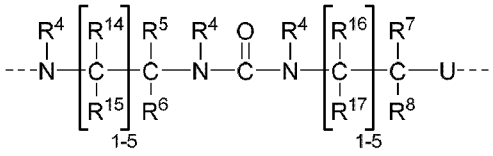
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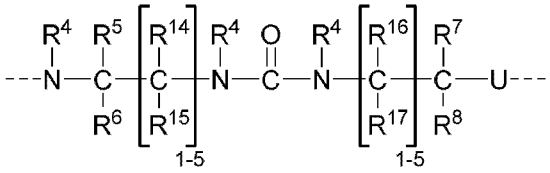
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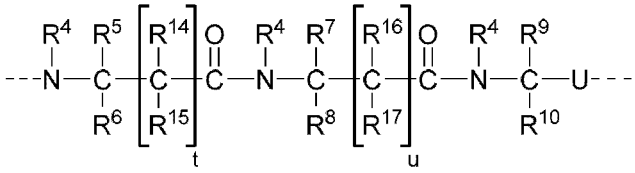
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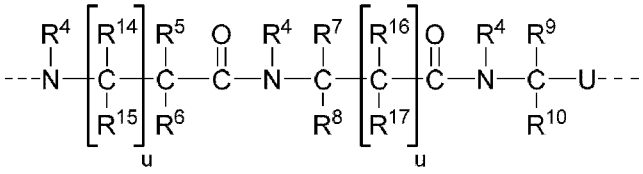
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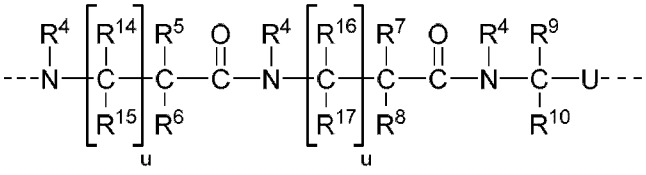
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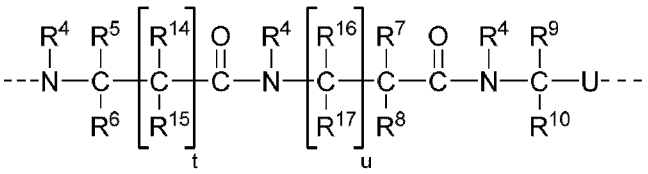
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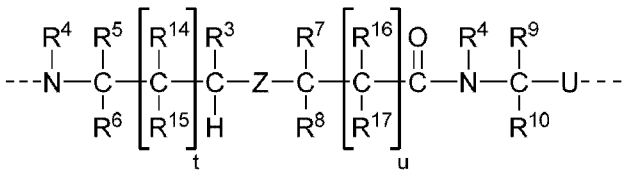
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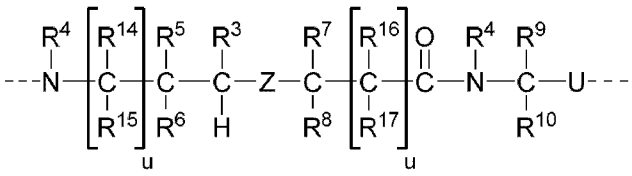
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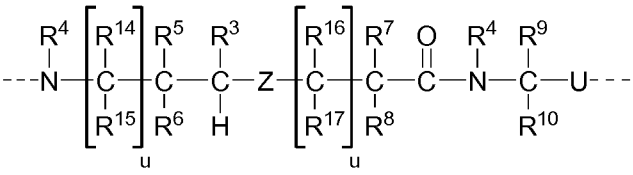
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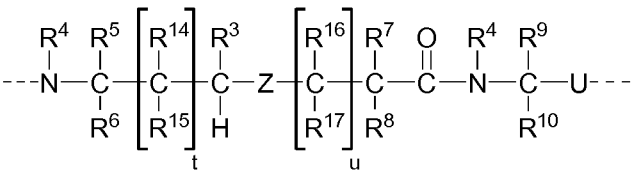
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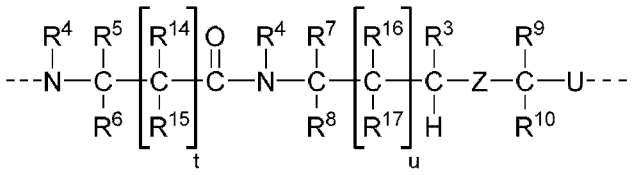
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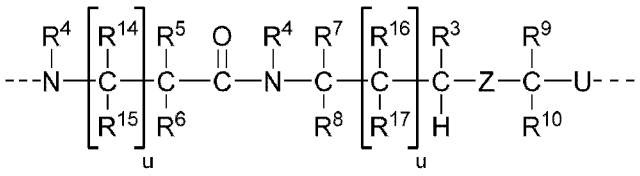
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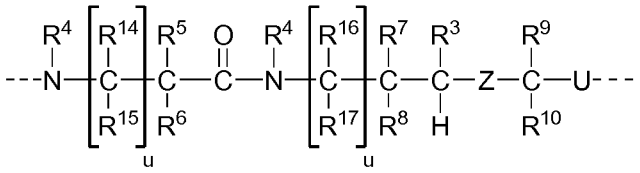
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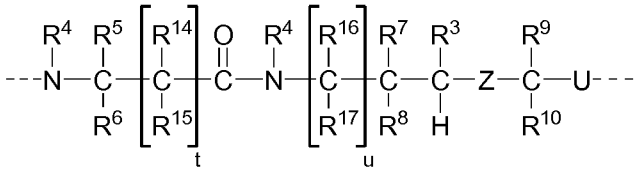
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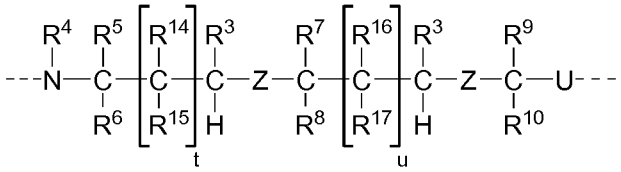
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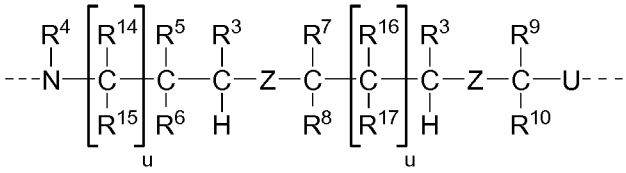
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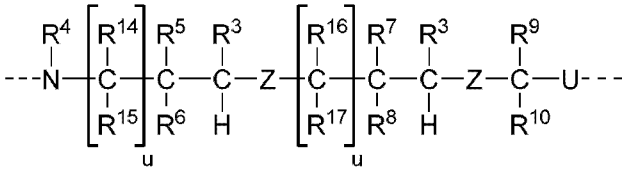
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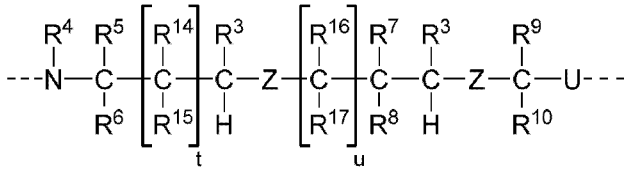
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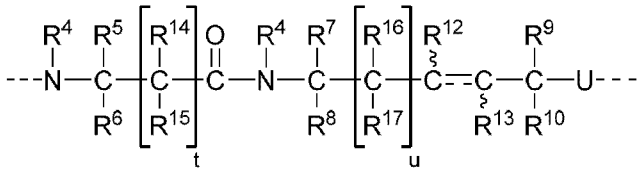
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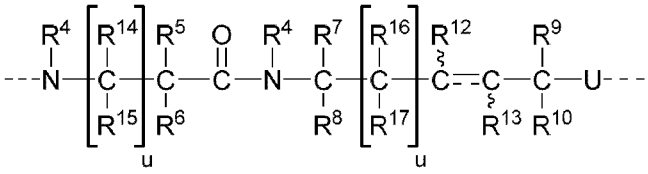
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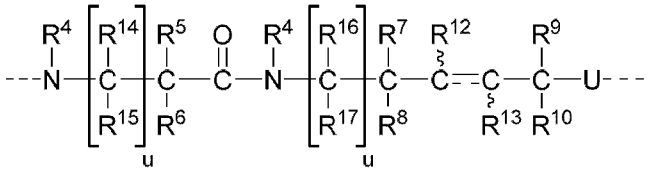
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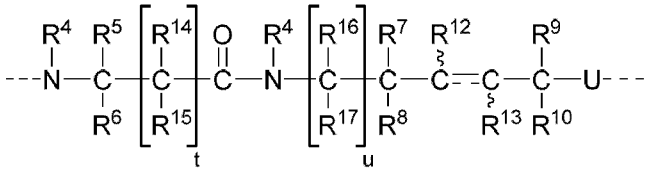
C70



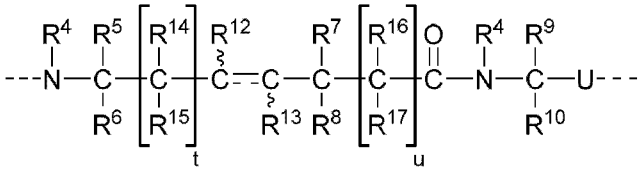
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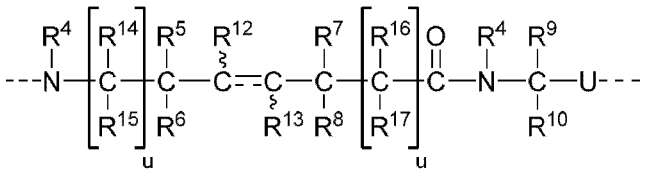
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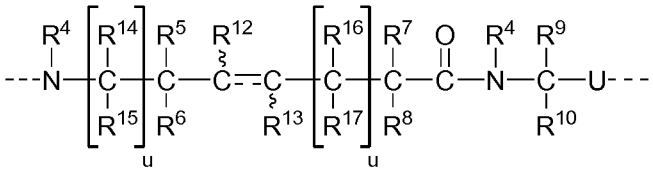
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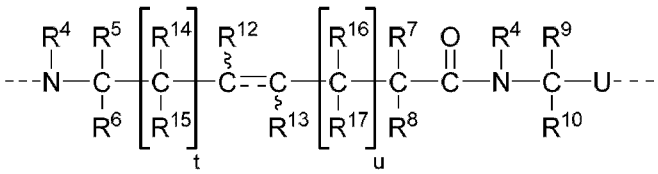
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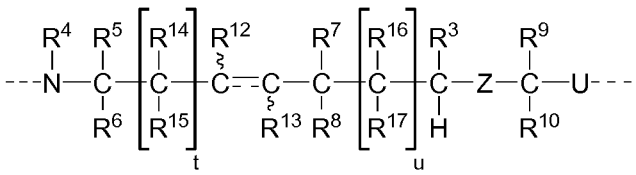
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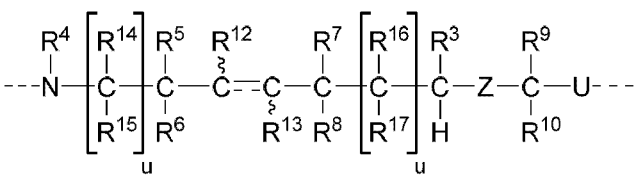
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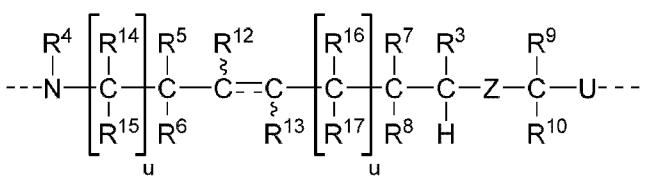
C77



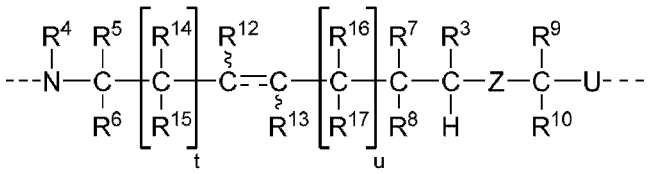
C78



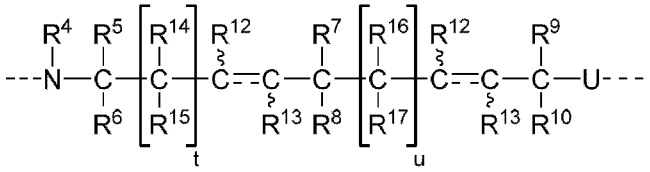
C79



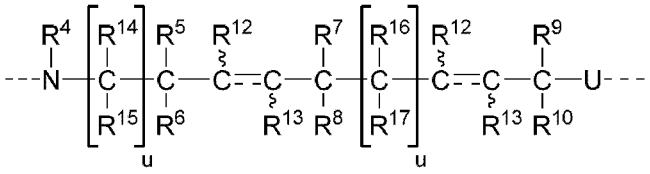
C80



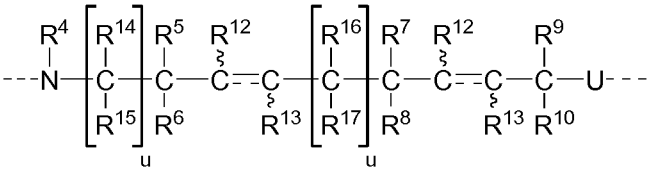
C81



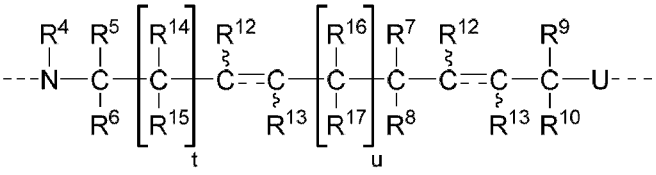
C82



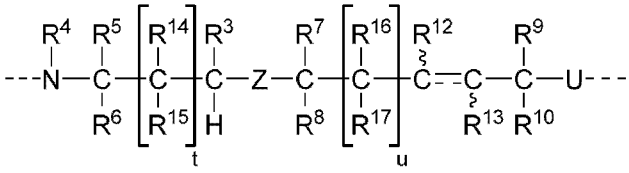
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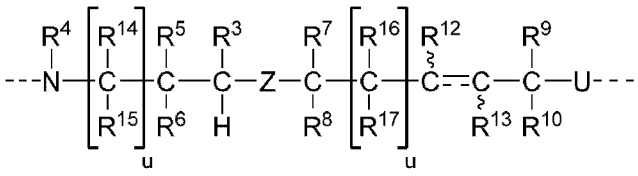
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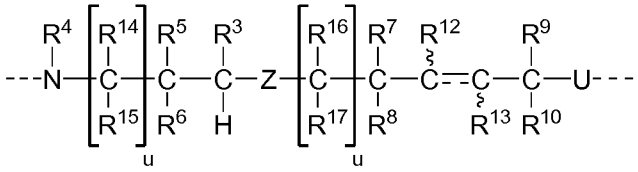
C85



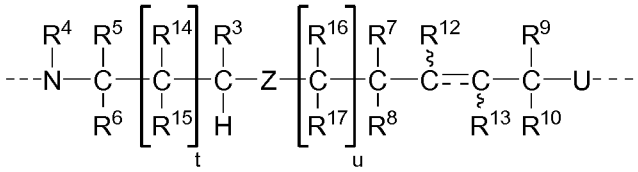
C86



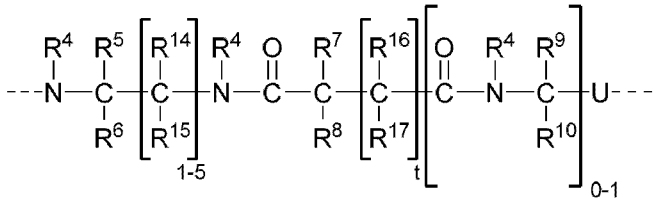
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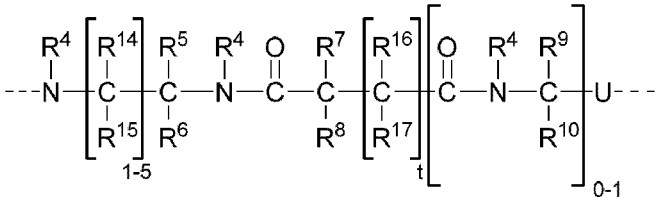
C88



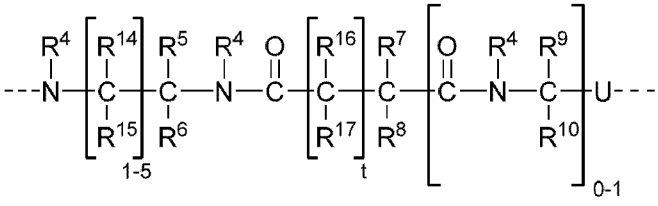
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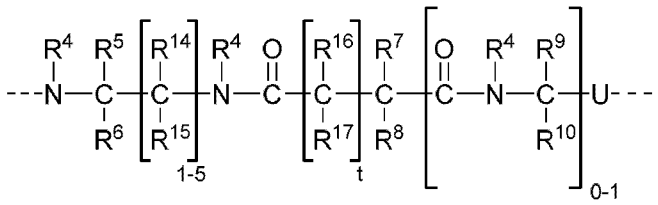
C90



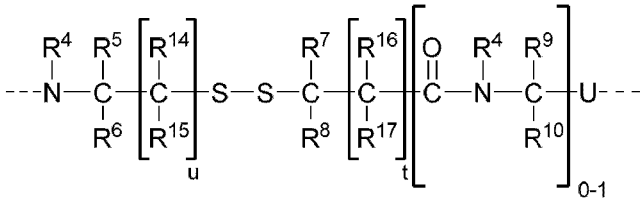
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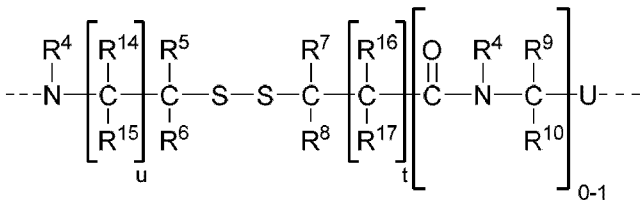
C92



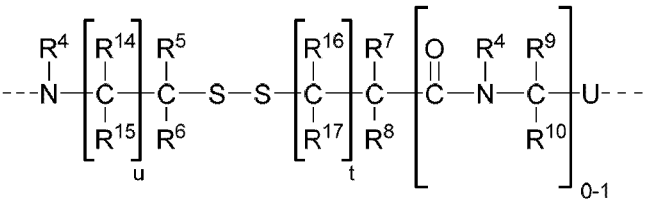
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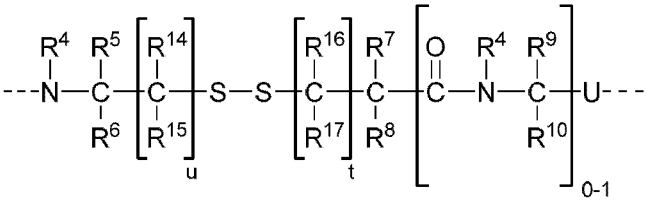
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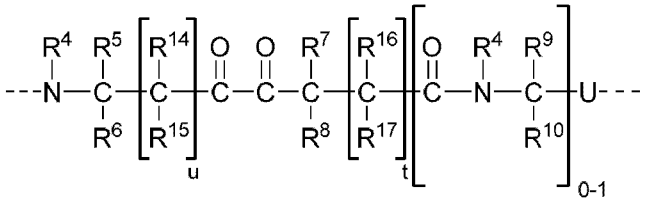
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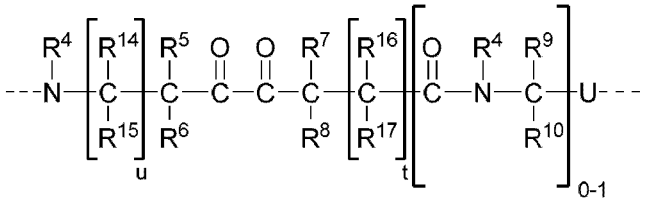
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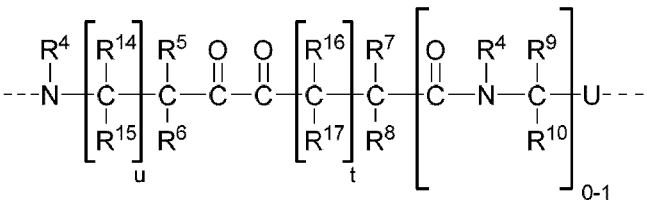
C97



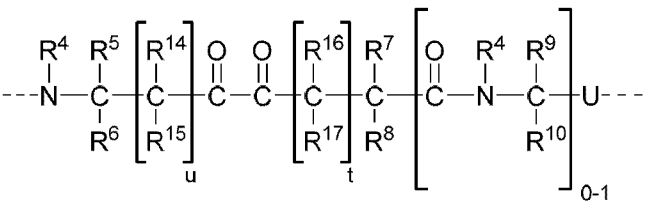
C98



C99



C100



C101

According to the preceding explanations, products of type **I** contain at least two amide bonds. As mentioned in the introduction, tertiary amide containing products generally show various ratios of *cis* and *trans* amide bond conformations in solution; this preference is in contrast to secondary amides that generally adopt *trans* conformations only. The occurrence of *cis* and/or *trans* conformations in macrocyclic natural products containing tertiary amides is well documented. In some cases a rapid equilibration between the *cis* and *trans* amide bonds, the so-called "peptidyl *cis/ trans* isomerization", is

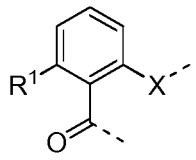
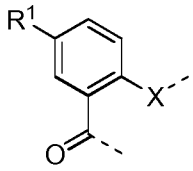
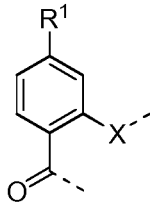
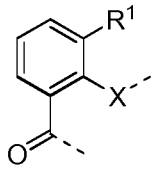
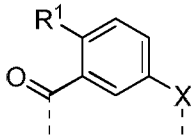
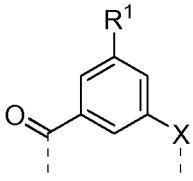
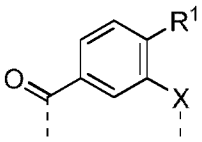
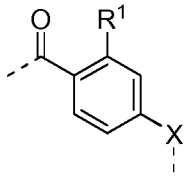
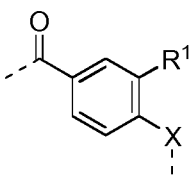
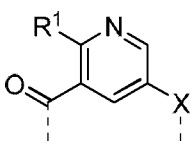
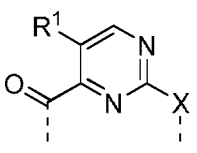
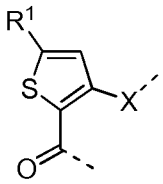
observed; whereas in other cases discrete *cis* and *trans* tertiary amide bonds are detected as two stable conformers in solution at room temperature.

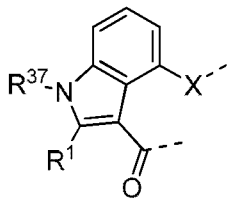
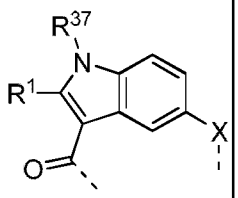
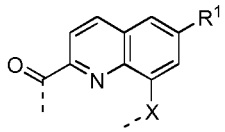
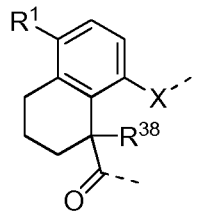
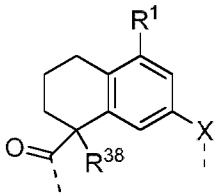
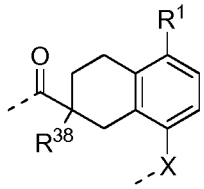
All possible stereoisomers, including atropisomers, and distinct conformers or rotamers of macrocycles of type **I** are part of this invention.

Within the general scope of building blocks **A** preferred radicals are:

Within the general scope of building blocks **A** preferred radicals are **A1**(a1); **A2**(a1); **A3**(a1); **A4**(a1); **A5**(a1); **A6**(a1); **A7**(a1); **A9**(a1); **A10**(a1); **A73**(a2); **A170**(a4); **A209**(a7); **A240**(a10); **A272**(a10); **A532**(a18); **A609**(a24); **A612**(a24) and **A614**(a24) (**Table 13**).

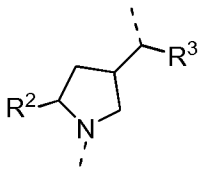
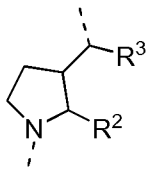
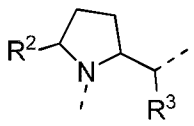
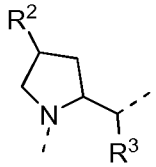
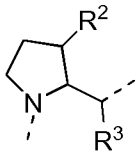
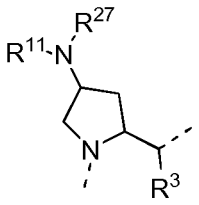
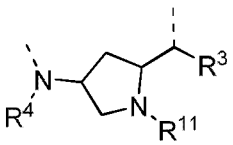
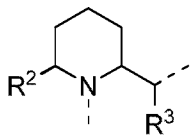
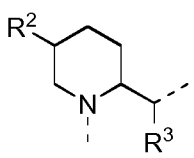
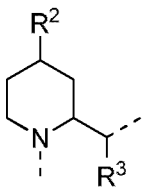
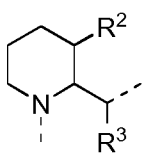
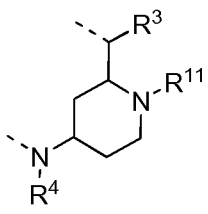
Table 13: Preferred Building Blocks of Type **A**

 **A1**(a1)	 **A2**(a1)	 **A3**(a1)	 **A4**(a1)
 **A5**(a1)	 **A6**(a1)	 **A7**(a1)	 **A9**(a1)
 **A10**(a1)	 **A73**(a2)	 **A170**(a4)	 **A209**(a7)

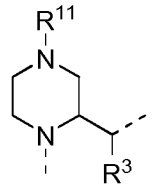
 **A240** (a10)	 **A272** (a10)	 **A532** (a18)	 **A609** (a24)
 **A612** (a24)	 **A614** (a24)		

Preferred building blocks of type **B** are **B4** (b3); **B5** (b3); **B6** (b3); **B7** (b3); **B8** (b3); **B9** (b3); **B10** (b3); **B12** (b4); **B13** (b4); **B14** (b4); **B15** (b4); **B16** (b4) and **B17** (b5) (**Table 14**).

Table 14: Preferred Building Blocks of Type **B**

 **B4** (b3)	 **B5** (b3)	 **B6** (b3)	 **B7** (b3)
 **B8** (b3)	 **B9** (b3)	 **B10** (b3)	 **B12** (b4)
			

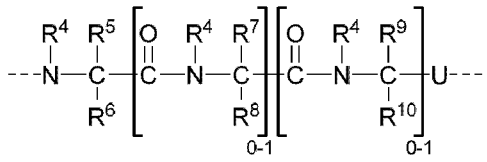
B13 (b4)	B14 (b4)	B15 (b4)	B16 (b4)



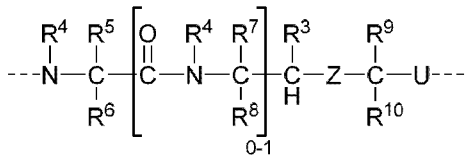
B17 (b5)

Preferred embodiments of linker **C** are shown in **Table 15.**

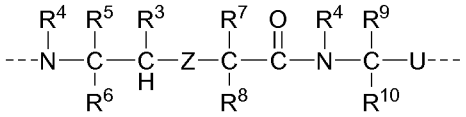
Table 15: Preferred Linker of type **C**



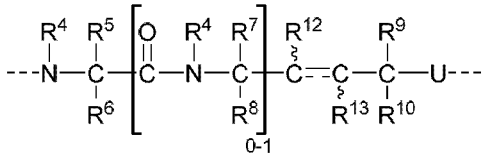
C1



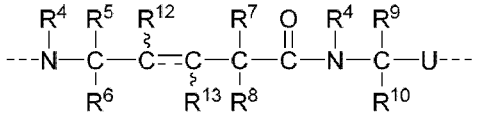
C2



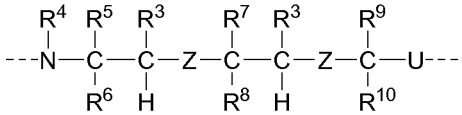
C3



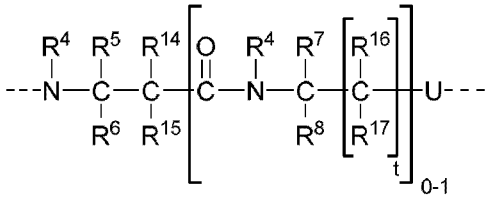
C4



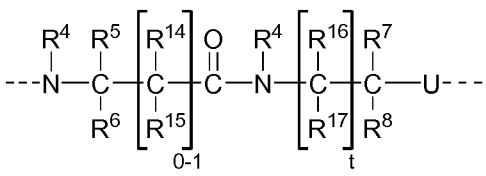
C5



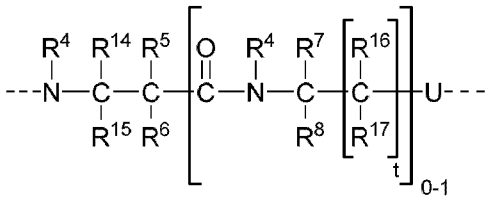
C6



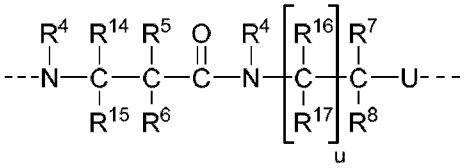
C7



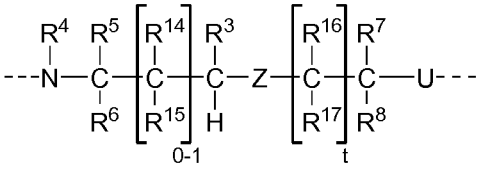
C8



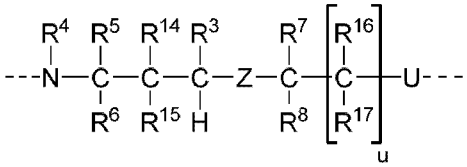
C9



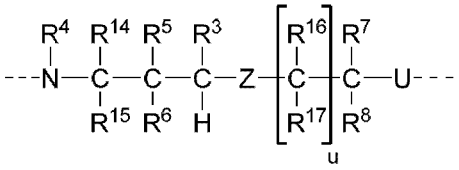
C10



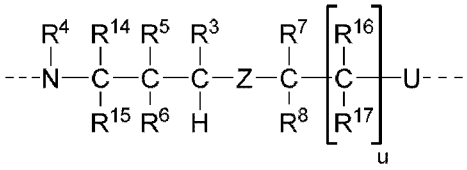
C11



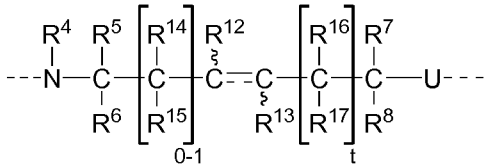
C12



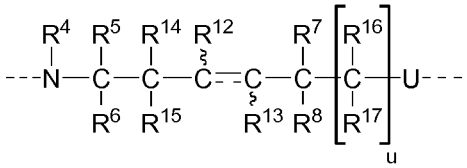
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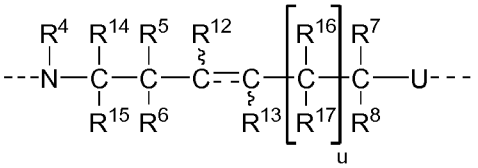
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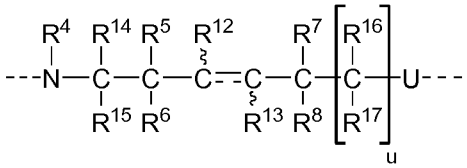
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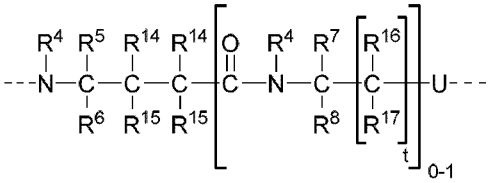
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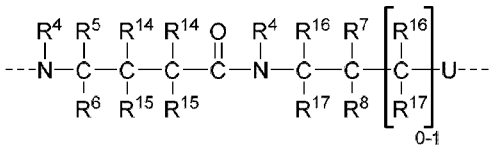
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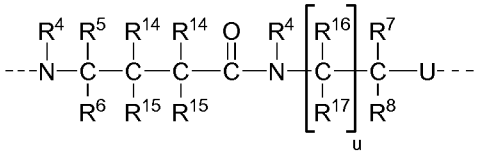
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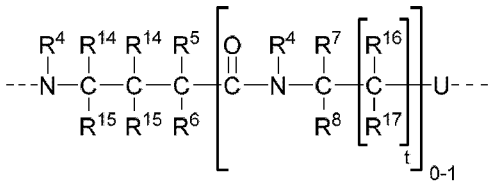
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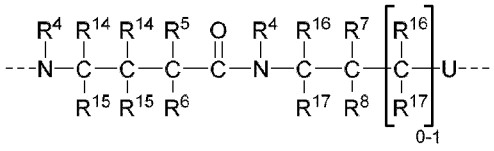
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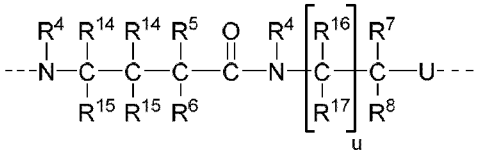
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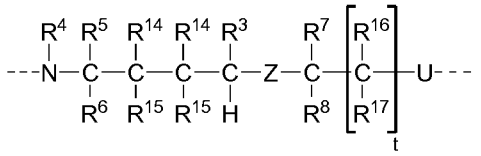
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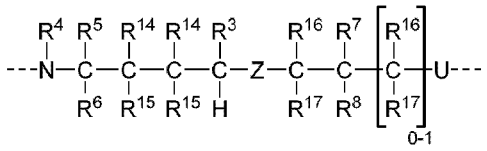
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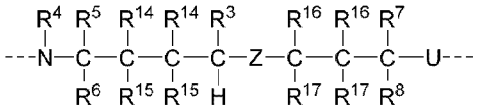
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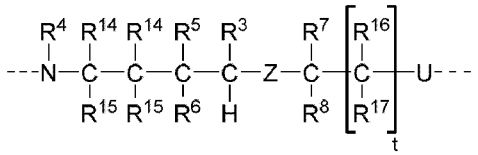
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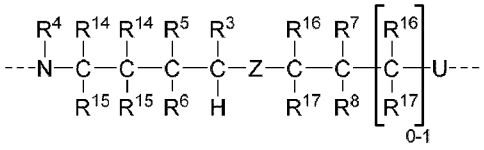
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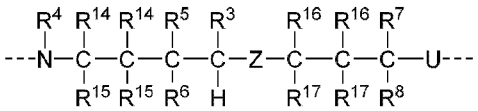
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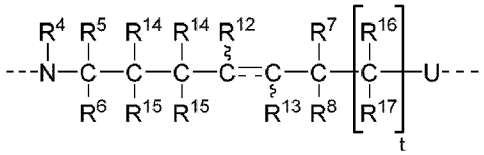
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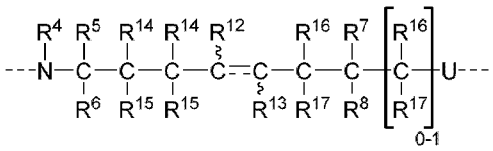
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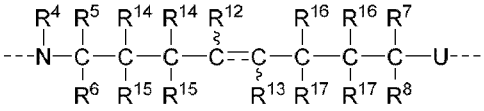
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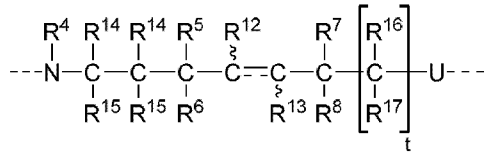


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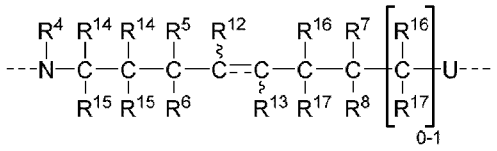


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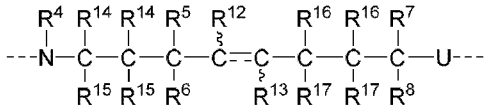




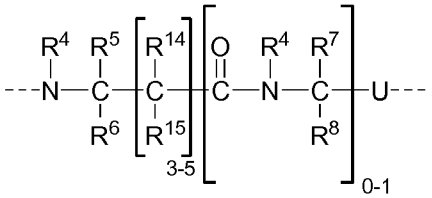
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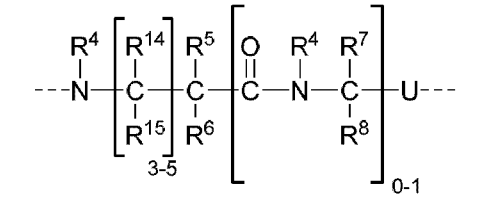
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C44



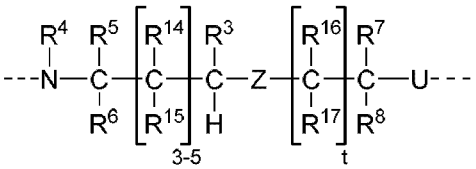
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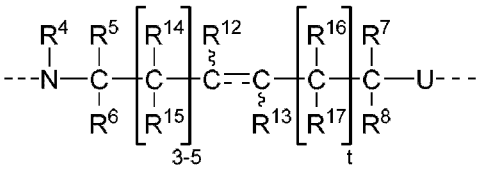
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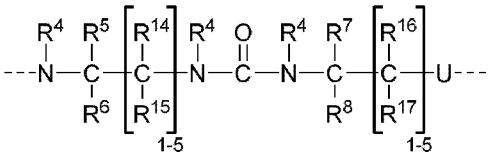
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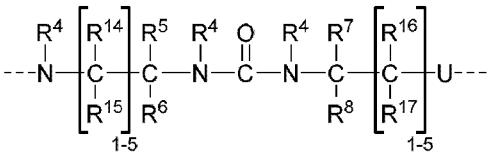
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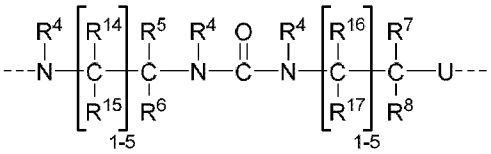
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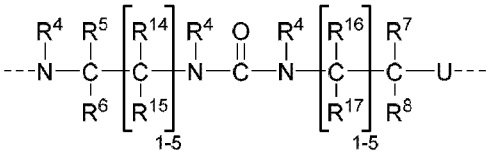
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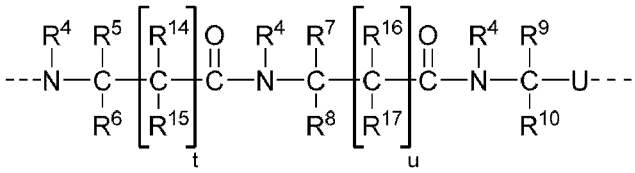
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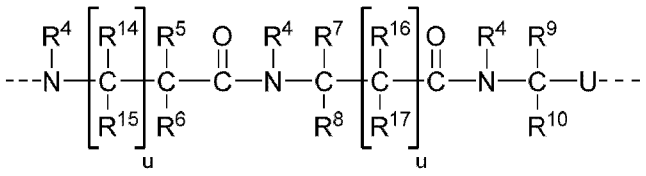


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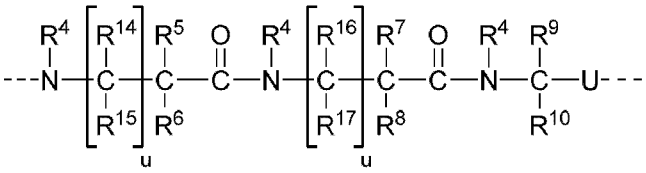


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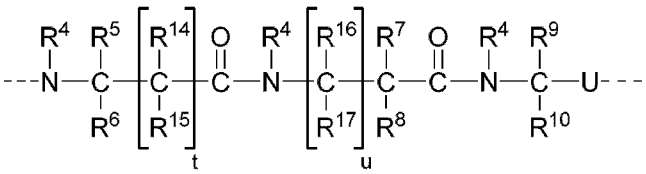




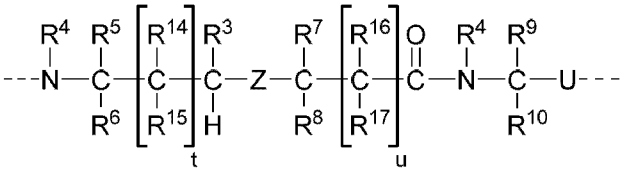
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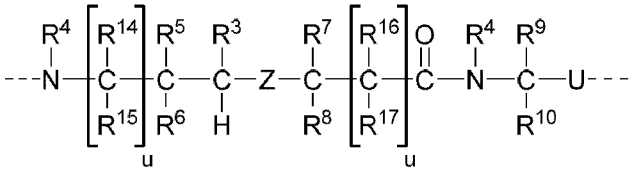
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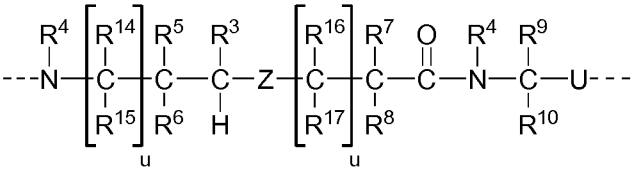
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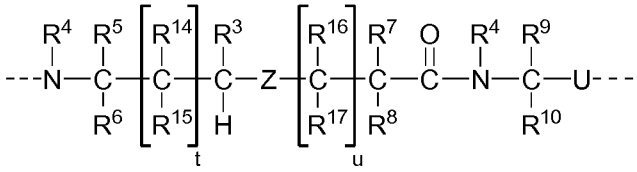
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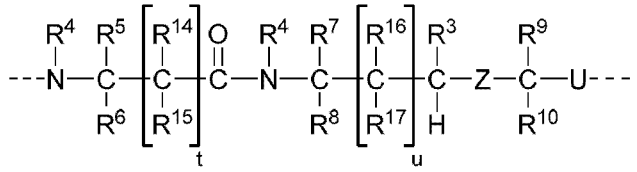
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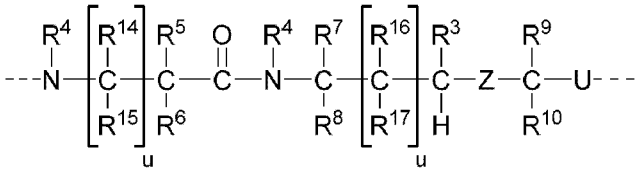
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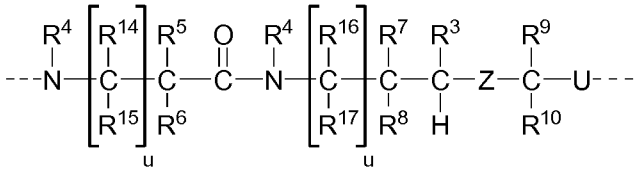
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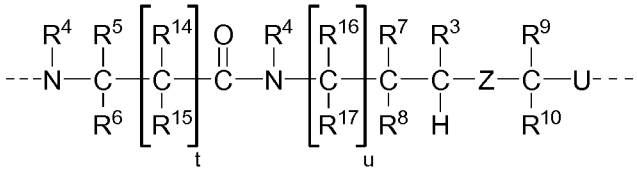
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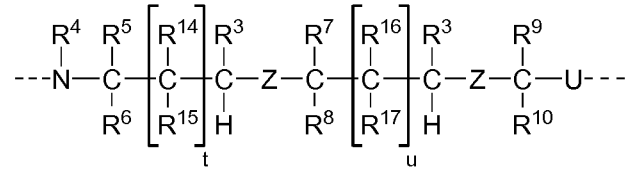
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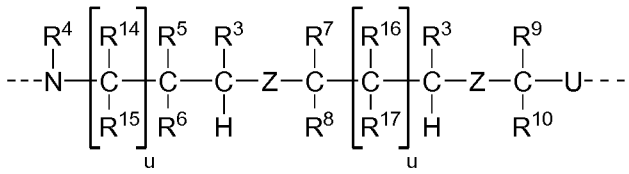
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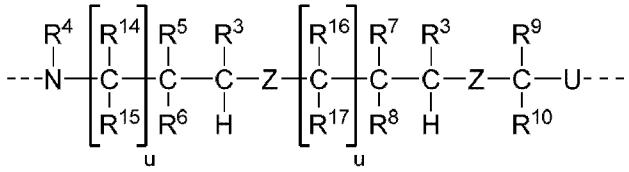
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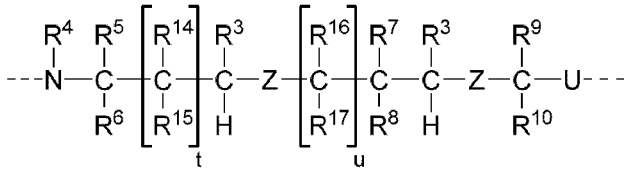
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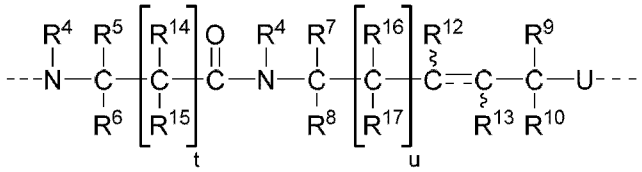
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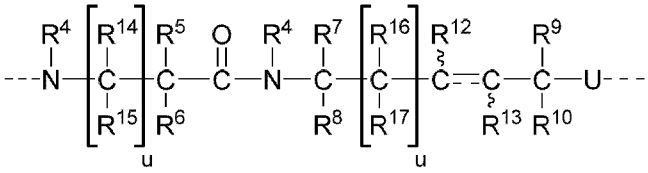
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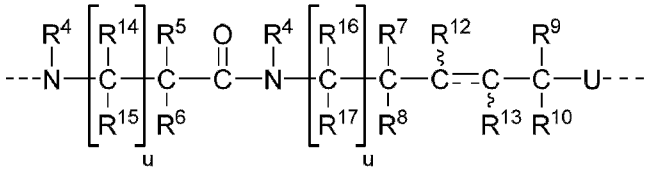
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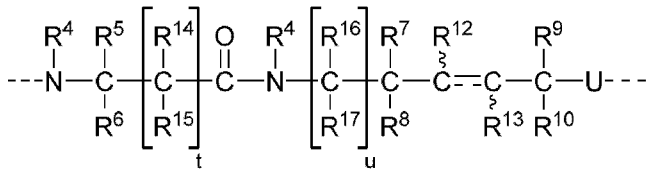
C70



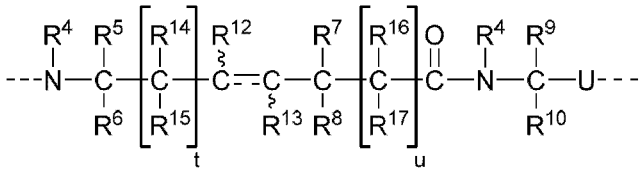
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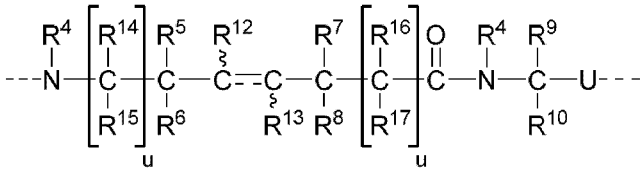
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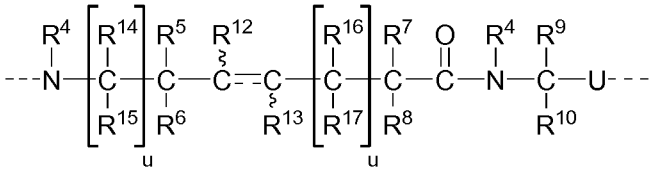
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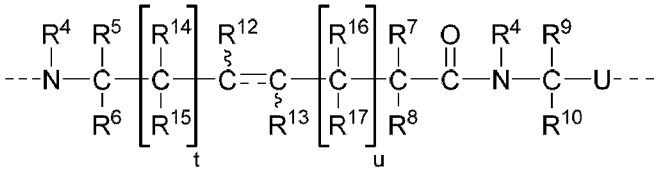
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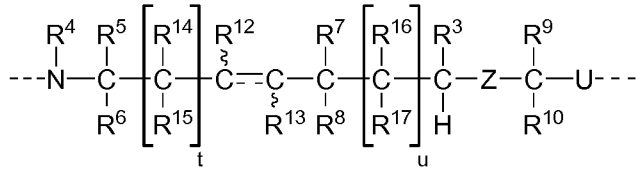
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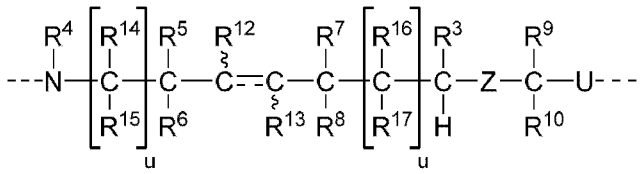
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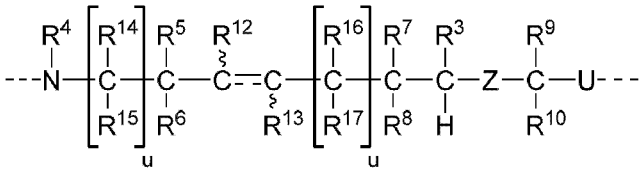
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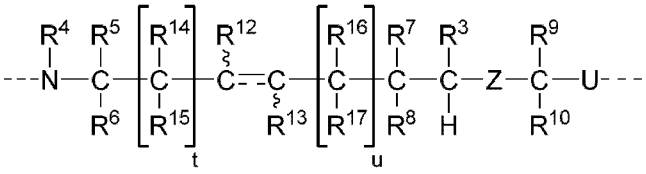
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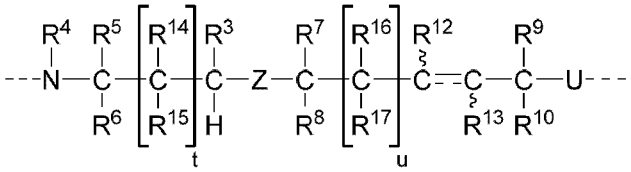
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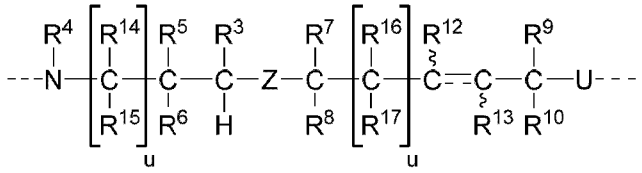
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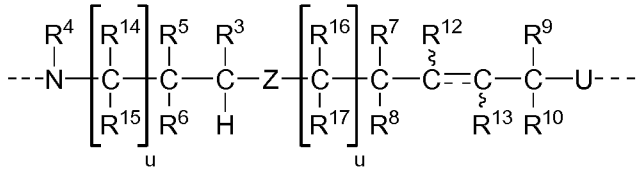
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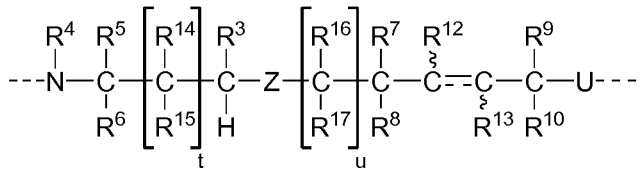
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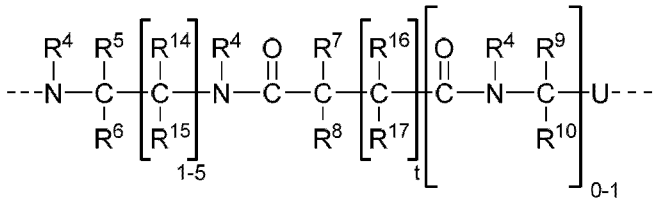
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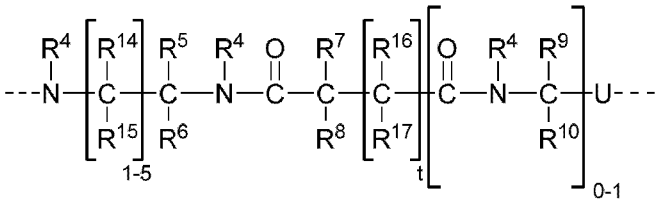
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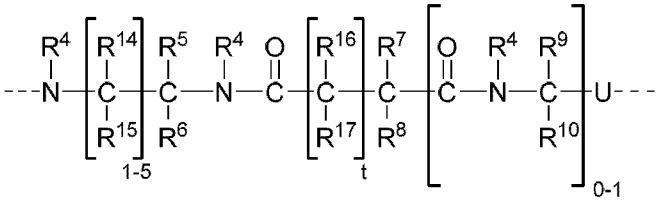
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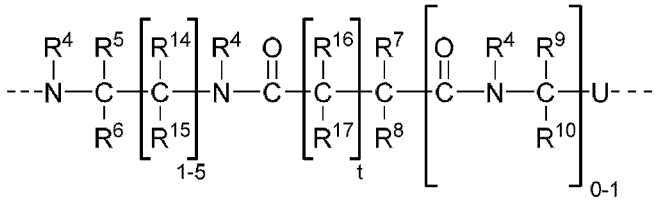
C90



C91



C92



C93

The preferred substituents of the preferred building blocks **A**, **B** and **C** are defined as:

R^1: H; F; Cl; Br; I; CF_3; OCF_3; $OCHF_2$; NO_2; CN; lower alkyl; lower alkenyl; lower alkynyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl;
$-(CR^{18}R^{19})_qOR^{20}$; $-(CR^{18}R^{19})_qNR^4R^{11}$; $-(CR^{18}R^{19})_qNR^4COOR^{21}$;
$-(CR^{18}R^{19})_qNR^4COR^{22}$; $-(CR^{18}R^{19})_qNR^4CONR^4R^{11}$; $-(CR^{18}R^{19})_qNR^4SO_2R^{23}$;
$-(CR^{18}R^{19})_qNR^4SO_2NR^4R^{11}$; $-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{11}$;
$-(CR^{18}R^{19})_qSO_2NR^4R^{11}$; $-(CR^{18}R^{19})_qPO(OR^{21})_2$; $-(CR^{18}R^{19})_qCOR^{22}$;
$-(CR^{18}R^{19})_qSO_2R^{23}$; $-(CR^{18}R^{19})_qOSO_3R^{21}$; $-(CR^{18}R^{19})_qR^{24}$; $-(CR^{18}R^{19})_qR^{25}$; or
$-(CR^{18}R^{19})_qR^{26}$.

R^2: H; CF_3; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl;
$-(CR^{18}R^{19})_qOR^{20}$; $-(CR^{18}R^{19})_qNR^4R^{11}$; $-(CR^{18}R^{19})_qNR^4COOR^{21}$;
$-(CR^{18}R^{19})_qNR^4COR^{22}$; $-(CR^{18}R^{19})_qNR^4CONR^4R^{11}$; $-(CR^{18}R^{19})_qNR^4SO_2R^{23}$;
$-(CR^{18}R^{19})_qNR^4SO_2NR^4R^{11}$;
$-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{11}$; $-(CR^{18}R^{19})_qSO_2NR^4R^{11}$;
$-(CR^{18}R^{19})_qPO(OR^{21})_2$; $-(CR^{18}R^{19})_qCOR^{22}$; $-(CR^{18}R^{19})_qSO_2R^{23}$;
$-(CR^{18}R^{19})_qR^{24}$; $-(CR^{18}R^{19})_qR^{25}$; or $-(CR^{18}R^{19})_qR^{26}$.

R^3: Defined as above.

R^4: H; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; or a suitable *N*-protecting group.

R^5, R^7 and R^9 are independently defined as: H; F; CF_3; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl;
$-(CR^{18}R^{19})_sOR^{20}$; $-(CR^{18}R^{19})_sNR^4R^{11}$; $-(CR^{18}R^{19})_sNR^4COOR^{21}$;
$-(CR^{18}R^{19})_sNR^4COR^{22}$; $-(CR^{18}R^{19})_sNR^4CONR^4R^{11}$; $-(CR^{18}R^{19})_sNR^4SO_2R^{23}$;
$-(CR^{18}R^{19})_sNR^4SO_2NR^4R^{11}$; $-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{11}$;
$-(CR^{18}R^{19})_qSO_2NR^4R^{11}$; $-(CR^{18}R^{19})_qPO(OR^{21})_2$; $-(CR^{18}R^{19})_qCOR^{22}$;
$-(CR^{18}R^{19})_qSO_2R^{23}$; $-(CR^{18}R^{19})_qR^{24}$; $-(CR^{18}R^{19})_qR^{25}$; or $-(CR^{18}R^{19})_qR^{26}$.

R^6, R^8 and R^{10} are independently defined as: H; CF_3; or lower alkyl.

R^{11}: H; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; a suitable protecting group; $-(CR^{18}R^{19})_rOR^{20}$; $-(CR^{18}R^{19})_rNR^4R^{27}$; $-(CR^{18}R^{19})_rNR^4COOR^{21}$; $-(CR^{18}R^{19})_rNR^4CONR^4R^{27}$; $-(CR^{18}R^{19})_rNR^4SO_2R^{23}$; $-(CR^{18}R^{19})_rNR^4SO_2NR^4R^{27}$; $-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{27}$; $-(CR^{18}R^{19})_qCOR^{22}$; $-(CR^{18}R^{19})_qSO_2R^{23}$; $-(CR^{18}R^{19})_qSO_2NR^4R^{27}$; $-(CR^{18}R^{19})_qR^{24}$; $-(CR^{18}R^{19})_sR^{25}$; or $-(CR^{18}R^{19})_qR^{26}$.

R^{12} and R^{13} are independently defined as H; or lower alkyl.

R^{14} and R^{16} are independently defined as: H; F; CF_3; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{18}R^{19})_sOR^{20}$; $-(CR^{18}R^{19})_sNR^4R^{11}$; $-(CR^{18}R^{19})_sNR^4COOR^{21}$; $-(CR^{18}R^{19})_sNR^4COR^{22}$; $-(CR^{18}R^{19})_sNR^4CONR^4R^{11}$; $-(CR^{18}R^{19})_sNR^4SO_2R^{23}$; $-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{11}$; $-(CR^{18}R^{19})_qCOR^{22}$.

R^{15} and R^{17} are independently defined as: H; CF_3; lower alkyl.

R^{18}: H; F; CF_3; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{29}R^{30})_sOR^{31}$; $-(CR^{29}R^{30})_sNR^{28}R^{31}$; $-(CR^{29}R^{30})_sNR^{28}COOR^{21}$; $-(CR^{29}R^{30})_sNR^{28}COR^{31}$; $-(CR^{29}R^{30})_sNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_sNR^{28}SO_2R^{23}$; $-(CR^{29}R^{30})_sNR^{28}SO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_qSO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qPO(OR^{21})_2$; $-(CR^{29}R^{30})_qCOR^{31}$; $-(CR^{29}R^{30})_qSO_2R^{23}$; $-(CR^{29}R^{30})_qR^{24}$; $-(CR^{29}R^{30})_qR^{25}$; or $-(CR^{29}R^{30})_qR^{26}$.

R^{19}: H; CF_3; or lower alkyl.

R^{20}: H; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{29}R^{30})_rOR^{31}$; $-(CR^{29}R^{30})_rNR^{28}R^{31}$; $-(CR^{29}R^{30})_rNR^{28}COOR^{21}$; $-(CR^{29}R^{30})_rNR^{28}COR^{31}$; $-(CR^{29}R^{30})_rNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_rNR^{28}SO_2R^{23}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_qSO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOR^{31}$; $-(CR^{29}R^{30})_qSO_2R^{23}$; $-(CR^{29}R^{30})_qR^{24}$; $-(CR^{29}R^{30})_qR^{25}$; or $-(CR^{29}R^{30})_qR^{26}$.

R^{21} and R^{23}: Defined as above.

R^{22}: lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{29}R^{30})_sOR^{31}$; $-(CR^{29}R^{30})_sNR^{28}R^{31}$; $-(CR^{29}R^{30})_sNR^{28}COOR^{21}$; $-(CR^{29}R^{30})_sNR^{28}COR^{31}$; $-(CR^{29}R^{30})_sNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_sNR^{28}SO_2R^{23}$; $-(CR^{29}R^{30})_sCOOR^{21}$; $-(CR^{29}R^{30})_sCONR^{28}R^{31}$; $-(CR^{29}R^{30})_sSO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_tCOR^{31}$; $-(CR^{29}R^{30})_sSO_2R^{23}$; $-(CR^{29}R^{30})_tR^{24}$; $-(CR^{29}R^{30})_tR^{25}$; or $-(CR^{29}R^{30})_tR^{26}$.

R^{24}, R^{25} and R^{26}: Defined as above.

R^{27} and R^{28}: Defined as above.

R^{29}: H; F; CF_3; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{32}R^{33})_sOR^{31}$; $-(CR^{32}R^{33})_sNR^{28}R^{31}$; $-(CR^{32}R^{33})_sNR^{28}COOR^{21}$; $-(CR^{32}R^{33})_sNR^{28}COR^{31}$; $-(CR^{32}R^{33})_sNR^{28}CONR^{28}R^{31}$; $-(CR^{32}R^{33})_sNR^{28}SO_2R^{23}$; $-(CR^{32}R^{33})_qCOOR^{21}$; $-(CR^{32}R^{33})_qCONR^{28}R^{31}$; $-(CR^{32}R^{33})_qSO_2NR^{28}R^{31}$; $-(CR^{32}R^{33})_qPO(OR^{21})_2$; $-(CR^{32}R^{33})_qCOR^{31}$; $-(CR^{32}R^{33})_qSO_2R^{23}$; $-(CR^{32}R^{33})_qR^{31}$.

R^{30} and R^{33}: H; CF_3; lower alkyl.

R^{31} and R^{32}: Defined as above.

R^{34} and R^{35} are independently defined as H; F; Cl; CF_3; OCF_3; $OCHF_2$; NO_2; CN; lower alkyl; lower alkenyl; lower alkynyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{29}R^{30})_qOR^{31}$; $-(CR^{29}R^{30})_qNR^{28}R^{31}$; $-(CR^{29}R^{30})_qNR^{28}COOR^{21}$; $-(CR^{29}R^{30})_qNR^{28}COR^{31}$; $-(CR^{29}R^{30})_qNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_qNR^{28}SO_2R^{23}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_qSO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOR^{31}$; $-(CR^{29}R^{30})_qSO_2R^{23}$; or $-(CR^{29}R^{30})_qR^{31}$.

R^{36}: Defined as above.

R^{37}: H; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; a suitable *N*-protecting group; $-(CR^{29}R^{30})_rOR^{31}$; $-(CR^{29}R^{30})_rNR^{28}R^{31}$; $-(CR^{29}R^{30})_rNR^{28}COOR^{21}$; $-(CR^{29}R^{30})_rNR^{28}COR^{31}$; $-(CR^{29}R^{30})_rNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_rNR^{28}SO_2R^{23}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_rSO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOR^{31}$; $-(CR^{29}R^{30})_qSO_2R^{23}$; or $-(CR^{29}R^{30})_qR^{31}$.

R^{38}: H; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{29}R^{30})_qOR^{31}$; $-(CR^{29}R^{30})_qNR^{28}R^{31}$; $-(CR^{29}R^{30})_qNR^{28}COOR^{21}$; $-(CR^{29}R^{30})_qNR^{28}COR^{31}$; $-(CR^{29}R^{30})_qNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOR^{31}$; or $-(CR^{29}R^{30})_qR^{31}$.

R^{39}; R^{40}; R^{41}; R^{42}; R^{43}; R^{44}; R^{45}; R^{46}; R^{47}; R^{48}; R^{49} and R^{50}: Defined as above.

In the aforementioned preferred structures the variable heteroatom Z and the connector U are defined as:

Z: O; S(=O); or $S(=O)_2$.

U: $-C(=O)-$; $-NR^4-C(=O)-$; $-C(=O)-C(=O)-$; or $-C(-OR^{20})_2-C(=O)-$.

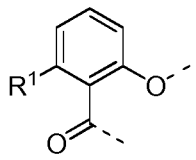
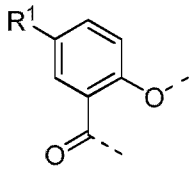
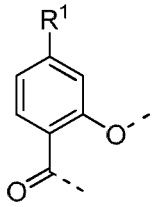
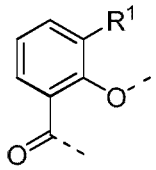
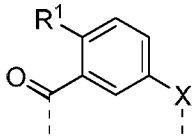
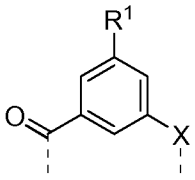
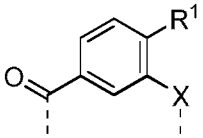
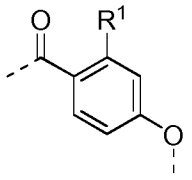
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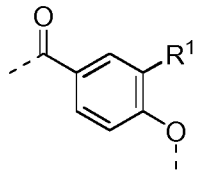
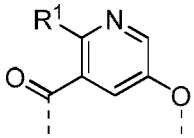
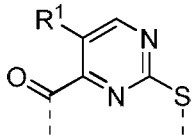
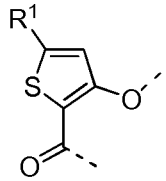
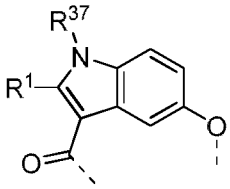
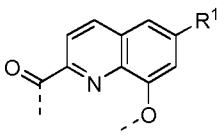
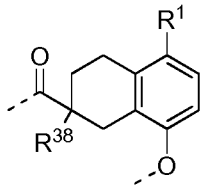
- Substituents that can be pairwise taken together and form optionally substituted cycloalkyl or heterocycloalkyl moieties.
- Structural elements that can form one of the groups of formulae **H111-H118** (**Table 9**).
- Variable heteroatoms Q, T, X and Y.
- Indices q-u.

The above preferred structures include all possible stereoisomers, explicitly also including rotamers and atropisomers, of macrocycles of type **I**.

Particularly preferred among the building blocks of type **A** are **A1**(a1); **A2**(a1); **A3**(a1); **A4**(a1); **A5**(a1); **A6**(a1); **A7**(a1); **A9**(a1); **A10**(a1); **A73**(a2); **A170**(a4); **A209**(a7); **A240**(a10); **A272**(a10); **A532**(a18); **A614**(a24). For most of these building blocks, oxygen is the preferred nucleophilic moiety. However in the case of **A170** it consists of a sulfur atom; and in the case of the three building blocks **A5-A7**, both oxygen and sulfur derivatives are part of the invention (**Table 16**).

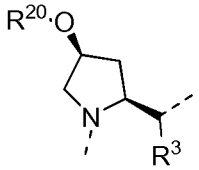
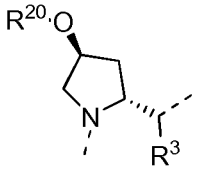
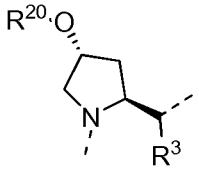
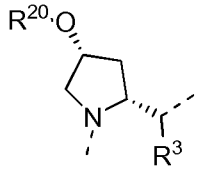
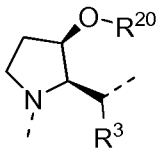
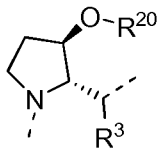
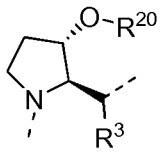
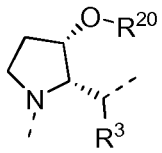
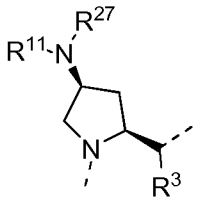
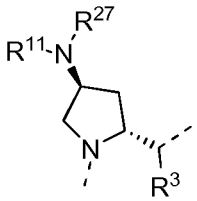
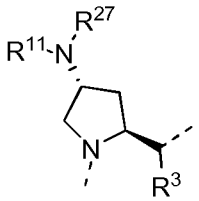
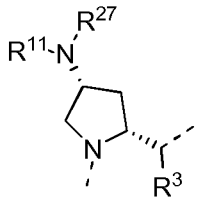
Table 16: Particularly Preferred Building Blocks of Type **A**

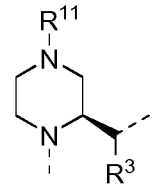
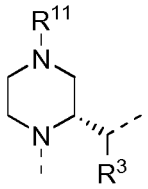
 **A1**(a1)	 **A2**(a1)	 **A3**(a1)	 **A4**(a1)
 **A5**(a1)	 **A6**(a1)	 **A7**(a1)	 **A9**(a1)

 **A10** (a1)	 **A73** (a2)	 **A170** (a4)	 **A209** (a7)
 **A272** (a10)	 **A532** (a18)	 **A614** (a24)	

Among the building blocks of type **B** particularly preferred are **B7, B8, B9** and **B-17** as shown in **Table 17.**

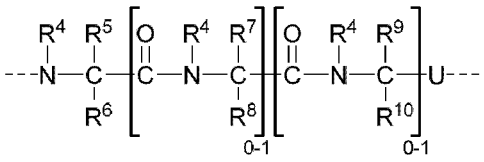
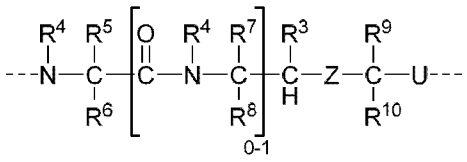
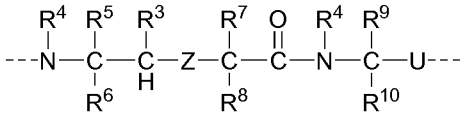
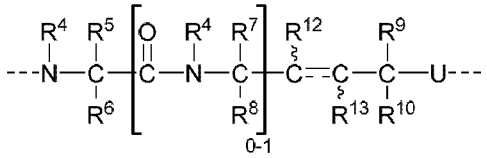
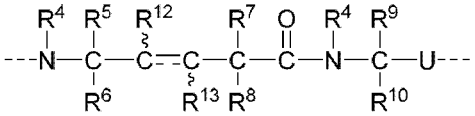
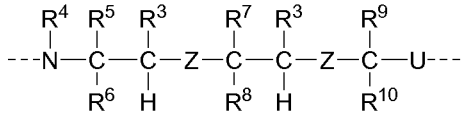
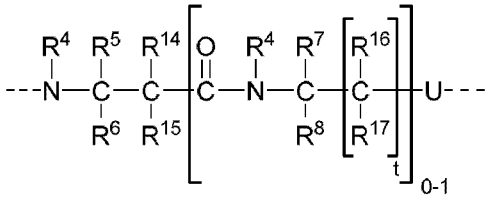
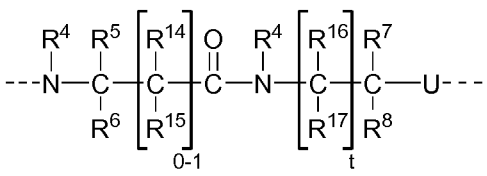
Table 17: Particularly Preferred Building Blocks of Type **B**

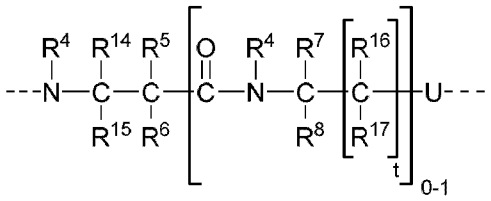
 **B7-1**	 **B7-2**	 **B7-3**	 **B7-4**
 **B8-1**	 **B8-2**	 **B8-3**	 **B8-4**
 **B9-1**	 **B9-2**	 **B9-3**	 **B9-4**

 B17-1	 B17-2

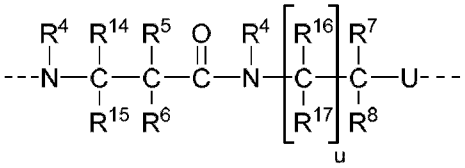
Particularly preferred embodiments of the linker **C** are listed in **Table 18.**

Table 18: Particularly Preferred Embodiments of Linker **C**

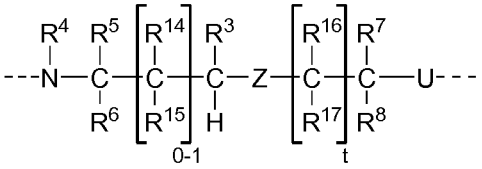
 C1	 C2
 C3	 C4
 C5	 C6
 C7	 C8



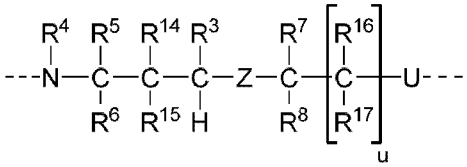
C9



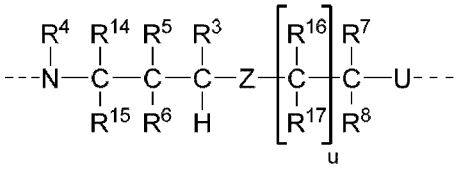
C10



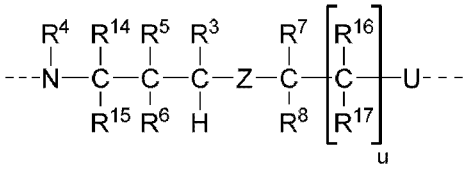
C11



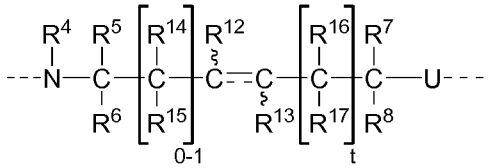
C12



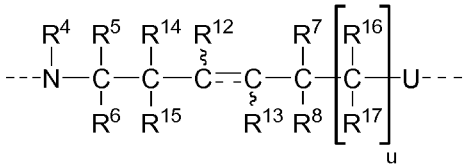
C13



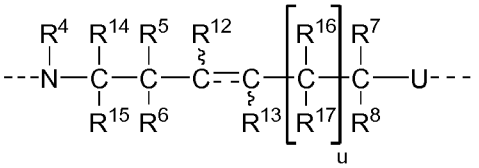
C14



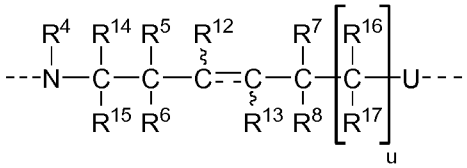
C15



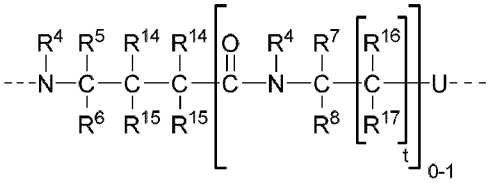
C16



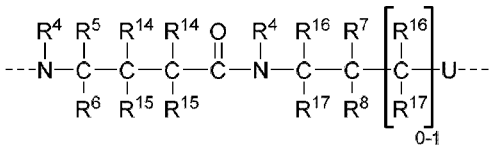
C17



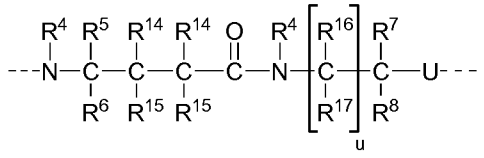
C18



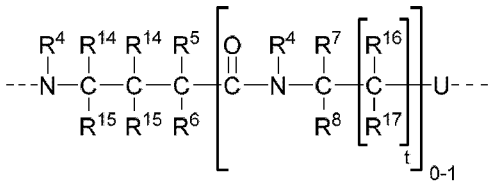
C19



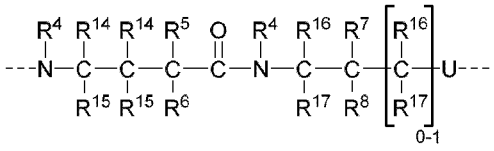
C20



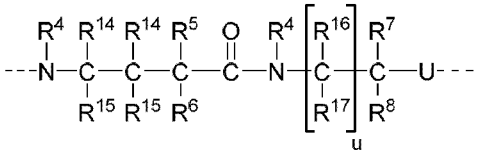
C21



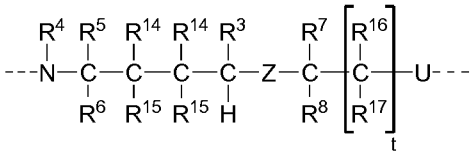
C25



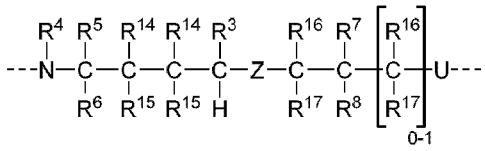
C26



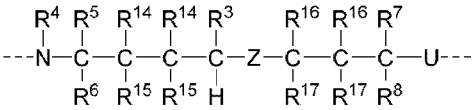
C27



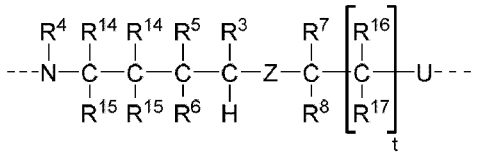
C28



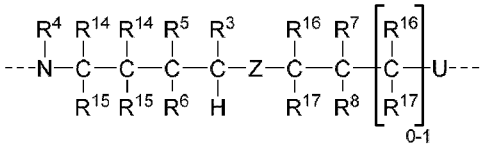
C29



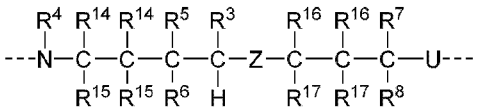
C30



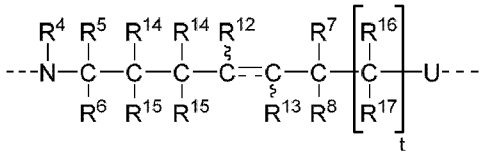
C34



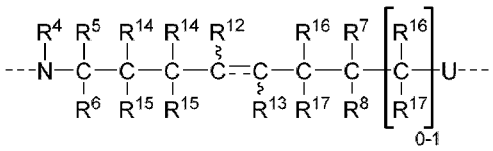
C35



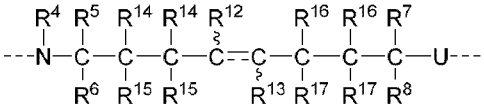
C36

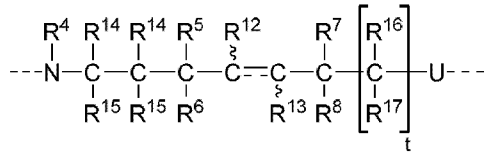


C37

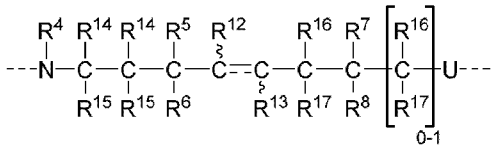


C38

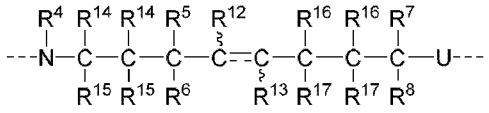




C39

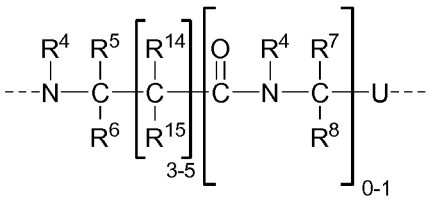


C43

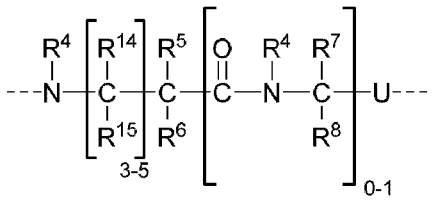


C44

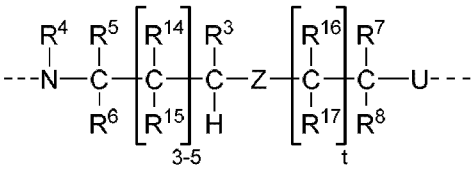
C45



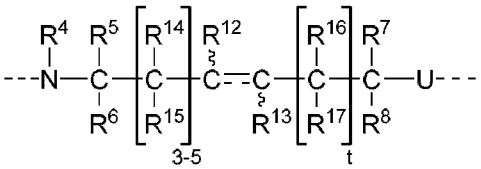
C46



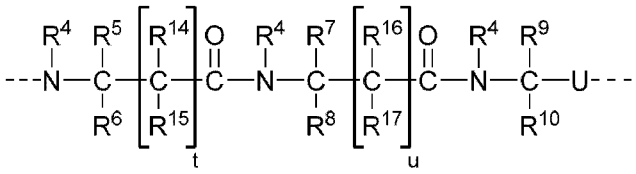
C47



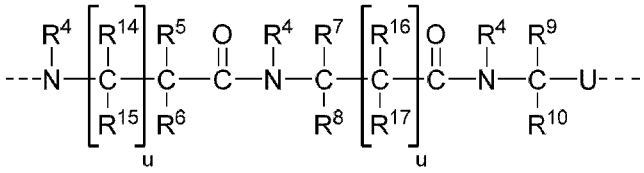
C48



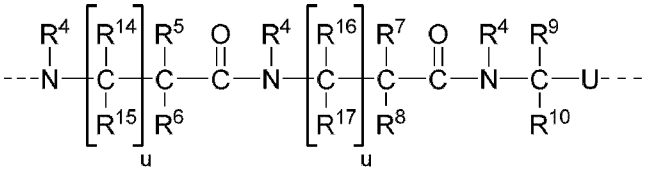
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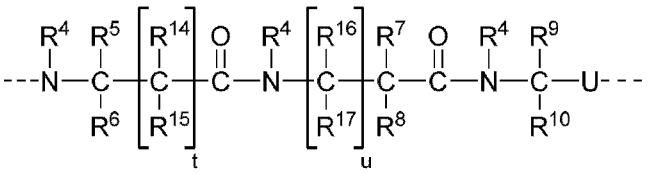
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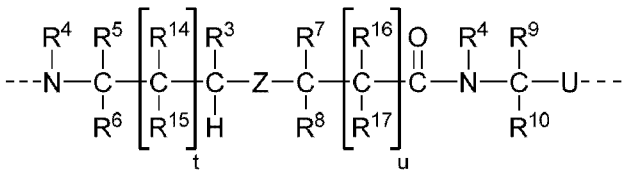
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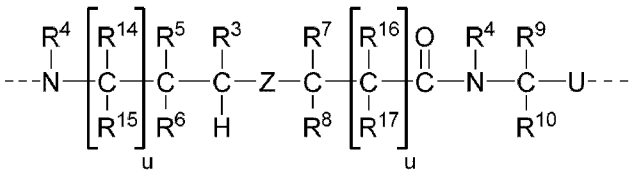
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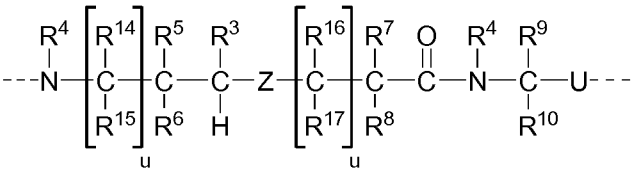
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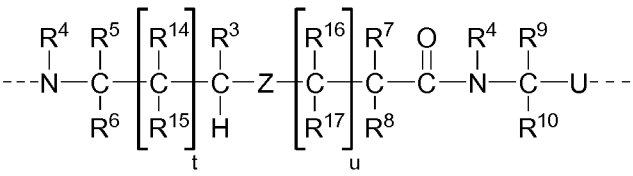
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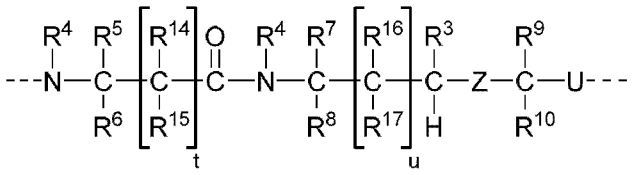
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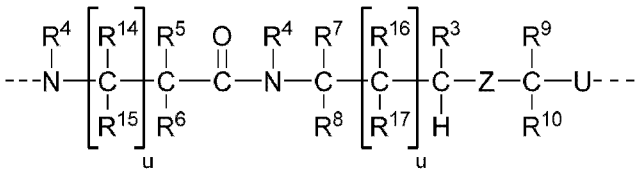
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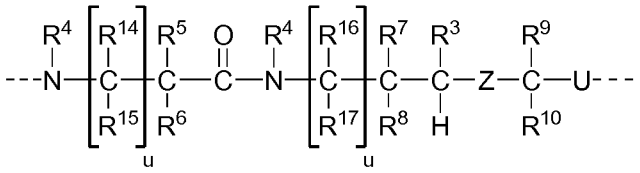
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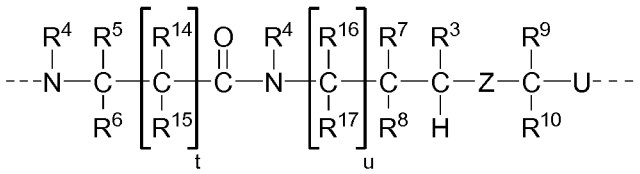
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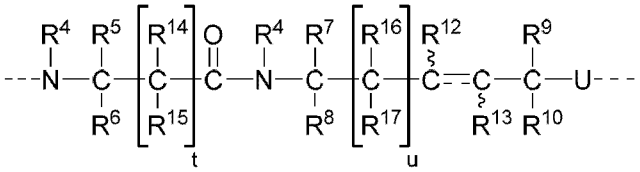
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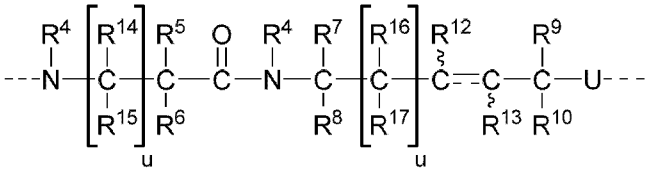
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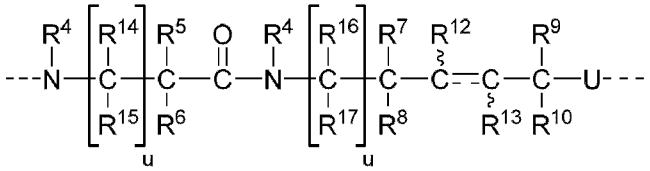
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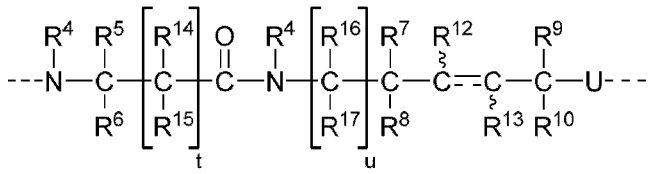
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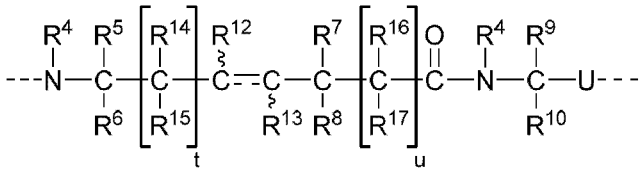
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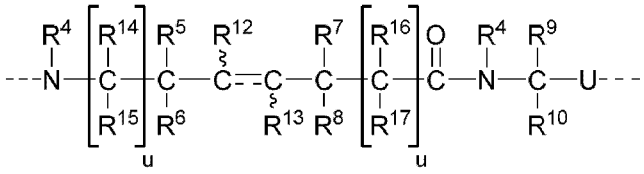
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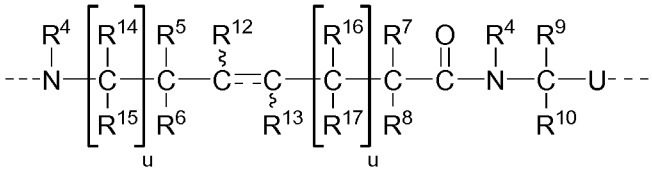
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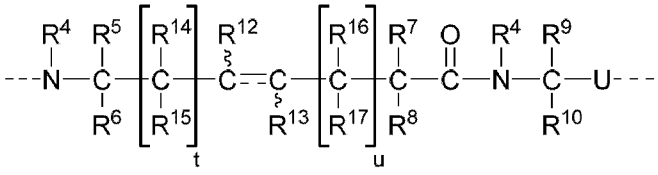
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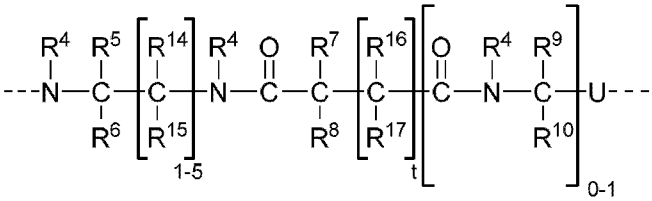
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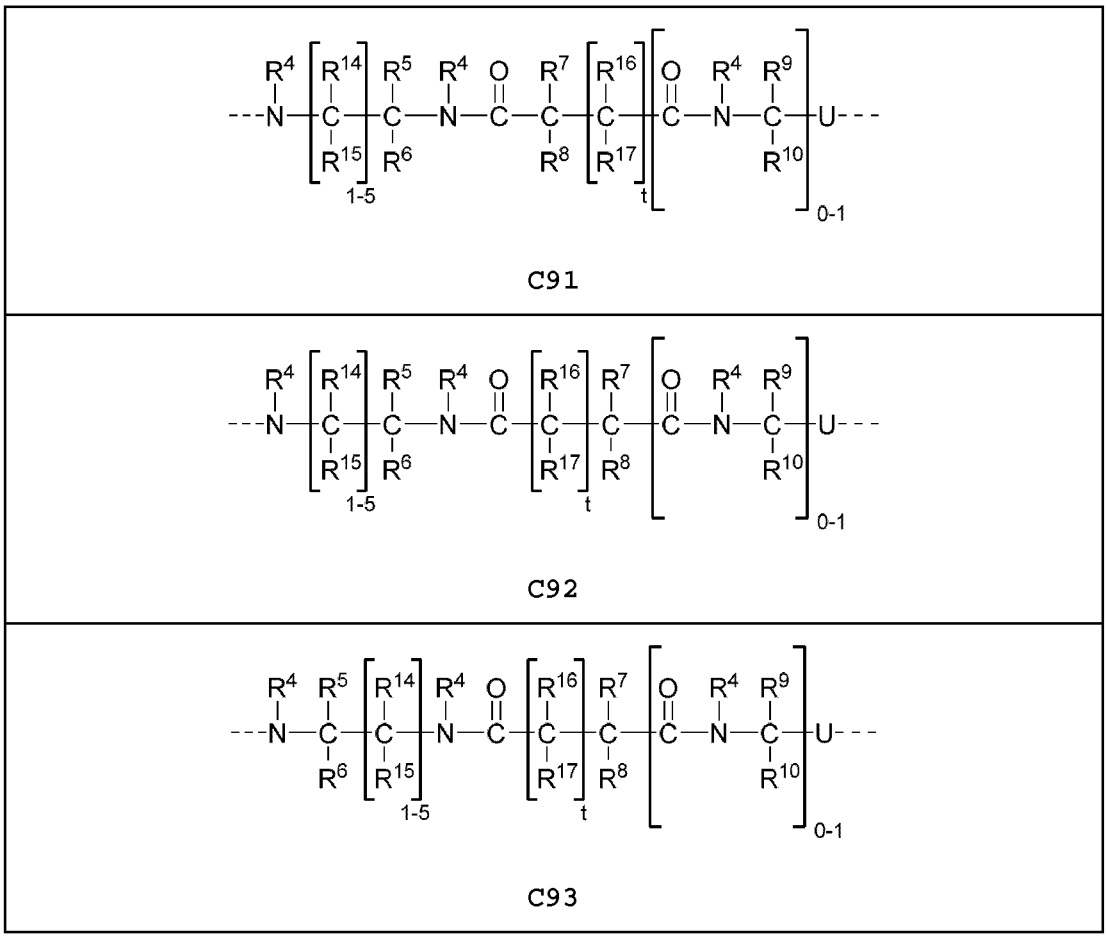
C76



C77



C90



C91

C92

C93

The particularly preferred substituents on the particularly preferred building blocks **A**, **B** and **C** are defined as:

R^1: H; F; Cl; CF_3; OCF_3; $OCHF_2$; NO_2; CN; lower alkyl; lower alkenyl; lower alkynyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl;
$-(CR^{18}R^{19})_qOR^{20}$; $-(CR^{18}R^{19})_qNR^4R^{11}$; $-(CR^{18}R^{19})_qNR^4COR^{22}$; $-(CR^{18}R^{19})_qNR^4CONR^4R^{11}$; $-(CR^{18}R^{19})_qNR^4SO_2R^{23}$; $-(CR^{18}R^{19})_qNR^4SO_2NR^4R^{11}$; $-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{11}$; $-(CR^{18}R^{19})_qSO_2NR^4R^{11}$; $-(CR^{18}R^{19})_qCOR^{22}$; $-(CR^{18}R^{19})_qSO_2R^{23}$; $-(CR^{18}R^{19})_qR^{24}$; $-(CR^{18}R^{19})_qR^{25}$; or $-(CR^{18}R^{19})_qR^{26}$.

R^2: H; CF_3; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl;

lower heteroarylalkyl; -$(CR^{18}R^{19})_qOR^{20}$; -$(CR^{18}R^{19})_qNR^4R^{11}$; -$(CR^{18}R^{19})_qNR^4COR^{22}$; -$(CR^{18}R^{19})_qNR^4CONR^4R^{11}$; -$(CR^{18}R^{19})_qNR^4SO_2R^{23}$; -$(CR^{18}R^{19})_qNR^4SO_2NR^4R^{11}$; -$(CR^{18}R^{19})_qCOOR^{21}$; -$(CR^{18}R^{19})_qCONR^4R^{11}$; -$(CR^{18}R^{19})_qSO_2NR^4R^{11}$; -$(CR^{18}R^{19})_qCOR^{22}$; -$(CR^{18}R^{19})_qSO_2R^{23}$; -$(CR^{18}R^{19})_qR^{24}$; -$(CR^{18}R^{19})_qR^{25}$; or -$(CR^{18}R^{19})_qR^{26}$.

R^3: Defined as earlier hereinabove.

R^4: H; lower alkyl; lower alkenyl; or a suitable *N*-protecting group.

R^5, R^7 and R^9 are independently defined as: H; CF_3; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; -$(CR^{18}R^{19})_sOR^{20}$; -$(CR^{18}R^{19})_sNR^4R^{11}$; -$(CR^{18}R^{19})_sNR^4COR^{22}$; -$(CR^{18}R^{19})_sNR^4CONR^4R^{11}$; -$(CR^{18}R^{19})_sNR^4SO_2R^{23}$; -$(CR^{18}R^{19})_qCOOR^{21}$; -$(CR^{18}R^{19})_qCONR^4R^{11}$; -$(CR^{18}R^{19})_qSO_2NR^4R^{11}$; -$(CR^{18}R^{19})_qCOR^{22}$; -$(CR^{18}R^{19})_qSO_2R^{23}$; -$(CR^{18}R^{19})_qR^{24}$; -$(CR^{18}R^{19})_qR^{25}$; or -$(CR^{18}R^{19})_qR^{26}$.

R^6, R^8 and R^{10} are independently defined as: H; CF_3; or CH_3.

R^{11}: H; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; a suitable protecting group; -$(CR^{18}R^{19})_rOR^{20}$; -$(CR^{18}R^{19})_rNR^4R^{27}$; -$(CR^{18}R^{19})_rNR^4CONR^4R^{27}$; -$(CR^{18}R^{19})_rNR^4SO_2R^{23}$; -$(CR^{18}R^{19})_qCOOR^{21}$; -$(CR^{18}R^{19})_qCONR^4R^{27}$; -$(CR^{18}R^{19})_qCOR^{22}$; -$(CR^{18}R^{19})_qR^{24}$; -$(CR^{18}R^{19})_sR^{25}$; or -$(CR^{18}R^{19})_qR^{26}$.

R^{12} and R^{13} are independently defined as H; or lower alkyl.

R^{14} and R^{16} are independently defined as: H; F; CF_3; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl;

aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{18}R^{19})_sOR^{20}$; $-(CR^{18}R^{19})_sNR^4R^{11}$; $-(CR^{18}R^{19})_sNR^4COR^{22}$; $-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{11}$.

R^{15} and R^{17} are independently defined as: H; CF_3; or CH_3.

R^{18}: H; F; CF_3; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{29}R^{30})_sOR^{31}$; $-(CR^{29}R^{30})_sNR^{28}R^{31}$; $-(CR^{29}R^{30})_sNR^{28}COR^{31}$; $-(CR^{29}R^{30})_sNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_sNR^{28}SO_2R^{23}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_qSO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOR^{31}$; $-(CR^{29}R^{30})_qSO_2R^{23}$; $-(CR^{29}R^{30})_qR^{24}$; $-(CR^{29}R^{30})_qR^{25}$; or $-(CR^{29}R^{30})_qR^{26}$.

R^{19}: H; CF_3; or CH_3.

R^{20}: H; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{29}R^{30})_rOR^{31}$; $-(CR^{29}R^{30})_rNR^{28}R^{31}$; $-(CR^{29}R^{30})_rNR^{28}COR^{31}$; $-(CR^{29}R^{30})_rNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_rNR^{28}SO_2R^{23}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_qSO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOR^{31}$; $-(CR^{29}R^{30})_qSO_2R^{23}$; $-(CR^{29}R^{30})_qR^{24}$; $-(CR^{29}R^{30})_qR^{25}$; or $-(CR^{29}R^{30})_qR^{26}$.

R^{21} and R^{23}: Defined as above

R^{22}: lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{29}R^{30})_sOR^{31}$; $-(CR^{29}R^{30})_sNR^{28}R^{31}$; $-(CR^{29}R^{30})_sNR^{28}COR^{31}$; $-(CR^{29}R^{30})_sNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_sNR^{28}SO_2R^{23}$; $-(CR^{29}R^{30})_sCOOR^{21}$; $-(CR^{29}R^{30})_sCONR^{28}R^{31}$; $-(CR^{29}R^{30})_sSO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_tCOR^{31}$; $-(CR^{29}R^{30})_sSO_2R^{23}$; $-(CR^{29}R^{30})_tR^{24}$; $-(CR^{29}R^{30})_tR^{25}$; or $-(CR^{29}R^{30})_tR^{26}$.

R^{24}, R^{25} and R^{26}: Defined as above.

R^{27} and R^{28}: Defined as above.

R^{29}: H; F; CF_3; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{32}R^{33})_sOR^{31}$; $-(CR^{32}R^{33})_sNR^{28}R^{31}$; $-(CR^{32}R^{33})_sNR^{28}COR^{31}$; $-(CR^{32}R^{33})_sNR^{28}CONR^{28}R^{31}$; $-(CR^{32}R^{33})_qCOOR^{21}$; $-(CR^{32}R^{33})_qCONR^{28}R^{31}$; $-(CR^{32}R^{33})_qCOR^{31}$; $-(CR^{32}R^{33})_qR^{31}$.

R^{30} and R^{33}: H; CF_3; or CH_3.

R^{31} and R^{32}: Defined as above

R^{34} and R^{35} are independently defined as H; F; Cl; CF_3; OCF_3; $OCHF_2$; lower alkyl; lower alkenyl; lower alkynyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{29}R^{30})_qOR^{31}$; $-(CR^{29}R^{30})_qNR^{28}R^{31}$; $-(CR^{29}R^{30})_qNR^{28}COR^{31}$; $-(CR^{29}R^{30})_qNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_qNR^{28}SO_2R^{23}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_qSO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOR^{31}$; $-(CR^{29}R^{30})_qSO_2R^{23}$; or $-(CR^{29}R^{30})_qR^{31}$.

R^{36}: Defined as in Part 3 "General Scope of the Invention".

R^{37}: H; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; a suitable *N*-protecting group; $-(CR^{29}R^{30})_rOR^{31}$; $-(CR^{29}R^{30})_rNR^{28}R^{31}$; $-(CR^{29}R^{30})_rNR^{28}COOR^{21}$; $-(CR^{29}R^{30})_rNR^{28}COR^{31}$; $-(CR^{29}R^{30})_rNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOR^{31}$; or $-(CR^{29}R^{30})_qR^{31}$.

R^{38}: H; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{29}R^{30})_qOR^{31}$; $-(CR^{29}R^{30})_qNR^{28}R^{31}$; $-(CR^{29}R^{30})_qNR^{28}COR^{31}$; $-(CR^{29}R^{30})_qNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOR^{31}$; or $-(CR^{29}R^{30})_qR^{31}$.

R^{39}; R^{40}; R^{41}; R^{42}; R^{43}; R^{44}; R^{45}; R^{46}; R^{47}; R^{48}; R^{49} and R^{50}: Defined as above.

In the aforementioned structures the variable heteroatom Z and the connector U are defined as:

Z: O; or $S(=O)_2$.

U: $-C(=O)-$; $-NR^4-C(=O)-$; or $-C(=O)-C(=O)-$.

Defined as above are:

- Substituents that can be pairwise taken together and form optionally substituted cycloalkyl or heterocycloalkyl moieties.
- Structural elements that can form one of the groups of formulae **H111-H118** (**Table 9**).
- Variable heteroatoms Q, T, X and Y.
- Indices q-u.

The above particularly preferred structures include all posible stereoisomers, exlicity also rotamers and atropisomers, of macrocycles of type **I**.

Examples of, but not limited to, readily accessible substances that define possible subunits of the linker **C** are listed in **Table 19**.

Table 19: Substances Representing Subunits of Particularly Preferred Linkers **C**

Code	Chemical Name
Ala	L-Alanine
[D]Ala	D-Alanine
Arg	L-Arginine
[D]Arg	D-Arginine
Asn	L-Asparagine
[D]Asn	D-Asparagine
Asp	L-Aspartic acid
[D]Asp	D-Aspartic acid
Cys	L-Cysteine
[D]Cys	D-Cysteine
Glu	L-Glutamic acid
[D]Glu	D-Glutamic acid
Gln	L-Glutamine
[D]Gln	D-Glutamine
Gly	Glycine
His	L-Histidine
[D]His	D-Histidine
Ile	L-Isoleucine
[D]Ile	D-Isoleucine
Leu	L-Leucine
[D]Leu	D-Leucine
Lys	L-Lysine
[D]Lys	D-Lysine
Met	L-Methionine
[D]Met	D-Methionine
Phe	L-Phenylalanine
[D]Phe	D-Phenylalanine
Pro	L-Proline
[D]Pro	D-Proline
Ser	L-Serine
[D]Ser	D-Serine
Thr	L-Threonine
[D]Thr	D-Threonine
Trp	L-Tryptophan
[D]Trp	D-Tryptophan
Tyr	L-Tyrosine

Code	Chemical Name
^{D}Tyr	D-Tyrosine
Val	L-Valine
^{D}Val	D-Valine
Apa	3-Amino-propanoic acid
H-β^3-HAla-OH	(3S)-3-Amino-butyric acid
H-β^3-HVal-OH	(3R)-3-Amino-4-methyl-valeric acid
H-β^3-HIle-OH	(3R, 4S)-3-Amino-4-methyl-hexanoic acid
H-β^3-HLeu-OH	(3S)-3-Amino-5-methyl-hexanoic acid
H-β^3-HMet-OH	(3S)-3-Amino-5-methylthio pentanoic acid
H-β^3-HTyr-OH	(3S)-3-Amino-4-(4'-hydroxyphenyl)-butyric acid
H-β^3-HHis-OH	(3S)-3-Amino-4-(imidazole-4'-yl)-butyric acid
H-β^3-HPhe-OH	(3S)-3-Amino-4-phenyl butyric acid
H-β^3-HTrp-OH	(3S)-3-Amino-4-(indol-3'-yl)-butyric acid
H-β^3-HSer-OH	(3R)-3-Amino-4-hydroxy-butyric acid
H-β^3-HAsp-OH	3-Amino-pentanedioic acid
H-β^3-HGlu-OH	(3S)-3-Amino-hexanedioic acid
H-β^3-HLys-OH	(3S)-3,7-Diamino-heptanoic acid
H-β^3-HArg-OH	(3S)-3-Amino-6-guanidino-hexanoic-acid
H-β^3-HCys-OH	(3R)-3-Amino-4-mercapto-butyric acid
H-β^3-HAsn-OH	(3S)-3-Amino-4-carbamoyl-butyric acid
H-β^3-HGln-OH	(3S)-3-Amino-5-carbamoyl-pentanoic acid
H-β^3-HThr-OH	(3R,4R)-3-Amino-4-hydroxy-pentanoic acid
Gaba	4-Amino-butyric acid
H-γ^4-DiHAla-OH	(4S)-4-Amino-pentanoic acid
H-γ^4-DiHVal-OH	(4R)-4-Amino-5-methyl-hexanoic acid
H-γ^4-DiHIle-OH	(4R, 5S)-4-Amino-5-methyl-heptanoic acid
H-γ^4-DiHLeu-OH	(4R)-4-Amino-6-methyl-heptanoic acid
H-γ^4-DiHMet-OH	(4R)-4-Amino-6-methylthio-hexanoic acid
H-γ^4-DiHTyr-OH	(4R)-4-Amino-5-(4'-hydroxyphenyl)-pentanoic acid
H-γ^4-DiHHis-OH	(4R)-4-Amino-5-(imidazole-4'-yl)-pentanoic acid
H-γ^4-DiHPhe-OH	(4R)-4-Amino-5-phenyl-pentanoic acid

Code	Chemical Name
H-γ^4-DiHTrp-OH	(4R)-4-Amino-5-(indol-3'-yl)-pentanoic acid
H-γ^4-DiHSer-OH	(4R)-4-Amino-5-hydroxy-pentanoic acid
H-γ^4-DiHAsp-OH	(4R)-4-Amino-hexanedioic acid
H-γ^4-DiHGlu-OH	4-Amino-heptanedioic acid
H-γ^4-DiHLys-OH	(4S)-4,8-Diamino-octanoic acid
H-γ^4-DiHArg-OH	(4S)-4-Amino-7-guanidino-heptanoic-acid
H-γ^4-DiHCys-OH	(4R)-4-Amino-5-mercapto-pentanoic acid
H-γ^4-DiHAsn-OH	(4R)-4-Amino-5-carbamoyl-pentanoic acid
H-γ^4-DiHGln-OH	(3S)-3-Amino-5-carbamoyl-hexanoic acid
H-γ^4-DiHThr-OH	(4R, 5R)-4-Amino-5-hydroxy- hexanoic acid
Cit	L-Citrulline
^{D}Cit	D-Citrulline
Orn	L-Ornithine
^{D}Orn	D-Ornithine
tBuA	L-t-Butylalanine
^{D}tBuA	D-t-Butylalanine
Sar	Sarcosine
Pen	L-Penicillamine
^{D}Pen	D-Penicillamine
tBuG	L-tert.-Butylglycine
^{D}tBuG	D-tert.-Butylglycine
4AmPhe	L-para-Aminophenylalanine
^{D}4AmPhe	D-para-Aminophenylalanine
3AmPhe	L-meta-Aminophenylalanine
^{D}3AmPne	D-meta-Aminophenylalanine
2AmPhe	L-ortho-Aminophenylalanine
^{D}2AmPhe	D-ortho-Aminophenylalanine
Phe(mC(NH_2)=NH)	L-meta-Amidinophenylalanine
^{D}Phe(mC(NH_2)=NH)	D-meta-Amidinophenylalanine
Phe(pC(NH_2)=NH)	L-para-Amidinophenylalanine
^{D}Phe(pC(NH_2)=NH)	D-para-Amidinophenylalanine
Phe(mNHC(NH_2)=NH)	L-meta-Guanidinophenylalanine
^{D}Phe(mNHC(NH_2)=NH)	D-meta-Guanidinophenylalanine

Code	Chemical Name
Phe(pNHC(NH_2)=NH)	L-para-Guanidinophenylalanine
^{D}Phe(pNHC(NH_2)=NH)	D-para-Guanidinophenylalanine
2Pal	(2S)-2-Amino-3-(pyridine-2'-yl)-propionic acid
^{D}2Pal	(2R)-2-Amino-3-(pyridine-2'-yl)-propionic acid
4Pal	(2S)-2-Amino-3-(pyridine-4'-yl)-propionic acid
^{D}4Pal	(2R)-2-Amino-3-(pyridine-4'-yl)-propionic acid
Phg	L-Phenylglycine
^{D}Phg	D-Phenylglycine
Cha	L-Cyclohexylalanine
^{D}Cha	D-Cyclohexylalanine
C_4al	L-3-Cyclobutylalanine
$^{D}C_4$al	D-3-Cyclobutylalanine
C_5al	L-3-Cyclopentylalanine
$^{D}C_5$al	D-3-Cyclopentylalanine
Nle	L-Norleucine
^{D}Nle	D-Norleucine
2-Nal	L-2-Naphthylalanine
^{D}2Nal	D-2-Naphthylalanine
1-Nal	L-1-Naphthylalanine
^{D}1Nal	D-1-Naphthylalanine
4ClPhe	L-4-Chlorophenylalanine
^{D}4ClPhe	D-4-Chlorophenylalanine
3ClPhe	L-3-Chlorophenylalanine
^{D}3ClPhe	D-3-Chlorophenylalanine
2ClPhe	L-2-Chlorophenylalanine
^{D}2ClPhe	D-2-Chlorophenylalanine
3,4Cl_2Phe	L-3,4-Dichlorophenylalanine
^{D}3,4Cl_2Phe	D-3,4-Dichlorophenylalanine
4FPhe	L-4-Fluorophenylalanine
^{D}4FPhe	D-4-Fluorophenylalanine
3FPhe	L-3-Fluorophenylalanine
^{D}3FPhe	D-3-Fluorophenylalanine
2FPhe	L-2-Fluorophenylalanine

Code	Chemical Name
^{D}2FPhe	D-2-Fluorophenylalanine
Thi	L-β-2-Thienylalanine
^{D}Thi	D-β-2-Thienylalanine
Tza	L-2-Thiazolylalanine
^{D}Tza	D-2-Thiazolylalanine
Mso	L-Methionine sulfoxide
^{D}Mso	D-Methionine sulfoxide
AcLys	N-Acetyllysine
^{D}AcLys	N-Acetyl-D-lysine
Dap	2,3-Diaminopropionic acid
^{D}Dap	D-2,3-Diaminopropionic acid
Dab	2,4-Diaminobutyric acid
^{D}Dab	(2R)-2,4-Diaminobutyric acid
Dbu	(2S)-2,3-Diamino-butyric acid
^{D}Dbu	(2R)-2,3-Diamino-butyric acid
Abu	γ-Aminobutyric acid (GABA)
Aha	ε-Aminohexanoic acid
Aib	α-Aminoisobutyric acid
Cyp	1-Amino cyclopentane carboxylic acid
Y(Bzl)	L-O-Benzyltyrosine
^{D}Y(Bzl)	D-O-Benzyltyrosine
H(Bzl)	(3S)-2-Amino-3-(1'-benzylimidazole-4'-yl)-propionic acid
^{D}H(Bzl)	(3R)- 2-Amino-3-(1'-benzylimidazole-4'-yl)-propionic acid
Bip	L-(4-phenyl)phenylalanine
^{D}Bip	D-(4-phenyl)phenylalanine
S(Bzl)	L-O-Benzylserine
^{D}S(Bzl)	D-O-Benzylserine
T(Bzl)	L-O-Benzylthreonine
^{D}T(Bzl)	D-O-Benzylthreonine
alloT	(2S, 3S)-2-Amino-3-hydroxy-butyric acid
^{D}alloT	(2R, 3S)-2-Amino-3-hydroxy-butyric acid
Leu3OH	(2S, 3R)-2-Amino-3-hydroxy-4-methyl-pentanoic acid
^{D}Leu3OH	(2R, 3R)-2-Amino-3-hydroxy-4-methyl-pentanoic acid
hAla	L-Homo-alanine

Code	Chemical Name
^{D}hAla	D-Homo-alanine
hArg	L-Homo-arginine
^{D}hArg	D-Homo-arginine
hCys	L-Homo-cysteine
^{D}hCys	D-Homo-cysteine
hGlu	L-Homo-glutamic acid
^{D}hGlu	D-glutamic acid
hGln	L-Homo-glutamine
^{D}hGln	D-Homo-glutamine
hHis	L-Homo-histidine
^{D}hHis	D-Homo-histidine
hIle	L-Homo-isoleucine
^{D}hIle	D-Homo-isoleucine
hLeu	L-Homo-leucine
^{D}hLeu	D-Homo-leucine
hNle	L-Homo-norleucine
^{D}hNle	D-Homo-norleucine
hLys	L-Homo-lysine
^{D}hLys	D-Homo-lysine
hMet	L-Homo-Methionine
^{D}hMet	D-Homo-Methionine
hPhe	L-Homo-phenylalanine
^{D}hPhe	D-Homo-phenylalanine
hSer	L-Homo-serine
^{D}hSer	D-Homo-serine
hThr	L-Homo-threonine
^{D}hThr	D-Homo-threonine
hTrp	L-Homo-tryptophan
^{D}hTrp	D-Homo-tryptophan
hTyr	L-Homo-tyrosine
^{D}hTyr	D-Homo-tyrosine
hVal	L-Homo-valine
^{D}hVal	D-Homo-valine
hCha	L-Homo-cyclohexylalanine
^{D}hCha	D-Homo-cyclohexylalanine

Code	Chemical Name
Bpa	L-4-Benzoylphenylalanine
[D]Bpa	D-4-Benzoylphenylalanine
OctG	L-Octylglycine
[D]OctG	D-Octylglycine
Tic	(3S)-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid
[D]Tic	(3R)-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid
Tiq	(1S)-1,2,3,4-Tetrahydroisoquinoline-1-carboxylic acid
[D]Tiq	(1R)-1,2,3,4-Tetrahydroisoquinoline-1-carboxylic acid
Oic	(2S, 3aS, 7aS)-1-Octahydro-1H-indole-2-carboxylic acid
[D]Oic	(2R, 3aS, 7aS)-1-Octahydro-1H-indole-2-carboxylic acid
4AmPyrr1	(2S, 4S)-4-Amino-pyrrolidine-2-carboxylic acid
[D]4AmPyrr1	(2R, 4S)-4-Amino-pyrrolidine-2-carboxylic acid
4AmPyrr2	(2S, 4R)-4-Amino-pyrrolidine-2-carboxylic acid
[D]4AmPyrr2	(2R, 4R)-4-Amino-pyrrolidine-2-carboxylic acid
4PhePyrr1	(2S, 4R)-4-Phenyl-pyrrolidine-2-carboxylic acid
[D]4PhePyrr1	(2R, 4R)-4-Phenyl-pyrrolidine-2-carboxylic acid
4PhePyrr2	(2S, 4S)-4-Phenyl-pyrrolidine-2-carboxylic acid
[D]4PhePyrr2	(2R, 4S)-4-Phenyl-pyrrolidine-2-carboxylic acid
5PhePyrr1	(2S, 5R)-5-Phenyl-pyrrolidine-2-carboxylic acid
[D]5PhePyrr1	(2R, 5R)-5-Phenyl-pyrrolidine-2-carboxylic acid
5PhePyrr2	(2S, 5S)-5-Phenyl-pyrrolidine-2-carboxylic acid
[D]5PhePyrr2	(2R, 5S)-5-Phenyl-pyrrolidine-2-carboxylic acid
4Hyp1	(4S)-L-Hydroxyproline
[D]4Hyp1	(4S)-D-Hydroxyproline
4Hyp2	(4R)-L-Hydroxyproline
[D]4Hyp2	(4R)-D-Hydroxyproline
4Mp1	(4S)-L-Mercaptoproline
[D]4Mp1	(4S)-D-Mercaptoproline

Code	Chemical Name
4Mp2	(4R)-L-Mercaptoproline
^{D}4Mp2	(4R)-D-Mercaptoproline
Pip	L-Pipecolic acid
^{D}Pip	D-Pipecolic acid
H-β^3-HCit-OH	(3S)-3-Amino-6-carbamidyl-hexanoic acid
H-β^3-HOrn-OH	(3S)-3,6-Diamino-hexanoic acid
H-β^3-HtBuA-OH	(3S)-3-Amino-5,5-dimethyl-hexanoic acid
H-β^3-HSar-OH	N-Methyl-3-amino-propionic acid
H-β^3-HPen-OH	(3R)-3-Amino-4-methyl-4-mercapto-pentanoic acid
H-β^3-HtBuG-OH	(3R)-3-Amino-4,4-dimethyl-pentanoic acid
H-β^3-H4AmPhe-OH	(3S)-3-Amino-4-(4'-aminophenyl)-butyric acid
H-β^3-H3AmPhe-OH	(3S)-3-Amino-4-(3'-aminophenyl)-butyric acid
H-β^3-H2AmPhe-OH	(3S)-3-Amino-4-(2'-aminophenyl)-butyric acid
H-β^3-HPhe(mC(NH_2)=NH)-OH	(3S)-3-Amino-4-(3'-amidinophenyl)-butyric acid
H-β^3-HPhe(pC(NH_2)=NH)-OH	(3S)-3-Amino-4-(4'-amidinophenyl)-butyric acid
H-β^3-HPhe(mNHC(NH_2)=NH)-OH	(3S)-3-Amino-4-(3'-guanidinophenyl)-butyric acid
H-β^3-HPhe(pNHC(NH_2)=NH)-OH	(3S)-3-Amino-4-(4'-guanidino-phenyl)-butyric acid
H-β^3-H2Pal-OH	(3S)-3-Amino-4-(pyridine-2'-yl)-butyric acid
H-β^3-H4Pal-OH	(3S)-3-Amino-4-(pyridine-4'-yl)-butyric acid
H-β^3-HPhg-OH	(3R)-3-Amino-3-phenyl-propionic acid
H-β^3-HCha-OH	(3S)-3-Amino-4-cyclohexyl-butyric acid
H-β^3-HC$_4$al-OH	(3S)-3-Amino-4-cyclobutyl-butyric acid
H-β^3-HC$_5$al-OH	(3S)-3-Amino-4-cyclopentyl-butyric acid
H-β^3-HNle-OH	(3S)-3-Amino-heptanoic acid
H-β^3-H2Nal-OH	(3S)-3-Amino-4-(2'-naphthyl)-butyric acid
H-β^3-H1Nal-OH	(3S)-3-Amino-4-(1'-naphthyl)-butyric acid
H-β^3-H4ClPhe-OH	(3S)-3-Amino-4-(4'-chlorophenyl)-butyric acid
H-β^3-H3ClPhe-OH	(3S)-3-Amino-4-(3'-chlorophenyl)-butyric acid

Code	Chemical Name
H-β³-H2ClPhe-OH	(3S)-3-Amino-4-(2'-chlorophenyl)-butyric acid
H-β³-H3,4Cl₂Phe-OH	(3S)-3-Amino-4-(3',4'-dichlorophenyl)-butyric acid
H-β³-H4FPhe-OH	(3S)-3-Amino-4-(4'-fluorophenyl)-butyric acid
H-β³-H3FPhe-OH	(3S)-3-Amino-4-(3'-fluorophenyl)-butyric acid
H-β³-H2FPhe-OH	(3S)-3-Amino-4-(2'-fluorophenyl)-butyric acid
H-β³-HThi-OH	(3R)-3-Amino-4-(2'-thienyl)-butyric acid
H-β³-HTza-OH	(3R)-3-Amino-4-(2'-thiazolyl)-butyric acid
H-β³-HMso-OH	(3R)-3-Amino-4-methylsulfoxyl-butyric acid
H-β³-HAcLys-OH	(3S)-7-Acetylamino-3-amino-heptanoic acid
H-β³-HDpr-OH	(3R)-3,4-diamino-butyric acid
H-β³-HA₂Bu-OH	(3S)-3,5-Diamino-pentanoic acid
H-β³-HDbu-OH	(3R)-3,4-Diamino-pentanoic acid
H-β³-HAib-OH	Amino-dimethyl acetic acid
H-β³-HCyp-OH	1-Amino-cyclopentane-1-yl-acetic acid
H-β³-HY(Bzl)-OH	(3S)-3-Amino-4-(4'-benzyloxyphenyl)-butyric acid
H-β³-HH(Bzl)-OH	(3S)-3-Amino-4-(1'-benzylimidazole-4'-yl)-butyric acid
H-β³-HBip-OH	(3S)-3-Amino-4-biphenylyl-butyric acid
H-β³-HS(Bzl)-OH	(3S)-3-Amino-4-(benzyloxy)-butyric acid
H-β³-HT(Bzl)-OH	(3R, 4R)-3-Amino-4-benzyloxy-pentanoic acid
H-β³-HalloT-OH	(3R, 4S)-3-Amino-4-hydroxy-pentanoic acid
H-β³-HLeu3OH-OH	(3R, 4R)-3-Amino-4-hydroxy-5-methyl-hexanoic acid
H-β³-HhAla-OH	(3S)-3-Amino-pentanoic acid
H-β³-HhArg-OH	(3S)-3-Amino-7-guanidino-heptanoic acid
H-β³-HhCys-OH	(3R)-Amino-5-mercapto-pentanoic acid
H-β³-HhGlu-OH	(3S)-3-Amino-heptanedioic acid
H-β³-HhGln-OH	(3S)-3-Amino-6-carbamoyl hexanoic acid
H-β³-HhHis-OH	(3S)-3-Amino-5-(imidazole-4'-yl)-pentanoic acid
H-β³-HhIle-OH	(3S, 5S)-3-Amino-5-methyl-heptanoic acid
H-β³-HhLeu-OH	(3S)-3-Amino-6-methyl-heptanoic acid

