

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 (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 into well-defined spatial orientation. 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 semi-rigid scaffolds 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**).

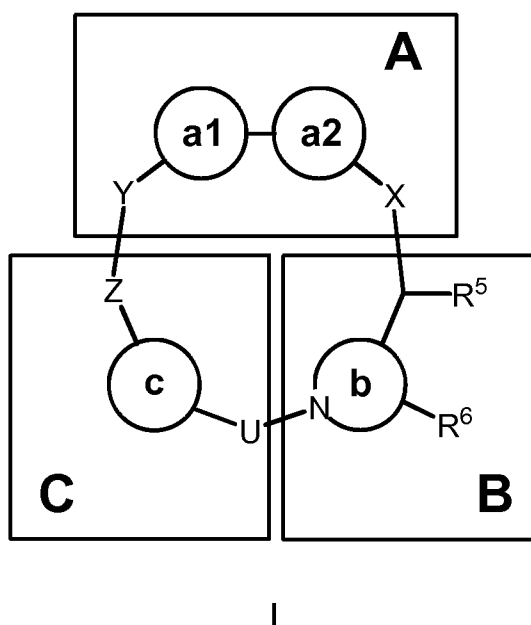
Macrocyclic natural and synthetic products are generally classified according to the chemical nature of the backbone, e.g. cyclic peptides (Y. Hamady, T. Shioiri, *Chem. Rev.* **2005**, *105*, 4441-4482; N.-H. Tan, J. Zhou, *Chem. Rev.* **2006**, *106*, 840-895); cyclic depsipeptides (F. Sarabia, S. Chammaa, A. S. Ruiz, L. M. Ortiz, F. J. Herrera, *Curr. Med. Chem.* **2004**, *11*, 1309-1332); macrocyclic lactones (macrolactones) and macrolides; macrocyclic lactams (macrolactams), 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 created a virtually unlimited repertoire of molecular diversity. Despite their

undisputed interesting biological properties, many natural products show limitations for drug development, such as low metabolic stability, i.e. short half lives, lack of or insufficient oral bioavailability as well as low tissue penetration and membrane permeability which renders them not amenable for intracellular targets. In addition, their high structural complexity imposes severe limitations to synthetic accessibility, often leaving fermentation or recombinant methods as sole options; thus making complex quality control and development processes necessary and leading to high production costs.

- 10 The present invention describes novel, fully synthetic, macrocyclic natural product-like molecules of type I (Scheme 1), accessible through a modular approach by connecting suitably protected building blocks **A**, **B** and **C** to a linear precursor followed by subsequent intramolecular cyclization.

Building blocks **A** serve as conformation-inducing templates ("Template") and are based on appropriately substituted and protected divalent biaryl-derivatives. Biaryl as used in this context shall comprise all possible pairwise combinations of aromatic carbocyclic and/or aromatic heterocyclic ring systems connected by a $C_{sp^2}-C_{sp^2}$ single bond, i.e. aryl-aryl, heteroaryl-heteroaryl, aryl-heteroaryl and heteroaryl-aryl.

- 20 **Scheme 1: Macrocycles of Type I**

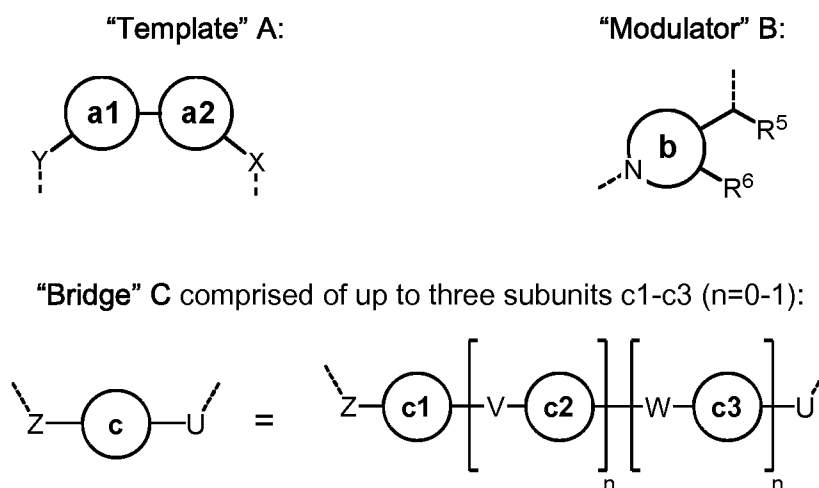


Building blocks **B** are corresponding to appropriately substituted and protected primary, secondary or tertiary aminoalcohols and are functioning as conformational

modulators ("Modulator") by influencing the conformation of the macrocycle, e.g. through *cis/trans*-isomerization of amides.

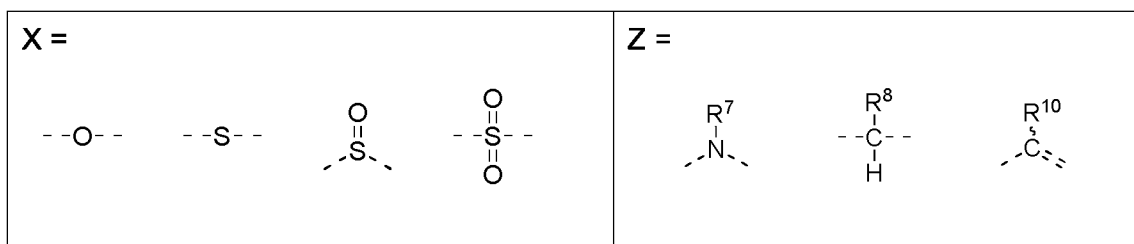
- 5 Within the macrocycles backbone of I the building blocks **A** and **B** are connected via the "Bridge" **C** composed of one to three appropriately and independently substituted subunits **c1**, **c2** and **c3**, which in turn are derived from suitably substituted and protected precursors, like, but not limited to, appropriately substituted and protected amino acids or amine derivatives.

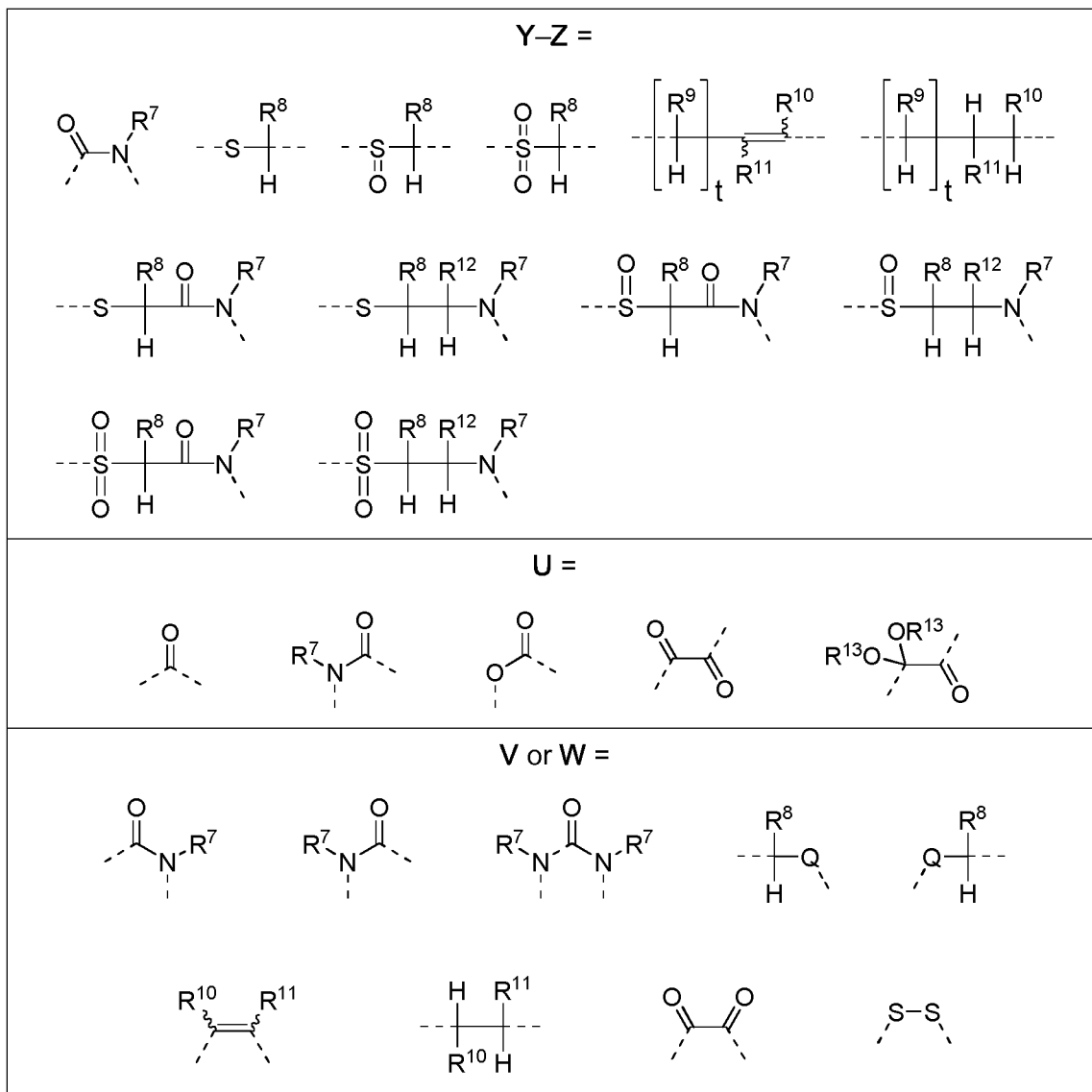
10 **Scheme 2: Building Blocks of Macrocycle I**



- The connectivity $-X-$ between Template **A** and Modulator **B** is defined by an ether ($X=O$) or thioether ($X=S$) bond; while that between **A** and Bridge **C** is defined by the structural element $-Y-Z-$ as detailed below. As sulfur atoms of such a thioether linkage can easily and selectively be oxidized to the corresponding sulfoxides ($S=O$) or sulfones ($S(=O)_2$), these higher oxidation states are also part of the invention.
- 15

Scheme 3: Connectivities of Macrocycle I (*continued on the following page*)





- The generic connection -Y-Z- between **A** and **C** corresponds in most exemplified cases to a secondary or tertiary amide bond (-C(=O)-NR⁷-). Alternative connectivities -Y-Z- are thioethers (-S-CHR⁸-) and its oxidation products, i.e. sulfoxides (-S(=O)-CHR⁸-) or sulfones (-S(=O)₂-CHR⁸-), as well as olefinic moieties (-CH(R⁹)_t-CR¹¹=CR¹⁰-) and their reduced aliphatic analogs (-CH(R⁹)_t-CH(R¹¹)-CH(R¹⁰)-). Furthermore, in case of Templates **A** carrying a thiophenolic Y-group (Y=S) an additional two carbon spacer can be easily introduced by reacting with β-halo carboxyl or β-halo carbonyl compounds prior to processing with the **C** building blocks; thus providing access to -Y-Z- groups of type -S-CHR⁸-C(=O)-NR⁷-, -S-CHR⁸-CH(R¹²)-NR⁷-, -S-CHR⁸-CH(R¹²)-NR⁷- and their corresponding S-oxidized congeners.

The functional moiety **U** connects Bridge **C** with the nitrogen atom of Modulator **B**. In most cases this is realized by an amide bond, in which case the moiety **U** corresponds to a carbonyl group ($-\text{C}(=\text{O})-$). Alternatively, **U** can be defined as a carbamoyl moiety ($-\text{NR}^7-\text{C}(=\text{O})-$) leading to a urea (including the *N*-atom of **B**) as functional connection between **B** and **C**. Similarly, a carboxyl group ($-\text{O}-\text{C}(=\text{O})-$) as **U** describes a carbamate linkage between **B** and **C**. In addition, **U** can represent an oxalyl group ($-\text{C}(=\text{O})-\text{C}(=\text{O})-$) or the corresponding acetal ($-\text{C}(\text{OR}^{13})_2-\text{C}(=\text{O})-$).

As mentioned before, the Bridge **C** itself comprises one to three (1-3) appropriately and independently substituted subunits **c1**, **c2** and **c3**, which in turn are independently connected to each other by the generic groups **V** or **W** which can correspond to an amide bond ($-\text{C}(=\text{O})\text{NR}^7-$) and the corresponding inverse amide ($-\text{NR}^7\text{C}(=\text{O})-$), the methylene-heteroatom linkages $-\text{CHR}^8-\text{Q}-$ and $-\text{Q}-\text{CHR}^8-$, an alkene[1,2]diyl moiety ($-\text{CHR}^{10}=\text{CHR}^{11}-$) or its reduced form as alkane[1,2]diyl ($-\text{CHR}^{10}-\text{CHR}^{11}-$), an oxalyl group ($-\text{C}(=\text{O})-\text{C}(=\text{O})-$) or a disulfide bridge ($-\text{S}-\text{S}-$).

The spatial orientation of the substituents in macrocycles **I** is modulated by the ring size and the stereochemical connectivity within building blocks **A**, **B** and **C**. Therefore the macrocyclic backbone as well as the substituents contribute to the biological activity of compounds of type **I**.

Compounds of this invention are characterized by macrocyclic backbones containing an aromatic ether/thioether linkage and one or more tertiary amide bonds. In other cases secondary amide bonds, aliphatic ether linkages, ethylidene or ethylene moieties are exemplified as part of the backbone.

Ether linkages in macrocyclic molecules favorably influence physico-chemical and pharmacological properties, such as solubility in aqueous solutions, metabolic stability against proteolytic degradation, cell permeability and oral absorption (K. X. Chen et al., *J. Med. Chem.* **2006**, *49*, 995-1005). In addition, tertiary amide bonds containing macrocycles are well-known for 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 instance, 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).

- 5 A well documented process in protein folding events is the peptidyl *cis/trans* isomerization of proline or pipecolic acid containing polypeptides and proteins. *In vivo* this process is 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
- 10 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. In the context of this invention it is worth mentioning that both FK506 and cyclosporin A are macrocyclic natural products interacting with the FK506-binding protein and cyclophilins, respectively.

15

- An interesting structural motif found in several natural products consist of a macrocyclic ring sytem with a biaryl moiety as backbone element. Such biaryls, which are composed of two aromatic or heteroaromatic rings connected via a single bond, are the outstanding characteristic of a number of antibacterial macrocyclic peptide
- 20 classes, like the biphenomycins, arylomycins and aciculitins; not to mention the glycopeptide antibiotics with the vancomycins as most prominent representatives (L. Feliu, M. Planas, *Int. J. Pept. Res. Ther.* **2005**, *11*, 53-97).

- For many extra- and intracellular biological targets the quest for small molecule hits
- 25 has been disappointing; this is especially true if protein-protein interactions are involved (J. A. Robinson, S. DeMarco, F. Gombert, K. Moehle, D. Obrecht, *Drug Disc. Today* **2008**, *13*, 944-951). These so-called "difficult targets" include e.g. receptor tyrosine kinases, growth factor receptors, transcription modulators, and chaperones. Interestingly, several natural and synthetic macrocyclic compounds have
- 30 been described as promising starting points for drug discovery programs around such difficult targets (D. Obrecht, J. A. Robinson, F. Bernardini, C. Bisang, S. J. DeMarco, K. Moehle, F. O. Gombert, *Curr. Med. Chem.* **2009**, *16*, 42-65).

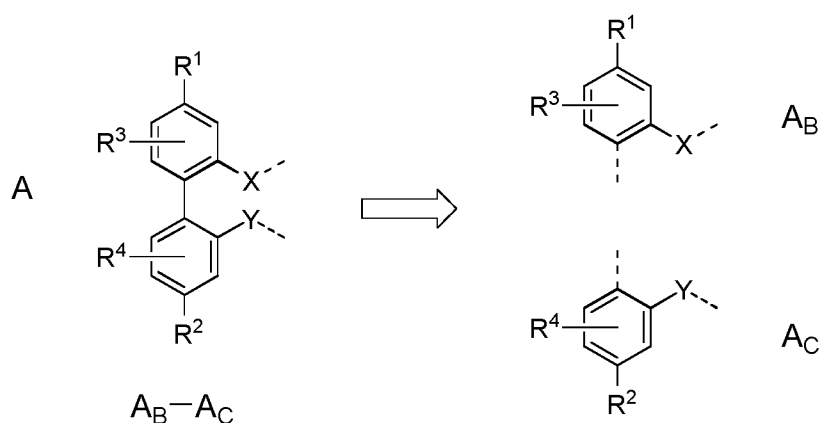
- The novel macrocycles of type I described in the embodiments of this invention are
- 35 designed to combine unique features of natural macrocyclic compounds with beneficial physico-chemical and pharmacological properties of small molecules, e.g.:

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

The **Main Embodiment** of the current invention of novel and fully synthetic
15 macrocyclic compounds I according Scheme 1 (detailed in Scheme 2 and Scheme 3)
is defined by groups of selected building blocks **A**, **B** and **C** as shown in Table 1 to
Table 3 and by the appending substituents R¹-R⁵⁷ as detailed below.

As shortly indicated before, **Template A** exerts an important conformational constraint
20 on products of type I. These structural effects of **A** depend on (i) the dihedral angle
between the two C_{sp}²-C_{sp}² connected aromatic rings **A_B** and **A_C** that are defining the
Template A entity; (ii) the relative orientation of the attachment vectors of -X- and
-Y- and (iii) the spatial distance between the groups -X- and -Y-.

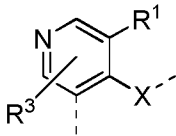
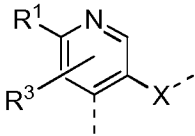
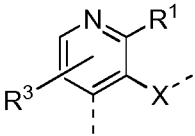
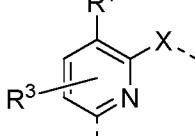
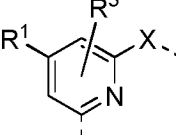
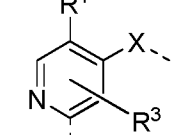
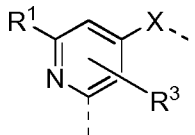
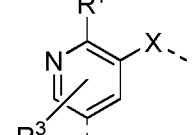
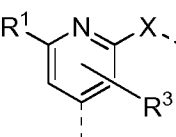
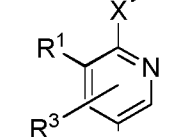
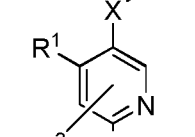
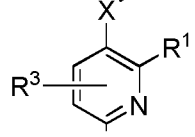
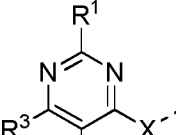
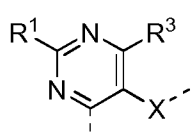
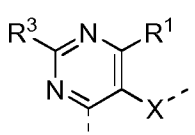
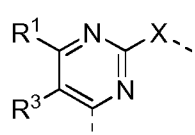
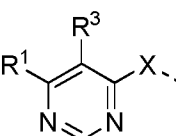
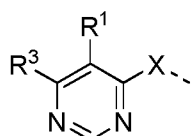
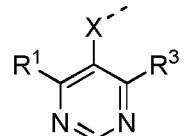
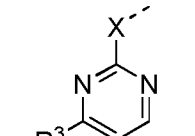
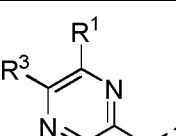
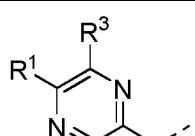
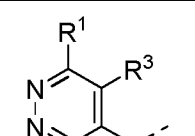
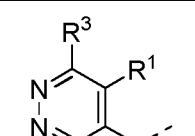
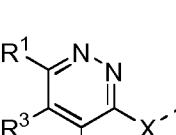
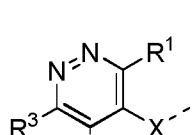
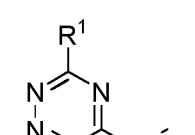
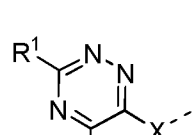
One possible general preparative access to the corresponding building blocks of type
25 **A** consists of an C_{sp}²-C_{sp}²-coupling between appropriately functionalized arene
and/or heteroarenes (R. M. Kellogg et al., *Org. Process Res. Dev.* **2010**, *14*, 30-47; A.
de Meijere, F. Diederich (eds), *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.,
Wiley-VCH **2004**; especially for macrocyclic biaryls cf. Q. Wang, J. Zhu, *Chimia* **2011**,
65, 168-174, and literature cited therein). Therefore the template **A** can be described
30 by its two aryl/ heteroaryl constituents **A_B** and **A_C**, wherein **A_B** is defined as that
structural half of **A** that is directly connected with building block **B** and **A_C** as that half
that is directly bound to building block **C**. In case of a biphenyl derivative as Template
A such disconnection can be illustrated e.g. as:

Scheme 4: Dissection of Template **A** into its constituents **A_B** and **A_C**

In general, Template **A** of this invention is a divalent radical that is defined by the
 5 combinatorial connection of its two constituent aryl/heteroaryl moieties **A_B** and **A_C**
 selected from Table 1 and Table 2.

Table 1: Constituents **A_B1-A_B65** of Template **A** (continued on the following pages)

A_B1	A_B2	A_B3	A_B4
A_B5	A_B6	A_B7	A_B8
A_B9	A_B10	A_B11	A_B12

 AB13	 AB14	 AB15	 AB16
 AB17	 AB18	 AB19	 AB20
 AB21	 AB22	 AB23	 AB24
 AB25	 AB26	 AB27	 AB28
 AB29	 AB30	 AB31	 AB32
 AB33	 AB34	 AB35	 AB36
 AB37	 AB38	 AB39	 AB40

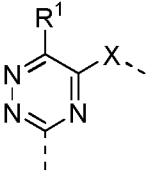
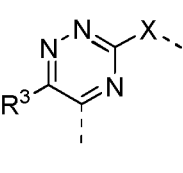
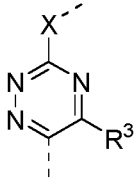
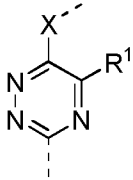
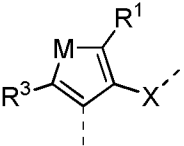
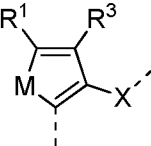
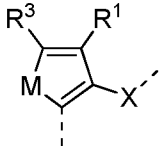
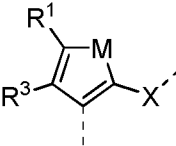
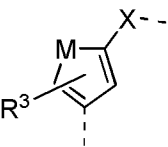
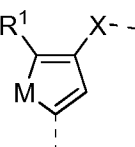
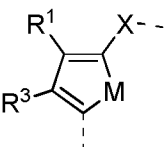
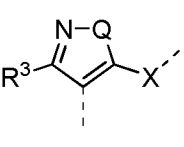
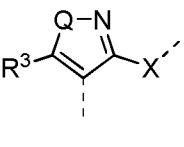
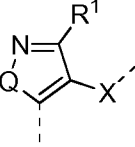
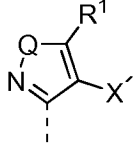
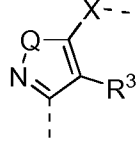
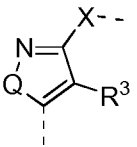
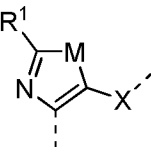
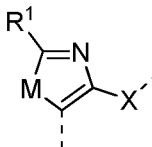
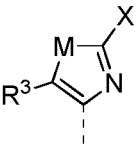
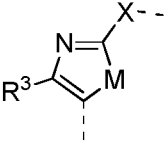
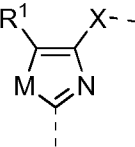
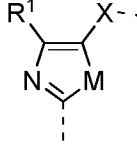
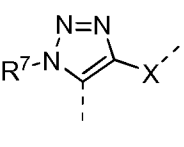
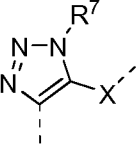
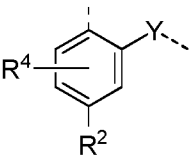
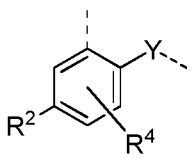
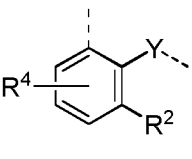
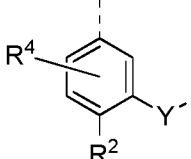
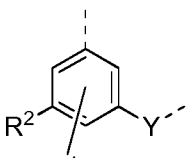
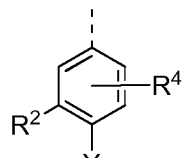
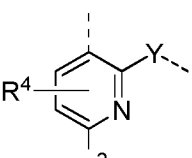
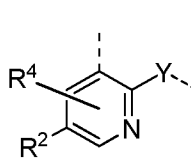
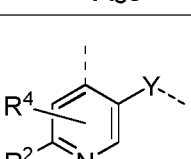
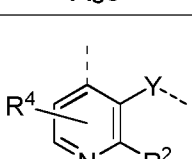
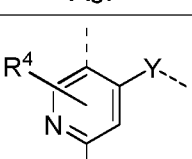
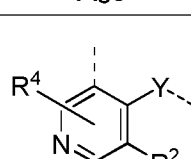
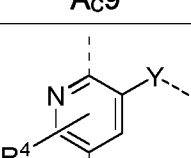
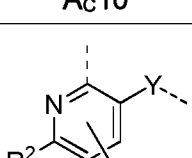
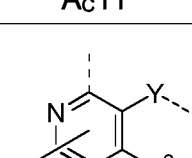
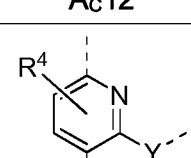
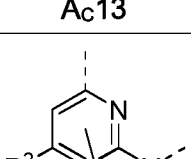
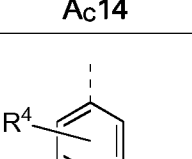
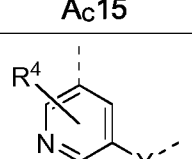
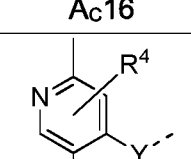
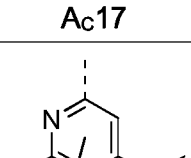
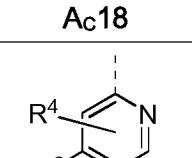
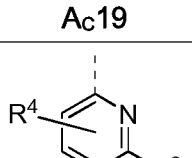
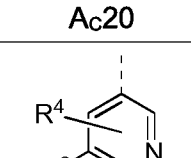
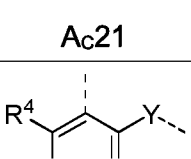
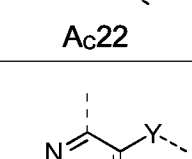
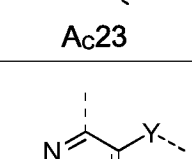
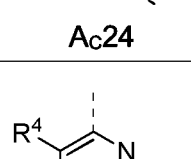
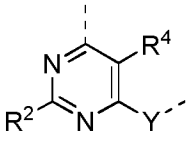
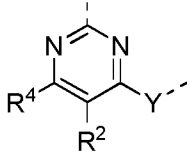
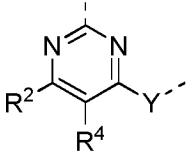
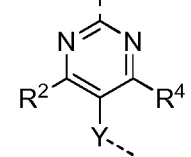
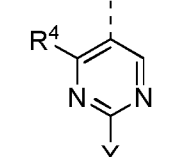
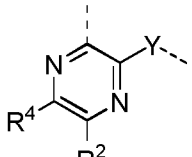
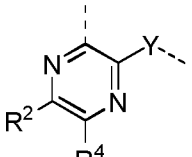
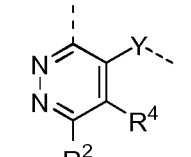
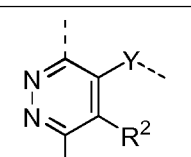
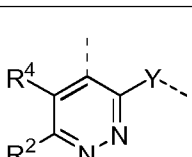
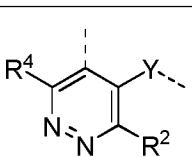
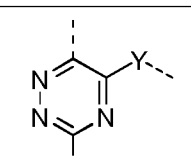
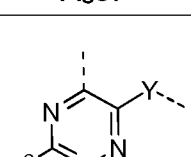
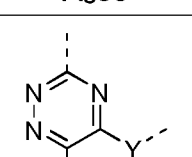
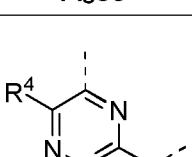
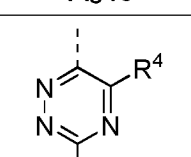
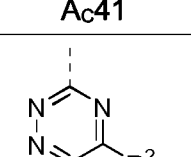
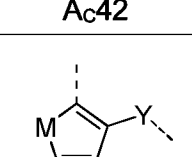
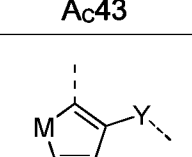
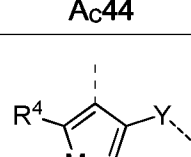
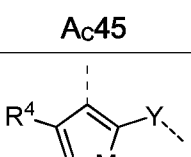
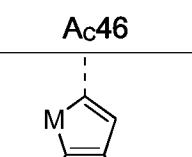
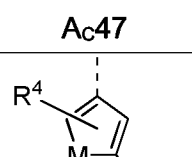
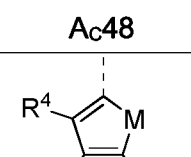
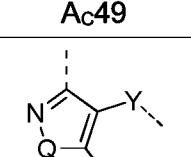
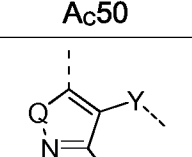
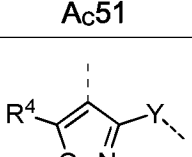
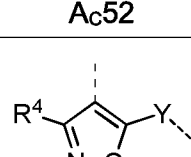
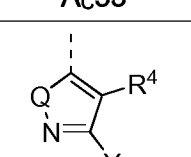
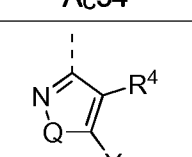
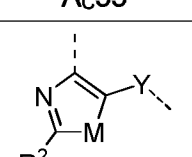
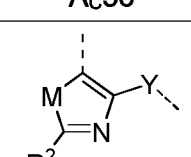
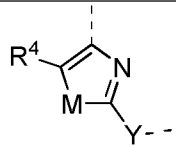
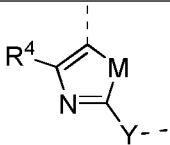
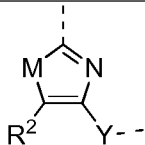
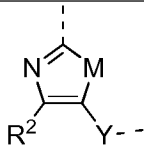
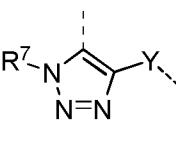
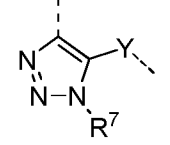
 A_B41	 A_B42	 A_B43	 A_B44
 A_B45	 A_B46	 A_B47	 A_B48
 A_B49	 A_B50	 A_B51	 A_B52
 A_B53	 A_B54	 A_B55	 A_B56
 A_B57	 A_B58	 A_B59	 A_B60
 A_B61	 A_B62	 A_B63	 A_B64
 A_B65			

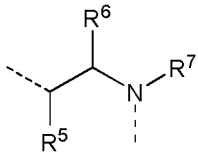
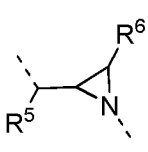
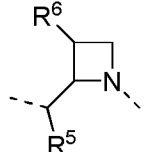
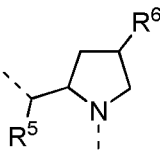
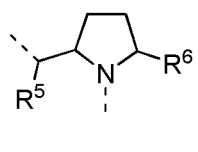
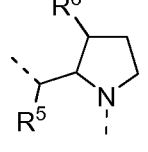
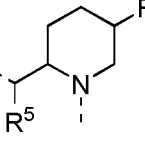
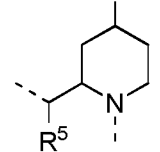
Table 2: Constituents Ac1-Ac66 of Template A (continued on the following pages)

 Ac1	 Ac2	 Ac3	 Ac4
 Ac5	 Ac6	 Ac7	 Ac8
 Ac9	 Ac10	 Ac11	 Ac12
 Ac13	 Ac14	 Ac15	 Ac16
 Ac17	 Ac18	 Ac19	 Ac20
 Ac21	 Ac22	 Ac23	 Ac24
 Ac25	 Ac26	 Ac27	 Ac28

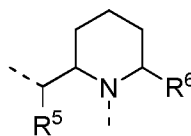
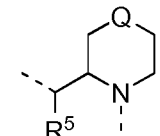
 Ac29	 Ac30	 Ac31	 Ac32
 Ac33	 Ac34	 Ac35	 Ac36
 Ac37	 Ac38	 Ac39	 Ac40
 Ac41	 Ac42	 Ac43	 Ac44
 Ac45	 Ac46	 Ac47	 Ac48
 Ac49	 Ac50	 Ac51	 Ac52
 Ac53	 Ac54	 Ac55	 Ac56
 Ac57	 Ac58	 Ac59	 Ac60

 Ac61	 Ac62	 Ac63	 Ac64
 Ac65	 Ac66		

- The **Modulator B** is a divalent radical selected from the groups of Table 3. **B1-B10** are optionally substituted primary or secondary amines carrying a moiety of type $-\text{CHR}^5-\text{LG}$, wherein LG is a suitable leaving group that can be replaced by the nucleophilic groups on Template **A** forming an ether ($-\text{O}-$) or a thioether ($-\text{S}-$) linkage (as well as its oxidized variations $-\text{S}(=\text{O})-$ and $-\text{S}(=\text{O})_2-$) between building blocks of type **A** and **B**. Examples of appropriate LGs include $-\text{OH}$, which is *in situ* transformed into the active LG during Mitsunobu reactions, or halogens, like $-\text{Br}$ or $-\text{I}$, which are amenable to S_N reactions.
- For most examples of this invention, the amine nitrogen of Modulator **B** forms a secondary or tertiary amide bond with the carboxyl group of the Bridge **C**. By virtue of inducing peptidyl *cis-trans* isomerizations or stabilizing *cis* amide bonds, building blocks of type **B** can function as conformational modulators in macrocycles of type I.
- Table 3: Radicals B1-B10 (continued on the following page)**

 B1	 B2	 B3	 B4
 B5	 B6	 B7	 B8

14

 B9	 B10		
--	---	--	--

The **Bridge C** is a divalent radical selected from the groups of Table 4. This divalent moiety **C** may consist of one to three (1-3) subunits **c1** to **c3**, i.e. (i) $-Z-c1-U-$, (ii) $-Z-c1-V-c2-U-$ and (iii) $-X-c1-V-c2-W-c3-U-$. As a consequence Bridge **C** directly influences the ring size of the macrocycle and can therefore be regarded as spacer or linker. This Bridge **C** is joined to Template **A** via its terminal group Z (i.e. *N*-terminus in case of an amino acid) and to Modulator **B** via its terminal group U (i.e. *C*-terminus in case of an amino acid) to form the macrocyclic ring of type I. Thus **C** contributes to the backbone of macrocycle I with its carbon chains as well as with its functional groups Z, W, V and U (cf. Scheme 2 and 3).

Table 4: Generic Representations of Bridge **C**

$ \begin{array}{c} \begin{array}{c} R^{14} \quad [R^{16}] \quad [R^{18}] \\ \quad \quad \\ \text{---}Z-C-C-C-U\text{---} \\ \quad \quad \\ R^{15} \quad [R^{17}] \quad [R^{19}] \end{array} \\ \begin{array}{c} m \quad n \end{array} \end{array} $ C1
$ \begin{array}{c} \begin{array}{c} R^{14} \quad [R^{16}] \quad [R^{18}] \\ \quad \quad \\ \text{---}Z-C-C-C-V-C-C-C-U\text{---} \\ \quad \quad \quad \quad \quad \\ R^{15} \quad [R^{17}] \quad [R^{19}] \quad R^{20} \quad [R^{22}] \quad [R^{24}] \\ \quad \quad \quad p \quad n \quad \quad \quad p \quad n \end{array} \end{array} $ C2
$ \begin{array}{c} \begin{array}{c} R^{14} \quad [R^{16}] \quad [R^{18}] \\ \quad \quad \\ \text{---}Z-C-C-C-V-C-C-C-W-C-C-C-U\text{---} \\ \quad \quad \quad \quad \quad \quad \quad \quad \\ R^{15} \quad [R^{17}] \quad [R^{19}] \quad R^{20} \quad [R^{22}] \quad [R^{24}] \quad R^{26} \quad [R^{28}] \quad [R^{30}] \\ \quad \quad \quad p \quad n \quad \quad \quad p \quad n \quad \quad \quad p \quad n \end{array} \end{array} $ C3

According to the preceding definitions, macrocycles I contain at least one amide bond or isosteric surrogate thereof. As emphasized in the introduction, tertiary amides generally show various ratios of *cis* and *trans* conformations in solution. In striking

contrast secondary amides strongly prefer *trans* conformations. Such occurrence of *cis* and/or *trans* conformations in macrocyclic natural products containing tertiary amide groups is well documented. In some cases a rapid equilibration by 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. Consequently all possible stereoisomers, explicitly including atropisomers, conformers or rotamers of macrocycles of type I are part of this invention.

The substituents attached to the Main Embodiment of macrocycle I or its constituents A, B or C, are defined as follows:

R¹ and R² are independently defined as H; F; Cl; Br; I; CF₃; OCF₃; OCHF₂; NO₂; CN; C₁₋₂₄-alkyl; C₂₋₂₄-alkenyl; C₂₋₁₀-alkynyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl-C₁₋₁₂-alkyl; heteroaryl-C₁₋₁₂-alkyl; $-(CR^{32}R^{33})_qOR^{34}$; $-(CR^{32}R^{33})_qSR^{34}$; $-(CR^{32}R^{33})_qNR^7R^{35}$; $-(CR^{32}R^{33})_qOCONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7COOR^{36}$; $-(CR^{32}R^{33})_qNR^7COR^{37}$; $-(CR^{32}R^{33})_qNR^7CONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7SO_2R^{38}$; $-(CR^{32}R^{33})_qNR^7SO_2NR^7R^{35}$; $-(CR^{32}R^{33})_qCOOR^{36}$; $-(CR^{32}R^{33})_qCONR^7R^{35}$; $-(CR^{32}R^{33})_qSO_2NR^7R^{35}$; $-(CR^{32}R^{33})_qCOR^{37}$; $-(CR^{32}R^{33})_qSO_2R^{38}$; $-(CR^{32}R^{33})_qR^{39}$; $-(CR^{32}R^{33})_qR^{40}$; $-(CR^{32}R^{33})_qR^{41}$; or $-(CR^{32}R^{33})_qR^{44}$;

20

R³ and R⁴ are independently defined as H; F; Cl; CF₃; OCF₃; OCHF₂; NO₂; CN; C₁₋₂₄-alkyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl-C₁₋₁₂-alkyl; heteroaryl-C₁₋₁₂-alkyl; C₁₋₁₂-alkoxy or aryloxy;

R⁵ is H; CF₃; C₁₋₂₄-alkyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl-C₁₋₁₂-alkyl; or heteroaryl-C₁₋₁₂-alkyl;

R⁶ is H; CF₃; C₁₋₂₄-alkyl; C₂₋₂₄-alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl-C₁₋₁₂-alkyl; heteroaryl-C₁₋₁₂-alkyl; $-(CR^{32}R^{33})_qOR^{34}$; $-(CR^{32}R^{33})_qSR^{34}$; $-(CR^{32}R^{33})_qNR^7R^{35}$; $-(CR^{32}R^{33})_qOCONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7COOR^{36}$; $-(CR^{32}R^{33})_qNR^7COR^{37}$; $-(CR^{32}R^{33})_qNR^7CONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7SO_2R^{38}$; $-(CR^{32}R^{33})_qNR^7SO_2NR^7R^{35}$; $-(CR^{32}R^{33})_qCOOR^{36}$; $-(CR^{32}R^{33})_qCONR^7R^{35}$; $-(CR^{32}R^{33})_qSO_2NR^7R^{35}$; $-(CR^{32}R^{33})_qCOR^{37}$; $-(CR^{32}R^{33})_qSO_2R^{38}$; $-(CR^{32}R^{33})_qR^{39}$; $-(CR^{32}R^{33})_sR^{40}$; or $-(CR^{32}R^{33})_qR^{41}$; or $-(CR^{32}R^{33})_qR^{44}$;

35

R⁷ is H; C₁₋₂₄-alkyl; C₂₋₂₄-alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl-C₁₋₁₂-alkyl; heteroaryl-C₁₋₁₂-alkyl; or an *N*-protecting group;

R⁸ and R⁹ are independently defined as H; F; CF₃; C₁₋₂₄-alkyl; C₂₋₂₄-alkenyl;
5 cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl-C₁₋₁₂-alkyl; or heteroaryl-C₁₋₁₂-alkyl;

R¹⁰, R¹¹ and R¹² are independently defined as H; C₁₋₂₄-alkyl; or cycloalkyl;

R¹³ is C₁₋₂₄-alkyl or cycloalkyl;
10

R¹⁴, R²⁰ and R²⁶ are independently defined as H; F; CF₃; C₁₋₂₄-alkyl; C₂₋₂₄-alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl-C₁₋₁₂-alkyl; heteroaryl-C₁₋₁₂-alkyl; $-(CR^{32}R^{33})_qOR^{34}$; $-(CR^{32}R^{33})_qSR^{34}$; $-(CR^{32}R^{33})_qNR^7R^{35}$; $-(CR^{32}R^{33})_qOCONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7COOR^{36}$; $-(CR^{32}R^{33})_qNR^7COR^{37}$;
15 $-(CR^{32}R^{33})_qNR^7CONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7SO_2R^{38}$; $-(CR^{32}R^{33})_qNR^7SO_2NR^7R^{35}$; $-(CR^{32}R^{33})_qCOOR^{36}$; $-(CR^{32}R^{33})_qCONR^7R^{35}$; $-(CR^{32}R^{33})_qSO_2NR^7R^{35}$; $-(CR^{32}R^{33})_qCOR^{37}$; $-(CR^{32}R^{33})_qSO_2R^{38}$; $-(CR^{32}R^{33})_qR^{39}$; $-(CR^{32}R^{33})_sR^{40}$; $-(CR^{32}R^{33})_qR^{41}$; or $-(CR^{32}R^{33})_qR^{44}$;

R¹⁵, R¹⁷, R¹⁹, R²¹, R²³, R²⁵, R²⁷, R²⁹ and R³¹ are independently defined as H; C₁₋₂₄-alkyl; cycloalkyl; or heterocycloalkyl;
20

R¹⁶, R²² and R²⁸ are independently defined as H; CF₃; C₁₋₂₄-alkyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl-C₁₋₁₂-alkyl; or heteroaryl-C₁₋₁₂-alkyl;
25

R¹⁸, R²⁴ and R³⁰ are independently defined as H; F; CF₃; C₁₋₂₄-alkyl; C₂₋₂₄-alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl-C₁₋₁₂-alkyl; heteroaryl-C₁₋₁₂-alkyl; $-(CR^{32}R^{33})_qOR^{34}$; $-(CR^{32}R^{33})_qNR^7R^{35}$; $-(CR^{32}R^{33})_qOCONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7COOR^{36}$; $-(CR^{32}R^{33})_qNR^7COR^{37}$; $-(CR^{32}R^{33})_qNR^7CONR^7R^{35}$;
30 $-(CR^{32}R^{33})_qNR^7SO_2R^{38}$; $-(CR^{32}R^{33})_qNR^7SO_2NR^7R^{35}$; $-(CR^{32}R^{33})_qCOOR^{36}$; $-(CR^{32}R^{33})_qCONR^7R^{35}$; $-(CR^{32}R^{33})_qSO_2NR^7R^{35}$; $-(CR^{32}R^{33})_qCOR^{37}$; or $-(CR^{32}R^{33})_qR^{44}$;

R³² is H; F; CF₃; C₁₋₂₄-alkyl; C₂₋₂₄-alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl-C₁₋₁₂-alkyl; heteroaryl-C₁₋₁₂-alkyl; $-(CR^{51}R^{53})_qOR^{45}$; $-(CR^{51}R^{53})_qSR^{45}$;
35 $-(CR^{51}R^{53})_qNR^7R^{45}$; $-(CR^{51}R^{53})_qOCONR^7R^{45}$; $-(CR^{51}R^{53})_qNR^7COOR^{36}$; $-(CR^{51}R^{53})_qNR^7COR^{37}$; $-(CR^{51}R^{53})_qNR^7CONR^7R^{45}$; $-(CR^{51}R^{53})_qNR^7SO_2R^{38}$;

$-(\text{CR}^{51}\text{R}^{53})_q\text{NR}^7\text{SO}_2\text{NR}^7\text{R}^{45}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{COOR}^{36}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{CONR}^7\text{R}^{45}$;
 $-(\text{CR}^{51}\text{R}^{53})_q\text{SO}_2\text{NR}^7\text{R}^{45}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{COR}^{37}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{SO}_2\text{R}^{38}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{R}^{39}$;
 $-(\text{CR}^{51}\text{R}^{53})_s\text{R}^{40}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{R}^{41}$; or $-(\text{CR}^{51}\text{R}^{53})_q\text{R}^{44}$;

- 5 R^{33} is H; C_{1-24} -alkyl; C_{2-24} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-12} -alkyl; or heteroaryl- C_{1-12} -alkyl;

- R^{34} is H; C_{1-24} -alkyl; C_{2-24} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl;
 aryl- C_{1-12} -alkyl; heteroaryl- C_{1-12} -alkyl; $-(\text{CR}^{51}\text{R}^{53})_r\text{OR}^{45}$; $-(\text{CR}^{51}\text{R}^{53})_r\text{NR}^7\text{R}^{45}$;
 10 $-(\text{CR}^{51}\text{R}^{53})_r\text{OCONR}^7\text{R}^{35}$; $-(\text{CR}^{51}\text{R}^{53})_r\text{NR}^7\text{COOR}^{36}$; $-(\text{CR}^{51}\text{R}^{53})_r\text{NR}^7\text{COR}^{38}$;
 $-(\text{CR}^{51}\text{R}^{53})_r\text{NR}^7\text{CONR}^7\text{R}^{45}$; $-(\text{CR}^{51}\text{R}^{53})_r\text{NR}^7\text{SO}_2\text{R}^{38}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{COOR}^{36}$;
 $-(\text{CR}^{51}\text{R}^{53})_q\text{CONR}^7\text{R}^{45}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{SO}_2\text{NR}^7\text{R}^{45}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{COR}^{38}$;
 $-(\text{CR}^{51}\text{R}^{53})_q\text{SO}_2\text{R}^{38}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{R}^{39}$; $-(\text{CR}^{51}\text{R}^{53})_s\text{R}^{40}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{R}^{41}$; or
 $-(\text{CR}^{51}\text{R}^{53})_q\text{R}^{44}$;

15

- R^{35} is H; C_{1-24} -alkyl; C_{2-24} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl;
 aryl- C_{1-12} -alkyl; heteroaryl- C_{1-12} -alkyl; an *N*-protecting group; $-(\text{CR}^{32}\text{R}^{33})_r\text{OR}^{45}$;
 $-(\text{CR}^{32}\text{R}^{33})_r\text{NR}^7\text{R}^{45}$; $-(\text{CR}^{32}\text{R}^{33})_r\text{OCONR}^7\text{R}^{45}$; $-(\text{CR}^{32}\text{R}^{33})_r\text{NR}^7\text{COOR}^{36}$;
 $-(\text{CR}^{32}\text{R}^{33})_r\text{NR}^7\text{CONR}^7\text{R}^{50}$; $-(\text{CR}^{32}\text{R}^{33})_r\text{NR}^7\text{SO}_2\text{R}^{38}$; $-(\text{CR}^{32}\text{R}^{33})_r\text{NR}^7\text{SO}_2\text{NR}^7\text{R}^{50}$;
 20 $-(\text{CR}^{32}\text{R}^{33})_q\text{COOR}^{36}$; $-(\text{CR}^{32}\text{R}^{33})_r\text{NR}^7\text{COR}^{37}$; $-(\text{CR}^{32}\text{R}^{33})_q\text{CONR}^7\text{R}^{50}$;
 $-(\text{CR}^{32}\text{R}^{33})_q\text{COR}^{37}$; $-(\text{CR}^{32}\text{R}^{33})_q\text{SO}_2\text{R}^{38}$; $-(\text{CR}^{32}\text{R}^{33})_q\text{SO}_2\text{NR}^7\text{R}^{50}$; $-(\text{CR}^{32}\text{R}^{33})_q\text{R}^{39}$;
 $-(\text{CR}^{32}\text{R}^{33})_s\text{R}^{40}$; $-(\text{CR}^{32}\text{R}^{33})_q\text{R}^{41}$; or $-(\text{CR}^{32}\text{R}^{33})_q\text{R}^{44}$;

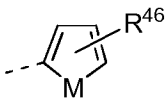
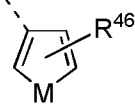
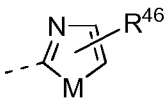
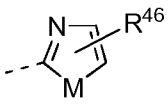
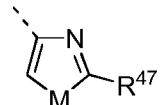
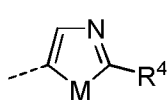
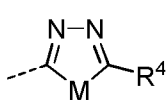
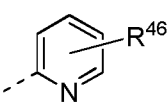
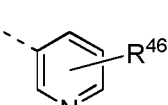
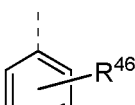
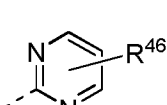
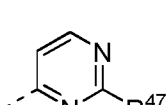
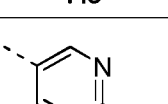
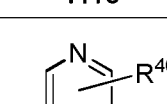
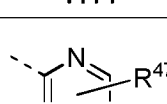
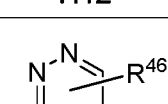
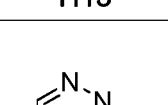
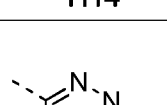
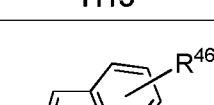
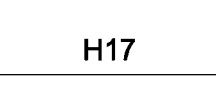
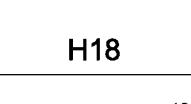
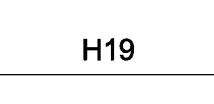
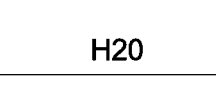
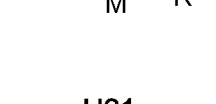
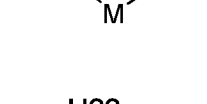
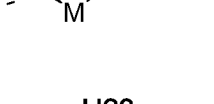
- R^{36} is H; C_{1-24} -alkyl; C_{2-24} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl;
 25 aryl- C_{1-12} -alkyl; heteroaryl- C_{1-12} -alkyl; or an *O/S*-protecting group;

- R^{37} is C_{1-24} -alkyl; C_{2-24} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl;
 aryl- C_{1-12} -alkyl; heteroaryl- C_{1-12} -alkyl; $-(\text{CR}^{51}\text{R}^{53})_q\text{OR}^{45}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{SR}^{45}$;
 $-(\text{CR}^{51}\text{R}^{53})_q\text{NR}^7\text{R}^{45}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{OCONR}^7\text{R}^{45}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{NR}^7\text{COOR}^{36}$;
 30 $-(\text{CR}^{51}\text{R}^{53})_q\text{NR}^7\text{COR}^{38}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{NR}^7\text{CONR}^7\text{R}^{45}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{NR}^7\text{SO}_2\text{R}^{38}$;
 $-(\text{CR}^{51}\text{R}^{53})_q\text{NR}^7\text{SO}_2\text{NR}^7\text{R}^{45}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{COOR}^{36}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{CONR}^7\text{R}^{45}$;
 $-(\text{CR}^{51}\text{R}^{53})_q\text{SO}_2\text{NR}^7\text{R}^{45}$; $-(\text{CR}^{51}\text{R}^{53})_t\text{COR}^{44}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{SO}_2\text{R}^{38}$; $-(\text{CR}^{51}\text{R}^{53})_t\text{R}^{39}$;
 $-(\text{CR}^{51}\text{R}^{53})_u\text{R}^{40}$; $-(\text{CR}^{51}\text{R}^{53})_t\text{R}^{41}$; or $-(\text{CR}^{51}\text{R}^{53})_t\text{R}^{44}$;

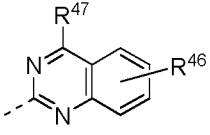
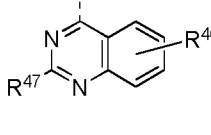
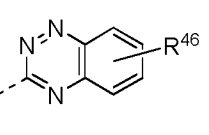
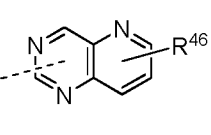
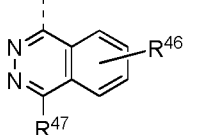
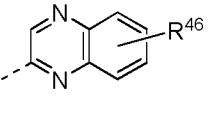
- 35 R^{38} is C_{1-24} -alkyl; C_{2-24} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl;
 aryl- C_{1-12} -alkyl; or heteroaryl- C_{1-12} -alkyl;

R^{39} is aryl; heteroaryl; $-C_6H_2R^3R^4R^{46}$; or a group of one of the formulae H1-H34 listed in Table 5.

Table 5: Groups of Formulae H1-H34 (continued on the following page)

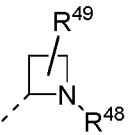
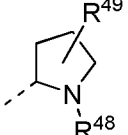
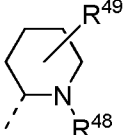
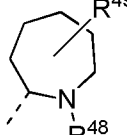
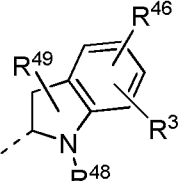
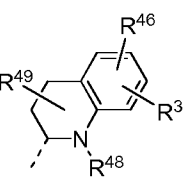
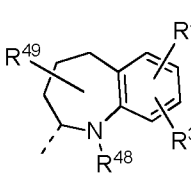
			
H1	H2	H3	H4
			
H5	H6	H7	H8
			
H9	H10	H11	H12
			
H13	H14	H15	H16
			
H17	H18	H19	H20
			
H21	H22	H23	H24
			
H25	H26	H27	H28

19

			
H29	H30	H31	H32
			
H33	H34		

R⁴⁰ is a group of one of formulae **H35-H41** as shown in Table 6 below.

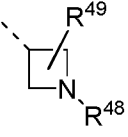
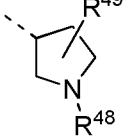
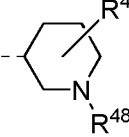
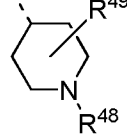
Table 6: Groups of Formulae **H35-H41**

			
H35	H36	H37	H38
			
H39	H40	H41	

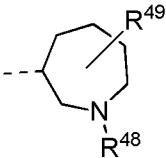
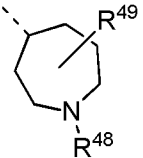
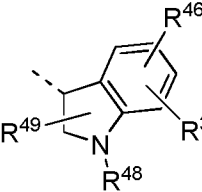
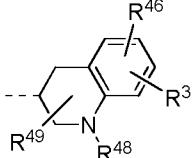
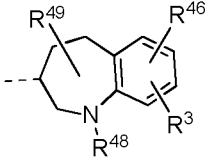
5

R⁴¹ is a group of one of formulae **H42-H50** as shown in Table 7 below.

Table 7: Groups of Formulae **H42-H50** (continued on the following page)

			
H42	H43	H44	H45

20

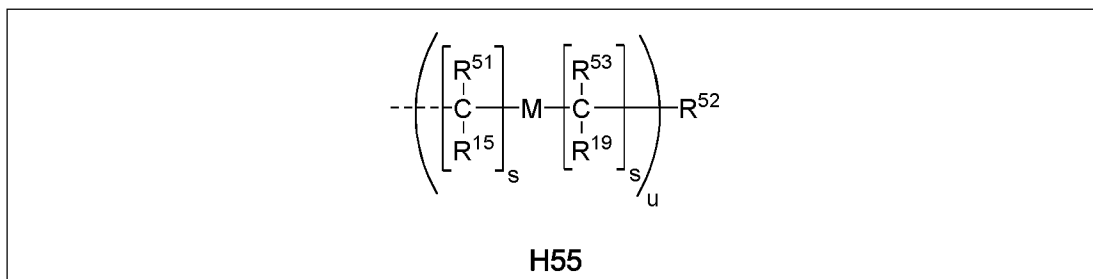
 H46	 H47	 H48	 H49
 H50			

R^{42} and R^{43} are independently defined as H; F; CF_3 ; C_{1-24} -alkyl; C_{2-24} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-12} -alkyl; or heteroaryl- C_{1-12} -alkyl;

- 5 R^{44} is H; C_{1-24} -alkyl; C_{2-24} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-12} -alkyl; heteroaryl- C_{1-12} -alkyl; or a group of one of the formulae **H51-H55** as shown in Table 8 below.

Table 8: Groups of Formulae **H51-H55** (continued on the following page)

$\text{---} \left[\begin{array}{c} R^{51} \\ \\ C \\ \\ R^{15} \end{array} \right]_{0-20} R^{52}$ H51	$\text{---} \left(\begin{array}{c} R^{51} \\ \\ C \\ \\ R^{15} \end{array} \right)_q \left[\begin{array}{c} OR^{36} \\ \\ C \\ \\ R^{17} \end{array} \right]_s \left[\begin{array}{c} R^{53} \\ \\ C \\ \\ R^{19} \end{array} \right]_q R^{52}$ H52
$\text{---} \left(\begin{array}{c} R^{51} \\ \\ C \\ \\ R^{15} \end{array} \right)_q \left[\begin{array}{c} NR^{45}R^7 \\ \\ C \\ \\ R^{17} \end{array} \right]_s \left[\begin{array}{c} R^{53} \\ \\ C \\ \\ R^{19} \end{array} \right]_q R^{52}$ H53	$\text{---} \left(\begin{array}{c} R^{51} \\ \\ C \\ \\ R^{15} \end{array} \right)_q \left[\begin{array}{c} R^{10} \\ \\ C = C \\ \\ R^{11} \end{array} \right]_s \left[\begin{array}{c} R^{53} \\ \\ C \\ \\ R^{19} \end{array} \right]_q R^{52}$ H54



- R^{45} is H; C_{1-24} -alkyl; C_{2-24} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-12} -alkyl; heteroaryl- C_{1-12} -alkyl; an *N*-protecting group; $\text{---}(\text{CR}^{51}\text{R}^{53})_r\text{OR}^{36}$;
- 5 $\text{---}(\text{CR}^{51}\text{R}^{53})_r\text{NR}^7\text{R}^{57}$; $\text{---}(\text{CR}^{51}\text{R}^{53})_r\text{OCONR}^7\text{R}^{57}$; $\text{---}(\text{CR}^{51}\text{R}^{53})_r\text{NR}^7\text{CONR}^7\text{R}^{57}$;
 $\text{---}(\text{CR}^{51}\text{R}^{53})_r\text{NR}^7\text{COR}^{38}$; $\text{---}(\text{CR}^{51}\text{R}^{53})_r\text{NR}^7\text{SO}_2\text{NR}^7\text{R}^{57}$; $\text{---}(\text{CR}^{51}\text{R}^{53})_r\text{NR}^7\text{SO}_2\text{R}^{38}$;
 $\text{---}(\text{CR}^{51}\text{R}^{53})_q\text{COOR}^{36}$; $\text{---}(\text{CR}^{51}\text{R}^{53})_q\text{COR}^{38}$; $\text{---}(\text{CR}^{51}\text{R}^{53})_q\text{SO}_2\text{R}^{38}$; $\text{---}(\text{CR}^{51}\text{R}^{53})_q\text{R}^{39}$;
 $\text{---}(\text{CR}^{51}\text{R}^{53})_s\text{R}^{40}$; $\text{---}(\text{CR}^{51}\text{R}^{53})_q\text{R}^{41}$; or $\text{---}(\text{CR}^{51}\text{R}^{53})_s\text{R}^{44}$;
- 10 R^{46} is H; F; Cl; CF_3 ; OCF_3 ; OCHF_2 ; NO_2 ; CN; C_{1-24} -alkyl; C_{2-24} -alkenyl; C_{2-10} -alkynyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-12} -alkyl; heteroaryl- C_{1-12} -alkyl; $\text{---}(\text{CR}^{51}\text{R}^{53})_q\text{OR}^{36}$; $\text{---}(\text{CR}^{51}\text{R}^{53})_q\text{SR}^{36}$; $\text{---}(\text{CR}^{51}\text{R}^{53})_q\text{NR}^7\text{R}^{57}$;
 $\text{---}(\text{CR}^{51}\text{R}^{53})_q\text{OCONR}^7\text{R}^{57}$; $\text{---}(\text{CR}^{51}\text{R}^{53})_q\text{NR}^7\text{COOR}^{36}$; $\text{---}(\text{CR}^{51}\text{R}^{53})_q\text{NR}^7\text{COR}^{38}$;
 $\text{---}(\text{CR}^{51}\text{R}^{53})_q\text{NR}^7\text{CONR}^7\text{R}^{45}$; $\text{---}(\text{CR}^{51}\text{R}^{53})_q\text{NR}^7\text{SO}_2\text{R}^{38}$; $\text{---}(\text{CR}^{51}\text{R}^{53})_q\text{NR}^7\text{SO}_2\text{NR}^7\text{R}^{45}$;
- 15 $\text{---}(\text{CR}^{51}\text{R}^{53})_q\text{COOR}^{36}$; $\text{---}(\text{CR}^{51}\text{R}^{53})_q\text{CONR}^7\text{R}^{45}$; $\text{---}(\text{CR}^{51}\text{R}^{53})_q\text{SO}_2\text{NR}^7\text{R}^{45}$;
 $\text{---}(\text{CR}^{51}\text{R}^{53})_q\text{COR}^{38}$; $\text{---}(\text{CR}^{51}\text{R}^{53})_q\text{SO}_2\text{R}^{38}$; or $\text{---}(\text{CR}^{51}\text{R}^{53})_q\text{R}^{44}$;
- R^{47} is H; C_{1-24} -alkyl; C_{2-24} -alkenyl; C_{2-10} -alkynyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-12} -alkyl; heteroaryl- C_{1-12} -alkyl; or $\text{---NR}^7\text{R}^{45}$;
- 20 R^{48} is H; C_{1-24} -alkyl; C_{2-24} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-12} -alkyl; heteroaryl- C_{1-12} -alkyl; an *N*-protecting group; $\text{---}(\text{CR}^{51}\text{R}^{53})_r\text{OR}^{45}$;
 $\text{---}(\text{CR}^{51}\text{R}^{53})_r\text{SR}^{45}$; $\text{---}(\text{CR}^{51}\text{R}^{53})_r\text{NR}^7\text{R}^{45}$; $\text{---}(\text{CR}^{51}\text{R}^{53})_r\text{OCONR}^7\text{R}^{45}$;
 $\text{---}(\text{CR}^{51}\text{R}^{53})_r\text{NR}^7\text{COOR}^{36}$; $\text{---}(\text{CR}^{51}\text{R}^{53})_r\text{NR}^7\text{COR}^{38}$; $\text{---}(\text{CR}^{51}\text{R}^{53})_r\text{NR}^7\text{CONR}^7\text{R}^{45}$;
- 25 $\text{---}(\text{CR}^{51}\text{R}^{53})_r\text{NR}^7\text{SO}_2\text{R}^{38}$; $\text{---}(\text{CR}^{51}\text{R}^{53})_r\text{NR}^7\text{SO}_2\text{NR}^7\text{R}^{45}$; $\text{---}(\text{CR}^{51}\text{R}^{53})_q\text{COOR}^{36}$;
 $\text{---}(\text{CR}^{51}\text{R}^{53})_q\text{CONR}^7\text{R}^{45}$; $\text{---}(\text{CR}^{51}\text{R}^{53})_r\text{SO}_2\text{NR}^7\text{R}^{45}$; $\text{---}(\text{CR}^{51}\text{R}^{53})_q\text{COR}^{38}$;
 $\text{---}(\text{CR}^{51}\text{R}^{53})_q\text{SO}_2\text{R}^{38}$; or $\text{---}(\text{CR}^{51}\text{R}^{53})_s\text{R}^{44}$;
- R^{49} is H; C_{1-24} -alkyl; C_{2-24} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl;
- 30 aryl- C_{1-12} -alkyl; heteroaryl- C_{1-12} -alkyl; $\text{---}(\text{CR}^{51}\text{R}^{53})_q\text{OR}^{36}$; $\text{---}(\text{CR}^{51}\text{R}^{53})_q\text{SR}^{36}$;

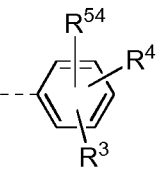
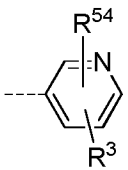
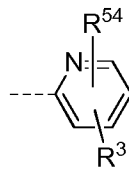
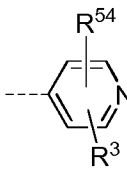
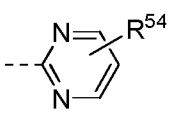
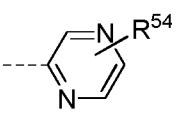
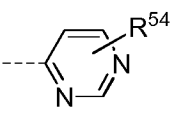
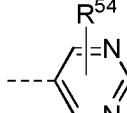
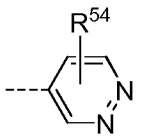
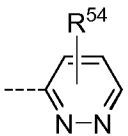
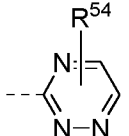
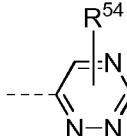
$-(\text{CR}^{51}\text{R}^{53})_q\text{NR}^7\text{R}^{45}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{NR}^7\text{COOR}^{36}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{NR}^7\text{COR}^{38}$;
 $-(\text{CR}^{51}\text{R}^{53})_q\text{NR}^7\text{SO}_2\text{R}^{38}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{NR}^7\text{CONR}^7\text{R}^{45}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{COOR}^{36}$;
 $-(\text{CR}^{51}\text{R}^{53})_q\text{CONR}^7\text{R}^{45}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{COR}^{38}$; or $-(\text{CR}^{51}\text{R}^{53})_q\text{R}^{44}$;

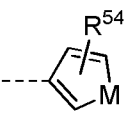
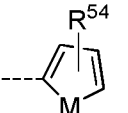
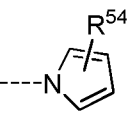
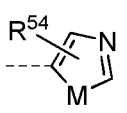
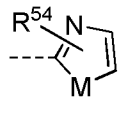
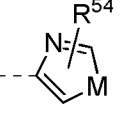
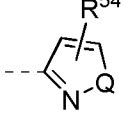
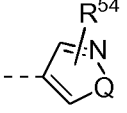
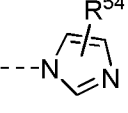
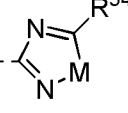
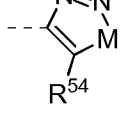
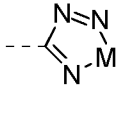
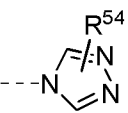
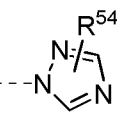
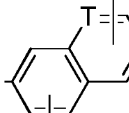
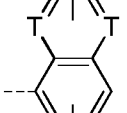
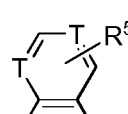
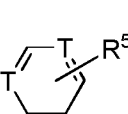
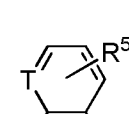
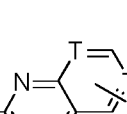
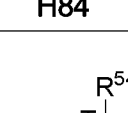
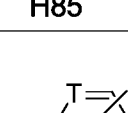
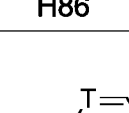
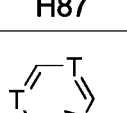
- 5 R^{50} is H; C_{1-24} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; or an *N*-protecting group;

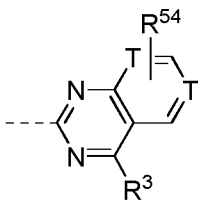
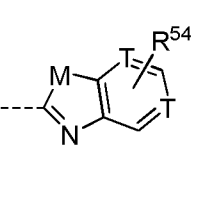
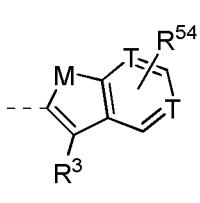
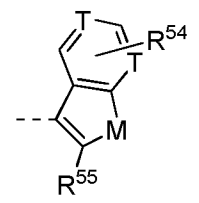
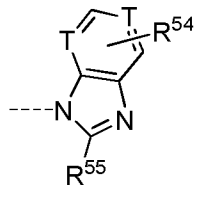
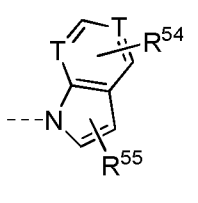
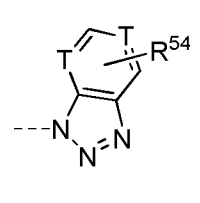
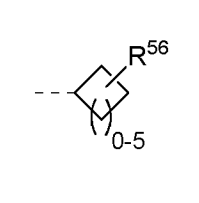
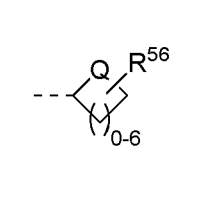
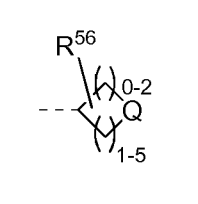
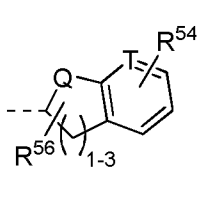
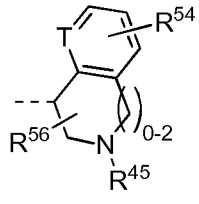
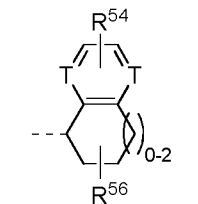
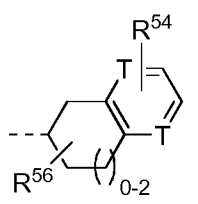
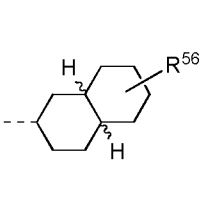
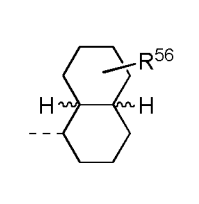
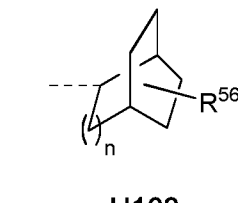
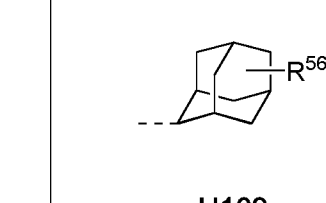
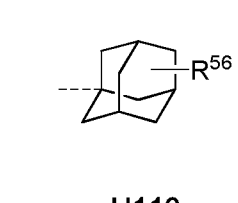
- R^{51} and R^{53} are independently defined as H; F; CF_3 ; C_{1-24} -alkyl; C_{2-24} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-12} -alkyl; heteroaryl- C_{1-12} -alkyl;
 10 $-(\text{CR}^{42}\text{R}^{43})_t\text{OR}^{36}$; $-(\text{CR}^{42}\text{R}^{43})_t\text{NR}^7\text{R}^{57}$; $-(\text{CR}^{42}\text{R}^{43})_t\text{COOR}^{36}$; or $-(\text{CR}^{42}\text{R}^{43})_t\text{CONR}^7\text{R}^{57}$;

- R^{52} is H; CF_3 ; C_{1-24} -alkyl; C_{2-24} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-12} -alkyl; heteroaryl- C_{1-12} -alkyl; $-\text{OR}^{36}$; $-\text{NR}^7\text{R}^{57}$; $-\text{NR}^7\text{COR}^{38}$;
 $-\text{NR}^7\text{COOR}^{36}$; $-\text{NR}^7\text{SO}_2\text{R}^{38}$; $-\text{NR}^7\text{CONR}^7\text{R}^{57}$; $-\text{COOR}^{36}$; $-\text{CONR}^7\text{R}^{57}$;
 15 $-\text{C}(=\text{NR}^7)\text{NR}^7\text{R}^{57}$; $-\text{NR}^7\text{C}(=\text{NR}^7)\text{NR}^7\text{R}^{57}$; or a group of one of the formulae **H56-H110** as shown in Table 9 below.

Table 9: Groups of Formulae **H56-H110** (continued on the following pages)

 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	 H107
 H108	 H109	 H110	

R^{54} is H; F; CF_3 ; OCF_3 ; $OCHF_2$; NO_2 ; CN; C_{1-24} -alkyl; C_{2-24} -alkenyl; C_{2-10} -alkynyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-12} -alkyl; heteroaryl- C_{1-12} -alkyl; $-OR^{36}$; $-NR^7R^{57}$; $-NR^7COR^{38}$; $-NR^7SO_2R^{38}$; $-NR^7CONR^7R^{57}$; $-COR^{38}$; or $-SO_2R^{38}$;

R^{55} is H; CF_3 ; C_{1-24} -alkyl; C_{2-24} -alkenyl; C_{2-10} -alkynyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-12} -alkyl; heteroaryl- C_{1-12} -alkyl; $-COOR^{36}$; or $-CONR^7R^{45}$;

- 5 R^{56} is H; F; CF_3 ; C_{1-24} -alkyl; C_{2-24} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-12} -alkyl; heteroaryl- C_{1-12} -alkyl; $-(CR^{42}R^{43})_sOR^{36}$; $-(CR^{42}R^{43})_sNR^7R^{45}$; $-(CR^{42}R^{43})_qCOOR^{36}$; or $-(CR^{42}R^{43})_qCONR^7R^{45}$;

R^{57} is H; C_{1-24} -alkyl; C_{2-24} -alkenyl; cycloalkyl; aryl; aryl- C_{1-12} -alkyl; or an *N*-protecting group.

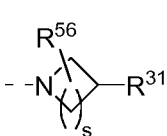
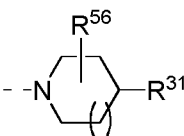
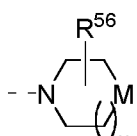
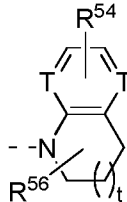
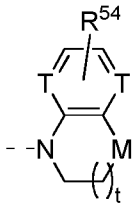
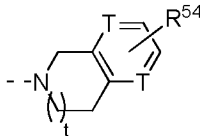
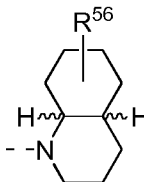
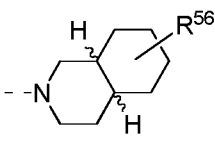
10

Taken together, the following pairs of substituents can form optionally substituted cycloalkyl or heterocycloalkyl moieties: (R^5 and R^6); (R^7 and R^{14}); (R^7 and R^{16}); (R^7 and R^{18}); (R^7 and R^{20}); (R^7 and R^{22}); (R^7 and R^{24}); (R^7 and R^{26}); (R^7 and R^{28}); (R^7 and R^{30}); (R^7 and R^{35}); (R^7 and R^{45}); (R^7 and R^{57}); (R^{13} and R^{13}); (R^{14} and R^{16}); (R^{14} and R^{18}); (R^{15} and R^{51}); (R^{19} and R^{51}); (R^{20} and R^{22}); (R^{20} and R^{24}); (R^{26} and R^{28}); (R^{26} and R^{30}); (R^{32} and R^{33}); (R^{42} and R^{43}); or (R^{51} and R^{53}).

15

In addition, the structural elements $-NR^7R^{35}$; or $-NR^{44}R^{45}$ can form one of the groups of formulae H111–H118 as shown in Table 10 below.

20 **Table 10:** Heterocyclic Groups Defined by Linking the Residues of the Disubstituted Amino Groups $-NR^7R^{35}$ or $-NR^{44}R^{45}$.

 H111	 H112	 H113	 H114
 H115	 H116	 H117	 H118

Generic atoms and connector groups in the aforementioned structures are:

Z, Y, X, W, V, U as defined by Scheme 3;

T is CR⁵⁴ or N;

Q is O; S; or NR³⁵;

M is O; S; or NR⁷.

5 The indices in the aforementioned structures are defined as:

m is an integer of 0-8;

n is an integer of 0-1;

p is an integer of 0-4;

q is an integer of 0-4;

10 r is an integer of 2-4;

s is an integer of 1-4;

t is an integer of 0-2;

u is an integer of 1-2.

15 For the avoidance of doubt, some of the aforementioned substituents, for example, but not limited to, R⁷, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²², R²³, R²⁴, R²⁵, R²⁸, R²⁹, R³⁰, R³¹, R³², R³³, R⁴², R⁴³, R⁴⁵, R⁴⁶, and R⁴⁹; the indices as well as the generic atoms/connector groups (Z, Y, X, W, V, U, T, Q, M) can occur several times within the same molecular entity. In such a case each of them shall be selected independently from others specified by
20 the same symbol.

“Salts” as understood herein are especially, but not limited to, the pharmaceutically acceptable salts of compounds of formula I. Such salts are formed, for example, as acid addition salts with organic or inorganic acids, from compounds of type I with a
25 basic nitrogen atom. 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; like 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,
30 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-methylbenzene-sulfonic acid, methylsulfuric acid, ethylsulfuric acid, dodecylsulfuric acid, *N*-
35

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.e. as part of another group, such as "aryl-C₁₋₆-alkyl"), designates saturated, straight-chain or branched hydrocarbon radicals and may be optionally substituted. The term "C_{x-y}-alkyl" (x and y each being an integer) refers to an alkyl group as defined before containing x to y carbon atoms. For example a C₁₋₆-alkyl group contains one to six carbon atoms. Representative examples of alkyl groups include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *n*-hexyl and the like.

The term "alkenyl", taken alone or in combinations, designates straight chain or branched hydrocarbon radicals containing at least one or, depending on the chain length, up to four olefinic double bonds. Such alkenyl moieties are optionally substituted and can independently exist as E or Z configurations per double bond, which are all part of the invention. The term "C_{x-y}-alkenyl" (x and y each being an integer) refers to an alkenyl group as defined before, containing x to y carbon atoms.

The term "alkynyl" designates straight chain or branched hydrocarbon radicals containing at least one or, depending on the chain length, up to four triple bonds. The term "C_{x-y}-alkynyl" (x and y each being an integer) refers to an alkynyl group as defined before, containing x to y carbon atoms.

The term "cycloalkyl" refers to a saturated or partially unsaturated alicyclic moiety having from three to ten carbon atoms and may be optionally substituted. Examples of this moiety include, but are not limited to, cyclohexyl, norbornyl, decalinyl and the like.

The term "heterocycloalkyl" describes a saturated or partially unsaturated mono- or bicyclic moiety having from two to nine ring carbon atoms and one or more ring heteroatoms selected from nitrogen, oxygen or sulphur. This term includes, for example, morpholino, piperazino, azetidiny, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, octahydro-1H-indolyl, 1,7-diazaspiro[4.4]nonane and the like. Said heterocycloalkyl ring(s) might be optionally substituted.

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 optionally substituted by up to three substituents such as F, Cl, Br, CF₃, OH, OCF₃, OCHF₂, NH₂, N(CH₃)₂, NO₂, CN, C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, phenyl or phenoxy.

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 four 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 "aryl-C_{x-y}-alkyl", as used herein, refers to an C_{x-y}-alkyl group as defined above, substituted by an aryl group, as defined above. Representative examples of aryl-C_{x-y}-alkyl moieties include, but are not limited to, benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 2-phenylpropyl and the like.

The term "heteroaryl-C_{x-y}-alkyl", as used herein, refers to an C_{x-y}-alkyl group as defined above, substituted by a heteroaryl group, as defined above. Examples of heteroaryl-C_{x-y}-alkyl groups include pyridin-3-ylmethyl, (1H-pyrrol-2-yl)ethyl and the like.

The terms "alkoxy" and "aryloxy", taken alone or in combinations, refer to the groups of -O-alkyl and -O-aryl respectively, wherein an alkyl group or an aryl group is as defined above. The term "C_{x-y}-alkoxy" (x and y each being an integer) refers to an -O-alkyl group as defined before containing x to y carbon atoms attached to an oxygen atom. Representative examples of alkoxy groups include methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *tert*-butoxy and the like. Examples of aryloxy include e.g. phenoxy.

"Amino" designates primary, secondary or tertiary amines. Particular secondary and tertiary amines are alkylamines, dialkylamines, arylamines, diarylamines, arylalkylamines and diarylamines wherein the alkyl or aryl is as herein defined and optionally substituted.

The term “N-protecting group”, as use herein, refers to the following commonly known groups, suitable to protect a nitrogen atom: allyloxycarbonyl (Alloc), *tert*-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz), 9-fluorenylmethoxycarbonyl (Fmoc), 2- or 4-nitrobenzenesulfonyl (Ns), 2-(trimethylsilyl)ethoxycarbonyl (Teoc), 2,2,2-Trichloroethoxycarbonyl (Troc), *p*-methoxybenzyl (PMB), 3,4-dimethoxybenzyl (DMB), triphenylmethyl (trityl, Tr), or 2-chlorotrityl (CTC).

The term “O/S-protecting group”, as use herein, refers to the following commonly known groups, suitable to protect either an oxygen and/or a sulfur atom: *tert*-butyldimethylsilyl (TBDMS), *tert*-butyldiphenylsilyl (TBDPS), acetyl (Ac), pivaloyl (Piv), *tert*-butyl, 2-(trimethylsilyl)ethoxymethyl (SEM), methoxymethyl (MOM), triphenylmethyl (trityl, Tr), *p*-methoxybenzyl (PMB), 3,4-dimethoxybenzyl (DMB), or 2-(Trimethylsilyl)ethyl (TMSE).

A person skilled in the art might find easily corresponding equivalents for the above mentioned protecting groups which are considered to be as well comprised by the gist of the current invention. Examples of suitable protecting groups are as detailed in P.G.M. Wuts, T.W. Greene, *Greene's Protective Groups in Organic Synthesis*, John Wiley and Sons, 4th Edition, 2006.

The term “optionally substituted” is in general intended to mean that a group, such as, but not limited to C_{x-y}-alkyl, C_{x-y}-alkenyl, C_{x-y}-alkynyl, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, C_{x-y}-alkoxy and aryloxy may be substituted with one or more substituents independently selected from amino (-NH₂), dimethylamino, nitro (-NO₂), halogen (F, Cl, Br, I), CF₃, cyano (-CN), hydroxy, methoxy, ethoxy, phenyloxy, benzyloxy, acetoxy, oxo (=O), carboxy, carboxamide, methyl, ethyl, *n*-propyl, *iso*-propyl, *cyclo*-propyl, phenyl, benzyl, sulfonic acid, sulfate, phosphonic acid, phosphate, phosphonate, or

-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)NR^bR^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^aS(O)₂R^b, wherein R^a, R^b, R^c, and R^d are each independently hydrogen, C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-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 one or more moieties selected from the group consisting of halogen (F, Cl, Br, or I), hydroxyl, amino, *mono*-,

di- or *tri-*C₁₋₆-alkylamino, *mono-*, *di-* or *tri-*aryl amino, hydroxy, carboxy, C₁₋₆-alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate.

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

The embodiments of the present invention shall include 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.

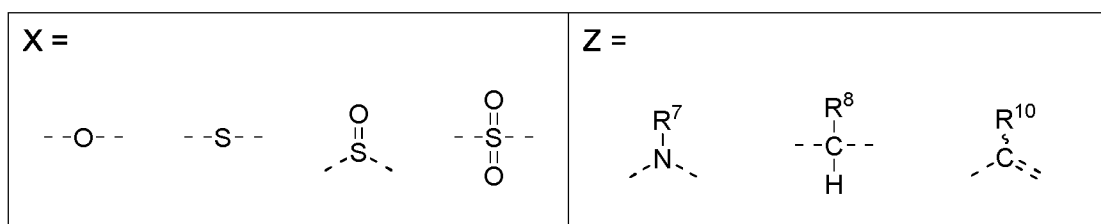
- 10 Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in Hans Bundgaard, *Design of Prodrugs*, Elsevier, **1985**; and in Valentino J. Stella et al., *Prodrugs: Challenges and Rewards*, Springer, 1st ed., **2007**.

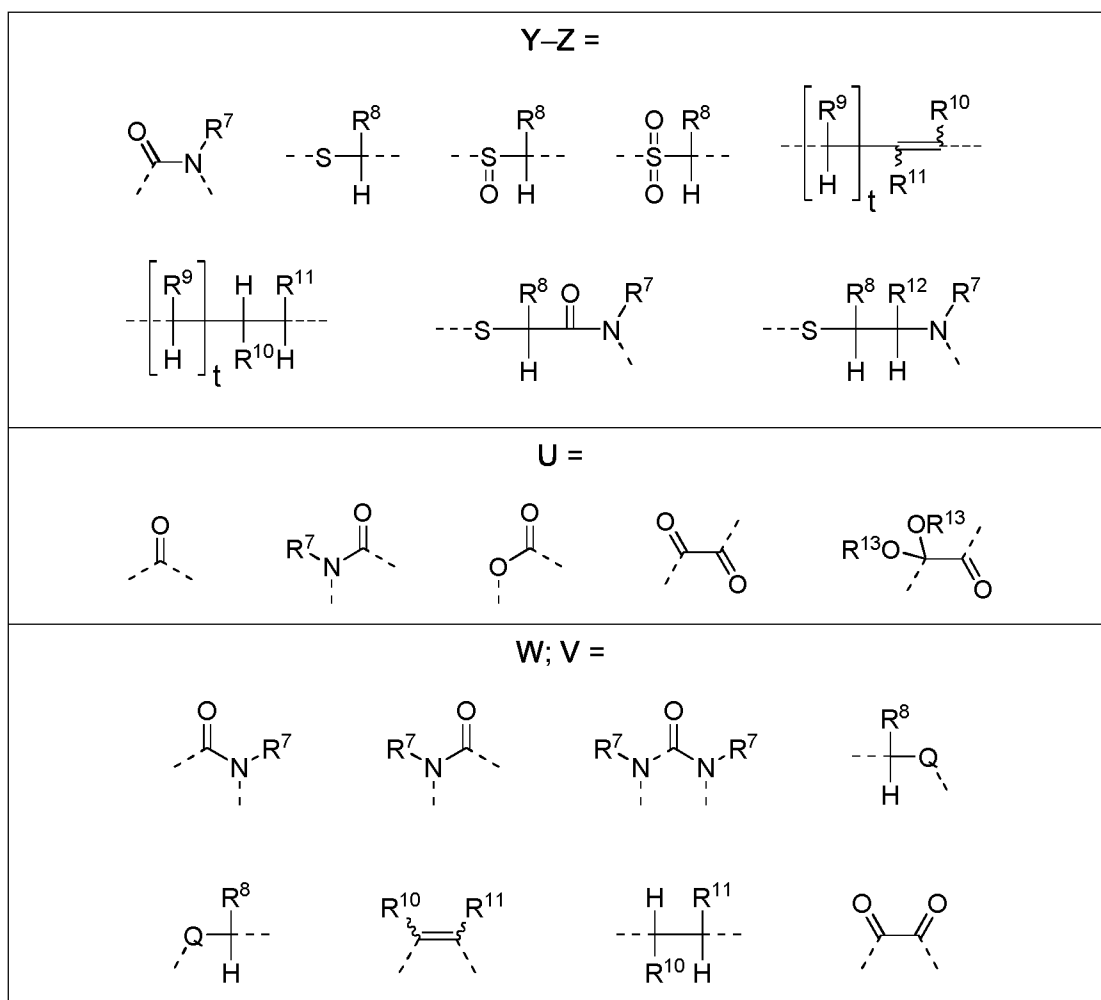
- 15 The term “isomer” comprises species of identical chemical formula, constitution and thus molecular mass, such as but not limited to C=C-double bond or amide *cis/trans* isomers, rotamers, conformers and diastereomers.

- 20 All possible stereoisomers - explicitly including atropisomers - conformers and rotamers as well as salts, solvates, clathrates, *N*-oxides, or isotopically enriched or enantiomerically enriched versions of the macrocycles of type I are part of this invention.

- 25 In a **Preferred Embodiment** of this invention, macrocycles of type I are defined by groups of selected building blocks **A**, **B** and **C** and substituents R¹-R⁵⁷. The connectivities between the building blocks of the preferred embodiment are defined as shown in Scheme 5.

- 30 **Scheme 5:** Connectivities of Preferred Embodiment of Macrocycle I (*continued on the following page*)





The biaryl Template A of the Preferred Embodiment is selected from

- AB1-AC1; AB1-AC2; AB1-AC3; AB1-AC4; AB1-AC5; AB1-AC6; AB1-AC8;
 5 AB1-AC9; AB1-AC11; AB1-AC12; AB1-AC13; AB1-AC19; AB1-AC22; AB1-AC24;
 AB1-AC49; AB1-AC51; AB2-AC1; AB2-AC2; AB2-AC3; AB2-AC4; AB2-AC5; AB2-AC11;
 AB2-AC12; AB2-AC51; AB3-AC1; AB3-AC2; AB3-AC3; AB3-AC4; AB3-AC5; AB3-AC11;
 AB3-AC12; AB4-AC1; AB4-AC2; AB4-AC3; AB4-AC4; AB4-AC5; AB4-AC6; AB4-AC11;
 AB4-AC12; AB4-AC19; AB4-AC22; AB4-AC24; AB4-AC49; AB4-AC51; AB4-AC59;
 10 AB5-AC1; AB5-AC2; AB5-AC3; AB5-AC4; AB5-AC5; AB5-AC11; AB5-AC12; AB5-AC51;
 AB5-AC59; AB6-AC1; AB6-AC4; AB6-AC8; AB6-AC9; AB6-AC11; AB6-AC13; AB6-AC16;
 AB6-AC18; AB6-AC19; AB6-AC20; AB6-AC30; AB6-AC31; AB6-AC49; AB6-AC51;
 AB9-AC6; AB9-AC49; AB10-AC6; AB11-AC6; AB12-AC2; AB12-AC5; AB12-AC11;
 AB12-AC12; AB13-AC2; AB13-AC5; AB13-AC11; AB13-AC12; AB13-AC5; AB13-AC11;
 15 AB13-AC12; AB14-AC49; AB20-AC2; AB20-AC6; AB20-AC49; AB23-AC4; AB23-AC49;
 AB26-AC2; AB26-AC5; AB26-AC11; AB26-AC12; AB40-AC2; AB40-AC5; AB40-AC11;

- A_B40-A_C12 ; A_B45-A_C49 ; A_B45-A_C52 ; A_B45-A_C57 ; A_B45-A_C58 ; A_B45-A_C65 ;
 A_B45-A_C66 ; A_B46-A_C57 ; A_B46-A_C58 ; A_B47-A_C58 ; A_B49-A_C49 ; A_B50-A_C57 ;
 A_B50-A_C58 ; A_B50-A_C61 ; A_B51-A_C49 ; A_B51-A_C61 ; A_B53-A_C2 ; A_B53-A_C5 ; A_B53-A_C11 ;
 A_B53-A_C12 ; A_B58-A_C2 ; A_B58-A_C5 ; A_B58-A_C11 ; A_B58-A_C12 ; A_B59-A_C2 ; A_B59-A_C5 ;
 5 A_B59-A_C11 ; A_B59-A_C12 ; or A_B59-A_C61 .

The preferred Modulator **B** is selected from

B1; B4; B5; B6; B7; B8; B9 or B10;

and the preferred Bridge **C** from

- 10 **C1; C2; or C3.**

The substituents R^1 - R^{57} attached to the Preferred Embodiment of macrocycle **I** are as defined as shown below.

- 15 R^1 and R^2 are independently defined as H; F; Cl; Br; I; CF_3 ; OCF_3 ; $OCHF_2$;
 NO_2 ; CN; C_{1-6} -alkyl; C_{2-6} -alkenyl; C_{2-6} -alkynyl; cycloalkyl; heterocycloalkyl; aryl- C_{1-6} -
 alkyl; heteroaryl- C_{1-6} -alkyl; $-(CR^{32}R^{33})_qOR^{34}$; $-(CR^{32}R^{33})_qSR^{34}$; $-(CR^{32}R^{33})_qNR^7R^{35}$;
 $-(CR^{32}R^{33})_qOCONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7COOR^{36}$; $-(CR^{32}R^{33})_qNR^7COR^{37}$;
 $-(CR^{32}R^{33})_qNR^7CONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7SO_2R^{38}$; $-(CR^{32}R^{33})_qNR^7SO_2NR^7R^{35}$;
 20 $-(CR^{32}R^{33})_qCOOR^{36}$; $-(CR^{32}R^{33})_qCONR^7R^{35}$; $-(CR^{32}R^{33})_qSO_2NR^7R^{35}$;
 $-(CR^{32}R^{33})_qCOR^{37}$; $-(CR^{32}R^{33})_qSO_2R^{38}$; $-(CR^{32}R^{33})_qR^{39}$; $-(CR^{32}R^{33})_qR^{40}$;
 $-(CR^{32}R^{33})_qR^{41}$; or $-(CR^{32}R^{33})_qR^{44}$;

- R^3 and R^4 are independently defined as H; F; Cl; CF_3 ; OCF_3 ; $OCHF_2$; NO_2 ;
 25 CN; C_{1-6} -alkyl; cycloalkyl; C_{1-6} -alkoxy or aryloxy;

R^5 is H; CF_3 ; C_{1-6} -alkyl; or cycloalkyl;

- R^6 is H; CF_3 ; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl;
 30 heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; $-(CR^{32}R^{33})_qOR^{34}$; $-(CR^{32}R^{33})_qSR^{34}$;
 $-(CR^{32}R^{33})_qNR^7R^{35}$; $-(CR^{32}R^{33})_qOCONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7COOR^{36}$;
 $-(CR^{32}R^{33})_qNR^7COR^{37}$; $-(CR^{32}R^{33})_qNR^7CONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7SO_2R^{38}$;
 $-(CR^{32}R^{33})_qNR^7SO_2NR^7R^{35}$; $-(CR^{32}R^{33})_qCOOR^{36}$; $-(CR^{32}R^{33})_qCONR^7R^{35}$;
 $-(CR^{32}R^{33})_qSO_2NR^7R^{35}$; $-(CR^{32}R^{33})_qCOR^{37}$; $-(CR^{32}R^{33})_qSO_2R^{38}$; $-(CR^{32}R^{33})_qR^{39}$;
 35 $-(CR^{32}R^{33})_sR^{40}$; $-(CR^{32}R^{33})_qR^{41}$; or $-(CR^{32}R^{33})_qR^{44}$;

R^7 is H; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; or an *N*-protecting group;

5 R^8 and R^9 are independently defined as H; CF_3 ; C_{1-6} -alkyl; cycloalkyl; heterocycloalkyl;

R^{10} , R^{11} and R^{12} are independently defined as H; C_{1-6} -alkyl; or cycloalkyl;

10 R^{13} is C_{1-6} -alkyl;

R^{14} , R^{20} and R^{26} are independently defined as H; F; CF_3 ; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; $-(CR^{32}R^{33})_qOR^{34}$; $-(CR^{32}R^{33})_qSR^{34}$; $-(CR^{32}R^{33})_qNR^7R^{35}$;
 15 $-(CR^{32}R^{33})_qOCONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7COOR^{36}$; $-(CR^{32}R^{33})_qNR^7COR^{37}$;
 $-(CR^{32}R^{33})_qNR^7CONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7SO_2R^{38}$; $-(CR^{32}R^{33})_qNR^7SO_2NR^7R^{35}$;
 $-(CR^{32}R^{33})_qCOOR^{36}$; $-(CR^{32}R^{33})_qCONR^7R^{35}$; $-(CR^{32}R^{33})_qSO_2NR^7R^{35}$;
 $-(CR^{32}R^{33})_qCOR^{37}$; $-(CR^{32}R^{33})_qSO_2R^{38}$; $-(CR^{32}R^{33})_qR^{39}$; $-(CR^{32}R^{33})_sR^{40}$;
 $-(CR^{32}R^{33})_qR^{41}$; or $-(CR^{32}R^{33})_qR^{44}$;

20 R^{15} , R^{17} , R^{19} , R^{21} , R^{23} , R^{25} , R^{27} , R^{29} and R^{31} are independently defined as H; or C_{1-6} -alkyl;

R^{16} , R^{22} and R^{28} are independently defined as H; CF_3 ; or C_{1-6} -alkyl;

25 R^{18} , R^{24} and R^{30} are independently defined as H; F; CF_3 ; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl;
 $-(CR^{32}R^{33})_qOR^{34}$; $-(CR^{32}R^{33})_qNR^7R^{35}$; $-(CR^{32}R^{33})_qOCONR^7R^{35}$;
 $-(CR^{32}R^{33})_qNR^7COOR^{36}$; $-(CR^{32}R^{33})_qNR^7COR^{37}$; $-(CR^{32}R^{33})_qNR^7CONR^7R^{35}$;
 30 $-(CR^{32}R^{33})_qNR^7SO_2R^{38}$; $-(CR^{32}R^{33})_qNR^7SO_2NR^7R^{35}$; $-(CR^{32}R^{33})_qCOOR^{36}$;
 $-(CR^{32}R^{33})_qCONR^7R^{35}$; $-(CR^{32}R^{33})_qSO_2NR^7R^{35}$; $-(CR^{32}R^{33})_qCOR^{37}$; or $-(CR^{32}R^{33})_qR^{44}$;

R^{32} is H; F; CF_3 ; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; $-(CR^{42}R^{51})_qOR^{45}$; $-(CR^{42}R^{51})_qSR^{45}$;
 35 $-(CR^{42}R^{51})_qNR^7R^{45}$; $-(CR^{42}R^{51})_qOCONR^7R^{45}$; $-(CR^{42}R^{51})_qNR^7COOR^{36}$;
 $-(CR^{42}R^{51})_qNR^7COR^{38}$; $-(CR^{42}R^{51})_qNR^7CONR^7R^{45}$; $-(CR^{42}R^{51})_qNR^7SO_2R^{38}$;

$-(\text{CR}^{42}\text{R}^{51})_q\text{NR}^7\text{SO}_2\text{NR}^7\text{R}^{45}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{COOR}^{36}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{CONR}^7\text{R}^{45}$;
 $-(\text{CR}^{42}\text{R}^{51})_q\text{SO}_2\text{NR}^7\text{R}^{45}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{COR}^{38}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{SO}_2\text{R}^{38}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{R}^{39}$;
 $-(\text{CR}^{42}\text{R}^{51})_s\text{R}^{40}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{R}^{41}$; or $-(\text{CR}^{42}\text{R}^{51})_q\text{R}^{44}$;

5 R^{33} is H; or C_{1-6} -alkyl;

R^{34} is H; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl;
 heteroaryl- C_{1-6} -alkyl; $-(\text{CR}^{42}\text{R}^{51})_r\text{OR}^{45}$; $-(\text{CR}^{42}\text{R}^{51})_r\text{NR}^7\text{R}^{45}$; $-(\text{CR}^{42}\text{R}^{51})_r\text{OCONR}^7\text{R}^{35}$;
 $-(\text{CR}^{42}\text{R}^{51})_r\text{NR}^7\text{COOR}^{36}$; $-(\text{CR}^{42}\text{R}^{51})_r\text{NR}^7\text{COR}^{38}$; $-(\text{CR}^{42}\text{R}^{51})_r\text{NR}^7\text{CONR}^7\text{R}^{45}$;
 10 $-(\text{CR}^{42}\text{R}^{51})_r\text{NR}^7\text{SO}_2\text{R}^{38}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{COOR}^{36}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{CONR}^7\text{R}^{45}$;
 $-(\text{CR}^{42}\text{R}^{51})_q\text{SO}_2\text{NR}^7\text{R}^{45}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{COR}^{38}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{SO}_2\text{R}^{38}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{R}^{39}$;
 $-(\text{CR}^{42}\text{R}^{51})_s\text{R}^{40}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{R}^{41}$; or $-(\text{CR}^{42}\text{R}^{51})_q\text{R}^{44}$;

R^{35} is H; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl;
 15 aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; an *N*-protecting group; $-(\text{CR}^{32}\text{R}^{33})_r\text{OR}^{45}$;
 $-(\text{CR}^{32}\text{R}^{33})_r\text{NR}^7\text{R}^{45}$; $-(\text{CR}^{32}\text{R}^{33})_r\text{OCONR}^7\text{R}^{45}$; $-(\text{CR}^{32}\text{R}^{33})_r\text{NR}^7\text{COOR}^{36}$;
 $-(\text{CR}^{32}\text{R}^{33})_r\text{NR}^7\text{COR}^{37}$; $-(\text{CR}^{32}\text{R}^{33})_r\text{NR}^7\text{CONR}^7\text{R}^{45}$; $-(\text{CR}^{32}\text{R}^{33})_r\text{NR}^7\text{SO}_2\text{R}^{38}$;
 $-(\text{CR}^{32}\text{R}^{33})_r\text{NR}^7\text{SO}_2\text{NR}^7\text{R}^{45}$; $-(\text{CR}^{32}\text{R}^{33})_q\text{COOR}^{36}$; $-(\text{CR}^{32}\text{R}^{33})_q\text{CONR}^7\text{R}^{45}$;
 $-(\text{CR}^{32}\text{R}^{33})_q\text{COR}^{37}$; $-(\text{CR}^{32}\text{R}^{33})_q\text{SO}_2\text{R}^{38}$; $-(\text{CR}^{32}\text{R}^{33})_q\text{SO}_2\text{NR}^7\text{R}^{50}$; $-(\text{CR}^{32}\text{R}^{33})_q\text{R}^{39}$;
 20 $-(\text{CR}^{32}\text{R}^{33})_s\text{R}^{40}$; $-(\text{CR}^{32}\text{R}^{33})_q\text{R}^{41}$; or $-(\text{CR}^{32}\text{R}^{33})_q\text{R}^{44}$;

R^{36} is H; C_{1-6} -alkyl; cycloalkyl; aryl; aryl- C_{1-6} -alkyl; or an *O/S*-protecting group;

R^{37} is C_{1-6} -alkyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl;
 25 heteroaryl- C_{1-6} -alkyl; $-(\text{CR}^{42}\text{R}^{51})_q\text{OR}^{45}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{SR}^{45}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{NR}^7\text{R}^{45}$;
 $-(\text{CR}^{42}\text{R}^{51})_s\text{OCONR}^7\text{R}^{45}$; $-(\text{CR}^{42}\text{R}^{51})_s\text{NR}^7\text{COOR}^{36}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{NR}^7\text{COR}^{44}$;
 $-(\text{CR}^{42}\text{R}^{51})_s\text{NR}^7\text{CONR}^7\text{R}^{45}$; $-(\text{CR}^{42}\text{R}^{51})_s\text{NR}^7\text{SO}_2\text{R}^{38}$; $-(\text{CR}^{42}\text{R}^{51})_s\text{NR}^7\text{SO}_2\text{NR}^7\text{R}^{45}$;
 $-(\text{CR}^{42}\text{R}^{51})_q\text{COOR}^{36}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{CONR}^7\text{R}^{45}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{SO}_2\text{NR}^7\text{R}^{45}$;
 $-(\text{CR}^{42}\text{R}^{51})_t\text{COR}^{38}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{SO}_2\text{R}^{38}$; $-(\text{CR}^{42}\text{R}^{51})_t\text{R}^{39}$; $-(\text{CR}^{42}\text{R}^{51})_u\text{R}^{40}$;
 30 $-(\text{CR}^{42}\text{R}^{51})_t\text{R}^{41}$; or $-(\text{CR}^{42}\text{R}^{51})_t\text{R}^{44}$;

R^{38} is C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl-
 C_{1-6} -alkyl; or heteroaryl- C_{1-6} -alkyl;

35 R^{39} , R^{40} , and R^{41} are as defined in the Main Embodiment;

R^{42} and R^{43} are independently defined as H; F; CF_3 ; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl- C_{1-6} -alkyl; or heteroaryl- C_{1-6} -alkyl;

R^{44} is H; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; or a group of one of the formulae **H51-H55** as shown in Table 8 above.

R^{45} is H; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; an *N*-protecting group; $-(CR^{42}R^{51})_rOR^{36}$;
 10 $-(CR^{42}R^{51})_rNR^7R^{57}$; $-(CR^{42}R^{51})_rOCONR^7R^{57}$; $-(CR^{42}R^{51})_rNR^7CONR^7R^{57}$;
 $-(CR^{42}R^{51})_rNR^7COR^{38}$; $-(CR^{42}R^{51})_rNR^7SO_2R^{38}$; $-(CR^{42}R^{51})_rNR^7SO_2NR^7R^{57}$;
 $-(CR^{42}R^{51})_qCOOR^{36}$; $-(CR^{42}R^{51})_qCOR^{38}$; $-(CR^{42}R^{51})_qSO_2R^{33}$; $-(CR^{42}R^{51})_qR^{39}$;
 $-(CR^{42}R^{51})_sR^{40}$; $-(CR^{42}R^{51})_qR^{41}$; or $-(CR^{42}R^{51})_sR^{44}$;

15 R^{46} is H; F; Cl; CF_3 ; OCF_3 ; $OCHF_2$; NO_2 ; CN; C_{1-6} -alkyl; C_{2-6} -alkenyl; C_{2-6} -alkynyl; cycloalkyl; heterocycloalkyl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl;
 $-(CR^{42}R^{51})_qOR^{36}$; $-(CR^{42}R^{51})_qSR^{36}$; $-(CR^{42}R^{51})_qNR^7R^{57}$; $-(CR^{42}R^{51})_qOCONR^7R^{57}$;
 $-(CR^{42}R^{51})_qNR^{44}COOR^{36}$; $-(CR^{42}R^{51})_qNR^7COR^{38}$; $-(CR^{42}R^{51})_qNR^7CONR^7R^{45}$;
 $-(CR^{42}R^{51})_qNR^7SO_2R^{38}$; $-(CR^{42}R^{51})_qNR^7SO_2NR^7R^{45}$; $-(CR^{42}R^{51})_qCOOR^{36}$;
 20 $-(CR^{42}R^{51})_qCONR^7R^{45}$; $-(CR^{42}R^{51})_qSO_2NR^7R^{45}$; $-(CR^{42}R^{51})_qCOR^{38}$;
 $-(CR^{42}R^{51})_qSO_2R^{38}$; or $-(CR^{42}R^{51})_qR^{44}$;

R^{47} is H; C_{1-6} -alkyl; C_{2-6} -alkenyl; C_{2-6} -alkynyl; cycloalkyl; heterocycloalkyl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; or $-NR^7R^{45}$;

25

R^{48} is H; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; an *N*-protecting group; $-(CR^{42}R^{51})_rOR^{45}$;
 $-(CR^{42}R^{51})_rSR^{45}$; $-(CR^{42}R^{51})_rNR^7R^{45}$; $-(CR^{42}R^{51})_rOCONR^7R^{45}$;
 $-(CR^{42}R^{51})_rNR^7COOR^{36}$; $-(CR^{42}R^{51})_rNR^7COR^{38}$; $-(CR^{42}R^{51})_rNR^7CONR^7R^{45}$;
 30 $-(CR^{42}R^{51})_rNR^7SO_2R^{38}$; $-(CR^{42}R^{51})_rNR^7SO_2NR^7R^{45}$; $-(CR^{42}R^{51})_qCOOR^{36}$;
 $-(CR^{42}R^{51})_qCONR^7R^{45}$; $-(CR^{42}R^{51})_rSO_2NR^7R^{45}$; $-(CR^{42}R^{51})_qCOR^{38}$;
 $-(CR^{42}R^{51})_qSO_2R^{38}$; or $-(CR^{42}R^{51})_sR^{44}$;

R^{49} is H; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; $-(CR^{42}R^{51})_qOR^{36}$; $-(CR^{42}R^{51})_qSR^{36}$;
 35 $-(CR^{42}R^{51})_qNR^7R^{45}$; $-(CR^{42}R^{51})_qNR^7COOR^{36}$; $-(CR^{42}R^{51})_qNR^7COR^{38}$;

36

$-(\text{CR}^{42}\text{R}^{51})_q\text{NR}^7\text{SO}_2\text{R}^{38}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{NR}^7\text{CONR}^7\text{R}^{45}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{COOR}^{36}$;
 $-(\text{CR}^{42}\text{R}^{51})_q\text{CONR}^7\text{R}^{45}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{COR}^{38}$; or $-(\text{CR}^{42}\text{R}^{51})_q\text{R}^{44}$;

R^{50} is H; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl;
 5 aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; or an *N*-protecting group;

R^{51} and R^{53} are independently defined as H; F; CF_3 ; C_{1-6} -alkyl; C_{2-6} -alkenyl;
 cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl;
 $-(\text{CR}^{42}\text{R}^{43})_l\text{OR}^{36}$; $-(\text{CR}^{42}\text{R}^{43})_l\text{NR}^7\text{R}^{57}$; $-(\text{CR}^{42}\text{R}^{43})_l\text{COOR}^{36}$; or $-(\text{CR}^{42}\text{R}^{43})_l\text{CONR}^7\text{R}^{57}$;
 10

R^{52} is H; CF_3 ; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl;
 heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; $-\text{OR}^{36}$; $-\text{NR}^7\text{R}^{57}$; $-\text{NR}^7\text{COR}^{38}$;
 $-\text{NR}^7\text{COOR}^{36}$; $-\text{NR}^7\text{SO}_2\text{R}^{38}$; $-\text{NR}^7\text{CONR}^7\text{R}^{57}$; $-\text{COOR}^{36}$; $-\text{CONR}^7\text{R}^{57}$;
 $-\text{C}(=\text{NR}^7)\text{NR}^7\text{R}^{57}$; $-\text{NR}^7\text{C}(=\text{NR}^7)\text{NR}^7\text{R}^{57}$; or a group of one of the formulae **H56-H110**
 15 as shown in Table 9 above.

R^{54} is H; F; CF_3 ; OCF_3 ; OCHF_2 ; NO_2 ; CN; C_{1-6} -alkyl; C_{2-6} -alkenyl; C_{2-6} -alkynyl;
 cycloalkyl; heterocycloalkyl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; $-\text{OR}^{36}$; $-\text{NR}^7\text{R}^{57}$;
 $-\text{NR}^7\text{COR}^{38}$; $-\text{NR}^7\text{SO}_2\text{R}^{38}$; $-\text{NR}^7\text{CONR}^7\text{R}^{57}$; $-\text{COR}^{38}$; or $-\text{SO}_2\text{R}^{38}$;
 20

R^{55} is H; CF_3 ; C_{1-6} -alkyl; C_{2-6} -alkenyl; C_{2-6} -alkynyl; cycloalkyl; heterocycloalkyl;
 aryl; heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; $-\text{COOR}^{36}$; or $-\text{CONR}^7\text{R}^{45}$;

R^{56} is H; F; CF_3 ; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl;
 25 heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; $-(\text{CR}^{42}\text{R}^{43})_s\text{OR}^{36}$; $-(\text{CR}^{42}\text{R}^{43})_s\text{NR}^7\text{R}^{45}$;
 $-(\text{CR}^{42}\text{R}^{43})_q\text{COOR}^{36}$; or $-(\text{CR}^{42}\text{R}^{43})_q\text{CONR}^7\text{R}^{45}$;

R^{57} is H; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; aryl- C_{1-6} -alkyl; or an *N*-protecting
 group.

30

Defined as for the Main Embodiment (vide supra) are i) the generic atoms and
 connector groups Z, Y, X, W, V, U, T, Q and M; ii) the indices m, n, p, q, r, s, t and u;
 as well as iii) pairs of substituents that can be define additional cyclic structural
 elements.

35

In a **Further Preferred Embodiment** of this invention, the macrocycles of type I are defined by groups of selected building blocks **A**, **B** and **C** and substituents R^1 - R^{57} as follows. The connectivities between these building blocks are defined as for the Preferred Embodiment and as shown in Scheme 5 above.

5

The biaryl Template **A** of the Further Preferred Embodiment is selected from

A_B1-A_C1 ; A_B1-A_C4 ; A_B1-A_C6 ; A_B1-A_C8 ; A_B1-A_C9 ; A_B1-A_C11 ; A_B1-A_C13 ;
 A_B1-A_C19 ; A_B1-A_C22 ; A_B1-A_C24 ; A_B1-A_C49 ; A_B1-A_C51 ; A_B2-A_C4 ; A_B2-A_C51 ;
 A_B4-A_C1 ; A_B4-A_C4 ; A_B4-A_C6 ; A_B4-A_C19 ; A_B4-A_C22 ; A_B4-A_C24 ; A_B4-A_C49 ;
 10 A_B4-A_C51 ; A_B4-A_C59 ; A_B5-A_C51 ; A_B5-A_C59 ; A_B6-A_C1 ; A_B6-A_C4 ; A_B6-A_C8 ; A_B6-A_C9 ;
 A_B6-A_C11 ; A_B6-A_C13 ; A_B6-A_C16 ; A_B6-A_C18 ; A_B6-A_C19 ; A_B6-A_C20 ; A_B6-A_C30 ;
 A_B6-A_C31 ; A_B6-A_C49 ; A_B6-A_C51 ; A_B9-A_C6 ; A_B9-A_C49 ; A_B14-A_C49 ; A_B20-A_C6 ;
 A_B20-A_C49 ; A_B23-A_C4 ; A_B23-A_C49 ; A_B45-A_C49 ; A_B45-A_C52 ; A_B45-A_C57 ;
 A_B45-A_C58 ; A_B45-A_C65 ; A_B45-A_C66 ; A_B46-A_C57 ; A_B46-A_C58 ; A_B49-A_C49 ;
 15 A_B50-A_C57 ; A_B50-A_C58 ; A_B50-A_C61 ; A_B51-A_C49 ; A_B51-A_C61 ; or A_B59-A_C61 .

The further preferred Modulator **B** is selected from

B1; **B4**; **B5**; **B6**; or **B7**;

and the further preferred Bridge of type **C** from

20 **C1**; **C2**; or **C3**.

The substituents R^1 - R^{57} attached to the Further Preferred Embodiment of macrocycle I are as defined as described below.

25 R^1 and R^2 are independently defined as H; F; Cl; Br; I; CF_3 ; OCF_3 ; $OCHF_2$;
 NO_2 ; CN; C_{1-6} -alkyl; C_{2-6} -alkenyl; C_{2-6} -alkynyl; cycloalkyl; heterocycloalkyl; aryl- C_{1-6} -
 alkyl; heteroaryl- C_{1-6} -alkyl; $-(CR^{32}R^{33})_qOR^{34}$; $-(CR^{32}R^{33})_qSR^{34}$; $-(CR^{32}R^{33})_qNR^7R^{35}$;
 $-(CR^{32}R^{33})_qOCONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7COOR^{36}$; $-(CR^{32}R^{33})_qNR^7COR^{37}$;
 $-(CR^{32}R^{33})_qNR^7CONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7SO_2R^{38}$; $-(CR^{32}R^{33})_qCOOR^{36}$;
 30 $-(CR^{32}R^{33})_qCONR^7R^{35}$; $-(CR^{32}R^{33})_qSO_2NR^7R^{35}$; $-(CR^{32}R^{33})_qCOR^{37}$; $-(CR^{32}R^{33})_qR^{39}$;
 $-(CR^{32}R^{33})_qR^{40}$; $-(CR^{32}R^{33})_qR^{41}$; or $-(CR^{32}R^{33})_qR^{44}$.

R^3 and R^4 are independently defined as H; F; Cl; CF_3 ; OCF_3 ; $OCHF_2$; NO_2 ;
 CN; C_{1-6} -alkyl; or C_{1-6} -alkoxy;

35

R⁵ is H; CF₃; or C₁₋₆-alkyl;

R⁶ is H; CF₃; C₁₋₆-alkyl; C₂₋₆-alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl-C₁₋₆-alkyl; heteroaryl-C₁₋₆-alkyl; $-(CR^{32}R^{33})_qOR^{34}$; $-(CR^{32}R^{33})_qSR^{34}$; $-(CR^{32}R^{33})_qNR^7R^{35}$; $-(CR^{32}R^{33})_qOCONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7COOR^{36}$; $-(CR^{32}R^{33})_qNR^7COR^{37}$; $-(CR^{32}R^{33})_qNR^7CONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7SO_2R^{38}$; $-(CR^{32}R^{33})_qCOOR^{36}$; $-(CR^{32}R^{33})_qCONR^7R^{35}$; $-(CR^{32}R^{33})_qSO_2NR^7R^{35}$; $-(CR^{32}R^{33})_qCOR^{37}$; $-(CR^{32}R^{33})_qR^{39}$; $-(CR^{32}R^{33})_sR^{40}$; $-(CR^{32}R^{33})_qR^{41}$; or $-(CR^{32}R^{33})_qR^{44}$;

R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹² and R¹³ are defined as in the Preferred Embodiment;

R¹⁴, R²⁰ and R²⁶ are independently defined as H; F; CF₃; C₁₋₆-alkyl; C₂₋₆-alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl-C₁₋₆-alkyl; heteroaryl-C₁₋₆-alkyl; $-(CR^{32}R^{33})_qOR^{34}$; $-(CR^{32}R^{33})_qSR^{34}$; $-(CR^{32}R^{33})_qNR^7R^{35}$; $-(CR^{32}R^{33})_qOCONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7COOR^{36}$; $-(CR^{32}R^{33})_qNR^7COR^{37}$; $-(CR^{32}R^{33})_qNR^7CONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7SO_2R^{38}$; $-(CR^{32}R^{33})_qCOOR^{36}$; $-(CR^{32}R^{33})_qCONR^7R^{35}$; $-(CR^{32}R^{33})_qSO_2NR^7R^{35}$; $-(CR^{32}R^{33})_qCOR^{37}$; $-(CR^{32}R^{33})_qR^{39}$; $-(CR^{32}R^{33})_sR^{40}$; $-(CR^{32}R^{33})_qR^{41}$; or $-(CR^{32}R^{33})_qR^{44}$;

R¹⁵, R¹⁶, R¹⁷, R¹⁹, R²¹, R²², R²³, R²⁵, R²⁷, R²⁸, R²⁹ and R³¹ are defined as in the Preferred Embodiment;

R¹⁸, R²⁴ and R³⁰ are independently defined as H; F; CF₃; C₁₋₆-alkyl; C₂₋₆-alkenyl; cycloalkyl; heterocycloalkyl; aryl-C₁₋₆-alkyl; heteroaryl-C₁₋₆-alkyl; $-(CR^{32}R^{33})_qOR^{34}$; $-(CR^{32}R^{33})_qNR^7R^{35}$; $-(CR^{32}R^{33})_qOCONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7COOR^{36}$; $-(CR^{32}R^{33})_qNR^7COR^{37}$; $-(CR^{32}R^{33})_qNR^7CONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7SO_2R^{38}$; $-(CR^{32}R^{33})_qCOOR^{36}$; $-(CR^{32}R^{33})_qCONR^7R^{35}$; $-(CR^{32}R^{33})_qCOR^{37}$; or $-(CR^{32}R^{33})_qR^{44}$;

R³² is H; F; CF₃; C₁₋₆-alkyl; C₂₋₆-alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl-C₁₋₆-alkyl; heteroaryl-C₁₋₆-alkyl; $-(CR^{42}R^{43})_qOR^{45}$; $-(CR^{42}R^{43})_qSR^{45}$; $-(CR^{42}R^{43})_qNR^7R^{45}$; $-(CR^{42}R^{43})_qNR^7COOR^{36}$; $-(CR^{42}R^{43})_qNR^7COR^{38}$; $-(CR^{42}R^{43})_qCOOR^{36}$; $-(CR^{42}R^{43})_qCONR^7R^{45}$; $-(CR^{42}R^{43})_qCOR^{38}$; $-(CR^{42}R^{43})_qR^{39}$; $-(CR^{42}R^{43})_sR^{40}$; $-(CR^{42}R^{43})_qR^{41}$; or $-(CR^{42}R^{43})_qR^{44}$;

R^{33} is H; or C_{1-6} -alkyl;

R^{34} is H; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl;

$-(CR^{42}R^{43})_rOR^{45}$; $-(CR^{42}R^{43})_rNR^7R^{45}$; $-(CR^{42}R^{43})_rOCONR^7R^{35}$;

5 $-(CR^{42}R^{43})_rNR^7COOR^{36}$; $-(CR^{42}R^{43})_rNR^7COR^{38}$; $-(CR^{42}R^{43})_rNR^7CONR^7R^{45}$;

$-(CR^{42}R^{43})_rNR^7SO_2R^{38}$; $-(CR^{42}R^{43})_qCOOR^{36}$; $-(CR^{42}R^{43})_qCONR^7R^{45}$;

$-(CR^{42}R^{43})_qCOR^{38}$; $-(CR^{42}R^{43})_qR^{39}$; $-(CR^{42}R^{43})_sR^{40}$; $-(CR^{42}R^{43})_qR^{41}$; or

$-(CR^{42}R^{43})_qR^{44}$;

10 R^{35} is H; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl;

aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; an *N*-protecting group; $-(CR^{32}R^{33})_rOR^{45}$;

$-(CR^{32}R^{33})_rNR^7R^{45}$; $-(CR^{32}R^{33})_rOCONR^7R^{45}$; $-(CR^{32}R^{33})_rNR^7COOR^{36}$;

$-(CR^{32}R^{33})_rNR^7COR^{37}$; $-(CR^{32}R^{33})_rNR^7CONR^7R^{50}$; $-(CR^{32}R^{33})_rNR^7SO_2R^{38}$;

$-(CR^{32}R^{33})_qCOOR^{36}$; $-(CR^{32}R^{33})_qCONR^7R^{45}$; $-(CR^{32}R^{33})_qCOR^{38}$; $-(CR^{32}R^{33})_qR^{39}$;

15 $-(CR^{32}R^{33})_sR^{40}$; $-(CR^{32}R^{33})_qR^{41}$; or $-(CR^{32}R^{33})_qR^{44}$;

R^{36} is H; C_{1-6} -alkyl; cycloalkyl; aryl; aryl- C_{1-6} -alkyl; or an *O/S*-protecting group;

R^{37} is C_{1-6} -alkyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl;

20 heteroaryl- C_{1-6} -alkyl; $-(CR^{42}R^{43})_qOR^{45}$; $-(CR^{42}R^{43})_qSR^{45}$; $-(CR^{42}R^{43})_qNR^7R^{45}$;

$-(CR^{42}R^{43})_sOCONR^7R^{45}$; $-(CR^{42}R^{43})_sNR^7COOR^{36}$; $-(CR^{42}R^{43})_sNR^7COR^{44}$;

$-(CR^{42}R^{43})_sNR^7CONR^7R^{45}$; $-(CR^{42}R^{43})_sNR^7SO_2R^{38}$; $-(CR^{42}R^{43})_qCOOR^{36}$;

$-(CR^{42}R^{43})_qCONR^7R^{45}$; $-(CR^{42}R^{43})_iCOR^{38}$; $-(CR^{42}R^{43})_iR^{39}$; $-(CR^{42}R^{43})_uR^{40}$;

$-(CR^{42}R^{43})_iR^{41}$; or $-(CR^{42}R^{43})_iR^{44}$;

25

R^{38} , R^{42} , R^{43} and R^{44} are defined as in the Preferred Embodiment;

R^{39} , R^{40} , and R^{41} are as defined in the Main Embodiment;

30 R^{45} is H; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl;

aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; an *N*-protecting group; $-(CR^{42}R^{43})_rOR^{36}$;

$-(CR^{42}R^{43})_rNR^7R^{57}$; $-(CR^{42}R^{43})_rOCONR^7R^{57}$; $-(CR^{42}R^{43})_rNR^7CONR^7R^{57}$;

$-(CR^{42}R^{43})_rNR^7COR^{38}$; $-(CR^{42}R^{43})_rNR^7SO_2R^{38}$; $-(CR^{42}R^{43})_qCOOR^{36}$;

$-(CR^{42}R^{43})_qCOR^{38}$; $-(CR^{42}R^{43})_qR^{39}$; $-(CR^{42}R^{43})_sR^{40}$; $-(CR^{42}R^{43})_qR^{41}$; or

35 $-(CR^{42}R^{43})_sR^{44}$;

R⁴⁶ is H; F; Cl; CF₃; OCF₃; OCHF₂; NO₂; CN; C₁₋₆-alkyl; C₂₋₆-alkenyl; C₂₋₆-alkynyl; cycloalkyl; heterocycloalkyl; aryl-C₁₋₆-alkyl; heteroaryl-C₁₋₆-alkyl; $-(\text{CR}^{42}\text{R}^{43})_q\text{OR}^{36}$; $-(\text{CR}^{42}\text{R}^{43})_q\text{NR}^7\text{R}^{57}$; $-(\text{CR}^{42}\text{R}^{43})_q\text{NR}^7\text{COR}^{38}$; $-(\text{CR}^{42}\text{R}^{43})_q\text{COOR}^{36}$; $-(\text{CR}^{42}\text{R}^{43})_q\text{CONR}^7\text{R}^{45}$; $-(\text{CR}^{42}\text{R}^{43})_q\text{SO}_2\text{NR}^7\text{R}^{45}$; $-(\text{CR}^{42}\text{R}^{43})_q\text{COR}^{38}$; or $-(\text{CR}^{42}\text{R}^{43})_q\text{R}^{44}$;

5

R⁴⁷ is H; C₁₋₆-alkyl; C₂₋₆-alkenyl; C₂₋₆-alkynyl; cycloalkyl; heterocycloalkyl; aryl-C₁₋₆-alkyl; heteroaryl-C₁₋₆-alkyl; or $-\text{NR}^7\text{R}^{45}$.

R⁴⁸ is H; C₁₋₆-alkyl; C₂₋₆-alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl-C₁₋₆-alkyl; heteroaryl-C₁₋₆-alkyl; an *N*-protecting group; $-(\text{CR}^{42}\text{R}^{43})_r\text{OR}^{45}$; $-(\text{CR}^{42}\text{R}^{43})_r\text{SR}^{45}$; $-(\text{CR}^{42}\text{R}^{43})_r\text{NR}^7\text{R}^{45}$; $-(\text{CR}^{42}\text{R}^{43})_r\text{OCONR}^7\text{R}^{45}$; $-(\text{CR}^{42}\text{R}^{43})_r\text{NR}^7\text{COOR}^{36}$; $-(\text{CR}^{42}\text{R}^{43})_r\text{NR}^7\text{COR}^{38}$; $-(\text{CR}^{42}\text{R}^{43})_r\text{NR}^7\text{CONR}^7\text{R}^{45}$; $-(\text{CR}^{42}\text{R}^{43})_r\text{NR}^7\text{SO}_2\text{R}^{38}$; $-(\text{CR}^{42}\text{R}^{43})_q\text{COOR}^{36}$; $-(\text{CR}^{42}\text{R}^{43})_q\text{CONR}^7\text{R}^{45}$; $-(\text{CR}^{42}\text{R}^{43})_q\text{COR}^{38}$; or $-(\text{CR}^{42}\text{R}^{43})_s\text{R}^{44}$;

15

R⁴⁹ is H; C₁₋₆-alkyl; C₂₋₆-alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl-C₁₋₆-alkyl; heteroaryl-C₁₋₆-alkyl; $-(\text{CR}^{42}\text{R}^{43})_q\text{OR}^{36}$; $-(\text{CR}^{42}\text{R}^{43})_q\text{NR}^7\text{R}^{45}$; $-(\text{CR}^{42}\text{R}^{43})_q\text{NR}^7\text{COR}^{38}$; $-(\text{CR}^{42}\text{R}^{43})_q\text{NR}^7\text{SO}_2\text{R}^{38}$; $-(\text{CR}^{42}\text{R}^{43})_q\text{COOR}^{36}$; $-(\text{CR}^{42}\text{R}^{43})_q\text{CONR}^7\text{R}^{45}$; $-(\text{CR}^{42}\text{R}^{43})_q\text{COR}^{38}$; or $-(\text{CR}^{42}\text{R}^{43})_q\text{R}^{44}$;

20

R⁵⁰ is H; C₁₋₆-alkyl; C₂₋₆-alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl-C₁₋₆-alkyl; heteroaryl-C₁₋₆-alkyl; or an *N*-protecting group;

R⁵¹ and R⁵³ are independently defined as H; F; CF₃; C₁₋₆-alkyl; C₂₋₆-alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl-C₁₋₆-alkyl; heteroaryl-C₁₋₆-alkyl; $-(\text{CR}^{42}\text{R}^{43})_t\text{OR}^{36}$; $-(\text{CR}^{42}\text{R}^{43})_t\text{NR}^7\text{R}^{57}$; $-(\text{CR}^{42}\text{R}^{43})_t\text{COOR}^{36}$; or $-(\text{CR}^{42}\text{R}^{43})_t\text{CONR}^7\text{R}^{57}$;

25

R⁵² is defined as in the Preferred Embodiment;

R⁵⁴ is H; F; CF₃; OCF₃; OCHF₂; NO₂; CN; C₁₋₆-alkyl; C₂₋₆-alkenyl; C₂₋₆-alkynyl; cycloalkyl; heterocycloalkyl; aryl-C₁₋₆-alkyl; heteroaryl-C₁₋₆-alkyl; $-\text{OR}^{36}$; $-\text{NR}^7\text{R}^{57}$; $-\text{NR}^7\text{COR}^{38}$; $-\text{NR}^7\text{SO}_2\text{R}^{38}$; $-\text{NR}^7\text{CONR}^7\text{R}^{57}$; $-\text{COR}^{38}$; or $-\text{SO}_2\text{R}^{38}$;

30

R⁵⁵ is H; CF₃; C₁₋₆-alkyl; C₂₋₆-alkenyl; C₂₋₆-alkynyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl-C₁₋₆-alkyl; heteroaryl-C₁₋₆-alkyl; $-\text{COOR}^{36}$; or $-\text{CONR}^7\text{R}^{45}$;

35

R^{56} is H; F; CF_3 ; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; $-(CR^{42}R^{43})_sOR^{36}$; $-(CR^{42}R^{43})_sNR^7R^{45}$; $-(CR^{42}R^{43})_qCOOR^{36}$; or $-(CR^{42}R^{43})_qCONR^7R^{45}$;

5 R^{57} is defined as in the Preferred Embodiment;

as are (vide supra) i) the generic atoms and connector groups Z, Y, X, W, V, U, T, Q and M; ii) the indices m, n, p, q, r, s, t and u; as well as iii) the pairs of substituents that can be define additional cyclic structural elements.

10

In a **Particularly Preferred Embodiment** of this invention, the macrocycles of type I are defined by groups of selected building blocks **A**, **B** and **C** and substituents R^1 - R^{57} as follows. The connectivities between these building blocks are defined as for the Preferred Embodiment and as shown in Scheme 5 above.

15

The biaryl Template **A** of the Particularly Preferred Embodiment is selected from

A_B1-A_C1 ; A_B1-A_C4 ; A_B1-A_C19 ; A_B2-A_C4 ; A_B4-A_C1 ; A_B4-A_C4 ; A_B4-A_C19 ; A_B4-A_C59 ; A_B5-A_C51 ; A_B5-A_C59 ; A_B6-A_C31 ; A_B9-A_C6 ; or A_B46-A_C58 .

20 The particularly preferred Modulator building block of type **B** and the Bridge of type **C** are selected as described in the Further Preferred Embodiment.

The substituents R^1 - R^{57} attached to the Particularly Preferred Embodiment of macrocycle I are as defined as described below.

25

R^1 and R^2 are defined as in the Further Preferred Embodiment;

R^3 and R^4 are independently defined as H; F; CF_3 ; OCF_3 ; $OCHF_2$; CN; or C_{1-6} -alkoxy;

30

R^5 is H; CF_3 ; or C_{1-6} -alkyl;

R^6 is defined as in the Further Preferred Embodiment;

35 R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} and R^{13} are defined as in the Preferred Embodiment;

R¹⁴, R²⁰ and R²⁶ are defined as in the Further Preferred Embodiment;

R¹⁵, R¹⁶, R¹⁷, R¹⁹, R²¹, R²², R²³, R²⁵, R²⁷, R²⁸, R²⁹ and R³¹ are defined as in the Preferred Embodiment,

5

R¹⁸, R²⁴, R³⁰ and R³² are defined as in the Further Preferred Embodiment;

R³³ is H; or C₁₋₆-alkyl;

10

R³⁴, R³⁵, R³⁶ and R³⁷ are defined as in the Further Preferred Embodiment;

R³⁸, R⁴², R⁴³ and R⁴⁴ are defined as in the Preferred Embodiment;

R³⁹, R⁴⁰, and R⁴¹ are as defined in the Main Embodiment;

15

R⁴⁵ is defined as in the Further Preferred Embodiment;

R⁴⁶ is H; F; Cl; CF₃; OCF₃; OCHF₂; NO₂; CN; C₁₋₆-alkyl; C₂₋₆-alkenyl; C₂₋₆-alkynyl; cycloalkyl; heterocycloalkyl; aryl-C₁₋₆-alkyl; heteroaryl-C₁₋₆-alkyl; or

20

-(CR⁴²R⁴³)_qR⁴⁴;

R⁴⁷ is H; C₁₋₆-alkyl; C₂₋₆-alkenyl; C₂₋₆-alkynyl; cycloalkyl; heterocycloalkyl; aryl-C₁₋₆-alkyl; heteroaryl-C₁₋₆-alkyl; or -NR⁷R⁴⁵;

25

R⁴⁸ is defined as in the Further Preferred Embodiment;

R⁴⁹ is H; C₁₋₆-alkyl; C₂₋₆-alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl-C₁₋₆-alkyl; heteroaryl-C₁₋₆-alkyl; or -(CR⁴²R⁴³)_qR⁴⁴;

30

R⁵⁰ is defined as in the Further Preferred Embodiment;

R⁵¹ and R⁵³ are independently defined as H; F; CF₃; C₁₋₆-alkyl; C₂₋₆-alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl-C₁₋₆-alkyl; heteroaryl-C₁₋₆-alkyl; -(CR⁴²R⁴³)_iOR³⁶; -(CR⁴²R⁴³)_iNR⁷R⁵⁷; -(CR⁴²R⁴³)_iCOOR³⁶; or -(CR⁴²R⁴³)_iCONR⁷R⁵⁷;

35

R⁵² is defined as in the Preferred Embodiment;

R^{54} is H; F; CF_3 ; OCF_3 ; $OCHF_2$; NO_2 ; CN; C_{1-6} -alkyl; C_{2-6} -alkenyl; C_{2-6} -alkynyl; cycloalkyl; heterocycloalkyl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; $-OR^{36}$; $-NR^7R^{57}$; $-NR^7COR^{38}$; $-NR^7SO_2R^{38}$; $-NR^7CONR^7R^{57}$; $-COR^{38}$; or $-SO_2R^{38}$;

5

R^{55} is H; CF_3 ; C_{1-6} -alkyl; C_{2-6} -alkenyl; C_{2-6} -alkynyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; $-COOR^{36}$; or $-CONR^7R^{45}$;

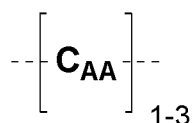
R^{56} is H; F; CF_3 ; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; $-(CR^{42}R^{43})_sOR^{36}$; $-(CR^{42}R^{43})_sNR^7R^{45}$; $-(CR^{42}R^{43})_qCOOR^{36}$; or $-(CR^{42}R^{43})_qCONR^7R^{45}$;

R^{57} is defined as in the Preferred Embodiment;

as are (vide supra) i) the generic atoms and connector groups Z, Y, X, W, V, U, T, Q and M; ii) the indices m, n, p, q, r, s, t and u; as well as iii) the pairs of substituents that can be define additional cyclic structural elements.

In an **Specific Representation of the Particularly Preferred Embodiment**

the **Bridge C** is represented by



wherein

C_{AA} is an amino acid selected from the readily accessible amino acids listed in Table 11. Even though only one stereoisomer, usually the L-enantiomer, is cited within Table 11, it is understood that the complementary enantiomer is also part to the embodiment. Also not listed explicitly, but part of the embodiment are the simple *N*-methyl derivatives of the listed amino acids.

Table 11: Structures representing subunits C_{AA} of Bridge C (*continued on the following pages*)

Code	Chemical Name
Ala	L-Alanine

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

Code	Chemical Name
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
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
Orn	L-Ornithine
tBuA	L-t-Butylalanine
Sar	Sarcosine
Pen	L-Penicillamine
tBuG	L-tert-Butylglycine
4AmPhe	L-para-Aminophenylalanine
3AmPhe	L-meta-Aminophenylalanine
2AmPhe	L-ortho-Aminophenylalanine

Code	Chemical Name
Phe(mC(NH ₂)=NH)	L-meta-Amidinophenylalanine
Phe(pC(NH ₂)=NH)	L-para-Amidinophenylalanine
Phe(mNHC(NH ₂)=NH)	L-meta-Guanidinophenylalanine
Phe(pNHC(NH ₂)=NH)	L-para-Guanidinophenylalanine
2Pal	(2S)-2-Amino-3-(pyridine-2'-yl)-propionic acid
4Pal	(2S)-2-Amino-3-(pyridine-4'-yl)-propionic acid
Phg	L-Phenylglycine
Cha	L-Cyclohexylalanine
C ₄ al	L-3-Cyclobutylalanine
C ₅ al	L-3-Cyclopentylalanine
Nle	L-Norleucine
2-Nal	L-2-Naphthylalanine
1-Nal	L-1-Naphthylalanine
4ClPhe	L-4-Chlorophenylalanine
3ClPhe	L-3-Chlorophenylalanine
2ClPhe	L-2-Chlorophenylalanine
3,4Cl ₂ Phe	L-3,4-Dichlorophenylalanine
4FPhe	L-4-Fluorophenylalanine
3FPhe	L-3-Fluorophenylalanine
2FPhe	L-2-Fluorophenylalanine
Thi	L-β-2-Thienylalanine
Tza	L-2-Thiazolylalanine
Mso	L-Methionine sulfoxide
AcLys	N-Acetyllysine
Dap	2,3-Diaminopropionic acid
Dab	2,4-Diaminobutyric acid
Dbu	(2S)-2,3-Diamino-butyric acid
Abu	γ-Aminobutyric acid (GABA)
Aha	ε-Aminohexanoic acid
Aib	α-Aminoisobutyric acid
ACC	1-Amino cyclopropane carboxylic acid
ACBC	1-Amino cyclobutane carboxylic acid
ACPC	1-Amino cyclopentane carboxylic acid
1-ACHC	1-Amino cyclohexane carboxylic acid

Code	Chemical Name
2-ACHC	2-Amino cyclohexane carboxylic acid
3-ACHC	3-Amino cyclohexane carboxylic acid
4-ACHC	4-Amino cyclohexane carboxylic acid
Y(Bzl)	L-O-Benzyltyrosine
H(Bzl)	(3S)-2-Amino-3-(1'-benzylimidazole-4'-yl)-propionic acid
Bip	L-(4-phenyl)phenylalanine
S(Bzl)	L-O-Benzylserine
T(Bzl)	L-O-Benzylthreonine
alloT	(2S, 3S)-2-Amino-3-hydroxy-butyric acid
Leu3OH	(2S, 3R)-2-Amino-3-hydroxy-4-methyl-pentanoic acid
hAla	L-Homo-alanine
hArg	L-Homo-arginine
hCys	L-Homo-cysteine
hGlu	L-Homo-glutamic acid
hGln	L-Homo-glutamine
hHis	L-Homo-histidine
hIle	L-Homo-isoleucine
hLeu	L-Homo-leucine
hNle	L-Homo-norleucine
hLys	L-Homo-lysine
hMet	L-Homo-Methionine
hPhe	L-Homo-phenylalanine
hSer	L-Homo-serine
hThr	L-Homo-threonine
hTrp	L-Homo-tryptophan
hTyr	L-Homo-tyrosine
hVal	L-Homo-valine
hCha	L-Homo-cyclohexylalanine
Bpa	L-4-Benzoylphenylalanine
OctG	L-Octylglycine
Tic	(3S)-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid
Tiq	(1S)-1,2,3,4-Tetrahydroisoquinoline-1-carboxylic acid
Oic	(2S, 3aS, 7aS)-1-Octahydro-1H-indole-2-carboxylic acid
4AmPyrr1	(2S, 4S)-4-Amino-pyrrolidine-2-carboxylic acid

Code	Chemical Name
4AmPyr2	(2S, 4R)-4-Amino-pyrrolidine-2-carboxylic acid
4PhePyr1	(2S, 4R)-4-Phenyl-pyrrolidine-2-carboxylic acid
4PhePyr2	(2S, 4S)-4-Phenyl-pyrrolidine-2-carboxylic acid
5PhePyr1	(2S, 5R)-5-Phenyl-pyrrolidine-2-carboxylic acid
5PhePyr2	(2S, 5S)-5-Phenyl-pyrrolidine-2-carboxylic acid
4Hyp1	(4S)-L-Hydroxyproline
4Hyp2	(4R)-L-Hydroxyproline
4Mp1	(4S)-L-Mercaptoproline
4Mp2	(4R)-L-Mercaptoproline
Pip	L-Pipecolic acid
H- β^3 -HCit-OH	(3S)-3-Amino-6-carbamidyl-hexanoic acid
H- β^3 -HO ^{rn} -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

Code	Chemical Name
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
H- β^3 -H2ClPhe-OH	(3S)-3-Amino-4-(2'-chlorophenyl)-butyric acid
H- β^3 -H3,4Cl ₂ Phe-OH	(3S)-3-Amino-4-(3',4'-dichlorophenyl)-butyric acid
H- β^3 -H4FPhe-OH	(3S)-3-Amino-4-(4'-fluorophenyl)-butyric acid
H- β^3 -H3FPhe-OH	(3S)-3-Amino-4-(3'-fluorophenyl)-butyric acid
H- β^3 -H2FPhe-OH	(3S)-3-Amino-4-(2'-fluorophenyl)-butyric acid
H- β^3 -HThi-OH	(3R)-3-Amino-4-(2'-thienyl)-butyric acid
H- β^3 -HTza-OH	(3R)-3-Amino-4-(2'-thiazolyl)-butyric acid
H- β^3 -HMso-OH	(3R)-3-Amino-4-methylsulfoxyl-butyric acid
H- β^3 -HAcLys-OH	(3S)-7-Acetylamino-3-amino-heptanoic acid
H- β^3 -HDpr-OH	(3R)-3,4-diamino-butyric acid
H- β^3 -HA ₂ Bu-OH	(3S)-3,5-Diamino-pentanoic acid
H- β^3 -HDbu-OH	(3R)-3,4-Diamino-pentanoic acid
H- β^3 -HAib-OH	Amino-dimethyl acetic acid
H- β^3 -HCyp-OH	1-Amino-cyclopentane-1-yl-acetic acid
H- β^3 -HY(Bzl)-OH	(3S)-3-Amino-4-(4'-benzyloxyphenyl)-butyric acid
H- β^3 -HH(Bzl)-OH	(3S)-3-Amino-4-(1'-benzylimidazole-4'-yl)-butyric acid
H- β^3 -HBip-OH	(3S)-3-Amino-4-biphenyl-butyl-butyric acid
H- β^3 -HS(Bzl)-OH	(3S)-3-Amino-4-(benzyloxy)-butyric acid
H- β^3 -HT(Bzl)-OH	(3R, 4R)-3-Amino-4-benzyloxy-pentanoic acid
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

Code	Chemical Name
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 -H4AmPyr1-OH	(2S, 4S)-4-Amino-pyrrolidine-2-acetic acid
H- β^3 -H4AmPyr2-OH	(2S, 4R)-4-Amino-pyrrolidine-2-acetic acid
H- β^3 -H4PhePyr1-OH	(2S, 4R)-4-Phenyl-pyrrolidine-2-acetic acid
H- β^3 -H4PhePyr2-OH	(2S, 4S)-4-Phenyl-pyrrolidine-2-acetic acid
H- β^3 -H5PhePyr1-OH	(2S, 5R)-5-Phenyl-pyrrolidine-2-acetic acid
H- β^3 -H5PhePyr2-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
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

Code	Chemical Name
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 ₄ al-OH	(4R)-4-Amino-5-cyclobutyl-pentanoic acid
H- γ^4 -DiHC ₅ al-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 ₂ Phe-OH	(4R)-4-Amino-5-(3',4'-dichloro-phenyl)-pentanoic acid
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-octanoic acid

Code	Chemical Name
H- γ^4 -DiHDpr-OH	(4R)-4,5-diamino-pentanoic acid
H- γ^4 -DiHA ₂ Bu-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-biphenyl-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 -DiHaloT-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
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)-hexanoic acid
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

Code	Chemical Name
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
(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

Code	Chemical Name
(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
Nip	(S)-Nipecotic acid/ (S)-3-Piperidinecarboxylic acid
INip	Isonipecotic acid/ 4-Piperidinecarboxylic acid
PCA	(S)-2-Piperazinecarboxylic acid
(S)betaPro	(S)- β -Proline/ (S)-Pyrrolidine-3-carboxylic acid

In a **Specific Embodiment** of this invention, the macrocycles of formula I are selected from the following list (Table 12).

5 **Table 12:** IUPAC Names of the Examples (*continued on the following pages*)

Example	IUPAC Name
Ex.1	benzyl N-[(12R,16S,18S)-16-[(<i>tert</i> -butoxycarbonyl)amino]-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]carbamate

Ex.2	<i>tert</i> -butyl <i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-12-amino-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-16-yl]carbamate
Ex.3	benzyl <i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-16-amino-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]carbamate
Ex.4	<i>tert</i> -butyl <i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-12-{[2-(1-naphthyl)acetyl]amino}-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-16-yl]carbamate
Ex.5	<i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-16-amino-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]-2-(1-naphthyl)acetamide
Ex.6	methyl <i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-12-{[2-(1-naphthyl)acetyl]amino}-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-16-yl]carbamate
Ex.7	<i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-8,13-dioxo-16-{[2-(1-pyrrolidinyl)acetyl]amino}-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]-2-(1-naphthyl)acetamide
Ex.8	<i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-16-(dimethylamino)-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]-2-(1-naphthyl)acetamide
Ex.9	(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-12,16-diamino-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaene-8,13-dione
Ex.10	benzyl <i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-16-{[2-(2-naphthyl)acetyl]amino}-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]carbamate
Ex.11	<i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-12-amino-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-16-yl]-2-(2-naphthyl)acetamide
Ex.12	2-(dimethylamino)- <i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-16-{[2-(2-naphthyl)acetyl]amino}-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]acetamide

Ex.13	3-methyl- <i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-16-{[2-(2-naphthyl)acetyl]amino}-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]butanamide
Ex.14	benzyl <i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-8,13-dioxo-16-[(phenoxycarbonyl)amino]-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]carbamate
Ex.15	benzyl <i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-12-[(<i>tert</i> -butoxycarbonyl)amino]-20-methyl-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]carbamate
Ex.16	<i>tert</i> -butyl <i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-16-amino-20-methyl-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-12-yl]carbamate
Ex.17	benzyl <i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-12-amino-20-methyl-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]carbamate
Ex.18	benzyl <i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-20-methyl-12-{[2-(2-naphthyl)acetyl]amino}-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]carbamate
Ex.19	<i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-16-amino-20-methyl-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-12-yl]-2-(2-naphthyl)acetamide
Ex.20	2-(dimethylamino)- <i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-20-methyl-12-{[2-(2-naphthyl)acetyl]amino}-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]acetamide
Ex.21	<i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-16-[(cyclopropylsulfonyl)amino]-20-methyl-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-12-yl]-2-(2-naphthyl)acetamide
Ex.22	<i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-20-methyl-16-[(methylamino)carbonyl]amino]-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-12-yl]-2-(2-naphthyl)acetamide
Ex.23	2-methoxy- <i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-20-methyl-12-{[2-(2-naphthyl)acetyl]amino}-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]acetamide

Ex.24	3-methyl- <i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-20-methyl-12-[[2-(2-naphthyl)acetyl]amino]-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]butanamide
Ex.25	<i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-20-methyl-15,21-dioxo-16-[(2-phenylacetyl)amino]-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-12-yl]-2-(2-naphthyl)acetamide
Ex.26	<i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-20-methyl-12-[[2-(2-naphthyl)acetyl]amino]-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]benzamide
Ex.27	<i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-20-methyl-12-[[2-(2-naphthyl)acetyl]amino]-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]butanamide
Ex.28	<i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-20-methyl-12-[[2-(2-naphthyl)acetyl]amino]-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]pentanamide
Ex.29	2-[[[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-16-[[2-(dimethylamino)acetyl]amino]-20-methyl-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-12-yl]amino}acetic acid
Ex.30	2-(dimethylamino)- <i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-20-methyl-12-[[[(methylamino)carbothioyl]amino]-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]acetamide
Ex.31	2-(dimethylamino)- <i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-20-methyl-15,21-dioxo-12-[(2-sulfanylacetyl)amino]-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]acetamide
Ex.32	2-(dimethylamino)- <i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-20-methyl-15,21-dioxo-12-[[2-(tritylsulfanyl)acetyl]amino]-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]acetamide
Ex.33	2-(dimethylamino)- <i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-20-methyl-12-[[[(methylamino)carbonyl]amino]-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]acetamide

Ex.34	2-(dimethylamino)- <i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-12-({[3-(dimethylamino)anilino]carbonyl}amino)-20-methyl-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]acetamide
Ex.35	2-(dimethylamino)- <i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-20-methyl-12-{{(2-naphthylamino)carbonyl}amino}-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]acetamide
Ex.36	2-(dimethylamino)- <i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-20-methyl-12-[(methylsulfonyl)amino]-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]acetamide
Ex.37	<i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-12-[(benzylsulfonyl)amino]-20-methyl-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]-2-(dimethylamino)acetamide
Ex.38	<i>tert</i> -butyl <i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-16-{{[2-(dimethylamino)acetyl]amino}-20-methyl-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-12-yl]carbamate
Ex.39	<i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-12-amino-20-methyl-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]-2-(dimethylamino)acetamide
Ex.40	ethyl 2-{{[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-16-{{[2-(dimethylamino)acetyl]amino}-20-methyl-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-12-yl]amino}acetate
Ex.41	benzyl (10 <i>R</i> ,15 <i>S</i>)-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxylate
Ex.42	(10 <i>R</i> ,15 <i>S</i>)-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxylic acid
Ex.43	(10 <i>R</i> ,15 <i>S</i>)-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide

Ex.44	(10 <i>R</i> ,15 <i>S</i>)-4-methoxy- <i>N</i> ,10,16-trimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide
Ex.45	(10 <i>R</i> ,15 <i>S</i>)-4-methoxy-10,16-dimethyl-12,17-dioxo- <i>N</i> -phenyl-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide
Ex.46	(10 <i>R</i> ,15 <i>S</i>)-4-methoxy-10,16-dimethyl-15-(1-pyrrolidinylcarbonyl)-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-12,17-dione
Ex.47	(10 <i>R</i> ,15 <i>S</i>)- <i>N</i> -[2-(dimethylamino)ethyl]-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide
Ex.48	<i>tert</i> -butyl <i>N</i> -[3-({[(10 <i>R</i> ,15 <i>S</i>)-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaen-15-yl]carbonyl}amino)propyl]carbamate
Ex.49	(10 <i>R</i> ,15 <i>S</i>)- <i>N</i> -(3-aminopropyl)-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide
Ex.50	(10 <i>R</i> ,15 <i>S</i>)-4-methoxy-10,16-dimethyl-12,17-dioxo- <i>N</i> -(3-pyridinylmethyl)-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide
Ex.51	(10 <i>R</i> ,15 <i>S</i>)-4-methoxy- <i>N</i> -(2-methoxyethyl)-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide
Ex.52	(10 <i>R</i> ,15 <i>S</i>)- <i>N</i> -cyclopropyl-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide
Ex.53	(10 <i>R</i> ,15 <i>S</i>)-4-methoxy-10,16-dimethyl-12,17-dioxo- <i>N</i> -(2,2,2-trifluoroethyl)-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide
Ex.54	(10 <i>R</i> ,15 <i>S</i>)- <i>N</i> -isobutyl-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide

Ex.55	(10 <i>R</i> ,15 <i>S</i>)- <i>N</i> -(2-hydroxyethyl)-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide
Ex.56	<i>tert</i> -butyl 2-({[(10 <i>R</i> ,15 <i>S</i>)-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaen-15-yl]carbonyl}amino)acetate
Ex.57	2-({ [(10 <i>R</i> ,15 <i>S</i>)-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaen-15-yl]carbonyl}amino)acetic acid
Ex.58	(10 <i>R</i> ,15 <i>S</i>)-4-methoxy-10,16-dimethyl-12,17-dioxo- <i>N</i> -[(1 <i>S</i>)-1-phenylethyl]-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide
Ex.59	(10 <i>R</i> ,15 <i>S</i>)- <i>N</i> -[2-(dimethylamino)ethyl]-4-methoxy- <i>N</i> ,10,16-trimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide
Ex.60	(10 <i>R</i> ,15 <i>S</i>)-4-methoxy-10,16-dimethyl- <i>N</i> -(1-naphthylmethyl)-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide
Ex.61	(10 <i>R</i> ,15 <i>S</i>)-4-methoxy-10,16-dimethyl- <i>N</i> -(2-naphthylmethyl)-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide
Ex.62	(10 <i>R</i> ,15 <i>S</i>)-15-(hydroxymethyl)-4-methoxy-10,16-dimethyl-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-12,17-dione
Ex.63	(10 <i>R</i> ,15 <i>S</i>)-4-methoxy-10,16-dimethyl-15-[(3-pyridinyloxy)methyl]-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-12,17-dione
Ex.64	(10 <i>R</i> ,15 <i>S</i>)-15-(azidomethyl)-4-methoxy-10,16-dimethyl-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-12,17-dione
Ex.65	(10 <i>R</i> ,15 <i>S</i>)-15-(aminomethyl)-4-methoxy-10,16-dimethyl-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-12,17-dione
Ex.66	<i>N</i> -{[(10 <i>R</i> ,15 <i>S</i>)-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaen-15-yl]methyl}-2-phenylacetamide

Ex.67	[(10 <i>R</i> ,15 <i>S</i>)-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaen-15-yl]methyl <i>N</i> -phenylcarbamate
Ex.68	benzyl (9 <i>S</i> ,14 <i>S</i>)-9,15-dimethyl-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxylate
Ex.69	(9 <i>S</i> ,14 <i>S</i>)-9,15-dimethyl-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxylic acid
Ex.70	(9 <i>S</i> ,14 <i>S</i>)- <i>N</i> ,9,15-trimethyl-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide
Ex.71	(9 <i>S</i> ,14 <i>S</i>)-9,15-dimethyl-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide
Ex.72	(9 <i>S</i> ,14 <i>S</i>)-9,15-dimethyl-11,16-dioxo- <i>N</i> -phenyl-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide
Ex.73	(9 <i>S</i> ,14 <i>S</i>)-9,15-dimethyl-11,16-dioxo- <i>N</i> -phenethyl-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide
Ex.74	(9 <i>S</i> ,14 <i>S</i>)-9,15-dimethyl- <i>N</i> -(1-naphthylmethyl)-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide
Ex.75	(9 <i>S</i> ,14 <i>S</i>)-9,15-dimethyl-11,16-dioxo- <i>N</i> -(3-pyridinylmethyl)-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide
Ex.76	(9 <i>S</i> ,14 <i>S</i>)-9,15-dimethyl-11,16-dioxo- <i>N</i> -[(1 <i>S</i>)-1-phenylethyl]-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide
Ex.77	(9 <i>S</i> ,14 <i>S</i>)- <i>N</i> -(2-methoxyethyl)-9,15-dimethyl-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide

Ex.78	(9 <i>S</i> ,14 <i>S</i>)-9,15-dimethyl-11,16-dioxo- <i>N</i> -(2,2,2-trifluoroethyl)-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide
Ex.79	(9 <i>S</i> ,14 <i>S</i>)- <i>N</i> -cyclopropyl-9,15-dimethyl-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide
Ex.80	(9 <i>S</i> ,14 <i>S</i>)- <i>N</i> -isobutyl-9,15-dimethyl-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide
Ex.81	(9 <i>S</i> ,14 <i>S</i>)- <i>N</i> -(2-hydroxyethyl)-9,15-dimethyl-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide
Ex.82	<i>tert</i> -butyl 2-({[(9 <i>S</i> ,14 <i>S</i>)-9,15-dimethyl-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaen-14-yl]carbonyl}amino)acetate
Ex.83	2-({[(9 <i>S</i> ,14 <i>S</i>)-9,15-dimethyl-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaen-14-yl]carbonyl}amino)acetic acid
Ex.84	(9 <i>S</i> ,14 <i>S</i>)- <i>N</i> -[2-(dimethylamino)ethyl]-9,15-dimethyl-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide
Ex.85	(9 <i>S</i> ,14 <i>S</i>)-9,15-dimethyl-11,16-dioxo- <i>N</i> -[3-(1-pyrrolidinyl)propyl]-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide
Ex.86	(9 <i>S</i> ,14 <i>S</i>)-14-(1-azetanylcabonyl)-9,15-dimethyl-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-11,16-dione
Ex.87	(9 <i>S</i> ,14 <i>S</i>)-9,15-dimethyl-14-(morpholinocarbonyl)-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-11,16-dione
Ex.88	(9 <i>S</i> ,14 <i>S</i>)-9,15-dimethyl- <i>N</i> -[(1-methyl-1 <i>H</i> -imidazol-4-yl)methyl]-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide

Ex.89	(9 <i>S</i> ,14 <i>S</i>)-9,15-dimethyl- <i>N</i> -(2-naphthylmethyl)-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide
Ex.90	benzyl (9 <i>S</i> ,11 <i>R</i>)-11-[(<i>tert</i> -butoxycarbonyl)amino]-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaene-16-carboxylate
Ex.91	<i>tert</i> -butyl <i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]carbamate
Ex.92	benzyl (9 <i>S</i> ,11 <i>R</i>)-11-amino-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaene-16-carboxylate
Ex.93	(9 <i>S</i> ,11 <i>R</i>)-11-amino-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaene-14,20-dione
Ex.94	<i>tert</i> -butyl <i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-methyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]carbamate
Ex.95	(9 <i>S</i> ,11 <i>R</i>)-11-amino-16-methyl-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaene-14,20-dione
Ex.96	<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-methyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(2-naphthyl)acetamide
Ex.97	<i>tert</i> -butyl <i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-(3-fluorobenzyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]carbamate
Ex.98	(9 <i>S</i> ,11 <i>R</i>)-11-amino-16-(3-fluorobenzyl)-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaene-14,20-dione
Ex.99	<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-methyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]acetamide

Ex.100	<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-(3-fluorobenzyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]acetamide
Ex.101	<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-methyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(1-naphthyl)acetamide
Ex.102	<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-methyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]- <i>N'</i> -phenylurea
Ex.103	<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-methyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]benzenesulfonamide
Ex.104	<i>tert</i> -butyl <i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-[2-(dimethylamino)acetyl]-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]carbamate
Ex.105	(9 <i>S</i> ,11 <i>R</i>)-11-amino-16-[2-(dimethylamino)acetyl]-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaene-14,20-dione
Ex.106	<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-[2-(dimethylamino)acetyl]-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-phenylacetamide
Ex.107	<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-[2-(dimethylamino)acetyl]-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]cyclopropanesulfonamide
Ex.108	<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-[2-(dimethylamino)acetyl]-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]- <i>N'</i> -methylurea
Ex.109	<i>tert</i> -butyl <i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-(cyclopropylsulfonyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]carbamate
Ex.110	(9 <i>S</i> ,11 <i>R</i>)-11-amino-16-(cyclopropylsulfonyl)-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaene-14,20-dione

Ex.111	<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-(cyclopropylsulfonyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]benzamide
Ex.112	<i>tert</i> -butyl <i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-[(methylamino)carbonyl]-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]carbamate
Ex.113	(9 <i>S</i> ,11 <i>R</i>)-11-amino- <i>N</i> -methyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaene-16-carboxamide
Ex.114	(9 <i>S</i> ,11 <i>R</i>)-11-[(3-fluorobenzoyl)amino]- <i>N</i> -methyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaene-16-carboxamide
Ex.115	allyl <i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-14-oxo-18-oxa-8-thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]carbamate
Ex.116	(13 <i>S</i> ,16 <i>R</i>)-13-amino-16-methyl-18-oxa-8-thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-14-one
Ex.117	<i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-14-oxo-18-oxa-8-thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]-2-(1-naphthyl)acetamide
Ex.118	<i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-14-oxo-18-oxa-8-thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]-2-(2-naphthyl)acetamide
Ex.119	<i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-14-oxo-18-oxa-8-thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]-2-(1-pyrrolidinyl)acetamide
Ex.120	<i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-14-oxo-18-oxa-8-thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]nicotinamide
Ex.121	3-methyl- <i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-14-oxo-18-oxa-8-thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]butanamide
Ex.122	methyl <i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-14-oxo-18-oxa-8-thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]carbamate
Ex.123	<i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-14-oxo-18-oxa-8-thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]cyclopropanesulfonamide

Ex.124	<i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-14-oxo-18-oxa-8-thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]benzenesulfonamide
Ex.125	<i>N</i> -methyl- <i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-14-oxo-18-oxa-8-thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]urea
Ex.126	<i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-14-oxo-18-oxa-8-thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]- <i>N</i> -(3-pyridinyl)urea
Ex.127	(13 <i>S</i> ,16 <i>R</i>)-13-(isobutylamino)-16-methyl-18-oxa-8-thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-14-one
Ex.128	(13 <i>S</i> ,16 <i>R</i>)-13-(isopentylamino)-16-methyl-18-oxa-8-thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-14-one
Ex.129	allyl <i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-8,8,14-trioxo-18-oxa-8λ ⁶ -thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]carbamate
Ex.130	(13 <i>S</i> ,16 <i>R</i>)-13-amino-16-methyl-18-oxa-8λ ⁶ -thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaene-8,8,14-trione
Ex.131	<i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-8,8,14-trioxo-18-oxa-8λ ⁶ -thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]-2-(1-naphthyl)acetamide
Ex.132	<i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-8,8,14-trioxo-18-oxa-8λ ⁶ -thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]-2-(2-naphthyl)acetamide
Ex.133	<i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-8,8,14-trioxo-18-oxa-8λ ⁶ -thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]-2-(1-pyrrolidinyl)acetamide
Ex.134	<i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-8,8,14-trioxo-18-oxa-8λ ⁶ -thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]nicotinamide
Ex.135	3-methyl- <i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-8,8,14-trioxo-18-oxa-8λ ⁶ -thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]butanamide
Ex.136	methyl <i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-8,8,14-trioxo-18-oxa-8λ ⁶ -thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]carbamate
Ex.137	<i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-8,8,14-trioxo-18-oxa-8λ ⁶ -thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]cyclopropanesulfonamide

Ex.138	<i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-8,8,14-trioxo-18-oxa-8λ ⁶ -thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]benzenesulfonamide
Ex.139	<i>N</i> -methyl- <i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-8,8,14-trioxo-18-oxa-8λ ⁶ -thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]urea
Ex.140	<i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-8,8,14-trioxo-18-oxa-8λ ⁶ -thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]- <i>N</i> -(3-pyridinyl)urea
Ex.141	(13 <i>S</i> ,16 <i>R</i>)-13-(isobutylamino)-16-methyl-18-oxa-8λ ⁶ -thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaene-8,8,14-trione
Ex.142	(13 <i>S</i> ,16 <i>R</i>)-13-(isopentylamino)-16-methyl-18-oxa-8λ ⁶ -thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaene-8,8,14-trione
Ex.143	allyl <i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]carbamate
Ex.144	(10 <i>R</i> ,13 <i>S</i>)-13-amino-10-methyl-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-12-one
Ex.145	(10 <i>R</i> ,13 <i>S</i>)-13-(dimethylamino)-10-methyl-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-12-one
Ex.146	(10 <i>R</i> ,13 <i>S</i>)-13-(isobutylamino)-10-methyl-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-12-one
Ex.147	(10 <i>R</i> ,13 <i>S</i>)-13-[(3-fluorobenzyl)amino]-10-methyl-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-12-one
Ex.148	<i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]acetamide
Ex.149	2-methoxy- <i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]acetamide
Ex.150	2-(dimethylamino)- <i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]acetamide
Ex.151	<i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]nicotinamide
Ex.152	3-methyl- <i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]butanamide

Ex.153	<i>tert</i> -butyl <i>N</i> -(3-[(<i>10R</i> , <i>13S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]amino}-3-oxopropyl)carbamate
Ex.154	3-amino- <i>N</i> [(<i>10R</i> , <i>13S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]propanamide
Ex.155	<i>N</i> [(<i>10R</i> , <i>13S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]-2-(1-naphthyl)acetamide
Ex.156	<i>N</i> [(<i>10R</i> , <i>13S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]-2-(2-naphthyl)acetamide
Ex.157	3,3,3-trifluoro- <i>N</i> [(<i>10R</i> , <i>13S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]propanamide
Ex.158	3-fluoro- <i>N</i> [(<i>10R</i> , <i>13S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]benzamide
Ex.159	<i>N</i> [(<i>10R</i> , <i>13S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]- <i>N</i> -(3-pyridinyl)urea
Ex.160	<i>N</i> -methyl- <i>N</i> [(<i>10R</i> , <i>13S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]urea
Ex.161	<i>tert</i> -butyl 3-[(<i>10R</i> , <i>13S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]amino}carbonyl)amino]propanoate
Ex.162	3-[(<i>10R</i> , <i>13S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]amino}carbonyl)amino]propanoic acid
Ex.163	<i>N</i> [(<i>10R</i> , <i>13S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]methanesulfonamide
Ex.164	<i>N</i> [(<i>10R</i> , <i>13S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]cyclopropanesulfonamide

Ex.165	<i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]benzenesulfonamide
Ex.166	methyl <i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]carbamate
Ex.167	2-methoxyethyl <i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]carbamate
Ex.168	allyl <i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]carbamate
Ex.169	(10 <i>R</i> ,13 <i>S</i>)-13-amino-10-methyl-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaene-12,18,18-trione
Ex.170	(10 <i>R</i> ,13 <i>S</i>)-13-(dimethylamino)-10-methyl-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaene-12,18,18-trione
Ex.171	(10 <i>R</i> ,13 <i>S</i>)-13-(isobutylamino)-10-methyl-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaene-12,18,18-trione
Ex.172	(10 <i>R</i> ,13 <i>S</i>)-13-[(3-fluorobenzyl)amino]-10-methyl-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaene-12,18,18-trione
Ex.173	<i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]acetamide
Ex.174	2-methoxy- <i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]acetamide
Ex.175	2-(dimethylamino)- <i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]acetamide
Ex.176	<i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]nicotinamide
Ex.177	3-methyl- <i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]butanamide
Ex.178	<i>tert</i> -butyl <i>N</i> -(3-[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]amino}-3-oxopropyl)carbamate

Ex. 179	3-amino- <i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]propanamide
Ex. 180	<i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]-2-(1-naphthyl)acetamide
Ex. 181	<i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]-2-(2-naphthyl)acetamide
Ex. 182	3,3,3-trifluoro- <i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]propanamide
Ex. 183	3-fluoro- <i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]benzamide
Ex. 184	<i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]- <i>N</i> -(3-pyridinyl)urea
Ex. 185	<i>N</i> -methyl- <i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]urea
Ex. 186	<i>tert</i> -butyl 3-[(<i>[(10<i>R</i>,13<i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18λ^6-thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]amino</i> carbonyl)amino]propanoate
Ex. 187	3-[(<i>[(10<i>R</i>,13<i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18λ^6-thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]amino</i> carbonyl)amino]propanoic acid
Ex. 188	<i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]methanesulfonamide
Ex. 189	<i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]cyclopropanesulfonamide
Ex. 190	<i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]benzenesulfonamide

Ex.191	methyl <i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]carbamate
Ex.192	2-methoxyethyl <i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]carbamate
Ex.193a	(9 <i>S</i> ,16 <i>S</i> ,19 <i>R</i>)-16-benzyl-19,20-dimethyl-7-oxa-13,17,20,24-tetraazatetracyclo[20.3.1.1 ^{2,6} .0 ^{9,13}]heptacos-1(26),2(27),3,5,22,24-hexaene-14,18,21-trione
Ex.193c	(9 <i>S</i> ,19 <i>S</i>)-19-benzyl-20-methyl-7-oxa-13,17,20,24-tetraazatetracyclo[20.3.1.1 ^{2,6} .0 ^{9,13}]heptacos-1(26),2(27),3,5,22,24-hexaene-14,18,21-trione
Ex.193d	(9 <i>S</i> ,19 <i>S</i>)-19-benzyl-7-oxa-13,17,20,24-tetraazatetracyclo[20.3.1.1 ^{2,6} .0 ^{9,13}]heptacos-1(26),2(27),3,5,22,24-hexaene-14,18,21-trione
Ex.193e	(9 <i>S</i> ,16 <i>R</i> ,19 <i>S</i>)-19-benzyl-16,17,20-trimethyl-7-oxa-13,17,20,24-tetraazatetracyclo[20.3.1.1 ^{2,6} .0 ^{9,13}]heptacos-1(26),2(27),3,5,22,24-hexaene-14,18,21-trione
Ex.193f	(9 <i>S</i> ,16 <i>R</i>)-16,17,20-trimethyl-7-oxa-13,17,20,24-tetraazatetracyclo[20.3.1.1 ^{2,6} .0 ^{9,13}]heptacos-1(26),2(27),3,5,22,24-hexaene-14,18,21-trione
Ex.193g	(9 <i>S</i> ,16 <i>R</i> ,19 <i>S</i>)-19-benzyl-16,17-dimethyl-7-oxa-13,17,20,24-tetraazatetracyclo[20.3.1.1 ^{2,6} .0 ^{9,13}]heptacos-1(26),2(27),3,5,22,24-hexaene-14,18,21-trione
Ex.193h	(9 <i>S</i> ,16 <i>S</i>)-16-benzyl-21-methyl-7-oxa-13,17,21,25-tetraazatetracyclo[21.3.1.1 ^{2,6} .0 ^{9,13}]octacos-1(27),2(28),3,5,23,25-hexaene-14,18,22-trione
Ex.194b	3-[(9 <i>S</i> ,16 <i>R</i> ,19 <i>S</i>)-16,17,20-trimethyl-14,18,21-trioxo-7-oxa-13,17,20,24-tetraazatetracyclo[20.3.1.1 ^{2,6} .0 ^{9,13}]heptacos-1(26),2(27),3,5,22,24-hexaen-19-yl]propanoic acid
Ex.195a	(9 <i>S</i> ,16 <i>R</i> ,22 <i>S</i>)-16,17,20,22,23-pentamethyl-7-oxa-13,17,20,23,27-pentaazatetracyclo[23.3.1.1 ^{2,6} .0 ^{9,13}]triaconta-1(29),2(30),3,5,25,27-hexaene-14,18,21,24-tetrone
Ex.195b	(9 <i>S</i> ,16 <i>R</i> ,22 <i>S</i>)-16,17,22-trimethyl-7-oxa-13,17,20,23,27-pentaazatetracyclo[23.3.1.1 ^{2,6} .0 ^{9,13}]triaconta-1(29),2(30),3,5,25,27-hexaene-14,18,21,24-tetrone

Ex.195e	(9 <i>S</i> ,19 <i>R</i> ,22 <i>S</i>)-16,19,20,22,23-pentamethyl-7-oxa-13,16,20,23,27-pentaazatetracyclo[23.3.1.1 ^{2,6} .0 ^{9,13}]triaconta-1(29),2(30),3,5,25,27-hexaene-14,17,21,24-tetrone
Ex.195f	(9 <i>S</i> ,18 <i>S</i> ,22 <i>R</i>)-16,18,19,22,23-pentamethyl-7-oxa-13,16,19,23,27-pentaazatetracyclo[23.3.1.1 ^{2,6} .0 ^{9,13}]triaconta-1(29),2(30),3,5,25,27-hexaene-14,17,20,24-tetrone
Ex.195g	(9 <i>S</i> ,18 <i>S</i> ,21 <i>R</i>)-18-benzyl-21,22-dimethyl-7-oxa-13,16,19,22,26-pentaazatetracyclo[22.3.1.1 ^{2,6} .0 ^{9,13}]nonacosa-1(28),2(29),3,5,24,26-hexaene-14,17,20,23-tetrone
Ex.195h	(9 <i>S</i> ,18 <i>S</i> ,21 <i>R</i>)-18-benzyl-16,21-dimethyl-7-oxa-13,16,19,22,26-pentaazatetracyclo[22.3.1.1 ^{2,6} .0 ^{9,13}]nonacosa-1(28),2(29),3,5,24,26-hexaene-14,17,20,23-tetrone
Ex.195j	(9 <i>S</i> ,18 <i>S</i> ,21 <i>R</i>)-18-benzyl-16,21,22-trimethyl-7-oxa-13,16,19,22,26-pentaazatetracyclo[22.3.1.1 ^{2,6} .0 ^{9,13}]nonacosa-1(28),2(29),3,5,24,26-hexaene-14,17,20,23-tetrone
Ex.196c	3-[(9 <i>S</i> ,16 <i>R</i> ,19 <i>S</i> ,22 <i>S</i>)-16,17,19,23-tetramethyl-14,18,21,24-tetraoxo-7-oxa-13,17,20,23,27-pentaazatetracyclo[23.3.1.1 ^{2,6} .0 ^{9,13}]triaconta-1(29),2(30),3,5,25,27-hexaen-22-yl]propanoic acid
Ex.196i	3-[(9 <i>S</i> ,15 <i>S</i> ,18 <i>R</i> ,21 <i>S</i>)-18-benzyl-15,22-dimethyl-14,17,20,23-tetraoxo-7-oxa-13,16,19,22,26-pentaazatetracyclo[22.3.1.1 ^{2,6} .0 ^{9,13}]nonacosa-1(28),2(29),3,5,24,26-hexaen-21-yl]propanoic acid
Ex.196k	3-[(9 <i>S</i> ,15 <i>R</i> ,18 <i>S</i> ,21 <i>S</i>)-18-benzyl-15,22-dimethyl-14,17,20,23-tetraoxo-7-oxa-13,16,19,22,26-pentaazatetracyclo[22.3.1.1 ^{2,6} .0 ^{9,13}]nonacosa-1(28),2(29),3,5,24,26-hexaen-21-yl]propanoic acid
Ex.197d	(9 <i>S</i> ,16 <i>R</i> ,19 <i>S</i> ,22 <i>R</i>)-19-(4-aminobutyl)-16,17,22-trimethyl-7-oxa-13,17,20,23,27-pentaazatetracyclo[23.3.1.1 ^{2,6} .0 ^{9,13}]triaconta-1(29),2(30),3,5,25,27-hexaene-14,18,21,24-tetrone
Ex.198	benzyl (10 <i>S</i> ,12 <i>S</i>)-12-[(<i>tert</i> -butoxycarbonyl)amino]-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaene-17-carboxylate
Ex.199	benzyl (10 <i>S</i> ,12 <i>S</i>)-12-amino-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaene-17-carboxylate

Ex.200	<i>tert</i> -butyl <i>N</i> -[(10 <i>S</i> ,12 <i>S</i>)-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaen-12-yl]carbamate
Ex.201	<i>tert</i> -butyl <i>N</i> -[(10 <i>S</i> ,12 <i>S</i>)-17-methyl-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaen-12-yl]carbamate
Ex.202	(10 <i>S</i> ,12 <i>S</i>)-12-amino-17-methyl-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaene-15,21-dione
Ex.203	<i>N</i> -[(10 <i>S</i> ,12 <i>S</i>)-17-methyl-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaen-12-yl]-2-(1-naphthyl)acetamide
Ex.204	3-methyl- <i>N</i> -[(10 <i>S</i> ,12 <i>S</i>)-17-methyl-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaen-12-yl]butanamide
Ex.205	<i>N</i> -[(10 <i>S</i> ,12 <i>S</i>)-17-methyl-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaen-12-yl]- <i>N</i> -(3-pyridinyl)urea
Ex.206	<i>N</i> -[(10 <i>S</i> ,12 <i>S</i>)-17-methyl-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaen-12-yl]benzenesulfonamide
Ex.207	<i>tert</i> -butyl <i>N</i> -[(10 <i>S</i> ,12 <i>S</i>)-17-[2-(dimethylamino)acetyl]-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaen-12-yl]carbamate
Ex.208	(10 <i>S</i> ,12 <i>S</i>)-12-amino-17-[2-(dimethylamino)acetyl]-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaene-15,21-dione
Ex.209	<i>N</i> -[(10 <i>S</i> ,12 <i>S</i>)-17-[2-(dimethylamino)acetyl]-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaen-12-yl]-2-phenylacetamide
Ex.210	<i>N</i> -[(10 <i>S</i> ,12 <i>S</i>)-17-[2-(dimethylamino)acetyl]-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaen-12-yl]- <i>N</i> -methylurea

Ex.211	<i>N</i> -[(10 <i>S</i> ,12 <i>S</i>)-17-[2-(dimethylamino)acetyl]-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaen-12-yl]cyclopropanesulfonamide
Ex.212	benzyl (10 <i>S</i> ,12 <i>S</i>)-12-(acetylamino)-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaene-17-carboxylate
Ex.213	<i>N</i> -[(10 <i>S</i> ,12 <i>S</i>)-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaen-12-yl]acetamide
Ex.214	<i>N</i> -[(10 <i>S</i> ,12 <i>S</i>)-17-(3-fluorobenzyl)-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaen-12-yl]acetamide
Ex.215	<i>N</i> -[(10 <i>S</i> ,12 <i>S</i>)-15,21-dioxo-17-[2-(1-pyrrolidinyl)acetyl]-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaen-12-yl]acetamide
Ex.216	(10 <i>S</i> ,12 <i>S</i>)-12-(acetylamino)-15,21-dioxo- <i>N</i> -phenyl-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaene-17-carboxamide
Ex.217	<i>N</i> -[(10 <i>S</i> ,12 <i>S</i>)-15,21-dioxo-17-(phenylsulfonyl)-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaen-12-yl]acetamide
Ex.218	3-({[(10 <i>S</i> ,12 <i>S</i>)-12-(acetylamino)-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaen-17-yl]carbonyl}amino)propanoic acid
Ex.219	<i>tert</i> -butyl 3-({[(10 <i>S</i> ,12 <i>S</i>)-12-(acetylamino)-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaen-17-yl]carbonyl}amino)propanoate
Ex.220	methyl (8 <i>S</i> ,17 <i>S</i> ,19 <i>S</i>)-17-[(<i>tert</i> -butoxycarbonyl)amino]-24-fluoro-6,14-dioxo-10,21-dioxa-4-thia-7,15-diazatetracyclo[20.3.1.1 ^{2,5} .0 ^{15,19}]heptacosa-1(26),2,5(27),12,22,24-hexaene-8-carboxylate
Ex.221	methyl (8 <i>S</i> ,17 <i>S</i> ,19 <i>S</i>)-17-[(<i>tert</i> -butoxycarbonyl)amino]-24-fluoro-6,14-dioxo-10,21-dioxa-4-thia-7,15-diazatetracyclo[20.3.1.1 ^{2,5} .0 ^{15,19}]heptacosa-1(26),2,5(27),22,24-pentaene-8-carboxylate

Ex.222	methyl (8 <i>S</i> ,17 <i>S</i> ,19 <i>S</i>)-17-amino-24-fluoro-6,14-dioxo-10,21-dioxo-4-thia-7,15-diazatetracyclo[20.3.1.1 ^{2,5} .0 ^{15,19}]heptacosa-1(26),2,5(27),22,24-pentaene-8-carboxylate
Ex.223	methyl (8 <i>S</i> ,17 <i>S</i> ,19 <i>S</i>)-24-fluoro-6,14-dioxo-17-[(2-phenylacetyl)amino]-10,21-dioxo-4-thia-7,15-diazatetracyclo[20.3.1.1 ^{2,5} .0 ^{15,19}]heptacosa-1(26),2,5(27),22,24-pentaene-8-carboxylate
Ex.224	(8 <i>S</i> ,17 <i>S</i> ,19 <i>S</i>)-24-fluoro-6,14-dioxo-17-[(2-phenylacetyl)amino]-10,21-dioxo-4-thia-7,15-diazatetracyclo[20.3.1.1 ^{2,5} .0 ^{15,19}]heptacosa-1(26),2,5(27),22,24-pentaene-8-carboxylic acid
Ex.225	(8 <i>S</i> ,17 <i>S</i> ,19 <i>S</i>)-24-fluoro-6,14-dioxo-17-[(2-phenylacetyl)amino]-10,21-dioxo-4-thia-7,15-diazatetracyclo[20.3.1.1 ^{2,5} .0 ^{15,19}]heptacosa-1(26),2,5(27),22,24-pentaene-8-carboxamide
Ex.226	(8 <i>S</i> ,17 <i>S</i> ,19 <i>S</i>)-24-fluoro- <i>N</i> -isobutyl-6,14-dioxo-17-[(2-phenylacetyl)amino]-10,21-dioxo-4-thia-7,15-diazatetracyclo[20.3.1.1 ^{2,5} .0 ^{15,19}]heptacosa-1(26),2,5(27),22,24-pentaene-8-carboxamide
Ex.227	methyl (8 <i>S</i> ,12 <i>E</i> ,18 <i>S</i> ,20 <i>S</i>)-18-[(<i>tert</i> -butoxycarbonyl)amino]-25-fluoro-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacosa-1(27),2,5(28),12,23,25-hexaene-8-carboxylate
Ex.228	(8 <i>S</i> ,12 <i>E</i> ,18 <i>S</i> ,20 <i>S</i>)-18-[(<i>tert</i> -butoxycarbonyl)amino]-25-fluoro-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacosa-1(27),2,5(28),12,23,25-hexaene-8-carboxylic acid
Ex.229	methyl (8 <i>S</i> ,12 <i>E</i> , 18 <i>S</i> ,20 <i>S</i>)-18-amino-25-fluoro-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacosa-1(27),2,5(28),12,23,25-hexaene-8-carboxylate
Ex.230	methyl (8 <i>S</i> ,12 <i>E</i> , 18 <i>S</i> ,20 <i>S</i>)-25-fluoro-18-[2-(2-naphthyl)acetyl]amino-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacosa-1(27),2,5(28),12,23,25-hexaene-8-carboxylate
Ex.231	<i>tert</i> -butyl <i>N</i> -[(8 <i>S</i> ,12 <i>E</i> , 18 <i>S</i> ,20 <i>S</i>)-25-fluoro-8-[(isobutylamino)carbonyl]-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacosa-1(27),2,5(28),12,23,25-hexaen-18-yl]carbamate
Ex.232	(8 <i>S</i> ,12 <i>E</i> ,18 <i>S</i> ,20 <i>S</i>)-18-amino-25-fluoro- <i>N</i> -isobutyl-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacosa-1(27),2,5(28),12,23,25-hexaene-8-carboxamide

Ex.233	(8 <i>S</i> ,12 <i>E</i> ,18 <i>S</i> ,20 <i>S</i>)-25-fluoro- <i>N</i> -isobutyl-6,15-dioxo-18-[(3-pyridinylcarbonyl)amino]-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaene-8-carboxamide
Ex.234	<i>tert</i> -butyl <i>N</i> -[(8 <i>S</i> ,12 <i>E</i> ,18 <i>S</i> ,20 <i>S</i>)-8-(anilinocarbonyl)-25-fluoro-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaen-18-yl]carbamate
Ex.235	(8 <i>S</i> ,12 <i>E</i> ,18 <i>S</i> ,20 <i>S</i>)-18-amino-25-fluoro-6,15-dioxo- <i>N</i> -phenyl-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaene-8-carboxamide
Ex.236	methyl (8 <i>S</i> ,12 <i>E</i> ,18 <i>S</i> ,20 <i>S</i>)-25-fluoro-6,15-dioxo-18-[(2-phenylacetyl)amino]-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaene-8-carboxylate
Ex.237	(8 <i>S</i> ,12 <i>E</i> ,18 <i>S</i> ,20 <i>S</i>)-25-fluoro-6,15-dioxo-18-[(2-phenylacetyl)amino]-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaene-8-carboxylic acid
Ex.238	methyl (8 <i>S</i> ,12 <i>E</i> ,18 <i>S</i> ,20 <i>S</i>)-18-[(3-chlorobenzoyl)amino]-25-fluoro-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaene-8-carboxylate
Ex.239	(8 <i>S</i> ,12 <i>E</i> ,18 <i>S</i> ,20 <i>S</i>)-18-[(3-chlorobenzoyl)amino]-25-fluoro-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaene-8-carboxylic acid
Ex.240	(8 <i>S</i> ,12 <i>E</i> ,18 <i>S</i> ,20 <i>S</i>)-25-fluoro- <i>N</i> -isobutyl-18-[[2-(2-naphthyl)acetyl]amino]-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaene-8-carboxamide
Ex.241	(8 <i>S</i> ,12 <i>E</i> ,18 <i>S</i> ,20 <i>S</i>)-25-fluoro-18-[[2-(2-naphthyl)acetyl]amino]-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaene-8-carboxylic acid
Ex.242	methyl (8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-18-[(<i>tert</i> -butoxycarbonyl)amino]-25-fluoro-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaene-8-carboxylate

Ex.243	(8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-18-[(<i>tert</i> -butoxycarbonyl)amino]-25-fluoro-6,15-dioxo-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaene-8-carboxylic acid
Ex.244	methyl (8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-18-amino-25-fluoro-6,15-dioxo-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaene-8-carboxylate
Ex.245	methyl (8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-25-fluoro-18-[[2-(2-naphthyl)acetyl]amino]-6,15-dioxo-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaene-8-carboxylate
Ex.246	<i>tert</i> -butyl <i>N</i> -[(8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-8-(anilincarbonyl)-25-fluoro-6,15-dioxo-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaen-18-yl]carbamate
Ex.247	(8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-18-amino-25-fluoro-6,15-dioxo- <i>N</i> -phenyl-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaene-8-carboxamide
Ex.248	methyl (8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-25-fluoro-6,15-dioxo-18-[(2-phenylacetyl)amino]-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaene-8-carboxylate
Ex.249	(8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-18-[(3-chlorobenzoyl)amino]-25-fluoro-6,15-dioxo-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaene-8-carboxylic acid
Ex.250	methyl (8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-18-[(3-chlorobenzoyl)amino]-25-fluoro-6,15-dioxo-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaene-8-carboxylate
Ex.251	(8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-25-fluoro-6,15-dioxo-18-[(2-phenylacetyl)amino]-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaene-8-carboxylic acid
Ex.252	(8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-25-fluoro-18-[[2-(2-naphthyl)acetyl]amino]-6,15-dioxo-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaene-8-carboxylic acid
Ex.253	<i>tert</i> -butyl <i>N</i> -[(8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-25-fluoro-8-[(isobutylamino)carbonyl]-6,15-dioxo-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaen-18-yl]carbamate

Ex.254	(8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-18-amino-25-fluoro- <i>N</i> -isobutyl-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaene-8-carboxamide
Ex.255	(8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-25-fluoro- <i>N</i> -isobutyl-6,15-dioxo-18-[(3-pyridinylcarbonyl)amino]-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaene-8-carboxamide
Ex.256	<i>tert</i> -butyl <i>N</i> -[(8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-8-[(4-chloroanilino)carbonyl]-25-fluoro-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaen-18-yl]carbamate
Ex.257	(8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-18-amino- <i>N</i> -(4-chlorophenyl)-25-fluoro-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaene-8-carboxamide
Ex.258	<i>tert</i> -butyl <i>N</i> -[(8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-25-fluoro-6,15-dioxo-8-(3-toluidinocarbonyl)-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaen-18-yl]carbamate
Ex.259	(8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-18-amino-25-fluoro- <i>N</i> -(3-methylphenyl)-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaene-8-carboxamide
Ex.260	<i>tert</i> -butyl <i>N</i> -[(8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-8-[(benzylamino)carbonyl]-25-fluoro-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaen-18-yl]carbamate
Ex.261	(8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-18-amino- <i>N</i> -benzyl-25-fluoro-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaene-8-carboxamide
Ex.262	benzyl <i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-[(4-bromobenzyl)oxy]-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricos-1(22),2(6),4,20(23)-tetraen-15-yl]carbamate
Ex.263	(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-15-amino-11-hydroxy-18,21-dimethyl-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricos-1(22),2(6),4,20(23)-tetraene-14,19-dione
Ex.264	(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-15-amino-11-(benzyloxy)-18,21-dimethyl-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricos-1(22),2(6),4,20(23)-tetraene-14,19-dione

Ex.265	<i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]-2-(2-naphthyl)acetamide
Ex.266	<i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-(benzyloxy)-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]acetamide
Ex.267	<i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]-2-(1-naphthyl)acetamide
Ex.268	<i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]-3-methylbutanamide
Ex.269	3-fluoro- <i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]benzamide
Ex.270	<i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]benzenesulfonamide
Ex.271	<i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]methanesulfonamide
Ex.272	methyl <i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]carbamate
Ex.273	<i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]- <i>N</i> '-methylurea
Ex.274	<i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]- <i>N</i> '-(3-pyridinyl)urea
Ex.275	<i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-methoxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]-2-(2-naphthyl)acetamide

Ex.276	<i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]- <i>N'</i> -(2-naphthyl)urea
Ex.277	<i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]-2-phenylacetamide
Ex.278	<i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]-3-methoxybenzamide
Ex.279	<i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]-2-naphthalenesulfonamide
Ex.280	3-(4-fluorophenyl)- <i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]propanamide
Ex.281	<i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]-2-(1 <i>H</i> -indol-3-yl)acetamide
Ex.282	(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-hydroxy-18,21-dimethyl-15-[[2-(2-naphthyl)ethyl]amino]-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraene-14,19-dione
Ex.283	(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-15-[(4-fluorobenzyl)amino]-11-hydroxy-18,21-dimethyl-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraene-14,19-dione
Ex.284a	benzyl <i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-4,8-dimethyl-23-nitro-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacosa-1(24),2(27),3,5,22,25-hexaen-13-yl]carbamate
EX.284b	benzyl <i>N</i> -[(13 <i>R</i> ,19 <i>S</i>)-4,8-dimethyl-23-nitro-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacosa-1(24),2(27),3,5,22,25-hexaen-13-yl]carbamate
Ex.285	(13 <i>S</i> ,19 <i>S</i>)-13-amino-4,8-dimethyl-23-nitro-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacosa-1(24),2(27),3,5,22,25-hexaene-7,14-dione

Ex.286	benzyl <i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-23-amino-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacosa-1(24),2(27),3,5,22,25-hexaen-13-yl]carbamate
Ex.287	benzyl <i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-23-(acetylamino)-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacosa-1(24),2(27),3,5,22,25-hexaen-13-yl]carbamate
Ex.288	<i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-13-amino-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacosa-1(24),2(27),3,5,22,25-hexaen-23-yl]acetamide
Ex.289	<i>N</i> -(2-chlorophenyl)- <i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-4,8-dimethyl-23-nitro-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacosa-1(24),2(27),3,5,22,25-hexaen-13-yl]urea
Ex.290	<i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-23-amino-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacosa-1(24),2(27),3,5,22,25-hexaen-13-yl]- <i>N</i> -(2-chlorophenyl)urea
Ex.291	<i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-13-[(2-chloroanilino)carbonyl]amino}-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacosa-1(24),2(27),3,5,22,25-hexaen-23-yl]methanesulfonamide
Ex.292	<i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-4,8-dimethyl-23-nitro-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacosa-1(24),2(27),3,5,22,25-hexaen-13-yl]cyclopropanecarboxamide
Ex.293	<i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-23-amino-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacosa-1(24),2(27),3,5,22,25-hexaen-13-yl]cyclopropanecarboxamide
Ex.294	<i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-4,8-dimethyl-23-[(methylsulfonyl)amino]-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacosa-1(24),2(27),3,5,22,25-hexaen-13-yl]cyclopropanecarboxamide
Ex.295	<i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-13-amino-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacosa-1(24),2(27),3,5,22,25-hexaen-23-yl]methanesulfonamide
Ex.296	benzyl <i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-4,8-dimethyl-23-[(methylsulfonyl)amino]-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacosa-1(24),2(27),3,5,22,25-hexaen-13-yl]carbamate

Ex.297	benzyl <i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-4,8-dimethyl-7,14-dioxo-23-(2-pyrimidinylamino)-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-13-yl]carbamate
Ex.298	(13 <i>S</i> ,19 <i>S</i>)-13-amino-4,8-dimethyl-23-(2-pyrimidinylamino)-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaene-7,14-dione
Ex.299	<i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-13-(dimethylamino)-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-23-yl]acetamide
Ex.300	<i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-23-(acetylamino)-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-13-yl]-2-phenylacetamide
Ex.301	<i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-13-[(3-chlorophenyl)sulfonyl]amino]-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-23-yl]acetamide
Ex.302	<i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-13-[(isobutylamino)carbonyl]amino]-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-23-yl]acetamide
Ex.303	<i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-4,8-dimethyl-23-[(methylsulfonyl)amino]-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-13-yl]-4-fluorobenzamide
Ex.304	<i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-13-[(3-fluorobenzyl)amino]-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-23-yl]methanesulfonamide
Ex.305	benzyl <i>N</i> -[(15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]carbamate
Ex.306	(15 <i>R</i> ,16 <i>aS</i>)-15-amino-10-methyl-10,11,15,16,16 <i>a</i> ,17-hexahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecine-9,12-dione
Ex.307	(15 <i>R</i> ,16 <i>aS</i>)-15-(dimethylamino)-10-methyl-10,11,15,16,16 <i>a</i> ,17-hexahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecine-9,12-dione

Ex.308	<i>N</i> -[(15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]acetamide
Ex.309	<i>N</i> -[(15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]-3-methylbutanamide
Ex.310	<i>N</i> -[(15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]-2-(2-naphthyl)acetamide
Ex.311	<i>N</i> -[(15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]-2-(1-naphthyl)acetamide
Ex.312	<i>N</i> -[(15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]-2-(dimethylamino)acetamide
Ex.313	<i>tert</i> -butyl <i>N</i> -(3-[(15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]amino-3-oxopropyl)carbamate
Ex.314	<i>N</i> -[(15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]-3-aminopropanamide
Ex.315	<i>N</i> -[(15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]-3-fluorobenzamide
Ex.316	<i>N</i> -[(15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]isonicotinamide
Ex.317	<i>N</i> -[(15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]- <i>N</i> -methylurea
Ex.318	<i>N</i> -[(15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]- <i>N</i> -(3-pyridinyl)urea

Ex.319	2-methoxyethyl <i>N</i> -[(15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]carbamate
Ex.320	<i>tert</i> -butyl 3-[(<i>[(</i> (15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]amino}carbonyl)amino]propanoate
Ex.321	3-[(<i>[(</i> (15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]amino}carbonyl)amino]propanoic acid
Ex.322	<i>N</i> -[(15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]methanesulfonamide
Ex.323	<i>N</i> -[(15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]benzenesulfonamide
Ex.324	(15 <i>R</i> ,16 <i>aS</i>)-15-[(3-fluorobenzyl)amino]-10-methyl-10,11,15,16,16 <i>a</i> ,17-hexahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecine-9,12-dione
Ex.325	(15 <i>R</i> ,16 <i>aS</i>)-15-(isobutylamino)-10-methyl-10,11,15,16,16 <i>a</i> ,17-hexahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecine-9,12-dione
Ex.326	<i>N'</i> -[(15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]- <i>N,N,N,N</i> -tetramethylguanidine
Ex.327	benzyl (16 <i>S</i> ,18 <i>S</i>)-16-[(<i>tert</i> -butoxycarbonyl)amino]-7,13-dioxo-4-(trifluoromethyl)-5,20-dioxa-3,8,11,14-tetraazatetracyclo[19.3.1.0 ^{2,6} .0 ^{14,18}]pentacosa-1(25),2(6),3,21,23-pentaene-11-carboxylate
Ex.328	<i>tert</i> -butyl <i>N</i> -[(16 <i>S</i> ,18 <i>S</i>)-7,13-dioxo-4-(trifluoromethyl)-5,20-dioxa-3,8,11,14-tetraazatetracyclo[19.3.1.0 ^{2,6} .0 ^{14,18}]pentacosa-1(25),2(6),3,21,23-pentaen-16-yl]carbamate
Ex.329	benzyl (16 <i>S</i> ,18 <i>S</i>)-16-amino-7,13-dioxo-4-(trifluoromethyl)-5,20-dioxa-3,8,11,14-tetraazatetracyclo[19.3.1.0 ^{2,6} .0 ^{14,18}]pentacosa-1(25),2(6),3,21,23-pentaene-11-carboxylate

Ex.330	allyl <i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-16-[(<i>tert</i> -butoxycarbonyl)amino]-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]carbamate
Ex.331	allyl <i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-16-amino-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]carbamate
Ex.332	2-(1 <i>H</i> -imidazol-1-yl)- <i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-12-{[2-(1-naphthyl)acetyl]amino}-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-16-yl]acetamide
Ex.333	<i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-8,13-dioxo-16-{[(3-pyridinylamino)carbonyl]amino}-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]-2-(1-naphthyl)acetamide
Ex.334	2-(3-chlorophenyl)- <i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-8,13-dioxo-16-{[2-(1-pyrrolidinyl)acetyl]amino}-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]acetamide
Ex.335	2-cyclohexyl- <i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-8,13-dioxo-16-{[2-(1-pyrrolidinyl)acetyl]amino}-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]acetamide
Ex.336	<i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-12-{[(1-naphthylamino)carbonyl]amino}-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-16-yl]-2-(1-pyrrolidinyl)acetamide
Ex.337	<i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-12-[(benzylsulfonyl)amino]-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-16-yl]-2-(1-pyrrolidinyl)acetamide
Ex.338	benzyl <i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-8,13-dioxo-16-{[2-(1-pyrrolidinyl)acetyl]amino}-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]carbamate
Ex.339	<i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-12-amino-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-16-yl]-2-(1-pyrrolidinyl)acetamide

Ex.340	<i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-12-{[2-(1-naphthyl)ethyl]amino}-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-16-yl]-2-(1-pyrrolidinyl)acetamide
Ex.341	<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-(3-fluorobenzyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(1-naphthyl)acetamide
Ex.342	<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-(3-fluorobenzyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(2-naphthyl)acetamide
Ex.343	<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-(3-fluorobenzyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]- <i>N'</i> -(2-naphthyl)urea
Ex.344	<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-(3-fluorobenzyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-naphthalenesulfonamide
Ex.345	<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-(3-fluorobenzyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-3-(2-naphthyl)propanamide
Ex.346	<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-(3-fluorobenzyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-3-phenylpropanamide
Ex.347	2-(dimethylamino)- <i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-(3-fluorobenzyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]acetamide
Ex.348	benzyl (9 <i>S</i> ,11 <i>R</i>)-11-{[2-(2-naphthyl)acetyl]amino}-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaene-16-carboxylate
Ex.349	<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(2-naphthyl)acetamide
Ex.350	<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-(3-fluorobenzoyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(2-naphthyl)acetamide

Ex.351	<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-benzyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(2-naphthyl)acetamide
Ex.352	<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-14,20-dioxo-16-phenethyl-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(2-naphthyl)acetamide
Ex.353	<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-14,20-dioxo-16-(3-phenylpropyl)-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(2-naphthyl)acetamide
Ex.354	<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-isopentyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(2-naphthyl)acetamide
Ex.355	<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-isobutyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(2-naphthyl)acetamide
Ex.356	2-(dimethylamino)ethyl (9 <i>S</i> ,11 <i>R</i>)-11-[[2-(2-naphthyl)acetyl]amino]-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaene-16-carboxylate
Ex.357	<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-[2-(dimethylamino)ethyl]-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(2-naphthyl)acetamide
Ex.358	3,3-dimethyl- <i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-methyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]butanamide

Synthesis of the Building Blocks

- 5 Readily available examples of amino acids representing subunits of the Bridge **C** are detailed to the level of fully-defined structures in Table 11. Additional analogs can be accessed smoothly, and a plethora of literature precedents are published. Therefore this section focuses on synthetic approaches towards building blocks of the Template **A** and the Modulator **B**.
- 10 Functional groups not involved in ring connections of the macrocyclic backbone can be diversified by standard methods of organic synthesis, preferably by

parallel/combinatorial chemistry introducing so-called high variation substituents. These derivatization methods are well-known to those skilled in the art and do not require further exemplification (selected references: A. R. Katritzky et al. (eds), *Comprehensive Functional Group Transformations*, Pergamon, **1995**; S. Patai, Z. Rappoport (eds), *Chemistry of Functional Groups*, Wiley, **1999**; J. March, *Advanced Organic Chemistry*, 4 ed., Wiley, **1992**; D. Obrecht, J.M. Villalgordo (eds), *Solid-Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound Libraries*, Pergamon, **1998**; W. Bannwarth et al. (eds), *Combinatorial Chemistry: From Theory to Application*, 2 ed., Wiley-VCH **2006**).

10

a) Synthesis of Template A Building Blocks

Over the last decades the coupling to suitably functionalized aromatic or heteroaromatic compounds has reached a highly mature status providing an easy and reliable route to biaryl derivatives of nearly any substitution pattern (cf. leading reviews covering several types of coupling reactions and the references cited therein: R. M. Kellogg et al., *Org. Process Res. Dev.* **2010**, *14*, 30–47; A. de Meijere, F. Diederich (eds), *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed., Wiley-VCH **2004**; with focus on heteroaromatic substrates: G. Zeni, R. C. Larock, *Chem. Rev.* **2006**, *106*, 4644–4680; especially for macrocyclic biaryls: Q. Wang, J. Zhu, *Chimia* **2011**, *65*, 168–174). Most prominent among these coupling reactions is definitely the Suzuki-Miyaura cross coupling of aryl boronic acid derivatives with aryl halides under palladium catalysis (N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483; S. Kotha et al., *Tetrahedron* **2002**, *58*, 9633–9695; S. L. Buchwald et al., *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696). Special catalysts, especially the Nolan's catalysts make the Suzuki-Miyaura reaction also amenable to highly sterically hindered substrates (S. P. Nolan et al., *J. Am. Chem. Soc.* **2003**, *125*, 16194–16195; S. P. Nolan et al., *Org. Lett.* **2005**, *7*, 1829–1832). More recent developments broadened the scope of the Suzuki coupling from aryl halides to other substrates like aryl mesylates (F.Y. Kwong et al., *Angew. Chem. Int. Ed.* **2008**, *47*, 8059–8063) or aryl carbamates, carbonates and sulfamates (N. K. Garg et al., *J. Am. Chem. Soc.* **2009**, *131*, 17748–17749).

The biaryl compounds obtained by such coupling protocols might require further functional group transformations as described below.

35

General Functional Group Interconversions

The majority of the Templates **A** are carrying an aromatic or heteroaromatic hydroxy (–OH) or sulfanyl (thiol) group (–SH) in the **A_B** substructure and a carboxylic acid group (–COOH) or sulfanyl moiety (–SH) or its respective oxidation products in the **A_C** substructure.

As more phenolic precursors are commercially available than the corresponding thiophenols, a transformation of a phenol into a thiophenol might be required. Alternatively thiophenols might be derived from the corresponding aryl halides or diazonium salts. Selected functional group transformations for introducing a sulfanyl group (–SH), i.e. Ar/Hetar–X → Ar/Hetar–SH (X= OH, F, Cl, Br, I, N₂⁺), are the compiled below (T-I to T-VII):

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., *Bioorg. 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 (i.e. equivalent to the pyridone tautomer) can be accomplished by heating with P₂S₅ (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 surrogate 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 (–N₂⁺) can be replaced (C. Mukherjee, E. Biehl, *Heterocycles* **2004**, *63*, 2309-2318).

T-V: In positions not activated for an S_NAr 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). Alternatively, transition metal-catalyzed transformations are feasible for this type of reaction, e.g. Cu-catalyzed substitution with benzoithioic S-acid (N. Sawada et al., *Tetrahedron Lett.* **2006**, *47*, 6595-6597), or

Pd-catalyzed substitution with $\text{KS-Si}(i\text{-Pr})_3$ followed by desilylation of the introduced $-\text{SSi}(i\text{-Pr})_3$ group (A. M. Rane et al., *Tetrahedron Lett.* **1994**, 35, 3225-3226).

5 The thus introduced $-\text{SH}$ moieties constitute a thia-bridge $-\text{S}-$ in the later macrocyclic products and can be selectively transformed into higher oxidation states. Therefore the building blocks with sulfanyl moieties are also regarded as building blocks for the introduction of sulfinyl ($-\text{S}(=\text{O})-$; i.e. sulfoxide) and sulfonyl ($-\text{S}(=\text{O})_2-$; i.e. sulfone) moieties. Suitable oxidation methods are:

10 T-VI: The selective oxidation of a thioether ($-\text{S}-$) to a sulfoxide ($-\text{S}(=\text{O})-$) can be highly selectively and mildly achieved with hexamethylenetetramine-bromine HMTAB (K. Choudhary et al.; *J. Phys. Org. Chem.* **2000**, 13, 283-292); under these conditions primary hydroxyl groups for example are not affected. In a number of related reactions chlorotrimethylsilane showed high selectivity, too (Y.-J. Chen et al., *Tetrahedron Lett.* **2000**, 41, 5233-5236).

15 T-VII: Stronger oxidants directly transfer the sulfanyl ($-\text{S}-$) into the sulfonyl group ($-\text{S}(=\text{O})_2-$). Among the many reagents mentioned in literature the system periodic acid/ chromium(VI)oxide for example can be applied in the presence of C=C-double bonds (US2007/293548 A1).

20 Hydroxyl groups attached to aromatic rings (Ar-OH or Heteroaryl-OH) in turn, if not already part of a synthesized or commercially available biaryl, can be introduced by various methods, e.g. H-I to H-IV:

25 H-I: Analogously to T-III) the hydroxy group or its surrogate can be introduced by an $\text{S}_{\text{N}}\text{Ar}$ 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).

30 H-III: The substitution of halogen atoms (esp. Br and I), which are not activated for an $\text{S}_{\text{N}}\text{Ar}$, 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 find application, like Cu-catalysts (J.E. Ellis, S.R. Lenger, *Synth. Commun.* **1998**, 28, 1517-1524).

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).

- 5 The carboxylic acid group of the biaryl **A** building blocks, if not already present in commercially available coupling precursors, can be introduced by standard procedures like C-I to C-IV:

C-I: The oxidation of functional groups like hydroxymethyl ($-\text{CH}_2\text{OH}$) or aldehyde ($-\text{C}(=\text{O})\text{H}$) 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).
10 Also methyl groups on benzene rings can be oxidized; however, as harsh reaction conditions are usually required, its applicability is limited. In contrast, the relatively 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 analogs (T. R. Kelly,
15 F. Lang, *J. Org. Chem.* **1996**, 61, 4623-4633).

C-II: Halogen atoms can easily be replaced by a carboxyl group or surrogate 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 cyanofomate)(A. Lepretre et al., *Tetrahedron* **2000**, 56, 265-274).
20

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
25 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 or biaryls obtained by coupling route, these general transformations offer a tool box for accessing a huge variety of
30 Templates **A**. Additional literature examples are cited below within the sections on specific derivatives.

b) Synthesis of Modulator B Building Blocks

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

If not already present in a commercial building block, the substituent R⁶ can be introduced by standard nucleophilic addition of organometallic reagents to carbonyl or carboxyl derivatives. Alkyl (as R⁶) substituted analogs of **B1** and derivatives of **B2-B10** with no additional C-substituent on their ring system are commercially available, as are many derivatives with an amino (–NH₂) or alcohol (–OH) substituent as R⁶. In the such cases the diversification of the substitution pattern can be easily achieved by standard transformations of the free amine or hydroxy functionalities.

Possible pathways to more complex pyrrolidine derivatives of type **B4-B6** or piperidine derivatives of type **B7-B9** rely on the same strategy: Intramolecular cyclization reactions are the predominant route applicable to diversely substituted substrates. Amines carrying a residue with a leaving group in the ω-position lead directly to the desired saturated ring systems by intramolecular nucleophilic 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 into the desired compounds by a Hofmann–Löffler–Freitag 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 partially unsaturated ring to the saturated heterocycle.

Another possible access, reduction of aromatic five- or six-membered heterocycles to their saturated analogs, is described in the literature. Due to the large number of commercially available pyridines this approach is especially useful for 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).

General processes for the synthesis of macrocyclic compounds I

General procedures for the synthesis of libraries of macrocyclic compounds of general structure I are described below. It will be immediately apparent to those skilled in the art how these procedures have to be modified for the synthesis of individual macrocyclic compounds of type I.

The macrocyclic compounds of this invention are obtained by cyclization of suitable linear precursors which are derived from optionally substituted bifunctional hydroxy-

or mercapto biaryls/heteroaryls $X-A_B-A_C-Y$ (Template A_B-A_C), substituted amino alcohols **B** (Modulator), and one to three building blocks forming Bridge **C**.

Hydroxy- or mercapto biaryls/heteroaryls $X-A_B-A_C-Y$ consist of two optionally substituted building blocks $X-A_B$ and A_C-Y . Building blocks $X-A_B$ comprise
 5 hydroxyaryl, hydroxyheteroaryl-, mercaptoaryl- and mercaptoheteroaryl compounds. Building blocks A_C-Y comprise carboxyaryl-, carboxyheteroaryl-, mercaptoaryl-, mercaptoheteroaryl, alkenylaryl, and alkenylheteroaryl compounds. $X-A_B$ and A_C-Y are six-membered aromatic or five- or six-membered heteroaromatic rings. Templates $X-A_B-A_C-Y$ can be obtained by combination of two six-membered rings,
 10 two five-membered rings or a five- and a six-membered ring. The building blocks $X-A_B$ and A_C-Y are connected by a carbon-carbon bond to form the biaryls $X-A_B-A_C-Y$.

Variable substituents are introduced by pre- or postcyclative derivatization of one or more orthogonally protected functional group (e.g. amino groups, carboxyl groups,
 15 hydroxyl groups) attached to **B**, **C** or **A**. Variable R-groups may also be introduced as side chain motifs of the subunits of Bridge **C**.

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

The essential ring closure reaction is possible between any of the building blocks;
 20 and macrocycles **I** are obtained by e.g.

- Macrolactamization between **C** and **B**;
- Macrolactamization between A_B-A_C and **C**;
- Macrolactamization between any two subunits of Bridge **C**;
- Arylether or arylthioether formation between A_B-A_C and **B**;
- 25 • Arylthioether formation between A_B-A_C and **C**;
- Biaryl synthesis by coupling reaction (e.g. Suzuki coupling) between A_B and A_C ;
- Ring closing metathesis (RCM) reaction between any two subunits of **C** or upon formation of such a subunit;
- 30 • Ring closing metathesis reaction between A_B-A_C and **C**.

SW-1: Synthesis workflow for the preparation of side-chain protected macrocycles **I by macrolactamization in solution**

Macrocycles of structure **I** with orthogonally protected exocyclic functional groups
 35 (attachment points for derivatizations) are prepared in solution by the process

outlined below. Throughout all steps the orthogonal protection of the side chains stays intact and is not affected by protecting group manipulations of the main chain.

a1) Condensation of an appropriately protected hydroxy- or mercapto-biaryl/heteroaryl carboxylic acid $PG^1-X-A_B-A_C-CO_2H$ and a suitable C-terminally and side-chain protected C-subunit building block $H-NR^7-c1-CO-OPG^2$ to form $PG^1-X-A_B-A_C-CONR^7-c1-CO-OPG^2$;

b1) If required, deprotection of the aryl/heteroaryl hydroxy or mercapto group;

c1) Aryl/heteroaryl ether or thioether formation with a suitably N-protected amino alcohol PG^3-B-OH leading to the fully protected linear precursor $PG^3-B-X-A_B-A_C-CONR^7-c1-CO-OPG^2$;

d1) Cleavage of the "main chain" protective groups affording the free amino acid $H-B-X-A_B-A_C-CONR^7-c1-CO-OH$, which is subjected to macrocyclization

e1) Intramolecular amide coupling to $cyclo(B-X-A_B-A_C-CONR^7-c1-CO-)$ as macrocyclic product.

15

In addition to the steps described above, chain elongation by one or two additional C-subunits (**c2**, **c3**) and subsequent macrolactamization starts with coupling of a second suitably C-protected amino acid to the free carboxylic acid functionality of the product obtained by N-reprotection of the product of step d1. Cleavage of the main chain protective groups and either macrolactamization or repetition of the chain elongation steps and macrolactamization provides either $cyclo(B-X-A_B-A_C-CONR^7-c1-CONR^7-c2-CO-)$ or $cyclo(B-X-A_B-A_C-CONR^7-c1-CONR^7-c2-CONR^7-c3-CO-)$.

The free carboxylic acid functionality of the N-reprotected product derived from any of the three linear macrolactamization precursors (product of step d1, or corresponding product after coupling of one or two additional C-subunits) can be further elaborated by chain extensions/ homologizations (e.g. Arndt-Eistert reaction) or functional group interconversions like Curtius rearrangement ultimately affording homologous macrocycles or those where the connection between Modulator B and Bridge C corresponds to a urea moiety.

30

SW-2: Synthesis workflow for the preparation of side-chain protected macrocycles I by macrolactamization in solution

As an alternative to SW-1 the intermediate $H-X-A_B-A_C-Y-Z-c1-CO-OPG^2$ (product of step b1) can be prepared by

a2) S-alkylation of a suitable mercapto-substituted haloaryl/heteroaryl compound $Hal-A_C-SH$ (Hal represents a halogen atom) with a C-terminally and side-chain protected

35

C-subunit building block $\text{LG}-\text{CHR}^8-\text{c1}-\text{CO}-\text{OPG}^2$ (LG represents a leaving group like halide, alkyl-, arylsulfonate or activated OH like e.g. under Mitsunobu conditions);

b2) Suzuki coupling reaction between the product of step a2) and a suitable hydroxyl-substituted boronic acid or boronic ester $\text{HX}-\text{A}_\text{B}-\text{B}(\text{OR})_2$ leading to $\text{HX}-\text{A}_\text{B}-\text{A}_\text{C}-\text{S}-\text{CHR}^8-\text{c1}-\text{CO}-\text{OPG}^2$.

In analogy, amide coupling of a suitable C-terminally and side-chain protected C-subunit building block $\text{H}-\text{NR}^7-\text{c1}-\text{CO}-\text{OPG}^2$ to a haloaryl/heteroaryl carboxylic acid $\text{Hal}-\text{A}_\text{C}-\text{CO}-\text{OH}$ and subsequent Suzuki biaryl coupling reaction with a suitable hydroxyl-substituted boronic acid or boronic ester would provide $\text{H}-\text{X}-\text{A}_\text{B}-\text{A}_\text{C}-\text{CONR}^7-\text{c1}-\text{CO}-\text{OPG}^2$.

Possible subsequent steps are as described in SW-1, providing *cyclo*($\text{B}-\text{X}-\text{A}_\text{B}-\text{A}_\text{C}-\text{Y}-\text{Z}-\text{c1}-\text{CO}-$) with $\text{Y}-\text{Z} = \text{CONR}^7, \text{S}-\text{CHR}^8$.

Oxidation of *cyclo*($\text{B}-\text{X}-\text{A}_\text{B}-\text{A}_\text{C}-\text{S}-\text{CHR}^8-\text{c1}-\text{CO}-$) leads to the corresponding sulfoxides *cyclo*($\text{B}-\text{X}-\text{A}_\text{B}-\text{A}_\text{C}-\text{SO}-\text{CHR}^8-\text{c1}-\text{CO}-$) or sulfone *cyclo*($\text{B}-\text{X}-\text{A}_\text{B}-\text{A}_\text{C}-\text{SO}_2-\text{CHR}^8-\text{c1}-\text{CO}-$).

SW-3: Synthesis workflow for the preparation of side-chain protected macrocycles I by macrolactamization in solution

As an alternative to SW-1 the protected cyclization precursor $\text{PG}^3-\text{B}-\text{X}-\text{A}_\text{B}-\text{A}_\text{C}-\text{CONR}^7-\text{c1}-\text{CO}-\text{OPG}^2$ can also be synthesized by an inverted order of reaction steps:

a3) Arylether or arylthioether formation between a hydroxyl or mercapto-aryl/heteroaryl ester $\text{H}-\text{X}-\text{A}_\text{B}-\text{A}_\text{C}-\text{CO}-\text{OPG}^4$ and a suitably protected amino alcohol $\text{PG}^3-\text{B}-\text{OH}$ to afford $\text{PG}^3-\text{B}-\text{X}-\text{A}_\text{B}-\text{A}_\text{C}-\text{CO}-\text{OPG}^4$.

Further more, $\text{PG}^3-\text{B}-\text{X}-\text{A}_\text{B}-\text{A}_\text{C}-\text{CO}-\text{OPG}^4$ can also be obtained by arylether or arylthio ether formation between a suitably protected aminoalcohol $\text{PG}^3-\text{B}-\text{OH}$ and an optionally substituted hydroxyl- or mercaptoaryl halide or heteroaryl halide $\text{HX}-\text{A}_\text{B}-\text{Hal}$ leading to $\text{PG}^3-\text{B}-\text{X}-\text{A}_\text{B}-\text{Hal}$ and subsequent coupling of an optionally substituted alkoxy carbonyl aryl or heteroaryl boronic acid or boronic ester $(\text{RO})_2\text{B}-\text{A}_\text{C}-\text{CO}-\text{OPG}^4$.

b3) Deprotection of the carboxylic acid group to $\text{PG}^3-\text{B}-\text{X}-\text{A}_\text{B}-\text{A}_\text{C}-\text{CO}-\text{OH}$;

c3) Condensation with a C-terminally and side-chain protected building block $\text{H}-\text{NR}^7-\text{c1}-\text{CO}-\text{OPG}^2$ to $\text{PG}^3-\text{B}-\text{X}-\text{A}_\text{B}-\text{A}_\text{C}-\text{CONR}^7-\text{c1}-\text{CO}-\text{OPG}^2$.

Possible subsequent steps are as described in SW-1.

In analogy to step c3), $\text{PG}^3-\text{B}-\text{X}-\text{A}_\text{B}-\text{A}_\text{C}-\text{CO}_2\text{H}$ can be coupled to a previously formed di- or tripeptide leading to protected cyclization precursors such as $\text{PG}^3-\text{B}-\text{X}-\text{A}_\text{B}-$

$A_C-CONR^7-c1-CONR^7-c2-CO-OPG^2$ or $PG^3-B-X-A_B-A_C-CONR^7-c1-CONR^7-c2-CONR^7-c3-CO-OPG^2$. If applying this approach for the synthesis of macrocycles I, the synthesis is best performed by preparation of the linear *N*-terminal deprotected cyclization precursor on solid support, followed by release from resin and cyclization as well as cleavage of side chain protective groups in solution, as detailed in SW4.

SW-4: Synthesis workflow for the preparation of side-chain protected macrocycles I by combined solid phase and solution phase chemistry

Macrocyclic compounds of general formula I with highly variable side chain motifs in Bridge C can advantageously be prepared in parallel array synthesis applying a combination of solid phase and solution phase synthesis methodologies.

The solid support (polymer, resin) is preferably a trityl resin e.g. chlorotrityl chloride resin (cross-linked with 1–5% divinylbenzene), which is useful as polymer-bound protective group for carboxylic acids (D. Obrecht, J.-M. Villalgordo, *Solid-Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound Libraries*, Tetrahedron Organic Chemistry Series, Vol. 17, Pergamon **1998**; K. Barlos et al., *Int. J. Peptide Protein Res.* **1991**, 37, 513-520; K. Barlos et al., *Angew. Chem. Int. Ed.* **1991**, 30, 590-593).

a4) The suitably side-chain protected C-subunit $PG^5NR^7-c2-CO-OH$ is attached to the solid support;

b4) The *N*-terminal protective group is cleaved;

c4) The suitably side-chain protected C-subunit $PG^5NR^7-c1-CO-OH$ is coupled; subsequent *N*-terminal deprotection leads to $HNR^7-c1-CO-NR^7-c2-CO-O$ -chlorotrityl resin;

d4) Coupling of a suitably side chain protected building block $PG^3-B-X-A_B-A_C-CO-OH$ (cf. SW-3, product of step b3) and cleavage of the *N*-terminal protective group;

e4) Release of the linear main-chain deprotected macrolactamization precursor $H-B-X-A_B-A_C-CONR^7-c1-CONR^7-c2-CO-OH$ from the resin;

f4) Macrolactamization to *cyclo*($B-X-A_B-A_C-CONR^7-c1-CONR^7-c2-CO-$).

g4) Optional: Cleavage of protective groups of side-chain functions.

Immobilization of an amino acid $PG^5NR^7-c3-CO-OH$ and two additional amino acid coupling/deprotection cycles would lead to $HNR^7-c1-CO-NR^7-c2-CO-NR^7-c3-CO-O$ -chlorotrityl resin. Possible subsequent steps are as described above, providing *cyclo*($B-X-A_B-A_C-CONR^7-c1-CONR^7-c2-CO-NR^7-c3-CO-$).

The ring closure of linear precursors like $\text{H-B-X-A}_\text{B}\text{-A}_\text{C}\text{-CONR}^7\text{-c1-CONR}^7\text{-c2-CO-OH}$ may be achieved using soluble coupling reagents as described below or by engaging polymer-supported coupling reagents such as *N*-cyclohexyl-carbodiimide-*N*'-methylpolystyrene or *N*-alkyl-2-chloro pyridinium triflate resin (S. Crosignani et al, 5 *Org. Lett.* **2004**, 6, 4579–4582).

Further viable alternatives for the synthesis of macrocycles I by combined application of solid phase and solution phase conditions could involve macrolactamization in other positions, e.g. between two subunits in Bridge C. Alternative cyclization 10 precursors like $\text{H-NR}^7\text{-c2-CO-B-X-A}_\text{B}\text{-A}_\text{C}\text{-CONR}^7\text{-c1-CO-OH}$ can be obtained from the same building blocks (as described for SW4) by changing the sequence of coupling/deprotection steps.

15 **SW-5: Synthesis workflow for the preparation of side-chain protected macrocycles I by ring-closing metathesis in solution**

Ring-closing metathesis (RCM) of olefinic precursors was applied for the synthesis of subunits of Bridge C, wherein e.g. $\text{c2} = \text{c2}'\text{-c2}''$:

a5) Coupling of an optionally substituted alkenyl amine building block $\text{H-NR}^7\text{-c1-V-c2}'\text{=CH}_2$ with suitably protected carboxylic acid derivatives $\text{PG}^1\text{-X-A}_\text{B}\text{-A}_\text{C}\text{-CO}_2\text{H}$ 20 afford $\text{PG}^1\text{-X-A}_\text{B}\text{-A}_\text{C}\text{-CO-NR}^7\text{-c1-V-c2}'\text{=CH}_2$;

b5) if required release of the aryl/heteroaryl hydroxyl or mercapto group;

c5) Arylether or arylthioether formation between $\text{H-X-A}_\text{B}\text{-A}_\text{C}\text{-CO-NR}^7\text{-c1-V-c2}'\text{=CH}_2$ and $\text{PG}^3\text{-B-OH}$ leading to $\text{PG}^3\text{-B-X-A}_\text{B}\text{-A}_\text{C}\text{-CO-NR}^7\text{-c1-V-c2}'\text{=CH}_2$

d5) Cleavage of the N-terminal protective group leading to $\text{H-B-X-A}_\text{B}\text{-A}_\text{C}\text{-CO-NR}^7\text{-c1-V-c2}'\text{=CH}_2$ 25

e5) Coupling of a suitable (optionally substituted and suitably protected) enoic acid to $\text{H}_2\text{C=c2}''\text{-CO-B-X-A}_\text{B}\text{-A}_\text{C}\text{-CO-NR}^7\text{-c1-V-c2}'\text{=CH}_2$;

f5) Ring-closing metathesis to *cyclo*($\text{c2}''\text{-CO-B-X-A}_\text{B}\text{-A}_\text{C}\text{-CO-NR}^7\text{-c1-V-c2}'$)

[= *cyclo*($\text{B-X-A}_\text{B}\text{-A}_\text{C}\text{-CO-NR}^7\text{-c1-V-c2-CO-}$)]

g5) Optional: Hydrogenation of the newly formed C-C double bond of the metathesis product. 30

In addition, it is also feasible to prepare olefinic macrocycles with modified Bridges C such as *cyclo*($\text{B-X-A}_\text{B}\text{-A}_\text{C}\text{-Y-Z-c1-V-c2-CO-NR}^7\text{-c3-CO-}$), or *cyclo*($\text{B-X-A}_\text{B}\text{-A}_\text{C}\text{-Y-Z-c1-CO-}$), and subsequently the respective hydrogenated analogs.