Code	Chemical Name
H-β^3-HhNle-OH	(3S)-3-Amino-octanoic acid
H-β^3-DiAoc-OH	(3S)-3,8-Diamino-octanoic acid
H-β^3-HhMet-OH	(3S)-3-Amino-6-methylthio-hexanoic acid
H-β^3-HhPe-OH	(3S)-3-Amino-5-phenyl-pentanoic acid
H-β^3-HhSer-OH	(3S)-3-Amino-5-hydroxy-pentanoic acid
H-β^3-HhThr-OH	(3S, 5R)-3-Amino-5-hydroxy-hexanoic acid
H-β^3-HhTrp-OH	(3S)-3-Amino-5-(indol-3'-yl)-pentanoic acid
H-β^3-HhThr-OH	(3S)-3-Amino-5-(4'-hydroxyphenyl)-pentanoic acid
H-β^3-HhCha-OH	(3S)-3-Amino-5-cyclohexyl-pentanoic acid
H-β^3-HBpa-OH	(3S)-3-Amino-4-(4'-benzoylphenyl)-butyric acid
H-β^3-HOctG-OH	(3S)-3-Amino-undecanoic acid
H-β^3-HNle-OH	(3S)-3-Amino-heptanoic acid
H-β^3-HTic-OH	(3S)-1,2,3,4-Tetrahydroisoquinoline-3-yl-acetic acid
H-β^3-HTiq-OH	(1S)-1,2,3,4-Tetrahydroisoquinoline-1-acetic acid
H-β^3-HOic-OH	(2S, 3aS, 7aS)-1-Octahydro-1H-indole-2-yl-acetic acid
H-β^3-H4AmPyrr1-OH	(2S, 4S)-4-Amino-pyrrolidine-2-acetic acid
H-β^3-H4AmPyrr2-OH	(2S, 4R)-4-Amino-pyrrolidine-2-acetic acid
H-β^3-H4PhePyrr1-OH	(2S, 4R)-4-Phenyl-pyrrolidine-2-acetic acid
H-β^3-H4PhePyrr2-OH	(2S, 4S)-4-Phenyl-pyrrolidine-2-acetic acid
H-β^3-H5PhePyrr1-OH	(2S, 5R)-5-Phenyl-pyrrolidine-2-acetic acid
H-β^3-H5PhePyrr2-OH	(2S, 5S)-5-Phenyl-pyrrolidine-2-acetic acid
H-β^3-H4Hyp1-OH	(2S, 4S)-4-Hydroxy-pyrrolidine-2-acetic acid
H-β^3-H4Hyp2-OH	(2S, 4R)-4-Hydroxy-pyrrolidine-2-acetic acid
H-β^3-H4Mp1-OH	(2R, 4S)-4-Mercapto-pyrrolidine-2-acetic acid
H-β^3-H4Mp2-OH	(2R, 4R)-4-Mercapto-pyrrolidine-2-acetic acid
H-β^3-HPip-OH	(2S)-piperidine-2-acetic acid
H-β^3-HPro-OH	(2S)-pyrrolidine-2-acetic acid
H-β^3-H^{D}Pro-OH	(2R)-pyrrolidine-2-acetic acid

Code	Chemical Name
Ahb	4-Amino-2-hydroxy butyric acid
H-γ^4-DiHCit-OH	(4S)-4-Amino-7-carbamidyl-heptanoic acid
H-γ^4-DiHOrn-OH	(4S)-4,7-Diamino-heptanoic acid
H-γ^4-DiHtBuA-OH	(4R)-4-Amino-6,6-dimethyl-heptanoic acid
H-γ^4-DiHSar-OH	N-Methyl-4-amino-butyric acid
H-γ^4-DiHPen-OH	(4R)-4-Amino-5-methyl-5-mercapto-hexanoic acid
H-γ^4-DiHtBuG-OH	(4R)-4-Amino-5,5-dimethyl-hexanoic acid
H-γ^4-DiH4AmPhe-OH	(4R)-4-Amino-5-(4'-aminophenyl)-pentanoic acid
H-γ^4-DiH3AmPhe-OH	(4R)-4-Amino-5-(3'-aminophenyl)-pentanoic acid
H-γ^4-DiH2AmPhe-OH	(4R)-4-Amino-5-(2'-aminophenyl)-pentanoic acid
H-γ^4-DiHPhe(mC(NH_2)=NH)-OH	(4R)-4-Amino-5-(3'-amidinophenyl)-pentanoic acid
H-γ^4-DiHPhe(pC(NH_2)=NH)-OH	(4R)-4-Amino-5-(4'-amidinophenyl)-pentanoic acid
H-γ^4-DiHPhe(mNHC(NH_2)=NH)-OH	(4R)-4-Amino-5-(3'-guanidino-phenyl)-pentanoic acid
H-γ^4-DiHPhe(pNHC(NH_2)=NH)-OH	(4R)-4-Amino-5-(4'-guanidino-phenyl)-pentanoic acid
H-γ^4-DiH2Pal-OH	(4R)-4-Amino-5-(pyridine-4'-yl)-pentanoic acid
H-γ^4-DiH4Pal-OH	(4R)-4-Amino-5-(pyridine-4'-yl)-pentanoic acid
H-γ^4-DiHPhg-OH	(4R)-4-Amino-4-phenyl-butyric acid
H-γ^4-DiHCha-OH	(4R)-4-Amino-5-cyclohexyl-pentanoic acid
H-γ^4-DiHC_4al-OH	(4R)-4-Amino-5-cyclobutyl-pentanoic acid
H-γ^4-DiHC_5al-OH	(4R)-4-Amino-5-cyclopentyl-pentanoic acid
H-γ^4-DiHNle-OH	(4S)-4-Amino-octanoic acid
H-γ^4-DiH2Nal-OH	(4S)-4-Amino-5-(2'-naphthyl)-pentanoic acid
H-γ^4-DiH1Nal-OH	(4S)-4-Amino-5-(1'-naphthyl)-pentanoic acid
H-γ^4-DiH4ClPhe-OH	(4R)-4-Amino-5-(4'-chlorophenyl)-pentanoic acid
H-γ^4-DiH3ClPhe-OH	(4R)-4-Amino-5-(3'-chlorophenyl)-pentanoic acid
H-γ^4-DiH2ClPhe-OH	(4R)-4-Amino-5-(2'-chlorophenyl)-pentanoic acid
H-γ^4-DiH3,4Cl_2Phe-OH	(4R)-4-Amino-5-(3',4'-dichloro-phenyl)-pentanoic acid

Code	Chemical Name
H-γ^4-DiH4FPhe-OH	(4R)-4-Amino-5-(4'-fluorophenyl)-pentanoic acid
H-γ^4-DiH3FPhe-OH	(4R)-4-Amino-5-(3'-fluorophenyl)-pentanoic acid
H-γ^4-DiH2FPhe-OH	(4R)-4-Amino-5-(2'-fluorophenyl)-pentanoic acid
H-γ^4-DiHThi-OH	(4R)-4-Amino-5-(2'-thienyl)-pentanoic acid
H-γ^4-DiHTza-OH	(4R)-4-Amino-5-(2'- thiazolyl)-pentanoic acid
H-γ^4-DiHMso-OH	(4R)-4-Amino-5-methylsulfoxyl-pentanoic acid
H-γ^4-DiHAcLys-OH	(4S)-8-Acetylamino-4-amino-ocatanoic acid
H-γ^4-DiHDpr-OH	(4R)-4,5-diamino-pentanoic acid
H-γ^4-DiHA_2Bu-OH	(4R)-4,5-Diamino-hexanoic acid
H-γ^4-DiHDbu-OH	(4R)-4,5-Diamion-hexanoic acid
H-γ^4-DiHAib-OH	3-Amino-3,3-dimethyl propionic acid
H-γ^4-DiHCyp-OH	(1'-Amino-cyclopentane-1'-yl)-3-propionic acid
H-γ^4-DiHY(Bzl)-OH	(4R)-4-Amino-5-(4'-benzyloxyphenyl)-pentanoic acid
H-γ^4-DiHH(Bzl)-OH	(4R)-4-Amino-5-(1'-benzylimidazole-4'-yl)-pentanoic acid
H-γ^4-DiHBip-OH	(4R)-4-Amino-5-biphenylyl-pentanoic acid
H-γ^4-DiHS(Bzl)-OH	(4S)-4-Amino-5-(benzyloxy)-pentanoic acid
H-γ^4-DiHT(Bzl)-OH	(4R, 5R)-4-Amino-5-benzyloxy-hexanoic acid
H-γ^4-DiHalloT-OH	(4R, 5S)-4-Amino-5-hydroxy-hexanoic acid
H-γ^4-DiHLeu3OH-OH	(4R, 5R)-4-Amino-5-hydroxy-6-methyl-heptanoic acid
H-γ^4-DiHhAla-OH	(4S)-4-Amino-hexanoic acid
H-γ^4-DiHhArg-OH	(4S)-4-Amino-8-guanidino-octanoic acid
H-γ^4-DiHhCys-OH	(4R)-Amino-6-mercapto-hexanoic acid
H-γ^4-DiHhGlu-OH	(4S)-4-Amino-ocatanedioic acid
H-γ^4-DiHhGln-OH	(4S)-4-Amino-7-carbamoyl-heptanoic acid
H-γ^4-DiHhHis-OH	(4S)-4-Amino-6-(imidazole-4'-yl)-hexanoic acid
H-γ^4-DiHhIle-OH	(4S, 6S)-4-Amino-6-methyl-octanoic acid
H-γ^4-DiHhLeu-OH	(4S)-4-Amino-7-methyl-ocatanoic acid
H-γ^4-DiHhNle-OH	(4S)-4-Amino-nonanoic acid
H-γ^4-DiHhLys-OH	(4S)-4,9-Diamino-nonanoic acid

Code	Chemical Name
H-γ^4-DiHhMet-OH	(4R)-4-Amino-7-methylthioheptanoic acid
H-γ^4-DiHhPhe-OH	(4S)-4-Amino-6-phenyl-hexanoic acid
H-γ^4-DiHhSer-OH	(4R)-4-Amino-6-hydroxy-hexanoic acid
H-γ^4-DiHhThr-OH	(4R, 6R)-4-Amino-6-hydroxy-heptanoic acid
H-γ^4-DiHhTrp-OH	(4S)-4-Amino-6-(indol-3'-yl)-hexanoi cacid
H-γ^4-DiHhTyr-OH	(4S)-4-Amino-6-(4'-hydroxyphenyl)-hexanoic acid
H-γ^4-DiHhCha-OH	(4R)-4-Amino-5-cyclohexyl-pentanoic acid
H-γ^4-DihBpa-OH	(4R)-4-Amino-5-(4'-benzoylphenyl)-pentanoic acid
H-γ^4-DiHOctG-OH	(4S)-4-Amino-dodecanoic acid
H-γ^4-DiHNle-OH	(4S)-4-Amino-octanoic acid
H-γ^4-DiHTic-OH	(3R)-1',2',3',4'-Tetrahydroisoquinoline-3'-yl-3-propionic acid
H-γ^4-DiHTiq-OH	(1'R)-1',2',3',4'-Tetrahydroisoquinoline-1'-yl-3-propionic acid
H-γ^4-DiHOic-OH	(2'S, 3'aS, 7'aS)-1'-Octahydro-1H-indole-2'-yl-3-propionic acid
H-γ^4-DiH4AmPyrr1-OH	(2'R, 4'S)-4'-Amino-pyrrolidine-2'-yl-3-propionic acid
H-γ^4-DiH4AmPyrr2-OH	(2'R, 4'R)-4'-Amino-pyrrolidine-2'-yl-3-propionic acid
H-γ^4-DiH4PhePyrr1-OH	(2'R, 4'R)-4'-Phenyl-pyrrolidine-2'-yl-3-propionic acid
H-γ^4-DiH4PhePyrr2-OH	(2'R, 4'S)-4'-Phenyl-pyrrolidine-2'-yl-3-propionic acid
H-γ^4-DiH5PhePyrr1-OH	(2'S, 5'R)-5'-Phenyl-pyrrolidine-2'-yl-3-propionic acid
H-γ^4-DiH5PhePyrr2-OH	(2'S, 5'S)-5'-Phenyl-pyrrolidine-2'-yl-3-propionic acid
H-γ^4-DiH4Hyp1-OH	(2'R, 4'S)-4'-Hydroxy-pyrrolidine-2'-yl-2-propionic acid
H-γ^4-DiH4Hyp2-OH	(2'R, 4'R)-4'-Hydroxy-pyrrolidine-2'-yl-3-propionic acid
H-γ^4-DiH4Mp1-OH	(2'R, 4'S)-4'-Mercapto-pyrrolidine-2'-yl-3-propionic acid
H-γ^4-DiH4Mp2-OH	(2'R, 4'R)-4'-Mercapto-pyrrolidine-2'-yl-3-propionic acid
H-γ^4-DiHPip-OH	(2'S)-Piperidine-2'-yl-3-propionic acid
H-γ^4-DiHPro-OH	(2'S)-Pyrrolidine-2'-yl-3-propionic acid
(AEt)G	N-(2-Aminoethyl)glycine
(APr)G	N-(3-Amino-n-propyl)glycine
(ABu)G	N-(4-Amino-n-butyl)glycine

Code	Chemical Name
(APe)G	N-(5-Amino-n-pentyl)glycine
(GuEt)G	N-(2-Guanidinoethyl)glycine
(GuPr)G	N-(3-Guanidino-n-propyl)glycine
(GuBu)G	N-(4-Guanidino-n-butyl)glycine
(GuPe)G	N-(5-Guanidino-n-pentyl)glycine
(PEG_3-NH_2)G	N-[H_2N-$(CH_2)_3$-$(OCH_2$-$CH_2)_2$-O$(CH_2)_3$]glycine
(Me)G	N-Methylglycine
(Et)G	N-Ethylglycine
(Bu)G	N-Butylglycine
(Pe)G	N-Pentylglycine
(Ip)G	N-Isopropylglycine
(2MePr)G	N-(2-Methylpropyl)glycine
(3MeBu)G	N-(3-Methylbutyl)glycine
(1MePr)G	(1S)-N-(1-Methylpropyl)glycine
(2MeBu)G	(2S)-N-(2-Methylbutyl)glycine
(MthEt)G	N-(Methylthioethyl)glycine
(MthPr)G	N-(Methylthiopropyl)glycine
(Ben)G	N-(Benzyl)glycine
(PhEt)G	N-(2-Phenylethyl)glycine
(HphMe)G	N-([4'-hydroxyphenyl]methyl)glycine
(HphEt)G	N-(2-[4'-hydroxyphenyl]ethyl)glycine
(ImMe)G	N-(Imidazol-5-yl-methyl)glycine
(ImEt)G	N-(2-(Imidazol-5'-yl)ethyl)glycine
(InMe)G	N-(Indol-2-yl-methyl)glycine
(InEt)G	N-(2-(Indol-2'-yl)ethyl)glycine
(CboMe)G	N-(Carboxymethyl)glycine
(CboEt)G	N-(2-Carboxyethyl)glycine
(CboPr)G	N-(3-Carboxypropyl)glycine
(CbaMe)G	N-(Carbamoylmethyl)glycine
(CbaEt)G	N-(2-Carbamoylethyl)glycine
(CbaPr)G	N-(3-Carbamoylpropyl)glycine
(HyEt)G	N-(2-Hydroxyethyl)glycine
(HyPr)G	(2R)-N-(2-Hydroxypropyl)glycine
(Mcet)G	N-(2-Mercaptoethyl)glycine
NMeAla	L-N-Methylalanine
$NMe^{D}Ala$	D-N-Methylalanine
NMeVal	L-N-Methylvaline
$NMe^{D}Val$	D-N-Methylvaline
NMeIle	L-N-Methylisoleucine

Code	Chemical Name
NMe^{D}Ile	D-N-Methylisoleucine
NMeLeu	L-N-Methylleucine
NMe^{D}Leu	D-N-Methylleucine
NMeNle	L-N-Methylnorleucine
NMe^{D}Nle	D-N-Methylnorleucine
NMeMet	L-N-Methylmethionine
NMe^{D}Met	D-N-Methylmethionine
NMeTyr	L-N-Methyltyrosine
NMe^{D}Tyr	D-N-Methyltyrosine
NMeHis	L-N-Methylhistidine
NMe^{D}His	D-N-Methylhistidine
NMePhe	L-N-Methylphenylalanine
NMe^{D}Phe	D-N-Methylphenylalanine
NMeTrp	L-N-Methyltryptophane
NMe^{D}Trp	D-N-Methyltryptophane
NMeSer	L-N-Methylserine
NMe^{D}Ser	D-N-Methylserine
NMeAsp	L-N-Methylaspartic acid
NMe^{D}Asp	D-N-Methylaspartic acid
NMeGlu	L-N-Methylglutamic acid
NMe^{D}Glu	D-N-Methylglutamic acid
NMeLys	L-N-Methyllysine
NMe^{D}Lys	D-N-Methyllysine
NMeArg	L-N-Methylarginine
NMe^{D}Arg	D-N-Methylarginine
NMeDab	L-N-Methyl-2,4-diamino butyric acid
NMe^{D}Dab	D-N-Methyl-2,4-diamino butyric acid
NMeCys	L-N-Methylcysteine
NMe^{D}Cys	D-N-Methylcysteine
NMeAsn	L-N-Methylasparagine
NMe^{D}Asn	D-N-Methylasparagine
NMeGln	L-N-Methylglutamine
NMe^{D}Gln	D-N-Methylglutamine
NMeThr	L-N-Methylthreonine
NMe^{D}Thr	D-N-Methylthreonine

Particularly preferred macrocyclic compounds of formula **I** are the examples: **Ex.9**, **Ex.11**, **Ex.12**, **Ex.16**, **Ex.30**, **Ex.49**, **Ex.184**, **Ex.200**, and **Ex.213**.

Synthesis of the Building Blocks

Building blocks **C** used in the synthesis of the macrocyclic compounds of the invention are detailed to the level of fully-defined structures shown in **Table 19**, above and are easily available. Possible synthetic approaches to the modulator building blocks **B** and, especially, the production of the template building blocks **A** are described in some detail hereinbelow.

Synthesis of the Template Building Blocks A

General Transformations

Building blocks of type **A** are based on readily available substances carrying a carboxylic acid group and either a phenolic (Ar/Hetar-OH) or a thiophenolic moiety (Ar/Hetar-SH). The -COOH group may be attached to the same ring as the -OH/ -SH group or to an annelated ring which in turn may be aromatic or partially unsaturated.

In general phenol derivatives are more abundantly described in the literature than the corresponding thiophenols. However, transformations of phenols into thiophenols are well established. Therefore the phenolic systems can be regarded as precursors towards their thio-analogs. Alternatively thiophenols might be derived from the corresponding aryl halides or diazonium salts.

Selected examples of general scope for the transformations Ar/Hetar-X → Ar/Hetar-SH (X=OH, F, Cl, Br, I, N_2^+) are introduced below:

T-I) A sequence of broad applicability is the transformation of a phenol into a thiocarbamate with *N,N*-dimethylthiocarbamoyl chloride, followed by Newman-Kwart rearrangement and subsequent hydrolysis (A. Gallardo-Godoy et al., *J. Med. Chem.* **2005**, *48*, 2407-2419; P. Beaulieu et al., *Biorg. Med. Chem. Lett.* **2006**, *16*, 4987-4993; H. Sugiyama et al., *Chem. Pharm. Bull.* **2007**, *55*, 613-624; S. Lin et al., *Org. Prep. Proced. Int.* **2000**; 547-556).

T-II) The direct transformation of an -OH adjacent to a pyridinic nitrogen (equivalent to the pyridone tautomer) can be accomplished by heating with P_2S_5 (K. Hirai et al., *Heterocycles* **1994**, *38*, 277-280).

T-III) As an alternative to phenols, halogen-substituted (esp. with F or Cl) aromatic ring systems might serve as precursors. In case the halogen is in a position activated by an electron withdrawing group in *ortho*- or *para*-position the -SH moiety or a protected analog can be introduced under mild conditions by nucleophilic aromatic substitution reactions (S_NAr) (G. J. Atwell et al., *J. Med. Chem.* **1994**, *37*, 371-380). Especially in the field of heterocyclic compounds, where the electron withdrawing effect is exerted by pyridine-like nitrogen atoms, this type of substitution is often utilized (S. McCombie et al., *Heterocycles*, **1993**, 35, 93-97).

T-IV) Similarly, in Sandmeyer-type reactions a diazonium group ($-N_2^+$) is replaced (C. Mukherjee, E. Biehl, *Heterocycles* **2004**, *63*, 2309-2318).

T-V) In non-activated positions the substitution of halogen atoms (esp. Br or I) can be accomplished via the corresponding organolithium or Grignard reagents (J. L. Kice, A. G. Kutateladze, *J. Org. Chem.* **1993**, *58*, 917-923; P. C. Kearney et al., *J. Am. Chem. Soc.* **1993**, *115*, 9907-9919; K.-Y. Jen, M. P. Cava, *Tetrahedron Lett.* **1982**, 23, 2001-2004). Alternatively, transition metal-catalyzed transformations are feasible for this type of reaction, e.g. Cu-catalyzed substitution with benzothioic *S*-acid (N. Sawada et al., *Tetrahedron Lett.* **2006**, *47*, 6595-6597), or Pd-catalyzed substitution with KS-Si(*i*-Pr)$_3$ followed by desilylation of the thus introduced -SSi(*i*-Pr)$_3$

group (A. M. Rane et al., *Tetrahedron Lett.* **1994**, *35*, 3225-3226).

The hydroxyl group attached to the aromatic ring (Ar-OH or Hetar-OH) in turn, if not part of a commercially available substance, can be introduced by various methods:

H-I) Analogously to T-III) the hydroxy group or a surrogate can be introduced by an S_NAr reaction of halogen atoms, esp. Cl or F, *ortho* or *para* to an electron withdrawing substituent (W. Cantrell, *Tetrahedron Lett.* **2006**, *47*, 4249-4251) or to a pyridinic nitrogen atom (S. D. Taylor et al., *J. Org. Chem.* **2006**, *71*, 9420-9430).

H-II) Sandmeyer-type hydroxylations of aromatic amines via intermediate diazonium salts (P. Madsen et al., *J. Med. Chem.* **2002**, *45*, 5755-5775).

H-III) The substitution of halogen atoms (esp. Br and I), not activated for an S_NAr, can be achieved by transition metal-catalyzed C-O-couplings; predominant are Pd-catalysts (K. W. Anderson et al., *J. Am. Chem. Soc.* **2006**, *128*, 10694-10695; B. J. Gallon et al., *Angew. Chem., Int. Ed.* **2007**, *46*, 7251-7254), but also others, like Cu-catalysts (J. E. Ellis, S. R. Lenger, *Synth. Commun.* **1998**, *28*, 1517-1524), find application.

H-IV) Of broad scope is also a two-step process which first transforms halogen atoms (Cl, Br and I) into a boronate and then oxidatively cleaves the carbon-boron bond to the phenol (J. R. Vyvyan et al., *J. Org. Chem.* **2004**, 69, 2461-2468).

The carboxylic acid groups of template building blocks **A**, if not already present in a commercial available building block, can be introduced by standard procedures:

C-I) The oxidation of functional groups like hydroxymethyl (-CH_2-OH) or aldehyde (-C(=O)H) can be achieved under mild conditions (G. V. M. Sharma et al., *Synth. Commun.* **2000**, *30*, 397-406; C. Wiles et al., *Tetrahedron Lett.* **2006**, *47*, 5261-5264). Also methyl groups on benzene rings can be oxidized; however, as harsh reaction conditions are usually required, its

applicability is limited. In contrast, the relative acidic methyl groups *ortho* or *para* to a pyridine nitrogen can be oxidized under milder conditions; making this the method of choice for many pyridine ring analogs (T. R. Kelly, F. Lang, *J. Org. Chem.* **1996**, *61*, 4623-4633).

C-II) Halogen atoms can easily be replaced by a carboxyl group or surrogates thereof, e.g. by halogen metal exchange and subsequent carboxylation of the intermediate Grignard or organolithium species (C. G. Screttas, B. R. Steele, *J. Org. Chem.* **1989**, *54*, 1013-1017), or by utilizing Mander's reagent (methyl cyanoformate)(A. Lepretre et al., *Tetrahedron* **2000**, *56*, 265-274).

C-III) In the case that acidified ring positions are to be carboxylated, a viable method is deprotonation with a strong base (usually *tert*-butyl lithium) followed by carboxylation of the intermediate organolithium species in analogy to C-II).

C-IV) Hydrolysis of ester, amide or nitrile groups. The CN group in turn can easily be introduced by treating organic halides with CuCN (Rosenmund-von Braun reaction: C. F. Koelsch, A. G. Whitney, *J. Org. Chem.*, **1941**, *6*, 795-803).

Applied to commercially available starting materials these general transformations offer a tool box for accessing templates A. Further literature example are cited within the category of each embodiment below.

A1-A59 Phenyl Derivatives

A plethora of hydroxy benzoic acids with diverse substitution patterns are commercially available and can be directly incorporated as template **A** into the macrocyclic backbone. In several other cases the presence of an optional substituent provides a suitable functionality that can be further extended into more complex high variation substituents by standard methods of organic synthesis and parallel/combinatorial chemistry.

Even not so common tetrasubstituted hydroxy benzoic acids (**A53-A59**) can be built up by procedures in accordance with the general methods mentioned above, for example by carboxylation of pentasubstituted phenol derivatives (K. Sung, R. J. Lagow, *J. Mater. Chem.* **1996**, *6*, 917-918; E. Marzi, M. Schlosser, *Tetrahedron* **2005**, 61, 3393-3402; K. C. Nicolaou et al., *Angew. Chem., Int. Ed.* **1999**, *38*, 3334-3339). Alternative approaches to tetrasubstituted hydroxy benzoic acids involve, for example, the oxidation of benzaldehydes followed by the introduction of substituents into remaining free positions, also feasible to build up polysubstituted benzoic acids from less substituted ones (K. C. Nicolaou et al., *Chem. Eur. J.* **2000**, 6, 3095-3115).

A60-A143 Pyridine Derivatives

As in the case of the above class of compounds also for pyridine derivatives a very large number of substances are commercially available which can be incorporated into the macrocycle directly, or can easily be transformed into suitable hydroxyl pyridine carboxylic acids by the general methods mentioned above: selected literature examples can be cited for transformations of type C-III (M. Shimano et al. *Tetrahedron Lett.* **1998**, *39*; 4363-4366; ibid., *Tetrahedron* **1998**, *54*, 12745-12774); for H-II (L. Carpino et al., *J. Org. Chem.* **2004**, *69*; 54-61); and for C-I (T. R. Kelly, F. Lang, *Tetrahedron Lett.* **1995**, *36*, 5319-5322), or for C-IV (J. L. LaMattina, R. L. Taylor, *J. Org. Chem.* **1981**, *46*, 4179-4182).

A144- A165 Pyridazine Derivatives

In analogy to general transformations which are readily available, suitably substituted methyl pyridazines can be oxidized to the corresponding 3- or 4-carboxylic acids with dichromate (M. Morishita et al., *Chem. Pharm. Bull.* **1994**, *42*, 371-372; M. Winn et al., *J. Med. Chem.* **1993**, *36*, 2676-2688). Of similarly broad scope is the hydrolysis of the corresponding nitriles under chemical conditions (hydroxide; G. Heinisch, D. Lassnigg, *Arch. Pharm. (Weinheim, Ger.)* **1987**, 320, 1222-1226)

or under enzymatic conditions (nitrilase from Rhodococcus sp.; N. Klempier et al., *Tetrahedron Lett.* **1991**, *32*, 341-344).

One possibility to construct the heterocyclic pyridazine core from non-cyclic precursors starts with β-ketoesters which can be subjected to a Staudinger reaction followed by a aza-Wittig-cyclization of the intermediate azides (S. V. Galiullina et al., *Russ. J. Org. Chem.* 2007, 43, 607-614; M. Guillaume et al., *Synthesis* **1995**, 8, 920-922) or directly cyclocondensed with monohydrazone(E. E. Schweizer, K.-J. Lee, J. Org. Chem. **1982**, *47*, 2768-2773).

A166- A189 Pyrimidine Derivatives

Similarly as with the pyridine derivatives, a large number of suitable building blocks are commercially available and can be directly incorporated into the macrocycle, or they can easily be ransformed into the target compounds by the standard procedures mentioned above, including selected examples for transformations of type C-I (Y. Honma et al., *Chem. Pharm. Bull.* **1982**, *30*, 4314-4324); and C-IV (I. V. Oleinik, O. A. Zagulyaeva, Chem. Heterocycl. Compd. **1993**, *29*, 427-431). In addition, the pyrimidine core can easily be constructed by cyclocondensation of oxalylic compounds with malonamidine derivative (G. A. Howard et al., *J. Chem. Soc.* **1944**, 476-477) or of malonates with amidine derivatives (M. Otsuka et al., *Chem. Pharm. Bull.* **1985**, *33*, 515-519).

A190- A200 Pyrazine Derivatives

Pyrazine carboxylic acids are easily obtained by cyclocondensation of α,β-diaminopropionic acid with α,β-dicarbonyl derivatives (J. Bostroem et al., *Bioorg. Med. Chem.* **2007**, *15*, 4077-4084). Standard protocol examples are for C-I (J. R. Young et al., *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1723-1728); for C-III (N. Ple et al., *Tetrahedron* **1998**, *54*, 9701-9710); and for H-II (A. P. Krapcho et al., *J. Heterocycl. Chem.* **1997**, *34*, 27-32). Highly chemosoelective oxidations of type C-I can be

achived by biotransformations with *Pseudomonas putida* (A. Kiener, *Ang. Chem.* **1992**, *104*, 748-749).

A201-A206 Triazine Derivatives

A possible route to suitably substituted precursors of difunctional triazines is the cyclocondensation of amidrazones with α,β-diketones or α,β-diketoesters (M. Sagi et al., *Heterocycles* **1990**, *30*, 1009-1021). Also α,γ-diketoesters are described as suitable starting materials, in this case, however, a multi step reaction sequence being required that proceeds via intermediate 4-nitrosopyrazoles (R. Fusco, S. Rossi, Tetrahedron **1958**, *3*, 209-224).

A207-A228 Furan, Thiophene and Pyrrole Derivatives

The furans **A207** and **A208** can be synthesized from suitably substituted 2-formyl- or 2-acetyl-3-oxo-butanoates by bromination followed by cyclization (A. Becker, *Helv. Chim. Acta* **1949**, *32*, 1114-1122; R. Richter, *Helv. Chim. Acta* **1949**, *32*, 1123-1136). The thiophenes **A207** and **A208** can be prepared from (substituted) 3-methoxycarbonyl-tetrahydrothiophene-4-one by oxidation (M. R. Banks et al., *J. Chem. Res. (M)* **1984**, 369-389) or by condensation with aldehydes followed by isomerization (R. Jaunin, *Helv. Chim. Acta* **1980**, 63, 1542-1553). The pyrroles **A207** and **A208** (X = O) can be obtained from N-protected, suitably substituted 3-amino-acrylates by reaction with (substituted) 2-chloroacetyl chlorides followed by base-induced cyclization (E. Benary, R. Konrad, *Chem. Ber.* **1923**, *56*, 44-52). The thioanalogues (X = S) can be synthesized from 3-methoxycarbonyl-furan by dibromination/methanolysis, subsequent reaction with 3-mercapto-propionate and amines, followed by acid-induced cyclization and S-deprotection (F. Eiden, U. Grusdt, *Arch. Pharm.* **1989**, *322*, 807-810).

The furans **A209** and **A210** (X = O) are accessible from (substituted) acetyl(methoxycarbonyl)methylene]-triphenylphosphorane by reaction with aldehydes followed by

ozonolysis and acid-induced isomerization (H. H. Wasserman, G. M. Lee, *Tetrahedron Lett.* **1994**, *35*, 9783-9786). The thiophenes **A209** and **A210** can be prepared from 2-mercaptoacetate and (substituted) acetylene carboxylates (H. Fiesselmann, G. Pfeiffer, *Chem. Ber.* **1954**, *87*, 848-856) or from acetyl acetates and 2-mercaptoacetate followed by base-induced cyclization (H. Fiesselmann, F. Thoma, *Chem. Ber.* **1956**, *89*, 1907-1912).

The pyrroles **A209** and **A210** can be obtained by condensation of beta-alanine ethyl ester and (substituted) 2,3-dioxo-pent-4-enoic esters (H. H. Wasserman et al., *Tetrahedron Lett.* **1989**, *30*, 1721-1724) or by reaction of suitably substituted 3-oxo-propanoates with glycine esters (A. Treibs, A. Ohorodnik, *Liebigs Ann. Chem.* **1958**, *611*, 139-149). The thioanalogues (X = S) can be synthesized from (substituted) pyrrolidine-2-carboxylates by subsequent reaction with bistosylsulfur diimide and trimethylphosphite followed by demethylation (J. Häusler, *Monatsh. Chem.* **1986**, *117*, 269-274).

The furans of type **A211** and **A212** can be synthesized from diazomalonates and suitably substituted alkynes in a two-step-procedure catalyzed by rhodium(II)-acetate (P. Müller, C. Gränicher, *Helv. Chim. Acta* **1993**, *76*, 521-534). The thioanalogues (X = S) can be obtained from suitably substituted oxazoles by deprotonation and reaction with dimethyl disulfide, then bromination, lithiation and carboxylation followed by demethylation (S. M. Nolan, T. Cohen, *J. Org. Chem.* **1981**, *46*, 2473-2476). The thiophenes **A211** and **A212** are accessible from (substituted) thiophenes by 5-alkylation and/or 3-carboxylation by deprotonation or lithiation (J. Sicé, *J. Am. Chem. Soc.* **1953**, *75*, 3697-3700). The thioanalogues (X = S) can be obtained from (substituted) 2-trimethylsilyloxy-cyclopropanecarboxylates by reaction with carbon disulfide (C. Brückner, H.-U. Reissig, *Liebigs Ann. Chem.* **1988**, 465-470).

The pyrroles **A211** and **A212** can be prepared from suitably substituted 2-chloroethylidene-malonates by substitution with sodium azide followed by cyclization in the presence of triphenylphosphine (F.-P. Montforts et al., *Liebigs Ann. Chem.*

1990, 1037-1043). The thioanalogues (X = S) can be obtained from suitably substituted 2-oxoethyl-malonates by reaction with isothiocyanates followed by acid-induced cyclization and decarboxylation (J. Fuentes et al., *Tetrahedron: Asymm.* **1998**, *9*, 2517-2532).

Furans of type **A213** and **A214** are accessible either by 5-lithiation/carboxylation of (substituted) O-protected 2-hydroxy-furans or by 5-bromination of furan-2-carboxylates followed by substitution with methylate and demethylation (D. G. Manly, E. D. Amstutz, *J. Org. Chem.* **1956**, *21*, 516-519). The thioanalogues (X = S) can be obtained from (substituted) 1,1-bis(methylthio)prop-1-en-3-one and bromoacetate followed by demethylation (A. Datta et al., *Tetrahedron* **1989**, *45*, 7631-7641). The thiophenes **A213** and **A214** can be prepared analogously as for the compounds **A211** and **A212** (J. Sicé, *J. Am. Chem. Soc.* **1953**, *75*, 3697-3700). The thioanalogues of thiophenes **A213** and **A214** (X = S) can be synthesized from suitably substituted 2-chloro-thiophenes by 5-carboxylation and subsequent substitution with sodium hydrogensulfide (K. Clarke et al., *J. Chem. Soc., Perkin Trans. 1* **1980**, 1029-1037). The pyrrols **A213** and **A214** can be obtained from suitably substituted, N-protected glutamate, which is transformed into the didehydro derivative and cyclized in the presence of $LiCuMe_2$ (M. M. Paz., F. J. Sardina, *J. Org. Chem.* **1993**, *58*, 6990-6995).

The thiophenes **A215** and **A216** (X = S) can be synthesized from (substituted) 3-bromo-thiophenes by a sequence of 3-lithiation/sulfanylation, 2-bromination, 4-lithiation/carboxylation, 2-debromination and 3-demethylation (E. C. Taylor, D. E. Vogel, *J. Org. Chem.* **1985**, *50*, 1002-1004). The pyrroles **A215** and **A216** can be prepared from aminooxoacetate and oxalyl chloride, alcoholysis of the isocyanate, reaction with (3-bromoacetonyl)triphenylphosphonium bromide and N-deprotection (J. P. Bazureau et al., *Tetrahedron Lett.* **1988**, *29*, 1921-1922), or from (substituted) N-Pfp-protected 3-oxo-prolinates by subsequent reaction with base and acid (F.-A. Marcotte, W. D. Lubell, *Org. Lett.* **2002**, *4*, 2601-2603). The

thioanalogues (X = S) can be obtained from suitably substituted pyrrole-2-carboxylates by subsequent reaction with dicyanodisulfane and zinc/acetic acid (A. Berlin et al., *J. Chem. Soc, Perkin Trans. 2* **1990**, *5*, 699-704).

The furans **A217** and **A218** may be obtained from (substituted) acetylene carboxylates by reaction with suitably substituted ethoxyvinylidene-tetracarbonyl-ferrocene complexes followed by O-deprotection (Atiq-ur-Rehman et al., *J. Am. Chem. Soc.* **1993**, *115*, 9848-9849). The thioanalogues (X = S) can be synthesized from suitably substituted furan-3-carboxylates by subsequent 5-bromination, reaction with dimethyl disulfide and S-deprotection (G. Majetich et al., *Tetrahedron Lett.* **1994**, *35*, 4887-4890). The thiophenes **A217** and **A218** should be accessible from (substituted) formylsuccinates by cyclization in the presence of methanol, hydrogen chloride and hydrogen sulfide, followed by demethylation (S. Mitra et al., *J. Chem. Soc.* **1939**, 1116-1117); or from (substituted) 2,4-dibromothiophene by subsequent reaction with methanol, butyllithium and carbon dioxide followed by demethylation (D. Spinelli et al., *J. Chem. Res. (M)* **1993**, *8*, 1873-1890). The pyrroles **A217** and **A218** (keto-tautomer) can be obtained from suitably substituted aminomethylene succinates by base-induced cyclization (C. A. Grob, P. Ankli, *Helv. Chim. Acta* **1949**, *32*, 2023-2038). The thioanalogues (X = S) can be synthesized from (substituted) dimethyl (trimethylsilyl)methyl-carbonimidodithioate and (substituted) acetylene carboxylates in the presence of silver fluoride (A. Padwa et al., *J. Org. Chem.* **1987**, *52*, 1027-1035).

A229-A234 Oxazole, Thiazole and Imidazole derivatives

The oxazoles of type **A229** can be obtained by reaction of acetyl isocyanates and diazoacetate followed by cyclization (O. Tsuge et al., *Tetrahedron* **1973**, *29*, 1983-1990), whereas the thiazoles **A229** can be synthesized from bromomalonates and thioamides (F. A. J. Kerdesky et al., *J. Med. Chem.* **1991**, *34*, 2158-2165). The imidazoles **A229** are accessible by reaction of aminomalonate

with substituted acetimidates (M. S. Poonian, E. F. Nowoswiat, *J. Org. Chem.* **1980**, *45*, 203-208).

The oxazoles and thiazoles of type **A230** are accessible by cyclizing monoethyl acetamidomalonate in the presence of trifluoroacetic anhydride (to the oxazoles; J. Morgan et al., *J. Chem. Soc., Perkin Trans. 1* **1997**, *5*, 613-620), or in the presence of phosphorus pentasulfide (to the thiazoles; A. G. Long, A. Tulley, *J. Chem. Soc.* **1964**, 1190-1192). The thiazoles **A230** (with X = S) can be synthesized either from N-thioacetyl-glycine by PCl_3-mediated cyclization followed by subsequent reaction with the Vilsmeyer reagent and hydrosulfide and oxidation of the intermediate aldehyde (to give 2-substituted 5-mercapto-thiazoles; I. Y. Kvitko et al., *Chem. Heterocycl. Comp.* **1980**, *16*, 28-31) or from (substituted) 3-bromo-2-oxo-propionic acid by reaction with thiourea, 2-deamination via diazotation, 5-bromination, substitution and deprotection (to give 2-unsubstituted 5-mercapto-thiazoles; B. Blank et al., J. Med. Chem. 1977, 20, 572-576). The imidazoles **A230** (X = O) can be obtained from aminomalonate by reaction with trimethylorthoformiate followed by cyclization in the presence of ammonia or amines (R. S. Hosmane, B. B. Lim, *Tetrahedron Lett.* **1985**, *26*, 1915-1918) or, for (X = S) by subsequent reaction of 2-amino-2-cyano-acetate with (substituted) trimethylorthoformiate and hydrogen sulfide A. K. Sen, A. K. Mukhopadhyay, *Indian J. Chem. B.* **1981**, *20*, 275-278).

The oxazoles **A231** (X = S) should be obtainable starting from hydroxyacetaldehyde dimer and potassium thiocyanate followed by S-methylation, lithiation/acylation with chloroformiate and demethylation (C. M. Shafer, T. F. Molinski, *J. Org. Chem.* **1998**, *63*, 551-555). The corresponding thiazoles **A231** (X = S) may be synthesized from suitably substituted beta-ketoesters by subsequent reaction with [hydroxy(tosyloxy)iodo]benzene and ammonium dithiocarbamate (P.-F. Zhang, Z.-C. Chen, *Synth. Comm.* **2001**, *31*, 415-420). The imidazoles **A231** (X = S) can be prepared from N-protected glycine by subsequent reaction with formic acid, methyl formiate and potassium thiocyanate (G. van Lommen

et al., *Bioorg. Med. Chem. Lett.* **2005**, *15*, 497-500), or by C-alkylation of N-protected glycine with suitably substituted chloroacetates followed by reaction with potassium thiocyanate (J. Singh et al., *Tetrahedron Lett.* **1993**, *34*, 211-214).

Oxazoles of type **A232** can be prepared from suitably substituted diazoacetates by rhodium-catalyzed reaction with cyanoformiate (G. Shi et al., *J. Fluorine Chem.* **1991**, *52*, 149-157).

Oxazoles of type **A233** can be obtained by heating suitably substituted acetylene carboxylates with diazoacetate followed by demethylation (R. Huisgen, H. Blaschke, *Chem. Ber.* **1965**, *98*, 2985-2997).The S-analogues of oxazoles **A233** (X = S) are accessible from N-(bismethylthio)glycine esters by reaction with DMF-acetals followed by acid-induced cyclization and demethylation (R. Gompper, U. Heinemann, *Angew. Chem.* **1981**, *93*, 297-298). The thiazoles **A233** (X = O) can be prepared from suitably substituted cysteine ethyl ester by reaction with diphosgene followed by bromination/elimination (G. Serra et al., *Heterocycles* **1995**, *41*, 2701-2711).

The oxazoles **A234** (X = O) can be prepared from suitably substituted hydroxyacetonitriles and oxalyl chloride followed by methanolysis of the intermediate and demethylation (K. van Aken, G. Hoornaert, *J. Chem. Soc., Chem. Comm.* **1992**, *12*, 895-896). The thiazoles **A234** (X = O) are accessible from suitably substituted 2-mercaptoacetate and cyanoformiate (G. Satzinger, *Liebigs Ann. Chem.* **1978**, 473-511). The corresponding thioanalogues (X = S) can be prepared from (substituted) S-methyl 3-oxopropanedithioates and glycine esters followed by cyclization induced by thionyl chloride and demethylation (A. Rahman et al., *Synthesis* **1984**, 250-252).

A235-A239 Isoxazole, Isothiazole and Pyrazole Derivatives

Isoxazoles **A235** can be synthesized from (2-methoxymethylene)-malonate substituted in 2-position by reaction with hydroxylamine followed by aqueous HCl (K. Bowden et al., *J. Chem. Soc. C* **1968**, 172-185). The corresponding pyrazoles **A235** can be prepared similarly but with hydrazine instead of

hydroxylamine (T. M. Willson et al., *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1047-1050).

The isothiazoles **A236** can be obtained from suitably substituted O-toluenesulfonyloxyiminoacetates by reaction with thioglycolates (B. Rezessy et al., *Tetrahedron Lett.* **1992**, *33*, 6523-6526). The corresponding pyrazoles **A236** can be prepared either from suitably substituted 2-oxopropionates by reaction with ethyl hydrazinoacetate followed by methoxide-mediated cyclization (R. N. Comber et al., *Carbohyd. Res.* **1992**, *216*, 441-452) or from substituted 3-oxopropionates by 2-diazotation followed by cyclization in the presence of sodium hydride (F. J. L. Herrera, C. U. Baelo, *Carbohyd. Res.* **1985**, *143*, 161-174).

The isoxazoles **A237** are accessible by reaction of 4-chloro-3-oxo-butanoates substituted in 4-position with isopentylnitrite (G. Hesse, G. Krehbiel, *Chem. Ber.* **1955**, *88*, 130-133). The pyrazoles **A237** can be obtained from suitably substituted malonates by reaction with diazoacetate (A. Bertho, H. Nüssel, *Liebigs Ann. Chem.* **1927**, *457*, 278-307). The pyrazoles of type **A238** (keto-isomers) can be synthesized from suitably substituted ketosuccinic acids by reaction with hydrazines in the presence of acetic acid (K. J. Duffy et al., *J. Med. Chem.* **2001**, *44*, 3730-3745).

Isoxazoles of type **A239** can be obtained from 3-substituted 2-bromomaleic acids by esterification followed by reaction with hydroxyurea (C. Bennouna et al., *Bull. Soc. Chim. Fr.* **1980**, *2*, 478-480). The isothiazoles **A239** can be prepared from 3-substituted 2-aminofurmaramides by subsequent reaction with hydrogen sulfide and bromine followed by hydrolysis of the formed amides (J. Lykkeberg, P. Krogsgaard-Larsen, *Acta Chem. Scand. B* **1976**, *30*, 781-785). The corresponding pyrazoles are accessible from (substituted) maleates by reaction with hydrazines followed by oxidation to give the pyrazole ring (G. P. Lahm et al., *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6274-6279).

A240-A357 Benzofurane, Benzothiophene and Indole derivatives

The benzothiophenes **A240** can be prepared in a multistep sequence starting from suitably substituted 2-hydroxy-benzaldehydes, which are transformed into the 3-isopropoxy-2,3-dihydrobenzothiophen-2-ones and then further on functionalized in 2-position and carboxylated in 3-position (A. V. Kalinin et al., *J. Org. Chem.* **2003**, *68*, 5992-5999).

A possible route to benzofuranes of type **A241-A243** involves condensation of suitably substituted cyclohexane-1,3-diones and 3-bromo-2-oxo-propionic acid followed by Pd-catalyzed dehydrogenation (G. Kneen, P. J. Maddocks, *Synth. Comm.* **1986**, *16*, 1635-1640). The indoles **A244-A247** can be obtained from suitably substituted 2-bromo-3-nitro-benzoates by a Stille coupling to the corresponding 1-ethoxy-styrene followed by a Pd-catalyzed reductive cyclization in the presence of CO and subsequent deprotection of the alcohol and acid (R. W. Clawson et al., *Tetrahedron* **2006**, *62*, 10829-10834).

The benzofuranes of type **A248-A251** can be synthesized from suitably substituted 2,6-dihydroxy-benzoates by reaction with 2-chloroketones (F. H. Curd, A. Robertson, *J. Chem. Soc.* **1933**, 714-720) or with chloroacetonitrile in the presence of Lewis acids and HCl followed by acetylation and reductive deoxygenation in 3-position (W. Gruber, K. Horvath, *Mh. Chem.* **1950**, *81*, 828-836). The corresponding indoles **A250** and **A251** should accessible from 6-hydroxy-3-methyl-2-nitro-benzoic acid, which is reacted with dimethylformamide followed by hydrogenation of the nitro group, cyclization, diazotation of the amine and hydroxylation (H. D. Hollis Showalter et al., *J. Org. Chem.* **1996, 61**, 1155-1158). The benzothiophenes **A250** and **A251** could be obtained from suitably substituted 2-(thiophen-3-yl-)acetaldehydes by reaction with propargyl alcohol followed by iodo-cyclization, oxidation of the alcohol to the acid and transformation of the 6-iodo-compound into the alcohol (J. P. Waldo et al., *J. Org. Chem.* **2008**, *73*, 6679-6685).

The benzothiophenes of type **A252-A255** are accessible from suitably substituted methyl 3-methyl-thiophene-2-carboxylate, which is first transformed into the 3-toluenesulfinylmethyl

compound and then further reacted with suitably substituted acrylates in the presence of base to give the methyl esters of **A252-A255** (J. W. Terpstra, A. M. van Leusen, *J. Org. Chem.* **1986**, *51*, 230-238). Indoles **A252-A255** can be synthesized from methyl 2-methoxy-4-methyl-benzoates, which are subsequently brominated in 5-position, nitrated in 3-position, then reacted with dimethylformamide and reduced with Ra/Ni and hydrazine, which triggers a cyclization to the 7-methoxy-6-methoxycarbonyl-indoles. These intermediates can then be deprotected to the indoles **A252-A255** (P. L. Beaulieu et al., *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4987-4993).

Possible precursors for benzofuranes **A256-A259** and **A264-A267** are suitably substituted 2,4-dihydroxy-benzoates which are subjected to alkylation in 4-position with bromoacetaldehyde diethyl acetal followed by cyclization mediated by Amberlyst A15 (M. Dixit et al., *Synlett* **2006**, *10*, 1497-1502). Indoles of type **A256-A259** (TMS-protected in 4-position, if there is no other substituent) and **A264-A267** can be obtained from suitably substituted 5-hydroxy-indoles by formation of the diethyl carbamate followed by anionic Fries rearrangement to the diethyl amide, which is subsequently hydrolyzed with aqueous sodium hydroxide or perchloric acid (E. J. Griffen et al., *J. Org. Chem.* **1995**, *60*, 1484-1485). The benzothiophenes of type **A260** and **A263** should accessible from 4,6-dibromo-benzene-1,3-carbaldehyde (substituted in 2- or 5-position) by subsequent substitution of the bromides with methoxide and with 2-mercaptoacetate followed by cyclization, decarboxylation, demethylation and oxidation of the aldehyde to the acid (A. E. Jakobs et al., *Tetrahedron* **1994**, *50*, 9315-9324).

Benzofuranes of type **A268-A271** can be synthesized from the corresponding 4-hydroxy-benzofuranes by carboxylation with carbon dioxide in the presence of methoxide (T. Reichstein, R. Hirt, *Helv. Chim. Acta* **1933**, *16*, 121-129) or from suitably substituted 5-carbomethoxy-6-hydroxy-salicylaldehydes by reaction with bromoacetates followed by saponification and cyclization in the presence of acetic anhydride (R. T. Foster,

A. Robertson, *J. Chem. Soc.* **1948**, 115-116). The preparation of the corresponding benzothiophenes **A268-A271** should be possible from suitably substituted 4-oxo-tetrahydrobenzothiophene by acylation with dimethyl carbonate followed by aromatization with DDQ (P. P. Yadav et al., *Bioorg. Med. Chem.* **2005**, *13*, 1497-1505). The indoles **A268-A271** can be prepared similarly from the 4-oxo-tetrahydroindoles, or alternatively from suitably substituted N-protected 4-amino-salicylic acid via Claisen rearrangement of the O-allyl ether followed by cleavage of the double bond and cyclization (T. Kakigami et al., *Chem. Pharm. Bull.* **1988**, *46*, 42-52). Benzofuranes of type **A273-A275** can be obtained from 4-O-protected 4-hydroxy-salicylaldehydes by reaction with ethyl diazoacetate in the presence of tetrafluoroboric acid followed by dehydration and deprotection (M. E. Dudley et al., *Synthesis* **2006**, 1711-1714). The benzothiophenes **A272-A275** are accessible from 5-bromo-benzothiophene (which, in turn, can be prepared from suitably substituted 4-bromo-thiophenols and bromoacetaldehyde diethyl acetal) by Friedel-Crafts acylation, conversion of the methyl ketone into the carboxylate, substitution of the bromide with methoxide and demethylation (S. Mitsumori et al., *J. Med. Chem.* **2003**, *46*, 2446-2455). The synthesis of corresponding indoles **A272-A275** should be possible by the reaction of suitably substituted para-benzoquinones with substituted 2-aminoacrylates in a Nenitzescu reaction (E. A. Steck et al., *J. Org. Chem.* **1959**, *24*, 1750-1752) Benzofuranes of type **A276-A279** can be obtained from the 3-acetyl-4-hydroxy-benzoates by bromination of the methyl ketone followed by base-induced cyclization to the keto-tautomer of **A276-A279** (G. Doria et al., *Farmaco* **1980**, *35*, 674-680). The synthesis of 2-substituted benzofuranes **A278** can be achieved by alkylation or acylation. The corresponding benzothiophenes **A276-A279** may be prepared from suitably substituted 4-fluorobenzoates and thioglycolate by $AlCl_3$-induced intramolecular Fridel-Crafts acylation of the intermediate 4-alkoxycarbonyl-phenylsulfanyl acetates (D. L. Gernert et al., *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2759-2764).

The benzofuranes and benzothiophenes of type **A284-A287** can be synthesized from suitably substituted 3-furaldehydes or 3-formyl-thiophenes by condensation with diethyl succinate followed by cyclization in the presence of acetic anhydride and then base (D. Simoni et al., *J. Med. Chem.* **2006**, *49*, 3143-3152). The indoles of type **A284** and **A287** are accessible from 3-methoxy-4-amino-benzoates by subsequent 5-iodination, Sonogashira coupling with TMS-acetylene and CuI-mediated cyclization followed by demethylation (J. Ezquerra et al., *J. Org. Chem.* **1996**, *61*, 5804-5812). Benzofuranes and benzothiophenes of type **A288-A291** can be obtained from suitably substituted 2-furaldehydes similarly as described for **A284-A287** (D. Simoni et al., *J. Med. Chem.* **2006**, *49*, 3143-3152). The indoles **A288-A291** can be synthesized similarly from pyrrole-2-carbaldehydes and diethyl succinate followed by base-induced cyclization (C. Fuganti, S. Serra, *J. Chem. Res. (M)* **1998**, *10*, 2769-2782).

The indoles of type **A292-A295** can be prepared from N-protected ethyl furo[3,2-b]pyrrole-5-carboxylates by decarboxylation with copper chromite in quinoline followed by Diels-Alder reaction with ethyl propiolate and subsequent deprotection (A. Krutosikova, M. Hanes, *Collect. Czech. Chem. Comm.* **1992**, *57*, 1487-1494).

Benzofuranes of type **A296-A299** can be obtained from suitably substituted (p-acetoxyphenoxy)acetyl chlorides by reaction with cyanide followed by cyclization with 1,3-dihydroxy-benzene mediated by zinc(II)-chloride and hydrogen chloride (L. Crombie et al., *J. Chem. Soc., Perkin Trans. 1* **1987**, 2783-2786). The corresponding benzothiophenes **A296-A299** can be synthesized from suitably substituted 3-bromothiophenols similarly to the synthesis of **A272-A275** (S. Mitsumori et al., *J. Med. Chem.* **2003**, *46*, 2446-2455). The access of the indoles **A296-A299** can be achieved either from O-protected 6-hydroxyindoles by acylation in 3-position with trichloroacetyl chloride and methanolysis followed by deprotection (M. Fedouloff et al., *Bioorg. Med. Chem.* **2001**, *9*, 2119-2128) or by acylation of suitably

substituted indoles in 3-position followed by 6-hydroxylation via a Friedel-Crafts acylation/Baeyer-Villiger oxidation sequence (S. Nakatsuka et al., *Heterocycles* **1987**, *26*, 1471-1474).

The benzofuranes **A300-A303** can be obtained from suitably substituted 3-acetyl-furanes by transformation into the silylenol ether followed by Diels-Alder reaction, elimination and dehydrogenation (A. Benitez et al., *J. Org. Chem.* **1996**, *61*, 1487-1492).

The benzofuranes **A304-A307** can be synthesized either from substituted 2-allyl-3-allyloxy-4-methoxy-benzaldehydes by isomerization/metathesis followed by oxidation of the aldehyde and demethylation (W. A. L. van Otterlo et al., *Tetrahedron* **2005**, *61*, 7746-7755) or from substituted 2-hydroxy-3-methoxy-6-bromo-benzaldehydes by reduction of the alcohol, formation of the phosphonium salt and cyclization in the presence of an acid chloride followed by lithiation/carboxylation and demethylation (K. Hagihara et al., *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1616-1621). The corresponding benzothiophenes **A304-A307** are accessible from suitably substituted methyl thiophene-2-carboxylates by transformation into the 1-(2'-thienyl)-1,4-dioxobutanes followed by BF_3-mediated cyclization, 4-carbonylation by Vilsmeyer-Haack reaction, oxidation of the aldehyde and demethylation (S. S. Samanta et al., *J. Chem. Soc., Perkin Trans. 1* **1997**, 3673-3678).

The indoles **A304-A307** can be obtained either by Diels-Alder reaction of the silylenolate of N-protected 2-acetylpyrrole with propiolate followed by air oxidation (M. Ohno et al., *Heterocycles* **1991**, *32*, 1199-1202) or from suitably substituted 4-benzyloxy-2-methyl-3-nitro-benzoates (prepared from the 3-methylphenols in a multistep sequence) by subsequent reaction with dimethylformamide and zinc/acetic acid followed by deprotection (M. Tanaka et al., *Eur. J. Med. Chem.* **1996**, *31*, 187-198).

A358-A372 Pyrrolo[2,3-*b*]pyridine Derivatives

The pyrrolopyridines **A365** and **A366** can be synthesized from 7-azaindole, which is first transformed into N-protected 4-chloro-7-azaindole via the pyridyl-N-oxide (X. Wang et al., *J. Org. Chem.* **2006**, *71*, 4021-4023), followed by 5-lithiation and carboxylation, hydrolysis of the chloride and of the ester and N-deprotection (A. L'Heureux et al., *Tetrahedron Lett.* **2004**, *45*, 2317-2320). The pyrrolopyridines of type **A367** and **A368** can be obtained from suitably substituted 4-chloro-3-formyl-pyridines by reaction with azidoacetate followed by a Hemetsberger-Knittel reaction(P. J. Roy et al., *Synthesis* **2005**, 2751-2757). The pyrrolopyridines of type **A369** and **A370** may be accessible from the corresponding substituted 5-chloro-pyrrolopyridine by formylation in a Duff reaction, oxidation to the acid and hydrolysis of the chloride (R. H. Bahekar et al., *Bioorg. Med. Chem.* **2007**, *15*, 6782-6795) The synthesis of pyrrolopyridines **A371** and **A372** may be possible from 4-chloro-7-azaindole by pyridyl-N-oxidation and –methylation followed by substitution with cyanide and hydrolysis of the nitrile and chloride (T. Storz et al., *Synthesis* **2008**, 201-214).

A373-A385 Pyrrolo[2,3-*c*]pyridine Derivatives

The pyrrolopyridine **A379** might be obtained from suitably substituted 4-iodo-3-nitro-pyridines by a Sonogashira coupling, ethanolysis of the alkyne, reduction of the nitro group and $TiCl_4$-mediated cyclization (T. Sakamoto et al., *Chem. Pharm. Bull.* **1986**, *34*, 2362-2368). The pyrrolopyridines of type **A382** and **A383** can be prepared from 2-methoxy-4-iodo-5-aminopyridines by Sonogashira coupling with TMS-acetylene, CuI-mediated cyclization, formylation (and oxidation) in 3-position and demethylation (D. Mazeas et al., *Heterocycles* **1999**, *50*, 1065-1080).

Pyrrolopyridines of type **A384** and **A385** are accessible from suitably substituted 4-methoxy-pyrrole-2-carbaldehyde by reductive amination with 3,3-diethoxy-2-amino-propionate, $TiCl_4$-mediated cyclization and demethylation (S. K. Singh et al., *Heterocycles* **1997**, *44*, 379-392).

A386-A398 Pyrrolo[3,2-*c*]pyridine Derivatives

The pyrrolopyridines **A387** and **A388** could be accessible starting from suitably substituted N-alkylated 2-formyl-pyrroles via the 2-pyrrylacryl azides, which are then cyclized to the pyrrolopyridinones. These intermediates are then transformed into the 3-carboxy compounds via the corresponding aldehydes (J. S. New et al., *J. Med. Chem.* **1989**, *32*, 1147-1156). The pyrrolopyridines of type **A389** and **A390** can be obtained from suitably substituted 2-methoxy-3-formyl-pyridines by reaction with azidoacetate followed by a Hemetsberger-Knittel reaction, similarly to the synthesis of **A367** and **A368** (P. J. Roy et al., *Synthesis* **2005**, 2751-2757).

A399-A413 Pyrrolo[3,2-*b*]pyridine Derivatives

Pyrrolopyridines of type **A406** and **A407** can be obtained from substituted 2-(6-methoxy-3-nitro-2-pyridyl)-acetates by Knoevenagel reaction with formaldehyde followed by Pd-catalyzed cyclization in the presence of hydrogen and CO (B. C. G. Soederberg et al., *Synthesis* **2008**, *6*, 903-912).
Pyrrolopyridines **A410** and **A413** can be synthesized from suitably substituted 2-chloro-3-nicotinonitriles by Sonogashira coupling with TMS-acetylene followed by ethanolysis of the alkyne and degradation of the nitrile and finally acid-induced cyclization (T. Sakamoto et al., *Chem. Pharm. Bull.* **1986**, *34*, 2362-2368). Alternatively, the synthesis of **A410** and **A413** can be achieved by reaction of suitably substituted 3-nitro-pyridines with vinylmagnesium bromide (Z. Zhang et al., *J. Org. Chem.* **2002**, *67*, 2345-2347). The pyrrolopyridines **A408** and **A412** can be obtained from 2-alkynyl-3-amino-pyridines by CuI-catalyzed cyclization (A. M. Palmer et al., *Bioorg. Med. Chem.* **2008**, *16*, 1511-1530).

A414-A449 Benzoxazole, Benzothiazole and Benzoimidazole Derivatives

Benzoxazoles **A415** and **A416** can be prepared starting from N-acylated 3-chloro-4-anisidines via benzyne-formation and

carboxylation (D. R. Reavill, S. K. Richardson, *Synth. Comm.* **1990**, *20*, 1423-1436). The corresponding benzimidazoles **A415** and **A416** are accessible from of 2-amino-3-halo-benzoates by acylation of the amine, nitration in 6-position, alkylation of the amide and cyclization under reductive conditions (K. Kubo et al., *J. Med. Chem.* **1993**, *36*, 1772-1784).

Benzimidazoles of type **A417-A419** can be obtained from 4-acetamido-2-methoxy-benzoates by subsequent chlorination in 5-position and nitration in 3-position, followed by reductive cyclization of the obtained 3-nitro-4-amino-benzoates in the presence of carboxylic acids or formic acid (S. Bolgunas et al., *J. Med. Chem.* **2006**, *49*, 4762-4766). This reductive cyclization procedure might also be applicable to the synthesis of other benzimidazoles. Benzimidazoles **A420-A422** are accessible from the corresponding 5-methoxy-6-methyl-benzimidazoles by demethylation and oxidation of the methyl group to the carboxylate (B. D. Palmer et al., *J. Med. Chem.* **1999**, *42*, 2373-2382). Benzoxazoles of type **A423-A425** can be obtained by condensation of substituted 4-methylene-2-oxazolin-5-ones and 4-triphenylphosphoranylidene-3-oxobutanoates followed by iodine-mediated aromatization (F. Clerici et al., *Tetrahedron* **1991**, *47*, 8907-8916). The synthesis of the corresponding benzimidazoles **A423-A425** should be possible starting from 4-amino-2-hydroxy-5-nitrobenzoates via acylation, then reduction of the nitro group and cyclization, as is described for the 2-chloro-benzoates (A. Tanaka et al., *Chem. Pharm. Bull.* **1994**, *42*, 560-569). Benzoxazoles of type **A426-A428** can be synthesized starting from 2,5-dihydroxybenzoate, which is aminated in 6-position in a multistep sequence, then acylated and cyclized (D. Diez-Martin et al., *Tetrahedron* **1992**, *48*, 7899-7939).

The benzimidazoles **A429-A431** should be accessible from O-protected 3,4-diamino-2-hydroxy-benzoates, which are mono-acylated and then cyclized under acidic conditions (Y. Hirokawa et al., *Chem. Pharm. Bull.* **2002**, *50*, 941-959; A. Viger, P. B. Dervan, *Bioorg. Med. Chem.* **2006**, *14*, 8539-8549). Benzothiazoles of type **A438-A440** can be synthesized by heating suitably

substituted 4-amino-3-methoxy-benzoates with potassium thiocyanate in the presence of copper(II)-sulfate and subsequent 2-desamination and 3-demethylation (I. A. Ismail et al., *J. Org. Chem.* **1980**, *45*, 2243-2246). Benzimidazoles **A441-A443** can be prepared by a multi-step sequence from 8-aminoquinolines via the corresponding 5,6-dihydro-4H-imidazoquinolines (R. C. Elderfield, F. J. Kreysa, *J. Am. Chem. Soc.* **1948**, *70*, 44-48). Benzimidazoles **A444** and **A447** can be obtained by reaction of suitably substituted 3-amino-4-methoxy-benzoates with nitriles followed by NaOCl-induced cyclization and subsequent deprotection (J. Reagn et al., *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2737-2742).

A450-A459 Benzoisoxazole, Benzoisothiazole and Indazole Derivatives

Benzoisoxazoles of type **A456** and **A459** can be synthesized starting from 2,6-dihydroxy-3-formyl-4-methyl-benzoates by reaction with hydroxylamine followed by thermal cyclization (D. H. R. Barton et al., *J. Chem. Soc. C* **1971**, 2166-2174). The application of this method to the synthesis of the other benzisoxazoles (**A450-A455**, **A457** and **A458**) should be possible. The preparation of indazoles **A457** has been described by reaction of 3-amino-2-methoxy-4-methylbenzoate with isoamylnitrite followed by demethylation (S. Bolgunas et al., *J. Med. Chem.* **2006**, *49*, 4762-4766); the application to other indazoles (**A450-A456** and **A458**) appears feasible.

A460-A515 Naphthalene derivatives

A relatively large number of suitably substitued naphthalene derivatives is commercially available. In addition, naphthalenes of type **A460-A465** and **A496-A499** can be obtained from the corresponding 2-hydroxy-naphthalenes via lithiation and carboxylation (K. Takahashi et al., *Tetrahedron* **1994**, *50*, 1327-1340). Alternatively, the demethylation of 2-methoxynaphthalene carboxylic acids has been described (Y. Gao et al., *J. Med. Chem.* **2001**, *44*, 2869-2878). Higher substituted

compounds can be prepared in a multistep sequence from suitably substituted 2-bromotoluenes via 2-tetralone-1-carboxylates analogously to the method described by F. C. Goerth et al., *Eur. J. Org. Chem.* **2000**, 2605-2612.

Naphthalenes of type **A478-A483** and **A508-A511** can be prepared either by demethylation of the 3-methoxynaphthalene-1-carboxylates (R. E. Royer et al., *J. Med. Chem.* **1995**, *38*, 2427-2432) or by diazotation and subsequent hydrolysis of the corresponding 3-aminonaphthalene-1-carboxylates (K. J. Duffy et al., *J. Med. Chem.* **2001**, *44*, 3730-3745).

The naphthalenes of type **A484-A489** and **A504-A507** can be easily built up by a condensation reaction with succinic esters, starting either from suitably substituted benzaldehydes (A. M. El-Abbady et al., *J. Org. Chem.* **1961**, *26*, 4871-4873; M. Kitamura et al., *Angew. Chem. Int. Ed.* **1999**, *38*, 1229-1232) or from benzophenones (F. G. Baddar et al., *J. Chem. Soc.* **1955**, 1714-1718), depending on the substitution pattern in the desired product.

Naphthalene derivatives of type **A490-A495** and **A512-A515** can be obtained from 2-methoxynaphthalenes by bromination in 4-position, lithiation of the bromide followed by carboxylation and demethylation (J. A. O'Meara et al., *J. Med. Chem.* **2005**, *48*, 5580-5588) or from 2-chloro-naphthalene by reaction with phthalic anhydride followed by KOH-induced cleavage (G. Heller, *Chem. Ber.* **1912**, *45*, 674-679).

A516-A548 Quinoline Derivatives

The synthesis of quinolines of type **A516-A518** can be accomplished by reaction of suitably substituted isatins with substituted phenacylbromides (H. John, *J. Prakt. Chem.* **1932**, *133*, 259-272; E. J. Cragoe et al., *J. Org. Chem.* **1953**, *18*, 552-560).

Quinolines of type **A522-A524** are easily accessible from suitably substituted 2-amino-benzaldehydes via a modified Friedländer synthesis (D. L. Boger, J.-H. Chen, *J. Org. Chem.* **1995**, *60*, 7369-7371). Similarly, quinoline derivatives **A527-**

A529 can be obtained from 2-aminobenzaldehydes by condensation with malonic acid (J. Troeger, C. Cohaus, *J. Prakt. Chem.* **1927**, *117*, 97-116).

Quinolines **A525** can be synthesized from the corresponding 2-cyanoquinoline-1-oxides by rearrangement (C. Kaneko, S. Yamada, *Chem. Pharm. Bull.* **1967**, *15*, 663-669). The quinolines **A526** (with a substitution in 4-position) are in principle accessible from substituted 2-aminoacetophenones (with the substitution on the acetyl moiety) by reaction with 3-chloro-3-oxopropionate and subsequent base-induced cyclization (A. Capelli et al., *Bioorg. Med. Chem.* **2002**, *10*, 779-802).

Quinolines of type **A530-A533** can be built up starting from 2-anisidines by reaction with 2-oxosuccinic esters followed by thermal cyclization, demethylation and removal of the 4-hydroxy group via hydrogenation of the corresponding chloride (L. Musajo, M. Minchilli, *Chem. Ber.* **1941**, *74*, 1839-1843).

For the synthesis of quinolines of type **A543-A545** the condensation of suitably substituted isatins with malonic acid has been described (e.g. W. Borsche, W. Jacobs, *Chem. Ber.* **1914**, *47*, 354-363; J. A. Aeschlimann, *J. Chem. Soc.* **1926**, 2902-2911).

A549-A564 Isoquinoline Derivatives

Isoquinolines of type **A549-A553** with the carboxylate in the 1-position can be prepared from suitably substituted benzaldehydes, which are transformed into the aminoethanes followed by reaction with oxalic ester aldehyde or acid chloride, cyclization, oxidative aromatization and finally saponification (M. Keizo et al., *Chem. Pharm. Bull.* **1982**, *30*, 4170-4174; S. Naoki et al., *Chem. Pharm. Bull.* **1989**, *37*, 1493-1499).

Isoquinoline-3-carboxylates (**A554-A556**) are accessible from hydroxylated phenylalanines via a Bischler-Napieralski reaction followed by oxidative aromatization, or alternatively from suitably substituted 2-methyl benzaldehydes, which are reacted with methyl azidoacetate and then cyclized under thermal conditions followed by aromatization (Y. Fukuda et al., *J. Med.*

Chem. **1999**, *42*, 1448-1458; T. R. Burke et al., *Heterocycles* **1992**, *34*, 757-764).

Compounds of type **A557** and **A558** can be built up by reaction between suitably substituted 2-aminobenzoic acids and 5-chloro-3-carboxy-1,2,4-pyrazines in the presence of amylnitrite followed by hydrolysis (A. M. d'A. Rocha Gonsalves, T. M. V. D. Pinho e Melo, *Tetrahedron* **1992**, *48*, 6821-6826), whereas isoquinolines **A559** and **A560** can be prepared by reaction of 2-formylbenzoic acids with 2-thioxothiazolidin-4-one followed by cyclization and transformation of the isothiochromenone into the isoquinoline with ethanolic ammonia (D. J. Dijksman, G. T. Newbold, *J. Chem. Soc.* **1951**, 1213-1217).

The access to isoquinolines **A561** and **A562** might be possible by transformation of suitably substituted isquinolines into the corresponding Reissert compounds, nitration in 4-position and hydrolysis of the nitrile (M. Sugiura et al., *Chem. Pharm. Bull.* **1992**, *40*, 2262-2266) followed by hydrogenation of the nitro group, diazotation of the amine and transformation into the hydroxyl group.

Isoquinolines of type **A563** and **A564** are accessible from suitably substituted (2-methoxycarbonyl-phenyl-)acetic acids via reaction with methyl formiate followed by cyclization of the formed enol and amination of the isochromenone (H. E. Ungnade et al., *J. Org. Chem.* **1945**, *10*, 533-536).

A565-A577 Quinazoline Derivatives

The most general routes to quinazolines use appropriately substituted phenyl derivatives onto which the pyrimido ring is cyclized, e.g. the cyclocondensation of 2-amino benzamides with oxalates (M. Suesse et al., *Helv. Chim. Acta* **1986**, *69*, 1017-1024), of *ortho*-carbonyl substituted phenyl oxalamic acid esters with ammonium formate (S. Ferrini et al., *Org. Lett.* **2007**, 9, 69-72), or of 2-amino benzonitriles with carbonylformimidate or chloroformamidine (A. McKillop et al., *Tetrahedron Lett.* **1982**, *23*, 3357-3360; N. Harris et al., *J. Med. Chem.* **1990**, *33*, 434-444), or of *ortho*-oxalyl anilides with

ammonia (M. T. Bogert, F. P. Nabenhauer, *J. Am. Chem. Soc.* **1924**, *46*, 1702-1707).

A578-A587 Quinoxaline Derivatives

The synthesis of quinoxalines of types **A578-581** via their 2-carbaldehydes is well-described (E. Lippmann et al., *Zeitschr. Chem.* **1990**, 30, 251-252). The other representatives of these groups **A582-587** are available by cyclocondensation of β-dicarbonyl derivatives or β-keto-esters with appropriately substituted *ortho*-phenylendiamines (S. Grivas et al., *Acta Chem. Scand.* **1993**, 47, 521-528; A. Zychilinski, I. Ugi, *Heterocycles* **1998**, 49, 29-32; D. Zhou et al., *Bioorg. Med. Chem.* **2008**, 16, 6707-6723). Unique to the quinoxaline is the possibility to introduce a carboxyl group in the 2-position by enzyme catalyst biotransformation applying *Arthrobacter nicotianae* (T. Yoshida et al., *Biosci. Biotech. Biochem.* **2002**, 66, 2388-2394).

A588-A601 Pyrido[5,4-*d*]pyrimidine Derivatives

The bicyclic core can be accessed by annelating suitably substituted pyridines by cyclocondensation reactions. Feasible starting materials include pyridine-2,3-dicarboxylic acids (A. Tikad et al., *Synlett* **2006**, *12*, 1938-1942), 3-aminopyridine-2-carboxylates (M. Hayakawa et al., *Bioorg. Med. Chem.* **2006**, *14*, 6847-6858) or 3-aminopyridine-2-nitriles (J. B. Smaill et al., *J. Med. Chem.* **2000**, *43*, 1380-1397).

A602-A608 Pyrimido[5,4-*d*]pyrimidine Derivatives

Access to the pyrimidopyrimidine group of templates might be achieved via the literature-known 4,6-dichloro derivative (G. Rewcastle et al., *J. Med. Chem.* **1997**, *40*; 12, 1820-1826) or the corresponding 2,4,6,8-tetrachloro derivative (J. Northen et al., *J. Chem. Soc., Perkin Trans. 1*, **2002**, 108-115) using the general methods described above and separation of the expected isomeric mixtures.

A609-A618 Tetraline Derivatives

A large number of reaction sequences that lead to tetraline derivatives involve an intramolceular Friedel-Crafts acylation as a key step, and the prerequisite cyclization precusors can be elaborated from phenylacetonitriles, 2-phenyl malonates (R. S. Natekar, S. D. Samant, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2002**, 41, 187-190; L. Gong, H. Parnes, *J. Labelled Compd. Radiopharm.* **1996**, 38, 425-434). Alternatively, the intramolecular cyclization can be achieved by a Buchner Reaction (A. Cheung et al., *Bioorg. Med. Chem. Lett.* **2003**, *13*, 133-138). Subsequently, the carbonyl groups of the thus obtained 1- or 2- tetralones can easily be converted into carboxyl moieties (M. Meyer et al., *J. Med. Chem.* **1997**, *40*, 104-1062; F. Berardi et al., *J. Med. Chem.* **2004**, *47*, 2308-2317).

A619-A626 Indane Derivatives

Indane derivatives of types **A619-A623** with a carboxyl group in the 1-position are accessible from appropriately substituted and easily available 3-cyano-indenes by hydrogenation to the indane core followed by hydrolysis to the carboxyxlic acid moiety (T. McLean et al., J. Med. Chem. **2006**, *49*, 4269 – 4274). Also indan-1-ones can be transferred into indane-1-caboxylic acids, for example via oxiranes (D.-I. Kato et al., *J. Org. Chem.* **2003**, 68, 7234 – 7242), or in a Corey-Seebach-type reaction via 1,3-dithianes (Y.-P. Pang et al., J. Org. Chem. **1991**, 56, 4499 – 4508).

Indane derivatives of types **A624-A626** with a carboxyl group in 2-position can be obtained from readily accessible, suitably substituted indan-1-ones by treatment of the corresponding enolate with a dimethyl carbonate, hydrogenation of the carbonyl group and hydrolysis of the introduced ester group (T. Tanaka et al., *Chem. Pharm. Bull.* **1994**, 42, 1756 – 1759; U. Hacksell et al. *J. Med. Chem.* **1981**, 24, 429 – 434).

Alternatively the indane ring system can be built up starting from *ortho*-xylenes by NBS bromination of both methyl residues, alkylation-spirocyclization with the enolate of barbituric acid

and finally decarboxylative ring cleavage to indane-2-caboxylic acids (G. A. Kraus et al., *J. Org. Chem.* **2002**, 67, 5857 - 5859).

Synthesis of Building Blocks for the Modulators B

The Modulator moieties **B** of the macrocycle **I** are derived from appropriately substituted aminoalcohols, wherein the amino and alcohol group, which contribute to the ring connectivity, are separated from by 2-4 C-atoms.

If not already present in a commercial building block, the substituent R^3 can be introduced by standard nucleophilic addition of organo metallic reagents to carbonyl or carboxyl derivatives. For **B18-B21**, carrying no additional C-substituent on their ring system, such precursors are commercially available. Similarly, in the case of **B9**, **B10**, **B16** and **B17** the diversification of the substituent pattern can be easily achieved by standard transformations of the commercial analogs with free amine functionalities (i.e. $-NH_2 \rightarrow -NR^{11}R^{27}$ in the case of **B9** and $-NH \rightarrow -NR^{11}$ for **B10**, **B16** and **B17**).

B1 Aziridine Derivatives

Usually, the access to hydroxymethyl aziridines relies on reaction sequences involving the construction of the aziridine ring. The starting materials with the broadest applicability are β-ketoesters: Transformation into the β-hyroxyimino analog, intramolecular cyclisation to the aziridine ring and reduction of the ester to the alcohol group leads to building blocks of type **B1** (e.g. T. Sakai et al., *J. Org. Chem.* **2005**, *70*, 1369 - 1375). An alternative approach uses α,β-dihaloester which are converted into substances of type **B1** via aziridination with ammonia and reduction of the ester group (P. Davoli et al., *Tetrahedron* **2001**, *57*, 1801 - 1812).

B2-B3 Azetidine Derivatives

The standard approaches to hydroxymethyl azetidines comprises subjecting easily accessible *O*-protected glycidols to,

successively, an epoxide-ring opening with azide, transformation of the OH group of the thus obtained alcohol into a suitable leaving group (e.g. tosylate or sulfate), reduction of the azide to an amine and concomitant intramolceular cyclization (F. Hosono et al., *Tetrahedron* **1994**, *50*, 13335-13346; D.-G. Liu, G.-Q. Lin, *Tetrahedron Lett.* **1999**, 40, 337-340).

B4-B8 Pyrrolidine Derivatives and **B11-B15** Piperidine Derivatives

The synthetic approaches to the pyrrolidine and piperidine classes of building blocks **B** rely on the same strategies and are therefore discussed together. Intramolecular cyclization reactions are the predominant routes applicable to a broad number of diversely substituted substrates: Amines carrying a residue with a leaving group in the ω-position lead directly to the desired saturated ring systems by an intramoleular nulceophilic substitution (G. Ceulemans et al., *Tetrahedron* **1997**, *53*, 14957-14974; S. H. Kang, D. H. Ryu, *Tetrahedron Lett.* **1997**, *38*, 607-610; J. L. Ruano et al., *Synthesis* **2006**, 687-691). Also *N*-haloamines can be directly transformed to the desired compounds by the Hofmann-Löffler-Freytag reaction (M. E. Wolff, *Chem. Rev.* **1963**, *63*, 55-64). Alternatively amines carrying two substituents, each with an alkene or alkyne bond, can be subjected to a ring closing metathesis (RCM) reaction (Y. Coquerel, J. Rodriguez, *Eur. J. Org. Chem.* **2008**, 1125-1132) and subsequent reduction of the thus obtained partially unsaturated ring to the saturated heterocycle.

Also the reduction of the corresponding aromatic five- and six-membered heterocycles to their saturated analogs is described in the literature. However, due to the large number of commercially available pyridines this approach is mainly applied to the synthesis of the piperidine system (J. Bolos et al., *J. Heterocycl. Chem.* **1994**, *31*, 1493-1496; A. Solladie-

Cavallo et al., *Tetrahedron Lett.* **2003**, *44*, 8501-8504; R. Naef et al., *J. Agric. Food Chem.* **2005**, *53*, 9161-9164).

Procedures for the synthesis of libraries of macrocyclic compounds of general structure **I** are described below but it will immediately apparent to those skilled in the art how these procedures have to be modified if it is intended to synthesize one single macrocyclic compound of formula I.

The macrocyclic compounds of the invention are obtained by cyclization of suitable linear precursors which are derived from optionally substituted hydroxyaryl, hydroxyheteroaryl, mercaptoaryl, or mercaptoheteroaryl carboxylic acids **A** ("template", **a**), substituted amino alcohols **B** ("modulator", **b**) and one to three building blocks of type **C** forming the "bridge", **c**.

Variable substituents are introduced by pre- or postcyclative derivatization of one or more orthogonally protected attachment points (e.g. amino groups, carboxyl groups, hydroxyl groups) on building blocks **B** and **C**, and optionally **A**. Variable R-groups may also be introduced as side chain motifs in building blocks **C**.

The macrocyclic products of the invention can be prepared either in solution or on a solid support.

In accordance with the present invention, the ring closure reaction is, in principle, possible between any of the building blocks.

Macrocycles of general structure **I** with building block **c** forming the bridge **c** are obtained by either

a) macrolactamisation between **c** and **B**; or

b) macrolactamisation between **A** and **c**; or

c) aryl- or thioaryl ether formation between **A** and **B**; or, alternatively,

d) Ring closure metathesis reaction within building blocks of type **C** is also possible.

Macrocycles of structure **I** with orthogonally protected exocyclic functional groups (attachment points for derivatization) are prepared in solution by a process which comprises:

a^1) condensation of an appropriately protected hydroxy- or mercapto-aryl/heteroaryl carboxylic acid PG-**A**-OH and a suitably C-terminal- and appropriately side-chain-protected building block H-**c1**-OPG to form PG-**A**-**c1**-OPG;

b^1) if required release of the aryl/heteroaryl (phenolic) OH group or mercapto group, respectively;

c^1) aryl/heteroaryl ether or thioether formation with a suitably N-protected amino alcohol HO-**B**-PG leading to the fully protected linear cyclization precursor PG-**B**-**A**-**c1**-OPG;

d^1) cleavage of the "main chain" protective groups (PG) affording the free amino acid H-**B**-**A**-**c1**-OH (still carrying appropriately protected side chain functional groups); followed by either

e^1) intramolecular amide coupling affording protected macrocycles of general formula **I** (yielding cyclo-(**B**-**A**-**c1**) still carrying orthogonally protected side chain functional groups); or

f^1) N-reprotection of the product obtained in step d^1);

g^1) coupling of a suitably C-protected amino acid H-**c2**-OPG;

h^1) cleavage of the "main chain" protective groups affording the free amino acid H-**B**-**A**-**c1**-**c2**-OH (still carrying appropriately protected side chain functional groups);

i^1) intramolecular amide coupling affording the protected macrocycles of general formula **I** (yielding cyclo-(**B**-**A**-**c1**-**c2**);

still carrying orthogonally protected side chain functional groups); or

j^1) N-protection of the product obtained in step d^1);

k^1) coupling of a suitably C-protected amino acid H-**c2**-OPG

l^1) cleavage of the C-terminal protective group or cleavage of N- and C-terminal main chain protective groups and reprotection of the N-terminus;

m^1) coupling of a suitably C-protected amino acid H-**c3**-OPG;

n^1) release of the "main chain" protective groups affording the free amino acid H-**B**-**A**-**c1**-**c2**-**c3**-OH (still carrying protected side chain functional groups); and

o^1) intramolecular amide coupling affording the protected macrocycles of general formula **I** (yielding cyclo-(**B**-**A**-**c1**-**c2**-**c3**), still carrying protected side chain functional groups).

The appropriately protected, preferably acyloxy- or acylmercapto-, most preferably acetyloxy- or acetylmercapto-substituted aryl/heteroaryl carboxylic acid (PG^1-**A**-OH) is converted into the corresponding acid chloride and condensed with a suitably protected amino acid ester H-**c1**-OPG^2 in the presence of an auxiliary base (e.g $i\text{-}Pr_2NEt$, Et_3N, pyridine, collidine) and in solvents like CH_2Cl_2, $CHCl_3$, THF to afford after deacylation (preferably by aminolysis) the hydroxyl or mercapto aryl/heteroaryl amide H-**A**-**c1**-OPG^2.

The aminolysis is advantageously carried out with a dialkylaminoalkyl amine in solvents like THF at 0-25°C. Acyl amine side products formed in the course of the reaction can thus be removed by extraction with acidic aqueous solutions.

Alternatively, the acyloxy or acylmercapto aryl/heteroaryl carboxylic acid (PG^1-**A**-OH) can be coupled in the presence of a coupling reagent (such as benzotriazol derivatives like HBTU, HCTU, PyBOP, or their aza analogs such as HATU, or carbodiimides such as EDC) to the amino acid ester H-**c1**-OPG^2 to

afford, after deacylation, the phenol or thiophenol H-**A**-**c1**-OPG^2.

The phenol H-**A**-**c1**-OPG^2 can also be directly obtained from the hydroxyaryl/heteroaryl carboxylic acid H-**A**-OH and the amino acid ester H-**c1**-OPG^2 in the presence of a coupling reagent.

Alkylation of the phenol or thiophenol H-**A**-$\mathbf{C_1}$-OPG^2 with a suitably N-protected amino alcohol HO-**B**-PG^3 to give the ether or thioether PG^3-**B**-**A**-**c1**-OPG^2 is achieved using azodicarboxylic acid derivatives such as DEAD, DIAD or ADDP in the presence of trialkyl or triaryl phosphines in solvents like benzene, toluene, CH_2Cl_2, $CHCl_3$ or THF at 0°C to room temperature. As a variation, the reaction can be induced with CMBP in toluene at temperatures ranging from 20 – 110°C.

As an alternative, the alcohol HO-**B**-PG^3 can be converted into a corresponding sulfonates (such as for example the mesylate, tosylate, triflate) or a corresponding halide (such as chloride, bromide and iodide) and subsequently be treated with the phenol or thiophenol H-**A**-**c1**-OPG^2 in the presence of an auxiliary base such as for example NaH or K_2CO_3 in solvents like DMF, DMSO, NMP, HMPA, THF, to give the ether or thioether PG^3-**B**-**A**-**c1**-OPG^2.

Simultaneous or stepwise cleavage of the main chain protective groups provides the linear amino acid cyclization precursor H-**B**-**A**-**c1**-OH. Alloc (for PG^3) and allylester groups (for PG^2) are preferred as protecting groups and best cleaved simultaneously mediated by palladium catalysts, e.g. $Pd(PPh_3)_4$, in the presence of 1,3-dimethyl barbituric acid in solvents like CH_2Cl_2 or EtOAc or mixtures thereof.

Macrolactamization occurs upon treatment of the cyclization precursor
H-**B**-**A**-**c1**-OH – if required in the presence of an auxiliary base such as i-Pr_2NEt – with coupling reagents like T3P or FDPP in solvents like CH_2Cl_2 or DMF under high dilution conditions and at temperatures ranging from 20 to 100°C to yield cyclo-(**B**-**A**-**c1**).
For examples of macrolactamizations mediated by FDPP see J. Dudash, J. Jiang, S.C. Mayer, M.M. Joullié, Synth. Commun. **1993**, 23 (3), 349 – 356; R. Samy, H.Y. Kim, M. Brady, and P.L. Toogood, J. Org. Chem. **1999**, 64, 2711 – 2728.

It is well known that many other coupling reagents have been used in such head to tail cyclizations to prepare macrolactams, and such other coupling reagents might, alternatively, be engaged in the above mentioned reactions. Examples include benzotriazole derivatives such as HBTU, HCTU, PyBOP and their aza analogs such as HATU, as well as DPPA, and carbodiimides like EDC, DIPCDI; for examples see P. Li, P.P. Roller, Current Topics in Mecicinal Chemistry **2002**, 2, 325 – 341; D.L. Boger, S. Miyazaki, S.H. Kim, J. H. Wu, S.L. Castle, O. Loiseleur, and Q. Jin, J. Am. Chem. Soc. **1999**, 121, 10004 – 10011).

Another option to obtain macrolactams comprises the intramolecular reaction of an active ester with an *in situ* released amino group (carbamate deprotection, azide reduction) as demonstrated for example in the synthesis of peptide alkaloids and vancomycin model systems (U. Schmidt, A. Lieberknecht, H. Griesser, J. Talbiersky, J. Org. Chem. **1982**, 47, 3261 – 3264; K.C. Nicolaou, J.M. Ramanjulu, S. Natarajan, S. Bräse, H. Li, C.N.C. Boddy, F. Rübsam, Chem. Commun. **1997**, 1899 - 1900.)

N-reprotection of H-**B**-**A**-**c1**-OH can be achieved applying standard amino acid protection protocols. Chloroformates or N-hydroxy-

succinimidyl carbonates in solvents like dioxane, if required in the presence of a base such as aqueous K_2CO_3 solution, react to give the N-protected amino acid PG^3-**B**-**A**-**c1**-OH.

Coupling of an additional amino acid can be effected applying classical peptide coupling conditions.

Building blocks **c1** – **c3** can be derived from tri-functionalized aminoacids (e.g. derivatives of Dap, Dab, Orn, Lys, Asp, Glu), main chain- or side chain- functional groups of which may be part of the macrocyclic scaffold.
Non proteinogenic tri-functionalized amino acid building blocks can be obtained by various synthetic methods, among others formal alkylation of the side chain hydroxyl group of Ser, HomoSer, Thr or derivation of the mercapto group of Cys, HomoCys with Ω-haloalkyl carboxylic esters.

An alternative route for synthesizing macrocyclic compounds of the invention comprises
a^2) synthesis of the H-**A**-**c1**-OPG^2 fragment as described above;
b^2) N-acylation of the aminoalcohol HO-**B**-H with a suitably N-terminal protected amino acid PG^4-**c2**-OH to afford the amidoalcohol PG^4-**c2**-**B**-OH;
c^2) aryl or thioaryl ether synthesis starting from H-**A**-**c1**-OPG^2 and
PG^4-**c2**-**B**-OH, applying conditions as described above;
d^2) release of the "main chain" protective groups to give the cyclization precursor H-**c2**-**B**-**A**-**c1**-OH; and
e^2) macrolactamization as described above, affording the protected macrocycles of general formula **I** (cyclo-(**c2**-**B**-**A**-**c1**), side chain functional groups still carrying orthogonal protective groups).

The fragment PG^4-**c3**-**B**-OH can be prepared by N-Acylation of the amino alcohol HO-**B**-H with suitable N-terminal protected amino acid PG4-**C3**-OH. N-deprotection and coupling to an appropriately N-terminal protected amino acid PG^5-**c2**-OH affords the alcohol PG^5-**c2**-**c3**-**B**-OH which can then be converted - by effecting steps corresponding to c^2), d^2) and e^2) - into the protected macrocycles of general formula **I** (cyclo(**c2-c3-B-A-c1**), side chain functional groups still carrying orthogonal protective groups).

As a further alternative, cyclization can be obtained by ring closing metathesis. The orthogonally protected macrocycles of general structure **I** are synthesized applying a process which comprises

a^3) coupling of an optionally substituted alkenyl amine containing building block **c1**(alkenyl) of type **C** to the acyloxy or hydroxy or acylmercapto aryl/heteroaryl carboxylic acid PG^1-**A**-OH;

b^3) if required release of the aryl/heteroaryl (phenolic) OH group or mercapto group, respectively;

c^3) N-acylation of the aminoalcohol HO-**B**-H with an optionally suitably substituted alkenyl carboxylic acid PG^6-**c2**(alkenyl)-OH to afford the amido alcohol PG^6-**c2**(alkenyl)-**B**-OH;

d^3) aryl or thioaryl ether formation as described above to yield the cyclization precursor PG^6-**c2**(alkenyl)-**B**-**A**-**c1**(alkenyl);

e^3) ring closure metathesis; and

f^3) optional hydrogenation of the newly generated olefinic double bond of the metathesis product of step e^3).

Ring closure metathesis to form macrocyclic compounds from olefinic precursors is well known (for examples see A. Fürstner, O. Guth, A. Duffels, G. Seidel, M. Liebl, B. Gabor, and R. Mynott, Chem. Eur. J. **2001**, 7 (22), 4811 - 4820).

Ring closure metathesis of PG^6-**c2**(alkenyl)-**B**-**A**-**c1**(alkenyl) is conveniently performed in suitable solvents, like CH_2Cl_2 or toluene, at 20 to 100°C in the presence of indenylidene-ruthenium complexes including dichloro-(3-phenyl-1H-inden-1-ylidene)bis(tricyclohexylphosphine)-ruthenium (II), [1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]-dichloro-(3-phenyl-1H-inden-1-ylidene(tricyclohexylphosphine)-ruthenium(II), [1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]-dichloro-(3-phenyl-1H-inden-1-ylidene)(pyridyl)ruthenium(II) (see S. Monsaert, R. Drozdzak, V. Dragutan, I. Dragutan, and F. Verpoort, Eur. J. Inorg. Chem. **2008**, 432 – 440 and references therein).

Derivatization of the macrocyclic core structures with variable R-groups can be effected as described hereinbelow.

Orthogonally protected attachment points (e.g. exocyclic amino groups, carboxyl groups, hydroxyl groups) allow stepwise deprotection and derivatization.

The reactions can be carried out in a parallel fashion to generate libraries of final products. The following general process can be applied:

a^4) Cleavage of the first protective group;

b^4) derivatization of the free functional group;

c^4) cleavage of the second protective group, and

d^4) derivatiszation or the free functional group.

Amine protecting groups such as preferably Boc, Cbz, Teoc, Alloc, Fmoc are removed applying standard conditions, cf. T.W. Greene, P.G.M. Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons, **1999**; P.J. Koncienski, Protecting Groups, 3rd edition, Georg Thieme Verlag, **2005**.

Carboxylic acid protecting groups such as tert.butyl, benzyl, allyl, methyl are removed applying standard conditions.

Alcohol protecting groups such as tert.butyl, benzyl, allyl, acetyl, benzoyl, pivaloyl are removed applying standard conditions.

Attachment point amino groups can be converted into amides by reaction with carbonyl chlorides, carboxylic acid anhydrides active esters or by treatment with carboxylic acids in the presence of soluble or polymer-supported coupling reagents such as for example HATU, T3P or polymer-supported carbodiimides.

Reductive alkylation of the attachment point amino groups or their reaction with alkyl halides, alkylsulfonates or Michael acceptors affords higher alkylated amines.

The reaction of attachment point amino groups with isocyanates or equivalents like carbamoyl chlorides or hydoxysuccinimidyl esters affords ureas.

The reaction of attachment point amino groups with isothiocyanates provides thioureas.

The reaction of attachment point amino groups with chloroformates or equivalents such as hydroxysuccinimidyl carbonates affords carbamates.

The reaction of attachment point amino groups with sulfonyl chlorides yields sulfonamides.

The reaction of attachment point amino groups with suitably activated aromatic or heteroaromatic halides or sulfonates - in the presence of auxiliary base and if required a Pd catalyst

(e.g. Buchwald couplings) - affords the corresponding N-aryl or N-heteroaryl derivatives.

Attachment point carboxyl groups are converted into amides using amines and coupling reagents.

Attachment point alcoholic hydroxyl groups can be alkylated with alkyl halides or alkylsulfonates to give alkylethers. Their reaction with phenols in the presence of azodicarboxylic acid derivatives and triaryl or trialkyl phosphines as well as their reaction with suitably activated aryl or heteroaryl halides or sulfonates affords aryl or heteroaryl ethers.

Attachment point secondary alcoholic hydroxyl groups can be oxidized to the corresponding ketones which in turn may be submitted to a reductive amination using amines and a suitable reducing agent.
Attachment point alcoholic hydroxyl groups can be converted into esters.
Appropriate macrocyclic compounds of general formula **I** with one or more (orthogonally) protected exocyclic functional groups and a free primary amino group can be converted into fully derivatized products on solid support.

A process, which allows an efficient parallel array derivatization, comprises
a^5) attachment of the macrocyclic amine to an appropriately functionalized solid support in a reductive amination step;
b^5) acylation, carbamoylation, oxycarbonylation or sulfonylation of the secondary amine thus obtained in step a^5);
c^5) Removal of the protective group of the next attachment point;
d^5) Derivatisation of the second free functional group whereby

amino groups can be converted into amides, ureas, thioureas carbamates, or sulfonamides, or can be alkylated; and carboxylic acids can be converted into amides;

e^5) repetition of steps c^5) and d^5) if an additional derivatisation site is available; and

f^5) Release of the final product from solid support.

In priniciple a macrocyclic carbocylic acid can be coupled to polymer-supported amines and be converted into final products by effecting steps corresponding c^5) to f^5).

The functionalized solid support is a derivative of polystyrene cross- linked with preferably 1-5% divinylbenzene, of polystyrene coated with polyethyleneglycol (Tentagel^R), and of polyacrylamid resins (see D. Obrecht, J.-M. Villalgordo, "Solid-Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound Libraries", Tetrahedron Organic Chemistry Series, Vol. 17, Pergamon, Elsevier Science, **1998**).

The solid support is functionalized by means of a linker, i.e. a bifunctional spacer molecule which contains on one end an anchoring group for attachment to the solid support and on the other end a selectively cleavable functional group used for the subsequent chemical transformations and cleavage procedures. For the purposes of the present invention, linkers are used which are designed to release an N-acyl derivative (amide, urea, carbamate) or a sulfonamide under acidic conditions. Such linkers have been applied in the backbone amide linker (BAL) strategy for solid-phase synthesis of C-terminal modified and cyclic peptides (K.J. Jensen, J. Alsina, M.F. Songster, J. Vagner, F. Albericio, and G. Barnay, J. Am. Chem. Soc. **1998**, 120, 5441 – 5452; J. Alsina, K.J. Jensen, F. Albericio, and G. Barany, Chem. Eur. J. **1999**, 5 (10), 2787 - 2795) as well as for the synthesis of heterocyclic compounds (T.F. Herpin, K.G. Van Kirk, J. M. Savino, S. T. Yu, and R. F. Labaudinière, J. Comb. Chem. **2000**, 2, 513 – 521, M. del Fresno, J. Alsina, M. Royo, G.

Barany, and F. Albericio, Tetrahedron Lett. **1998**, 39, 2639 - 2642; N. S. Gray, S.Kwon, P.G. Schultz, Tetrahedron Lett. **1997**, 38 (7), 1161 - 1164).

Examples of resins functionalized by such linker structures include DFPE polystyrene (2-(3,5-dimethoxy-4-formylphenoxy)ethyl polystyrene), DFPEM polystyrene (2-(3,5-dimethoxy-4-formylphenoxy)ethoxymethyl polystyrene), FMPB resins (4-(4-formyl-3-methoxyphenoxy)butyryl AM resin), FMPE polystyrene HL (2-(4-formyl-3-methoxyphenoxy)ethyl polystyrene HL), FMPB NovaGel™ (4-(4-formyl-3-methoxyphenoxy)butyryl NovaGelTM; a PEG PS resin).

The macrocyclic primary amine is attached to such solid support by means of reductive amination preferably using $NaBH(OAc)_3$ in 1,2 dichloroethane in the presence of trimethyl orthoformate.

The use of reductive amination to couple amines to resins with the above mentioned linker is well documented; for example $NaBH_3CN$ in DMF or in methanol, or $NaBH(OAc)_3$ in DMF / acetic acid or in dichloromethane / acetic acid have been used (see K.J. Jensen, J. Alsina, M.F. Songster, J. Vagner, F. Albericio, and G. Barany, J. Am. Chem. Soc. **1998**, 120, 5441 - 5452; J. Alsina, K.J. Jensen, F. Albericio, and G. Barnay, Chem. Eur. J. **1999**, 5 (10), 2787 - 2795; T.F. Herpin, K.G. Van Kirk, J. M. Savino, S. T. Yu, and R. F. Labaudinière, J. Comb. Chem. **2000**, 2, 513 - 521; A. L. Vergnon, R.S. Pottorf, M. R. Player, J. Comb. Chem. **2004**, 6, 91 - 98.). These authors also describe a variety of conditions for the acylation of the resulting secondary amine, using carboxylic acid and coupling reagents including PyBOP, PyBroP, HATU as well as carboxylic acid fluorides or carboxylic acid anhydrides.

The second functional group is an Alloc or Fmoc protected amino group or a carboxyl group protected as allyl ester. Standard

conditions are applied to deprotect and derivatize these functional groups.

The final products are detached from the solid support by means of acid in organic solvents or in H_2O. The use of TFA in dichloromethane, TFA in dichloromethane in the presence of a scavenger such as H_2O or dimethyl sulfide, or of TFA /H_2O and TFA/H_2O/dimethylsulfide has been described, references see above.

Macrocyclic compounds of general formula **I** with highly variable amino acid side chain motifs in bridge **c** can advantageously be prepared in a parallel array synthesis on solid support. This synthesis comprises immobilization of an appropriately protected and functionalized precursor comprising building blocks **A**, **B** and subsequent coupling of one to three amino acids **c1**, **c2** and **c3**, followed by cylization and release of the product thus obtained.

The corresponding process comprises:

a^6) condensation of a suitable hydroxy or mercapto aryl/heteroaryl carboxylic acid ester H-**A**-OPG^7 with an appropriately N-protected amino alcohol HO-**B**-PG^8, substituted with an orthogonally protected primary amino group, applying the methods discussed above;

b^6) removal of the protective group of the primary amine;

c^6) attachment of the product obtained in step b^6) to the solid support in a reductive alkylation step in analogy to the previously described process providing a polymer-supported fragment PG^8-**B**-**A**-O-PG^7 with free secondary side chain amino group;

d^6) acylation, carbamoylation, oxycarbonylation or sulfonylation of the secondary amine obtained in step c^6);

e^6) cleavage of the "main chain" amine protective group (PG^8);

f^6) coupling of a appropriately N-terminal protected amino acid PG^9-**c3**-OH;

g^6) removal of the N-terminal protective group (PG^9) of the product obtained in step f^6);

h^6) next coupling to introduce amino acid PG^9-**c1**-OH (for target compounds with bridges comprising two amino acid building blocks), or coupling/deprotection cycle to introduce amino PG^9-**c2**-OH followed by coupling of amino acid PG^9-**c1**-OH (for target compounds with bridges comprising three amino acid building blocks) by effecting steps corresponding to f^6) and g^6);

i^6) cleavage of the aryl/heteroaryl ester group (PG^7);

j^6) cleavage of the N-terminal protective group (PG^9);

k^6) macrolactamization of the linear cyclization precursor on solid support (for an example of cyclization on solid support see the synthesis of cyclic peptides attached to the solid support with the side chain as described by C. Cabrele, M. Langer, and A.G. Beck-Sickinger, J. Org. Chem. **1999**, 64, 4353 – 4361.); and

l^6) detachment of the final product.

As an alternative, the linear cyclization precursor obtained in step j^6) can be released from the solid support and cyclized in solution by

$k^{6\prime}$) detachment of the linear cyclization precursor; and

$l^{6\prime}$) macrolactamization in solution.

In a parallel array synthesis soluble coupling reagents as described above as well as polymer supported coupling reagents such as N-cyclohexyl-carbodiimide-N'-methylpolystyrene or N-alkyl-2-chloro pyridinium triflate resin (S. Crosignani, J. Gonzales, D. Swinnen, Org. Lett. **2004**, 6 (24), 4579 – 4582) may be used.

Further alternatives include ring closure in other positions, for example between amino acids **c1** and **c2**.

Thus a precursor with two amino acids coupled to the immobilized precursor would be prepared (polymer supported PG^9-**c2**-**c3**-**B**-**A**-OPG^7) by effecting steps corresponding to steps a^6) to h^6) described in the above paragraph. The subsequent steps then comprise

i^6') cleavage of the aryl/heteroaryl ester group (PG^7);

j^6') coupling of an appropriately C-terminal protected amino acid

H-**c1**-OGP^7;

k^6') cleavage of the c-terminal protective group (PG^7);

l^6') cleavage of the N-terminal protective group (PG^9) and

m^6') macrolactamization either on solid support or in solution after detachment of the linear precursor from the solid support.

The macrocycles of formula **I** of the present invention interact with specific biological targets. In particular, they show agonistic or antagonistic activity on the motilin receptor (MR receptor), on the serotonin receptor of subtype 5-HT_{2B} (5-HT_{2B} receptor), and on the prostaglandin F2α receptor (FP receptor). Accordingly, these compounds are useful for the treatment of hypomotility disorders of the gastrointestinal tract such as diabetic gastroparesis and constipation type irritable bowl syndrome; for the treatment of CNS related diseases like migraine, schizophrenia, psychosis or depression; for the treatment of ocular hypertension such as associated with glaucoma and for preterm labour.

The macrocycles, as such or after further optimization, may be administered per se or may be applied as an appropriate formulation together with carriers, diluents or excipients well-known in the art.

When used to treat or prevent the diseases mentioned above the macrocycles can be administered singly, as mixtures of several macrocycles, or in combination with other pharmaceutically

active agents. The macrocycles can be administered per se or as pharmaceutical compositions.

Pharmaceutical compositions comprising macrocycles of the invention may be manufactured by means of conventional mixing, dissolving, granulating, coated tablet-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes. Pharmaceutical compositions may be formulated in conventional manner using one or more physiologically acceptable carriers, diluents, excipients or auxiliaries which facilitate processing of the active macrocycles into preparations which can be used pharmaceutically. Proper formulation depends upon the method of administration chosen.

For topical administration the macrocycles of the invention may be formulated as solutions, gels, ointments, creams, suspensions, etc. as are well-known in the art.

Systemic formulations include those designed for administration by injection, e.g. subcutaneous, intravenous, intramuscular, intrathecal or intraperitoneal injection, as well as those designed for transdermal, transmucosal, oral or pulmonary administration.

For injections, the macrocycles of type **I** may be formulated in adequate solutions, preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer. The solutions may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the macrocycles of the invention may be in powder form for combination with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation as known in the art.

For oral administration, the compounds can be readily formulated per se or by combining the active macrocycle of the invention with pharmaceutically acceptable carriers well known in the art. Such carriers enable the macrocycles of type **I** to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions etc., for oral ingestion by a patient to be treated. For oral formulations such as, for example, powders, capsules and tablets, suitable excipients include fillers such as sugars, (e.g. lactose, sucrose, mannitol or sorbitol) or such as cellulose preparations (e.g. maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl cellulose, sodium carboxymethylcellulose); and/or granulating agents; and/or binding agents such as polyvinylpyrrolidone (PVP). If desired, desintegrating agents may be added, such as cross-linked polyvinylpyrrolidones, agar, or alginic acid or a salt thereof, such as sodium alginate. If desired, solid dosage forms may be sugar-coated or enteric-coated using standard techniques.

For oral liquid preparations such as, for example, suspensions, elixirs and solutions, suitable carriers, excipients or diluents include water, glycols, oils, alcohols, etc. In addition, flavoring agents, preservatives, coloring agents and the like may be added.

For buccal administration, the composition may take the form of tablets, lozenges, etc. formulated as usual.

For administration by inhalation, the macrocycles of the invention are conveniently delivered in form of an aerosol spray from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g. hydrofluoroalkanes (HFA) such as HFA 134a (1,1,1,2,-tetrafluoroethane); carbon dioxide or another suitable gas. In the case of a pressurized aerosol the dose

unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the macrocycles of the invention and a suitable powder base such as lactose or starch.

The compounds may also be formulated in rectal or vaginal compositions such as suppositories together with appropriate suppository bases like cocoa butter or other glycerides.

In addition to the formulations described afore, the macrocycles of the invention may also be formulated as depot preparations. Such slow release, long acting formulations may be administered by implantation (e.g. subcutaneously or intramuscularly) or by intramuscular injection. For the manufacture of such depot preparations the macrocycles of the invention may be formulated with suitable polymeric or hydrophobic materials (e.g. as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble salts.

In addition, other pharmaceutical delivery systems may be employed such as liposomes and emulsions well known in the art. Certain organic solvents such as dimethylsulfoxide may also be employed. Additionally, the macrocycles of type **I** may be delivered using a sustained-release system, such as semi-permeable matrices of solid polymers containing the therapeutic agent. Various sustained-release materials have been established and are well-known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds over a period of a few days up to several months. Depending on the chemical nature and the biological stability of the therapeutic agent, additional strategies for stabilization may be employed.

As the macrocycles of the invention may contain charged residues, they may be included in any of the above-described

formulations as such or as pharmaceutically acceptable salts. Pharmaceutically acceptable salts tend to be more soluble in aqueous and other protic solvents than the corresponding free base or acid forms.

The macrocycles of the invention, or compositions thereof, will generally be used in an amount effective to achieve the intended purpose. It is to be understood that the amount used will depend on a particular application.

For example, the therapeutically effective dose for an systemic administration can be estimated initially from in vitro assays: A dose can be formulated in animal models to achieve a circulating macrocycle concentration range that includes the IC_{50} or EC_{50} as determined in the cell culture (i.e. the concentration of a test compound that shows half maximal inhibitory concentration in case of antagonists or half maximal effective concentration in case agonists). Such information can be used to more accurately determine useful doses in humans. Initial dosages can also be determined from in vivo data, e.g. animal models, using techniques that are well known in the art. One having ordinary skill in the art could readily optimize administration to humans based on animal data.

Dosage amounts for applications such as gastroparesis or schizophrenia etc. may be adjusted individually to provide plasma levels of the active compound that are sufficient to maintain the therapeutic effect. Therapeutically effective serum levels may be achieved by administering multiple doses each day.

In cases of local administration or selective uptake, the effective local concentration of the macrocycles of the invention may not be related to plasma concentration. Those having the ordinary skill in the art will be able to optimize therapeutically effective local dosages without undue experimentation.

The amount of macrocycle administered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration and the judgment of the prescribing physician.

Normally, a therapeutically effective dose of the macrocycles described herein will provide therapeutic benefit without causing substantial toxicity.

Toxicity of the macrocycles of the invention can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., by determining the LD_{50} (the dose lethal to 50% of the population) or the LD_{100} (the dose lethal to 100% of the population). The dose ratio between toxic and therapeutic effect is the therapeutic index. Compounds which exhibit high therapeutic indices are preferred. The data obtained from cell culture assays and animal studies can be used in formulating a dosage range that is not toxic for use in humans. The dosage of the macrocycles of the invention lies preferably within a range of circulating concentrations that include the effective dose with little or no toxicity. The dosage may vary within the range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dose can be chosen by the individual physician in view of the patient's condition (cf. E. Fingl et al., *The Pharmacological Basis of Therapeutics*, 5th ed. **1975** (Ed. L. Goodman und A. Gilman), Ch.1, p.1).

A further embodiment of the present invention may also include compounds, which are identical to the compounds of formula I, except that one or more atoms are replaced by an atom having an atomic mass number or mass different from the atomic mass number or mass usually found in nature, e.g. compounds enriched in ^{2}H (D), ^{3}H, ^{11}C, ^{14}C, ^{125}I etc. These isotopic analogs and

their pharmaceutical salts and formulations are considered useful agents in the therapy and/or diagnostic, for example, but not limited to, where a fine-tuning of *in vivo* half-life time could let to an optimized dosage regimen.

Examples

The following Examples illustrate the invention in more detail but are not intended to limit its scope in any way. The following abbreviations are used in these Examples:

ADDP: azodicarboxylic dipiperidide
All: allyl
Alloc: allyloxycarbonyl
AllocCl: allyl chloroformate
AllocOSu: allyloxycarbonyl-N-hydroxysuccinimide
AM-resin: aminomethyl resin
aq.: aqueous
arom.: aromatic
BnBr: benzyl bromide
Boc: *tert*-butoxycarbonyl
br.: broad
Cbz: benzyloxycarbonyl
CbzOSu: N-(benzyloxycarbonyloxy)succinimide
Cl-HOBt: 6-chloro-1-hydroxybenzotriazole
CMBP: cyanomethylenetributyl-phosphorane
m-CPBA: 3-chloroperbenzoic acid
d: day(s) or doublet (spectral)
DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene
DCE: 1,2-dichloroethane
DEAD: diethyl azodicarboxylate
DFPE polystyrene: 2-(3,5-dimethoxy-4-formylphenoxy)ethyl polystyrene
DIAD: diisopropyl azodicarboxylate

DIC: N,N'-diisopropylcarbodiimide

DMF: dimethylformamide

DMSO: dimethyl sulfoxide

DPPA: diphenyl phosphoryl azide

DVB: divinylbenzene

EDC: 1-[3-(dimethylamino)propyl-3-ethylcarbodiimide

equiv.: equivalent

Et_3N: triethylamine

EtOAc: ethyl acetate

FC: flash chromatography

FDPP: pentafluorophenyl diphenylphosphinate

Fmoc: 9-fluorenylmethoxycarbonyl

h: hour(s)

HATU: O-(7-azobenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate

HBTU: O-(benoztriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate

HCTU: O-(1H-6-chlorobenoztriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate

HOAt: 1-hydroxy-7-azabenzotriazole

$HOBt.H_2O$: 1-hydroxybenzotriazole hydrate

HMPA: hexamethylphosphoramide

i.v.: in vacuo

m: multiplet (spectral)

MeOH: methanol

NMP: 1-methyl-2-pyrrolidinone

$Pd(PPh_3)_4$: Tetrakis(triphenylphosphine)palladium(0)

PEG PS resin: polyethyleneglycol coated polystyrene resin

PG: protective group

PPh_3: triphenylphosphine

prep.: preparative

i-Pr_2NEt: N-etyl-N,N-diisopropylamine

PyBOP: (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate

PyBroP: Bromotripyrrolidinophosphonium hexafluorophosphate

q: quartet (spectral)

quant.: quantitative

sat.: saturated

soln: solution

t: triplet (spectral)

TBAF: tetrabutylammonium fluoride

Teoc: 2-(trimethylsilyl)ethoxycarbonyl

TeocONp: 2-(trimethylsilyl)ethyl 4-nitrophenyl carbonate

TFA: trifluoroacetic acid

THF: tetrahydrofuran

tlc: thin layer chromatography

T3P™: propanphosphonic acid cyclic anhydride

p-TsOH: p-toluenesulfonic acid

General Methods

TLC: Merck (silica gel 60 F254, 0.25 mm).

Flash chromatography (FC): *Fluka* silica gel 60 (0.04-0.063 mm) and Interchim Puriflash IR 60 silica gel (0.04-0.063 mm).

I. Analytical HPLC-MS methods:

R_t in min (purity at 220 nm in %), m/z $[M+H]^+$

Volume of injection: 5 µL for all methods

Method 1a and 1b

Column: XBridge C18 2.5 µm, 2.1x50 mm (186003085 - Waters)

Mobile Phases **A:** 0.1% TFA in Water
0.085% TFA in
B: Acetonitrile

Column oven temp. 45° C

Gradient	**Time (min.)**	**Flow (µl/min)**	**%A**	**%B**
	0	500	97	3
	0.1	500	97	3
	3	500	3	97

3.6	500	3	97
3.7	500	97	3
4.3	500	97	3

Method 1, cont.

UV Wavelenght: 220 nm 254 nm

Method 1a

100-800 Da

Method 1b Centroid

MS scan Range: 300-2000 Da mode

Scan Time: 1 sec.

Ionization type: Electrospray

Method 2

Column: Gemini NX C18 3 µm, 2.1x50 mm (00B-4453-B0 - Phenomenex)

Mobile Phases **A:** 0.1% TFA in Water
0.085% TFA in
B: Acetonitrile

Column oven temp. 45° C

Gradient	**Time (min.)**	**Flow (µl/min)**	**%A**	**%B**
	0	800	97	3
	0.1	800	97	3
	2.2	800	3	97
	2.5	800	3	97
	2.55	1000	97	3
	2.75	1000	97	3
	2.8	800	97	3

UV Wavelenght: 220 nm 254 nm

MS scan Range: 100-2000 Da Centroid mode

Scan Time: 1 sec.

Ionization type: Electrospray

Method 3

Column: Gemini NX C18 3 µm, 2.1x50 mm (00B-4453-B0 - Phenomenex)

Mobile Phases **A:** 1 mM ammonium bicarbonate pH 10
B: Acetonitrile

Column oven temp. 45° C

Gradient	**Time (min.)**	**Flow (µl/min)**	**%A**	**%B**
	0	800	97	3
	0.1	800	97	3

	2.2	800	3	97
	2.5	800	3	97
	2.55	1000	97	3
	2.75	1000	97	3
	2.8	800	97	3

Method 3, cont.

UV Wavelenght: 220 nm 254 nm

MS scan Range: 100-2000 Da Centroid mode

Scan Time: 1 sec.

Ionization type: Electrospray

Method 4a-4b

Column: Gemini NX C18 3 µm, 2.1x50 mm (00B-4453-B0 - Phenomenex)

Mobile Phases **A:** 0.1% TFA in Water
B: 0.085% TFA in Acetonitrile

Column oven temp. 45° C

Gradient	**Time (min.)**	**Flow (µl/min)**	**%A**	**%B**
	0	800	97	3
	0.1	800	97	3
	2.7	800	3	97
	3	800	3	97
	3.05	1000	97	3
	3.25	1000	97	3
	3.3	800	97	3

UV Wavelenght: 220 nm 254 nm

MS scan Range: **Method 4a** 100-2000 Da Centroid mode **Method 4b** 350-2000 Da Profile mode

Scan Time: 1 sec.

Ionization type: Electrospray

Method 5a-5b

Column: Gemini NX C18 3 µm, 2.1x50 mm (00B-4453-B0 - Phenomenex)

Mobile Phases **A:** 1 mM ammonium bicarbonate pH 10
B: Acetonitrile

Column oven temp. 45° C

Gradient	**Time (min.)**	**Flow (µl/min)**	**%A**	**%B**
	0	800	97	3

175

0.1	800	97	3
2.7	800	3	97
3	800	3	97
3.05	1000	97	3
3.25	1000	97	3
3.3	800	97	3

Method 5, cont.

UV Wavelenght: 220 nm 254 nm

MS scan Range: **Method 5a** 100-2000 Da Centroid mode; **Method 5b** 350 – 2000 Da Profile mode

Scan Time: 1 sec.

Ionization type: Electrospray

Method 6

Column: Acquity UPLC BEH C18 1.7 µm, 2.1x50 mm (cod. 186002350 - Waters)

Mobile Phases **A:** 0.1% TFA in Water
B: 0.085% TFA in Acetonitrile

Column oven temp. 55° C

Gradient	**Time (min.)**	**Flow (µl/min)**	**%A**	**%B**
	0	1250	97	3
	0.05	1250	97	3
	1.65	1250	3	97
	1.95	1250	3	97
	2.00	1250	97	3
	2.30	1250	97	3

UV Wavelenght: 220 nm 254 nm

MS scan Range: 100-1650 Da Centroid mode

Scan Time: 0.5 sec.