General procedures for synthetic steps utilized in SW-1 to SW-5

In all general procedures below Y-Z represents CONRⁿ or SCHRⁿ.

Amidation reactions (steps a1, c3, a5, e5)

- 5 An appropriately protected (preferably as acetyloxy or acetylmercapto) and optionally substituted biaryl/heteroaryl carboxylic acid (PG³-X-A_B-A_C-CO₂H) or a more advanced intermediate like PG³-B-X-A_B-A_C-CO₂H is condensed with a suitably protected amino acid ester H-NR⁷-c1-CO-OPG² or an amine H-NR⁷-c1-V-c2'=CH₂ in the presence of a coupling reagent (e.g. benzotriazole derivatives like HBTU, HCTU, BOP, PyBOP; their aza analogs like HATU; or carbodiimides like EDC; others like PyClu, T3P), an auxiliary base (e.g. *i*-Pr₂NEt, Et₃N, pyridine, collidine) in solvents like CH₂Cl₂, DMF, pyridine. Benzotriazole-based coupling reagents and carbodiimides can be used together with suitable auxiliary reagents HOBt or HOAt.
- 10 Hydroxybiaryl/heteroaryl carboxylic acids H-X-A_B-A_C-CO₂H do not necessarily require protection of the phenolic OH-group and can directly be coupled with the H-NR⁷-c1-CO-OPG² to the free phenol derivative H-X-A_B-A_C-CONR⁷-c1-CO-OPG².

As an alternative, the amidation can also be accomplished with the corresponding acid derivatives like acid chlorides, anhydrides, or active esters.

- 20 Deprotection of aromatic hydroxy or mercapto groups (steps b1, b5)
- Deacylation of PG¹-X-A_B-A_C-CONR⁷-c1-CO-OPG² or PG¹-X-A_B-A_C-CO-NR⁷-c1-V-c2'=CH₂ to the corresponding free hydroxyl or mercapto aryl/heteroaryl amide H-X-A_B-A_C-CONR⁷-c1-CO-OPG² or H-X-A_B-A_C-CO-NR⁷-c1-V-c2'=CH₂ is achieved by aminolysis, which is advantageously carried out with a dialkylaminoalkyl amine in solvents like degassed THF at 0-25°C. Acyl amine side products formed in the course of the reaction are easily removed by extraction with acidic aqueous solutions.

Arylether or arylthioether formation between A and B (steps c1, a3, c5)

- Alkylation of the phenol or thiophenol like H-X-A_B-A_C-Y-Z-c1-CO-OPG², H-X-A_B-A_C-CO-OPG⁴, or H-X-A_B-A_C-CO-NR⁷-c1-V-c2'=CH₂ with a suitably N-protected amino alcohol PG³-B-OH to the ether or thioether PG³-B-X-A_B-A_C-Y-Z-c1-CO-OPG², PG³-B-X-A_B-A_C-CO-OPG⁴, or PG³-B-X-A_B-A_C-CO-NR⁷-c1-V-c2'=CH₂ is accomplished with azodicarboxylic acid derivatives such as DEAD, DIAD, TMAD or ADDP in the presence of trialkyl or triaryl phosphines in solvents like benzene, toluene, CH₂Cl₂, CHCl₃ or THF at 0°C to room temperature. As a variation,
- 35 the reaction is performed with CMBP in toluene at temperatures of 20-110°C.

In an alternative approach, the alcohol $\text{PG}^3\text{-B-OH}$ is converted into the corresponding sulfonate (e.g. mesylate, tosylate or triflate) or halide (e.g. chloride, bromide or iodide) and subsequently treated with the phenol/thiophenol $\text{H-X-A}_\text{B}\text{-A}_\text{C}\text{-CO-OPG}^4$ in the presence of an auxiliary base such as NaH or K_2CO_3 in solvents like DMF, DMSO, NMP, HMPA, or THF, to yield $\text{PG}^3\text{-B-X-A}_\text{B}\text{-A}_\text{C}\text{-CO-OPG}^4$.

Cleavage of the main chain protective groups (step d1)

Simultaneous or stepwise cleavage of the main chain protective groups provides the linear amino acids as cyclization precursors. The preferred protecting groups are Alloc as PG^3 and/or allylester as PG^2 , which can be cleaved simultaneously by palladium catalysts (e.g. $\text{Pd}(\text{PPh}_3)_4$) in the presence of 1,3-dimethyl barbituric acid in solvents like CH_2Cl_2 or EtOAc or mixtures thereof.

Also applied were Boc as PG^3 and methyl, ethyl or tert-butyl ester as PG^2 . Boc and groups and t-Bu esters are cleaved either with TFA in CH_2Cl_2 or with HCl-dioxane. Methyl or ethyl esters are best saponified with aq. LiOH in mixtures of MeOH and THF.

Macrolactamization (steps e1, f4)

Macrolactamization occurs upon treatment of the cyclization precursor with coupling reagents like T3P or FDPP (if required in the presence of an auxiliary base such as $i\text{-Pr}_2\text{NEt}$) in solvents like CH_2Cl_2 or DMF under high dilution conditions and at temperatures ranging from 20 to 100°C .

Due to their synthetic importance, macrolactamizations are a well-investigated class of transformations. The favorable application of FDPP as cyclization mediator is described e.g. by J. Dudash et al., *Synth. Commun.* **1993**, 23, 349–356; and R. Samy et al., *J. Org. Chem.* **1999**, 64, 2711–2728. Many other coupling reagents were successfully utilized in related head to tail cyclizations and might be applied instead; examples include benzotriazole derivatives like HBTU, HCTU, PyBOP; or their aza analogs such as HATU, as well as DPPA, and carbodiimides like EDC or DIC (P. Li, P.P. Roller, *Curr. Top. Med. Chem.* **2002**, 2, 325–341; D.L. Boger et al., *J. Am. Chem. Soc.* **1999**, 121, 10004–10011). Still another route to macrolactams relies on the intramolecular reaction of an active ester with an *in situ* released amino group (e.g. by carbamate deprotection or azide reduction) as demonstrated in the synthesis of peptide alkaloids and vancomycin model systems (U. Schmidt et al., *J. Org. Chem.* **1982**, 47, 3261–3264; K.C. Nicolaou et al., *Chem. Commun.* **1997**, 1899–1900).

Ring-closing metathesis (RCM) (step f5)

Ring-closing metathesis (RCM) of olefinic precursors to macrocyclic compounds is well documented (e.g. A. Fürstner et al., *Chem. Eur. J.* **2001**, 7, 4811–4820) and supplements the macrocyclization strategies described above.

- 5 The ring-closing metathesis is conveniently performed in solvents like CH₂Cl₂ or toluene at temperatures of 20-100°C in the presence of indenylidene-ruthenium complexes such as [1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro-[(2-isopropoxy)(5-pentafluorobenzoylamino)benzylidene]ruthenium(II); dichloro-(3-phenyl-1*H*-inden-1-ylidene)bis(tricyclohexyl-phosphine)-ruthenium(II); [1,3-bis(2,4,6-
- 10 trimethylphenyl)-2-imidazolidinylidene]-dichloro-(3-phenyl-1*H*-inden-1-ylidene)(tri-cyclohexylphosphine)-ruthenium(II); or [1,3-bis(2,4,6-tri-methylphenyl)-2-imidazolidinylidene]-dichloro-(3-phenyl-1*H*-inden-1-ylidene)(pyridyl)ruthenium(II) (S. Monsaert et al., *Eur. J. Inorg. Chem.* **2008**, 432–440 and references cited therein).
- 15 In addition to ring closing transformations described above, biaryl coupling reactions such as intramolecular Suzuki coupling and Suzuki-Miyaura conditions have been applied to prepare macrocyclic compounds with biaryl motifs (M. Kaiser et al., *Org. Lett.* **2003**, 5, 3435 – 3437; R. Lépine et al., *Org. Lett.* **2005**, 7, 2981-2984).
- The coupling of arylboronate-carboxylic acids to amines is also described (cf ref. above, M. Kaiser et al., R. Lépine et al.); therefore the synthesis of linear precursors
- 20 Hal-A_B-X-B-CO-c1-NR⁷-CO-A_C-B(OR)₂ (Hal represents a halogen atom or a triflate, B(OR)₂ a boronic acid or boronic ester functionality) and their cyclization in a Pd-catalyzed coupling reaction is a feasible alternative.

25 **General procedures for synthetic steps in SW-4**

Synthesis of linear cyclization precursors on solid support (steps a4 to e4)

- Chlorotrityl resins are frequently used in solid phase peptide synthesis. Therefore, attachment of Fmoc- or Alloc-protected amino acids to these resins as well as subsequent deprotection steps and coupling/deprotection of additional amino acids
- 30 are well described (K. Barlos et al., *Int. J. Peptide Protein Res.* **1991**, 37, 513-520; K. Barlos et al., *Angew. Chem. Int. Ed.* **1991**, 30, 590-593). For the examples of the present invention, chlorotrityl chloride resin (matrix: copoly(styrene-1%DVB) is treated with an N-terminally Fmoc-protected amino acid in CH₂Cl₂ in the presence of an auxiliary base like *i*-Pr₂NEt. Fmoc deprotection (DBU, DMF) and
- 35 coupling/deprotection of Fmoc- or Alloc-protected amino acids provides a linear, N-terminally deprotected cyclization precursor, still attached to the resin. Fmoc- or

Alloc-protected amino acids are coupled in the presence of reagents like HATU or PyBOP in DMF in the presence of *i*-Pr₂NEt. Alloc protective groups were removed by treatment of the carbamate with Pd(PPh₃)₄ and phenylsilane in CH₂Cl₂. The linear cyclization precursor is then released by treatment of the resin with HFIP in CH₂Cl₂ (R. Bollhagen et al. *J. Chem. Soc. Chem. Commun.* **1994**, 2559-2560). It is well known, that peptides can also be cleaved from the resin using TFA in CH₂Cl₂ or mixtures of acetic acid, 2,2,2-trifluoroethanol and CH₂Cl₂ (K. Barlos et al., *Int. J. Peptide Protein Res.* **1991**, 37, 513-520). The subsequent macrolactaminization step is described above.

10

SW-6: Synthesis workflow for derivatizations of attachment points in solution

The macrocyclic compounds obtained according to SW-1 to SW-3 and SW-5 can be further modified by transformations involving functional groups like, but not limited to, amino, carboxyl or hydroxyl groups. In addition, aromatic halides or sulfonates can be subjected to transition-metal catalyzed C-C or C-heteroatom-coupling reactions. The orthogonal protection of the attachment points allows stepwise deprotections and derivatizations which are carried out in a parallel fashion to generate substance libraries:

15

- a6) Cleavage of the first protective group;
- b6) Derivatization of the unmasked functional group;
- c6) Cleavage of the second protective group;
- d6) Derivatization of the liberated functional group; etc.

20

General procedures for synthetic steps utilized in SW-6

25 Protecting group cleavage (steps a6 and c6)

The utilized amine protecting groups (e.g. Boc, Cbz, Teoc, Alloc, Fmoc, etc.), carboxylic acid protecting groups (e.g. *tert*-butyl, benzyl, allyl, methyl, etc.) or alcohol protecting groups (e.g. *tert*-butyl, benzyl, allyl, acetyl, benzoyl, pivaloyl) are removed under standard conditions (P.G.M. Wuts, T.W. Greene, *Greene's Protective Groups in Organic Synthesis*, John Wiley and Sons, 4th Edition, **2006**; P.J. Koncinski, *Protecting Groups*, 3rd ed., Georg Thieme Verlag **2005**).

30

Aryl nitro groups are reduced to anilines.

Attachment point derivatizations (steps b6 and d6)

Derivatizations of the liberated functional groups are based on standard synthesis procedures (A. R. Katritzky et al. (eds), *Comprehensive Functional Group*

35

Transformations, Pergamon, **1995**; S. Patai, Z. Rappoport (eds), *Chemistry of Functional Groups*, Wiley, **1999**; J. March, *Advanced Organic Chemistry*, 4 ed., Wiley, **1992**; leading reviews for Mitsunobu reaction: O. Mitsunobu, *Synthesis* **1981**, 1-28; D.L. Hughes, *Org. Reactions*; Wiley, **1992**, Vol. 42; leading reviews for reductive amination/alkylation: A.F. Abdel-Magid et al., *J. Org. Chem.* **1996**, 61, 3849; E.W. Baxter, A.B. Reitz, *Org. Reactions*, Wiley, **2002**, Vol. 59).

Such prototypical transformations include, but are not limited to:

(i) Amino group derivatizations such as

- Amidations with carbonyl chlorides, carboxylic acid anhydrides, active esters; or with carboxylic acids in the presence of coupling reagents (cf. the general procedures);
- Formation of sulfonamides with sulfonyl chlorides;
- Reductive alkylation with carbonyl compounds; or alkylation with alkyl halides, alkylsulfonates or Michael acceptors;
- Formation of ureas by reacting with isocyanates or their equivalents like carbamoyl chlorides or hydroxysuccinimidyl esters;
- Transformation into thioureas with isothiocyanates or their equivalents;
- Carbamate formation by reacting with chloroformates or their surrogates such as hydroxysuccinimidyl carbonates;
- *N*-arylation to the corresponding *N*-aryl or *N*-heteroaryl derivatives with activated aromatic or heteroaromatic halides or sulfonates in the presence of an auxiliary base and/or transition metal catalyst like Pd or Cu catalyst (e.g. Buchwald-Hartwig coupling).

(ii) Carboxyl group derivatizations like

- Amidation with amines in the presence of a coupling reagent;
- Esterification with alcohols.
- Reduction to alcohols (also obtained by reduction of the corresponding esters)

(iii) Alcoholic hydroxyl group derivatizations such as

- Alkylation to alkyl ethers with alkyl halides or alkylsulfonates, trialkyloxonium tetrafluoroborates;
- Transformation into aryl or heteroaryl ethers by reaction with (a) phenols in the presence of azodicarboxylic acid derivatives and triaryl or trialkyl phosphines (Mitsunobu type reactions); or (b) suitably activated aryl or heteroaryl halides or sulfonates;
- Conversion into carbamates by reaction with isocyanates;

- Conversion into primary amines (obtained e.g. by hydrogenation of azides, which in turn are prepared by the reaction of an alcohol with DPPA, PPh₃, and DEAD) and derivatization of these amines as described above;
- Oxidation to carbonyl compounds, which in turn can be further elaborated by e.g. reductive amination, Wittig reaction or related olefination reactions, etc.;
- Esterification with carboxylic acids or their activated surrogates.

(iv) Aryl halide or sulfonate derivatizations by e.g. Suzuki, Sonogashira, Buchwald, Negishi or Kumada coupling reactions etc.

10 **SW-7: Synthesis workflow for derivatizations of functional groups at the solid phase**

As a possible alternative to SW-6, macrocyclic compounds I with one or more orthogonally protected exocyclic functional groups and one free primary amino group can be converted into fully derivatized products on solid support as previously described for related macrocyclic compounds (WO2011/014973) by:

- 15 a7) Attachment of the macrocyclic amine to an appropriately functionalized solid support by reductive amination;
- b7) Acylation, carbamoylation, or sulfonylation, of the secondary amine functionality generated in the previous step a7 or conversion of this secondary amine functionality into carbamates;
- 20 c7) Removal of the protecting group from the second attachment point;
- d7) Derivatization of the liberated second functional group whereby e.g. amino groups can be alkylated or converted into amides, ureas, thioureas carbamates, or sulfonamides; and carboxylic acid moieties can be transformed into amides or esters;
- e7) Repetitions of steps c7 and d7 if a third, fourth etc. attachment point is available;
- 25 f7) Release of the final product from the solid support.

In case of macrocyclic carboxylic acids the attachment to a polymer-supported amine is followed by derivatizations and release in analogy to c7 to f7:

- a8) Attachment of an amine to an appropriately functionalized solid support by reductive amination;
- 30 b8) Coupling of the macrocyclic carboxylic acid to the polymer-supported amine of step a8;
- c8-f8) Derivatizations and release in analogy to steps c7-f7.

35 **General procedures for synthetic steps utilized in SW-7**

The functionalized solid support

The solid support (polymer, resin) is preferably a derivative of polystyrene cross-linked with 1–5% divinylbenzene, of polystyrene coated with polyethyleneglycol (Tentagel™), or of polyacrylamide (D. Obrecht, J.-M. Villalgordo, *Solid-Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound Libraries*, 5 Tetrahedron Organic Chemistry Series, Vol. 17, Pergamon 1998). It is functionalized by means of a linker, i.e. an α,ω -bifunctional spacer molecule with an anchoring group for the solid support on one end, and on the other end by means of a selectively cleavable functional group that is used for subsequent transformations and finally for release of the product. For the examples of the present invention 10 linkers are used that release an *N*-acyl (amide, urea, carbamate) or an *N*-sulfonyl (sulfonamide) derivative under acidic conditions. These kinds of linkers have been applied in the backbone amide linker (BAL) strategy for solid-phase synthesis of linear and cyclic peptides (K.J. Jensen et al., *J. Am. Chem. Soc.* 1998, 120, 5441-5452; J. Alsina et al., *Chem. Eur. J.* 1999, 5, 2787-2795) and heterocyclic 15 compounds as well (T.F. Herpin et al., *J. Comb. Chem.* 2000, 2, 513-521; M. del Fresno et al., *Tetrahedron Lett.* 1998, 39, 2639-2642; N.S. Gray et al., *Tetrahedron Lett.* 1997, 38, 1161-1164).

Examples of such functionalized resins include DFPE polystyrene (2-(3,5-dimethoxy-4-formylphenoxy)ethyl polystyrene), DFPEM polystyrene (2-(3,5-dimethoxy-4- 20 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 NovaGel; a PEG PS resin).

Attachment of the macrocyclic amine to the functionalized resin (steps a7 and b7) 25 and subsequent *N*-acylation or *N*-sulfonylation

The macrocyclic primary amine is attached to the functionalized solid support by reductive amination preferably with $\text{NaBH}(\text{OAc})_3$ as reducing agent in 1,2-dichloroethane and in the presence of trimethyl orthoformate or $i\text{-Pr}_2\text{NEt}$.

The use of reductive aminations for such processes as well as the subsequent *N*-acylation or *N*-sulfonylation are well-documented; for example NaBH_3CN in DMF or in 30 methanol, or $\text{NaBH}(\text{OAc})_3$ in DMF/acetic acid or in dichloromethane/acetic acid have been used (cf. references cited for the functionalized solid support). The *N*-acylation is favorably conducted with carboxylic acids in the presence of coupling reagents like PyBOP, PyBroP, or HATU or with carboxylic acid fluorides/ chlorides or carboxylic 35 acid anhydrides.

Deprotection (steps c7)

The second attachment point is an Alloc or Fmoc protected amino group or a carboxyl group protected as allyl ester. Standard methods (cf. SW-6) are applied for their deprotection and derivatization.

Release from the resin (step f7)

- 5 The final products are detached from the solid support by acids dissolved in organic solvents and/or H₂O. The use of TFA in dichloromethane, of TFA in dichloromethane in the presence of a scavenger such as H₂O or dimethyl sulfide, or of TFA/H₂O and TFA/H₂O/dimethylsulfide has been described (cf. references cited for the functionalized solid support).

- 10 Attachment of the macrocyclic carboxylic acid to the functionalized resin (steps a8 and b8)

A primary amine is attached to the functionalized solid support by reductive amination preferably using NaBH(OAc)₃ in 1,2-dichloroethane in the presence of trimethyl orthoformate.

- 15 Subsequent acylation with the macrocyclic carboxylic acids is favorably conducted in the presence of coupling reagents like HATU, PyBOP, or PyBroP.

It is worth mentioning that the initially attached primary amine corresponds to an attachment point derivatization of the carboxylic acid.

20

Properties and usefulness

- The macrocycles of type I of the present invention interact with specific biological targets. In particular, they show i) inhibitory activity on endothelin converting enzyme
25 of subtype 1 (ECE-1), ii) inhibitory activity on the cysteine protease cathepsin S (CatS), iii) antagonistic activity on the oxytocin (OT) receptor), iv) antagonistic activity on the thyrotropin-releasing hormone (TRH) receptor), v) agonistic activity on the bombesin 3 (BB3) receptor, vi) antagonistic activity on the leukotriene B4 (LTB4) receptor, and/or vii) antimicrobial activity against at least one bacterial strain, in
30 particular *Staphylococcus aureus* or *Streptococcus pneumoniae*.

- Accordingly, these compounds are useful for the prevention or treatment of i) diseases resulting from abnormally high plasma or tissue levels of the potent vasoconstrictive peptide endothelin-1 (ET-1), like systemic and pulmonary hypertension, cerebral vasospasm and stroke, asthma, cardiac and renal failure,
35 atherosclerosis, preeclampsia, benign prostatic hyperplasia, and carcinogenesis (S. De Lombaert et al., *J. Med. Chem.* **2000**, 43, 488-504); ii) a wide range of diseases

related to Cathepsin S, including neuropathic hyperalgesia, obesity, and in particular diseases of the immune system, like rheumatoid arthritis (RA), multiple sclerosis (MS), myasthenia gravis, transplant rejection, diabetes, Sjögrens syndrome, Grave's disease, systemic lupus erythematosus, osteoarthritis, psoriasis, idiopathic thrombocytopenic purpura, allergic rhinitis, asthma, atherosclerosis, and chronic obstructive pulmonary disease (COPD) (O. Irie et al., *J. Med. Chem.* **2008**, *51*, 5502–5505; WO2009/1112826); iii) diseases and conditions associated to an overexpression of oxytocin (OT), like preterm delivery (P. D. Williams, D. J. Pettibone, *Curr. Pharm. Des.* **1996**, *2*, 41-58; A. D. Borthwick, *J. Med. Chem.* **2010**, *53*, 6525–6538); iv) diseases related to a dysfunction in the homeostatic system of the thyrotropin-releasing hormone (TRH), such as infantile spasms, generalized and refractory partial seizures, edematous and destructive forms of acute pancreatitis, and certain inflammatory disorders (e.g. autoimmune diseases, inflammatory bowel diseases, cancer-related fatigue or depression, and Alzheimer's disease) (P.-Y. Deng et al., *J. Physiol.* **2006**, 497-511; J. Kamath et al., *Pharmacol. Ther.* **2009**, *121*, 20-28); v) diseases related to a dysfunction of the bombesin 3 (BB3) receptor, like obesity and impairment of glucose metabolism, disorders of lung development, pulmonary diseases, CNS disorders and carcinogenesis (R. T. Jensen, *Pharmacol. Rev.* **2008**, *60*, 1-42); vi) diseases potentially treatable by blockade of the leukotriene B4 (LTB4) receptor, especially inflammatory and allergic diseases like asthma, acute respiratory distress syndrome (ARDS), acute lung injury (ALI), chronic obstructive pulmonary disease (COPD), rheumatoid arthritis (RA) and inflammatory bowel disease (IBD), allergic rhinitis, atopic dermatitis, allergic conjunctivitis, obliterative bronchiolitis after lung transplantation, or interstitial lung diseases (R.A. Goodnow, Jr., et al., *J. Med. Chem.* **2010**, *53*, 3502-3516; E.W. Gelfand et al., H. Ohnishi et., *Allergol. Int.* **2008**, *57*, 291-298); and/or vii) a wide range of infections caused by microorganisms, in particular strains of *Staphylococcus aureus* or *Streptococcus pneumonia*, comprising infections related to: a) respiratory diseases like cystic fibrosis, emphysema, asthma or pneumonia, b) skin or soft tissue diseases such as surgical wounds, traumatic wounds, burn wounds or herpes, smallpox, rubella or measles, c) gastrointestinal diseases including epidemic diarrhea, necrotizing enterocolitis, typhlitis or gastroenteritis or pancreatitis, d) eye diseases such as keratitis and endophthalmitis, e) ear diseases, e.g. otitis, f) CNS diseases including brain abscess and meningitis or encephalitis, g) bone diseases such as osteochondritis and osteomyelitis, h) cardiovascular diseases like endocarditis and pericarditis, or i) genitourinal diseases such as epididymitis, prostatitis and urethritis

(R.P. Rennie, *Handb. Exp. Pharmacol.* **2012**, 211, 45-65; W. Bereket et al., *Eur. Rev. Med. Pharmacol. Sci.* **2012**, 16, 1039-1044; D.P. Calfee, *Curr. Opin. Infect. Dis.* **2012**, 25, 385-394). Additional uses of antimicrobial macrocycles of type I comprise the treatment or prevention of microbial infections in plants and animals or as
5 disinfectants or preservatives for materials such as foodstuff, cosmetics, medicaments and other nutrient-containing materials.

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
10 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
15 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
20 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
25 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.

30 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
35 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
5 combining the active macrocycles 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
10 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
15 cross-linked polyvinylpyrrolidones, agar, or alginic acid or a salt thereof, such as sodium alginate. 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
20 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
25 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
30 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.

35 In addition to the formulations described above, 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 with ion exchange resins, or as sparingly soluble salts.

Furthermore, other pharmaceutical delivery systems may be employed such as liposomes and emulsions. 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 understood that the amount used will depend on a particular application.

For example, the therapeutically effective dose for 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.

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.

- 5 Those having the ordinary skill in the art will be able to optimize therapeutically effective 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 method of
10 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 can be determined by standard pharmaceutical
15 procedures in cell cultures or experimental animals, e.g., by determining the LD₅₀ (the dose lethal to 50% of the population) or the LD₁₀₀ (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
20 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 and the route of administration. The exact formulation, route of administration and dose can be chosen by the individual
25 physician in view of the patient's condition (cf. E. Fingl et al. in L. Goodman und A. Gilman (eds), *The Pharmacological Basis of Therapeutics*, 5th ed. 1975, Ch.1, p.1).

- Another 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
30 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 ²H (D), ³H, ¹¹C, ¹⁴C, ¹²⁵I etc. These isotopic analogs and their pharmaceutical salts and formulations are considered useful agents in therapy and/or diagnostics, for example, but not limited to, fine-tuning of *in vivo* half-life.

Examples

The following examples illustrate the invention in more detail but are not intended to limit its scope in any way. Before specific examples are described in detail the used abbreviations and applied general methods are listed.

5

Ac: acetyl

addn: addition

ADDP: azodicarboxylic dipiperidide

Alloc: allyloxycarbonyl

10

AllocCl: allyl chloroformate

AllocOSu: allyloxycarbonyl-*N*-hydroxysuccinimide

AM-resin: aminomethyl resin

AM-PS: aminomethyl polystyrene

aq.: aqueous

15

arom.: aromatic

Bn: benzyl

BOP: (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate

Boc: *tert*-butoxycarbonyl

br.: broad

20

Cbz: benzyloxycarbonyl

CbzCl: benzyl chloroformate

CbzOSu: *N*-(benzyloxycarbonyloxy)succinimide

Cl-HOBt: 6-chloro-1-hydroxybenzotriazole

CMBP: cyanomethylenetriethyl-phosphorane

25

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

30

DFPE polystyrene: 2-(3,5-dimethoxy-4-formylphenoxy)ethyl polystyrene

DIAD: diisopropyl azodicarboxylate

DIC: *N,N'*-diisopropylcarbodiimide

DMAP: 4-(dimethylamino)pyridine

DME: 1,2-dimethoxyethane

35

DMF: dimethylformamide

DMSO: dimethyl sulfoxide

- DPPA: diphenyl phosphoryl azide
DVB: divinylbenzene
EDC: 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide
equiv.: equivalent
- 5 Et: ethyl
Et₃N: triethylamine
Et₂O: diethyl ether
EtOAc: ethyl acetate
EtOH: ethanol
- 10 exp.: experimental
FC: flash chromatography
FDPP: pentafluorophenyl diphenylphosphinate
FI-MS: flow injection mass spectrometry
Fmoc: 9-fluorenylmethoxycarbonyl
- 15 Fmoc-Cl: Fmoc chloride, 9-fluorenylmethyl chloroformate
Fmoc-OSu: (9H-fluoren-9-yl)methyl 2,5-dioxopyrrolidin-1-yl carbonate (or 9-fluorenylmethyl-succinimidyl carbonate)
h: hour(s)
HATU: *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexa-
- 20 fluorophosphate
HBTU: *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
mCPBA: 3-chloroperbenzoic acid
HCTU: *O*-(6-chlorobenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
- 25 HFIP: Hexafluoroisopropanol (1,1,1,3,3,3-hexafluoro-2-propanol)
HL: high loading
HOAt: 1-hydroxy-7-azabenzotriazole
HOBt·H₂O: 1-hydroxybenzotriazole hydrate
HMPA: hexamethylphosphoramide
- 30 i.v.: in vacuo
m: multiplet (spectral)
MeCN: acetonitrile
MeOH: methanol
Me: methyl
- 35 NMP: 1-methyl-2-pyrrolidinone
Ns: 2-nitrobenzenesulfonyl; 4-nitrobenzenesulfonyl

- $\text{PdCl}_2(\text{PPh}_3)_2$: bis(triphenylphosphine)palladium (II) dichloride
 $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$: [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with dichloromethane
 $\text{Pd}(\text{PPh}_3)_4$: tetrakis(triphenylphosphine)palladium(0)
- 5 PEG PS resin: polyethyleneglycol coated polystyrene resin
PG: protective group
Ph: phenyl
 PPh_3 : triphenylphosphine
prep.: preparative
- 10 i-Pr: isopropyl
i-Pr₂NEt: *N*-ethyl-*N,N*-diisopropylamine
i-PrOH: isopropanol
PyBOP: (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
PyBroP: bromotripyrrolidinophosphonium hexafluorophosphate
- 15 PyClu: *N,N,N',N'*-bis-(tetramethylene)-chloroformidinium hexafluorophosphate
q: quartet (spectral)
quant.: quantitative
quint : quintet (spectral)
rt: room temperature
- 20 s : singlet (spectral)
sat.: saturated
soln: solution
TBAF : tetrabutylammonium fluoride
t: triplet (spectral)
- 25 Teoc: 2-(trimethylsilyl)ethoxycarbonyl
tert.: tertiary
TFA: trifluoroacetic acid
THF: tetrahydrofuran
TLC: thin layer chromatography
- 30 TMAD: tetramethylazodicarboxamide
T3P = T3P™: propanephosphonic acid cyclic anhydride
p-TsOH: p-toluenesulfonic acid
Umicore M72 SiMes (RD): [1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro-[(2-isopropoxy)(5-pentafluorobenzoylamino)benzylidene]ruthenium(II)
- 35

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

- 5 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 $[M+H]^+$

UV wave length 220 nm, 254 nm

MS: Electrospray Ionization

- 10 Volume of injection: 5 μ L

Method 1

LC-MS: Agilent HP1100 (DAD detector)

Column: Ascentis Express™ C18 2.7 μ m, 3x50 mm (53811U – Supelco Inc.)

Mobile Phases: A: 0.1% TFA in Water; B: 0.085% TFA in MeCN

- 15 Column oven temperature: 55°C

Gradient:

Time [min.]	Flow [mL/min]	%A	%B
0	1.3	97	3
0.05	1.3	97	3
2.95	1.3	3	97
3.15	1.3	3	97
3.17	1.3	97	3
3.2	1.3	97	3

Method 1a: MS scan range: 95 – 1800 Da; centroid mode, positive mode 40V,
scan time: 1 sec

- 20 **Method 1b:** MS scan range: 95 – 800 Da; centroid mode, positive mode 40V,
scan time: 1 sec

Method 1c: MS scan range: 95 – 1800 Da; centroid mode, positive mode 20V,
scan time: 1 sec

Method 1d: MS scan range: 95 – 1800 Da; profile mode, positive mode 40V,
scan time: 1 sec

- 25 **Method 1e:** MS scan range: 95 – 1800 Da; profile mode, positive mode 80V,
scan time: 1 sec

Method 1f: MS scan range: 95 – 1800 Da; profile mode, positive mode 20V,

scan time: 1 sec

Method 1g: MS scan range: 95 – 1800 Da; centroid mode, positive mode 80V,
scan time: 1 sec

5 Method 2

LC-MS: Agilent HP1100 (DAD detector)

Column: Ascentis Express™ C18 2.7 µm, 3x50 mm (53811U – Supelco Inc.)

Mobile Phases: A: Ammonium Bicarbonate 1 mM in Water – pH=10 in Water; B:
MeCN

10 Column oven temperature: 55°C

Gradient:

Time [min.]	Flow [mL/min]	%A	%B
0	1.3	97	3
0.05	1.3	97	3
2.95	1.3	3	97
3.15	1.3	3	97
3.17	1.3	97	3
3.2	1.3	97	3

Method 2a: MS scan range: 95 – 800 Da; centroid mode, negative mode 40V
scan time: 1 sec

Method 2b: MS scan range: 95 – 1800 Da; centroid mode, negative mode 40V

15 scan time: 1 sec

Method 2c: MS scan range: 95 – 1800 Da; centroid mode, positive mode 40V
scan time: 1 sec

Method 2d: MS scan range: 95 – 1800 Da; centroid mode, positive mode 20V
scan time: 1 sec

20 **Method 2e:** MS scan range: 95 – 800 Da; centroid mode, positive mode 40V
scan time: 1 sec

Method 2f: MS scan range: 95 – 1800 Da; profile mode, positive mode 40V
scan time: 1 sec

25 Method 3

LC-MS: Dionex Ultimate 3000 RS (DAD detector)

Column: Ascentis Express™ C18 2.7 µm, 2.1x50 mm (53822-U – Supelco Inc.)

Mobile Phases: A: 0.1% TFA in Water; B: 0.085% TFA in MeCN

Column oven temperature: 55°C

Gradient:

Time [min.]	Flow [mL/min]	%A	%B
0	1.4	97	3
0.05	1.4	97	3
1.95	1.4	3	97
2.15	1.4	3	97
2.18	1.4	97	3
2.3	1.4	97	3

Method 3a: MS scan range: 95 – 1800 Da; centroid mode, positive mode 40V

5 scan time: 1 sec

Method 3b: MS scan range: 95 – 1800 Da; profile mode, positive mode 40V

scan time: 1 sec

Method 4

10 LC-MS: Agilent HP1100 (DAD detector)

Column: Ascentis Express™ F5 2.7 µm, 3x50 mm (53576-U – Supelco Inc.)

Mobile Phases: A: 0.1%TFA in Water; B: 0.085% TFA in MeCN

Column oven temperature: 55°C

Method 4a and method 4b

15 Gradient:

Time [min.]	Flow [mL/min]	%A	%B
0	1.3	70	30
0.05	1.3	70	30
2.95	1.3	30	97
3.15	1.3	30	97
3.17	1.3	70	30
3.2	1.3	70	30

Method 4a: MS scan range: 95 – 1800 Da; centroid mode, positive mode 40V,

scan time: 1sec

Method 4b: MS scan range: 95 – 1800 Da; profile mode, positive mode 40V,

scan time: 1sec

Method 4c

Gradient:

Time [min.]	Flow [mL/min]	%A	%B
0	1.3	97	3
0.05	1.3	97	3
2.95	1.3	3	97
3.15	1.3	3	97
3.17	1.3	97	3
3.2	1.3	97	3

Method 4c: MS scan range: 95 – 1800 Da; centroid mode, positive mode 20V,
scan time: 1sec

5

Method 5

LC-MS: Agilent HP1100 (DAD detector)

Column: Atlantis™ T3 3 µm, 2.1x50 mm (186003717 – Waters AG)

Mobile Phases: A: 0.1% TFA in Water; B: 0.085% TFA in MeCN

10 Column oven temperature: 55 °C

Gradient:

Time [min.]	Flow [mL/min]	%A	%B
0	0.8	100	0
0.1	0.8	100	0
2.9	0.8	50	50
2.95	0.8	3	97
3.2	0.8	3	97
3.22	0.8	100	100
3.3	0.8	100	100

Method 5a: MS scan range: 95 – 1800 Da; centroid mode, positive mode 40V,
scan time: 1sec

15

II. Preparative HPLC methods:**1. Reverse Phase – Acidic conditions****Method 1a**

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

5 Mobile phases:

A: 0.1% TFA in Water/Acetonitrile 98/2 v/v

B: 0.1% TFA Acetonitrile

Method 1b

Column: XBridge™ C18 5 µm, 30 x 100 mm (Waters AG)

10 Mobile phases:

A: 0.1% TFA in Water/Acetonitrile 98/2 v/v

B: 0.1% TFA Acetonitrile

Method 1c

Column: Gemini-NX™ C18 5 µm, 30 x 100 mm (Phenomenex Inc.)

15 Mobile phases:

A: 0.1% TFA in Water/Acetonitrile 98/2 v/v

B: 0.1% TFA Acetonitrile

Method 1d

Column: XBridge™ Prep C18 10 µm, 50 x 250 mm (Waters AG)

20 Mobile phases:

A: 0.1% TFA in Water/Acetonitrile 98/2 v/v

B: Acetonitrile

Flow rate: 150 mL/min

2. Reverse Phase - Basic conditions**25 Method 2a**

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

Mobile phases:

A: 10 mM Ammonium Bicarbonate pH 10/Acetonitrile 98/2 v/v

B: Acetonitrile

30 Method 2b

Column: XBridge™ C18 5 µm, 30 x 100 mm (Waters AG)

Mobile phases:

A: 10 mM Ammonium Bicarbonate pH 10/Acetonitrile 98/2 v/v

B: Acetonitrile

35 3. Normal Phase

Method 3

Column: VP 100/21 NUCLEOSIL™ 50-10, 21 x 100 mm (Macherey-Nagel AG)

Mobile phases: A: Hexane
 B: Ethylacetate
 C: Methanol

5

FI-MS: Agilent HP1100; m/z [M+H]⁺

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

Specific Examples

15 In the examples below and if no other sources are cited, leading reference for standard conditions of protecting group manipulations (protection and deprotection) are 1) P.G.M. Wuts, T.W. Greene, *Greene's Protective Groups in Organic Synthesis*, John Wiley and Sons, 4th Edition, **2006**; 2) P.J. Koncinski, *Protecting Groups*, 3rd ed., Georg Thieme Verlag **2005**; and 3) M. Goodman (ed.), *Methods of Organic Chemistry (Houben-Weyl)*, Vol E22a, Synthesis of Peptides and Peptidomimetics, Georg Thieme Verlag **2004**.

20

Starting materials

Template A building blocks (Scheme 5):

25

3'-Hydroxybiphenyl-2-carboxylic acid (**1**) is commercially available.

Methyl 3'-hydroxybiphenyl-2-carboxylate (**2**)

30 Thionyl chloride (7.7 mL, 105 mmol) was added at 0°C to a soln of **1** (4.5 g, 21.0 mmol) in MeOH (55 mL). The mixture was stirred for 10 min at 0°C and then heated to reflux for 4 h. Evaporation of the volatiles, aqueous workup (EtOAc, sat. aq. NaHCO₃ soln; Na₂SO₄) and FC (hexane/EtOAc 5:1) afforded the ester **2** (4.34 g, 90%).

35 Data of **2**: C₁₄H₁₂O₃ (228.2). ¹H-NMR (DMSO-d₆): 9.52 (br. s, OH); 7.68 (dd, J = 1.1, 7.6, 1 H); 7.59 (dt, J = 1.5, 7.6, 1 H); 7.47 (dt, J = 1.3, 7.5, 1 H); 7.40 (dd, J = 0.9, 7.6, 1 H); 7.20 (t-like m, J = 8.0, 1 H); 6.75 (m, 1 H); 6.70 – 6.67 (m, 2 H); 3.59 (s, 3 H).

2'-Hydroxybiphenyl-3-carboxylic acid (**3**) is commercially available.

Methyl 2'-hydroxybiphenyl-3-carboxylate (**4**)

- 5 Thionyl chloride (6.8 mL, 93 mmol) was added at 0°C to a soln of **3** (4.0 g, 18.6 mmol) in MeOH (60 mL). The mixture was stirred for 10 min at 0°C and then heated to reflux for 3 h. Evaporation of the volatiles and aqueous workup (EtOAc, sat. aq. NaHCO₃ soln; Na₂SO₄) afforded the ester **4** (3.68 g, 86%).

Data of **4**: C₁₄H₁₂O₃ (228.2). LC-MS (method 2a): R_t = 1.95 (98), 226.9 ([M-H]⁻). ¹H-NMR (DMSO-d₆): 9.66 (s, 1 H); 8.16 (t, J = 1.6, 1 H); 7.89 (d-like m, 1 H); 7.81 (d-like m, 1 H); 7.56 (t, J = 7.7, 1 H); 7.29 (dd, J = 1.7, 7.6, 1 H); 7.20 (t-like m, 1 H); 6.98 – 6.88 (m, 2 H); 3.87 (s, 3 H).

2'-Hydroxy-5'-methoxybiphenyl-3-carboxylic acid (**5**) is commercially available.

15

Methyl 2'-hydroxy-5'-methoxybiphenyl-3-carboxylate (**6**)

- Thionyl chloride (5.14 mL, 71 mmol) was added at 0°C to a soln of **5** (5.74 g, 23.5 mmol) in MeOH (100 mL). The mixture was heated to reflux for 2 h. Evaporation of the volatiles, aqueous workup (EtOAc, sat. aq. NaHCO₃ soln; Na₂SO₄) and FC (hexane/EtOAc 4:1) afforded the ester **6** (5.1 g, 84%).

Data of **6**: C₁₅H₁₄O₄ (258.3). ¹H-NMR (DMSO-d₆): 9.18 (s, OH); 8.17 (t, J = 1.7, 1 H); 7.89 (td, J = 1.4, 7.8, 1 H); 7.82 (td, J = 1.5, 8.0, 1 H); 7.56 (t, J = 7.8, 1 H); 6.91 – 6.78 (m, 3 H); 3.87 (s, 3 H); 3.72 (s, 3 H).

- 25 3'-Hydroxybiphenyl-3-carboxylic acid (**7**) is commercially available.

Methyl 3'-hydroxybiphenyl-3-carboxylate (**8**)

- Thionyl chloride (4.1 mL, 56 mmol) was added at 0°C to a soln of **7** (4.0 g, 18.6 mmol) in MeOH (160 mL). The mixture was heated to reflux for 2 h. Evaporation of the volatiles, filtration of the residue through a pad of silica gel (EtOAc) and FC (hexane/EtOAc 93:7 to 0:100) afforded the ester **8** (4.0 g, 94%).

Data of **8**: C₁₄H₁₂O₃ (228.2). LC-MS (method 2a): R_t = 1.90 (98), 227.3 ([M-H]⁻). ¹H-NMR (DMSO-d₆): 9.63 (br. s, OH); 8.13 (t, J = 1.6, 1 H); 7.96 – 7.88 (m, 2 H); 7.61 (t, J = 7.7, 1 H); 7.29 (t, J = 7.8, 1 H); 7.10 (m, 1 H); 7.06 (t, J = 2.0, 1 H); 6.81 (m, 1 H); 3.89 (s, 3 H).

5-(3-Hydroxyphenyl)nicotinic acid (**9**) is commercially available.

5-(3-Acetoxyphenyl)nicotinic acid (**10**)

At 0°C acetic anhydride (18.8 mL, 0.2 mol) was added dropwise to a soln of 5-(3-hydroxyphenyl)nicotinic acid (**9**; 7.13 g, 0.033 mol) in 4 M aq. NaOH soln (41.4 mL, 0.166 mol). The mixture was stirred for 1 h. A precipitate was formed. The mixture was diluted with 4 M aq. NaOH soln (41.4 mL, 0.166 mol). More acetic anhydride (18.8 mL, 0.2 mol) was added and stirring was continued for 2 h followed by the addition of H₂O (50 mL). The mixture was acidified to pH 1 by addition of 3 M aq. HCl soln. The solid was filtered, washed (H₂O) and dried i.v. to afford **10**·HCl (8.22 g, 84%).

Data of **10**·HCl: C₁₄H₁₁NO₄·HCl (257.2, free base). LC-MS (method 1b): R_t = 1.22 (99), 258.0 ([M+H]⁺). ¹H-NMR (DMSO-d₆): 13.62 (very br. s, 1 H); 9.12 (d, J = 2.0, 1 H); 9.07 (d, J = 1.3, 1 H); 8.46 (s, 1 H); 7.71 (d, J = 7.7, 1 H); 7.63 (s, 1 H); 7.57 (t, J = 7.9, 1 H); 7.23 (d, J = 8.0, 1 H); 2.31 (s, 3 H).

2-Bromothiophenol (**11**) is commercially available.

3-Hydroxyphenylboronic acid (**12**) is commercially available.

20

5-Bromopyridine-3-thiol (**13**) was prepared as described in the literature (S.A. Thomas et al. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3740 – 3744).

2-Hydroxyphenylboronic acid (**14**) is commercially available.

25

4-(3-Hydroxypyridin-2-yl)benzoic acid (**92**) is commercially available.

Methyl 4-(3-hydroxypyridin-2-yl)benzoate (**93**)

Thionyl chloride (7.6 mL, 104 mmol) was added at 4°C to a soln of **92** (4.5 g, 21.0 mmol) in MeOH (130 mL). The mixture was heated to 70°C for 14 h and concentrated. The residue was dissolved in CHCl₃ (200 mL) and EtOH (20 mL) and treated with aq. NaHCO₃ soln (100 mL). The organic phase was separated, the aq. phase was extracted repeatedly with CHCl₃. The combined organic phases were dried (Na₂SO₄), filtered and concentrated to afford the ester **93** (4.45 g, 92%).

30

Data of **93**: $C_{13}H_{11}NO_3$ (229.2). LC-MS (method 1a): R_t = 1.07 (90), 230.1 ($[M+H]^+$). ^1H -NMR (DMSO- d_6): 10.40 (br. s, OH), 8.32 – 8.18 (m, 3 H); 8.02 (d, J = 8.6, 2 H), 7.38 (dd, J = 1.4, 8.2, 1 H); 7.26 (dd, J = 4.4, 8.2, 1 H); 3.88 (s, 3 H).

5 4-(3-Fluoro-5-hydroxyphenyl)thiophene-2-carboxylic acid (**98**)

At rt, a solution of tert-butyl 2,2,2-trichloroacetimidate (27.7 mL, 155 mmol) in CH_2Cl_2 (50 mL) was added dropwise to a soln of 4-bromothiophene-2-carboxylic acid (**94**; 16.0 g, 77.3 mmol) in CH_2Cl_2 (150 mL). The mixture was stirred for 16 h. A precipitate was formed, which was removed by filtration. The filtrate was concentrated. FC (hexane/EtOAc 99:1 to 97:3) yielded **95** (18.7 g, 92%).

Sat. aq. $NaHCO_3$ soln (183 mL) was added to a soln of **95** (17.2 g, 65.2 mmol), 3-fluoro-5-hydroxyphenylboronic acid (**96**; 15.3 g, 97.9 mmol) and $Pd(PPh_3)_4$ (3.77 g, 3.26 mmol) in dioxane (517 mL). The mixture was heated to reflux for 2 h. Aqueous workup (EtOAc, sat. aq. Na_2CO_3 soln, sat. aq. $NaCl$ soln; Na_2SO_4) and FC (hexane/EtOAc 90:10) afforded **97** (12.55 g, 65%).

TFA (150 mL) was added at rt to a mixture of **97** (12.5 g, 42.6 mmol) in CH_2Cl_2 (150 mL). The soln was stirred for 2.5 h and concentrated to give **98** (10.3 g, quant. yield). Data of **98**: $C_{11}H_7FO_3S$ (238.2). ^1H -NMR (DMSO- d_6): 13.23 (br. s, 1 H); 10.03 (br. s, 1 H); 8.21 (d, J = 1.6, 1 H); 8.05 (d, J = 1.6, 1 H); 7.05 (m, 1 H); 6.95 (t, J = 1.7, 1 H), 6.53 (td, J = 2.2, 10.7, 1 H).

3-(Allyloxy)-N-methoxy-N-methylthiophene-2-carboxamide (**102**)

At 0°C, allyl bromide (18.1 mL, 209 mmol) was added dropwise to a mixture of 3-hydroxythiophene-2-carboxylic acid (**99**; 10.0 g, 69.8 mmol) and K_2CO_3 (48.2 g, 349 mmol) in DMF (255 mL). The mixture was allowed to stir for 2 h at 0°C to rt. The mixture was filtered and the residue was washed with EtOAc. The filtrate was concentrated, followed by an aqueous workup (Et_2O , 1 M aq. HCl soln, sat. aq. $NaHCO_3$ soln, H_2O ; Na_2SO_4) to give ester **100** (15.5 g).

At rt, 2 M aq. LiOH soln (346 mL, 691 mmol) was added to a soln of the crude ester **100** (15.5 g) in DME (315 mL). The mixture was heated to 50°C for 16 h and concentrated. The residue was distributed between H_2O and EtOAc. The aqueous phase was acidified with 1 M aq. HCl soln and repeatedly extracted with EtOAc. The combined organic layer was dried (Na_2SO_4), filtered and concentrated to afford the acid **101** (11.5 g, 90%).

At 5°C, i - Pr_2NEt (42.3 mL, 249 mmol) was added dropwise to a mixture of **101** (11.45 g, 62.2 mmol), N,O -dimethylhydroxylamine hydrochloride (7.28 g, 74.6 mmol),

EDC-HCl (14.3 g, 74.6 mmol), HOBt·H₂O (11.4 g, 74.6 mmol) and DMAP (1.52 g, 12.4 mmol) in DMF (116 mL). The mixture was allowed to warm to rt over 5 h followed by an aqueous workup (EtOAc, 1 M aq. HCl soln; Na₂SO₄) and FC (hexane/EtOAc 2:1) to afford **102** (9.69 g, 69%).

- 5 Data of **102**: C₁₀H₁₃NO₃S (227.3). LC-MS (method 1c): R_t = 1.59 (92), 228.1 ([M+H]⁺).

tert-Butyl 3-(3-hydroxythiophen-2-yl)-1-methyl-1H-pyrazole-5-carboxylate (**106**)

- n-Butyllithium (1.6 M in hexane; 41.9 mL, 67.0 mmol) was added dropwise within 10 min at -55 to -50°C to a soln of tert-butyl propiolate (**103**; 8.76 mL, 63.8 mmol) in dry THF (200 mL). The mixture was allowed to stir at -40°C for 1.5 h. The mixture was cooled to -78°C. A soln of **102** (7.25 g, 31.9 mmol) in THF (66 mL) was added within 10 min with the temperature not exceeding -64°C. The mixture was stirred for 0.5 h at -78°C, then warmed to -40°C and allowed to slowly warm to 0°C over 3 h. The mixture was poured into 1M aq. KHSO₄ soln and extracted with EtOAc. The organic phase was dried (Na₂SO₄) and concentrated. FC (hexane/EtOAc 90:10 to 70:30) afforded the ketone **104** (8.34 g, 89%).
- 10
- 15

- Methylhydrazine (1.0 mL, 18.8 mmol) was added at rt to a soln of **104** (4.6 g, 16 mmol) in EtOH (62 mL). Stirring was continued for 1 h and the volatiles were evaporated. Aqueous workup (EtOAc, sat. aq. NaHCO₃ soln; Na₂SO₄) and FC (hexane/EtOAc 90:10) gave pyrazole **105** (4.25 g, 84%).
- 20

Data of **105**: C₁₆H₂₀N₂O₃S (320.4). LC-MS (method 4a): R_t = 1.80 (96), 321.2 ([M+H]⁺). ¹H-NMR (DMSO-d₆): 7.40 (d, J = 5.5, 1 H); 7.08 (s, 1 H); 7.07 (d, J ca 5.9, 1 H); 6.06 (m, 1 H); 5.43 (qd, J = 1.7, 17.3, 1 H); 5.29 (qd, J = 1.6, 10.6, 1 H); 4.69 (td, J = 1.6, 5.0, 2 H); 4.05 (s, 3 H); 1.55 (s, 9 H).

- 25 Phenylsilane (15.0 mL, 121 mmol) was added to a soln of **105** (7.75 g, 24 mmol) and Pd(PPh₃)₄ (1.4 g, 1.2 mmol) in THF (78 mL). The mixture was stirred at rt for 16 h. More Pd(PPh₃)₄ (0.8 g, 0.7 mmol) and phenylsilane (6.0 mL, 48 mmol) were added and stirring was continued for 24 h. The volatiles were evaporated followed by an aqueous workup (EtOAc, 1 M NH₄Cl soln) and FC (hexane/EtOAc 90:10) to yield **106** (5.75 g, 84%).
- 30

Data of **106**: C₁₃H₁₆N₂O₃S (280.3). LC-MS (method 1a): R_t = 2.40 (94), 281.2 ([M+H]⁺). ¹H-NMR (DMSO-d₆): 10.01 (br. s, 1 H); 7.24 (d, J = 5.3, 1 H); 7.04 (s, 1 H); 6.72 (d, J = 5.3, 1 H); 4.04 (s, 3 H); 1.55 (s, 9 H).

2-(4-Hydroxy-3-nitrophenyl)-6-methylpyrimidine-4-carboxylic acid (**110**)

Sat. aq. Na_2CO_3 soln (52.5 mL) was added to a soln of methyl 2-chloro-6-methylpyrimidine-4-carboxylate (**107**; 5.0 g, 26.8 mmol), 4-methoxy-3-nitrophenylboronic acid (**108**; 6.86 g, 34.8 mmol) and $\text{PdCl}_2(\text{PPh}_3)_2$ (0.94 g, 1.3 mmol) in dioxane (175 mL). The mixture was heated to reflux for 4 h and partially concentrated, followed by an aqueous workup (EtOAc, 1 M aq. HCl soln; sat. aq. NaCl soln; Na_2SO_4). The crude product was suspended in $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 2:1; the solid was filtered, washed (MeOH) and dried i.v to afford **109**·HCl (3.7 g, 42%). The filtrate was concentrated and purified by FC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 100:0 to 70:30) to give **109**·HCl (3.87g, 44%).

A mixture of **109**·HCl (7.5 g, 23.1 mmol) and LiCl (4.9 g, 11.5 mmol) in DMF (100 mL) was heated to 145°C for 18 h. The volatiles were mostly evaporated. The residue was cooled to 0°C and treated with 1 M aq. HCl soln (250 mL). The resulting suspension was sonicated and filtered. The solid material was washed (Et_2O) and dried. The solid material was suspended in $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ 1:4, filtered and dried to give **110**·HCl (6.5 g, 80%).

Data of **110**·HCl: $\text{C}_{12}\text{H}_9\text{N}_3\text{O}_5\cdot\text{HCl}$ (free base, 275.2). LC-MS (method 1a): R_t = 1.73 (83), 276.0 ($[\text{M}+\text{H}]^+$). ^1H -NMR ($\text{DMSO}-d_6$): 8.91 (d, J = 1.9, 1 H); 8.56 (dd, J = 1.9, 8.8, 1 H); 7.80 (s, 1 H); 7.30 (d, J = 8.8, 1 H); 2.63 (s, 3 H).

20

2-Iodophenol (**111**) is commercially available.

2-(Ethoxycarbonyl)phenylboronic acid (**112**) is commercially available.

Ethyl 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (**113**) is commercially available.

4-(3-Hydroxyphenyl)-2-(trifluoromethyl)oxazole-5-carboxylic acid (**117**)

The aminoacrylic acid ester **115** was prepared according to J.H. Lee et al, *J. Org. Chem.* **2007**, 72, 10261.

The 2-(trifluoromethyl)oxazole **116** was prepared as described by F. Zhao et al. *J. Org. Chem.* **2011**, 76, 10338 for similar compounds:

A degassed soln of **115** (2.15 g, 9.72 mmol) in DCE (500 mL) was warmed to 45°C. [Bis(trifluoroacetoxy)iodo]benzene (5.02 g, 11.67 mmol) was added in one portion, and stirring at 45°C was continued for 16 h. Evaporation of the volatiles and FC (hexane/EtOAc 98:2) afforded **116** (1.55 g, 50%).

Data of **116**: $C_{14}H_{12}F_3NO_4$ (315.2). ^1H -NMR (DMSO- d_6): 7.62 – 7.57 (m, 2 H); 7.45 (t, J = 8.0, 1 H); 7.11 (m, 1 H); 4.38 (q, J = 7.1, 2 H); 3.81 (s, 3 H); 1.31 (t, J = 7.1, 3 H).

At 0°C, BBr_3 (1 M in THF; 24.2 mL, 24.2 mmol) was added dropwise to a soln of **116** (1.5 g, 4.85 mmol) in CH_2Cl_2 (3.5 mL). The mixture was stirred for 16 h at 0°C to rt, slowly added onto ice-cold water (500 mL) and extracted with EtOAc. The organic phase was washed (sat. aq. NaCl soln), dried (Na_2SO_4), filtered and concentrated. FC (hexane/EtOAc 75:25 to 0:100, then CH_2Cl_2 /MeOH 90:10) afforded **117** (1.24 g, 95%).

Data of **117**: $C_{11}H_6F_3NO_4$ (273.2). ^1H -NMR (DMSO- d_6): 9.54 (br. s, 1 H), 7.71 – 7.65 (m, 2 H); 7.23 (t, J = 7.9, 1 H); 6.80 (m, 1 H).

Modulator B building blocks (Scheme 6):

tert-Butyl (3S,5S)-5-(hydroxymethyl)pyrrolidin-3-ylcarbamate hydrochloride (**15**·HCl) is commercially available.

(2S,4S)-Allyl 4-(tert-butoxycarbonylamino)-2-(hydroxymethyl)-pyrrolidine-1-carboxylate (**16**) was prepared by Alloc protection of the secondary amino group of **15**·HCl with allyl chloroformate in CH_2Cl_2 in the presence of aq. $NaHCO_3$ soln applying standard conditions.

Data of **16**: $C_{14}H_{24}N_2O_5$ (300.4). ^1H -NMR (DMSO- d_6): 7.12 (br. d, J = 6.1, 1 H); 5.91 (m, 1 H); 5.27 (m, 1 H); 5.18 (m, 1 H); 4.49 (m, 2 H); ca 3.9 (br. m, 1 H); 3.89 – 3.57 (several m, 4 H); 3.48 (dd, J = 3.1, 10.6, 1 H); 2.95 (br. m, 1 H); 2.21 (br. m, 1 H); 1.75 (br. m, 1 H); 1.38 (s, 9 H).

tert-Butyl (3R,5S)-5-(hydroxymethyl)pyrrolidin-3-ylcarbamate hydrochloride (**17**·HCl) is commercially available.

(2S,4R)-Allyl 4-(tert-butoxycarbonylamino)-2-(hydroxymethyl)-pyrrolidin-1-carboxylate (**18**) was prepared by Alloc protection of the secondary amino group of **17**·HCl with allyl chloroformate in CH_2Cl_2 in the presence of aq. $NaHCO_3$ soln applying standard conditions.

Data of **18**: $C_{14}H_{24}N_2O_5$ (300.4). ^1H -NMR (DMSO- d_6): 7.08 (br. d, J = 7.1, 1 H); 5.91 (m, 1 H); 5.26 (br. m, 1 H); 5.18 (br. d, J ca 10.4, 1 H); 4.52 (br. m, 2 H), ca 4.1 (br.

m, 2 H); 3.82 (br. m, 1 H); ca 3.5- 3.35 (br. s-like m, 3 H); 3.19 (br. m, 1 H); 2.05 (br. m, 1 H); 1.79 (br. m, 1 H); 1.38 (s, 9 H).

N-Boc-L-alaninol (**19**) is commercially available.

5

N-Boc-D-alaninol (**20**) is commercially available.

(S)-tert-Butyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate (**21**) is commercially available.

10

(2S,4S)-Allyl 4-(4-bromobenzyloxy)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (**118**) was prepared as described in the preceding patent application (WO 2011/014973 A2).

15 (S)-(+)-Prolinol (**119**) is commercially available.

(S)-Allyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate (**120**) was prepared by Alloc protection of the secondary amino group of (S)-(+)-prolinol (**119**) with allyl chloroformate in dioxane in the presence of aq. NaHCO₃ soln applying standard conditions.

20

Data of **120**: C₉H₁₅NO₃ (185.2). FI-MS: 186.1 ([M+H]⁺). ¹H-NMR (DMSO-d₆): 5.92 (m, 1 H); 5.28 (br. dd-like m, 1 H); 5.18 (br. dd-like m, 1 H); 4.72 (br. not resolved m, 1 H); 4.60 – 4.45 (br. not resolved m, 2 H); 3.73 (br. not resolved m, 1 H); 3.50 (br. not resolved m, 1 H); 3.35 – 3.25 (br. not resolved m, 3 H); 2.0 – 1.75 (br. not resolved m, 4 H).

25

(2S,4R)-tert-Butyl 4-amino-2-(hydroxymethyl)pyrrolidine-1-carboxylate hydrochloride (**121**·HCl) is commercially available.

30 (2S,4R)-tert-Butyl 4-(benzyloxycarbonylamino)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (**122**) was prepared by Cbz protection of the primary amino group of **121**·HCl with benzyl chloroformate in CH₂Cl₂ in the presence of aq. Na₂CO₃ soln applying standard conditions.

Data of **122**: C₁₈H₂₆N₂O₅ (350.4). LC-MS (method 1c): R_t = 1.89 (95), 351.3 ([M+H]⁺).

35 ¹H-NMR (DMSO-d₆): 7.49 (d, J = 6.8, 1 H); 7.42 – 7.28 (m, 5 H); 5.02 (s, 2 H); 4.76 (br. s, 1 H); 4.13 (br. not resolved m, 1 H), 3.76 (br. not resolved m, 1 H); 3.40 (m, 3

H; partially superimposed by H₂O signal); 3.11 (dd; J = 6.4, 10.6, 1 H); 2.07 (br. not resolved m, 1 H); 1.82 (br. not resolved m, 1 H); 1.38 (s, 9 H).

5 **Building blocks for subunits of bridge C (Scheme 7):**

(R)-Allyl 4-amino-2-(benzyloxycarbonylamino)butanoate toluene-4-sulfonate (**22**·pTsOH) was prepared as described for the (S)-enantiomer in the preceding patent application (WO 2011/014973 A2).

(S)-Allyl 2-(benzyloxycarbonylamino)-(5-methylamino)pentanoate hydrochloride (**23**·HCl), (S)-5-allyl 1-benzyl 2-(methylamino)pentanedioate hydrochloride (**24**·HCl) and (S)-5-allyl 1-benzyl 2-aminopentanedioate hydrochloride (**25**·HCl) were prepared as described in the preceding patent application (WO 2011/014973 A2).

Ethyl 2-((2-aminoethyl)(benzyloxycarbonyl)amino)acetate hydrochloride (**28**·HCl)

15 Ethyl 2-(2-(tert-butoxycarbonylamino)ethylamino)acetate hydrochloride (**26**·HCl; 25.0 g, 88 mmol) was added to a mixture of dioxane (250 mL) and 1 M aq. Na₂CO₃ soln (250 mL). After 5 min, CbzCl (17.0 g, 98 mmol) was slowly added and the mixture was stirred for 2 h. Aqueous workup (EtOAc, sat. aq. NaHCO₃; Na₂SO₄) and FC (hexane/EtOAc 8:2 to 1:1) afforded **27** (29.0 g, 85%). A solution of **27** (29.5 g, 77.5 mmol) in 4 M HCl-dioxane (300 mL) was stirred at rt for 2 h and concentrated. The residue was washed with Et₂O to give **28**·HCl (24.3 g, 99%).

20 Data of **28**·HCl: C₁₄H₂₀N₂O₄·HCl (280.3, free base). LC-MS (method 1a): R_t = 1.33 (99), 281.1 ([M+H]⁺). ¹H-NMR (DMSO-d₆): 8.05 (br. s, NH₃⁺); 7.39 – 7.28 (m, 5 arom. H); 5.12, 5.07 (2 s; 2 H); 4.16 – 4.04 (m, 4 H); 3.54 (m, 2 H); 2.97 (br m, 2 H); 1.19, 1.32 (2 t, J = 7.1, 3 H).

(S)-Methyl 2-(tert-butoxycarbonylamino)-6-hydroxyhexanoate (**30**)

30 At 0°C, iodomethane (8.18 mL, 131 mmol) was added to a suspension of Boc-L-6-hydroxynorleucine (**29**; 25 g, 101 mmol) and NaHCO₃ (42.5 g, 505 mmol) in DMF (790 mL). The mixture was stirred at 0°C to rt for 16 h. The mixture was filtered. The filtrate was distributed between EtOAc and 1 M aq. HCl soln. The organic layer was subsequently washed with H₂O, sat. aq. NaHCO₃ soln and sat. aq. NaCl soln. The organic phase was dried (Na₂SO₄), filtered, and concentrated to afford **30** (24.54 g, 92%).

35 Data of **30**: C₁₂H₂₃NO₅ (261.3). FI-MS: 262.0 ([M+H]⁺). ¹H-NMR (DMSO-d₆): 7.21 (d, J = 7.8, 1 H); 4.36 (t, J = 5.2, 1 H); 3.92 (m, 1 H); 3.61 (s, 3 H); 3.36 (q, J = 5.8, 2 H);

1.59 (m, 2 H); 1.44 (s, 9 H); 1.44 – 1.26 (m, 4 H).

(S)-3-(((9H-Fluoren-9-yl)methoxy)carbonylamino)-4-phenylbutanoic acid (**31**; Fmoc- β^3 -homoPhe-OH) is commercially available.

5

3-(((9H-Fluoren-9-yl)methoxy)carbonyl)(methylamino)propanoic acid (**33**; Fmoc-NMe- β -Ala-OH) was prepared from 3-(methylamino)propanoic acid hydrochloride (**32**·HCl) applying Fmoc-OSu and Na₂CO₃ in H₂O and dioxane.

Data of **33**: C₁₉H₁₉NO₄ (325.3). LC-MS (method 1a): R_t = 1.95 (96), 326.0 ([M+H]⁺).

10

3-(((9H-Fluoren-9-yl)methoxy)carbonylamino)propanoic acid (**34**; Fmoc- β -Ala-OH) is commercially available.

Synthesis of (R)-3-(((9H-Fluoren-9-yl)methoxy)carbonyl)(methylamino)butanoic acid (**40**; Fmoc-NMe- β^3 -homoDAla-OH)

15

At 0°C, 4 M HCl-dioxane (37.8 mL, 151 mmol) was added dropwise to a mixture of (R)-homo- β -alanine (**35**; 13.0 g, 126 mmol) in CH₂Cl₂ (170 mL). PCl₅ (31.5 g, 151 mmol) was added to the suspension. The mixture was stirred at 0°C to rt for 15 h. A clear solution resulted. The volatiles were evaporated. The residue was dissolved in CH₂Cl₂ (150 mL). Allyl alcohol (10.3 mL, 151 mmol) was added slowly and the mixture was stirred for 2 h at rt. The volatiles were evaporated to afford crude **36**·HCl (25.6 g).

20

Pyridine (115 mL) was added to a soln of crude **36**·HCl (25.5 g) in CH₂Cl₂ (275 mL). The mixture was cooled to 0°C, followed by the addition of 4-nitrobenzenesulfonyl chloride (63 g, 284 mmol). The mixture was stirred at 0°C to rt for 16 h. Aq. workup (CH₂Cl₂, 1 M aq. HCl soln; Na₂SO₄) and FC (hexane/EtOAc 9:1 to 1:1) yielded **37** (26.7 g, 64%).

25

K₂CO₃ (56 g, 404 mmol) was added to a solution of **37** (26.5 g, 81 mmol) in DMF (295 mL). Iodomethane (50 mL, 807 mmol) was added at 0°C and the mixture was allowed to warm to rt over 3 h. Aq. workup (EtOAc, 1 M aq. HCl soln, sat. aq. NaCl soln; Na₂SO₄) gave crude **38** (27.6 g).

30

K₂CO₃ (16.7 g, 121 mmol) was added to a soln of crude **38** (13.8 g, ca 40 mmol) in CH₃CN (275 mL). The mixture was degassed, cooled to 0°C and treated with thiophenol (6.15 mL, 60 mmol). The mixture was stirred at 0°C to rt for 15 h. H₂O (115 mL) and (in portions) Fmoc-Cl (10.5 g, 40.3 mmol) were added. Stirring was continued for 3 h followed by an aq. workup (EtOAc, sat. aq. Na₂CO₃; Na₂SO₄) and

35

FC (hexane/EtOAc 95:5 to 70:30). The material obtained (11.5 g) was purified again by FC (hexane/CH₂Cl₂ 8:2, then CH₂Cl₂, then CH₂Cl₂/EtOAc) to give **39** (9.2 g, 60%). A degassed soln of **39** (18.3 g, 48.2 mmol) in CH₂Cl₂ (175 mL) / EtOAc (210 mL) was treated with Pd(PPh₃)₄ (0.9 g, 0.77 mmol) and 1,3-dimethylbarbituric acid (9.04 g, 57.9 mmol) for 3 h at rt. The volatiles were evaporated. FC (CH₂Cl₂/MeOH 100:0 to 80:20) afforded **40** (7.55 g, 46%) and impure material which was further purified by prep. HPLC (method 1d) to give more **40** (5.61 g, 34%).

Data of **40**: C₂₀H₂₁NO₄ (339.4). LC-MS (method 1a): R_t = 2.03 (96), 340.1 ([M+H]⁺).

¹H-NMR (DMSO-d₆): 12.2 (br. s, 1 H); 7.89 (d, J = 7.4, 2 H); 7.65 (br. s, 2 H); 7.41 (t, J = 7.4, 2 H); 7.33 (t, J = 7.3, 2 H); 4.40 – 4.24 (m, 4 H), 2.67 (s, 3 H); 2.45– 2.30 (br. m, 2 H); 1.37 (br. d, 3 H).

Allyl 2-((2-aminoethyl)(benzyloxycarbonyl)amino)acetate hydrochloride (**125**·HCl)

At 4°C, LiOH·H₂O (6.36 g, 152 mmol) was added to a soln of **27** (28.82 g, 75.8 mmol) in MeOH (86 mL), H₂O (85 mL) and THF (270 mL). The mixture was stirred for 18 h at rt, acidified with 1 M aq. HCl soln (500 mL) and extracted with EtOAc. The organic phase was dried (Na₂SO₄), filtered and concentrated to give **123** (26.5 g, 99%).

NaHCO₃ (17.7 g, 210 mmol) was added to a soln of **123** (37.1 g, 105.4 mmol) in DMF (530 mL). The mixture was stirred for 5 min followed by the addn of allyl bromide (18.0 mL; 208 mmol). The mixture was stirred at rt for 18 h. More NaHCO₃ (2.0 g, 24 mmol) and allyl bromide (2.0 mL; 23.1 mmol) were added and stirring was continued for 4 h. Aq. Workup (EtOAc, 1 M aq. HCl soln; Na₂SO₄) and FC (CH₂Cl₂/MeOH 99.5:0.5 to 98:2) afforded **124** (38.8 g, 94%).

A soln of **124** (22.5 g, 53.3 mmol) in dioxane (23 mL) was treated at rt with 4 M HCl in dioxane (80 mL) for 3 h. Dioxane (50 mL) was added and stirring was continued for 1 h. The volatiles were evaporated and the residue was washed (Et₂O) and dried i.v. to yield **125**·HCl (17.0 g, 97%).

Data of **125**·HCl: C₁₅H₂₀N₂O₄·HCl (free base, 292.3). FI-MS: 292.9 ([M+H]⁺).

¹H-NMR (DMSO-d₆): 8.03 (br s, 3 H); 7.39 – 7.28 (m, 5 H); 5.87 (m, 1 H); 5.35 – 5.17 (m, 2 H); 5.12, 5.07 (2 s, 2 H); 4.59 (m, 2 H); 4.16 (d, J = 7.5, 2 H); 3.54 (q-like m, 2 H); 2.97 (br m, 2 H).

All Fmoc-α-amino acids and Fmoc-N-methyl-α-amino acids applied in the synthesis of Core 10 and Core 11 are commercially available:

Fmoc-L-alanine (Fmoc-Ala-OH)

Fmoc-N-methyl-L-alanine (Fmoc-NMe-Ala-OH)

Fmoc-D-alanine (Fmoc-DAla-OH)

Fmoc-N-methyl-D-alanine (Fmoc-NMe-DAla-OH)

Fmoc-N-methyl-L-glutamic acid 5 tert.-butyl ester (Fmoc-NMe-Glu(OtBu)-OH)

Fmoc-glycine (Fmoc-Gly-OH)

5 N- α -Fmoc-N- ϵ -Boc-L-lysine (Fmoc-Lys(Boc)-OH)

Fmoc-L-phenylalanine (Fmoc-Phe-OH)

Fmoc-N-methyl-L-phenylalanine (Fmoc-NMe-Phe-OH)

Fmoc-D-phenylalanine (Fmoc-DPhe-OH)

Fmoc-N-methyl-D-phenylalanine (Fmoc-NMe-DPhe-OH)

10 Fmoc-sarcosine (Fmoc-Sar-OH)

(S)-Methyl 3-(allyloxy)-2-aminopropanoate hydrochloride (**129**)

A soln of Boc-serine (**126**; 14.0 g, 68.2 mmol) in DMF (143 mL) was cooled to 0°C. NaHCO₃ (17.2 g 205 mmol) was added and the mixture was stirred for 15 min.

15 Iodomethane (8.5 mL, 136 mmol) was added dropwise. The mixture was stirred at 0°C to rt for 16 h and again cooled to 0°C. More iodomethane (4.2 mL, 67 mmol) was slowly added and stirring was continued for 3 h. The mixture was diluted with H₂O and extracted with EtOAc. The organic phase was washed (sat. aq. NaCl soln), dried (Na₂SO₄), filtered and concentrated to give crude **127** (14.2 g).

20 A soln of crude **127** (14.2 g) and Pd(PPh₃)₄ (0.64 g) in THF (416 mL) was degassed. Carbonic acid allyl methyl ester (9.6 g, 82.8 mmol) was added and the mixture was heated to 60°C for 2 h. The volatiles were evaporated. FC (hexane/EtOAc 9:1) afforded **128** (11.4 g, 79%)

A soln of **128** (11.4 g, 43.9 mmol) in dioxane (110 mL) was treated with 4 M HCl in dioxane (110 mL) for 4 h at rt. Additional 4 M HCl in dioxane (30 mL) was added and stirring was continued for 30 min. The volatiles were evaporated and the residue was washed with Et₂O to give **129**-HCl (8.3 g, 96%).

25 Data of **129**-HCl: C₇H₁₃NO₃·HCl (159.2, free base). FI-MS: 160.0 ([M+H]⁺). ¹H-NMR (DMSO-d₆): 8.70 (br. s, 3 H); 5.85 (m, 1 H); 5.29 (qd, J = 1.7, 17.3, 1 H), 5.19 (qd, J = 1.5, 10.4, 1 H); 4.33 (t, J = 3.6, 1 H); 4.07 – 3.93 (m, 2 H); 3.86 – 3.78 (m, 2 H); 3.76 (s, 3 H).

(S)-Allyl 2-(benzyloxycarbonylamino)-4-(methylamino)butanoate hydrochloride (**130**-HCl) and

(S)-Allyl 2-(benzyloxycarbonylamino)-6-(methylamino)hexanoate hydrochloride (**131**·HCl) were prepared described in the preceding patent application (WO 2011/014973 A2).

- 5 Sarcosine tert-butylester hydrochloride (**132**·HCl) is commercially available.

Core 01: Synthesis of Ex.1, Ex.2 and Ex.3 (Scheme 8)

Synthesis of the Mitsunobu product **41**

- 10 At 0°C, ADDP (7.08 g, 28.1 mmol) was added in portions to a mixture of phenol **2** (4.27 g, 18.7 mmol), alcohol **16** (6.18 g, 20.6 mmol) and PPh₃ (7.36 g, 28.1 mmol) in CHCl₃ (110 mL). The stirred mixture was allowed to warm to rt over 15 h. The volatiles were evaporated. The residue was suspended in CH₂Cl₂ and filtered. The filtrate was concentrated and purified by FC (hexane/EtOAc 4:1) to yield **41** (5.98 g, 62%).

15 Data of **41**: C₂₈H₃₄N₂O₇ (510.6). LC-MS (method 1a): R_t = 2.58 (94), 511.2 ([M+H]⁺).

Synthesis of the acid **42**

- 20 Aq. LiOH soln (2 M; 11 mL, 22.0 mmol) was added to a solution of ester **41** (5.65 g, 11.1 mmol) in MeOH (11 mL) and THF (19 mL). The mixture was heated to 65°C for 4 h, partially concentrated, acidified with 1 M aq. HCl soln to pH 1 and extracted twice with EtOAc. The combined organic layer was washed (sat. aq. NaCl soln), dried (Na₂SO₄), filtered and concentrated to give **42** (4.46 g, 81%).

25 Data of **42**: C₂₇H₃₂N₂O₇ (496.6). LC-MS (method 1a): R_t = 2.28 (90), 497.2 ([M+H]⁺).

Synthesis of the amide **43**

- 30 A solution of acid **42** (4.46 g, 9.0 mmol), amine **22**-pTsOH (5.6 g, 11 mmol), HATU (5.1 g, 13 mmol), HOAt (1.8 g, 13 mmol) in DMF (70 mL) was cooled to 0°C, followed by the addition of i-Pr₂NEt (6.2 mL, 36 mmol). The mixture was allowed to warm to rt over 15 h. The mixture was diluted with 0.5 M aq. HCl soln and extracted twice with EtOAc. The combined organic layer was washed (sat. aq. NaCl soln), dried (Na₂SO₄), filtered and concentrated. FC (hexane/EtOAc 1:1) of the crude product afforded **43** (5.56 g, 80%).

35 Data of **43**: C₄₂H₅₀N₄O₁₀ (770.9). LC-MS (method 1a): R_t = 2.55 (95), 771.3 ([M+H]⁺).

Synthesis of amino acid **44**

A degassed solution of amide **43** (5.55 g, 7.2 mmol) and 1,3-dimethylbarbituric acid (2.5 g, 16 mmol) in CH₂Cl₂ (40 mL) and EtOAc (40 mL) was treated with Pd(PPh₃)₄ (0.41 g, 0.36 mmol) at rt. After 2 h, more CH₂Cl₂ (40 mL) and Pd(PPh₃)₄ (0.41 g, 0.36 mmol) were added and stirring was continued for 1 h. The volatiles were evaporated. The solid was suspended in EtOAc, filtered, washed (EtOAc) and dried i.v. to afford **44** (3.94 g, 83%).

Data of **44**: C₃₅H₄₂N₄O₈ (646.7). LC-MS (method 1a): R_t = 1.75 (97), 647.2 ([M+H]⁺).

10 Synthesis of Ex.1

The amino acid **44** (2.77 g, 4.28 mmol) was added in portions over 2 h to a solution of T3P (50% in EtOAc; 13 mL, 22.1 mmol) and i-Pr₂NEt (5.8 mL, 34.3 mmol) in dry CH₂Cl₂ (800 mL). Stirring was continued for 30 min. The mixture was washed (sat. aq. NaHCO₃ soln.), dried (Na₂SO₄), filtered and concentrated. FC (CH₂Cl₂/THF 9:1) of the crude product yielded Ex.1 (2.35 g, 87%).

Data of Ex.1: C₃₅H₄₀N₄O₇ (628.7). LC-MS (method 1a): R_t = 2.17 (94), 629.2 ([M+H]⁺). ¹H-NMR (DMSO-d₆): 8.18 (br. t, 1 H); 7.67 (d, J = 7.2, 1 H); 7.52 – 7.23 (m, 11 H); 7.11 – 7.06 (m, 2 H); 6.98 (d, J = 8.1, 1 H); 4.98 (s, 2 H); 4.64 (br. m, 1 H); ca 4.3 – 4.0 (several br. m, 4 H); 3.85 (br. m, 1 H); 3.10 (br. m, 1 H); 2.98 (m, 1 H); 2.31 (br. m, 1 H); ca 2.0 – 1.75 (br. m, 2 H); 1.53 (br. m, 1 H); 1.41 (s, 9 H); 0.83 (br. m, 1 H).

Synthesis of Ex.2

A soln of Ex.1 (300 mg, 0.477 mmol) in MeOH (6.0 mL) was hydrogenated for 16 h at rt and normal pressure in the presence of palladium hydroxide on activated charcoal (moistened with 50% H₂O; 63 mg). The mixture was filtered through a pad of celite. The solid was washed with MeOH. The combined filtrate and washings were concentrated. FC (CH₂Cl₂/MeOH 95:5 to 80:20) gave Ex.2 (206 mg, 87%).

Data of Ex.2: C₂₇H₃₄N₄O₅ (494.6). LC-MS (method 1a): R_t = 1.60 (99), 495.2 ([M+H]⁺). ¹H-NMR (DMSO-d₆): 8.21 (t-like m, 1 H); 7.52 – 7.36 (m, 5 H); 7.21 (br. d, 1 H), 7.15 – 7.00 (m, 2 H); 7.00 (s, 1 H), 4.43 (br. not resolved m, 1 H); 4.24 – 4.01 (m, 3 H); 3.89 (q-like m, 1 H); 3.58 – 3.12 (several br. m, 3 H); 2.98 (dd, J = 6.2, 12.1, 1 H); 2.33 (m, 1 H); 1.89 (m, 1 H); 1.65 – 1.55 (br. not resolved m, 2 H); 1.41 (s, 9 H).

Synthesis of Ex.3

A soln of Ex.1 (750 mg, 1.19 mmol) in CH₂Cl₂ (5 mL) was cooled to 0°C. TFA (2.0 mL) was slowly added and the mixture was stirred at 0°C to rt for 4 h. The volatiles were evaporated. The residue was taken up in CHCl₃ and concentrated.

- 5 The residue was taken up in CH₂Cl₂ (6 mL), treated with 4 M HCl in dioxane (2 mL) to give a precipitate. The volatiles were evaporated. The treatment with CH₂Cl₂/4 M HCl in dioxane was repeated. The residue was suspended in Et₂O, filtered, washed (Et₂O) and dried i.v. to afford Ex.3·HCl (613 mg, 90%).

Data of Ex.3·HCl: C₃₀H₃₂N₄O₅·HCl (528.6, free base). LC-MS (method 1a): R_t = 1.55 (99), 529.1 ([M+H]⁺).

10

Core 01: Synthesis of Ex.330, Ex.331 and the resin 133 (Scheme 8)

Synthesis of Ex.330

- Sat. aq. NaHCO₃ soln (131 mL) and H₂O (53.5 mL) were added to a soln of Ex.2 (14.4 g, 29 mmol) in dioxane (131 mL) and THF (78 mL). The mixture was cooled to 0°C. Allyl chloroformate (3.71 mL, 34.9 mmol) was slowly added. Stirring was continued for 2 h at 0°C to rt. The mixture was diluted with sat. aq. Na₂CO₃ soln and extracted with CH₂Cl₂. The organic phase was dried (Na₂SO₄), filtered and concentrated to give Ex.330 (16.18 g, 96%).
- 15

20 Data of Ex.330: C₃₁H₃₈N₄O₇ (578.6). LC-MS (method 1c): R_t = 2.06 (97), 578.9 ([M+H]⁺).

Synthesis of Ex.331

- At 0°C, TFA (40.6 mL) was added to a soln of Ex.330 (15.8 g, 27.3 mmol) in CH₂Cl₂ (160 mL). The cooling bath was removed and stirring was continued for 2 h. The volatiles were evaporated. The residue was dissolved in CHCl₃ (76 mL) and 4 M HCl in dioxane (14.0 mL) was added. The volatiles were evaporated. The residue was again taken up in CHCl₃ (76 mL), treated with 4 M HCl in dioxane (14.0 mL) and concentrated. The residue was distributed between sat. aq. Na₂CO₃ soln and EtOAc.
- 25
- 30 The organic layer was separated, the aqueous layer repeatedly extracted with EtOAc. The combined organic phases were concentrated. The residue was dissolved in CH₂Cl₂ (200 mL). Then 4 M HCl in dioxane (17.7 mL) was slowly added to give a thick precipitate. The volatiles were evaporated. The residue was suspended in Et₂O, filtered, washed (Et₂O) and dried i.v. to afford Ex.331·HCl (12.5 g, 89%).

35 Data of Ex.331·HCl: C₂₆H₃₀N₄O₅·HCl (free base, 478.5). LC-MS (method 1a): R_t = 1.36 (96), 479.2 ([M+H]⁺). ¹H-NMR (DMSO-d₆): 8.43 (br. s, 3 H); 8.27 (br. t, J ca 5.3,

134

1 H); 7.67 (d, J = 6.9, 1 H); 7.52 – 7.37 (m, 5 H); 7.12 – 7.09 (m, 2 H); 7.02 (d, J = 8.8, 1 H); 5.88 (m, 1 H); 5.26 (dd, J = 1.2, 17.2, 1 H); 5.17 (dd, J = 1.1, 10.4, 1 H); 4.67 (br. m, not resolved, 1 H); 4.43 (d, J = 5.2, 2 H); 4.31 – 4.11 (m, 4 H); 3.56 (br. m, not resolved, 1 H); 3.31 – 3.16 (br. m, 2 H); 3.19 (dd, J = 8.1, 12.1, 1 H); 2.60 (m, 1 H); 2.12 (m, 1 H); 1.83 (br. m, 1 H); 1.47 (br. m, 1 H).

Synthesis of the resin **133**

Under Ar, DFPE polystyrene (1% DVB, 100 – 200 mesh, loading 0.87 mmol/g; 11.1 g, 9.6 mmol) was swollen in DCE (110 mL) for 1 h. **Ex.331**-HCl (5.7 g, 10.6 mmol) and *i*-Pr₂NEt (4.9 mL, 28.9 mmol) were added. The mixture was shaken at rt for 1 h. NaBH(OAc)₃ (4.09 g, 19.3 mmol) was added and the mixture was shaken for 20 h. The resin was filtered and successively washed with MeOH twice, then three times each with DCE, 10% *i*-Pr₂NEt in DMF, DMF, CH₂Cl₂ and MeOH. The resin was dried i.v. to give **133** (15.73 g; loading 0.6 mmol/g).

Procedure D:Core 01: Synthesis of final products on solid supportSynthesis of resin **134**

1) First derivatization step

Resin **133** (loading 0.6 mmol/g; 96 mg, 0.055 mmol) was swollen in DMF (1 mL) for 60 min and filtered. The resin was resuspended in DMF/CH₂Cl₂ 1:1 (1 mL). *i*-Pr₂NEt (8 equiv.) the carboxylic acid R^{III}CO₂H (4 equiv.) and HATU (4 equiv.) or the succinimidyl carbamate R^{III}NHCO₂Su (4 equiv.) were added. The mixture was shaken for 1 h and filtered. The resin was washed with DMF. The coupling step was repeated. The resin was washed three times with DMF.

2) Cleavage of the Alloc group

The resin was suspended in CH₂Cl₂ (1 mL). Phenylsilane (10 equiv.) and Pd(PPh₃)₄ (0.2 equiv.) were added, then the mixture was shaken for 15 min and filtered. The deprotection step was repeated. The resin was filtered, washed three times each with CH₂Cl₂, DMF, twice with MeOH and three times with CH₂Cl₂.

3) Second derivatization step

The resin was resuspended in DMF/CH₂Cl₂ 1:1 (1 mL). *i*-Pr₂NEt (8 equiv.) and the carboxylic acid R^{IV}CO₂H (4 equiv.) and PyBOP (4 equiv.) or the isocyanate R^{IV}NCO (4 equiv.) or the sulfonyl chlorides R^{IV}SO₂Cl (4 equiv.) and DMAP (1 equiv.) were

added. The mixture was shaken for 1 h and filtered. The resin was filtered, washed three times with DMF to afford resin **134**.

Release of the final products

- 5 The resin **134** was treated with 20% TFA in CH_2Cl_2 (1 mL) for 30 min, filtered and washed with CH_2Cl_2 . The cleavage step was repeated once. 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 normal phase or reverse phase prep. HPLC afforded **Ex. 7** and **Ex.332 – Ex.337**.

10

Core 01: Synthesis of selected advanced intermediates and final products

(Scheme 8)

Synthesis on solid support:

- 15 **Ex.7** $\text{CF}_3\text{CO}_2\text{H}$ (6.6 mg, 15%) was obtained by treatment of resin **133** (0.6 mmol/g, 96 mg, 0.055 mmol) with 1-pyrrolidineacetic acid (in total 57 mg, 0.44 mmol; first coupling step) and with 1-naphthaleneacetic acid (41 mg, 0.22 mmol, second coupling step) according to procedure D. The product was purified by prep. HPLC (method 1a).

Data of **Ex.7** $\text{CF}_3\text{CO}_2\text{H}$: cf. Table 13b.

- 20 $^1\text{H-NMR}$ (DMSO-d_6): 9.94 (br. s, 1 H); 8.77 (d, $J = 5.3$, 1 H); 8.65 (d, $J = 7.7$, 1 H); 8.06 (t, $J = 5.4$, 1 H); 8.01 (m, 1 H); 7.92 (m, 1 H); 7.81 (d, $J = 7.9$, 1 H); 7.55 – 7.37 (m, 8 H); 7.34 (t, $J = 8.0$, 1 H); 7.09 – 7.05 (m, 2 H); 6.91 (dd, $J = 2.0, 8.2$, 1 H); 4.58 (br. not resolved m, 1 H); 4.44 (br. not resolved m, 1 H); 4.19 (dd, $J = 4.9, 11.5$, 1 H); 4.12 – 4.00 (m, 5 H); 3.94 (d, $J = 14.9$, 1 H); 3.87 (d, $J = 14.9$, 1 H); ca 3.6 – 3.5 (br m, 25 2 H), 3.30 (1 H, superimposed by H_2O signal); 3.07 – 3.02 (br. m, 4 H); 2.15 – 1.84 (br. m, 7 H); 1.67 (br. m, 1 H).

- Ex.332** $\text{CF}_3\text{CO}_2\text{H}$ (21 mg, 48%) was obtained by treatment of resin **133** (0.6 mmol/g, 96 mg, 0.055 mmol) with imidazol-1-yl acetic acid (in total 55 mg, 0.44 mmol; first 30 coupling step) and with 1-naphthaleneacetic acid (41 mg, 0.22 mmol, second coupling step) according to procedure D. The product was purified by prep. HPLC (method 1a).

Data of **Ex.332** $\text{CF}_3\text{CO}_2\text{H}$: cf. Table 13b.

- 35 **Ex.333** $\text{CF}_3\text{CO}_2\text{H}$ (29 mg, 65%) was obtained by treatment of resin **133** (0.6 mmol/g, 96 mg, 0.055 mmol) with 2,5-dioxopyrrolidin-1-yl pyridine-3-ylcarbamate (in total 103

mg, 0.44 mmol; first coupling step) and with 1-naphthaleneacetic acid (41 mg, 0.22 mmol, second coupling step) according to procedure D. The product was purified by prep. HPLC (method 1a).

Data of **Ex.333**-CF₃CO₂H: cf. Table 13b.

5

Ex.334-CF₃CO₂H (16 mg, 38%) was obtained by treatment of resin **133** (0.6 mmol/g, 96 mg, 0.055 mmol) with 1-pyrrolidineacetic acid (in total 57 mg, 0.44 mmol; first coupling step) and with 3-chlorophenylacetic acid (37 mg, 0.22 mmol, second coupling step) according to procedure D. The product was purified by prep. HPLC (method 1a).

10

Data of **Ex.334**-CF₃CO₂H: cf. Table 13b.

Ex.335-CF₃CO₂H (11 mg, 26%) was obtained by treatment of resin **133** (0.6 mmol/g, 96 mg, 0.055 mmol) with 1-pyrrolidineacetic acid (in total 57 mg, 0.44 mmol; first coupling step) and with cyclohexylacetic acid (31 mg, 0.22 mmol, second coupling step) according to procedure D. The product was purified by prep. HPLC (method 1a).

15

Data of **Ex.335**-CF₃CO₂H: cf. Table 13b.

Ex.336-CF₃CO₂H (6 mg, 13%) was obtained by treatment of resin **133** (0.6 mmol/g, 96 mg, 0.055 mmol) with 1-pyrrolidineacetic acid (in total 57 mg, 0.44 mmol; first coupling step) and with 1-naphthyl isocyanate (0.031 mL, 0.22 mmol, second coupling step) according to procedure D. The product was purified by prep. HPLC (method 1a).

20

Data of **Ex.336**-CF₃CO₂H: cf. Table 13b.

¹H-NMR (DMSO-d₆): 9.94 (br. s, 1 H); 8.81 (d, J = 4.9, 1 H); 8.63 (s, 1 H); 8.27 (t, J = 5.6, 1 H); 8.06 (d, J = 8.0, 1 H); 7.96 (dd, J = 1.0, 7.6, 1 H); 7.89 (d, J ca 9.3, 1 H); 7.59 – 7.38 (m, 9 H); 7.16 – 7.13 (m, 2 H); 7.04 – 6.99 (t-like m, 2 H); 4.82 (br. not resolved m, 1 H); 4.45 (t-like m, 1 H); 4.29 (dd, J = 5.9, 11.5, 1 H); 4.22 – 4.13 (br. m, 3 H); 4.01 (s, 2 H); 3.65 – 3.45 (br. m, 3 H); 3.25 – 3.0 (br. m, 4 H); 2.45 (m, 1 H); 2.10 – 1.70 (br. m, 7 H).

25

30

Synthesis in solution:

Synthesis of **Ex.4**

At rt, i-Pr₂NEt (0.27 mL, 1.57 mmol) was added to a soln of **Ex.2** (258 mg, 0.52 mmol), 1-naphthaleneacetic acid (117 mg, 0.63 mmol), HATU (298 mg, 0.78 mmol)

35

and HOAt (107 mg, 0.78 mmol) in DMF (4.3 mL). The mixture was stirred at rt for 15 h and distributed between CH₂Cl₂ and 1 M aq. Na₂CO₃ soln. The organic phase was separated, washed (H₂O), dried (Na₂SO₄), filtered and concentrated. FC (hexane/EtOAc 34:66 to 0:100) afforded **Ex.4** (267 mg, 77%).

5 Data of **Ex.4**: cf. Table 13b

Synthesis of **Ex.5**

A soln of **Ex.4** (220 mg, 0.33 mmol) in dioxane (4.0 mL) was treated with 4 M HCl-dioxane (1.0 mL) for 2h. The volatiles were evaporated to afford **Ex.5**-HCl (208 mg, quant.)

10

Data of **Ex.5**-HCl: cf. Table 13b

Synthesis of **Ex.7**

At rt, i-Pr₂NEt (0.057 mL, 0.33 mmol) was added to a soln of **Ex.5**-HCl (50 mg, 0.08 mmol), 1-Pyrrolidineacetic acid (22 mg, 0.17 mmol), HATU (63 mg, 0.17 mmol) and HOAt (23 mg, 0.17 mmol) in DMF (1.2 mL). The mixture was stirred at rt for 4 h and distributed between EtOAc and sat. aq. NaHCO₃ soln. The organic phase was dried (Na₂SO₄), filtered and concentrated. FC (CH₂Cl₂/MeOH 100:0 to 95:5) afforded **Ex.7** (40 mg, 71%).

15

20 Data of **Ex.7**: C₄₀H₄₃N₅O₅ (673.8). LC-MS (method 1a): R_t = 1.70 (96), 674.2 ([M+H]⁺).

Synthesis of **Ex.14**

At 0°C, phenyl chloroformate (87 mg, 0.55 mmol) was slowly added to a mixture of **Ex.3** (285 mg, 0.50 mmol) in CH₂Cl₂ (5 mL) and sat. aq. Na₂CO₃ soln (1.7 mL). Stirring was continued for 2 h. Aqueous workup (EtOAc, sat. aq. NaHCO₃ soln., Na₂SO₄) and FC (EtOAc) afforded **Ex.14** (315 mg, 96%)

25

Data of **Ex.14**: cf. Table 13b

30 **Core 02: Synthesis of Ex.15, Ex.16 and Ex.17** (Scheme 9)

Synthesis of the Mitsunobu product **45**

At 0°C, a solution of TMAD (7.57 g, 43.9 mmol) in benzene (80 mL) was added dropwise to a degassed solution of the phenol **4** (3.68 g, 16.1 mmol), alcohol **16** (4.40 g, 14.65 mmol) and PPh₃ (11.5 g, 43.9 mmol) in benzene (80 mL). The stirred mixture was allowed to warm to rt over 15 h.

35

The volatiles were evaporated. The residue was suspended in hexane and filtered. The filtrate was concentrated and purified by FC (hexane/EtOAc 5:1) to yield **45** (5.45 g, 73%).

Data of **45**: $C_{28}H_{34}N_2O_7$ (510.6). LC-MS (method 1c): $R_t = 2.67$ (97), 511.2 ($[M+H]^+$).

5

Synthesis of the acid **46**

At 0°C, aq. LiOH soln (2 M; 10.6 mL, 21.1 mmol) was added to a solution of ester **45** (5.4 g, 10.6 mmol) in MeOH (10 mL) and THF (20 mL). The mixture was allowed to warm to rt over 16 h. The volatiles were evaporated. The residue was taken up in 1 M aq. HCl soln and extracted twice with EtOAc. The combined organic layer was dried (Na₂SO₄), filtered and concentrated. FC (hexane/EtOAc 2:1 to 0:100 then EtOAc/MeOH 100:0 to 90:10) gave **46** (4.48 g, 85%).

10

Data of **46**: $C_{27}H_{32}N_2O_7$ (496.6). LC-MS (method 1c): $R_t = 2.29$ (99), 497.2 ($[M+H]^+$).

15 Synthesis of the amide **47**

A solution of acid **46** (4.28 g, 8.6 mmol), amine **23**-HCl (4.6 g, 10.3 mmol), HATU (4.9 g, 12.9 mmol) and HOAt (1.76 g, 12.9 mmol) in DMF (80 mL) was cooled to 0°C, followed by the addition of i-Pr₂NEt (5.9 mL, 34.5 mmol). The mixture was allowed to warm to rt over 15 h. The mixture was diluted with H₂O and EtOAc. The organic layer was washed (aq. 1 M HCl soln, sat. aq. NaCl soln), dried (Na₂SO₄), filtered and concentrated. FC (hexane/EtOAc 1:1) of the crude product afforded **47** (6.1 g, 89%).

20

Data of **47**: $C_{44}H_{54}N_4O_{10}$ (798.9). LC-MS (method 1a): $R_t = 2.72$ (97), 799.4 ($[M+H]^+$).

Synthesis of amino acid **48**

A degassed solution of **47** (6.14 g, 7.7 mmol) and 1,3-dimethylbarbituric acid (2.64 g, 16.9 mmol) in CH₂Cl₂ (70 mL) and EtOAc (42 mL) was treated with Pd(PPh₃)₄ (0.44 g, 0.38 mmol) at rt for 1 h. The volatiles were evaporated. FC (EtOAc, then CH₂Cl₂/MeOH 98:2 to 80:20) afforded **48** (4.64 g, 89%).

25

Data of **48**: $C_{37}H_{46}N_4O_8$ (674.8). LC-MS (method 1a): $R_t = 1.86$ (97), 675.3 ($[M+H]^+$).

30

Synthesis of Ex.15

A soln of the amino acid **48** (1.12 g, 1.66 mmol) in CH₂Cl₂ (60 mL) was added dropwise over 2 h by syringe pump to a soln of T3P (50% in EtOAc; 2.45 mL, 4.15 mmol) and i-Pr₂NEt (1.14 mL, 6.64 mmol) in dry CH₂Cl₂ (770 mL). Evaporation of the volatiles, aq. workup (EtOAc, sat. aq. NaHCO₃ soln; Na₂SO₄) and FC (hexane/EtOAc 50:50 to 0:100) yielded Ex.15 (0.96 g, 88%).

35

Data of **Ex.15**: $C_{37}H_{44}N_4O_7$ (656.7). LC-MS (method 1d): $R_t = 2.29$ (97), 657.3 ([M+H]⁺). ¹H-NMR (DMSO-d₆): 7.6 – 7.0 (br. m, 13 H); 7.13 (d, J = 7.9, 1 H); 7.03 (t, J = 7.3, 1 H); 5.01 (br. s, 2 H); 4.37 (br. d, J ca 9.7, 1 H); ca 4.25 – 3.7 (several br. m, 4 H); 3.25 (br. m, 1 H); 2.95 (br. s, 3 H); 2.64 (br. m, 1 H); 2.40 (br. m, 1 H); 2.18 (br. m, 1 H); ca. 1.85 – 1.0 (several br. m, 6 H); 1.37 (s, 9 H).

Synthesis of **Ex.16**

A soln of **Ex.15** (1.3 g, 2.0 mmol) in MeOH (60 mL) was hydrogenated for 4 h at rt and normal pressure in the presence of palladium hydroxide on activated charcoal (moistened with 50% H₂O; 240 mg). The mixture was filtered through a pad of celite and Na₂SO₄. The solid was washed with MeOH. The combined filtrate and washings were concentrated to give **Ex.16** (1.03 g, 99%).

Data of **Ex.16**: $C_{29}H_{38}N_4O_5$ (522.6). LC-MS (method 1a): $R_t = 1.68$ (97), 523.1 ([M+H]⁺).

Synthesis of **Ex.17**

A soln of **Ex.15** (600 mg, 0.91 mmol) in dioxane (6 mL) was treated with 4 M HCl in dioxane (6 mL) at rt for 1 h followed by evaporation of the volatiles. The residue was taken up in CHCl₃ and concentrated to afford **Ex.17** (571 mg, quant. yield).

Data of **Ex.17**·HCl: $C_{32}H_{36}N_4O_5$ ·HCl (556.6, free base). LC-MS (method 1a): $R_t = 1.65$ (96), 557.2 ([M+H]⁺).

Core 02: Synthesis of selected advanced intermediates and final products (Scheme 9)

25 Synthesis of **Ex.18**

At 0°C, i-Pr₂NEt (0.635 mL, 3.71 mmol) was added dropwise to a soln of **Ex.17**·HCl (550 mg, 0.93 mmol), 2-naphthaleneacetic acid (207 mg, 1.11 mmol), HATU (529 mg, 1.39 mmol) and HOAt (189 mg, 1.39 mmol) in DMF (10 mL). The mixture was stirred at 0°C for 4 h and distributed between EtOAc and 0.2 M aq. HCl soln. The organic phase was separated, washed (H₂O, sat. aq. NaCl soln), dried (Na₂SO₄), filtered and concentrated. FC (EtOAc) afforded **Ex.18** (530 mg, 79%).

Data of **Ex.18**: cf. Table 14b

Synthesis of **Ex.19**

A soln of **Ex.18** (520 mg, 0.72 mmol) in MeOH (5 mL) was hydrogenated for 4 h at rt and normal pressure in the presence of palladium hydroxide on activated charcoal

(moistened with 50% H₂O; 94 mg). The mixture was filtered through a pad of celite. The solid was washed with MeOH. The combined filtrate and washings were concentrated to give **Ex.19** (412 mg, 97%).

Data of **Ex.19**: cf. Table 14b

5

Synthesis of **Ex.20**

i-Pr₂NEt (0.043 mL, 0.25 mmol) was added to a soln of **Ex.19** (50 mg, 0.085 mmol), 2-(dimethylamino)acetic acid (17 mg, 0.17 mmol), HATU (64 mg, 0.17 mmol) and HOAt (23 mg, 0.17 mmol). The mixture was stirred at rt for 15 h and distributed
10 between CH₂Cl₂ and sat. aq. Na₂CO₃ soln. The organic phase was separated, dried (Na₂SO₄), filtered and concentrated. FC (CH₂Cl₂/MeOH 95:5 to 90:10) afforded **Ex.20** (17 mg, 30%).

Data of **Ex.20**: cf. Table 14b

15

Synthesis of **Ex.25**

Phenylacetyl chloride (0.013 mL, 0.098 mmol) was added at 0°C to a soln of **Ex.19** (50 mg, 0.085 mmol) and pyridine (0.034 mL, 0.42 mmol) in CH₂Cl₂ (0.5 mL). The mixture was stirred at 0°C for 2 h followed by the addition of more phenylacetyl chloride (0.006 mL, 0.045 mmol). Stirring was continued for 1 h. Evaporation of the
20 volatiles and prep. HPLC (method 1a) afforded **Ex.25** (36 mg, 60%).

Data of **Ex.25**: cf. Table 14b

Synthesis of **Ex.26**

Benzoyl chloride (0.012 mL, 0.10 mmol) was added at 0°C to a soln of **Ex.19** (50 mg, 0.085 mmol) and pyridine (0.034 mL, 0.42 mmol) in CH₂Cl₂ (0.5 mL). The mixture
25 was stirred at 0°C for 2 h followed by evaporation of the volatiles and prep. HPLC (method 1a) to afford **Ex.26** (40 mg, 67%).

Data of **Ex.26**: cf. Table 14b

30

Core 03: Synthesis of Ex.41, Ex.42, Ex.50 and Ex.62 – Ex.67 (Scheme 10)

Synthesis of the Mitsunobu product **49**

At 0°C, ADDP (7.32 g, 29.0 mmol) was added in portions to a mixture of phenol **6** (5.0 g, 19.4 mmol), alcohol **20** (5.08 g, 29.0 mmol) and PPh₃ (7.62 g, 29.0 mmol) in
35 CHCl₃ (82 mL). The stirred mixture was allowed to warm to rt over 15 h.

More **20** (5.08 g, 29.0 mmol), PPh_3 (7.62 g, 29.0 mmol) and finally ADDP (7.32 g, 29.0 mmol) were added at 0°C. Stirring was continued at rt for 6 h. The mixture was filtered. The filtrate was concentrated and purified by FC (hexane/EtOAc 90:10 to 80:20) to yield **49** (7.57 g, 94%).

- 5 Data of **49**: $\text{C}_{23}\text{H}_{29}\text{NO}_6$ (415.5). LC-MS (method 1a): $R_t = 2.54$ (99), 416.2 ($[\text{M}+\text{H}]^+$).

Synthesis of the acid **50**

- At 0°C, aq. LiOH soln (2 M; 27 mL, 54.0 mmol) was added dropwise to a solution of ester **49** (7.44 g, 17.9 mmol) in MeOH (27 mL) and THF (50 mL). The mixture was stirred at rt for 5 h, partially concentrated, acidified with 1 M aq. HCl soln and extracted twice with EtOAc. The combined organic layer was dried (Na_2SO_4), filtered and concentrated to give **50** (7.1 g, 98%).
- 10

Data of **50**: $\text{C}_{22}\text{H}_{27}\text{NO}_6$ (401.4). LC-MS (method 1a): $R_t = 2.20$ (98), 402.1 ($[\text{M}+\text{H}]^+$).

- 15 Synthesis of the amide **51**

- A solution of acid **50** (7.0 g, 17.4 mmol), amine **24**·HCl (6.86 g, 20.9 mmol), HATU (9.95 g, 26.2 mmol) and HOAt (3.56 g, 26.2 mmol) in DMF (180 mL) was cooled to 0°C, followed by the addition of $i\text{-Pr}_2\text{NEt}$ (11.9 mL, 69.7 mmol). The mixture was allowed to warm to rt over 7 h. More **24**·HCl (6.86 g, 20.9 mmol) was added and stirring continued for 15 h. The mixture was diluted with 1 M aq. HCl soln and extracted twice with EtOAc. The combined organic layer was washed (H_2O , sat. aq. NaCl soln), dried (Na_2SO_4), filtered and concentrated. FC (hexane/EtOAc 2:1) of the crude product afforded **51** (10.05 g, 85%).
- 20

Data of **51**: $\text{C}_{38}\text{H}_{46}\text{N}_2\text{O}_9$ (674.8). LC-MS (method 1a): $R_t = 2.69$ (97), 675.2 ($[\text{M}+\text{H}]^+$).

- 25

Synthesis of the amino ester **52**

- A soln of **51** (10.0 g, 14.8 mmol) in dioxane (10 mL) was treated at rt with 4 M HCl in dioxane (40 mL) for 5 h. The volatiles were evaporated. The residue was taken up in CH_2Cl_2 and concentrated to afford **52**·HCl (9.2 g, quant. yield).
- 30 Data of **52**·HCl: $\text{C}_{33}\text{H}_{38}\text{N}_2\text{O}_7\text{HCl}$ (574.6, free base). LC-MS (method 1a): $R_t = 1.94$ (94), 575.2 ($[\text{M}+\text{H}]^+$).

Synthesis of amino acid **53**

- 35 A degassed solution of ester **52** (9.2 g, 15 mmol) and 1,3-dimethylbarbituric acid (2.8 g, 18 mmol) in CH_2Cl_2 (30 mL) and EtOAc (60 mL) was treated with $\text{Pd}(\text{PPh}_3)_4$ (1.8 g,

1.5 mmol) at rt for 2 h. The volatiles were evaporated. FC (CH₂Cl₂/MeOH 98:2 to 70:30) afforded **53** (8.2 g, quant.).

Data of **53**: C₃₀H₃₄N₂O₇ (534.6). LC-MS (method 1a): R_t = 1.70 (94), 535.2 ([M+H]⁺).

5 Synthesis of Ex.41

A soln of the amino acid **53** (4.0 g, 7.5 mmol) in CH₂Cl₂ (80 mL) was added dropwise over 2 h by syringe pump to a soln of T3P (50% in EtOAc; 11.0 mL, 18.7 mmol) and i-Pr₂NEt (5.12 mL, 29.9 mmol) in dry CH₂Cl₂ (1360 mL). Evaporation of the volatiles, aq. workup (CH₂Cl₂, sat. aq. NaHCO₃ soln; Na₂SO₄) and FC (hexane/EtOAc 20:80 to 0:100) yielded **Ex.41** (3.0 g, 77%).

Data of **Ex.41**: C₃₀H₃₂N₂O₆ (516.5). LC-MS (method 1d): R_t = 2.14 (96), 517.0 ([M+H]⁺). ¹H-NMR (CDCl₃): 7.78 (s, 1 H); 7.50 – 7.35 (m, 7 H); 7.25 (m, 1 H), 6.92 – 6.82 (m, 3 H); 5.59 (d, J = 8.4, 1 H); 5.32 (d, J = 12.2, 1 H); 5.26 (d, J = 12.2, 1 H); 4.78 (d, J = 11.9, 1 H); 4.16 (q-like m, 1 H); 3.81 (s, 3 H); 3.71 (d, J = 9.0, 1 H); 3.38 (t-like m, 1 H); 2.98 (s, 3 H); 2.64 (br. t, J ca. 12.7, 1 H); 2.37 (dd, J = 5.6, 16.2, 1 H); 2.01 – 1.90 (m, 2 H); 1.24 (d, J = 6.8, 3 H).

Synthesis of Ex.42

A soln of **Ex.41** (2.0 g, 3.87 mmol) in MeOH (30 mL) was hydrogenated for 2 h at rt and normal pressure in the presence of palladium hydroxide on activated charcoal (moistened with 50% H₂O; 220 mg). The mixture was filtered through a pad of celite. The solid was washed with MeOH. The combined filtrate and washings were concentrated to give **Ex.42** (1.77 g, quant. yield).

Data of **Ex.42**: C₂₃H₂₆N₂O₆ (426.5). LC-MS (method 1d): R_t = 1.55 (93), 427.0 ([M+H]⁺). ¹H-NMR (DMSO-d₆): 13.2 (br. s, 1 H); 8.03 (d, J = 8.2, 1 H); 7.59 (s, 1 H); 7.46 – 7.41 (m, 2 H); 7.16 (m, 1 H); 7.04 (d, J = 8.9, 1 H); 6.90 (dd, J = 3.0, 8.8, 1 H); 6.83 (d, J = 3.0, 1 H); 4.13 (dd, J = 3.0, 12.2, 1 H); 4.03 – 3.91 (m, 2 H); 3.74 (s, 3 H); 3.52 (t, J = 9.2, 1 H); 2.86 (s, 3 H); 2.39 (br. t, J ca 13.2, 1 H); 2.19 (br. dd, J ca 4.9, 15.9, 1 H); 1.99 (d-like m, 1 H); 1.86 (m, 1 H); 1.03 (d, J = 6.6, 3 H).

30

Core 03: Synthesis of selected advanced intermediates and final products (Scheme 10)

Synthesis of Ex.62

A soln of **Ex.41** (50 mg, 0.1 mmol) in THF (1 mL) was cooled to 0°C. LiBH₄ (5 mg, 0.213 mmol) and MeOH (3.9 µL, 0.1 mmol) in THF (0.5 mL) were added. The mixture was stirred at rt for 20 h followed by the addition of acetone (0.1 mL). Aqueous

35

workup (CHCl₃, 1 M aq. HCl soln, H₂O, sat. aq. NaHCO₃ soln, sat. aq. NaCl soln; Na₂SO₄) and FC (CH₂Cl₂/MeOH 100:0 to 90:10) yielded **Ex.62** (25 mg, 61%).

Data of **Ex.62**: C₂₃H₂₈N₂O₅ (412.5). LC-MS (method 1a): R_t = 1.49 (97), 413.0 ([M+H]⁺). ¹H-NMR (DMSO-d₆): 7.90 (d, J = 8.2, 1 H); 7.56 – 7.53 (m, 2 H); 7.41 – 7.32 (m, 2 H); 7.00 (d, J = 8.9, 1 H); 6.89 (dd, J = 3.1, 8.9, 1 H); 6.80 (d, J = 3.1, 1 H); 5.05 (t, J = 5.3, 1 H); 4.01 – 3.87 (m, 2 H); 3.74 (s, 3 H); 3.74 (m, 1 H); 3.61 – 3.38 (m, 3 H); 2.78 (s, 3 H); 2.11 (dd, J = 5.6, 15.9, 1 H); 1.99 (br.t, 1 H); 1.85 (br.t, 1 H); 1.45 (dt, J = 6.1, 12.7, 1 H); 1.00 (d, J = 6.7, 3 H).

10 Synthesis of **Ex.63**

At 0°C, DEAD (40% in toluene; 0.05 mL, 0.109 mmol) was slowly added to a soln of **Ex.62** (30 mg, 0.073 mmol), 3-hydroxypyridine (8.3 mg, 0.087 mmol) and PPh₃ (29 mg, 0.109 mmol) in degassed benzene/THF 1:1 (2 mL). The mixture was stirred at rt for 16 h and concentrated. FC (CH₂Cl₂/MeOH 100:0 to 90:10) afforded **Ex.63** (26 mg, 73%).

Data of **Ex.63**: C₂₈H₃₁N₃O₅ (489.5). LC-MS (method 1a): R_t = 1.44 (95), 490.1 ([M+H]⁺).

Synthesis of **Ex.64**

20 At 0°C, DEAD (40% in toluene; 0.83 mL, 1.82 mmol) was slowly added to a soln of **Ex.62** (250 mg, 0.61 mmol), PPh₃ (477 mg, 1.82 mmol) and DPPA (0.394 mL; 1.82 mmol) in degassed benzene (10 mL). The mixture was stirred for 30 min at rt and for 1 h at 50°C. The volatiles were evaporated. The residue was suspended in Et₂O. The solid was collected to afford **Ex.64** (169 mg, 63%).

25 Data of **Ex.64**: C₂₃H₂₇N₅O₄ (437.5). LC-MS (method 1a): R_t = 1.86 (94), 438.2 ([M+H]⁺).

Synthesis of **Ex.65**

30 A soln of **Ex.64** (166 mg, 0.38 mmol) in MeOH/CH₂Cl₂ 2:1 (3 mL) was hydrogenated at rt for 4 h in the presence of palladium hydroxide on activated charcoal (moistened with 50% H₂O; 71 mg). The mixture was filtered through a pad of celite. The solid was washed with MeOH. The combined filtrate and washings were concentrated. The residue was dissolved in CHCl₃ and evaporated. The residue was dissolved in CH₂Cl₂ (3 mL), treated with 4 M HCl-dioxane (0.285 mL, 1.1 mmol). A precipitate was
35 obtained which was filtered and washed (EtOAc) to afford **Ex.65-HCl** (149 mg, 87%).

Data of **Ex.65**·HCl: $C_{23}H_{29}N_3O_4$ (411.5). LC-MS (method 1a): $R_t = 1.35$ (86), 412.2 ($[M+H]^+$).

Synthesis of **Ex.66**

- 5 At 0°C, *i*-Pr₂NEt (0.076 mL, 0.45 mmol) was added dropwise to a soln of **Ex.65**·HCl (50 mg, 0.11 mmol), phenylacetic acid (18 mg, 0.13 mmol), HATU (64 mg, 0.17 mmol) and HOAt (23 mg, 0.167 mmol) in DMF (0.5 mL). The mixture was stirred at 0°C for 2 h. Aq. workup (EtOAc, 0.2 M HCl soln, H₂O, sat. aq. NaCl soln; Na₂SO₄) and prep. HPLC (method 3) afforded **Ex.66** (33 mg, 55%).
- 10 Data of **Ex.66**: $C_{31}H_{35}N_3O_5$ (529.6). LC-MS (method 1a): $R_t = 1.89$ (91), 530.2 ($[M+H]^+$).

Synthesis of **Ex.67**

- i*-Pr₂NEt (0.031 mL, 0.18 mmol) was added to a soln of **Ex.62** (50 mg, 0.12 mmol)
- 15 and phenyl isocyanate (17 mg, 0.15 mmol) in THF / DMF 1:1 (1.0 mL). The mixture was stirred at rt for 16 h followed by an aq. workup (CHCl₃, sat. aq. Na₂CO₃ soln; Na₂SO₄) and prep. HPLC (method 3) to afford **Ex.67** (46 mg, 72%).
- Data of **Ex.67**: $C_{30}H_{33}N_3O_6$ (531.6). LC-MS (method 1a): $R_t = 2.06$ (90), 532.2 ($[M+H]^+$).

20

Synthesis of **Ex.50**

- 3-Picolylamine (0.014 mL, 0.141 mmol) and *i*-Pr₂NEt (0.06 mL, 0.352 mmol) were slowly added to a cold solution of **Ex.42** (50 mg, 0.117 mmol), HATU (67 mg, 0.176 mmol) and HOAt (24 mg, 0.176 mmol) in DMF (0.5 mL). The mixture was stirred for 2
- 25 h at 4°C, followed by an aqueous workup (CH₂Cl₂, 1 M aq. HCl soln, sat. aq. NaCl soln; Na₂SO₄) and purification by prep HPLC (method 1c) to give **Ex.50**·CF₃CO₂H (28 mg, 37%).

Data of **Ex.50**·CF₃CO₂H: cf. Table 15b.

- ¹H-NMR (DMSO-*d*₆ and D₂O): 8.90 (br. s, 1 H); 8.50 (very br. s, 1 H); 7.56 (s, 1 H);
- 30 7.40 (br. s, 1 H); 7.30 (very br. s, 1 H); 7.01 (m, 2 H); 6.88 (dd, *J* = 2.9, 8.9, 1 H); 6.78 (d, *J* = 2.7, 1 H); 4.60 (br. not resolved m, 2 H); 4.08 (br. d, *J* = 9.8, 1 H); 3.98 – 3.89 (br. m, 2 H); 3.71 (s, 3 H); 3.51 (t, *J* = 9.2, 1 H); 2.84 (s, 3 H); 2.43 (br. not resolved m, 1 H); 2.21 (br. m, 1 H); 1.96 – 1.76 (m, 2 H); 1.00 (d, *J* = 6.5, 3 H).

- An analytical sample of **Ex.50**·CF₃CO₂H was dissolved in CH₂Cl₂ and washed with
- 35 sat. aq. Na₂CO₃ soln. The organic phase was separated, dried (Na₂SO₄) and concentrated to give **Ex.50**.

Data of **Ex.50**: $^1\text{H-NMR}$ (DMSO-d_6): 8.88 (t, $J = 6.0$, 1 H); 8.59 (d, $J = 1.6$, 1 H); 8.56 (dd, $J = 1.5$, 4.8, 1 H); 8.09 (d, $J = 8.2$, 1 H); 7.82 (td, $J = 1.9$, 7.9, 1 H); 7.67 (s, 1 H); 7.50 – 7.44 (m, 2 H); 7.32 (t, $J = 7.6$, 1 H); 7.13 – 7.08 (m, 2 H); 6.95 (dd; $J = 3.1$, 8.9, 1 H); 6.87 (d, $J = 3.1$, 1 H); 4.43 – 4.40 (m, 2 H); 4.15 – 3.96 (m, 3 H); 3.80 (s, 3 H);
5 3.57 (t, J ca 9.0, 1 H); 2.91 (s, 3 H); ca 2.5 (1 H, superimposed by DMSO-d signal); 2.26 (br. dd, 1 H); 1.98 (br. dd, 1 H), 1.81 (dt; $J = 5.3$, 10.0, 1 H); 1.08 (d, $J = 6.7$, 3 H).

10 **Core 04: Synthesis of Ex.68 and Ex.69** (Scheme 11)

Synthesis of the Mitsunobu product **54**

ADDP (6.61 g, 26.2 mmol) was added to a mixture of the phenol **8** (3.98 g, 17.5 mmol), the alcohol **19** (4.59 g, 26.2 mmol) and PPh_3 (6.87 g, 26.2 mmol) in CHCl_3 (160 mL). The mixture was stirred at rt for 15 h. Silica gel (20 g) was added. The
15 volatiles were evaporated and the residue was purified by FC (hexane/EtOAc 5:1) to give **54** (3.2 g, 48%).

Data of **54**: $\text{C}_{22}\text{H}_{27}\text{NO}_5$ (385.5). LC-MS (method 2b): $R_t = 2.56$ (90), 384.0 ($[\text{M-H}]^-$).

Synthesis of the acid **55**

20 $\text{LiOH}\cdot\text{H}_2\text{O}$ (1.6 g, 38 mmol) was added to a solution of ester **54** (4.89 g, 12.7 mmol) in THF (72 mL), MeOH (24 mL) and H_2O (24 mL). The mixture was stirred at rt for 4.5 h, partially concentrated, diluted with H_2O (30 mL), acidified with 1 M aq. HCl soln (ca 40 mL) and extracted twice with EtOAc. The combined organic layer was dried (Na_2SO_4), filtered and concentrated to give **55** (4.67 g, 99%).

25 Data of **55**: $\text{C}_{21}\text{H}_{25}\text{NO}_5$ (371.4). LC-MS (method 2a): $R_t = 1.32$ (98), 369.9 ($[\text{M-H}]^-$).

Synthesis of the amide **56**

PyClu (2.2 g, 6.62 mmol) and $i\text{-Pr}_2\text{NEt}$ (2.95 mL, 17.3 mmol) were successively added to a solution of acid **55** (2.14 g, 5.76 mmol) and amine **24**·HCl (2.52 g, 7.7 mmol), in DMF (50 mL). The mixture was stirred at rt for 1 h followed by an aq. workup (Et_2O , 0.5 M aq. HCl soln, H_2O , sat. aq. NaCl soln; Na_2SO_4). FC (hexane/EtOAc 7:3 to 4:6) afforded **56** (2.29 g, 61%).
30

Data of **56**: $\text{C}_{37}\text{H}_{44}\text{N}_2\text{O}_8$ (644.8). LC-MS (method 1a): $R_t = 2.69$ (95), 645.3 ($[\text{M+H}]^+$).

Synthesis of the amino ester **57**

A soln of **56** (5.6 g, 8.66 mmol) in dry CH_2Cl_2 (75 mL) was treated with TFA (15 mL) at rt for 1 h. The volatiles were evaporated. Aq. workup (CH_2Cl_2 , sat. aq. NaHCO_3 soln, sat. aq. NaCl soln; Na_2SO_4) of the residue gave **57** (4.93 g, quant. yield).

- 5 Data of **57**: $\text{C}_{32}\text{H}_{36}\text{N}_2\text{O}_6$ (544.6). LC-MS (method 1a): $R_t = 1.88$ (93), 545.2 ($[\text{M}+\text{H}]^+$).

Synthesis of amino acid **58**

- 10 A degassed solution of ester **57** (4.7 g, 8.66 mmol) and 1,3-dimethylbarbituric acid (1.62 g, 10.4 mmol) in CH_2Cl_2 (73 mL) and EtOAc (73 mL) was treated with $\text{Pd}(\text{PPh}_3)_4$ (0.3 g, 0.26 mmol) at rt for 1.5 h. The volatiles were evaporated. The solid was suspended in EtOAc (200 mL), filtered and washed (EtOAc). The solid was suspended in CH_2Cl_2 . The volatiles were evaporated. The residue was dried i.v. to yield **58** (3.94 g, 90%).

- 15 Data of **58**: $\text{C}_{29}\text{H}_{32}\text{N}_2\text{O}_6$ (504.6). LC-MS (method 1a): $R_t = 1.61$ (91), 505.2 ($[\text{M}+\text{H}]^+$).

Synthesis of **Ex.68**

- 20 A soln of the amino acid **58** (3.45 g, 6.8 mmol) in CH_2Cl_2 (150 mL) was added dropwise over 2 h by syringe pump to a soln of T3P (50% in EtOAc; 10 mL, 17.1 mmol) and $i\text{-Pr}_2\text{NEt}$ (4.7 mL, 27.4 mmol) in dry CH_2Cl_2 (1250 mL). Partial evaporation of the volatiles, aq. workup (sat. aq. NaHCO_3 soln; Na_2SO_4) and FC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 98.5:1.5) yielded **Ex.68** (2.57 g, 78%).

Data of **Ex.68**: $\text{C}_{29}\text{H}_{30}\text{N}_2\text{O}_5$ (486.5). LC-MS (method 1d): $R_t = 2.23$ (95), 486.9 ($[\text{M}+\text{H}]^+$).

25 Synthesis of **Ex.69**

- A soln of **Ex.68** (2.5 g, 5.2 mmol) in MeOH (50 mL) and CH_2Cl_2 (25 mL) was hydrogenated for 2 h at rt and normal pressure in the presence of palladium on activated charcoal (moistened with 50% H_2O ; 1.9 g). The mixture was filtered through a pad of celite. The solid was washed with MeOH/ CH_2Cl_2 2:1. The combined filtrate and washings were concentrated to give **Ex.69** (2.0 g, 98%).

- 30 Data of **Ex.69**: $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_5$ (396.4). LC-MS (method 1a): $R_t = 1.58$ (98), 397.1 ($[\text{M}+\text{H}]^+$). $^1\text{H-NMR}$ (DMSO-d_6): 13.05 (br. s, 1 H); 8.21 (br. s, 1 H); 7.86 – 7.17 (several m, 6.33 H); 7.06 (s, 0.66 H); 6.96 (d, $J = 8.2$, 0.66 H); 6.90 (dd, $J = 1.9$, 8.2, 0.33 H); 4.49 – 4.31 (m, 1.66 H); 4.15 (s, 2 H); 3.57 (t, $J = 11.8$, 0.33 H); 2.91, 2.86 (2 br. s, 3 H); 2.45 – 2.20 (m, 2.33 H); 2.2 – 2.0 (m, 1.66 H); 1.15 – 1.12 (2 d, 3 H).
- 35

Core 05: Synthesis of Ex.90, Ex.91 and Ex.92 (Scheme 12)**Synthesis of amide 59**

A mixture of acid **10**·HCl (9.34 g, 31.8 mmol), amine **28**·HCl (13.1 g, 41.3 mmol), HATU (19.3 g, 51 mmol) and HOAt (6.93 g, 51 mmol) in DMF (75 mL) was cooled to 0°C, followed by the addition of i-Pr₂NEt (21.6 mL, 127 mmol). The mixture was stirred for 4 h and concentrated to ca 50% of its volume. The mixture was diluted with 1 M aq. HCl soln and extracted twice with EtOAc. The combined organic layer was washed (H₂O, sat. aq. NaHCO₃ soln.), dried (Na₂SO₄), filtered and concentrated. FC (hexane/EtOAc 50:50 to 20:80) of the crude product afforded **59** (13.4g, 80%).

10 Data of **59**: C₂₈H₂₉N₃O₇ (519.5). LC-MS (method 1a): R_t = 1.89 (98), 520.0 ([M+H]⁺).

Synthesis of phenol 60

At 0°C 3-(dimethylamino)propylamine (12.0 mL, 95.4 mmol) was slowly added to a soln of **59** (16.53 g, 31.8 mmol) in THF (110 mL). The soln was allowed to warm to rt over 2 h. Aqueous workup (EtOAc, 1 M aq. HCl soln, sat. aq. NaHCO₃ soln; Na₂SO₄) yielded **60** (14.45 g, 95%).

15 Data of **60**: C₂₆H₂₇N₃O₆ (477.5). LC-MS (method 1a): R_t = 1.67 (97), 478.1 ([M+H]⁺).

Synthesis of the Mitsunobu product 61

20 The phenol **60** (4.35 g, 9.1 mmol) and the alcohol **18** (3.56 g, 11.8 mmol) were dissolved in toluene (39 mL). CMBP (3.0 mL, 11.4 mmol) was added and the mixture was heated to reflux for 0.5 h. More CMBP (0.31 mL, 1.2 mmol) was added and the mixture was refluxed for 0.5 h followed by evaporation of the volatiles and FC (hexane/EtOAc 50:50 to 0:100) to afford **61** (5.25 g, 77%).

25 Data of **61**: C₄₀H₄₉N₅O₁₀ (759.8). LC-MS (method 1a): R_t = 2.24 (92), 760.2 ([M+H]⁺).

Synthesis of the amino acid 63

A soln of **61** (11.8 g, 16 mmol) in THF (59 mL) and MeOH (30 mL) was treated with 2 M aq. LiOH soln (31 mL, 62 mmol) at rt for 2 h. The volatiles were partially evaporated. The remaining mixture was acidified to pH ca 1 by addition of 3 M aq. HCl soln and repeatedly extracted with EtOAc. The combined organic phase was dried (Na₂SO₄) and concentrated to afford crude acid **62** (12.6 g).

30 1,3-Dimethylbarbituric acid (3.2 g, 20.5 mmol) and acid **62** (12.5 g) were dissolved in CH₂Cl₂/EtOAc 1:1 (300 mL). The mixture was degassed, treated with Pd(PPh₃)₄ (1.98 g, 1.71 mmol) and stirred at rt for 2 h. The volatiles were evaporated. The residue was suspended in EtOAc and filtered to give **63** (9.80 g, 97%).

35

Data of **63**: $C_{34}H_{41}N_5O_8$ (647.7). LC-MS (method 1c): $R_t = 1.51$ (83), 648.1 ($[M+H]^+$).

Synthesis of Ex.90

A soln of the amino acid **63** (2.0 g, 3.1 mmol) in DMF (50 mL) was added dropwise over 2 h by syringe pump to a soln of T3P (50% in EtOAc; 9.1 mL, 15 mmol) and *i*-Pr₂NEt (4.2 mL, 25 mmol) in dry CH₂Cl₂ (600 mL). Partial evaporation of the volatiles, aq. workup (sat. aq. NaHCO₃ soln; Na₂SO₄) and FC (CH₂Cl₂/MeOH 100:0 to 97:3) yielded **Ex.90** (1.18 g, 60%).

Data of **Ex.90**: $C_{34}H_{39}N_5O_7$ (629.7). LC-MS (method 1d): $R_t = 2.00$ (99), 630.0 ($[M+H]^+$). ¹H-NMR (DMSO-*d*₆): 9.68, 9.62 (2 s, 1 H); 9.18 (s, 1 H); 9.11 (s, 1 H); 8.97 (s, 1 H); 8.41 (br. s, 1 H); 7.58 (d, *J* = 7.5, 1 H); 7.40 (t, *J* = 7.9, 1 H); 7.40 – 7.20 (m, 5 H); 7.17 (m, 1 H); 6.94 (d, *J* = 8.0, 1 H); 5.15 (d, *J* = 12.1, 0.5 H); 5.12 (s, 1 H); 5.01 (d, *J* = 12.9, 0.5 H); 4.55 – 4.15 (m, 4 H); 4.15 – 3.5 (several m, 5 H); 3.5 – 3.1 (several m, 3 H); 2.11 (m, 1 H); 1.91 (m, 1 H); 1.40 (s, 9 H).

15 Synthesis of Ex.91

A soln of **Ex.90** (200 mg, 0.32 mmol) in MeOH (5 mL) was hydrogenated for 2 h at rt and normal pressure in the presence of palladium hydroxide on activated charcoal (moistened with 50% H₂O; 50 mg). The mixture was filtered through a pad of celite. The solid was washed with MeOH. The combined filtrate and washings were concentrated to give **Ex.91** (150 mg, 95%).

Data of **Ex.91**: $C_{26}H_{33}N_5O_5$ (495.6). LC-MS (method 1a): $R_t = 1.48$ (97), 496.1 ($[M+H]^+$). ¹H-NMR (DMSO-*d*₆): 9.73 (br. s, 1 H); 9.26 (t, *J* = 1.9, 1 H); 9.18 (d, *J* = 1.9, 1 H); 8.94 (d, *J* = 1.9, 1 H); 8.51 (s, 1 H); 7.59 (d, *J* = 7.7, 1 H); 7.40 (t, *J* = 7.9, 1 H); 7.26 (d, *J* = 6.5, 1 H); 6.94 (dd; *J* = 1.9, 8.1, 1 H); 4.5 – 4.4 (m, 2 H); 4.26 (m, 1 H); 3.89 (t, *J* ca. 11.5, 1 H); 3.67 (dd, *J* = 7.2, 9.7, 1 H); 3.53 (d, *J* = 17.9, 1 H); 3.39 (d, *J* = 17.8, 1 H); 3.21 – 3.08 (m, 3 H); 2.55 (m, 1 H); ca 2.45 (m, 1 H); 2.11 (m, 1 H); 1.89 (m, 1 H); 1.40 (s, 9 H).

Synthesis of Ex.92

30 A soln of **Ex.90** (200 mg, 0.32 mmol) in dioxane (2 mL) was treated with 4 M HCl in dioxane (2 mL) for 15 h. The volatiles were evaporated. Purification by prep. HPLC (method 1c) afforded **Ex.92-2** CF₃CO₂H (89 mg, 37%) and **Ex.93-3** CF₃CO₂H (34 mg, 17%).

Data of **Ex.92-2** CF₃CO₂H: $C_{29}H_{31}N_5O_5$ (529.6, free base). LC-MS (method 1a): $R_t = 1.38$ (98), 530.1 ($[M+H]^+$).

Data of **Ex.93-3** CF₃CO₂H: Cf Table 17b

Core 05: Synthesis of selected advanced intermediates and final products(Scheme 12)Synthesis of **Ex.94**

- 5 A soln of **Ex.91** (137 mg, 0.28 mmol) in DCE (4.0 mL) was cooled to 0°C. Aq. formaldehyde soln. (36.5%; 0.104 mL, 1.38 mmol) was added followed by acetic acid (0.019 mL, 0.332 mmol) and NaBH(OAc)₃ (234 mg, 1.106 mmol). The mixture was stirred at 0°C for 4 h followed by an aq. workup (CH₂Cl₂, sat. aq. NaHCO₃ soln). FC (CH₂Cl₂/MeOH 100:0 to 95:5) afforded **Ex.94** (119 mg, 84%).
- 10 Data of **Ex.94**: cf. Table 17b
- ¹H-NMR (DMSO-d₆): 9.60 (br.s, 1 H); 9.21 (t, J = 1.9, 1 H); 9.17 (d, J = 1.9, 1 H); 8.93 (d, J = 1.9, 1 H), 8.48 (s, 1 H); 7.58 (d, J = 7.7, 1 H); 7.39 (t, J = 8.0, 1 H); 7.28 (d, J = 6.4, 1 H); 6.94 (dd, J = 1.9, 8.1, 1 H); 4.45 – 4.41 (br, m, 2 H); 4.26 (m, 1 H); 3.88 (br. t, J ca 11.5, 1 H); 3.68 (dd, J = 7.2, 9.7, 1 H); 3.45 (d, J = 17.6, 1 H); 3.89 – 3.21 (m, 3
- 15 H, signal partially superimposed by H₂O signal); 3.15 (t-like m, J ca 9, 1 H); 2.62 (br. not resolved m, 2 H), 2.37 (s, 3 H); 2.11 (m, 1 H); 1.90 (m, 1 H); 1.41 (s, 9 H).

Synthesis of **Ex.95**

- A soln of **Ex.94** (100 mg, 0.196 mmol) in dioxane (1.0 mL) was treated with 4 M HCl-dioxane (1.0 mL) for 2 h. The volatiles were evaporated to afford **Ex.95**·3HCl (116 mg, quant.).
- 20

Data of **Ex.95**·3HCl: cf. Table 17b

Synthesis of **Ex.96**

- 25 At 0°C, i-Pr₂NEt (0.11 mL, 0.65 mmol) was slowly added to a soln of **Ex.95**·3HCl (97 mg, 0.19 mmol), 2-naphthaleneacetic acid (49 mg, 0.26 mmol), HATU (124 mg, 0.326 mmol) and HOAt (44 mg, 0.323 mmol) in DMF (1.0 mL). The mixture was stirred at at 0°C for 2 h and distributed between CH₂Cl₂ and 1 M aq. HCl soln. The organic phase was washed (sat. aq. NaCl soln), dried (Na₂SO₄), filtered and concentrated. FC (CH₂Cl₂/MeOH 100:0 to 95:5) and prep. HPLC (method 1b) afforded **Ex.96**·2CF₃CO₂H (62 mg, 41%).
- 30

Data of **Ex.96**: cf. Table 17b

- ¹H-NMR (DMSO-d₆): Ca. 9.7 (very br. s, 1H); 9.28 (very br. s, 1 H); 9.14 (br. s, 1 H); 8.96 (very br. s, 1 H); 8.62 (d, J = 5.4, 1 H); 8.54 (br. s, 1 H); 8.30 (br. s, 1 H); 7.90 – 7.85 (m, 3 H); 7.77 (s, 1 H); 7.65 (d, J = 7.6, 1 H); 7.53 – 7.41 (m, 4 H); 6.98 (d, J = 8.3, 1 H); 4.55 – 4.33 (2 br. not resolved m, 5 H); 4.01 (t, J = 11.2, 1 H); 3.85 (br. t, J
- 35

ca 8.4, 1 H); 3.65 (br. not resolved m, 2 H); 3.63 (s, 2 H); 3.39 (br. not resolved m, 2 H); 3.11 (t, J = 9.0, 1 H); 2.89 (s, 3 H); 2.26 (m, 1 H); 2.04 (m, 1 H).

Synthesis of Ex.101

- 5 A soln of 1-naphthaleneacetic acid (43 mg, 0.23 mmol) and T3P (50% in DMF; 0.17 mL; 0.29 mmol) in DMF (0.3 mL) was added dropwise to a suspension of Ex.95·3HCl (50 mg, 0.096 mmol) in DMF (0.2 mL). The mixture was stirred at rt for 15 h followed by an aqueous workup (CHCl₃, sat. aq. Na₂CO₃ soln; Na₂SO₄) and purification by prep. HPLC (method 1a) to afford Ex.101·2 CF₃CO₂H (38 mg, 49%).
- 10 Data of Ex.101·2 CF₃CO₂H: cf. Table 17b
- ¹H-NMR (DMSO-d₆): 9.71 (very br. s, 1 H); 9.26 (d, J = 1.9, 1 H); 9.13 (br. s, 1 H); 8.93 (d, J = 1.5, 1 H); 8.68 (d, J = 5.6, 1 H); 8.52 (br. s, 1 H); 8.30 (s, 1 H); 8.10 (m, 1 H); 7.93 (m, 1 H); 7.84 (dd, J = 1.9, 7.3, 1 H); 7.66 (d, J = 7.7, 1 H); 7.57 – 7.41 (m, 5 H); 6.98 (dd, J = 1.8, 8.3, 1 H); 4.55 – 4.39 (2 br. not resolved m, 5 H); 4.04 – 3.94 (m, 3 H); 3.83 (br. t, J ca 8.5, 1 H); 3.68 (br. not resolved m, 2 H); 3.41 (br. not resolved m, 2 H); 3.12 (t, J = 9.0, 1 H); 2.89 (s, 3 H); 2.26 (m, 1 H); 2.03 (m, 1 H).

Synthesis of Ex.103

- At 4°C, Et₃N (0.04 mL, 0.29 mmol) and then benzenesulfonyl chloride (17 mg, 0.096 mmol) were added to a soln of Ex.95·3HCl (50 mg, 0.096 mmol) in CH₂Cl₂ (0.5 mL). The mixture was stirred at rt for 15 h; i-Pr₂NEt (0.049 mL, 0.29 mmol) and more benzenesulfonyl chloride (17 mg, 0.096 mmol) were added. Stirring was continued for 1 h followed by an aqueous workup (CHCl₃, sat. aq. Na₂CO₃ soln, Na₂SO₄) and purification by prep. HPLC (method 1a) to afford Ex.103·2 CF₃CO₂H (33 mg, 44%).
- 25 Data of Ex.103·2 CF₃CO₂H: cf. Table 17b
- ¹H-NMR (DMSO-d₆): 9.69 (br. s, 1 H); 9.24 (d, J = 1.9, 1 H); 9.09 (br. s, 1 H); 8.92 (d, J = 1.6, 1 H); 8.47 (br. s, 1 H); 8.30 (br. s, 1 H); 8.22 (br. s, 1 H); 7.90 – 7.88 (m, 2 H); 7.74 – 7.63 (m, 4 H); 7.41 (t, J = 7.9, 1 H); 6.93 (dd; J = 1.9, 8.2, 1 H); ca. 4.5 – 4.2 (m, 4 H); 4.00 (br. not resolved m, 1 H); 3.89 (t, J ca. 11.4, 1 H); 3.69 – 3.63 (m, 3 H); 3.42 (br. not resolved m, 2 H); 3.23 (dd, J = 8.4, 9.7; 1 H); 2.91 (s, 3 H); 2.02 (m, 1 H); 1.88 (m, 1 H).

Synthesis of Ex.97

- 3-Fluorobenzaldehyde (50 mg, 0.40 mmol) was added to a soln of Ex.91 (120 mg, 0.24 mmol) in THF (1.5 mL). The soln was stirred at rt for 1 h followed by the addn of acetic acid (0.015 mL, 0.27 mmol) and NaBH(OAc)₃ (154 mg, 0.73 mmol). The

mixture was stirred at rt for 16 h. More 3-fluorobenzaldehyde (15 mg, 0.12 mmol) was added and stirring continued. Aq. workup (CH_2Cl_2 , sat. aq. Na_2CO_3 soln; Na_2SO_4) and FC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$) afforded **Ex.97** (117 mg, 80%).

Data of **Ex.97**: cf. Table 17b

5

Synthesis of **Ex.98**

A soln of **Ex.97** (94 mg, 0.156 mmol) in dioxane (0.8 mL) was treated with 4 M HCl-dioxane (0.8 mL) for 2 h. The volatiles were evaporated to afford **Ex.98**·3HCl (91 mg, 95%).

10 Data of **Ex.98**·3HCl: cf. Table 17b

Synthesis of **Ex.100**

A soln of **Ex.98**·3HCl (62 mg, 0.10 mmol) in CH_2Cl_2 (0.6 mL) was treated with pyridine (0.041 mL, 0.51 mmol) and acetyl chloride (16 mg, 0.2 mmol) at rt for 16 h. $i\text{-Pr}_2\text{NEt}$ (0.052 mL, 0.3 mmol) and more acetyl chloride (16 mg, 0.2 mmol) were added and stirring was continued for 24 h followed by an aqueous workup (CHCl_3 , sat. aq. Na_2CO_3 soln; Na_2SO_4) and purification by prep. HPLC (method 1a) to afford **Ex.100**·2 $\text{CF}_3\text{CO}_2\text{H}$ (50 mg, 64%).

Data of **Ex.100**·2 $\text{CF}_3\text{CO}_2\text{H}$: cf. Table 17b

20 $^1\text{H-NMR}$ (DMSO-d_6): Ca. 9.5 (br. s, 1 H); 9.23 (s, 2 H); 8.96 (d, $J = 1.0$, 1 H); 8.45 (br. s, 1 H); 8.17 (d, $J = 6.5$, 1 H); 7.62 (d, $J = 7.7$, 1 H); 7.42 (t, $J = 7.9$, 1 H); ca 7.4 (br. not resolved m, 1 H); ca 7.35 – 7.25 (br. not resolved m, 2 H); 7.15 (br. t-like m, 1 H); 6.97 (dd; $J = 1.9$, 8.2, 1 H); 4.52 – 4.39 (m, 4 H); ca 4.2 – 3.8 (br. not resolved m, 3 H); 3.90 (t, $J = 11.3$, 1 H); 3.71 (t-like m, 2 H); 3.49 (m, 1 H); 3.33 (br. t-like m, 1 H);
25 3.07 (t, $J = 9.0$, 1 H); 2.95 (br. not resolved m, 2 H); 2.14 (m, 1 H); 1.89 (m, 1 H); 1.81 (s, 3 H).

Core 06 / 07: Synthesis of **Ex.115**, **Ex.116** and **Ex.129**, **Ex.130** (Scheme 13)

30 Synthesis of the arylbromide **65**

2-Bromothiophenol (**11**; 2.71 mL, 23 mmol) was added to a soln of **30** (5.0 g, 19.1 mmol) and CMBP (6.02 mL, 23 mmol) in toluene (50 mL). The mixture was heated to reflux for 1 h. The volatiles were evaporated. FC (hexane/EtOAc 4:1) afforded **65** 7.31 g, 88%).

35 Data of **65**: $\text{C}_{18}\text{H}_{26}\text{BrNO}_4\text{S}$ (432.3). LC-MS (method 1c): $R_t = 2.58$ (97), 434.0/431.9 ($[\text{M}+\text{H}]^+$).

Synthesis of the biphenyl **66**

Sat. aq. NaHCO_3 soln (37.8 mL) was added dropwise to a soln of **65** (5.0 g, 11.6 mmol), 3-hydroxyphenylboronic acid (**12**, 4.79 g, 34.7 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (1.34 g, 1.16 mmol) in DME (150 mL). The mixture was heated to reflux for 4 h. The volatiles were evaporated and the residue was distributed between EtOAc and sat. aq. Na_2CO_3 soln. The organic phase was repeatedly washed (sat. aq. Na_2CO_3 soln), dried (Na_2SO_4), filtered and concentrated. FC ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 100:0 to 95:5) afforded **66** (3.91 g, 75%).

10 Data of **66**: $\text{C}_{24}\text{H}_{31}\text{NO}_5\text{S}$ (445.5). LC-MS (method 1a): $R_t = 2.46$ (94), 446.1 ($[\text{M}+\text{H}]^+$).

Synthesis of the phenol **68**

At 0°C , TFA (11.9 mL) was slowly added to a soln of **66** (2.38 g, 5.34 mmol) in CH_2Cl_2 (24 mL). Stirring was continued for 1 h followed by evaporation of the volatiles. The residue was dissolved in CHCl_3 and concentrated to afford **67**· $\text{CF}_3\text{CO}_2\text{H}$ as a brown oil which was dissolved in CH_2Cl_2 (12 mL) and cooled to 0°C . $i\text{-Pr}_2\text{NEt}$ (2.73 mL, 16.0 mmol) was slowly added. Allyl chloroformate (0.63 mL, 5.88 mmol) in CH_2Cl_2 (12 mL) was added over 30 min. The mixture was stirred for 2 h followed by evaporation of the volatiles. Aqueous workup (EtOAc, sat. aq. NaHCO_3 soln; Na_2SO_4) and FC (hexane/EtOAc 9:1 to 7:3) yielded **68** (2.02 g, 88%).

20 Data of **68**: $\text{C}_{23}\text{H}_{27}\text{NO}_5\text{S}$ (429.5). LC-MS (method 1a): $R_t = 2.29$ (92), 430.1 ($[\text{M}+\text{H}]^+$).

Synthesis of the ether **69**

A soln of ADDP (1.34 g, 5.31 mmol) in degassed CHCl_3 (5.0 mL) was added at 0°C to a soln of **68** (1.52 g, 3.54 mmol), Boc-D-alaninol (**20**; 0.93 g, 5.31 mmol) and PPh_3 (1.39 g, 5.31 mmol) in CHCl_3 (20 mL). The mixture was stirred at 0°C to rt for 16 h. More Boc-D-alaninol (**20**; 0.93 g, 5.31 mmol) and PPh_3 (1.39 g, 5.31 mmol) were added. The mixture was cooled to 0°C followed by the slow addition of ADDP (1.34 g, 5.31 mmol) in CHCl_3 (5.0 mL). The mixture was stirred at rt for 16 h. The volatiles were evaporated. The residue was suspended in Et_2O and filtered. The filtrate was concentrated and purified by FC (hexane/EtOAc 4:1 to 3:1) to afford **69** (1.6 g, 77%).

30 Data of **69**: $\text{C}_{31}\text{H}_{42}\text{N}_2\text{O}_7\text{S}$ (586.7). LC-MS (method 1a): $R_t = 2.78$ (97), 587.1 ($[\text{M}+\text{H}]^+$).

Synthesis of the amino acid **71**

35 A soln of **69** (3.2 g, 5.5 mmol) in THF (17 mL) and MeOH (17 mL) was treated at 0°C with 1 M aq. LiOH soln (6.5 mL, 6.5 mmol). The mixture was allowed to stir at 0°C to

rt for 16 h. The volatiles were evaporated. The residue was distributed between EtOAc and 0.2 M aq. HCl soln. The organic phase was dried (Na_2SO_4) and concentrated to afford crude acid **70** (3.02 g) which was dissolved in dioxane (12.5 mL) and treated with 4 M HCl-dioxane (7.9 mL) for 4 h. The volatiles were evaporated. The residue was taken up in CHCl_3 and concentrated to afford crude **71**·HCl (2.84 g, quant. yield) which was used without further purification.

Data of **71**·HCl: $\text{C}_{25}\text{H}_{32}\text{N}_2\text{O}_5\text{S}\cdot\text{HCl}$ (472.6, free base). LC-MS (method 1a): $R_t = 1.76$ (89), 473.1 ($[\text{M}+\text{H}]^+$).

10 Synthesis of Ex.115

A soln of crude **71**·HCl (0.94 g, 1.8 mmol) in CH_2Cl_2 (45 mL) was added over 2 h to a soln of T3P (50% in EtOAc; 2.7 mL, 4.6 mmol) and $i\text{-Pr}_2\text{NEt}$ (1.3 mL, 7.4 mmol) in CH_2Cl_2 (1810 mL). The soln was partially concentrated, washed with sat. aq. NaHCO_3 soln, dried (Na_2SO_4), filtered and concentrated. FC (hexane/EtOAc 8:2 to 1:1) gave **Ex.115** (0.63 g, 75%).

Data of **Ex.115**: $\text{C}_{25}\text{H}_{30}\text{N}_2\text{O}_4\text{S}$ (454.6). LC-MS (method 1d): $R_t = 2.35$ (95), 455.0 ($[\text{M}+\text{H}]^+$). $^1\text{H-NMR}$ (DMSO-d_6): 7.57 – 7.52 (m, 2 H); 7.38 – 7.21 (m, 5 H); 7.01 – 6.95 (m, 2 H); 6.90 (d, $J = 7.9$, 1 H); 5.90 (m, 1 H); 5.29 (d, $J = 17.2$, 1 H); 5.17 (d, $J = 10.0$, 1 H); 4.47 – 4.45 (m, 2 H); 4.13 – 3.97 (m, 3 H); 3.82 (q, $J = 6.5$, 1 H); 2.60 – 2.57 (m, 2 H); 1.57 – 1.09 (m, 6 H); 1.19 (d, $J = 6.5$, 3 H).

Synthesis of Ex.116

A soln of **Ex.115** (120 mg, 0.26 mmol) in degassed EtOAc/ CH_2Cl_2 1:1 (2.1 mL) was treated at rt for 16 h with $\text{Pd}(\text{PPh}_3)_4$ (1.2 mg) and 1,3-dimethylbarbituric acid (49 mg, 0.32 mmol). The volatiles were evaporated and the residue purified by FC (hexane/EtOAc 50:50 to 0:100, then $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 100:0 to 90:10) to afford **Ex.116** (82 mg, 83%).

Data of **Ex.116**: $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_2\text{S}$ (370.5). LC-MS (method 1a): $R_t = 1.74$ (95), 371.1 ($[\text{M}+\text{H}]^+$).

$^1\text{H-NMR}$ (DMSO-d_6): 7.76 (d, $J = 7.1$, 1 H); 7.55 (m, 1 H); 7.37 – 7.26 (m, 4 H); 7.07 (t-like m, 1 H); 6.98 (dd-like m, 1 H); 6.87 (d-like m, J ca 7.9, 1 H); 4.14 – 4.01 (m, 3 H); 3.32 (t, $J = 5.0$, 1 H); 2.67 – 2.55 (m, 2 H); ca 2.6 (very br. s, 2 H); 1.56 (m, 1 H); 1.38 – 1.03 (m, 5 H); 1.21 (d, $J = 6.3$, 3 H).

Synthesis of Ex.129

At 0°C, mCPBA (70%, 876 mg, 3.55 mmol) was added in portions to a soln of Ex.115 (808 mg, 1.78 mmol) in CH₂Cl₂ (17 mL). The mixture was stirred at 0°C to rt for 2 h and concentrated, followed by an aq. workup (EtOAc, sat. aq. NaHCO₃ soln, 1 M aq. Na₂S₂O₃ soln; Na₂SO₄). FC (hexane/EtOAc 50:50 to 0:100) gave Ex.129 (788 mg, 91%).

Data of Ex.129: C₂₅H₃₀N₂O₆S (486.6). LC-MS (method 1a): R_t = 1.91 (93), 487.1 ([M+H]⁺). ¹H-NMR (DMSO-d₆): 8.06 (dd, J = 1.3, 7.9, 1 H); 7.77 (dt, J = 1.4, 7.5, 1 H); 7.68 (dt, J = 1.4, 7.7, 1 H); 7.49 – 7.44 (m, 2 H); 7.39 (t, J = 8.0, 1 H); 7.09 – 7.03 (m, 3 H); 6.73 (s, 1 H); 5.88 (m, 1 H); 5.27 (d, J = 17.3, 1 H); 5.17 (d, J = 10.3, 1 H); 4.45 (d, J = 4.9, 2 H); 4.08 – 3.96 (m, 3 H); 3.75 (q-like m, J = 7.6, 1 H); 2.45 (br. m, 2 H); 1.45 – 1.01 (m, 5 H); 1.23 (d, J = 6.8, 3 H); 1.01 (m, 1 H).

Synthesis of Ex.130

A soln of Ex.129 (100 mg, 0.21 mmol) in degassed EtOAc/CH₂Cl₂ 1:1 (1.7 mL) was treated at rt for 3 h with Pd(PPh₃)₄ (1.0 mg) and 1,3-dimethylbarbituric acid (39 mg, 0.25 mmol). The volatiles were evaporated and the residue purified by FC (hexane/EtOAc 50:50 to 0:100, then CH₂Cl₂/MeOH 100:0 to 90:10) to afford Ex.130 (82 mg, 98%).

Data of Ex.130: C₂₁H₂₆N₂O₄S (402.5). LC-MS (method 1a): R_t = 1.48 (94), 403.0 ([M+H]⁺).

Core 06: Synthesis of selected advanced intermediates and final products
(Scheme 13)

25 Synthesis of Ex.119

At 0°C, i-Pr₂NEt (0.055 mL, 0.324 mmol) was slowly added to a solution of Ex.116 (40 mg, 0.108 mmol), 1-pyrrolidineacetic acid (17 mg, 0.13 mmol), HATU (62 mg, 0.162 mmol) and HOAt (22 mg, 0.162 mmol) in DMF (0.5 mL). The mixture was stirred for 2 h at 0°C, followed by an aqueous workup (EtOAc, sat. aq. NaHCO₃ soln, H₂O, sat. aq. NaCl soln; Na₂SO₄) and purification by prep HPLC (method 3) to give Ex.119 (30 mg, 57%).

Data of Ex.119: cf. Table 18b.

Core 08 / 09: Synthesis of Ex.143, Ex.144 and Ex.168, Ex.169 (Scheme 14)**Synthesis of thioether 72**

5-Bromopyridine-3-thiol (**13**; 1.0 g, 5.3 mmol) was added to a soln of alcohol **30** (1.06 g, 4.0 mmol) and CMBP (1.17 g, 4.85 mmol) in toluene (15 mL). The mixture was heated to reflux for 1 h. The volatiles were evaporated. FC (hexane/EtOAc 4:1) of the residue gave **72** (1.35 g, 77%).

Data of **72**: $C_{17}H_{25}BrN_2O_4S$ (433.6). LC-MS (method 1c): $R_t = 2.37$ (93), 433.0/435.0 ($[M+H]^+$).

10 Synthesis of phenol 73

At rt, sat. aq. $NaHCO_3$ soln (17.1 mL) was added to a soln of **72** (2.65 g, 6.1 mmol), 2-hydroxyphenylboronic acid (**14**; 2.53 g, 18.3 mmol) and $Pd(PPh_3)_4$ (707 mg, 0.61 mmol) in DME (78 mL). The mixture was heated to reflux for 1 h followed by an aq. workup (EtOAc, sat. aq. Na_2CO_3 soln; Na_2SO_4) and FC (hexane/EtOAc 2:1 to 1:1) to afford **73** (2.42 g, 88%).

Data of **73**: $C_{23}H_{30}N_2O_5S$ (446.6). LC-MS (method 1a): $R_t = 1.82$ (96), 447.1 ($[M+H]^+$).

Synthesis of phenol 75

At 0°C, a soln of **73** (500 mg, 1.12 mmol) in CH_2Cl_2 (4.0 mL) was treated with TFA (3.0 mL) for 2 h and concentrated. Aq. workup (EtOAc, sat. aq. $NaHCO_3$ soln; Na_2SO_4) afforded crude **74** which was dissolved in CH_2Cl_2 (4.0 mL). The soln was cooled to 0°C. A soln of AllocOSu (245 mg, 1.23 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise. Stirring was continued for 2 h followed by an aq. workup (CH_2Cl_2 , sat. aq. $NaHCO_3$ soln; Na_2SO_4) and FC (hexane/EtOAc 1:1) to yield **75** (310 mg, 64%).

Data of **75**: $C_{22}H_{26}N_2O_5S$ (430.5). LC-MS (method 1a): $R_t = 1.68$ (94), 431.1 ($[M+H]^+$).

Synthesis of the ether 76

At 0°C, ADDP (967 mg, 3.83 mmol) was added in portions to a soln of alcohol **20** (672 mg, 3.83 mmol), phenol **75** (1.1 g, 2.55 mmol) and PPh_3 (1.0 g, 3.83 mmol) in $CHCl_3$ (15 mL). The mixture was stirred for 4 h at rt and concentrated. FC (hexane/EtOAc 4:1 to 2:1) afforded **76** (450 mg, 30%).

Data of **76**: $C_{30}H_{41}N_3O_7S$ (587.7). LC-MS (method 1a): $R_t = 2.33$ (87), 588.2 ($[M+H]^+$).

Synthesis of the amino acid **78**

At 0°C, 1 M aq. LiOH (0.67 mL, 0.67 mmol) was added to a soln of **76** (430 mg, 0.73 mmol) in THF/MeOH 2:1 (1.5 mL). The mixture was stirred at 0°C to rt for 5 h and distributed between EtOAc and 0.2 M aq. HCl soln. The organic phase was separated, dried (Na₂SO₄), filtered and concentrated. FC (CH₂Cl₂/MeOH 100:0 to 80:20) gave acid **77** (288 mg) which was dissolved in dioxane (1 mL) and treated with 4 M HCl-dioxane (1.15 mL) for 6 h at rt. The volatiles were evaporated. The residue was suspended in EtOAc, filtered and dried i.v. to afford **78**·2HCl (256 mg, 64%).

Data of **78**·2HCl: C₂₄H₃₁N₃O₅S·2HCl (473.6, free base). LC-MS (method 1c): R_t = 1.39 (92), 474.1 ([M+H]⁺).

Synthesis of **Ex.143**

A soln of **78**·2HCl (200 mg, 0.37 mmol) and i-Pr₂NEt (0.125 mL, 0.73 mmol) in CH₂Cl₂ (5 mL) was added dropwise over 2 h (syringe pump) to a soln of T3P (50% in EtOAc; 0.65 mL, 1.1 mmol) and i-Pr₂NEt (0.188 mL, 1.1 mmol) in CH₂Cl₂ (177 mL). Aq. Workup (CH₂Cl₂, sat. aq. NaHCO₃ soln; Na₂SO₄) and FC (hexane/EtOAc 50:50 to 0:100) afforded **Ex.143** (105 mg, 63%).

Data of **Ex.143**: C₂₄H₂₉N₃O₄S (455.5). LC-MS (method 1d): R_t = 1.66 (98), 456.0 ([M+H]⁺). ¹H-NMR (DMSO-d₆): 8.52 (d, J = 2.2, 1 H); 8.40 (d, J = 1.9, 1 H); 8.36 (s, 1 H); 8.11 (d, J = 5.5, 1 H); 7.45 – 7.39 (m, 2 H); 7.20 (d, J = 7.6, 1 H); 7.14 (d, J = 8.2, 1 H); 7.08 (t, J = 7.5, 1 H); 5.88 (m, 1 H); 5.28 (d, J = 16.5, 1 H); 5.16 (d, J = 10.4, 1 H); 4.44 (d, J = 5.2, 2 H); 4.17 – 3.97 (m, 4 H); 3.06 (m, 1 H); 2.89 (m, 1 H); 1.85 (m, 1 H); ca 1.6 – 1.3 (m, 5 H); 1.09 (d, J = 6.3, 3 H).

Synthesis of **Ex.144**

A degassed solution of **Ex.143** (200 mg, 0.44 mmol) in degassed CH₂Cl₂/EtOAc 1:1 (11 mL) was treated at rt for 2 h with Pd(PPh₃)₄ (2.0 mg) and 1,3-dimethylbarbituric acid (82 mg, 0.53 mmol). The volatiles were evaporated. FC (hexane/EtOAc 50:50 to 0:100 and then CH₂Cl₂/MeOH 99:1 to 95:5) gave **Ex.144** (128 mg, 78%).

Data of **Ex.144**: C₂₀H₂₅N₃O₂S (371.5). LC-MS (method 1a): R_t = 1.30 (97), 371.9 ([M+H]⁺). ¹H-NMR (DMSO-d₆): 8.52 (d, J = 2.2, 1 H); 8.40 (d, J = 2.0, 1 H); 8.16 (t, J = 2.1, 1 H); 7.77 (d, J = 6.4, 1 H); 7.45 – 7.39 (m, 2 H); 7.16 (d, J = 7.9, 1 H); 7.07 (dt; J = 0.8, 7.1, 1 H); 4.13 – 4.04 (m, 2 H); 3.97 (br. not resolved m, 1 H); 3.21 (t-like m, 1 H); 3.08 – 2.89 (m, 2 H); 2.01 (br. s, 2 H); 1.74 – 1.18 (several m, 6 H); 1.12 (d, J = 6.5, 3 H).

Synthesis of Ex.168

H₂O₂ (35% in H₂O; 0.043 mL; 0.49 mmol) was added to a soln of Ex.143 (32 mg, 0.07 mmol) in AcOH (1.0 mL). The mixture was stirred at rt for 20 h; after 2h and after 3 h, 16 h and 17 h more H₂O₂ (35% in H₂O; 0.043 mL; 0.49 mmol) had been added. The mixture was diluted with H₂O and extracted with EtOAc. The organic phase was dried (Na₂SO₄), filtered and concentrated to yield Ex.168 (28 mg, 82%).

Data of Ex.168: C₂₄H₂₉N₃O₆S (487.5). LC-MS (method 1a): R_t = 1.78 (92), 488.1 ([M+H]⁺). ¹H-NMR (DMSO-d₆): 8.99 (d, J = 2.2, 1 H); 8.91 (d, J = 1.9, 1 H); 8.52 (s, 1 H); 7.86 (d, J = 4.9, 1 H); 7.49 – 7.44 (m, 2 H); 7.17 – 7.08 (m, 3 H); 5.86 (m, 1 H); 5.26 (d, J = 18.6, 1 H); 5.15 (d, J = 9.9, 1 H); 4.42 (m, 2 H); 4.11 – 3.95 (m, 3 H); 3.87 (q-like m, 1 H); 3.56 (m, 1 H); 3.35 (m, 1 H); ca 1.70 (m, 1 H); ca 1.65 (m, 1 H); 1.40 – 1.10 (m, 4 H); 1.06 (d, J = 6.1, 3 H).

Synthesis of Ex.169

A soln of Ex.168 (2.19 g, 4.5 mmol) and 1,3-dimethylbarbituric acid (2.1 g, 13.5 mmol) in degassed EtOAc/CH₂Cl₂ 1:1 (65 mL) was treated at rt for 2 h with Pd(PPh₃)₄ (260 mg). The volatiles were evaporated and the residue purified by FC (CH₂Cl₂/MeOH 100:0 to 95:5) to afford Ex.169 (1.81 g, quant. yield).

Data of Ex.169: C₂₀H₂₅N₃O₄S (403.5). LC-MS (method 1a): R_t = 1.34 (96), 403.9 ([M+H]⁺). ¹H-NMR (DMSO-d₆): 8.97 (d, J = 2.2, 1 H); 8.92 (d, J = 2.0, 1 H); 8.39 (t, J = 2.1, 1 H); 7.64 (d, J = 6.5, 1 H); 7.49 – 7.42 (m, 2 H); 7.17 (d, J = 8.0, 1 H); 7.11 (t, J = 7.4, 1 H); 4.11 – 3.97 (m, 3 H); 3.63 (m, 1 H); 3.40 (m, 1 H); 3.07 (m, 1 H); 1.98 (br. s, 2 H); 1.58 (quint, J = 7.1, 2 H); 1.27 – 1.16 (m, 2 H); 1.09 (d, J = 6.0, 3 H); 1.09 (m, 1 H), 0.97 (m, 1 H).

Core 10 / 11: Synthesis of the B-A_B-A_C fragment 84 (Scheme 15)

Synthesis of the allylester 79

Oxalyl chloride (1.8 mL, 20.4 mmol) and DMF (26 µL) were added to a suspension of 10·HCl (2.0 g, 6.8 mmol) in CHCl₃ (50 mL). The mixture was stirred at rt for 1 h and concentrated (at 35°C). The residue was suspended in THF (50 mL) and cooled to 0°C. Allyl alcohol (1.4 mL, 20.4 mmol) and Et₃N (2.9 mL, 20.4 mmol) were added. The mixture was stirred at rt for 1 h followed by an aq. workup (EtOAc, 1 M aq. HCl soln, sat. aq. NaHCO₃ soln, sat. aq. NaCl soln; Na₂SO₄). FC (hexane/EtOAc 3:1) yielded 79 (1.78 g, 88%).

Data of 79: C₁₇H₁₅NO₄ (297.3). LC-MS (method 1b): R_t = 1.96 (99), 298.0 ([M+H]⁺).

Synthesis of the phenol **80**

3-Dimethylaminopropylamine (2.3 mL, 17.9 mmol) was added at rt to a soln of **79** (1.77 g, 5.9 mmol) in THF (65 mL). The soln was stirred at rt for 3 h followed by an
5 aq. workup (EtOAc, 1 M aq. HCl soln, sat. aq. NaHCO₃ soln, sat. aq. NaCl soln; Na₂SO₄) to afford **80** (1.27 g, 83%).

Data of **80**: C₁₅H₁₃NO₃ (255.3). LC-MS (method 1a): R_t = 1.65 (91), 255.9 ([M+H]⁺).

Synthesis of the aryether **81**

10 A soln of ADDP (1.56 g, 6.2 mmol) in degassed CHCl₃ (10 mL) was slowly added to a soln of **80** (1.26 g, 4.9 mmol), (S)-tert-butyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate (**21**; 0.83 g, 4.12 mmol) and PPh₃ (1.62 g, 6.2 mmol) in degassed CHCl₃ (20 mL). The soln was stirred at rt for 15 h followed by evaporation of the volatiles. The residue was suspended in Et₂O and filtered. The filtrate was concentrated and
15 purified by FC (hexane/EtOAc 4:1) to afford **81** (1.78 g, 98%).

Data of **81**: C₂₅H₃₀N₂O₅ (438.5). LC-MS (method 1a): R_t = 2.58 (98), 439.1 ([M+H]⁺).

Synthesis of acid **84**

A soln of **81** (1.76 g, 4.0 mmol) in MeOH/THF 1:1 (30 mL) was treated with 2 M aq. LiOH soln (4.0 mL, 8.0 mmol) for 1 h at rt. The mixture was concentrated. The residue was distributed between EtOAc and 1 M aq. HCl soln. The organic phase was washed (sat. aq. NaCl soln), dried (Na₂SO₄), filtered and concentrated to give crude **82**·HCl (1.5 g) which was dissolved in dioxane (15 mL) and treated with 4 M HCl-dioxane (30 mL) for 2.5 h at rt. The mixture was concentrated and repeatedly treated
25 with CHCl₃ and concentrated to obtain crude **83**·2HCl (1.79 g).

To a soln of crude **83**·2HCl (1.24 g) in THF (11 mL) was added 2 M aq NaOH soln (5.3 mL). The mixture was cooled to 0°C. A soln of allyl chloroformate (0.34 mL, 3.2 mmol) in THF (5 mL) was added dropwise over 30 min (syringe pump). Stirring was continued for 30 min followed by an aq. workup (CH₂Cl₂, 1 M aq. HCl soln; Na₂SO₄)
30 and purification by prep. HPLC (method 1d) to yield **84**·CF₃CO₂H (0.93 g, 67%).

Data of **84**·CF₃CO₂H: C₂₁H₂₂N₂O₅·CF₃CO₂H (382.4, free form). LC-MS (method 1a): R_t = 1.80 (99), 383.0 ([M+H]⁺). ¹H-NMR (DMSO-d₆): ca 13.5 (br. s, 1 H); 9.12 (s, 1 H); 9.06 (d, J = 1.9, 1 H); 8.48 (s, 1 H); 7.46 – 7.34 (m, 3 H); 7.06 (d, J = 7.4, 1 H); 5.92 (m, 1 H); 5.31 – 5.15 (m, 2 H); 4.61 – 4.48 (m, 2 H); 4.23 – 4.02 (m, 3 H); 3.37 – 3.35
35 (m, 2 H); ca 2.1 – 1.8 (m, 4 H).

Core 10: Synthesis of Ex.193a,c-h and Ex.194b (Scheme 15)Procedure C.1:General Procedure for the synthesis of Ex.193a-h and Ex.194b (Scheme 15)5 1. Synthesis of resins **85a-h**: Immobilisation of Fmoc-AA1-OH

2-Chlorotriyl chloride resin (matrix: copoly(styrene-1% DVB), 100 – 200 mesh, loading: 1.3 mmol/g; 10 g, 13 mmol) was suspended in dry CH₂Cl₂ (100 mL), shaken for 50 min and filtered. The resin was suspended in dry CH₂Cl₂ (80 mL). A soln of Fmoc-AA1-OH (10.3 mmol) and i-Pr₂NEt (4.4 mL, 26 mmol) in DMF (20 mL) was added. The mixture was shaken at rt for 2.7 h with N₂ bubbling through. The resin was filtered and washed (CH₂Cl₂, DMF, CH₂Cl₂). Capping: The resin was shaken in CH₂Cl₂/MeOH/i-Pr₂NEt 15:2:3 (100 mL) for 0.5 h and filtered. The capping step was repeated twice. The resin was filtered, washed (CH₂Cl₂, DMF, CH₂Cl₂, MeOH) and dried i.v. to afford resin **85**.

Resin	Chlorotriyl-chlorid resin	Fmoc-AA1-OH	Yield / Loading (mass increase)
85a,h	5 g	Fmoc-β ³ -homoPhe-OH	6.79 g / 0.72 mmol/g
85b,e,f,g	10 g	Fmoc-NMe-β ³ -homoDAla-OH	13.0 g / 0.78 mmol/g
85c,d	10 g	Fmoc-β-Ala-OH	12.5 g / 0.73 mmol/g

15

2. Synthesis of Ex.193a,c-h and Ex.194b

Fmoc Cleavage: The resin **85** (90 - 110 mg, ca 70 μmol) was swollen, in DMF (1 mL) for 1 h and filtered. Then it was suspended in a soln of 2%v/v DBU in DMF (1 mL), shaken for 10 min, filtered off and washed (DMF). The deprotection step was repeated once. The resin was filtered and washed (DMF).

Coupling of Fmoc-AA2-OH: The resin **86** was suspended in DMF (1 mL). i-Pr₂NEt (280 μmol), Fmoc-AA2-OH (140 μmol) and HATU (140 μmol) were added. The mixture was shaken for 40 min, filtered and washed (DMF). The coupling step was repeated once. The resin **87** was filtered and washed (DMF).

25 Fmoc Cleavage: The resin was treated with 2%v/v DBU in DMF (1 mL) as described above to yield resin **88**.

Coupling of Alloc-protected amino acid **84**: The resin **88** was suspended in DMF (1mL)¹⁾. i-Pr₂NEt (560 μmol), **84** (35 mg, 70 μmol) and PyBOP (140 μmol) were added. The mixture was shaken for 1 h and filtered. The resin was washed (DMF).

The coupling step was repeated once. The resin **89** was filtered and washed (DMF, CH₂Cl₂).

Alloc Cleavage: The resin **89** was suspended in CH₂Cl₂ (1 mL). Phenylsilane (0.18 mL; 1.45 mmol)²⁾ and Pd(PPh₃)₄ (8 mg, 7 μmol) were added. The mixture was shaken
5 for 15 min and filtered. The deprotection step was repeated once. The resin **90** was filtered and washed (CH₂Cl₂, DMF, MeOH, CH₂Cl₂).

Release of the cyclization precursor: The resin **90** was treated with HFIP/CH₂Cl₂ 2:3 (1 mL) for 30 min, filtered and washed (CH₂Cl₂). The cleavage step was repeated once. The combined filtrates and washings were concentrated and dried i.v. to afford
10 crude **91a-h**.

Ring closure and cleavage of side chain protective groups: Crude **91** was dissolved in dry DMF (4 mL)³⁾ and i-Pr₂NEt (96 μL; 560 μmol) was added. This soln was then added dropwise to a soln of FDPP (40 mg, 105 μmol) in DMF (20 mL)³⁾. The soln was stirred at rt for 15 h and the volatiles were evaporated. The residue was treated with
15 sat. aq. Na₂CO₃ soln (4 mL) and extracted with CHCl₃ (9 mL). The organic layer was filtered through a pad of MgSO₄. The filtrate was concentrated and purified by prep. HPLC to afford Ex.193a,c-h.

Crude Ex.193b was dissolved in CH₂Cl₂ (0.7 mL) and treated with TFA (0.3 mL) at rt for 3 h. The volatiles were evaporated and the residue was purified by prep. HPLC to
20 give Ex.194b.

1) Ex.193c,d: Coupling of **84** was performed in DMF/NMP 6:1

2) Ex.193c,d: 0.09 mL / 0.7 mmol Phenylsilane was used

3) Ex.193c,d: Ring closure was performed in a total volume of 12 mL of DMF

Purification methods applied, yields, LC-MS data and systematic names of
25 Ex.193a,c-h and Ex.194b are indicated in Table 22.

Ex.193a: ¹H-NMR (DMSO-d₆): 9.21 (d, J = 2.1, 1 H); 8.80 (t, J = 2.0, 1 H); 8.64 (d, J = 1.8, 1 H); 8.50 (d, J = 9.0, 1 H); 8.30 (s, 1 H); 7.65 (d, J = 7.7, 1 H); 7.40 (t, J = 7.9, 1 H); 7.30 - 7.10 (m, 5 H); 6.94 (dd, J = 1.8, 8.2, 1 H); 5.23 (q, J = 7.2, 1 H); 4.50 (d, J = 11.6, 1 H); 4.36 - 4.26 (m, 2 H); 3.82 (t, J = 11.2, 1 H); 3.20 - 3.17 (m, 2 H); 2.99 -
30 2.70 (m, 2 H); 2.81 (s, 3 H); ca 2.50 (m, 2 H; superimposed by DMSO-d signal); 2.09 - 1.77 (m, 4 H); 1.34 (d, J = 7.2, 3 H).

Ex.194b: ¹H-NMR (DMSO-d₆, addition of D₂O): Two sets of signals were observed; ratio 9:1; signals of major isomer: 9.17 (d, J = 2.0, 1 H); 8.64 (s, 1 H); 8.59 (d, J = 1.7,
35 1 H); 8.09 (s, 1 H); 7.57 (d, J = 7.8, 1 H); 7.40 (t, J = 7.9, 1 H); 6.93 (dd, J = 1.6, 8.2, 1 H); 5.54 (t-like m, 1 H); 4.56 - 4.53 (m, 2 H); 4.31 (m, 1 H); 3.68 (t, J = 11.3, 1 H);

3.55 (br. t-like m, 1 H); 3.36 (br. q-like m, 1 H); 2.81 (s, 3H); 2.80 (s, 3 H); 2.62 – 2.60 (m, 2 H); 2.31 – 2.27 (m, 2 H); ca 2.1 – 1.75 (m, 6 H); 1.12 (d, J = 6.8; 3 H).

5 **Core 11: Synthesis of Ex.195a,b,e-h,j; Ex.196c,i,k and Ex.197d** (Scheme 16)

Procedure C.2:

General Procedure for the synthesis of Ex.195a,b,e-h,j; Ex.196c,i,k and Ex.197d
(Scheme 16)

1. Synthesis of resins **135a-k**: Immobilisation of Fmoc-AA1-OH

- 10 2-Chlorotriyl chloride resin (matrix: copoly(styrene-1% DVB), 100 – 200 mesh, loading: 1.3 mmol/g; 10 g, 13 mmol) was suspended in dry CH₂Cl₂ (100 mL), shaken for 50 min and filtered. The resin was suspended in dry CH₂Cl₂ (80 mL). A soln of Fmoc-AA1-OH (10.3 mmol) and i-Pr₂NEt (4.4 mL, 26 mmol) in DMF (20 mL) was added. The mixture was shaken at rt for 2.7 h with N₂ bubbling through. The resin
- 15 was filtered and washed (CH₂Cl₂, DMF, CH₂Cl₂). Capping: The resin was shaken in CH₂Cl₂/MeOH/i-Pr₂NEt 15:2:3 (100 mL) for 0.5 h and filtered. The capping step was repeated twice. The resin was filtered, washed (CH₂Cl₂, DMF, CH₂Cl₂, MeOH) and dried i.v. to afford resin **135**.

Resin	Chlorotriyl-chlorid resin	Fmoc-AA1-OH	Yield / Loading (mass increase)
135a-d	10 g	Fmoc-NMe-β ³ -homoDAla-OH	13.0 g / 0.78 mmol/g
135e,f,h,j	1 g	Fmoc-Sar-OH	1.34 g / 0.80 mmol/g
135g	1 g	Fmoc-Gly-OH	1.22 g / 0.70 mmol/g
135i	1 g	Fmoc-Ala-OH	1.28 g / 0.67 mmol/g
135k	2 g	Fmoc-DAla-OH	2.35 g / 0.71 mmol/g

20 2. Synthesis of Ex.195a,b,e-h,j; Ex.196c,i,k and Ex.197d

Fmoc Cleavage: The resin **135** (90 - 107 mg, ca 70 μmol) was swollen in DMF (1 mL) for 1 h and filtered. Then it was suspended in a soln of 2%v/v DBU in DMF (1 mL), shaken for 10 min filtered and washed (DMF). The deprotection step was repeated once. The resin **136** was filtered and washed (DMF).

- 25 Coupling of Fmoc-AA2-OH: The resin **136** was suspended in DMF (1 mL). i-Pr₂NEt (280 μmol), Fmoc-AA2-OH (140 μmol) and HATU (140 μmol) were added. The mixture was shaken for 40 min, filtered and washed (DMF). The coupling step was repeated once. The resin **137** was filtered and washed (DMF).

Fmoc Cleavage: The resin **137** was treated with 2%v/v DBU in DMF (1 mL) as described above to afford resin **138**.

Coupling of Fmoc-AA3-OH: The resin **138** was suspended in DMF (1 mL). *i*-Pr₂NEt (280 μmol), Fmoc-AA3-OH (140 μmol) and HATU (140 μmol) were added. The mixture was shaken for 40 min, filtered and washed (DMF). The coupling step was repeated once. The resin **139** was filtered and washed (DMF).

Fmoc Cleavage: The resin **139** was treated with 2%v/v DBU in DMF (1 mL) as described above to afford resin **140**.

Coupling of Alloc-protected amino acid **84**: The resin **140** was suspended in DMF (1 mL). *i*-Pr₂NEt (560 μmol), **84** (36 mg, 84 μmol) and PyBOP (140 μmol) were added. The mixture was shaken for 1 h and filtered. The resin **141** was washed (DMF). The coupling step was repeated once. The resin was filtered and washed (DMF, CH₂Cl₂).

Alloc Cleavage: The resin **141** was suspended in CH₂Cl₂ (1 mL). Phenylsilane (0.18 mL; 1.4 mmol) and Pd(PPh₃)₄ (8 mg, 7 μmol) were added. The mixture was shaken for 15 min and filtered. The deprotection step was repeated once. The resin **142** was filtered and washed (CH₂Cl₂, DMF, MeOH, CH₂Cl₂).

Release of the cyclization precursor: The resin **142** was treated with HFIP/CH₂Cl₂ 2:3 (1 mL) for 30 min, filtered and washed (CH₂Cl₂). The cleavage step was repeated once. The combined filtrates and washings were concentrated, taken up in CH₃CN (3 mL), concentrated and dried i.v. to afford crude **143a-k**.

Ring closure and cleavage of side chain protective groups: Crude **143** was dissolved in a soln of *i*-Pr₂NEt (98 μL; 570 μmol) in dry DMF (4 mL). This soln was then added dropwise to a soln of FDPP (41 mg, 106 μmol) in DMF (20 mL). The soln was stirred at rt for 5 h and the volatiles were evaporated. The residue was treated with sat. aq. Na₂CO₃ soln (4 mL) and extracted with CHCl₃ (9 mL). The organic layer was filtered through a pad of MgSO₄. The filtrate was concentrated to afford crude **Ex.195a-k**. Crude products **Ex.195a,b,e-h,j** were purified by prep. HPLC to afford **Ex.195a,b,e-h,j**.

A soln of crude product **Ex.195c,d,i or k** in TFA/CH₂Cl₂ 3:7 (1 mL) was stirred at rt for 3 h. The volatiles were evaporated. The residue was dissolved in CH₂Cl₂, concentrated, dried i.v. and purified by prep. HPLC to afford **Ex.196c,i,k** or **Ex.197d**, respectively.

Purification methods applied, yields, LC-MS data and systematic names of **Ex.195a,b,e-h,j**; **Ex.196c,i,k** and **Ex.197d** are indicated in Table 23a.

Ex.195b: $^1\text{H-NMR}$ (CD_3OD): 9.16 (d, $J = 2.1$, 1 H); 8.97 (t, $J = 2.1$, 1 H); 8.94 (d, $J = 2.0$, 1 H); 7.57 – 7.39 (m, 3 H); 7.00 (m, 1 H); 5.23 (m, 1 H); ca 4.8 (1 H, superimposed by HDO signal); 4.40 (d, $J = 16.8$, 1 H); ca. 4.4 (br. m, 1 H), 4.28 (dd; $J = 3.8$, 8.1, 1 H); 3.73 (d, $J = 16.8$, 1 H); 3.77 – 3.60 (m, 3 H); 2.98 (s, 3 H); 2.65 (dd, $J = 2.4$, 13.6, 1 H); 2.37 (t, $J = 12.8$, 1 H); 2.20 – 2.02 (m, 4 H); 1.46 (d, $J = 7.0$, 3 H); 1.15 (d, $J = 7.0$, 3 H).

Ex.195h: $^1\text{H-NMR}$ (CD_3OD): Two sets of signals were observed; ratio 1:1; 9.06 (d, $J = 2.0$, 0.5 H); 9.00 (d, $J = 2.0$, 0.5 H); 8.97 (d, $J = 1.9$, 0.5 H); 8.84 (d, $J = 1.9$, 0.5 H); 8.72 (t, $J = 2.1$, 0.5 H); 8.50 (t, $J = 2.1$, 0.5 H); 7.88 (s, 0.5 H); 7.65 (s, 0.5 H); 7.50 – 7.35 (m, 2 H); 7.32 – 7.19 (m, 3.5 H); 7.09 – 6.93 (m, 2.5 H); 5.89 (d, $J = 16.7$, 0.5 H); 5.26 – 5.20 (q-like m, 1 H), 4.79 (q, $J = 7.2$, 0.5 H); 4.65 (dd, J ca 4.7, 11.8, 1 H); 4.51 (dt-like m, 1 H); 4.50 (br. m, 0.5 H); 4.05 (d, $J = 7.2$, 1 H); 3.90 (t, $J = 9.6$, 0.5 H); 3.75 – 3.44 (m, 3.5 H); 3.23 (dd, $J = 4.5$, 13.9, 0.5 H); 3.12 – 3.05 (m, 1 H); 2.98 (s, 3 H); 2.24 – 2.04 (m, 4 H); 1.43 (d, $J = 7.0$, 1.5 H); 1.36 (d, $J = 7.2$, 1.5 H).

Core 12: Synthesis of Ex.198, Ex.199 and Ex.200 (Scheme 17)

Synthesis of the Mitsunobu product **144**

CMBP (9.9 mL, 38 mmol) was added to a soln of the hydroxypyridine **93** (4.32 g, 19 mmol) and the alcohol **16** (6.5 g, 22 mmol) in toluene (200 mL). The mixture was heated to 80°C for 1 h. The volatiles were evaporated. FC (hexane/EtOAc/MeOH gradient) afforded **144** (8.60 g, 90%).

Data of **144**: $\text{C}_{27}\text{H}_{33}\text{N}_3\text{O}_7$ (511.6). LC-MS (method 1a): $R_t = 1.91$ (98), 512.3 ($[\text{M}+\text{H}]^+$).

Synthesis of the carboxylic acid **145**

A soln of the ester **144** (6.56 g, 13 mmol) in MeOH (23 mL), THF (92 mL) and H_2O (23 mL) was treated with $\text{LiOH}\cdot\text{H}_2\text{O}$ (1.6 g, 38 mmol) at rt for 16 h. H_2O (50 mL) was added followed by 1 M aq. HCl soln (100 mL). The mixture was repeatedly extracted with EtOAc. The combined organic phases were washed (sat. aq. NaCl soln), dried (Na_2SO_4), filtered and concentrated to give **145** (6.19 g, 96%).

Data of **145**: $\text{C}_{26}\text{H}_{31}\text{N}_3\text{O}_7$ (497.5). LC-MS (method 1a): $R_t = 1.62$ (97), 498.0 ($[\text{M}+\text{H}]^+$).

Synthesis of amide **146**

A mixture of acid **145** (6.19 g, 12 mmol), amine **28**·HCl (3.6 g, 11 mmol), and HATU (5.7 g, 15 mmol) was dissolved in DMF (197 mL), followed by the addition of $i\text{-Pr}_2\text{NEt}$ (6.6 mL, 39 mmol). The mixture was stirred for 2 h. The mixture was diluted with sat.

aq. Na_2CO_3 soln and extracted with CH_2Cl_2 . The organic layer was dried (Na_2SO_4), filtered and concentrated. The residue was dissolved in EtOAc, washed (H_2O , sat. aq. NaCl soln), dried (Na_2SO_4), filtered and concentrated. FC (hexane/EtOAc 1:3) afforded **146** (7.1g, 74%).

- 5 Data of **146**: $\text{C}_{40}\text{H}_{49}\text{N}_5\text{O}_{10}$ (759.8). LC-MS (method 1a): $R_t = 2.04$ (92), 760.1 ($[\text{M}+\text{H}]^+$).

Synthesis of the carboxylic acid **147**

- 10 A soln of the ester **146** (7.07 g, 9.3 mmol) in MeOH (57 mL), THF (171 mL) and H_2O (57 mL) was treated with $\text{LiOH}\cdot\text{H}_2\text{O}$ (1.2 g, 28 mmol) at rt for 16 h. The mixture was poured onto ice / 1 M aq. HCl soln (50 mL) and repeatedly extracted with EtOAc. The combined organic phases were washed (sat. aq. NaCl soln), dried (Na_2SO_4), filtered and concentrated to give **147** (6.8 g, quant. yield).

Data of **147**: $\text{C}_{38}\text{H}_{45}\text{N}_5\text{O}_{10}$ (731.8). LC-MS (method 1c): $R_t = 1.81$ (94), 731.9 ($[\text{M}+\text{H}]^+$).

- 15 Synthesis of amino acid **148**

A degassed solution of ester **147** (6.8 g, 9.3 mmol) and 1,3-dimethylbarbituric acid (4.4 g, 28 mmol) in CH_2Cl_2 (67 mL) and EtOAc (68 mL) was treated with $\text{Pd}(\text{PPh}_3)_4$ (0.54 g, 0.46 mmol) at rt for 2 h. The volatiles were evaporated. FC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 99:1 to 80:20) afforded **148** (5.6 g, 93%).

- 20 Data of **148**: $\text{C}_{34}\text{H}_{41}\text{N}_5\text{O}_8$ (647.7). LC-MS (method 1a): $R_t = 1.45$ (91), 648.0 ($[\text{M}+\text{H}]^+$).

Synthesis of Ex.198

- 25 A solution of **148** (1.08 g, 1.7 mmol) and $i\text{-Pr}_2\text{NEt}$ (0.86 mL, 5.0 mmol) in dry DMF (40 mL) was added over 3 h (syringe pump) to a soln of HATU (1.27 g, 3.33 mmol) in DMF (1620 mL). The volatiles were evaporated. Aq. Workup (EtOAc, sat. aq. NaHCO_3 soln, H_2O , sat. aq. NaCl soln; Na_2SO_4) and FC (EtOAc/MeOH 95:5) afforded Ex.198 (0.65 g, 62%).

- 30 Data of Ex.198: $\text{C}_{34}\text{H}_{39}\text{N}_5\text{O}_7$ (629.7). LC-MS (method 1d): $R_t = 1.61$ (99), 630.3 ($[\text{M}+\text{H}]^+$). $^1\text{H-NMR}$ (DMSO-d_6): Three sets of broad signals were observed; 8.44 (br. d, J ca 3.7, 0.5 H); 8.32, 8.28 (2 d, $J = 3.8, 3.9, 0.5$ H); 7.86 – 7.18 (m, 13 H); 5.12 – 4.83 (m, 2 H); 4.59 – 3.46 (several m, 7 H); 3.32 – 2.72 (several m, 5 H); 2.40 – 2.25 (m, 1 H), 2.15 – 1.90 (m, 1 H); 1.40, 1.39 (2 s, 9 H).

Synthesis of Ex.199

- 35 A soln of Ex.198 (0.85 g, 1.34 mmol) in dioxane (17 mL) was treated with 4 M HCl dioxane soln (17 mL) for 1 h at rt. The volatiles were evaporated. The residue was

suspended in Et₂O, filtered, washed with Et₂O and dried to afford **Ex.199**·2HCl (836 mg; quant. yield).

Data of **Ex.199**·2 HCl: C₂₉H₃₁N₅O₅·2 HCl (529.6, free base). LC-MS (method 2c): R_t = 1.40 (94), 530.2 ([M+H]⁺).

5

Synthesis of **Ex.200**

A soln of **Ex.198** (1.2 g, 1.91 mmol) in MeOH (40 mL) was hydrogenated for 2 h at rt and normal pressure in the presence of palladium hydroxide on activated charcoal (moistened with 50% H₂O; 250 mg). The mixture was filtered through a pad of celite.

10 The solid was washed with MeOH. The combined filtrate and washings were concentrated to give **Ex.200** (0.87 g, 92%).

Data of **Ex.200**: C₂₆H₃₃N₅O₅ (495.6). LC-MS (method 1a): R_t = 1.15 (97), 496.2 ([M+H]⁺). ¹H-NMR (DMSO-d₆): two sets of signals were observed; 8.38 (br. s, 0.3 H); 8.33 (d, J = 4.2, 0.7 H), 7.75 – 7.41 (m, 7 H), 7.18 (br. s, 1 H); 4.20 – 4.13 (m, 2 H);
15 3.93 – 3.87 (t-like m, 2 H); 3.76 – 3.73 (d-like m, 1 H); 3.14 – 2.70 (several m, 4 H); 2.45 – 2.30 (m, 2 H), 2.01 (d, J = 15.9, 1 H), 1.85 (br. not resolved m, 1 H); 1.70 (d-like m, 1 H); 1.41, 1.37 (2 s, 9 H).

20 **Core 13 – 15: Synthesis of the common precursor 151** (Scheme 18)

Synthesis of the amide **149**

A soln of **98** (7.96 g, 33.4 mmol), **129**·HCl (7.19 g, 36.8 mmol) and BOP (16.3 g, 36.8 mmol) in DMF (120 mL) was cooled to 0°C. i-Pr₂NEt (22.7 mL, 134 mmol) was slowly added and stirring was continued for 30 min. Aqueous workup (EtOAc, aq. 1 M HCl
25 soln, sat. aq. NaHCO₃ soln, sat. aq. NaCl soln; Na₂SO₄) followed by FC (hexane/EtOAc 2:1) afforded **149** (10.8 g, 85%).

Data of **149**: C₁₈H₁₈FNO₅S (379.4). LC-MS (method 1a): R_t = 1.98 (90), 380.2 ([M+H]⁺)

30 Synthesis of the amine **151**

A suspension of phenol **149** (8.79 g, 23.2 mmol), alcohol **16** (8.35 g, 27.8 mmol) and PPh₃ (9.11 g, 34.8 mmol) in benzene (278 mL) was degassed and cooled to 0°C. DEAD (40% in toluene; 15.9 mL, 34.8 mmol) was added dropwise. The mixture was stirred at rt for 16 h and concentrated. The residue was suspended in Et₂O and
35 filtered. The filtrate was concentrated and purified by FC (hexane/EtOAc, Et₃N 66:33:1) to give **150** (15.4 g).

A degassed soln of **150** (15.4 g) and 1,3-dimethylbarbituric acid (5.45 g, 34.9 mmol) in CH₂Cl₂ (150 mL) and EtOAc (450 mL) was treated with Pd(PPh₃)₄ (0.67 g, 0.58 mmol) at rt for 1 h. Aqueous workup (EtOAc, sat.aq. NaHCO₃ soln, sat. aq. NaCl soln; Na₂SO₄) and FC (EtOAc, then CH₂Cl₂/MeOH 95:5) afforded **151** (8.18 g, 61%).

- 5 Data of **151**: C₂₈H₃₆FN₃O₇S (577.6). LC-MS (method 1a): R_t = 1.87 (96), 578.4 ([M+H]⁺)

Core 13: Synthesis of Ex.220 , Ex.221 and Ex.222 (Scheme 18)

10 Synthesis of amide **152**

At 0°C, acryloyl chloride (0.37 mL, 4.57 mmol) was slowly added to a soln of **151** (2.2 g, 3.81 mmol) and i-Pr₂NEt (0.78 mL, 4.57 mmol) in CH₂Cl₂ (33 mL). The mixture was stirred for 0.5 h followed by an aqueous workup (CH₂Cl₂, 0.1 M aq. HCl soln, sat. aq. NaHCO₃ soln, sat. aq. NaCl soln; Na₂SO₄) and FC (hexane/EtOAc 1:1 to 3:7) to afford **152** (2.21 g, 91%).

- 15 Data of **152**: C₃₁H₃₈FN₃O₈S (631.7). LC-MS (method 4a): R_t = 1.60 (94), 632.1 ([M+H]⁺)

Synthesis of **Ex.220**

- 20 The catalyst Umicore M72 SIMes (RD) (64 mg, 0.075 mmol) was added in one portion to a degassed solution of **152** (240 mg, 0.38 mmol) in toluene (380 mL) and heated to 100°C for 0.5 h. The mixture was cooled to rt. More Umicore M72 SIMes (RD) catalyst (64 mg) was added and the mixture was heated to 100°C for 30 min; this operation was repeated once again. 2-Mercaptonicotinic acid (59 mg, 0.38 mmol) was added and the heating to 100°C was continued for 1 h. The mixture was concentrated. Aqueous workup (EtOAc, sat. aq. NaHCO₃ soln; Na₂SO₄) and FC (hexane/EtOAc 50:50 to 0:100) followed by prep. HPLC (method 3) afforded **Ex.220** (42 mg, 18%).

- 25 Data of **Ex.220**: C₂₉H₃₄FN₃O₈S (603.6). LC-MS (method 1f): R_t = 2.18 (89), 604.0 ([M+H]⁺)
- 30

Synthesis of **Ex.221**

- A soln of **Ex.220** (0.49 g, 0.8 mmol) in MeOH (80 mL) was hydrogenated for 2 h at rt and normal pressure in the presence palladium hydroxide on activated charcoal (moistened with 50% H₂O; 304 mg). The mixture was filtered through a pad of
- 35

Na₂SO₄ and celite. The solid was washed with CH₂Cl₂/MeOH 1:1 (300 mL). The combined filtrate and washings were concentrated to give **Ex.221** (0.25 g, 51%).

Data of **Ex.221**: C₂₉H₃₆FN₃O₈S (605.7). LC-MS (method 2f): R_t = 2.43 (90), 606.2 ([M+H]⁺). ¹H-NMR (CDCl₃): 8.67 (d, J = 1.2, 1 H); 8.01 (s, 1 H); 7.69 (d, J = 1.2, 1 H); 7.52 (d, J = 8.5, 1 H); 6.98 (d, J = 8.7, 1 H); 6.55 (td, J = 2.2, 10.2, 1 H); 4.97 (td, J = 2.9, 8.7, 1 H); 4.82 (br. m, not resolved, 1 H); 4.69 (d-like m, 1 H); 4.61 (br. not resolved m, 1 H); 4.31 – 4.22 (m, 2 H); 4.04 – 3.90 (m, 3 H); 3.80 (s, 3 H); 3.74 (dd, J = 2.8, 10.8, 1 H); 3.65 (m, 1 H); 3.46 (m, 1 H); 2.53 – 2.41 (m, 3 H); 2.02 – 1.88 (m, 3 H); 1.48 (s, 9 H).

10

Synthesis of **Ex.222**

A soln of **Ex.221** (233 mg, 0.39 mmol) in dioxane (1 mL) was treated with 4 M HCl in dioxane (5 mL) for 2 h at rt. The volatiles were evaporated. The residue was suspended in Et₂O, filtered and dried i.v. to afford **Ex.222**·HCl (180 mg, 86%).

15 Data of **Ex.222**·HCl: C₂₄H₂₈FN₃O₆S (505.6, free base). LC-MS (method 1d): R_t = 1.55 (92), 506.2 ([M+H]⁺).

Core 14: Synthesis of **Ex.227**, **Ex.228** and **Ex.229** (Scheme 18)

20 Synthesis of amide **153**

At 0°C, i-Pr₂NEt (2.2 mL, 13.0 mmol) was added dropwise to a soln of **151** (2.5 g, 4.3 mmol), but-3-enoic acid (0.48 g, 5.6 mmol), HATU (2.47 g, 6.5 mmol) and HOAt (0.88 g, 6.5 mmol) in DMF (60 mL). The mixture was stirred for 1.5 h at 0°C followed by an aqueous workup (EtOAc, 1 M aq. HCl soln, sat. aq. NaHCO₃ soln, sat. aq. NaCl soln; Na₂SO₄) and FC (hexane/EtOAc 2:1 to 1:2) to give **153** (2.36 g, 84%).

25 Data of **153**: C₃₂H₄₀FN₃O₈S (645.7). LC-MS (method 4b): R_t = 1.67 (96), 646.2 ([M+H]⁺).

Synthesis of **Ex.227**

30 A solution of **153** (110 mg, 0.17 mmol) and the catalyst Umicore M72 SIMes (RD) (58 mg, 0.068 mmol) in CH₂Cl₂ (70 mL) was degassed and heated to reflux for 2 h. The mixture was allowed to cool to rt. 2-Mercaptonicotinic acid (106 mg, 0.68 mmol) was added. The mixture was heated to reflux for 1 h. The mixture was washed with sat. aq. NaHCO₃ soln. The organic phase was dried (Na₂SO₄), filtered and concentrated.

35 The crude product was purified by prep. HPLC (method 3) to afford **Ex.227** (56 mg, 53%).

Data of **Ex.227**: $C_{30}H_{36}FN_3O_8S$ (617.7). LC-MS (method 1d): $R_t = 2.32$ (87), 618.2 ($[M+H]^+$). ^1H -NMR (DMSO- d_6): 8.38 (s, 1 H), 8.27 – 8.24 (m, 2 H); 7.90 (s, 1 H); 7.28 – 7.18 (m, 2 H); 6.70 (td, $J = 2.1, 10.6$, 1 H); 5.97 (td, $J = 5.9, 15.8$, 1 H); 5.66 (td, $J = 4.6, 15.7$, 1 H); 4.75 – 4.63 (m, 2 H); 4.31 (br. not resolved m, 1 H); 4.06 – 3.67 (m, 7 H); 3.67 (s, 3 H); 3.24 (dd, $J = 6.4, 10.5$, 1 H); 3.11 (br. m, 2 H); 2.30 (m, 1 H); 1.92 (m, 1 H); 1.39 (s, 9 H).

Synthesis of **Ex.228**

Trimethyltin hydroxide (263 mg; 1.46 mmol) was added to a solution of **Ex.227** (300 mg, 0.49 mmol) in DCE (15 mL). The mixture was heated to 80°C for 16 h, followed by aqueous workup (CH_2Cl_2 , 1 M aq. HCl soln, sat. aq. NaCl soln; Na_2SO_4) to afford **Ex.228** (350 mg, containing tin salts). An analytical sample was purified by prep. RP-HPLC (method 2a) followed by aqueous extraction (CH_2Cl_2 , 1 M aq. HCl soln; Na_2SO_4) to give **Ex.228** (13 mg).

Data of **Ex.228**: $C_{29}H_{34}FN_3O_8S$ (603.6). LC-MS (method 1a): $R_t = 2.17$ (92), 604.0 ($[M+H]^+$).

Synthesis of **Ex.229**

A soln of **Ex.227** (287 mg, 0.46 mmol) in dioxane (5 mL) was treated with 4 M HCl in dioxane (5 mL) for 5 h at rt and concentrated. The residue was suspended in Et_2O and filtered to afford **Ex.229**-HCl (240 mg, 93%).

Data of **Ex.229**-HCl: $C_{25}H_{28}FN_3O_6S \cdot HCl$ (517.6, free base). LC-MS (method 1a): $R_t = 1.49$ (92), 518.1 ($[M+H]^+$). ^1H -NMR (DMSO- d_6): 8.38 (br. s, 4 H), 8.28 (s, 1 H); 8.22 (d, $J = 8.0$, 1 H); 7.82 (s, 1 H); 7.29 (d, $J = 9.4$, 1 H); 6.73 (d, $J = 10.6$, 1 H); 5.98 (td, $J = 6.0, 15.6$, 1 H); 5.69 (td, $J = 4.8, 15.8$, 1 H); 4.74 – 4.65 (m, 2 H); 4.39 (m, 1 H); 4.04 – 3.85 (m, 5 H); 3.85 – 3.65 (m, 2 H); 3.67 (s, 3 H); 3.44 (dd, $J = 7.1, 10.5$, 1 H); 3.14 (d, $J = 5.6, 2$ H), 2.50 (m, 1 H); 2.04 (m, 1 H).

30 **Core 15: Synthesis of Ex.242, Ex.243 and Ex.244** (Scheme 18)

Synthesis of **Ex.242**

A soln of **Ex.227** (1.5 g, 2.4 mmol) in MeOH (75 mL) was hydrogenated for 2.5 h at rt and normal pressure in the presence of 5% palladium on activated charcoal (moistened with 50% H_2O ; 300 mg). The mixture was filtered through a pad of celite.
The solid was washed with MeOH. The combined filtrate and washings were concentrated. FC (hexane/EtOAc 1:2) gave **Ex.242** (1.37 g, 91%).

Data of **Ex.242**: $C_{30}H_{38}FN_3O_8S$ (619.7). LC-MS (method 1a): $R_t = 2.47$ (92), 620.0 ($[M+H]^+$). ^1H -NMR (DMSO- d_6): 8.51 (d, $J = 1.1$, 1 H); 8.29 (d, $J = 1.1$, 1 H); 8.07 (d, $J = 7.9$, 1 H); 7.95 (s, 1 H); 7.30 – 7.26 (m, 2 H), 6.70 (td, $J = 2.1$, 10.5, 1 H); 4.70 (m, 1 H); 4.60 (br. dd, 1 H); 4.29 (br. not resolved m, 1 H); 4.04 – 3.67 (m, 5 H); 3.67 (s, 3 H); 3.48 (br. not resolved m, 2 H); 3.28 (m, 1 H); 2.38 – 2.23 (m, 3 H); 1.91 (m, 1 H), 1.77 (m, 1 H); 1.68 – 1.51 (m, 3 H); 1.39 (s, 9 H).

Synthesis of **Ex.243**

Trimethyltin hydroxide (175 mg; 0.97 mmol) was added to a solution of **Ex.242** (200 mg, 0.32 mmol) in DCE (10 mL). The mixture was heated to 80°C for 16 h, followed by aqueous workup (CH_2Cl_2 , 1 M aq. HCl soln, sat. aq. NaCl soln; Na_2SO_4) to afford **Ex.243** (236 mg, containing tin salts). An analytical sample was purified by prep. RP-HPLC (method 2a) followed by aqueous extraction (CH_2Cl_2 , 1 M aq. HCl soln; Na_2SO_4) to give **Ex.243** (14 mg).

Data of **Ex.243**: $C_{29}H_{36}FN_3O_8S$ (605.7). LC-MS (method 1a): $R_t = 2.27$ (97), 606.2 ($[M+H]^+$).

Synthesis of **Ex.244**

A soln of **Ex.242** (265 mg, 0.43 mmol) in dioxane (5 mL) was treated with 4 M HCl in dioxane (5 mL) for 6 h at rt and concentrated. The residue was taken up in $CHCl_3$ and concentrated to afford **Ex.244**·HCl (205 mg, 86%).

Data of **Ex.244**·HCl: $C_{25}H_{30}FN_3O_6S \cdot HCl$ (519.6, free base). LC-MS (method 1d): $R_t = 1.55$ (92), 520.0 ($[M+H]^+$). ^1H -NMR (DMSO- d_6): 8.48 (s, 1 H); 8.40 – 8.25 (br. s, 4 H); 8.05 (d, $J = 7.9$, 1 H); 7.86 (s, 1 H); 7.31 (d, $J = 8.8$, 1 H); 6.73 (d, $J = 10.6$, 1 H); 4.72 – 4.61 (m, 2 H); ca 4.4 – 4.3 (br. m, 2 H); 4.00 – 3.68 (m, 5 H); 3.68 (s, 3 H); 3.49 – 3.43 (m, not resolved, 2 H), ca 2.5 (m, superimposed by DMSO- d signal, 1 H); 2.40 – 2.25 (m, 2 H), 2.02 (m, 1 H); 1.79 – 1.52 (m, 4 H).

Core 15: Synthesis of selected advanced intermediates and final products

(Scheme 18)

Synthesis of **Ex.246**

At 0°C, i -Pr $_2$ NEt (0.054 mL, 0.32 mmol) was added to a soln of **Ex.243** (ca. 70% w/w; 55 mg, 0.064 mmol), HATU (36 mg, 0.095 mmol), HOAt (13 mg, 0.095 mmol) and aniline (0.029 mL, 0.32 mmol) in CH_2Cl_2 (1.5 mL) and DMF (0.5 mL). The mixture was stirred for 30 min followed by an aqueous workup (CH_2Cl_2 , 1 M aq. HCl soln, sat.

aq. NaHCO_3 soln, sat. aq. NaCl soln; Na_2SO_4) and FC (hexane/EtOAc 2:1 to 1.1) to afford **Ex.246** (27 mg, 62%).

Data of **Ex.246**: cf. Table 27b

5 Synthesis of **Ex.247**

At 0°C , 4 M HCl in dioxane (0.20 mL) was added to a soln of **Ex.246** (25 mg, 0.037 mmol) in dioxane (0.6 mL). The mixture was stirred for 5 h at 0°C to rt. More 4 M HCl in dioxane (0.15 mL) was added and the mixture was stirred at rt for 16 h. The volatiles were evaporated. The residue was treated with TFA (0.15 mL) in CH_2Cl_2 (0.75 mL) for 1 h at 0°C , followed by evaporation of the solvents, aqueous workup (EtOAc, sat.aq. Na_2CO_3 soln; Na_2SO_4) and FC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 100:0 to 90:10). The purified product (13 mg) was dissolved in dioxane (0.3 mL) and treated with 4 M HCl in dioxane (0.05 mL). The volatiles were evaporated to give **Ex.247**· HCl (14 mg, 60%).

15 Data of **Ex.247**· HCl : cf. Table 27b

^1H -NMR (DMSO-d_6): 10.18 (s, 1 H); 8.48 (s, 1 H); 8.30 (s, 1 H); 8.15 (d, $J = 7.1$, 1 H); 8.15 (br. s, 3 H); 7.85 (s, 1 H); 7.59 (d, $J = 7.7$, 2 H); 7.36 – 7.27 (m, 3 H); 7.06 (t, $J = 7.4$, 1 H); 6.74 (dt-like m, 1 H); 4.73 – 4.63 (m, 2 H); 4.40 (br. not resolved m, 1 H); 4.01 – 3.59 (m, 5 H); 3.50 – 3.41 (m, 3 H); 2.36 (br. t-like m, 2 H); 2.04 (m, 1 H); 1.90 – 1.45 (several not resolved m, 5 H).

Synthesis of **Ex.256**

Ex.256 (8 mg, 14%) was obtained from **Ex.243** (ca. 70% w/w; 65 mg, 0.075 mmol) and 4-chloroaniline (48 mg, 0.38 mmol) by applying the method described for the synthesis of **Ex.246**.

Data of **Ex.256**: cf. Table 27b

Synthesis of **Ex.257**

Ex.257· HCl (4 mg, 66%) was obtained from **Ex.256** (7 mg, 0.01 mmol) by applying the method described for the synthesis of **Ex.247**· HCl .

Data of **Ex.257**· HCl : cf. Table 27b

Synthesis of **Ex.258**

Ex.258 (19 mg, 43%) was obtained from **Ex.243** (ca. 70% w/w; 55 mg, 0.064 mmol) and m-toluidine (0.034 mL, 0.32 mmol) by applying the method described for the synthesis of **Ex.246**.

Data of **Ex.258**: cf. Table 27b

Synthesis of **Ex.259**

Ex.259-HCl (10 mg, 66%) was obtained from **Ex.258** (17 mg, 0.024 mmol) by
5 applying the method described for the synthesis of **Ex.247**-HCl.

Data of **Ex.259**-HCl: cf. Table 27b

¹H-NMR (DMSO-d₆): 10.07 (s, 1 H); 8.47 (s, 1 H); 8.30 (s, 1 H); 8.12 (d, J = 7.6, 1 H);
8.12 (br. s, 3 H); 7.85 (s, 1 H); 7.42 – 7.30 (m, 3 H), 7.18 (t, J = 7.4, 1 H); 6.88 (d, J ca
7.6, 1 H); 6.74 (d, J = 10.3, 1 H); 4.78 – 4.60 (m, 2 H); 4.40 (br. not resolved m, 1 H);
10 4.05 – 3.65 (m, 5 H); 3.51 – 3.40 (m, 3 H); 2.37 (br. t-like m, 2 H); 2.27 (s, 3 H); 2.01
(m, 1 H); 1.90 – 1.45 (several not resolved m, 5 H).

Core 16: Synthesis of Ex.262, Ex.263 and Ex.264 (Scheme 19)

15 Synthesis of the Mitsunobu product **154**

CMBP (8.5 mL, 32 mmol) was added to a soln of hydroxythiophene **106** (5.69 g, 20
mmol) and alcohol **118** (9.8 g, 26 mmol) in toluene (77 mL). The mixture was heated
to reflux for 2 h and concentrated. FC (hexane/EtOAc 90:10 to 20:80) gave **154**
(12.68 g, 98%).

20 Data of **154**: C₂₉H₃₄BrN₃O₆S (632.6). LC-MS (method 4a): R_t = 2.29 (93), 634.3/632.3
([M+H]⁺).

Synthesis of the amino acid **157**

A soln of **154** (12.6 g, 20 mmol) in CH₂Cl₂ (128 mL) was treated with TFA (148 mL)
25 and heated to reflux for 3 h. The volatiles were evaporated. The residue was
suspended in toluene, concentrated and dried i.v. to give crude **155** (16.15 g,
containing residual solvent), which was used without further purification.

At 0°C, i-Pr₂NEt (6.85 mL, 40.3 mmol) was added to a soln of crude carboxylic acid
155 (9.27 g, ca 11.5 mmol), amine **130**-HCl (5.52 g, 16.1 mmol), HATU (7.66 g, 20.1
30 mmol) and HOAt (2.74 g, 20.1 mmol) in DMF (170 mL). The mixture was stirred at rt
for 2 h, followed by an aqueous workup (EtOAc, 1 M aq. HCl soln, sat. aq. NaHCO₃
soln; Na₂SO₄) and FC (CH₂Cl₂/MeOH 100:0 to 95:5) to afford **156** (11.7 g; containing
residual DMF), used without further purification.

A degassed solution of **156** (11.6 g) and 1,3-dimethylbarbituric acid (6.3 g, 40 mmol)
35 in CH₂Cl₂ (39 mL) and EtOAc (78 mL) was treated with Pd(PPh₃)₄ (1.6 g, 1.3 mmol)

at rt for 4 h. The volatiles were evaporated. FC (EtOAc, then CH₂Cl₂/MeOH 100:0 to 80:20) afforded **157** (7.6 g, 89% over the three steps).

Data of **157**: C₃₄H₃₈BrN₅O₇S (740.6). LC-MS (method 1a): R_t = 1.91 (87), 740.1/742.1 ([M+H]⁺).

5

Synthesis of Ex.262

A soln of **157** (1.9 g, 2.57 mmol) in CH₂Cl₂ (40 mL) was added dropwise over 2 h (syringe pump) to a soln of T3P (50% in EtOAc, 7.56 mL, 12.8 mmol) and i-Pr₂NEt (1.96 mL, 11.5 mmol) in CH₂Cl₂ (1190 mL). Stirring at rt was continued for 4 h. The volatiles were evaporated. Aqueous workup (CH₂Cl₂, sat. aq. NaHCO₃ soln.; Na₂SO₄) and FC (hexane/EtOAc 50:50 to 0:100) afforded **Ex.262** (1.63 g, 88%).

Data of **Ex.262**: C₃₄H₃₆BrN₅O₆S (722.6). LC-MS (method 1d): R_t = 2.52 (99), 722.0/724.0 ([M+H]⁺). ¹H-NMR (DMSO-d₆): 7.65 (d, J = 6.8, 1 H); 7.49 (d, J = 8.0, 2 H); 7.41 – 7.26 (m, 8 H); 7.08 (d, J = 5.4, 1 H); 6.64 (s, 1 H); 5.06 (s, 2 H); ca 4.5 – 4.4 (br. m, 2 H); 4.48 (s, 2 H); 4.32 (br. d, J ca 8.8, 1 H); 4.16 (br. m, 2 H); 4.01 (m, 1 H); 3.86 (s, 3 H); 3.69 (br. m, 1 H); 3.46– 3.32 (m, 2 H); 2.96 (s, 3 H); 2.40 – 2.25 (br. m, 2 H), 2.10 – 1.90 (br. m, 2 H).

20 Synthesis of Ex.263

At 0°C, BCl₃ (16 mL, 16 mmol) was added dropwise to a soln of **Ex.262** (2.34 g, 3.2 mmol) in CH₂Cl₂ (83 mL). The mixture was allowed to stir at 0°C to rt for 16 h. The mixture was cooled to 0°C and poured slowly into MeOH. The mixture was concentrated. Aqueous workup (CH₂Cl₂, sat. aq. NaHCO₃ soln; Na₂SO₄) afforded **Ex.263** (1.21 g, 89%).

Data of **Ex.263**: C₁₉H₂₅N₅O₄S (419.5). LC-MS (method 1d): R_t = 1.11 (98), 420.0 ([M+H]⁺). ¹H-NMR (DMSO-d₆): 7.40 (d, J = 5.5, 1 H); 7.08 (d, J = 5.5, 1 H); 6.63 (s, 1 H); 5.17 (d, J = 5.1, 1 H); 4.35 – 4.29 (m, 2 H); 4.24 (dd, J = 6.6, 11.9, 1 H); 4.12 – 3.97 (m, 3 H); 3.85 (s, 3 H); 3.68 (d, J = 7.4, 1 H); 3.61 (m, 1 H); 3.17 (dd, J = 6.6, 10.2, 1 H); 2.97 (s, 3 H); 2.28 – 2.19 (m, 2 H); 1.95 (m, 1 H), 1.90 – 1.75 (br. not resolved m, 3 H).

Synthesis of Ex.264

At rt, TBAF (1 M in THF; 0.119 mL, 0.119 mmol) was slowly added to a soln of **Ex.262** (160 mg, 0.221 mmol) in THF (2.5 mL). The mixture was heated to reflux for 2 h, filtered through a pad of celite and concentrated. Aqueous workup (CH₂Cl₂, sat. aq.

35

NaHCO₃ soln; Na₂SO₄) and FC (CH₂Cl₂/MeOH 85:15) afforded a white solid (100 mg) was dissolved in DMF (4.0 mL) and hydrogenated for 2 h at rt and normal pressure in the presence of palladium hydroxide on activated charcoal (moistened with 50% H₂O; 23 mg). The volatiles were evaporated. The crude product was purified by FC (CH₂Cl₂/MeOH 100:0 to 80:20) to give **Ex.264** (45 mg, 40%).

Data of **Ex.264**: C₂₆H₃₁N₅O₄S (509.6). LC-MS (method 1a): R_t = 1.62 (99), 510.1 ([M+H]⁺). ¹H-NMR (DMSO-d₆): 7.40 (d, J = 5.5, 1 H); 7.33 – 7.27 (m, 5 H); 7.08 (d, J = 5.5, 1 H); 6.65 (s, 1 H); 4.53 (s, 2 H); 4.41 – 4.17 (m, 5 H); 3.98 (dd, J = 5.1, 9.4, 1 H); 3.85 (s, 3 H); 3.72 (d, J = 7.0, 1 H); 3.61 (m, 1 H); ca 3.3 (m, superimposed by H₂O signal, 1 H); 2.97 (s, 3 H); 2.40 – 1.80 (several br. m, 6 H).

Core 16: Synthesis of selected advanced intermediates and final products

(Scheme 19)

Synthesis of **Ex.265**

At 0°C, oxalyl chloride (0.104 mL, 1.19 mmol) and one drop of DMF were added to a soln of 2-naphthaleneacetic acid (53 mg, 0.29 mmol) in CH₂Cl₂ (6 mL). The mixture was stirred at rt for 1 h and concentrated. The residue was dissolved in CH₂Cl₂ (2.5 mL) and added dropwise to a soln of **Ex.263** (100 mg, 0.24 mmol) and i-Pr₂NEt (0.204 mL, 1.19 mmol) in CH₂Cl₂ (3.5 mL). The mixture was stirred at 0°C for 1 h followed by an aqueous workup (CH₂Cl₂, sat. aq. NaHCO₃ soln; Na₂SO₄) and FC (CH₂Cl₂/i-PrOH 100:0 to 95:5) to yield **Ex.265** (110 mg, 78%).

Data of **Ex.265**: cf. Table 28b

¹H-NMR (DMSO-d₆): 8.54 (d, J = 7.5, 1 H); 7.89 – 7.85 (m, 3 H); 7.78 (s, 1 H); 7.52 – 7.44 (m, 3 H); 7.40 (d, J = 5.5, 1 H); 7.09 (d, J = 5.5, 1 H); 6.44 (s, 1 H); 5.14 (d, J = 4.9, 1 H); 4.65 (br. t, J = 8.0, 1 H); 4.40 – 4.31 (m, 2 H); 4.11 (q, J ca 5.8, 1 H); 4.03 (m, 1 H); 3.84 (m, 1 H); 3.84 (s, 3 H); 3.68 (s, 2 H); 3.64 (m, 1 H); ca 3.30 (m, 1 H, partially superimposed by H₂O signal); 3.17 (dd, J = 6.3, 10.5, 1 H); 2.91 (s, 3 H); 2.35 (m, 1 H); 2.18 (m, 1 H); 1.91 – 1.82 (m, 2 H).

Synthesis of **Ex.275**

Trimethyloxonium tetrafluoroborate (15 mg, 0.10 mmol) was added at 0°C to a solution of **Ex.265** (40 mg, 0.068 mmol) and N,N,N',N'-tetramethyl-1,8-naphthalenediamine (22 mg, 0.102 mmol) in CH₂Cl₂ (1.0 mL). The mixture was stirred at 0°C to rt for 4.5 h. More N,N,N',N'-tetramethyl-1,8-naphthalenediamine (32 mg, 0.15 mmol) and trimethyloxonium tetrafluoroborate (22 mg, 0.15 mmol) were added at 0°C and stirring was continued at rt for 16 h. Aqueous workup (CH₂Cl₂, 2 M

aq. HCl soln; Na₂SO₄). The residue was suspended in CH₂Cl₂ and filtered. The filtrate was purified by FC (EtOAc/MeOH 100:0 to 97:3) and by prep. RP-HPLC (method 1a) to afford **Ex.275** (5 mg, 12%).

Data of **Ex.275**: cf. Table 28b

- 5 ¹H-NMR (DMSO-d₆): 8.57 (d, J = 7.5, 1 H); 7.90 – 7.85 (m, 3 H); 7.80 (s, 1 H); 7.54 – 7.45 (m, 3 H); 7.39 (d, J = 5.5, 1 H); 7.07 (d, J = 5.5, 1 H); 6.62 (s, 1 H); 4.65 (br. t, J = 7.8, 1 H); 4.40 (br. not resolved m, 1 H); 4.29 (dd; J = 2.7, 9.5, 1 H); 3.96 – 3.83 (m, 2 H); 3.83 (s, 3 H); 3.75 – 3.60 (m, 2 H); 3.67 (s, 2 H); ca 3.3 – 3.2 (m, 2 H, partially superimposed by H₂O signal); 3.05 (s, 3 H); 2.92 (s, 3 H); 2.36 (m, 1 H); 2.16 (m, 1 H); 1.96 – 1.83 (m, 2 H).
- 10

Synthesis of **Ex.276**

- At 0°C, i-Pr₂NEt (0.061 mL, 0.36 mmol) and 2-naphthylisocyanate (22 mg, 0.131 mmol) were added to a soln of **Ex.263** (50 mg, 0.12 mmol) in CH₂Cl₂ (1.0 mL). The mixture was stirred at 0°C to rt for 60 min. Aqueous workup (CHCl₃, sat. aq. Na₂CO₃ soln; Na₂SO₄) and purification by prep. HPLC (method 3) afforded **Ex.276** (50 mg, 71%).
- 15

Data of **Ex.276**: cf. Table 28b

- ¹H-NMR (DMSO-d₆): 9.00 (s, 1 H) 8.05 (d, J = 1.8, 1 H); 7.81 – 7.74 (m, 3 H); 7.45 – 7.40 (m, 3 H); 7.32 (dt, J = 1.2, 7.5, 1 H); 7.11 (d, J = 5.5, 1 H); 6.74 (d, J = 7.3, 1 H); 6.68 (s, 1 H); 5.24 (d, J = 5.0, 1 H); 4.77 (br. t, J = 7.1, 1 H); 4.38 – 4.32 (m, 2 H); 4.29 (q-like m, 1 H); 4.07 – 4.00 (m, 2 H), 3.88 (s, 3 H); 3.85 (m, 1H); ca 3.30 – 3.20 (m, 2 H, partially superimposed by H₂O signal); 2.98 (s, 3 H); ca 2.5 (m, 1 H, superimposed by DMSO-d signal); 2.27 (m, 1 H); 2.00 – 1.92 (m, 2 H).
- 20
- 25

Core 17: Synthesis of **Ex.284a**, **Ex.285** and **Ex.286** (Scheme 20)

Synthesis of amide **158**

- A suspension of **110**·HCl (6.2 g, 19.9 mmol) in CH₂Cl₂ (310 mL) was cooled to 0°C. Oxalyl chloride (5.1 mL, 59.7 mmol) was added followed by DMF (0.37 mL). The mixture was stirred for 1.5 h at rt and concentrated. The residue was suspended in CH₂Cl₂ and concentrated; this operation was repeated once and the residue was then dried i.v. The residue was suspended in CH₂Cl₂ (180 mL). A soln of **131**·HCl (8.86 g, 23.9 mmol) in CH₂Cl₂ (120 mL) was added. The mixture was cooled to 0°C followed by the slow addn of i-Pr₂NEt (17.0 mL, 99.5 mmol). The mixture was stirred for 1 h at
- 30
- 35

0°C. Aqueous workup (CH₂Cl₂, 1 M aq. HCl soln, sat. aq. NaHCO₃ soln; Na₂SO₄) and FC (hexane/EtOAc gradient) gave **158** (8.1 g, 69%).