Ionization type: Electrospray

Method 7

Column: Acquity UPLC BEH C18 1.7 µm, 2.1x50 mm (cod. 186002350 - Waters)

Mobile Phases **A:** 0.1% TFA in Water
B: 0.085% TFA in Acetonitrile

Column oven temp. 55° C

Gradient	**Time (min.)**	**Flow (µl/min)**	**%A**	**%B**

0	1250	97	3
0.05	1250	97	3
1.65	1250	3	97
1.95	1250	3	97
2.00	1250	97	3
2.30	1250	97	3

Method 7, cont.

UV Wavelenght: 220 nm 254 nm

MS scan Range: 100-1650 Da Profile mode

Scan Time: 0.5 sec.

Ionization type: Electrospray

Method 8

Column: Acquity UPLC BEH C18 1.7 µm, 2.1x50 mm (cod. 186002350 - Waters)

Mobile Phases **A:** 1 mM ammonium bicarbonate pH 10

B: Acetonitrile

Column oven temp. 55° C

Volume of injection: 5 µl

Gradient

Time (min.)	Flow (µl/min)	%A	%B
0	1250	97	3
0.05	1250	97	3
1.65	1250	3	97
1.95	1250	3	97
2.00	1250	97	3
2.30	1250	97	3

UV Wavelenght: 220 nm 254 nm

MS scan Range: 100-1650 Da Profile mode

Scan Time: 0.5 sec.

Ionization type: Electrospray

Method 9a-9c

Column: Acquity UPLC BEH C18 1.7 µm, 2.1x100 mm

(cod. 186002352 - Waters)

Mobile Phases	**A:**	0.1% TFA in Water / Acetonitrile 95/5 v/v
	B:	0.085% TFA in Acetonitrile
Column oven temp.	55° C	

Method 9, cont. Gradient	**Time (min.)**	**Flow (µl/min)**	**%A**	**%B**
	0	700	99	1
	0.2	700	99	1
	2.5	700	3	97
	2.85	700	3	97
	2.86	700	99	1
	3.20	700	99	1

UV Wavelenght:	220 nm	
MS scan Range:	**Method 9a:** 100-800 Da; **Method 9b:** 100 – 1200 Da; **Method 9c:** 200 – 1400 Da	Profile mode
Scan Time:	1 sec.	
Ionization type:	Electrospray	

Analytical HPLC (x% CH_3CN): R_t in min (purity at 220 nm in %)

Column: Develosil RPAq 5 µM, 4.6 x 50 mm;

Flow rate: 1.5 ml/min

0.0-0.5 min (x% CH_3CN, 100-x% H_2O containing 0.1% TFA);

0.5-5.0 min (x% CH_3CN, 100-x% H_2O containing 0.1% TFA to 100% CH_3CN)

5.0-6.2 min (100% CH_3CN)

II. Preparative HPLC methods:

1. Reverse Phase - *Acidic conditions*

Column: XBridge C18 5 µm, 30 x 150 mm (Waters)

Mobile phases:

A: 0.1% TFA in Water/Acetonitrile 95/5 v/v

B: 0.1% TFA in Water/Acetonitrile 5/95 v/v

2. Reverse Phase - *Basic conditions*

Column: XBridge C18 5 µm, 30 x 150 mm (Waters)
Mobile phases:
A: 10 mM Ammonium Bicarbonate pH 10/Acetonitrile 95/5 v/v
B: Acetonitrile

3. Normal Phase

Column: VP 100/21 NUCLEOSIL 50-10, 21 x 100 mm (Macherey-Nagel)
Mobile phases: ***A***: Hexane
B: Ethylacetate
C: Methanol

NMR Spectroscopy: Bruker Avance 300, ^{1}H-NMR (300 MHz) in the indicated solvent at ambient temperature. Chemical shifts δ in ppm, coupling constants J in Hz.

The term "isomers" comprises in the present invention species of identical chemical formula, constitution and thus molecular mass, such as but not limited to amide cis/trans isomers, rotamers, conformers, diastereomers.

Examples

Starting materials
Building Blocks of Type A (Scheme 1):

2-Acetoxy-5-fluoro benzoic acid (**2**) was prepared according to the method of C. M. Suter and A. W. Weston, *J. Am. Chem. Soc.* **1939**, *61*, 2317-2318.

3-Acetoxybenzoic acid (**3**) is commercially available.

4-Acetoxybenzoic acid (**4**) is commercially available.

5-Hydroxy nicotinic acid (**5**) is commercially available.

8-Acetoxyquinoline-2-carboxylic acid (**8**) was prepared according to the method of R.W. Hay, C.R. Clark, *J. Chem. Soc. Dalton* **1977**, 1993-1998.

(*S*)-2-tert-Butoxycarbonylamino-8-hydroxy-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid (**10**) was prepared according to the method of M. M. Altorfer, Dissertation Universität Zürich, **1996**.

3-Mercaptobenzoic acid (**11**) is commercially available

Building Blocks of Type B (Scheme 2):

tert-Butyl (3*S*,5*S*)-5-(hydroxymethyl)pyrrolidin-3-ylcarbamate (**13**) as well as the corresponding HCl salt (**13**·HCl) are commercially available.

tert-Butyl (3*R*,5*S*)-5-(hydroxymethyl)pyrrolidin-3-ylcarbamate (**17**) as well as the corresponding HCl salt (**17**·HCl) are commercially available.

(*S*)-tert-Butyl 3-(hydroxymethyl)piperazine-1-carboxylate hydrochloride (**21**·HCl) is commercially available.

(*R*)-tert-Butyl 3-(hydroxymethyl)piperazine-1-carboxylate hydrochloride (**83**·HCl) (Scheme 5) is commercially available.

(2*S*,4*S*)-Allyl 2-(hydroxymethyl)-4-((2-(trimethylsilyl)ethoxy)carbonylamino)pyrrolidine-1-carboxylate

(**16**) was prepared in three steps (1. Alloc protection of the secondary amino group with allyloxycarbonyl-N-hydroxysuccinimide (AllocOSu) in CH_2Cl_2, 2. cleavage of the Boc group with dioxane-HCl;

3. Teoc protection of the primary amino group with 2-(trimethylsilyl)ethyl 4-nitrophenyl carbonate (Teoc-ONp) in CH_2Cl_2 in the presence of Et_3N) from amino alcohol **13**, applying standard conditions; as leading references cf. T.W. Greene, P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, **1999**; P.J. Kocienski, *Protecting Groups*, 3rd edition, Georg Thieme Verlag, **2005**.

Data of **16**: $C_{15}H_{28}N_2O_5Si$ (344.5): Flow injection MS (APCI): 689 ($[2M+H]^+$), 345 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 7.28 (d, J = 6.1, 1 H), 5.90 (m, 1 H), 5.25 (qd, J = 1.7, 17.2, 1 H), 5.16 (qd, J = 1.5, 10.5, 1 H), 4.90 (br. t, 1 H), 4.54-4.42 (m, 2 H), 4.04-3.97 (m, 2 H), 3.90 (q, J = 6.8, 1 H), 3.80-3.66 (br. m and dd, 2 H), 3.57-3.43 (br. m, 2 H), 2.96 (br. m, 1 H), 2.19 (br. m, 1 H), 1.78 (br. m, 1 H), 0.89 (t, J ca 8.3, 2 H), 0.00 (s, 9 H)

(2*S*,4*R*)-Allyl 2-(hydroxymethyl)-4-((2-(trimethylsilyl)ethoxy)carbonylamino)pyrrolidine-1-carboxylate (**20**) was prepared from amino alcohol hydrochloride **17**·HCl, applying the same transformations as described for the synthesis of diastereomer **16** with the exception of the Alloc protection step which was performed using allyl chloroformate in CH_2Cl_2 in the presence of aqueous $NaHCO_3$ solution.

Data of **20**: $C_{15}H_{28}N_2O_5Si$ (344.5): LC-MS (method 9a): R_t = 1.98, 345 ($[M+H]^+$); 317; 259. ^{1}H-NMR (DMSO-d_6): 7.26 (d, J = 6.6, 1 H), 5.89 (m, 1 H), 5.25 (br. d, J = 17.0, 1 H), 5.15 (br. d, J = 10.2, 1 H), 4.75 (m, 1 H), 4.48 (m, 2 H), 4.16-3.98 (m, 3 H), 3.82 (br. m, 1 H), 3.48-3.30 (m, 3 H), 3.21 (m, 1 H), 2.01 (m, 1 H), 1.80 (m, 1 H), 0.89 (t, J = 8.3, 2 H), 0.00 (s, 9 H).

(*S*)-1-Allyl 4-tert-butyl 2-(hydroxymethyl)piperazine-1,4-dicarboxylate (**22**) was prepared from amino alcohol hydrochloride **21**·HCl, applying allyl chloroformate in CH_2Cl_2 in the presence of aqueous $NaHCO_3$ solution; as leading references cf. T.W. Greene, P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, **1999**; P.J. Kocienski, *Protecting Groups*, 3rd edition, Georg Thieme Verlag, **2005**.

Data of **22**: $C_{14}H_{24}N_2O_5$ (300.4): LC-MS (method 9a): R_t = 1.70, 201 ([M+H]$^+$). ^{1}H-NMR (DMSO-d_6): 5.90 (m, 1 H), 5.29 (qd, J = 1.7, 17.3, 1 H), 5.18 (qd, J = 1.5, 10.5, 1 H), 4.81 (t, J = 4.9, 1 H), 4.53 (d-like m, J ca. 5.1, 2 H), 4.04-3.75 (br. m, 4 H), 3.39 (m, 2 H), 2.95-2.70 (br. m, 3 H), 1.40 (s, 9 H).

Building Blocks of Type C (Scheme 3):

(*S*)-5-Allyl 1-benzyl 2-(methylamino)pentanedioate hydrochloride (**27**·HCl)

A mixture of Boc-L-Glu(OAll)OH (**23**; 33 g, 115 mmol) and $NaHCO_3$ (27 g, 322 mmol) in DMF (500 mL) was stirred for 1 h at room temperature followed by the slow addition of benzyl bromide (35 mL, 299 mmol) in DMF (15 mL). Stirring was continued for 16 h followed by aqueous workup (diethyl ether, sat. aq. $NaHCO_3$ soln, sat aq. NaCl soln) and purification by FC (CH_2Cl_2/MeOH 100:0 to 98:2) to give the corresponding benzyl ester (34.4 g, 79%), which was dissolved in dioxane (40 mL) and treated with 4 M HCl-dioxane (400 mL) for 1 h. The volatiles were evaporated. The residue was crystallized from diethyl ether to afford **24**·HCl (23.8 g, 83%).

4-Nitrobenzenesulfonyl chloride (39 g, 178 mmol) was added at 0°C to a solution of **24**·HCl (46.5 g, 148 mmol) and pyridine (42 mL, 519 mmol) in CH_2Cl_2 (700 mL). The mixture was stirred for 15 h followed by aqueous workup (CH_2Cl_2, 1 M aq. HCl soln) and

purification of the crude by FC (hexane/EtOAc 80:20 to 75:25) to yield **25** (55.54 g, 81%).

A solution of **25** (41.3 g, 89 mmol) in dry DMF (200 mL) was cooled to 0°C. Methyliodide (5.8 mL, 94 mmol) in DMF (100 mL) was slowly added, followed by a solution of DBU (14 mL, 94 mmol) in DMF (100 mL). The mixture was stirred for 4 h at room temperature followed by aqueous workup (EtOAc, 1 M aq. HCl soln., H_2O, sat. aq. $NaHCO_3$ soln, sat. aq. NaCl soln) to afford **26** (42.8 g, 99%).

A solution of **26** (17.4 g, 37 mmol) in dry, degassed CH_3CN (270 mL) was treated with thiophenol (6.7 mL, 66 mmol) and Cs_2CO_3 (39 g, 121 mmol) at room temperature for 16 h. The mixture was filtered and the residue was washed with diethyl ether. The filtrate was carefully concentrated (bath temperature 20°C) and immediately purified by FC (hexane/EtOAc 80:20 to 50:50). The combined product fractions were carefully concentrated, immediately treated with 4 M HCl-dioxane (20 mL) for 5 min and concentrated to give **27**·HCl (8.62 g, 72%).

Data of **27**·HCl: $C_{16}H_{21}NO_4$·HCl (291.3, free base). LC-MS (method 9b): R_t = 1.44, 292 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 9.57 (br. s, NH_2^+), 7.45-7.34 (m, 5 arom. H), 5.88 (M, 1 H), 5.32-5.19 (m, 4 H), 4.53 (td, J = 1.3, 5.4, 1 H), 4.13 (br. t, J ca. 6.0, 1 H), 2.69-2.40 (m, 2 H), 2.56 (s, 3 H), 2.30-2.05 (m, 2 H).

(*R*)-5-Allyl 1-benzyl 2-(methylamino)pentanedioate hydrochlorided (**29**·HCl) was prepared from Boc-D-Glu(OAll)OH (**28**) applying the methods described above for the synthesis of the enantiomer (**27**·HCl).

Data of **29**·HCl: $C_{16}H_{21}NO_4$·HCl (291.3, free base). LC-MS (method 9b): R_t = 1.44, 292 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 9.92 (br. s, NH^+), 9.54 (br. s, NH^+), 7.45-7.34 (m, 5 arom. H), 5.88 (M, 1 H), 5.32-5.19 (m, 4 H), 4.53 (td, J = 1.3, 5.4, 1 H), 4.13 (br. t, J ca. 6.0, 1 H), 2.69-2.40 (m, 2 H), 2.56 (s, 3 H), 2.30-2.05 (m, 2 H).

(*S*)-Allyl 2-(benzyloxycarbonylamino)-3-(methylamino)propanoate hydrochloride (**32**·HCl)

Cbz-L-SerOH (**30**) was converted into amino acid **31** by β-lactone formation and opening with $HNCH_3Si(CH_3)_3$ (see J. Kim, S. G. Bott, D.M. Hoffman *Inorg. Chem.* **1998**, *37*, 3835-3841), following the procedures of J.K. Kretsinger and J.P. Schneider, *J. Am. Chem. Soc.* **2003**, *125*, 7907-7913 and E.S. Ratemi and J.C. Vederas, *Tetrahedron Lett.* **1994**, *35*, 7605-7608.

A solution of **31**·HCl (2.2 g, 7.6 mmol) in allyl alcohol (55 mL) was treated with thionyl chloride (1.7 mL, 23 mmol) for 15 min at room temperature and for 1.5 h at 70°C. The volatiles were evaporated. The crude product was dissolved in CH_2Cl_2 and washed with aq. $NaHCO_3$ solution. The aqueous layers were extracted with CH_2Cl_2 and with EtOAc. The combined organic phase was dried (Na_2SO_4), filtered, and concentrated. The resulting oil (2.18 g) was dissolved in CH_2Cl_2 (80 mL), treated with 4 M HCl-dioxane (20 mL), stirred for 5 min and concentrated to afford **32**·HCl (2.5 g, quantitative).

Data of **32**·HCl: $C_{15}H_{20}N_2O_4$·HCl (292.3, free base). LC-MS (method 9a): R_t = 1.26, 293 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 9.20 (br. s, NH^+), 9.03 (br. s, NH^+), 8.02 (d, J = 8.2, NH), 7.38-7.30 (m, 5 arom. H), 5.89 (m, 1 H), 5.33 (d, J = 17.3, 1 H), 5.23 (d, J = 10.5, 1 H), 5.08 (s, 2 H), 4.63 (d, J = 5.3, 2 H), 4.56 (m, 1 H), 3.35 (br. m, 1 H), 3.25 (br. m, 1 H), 2.56 (br. s, 3 H).

As an alternative, **32**·HCl was prepared from Cbz-L-DapOH applying the method described below for the synthesis of the enantiomer **36**·HCl.

(*R*)-Allyl 2-(benzyloxycarbonylamino)-3-(methylamino)propanoate hydrochloride (**36**·HCl)

Cbz-D-DapOH was converted into the allylester-pTsOH salt **33**·pTsOH according to the procedure of T.M. Kamenecka and S.J. Danishefsky, *Chem. Eur. J.* **2001**, 7, 41-63, describing the synthesis of D-threonine allyl ester.

The amino ester **33**·pTsOH was converted into the free base by extraction (CH_2Cl_2, sat. aq. $NaHCO_3$ soln) and treated with 4-nitrobenzenesulfonyl chloride (1.05 equiv.) in CH_2Cl_2 in the presence of pyridine (3.0 equiv.) to give the p-nitrophenyl sulfonamide **34**.

At 0°C, a solution of methyl iodide (2.3 mL, 37 mmol) in DMF (80 mL) was added to a solution of **34** (16.4 g, 35 mmol) in DMF (80 mL). A solution of DBU (5.6 mL, 37 mmol) in DMF (80 mL) was slowly added over 2 h. The mixture was stirred at room temperature for 1.5 h, followed by an aqueous workup (EtOAC, 1 M HCl soln, H_2O, sat. aq. $NaHCO_3$ soln, sat. aq. NaCl soln) to afford **35** (17.07 g, quant.).

At 0°C, thiophenol (3.02 mL, 29.6 mmol) was added (dropwise, rapidly) to a mixture of **35** (7,85 g, 16.5 mmol) and K_2CO_3 (7.95 g, 57.5 mmol) in DMF (78 mL). The mixture was stirred for 2.5 h at 0-10°C. The mixture was diluted with EtOAc and washed with H_2O and sat. aq. NaCl soln. The organic layer was extracted with ice-cold 1 M aqueous HCl soln. The aqueous phase (base extract) was poured onto aqueous Na_2CO_3 soln to reach pH ca 7; 2 M aq. NaOH soln. was added to reach pH ca 10, followed by extraction with EtOAc. The organic phase was dried (Na_2SO_4) and concentrated. The remaining oil (2.72 g) was dissolved in CH_2Cl_2 (30 mL) and treated with 4 M HCl-dioxane (10 mL) to afford after evaporation of the volatiles **36**·HCl (3.34 g, 62%).

Data of **36**·HCl: $C_{15}H_{20}N_2O_4$·HCl (292.3, free base). LC-MS (method 7): R_t = 0.88, 293 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 9.06 (br. s, NH^+), 8.94 (br. s, NH^+), 8.00 (d, J = 8.3, NH), 7.38-7.30 (m, 5 arom. H), 5.88 (m, 1 H), 5.33 (d, J = 17.3, 1 H), 5.23 (d, J = 10.5, 1 H), 5.08 (s, 2 H), 4.63 (d, J = 5.3, 2 H), 4.56 (m, 1 H), 3.35 (br. m, 1 H), 3.20 (br. m, 1 H), 2.57 (br. s, 3 H).

(*S*)-Allyl 2-(benzyloxycarbonylamino)-4-(methylamino)butanoate hydrochloride (**40**·HCl)

Cbz-L-DabOH (**37**) was converted into the allylester-pTsOH salt **38**·pTsOH according to the procedure of T.M. Kamenecka and S.J. Danishefsky, *Chem. Eur. J.* **2001**, 7, 41-63, describing the synthesis of D-threonine allyl ester.

A mixture of **38**·pTsOH (45 g, 97 mmol) in CH_2Cl_2 (600 mL) was cooled to 0°C. MeOH (60 mL) was added, followed by ethyl trifluoroacetate (23 mL, 194 mmol). Et_3N (53 mL, 387 mmol) was added dropwise. The mixture was stirred at 0°C for 15 min, then at room temperature for 4 h. The volatiles were evaporated. The residue was dissolved in EtOAc, washed (1 M aq. HCl soln, sat. aq. Na_2CO_3 soln), dried (Na_2SO_4), filtered and concentrated to afford the corresponding trifluoroacetamide (32 g, 84%). N-Methylation of the acetamide (21.78 g, 56 mmol; applying CH_3I and K_2CO_3 in DMF) following the procedure described by Chu-Biao Xue et al. *J. Med. Chem.* **2001**, *44*, 2636-2660 - with the exception that the transformation was performed at room temperature for 4 h - afforded **39** (25 g, ca 90%).

Treatment of **39** (8.0 g, ca 18 mmol) in THF (80 mL) with $Pd(PPh_3)_4$ (0.2 g) and morpholine (8.5 mL, 98 mmol) at room temperature for 3 h afforded after aqueous workup (EtOAc, 1 M aq HCl soln.) the corresponding trifluoroacetamido acid (7.3 g) which was treated with NH_3 (25% in H_2O; 50 mL) for 2 h and concentrated to give the corresponding aminoacid (8 g). This material was dissolved in allyl alcohol (150 mL) and treated at 0°C with thionyl chloride (6.6 mL, 91 mmol). The mixture was stirred at 0°C for 15 min and at room temperature for 3 h and concentrated to give **40**·HCl (7.6 g, used in the next step without further purification)

Data of **40**·HCl: $C_{16}H_{22}N_2O_4$·HCl (306.3, free base). Flow injection MS (ESI, positive modus): 307 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 8.97 (br. s, NH_2^+), 7.92 (d, J = 7.8, NH), 7.40-7.25 (m, 5 arom. H), 5.88 (m, 1 H), 5.32 (d, J = 17.2, 1 H), 5.22 (d, J = 10.5, 1 H), 5.05 (s, 2 H), 4.60 (d, J = 5.2, 2 H), 4.22 (m, 1 H), 2.94

(m, 2 H), 2.50 (s, 3 H, superimposed by DMSO-d signal), 2.10 (m, 1 H), 2.00 (m, 1 H).

(*S*)-Allyl 2-(benzyloxycarbonylamino)-5-(methylamino)pentanoate hydrochloride (**44**·HCl)

Cbz-L-OrnOH (**41**) was converted into the allylester-pTsOH salt **42**·pTsOH according to the procedure of T.M. Kamenecka and S.J. Danishefsky, *Chem. Eur. J.* **2001**, 7, 41-63, describing the synthesis of D-threonine allyl ester.

The ester **42**·pTsOH (5.5 g, 11 mmol) was converted into **43** (3.97 g, 83%) applying the conditions described for the synthesis of **39**, with the exception that the N-methylation was continued at room temperature for 8 h.

The allyl ester group was then cleaved applying the conditions described for the treatment of **39**. The saponification of the resulting trifluoroacetamido acid was performed according to the procedure of Chu-Biao Xue et al. *J. Med. Chem.* **2001**, *44*, 2636-2660, with the exception that 2 equiv. of LiOH were used. The resulting amino acid (3.80 g, containing LiCl ca. 9 mmol) was treated at room temperature with allyl alcohol (100 mL) and thionyl chloride (3.0 mL, 41 mmol). The mixture was heated for 2 h at 70°C. Stirring was continued at room temperature for 17 h. The volatiles were evaporated. The resulting solid was washed with CH_2Cl_2 to afford **44**·HCl (3.62 g, ca 75% w/w; yield 83%, used without further purification).

Data of **44**·HCl: $C_{17}H_{24}N_2O_4$·HCl (320.4, free base). LC-MS (method 9b): R_t = 1.48, 321 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 9.26 (br. s, NH_2^+), 7.86 (d, J = 7.7, NH), 7.39-7.13 (m, 5 arom. H), 5.89 (m, 1 H), 5.31 (br. d, J = 17.3, 1 H), 5.20 (br. d, J = 10.4, 1 H), 5.04 (s, 2 H), 4.58 (d, J = 5.2, 2 H), 4.05 (br. m, 1 H), 2.81 (br. m, 2 H), 2.44 (s, 3 H), 1.80-1.60 (br. m, 4 H),

Sarcosine allyl ester (**46**) was prepared as p-TsOH salt applying the procedure of T.M. Kamenecka and S.J. Danishefsky, *Chem. Eur. J.* **2001**, 7, 41-63, describing the synthesis of D-threonine allyl ester.

2-((Allyloxycarbonyl)(methyl)amino)acetic acid (**47**) was prepared according to the method of M. Mori, A. Somada, S. Oida, *Chem. Pharm. Bull.* **2000**, *48*, 716-728.

3-((Allyloxycarbonyl)(methyl)amino)propanoic acid (**49**) was prepared applying the method of M. Mori, A. Somada, S. Oida, *Chem. Pharm. Bull.* **2000**, *48*, 716-728, describing the synthesis of N-allyloxycarbonylsarcosine.

(*S*)-2-(Benzyloxycarbonylamino)pent-4-enoic acid (**51**) was prepared from (S)-allylglycine by N-protection (CBzOSu, dioxane, aqueous Na_2CO_3) in analogy to the procedure of D.R. Ijzendoorn, P.N.M. Botman, R.H.Blaauw, *Org. Lett* **2006**, *8*, 239-242.
Acid **51** was also described by Z-Y Sun, C-H. Kwon, J. N.D. Wurpel, *J. Med. Chem.* **1994**, *37*, 2841-2845.

General Procedures

Synthesis of the A-c1 Fragment

Procedure A

A.1: Acid chloride formation

Oxalyl chloride (3.5-5.0 equiv.) was added to a mixture of the acetoxyaryl carboxylic acid (Ac-**A**-OH) and dry diethyl ether or CH_2Cl_2. The resulting mixture was stirred at room temperature for 15 min followed by the addition of a few drops (ca 50-100 µL) of dry DMF. Stirring was continued for 16 h. The mixture was filtered. The filtrate was concentrated and the residue dried i.v. to afford the crude acetoxyaryl carboxylic acid chloride (Ac-**A**-Cl), which was immediately used in the next step.

A.2: Amide coupling

A mixture of the amino ester salt (H-**c1**-OAll·HCl), the crude acetoxyaryl carboxylic acid chloride (Ac-**A**-Cl, 1.1-1.5 equiv.) and dry CH_2Cl_2 or THF was cooled to 0°C. An auxiliary base (sym-collidine or *i*-Pr_2NEt; 3.0 equiv.) was added dropwise. The mixture was stirred at room temperature for 16 h. The mixture was distributed between EtOAc and 1 M aq. HCl solution. The organic phase was washed (1 M aq. HCl soln., then sat. aq. $NaHCO_3$ soln. or sat aq. NaCl soln.), dried (Na_2SO_4), filtered and concentrated. FC (hexane/EtOAc gradients) gave the acetoxyaryl amide (Ac-**A**-**c1**-OAll).

A.3: Deacetylation

A solution of acetoxyarylamide (Ac-**A**-**c1**-OAll) in dry THF was treated at 0°C with 3-dimethylaminopropylamine (3.0-4.5 equiv.). The solution was stirred at room temperature for 1-5 h. The mixture was distributed between EtOAc and icecold 0.1 M or 1 M aq. HCl solution. The organic phase was washed (0.1 or 1 M aq. HCl soln., sat. aq. NaCl soln.), dried (Na_2SO_4), filtered and concentrated to afford the hydroxyaryl amide (H-**A**-**c1**-OAll).

Synthesis of the linear cyclization precursor H-B-A-c1-OH

Procedure B

B.1.1: Mitsunobu aryl ether synthesis using PPh_3/DEAD
A mixture of the hydroxyaryl amide (H-**A**-**c1**-OAll) and PPh_3 (1.5 equiv.) was dried i.v. for 15 min. Under argon a solution of alcohol (HO-**B**-Alloc, 1.2 equiv.) in dry benzene was added and the resulting solution was cooled to 0°C. A solution DEAD (40% in toluene, 1.2 equiv.) in benzene was slowly added (by syringe pump). The mixture was stirred at room temperature for 18 h and concentrated. FC (hexane/EtOAc gradients) gave the protected amino acid (Alloc-**B**-**A**-**c1**-OAll, sometimes contaminated with byproducts such as e.g. triphenylphosphine oxide, however acceptable for the use in the next step without further purification).

B.1.2: Mitsunobu aryl ether synthesis using CMBP
A solution of the hydroxyaryl amide (HO-**A**-**c1**-OAll), the alcohol (HO-**B**-Alloc, 1.2-1.3 equiv) and CMBP (2 equiv) was heated in dry toluene at reflux for 3-4 h. The solution was concentrated. FC (hexane/EtOAc gradients) afforded the protected amino acid (Alloc-**B**-**A**-**c1**-OAll).

B.2: Cleavage of the allyl/alloc protective groups
$Pd(PPh_3)_4$ (0.05-0.1 equiv.) was added to a mixture of the protected amino acid (Alloc-**B**-**A**-**c1**-OAll) and 1,3-dimethylbarbituric acid (2.5 equiv.) in degassed EtOAc/CH_2Cl_2 (ca. 1:1). The resulting solution was stirred at room temperature for 1-3 h and concentrated. FC (EtOAC, CH_2Cl_2/EtOH, or CH_2Cl_2/MeOH gradients) afforded the free amino acid (H-**B**-**A**-**c1**-OH)

Synthesis of the linear cyclization precursor H-B-A-c1-c2-OH

Procedure C

C.1: Alloc carbamate formation

At 0°C, allylchloroformate (1.1 equiv.) was slowly added to a mixture of aminoacid (H-**B**-**A**-**c1**-OH) and Na_2CO_3 (1.5-3 equiv.) in dioxane/H_2O 1:1. The mixture was stirred at room temperature for 15 h. The mixture was diluted with EtOAc and treated with 1 M aq. HCl solution until pH ca 2 was reached. The organic phase was separated, washed (sat. aq. NaCl soln.), dried (Na_2SO_4), filtered, concentrated and dried i.v. to afford the alloc protected amino acid (Alloc-**B**-**A**-**c1**-OH).

C.2: Amid coupling

i-Pr_2NEt (5.0 equiv.) was slowly added to a mixture of the alloc protected amino acid (Alloc-**B**-**A**-**c1**-OH), the aminoacid ester salt (H-**c2**-OAll.p-TsOH, 1.2 equiv.), HOAt (1.5 equiv.) and HATU (1.5 equiv.) in DMF. The mixture was stirred at room temperature for 20 h followed by distribution between EtOAc and ice-cold 0.5 M aq, HCl solution. The organic phase was washed (0.5 M aq. HCl soln., H_2O, sat. aq. $NaHCO_3$ soln., sat. aq. NaCl soln.), dried (Na_2SO_4), filtered and concentrated. FC (hexane/EtOAc gradients) afforded the protected amino acid (Alloc-**B**-**A**-**c1**-**c2**-OAll)

C.3: Cleavage of the allyl/alloc protective groups

$Pd(PPh_3)_4$ (0.1 equiv.) was added to a mixture of the protected amino acid (Alloc-**B**-**A**-**c1**-**c2**-OAll) and 1,3-dimethylbarbituric acid (2.5 equiv.) in degassed EtOAc/CH_2Cl_2 1:1. The resulting solution was stirred at room temperature for 1-2 h and concentrated. FC (EtOAC, CH_2Cl_2/EtOH, or CH_2Cl_2/MeOH gradients) afforded the free amino acid (H-**B**-**A**-**c1**-**c2**-OH).

Synthesis of the c2-B Fragment

Procedure D

Synthesis in two steps, via amidoester and subsequent saponification

i-Pr_2NEt (5.0 equiv.) was slowly added to a mixture of the N-protected amino acid (Alloc-**c2**-OH, 2.2 equiv.), the aminoalcohol hydrochloride (HO-**B**-H·HCl), Cl-HOBt (0.25 equiv.) and HCTU (2.5 equiv.) in DMF. The resulting solution was stirred at room temperature for 17 h, followed by distribution between EtOAc and sat. aq. Na_2CO_3 solution. The organic phase was washed (1 M aq. HCl soln, sat. aq. NaCl soln), dried (Na_2SO_4), filtered and concentrated. FC (hexane/EtOAc or CH_2Cl_2/MeOH gradients) afforded the corresponding amidoester, which was dissolved in THF/H_2O 4:1 and treated with lithium hydroxide monohydrate (3.0 equiv.) for 2 h at room temperature. The mixture was concentrated to about 50% of the original volume, diluted with EtOAc and extracted with 1 M aq. NaOH solution. The organic phase was washed (H_2O, sat. aq. NaCl soln), dried (Na_2SO_4), filtered and concentrated to afford the amidoalcohol (HO-**B**-**c2**-Alloc).

Synthesis of the linear cyclization precursor H-c2-B-A-c1-OH

Procedure E

E.1.1: Mitsunobu aryl ether synthesis using PPh_3/DEAD

A mixture of the hydroxyaryl amide (HO-**A**-**c1**-OAll) and PPh_3 (1.5-4.5 equiv.) was dissolved in benzene. The solution was concentrated and the residue was dried i.v. for 15-30 min. Under argon, a solution of the alcohol (HO-**B**-**c2**-Alloc, 1.2-2.3 equiv.) in dry and degassed benzene was added and the resulting mixture was cooled to 0°C. A solution of DEAD (40% in toluene, 1.2-4.5 equiv.) was slowly added. The mixture was stirred at

room temperature for 18 h. In case of incomplete consumption of the hydroxyaryl amide, additional triphenylphosphine (1.0-1.3 equiv.) and DEAD (40% in toluene, 1.0 equiv.) and alcohol (1.0 equiv.) – if consumed according to tlc - were added and stirring was continued for 18 h. The mixture was concentrated. FC (hexane/EtOAc, CH_2Cl_2/EtOH, or CH_2Cl_2/MeOH gradients) afforded Alloc-**c2**-**B**-**A**-**c1**-OAll (possibly contaminated with byproducts such as e.g. triphenylphosphine oxide, however acceptable for the use in the next step without further purification).

E.1.2: Mitsunobu aryl ether synthesis using CMBP
CMBP (2-3 equiv.) was added to a mixture of the hydroxyaryl amide (H-**A**-**c1**-OAll) and the alcohol (HO-**B**-**c2**-Alloc, 1.2-2.2 equiv.) in dry toluene. The mixture was heated at reflux for 16 h and concentrated. FC (hexane/EtOAc gradients) afforded the protected amino acid (Alloc-**c2**-**B**-**A**-**c1**-OAll).

E.2: Cleavage of the allyl/alloc protective groups
$Pd(PPh_3)_4$ (0.05-0.1 equiv.) was added to a mixture of the protected amino acid (Alloc-**c2**-**B**-**A**-**c1**-OAll) and 1,3-dimethylbarbituric acid (2.4 equiv.) in degassed EtOAc/CH_2Cl_2 1:1. The resulting solution was stirred at room temperature for 1-3 h and concentrated. FC(EtOAC, CH_2Cl_2/EtOH, or CH_2Cl_2/MeOH gradients) afforded the free amino acid (H-**c2**-**B**-**A**-**c1**-OH).

Synthesis of the macrocycles *cyclo*-(**B-A-c1**), and *cyclo*-(**c2-B-A-c1**)

Procedure F

The macrolactamization was typically performed at final concentrations ranging from 0.01 M to 0.001 M

F.1.1: T3P mediated lactam formation

A solution of the precursor (H-**B**-**A**-**c1**-OH or H-**c2**-**B**-**A**-**c1**-OH or H-**B**-**A**-**c1**-**c2**-OH, respectively) in dry CH_2Cl_2 was added within 2 h by syringe pump to a solution of T3P (50% in EtOAc, 2 equiv.) and *i*-Pr_2NEt (4 equiv.) in dry CH_2Cl_2. The solution was stirred at room temperature for 20 h, extracted with sat. aq. Na_2CO_3 solution and with H_2O, dried (Na_2SO_4), filtered and then concentrated. FC (hexane/EtOAc/MeOH or CH_2Cl_2/MeOH gradients) afforded the macrocyclic compound (*cyclo*-(**B**-**A**-**c1**) or *cyclo*-(**c2**-**B**-**A**-**c1**), respectively).

F.1.2: FDPP mediated lactam formation

A solution of the precursor (H-**B**-**A**-**c1**-OH or H-**c2**-**B**-**A**-**c1**-OH or H-**B**-**A**-**c1**-**c2**-OH, respectively) in dry DMF was added within 2 h to a solution of FDPP (2.0 equiv.) in dry DMF. The solution was stirred at room temperature for 20 h. The volatiles were evaporated and the residue taken up in EtOAc and washed (sat. aq. $NaHCO_3$ soln, H_2O, sat. aq. NaCl soln). The organic phase was dried (Na_2SO_4), filtered and concentrated. FC (hexane/EtOAc/MeOH or CH_2Cl_2/MeOH gradients gradients) afforded the macrocyclic compound (*cyclo*-(**B**-**A**-**c1**) or *cyclo*-(**c2**-**B**-**A**-**c1**), respectively).

Attachment of substituents to the macrocyclic core structures: Synthesis of the final products

Procedure H

A solution of a macrocyclic benzylester in MeOH or MeOH/THF (ca 100 mL per g of starting material) was hydrogenated for 2 h at room temperature and at normal pressure in the presence of palladium hydroxide on activated charcoal (moistened with 50% H_2O; 0.5 g per g of starting material). The mixture was filtered trough a pad of celite. The residue was washed (MeOH,

MeOH/CH_2Cl_2 1:1, THF). The combined filtrate and washings were concentrated to obtain a macrocyclic acid.

Procedure I

I.1: Teoc deprotection with dioxane-HCl

A solution of a macrocyclic Teoc-amine (1.5 mmol) in dioxane (18 mL) was treated with 4 M HCl in dioxane (18 mL) and stirred at room temperature for 4-16 h. The mixture was treated with diethyl ether and filtered. The solid was washed with diethyl ether and dried i.v. to give the macrocyclic amine hydrochloride.

I.2: Teoc deprotection with TBAF in THF

A solution of TBAF (1 M in THF, 3 equiv.) was added at 0°C to a solution of a macrocyclic Teoc-amine (1.3 mmol) in THF (34 mL). Stirring at 0°C to room temperature was continued for 3 h. The solution was distributed between CH_2Cl_2 and H_2O. The organic phase was washed (H_2O), dried (Na_2SO_4), filtered and concentrated to provide after FC the macrocyclic amine.

Procedure J

A solution of a macrocyclic Boc-amine in dioxane (10 mL per g of starting material) was treated with 4 M HCl in dioxane (20 mL per g of starting material) and stirred at room temperature for 2 h. The mixture was filtered. The solid was washed with diethyl ether and dried i.v. to give the macrocyclic amine hydrochloride.

Procedure K

A solution of a macrocyclic benzylcarbamate (0.9 mmol) in MeOH (52 mL) was hydrogenated for 4 h at room temperature and at normal pressure in the presence of palladium hydroxide on

activated charcoal (moistened with 50% H_2O; 0.3 g). The mixture was filtered trough a pad of celite. The residue was washed (MeOH). The combined filtrate and washings were concentrated to obtain the macrocyclic amine.

Procedure L

Amide coupling

L.1.1: with carboxylic acid anhydrides or acylchlorides

A solution of an amino macrocycle (free amine or hydrochloride; 0.09 mmol) in CH_2Cl_2 (1 mL) was at 0°C subsequently treated with pyridine (10 equiv.) and the carboxylic acid anhydride (1.05-5 equiv.) or a carboxylic acid chloride (1.05-2.0 equiv.), respectively. The solution was stirred at room temperature for 15 h. After the addition of MeOH (0.1 mL) the solution was stirred for 10 min and concentrated. The resulting crude product was coevaporated with toluene and purified by chromatography (FC, normal phase or reversed phase prep. HPLC) to give an N-acylamino macrocycle.

L.1.2: with carboxylic acid and polymersupported carbodiimide

A solution of an amino macrocycle (free amine or hydrochloride; 0.09 mmol), a carboxylic acid (1.2 equiv.), HOBt.H_2O (1.2 equiv.) in CH_2Cl_2 (1 mL) was treated with N-cyclohexyl-carbodiimide-N'-methylpolystyrene (1.9 mmol/g; 1.5 equiv.) and *i*-Pr_2NEt (3.0 equiv.). The mixture was stirred for 15 h at room temperature. (Polystyrylmethyl)trimethylammonium bicarbonate (3.5 mmol/g; 3 equiv.) was added and stirring was continued for 1 h. The mixture was diluted with CH_2Cl_2/MeOH 9:1 (2 mL) and filtered. The polymer was washed twice with CH_2Cl_2/MeOH 8:2 (5 mL). The combined filtrate and washings were concentrated. Purification of the crude product by chromatography (FC, normal phase or reversed phase prep. HPLC) afforded an N-acylamino macrocycle

L.1.3: with a carboxylic acid and HATU

A solution of an amino macrocycle (free amine or hydrochloride; 0.145 mmol), a carboxylic acid (2.0 equiv.), HATU (2.0 equiv.), HOAt (2.0 equiv.) in DMF (2 mL) was treated with *i*-Pr_2NEt (4.0 equiv.). The mixture was stirred for 15 h at room temperature. The solvent was removed. The residue was distributed between $CHCl_3$ and sat. aq. $NaHCO_3$ solution. The organic phase was washed (H_2O), dried (Na_2SO_4), filtered and concentrated. Purification of the crude product by chromatography (FC, normal phase or reversed phase prep. HPLC) afforded an N-acylamino macrocycle.

L.2: with an amine and HATU

A solution of a macrocyclic carboxylic acid (0.78 mmol), an amine (2.0 equiv.), HATU (2.0 equiv.), HOAt (2.0 equiv.) in DMF (6 mL) was treated with *i*-Pr_2NEt (4.0 equiv.). The mixture was stirred for 15 h at room temperature. The solvent was removed. The residue was distributed between $CHCl_3$ and sat. aq. $NaHCO_3$ solution. The organic phase was washed (H_2O), dried (Na_2SO_4), filtered and concentrated. Purification of the crude product by chromatography (FC, normal phase or reversed phase prep. HPLC) afforded a macrocycle amide.

Procedure M

N,N-Diethylamino macrocycles by reductive amination

At 0°C $NaBH(OAc)_3$ (5 equiv.) and acetaldehyde (1 mL) were added to a solution of an the amino macrocycle (free amine or hydrochloride; 0.09 mmol) in THF (1 mL). The mixture was stirred at 0°C to room temperature for 15 h. The mixture was diluted with $CHCl_3$ and washed with sat. aq. $NaHCO_3$ soln. The organic phase was dried (Na_2SO_4), filtered and concentrated. Purification of the crude product by chromatography (FC, normal

phase or reversed phase prep. HPLC) afforded the diethylamino macocycle.

Procedure N

Methylester cleavage

A solution of the methylester (57 μMol) in THF (1.5 mL) and MeOH (0.5 mL) was treated with H_2O (0.5 mL) and lithium hydroxide monohydrate (3 equiv.) for 2 h at room temperature. The mixture was acidified by addition of aqueous 1 M HCl and concentrated. The crude product was purified by prep. HPLC.

Synthesis of A-c1 Fragments

1. Synthesis of (*S*)-5-allyl 1-benzyl 2-(5-fluoro-2-hydroxy-*N*-methylbenzamido)pentanedioate (**54**) (Scheme 4)

Following procedure **A** (steps **A.1-A.3**), the reaction of 2-acetoxy-5-fluoro benzoic acid (**2**, 11.78 g, 59 mmol) and oxalylchloride (18 mL, 206 mmol)in dry CH_2Cl_2 (516 mL) in the presence of DMF (50 μL) afforded 2-acetoxy-5-fluoro benzoyl chloride (**52**).

Reaction of acid chloride **52** with (*S*)-5-allyl 1-benzyl 2-(methylamino)pentanedioate hydrochloride (**27**·HCl, 15.0 g, 46 mmol) in THF (260 mL) in the presence of *i*-Pr_2NEt (23 mL, 137 mmol) yielded the acetate **53** (19.35 g, 90%), which was treated with 3-dimethylamino-1-propylamine (23 mL, 185 mmol) in THF (200 mL) to afford after aqueous workup (EtOAc, 0.1 M aq. HCl soln, sat. aq. NaCl soln) and after FC (hexane/EtOAc 8:2 to 7:3) the phenol **54** (14.4 g, 81%).

Data of **54**: $C_{23}H_{24}FNO_6$ (429.4). HPLC (30% CH_3CN): R_t = 3.79 (87 %). LC-MS (method 9a): R_t = 2.09, 430 ($[M+H]^+$).

2. Synthesis of (*R*)-5-allyl 1-benzyl 2-(5-fluoro-2-hydroxy-*N*-methylbenzamido)pentanedioate (**56**) (Scheme 4)

Following procedure **A** (steps **A.1-A.3**), the reaction of 2-acetoxy-5-fluoro benzoic acid (**2**, 13.0 g, 67 mmol) and oxalylchloride (20 mL, 233 mmol)in dry CH_2Cl_2 (585 mL) in the presence of DMF (50 µL) afforded 2-acetoxy-5-fluoro benzoyl chloride (**52**).

Reaction of acid chloride **52** with (*R*)-5-allyl 1-benzyl 2-(methylamino)pentanedioate hydrochloride (**29**·HCl, 17.0 g, 52 mmol) in THF (280 mL) in the presence of *i*-Pr_2NEt (27 mL, 156 mmol) yielded **55** (21.5 g, 88%), which was treated with 3-dimethylamino-1-propylamine (26 mL, 205 mmol) in THF (200 mL) to afford after aqueous workup (EtOAc, 0.1 M aq. HCl soln, sat. aq. NaCl soln) and after FC (hexane/EtOAc 8:2 to 7:3) the phenol **56** (14.8 g, 75%).

Data of **56**: $C_{23}H_{24}FNO_6$ (429.4). HPLC (30% CH_3CN): R_t = 3.79 (89). LC-MS (method 9c): R_t = 2.11, 430 ($[M+H]^+$).

3. Synthesis of (*S*)-allyl 2-(benzyloxycarbonylamino)-3-(3-hydroxy-*N*-methylbenzamido)propanoate (**59**) (Scheme 4)

Following procedure **A** (steps **A.1-A.3**), the reaction of 3-acetoxybenzoic acid (**3**, 6.0 g, 33 mmol) and oxalylchloride (14 mL, 164 mmol) in dry diethyl ether (216 mL) in the presence of DMF (50 µL) afforded 3-acetoxybenzoyl chloride (**57**, 7.0 g, quant.).

Reaction of **57** (7.0 g, 35 mmol) with (*S*)-allyl 2-(benzyloxycarbonylamino)-3-(methylamino)propanoate hydrochloride (**32**·HCl, 10.5 g, 32 mmol) in CH_2Cl_2 (285 mL) in the presence of 2,4,6-collidine (12.8 mL, 96 mmol) yielded **58** (12.34 g, 82%).

The acetate **58** (12.82 g, 28.2 mmol) was treated with 3-dimethylamino-1-propylamine (10.6 mL, 84.6 mmol) in THF (114 mL) to afford the phenol **59** (10.45 g, 90%).

Data of **59**: $C_{22}H_{24}N_2O_6$ (412.4). HPLC (10% CH_3CN): R_t = 3.91 (96). LC-MS (method 9a): R_t = 1.77, 413 ($[M+H]^+$).

4. Synthesis of (*R*)-allyl 2-(benzyloxycarbonylamino)-3-(3-hydroxy-*N*-methylbenzamido)propanoate (**61**) (Scheme 4)

Following procedure **A** (steps **A.1-A.3**), the reaction of 3-acetoxybenzoic acid (**3**, 5.82 g, 32.3 mmol) and oxalylchloride (11.1 mL, 129 mmol) in dry diethyl ether (210 mL) in the presence of DMF (50 μL) afforded 3-acetoxybenzoyl chloride (**57**, 6.5 g, 100%).

Reaction of **57** (6.5 g, 32.3 mmol) with (*R*)-allyl 2-(benzyloxycarbonylamino)-3-(methylamino)propanoate hydrochloride (**36**·HCl, 8.5 g, 26 mmol) in CH_2Cl_2 (220 mL) in the presence of 2,4,6-collidine (10.3 mL, 77.6 mmol) yielded **60** (10.73 g, 92%).

The acetate **60** (15.46 g, 34 mmol) was treated with 3-dimethylamino-1-propylamine (12.8 mL, 102 mmol) in THF (140 mL) to afford the phenol **61** (12.92 g, 92%).

Data of **61**: $C_{22}H_{24}N_2O_6$ (412.4). LC-MS (method 2): R_t = 1.77 (98), 413 ($[M+H]^+$).

5. Synthesis of (*S*)-allyl 2-(benzyloxycarbonylamino)-4-(3-hydroxy-*N*-methylbenzamido)butanoate (**63**) (Scheme 4)

Following procedure **A** (steps **A.1-A.3**), the reaction of 3-acetoxybenzoic acid (**3**, 7.65 g, 43 mmol) and oxalylchloride (18.2 mL, 213 mmol) in dry CH_2Cl_2 (140 mL) in the presence of DMF (300 μL) afforded after 3 h at room temperature 3-acetoxybenzoyl chloride (**57**).

Reaction of **57** thus obtained with (*S*)-allyl 2-(benzyloxycarbonylamino)-5-(methylamino)butanoate hydrochloride (**40**·HCl, 8.7 g, 28 mmol) in THF (140 mL) in the presence of *i*-Pr_2NEt (15 mL, 85 mmol) yielded **62** (8.1g, 61%).

The acetate **62** (4.85 g, 10 mmol) was treated with 3-dimethylamino-1-propylamine (3.8 mL, 31 mmol) in THF (90 mL) to afford the phenol **63** (4.23 g, 95%).
Data of **63**: $C_{23}H_{26}N_2O_6$ (426.5). LC-MS: (method 6): R_t = 1.06 (99), 427 ($[M+H]^+$).

6. Synthesis of (*S*)-allyl 2-(benzyloxycarbonylamino)-5-(3-hydroxy-*N*-methylbenzamido)pentanoate (**65**) (Scheme 4)
Following procedure **A** (steps **A.1-A.3)**, the reaction of 3-acetoxybenzoic acid (**3**, 10 g, 58 mmol) and oxalylchloride (19 mL, 218 mmol) in dry CH_2Cl_2 (450 mL) in the presence of DMF (500 µL) afforded 3-acetoxybenzoyl chloride (**57**).
Reaction of **57** thus obtained with (S)-allyl 2-(benzyloxycarbonylamino)-5-(methylamino)pentanoate hydrochloride (**44**·HCl, 17.3 g, 48 mmol) in THF (200 mL) in the presence of *i*-Pr_2NEt (25 mL, 145 mmol) yielded **64** (12.08 g, 51%), which was treated with 3-dimethylamino-1-propylamine (9.3 mL, 75 mmol) in THF (240 mL) to afford after aqueous workup (EtOAc, 1 M aq. HCl soln, sat. aq. $NaHCO_3$ soln, sat.- aq. NaCl soln) the phenol **65** (10.84 g, 98%).
Data of **65**: $C_{24}H_{28}N_2O_6$ (440.5). LC-MS (method 6): R_t = 1.15 (91), 441 ($[M+H]^+$).

7. Synthesis of (*S*)-5-allyl 1-benzyl 2-(4-hydroxy-*N*-methylbenzamido)pentanedioate (**68**) (Scheme 4)
Following procedure **A** (steps **A.1-A.3)**, the reaction of 4-acetoxybenzoic acid (**4**, 10.7 g, 59.5 mmol) and oxalylchloride (17.7 mL, 206 mmol) in dry CH_2Cl_2 (350 mL) in the presence of DMF (50 µL) afforded 4-acetoxybenzoyl chloride (**66**).
Reaction of **66** with (*S*)-5-allyl 1-benzyl 2-(methylamino)pentanedioate hydrochloride (**27**·HCl, 15.0 g, 46 mmol) in THF (250 mL) in the presence of *i*-Pr_2NEt (23.3 mL, 137 mmol) yielded **67** (16.24 g, 78%).

The treatment of **67** (15.2 g, 33.5 mmol) with 3-dimethylamino-1-propylamine (12.6 mL, 101 mmol) in THF (140 mL) afforded the phenol **68** (14.86 g, quant.; the product was contaminated with 9% EtOAc).

Data of **68**: $C_{23}H_{25}NO_6$ (411.4). LC-MS (method 9b): R_t = 1.96, 412 ($[M+H]^+$).

8. Synthesis of (*S*)-allyl 2-(benzyloxycarbonylamino)-3-(5-hydroxy-*N*-methylnicotinamido)propanoate (**71**) (Scheme 4)

A mixture of 5-hydroxy nicotinic acid (**5**, 3.5 g, 25.1 mmol) and acetic anhydride (23 mL, 243 mmol) was heated at 95°C for 45 min and cooled to room temperature. The mixture was filtered. The solid was washed (H_2O, diethyl ether) and dried i.v. to give 5-acetoxynicotinic acid (**6**; 3.76 g, 82%) (Scheme 1)

5-Acetoxynicotinic acid (**6**; 5.7 g, 31.5 mmol) was suspended in $CHCl_3$ (stabilized with amylene, 230 mL). Oxalylchloride (9.0 mL, 105 mmol) was added followed by DMF (ca. 50 µL). The mixture was stirred at room temperature for 15 h, then concentrated, coevaporated with dry CH_2Cl_2 and dried i.v. to afford 5-acetoxynicotinoyl chloride (**69**). (*S*)-allyl 2-(benzyloxycarbonylamino)-3-(methylamino)propanoate hydrochloride (**32**, 8.6 g, 26.2 mmol) and THF (225 mL) were added. The mixture was cooled to 0°C. Et_3N (13 mL, 92 mmol) was slowly added. The mixture was stirred at 0°C to room temperature for 18 h. 3-dimethylamino-1-propylamine (9.9 mL, 78.6 mmol) was added and stirring at room temperature was continued for 2 h. The mixture was distributed between EtOAc and 1 M aq. NaH_2PO_4 solution. The organic layer was separated, washed (sat. aq. NaCl soln), dried (Na_2SO_4), filtered and concentrated. FC (CH_2Cl_2/MeOH 19:1) afforded the phenol **71** (8.81 g, 81%).

Data of **71**: $C_{21}H_{23}N_3O_6$ (413.4). LC-MS (method 6): R_t = 0.94 (92), 414 ($[M+H]^+$).

9. Synthesis of allyl (2*S*)-2-[(benzyloxy)carbonyl]amino-3-[((2*S*)-2-[(*tert*-butoxycarbonyl)amino]-8-hydroxy-1,2,3,4-tetrahydro-2-naphthalenylcarbonyl)(methyl)amino]propanoate (**72**) (Scheme 4)

A mixture of **10** (3.0 g, 9.76 mmol), HATU (5.57 g, 14.6 mmol), HOAt (1.99 g, 14.6 mmol) and **32**·HCl (6.4 g, 19.5 mmol) were dissolved in DMF (113 mL). *i*-Pr_2NEt (8.36 mL, 48.8 mmol) was added. The mixture was stirred at room temperature for 3 d. The mixture was distributed between H_2O and EtOAc. The organic phase was dried (Na_2SO_4), filtered, and concentrated. FC (hexane/EtOAc 75:25 to 50:50) afforded **72** (2.58 g, 45%).

Data of **72**: $C_{31}H_{39}N_3O_8$ (581.3). LC-MS (method 7): R_t = 1.27 (97), 582 ($[M+H]^+$).

10. Synthesis of 5-allyl 1-benzyl (2S)-2-[[(8-hydroxy-2-quinolinyl)carbonyl](methyl)amino]pentanedioate(**75**) (Scheme 4)

Following procedure **A** (steps **A.1-A.3)**, the reaction of 8-Acetoxyquinoline-2-carboxylic acid (**8**, 2.22 g 9.6 mmol) and oxalylchloride (2.1 mL, 24 mmol) in dry CH_2Cl_2 (90 mL) (no addition of DMF) afforded after 2 h at room temperature acetoxyquinoline-2-carboxylic acid chloride (**73**).

Reaction of **73** with (*S*)-5-allyl 1-benzyl 2-(methylamino)pentanedioate hydrochloride (**27**·HCl, 2.3 g, 8.0 mmol) in CH_2Cl_2 (200 mL) in the presence of *i*-Pr_2NEt (5.5 mL, 32 mmol) yielded after 2.5 h at room temperature and purification by FC (hexane/EtOAc gradient) **74** (3.03 g, 74%), which was treated with 3-dimethylamino-1-propylamine (2.3 mL, 18 mmol) in THF (54 mL) to afford after aqueous workup (EtOAc, 1 M aq. HCl soln, sat. aq. $NaHCO_3$ soln, sat.- aq. NaCl soln) the phenol **75** (2.79 g, 99%).

Data of **75**: $C_{26}H_{26}N_2O_6$ (462.5). LC-MS (method 7): R_t = 1.29 (94), 463 ($[M+H]^+$).

11. Synthesis of *N*-allyl-3-hydroxy-*N*-methylbenzamide (**77**) (Scheme 4)

Following procedure **A** (steps **A.1-A.3)**, the reaction of 3-acetoxybenzoic acid (**3**, 23.7 g, 132 mmol) and oxalylchloride (45.3 mL, 527 mmol) in dry diethyl ether (800 mL) in the presence of DMF (100 μL) afforded 3-acetoxybenzoyl chloride (**57**).

Reaction of **57** thus obtained with *N*-allylmethylamine (10.1 ml, 105 mmol) in CH_2Cl_2 (500 mL) in the presence of 2,4,6-collidine (42 mL, 316 mmol) yielded **76** (24 g, 98%).

The acetate **76** (10.9 g, 46.7 mmol) was treated with 3-dimethylamino-1-propylamine (17.5 mL, 140 mmol) in THF (90 mL) to afford after aqueous workup (EtOAc, 1 M aq. HCl soln, sat. aq. NaCl soln) the phenol **77** (9.0 g, 100%).

Data of **77**: $C_{11}H_{13}NO_2$ (191.2). LC-MS (method 2): R_t = 1.52 (99), 192 ($[M+H]^+$).

12. Synthesis of (*S*)-5-allyl-1-benzyl 2-(3-mercapto-*N*-methylbenzamido)pentanedioate (**80**)

(Scheme 4)

Acetic anhydride (0.46 mL, 4.86 mmol) was added at 0°C to a solution of 3-mercaptobenzoic acid (**11**, 250 mg, 1.62 mmol) in 1 M aqueous NaOH solution (5.0 mL, 5.0 mmol). The mixture was stirred at 0°C for 1 h. A precipitate was formed. The mixture was acidified by the addition of 1 M aqueous HCl solution and filtered. The solid was dried i.v. to afford 3-(acetylthio)benzoic acid (**12**; 280 mg, 88%).

Oxalyl chloride (0.34 mL, 3.97 mmol) was added to a mixture of **12** (260 mg, 1.33 mmol) and $CHCl_3$ (stabilized with amylene; 16 mL). DMF (7 μL) was added. The mixture was stirred at room temperature for 2 h. The volatiles were evaporated to afford 3-(acetylthio)benzoyl chloride (**78**).

(*S*)-5-allyl 1-benzyl 2-(methylamino)pentanedioate hydrochloride (**27**·HCl, 434 mg, 1.33 mmol) and dry THF (5 mL) were added. The mixture was cooled to 0°C, followed by the addition of *i*-Pr_2NEt (0.79 mL, 4.6 mmol). The mixture was stirred at room temperature for 16 h and distributed between EtOAc and 1 M aqueous HCl solution. The organic phase was separated, dried (Na_2SO_4), filtered and concentrated. FC (hexane/EtOAc 2:1) afforded the acetate **79** (420 mg, 67%).

At room temperature, a solution of **79** (246 mg, 0.52 mmol) in degassed THF (3.6 mL) was treated with 3-dimethylamino-1-propylamine (0.13 mL, 1.05 mmol) for 1 h. The mixture was distributed between EtOAc and 1 M aqueous HCl solution. The organic phase was separated, dried (Na_2SO_4), filtered and concentrated. FC (hexane/EtOAc 2:1) afforded **80** (153 mg, 68%).

Data of **80**: $C_{23}H_{25}NO_5S$ (427.5): LC-MS (method 7): R_t = 1.39 (84), 428 ($[M+H]^+$).

Synthesis of c2-B Fragments

1. Synthesis of allyl *N*-2-[(2*S*,4*S*)-4-[(*tert*-butoxycarbonyl)amino]-2-(hydroxymethyl)tetrahydro-1*H*-pyrrol-1-yl]-2-oxoethyl-*N*-methylcarbamate (**81**) (Scheme 5)

A solution of (2-((allyloxycarbonyl)(methyl)amino)acetic acid (**47**, 8.0 g, 46 mmol) and aminoalcohol **13** (11.0 g, 51 mmol) in DMF (120 mL) was cooled to 0°C. 2,4,6-Collidine (11 mL, 82 mmol) was added followed by HATU (22 g, 58 mmol). The mixture was stirred for 1 h at 0°C then for 16 h at room temperature followed by distribution between EtOAc and sat. aq. Na_2CO_3 solution. The organic phase was washed (1 M aq. HCl soln, sat. aq. NaCl soln), dried (Na_2SO_4), filtered and concentrated. FC (EtOAc/MeOH 100:0 to 95:5) afforded the amidoalcohol **81** (14.7 g, 86%).

Data of **81**: $C_{17}H_{29}N_3O_6$ (371.4). HPLC (20% CH_3CN): R_t = 2.94 (97). LC-MS (method 9c): R_t = 1.55; 743 ($[2M+H]^+$), 372 ($[M+H]^+$).

2. Synthesis of allyl *N*-2-[(2*S*,4*R*)-4-[(*tert*-butoxycarbonyl)amino]-2-(hydroxymethyl)tetrahydro-1*H*-pyrrol-1-yl]-2-oxoethyl-*N*-methylcarbamate (**82**) (Scheme 5)

Following procedure **D**, the reaction of the amnioalcohol **17**·HCl (10.0 g, 39.6 mmol) and 2-((allyloxycarbonyl)(methyl)amino)acetic acid (**47**, 15.1 g, 87 mmol) in DMF (100 mL) in the presence of HCTU (40.9 g, 98.9 mmol), Cl-HOBt (1.68 g, 9.89 mmol) and *i*-Pr_2NEt (33.6 mL, 198 mmol) afforded after FC (hexane/EtOAc 20:80 to 0:100) the corresponding amido ester intermediate (13.7 g) which was saponified with lithium hydroxide monohydrate (3.28 g, 78.1 mmol) in THF (350 mL) and H_2O (90 mL) to yield the amidoalcohol **82** (8.89 g, 61%).

Data of **82**: $C_{17}H_{29}N_3O_6$ (371.4). LC-MS (method 9b): R_t = 1.57; 372 ($[M+H]^+$), 316, 272 ($[M+H-Boc]^+$), 156.

3. Synthesis of *tert*-butyl (3*R*)-4-{2-[[(allyloxy)carbonyl](methyl)amino]acetyl}-3-(hydroxymethyl)tetrahydro-1(2H)-pyrazinecarboxylate (**84**) (Scheme 5)

Following procedure **D**, the reaction of (*R*)-tert-butyl 3-(hydroxymethyl)piperazine-1-carboxylate hydrochloride (**83**·HCl, 19.7 g, 78 mmol) and 3-((allyloxycarbonyl)(methyl)amino)acetic acid (**47**, 30 g, 172 mmol) in DMF (188 mL) in the presence of HCTU (81.0 g, 195 mmol), Cl-HOBt (3.3 g, 19 mmol) and *i*-Pr_2NEt (67 mL, 390 mmol) afforded after FC (EtOAc) the corresponding amido ester intermediate (40 g) which was saponified with lithium hydroxide monohydrate (9.5 g, 228 mmol) in THF (1020 mL) and H_2O (245 mL) to yield after FC (EtOAc) amidoalcohol **84**; 22.8g, 79%).

Data of **84**: $C_{17}H_{29}N_3O_6$ (371.4). LC-MS (method 7): R_t = 0.99 (93), 372 ($[M+H]^+$).

4. Synthesis of benzyl *N*-((1*S*)-1-[(2*S*,4*S*)-4-[(*tert*-butoxycarbonyl)amino]-2-(hydroxymethyl)tetrahydro-1*H*-pyrrol-1-yl]carbonyl-3-butenyl)carbamate (**85**) (Scheme 5)

Aminoalcohol-hydrochloride **13**·HCl (3.7 g, 14.7 mmol) was added to a solution of acid **51** (5.22 g, 14.7 mmol) in DMF (80 ml). The mixture was cooled to 0°C. HATU (7.0 g, 18.4 mmol) and 2,4,6-collidine (3.51 ml, 26.4 mmol) were added. The solution was stirred at 0°C to room temperature for 17 h, followed by distribution between EtOAc and sat. aq. Na_2CO_3 solution. The organic phase was washed (1 M aq. HCl soln, sat. aq. $NaHCO_3$ soln, sat. aq. NaCl soln), dried (Na_2SO_4), filtered and concentrated. FC (hexane/EtOAc 30:70 to 20:80) afforded the amidoalcohol (**85**, 5.78 g, 88%)

Data of **85**: $C_{23}H_{33}N_3O_6$ (447.5). LC-MS (method 2): R_t = 1.92 (92), 448 ($[M+H]^+$).

5. Synthesis of allyl *N*-3-[(2*S*,4*R*)-4-[(*tert*-butoxycarbonyl)amino]-2-(hydroxymethyl)tetrahydro-1*H*-pyrrol-1-yl]-3-oxopropyl-*N*-methylcarbamate (**86**) (Scheme 5)

Following procedure **D**, the reaction of aminoalcohol **17**·HCl (7.5 g, 30 mmol) and 3-((allyloxycarbonyl)(methyl)amino)propanoic acid (**49**, 12.3 g, 66 mmol) in DMF (77 mL) in the presence of HCTU (31.0 g, 75.0 mmol), Cl-HOBt (1.27 g, 7.5 mmol) and *i*-Pr_2NEt (25.6 mL, 150 mmol) afforded after FC (CH_2Cl_2/MeOH 100:0 to 97:3) the corresponding amido ester intermediate (17.1 g) which was saponified with lithium hydroxide monohydrate (3.8 g, 90 mmol) in THF (388 mL) and H_2O (105 mL) to yield the amidoalcohol **86** (10.48 g, 86%).

Data of **86**: $C_{18}H_{31}N_3O_6$ (385.4). HPLC (10% CH_3CN): R_t = 3.49 (88). LC-MS (method 9a): R_t = 1.62; 386 ($[M+H]^+$), 330 ($[M+H-tBu]^+$), 286 ($[M+H-Boc]^+$).

Core 01: Synthesis of Ex.1 (Scheme 6)

Synthesis of the Mitsunobu product **87**

To a solution of **54** (350 mg, 0.82 mmol), **16** (590 mg, 1,7 mmol) and PPh_3 (1069 mg, 4.08 mmol) in dry degassed $CHCl_3$ (11 mL) was added ADDP (1028 mg, 4.08 mmol) in one portion at 0°C, under a N_2 atmosphere. The resulting mixture was stirred for 16 h at room temperature. The mixture was filtered and the slurry washed further with diethyl ether. The combined filtrates were concentrated *in vacuo*. The crude residue was purified by FC (CH_2Cl_2/EtOH 100:0 to 99:1) to afford **87** (1.05 g, contains triphenylphosphine oxide; used in the next step without further purification).

Synthesis of the amino acid **88**

Following procedure **B.2**, the reaction of **87** (441 mg, contaminated with triphenylphosphine oxide, ca 0.5 mmol), 1,3-dimethylbarbituric acid (219 mg, 1.4 mmol) and $Pd(PPh_3)_4$ (34 mg) in EtOAc/CH_2Cl_2 (55:45, 10 mL) yielded after 1,5 h and subsequent FC (CH_2Cl_2/MeOH 100:0 to 80:20) amino acid **88** (267 mg, 72%).

Data of **88**: $C_{31}H_{42}FN_3O_8Si$ (631.7). LC-MS (method 9a): R_t = 2.02, 632 ($[M+H]^+$). HPLC (30% CH_3CN): R_t = 3.41 (96).

Synthesis of the macrolactam **Ex.1**

According to procedure **F.1.1** the amino acid **88** (75 mg, 0.12 mmol) in dry CH_2Cl_2 (6 mL) was added within 4 h to T3P (50% in EtOAc, 0.21 mL, 0.36 mmol) and *i*-Pr_2NEt (0.1 mL, 0.59 mmol) in dry CH_2Cl_2 (6 mL) to give after FC (CH_2Cl_2/MeOH 100:0 to 96:4) the macrolactam **Ex.1** (45 mg, 61%).

Data of **Ex.1**: $C_{31}H_{40}FN_3O_7Si$ (613.7). LC-MS (method 7): R_t = 1.45 (41), 614 ($[M+H]^+$); 1.47 (44), 614 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): complex spectrum, several isomers; 7.45-7.01 (m, 8 H), 6,78-6.58 (2 m, 1 H), 5.42-5.06 (m, 3 H), 4.50-3.50 (several m, 7 H), 3.30-1.40 (several m, 7 H), 2.84, 2.70, 2.66 (s, 3 H),0.97-0.82 (m, 2 H), 0.03, 0.02, 0.00 (s 9 H).

Core 02: Synthesis of Ex.2 (Scheme 11)

Synthesis of the protected macrolactam **Ex.2**

A solution of T3P (50% in EtOAc, 0.75 mL, 1.27 mmol) and *i*-Pr_2NEt (0.36 mL, 2.2 mmol) in dry CH_2Cl_2 (20 mL) was added within 2 h to a solution of the amino acid **98** (250 mg, 0.43 mmol) in dry CH_2Cl_2 (730 mL). The solution was stirred at room temperature for 20 h, followed by extraction with sat. aq. Na_2CO_3 solution. The organic phase was dried (Na_2SO_4), filtered and concentrated. FC (CH_2Cl_2/MeOH 100:0 to 95:5) afforded **Ex.2** (187 mg, 77%).

Data of **Ex.2**: $C_{30}H_{36}FN_3O_7$ (569.6) LC-MS (method 7): R_t = 1.35 (62), 570 ($[M+H]^+$); 1.39 (15), 570 ($[M+H]^+$) ^{1}H-NMR (DMSO-d_6): complex spectrum, several isomers; 7.46-7.30 (m, 5 H), 7.27-7.06 (m, 2 H), 6.98-6.67 (4 dd, 1 H), 5.54-5.06 (m, 3 H), 4.68-3.48 (m, 6 H), 3.05-1.98 (m 10 H; s at 2.82, 2.69, 2.64), 1.44-1.41 (3 s, 9 H).

Core 03: Synthesis of Ex.3, Ex.4, and Ex.5 (Scheme 7)

Synthesis of the Mitsunobu product **89**

Following procedure **E.1.1**, the reaction of phenol **54** (7.8 g, 18 mmol), alcohol **81** (16 g, 43 mmol), DEAD (40% in toluene, 37 mL, 82 mmol), and PPh_3 (21 g, 80 mmol) in dry benzene (250 mL) afforded after FC (CH_2Cl_2/EtOH 100:0 to 95:5) the protected amino acid **89** (15.9 g, contaminated with ca. 30% triphenylphosphine oxide; used in the next step without further purification).

Synthesis of the amino acid **90**

Following procedure **E.2**, the reaction of **89** (9.6 g, contaminated with triphenylphosphine oxide, ca 9 mmol), 1,3-dimethylbarbituric acid (5.0 g, 32.0 mmol) and $Pd(PPh_3)_4$ (0.4 g) in EtOAc/CH_2Cl_2 (55:45, 266 mL) yielded after 1,5 h and after FC (CH_2Cl_2/MeOH 90:10 to 50:50) amino acid **90** (4.34 g, 76%).

Data of **90**: $C_{33}H_{43}FN_4O_9$ (658.7). HPLC (10% CH_3CN): R_t = 3.87 (99). LC-MS (method 9a): R_t = 1.77, 659 ($[M+H]^+$).

Synthesis of the protected macrolactam **Ex.3**

According to procedure **F.1.2**, the amino acid **90** (2.5 g, 3.80 mmol)in dry DMF (50 mL) was treated with FDPP (2.51 g, 6.53 mmol) in DMF (400 mL) to afford after FC (EtOAc/MeOH 100:0 to 95:5) the macrolactam **Ex.3** (2.29 g, 94%).

Data of **Ex.3**: $C_{33}H_{41}FN_4O_8$ (640.7). HPLC (30% CH_3CN): R_t = 3.20 (96). LC-MS (method 9c): R_t = 2.06, 641 ($[M+H]^+$). ^{1}H-NMR ($CDCl_3$): 7.45-7.32 (m, 5 H), 7.06 (m, 1 H), 6.94-6.88 (m, 2 H), 5.57 (dd, J = 2.8, 12.6, 1 H), 5.42 (br. m, 1 H), 5.26 (d, J = 12.2, 1 H), 5.15 (d, J = 12.2, 1 H), 4.90 (dd, J = 2.5, 11.0, 1 H), 4.34 (d, J = 17.2, 1 H), 4.35-4.11 (m, 3 H), 3.82 (br. t, J ca. 8.5, 1 H), 3.65 (d, J = 17.3, 1 H), 3.29 (t, J ca 8.8, 1 H), 3.14 (s, 3 H), 2.65 (s, 3 H), 2.51-1.98 (several m, 5 H), 1.76 (td, J = 8.2, 12.7, 1 H), 1.36 (s, 9 H).

Synthesis of the acid **Ex.4**:
According to procedure **H**, ester **Ex.3** (2.0 g, 3.1 mmol) was hydrogenated in MeOH (120 mL)/THF (40 mL) in the presence of the catalyst (1 g) for 2 h to afford **Ex.4** (1.68 g, 97%).
Data of **Ex.4**: $C_{26}H_{35}FN_4O_8$ (550.6). HPLC (5% CH_3CN): R_t = 3.60 (86). LC-MS: (method 9c): R_t = 1.53; 551 ($[M+H]^+$), 451 ($[M+H-Boc]^+$).

Synthesis of the amine **Ex.5**:
According to procedure **J**, ester **Ex.3** (100 mg, 0.16 mmol) in dioxane (3 mL) was treated with 4 M HCl-dioxane (3 mL) to afford **Ex.5**·HCl (100 mg, quant.).
Data of **Ex.5**·HCl: $C_{28}H_{33}FN_4O_6$·HCl (540.6, free base). LC-MS: (method 9c): R_t = 1.44, 541 ($[M+H]^+$).

Core 04: Synthesis of Ex.56 and Ex.57 (Scheme 8)

Synthesis of the Mitsunobu product **91**
Following procedure **E.1.1** the reaction of phenol **54** (8.0 g, 19 mmol), alcohol **82** (16.0 g, 43 mmol), DEAD (40% in toluene, 38 mL, 84 mmol), and PPh_3 (22 g, 84 mmol) in dry benzene (260 mL) afforded after FC the protected amino acid **91** (33.5 g, contaminated with triphenylphosphine oxide. The material was used in the next step without further purification).

Synthesis of the amino acid **92**
Following procedure **E.2**, the reaction of **91** (33.5 g, impure material), 1,3-dimethylbarbituric acid (16 g, 102 mmol) and $Pd(PPh_3)_4$ (0.2 g) in EtOAc/CH_2Cl_2 (45:55, 340 mL) yielded after 3 h and after FC (CH_2Cl_2/EtOH 100:0 to 70:30 then CH_2Cl_2/MeOH

90:10 to 70:30) amino acid **92** (4.8 g, 39% over the two steps, based on phenol **54**).

Data of **92**: $C_{33}H_{43}FN_4O_9$ (658.7). HPLC (10% CH_3CN): R_t = 3.80 (95). LC-MS (method 9c): R_t = 1.81, 659 ($[M+H]^+$).

Synthesis of the protected macrolactam **Ex.56**

According to procedure **F.1.1**, amino acid **92** (3.8 g, 5.80 mmol) in dry CH_2Cl_2 (40 mL) was treated with T3P (50% in EtOAc, 6.8 mL, 12 mmol) and *i*-Pr_2NEt (4.0 mL, 23 mmol) in dry CH_2Cl_2 (510 mL) to afford after FC (EtOAc/MeOH 100:0 to 95:5) the macrolactam **Ex.56** (3.23 g, 87%).

Data of **Ex.56**: $C_{33}H_{41}FN_4O_8$ (640.7). HPLC (30% CH_3CN): R_t = 3.49 (88). LC-MS (method 9c): R_t = 2.02, 641 ($[M+H]^+$). ^{1}H-NMR ($CDCl_3$): 7.41-7.32 (m, 5 H), 7.04 (m, 1 H), 6.94-6.83 (m, 2 H), 5.54 (dd, J = 3.0, 12.7, 1 H), 5.25 (d, J = 12.2, 1 H), 5.14 (d, J = 12.2, 1 H), 4.89 (dd, J = 2.1, 11.0, 1 H), 4.63 (br. m, 1 H), 4.39-4.10 (m, 4 H), 3.79-3.64 (m, 2 H), 3.49 (br. m, 1 H), 3.12 (s, 3 H), 2.64 (s, 3 H), 2.51-2.36 (m, 2 H), 2.23-1.98 (m, 4 H),1.44 (s, 9 H).

Synthesis of the acid **Ex.57**:

According to procedure **H**, the ester **Ex.56** (2.25 g, 3.5 mmol) was hydrogenated in MeOH (120 mL)/THF (40 mL) in the presence of the catalyst (1.1 g) for 2 h to afford - after washing of the filtration residue with warm (50°C) MeOH/THF 3:1-the acid **Ex.57** (1.9 g, 98%).

Data of **Ex.57**: $C_{26}H_{35}FN_4O_8$ (550.6). HPLC LC-MS: (method 2): R_t = 1.54 (82), 551 ($[M+H]^+$).

Core 05: Synthesis of Ex.85 and Ex.86 (Scheme 9)

Synthesis of the Mitsunobu product **93**

Following procedure **E.1.1**, the reaction of phenol **56** (6.6 g, 15 mmol), alcohol **81** (13 g, 35 mmol), DEAD (40% in toluene, 32 mL, 69 mmol), and PPh_3 (18 g, 69 mmol) in dry benzene (220 mL) afforded after FC (CH_2Cl_2/MeOH 100:0 to 94:6) the protected amino acid **93** (34.5 g, contaminated with triphenylphosphine oxide and diethyl hydrazine-1,2-dicarboxylate; acceptable for the use in the next step without further).

Synthesis of the amino acid **94**

Following procedure **E.2**, the reaction of **93** (34.5 g, impure material), 1,3-dimethylbarbituric acid (17 g, 106 mmol) and $Pd(PPh_3)_4$ (0.1 g) in EtOAc/CH_2Cl_2 (55:45, 350 mL) yielded after 3 h and after FC (CH_2Cl_2/EtOH 100:0 to 70:30 then CH_2Cl_2/MeOH 90:10 to 70:30) the amino acid **94** (5.6 g, 55% over the two steps, based on phenol **56**).

Data of **94**: $C_{33}H_{43}FN_4O_9$ (658.7). HPLC (10% CH_3CN): R_t = 3.79 (96). LC-MS (method 9c): R_t = 1.77, 659 ($[M+H]^+$).

Synthesis of the protected macrolactam **Ex.85**

According to procedure **F.1.1**, amino acid **94** (2.75 g, 4.2 mmol) in dry CH_2Cl_2 (35 mL) was treated with T3P (50% in EtOAc, 4.9 mL, 8.3 mmol) and *i*-Pr_2NEt (2.9 mL, 17 mmol) in dry CH_2Cl_2 (355 mL) to yield after FC (EtOAc/MeOH 100:0 to 95:5) macrolactam **Ex.85** (2.47 g, 92%).

Data of **Ex.85**: $C_{33}H_{41}FN_4O_8$ (640.7). HPLC (30% CH_3CN): R_t = 3.52 (96). LC-MS (method 9c): R_t = 2.06; 641 ($[M+H]^+$), 541 ($[M+H-Boc]^+$). ^{1}H-NMR ($CDCl_3$): two isomers, ratio 85:15, 7.42-7.31 (m, 5 H), 7.08-6.77 (m, 3 H), 5.33 (d, J = 8.3, 1 H), 5.23 (d, J = 12.2, 1 H), 5.17 (d, J = 12.1, 1 H), 4.84 (dd, J = 2.9, 8.9, 1 H), 4.37-4.25 (m, 3 H), 4.11 (dd, J = 4.2, 12.0, 1 H), 3.89 (t, J = 8.3, 1 H), 3.80 (d, J = 8.9, 1 H), 3.61 (d, J = 17.1, 1 H), 3.16 (t, J = 9.1, 1 H), 3.13 (s, 2.55 H, NCH_3 of major isomer), 3.03 (s, 0.45 H, NCH_3 of minor isomer), 2.98 (s, 2.55 H, NCH_3

of major isomer), 2.87 (0.45 H, NCH_3 of minor isomer), 2.64-2.41 (m, 2 H), 2.27-2.09 (m, 1 H), 1.98-1.83 (m, 2 H), 1.79-1.66 (m, 2 H), 1.45 (s, 7.65 H, Boc, major isomer), 1.35 (s, 1.35 H, Boc, minor isomer).

Synthesis of the acid **Ex.86**:
According to procedure **H**, ester **Ex.85** (2.0 g, 3.1 mmol) was hydrogenated in MeOH (120 mL) / THF (40 mL) in the presence of the catalyst (1 g) for 2 h to afford - after washing of the filtration residue with warm (50°C) MeOH/TFH 3:1 - the acid **Ex.86** (1.67 g, 97%).
Data of **Ex.86**: $C_{26}H_{35}FN_4O_8$ (550.6). LC-MS: (method 3): R_t = 1.10 (83), 551 ($[M+H]^+$); 1.17 (15), 551 ($[M+H]^+$).

Core 06: Synthesis of Ex.104 and Ex.105 (Scheme 10)

Synthesis of the Mitsunobu product **95**
Following procedure **E.1.2**, the reaction of phenol **56** (13.1 g, 30.5 mmol), alcohol **82** (13.6 g, 36.6 mmol), and CMBP (14.7 g, 61 mmol) in dry toluene (500 mL) afforded after FC (hexane/EtOAc 50:50 to 30:70) the protected amino acid **95** (16 g, 67%).

Synthesis of the amino acid **96**
Following procedure **E.2**, the reaction of **95** (16.0 g, 20 mmol), 1,3-dimethylbarbituric acid (8 g, 49 mmol) and $Pd(PPh_3)_4$ (0.1 g) in EtOAc/CH_2Cl_2 (55:45, 220 mL) yielded after 3 h and after FC (CH_2Cl_2/EtOH 100:0 to 70:30 then CH_2Cl_2/MeOH 90:10 to 70:30) amino acid **96** (11 g, 81%).
Data of **96**: $C_{33}H_{43}FN_4O_9$ (658.7). LC-MS (method 2): R_t = 1.63 (97), 659 ($[M+H]^+$).

Synthesis of the protected macrolactam **Ex.104**

According to procedure **F.1.1**, amino acid **96** (4.0 g, 6.1 mmol) in dry CH_2Cl_2 (40 mL) was treated with T3P (50% in EtOAc, 7.2 mL, 12.1 mmol) and *i*-Pr_2NEt (4.2 mL, 24.3 mmol) in dry CH_2Cl_2 (1160 mL) to give after FC (CH_2Cl_2/MeOH 100:0 to 95:5) macrolactam **Ex.104** (2.32 g, 60%).

Data of **Ex.104**: $C_{33}H_{41}FN_4O_8$ (640.7). LC-MS (method 7): R_t = 1.21 (47), 641 ($[M+H]^+$); 1.24 (53), 641 ([M+H]). ^{1}H-NMR (DMSO-d_6): complex spectrum, mixture of isomers, 7.44-6.65 (m, 9 H), 5.32-5.05 (m, 2 H), 4.70-3.30 (several m, 9 H), 2.92 (s, NCH_3 of major isomer), 2.84 (s, NCH_3 of major isomer), 2.30-1.70 (several m, 6 H), 1.40, 1.38 (2 s, 9 H).

Synthesis of the acid **Ex.105**:

According to procedure **H**, ester **Ex.104** (2.15 g, 3.3 mmol) was hydrogenated in MeOH (215 mL) in the presence of the catalyst (1.07 g) for 4 h to afford acid **Ex.105** (1.72 g, 93%).

Data of **Ex.105**: $C_{26}H_{35}FN_4O_8$ (550.6). LC-MS: (method 7): R_t = 0.91 (45), 551 ($[M+H]^+$); 0.95 (38), 551 ($[M+H]^+$).

Core 07: Synthesis of Ex.115 and Ex.116 (Scheme 11)

Synthesis of the Mitsunobu product **97**

A mixture of the phenol **54** (6.42 g, 14.9 mmol), alcohol **22** (4.04 g, 13.5 mmol), and PPh_3 (9.73 g, 37.1 mmol) was dried i.v. for 15 min. and dissolved in dry, degassed chloroform (130 mL). The solution was cooled to 0°C. A solution of ADDP (9.36 g, 37.1 mmol) in chloroform (20 mL) was slowly added. The mixture was stirred at room temperature for 3 h followed by the addition of more **22** (4.04 g, 13.5 mmol) and PPh_3 (5.97 g, 22.8

mmol) in chloroform (20 mL). The mixture was cooled to 0°C. A solution of ADDP (5.74 g, 22.7 mmol) in chloroform (20 mL) was slowly added. The solution was stirred at room temperature for 16 h and concentrated. The residue was suspended in diethyl ether and filtered. The solid was washed with diethyl ether. The combined filtrate and washings were concentrated. FC (CH_2Cl_2/EtOAc 10:1) gave **97** (7.73 g, 73%).

Synthesis of the amino acid **98**

Following procedure **B.2**, the reaction of **97** (7.72 g, 11 mmol), 1,3-dimethylbarbituric acid (4.1 g, 26.0 mmol) and $Pd(PPh_3)_4$ (0.63 g) in EtOAc/CH_2Cl_2 (53:47, 190 mL) yielded after 2 h and after FC (EtOAc, then CH_2Cl_2/MeOH 95:5 to 90:10) amino acid **98** (4.31 g, 67%).

Data of **98**: $C_{30}H_{38}FN_3O_8$ (587.6). HPLC (10% CH_3CN): R_t = 3.86 (84). LC-MS (method 9a): R_t = 1.76; 588 ($[M+H]^+$), 488 ($[M+H-Boc]^+$).

Synthesis of the Alloc protected amino acid **99**

Following procedure **C.1**, the reaction of the amino acid **98** (4.3 g, 7.3 mmol), allyl choroformate (0.86 mL, 8.0 mmol) and Na_2CO_3 (1.2 g, 11 mmol) in dioxane (62 mL) and H_2O (60 mL) gave acid **99** (5.07 g, 100%).

Synthesis of the protected diamide **100**

Following procedure **C.2**, the acid **99** (4.9 g, 7.3 mmol) was reacted with sarcosine allylester p-toluenesufonate (**46**.p-TsOH, 2.6 g, 8.8 mmol), HOAt (1.5 g, 11 mmol), HATU (4.2 g, 11 mmol) and *i*-Pr_2NEt (6.2 mL, 36 mmol) in DMF (75 mL) to afford the protected amino acid **100** (4.37 g, 76%).

Data of **100**: $C_{40}H_{51}FN_4O_{11}$ (782.8). HPLC (50% CH_3CN): R_t = 3.56 (99). LC-MS (method 9a): R_t = 2.45; 783 ($[M+H]^+$), 683 ($[M+H-Boc]^+$).

Synthesis of the deprotected amino acid **101**

Following procedure **C.3**, the reaction of the protected amino acid **100** (4.36 g, 5.6 mmol), 1,3-dimethylbarbituric acid (2.1 g, 13 mmol) and $Pd(PPh_3)_4$ (0.32 g) in EtOAc/CH_2Cl_2 (45:55, 106 mL) yielded amino acid **101** (3.46 g, 93%).

Data of **101**: $C_{33}H_{43}FN_4O_9$ (658.7). LC-MS (method 9b): R_t = 1.74; 659 ($[M+H]^+$), 559 ($[M+H-Boc]^+$).

Synthesis of the protected macrolactam **Ex.115**

According to procedure **F.1.1**, amino acid **101** (3.44 g, 5.2 mmol) in dry CH_2Cl_2 (50 mL) was treated with T3P (50% in EtOAc, 6.2 mL, 10 mmol) and *i*-Pr_2NEt (3.6 mL, 21 mmol) in dry CH_2Cl_2 (470 mL) to give after FC (CH_2Cl_2/MeOH 95:5) macrolactam **Ex.115** (2.95 g, 90%).

Data of **Ex.115**: $C_{33}H_{41}FN_4O_8$ (640.7). HPLC (20% CH_3CN): R_t = 4.05 (93). LC-MS (method 9c): R_t = 2.08; 641 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): complex spectrum, mixture of isomers, 7.38 (s, 5 H), 7.35-6.95 (several m, 2 H), 6.81-6.72 (several m, 0.4 H), 6.64 (dd, J = 3.1, 8.2, 0.25 H), 6.39 (dd, J = 3.2, 7.7, 0.25 H), 6.30 (dd, J = 3.3, 8.2, 0.1 H), 5.37-4.99 (m, 3 H), 4.60-3.60 (several m, 9 H), 3.20-2.60 (several m and s, 8 H), 2.40-1.70 (several m, 4 H), 1.45, 1.43, 1.42, 1.38 (4 s, Boc).

Synthesis of the acid **Ex.116**:

According to procedure **H**, the ester **Ex.115** (1.2 g, 1.9 mmol) was hydrogenated in MeOH (120 mL) in the presence of the catalyst (0.6 g) for 2 h to afford the acid **Ex.116** (1.02 g, 99%).

Data of **Ex.116**: $C_{26}H_{35}FN_4O_8$ (550.6). HPLC (10% CH_3CN): R_t = 3.47 (20), 3.55 (75). LC-MS: (method 9c): R_t = 1.53, 1.58; 551 ($[M+H]^+$).

Core 08: Synthesis of Ex.132 and Ex.133 (Scheme 12)

Synthesis of the Mitsunobu product **102**

Following procedure **E.1.2**, the reaction of phenol **56** (2.0 g, 4.7 mmol), alcohol **84** (2.08 g, 5.6 mmol), and CMBP (2.25 g, 9.3 mmol) in dry toluene (80 mL) afforded after 3 h and after FC (hexane/EtOAc 1:1 to 1:2) the protected amino acid **102** (2.06 g, 56%).

Synthesis of the amino acid **103**

Following procedure **E.2**, the reaction of **102** (2.05 g, 2.6 mmol), 1,3-dimethylbarbituric acid (1.0 g, 6.3 mmol) and $Pd(PPh_3)_4$ (0.15 g) in EtOAc/CH_2Cl_2 (55:45; 45 mL) yielded after 2 h and after FC (EtOAc, then CH_2Cl_2/MeOH 95:5 to 70:30) amino acid **103** (1.45 g, 85%).

Data of **103**: $C_{33}H_{43}FN_4O_9$ (658.7). HPLC (5% CH_3CN): R_t = 4.04 (97). LC-MS (method 9c): R_t = 1.87, 659 ($[M+H]^+$).

Synthesis of the protected macrolactam **Ex.132**

According to procedure **F.1.1**, the amino acid **103** (1.44 g, 2.19 mmol) in dry CH_2Cl_2 (40 mL) was treated with T3P (50% in EtOAc, 2.6 mL, 4.37 mmol) and *i*-Pr_2NEt (1.5 mL, 8.74 mmol) in dry CH_2Cl_2 (170 mL) to give after FC (CH_2Cl_2/MeOH 95:5) the macrolactam **Ex.132** (1.36 g, 96%).

Data of **Ex.132**: $C_{33}H_{41}FN_4O_8$ (640.7). LC-MS (method 2): R_t = 1.93 (100), 641 ($[M+H]^+$); LC-MS (method 9c): R_t = 2.12, 641 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): complex spectrum, mixture of isomers, 7.38 (s, 5 H), 7.35-6.99 (several m, 2 H), 6.85-6.73 (several m, 0.4 H), 6.65 (dd, J = 3.1, 8.2, 0.25 H), 6.39 (dd, J = 3.1, 7.9, 0.25 H), 6.30 (dd, J = 3.3, 8.1, 0.1 H), 5.37-4.99 (m, 3 H), 4.6-3.6 (several m, 9 H), 3.2-2.6 (several m and s, 8 H), 2.4-1.7 (several m, 4 H), 1.45, 1.43, 1.41, 1.38 (4 s, Boc).

Synthesis of the acid **Ex.133**:

According to procedure **H**, ester **Ex.132** (1.13 g, 1.7 mmol) was hydrogenated in MeOH (110 mL) in the presence of the catalyst (0.56 g) for 4 h to afford acid **Ex.133** (0.92 g, 94%).

Data of **Ex.133**: $C_{26}H_{35}FN_4O_8$ (550.6). HPLC (5% CH_3CN): R_t = 3.65 (27), 3.72 (71). LC-MS: (method 9c): R_t = 1.53, 551 ($[M+H]^+$); 1.57, 551 ($[M+H]^+$).

Core 09: Synthesis of Ex.142 and Ex.143 (Scheme 13)

Synthesis of the Mitsunobu product **104**

Following procedure **E.1.2**, the reaction of the phenol **54** (3.1 g, 7.2 mmol), alcohol **86** (3.34 g, 8.7 mmol), and CMBP (3.49 g, 14.4 mmol) in dry toluene (123 mL) afforded after 3 h and after FC (hexane/EtOAc 1:1 to 1:2) the protected amino acid **104** (4.11 g, 71%).

Synthesis of the amino acid **105**

Following procedure **E.2**, the reaction of **104** (4.07 g, 5.1 mmol), 1,3-dimethylbarbituric acid (1.9 g, 12 mmol) and $Pd(PPh_3)_4$ (0.3 g) in EtOAc/CH_2Cl_2 (45:55, 90 mL) yielded after 2 h and after FC (EtOAc, then CH_2Cl_2/MeOH 95:5 to 70:30) the amino acid **105** (3.19 g, 93%).

Data of **105**: $C_{34}H_{45}FN_4O_9$ (672.7). HPLC (5% CH_3CN): R_t = 3.96 (88). LC-MS (method 9c): R_t = 1.83, 673 ($[M+H]^+$).

Synthesis of the protected macrolactam **Ex.142**

According to procedure **F.1.1**, amino acid **105** (2.4 g, 3.6 mmol) in dry CH_2Cl_2 (40 mL) was treated with T3P (50% in EtOAc, 4.2

mL, 7.1 mmol) and *i*-Pr_2NEt (2.4 mL, 14.2 mmol) in dry CH_2Cl_2 (300 mL) to give after FC (CH_2Cl_2/MeOH 95:5) the macrolactam **Ex.142** (1.92 g, 82%).

Data of **Ex.142**: $C_{34}H_{43}FN_4O_8$ (654.7). HPLC (30% CH_3CN): R_t = 3.50 (89). LC-MS (method 9b): R_t = 2.01; 655 ($[M+H]^+$), 599 ($[M+H-tBu]^+$), 555 ($[M+H-Boc]^+$). ^{1}H-NMR (DMSO-d_6): complex spectrum, mixture of isomers, 7.41-7.38 (m, 5 H), 7.37-7.14 (m, 3 H), 6.80-6.67 (m, 1 H), 5.45-5.13 (m, 3 H), 4.60-3.30 (several m, 8 H), 3.10-2.50 (several m and s, 8 H), 2.50-1.80 (several m, 6 H), 1.39, 1.38, 1.36 (3 s, Boc).

Synthesis of the acid **Ex.143**:

According to procedure **H**, ester **Ex.142** (1.07 g, 1.6 mmol) was hydrogenated in MeOH (100 mL) in the presence of the catalyst (0.53 g) for 4 h to afford acid **Ex.143** (0.92 g, 99%).

Data of **Ex.143**: $C_{27}H_{37}FN_4O_8$ (564.6). LC-MS: (method 2): R_t = 1.54 (91), 565 ($[M+H]^+$).

Core 10: Synthesis of Ex.164 and Ex.165 (Scheme 14)

Synthesis of the Mitsunobu product **106**

Following procedure **B.1.2**, the reaction of phenol **63** (4.2 g, 9.8 mmol), alcohol **16** (4.4 g, 13 mmol), and CMBP (4.8 g, 20 mmol) in dry toluene (120 mL) afforded after 4 h and FC (hexane/EtOAc 50:50) the protected amino acid **106** (6.37 g, 86%).

Synthesis of the amino acid **107**

Following procedure **B.2**, the reaction of **106** (1.18 g, 1.6 mmol), 1,3-dimethylbarbituric acid (0.6 g, 3.8 mmol) and $Pd(PPh_3)_4$ (90 mg) in EtOAc/CH_2Cl_2 (60:40, 15 mL) yielded after 3 h and after FC (CH_2Cl_2/EtOH 100:0 to 80:20) the amino acid **107** (0.86 g, 87%).

Data of **107**: $C_{31}H_{44}N_4O_8Si$ (628.8). LC-MS: (method 6): R_t = 1.08 (88), 629 ($[M+H]^+$).

Synthesis of the protected macrolactam **Ex.164**

According to procedure **F.1.2**, amino acid **107** (310 mg, 0.49 mmol) in dry DMF (5 mL) was treated with FDPP (379 mg, 0.99 mmol) in dry DMF (500 mL) to afford after FC (hexane/EtOAc/MeOH 50:50:0 to 0:95:5) the macrolactam **Ex.164** (131 mg, 43%).

Data of **Ex.164**: $C_{31}H_{42}N_4O_7Si$ (610.8). LC-MS: (method 7): R_t = 1.34 (98), 611 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 7.42-7.27 (m, 8 H), 6.98 (dd, J = 1.4, 8.2, 1 H), 6.91 (d, J = 7.5, 1 H), 6.84 (s, 1 H), 4.98 (s, 2 H), 4.50 (d, J = 11.9, 1 H), 4.35-4.15 (m, 3 H), 4.06-3.96 (m, 4 H), 3.21 (m, 1 H), 3.10-2.95 (m, 2 H), 2.87 (s, 3 H), 2.30-1.80 (m, 4 H), 0.91 (t, J = 8.3, 2 H), 0.00 (s, 9 H).

Synthesis of the amine **Ex.165**

At 0°C, a solution of TBAF in THF (1 M, 3.9 mL, 3.9 mmol) was added to a solution of **Ex.164** (1.2 g, 1.96 mmol) in THF (42 mL). The solution was allowed to stir at 0°C to room temperature for 15 h, followed by the addition of more TBAF in THF (1 M, 1.18 mL, 1.18 mmol). Stirring was continued for 2 h. The solution was distributed between CH_2Cl_2 and H_2O. The aqueous phase was repeatedly extracted with CH_2Cl_2. The combined organic phase was dried (Na_2SO_4), filtered and concentrated. FC (CH_2Cl_2/MeOH 100:0 to 90:10) afforded **Ex.165** (0.76 g, 83%).

Data of **Ex.165**:$C_{25}H_{30}N_4O_5$ (466.52). LC-MS: (method 4a): R_t = 1.49 (99), 467 ($[M+H]^+$).

Core 11: Synthesis of Ex.181 and Ex.182 (Scheme 15)

Synthesis of the Mitsunobu product **108**

Following procedure **B.1.2**, the reaction of phenol **65** (10.7 g, 24 mmol), alcohol **16** (10.0 g, 29 mmol), and CMBP (12.0 g, 49 mmol) in dry toluene (362 mL) afforded after FC (hexane/EtOAc 50:50 to 70:30) the protected amino acid **108** (14.55 g, 78%).

Synthesis of the amino acid **109**

Following procedure **B.2**, the reaction of **108** (14.50 g, 19 mmol), 1,3-dimethylbarbituric acid (7.0 g, 47.0 mmol) and $Pd(PPh_3)_4$ (0.1 g) in EtOAc/CH_2Cl_2 (55:45, 203 mL) yielded after 3 h and after FC (CH_2Cl_2/MeOH 99:1 to 90:10) the amino acid **109** (11.26 g, 92%).

Data of **109**: $C_{32}H_{46}N_4O_8Si$ (642.8). LC-MS: (method 6): R_t = 1.13 (94), 643 ($[M+H]^+$).

Synthesis of the protected macrolactam **Ex.181**

According to procedure **F.1.1**, the amino acid **109** (4.0 g, 6.2 mmol) in dry CH_2Cl_2 (100 mL) was treated with T3P (50% in EtOAc, 7.4 mL, 12.4 mmol) and *i*-Pr_2NEt (4.3 mL, 24.8 mmol) in dry CH_2Cl_2 (560 mL). Prior to aqueous workup, the CH_2Cl_2 was replaced by EtOAc. FC (hexane/EtOAc 50:50 to 0:100) afforded the macrolactam **Ex.181** (2.11 g, 54%).

Data of **Ex.181**: $C_{32}H_{44}N_4O_7Si$ (624.8). LC-MS (method 7): R_t = 1.37 (99), 625 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 7.46 (d, J = 8.0, 1 H), 7.42 (d, J = 7.2, 1 H), 7.34-7.23 (m, 6 H), 7.06 (d, J = 8.2, 1 H), 6.82 (d, J = 7.4, 1 H), 6.78 (s, 1 H), 5.02-4.86 (m, 3 H), 4.13 (t, J = 8.5, 1 H), 4.06-3.67 (m, 7 H), 3.05 (br. m, 1 H), 2.88 (br. m, 1 H), 2.88 (s, 3 H), 2.15 (m, 2 H), 1.51 (br. m, 2 H), 1.33 (br. m, 1 H), 1.12 (br. m, 1 H), 0.91 (t-like m, J ca. 8.4, 2 H), 0.00 (s, 9 H).

Synthesis of the amine **Ex.182**

According to procedure **I.2**, carbamate **Ex.181** (844 mg, 1.3 mmol) in THF (34 mL) was treated with TBAF solution (4.1 mL) to

afford after FC (CH_2Cl_2/MeOH 90:10) the amine **Ex.182** (620 mg, 95%)

Data of **Ex.182**: $C_{26}H_{32}N_4O_5$ (480.5). LC-MS: (method 2): R_t = 1.35 (99), 481 ($[M+H]^+$).

Core 12: Linear synthesis of Ex.196 and Ex.197 (Scheme 16)

Synthesis of the Mitsunobu product **110**

Following procedure **B.1.1**, the reaction of phenol **59** (5.22 g, 12.6 mmol), alcohol **16** (5.2 g, 15.2 mmol), PPh_3 (5.0 g, 19 mmol) in dry benzene (124 mL) and DEAD (40% in toluene, 7.0 mL, 15.2 mmol) in dry benzene (36 mL) afforded after FC (hexane/EtOAc 60:40 to 40:60) the protected amino acid **110** (8.3 g, 88%, contaminated with some triphenylphosphine oxide; acceptable for the use in the next stop without further purification).

Synthesis of the amino acid **111**

Following procedure **B.2**, the reaction of **110** (4.15 g, 5.62 mmol), 1,3-dimethylbarbituric acid (2.19 g, 14.0 mmol) and $Pd(PPh_3)_4$ (0.71 g) in EtOAc/CH_2Cl_2 1:1 (60 mL) yielded after 1 h and after FC (CH_2Cl_2/EtOH 95:5 to 90:10 then CH_2Cl_2/MeOH 90:10 to 70:30) amino acid **111** (2.75 g, 80%).

Data of **111**: $C_{30}H_{42}N_4O_8Si$ (614.8). HPLC (10% CH_3CN): R_t = 3.82 (99). LC-MS (method 9a): R_t = 1.81; 615 ($[M+H]^+$).

Synthesis of the alloc protected amino acid **112**

Following procedure **C.1**, the reaction of the amino acid **111** (1.5 g, 2.4 mmol), allyl choroformate (0.29 mL, 2.68 mmol) and Na_2CO_3 (0.72 g, 6.83 mmol) in dioxane (40 mL) and H_2O (40 mL) gave acid **112** (1.7 g, 100%).

Synthesis of the protected amino acid **113**

Following procedure **C.2**, the acid **112** (1.7 g, 2.4 mmol) was reacted with sarcosine allylester p-toluenesufonate (**46**.p-TsOH, 0.88 g, 2.9 mmol), HOAt (0.5 g, 3.6 mmol), HATU (1.4 g, 3.6 mmol) and *i*-Pr_2NEt (2.1 mL, 12 mmol) in DMF (25 mL) to afford the protected amino acid **113** (1.51 g, 75%).

Data of **113**: $C_{40}H_{55}N_5O_{11}Si$ (809.9). HPLC (40% CH_3CN): R_t = 4.43 (91). LC-MS (method 9c): R_t = 2.51, 810 ($[M+H]^+$).

Deprotection to amino acid **114**

Following procedure **C.3**, the reaction of the protected amino acid **113** (1.5 g, 1.85 mmol), 1,3-dimethylbarbituric acid (0.72 g, 4.6 mmol) and $Pd(PPh_3)_4$ (0.23 g) in EtOAc/CH_2Cl_2 (1:1, 25 mL) yielded amino acid **114** (1.05 g, 83%).

Data of **114**: $C_{33}H_{47}N_5O_9Si$ (685.8). HPLC (10% CH_3CN): R_t = 3.85 (95). LC-MS (method 9c): R_t = 1.78, 686 ($[M+H]^+$).

Synthesis of the protected macrolactam **Ex.196**

According to procedure **F.1.2**, amino acid **114** (1.0 g, 1.46 mmol) in dry DMF (20 mL) was treated with FDPP (1.12 g, 2.92 mmol) in dry DMF (130 mL) to yield after FC (EtOAc) the macrolactam **Ex.196** (0.61 g, 63%).

Data of **Ex.196**: $C_{33}H_{45}N_5O_8Si$ (667.8). LC-MS (method 1a): R_t = 2.66 (100), 668 ($[M+H]^+$). LC-MS (method 9c): R_t = 2.12, 668 ($[M+H]^+$), 640. ^{1}H-NMR ($CDCl_3$): 7.34-7.26 (m, 6 H), 7.17 (d, J = 7.6, 1 H), 7.02 (s, 1 H), 6.91 (d, J = 9.5, 1 H), 5.49 (d, J = 9.5, 2 H), 5.10 (m, 1 H), 5.06 (s, 2 H), 4.39-4.13 (m, 5 H), 4.00-3.95 (m, 2 H), 3.65 (m, 1 H), 3.36 (br. s, 2 H), 3.14 (m, 2 H), 3.09 (s, 3 H), 2.74 (s, 3 H), 2.45 (m, 1 H), 2.08 (m, 1 H), 0.98 (m, 2 H), 0.00 (s, 9 H). ^{1}H-NMR (DMSO-d_6): 7.98 (d, J = 9.9, 1 H), 7.52 (d, J = 7.9, 1 H), 7.36-7.27 (m, 6 H), 7.18 (s, 1 H), 7.06 (dd, J = 1.8, 8.1, 1 H), 6.83 (d, J = 7.5, 1 H), 5.12 (d, J = 12.5, 1 H), 5.04 (d, J = 12.5, 1 H), 4.87 (d, J =

8.8, 1 H), 4.25-3.89 (m, 8 H), 3.71-3.66 (m, 2 H), 3.20 (m, 1 H), 3.02 (m, 1 H), 2.97 (s, 3 H), 2.65 (s, 3 H), 2.20 (m, 1 H), 2.09 (m, 1 H), 0.92 (t, J = 8.2, 2 H), 0.00 (s, 9 H).

Synthesis of the amine **Ex.197**

According to procedure **I.1**, carbamate **Ex.196** (120 mg, 0.18 mmol) in dioxane (3 mL) was treated with 4 M HCl-dioxane (3 mL) to afford **Ex.197**·HCl (59 mg, 58%).

Data of **Ex.197**·HCl: $C_{27}H_{33}N_5O_6$·HCl (523.5, free base). HPLC (5% CH_3CN): R_t = 3.05 (83). LC-MS (method 9c): R_t = 1.12, 524 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 8.53 (br. s, NH_3^+), 8.03 (d, J = 9.9, 1 H), 7.41-7.31 (m, 7 H), 7.15 (m, 1 H), 6.85 (d, J = 7.5, 1 H), 5.14 (d, J = 12.5, 1 H), 5.04 (d, J = 12.5, 1 H), 4.86 (dd, J ca. 2.2, 11.0, 1 H), 4.42-4.13 (m, 2 H), 4.05 (t, J = 8.5, 1 H), 3.96 (d, J = 17.8, 1 H), 3.85-3.75 (m, 2 H), 3.65 (br. m, 1 H), ca. 3.3-3.1 (m, 3 H, partially superimposed by the H_2O signal), 2.97 (s, 3 H), 2.67 (s, 3 H), 2.42 (m, 1 H), 2.18 (br. q, J ca. 11.1, 1 H).

Core 12: Convergent synthesis of Ex.197 and Ex.198

(Scheme 17)

Synthesis of the Mitsunobu product **115**

Following procedure **E.1.1**, phenol **59** (4.6 g, 11 mmol) was treated for 40 h with alcohol **81** (5.0 g, 13 mmol), DEAD (40% in toluene, 6.1 mL, 13 mmol) and PPh_3 (4.4 g, 17 mmol) in dry benzene (150 mL). After 2h and after 18 h, more PPh_3 (1.82 g, 6.9 mmol), alcohol **81** (2.04 g, 5.5 mmol) in benzene (50 mL), and DEAD (40% in toluene, 2.55 mL, 5.6 mmol) in benzene (13 mL) were added. FC (hexane/EtOAc 50:50 to 90:10) afforded the protected amino acid **115.1** (2.5 g, 29%).

Following procedure **E.1.2**, the reaction of phenol **59** (2.9 g, 7.0 mmol), alcohol **81**, (5.7 g, 15 mmol) and CMBP (5.1 g, 21 mmol) in dry toluene (121 mL) afforded after FC (hexane/EtOAc 20:80 to 90:10) the protected amino acid **115.2** (2.92 g, 54%).

Synthesis of the amino acid **116**

Following procedure **E.2**, the reaction of **115.1** (3.17 g, 4.14 mmol), 1,3-dimethylbarbituric acid (1.62 g, 10.3 mmol) and $Pd(PPh_3)_4$ (0.53 g) in EtOAc/CH_2Cl_2 (1:1, 46 mL) yielded after 1 h and after FC (CH_2Cl_2/MeOH 90:10 to 70:30) the amino acid **116.1** (1.86 g, 70%).

Data of **116.1**: $C_{32}H_{43}N_5O_9$ (641.7). HPLC (5% CH_3CN): R_t = 3.65 (100). LC-MS (method 9c): R_t = 1.60, 642 ($[M+H]^+$).

Following procedure **E.2**, the reaction of **115.2** (2.9 g, 3.8 mmol), 1,3-dimethylbarbituric acid (1.5 g, 9.5 mmol) and $Pd(PPh_3)_4$ (0.48 g) in EtOAc/CH_2Cl_2 (1:1, 46 mL) yielded after 1 h and after FC (CH_2Cl_2/MeOH 90:10 to 70:30) the amino acid **116.2** (2.0 g, 83%).

Data of **116.2**: $C_{32}H_{43}N_5O_9$ (641.7). HPLC (5% CH_3CN): R_t = 3.73 (98). LC-MS (method 9c): R_t = 1.61, 642 ($[M+H]^+$).

Synthesis of the protected macrolactam **Ex.198**

According to procedure **F.1.1**, the amino acid **116.1** (1.0 g, 1.6 mmol) in dry CH_2Cl_2 (200 mL) was treated with T3P (50% in EtOAc, 1.8 mL, 3.1 mmol) and *i*-Pr_2NEt (1.1 mL, 6.2 mmol) in dry CH_2Cl_2 (1400 mL) to afford after FC (EtOAc/MeOH 95:5 to 80:20) the macrolactam **Ex.198** (containing 15% of the epimer **Ex.231**; 0.38 g, 39%).

Data of **Ex.198**: $C_{32}H_{41}N_5O_8$ (623.7). LC-MS: (method 2): R_t = 1.78 (84), 624 ($[M+H]^+$); 1.82 (15). LC-MS (method 9c): R_t = 1.87, 624 ($[M+H]^+$).

^{1}H-NMR ($CDCl_3$): 7.42-7.25 (m, 7 H), 7.07 (s, 1 H), 7.00 (d, J = 8.2, 1 H), 5.59 (d, J = 9.5, 1 H), 5.38 (br. d, J ca 7.9, 1 H), 5.18 (dd, J = 2.5, 12.2, 1 H), 5.13 (s, 2 H), 4.43-4.01 (m, 5 H), 3.73 (m, 1 H), 3.47 (d, J = 17.7, 1 H), 3.33 (d, J = 17.7, 1 H), 3.20-3.11 (m, 2 H), 3.17 (s, 3 H), 2.81 (s, 3 H), 2.50 (m, 1 H), 2.15 (m, 1 H), 1.51 (s, Boc, major isomer), 1.45 (s, Boc, minor isomer); ^{1}H-NMR (DMSO-d_6): 7.97 (d, J = 10.3, 1 H), 7.41-7.30 (m, 7 H), 7.18 (s, 1 H), 7.09 (d, J = 8.2, 1 H), 6.85 (J = 7.6, 1 H), 5.12 (d, J = 12.5, 1 H), 5.05 (d, J = 12.6, 1 H), 4.89 (J = 9.6, 1 H), 4.30-3.55 (m, 6 H), 3.40 (2 H, superimposed by H_2O signal), 3.25-3.00 (m, 2 H), 2.99 (s, 3 H), 2.65 (s, 3 H), 2.22 (m, 1 H), 2.05 (br. q, 1 H), 1.41, (s, 9 H).

According to procedure **F.1.1**, amino acid **116.2** (0.85 g, 1.3 mmol) in dry CH_2Cl_2 (170 mL) was treated with T3P (50% in EtOAc, 1.56 mL, 2.6 mmol) and *i*-Pr_2NEt (0.91 mL, 5.3 mmol) in dry CH_2Cl_2 (1190 mL) to afford after FC (EtOAc/MeOH 95:5 to 80:20) the macrolactam **Ex.198** and its epimer **Ex.231** (ca 1:1 mixture; 0.61 g, 73%).

Data of the mixture **Ex.198/Ex.231**: $C_{32}H_{41}N_5O_8$ (623.7). LC-MS: (method 2): R_t = 1.78 (44), 624 ($[M+H]^+$); 1.82 (56), 624 ($[M+H]^+$). ^{1}H-NMR ($CDCl_3$): complex spectrum, mixture of epimers, 7.41-7.20 (m, 6 H), 7.07-6.92 (m, 3 H) 5.8-4.8 (several m, 5 H), 4.3-3.0 (several m, 10 H), 3.16 (s, NCH_3), 2.81 (s, NCH_3), 2.58-2.45 (m, 1 H), 2.19-2.03 (m, 1 H), 1.51, 1.41 (2 s, 9 H)

Synthesis of the amine **Ex.197**

According to procedure **J**, carbamate **Ex.198/Ex.231** (ca. 85:15, 749 mg, 1.2 mmol) in dioxane (7.5 mL) was treated with 4 M HCl-dioxane (15 mL) to afford **Ex.197**·HCl/**Ex.232**·HCl (607 mg, 90%).

Data of **Ex.197**·HCl/**Ex.232**·HCl: $C_{27}H_{33}N_5O_6$·HCl (523.5, free base). LC-MS (method 2): R_t = 1.26 (75), 1.33 (14); 524 ($[M+H]^+$).

^{1}H-NMR (DMSO-d_6), major component **Ex.197**·HCl: spectrum identical with the one described above for compound **Ex.197**·HCl (cf. Scheme 16).

According to procedure **J**, carbamate **Ex.198/Ex.231** (ca. 1:1, 1.32 g, 2.12 mmol) in dioxane (13 mL) was treated with 4 M HCl-dioxane (26 mL) to afford after separation of the isomers by preparative RP-HPLC (method 1) **Ex.197**·TFA (460 mg, 34%) and **Ex.232**·TFA (470 mg, 35%).

Data of **Ex.197**·TFA: $C_{27}H_{33}N_5O_6 \cdot C_2HF_3O_2$ (523.5, free base). LC-MS (method 2): R_t = 1.25 (99), 524 ($[M+H]^+$). LC-MS (method 7): R_t = 0.74 (97), 524 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 8.34 (br. s, NH_3^+), 8.07 (d, J = 9.9, 1 H), 7.43-7.33 (m, 6 H), 7.20 (s, 1 H), 7.10 (dd, J = 1.5, 8.2, 1 H), 6.87 (d, J = 7.4, 1 H), 5.17 (d, J = 12.5, 1 H), 5.05 (d, J = 12.5, 1 H), 4.87 (br. dd, 1 H), 4.27-4.16 (m, 2 H), 4.06 (t, J = 8.6, 1 H), 4.01-3.91 (m, 2 H), 3.82 (t-like dd, J ca. 8.1, 1 H), 3.70 (br. m, 1 H), 3.35-3.20 (m, 3 H), 2.98 (s, 3 H), 2.70 (s, 3 H), 2.49 (m, 1 H), 2.18 (br. q, J ca 11.0, 1 H).

Data of **Ex.232**·TFA: See below; Core 14.

Core 13: Synthesis of Ex.215 and Ex.216 (Scheme 18)

Synthesis of the Mitsunobu product **117**

Following procedure **B.1.1**, the reaction of phenol **59** (2.1 g, 5.1 mmol), alcohol **20** (2.1 g, 6.1 mmol), PPh_3 (2.0 g, 7.6 mmol) in dry benzene (50 mL) and DEAD (40% in toluene, 2.8 mL, 6.1 mmol) in dry benzene (14 mL) afforded, after further addition of PPh_3 (0.84 g, 3.2 mmol), alcohol **20** (0.88 g, 2.6 mmol) in benzene (21 mL) and DEAD (40% in toluene, 1.2 mL, 2.6 mmol) in benzene (6 mL) and after FC (hexane/EtOAc 50:50) the protected amino acid **117** (3.8 g, 100%).

Synthesis of the amino acid **118**

Following procedure **B.2**, the reaction of **117** (7.63 g, 10.3 mmol), 1,3-dimethylbarbituric acid (4.03 g, 25.8 mmol) and $Pd(PPh_3)_4$ (1.31 g) in EtOAc/CH_2Cl_2 (1:1, 110 mL) yielded after 1 h and after FC (CH_2Cl_2/MeOH 95:5 to 70:30) the amino acid **118** (3.48 g, 60%).

Data of **118**: $C_{30}H_{42}N_4O_8Si$ (614.8). HPLC (10% CH_3CN): R_t = 3.88 (100). LC-MS (method 9a): R_t = 1.80, 615 ($[M+H]^+$).

Synthesis of the alloc protected amino acid **119**

Following procedure **C.1**, the reaction of the amino acid **118** (3.36 g, 5.5 mmol), allyl choroformate (0.64 mL, 6.0 mmol) and Na_2CO_3 (0.87 g, 8.2 mmol) in dioxane (51 mL) and H_2O (51 mL) gave the acid **119** (3.51 g, 92%).

Synthesis of the protected amino acid **120**

Following procedure **C.2**, acid **119** (3.47 g, 5.0 mmol) was reacted with sarcosine allylester p-toluenesufonate (**46**.p-TsOH, 1.8 g, 6.0 mmol), HOAt (1.0 g, 7.4 mmol), HATU (2.8 g, 7.4 mmol) and *i*-Pr_2NEt (4.2 mL, 25 mmol) in DMF (108 mL) to afford the protected amino acid **120** (3.52 g, 88%).

Data of **120**: $C_{40}H_{55}N_5O_{11}Si$ (809.9). LC-MS: (method 4b): R_t = 2.51 (95), 810 ($[M+H]^+$)

Deprotection to amino acid **121**

Following procedure **C.3**, the reaction of the protected amino acid **120** (3.49 g, 4.31 mmol), 1,3-dimethylbarbituric acid (1.68 g, 10.8 mmol) and $Pd(PPh_3)_4$ (0.55 g) in EtOAc/CH_2Cl_2 (1:1; 50 mL) yielded the amino acid **121** (2.72 g,92%).

Data of **121**: $C_{33}H_{47}N_5O_9Si$ (685.8). LC-MS: (method 4b): R_t = 1.84 (94), 686 ($[M+H]^+$)

Synthesis of the protected macrolactam **Ex.215**

According to procedure **F.1.2**, amino acid **121** (1.33 g, 1.94 mmol) in dry DMF (27 mL) was treated with FDPP (1.49 g, 3.88 mmol) in dry DMF (164 mL) to yield after FC (EtOAc/MeOH 95:5) macrolactam **Ex.215** (0.89 g, 68%).

Data of **Ex.215**: $C_{33}H_{45}N_5O_8Si$ (667.8). LC-MS: (method 1b): R_t = 2.60 (99), 668 ($[M+H]^+$). LC-MS: (method 9c): R_t = 2.14, 668 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 7.94 (d, J = 9.8, 1 H), 7.39-7.27 (m, 7 H), 7.11 (s, 1 H), 6.97 (dd, J = 1.5, 8.2, 1 H), 6.82 (d, J = 7.5, 1 H), 5.05 (s, 2 H), 4.83 (br. d, 1 H), 4.25 (br. m, 1 H), 4.17-3.96 (m, 5 H), 3.73 (br. q, J ca. 16.8, 2 H), 3.47 (m, 1 H), 3.33 (m, 1 H), 3.19 (m, 2 H), 2.96 (s, 3 H), 2.67 (s, 3 H), 2.20 (m, 1 H), 2.00 (m, 1 H), 0.91 (t, J = 8.4, 2 H), 0.00 (s, 9 H).

Synthesis of the amine **Ex.216**

According to procedure **I.1**, carbamate **Ex.215** (881 mg, 1.3 mmol) in dioxane (16 mL) was treated with 4 M HCl-dioxane (16 mL) to afford **Ex.216**·HCl (666 mg, 90%).

Data of **Ex.216**·HCl: $C_{27}H_{33}N_5O_6$·HCl (523.5, free base). HPLC (5% CH_3CN): R_t = 3.11 (91). LC-MS (method 9c): R_t = 1.19, 524 ($[M+H]^+$).

Core 14: Synthesis of Ex.231 and Ex.232 (Scheme 19)

Synthesis of the Mitsunobu product **122**

A mixture of phenol **61** (4.6 g, 11.2 mmol) and PPh_3 (5.27 g, 20.1 mmol) was dissolved in benzene. The solution was concentrated and the residue was dried i.v. for 20 min. A solution of the alcohol **81**, (7.46 g, 20.1 mmol) in dry, degassed benzene (120 mL) was added. The resulting mixture was cooled to 0°C. DEAD (40% in toluene, 11.5 mL, 25.1 mmol)

in benzene (10 mL) was slowly added. The solution was stirred at room temperature for 16 h. More PPh_3 (1.46 g, 5.6 mmol), alcohol **81** (1.04 g, 2.8 mmol) and at 0°C, a solution of DEAD (40% in toluene, 2.6 mL, 5.7 mmol) in benzene (2 mL) were added and stirring at room temperature was continued for 7 h. More PPh_3 (1.46 g, 5.6 mmol), alcohol **81** (1.04 g, 2.8 mmol), and at 0°C, a solution of DEAD (40% in toluene, 2.6 mL, 5.7 mmol) in benzene (2 mL) were added. Stirring at room temperature was continued for 16 h. The mixture was concentrated. FC (hexane/EtOAc 30:70 to 0:100) afforded **122** (12.8 g, contaminated with ca 40% triphenylphosphinoxide, yield ca 90%). The material was used for the next step without further purification)

Synthesis of the amino acid **123**

Following procedure **E.2**, the reaction of the protected amino acid **122** (contaminated with ca 40% of triphenylphosphine oxide, 12.8 g, ca 10 mmol), 1,3-dimethylbarbituric acid (3.91 g, 25.1 mmol) and $Pd(PPh_3)_4$ (1.27 g) in EtOAc/CH_2Cl_2 (1:1, 120 mL) yielded after 1 h and after FC (CH_2Cl_2/MeOH 100:0 to 70:30 then $CHCl_3$/MeOH 70:30) the amino acid **123** (2.80 g, 44%).

Data of **123**: $C_{32}H_{43}N_5O_9$ (641.7). LC-MS: (method 2): R_t = 1.56 (94), 642 ($[M+H]^+$).

Synthesis of the protected macrolactam **Ex.231**

According to procedure **F.1.2**, amino acid **123** (3.29 g, 5.13 mmol) in dry DMF (150 mL) was added within 4 h at 60°C to FDPP (3.94 g, 10.3 mmol) in dry DMF (4980 mL) to afford after 16 h at 60°C and after FC (EtOAc/MeOH 100:0 to 95:5) the macrolactam **Ex.231** (contained ca 15% of its epimer **Ex.198**; 2.5 g, 78%).

Data of **Ex.231**: $C_{32}H_{41}N_5O_8$ (623.7). LC-MS: (method 2): R_t = 1.78 (12), 1.82 (83), 624 ($[M+H]^+$). LC-MS: (method 7): R_t = 1.16 (18), 624 ($[M+H]^+$); 1.18 (80), 624 ($[M+H]^+$). ^{1}H-NMR ($CDCl_3$): complex spectrum, two epimers; 7.38-7.22 (m, 6 H), 7.06-6.90

(m, 3 H), 5.80-4.80 (several m, 4 H), 5.08, 5.12 (2 s, 2 H), 4.43-2.80 (several br. m, 15 H), 2.51 (m, 1 H), 2.19-2.03 (m, 1 H), 1.50, 1.42 (2 s, 9 H).

Synthesis of the amine **Ex.232**

According to procedure **J**, carbamate **Ex.231** (containing 15% of the epimer **Ex.198**; 1.42 g, 2.3 mmol) in dioxane (30 mL) was treated with 4 M HCl-dioxane (45 mL) to afford after preparative RP-HPLC (method 1) **Ex.232**·TFA (1.10 g, 71%) and **Ex.197**·TFA (0.27 g, 17%).

Data of **Ex.232**·TFA: $C_{27}H_{33}N_5O_6 \cdot C_2HF_3O_2$ (523.5, free base). LC-MS (method 2): R_t = 1.32 (99), 524 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): complex spectrum, mixture of isomers; 8.40 (br. s), 8.20 (br. s), 7.84 (d, J = 7.1), 7.50-6.80 (several m), 5.25-3.40 (several m, partially superimposed by the H_2O signal), 3.30-2.80 (m), 3.04 (s, NCH_3), 2.98 (s, NCH_3), 2.67 (s, NCH_3), 2.64 (s, NCH_3), 2.6-1.9 (several m).

Data of **Ex.197**·TFA: See above; Core 12.

Core 15 and Core 16:

Synthesis of Ex.238 and Ex.239 (Scheme 20)

Synthesis of the Mitsunobu product **124**

Following procedure **E.1.1**, phenol **77** (1.63 g, 8.5 mmol), alcohol **85** (5.72 g, 12.8 mmol) and PPh_3 (4.02 g, 15.3 mmol) in dry benzene (80 mL) were treated with DEAD (40% in toluene, 8.79 mL, 19.2 mmol) for 20 h. Purification by FC(hexane/EtOAc 20:80 to 100:0) then (hexane/EtOAc 50:50 to 20:80) afforded the protected amino acid **124** (1.96 g, 37%).

Synthesis of the macrocycle **Ex.238**

Dichloro-[1,3-bis(mesityl)-2-imidazoldinylidene]-(3-phenyl-1H-inden-1-ylidene)(tricyclohexylphosphine)ruthenium (II) (Umicore M2 catalyst; 88 mg) was added to a solution of **124** (1160 mg, 1.29 mmol) in dry, degassed CH_2Cl_2 (170 mL). The solution was stirred in a sealed tube at 40°C for 68 h, followed by 45 h at room temperature. During this period further equal portions of catalyst (in total 350 mg) were added after 20 h, 28 h, 44 h, and 52 h. The solution was concentrated. FC (hexane/EtOAc 70:30 to 0:100) gave **Ex.238** (350 mg, 46%, mixture of two isomers, ratio > 9:1, acceptable for the use in the next step). An analytical sample (69 mg) was further purified by preparative RP-HPLC (method 2) to afford pure **Ex.238** (major isomer; 45 mg).

Data of **Ex.238** (major isomer): $C_{32}H_{40}N_4O_7$ (592.6). LC-MS: (method 4a): R_t = 2.23 (92), 593 ($[M+H]^+$). ^{1}H-NMR ($CDCl_3$): 7.62-7.31 (m, 6 H), 7.07 (d, J = 7.6, 1 H), 6.99 (dd, J = 2.0, 7.9, 1 H), 6.85 (s, 1 H), 5.69-5.61 (m, 2 H), 5.48 (d, J = 8.2, 1 H), 5.21 (m, 1 H), 5.10 (s, 2 H), 4.76 (d, J = 10.1, 1 H), 4.54 (dt, J = 3.5, 7.9, 1 H), 4.41-4.25 (m, 2 H), 4.13 (d, J = 10.7, 1 H), 3.97 (m, 1 H), 3.62 (m, 2 H), 3.48 (m, 1 H), 3.10 (s, 3 H), 2.73 (m, 1 H), 2.60-2.45 (m, 2 H), 2.02 (m, 1 H), 1.46 (s, 9 H).

Synthesis of amine **Ex.239**

A solution of **Ex.238** (430 mg, 0.73 mmol) in MeOH/THF 1:3, 36 mL) was hydrogenated for 3.5 h at room temperature and at normal pressure in the presence of palladium hydroxide on activated charcoal (moistened with 50% H_2O; 215 mg). The mixture was filtered through a pad of celite. The filtrate was concentrated to give **Ex.239** (355 mg, quantitative; used in the next step without further purification).

An analytical sample (68 mg) was purified by preparative RP-HPLC (method 2) to afford pure **Ex.239** (37 mg).

Data of **Ex.239**: $C_{24}H_{36}N_4O_5$ (460.6): LC-MS (method 7): R_t = 0.88 (97), 461 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 7.36 (t, J = 7.8, 1 H),

7.25 (d, J = 6.1, 1 H), 7.03 (dd, J = 1.6, 8.2, 1 H), 6.88-6.65 (m, 2 H), 4.51 (d, J = 8.3, 1 H), 4.18 (t, J = 10.3, 2 H), 4.09 (br. s, 1 H), 3.96 (br. m, 2 H), 3.19-2.72 (m, 3 H), 2.92 (s, 3 H), 2.34 (m, 2 H), 2.05 (br. q, 1 H), 1.82 (m, 1 H), 1.60-0.85 (m, 5 H), 1.40 (s, 9 H), 0.82 (m, 1 H).

Core 17: Synthesis of Ex.248 and Ex.249 (Scheme 21)

Synthesis of the Mitsunobu product **125**

Following procedure **E.1.1**, phenol **68** (6.0 g, 14.6 mmol), alcohol **82** (9.75 g, 26.2 mmol), and PPh_3 (6.88 g, 26.2 mmol) were treated in dry benzene (160 mL) with DEAD (40% in toluene, 15 mL, 32.8 mmol) for 40 h. After 18 h and after 25 h, more PPh_3 (1.27 g, 4.8 mmol) and DEAD (40% in toluene, 2.23 mL, 4.9 mmol) in benzene (2 mL) were added. FC (hexane/EtOAc 30:70 to 20:80) afforded the protected amino acid **125** (16.85 g, contaminated with ca 40% triphenylphosphinoxide, yield ca 85%). The material was used for the next step without further purification)

Synthesis of the amino acid **126**

Following procedure **E.2**, the reaction of **125** (16.8 g, contaminated with ca 40% of triphenylphosphine oxide, ca. 12 mmol), 1,3-dimethylbarbituric acid (4.80 g, 30.8 mmol) and $Pd(PPh_3)_4$ (1.56 g) in EtOAc/CH_2Cl_2 (1:1, 170 mL) yielded after 1 h and after FC (CH_2Cl_2/MeOH 0:100 to 70:30, then $CHCl_3$/MeOH 70:30) amino acid **126** (4.15 g, ca. 52%).

Data of **126**: $C_{33}H_{44}N_4O_9$ (640.7). HPLC (10% CH_3CN): R_t = 3.67 (69). LC-MS (method 9c): R_t = 1.75, 641 ($[M+H]^+$).

Synthesis of the protected macrolactam **Ex.248**

According to procedure **F.1.1**, amino acid **126** (4.55 g, 7.1 mmol) in dry CH_2Cl_2 (120 mL) was added within 3 h to T3P (50% in EtOAc, 8.37 ml, 14.2 mmol) and *i*-Pr_2NEt (4.83 ml, 28.4 mmol) in dry CH_2Cl_2 (6660 mL). Prior to aqueous workup, CH_2Cl_2 was replaced with EtOAc. FC (CH_2Cl_2/MeOH 100:0 to 95:5) yielded the macrolactam **Ex.248** (2.38 g, 54%).

Data of **Ex.248**: $C_{33}H_{42}N_4O_8$ (622.7). LC-MS: (method 2): R_t = 1.83 (100), 623 ($[M+H]^+$). LC-MS: (method 9c): R_t = 1.97, 623 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 7.45-7.34 (m, 5 H), 7.15-6.78 (m, 5 H), 5.25 (s, 2 H), 5.08 (d, J = 12.8, 1 H), 4.62 (d, J = 13.5, 2 H), 4.29 (m, 1 H), 4.09 (d, J = 7.3, 1 H), 3.89 (d, J = 12.4, 1 H), 3.54 (br. t, 1 H), 3.27 (m, 1 H), 3.07 (s, 3 H), 2.80 (m, 1 H), 2.71 (s, 3 H), 2.28-2.06 (m, 4 H), 1.94 (m, 1 H), 1.71 (m, 1 H), 1.39 (s, 9 H).

Synthesis of the acid **Ex.249**:

According to procedure **H**, the ester **Ex.248** (2.16 g, 3.5 mmol) was hydrogenated in MeOH (130 mL)/THF (40 mL) in the presence of the catalyst (1.09 g) for 2.5 h to afford the acid **Ex.249** (1.83 g, 99%).

Data of **Ex.249**: $C_{26}H_{36}N_4O_8$ (532.6). LC-MS: (method 2): R_t = 1.42 (95), 533 ($[M+H]^+$).

Core 18: Synthesis of Ex.272, Ex.273, and Ex.274 (Scheme 22)

Synthesis of the Mitsunobu product **127**

Following procedure **E.1.1**, the reaction of phenol **71** (6.47 g, 15,7 mmol), the alcohol **81** (10.5 g, 28.2 mmol), DEAD (40% in toluene, 26 mL, 56.3 mmol), and PPh_3 (14.8 g, 56.3 mmol) in dry benzene (380 mL) afforded after 2 h at room temperature and after aqueous workup (EtOAc, sat. aq. Na_2CO_3 soln, sat. aq. NaCl soln), drying (Na_2SO_4), concentration of the organic layer

and FC (hexane/EtOAc 30:70, 0:100, then CH_2Cl_2/MeOH 90:10) the protected amino acid **127** (12.0 g, 99%).

Synthesis of the amino acid **128**

Following procedure **E.2**, the reaction of **127** (12.0 g, 16 mmol), 1,3-dimethylbarbituric acid (5.9 g, 38.0 mmol) and $Pd(PPh_3)_4$ (0.9 g) in EtOAc/CH_2Cl_2 (55:45, 275 mL) yielded after 2 h and after FC (EtOAc, then CH_2Cl_2/MeOH 90:10 to 60:40) the amino acid **128** (9.05 g, 90%).

Data of **128**: $C_{31}H_{42}N_6O_9$ (642.7). LC-MS: (method 7): R_t = 0.90 (94), 643 ($[M+H]^+$).

Synthesis of the protected macrolactam **Ex.272**

According to procedure **F.1.1**, the amino acid **128** (5.04 g, 7.8 mmol) in dry CH_2Cl_2 (100 mL) was treated with T3P (50% in EtOAc, 9.2 mL, 16 mmol) and *i*-Pr_2NEt (5.4 mL, 31 mmol) in dry CH_2Cl_2 (700 mL) to afford after FC (CH_2Cl_2/MeOH 39:1 to 19:1) the epimeric macrolactams **Ex.272** (1.90 g, 38%).

Data of **Ex.272**: $C_{31}H_{40}N_6O_8$ (624.7). LC-MS: (method 2): R_t = 1.61 (99), 625 ($[M+H]^+$). LC-MS: (method 7): R_t = 1.01 (99), 625 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 8.47 (d, J = 2.6, 1 H), 8.12 (s, 1 H), 7.95 (d, J = 9.6, 1 H), 7.61 (s, 1 H), 7.40-7.29 (m, 6 H), 5.10 (d, J = 12.6, 1 H), 5.04 (d, J = 12.6, 1 H), 4.98 (br. d, J = 10.7, 1 H), 4.16 (br. d, J = 11.8, 1 H), 4.10-3.90 (m, 4 H), 3.71 (br. t, J ca. 8.4, 1 H), 3.65-3.40 (m, 2 H), 3.23 (br. dd, J = 11.1, 15.2, 1 H), 3.04 (s, 3 H), 2.92 (t, J = 9.6, 1 H), 2.66 (s, 3 H), 2.12 (m, 1 H), 2.09 (br. q, 1 H), 1.42 (s, 9 H).

Synthesis of the amine **Ex.273**

According to procedure **J**, carbamate **Ex.272** (3.12 g, 5 mmol) in dioxane (31 mL) was treated with 4 M HCl-dioxane (62 mL) to afford **Ex.273**.2HCl (2.9 g, 97%)

Data of **Ex.273**.2HCl: $C_{26}H_{32}N_6O_6$.2HCl (524.5, free base). LC-MS (method 2): R_t = 1.31 (92), 525 ($[M+H]^+$).

Synthesis of the amine **Ex.274**

According to procedure **K**, carbamate **Ex.272** (200 mg, 0.32 mmol) was hydrogenated in MeOH (20 mL) in the presence of the catalyst (100 mg) to afford **Ex.274** (154 mg, 97%).

Data of **Ex.274**: $C_{23}H_{34}N_6O_6$. (490.5). LC-MS (method 2): R_t = 1.26 (98), (491 ($[M+H]^+$).

Core 19: Synthesis of Ex.297 and Ex.298 (Scheme 23)

Synthesis of the Mitsunobu product **129**

Following procedure **E.1.2**, the reaction of phenol **75** (4.58 g, 9.9 mmol), alcohol **81** (5.5 g, 15 mmol), and CMBP (4.8 g, 20 mmol) in dry toluene (24 mL) afforded after FC (hexane/EtOAc 1:3) the protected amino acid **129** (5.54 g, 68%).

Synthesis of the amino acid **130**

Following procedure **E.2**, the reaction of **129** (5.53 g, 6.8 mmol), 1,3-dimethylbarbituric acid (2.5 g, 16 mmol) and $Pd(PPh_3)_4$ (0.39 g) in EtOAc/CH_2Cl_2 55:45 (118 mL) yielded after 2 h and after FC (CH_2Cl_2/MeOH 95:5 to 70:30) the amino acid **130** (1.45 g, 85%).

Data of **130**: $C_{36}H_{45}N_5O_9$ (691.7). LC-MS (method 7): R_t = 1.09 (96), 692 ($[M+H]^+$).

Synthesis of the protected macrolactam **Ex.297**

According to procedure **F.1.1**, amino acid **130** (2.57 g, 3.7 mmol) in dry CH_2Cl_2 (40 mL) was treated with T3P (50% in EtOAc, 4.4 mL, 7.4 mmol) and *i*-Pr_2NEt (2.5 mL, 14.9 mmol) in dry CH_2Cl_2

(330 mL) to give after FC (CH_2Cl_2/MeOH 99:1 to 90:10) the macrolactam **Ex.297** (2.5 g, contaminated with ca 20% *i*-Pr_2NEt; yield 80%).

Data of **Ex.297**: $C_{36}H_{43}N_5O_8$ (673.7). LC-MS: (method 7): R_t = 1.18 (93), 674 ($[M+H]^+$).

Aqueous workup (EtOAc, 1 M aq. NaH_2PO_4 soln) of ananalytical sample (100 mg) afforded pure **Ex.297** (81 mg).

LC-MS: (method 2): R_t = 2.20 (93), 674 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6):complex spectrum, several isomers, 8.51 (d, J = 8.5, 0.2 H), 8.47 (d, J = 8.7, 0.1 H), 8.40 (d, J = 8.5, 0.55 H), 8.32 (d, J = 8.5, 0.15 H), 7.68-7.10 (several m, 10 H), 5.96 (br. s, 0.3 H), 5.90 (br. s, 0.3 H), 5.4-5.0 (m, 2.4 H), 4.8-3.8 (several m, 8 H), 3.3-2.5 (several m and s, 8 H), 2.5-1.6 (several m, 4 H), 1.42, 1.41, 1.36, 1.26 (4 s, Boc).

Synthesis of the acid **Ex.298**:

According to procedure **H**, the ester **Ex.297** (2.0 g, contaminated with ca 20% *i*-Pr_2NEt 2.4 mmol) was hydrogenated in MeOH (200 mL) in the presence of the catalyst (1 g) for 3 h.

The crude product was suspended in diethyl ether (20 mL) stirred for 20 min, filtered, washed (diethyl ether) and dried to afford **Ex.298** (1.63 g, contaminated with 15% *i*-Pr_2NEt, quantitative yield).

Aqueous workup (CH_2Cl_2, 1 M aq. NaH_2PO_4 soln) of an analytical sample (200 mg) afforded pure **Ex.298** (135 mg).

Data of **Ex.298**: $C_{29}H_{37}N_5O_8$ (583.6). LC-MS: (method 4a): R_t = 1.78 (86), 584 ($[M+H]^+$).

Core 20: Synthesis of Ex.311 (Scheme 24)

Synthesis of the Mitsunobu product **131**

A solution of phenol **72** (200 mg, 0.34 mmol), alcohol **16** (178 mg, 0.52 mmol) and PPh_3 (180 mg, 0.69 mmol) in benzene (5 mL)

was degassed. At 0°C, DEAD (40% in toluene, 0.32 mL, 0.69 mmol) was added. The mixture was stirred at room temperature for 15 h. More of alcohol **16** (178 mg, 0.52 mmol) and PPh_3 (180 mg, 0.69 mmol) were added. DEAD (40% in toluene, 0.32 mL, 0.69 mmol) was added at 0°C. The mixture was stirred for 20 h and concentrated. FC (CH_2Cl_2/EtOAc 100:0 to 80:20) afforded **131** (containing ca. 20% of diethyl hydrazine-1,2-dicarboxylate; used without any further purification).

Synthesis of the amino acid **132**

Following procedure **B.2**, the reaction of **131** (250 mg, ca. 80%, 0.22 mmol), 1.3-dimethylbarbituric acid (107 mg, 0.69 mmol) and $Pd(PPh_3)_4$ (16 mg) in EtOAc/CH_2Cl_2 (55:45, 4.8 mL) yielded after 3 h and after FC (EtOAc/MeOH 100:0 to 90:10, then CH_2Cl_2/MeOH 90:10 to 80:20) **132** (177 mg, yield over the two steps: 73%).
Data of **132**: $C_{39}H_{57}N_5O_{10}Si$ (784.0): LC-MS: (method 7): R_t = 1.31, 784.2 ($[M+H]^+$).

Synthesis of the alloc protected amino acid **133**

Following procedure **C.1**, the reaction of **132** (150 mg, 0.19 mmol), allyl chloroformate (23 µL, 0.21 mmol) and Na_2CO_3 (61 mg, 0.57 mmol) in dioxane (1.5 mL) and H_2O (1.5 mL) gave, after 2 h at 0°C, acid **133** (154 mg, 92%).

Synthesis of the protected amino acid **134**

Following procedure **C.2**, acid **133** (140 mg, 0.16 mmol) was reacted with sarcosine allylester p-toluenesulfonate (**46**·pTsOH, 58 mg, 0.194 mmol), HOAt (33 mg, 0.24 mmol), HATU (92 mg, 0.24 mmol) and *i*-Pr_2NEt (0.138 mL, 0.81 mmol) in DMF (2.4 mL) to afford the protected amino acid **134** (106 mg, 67%).
Data of **134**: $C_{49}H_{70}N_6O_{13}Si$ (979.2). LC-MS: (method 7): R_t = 1.68, 979.3 ($[M+H]^+$).

Synthesis of amino acid **135**

Following procedure **C.3**, the reaction of the protected amino acid **134** (100 mg, 0.10 mmol), 1.3-dimethylbarbituric acid (38 mg, 0.25 mmol) and $Pd(PPh_3)_4$ (6 mg) in EtOAc/CH_2Cl_2 (45:55, 1.9 mL) yielded after 16 h and after FC (EtOAc, then CH_2Cl_2/MeOH 90:10) **135** (70 mg, 80%).

Data of **135**: $C_{42}H_{62}N_6O_{11}Si$ (855.1). LC-MS: (method 7): R_t = 1.30, 855.5 ($[M+H]^+$).

Synthesis of the protected macrolactam **Ex.311**

According to procedure **F.1.1**, a solution of the amino acid **135** (60 mg, 0.07 mmol) in dry CH_2Cl_2 (2 mL), was added within 2 h to T3P (50% in EtOAc; 84 µL, 0.14 mmol) and *i*-Pr_2NEt (48 µL, 0.28 mmol) in CH_2Cl_2 (5 mL). Then sat. aq. $NaHCO_3$ solution was added and the mixture was extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4), filtered and concentrated. FC (EtOAc) afforded **Ex.311** (26 mg, 44%).

Data of **Ex.311**: ($C_{42}H_{60}N_6O_{10}Si$ (837.0). LC-MS: (method 7): R_t = 1.51 (90), 837.4 ($[M+H]^+$). ^{1}H-NMR ($CDCl_3$): 7.26 (s, 5 H), 7.09 (t, J = 8.4, 1 H), 6.78 (d-like m, 1 H), 6.61 (d, J = 7.4, 1 H), 5.50-4.90 (several br. m, 5 H), 4.90-3.80 (several br. m, 8 H), 3.69 (br. t, J ca. 8.5, 1 H), 3.6-2.3 (several br. m, 14 H), 2.12 (m, 1 H), 1.61 (m, 1 H), 1.38 (s, 9 H), 1.24 (s, 2 H), 0.93 (br. t, J ca. 8.0, 2 H), 0.00, -0.03 (2 s, 9 H).

Core 21: Synthesis of Ex.312 and Ex.313 (Scheme 25)

Synthesis of the Mitsunobu product **136**

Alcohol **82** (217 mg, 0.58 mmol) and CMBP (212 mg, 0.88 mmol) were dissolved in dry degassed toluene (7 mL) and heated at

100°C for 30 min. A solution of **80** (250 mg, 0.58 mmol) in toluene (2 mL) was added dropwise. Stirring at 100°C was continued for 1 h. The volatiles were evaporated. FC (hexane/EtOAc 2:1 to 1:1) yielded **136** (290 mg, 63%).

Synthesis of aminoacid **137**

Following procedure **E.2** the reaction of **136** (250 mg, 0.32 mmol), 1,3-dimethylbarbituric acid (120 mg, 0.77 mmol) and $Pd(PPh_3)_4$ (18 mg) in EtOAc/CH_2Cl_2 (45:55, 5.5 mL) yielded after 0.5 h and after FC (CH_2Cl_2/MeOH 95:5 to 70:30) the aminoacid **137** (164 mg, 78%).

Data of **137**: $C_{33}H_{44}N_4O_8S$ (656.8). LC-MS (method 7): R_t = 1.15 (95), 657 ($[M+H]^+$).

Synthesis of the protected macrolactam **Ex.312**

According to procedure **F.1.1**, a solution of the amino acid **137** (100 mg, 0.15 mmol) in dry CH_2Cl_2 (2 mL) was added over 2 h to T3P (50% in EtOAc, 0.18 mL, 0.31 mmol) and *i*-Pr_2NEt (0.1 mL, 0.61 mmol) in dry CH_2Cl_2 (13 mL). Stirring at room temperature was continued for 1 h, followed by aqueous workup (EtOAc, sat. aq. $NaHCO_3$ soln, Na_2SO_4) and FC (EtOAc) to afford **Ex.312** (56 mg, 57%).

Data of **Ex.312**: $C_{33}H_{42}N_4O_7S$ (638.7). LC-MS (method 7): R_t = 1.33 (95), 639 ($[M+H]^+$). ^{1}H-NMR ($CDCl_3$): 7.37-7.23 (m, 8 H), 6.92 (br. s, 1 H), 5.25 (m, 2 H), 5.17 (s, 1 H), 4.88 (d, J = 16.2, 1 H), 4.62 (br. m, 1 H), 4.46 (br. t-like m, 1 H), 4.31 (br. m, 1 H), 4.17 (dd, J = 4.1, 14.2, 1 H), 3.72 (dd, J = 4.8, 10.7, 1 H), 3.50 (m, 1 H), 3.30-2.80 (several m, 2 H), 3.14 (s, 3 H), 3.01 (s, 3 H), 2.60-1.90 (several m, 6 H), 1.46 (s, 9 H).

Synthesis of sulfon **Ex.313**

m-CPBA (70% w/w; 10 mg, 41 μmol) was added at 0°C to a solution of **Ex.312** (20 mg, 31 μmol) in CH_2Cl_2 (0.5 mL). The mixture was stirred for 15 min followed by the addition of m-CPBA (9 mg, 37 μmol). The mixture was allowed to warm to room temperature over 1 h, diluted with CH_2Cl_2 and washed with aq. $Na_2S_2O_3$ soln and with aq. $NaHCO_3$ soln. The organic phase was dried (Na_2SO_4), filtered and concentrated. FC (EtOAc/MeOH 100:0 to 90:10) afforded **Ex.313** (8 mg, 38%).

Data of **Ex.313**: $C_{33}H_{42}N_4O_9S$ (670.7). LC-MS (method 6): R_t = 1.24 (95), 671 ($[M+H]^+$). ^{1}H-NMR ($CDCl_3$): 7.89 (td, J = 1.7, 7.3, 1 H), 7.71 (s, 1 H), 7.43-7.28 (m, 7 H), 5.17 (d, J = 12.0, 1 H), 5.10 (d, J = 12.0, 1 H), 5.01 (dd, J = 5.9, 9.1, 1 H), 4.96-4.85 (m, 2 H), 4.71 (d, J = 15.4, 1 H), 4.57 (br. m, 1 H), 4.33 (br. m, 2 H), 3.85 (dd, J = 7.8, 12.3, 1 H), 3.25 (s, 3 H), 3.20 (m, 1 H), 3.10 (m, 1 H), 2,97 (s, 3 H), 2.73-2.54 (m, 2 H), 2.45-2.23 (m, 2 H), 2.17 (m, 1 H), 1.99 (m, 1 H), 1.46 (s, 9 H).

Synthesis of final products

Advanced macrocyclic intermediates and final products depicted in **Tables 21a-36a** (Scheme 26) and were prepared starting from the suitable precursor macrocyclic acid or macrocyclic amine applying the general procedures (H-N) described above.
Deviations from general procedures are indicated in **Tables 21a-36a.**
Analytical data of these intermediates and final products are depicted in **Tables 21b-36b.**
IUPAC names of all examples are listed in **Tables 20, 21c-36c,** and **37.**

Detailed description of selected examples:

Core 03:

Synthesis of selected advanced intermediates and final products (Scheme 27)

Synthesis of amide **Ex.27**

A mixture of **Ex.4** (432 mg, 0.79 mmol), HATU (597 mg, 1.57 mmol) and HOAt (214 mg, 1.57 mmol) was dissolved in DMF (6 mL). N,N-dimethylethylenediamine (173 µL, 1.57 mmol) and *i*-Pr_2NEt (537 µL, 3.14 mmol) were added. The solution was stirred at room temperature for 15 h and concentrated. The residue was dissolved in $CHCl_3$ and washed with sat. aq. $NaHCO_3$ solution and with H_2O. The organic phase was dried (Na_2SO_4), filtered and concentrated. FC (CH_2Cl_2/MeOH/conc. aq. NH_3 soln 100:0:0 to 90:10:0.5) afforded **Ex.27** (405 mg, 83%).

Data of **Ex.27**: Cf. **Table 21b**

Synthesis of amine **Ex.28**

A solution of **Ex.27** (400 mg, 0.64 mmol) in dioxane (4 mL) was treated at room temperature with 4 M HCl-dioxane (8 mL) for 2 h. The volatiles were evaporated. The residue was dissolved in CH_2Cl_2/MeOH, concentrated and dried i.v. to afford **Ex.28**·HCl (343 mg, 90%).

Data of **Ex.28**: Cf. **Table 21b**

Synthesis of amide **Ex.11**

A mixture of **Ex.28**·HCl (75 mg, 0.126 mmol), ^{1}H-indole-3-acetic acid (44 mg, 0.253 mmol), HATU (96 mg, 0.253 mmol) and HOAt (34 mg, 0.253 mmol) was dissolved in DMF (2 mL). *i*-Pr_2NEt (87 µL, 0.505 mmol) was added. The solution was stirred at room temperature for 15 h and concentrated. The residue was dissolved in $CHCl_3$ and washed with sat. aq. $NaHCO_3$ solution and with H_2O. The organic phase was dried (Na_2SO_4), filtered and

concentrated. FC (CH_2Cl_2/MeOH/conc. aq. NH_3 soln 100:0:0 to 90:10:1) afforded **Ex.11** (50 mg, 58%).

Data of **Ex.11**: Cf. **Table 21b**

^{1}H-NMR (DMSO-d_6): 10.81 (s, 1 H), 8.26 (d, J = 7.4, 1 H), 7.62 (t, J = 5.5, 1 H), 7.46 (d, J = 7.9, 1 H), 7.37-7.15 (m, 4 H), 7.09 (d, J = 2.2, 1 H), 7.04 (t, J = 7.5, 1 H), 6.92 (t, J ca. 7.4, 1 H), 5.08 (d, J ca. 12.5, 1 H), 4.74 (d, J = 8.9, 1 H), 4.37 (d, J = 11.0, 1 H), 4.25 (d, J = 17.7, 1 H), 4.22-4.13 (m, 2 H), 3.97 (d, J = 17.6, 1 H), 3.78 (t, J = 8.3, 1 H), 3.41 (s, 2 H), 3.24 (m, 1 H), 3.15 (m, 1 H), 2.98 (t, J = 9.2, 1 H), 2.88 (s, 3 H), 2.53 (s, 3 H), 2.41- 2.27 (m, 4 H), 2.17 (s, 6 H), 2.04 (m, 1 H), 1.83 (t-like m, 2 H), 1.69 (q-like m, 1 H).

Synthesis of amide **Ex.49**

A mixture of **Ex.28**·HCl (60 mg, 0.101 mmol), 1-naphthylacetic acid (23 mg, 0.121 mmol), and HOBt.H_2O (19 mg, 0.121 mmol) was dissolved in CH_2Cl_2 (1 mL). *N*-Cyclohexyl-carbodiimide-*N'*-methylpolystyrene (1.9 mmol/g; 80 mg, 0.152 mmol) and *i*-Pr_2NEt (52 µL, 0.303 mmol) were added. The mixture was stirred for 15 h at room temperature. (Polystyrylmethyl)-trimethylammonium bicarbonate (3.5 mmol/g; 87 mg, 0.303 mmol) was added and stirring was continued for 1 h. The mixture was diluted with CH_2Cl_2/MeOH 9:1 (2 mL) and filtered. The polymer was washed with twice with CH_2Cl_2/MeOH 8:2 (5 mL). The combined filtrate and washings were concentrated. Purification of the crude product by FC (CH_2Cl_2/MeOH/conc. aq. NH_3 soln. 100:0:0 to 90:10:1) afforded **Ex.49** (58 mg, 83%).

Data of **Ex.49**: Cf. **Table 21b**

^{1}H-NMR (DMSO-d_6): 8.45 (d, J = 7.3, 1 H), 8.00-7.87 (m, 2 H), 7.79 (d, J = 8.0, 1 H), 7.62 (t, J = 5.5, 1 H), 7.53-7.25 (m, 6 H), 7.19 (dd, J = 3.0, 8.4, 1 H), 5.10 (d, J = 12.3, 1 H), 4.75 (d, J = 8.9, 1 H), 4.39 (d, J = 10.8, 1 H), 4.27 (d, J = 17.8, 1 H), 4.28-4.08 (m, 2 H), 3.95 (d, J = 17.9, 1 H), 3.83 (m, 1 H), 3.81 (s, 2 H), 3.24 (m, 1 H), 3.16 (m, 1 H), 3.03 (t, J =

9.2, 1 H), 2.87 (s, 3 H), 2.54 (s, 3 H), 2.42-2.27 (m, 4 H), 2.16 (s, 6 H), 2.02 (m, 1 H), 1.84 (t-like m, 2 H), 1.71 (q, J ca. 9.4, 1 H).

Synthesis of amide **Ex.30**

A mixture of **Ex.4** (400 mg, 0.73 mmol), HATU (552 mg, 1.45 mmol), HOAt (198 mg, 1.45 mmol) and tryptamine (233 mg, 1.45 mmol) was dissolved in DMF (6 mL). *i*-Pr_2NEt (497 µL, 2.91 mmol) was added. The solution was stirred at room temperature for 15 h followed by aqueous workup ($CHCl_3$, sat. aq. $NaHCO_3$ soln, H_2O). The organic phase was dried (Na_2SO_4), filtered and concentrated. FC (CH_2Cl_2/MeOH 100:0 to 95:5) afforded **Ex.30** (410 mg, 81%).

Data of **Ex.30**: Cf. **Table 21b**

^{1}H-NMR (DMSO-d_6): 10.80 (s, 1 H), 7.91 (t, J = 5.6, 1 H), 7.56 (d, J = 7.7, 1 H), 7.32 (d, J = 8.0, 1 H), 7.27-7.12 (m, 5 H), 7.06 (t, J = 7.5, 1 H), 6.97 (t, J = 7.4, 1 H), 5.08 (d, J =12.4, 1 H), 4.75 (d, J = 9.3, 1 H), 4.34 (d, J = 10.9, 1 H), 4.24 (d, J = 17.8, 1 H), 4.10 (t-like m, 1 H), 3.97 (d, J = 17.7, 1 H), 3.86 (m, 1 H), 3.77 (m, 1 H), 3.42-3.30 (m, 2 H), 2.96-2.83 (m, 3 H), 2.89 (s, 3 H), 2.50 (s, 3 H, superimposed by DMSO-d signal), 2.27 (m, 2 H), 2.08 (m, 1 H), 1.84 (t-like m, 2 H), 1.65 (q, J = 10.8, 1 H), 1.34 (s, 9 H).

Synthesis of amine **Ex.55**

A solution of **Ex.30** (380 mg, 0.55 mmol) in dioxane (4 mL) was treated at room temperature with 4 M HCl-dioxane (8 mL) for 4 h. The volatiles were evaporated. The residue was dissolved in dioxane (4 mL) and treated again for 2 h with 4 M HCl-dioxane (8 mL). The volatiles were evaporated. The residue was washed with diethyl ether and purified by FC (CH_2Cl_2/MeOH/conc. aq. NH_3 soln 90:10:0 to 90:10:1) to afford **Ex.55** (136 mg, 42%).

Data of **Ex.55**: Cf. **Table 21b**

Synthesis of amide **Ex.12**

A mixture of **Ex.55** (68 mg, 0.092 mmol), 1H-indole-3-acetic acid (32 mg, 0.184 mmol), HATU (70 mg, 0.184 mmol) and HOAt (25 mg, 0.184 mmol) was dissolved in DMF (2 mL). *i*-Pr_2NEt (63 µL, 0.367 mmol) was added. The solution was stirred at room temperature for 15 h and concentrated. The residue was dissolved in $CHCl_3$ and washed with sat. aq. $NaHCO_3$ solution and with H_2O. The organic phase was dried (Na_2SO_4), filtered and concentrated. Purification by prep. HPLC, method 1, afforded **Ex.12** (38 mg, 55%).

Data of **Ex.12**: Cf. **Table 21b**

^{1}H-NMR (DMSO-d_6): 10.81 (s, 2 H), 8.26 (d, J = 7.2, 1 H), 7.93 (t, J = 5.7, 1 H), 7.57 (d, J = 7.8, 1 H), 7.46 (d, J = 7.7, 1 H), 7.38-6.90 (m, 11 H); 5.10 (d, J = 12.1, 1 H), 4.76 (d, J = 9.3, 1 H), 4.38 (d, J = 10.8, 1 H), 4.26 (d, J = 17.8, 1 H), 4.23-4.11 (m, 2 H), 3.96 (d, J = 18.0, 1 H), 3.78 (t, J = 8.3, 1 H), 3.7-3.25 (m, 3 H), 3.60 (s, 2 H), 3.01 -2.81 (m, 2 H), 2.88 (s, 3 H), ca. 2.5 (s, 3 H, superimposed by DMSO-d signal), 2.33 (m, 2 H), 2.06 (m, 1 H), 1.85 (t-like m, 2 H), 1.63 (q, J ca. 10.7, 1 H).

Synthesis of amide **Ex.16**

A mixture of **Ex.55** (68 mg, 0.092 mmol), N,N-dimethyl glycine (19 mg, 0.184 mmol), HATU (70 mg, 0.184 mmol) and HOAt (25 mg, 0.184 mmol) was dissolved in DMF (2 mL). *i*-Pr_2NEt (63 µL, 0.367 mmol) was added. The solution was stirred at room temperature for 15 h and concentrated. The residue was dissolved in $CHCl_3$ and washed with sat. aq. $NaHCO_3$ solution and with H_2O. The organic phase was dried (Na_2SO_4), filtered and concentrated. Purification by prep. HPLC, method 1, afforded **Ex.16**·TFA (40 mg, 55%).

Data of **Ex.16**·TFA: Cf. **Table 21b**

^{1}H-NMR (DMSO-d_6): 10.81 (s, 1 H), 9.66 (br. s, NH^+), 8.75 (d, J = 6.9, 1 H), 7.90 (t, J = 5.6, 1 H), 7.56 (d, J = 7.8, 1 H), 7.34-7.14 (m, 5 H), 7.06 (t, J ca. 7.5, 1 H), 6.97 (t, J = 7.4, 1 H), 5.08 (d, J = 12.3, 1 H), 4.78 (d, J = 9.2, 1 H), 4.39 (d, J = 10.7, 1 H), 4.24 (d, J = 17.8, 1 H), 4.24-4.14 (m, 2 H), 4.00 (d, J = 17.8, 1 H), 3.96-3.75 (m, 3 H), 3.45-3.35 (m, 2 H), 3.0-2.67 (m, 3 H), 2.90 (s, 3 H), 2.75 (s, 6 H), 2.50 (s, 3 H, superimposed by DMSO-d signal), 2.5-2.27 (m, 2 H), 2.08 (m, 1 H), 1.85 (t-like m, 2 H), 1.64 (q, J = 10.8, 1 H).

Synthesis of amide **Ex.53**

Pyridine (2 mL) and acetic anhydride (0.14 mL, 1.48 mmol) were added to a solution of **Ex.5**·HCl (95 mg, 0.15 mmol) in dry CH_2Cl_2 (2 mL). The solution was stirred at room temperature for 20 h. The solution was diluted with EtOAc and washed with 1 M aq. HCl soln, sat. aq. NaCl soln, sat. aq. $NaHCO_3$ soln, and sat. aq. NaCl soln. The organic phase was dried (Na_2SO_4), filtered and concentrated. FC of the crude product afforded **Ex.53** (60 mg, 70%).

Data of **Ex.53**: Cf. **Table 21b**

Synthesis of acid **Ex.54**

A solution of **Ex.53** (58 mg, 0.01 mmol) in MeOH (5 mL) was hydrogenated at room temperature and normal pressure for 2 h in the presence of palladium hydroxide on activated charcoal (moistened with 50% H_2O; 50 mg). The mixture was filtered through a pad of celite. The residue was washed (MeOH). The combined filtrate and washings were concentrated and dried i.v. to yield **Ex.54** (45 mg, 92%).

Data of **Ex.54**: Cf. **Table 21b**

Synthesis of amide **Ex.9**

A mixture of **Ex.54** (45 mg, 0.091 mmol), HATU (52 mg, 0.137 mmol) HOAt (19 mg, 0.137 mmol) and tryptamine (22 mg, 0.137 mmol) was dissolved in DMF (1 mL). *i*-Pr_2NEt (47 µL, 0.274 mmol) was added. The solution was stirred at room temperature for 20 h followed by aqueous workup ($CHCl_3$, sat. aq. $NaHCO_3$ soln, H_2O). The organic phase was dried (Na_2SO_4), filtered and concentrated. FC (CH_2Cl_2/MeOH 100:0 to 86:14) afforded **Ex.9** (36 mg, 62%).

Data of **Ex.9**: Cf. **Table 21b**

^{1}H-NMR (DMSO-d_6): 10.81 (s, 1 H), 8.06 (d, J = 7.0, 1 H), 7.93 (t, J = 5.6, 1 H), 7.56 (d, J = 7.8, 1 H), 7.34-7.14 (m, 5 H), 7.05 (t, J ca. 7.5, 1 H), 6.97 (t, J ca. 7.4, 1 H), 5.09 (d, J = 12.4, 1 H), 4.75 (d, J = 9.1, 1 H), 4.38 (d, J = 10.8, 1 H), 4.26 (d, J = 17.7, 1 H), 4.19-4.10 (m, 2 H), 3.97 (d, J = 17.9, 1 H), 3.78 (t, J = 8.3, 1 H), 3.43-3.30 (m, 2 H), 2.96-2.83 (m, 3 H), 2.89 (s, 3 H), 2.50 (s, 3 H, superimposed by DMSO-d signal), 2.40-2.27 (m, 2 H), 2.08 (m, 1 H), 1.85 (m, 2 H), 1.71 (s, 3 H), 1.62 (q, J ca. 10.6, 1 H).

Core 11 and Core 12:

Synthesis of selected advanced intermediates and final products (Scheme 28)

Synthesis of amide **Ex.184**

A mixture of **Ex 182** (500 mg, 1.04 mmol), 2-naphthylacetic acid (232 mg, 1.25 mmol), HATU (791 mg, 2.08 mmol) and HOAt (283 mg, 2.08 mmol) was dissolved in DMF (15 mL). *i*-Pr_2NEt (712 µL, 4.16 mmol) was added. The solution was stirred at room temperature for 20 h and concentrated. The residue was dissolved in $CHCl_3$ and washed with sat. aq. $NaHCO_3$ solution and with H_2O. The organic phase was dried (Na_2SO_4), filtered and concentrated. FC (EtOAc, then CH_2Cl_2/MeOH 95:5) afforded **Ex.184** (637 mg, 94%).

Data of **Ex.184**: Cf. **Table 29b**

^{1}H-NMR (DMSO-d_6): 8.41 (d, J = 7.0, 1 H), 7.90-7.83 (m, 3 H), 7.77 (s, 1 H), 7.53-7.44 (m, 4 H), 7.32-7.22 (m, 6 H), 7.04 (d, J = 8.4, 1 H), 6.86 (d, J = 7.4, 1 H), 6.81 (s, 1 H), 5.02-4.90 (m, 3 H), 4.19 (t, J ca. 8.6, 1 H), 4.14-3.96 (m, 2 H), 3.83 (t-like m, 2 H), 3.63 (s, 2 H), ca. 3.3 (m, 1 H, superimposed by H_2O signal), 3.05 (m, 1 H), 2.95 (m, 1 H), 2.91 (s, 3 H), 2.27 (m, 1 H), 2.16 (br. q, J ca. 11.3, 1 H), 1.54 (m, 2 H), 1.31 (m, 1 H), 1.15 (m, 1 H).

Synthesis of amide **Ex.200**

A mixture of **Ex.197**·TFA (60 mg, 0.094 mmol), 1H-indole-3-acetic acid (25 mg, 0.14 mmol), HATU (54 mg, 0.14 mmol) and HOAt (19 mg, 0.14 mmol) was dissolved in DMF (1.5 mL). *i*-Pr_2NEt (81 μL, 0.471 mmol) was added. The solution was stirred for 18 h at room temperature and concentrated. The residue was dissolved in $CHCl_3$ and washed (sat. aq. $NaHCO_3$ soln, H_2O). The organic phase was dried (Na_2SO_4), filtered and concentrated, followed by FC (EtOAc, then CH_2Cl_2/MeOH 95:5) to afford **Ex.200** (50 mg, 78%).

Data of **Ex.200**: Cf. **Table 30b**

^{1}H-NMR (DMSO-d_6): 10.86 (s, 1 H), 8.42 (d, J = 7.8, 1 H), 8.01 (d, J = 10.0, 1 H), 7.58 (d, J = 7.8, 1 H), 7.36-7.19 (m, 9 H), 7.07-7.02 (m, 2 H), 6.97 (t, J = 7.1, 1 H), 6.86 (d, J = 7.6, 1 H), 5.08 (s, 2 H), 4.88 (d, J = 8.7, 1 H), 4.30-4.10 (m, 2 H), 4.13 (d, J = 10.9, 1 H), 4.01 (t-like m, 1 H), 3.95 (d, J = 18.0, 1 H), 3.75-3.70 (m, 2 H), 3.56 (s, 2 H), 3.4-3.2 (m, 2 H, partially superimposed by H_2O signal), 3.04 (t, J = 9.9, 1 H), 2.98 (s, 3 H), 2.65 (s, 3 H), 2.27 (m, 1 H), 2.09 (q, J = 11.7, 1 H).

Synthesis of amine **Ex.202**

A solution of **Ex.200** (320 mg, 0.47 mmol) in MeOH (28 mL) was hydrogenated at normal pressure and at room temperature for 4 h in the presence of palladium hydroxide on activated charcoal

(moistened with 50% H_2O; 158 mg). The mixture was filtered through a pad of celite. The residue was washed (MeOH). The combined filtrate and washings were concentrated and dried i.v. to yield **Ex.202** (250 mg, 97%).

Data of **Ex.202**: Cf. **Table 30b**

Synthesis of amide **Ex.213**

A solution of **Ex.202** (60 mg, 0.11 mmol) in dry CH_2Cl_2 (1 mL) was treated with pyridine (89 µL, 1.1 mmol). Decanoyl chloride (46 µL, 0.22 mmol) was slowly added at 0°C. The mixture was stirred at 0°C to room temperature for 18 h followed by the addition of MeOH (0.1 mL). Stirring was continued for 10 min. The volatiles were evaporated. The residue was three times treated with toluene and evaporated. Purification by prep. HPLC, method 1 and subsequent FC (EtOAc/MeOH 90:10 to 80:20) afforded **Ex.213** (27 mg, 35%).

Data of **Ex.213**: Cf. **Table 30b**

^{1}H-NMR (DMSO-d_6): 10.86 (s, 1 H), 8.53 (d, J = 9.8, 1 H), 8.44 (d, J = 7.7, 1 H), 7.57 (d, J = 7.7, 1 H), 7.35-7.30 (m, 3 H), 7.27 (s, 1 H), 7.19-6.95 (m, 3 H), 6.84 (d, J = 7.5, 1 H), 4.86 (dd, J = 2.4, 11.2, 1 H), 4.60 (q, J = 8.4, 1 H), 4.25 (q-like m, 1 H), 4.14 (d, J = 10.7, 1 H), 4.04-3.82 (m, 3 H), 3.73 (t, J ca. 8.5, 1 H), 3.55 (s, 2 H), 3.24 (d, J = 7.8, 2 H), 3.09 (t, J = 9.5, 1 H), 2.99 (s, 3 H), 2.67 (s, 3 H), 2.26 (m, 1 H), 2.15 (t, J = 7.2, 2 H), 2.09 (m, 1 H), 1.51 (t-like m, 2 H), 1.24 (s, 12 H), 0.85 (t, J = 6.6, 3 H).

Core 11:

Synthesis of Ex.186 on solid support (Scheme 29)

Synthesis of amine **139**

A solution of **Ex.181** (2.0 g, 3.2 mmol) in MeOH (200 mL) was hydrogenated for 3 h at room temperature and at normal pressure in the presence of palladium hydroxide on activated charcoal (15-20% Pd, moistened with 50% H_2O; 400 mg). The mixture was filtered through a pad of celite. The residue was washed (MeOH). The combined filtrate and washings were concentrated and dried i.v. to give the corresponding amine (1.57 g), which was dissolved in CH_2Cl_2 (8 mL) and treated with sat. aqueous $NaHCO_3$ solution (2.9 mL) and allyl chloroformate (0.36 mL, 3.43 mmol). The mixture was stirred at room temperature for 2 h. The organic phase was separated and concentrated. Purification of the residue by FC (EtOAc) afforded the allyl carbamate **138** (1.65 g, 92%).

TBAF solution (1 M in THF, 7 mL, 7 mmol) was added at 0°C to a solution of **138** (1.29 g, 2.24 mmol) in THF (53 mL). The solution was stirred at 0°C to room temperature for 3 h and concentrated. The residue was distributed between CH_2Cl_2 and sat. aq. $NaHCO_3$ solution. The aqueous phase was separated and extracted with CH_2Cl_2. The combined organic phase was dried (Na_2SO_4), filtered and concentrated. The residue was dissolved in CH_2Cl_2 (10 mL) and treated for 20 min with 25% aq. HCl solution (0.29 mL). The volatiles were evaporated and the residue was dried i.v. to afford **139**·HCl (1.14 g; contaminated with ca 15% tetrabutylammonium salt and used without further purification; yield ca 90%)

Data of **139**·HCl: $C_{22}H_{30}N_4O_5$·HCl (430.5, free base). LC-MS (method 4a): R_t = 1.22 (92), 431.3 $[M+H]^+$.

Synthesis of the resin **140**

DFPE polystyrene (1% DVB, 100-200 mesh, loading 0.89 mmol/g; 200 mg, 0.178 mmol) was swollen in DCE (2 mL) for 1 h. The resin was filtered. A solution of amine hydrochloride **139**·HCl (ca 85% w/w, 166 mg, 0.303 mmol) in DCE (1.33 mL) and trimethyl orthoformate (0.66 mL, 6.02 mmol) were added. The resin was shaken for 1 h at room temperature, followed by the addition of

sodium triacetoxyborohydride (75 mg, 0.356 mmol). The mixture was shaken for 15 h and the resin was filtered. The resin was successively washed three times each with DMF, 10% *i*-Pr_2NEt in DMF, DMF, CH_2Cl_2 and dried i.v. to afford resin **140** (293 mg).

Synthesis of the resin **141**

1st Acid coupling step: The resin **140** (loading 0.77 mmol/g; 50 mg, 0.038 mmol) was swollen in DMF (1 mL) for 30 min and filtered. CH_2Cl_2 (0.5 mL), DMF (0.5 mL), 2-naphthylacetic acid (65 mg, 0.35 mmol), *i*-Pr_2NEt (0.13 mL, 0.76 mmol) and HATU (144 mg, 0.38 mmol) were successively added. The resin was shaken for 1 h, filtered and washed with DMF. CH_2Cl_2 (0.5 mL), DMF (0.5 mL) 2-naphthylacetic acid (65 mg, 0.35 mmol), *i*-Pr_2NEt (0.13 mL, 0.76 mmol) and then HATU (144 mg, 0.38 mmol) were added to the resin. The mixture was shaken for 1 h and filtered. The resin was washed three times with DMF and two times with CH_2Cl_2.

Cleavage of the Alloc group: CH_2Cl_2 (1 mL), phenylsilane (41 mg, 0.375 mmol) and $Pd(PPh_3)_4$ (9 mg) were added to the resin. The mixture was shaken for 15 min and filtered. The resin was washed with CH_2Cl_2 and treated again for 15 min with CH_2Cl_2 (1 mL), phenylsilane (41 mg, 0.375 mmol) and $Pd(PPh_3)_4$ (9 mg). The resin was filtered, washed three times each with CH_2Cl_2, DMF and twice with MeOH and CH_2Cl_2.

2nd Acid coupling step: DMF (0.5 mL), CH_2Cl_2 (1 mL), 2-naphthylacetic acid (70 mg, 0.375 mmol), *i*-Pr_2NEt (0.13 mL, 0.75 mmol) and PyBOP (195 mg, 0.375 mmol) were added to the resin. The mixture was shaken for 1 h and filtered. The resin was washed three times each with DMF and CH_2Cl_2 to afford resin **141**, which was immediately used in the next step.

Release of the amide **Ex.186**

The resin **141** was treated with 20% TFA in CH_2Cl_2 (1 mL) for 10 min, filtered and washed with CH_2Cl_2. The resin was treated

again for 10 min with 20% TFA in CH_2Cl_2 (1 mL), filtered and washed three times with CH_2Cl_2. The combined filtrates and washings were concentrated. The residue was treated with CH_3CN, evaporated and dried i.v. Purification of the crude product by prep. HPLC, method 3, afforded **Ex.186** (11 mg, yield: overall 32% based on **139**).

Data of **Ex.186**: $C_{42}H_{42}N_4O_5$ (682.8). LC-MS (method 4a): R_t = 2.26 (98). ^{1}H-NMR (DMSO-d_6): 8.38 (d, J = 7.0, 2 H), 7.91-7.69 (m, 8 H), 7.54-7.27 (m, 7 H), 7.03 (dd, J = 1.5, 8.2, 1 H), 6.86-6.82 (m, 2 H), 4.94 (d, J = 12.7, 1 H), 4.19 (t, J = 8.6, 1 H), 4.11-3.94 (m, 3 H), 3.71 (dd, J = 9.2, 16.5, 1 H), 3.62 (s, 2 H), 3.58 (s, 2 H), 3.08 (m, 1 H), 2.89 (m, 1 H), 2.89 (s, 3 H), 2.5 (m, 1 H, superimposed by DMSO-d signal), 2.30 (m, 1 H), 2.14 (q-like m, 1 H), 1.64-1.49 (m, 2 H), 1.34 (m, 1 H), 1.14 (m, 1 H).

The ^{1}H-NMR spectrum is identical with the spectrum of the sample prepared in solution, cf. **Table 29**

Table 20: Examples of Core 01 and Core 02 (**Ex.1-Ex.2**)

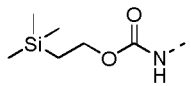
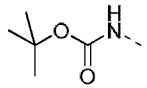
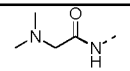
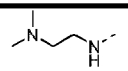
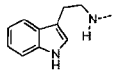
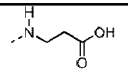
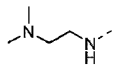
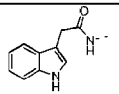
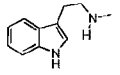
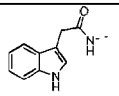
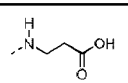
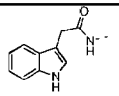
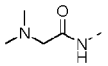
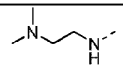
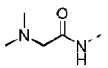
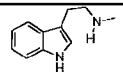
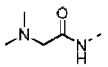
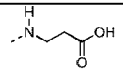
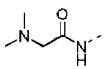
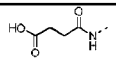
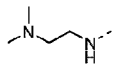
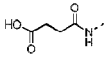
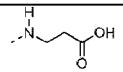
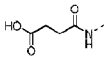
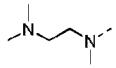
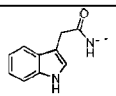
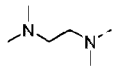
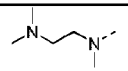
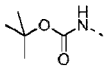
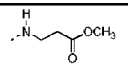
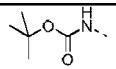
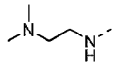
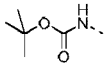
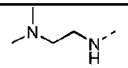
No			IUPAC name
Core 01	**R2**	**R50**	
Ex.1		OCH_2Ph	8-benzyl 2-[2-(trimethylsilyl)ethyl] (2S,8S,16aS)-12-fluoro-9-methyl-5,10-dioxo-2,3,5,6,7,8,9,10,16,16a-decahydro-1H-pyrrolo[2,1-c][1,4,9]benzoxadiazacyclododecine-2,8-dicarboxylate
Core 02	**R11**	**R50**	
Ex.2		OCH_2Ph	9-benzyl 2-(tert-butyl) (9S,17aS)-13-fluoro-10-methyl-6,11-dioxo-3,4,6,7,8,9,10,11,17,17a-decahydropyrazino[2,1-c][1,4,9]benzoxadiazacyclododecine-2,9(1H)-dicarboxylate

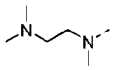
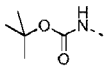
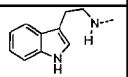
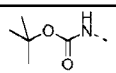
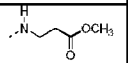
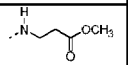
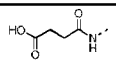
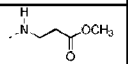
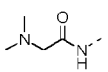
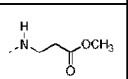
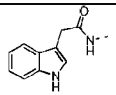
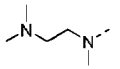
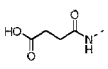
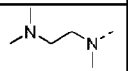
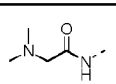
Table 21a: Examples of Core 03 (**Ex.3-Ex.55,** *continued on the following pages*)

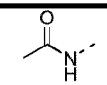
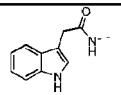
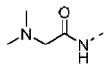
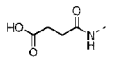
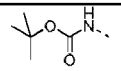
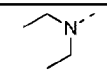
No	R50	R2	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.3-Ex.5: *cf. experimental description*							
Ex.6	OH		**Ex.52**	H	H_2, $Pd(OH)_2$-C*)	Crude product	70%
Ex.7			**Ex.25**	L.1.1	acetic anhydride (5 equiv.)	prep. HPLC, method 1	56%

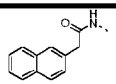
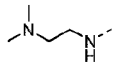
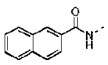
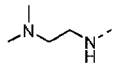
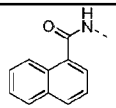
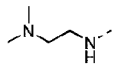
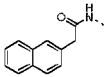
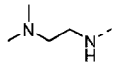
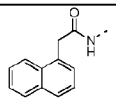
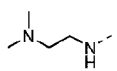
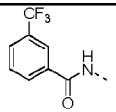
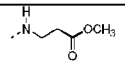
No	R50	R2	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.8			**Ex.28**	L.1.1	acetic anhydride (10 equiv.)	prep. HPLC, method 1	26% (TFA salt)
Ex.9			**Ex.53**	L.2	tryptamine (1.5 equiv.) HATU (1.5 equiv.) HOAt (1.5 equiv.) i-Pr_2Net (3 equiv.)	FC (CH_2Cl_2/MeOH)	62%
Ex.10			**Ex.31**	N	$LiOH \cdot H_2O$	prep. HPLC, method 1	57%
Ex.11			**Ex.28**	L.1.3	3-indoleacetic acid	FC (CH_2Cl_2/MeOH/aq. NH_3)	58%
Ex.12			**Ex.55**	L.1.3	3-indoleacetic acid	prep. HPLC, method 1	55%
Ex.13			**Ex.34**	N	$LiOH \cdot H_2O$	prep. HPLC, method 1	60%

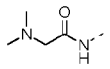
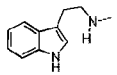
No	R50	R2	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.14			**Ex.25**	**)	N,N-dimethyl glycine	prep. HPLC, method 1	22% (TFA salt)
Ex.15			**Ex.28**	L.1.3	N,N-dimethyl glycine	prep. HPLC, method 1	42% (TFA salt)
Ex.16			**Ex.55**	L.1.3	N,N-dimethyl glycine	prep. HPLC, method 1	56% (TFA salt)
Ex.17			**Ex.33**	N	$LiOH \cdot H_2O$	prep. HPLC, method 1	77% (TFA salt)
Ex.18			**Ex.25**	L.1.1	succinic anhydride (1.05 equiv)	prep. HPLC, method 1	62%
Ex.19			**Ex.28**	L.1.1	succinic anhydride (1.05 equiv) pyridine (49 equiv.)	prep. HPLC, method 1	67% (TFA salt)
Ex.20			**Ex.32**	N	$LiOH \cdot H_2O$	prep. HPLC, method 1	72%
Ex.21			**Ex.23**	L.1.3	3-indoleacetic acid	prep. HPLC, method 1	32%

No	R50	R2	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.22			**Ex.23**	L.1.1	acetic anhydride (10 equiv) pyridine (120 equiv.)	prep. HPLC, method 1	53% (TFA salt)
Ex.23		NH_2	**Ex.29**	J	HCl-dioxane	prep. HPLC, method 1	52% (TFA salt)
Ex.24			**Ex.4**	L.2	methylamine-HCl (10 equiv.), HATU (1.5 equiv.) HOAt (1.5 equiv.) i-Pr_2NEt (13 equiv.)	FC (CH_2Cl_2/MeOH)	89%
Ex.25		NH_2	**Ex.24**	J	HCl-dioxane	crude product	84% (HCl salt)
Ex.26			**Ex.4**	L.2	β-alaninemethylester hydrochloride	FC (CH_2Cl_2/MeOH)	97%
Ex.27			**Ex.4**	L.2	N,N-dimethyl-ethylenediamine	FC (CH_2Cl_2/MeOH/aq. NH_3)	83%
Ex.28		NH_2	**Ex.27**	J	HCl-dioxane	(crude product)	90% (HCl salt)

No	R50	R2	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.29			**Ex.4**	L.2	N,N,N'-trimethyl-ethylenediamine	FC (CH_2Cl_2/MeOH/aq. NH_3)	74%
Ex.30			**Ex.4**	L.2	tryptamine	FC (CH_2Cl_2/MeOH)	81%
Ex.31			**Ex.51**	L.1.1	acetic anhydride (5 equiv)	prep. HPLC, method 1	72%
Ex.32			**Ex.51**	L.1.1	succinic anhydride (1.05 equiv)	prep. HPLC, method 1	68%
Ex.33			**Ex.51**	L.1.3	N,N-dimethyl glycine	prep. HPLC, method 1	64% (TFA salt)
Ex.34			**Ex.51**	L.1.3	3-indoleacetic acid	prep. HPLC, method 1	24%
Ex.35			**Ex.23**	L.1.1	succinic anhydride (1.05 equiv)	prep. HPLC, method 1	63% (TFA salt)
Ex.36			**Ex.23**	L.1.3	N,N-dimethyl glycine	prep. HPLC, method 1	40% (TFA salt)

No	R50	R2	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.37			**Ex.42**	L.1.1	acetic anhydride (5 equiv)	prep. HPLC, method 1	61%
Ex.38			**Ex.42**	L.1.3	3-indoleacetic acid	prep. HPLC, method 1	43%
Ex.39			**Ex.42**	L.1.3	N,N-dimethyl glycine	prep. HPLC, method 1	56% (TFA salt)
Ex.40			**Ex.42**	L.1.1	succinic anhydride (1.05 equiv)	prep. HPLC, method 1	37%
Ex.41			**Ex.4**	L.2	pyrrolidine	FC (CH_2Cl_2/MeOH)	76%
Ex.42		NH_2	**Ex.41**	J	HCl-dioxane	(crude product)	90% (HCl salt)
Ex.43			**Ex.42**	M	acetaldehyde	prep. HPLC, method 1	67% (TFA salt)
Ex.44			**Ex.25**	M	acetaldehyde	prep. HPLC, method 1	33% (TFA salt)

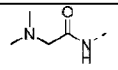
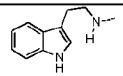
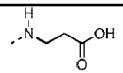
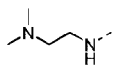
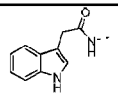
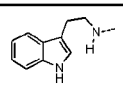
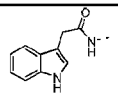
No	R50	R2	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.45			**Ex.25**	L.1.3	2-naphthylacetic acid	prep. HPLC, method 1	46%
Ex.46			**Ex.28**	L.1.1	2-naphthoyl chloride (3.6 equiv.)	FC (CH_2Cl_2/MeOH/aq. NH_3)	85%
Ex.47			**Ex.28**	L.1.2	1-naphthoic acid	FC (CH_2Cl_2/MeOH/aq. NH_3)	85%
Ex.48			**Ex.28**	L.1.2	2-naphthylacetic acid	FC (CH_2Cl_2/MeOH/aq. NH_3)	83%
Ex.49			**Ex.28**	L.1.2	1-naphthylacetic acid	FC (CH_2Cl_2/MeOH/aq. NH_3)	83%
Ex.50			**Ex.28**	L.1.1	3-(trifluoromethyl)-benzoyl chloride (4 equiv.)	FC (CH_2Cl_2/MeOH/aq. NH_3)	24%
Ex.51		NH_2	**Ex.26**	J	HCl-dioxane	crude product	93% (HCl salt)

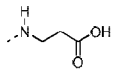
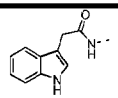
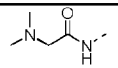
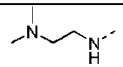
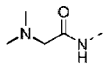
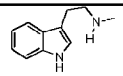
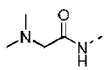
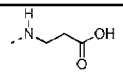
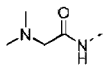
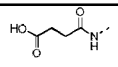
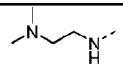
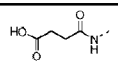
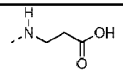
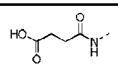
No	R50	R2	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.52	OCH_2Ph		**Ex.5**	L.1.3	N,N-dimethylglycine (1.7 equiv.) HATU (1.0 equiv.) HOAt (2.0 equiv.) i-Pr_2NEt (4.0 equiv.)	prep. HPLC, method 1	88% (TFA salt)
Ex.53	OCH_2Ph		**Ex.5**	L.1.1	Acetic anhydride (10 equiv.) pyridine/CH_2Cl_2 1:1	FC	70%
Ex.54	OH		**Ex.54**	H	H_2, $Pd(OH)_2$-C	crude product	92%
Ex.55		NH_2	**Ex.30**	J	HCl-dioxane	FC (CH_2Cl_2/MeOH/aq. NH_3)	42%

*) Prior to debenzylation, the starting material **Ex.52**·TFA was converted into the free base ($CHCl_3$, aq. Na_2CO_3 soln.)

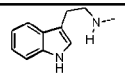
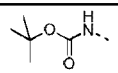
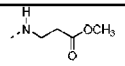
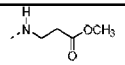
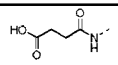
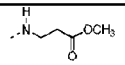
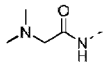
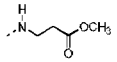
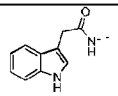
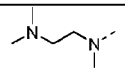
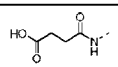
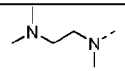
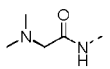
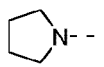
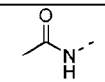
**)The amide coupling reaction was performed at room temperature with N,N-dimethyl glycine (2.2 equiv.) in CH_2Cl_2, in the presence of T3P (50% in EtOAc; 2.2 equiv.) and i-Pr_2NEt (3 equiv.).

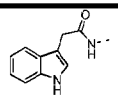
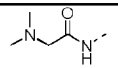
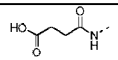
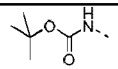
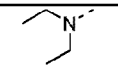
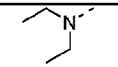
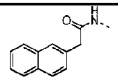
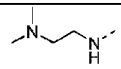
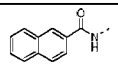
Table 21b: Examples of Core 03 (**Ex.3-Ex.55,** *continued on the following pages*)

No	R50	R2	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.3-Ex.5: *cf. experimental description*							
Ex.6	OH		C25H34FN5O7	535.2	1.05 (99)	536.3	Method 2
Ex.7			C24H32FN5O6	505.2	1.21 (87)	506.3	Method 2
Ex.9			C33H39FN6O6	634.3	2.12 (99)	635.4	Method 1a
Ex.10			C26H34FN5O8	563.2	1.20 (91)	564.2	Method 2
Ex.11			C35H44FN7O6	677.3	1.34 (93)	678.4	Method 2
Ex.12			C41H44FN7O6	749.3	1.73 (92)	750.4	Method 2

No	R50	R2	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.13			C34H39FN6O8	678.3	1.45 (87)	679.3	Method 2
Ex.14			C26H37FN6O6	548.3	1.08 (88)	549.3	Method 2
Ex.15			C29H44FN7O6	605.3	0.99 (96)	606.4	Method 2
Ex.16			C35H44FN7O6	677.3	1.41 (97)	678.4	Method 2
Ex.17			C28H39FN6O8	606.3	1.09 (94)	607.3	Method 2
Ex.18			C26H34FN5O8	563.2	1.20 (88)	564.3	Method 2
Ex.19			C29H41FN6O8	620.3	1.08 (100)	621.3	Method 2
Ex.20			C28H36FN5O10	621.2	1.18 (91)	622.2	Method 2

No	R50	R2	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.21			C36H46FN7O6	691.4	1.35 (88)	692.4	Method 2
Ex.22			C28H41FN6O6	576.3	1.12 (96)	577.4	Method 2
Ex.23		NH_2	C26H39FN6O5	534.3	0.96 (88)	535.4	Method 2
Ex.24			C27H38FN5O7	563.3	1.54 (93)	564.3	Method 2
Ex.25		NH_2	C22H30FN5O5	463.2	1.06 (91)	464.2	Method 2
Ex.26			C30H42FN5O9	635.3	1.61 (87)	636.4	Method 2
Ex.27			C30H45FN6O7	620.3	1.53 (92)	621.3	Method 4a
Ex.28		NH_2	C25H37FN6O5	520.3	0.93 (94)	521.3	Method 2
Ex.29			C31H47FN6O7	634.4	1.41 (96)	635.4	Method 2

No	R50	R2	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.30			C36H45FN6O7	692.3	1.79 (99)	693.4	Method 2
Ex.31			C27H36FN5O8	577.3	1.32 (90)	578.3	Method 2
Ex.32			C29H38FN5O10	635.3	1.30 (83)	636.2	Method 2
Ex.33			C29H41FN6O8	620.3	1.18 (100)	621.3	Method 2
Ex.34			C35H41FN6O8	692.3	1.56 (90)	693.3	Method 2
Ex.35			C30H43FN6O8	634.3	1.10 (94)	635.3	Method 2
Ex.36			C30H46FN7O6	619.4	1.00 (91)	620.3	Method 2
Ex.37			C27H36FN5O6	545.3	1.36 (93)	546.3	Method 2

No	R50	R2	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.38			C35H41FN6O6	660.3	1.60 (94)	661.3	Method 2
Ex.39			C29H41FN6O6	588.3	1.19 (94)	589.3	Method 2
Ex.40			C29H38FN5O8	603.3	1.33 (94)	604.3	Method 2
Ex.41			C30H42FN5O7	603.3	1.67 (90)	604.3	Method 2
Ex.42		NH_2	C25H34FN5O5	503.3	1.17 (92)	504.2	Method 2
Ex.43			C29H42FN5O5	559.3	1.26 (96)	560.3	Method 2
Ex.44			C26H38FN5O5	519.3	1.13 (97)	520.3	Method 2
Ex.45			C34H38FN5O6	631.3	1.65 (97)	632.2	Method 2
Ex.46			C36H43FN6O6	674.3	1.49 (97)	675.5	Method 2

No	R50	R2	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.47			C36H43FN6O6	674.3	1.43 (96)	675.5	Method 2
Ex.48			C37H45FN6O6	688.3	1.50 (95)	689.5	Method 2
Ex.49			C37H45FN6O6	688.3	1.48 (95)	689.5	Method 2
Ex.50			C33H40F4N6O6	692.3	1.49 (97)	693.5	Method 2
Ex.51		NH_2	C25H34FN5O7	535.2	1.05	536.3	Method 9c
Ex.52	OCH_2Ph		C32H40FN5O7	625.3	1.47	626.3	Method 9c
Ex.53	OCH_2Ph		C30H35FN4O7	582.3	1.65	582.9	Method 9c

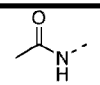
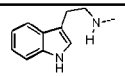
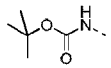
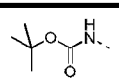
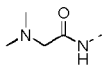
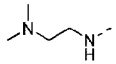
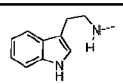
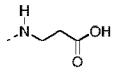
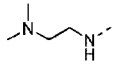
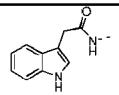
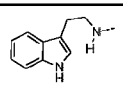
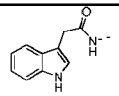
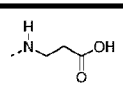
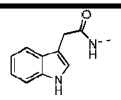
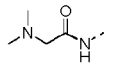
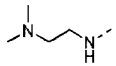
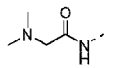
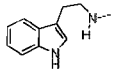
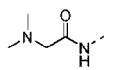
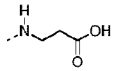
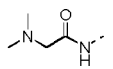
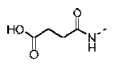
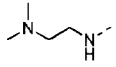
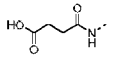
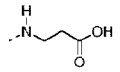
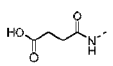
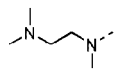
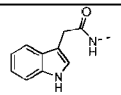
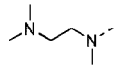
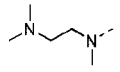
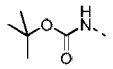
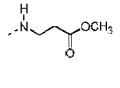
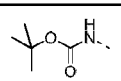
No	R50	R2	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.54	OH		C23H29FN4O7	492.2	1.04	493.1	Method 9c
Ex.55		NH_2	C31H37FN6O5	592.3	1.38	593.0	Method 9c

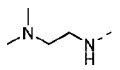
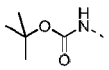
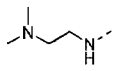
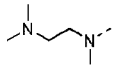
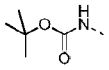
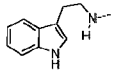
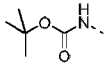
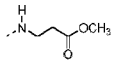
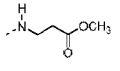
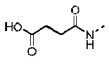
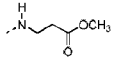
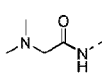
Table 21c: Examples of Core 03 (**Ex.3-Ex.55**, *continued on the following pages*)

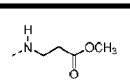
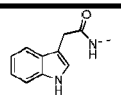
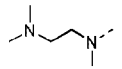
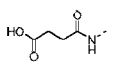
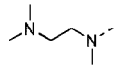
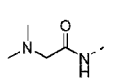
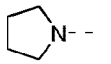
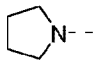
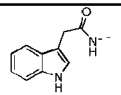
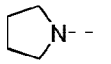
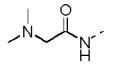
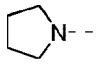
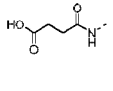
No	R50	R2	IUPAC name
Ex.3	OCH_2Ph		benzyl (2S,11S,19aS)-2-[(tert-butoxycarbonyl)amino]-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxylate
Ex.4	OH		(2S,11S,19aS)-2-[(tert-butoxycarbonyl)amino]-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxylic acid
Ex.5	OCH_2Ph	NH_2	benzyl (2S,11S,19aS)-2-amino-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxylate

No	R50	R2	IUPAC name
Ex.6	OH		(2S,11S,19aS)-2-{[2-(dimethylamino)acetyl]amino}-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxylic acid
Ex.7			(2S,11S,19aS)-2-(acetylamino)-15-fluoro-N,7,12-trimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.8			(2S,11S,19aS)-2-(acetylamino)-N-[2-(dimethylamino)ethyl]-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.9			(2S,11S,19aS)-2-(acetylamino)-15-fluoro-N-[2-(1H-indol-3-yl)ethyl]-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.10			3-({[(2S,11S,19aS)-2-(acetylamino)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-11-yl]carbonyl}amino)propanoic acid
Ex.11			(2S,11S,19aS)-N-[2-(dimethylamino)ethyl]-15-fluoro-2-{[2-(1H-indol-3-yl)acetyl]amino}-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.12			(2S,11S,19aS)-15-fluoro-2-{[2-(1H-indol-3-yl)acetyl]amino}-N-[2-(1H-indol-3-yl)ethyl]-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide

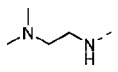
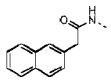
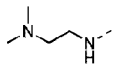
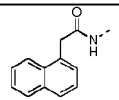
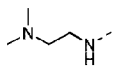
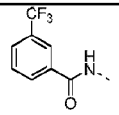
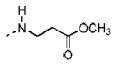
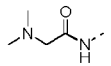
No	R50	R2	IUPAC name
Ex.13			3-{[((2S,11S,19aS)-15-fluoro-2-{[2-(1H-indol-3-yl)acetyl]amino}-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-11-yl)carbonyl]amino}propanoic acid
Ex.14			(2S,11S,19aS)-2-{[2-(dimethylamino)acetyl]amino}-15-fluoro-N,7,12-trimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.15			(2S,11S,19aS)-2-{[2-(dimethylamino)acetyl]amino}-N-[2-(dimethylamino)ethyl]-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.16			(2S,11S,19aS)-2-{[2-(dimethylamino)acetyl]amino}-15-fluoro-N-[2-(1H-indol-3-yl)ethyl]-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.17			3-{[((2S,11S,19aS)-2-{[2-(dimethylamino)acetyl]amino}-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-11-yl)carbonyl]amino}propanoic acid
Ex.18			4-({(2S,11S,19aS)-15-fluoro-7,12-dimethyl-11-[(methylamino)carbonyl]-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-2-yl}amino)-4-oxobutanoic acid
Ex.19			4-{[(2S,11S,19aS)-11-({[2-(dimethylamino)ethyl]amino}carbonyl)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]amino}-4-oxobutanoic acid

No	R50	R2	IUPAC name
Ex.20			4-[((2S,11S,19aS)-15-fluoro-11-{[(3-hydroxy-3-oxopropyl)amino]carbonyl}-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-2-yl)amino]-4-oxobutanoic acid
Ex.21			(2S,11S,19aS)-N-[2-(dimethylamino)ethyl]-15-fluoro-2-{[2-(1H-indol-3-yl)acetyl]amino}-N,7,12-trimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.22			(2S,11S,19aS)-2-(acetylamino)-N-[2-(dimethylamino)ethyl]-15-fluoro-N,7,12-trimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.23		NH_2	(2S,11S,19aS)-2-amino-N-[2-(dimethylamino)ethyl]-15-fluoro-N,7,12-trimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.24			tert-butyl N-{(2S,11S,19aS)-15-fluoro-7,12-dimethyl-11-[(methylamino)carbonyl]-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-2-yl}carbamate
Ex.25		NH_2	(2S,11S,19aS)-2-amino-15-fluoro-N,7,12-trimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.26			methyl 3-[({(2S,11S,19aS)-2-[(tert-butoxycarbonyl)amino]-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-11-yl}carbonyl)amino]propanoate

No	R50	R2	IUPAC name
Ex.27			tert-butyl N-[(2S,11S,19aS)-11-({[2-(dimethylamino)ethyl]amino}carbonyl)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]carbamate
Ex.28		NH_2	(2S,11S,19aS)-2-amino-N-[2-(dimethylamino)ethyl]-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.29			tert-butyl N-((2S,11S,19aS)-11-{[[2-(dimethylamino)ethyl](methyl)amino]carbonyl}-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-2-yl)carbamate
Ex.30			tert-butyl N-[(2S,11S,19aS)-15-fluoro-11-({[2-(1H-indol-3-yl)ethyl]amino}carbonyl)-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]carbamate
Ex.31			methyl 3-({[(2S,11S,19aS)-2-(acetylamino)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-11-yl]carbonyl}amino)propanoate
Ex.32			4-[((2S,11S,19aS)-15-fluoro-11-{[(3-methoxy-3-oxopropyl)amino]carbonyl}-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-2-yl)amino]-4-oxobutanoic acid
Ex.33			methyl 3-{[((2S,11S,19aS)-2-{[2-(dimethylamino)acetyl]amino}-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-11-yl)carbonyl]amino}propanoate

No	R50	R2	IUPAC name
Ex.34			methyl 3-{[((2S,11S,19aS)-15-fluoro-2-{[2-(1H-indol-3-yl)acetyl]amino}-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-11-yl)carbonyl]amino}propanoate
Ex.35			4-[((2S,11S,19aS)-11-{[[2-(dimethylamino)ethyl](methyl)amino]carbonyl}-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-2-yl)amino]-4-oxobutanoic acid
Ex.36			(2S,11S,19aS)-2-{[2-(dimethylamino)acetyl]amino}-N-[2-(dimethylamino)ethyl]-15-fluoro-N,7,12-trimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.37			N-[(2S,11S,19aS)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]acetamide
Ex.38			N-[(2S,11S,19aS)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]-2-(1H-indol-3-yl)acetamide
Ex.39			N-[(2S,11S,19aS)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]-2-(dimethylamino)acetamide
Ex.40			4-{[(2S,11S,19aS)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]amino}-4-oxobutanoic acid

No	R50	R2	IUPAC name
Ex.41			tert-butyl N-[(2S,11S,19aS)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]carbamate
Ex.42		NH_2	(2S,11S,19aS)-2-amino-15-fluoro-7,12-dimethyl-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,9,10,11,12,19,19a-decahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-5,8,13-trione
Ex.43			(2S,11S,19aS)-2-(diethylamino)-15-fluoro-7,12-dimethyl-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,9,10,11,12,19,19a-decahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-5,8,13-trione
Ex.44			(2S,11S,19aS)-2-(diethylamino)-15-fluoro-N,7,12-trimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.45			(2S,11S,19aS)-15-fluoro-N,7,12-trimethyl-2-{[2-(2-naphthyl)acetyl]amino}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.46			(2S,11S,19aS)-N-[2-(dimethylamino)ethyl]-15-fluoro-7,12-dimethyl-2-(2-naphthoylamino)-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.47			(2S,11S,19aS)-N-[2-(dimethylamino)ethyl]-15-fluoro-7,12-dimethyl-2-(1-naphthoylamino)-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide

No	R50	R2	IUPAC name
Ex.48			(2S,11S,19aS)-N-[2-(dimethylamino)ethyl]-15-fluoro-7,12-dimethyl-2-{[2-(2-naphthyl)acetyl]amino}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.49			(2S,11S,19aS)-N-[2-(dimethylamino)ethyl]-15-fluoro-7,12-dimethyl-2-{[2-(1-naphthyl)acetyl]amino}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.50			(2S,11S,19aS)-N-[2-(dimethylamino)ethyl]-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2-{[3-(trifluoromethyl)benzoyl]amino}-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.51		NH_2	methyl 3-({[(2S,11S,19aS)-2-amino-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-11-yl]carbonyl}amino)propanoate
Ex.52	OCH_2Ph		benzyl (2S,11S,19aS)-2-{[2-(dimethylamino)acetyl]amino}-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxylate
Ex.53	OCH_2Ph		benzyl (2S,11S,19aS)-2-(acetylamino)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxylate
Ex.54	OH		(2S,11S,19aS)-2-(acetylamino)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxylic acid

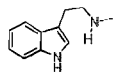
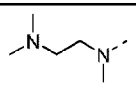
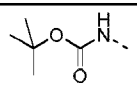
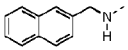
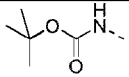
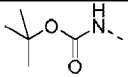
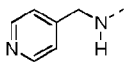
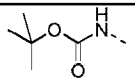
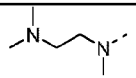
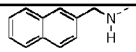
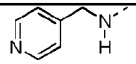
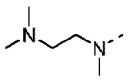
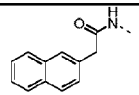
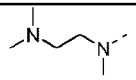
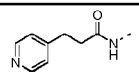
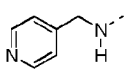
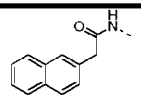
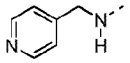
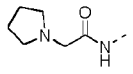
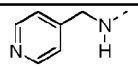
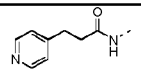
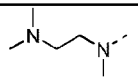
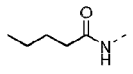
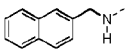
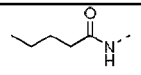
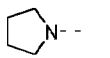
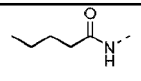
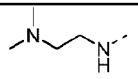
No	R50	R2	IUPAC name
Ex.55		NH_2	(2S,11S,19aS)-2-amino-15-fluoro-N-[2-(1H-indol-3-yl)ethyl]-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide

Table 22a: Examples of Core 04 (**Ex.56-Ex.84,** *continued on the following pages*)

No	R50	R2	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.56-Ex.57: *cf. experimental description*							
Ex.58			**Ex.57**	L.2	N,N,N'-trimetylethylene-diamine	FC (CH_2Cl_2/MeOH/aq. NH_3)	86%
Ex.59			**Ex.57**	L.2	2-naphthylmethylamine	FC (CH_2Cl_2/MeOH)	91%

No	R50	R2	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.60			**Ex.57**	L.2	pyrrolidine	FC (CH_2Cl_2/MeOH)	79%
Ex.61			**Ex.57**	L.2	4-(aminomethyl)pyridine	FC (CH_2Cl_2/MeOH)	81%
Ex.62		NH_2	**Ex.58**	J	HCl-dioxane	crude product	98% (HCl salt)
Ex.63		NH_2	**Ex.59**	J	HCl-dioxane	crude product	76% (HCl salt)
Ex.64		NH_2	**Ex.60**	J	HCl-dioxane	crude product	94% (HCl salt)
Ex.65		NH_2	**Ex.61**	J	HCl-dioxane	crude product	91% (HCl salt)
Ex.66			**Ex.62**	L.1.3	2-naphthylacetic acid	prep. HPLC, method 1	67% (TFA salt)
Ex.67			**Ex.62**	L.1.2	3-(pyridine-4-yl)propanoic acid	prep. HPLC, method 2	56%

No	R50	R2	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.68			Ex.62	L.1.2	1-naphthylacetic acid (1.5 equiv.)	prep. HPLC, method 1	24% (TFA salt)
Ex.69			Ex.63	L.1.1	acetic anhydride (5 equiv.)	prep. HPLC, method 1	75%
Ex.70			Ex.63	L.1.3	1-pyrrolidinacetic acid	prep. HPLC, method 1	62% (TFA salt)
Ex.71			Ex.63	L.1.2	3-(pyridine-4-yl)propanoic acid	prep. HPLC, method 1	22% (TFA salt)
Ex.72			Ex.64	L.1.3	2-naphthylacetic acid	prep. HPLC, method 2	51%
Ex.73			Ex.64	L.1.2	1-pyrrolidinacetic acid (1.7 equiv.)	prep. HPLC, method 1	39% (TFA salt)
Ex.74			Ex.64	L.1.2	3-(pyridine-4-yl)propanoic acid	prep. HPLC, method 2	29%

No	R50	R2	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.75			**Ex.65**	L.1.3	2-naphthylacetic acid	prep. HPLC, method 1	37% (TFA salt)
Ex.76			**Ex.65**	L.1.2	1-pyrrolidinacetic acid (1.7 equiv.)	prep. HPLC, method 2	45%
Ex.77			**Ex.65**	L.1.2	3-(pyridine-4-yl)propanoic acid	prep. HPLC, method 2	45%
Ex.78			**Ex.62**	L.1.1	valeroyl chloride (1.6 equiv.)	prep. HPLC, method 1	56%
Ex.79			**Ex.63**	L.1.1	valeroyl chloride (1.6 equiv.)	prep. HPLC, method 1	77%
Ex.80			**Ex.64**	L.1.1	valeroyl chloride (1.3 equiv.)	prep. HPLC, method 1	46%
Ex.81		NH_2	**Ex.84**	J	HCl-dioxane	crude product	99% (HCl salt)

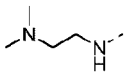
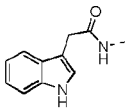
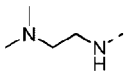
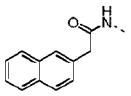
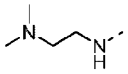
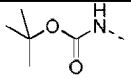
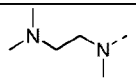
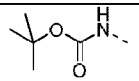
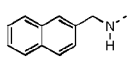
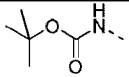
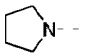
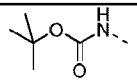
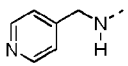
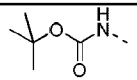
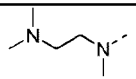
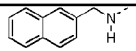
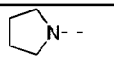
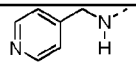
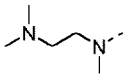
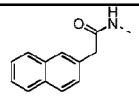
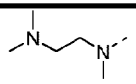
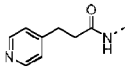
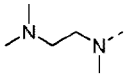
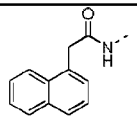
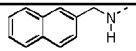
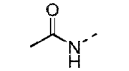
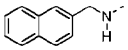
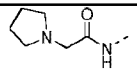
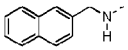
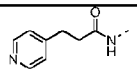
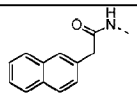
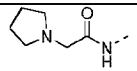
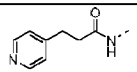
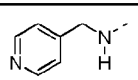
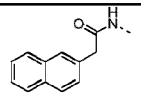
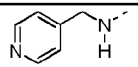
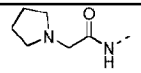
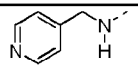
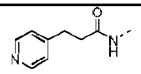
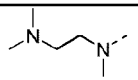
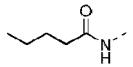
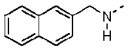
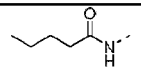
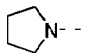
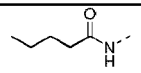
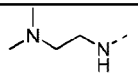
No	R50	R2	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.82			**Ex.81**	L.1.3	3-indoleacetic acid (1.5 equiv.) HATU (1.5 equiv.) HOAt (1.5 equiv.) i-Pr_2NEt (5 equiv.)	prep. HPLC, method 1, then FC (CH_2Cl_2/MeOH/aq. NH_3)	15%
Ex.83			**Ex.81**	L.1.3	2-naphthylacetic acid (1.2 equiv.)	FC (CH_2Cl_2/MeOH/aq. NH_3), then prep. HPLC, method 1	58%
Ex.84			**Ex.57**	L.2	2-dimethylaminoethyl-amine	FC (CH_2Cl_2/MeOH)	89%

Table 22b: Examples of Core 04 (**Ex.56-Ex.84,** *continued on the following pages*)

No	R50	R2	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.56-Ex.57: *cf. experimental description*							
Ex.58			C31H47FN6O7	634.4	1.44 (91)	635.5	Method 2

No	R50	R2	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.59			C37H44FN5O7	689.3	1.89 (87)	690.5	Method 2
Ex.60			C30H42FN5O7	603.3	1.67 (84)	604.4	Method 2
Ex.61			C32H41FN6O7	640.3	1.42 (92)	641.4	Method 2
Ex.62		NH_2	C26H39FN6O5	534.3	0.97 (91)	535.4	Method 2
Ex.63		NH_2	C32H36FN5O5	589.3	1.53 (95)	590.4	Method 2
Ex.64		NH_2	C25H34FN5O5	503.3	1.23 (82)	504.3	Method 2
Ex.65		NH_2	C27H33FN6O5	540.3	0.97 (97)	541.4	Method 2
Ex.66			C38H47FN6O6	702.4	1.51 (97)	703.5	Method 2

No	R50	R2	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.67			C34H46FN7O6	667.4	1.08 (94)	668.5	Method 2
Ex.68			C38H47FN6O6	702.4	1.51 (88)	703.5	Method 2
Ex.69			C34H38FN5O6	631.3	1.66 (90)	632.3	Method 2
Ex.70			C38H45FN6O6	700.3	1.56 (95)	701.5	Method 2
Ex.71			C40H43FN6O6	722.3	1.55 (93)	723.5	Method 2
Ex.72			C37H42FN5O6	671.3	1.73 (87)	672.4	Method 2
Ex.73			C31H43FN6O6	614.3	1.28 (90)	615.4	Method 2
Ex.74			C33H41FN6O6	636.3	1.29 (91)	637.4	Method 2

No	R50	R2	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.75			C39H41FN6O6	708.3	1.50 (92)	709.4	Method 2
Ex.76			C33H42FN7O6	651.3	1.07 (91)	652.4	Method 2
Ex.77			C35H40FN7O6	673.3	1.07 (90)	674.5	Method 2
Ex.78			C31H47FN6O6	618.4	1.33(98)	619.4	Method 2
Ex.79			C37H44FN5O6	673.3	1.81 (91)	674.4	Method 2
Ex.80			C30H42FN5O6	587.3	1.56 (93)	588.4	Method 2
Ex.81		NH_2	C25H37FN6O5	520.3	1.10 (88)	521.4	Method 2

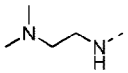
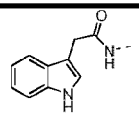
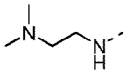
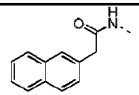
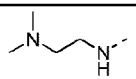
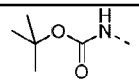
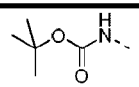
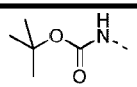
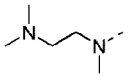
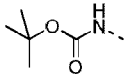
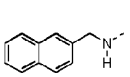
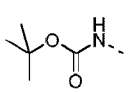
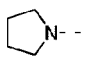
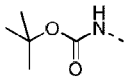
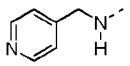
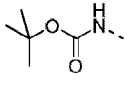
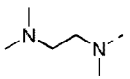
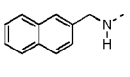
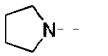
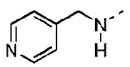
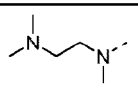
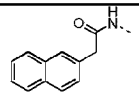
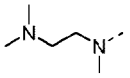
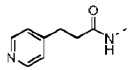
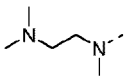
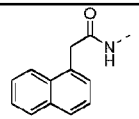
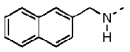
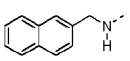
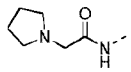
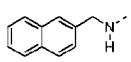
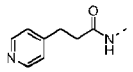
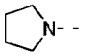
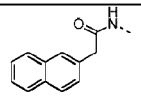
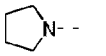
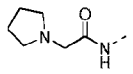
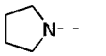
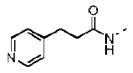
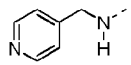
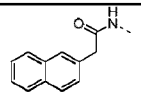
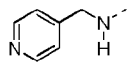
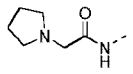
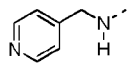
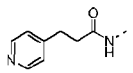
No	R50	R2	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.82			C35H44FN7O6	677.3	1.36 (93)	678.5	Method 2
Ex.83			C37H45FN6O6	688.3	1.49 (93)	689.5	Method 2
Ex.84			C30H45FN6O7	620.3	1.38 (87)	621.5	Method 2

Table 22c: Examples of Core 04 (**Ex.56-Ex.84,** *continued on the following pages*)

No	R50	R2	IUPAC name
Ex.56	OCH_2Ph		benzyl (2R,11S,19aS)-2-[(tert-butoxycarbonyl)amino]-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxylate

No	R50	R2	IUPAC name
Ex.57	OH		(2R,11S,19aS)-2-[(tert-butoxycarbonyl)amino]-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxylic acid
Ex.58			tert-butyl N-((2R,11S,19aS)-11-{[[2-(dimethylamino)ethyl](methyl)amino]carbonyl}-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-2-yl)carbamate
Ex.59			tert-butyl N-((2R,11S,19aS)-15-fluoro-7,12-dimethyl-11-{[(2-naphthylmethyl)amino]carbonyl}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-2-yl)carbamate
Ex.60			tert-butyl N-[(2R,11S,19aS)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]carbamate
Ex.61			tert-butyl N-((2R,11S,19aS)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-11-{[(4-pyridinylmethyl)amino]carbonyl}-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-2-yl)carbamate
Ex.62		NH_2	(2R,11S,19aS)-2-amino-N-[2-(dimethylamino)ethyl]-15-fluoro-N,7,12-trimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.63		NH_2	(2R,11S,19aS)-2-amino-15-fluoro-7,12-dimethyl-N-(2-naphthylmethyl)-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide

No	R50	R2	IUPAC name
Ex.64		NH_2	(2R,11S,19aS)-2-amino-15-fluoro-7,12-dimethyl-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,9,10,11,12,19,19a-decahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-5,8,13-trione
Ex.65		NH_2	(2R,11S,19aS)-2-amino-15-fluoro-7,12-dimethyl-5,8,13-trioxo-N-(4-pyridinylmethyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.66			(2R,11S,19aS)-N-[2-(dimethylamino)ethyl]-15-fluoro-N,7,12-trimethyl-2-{[2-(2-naphthyl)acetyl]amino}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.67			(2R,11S,19aS)-N-[2-(dimethylamino)ethyl]-15-fluoro-N,7,12-trimethyl-5,8,13-trioxo-2-{[3-(4-pyridinyl)propanoyl]amino}-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.68			(2R,11S,19aS)-N-[2-(dimethylamino)ethyl]-15-fluoro-N,7,12-trimethyl-2-{[2-(1-naphthyl)acetyl]amino}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.69			(2R,11S,19aS)-2-(acetylamino)-15-fluoro-7,12-dimethyl-N-(2-naphthylmethyl)-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.70			(2R,11S,19aS)-15-fluoro-7,12-dimethyl-N-(2-naphthylmethyl)-5,8,13-trioxo-2-{[2-(1-pyrrolidinyl)acetyl]amino}-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide

No	R50	R2	IUPAC name
Ex.71			(2R,11S,19aS)-15-fluoro-7,12-dimethyl-N-(2-naphthylmethyl)-5,8,13-trioxo-2-{[3-(4-pyridinyl)propanoyl]amino}-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.72			N-[(2R,11S,19aS)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]-2-(2-naphthyl)acetamide
Ex.73			N-[(2R,11S,19aS)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]-2-(1-pyrrolidinyl)acetamide
Ex.74			N-[(2R,11S,19aS)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]-3-(4-pyridinyl)propanamide
Ex.75			(2R,11S,19aS)-15-fluoro-7,12-dimethyl-2-{[2-(2-naphthyl)acetyl]amino}-5,8,13-trioxo-N-(4-pyridinylmethyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.76			(2R,11S,19aS)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-N-(4-pyridinylmethyl)-2-{[2-(1-pyrrolidinyl)acetyl]amino}-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.77			(2R,11S,19aS)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-N-(4-pyridinylmethyl)-2-{[3-(4-pyridinyl)propanoyl]amino}-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide

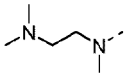
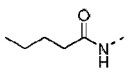
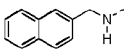
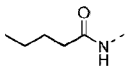
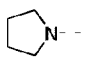
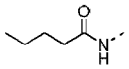
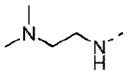
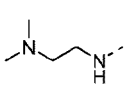
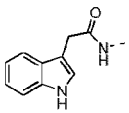
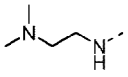
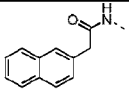
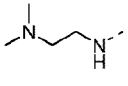
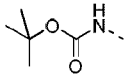
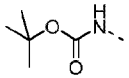
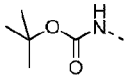
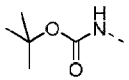
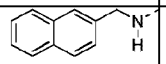
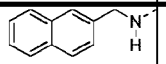
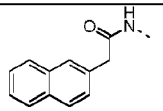
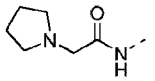
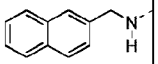
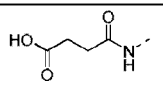
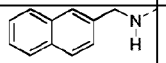
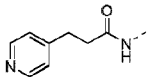
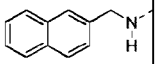
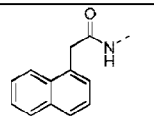
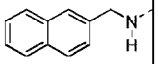
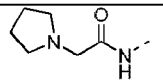
No	R50	R2	IUPAC name
Ex.78			(2R,11S,19aS)-N-[2-(dimethylamino)ethyl]-15-fluoro-N,7,12-trimethyl-5,8,13-trioxo-2-(pentanoylamino)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.79			(2R,11S,19aS)-15-fluoro-7,12-dimethyl-N-(2-naphthylmethyl)-5,8,13-trioxo-2-(pentanoylamino)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.80			N-[(2R,11S,19aS)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]pentanamide
Ex.81		NH_2	(2R,11S,19aS)-2-amino-N-[2-(dimethylamino)ethyl]-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.82			(2R,11S,19aS)-N-[2-(dimethylamino)ethyl]-15-fluoro-2-{[2-(1H-indol-3-yl)acetyl]amino}-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.83			(2R,11S,19aS)-N-[2-(dimethylamino)ethyl]-15-fluoro-7,12-dimethyl-2-{[2-(2-naphthyl)acetyl]amino}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.84			tert-butyl N-[(2R,11S,19aS)-11-({[2-(dimethylamino)ethyl]amino}carbonyl)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]carbamate

Table 23a: Examples of Core 05 (**Ex.85-Ex.103**, continued on the following pages)

No	R2	R50	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.85-Ex.86: *cf. experimental description*							
Ex.87			**Ex.86**	L.2	methylamine-hydrochloride (10 equiv.) HATU (1.5 equiv.) HOAt (1.5 equiv.) i-Pr_2NEt (13 equiv.)	FC (CH_2Cl_2/MeOH)	76%
Ex.88			**Ex.86**	L.2	pyrrolidine	FC (CH_2Cl_2/MeOH) then prep. HPLC, method 2	64%
Ex.89			**Ex.86**	L.2	2-naphthylmethylamine	FC (EtOAc/MeOH)	93%
Ex.90	NH_2		**Ex.87**	J	HCl-dioxane	crude product	86% (HCl salt)

No	R2	R50	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.91	NH_2		**Ex.89**	J	HCl-dioxane	crude product	98% (HCl salt)
Ex.92	NH_2		**Ex.88**	J	HCl-dioxane	crude product	94% (HCl salt)
Ex.93			**Ex.90**	L.1.2	2-naphthylacetic acid	prep. HPLC, method 3	66%
Ex.94			**Ex.91**	L.1.2	1-pyrrolidineacetic acid (1.7 equiv.)	prep. HPLC, method 1	46% (TFA salt)
Ex.95			**Ex.91**	L.1.1	succinic anhydride (1.05 equiv.)	prep. HPLC, method 2	47% ($NH4^+$ salt)
Ex.96			**Ex.91**	L.1.2	3-(pyridine-4-yl)propanoic acid (3.7 equiv.)	FC (CH_2Cl_2/MeOH)	74%
Ex.97			**Ex.91**	L.1.2	1-naphthylacetic acid (1.4 equiv.)	prep. HPLC, method 3	72%
Ex.98			**Ex.92**	L.1.2	1-pyrrolidineacetic acid	prep. HPLC, method 1	68% (TFA salt)

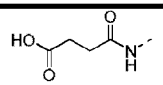
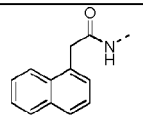
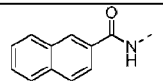
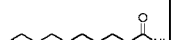
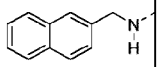
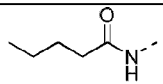
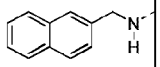
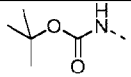
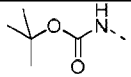
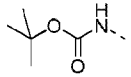
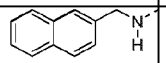
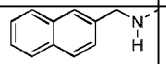
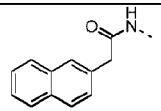
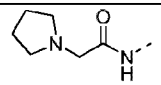
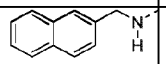
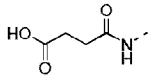
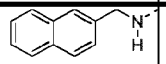
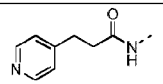
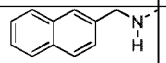
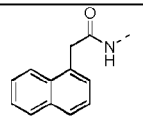
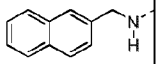
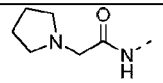
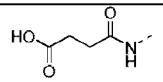
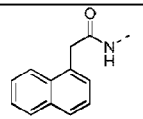
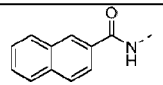
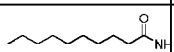
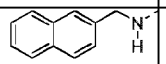
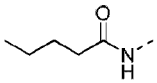
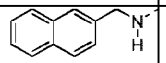
No	R2	R50	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.99			**Ex.92**	L.1.1	succinic anhydride (1.05 equiv.)	prep. HPLC, method 2	40% ($NH4^+$ salt)
Ex.100			**Ex.92**	L.1.2	1-naphthylacetic acid	FC (EtOAc/MeOH)	83%
Ex.101			**Ex.92**	L.1.1	2-naphthoyl chloride (1.6 equiv.)	FC (EtOAc/MeOH)	84%
Ex.102			**Ex.91**	L.1.1	decanoyl chloride (4.1 equiv.) pyridine (15 equiv.)	prep. HPLC, method 3	64%
Ex.103			**Ex.91**	L.1.1	valeroyl chloride (2.0 equiv.)	prep. HPLC, method 3	87%

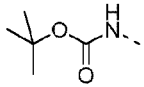
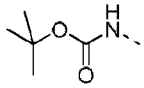
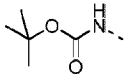
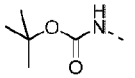
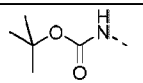
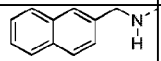
Table 23b: Examples of Core 05 (**Ex.85-Ex.103**, *continued on the following pages*)

No	R2	R50	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.85-Ex.86: *cf. experimental description*							
Ex.87			C27H38FN5O7	563.3	1.52 (78)	564.4	Method 2
Ex.88			C30H42FN5O7	603.3	1.59 (64), 1.63 (27)	604.4/604.4	Method 2
Ex.89			C37H44FN5O7	689.3	1.89 (97)	690.5	Method 2
Ex.90	NH_2		C22H30FN5O5	463.2	1.02 (95)	464.3	Method 2
Ex.91	NH_2		C32H36FN5O5	589.3	1.51 (98)	590.4	Method 2
Ex.92	NH_2		C25H34FN5O5	503.3	1.20 (97)	504.3	Method 2
Ex.93			C34H38FN5O6	631.3	1.65 (98)	632.3	Method 2
Ex.94			C38H45FN6O6	700.3	1.55 (100)	701.5	Method 2

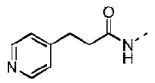
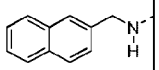
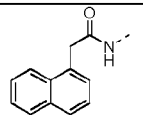
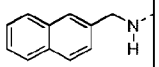
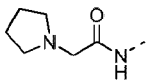
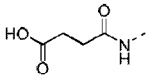
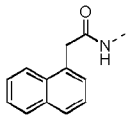
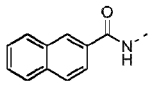
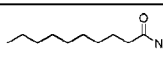
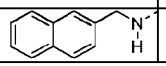
No	R2	R50	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.95			C36H40FN5O8	689.3	1.65 (98)	690.5	Method 2
Ex.96			C40H43FN6O6	722.3	1.51 (96)	723.5	Method 2
Ex.97			C44H44FN5O6	757.3	1.96 (92)	758.5	Method 2
Ex.98			C31H43FN6O6	614.3	1.25 (98)	615.3	Method 2
Ex.99			C29H38FN5O8	603.3	1.34 (100)	604.4	Method 2
Ex.100			C37H42FN5O6	671.3	1.73 (85)	672.4	Method 3
Ex.101			C36H40FN5O6	657.3	1.73 (98)	658.4	Method 2
Ex.102			C42H54FN5O6	743.4	2.16 (95)	744.6	Method 3
Ex.103			C37H44FN5O6	673.3	1.83 (96)	674.5	Method 2

No	R2	R50	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method

Table 23c: Examples of Core 05 (**Ex.85-Ex.103**, *continued on the following pages*)

No	R2	R50	IUPAC name
Ex.85		OCH_2Ph	benzyl (2S,11R,19aS)-2-[(tert-butoxycarbonyl)amino]-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxylate
Ex.86		OH	(2S,11R,19aS)-2-[(tert-butoxycarbonyl)amino]-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxylic acid
Ex.87			tert-butyl N-{(2S,11R,19aS)-15-fluoro-7,12-dimethyl-11-[(methylamino)carbonyl]-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-2-yl}carbamate
Ex.88			tert-butyl N-[(2S,11R,19aS)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]carbamate
Ex.89			tert-butyl N-((2S,11R,19aS)-15-fluoro-7,12-dimethyl-11-{[(2-naphthylmethyl)amino]carbonyl}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-

No	R2	R50	IUPAC name
			dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-2-yl)carbamate
Ex.90	NH_2		(2S,11R,19aS)-2-amino-15-fluoro-N,7,12-trimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.91	NH_2		(2S,11R,19aS)-2-amino-15-fluoro-7,12-dimethyl-N-(2-naphthylmethyl)-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.92	NH_2		(2S,11R,19aS)-2-amino-15-fluoro-7,12-dimethyl-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,9,10,11,12,19,19a-decahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-5,8,13-trione
Ex.93			(2S,11R,19aS)-15-fluoro-N,7,12-trimethyl-2-{[2-(2-naphthyl)acetyl]amino}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.94			(2S,11R,19aS)-15-fluoro-7,12-dimethyl-N-(2-naphthylmethyl)-5,8,13-trioxo-2-{[2-(1-pyrrolidinyl)acetyl]amino}-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.95			4-[({(2S,11R,19aS)-15-fluoro-7,12-dimethyl-11-{[(2-naphthylmethyl)amino]carbonyl}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-2-yl)amino]-4-oxobutanoic acid

No	R2	R50	IUPAC name
Ex.96			(2S,11R,19aS)-15-fluoro-7,12-dimethyl-N-(2-naphthylmethyl)-5,8,13-trioxo-2-{[3-(4-pyridinyl)propanoyl]amino}-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.97			(2S,11R,19aS)-15-fluoro-7,12-dimethyl-2-{[2-(1-naphthyl)acetyl]amino}-N-(2-naphthylmethyl)-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.98			N-[(2S,11R,19aS)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]-2-(1-pyrrolidinyl)acetamide
Ex.99			4-{[(2S,11R,19aS)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]amino}-4-oxobutanoic acid
Ex.100			N-[(2S,11R,19aS)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]-2-(1-naphthyl)acetamide
Ex.101			N-[(2S,11R,19aS)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]-2-naphthamide
Ex.102			(2S,11S,19aS)-2-(decanoylamino)-15-fluoro-7,12-dimethyl-N-(2-naphthylmethyl)-

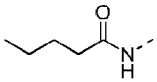
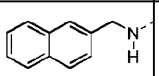
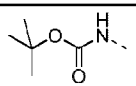
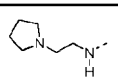
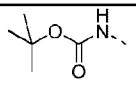
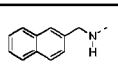
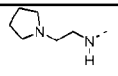
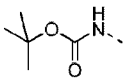
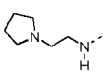
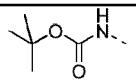
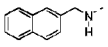
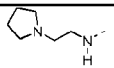
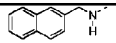
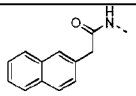
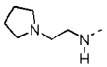
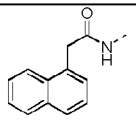
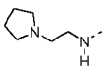
No	R2	R50	IUPAC name
			5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.103			(2S,11S,19aS)-15-fluoro-7,12-dimethyl-N-(2-naphthylmethyl)-5,8,13-trioxo-2-(pentanoylamino)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide

Table 24a: Examples of Core 06 (**Ex.104-Ex.114,** *continued on the following pages*)

No	R2	R50	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.104-Ex.105: *cf. experimental description*							
Ex.106			**Ex.105**	L.2	N-(2-aminoethyl)pyrolidine	FC (CH_2Cl_2/MeOH/aq.NH_3)	78%
Ex.107			**Ex.105**	L.2	2-naphthylmethylamine	FC (CH_2Cl_2/MeOH)	96%
Ex.108	NH_2		**Ex.106**	J	HCl-dioxane	crude product	99% (HCl salt)

No	R2	R50	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.109	NH_2		Ex.107	J	HCl-dioxane	crude product	95% (HCl salt)
Ex.110			Ex.108	L.1.2	2-naphthylacetic acid	prep. HPLC, method 1 and workup ($CHCl_3$/aq. $NaHCO_3$ soln.)	51%
Ex.111			Ex.108	L.1.2	1-naphthylacetic acid	prep. HPLC, method 1	55% (TFA salt)
Ex.112			Ex.108	M	acetaldehyde	FC (CH_2Cl_2/MeOH/aq.NH_3)	48%
Ex.113			Ex.109	L.1.2	1-naphthylacetic acid (3.7 equiv.)	prep. HPLC, method 3	77%
Ex.114			Ex.109	L.1.1	valeroyl chloride (2 equiv.)	prep. HPLC, method 3	84%

Table 24b: Examples of Core 06 (**Ex.104-Ex.114,** *continued on the following pages*)

No	R2	R50	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.104-Ex.105: *cf. experimental description*							
Ex.106			C32H47FN6O7	646.4	1.36 (43), 1.42(27), 1.44 (27)	647.5/647.5 647.5	Method 2
Ex.107			C37H44FN5O7	689.3	1.94 (42)/1.98 (50)	690.5/690.5	Method 2
Ex.108	NH_2		C27H39FN6O5	546.3	1.37 (50), 1.44 (38)	547.5/547.5	Method 3
Ex.109	NH_2		C32H36FN5O5	589.3	1.55 (96)	590.3	Method 2
Ex.110			C39H47FN6O6	714.4	1.62 (44), 1.66 (52)	715.4/715.4	Method 2
Ex.111			C39H47FN6O6	714.4	1.51 (46),1.56 (54)	715.5/715.5	Method 2

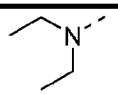
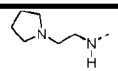
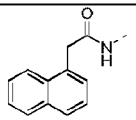
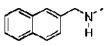
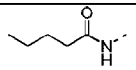
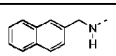
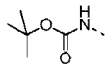
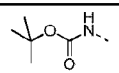
No	R2	R50	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.112			C31H47FN6O5	602.4	1.14 (57), 1.18 (39)	603.4/603.5	Method 2
Ex.113			C44H44FN5O6	757.3	2.15 (52), 2.19 (41)	758.4/758.4	Method 4a
Ex.114			C37H44FN5O6	673.3	2.00 (58), 2.05 (41)	674.4/674.4	Method 4a

Table 24c: Examples of Core 06 (**Ex.104-Ex.114,** *continued on the following pages*)

No	R2	R50	IUPAC name
Ex.104		OCH_2Ph	benzyl (2R,11R,19aS)-2-[(tert-butoxycarbonyl)amino]-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxylate
Ex.105		OH	(2R,11R,19aS)-2-[(tert-butoxycarbonyl)amino]-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-

No	R2	R50	IUPAC name
			c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxylic acid
Ex.106			tert-butyl N-[(2R,11R,19aS)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-11-({[2-(1-pyrrolidinyl)ethyl]amino}carbonyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]carbamate
Ex.107			tert-butyl N-((2R,11R,19aS)-15-fluoro-7,12-dimethyl-11-{[(2-naphthylmethyl)amino]carbonyl}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-2-yl)carbamate
Ex.108	NH_2		(2R,11R,19aS)-2-amino-15-fluoro-7,12-dimethyl-5,8,13-trioxo-N-[2-(1-pyrrolidinyl)ethyl]-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.109	NH_2		(2R,11R,19aS)-2-amino-15-fluoro-7,12-dimethyl-N-(2-naphthylmethyl)-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.110			(2R,11R,19aS)-15-fluoro-7,12-dimethyl-2-{[2-(2-naphthyl)acetyl]amino}-5,8,13-trioxo-N-[2-(1-pyrrolidinyl)ethyl]-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.111			(2R,11R,19aS)-15-fluoro-7,12-dimethyl-2-{[2-(1-naphthyl)acetyl]amino}-5,8,13-trioxo-N-[2-(1-pyrrolidinyl)ethyl]-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide

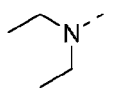
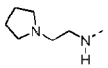
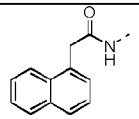
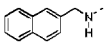
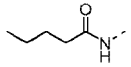
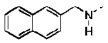
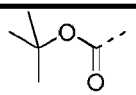
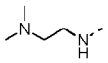
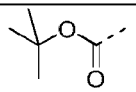
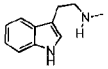
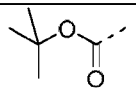
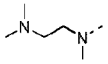
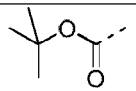
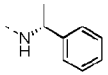
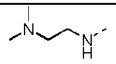
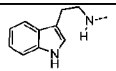
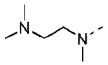
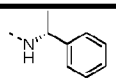
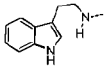
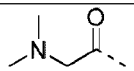
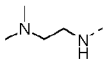
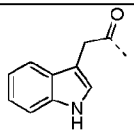
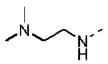
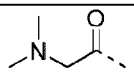
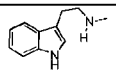
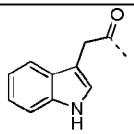
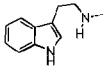
No	R2	R50	IUPAC name
Ex.112			(2R,11R,19aS)-2-(diethylamino)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-N-[2-(1-pyrrolidinyl)ethyl]-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.113			(2R,11R,19aS)-15-fluoro-7,12-dimethyl-2-{[2-(1-naphthyl)acetyl]amino}-N-(2-naphthylmethyl)-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.114			(2R,11R,19aS)-15-fluoro-7,12-dimethyl-N-(2-naphthylmethyl)-5,8,13-trioxo-2-(pentanoylamino)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide

Table 25a: Examples of Core 07 (**Ex.115-Ex.131**, *continued on the following pages*)

No	R11	R50	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.115-Ex.116: *cf. experimental description*							

No	R11	R50	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.117			**Ex.116**	L.2	N,N-dimethylethylendiamine	FC (CH_2Cl_2/MeOH/aq. NH_3)	73%
Ex.118			**Ex.116**	L.2	tryptamine	FC (CH_2Cl_2/MeOH)	98%
Ex.119			**Ex.116**	L.2	N,N,N'-trimethylethylenediamine	FC (CH_2Cl_2/MeOH)	79%
Ex.120			**Ex.116**	L.2	D-(+)-α-methylbenzylamine	prep. HPLC, method 1	70%
Ex.121	H		**Ex.117**	J	HCl-dioxane	crude product	98% (HCl salt)
Ex.122	H		**Ex.118**	J	HCl-dioxane	crude product	98% (HCl salt)
Ex.123	H		**Ex.119**	J	HCl-dioxane THF/CH_2Cl_2 as cosolvent	crude product	quant. (HCl salt)

No	R11	R50	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.124	H		**Ex.120**	J	HCl-dioxane	crude product	95% (HCl salt)
Ex.125			**Ex.122**	L.1.1	acetic anhydride (1.1 equiv.) pyridine/CH_2Cl_2 1:1 (3 mL)	prep. HPLC, method 1	62%
Ex.126			**Ex.121**	L.1.3	N,N-dimethylglycine	prep. HPLC, method 1	39% (TFA salt)
Ex.127			**Ex.121**	L.1.3	3-indoleacetic acid	prep. HPLC, method 1	20% (TFA salt)
Ex.128			**Ex.122**	L.1.3	N,N-dimethylglycine	prep. HPLC, method 1	21% (TFA salt)
Ex.129			**Ex.122**	L.1.3	3-indoleacetic acid	prep. HPLC, method 1	45%