Data of **158**: C₃₀H₃₃N₅O₈ (591.6). LC-MS (method 1a): R_t = 2.43 (94), 592.1 ([M+H]⁺).

5 Synthesis of the Mitsunobu product **159**

A soln of CMBP (6.58 g, 27.3 mmol) in toluene (30 mL) was added to a soln of phenol **158** (8.07 g, 13.6 mmol) and alcohol **120** (3.28 g, 17.7 mmol) in toluene (131 mL). The mixture was heated to reflux for 1 h and concentrated. FC (hexane/EtOAc 50:50 to 0:100) yielded **159** (7.9 g, 76%).

10 Data of **159**: C₃₉H₄₆N₆O₁₀ (758.8). LC-MS (method 4a): R_t = 1.91 (90), 759.2 ([M+H]⁺).

Synthesis of the amino acid **160**

A degassed solution of **159** (8.9 g, 11.8 mmol) and 1,3-dimethylbarbituric acid (4.4 g, 28.3 mmol) in CH₂Cl₂ (180 mL) and EtOAc (45 mL) was treated with Pd(PPh₃)₄ (1.36 g, 1.18 mmol) at rt for 2 h. The volatiles were evaporated. FC (EtOAc, then CH₂Cl₂/MeOH 100:0 to 40:60) afforded **160** (7.33 g, 98%; containing some impurities; used without further purification).

Data of **160**: C₃₂H₃₈N₆O₈ (634.7). LC-MS (method 1a): R_t = 1.65 (88), 635.2 ([M+H]⁺).

20 Synthesis of **Ex.284a** and **Ex.284b**

A soln of **160** (500 mg, 0.79 mmol) in pyridine (40 mL) was added dropwise over 2 h (syringe pump) to a soln of HATU (900 mg, 2.36 mmol) and HOAt (322 mg, 2.36 mmol) in pyridine (1500 mL). An additional portion of HATU (900 mg, 2.36 mmol) and HOAt (322 mg, 2.36 mmol) was added to the solution. Again a soln of **160** (500 mg, 0.79 mmol) in pyridine (40 mL) was added dropwise over 2 h (syringe pump).

The volatiles were evaporated. Aqueous workup (CH₂Cl₂, sat. aq. NaHCO₃ soln, H₂O, Na₂SO₄). Purification by preparative HPLC (method 1d) afforded **Ex.284a**·CF₃CO₂H (480 mg) and **Ex.284b**·CF₃CO₂H (186 mg, 16%).

Ex.284a·CF₃CO₂H (480 mg) was dissolved in CH₂Cl₂ and washed with sat. aq. NaHCO₃ soln. The organic phase was dried (Na₂SO₄), filtered and concentrated to afford **Ex.284a** (442 mg, 45%).

Data of **Ex.284a**: C₃₂H₃₆N₆O₇ (616.6). LC-MS (method 1d): R_t = 2.24 (99), 617.2 ([M+H]⁺). ¹H-NMR (DMSO-d₆): 8.66 (d, J = 2.1, 1 H); 8.40 (dd, J = 2.1, 8.9, 1 H); 7.53 – 7.49 (m, 2 H); 7.36 – 7.26 (m, 6 H); 5.06 (br. d, J = 12.6, 1 H); 4.92 (s, 2 H); 4.37 (br. dd, J ca 2.6, 13.0, 1 H); 4.15 (t-like m, 1 H); 3.65 (br. t, J ca 8.7, 1 H); 3.55 (q-like

m, 1 H); 3.27 (m, 1 H); 3.01 (s, 3 H); 2.95 – 2.82 (m, 2 H), 2.61 (s, 3 H); 1.97 – 1.68 (several m, 6 H), 1.23 – 0.90 (br. m, 4 H).

Data of **Ex.284b**-CF₃CO₂H: C₃₂H₃₆N₆O₇-CF₃CO₂H (free base 616.6). LC-MS (method 1d): R_t = 2.14 (99), 617.2 ([M+H]⁺).

5

Synthesis of **Ex.285**

A soln of **Ex.284a** (380 mg, 0.62 mmol) in THF (19 mL) was treated with TBAF (1 M in THF; 0.6 mL, 0.6 mmol) at 75°C for 7 h. The mixture was cooled to rt and TBAF (1 M in THF; 0.3 mL, 0.3 mmol) was added. Stirring at 75°C was continued for 8 h. The volatiles were evaporated. FC (CH₂Cl₂/MeOH 95:5 to 90:10) afforded **Ex.285** (182 mg, ca 60%; containing ca 5% of tetrabutylammonium salts). An analytical sample (15 mg) was further purified by preparative HPLC (method 2a) to afford **Ex.285** (9 mg).

15 Data of **Ex.285**: C₂₄H₃₀N₆O₅ (482.5). LC-MS (method 1d): R_t = 1.47 (95), 483.2 ([M+H]⁺). ¹H-NMR (DMSO-d₆): 8.66 (d, J = 2.2, 1 H); 8.41 (dd, J = 2.2, 9.0, 1 H); 7.51 (s, 1 H); 7.47 (d, J = 9.1, 1 H); 5.17 (d, J = 12.5, 1 H); 4.30 (dd, J = 2.3, 12.7, 1 H); 4.14 (t, J = 7.0, 1 H); 3.51 (m, 1 H); ca. 3.2 (m, 1 H), 3.02 (s, 3 H); 2.97 (m, 1 H); 2.81 – 2.68 (m, 2 H); 2.61 (s, 3 H); 2.0 – 1.7 (several m, 8 H); 1.4 – 0.6 (several m, 4 H).

20

Synthesis of **Ex.286**

A soln. of **Ex.284a** (1.2 g, 1.95 mmol) in MeOH (120 mL) was hydrogenated in the presence of platinum (IV) oxide hydrate (120 mg) for 8 h at rt and normal pressure. More platinum (IV) oxide hydrate (60 mg) was added and the hydrogenation was continued for 6 h. The mixture was filtered through a pad of celite. The solid was washed (MeOH). The combined filtrate and washings were concentrated. FC (hexane/EtOAc 50:50:0 to 0:100 then CH₂Cl₂/MeOH 90:10) yielded **Ex.286** (0.75 g, 66%).

30 Data of **Ex.286**: C₃₂H₃₈N₆O₅ (586.7). LC-MS (method 1d): R_t = 1.68 (90), 587.2 ([M+H]⁺). ¹H-NMR (DMSO-d₆): 7.67 (d, J = 2.0, 1 H); 7.48 – 7.43 (m, 2 H); 7.39 – 7.27 (m, 6 H); 6.87 (d, J = 8.6, 1 H); 5.06 – 4.93 (m, 5 H); 4.11 (br. m, not resolved, 1 H); 4.00 (br. d, J ca 11.7, 1 H); 3.60 (br. t, J ca. 8.4, 1 H); 3.49 (q-like m, 1 H); 3.15 (m, 1 H), 2.99 (s, 3 H); 2.96 (m, 1 H); 2.78 (m, 1 H); 2.54 (s, 3 H); 2.21 (m, 1 H); 2.15 – 1.15 (several br. m, 8 H); 0.66 (br. m, 1 H).

35

Core 18: Synthesis of Ex.305 and Ex.306 (Scheme 21)Synthesis of the Mitsunobu product **161**

DEAD (40% in toluene; 11.1 mL, 24.3 mmol) was slowly added to a soln of alcohol **122** (5.66 g, 16.2 mmol), 2-iodophenol (**111**; 5.33 g, 24.3 mmol) and PPh₃ (6.36 g, 24.3 mmol) in toluene (345 mL). The mixture was stirred at rt for 4 h. The volatiles were evaporated. FC (hexane/EtOAc gradient) afforded **161** (6.85 g, 77%).

Data of **161**: C₂₄H₂₉IN₂O₅ (552.4). LC-MS (method 1a): R_t = 2.71 (99), 553.2 ([M+H]⁺). ¹H-NMR (DMSO-d₆): 7.76 (d, J = 7.7, 1 H); 7.60 (d, J = 6.5, 1 H); 7.40 – 7.28 (m, 6 H); 7.02 (d, J = 8.2, 1 H); 6.76 (t, J = 7.5, 1 H); 5.03 (s, 2 H); 4.33 (br. m, 1 H); 4.17 – 4.07 (br. m, 3 H); 3.59 (br. m, 1 H); 3.29 (br. m, 1 H); 2.26 (br. m, 1 H); 2.02 (br. m, 1 H); 1.38 (s, 9 H).

Synthesis of the biphenyl **162**

Pd(dppf)Cl₂·CH₂Cl₂ (1.0 g, 1.2 mmol) was added to a mixture of **161** (6.8 g, 12.3 mmol), ethyl 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (**113**; 3.0 g, 10.8 mmol), 2-(ethoxycarbonyl)phenylboronic acid (**112**; 2.3 g, 11.8 mmol) in DME (325 mL), EtOH (32 mL) and 1 M aq. Na₂CO₃ soln (37 mL). The mixture was heated to 80°C for 3 h. The mixture was diluted with sat. aq. NaHCO₃ soln and repeatedly extracted with CH₂Cl₂. The combined organic layer was dried (Na₂SO₄), filtered and concentrated. FC (hexane/EtOAc gradient) gave **162** (6.6 g, 94%).

Data of **162**: C₃₃H₃₈N₂O₇ (574.6). LC-MS (method 4c): R_t = 2.48 (96), 575.4 ([M+H]⁺). ¹H-NMR (DMSO-d₆): 7.80 (d, J = 7.5, 1 H); 7.58 (t, J = 7.3, 1 H); 7.46 – 7.25 (m, 9 H); 7.12 (m, 1 H); 7.03 – 7.00 (m, 2 H); 4.99 (s, 2 H); 3.99 – 3.83 (br. m, 6 H); 3.78 (br. not resolved m, 1 H); 3.01 (br. not resolved m, 1 H); 1.81 (br. not resolved m, 1 H); 1.72 (br. not resolved m, 1 H); 1.33 (s, 9 H); 0.88 (br. t, 3 H).

Synthesis of the carboxylic acid **164**

A soln of **162** (5.2 g, 9.1 mmol) in EtOH (50 mL) was hydrogenated for 3 h at rt and normal pressure in the presence of palladium hydroxide on activated charcoal (moistened with 50% H₂O; 0.5 g). The mixture was filtered through a pad of celite. The residue was washed with EtOH. The combined filtrate and washings were concentrated to give crude **163** (4.0 g) which was dissolved in EtOH (84 mL). KOH (10.2 g, 182 mmol) dissolved in H₂O (28 mL) was added and the mixture was stirred at 45°C for 18 h. The solution was cooled to rt. NaHCO₃ (15.2 g, 182 mmol) and CH₂Cl₂ (100 mL) followed by CbzOSu (2.7 g, 10.8 mmol) were successively added and the mixture was allowed to stir for 3 h. The mixture was acidified by addn of 3 M

aq. HCl soln and extracted with CH₂Cl₂. The organic layer was dried (Na₂SO₄), filtered and concentrated. FC (EtOAc) afforded **164** (4.87 g, 98%)

Data of **164**: C₃₁H₃₄N₂O₇ (546.6). LC-MS (method 1c): R_t = 2.44 (88), 547.1 ([M+H]⁺).

5 Synthesis of the amide **165**

EDC-HCl (3.4 g, 17.8 mmol) was added to a soln of **164** (4.8 g, 8.9 mmol) and sarcosine tert.-butylester hydrochloride (**132**; 3.2 g, 17.8 mmol) in pyridine (150 mL). The mixture was stirred at rt for 3 h. Aqueous workup (CH₂Cl₂, aq. 2 M HCl soln, sat. aq. NaHCO₃ soln; Na₂SO₄) and FC (hexane/EtOAc gradient) afforded **165** (4.9 g, 82%).

Data of **165**: C₃₈H₄₇N₃O₈ (673.8). LC-MS (method 1a): R_t = 2.71 (97), 674.2 ([M+H]⁺).

Synthesis of Ex.305

A soln of **165** (4.9 g, 7.3 mmol) in CH₂Cl₂ (50 mL) was treated with TFA (25 mL) for 4 h at rt. Evaporation of the volatiles afforded the crude amino acid **166**·CF₃CO₂H (5.3 g, containing residual solvent) which was used without further purification.

The ring closing reaction was performed in four batches:

A soln of crude **166**·CF₃CO₂H (1.3 g) and i-Pr₂NEt (1.5 mL, 8.7 mmol) in CH₂Cl₂ (40 mL) was added dropwise over 2 h (syringe pump) to a soln of T3P (50% in EtOAc, 2.2 mL, 3.7 mmol) in CH₂Cl₂ (1200 mL). The mixture was stirred for 1 h at rt and concentrated.

The four batches were combined and purified by FC (hexane/EtOAc/MeOH gradient) to give Ex.305 (3.7 g, quant. yield).

Data of Ex.305: C₂₉H₂₉N₃O₅ (499.5). LC-MS (method 1a): R_t = 2.00 (98), 500.1 ([M+H]⁺). ¹H-NMR (CD₃OD): Two sets of signals were observed; ratio 7:3; 7.48 – 7.21 (m, 11 H), 7.12 – 6.96 (m, 1.3 H); 6.91 (t, J = 7.5, 0.7 H); 5.10 – 5.04 (m, 2 H); 4.72 (dd, J = 4.2, 9.7, 0.7 H); 4.40 – 4.28 (m, 1.3 H); 4.16 – 4.06 (m, 1.6 H); 4.03 (dt, J = 4.0, 7.8, 0.7 H); 3.93 (br. not resolved m, 0.7 H); 3.78 (d, J = 14.6, 0.3 H); 3.69 (br. d, 0.7 H); 3.59 – 3.50 (m, 1.3 H); 3.10, 3.07 (2 s, 3 H); 2.99 (br. d, J ca 10.0, 0.7 H); 2.10 – 1.93 (m, 2 H).

Synthesis of Ex.306

A soln of Ex.305 (3.68 g, 7.3 mmol) in MeOH (50 mL) was hydrogenated for 4 h at rt and normal pressure in the presence of palladium hydroxide on activated charcoal (moistened with 50% H₂O; 0.38 g). The mixture was filtered through a pad of celite.

The residue was washed (MeOH). The combined filtrate and washings were concentrated. FC (hexane/EtOAc/MeOH gradient) afforded **Ex.306** (2.4 g, 89%).

Data of **Ex.306**: $C_{21}H_{23}N_3O_3$ (365.4). LC-MS (method 1a): $R_t = 1.17$ (96), 366.0 ($[M+H]^+$).

5

Core 19: Synthesis of **Ex.327**, **Ex.328** and **Ex.329** (Scheme 22)

Synthesis of the amide **167**

At 0°C, *i*-Pr₂NEt (4.5 mL, 26.3 mmol) was added dropwise to a soln of **117** (1.2 g, 4.4 mmol), **125**-HCl (1.73 g, 5.2 mmol), HATU (1.67 g, 4.4 mmol) and HOAt (0.60 g, 4.4 mmol) in DMF (30 mL) and THF (45 mL). The mixture was stirred at rt for 1.5 h. Aqueous workup (EtOAc, 0.1 M aq. HCl soln, sat. aq. NaCl soln; Na₂SO₄) and FC (hexane/EtOAc 2:1 to 1:1) afforded **167** (1.24 g, 51%).

Data of **167**: $C_{26}H_{24}F_3N_3O_7$ (547.5). LC-MS (method 1c): $R_t = 2.37$ (89), 548.2 ($[M+H]^+$).

15

Synthesis of the Mitsunobu product **168**

A soln of phenol **167** (1.23 g, 2.2 mmol), alcohol **16** (0.81 g, 2.7 mmol) and CMBP (1.36 g, 5.6 mmol) in toluene (30 mL) was heated to reflux for 1.5 h. Evaporation of the volatiles and FC (CH₂Cl₂/EtOAc 3:1 to 1:1) afforded **168** (1.84 g, 99%).

Data of **168**: $C_{40}H_{46}F_3N_5O_{11}$ (829.8). LC-MS (method 4a): $R_t = 2.00$ (92), 830.4 ($[M+H]^+$).

20

Synthesis of the amino acid **169**

A degassed solution of **168** (1.8 g, 2.2 mmol) and 1,3-dimethylbarbituric acid (0.8 g, 5.3 mmol) in CH₂Cl₂ (15 mL) and EtOAc (15 mL) was treated with Pd(PPh₃)₄ (0.13 g, 0.1 mmol) at rt for 1 h. The volatiles were evaporated. FC (CH₂Cl₂/MeOH 99:1 to 80:20) afforded **169** (1.32 g, 85%).

Data of **169**: $C_{33}H_{38}F_3N_5O_9$ (705.7). LC-MS (method 1a): $R_t = 1.95$ (94), 706.3 ($[M+H]^+$).

30

Synthesis of **Ex.327**

A mixture of **169** (1.33 g, 1.9 mmol), *i*-Pr₂NEt (1.6 mL, 9.4 mmol) and CH₂Cl₂ (40 mL) was slowly added over 2 h (syringe pump) to a soln of T3P (50% in EtOAc; 3.3 mL, 5.6 mmol) and *i*-Pr₂NEt (1.6 mL, 9.4 mmol) in CH₂Cl₂ (1880 mL). The volatiles were partially evaporated. The soln was washed (sat. aq. NaHCO₃ soln), dried (Na₂SO₄),

35

filtered and concentrated. FC (hexane/EtOAc 25:75 to 0:100) afforded **Ex.327** (0.96 g, 74%).

Data of **Ex.327**: $C_{33}H_{36}F_3N_5O_8$ (687.6). LC-MS (method 1f): $R_t = 2.43$ (89), 688.3 ($[M+H]^+$). ^1H -NMR (DMSO- d_6): Three sets of signals were observed; ratio 2:1:1; 9.16 (br. s, 0.5 H); 8.65 (br. s, 0.25 H); 8.50 (br. s, 0.25 H); 7.56 – 7.08 (m, 10 H); 5.13 – 4.92 (several d, 2 H); 4.40 – 2.98 (several br. not resolved m, 12 H); 2.43 – 2.04 (br. not resolved m, 1 H); 1.95 – 1.70 (br. not resolved m, 1 H); 1.41, 1.39 (2 s, 9 H).

Synthesis of **Ex.328**

10 A soln of **Ex.327** (60 mg, 0.087 mmol) in EtOAc (5 mL) was hydrogenated for 3 h at rt and normal pressure in the presence of palladium hydroxide on activated charcoal (moistened with 50% H_2O ; 30 mg). The mixture was filtered through a pad of celite. The residue was washed (EtOAc). The combined filtrate and washings were concentrated. FC (CH_2Cl_2 /MeOH 95:5 to 90:10) afforded **Ex.328** (37 mg, 77%).

15 Data of **Ex.328**: $C_{25}H_{30}F_3N_5O_6$ (553.5). LC-MS (method 1d): $R_t = 1.84$ (96), 554.2 ($[M+H]^+$). ^1H -NMR (DMSO- d_6): Two sets of signals were observed; ratio 4:6; 9.19 (t-like m, 0.4 H), 8.72 (t-like m, 0.6 H); 7.57 (not resolved m, 1 H); 7.48 – 7.30 (m, 2 H); 7.23 (d, $J = 5.1$, 1 H); 7.04 (not resolved m, 1 H); 4.50 – 4.34 (2 m, 1 H); 4.20 – 4.13 (m, 2 H); 4.07 – 3.94 (m, 2 H); 3.84 – 3.30 (several m, 3 H); 3.19 – 2.66 (several m, 5 H); 2.42, 2.26 (2 m, 1 H); 1.95, 1.70 (2 m, 1 H); 1.40 (s, 9 H).

Synthesis of **Ex.329**

Ex.327 (50 mg, 0.073 mmol) was dissolved in CH_2Cl_2 (2 mL). At 0°C, TFA (0.03 mL, 0.36 mmol) was added and the soln was stirred for 1.5 h. Aqueous workup (EtOAc, 25 sat. aq. $NaHCO_3$ soln, sat aq. $NaCl$ soln; Na_2SO_4) and treatment of the product with HCl in dioxane afforded **Ex.329**·HCl (33 mg, 73%).

Data of **Ex.329**·HCl: $C_{28}H_{28}F_3N_5O_6 \cdot HCl$ (free base; 587.5). LC-MS (method 1d): $R_t = 1.69$ (97), 588.2 ($[M+H]^+$).

General Procedures

Attachment of substituents to the macrocyclic core structures:

Synthesis of the final products

5 Acylation, carbamoylation, sulfonylation, and alkylation reactions

Procedure A

A.1.: Amide coupling of a macrocyclic amine with

A.1.1: Carboxylic acid and HATU

A soln of an amino macrocycle (free amine or hydrochloride; 0.085 mmol), a
10 carboxylic acid (1.2 equiv.), HATU (1.5 equiv.) and HOAt (1.5 equiv.) in DMF (0.5 mL)
was treated at rt with $i\text{-Pr}_2\text{NEt}$ (3.0 equiv.). The mixture was stirred at rt for 2 - 15 h.
The mixture was distributed between CH_2Cl_2 and 1 M aq. HCl soln. The organic
phase was washed (sat. aq. NaCl soln), dried (Na_2SO_4), filtered and concentrated.
Purification of the crude product by chromatography (FC, normal phase or reversed
15 phase prep. HPLC) afforded a macrocyclic N-acyl amine.

A.1.2: Acyl chloride or carboxylic acid anhydride

At 0°C , a soln of an amino macrocycle (free amine or hydrochloride; 0.085 mmol) in
 CH_2Cl_2 (0.5 mL) was successively treated with pyridine (5 equiv.) and carboxylic acid
chloride (1.05 – 2 equiv.) or carboxylic acid anhydride (1.05 – 2 equiv.). The mixture
20 was stirred at 0°C to rt for 2 - 15 h. After the addn of MeOH (0.01 mL) the soln was
stirred for 10 min and concentrated. Toluene was added to the crude product and
evaporated. Purification of the residue by chromatography (FC, normal phase or
reversed phase prep. HPLC) afforded a macrocyclic N-acyl amine.

A.1.2.1: Acyl chloride

25 Like A.1.2 and after 15 h at rt more carboxylic acid chloride (2 equiv.) and $i\text{-Pr}_2\text{NEt}$ (3
equiv.) were added. Stirring was continued for 24 h followed by an aq. workup
(CHCl_3 , sat. aq. Na_2CO_3 soln; Na_2SO_4).

A.1.2.2: Acyl chloride

At 0°C , a soln of an amino macrocycle (free amine or hydrochloride; 1 mmol) in
30 CH_2Cl_2 (7 mL) was successively treated with $i\text{-Pr}_2\text{NEt}$ (5 equiv.) and carboxylic acid
chloride (1.05 – 2 equiv.). The mixture was stirred at 0°C to rt for 2 - 15 h. Aq. workup
(CHCl_3 , sat. aq. Na_2CO_3 soln; Na_2SO_4). Purification of the crude product by
chromatography (FC, normal phase or reversed phase prep. HPLC) afforded a
macrocyclic N-acyl amine.

35 A.1.3: Carboxylic acid and T3P

A soln of a carboxylic acid (2.4 equiv.), T3P (50% in DMF; 3 equiv.) and *i*-Pr₂NEt (4.0 equiv.) in DMF (0.3 mL) was slowly added to a mixture of an amino macrocycle (free amine or hydrochloride; 0.1 mmol) and DMF (0.2 mL). The mixture was stirred at rt for 2 - 15 h followed by an aq. workup (CHCl₃, sat. aq. Na₂CO₃ soln; Na₂SO₄).

- 5 Purification of the crude product by chromatography (FC, normal phase or reversed phase prep. HPLC) afforded a macrocyclic N-acyl amine.

A.2: Amide coupling of a macrocyclic carboxylic acid with an amine and HATU

- A soln of a macrocyclic carboxylic acid (0.12 mmol), an amine (1.2 equiv.), HATU (1.5 equiv.) and HOAt (1.5 equiv.) in DMF (0.5 mL) was treated at 4°C with *i*-Pr₂NEt (3.0 equiv.). The mixture was stirred at 4°C for 2 h. The mixture was distributed between CH₂Cl₂ and 1 M aq. HCl soln. The organic phase was washed (sat. aq. NaCl soln), dried (Na₂SO₄), filtered and concentrated.
- 10

Purification of the crude product by chromatography (FC, normal phase or reversed phase prep. HPLC) afforded a macrocyclic amide.

- 15 Procedure A.3: Urea formation with isocyanates or equivalents of isocyanates

- A soln of an amino macrocycle (free amine or hydrochloride; 0.1 mmol) in CH₂Cl₂ (0.5 mL) was treated at rt for 2 - 15 h with an isocyanate (1.1 equiv.) (or with a succinimidyl carbamate (1.1 equiv.)) and *i*-Pr₂NEt (3 equiv.) followed by aq. workup (CHCl₃, sat. aq. Na₂CO₃ soln; Na₂SO₄). The crude product was purified by chromatography (FC, normal phase or reversed phase prep. HPLC) to afford the targeted macrocyclic urea.
- 20

Procedure A.4: Carbamate formation with chloroformates

- At 0°C the chloroformate (1.1 equiv.) was added to a stirred mixture of CH₂Cl₂ (0.9 mL) and sat. aq. Na₂CO₃ soln (0.35 mL). The amino macrocycle (free amine or hydrochloride; 0.085 mmol) and H₂O (0.75 mL) were added. The mixture was stirred at rt for 2 - 15 h followed by aq. workup (EtOAc, sat. aq. NaHCO₃ soln; Na₂SO₄). The crude product was purified by chromatography (FC, normal phase or reversed phase prep. HPLC) to afford the targeted macrocyclic carbamate.
- 25

Procedure A.5: Sulfonamide formation with sulfonyl chlorides

- At 0°C a soln of an amino macrocycle (free amine or hydrochloride; 0.1 mmol) in CH₂Cl₂ (0.5 mL) was successively treated with triethylamine (3.0 equiv.) and the sulfonyl chloride (1.0 equiv.). The mixture was stirred at 0°C to rt for 2 - 15 h. (In case of incomplete transformation, more sulfonyl chloride (1.0 equiv.) and auxiliary base (3.0 equiv.) were added and stirring continued.) Aq. workup (CHCl₃, sat. aq. Na₂CO₃ soln; Na₂SO₄) and purification of the crude product by chromatography (FC, normal
- 30
- 35

phase or reversed phase prep. HPLC) afforded the targeted macrocyclic sulfonamide.

Procedure A.6: N-Alkylation by reductive amination

A.6.1. N,N-Dimethylamino macrocycles by reductive amination

- 5 To a soln. of the amino macrocycle (free amine or hydrochloride; 0.085 mmol) in DCE (1.2 mL) was added formaldehyde soln (36.5% in H₂O; 5 equiv.) followed by NaBH(OAc)₃ (4 equiv.). The mixture was stirred at rt for 4 h.

Aq. workup (EtOAc, sat. aq. NaHCO₃ soln; Na₂SO₄) and purification of the crude product by chromatography (FC, normal phase or reversed phase prep. HPLC) afforded a dimethylamino macrocycle.

A.6.2: Synthesis of tertiary amines by N-methylation of secondary amines

- At 0°C formaldehyde soln (36.5% in H₂O; 5 equiv.), acetic acid (1.2 equiv.) and NaBH(OAc)₃ (4.0 equiv.) were added to a soln of the macrocyclic amine (0.25 mmol) in DCE (4 mL). The mixture was stirred at rt for 4 h followed by aqueous workup (CH₂Cl₂, sat. aq. NaHCO₃ soln; Na₂SO₄). Purification of the crude product by chromatography (FC, normal phase or reverse phase prep. HPLC) afforded the desired N-methyl-N,N-dialkylamino macrocycle.

A.6.3: Synthesis of tertiary amines by reductive amination of secondary amines

- The aldehyde (1.5 equiv.) was added to a mixture of the macrocyclic amine (0.25 mmol) and THF (1.5 mL). The mixture was stirred at rt for 1 h. Acetic acid (1.2 equiv.) and NaBH(OAc)₃ (3 equiv.) were added and stirring was continued for 15 h. (In case of incomplete transformation, more aldehyde (0.5 equiv.) was added and stirring continued.) After aqueous workup (CH₂Cl₂, 1 M aq. Na₂CO₃ soln; Na₂SO₄) the crude product was purified by chromatography (FC, normal phase or reverse phase prep. HPLC) to afford the macrocyclic tertiary amine.

A.6.4: Synthesis of secondary amines by reductive amination

- Activated molecular sieve powder (3 Å; 2 mg per mg of starting material) was added at rt to a soln of an amino macrocycle (0.1 mmol) and an aldehyde (1.1 equiv.) in THF (0.5 mL). The suspension was stirred for 2 - 4 h at rt, followed by the addition of acetic acid (1.1 equiv.) and NaBH(OAc)₃ (3.0 equiv.). The mixture was stirred for 18 h and filtered. Aqueous workup of the filtrate (CH₂Cl₂, sat. aq. Na₂CO₃ soln; Na₂SO₄) and purification of the crude product by chromatography (FC, normal phase or reverse phase prep. HPLC) afforded the alkylamino macrocycle.

Deprotection reactions**Procedure B**Procedure B.1: Boc cleavage

A soln of a macrocyclic Boc-amine in dioxane (1 mL per 100 mg) was treated with 4
5 M HCl in dioxane (1 mL per 100 mg) and stirred at rt for 2 - 16 h. The volatiles were evaporated. The residue was taken up in CHCl₃, concentrated and dried i.v.. Solid residues were then washed with Et₂O/CH₂Cl₂.

Procedure B.2: tert.-Butyl ester cleavage or Boc cleavage

Tert.-Butyl ester cleavage:

10 TFA (1 mL per 100 mg) was slowly added to a soln of a macrocyclic tert.-butyl ester in CH₂Cl₂ (5 mL per 100 mg). The mixture was stirred for 2 h at rt and concentrated. The residue was twice taken up in toluene and concentrated. The residue was then twice taken up in CHCl₃ and concentrated followed by washing with Et₂O/CH₂Cl₂.

Boc cleavage:

15 TFA (1 mL per 100 mg of starting material) was slowly added to a soln of the macrocyclic Boc-amine in CH₂Cl₂ (3 mL per 100 mg). The mixture was stirred at rt for 3 h and concentrated. The residue was dried i.v.

Procedure B.3: Cbz cleavage

A soln of the macrocyclic benzyl carbamate (500 mg) in MeOH (10 mL) or 2,2,2-trifluoroethanol (10 mL) was hydrogenated for 4 h at rt and at normal pressure in the presence of palladium hydroxide on activated charcoal (moistened with 50% H₂O; 15
20 – 20% Pd; 0.1 g). The mixture was filtered through a pad of celite. The residue was washed (MeOH). The combined filtrates and washings were concentrated to obtain the macrocyclic amine.

25 Procedure B.4: Nitro reduction

A soln of the macrocyclic aryl nitro compound (50 mg) in MeOH (5 mL) was hydrogenated for 15 h at rt and at normal pressure in the presence of platinum (IV) oxide hydrate (5 mg). The mixture was filtered through a pad of celite. The residue was washed (MeOH). The combined filtrates and washings were concentrated to
30 obtain the macrocyclic aniline.

B.5: Methyl ester cleavage

A soln of the macrocyclic methyl ester (0.07 mmol) in DCE (2 mL) was treated with trimethyltin hydroxide (3 equiv.) at 80°C for 16 h. Aqueous workup (CH₂Cl₂, 1 M aq. HCl soln; Na₂SO₄) and purification by reverse phase prep. HPLC afforded the
35 corresponding macrocyclic carboxylic acids.

Procedures for the synthesis on solid support

Procedure C: Description of examples of **core 10** and **core 11**

Procedure D: Description of examples of **core 01**

5

Synthesis of final products

Advanced macrocyclic intermediates and final products depicted in **Tables 13-31** (related cores cf. **Scheme 23**) were prepared starting from the suitable precursor macrocyclic acid, macrocyclic amine, or macrocyclic alcohol applying the general procedures (**A.1–A.6**; **B.1–B.5**) or specific procedures described above (as indicated in the corresponding Tables). Deviations from general procedures are indicated in **Tables 13a-31a**.

Final products of Core 01 prepared on solid support were obtained following the general **procedure D** (vide supra; **Core 01: Synthesis of final products on solid support**).

Final products of Cores 10 and 11 were prepared following the general procedure described in the text (vide supra; **Procedure C.1: Core 10: Synthesis of Ex.193a,c-h and Ex.194b** and **Procedure C.2: Core 11: Synthesis of Ex.195a,b,e-h,j; Ex.196c,i,k and Ex.197d**)

Analytical data of these intermediates and final products are depicted in **Tables 13b-31b**.

IUPAC names of all examples are listed in **Tables 13c-31c**.

The generic macrocyclic ring structures (Cores) related to **Tables 13–31** are depicted in **Scheme 23** in the order of their core numbers

25

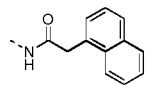
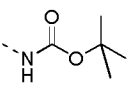
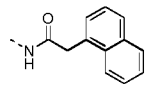
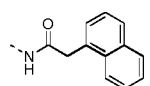
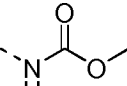
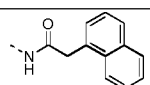
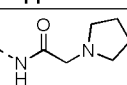
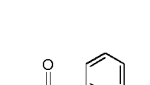
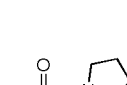
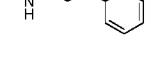
Reagents used in the derivatizations are commercially available with the exception of few N-succinimidyl carbamates which were synthesized from amines, anilines or heteroaryl amines according to the procedure of K. Takeda et al. *Tetrahedron Lett.* **1983**, 24, 4569 – 4572.

The synthesis of selected advanced intermediates and final products is described in detail in the text above; cf. corresponding core description.

35

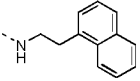
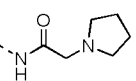
The generic macrocyclic ring structures (Cores) related to **Tables 13-31** are depicted in **Scheme 23** in the order of their core numbers.

Table 13a: Examples of Core 01 (Ex.1-Ex.14 and Ex.330-Ex.340; *continued on the following page*)

No	R ^A	R ^B	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.1-Ex.3 and Ex.330-Ex.331: <i>cf. experimental description</i>							
Ex.4			Ex.2	A.1.1; ¹⁾	1-Naphthaleneacetic acid	FC (hexane/EtOAc)	77%
Ex.5		NH ₂	Ex.4	B.1; ¹⁾	HCl-dioxane	crude product	quant. (HCl salt)
Ex.6			Ex.5	A.4	Methyl chloroformate	FC (CH ₂ Cl ₂ /MeOH)	82%
Ex.7			Ex.5	A.1.1 ; ¹⁾	1-Pyrrolidineacetic acid	FC (CH ₂ Cl ₂ /MeOH)	71%
Ex.7			133	D ; ¹⁾	1. 1-Pyrrolidineacetic acid 2. 1-Naphthaleneacetic acid	prep. HPLC method 1a	15% (TFA salt)
Ex.8		N(CH ₃) ₂	Ex.5	A.6.1	Formaldehyde (36.5% in H ₂ O)	FC (CH ₂ Cl ₂ /MeOH)	79%
Ex.9	NH ₂	NH ₂	Ex.2	B.1	HCl-dioxane rt, 16 h	crude product	97% (HCl salt)

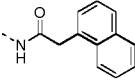
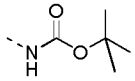
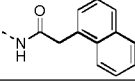
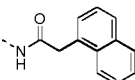
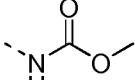
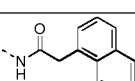
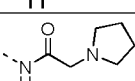
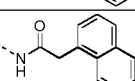
No	R ^A	R ^B	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.10			Ex.3	A.1.1	2-Naphthaleneacetic acid 4°C, 1 h	FC (hexane/EtOAc/MeOH 80 :20 :0 to 0 :90 :10)	31%
Ex.11	NH ₂		Ex.10	B.3	H ₂ , Pd(OH) ₂ -C 2,2,2-trifluoroethanol	crude product	90%
Ex.12			Ex.11	A.1.1	2-(Dimethylamino)acetic acid 0°C, 2 h	prep. HPLC method 1b	48% (TFA salt)
Ex.13			Ex.11	A.1.1	3-Methylbutanoic acid 0°C, 2 h	prep. HPLC method 1b	55%
Ex.14			Ex.3	A.4 ¹⁾	Phenyl chloroformate 0°C, 2 h	FC (EtOAc)	96%
Ex.332			133	D; ¹⁾	1. Imidazol-1-yl-acetic acid 2. 1-Naphthaleneacetic acid	prep. HPLC method 1a	48% (TFA salt)
Ex.333			133	D; ¹⁾	1. 2,5-Dioxypyrrolidin-1-yl pyridin-3-yl carbamate 2. 1-Naphthaleneacetic acid	prep. HPLC method 1a	65% (TFA salt)

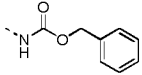
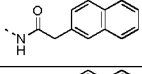
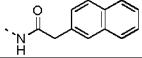
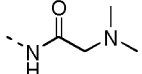
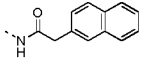
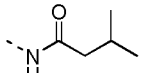
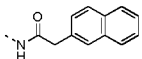
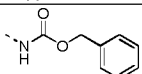
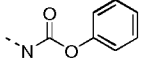
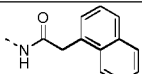
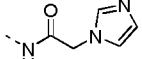
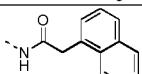
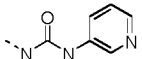
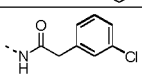
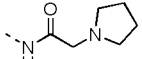
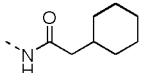
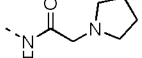
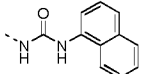
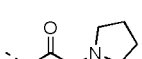
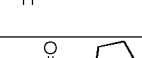
No	R ^A	R ^B	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.334			133	D; ¹⁾	1. 1-Pyrrolidineacetic acid 2. 3-Chlorophenylacetic acid	prep. HPLC method 1a	38% (TFA salt)
Ex.335			133	D; ¹⁾	1. 1-Pyrrolidineacetic acid 2. Cyclohexylacetic acid	prep. HPLC method 1a	26% (TFA salt)
Ex.336			133	D; ¹⁾	1. 1-Pyrrolidineacetic acid 2. 1-Naphthyl isocyanate	prep. HPLC method 1a	13% (TFA salt)
Ex.337			133	D	1. 1-Pyrrolidineacetic acid 2. Benzylsulfonyl chloride	prep. HPLC method 1a	21% (TFA salt)
Ex.338			Ex.3	A.1.3	1-Pyrrolidineacetic acid i-Pr ₂ NEt (5 equiv.) Workup: CH ₂ Cl ₂ , sat. aq. NaHCO ₃ soln	FC (CH ₂ Cl ₂ /MeOH)	80%
Ex.339	NH ₂		Ex.338	B.3	H ₂ , Pd(OH) ₂ -C, MeOH	crude product	98%

No	R ^A	R ^B	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.340			Ex.339	A.6.4	1-Naphthaleneacet aldehyde, 3h; NaBH(OAc) ₃ (3 eq.) Workup: CHCl ₃ , sat. aq. NaHCO ₃ soln	FC (CH ₂ Cl ₂ /MeOH) and prep. HPLC method 1a	20% (TFA salt)

¹⁾ Cf. experimental description for detailed procedure

Table 13b: Examples of Core 01 (Ex.1-Ex.14 and Ex.330-Ex.340; continued on the following page)

No	R ^A	R ^B	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.1-Ex.3 and Ex.330-Ex.331: cf. experimental description							
Ex.4			C ₃₉ H ₄₂ N ₄ O ₆	662.3	2.27 (86)	663.2	method 1a
Ex.5		NH ₂	C ₃₄ H ₃₄ N ₄ O ₄	562.3	1.61 (91)	563.2	method 1a
Ex.6			C ₃₆ H ₃₆ N ₄ O ₆	620.3	2.01 (90)	621.0	method 1a
Ex.7			C ₄₀ H ₄₃ N ₅ O ₅	673.3	2.13 (99)	674.3	method 2c
Ex.8		N(CH ₃) ₂	C ₃₆ H ₃₈ N ₄ O ₄	590.3	1.65 (97)	591.1	method 1a

No	R ^A	R ^B	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.9	NH ₂	NH ₂	C ₂₂ H ₂₆ N ₄ O ₃	394.2	1.01 (96)	395.2	method 1a
Ex.10			C ₄₂ H ₄₀ N ₄ O ₆	696.3	2.25 (91)	697.1	method 1a
Ex.11	NH ₂		C ₃₄ H ₃₄ N ₄ O ₄	562.3	1.73 (91)	563.1	method 1a
Ex.12			C ₃₈ H ₄₁ N ₅ O ₅	647.3	1.71 (96)	648.1	method 1a
Ex.13			C ₃₉ H ₄₂ N ₄ O ₅	646.3	2.09 (89)	647.2	method 1a
Ex.14			C ₃₇ H ₃₆ N ₄ O ₇	648.3	2.22 (97)	649.1	method 1a
Ex.332			C ₃₉ H ₃₈ N ₆ O ₅	670.3	1.84 (99)	671.3	method 2c
Ex.333			C ₄₀ H ₃₈ N ₆ O ₅	682.3	1.94 (99)	683.2	method 2c
Ex.334			C ₃₆ H ₄₀ ClN ₅ O ₅	657.3	2.08 (99)	658.2	method 2c
Ex.335			C ₃₆ H ₄₇ N ₅ O ₅	629.4	2.10 (99)	630.3	method 2c
Ex.336			C ₃₉ H ₄₂ N ₆ O ₅	674.3	2.09 (98)	675.3	method 2c
Ex.337			C ₃₅ H ₄₁ N ₅ O ₆ S	659.3	1.59 (99)	660.3	method 1a

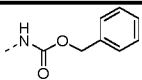
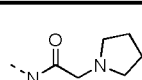
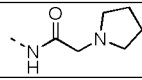
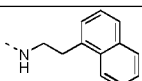
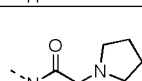
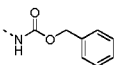
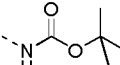
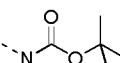
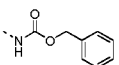
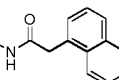
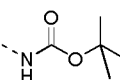
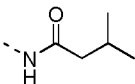
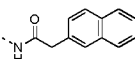
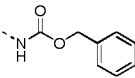
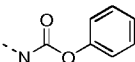
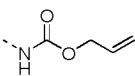
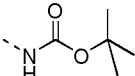
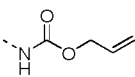
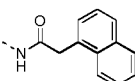
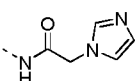
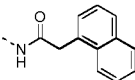
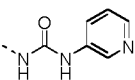
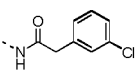
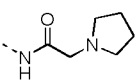
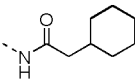
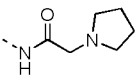
No	R ^A	R ^B	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.338			C ₃₆ H ₄₁ N ₅ O ₆	639.3	1.63 (99)	640.2	method 1a
Ex.339	NH ₂		C ₂₈ H ₃₅ N ₅ O ₄	505.3	1.15 (97)	506.2	method 1c
Ex.340			C ₄₀ H ₄₅ N ₅ O ₄	659.3	1.60 (87)	660.3	method 1a

Table 13c: Examples of Core 01 (Ex.1-Ex.14 and Ex.330-Ex.340; continued on the following page)

No	R ^A	R ^B	IUPAC name
Ex.1			benzyl <i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-16-[(<i>tert</i> -butoxycarbonyl)amino]-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]carbamate
Ex.2	NH ₂		<i>tert</i> -butyl <i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-12-amino-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-16-yl]carbamate
Ex.3		NH ₂	benzyl <i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-16-amino-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]carbamate
Ex.4			<i>tert</i> -butyl <i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-12-[[2-(1-naphthyl)acetyl]amino]-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-16-yl]carbamate

No	R ^A	R ^B	IUPAC name
Ex.5		NH ₂	<i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-16-amino-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]-2-(1-naphthyl)acetamide
Ex.6			methyl <i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-12-[[2-(1-naphthyl)acetyl]amino]-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-16-yl]carbamate
Ex.7			<i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-8,13-dioxo-16-[[2-(1-pyrrolidinyl)acetyl]amino]-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]-2-(1-naphthyl)acetamide
Ex.8		N(CH ₃) ₂	<i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-16-(dimethylamino)-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]-2-(1-naphthyl)acetamide
Ex.9	NH ₂	NH ₂	(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-12,16-diamino-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaene-8,13-dione
Ex.10			benzyl <i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-16-[[2-(2-naphthyl)acetyl]amino]-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]carbamate
Ex.11	NH ₂		<i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-12-amino-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-16-yl]-2-(2-naphthyl)acetamide
Ex.12			2-(dimethylamino)- <i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-16-[[2-(2-naphthyl)acetyl]amino]-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]acetamide

No	R ^A	R ^B	IUPAC name
Ex.13			3-methyl- <i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-16-[[2-(2-naphthyl)acetyl]amino]-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]butanamide
Ex.14			benzyl <i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-8,13-dioxo-16-[(phenoxy carbonyl)amino]-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]carbamate
Ex.330			allyl <i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-16-[(<i>tert</i> -butoxycarbonyl)amino]-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]carbamate
Ex.331		NH ₂	allyl <i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-16-amino-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]carbamate
Ex.332			2-(1 <i>H</i> -imidazol-1-yl)- <i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-12-[[2-(1-naphthyl)acetyl]amino]-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-16-yl]acetamide
Ex.333			<i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-8,13-dioxo-16-[[3-(3-pyridinylamino)carbonyl]amino]-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]-2-(1-naphthyl)acetamide
Ex.334			2-(3-chlorophenyl)- <i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-8,13-dioxo-16-[[2-(1-pyrrolidinyl)acetyl]amino]-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]acetamide
Ex.335			2-cyclohexyl- <i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-8,13-dioxo-16-[[2-(1-pyrrolidinyl)acetyl]amino]-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]acetamide

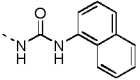
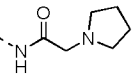
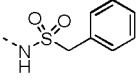
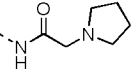
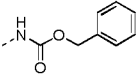
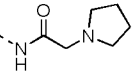
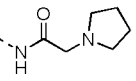
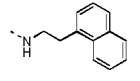
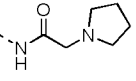
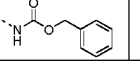
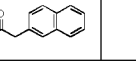
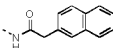
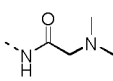
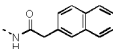
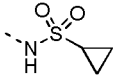
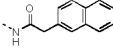
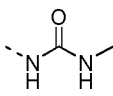
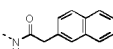
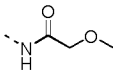
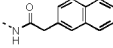
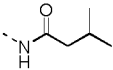
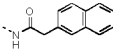
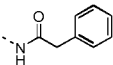
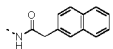
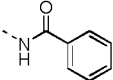
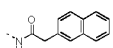
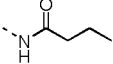
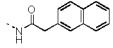
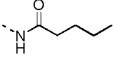
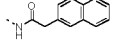
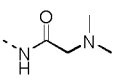
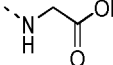
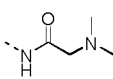
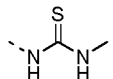
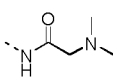
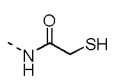
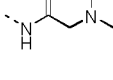
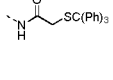
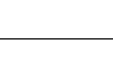
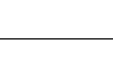
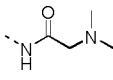
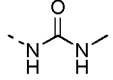
No	R ^A	R ^B	IUPAC name
Ex.336			<i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-12-[[1-naphthylamino]carbonyl]amino]-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-16-yl]-2-(1-pyrrolidinyl)acetamide
Ex.337			<i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-12-[(benzylsulfonyl)amino]-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-16-yl]-2-(1-pyrrolidinyl)acetamide
Ex.338			benzyl <i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-8,13-dioxo-16-[[2-(1-pyrrolidinyl)acetyl]amino]-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]carbamate
Ex.339	NH ₂		<i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-12-amino-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-16-yl]-2-(1-pyrrolidinyl)acetamide
Ex.340			<i>N</i> -[(12 <i>R</i> ,16 <i>S</i> ,18 <i>S</i>)-12-[[2-(1-naphthyl)ethyl]amino]-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0 ^{2,7} .0 ^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-16-yl]-2-(1-pyrrolidinyl)acetamide

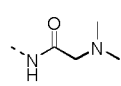
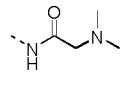
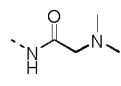
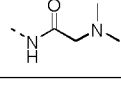
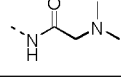
Table 14a: Examples of Core 02 (Ex.15-Ex.40; continued on the following pages)

No	R ^A	R ^B	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.15-Ex.17: cf. experimental description							
Ex.18			Ex.17	A.1.1; 4)	2-Naphthaleneacetic acid	FC (EtOAc)	79%

No	R ^A	R ^B	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.19	NH ₂		Ex.18	B.3; ⁴⁾	H ₂ , Pd(OH) ₂ -C MeOH	crude product	97%
Ex.20			Ex.19	A.1.1; ⁴⁾	2-(Dimethylamino)acetic acid	FC (CH ₂ Cl ₂ /MeOH)	30%
Ex.21			Ex.19	A.5	Cyclopropanesulfonyl chloride (1.5 equiv.) Et ₃ N (3 equiv.) DMAP (0.1 equiv) CHCl ₃ (0.25 mL), 50°C, 15 h Workup: CH ₂ Cl ₂ , half-sat. aq. NaHCO ₃ soln.; Na ₂ SO ₄	FC (EtOAc; then CH ₂ Cl ₂ /MeOH)	86%
Ex.22			Ex.19	A.3	N-Succinimidyl N-methylcarbamate (1.3 equiv.) i-Pr ₂ NEt (3 equiv) THF/CHCl ₃ 1:1 (1.0 mL) rt, 3 h	FC (CH ₂ Cl ₂ /MeOH)	63%
Ex.23			Ex.19	A.1.2	2-Methoxyacetyl chloride (1.5 equiv.) rt, 3 h	FC (CH ₂ Cl ₂ /MeOH)	51%

No	R ^A	R ^B	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.24			Ex.19	A.1.2	3-Methylbutanoyl chloride (1.2 equiv.) 0°C, 2 h (Mixture was concentrated without addn of MeOH.)	prep. HPLC method 1a	73%
Ex.25			Ex.19	A.1.2; ⁴⁾	Phenylacetyl chloride	prep. HPLC method 1a	60%
Ex.26			Ex.19	A.1.2; ⁴⁾	Benzoyl chloride	prep. HPLC method 1a	67%
Ex.27			Ex.19	A.1.2	Butyryl chloride (1.2 equiv.) 0°C, 2 h (Mixture was concentrated without addn of MeOH.)	prep. HPLC method 1a	67%
Ex.28			Ex.19	A.1.2	Pentanoyl chloride (1.2 equiv.) 0°C, 2 h (Mixture was concentrated without addn of MeOH.)	prep. HPLC method 1a	66%
Ex.29			Ex.40	¹⁾	LiOH ¹⁾	prep. HPLC method 1a	47%

No	R ^A	R ^B	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.30			Ex.39	2)	Methyl isothiocyanate 2)	prep. HPLC method 1a	48%
Ex.31			Ex.32	3)	3)	FC (CH ₂ Cl ₂ /MeOH 100:0 to 80:20)	57%
Ex.32			Ex.39	A.1.1	2-(Tritylthio)acetic acid i-Pr ₂ NEt (5 equiv.) 0°C, 2 h Workup: CH ₂ Cl ₂ , sat. aq. NaHCO ₃ soln	FC (CH ₂ Cl ₂ /MeOH 90:10)	85%
Ex.33			Ex.39	A.3	N-Succinimidyl N-methylcarbamate (1.4 equiv.) i-Pr ₂ NEt (5.0 equiv.)	prep. HPLC method 1a	77% (TFA salt)
Ex.34			Ex.39	A.3	2,5-Dioxopyrrolidin-1-yl-3-(dimethylamino)phenylcarbamate (1.4 equiv.) i-Pr ₂ NEt (5.0 equiv.)	prep. HPLC method 1a	77% (TFA salt)
Ex.35			Ex.39	A.3	2-Naphthyl isocyanate (1.4 equiv.) i-Pr ₂ NEt (5.0 equiv.)	prep. HPLC method 1a	77% (TFA salt)

No	R ^A	R ^B	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.36			Ex.39	A.5	Methanesulfonyl chloride (1.3 equiv.) Et ₃ N (5 equiv.)	prep. HPLC method 1a	64% (TFA salt)
Ex.37			Ex.39	A.5	Phenylmethanesulfonyl chloride (1.3 equiv.) Et ₃ N (5 equiv.)	prep. HPLC method 1a	43% (TFA salt)
Ex.38			Ex.16	A.1.3	2-(Dimethylamino)acetic acid Workup: CH ₂ Cl ₂ , 1 M aq. HCl soln; sat. aq. NaHCO ₃ soln, sat. aq. NaCl soln; Na ₂ SO ₄	FC (CH ₂ Cl ₂ /MeOH/ conc. aq. NH ₃ soln 95:5:2)	86%
Ex.39		NH ₂	Ex.38	B.1	HCl-dioxane rt, 2 h	crude product	quant. (HCl salt)
Ex.40			Ex.39	A.6.4	Ethyl glyoxylate (1.2 equiv.)	FC (CH ₂ Cl ₂ /MeOH 9:1)	37%

- 1) A soln of the macrocyclic ethylester **Ex.40** (63 mg, 0.11 mmol) in THF/MeOH 1:1 (1 mL) was treated at 0°C for 2 h with 2 M aq. LiOH soln (0.16 mL, 0.32 mmol). The mixture was concentrated. The residue was treated with 1 M aq. HCl soln and concentrated. Purification by reverse phase prep. HPLC afforded **Ex.29** (40 mg, 47%).
- 2) Methyl isothiocyanate (6 mg, 0.11 mmol) was added to a soln of **Ex.39** (50 mg, 0.078 mmol) and i-Pr₂NEt (0.07 mL, 0.39 mmol) in CH₂Cl₂ (0.5 mL). The mixture was stirred for 16 h at rt. More methyl isothiocyanate (2 mg) was added and stirring continued for 1 h. Aq. Workup (CHCl₃, sat. aq. Na₂CO₃ soln; Na₂SO₄) and purification by prep. HPLC (method 1a) afforded **Ex.30** (26 mg, 48%).

- 3) Triisopropylsilane (0.12 mL, 0.58 mmol) was added to a soln of **Ex.32** (50 mg, 0.115 mmol) in CH₂Cl₂ (0.4 mL). The mixture was cooled to 0°C followed by the addition of TFA (0.4 mL). The mixture was stirred for 30 min at 0°C and concentrated. FC (CH₂Cl₂/MeOH 100:0 to 80:20) afforded **Ex.31** (46 mg, 57%).
- 4) Cf. experimental description for detailed procedure

Table 14b: Examples of Core 02 (**Ex.15-Ex.40**; *continued on the following page*)

No	R ^A	R ^B	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.15-Ex.17: <i>cf. experimental description</i>							
Ex.18			C44H44N4O6	724.3	2.36 (98)	725.2	method 1a
Ex.19	NH ₂		C36H38N4O4	590.3	1.76 (97)	591.2	method 1a
Ex.20			C40H45N5O5	675.3	1.82 (95)	676.3	method 1a
Ex.21			C39H42N4O6S	694.3	2.10 (97)	695.2	method 1a
Ex.22			C38H41N5O5	647.3	1.96 (98)	648.2	method 1a
Ex.23			C39H42N4O6	662.3	2.04 (99)	663.2	method 1a
Ex.24			C41H46N4O5	674.3	2.20 (98)	675.2	method 1a
Ex.25			C44H44N4O5	708.3	2.27 (99)	709.2	method 1a
Ex.26			C43H42N4O5	694.3	2.26 (99)	695.2	method 1a

No	R ^A	R ^B	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.27			C40H44N4O5	660.3	2.15 (99)	661.2	method 1a
Ex.28			C41H46N4O5	674.3	2.24 (99)	675.3	method 1a
Ex.29			C30H39N5O6	565.3	1.25 (99)	566.2	method 1a
Ex.30			C30H40N6O4S	580.3	1.38 (95)	581.2	method 3a
Ex.31			C30H39N5O5S	581.3	1.49 (90)	582.0	method 1a
Ex.32			C49H53N5O5S	823.4	2.18 (90)	824.3	method 1a
Ex.33			C30H40N6O5	564.3	1.40 (99)	565.1	method 1a
Ex.34			C37H47N7O5	669.4	1.37 (97)	670.2	method 1a
Ex.35			C39H44N6O5	676.3	1.84 (98)	677.3	method 1a
Ex.36			C29H39N5O6S	585.3	1.44 (99)	586.0	method 1a
Ex.37			C35H43N5O6S	661.3	1.68 (97)	661.8	method 1e
Ex.38			C33H45N5O6	607.3	1.73 (93)	608.1	method 1a
Ex.39		NH ₂	C28H37N5O4	507.3	1.23 (93)	508.2	method 1a
Ex.40			C32H43N5O6	593.3	1.38 (96)	594.1	method 1a

Table 14c: Examples of Core 02 (Ex.15-Ex.40; continued on the following pages)

No	R ^A	R ^B	IUPAC name
Ex.15			benzyl <i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-12-[(<i>tert</i> -butoxycarbonyl)amino]-20-methyl-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]carbamate
Ex.16	NH ₂		<i>tert</i> -butyl <i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-16-amino-20-methyl-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-12-yl]carbamate
Ex.17		NH ₂	benzyl <i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-12-amino-20-methyl-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]carbamate
Ex.18			benzyl <i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-20-methyl-12-{[2-(2-naphthyl)acetyl]amino}-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]carbamate
Ex.19	NH ₂		<i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-16-amino-20-methyl-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-12-yl]-2-(2-naphthyl)acetamide
Ex.20			2-(dimethylamino)- <i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-20-methyl-12-{[2-(2-naphthyl)acetyl]amino}-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]acetamide
Ex.21			<i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-16-[(cyclopropylsulfonyl)amino]-20-methyl-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-12-yl]-2-(2-naphthyl)acetamide

No	R ^A	R ^B	IUPAC name
Ex.22			<i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-20-methyl-16-[[[(methylamino)carbonyl]amino}-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-12-yl]-2-(2-naphthyl)acetamide
Ex.23			2-methoxy- <i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-20-methyl-12-[[2-(2-naphthyl)acetyl]amino}-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]acetamide
Ex.24			3-methyl- <i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-20-methyl-12-[[2-(2-naphthyl)acetyl]amino}-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]butanamide
Ex.25			<i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-20-methyl-15,21-dioxo-16-[(2-phenylacetyl)amino]-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-12-yl]-2-(2-naphthyl)acetamide
Ex.26			<i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-20-methyl-12-[[2-(2-naphthyl)acetyl]amino}-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]benzamide
Ex.27			<i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-20-methyl-12-[[2-(2-naphthyl)acetyl]amino}-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]butanamide
Ex.28			<i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-20-methyl-12-[[2-(2-naphthyl)acetyl]amino}-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]pentanamide
Ex.29			2-[[[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-16-[[2-(dimethylamino)acetyl]amino}-20-methyl-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-12-yl]amino}acetic acid

No	R ^A	R ^B	IUPAC name
Ex.30			2-(dimethylamino)- <i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-20-methyl-12-[[[(methylamino)carbothioyl]amino]-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]acetamide
Ex.31			2-(dimethylamino)- <i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-20-methyl-15,21-dioxo-12-[(2-sulfanylacetyl)amino]-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]acetamide
Ex.32			2-(dimethylamino)- <i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-20-methyl-15,21-dioxo-12-[[2-(tritylsulfanyl)acetyl]amino]-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]acetamide
Ex.33			2-(dimethylamino)- <i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-20-methyl-12-[[[(methylamino)carbonyl]amino]-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]acetamide
Ex.34			2-(dimethylamino)- <i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-12-([3-(dimethylamino)anilino]carbonyl)amino]-20-methyl-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]acetamide
Ex.35			2-(dimethylamino)- <i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-20-methyl-12-[[[(2-naphthylamino)carbonyl]amino]-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]acetamide
Ex.36			2-(dimethylamino)- <i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-20-methyl-12-[(methylsulfonyl)amino]-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]acetamide

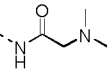
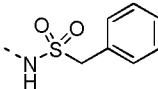
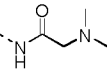
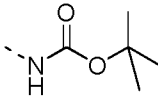
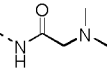
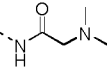
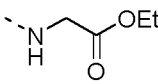
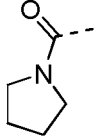
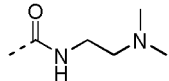
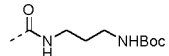
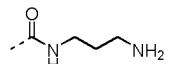
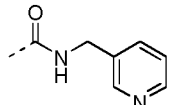
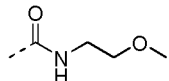
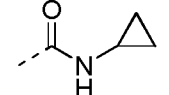
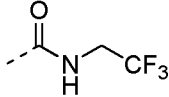
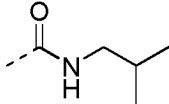
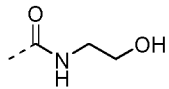
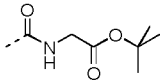
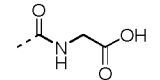
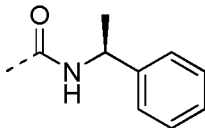
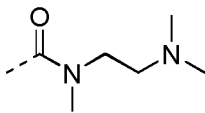
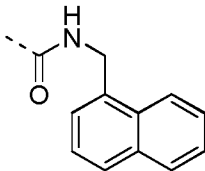
No	R ^A	R ^B	IUPAC name
Ex.37			<i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-12-[(benzylsulfonyl)amino]-20-methyl-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]-2-(dimethylamino)acetamide
Ex.38			<i>tert</i> -butyl <i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-16-{[2-(dimethylamino)acetyl]amino}-20-methyl-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-12-yl]carbamate
Ex.39		NH ₂	<i>N</i> -[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-12-amino-20-methyl-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]-2-(dimethylamino)acetamide
Ex.40			ethyl 2-{[(10 <i>S</i> ,12 <i>S</i> ,16 <i>S</i>)-16-{[2-(dimethylamino)acetyl]amino}-20-methyl-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0 ^{2,7} .0 ^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-12-yl]amino}acetate

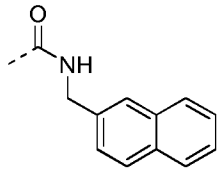
Table 15a: Examples of Core 03 (Ex.41-Ex.67; continued on the following pages)

No	R ^E	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.41-Ex.42, Ex.62–Ex.67: <i>cf. experimental description</i>						

No	R ^E	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.43	CONH ₂	Ex.42	A.2	NH ₄ Cl (4 equiv.) HATU (2.0 equiv.) HOAT (2.0 equiv.) i-Pr ₂ NEt (6 equiv.) rt, 2 h Workup: Sat. aq. Na ₂ CO ₃ , CH ₂ Cl ₂	prep. HPLC method 3	64%
Ex.44	CONHCH ₃	Ex.42	A.2	CH ₃ NH ₃ Cl (4 equiv.) HATU (2.0 equiv.) HOAT (2.0 equiv.) i-Pr ₂ NEt (6 equiv.) 4°C, 1 h Workup: Sat. aq. Na ₂ CO ₃ , CH ₂ Cl ₂	prep. HPLC method 3	71%
Ex.45	CONHPh	Ex.42	A.2	Aniline	prep. HPLC method 3	80%
Ex.46		Ex.42	A.2	Pyrrolidine	prep. HPLC method 3	53%

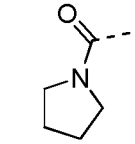
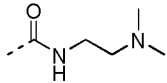
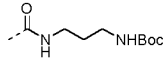
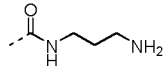
No	R ^E	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.47		Ex.42	A.2	N,N-Dimethyl-ethylenediamine (1.0 equiv.) Workup: Sat. aq. Na ₂ CO ₃ , CH ₂ Cl ₂	prep. HPLC method 1a	61% (TFA salt)
Ex.48		Ex.42	A.2	tert.-Butyl-3-aminopropylcarbamate	prep. HPLC method 3	65%
Ex.49		Ex.48	B.1	HCl-dioxane rt, 2 h	crude product	74% (HCl salt)
Ex.50		Ex.42	A.2 ¹⁾	3-Picolylamine	prep. HPLC method 1c	37% (TFA salt)
Ex.51		Ex.42	A.2	2-Methoxyethylamine	prep. HPLC method 3	63%
Ex.52		Ex.42	A.2	Cyclopropylamine	prep. HPLC method 3	84%
Ex.53		Ex.42	A.2	2,2,2-Trifluoroethylamine	prep. HPLC method 3	66%
Ex.54		Ex.42	A.2	Isobutylamine	prep. HPLC method 3	66%
Ex.55		Ex.42	A.2	2-Aminoethanol 4°C 2 h and rt 3 h	prep. HPLC method 1c	82%

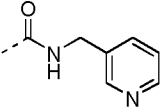
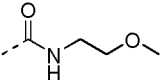
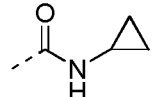
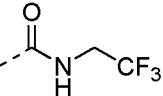
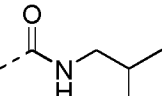
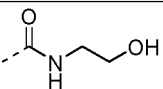
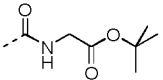
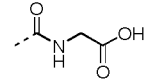
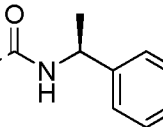
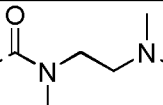
No	R ^E	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.56		Ex.42	A.2	Glycine-tert.-butyl ester hydrochloride (1.5 equiv.) HATU 2.0 equiv.) HOAt (2.0 equiv.) i-Pr ₂ NEt (3.0 equiv.) 4°C, 2 h	prep. HPLC method 3	76%
Ex.57		Ex.56	B.2	TFA, CH ₂ Cl ₂	crude product	80%
Ex.58		Ex.42	A.2	(L)-α-Methylbenzylamine 4°C 2 h and rt 2 h	prep. HPLC method 3	55%
Ex.59		Ex.42	A.2	N,N,N'-Trimethylethylene-diamine	FC (CH ₂ Cl ₂ / MeOH/ aq. NH ₃ soln)	83%
Ex.60		Ex.42	A.2	Naphthalen-1-ylmethanamine	prep. HPLC method 3	57%

No	R ^E	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.61		Ex.42	A.2	Naphthalen-2-ylmethanamine	prep. HPLC method 3 and prep. HPLC method 2a	29%

1) Cf. experimental description for detailed procedure

Table 15b: Examples of Core 03 (Ex.41-Ex.67; continued on the following pages)

No	R ^E	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.41-Ex.42, Ex.62-Ex.67: cf. experimental description						
Ex.43	CONH ₂	C ₂₃ H ₂₇ N ₃ O ₅	425.2	1.47 (95)	426.1	method 1a
Ex.44	CONHCH ₃	C ₂₄ H ₂₉ N ₃ O ₅	439.2	1.49 (99)	440.1	method 1a
Ex.45	CONHPh	C ₂₉ H ₃₁ N ₃ O ₅	501.2	1.97 (97)	502.1	method 1a
Ex.46		C ₂₇ H ₃₃ N ₃ O ₅	479.2	1.74 (98)	480.1	method 1a
Ex.47		C ₂₇ H ₃₆ N ₄ O ₅	496.3	1.32 (99)	497.2	method 1a
Ex.48		C ₃₁ H ₄₂ N ₄ O ₇	582.3	1.91 (99)	583.1	method 1a
Ex.49		C ₂₆ H ₃₄ N ₄ O ₅	482.2	1.32 (95)	483.1	method 1a

No	R ^E	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.50		C ₂₉ H ₃₂ N ₄ O ₅	516.2	1.32 (99)	517.1	method 1a
Ex.51		C ₂₆ H ₃₃ N ₃ O ₆	483.2	1.57 (95)	484.1	method 1a
Ex.52		C ₂₆ H ₃₁ N ₃ O ₅	465.2	1.67 (99)	466.1	method 1a
Ex.53		C ₂₅ H ₂₈ F ₃ N ₃ O ₅	507.2	1.80 (94)	508.0	method 1a
Ex.54		C ₂₇ H ₃₅ N ₃ O ₅	481.2	1.85 (95)	482.1	method 1a
Ex.55		C ₂₅ H ₃₁ N ₃ O ₆	469.2	1.40 (94)	470.1	method 1a
Ex.56		C ₂₉ H ₃₇ N ₃ O ₇	539.3	1.91 (93)	540.0	method 1a
Ex.57		C ₂₅ H ₂₉ N ₃ O ₇	483.2	1.47 (85)	484.1	method 1a
Ex.58		C ₃₁ H ₃₅ N ₃ O ₅	529.2	2.00 (93)	530.1	method 1a
Ex.59		C ₂₈ H ₃₈ N ₄ O ₅	510.3	1.37 (97)	511.2	method 1a

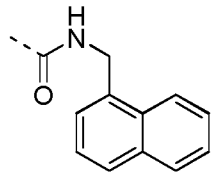
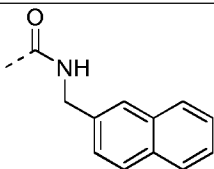
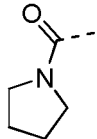
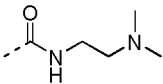
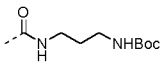
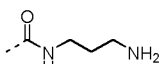
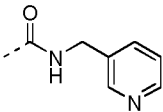
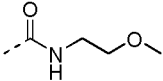
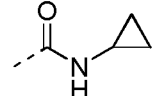
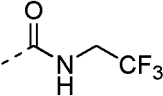
No	R ^E	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.60		C ₃₄ H ₃₅ N ₃ O ₅	565.2	2.09 (97)	566.1	method 1a
Ex.61		C ₃₄ H ₃₅ N ₃ O ₅	565.2	2.12 (100)	566.1	method 1a

Table 15c: Examples of Core 03 (Ex.41-Ex.67; continued on the following pages)

No	R ^E	IUPAC name
Ex.41	CO ₂ CH ₂ Ph	benzyl (10 <i>R</i> ,15 <i>S</i>)-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxylate
Ex.42	CO ₂ H	(10 <i>R</i> ,15 <i>S</i>)-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxylic acid
Ex.43	CONH ₂	(10 <i>R</i> ,15 <i>S</i>)-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide
Ex.44	CONHCH ₃	(10 <i>R</i> ,15 <i>S</i>)-4-methoxy- <i>N</i> ,10,16-trimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide

No	RE	IUPAC name
Ex.45	CONHPh	(10 <i>R</i> ,15 <i>S</i>)-4-methoxy-10,16-dimethyl-12,17-dioxo- <i>N</i> -phenyl-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide
Ex.46		(10 <i>R</i> ,15 <i>S</i>)-4-methoxy-10,16-dimethyl-15-(1-pyrrolidinylcarbonyl)-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-12,17-dione
Ex.47		(10 <i>R</i> ,15 <i>S</i>)- <i>N</i> -[2-(dimethylamino)ethyl]-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide
Ex.48		<i>tert</i> -butyl <i>N</i> -[3-(((10 <i>R</i> ,15 <i>S</i>)-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaen-15-yl)carbonyl)amino)propyl]carbamate
Ex.49		(10 <i>R</i> ,15 <i>S</i>)- <i>N</i> -(3-aminopropyl)-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide
Ex.50		(10 <i>R</i> ,15 <i>S</i>)-4-methoxy-10,16-dimethyl-12,17-dioxo- <i>N</i> -(3-pyridinylmethyl)-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide
Ex.51		(10 <i>R</i> ,15 <i>S</i>)-4-methoxy- <i>N</i> -(2-methoxyethyl)-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide
Ex.52		(10 <i>R</i> ,15 <i>S</i>)- <i>N</i> -cyclopropyl-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide
Ex.53		(10 <i>R</i> ,15 <i>S</i>)-4-methoxy-10,16-dimethyl-12,17-dioxo- <i>N</i> -(2,2,2-trifluoroethyl)-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide

No	RE	IUPAC name
Ex.54		(10 <i>R</i> ,15 <i>S</i>)- <i>N</i> -isobutyl-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide
Ex.55		(10 <i>R</i> ,15 <i>S</i>)- <i>N</i> -(2-hydroxyethyl)-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide
Ex.56		<i>tert</i> -butyl 2-({[(10 <i>R</i> ,15 <i>S</i>)-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaen-15-yl]carbonyl}amino)acetate
Ex.57		2-({[(10 <i>R</i> ,15 <i>S</i>)-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaen-15-yl]carbonyl}amino)acetic acid
Ex.58		(10 <i>R</i> ,15 <i>S</i>)-4-methoxy-10,16-dimethyl-12,17-dioxo- <i>N</i> -[(1 <i>S</i>)-1-phenylethyl]-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide
Ex.59		(10 <i>R</i> ,15 <i>S</i>)- <i>N</i> -[2-(dimethylamino)ethyl]-4-methoxy- <i>N</i> ,10,16-trimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide
Ex.60		(10 <i>R</i> ,15 <i>S</i>)-4-methoxy-10,16-dimethyl- <i>N</i> -(1-naphthylmethyl)-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide

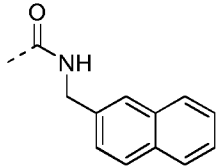
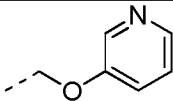
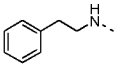
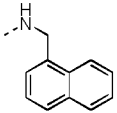
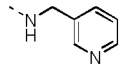
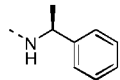
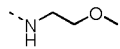
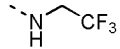
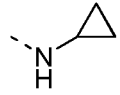
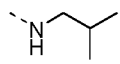
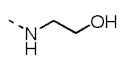
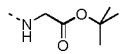
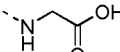
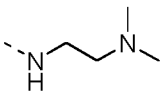
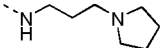
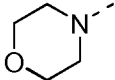
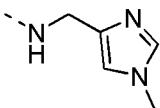
No	RE	IUPAC name
Ex.61		(10 <i>R</i> ,15 <i>S</i>)-4-methoxy-10,16-dimethyl- <i>N</i> -(2-naphthylmethyl)-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide
Ex.62	CH ₂ OH	(10 <i>R</i> ,15 <i>S</i>)-15-(hydroxymethyl)-4-methoxy-10,16-dimethyl-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-12,17-dione
Ex.63		(10 <i>R</i> ,15 <i>S</i>)-4-methoxy-10,16-dimethyl-15-[(3-pyridinyloxy)methyl]-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-12,17-dione
Ex.64	CH ₂ N ₃	(10 <i>R</i> ,15 <i>S</i>)-15-(azidomethyl)-4-methoxy-10,16-dimethyl-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-12,17-dione
Ex.65	CH ₂ NH ₂	(10 <i>R</i> ,15 <i>S</i>)-15-(aminomethyl)-4-methoxy-10,16-dimethyl-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-12,17-dione
Ex.66	CH ₂ NHCOCH ₂ Ph	<i>N</i> -{[(10 <i>R</i> ,15 <i>S</i>)-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaen-15-yl]methyl}-2-phenylacetamide
Ex.67	CH ₂ OCONHPh	[(10 <i>R</i> ,15 <i>S</i>)-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0 ^{2,7}]docosa-1(22),2,4,6,18,20-hexaen-15-yl]methyl <i>N</i> -phenylcarbamate

Table 16a: Examples of Core 04 (Ex.68-Ex.89; continued on the following pages)

No	R ^c	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.68 -Ex.69: cf. experimental description						
Ex.70	NHCH ₃	Ex.69	A.2	CH ₃ NH ₃ Cl (4 equiv.) HATU (2.0 equiv.) HOAT (2.0 equiv.) i-Pr ₂ NEt (6 equiv.) rt, 2 h Workup: Sat. aq. Na ₂ CO ₃ , CH ₂ Cl ₂	FC (CH ₂ Cl ₂ /MeOH)	50%
Ex.71	NH ₂	Ex.69	A.2	NH ₄ Cl (4 equiv.) HATU (2.0 equiv.) HOAT (2.0 equiv.) i-Pr ₂ NEt (6 equiv.) rt, 2 h Workup: Sat. aq. Na ₂ CO ₃ , CH ₂ Cl ₂	prep. HPLC method 3	95
Ex.72	NHPh	Ex.69	A.2	Aniline	prep. HPLC method 3	68
Ex.73		Ex.69	A.2	2-Phenylethylamine	prep. HPLC method 3	71
Ex.74		Ex.69	A.2	Naphthalen-1-ylmethanamine 0°C, 1 h	prep. HPLC method 3 and FC (EtOAc)	70%

No	R ^c	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.75		Ex.69	A.2	3-Picolylamine 4°C, 1 h Workup: Sat. aq. Na ₂ CO ₃ , CHCl ₃	prep. HPLC method 3	55%
Ex.76		Ex.69	A.2	(L)-α-Methylbenzylamine	prep. HPLC method 3	60%
Ex.77		Ex.69	A.2	2-Methoxyethylamine	prep. HPLC method 3	66%
Ex.78		Ex.69	A.2	2,2,2-Trifluoroethylamine	prep. HPLC method 3	72%
Ex.79		Ex.69	A.2	Cyclopropylamine	prep. HPLC method 3 then prep. HPLC method 1a	32%
Ex.80		Ex.69	A.2	Isobutylamine 4°C, 1 h	prep. HPLC method 3	77%
Ex.81		Ex.69	A.2	2-Aminoethanol 4°C 2 h and rt 1 h	prep. HPLC method 1a	56%

No	R ^c	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.82		Ex.69	A.2	Glycine-tert.-butyl ester hydrochloride (2.2 equiv.) HATU (2.5 equiv.) HOAt (2.5 equiv.) i-Pr ₂ NEt (6.0 equiv.) 4°C, 3 h	FC (EtOAc)	78%
Ex.83		Ex.82	B.2	TFA, CH ₂ Cl ₂ rt, 4 h	prep. HPLC method 1a	78%
Ex.84		Ex.69	A.2	N,N-Dimethylethylenediamine 4°C, 1 h Workup: Sat. aq. Na ₂ CO ₃ , EtOAc	prep. HPLC method 3	47%
Ex.85		Ex.69	A.2	1-(3-Aminopropyl)pyrrolidine	prep. HPLC method 1a	57% (TFA salt)
Ex.86		Ex.69	A.2	Azetidine	prep. HPLC method 3	80%
Ex.87		Ex.69	A.2	Morpholine	prep. HPLC method 3	74%
Ex.88		Ex.69	A.2	(1-Methyl-1H-imidazol-4-yl)methanamine 4°C, 2 h and rt, 1 h	prep. HPLC method 1a	27% (TFA salt)

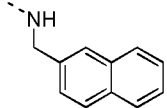
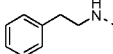
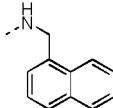
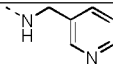
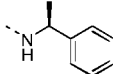
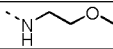
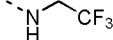
No	R ^c	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.89		Ex.69	A.2	Naphthalen-2-ylmethanamine 0°C, 3 h	prep. HPLC method 3 and FC (EtOAc)	73%

Table 16b: Examples of Core 04 (Ex.68-Ex.89; continued on the following page)

No	R ^c	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.68-Ex.69: cf. experimental description						
Ex.70	NHCH ₃	C23H27N3O4	409.2	1.57 (96)	410.1	method 1a
Ex.71	NH ₂	C22H25N3O4	395.2	1.53 (95)	396.1	method 1a
Ex.72	NHPh	C28H29N3O4	471.2	1.96 (92)	472.1	method 1a
Ex.73		C30H33N3O4	499.2	1.97 (99)	500.1	method 1a
Ex.74		C33H33N3O4	535.2	2.11 (96)	536.2	method 1a
Ex.75		C28H30N4O4	486.2	1.40 (93)	487.1	method 1a
Ex.76		C30H33N3O4	499.2	1.99 (96)	500.1	method 1a
Ex.77		C25H31N3O5	453.2	1.60 (99)	454.1	method 1a
Ex.78		C24H26F3N3O4	477.2	1.82 (96)	478.0	method 1a

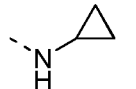
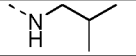
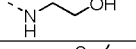
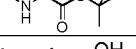
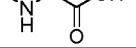
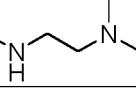
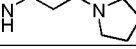
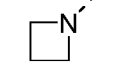
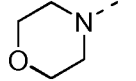
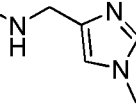
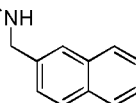
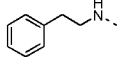
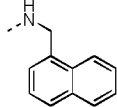
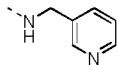
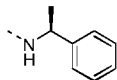
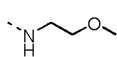
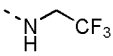
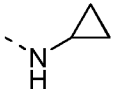
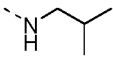
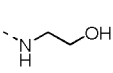
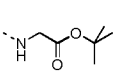
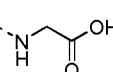
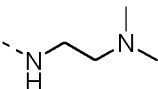
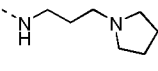
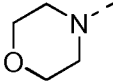
No	R ^c	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
<i>Ex.68-Ex.69: cf. experimental description</i>						
Ex.79		C ₂₅ H ₂₉ N ₃ O ₄	435.2	1.71 (98)	436.1	method 1a
Ex.80		C ₂₆ H ₃₃ N ₃ O ₄	451.2	1.90 (98)	452.1	method 1a
Ex.81		C ₂₄ H ₂₉ N ₃ O ₅	439.2	1.50 (91)	440.1	method 1a
Ex.82		C ₂₈ H ₃₅ N ₃ O ₆	509.2	1.97 (95)	510.1	method 1a
Ex.83		C ₂₄ H ₂₇ N ₃ O ₆	453.2	1.50 (98)	454.1	method 1a
Ex.84		C ₂₆ H ₃₄ N ₄ O ₄	466.2	1.40 (99)	467.1	method 1a
Ex.85		C ₂₉ H ₃₈ N ₄ O ₄	506.3	1.46 (99)	507.2	method 1a
Ex.86		C ₂₅ H ₂₉ N ₃ O ₄	435.2	1.63 (92)	436.1	method 1a
Ex.87		C ₂₆ H ₃₁ N ₃ O ₅	465.2	1.64 (92)	466.1	method 1a
Ex.88		C ₂₇ H ₃₁ N ₅ O ₄	489.2	1.43 (99)	490.1	method 1a
Ex.89		C ₃₃ H ₃₃ N ₃ O ₄	535.2	2.14 (93)	536.1	method 1a

Table 16c: Examples of Core 04 (Ex.68-Ex.89; continued on the following pages)

No	R ^c	IUPAC name
Ex.68	OCH ₂ Ph	benzyl (9 <i>S</i> ,14 <i>S</i>)-9,15-dimethyl-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxylate
Ex.69	OH	(9 <i>S</i> ,14 <i>S</i>)-9,15-dimethyl-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxylic acid
Ex.70	NHCH ₃	(9 <i>S</i> ,14 <i>S</i>)- <i>N</i> ,9,15-trimethyl-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide
Ex.71	NH ₂	(9 <i>S</i> ,14 <i>S</i>)-9,15-dimethyl-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide
Ex.72	NHPh	(9 <i>S</i> ,14 <i>S</i>)-9,15-dimethyl-11,16-dioxo- <i>N</i> -phenyl-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide
Ex.73		(9 <i>S</i> ,14 <i>S</i>)-9,15-dimethyl-11,16-dioxo- <i>N</i> -phenethyl-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide
Ex.74		(9 <i>S</i> ,14 <i>S</i>)-9,15-dimethyl- <i>N</i> -(1-naphthylmethyl)-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide
Ex.75		(9 <i>S</i> ,14 <i>S</i>)-9,15-dimethyl-11,16-dioxo- <i>N</i> -(3-pyridinylmethyl)-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide
Ex.76		(9 <i>S</i> ,14 <i>S</i>)-9,15-dimethyl-11,16-dioxo- <i>N</i> -[(1 <i>S</i>)-1-phenylethyl]-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide
Ex.77		(9 <i>S</i> ,14 <i>S</i>)- <i>N</i> -(2-methoxyethyl)-9,15-dimethyl-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide

No	R ^c	IUPAC name
Ex.78		(9 <i>S</i> ,14 <i>S</i>)-9,15-dimethyl-11,16-dioxo- <i>N</i> -(2,2,2-trifluoroethyl)-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide
Ex.79		(9 <i>S</i> ,14 <i>S</i>)- <i>N</i> -cyclopropyl-9,15-dimethyl-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide
Ex.80		(9 <i>S</i> ,14 <i>S</i>)- <i>N</i> -isobutyl-9,15-dimethyl-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide
Ex.81		(9 <i>S</i> ,14 <i>S</i>)- <i>N</i> -(2-hydroxyethyl)-9,15-dimethyl-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide
Ex.82		<i>tert</i> -butyl 2-({[(9 <i>S</i> ,14 <i>S</i>)-9,15-dimethyl-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaen-14-yl]carbonyl}amino)acetate
Ex.83		2-({[(9 <i>S</i> ,14 <i>S</i>)-9,15-dimethyl-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaen-14-yl]carbonyl}amino)acetic acid
Ex.84		(9 <i>S</i> ,14 <i>S</i>)- <i>N</i> -[2-(dimethylamino)ethyl]-9,15-dimethyl-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide
Ex.85		(9 <i>S</i> ,14 <i>S</i>)-9,15-dimethyl-11,16-dioxo- <i>N</i> -[3-(1-pyrrolidinyl)propyl]-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide
Ex.86		(9 <i>S</i> ,14 <i>S</i>)-14-(1-azetanylcarbonyl)-9,15-dimethyl-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-11,16-dione
Ex.87		(9 <i>S</i> ,14 <i>S</i>)-9,15-dimethyl-14-(morpholinocarbonyl)-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-11,16-dione

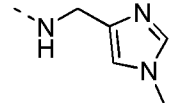
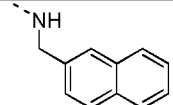
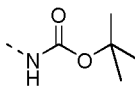
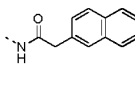
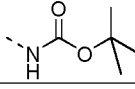
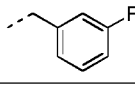
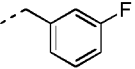
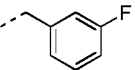
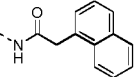
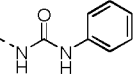
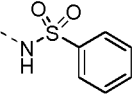
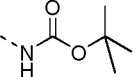
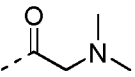
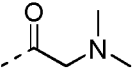
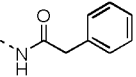
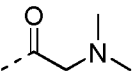
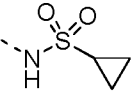
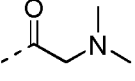
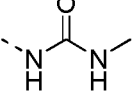
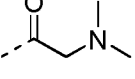
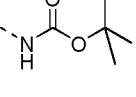
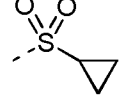
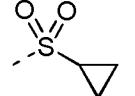
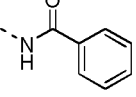
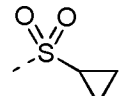
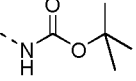
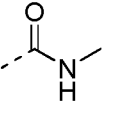
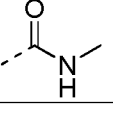
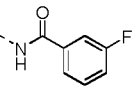
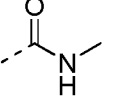
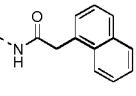
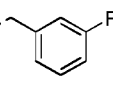
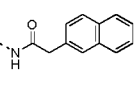
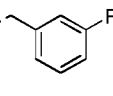
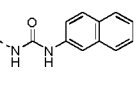
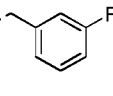
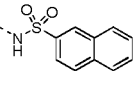
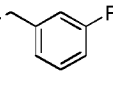
No	R ^c	IUPAC name
Ex.88		(9S,14S)-9,15-dimethyl-N-[(1-methyl-1H-imidazol-4-yl)methyl]-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide
Ex.89		(9S,14S)-9,15-dimethyl-N-(2-naphthylmethyl)-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1 ^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide

Table 17a: Examples of Core 05 (Ex.90-Ex.114 and Ex.341-Ex.358; continued on the following pages)

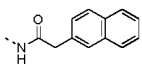
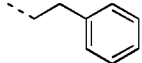
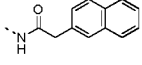
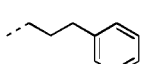
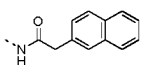
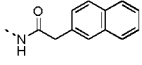
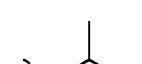
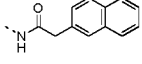
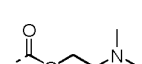
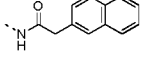
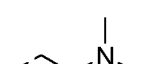
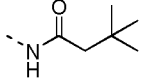
No	R ^B	R ^D	Starting Material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.90-Ex.92 <i>cf. experimental description</i>							
Ex.93	NH ₂	H	Ex.90	B.1 ¹⁾	HCl-dioxane rt, 16 h	prep. HPLC method 1c	17% (TFA salt)
Ex.94		CH ₃	Ex.91	A.6.2 ; ⁵⁾	Formaldehyde (36.5% in H ₂ O)	FC (CH ₂ Cl ₂ /MeOH)	84%
Ex.95	NH ₂	CH ₃	Ex.94	B.1; ⁵⁾	HCl-dioxane rt, 2 h	crude product	quant. (HCl salt)
Ex.96		CH ₃	Ex.95	A.1.1; ⁵⁾	2-Naphthaleneacetic acid	FC (CH ₂ Cl ₂ /MeOH) and prep. HPLC method 1b	41% (TFA salt)
Ex.97			Ex.91	A.6.3; ⁵⁾	3-Fluorobenzaldehyde	FC (CH ₂ Cl ₂ /MeOH)	80%

No	R ^B	R ^D	Starting Material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.98	NH ₂		Ex.97	B.1; ⁵⁾	HCl-dioxane rt, 2 h	crude product	95% (HCl salt)
Ex.99	NHCOCH ₃	CH ₃	Ex.95	A.1.2.1	Acetyl chloride (4.0 equiv. in total)	prep. HPLC method 1a	61% (TFA salt)
Ex.100	NHCOCH ₃		Ex.98	A.1.2.1; ⁵⁾	Acetyl chloride (4.0 equiv. in total)	prep. HPLC method 1a	64% (TFA salt)
Ex.101		CH ₃	Ex.95	A.1.3; ⁵⁾	1-Naphthaleneacetic acid	prep. HPLC method 1a	49% (TFA salt)
Ex.102		CH ₃	Ex.95	A.3	Phenyl isocyanate rt, 15 h	prep. HPLC method 1a	57% (TFA salt)
Ex.103		CH ₃	Ex.95	A.5; ⁵⁾	Benzenesulfonyl chloride (2.0 equiv.) Et ₃ N (3.0 equiv.) i-Pr ₂ NEt (3.0 equiv.)	prep. HPLC method 1a	44% (TFA salt)
Ex.104			Ex.91	A.1.3	2-(Dimethylamino)- acetic acid rt, 2 h	FC (CH ₂ Cl ₂ /MeOH)	83%
Ex.105	NH ₂		Ex.104	B.1	HCl-dioxane rt, 2 h	crude product	90%
Ex.106			Ex.105	A.1.3	2-Phenylacetic acid (4.8 equiv.) rt, 40 h	prep. HPLC method 1a	41% (TFA salt)

No	R ^B	R ^D	Starting Material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.107			Ex.105	A.5	Cyclopropanesulfonyl chloride (3.0 equiv.) Et ₃ N (8.0 equiv.) rt, 16 h	prep. HPLC method 1a	32% (TFA salt)
Ex.108			Ex.105	A.3	N-Succinimidyl N-methylcarbamate (1.4 equiv.) i-Pr ₂ NEt (5.0 equiv.) rt, 16 h	prep. HPLC method 1a	55% (TFA salt)
Ex.109			Ex.91	A.5	Cyclopropanesulfonyl chloride (5.2 equiv.) Et ₃ N (5.0 equiv.), DMAP (0.1 equiv.) 45°C, 48 h	FC (CH ₂ Cl ₂ /MeOH)	64%
Ex.110	NH ₂		Ex.109	B.1	HCl-dioxane rt, 3 h	crude product	quant. (HCl salt)
Ex.111			Ex.110	A.1.2.1	Benzoyl chloride (2.0 equiv) i-Pr ₂ NEt (5.0 equiv.) rt, 16 h	prep. HPLC method 1a	19% (TFA salt)

No	R ^B	R ^D	Starting Material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.112			Ex.91	A.3	N-Succinimidyl N-methylcarbamate (1.4 equiv.) i-Pr ₂ NEt (5.0 equiv.) rt, 16 h	FC (CH ₂ Cl ₂ /MeOH)	82%
Ex.113	NH ₂		Ex.112	B.1	HCl-dioxane rt, 4 h	crude product	quant. (HCl salt)
Ex.114			Ex.113	A.1.2.1	3-Fluorobenzoyl chloride (4.0 equiv. in total)	prep. HPLC method 1a	5% (TFA salt)
Ex.341			Ex.98	A.1.3	1-Naphthaleneacetic acid i-Pr ₂ NEt (9 equiv.)	prep. HPLC method 1a and FC (CH ₂ Cl ₂ /MeOH)	47%
Ex.342			Ex.98	A.1.3	2-Naphthaleneacetic acid i-Pr ₂ NEt (9 equiv.)	prep. HPLC method 1a and FC (CH ₂ Cl ₂ /MeOH)	34%
Ex.343			Ex.98	A.3	2-Naphthylisocyanate i-Pr ₂ NEt (5 equiv.)	prep. HPLC method 1a and FC (CH ₂ Cl ₂ /MeOH)	63%
Ex.344			Ex.98	A.5	Naphthalene-2-sulfonyl chloride i-Pr ₂ NEt (5 equiv.)	prep. HPLC method 1a	41% (TFA salt)

No	R ^B	R ^D	Starting Material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.345			Ex.98	A.1.3	2- Naphthalene- propanoic acid i-Pr ₂ NEt (9 equiv.)	prep. HPLC method 1a	40% (TFA salt)
Ex.346			Ex.98	A.1.3	3-Phenylpropionic acid i-Pr ₂ NEt (9 equiv.)	prep. HPLC method 1a	37% (TFA salt)
Ex.347			Ex.98	A.1.3	N, N-Dimethylglycine i-Pr ₂ NEt (9 equiv.)	prep. HPLC method 1a	9% (TFA salt)
Ex.348			Ex.92	A.1.3	2- Naphthaleneacetic acid i-Pr ₂ NEt (6 equiv.)	FC (CH ₂ Cl ₂ /MeOH)	80%
Ex.349		H	Ex.348	B.3	H ₂ , Pd(OH) ₂ -C, MeOH	crude product	97%
Ex.350			Ex.349	A.1.3	3-Fluorobenzoic acid	prep. HPLC method 1a	55% (TFA salt)
Ex.351			Ex.349	A.6.3	Benzaldehyde Workup : CH ₂ Cl ₂ , sat. aq. Na ₂ CO ₃ soln	prep. HPLC method 1a	51% (TFA salt)

No	R ^B	R ^D	Starting Material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.352			Ex.349	A.6.3	Phenylacetaldehyde Workup : CH ₂ Cl ₂ , sat. aq. Na ₂ CO ₃ soln	prep. HPLC method 1a	37% (TFA salt)
Ex.353			Ex.349	A.6.3	3-Phenylpropion- aldehyde Workup : CH ₂ Cl ₂ , sat. aq. Na ₂ CO ₃ soln	prep. HPLC method 1a	30% (TFA salt)
Ex.354			Ex.349	A.6.3	Isovaleraldehyde (1.7 equiv.) Workup : CH ₂ Cl ₂ , sat. aq. Na ₂ CO ₃ soln	prep. HPLC method 1a	32% (TFA salt)
Ex.355			Ex.349	A.6.3	Isobutyraldehyde Workup : CH ₂ Cl ₂ , sat. aq. Na ₂ CO ₃ soln	prep. HPLC method 1a	68% (TFA salt)
Ex.356			Ex.349	2)	2-Dimethylaminoethyl- chlorid hydrochloride	FC (CH ₂ Cl ₂ /MeOH)	21%
Ex.357			Ex.349	3)	2-Dimethylaminoethyl- chlorid hydrochloride	prep. HPLC method 2a and FC (CH ₂ Cl ₂ /MeOH)	17%
Ex.358		CH ₃	Ex.95	4)	3,3-Dimethylbutyryl chloride	FC (CH ₂ Cl ₂ /MeOH)	83%

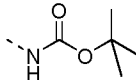
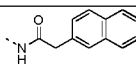
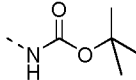
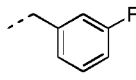
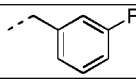
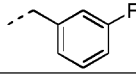
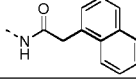
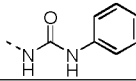
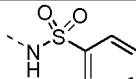
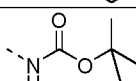
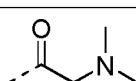
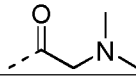
- 1) **Ex.93** was obtained as a side product upon treatment of **Ex.90** with HCl-dioxane; see description of synthesis of **Ex.92**.
- 2) 2-Dimethylaminoethylchloride hydrochloride (13 mg, 0.089 mmol) was added to a mixture of **Ex.349** (50 mg, 0.089 mmol) and dry K₂CO₃ (61 mg, 0.44 mmol) in DCE (0.5 mL). The mixture was stirred at 50°C for 16 h. More 2-dimethylaminoethylchloride hydrochloride (6.4 mg, 0.044 mmol) was added and stirring at 50°C continued for 2 h. Aqueous workup (CH₂Cl₂, sat. aq. Na₂CO₃ soln; Na₂SO₄) and FC (CH₂Cl₂/MeOH 100:0 to 80:20) afforded **Ex.356** (13 mg, 21%).
- 3) 2-Dimethylaminoethylchloride hydrochloride (64 mg, 0.44 mmol) was added to a mixture of **Ex.349** (60 mg, 0.106 mmol) and i-Pr₂NEt (0.121 mL; 0.71 mmol) in DMF (1 mL). The mixture was stirred at 50°C for 3 d. More 2-dimethylaminoethylchloride hydrochloride (64 mg, 0.44 mmol) and i-Pr₂NEt (0.121 mL; 0.71 mmol) were added and stirring at 50°C was continued for 1 d. Aqueous workup (EtOAc, sat. aq. Na₂CO₃ soln; Na₂SO₄) and FC (CH₂Cl₂/MeOH(conc. aq. NH₃ soln 100:0:0.1 to 90:10:0.1) afforded **Ex.357** (12 mg, 17%).
- 4) Synthesis of **Ex.358**
3,3-Dimethylbutyryl chloride (0.019 mL, 0.14 mmol) was added at 0°C to a suspension of **Ex.95** (60 mg, 0.116 mmol) and pyridine (0.047 mL, 0.58 mmol) in CH₂Cl₂ (1.2 mL). The mixture was stirred at rt for 1 h and cooled to 0°C. Then i-Pr₂NEt (0.059 mL; 0.35 mmol) and 3,3-dimethylbutyryl chloride (0.019 mL, 0.14 mmol) were added. The resulting clear soln was stirred for 30 min. MeOH (0.01 mL) was added and stirring continued for 10 min. The volatiles were evaporated. FC (CH₂Cl₂/MeOH 100:0 to 95:5) afforded **Ex.358** (49 mg, 83%).

Data of **Ex.358**: cf. Table 17b

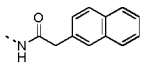
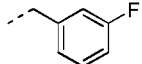
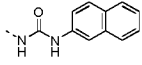
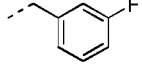
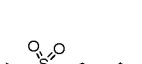
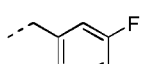
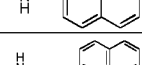
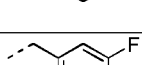
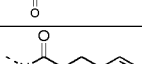
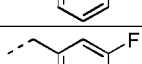
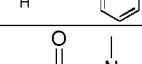
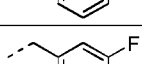
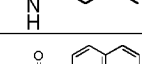
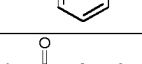
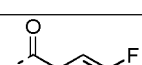
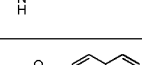
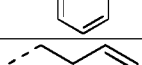
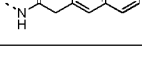
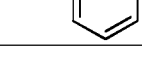
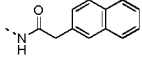
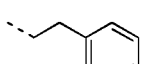
¹H-NMR (DMSO-d₆): 9.62 (br. s, 1 H); 9.22 (t, J ca. 1.9, 1 H); 9.18 (d, J = 2.0, 1 H); 8.93 (d, J = 1.9, 1 H); 8.40 (br.s, 1 H); 8.08 (d, J = 6.5, 1 H); 7.59 (d, J = 7.6, 1 H); 7.40 (t, J = 7.9, 1 H); 6.82 (dd; J = 2.0, 8.3, 1 H); 4.53 – 4.41 (br. not resolved m, 3 H); 3.91 (t, J = 11.2, 1 H); 3.72 (dd; J = 7.0, 9.7, 1 H); 3.46 (d, J = 17.6, 1 H); 3.38 – 3.24 (m, 3 H, partially superimposed by H₂O signal); 3.13 (dd-like m, 1 H); 2.62 (m, 2 H); 2.37 (s, 3 H); 2.14 (m, 1 H); 1.96 (s, 2 H); 1.93 (m, 1 H); 0.96 (s, 9 H).