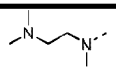
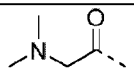
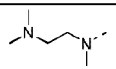
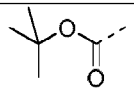
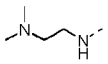
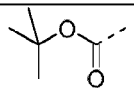
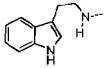
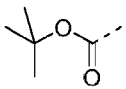
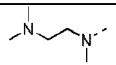
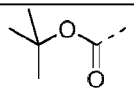
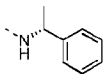
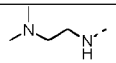
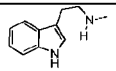
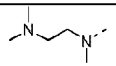
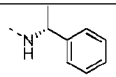
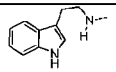
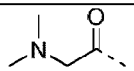
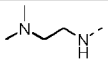
No	R11	R50	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.130			**Ex.123**	L.1.1	acetic anhydride (5 equiv.)	prep. HPLC, method 1	14% (TFA salt)
Ex.131			**Ex.123**	L.1.3	N,N-dimethylglycine	prep. HPLC, method 1	44% (TFA salt)

Table 25b: Examples of Core 07 (**Ex.115-Ex.131,** *continued on the following pages*)

No	R11	R50	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.115-Ex.116: *cf. experimental description*							
Ex.117			C30H45FN6O7	620.3	1.45	621.2	Method 9c
Ex.118			C36H45FN6O7	692.3	1.94	693.1	Method 9c
Ex.119			C31H47FN6O7	634.4	1.48	635.4	Method 9c

No	R11	R50	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.120			C34H44FN5O7	653.3	1.99	653.9	Method 9c
Ex.121	H		C25H37FN6O5	520.3	1.23 (17), 1.29 (80)	521.3/521.3	Method 3
Ex.122	H		C31H37FN6O5	592.3	1.40 (89)	593.3	Method 2
Ex.123	H		C26H39FN6O5	534.3	1.32 (96)	535.3	Method 3
Ex.124	H		C29H36FN5O5	553.3	1.41 (98)	554.3	Method 2
Ex.125			C33H39FN6O6	634.3	1.54 (100)	635.3	Method 2
Ex.126			C29H44FN7O6	605.3	1.37 (83)	606.4	Method 3

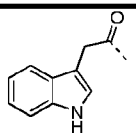
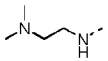
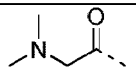
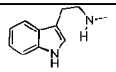
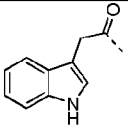
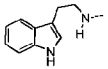
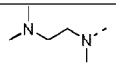
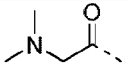
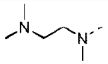
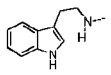
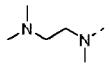
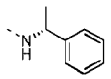
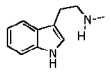
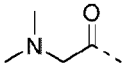
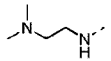
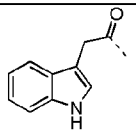
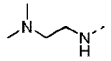
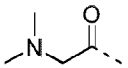
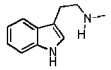
No	R11	R50	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.127			C35H44FN7O6	677.3	1.32 (12), 1.38 (84)	678.3/678.3	Method 2
Ex.128			C35H44FN7O6	677.3	1.40 (98)	678.4	Method 2
Ex.129			C41H44FN7O6	749.3	1.73 (85)	750.4	Method 2
Ex.130			C28H41FN6O6	576.3	1.10 (98)	577.3	Method 2
Ex.131			C30H46FN7O6	619.4	1.41 (96)	620.4	Method 3

Table 25c: Examples of Core 07 (**Ex.115-Ex.131,** *continued on the following pages*)

No	R11	R50	IUPAC name
Ex.115		OCH_2Ph	12-benzyl 2-(tert-butyl) (12S,20aS)-16-fluoro-8,13-dimethyl-6,9,14-trioxo-3,4,7,8,9,10,11,12,13,14,20,20a-dodecahydro-6H-pyrazino[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-2,12(1H)-dicarboxylate
Ex.116		OH	(12S,20aS)-2-(tert-butoxycarbonyl)-16-fluoro-8,13-dimethyl-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6H-pyrazino[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxylic acid
Ex.117			tert-butyl (12S,20aS)-12-({[2-(dimethylamino)ethyl]amino}carbonyl)-16-fluoro-8,13-dimethyl-6,9,14-trioxo-3,4,7,8,9,10,11,12,13,14,20,20a-dodecahydro-6H-pyrazino[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-2(1H)-carboxylate
Ex.118			tert-butyl (12S,20aS)-16-fluoro-12-({[2-(1H-indol-3-yl)ethyl]amino}carbonyl)-8,13-dimethyl-6,9,14-trioxo-3,4,7,8,9,10,11,12,13,14,20,20a-dodecahydro-6H-pyrazino[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-2(1H)-carboxylate
Ex.119			tert-butyl (12S,20aS)-12-{[[2-(dimethylamino)ethyl](methyl)amino]carbonyl}-16-fluoro-8,13-dimethyl-6,9,14-trioxo-3,4,7,8,9,10,11,12,13,14,20,20a-dodecahydro-6H-pyrazino[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-2(1H)-carboxylate
Ex.120			tert-butyl (12S,20aS)-16-fluoro-8,13-dimethyl-6,9,14-trioxo-12-({[(1R)-1-phenylethyl]amino}carbonyl)-3,4,7,8,9,10,11,12,13,14,20,20a-dodecahydro-6H-pyrazino[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-2(1H)-carboxylate
Ex.121	H		(12S,20aS)-N-[2-(dimethylamino)ethyl]-16-fluoro-8,13-dimethyl-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6H-pyrazino[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxamide

No	R11	R50	IUPAC name
Ex.122	H		(12S,20aS)-16-fluoro-N-[2-(1H-indol-3-yl)ethyl]-8,13-dimethyl-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6H-pyrazino[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxamide
Ex.123	H		(12S,20aS)-N-[2-(dimethylamino)ethyl]-16-fluoro-N,8,13-trimethyl-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6H-pyrazino[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxamide
Ex.124	H		(12S,20aS)-16-fluoro-8,13-dimethyl-6,9,14-trioxo-N-[(1R)-1-phenylethyl]-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6H-pyrazino[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxamide
Ex.125			(12S,20aS)-2-acetyl-16-fluoro-N-[2-(1H-indol-3-yl)ethyl]-8,13-dimethyl-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6H-pyrazino[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxamide
Ex.126			(12S,20aS)-2-[2-(dimethylamino)acetyl]-N-[2-(dimethylamino)ethyl]-16-fluoro-8,13-dimethyl-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6H-pyrazino[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxamide
Ex.127			(12S,20aS)-N-[2-(dimethylamino)ethyl]-16-fluoro-2-[2-(1H-indol-3-yl)acetyl]-8,13-dimethyl-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6H-pyrazino[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxamide
Ex.128			(12S,20aS)-2-[2-(dimethylamino)acetyl]-16-fluoro-N-[2-(1H-indol-3-yl)ethyl]-8,13-dimethyl-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6H-pyrazino[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxamide

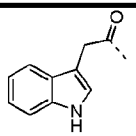
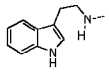
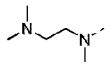
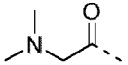
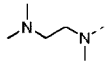
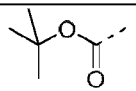
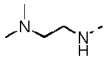
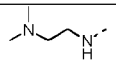
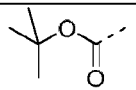
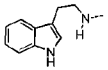
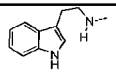
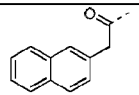
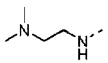
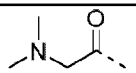
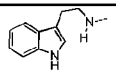
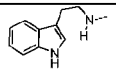
No	R11	R50	IUPAC name
Ex.129			(12S,20aS)-16-fluoro-2-[2-(1H-indol-3-yl)acetyl]-N-[2-(1H-indol-3-yl)ethyl]-8,13-dimethyl-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6H-pyrazino[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxamide
Ex.130			(12S,20aS)-2-acetyl-N-[2-(dimethylamino)ethyl]-16-fluoro-N,8,13-trimethyl-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6H-pyrazino[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxamide
Ex.131			(12S,20aS)-2-[2-(dimethylamino)acetyl]-N-[2-(dimethylamino)ethyl]-16-fluoro-N,8,13-trimethyl-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6H-pyrazino[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxamide

Table 26a: Examples of Core 08 (**Ex.132-Ex.141**, *continued on the following pages*)

No	R11	R50	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.132-Ex.133: *cf. experimental description*							
Ex.134			**Ex.133**	L.2	N,N-dimethylethylenediamine	FC (CH_2Cl_2/MeOH/aq. NH_3)	80%
Ex.135	H		**Ex.134**	J	HCl-dioxane	crude product	100% (HCl salt)
Ex.136			**Ex.133**	L.2	tryptamine	FC (CH_2Cl_2/MeOH/aq. NH_3)	89%
Ex.137	H		**Ex.136**	J	HCl-dioxane	crude product	100% (HCl salt)
Ex.138			**Ex.135**	L.1.2	2-naphthylacetic acid	prep. HPLC, method 1	71% (TFA salt)
Ex.139			**Ex.137**	L.1.2	N,N-dimethyl glycine	prep. HPLC, method 1	40% (TFA salt)
Ex.140			**Ex.137**	L.1.1	acetic anhydride (5 equiv.)	prep. HPLC, method 1	50%

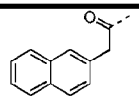
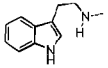
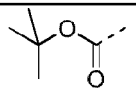
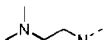
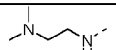
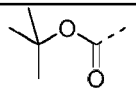
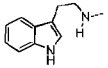
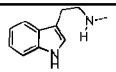
No	R11	R50	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.141			**Ex.137**	L.1.2	2-naphthylacetic acid	prep. HPLC, method 3, then FC (EtOAc/MeOH)	39%

Table 26b: Examples of Core 08 (**Ex.132-Ex.141,** *continued on the following pages*)

No	R11	R50	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.132-Ex.133: *cf. experimental description*							
Ex.134			C30H45FN6O7	620.3	1.40 (20), 1.45 (77)	621.5/621.5	Method 2
Ex.135	H		C25H37FN6O5	520.3	0.94 (85)	521.4	Method 2
Ex.136			C36H45FN6O7	692.3	1.83 (91)	693.5	Method 2
Ex.137	H		C31H37FN6O5	592.3	1.41 (80)	593.4	Method 2

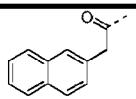
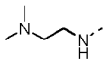
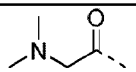
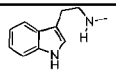
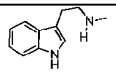
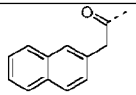
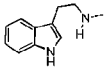
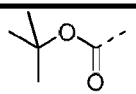
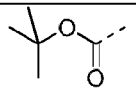
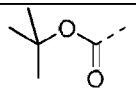
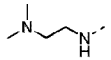
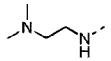
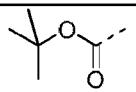
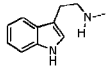
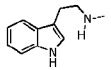
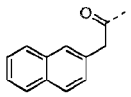
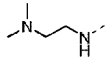
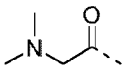
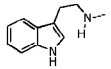
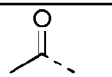
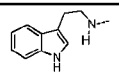
No	R11	R50	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.138			C37H45FN6O6	688.3	1.46 (15), 1.51 (84)	689.5/689.5	Method 2
Ex.139			C35H44FN7O6	677.3	1.43 (92)	678.5	Method 2
Ex.140			C33H39FN6O6	634.3	1.57 (97)	635.5	Method 2
Ex.141			C43H45FN6O6	760.3	1.86 (95)	761.5	Method 2

Table 26c: Examples of Core 08 (**Ex.132-Ex.141,** *continued on the following pages*)

No	R11	R50	IUPAC name
Ex.132		OCH_2Ph	12-benzyl 2-(tert-butyl) (12R,20aR)-16-fluoro-8,13-dimethyl-6,9,14-trioxo-3,4,7,8,9,10,11,12,13,14,20,20a-dodecahydro-6H-pyrazino[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-2,12(1H)-dicarboxylate
Ex.133		OH	(12R,20aR)-2-(tert-butoxycarbonyl)-16-fluoro-8,13-dimethyl-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6H-pyrazino[2,1-

No	R11	R50	IUPAC name
			c][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxylic acid
Ex.134			tert-butyl (12R,20aR)-12-({[2-(dimethylamino)ethyl]amino}carbonyl)-16-fluoro-8,13-dimethyl-6,9,14-trioxo-3,4,7,8,9,10,11,12,13,14,20,20a-dodecahydro-6H-pyrazino[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-2(1H)-carboxylate
Ex.135	H		(12R,20aR)-N-[2-(dimethylamino)ethyl]-16-fluoro-8,13-dimethyl-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6H-pyrazino[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxamide
Ex.136			tert-butyl (12R,20aR)-16-fluoro-12-({[2-(1H-indol-3-yl)ethyl]amino}carbonyl)-8,13-dimethyl-6,9,14-trioxo-3,4,7,8,9,10,11,12,13,14,20,20a-dodecahydro-6H-pyrazino[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-2(1H)-carboxylate
Ex.137	H		(12R,20aR)-16-fluoro-N-[2-(1H-indol-3-yl)ethyl]-8,13-dimethyl-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6H-pyrazino[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxamide
Ex.138			(12R,20aR)-N-[2-(dimethylamino)ethyl]-16-fluoro-8,13-dimethyl-2-[2-(2-naphthyl)acetyl]-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6H-pyrazino[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxamide
Ex.139			(12R,20aR)-2-[2-(dimethylamino)acetyl]-16-fluoro-N-[2-(1H-indol-3-yl)ethyl]-8,13-dimethyl-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6H-pyrazino[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxamide
Ex.140			(12R,20aR)-2-acetyl-16-fluoro-N-[2-(1H-indol-3-yl)ethyl]-8,13-dimethyl-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6H-pyrazino[2,1-

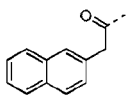
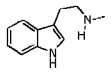
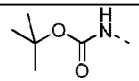
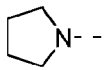
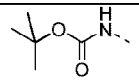
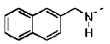
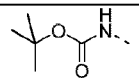
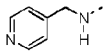
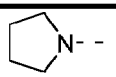
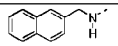
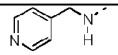
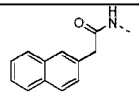
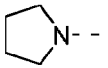
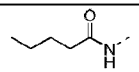
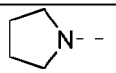
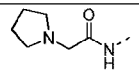
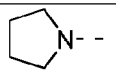
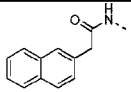
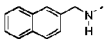
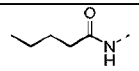
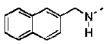
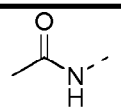
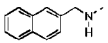
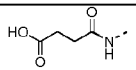
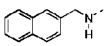
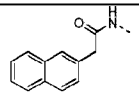
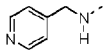
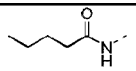
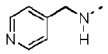
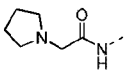
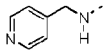
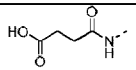
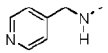
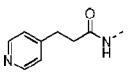
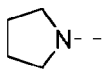
No	R11	R50	IUPAC name
			c][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxamide
Ex.141			(12R,20aR)-16-fluoro-N-[2-(1H-indol-3-yl)ethyl]-8,13-dimethyl-2-[2-(2-naphthyl)acetyl]-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6H-pyrazino[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxamide

Table 27a: Examples of Core 09 (**Ex.142-Ex.163,** *continued on the following pages*)

No	R2	R50	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.142-Ex.143: *cf. experimental description*							
Ex.144			**Ex.143**	L.2	pyrrolidine	FC (CH_2Cl_2/MeOH)	91%
Ex.145			**Ex.143**	L.2	2-naphthylmethylamine	FC (CH_2Cl_2/MeOH)	72%
Ex.146			**Ex.143**	L.2	4-(aminomethyl)pyridine	FC (CH_2Cl_2/MeOH)	87%

No	R2	R50	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.147	NH_2		**Ex.144**	J	HCl-dioxane	crude product	100% (HCl salt)
Ex.148	NH_2		**Ex.145**	J	HCl-dioxane	crude product	97% (HCl salt)
Ex.149	NH_2		**Ex.146**	J	HCl-dioxane	crude product	87% (HCl salt)
Ex.150			**Ex.147**	L.1.2	2-naphthylacetic acid	Prep. HPLC, method 3	72%
Ex.151			**Ex.147**	L.1.1	valeroyl chloride (2.0 equiv.)	Prep. HPLC, method 3	73%
Ex.152			**Ex.147**	L.1.2	1-pyrriolidinacetic acid	Prep. HPLC, method 2	26%
Ex.153			**Ex.148**	L.1.2	2-naphthylacetic acid	Prep. HPLC, method 3	68%
Ex.154			**Ex.148**	L.1.1	valeroyl chloride (2.0 equiv.)	Prep. HPLC, method 3	76%

No	R2	R50	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.155			**Ex.148**	L.1.1	acetic anhydride (5.0 equiv.)	Prep. HPLC, method 3	72%
Ex.156			**Ex.148**	L.1.1	succinic anhydride (1.05 equiv.)	Prep. HPLC, method 2	69% ($NH4^+$ salt)
Ex.157			**Ex.149**	L.1.2	2-naphthylacetic acid (1.7 equiv.)	Prep. HPLC, method 2	24%
Ex.158			**Ex.149**	L.1.1	valeroyl chloride (2.0 equiv.)	Prep. HPLC, method 2	42%
Ex.159			**Ex.149**	L.1.2	1-pyrriolidinacetic acid (2.5 equiv.)	Prep. HPLC, method 2	55%
Ex.160			**Ex.149**	L.1.1	succinic anhydride (1.05 equiv.)	Prep. HPLC, method 2	69% ($NH4^+$ salt)
Ex.161			**Ex.147**	L.1.2	3-(pyridine-4-yl)propanoic acid	Prep. HPLC, method 2	53%

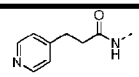
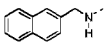
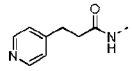
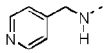
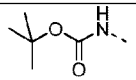
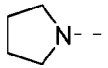
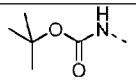
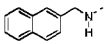
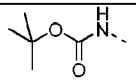
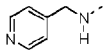
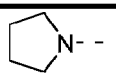
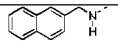
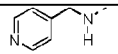
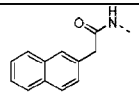
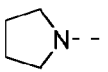
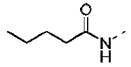
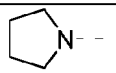
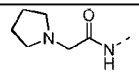
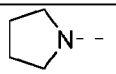
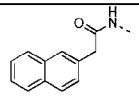
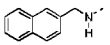
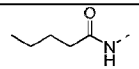
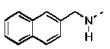
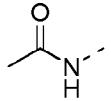
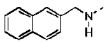
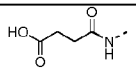
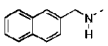
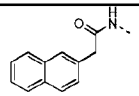
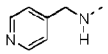
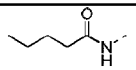
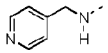
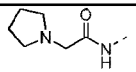
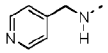
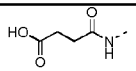
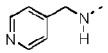
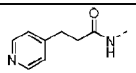
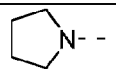
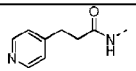
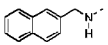
No	R2	R50	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.162			**Ex.148**	L.1.2	3-(pyridine-4-yl)propanoic acid	Prep. HPLC, method 2	48%
Ex.163			**Ex.149**	L.1.2	3-(pyridine-4-yl)propanoic acid (1.7 equiv.)	Prep. HPLC, method 2	63%

Table 27b: Examples of Core 09 (**Ex.142-Ex.163,** *continued on the following pages*)

No	R2	R50	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.142-Ex.143: *cf. experimental description*							
Ex.144			C31H44FN5O7	617.3	1.66 (90)	618.4	Method 2
Ex.145			C38H46FN5O7	703.3	1.90 (90)	704.5	Method 2
Ex.146			C33H43FN6O7	654.3	1.39 (92)	655.5	Method 2

No	R2	R50	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.147	NH_2		C26H36FN5O5	517.3	1.36 (79)	518.4	Method 3
Ex.148	NH_2		C33H38FN5O5	603.3	1.53 (98)	604.4	Method 2
Ex.149	NH_2		C28H35FN6O5	554.3	1.25 (8), 1.31 (85)	555.4	Method 3
Ex.150			C38H44FN5O6	685.3	1.72 (98)	686.5	Method 2
Ex.151			C31H44FN5O6	601.3	1.55 (98)	602.5	Method 2
Ex.152			C32H45FN6O6	628.3	1.52 (94)	629.5	Method 3
Ex.153			C45H46FN5O6	771.3	1.94 (96)	772.5	Method 2
Ex.154			C38H46FN5O6	687.3	1.82 (97)	688.5	Method 2

No	R2	R50	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.155			C35H40FN5O6	645.3	1.67 (99)	646.4	Method 2
Ex.156			C37H42FN5O8	703.3	1.65 (99)	704.5	Method 2
Ex.157			C40H43FN6O6	722.3	1.48 (94)	723.8	Method 2
Ex.158			C33H43FN6O6	638.3	1.50 (95)	639.5	Method 3
Ex.159			C34H44FN7O6	665.3	1.47 (96)	666.5	Method 3
Ex.160			C32H39FN6O8	654.3	1.04 (96)	655.4	Method 3
Ex.161			C34H43FN6O6	650.3	1.47 (91)	651.5	Method 3
Ex.162			C41H45FN6O6	736.3	1.55 (96)	737.6	Method 2

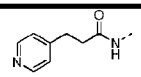
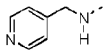
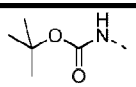
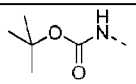
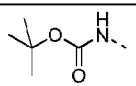
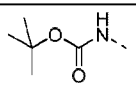
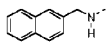
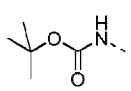
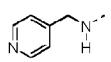
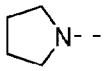
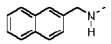
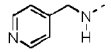
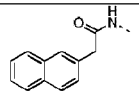
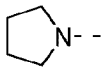
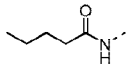
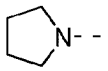
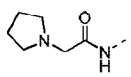
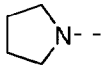
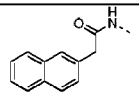
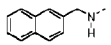
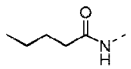
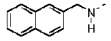
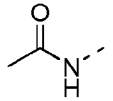
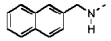
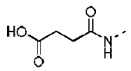
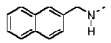
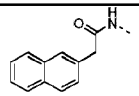
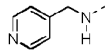
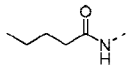
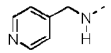
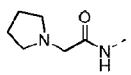
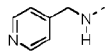
No	R2	R50	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.163			C36H42FN7O6	687.3	1.42 (99)	688.5	Method 3

Table 27c: Examples of Core 09 (**Ex.142-Ex.163**, *continued on the following pages*)

No	R2	R50	IUPAC name
Ex.142		OCH_2Ph	benzyl (2R,12S,20aS)-2-[(tert-butoxycarbonyl)amino]-16-fluoro-8,13-dimethyl-5,9,14-trioxo-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1H-pyrrolo[2,1-c][1,4,8,13]benzoxatriazacyclohexadecine-12-carboxylate
Ex.143		OH	(2R,12S,20aS)-2-[(tert-butoxycarbonyl)amino]-16-fluoro-8,13-dimethyl-5,9,14-trioxo-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1H-pyrrolo[2,1-c][1,4,8,13]benzoxatriazacyclohexadecine-12-carboxylic acid
Ex.144			tert-butyl N-[(2R,12S,20aS)-16-fluoro-8,13-dimethyl-5,9,14-trioxo-12-(1-pyrrolidinylcarbonyl)-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1H-pyrrolo[2,1-c][1,4,8,13]benzoxatriazacyclohexadecin-2-yl]carbamate
Ex.145			tert-butyl N-((2R,12S,20aS)-16-fluoro-8,13-dimethyl-12-{[(2-naphthylmethyl)amino]carbonyl}-5,9,14-trioxo-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1H-pyrrolo[2,1-c][1,4,8,13]benzoxatriazacyclohexadecin-2-

No	R2	R50	IUPAC name
			yl)carbamate
Ex.146			tert-butyl N-((2R,12S,20aS)-16-fluoro-8,13-dimethyl-5,9,14-trioxo-12-{[(4-pyridinylmethyl)amino]carbonyl}-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1H-pyrrolo[2,1-c][1,4,8,13]benzoxatriazacyclohexadecin-2-yl)carbamate
Ex.147	NH_2		(2R,12S,20aS)-2-amino-16-fluoro-8,13-dimethyl-12-(1-pyrrolidinylcarbonyl)-2,3,7,8,10,11,12,13,20,20a-decahydro-1H-pyrrolo[2,1-c][1,4,8,13]benzoxatriazacyclohexadecine-5,9,14(6H)-trione
Ex.148	NH_2		(2R,12S,20aS)-2-amino-16-fluoro-8,13-dimethyl-N-(2-naphthylmethyl)-5,9,14-trioxo-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1H-pyrrolo[2,1-c][1,4,8,13]benzoxatriazacyclohexadecine-12-carboxamide
Ex.149	NH_2		(2R,12S,20aS)-2-amino-16-fluoro-8,13-dimethyl-5,9,14-trioxo-N-(4-pyridinylmethyl)-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1H-pyrrolo[2,1-c][1,4,8,13]benzoxatriazacyclohexadecine-12-carboxamide
Ex.150			N-[(2R,12S,20aS)-16-fluoro-8,13-dimethyl-5,9,14-trioxo-12-(1-pyrrolidinylcarbonyl)-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1H-pyrrolo[2,1-c][1,4,8,13]benzoxatriazacyclohexadecin-2-yl]-2-(2-naphthyl)acetamide
Ex.151			N-[(2R,12S,20aS)-16-fluoro-8,13-dimethyl-5,9,14-trioxo-12-(1-pyrrolidinylcarbonyl)-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1H-pyrrolo[2,1-c][1,4,8,13]benzoxatriazacyclohexadecin-2-yl]pentanamide
Ex.152			N-[(2R,12S,20aS)-16-fluoro-8,13-dimethyl-5,9,14-trioxo-12-(1-pyrrolidinylcarbonyl)-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1H-

No	R2	R50	IUPAC name
			pyrrolo[2,1-c][1,4,8,13]benzoxatriazacyclohexadecin-2-yl]-2-(1-pyrrolidinyl)acetamide
Ex.153			(2R,12S,20aS)-16-fluoro-8,13-dimethyl-2-{[2-(2-naphthyl)acetyl]amino}-N-(2-naphthylmethyl)-5,9,14-trioxo-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1H-pyrrolo[2,1-c][1,4,8,13]benzoxatriazacyclohexadecine-12-carboxamide
Ex.154			(2R,12S,20aS)-16-fluoro-8,13-dimethyl-N-(2-naphthylmethyl)-5,9,14-trioxo-2-(pentanoylamino)-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1H-pyrrolo[2,1-c][1,4,8,13]benzoxatriazacyclohexadecine-12-carboxamide
Ex.155			(2R,12S,20aS)-2-(acetylamino)-16-fluoro-8,13-dimethyl-N-(2-naphthylmethyl)-5,9,14-trioxo-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1H-pyrrolo[2,1-c][1,4,8,13]benzoxatriazacyclohexadecine-12-carboxamide
Ex.156			4-[((2R,12S,20aS)-16-fluoro-8,13-dimethyl-12-{[(2-naphthylmethyl)amino]carbonyl}-5,9,14-trioxo-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1H-pyrrolo[2,1-c][1,4,8,13]benzoxatriazacyclohexadecin-2-yl)amino]-4-oxobutanoic acid
Ex.157			(2R,12S,20aS)-16-fluoro-8,13-dimethyl-2-{[2-(2-naphthyl)acetyl]amino}-5,9,14-trioxo-N-(4-pyridinylmethyl)-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1H-pyrrolo[2,1-c][1,4,8,13]benzoxatriazacyclohexadecine-12-carboxamide
Ex.158			(2R,12S,20aS)-16-fluoro-8,13-dimethyl-5,9,14-trioxo-2-(pentanoylamino)-N-(4-pyridinylmethyl)-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1H-pyrrolo[2,1-c][1,4,8,13]benzoxatriazacyclohexadecine-12-carboxamide
Ex.159			(2R,12S,20aS)-16-fluoro-8,13-dimethyl-5,9,14-trioxo-N-(4-pyridinylmethyl)-2-{[2-(1-pyrrolidinyl)acetyl]amino}-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-

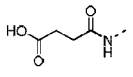
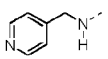
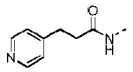
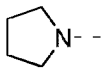
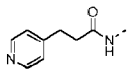
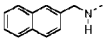
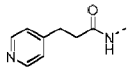
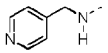
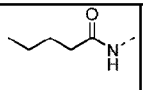
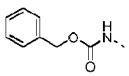
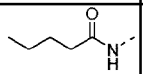
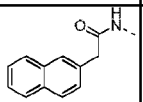
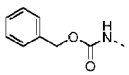
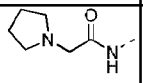
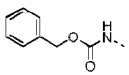
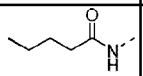
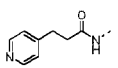
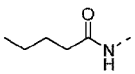
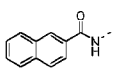
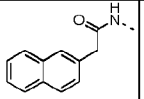
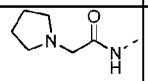
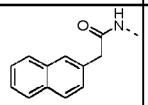
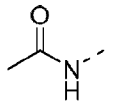
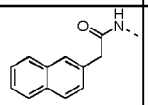
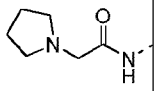
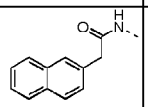
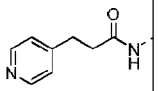
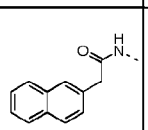
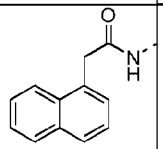
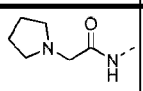
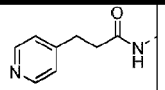
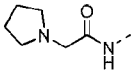
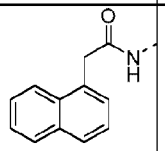
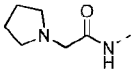
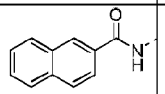
No	R2	R50	IUPAC name
			1H-pyrrolo[2,1-c][1,4,8,13]benzoxatriazacyclohexadecine-12-carboxamide
Ex.160			4-[((2R,12S,20aS)-16-fluoro-8,13-dimethyl-5,9,14-trioxo-12-{[(4-pyridinylmethyl)amino]carbonyl}-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1H-pyrrolo[2,1-c][1,4,8,13]benzoxatriazacyclohexadecin-2-yl)amino]-4-oxobutanoic acid
Ex.161			N-[(2R,12S,20aS)-16-fluoro-8,13-dimethyl-5,9,14-trioxo-12-(1-pyrrolidinylcarbonyl)-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1H-pyrrolo[2,1-c][1,4,8,13]benzoxatriazacyclohexadecin-2-yl]-3-(4-pyridinyl)propanamide
Ex.162			(2R,12S,20aS)-16-fluoro-8,13-dimethyl-N-(2-naphthylmethyl)-5,9,14-trioxo-2-{[3-(4-pyridinyl)propanoyl]amino}-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1H-pyrrolo[2,1-c][1,4,8,13]benzoxatriazacyclohexadecine-12-carboxamide
Ex.163			(2R,12S,20aS)-16-fluoro-8,13-dimethyl-5,9,14-trioxo-N-(4-pyridinylmethyl)-2-{[3-(4-pyridinyl)propanoyl]amino}-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1H-pyrrolo[2,1-c][1,4,8,13]benzoxatriazacyclohexadecine-12-carboxamide

Table 28a: Examples of Core 10 (**Ex.164-Ex.180,** *continued on the following pages*)

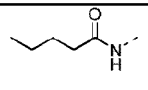
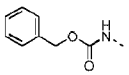
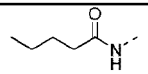
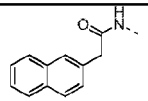
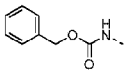
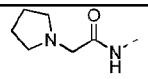
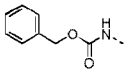
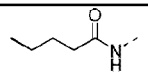
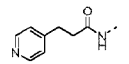
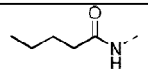
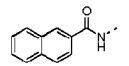
No	R2	R5	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.164-Ex.165: *cf. experimental description*							
Ex.166			**Ex.165**	L.1.1	valeroyl chloride (2.0 equiv.)	FC (EtOAc/MeOH)	ca.70%
Ex.167		NH_2	**Ex.166**	K	H_2, $Pd(OH)_2$-C	crude product	quant.
Ex.168			**Ex.165**	L.1.3	2-naphthylacetic acid	FC (EtOAc)	68%
Ex.169			**Ex.165**	L.1.3	1-pyrrolidinacetic acid	FC (EtOAc/MeOH)	76%
Ex.170			**Ex.167**	L.1.2	3-(pyridine-4-yl)propanoic acid	FC (CH_2Cl_2/MeOH)	78%
Ex.171			**Ex.167**	L.1.1	2-naphthoyl chloride (2.6 equiv.)	Prep. HPLC, method 3	42%

No	R2	R5	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.172		NH_2	**Ex.168**	K	H_2, $Pd(OH)_2$-C	crude product	97%
Ex.173		NH_2	**Ex.169**	K	H_2, $Pd(OH)_2$-C	crude product	96%
Ex.174			**Ex.172**	L.1.1	acetic anhydride (5 equiv.)	Prep. HPLC, method 3	97%
Ex.175			**Ex.172**	L.1.2	1-pyrrolidinacetic acid (2.2 equiv.)	Prep. HPLC, method 3	58%
Ex.176			**Ex.172**	L.1.2	3-(pyridine-4-yl)propanoic acid	Prep. HPLC, method 3	71%
Ex.177			**Ex.172**	L.1.2*)	1-naphthylacetic acid	Prep. HPLC, method 3	68%

No	R2	R5	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.178			**Ex.173**	L.1.2	3-(pyridine-4-yl)propanoic acid	Prep. HPLC, method 2	48%
Ex.179			**Ex.173**	L.1.2*)	1-naphthylacetic acid	Prep. HPLC, method 3	84%
Ex.180			**Ex.173**	L.1.1*)	2-naphthoyl chloride (1.5 equiv.)	Prep. HPLC, method 3	78%

*) The treatment with (polystyrylmethyl)trimethylammonium bicarbonate was replaced by an aqueous workup ($CHCl_3$, sat. aq. $NaHCO_3$ soln)

Table 28b: Examples of Core 10 (**Ex.164-Ex.180,** *continued on the following pages*)

No	R2	R5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.164-Ex.165: *cf. experimental description*							
Ex.166			C30H38N4O6	550.3	1.96 (99)	551.3	Method 4a
Ex.167		NH_2	C22H32N4O4	416.2	1.4 (99)	417.3	Method 4a
Ex.168			C37H38N4O6	634.3	2.2 (98)	635.3	Method 4a
Ex.169			C31H39N5O6	577.3	1.57 (99)	578.4	Method 4a
Ex.170			C30H39N5O5	549.3	1.47 (97)	550.4	Method 4a
Ex.171			C33H38N4O5	570.3	2.1 (100)	571.3	Method 4a

No	R2	R5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.172		NH_2	C29H32N4O4	500.2	1.60 (91)	501.3	Method 4a
Ex.173		NH_2	C23H33N5O4	443.3	1.48 (99)	444.2	Method 5a
Ex.174			C31H34N4O5	542.3	1.82 (99)	543.2	Method 4a
Ex.175			C35H41N5O5	611.3	1.69 (96)	612.2	Method 4a
Ex.176			C37H39N5O5	633.3	1.68 (99)	634.3	Method 4a
Ex.177			C41H40N4O5	668.3	2.24 (92)	669.3	Method 4a

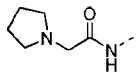
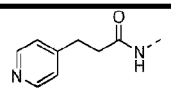
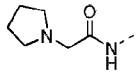
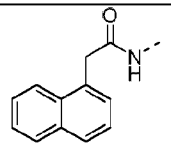
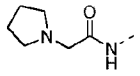
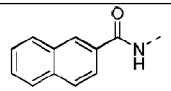
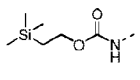
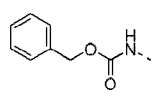
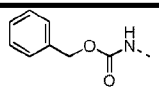
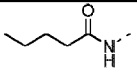
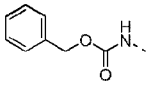
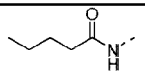
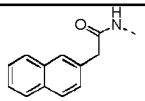
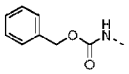
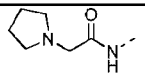
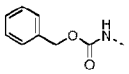
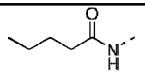
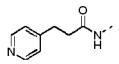
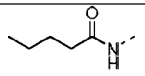
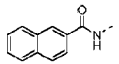
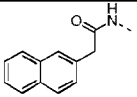
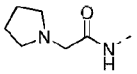
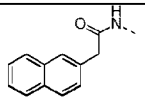
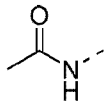
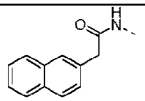
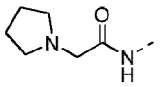
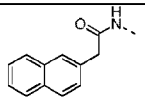
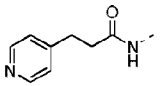
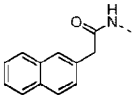
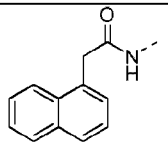
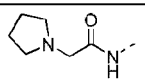
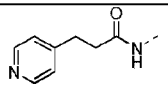
No	R2	R5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.178			C31H40N6O5	576.3	1.07 (98)	577.3	Method 4a
Ex.179			C35H41N5O5	611.3	1.69 (93)	612.3	Method 4a
Ex.180			C34H39N5O5	597.3	1.69 (97)	597.8	Method 4a

Table 28c: Examples of Core 10 (**Ex.164-Ex.180,** *continued on the following pages*)

No	R2	R5	IUPAC name
Ex.164			benzyl N-[(4S,6S,10S)-13-methyl-9,14-dioxo-6-({[2-(trimethylsilyl)ethoxy]carbonyl}amino)-2-oxa-8,13-diazatricyclo[13.3.1.$0^{4,8}$]nonadeca-1(19),15,17-trien-10-yl]carbamate

No	R2	R5	IUPAC name
Ex.165	NH_2		benzyl N-[(4S,6S,10S)-6-amino-13-methyl-9,14-dioxo-2-oxa-8,13-diazatricyclo[13.3.1.$0^{4,8}$]nonadeca-1(19),15,17-trien-10-yl]carbamate
Ex.166			benzyl N-[(4S,6S,10S)-13-methyl-9,14-dioxo-6-(pentanoylamino)-2-oxa-8,13-diazatricyclo[13.3.1.$0^{4,8}$]nonadeca-1(19),15,17-trien-10-yl]carbamate
Ex.167		NH_2	N-[(4S,6S,10S)-10-amino-13-methyl-9,14-dioxo-2-oxa-8,13-diazatricyclo[13.3.1.$0^{4,8}$]nonadeca-1(19),15,17-trien-6-yl]pentanamide
Ex.168			benzyl N-[(4S,6S,10S)-13-methyl-6-{[2-(2-naphthyl)acetyl]amino}-9,14-dioxo-2-oxa-8,13-diazatricyclo[13.3.1.$0^{4,8}$]nonadeca-1(19),15,17-trien-10-yl]carbamate
Ex.169			benzyl N-[(4S,6S,10S)-13-methyl-9,14-dioxo-6-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,13-diazatricyclo[13.3.1.$0^{4,8}$]nonadeca-1(19),15,17-trien-10-yl]carbamate
Ex.170			N-[(4S,6S,10S)-13-methyl-9,14-dioxo-10-{[3-(4-pyridinyl)propanoyl]amino}-2-oxa-8,13-diazatricyclo[13.3.1.$0^{4,8}$]nonadeca-1(19),15,17-trien-6-yl]pentanamide
Ex.171			N-[(4S,6S,10S)-13-methyl-9,14-dioxo-6-(pentanoylamino)-2-oxa-8,13-diazatricyclo[13.3.1.$0^{4,8}$]nonadeca-1(19),15,17-trien-10-yl]-2-naphthamide
Ex.172		NH_2	N-[(4S,6S,10S)-10-amino-13-methyl-9,14-dioxo-2-oxa-8,13-diazatricyclo[13.3.1.$0^{4,8}$]nonadeca-1(19),15,17-trien-6-yl]-2-(2-naphthyl)acetamide

No	R2	R5	IUPAC name
Ex.173		NH_2	N-[(4S,6S,10S)-10-amino-13-methyl-9,14-dioxo-2-oxa-8,13-diazatricyclo[13.3.1.$0^{4,8}$]nonadeca-1(19),15,17-trien-6-yl]-2-(1-pyrrolidinyl)acetamide
Ex.174			N-[(4S,6S,10S)-10-(acetylamino)-13-methyl-9,14-dioxo-2-oxa-8,13-diazatricyclo[13.3.1.$0^{4,8}$]nonadeca-1(19),15,17-trien-6-yl]-2-(2-naphthyl)acetamide
Ex.175			N-[(4S,6S,10S)-13-methyl-9,14-dioxo-10-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,13-diazatricyclo[13.3.1.$0^{4,8}$]nonadeca-1(19),15,17-trien-6-yl]-2-(2-naphthyl)acetamide
Ex.176			N-[(4S,6S,10S)-13-methyl-6-{[2-(2-naphthyl)acetyl]amino}-9,14-dioxo-2-oxa-8,13-diazatricyclo[13.3.1.$0^{4,8}$]nonadeca-1(19),15,17-trien-10-yl]-3-(4-pyridinyl)propanamide
Ex.177			N-[(4S,6S,10S)-13-methyl-6-{[2-(2-naphthyl)acetyl]amino}-9,14-dioxo-2-oxa-8,13-diazatricyclo[13.3.1.$0^{4,8}$]nonadeca-1(19),15,17-trien-10-yl]-2-(1-naphthyl)acetamide
Ex.178			N-[(4S,6S,10S)-13-methyl-9,14-dioxo-6-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,13-diazatricyclo[13.3.1.$0^{4,8}$]nonadeca-1(19),15,17-trien-10-yl]-3-(4-pyridinyl)propanamide

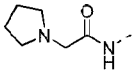
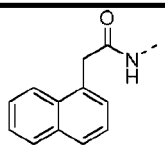
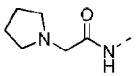
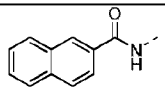
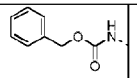
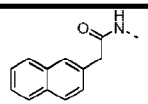
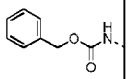
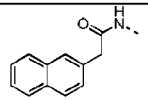
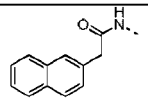
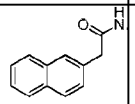
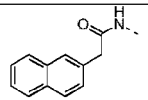
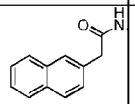
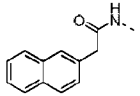
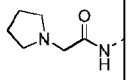
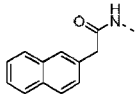
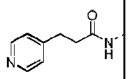
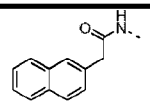
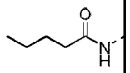
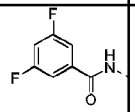
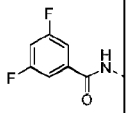
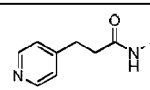
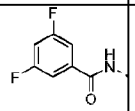
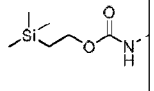
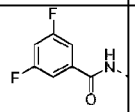
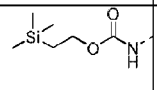
No	R2	R5	IUPAC name
Ex.179			N-[(4S,6S,10S)-13-methyl-9,14-dioxo-6-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,13-diazatricyclo[13.3.1.$0^{4,8}$]nonadeca-1(19),15,17-trien-10-yl]-2-(1-naphthyl)acetamide
Ex.180			N-[(4S,6S,10S)-13-methyl-9,14-dioxo-6-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,13-diazatricyclo[13.3.1.$0^{4,8}$]nonadeca-1(19),15,17-trien-10-yl]-2-naphthamide

Table 29a: Examples of Core 11 (**Ex.181-Ex.195,** *continued on the following pages*)

No	R2	R5	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.181-Ex.182: *cf. experimental description*							
Ex.183			**Ex.182**	L.1.1	acetic anhydride (5 equiv.)	FC (CH_2Cl_2/MeOH)	75%

No	R2	R5	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.184			**Ex.182**	L.1.3	2-naphthylacetic acid (1.2 equiv.)	FC (EtOAc, then CH_2Cl_2/MeOH)	94%
Ex.185		NH_2	**Ex.184**	K	H_2, $Pd(OH)_2$-C	crude product	99%
Ex.186			**Ex.185**	L.1.3	2-naphthylacetic acid (1.2 equiv.)	prep. HPLC, method 3	60%
Ex.186			**139**	Synthesis on solid support	2-naphthylacetic acid	prep. HPLC, method 3	32%
Ex.187			**Ex.185**	L.1.3	pyrrolidin-1-acetic acid (1.2 equiv.)	prep. HPLC, method 3 then prep. HPLC, method 1	38% (TFA salt)
Ex.188			**Ex.185**	L.1.3	3-(pyridine-4-yl)propanoic acid (1.2 equiv.)	prep. HPLC, method 3 then prep. HPLC, method 1	32% (TFA salt)

No	R2	R5	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.189			**Ex.185**	L.1.1	valeroyl chloride (2 equiv.)	prep. HPLC, method 3	52%
Ex.190	NH_2		**Ex.193**	I.2	TBAF (4 equiv.) in THF	crude product, contaminated with TBAF	ca 70%
Ex.191			**Ex.190**	L.1.1	Acetic anhydride (10 equiv.) Pyridine/CH_2Cl_2 1:1 (3 mL)	prep. HPLC, method 3	62%
Ex.192			**Ex.190**	L.1.3	3-(pyridine-4-yl)propanoic acid (1.2 equiv.)	prep. HPLC, method 3	63%
Ex.193			**Ex.194**	L.1.1	3,5-difluorbenzoyl chloride (2 equiv.)	FC (EtOAc)	85%
Ex.194		NH_2	**Ex.181**	K	H_2, $Pd(OH)_2$-C	crude product	quant.

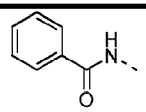
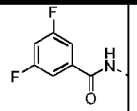
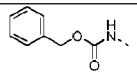
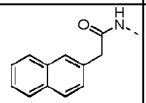
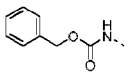
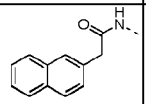
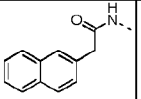
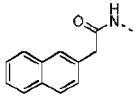
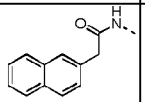
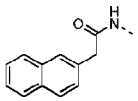
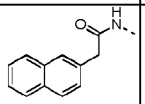
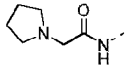
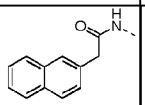
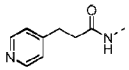
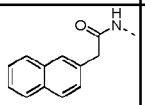
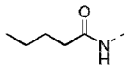
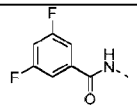
No	R2	R5	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.195			**Ex.190**	L.1.1	benzoyl chloride (2 equiv.)	preparative HPLC 3ethod 3	78%

Table 29b: Examples of Core 11 (**Ex.181-Ex.195,** *continued on the following pages*)

No	R2	R5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.181-Ex.182: *cf. experimental description*							
Ex.183			C28H34N4O6	522.3	1.56 (99)	523.3	Method 2
Ex.184			C38H40N4O6	648.3	1.92 (96)	649.5	Method 2
Ex.185		NH_2	C30H34N4O4	514.3	1.48 (98)	515.4	Method 2

No	R2	R5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.186			C42H42N4O5	682.3	2.00 (91)	683.5	Method 2
Ex.186			C42H42N4O5	682.3	2.26 (98)	683.3	Method 4a
Ex.187			C36H43N5O5	625.3	1.62 (100)	626.4	Method 2
Ex.188			C38H41N5O5	647.3	1.60 (99)	648.3	Method 2
Ex.189			C35H42N4O5	598.3	1.88 (85), 1.93 (8)	599.5	Method 2
Ex.190	NH_2		C25H28F2N4O4	486.2	1.42 (98)	487.3	Method 4a

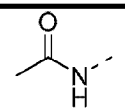
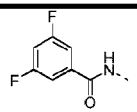
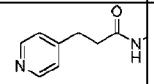
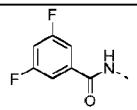
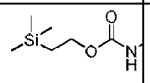
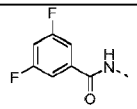
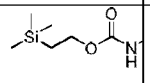
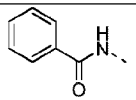
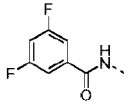
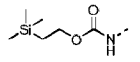
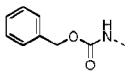
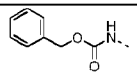
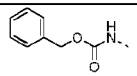
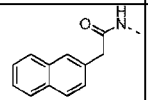
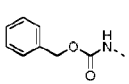
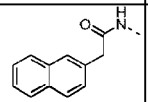
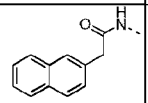
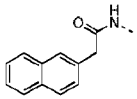
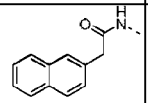
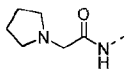
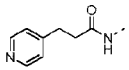
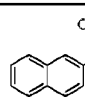
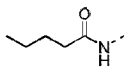
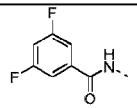
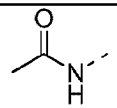
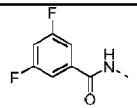
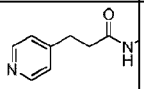
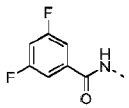
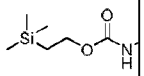
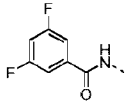
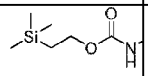
No	R2	R5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.191			C27H30F2N4O5	528.2	1.69 (99)	529.3	Method 4a
Ex.192			C33H35F2N5O5	619.3	1.50 (99)	620.3	Method 4a
Ex.193			C31H40F2N4O6Si	630.3	2.13 (97)	631.4	Method 2
Ex.194		NH_2	C24H38N4O5Si	490.3	1.62 (99)	491.3	Method 2
Ex.195			C32H32F2N4O5	590.2	1.99 (98)	591.3	Method 4a

Table 29c: Examples of Core 11 (**Ex.181-Ex.195,** *continued on the following pages*)

No	R2	R5	IUPAC name
Ex.181			benzyl N-[(4S,6S,10S)-14-methyl-9,15-dioxo-6-({[2-(trimethylsilyl)ethoxy]carbonyl}amino)-2-oxa-8,14-diazatricyclo[14.3.1.0^{4,8}]icosa-1(20),16,18-trien-10-yl]carbamate
Ex.182	NH_2		benzyl N-[(4S,6S,10S)-6-amino-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.0^{4,8}]icosa-1(20),16,18-trien-10-yl]carbamate
Ex.183			benzyl N-[(4S,6S,10S)-6-(acetylamino)-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.0^{4,8}]icosa-1(20),16,18-trien-10-yl]carbamate
Ex.184			benzyl N-[(4S,6S,10S)-14-methyl-6-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.0^{4,8}]icosa-1(20),16,18-trien-10-yl]carbamate
Ex.185		NH_2	N-[(4S,6S,10S)-10-amino-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.0^{4,8}]icosa-1(20),16,18-trien-6-yl]-2-(2-naphthyl)acetamide
Ex.186			N-[(4S,6S,10S)-14-methyl-10-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.0^{4,8}]icosa-1(20),16,18-trien-6-yl]-2-(2-naphthyl)acetamide
Ex.187			N-[(4S,6S,10S)-14-methyl-9,15-dioxo-10-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,14-diazatricyclo[14.3.1.0^{4,8}]icosa-1(20),16,18-trien-6-yl]-2-(2-naphthyl)acetamide

No	R2	R5	IUPAC name
Ex.188			N-[(4S,6S,10S)-14-methyl-6-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-3-(4-pyridinyl)propanamide
Ex.189			N-[(4S,6S,10S)-14-methyl-6-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]pentanamide
Ex.190	NH_2		N-[(4S,6S,10S)-6-amino-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-3,5-difluorobenzamide
Ex.191			N-[(4S,6S,10S)-6-(acetylamino)-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-3,5-difluorobenzamide
Ex.192			3,5-difluoro-N-[(4S,6S,10S)-14-methyl-9,15-dioxo-6-{[3-(4-pyridinyl)propanoyl]amino}-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]benzamide
Ex.193			2-(trimethylsilyl)ethyl N-[(4S,6S,10S)-10-[(3,5-difluorobenzoyl)amino]-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]carbamate
Ex.194		NH_2	2-(trimethylsilyl)ethyl N-[(4S,6S,10S)-10-amino-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]carbamate

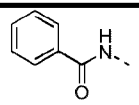
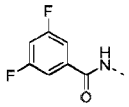
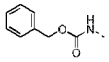
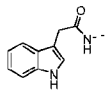
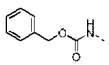
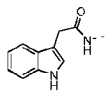
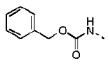
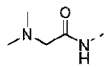
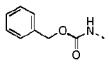
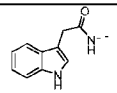
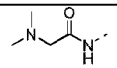
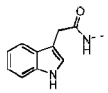
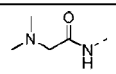
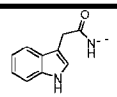
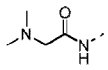
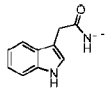
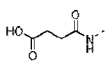
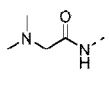
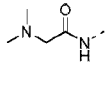
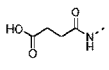
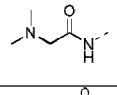
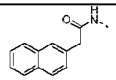
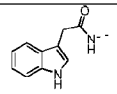
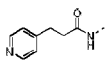
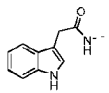
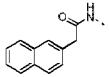
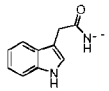
No	R2	R5	IUPAC name
Ex.195			N-[(4S,6S,10S)-6-(benzoylamino)-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-3,5-difluorobenzamide

Table 30a: Examples of Core 12 (**Ex.196-Ex.214,** *continued on the following pages*)

No	R2	R5	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.196-Ex.198: *cf. experimental description*							
Ex.199			**Ex.197**·HCl	L.1.1	acetic anhydride (10 equiv.) pyridine (2 mL)	FC (CH_2Cl_2/MeOH) then prep HPLC, method 1	36%
Ex.200			**Ex.197**·HCl	L.1.3	3-indoleacetic acid (1.5 equiv.), HATU (1.5 equiv.), HOAt (1.5 equiv), i-Pr_2NEt (5 equiv.)	FC (CH_2Cl_2/MeOH) then prep HPLC, method 1	22%

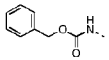
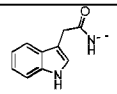
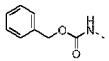
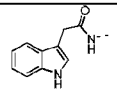
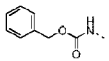
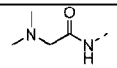
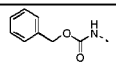
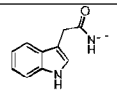
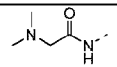
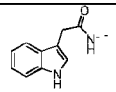
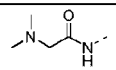
No	R2	R5	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.200			**Ex.197** ·TFA	L.1.3	3-indoleacetic acid (1.5 equiv.), HATU (1.5 equiv.), HOAt (1.5 equiv), i-Pr_2NEt (5 equiv.)	FC (EtOAc, then CH_2Cl_2/MeOH)	78%
Ex.201			**Ex.197** ·HCl	L.1.3	N,N-dimethyl glycine (1.7 equiv.)	FC (CH_2Cl_2/MeOH) and prep HPLC, method 1	91%*) (TFA salt)
Ex.202		NH_2	**Ex.200**	K	H_2, $Pd(OH)_2$-C	crude product	97%
Ex.203		NH_2	**Ex.201**	K	H_2, $Pd(OH)_2$-C	crude product	99%
Ex.204			**Ex.214**	L.1.3	3-indoleacetic acid (1.2 equiv.), HATU (1.5 equiv.), HOAt (1.5 equiv), i-Pr_2NEt (3 equiv.)	FC (CH_2Cl_2/MeOH)	64%
Ex.205			**Ex.214**	L.1.3	N,N-dimethyl glycine (1.7 equiv.)	prep HPLC, method 1	47% (TFA salt)

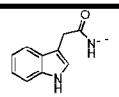
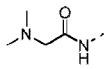
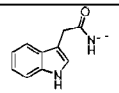
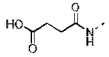
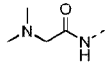
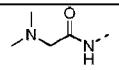
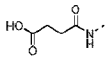
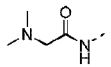
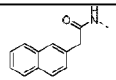
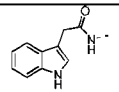
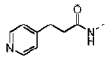
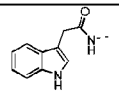
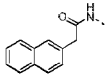
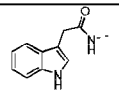
No	R2	R5	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.206			**Ex.202**	L.1.3	N,N-dimethyl glycine (1.7 equiv.)	prep HPLC, method 1	39% (TFA salt)
Ex.207			**Ex.202**	L.1.1	succinic anhydride (1.05 equiv.) pyridine (49 equiv.)	prep HPLC, method 2	48%
Ex.208			**Ex.203**	L.1.1	acetic anhydride (10 equiv.) pyridine/CH_2Cl_2 1.1 (3 mL)	prep HPLC, method 2	59%
Ex.209			**Ex.203**	L.1.1	succinic anhydride (1.05 equiv.) pyridine (49 equiv.)	prep HPLC, method 2	35%
Ex.210			**Ex.203**	L.1.3	2-naphthylacetic acid (1.2 equiv.)	prep HPLC, method 1	38% (TFA salt)
Ex.211			**Ex.202**	L.1.2	3-(pyridine-4-yl)propanoic acid	prep HPLC, method 1	44% (TFA salt)

No	R2	R5	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.212			**Ex.202**	L.1.3	2-naphthylacetic acid (1.2 equiv.)	prep HPLC, method 1 then FC (EtOAc/MeOH)	53%
Ex.213		$CH_3(CH_2)_8CONH$	**Ex.202**	L.1.1	decanoyl chloride (2 equiv.)	prep HPLC, method 1 then FC (EtOAc/MeOH)	35%
Ex.214		NH_2	**Ex.199**	K	H_2, $Pd(OH)_2$-C	crude product	98%

*) An analytical sample was further purified by prep. HPLC (method 1), to afford the TFA salt of the corresponding product

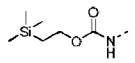
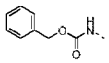
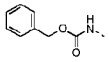
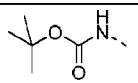
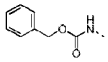
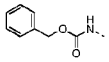
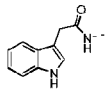
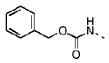
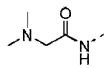
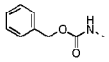
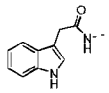
Table 30b: Examples of Core 12 (**Ex.196-Ex.214,** *continued on the following pages*)

No	R2	R5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.196-Ex.198: *cf. experimental description*							
Ex.199			C29H35N5O7	565.3	1.92 (100)	566.4	Method 1a
Ex.200			C37H40N6O7	680.3	2.23 (98)	681.4	Method 1a
Ex.200			C37H40N6O7	680.3	1.68 (93)	681.5	Method 2
Ex.201			C31H40N6O7	608.3	1.28 (99)	609.4	Method 2
Ex.202		NH_2	C29H34N6O5	546.3	1.32 (76)	547.4	Method 2
Ex.203		NH_2	C23H34N6O5	474.3	0.77	475.5	Method 9c
Ex.204			C31H36N6O6	588.3	1.49 (87)	589.2	Method 4a
Ex.205			C25H36N6O6	516.3	1.42 (100)	517.3	Method 1a

No	R2	R5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.206			C33H41N7O6	631.3	1.84 (97)	632.4	Method 1a
Ex.207			C33H38N6O8	646.3	1.42 (100)	647.4	Method 2
Ex.208			C25H36N6O6	516.3	0.95 (100)	517.4	Method 2
Ex.209			C27H38N6O8	574.3	1.02 (92)	575.4	Method 3
Ex.210			C35H42N6O6	642.3	1.37 (100)	643.4	Method 2
Ex.211			C37H41N7O6	679.3	1.34 (92)	680.5	Method 2
Ex.212			C41H42N6O6	714.3	1.75 (86)	715.5	Method 2
Ex.213		$CH_3(CH_2)_8CONH$	C39H52N6O6	700.4	1.96 (99)	701.6	Method 2
Ex.214		NH_2	C21H29N5O5	431.2	0.81*)	432.2	Method 9c

*) Analytical HPLC (5% CH_3CN): 2.52 (93)

Table 30c: Examples of Core 12 (**Ex.196-Ex.214,** *continued on the following pages*)

No	R2	R5	IUPAC name
Ex.196			benzyl N-[(4S,6S,13S)-11,15-dimethyl-9,12,16-trioxo-6-({[2-(trimethylsilyl)ethoxy]carbonyl}amino)-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.197	NH_2		benzyl N-[(4S,6S,13S)-6-amino-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.198			benzyl N-[(4S,6S,13S)-6-[(tert-butoxycarbonyl)amino]-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.199			benzyl N-[(4S,6S,13S)-6-(acetylamino)-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.200			benzyl N-[(4S,6S,13S)-6-{[2-(1H-indol-3-yl)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.201			benzyl N-[(4S,6S,13S)-6-{[2-(dimethylamino)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.202		NH_2	N-[(4S,6S,13S)-13-amino-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]-2-(1H-indol-3-yl)acetamide

No	R2	R5	IUPAC name
Ex.203		NH_2	N-[(4S,6S,13S)-13-amino-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.0^{4,8}]henicosa-1(21),17,19-trien-6-yl]-2-(dimethylamino)acetamide
Ex.204			N-[(4S,6S,13S)-6-(acetylamino)-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.0^{4,8}]henicosa-1(21),17,19-trien-13-yl]-2-(1H-indol-3-yl)acetamide
Ex.205			N-[(4S,6S,13S)-6-(acetylamino)-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.0^{4,8}]henicosa-1(21),17,19-trien-13-yl]-2-(dimethylamino)acetamide
Ex.206			2-(dimethylamino)-N-[(4S,6S,13S)-6-{[2-(1H-indol-3-yl)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.0^{4,8}]henicosa-1(21),17,19-trien-13-yl]acetamide
Ex.207			4-{[(4S,6S,13S)-6-{[2-(1H-indol-3-yl)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.0^{4,8}]henicosa-1(21),17,19-trien-13-yl]amino}-4-oxobutanoic acid
Ex.208			N-[(4S,6S,13S)-13-(acetylamino)-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.0^{4,8}]henicosa-1(21),17,19-trien-6-yl]-2-(dimethylamino)acetamide
Ex.209			4-{[(4S,6S,13S)-6-{[2-(dimethylamino)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.0^{4,8}]henicosa-1(21),17,19-trien-13-yl]amino}-4-oxobutanoic acid

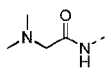
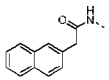
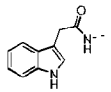
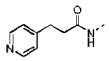
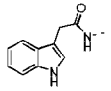
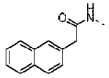
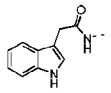
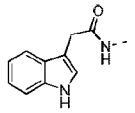
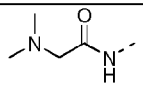
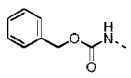
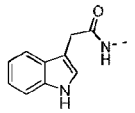
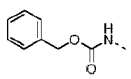
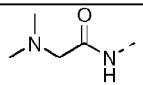
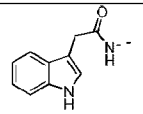
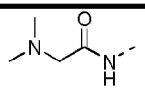
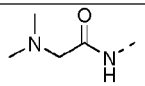
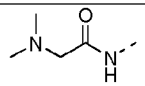
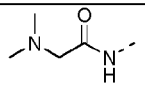
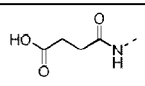
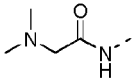
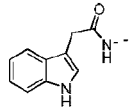
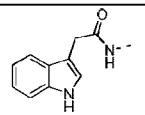
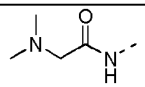
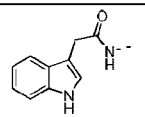
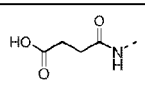
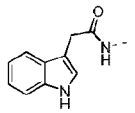
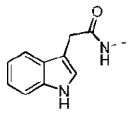
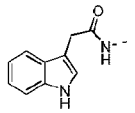
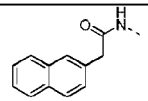
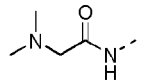
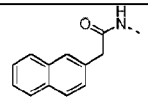
No	R2	R5	IUPAC name
Ex.210			2-(dimethylamino)-N-[(4S,6S,13S)-11,15-dimethyl-13-{[2-(2-naphthyl)acetyl]amino}-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]acetamide
Ex.211			N-[(4S,6S,13S)-6-{[2-(1H-indol-3-yl)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]-3-(4-pyridinyl)propanamide
Ex.212			N-[(4S,6S,13S)-11,15-dimethyl-13-{[2-(2-naphthyl)acetyl]amino}-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]-2-(1H-indol-3-yl)acetamide
Ex.213		$CH_3(CH_2)_8CONH$	N-[(4S,6S,13S)-6-{[2-(1H-indol-3-yl)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]decanamide
Ex.214		NH_2	N-[(4S,6S,13S)-13-amino-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]acetamide

Table 31a: Examples of Core 13 (**Ex.215-Ex.230,** *continued on the following pages*)

No	R2	R5	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.215-Ex.216: *cf. experimental description*							
Ex.217			**Ex.221**	L.1.1	acetic anhydride (10 equiv.) pyridine/CH_2Cl_2 1:1 (2 mL)	prep. HPLC, method 1	41%
Ex.218			**Ex.216** ·HCl	L.1.3	N,N-dimetyl glycine (1.7 equiv.)	FC (CH_2Cl_2/MeOH)	85%*)
Ex.219			**Ex.216** ·HCl	L.1.3	3-indoleacetic acid (1.1 equiv.) HATU (1.5 equiv.) HOAt (1.5 equiv.) i-Pr_2NEt (5 equiv.)	FC (CH_2Cl_2/MeOH)	63%
Ex.220		NH_2	**Ex.218**	K	H_2, $Pd(OH)_2$-C	crude product	93%*)
Ex.221		NH_2	**Ex.219**	K	H_2, $Pd(OH)_2$-C	crude product	94%*)

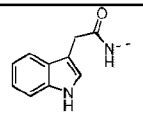
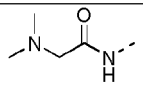
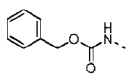
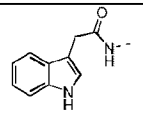
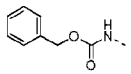
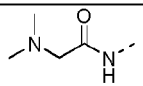
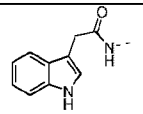
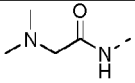
No	R2	R5	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.222			**Ex.220**	L.1.1	acetic anhydride (5 equiv.)	prep. HPLC, method 1	25% (TFA salt)
Ex.223			**Ex.220**	L.1.3	N,N-dimetyl glycine (1.7 equiv.)	prep. HPLC, method 1	24% (TFA salt)
Ex.224			**Ex.220**	L.1.1	succinic anhydride (1.05 equiv.)	prep. HPLC, method 1	37% (TFA salt)
Ex.225			**Ex.220**	L.1.3	3-indoleacetic acid (1.2 equiv.) HATU (1.5 equiv.) HOAt (1.5 equiv.) i-Pr_2NEt (3 equiv.)	prep. HPLC, method 1	28% (TFA salt)
Ex.226			**Ex.221**	L.1.3	N,N-dimetyl glycine (1.7 equiv.)	prep. HPLC, method 1	45% (TFA salt)
Ex.227			**Ex.221**	L.1.1	succinic anhydride (1.05 equiv.) pyridine (49 equiv.)	prep. HPLC, method 1	49%

No	R2	R5	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.228			**Ex.221**	L.1.3	3-indoleacetic acid (1.2 equiv.) HATU (1.5 equiv.) HOAt (1.5 equiv.) i-Pr_2NEt (3 equiv.)	prep. HPLC, method 1	33%
Ex.229			**Ex.221**	L.1.3	2-naphthylacetic acid (1.2 equiv.)	prep. HPLC, method 1	56%
Ex.230			**Ex.220**	L.1.3	2-naphthylacetic acid (1.2 equiv.)	prep. HPLC, method 1	52% (TFA salt)

*) Analytical sample further purified by prep. HPLC, method 1 to afford the TFA salt of the corresponding product

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Table 31b: Examples of Core 13 (**Ex.215-Ex.230,** *continued on the following pages*)

No	R2	R5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.215-Ex.216: *cf. experimental description*							
Ex.217			C31H36N6O6	588.3	1.82 (94)	589.2	Method 1b
Ex.218			C31H40N6O7	608.3	1.36 (100)	609.2	Method 4b
Ex.219			C37H40N6O7	680.3	1.64 (96)	681.3	Method 2
Ex.220		NH_2	C23H34N6O5	474.3	1.19 (92)	475.2	Method 5b
Ex.221		NH_2	C29H34N6O5	546.3	1.38 (96)	547.2	Method 4b
Ex.222			C25H36N6O6	516.3	1.23 (97)	517.2	Method 5b

No	R2	R5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.223			C27H41N7O6	559.3	1.33 (94)	560.3	Method 5b
Ex.224			C27H38N6O8	574.3	1.04 (100)	575.2	Method 5b
Ex.225			C33H41N7O6	631.3	1.30 (97)	632.3	Method 4b
Ex.226			C33H41N7O6	631.3	1.39 (92)	632.2	Method 4b
Ex.227			C33H38N6O8	646.3	1.49 (94)	647.2	Method 4b
Ex.228			C39H41N7O6	703.3	1.75 (91)	704.3	Method 4b
Ex.229			C41H42N6O6	714.3	1.91 (92)	715.3	Method 4b

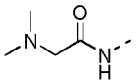
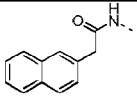
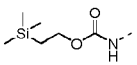
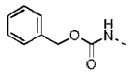
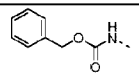
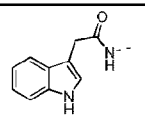
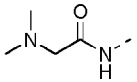
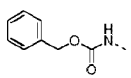
No	R2	R5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.230			C35H42N6O6	642.3	1.50 (100)	643.2	Method 4b

Table 31c: Examples of Core 13 (**Ex.215-Ex.230,** *continued on the following pages*)

No	R2	R5	IUPAC name
Ex.215			benzyl N-[(4S,6R,13S)-11,15-dimethyl-9,12,16-trioxo-6-({[2-(trimethylsilyl)ethoxy]carbonyl}amino)-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.216	NH_2		benzyl N-[(4S,6R,13S)-6-amino-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.217			N-[(4S,6R,13S)-13-(acetylamino)-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]-2-(1H-indol-3-yl)acetamide
Ex.218			benzyl N-[(4S,6R,13S)-6-{[2-(dimethylamino)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate

No	R2	R5	IUPAC name
Ex.219			benzyl N-[(4S,6R,13S)-6-{[2-(1H-indol-3-yl)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.0^{4,8}]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.220		NH_2	N-[(4S,6R,13S)-13-amino-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.0^{4,8}]henicosa-1(21),17,19-trien-6-yl]-2-(dimethylamino)acetamide
Ex.221		NH_2	N-[(4S,6R,13S)-13-amino-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.0^{4,8}]henicosa-1(21),17,19-trien-6-yl]-2-(1H-indol-3-yl)acetamide
Ex.222			N-[(4S,6R,13S)-13-(acetylamino)-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.0^{4,8}]henicosa-1(21),17,19-trien-6-yl]-2-(dimethylamino)acetamide
Ex.223			2-(dimethylamino)-N-[(4S,6R,13S)-13-{[2-(dimethylamino)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.0^{4,8}]henicosa-1(21),17,19-trien-6-yl]acetamide
Ex.224			4-{[(4S,6R,13S)-6-{[2-(dimethylamino)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.0^{4,8}]henicosa-1(21),17,19-trien-13-yl]amino}-4-oxobutanoic acid
Ex.225			2-(dimethylamino)-N-[(4S,6R,13S)-13-{[2-(1H-indol-3-yl)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.0^{4,8}]henicosa-1(21),17,19-trien-6-yl]acetamide

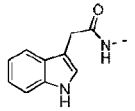
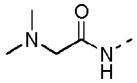
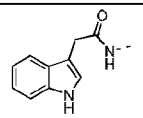
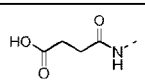
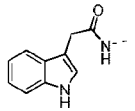
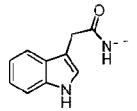
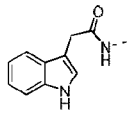
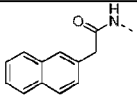
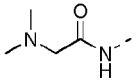
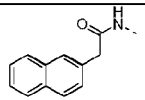
No	R2	R5	IUPAC name
Ex.226			2-(dimethylamino)-N-[(4S,6R,13S)-6-{[2-(1H-indol-3-yl)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]acetamide
Ex.227			4-{[(4S,6R,13S)-6-{[2-(1H-indol-3-yl)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]amino}-4-oxobutanoic acid
Ex.228			2-(1H-indol-3-yl)-N-[(4S,6R,13S)-13-{[2-(1H-indol-3-yl)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]acetamide
Ex.229			N-[(4S,6R,13S)-11,15-dimethyl-13-{[2-(2-naphthyl)acetyl]amino}-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]-2-(1H-indol-3-yl)acetamide
Ex.230			2-(dimethylamino)-N-[(4S,6R,13S)-11,15-dimethyl-13-{[2-(2-naphthyl)acetyl]amino}-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]acetamide

Table 32a: Examples of Core 14 (**Ex.231-Ex.237,** *continued on the following page*)

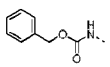
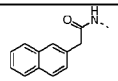
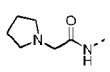
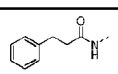
No	R2	R5	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.231-Ex.232: *cf. experimental description*							
Ex.233			**Ex.232**·TFA	L.1.3	3-indoleacetic acid (1.5 equiv.) HATU (1.5 equiv.) HOAt (1.5 equiv.) i-Pr_2NEt (5 equiv)	FC (EtOAc, then CH_2Cl_2/MeOH)	68%
Ex.234		NH_2	**Ex.233**	K	H_2, $Pd(OH)_2$-C	crude product	99%
Ex.235			**Ex.234**	L.1.3	2-naphthylacetic acid (1.2 equiv.)	prep. HPLC, method 3	68%
Ex.236			**Ex.234**	L.1.3	pyrrolidin-1-acetic acid (1,2 equiv.)	prep. HPLC, method 3	28%
Ex.237			**Ex.234**	L.1.3	3-phenylpropionic acid	prep. HPLC, method 3	66%

Table 32b: Examples of Core 14 (**Ex.231-Ex.237,** *continued on the following page*)

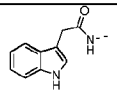
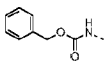
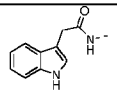
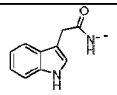
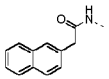
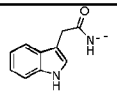
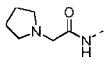
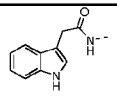
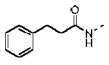
No	R2	R5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.231-Ex.232: *cf. experimental description*							
Ex.233			C37H40N6O7	680.3	1.80 (96)	681.4	Method 2
Ex.234		NH_2	C29H34N6O5	546.3	1.47 (93)	547.3	Method 2
Ex.235			C41H42N6O6	714.3	1.80 (90)	715.4	Method 2
Ex.236			C35H43N7O6	657.3	1.45 (94)	658.4	Method 2
Ex.237			C38H42N6O6	678.3	1.81 (96)	679.4	Method 2

Table 32c: Examples of Core 14 (**Ex.231-Ex.237,** *continued on the following page*)

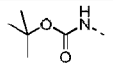
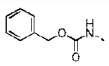
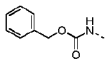
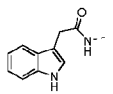
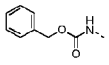
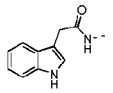
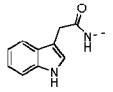
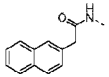
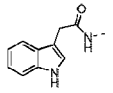
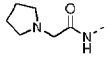
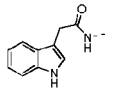
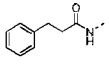
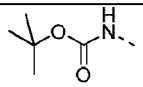
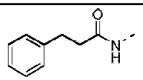
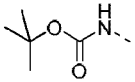
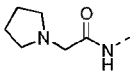
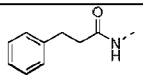
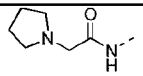
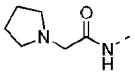
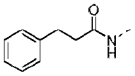
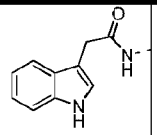
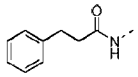
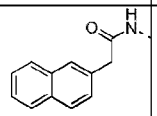
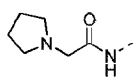
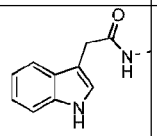
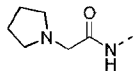
No	R2	R5	IUPAC name
Ex.231			benzyl N-[(4S,6S,13R)-6-[(tert-butoxycarbonyl)amino]-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.232	NH_2		benzyl N-[(4S,6S,13R)-6-amino-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.233			benzyl N-[(4S,6S,13R)-6-{[2-(1H-indol-3-yl)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.234		NH_2	N-[(4S,6S,13R)-13-amino-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]-2-(1H-indol-3-yl)acetamide
Ex.235			N-[(4S,6S,13R)-11,15-dimethyl-13-{[2-(2-naphthyl)acetyl]amino}-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]-2-(1H-indol-3-yl)acetamide
Ex.236			N-[(4S,6S,13R)-11,15-dimethyl-9,12,16-trioxo-13-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]-2-(1H-indol-3-yl)acetamide
Ex.237			N-[(4S,6S,13R)-6-{[2-(1H-indol-3-yl)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]-3-phenylpropanamide

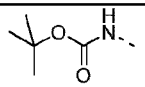
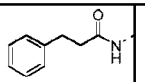
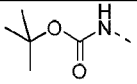
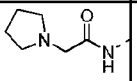
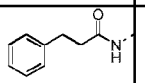
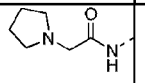
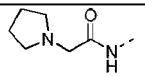
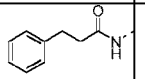
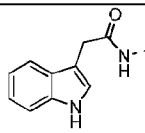
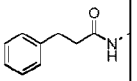
Table 33a: Examples of Core 15 and Core 16 (**Ex.238-Ex.247**, *continued on the following page*)

No	R2	R5	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.238-Ex.239: *cf. experimental description*							
Ex.240			**Ex.239**	L.1.3	3-phenylpoanoic acid	FC (EtOAc/MeOH)*)	47%
Ex.241			**Ex.239**	L.1.3	pyrrolidin-1-acetic acid	FC (CH_2Cl_2/MeOH/aq. NH_3)	56%
Ex.242	NH_2		**Ex.240**	J	HCl-dioxane	crude product	quant. (HCl salt)
Ex.243	NH_2		**Ex.241**	J	HCl-dioxane	crude product	quant. (HCl salt)
Ex.244			**Ex.242**	L.1.3	pyrrolidin-1-acetic acid	FC (CH_2Cl_2/MeOH/aq. NH_3)	81%

No	R2	R5	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.245			**Ex.242**	L.1.3	3-indoleacetic acid	FC (CH_2Cl_2/MeOH/aq. NH_3)	59%
Ex.246			**Ex.243**	L.1.3	2-naphthylacetic acid	FC (CH_2Cl_2/MeOH/aq. NH_3)	51%
Ex.247			**Ex.243**	L.1.3	3-indoleacetic acid	FC (CH_2Cl_2/MeOH/aq. NH_3)	58%

*) An analytical sample was further purified by prep. HPLC, method 2

Table 33b: Examples of Core 15 and Core 16 (**Ex.238-Ex.247**, *continued on the following page*)

No	R2	R5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.238-Ex.239: *cf. experimental description*							
Ex.240			C33H44N4O6	592.3	2.12 (90)	593.3	Method 4a
Ex.241			C30H45N5O6	571.3	1.58 (91)	572.3	Method 4a
Ex.242	NH_2		C28H36N4O4	492.3	1.53 (88), 1.59 (6)	493.2	Method 4a
Ex.243	NH_2		C25H37N5O4	471.3	1.08 (91)	472.4	Method 4a
Ex.244			C34H45N5O5	603.3	1.63 (93)	604.4	Method 4a
Ex.245			C38H43N5O5	649.3	2.01 (91)	650.3	Method 4a

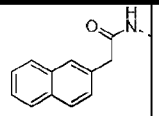
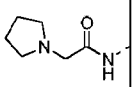
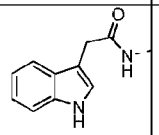
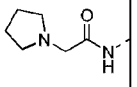
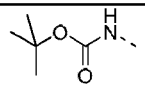
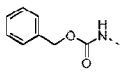
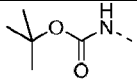
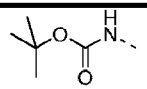
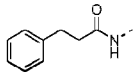
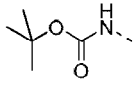
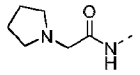
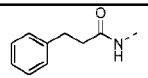
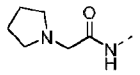
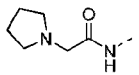
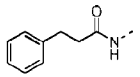
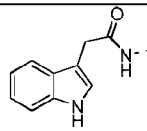
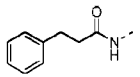
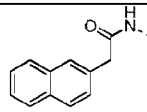
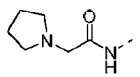
No	R2	R5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.246			C37H45N5O5	639.3	1.69 (90)	640.3	Method 4a
Ex.247			C35H44N6O5	628.3	1.52 (94)	629.3	Method 4a

Table 33c: Examples of Core 15 and Core 16 (**Ex.238-Ex.247**, *continued on the following page*)

No	R2	R5	IUPAC name
Core 15			
Ex.238			benzyl N-[(4S,6S,10S)-6-[(tert-butoxycarbonyl)amino]-15-methyl-9,16-dioxo-2-oxa-8,15-diazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),12,17,19-tetraen-10-yl]carbamate
Core 16			
Ex.239		NH_2	tert-butyl N-[(4S,6S,10S)-10-amino-15-methyl-9,16-dioxo-2-oxa-8,15-diazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]carbamate

No	R2	R5	IUPAC name
Ex.240			tert-butyl N-[(4S,6S,10S)-15-methyl-9,16-dioxo-10-[(3-phenylpropanoyl)amino]-2-oxa-8,15-diazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]carbamate
Ex.241			tert-butyl N-[(4S,6S,10S)-15-methyl-9,16-dioxo-10-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,15-diazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]carbamate
Ex.242	NH_2		N-[(4S,6S,10S)-6-amino-15-methyl-9,16-dioxo-2-oxa-8,15-diazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-10-yl]-3-phenylpropanamide
Ex.243	NH_2		N-[(4S,6S,10S)-6-amino-15-methyl-9,16-dioxo-2-oxa-8,15-diazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-10-yl]-2-(1-pyrrolidinyl)acetamide
Ex.244			N-[(4S,6S,10S)-15-methyl-9,16-dioxo-6-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,15-diazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-10-yl]-3-phenylpropanamide
Ex.245			N-[(4S,6S,10S)-6-{[2-(1H-indol-3-yl)acetyl]amino}-15-methyl-9,16-dioxo-2-oxa-8,15-diazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-10-yl]-3-phenylpropanamide
Ex.246			N-[(4S,6S,10S)-15-methyl-9,16-dioxo-10-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,15-diazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]-2-(2-naphthyl)acetamide

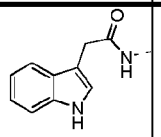
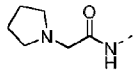
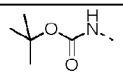
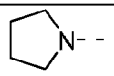
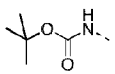
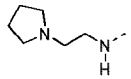
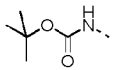
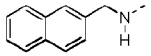
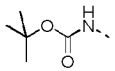
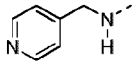
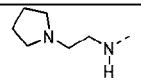
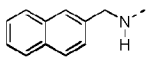
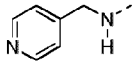
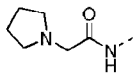
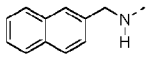
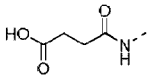
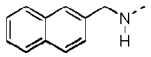
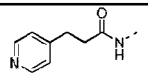
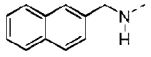
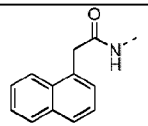
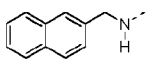
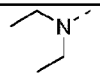
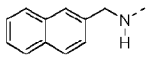
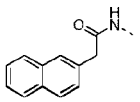
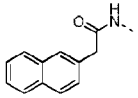
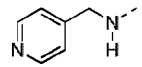
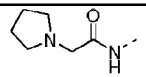
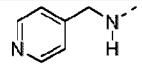
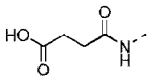
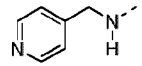
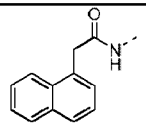
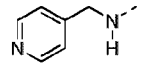
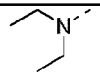
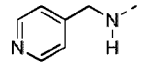
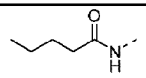
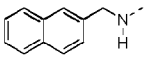
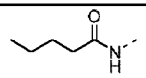
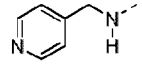
No	R2	R5	IUPAC name
Ex.247			2-(1H-indol-3-yl)-N-[(4S,6S,10S)-15-methyl-9,16-dioxo-10-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,15-diazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]acetamide

Table 34a: Examples of Core 17 (**Ex.248-Ex.271,** *continued on the following pages*)

No	R2	R50	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.248-Ex.249: *cf. experimental description*							
Ex.250			**Ex.249**	L.2	pyrrolidine	FC (CH_2Cl_2/MeOH)	81%
Ex.251			**Ex.249**	L.2	N-(2-aminoethyl) pyrrolidine	FC (CH_2Cl_2/MeOH/aq. NH_3 soln.)	88%

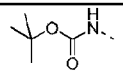
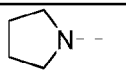
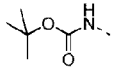
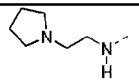
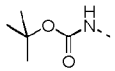
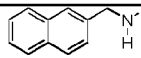
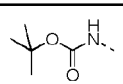
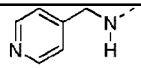
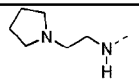
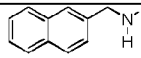
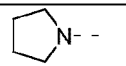
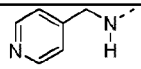
No	R2	R50	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.252			**Ex.249**	L.2	2-naphthylmethylamine (1.5 equiv.) HATU (1.5 equiv.) HOAt (1.5 equiv.) i-Pr_2NEt (3 equiv.)	FC (CH_2Cl_2/MeOH)	91%
Ex.253			**Ex.249**	L.2	4-(aminomethyl)pyridine (1.5 equiv.) HATU (1.5 equiv.) HOAt (1.5 equiv.) i-Pr_2NEt (3 equiv.)	FC (CH_2Cl_2/MeOH)*)	97%
Ex.254	NH_2		**Ex.251**	J	HCl-dioxane	crude product	96% (HCl salt)
Ex.255	NH_2		**Ex.252**	J	HCl-dioxane	crude product	100% (HCl salt)
Ex.256	NH_2		**Ex.250**	J	HCl-dioxane	crude product	93% (HCl salt)
Ex.257	NH_2		**Ex.253**	J	HCl-dioxane	crude product	91% (HCl salt)

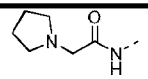
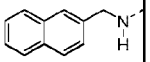
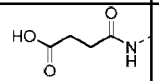
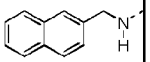
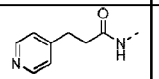
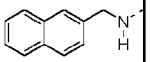
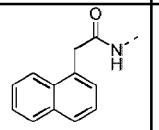
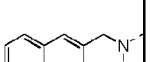
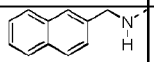
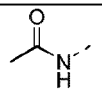
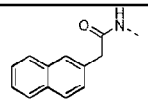
No	R2	R50	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.258			Ex.255	L.1.2	1-pyrrolidinacetic acid (2.7 equiv.) i-Pr_2NEt v(4 equiv.)	FC (CH_2Cl_2/MeOH)	61%
Ex.259			Ex.255	L.1.1	succininc anhydride (1.05 equiv.) pyridine (49 equiv.)	prep. HPLC, method 1	15%
Ex.260			Ex.255	L.1.2	3-(pyridine-4-yl)propanoic acid	prep. HPLC, method 1	55% (TFA salt)
Ex.261			Ex.255	L.1.3	1-naphthylacetic acid (1.2 equiv.)	prep. HPLC, method 1	69%
Ex.262			Ex.255	M	acetaldehyde	prep. HPLC, method 1	76% (TFA salt)
Ex.263			Ex.256	L.1.1	acetic anhydride (10 equiv.) Pyridine/CH_2Cl_2 1:1 (3 mL)	prep. HPLC, method 1	82%
Ex.264			Ex.256	L.1.3	2-naphthylacetic acid (1.2 equiv.)	prep. HPLC, method 1	61%

No	R2	R50	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.265			Ex.257	L.1.3	2-naphthylacetic acid (1.2 equiv.)	prep. HPLC, method 1	59% (TFA salt)
Ex.266			Ex.257	L.1.2	1-pyrrolidinacetic acid	prep. HPLC, method 2	71%
Ex.267			Ex.257	L.1.1	succininc anhydride (1.5 equiv.) pyridine (49 equiv.)	prep. HPLC, method 1	89% (TFA salt)
Ex.268			Ex.257	L.1.3	1-naphthylacetic acid (1.2 equiv.)	prep. HPLC, method 2	45%
Ex.269			Ex.257	M	Acetaldehyde (0.75 mL)	prep. HPLC, method 2	70%
Ex.270			Ex.255	L.1.1	valeroyl chloride (2 equiv.)	prep. HPLC, method 1	77%
Ex.271			Ex.257	L.1.1	valeroyl chloride (2 equiv.)	prep. HPLC, method 1	58% (TFA salt)

*) An analytical sample was further purified by prep HPLC, method 1

Table 34b: Examples of Core 17 (**Ex.248-Ex.271,** *continued on the following pages*)

No	R2	R50	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.248-Ex.249: *cf. experimental description*							
Ex.250			C30H43N5O7	585.4	1.58 (96)	586.4	Method 2
Ex.251			C32H48N6O7	628.4	1.35 (98)	629.5	Method 2
Ex.252			C37H45N5O7	671.3	1.86 (88)	672.4	Method 2
Ex.253			C32H42N6O7	622.3	1.29 (92)	623.4	Method 2
Ex.254	NH_2		C27H40N6O5	528.3	1.31 (97)	529.5	Method 3
Ex.255	NH_2		C32H37N5O5	571.3	1.45 (94)	572.4	Method 2
Ex.256	NH_2		C25H35N5O5	485.3	1.06 (96)	486.4	Method 2
Ex.257	NH_2		C27H34N6O5	522.3	0.85 (96)	523.3	Method 2

No	R2	R50	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.258			C38H46N6O6	682.4	1.47 (95)	683.5	Method 2
Ex.259			C36H41N5O8	671.3	1.59 (87)	672.4	Method 2
Ex.260			C40H44N6O6	704.3	1.47 (100)	705.5	Method 2
Ex.261			C44H45N5O6	739.3	1.93 (99)	740.5	Method 2
Ex.262			C36H45N5O5	627.3	1.50 (100)	628.5	Method 2
Ex.263			C27H37N5O6	527.3	1.23 (99)	528.3	Method 2
Ex.264			C37H43N5O6	653.3	1.68 (100)	654.4	Method 2

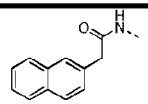
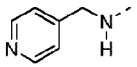
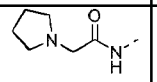
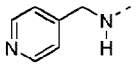
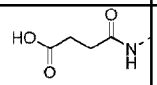
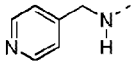
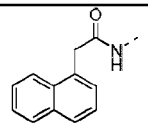
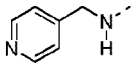
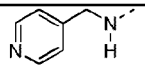
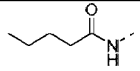
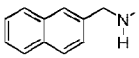
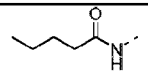
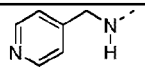
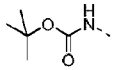
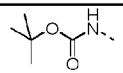
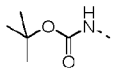
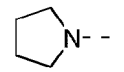
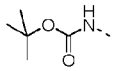
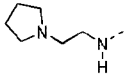
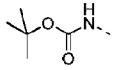
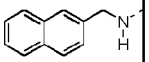
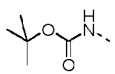
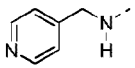
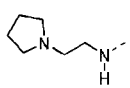
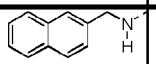
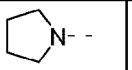
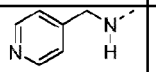
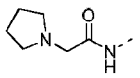
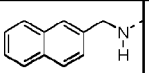
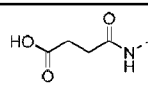
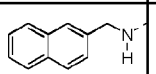
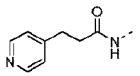
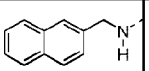
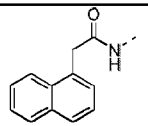
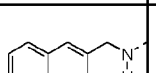
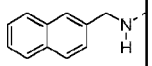
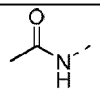
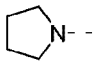
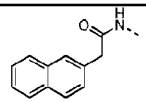
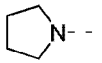
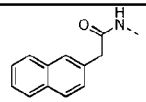
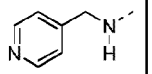
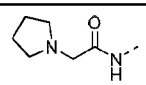
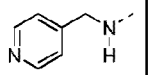
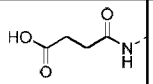
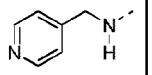
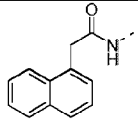
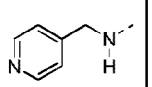
No	R2	R50	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.265			C39H42N6O6	690.3	1.44 (99)	691.5	Method 2
Ex.266			C33H43N7O6	633.3	0.99 (94)	634.5	Method 2
Ex.267			C31H38N6O8	622.3	1.05 (94)	623.3	Method 2
Ex.268			C39H42N6O6	690.3	1.68 (93)	691.5	Method 3
Ex.269			C31H42N6O5	578.3	0.96 (96)	579.5	Method 2
Ex.270			C37H45N5O6	655.3	1.81 (100)	656.4	Method 2
Ex.271			C32H42N6O6	606.3	1.25 (100)	607.4	Method 2

Table 34c: Examples of Core 17 (**Ex.248-Ex.271,** *continued on the following pages*)

No	R2	R50	IUPAC name
Ex.248		OCH_2Ph	benzyl (4S,6R,15S)-6-[(tert-butoxycarbonyl)amino]-11,16-dimethyl-9,12,17-trioxo-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-triene-15-carboxylate
Ex.249		OH	(4S,6R,15S)-6-[(tert-butoxycarbonyl)amino]-11,16-dimethyl-9,12,17-trioxo-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-triene-15-carboxylic acid
Ex.250			tert-butyl N-[(4S,6R,15S)-11,16-dimethyl-9,12,17-trioxo-15-(1-pyrrolidinylcarbonyl)-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-trien-6-yl]carbamate
Ex.251			tert-butyl N-[(4S,6R,15S)-11,16-dimethyl-9,12,17-trioxo-15-({[2-(1-pyrrolidinyl)ethyl]amino}carbonyl)-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-trien-6-yl]carbamate
Ex.252			tert-butyl N-[(4S,6R,15S)-11,16-dimethyl-15-{[(2-naphthylmethyl)amino]carbonyl}-9,12,17-trioxo-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-trien-6-yl]carbamate
Ex.253			tert-butyl N-[(4S,6R,15S)-11,16-dimethyl-9,12,17-trioxo-15-{[(4-pyridinylmethyl)amino]carbonyl}-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-trien-6-yl]carbamate
Ex.254	NH_2		(4S,6R,15S)-6-amino-11,16-dimethyl-9,12,17-trioxo-N-[2-(1-pyrrolidinyl)ethyl]-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-triene-15-carboxamide

No	R2	R50	IUPAC name
Ex.255	NH_2		(4S,6R,15S)-6-amino-11,16-dimethyl-N-(2-naphthylmethyl)-9,12,17-trioxo-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-triene-15-carboxamide
Ex.256	NH_2		(4S,6R,15S)-6-amino-11,16-dimethyl-15-(1-pyrrolidinylcarbonyl)-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-triene-9,12,17-trione
Ex.257	NH_2		(4S,6R,15S)-6-amino-11,16-dimethyl-9,12,17-trioxo-N-(4-pyridinylmethyl)-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-triene-15-carboxamide
Ex.258			(4S,6R,15S)-11,16-dimethyl-N-(2-naphthylmethyl)-9,12,17-trioxo-6-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-triene-15-carboxamide
Ex.259			4-{[(4S,6R,15S)-11,16-dimethyl-15-{[(2-naphthylmethyl)amino]carbonyl}-9,12,17-trioxo-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-trien-6-yl]amino}-4-oxobutanoic acid
Ex.260			(4S,6R,15S)-11,16-dimethyl-N-(2-naphthylmethyl)-9,12,17-trioxo-6-{[3-(4-pyridinyl)propanoyl]amino}-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-triene-15-carboxamide
Ex.261			(4S,6R,15S)-11,16-dimethyl-6-{[2-(1-naphthyl)acetyl]amino}-N-(2-naphthylmethyl)-9,12,17-trioxo-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-triene-15-carboxamide

No	R2	R50	IUPAC name
Ex.262			(4S,6R,15S)-6-(diethylamino)-11,16-dimethyl-N-(2-naphthylmethyl)-9,12,17-trioxo-2-oxa-8,11,16-triazatricyclo[16.2.2.0^{4,8}]docosa-1(20),18,21-triene-15-carboxamide
Ex.263			N-[(4S,6R,15S)-11,16-dimethyl-9,12,17-trioxo-15-(1-pyrrolidinylcarbonyl)-2-oxa-8,11,16-triazatricyclo[16.2.2.0^{4,8}]docosa-1(20),18,21-trien-6-yl]acetamide
Ex.264			N-[(4S,6R,15S)-11,16-dimethyl-9,12,17-trioxo-15-(1-pyrrolidinylcarbonyl)-2-oxa-8,11,16-triazatricyclo[16.2.2.0^{4,8}]docosa-1(20),18,21-trien-6-yl]-2-(2-naphthyl)acetamide
Ex.265			(4S,6R,15S)-11,16-dimethyl-6-{[2-(2-naphthyl)acetyl]amino}-9,12,17-trioxo-N-(4-pyridinylmethyl)-2-oxa-8,11,16-triazatricyclo[16.2.2.0^{4,8}]docosa-1(20),18,21-triene-15-carboxamide
Ex.266			(4S,6R,15S)-11,16-dimethyl-9,12,17-trioxo-N-(4-pyridinylmethyl)-6-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,11,16-triazatricyclo[16.2.2.0^{4,8}]docosa-1(20),18,21-triene-15-carboxamide
Ex.267			4-{[(4S,6R,15S)-11,16-dimethyl-9,12,17-trioxo-15-{[(4-pyridinylmethyl)amino]carbonyl}-2-oxa-8,11,16-triazatricyclo[16.2.2.0^{4,8}]docosa-1(20),18,21-trien-6-yl]amino}-4-oxobutanoic acid
Ex.268			(4S,6R,15S)-11,16-dimethyl-6-{[2-(1-naphthyl)acetyl]amino}-9,12,17-trioxo-N-(4-pyridinylmethyl)-2-oxa-8,11,16-triazatricyclo[16.2.2.0^{4,8}]docosa-1(20),18,21-triene-15-carboxamide

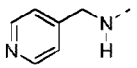
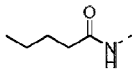
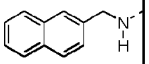
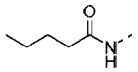
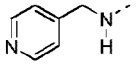
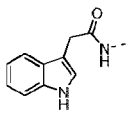
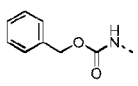
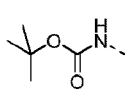
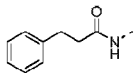
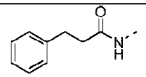
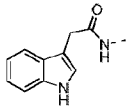
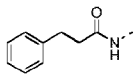
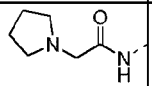
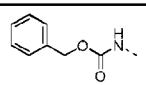
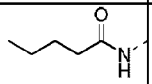
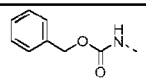
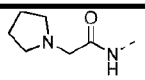
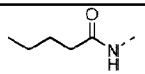
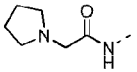
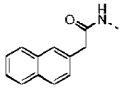
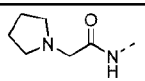
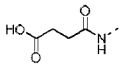
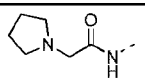
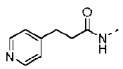
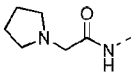
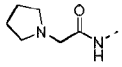
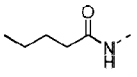
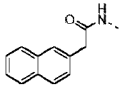
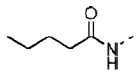
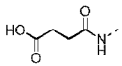
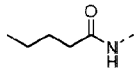
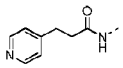
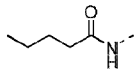
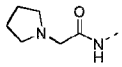
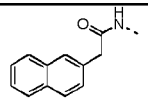
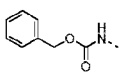
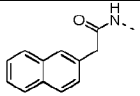
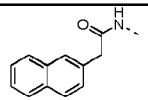
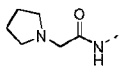
No	R2	R50	IUPAC name
Ex.269			(4S,6R,15S)-6-(diethylamino)-11,16-dimethyl-9,12,17-trioxo-N-(4-pyridinylmethyl)-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-triene-15-carboxamide
Ex.270			(4S,6R,15S)-11,16-dimethyl-N-(2-naphthylmethyl)-9,12,17-trioxo-6-(pentanoylamino)-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-triene-15-carboxamide
Ex.271			(4S,6R,15S)-11,16-dimethyl-9,12,17-trioxo-6-(pentanoylamino)-N-(4-pyridinylmethyl)-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-triene-15-carboxamide

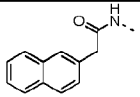
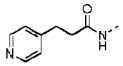
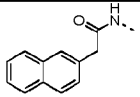
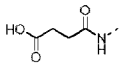
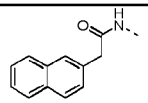
Table 35a: Examples of Core 18 (**Ex.272-Ex.296,** *continued on the following pages*)

No	R2	R5	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.272-Ex.274: *cf. experimental description*							
Ex.275			**Ex.273** (HCl salt)	L.1.3	3-indoleacetic acid (1.1 equiv.) HATU (1.5 equiv.) HOAt (1.5 equiv.) i-Pr_2NEt (5 equiv.)	FC (CH_2Cl_2/MeOH)	53%

No	R2	R5	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.276			**Ex.274**	L.1.3	3-phenylpropanoic acid (1.2 equiv.) HATU (1.5 equiv.) HOAt (1.5 equiv.) i-Pr_2NEt (3 equiv.)	FC (CH_2Cl_2/MeOH)	72%
Ex.277	NH_2		**Ex.276**	J	HCl-dioxane	crude product	quant. (HCl salt)
Ex.278			**Ex.277**	L.1.3	3-indoleacetic acid (1.1 equiv.) HATU (1.5 equiv.) HOAt (1.5 equiv.) i-Pr_2NEt (5 equiv.)	FC (CH_2Cl_2/MeOH)	75%
Ex.279			**Ex.273** (HCl salt)	L.1.3	pyrrolidine-1-acetic acid (1.2 equiv.)	FC (EtOAc/MeOH)	67%
Ex.280			**Ex.273** (HCl salt)	L.1.1	valeroyl chloride (2 equiv.)	FC (EtOAc/MeOH)	71%

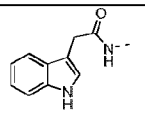
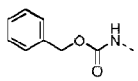
No	R2	R5	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.281		NH_2	**Ex.279**	K	H_2, $Pd(OH)_2$-C	crude product	quant.
Ex.282		NH_2	**Ex.280**	K	H_2, $Pd(OH)_2$-C	crude product	quant.
Ex.283			**Ex.281**	L.1.3	2-naphthylacetic acid (1.2 equiv.)	Prep. HPLC, method 3	27%
Ex.284			**Ex.281**	L.1.1	succinic anhydride (1.5 equiv.) Pyridine (49 equiv.)	Prep. HPLC, method 2	51%
Ex.285			**Ex.281**	L.1.3	3-(pyridine-4-yl)propanoic acid (1.2 equiv.)	Prep. HPLC, method 2	12%
Ex.286			**Ex.281**	L.1.3	pyrrolidine-1-acetic acid (1.2 equiv.)	Prep. HPLC, method 2	16%
Ex.287			**Ex.282**	L.1.3	2-naphthylacetic acid (1.2 equiv.)	FC (CH_2Cl_2/MeOH/aq. NH_3)	79%

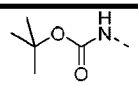
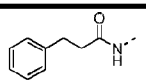
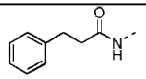
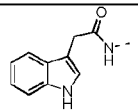
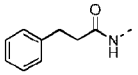
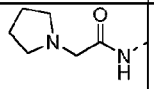
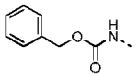
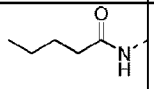
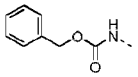
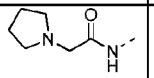
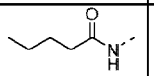
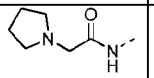
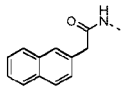
No	R2	R5	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.288			**Ex.282**	L.1.1	succinic anhydride (1.5 equiv.) Pyridine (49 equiv.)	Prep. HPLC, method 2	57%
Ex.289			**Ex.282**	L.1.3	3-(pyridine-4-yl)propanoic acid (1.2 equiv.)	Prep. HPLC, method 3	17%
Ex.290			**Ex.282**	L.1.3	pyrrolidine-1-acetic acid (1.2 equiv.)	FC (CH_2Cl_2/MeOH/aq. NH_3)	65%
Ex.291			**Ex.273** (HCl salt)	L.1.3	2-naphthylacetic acid (1.2 equiv.)	FC (EtOAc/MeOH) *)	79%
Ex.292		NH_2	**Ex.291**	K	H_2, $Pd(OH)_2$-C	FC (EtOAc/MeOH)	69%
Ex.293			**Ex.292**	L.1.3	pyrrolidine-1-acetic acid (1.2 equiv.)	Prep. HPLC, method 3	64%

No	R2	R5	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.294			**Ex.292**	L.1.3	3-(pyridine-4-yl)propanoic acid (1.2 equiv.)	Prep. HPLC, method 3	70%
Ex.295			**Ex.292**	L.1.1	succinic anhydride (1.5 equiv.) Pyridine (49 equiv.)	Prep. HPLC, method 2	73%
Ex.296		$CH_3(CH_2)_8$ CONH	**Ex.292**	L.1.1	decanoyl chloride (2 equiv.)	Prep. HPLC, method 3	40%

*) An analytical sample was further purified by prep. HPLC, method 3

Table 35b: Examples of Core 18 (**Ex.272-Ex.296,** *continued on the following pages*)

No	R2	R5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.272-Ex.274: *cf. experimental description*							
Ex.275			C36H39N7O7	681.3	1.53 (97)	682.5	Method 2

No	R2	R5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.276			C32H42N6O7	622.3	1.57 (95)	623.4	Method 2
Ex.277	NH_2		C27H34N6O5	522.3	1.10 (98)	523.4	Method 2
Ex.278			C37H41N7O6	679.3	1.50 (98)	680.5	Method 2
Ex.279			C32H41N7O7	635.3	1.32 (98)	636.3	Method 2
Ex.280			C31H40N6O7	608.3	1.54 (98)	609.3	Method 2
Ex.281		NH_2	C24H35N7O5	501.3	1.32 (98)	502.3	Method 5a
Ex.282		NH_2	C23H34N6O5	474.3	1.24 (94)	475.1	Method 4a
Ex.283			C36H43N7O6	669.3	1.42 (95)	670.3	Method 4a

No	R2	R5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.284			C28H39N7O8	601.3	0.99 (100)	602.2	Method 5a
Ex.285			C32H42N8O6	634.3	1.47 (98)	635.2	Method 5a
Ex.286			C30H44N8O6	612.3	1.55 (99)	613.3	Method 5a
Ex.287			C35H42N6O6	642.3	1.77 (98)	643.3	Method 4a
Ex.288			C27H38N6O8	574.3	1.32 (100)	575.2	Method 4a
Ex.289			C31H41N7O6	607.3	1.25 (95)	608.3	Method 4a
Ex.290			C29H43N7O6	585.3	1.30 (95)	586.4	Method 4a

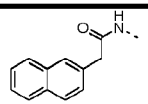
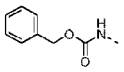
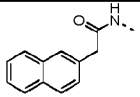
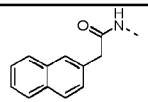
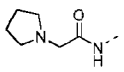
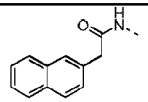
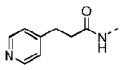
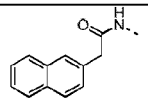
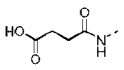
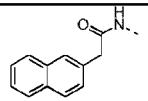
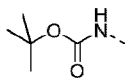
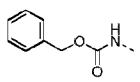
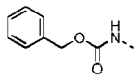
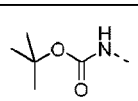
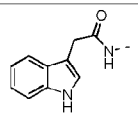
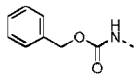
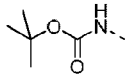
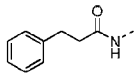
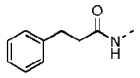
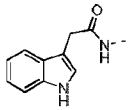
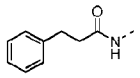
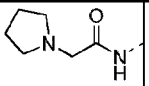
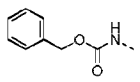
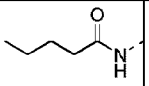
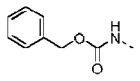
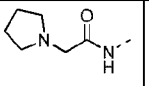
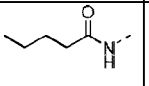
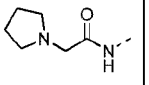
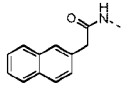
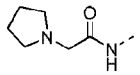
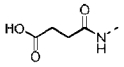
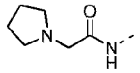
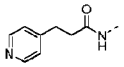
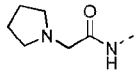
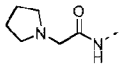
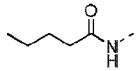
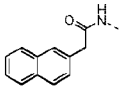
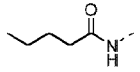
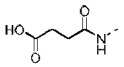
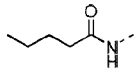
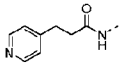
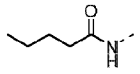
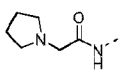
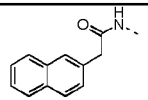
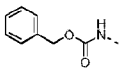
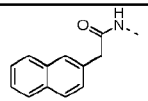
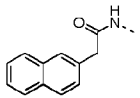
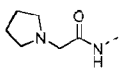
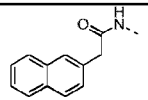
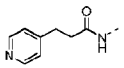
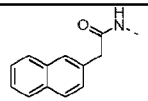
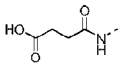
No	R2	R5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.291			C38H40N6O7	692.3	1.91 (97)	693.3	Method 4a
Ex.292		NH_2	C30H34N6O5	558.3	1.55 (99)	559.3	Method 4a
Ex.293			C36H43N7O6	669.3	1.52 (96)	670.3	Method 4a
Ex.294			C38H41N7O6	691.3	1.46 (97)	692.3	Method 4a
Ex.295			C34H38N6O8	658.3	1.58 (99)	659.2	Method 4a
Ex.296		$CH_3(CH_2)_8CONH$	C40H52N6O6	712.4	2.22 (99)	713.4	Method 4a

Table 35c: Examples of Core 18 (**Ex.272-Ex.296,** *continued on the following pages*)

No	R2	R5	IUPAC name
Ex.272			benzyl N-[(4S,6S,13S)-6-[(tert-butoxycarbonyl)amino]-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.273	NH_2		benzyl N-[(4S,6S,13S)-6-amino-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.274		NH_2	tert-butyl N-[(4S,6S,13S)-13-amino-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]carbamate
Ex.275			benzyl N-[(4S,6S,13S)-6-{[2-(1H-indol-3-yl)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.276			tert-butyl N-[(4S,6S,13S)-11,15-dimethyl-9,12,16-trioxo-13-[(3-phenylpropanoyl)amino]-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]carbamate
Ex.277	NH_2		N-[(4S,6S,13S)-6-amino-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]-3-phenylpropanamide

No	R2	R5	IUPAC name
Ex.278			N-[(4S,6S,13S)-6-{[2-(1H-indol-3-yl)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]-3-phenylpropanamide
Ex.279			benzyl N-[(4S,6S,13S)-11,15-dimethyl-9,12,16-trioxo-6-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.280			benzyl N-[(4S,6S,13S)-11,15-dimethyl-9,12,16-trioxo-6-(pentanoylamino)-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.281		NH_2	N-[(4S,6S,13S)-13-amino-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]-2-(1-pyrrolidinyl)acetamide
Ex.282		NH_2	N-[(4S,6S,13S)-13-amino-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]pentanamide
Ex.283			N-[(4S,6S,13S)-11,15-dimethyl-9,12,16-trioxo-6-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]-2-(2-naphthyl)acetamide

No	R2	R5	IUPAC name
Ex.284			4-{[(4S,6S,13S)-11,15-dimethyl-9,12,16-trioxo-6-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]amino}-4-oxobutanoic acid
Ex.285			N-[(4S,6S,13S)-11,15-dimethyl-9,12,16-trioxo-6-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]-3-(4-pyridinyl)propanamide
Ex.286			N-[(4S,6S,13S)-11,15-dimethyl-9,12,16-trioxo-13-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]-2-(1-pyrrolidinyl)acetamide
Ex.287			N-[(4S,6S,13S)-11,15-dimethyl-13-{[2-(2-naphthyl)acetyl]amino}-9,12,16-trioxo-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]pentanamide
Ex.288			4-{[(4S,6S,13S)-11,15-dimethyl-9,12,16-trioxo-6-(pentanoylamino)-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]amino}-4-oxobutanoic acid
Ex.289			N-[(4S,6S,13S)-11,15-dimethyl-9,12,16-trioxo-13-{[3-(4-pyridinyl)propanoyl]amino}-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]pentanamide

No	R2	R5	IUPAC name
Ex.290			N-[(4S,6S,13S)-11,15-dimethyl-9,12,16-trioxo-13-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]pentanamide
Ex.291			benzyl N-[(4S,6S,13S)-11,15-dimethyl-6-{[2-(2-naphthyl)acetyl]amino}-9,12,16-trioxo-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.292		NH_2	N-[(4S,6S,13S)-13-amino-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]-2-(2-naphthyl)acetamide
Ex.293			N-[(4S,6S,13S)-11,15-dimethyl-9,12,16-trioxo-13-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]-2-(2-naphthyl)acetamide
Ex.294			N-[(4S,6S,13S)-11,15-dimethyl-6-{[2-(2-naphthyl)acetyl]amino}-9,12,16-trioxo-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]-3-(4-pyridinyl)propanamide
Ex.295			4-{[(4S,6S,13S)-11,15-dimethyl-6-{[2-(2-naphthyl)acetyl]amino}-9,12,16-trioxo-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]amino}-4-oxobutanoic acid

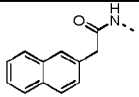
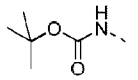
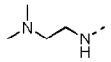
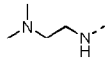
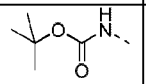
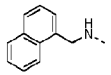
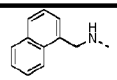
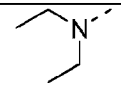
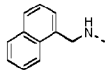
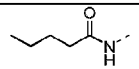
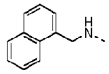
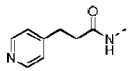
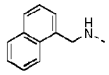
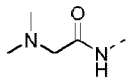
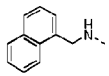
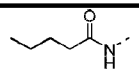
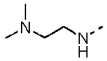
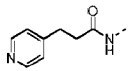
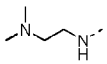
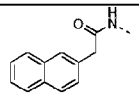
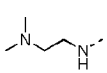
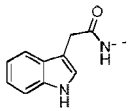
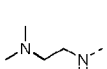
No	R2	R5	IUPAC name
Ex.296		$CH_3(CH_2)_8CONH$	N-[(4S,6S,13S)-11,15-dimethyl-6-{[2-(2-naphthyl)acetyl]amino}-9,12,16-trioxo-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]decanamide

Table 36a: Examples of Core 19 (**Ex.297-Ex.310,** *continued on the following pages*)

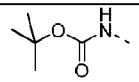
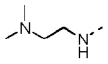
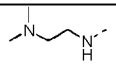
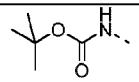
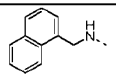
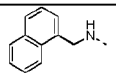
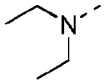
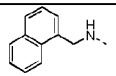
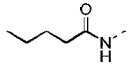
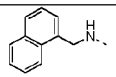
No	R2	R50	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.297-Ex.298: *cf. experimental description*							
Ex.299			**Ex.298**	L.2	N,N-dimethylethylene-diamine	Flash Chromatography	80%
Ex.300	NH_2		**Ex.299**	J	HCl-dioxane	No purification	quant. (HCl salt)
Ex.301			**Ex.298**	L.2	1-naphthylmethylamine	FC (CH_2Cl_2/MeOH)	75%

No	R2	R50	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.302	NH_2		**Ex.301**	J	HCl-dioxane	Crude product	quant. (HCl salt)
Ex.303			**Ex.302**	M	acetaldehyde	Prep. HPLC, method 2	45%
Ex.304			**Ex.302**	L.1.1	valeroyl chloride (5 equiv.)	Prep. HPLC, method 2	22%
Ex.305			**Ex.302**	L.1.2	3-(pyridine-4-yl)propanoic acid (3.7 equiv.) i-Pr_2NEt (4 equiv.) bicarbonate resin (4equiv.)	FC (CH_2Cl_2/MeOH/aq. NH_3) then Prep. HPLC, method 3	55%
Ex.306			**Ex.302**	L.1.2	N,N-dimethyl glycine (6.2 equiv.) carbodiimide resin (2.5 equiv.) i-Pr_2NEt (5 equiv.) bicarbonate resin (5 equiv.)	FC (CH_2Cl_2/MeOH)	43%

No	R2	R50	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.307			**Ex.300**	L.1.1	valeroyl chloride (2 equiv.)	Prep. HPLC, method 2	36%
Ex.308			**Ex.300**	L.1.2	3-(pyridine-4-yl)propanoic acid (1.2 equiv.) i-Pr_2NEt (4 equiv.), bicarbonate resin (4equiv.)	FC (CH_2Cl_2/MeOH)	77%
Ex.309			**Ex.300**	L.1.2*)	2-naphthylacetic acid i-Pr_2NEt (4 equiv.)	Prep. HPLC, method 2	58%
Ex.310			**Ex.300**	L.1.2	3-indoleacetic acid (3.7 equiv.) i-Pr_2NEt (4 equiv.) DMF (0.2 mL) bicarbonate resin (4equiv.)	Prep. HPLC, method 2	28%

*) The treatment with (polystyrylmethyl)trimethylammonium bicarbonate was replaced by an aqueous workup ($CHCl_3$, sat. aq. $NaHCO_3$ soln)

Table 36b: Examples of Core 19 (**Ex.297-Ex.310,** *continued on the following pages*)

No	R2	R50	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.297-Ex.298: *cf. experimental description*							
Ex.299			C33H47N7O7	653.4	1.62 (97)	654.4	Method 4a
Ex.300	NH_2		C28H39N7O5	553.3	1.11 (64), 1.08 (35)	554.3	Method 4a
Ex.301			C40H46N6O7	722.3	2.19 (89)	723.4	Method 4a
Ex.302	NH_2		C35H38N6O5	622.3	1.70 (79)	623.3	Method 4a
Ex.303			C39H46N6O5	678.4	1.75 (100)	679.4	Method 4a
Ex.304			C40H46N6O6	706.4	2.09 (100)	707.4	Method 4a

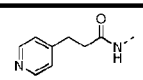
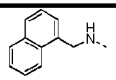
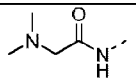
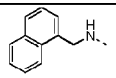
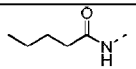
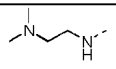
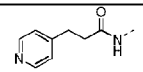
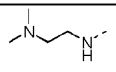
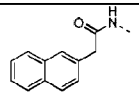
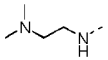
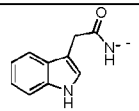
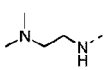
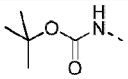
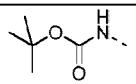
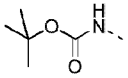
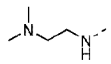
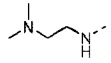
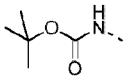
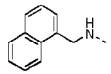
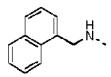
No	R2	R50	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.305			C43H45N7O6	755.3	1.67 (57), 1.70 (38)	756.4	Method 4a
Ex.306			C39H45N7O6	707.3	1.71 (86)	708.3	Method 4a
Ex.307			C33H47N7O6	637.4	1.50 (638.3)	638.3	Method 4a
Ex.308			C36H46N8O6	686.4	1.57 (92)	687.4	Method 5a
Ex.309			C40H47N7O6	721.4	1.68 (98)	722.4	Method 4a
Ex.310			C38H46N8O6	710.4	1.52 (97)	711.4	Method 4a

Table 36c: Examples of Core 19 (**Ex.297-Ex.310,** *continued on the following pages*)

No	R2	R50	IUPAC name
Ex.297		OCH_2Ph	benzyl (4S,6S,15S)-6-[(tert-butoxycarbonyl)amino]-11,16-dimethyl-9,12,17-trioxo-2-oxa-8,11,16,26-tetraazatetracyclo[16.6.2.$0^{4,8}$.$0^{21,25}$]hexacosa-1(24),18,20,22,25-pentaene-15-carboxylate
Ex.298		OH	(4S,6S,15S)-6-[(tert-butoxycarbonyl)amino]-11,16-dimethyl-9,12,17-trioxo-2-oxa-8,11,16,26-tetraazatetracyclo[16.6.2.$0^{4,8}$.$0^{21,25}$]hexacosa-1(24),18,20,22,25-pentaene-15-carboxylic acid
Ex.299			tert-butyl N-[(4S,6S,15S)-15-({[2-(dimethylamino)ethyl]amino}carbonyl)-11,16-dimethyl-9,12,17-trioxo-2-oxa-8,11,16,26-tetraazatetracyclo[16.6.2.$0^{4,8}$.$0^{21,25}$]hexacosa-1(24),18,20,22,25-pentaen-6-yl]carbamate
Ex.300	NH_2		(4S,6S,15S)-6-amino-N-[2-(dimethylamino)ethyl]-11,16-dimethyl-9,12,17-trioxo-2-oxa-8,11,16,26-tetraazatetracyclo[16.6.2.$0^{4,8}$.$0^{21,25}$]hexacosa-1(24),18,20,22,25-pentaene-15-carboxamide
Ex.301			tert-butyl N-[(4S,6S,15S)-11,16-dimethyl-15-{[(1-naphthylmethyl)amino]carbonyl}-9,12,17-trioxo-2-oxa-8,11,16,26-tetraazatetracyclo[16.6.2.$0^{4,8}$.$0^{21,25}$]hexacosa-1(25),18(26),19,21,23-pentaen-6-yl]carbamate
Ex.302	NH_2		(4S,6S,15S)-6-amino-11,16-dimethyl-N-(1-naphthylmethyl)-9,12,17-trioxo-2-oxa-8,11,16,26-tetraazatetracyclo[16.6.2.$0^{4,8}$.$0^{21,25}$]hexacosa-1(25),18(26),19,21,23-pentaene-15-carboxamide

No	R2	R50	IUPAC name
Ex.303			(4S,6S,15S)-6-(diethylamino)-11,16-dimethyl-N-(1-naphthylmethyl)-9,12,17-trioxo-2-oxa-8,11,16,26-tetraazatetracyclo[16.6.2.$0^{4,8}$.$0^{21,25}$]hexacosa-1(25),18(26),19,21,23-pentaene-15-carboxamide
Ex.304			(4S,6S,15S)-11,16-dimethyl-N-(1-naphthylmethyl)-9,12,17-trioxo-6-(pentanoylamino)-2-oxa-8,11,16,26-tetraazatetracyclo[16.6.2.$0^{4,8}$.$0^{21,25}$]hexacosa-1(25),18(26),19,21,23-pentaene-15-carboxamide
Ex.305			(4S,6S,15S)-11,16-dimethyl-N-(1-naphthylmethyl)-9,12,17-trioxo-6-{[3-(4-pyridinyl)propanoyl]amino}-2-oxa-8,11,16,26-tetraazatetracyclo[16.6.2.$0^{4,8}$.$0^{21,25}$]hexacosa-1(25),18(26),19,21,23-pentaene-15-carboxamide
Ex.306			(4S,6S,15S)-6-{[2-(dimethylamino)acetyl]amino}-11,16-dimethyl-N-(1-naphthylmethyl)-9,12,17-trioxo-2-oxa-8,11,16,26-tetraazatetracyclo[16.6.2.$0^{4,8}$.$0^{21,25}$]hexacosa-1(25),18(26),19,21,23-pentaene-15-carboxamide
Ex.307			(4S,6S,15S)-N-[2-(dimethylamino)ethyl]-11,16-dimethyl-9,12,17-trioxo-6-(pentanoylamino)-2-oxa-8,11,16,26-tetraazatetracyclo[16.6.2.$0^{4,8}$.$0^{21,25}$]hexacosa-1(25),18(26),19,21,23-pentaene-15-carboxamide
Ex.308			(4S,6S,15S)-N-[2-(dimethylamino)ethyl]-11,16-dimethyl-9,12,17-trioxo-6-{[3-(4-pyridinyl)propanoyl]amino}-2-oxa-8,11,16,26-tetraazatetracyclo[16.6.2.$0^{4,8}$.$0^{21,25}$]hexacosa-1(25),18(26),19,21,23-pentaene-15-carboxamide

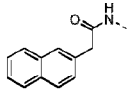
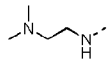
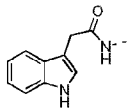
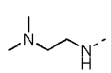
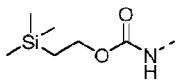
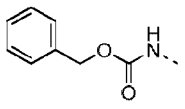
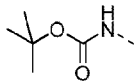
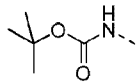
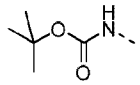
No	R2	R50	IUPAC name
Ex.309			(4S,6S,15S)-N-[2-(dimethylamino)ethyl]-11,16-dimethyl-6-{[2-(2-naphthyl)acetyl]amino}-9,12,17-trioxo-2-oxa-8,11,16,26-tetraazatetracyclo[16.6.2.$0^{4,8}$.$0^{21,25}$]hexacosa-1(25),18(26),19,21,23-pentaene-15-carboxamide
Ex.310			(4S,6S,15S)-N-[2-(dimethylamino)ethyl]-6-{[2-(1H-indol-3-yl)acetyl]amino}-11,16-dimethyl-9,12,17-trioxo-2-oxa-8,11,16,26-tetraazatetracyclo[16.6.2.$0^{4,8}$.$0^{21,25}$]hexacosa-1(25),18(26),19,21,23-pentaene-15-carboxamide

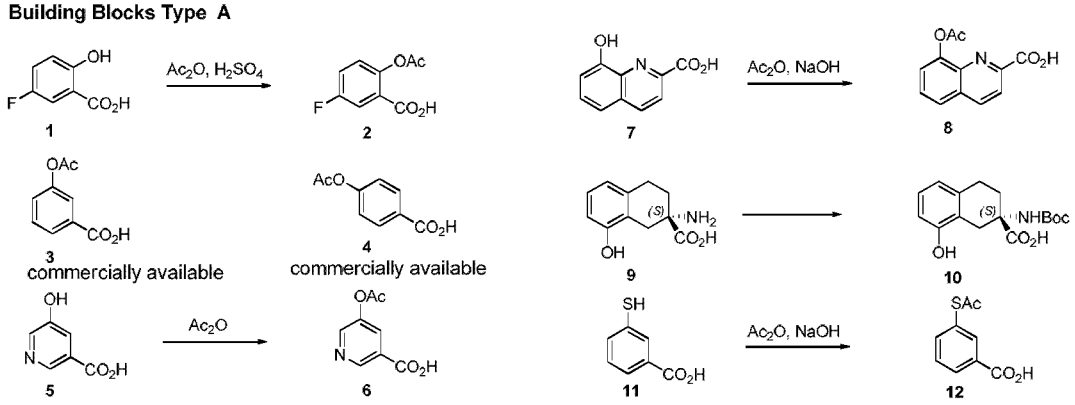
Table 37: Examples of Core 20 and Core 21 (**Ex.311-Ex.313,** *continued on the following page*)

No				IUPAC name
Core 20	**R2**	**R5**	**R38**	
Ex.311				benzyl N-[(4S,6S,13S,17S)-17-[(tert-butoxycarbonyl)amino]-11,15-dimethyl-9,12,16-trioxo-6-({[2-(trimethylsilyl)ethoxy]carbonyl}amino)-2-oxa-8,11,15-triazatetracyclo[15.6.2.$0^{4,8}$.$0^{20,24}$]pentacosa-1(24),20,22-trien-13-yl]carbamate

No				IUPAC name
Core 21	R2	R50		
Ex.312		OCH_2Ph		benzyl (4S,6R,15S)-6-[(tert-butoxycarbonyl)amino]-11,16-dimethyl-9,12,17-trioxo-2-thia-8,11,16-triazatricyclo[16.3.1.$0^{4,8}$]docosa-1(22),18,20-triene-15-carboxylate
Ex.313		OCH_2Ph		benzyl (4S,6R,15S)-6-[(tert-butoxycarbonyl)amino]-11,16-dimethyl-2,2,9,12,17-pentaoxo-2λ^6-thia-8,11,16-triazatricyclo[16.3.1.$0^{4,8}$]docosa-1(22),18,20-triene-15-carboxylate

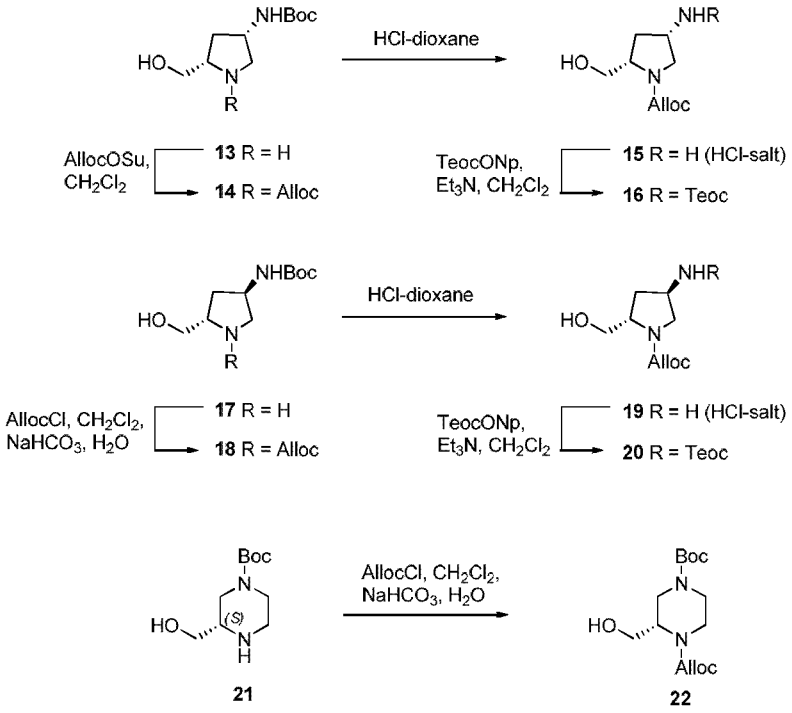
Scheme 1

Building Blocks Type A



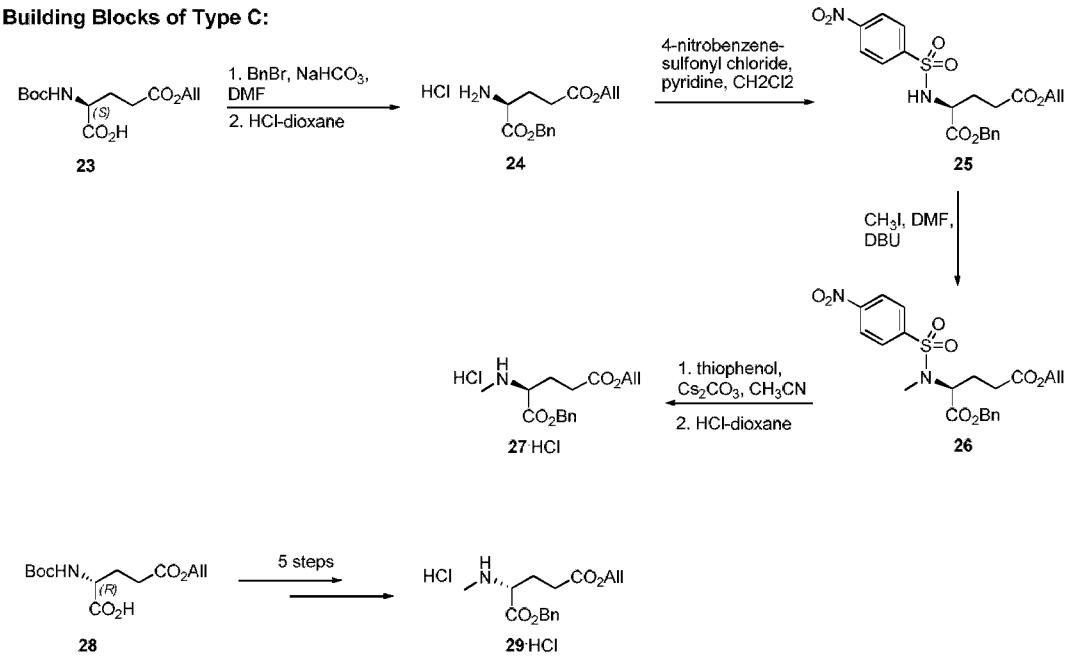
Scheme 2

Building Blocks of Type B



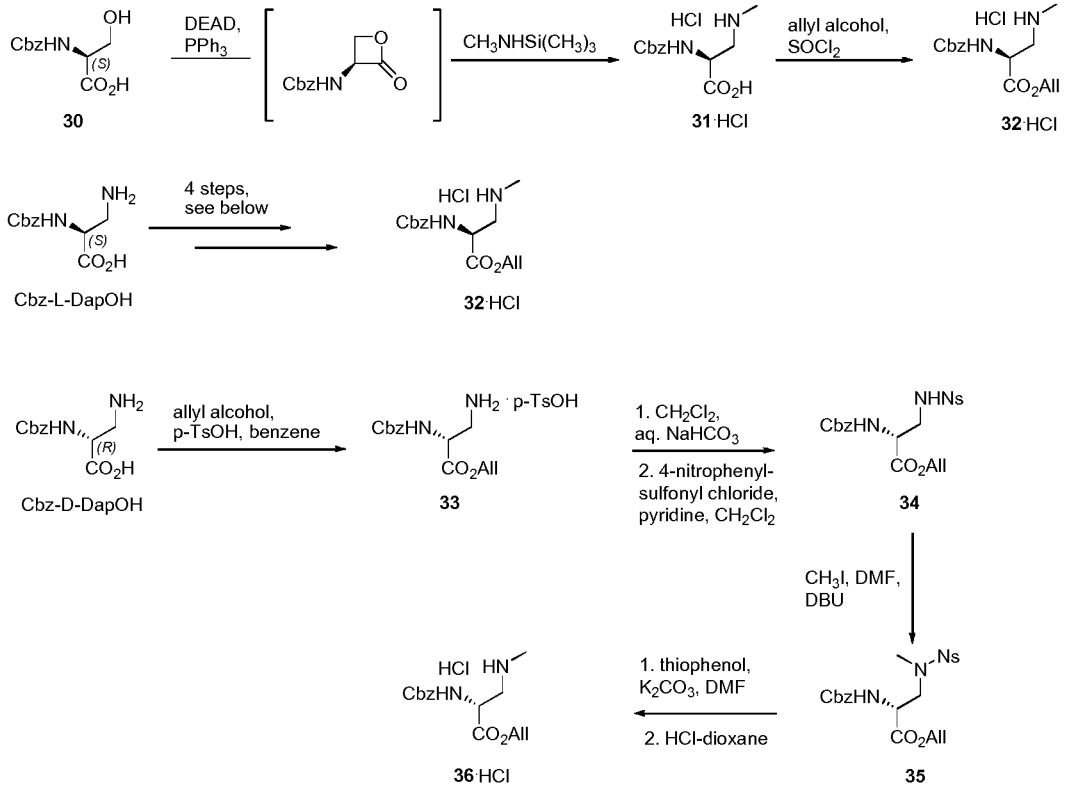
Scheme 3

Building Blocks of Type C:



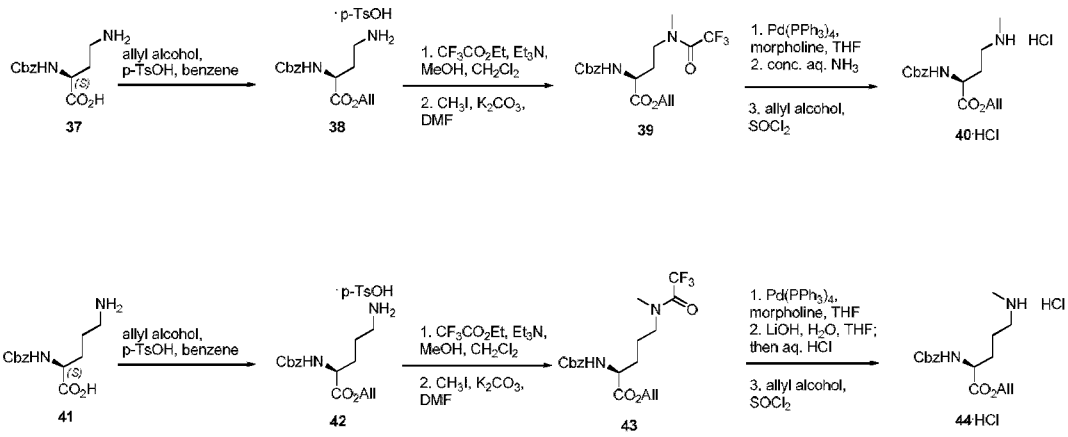
Scheme 3, cont.