- 5) Cf. experimental description for detailed procedure

Table 17b: Examples of Core 05 (Ex.90-Ex.114 and Ex.341-Ex.358; continued on the following pages)

No	R ^B	R ^D	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.90-Ex.92: cf. experimental description							
Ex.93	NH ₂	H	C ₂₁ H ₂₅ N ₅ O ₃	395.2	0.89 (97)	396.1	method 1a
Ex.94		CH ₃	C ₂₇ H ₃₅ N ₅ O ₅	509.3	1.49 (97)	510.1	method 1a
Ex.95	NH ₂	CH ₃	C ₂₂ H ₂₇ N ₅ O ₃	409.2	1.43 (98)	410.1	method 2c
Ex.96		CH ₃	C ₃₄ H ₃₅ N ₅ O ₄	577.3	1.59 (99)	578.1	method 1a
Ex.97			C ₃₃ H ₃₈ FN ₅ O ₅	603.3	2.44 (95)	604.0	method 2d
Ex.98	NH ₂		C ₂₈ H ₃₀ FN ₅ O ₃	503.2	1.31 (90)	504.2	method 1a
Ex.99	NHCOCH ₃	CH ₃	C ₂₄ H ₂₉ N ₅ O ₄	451.2	1.10 (96)	452.2	method 1a
Ex.100	NHCOCH ₃		C ₃₀ H ₃₂ FN ₅ O ₄	545.2	1.47 (97)	546.2	method 1a
Ex.101		CH ₃	C ₃₄ H ₃₅ N ₅ O ₄	577.3	1.59 (98)	578.2	method 1a
Ex.102		CH ₃	C ₂₉ H ₃₂ N ₆ O ₄	528.2	1.44 (98)	529.2	method 1a
Ex.103		CH ₃	C ₂₈ H ₃₁ N ₅ O ₅ S	549.2	1.43 (99)	550.1	method 1a
Ex.104			C ₃₀ H ₄₀ N ₆ O ₆	580.3	2.02 (96)	581.2	method 2d
Ex.105	NH ₂		C ₂₅ H ₃₂ N ₆ O ₄	480.2	0.97 (95)	481.1	method 1a

No	R ^B	R ^D	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.106			C33H38N6O5	598.3	1.45 (98)	599.2	method 1a
Ex.107			C28H36N6O6S	584.2	1.30 (95)	585.1	method 1a
Ex.108			C27H35N7O5	537.3	1.17 (97)	538.2	method 1a
Ex.109			C29H37N5O7S	599.2	1.87 (93)	600.1	method 1a
Ex.110	NH ₂		C24H29N5O5S	499.2	1.20 (91)	500.1	method 1a
Ex.111			C31H33N5O6S	603.2	1.73	604.0	method 1a
Ex.112			C28H36N6O6	552.3	1.67 (94)	553.1	method 1a
Ex.113	NH ₂		C23H28N6O4	452.2	1.04 (89)	453.1	method 1a
Ex.114			C30H31FN6O5	574.2	1.63 (95)	575.2	method 1a
Ex.341			C40H38FN5O4	671.3	2.37 (97)	672.0	method 2c

No	R ^B	R ^D	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.342			C ₄₀ H ₃₈ FN ₅ O ₄	671.3	2.38 (94)	672.0	method 2c
Ex.343			C ₃₉ H ₃₇ FN ₆ O ₄	672.3	2.41 (96)	673.0	method 2c
Ex.344			C ₃₈ H ₃₆ FN ₅ O ₅ S	693.2	2.42 (96)	694.0	method 2c
Ex.345			C ₄₁ H ₄₀ FN ₅ O ₄	685.3	2.41 (97)	686.0	method 2c
Ex.346			C ₃₇ H ₃₈ FN ₅ O ₄	635.3	2.26 (97)	635.8	method 2c
Ex.347			C ₃₂ H ₃₇ FN ₆ O ₄	588.3	2.01 (89)	588.5	method 2c
Ex.348			C ₄₁ H ₃₉ N ₅ O ₆	697.3	2.06 (97)	698.0	method 1a
Ex.349		H	C ₃₃ H ₃₃ N ₅ O ₄	563.2	1.94 (88)	563.9	method 2c
Ex.350			C ₄₀ H ₃₆ FN ₅ O ₅	685.3	1.97 (99)	686.0	method 1a
Ex.351			C ₄₀ H ₃₉ N ₅ O ₄	653.3	2.38 (98)	654.0	method 2c
Ex.352			C ₄₁ H ₄₁ N ₅ O ₄	667.3	2.40 (94)	667.9	method 2c
Ex.353			C ₄₂ H ₄₃ N ₅ O ₄	681.3	2.51 (97)	682.1	method 2c

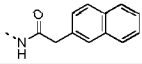
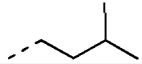
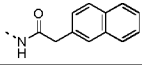
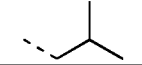
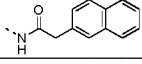
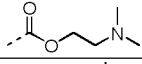
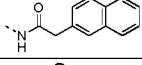
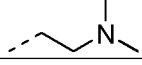
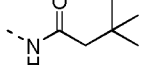
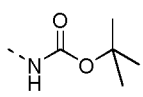
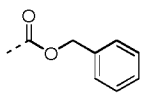
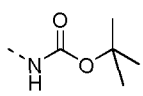
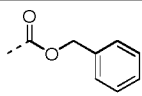
No	R ^B	R ^D	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.354			C ₃₈ H ₄₃ N ₅ O ₄	633.3	2.47 (98)	634.0	method 2c
Ex.355			C ₃₇ H ₄₁ N ₅ O ₄	619.3	2.41 (96)	619.9	method 2c
Ex.356			C ₃₈ H ₄₂ N ₆ O ₆	678.3	2.05 (96)	679.3	method 2e
Ex.357			C ₃₇ H ₄₂ N ₆ O ₄	634.3	2.20 (96)	635.3	method 2e
Ex.358		CH ₃	C ₂₈ H ₃₇ N ₅ O ₄	507.3	1.43 (99)	508.2	method 1c

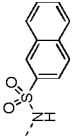
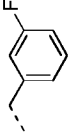
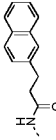
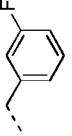
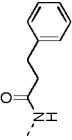
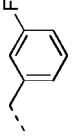
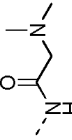
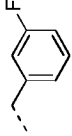
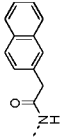
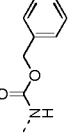
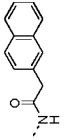
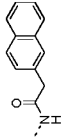
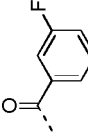
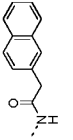
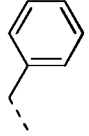
Table 17c: Examples of Core 05 (Ex.90-Ex.114 and Ex.341-Ex.358; continued on the following pages)

No	R ^B	R ^D	IUPAC name
Ex.90			benzyl (9 <i>S</i> ,11 <i>R</i>)-11-[(<i>tert</i> -butoxycarbonyl)amino]-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaene-16-carboxylate
Ex.91		H	<i>tert</i> -butyl <i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]carbamate
Ex.92	NH ₂		benzyl (9 <i>S</i> ,11 <i>R</i>)-11-amino-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaene-16-carboxylate
Ex.93	NH ₂	H	(9 <i>S</i> ,11 <i>R</i>)-11-amino-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaene-14,20-dione

No	R ^B	R ^D	IUPAC name
Ex.94		CH ₃	<i>tert</i> -butyl <i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-methyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacos-1(25),2(26),3,5,21,23-hexaen-11-yl]carbamate
Ex.95	NH ₂	CH ₃	(9 <i>S</i> ,11 <i>R</i>)-11-amino-16-methyl-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacos-1(25),2(26),3,5,21,23-hexaene-14,20-dione
Ex.96		CH ₃	<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-methyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacos-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(2-naphthyl)acetamide
Ex.97			<i>tert</i> -butyl <i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-(3-fluorobenzyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacos-1(25),2(26),3,5,21,23-hexaen-11-yl]carbamate
Ex.98	NH ₂		(9 <i>S</i> ,11 <i>R</i>)-11-amino-16-(3-fluorobenzyl)-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacos-1(25),2(26),3,5,21,23-hexaene-14,20-dione
Ex.99	NHCOCH ₃	CH ₃	<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-methyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacos-1(25),2(26),3,5,21,23-hexaen-11-yl]acetamide
Ex.100	NHCOCH ₃		<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-(3-fluorobenzyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacos-1(25),2(26),3,5,21,23-hexaen-11-yl]acetamide
Ex.101		CH ₃	<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-methyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacos-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(1-naphthyl)acetamide
Ex.102		CH ₃	<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-methyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacos-1(25),2(26),3,5,21,23-hexaen-11-yl]- <i>N</i> '-phenylurea

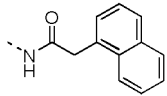
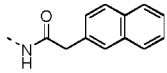
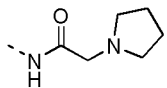
No	R ^B	R ^D	IUPAC name
Ex.103		CH ₃	<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-methyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]benzenesulfonamide
Ex.104			<i>tert</i> -butyl <i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-[2-(dimethylamino)acetyl]-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]carbamate
Ex.105	NH ₂		(9 <i>S</i> ,11 <i>R</i>)-11-amino-16-[2-(dimethylamino)acetyl]-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaene-14,20-dione
Ex.106			<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-[2-(dimethylamino)acetyl]-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-phenylacetamide
Ex.107			<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-[2-(dimethylamino)acetyl]-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]cyclopropanesulfonamide
Ex.108			<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-[2-(dimethylamino)acetyl]-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]- <i>N'</i> -methylurea
Ex.109			<i>tert</i> -butyl <i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-(cyclopropylsulfonyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]carbamate
Ex.110	NH ₂		(9 <i>S</i> ,11 <i>R</i>)-11-amino-16-(cyclopropylsulfonyl)-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaene-14,20-dione

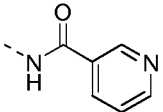
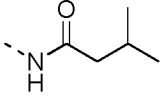
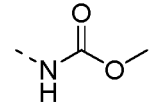
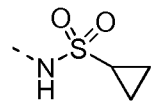
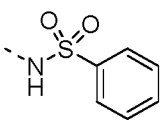
No	R ^B	R ^D	IUPAC name
Ex.111			<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-(cyclopropylsulfonyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]benzamide
Ex.112			<i>tert</i> -butyl <i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-[(methylamino)carbonyl]-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]carbamate
Ex.113	NH ₂		(9 <i>S</i> ,11 <i>R</i>)-11-amino- <i>N</i> -methyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaene-16-carboxamide
Ex.114			(9 <i>S</i> ,11 <i>R</i>)-11-[(3-fluorobenzoyl)amino]- <i>N</i> -methyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaene-16-carboxamide
Ex.341			<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-(3-fluorobenzyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(1-naphthyl)acetamide
Ex.342			<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-(3-fluorobenzyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(2-naphthyl)acetamide
Ex.343			<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-(3-fluorobenzyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]- <i>N</i> -(2-naphthyl)urea

No	R ^B	R ^D	IUPAC name
Ex.344			N-[(9S,11R)-16-(3-fluorobenzyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-naphthalenesulfonamide
Ex.345			N-[(9S,11R)-16-(3-fluorobenzyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-3-(2-naphthyl)propanamide
Ex.346			N-[(9S,11R)-16-(3-fluorobenzyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-3-phenylpropanamide
Ex.347			2-(dimethylamino)-N-[(9S,11R)-16-(3-fluorobenzyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]acetamide
Ex.348			benzyl (9S,11R)-1-1-[[2-(2-naphthyl)acetyl]amino]-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaene-16-carboxylate
Ex.349		H	N-[(9S,11R)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(2-naphthyl)acetamide
Ex.350			N-[(9S,11R)-16-(3-fluorobenzyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(2-naphthyl)acetamide
Ex.351			N-[(9S,11R)-16-benzyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(2-naphthyl)acetamide

No	R ^B	R ^D	IUPAC name
Ex.352			<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-14,20-dioxo-16-phenethyl-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(2-naphthyl)acetamide
Ex.353			<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-14,20-dioxo-16-(3-phenylpropyl)-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(2-naphthyl)acetamide
Ex.354			<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-isopentyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(2-naphthyl)acetamide
Ex.355			<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-isobutyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(2-naphthyl)acetamide
Ex.356			2-(dimethylamino)ethyl (9 <i>S</i> ,11 <i>R</i>)-11-[[2-(2-naphthyl)acetyl]amino]-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaene-16-carboxylate
Ex.357			<i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-[2-(dimethylamino)ethyl]-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(2-naphthyl)acetamide
Ex.358		CH ₃	3,3-dimethyl- <i>N</i> -[(9 <i>S</i> ,11 <i>R</i>)-16-methyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1 ^{2,6} .0 ^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]butanamide

Table 18a: Examples of Core 06 (Ex.115-Ex.128; continued on the following pages)

No	R ^A	Starting Material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.115-Ex.116: cf. experimental description						
Ex.117		Ex.116	A.1.1	1-Naphthaleneacetic acid 0°C, 2 h	prep. HPLC method 3, then washed with Et ₂ O, then FC (hexane/EtOAc)	66%
Ex.118		Ex.116	A.1.1	2-Naphthaleneacetic acid 0°C, 2 h	prep. HPLC method 3, then washed with Et ₂ O, then FC (hexane/EtOAc)	60%
Ex.119		Ex.116	A.1.1	1-Pyrrolidineacetic acid 0°C, 2 h aq. workup (EtOAc, sat. aq. NaHCO ₃ soln, H ₂ O, sat. aq. NaCl soln; Na ₂ SO ₄)	prep. HPLC method 3	57%

No	R ^A	Starting Material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.120		Ex.116	A.1.1	Nicotinic acid 0°C, 2 h aq. workup (EtOAc, sat. aq. NaHCO ₃ soln, H ₂ O, sat. aq. NaCl soln; Na ₂ SO ₄)	prep. HPLC method 3	72%
Ex.121		Ex.116	A.1.2	3-Methylbutanoyl chloride (1.2 equiv.) 0°C, 2 h	prep. HPLC method 3	38%
Ex.122		Ex.116	A.4	Methyl chloroformate 0°C to rt, 2 h	prep. HPLC method 3	83%
Ex.123		Ex.116	A.5	Cyclopropanesulfonyl chloride (2.0 equiv.) Et ₃ N (3 equiv.) DMAP (0.1 equiv) rt, 15 h Workup: CHCl ₃ , half-sat. aq. NaHCO ₃ soln.; Na ₂ SO ₄	prep. HPLC method 3	64%
Ex.124		Ex.116	A.5	Benzenesulfonyl chloride (1.5 equiv.) rt, 1 h	prep. HPLC method 3	54%

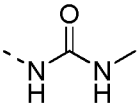
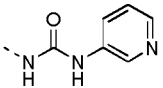
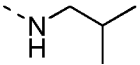
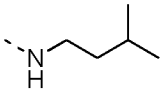
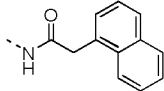
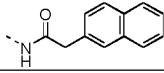
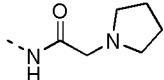
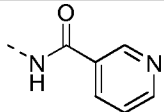
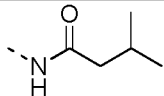
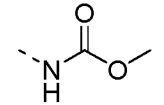
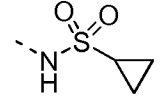
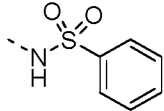
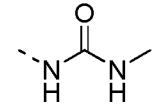
No	R ^A	Starting Material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.125		Ex.116	A.3	N-Succinimidyl N-methylcarbamate (1.8 equiv.) i-Pr ₂ NEt (4.5 equiv) THF/CHCl ₃ 1:1 (0.9 mL) rt, 16 h	no chromatography; washing of crude product with EtOH and Et ₂ O	73%
Ex.126		Ex.116	A.3	2,5-Dioxopyrrolidin-1-yl pyridin-3-ylcarbamate (1.3 equiv.) i-Pr ₂ NEt (3 equiv) THF/CHCl ₃ 1:1 (0.5 mL) rt, 15 h	no chromatography; washing of crude product with EtOH and Et ₂ O	70%
Ex.127		Ex.116	A.6.4	Isobutyraldehyde (1.05 equiv.)	prep. HPLC method 3	52%
Ex.128		Ex.116	A.6.4	3-Methylbutanal (1.05 equiv.)	prep. HPLC method 3 and prep. HPLC method 1a	8% (TFA salt)

Table 18b: Examples of Core 06 (Ex.115-Ex.128; continued on the following page)

No	R ^A	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.115-Ex.116: cf. experimental description						
Ex.117		C33H34N2O3S	538.2	2.55 (95)	539.2	method 1a
Ex.118		C33H34N2O3S	538.2	2.54 (95)	539.2	method 1a
Ex.119		C27H35N3O3S	481.2	1.82 (97)	482.2	method 1a
Ex.120		C27H29N3O3S	475.2	1.90 (92)	476.1	method 1a
Ex.121		C26H34N2O3S	454.2	2.32 (90)	455.2	method 1a
Ex.122		C23H28N2O4S	428.2	2.15 (97)	429.2	method 1a
Ex.123		C24H30N2O4S2	474.2	2.23 (93)	475.1	method 1a
Ex.124		C27H30N2O4S2	510.2	2.33 (82)	511.1	method 1a
Ex.125		C23H29N3O3S	427.2	1.97 (88)	428.2	method 1a

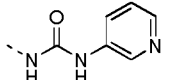
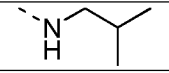
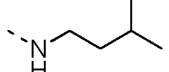
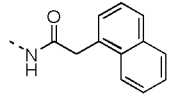
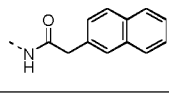
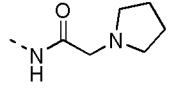
No	R ^A	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.126		C ₂₇ H ₃₀ N ₄ O ₃ S	490.2	1.80 (95)	491.2	method 1a
Ex.127		C ₂₅ H ₃₄ N ₂ O ₂ S	426.2	1.97 (97)	427.2	method 1a
Ex.128		C ₂₆ H ₃₆ N ₂ O ₂ S	440.2	2.05 (98)	441.2	method 1a

Table 18c: Examples of Core 06 (Ex.115-Ex.128; continued on the following page)

No	R ^A	IUPAC name
Ex.115	NHAlloc	allyl <i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-14-oxo-18-oxa-8-thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]carbamate
Ex.116	NH ₂	(13 <i>S</i> ,16 <i>R</i>)-13-amino-16-methyl-18-oxa-8-thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-14-one
Ex.117		<i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-14-oxo-18-oxa-8-thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]-2-(1-naphthyl)acetamide
Ex.118		<i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-14-oxo-18-oxa-8-thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]-2-(2-naphthyl)acetamide
Ex.119		<i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-14-oxo-18-oxa-8-thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]-2-(1-pyrrolidinyl)acetamide

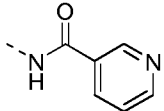
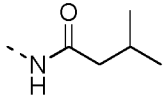
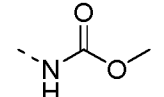
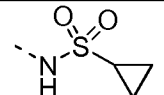
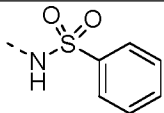
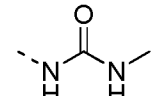
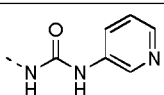
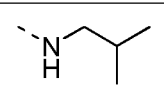
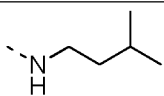
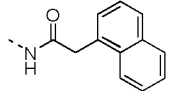
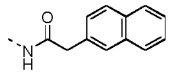
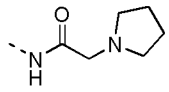
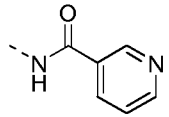
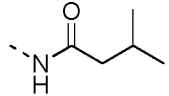
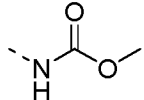
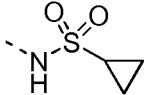
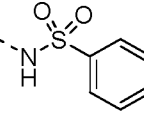
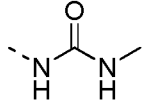
No	R ^A	IUPAC name
Ex.120		<i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-14-oxo-18-oxa-8-thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]nicotinamide
Ex.121		3-methyl- <i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-14-oxo-18-oxa-8-thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]butanamide
Ex.122		methyl <i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-14-oxo-18-oxa-8-thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]carbamate
Ex.123		<i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-14-oxo-18-oxa-8-thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]cyclopropanesulfonamide
Ex.124		<i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-14-oxo-18-oxa-8-thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]benzenesulfonamide
Ex.125		<i>N</i> -methyl- <i>N</i> '-[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-14-oxo-18-oxa-8-thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]urea
Ex.126		<i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-14-oxo-18-oxa-8-thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]- <i>N</i> '-(3-pyridinyl)urea
Ex.127		(13 <i>S</i> ,16 <i>R</i>)-13-(isobutylamino)-16-methyl-18-oxa-8-thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-14-one
Ex.128		(13 <i>S</i> ,16 <i>R</i>)-13-(isopentylamino)-16-methyl-18-oxa-8-thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-14-one

Table 19a: Examples of Core 07 (Ex.129-Ex.142; continued on the following pages)

No	R ^A	Starting Material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.129-Ex.130: cf. experimental description						
Ex.131		Ex.130	A.1.1	1-Naphthaleneacetic acid 0°C, 2 h	prep. HPLC method 3	71%
Ex.132		Ex.130	A.1.1	2-Naphthaleneacetic acid 0°C, 2 h	prep. HPLC method 3	73%
Ex.133		Ex.130	A.1.1	1-Pyrrolidineacetic acid 0°C, 2 h aq. workup (EtOAc, sat. aq. NaHCO ₃ soln, H ₂ O, sat. aq. NaCl soln; Na ₂ SO ₄)	prep. HPLC method 3	46%
Ex.134		Ex.130	A.1.1	Nicotinic acid 0°C, 2 h aq. workup (EtOAc, sat. aq. NaHCO ₃ soln, H ₂ O, sat. aq. NaCl soln; Na ₂ SO ₄)	prep. HPLC method 3	59%
Ex.135		Ex.130	A.1.2	3-Methylbutanoyl chloride (1.2 equiv.) 0°C, 2 h	prep. HPLC method 3	77%

No	R ^A	Starting Material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex. 136		Ex. 130	A.4	Methyl chloroformate 0°C to rt, 2 h	prep. HPLC method 3	20%
Ex. 137		Ex. 130	A.5	Cyclopropanesulfonyl chloride (1.5 equiv.) Et ₃ N (3 equiv.) DMAP (0.1 equiv) CHCl ₃ (0.5 mL) rt, 15 h Workup: CHCl ₃ , half-sat. aq. NaHCO ₃ soln.; Na ₂ SO ₄	prep. HPLC method 3	71%
Ex. 138		Ex. 130	A.5	Benzenesulfonyl chloride (1.5 equiv.)	prep. HPLC method 3	52%
Ex. 139		Ex. 130	A.3	N-Succinimidyl N-methylcarbamate (1.8 equiv.) i-Pr ₂ NEt (4.5 equiv) THF/CHCl ₃ 1:1 (0.9 mL) rt, 20 h	prep. HPLC method 3	49%

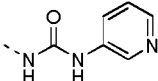
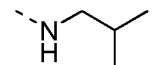
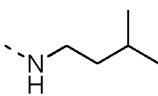
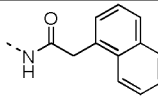
No	R ^A	Starting Material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.140		Ex.130	A.3	2,5-Dioxopyrrolidin-1-yl pyridin-3-ylcarbamate (1.3 equiv.) i-Pr ₂ NEt (3 equiv) THF/CHCl ₃ 1:1 (0.5 mL) rt, 15 h	prep. HPLC method 3	64%
Ex.141		Ex.130	A.6.4	Isobutyraldehyde (1.05 equiv.)	prep. HPLC method 3	57%
Ex.142		Ex.130	A.6.4	3-Methylbutanal (1.05 equiv.)	prep. HPLC method 3 and prep. HPLC method 1a	11% (TFA salt)

Table 19b: Examples of Core 07 (Ex.129-Ex.142; continued on the following page)

No	R ^A	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.129-Ex.130: cf. experimental description						
Ex.131		C ₃₃ H ₃₄ N ₂ O ₅ S	570.2	2.28 (91)	571.2	method 1a

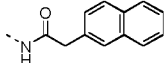
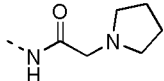
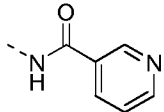
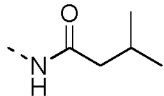
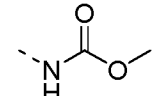
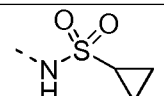
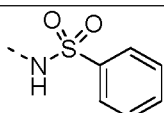
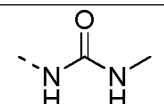
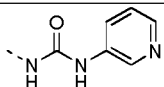
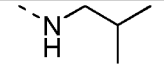
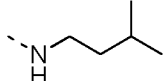
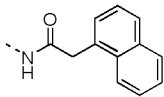
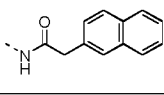
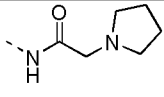
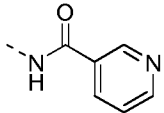
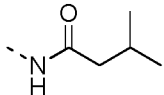
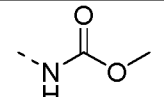
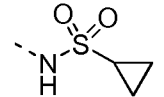
No	R ^A	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.132		C33H34N2O5S	570.2	2.20 (97)	571.2	method 1a
Ex.133		C27H35N3O5S	513.2	1.55 (93)	514.2	method 1a
Ex.134		C27H29N3O5S	507.2	1.59 (99)	509.0	method 1a
Ex.135		C26H34N2O5S	486.2	1.92 (99)	487.2	method 1a
Ex.136		C23H28N2O6S	460.2	1.74 (99)	461.0	method 1a
Ex.137		C24H30N2O6S2	506.2	1.84 (99)	507.1	method 1a
Ex.138		C27H30N2O6S2	542.2	2.02 (97)	543.1	method 1a
Ex.139		C23H29N3O5S	459.2	1.61 (99)	460.1	method 1a
Ex.140		C27H30N4O5S	522.2	1.53 (98)	523.2	method 1a
Ex.141		C25H34N2O4S	458.2	1.70 (99)	459.2	method 1a
Ex.142		C26H36N2O4S	472.3	1.78 (85)	473.2	method 1a

Table 19c: Examples of Core 07 (Ex.129-Ex.142; continued on the following page)

No	R ^A	IUPAC name
Ex.129	NHAlloc	allyl <i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-8,8,14-trioxo-18-oxa-8λ ⁶ -thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]carbamate
Ex.130	NH ₂	(13 <i>S</i> ,16 <i>R</i>)-13-amino-16-methyl-18-oxa-8λ ⁶ -thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaene-8,8,14-trione
Ex.131		<i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-8,8,14-trioxo-18-oxa-8λ ⁶ -thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]-2-(1-naphthyl)acetamide
Ex.132		<i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-8,8,14-trioxo-18-oxa-8λ ⁶ -thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]-2-(2-naphthyl)acetamide
Ex.133		<i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-8,8,14-trioxo-18-oxa-8λ ⁶ -thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]-2-(1-pyrrolidinyl)acetamide
Ex.134		<i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-8,8,14-trioxo-18-oxa-8λ ⁶ -thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]nicotinamide
Ex.135		3-methyl- <i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-8,8,14-trioxo-18-oxa-8λ ⁶ -thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]butanamide
Ex.136		methyl <i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-8,8,14-trioxo-18-oxa-8λ ⁶ -thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]carbamate
Ex.137		<i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-8,8,14-trioxo-18-oxa-8λ ⁶ -thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]cyclopropanesulfonamide

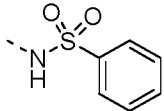
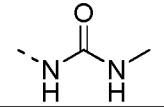
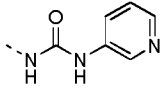
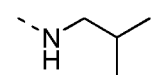
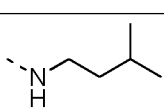
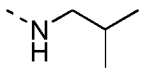
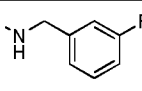
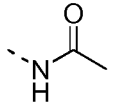
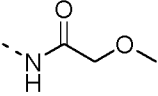
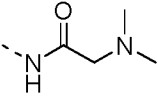
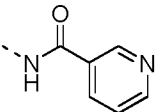
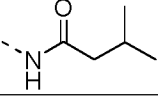
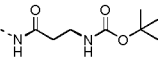
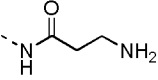
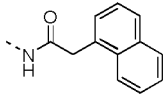
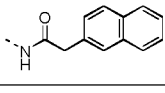
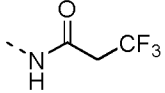
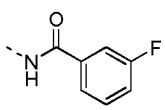
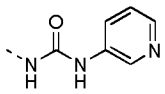
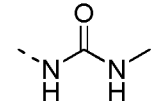
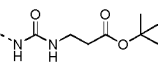
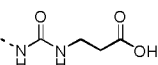
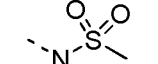
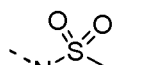
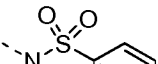
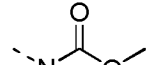
No	R ^A	IUPAC name
Ex.138		<i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-8,8,14-trioxo-18-oxa-8λ ⁶ -thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]benzenesulfonamide
Ex.139		<i>N</i> -methyl- <i>N'</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-8,8,14-trioxo-18-oxa-8λ ⁶ -thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]urea
Ex.140		<i>N</i> -[(13 <i>S</i> ,16 <i>R</i>)-16-methyl-8,8,14-trioxo-18-oxa-8λ ⁶ -thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]- <i>N'</i> -(3-pyridinyl)urea
Ex.141		(13 <i>S</i> ,16 <i>R</i>)-13-(isobutylamino)-16-methyl-18-oxa-8λ ⁶ -thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaene-8,8,14-trione
Ex.142		(13 <i>S</i> ,16 <i>R</i>)-13-(isopentylamino)-16-methyl-18-oxa-8λ ⁶ -thia-15-azatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaene-8,8,14-trione

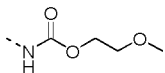
Table 20a: Examples of Core 08 (Ex.143- Ex.167; continued on the following pages)

No	R ^A	Starting Material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.143-Ex.144: cf. experimental description						
Ex.145	N(CH ₃) ₂	Ex.144	A.6.1	Formaldehyde (36% in H ₂ O)	prep. HPLC method 3	92%
Ex.146		Ex.144	A.6.4	Isobutyraldehyde	prep. HPLC method 3	16%
Ex.147		Ex.144	A.6.4	3-Fluorobenzaldehyde	prep. HPLC method 3	46%

No	R ^A	Starting Material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex. 148		Ex. 144	A.1.2	Acetic anhydrid (2.2 equiv.) Pyridine (7 equiv.); rt	prep. HPLC method 1a	94% (TFA salt)
Ex. 149		Ex. 144	A.1.1 ¹⁾	Methoxyacetic acid i-Pr ₂ NEt (5 equiv.)	prep. HPLC method 3	62%
Ex. 150		Ex. 144	A.1.3	2-(Dimethylamino)acetic acid i-Pr ₂ NEt (6 equiv.) Workup: CHCl ₃ , 10M aq NaOH soln	prep. HPLC method 3	49%
Ex. 151		Ex. 144	A.1.1	Nicotinic acid i-Pr ₂ NEt (5 equiv.) Workup: CHCl ₃ , 10M aq NaOH soln	prep. HPLC method 3	68%
Ex. 152		Ex. 144	A.1.1 ¹⁾	Isovaleric acid i-Pr ₂ NEt (5 equiv.)	prep. HPLC method 3	15%
Ex. 153		Ex. 144	A.1.1 ¹⁾	N-Boc-β-alanine i-Pr ₂ NEt (5 equiv.)	prep. HPLC method 3	88%
Ex. 154		Ex. 153	B.2	TFA, CH ₂ Cl ₂ rt, 2h	crude product	73% (TFA salt)

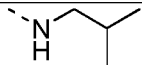
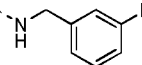
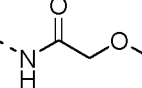
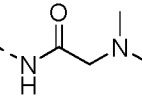
No	R ^A	Starting Material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex. 155		Ex. 144	A.1.1 ¹⁾	1-Naphthaleneacetic acid i-Pr ₂ NEt (5 equiv.)	prep. HPLC method 3 and FC (hexane/EtOAc)	69%
Ex. 156		Ex. 144	A.1.1 ¹⁾	2-Naphthaleneacetic acid i-Pr ₂ NEt (5 equiv.)	prep. HPLC method 3	66%
Ex. 157		Ex. 144	A.1.1 ¹⁾	3,3,3-Trifluoropropionic acid i-Pr ₂ NEt (5 equiv.)	prep. HPLC method 3	45%
Ex. 158		Ex. 144	A.1.1 ¹⁾	3-Fluorobenzoic acid i-Pr ₂ NEt (5 equiv.)	prep. HPLC method 3 and FC (hexane/EtOAc)	44%
Ex. 159		Ex. 144	A.3	2,5-Dioxopyrrolidin-1-yl pyridin-3-ylcarbamate (1.3 equiv) i-Pr ₂ NEt (5 equiv.)	prep. HPLC method 3	78%
Ex. 160		Ex. 144	A.3	N-Succinimidyl-N- methylcarbamate (1.3 equiv.) i-Pr ₂ NEt (5 equiv.)	prep. HPLC method 3	78%

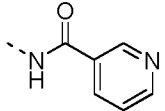
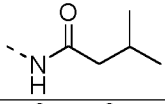
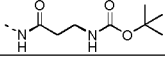
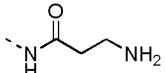
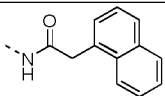
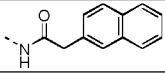
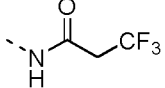
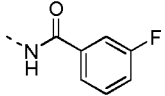
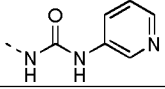
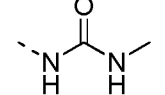
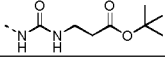
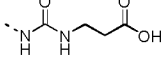
No	R ^A	Starting Material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.161		Ex.144	A.3	tert.-Butyl 3-((2,5-dioxopyrrolidin-1-yl)oxy)carbonylamino)propanoate (1.3 equiv.) i-Pr ₂ NEt (5 equiv.)	prep. HPLC method 3	84%
Ex.162		Ex.161	B.2	TFA, CH ₂ Cl ₂ rt, 2h	crude product	75% (TFA salt)
Ex.163		Ex.144	A.5	Methanesulfonyl chloride (3 equiv.) DMAP (0.1 equiv.) NEt ₃ (5 equiv.) CHCl ₃ , rt, 2 d	prep. HPLC method 3	71%
Ex.164		Ex.144	A.5	Cyclopropanesulfonyl chloride (3 equiv.) DMAP (0.1 equiv.) NEt ₃ (5 equiv.) CHCl ₃ , rt to 50°C, 3 d	prep. HPLC method 1a	55% (TFA salt)
Ex.165		Ex.144	A.5	Benzenesulfonyl chloride (3 equiv.) NEt ₃ (5 equiv.) CHCl ₃ , rt, 2 d	prep. HPLC method 3	57%
Ex.166		Ex.144	A.4	Methyl chloroformate (0.89 equiv.); rt, 2 h	prep. HPLC method 3	66%

No	R ^A	Starting Material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.167		Ex.144	A.4	2-Methoxyethyl chloroformate (0.96 equiv.); rt, 2 h	prep. HPLC method 3	52%

- 1) Method A.1.1; modified aq. workup: The (reaction) mixture was distributed between CH₂Cl₂ and 1 M aq. HCl soln. The organic phase was dried (Na₂SO₄), filtered and concentrated.

Table 20b: Examples of Core 08 (Ex.143-Ex.167; continued on the following pages)

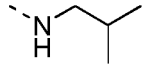
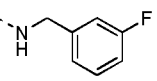
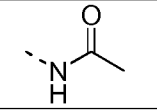
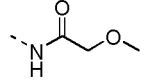
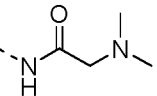
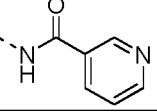
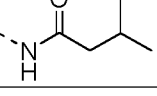
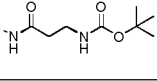
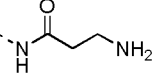
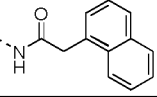
No	R ^A	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.143-Ex.144: cf. experimental description						
Ex.145	N(CH ₃) ₂	C ₂₂ H ₂₉ N ₃ O ₂ S	399.2	1.35 (98)	400.1	method 1a
Ex.146		C ₂₄ H ₃₃ N ₃ O ₂ S	427.2	1.46 (95)	428.2	method 1a
Ex.147		C ₂₇ H ₃₀ FN ₃ O ₂ S	479.2	1.53 (95)	480.2	method 1a
Ex.148		C ₂₂ H ₂₇ N ₃ O ₃ S	413.2	1.40 (99)	414.1	method 1a
Ex.149		C ₂₃ H ₂₉ N ₃ O ₄ S	443.2	1.49 (94)	444.2	method 1a
Ex.150		C ₂₄ H ₃₂ N ₄ O ₃ S	456.2	1.94 (96)	457.2	method 2c

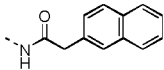
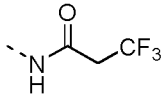
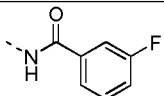
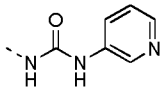
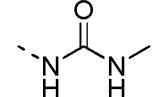
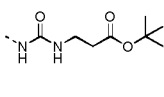
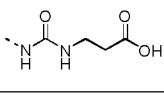
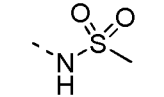
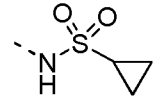
No	R ^A	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.151		C ₂₆ H ₂₈ N ₄ O ₃ S	476.2	1.86 (92)	477.0	method 2c
Ex.152		C ₂₅ H ₃₃ N ₃ O ₃ S	455.2	1.66 (90)	456.2	method 1a
Ex.153		C ₂₈ H ₃₈ N ₄ O ₅ S	542.3	1.70 (90)	543.2	method 1a
Ex.154		C ₂₃ H ₃₀ N ₄ O ₃ S	442.2	1.30 (87)	443.2	method 1c
Ex.155		C ₃₂ H ₃₃ N ₃ O ₃ S	539.2	1.91 (93)	540.1	method 1a
Ex.156		C ₃₂ H ₃₃ N ₃ O ₃ S	539.2	1.90 (97)	540.1	method 1a
Ex.157		C ₂₃ H ₂₆ F ₃ N ₃ O ₃ S	481.2	1.61 (96)	482.2	method 1a
Ex.158		C ₂₇ H ₂₈ FN ₃ O ₃ S	493.2	1.76 (99)	494.2	method 1a
Ex.159		C ₂₆ H ₂₉ N ₅ O ₃ S	491.2	1.86 (90)	492.1	method 2c
Ex.160		C ₂₂ H ₂₈ N ₄ O ₃ S	428.2	1.39 (99)	429.1	method 1a
Ex.161		C ₂₈ H ₃₈ N ₄ O ₅ S	542.3	2.13 (99)	543.1	method 2c
Ex.162		C ₂₄ H ₃₀ N ₄ O ₅ S	486.2	1.38 (98)	487.2	method 1a

No	R ^A	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.163		C ₂₁ H ₂₇ N ₃ O ₄ S ₂	449.1	1.46 (99)	450.1	method 1a
Ex.164		C ₂₃ H ₂₉ N ₃ O ₄ S ₂	475.2	1.55 (99)	476.0	method 1a
Ex.165		C ₂₆ H ₂₉ N ₃ O ₄ S ₂	511.2	1.72 (99)	512.1	method 1a
Ex.166		C ₂₂ H ₂₇ N ₃ O ₄ S	429.2	1.49 (99)	430.1	method 1a
Ex.167		C ₂₄ H ₃₁ N ₃ O ₅ S	473.2	1.52 (99)	474.2	method 1a

Table 20c: Examples of Core 08 (Ex.143-Ex.167; continued on the following pages)

No	R ^A	IUPAC name
Ex.143	NHAlloc	allyl N-[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricos-1(23),2,4,6,19,21-hexaen-13-yl]carbamate
Ex.144	NH ₂	(10 <i>R</i> ,13 <i>S</i>)-13-amino-10-methyl-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricos-1(23),2,4,6,19,21-hexaen-12-one
Ex.145	N(CH ₃) ₂	(10 <i>R</i> ,13 <i>S</i>)-13-(dimethylamino)-10-methyl-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricos-1(23),2,4,6,19,21-hexaen-12-one

No	R ^A	IUPAC name
Ex.146		(10 <i>R</i> ,13 <i>S</i>)-13-(isobutylamino)-10-methyl-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-12-one
Ex.147		(10 <i>R</i> ,13 <i>S</i>)-13-[(3-fluorobenzyl)amino]-10-methyl-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-12-one
Ex.148		<i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]acetamide
Ex.149		2-methoxy- <i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]acetamide
Ex.150		2-(dimethylamino)- <i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]acetamide
Ex.151		<i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]nicotinamide
Ex.152		3-methyl- <i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]butanamide
Ex.153		<i>tert</i> -butyl <i>N</i> -(3-[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]amino)-3-oxopropyl)carbamate
Ex.154		3-amino- <i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]propanamide
Ex.155		<i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]-2-(1-naphthyl)acetamide

No	R ^A	IUPAC name
Ex.156		<i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]-2-(2-naphthyl)acetamide
Ex.157		3,3,3-trifluoro- <i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]propanamide
Ex.158		3-fluoro- <i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]benzamide
Ex.159		<i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]- <i>N</i> -(3-pyridinyl)urea
Ex.160		<i>N</i> -methyl- <i>N'</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]urea
Ex.161		<i>tert</i> -butyl 3-[(<i>[(10R,13S)</i> -10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]amino}carbonyl)amino]propanoate
Ex.162		3-[(<i>[(10R,13S)</i> -10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]amino}carbonyl)amino]propanoic acid
Ex.163		<i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]methanesulfonamide
Ex.164		<i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]cyclopropanesulfonamide

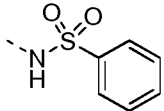
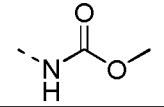
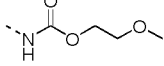
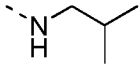
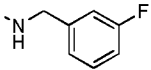
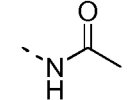
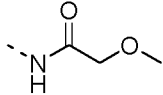
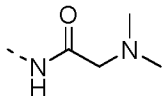
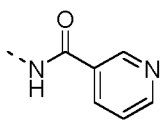
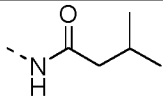
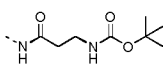
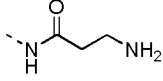
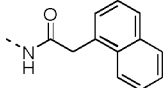
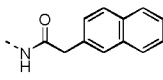
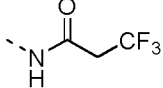
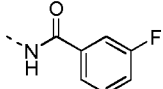
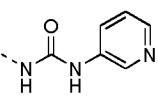
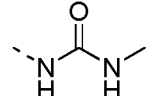
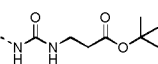
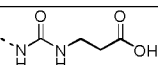
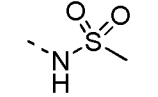
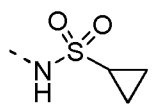
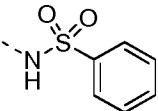
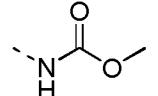
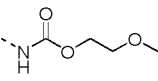
No	R ^A	IUPAC name
Ex.165		<i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]benzenesulfonamide
Ex.166		methyl <i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]carbamate
Ex.167		2-methoxyethyl <i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]carbamate

Table 21a: Examples of Core 09 (Ex.168–Ex.192; continued on the following pages)

No	R ^A	Starting Material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.168–Ex.169 <i>cf. experimental description</i>						
Ex.170	N(CH ₃) ₂	Ex.169	A.6.1	Formaldehyde (36% in H ₂ O)	prep. HPLC method 3	67%
Ex.171		Ex.169	A.6.4	Isobutyraldehyde	prep. HPLC method 3	44%
Ex.172		Ex.169	A.6.4	3-Fluorobenzaldehyde	prep. HPLC method 3	57%
Ex.173		Ex.169	A.1.2	Acetic anhydride (1.2 equiv.)	prep. HPLC method 3	79%

No	R ^A	Starting Material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex. 174		Ex. 169	A.1.1 ¹⁾	Methoxyacetic acid	prep. HPLC method 3	27%
Ex. 175		Ex. 169	A.1.3	2-(Dimethylamino)acetic acid Workup: CH ₂ Cl ₂	prep. HPLC method 3	9%
Ex. 176		Ex. 169	A.1.1	Nicotinic acid Workup: CH ₂ Cl ₂ , sat. aq. Na ₂ CO ₃	prep. HPLC method 3	26%
Ex. 177		Ex. 169	A.1.1 ¹⁾	Isovaleric acid	prep. HPLC method 3	18%
Ex. 178		Ex. 169	A.1.1 ¹⁾	N-Boc-β-alanine	prep. HPLC method 3	57%
Ex. 179		Ex. 178	B.2	TFA, CH ₂ Cl ₂ rt, 2h	crude product	41% (TFA salt)
Ex. 180		Ex. 169	A.1.1 ¹⁾	1-Naphthaleneacetic acid	prep. HPLC method 3	42%
Ex. 181		Ex. 169	A.1.1 ¹⁾	2-Naphthaleneacetic acid	prep. HPLC method 3	40%
Ex. 182		Ex. 169	A.1.1 ¹⁾	3,3,3-Trifluoropropionic acid	prep. HPLC method 3	22%
Ex. 183		Ex. 169	A.1.1 ¹⁾	3-Fluorobenzoic acid	prep. HPLC method 3	58%

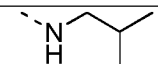
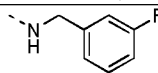
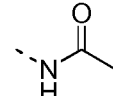
No	R ^A	Starting Material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex. 184		Ex. 169	A.3	2,5-Dioxopyrrolidin-1-yl pyridin-3-ylcarbamate (1.3 equiv.)	prep. HPLC method 3	73%
Ex. 185		Ex. 169	A.3	N-Succinimidyl N- methylcarbamate (1.3 equiv.)	prep. HPLC method 3	76%
Ex. 186		Ex. 169	A.3	tert.-Butyl 3-((2,5- dioxopyrrolidin-1- yloxy)carbonylamino)propan oate (1.3 equiv.)	prep. HPLC method 3	77%
Ex. 187		Ex. 186	B.2	TFA, CH ₂ Cl ₂	crude product	75%
Ex. 188		Ex. 169	A.5	Methanesulfonyl chloride (2 equiv.) DMAP (0.1 equiv.) Et ₃ N (3 equiv.) CHCl ₃ , rt, 2 d	prep. HPLC method 3	70%
Ex. 189		Ex. 169	A.5	Cyclopropanesulfonyl chloride DMAP (0.1 equiv.) Et ₃ N (3 equiv.) CHCl ₃ , rt, 2 d	prep. HPLC method 3	53%

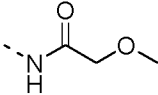
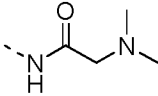
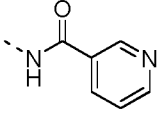
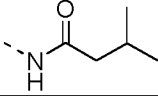
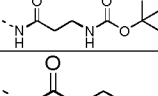
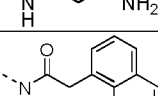
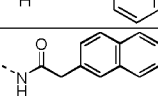
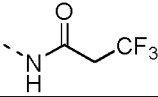
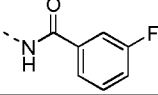
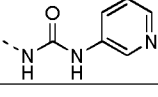
No	R ^A	Starting Material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex. 190		Ex. 169	A.5	Benzenesulfonyl chloride	prep. HPLC method 3	51%
Ex. 191		Ex. 169	A.4	Methyl chloroformate (0.86 equiv); rt, 2 h	prep. HPLC method 3	52%
Ex. 192		Ex. 169	A.4	2-Methoxyethyl chloroformate (0.97equiv); rt, 2 h	prep. HPLC method 3	55%

- 1) Method A.1.1; modified aq. workup: The (reaction) mixture was distributed between CH₂Cl₂ and 1 M aq. HCl soln. The organic phase was dried (Na₂SO₄), filtered and concentrated.

260

Table 21b: Examples of Core 09 (Ex.168–Ex.192; *continued on the following pages*)

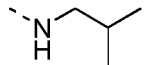
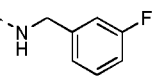
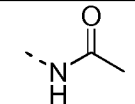
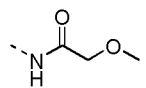
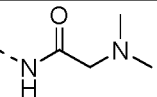
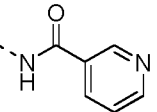
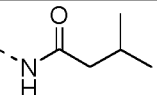
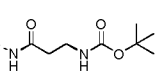
No	R ^A	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.168–Ex.169 <i>cf. experimental description</i>						
Ex. 170	N(CH ₃) ₂	C ₂₂ H ₂₉ N ₃ O ₄ S	431.2	1.39 (97)	432.1	method 1a
Ex. 171		C ₂₄ H ₃₃ N ₃ O ₄ S	459.2	1.53 (95)	460.1	method 1a
Ex. 172		C ₂₇ H ₃₀ FN ₃ O ₄ S	511.2	1.61 (96)	512.1	method 1a
Ex. 173		C ₂₂ H ₂₇ N ₃ O ₅ S	445.2	1.50 (100)	446.1	method 1a

No	R ^A	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.174		C ₂₃ H ₂₉ N ₃ O ₆ S	475.2	1.57 (96)	476.0	method 1a
Ex.175		C ₂₄ H ₃₂ N ₄ O ₅ S	488.2	1.38 (92)	489.1	method 1a
Ex.176		C ₂₆ H ₂₈ N ₄ O ₅ S	508.2	1.43 (98)	508.9	method 1a
Ex.177		C ₂₅ H ₃₃ N ₃ O ₅ S	487.2	1.77 (97)	488.2	method 1a
Ex.178		C ₂₈ H ₃₈ N ₄ O ₇ S	574.2	1.83 (98)	575.1	method 2c
Ex.179		C ₂₃ H ₃₀ N ₄ O ₅ S	474.2	1.35 (99)	475.2	method 1a
Ex.180		C ₃₂ H ₃₃ N ₃ O ₅ S	571.2	2.03 (97)	572.0	method 1a
Ex.181		C ₃₂ H ₃₃ N ₃ O ₅ S	571.2	2.05 (100)	572.1	method 1a
Ex.182		C ₂₃ H ₂₆ F ₃ N ₃ O ₅ S	513.2	1.74 (99)	514.1	method 1a
Ex.183		C ₂₇ H ₂₈ FN ₃ O ₅ S	525.2	1.90 (92)	526.1	method 1a
Ex.184		C ₂₆ H ₂₉ N ₅ O ₅ S	523.2	1.42 (99)	524.0	method 1a

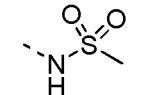
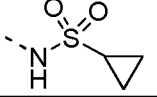
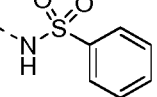
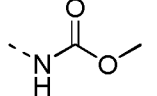
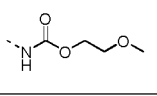
No	R ^A	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.185		C ₂₂ H ₂₈ N ₄ O ₅ S	460.2	1.48 (99)	461.0	method 1a
Ex.186		C ₂₈ H ₃₈ N ₄ O ₇ S	574.2	1.88 (98)	575.1	method 2c
Ex.187		C ₂₄ H ₃₀ N ₄ O ₇ S	518.2	1.45 (97)	519.1	method 1a
Ex.188		C ₂₁ H ₂₇ N ₃ O ₆ S ₂	481.1	1.58 (99)	482.1	method 1a
Ex.189		C ₂₃ H ₂₉ N ₃ O ₆ S ₂	507.1	1.68 (95)	508.0	method 1a
Ex.190		C ₂₆ H ₂₉ N ₃ O ₆ S ₂	543.1	1.85 (96)	544.1	method 1a
Ex.191		C ₂₂ H ₂₇ N ₃ O ₆ S	461.2	1.60 (98)	462.1	method 1a
Ex.192		C ₂₄ H ₃₁ N ₃ O ₇ S	505.2	1.63 (99)	506.2	method 1a

Table 21c: Examples of Core 09 (Ex.168–Ex.192; continued on the following pages)

No	R ^A	IUPAC name
Ex.168	NHAlloc	allyl N-[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]carbamate

No	R ^A	IUPAC name
Ex.169	NH ₂	(10 <i>R</i> ,13 <i>S</i>)-13-amino-10-methyl-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaene-12,18,18-trione
Ex.170	N(CH ₃) ₂	(10 <i>R</i> ,13 <i>S</i>)-13-(dimethylamino)-10-methyl-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaene-12,18,18-trione
Ex.171		(10 <i>R</i> ,13 <i>S</i>)-13-(isobutylamino)-10-methyl-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaene-12,18,18-trione
Ex.172		(10 <i>R</i> ,13 <i>S</i>)-13-[(3-fluorobenzyl)amino]-10-methyl-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaene-12,18,18-trione
Ex.173		<i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]acetamide
Ex.174		2-methoxy- <i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]acetamide
Ex.175		2-(dimethylamino)- <i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]acetamide
Ex.176		<i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]nicotinamide
Ex.177		3-methyl- <i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]butanamide
Ex.178		<i>tert</i> -butyl <i>N</i> -(3-[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]amino)-3-oxopropyl)carbamate

No	R ^A	IUPAC name
Ex.179		3-amino- <i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]propanamide
Ex.180		<i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]-2-(1-naphthyl)acetamide
Ex.181		<i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]-2-(2-naphthyl)acetamide
Ex.182		3,3,3-trifluoro- <i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]propanamide
Ex.183		3-fluoro- <i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]benzamide
Ex.184		<i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]- <i>N</i> -(3-pyridinyl)urea
Ex.185		<i>N</i> -methyl- <i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]urea
Ex.186		<i>tert</i> -butyl 3-([(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]amino)carbonyl)amino]propanoate
Ex.187		3-([(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]amino)carbonyl)amino]propanoic acid

No	R ^A	IUPAC name
Ex.188		<i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]methanesulfonamide
Ex.189		<i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]cyclopropanesulfonamide
Ex.190		<i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]benzenesulfonamide
Ex.191		methyl <i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]carbamate
Ex.192		2-methoxyethyl <i>N</i> -[(10 <i>R</i> ,13 <i>S</i>)-10-methyl-12,18,18-trioxo-8-oxa-18λ ⁶ -thia-11,21-diazatricyclo[17.3.1.0 ^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]carbamate

265

Table 22a: Examples of Core 10 (Ex.193a, c-h and Ex.194b; continued on the following page)

No	General Procedure	Fmoc-AA1-OH	Fmoc-AA2-OH	Purification Method	Yield (isolated salt)
Ex.193a	C.1	Fmoc-β ³ -homoPhe-OH	Fmoc-NMe-DAla-OH	prep. HPLC method 2b	20 mg / 53%
Ex.193c	C.1	Fmoc-β-Ala-OH	Fmoc-NMePhe-OH	prep. HPLC method 2b	7 mg / 19%
Ex.193d	C.1	Fmoc-β-Ala-OH	Fmoc-Phe-OH	prep. HPLC method 2b	2 mg / 6%

No	General Procedure	Fmoc-AA1-OH	Fmoc-AA2-OH	Purification Method	Yield (isolated salt)
Ex.193e	C.1	Fmoc-NMe- β^3 -homoDAIa-OH	Fmoc-NMePhe-OH	prep. HPLC method 2b	7 mg / 18%
Ex.193f	C.1	Fmoc-NMe- β^3 -homoDAIa-OH	Fmoc-Sar-OH	prep. HPLC method 2b	9 mg / 27%
Ex.193g	C.1	Fmoc-NMe- β^3 -homoDAIa-OH	Fmoc-Phe-OH	prep. HPLC method 2b	8 mg / 22%
Ex.193h	C.1	Fmoc- β^3 -homoPhe-OH	Fmoc-NMe- β -Ala-OH	prep. HPLC method 2b	13 mg / 33%
Ex.194b	C.1	Fmoc-NMe- β^3 -homoDAIa-OH	Fmoc-NMe-Glu(OtBu)-OH	prep. HPLC method 1a	14 mg / 31%

Table 22b: Examples of Core 10 (Ex. 193a, c-h and Ex. 194b; *continued on the following page*)

No	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.193a	C31H34N4O4	526.2	2.03 (99)	527.2	method 1d
Ex.193c	C30H32N4O4	512.2	1.94 (94)	513.0	method 1d
Ex.193d	C29H30N4O4	498.2	1.80 (93)	499.2	method 1d
Ex.193e	C32H36N4O4	540.2	2.07 (86)	541.2	method 1d
Ex.193f	C25H30N4O4	450.2	1.50 (99)	451.2	method 1d
Ex.193g	C31H34N4O4	526.2	1.94 (98)	527.2	method 1d
Ex.193h	C31H34N4O4	526.2	1.78 (98)	527.2	method 1d

No	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.194b	C ₂₈ H ₃₄ N ₄ O ₆	522.2	1.68 (97)	523.2	method 1d

Table 22c: Examples of Core 10 (Ex. 193a, c-h and Ex. 194b) (continued on the following page)

No	IUPAC name
Ex.193a	(9 <i>S</i> ,16 <i>S</i> ,19 <i>R</i>)-16-benzyl-19,20-dimethyl-7-oxa-13,17,20,24-tetraazatetracyclo[20.3.1.1 ^{2,6} .0 ^{9,13}]heptacos-1(26),2(27),3,5,22,24-hexaene-14,18,21-trione
Ex.193c	(9 <i>S</i> ,19 <i>S</i>)-19-benzyl-20-methyl-7-oxa-13,17,20,24-tetraazatetracyclo[20.3.1.1 ^{2,6} .0 ^{9,13}]heptacos-1(26),2(27),3,5,22,24-hexaene-14,18,21-trione
Ex.193d	(9 <i>S</i> ,19 <i>S</i>)-19-benzyl-7-oxa-13,17,20,24-tetraazatetracyclo[20.3.1.1 ^{2,6} .0 ^{9,13}]heptacos-1(26),2(27),3,5,22,24-hexaene-14,18,21-trione
Ex.193e	(9 <i>S</i> ,16 <i>R</i> ,19 <i>S</i>)-19-benzyl-16,17,20-trimethyl-7-oxa-13,17,20,24-tetraazatetracyclo[20.3.1.1 ^{2,6} .0 ^{9,13}]heptacos-1(26),2(27),3,5,22,24-hexaene-14,18,21-trione
Ex.193f	(9 <i>S</i> ,16 <i>R</i>)-16,17,20-trimethyl-7-oxa-13,17,20,24-tetraazatetracyclo[20.3.1.1 ^{2,6} .0 ^{9,13}]heptacos-1(26),2(27),3,5,22,24-hexaene-14,18,21-trione
Ex.193g	(9 <i>S</i> ,16 <i>R</i> ,19 <i>S</i>)-19-benzyl-16,17-dimethyl-7-oxa-13,17,20,24-tetraazatetracyclo[20.3.1.1 ^{2,6} .0 ^{9,13}]heptacos-1(26),2(27),3,5,22,24-hexaene-14,18,21-trione
Ex.193h	(9 <i>S</i> ,16 <i>S</i>)-16-benzyl-21-methyl-7-oxa-13,17,21,25-tetraazatetracyclo[21.3.1.1 ^{2,6} .0 ^{9,13}]octacos-1(27),2(28),3,5,23,25-hexaene-14,18,22-trione

No	IUPAC name
Ex.194b	3-[(9 <i>S</i> ,16 <i>R</i> ,19 <i>S</i>)-16,17,20-trimethyl-14,18,21-trioxo-7-oxa-13,17,20,24-tetraazatetracyclo[20.3.1.1 ^{2,6} .0 ^{9,13}]heptacos-1(26),2(27),3,5,22,24-hexaen-19-yl]propanoic acid

Table 23a: Examples of Core 11 (Ex. 195a,b,e-h,j; Ex. 196c,i,k and Ex. 197d; *continued on the following page*)

No	General Procedure	Fmoc-AA1-OH	Fmoc-AA2-OH	Fmoc-AA3-OH	Purification Method	Yield (isolated salt)
Ex.195a	C.2	Fmoc-NMe- β^3 -homoDAla-OH	Fmoc-Sar-OH	Fmoc-NMeAla-OH	prep. HPLC method 2a	31%
Ex.195b	C.2	Fmoc-NMe- β^3 -homoDAla-OH	Fmoc-Gly-OH	Fmoc-Ala-OH	prep. HPLC method 2a	18%
Ex.196c	C.2	Fmoc-NMe- β^3 -homoDAla-OH	Fmoc-Ala-OH	Fmoc-NMeGlu(OtBu)-OH	prep. HPLC method 1a	33% (TFA salt)
Ex.197d	C.2	Fmoc-NMe- β^3 -homoDAla-OH	Fmoc-Lys(Boc)-OH	Fmoc-DAla-OH	prep. HPLC method 2a	24%
Ex.195e	C.2	Fmoc-Sar-OH	Fmoc-NMe- β^3 -homoDAla-OH	Fmoc-NMeAla-OH	prep. HPLC method 2a	33%
Ex.195f	C.2	Fmoc-Sar-OH	Fmoc-NMeAla-OH	Fmoc-NMe- β^3 -homoDAla-OH	prep. HPLC method 2a	22%
Ex.195g	C.2	Fmoc-Gly -OH	Fmoc-Phe-OH	Fmoc-NMeDAla-OH	prep. HPLC method 2a	17%
Ex.195h	C.2	Fmoc-Sar-OH	Fmoc-Phe-OH	Fmoc-DAla-OH	prep. HPLC method 2a	13%

Ex.196i	C.2	Fmoc-Ala-OH	Fmoc-DPhe-OH	Fmoc-NMeGlu(OtBu)-OH	prep. HPLC method 1a	12% (TFA salt)
Ex.195j	C.2	Fmoc-Sar-OH	Fmoc-Phe-OH	Fmoc-NMeDAla-OH	prep. HPLC method 2a	13%
Ex.196k	C.2	Fmoc-DAla-OH	Fmoc-Phe-OH	Fmoc-NMeGlu(OtBu)-OH	prep. HPLC method 1a	10% (TFA salt)

Table 23b: Examples of Core 11 (Ex. 195a,b,e-h,j; Ex. 196c,i,k and Ex. 197d)

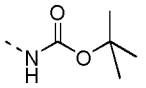
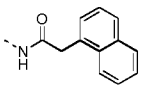
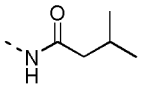
No	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.195a	C ₂₉ H ₃₇ N ₅ O ₅	535.3	1.50 (98)	536.2	method 1d
Ex.195b	C ₂₇ H ₃₃ N ₅ O ₅	507.3	1.44 (98)	508.2	method 1d
Ex.196c	C ₃₁ H ₃₉ N ₅ O ₇	593.3	1.47 (98)	594.2	method 1d
Ex.197d	C ₃₁ H ₄₂ N ₆ O ₅	578.3	2.10 (92)	579.2	method 2f
Ex.195e	C ₂₉ H ₃₇ N ₅ O ₅	535.3	1.53 (98)	536.3	method 1d
Ex.195f	C ₂₉ H ₃₇ N ₅ O ₅	535.2	1.40 (98)	536.2	method 1d
Ex.195g	C ₃₂ H ₃₅ N ₅ O ₅	569.3	1.71 (97)	569.9	method 1d
Ex.195h	C ₃₂ H ₃₅ N ₅ O ₅	569.3	1.67 (97)	570.2	method 1d
Ex.196i	C ₃₅ H ₃₉ N ₅ O ₇	641.3	1.41 (90)	642.3	method 2f
Ex.195j	C ₃₃ H ₃₇ N ₅ O ₅	583.3	1.72 (93)	584.0	method 1d
Ex.196k	C ₃₅ H ₃₉ N ₅ O ₇	641.3	1.71 (99)	642.2	method 1d

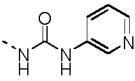
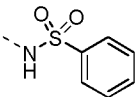
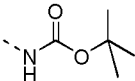
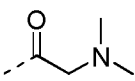
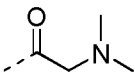
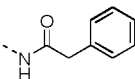
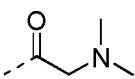
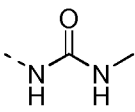
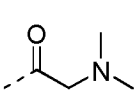
Table 23c: Examples of Core 11 (Ex. 195a,b,e-h,j; Ex. 196c,i,k and Ex. 197d) (continued on the following page)

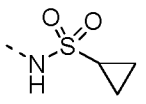
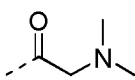
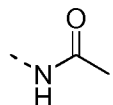
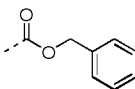
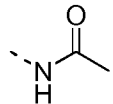
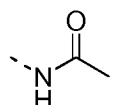
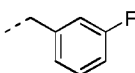
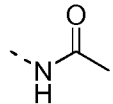
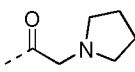
No	IUPAC name
Ex. 195a	(9 <i>S</i> ,16 <i>R</i> ,22 <i>S</i>)-16,17,20,22,23-pentamethyl-7-oxa-13,17,20,23,27-pentaazatetracyclo[23.3.1.1 ^{2,6} .0 ^{9,13}]triaconta-1(29),2(30),3,5,25,27-hexaene-14,18,21,24-tetrone
Ex. 195b	(9 <i>S</i> ,16 <i>R</i> ,22 <i>S</i>)-16,17,22-trimethyl-7-oxa-13,17,20,23,27-pentaazatetracyclo[23.3.1.1 ^{2,6} .0 ^{9,13}]triaconta-1(29),2(30),3,5,25,27-hexaene-14,18,21,24-tetrone
Ex. 196c	3-[(9 <i>S</i> ,16 <i>R</i> ,19 <i>S</i> ,22 <i>S</i>)-16,17,19,23-tetramethyl-14,18,21,24-tetraoxo-7-oxa-13,17,20,23,27-pentaazatetracyclo[23.3.1.1 ^{2,6} .0 ^{9,13}]triaconta-1(29),2(30),3,5,25,27-hexaen-22-yl]propanoic acid
Ex. 197d	(9 <i>S</i> ,16 <i>R</i> ,19 <i>S</i> ,22 <i>R</i>)-19-(4-aminobutyl)-16,17,22-trimethyl-7-oxa-13,17,20,23,27-pentaazatetracyclo[23.3.1.1 ^{2,6} .0 ^{9,13}]triaconta-1(29),2(30),3,5,25,27-hexaene-14,18,21,24-tetrone
Ex. 195e	(9 <i>S</i> ,19 <i>R</i> ,22 <i>S</i>)-16,19,20,22,23-pentamethyl-7-oxa-13,16,20,23,27-pentaazatetracyclo[23.3.1.1 ^{2,6} .0 ^{9,13}]triaconta-1(29),2(30),3,5,25,27-hexaene-14,17,21,24-tetrone
Ex. 195f	(9 <i>S</i> ,18 <i>S</i> ,22 <i>R</i>)-16,18,19,22,23-pentamethyl-7-oxa-13,16,19,23,27-pentaazatetracyclo[23.3.1.1 ^{2,6} .0 ^{9,13}]triaconta-1(29),2(30),3,5,25,27-hexaene-14,17,20,24-tetrone
Ex. 195g	(9 <i>S</i> ,18 <i>S</i> ,21 <i>R</i>)-18-benzyl-21,22-dimethyl-7-oxa-13,16,19,22,26-pentaazatetracyclo[22.3.1.1 ^{2,6} .0 ^{9,13}]nonacosa-1(28),2(29),3,5,24,26-hexaene-14,17,20,23-tetrone
Ex. 195h	(9 <i>S</i> ,18 <i>S</i> ,21 <i>R</i>)-18-benzyl-16,21-dimethyl-7-oxa-13,16,19,22,26-pentaazatetracyclo[22.3.1.1 ^{2,6} .0 ^{9,13}]nonacosa-1(28),2(29),3,5,24,26-hexaene-14,17,20,23-tetrone
Ex. 196i	3-[(9 <i>S</i> ,15 <i>S</i> ,18 <i>R</i> ,21 <i>S</i>)-18-benzyl-15,22-dimethyl-14,17,20,23-tetraoxo-7-oxa-13,16,19,22,26-pentaazatetracyclo[22.3.1.1 ^{2,6} .0 ^{9,13}]nonacosa-1(28),2(29),3,5,24,26-hexaen-21-yl]propanoic acid
Ex. 195j	(9 <i>S</i> ,18 <i>S</i> ,21 <i>R</i>)-18-benzyl-16,21,22-trimethyl-7-oxa-13,16,19,22,26-pentaazatetracyclo[22.3.1.1 ^{2,6} .0 ^{9,13}]nonacosa-1(28),2(29),3,5,24,26-hexaene-14,17,20,23-tetrone

No	IUPAC name
Ex.196k	3-[(9 <i>S</i> ,15 <i>R</i> ,18 <i>S</i> ,21 <i>S</i>)-18-benzyl-15,22-dimethyl-14,17,20,23-tetraoxo-7-oxa-13,16,19,22,26-pentaazatetracyclo[22.3.1.1 ^{2,6} .0 ^{9,13}]nonacos-1(28),2(29),3,5,24,26-hexaen-21-yl]propanoic acid

Table 24a: Examples of Core 12 (Ex.198-Ex.219; *continued on the following pages*)

No	R ^B	R ^D	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.198-Ex.200: <i>cf. experimental description</i>							
Ex.201		CH ₃	Ex.200	(A.6.2) ¹⁾	Formaldehyde (36.5% in H ₂ O); details cf. ¹⁾	FC (CH ₂ Cl ₂ /MeOH)	89%
Ex.202	NH ₂	CH ₃	Ex.201	B.1	HCl-dioxane	crude product	93% (HCl salt)
Ex.203		CH ₃	Ex.202	A.1.3	2-Naphthaleneacetic acid T3P 50% in EtOAc i-Pr ₂ NEt (7 equiv.)	prep. HPLC method 2a	6%
Ex.204		CH ₃	Ex.202	A.1.3	3-Methylbutanoic acid T3P 50% in EtOAc i-Pr ₂ NEt (7 equiv.)	prep. HPLC method 1a and prep. HPLC method 2a	7%

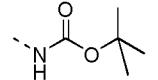
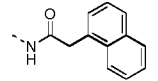
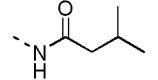
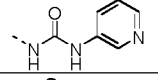
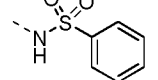
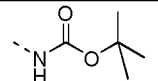
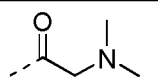
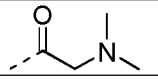
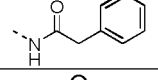
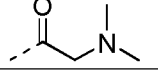
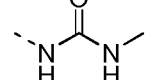
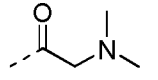
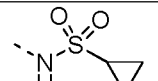
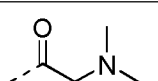
No	R ^B	R ^D	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.205		CH ₃	Ex.202	A.3	3-Pyridinyl isocyanate i-Pr ₂ NEt (5 equiv.)	prep. HPLC method 1a and prep. HPLC method 2a	24%
Ex.206		CH ₃	Ex.202	A.5	Benzenesulfonyl chloride (1.1 equiv.) NEt ₃ (5 equiv.)	prep. HPLC method 2a	68%
Ex.207			Ex.200	A.1.3	2-(Dimethylamino) acetic acid Workup: CH ₂ Cl ₂ , sat. aq. NaHCO ₃ soln	prep. HPLC method 2a	49%
Ex.208	NH ₂		Ex.207	B.1	HCl-dioxane	crude product	85% (HCl salt)
Ex.209			Ex.208	A.1.3	2-Phenylacetic acid (3.4 equiv.) i-Pr ₂ NEt (8 equiv.)	prep. HPLC method 1a and prep. HPLC method 2a	22%
Ex.210			Ex.208	A.3	N-Succinimidyl N- methylcarbamate i-Pr ₂ NEt (5 equiv.)	prep. HPLC method 1a and prep. HPLC method 2a	38%

No	R ^B	R ^D	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.211			Ex.208	A.5	Cyclopropanesulfonyl chloride NEt ₃ (5 equiv.)	prep. HPLC method 1a and prep. HPLC method 2a	30%
Ex.212			Ex.199	A.1.2.2	Acetyl chloride (2 equiv.); 0°C, 2 h	FC (CH ₂ Cl ₂ /MeOH)	68%
Ex.213		H	Ex.212	B.3	H ₂ , Pd(OH) ₂ -C, MeOH	crude product	86%
Ex.214			Ex.213	A.6.3	3-Fluorobenzaldehyde (1.8 equiv.) Acetic acid (1.5 equiv.) NaBH(OAc) ₃ (4 equiv.) Workup: CHCl ₃ , sat. aq. Na ₂ CO ₃ soln	prep. HPLC method 1a and prep. HPLC method 2a	8%
Ex.215			Ex.213	A.1.3	1-Pyrrolidineacetic acid	prep. HPLC method 1a and prep. HPLC method 2a	14%

No	R ^B	R ^D	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.216			Ex.213	A.3	Phenyl isocyanate (1.4 equiv.)	prep. HPLC method 1a and prep. HPLC method 2a	28%
Ex.217			Ex.213	A.5	Benzenesulfonyl chlorid	prep. HPLC method 1a and prep. HPLC method 2a	18%
Ex.218			Ex.219	B.2	TFA, CH ₂ Cl ₂ rt, 2 h	crude product	87% (TFA salt)
Ex.219			Ex.213	A.3	tert.-Butyl 3-((2,5-dioxopyrrolidin-1-yloxy) carbonylamino) propanoate	prep. HPLC method 1a and prep. HPLC method 2a	49%

- 1) At 0°C, formaldehyde (36.5% in H₂O; 0.48 mL, 6.4 mmol), acetic acid (0.088 mL, 1.5 mmol) and NaBH(OAc)₃ (1.09 g, 5.1 mmol) were added to a soln of **Ex.200** (0.635 g, 1.3 mmol) in DCE (20 mL). The mixture was stirred for 2 h at 0°C, followed by an aqueous workup (CH₂Cl₂, sat. aq. NaHCO₃ soln; Na₂SO₄). The crude product was dissolved in MeCN (3 mL) and treated with 25% aq. NH₃ soln (1 mL) for 3 h at rt. More 25% aq. NH₃ soln (1 mL) was added and stirrig was continued for 2 h. Aqueous workup (EtOAc, sat. aq. Na₂CO₃ soln, sat. aq. NaCl soln; Na₂SO₄) and FC (CH₂Cl₂/MeOH 9:1) afforded **Ex.201** (0.587g, 89%).

Table 24b: Examples of Core 12 (Ex.198-Ex.219; continued on the following page)

No	R ^B	R ^D	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.198-Ex.200: cf. experimental description							
Ex.201		CH ₃	C ₂₇ H ₃₅ N ₅ O ₅	509.3	1.58 (97)	510.3	method 2f
Ex.202	NH ₂	CH ₃	C ₂₂ H ₂₇ N ₅ O ₃	409.2	1.05 (95)	410.0	method 2f
Ex.203		CH ₃	C ₃₄ H ₃₅ N ₅ O ₄	577.3	1.58 (97)	578.1	method 2c
Ex.204		CH ₃	C ₂₇ H ₃₅ N ₅ O ₄	493.3	1.38 (99)	494.2	method 2c
Ex.205		CH ₃	C ₂₈ H ₃₁ N ₇ O ₄	529.2	1.20 (99)	530.2	method 2c
Ex.206		CH ₃	C ₂₈ H ₃₁ N ₅ O ₅ S	549.2	1.48 (99)	550.1	method 2c
Ex.207			C ₃₀ H ₄₀ N ₆ O ₆	580.3	1.18 (98)	581.2	method 1d
Ex.208	NH ₂		C ₂₅ H ₃₂ N ₆ O ₄	480.2	1.09 (95)	481.3	method 2f
Ex.209			C ₃₃ H ₃₈ N ₆ O ₅	598.3	1.44 (98)	599.1	method 2c
Ex.210			C ₂₇ H ₃₅ N ₇ O ₅	537.3	1.12 (99)	538.2	method 2c
Ex.211			C ₂₈ H ₃₆ N ₆ O ₆ S	584.2	1.28 (99)	585.1	method 2c

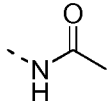
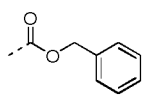
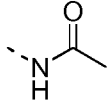
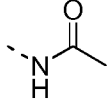
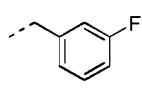
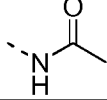
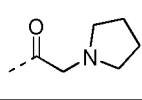
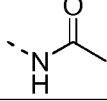
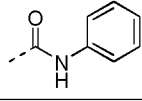
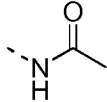
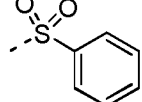
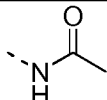
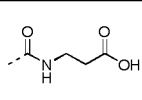
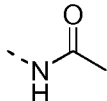
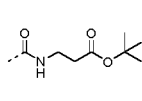
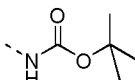
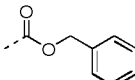
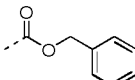
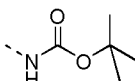
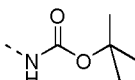
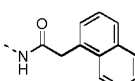
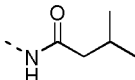
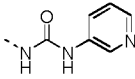
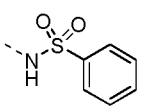
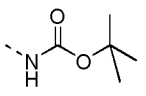
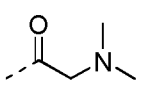
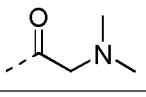
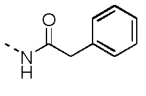
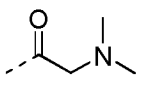
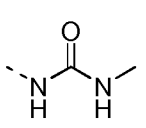
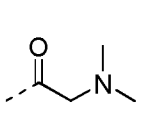
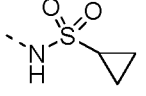
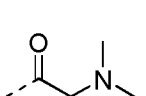
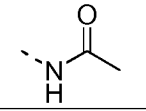
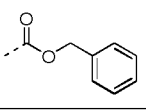
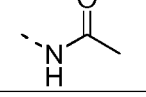
No	R ^B	R ^D	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.212			C31H33N5O6	571.2	1.18 (97)	572.0	method 1a
Ex.213		H	C23H27N5O4	437.2	1.32 (96)	438.1	method 5a
Ex.214			C30H32FN5O4	545.2	1.51 (99)	546.1	method 2c
Ex.215			C29H36N6O5	548.3	1.20 (99)	549.2	method 2c
Ex.216			C30H32N6O5	556.2	1.32 (97)	556.9	method 2c
Ex.217			C29H31N5O6S	577.2	1.37 (100)	578.1	method 2c
Ex.218			C27H32N6O7	552.2	1.50 (92)	553.1	method 5a
Ex.219			C31H40N6O7	608.3	1.42 (98)	609.2	method 2c

Table 24c: Examples of Core 12 (Ex.198-Ex.219; continued on the following pages)

No	R ^B	R ^D	IUPAC name
Ex.198			benzyl (10 <i>S</i> ,12 <i>S</i>)-12-[(<i>tert</i> -butoxycarbonyl)amino]-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaene-17-carboxylate
Ex.199	NH ₂		benzyl (10 <i>S</i> ,12 <i>S</i>)-12-amino-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaene-17-carboxylate
Ex.200		H	<i>tert</i> -butyl <i>N</i> -[(10 <i>S</i> ,12 <i>S</i>)-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaen-12-yl]carbamate
Ex.201		CH ₃	<i>tert</i> -butyl <i>N</i> -[(10 <i>S</i> ,12 <i>S</i>)-17-methyl-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaen-12-yl]carbamate
Ex.202	NH ₂	CH ₃	(10 <i>S</i> ,12 <i>S</i>)-12-amino-17-methyl-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaene-15,21-dione
Ex.203		CH ₃	<i>N</i> -[(10 <i>S</i> ,12 <i>S</i>)-17-methyl-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaen-12-yl]-2-(1-naphthyl)acetamide
Ex.204		CH ₃	3-methyl- <i>N</i> -[(10 <i>S</i> ,12 <i>S</i>)-17-methyl-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaen-12-yl]butanamide
Ex.205		CH ₃	<i>N</i> -[(10 <i>S</i> ,12 <i>S</i>)-17-methyl-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaen-12-yl]- <i>N</i> -(3-pyridinyl)urea

No	R ^B	R ^D	IUPAC name
Ex.206		CH ₃	<i>N</i> -[(10 <i>S</i> ,12 <i>S</i>)-17-methyl-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaen-12-yl]benzenesulfonamide
Ex.207			<i>tert</i> -butyl <i>N</i> -[(10 <i>S</i> ,12 <i>S</i>)-17-[2-(dimethylamino)acetyl]-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaen-12-yl]carbamate
Ex.208	NH ₂		(10 <i>S</i> ,12 <i>S</i>)-12-amino-17-[2-(dimethylamino)acetyl]-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaene-15,21-dione
Ex.209			<i>N</i> -[(10 <i>S</i> ,12 <i>S</i>)-17-[2-(dimethylamino)acetyl]-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaen-12-yl]-2-phenylacetamide
Ex.210			<i>N</i> -[(10 <i>S</i> ,12 <i>S</i>)-17-[2-(dimethylamino)acetyl]-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaen-12-yl]- <i>N</i> -methylurea
Ex.211			<i>N</i> -[(10 <i>S</i> ,12 <i>S</i>)-17-[2-(dimethylamino)acetyl]-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaen-12-yl]cyclopropanesulfonamide
Ex.212			benzyl (10 <i>S</i> ,12 <i>S</i>)-12-(acetamino)-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaene-17-carboxylate
Ex.213		H	<i>N</i> -[(10 <i>S</i> ,12 <i>S</i>)-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaen-12-yl]acetamide

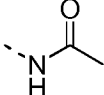
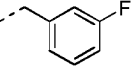
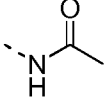
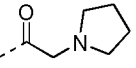
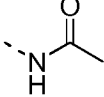
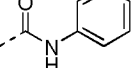
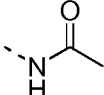
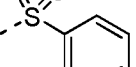
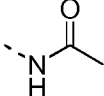
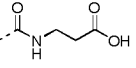
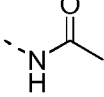
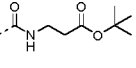
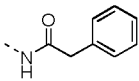
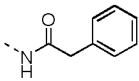
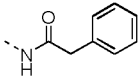
No	R ^B	R ^D	IUPAC name
Ex.214			<i>N</i> -[(10 <i>S</i> ,12 <i>S</i>)-17-(3-fluorobenzyl)-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaen-12-yl]acetamide
Ex.215			<i>N</i> -[(10 <i>S</i> ,12 <i>S</i>)-15,21-dioxo-17-[2-(1-pyrrolidinyl)acetyl]-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaen-12-yl]acetamide
Ex.216			(10 <i>S</i> ,12 <i>S</i>)-12-(acetamino)-15,21-dioxo- <i>N</i> -phenyl-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaene-17-carboxamide
Ex.217			<i>N</i> -[(10 <i>S</i> ,12 <i>S</i>)-15,21-dioxo-17-(phenylsulfonyl)-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaen-12-yl]acetamide
Ex.218			3-({[(10 <i>S</i> ,12 <i>S</i>)-12-(acetamino)-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaen-17-yl]carbonyl}amino)propanoic acid
Ex.219			<i>tert</i> -butyl 3-({[(10 <i>S</i> ,12 <i>S</i>)-12-(acetamino)-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0 ^{2,7} .0 ^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaen-17-yl]carbonyl}amino)propanoate

Table 25a: Examples of Core 13 (Ex.220-Ex.226; continued on the following pages)

No	R ^B	R ^E	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.220-Ex.222 <i>cf. experimental description</i>							
Ex.223		CO ₂ CH ₃	Ex.222	A.1.1	2-Phenylacetic acid i-Pr ₂ NEt added at 0°C 0°C to rt, 2 h Workup: EtOAc, 1M aq. HCl soln, H ₂ O, sat. aq. NaHCO ₃ soln	FC (CH ₂ Cl ₂ /MeOH)	93%
Ex.224		CO ₂ H	Ex.223	B.5	Trimethyltin hydroxide	FC (CH ₂ Cl ₂ /MeOH) and prep. HPLC method 1a	80%
Ex.225		CONH ₂	Ex.224	A.2	Ammonium chloride (5.2 equiv.) HATU (3.2 equiv.) HOAt (3.2 equiv.) i-Pr ₂ NEt (8.4 equiv.) Workup: EtOAc, 1M aq. HCl soln, H ₂ O, sat. aq. NaHCO ₃ soln, sat. aq. NaCl soln	FC (CH ₂ Cl ₂ /MeOH)	64%

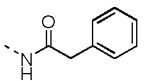
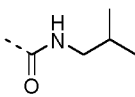
No	R ^B	R ^E	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.226			Ex.224	A.2	Isobutylamine Workup: EtOAc, 1M aq. HCl soln, H ₂ O, sat. aq. NaHCO ₃ soln, sat. aq. NaCl soln	FC (CH ₂ Cl ₂ /MeOH)	80%

Table 25b: Examples of Core 13 (Ex.220-Ex.226)

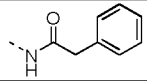
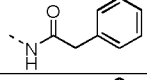
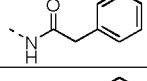
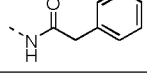
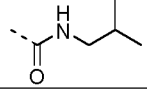
No	R ^B	R ^E	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.220-Ex.222.: cf. experimental description							
Ex.223		CO ₂ CH ₃	C32H34FN3O7S	623.2	2.31 (99)	624.3	method 1d
Ex.224		CO ₂ H	C31H32FN3O7S	609.2	2.05 (99)	610.2	method 1d
Ex.225		CONH ₂	C31H33FN4O6S	608.2	1.93 (99)	609.2	method 1d
Ex.226			C35H41FN4O6S	664.3	2.22 (89)	665.3	method 1d

Table 25c: Examples of Core 13 (Ex.220-Ex.226)

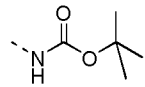
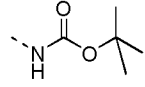
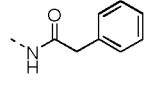
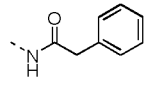
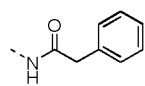
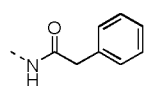
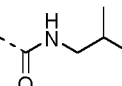
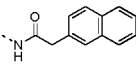
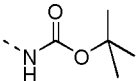
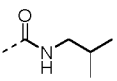
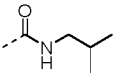
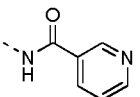
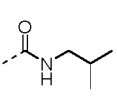
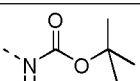
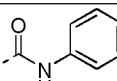
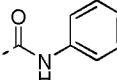
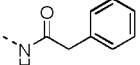
No	R ^B	R ^E	IUPAC name
Ex.220		CO ₂ CH ₃	methyl (8S,17S,19S)-17-[(<i>tert</i> -butoxycarbonyl)amino]-24-fluoro-6,14-dioxo-10,21-dioxa-4-thia-7,15-diazatetracyclo[20.3.1.1 ^{2,5} .0 ^{15,19}]heptacosa-1(26),2,5(27),12,22,24-hexaene-8-carboxylate
Ex.221		CO ₂ CH ₃	methyl (8S,17S,19S)-17-[(<i>tert</i> -butoxycarbonyl)amino]-24-fluoro-6,14-dioxo-10,21-dioxa-4-thia-7,15-diazatetracyclo[20.3.1.1 ^{2,5} .0 ^{15,19}]heptacosa-1(26),2,5(27),22,24-pentaene-8-carboxylate
Ex.222	NH ₂	CO ₂ CH ₃	methyl (8S,17S,19S)-17-amino-24-fluoro-6,14-dioxo-10,21-dioxa-4-thia-7,15-diazatetracyclo[20.3.1.1 ^{2,5} .0 ^{15,19}]heptacosa-1(26),2,5(27),22,24-pentaene-8-carboxylate
Ex.223		CO ₂ CH ₃	methyl (8S,17S,19S)-24-fluoro-6,14-dioxo-17-[(2-phenylacetyl)amino]-10,21-dioxa-4-thia-7,15-diazatetracyclo[20.3.1.1 ^{2,5} .0 ^{15,19}]heptacosa-1(26),2,5(27),22,24-pentaene-8-carboxylate
Ex.224		CO ₂ H	(8S,17S,19S)-24-fluoro-6,14-dioxo-17-[(2-phenylacetyl)amino]-10,21-dioxa-4-thia-7,15-diazatetracyclo[20.3.1.1 ^{2,5} .0 ^{15,19}]heptacosa-1(26),2,5(27),22,24-pentaene-8-carboxylic acid
Ex.225		CONH ₂	(8S,17S,19S)-24-fluoro-6,14-dioxo-17-[(2-phenylacetyl)amino]-10,21-dioxa-4-thia-7,15-diazatetracyclo[20.3.1.1 ^{2,5} .0 ^{15,19}]heptacosa-1(26),2,5(27),22,24-pentaene-8-carboxamide
Ex.226			(8S,17S,19S)-24-fluoro- <i>N</i> -isobutyl-6,14-dioxo-17-[(2-phenylacetyl)amino]-10,21-dioxa-4-thia-7,15-diazatetracyclo[20.3.1.1 ^{2,5} .0 ^{15,19}]heptacosa-1(26),2,5(27),22,24-pentaene-8-carboxamide

Table 26a: Examples of Core 14 (Ex.227-Ex.241; continued on the following page)

No	R ^B	R ^E	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.227-Ex.229: cf. experimental description							
Ex.230		CO ₂ CH ₃	Ex.229	A.1.2	2-Naphthaleneacetyl chloride (1.1 equiv.)	prep. HPLC method 3	57%
Ex.231			Ex.228	A.2	Isobutylamine	FC (hexane/EtOAc/MeOH)	40%
Ex.232	NH ₂		Ex.231	B.1	HCl-dioxane	crude product	93% (HCl salt)
Ex.233			Ex.232	A.1.1	Nicotinic acid (1.3 equiv.), 0°C, 2 h Workup : EtOAc, 1M aq. HCl soln, sat. aq. Na ₂ CO ₃ soln, sat. aq. NaCl soln	FC (CH ₂ Cl ₂ /MeOH)	14%
Ex.234			Ex.228	A.2	Aniline	FC (hexane/EtOAc)	4%
Ex.235	NH ₂		Ex.234	B.1	HCl-dioxane	prep. HPLC method 1a	44% (TFA salt)
Ex.236		CO ₂ CH ₃	Ex.229	A.1.2	Phenylacetyl chloride (1.1 equiv.)	prep. HPLC method 3	75%

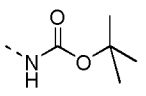
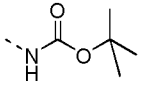
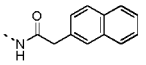
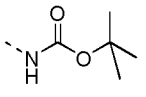
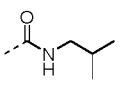
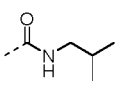
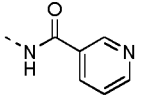
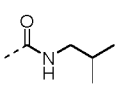
No	R ^B	R ^E	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.237		CO ₂ H	Ex.236	B.5	Trimethyltin hydroxide	prep. HPLC method 1a	78%
Ex.238		CO ₂ CH ₃	Ex.229	A.1.2	3-Chlorobenzoyl chloride (1.1 equiv.)	prep. HPLC method 3	62%
Ex.239		CO ₂ H	Ex.238	B.5	Trimethyltin hydroxide	prep. HPLC method 1a	70%
Ex.240			Ex.241	A.2	Isobutylamine	FC (hexane/EtOAc/MeOH)	78%
Ex.241		CO ₂ H	Ex.230	B.5	Trimethyltin hydroxide	FC (CH ₂ Cl ₂ /MeOH)	84%

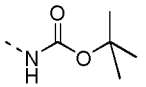
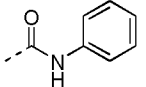
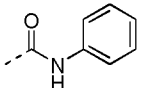
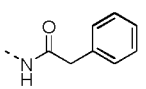
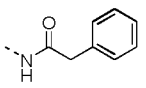
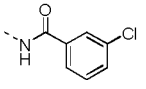
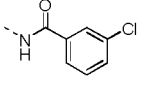
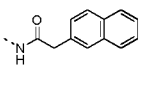
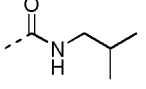
Table 26b: Examples of Core 14 (Ex.227-Ex.241; continued on the following page)

No	R ^B	R ^E	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.227-Ex.229: cf. experimental description							
Ex.230		CO ₂ CH ₃	C37H36FN3O7S	685.2	2.28 (96)	686.2	method 1a
Ex.231			C33H43FN4O7S	658.3	2.37 (95)	659.3	method 1a
Ex.232	NH ₂		C28H35FN4O5S	558.2	1.59 (93)	559.2	method 1a

No	R ^B	R ^E	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.233			C34H38FN5O6S	663.3	1.95 (87)	664.3	method 2c
Ex.234			C35H39FN4O7S	678.3	2.43 (77)	679.2	method 1a
Ex.235	NH ₂		C30H31FN4O5S	578.2	1.66 (95)	579.2	method 1a
Ex.236		CO ₂ CH ₃	C33H34FN3O7S	635.2	2.15 (91)	636.0	method 1a
Ex.237		CO ₂ H	C32H32FN3O7S	621.2	1.98 (96)	622.1	method 1c
Ex.238		CO ₂ CH ₃	C32H31ClFN3O7S	655.2	2.31 (97)	656.1	method 1a
Ex.239		CO ₂ H	C31H29ClFN3O7S	641.1	2.14 (97)	642.1	method 1a
Ex.240			C40H43FN4O6S	726.3	2.32 (79)	727.3	method 1a
Ex.241		CO ₂ H	C36H34FN3O7S	671.2	2.15 (88)	672.1	method 1a

Table 26c: Examples of Core 14 (Ex.227-Ex.241; continued on the following pages)

No	R ^B	R ^E	IUPAC name
Ex.227		CO ₂ CH ₃	methyl (8 <i>S</i> ,12 <i>E</i> ,18 <i>S</i> ,20 <i>S</i>)-18-[(<i>tert</i> -butoxycarbonyl)amino]-25-fluoro-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaene-8-carboxylate
Ex.228		CO ₂ H	(8 <i>S</i> ,12 <i>E</i> ,18 <i>S</i> ,20 <i>S</i>)-18-[(<i>tert</i> -butoxycarbonyl)amino]-25-fluoro-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaene-8-carboxylic acid
Ex.229	NH ₂	CO ₂ CH ₃	methyl (8 <i>S</i> ,12 <i>E</i> , 18 <i>S</i> ,20 <i>S</i>)-18-amino-25-fluoro-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaene-8-carboxylate
Ex.230		CO ₂ CH ₃	methyl (8 <i>S</i> ,12 <i>E</i> , 18 <i>S</i> ,20 <i>S</i>)-25-fluoro-18-[2-(2-naphthyl)acetyl]amino-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaene-8-carboxylate
Ex.231			<i>tert</i> -butyl <i>N</i> -[(8 <i>S</i> ,12 <i>E</i> , 18 <i>S</i> ,20 <i>S</i>)-25-fluoro-8-[(isobutylamino)carbonyl]-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaen-18-yl]carbamate
Ex.232	NH ₂		(8 <i>S</i> ,12 <i>E</i> ,18 <i>S</i> ,20 <i>S</i>)-18-amino-25-fluoro- <i>N</i> -isobutyl-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaene-8-carboxamide
Ex.233			(8 <i>S</i> ,12 <i>E</i> ,18 <i>S</i> ,20 <i>S</i>)-25-fluoro- <i>N</i> -isobutyl-6,15-dioxo-18-[(3-pyridinylcarbonyl)amino]-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaene-8-carboxamide

No	R ^B	R ^E	IUPAC name
Ex.234			<i>tert</i> -butyl <i>N</i> -[(8 <i>S</i> ,12 <i>E</i> ,18 <i>S</i> ,20 <i>S</i>)-8-(anilinoacarbonyl)-25-fluoro-6,15-dioxo-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaen-18-yl]carbamate
Ex.235	NH ₂		(8 <i>S</i> ,12 <i>E</i> ,18 <i>S</i> ,20 <i>S</i>)-18-amino-25-fluoro-6,15-dioxo- <i>N</i> -phenyl-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaene-8-carboxamide
Ex.236		CO ₂ CH ₃	methyl (8 <i>S</i> ,12 <i>E</i> ,18 <i>S</i> ,20 <i>S</i>)-25-fluoro-6,15-dioxo-18-[(2-phenylacetyl)amino]-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaene-8-carboxylate
Ex.237		CO ₂ H	(8 <i>S</i> ,12 <i>E</i> ,18 <i>S</i> ,20 <i>S</i>)-25-fluoro-6,15-dioxo-18-[(2-phenylacetyl)amino]-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaene-8-carboxylic acid
Ex.238		CO ₂ CH ₃	methyl (8 <i>S</i> ,12 <i>E</i> ,18 <i>S</i> ,20 <i>S</i>)-18-[(3-chlorobenzoyl)amino]-25-fluoro-6,15-dioxo-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaene-8-carboxylate
Ex.239		CO ₂ H	(8 <i>S</i> ,12 <i>E</i> ,18 <i>S</i> ,20 <i>S</i>)-18-[(3-chlorobenzoyl)amino]-25-fluoro-6,15-dioxo-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaene-8-carboxylic acid
Ex.240			(8 <i>S</i> ,12 <i>E</i> ,18 <i>S</i> ,20 <i>S</i>)-25-fluoro- <i>N</i> -isobutyl-18-{[2-(2-naphthyl)acetyl]amino}-6,15-dioxo-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaene-8-carboxamide

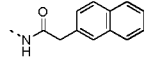
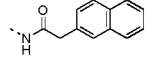
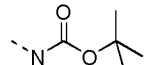
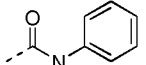
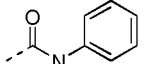
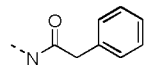
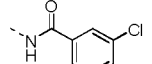
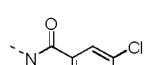
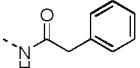
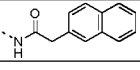
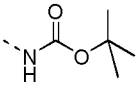
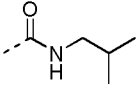
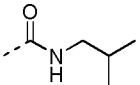
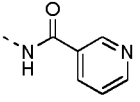
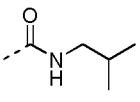
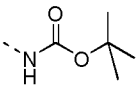
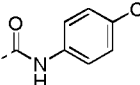
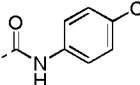
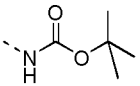
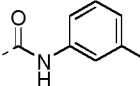
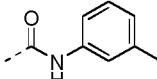
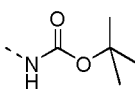
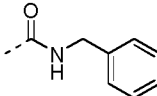
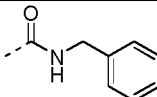
No	R ^B	R ^E	IUPAC name
Ex.241		CO ₂ H	(8 <i>S</i> ,12 <i>E</i> ,18 <i>S</i> ,20 <i>S</i>)-25-fluoro-18-[[2-(2-naphthyl)acetyl]amino]-6,15-dioxo-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaene-8-carboxylic acid

Table 27a: Examples of Core 15 (Ex.242-Ex.261; continued on the following pages)

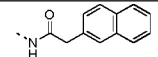
No	R ^B	R ^E	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.242-Ex.244: cf. experimental description							
Ex.245		CO ₂ CH ₃	Ex.244	1)	2-Naphthaleneacetyl chloride	FC (EtOAc) and FC (CH ₂ Cl ₂ /MeOH)	52%
Ex.246			Ex.243	2)	Aniline (5 equiv.)	FC (hexane/EtOAc)	62%
Ex.247	NH ₂		Ex.246	2)	HCl-dioxane then TFA, CH ₂ Cl ₂	FC (CH ₂ Cl ₂ /MeOH)	60% (HCl salt)
Ex.248		CO ₂ CH ₃	Ex.244	A.1.2	Phenylacetyl chloride (1.6 equiv.)	FC (hexane/EtOAc/MeOH)	90%
Ex.249		CO ₂ H	Ex.250	B.5	Trimethyltin hydroxide	prep. HPLC method 1a	65%
Ex.250		CO ₂ CH ₃	Ex.244	A.1.2	3-Chlorobenzoyl chloride (1.6 equiv.)	FC (hexane/EtOAc)	87%

No	R ^B	R ^E	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.251		CO ₂ H	Ex.248	B.5	Trimethyltin hydroxide	prep. HPLC method 1a	70%
Ex.252		CO ₂ H	Ex.245	B.5	Trimethyltin hydroxide	prep. HPLC method 1a	45%
Ex.253			Ex.243	A.2	Isobutylamine (1.5 equiv.) Workup: CH ₂ Cl ₂ , sat. aq. NaHCO ₃ soln, H ₂ O, sat.aq. NaCl soln	FC (hexane, EtOAc)	73%
Ex.254	NH ₂		Ex.253	B.1	HCl-dioxane	crude product	quant. (HCl salt)
Ex.255			Ex.254	A.1.1	Nicotinic acid (1.3 equiv.) 0°C, 2 h Workup: EtOAc, sat. aq. NaHCO ₃ soln, H ₂ O, sat. aq. NaCl soln,	FC (CH ₂ Cl ₂ /MeOH)	50%
Ex.256			Ex.243	2)	4-Chloroaniline (5 equiv.)	FC (hexane/EtOAc)	14%
Ex.257	NH ₂		Ex.256	2)	HCl-dioxane then TFA, CH ₂ Cl ₂	FC (CH ₂ Cl ₂ /MeOH)	66% (HCl salt)
Ex.258			Ex.243	2)	m-Toluidine (5 equiv.)	FC (hexane/EtOAc)	43%

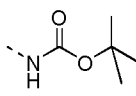
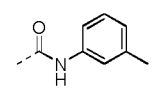
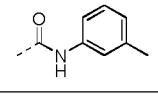
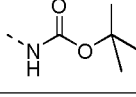
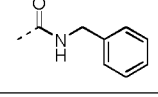
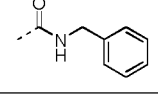
No	R ^B	R ^E	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.259	NH ₂		Ex.258	2)	HCl-dioxane then TFA, CH ₂ Cl ₂	FC (CH ₂ Cl ₂ /MeOH)	66% (HCl salt)
Ex.260			Ex.243	3)	Benzylamine (5 equiv.)	FC (hexane/EtOAc)	57%
Ex.261	NH ₂		Ex.260	3)	HCl-dioxane then TFA, CH ₂ Cl ₂	FC (CH ₂ Cl ₂ /MeOH)	74% (HCl salt)

- 1) 2-Naphthaleneacetic acid (41 mg, 0.22 mmol) in CH₂Cl₂ (3 mL) was treated at 0°C for 1 h with oxalyl chloride (0.08 mL, 0.93 mmol) and DMF (0.007 mL). The volatiles were evaporated. The residue was dissolved in CH₂Cl₂ (3 mL) and added dropwise to a mixture of **Ex.244**·HCl (103 mg, 0.19 mmol) and i-Pr₂NEt (0.2 mL; 0.93 mmol) in CH₂Cl₂ (3 mL). The solution was stirred at 0°C for 1 h, followed by an aqueous workup (CH₂Cl₂, sat. aq. NaHCO₃ soln; Na₂SO₄), FC (EtOAc) and FC (CH₂Cl₂/MeOH 99:1 to 97:3) to afford **Ex.245** (67 mg, 52%).
- 2) Cf. experimental description for detailed procedure
- 3) **Ex.260** was obtained by applying the method described for the synthesis of **Ex.246**; **Ex.261** was obtained by applying the method described for the synthesis of **Ex.247**.

Table 27b: Examples of Core 15 (Ex.242-Ex.261; continued on the following pages)

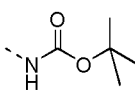
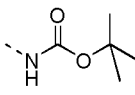
No	R ^B	R ^E	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.242-Ex.244.: cf. experimental description							
Ex.245		CO ₂ CH ₃	C ₃₇ H ₃₈ FN ₃ O ₇ S	687.2	1.62 (91)	688.2	method 4a

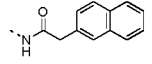
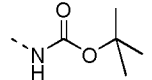
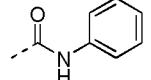
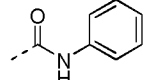
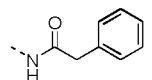
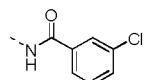
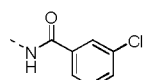
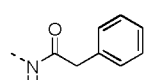
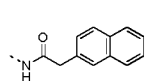
No	R ^B	R ^E	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.246			C35H41FN4O7S	680.3	2.48 (86)	681.3	method 1a
Ex.247	NH ₂		C30H33FN4O5S	580.2	1.66 (96)	581.2	method 1a
Ex.248		CO ₂ CH ₃	C33H36FN3O7S	637.2	2.21 (91)	638.2	method 1a
Ex.249		CO ₂ H	C31H31ClFN3O7S	643.2	2.22 (97)	644.1	method 1a
Ex.250		CO ₂ CH ₃	C32H33ClFN3O7S	657.2	2.40 (94)	658.1	method 1c
Ex.251		CO ₂ H	C32H34FN3O7S	623.2	2.06 (97)	624.1	method 1a
Ex.252		CO ₂ H	C36H36FN3O7S	673.2	2.23 (89)	674.2	method 1g
Ex.253			C33H45FN4O7S	660.3	2.45 (93)	661.2	method 1a
Ex.254	NH ₂		C28H37FN4O5S	560.2	1.60 (97)	561.2	method 1a
Ex.255			C34H40FN5O6S	665.3	2.00 (95)	666.2	method 2c
Ex.256			C35H40ClFN4O7S	714.2	2.59 (89)	715.4	method 1a
Ex.257	NH ₂		C30H32ClFN4O5S	614.2	1.80 (87)	615.2	method 1a

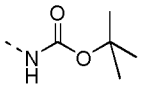
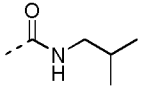
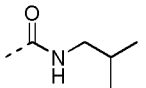
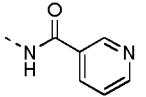
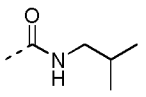
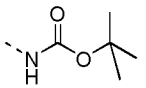
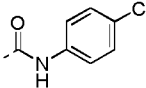
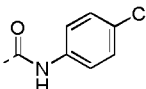
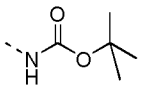
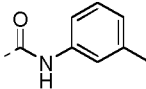
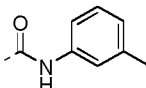
No	R ^B	R ^E	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.258			C ₃₆ H ₄₃ FN ₄ O ₇ S	694.3	2.55 (91)	695.4	method 1a
Ex.259	NH ₂		C ₃₁ H ₃₅ FN ₄ O ₅ S	594.2	1.74 (90)	595.3	method 1a
Ex.260			C ₃₆ H ₄₃ FN ₄ O ₇ S	694.3	2.44 (92)	695.3	method 1a
Ex.261	NH ₂		C ₃₁ H ₃₅ FN ₄ O ₅ S	594.2	1.63 (92)	595.2	method 1a

292

Table 27c: Examples of Core 15 (Ex.242-Ex.261; continued on the following pages)

No	R ^B	R ^E	IUPAC name
Ex.242		CO ₂ CH ₃	methyl (8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-18-[(<i>tert</i> -butoxycarbonyl)amino]-25-fluoro-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaene-8-carboxylate
Ex.243		CO ₂ H	(8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-18-[(<i>tert</i> -butoxycarbonyl)amino]-25-fluoro-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaene-8-carboxylic acid
Ex.244	NH ₂	CO ₂ CH ₃	methyl (8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-18-amino-25-fluoro-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaene-8-carboxylate

No	R ^B	R ^E	IUPAC name
Ex.245		CO ₂ CH ₃	methyl (8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-25-fluoro-18-[[2-(2-naphthyl)acetyl]amino]-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaene-8-carboxylate
Ex.246			<i>tert</i> -butyl <i>N</i> -[(8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-8-(anilino)-25-fluoro-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaen-18-yl]carbamate
Ex.247	NH ₂		(8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-18-amino-25-fluoro-6,15-dioxo- <i>N</i> -phenyl-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaene-8-carboxamide
Ex.248		CO ₂ CH ₃	methyl (8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-25-fluoro-6,15-dioxo-18-[(2-phenylacetyl)amino]-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaene-8-carboxylate
Ex.249		CO ₂ H	(8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-18-[(3-chlorobenzoyl)amino]-25-fluoro-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaene-8-carboxylic acid
Ex.250		CO ₂ CH ₃	methyl (8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-18-[(3-chlorobenzoyl)amino]-25-fluoro-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaene-8-carboxylate
Ex.251		CO ₂ H	(8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-25-fluoro-6,15-dioxo-18-[(2-phenylacetyl)amino]-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaene-8-carboxylic acid
Ex.252		CO ₂ H	(8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-25-fluoro-18-[[2-(2-naphthyl)acetyl]amino]-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaene-8-carboxylic acid

No	R ^B	R ^E	IUPAC name
Ex.253			<i>tert</i> -butyl <i>N</i> -[(8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-25-fluoro-8-[(isobutylamino)carbonyl]-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaen-18-yl]carbamate
Ex.254	NH ₂		(8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-18-amino-25-fluoro- <i>N</i> -isobutyl-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaene-8-carboxamide
Ex.255			(8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-25-fluoro- <i>N</i> -isobutyl-6,15-dioxo-18-[(3-pyridinylcarbonyl)amino]-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaene-8-carboxamide
Ex.256			<i>tert</i> -butyl <i>N</i> -[(8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-8-[(4-chloroanilino)carbonyl]-25-fluoro-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaen-18-yl]carbamate
Ex.257	NH ₂		(8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-18-amino- <i>N</i> -(4-chlorophenyl)-25-fluoro-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaene-8-carboxamide
Ex.258			<i>tert</i> -butyl <i>N</i> -[(8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-25-fluoro-6,15-dioxo-8-(3-toluidinocarbonyl)-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaen-18-yl]carbamate
Ex.259	NH ₂		(8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-18-amino-25-fluoro- <i>N</i> -(3-methylphenyl)-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacos-1(27),2,5(28),23,25-pentaene-8-carboxamide

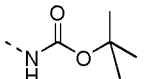
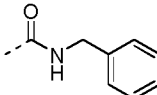
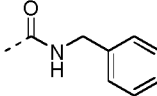
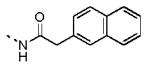
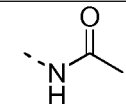
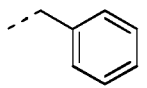
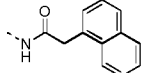
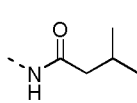
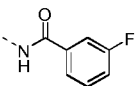
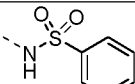
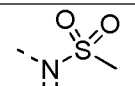
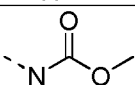
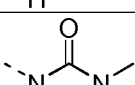
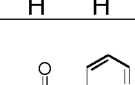
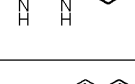
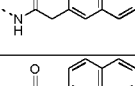
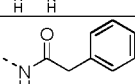
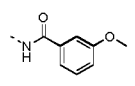
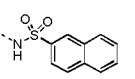
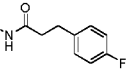
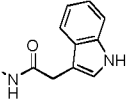
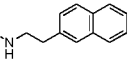
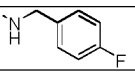
No	R ^B	R ^E	IUPAC name
Ex.260			<i>tert</i> -butyl <i>N</i> -[(8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-8-[(benzylamino)carbonyl]-25-fluoro-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacosa-1(27),2,5(28),23,25-pentaen-18-yl]carbamate
Ex.261	NH ₂		(8 <i>S</i> ,18 <i>S</i> ,20 <i>S</i>)-18-amino- <i>N</i> -benzyl-25-fluoro-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1 ^{2,5} .0 ^{16,20}]octacosa-1(27),2,5(28),23,25-pentaene-8-carboxamide

Table 28a: Examples of Core 16 (Ex.262-Ex.283; continued on the following pages)

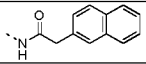
No	R ^A	R ^F	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.262-Ex.264: cf. experimental description							
Ex.265		H	Ex.263	1)	2-Naphthaleneacetyl chloride	FC (CH ₂ Cl ₂ /i-PrOH)	78%
Ex.266			Ex.264	A.1.2	Acetic anhydride (1.3 equiv.)	prep. HPLC method 1a	58% (TFA salt)
Ex.267		H	Ex.263	2)	1-Naphthaleneacetyl chloride	prep. HPLC method 3	58%
Ex.268		H	Ex.263	A.1.2	Isovaleryl chloride (1.6 equiv.) 0°C to rt, 16 h	prep. HPLC method 3	69%

No	R ^A	R ^F	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.269		H	Ex.263	A.1.2	3-Fluorobenzoyl chloride (1.1 equiv.)	prep. HPLC method 3	52%
Ex.270		H	Ex.263	A.5	Benzenesulfonyl chloride	prep. HPLC method 3	49%
Ex.271		H	Ex.263	A.5	Methanesulfonyl chloride	prep. HPLC method 3	39%
Ex.272		H	Ex.263	A.4	Methyl chloroformate	prep. HPLC method 3	69%
Ex.273		H	Ex.263	A.3	N-Succinimidyl N-methylcarbamate	prep. HPLC method 3	65%
Ex.274		H	Ex.263	A.3	2,5-Dioxopyrrolidin-1-yl pyridin-3-ylcarbamate 0°C to rt, 1 h	prep. HPLC method 3	64%
Ex.275		CH ₃	Ex.265	1)	Trimethyloxonium tetrafluoroborate	prep. HPLC method 1a	12%
Ex.276		H	Ex.263	1)	2-Naphthylisocyanate	prep. HPLC method 3	71%
Ex.277		H	Ex.263	A.1.1	Phenylacetic acid	prep. HPLC method 3	58%
Ex.278		H	Ex.263	A.1.2	m-Anisoyl chloride (1.1 equiv.)	prep. HPLC method 3	75%

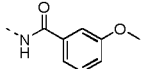
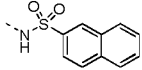
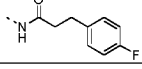
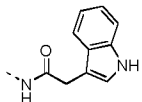
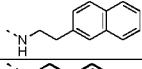
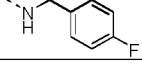
No	R ^A	R ^F	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.279		H	Ex.263	A.5	2-Naphthalenesulfonyl chloride	prep. HPLC method 3	76%
Ex.280		H	Ex.263	A.1.1	3-(4-Fluorophenyl)propionic acid	prep. HPLC method 3	42%
Ex.281		H	Ex.263	A.1.1	1H-indole-3-acetic acid	prep. HPLC method 3 and prep. HPLC method 2a	38%
Ex.282		H	Ex.263	A.6.4	2-Naphthylacetaldehyde (1.3 equiv.)	prep. HPLC method 2a	26%
Ex.283		H	Ex.263	A.6.4	4-Fluorobenzaldehyde	prep. HPLC method 3	52%

- 1) Cf. experimental description for detailed procedure
- 2) Ex.267 was prepared applying the protocol described for the synthesis of Ex.265.