Building Blocks of Type C:



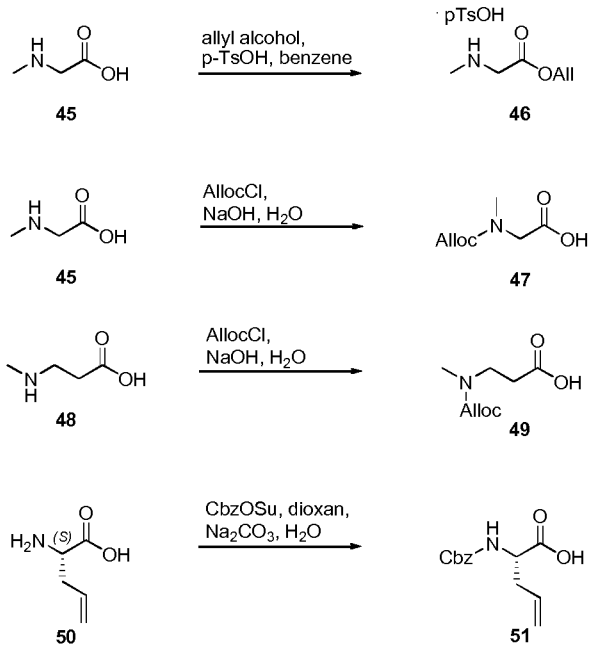
Scheme 3, cont.

Building Blocks of Type C:



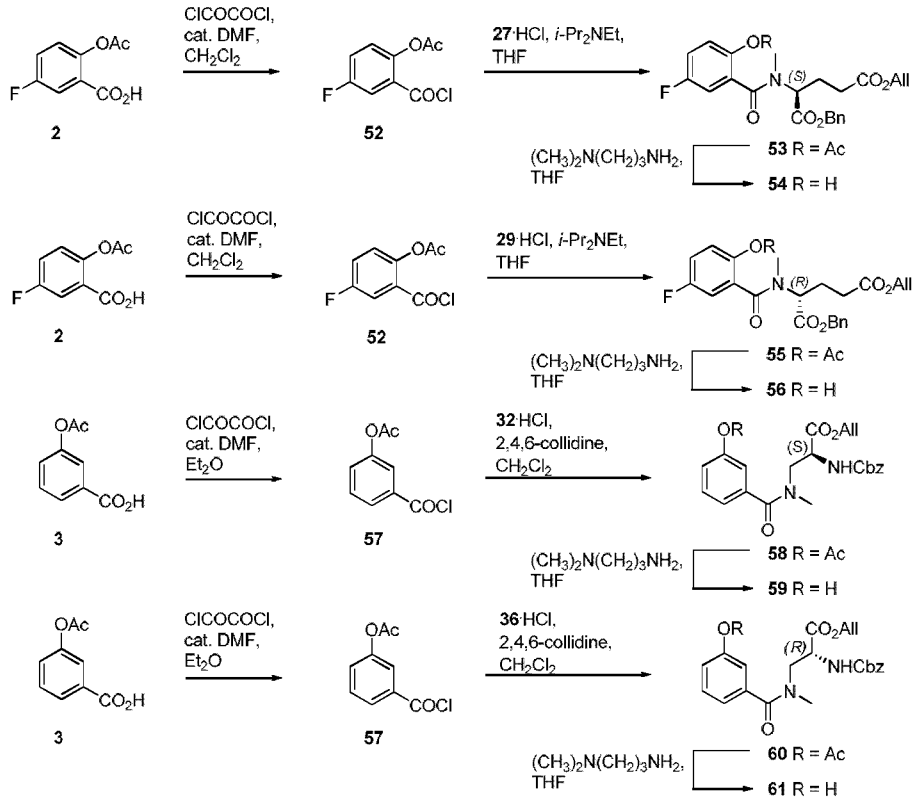
Scheme 3. cont.

Building Blocks of Type C:



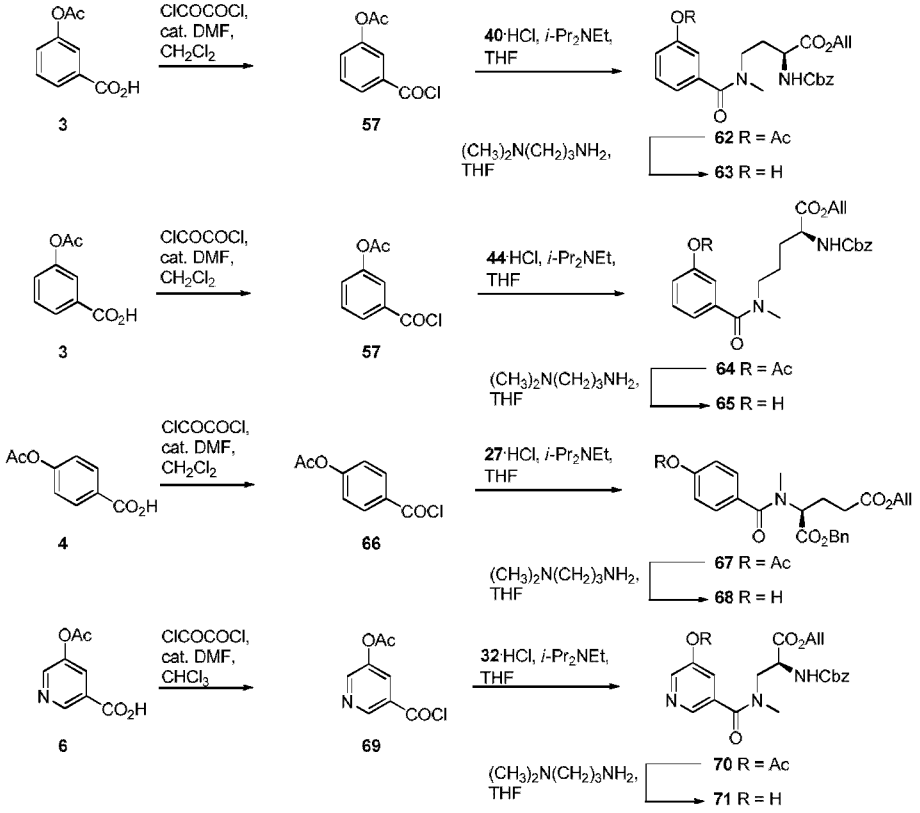
A-c1 Fragments

Scheme 4

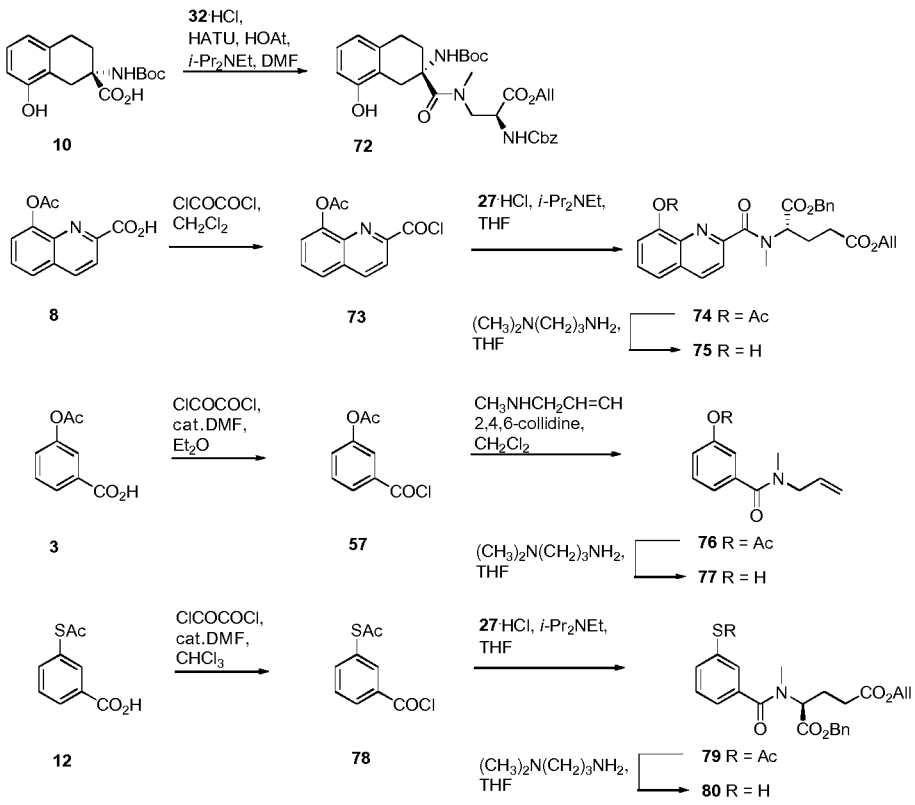


A-c1 Fragments

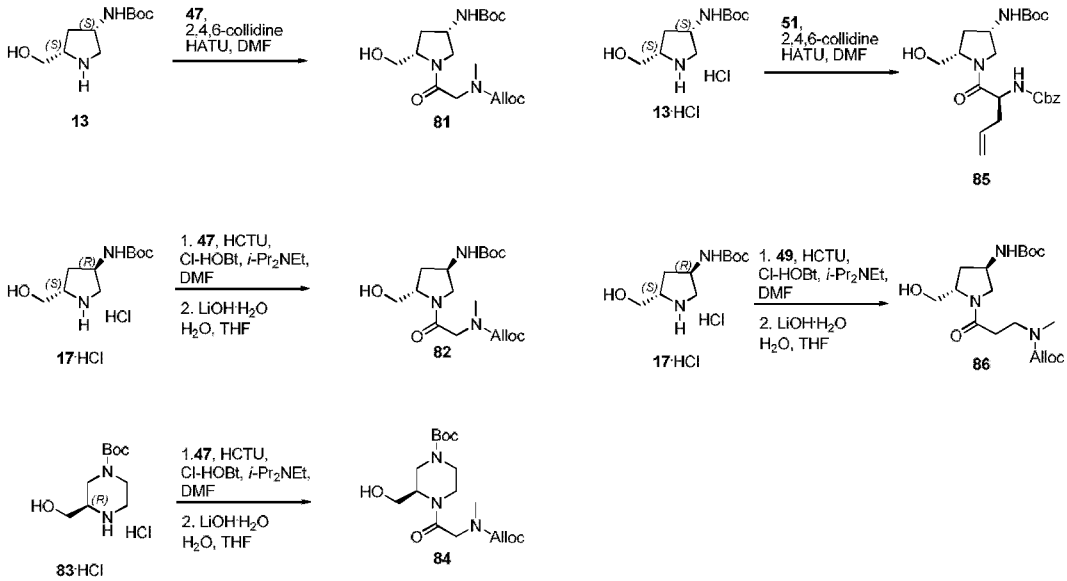
Scheme 4, cont.



A-c1 Fragments Scheme 4, cont.

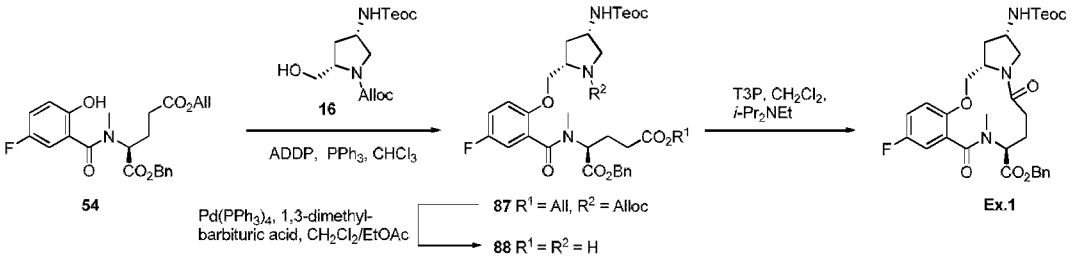


c2-B Fragments Scheme 5



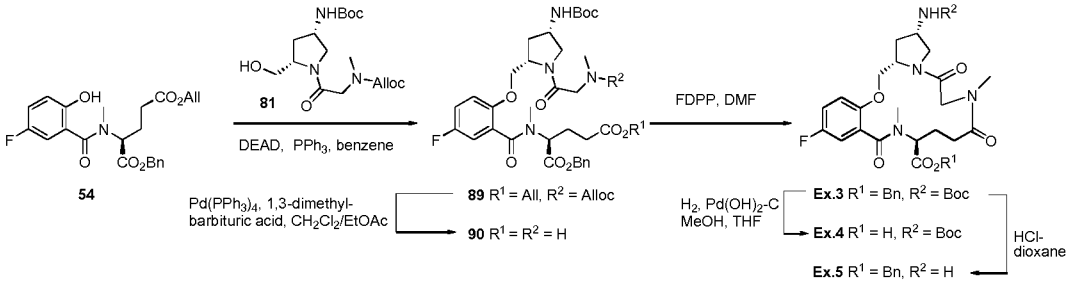
Core 01

Scheme 6



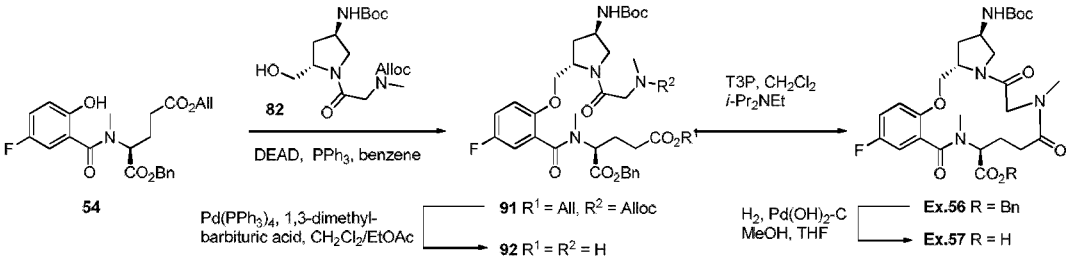
Core 03

Scheme 7



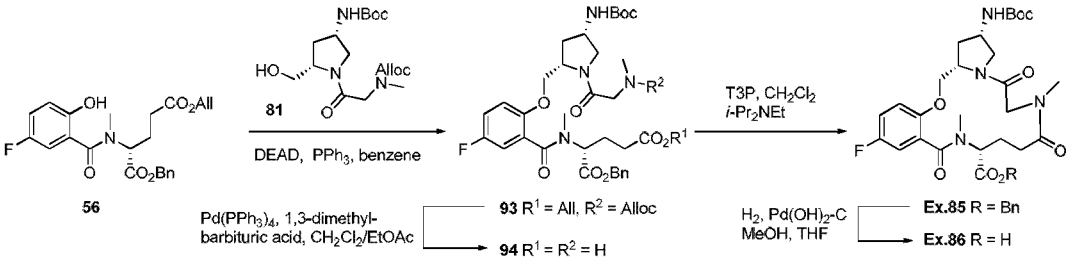
Core 04

Scheme 8



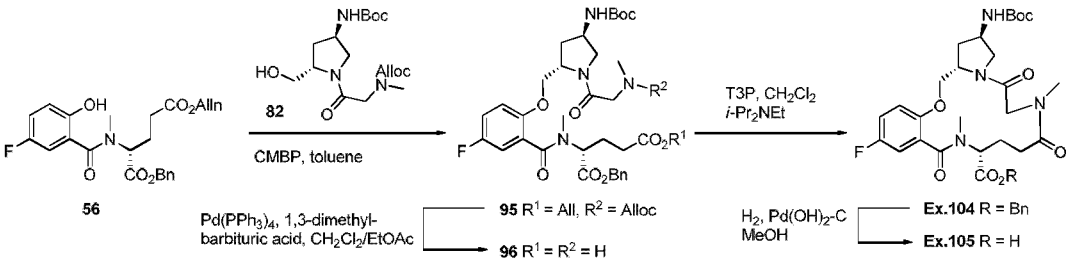
Core 05

Scheme 9



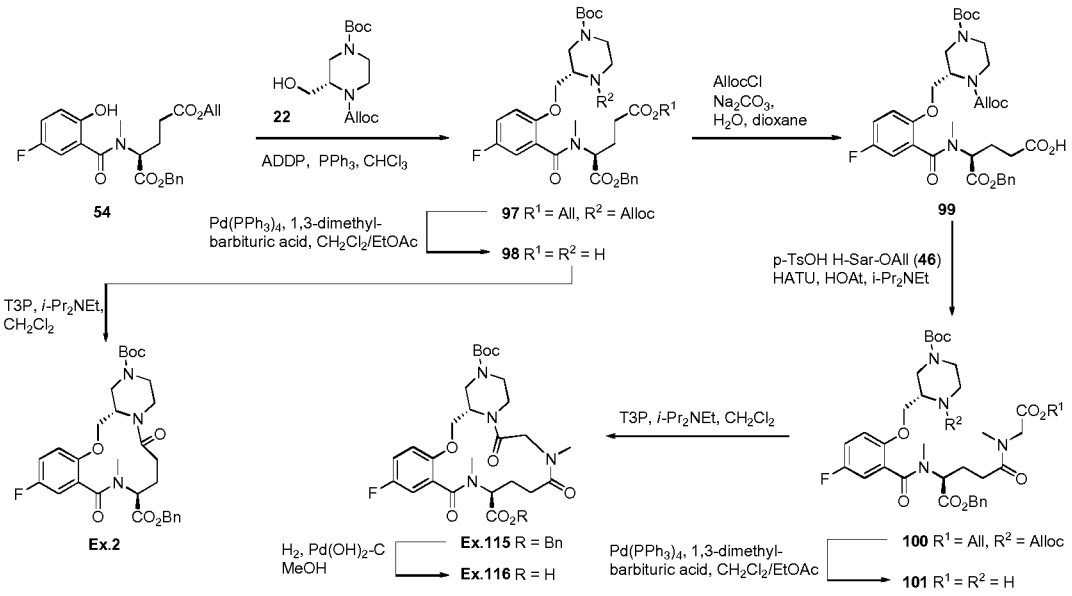
Core 06

Scheme 10



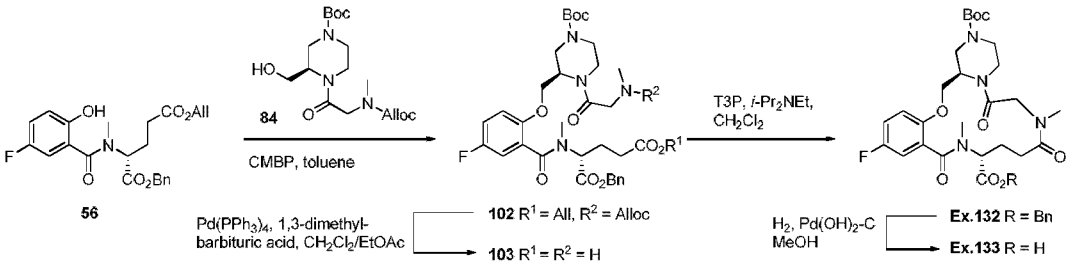
Core 02 and Core 07

Scheme 11



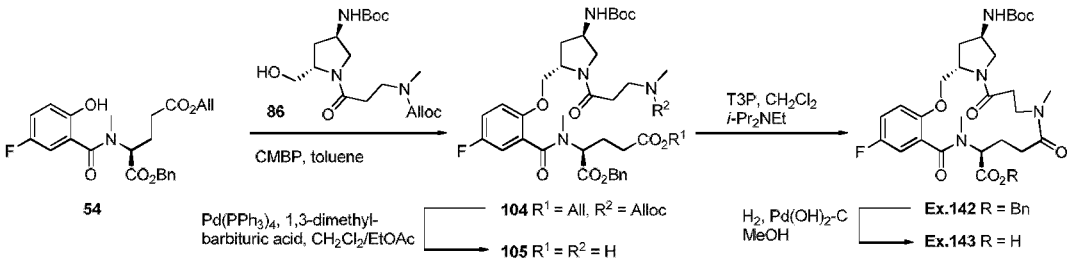
Core 08

Scheme 12



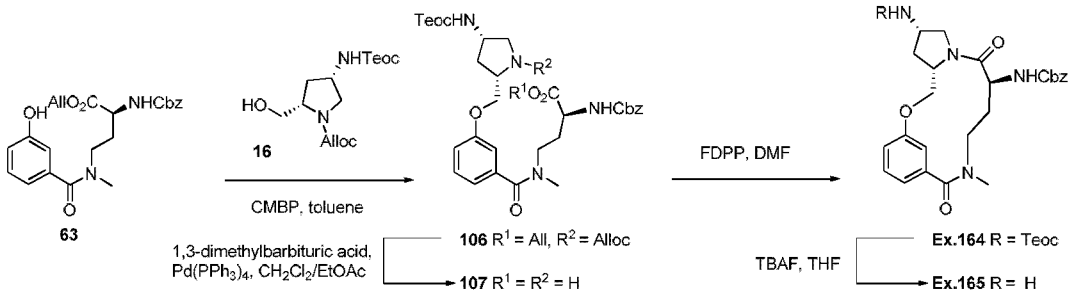
Core 09

Scheme 13



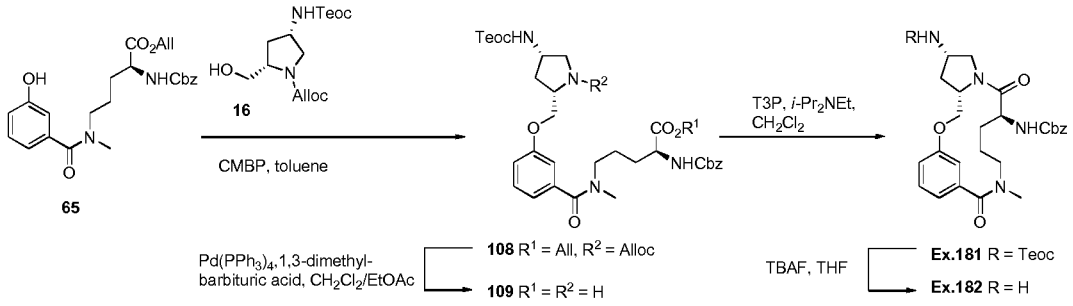
Scheme 14

Core 10

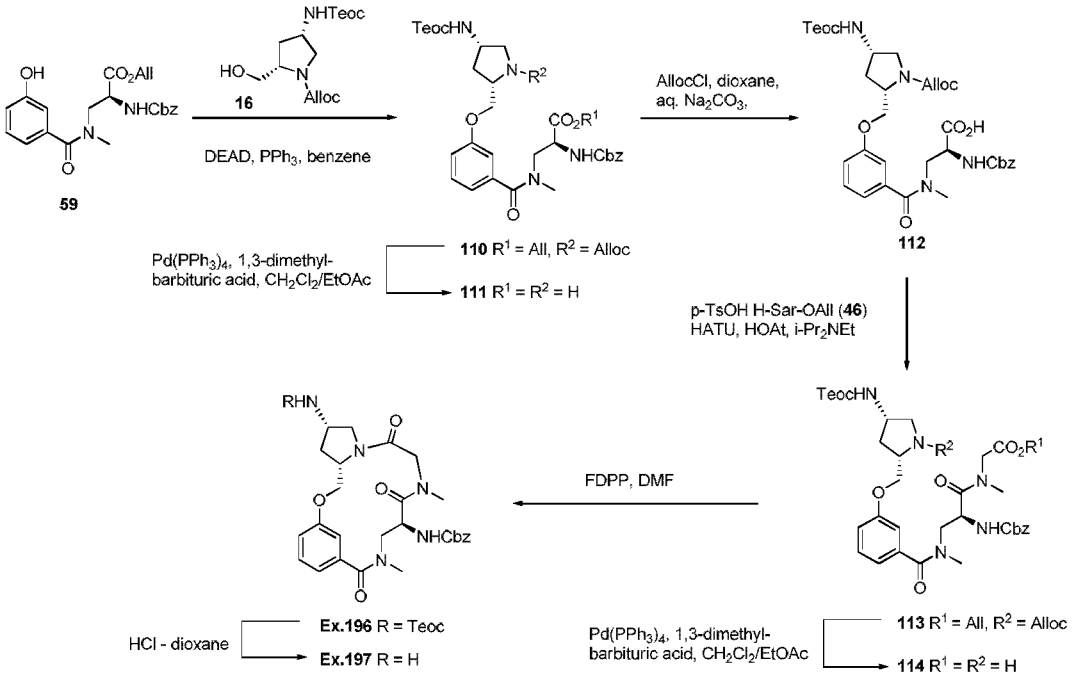


Core 11

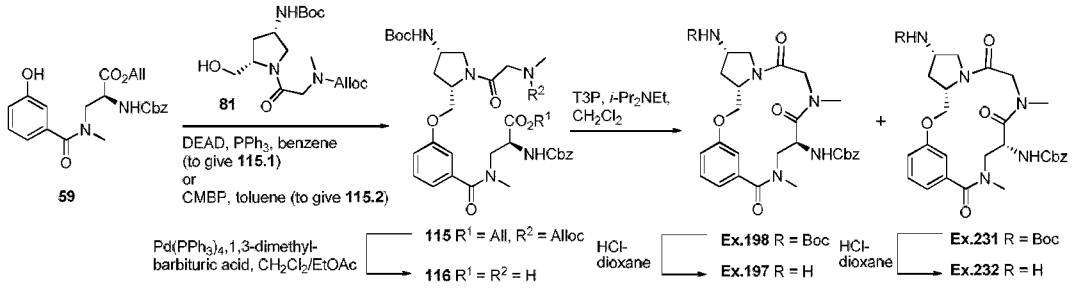
Scheme 15



Core 12 (linear synthesis) Scheme 16

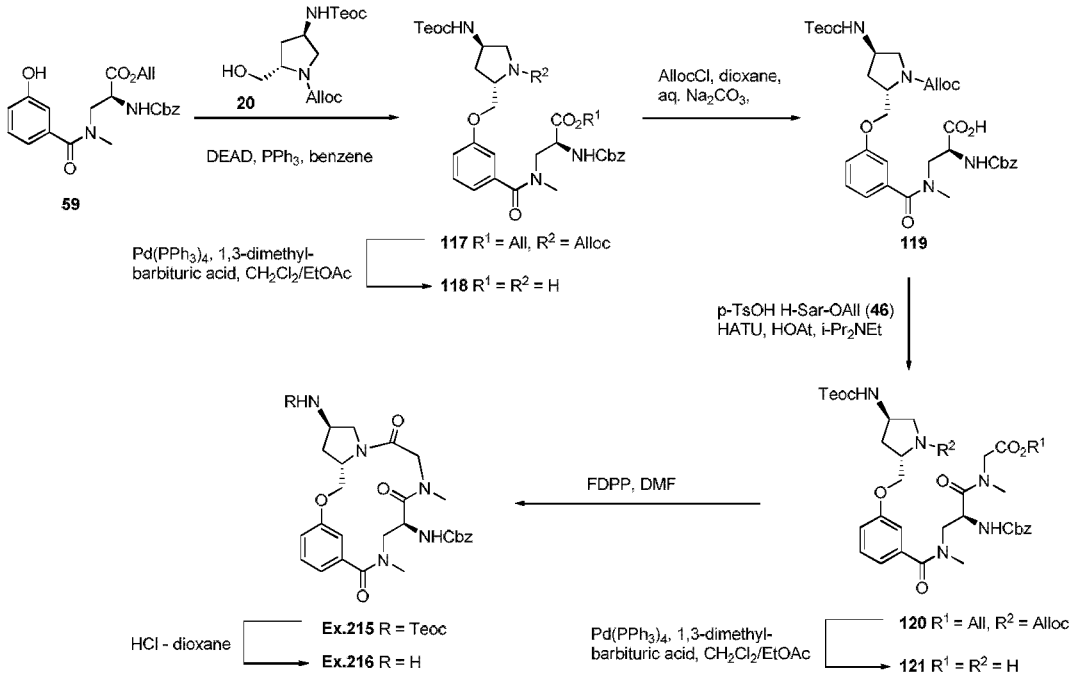


Core 12 (convergent synthesis) Scheme 17



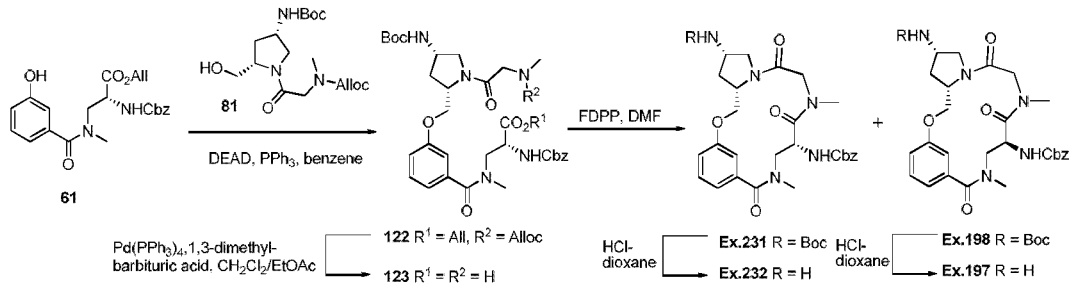
Core 13

Scheme 18



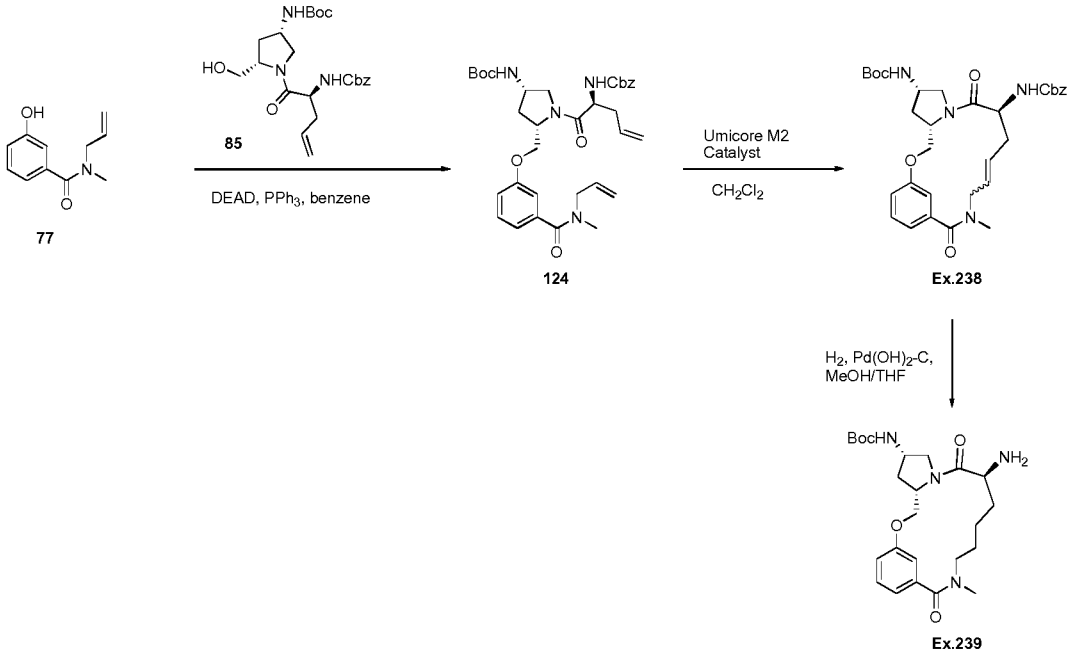
Core 14

Scheme 19



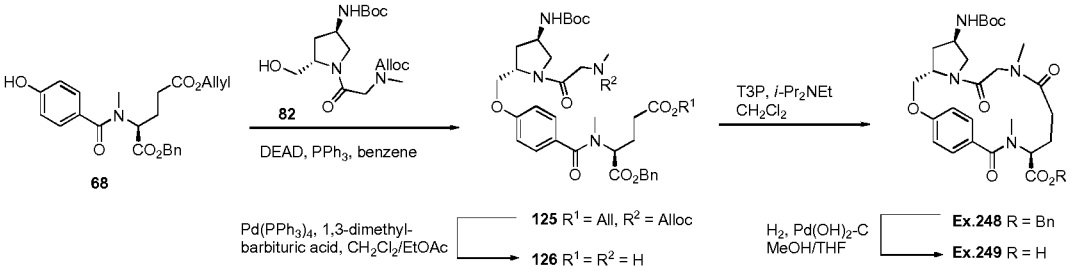
Core 15 and Core 16

Scheme 20



Core 17

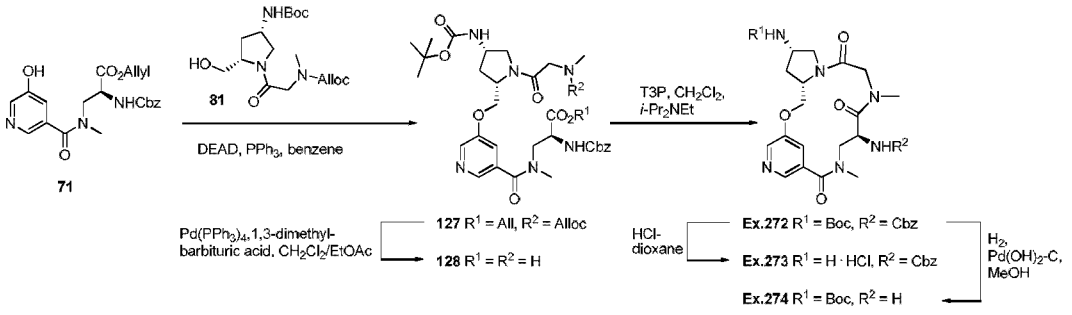
Scheme 21



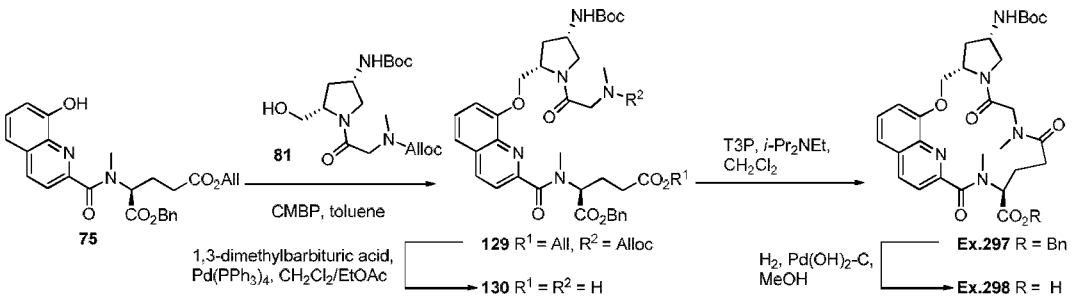
5

Core 18

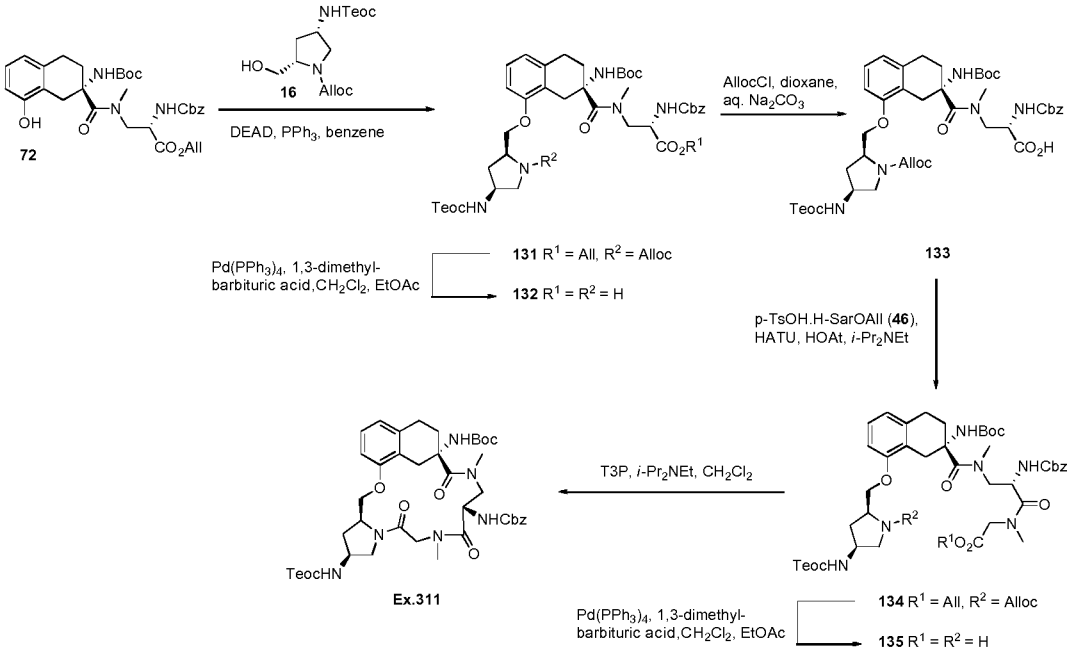
Scheme 22



Core 19 Scheme 23

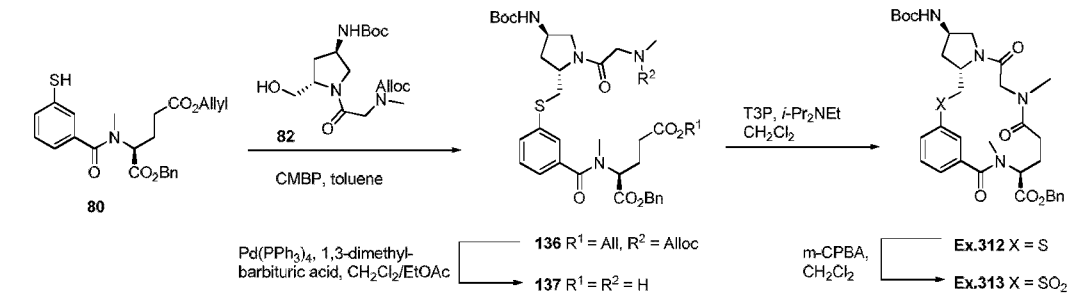


Core 20 Scheme 24

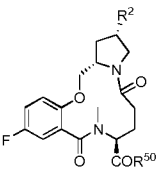


5

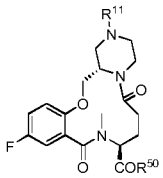
Core 21 Scheme 25



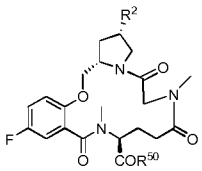
Structures of Examples Scheme 26



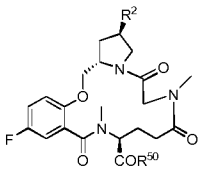
Core 01
Ex.1
definition of R-groups
cf. Table 20



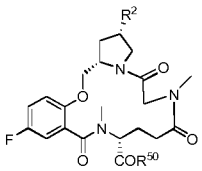
Core 02
Ex.2
definition of R-groups
cf. Table 20



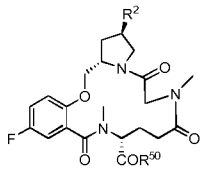
Core 03
Ex.3 - Ex.55
definition of R-groups
cf. Table 21



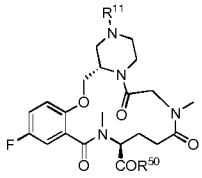
Core 04
Ex.56 - Ex.84
definition of R-groups
cf. Table 22



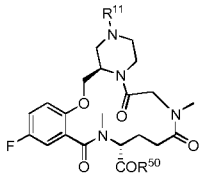
Core 05
Ex.85 - Ex.103
definition of R-groups
cf. Table 23



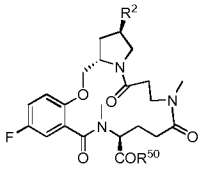
Core 06
Ex.104 - Ex.114
definition of R-groups
cf. Table 24



Core 07
Ex. 115 - Ex. 131
definition of R-groups
cf. Table 25

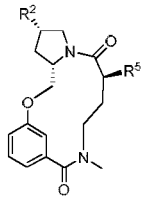


Core 08
Ex.132 - Ex.141
definition of R-groups
cf. Table 26

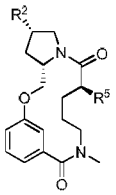


Core 09
Ex.142 - Ex.163
definition of R-groups
cf. Table 27

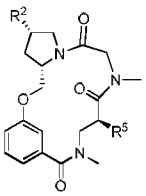
Structures of Examples Scheme 26, cont.



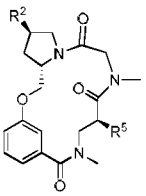
Core 10
Ex.164 - Ex.180
definition of R-groups
cf. Table28



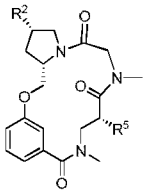
Core 11
Ex.181 - Ex.195
definition of R-groups
cf. Table 29



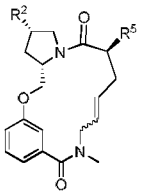
Core 12
Ex.196 - Ex.214
definition of R-groups
cf. Table 30



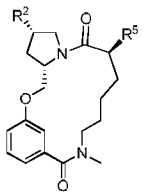
Core 13
Ex.215 - Ex.230
definition of R-groups
cf. Table 31



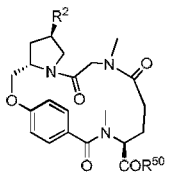
Core 14
Ex.231 - Ex.237
definition of R-groups
cf. Table 32



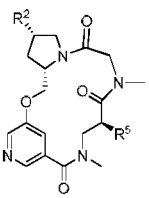
Core 15
Ex. 238
definition of R-groups
cf. Table 33



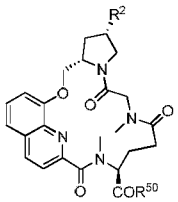
Core 16
Ex.239 - Ex.247
definition of R-groups
cf. Table 33



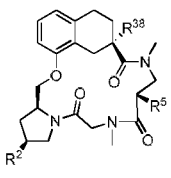
Core 17
Ex.248 - Ex.271
definition of R-groups
cf. Table 34



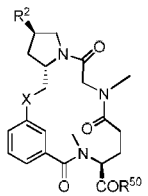
Core 18
Ex.272 - Ex.296
definition of R-groups
cf. Table 35



Core 19
Ex.297 - Ex.310
definition of R-groups
cf. Table 36



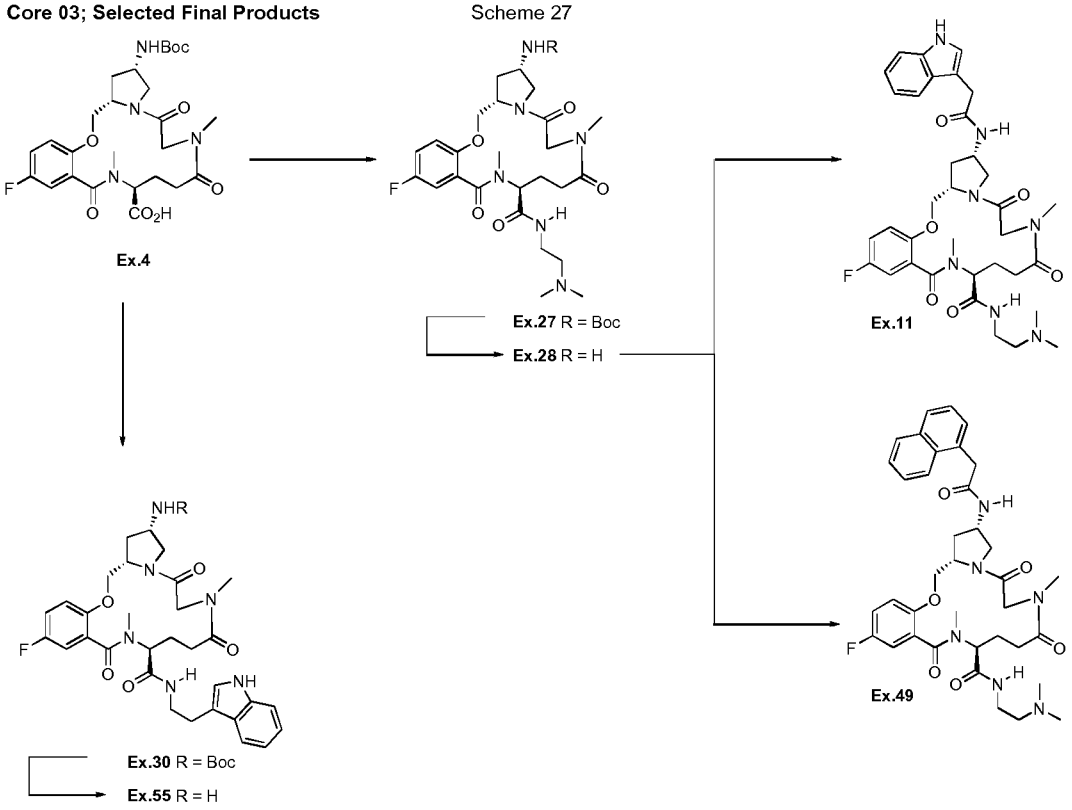
Core 20
Ex.311
definition of R-groups
cf. Table 37



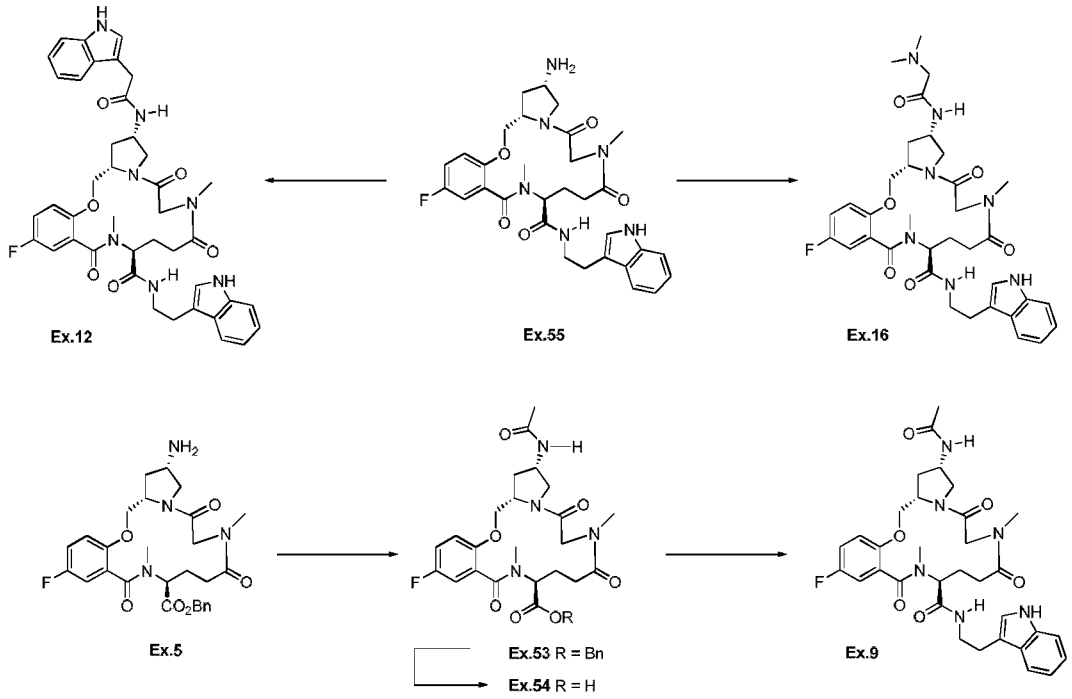
Core 21 (X = S, SO_2)
Ex.312 - Ex.313
definition of R-groups
cf. Table 37

5

Core 03; Selected Final Products Scheme 27

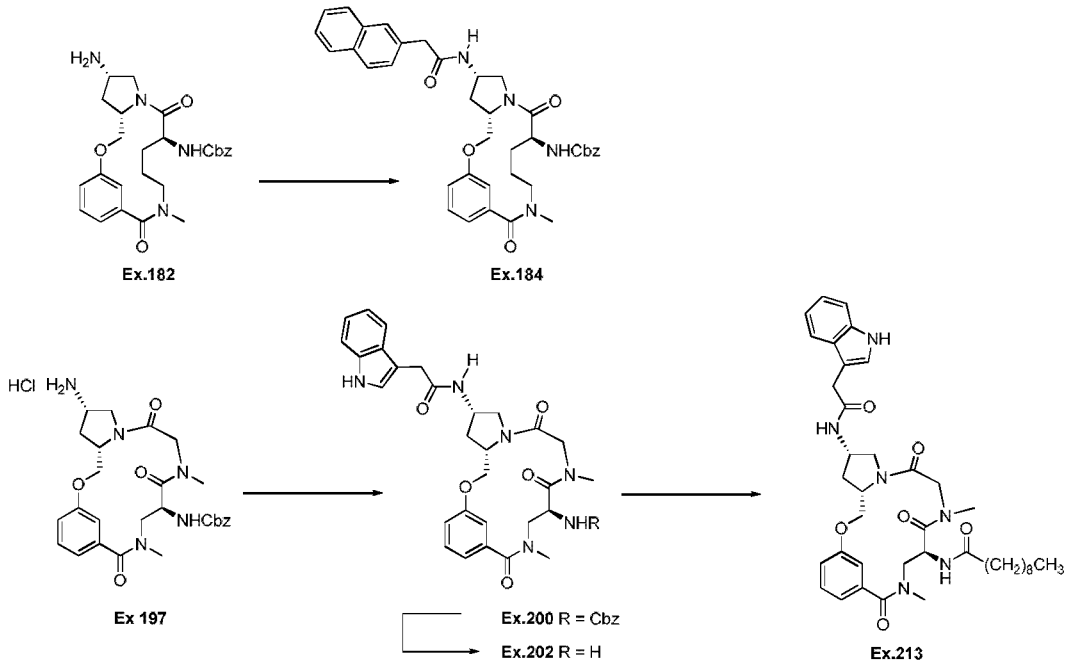


Core 03; Selected Final Products Scheme 27, cont.



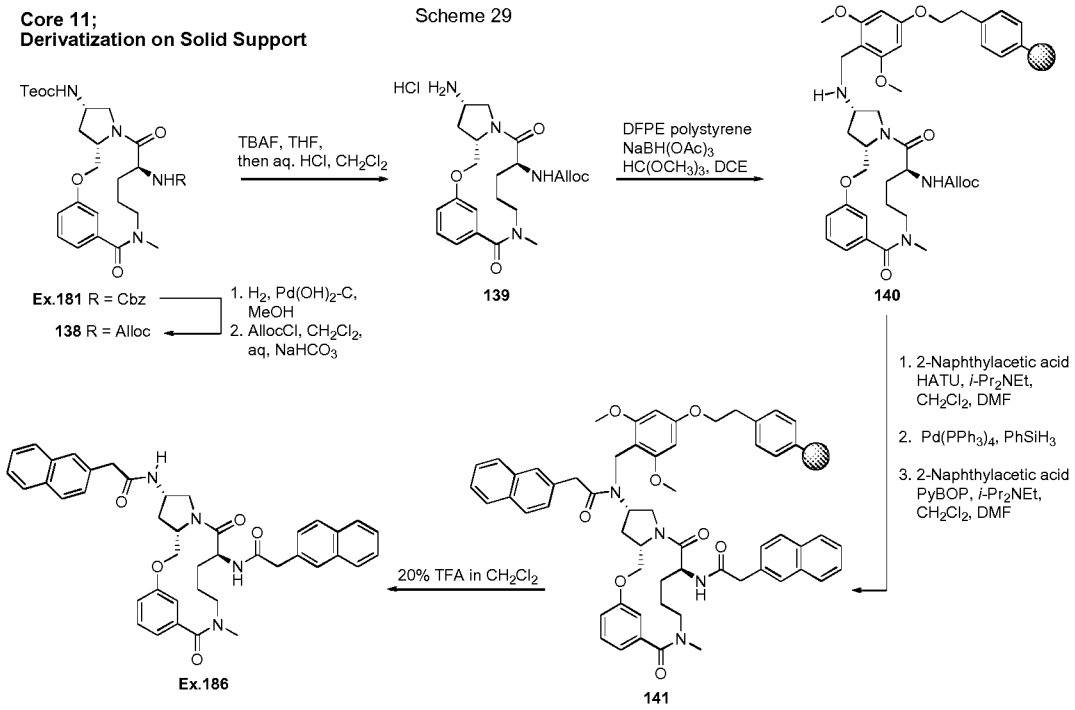
Core 11 and Core 12;
Selected Examples

Scheme 28



Core 11;
Derivatization on Solid Support

Scheme 29



Biological methods

1. Preparation of the example compounds

Example compounds were weighed on a Microbalance (Mettler MX5) and dissolved in 100% DMSO to a final concentration of 2.5 mM for Ca^{2+} assays.
Example compounds were dissolved in DMSO/H_2O 90:10 to a final concentration of 10 mM for plasma stability determination and metabolic stability determination.

2. Ca^{2+} assays: GPCR assays for motilin receptor, prostaglandin F (FP) receptor and 5-hydroxytryptamine 2B (5-HT_{2B}) receptor

Assays were performed using a FLIPR Tetra (Molecular Devices); the data analysis and FLIPR Tetra Operating-Soft ware was ScreenWorks version 2 (Molecular Devices).

Dose dependent agonist and antagonist activities were determined. Percentage activation and percentage inhibition values were determined.
Percentage activation was determined upon initial addition of the sample compounds followed by 10 minutes incubation at 25°C. Following compound incubation, reference agonists were added at EC_{80} to determine percentage inhibition.

Reference agonists were purchased from reputable commercial vendors and prepared according to specifications specific to each ligand. All handling of ligands were done to ensure proper control throughout the experiments.
Test compounds were serially diluted with DMSO. Once the appropriate concentrations were attained, the compounds were diluted into assay buffer.

GPCR assay buffer:
Assay buffer was a supplemented HBSS (Hank's Balanced Salt Solution). HBSS was supplemented with 20 mM HEPES (4-(2-hydroxyethyl)-piperazin-1-ethansulfonic acid) and 2.5 mM Probenecid (Sigma P8761).

Assay plate seeding:
GPCR assays were performed using Ca^{2+} optimized hematopoietic cell lines (rat) with cultures never exceeding 90% confluency. Cells were harvested and seeded (from cultures at less than 90% confluency) at 50000 cells/well for a 96-well plate (12500 cells/well for 384). After seeding, the assay plates were incubated for forty-five (45) minutes at room temperature. After room temperature incubation, the assay plates were incubated at 37°C 5% CO_2 for 24 hours prior to assaying.

Calcium Dye Loading:
All GPCR assays were performed using Fluo-8 Ca^{2+} dye. Ca^{2+} dye was prepared at 1 x dye concentration in GPCR assay buffer. After 24 hours of incubation, cells were washed with GPCR assay buffer, then Ca^{2+}-dye (100 µL/well) was added. The plates were incubated for 90 minutes at 30°C 5% CO_2 prior to FLIPR assay.

Agonist Assay:
Compound plates were prepared to add 50 µL/well during the agonist assay mode. During the FLIPR assay, 50 µL/well from the compound plate was diluted 3-fold into the existing 100 µL/well from the dye loading step. Therefore all compounds were prepared as 3x the final concentration desired in the assay.

After completion of the first single addition assay run, assay plate was removed from the FLIPR Tetra and placed at 25°C for seven (7) minutes before antagonist assay.

Antagonist Assay:
Using the EC_{80} values determined during the agonist assay, all pre-incubated sample compound and reference antagonist (if applicable) wells were stimulated with EC_{80} of reference agonist (motilin; prostaglandin F2α).
After the addition of the reference agonist fluorescence was monitored for 180 sec using FLIPR Tetra.

Data analysis:
From the FLIPR data, with negative control correction enabled, the maximum statistic for each well was exported and percentage activation relative to E_{max} control was calculated.

3. Plasma Stability

Human plasma (3-5 donors, Blutspendedienst SRK, Basel) and CD-1 mouse plasma (mixed gender pool >50 animals, Innovative Research, CA, USA) are both sodium citrate stabilized. The assay is performed in triplicates at 10 µM compound concentration and 37°C. Samples are taken at 0, 15, 60, and 240 minutes and stopped by precipitation with 2 volumes of acetonitrile. The supernatant is collected, evaporated and reconstituted in a 5% acetonitrile solution to be analyzed by HPLC/MS/MS. The resulting peak area counts are expressed in percent of the 0 value and used to determine the endpoint stability in % and the half life T½ in minutes. In order to monitor assay integrity the degradation of propantheline is assayed with every experimental set

4. Metabolic Stability

Microsomes from a human 50 donor mixed gender pool and 1:1 mixtures of microsomes from CD-1 mouse single-gender pools are

purchased from Celsis (Belgium). The enzymatic reaction is performed in a buffer containing an NADPH regeneration system and microsomes with the following end concentrations: 100 mM potassium phosphate buffer (all from Sigma), 1 mg/mL glucose-6-phosphate, 1 mg/mL β-nicotinamide adenine dinucleotide phosphate (NADP), 0.65 mg/mL magnesium chloride, 0.8 units/mL of glucose-6-phosphate dehydrogenase (prediluted with 5 mM citrate buffer), 10 µM compound and 1 mg/ml microsomal protein. Compounds are incubated at 37°C in duplicates and samples are taken after 0, 20 and 60 minutes. After acetonitrile precipitation (2 volumes) and HPLC/MS/MS analysis metabolic turnover is expressed in % of the initial 0 minutes value and half life T½ (min) is calculated. Verapamil for human and propranolol for mouse are used as reference and are assayed with every experimental set.

- F.P. Guengerich, *Analysis and Characterization of Enzymes*; in: *Principles and Methods of Toxicology*; A.W. Hayes (Ed.) Raven Press: New York, **1989**, 777-813.
- R. Singh et al., *In vitro metabolism of a potent HIV-protease inhibitor (141W94) using rat, monkey and human liver S9*, *Rapid Commun. Mass Spectrom.* **1996**, *10*, 1019-1026.

5. Results

The results of the experiments described under 1.-4. (above) are indicated in **Table 38** and **Table 39** herein below.

Table 38: Biological Data

No	Motilin receptor antagonist activity [% inhibition at 10 μM]	Motilin receptor antagonist activity IC_{50} [μM]]	FP receptor antagonist activity [% inhibition at 10 μM]	FP receptor antagonist activity IC_{50} [μM]	5-HT_{2B} receptor agonist activity [% activation at 12.5 μM]	5-HT_{2B} receptor agonist activity EC_{50} [μM]
Ex.9	n.d.	n.d.	n.d.	n.d.	48	12
Ex.11	79	0.78	n.d.	n.d.	n.d.	n.d.
Ex.12	95	2.7	44	n.d.	36	3.3
Ex.16	n.d.	n.d.	n.d.	n.d.	45	6.6
Ex.30	n.d.	n.d.	n.d.	n.d.	48	3.3
Ex.49	98	0.16	n.d.	n.d.	n.d.	n.d.
Ex.184	n.d.	n.d.	74	0.52	n.d.	n.d.
Ex.200	n.d.	n.d.	38	28	n.d.	n.d.
Ex.213	n.d.	n.d.	78	1.7	n.d.	n.d.

n.d. not determined

Table 39: Plasma Stability and Metabolic Stability (*continued on the following page*)

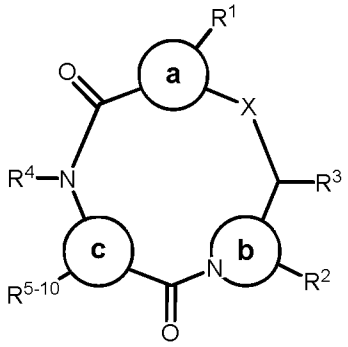
	Plasma Stability				Metabolic Stability			
No	T ½ [min] hum	240 min hum	T ½ min] mouse	240 min mouse	T ½ [min] hum	60 min hum	T ½ [min] mouse	60 min mouse
Ex.9	240	99	240	93	32	20	60	80
Ex.11	240	100	240	100	60	74	60	77
Ex.12	240	99	240	100	17	7	35	33
Ex.16	240	95	240	97	38	31	60	79
Ex.30	240	85	240	100	22	2	60	55
Ex.37	240	77	240	100	60	100	60	100
Ex.43	240	82	240	89	60	100	60	98
Ex.49	240	83	240	96	24	10	60	83
Ex.78	240	65	240	100	60	78	60	100
Ex.91	240	96	240	88	60	91	60	95
Ex.93	240	100	240	100	24	1	29	15
Ex.95	240	100	240	93	60	76	60	94
Ex.98	240	100	240	78	60	97	60	100
Ex.102	240	65	240	75	23	4	42	39
Ex.103	240	97	240	75	35	22	36	25
Ex.138	240	89	240	78	60	62	60	99
Ex.184	240	66	240	58	15	0	22	0

	Plasma Stability				Metabolic Stability			
No	T ½ [min] hum	240 min hum	T ½ min] mouse	240 min mouse	T ½ [min] hum	60 min hum	T ½ [min] mouse	60 min mouse
Ex.200	240	91	240	100	27	12	30	26
Ex.208	240	98	240	90	60	84	60	100
Ex.213	n.d.	n.d.	n.d.	n.d.	16	0	17	4
Ex.230	240	100	240	95	60	61	60	90
Ex.260	240	100	240	100	37	19	60	69
Ex.262	240	100	240	93	21	0	23	4
Ex.264	240	94	240	88	n.d.	n.d.	42	32
Ex.266	240	92	240	74	60	100	60	98
Ex.267	240	75	240	79	60	99	60	100
Ex.272	240	95	240	92	60	65	60	81

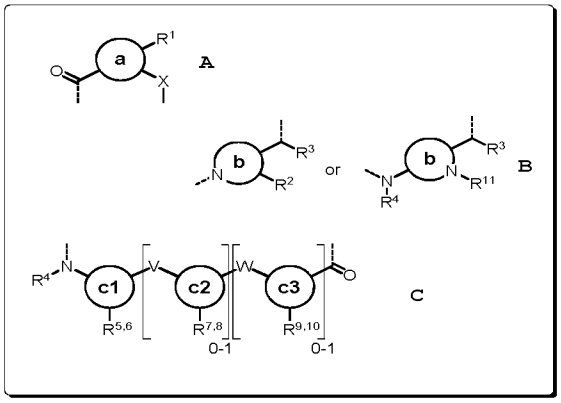
n.d. not determined

CLAIMS

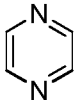
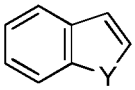
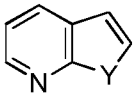
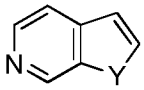
1. Compounds of the general formula **I** incorporating the building blocks **A**, **B** and **C**



I



wherein the encircled moieties **a** in building block **A**, **b** in building block B and **c1**–**C3** in building block **C** are derived from basic skeletons, appropriately and independently substituted as defined below, the basic skeletons of **a** and **b** corresponding to the ring systems depicted in Table 1 and Table 2, below;

 **a1**	 **a2**	 **a3**	 **a4**
 **a5**	 **a6**	 **a7**	 **a8**
 **a9**	 **a10**	 **a11**	 **a12**

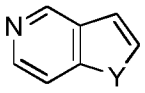
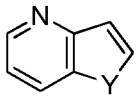
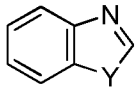
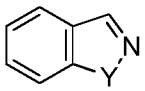
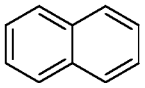
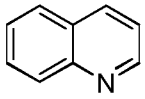
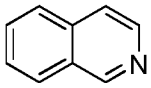
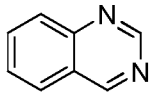
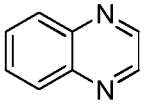
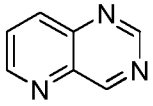
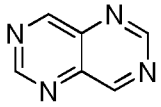
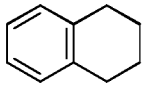
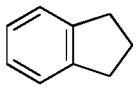
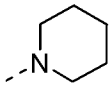
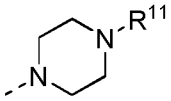
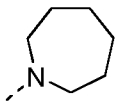
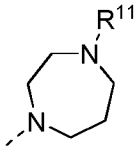
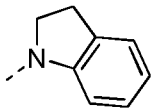
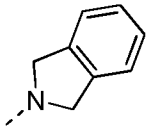
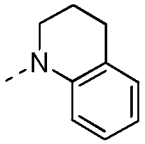
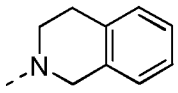
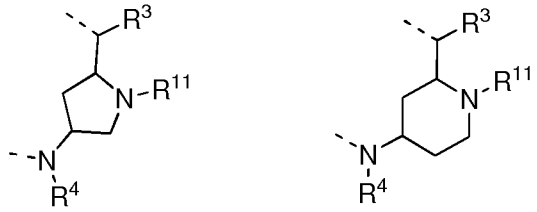
 a13	 a14	 a15	 a16
 a17	 a18	 a19	 a20
 a21	 a22	 a23	 a24
 a25			

Table 2: Ring Systems **b1**–**b11** of Building Blocks **B**

 b1	 b2	 b3	 b4
 b5	 b6	 b7	 b8
 b9	 b10	 b11	

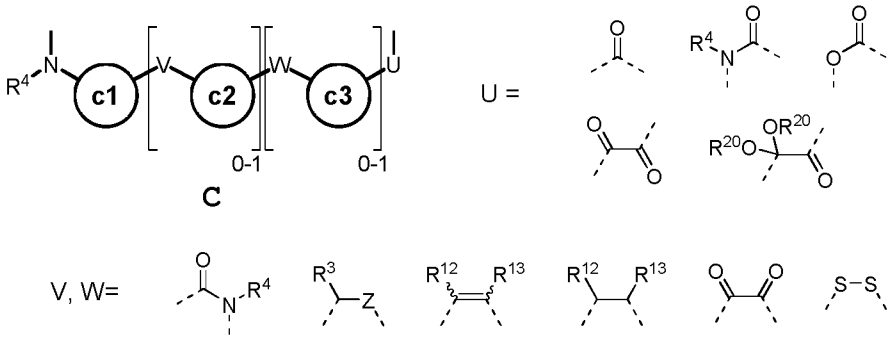
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depending on the substitution pattern of skeletons **b** alternative binding modes being feasible for skeletons **b3** and **b4** such incorporation via the excocyclic nitrogen atom being represented by the following two structures:

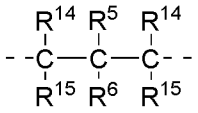
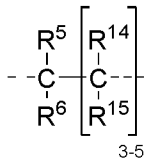
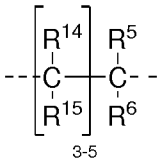
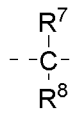
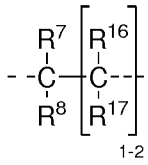
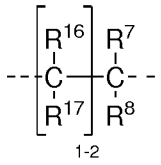
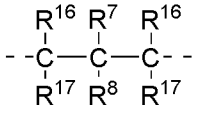
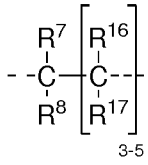
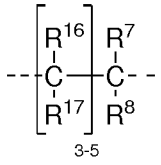
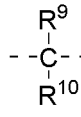
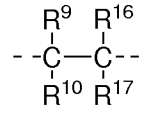
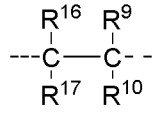


the encircled parts of the bridge subunits **c1**-**c3** representing optionally substituted groups, defintions of **c1-c3** being depicted in Table 3, below, each reading from the N-terminus to the C-terminus of the linker **C**, said linker **C** being, in the simplest case, constituted by one subunit **c1**, i.e. **c1-1** to **c1-6**,and for the embodiments consisting of two or three subunits all possible combinations of the subunits **c1-c3** and the connectivities U, V and W being possible;

Table 3: Scope of Subunits of **c1-c3** of the Linker Group **C**



c1	c1-1	c1-2	c1-3

	 **c1-4**	 **c1-5**	 **c1-6**
	 **c2-1**	 **c2-2**	 **c2-3**
	 **c2-4**	 **c2-5**	 **c2-6**
	 **c3-1**	 **c3-2**	 **c3-3**

the substituents directly attached to building block **A,B** and **C**, i.e. R^1–R^{17}, being defined as follows:

R^1: H; F; Cl; Br; I; CF_3; OCF_3; $OCHF_2$; NO_2; CN; alkyl; alkenyl; alkynyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{18}R^{19})_qOR^{20}$; $-(CR^{18}R^{19})_qSR^{20}$; $-(CR^{18}R^{19})_qNR^4R^{11}$; $-(CR^{18}R^{19})_qOCONR^4R^{11}$; $-(CR^{18}R^{19})_qOCOOR^{21}$; $-(CR^{18}R^{19})_qNR^4COOR^{21}$; $-(CR^{18}R^{19})_qNR^4COR^{22}$; $-(CR^{18}R^{19})_qNR^4CONR^4R^{11}$; $-(CR^{18}R^{19})_qNR^4SO_2R^{23}$; $-(CR^{18}R^{19})_qNR^4SO_2NR^4R^{11}$; $-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{11}$; $-(CR^{18}R^{19})_qSO_2NR^4R^{11}$; $-(CR^{18}R^{19})_qPO(OR^{21})_2$; $-(CR^{18}R^{19})_qOPO(OR^{21})_2$; $-(CR^{18}R^{19})_qCOR^{22}$; $-(CR^{18}R^{19})_qSO_2R^{23}$; $-(CR^{18}R^{19})_qOSO_3R^{21}$; $-(CR^{18}R^{19})_qR^{24}$; $-(CR^{18}R^{19})_qR^{25}$; or $-(CR^{18}R^{19})_qR^{26}$;

R^2:H; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{18}R^{19})_qOR^{20}$; $-(CR^{18}R^{19})_qSR^{20}$; $-(CR^{18}R1^9)_qNR^4R^{11}$; $-(CR^{18}R^{19})_qOCONR^4R^{11}$; $-(CR^{18}R^{19})_qOCOOR^{21}$; $-(CR^{18}R^{19})_qNR^4COOR^{21}$; $-(CR^{18}R^{19})_qNR^4COR^{22}$; $-(CR^{18}R^{19})_qNR^4CONR^4R^{11}$; $-(CR^{18}R^{19})_qNR^4SO_2R^{23}$; $-(CR^{18}R^{19})_qNR^4SO_2NR^4R^{11}$; $-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{11}$; $-(CR^{18}R^{19})_qSO_2NR^4R^{11}$; $-(CR^{18}R^{19})_qPO(OR^{21})_2$; $-(CR^{18}R^{19})_qCOR^{22}$; $-(CR^{18}R^{19})_qSO_2R^{23}$; $-(CR^{18}R^{19})_qR^{24}$; $-(CR^{18}R^{19})_qR^{25}$; or $-(CR^{18}R^{19})_qR^{26}$;

R^3: H; CF_3; alkyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl;

R^4: H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; or a suitable N-protecting group;

R^5, R^7 and R^9 are independently defined as: H; F; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{18}R^{19})_sOR^{20}$; $-(CR^{18}R^{19})_sSR^{20}$; $-(CR^{18}R^{19})_sNR^4R^{11}$; $-(CR^{18}R^{19})_sOCONR^4R^{11}$; $-(CR^{18}R^{19})_sOCOOR^{21}$; $-(CR^{18}R^{19})_sNR^4COOR^{21}$; $-(CR^{18}R^{19})_sNR^4COR^{22}$; $-(CR^{18}R^{19})_sNR^4CONR^4R^{11}$; $-(CR^{18}R^{19})_sNR^4SO_2R^{23}$; $-(CR^{18}R^{19})_sNR^4SO_2NR^4R^{11}$; $-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{11}$; $-(CR^{18}R^{19})_qSO_2NR^4R^{11}$; $-(CR^{18}R^{19})_qPO(OR^{21})_2$; $-(CR^{18}R^{19})_qCOR^{22}$; $-(CR^{18}R^{19})_qSO_2R^{23}$; $-(CR^{18}R^{19})_qR^{24}$; $-(CR^{18}R^{19})_qR^{25}$; or $-(CR^{18}R^{19})_qR^{26}$;

R^6, R^8 and R^{10} are independently defined as: H; F; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; or heteroarylalkyl;

R^{11}: H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; a suitable protecting group; $-(CR^{18}R^{19})_rOR^{20}$; $-(CR^{18}R^{19})_rSR^{20}$; $-(CR^{18}R^{19})_rNR^4R^{27}$; $-(CR^{18}R^{19})_rOCONR^4R^{27}$; $-(CR^{18}R^{19})_rOCOOR^{21}$; $-(CR^{18}R^{19})_rNR^4COOR^{21}$; $-(CR^{18}R^{19})_rNR^4CONR^4R^{27}$; $-(CR^{18}R^{19})_rNR^4SO_2R^{23}$; $-(CR^{18}R^{19})_rNR^4SO_2NR^4R^{27}$; $-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{27}$; $-(CR^{18}R^{19})_qCOR^{22}$; $-(CR^{18}R^{19})_qSO_2R^{23}$; $-(CR^{18}R^{19})_qSO_2NR^4R^{27}$; $-(CR^{18}R^{19})_qR^{24}$; $-(CR^{18}R^{19})_sR^{25}$; or $-(CR^{18}R^{19})_qR^{26}$;

R^{12} and R^{13} are independently defined as H; or alkyl;

R^{14} and R^{16} are independently defined as: H; F; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{18}R^{19})_sOR^{20}$; $-(CR^{18}R^{19})_sNR^4R^{11}$; $-(CR^{18}R^{19})_sNR^4COOR^{21}$; $-(CR^{18}R^{19})_sNR^4COR^{22}$; $-(CR^{18}R^{19})_sNR^4CONR^4R^{11}$; $-(CR^{18}R^{19})_sNR^4SO_2R^{23}$; $-(CR^{18}R^{19})_sNR^4SO_2NR^4R^{11}$; $-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{11}$; $-(CR^{18}R^{19})_qSO_2NR^4R^{11}$; or $-(CR^{18}R^{19})_qCOR^{22}$;

R^{15} and R^{17} are independently defined as: H; F; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; or heteroarylalkyl;

substituents introduced in the sub-definitions of the radicals R^1–R^{17} being defined as follows:

R^{18}: H; F; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{29}R^{30})_sOR^{31}$; $-(CR^{29}R^{30})_sSR^{31}$; $-(CR^{29}R^{30})_sNR^{28}R^{31}$; $-(CR^{29}R^{30})_sOCONR^{28}R^{31}$; $-(CR^{29}R^{30})_sOCOOR^{21}$; $-(CR^{29}R^{30})_sNR^{28}COOR^{21}$; $-(CR^{29}R^{30})_sNR^{28}COR^{31}$; $-(CR^{29}R^{30})_sNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_sNR^{28}SO_2R^{23}$; $-(CR^{29}R^{30})_sNR^{28}SO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_qSO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qPO(OR^{21})_2$; $-(CR^{29}R^{30})_qCOR^{31}$;

$-(CR^{29}R^{30})_qSO_2R^{23}$; $-(CR^{29}R^{30})_qR^{24}$; $-(CR^{29}R^{30})_qR^{25}$; or $-(CR^{29}R^{30})_qR^{26}$;

R^{19}: H; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl;

R^{20}: H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{29}R^{30})_rOR^{31}$; $-(CR^{29}R^{30})_rSR^{31}$; $-(CR^{29}R^{30})_rNR^{28}R^{31}$; $-(CR^{29}R^{30})_rOCONR^{28}R^{31}$; $-(CR^{29}R^{30})_rNR^{28}COOR^{21}$; $-(CR^{29}R^{30})_rNR^{28}COR^{31}$; $-(CR^{29}R^{30})_rNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_rNR^{28}SO_2R^{23}$; $-(CR^{29}R^{30})_rNR^{28}SO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_qSO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOR^{31}$; $-(CR^{29}R^{30})_qSO_2R^{23}$; $-(CR^{29}R^{30})_qR^{24}$; $-(CR^{29}R^{30})_qR^{25}$; or $-(CR^{29}R^{30})_qR^{26}$;

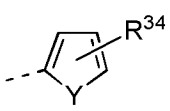
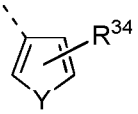
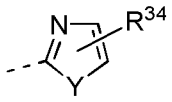
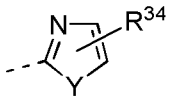
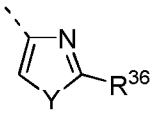
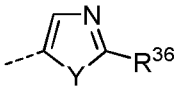
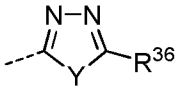
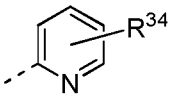
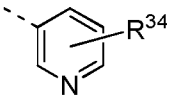
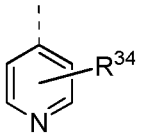
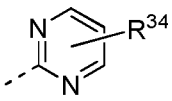
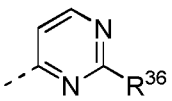
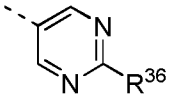
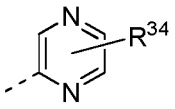
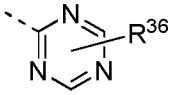
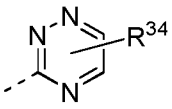
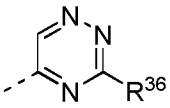
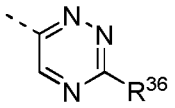
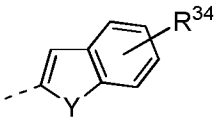
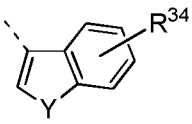
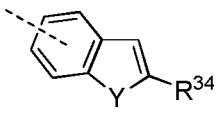
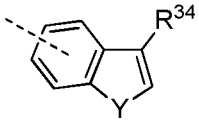
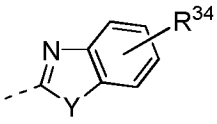
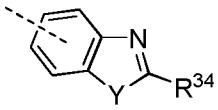
R^{21}: alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; or a suitable O-protecting group.

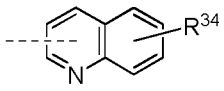
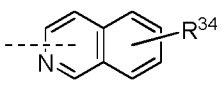
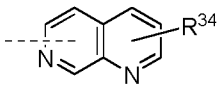
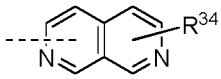
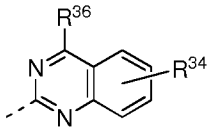
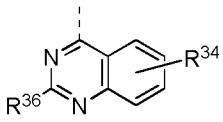
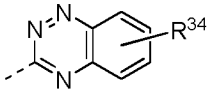
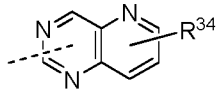
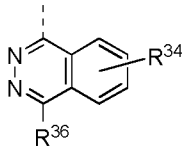
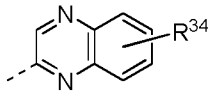
R^{22}: alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{29}R^{30})_sOR^{31}$; $-(CR^{29}R^{30})_sSR^{31}$; $-(CR^{29}R^{30})_sNR^{28}R^{31}$; $-(CR^{29}R^{30})_sOCONR^{28}R^{31}$; $-(CR^{29}R^{30})_sNR^{28}COOR^{21}$; $-(CR^{29}R^{30})_sNR^{28}COR^{31}$; $-(CR^{29}R^{30})_sNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_sNR^{28}SO_2R^{23}$; $-(CR^{29}R^{30})_sNR^{28}SO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_sCOOR^{21}$; $-(CR^{29}R^{30})_sCONR^{28}R^{31}$; $-(CR^{29}R^{30})_sSO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_tCOR^{31}$; $-(CR^{29}R^{30})_sSO_2R^{23}$; $-(CR^{29}R^{30})_tR^{24}$; $-(CR^{29}R^{30})_tR^{25}$; or $-(CR^{29}R^{30})_tR^{26}$;

R^{23}: H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; or $-(CR^{32}R^{33})_tR^{24}$;

R^{24}: aryl, preferably an optionally substituted phenyl group of type $C_6H_2R^{34}R^{35}R^{31}$; or a heteroaryl group, preferably one of the groups of formulae **H1-H34** as shown in Table 4, below;

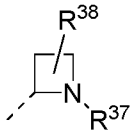
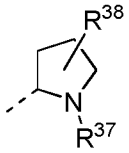
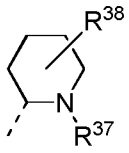
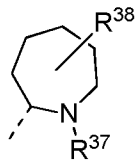
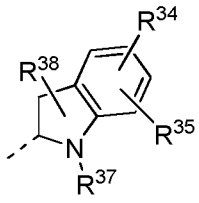
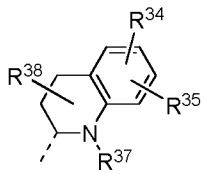
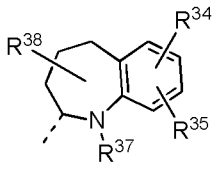
Table 4: Groups of Formulae **H1-H34**

 **H1**	 **H2**	 **H3**	 **H4**
 **H5**	 **H6**	 **H7**	 **H8**
 **H9**	 **H10**	 **H11**	 **H12**
 **H13**	 **H14**	 **H15**	 **H16**
 **H17**	 **H18**	 Umbruch **H19**	 **H20**
 **H21**	 **H22**	 **H23**	 **H24**

 **H25**	 **H26**	 **H27**	 **H28**
 **H29**	 **H30**	 **H31**	 **H32**
 **H33**	 **H34**		

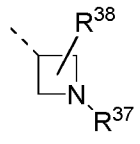
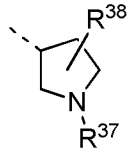
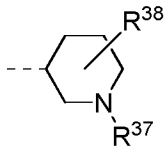
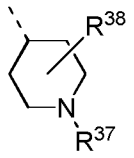
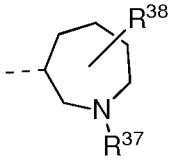
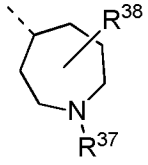
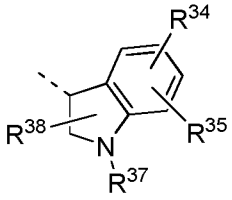
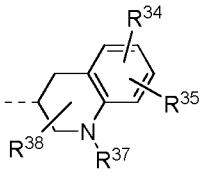
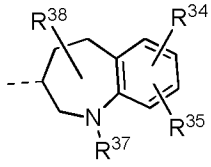
R^{25}: One of the groups of formulae **H35-H41** as shown in Table 5, below;

Table 5: Radicals of formulae **H35-H41**

 **H35**	 **H36**	 **H37**	 **H38**
 **H39**	 **H40**	 **H41**	

R^{26}: One of the groups of formulae **H42-H50** as shown in Table 6, below;

Table 6: Groups of Formulae **H43-H50**

 **H42**	 **H43**	 **H44**	 **H45**
 **H46**	 **H47**	 **H48**	 **H49**
 **H50**			

R^{27}: H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; a suitable protecting group; or
$-(CR^{29}R^{30})_qR^{24}$;

R^{28}: H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; a suitable N-protecting group;
$-(CR^{32}R^{33})_sOR^{21}$; $-(CR^{32}R^{33})_sNR^{43}R^{42}$; $-(CR^{32}R^{33})_sNR^{42}CONR^{43}R^{42}$; $-(CR^{32}R^{33})_sNR^{42}COR^{21}$; $-(CR^{32}R^{33})_sNR^{42}SO_2NR^{21}$; $-(CR^{32}R^{33})_qCOOR^{21}$; $-(CR^{32}R^{33})_qCOR^{23}$; $-(CR^{32}R^{33})_qSO_2R^{21}$;

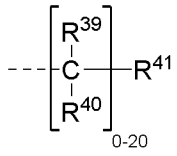
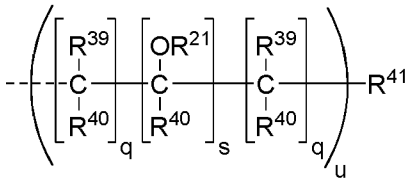
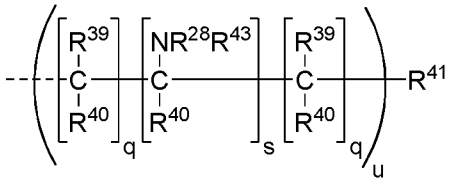
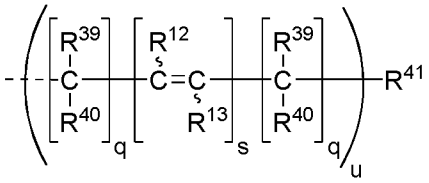
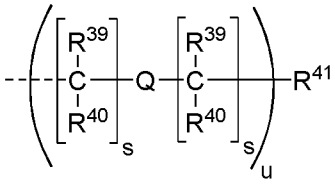
R^{29}: H; F; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{32}R^{33})_sOR^{31}$;

$-(CR^{32}R^{33})_sSR^{31}$; $-(CR^{32}R^{33})_sNR^{28}R^{31}$; $-(CR^{32}R^{33})_sOCONR^{28}R^{31}$;
$-(CR^{32}R^{33})_sOCOOR^{21}$; $-(CR^{32}R^{33})_sNR^{28}COOR^{21}$;
$-(CR^{32}R^{33})_sNR^{28}COR^{31}$; $-(CR^{32}R^{33})_sNR^{28}CONR^{28}R^{31}$; $-(CR^{32}R^{33})_sNR^{28}SO_2R^{23}$;
$-(CR^{32}R^{33})_sNR^{28}SO_2NR^{28}R^{31}$; $-(CR^{32}R^{33})_qCOOR^{21}$; $-(CR^{32}R^{33})_qCONR^{28}R^{31}$;
$-(CR^{32}R^{33})_qSO_2NR^{28}R^{31}$; $-(CR^{32}R^{33})_qPO(OR^{21})_2$; $-(CR^{32}R^{33})_qCOR^{31}$;
$-(CR^{32}R^{33})_qSO_2R^{23}$;
$-(CR^{32}R^{33})_qR^{31}$;

R^{30}: H; F; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl;

R^{31}: H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; or one of the groups of formulae **H51-H55** as shown in Table 7, below;

Table 7: Groups of Formulae **H51-H55**

 **H51**	 **H52**
 **H53**	 **H54**
 **H55**	

R^{32} and R^{33} are independently defined as H; F; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl;

R^{34} and R^{35} are independently defined as H; F; Cl; CF_3; OCF_3; $OCHF_2$; NO_2; CN; alkyl; alkenyl; alkynyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{29}R^{30})_qOR^{31}$; $-(CR^{29}R^{30})_qSR^{31}$; $-(CR^{29}R^{30})_qNR^{28}R^{31}$; $-(CR^{29}R^{30})_qOCONR^{28}R^{31}$; $-(CR^{29}R^{30})_qNR^{28}COOR^{21}$; $-(CR^{29}R^{30})_qNR^{28}COR^{31}$; $-(CR^{29}R^{30})_qNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_qNR^{28}SO_2R^{23}$; $-(CR^{29}R^{30})_qNR^{28}SO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_qSO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOR^{31}$; $-(CR^{29}R^{30})_qSO_2R^{23}$; or $-(CR^{29}R^{30})_qR^{31}$;

R^{36}: H; alkyl; alkenyl; alkynyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; or $-NR^{28}R^{31}$;

R^{37}: H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; a suitable N-protecting group; $-(CR^{29}R^{30})_rOR^{31}$; $-(CR^{29}R^{30})_rSR^{31}$; $-(CR^{29}R^{30})_rNR^{28}R^{31}$; $-(CR^{29}R^{30})_rOCONR^{28}R^{31}$; $-(CR^{29}R^{30})_rNR^{28}COOR^{21}$; $-(CR^{29}R^{30})_rNR^{28}COR^{31}$; $-(CR^{29}R^{30})_rNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_rNR^{28}SO_2R^{23}$; $-(CR^{29}R^{30})_rNR^{28}SO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_rSO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOR^{31}$; $-(CR^{29}R^{30})_qSO_2R^{23}$; or $-(CR^{29}R^{30})_qR^{31}$;

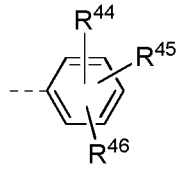
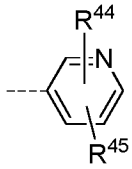
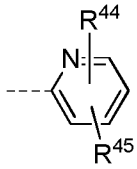
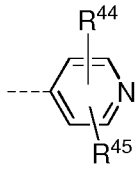
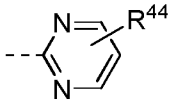
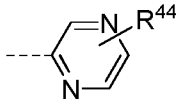
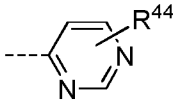
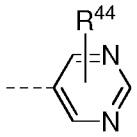
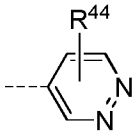
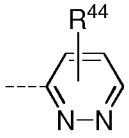
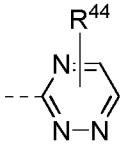
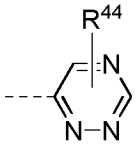
R^{38}: H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{29}R^{30})_qOR^{31}$; $-(CR^{29}R^{30})_qSR^{31}$; $-(CR^{29}R^{30})_qNR^{28}R^{31}$; $-(CR^{29}R^{30})_qNR^{28}COOR^{21}$; $-(CR^{29}R^{30})_qNR^{28}COR^{31}$; $-(CR^{29}R^{30})_qNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOR^{31}$; or $-(CR^{29}R^{30})_qR^{31}$;

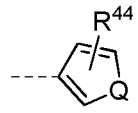
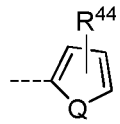
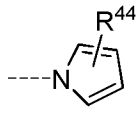
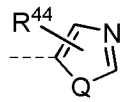
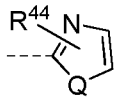
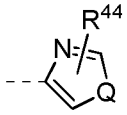
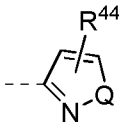
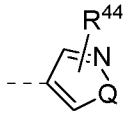
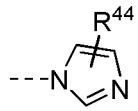
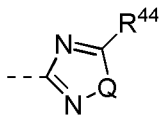
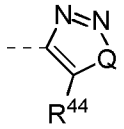
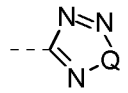
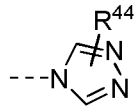
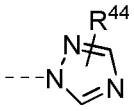
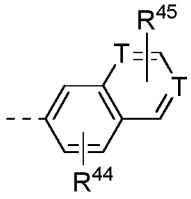
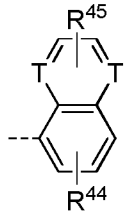
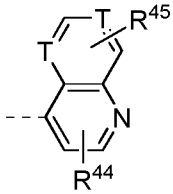
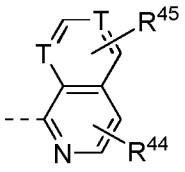
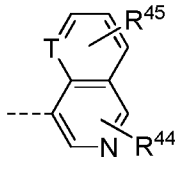
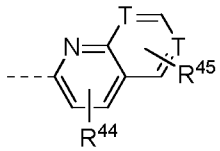
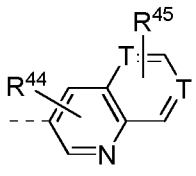
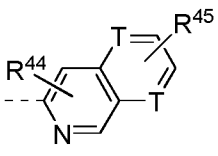
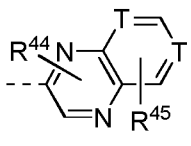
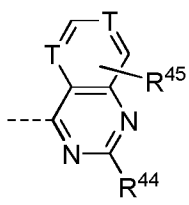
R^{39}: H; F; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{32}R^{33})_uOR^{21}$; $-(CR^{32}R^{33})_uNR^{28}R^{43}$; $-(CR^{32}R^{33})_tCOOR^{21}$; or $-(CR^{32}R^{33})_tCONR^{28}R^{43}$;

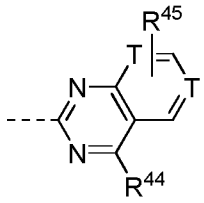
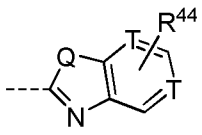
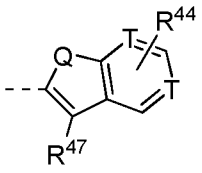
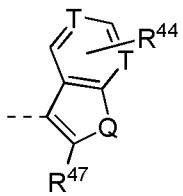
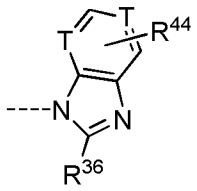
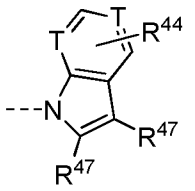
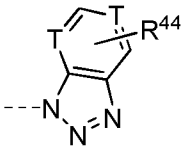
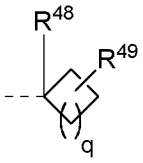
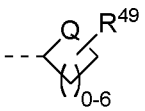
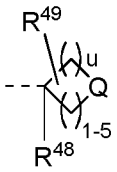
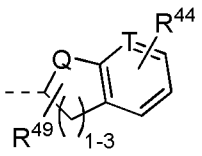
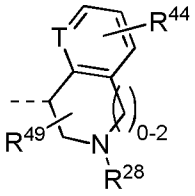
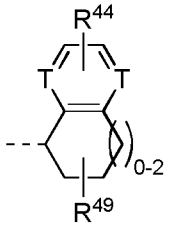
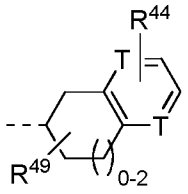
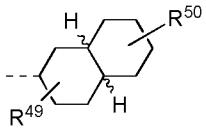
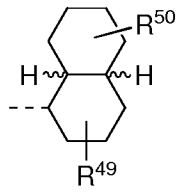
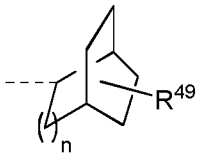
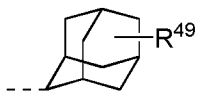
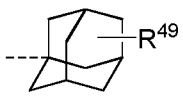
R^{40}: H; F; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{32}R^{33})_uOR^{21}$; $-(CR^{32}R^{33})_uNR^{28}R^{43}$; $-(CR^{32}R^{33})_tCOOR^{21}$; or $-(CR^{32}R^{33})_tCONR^{28}R^{43}$;

R^{41}: H; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-OR^{21}$; $-NR^{28}R^{43}$; $-NR^{28}COR^{23}$; $-NR^{28}COOR^{21}$; $-NR^{28}SO_2R2^3$; $-NR^{28}CONR^{28}R^{43}$; $-COOR^{21}$; $-CONR^{28}R^{43}$; $-C(=NR^{43})NR^{28}N^{43}$; $-NR^{28}C(=NR^{43})NR^{28}N^{43}$; or one of the groups of formulae **H56-H110** as shown in Table 8, below;

Table 8: Groups of Formulae **H56-H110**

 **H56**	 **H57**	 **H58**	 **H59**
 **H60**	 **H61**	 **H62**	 **H63**
 **H64**	 **H65**	 **H66**	 **H67**

 H68	 H69	 H70	 H71
 H72	 H73	 H74	 H75
 H76	 H77	 H78	 H79
 H80	 H81	 H82	 H83
 H84	 H85	 H86	 H87
 H88	 H89	 H90	 H91

 **H92**	 **H93**	 **H94**	 **H95**
 **H96**	 **H97**	 **H98**	 **H99**
 **H100**	 **H101**	 **H102**	 **H103**
 **H104**	 **H105**	 **H106**	 **H106**
 **H108**	 **H109**	 **H110**	

R^{42}: H; alkyl; alkenyl; cycloalkyl; cycloheteroalkyl; aryl; heteroaryl;

$-(CR^{23}R^{33})_sOR^{21}$; $-(CR^{23}R^{33})_sNR^{28}R^{43}$; $-(CR^{23}R^{33})_qCOOR^{21}$;

or $-(CR^{23}R^{33})_qCONR^{21}R^{43}$;

R^{43}: H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; or a suitable N-protecting group;

R^{44}, R^{45} and R^{46} are independently defined as H; F; CF_3; OCF_3; $OCHF_2$; NO_2; CN; alkyl; alkenyl; alkynyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-OR^{23}$; $-NR^{28}R^{43}$; $-NR^{28}COR^{23}$; $-NR^{28}SO_2R^{23}$; $-NR^{28}CONR^{28}R^{43}$; $-COR^{23}$; $-SO_2R^{23}$;

R^{47}: H; CF_3; alkyl; alkenyl; alkynyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-COOR^{21}$; or $-CONR^{28}R^{43}$;

R^{48}: H; F; CF_3; alkyl; alkenyl; cycloalkyl; cycloheteroalkyl; aryl; heteroaryl; $-(CR^{23}R^{33})_tOR^{21}$; $-(CR^{23}R^{33})_tNR^{28}R^{43}$; $-(CR^{23}R^{33})_tCOOR^{21}$; $-(CR^{23}R^{33})_tCONR^{21}R^{43}$;

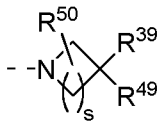
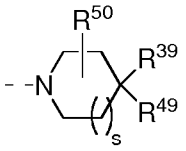
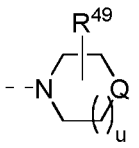
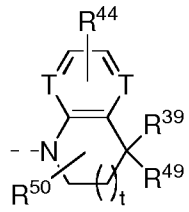
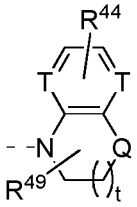
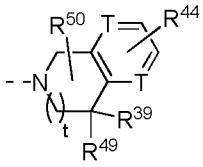
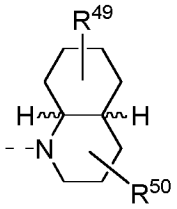
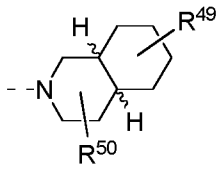
R^{49} and R^{50} are independently defined as H; F; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{32}R^{33})_qOR^{21}$; $-(CR^{32}R^{33})_qNR^{28}R^{43}$; $-(CR^{32}R^{33})_qCOOR^{21}$; or $-(CR^{32}R^{33})_qCONR^{28}R^{43}$;

taken together the following pairs of said substituents can define cyclic structural elements: (R^4 and R^{11}); (R^4 and R^{27}); (R^5 and R^6); (R^5 and R^7); (R^5 and R^9); (R^5 and R^{14}); (R^5 and R^{16}); (R^7 and R^8); (R^7 and R^9); (R^7 and R^{16}); (R^9 and R^{10}); (R^{14} and R^{15}); (R^{16} and R^{17}); (R^{18} and R^{19}); (R^{27} and R^{28}); (R^{28} and R^{31}); (R^{28} and R^{43}); (R^{29} and R^{30}); (R^{32} and R^{33}); (R^{34} and R^{35}); (R^{37} and R^{38}); (R^{39} and R^{40}); (R^{39} and R^{41}); (R^{39} and R^{49}); (R^{42} and R^{43}); (R^{44} and R^{45}); or (R^{44} and

R^{46}) can form optionally substituted cycloalkyl or heterocycloalkyl moieties;

in addition, the structural elements $-NR^4R^{11}$; $-NR^{27}R^{28}$; $-NR^{28}R^{31}$ or $-NR^{28}R^{43}$ can form one of the groups of formulae **H111–H118** as shown in Table 9, below;

Table 9: Heterocyclic Groups Defined by Linking the Residues of the Disubstituted Amino Groups $-NR^4R^{11}$; $-NR^{27}R^{28}$; $-NR^{28}R^{31}$ or $-NR^{28}R^{43}$.