Table 28b: Examples of Core 16 (Ex.262-Ex.283; continued on the following pages)

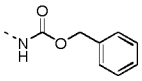
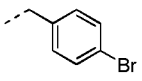
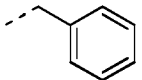
No	R ^A	R ^F	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.262 -Ex.264: cf. experimental description							
Ex.265		H	C ₃₁ H ₃₃ N ₅ O ₅ S	587.2	1.86 (93)	587.9	method 1a

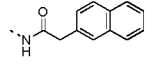
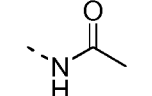
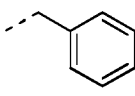
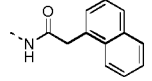
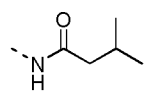
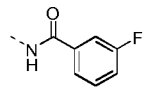
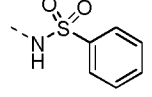
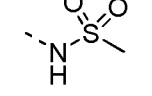
No	R ^A	R ^F	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.266			C ₂₈ H ₃₃ N ₅ O ₅ S	551.2	1.86 (96)	552.2	method 1d
Ex.267		H	C ₃₁ H ₃₃ N ₅ O ₅ S	587.2	1.85 (87)	588.0	method 1a
Ex.268		H	C ₂₄ H ₃₃ N ₅ O ₅ S	503.2	1.54 (98)	504.2	method 1a
Ex.269		H	C ₂₆ H ₂₈ N ₅ O ₅ S	541.2	1.66 (98)	542.1	method 1a
Ex.270		H	C ₂₅ H ₂₉ N ₅ O ₆ S ₂	559.2	1.58 (97)	560.0	method 1a
Ex.271		H	C ₂₀ H ₂₇ N ₅ O ₆ S ₂	497.1	1.30 (98)	498.0	method 1a
Ex.272		H	C ₂₁ H ₂₇ N ₅ O ₆ S	477.2	1.34 (99)	478.1	method 1a
Ex.273		H	C ₂₁ H ₂₈ N ₆ O ₅ S	476.2	1.23 (97)	476.9	method 1a
Ex.274		H	C ₂₅ H ₂₉ N ₇ O ₅ S	539.2	1.19 (99)	540.0	method 1a
Ex.275		CH ₃	C ₃₂ H ₃₅ N ₅ O ₅ S	601.2	2.05 (97)	602.2	method 1d
Ex.276		H	C ₃₀ H ₃₂ N ₆ O ₅ S	588.2	1.86 (99)	589.0	method 1a
Ex.277		H	C ₂₇ H ₃₁ N ₅ O ₅ S	537.2	1.62 (96)	538.2	method 1a

No	R ^A	R ^F	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.278		H	C ₂₇ H ₃₁ N ₅ O ₆ S	553.2	1.65 (96)	554.1	method 1a
Ex.279		H	C ₂₉ H ₃₁ N ₅ O ₆ S ₂	609.2	1.82 (96)	610.1	method 1a
Ex.280		H	C ₂₈ H ₃₂ FN ₅ O ₅ S	569.2	1.72 (92)	570.2	method 1a
Ex.281		H	C ₂₉ H ₃₂ N ₆ O ₅ S	576.2	1.61 (78)	577.1	method 1a
Ex.282		H	C ₃₁ H ₃₅ N ₅ O ₄ S	573.2	1.63 (89)	574.2	method 1d
Ex.283		H	C ₂₆ H ₃₀ FN ₅ O ₄ S	527.2	1.37 (97)	528.2	method 1a

299

Table 28c: Examples of Core 16 (Ex.262-Ex.283; continued on the following pages)

No	R ^A	R ^F	IUPAC name
Ex.262			benzyl N-[(9S,11S,15S)-11-[(4-bromobenzyl)oxy]-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]carbamate
Ex.263	NH ₂	H	(9S,11S,15S)-15-amino-11-hydroxy-18,21-dimethyl-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraene-14,19-dione
Ex.264	NH ₂		(9S,11S,15S)-15-amino-11-(benzyloxy)-18,21-dimethyl-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraene-14,19-dione

No	R ^A	R ^F	IUPAC name
Ex.265		H	<i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]-2-(2-naphthyl)acetamide
Ex.266			<i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-(benzyloxy)-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]acetamide
Ex.267		H	<i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]-2-(1-naphthyl)acetamide
Ex.268		H	<i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]-3-methylbutanamide
Ex.269		H	3-fluoro- <i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]benzamide
Ex.270		H	<i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]benzenesulfonamide
Ex.271		H	<i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]methanesulfonamide

No	R ^A	R ^F	IUPAC name
Ex.272		H	methyl <i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]carbamate
Ex.273		H	<i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]- <i>N</i> -methylurea
Ex.274		H	<i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]- <i>N</i> -(3-pyridinyl)urea
Ex.275		CH ₃	<i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-methoxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]-2-(2-naphthyl)acetamide
Ex.276		H	<i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]- <i>N</i> -(2-naphthyl)urea
Ex.277		H	<i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]-2-phenylacetamide
Ex.278		H	<i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]-3-methoxybenzamide

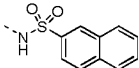
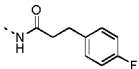
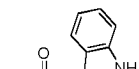
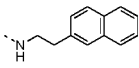
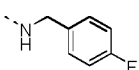
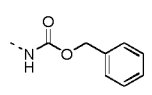
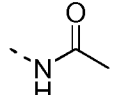
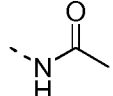
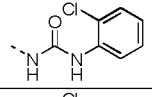
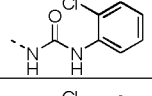
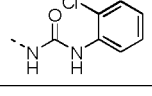
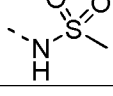
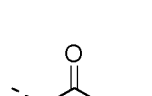
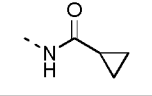
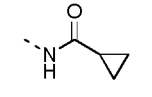
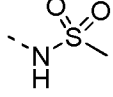
No	R ^A	R ^F	IUPAC name
Ex.279		H	<i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]-2-naphthalenesulfonamide
Ex.280		H	3-(4-fluorophenyl)- <i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]propanamide
Ex.281		H	<i>N</i> -[(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]-2-(1 <i>H</i> -indol-3-yl)acetamide
Ex.282		H	(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-11-hydroxy-18,21-dimethyl-15-[[2-(2-naphthyl)ethyl]amino]-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraene-14,19-dione
Ex.283		H	(9 <i>S</i> ,11 <i>S</i> ,15 <i>S</i>)-15-[(4-fluorobenzyl)amino]-11-hydroxy-18,21-dimethyl-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0 ^{2,6} .0 ^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraene-14,19-dione

Table 29a: Examples of Core 17 (Ex.284a-Ex.304; continued on the following pages)

No	R ^A	R ^G	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.284a-Ex.286: <i>cf. experimental description</i>							

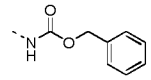
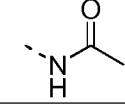
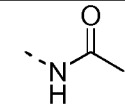
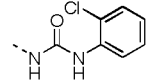
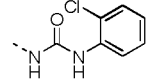
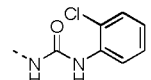
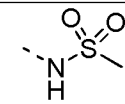
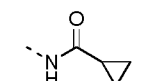
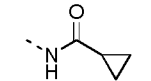
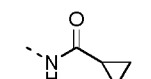
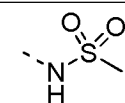
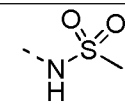
No	R ^A	R ^G	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.287			Ex.286	1)	Acetyl chloride	FC (hexane, EtOAc, MeOH)	77%
Ex.288	NH ₂		Ex.287	B.3	H ₂ , Pd(OH) ₂ -C, MeOH	crude product	78%
Ex.289		NO ₂	Ex.285	A.3	1-Chloro-2-isocyanatobenzene	FC (hexane, EtOAc, MeOH)	90%
Ex.290		NH ₂	Ex.289	B.4	H ₂ , PtO ₂	crude product	96%
Ex.291			Ex.290	A.5	Methanesulfonyl chloride (1.2 equiv.)	prep. HPLC method 1a	49% (TFA salt)
Ex.292		NO ₂	Ex.285	A.1.1	Cyclopropanecarboxylic acid, 0°C, 2 h Workup: EtOAc, 1 M aq. HCl soln, sat. aq. NaHCO ₃ soln, sat. aq. NaCl soln	FC (hexane, EtOAc, MeOH)	70%
Ex.293		NH ₂	Ex.292	B.4	H ₂ , PtO ₂	crude product	95%
Ex.294			Ex.293	A.5	Methanesulfonyl chloride (1.2 equiv.)	prep. HPLC method 1a	45%

No	R ^A	R ^G	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.295	NH ₂		Ex.296	B.3	H ₂ , Pd(OH) ₂ -C, MeOH	crude product	86%
Ex.296			Ex.286	A.5	Methanesulfonyl chloride (1.2 equiv.)	FC (hexane/ EtOAc) and prep. HPLC method 3	54%
Ex.297			Ex.286	2)	2-Chloropyrimidine	FC (EtOAc)	38%
Ex.298	NH ₂		Ex.297	B.3	H ₂ , Pd(OH) ₂ -C, MeOH	crude product	100%
Ex.299			Ex.288	A.6.1	Formaldehyde (36.5% in H ₂ O)	prep. HPLC method 1a	50% (TFA salt)
Ex.300			Ex.288	A.1.1	2-Phenylacetic acid (2.2 equiv.) HATU (2.5 equiv.) HOAt (2.5 equiv.) i-Pr ₂ NEt (6 equiv.) Workup: EtOAc, 1M aq. HCl soln, sat. aq. Na ₂ CO ₃ soln	prep. HPLC method 1a	17% (TFA salt)

No	R ^A	R ^G	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.301			Ex.288	A.5	3-Chlorobenzene-sulfonyl chloride	prep. HPLC method 1a	60% (TFA salt)
Ex.302			Ex.288	A.3	2,5-dioxopyrrolidin-1-yl isobutylcarbamate	prep. HPLC method 1a	70% (TFA salt)
Ex.303			Ex.295	A.1.1	4-Fluorobenzoic acid (2.2 equiv.) HATU (2.5 equiv.) HOAt (2.5 equiv.) i-Pr ₂ NEt (6 equiv.) Workup: EtOAc, 1M aq. HCl soln, sat. aq. Na ₂ CO ₃ soln, H ₂ O	prep. HPLC method 1a	11% (TFA salt)
Ex.304			Ex.295	A.6.4	3-Fluorobenzaldehyde	prep. HPLC method 1a	55% (TFA salt)

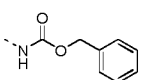
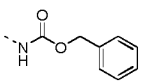
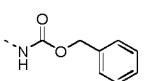
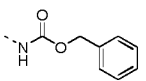
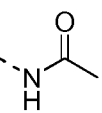
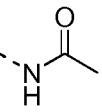
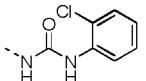
- 1) Acetyl chloride (0.109 mL, 1.5 mmol) was added at 0°C to a soln of **Ex.286** (450 mg, 0.77 mmol) and i-Pr₂NEt (0.394 mL, 2.3 mmol) in CH₂Cl₂ (16 mL). The soln was stirred at 0°C to rt for 2.5 h. MeOH (0.1 mL) was added and stirring continued for 10 min, followed by evaporation of the volatiles and FC (hexane/EtOAc/MeOH gradient) to afford **Ex.287** (371 mg, 77%).
- 2) A soln of **Ex.286** (115 mg, 0.196 mmol), 2-chloropyrimidine (27 mg, 0.235 mmol) and pTsOH·H₂O (45 mg, 0.235 mmol) in dioxane (3 mL) was heated to reflux for 8 h. More 2-chloropyrimidine (13 mg, 0.118 mmol) and pTsOH·H₂O (22mg, 0.118 mmol) were added and refluxing was continued for 6 h. The volatiles were evaporated. Aqueous workup (CH₂Cl₂, sat. aq. NaHCO₃ soln; Na₂SO₄) and FC (EtOAc) afforded **Ex.297** (50 mg, 38%).

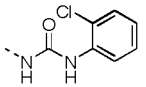
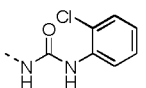
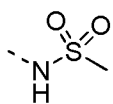
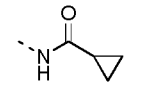
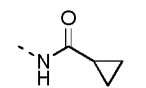
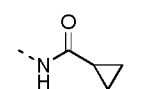
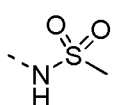
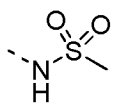
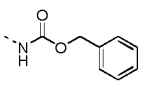
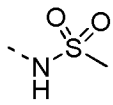
Table 29b: Examples of Core 17 (Ex.284a-Ex.304; continued on the following page)

No	R ^A	R ^G	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.284a-Ex.286: cf. experimental description							
Ex.287			C ₃₄ H ₄₀ N ₆ O ₆	628.3	1.89 (97)	629.3	method 1a
Ex.288	NH ₂		C ₂₆ H ₃₄ N ₆ O ₄	494.3	1.20 (92)	495.3	method 1a
Ex.289		NO ₂	C ₃₁ H ₃₄ ClN ₇ O ₆	635.2	2.26 (98)	636.2	method 1d
Ex.290		NH ₂	C ₃₁ H ₃₆ ClN ₇ O ₄	605.3	1.66 (95)	606.2	method 1a
Ex.291			C ₃₂ H ₃₈ ClN ₇ O ₆ S	683.2	1.98 (99)	684.3	method 1d
Ex.292		NO ₂	C ₂₈ H ₃₄ N ₆ O ₆	550.3	1.87 (96)	551.2	method 1a
Ex.293		NH ₂	C ₂₈ H ₃₆ N ₆ O ₄	520.3	1.32 (99)	521.3	method 1a
Ex.294			C ₂₉ H ₃₈ N ₆ O ₆ S	598.3	1.60 (99)	599.3	method 1d
Ex.295	NH ₂		C ₂₅ H ₃₄ N ₆ O ₅ S	530.2	1.24 (90)	531.2	method 1a

No	R ^A	R ^G	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.296			C33H40N6O7S	664.3	1.97 (91)	665.3	method 1a
Ex.297			C36H40N8O5	664.3	1.96 (86)	665.4	method 1d
Ex.298	NH ₂		C28H34N8O3	530.3	1.31 (87)	531.3	method 1d
Ex.299			C28H38N6O4	522.3	1.33 (100)	523.3	method 1d
Ex.300			C34H40N6O5	612.3	1.82 (97)	613.3	method 1d
Ex.301			C32H37ClN6O6S	668.2	2.03 (96)	669.3	method 1d
Ex.302			C31H43N7O5	593.3	1.24 (94)	594.0	method 3b
Ex.303			C32H37FN6O6S	652.2	1.95 (97)	653.3	method 1d
Ex.304			C32H39FN6O5S	638.3	1.51 (97)	639.3	method 1d

Table 29c: Examples of Core 17 (Ex.284a-Ex.304; continued on the following pages)

No	R ^A	R ^G	IUPAC name
Ex.284a		NO ₂	benzyl <i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-4,8-dimethyl-23-nitro-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-13-yl]carbamate
EX.284b		NO ₂	benzyl <i>N</i> -[(13 <i>R</i> ,19 <i>S</i>)-4,8-dimethyl-23-nitro-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-13-yl]carbamate
Ex.285	NH ₂	NO ₂	(13 <i>S</i> ,19 <i>S</i>)-13-amino-4,8-dimethyl-23-nitro-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaene-7,14-dione
Ex.286		NH ₂	benzyl <i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-23-amino-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-13-yl]carbamate
Ex.287			benzyl <i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-23-(acetamino)-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-13-yl]carbamate
Ex.288	NH ₂		<i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-13-amino-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-23-yl]acetamide
Ex.289		NO ₂	<i>N</i> -(2-chlorophenyl)- <i>N'</i> -[(13 <i>S</i> ,19 <i>S</i>)-4,8-dimethyl-23-nitro-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-13-yl]urea

No	R ^A	R ^G	IUPAC name
Ex.290		NH ₂	<i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-23-amino-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacosa-1(24),2(27),3,5,22,25-hexaen-13-yl]- <i>N</i> -(2-chlorophenyl)urea
Ex.291			<i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-13-[(2-chloroanilino)carbonyl]amino]-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacosa-1(24),2(27),3,5,22,25-hexaen-23-yl]methanesulfonamide
Ex.292		NO ₂	<i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-4,8-dimethyl-23-nitro-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacosa-1(24),2(27),3,5,22,25-hexaen-13-yl]cyclopropanecarboxamide
Ex.293		NH ₂	<i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-23-amino-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacosa-1(24),2(27),3,5,22,25-hexaen-13-yl]cyclopropanecarboxamide
Ex.294			<i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-4,8-dimethyl-23-[(methanesulfonyl)amino]-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacosa-1(24),2(27),3,5,22,25-hexaen-13-yl]cyclopropanecarboxamide
Ex.295	NH ₂		<i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-13-amino-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacosa-1(24),2(27),3,5,22,25-hexaen-23-yl]methanesulfonamide
Ex.296			benzyl <i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-4,8-dimethyl-23-[(methanesulfonyl)amino]-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacosa-1(24),2(27),3,5,22,25-hexaen-13-yl]carbamate

No	R ^A	R ^G	IUPAC name
Ex.297			benzyl <i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-4,8-dimethyl-7,14-dioxo-23-(2-pyrimidinylamino)-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-13-yl]carbamate
Ex.298	NH ₂		(13 <i>S</i> ,19 <i>S</i>)-13-amino-4,8-dimethyl-23-(2-pyrimidinylamino)-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaene-7,14-dione
Ex.299			<i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-13-(dimethylamino)-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-23-yl]acetamide
Ex.300			<i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-23-(acetamino)-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-13-yl]-2-phenylacetamide
Ex.301			<i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-13-[[3-chlorophenyl)sulfonyl]amino]-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-23-yl]acetamide
Ex.302			<i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-13-[(isobutylamino)carbonyl]amino]-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-23-yl]acetamide
Ex.303			<i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-4,8-dimethyl-23-[(methylsulfonyl)amino]-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-13-yl]-4-fluorobenzamide

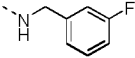
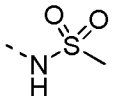
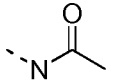
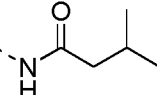
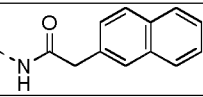
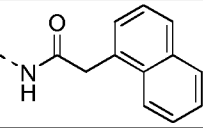
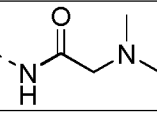
No	R ^A	R ^G	IUPAC name
Ex.304			<i>N</i> -[(13 <i>S</i> ,19 <i>S</i>)-13-[(3-fluorobenzyl)amino]-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1 ^{2,6} .0 ^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-23-yl]methanesulfonamide

Table 30a: Examples of Core 18 (Ex.305–Ex.326; continued on the following pages)

No	R ^B	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.305 – Ex.306: cf. experimental description						
Ex.307	N(CH ₃) ₂	Ex.306	A.6.1	Formaldehyde (36.5 % in H ₂ O)	prep. HPLC method 2a	72%
Ex.308		Ex.306	A.1.2	Acetyl chloride (2.0 equiv.)	prep. HPLC method 3	71%
Ex.309		Ex.306	A.1.1	3-Methylbutanoic acid	prep. HPLC method 3	65%
Ex.310		Ex.306	A.1.1	2-Naphthaleneacetic acid	prep. HPLC method 3	56%
Ex.311		Ex.306	A.1.1	1-Naphthaleneacetic acid	prep. HPLC method 3	70%
Ex.312		Ex.306	A.1.3	2-(Dimethylamino) acetic acid	prep. HPLC method 2a	56%

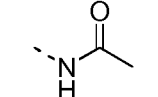
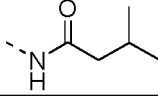
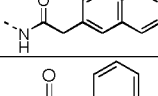
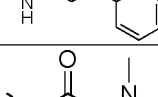
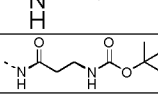
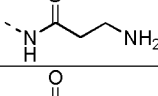
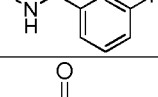
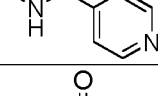
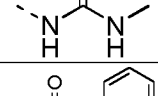
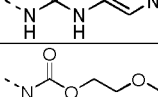
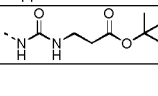
No	R ^B	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.313		Ex.306	A.1.1	N-Boc-β-alanine	FC (hexane/ EtOAc/MeOH)	80%
Ex.314		Ex.313	B.1	HCl-dioxane	prep. HPLC method 2a	43%
Ex.315		Ex.306	A.1.1	3-Fluorobenzoic acid	prep. HPLC method 3	43%
Ex.316		Ex.306	A.1.2	Isonicotinoyl chloride hydrochloride (2.5 equiv.) Pyridine (6.5 equiv.)	prep. HPLC method 2a	58%
Ex.317		Ex.306	A.3	N-Succinimidyl N- methylcarbamate	prep. HPLC method 3	67%
Ex.318		Ex.306	A.3	2,5-Dioxopyrrolidin-1-yl pyridin-3-ylcarbamate	prep. HPLC method 3	62%
Ex.319		Ex.306	A.4	2-Methoxyethyl chloro- formate	prep. HPLC method 3	70%
Ex.320		Ex.306	A.3	tert-Butyl 3-((2,5- dioxopyrrolidin-1- yloxy)carbonylamino) propanoate	FC (hexane/ EtOAc/MeOH)	82%
Ex.321		Ex.320	1)	HCl-dioxane	crude product	83%

No	R ^B	Starting Material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.322		Ex.306	A.5	Methanesulfonyl chloride	prep. HPLC method 3	75%
Ex.323		Ex.306	A.5	Benzenesulfonyl chloride	prep. HPLC method 3	61%
Ex.324		Ex.306	A.6.4	3-Fluorobenzaldehyde	prep. HPLC method 3	69%
Ex.325		Ex.306	A.6.4	Isobutyraldehyde	FC (hexane/EtOAc/MeOH)	60%
Ex.326		Ex.306	A.1.1	Side product from HATU coupling	prep. HPLC method 1a	-

- ¹⁾ A soln of **Ex.320** (82 mg, 0.15 mmol) in dioxane (0.8 mL) was treated with 4 M HCl-dioxane (0.8 mL) for 2 h at rt. Evaporation of the solvents and washing of the solid crude product with CH₂Cl₂/Et₂O yielded **Ex.321** (61 mg, 83%).

Table 30b: Examples of Core 18 (**Ex.305–Ex.326**; *continued on the following pages*)

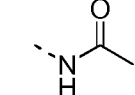
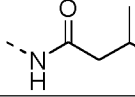
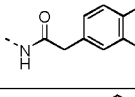
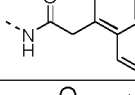
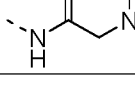
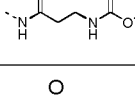
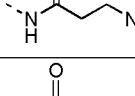
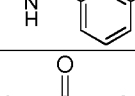
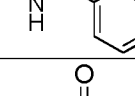
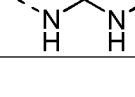
No	R ^B	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.305-Ex.306: <i>cf. experimental description</i>						
Ex.307	N(CH ₃) ₂	C ₂₃ H ₂₇ N ₃ O ₃	393.2	1.57 (98)	394.2	method 2c

Ex.308		C23H25N3O4	407.2	1.38 (97)	408.1	method 1a
Ex.309		C26H31N3O4	449.2	1.68 (98)	450.2	method 1a
Ex.310		C33H31N3O4	533.2	1.99 (93)	534.2	method 1a
Ex.311		C33H31N3O4	533.2	1.97 (95)	534.2	method 1a
Ex.312		C25H30N4O4	450.2	1.48 (98)	451.2	method 2c
Ex.313		C29H36N4O6	536.3	1.74 (91)	537.2	method 1a
Ex.314		C24H28N4O4	436.2	1.23 (99)	437.2	method 1a
Ex.315		C28H26FN3O4	487.2	1.83 (96)	488.2	method 1a
Ex.316		C27H26N4O4	470.2	1.51 (99)	471.2	method 2c
Ex.317		C23H26N4O4	422.2	1.37 (96)	423.2	method 1a
Ex.318		C27H27N5O4	485.2	1.33 (98)	486.2	method 1a
Ex.319		C25H29N3O6	467.2	1.58 (96)	468.2	method 1a
Ex.320		C29H36N4O6	536.3	1.79 (98)	537.2	method 1a

Ex.321		C25H28N4O6	480.2	0.99 (87)	481.2	method 2c
Ex.322		C22H25N3O5S	443.2	1.46 (97)	444.1	method 1a
Ex.323		C27H27N3O5S	505.2	1.82 (97)	506.1	method 1a
Ex.324		C28H28FN3O3	473.2	1.46 (98)	474.2	method 1a
Ex.325		C25H31N3O3	421.2	1.35 (98)	422.1	method 1a
Ex.326		C26H33N5O3	463.3	1.35 (95)	464.2	method 1a

Table 30c: Examples of Core 18 (Ex.305–Ex.326; continued on the following pages)

No	R ^B	IUPAC name
Ex.305		benzyl <i>N</i> -[(15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]carbamate
Ex.306	NH ₂	(15 <i>R</i> ,16 <i>aS</i>)-15-amino-10-methyl-10,11,15,16,16 <i>a</i> ,17-hexahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecine-9,12-dione
Ex.307	N(CH ₃) ₂	(15 <i>R</i> ,16 <i>aS</i>)-15-(dimethylamino)-10-methyl-10,11,15,16,16 <i>a</i> ,17-hexahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecine-9,12-dione

No	R ^B	IUPAC name
Ex.308		<i>N</i> -[(15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]acetamide
Ex.309		<i>N</i> -[(15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]-3-methylbutanamide
Ex.310		<i>N</i> -[(15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]-2-(2-naphthyl)acetamide
Ex.311		<i>N</i> -[(15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]-2-(1-naphthyl)acetamide
Ex.312		<i>N</i> -[(15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]-2-(dimethylamino)acetamide
Ex.313		<i>tert</i> -butyl <i>N</i> -(3-[(15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]amino-3-oxopropyl)carbamate
Ex.314		<i>N</i> -[(15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]-3-aminopropanamide
Ex.315		<i>N</i> -[(15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]-3-fluorobenzamide
Ex.316		<i>N</i> -[(15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]isonicotinamide
Ex.317		<i>N</i> -[(15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]- <i>N</i> '-methylurea

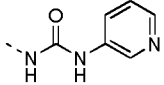
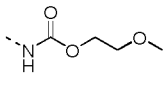
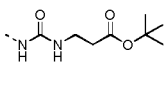
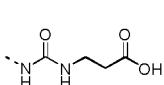
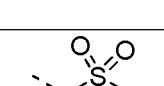
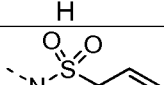
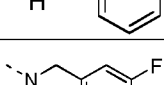
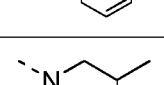
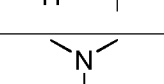
No	R ^B	IUPAC name
Ex.318		<i>N</i> -[(15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]- <i>N'</i> -(3-pyridinyl)urea
Ex.319		2-methoxyethyl <i>N</i> -[(15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]carbamate
Ex.320		<i>tert</i> -butyl 3-[[[[(15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]amino}carbonyl]amino]propanoate
Ex.321		3-[[[[(15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]amino}carbonyl]amino]propanoic acid
Ex.322		<i>N</i> -[(15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]methanesulfonamide
Ex.323		<i>N</i> -[(15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]benzenesulfonamide
Ex.324		(15 <i>R</i> ,16 <i>aS</i>)-15-[(3-fluorobenzyl)amino]-10-methyl-10,11,15,16,16 <i>a</i> ,17-hexahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecine-9,12-dione
Ex.325		(15 <i>R</i> ,16 <i>aS</i>)-15-(isobutylamino)-10-methyl-10,11,15,16,16 <i>a</i> ,17-hexahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecine-9,12-dione
Ex.326		<i>N''</i> -[(15 <i>R</i> ,16 <i>aS</i>)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16 <i>a</i> ,17-octahydro-14 <i>H</i> -dibenzo[<i>i,k</i>]pyrrolo[2,1- <i>c</i>][1,4,7]oxadiazacyclododecin-15-yl]- <i>N,N,N,N</i> -tetramethylguanidine

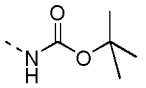
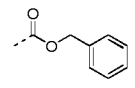
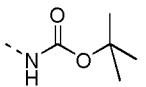
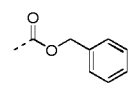
Table 31a: Examples of Core 19 (Ex.327-Ex.329)

No	R ^B	R ^D	Starting material	General Proced.	Reagent	Purification Method	Yield (isolated salt)
Ex.327-Ex.329: <i>cf. experimental description</i>							

Table 31b: Examples of Core 19 (Ex.327-Ex.329)

No	R ^B	R ^D	Formula	Monoisotopic Mass	Rt (purity at 220nm)	[M+H] ⁺ found	LC-MS-Method
Ex.327-Ex.329: <i>cf. experimental description</i>							

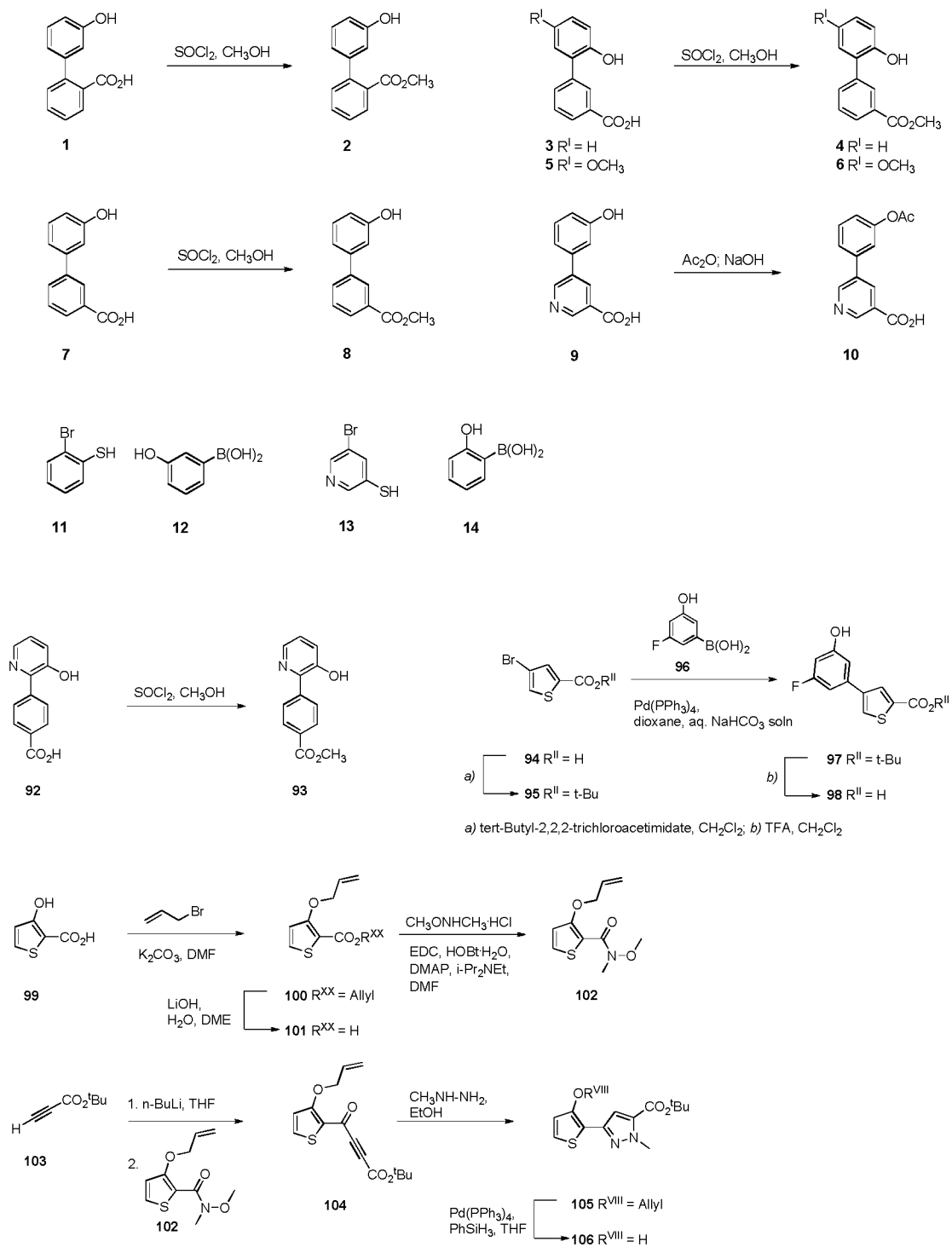
Table 31c: Examples of Core 19 (Ex.327-Ex.329)

No	R ^B	R ^D	IUPAC name
Ex.327			benzyl (16S,18S)-16-[(<i>tert</i> -butoxycarbonyl)amino]-7,13-dioxo-4-(trifluoromethyl)-5,20-dioxo-3,8,11,14-tetraazatetracyclo[19.3.1.0 ^{2,6} .0 ^{14,18}]pentacosa-1(25),2(6),3,21,23-pentaene-11-carboxylate
Ex.328		H	<i>tert</i> -butyl N-[(16S,18S)-7,13-dioxo-4-(trifluoromethyl)-5,20-dioxo-3,8,11,14-tetraazatetracyclo[19.3.1.0 ^{2,6} .0 ^{14,18}]pentacosa-1(25),2(6),3,21,23-pentaen-16-yl]carbamate
Ex.329	NH ₂		benzyl (16S,18S)-16-amino-7,13-dioxo-4-(trifluoromethyl)-5,20-dioxo-3,8,11,14-tetraazatetracyclo[19.3.1.0 ^{2,6} .0 ^{14,18}]pentacosa-1(25),2(6),3,21,23-pentaene-11-carboxylate

319

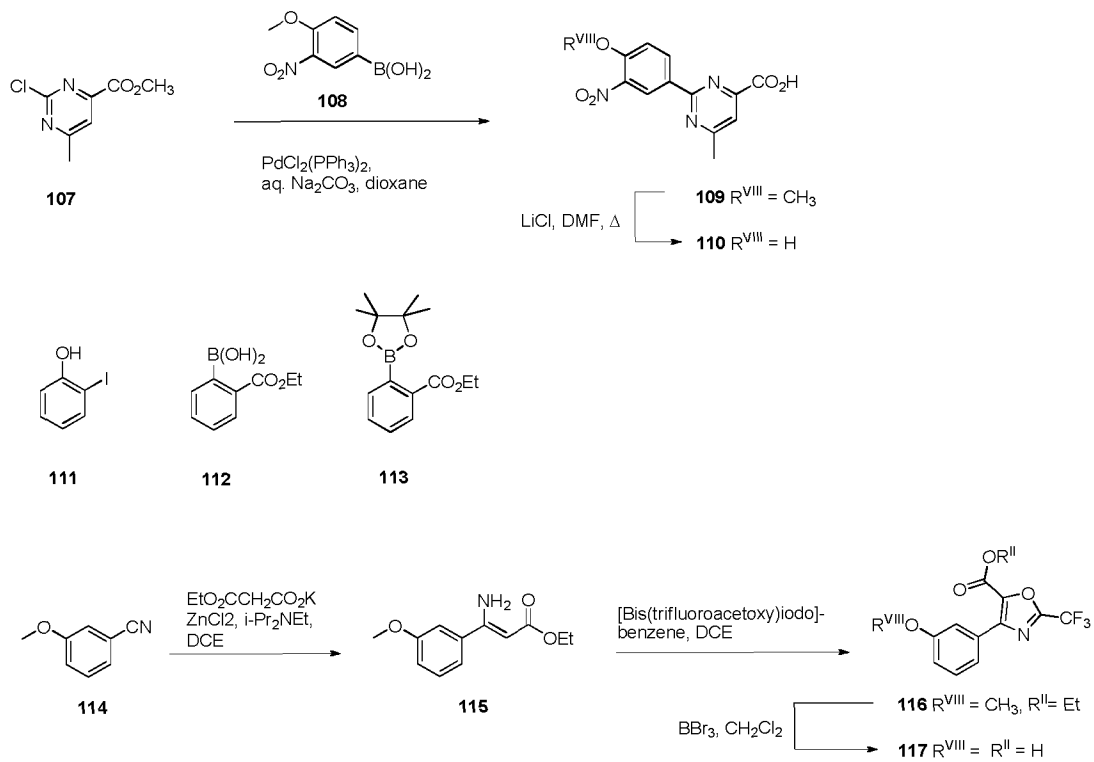
Building Blocks Type A

Scheme 5



320

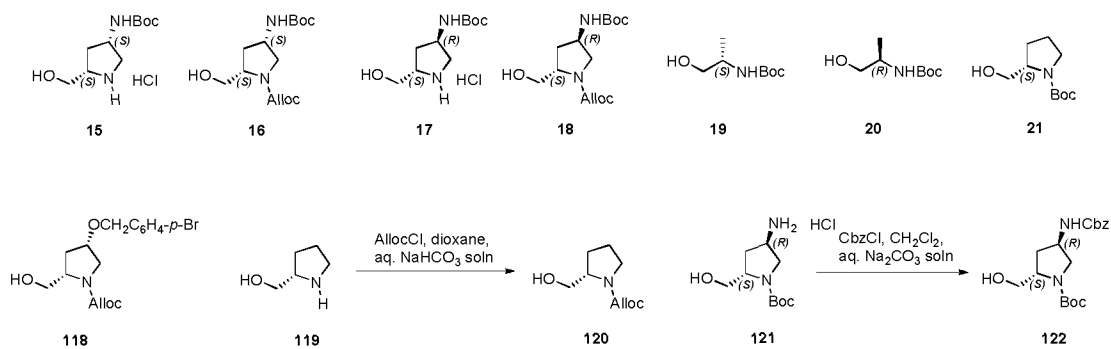
Scheme 5, cont.



5

Building Blocks Type B

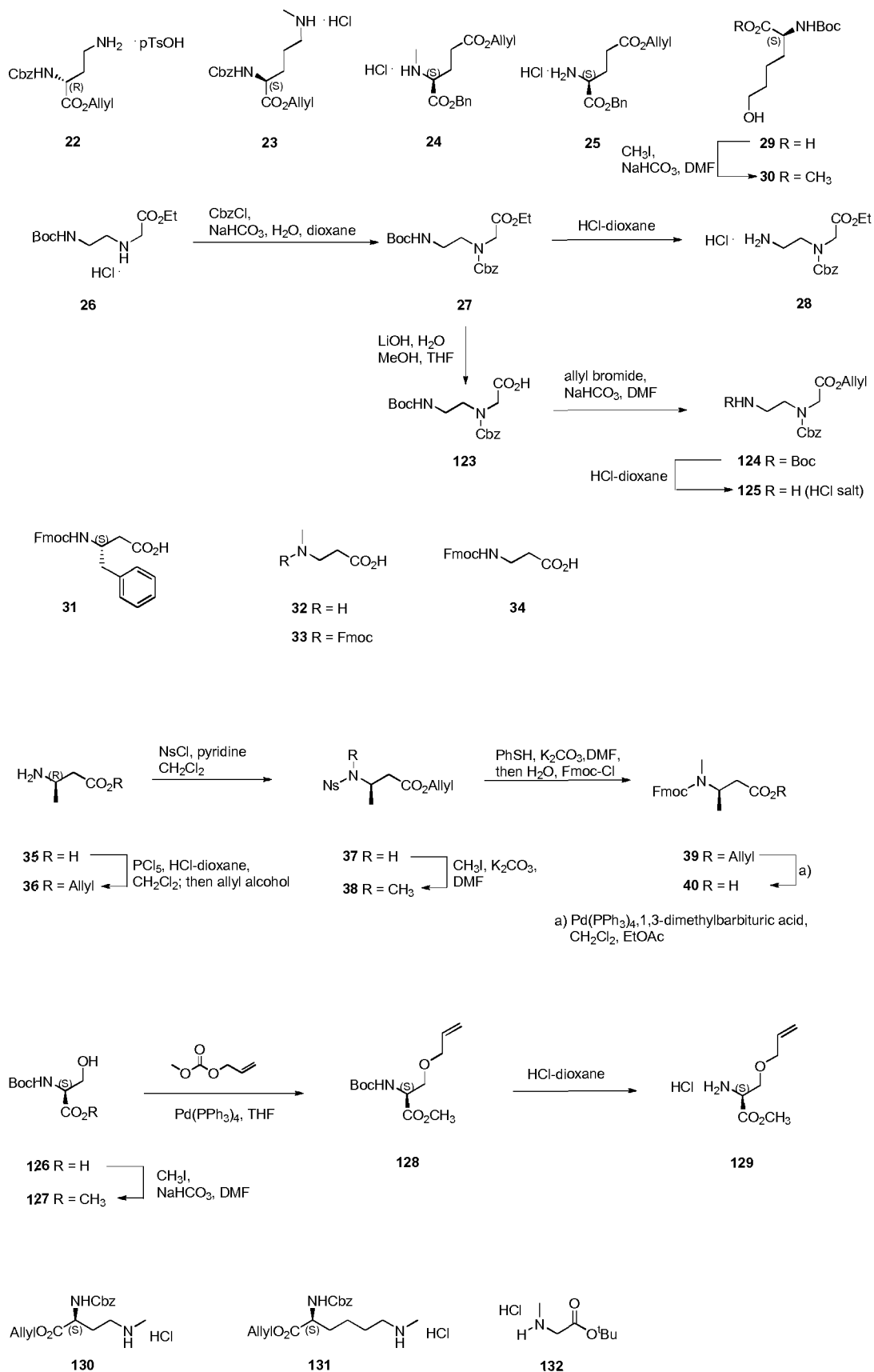
Scheme 6



321

Scheme 7

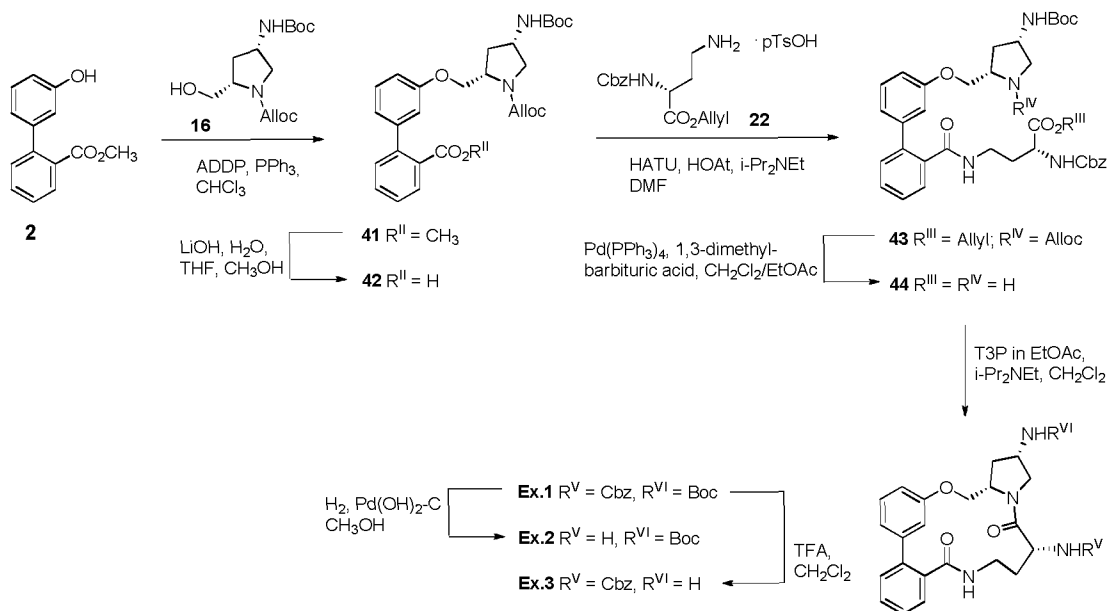
Building Blocks Type C



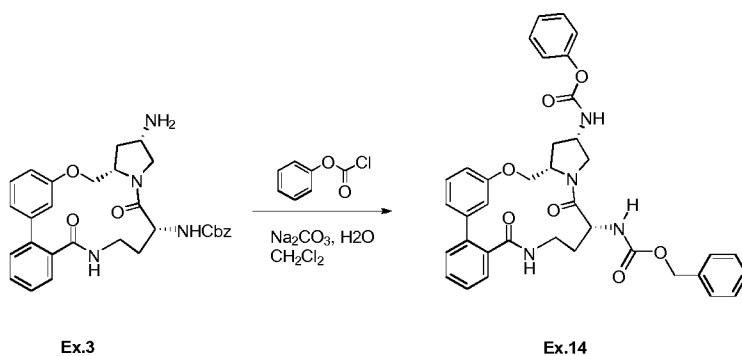
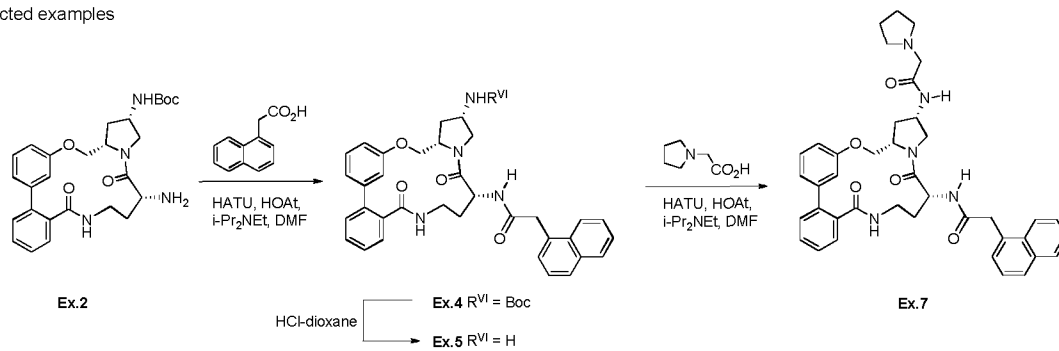
322

Core 01

Scheme 8

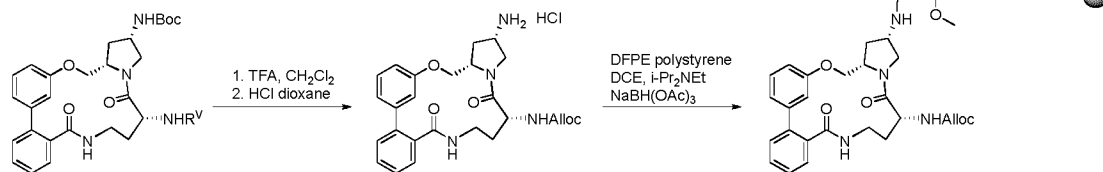


Selected examples



323

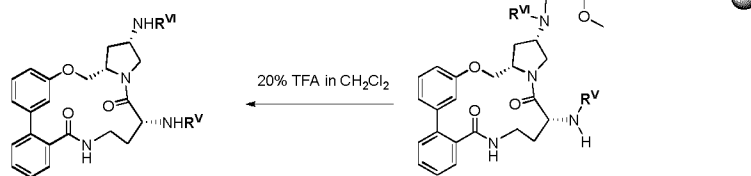
Scheme 8, cont.

**Core 01;
Derivatization on Solid Support**Ex.2 $R^V = H$ Ex.330 $R^V = Alloc$ AllocCl, dioxane, THF
aq, $NaHCO_3$

Ex.331

133

- a) $R^{II}CO_2H$, HATU
or $R^{III}NCO$ or $R^{III}NHCO_2Su$
 $i-Pr_2NEt$, CH_2Cl_2 , DMF
- b) $Pd(PPh_3)_4$, $PhSiH_3$, CH_2Cl_2
- c) $R^{IV}CO_2H$, PyBOP
or $R^{IV}NCO$ or $R^{IV}NHCO_2Su$
or $R^{IV}SO_2Cl$
 $i-Pr_2NEt$, CH_2Cl_2 , DMF


 $R^V = R^{IV}CO, R^{IV}NHCO, R^{IV}SO_2$
 $R^{VI} = R^{III}CO, R^{III}NHCO$

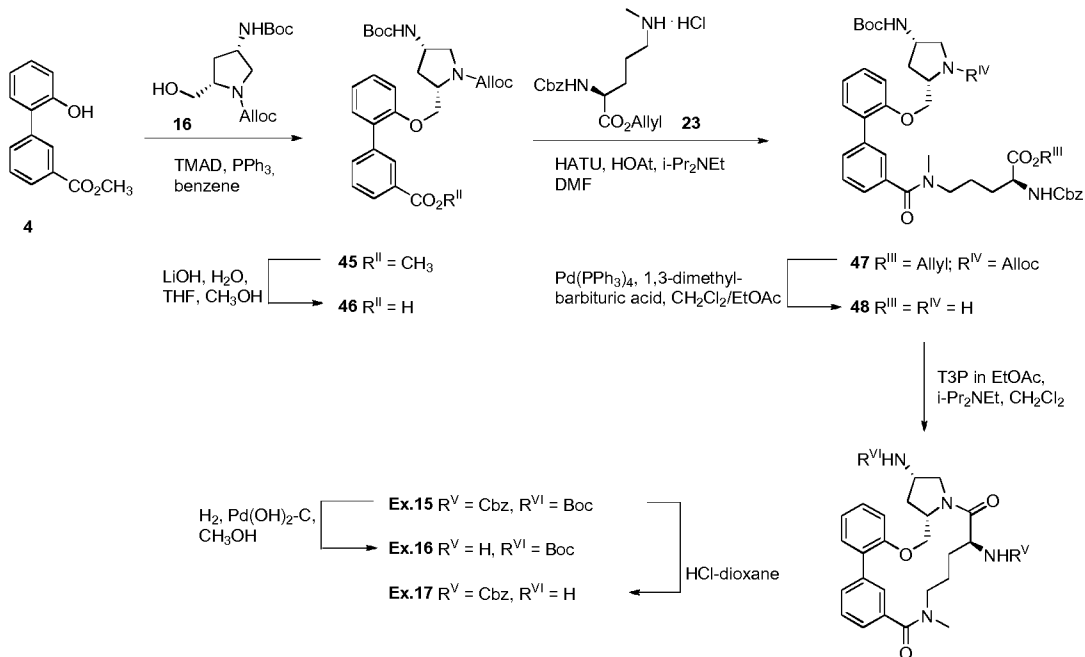
134

Ex.7, Ex.332- Ex.337
 $NHR^V = R^A$; $NHR^{VI} = R^B$;
 definitions of R^A and R^B cf. Tab. 13

5

Core 02

Scheme 9



LiOH, H_2O ,
THF, CH_3OH

45 $R^{II} = CH_3$
46 $R^{II} = H$

$Pd(PPh_3)_4$, 1,3-dimethyl-
barbituric acid, $CH_2Cl_2/EtOAc$

47 $R^{III} = Allyl$; $R^{IV} = Alloc$
48 $R^{III} = R^{IV} = H$

H_2 , $Pd(OH)_2-C$,
 CH_3OH

Ex.15 $R^V = Cbz$, $R^{VI} = Boc$
Ex.16 $R^V = H$, $R^{VI} = Boc$
Ex.17 $R^V = Cbz$, $R^{VI} = H$

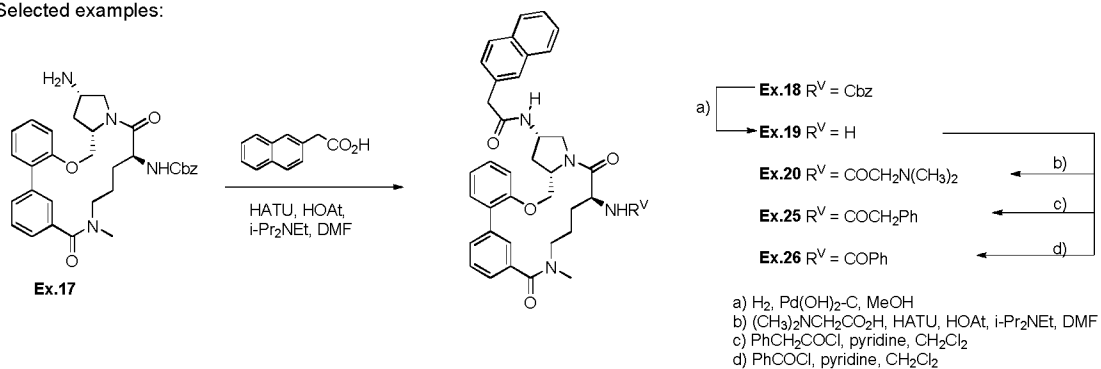
HCl-dioxane

T3P in EtOAc,
 $i-Pr_2NEt$, CH_2Cl_2

324

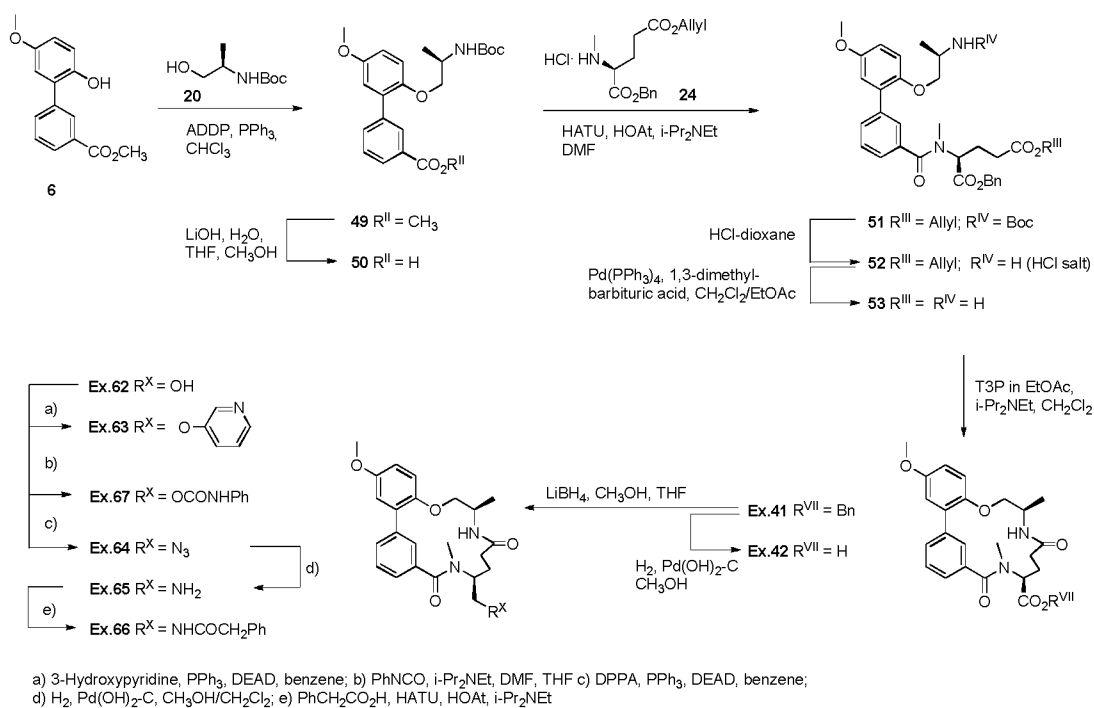
Scheme 9, cont.

Selected examples:

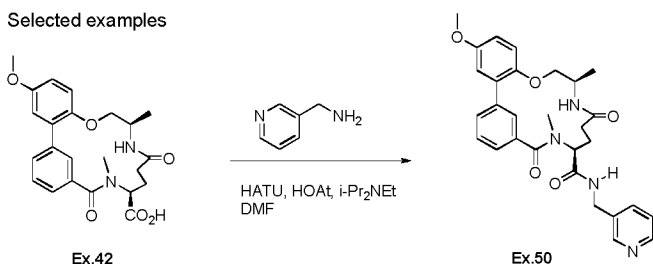


Core 03

Scheme 10



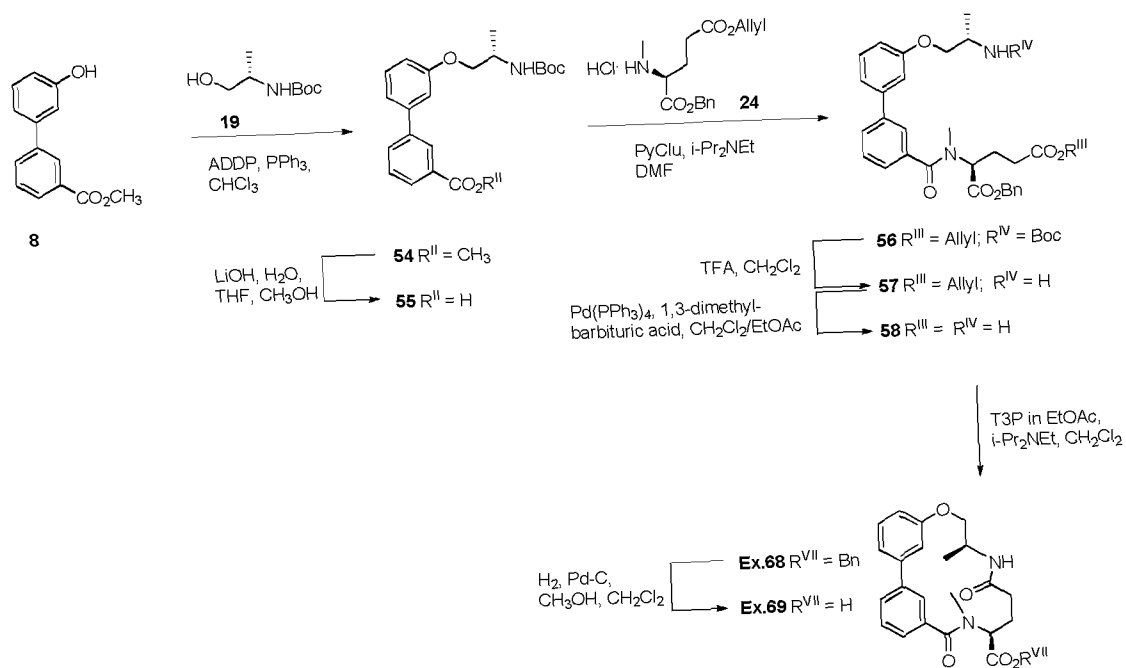
Selected examples



325

Scheme 11

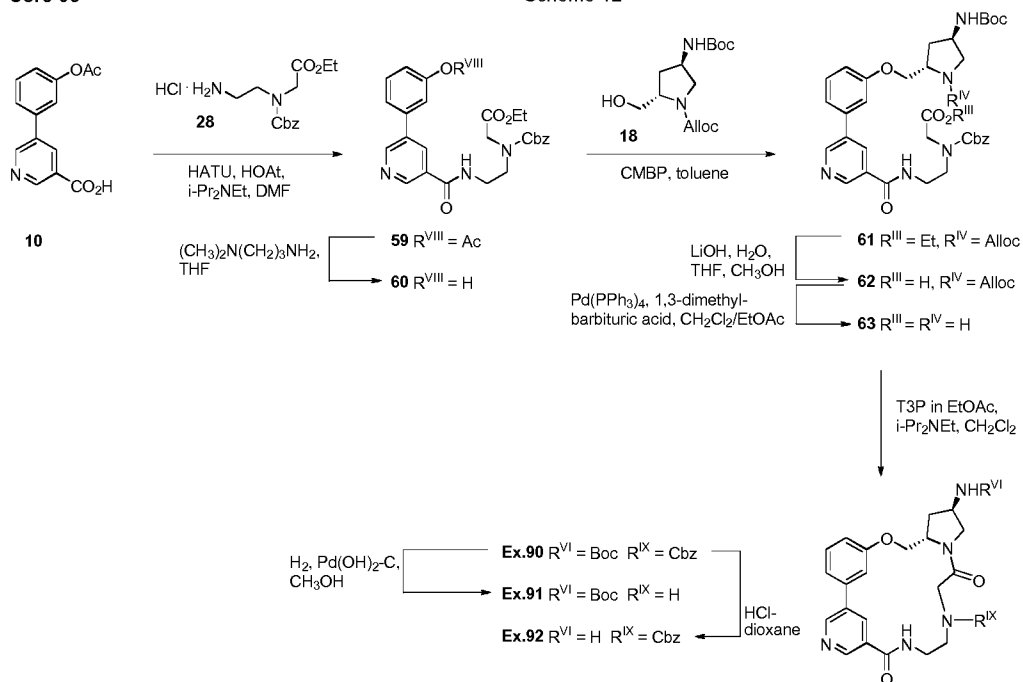
Core 04



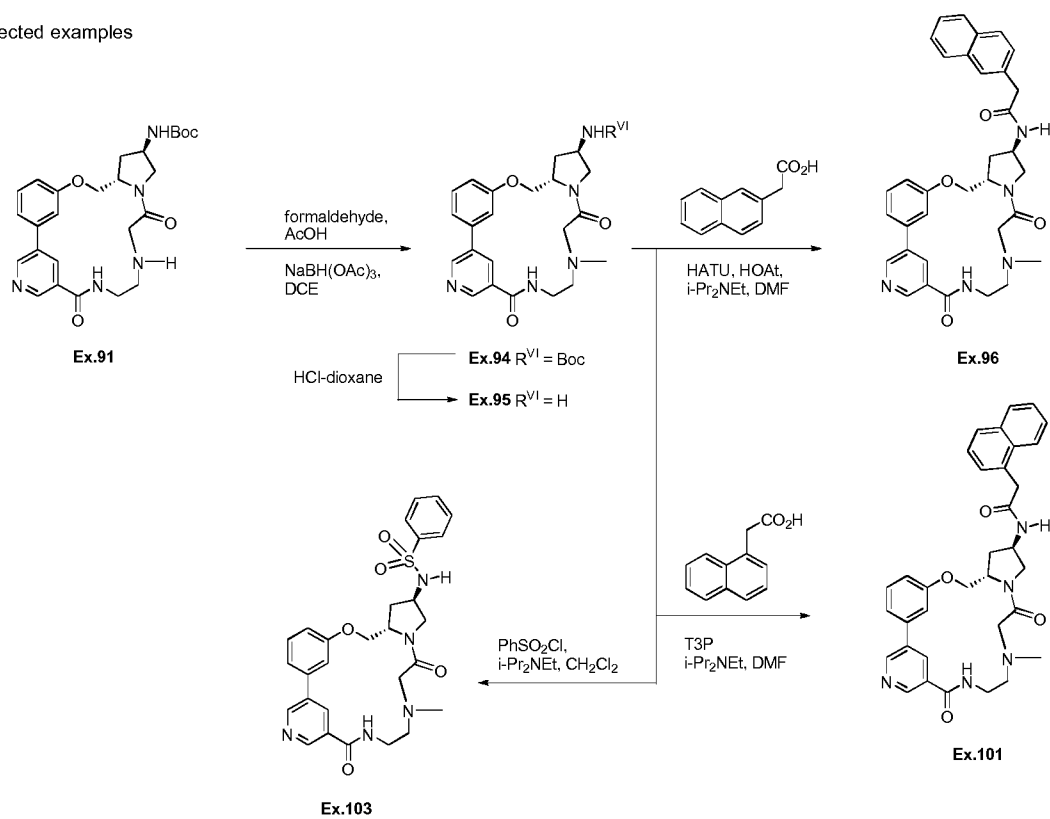
326

Core 05

Scheme 12

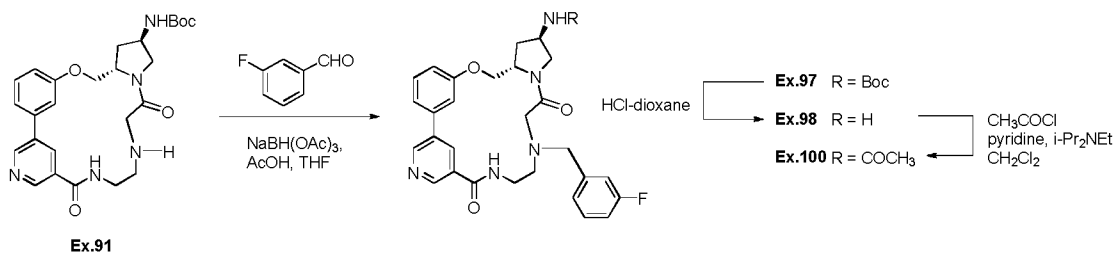


Selected examples



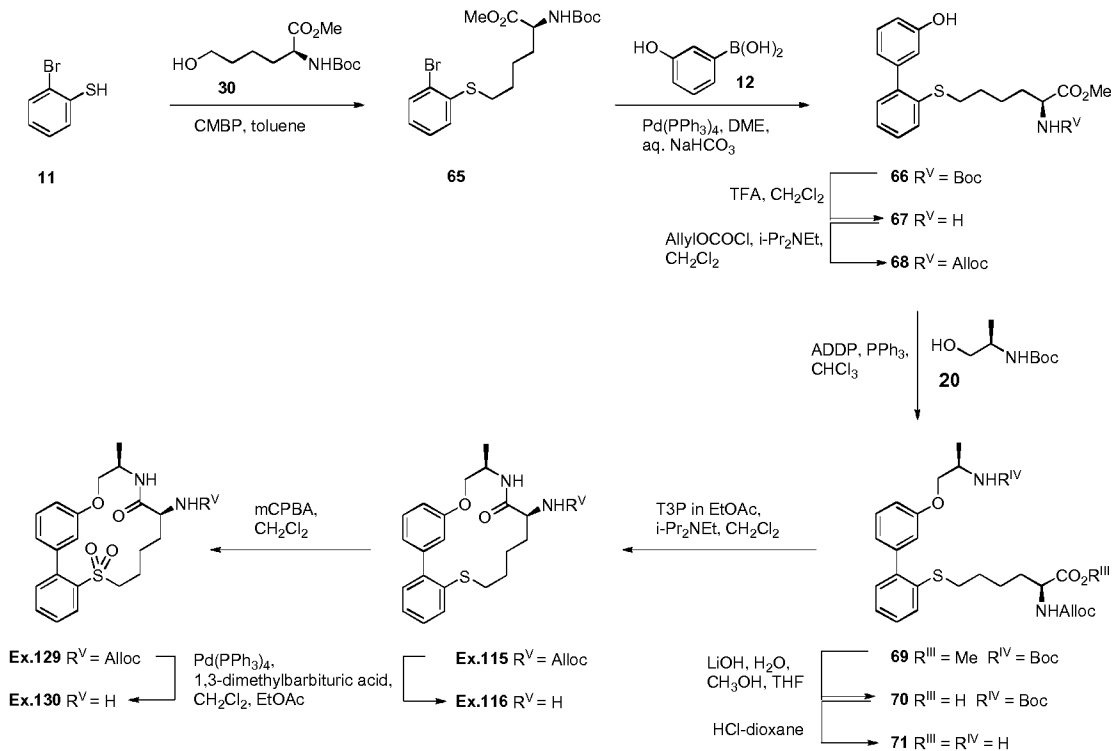
327

Scheme 12, cont.

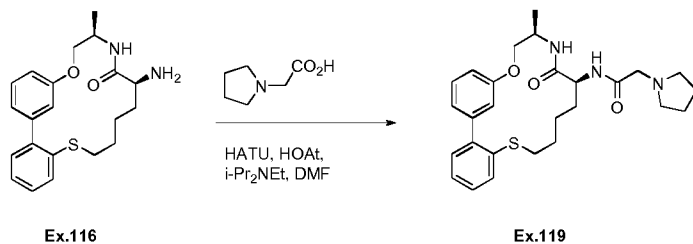


Core 06 / 07

Scheme 13



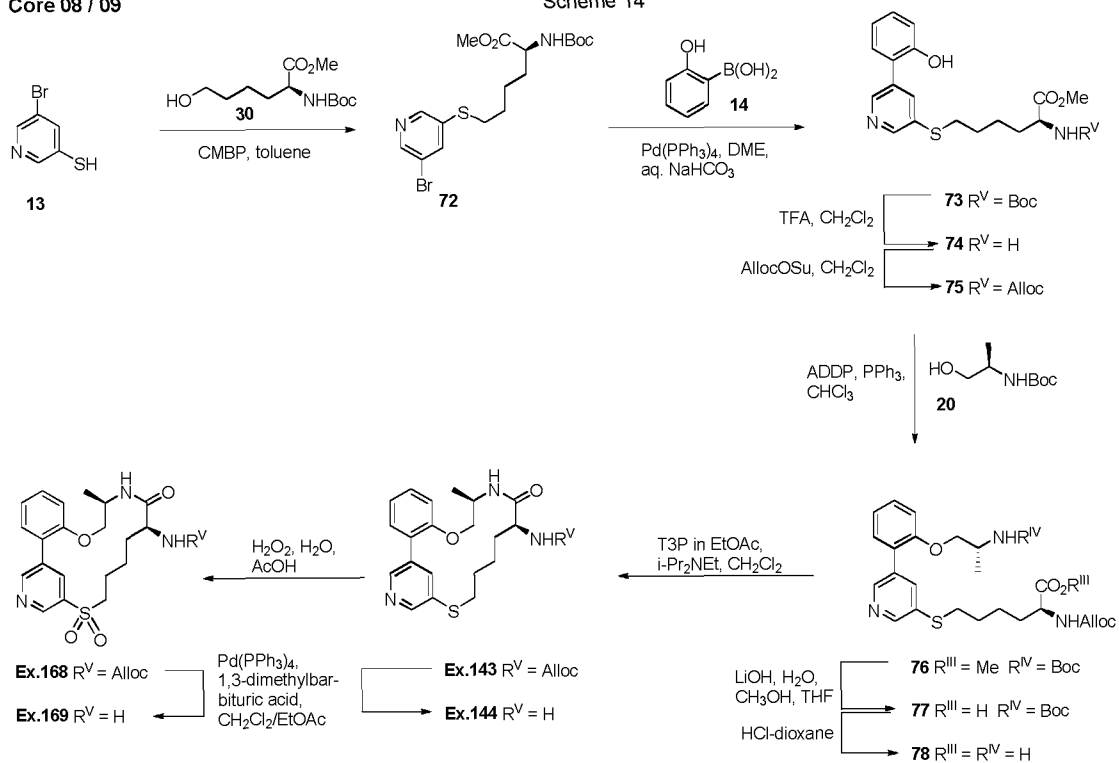
Selected examples



328

Core 08 / 09

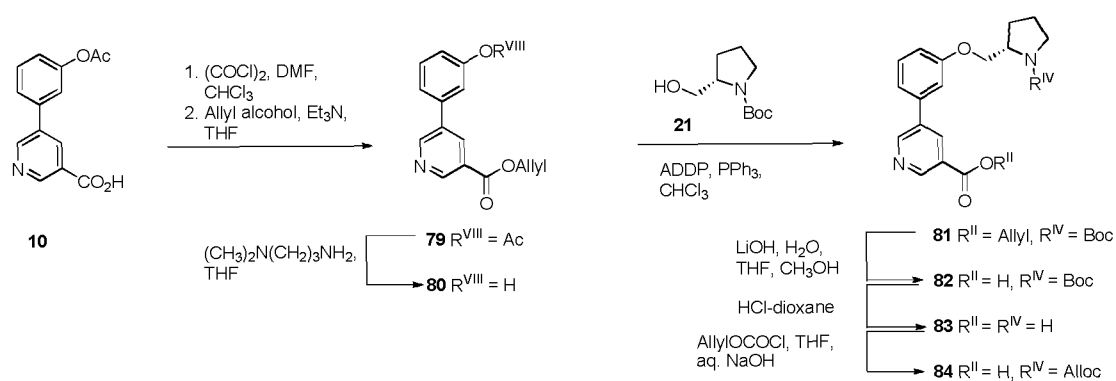
Scheme 14



5

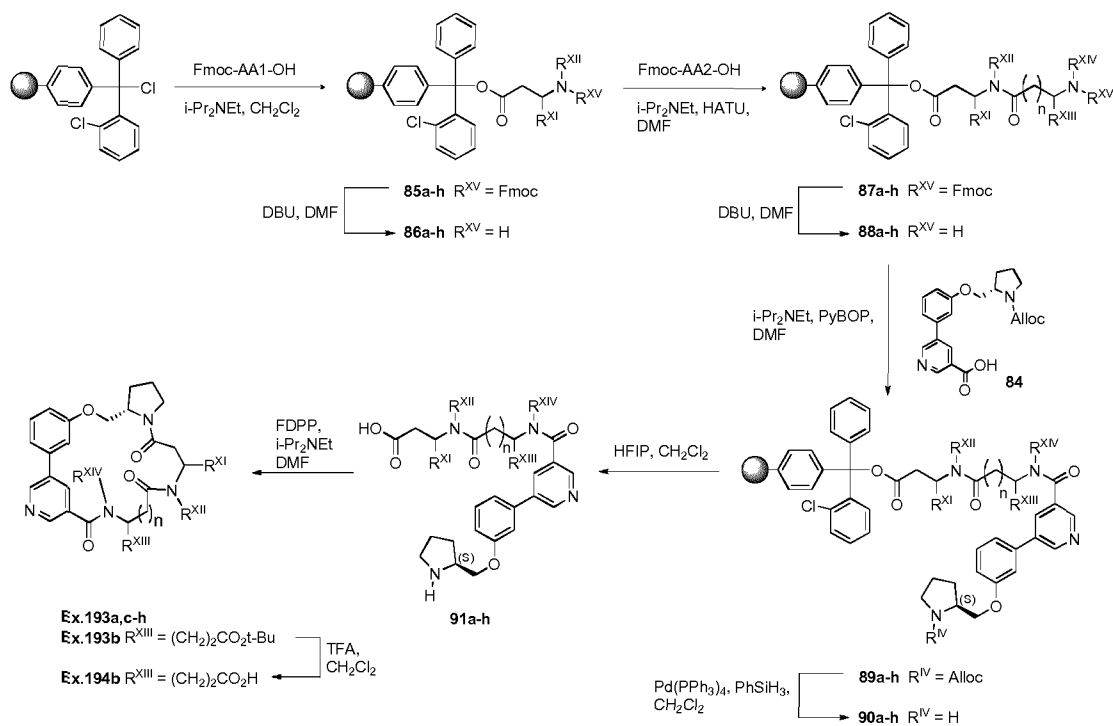
Core 10

Scheme 15



329

Scheme 15, cont.

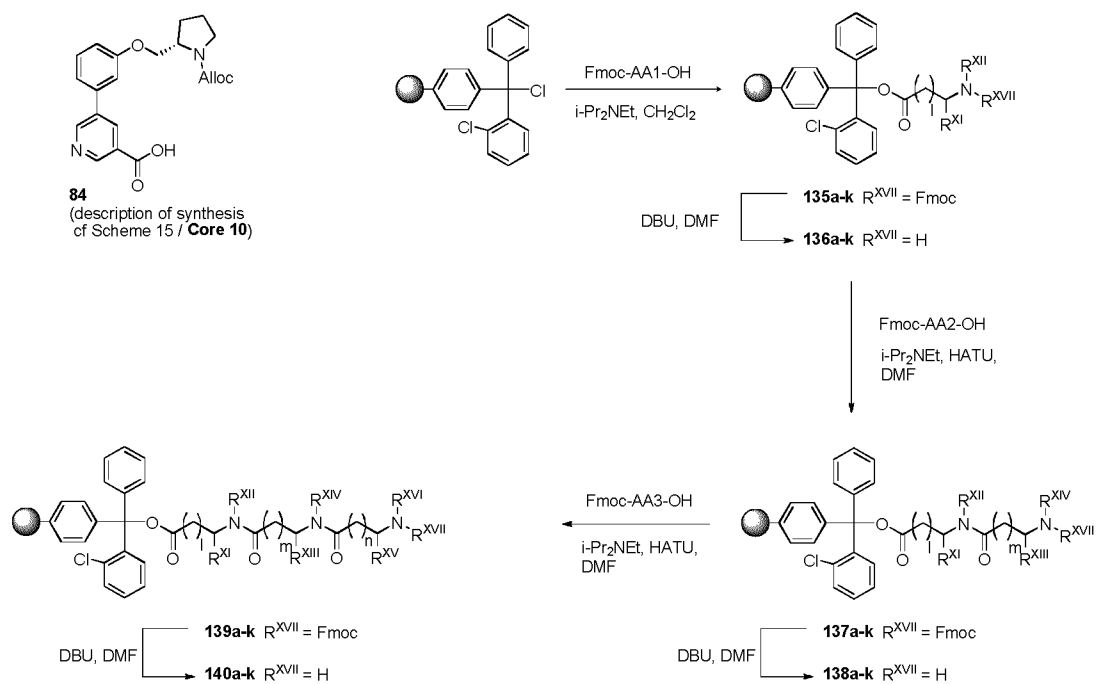
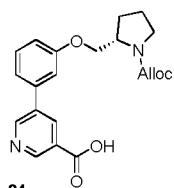


Cpd No	n	R ^{XI}	R ^{XII}	R ^{XIII}	R ^{XIV}	Fmoc-AA1-OH	Fmoc-AA2-OH
85a - Ex. 193a	0	CH ₂ Ph	H	CH ₃	CH ₃	Fmoc-β ³ -homoPhe-OH	Fmoc-NMeDAla-OH
85b - Ex. 193b	0	CH ₃	CH ₃	(CH ₂) ₂ CO ₂ tBu	CH ₃	Fmoc-NMe-β ³ -homoDAla-OH	Fmoc-NMeGlu(OtBu)-OH
85c - Ex. 193c	0	H	H	CH ₂ Ph	CH ₃	Fmoc-β-Ala-OH	Fmoc-NMePhe-OH
85d - Ex. 193d	0	H	H	CH ₂ Ph	H	Fmoc-β-Ala-OH	Fmoc-Phe-OH
85e - Ex. 193e	0	CH ₃	CH ₃	CH ₂ Ph	CH ₃	Fmoc-NMe-β ³ -homoDAla-OH	Fmoc-NMePhe-OH
85f - Ex. 193f	0	CH ₃	CH ₃	H	CH ₃	Fmoc-NMe-β ³ -homoDAla-OH	Fmoc-Sar-OH
85g - Ex. 193g	0	CH ₃	CH ₃	CH ₂ Ph	H	Fmoc-NMe-β ³ -homoDAla-OH	Fmoc-Phe-OH
85h - Ex. 193h	1	CH ₂ Ph	H	H	CH ₃	Fmoc-β ³ -homoPhe-OH	Fmoc-NMe-β-Ala-OH

330

Scheme 16

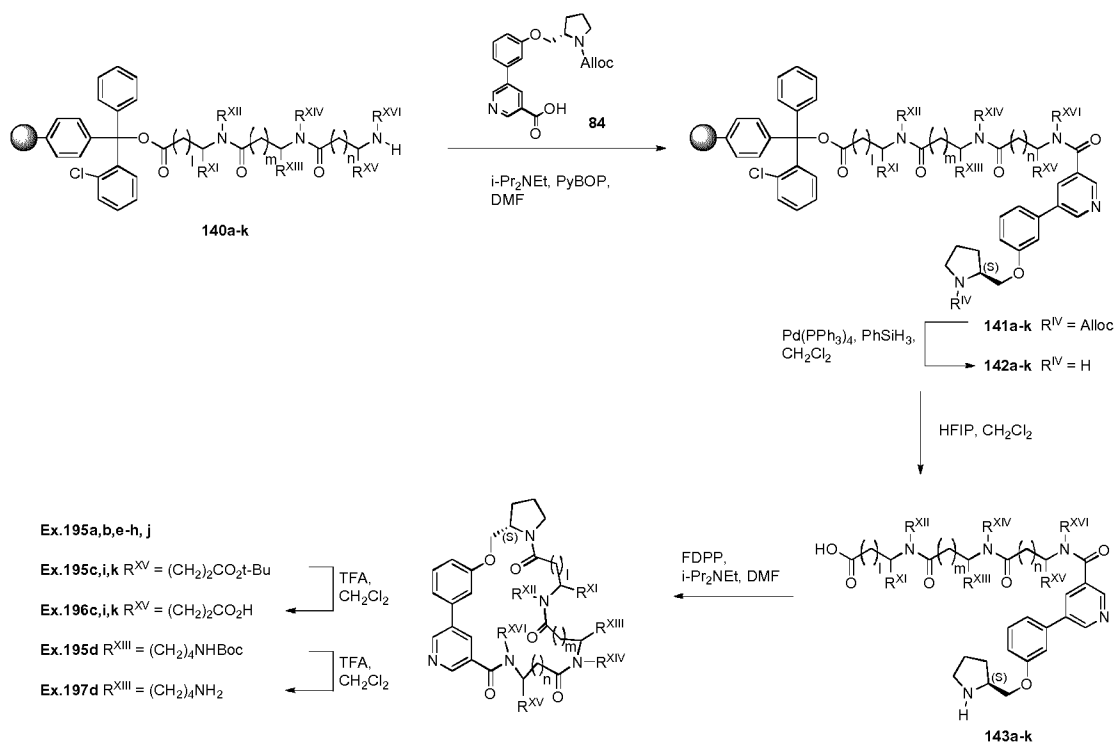
Core 11



331

Core 11

Scheme 16, cont



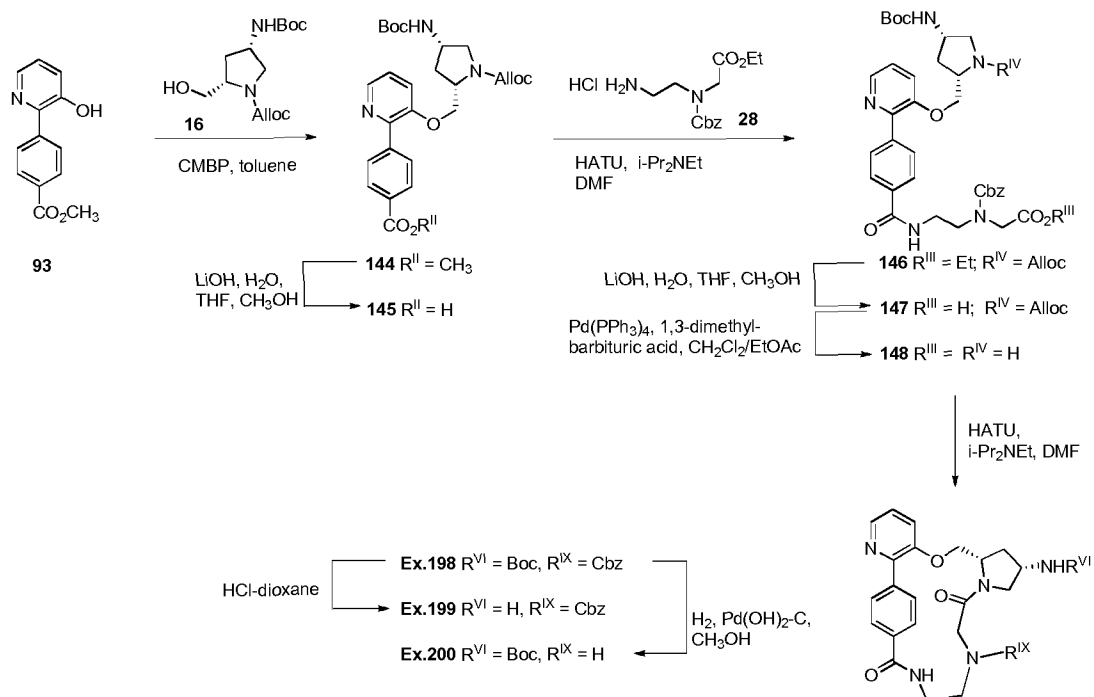
Cpd No	l	m	n	R ^{XI}	R ^{XII}	R ^{XIII}	R ^{XIV}	R ^{XV}	R ^{XVI}
135a – Ex. 195a	1	0	0	CH ₃	CH ₃	H	CH ₃	CH ₃	CH ₃
135b – Ex. 195b	1	0	0	CH ₃	CH ₃	H	H	CH ₃	H
135c – Ex. 195c	1	0	0	CH ₃	CH ₃	CH ₃	H	(CH ₂) ₂ CO ₂ tBu	CH ₃
135d – Ex. 195d	1	0	0	CH ₃	CH ₃	(CH ₂) ₄ NHBoc	H	CH ₃	H
135e – Ex. 195e	0	1	0	H	CH ₃	CH ₃	CH ₃	CH ₃	CH ₃
135f – Ex. 195f	0	0	1	H	CH ₃	CH ₃	CH ₃	CH ₃	CH ₃
135g – Ex. 195g	0	0	0	H	H	CH ₂ Ph	H	CH ₃	CH ₃
135h – Ex. 195h	0	0	0	H	CH ₃	CH ₂ Ph	H	CH ₃	H
135i – Ex. 195i	0	0	0	CH ₃	H	CH ₂ Ph	H	(CH ₂) ₂ CO ₂ tBu	CH ₃
135j – Ex. 195j	0	0	0	H	CH ₃	CH ₂ Ph	H	CH ₃	CH ₃
135k – Ex. 195k	0	0	0	CH ₃	H	CH ₂ Ph	H	(CH ₂) ₂ CO ₂ tBu	CH ₃

Cpd No	Fmoc-AA1-OH	Fmoc-AA2-OH	Fmoc-AA3-OH
135a – Ex. 195a	Fmoc-NMe-β ³ -homoDAla-OH	Fmoc-Sar-OH	Fmoc-NMeAla-OH
135b – Ex. 195b	Fmoc-NMe-β ³ -homoDAla-OH	Fmoc-Gly-OH	Fmoc-Ala-OH
135c – Ex. 195c	Fmoc-NMe-β ³ -homoDAla-OH	Fmoc-Ala-OH	Fmoc-NMeGlu(OtBu)-OH
135d – Ex. 195d	Fmoc-NMe-β ³ -homoDAla-OH	Fmoc-Lys(Boc)-OH	Fmoc-DAla-OH
135e – Ex. 195e	Fmoc-Sar-OH	Fmoc-NMe-β ³ -homoDAla-OH	Fmoc-NMeAla-OH
135f – Ex. 195f	Fmoc-Sar-OH	Fmoc-NMeAla-OH	Fmoc-NMe-β ³ -homoDAla-OH
135g – Ex. 195g	Fmoc-Gly-OH	Fmoc-Phe-OH	Fmoc-NMeDAla-OH
135h – Ex. 195h	Fmoc-Sar-OH	Fmoc-Phe-OH	Fmoc-DAla-OH
135i – Ex. 195i	Fmoc-Ala-OH	Fmoc-DPhe-OH	Fmoc-NMeGlu(OtBu)-OH
135j – Ex. 195j	Fmoc-Sar-OH	Fmoc-Phe-OH	Fmoc-NMeDAla-OH
135k – Ex. 195k	Fmoc-DAla-OH	Fmoc-Phe-OH	Fmoc-NMeGlu(OtBu)-OH

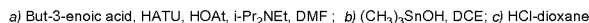
332

Scheme 17

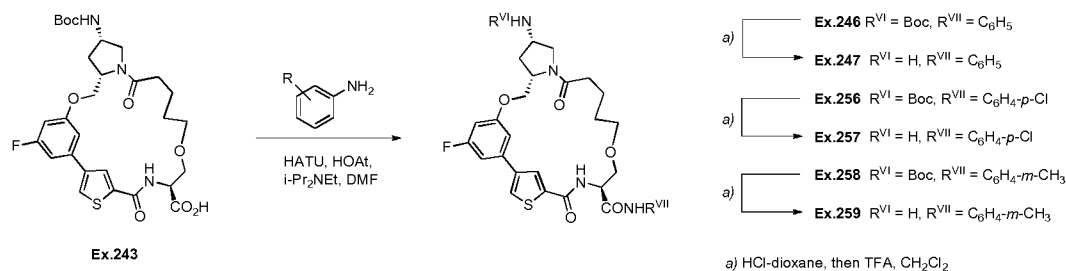
Core 12



Cores 13 - 15



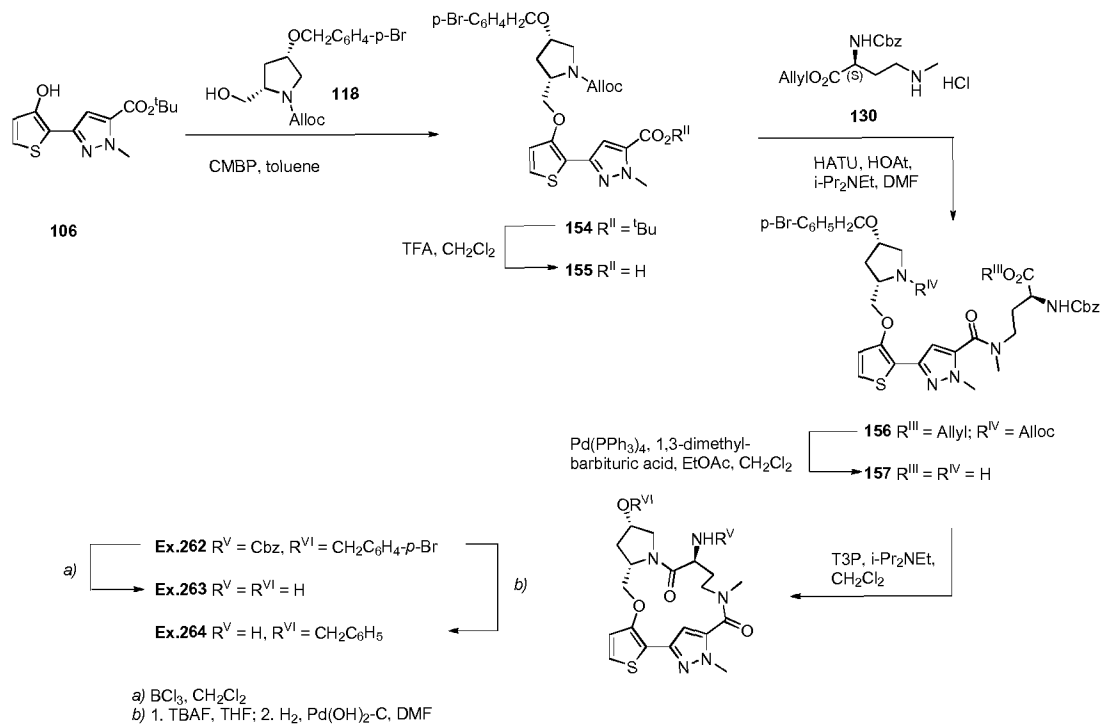
Selected examples:



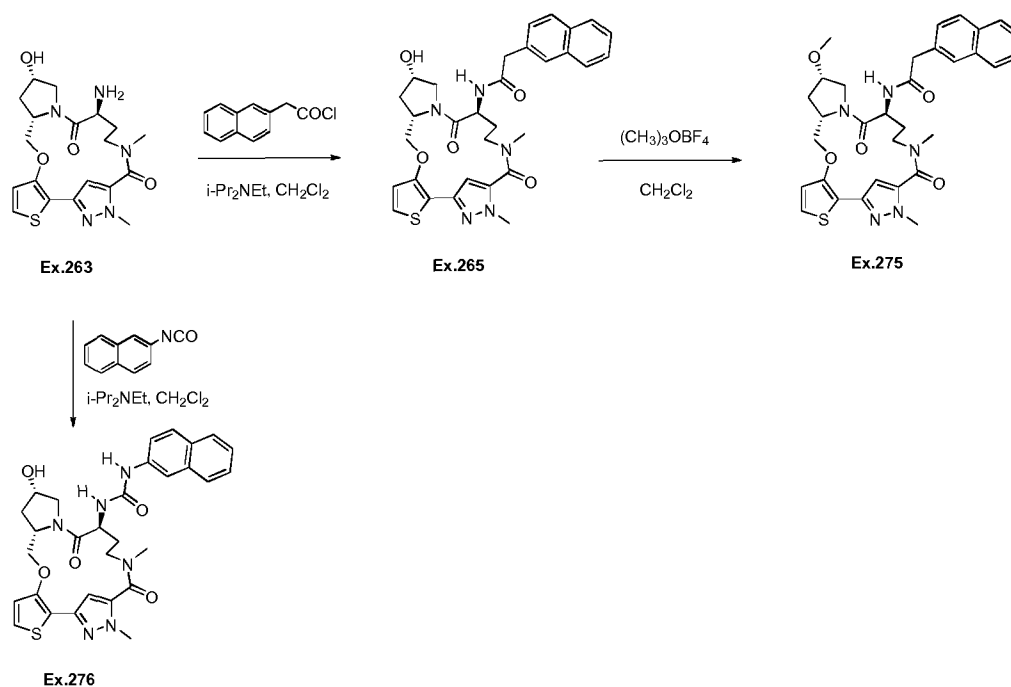
334

Scheme 19

Core 16



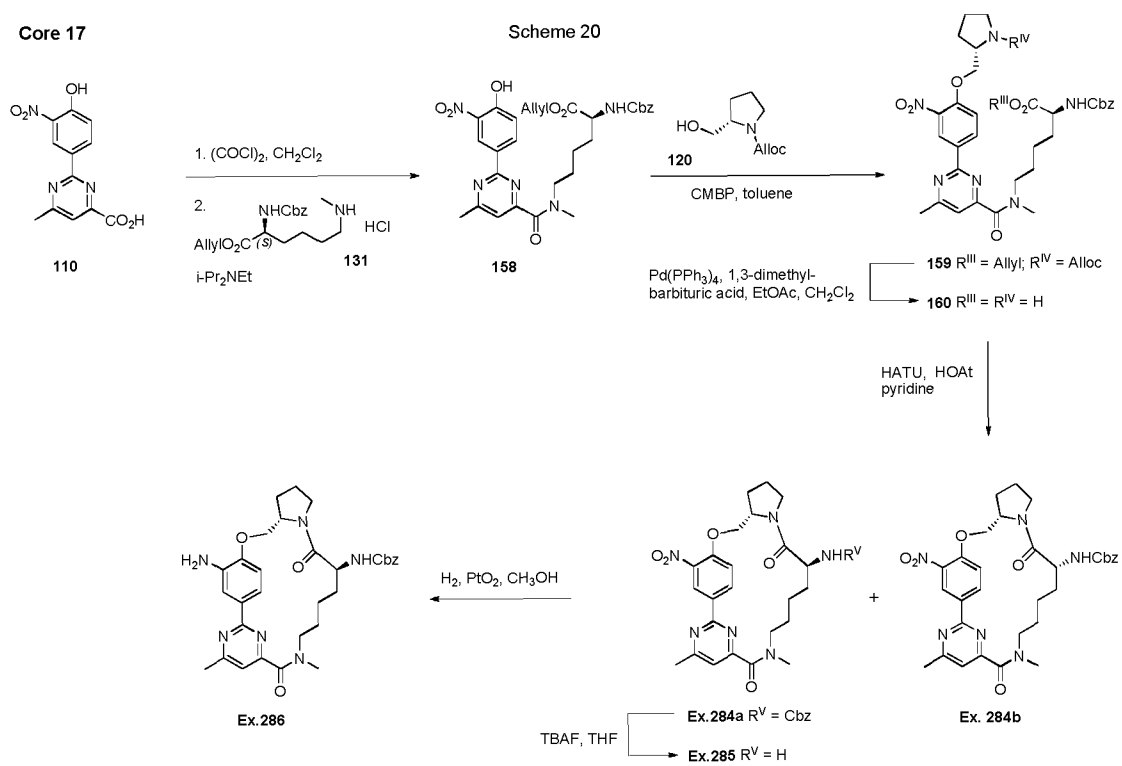
Selected examples



335

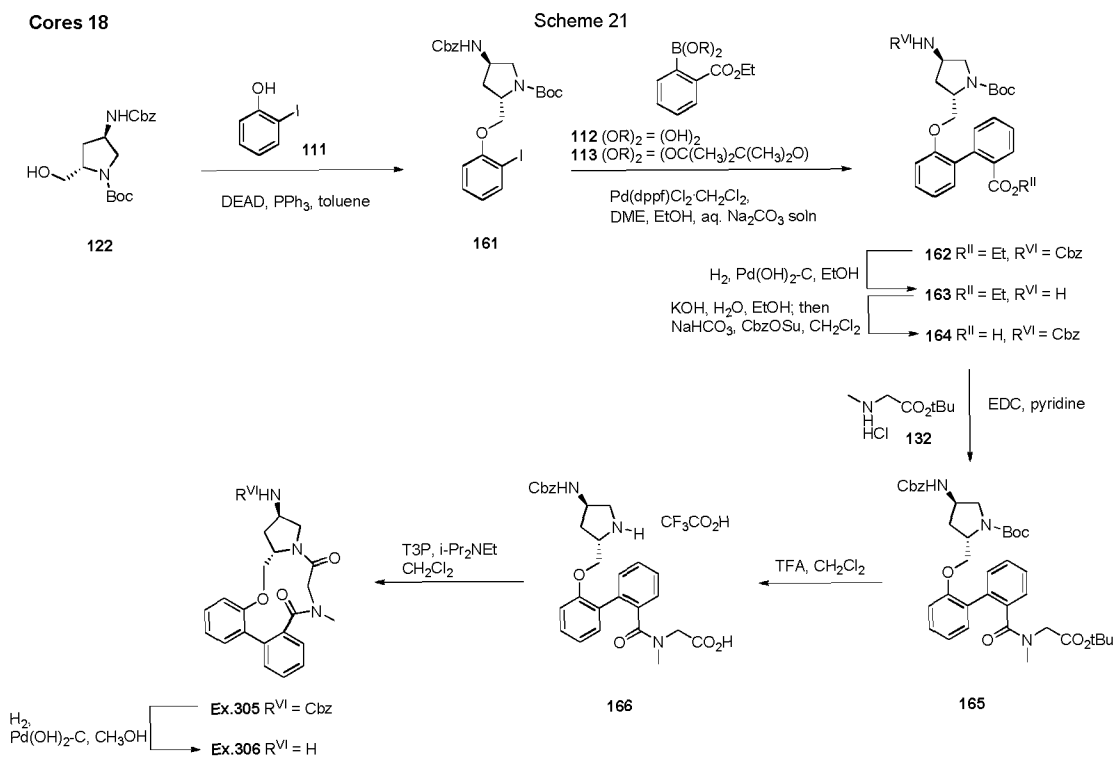
Core 17

Scheme 20



Cores 18

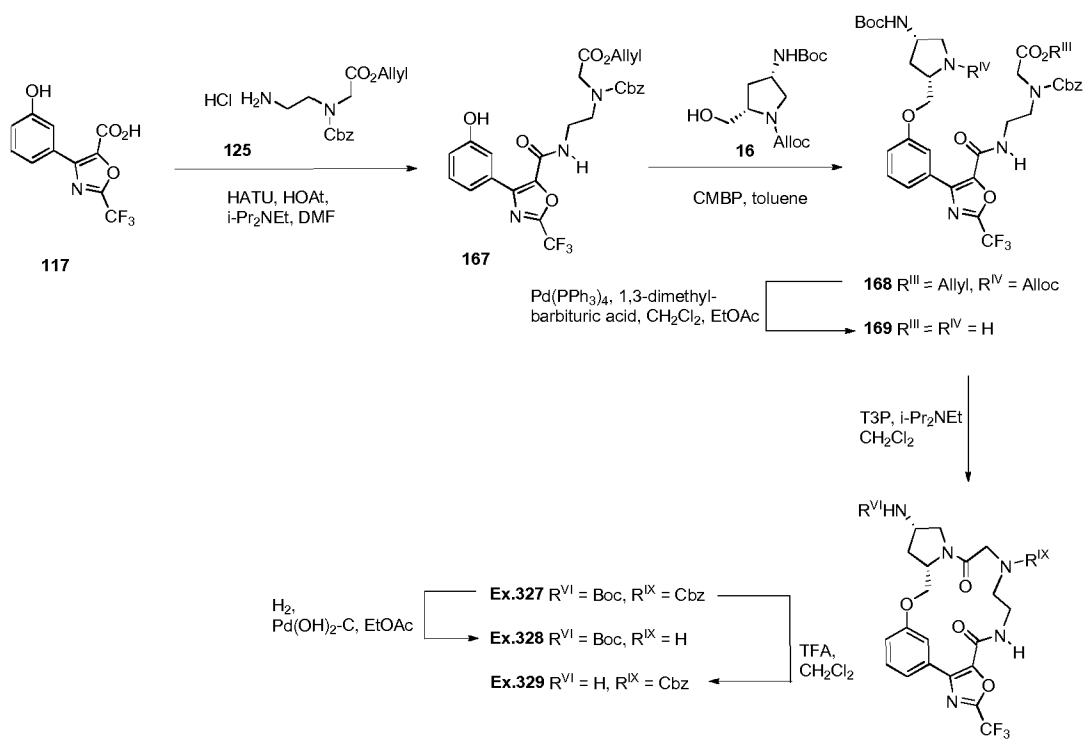
Scheme 21



Cores 19

336

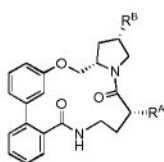
Scheme 22



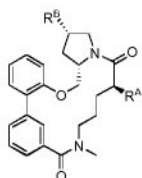
5

10

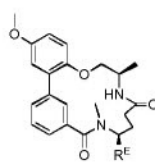
15



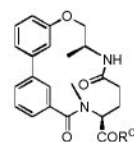
Core 01
Ex.1 - Ex.#14
and Ex.330 - Ex.340
definition of R-groups
cf. Table 13



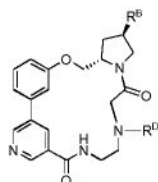
Core 02
Ex.15 - Ex.40
definition of R-groups
cf. Table 14



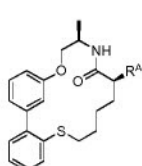
Core 03
Ex.41 - Ex.67
definition of R-groups
cf. Table 15



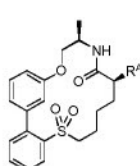
Core 04
Ex.68 - Ex.89
definition of R-groups
cf. Table 16



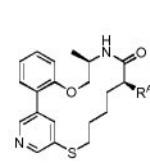
Core 05
Ex.90 - Ex.114
and Ex.341 - Ex.358
definition of R-groups
cf. Table 17



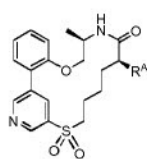
Core 06
Ex.115 - Ex.128
definition of R-groups
cf. Table 18



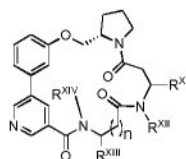
Core 07
Ex.129 - Ex.142
definition of R-groups
cf. Table 19



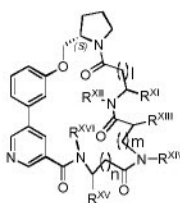
Core 08
Ex.143 - Ex.167
definition of R-groups
cf. Table 20



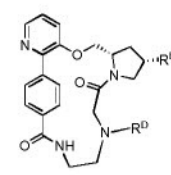
Core 09
Ex.168 - Ex.192
definition of R-groups
cf. Table 21



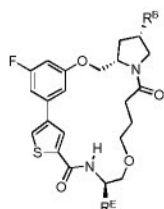
Core 10
Ex.193a, c-h; Ex.194b
definition of R-groups
cf. Table 22 and Scheme 15



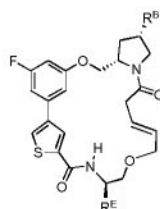
Core 11
Ex.195a,b,e-h j,
Ex.196c,i,k and Ex.197d
definition of R-groups
cf. Table 23 and Scheme 16



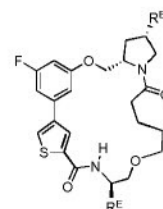
Core 12
Ex.198 - Ex.219
definition of R-groups
cf. Table 24



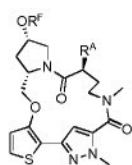
Core 13
Ex.221 - Ex.226
definition of R-groups
cf. Table 25



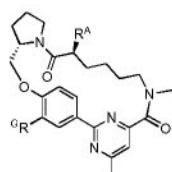
Core 14
Ex.227 - Ex.241
definition of R-groups
cf. Table 26



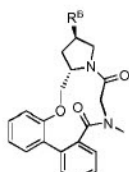
Core 15
Ex.242 - Ex.261
definition of R-groups
cf. Table 27



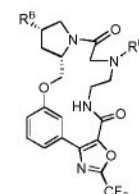
Core 16
Ex.262 - Ex.283
definition of R-groups
cf. Table 28



Core 17
Ex.284a - Ex.304
definition of R-groups
cf. Table 29



Core 18
Ex.305 - Ex.326
definition of R-groups
cf. Table 30



Core 19
Ex.327 - Ex.329
definition of R-groups
cf. Table 31

Biological and pharmacological methods

1. Ca^{2+} flux assays for the GPCRs oxytocin receptor (OT receptor), thyrotropin-releasing hormone receptor (TRH receptor) and bombesin receptor subtype 3 (BB3 receptor)

Assays were performed on a FLIPR^{TETRA} fluorometric imaging plate reader (Molecular Devices) with ScreenWorks Version 2 (Molecular Devices) as device operating and data analysis software.

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 each ligand's specifications. All handling of ligands were done to ensure proper control throughout the experiments.

Example compounds were weighed on a Microbalance (Mettler MX5) and dissolved in 100% DMSO to a final concentration of 2.5 mM and subsequently diluted into the assay buffer.

The 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 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, and 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.

5 Antagonist assay:

After completion of the first single addition assay run, assay plate was removed from the FLIPR Tetra and placed at 25°C for 7 minutes before antagonist assay.

Using the EC₈₀ values determined during the agonist assay, all pre-incubated sample compound and reference antagonist (if applicable) wells were stimulated at the EC₈₀ of the reference agonist. As reference ligands for these assays their obvious natural ligands oxytocin (OT), thyrotropin-releasing hormone (TRH) and bombesin (6-14) [BN(6-14)] were used.

After the addition of the reference agonist fluorescence was monitored for 180 sec using FLIPR Tetra.

15 Data analysis and results:

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.

The results of the GPCR assays are summarized in Table 32.3 to Table 32.5.

20

2. Enzyme assays for the peptidase endothelin converting enzyme-1 (ECE-1) and for the cysteine protease cathepsin S (CatS)

The assays were performed according to provider's (Ricerca Biosciences, LLC) protocols which in turn are based on literature procedures (for ECE-1 cf.: O. Valdenaire et al., *Eur. J. Biochem.* **1999**, 264, 341-349; F. D. Russell, A. P. Davenport, *Circ. Res.* **1999**, 84, 891-896; and for CatS: G P Shi et al., *J. Biol. Chem.* **1992**, 267, 7258-62; D Brömme et al., *J. Biol. Chem.* **1993** 268, 4832-4838.).

Procedures:

30 i) ECE-1 assay: Human recombinant ECE-1 expressed in murine myeloma cells NS0 is used. Test compound and/or vehicle is preincubated with 20 ng/ml enzyme in modified MES buffer pH 6.0 for 15 minutes at 25°C. The reaction is initiated by addition of 10 mM Mca-Arg-Pro-Pro-Gly-Phe-Ser-Ala-Phe-Lys(Dnp) for another 60 minutes' incubation period. Determination of the amount of Mca-Arg-Pro-Pro-Gly-Phe-Ser-Ala formed is read spectrophotometrically at 320 nm/405 nm. Compounds
35 are screened at 10 mM.

Reference Compound: Phosphoramidon (IC_{50} 0.0049 μ M)

- ii) CatS assay: Human recombinant cathepsin S expressed in a murine myeloma NS0 cells is used. Test compound and/or vehicle is preincubated with 0.1 μ g/ml enzyme in modified acetate buffer pH 4.5 for 15 minutes at 25°C. The reaction is initiated by addition of 10 mM Z-Leu-Arg-AMC for another 30 minutes' incubation period. Determination of the amount of AMC formed is read spectrofluorimetrically at 360 nm/465 nm. Compounds are screened at 10 mM.

Reference Compound: E-64 (IC_{50} 0.0014 μ M)

Data Analysis:

- 10 IC_{50} values were determined by a non-linear, least squares regression analysis using MathIQ™ (ID Business Solutions Ltd., UK). Inhibition constants K were calculated according to the equation of Cheng and Prusoff (Y. Cheng, W. H. Prusoff, *Biochem. Pharmacol.* **1973**, 22, 3099-3108) using the observed IC_{50} of the tested compound, the concentration of radioligand employed in the assay, and the historical values for the K_D of the ligand. The Hill coefficient (nH), defining the slope of the competitive binding curve, was calculated using MathIQ™.

The results of the assays are summarized in Table 32.1 and Table 32.2.

20 3. Human LTB₄ receptor cell-based assay

- CHO mito-i-Photina® cells (Axxam SpA) stably expressing the human leukotriene B₄ receptor (LTB₄R) were used for monitoring activation of the target LTB₄R, a GPCR (G α q), by measuring the flash luminescence of Ca²⁺ sensitive photoprotein as reporter system with FLIPR^{TETRA} screening instrumentation (Molecular Devices) upgraded with an ICCD Camera (MDC). For data quality check and data analysis a Genedata Screener 10.0.3 was used, and for curve fitting of reference agonist and antagonist GraphPad Prism Software.

- The reference agonist LTB₄ and antagonist U-75302 were purchased from reputable commercial vendors and prepared according to each ligand's specifications. All handling of ligands were done to ensure proper control throughout the experiments. The steps of the implemented workflow and data analysis are mainly as follows:

Assay plate seeding:

- mito-i-Photina cells are seeded (10000 c/w in 384 MTP; in complete medium 25 μ L/well) for 24 hours, removed from the incubator, equilibrated at room temperature for 1h, freed from the growth medium, loaded with 30 μ L/well of Tyrode's buffer containing 10 μ M coelenterazine, and incubated for 3 hours at rt.

Agonist/antagonist assay:

All compounds were tested at 10 μ M with triplicate data points.

After incubation, the volume in all the wells is flattened to 20 μ L by aspiration with CyBi®-Vario pipettor. The First Injection (10 μ L of test compounds or reference antagonist U-75302 in Tyrode's buffer + DMSO 0.5%) is performed by the FLIPR^{TETRA} and the kinetic response is monitored over a period of 120 seconds. Incubation at rt for 10 min. is followed by the Second Injection (15 μ L of LTB₄ at EC₈₀ in Tyrode's buffer) and monitoring of the kinetic response over a period of 120 seconds.

Data analysis and results:

10 The possible kinetic response is divided into two distinct phases: Monitoring the kinetic response after the First Injection is indicated as Compound Addition (CA) and measures the agonistic activity of compounds; monitoring the kinetic response after the Second Injection is indicated as Target Activation (TA) and measures the antagonistic activity of a compound.

15 The activity determination (IC₅₀ determination) experiment is performed using LTB₄ as agonist (100 nM corresponding to EC₈₀). Selected compound are tested in 8 doses intraplate dose response with quadruplicate data points.

The results of the LTB₄R assays are summarized in Table 32.6.

20

4. Antimicrobial Assays

The antimicrobial activities of the compounds were determined in 96-well plates (Greiner, polystyrene) by the standard NCCLS broth microdilution method (National Committee for Clinical Laboratory Standards 1993. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, 3rd ed. Approved standard M7-A6. National Committee for Clinical laboratory standards, Wayne, PA) with slight modifications. Inocula of the microorganisms were diluted into Mueller-Hinton II (MH, cation adjusted) broth + 0.002% P-80 and compared with a 0.5 McFarland standard to give appr. 10⁶ colony forming units (CFU)/mL. Aliquots (50 μ l) of inoculate were added to 50 μ l of MH broth + 0.002% P-80 containing the compounds in serial two-fold dilutions. The following microorganisms were used to determine antibiotic selectivity of the compounds: *S. pneumoniae* DSM 20566 11A11, 3313A6, 704CG4B21, 82BERG72; *S. aureus* ATCC 29213, ATCC 25923, DSM 11729, DSM 46320, *S. aureus* 39. Antimicrobial activities of the compounds were expressed as the minimal inhibitory concentration (MIC) in μ g/mL at which no visible growth was observed after 18-20 hours of incubation at 36 °C.

The results of the antimicrobial assays are summarized in Table 32.7 and Table 32.8.

5. Plasma and metabolic stability assays

- 5 Example compounds were dissolved in DMSO/H₂O 90:10 to a final concentration of 10 mM for plasma stability determination and metabolic stability determination.

The assays were conducted according to literature precedents (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).

Results of the stability assays are listed in Table 33 below.

Plasma stability assay

Human plasma (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, 30, 60, 120 and 240 minutes and stopped by precipitation with 3 volumes of acetonitrile/formic acid 98:2 and shaking (2 minutes, 600 rpm) followed by filtration (-20 mm Hg). The filtrate is collected. The filtrate (100 µL) is evaporated and reconstituted in the suitable solvent (cf. Table 33) 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 T_{1/2} in minutes. In order to monitor assay integrity the degradation of propantheline is assayed with every experimental set.

25

Metabolic stability assay

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.

35 Compounds are incubated at 37°C in duplicates and samples are taken after 0, 5, 10, 20 and 60 minutes. After acetonitrile precipitation (3 volumes), shaking (2 minutes,

600 rpm) followed by centrifugation (10 minutes, 3200 g), the supernatant is dried reconstituted in the suitable solvent (cf. Table 33) and analyzed by HPLC/MS/MS. Metabolic turnover is expressed in % of the initial 0 minutes value and half life $T_{1/2}$ (min) is calculated. Verapamil for human and propranolol for mouse are used as
5 reference and are assayed with every experimental set.

344

Table 32.1: Endothelin Converting Enzyme-1 Assay

No	[% Inhibition at 10 μ M]	IC ₅₀ [μ M]
Ex.18	98	3.01
Ex.25	97	4.28
Ex.26	98	4.07

Table 32.2: Cathepsin S Assay

No	[% Inhibition at 10 μ M]	IC ₅₀ [μ M]
Ex.18	82	3.65
Ex.20	45	14.7
Ex.21	75	n.d.
Ex.24	55	n.d.
Ex.25	87	3.18
Ex.26	81	3.83
Ex.27	50	n.d.
Ex.28	57	n.d.

5

Table 32.3: TRH (Thyrotropin-releasing hormone) receptor Assay

No	Antagonist activity [% Inhibition at 10 μ M]	Antagonist activity IC ₅₀ [μ M]
Ex.7	91	1.4
Ex.332	29	n.d.
Ex.333	35	n.d.
Ex.334	40	n.d.
Ex.335	34	n.d.
Ex.336	48	8.2

10

Table 32.4: OT (Oxytocin) receptor Assay

No	Antagonist activity [% Inhibition at 10 μ M]	Antagonist activity IC ₅₀ [μ M]
Ex.94	58	3.0
Ex.96	60	1.2
Ex.100	57	4.6
Ex.101	69	2.6
Ex.103	77	6.9

Table 32.5: BB3 (Bombesin) receptor Assay

No	Agonist activity [% activation at 12.5 μ M]	Agonist activity EC ₅₀ [nM]
Ex.265	84	630
Ex.267	61	> 50'000
Ex.275	60	780
Ex.276	75	480 *)
Ex.282	39	> 50'000

5

* Ca 75% of Bombesin efficacy

Table 32.6: LTB₄ (Leukotriene B₄) receptor Assay

No	Antagonist activity [% inhibition at 10 μ M]	Antagonist activity IC ₅₀ [μ M]
Ex.14	46	39.4
Ex.50	100	1.97
Ex.116	49	15.4
Ex.119	47	14.2
Ex.144	41	40.9

Table 32.7: Antimicrobial activity

No	<i>S. aureus</i> ATCC 29213 MIC [µg/mL]	<i>S. aureus</i> 39 MIC [µg/mL]	<i>S. aureus</i> ATCC 25923 MIC [µg/mL]	<i>S. aureus</i> DSM 11729 MIC [µg/mL]	<i>S. aureus</i> DSM 46320 MIC [µg/mL]	<i>S. pneumoniae</i> DSM 20566 MIC [µg/mL]
Ex.2	8 - 16	4	16	8-16	16 - >16	8
Ex.91	2 - 4	8	4	2	4	>16
Ex.94	4	8	8	4	8	>16

S. aureus: *Staphylococcus aureus*; *S. pneumoniae*: *Streptococcus pneumoniae*

Table 32.8: Antimicrobial activity

No	<i>S. pneumoniae</i> DSM 20566 MIC [µg/mL]	<i>S. pneumoniae</i> 11A11 MIC [µg/mL]	<i>S. pneumoniae</i> 3313A6 MIC [µg/mL]	<i>S. pneumoniae</i> 704CG4B21 MIC [µg/mL]	<i>S. pneumoniae</i> 82BERG72 MIC [µg/mL]
Ex.247	16	16	16	16	8
Ex.257	8	8	8	8	2
Ex.259	8	16	8	8	4

S. pneumoniae: *Streptococcus pneumonia*

Table 33: Plasma Stability and Metabolic Stability Assays of Selected Examples (continued on the following pages)

No	Solvent for reconstitution	Plasma Stability				Metabolic Stability			
		T ½ [min] hum	240 min hum [% remain.]	T ½ [min] mouse/ (rat)	240 min mouse/ (rat) [% remain.]	T ½ [min] hum	60 min hum [% remain.]	T ½ [min] mouse/ (rat)	60 min mouse/ (rat) [% remain.]
Ex.42	B	> 240	91	> 240	100	> 60	100	> 60	100
Ex.43	B	> 240	97	> 240	63	> 60	100	> 60	83
Ex.44	B	> 240	100	> 240	83	> 60	68	> 60	77
Ex.45	C	> 240	76	190	46	> 60	66	> 60	73
Ex.46	B	> 240	100	> 240	78	32	26	> 60	71
Ex.47	B	> 240	99	> 240	86	> 60	83	> 60	100
Ex.49	B	> 240	95	> 240	76	> 60	100	> 60	92
Ex.50	B	> 240	100	n.d.	n.d.	> 60	53	40	34
Ex.51	B	> 240	100	> 240	80	> 60	71	> 60	69
Ex.52	B	> 240	99	> 240	95	> 60	100	> 60	78
Ex.53	1)	n.d.	n.d.	> 240	86	> 60	100	> 60	92
Ex.54	B	> 240	100	> 240	100	> 60	60	> 60	82
Ex.55	B	n.d.	n.d.	> 240	80	> 60	97	> 60	98
Ex.57	B	> 240	100	> 240	74	> 60	100	> 60	100

No	Solvent for reconstitution	Plasma Stability				Metabolic Stability			
		T ½ [min] hum	240 min hum [% remain.]	T ½ [min] mouse/ (rat)	240 min mouse/ (rat) [% remain.]	T ½ [min] hum	60 min hum [% remain.]	T ½ [min] mouse/ (rat)	60 min mouse/ (rat) [% remain.]
Ex.58	D	> 240	95	n.d.	n.d.	> 60	87	> 60	70
Ex.59	B	> 240	74	> 240	67	> 60	94	> 60	81
Ex.60	C	> 240	97	n.d.	n.d.	8	0	25	19
Ex.69	1)	> 240	91	200	45	> 60	100	> 60	100
Ex.70	1)	> 240	99	> 240	61	> 60	100	> 60	77
Ex.71	B	> 240	100	> 240	92	> 60	100	> 60	89
Ex.72	B	> 240	100	> 240	65	22	14	35	30
Ex.73	B	> 240	89	n.d.	n.d.	2	0	1	0
Ex.74	C	> 240	100	> 240	67	7	1	3	0
Ex.75	B	> 240	93	> 240	55	21	12	53	48
Ex.76	D	> 240	88	n.d.	n.d.	16	4	15	9
Ex.77	B	> 240	96	> 240	85	44	41	> 60	75
Ex.78	B	> 240	100	> 240	86	> 60	99	> 60	92
Ex.79	B	> 240	100	> 240	60	> 60	95	> 60	73
Ex.80	1)	> 240	90	> 240	84	19	6	24	19

No	Solvent for reconstitution	Plasma Stability				Metabolic Stability			
		T ½ [min] hum	240 min hum [% remain.]	T ½ [min] mouse/ (rat)	240 min mouse/ (rat) [% remain.]	T ½ [min] hum	60 min hum [% remain.]	T ½ [min] mouse/ (rat)	60 min mouse/ (rat) [% remain.]
Ex.81	2)	> 240	88	> 240	100	> 60	100	> 60	97
Ex.83	3)	> 240	85	> 240	93	> 60	85	> 60	96
Ex.84	B	> 240	99	> 240	56	> 60	97	> 60	71
Ex.85	D	> 240	100	> 240	88	> 60	100	> 60	80
Ex.86	B	n.d.	n.d.	> 240	60	n.d.	n.d.	> 60	71
Ex.87	B	> 240	100	> 240	90	27	17	60	63
Ex.88	1)	n.d.	n.d.	> 240	81	56	49	> 60	62
Ex.89	C	> 240	100	> 240	76	13	8	10	2

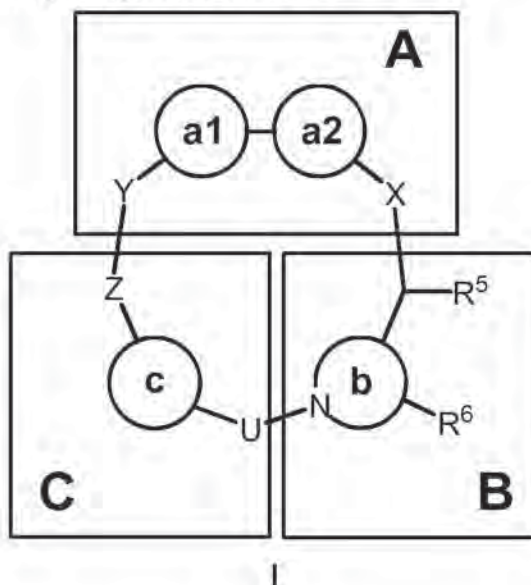
349

- 1) Reconstitution solvent for plasma stability determination: B; reconstitution solvent for metabolic stability determination: C
- 2) Reconstitution solvent for plasma stability determination; human: D; mouse B; reconstitution solvent for metabolic stability determination: D
- 3) Reconstitution solvent for plasma stability determination: B; reconstitution solvent for metabolic stability determination; human D; mouse B.