 **H111**	 **H112**	 **H113**	 **H114**
 **H115**	 **H116**	 **H117**	 **H118**

variable heteroatoms and connector groups in the aforementioned structures being as follows:

Z: O; S; S(=O); $S(=O)_2$; or NR^{28};

Y: O; S; or NR^{37};

X: O; S; S(=O); or $S(=O)_2$;

Q: O; S; or NR^{28};

U, V and W: as defined in Table 3, above;

T: CR^{46} or N;

in case T occurs several times in the same ring structure each T being defined independently of the other; and

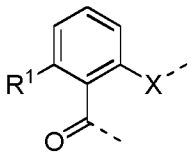
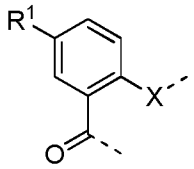
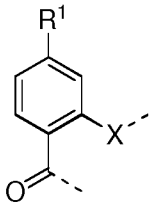
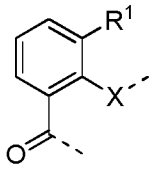
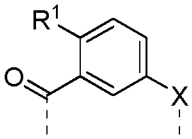
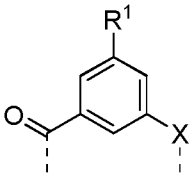
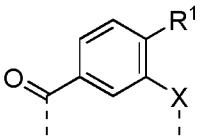
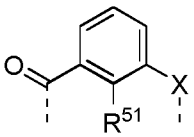
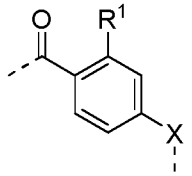
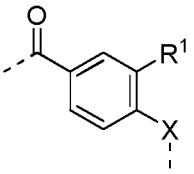
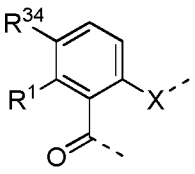
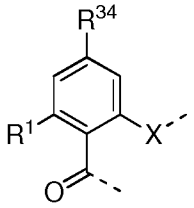
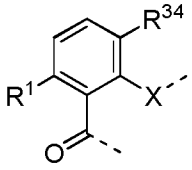
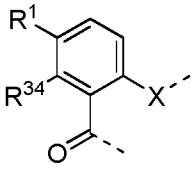
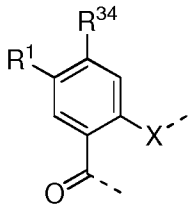
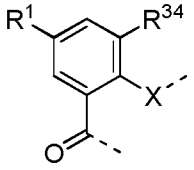
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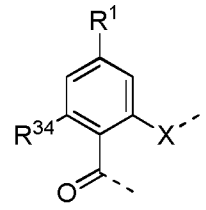
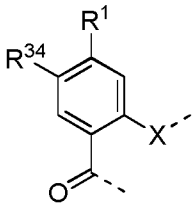
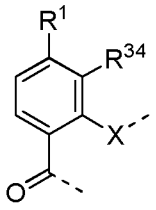
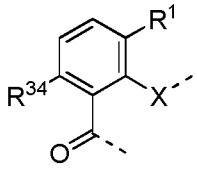
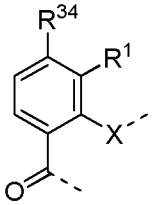
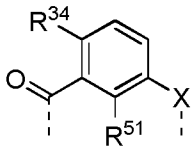
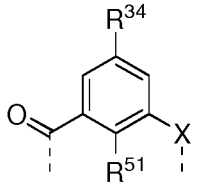
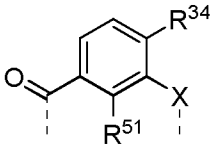
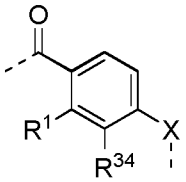
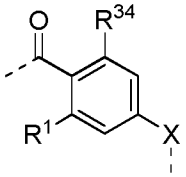
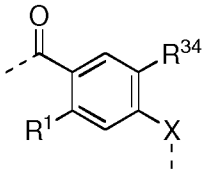
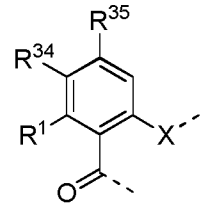
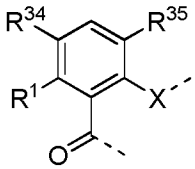
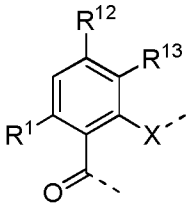
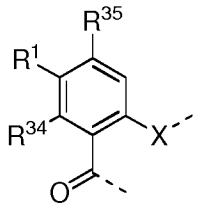
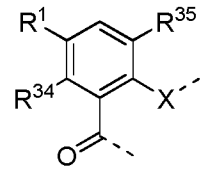
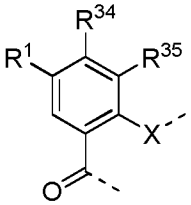
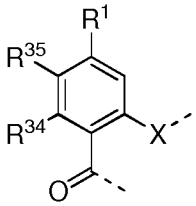
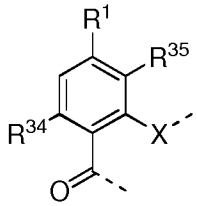
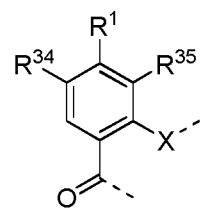
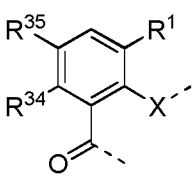
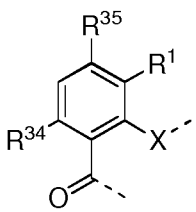
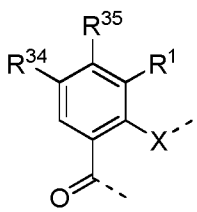
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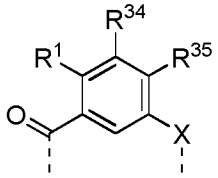
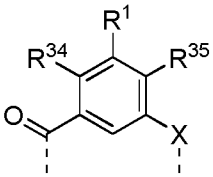
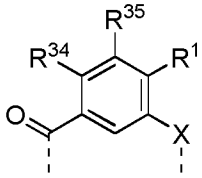
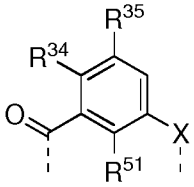
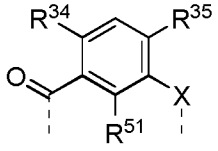
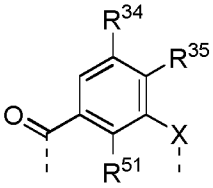
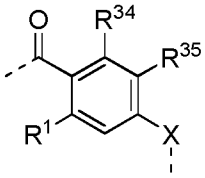
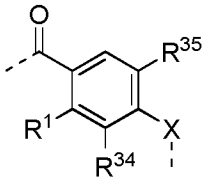
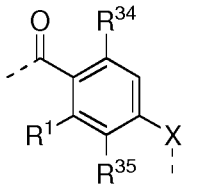
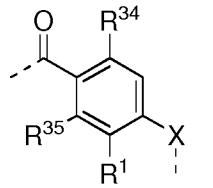
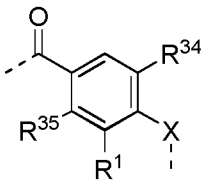
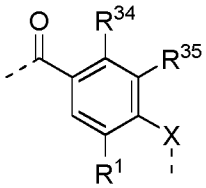
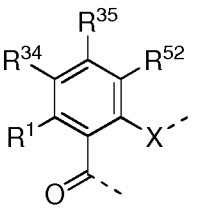
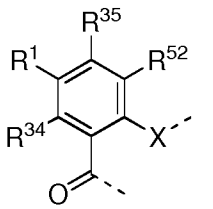
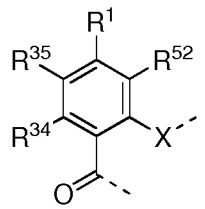
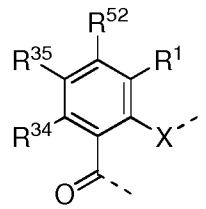
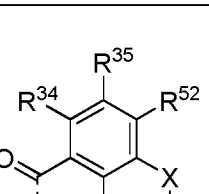
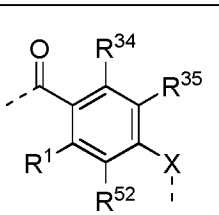
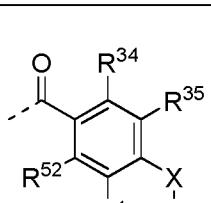
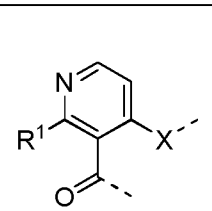
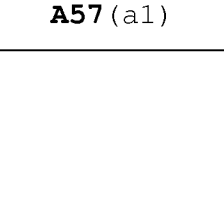
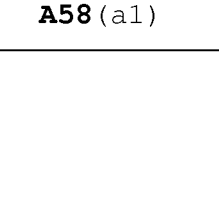
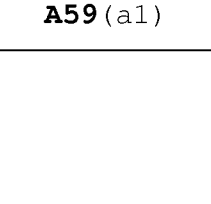
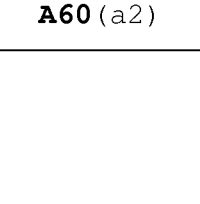
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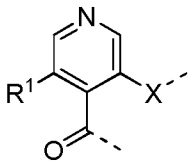
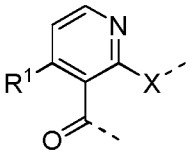
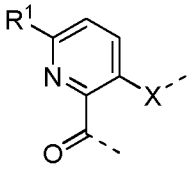
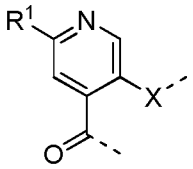
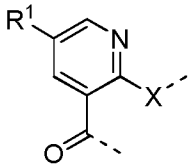
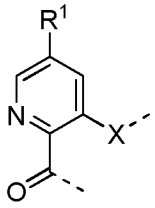
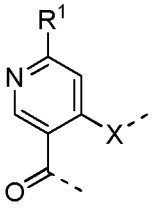
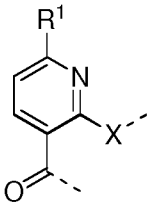
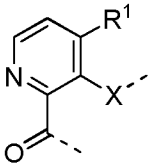
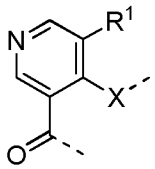
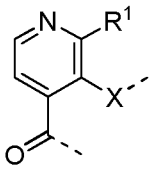
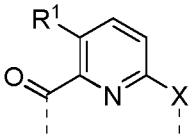
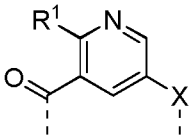
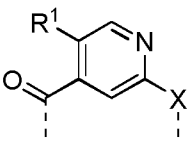
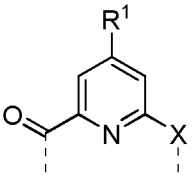
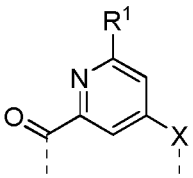
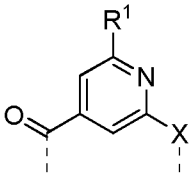
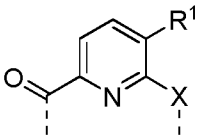
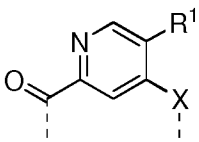
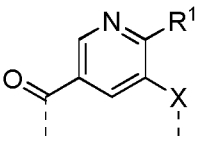
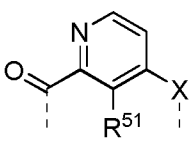
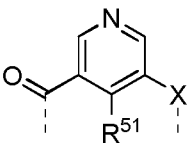
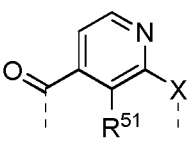
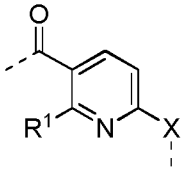
2. Compounds according to claim 1 wherein **A** is a bivalent radical selected from radicals **A1** - **A626** as depicted in Table 10, below;

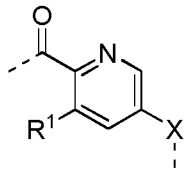
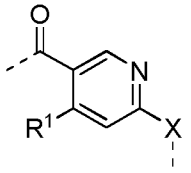
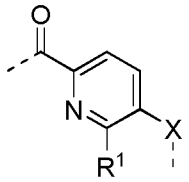
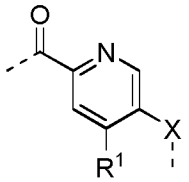
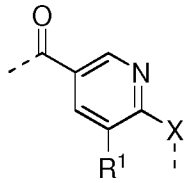
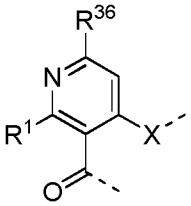
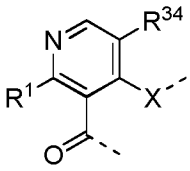
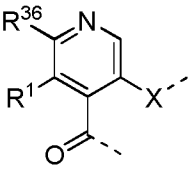
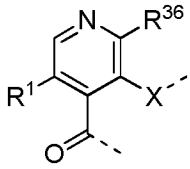
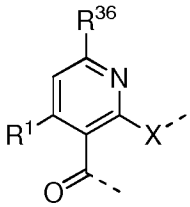
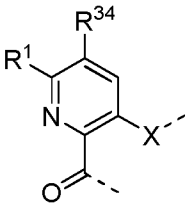
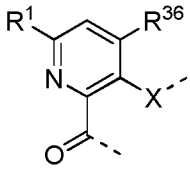
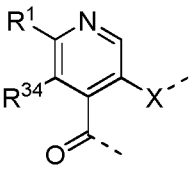
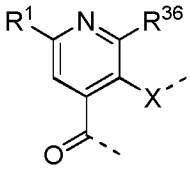
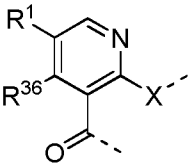
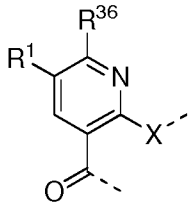
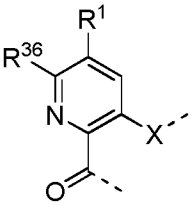
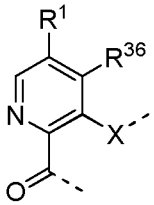
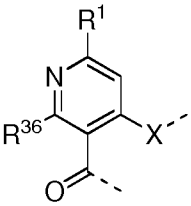
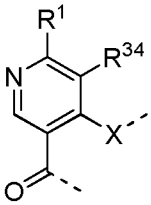
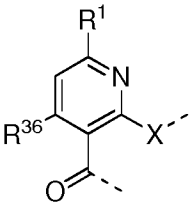
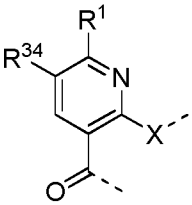
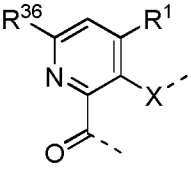
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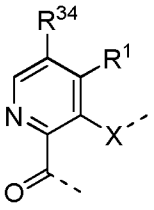
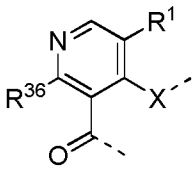
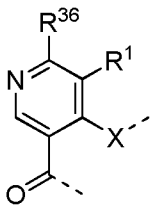
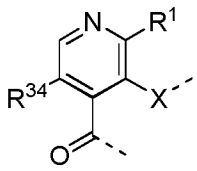
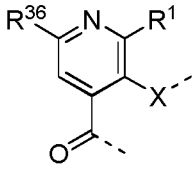
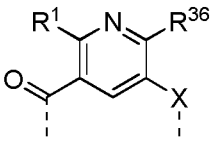
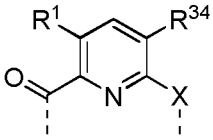
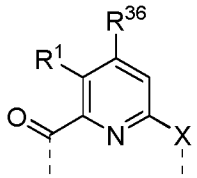
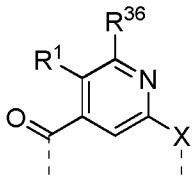
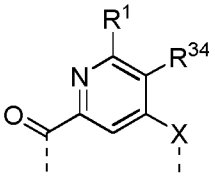
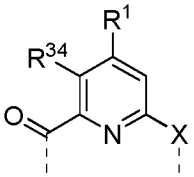
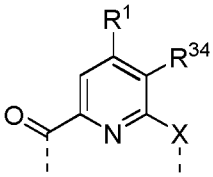
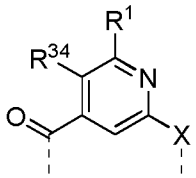
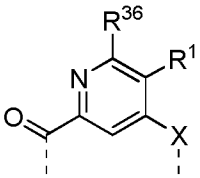
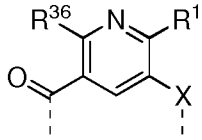
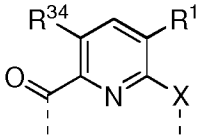
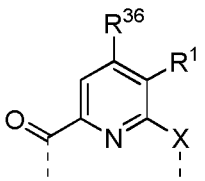
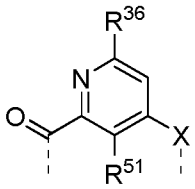
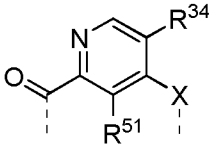
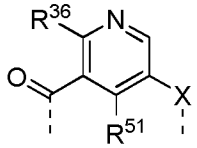
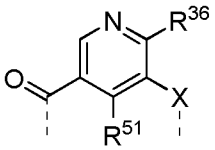
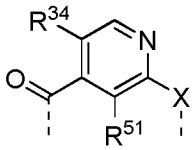
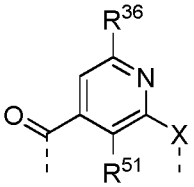
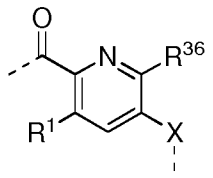
 **A1**(a1)	 **A2**(a1)	 **A3**(a1)	 **A4**(a1)
 **A5**(a1)	 **A6**(a1)	 **A7**(a1)	 **A8**(a1)
 **A9**(a1)	 **A10**(a1)	 **A11**(a1)	 **A12**(a1)
 **A13**(a1)	 **A14**(a1)	 **A15**(a1)	 **A16**(a1)

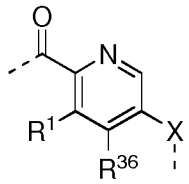
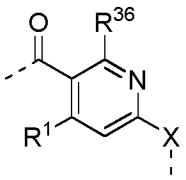
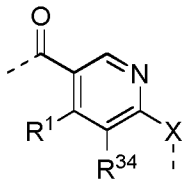
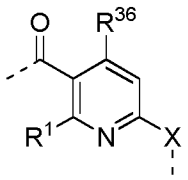
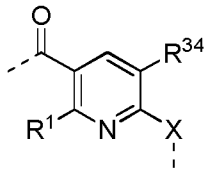
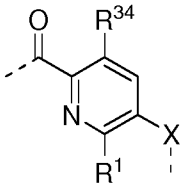
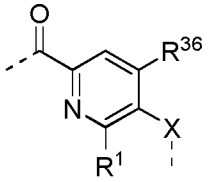
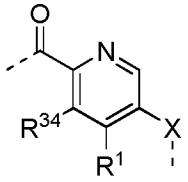
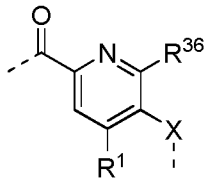
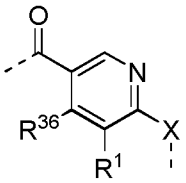
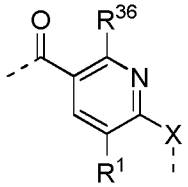
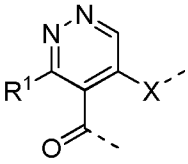
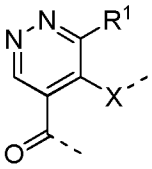
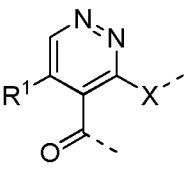
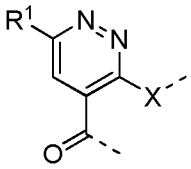
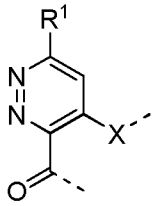
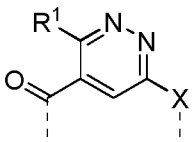
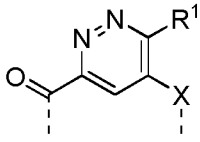
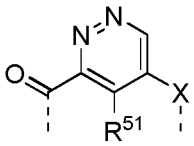
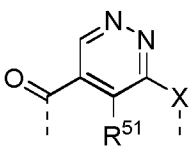
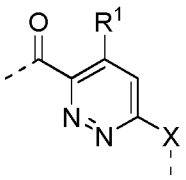
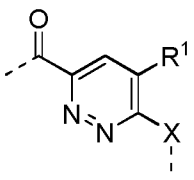
 **A17**(a1)	 **A18**(a1)	 **A19**(a1)	 **A20**(a1)
 **A21**(a1)	 **A22**(a1)	 **A23**(a1)	 **A24**(a1)
 **A25**(a1)	 **A26**(a1)	 **A27**(a1)	 **A28**(a1)
 **A29**(a1)	 **A30**(a1)	 **A31**(a1)	 **A32**(a1)
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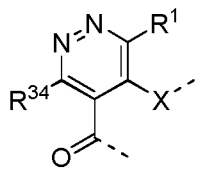
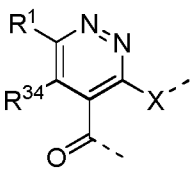
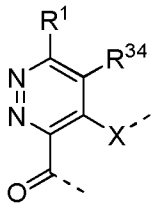
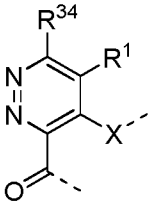
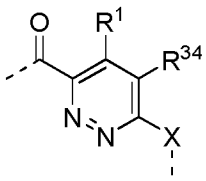
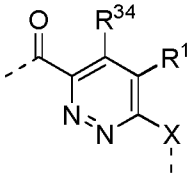
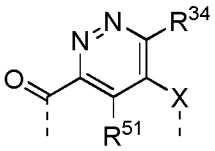
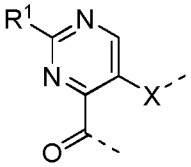
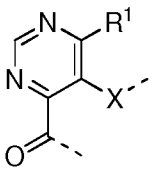
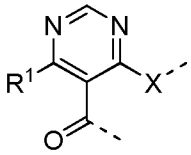
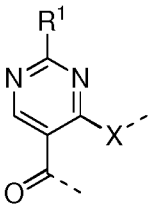
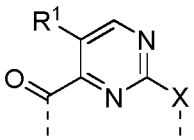
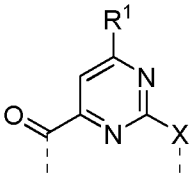
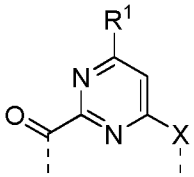
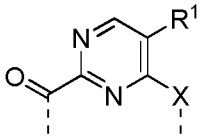
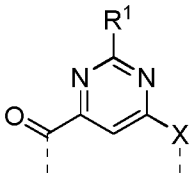
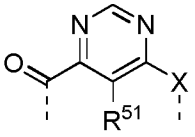
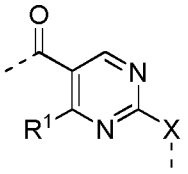
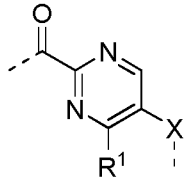
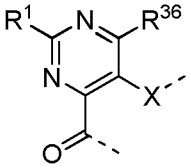
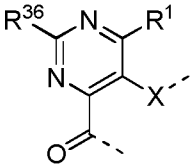
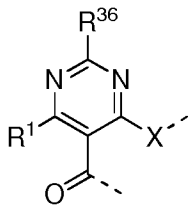
A37(a1)	**A38**(a1)	**A39**(a1)	**A40**(a1)
			
A41(a1)	**A42**(a1)	**A43**(a1)	**A44**(a1)
			
A45(a1)	**A46**(a1)	**A47**(a1)	**A48**(a1)
			
A49(a1)	**A50**(a1)	**A51**(a1)	**A52**(a1)
			
A53(a1)	**A54**(a1)	**A55**(a1)	**A56**(a1)
			
A57(a1)	**A58**(a1)	**A59**(a1)	**A60**(a2)
			

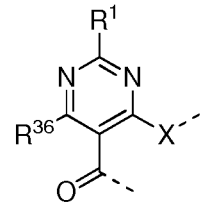
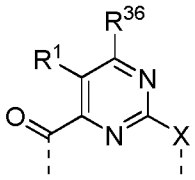
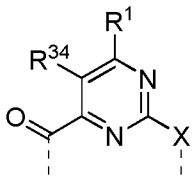
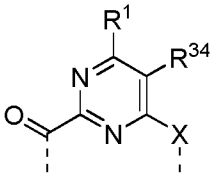
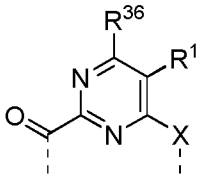
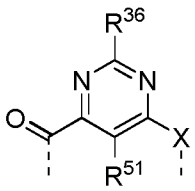
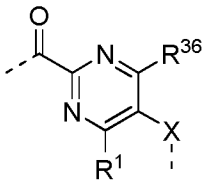
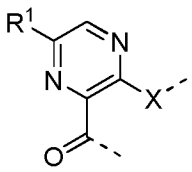
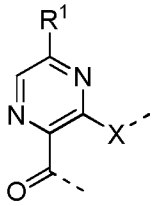
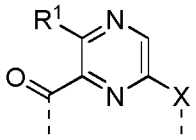
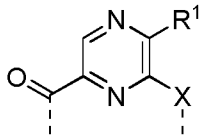
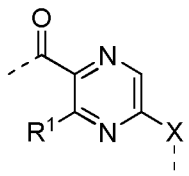
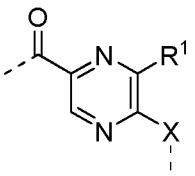
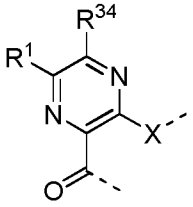
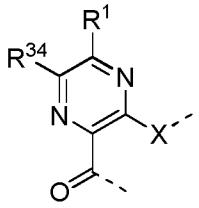
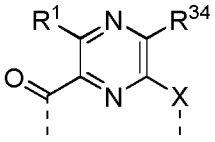
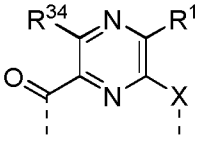
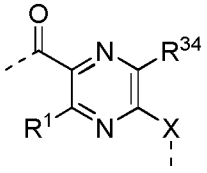
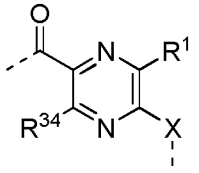
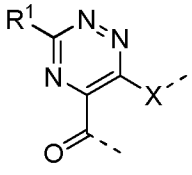
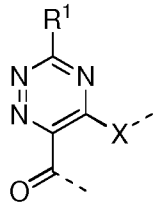
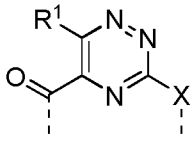
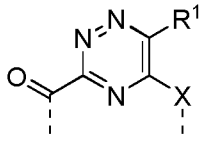
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 **A65** (a2)	 **A66** (a2)	 **A67** (a2)	 **A68** (a2)
 **A69** (a2)	 **A70** (a2)	 **A71** (a2)	 **A72** (a2)
 **A73** (a2)	 **A74** (a2)	 **A75** (a2)	 **A76** (a2)
 **A77** (a2)	 **A78** (a2)	 **A79** (a2)	 **A80** (a2)
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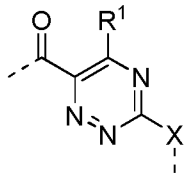
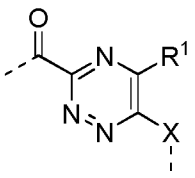
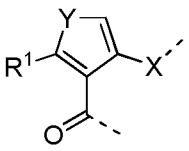
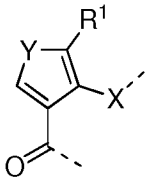
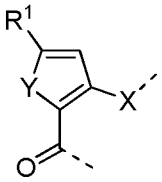
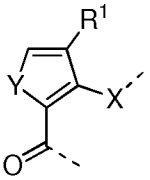
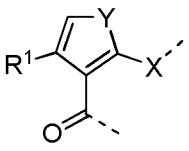
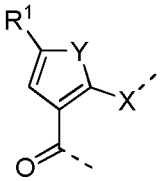
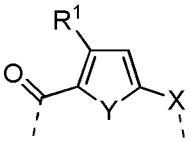
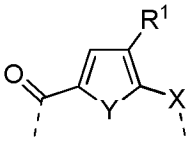
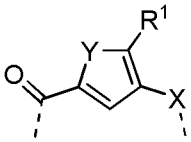
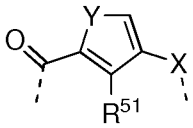
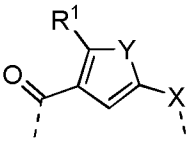
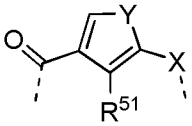
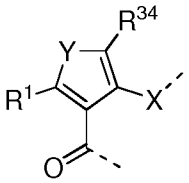
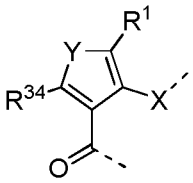
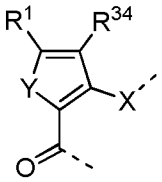
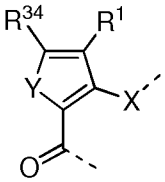
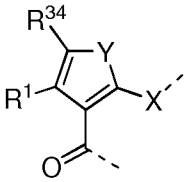
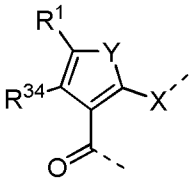
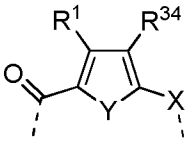
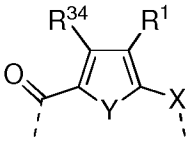
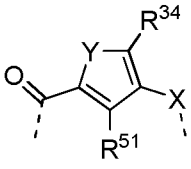
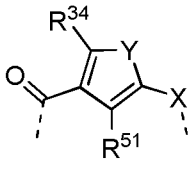
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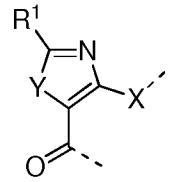
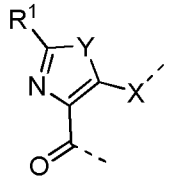
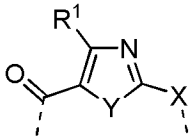
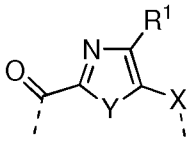
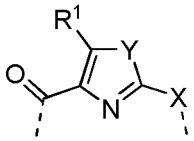
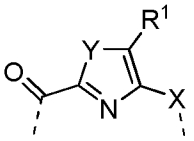
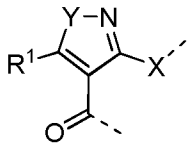
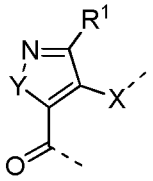
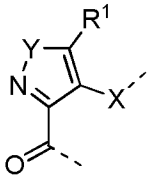
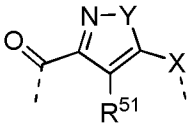
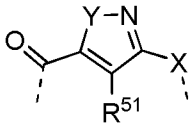
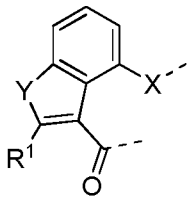
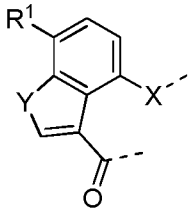
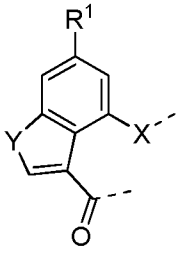
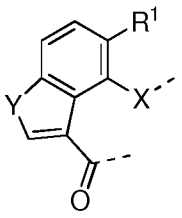
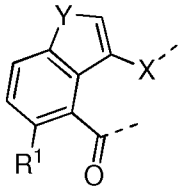
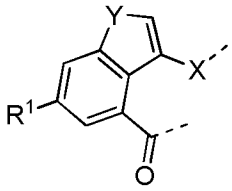
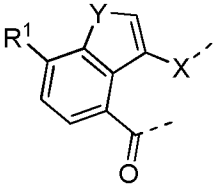
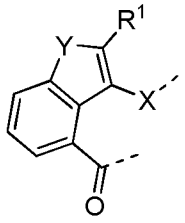
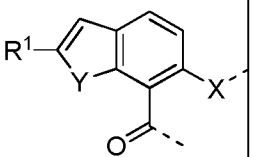
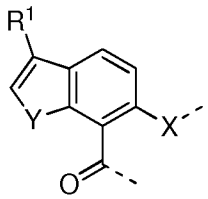
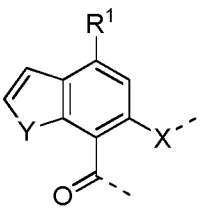
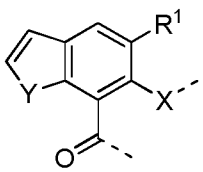
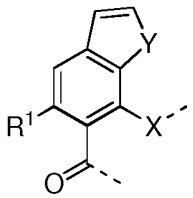
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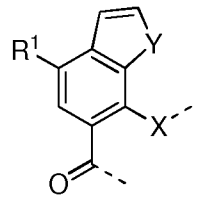
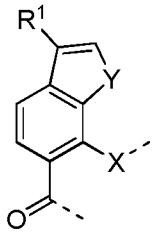
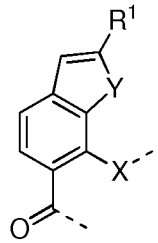
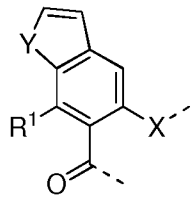
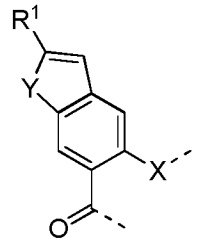
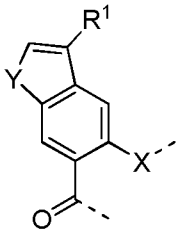
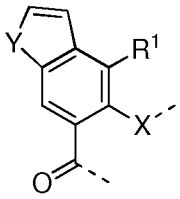
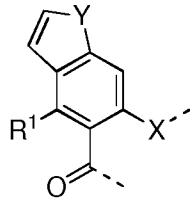
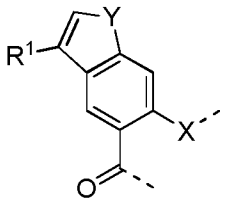
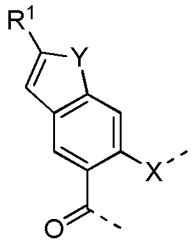
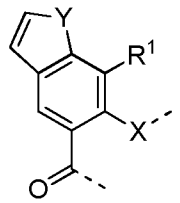
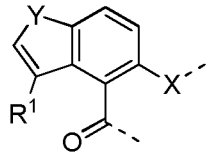
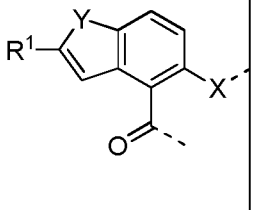
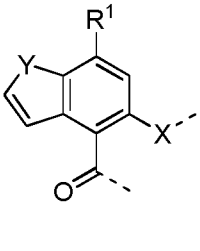
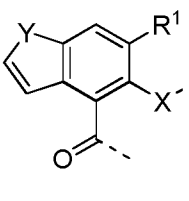
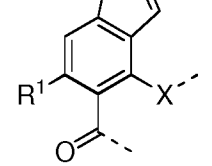
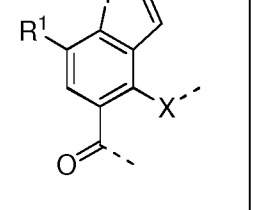
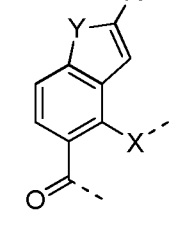
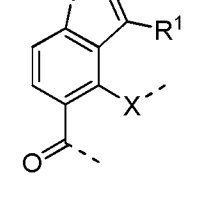
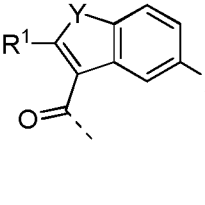
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 **A149** (a3)	 **A150** (a3)	 **A151** (a3)	 **A152** (a3)
 **A153** (a3)	 **A154** (a3)	 **A155** (a3)	 **A156** (a3)

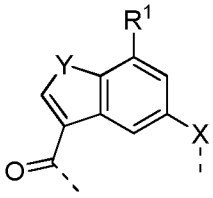
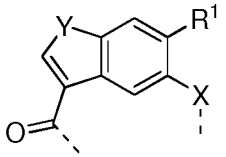
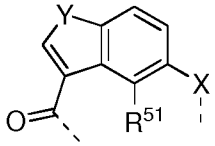
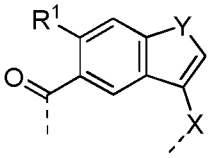
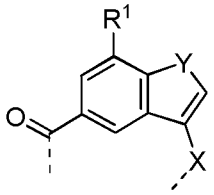
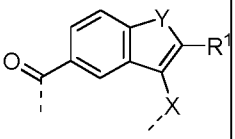
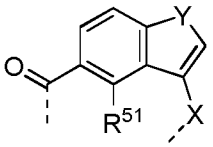
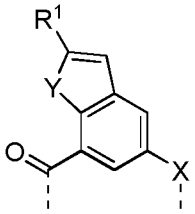
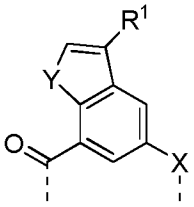
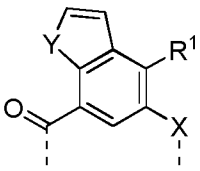
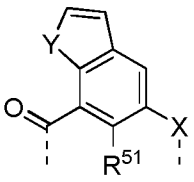
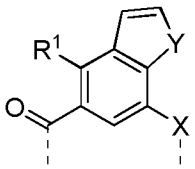
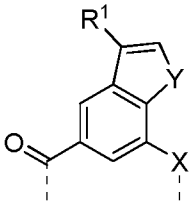
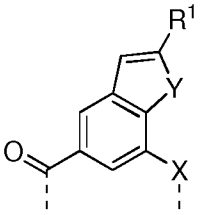
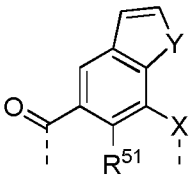
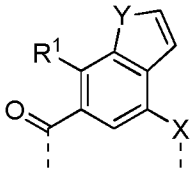
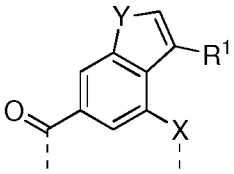
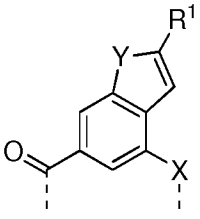
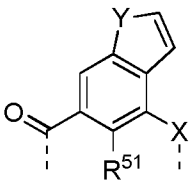
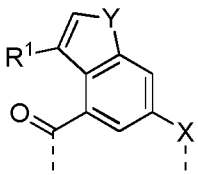
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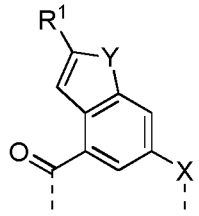
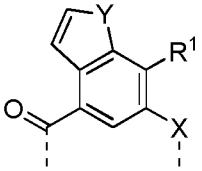
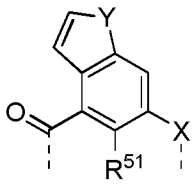
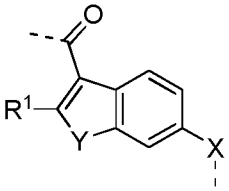
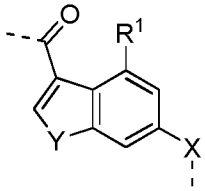
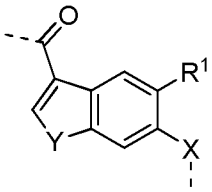
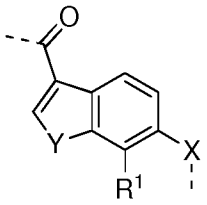
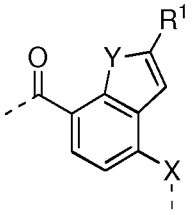
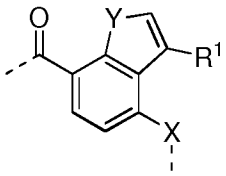
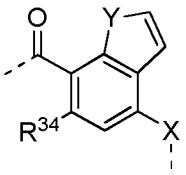
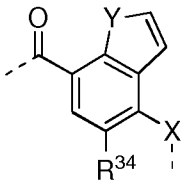
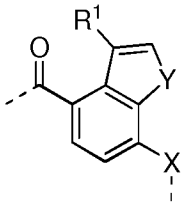
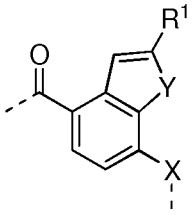
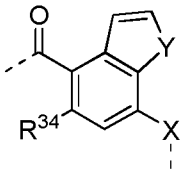
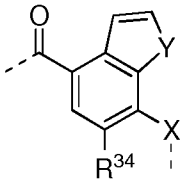
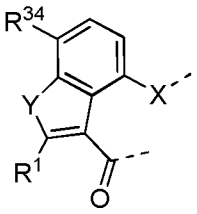
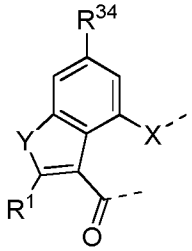
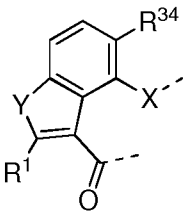
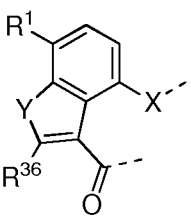
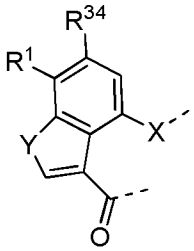
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 **A193** (a5)	 **A194** (a5)	 **A195** (a5)	 **A196** (a5)
 **A197** (a5)	 **A198** (a5)	 **A199** (a5)	 **A200** (a5)
 **A201** (a6)	 **A202** (a6)	 **A203** (a6)	 **A204** (a6)

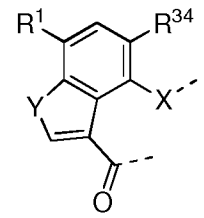
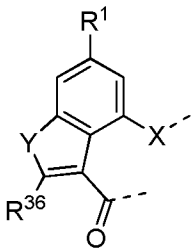
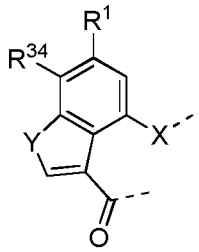
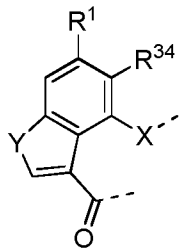
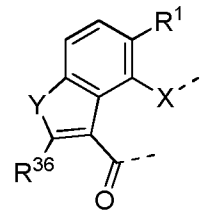
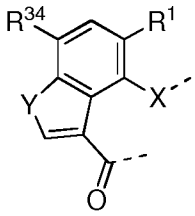
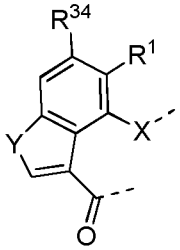
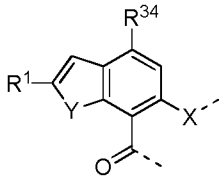
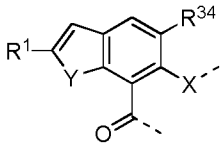
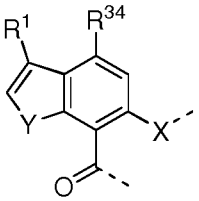
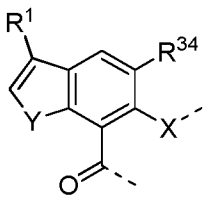
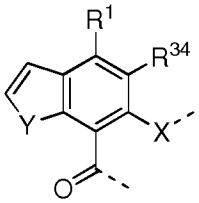
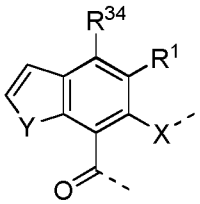
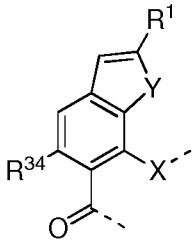
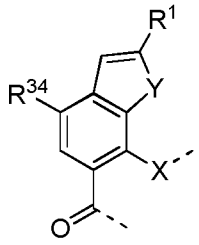
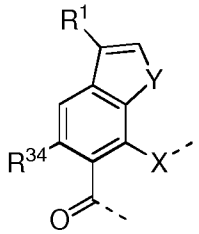
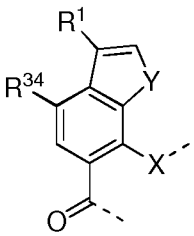
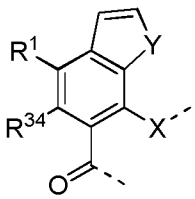
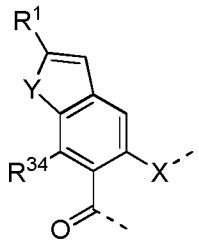
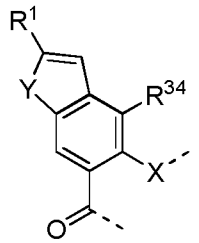
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 **A217** (a7)	 **A218** (a7)	 **A219** (a7)	 **A220** (a7)
 **A221** (a7)	 **A222** (a7)	 **A223** (a7)	 **A224** (a7)
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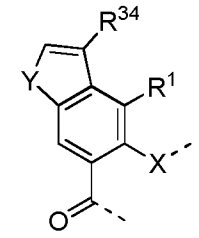
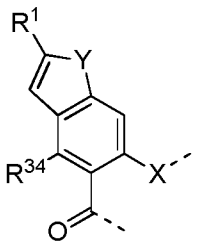
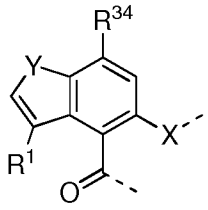
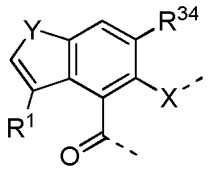
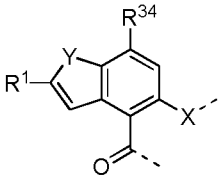
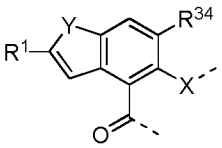
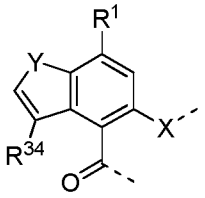
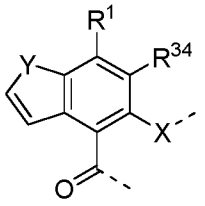
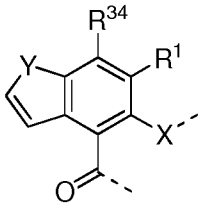
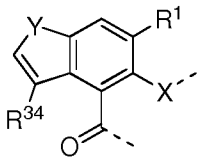
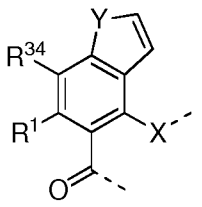
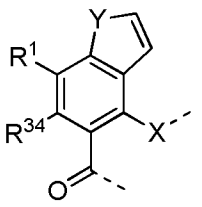
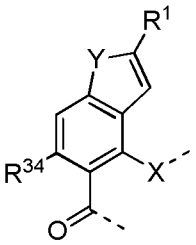
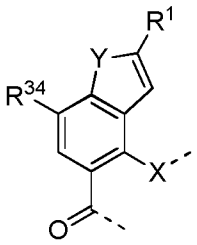
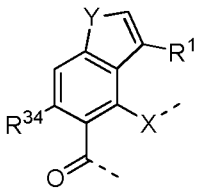
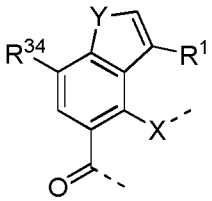
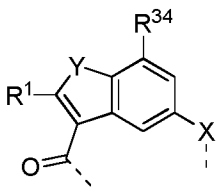
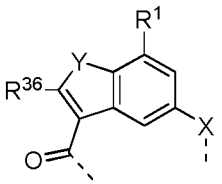
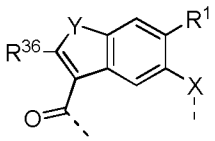
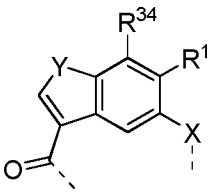
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 **A237** (a9)	 **A238** (a9)	 **A239** (a9)	 **A240** (a10)
 **A241** (a10)	 **A242** (a10)	 **A243** (a10)	 **A244** (a10)
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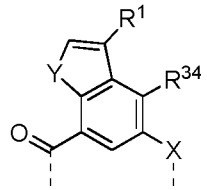
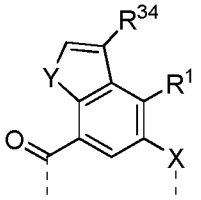
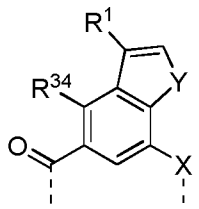
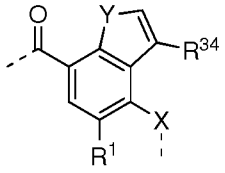
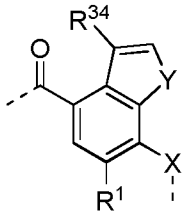
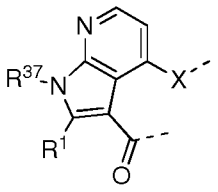
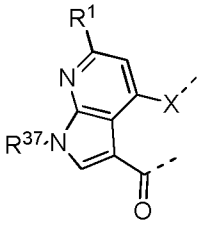
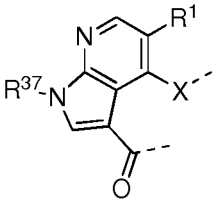
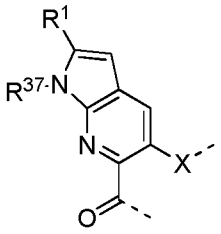
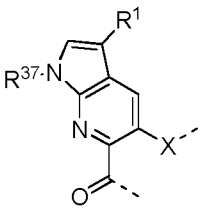
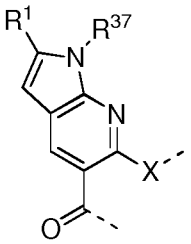
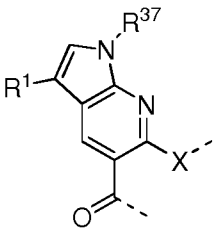
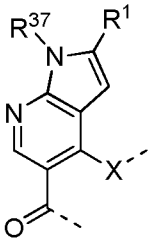
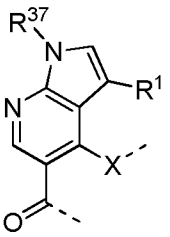
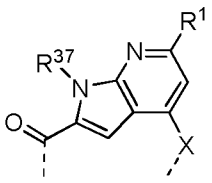
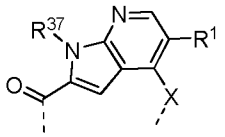
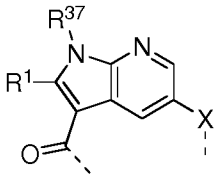
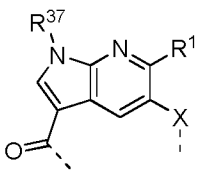
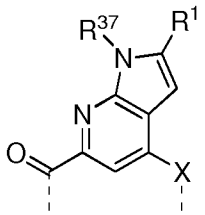
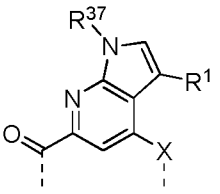
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A257 (a10)	**A258** (a10)	**A259** (a10)	**A260** (a10)
			
A261 (a10)	**A262** (a10)	**A263** (a10)	**A264** (a10)
			
A265 (a10)	**A266** (a10)	**A267** (a10)	**A268** (a10)
			
A269 (a10)	**A270** (a10)	**A271** (a10)	**A272** (a10)

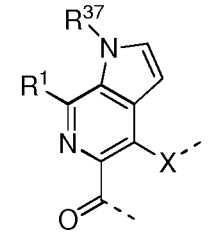
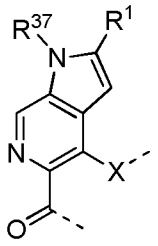
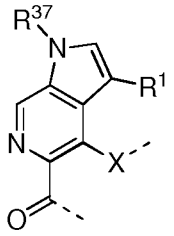
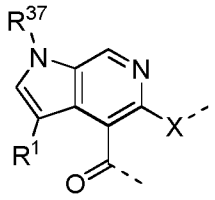
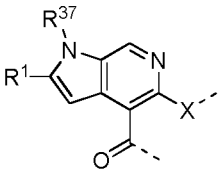
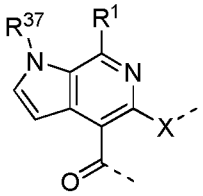
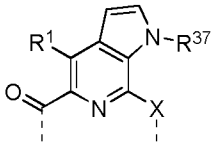
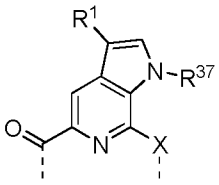
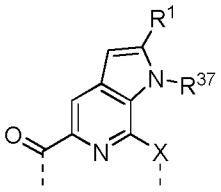
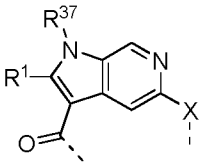
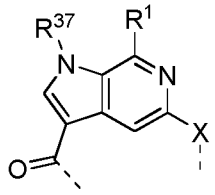
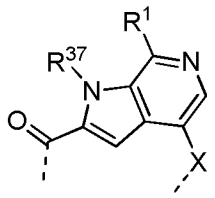
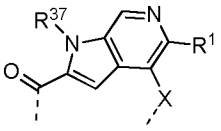
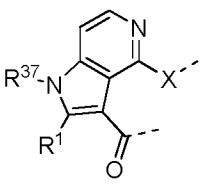
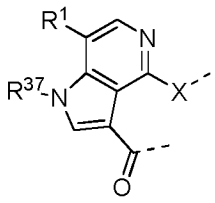
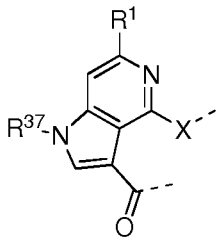
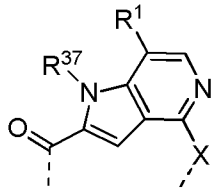
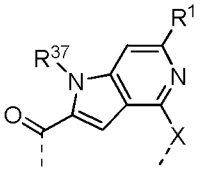
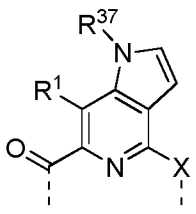
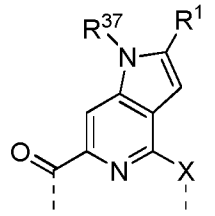
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 **A285** (a10)	 **A286** (a10)	 **A287** (a10)	 **A288** (a10)
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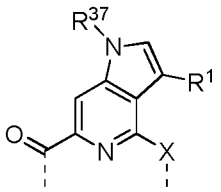
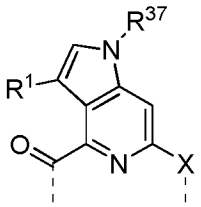
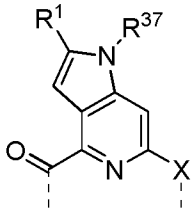
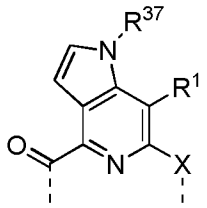
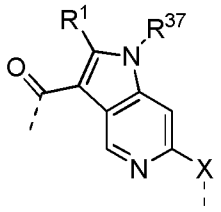
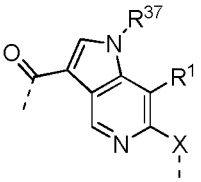
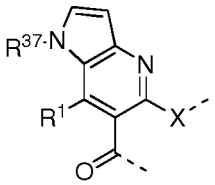
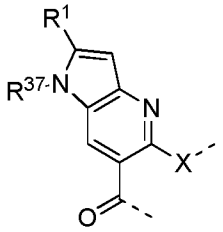
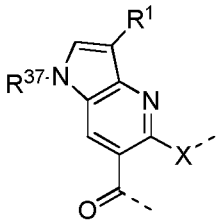
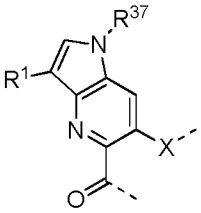
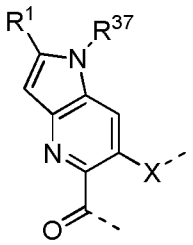
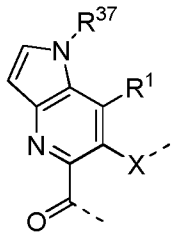
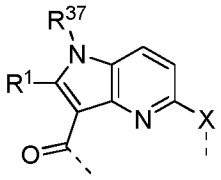
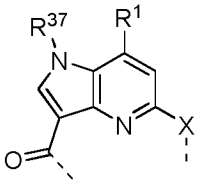
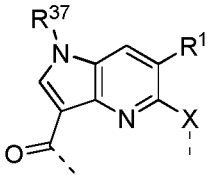
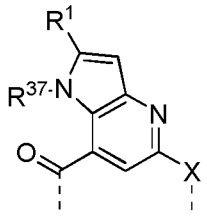
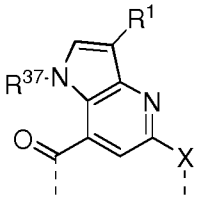
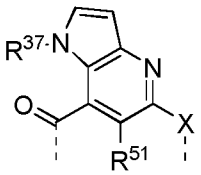
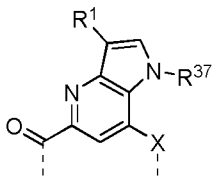
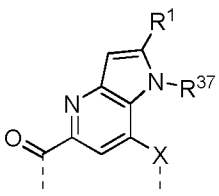
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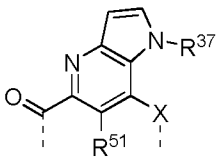
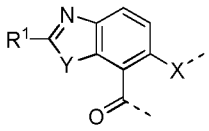
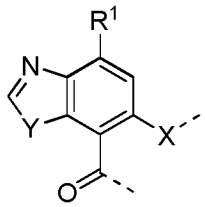
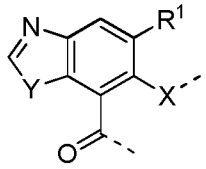
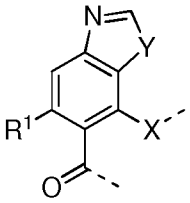
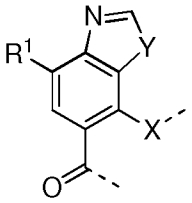
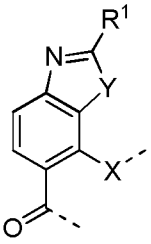
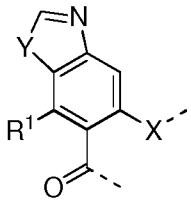
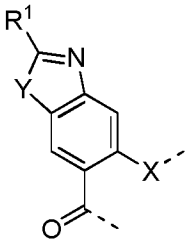
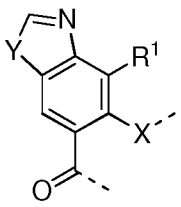
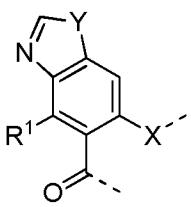
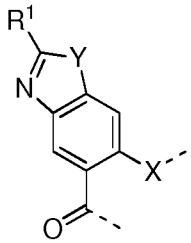
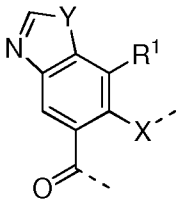
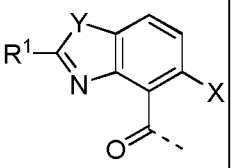
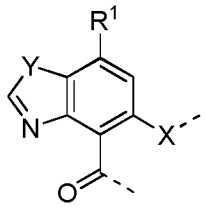
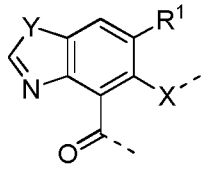
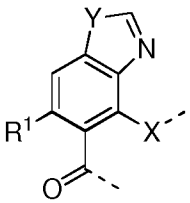
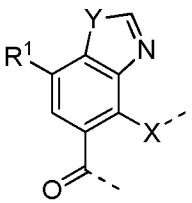
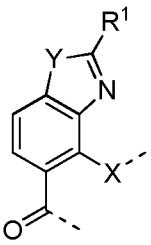
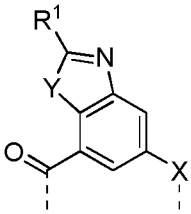
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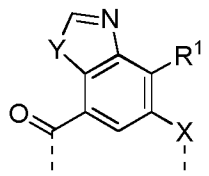
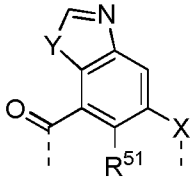
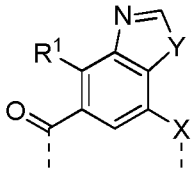
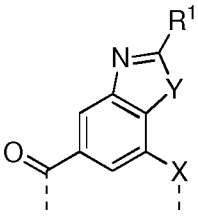
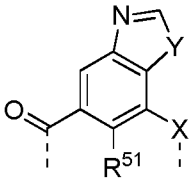
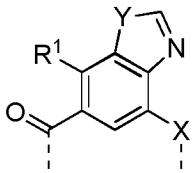
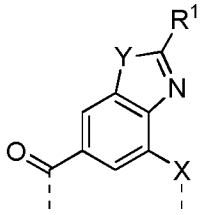
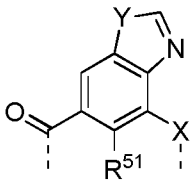
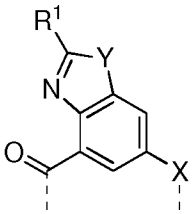
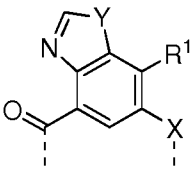
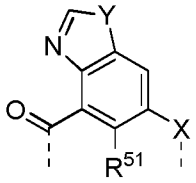
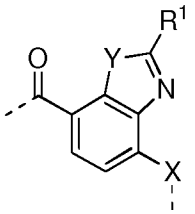
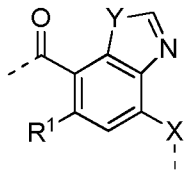
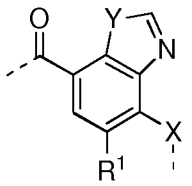
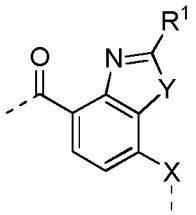
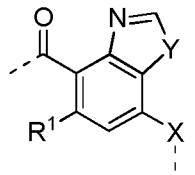
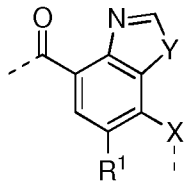
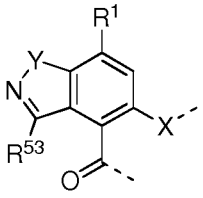
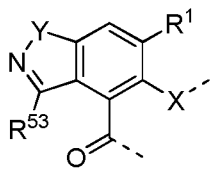
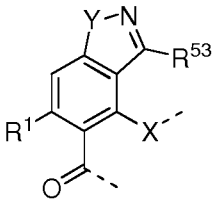
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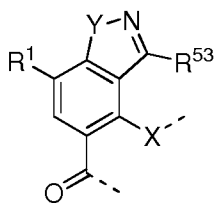
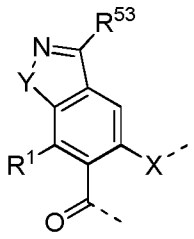
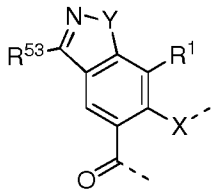
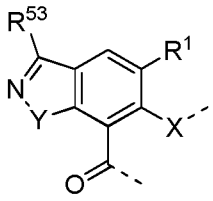
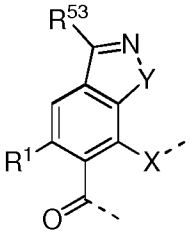
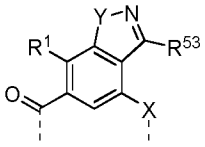
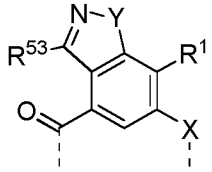
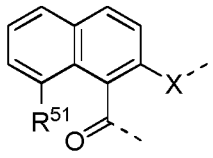
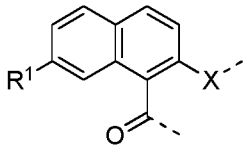
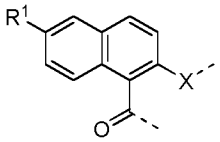
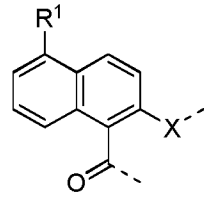
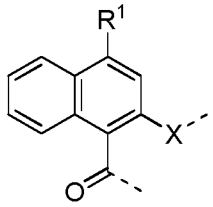
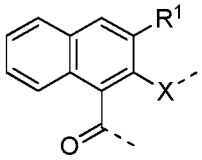
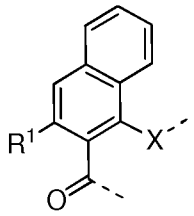
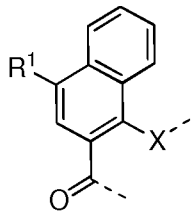
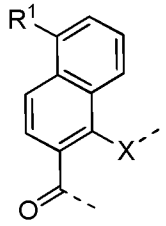
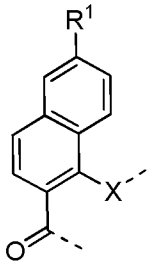
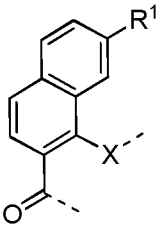
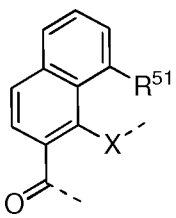
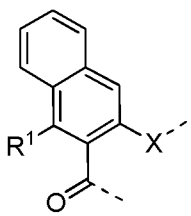
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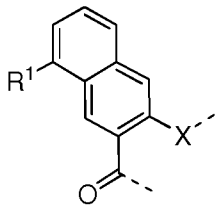
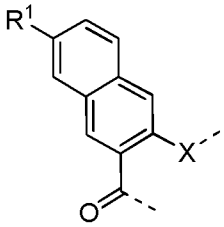
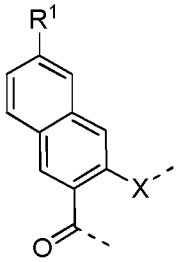
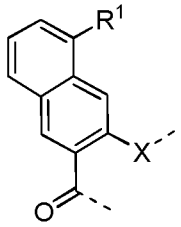
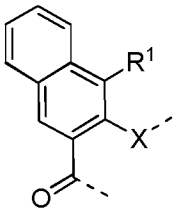
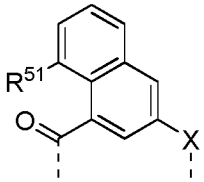
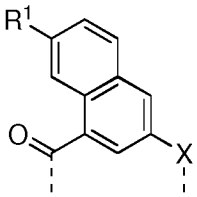
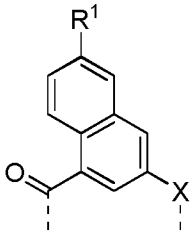
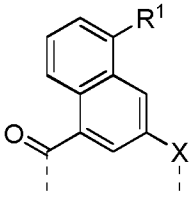
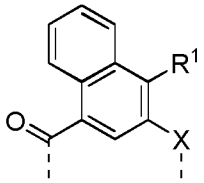
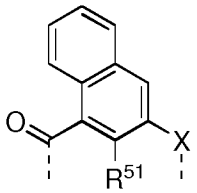
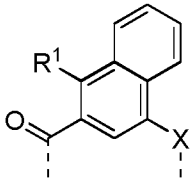
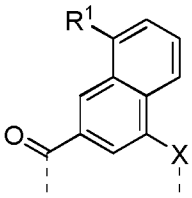
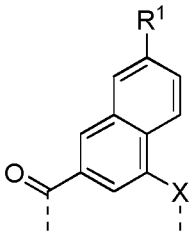
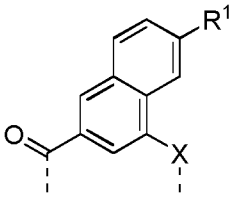
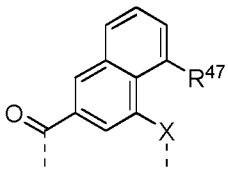
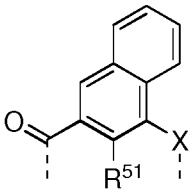
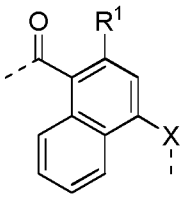
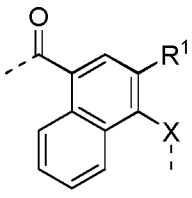
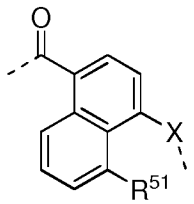
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 **A385** (a12)	 **A386** (a13)	 **A387** (a13)	 **A388** (a13)
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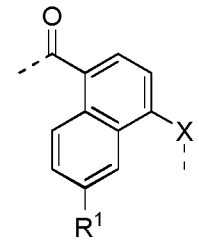
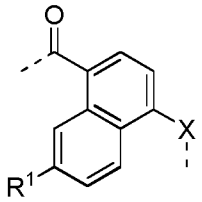
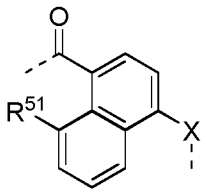
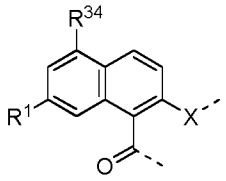
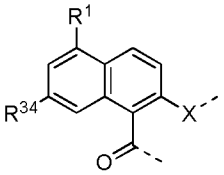
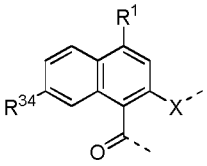
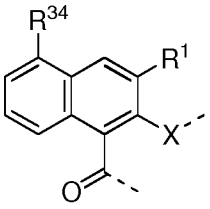
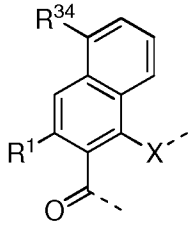
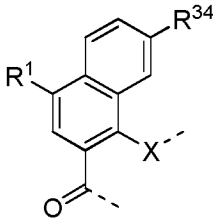
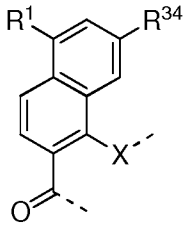
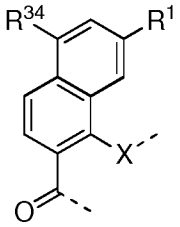
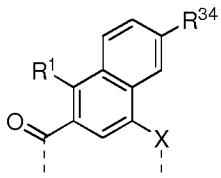
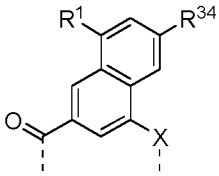
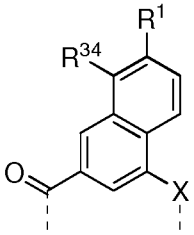
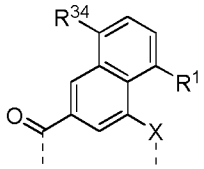
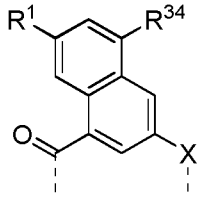
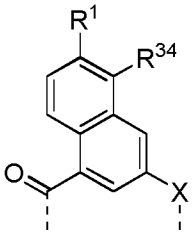
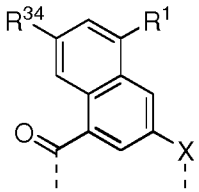
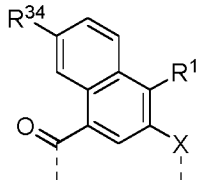
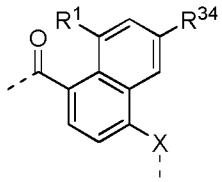
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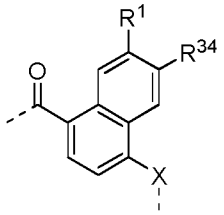
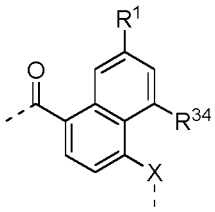
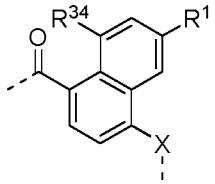
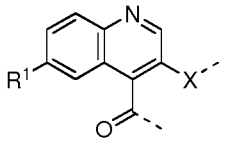
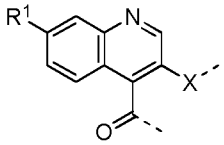
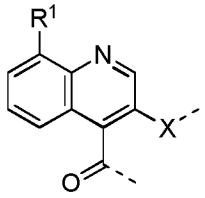
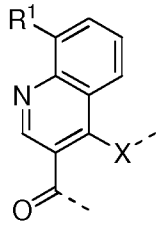
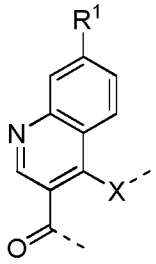
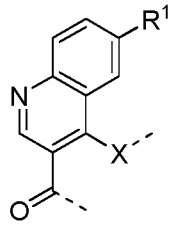
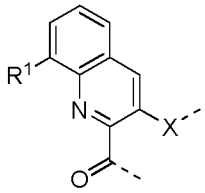
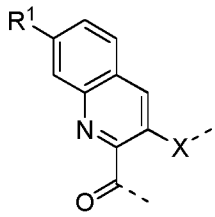
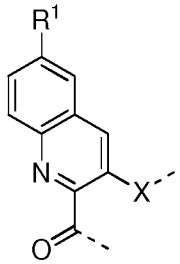
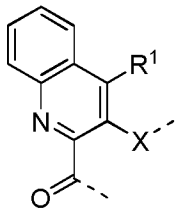
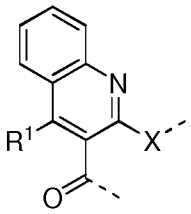
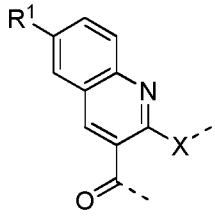
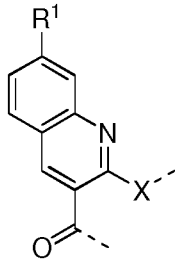
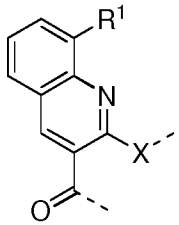
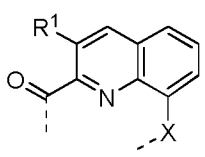
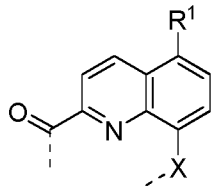
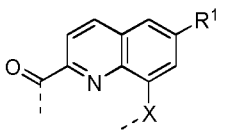
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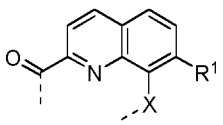
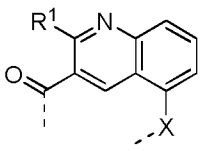
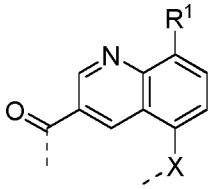
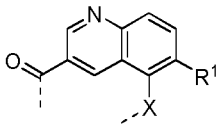
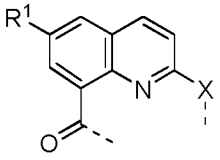
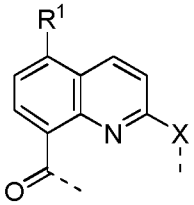
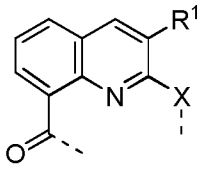
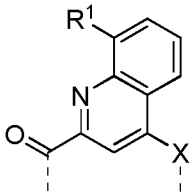
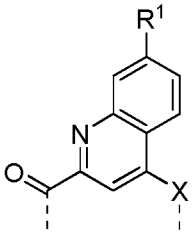
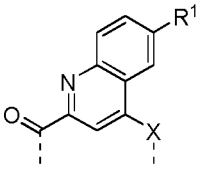
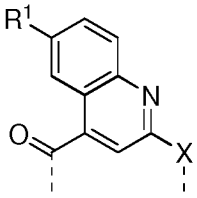
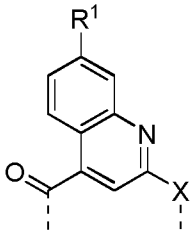
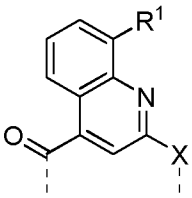
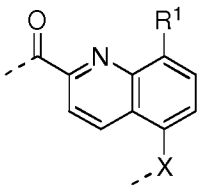
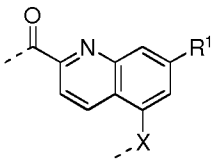
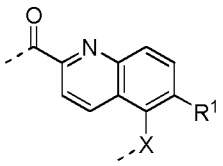
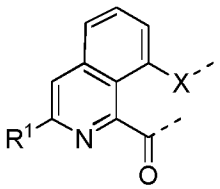
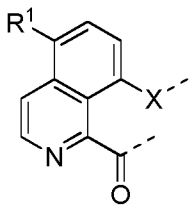
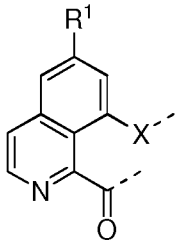
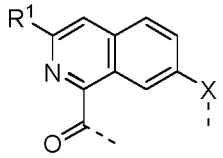
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 **A441** (a15)	 **A442** (a15)	 **A443** (a15)	 **A444** (a15)
 **A445** (a15)	 **A446** (a15)	 **A447** (a15)	 **A448** (a15)
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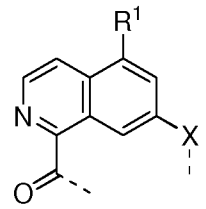
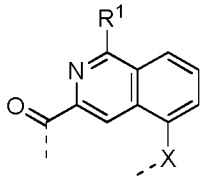
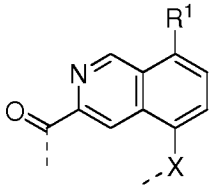
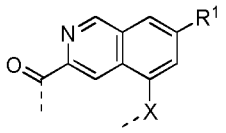
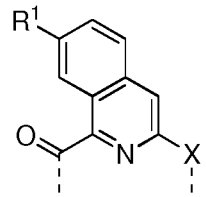
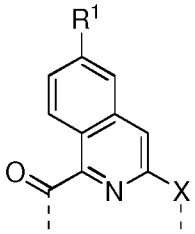
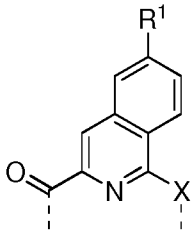
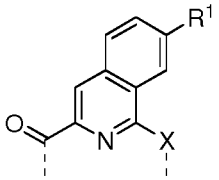
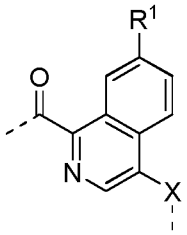
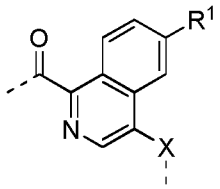
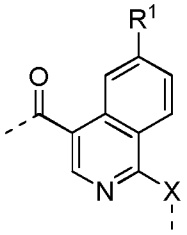
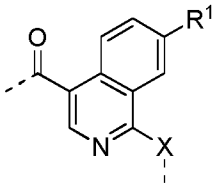
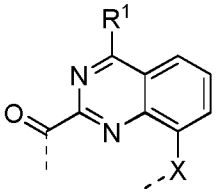
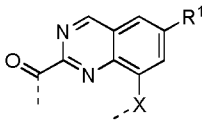
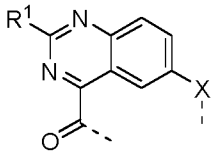
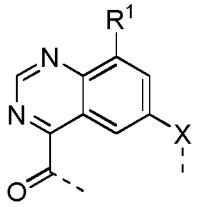
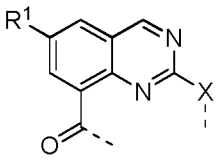
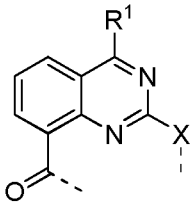
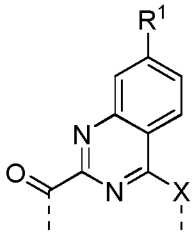
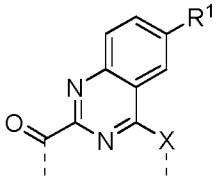
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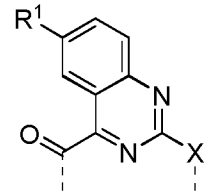
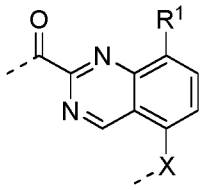
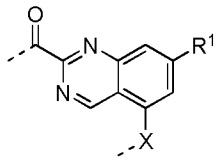
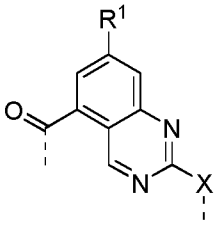
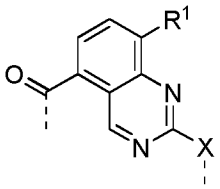
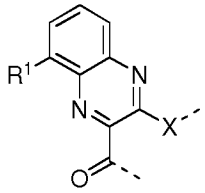
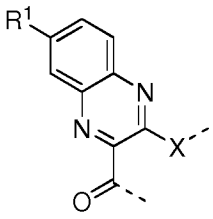
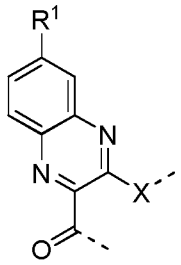
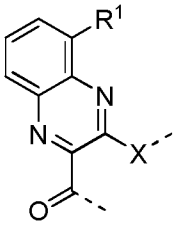
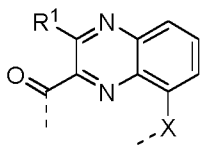
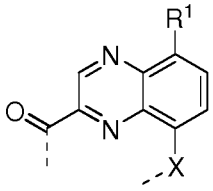
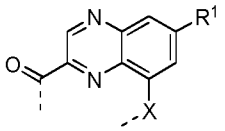
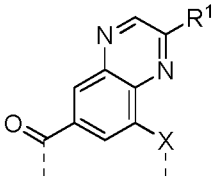
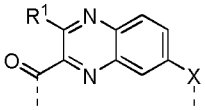
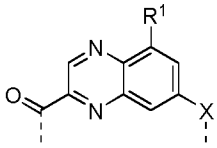
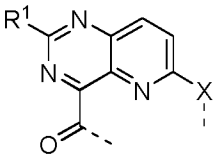
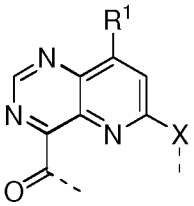
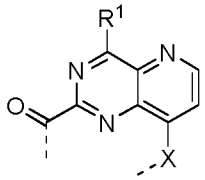
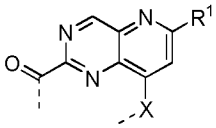
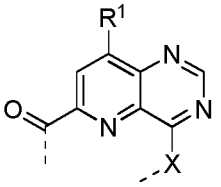
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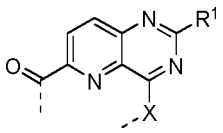
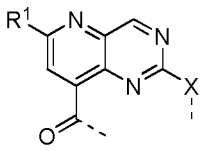
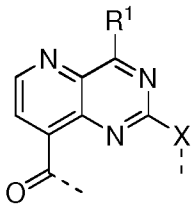
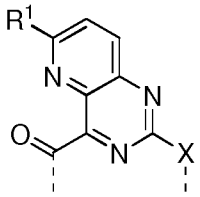
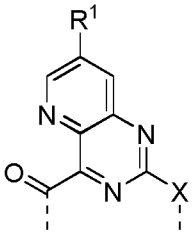
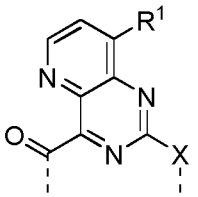
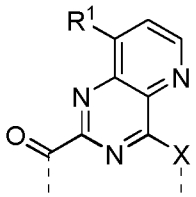
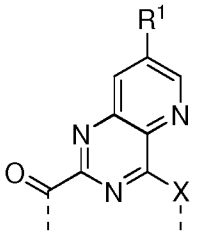
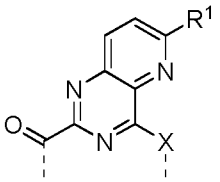
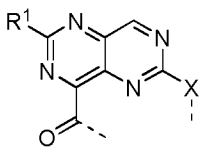
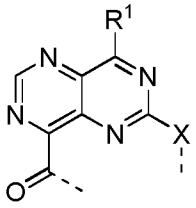
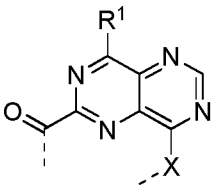
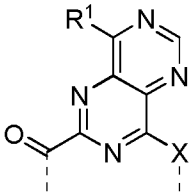
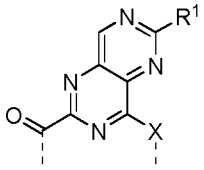
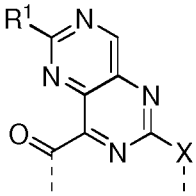
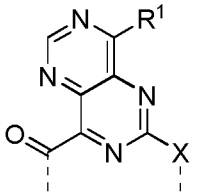
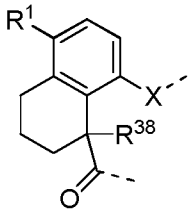
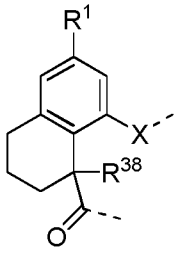
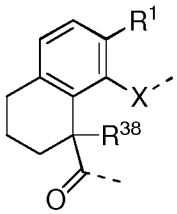
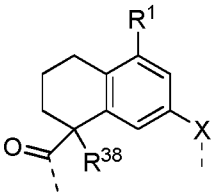
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 **A497** (a17)	 **A498** (a17)	 **A499** (a17)	 **A500** (a17)
 **A501** (a17)	 **A502** (a17)	 **A503** (a17)	 **A504** (a17)
 **A505** (a17)	 **A506** (a17)	 **A507** (a17)	 **A508** (a17)
 **A509** (a17)	 **A510** (a17)	 **A511** (a17)	 **A512** (a17)

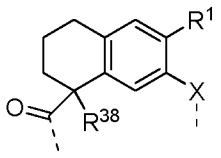
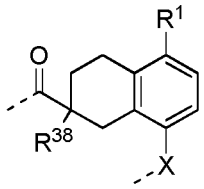
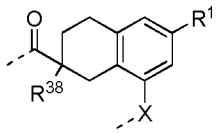
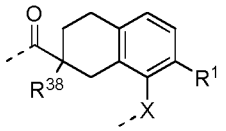
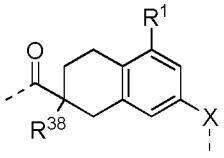
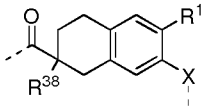
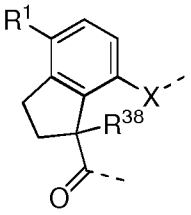
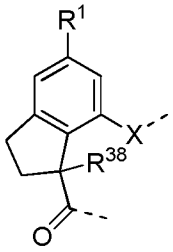
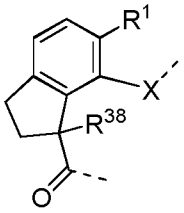
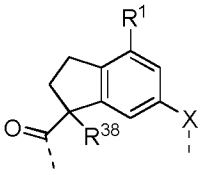
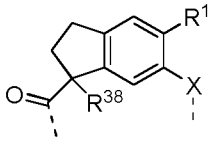
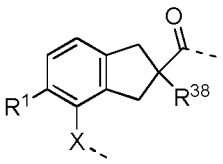
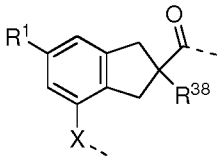
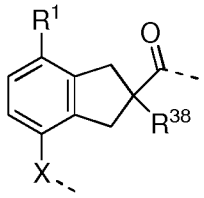
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 **A521** (a18)	 **A522** (a18)	 **A523** (a18)	 **A524** (a18)
 **A525** (a18)	 **A526** (a18)	 **A527** (a18)	 **A528** (a18)
 **A529** (a18)	 **A530** (a18)	 **A531** (a18)	 **A532** (a18)

 **A533** (a18)	 **A534** (a18)	 **A535** (a18)	 **A536** (a18)
 **A537** (a18)	 **A538** (a18)	 **A539** (a18)	 **A540** (a18)
 **A541** (a18)	 **A542** (a18)	 **A543** (a18)	 **A544** (a18)
 **A545** (a18)	 **A546** (a18)	 **A547** (a18)	 **A548** (a18)
 **A549** (a19)	 **A550** (a19)	 **A551** (a19)	 **A552** (a19)

 **A553** (a19)	 **A554** (a19)	 **A555** (a19)	 **A556** (a19)
 **A557** (a19)	 **A558** (a19)	 **A559** (a19)	 **A560** (a19)
 **A561** (a19)	 **A562** (a19)	 **A563** (a19)	 **A564** (a19)
 **A565** (a20)	 **A566** (a20)	 **A567** (a20)	 **A568** (a20)
 **A569** (a20)	 **A570** (a20)	 **A571** (a20)	 **A572** (a20)

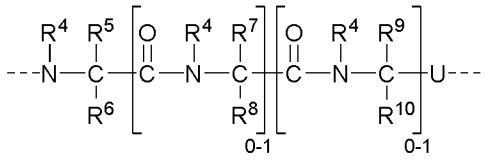
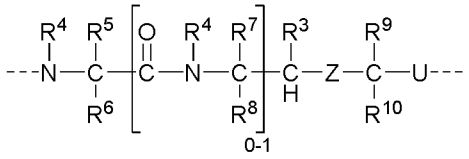
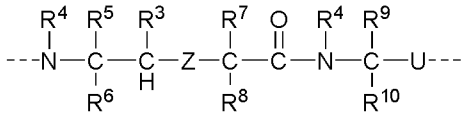
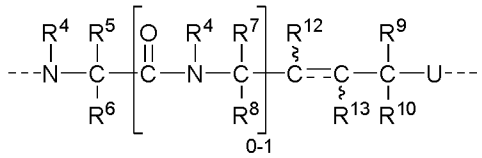
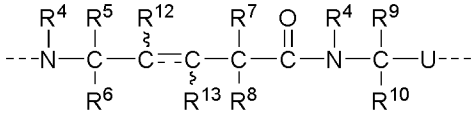
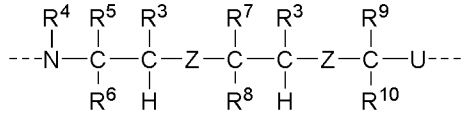
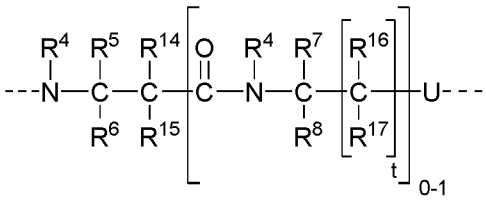
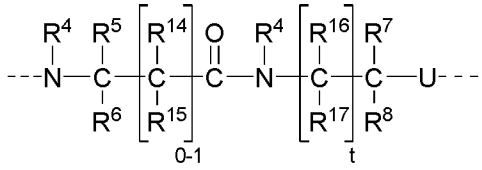
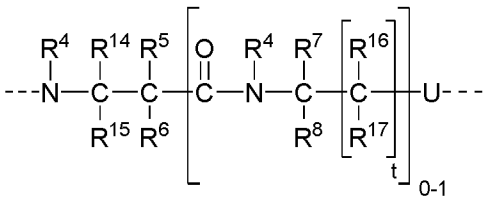
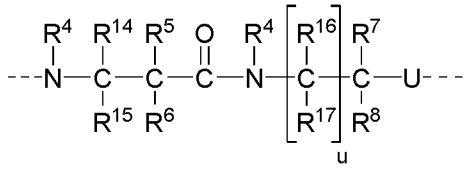
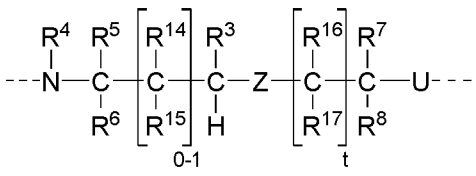
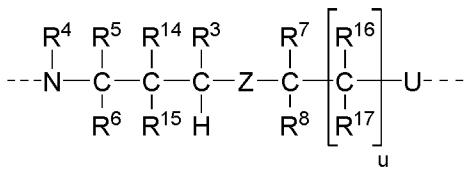
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 **A577** (a20)	 **A578** (a21)	 **A579** (a21)	 **A580** (a21)
 **A581** (a21)	 **A582** (a21)	 **A583** (a21)	 **A584** (a21)
 **A585** (a21)	 **A586** (a21)	 **A587** (a21)	 **A588** (a22)
 **A589** (a22)	 **A590** (a22)	 **A591** (a22)	 **A592** (a22)

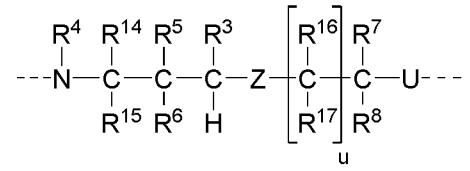
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 **A601** (a22)	 **A602** (a23)	 **A603** (a23)	 **A604** (a23)
 **A605** (a23)	 **A606** (a23)	 **A607** (a23)	 **A608** (a23)
 **A609** (a24)	 **A610** (a24)	 **A611** (a24)	 **A612** (a24)

 **A613** (a24)	 **A614** (a24)	 **A615** (a24)	 **A616** (a24)
 **A617** (a24)	 **A618** (a24)	 **A619** (a25)	 **A620** (a25)
 **A621** (a25)	 **A622** (a25)	 **A623** (a25)	 **A624** (a25)
 **A625** (a25)		 **A626** (a25)	

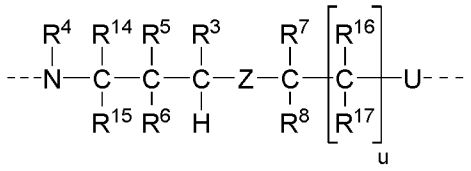
B is selected from the divalent building blocks **B1**-**B21** shown in Table 11, below which are based on optionally substituted cyclic secondary amines carrying a moiety of type $-CHR^3-LG$, wherein LG is a suitable leaving group that can be replaced by the nucleophilic groups of building blocks **A** thus forming an ether (-O-) or a thioether (-S-) linkage between building blocks of type **A** and **B**;

Table 12: Embodiments of Linker **C**

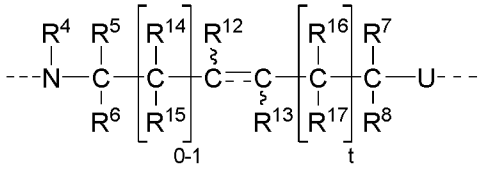
 **C1**	 **C2**
 **C3**	 **C4**
 **C5**	 **C6**
 **C7**	 **C8**
 **C9**	 **C10**
 **C11**	 **C12**



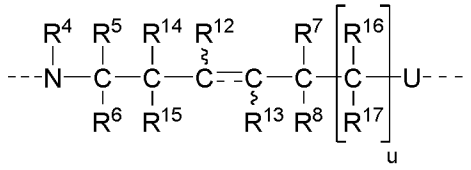
C13



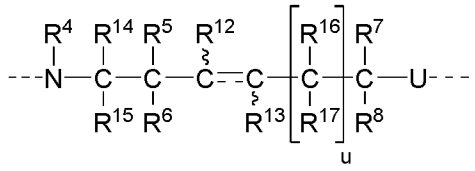
C14



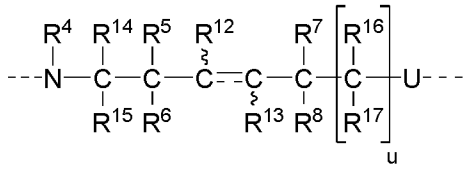
C15



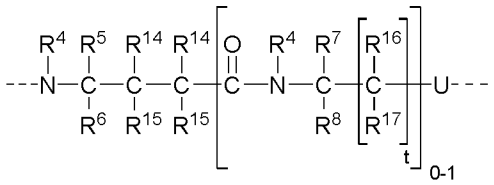
C16



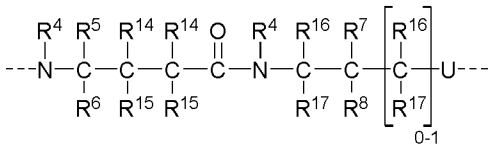
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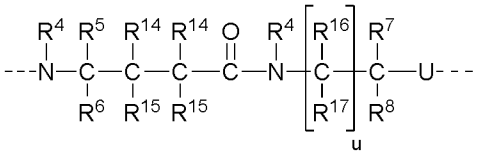
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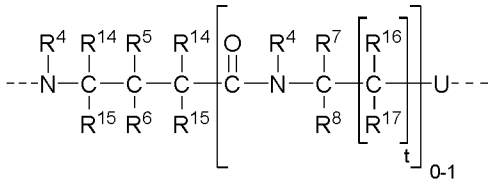
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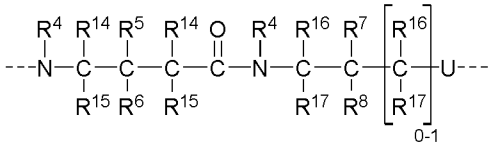
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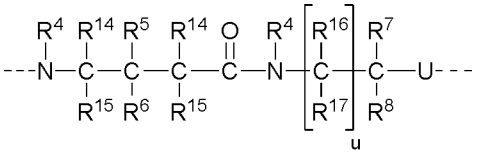
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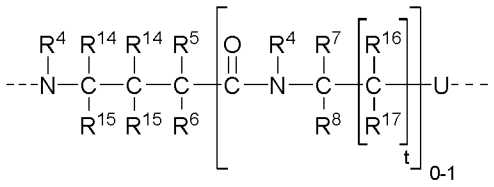
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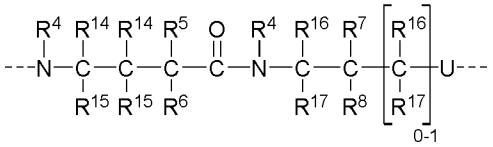
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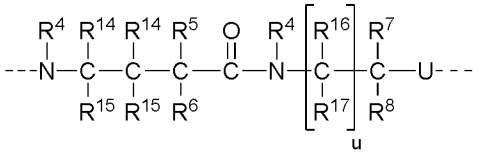
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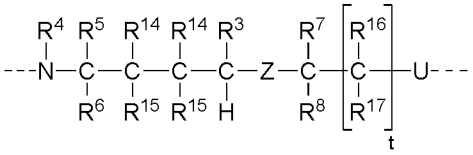
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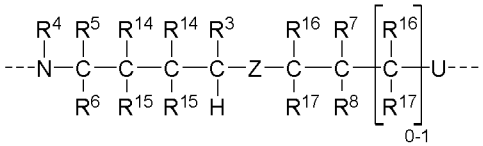
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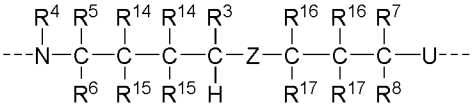
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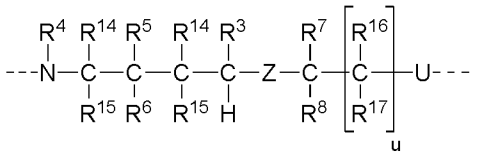
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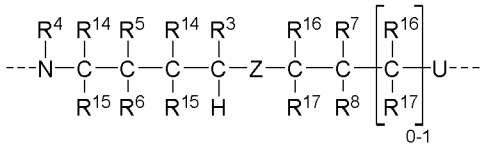
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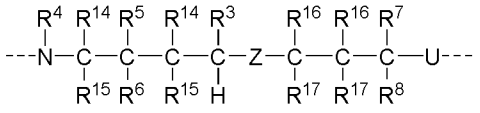
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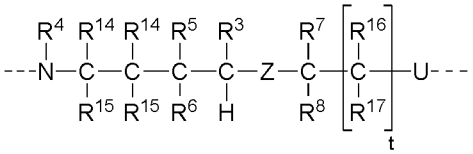
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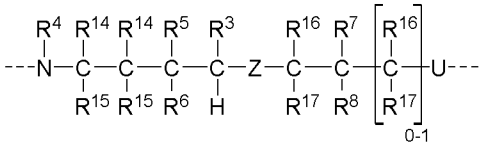
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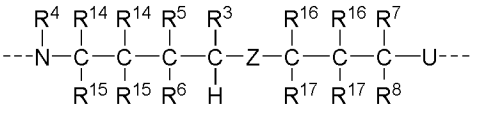
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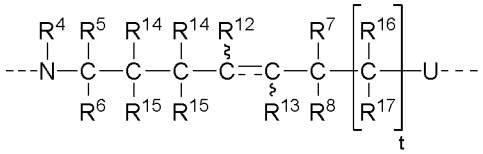
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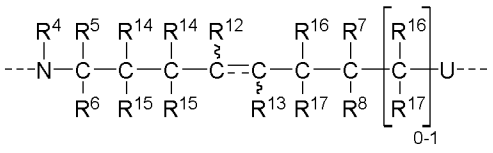


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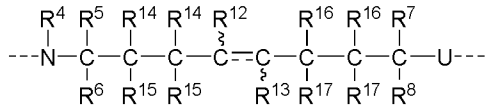


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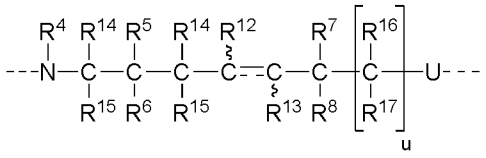




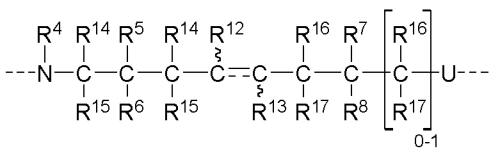
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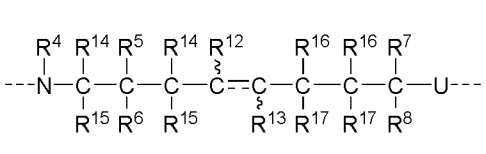
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C39



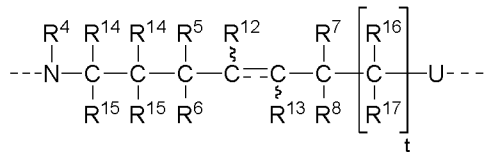
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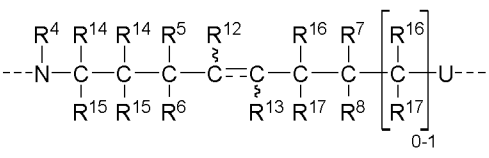
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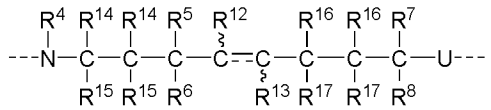
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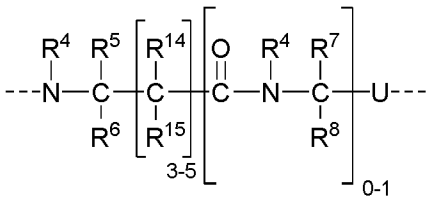
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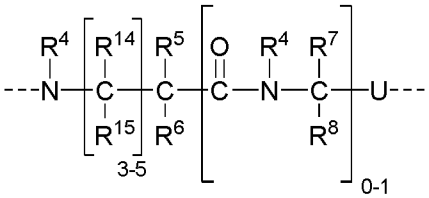
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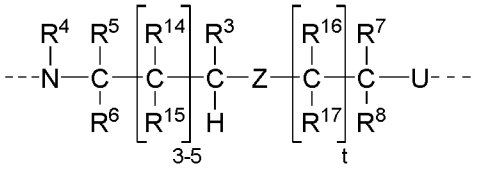
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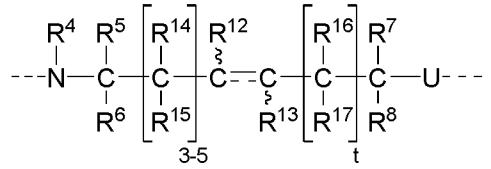
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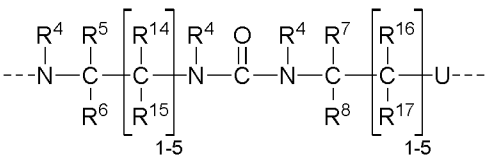
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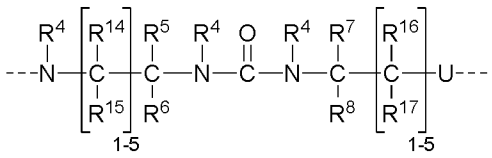


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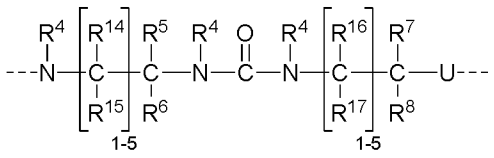


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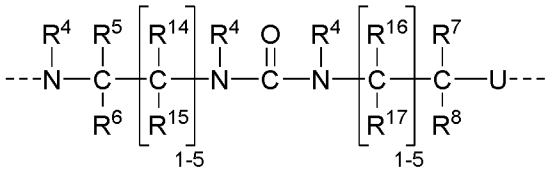




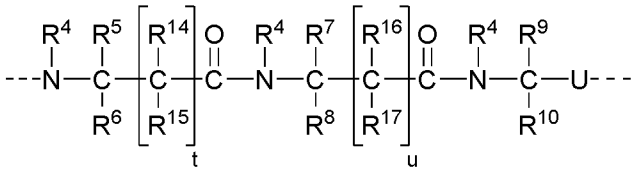
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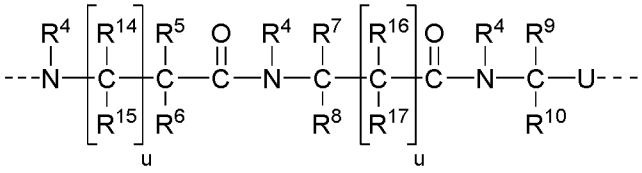
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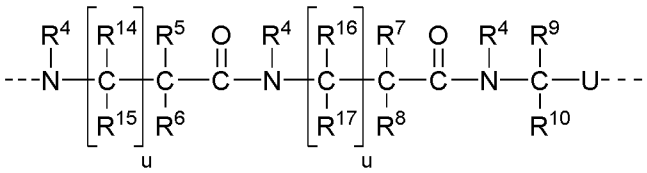
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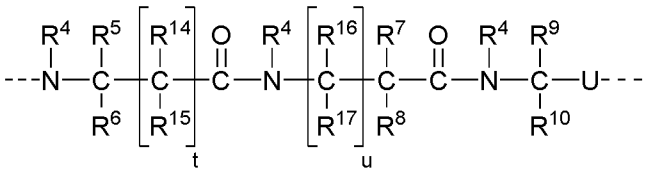
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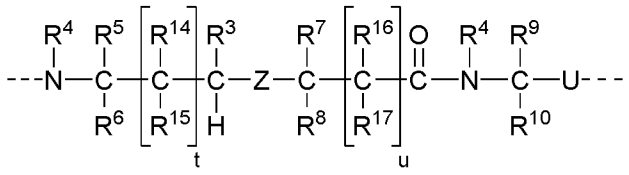
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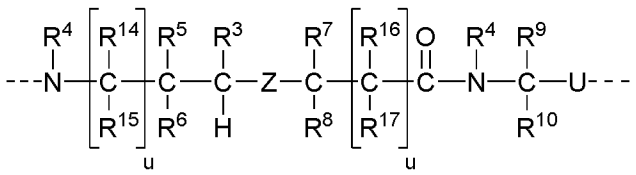
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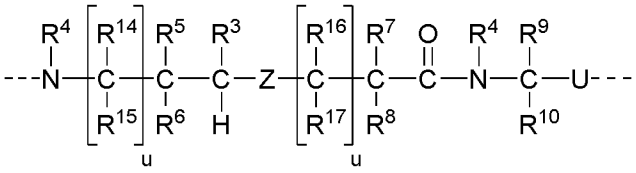
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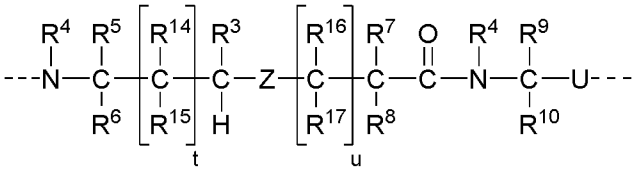
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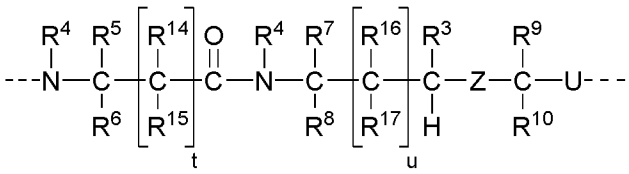
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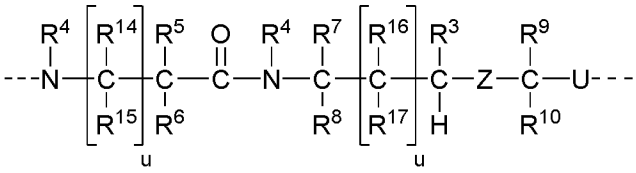
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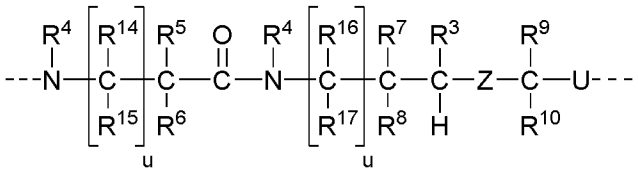
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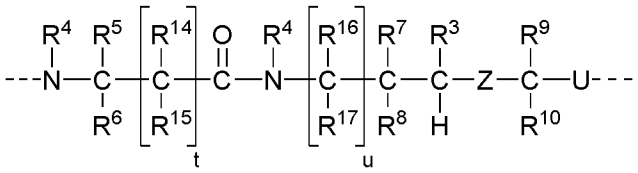
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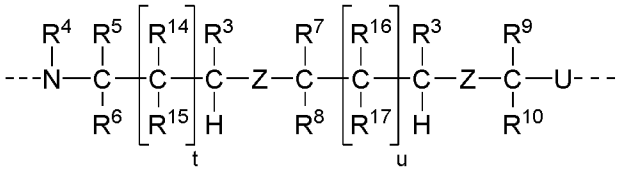
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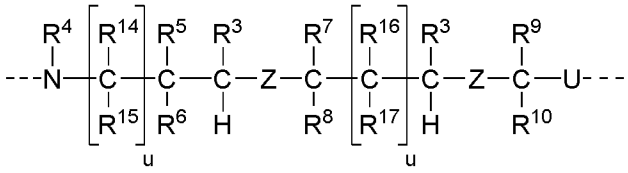
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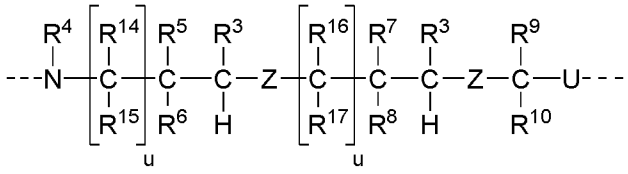
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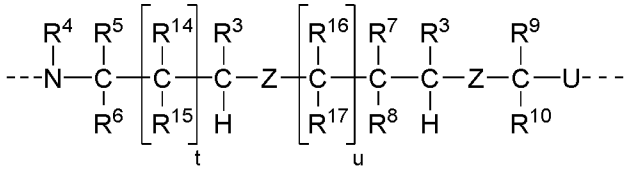
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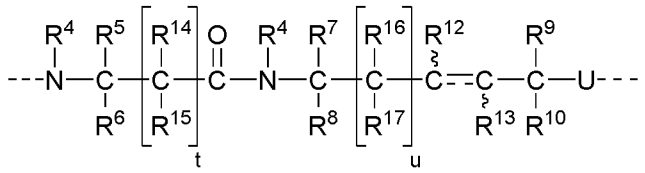
C67



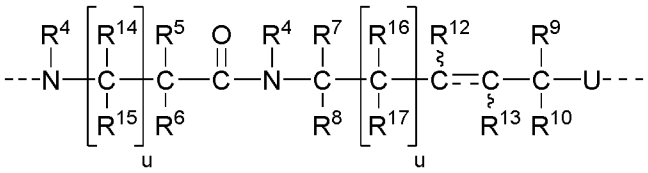
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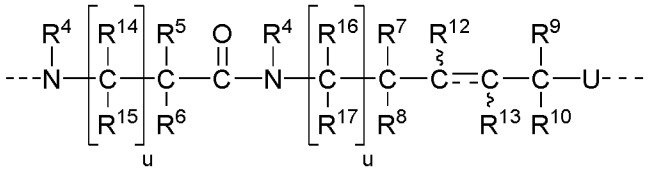
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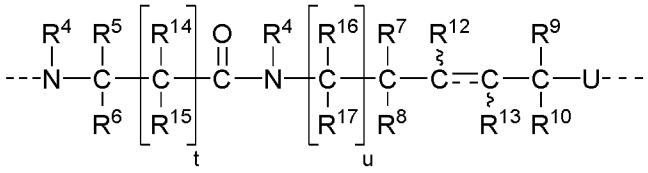
C70



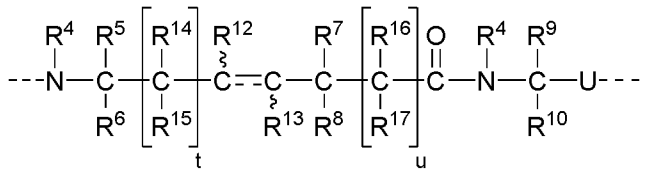
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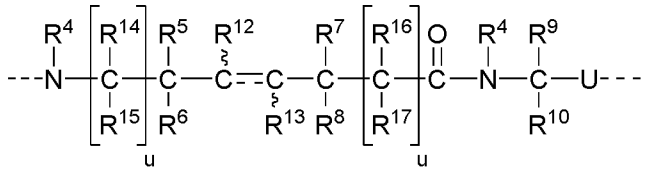
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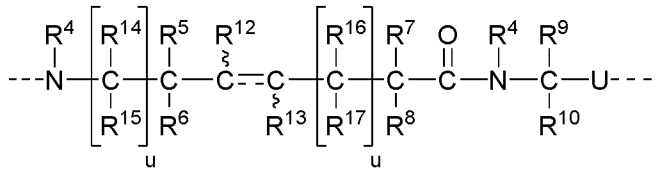
C73



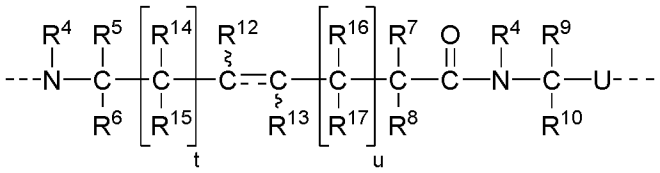
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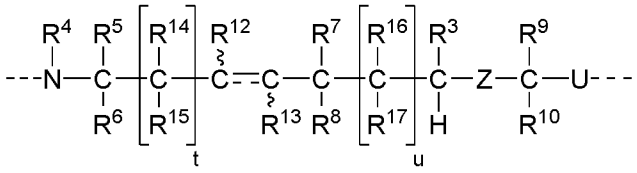
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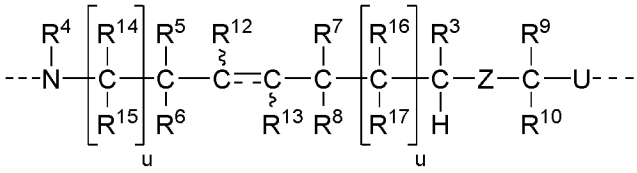
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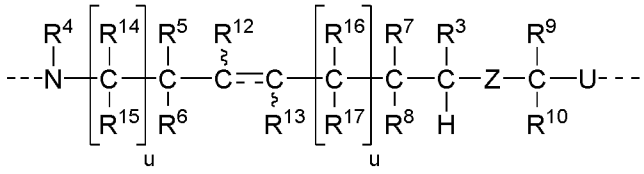
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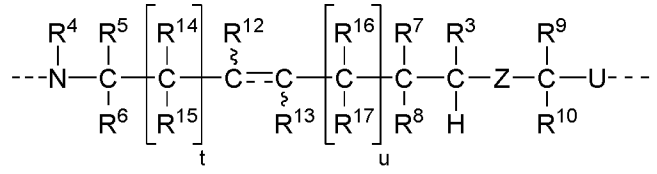
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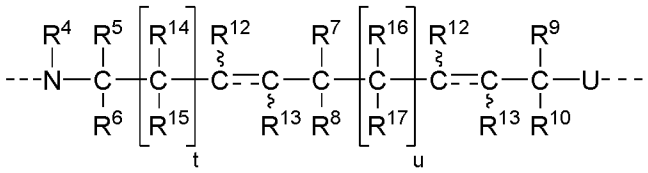
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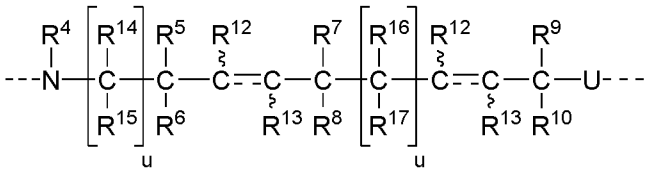
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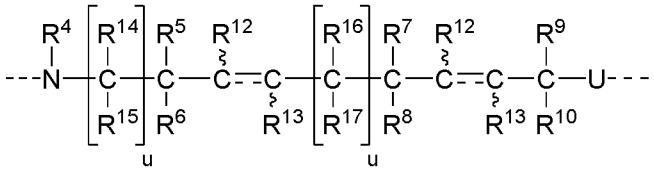
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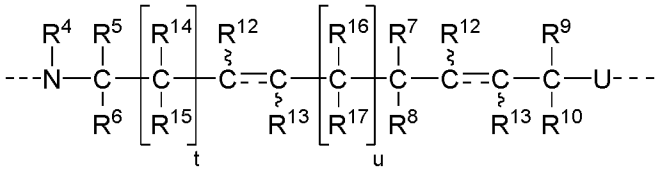
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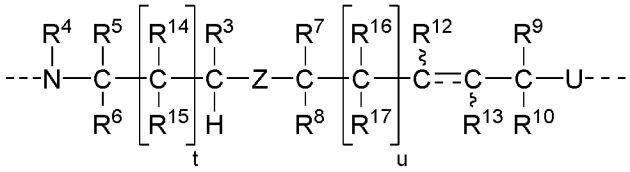
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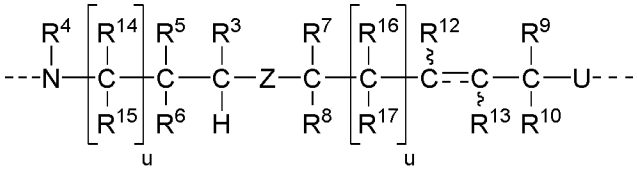
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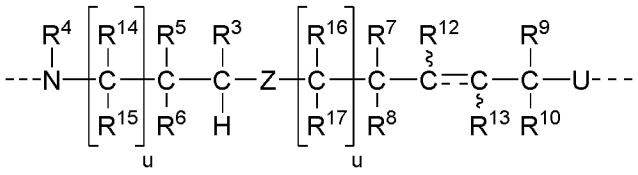
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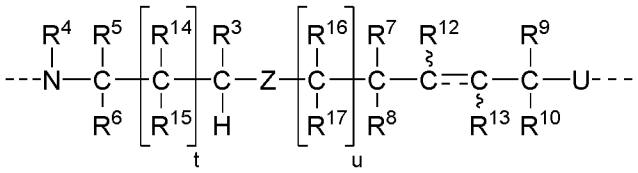
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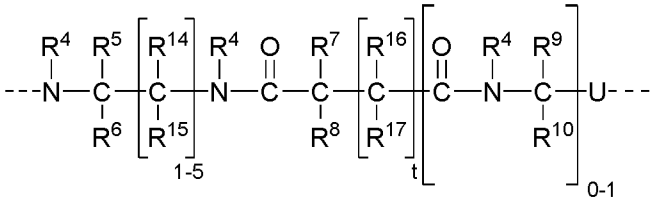
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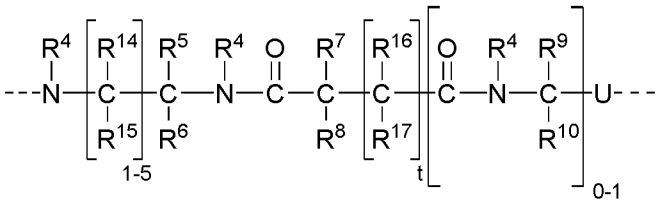
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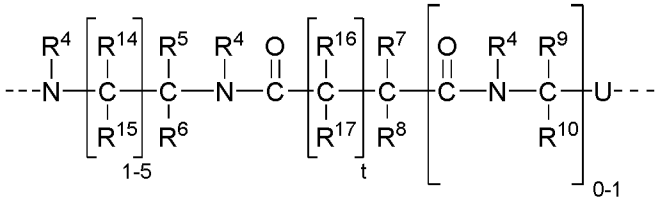
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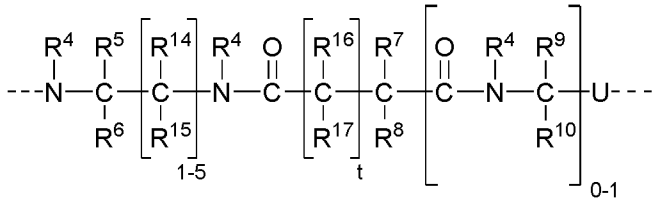
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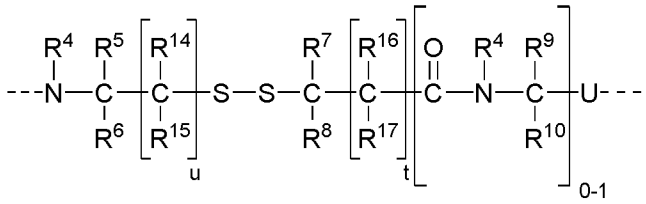
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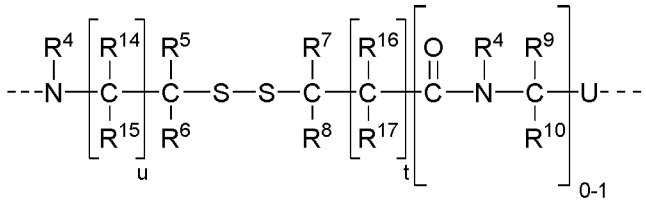
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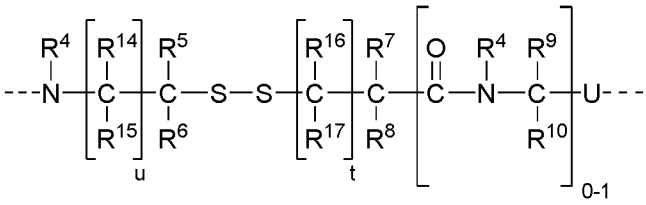
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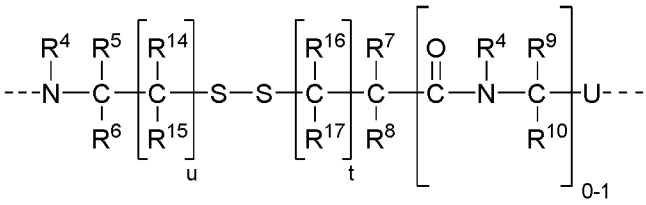
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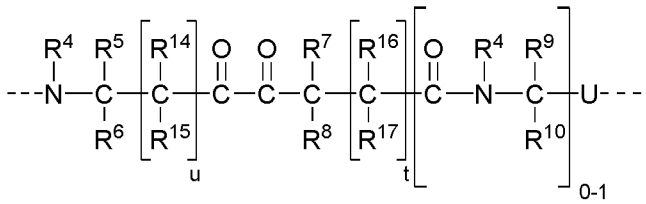
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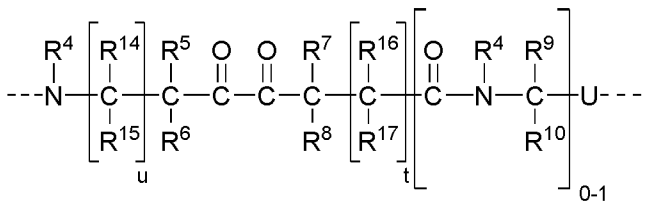
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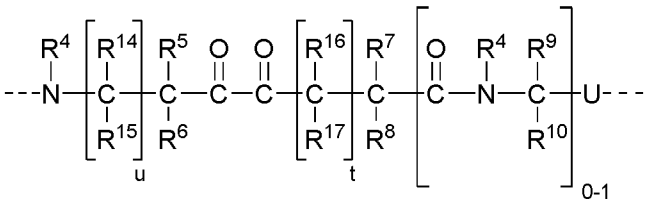
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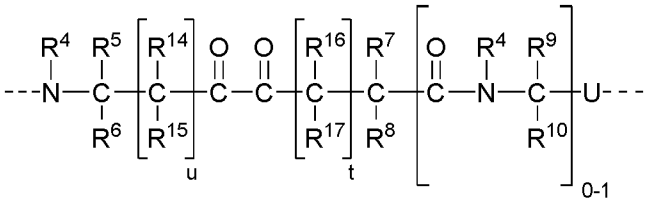
C98



C99



C100



C101

R^1 is H; F; Cl; Br; I; CF_3; OCF_3; $OCHF_2$; NO_2; CN; lower alkyl; lower alkenyl; lower alkynyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{18}R^{19})_qOR^{20}$; $-(CR^{18}R^{19})_qNR^4R^{11}$; $-(CR^{18}R^{19})_qNR^4COOR^{21}$; $-(CR^{18}R^{19})_qNR^4COR^{22}$; $-(CR^{18}R^{19})_qNR^4CONR^4R^{11}$; $-(CR^{18}R^{19})_qNR^4SO_2R^{23}$; $-(CR^{18}R^{19})_qNR^4SO_2NR^4R^{11}$; $-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{11}$; $-(CR^{18}R^{19})_qSO_2NR^4R^{11}$; $-(CR^{18}R^{19})_qPO(OR^{21})_2$; $-(CR^{18}R1^9)_qCOR^{22}$; $-(CR^{18}R^{19})_qSO_2R^{23}$; $-(CR^{18}R^{19})_qOSO_3R^{21}$; $-(CR^{18}R^{19})_qR^{24}$; $-(CR^{18}R^{19})_qR^{25}$; or $-(CR^{18}R^{19})_qR^{26}$;

R^2 is H; CF_3; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{18}R^{19})_qOR^{20}$; $-(CR^{18}R^{19})_qNR^4R^{11}$; $-(CR^{18}R^{19})_qNR^4COOR^{21}$; $-(CR^{18}R^{19})_qNR^4COR^{22}$; $-(CR^{18}R^{19})_qNR^4CONR^4R^{11}$; $-(CR^{18}R^{19})_qNR^4SO_2R^{23}$; $-(CR^{18}R^{19})_qNR^4SO_2NR^4R^{11}$; $-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{11}$; $-(CR^{18}R^{19})_qSO_2NR^4R^{11}$; $-(CR^{18}R^{19})_qPO(OR^{21})_2$; $-(CR^{18}R^{19})_qCOR^{22}$; $-(CR^{18}R^{19})_qSO_2R^{23}$; $-(CR^{18}R^{19})_qR^{24}$; $-(CR^{18}R^{19})_qR^{25}$; or $-(CR^{18}R^{19})_qR^{26}$;

R^3 is defined as in claim 1;

$R^4$is H; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; or a suitable N-protecting group;

R^5, R^7 and R^9 are independently defined as: H; F; CF_3; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl;
$-(CR^{18}R^{19})_sOR^{20}$; $-(CR^{18}R^{19})_sNR^4R^{11}$; $-(CR^{18}R^{19})_sNR^4COOR^{21}$;
$-(CR^{18}R^{19})_sNR^4COR^{22}$; $-(CR^{18}R^{19})_sNR^4CONR^4R^{11}$; $-(CR^{18}R^{19})_sNR^4SO_2R^{23}$;
$-(CR^{18}R^{19})_sNR^4SO_2NR^4R^{11}$; $-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{11}$;
$-(CR^{18}R^{19})_qSO_2NR^4R^{11}$; $-(CR^{18}R^{19})_qPO(OR^{21})_2$; $-(CR^{18}R^{19})_qCOR^{22}$;
$-(CR^{18}R^{19})_qSO_2R^{23}$; $-(CR^{18}R^{19})_qR^{24}$; $-(CR^{18}R^{19})_qR^{25}$; or $-(CR^{18}R^{19})_qR^{26}$;

R^6, R^8 and R^{10} are independently defined as: H; CF_3; or lower alkyl;

R^{11} is H; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; a suitable protecting group; $-(CR^{18}R^{19})_rOR^{20}$; $-(CR^{18}R^{19})_rNR^4R^{27}$; $-(CR^{18}R^{19})_rNR^4COOR^{21}$;
$-(CR^{18}R^{19})_rNR^4CONR^4R^{27}$; $-(CR^{18}R^{19})_rNR^4SO_2R^{23}$; $-(CR^{18}R^{19})_rNR^4SO_2NR^4R^{27}$;
$-(CR^{18}R^{19})_qCOOR^{21}$;
$-(CR^{18}R^{19})_qCONR^4R^{27}$; $-(CR^{18}R^{19})_qCOR^{22}$; $-(CR^{18}R^{19})_qSO_2R^{23}$;
$-(CR^{18}R^{19})_qSO_2NR^4R^{27}$; $-(CR^{18}R^{19})_qR^{24}$; $-(CR^{18}R^{19})_sR^{25}$;
or $-(CR^{18}R^{19})_qR^{26}$;

R^{12} and R^{13} are independently defined as H; or lower alkyl;

R^{14} and R^{16} are independently defined as: H; F; CF_3; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl;
$-(CR^{18}R^{19})_sOR^{20}$; $-(CR^{18}R^{19})_sNR^4R^{11}$; $-(CR^{18}R^{19})_sNR^4COOR^{21}$;
$-(CR^{18}R^{19})_sNR^4COR^{22}$; $-(CR^{18}R^{19})_sNR^4CONR^4R^{11}$; $-(CR^{18}R^{19})_sNR^4SO_2R^{23}$;
$-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{11}$; or $-(CR^{18}R^{19})_qCOR^{22}$;

R^{15} and R^{17} are independently defined as: H; CF_3; lower alkyl;

R^{18} is H; F; CF_3; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{29}R^{30})_sOR^{31}$; $-(CR^{29}R^{30})_sNR^{28}R^{31}$; $-(CR^{29}R^{30})_sNR^{28}COOR^{21}$; $-(CR^{29}R3^0)_sNR^{28}COR^{31}$; $-(CR^{29}R^{30})_sNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_sNR^{28}SO_2R^{23}$; $-(CR^{29}R^{30})_sNR^{28}SO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_qSO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qPO(OR^{21})_2$; $-(CR^{29}R^{30})_qCOR^{31}$; $-(CR^{29}R^{30})_qSO_2R^{23}$; $-(CR^{29}R^{30})_qR^{24}$; $-(CR^{29}R^{30})_qR^{25}$; or $-(CR^{29}R^{30})_qR^{26}$;

R^{19} is H; CF_3; or lower alkyl;

R^{20} is H; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{29}R^{30})_rOR^{31}$; $-(CR^{29}R^{30})_rNR^{28}R^{31}$; $-(CR^{29}R^{30})_rNR^{28}COOR^{21}$; $-(CR^{29}R^{30})_rNR^{28}COR^{31}$; $-(CR^{29}R^{30})_rNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_rNR^{28}SO_2R^{23}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_qSO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOR^{31}$; $-(CR^{29}R^{30})_qSO_2R^{23}$; $-(CR^{29}R^{30})_qR^{24}$; $-(CR^{29}R^{30})_qR^{25}$; or $-(CR^{29}R^{30})_qR^{26}$;

R^{21} and R^{23} are as defined in claim 1;

R^{22} is lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{29}R^{30})_sOR^{31}$; $-(CR^{29}R^{30})_sNR^{28}R^{31}$; $-(CR^{29}R^{30})_sNR^{28}COOR^{21}$; $-(CR^{29}R^{30})_sNR^{28}COR^{31}$; $-(CR^{29}R^{30})_sNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_sNR^{28}SO_2R^{23}$; $-(CR^{29}R^{30})_sCOOR^{21}$; $-(CR^{29}R^{30})_sCONR^{28}R^{31}$; $-(CR^{29}R^{30})_sSO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_tCOR^{31}$; $-(CR^{29}R^{30})_sSO_2R^{23}$; $-(CR^{29}R^{30})_tR^{24}$; $-(CR^{29}R^{30})_tR^{25}$; or $-(CR^{29}R^{30})_tR^{26}$;

R^{24}, R^{25}, R^{26}, R^{27} and R^{28} are as defined in claim 1;

R^{29} is H; F; CF_3; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{32}R^{33})_sOR^{31}$; $-(CR^{32}R^{33})_sNR^{28}R^{31}$; $-(CR^{32}R^{33})_sNR^{28}COOR^{21}$; $-(CR^{32}R^{33})_sNR^{28}COR^{31}$; $-(CR^{32}R^{33})_sNR^{28}CONR^{28}R^{31}$; $-(CR^{32}R^{33})_sNR^{28}SO_2R^{23}$; $-(CR^{32}R^{33})_qCOOR^{21}$; $-(CR^{32}R^{33})_qCONR^{28}R^{31}$; $-(CR^{32}R^{33})_qSO_2NR^{28}R^{31}$; $-(CR^{32}R^{33})_qPO(OR^{21})_2$; $-(CR^{32}R^{33})_qCOR^{31}$; $-(CR^{32}R^{33})_qSO_2R^{23}$; $-(CR^{32}R^{33})_qR^{31}$;

R^{30} and R^{33} are H; CF_3; or lower alkyl;

R^{31} and R^{32} are as defined in claim 1;

R^{34} and R^{35} are independently defined as H; F; Cl; CF_3; OCF_3; $OCHF_2$; NO_2; CN; lower alkyl; lower alkenyl; lower alkynyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{29}R^{30})_qOR^{31}$; $-(CR^{29}R^{30})_qNR^{28}R^{31}$; $-(CR^{29}R^{30})_qNR^{28}COOR^{21}$; $-(CR^{29}R^{30})_qNR^{28}COR^{31}$; $-(CR^{29}R^{30})_qNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_qNR^{28}SO_2R^{23}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_qSO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOR^{31}$; $-(CR^{29}R^{30})_qSO_2R^{23}$; or $-(CR^{29}R^{30})_qR^{31}$;

R^{36} is as defined in claim 1;

R^{37} is H; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; a suitable N-protecting group; $-(CR^{29}R^{30})_rOR^{31}$; $-(CR^{29}R^{30})_rNR^{28}R^{31}$; $-(CR^{29}R^{30})_rNR^{28}COOR^{21}$; $-(CR^{29}R^{30})_rNR^{28}COR^{31}$; $-(CR^{29}R^{30})_rNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_rNR^{28}SO_2R^{23}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_rSO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOR^{31}$; $-(CR^{29}R^{30})_qSO_2R^{23}$; or $-(CR^{29}R^{30})_qR^{31}$;

R^{38} is H; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{29}R^{30})_qOR^{31}$; $-(CR^{29}R^{30})_qNR^{28}R^{31}$; $-(CR^{29}R^{30})_qNR^{28}COOR^{21}$; $-(CR^{29}R^{30})_qNR^{28}COR^{31}$; $-(CR^{29}R^{30})_qNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOR^{31}$; or $-(CR^{29}R^{30})_qR^{31}$;

R^{39}; R^{40}; R^{41}; R^{42}; R^{43}; R^{44}; R^{45}; R^{46}; R^{47}; R^{48}; R^{49} and R^{50} are as defined in claim 1;

the variable heteroatom Z and the connector U are defined as

Z being O; S(=O); or $S(=O)_2$; and

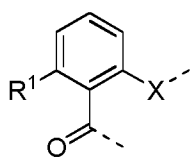
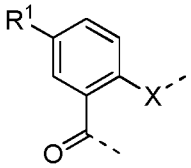
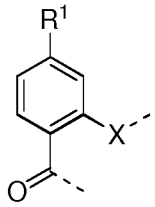
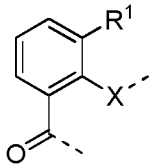
U being $-C(=O)-$; $-NR^4-C(=O)-$; $-C(=O)-C(=O)-$; or $-C(-OR^{20})_2-C(=O)-$; and

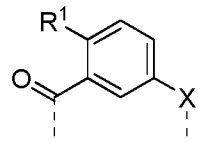
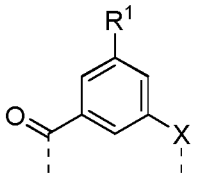
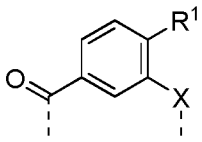
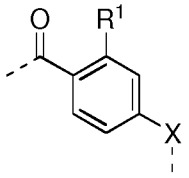
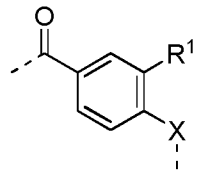
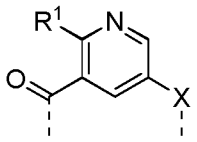
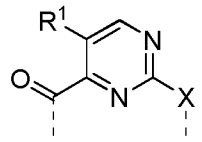
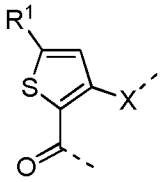
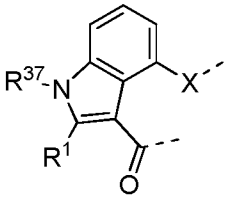
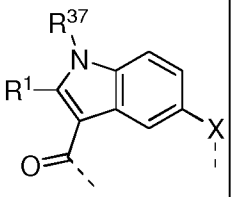
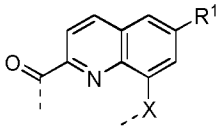
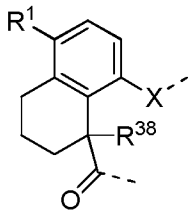
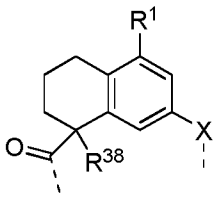
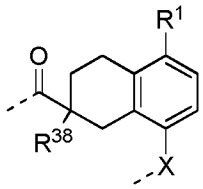
- substituents that can be pairwise taken together and form optionally substituted cycloalkyl or heterocycloalkyl moieties;
- structural elements that can form one of the groups of formulae **H111-H118** (Table 9);
- variable heteroatoms Q, T, X and Y; and
- indices q-u

being defined as in claim 1.

3. Compounds according to claim 2 wherein **A** is **A1**(a1); **A2**(a1); **A3**(a1); **A4**(a1); **A5**(a1); **A6**(a1); **A7**(a1); **A9**(a1); **A10**(a1); **A73**(a2); **A170**(a4); **A209**(a7); **A240**(a10); **A272**(a10); **A532**(a18); **A609**(a24); **A612**(a24) and **A614**(a24) as shown in Table 13, below;

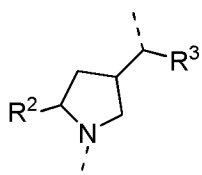
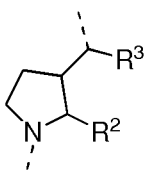
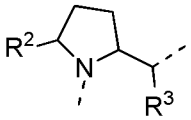
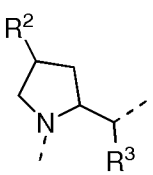
Table 13: Building Blocks of Type **A**

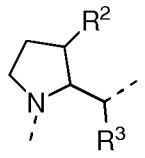
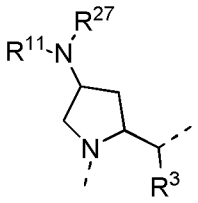
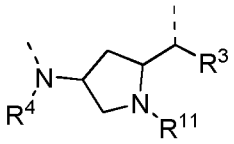
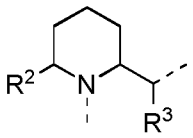
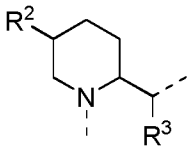
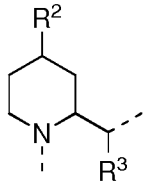
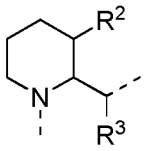
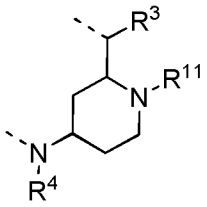
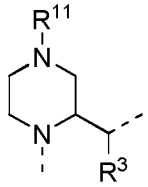
			
A1(a1)	**A2**(a1)	**A3**(a1)	**A4**(a1)

 **A5** (a1)	 **A6** (a1)	 **A7** (a1)	 **A9** (a1)
 **A10** (a1)	 **A73** (a2)	 **A170** (a4)	 **A209** (a7)
 **A240** (a10)	 **A272** (a10)	 **A532** (a18)	 **A609** (a24)
 **A612** (a24)		 **A614** (a24)	

B is **B4**(b3); **B5**(b3); **B6**(b3); **B7**(b3); **B8**(b3); **B9**(b3); **B10**(b3); **B12**(b4); **B13**(b4); **B14**(b4); **B15**(b4); **B16**(b4) or **B17**(b5) **as shown in** Table 14, below;

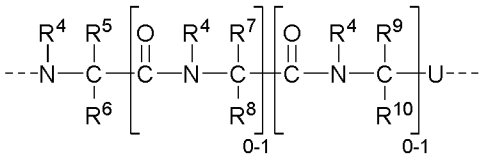
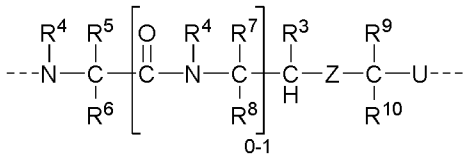
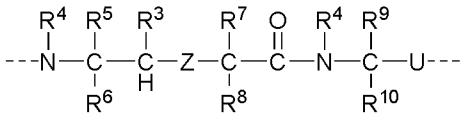
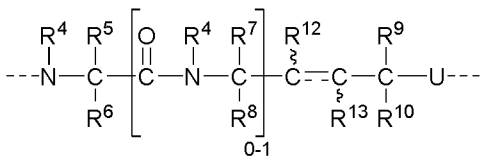
Table 14: Building Blocks of Type **B**

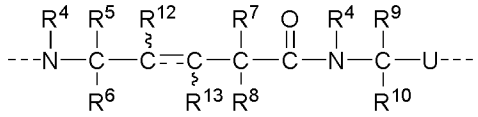
 **B4** (b3)	 **B5** (b3)	 **B6** (b3)	 **B7** (b3)

 **B8** (b3)	 **B9** (b3)	 **B10** (b3)	 **B12** (b4)
 **B13** (b4)	 **B14** (b4)	 **B15** (b4)	 **B16** (b4)
 **B17** (b5)			

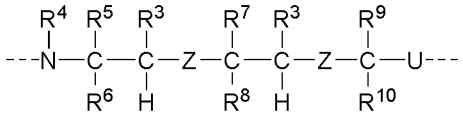
linker **C** is one of the groups shown in Table 15, below;

Table 15: Linkers of type **C**

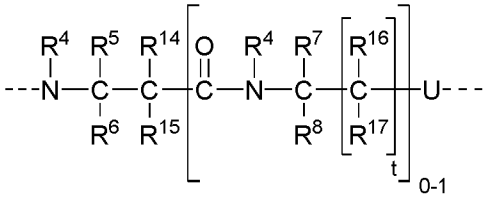
 **C1**	 **C2**
 **C3**	 **C4**



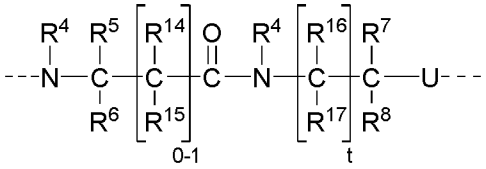
C5



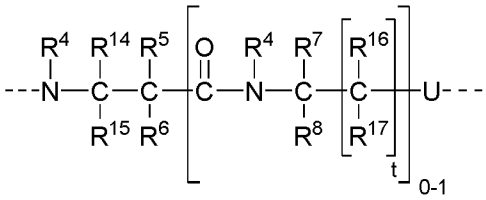
C6



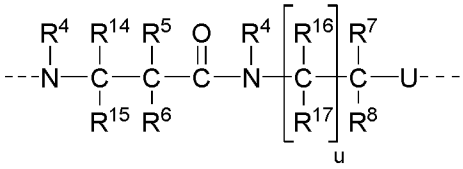
C7



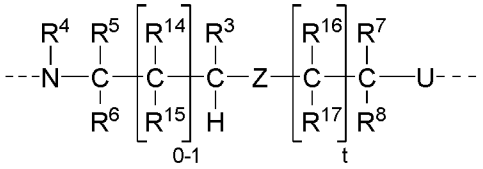
C8



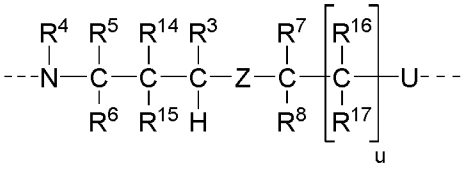
C9



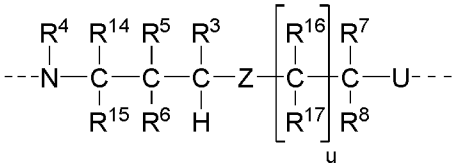
C10



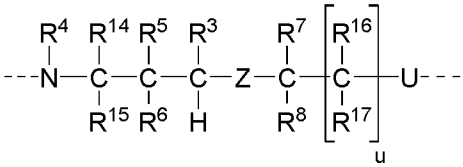
C11



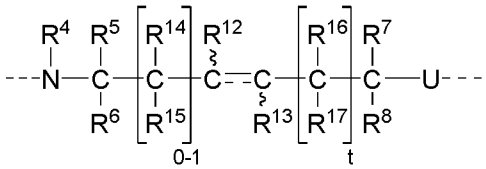
C12



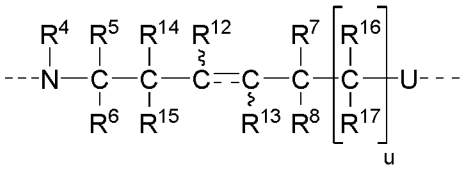
C13



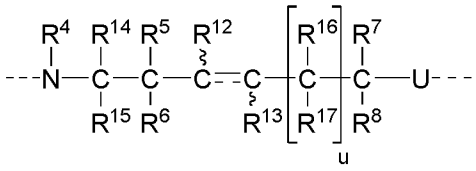
C14



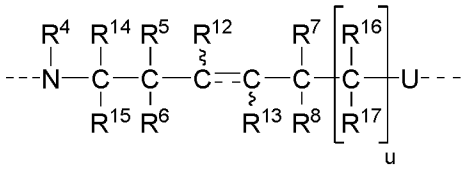
C15



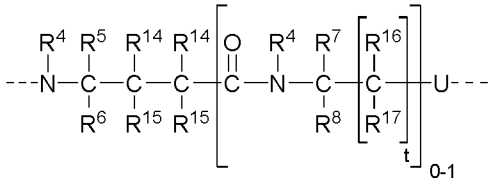
C16



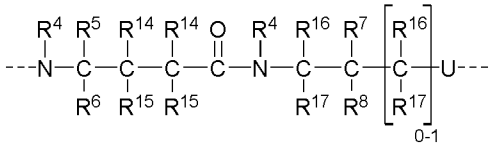
C17



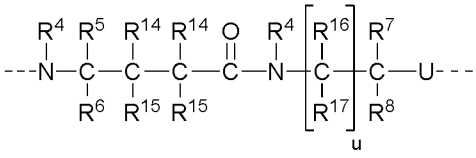
C18



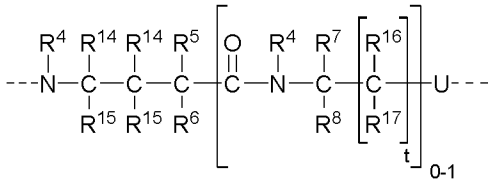
C19



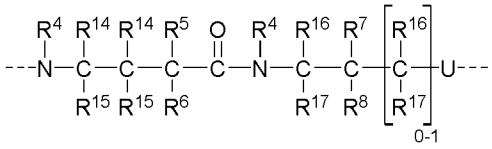
C20



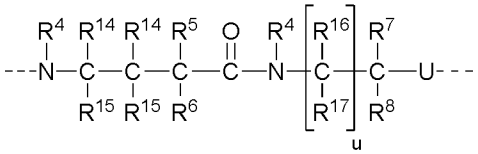
C21



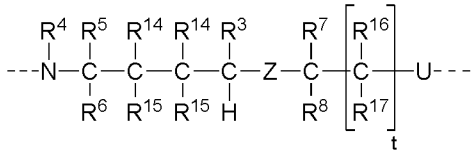
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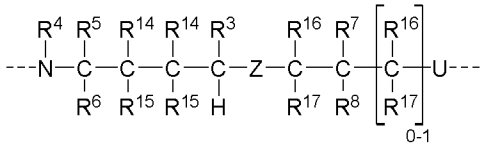
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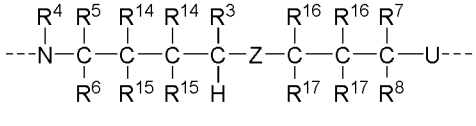
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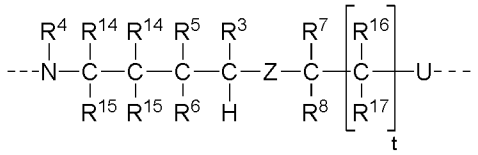
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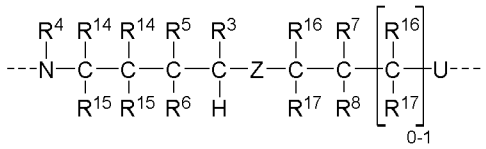
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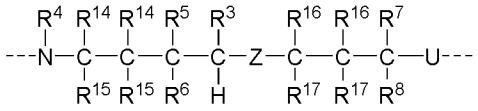
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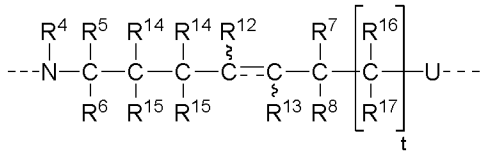
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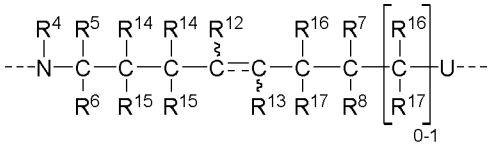
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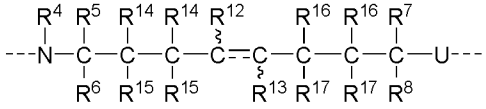
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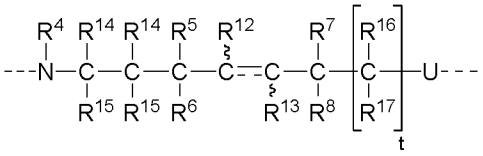
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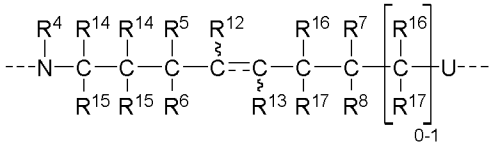
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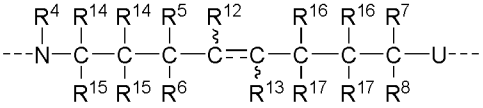
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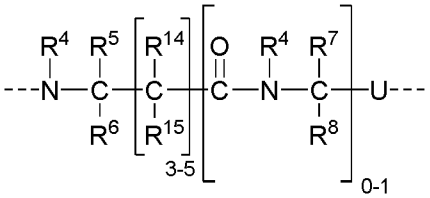
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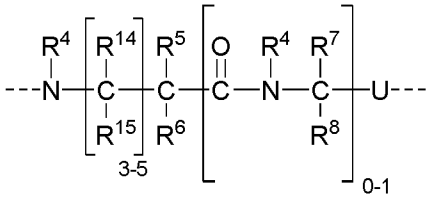
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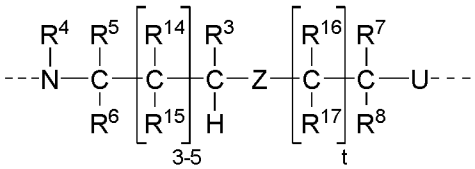
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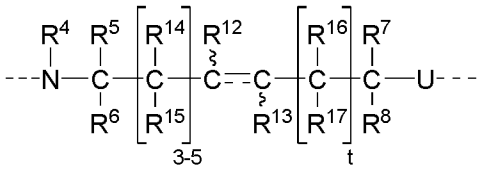
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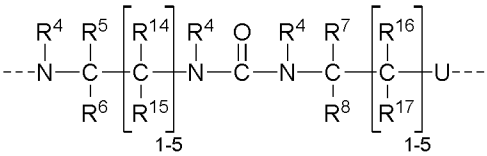
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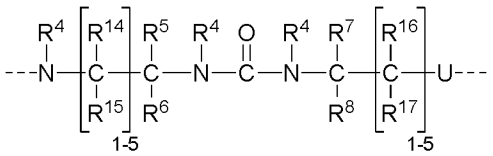


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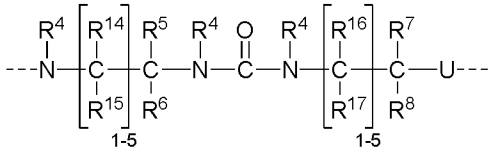


C49

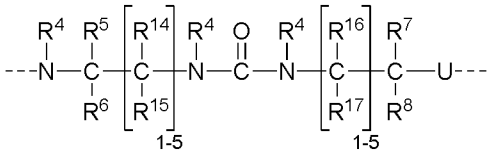




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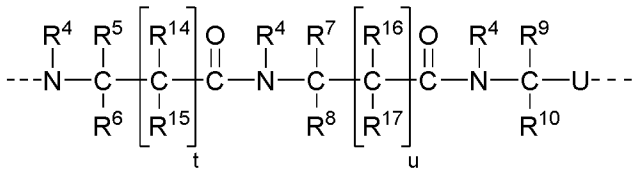


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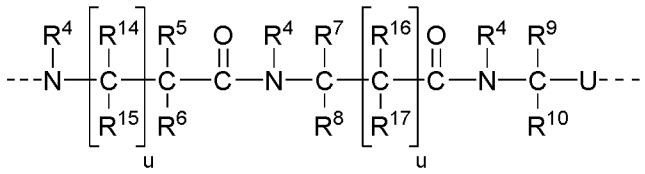


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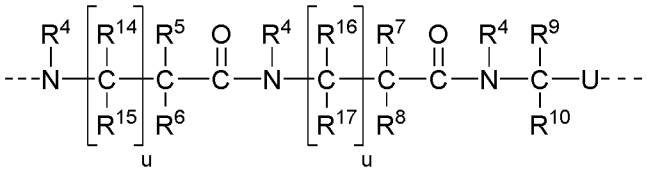
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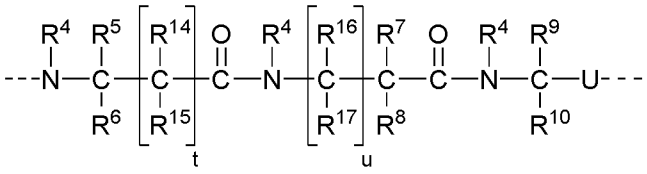
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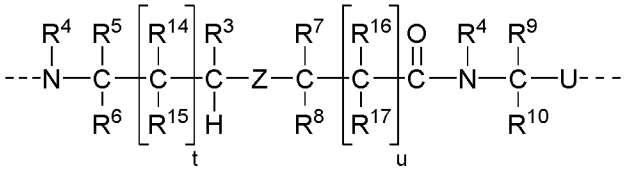
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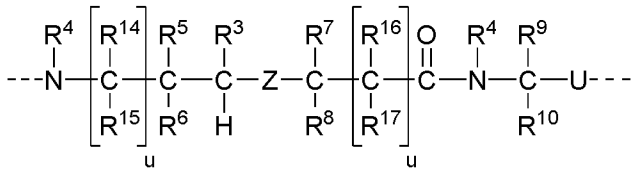
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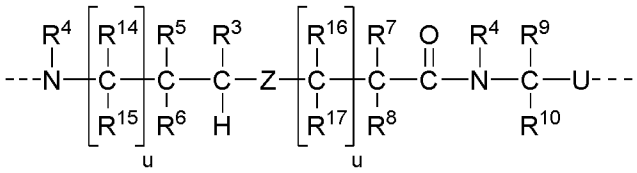
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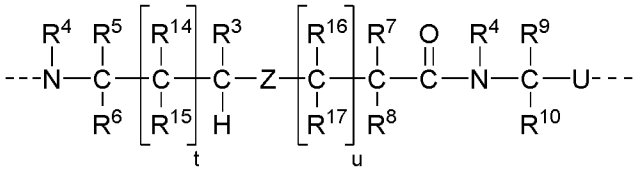
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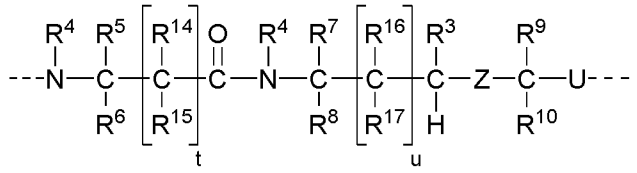
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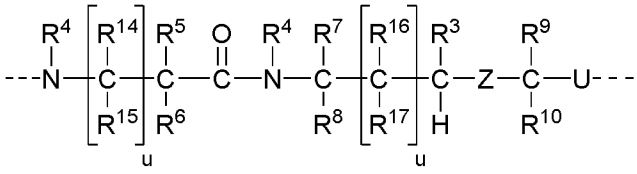
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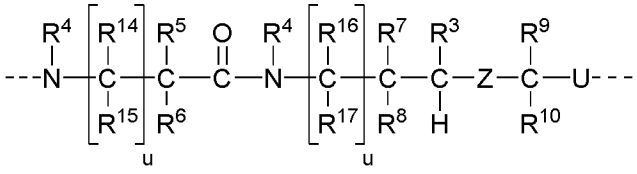
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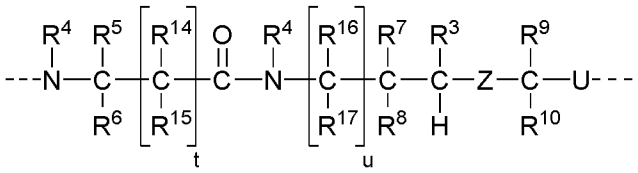
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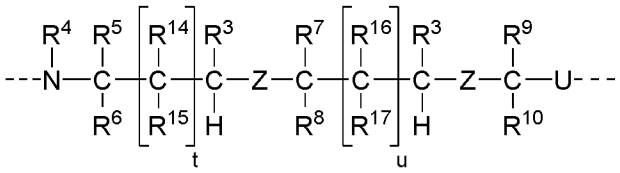
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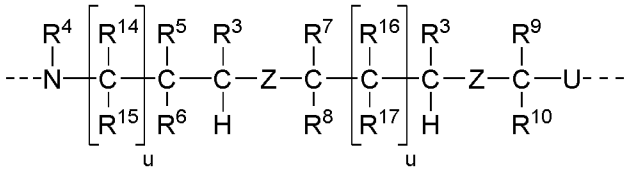
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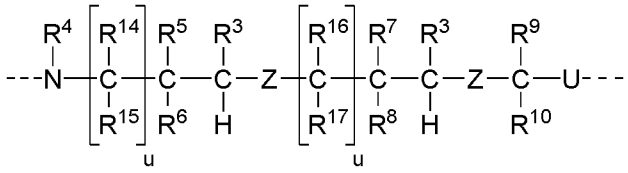
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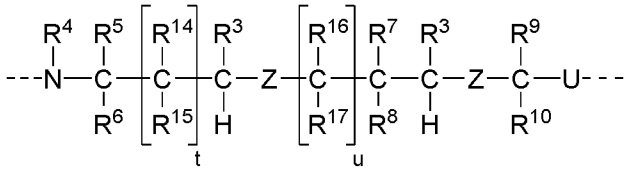
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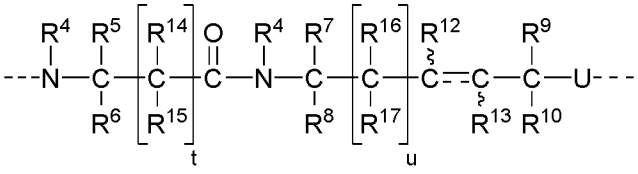
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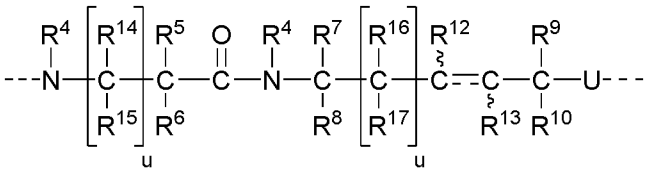
C68



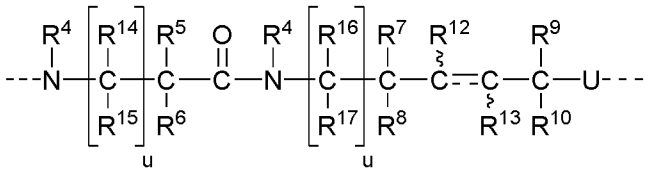
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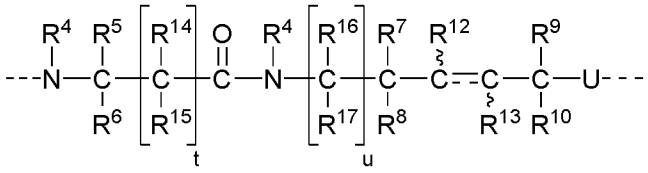
C70



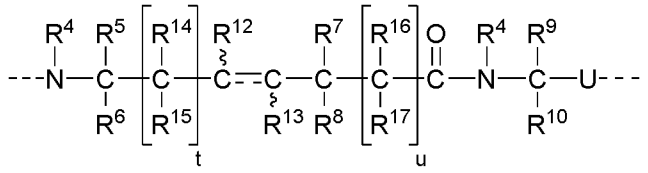
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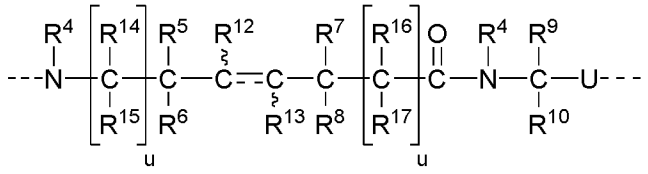
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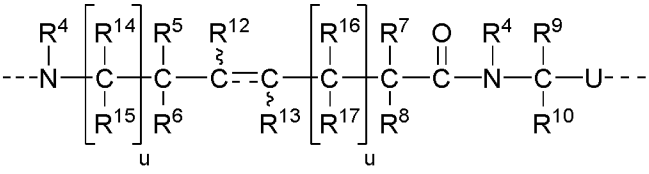
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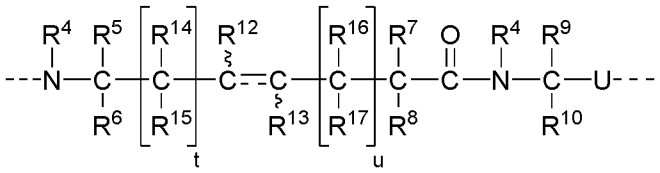
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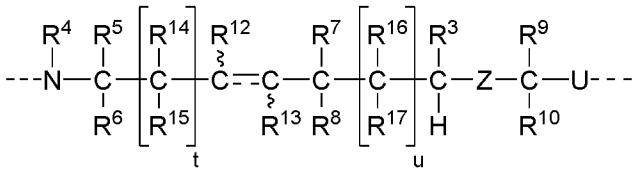
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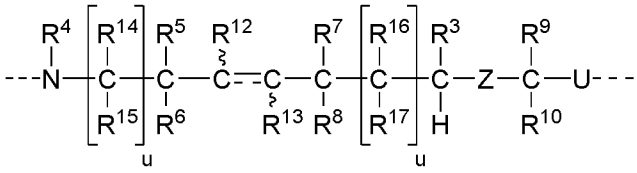
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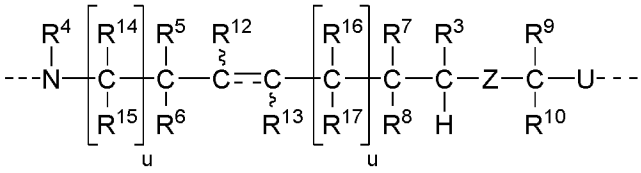
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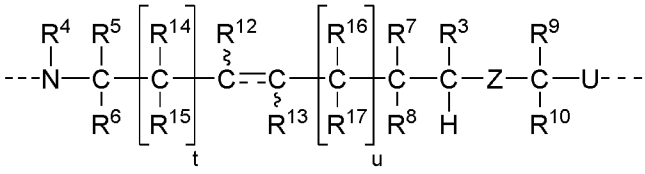
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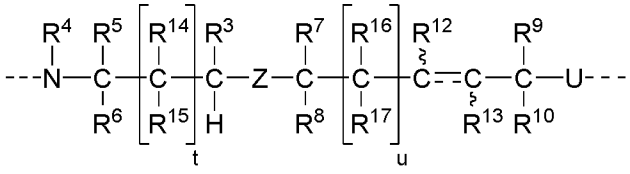
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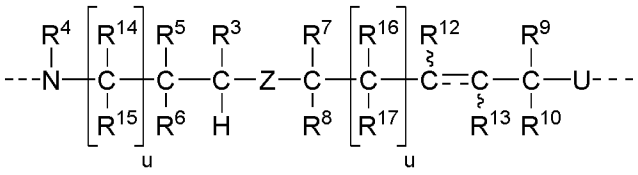
C80



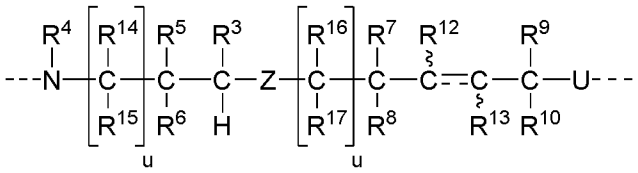
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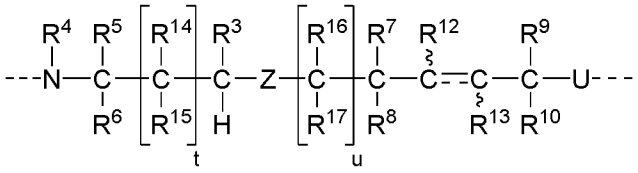
C86



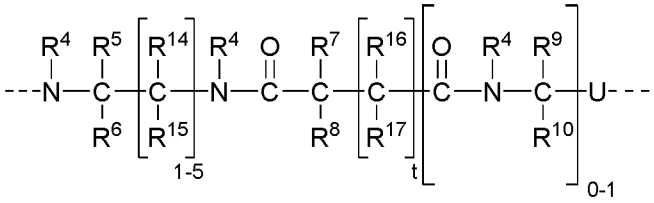
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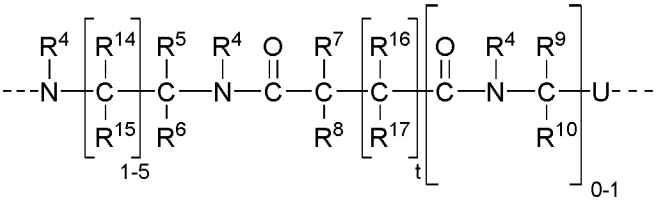
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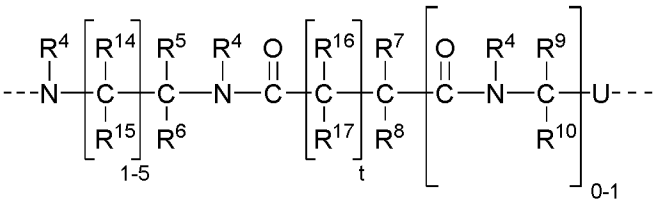
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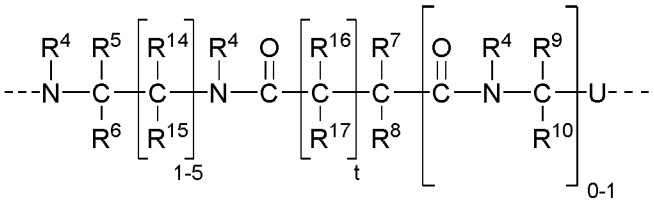
C90



C91



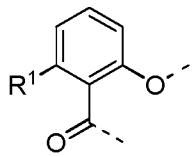
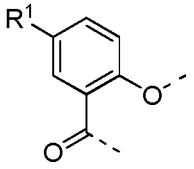
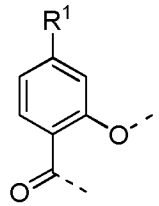
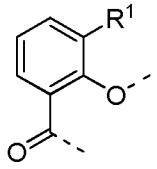
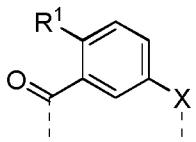
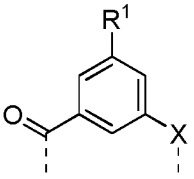
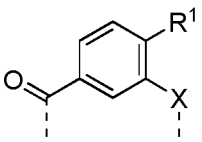
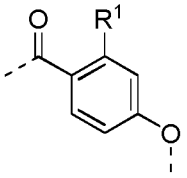
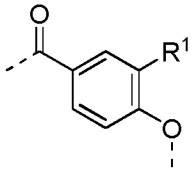
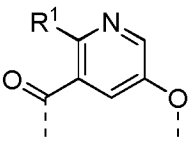
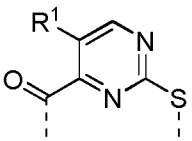
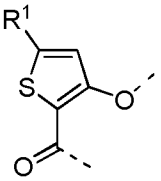
C92

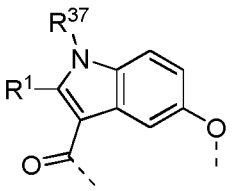
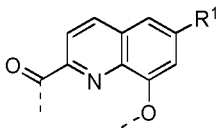
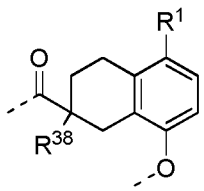


C93

4. Compounds according to claim 3 wherein the building blocks of type **A** are **A1**(a1); **A2**(a1); **A3**(a1); **A4**(a1); **A5**(a1); **A6**(a1); **A7**(a1); **A9**(a1); **A10**(a1); **A73**(a2); **A170**(a4); **A209**(a7); **A240**(a10); **A272**(a10); **A532**(a18); **A614**(a24) as shown in Table 16, below;

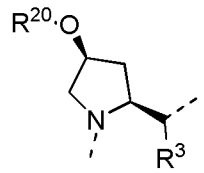
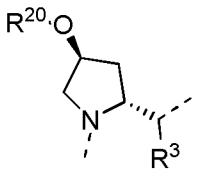
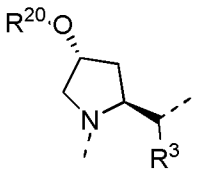
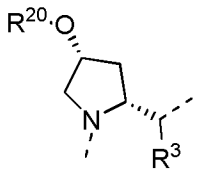
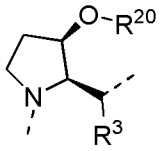
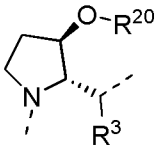
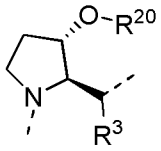
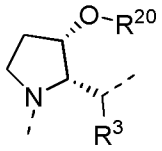
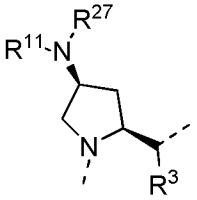
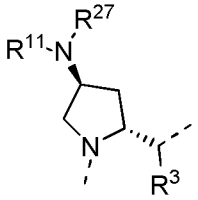
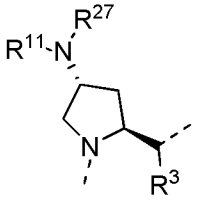
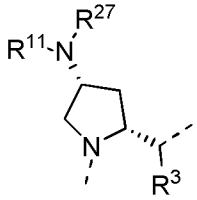
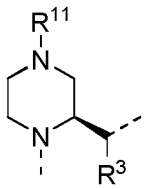
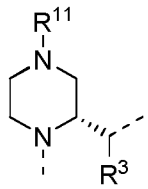
Table 16: Building Blocks of Type **A**

 **A1**(a1)	 **A2**(a1)	 **A3**(a1)	 **A4**(a1)
 **A5**(a1)	 **A6**(a1)	 **A7**(a1)	 **A9**(a1)
 **A10**(a1)	 **A73**(a2)	 **A170**(a4)	 **A209**(a7)

 **A272** (a10)	 **A532** (a18)	 **A614** (a24)

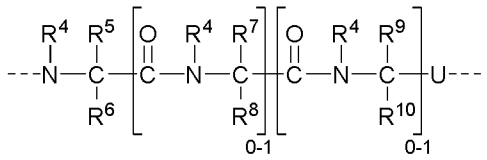
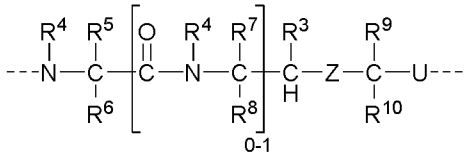
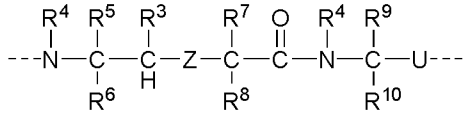
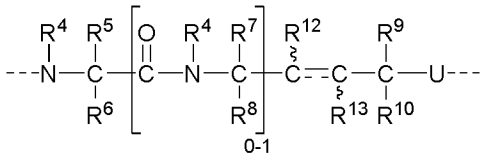
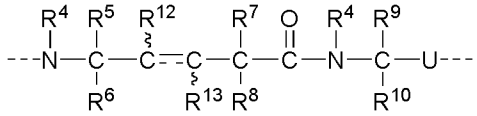
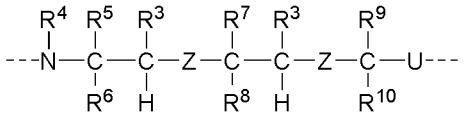
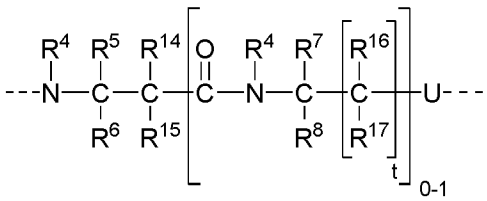
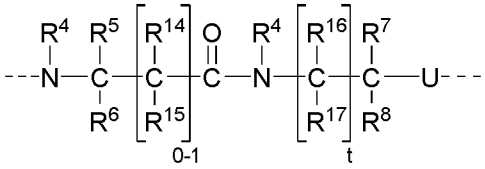
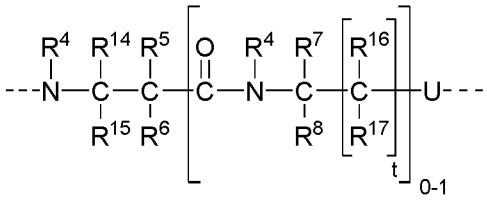
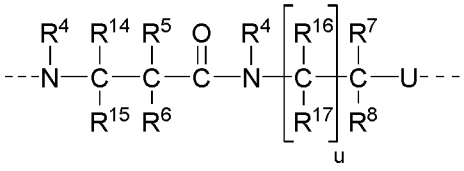
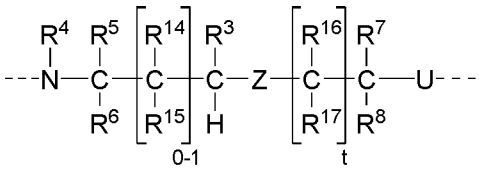
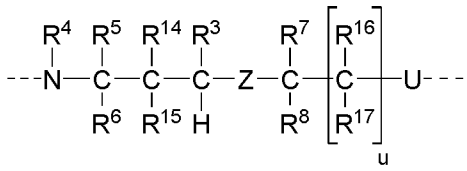
the building blocks of type **B** are **B7**, **B8**, **B9** and **B-17** as shown in Table 17, below;

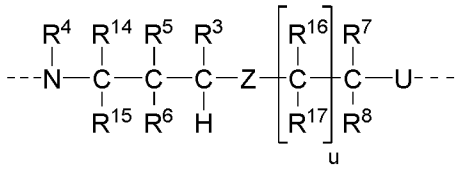
Table 17: Building Blocks of Type **B**

 **B7-1**	 **B7-2**	 **B7-3**	 **B7-4**
 **B8-1**	 **B8-2**	 **B8-3**	 **B8-4**
 **B9-1**	 **B9-2**	 **B9-3**	 **B9-4**
 **B17-1**		 **B17-2**	

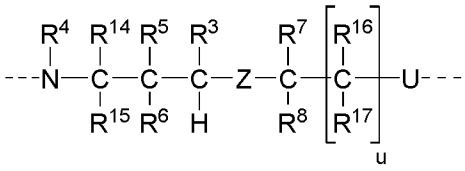
the linkers **C** are those listed in Table 18, below;

Table 18: Embodiments of Linker **C**

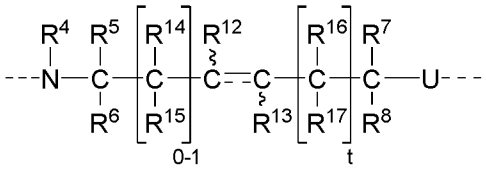
 **C1**	 **C2**
 **C3**	 **C4**
 **C5**	 **C6**
 **C7**	 **C8**
 **C9**	 **C10**
 **C11**	 **C12**



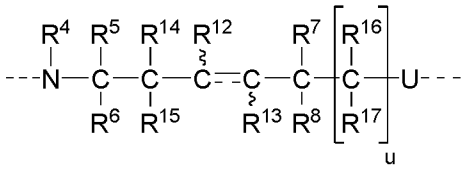
C13



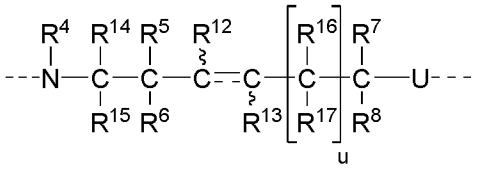
C14



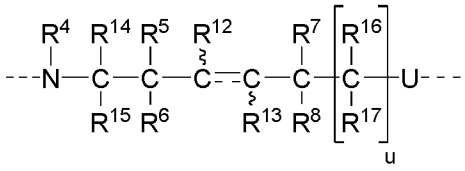
C15



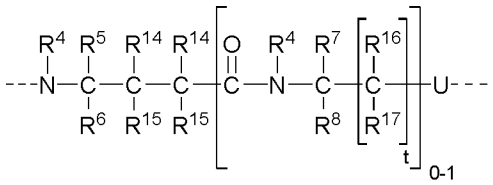
C16



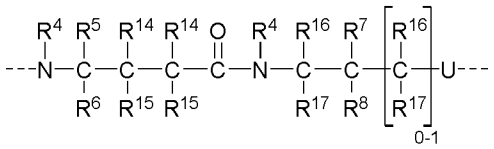
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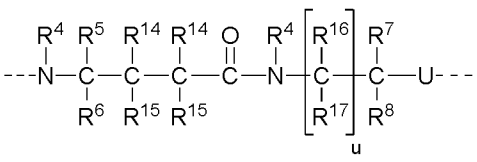
C18



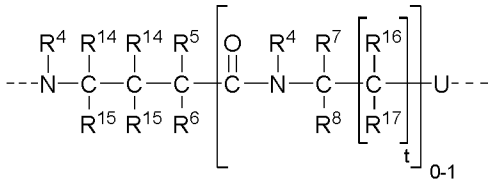
C19



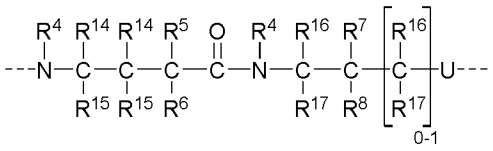
C20



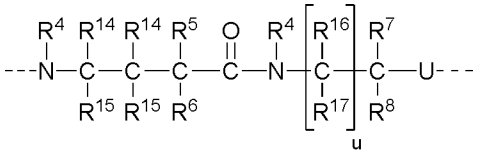
C21



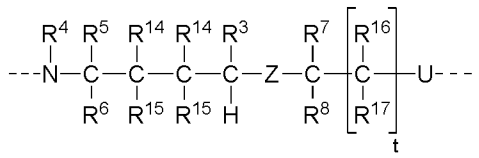
C25



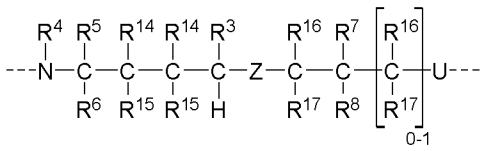
C26



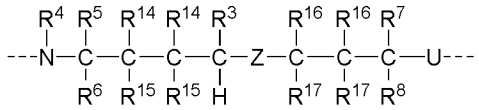
C27



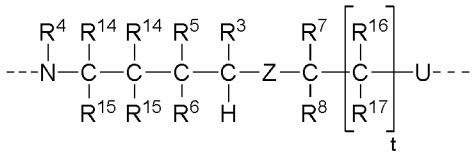
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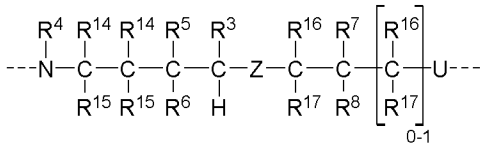
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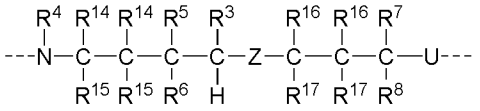
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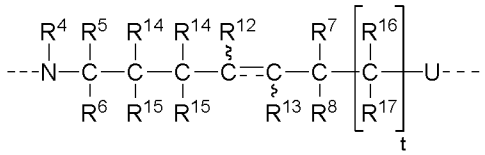
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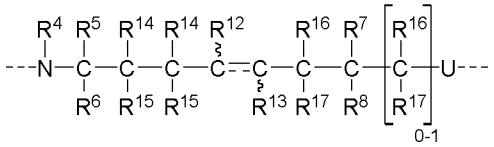
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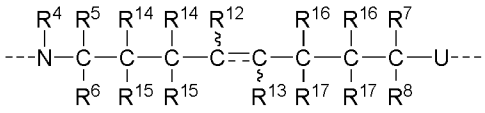
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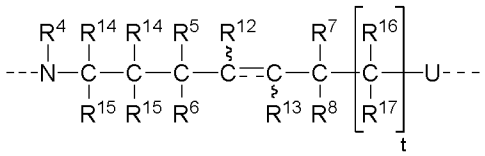
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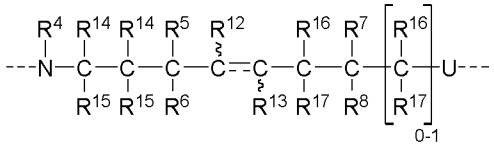
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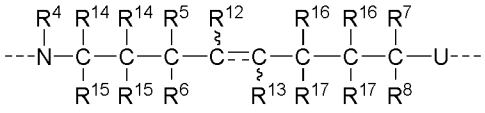
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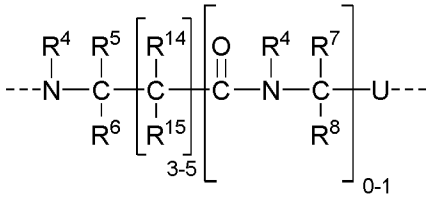
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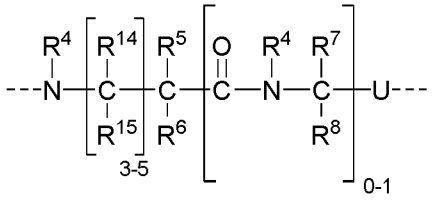


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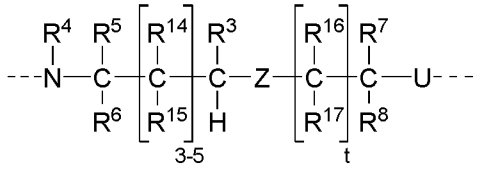


C45

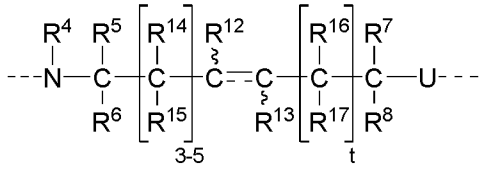




C46

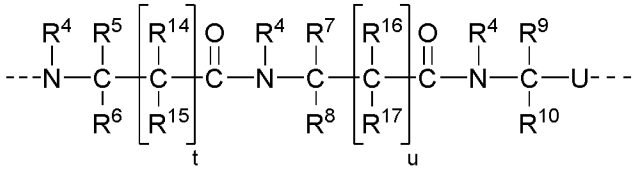


C47

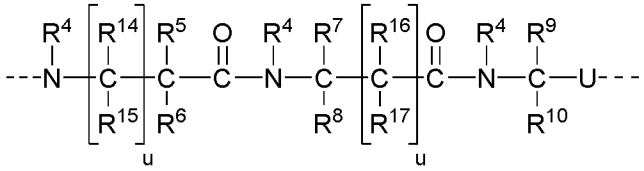


C48

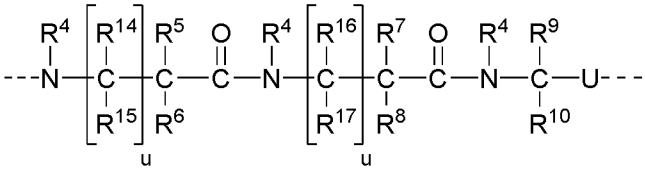
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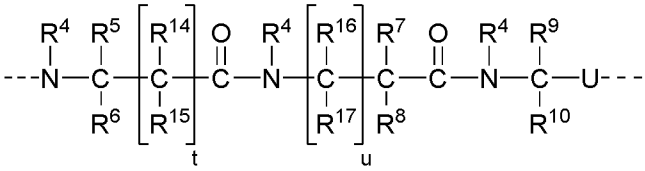
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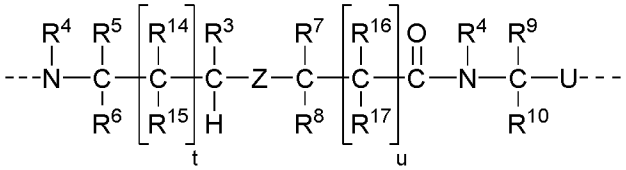
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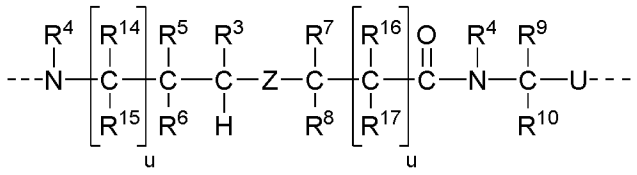
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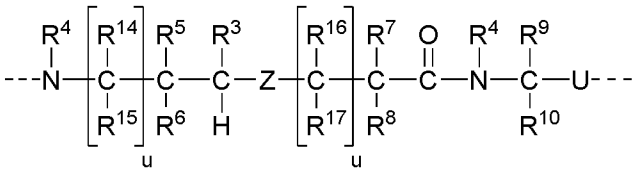
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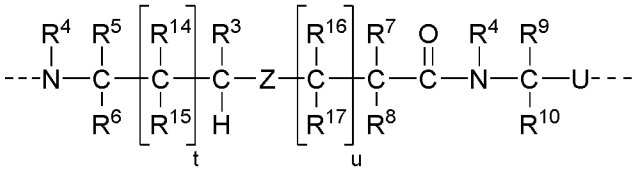
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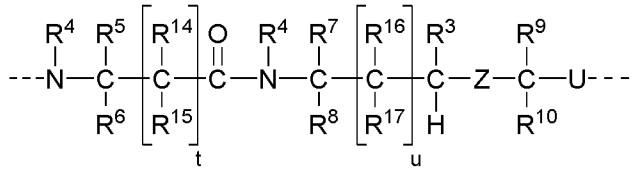
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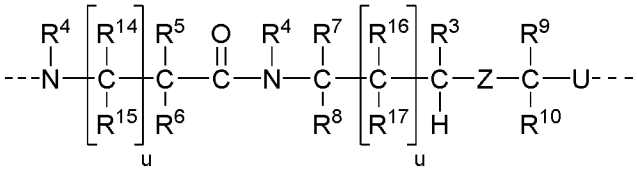
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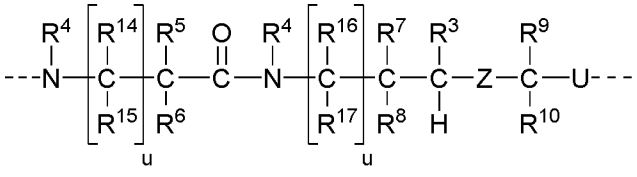
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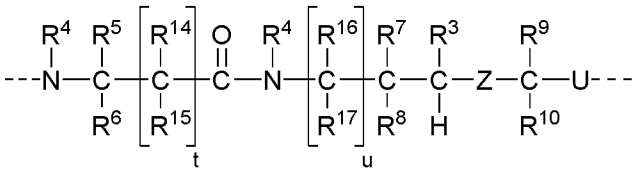
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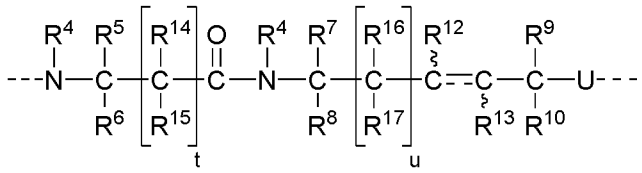
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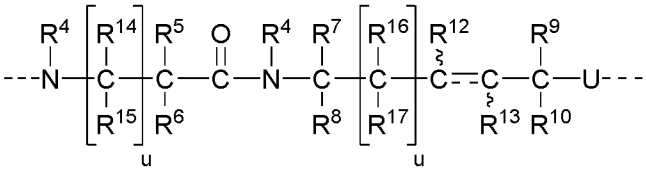
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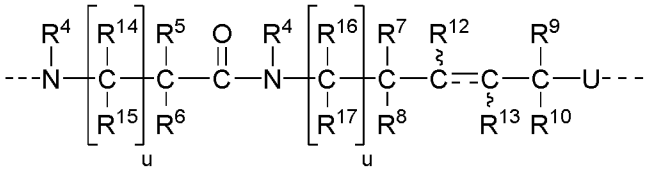
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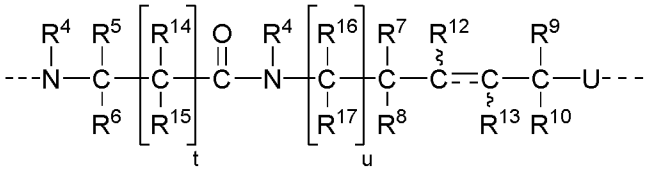
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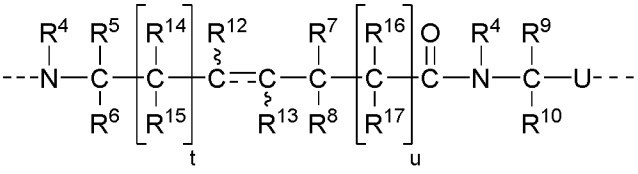
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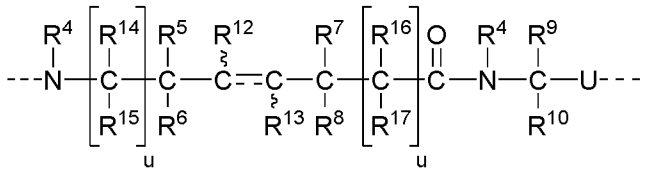
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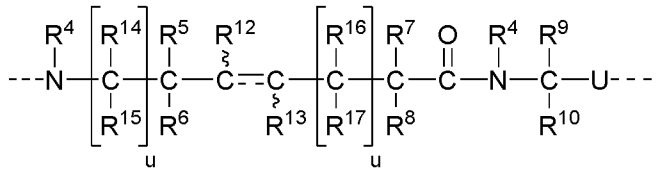
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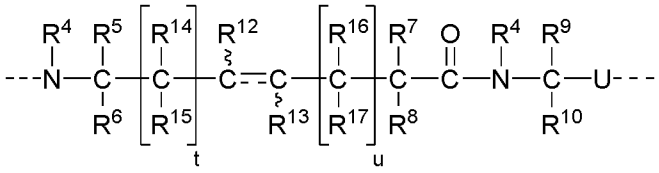
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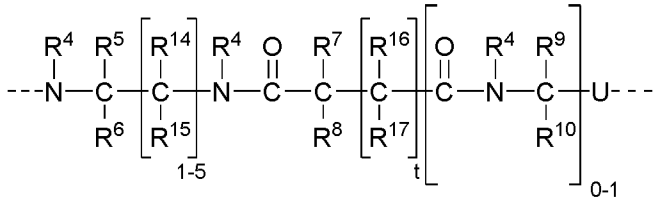
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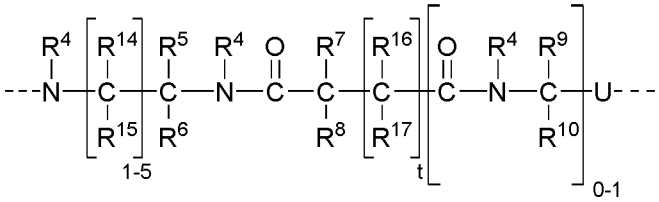
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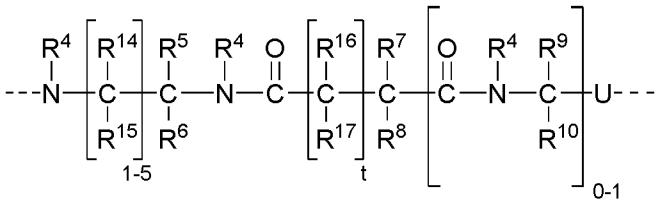
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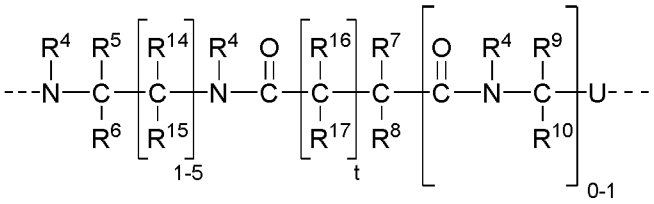
C90



C91



C92



C93

R^1 is H; F; Cl; CF_3; OCF_3; $OCHF_2$; NO_2; CN; lower alkyl; lower alkenyl; lower alkynyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl;
$-(CR^{18}R^{19})_qOR^{20}$; $-(CR^{18}R^{19})_qNR^4R^{11}$; $-(CR^{18}R^{19})_qNR^4COR^{22}$;
$-(CR^{18}R^{19})_qNR^4CONR^4R^{11}$; $-(CR^{18}R^{19})_qNR^4SO_2R^{23}$; $-(CR^{18}R^{19})_qNR^4SO_2NR^4R^{11}$;
$-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{11}$; $-(CR^{18}R^{19})_qSO_2NR^4R^{11}$;
$-(CR^{18}R^{19})_qCOR^{22}$; $-(CR^{18}R^{19})_qSO_2R^{23}$; $-(CR^{18}R^{19})_qR^{24}$; $-(CR^{18}R^{19})_qR^{25}$; or
$-(CR^{18}R^{19})_qR^{26}$;

R^2 is H; CF_3; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl;
$-(CR^{18}R^{19})_qOR^{20}$; $-(CR^{18}R^{19})_qNR^4R^{11}$; $-(CR^{18}R^{19})_qNR^4COR^{22}$;
$-(CR^{18}R^{19})_qNR^4CONR^4R^{11}$; $-(CR^{18}R^{19})_qNR^4SO_2R^{23}$; $-(CR^{18}R^{19})_qNR^4SO_2NR^4R^{11}$;
$-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{11}$; $-(CR^{18}R^{19})_qSO_2NR^4R^{11}$;
$-(CR^{18}R^{19})_qCOR^{22}$; $-(CR^{18}R^{19})_qSO_2R^{23}$; $-(CR^{18}R^{19})_qR^{24}$; $-(CR^{18}R^{19})_qR^{25}$; or $-(CR^{18}R^{19})_qR^{26}$.

R^3 is as defined in claim 1;

R^4 is H; lower alkyl; lower alkenyl; or a suitable N-protecting group;

R^5, R^7 and R^9 are independently defined as: H; CF_3; lower alkyl; lower alkenyl; lower cycloalkyl; lower

heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{18}R^{19})_sOR^{20}$; $-(CR^{18}R^{19})_sNR^4R^{11}$; $-(CR^{18}R^{19})_sNR^4COR^{22}$; $-(CR^{18}R^{19})_sNR^4CONR^4R^{11}$; $-(CR^{18}R^{19})_sNR^4SO_2R^{23}$; $-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{11}$; $-(CR^{18}R^{19})_qSO_2NR^4R^{11}$; $-(CR^{18}R^{19})_qCOR^{22}$; $-(CR^{18}R^{19})_qSO_2R^{23}$; $-(CR^{18}R^{19})_qR^{24}$; $-(CR^{18}R^{19})_qR^{25}$; or $-(CR^{18}R^{19})_qR^{26}$;

R^6, R^8 and R^{10} are independently defined as: H; CF_3; or CH_3;

R^{11} is H; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; a suitable protecting group; $-(CR^{18}R^{19})_rOR^{20}$; $-(CR^{18}R^{19})_rNR^4R^{27}$; $-(CR^{18}R^{19})_rNR^4CONR^4R^{27}$; $-(CR^{18}R^{19})_rNR^4SO_2R^{23}$; $-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{27}$; $-(CR^{18}R^{19})_qCOR^{22}$; $-(CR^{18}R^{19})_qR^{24}$; $-(CR^{18}R^{19})_sR^{25}$; or $-(CR^{18}R^{19})_qR^{26}$;

R^{12} and R^{13} are independently defined as H; or lower alkyl;

R^{14} and R^{16} are independently defined as: H; F; CF_3; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{18}R^{19})_sOR^{20}$; $-(CR^{18}R^{19})_sNR^4R^{11}$; $-(CR^{18}R^{19})_sNR^4COR^{22}$; $-(CR^{18}R^{19})_qCOOR^{21}$; or $-(CR^{18}R^{19})_qCONR^4R^{11}$;

R^{15} and R^{17} are independently defined as: H; CF_3; or CH_3;

R^{18} is H; F; CF_3; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{29}R^{30})_sOR^{31}$; $-(CR^{29}R^{30})_sNR^{28}R^{31}$; $-(CR^{29}R^{30})_sNR^{28}COR^{31}$; $-(CR^{29}R^{30})_sNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_sNR^{28}SO_2R^{23}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_qSO_2NR^{28}R^{31}$;

$-(CR^{29}R^{30})_qCOR^{31}$; $-(CR^{29}R^{30})_qSO_2R^{23}$; $-(CR^{29}R^{30})_qR^{24}$; $-(CR^{29}R^{30})_qR^{25}$; or $-(CR^{29}R^{30})_qR^{26}$;

R^{19} is H; CF_3; or CH_3;

R^{20} is H; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{29}R^{30})_rOR^{31}$; $-(CR^{29}R^{30})_rNR^{28}R^{31}$; $-(CR^{29}R^{30})_rNR^{28}COR^{31}$; $-(CR^{29}R^{30})_rNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_rNR^{28}SO_2R^{23}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_qSO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOR^{31}$; $-(CR^{29}R^{30})_qSO_2R^{23}$; $-(CR^{29}R^{30})_qR^{24}$; $-(CR^{29}R^{30})_qR^{25}$; or $-(CR^{29}R^{30})_qR^{26}$;

R^{21} and R^{23} are as defined in claim 1;

R^{22} is lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{29}R^{30})_sOR^{31}$; $-(CR^{29}R^{30})_sNR^{28}R^{31}$; $-(CR^{29}R^{30})_sNR^{28}COR^{31}$; $-(CR^{29}R^{30})_sN^{R28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_sNR^{28}SO_2R^{23}$; $-(CR^{29}R^{30})_sCOOR^{21}$; $-(CR^{29}R^{30})_sCONR^{28}R^{31}$; $-(CR^{29}R^{30})_sSO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_tCOR^{31}$; $-(CR^{29}R^{30})_sSO_2R^{23}$; $-(CR^{29}R^{30})_tR^{24}$; $-(CR^{29}R^{30})_tR^{25}$; or $-(CR^{29}R^{30})_tR^{26}$;

R^{24}, R^{25}, R^{26}, R^{27} and R^{28} are as defined in claim 1;

R^{29} is H; F; CF_3; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{32}R^{33})_sOR^{31}$; $-(CR^{32}R^{33})_sNR^{28}R^{31}$; $-(CR^{32}R^{33})_sNR^{28}COR^{31}$; $-(CR^{32}R^{33})_sNR^{28}CONR^{28}R^{31}$; $-(CR^{32}R^{33})_qCOOR^{21}$; $-(CR^{32}R^{33})_qCONR^{28}R^{31}$; $-(CR^{32}R^{33})_qCOR^{31}$; or $-(CR^{32}R^{33})_qR^{31}$;

R^{30} and R^{33} are H; CF_3; or CH_3;

R^{31} and R^{32} are as defined in claim 1;

R^{34} and R^{35} are independently defined as H; F; Cl; CF_3; OCF_3; $OCHF_2$; lower alkyl; lower alkenyl; lower alkynyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{29}R^{30})_qOR^{31}$; $-(CR^{29}R^{30})_qNR^{28}R^{31}$; $-(CR^{29}R^{30})_qNR^{28}COR^{31}$; $-(CR^{29}R^{30})_qNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_qNR^{28}SO_2R^{23}$; $-(CR^{29}R^{30})_qCOOR^{21}$;

$-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_qSO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOR^{31}$; $-(CR^{29}R^{30})_qSO_2R^{23}$; or $-(CR^{29}R^{30})_qR^{31}$;

R^{36} is as defined in claim 1;

R^{37} is H; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; a suitable N-protecting group; $-(CR^{29}R^{30})_rOR^{31}$; $-(CR^{29}R^{30})_rNR^{28}R^{31}$; $-(CR^{29}R^{30})_rNR^{28}COOR^{21}$; $-(CR^{29}R^{30})_rNR^{28}COR^{31}$; $-(CR^{29}R^{30})_rNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOR^{31}$; or $-(CR^{29}R^{30})_qR^{31}$;

R^{38} is H; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{29}R^{30})_qOR^{31}$; $-(CR^{29}R^{30})_qNR^{28}R^{31}$; $-(CR^{29}R^{30})_qNR^{28}COR^{31}$; $-(CR^{29}R^{30})_qNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOR^{31}$; or $-(CR^{29}R^{30})_qR^{31}$;

R^{39}; R^{40}; R^{41}; R^{42}; R^{43}; R^{44}; R^{45}; R^{46}; R^{47}; R^{48}; R^{49} and R^{50} are as defined in claim 1;

the variable heteroatom Z and the connector U are defined as:

Z: O; or $S(=O)_2$.

U: $-C(=O)-$; $-NR^4-C(=O)-$; or $-C(=O)-C(=O)-$; and

- substituents that can be pairwise taken together and form optionally substituted cycloalkyl or heterocycloalkyl moieties;
- structural elements that can form one of the groups of formulae **H111-H118** as shown in Table 9; and
- variable heteroatoms Q, T, X and Y;
- indices q-u;

are as defined in claim 1.

5. Compounds according to claim 1 wherein readily accessible substances that define possible subunits of the linker **C** are those listed in Table 19, below;

Code	Chemical Name
Ala	L-Alanine
^{D}Ala	D-Alanine
Arg	L-Arginine
^{D}Arg	D-Arginine
Asn	L-Asparagine
^{D}Asn	D-Asparagine
Asp	L-Aspartic acid
^{D}Asp	D-Aspartic acid
Cys	L-Cysteine
^{D}Cys	D-Cysteine
Glu	L-Glutamic acid
^{D}Glu	D-Glutamic acid
Gln	L-Glutamine
^{D}Gln	D-Glutamine
Gly	Glycine
His	L-Histidine
^{D}His	D-Histidine
Ile	L-Isoleucine

Code	Chemical Name
^{D}Ile	D-Isoleucine
Leu	L-Leucine
^{D}Leu	D-Leucine
Lys	L-Lysine
^{D}Lys	D-Lysine
Met	L-Methionine
^{D}Met	D-Methionine
Phe	L-Phenylalanine
^{D}Phe	D-Phenylalanine
Pro	L-Proline
^{D}Pro	D-Proline
Ser	L-Serine
^{D}Ser	D-Serine
Thr	L-Threonine
^{D}Thr	D-Threonine
Trp	L-Tryptophan
^{D}Trp	D-Tryptophan
Tyr	L-Tyrosine
^{D}Tyr	D-Tyrosine
Val	L-Valine
^{D}Val	D-Valine
Apa	3-Amino-propanoic acid
H-β^3-HAla-OH	(3S)-3-Amino-butyric acid
H-β^3-HVal-OH	(3R)-3-Amino-4-methyl-valeric acid
H-β^3-HIle-OH	(3R, 4S)-3-Amino-4-methyl-hexanoic acid
H-β^3-HLeu-OH	(3S)-3-Amino-5-methyl-hexanoic acid
H-β^3-HMet-OH	(3S)-3-Amino-5-methylthio pentanoic acid
H-β^3-HTyr-OH	(3S)-3-Amino-4-(4'-hydroxyphenyl)-butyric acid
H-β^3-HHis-OH	(3S)-3-Amino-4-(imidazole-4'-yl)-butyric acid
H-β^3-HPhe-OH	(3S)-3-Amino-4-phenyl butyric acid
H-β^3-HTrp-OH	(3S)-3-Amino-4-(indol-3'-yl)-butyric acid
H-β^3-HSer-OH	(3R)-3-Amino-4-hydroxy-butyric acid
H-β^3-HAsp-OH	3-Amino-pentanedioic acid
H-β^3-HGlu-OH	(3S)-3-Amino-hexanedioic acid

Code	Chemical Name
H-β^3-HLys-OH	(3S)-3,7-Diamino-heptanoic acid
H-β^3-HArg-OH	(3S)-3-Amino-6-guanidino-hexanoic-acid
H-β^3-HCys-OH	(3R)-3-Amino-4-mercapto-butyric acid
H-β^3-HAsn-OH	(3S)-3-Amino-4-carbamoyl-butyric acid
H-β^3-HGln-OH	(3S)-3-Amino-5-carbamoyl-pentanoic acid
H-β^3-HThr-OH	(3R,4R)-3-Amino-4-hydroxy-pentanoic acid
Gaba	4-Amino-butyric acid
H-•^{4}-DiHAla-OH	(4S)-4-Amino-pentanoic acid
H-•^{4}-DiHVal-OH	(4R)-4-Amino-5-methyl-hexanoic acid
H-•^{4}-DiHIle-OH	(4R, 5S)-4-Amino-5-methyl-heptanoic acid
H-•^{4}-DiHLeu-OH	(4R)-4-Amino-6-methyl-heptanoic acid
H-•^{4}-DiHMet-OH	(4R)-4-Amino-6-methylthio-hexanoic acid
H-•^{4}-DiHTyr-OH	(4R)-4-Amino-5-(4'-hydroxyphenyl)-pentanoic acid
H-•^{4}-DiHHis-OH	(4R)-4-Amino-5-(imidazole-4'-yl)-pentanoic acid
H-•^{4}-DiHPhe-OH	(4R)-4-Amino-5-phenyl-pentanoic acid
H-•^{4}-DiHTrp-OH	(4R)-4-Amino-5-(indol-3'-yl)-pentanoic acid
H-•^{4}-DiHSer-OH	(4R)-4-Amino-5-hydroxy-pentanoic acid
H-•^{4}-DiHAsp-OH	(4R)-4-Amino-hexanedioic acid
H-•^{4}-DiHGlu-OH	4-Amino-heptanedioic acid
H-•^{4}-DiHLys-OH	(4S)-4,8-Diamino-octanoic acid
H-•^{4}-DiHArg-OH	(4S)-4-Amino-7-guanidino-heptanoic-acid
H-•^{4}-DiHCys-OH	(4R)-4-Amino-5-mercapto-pentanoic acid
H-•^{4}-DiHAsn-OH	(4R)-4-Amino-5-carbamoyl-pentanoic acid
H-•^{4}-DiHGln-OH	(3S)-3-Amino-5-carbamoyl-hexanoic acid
H-•^{4}-DiHThr-OH	(4R, 5R)-4-Amino-5-hydroxy- hexanoic acid
Cit	L-Citrulline
^{D}Cit	D-Citrulline
Orn	L-Ornithine
^{D}Orn	D-Ornithine
tBuA	L-t-Butylalanine
^{D}tBuA	D-t-Butylalanine
Sar	Sarcosine
Pen	L-Penicillamine

Code	Chemical Name
^{D}Pen	D-Penicillamine
tBuG	L-tert.-Butylglycine
^{D}tBuG	D-tert.-Butylglycine
4AmPhe	L-para-Aminophenylalanine
^{D}4AmPhe	D-para-Aminophenylalanine
3AmPhe	L-meta-Aminophenylalanine
^{D}3AmPne	D-meta-Aminophenylalanine
2AmPhe	L-ortho-Aminophenylalanine
^{D}2AmPhe	D-ortho-Aminophenylalanine
Phe(mC(NH_2)=NH)	L-meta-Amidinophenylalanine
^{D}Phe(mC(NH_2)=NH)	D-meta-Amidinophenylalanine
Phe(pC(NH_2)=NH)	L-para-Amidinophenylalanine
^{D}Phe(pC(NH_2)=NH)	D-para-Amidinophenylalanine
Phe(mNHC(NH_2)=NH)	L-meta-Guanidinophenylalanine
^{D}Phe(mNHC(NH_2)=NH)	D-meta-Guanidinophenylalanine
Phe(pNHC(NH_2)=NH)	L-para-Guanidinophenylalanine
^{D}Phe(pNHC(NH_2)=NH)	D-para-Guanidinophenylalanine
2Pal	(2S)-2-Amino-3-(pyridine-2'-yl)-propionic acid
^{D}2Pal	(2R)-2-Amino-3-(pyridine-2'-yl)-propionic acid
4Pal	(2S)-2-Amino-3-(pyridine-4'-yl)-propionic acid
^{D}4Pal	(2R)-2-Amino-3-(pyridine-4'-yl)-propionic acid
Phg	L-Phenylglycine
^{D}Phg	D-Phenylglycine
Cha	L-Cyclohexylalanine
^{D}Cha	D-Cyclohexylalanine
C_4al	L-3-Cyclobutylalanine
$^{D}C_4$al	D-3-Cyclobutylalanine
C_5al	L-3-Cyclopentylalanine
$^{D}C_5$al	D-3-Cyclopentylalanine
Nle	L-Norleucine
^{D}Nle	D-Norleucine
2-Nal	L-2-Naphthylalanine
^{D}2Nal	D-2-Naphthylalanine

Code	Chemical Name
1-Nal	L-1-Naphthylalanine
^{D}1Nal	D-1-Naphthylalanine
4ClPhe	L-4-Chlorophenylalanine
^{D}4ClPhe	D-4-Chlorophenylalanine
3ClPhe	L-3-Chlorophenylalanine
^{D}3ClPhe	D-3-Chlorophenylalanine
2ClPhe	L-2-Chlorophenylalanine
^{D}2ClPhe	D-2-Chlorophenylalanine
3,4Cl$_2$Phe	L-3,4-Dichlorophenylalanine
^{D}3,4Cl$_2$Phe	D-3,4-Dichlorophenylalanine
4FPhe	L-4-Fluorophenylalanine
^{D}4FPhe	D-4-Fluorophenylalanine
3FPhe	L-3-Fluorophenylalanine
^{D}3FPhe	D-3-Fluorophenylalanine
2FPhe	L-2-Fluorophenylalanine
^{D}2FPhe	D-2-Fluorophenylalanine
Thi	L-β-2-Thienylalanine
^{D}Thi	D-β-2-Thienylalanine
Tza	L-2-Thiazolylalanine
^{D}Tza	D-2-Thiazolylalanine
Mso	L-Methionine sulfoxide
^{D}Mso	D-Methionine sulfoxide
AcLys	N-Acetyllysine
^{D}AcLys	N-Acetyl-D-lysine
Dap	2,3-Diaminopropionic acid
^{D}Dap	D-2,3-Diaminopropionic acid
Dab	2,4-Diaminobutyric acid
^{D}Dab	(2R)-2,4-Diaminobutyric acid
Dbu	(2S)-2,3-Diamino-butyric acid
^{D}Dbu	(2R)-2,3-Diamino-butyric acid
Abu	γ-Aminobutyric acid (GABA)
Aha	•-Aminohexanoic acid
Aib	•-Aminoisobutyric acid
Cyp	1-Amino cyclopentane carboxylic acid
Y(Bzl)	L-O-Benzyltyrosine
^{D}Y(Bzl)	D-O-Benzyltyrosine

Code	Chemical Name
H(Bzl)	(3S)-2-Amino-3-(1'-benzylimidazole-4'-yl)-propionic acid
^{D}H(Bzl)	(3R)- 2-Amino-3-(1'-benzylimidazole-4'-yl)-propionic acid
Bip	L-(4-phenyl)phenylalanine
^{D}Bip	D-(4-phenyl)phenylalanine
S(Bzl)	L-O-Benzylserine
^{D}S(Bzl)	D-O-Benzylserine
T(Bzl)	L-O-Benzylthreonine
^{D}T(Bzl)	D-O-Benzylthreonine
alloT	(2S, 3S)-2-Amino-3-hydroxy-butyric acid
^{D}alloT	(2R, 3S)-2-Amino-3-hydroxy-butyric acid
Leu3OH	(2S, 3R)-2-Amino-3-hydroxy-4-methyl-pentanoic acid
^{D}Leu3OH	(2R, 3R)-2-Amino-3-hydroxy-4-methyl-pentanoic acid
hAla	L-Homo-alanine
^{D}hAla	D-Homo-alanine
hArg	L-Homo-arginine
^{D}hArg	D-Homo-arginine
hCys	L-Homo-cysteine
^{D}hCys	D-Homo-cysteine
hGlu	L-Homo-glutamic acid
^{D}hGlu	D-glutamic acid
hGln	L-Homo-glutamine
^{D}hGln	D-Homo-glutamine
hHis	L-Homo-histidine
^{D}hHis	D-Homo-histidine
hIle	L-Homo-isoleucine
^{D}hIle	D-Homo-isoleucine
hLeu	L-Homo-leucine
^{D}hLeu	D-Homo-leucine
hNle	L-Homo-norleucine
^{D}hNle	D-Homo-norleucine
hLys	L-Homo-lysine
^{D}hLys	D-Homo-lysine
hMet	L-Homo-Methionine
^{D}hMet	D-Homo-Methionine

Code	Chemical Name
hPhe	L-Homo-phenylalanine
[D]hPhe	D-Homo-phenylalanine
hSer	L-Homo-serine
[D]hSer	D-Homo-serine
hThr	L-Homo-threonine
[D]hThr	D-Homo-threonine
hTrp	L-Homo-tryptophan
[D]hTrp	D-Homo-tryptophan
hTyr	L-Homo-tyrosine
[D]hTyr	D-Homo-tyrosine
hVal	L-Homo-valine
[D]hVal	D-Homo-valine
hCha	L-Homo-cyclohexylalanine
[D]hCha	D-Homo-cyclohexylalanine
Bpa	L-4-Benzoylphenylalanine
[D]Bpa	D-4-Benzoylphenylalanine
OctG	L-Octylglycine
[D]OctG	D-Octylglycine
Tic	(3S)-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid
[D]Tic	(3R)-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid
Tiq	(1S)-1,2,3,4-Tetrahydroisoquinoline-1-carboxylic acid
[D]Tiq	(1R)-1,2,3,4-Tetrahydroisoquinoline-1-carboxylic acid
Oic	(2S, 3aS, 7aS)-1-Octahydro-1H-indole-2-carboxylic acid
[D]Oic	(2R, 3aS, 7aS)-1-Octahydro-1H-indole-2-carboxylic acid
4AmPyrr1	(2S, 4S)-4-Amino-pyrrolidine-2-carboxylic acid
[D]4AmPyrr1	(2R, 4S)-4-Amino-pyrrolidine-2-carboxylic acid
4AmPyrr2	(2S, 4R)-4-Amino-pyrrolidine-2-carboxylic acid
[D]4AmPyrr2	(2R, 4R)-4-Amino-pyrrolidine-2-carboxylic acid
4PhePyrr1	(2S, 4R)-4-Phenyl-pyrrolidine-2-carboxylic acid
[D]4PhePyrr1	(2R, 4R)-4-Phenyl-pyrrolidine-2-carboxylic acid
4PhePyrr2	(2S, 4S)-4-Phenyl-pyrrolidine-2-carboxylic acid

Code	Chemical Name
^{D}4PhePyrr2	(2R, 4S)-4-Phenyl-pyrrolidine-2-carboxylic acid
5PhePyrr1	(2S, 5R)-5-Phenyl-pyrrolidine-2-carboxylic acid
^{D}5PhePyrr1	(2R, 5R)-5-Phenyl-pyrrolidine-2-carboxylic acid
5PhePyrr2	(2S, 5S)-5-Phenyl-pyrrolidine-2-carboxylic acid
^{D}5PhePyrr2	(2R, 5S)-5-Phenyl-pyrrolidine-2-carboxylic acid
4Hyp1	(4S)-L-Hydroxyproline
^{D}4Hyp1	(4S)-D-Hydroxyproline
4Hyp2	(4R)-L-Hydroxyproline
^{D}4Hyp2	(4R)-D-Hydroxyproline
4Mp1	(4S)-L-Mercaptoproline
^{D}4Mp1	(4S)-D-Mercaptoproline
4Mp2	(4R)-L-Mercaptoproline
^{D}4Mp2	(4R)-D-Mercaptoproline
Pip	L-Pipecolic acid
^{D}Pip	D-Pipecolic acid
H-β^3-HCit-OH	(3S)-3-Amino-6-carbamidyl-hexanoic acid
H-β^3-HOrn-OH	(3S)-3,6-Diamino-hexanoic acid
H-β^3-HtBuA-OH	(3S)-3-Amino-5,5-dimethyl-hexanoic acid
H-β^3-HSar-OH	N-Methyl-3-amino-propionic acid
H-β^3-HPen-OH	(3R)-3-Amino-4-methyl-4-mercapto-pentanoic acid
H-β^3-HtBuG-OH	(3R)-3-Amino-4,4-dimethyl-pentanoic acid
H-β^3-H4AmPhe-OH	(3S)-3-Amino-4-(4'-aminophenyl)-butyric acid
H-β^3-H3AmPhe-OH	(3S)-3-Amino-4-(3'-aminophenyl)-butyric acid
H-β^3-H2AmPhe-OH	(3S)-3-Amino-4-(2'-aminophenyl)-butyric acid
H-β^3-HPhe(mC(NH_2)=NH)-OH	(3S)-3-Amino-4-(3'-amidinophenyl)-butyric acid
H-β^3-HPhe(pC(NH_2)=NH)-OH	(3S)-3-Amino-4-(4'-amidinophenyl)-butyric acid
H-β^3-HPhe(mNHC(NH_2)=NH)-OH	(3S)-3-Amino-4-(3'-guanidinophenyl)-butyric acid
H-β^3-HPhe(pNHC(NH_2)=NH)-OH	(3S)-3-Amino-4-(4'-guanidino-phenyl)-butyric acid
H-β^3-H2Pal-OH	(3S)-3-Amino-4-(pyridine-2'-yl)-butyric acid

Code	Chemical Name
H-β³-H4Pal-OH	(3S)-3-Amino-4-(pyridine-4'-yl)-butyric acid
H-β³-HPhg-OH	(3R)-3-Amino-3-phenyl-propionic acid
H-β³-HCha-OH	(3S)-3-Amino-4-cyclohexyl-butyric acid
H-β³-HC$_4$al-OH	(3S)-3-Amino-4-cyclobutyl-butyric acid
H-β³-HC$_5$al-OH	(3S)-3-Amino-4-cyclopentyl-butyric acid
H-β³-HNle-OH	(3S)-3-Amino-heptanoic acid
H-β³-H2Nal-OH	(3S)-3-Amino-4-(2'-naphthyl)-butyric acid
H-β³-H1Nal-OH	(3S)-3-Amino-4-(1'-naphthyl)-butyric acid
H-β³-H4ClPhe-OH	(3S)-3-Amino-4-(4'-chlorophenyl)-butyric acid
H-β³-H3ClPhe-OH	(3S)-3-Amino-4-(3'-chlorophenyl)-butyric acid
H-β³-H2ClPhe-OH	(3S)-3-Amino-4-(2'-chlorophenyl)-butyric acid
H-β³-H3,4Cl$_2$Phe-OH	(3S)-3-Amino-4-(3',4'-dichlorophenyl)-butyric acid
H-β³-H4FPhe-OH	(3S)-3-Amino-4-(4'-fluorophenyl)-butyric acid
H-β³-H3FPhe-OH	(3S)-3-Amino-4-(3'-fluorophenyl)-butyric acid
H-β³-H2FPhe-OH	(3S)-3-Amino-4-(2'-fluorophenyl)-butyric acid
H-β³-HThi-OH	(3R)-3-Amino-4-(2'-thienyl)-butyric acid
H-β³-HTza-OH	(3R)-3-Amino-4-(2'-thiazolyl)-butyric acid
H-β³-HMso-OH	(3R)-3-Amino-4-methylsulfoxyl-butyric acid
H-β³-HAcLys-OH	(3S)-7-Acetylamino-3-amino-heptanoic acid
H-β³-HDpr-OH	(3R)-3,4-diamino-butyric acid
H-β³-HA$_2$Bu-OH	(3S)-3,5-Diamino-pentanoic acid
H-β³-HDbu-OH	(3R)-3,4-Diamino-pentanoic acid
H-β³-HAib-OH	Amino-dimethyl acetic acid
H-β³-HCyp-OH	1-Amino-cyclopentane-1-yl-acetic acid
H-β³-HY(Bzl)-OH	(3S)-3-Amino-4-(4'-benzyloxyphenyl)-butyric acid
H-β³-HH(Bzl)-OH	(3S)-3-Amino-4-(1'-benzylimidazole-4'-yl)-butyric acid
H-β³-HBip-OH	(3S)-3-Amino-4-biphenylyl-butyric acid
H-β³-HS(Bzl)-OH	(3S)-3-Amino-4-(benzyloxy)-butyric acid
H-β³-HT(Bzl)-OH	(3R, 4R)-3-Amino-4-benzyloxy-pentanoic acid

Code	Chemical Name
H-β^3-HalloT-OH	(3R, 4S)-3-Amino-4-hydroxy-pentanoic acid
H-β^3-HLeu3OH-OH	(3R, 4R)-3-Amino-4-hydroxy-5-methyl-hexanoic acid
H-β^3-HhAla-OH	(3S)-3-Amino-pentanoic acid
H-β^3-HhArg-OH	(3S)-3-Amino-7-guanidino-heptanoic acid
H-β^3-HhCys-OH	(3R)-Amino-5-mercapto-pentanoic acid
H-β^3-HhGlu-OH	(3S)-3-Amino-heptanedioic acid
H-β^3-HhGln-OH	(3S)-3-Amino-6-carbamoyl hexanoic acid
H-β^3-HhHis-OH	(3S)-3-Amino-5-(imidazole-4'-yl)-pentanoic acid
H-β^3-HhIle-OH	(3S, 5S)-3-Amino-5-methyl-heptanoic acid
H-β^3-HhLeu-OH	(3S)-3-Amino-6-methyl-heptanoic acid
H-β^3-HhNle-OH	(3S)-3-Amino-octanoic acid
H-β^3-DiAoc-OH	(3S)-3,8-Diamino-octanoic acid
H-β^3-HhMet-OH	(3S)-3-Amino-6-methylthio-hexanoic acid
H-β^3-HhPe-OH	(3S)-3-Amino-5-phenyl-pentanoic acid
H-β^3-HhSer-OH	(3S)-3-Amino-5-hydroxy-pentanoic acid
H-β^3-HhThr-OH	(3S, 5R)-3-Amino-5-hydroxy-hexanoic acid
H-β^3-HhTrp-OH	(3S)-3-Amino-5-(indol-3'-yl)-pentanoic acid
H-β^3-HhThr-OH	(3S)-3-Amino-5-(4'-hydroxyphenyl)-pentanoic acid
H-β^3-HhCha-OH	(3S)-3-Amino-5-cyclohexyl-pentanoic acid
H-β^3-HBpa-OH	(3S)-3-Amino-4-(4'-benzoylphenyl)-butyric acid
H-β^3-HOctG-OH	(3S)-3-Amino-undecanoic acid
H-β^3-HNle-OH	(3S)-3-Amino-heptanoic acid
H-β^3-HTic-OH	(3S)-1,2,3,4-Tetrahydroisoquinoline-3-yl-acetic acid
H-β^3-HTiq-OH	(1S)-1,2,3,4-Tetrahydroisoquinoline-1-acetic acid
H-β^3-HOic-OH	(2S, 3aS, 7aS)-1-Octahydro-1H-indole-2-yl-acetic acid
H-β^3-H4AmPyrr1-OH	(2S, 4S)-4-Amino-pyrrolidine-2-acetic acid
H-β^3-H4AmPyrr2-OH	(2S, 4R)-4-Amino-pyrrolidine-2-acetic acid
H-β^3-H4PhePyrr1-OH	(2S, 4R)-4-Phenyl-pyrrolidine-2-acetic acid
H-β^3-H4PhePyrr2-OH	(2S, 4S)-4-Phenyl-pyrrolidine-2-acetic acid

Code	Chemical Name
H-β^3-H5PhePyrr1-OH	(2S, 5R)-5-Phenyl-pyrrolidine-2-acetic acid
H-β^3-H5PhePyrr2-OH	(2S, 5S)-5-Phenyl-pyrrolidine-2-acetic acid
H-β^3-H4Hyp1-OH	(2S, 4S)-4-Hydroxy-pyrrolidine-2-acetic acid
H-β^3-H4Hyp2-OH	(2S, 4R)-4-Hydroxy-pyrrolidine-2-acetic acid
H-β^3-H4Mp1-OH	(2R, 4S)-4-Mercapto-pyrrolidine-2-acetic acid
H-β^3-H4Mp2-OH	(2R, 4R)-4-Mercapto-pyrrolidine-2-acetic acid
H-β^3-HPip-OH	(2S)-piperidine-2-acetic acid
H-β^3-HPro-OH	(2S)-pyrrolidine-2-acetic acid
H-β^3-H^{D}Pro-OH	(2R)-pyrrolidine-2-acetic acid
Ahb	4-Amino-2-hydroxy butyric acid
H-•^{4}-DiHCit-OH	(4S)-4-Amino-7-carbamidyl-heptanoic acid
H-•^{4}-DiHOrn-OH	(4S)-4,7-Diamino-heptanoic acid
H-•^{4}-DiHtBuA-OH	(4R)-4-Amino-6,6-dimethyl-heptanoic acid
H-•^{4}-DiHSar-OH	N-Methyl-4-amino-butyric acid
H-•^{4}-DiHPen-OH	(4R)-4-Amino-5-methyl-5-mercapto-hexanoic acid
H-•^{4}-DiHtBuG-OH	(4R)-4-Amino-5,5-dimethyl-hexanoic acid
H-•^{4}-DiH4AmPhe-OH	(4R)-4-Amino-5-(4'-aminophenyl)-pentanoic acid
H-•^{4}-DiH3AmPhe-OH	(4R)-4-Amino-5-(3'-aminophenyl)-pentanoic acid
H-•^{4}-DiH2AmPhe-OH	(4R)-4-Amino-5-(2'-aminophenyl)-pentanoic acid
H-•^{4}-DiHPhe(mC(NH_2)=NH)-OH	(4R)-4-Amino-5-(3'-amidinophenyl)-pentanoic acid
H-•^{4}-DiHPhe(pC(NH_2)=NH)-OH	(4R)-4-Amino-5-(4'-amidinophenyl)-pentanoic acid
H-•^{4}-DiHPhe(mNHC(NH_2)=NH)-OH	(4R)-4-Amino-5-(3'-guanidino-phenyl)-pentanoic acid
H-•^{4}-DiHPhe(pNHC(NH_2)=NH)-OH	(4R)-4-Amino-5-(4'-guanidino-phenyl)-pentanoic acid
H-•^{4}-DiH2Pal-OH	(4R)-4-Amino-5-(pyridine-4'-yl)-pentanoic acid
H-•^{4}-DiH4Pal-OH	(4R)-4-Amino-5-(pyridine-4'-yl)-pentanoic acid
H-•^{4}-DiHPhg-OH	(4R)-4-Amino-4-phenyl-butyric acid
H-•^{4}-DiHCha-OH	(4R)-4-Amino-5-cyclohexyl-pentanoic acid

Code	Chemical Name
H-•^{4}-DiHC$_{4}$al-OH	(4R)-4-Amino-5-cyclobutyl-pentanoic acid
H-•^{4}-DiHC$_{5}$al-OH	(4R)-4-Amino-5-cyclopentyl-pentanoic acid
H-•^{4}-DiHNle-OH	(4S)-4-Amino-octanoic acid
H-•^{4}-DiH2Nal-OH	(4S)-4-Amino-5-(2'-naphthyl)-pentanoic acid
H-•^{4}-DiH1Nal-OH	(4S)-4-Amino-5-(1'-naphthyl)-pentanoic acid
H-•^{4}-DiH4ClPhe-OH	(4R)-4-Amino-5-(4'-chlorophenyl)-pentanoic acid
H-•^{4}-DiH3ClPhe-OH	(4R)-4-Amino-5-(3'-chlorophenyl)-pentanoic acid
H-•^{4}-DiH2ClPhe-OH	(4R)-4-Amino-5-(2'-chlorophenyl)-pentanoic acid
H-•^{4}-DiH3,4Cl$_{2}$Phe-OH	(4R)-4-Amino-5-(3',4'-dichloro-phenyl)-pentanoic acid
H-•^{4}-DiH4FPhe-OH	(4R)-4-Amino-5-(4'-fluorophenyl)-pentanoic acid
H-•^{4}-DiH3FPhe-OH	(4R)-4-Amino-5-(3'-fluorophenyl)-pentanoic acid
H-•^{4}-DiH2FPhe-OH	(4R)-4-Amino-5-(2'-fluorophenyl)-pentanoic acid
H-•^{4}-DiHThi-OH	(4R)-4-Amino-5-(2'-thienyl)-pentanoic acid
H-•^{4}-DiHTza-OH	(4R)-4-Amino-5-(2'- thiazolyl)-pentanoic acid
H-•^{4}-DiHMso-OH	(4R)-4-Amino-5-methylsulfoxyl-pentanoic acid
H-•^{4}-DiHAcLys-OH	(4S)-8-Acetylamino-4-amino-ocatanoic acid
H-•^{4}-DiHDpr-OH	(4R)-4,5-diamino-pentanoic acid
H-•^{4}-DiHA$_{2}$Bu-OH	(4R)-4,5-Diamino-hexanoic acid
H-•^{4}-DiHDbu-OH	(4R)-4,5-Diamion-hexanoic acid
H-•^{4}-DiHAib-OH	3-Amino-3,3-dimethyl propionic acid
H-•^{4}-DiHCyp-OH	(1'-Amino-cyclopentane-1'-yl)-3-propionic acid
H-•^{4}-DiHY(Bzl)-OH	(4R)-4-Amino-5-(4'-benzyloxyphenyl)-pentanoic acid
H-•^{4}-DiHH(Bzl)-OH	(4R)-4-Amino-5-(1'-benzylimidazole-4'-yl)-pentanoic acid
H-•^{4}-DiHBip-OH	(4R)-4-Amino-5-biphenylyl-pentanoic acid
H-•^{4}-DiHS(Bzl)-OH	(4S)-4-Amino-5-(benzyloxy)-pentanoic acid
H-•^{4}-DiHT(Bzl)-OH	(4R, 5R)-4-Amino-5-benzyloxy-hexanoic acid
H-•^{4}-DiHalloT-OH	(4R, 5S)-4-Amino-5-hydroxy-hexanoic acid
H-•^{4}-DiHLeu3OH-OH	(4R, 5R)-4-Amino-5-hydroxy-6-methyl-heptanoic acid

Code	Chemical Name
H-•^{4}-DiHhAla-OH	(4S)-4-Amino-hexanoic acid
H-•^{4}-DiHhArg-OH	(4S)-4-Amino-8-guanidino-octanoic acid
H-•^{4}-DiHhCys-OH	(4R)-Amino-6-mercapto-hexanoic acid
H-•^{4}-DiHhGlu-OH	(4S)-4-Amino-ocatanedioic acid
H-•^{4}-DiHhGln-OH	(4S)-4-Amino-7-carbamoyl-heptanoic acid
H-•^{4}-DiHhHis-OH	(4S)-4-Amino-6-(imidazole-4'-yl)-hexanoic acid
H-•^{4}-DiHhIle-OH	(4S, 6S)-4-Amino-6-methyl-octanoic acid
H-•^{4}-DiHhLeu-OH	(4S)-4-Amino-7-methyl-ocatanoic acid
H-•^{4}-DiHhNle-OH	(4S)-4-Amino-nonanoic acid
H-•^{4}-DiHhLys-OH	(4S)-4,9-Diamino-nonanoic acid
H-•^{4}-DiHhMet-OH	(4R)-4-Amino-7-methylthioheptanoic acid
H-•^{4}-DiHhPhe-OH	(4S)-4-Amino-6-phenyl-hexanoic acid
H-•^{4}-DiHhSer-OH	(4R)-4-Amino-6-hydroxy-hexanoic acid
H-•^{4}-DiHhThr-OH	(4R, 6R)-4-Amino-6-hydroxy-heptanoic acid
H-•^{4}-DiHhTrp-OH	(4S)-4-Amino-6-(indol-3'-yl)-hexanoi cacid
H-•^{4}-DiHhTyr-OH	(4S)-4-Amino-6-(4'-hydroxyphenyl)-hexanoic acid
H-•^{4}-DiHhCha-OH	(4R)-4-Amino-5-cyclohexyl-pentanoic acid
H-•^{4}-DihBpa-OH	(4R)-4-Amino-5-(4'-benzoylphenyl)-pentanoic acid
H-•^{4}-DiHOctG-OH	(4S)-4-Amino-dodecanoic acid
H-•^{4}-DiHNle-OH	(4S)-4-Amino-octanoic acid
H-•^{4}-DiHTic-OH	(3R)-1',2',3',4'-Tetrahydroisoquinoline-3'-yl-3-propionic acid
H-•^{4}-DiHTiq-OH	(1'R)-1',2',3',4'-Tetrahydroisoquinoline-1'-yl-3-propionic acid
H-•^{4}-DiHOic-OH	(2'S, 3'aS, 7'aS)-1'-Octahydro-1H-indole-2'-yl-3-propionic acid
H-•^{4}-DiH4AmPyrr1-OH	(2'R, 4'S)-4'-Amino-pyrrolidine-2'-yl-3-propionic acid
H-•^{4}-DiH4AmPyrr2-OH	(2'R, 4'R)-4'-Amino-pyrrolidine-2'-yl-3-propionic acid
H-•^{4}-DiH4PhePyrr1-OH	(2'R, 4'R)-4'-Phenyl-pyrrolidine-2'-yl-3-propionic acid
H-•^{4}-DiH4PhePyrr2-OH	(2'R, 4'S)-4'-Phenyl-pyrrolidine-2'-yl-3-propionic acid
H-•^{4}-DiH5PhePyrr1-OH	(2'S, 5'R)-5'-Phenyl-pyrrolidine-2'-yl-3-propionic acid
H-•^{4}-DiH5PhePyrr2-OH	(2'S, 5'S)-5'-Phenyl-pyrrolidine-2'-yl-3-propionic acid

Code	Chemical Name
H-•^{4}-DiH4Hyp1-OH	(2'R, 4'S)-4'-Hydroxy-pyrrolidine-2'-yl-2-propionic acid
H-•^{4}-DiH4Hyp2-OH	(2'R, 4'R)-4'-Hydroxy-pyrrolidine-2'-yl-3-propionic acid
H-•^{4}-DiH4Mp1-OH	(2'R, 4'S)-4'-Mercapto-pyrrolidine-2'-yl-3-propionic acid
H-•^{4}-DiH4Mp2-OH	(2'R, 4'R)-4'-Mercapto-pyrrolidine-2'-yl-3-propionic acid
H-•^{4}-DiHPip-OH	(2'S)-Piperidine-2'-yl-3-propionic acid
H-•^{4}-DiHPro-OH	(2'S)-Pyrrolidine-2'-yl-3-propionic acid
(AEt)G	N-(2-Aminoethyl)glycine
(APr)G	N-(3-Amino-n-propyl)glycine
(ABu)G	N-(4-Amino-n-butyl)glycine
(APe)G	N-(5-Amino-n-pentyl)glycine
(GuEt)G	N-(2-Guanidinoethyl)glycine
(GuPr)G	N-(3-Guanidino-n-propyl)glycine
(GuBu)G	N-(4-Guanidino-n-butyl)glycine
(GuPe)G	N-(5-Guanidino-n-pentyl)glycine
(PEG$_3$-NH$_2$)G	N-[H$_2$N-(CH$_2$)$_3$-(OCH$_2$-CH$_2$)$_2$-O(CH$_2$)$_3$]glycine
(Me)G	N-Methylglycine
(Et)G	N-Ethylglycine
(Bu)G	N-Butylglycine
(Pe)G	N-Pentylglycine
(Ip)G	N-Isopropylglycine
(2MePr)G	N-(2-Methylpropyl)glycine
(3MeBu)G	N-(3-Methylbutyl)glycine
(1MePr)G	(1S)-N-(1-Methylpropyl)glycine
(2MeBu)G	(2S)-N-(2-Methylbutyl)glycine
(MthEt)G	N-(Methylthioethyl)glycine
(MthPr)G	N-(Methylthiopropyl)glycine
(Ben)G	N-(Benzyl)glycine
(PhEt)G	N-(2-Phenylethyl)glycine
(HphMe)G	N-([4'-hydroxyphenyl]methyl)glycine
(HphEt)G	N-(2-[4'-hydroxyphenyl]ethyl)glycine
(ImMe)G	N-(Imidazol-5-yl-methyl)glycine
(ImEt)G	N-(2-(Imidazol-5'-yl)ethyl)glycine
(InMe)G	N-(Indol-2-yl-methyl)glycine
(InEt)G	N-(2-(Indol-2'-yl)ethyl)glycine
(CboMe)G	N-(Carboxymethyl)glycine
(CboEt)G	N-(2-Carboxyethyl)glycine
(CboPr)G	N-(3-Carboxypropyl)glycine

Code	Chemical Name
(CbaMe)G	N-(Carbamoylmethyl)glycine
(CbaEt)G	N-(2-Carbamoylethyl)glycine
(CbaPr)G	N-(3-Carbamoylpropyl)glycine
(HyEt)G	N-(2-Hydroxyethyl)glycine
(HyPr)G	(2R)-N-(2-Hydroxypropyl)glycine
(Mcet)G	N-(2-Mercaptoethyl)glycine
NMeAla	L-N-Methylalanine
NMe^{D}Ala	D-N-Methylalanine
NMeVal	L-N-Methylvaline
NMe^{D}Val	D-N-Methylvaline
NMeIle	L-N-Methylisoleucine
NMe^{D}Ile	D-N-Methylisoleucine
NMeLeu	L-N-Methylleucine
NMe^{D}Leu	D-N-Methylleucine
NMeNle	L-N-Methylnorleucine
NMe^{D}Nle	D-N-Methylnorleucine
NMeMet	L-N-Methylmethionine
NMe^{D}Met	D-N-Methylmethionine
NMeTyr	L-N-Methyltyrosine
NMe^{D}Tyr	D-N-Methyltyrosine
NMeHis	L-N-Methylhistidine
NMe^{D}His	D-N-Methylhistidine
NMePhe	L-N-Methylphenylalanine
NMe^{D}Phe	D-N-Methylphenylalanine
NMeTrp	L-N-Methyltryptophane
NMe^{D}Trp	D-N-Methyltryptophane
NMeSer	L-N-Methylserine
NMe^{D}Ser	D-N-Methylserine
NMeAsp	L-N-Methylaspartic acid
NMe^{D}Asp	D-N-Methylaspartic acid
NMeGlu	L-N-Methylglutamic acid
NMe^{D}Glu	D-N-Methylglutamic acid
NMeLys	L-N-Methyllysine
NMe^{D}Lys	D-N-Methyllysine
NMeArg	L-N-Methylarginine
NMe^{D}Arg	D-N-Methylarginine
NMeDab	L-N-Methyl-2,4-diamino butyric acid

Code	Chemical Name
NMe^{D}Dab	D-N-Methyl-2,4-diamino butyric acid
NMeCys	L-N-Methylcysteine
NMe^{D}Cys	D-N-Methylcysteine
NMeAsn	L-N-Methylasparagine
NMe^{D}Asn	D-N-Methylasparagine
NMeGln	L-N-Methylglutamine
NMe^{D}Gln	D-N-Methylglutamine
NMeThr	L-N-Methylthreonine
NMe^{D}Thr	D-N-Methylthreonine

6. Compounds according to claim 1, selected from: (2S,11S,19aS)-2-(acetylamino)-15-fluoro-N-[2-(1H-indol-3-yl)ethyl]-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide; (2S,11S,19aS)-N-[2-(dimethylamino)ethyl]-15-fluoro-2-{[2-(1H-indol-3-yl)acetyl]amino}-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide; (2S,11S,19aS)-15-fluoro-2-{[2-(1H-indol-3-yl)acetyl]amino}-N-[2-(1H-indol-3-yl)ethyl]-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide; (2S,11S,19aS)-2-{[2-(dimethylamino)acetyl]amino}-15-fluoro-N-[2-(1H-indol-3-yl)ethyl]-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide; tert-butyl N-[(2S,11S,19aS)-15-fluoro-11-({[2-(1H-indol-3-yl)ethyl]amino}carbonyl)-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]carbamate; (2S,11S,19aS)-N-[2-(dimethylamino)ethyl]-15-fluoro-7,12-dimethyl-2-{[2-(1-naphthyl)acetyl]amino}-5,8,13-

trioxo-
2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide; benzyl N-[(4S,6S,10S)-14-methyl-6-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.0~4,8~]icosa-1(20),16,18-trien-10-yl]carbamate; benzyl N-[(4S,6S,13S)-6-{[2-(1H-indol-3-yl)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.0~4,8~]henicosa-1(21),17,19-trien-13-yl]carbamat; N-[(4S,6S,13S)-6-{[2-(1H-indol-3-yl)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.0~4,8~]henicosa-1(21),17,19-trien-13-yl]decanamide.

7. Compounds according to any one of claims 1-6 for use as therapeutically active substances.

8. Compounds according to claim 7 for use as therapeutically active substances having agonistic or antagonistic activity on the motilin receptor (MR receptor), on the serotonin receptor of subtype 5-HT_{2B} (5-HT_{2B} receptor), and on the prostaglandin F2• receptor (FP receptor).

9. A pharmaceutical composition containing a compound according to any one of claims 1-6 and a therapeutically inert carrier.

10. A composition according to claim 9 having agonistic or antagonistic activity on the motilin receptor (MR receptor), on the serotonin receptor of subtype 5-HT_{2B} (5-HT_{2B} receptor), and on the prostaglandin F2• receptor (FP receptor).

11. A composition according to claim 9 or 10 in a form suitable for oral, topical, transdermal, injection, buccal, transmucosal, pulmonary or inhalation administration.

12. Compositions according to claim 11 in form of tablets, dragees, capsules, solutions, liquids, gels, plaster, creams, ointments, syrup, slurries, suspensions, spray, nebuliser or suppositories.

13. The use of compounds according to any one of claims 1-6 for the manufacture of a medicament having agonistic or antagonistic activity on the motilin receptor (MR receptor), on the serotonin receptor of subtype 5-HT_{2B} (5-HT_{2B} receptor), and on the prostaglandin F2• receptor (FP receptor).

14. The use according to claim 13 wherein said medicament is intended for the treatment of hypomotility disorders of the gastrointestinal tract such as diabetic gastroparesis and constipation type irritable bowl syndrome; for the treatment of CNS related diseases like migraine, schizophrenia, psychosis or depression; for the treatment of ocular hypertension such as associated with glaucoma and preterm labour.

15. The use of compounds according to anyone of claims 1-5 for pharmaceutical lead finding.