Reconstitution solvents: **Solvent A:** DPBS (100 mg CaCl₂, 100 mg MgCl₂·6H₂O, 200 mg KCl, 200 mg KH₂PO₄, 8000 mg NaCl and 2160 mg Na₂HPO₄·7H₂O to be made up to 1000 mL by addition of H₂O); **Solvent B:** H₂O/CH₃CN 95:5 (v/v) + 0.2% formic acid; **Solvent C:** DMSO /(H₂O/CH₃CN 95:5)/DPBS 50:45:5 + 2% formic acid; **Solvent D:** H₂O/CH₃CN 1:1 (v/v) + 5% DPBS + 0.2% formic acid

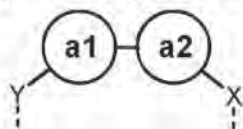
Claims

1. A compound consisting of a cyclic arrangement of the building blocks A, B and C and represented by the general formula I

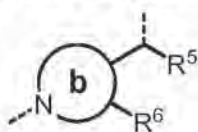


wherein

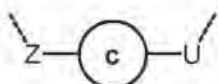
building block A ("Template") is represented by



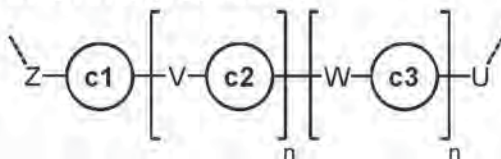
building block B ("Modulator") is represented by



building block C ("Bridge") is represented by



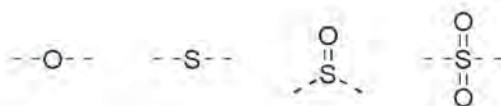
which in turn consists of



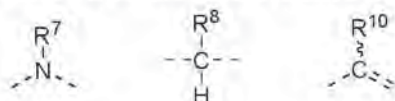
and wherein

X represents a divalent radical selected from the group of

351

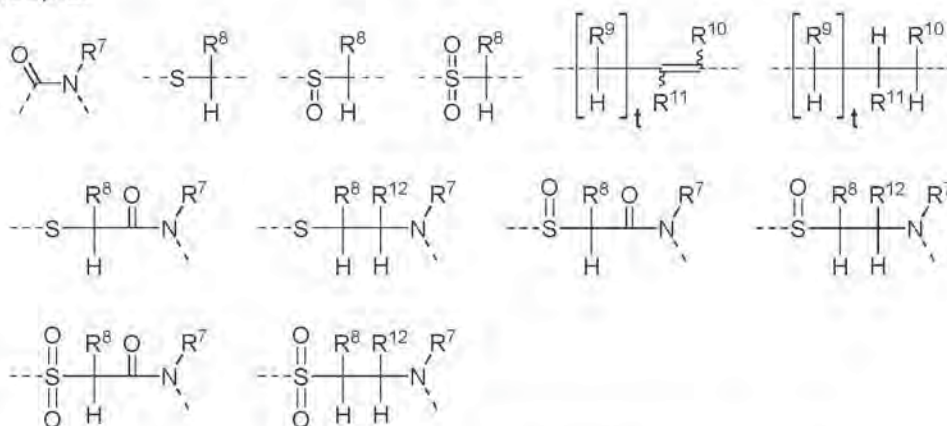


Z represents a divalent or trivalent radical selected from the group of

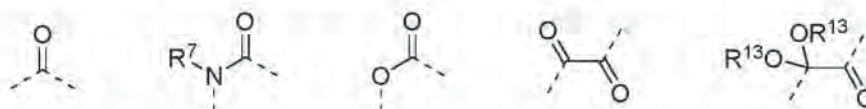


forming an integral part of the

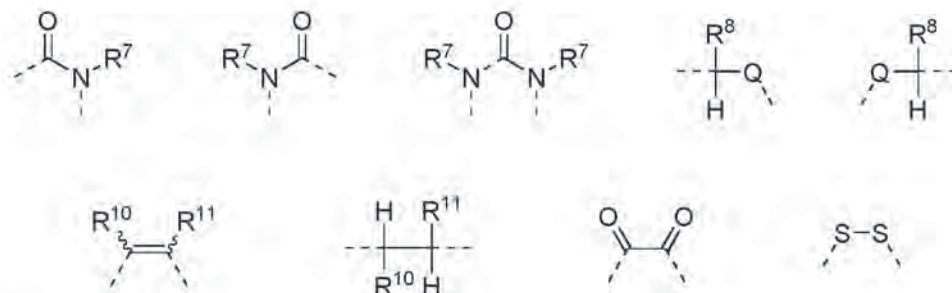
- 5 Y-Z connectivity which in turn represents a divalent radical selected from the group of



U represents a divalent radical selected from the group of



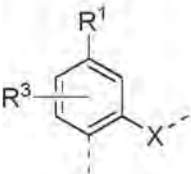
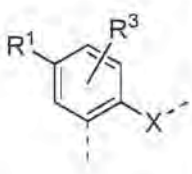
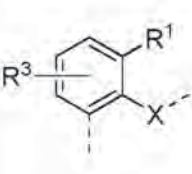
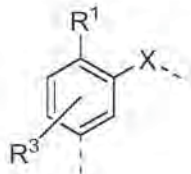
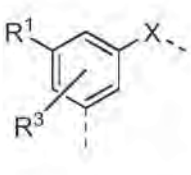
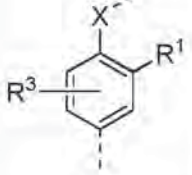
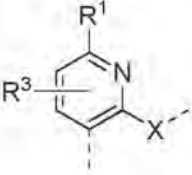
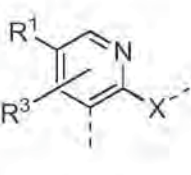
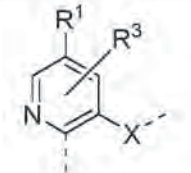
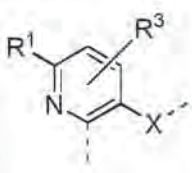
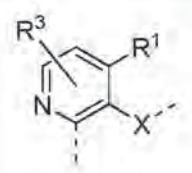
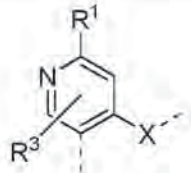
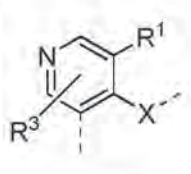
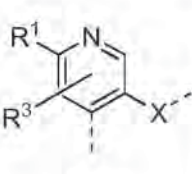
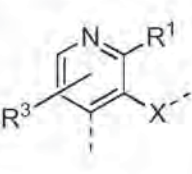
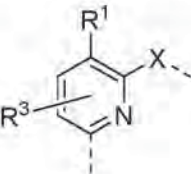
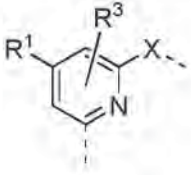
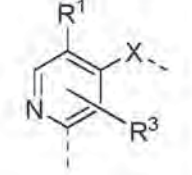
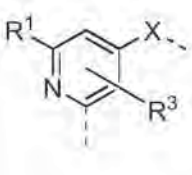
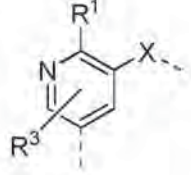
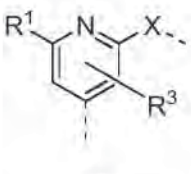
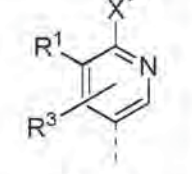
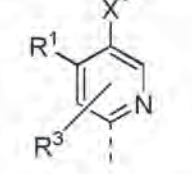
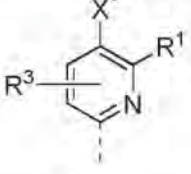
- 10 V and W are representing independently a divalent radical selected from the group of

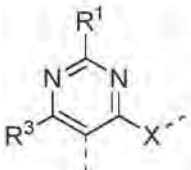
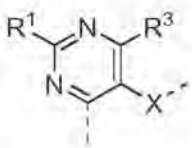
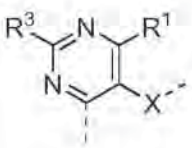
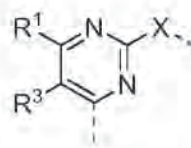
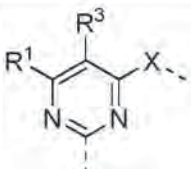
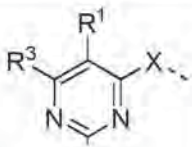
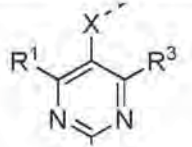
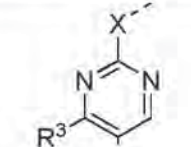
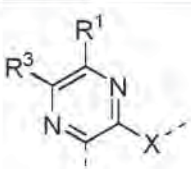
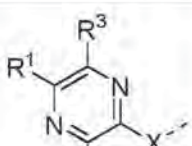
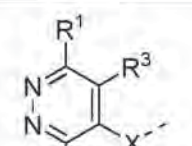
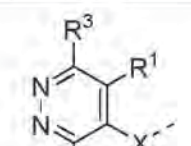
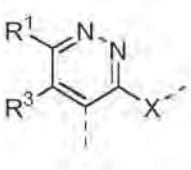
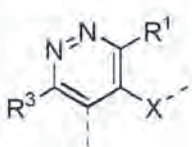
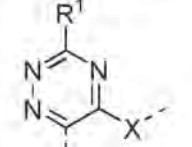
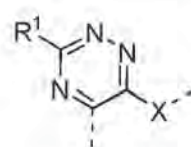
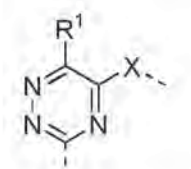
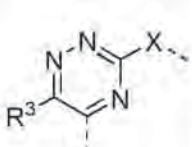
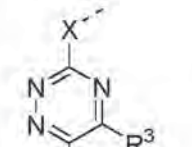
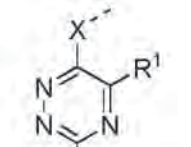
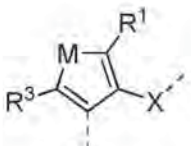
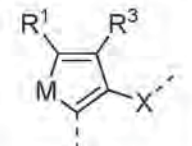
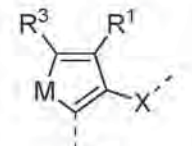
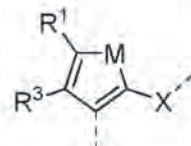
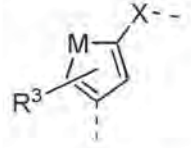
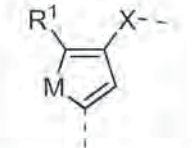
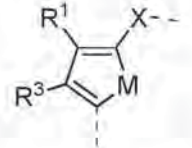
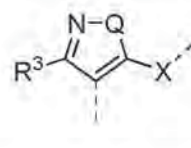


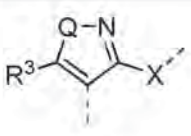
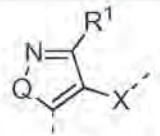
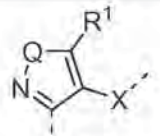
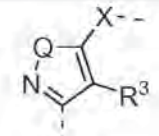
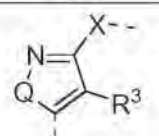
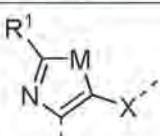
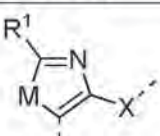
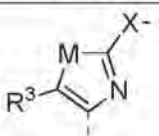
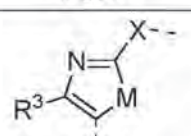
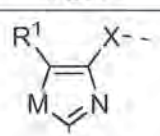
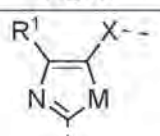
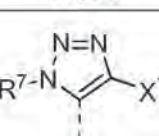
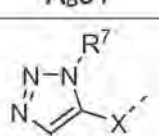
- 15 and wherein

said **Template A** is a bivalent radical consisting of all possible combinations of structure **A_B-A_C**

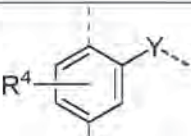
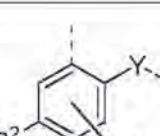
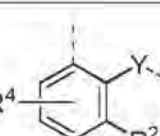
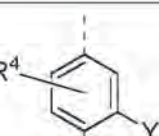
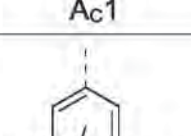
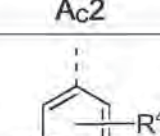
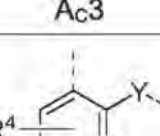
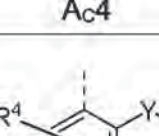
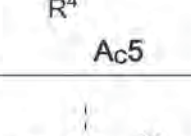
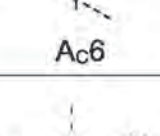
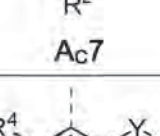
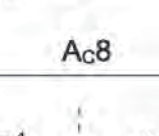
of which A_B is selected from the group of

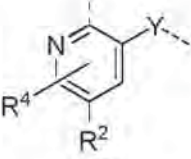
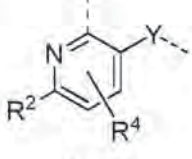
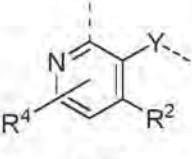
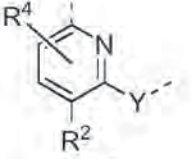
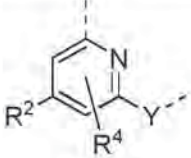
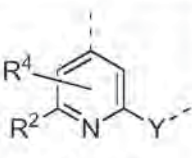
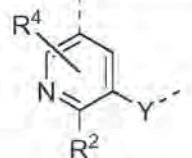
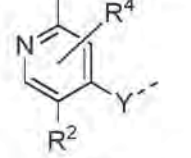
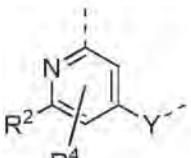
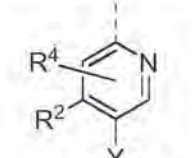
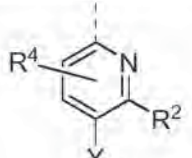
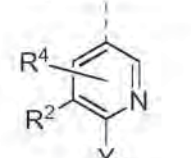
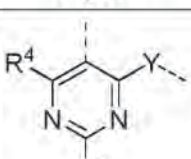
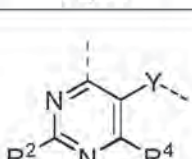
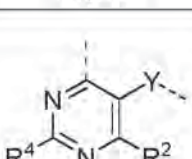
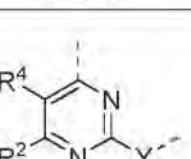
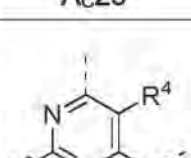
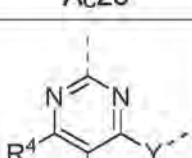
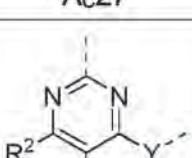
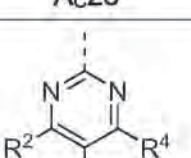
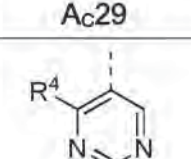
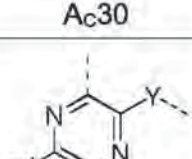
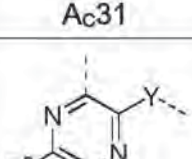
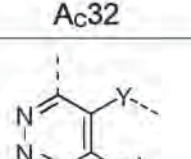
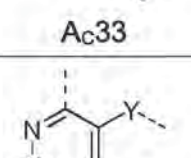
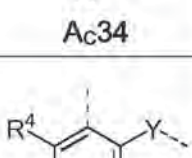
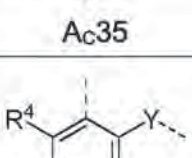
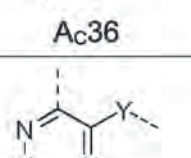
 A_{B1}	 A_{B2}	 A_{B3}	 A_{B4}
 A_{B5}	 A_{B6}	 A_{B7}	 A_{B8}
 A_{B9}	 A_{B10}	 A_{B11}	 A_{B12}
 A_{B13}	 A_{B14}	 A_{B15}	 A_{B16}
 A_{B17}	 A_{B18}	 A_{B19}	 A_{B20}
 A_{B21}	 A_{B22}	 A_{B23}	 A_{B24}

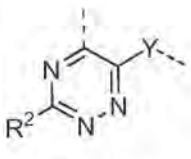
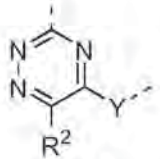
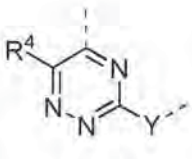
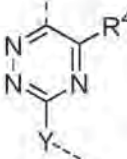
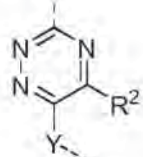
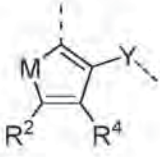
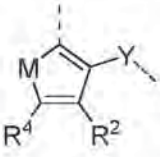
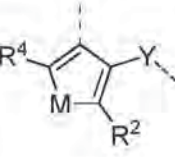
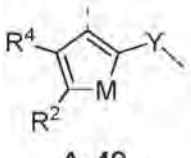
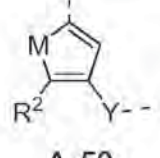
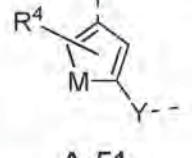
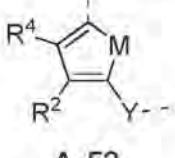
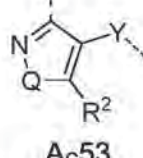
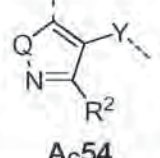
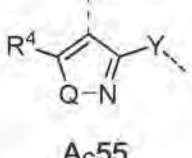
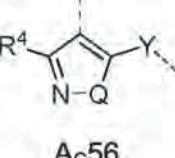
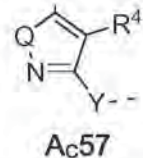
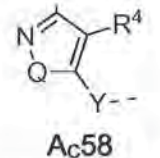
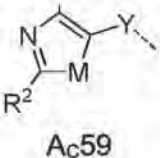
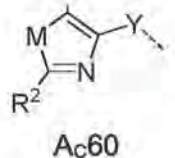
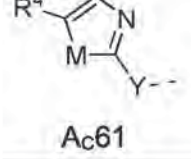
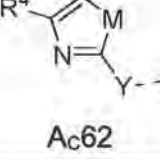
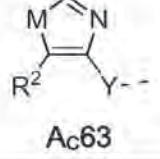
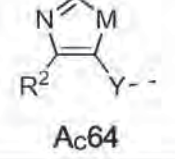
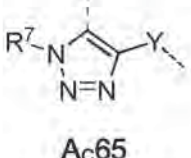
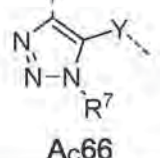
 A_B25	 A_B26	 A_B27	 A_B28
 A_B29	 A_B30	 A_B31	 A_B32
 A_B33	 A_B34	 A_B35	 A_B36
 A_B37	 A_B38	 A_B39	 A_B40
 A_B41	 A_B42	 A_B43	 A_B44
 A_B45	 A_B46	 A_B47	 A_B48
 A_B49	 A_B50	 A_B51	 A_B52

 A _B 53	 A _B 54	 A _B 55	 A _B 56
 A _B 57	 A _B 58	 A _B 59	 A _B 60
 A _B 61	 A _B 62	 A _B 63	 A _B 64
 A _B 65			

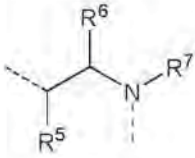
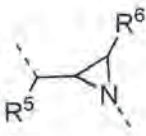
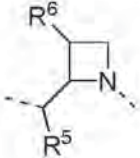
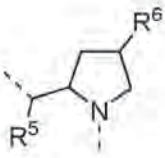
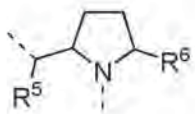
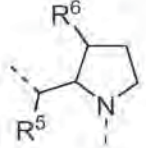
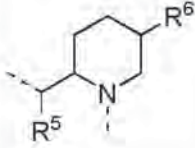
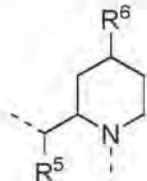
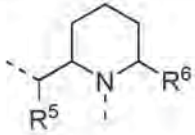
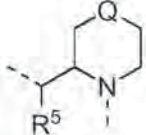
and A_C is selected from the group of

 A _C 1	 A _C 2	 A _C 3	 A _C 4
 A _C 5	 A _C 6	 A _C 7	 A _C 8
 A _C 9	 A _C 10	 A _C 11	 A _C 12

 Ac13	 Ac14	 Ac15	 Ac16
 Ac17	 Ac18	 Ac19	 Ac20
 Ac21	 Ac22	 Ac23	 Ac24
 Ac25	 Ac26	 Ac27	 Ac28
 Ac29	 Ac30	 Ac31	 Ac32
 Ac33	 Ac34	 Ac35	 Ac36
 Ac37	 Ac38	 Ac39	 Ac40

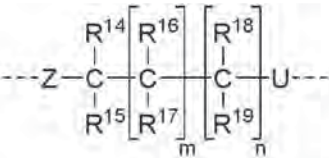
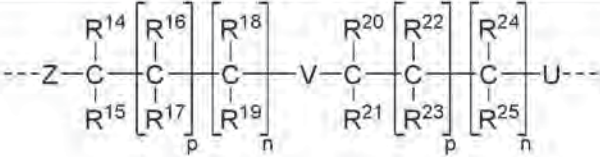
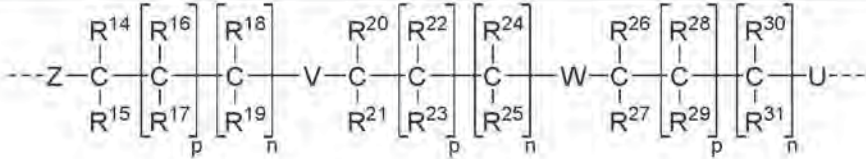
 Ac41	 Ac42	 Ac43	 Ac44
 Ac45	 Ac46	 Ac47	 Ac48
 Ac49	 Ac50	 Ac51	 Ac52
 Ac53	 Ac54	 Ac55	 Ac56
 Ac57	 Ac58	 Ac59	 Ac60
 Ac61	 Ac62	 Ac63	 Ac64
 Ac65	 Ac66		

wherein **Modulator B** is a bivalent radical selected from the group of

 B1	 B2	 B3	 B4
 B5	 B6	 B7	 B8
 B9	 B10		

and **Bridge C** is a bivalent radical selected from the group of

5

 C1
 C2
 C3

and wherein further

R¹ and R² are independently defined as H; F; Cl; Br; I; CF₃; OCF₃; OCHF₂; NO₂; CN; C₁₋₂₄-alkyl; C₂₋₂₄-alkenyl; C₂₋₁₀-alkynyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl-C₁₋₁₂-alkyl; heteroaryl-C₁₋₁₂-alkyl; $-(CR^{32}R^{33})_qOR^{34}$; $-(CR^{32}R^{33})_qSR^{34}$;
 5 $-(CR^{32}R^{33})_qNR^7R^{35}$; $-(CR^{32}R^{33})_qOCONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7COOR^{36}$;
 $-(CR^{32}R^{33})_qNR^7COR^{37}$; $-(CR^{32}R^{33})_qNR^7CONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7SO_2R^{38}$;
 $-(CR^{32}R^{33})_qNR^7SO_2NR^7R^{35}$; $-(CR^{32}R^{33})_qCOOR^{36}$; $-(CR^{32}R^{33})_qCONR^7R^{35}$;
 $-(CR^{32}R^{33})_qSO_2NR^7R^{35}$; $-(CR^{32}R^{33})_qCOR^{37}$; $-(CR^{32}R^{33})_qSO_2R^{38}$; $-(CR^{32}R^{33})_qR^{39}$;
 $-(CR^{32}R^{33})_qR^{40}$; $-(CR^{32}R^{33})_qR^{41}$; or $-(CR^{32}R^{33})_qR^{44}$;

10

R³ and R⁴ are independently defined as H; F; Cl; CF₃; OCF₃; OCHF₂; NO₂; CN; C₁₋₂₄-alkyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl-C₁₋₁₂-alkyl; heteroaryl-C₁₋₁₂-alkyl; C₁₋₁₂-alkoxy or aryloxy;

15

R⁵ is H; CF₃; C₁₋₂₄-alkyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl-C₁₋₁₂-alkyl; or heteroaryl-C₁₋₁₂-alkyl;

R⁶ is H; CF₃; C₁₋₂₄-alkyl; C₂₋₂₄-alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl-C₁₋₁₂-alkyl; heteroaryl-C₁₋₁₂-alkyl; $-(CR^{32}R^{33})_qOR^{34}$; $-(CR^{32}R^{33})_qSR^{34}$;
 20 $-(CR^{32}R^{33})_qNR^7R^{35}$; $-(CR^{32}R^{33})_qOCONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7COOR^{36}$;
 $-(CR^{32}R^{33})_qNR^7COR^{37}$; $-(CR^{32}R^{33})_qNR^7CONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7SO_2R^{38}$;
 $-(CR^{32}R^{33})_qNR^7SO_2NR^7R^{35}$; $-(CR^{32}R^{33})_qCOOR^{36}$; $-(CR^{32}R^{33})_qCONR^7R^{35}$;
 $-(CR^{32}R^{33})_qSO_2NR^7R^{35}$; $-(CR^{32}R^{33})_qCOR^{37}$; $-(CR^{32}R^{33})_qSO_2R^{38}$; $-(CR^{32}R^{33})_qR^{39}$;
 $-(CR^{32}R^{33})_sR^{40}$; or $-(CR^{32}R^{33})_qR^{41}$; or $-(CR^{32}R^{33})_qR^{44}$;

25

R⁷ is H; C₁₋₂₄-alkyl; C₂₋₂₄-alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl-C₁₋₁₂-alkyl; heteroaryl-C₁₋₁₂-alkyl; or an *N*-protecting group;

R⁸ and R⁹ are independently defined as H; F; CF₃; C₁₋₂₄-alkyl; C₂₋₂₄-alkenyl;
 30 cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl-C₁₋₁₂-alkyl; or heteroaryl-C₁₋₁₂-alkyl;

R¹⁰, R¹¹ and R¹² are independently defined as H; C₁₋₂₄-alkyl; or cycloalkyl;

R¹³ is C₁₋₂₄-alkyl or cycloalkyl;

35

R^{14} , R^{20} and R^{26} are independently defined as H; F; CF_3 ; C_{1-24} -alkyl; C_{2-24} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-12} -alkyl; heteroaryl- C_{1-12} -alkyl; $-(CR^{32}R^{33})_qOR^{34}$; $-(CR^{32}R^{33})_qSR^{34}$; $-(CR^{32}R^{33})_qNR^7R^{35}$;

$-(CR^{32}R^{33})_qOCONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7COOR^{36}$; $-(CR^{32}R^{33})_qNR^7COR^{37}$;

5 $-(CR^{32}R^{33})_qNR^7CONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7SO_2R^{38}$; $-(CR^{32}R^{33})_qNR^7SO_2NR^7R^{35}$;

$-(CR^{32}R^{33})_qCOOR^{36}$; $-(CR^{32}R^{33})_qCONR^7R^{35}$; $-(CR^{32}R^{33})_qSO_2NR^7R^{35}$;

$-(CR^{32}R^{33})_qCOR^{37}$; $-(CR^{32}R^{33})_qSO_2R^{38}$; $-(CR^{32}R^{33})_qR^{39}$; $-(CR^{32}R^{33})_sR^{40}$;

$-(CR^{32}R^{33})_qR^{41}$; or $-(CR^{32}R^{33})_qR^{44}$;

10 R^{15} , R^{17} , R^{19} , R^{21} , R^{23} , R^{25} , R^{27} , R^{29} and R^{31} are independently defined as H; C_{1-24} -alkyl; cycloalkyl; or heterocycloalkyl;

R^{16} , R^{22} and R^{28} are independently defined as H; CF_3 ; C_{1-24} -alkyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-12} -alkyl; or heteroaryl- C_{1-12} -alkyl;

15

R^{18} , R^{24} and R^{30} are independently defined as H; F; CF_3 ; C_{1-24} -alkyl; C_{2-24} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-12} -alkyl; heteroaryl- C_{1-12} -alkyl; $-(CR^{32}R^{33})_qOR^{34}$; $-(CR^{32}R^{33})_qNR^7R^{35}$; $-(CR^{32}R^{33})_qOCONR^7R^{35}$;

$-(CR^{32}R^{33})_qNR^7COOR^{36}$; $-(CR^{32}R^{33})_qNR^7COR^{37}$; $-(CR^{32}R^{33})_qNR^7CONR^7R^{35}$;

20 $-(CR^{32}R^{33})_qNR^7SO_2R^{38}$; $-(CR^{32}R^{33})_qNR^7SO_2NR^7R^{35}$; $-(CR^{32}R^{33})_qCOOR^{36}$;

$-(CR^{32}R^{33})_qCONR^7R^{35}$; $-(CR^{32}R^{33})_qSO_2NR^7R^{35}$; $-(CR^{32}R^{33})_qCOR^{37}$; or $-(CR^{32}R^{33})_qR^{44}$;

R^{32} is H; F; CF_3 ; C_{1-24} -alkyl; C_{2-24} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-12} -alkyl; heteroaryl- C_{1-12} -alkyl; $-(CR^{51}R^{53})_qOR^{45}$; $-(CR^{51}R^{53})_qSR^{45}$;

25 $-(CR^{51}R^{53})_qNR^7R^{45}$; $-(CR^{51}R^{53})_qOCONR^7R^{45}$; $-(CR^{51}R^{53})_qNR^7COOR^{36}$;

$-(CR^{51}R^{53})_qNR^7COR^{37}$; $-(CR^{51}R^{53})_qNR^7CONR^7R^{45}$; $-(CR^{51}R^{53})_qNR^7SO_2R^{38}$;

$-(CR^{51}R^{53})_qNR^7SO_2NR^7R^{45}$; $-(CR^{51}R^{53})_qCOOR^{36}$; $-(CR^{51}R^{53})_qCONR^7R^{45}$;

$-(CR^{51}R^{53})_qSO_2NR^7R^{45}$; $-(CR^{51}R^{53})_qCOR^{37}$; $-(CR^{51}R^{53})_qSO_2R^{38}$; $-(CR^{51}R^{53})_qR^{39}$;

$-(CR^{51}R^{53})_sR^{40}$; $-(CR^{51}R^{53})_qR^{41}$; or $-(CR^{51}R^{53})_qR^{44}$;

30

R^{33} is H; C_{1-24} -alkyl; C_{2-24} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-12} -alkyl; or heteroaryl- C_{1-12} -alkyl;

R^{34} is H; C_{1-24} -alkyl; C_{2-24} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl;

35 aryl- C_{1-12} -alkyl; heteroaryl- C_{1-12} -alkyl; $-(CR^{51}R^{53})_qOR^{45}$; $-(CR^{51}R^{53})_qNR^7R^{45}$;

- $-(\text{CR}^{51}\text{R}^{53})_r\text{OCONR}^7\text{R}^{35}$; $-(\text{CR}^{51}\text{R}^{53})_r\text{NR}^7\text{COOR}^{36}$; $-(\text{CR}^{51}\text{R}^{53})_r\text{NR}^7\text{COR}^{38}$;
 $-(\text{CR}^{51}\text{R}^{53})_r\text{NR}^7\text{CONR}^7\text{R}^{45}$; $-(\text{CR}^{51}\text{R}^{53})_r\text{NR}^7\text{SO}_2\text{R}^{38}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{COOR}^{36}$;
 $-(\text{CR}^{51}\text{R}^{53})_q\text{CONR}^7\text{R}^{45}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{SO}_2\text{NR}^7\text{R}^{45}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{COR}^{38}$;
 $-(\text{CR}^{51}\text{R}^{53})_q\text{SO}_2\text{R}^{38}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{R}^{39}$; $-(\text{CR}^{51}\text{R}^{53})_s\text{R}^{40}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{R}^{41}$; or
 5 $-(\text{CR}^{51}\text{R}^{53})_q\text{R}^{44}$;

- R^{35} is H; C_{1-24} -alkyl; C_{2-24} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl;
 aryl- C_{1-12} -alkyl; heteroaryl- C_{1-12} -alkyl; an *N*-protecting group; $-(\text{CR}^{32}\text{R}^{33})_r\text{OR}^{45}$;
 $-(\text{CR}^{32}\text{R}^{33})_r\text{NR}^7\text{R}^{45}$; $-(\text{CR}^{32}\text{R}^{33})_r\text{OCONR}^7\text{R}^{45}$; $-(\text{CR}^{32}\text{R}^{33})_r\text{NR}^7\text{COOR}^{36}$;
 10 $-(\text{CR}^{32}\text{R}^{33})_r\text{NR}^7\text{CONR}^7\text{R}^{50}$; $-(\text{CR}^{32}\text{R}^{33})_r\text{NR}^7\text{SO}_2\text{R}^{38}$; $-(\text{CR}^{32}\text{R}^{33})_r\text{NR}^7\text{SO}_2\text{NR}^7\text{R}^{50}$;
 $-(\text{CR}^{32}\text{R}^{33})_q\text{COOR}^{36}$; $-(\text{CR}^{32}\text{R}^{33})_r\text{NR}^7\text{COR}^{37}$; $-(\text{CR}^{32}\text{R}^{33})_q\text{CONR}^7\text{R}^{50}$;
 $-(\text{CR}^{32}\text{R}^{33})_q\text{COR}^{37}$; $-(\text{CR}^{32}\text{R}^{33})_q\text{SO}_2\text{R}^{38}$; $-(\text{CR}^{32}\text{R}^{33})_q\text{SO}_2\text{NR}^7\text{R}^{50}$; $-(\text{CR}^{32}\text{R}^{33})_q\text{R}^{39}$;
 $-(\text{CR}^{32}\text{R}^{33})_s\text{R}^{40}$; $-(\text{CR}^{32}\text{R}^{33})_q\text{R}^{41}$; or $-(\text{CR}^{32}\text{R}^{33})_q\text{R}^{44}$;

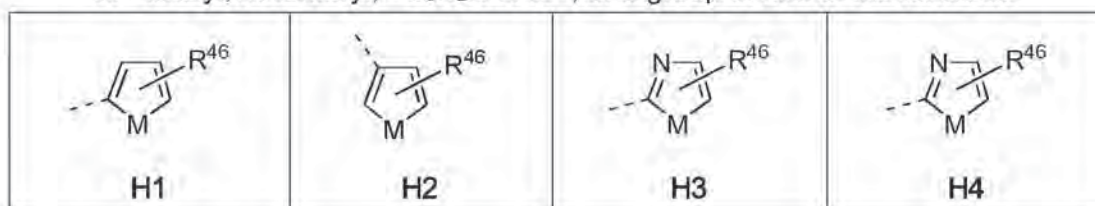
- 15 R^{36} is H; C_{1-24} -alkyl; C_{2-24} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl;
 aryl- C_{1-12} -alkyl; heteroaryl- C_{1-12} -alkyl; or an *O/S*-protecting group;

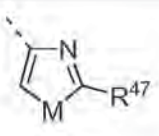
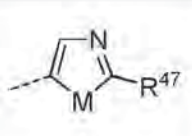
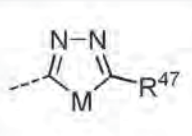
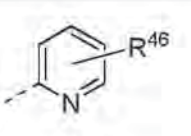
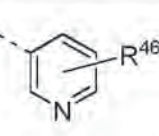
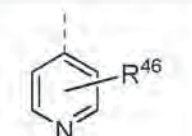
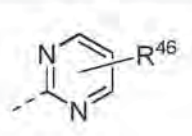
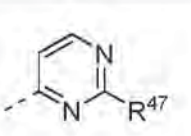
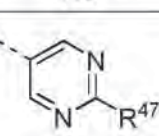
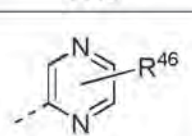
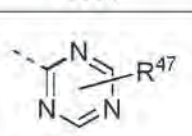
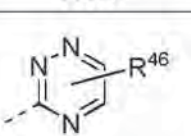
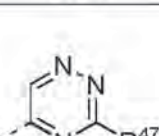
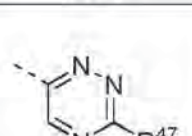
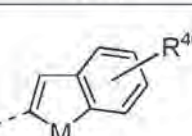
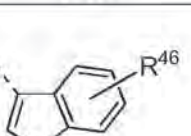
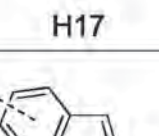
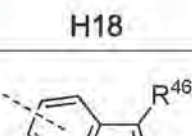
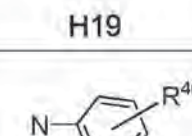
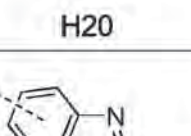
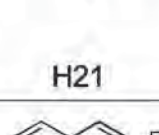
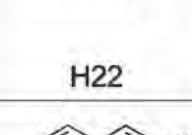
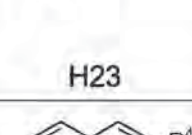
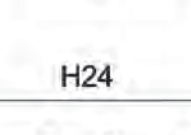
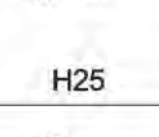
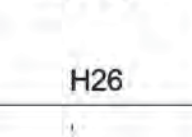
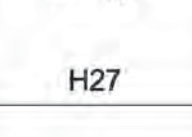
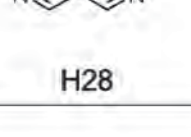
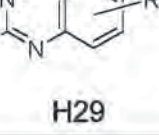
- R^{37} is C_{1-24} -alkyl; C_{2-24} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl;
 aryl- C_{1-12} -alkyl; heteroaryl- C_{1-12} -alkyl; $-(\text{CR}^{51}\text{R}^{53})_q\text{OR}^{45}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{SR}^{45}$;
 20 $-(\text{CR}^{51}\text{R}^{53})_q\text{NR}^7\text{R}^{45}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{OCONR}^7\text{R}^{45}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{NR}^7\text{COOR}^{36}$;
 $-(\text{CR}^{51}\text{R}^{53})_q\text{NR}^7\text{COR}^{38}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{NR}^7\text{CONR}^7\text{R}^{45}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{NR}^7\text{SO}_2\text{R}^{38}$;
 $-(\text{CR}^{51}\text{R}^{53})_q\text{NR}^7\text{SO}_2\text{NR}^7\text{R}^{45}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{COOR}^{36}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{CONR}^7\text{R}^{45}$;
 $-(\text{CR}^{51}\text{R}^{53})_q\text{SO}_2\text{NR}^7\text{R}^{45}$; $-(\text{CR}^{51}\text{R}^{53})_l\text{COR}^{44}$; $-(\text{CR}^{51}\text{R}^{53})_q\text{SO}_2\text{R}^{38}$; $-(\text{CR}^{51}\text{R}^{53})_l\text{R}^{39}$;
 $-(\text{CR}^{51}\text{R}^{53})_u\text{R}^{40}$; $-(\text{CR}^{51}\text{R}^{53})_l\text{R}^{41}$; or $-(\text{CR}^{51}\text{R}^{53})_l\text{R}^{44}$;

25

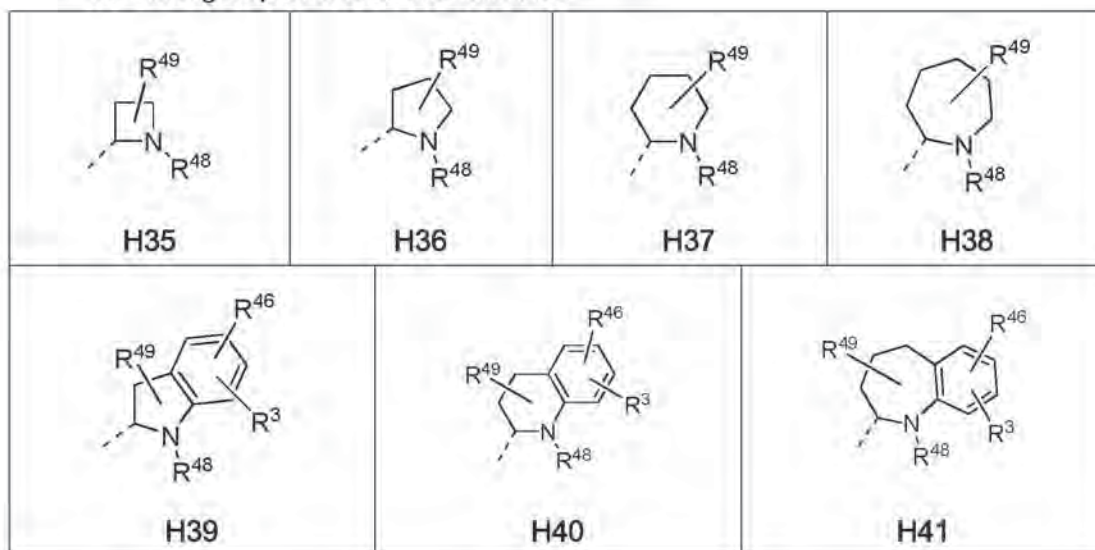
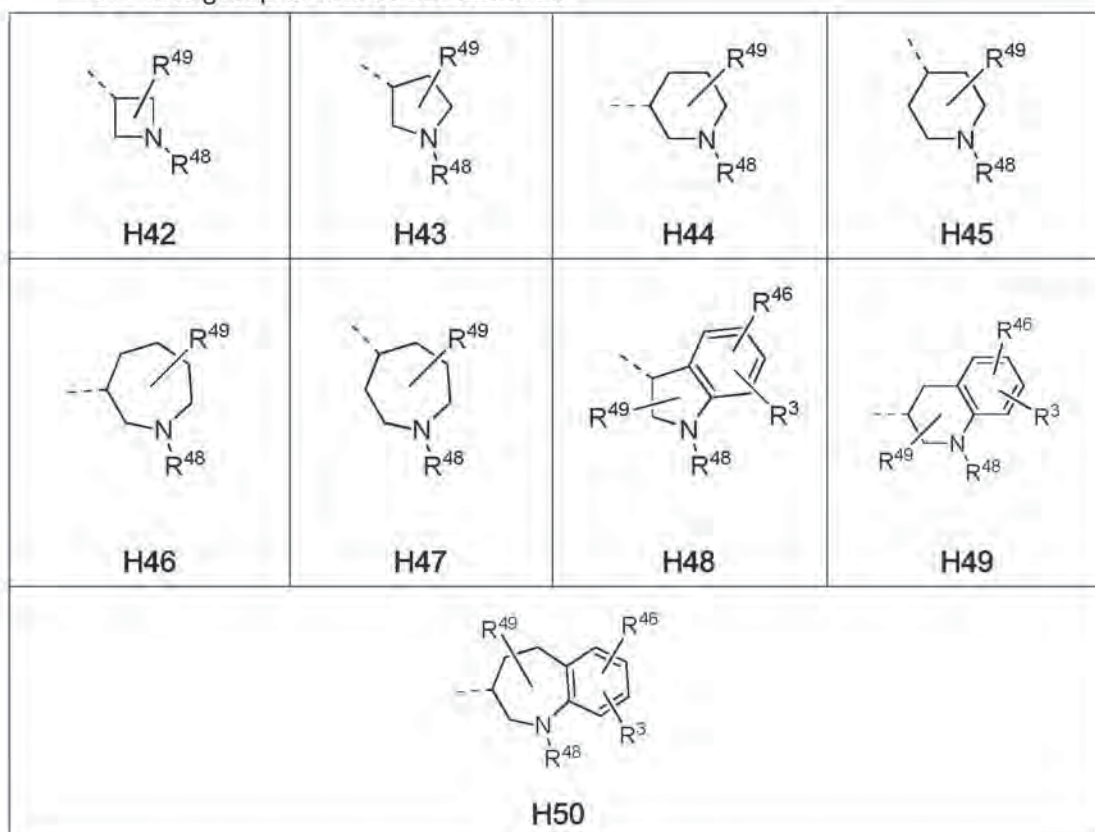
R^{38} is C_{1-24} -alkyl; C_{2-24} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl;
 aryl- C_{1-12} -alkyl; or heteroaryl- C_{1-12} -alkyl;

R^{39} is aryl; heteroaryl; $-\text{C}_6\text{H}_2\text{R}^3\text{R}^4\text{R}^{46}$; or a group of one of the formulae



			
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		

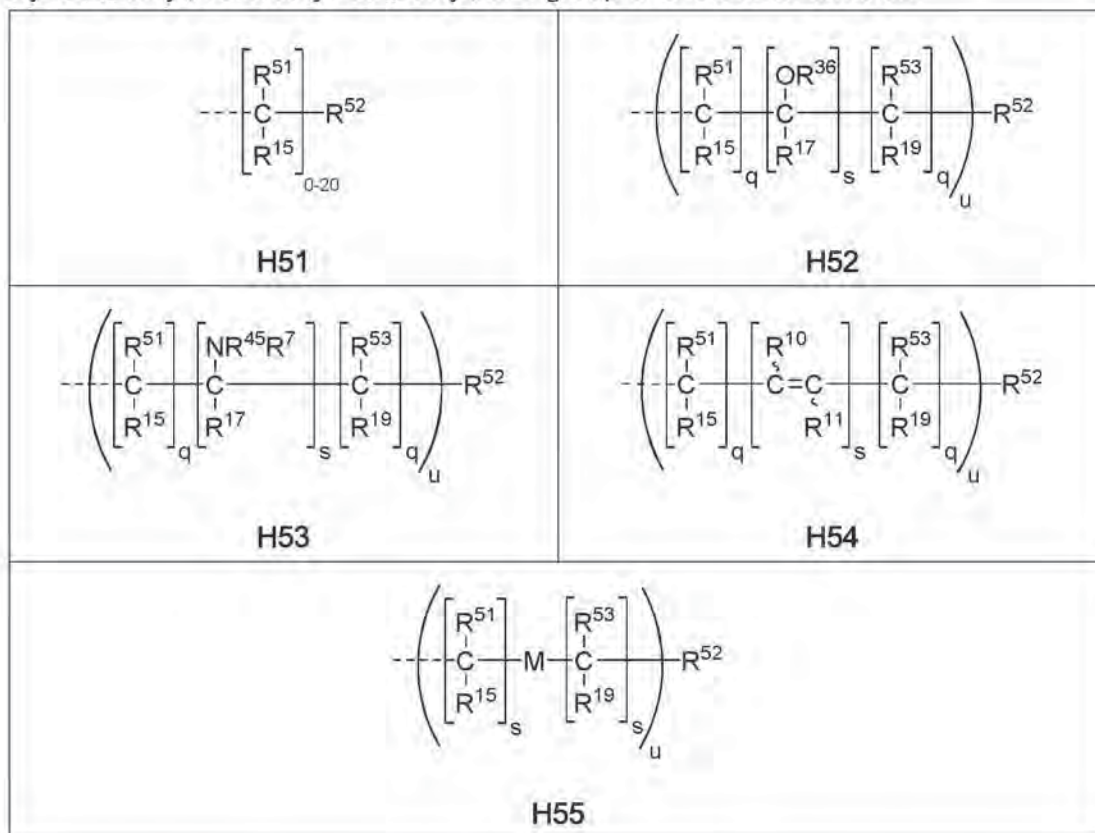
362

 R^{40} is a group of one of the formulae R^{41} is a group of one of the formulae

- 5 R^{42} and R^{43} are independently defined as H; F; CF_3 ; C_{1-24} -alkyl; C_{2-24} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-12} -alkyl; or heteroaryl- C_{1-12} -alkyl;

363

R^{44} is H; C_{1-24} -alkyl; C_{2-24} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-12} -alkyl; heteroaryl- C_{1-12} -alkyl; or a group of one of the formulae



- R^{45} is H; C_{1-24} -alkyl; C_{2-24} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl;
- 5 aryl- C_{1-12} -alkyl; heteroaryl- C_{1-12} -alkyl; an *N*-protecting group; $-(CR^{51}R^{53})_rOR^{36}$;
 $-(CR^{51}R^{53})_rNR^7R^{57}$; $-(CR^{51}R^{53})_rOCONR^7R^{57}$; $-(CR^{51}R^{53})_rNR^7CONR^7R^{57}$;
 $-(CR^{51}R^{53})_rNR^7COR^{38}$; $-(CR^{51}R^{53})_rNR^7SO_2NR^7R^{57}$; $-(CR^{51}R^{53})_rNR^7SO_2R^{38}$;
 $-(CR^{51}R^{53})_qCOOR^{36}$; $-(CR^{51}R^{53})_qCOR^{38}$; $-(CR^{51}R^{53})_qSO_2R^{38}$; $-(CR^{51}R^{53})_qR^{39}$;
 $-(CR^{51}R^{53})_sR^{40}$; $-(CR^{51}R^{53})_qR^{41}$; or $-(CR^{51}R^{53})_sR^{44}$;

10

- R^{46} is H; F; Cl; CF_3 ; OCF_3 ; $OCHF_2$; NO_2 ; CN; C_{1-24} -alkyl; C_{2-24} -alkenyl; C_{2-10} -alkynyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-12} -alkyl; heteroaryl- C_{1-12} -alkyl; $-(CR^{51}R^{53})_qOR^{36}$; $-(CR^{51}R^{53})_qSR^{36}$; $-(CR^{51}R^{53})_qNR^7R^{57}$;
 $-(CR^{51}R^{53})_qOCONR^7R^{57}$; $-(CR^{51}R^{53})_qNR^7COOR^{36}$; $-(CR^{51}R^{53})_qNR^7COR^{38}$;
- 15 $-(CR^{51}R^{53})_qNR^7CONR^7R^{45}$; $-(CR^{51}R^{53})_qNR^7SO_2R^{38}$; $-(CR^{51}R^{53})_qNR^7SO_2NR^7R^{45}$;
 $-(CR^{51}R^{53})_qCOOR^{36}$; $-(CR^{51}R^{53})_qCONR^7R^{45}$; $-(CR^{51}R^{53})_qSO_2NR^7R^{45}$;
 $-(CR^{51}R^{53})_qCOR^{38}$; $-(CR^{51}R^{53})_qSO_2R^{38}$; or $-(CR^{51}R^{53})_qR^{44}$;

R^{47} is H; C_{1-24} -alkyl; C_{2-24} -alkenyl; C_{2-10} -alkynyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-12} -alkyl; heteroaryl- C_{1-12} -alkyl; or $-NR^7R^{45}$;

R^{48} is H; C_{1-24} -alkyl; C_{2-24} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-12} -alkyl; heteroaryl- C_{1-12} -alkyl; an *N*-protecting group; $-(CR^{51}R^{53})_rOR^{45}$;

- 5 $-(CR^{51}R^{53})_rSR^{45}$; $-(CR^{51}R^{53})_rNR^7R^{45}$; $-(CR^{51}R^{53})_rOCONR^7R^{45}$;
 $-(CR^{51}R^{53})_rNR^7COOR^{36}$; $-(CR^{51}R^{53})_rNR^7COR^{38}$; $-(CR^{51}R^{53})_rNR^7CONR^7R^{45}$;
 $-(CR^{51}R^{53})_rNR^7SO_2R^{38}$; $-(CR^{51}R^{53})_rNR^7SO_2NR^7R^{45}$; $-(CR^{51}R^{53})_qCOOR^{36}$;
 $-(CR^{51}R^{53})_qCONR^7R^{45}$; $-(CR^{51}R^{53})_rSO_2NR^7R^{45}$; $-(CR^{51}R^{53})_qCOR^{38}$;
 $-(CR^{51}R^{53})_qSO_2R^{38}$; or $-(CR^{51}R^{53})_sR^{44}$;

10

R^{49} is H; C_{1-24} -alkyl; C_{2-24} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-12} -alkyl; heteroaryl- C_{1-12} -alkyl; $-(CR^{51}R^{53})_qOR^{36}$; $-(CR^{51}R^{53})_qSR^{36}$;

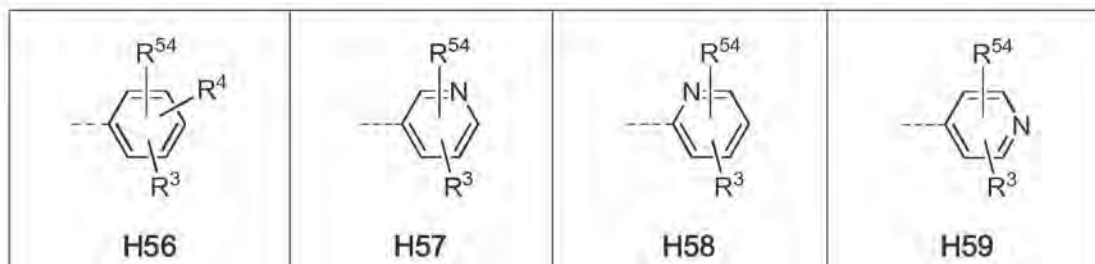
$-(CR^{51}R^{53})_qNR^7R^{45}$; $-(CR^{51}R^{53})_qNR^7COOR^{36}$; $-(CR^{51}R^{53})_qNR^7COR^{38}$;
 $-(CR^{51}R^{53})_qNR^7SO_2R^{38}$; $-(CR^{51}R^{53})_qNR^7CONR^7R^{45}$; $-(CR^{51}R^{53})_qCOOR^{36}$;

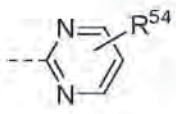
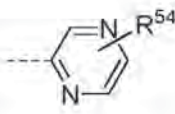
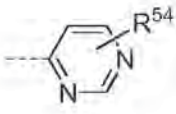
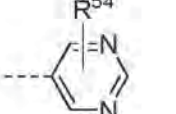
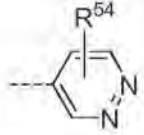
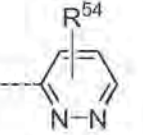
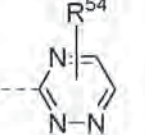
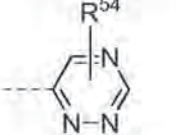
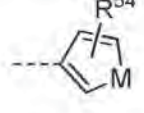
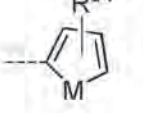
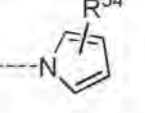
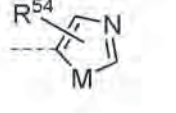
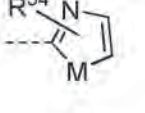
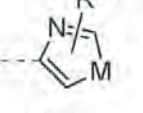
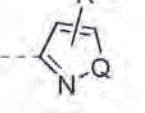
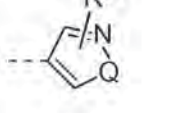
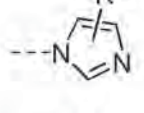
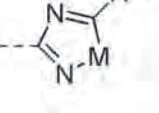
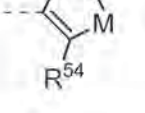
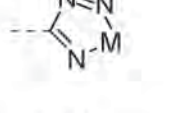
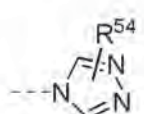
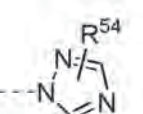
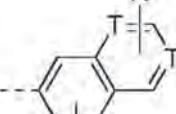
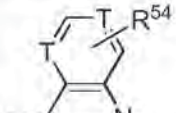
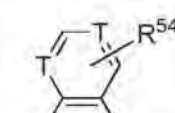
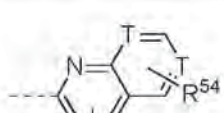
- 15 $-(CR^{51}R^{53})_qCONR^7R^{45}$; $-(CR^{51}R^{53})_qCOR^{38}$; or $-(CR^{51}R^{53})_qR^{44}$;

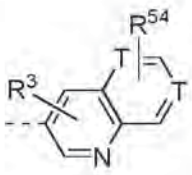
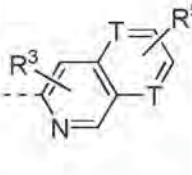
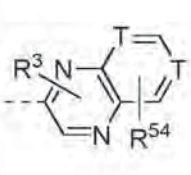
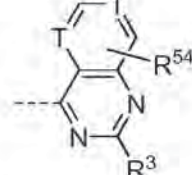
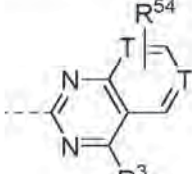
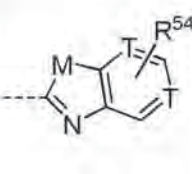
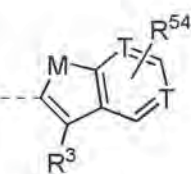
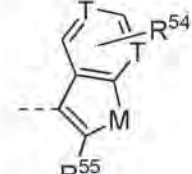
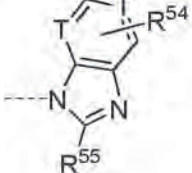
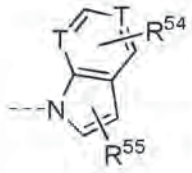
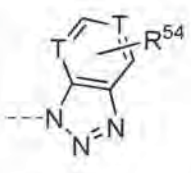
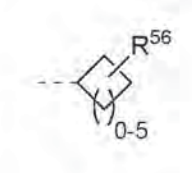
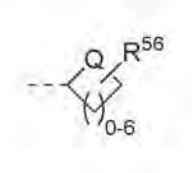
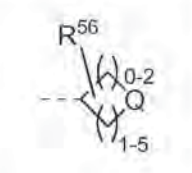
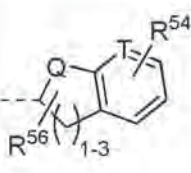
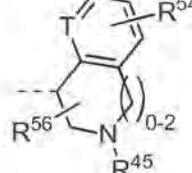
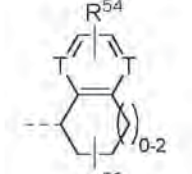
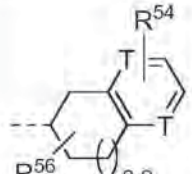
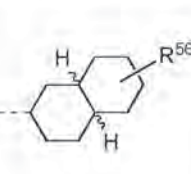
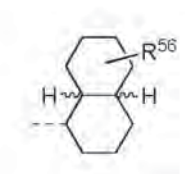
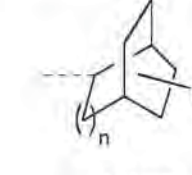
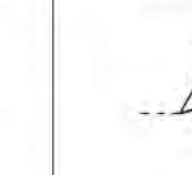
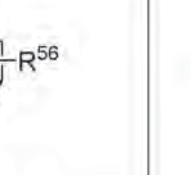
R^{50} is H; C_{1-24} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; or an *N*-protecting group;

- 20 R^{51} and R^{53} are independently defined as H; F; CF_3 ; C_{1-24} -alkyl; C_{2-24} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-12} -alkyl; heteroaryl- C_{1-12} -alkyl;
 $-(CR^{42}R^{43})_lOR^{36}$; $-(CR^{42}R^{43})_lNR^7R^{57}$; $-(CR^{42}R^{43})_lCOOR^{36}$; or $-(CR^{42}R^{43})_lCONR^7R^{57}$;

- 25 R^{52} is H; CF_3 ; C_{1-24} -alkyl; C_{2-24} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-12} -alkyl; heteroaryl- C_{1-12} -alkyl; $-OR^{36}$; $-NR^7R^{57}$; $-NR^7COR^{38}$;
 $-NR^7COOR^{36}$; $-NR^7SO_2R^{38}$; $-NR^7CONR^7R^{57}$; $-COOR^{36}$; $-CONR^7R^{57}$;
 $-C(=NR^7)NR^7R^{57}$; $-NR^7C(=NR^7)NR^7R^{57}$; or a group of one of the formulae



			
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	H107
			
H108	H109	H110	

R^{54} is H; F; CF_3 ; OCF_3 ; $OCHF_2$; NO_2 ; CN; C_{1-24} -alkyl; C_{2-24} -alkenyl; C_{2-10} -alkynyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-12} -alkyl; heteroaryl- C_{1-12} -alkyl; $-OR^{36}$; $-NR^7R^{57}$; $-NR^7COR^{38}$; $-NR^7SO_2R^{38}$; $-NR^7CONR^7R^{57}$; $-COR^{38}$; or $-SO_2R^{38}$;

5

R^{55} is H; CF_3 ; C_{1-24} -alkyl; C_{2-24} -alkenyl; C_{2-10} -alkynyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-12} -alkyl; heteroaryl- C_{1-12} -alkyl; $-COOR^{36}$; or $-CONR^7R^{45}$;

10

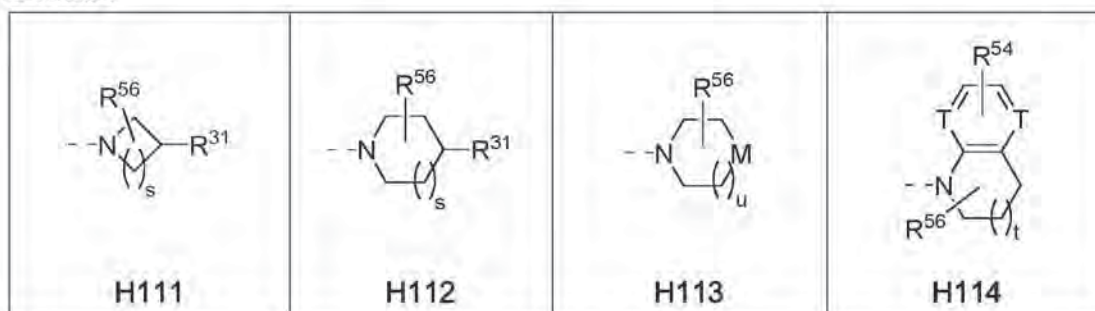
R^{56} is H; F; CF_3 ; C_{1-24} -alkyl; C_{2-24} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-12} -alkyl; heteroaryl- C_{1-12} -alkyl; $-(CR^{42}R^{43})_sOR^{36}$; $-(CR^{42}R^{43})_sNR^7R^{45}$; $-(CR^{42}R^{43})_qCOOR^{36}$; or $-(CR^{42}R^{43})_qCONR^7R^{45}$;

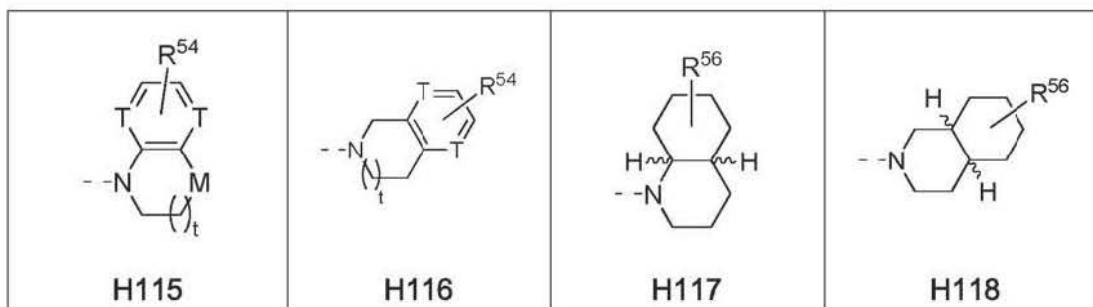
15

R^{57} is H; C_{1-24} -alkyl; C_{2-24} -alkenyl; cycloalkyl; aryl; aryl- C_{1-12} -alkyl; or an *N*-protecting group;

20

taken together (R^5 and R^6); (R^7 and R^{14}); (R^7 and R^{16}); (R^7 and R^{18}); (R^7 and R^{20}); (R^7 and R^{22}); (R^7 and R^{24}); (R^7 and R^{26}); (R^7 and R^{28}); (R^7 and R^{30}); (R^7 and R^{35}); (R^7 and R^{45}); (R^7 and R^{57}); (R^{13} and R^{13}); (R^{14} and R^{16}); (R^{14} and R^{18}); (R^{15} and R^{51}); (R^{19} and R^{51}); (R^{20} and R^{22}); (R^{20} and R^{24}); (R^{26} and R^{28}); (R^{26} and R^{30}); (R^{32} and R^{33}); (R^{42} and R^{43}); or (R^{51} and R^{53}) can form optionally substituted cycloalkyl or heterocycloalkyl moieties; and the structural elements $-NR^7R^{35}$; or $-NR^{44}R^{45}$ can form one of the groups of the formulae





T is CR⁵⁴ or N;

Q is O; S; or NR³⁵;

5 M is O; S; or NR⁷;

m is an integer of 0-8;

n is an integer of 0-1;

p is an integer of 0-4;

q is an integer of 0-4;

10 r is an integer of 2-4;

s is an integer of 1-4;

t is an integer of 0-2;

u is an integer of 1-2;

15 or a stereoisomer of such a compound; or a salt, solvate, clathrate, N-oxide, isotopically enriched or enantiomerically enriched version thereof, and

the Template A is selected from

20 A_{B1}-A_{C1}; A_{B1}-A_{C2}; A_{B1}-A_{C3}; A_{B1}-A_{C4}; A_{B1}-A_{C5}; A_{B1}-A_{C6}; A_{B1}-A_{C8};
A_{B1}-A_{C9}; A_{B1}-A_{C11}; A_{B1}-A_{C12}; A_{B1}-A_{C13}; A_{B1}-A_{C19}; A_{B1}-A_{C22}; A_{B1}-A_{C24};
A_{B1}-A_{C49}; A_{B1}-A_{C51}; A_{B2}-A_{C1}; A_{B2}-A_{C2}; A_{B2}-A_{C3}; A_{B2}-A_{C4}; A_{B2}-A_{C5}; A_{B2}-A_{C11};
A_{B2}-A_{C12}; A_{B2}-A_{C51}; A_{B3}-A_{C1}; A_{B3}-A_{C2}; A_{B3}-A_{C3}; A_{B3}-A_{C4}; A_{B3}-A_{C5}; A_{B3}-A_{C11};
A_{B3}-A_{C12}; A_{B4}-A_{C1}; A_{B4}-A_{C2}; A_{B4}-A_{C3}; A_{B4}-A_{C4}; A_{B4}-A_{C5}; A_{B4}-A_{C6}; A_{B4}-A_{C11};
25 A_{B4}-A_{C12}; A_{B4}-A_{C19}; A_{B4}-A_{C22}; A_{B4}-A_{C24}; A_{B4}-A_{C49}; A_{B4}-A_{C51}; A_{B4}-A_{C59};
A_{B5}-A_{C1}; A_{B5}-A_{C2}; A_{B5}-A_{C3}; A_{B5}-A_{C4}; A_{B5}-A_{C5}; A_{B5}-A_{C11}; A_{B5}-A_{C12}; A_{B5}-A_{C51};
A_{B5}-A_{C59}; A_{B6}-A_{C1}; A_{B6}-A_{C4}; A_{B6}-A_{C8}; A_{B6}-A_{C9}; A_{B6}-A_{C11}; A_{B6}-A_{C13}; A_{B6}-A_{C16};
A_{B6}-A_{C18}; A_{B6}-A_{C19}; A_{B6}-A_{C20}; A_{B6}-A_{C30}; A_{B6}-A_{C31}; A_{B6}-A_{C49}; A_{B6}-A_{C51};
A_{B9}-A_{C6}; A_{B9}-A_{C49}; A_{B10}-A_{C6}; A_{B11}-A_{C6}; A_{B12}-A_{C2}; A_{B12}-A_{C5}; A_{B12}-A_{C11};

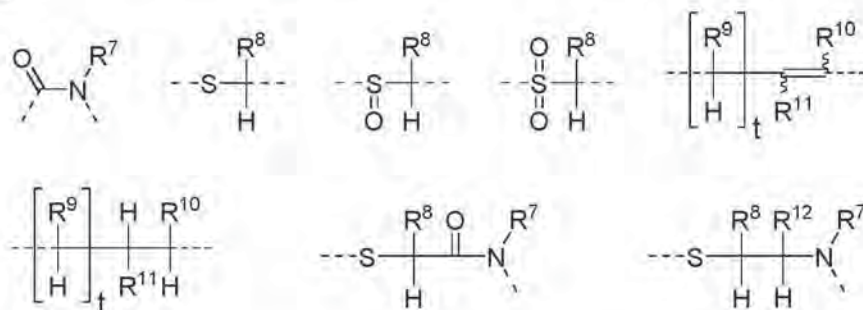
- A_B12-A_C12 ; A_B13-A_C2 ; A_B13-A_C5 ; A_B13-A_C11 ; A_B13-A_C12 ; A_B13-A_C5 ; A_B13-A_C11 ;
 A_B13-A_C12 ; A_B14-A_C49 ; A_B20-A_C2 ; A_B20-A_C6 ; A_B20-A_C49 ; A_B23-A_C4 ; A_B23-A_C49 ;
 A_B26-A_C2 ; A_B26-A_C5 ; A_B26-A_C11 ; A_B26-A_C12 ; A_B40-A_C2 ; A_B40-A_C5 ; A_B40-A_C11 ;
 A_B40-A_C12 ; A_B45-A_C49 ; A_B45-A_C52 ; A_B45-A_C57 ; A_B45-A_C58 ; A_B45-A_C65 ;
 5 A_B45-A_C66 ; A_B46-A_C57 ; A_B46-A_C58 ; A_B47-A_C58 ; A_B49-A_C49 ; A_B50-A_C57 ;
 A_B50-A_C58 ; A_B50-A_C61 ; A_B51-A_C49 ; A_B51-A_C61 ; A_B53-A_C2 ; A_B53-A_C5 ; A_B53-A_C11 ;
 A_B53-A_C12 ; A_B58-A_C2 ; A_B58-A_C5 ; A_B58-A_C11 ; A_B58-A_C12 ; A_B59-A_C2 ; A_B59-A_C5 ;
 A_B59-A_C11 ; A_B59-A_C12 ; or A_B59-A_C61 ;

- 10 the Modulator B is selected from
 $B1$; $B4$; $B5$; $B6$; $B7$; $B8$; $B9$ or $B10$;

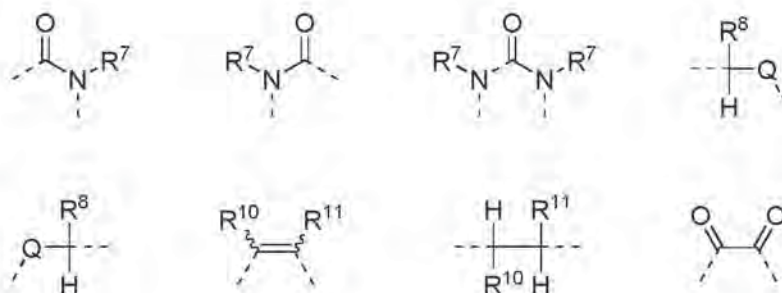
the Bridge C is selected from
 $C1$; $C2$; or $C3$.

15

and wherein the Y-Z connectivity representing a divalent radical is selected from the group of



- 20 V and W are representing independently a divalent radical selected from the group of



or a stereoisomer of such a compound; or a salt, solvate, clathrate, *N*-oxide, isotopically enriched or enantiomerically enriched version thereof.

2. A compound according to claim 1 or 2 wherein

R^1 and R^2 are independently defined as H; F; Cl; Br; I; CF_3 ; OCF_3 ; $OCHF_2$;
 5 NO_2 ; CN; C_{1-6} -alkyl; C_{2-6} -alkenyl; C_{2-6} -alkynyl; cycloalkyl; heterocycloalkyl; aryl- C_{1-6} -
 alkyl; heteroaryl- C_{1-6} -alkyl; $-(CR^{32}R^{33})_qOR^{34}$; $-(CR^{32}R^{33})_qSR^{34}$; $-(CR^{32}R^{33})_qNR^7R^{35}$;
 $-(CR^{32}R^{33})_qOCONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7COOR^{36}$; $-(CR^{32}R^{33})_qNR^7COR^{37}$;
 $-(CR^{32}R^{33})_qNR^7CONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7SO_2R^{38}$; $-(CR^{32}R^{33})_qNR^7SO_2NR^7R^{35}$;
 $-(CR^{32}R^{33})_qCOOR^{36}$; $-(CR^{32}R^{33})_qCONR^7R^{35}$; $-(CR^{32}R^{33})_qSO_2NR^7R^{35}$;
 10 $-(CR^{32}R^{33})_qCOR^{37}$; $-(CR^{32}R^{33})_qSO_2R^{38}$; $-(CR^{32}R^{33})_qR^{39}$; $-(CR^{32}R^{33})_qR^{40}$;
 $-(CR^{32}R^{33})_qR^{41}$; or $-(CR^{32}R^{33})_qR^{44}$;

R^3 and R^4 are independently defined as H; F; Cl; CF_3 ; OCF_3 ; $OCHF_2$; NO_2 ;
 CN; C_{1-6} -alkyl; cycloalkyl; C_{1-6} -alkoxy or aryloxy;

15

R^5 is H; CF_3 ; C_{1-6} -alkyl; or cycloalkyl;

R^6 is H; CF_3 ; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl;
 heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; $-(CR^{32}R^{33})_qOR^{34}$; $-(CR^{32}R^{33})_qSR^{34}$;
 20 $-(CR^{32}R^{33})_qNR^7R^{35}$; $-(CR^{32}R^{33})_qOCONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7COOR^{36}$;
 $-(CR^{32}R^{33})_qNR^7COR^{37}$; $-(CR^{32}R^{33})_qNR^7CONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7SO_2R^{38}$;
 $-(CR^{32}R^{33})_qNR^7SO_2NR^7R^{35}$; $-(CR^{32}R^{33})_qCOOR^{36}$; $-(CR^{32}R^{33})_qCONR^7R^{35}$;
 $-(CR^{32}R^{33})_qSO_2NR^7R^{35}$; $-(CR^{32}R^{33})_qCOR^{37}$; $-(CR^{32}R^{33})_qSO_2R^{38}$; $-(CR^{32}R^{33})_qR^{39}$;
 $-(CR^{32}R^{33})_sR^{40}$; $-(CR^{32}R^{33})_qR^{41}$; or $-(CR^{32}R^{33})_qR^{44}$;

25

R^7 is H; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl;
 aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; or an *N*-protecting group;

R^8 and R^9 are independently defined as H; CF_3 ; C_{1-6} -alkyl; cycloalkyl;
 30 heterocycloalkyl;

R^{10} , R^{11} and R^{12} are independently defined as H; C_{1-6} -alkyl; or cycloalkyl;

R^{13} is C_{1-6} -alkyl;

R^{14} , R^{20} and R^{26} are independently defined as H; F; CF_3 ; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; $-(CR^{32}R^{33})_qOR^{34}$; $-(CR^{32}R^{33})_qSR^{34}$; $-(CR^{32}R^{33})_qNR^7R^{35}$;

$-(CR^{32}R^{33})_qOCONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7COOR^{36}$; $-(CR^{32}R^{33})_qNR^7COR^{37}$;

5 $-(CR^{32}R^{33})_qNR^7CONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7SO_2R^{38}$; $-(CR^{32}R^{33})_qNR^7SO_2NR^7R^{35}$;

$-(CR^{32}R^{33})_qCOOR^{36}$; $-(CR^{32}R^{33})_qCONR^7R^{35}$; $-(CR^{32}R^{33})_qSO_2NR^7R^{35}$;

$-(CR^{32}R^{33})_qCOR^{37}$; $-(CR^{32}R^{33})_qSO_2R^{38}$; $-(CR^{32}R^{33})_qR^{39}$; $-(CR^{32}R^{33})_sR^{40}$;

$-(CR^{32}R^{33})_qR^{41}$; or $-(CR^{32}R^{33})_qR^{44}$;

10 R^{15} , R^{17} , R^{19} , R^{21} , R^{23} , R^{25} , R^{27} , R^{29} and R^{31} are independently defined as H; or C_{1-6} -alkyl;

R^{16} , R^{22} and R^{28} are independently defined as H; CF_3 ; or C_{1-6} -alkyl;

15 R^{18} , R^{24} and R^{30} are independently defined as H; F; CF_3 ; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl;

$-(CR^{32}R^{33})_qOR^{34}$; $-(CR^{32}R^{33})_qNR^7R^{35}$; $-(CR^{32}R^{33})_qOCONR^7R^{35}$;

$-(CR^{32}R^{33})_qNR^7COOR^{36}$; $-(CR^{32}R^{33})_qNR^7COR^{37}$; $-(CR^{32}R^{33})_qNR^7CONR^7R^{35}$;

$-(CR^{32}R^{33})_qNR^7SO_2R^{38}$; $-(CR^{32}R^{33})_qNR^7SO_2NR^7R^{35}$; $-(CR^{32}R^{33})_qCOOR^{36}$;

20 $-(CR^{32}R^{33})_qCONR^7R^{35}$; $-(CR^{32}R^{33})_qSO_2NR^7R^{35}$; $-(CR^{32}R^{33})_qCOR^{37}$; or $-(CR^{32}R^{33})_qR^{44}$;

R^{32} is H; F; CF_3 ; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; $-(CR^{42}R^{51})_qOR^{45}$; $-(CR^{42}R^{51})_qSR^{45}$;

$-(CR^{42}R^{51})_qNR^7R^{45}$; $-(CR^{42}R^{51})_qOCONR^7R^{45}$; $-(CR^{42}R^{51})_qNR^7COOR^{36}$;

25 $-(CR^{42}R^{51})_qNR^7COR^{38}$; $-(CR^{42}R^{51})_qNR^7CONR^7R^{45}$; $-(CR^{42}R^{51})_qNR^7SO_2R^{38}$;

$-(CR^{42}R^{51})_qNR^7SO_2NR^7R^{45}$; $-(CR^{42}R^{51})_qCOOR^{36}$; $-(CR^{42}R^{51})_qCONR^7R^{45}$;

$-(CR^{42}R^{51})_qSO_2NR^7R^{45}$; $-(CR^{42}R^{51})_qCOR^{38}$; $-(CR^{42}R^{51})_qSO_2R^{38}$; $-(CR^{42}R^{51})_qR^{39}$;

$-(CR^{42}R^{51})_sR^{40}$; $-(CR^{42}R^{51})_qR^{41}$; or $-(CR^{42}R^{51})_qR^{44}$;

30 R^{33} is H; or C_{1-6} -alkyl;

R^{34} is H; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; $-(CR^{42}R^{51})_rOR^{45}$; $-(CR^{42}R^{51})_rNR^7R^{45}$; $-(CR^{42}R^{51})_rOCONR^7R^{35}$;

$-(CR^{42}R^{51})_rNR^7COOR^{36}$; $-(CR^{42}R^{51})_rNR^7COR^{38}$; $-(CR^{42}R^{51})_rNR^7CONR^7R^{45}$;

35 $-(CR^{42}R^{51})_rNR^7SO_2R^{38}$; $-(CR^{42}R^{51})_qCOOR^{36}$; $-(CR^{42}R^{51})_qCONR^7R^{45}$;

$-(\text{CR}^{42}\text{R}^{51})_q\text{SO}_2\text{NR}^7\text{R}^{45}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{COR}^{38}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{SO}_2\text{R}^{38}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{R}^{39}$;
 $-(\text{CR}^{42}\text{R}^{51})_s\text{R}^{40}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{R}^{41}$; or $-(\text{CR}^{42}\text{R}^{51})_q\text{R}^{44}$;

R^{35} is H; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl;

- 5 aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; an *N*-protecting group; $-(\text{CR}^{32}\text{R}^{33})_r\text{OR}^{45}$;
 $-(\text{CR}^{32}\text{R}^{33})_r\text{NR}^7\text{R}^{45}$; $-(\text{CR}^{32}\text{R}^{33})_r\text{OCONR}^7\text{R}^{45}$; $-(\text{CR}^{32}\text{R}^{33})_r\text{NR}^7\text{COOR}^{36}$;
 $-(\text{CR}^{32}\text{R}^{33})_r\text{NR}^7\text{COR}^{37}$; $-(\text{CR}^{32}\text{R}^{33})_r\text{NR}^7\text{CONR}^7\text{R}^{45}$; $-(\text{CR}^{32}\text{R}^{33})_r\text{NR}^7\text{SO}_2\text{R}^{38}$;
 $-(\text{CR}^{32}\text{R}^{33})_r\text{NR}^7\text{SO}_2\text{NR}^7\text{R}^{45}$; $-(\text{CR}^{32}\text{R}^{33})_q\text{COOR}^{36}$; $-(\text{CR}^{32}\text{R}^{33})_q\text{CONR}^7\text{R}^{45}$;
 $-(\text{CR}^{32}\text{R}^{33})_q\text{COR}^{37}$; $-(\text{CR}^{32}\text{R}^{33})_q\text{SO}_2\text{R}^{38}$; $-(\text{CR}^{32}\text{R}^{33})_q\text{SO}_2\text{NR}^7\text{R}^{50}$; $-(\text{CR}^{32}\text{R}^{33})_q\text{R}^{39}$;
10 $-(\text{CR}^{32}\text{R}^{33})_s\text{R}^{40}$; $-(\text{CR}^{32}\text{R}^{33})_q\text{R}^{41}$; or $-(\text{CR}^{32}\text{R}^{33})_q\text{R}^{44}$;

R^{36} is H; C_{1-6} -alkyl; cycloalkyl; aryl; aryl- C_{1-6} -alkyl; or an *O/S*-protecting group;

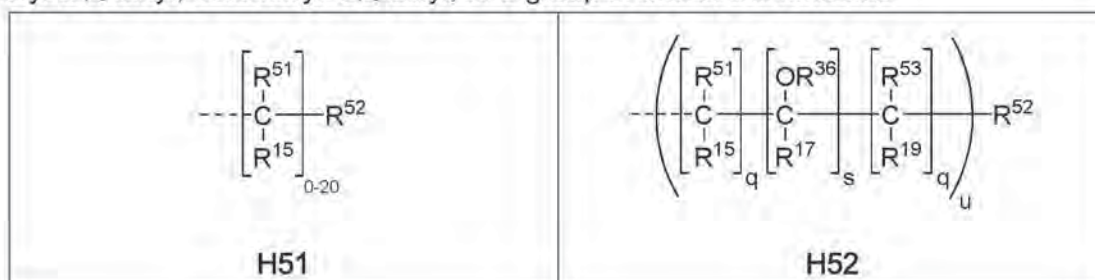
R^{37} is C_{1-6} -alkyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl;

- 15 heteroaryl- C_{1-6} -alkyl; $-(\text{CR}^{42}\text{R}^{51})_q\text{OR}^{45}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{SR}^{45}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{NR}^7\text{R}^{45}$;
 $-(\text{CR}^{42}\text{R}^{51})_s\text{OCONR}^7\text{R}^{45}$; $-(\text{CR}^{42}\text{R}^{51})_s\text{NR}^7\text{COOR}^{36}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{NR}^7\text{COR}^{44}$;
 $-(\text{CR}^{42}\text{R}^{51})_s\text{NR}^7\text{CONR}^7\text{R}^{45}$; $-(\text{CR}^{42}\text{R}^{51})_s\text{NR}^7\text{SO}_2\text{R}^{38}$; $-(\text{CR}^{42}\text{R}^{51})_s\text{NR}^7\text{SO}_2\text{NR}^7\text{R}^{45}$;
 $-(\text{CR}^{42}\text{R}^{51})_q\text{COOR}^{36}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{CONR}^7\text{R}^{45}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{SO}_2\text{NR}^7\text{R}^{45}$;
 $-(\text{CR}^{42}\text{R}^{51})_i\text{COR}^{38}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{SO}_2\text{R}^{38}$; $-(\text{CR}^{42}\text{R}^{51})_i\text{R}^{39}$; $-(\text{CR}^{42}\text{R}^{51})_u\text{R}^{40}$;
20 $-(\text{CR}^{42}\text{R}^{51})_i\text{R}^{41}$; or $-(\text{CR}^{42}\text{R}^{51})_i\text{R}^{44}$;

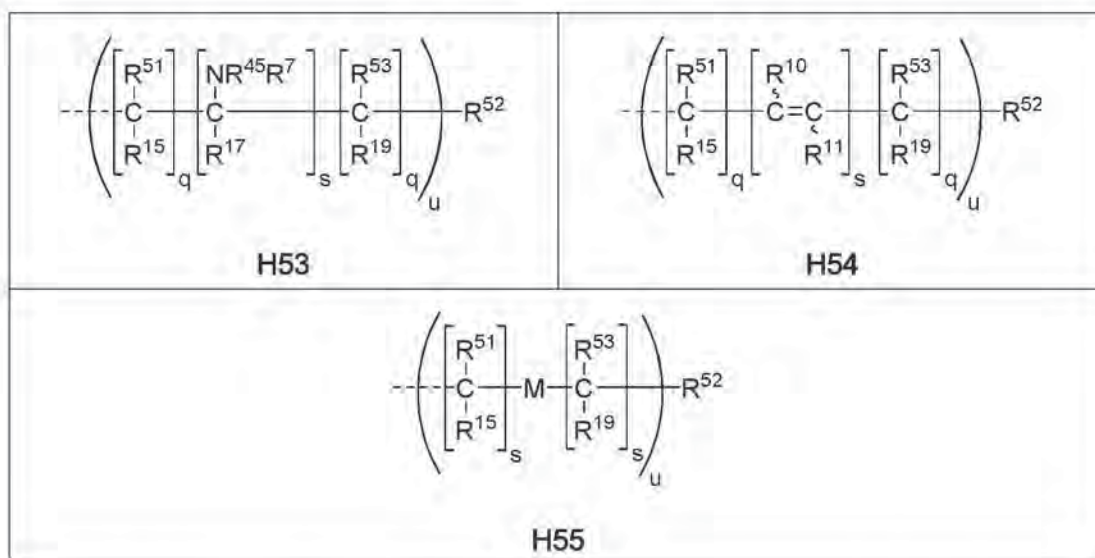
R^{38} is C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl; or heteroaryl- C_{1-6} -alkyl;

- 25 R^{42} and R^{43} are independently defined as H; F; CF_3 ; C_{1-6} -alkyl; C_{2-6} -alkenyl;
cycloalkyl; heterocycloalkyl; aryl- C_{1-6} -alkyl; or heteroaryl- C_{1-6} -alkyl;

R^{44} is H; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl;
aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; or a group of one of the formulae



373



- R^{45} is H; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; an *N*-protecting group; $-(CR^{42}R^{51})_rOR^{36}$; $-(CR^{42}R^{51})_rNR^7R^{57}$; $-(CR^{42}R^{51})_rOCONR^7R^{57}$; $-(CR^{42}R^{51})_rNR^7CONR^7R^{57}$;
- 5 $-(CR^{42}R^{51})_rNR^7COR^{38}$; $-(CR^{42}R^{51})_rNR^7SO_2R^{38}$; $-(CR^{42}R^{51})_rNR^7SO_2NR^7R^{57}$; $-(CR^{42}R^{51})_qCOOR^{36}$; $-(CR^{42}R^{51})_qCOR^{38}$; $-(CR^{42}R^{51})_qSO_2R^{33}$; $-(CR^{42}R^{51})_qR^{39}$; $-(CR^{42}R^{51})_sR^{40}$; $-(CR^{42}R^{51})_qR^{41}$; or $-(CR^{42}R^{51})_sR^{44}$;

- R^{46} is H; F; Cl; CF_3 ; OCF_3 ; $OCHF_2$; NO_2 ; CN; C_{1-6} -alkyl; C_{2-6} -alkenyl; C_{2-6} -alkynyl; cycloalkyl; heterocycloalkyl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl;
- 10 $-(CR^{42}R^{51})_qOR^{36}$; $-(CR^{42}R^{51})_qSR^{36}$; $-(CR^{42}R^{51})_qNR^7R^{57}$; $-(CR^{42}R^{51})_qOCONR^7R^{57}$; $-(CR^{42}R^{51})_qNR^{44}COOR^{36}$; $-(CR^{42}R^{51})_qNR^7COR^{38}$; $-(CR^{42}R^{51})_qNR^7CONR^7R^{45}$; $-(CR^{42}R^{51})_qNR^7SO_2R^{38}$; $-(CR^{42}R^{51})_qNR^7SO_2NR^7R^{45}$; $-(CR^{42}R^{51})_qCOOR^{36}$; $-(CR^{42}R^{51})_qCONR^7R^{45}$; $-(CR^{42}R^{51})_qSO_2NR^7R^{45}$; $-(CR^{42}R^{51})_qCOR^{38}$;
- 15 $-(CR^{42}R^{51})_qSO_2R^{38}$; or $-(CR^{42}R^{51})_qR^{44}$;

R^{47} is H; C_{1-6} -alkyl; C_{2-6} -alkenyl; C_{2-6} -alkynyl; cycloalkyl; heterocycloalkyl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; or $-NR^7R^{45}$;

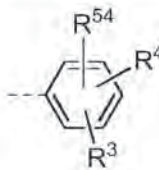
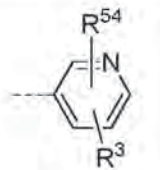
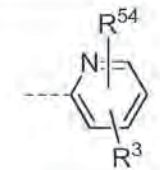
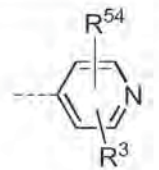
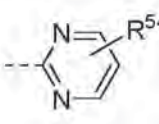
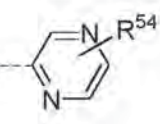
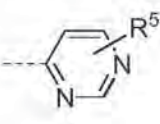
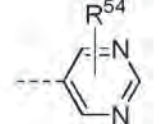
- R^{48} is H; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; an *N*-protecting group; $-(CR^{42}R^{51})_rOR^{45}$;
- 20 $-(CR^{42}R^{51})_rSR^{45}$; $-(CR^{42}R^{51})_rNR^7R^{45}$; $-(CR^{42}R^{51})_rOCONR^7R^{45}$; $-(CR^{42}R^{51})_rNR^7COOR^{36}$; $-(CR^{42}R^{51})_rNR^7COR^{38}$; $-(CR^{42}R^{51})_rNR^7CONR^7R^{45}$; $-(CR^{42}R^{51})_rNR^7SO_2R^{38}$; $-(CR^{42}R^{51})_rNR^7SO_2NR^7R^{45}$; $-(CR^{42}R^{51})_qCOOR^{36}$;

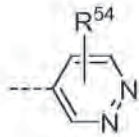
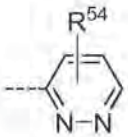
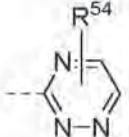
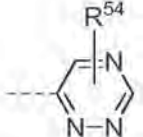
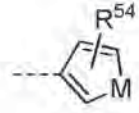
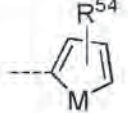
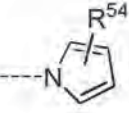
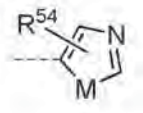
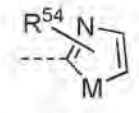
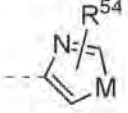
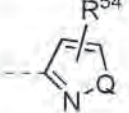
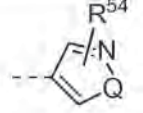
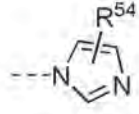
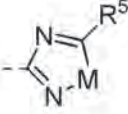
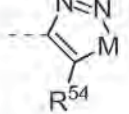
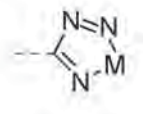
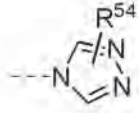
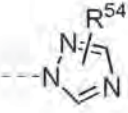
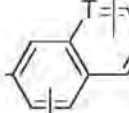
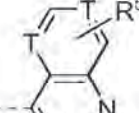
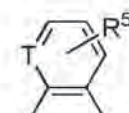
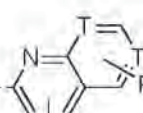
$-(\text{CR}^{42}\text{R}^{51})_q\text{CONR}^7\text{R}^{45}$; $-(\text{CR}^{42}\text{R}^{51})_r\text{SO}_2\text{NR}^7\text{R}^{45}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{COR}^{38}$;
 $-(\text{CR}^{42}\text{R}^{51})_q\text{SO}_2\text{R}^{38}$; or $-(\text{CR}^{42}\text{R}^{51})_s\text{R}^{44}$;

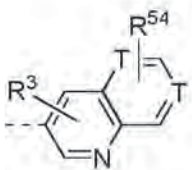
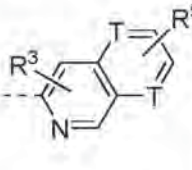
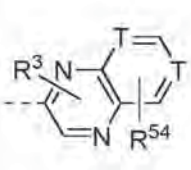
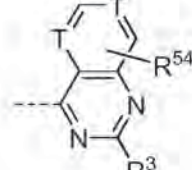
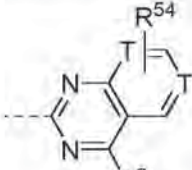
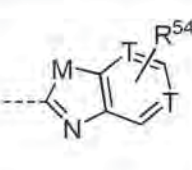
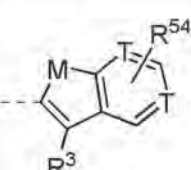
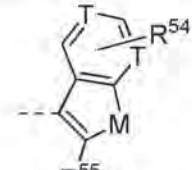
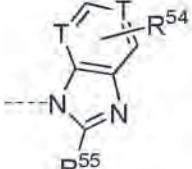
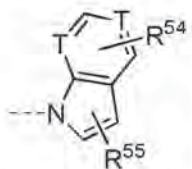
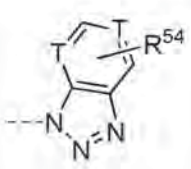
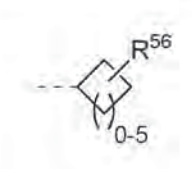
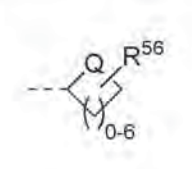
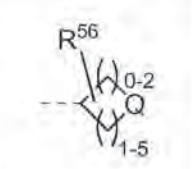
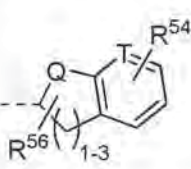
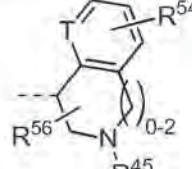
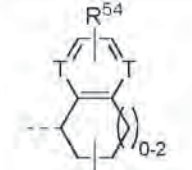
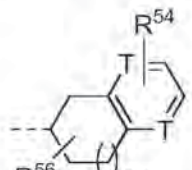
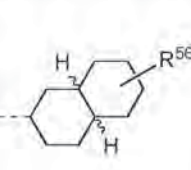
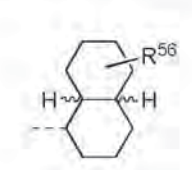
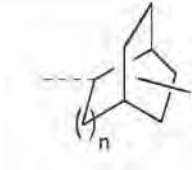
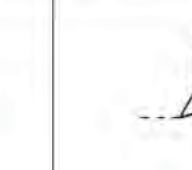
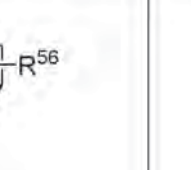
- R^{49} is H; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl;
 5 aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; $-(\text{CR}^{42}\text{R}^{51})_q\text{OR}^{36}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{SR}^{36}$;
 $-(\text{CR}^{42}\text{R}^{51})_q\text{NR}^7\text{R}^{45}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{NR}^7\text{COOR}^{36}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{NR}^7\text{COR}^{38}$;
 $-(\text{CR}^{42}\text{R}^{51})_q\text{NR}^7\text{SO}_2\text{R}^{38}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{NR}^7\text{CONR}^7\text{R}^{45}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{COOR}^{36}$;
 $-(\text{CR}^{42}\text{R}^{51})_q\text{CONR}^7\text{R}^{45}$; $-(\text{CR}^{42}\text{R}^{51})_q\text{COR}^{38}$; or $-(\text{CR}^{42}\text{R}^{51})_q\text{R}^{44}$;
- 10 R^{50} is H; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl;
 aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; or an *N*-protecting group;

- R^{51} and R^{53} are independently defined as H; F; CF_3 ; C_{1-6} -alkyl; C_{2-6} -alkenyl;
 cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl;
 15 $-(\text{CR}^{42}\text{R}^{43})_l\text{OR}^{36}$; $-(\text{CR}^{42}\text{R}^{43})_l\text{NR}^7\text{R}^{57}$; $-(\text{CR}^{42}\text{R}^{43})_l\text{COOR}^{36}$; or $-(\text{CR}^{42}\text{R}^{43})_l\text{CONR}^7\text{R}^{57}$;

- R^{52} is H; CF_3 ; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl;
 heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; $-\text{OR}^{36}$; $-\text{NR}^7\text{R}^{57}$; $-\text{NR}^7\text{COR}^{38}$;
 $-\text{NR}^7\text{COOR}^{36}$; $-\text{NR}^7\text{SO}_2\text{R}^{38}$; $-\text{NR}^7\text{CONR}^7\text{R}^{57}$; $-\text{COOR}^{36}$; $-\text{CONR}^7\text{R}^{57}$;
 20 $-\text{C}(=\text{NR}^7)\text{NR}^7\text{R}^{57}$; $-\text{NR}^7\text{C}(=\text{NR}^7)\text{NR}^7\text{R}^{57}$; or a group of one of the formulae

 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	H107
			
H108	H109	H110	

R⁵⁴ is H; F; CF₃; OCF₃; OCHF₂; NO₂; CN; C₁₋₆-alkyl; C₂₋₆-alkenyl; C₂₋₆-alkynyl; cycloalkyl; heterocycloalkyl; aryl-C₁₋₆-alkyl; heteroaryl-C₁₋₆-alkyl; -OR³⁶; -NR⁷R⁵⁷; -NR⁷COR³⁸; -NR⁷SO₂R³⁸; -NR⁷CONR⁷R⁵⁷; -COR³⁸; or -SO₂R³⁸;

- 5 R⁵⁵ is H; CF₃; C₁₋₆-alkyl; C₂₋₆-alkenyl; C₂₋₆-alkynyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl-C₁₋₆-alkyl; heteroaryl-C₁₋₆-alkyl; -COOR³⁶; or -CONR⁷R⁴⁵;

- R⁵⁶ is H; F; CF₃; C₁₋₆-alkyl; C₂₋₆-alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl-C₁₋₆-alkyl; heteroaryl-C₁₋₆-alkyl; -(CR⁴²R⁴³)_sOR³⁶; -(CR⁴²R⁴³)_sNR⁷R⁴⁵;
10 -(CR⁴²R⁴³)_qCOOR³⁶; or -(CR⁴²R⁴³)_qCONR⁷R⁴⁵;

R⁵⁷ is H; C₁₋₆-alkyl; C₂₋₆-alkenyl; cycloalkyl; aryl-C₁₋₆-alkyl; or an *N*-protecting group;

- 15 or a stereoisomer of such a compound; or a salt, solvate, clathrate, *N*-oxide, isotopically enriched or enantiomerically enriched version thereof.

3. A compound according to claim 1, 2 or 3 wherein the **Template A** is selected from

- 20 A_{B1}-A_{C1}; A_{B1}-A_{C4}; A_{B1}-A_{C6}; A_{B1}-A_{C8}; A_{B1}-A_{C9}; A_{B1}-A_{C11}; A_{B1}-A_{C13}; A_{B1}-A_{C19}; A_{B1}-A_{C22}; A_{B1}-A_{C24}; A_{B1}-A_{C49}; A_{B1}-A_{C51}; A_{B2}-A_{C4}; A_{B2}-A_{C51}; A_{B4}-A_{C1}; A_{B4}-A_{C4}; A_{B4}-A_{C6}; A_{B4}-A_{C19}; A_{B4}-A_{C22}; A_{B4}-A_{C24}; A_{B4}-A_{C49}; A_{B4}-A_{C51}; A_{B4}-A_{C59}; A_{B5}-A_{C51}; A_{B5}-A_{C59}; A_{B6}-A_{C1}; A_{B6}-A_{C4}; A_{B6}-A_{C8}; A_{B6}-A_{C9}; A_{B6}-A_{C11}; A_{B6}-A_{C13}; A_{B6}-A_{C16}; A_{B6}-A_{C18}; A_{B6}-A_{C19}; A_{B6}-A_{C20}; A_{B6}-A_{C30};
25 A_{B6}-A_{C31}; A_{B6}-A_{C49}; A_{B6}-A_{C51}; A_{B9}-A_{C6}; A_{B9}-A_{C49}; A_{B14}-A_{C49}; A_{B20}-A_{C6}; A_{B20}-A_{C49}; A_{B23}-A_{C4}; A_{B23}-A_{C49}; A_{B45}-A_{C49}; A_{B45}-A_{C52}; A_{B45}-A_{C57}; A_{B45}-A_{C58}; A_{B45}-A_{C65}; A_{B45}-A_{C66}; A_{B46}-A_{C57}; A_{B46}-A_{C58}; A_{B49}-A_{C49}; A_{B50}-A_{C57}; A_{B50}-A_{C58}; A_{B50}-A_{C61}; A_{B51}-A_{C49}; A_{B51}-A_{C61}; or A_{B59}-A_{C61};

- 30 the **Modulator B** is selected from

B1; B4; B5; B6; or B7;

and wherein

- R^1 and R^2 are independently defined as H; F; Cl; Br; I; CF_3 ; OCF_3 ; $OCHF_2$; NO_2 ; CN; C_{1-6} -alkyl; C_{2-6} -alkenyl; C_{2-6} -alkynyl; cycloalkyl; heterocycloalkyl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; $-(CR^{32}R^{33})_qOR^{34}$; $-(CR^{32}R^{33})_qSR^{34}$; $-(CR^{32}R^{33})_qNR^7R^{35}$; $-(CR^{32}R^{33})_qOCONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7COOR^{36}$; $-(CR^{32}R^{33})_qNR^7COR^{37}$;
- 5 $-(CR^{32}R^{33})_qNR^7CONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7SO_2R^{38}$; $-(CR^{32}R^{33})_qCOOR^{36}$; $-(CR^{32}R^{33})_qCONR^7R^{35}$; $-(CR^{32}R^{33})_qSO_2NR^7R^{35}$; $-(CR^{32}R^{33})_qCOR^{37}$; $-(CR^{32}R^{33})_qR^{39}$; $-(CR^{32}R^{33})_qR^{40}$; $-(CR^{32}R^{33})_qR^{41}$; or $-(CR^{32}R^{33})_qR^{44}$;

- R^3 and R^4 are independently defined as H; F; Cl; CF_3 ; OCF_3 ; $OCHF_2$; NO_2 ;
- 10 CN; C_{1-6} -alkyl; or C_{1-6} -alkoxy;

R^5 is H; CF_3 ; or C_{1-6} -alkyl;

- R^6 is H; CF_3 ; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl;
- 15 heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; $-(CR^{32}R^{33})_qOR^{34}$; $-(CR^{32}R^{33})_qSR^{34}$; $-(CR^{32}R^{33})_qNR^7R^{35}$; $-(CR^{32}R^{33})_qOCONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7COOR^{36}$; $-(CR^{32}R^{33})_qNR^7COR^{37}$; $-(CR^{32}R^{33})_qNR^7CONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7SO_2R^{38}$; $-(CR^{32}R^{33})_qCOOR^{36}$; $-(CR^{32}R^{33})_qCONR^7R^{35}$; $-(CR^{32}R^{33})_qSO_2NR^7R^{35}$; $-(CR^{32}R^{33})_qCOR^{37}$; $-(CR^{32}R^{33})_qR^{39}$; $-(CR^{32}R^{33})_sR^{40}$; $-(CR^{32}R^{33})_qR^{41}$; or
- 20 $-(CR^{32}R^{33})_qR^{44}$;

- R^{14} , R^{20} and R^{26} are independently defined as H; F; CF_3 ; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; $-(CR^{32}R^{33})_qOR^{34}$; $-(CR^{32}R^{33})_qSR^{34}$; $-(CR^{32}R^{33})_qNR^7R^{35}$;
- 25 $-(CR^{32}R^{33})_qOCONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7COOR^{36}$; $-(CR^{32}R^{33})_qNR^7COR^{37}$; $-(CR^{32}R^{33})_qNR^7CONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7SO_2R^{38}$; $-(CR^{32}R^{33})_qCOOR^{36}$; $-(CR^{32}R^{33})_qCONR^7R^{35}$; $-(CR^{32}R^{33})_qSO_2NR^7R^{35}$; $-(CR^{32}R^{33})_qCOR^{37}$; $-(CR^{32}R^{33})_qR^{39}$; $-(CR^{32}R^{33})_sR^{40}$; $-(CR^{32}R^{33})_qR^{41}$; or $-(CR^{32}R^{33})_qR^{44}$;

- R^{18} , R^{24} and R^{30} are independently defined as H; F; CF_3 ; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl;
- 30 $-(CR^{32}R^{33})_qOR^{34}$; $-(CR^{32}R^{33})_qNR^7R^{35}$; $-(CR^{32}R^{33})_qOCONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7COOR^{36}$; $-(CR^{32}R^{33})_qNR^7COR^{37}$; $-(CR^{32}R^{33})_qNR^7CONR^7R^{35}$; $-(CR^{32}R^{33})_qNR^7SO_2R^{38}$; $-(CR^{32}R^{33})_qCOOR^{36}$; $-(CR^{32}R^{33})_qCONR^7R^{35}$;
- 35 $-(CR^{32}R^{33})_qCOR^{37}$; or $-(CR^{32}R^{33})_qR^{44}$;

- R^{32} is H; F; CF_3 ; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; $-(CR^{42}R^{43})_qOR^{45}$; $-(CR^{42}R^{43})_qSR^{45}$; $-(CR^{42}R^{43})_qNR^7R^{45}$; $-(CR^{42}R^{43})_qNR^7COOR^{36}$; $-(CR^{42}R^{43})_qNR^7COR^{38}$; $-(CR^{42}R^{43})_qCOOR^{36}$; $-(CR^{42}R^{43})_qCONR^7R^{45}$; $-(CR^{42}R^{43})_qCOR^{38}$; $-(CR^{42}R^{43})_qR^{39}$;
 5 $-(CR^{42}R^{43})_sR^{40}$; $-(CR^{42}R^{43})_qR^{41}$; or $-(CR^{42}R^{43})_qR^{44}$;

R^{33} is H; or C_{1-6} -alkyl;

- R^{34} is H; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl;
 10 $-(CR^{42}R^{43})_rOR^{45}$; $-(CR^{42}R^{43})_rNR^7R^{45}$; $-(CR^{42}R^{43})_rOCONR^7R^{35}$;
 $-(CR^{42}R^{43})_rNR^7COOR^{36}$; $-(CR^{42}R^{43})_rNR^7COR^{38}$; $-(CR^{42}R^{43})_rNR^7CONR^7R^{45}$;
 $-(CR^{42}R^{43})_rNR^7SO_2R^{38}$; $-(CR^{42}R^{43})_qCOOR^{36}$; $-(CR^{42}R^{43})_qCONR^7R^{45}$;
 $-(CR^{42}R^{43})_qCOR^{38}$; $-(CR^{42}R^{43})_qR^{39}$; $-(CR^{42}R^{43})_sR^{40}$; $-(CR^{42}R^{43})_qR^{41}$; or
 $-(CR^{42}R^{43})_qR^{44}$;

15

- R^{35} is H; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; an *N*-protecting group; $-(CR^{32}R^{33})_rOR^{45}$;
 $-(CR^{32}R^{33})_rNR^7R^{45}$; $-(CR^{32}R^{33})_rOCONR^7R^{45}$; $-(CR^{32}R^{33})_rNR^7COOR^{36}$;
 $-(CR^{32}R^{33})_rNR^7COR^{37}$; $-(CR^{32}R^{33})_rNR^7CONR^7R^{50}$; $-(CR^{32}R^{33})_rNR^7SO_2R^{38}$;
 20 $-(CR^{32}R^{33})_qCOOR^{36}$; $-(CR^{32}R^{33})_qCONR^7R^{45}$; $-(CR^{32}R^{33})_qCOR^{38}$; $-(CR^{32}R^{33})_qR^{39}$;
 $-(CR^{32}R^{33})_sR^{40}$; $-(CR^{32}R^{33})_qR^{41}$; or $-(CR^{32}R^{33})_qR^{44}$;

R^{36} is H; C_{1-6} -alkyl; cycloalkyl; aryl; aryl- C_{1-6} -alkyl; or an *O/S*-protecting group;

- R^{37} is C_{1-6} -alkyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; $-(CR^{42}R^{43})_qOR^{45}$; $-(CR^{42}R^{43})_qSR^{45}$; $-(CR^{42}R^{43})_qNR^7R^{45}$;
 $-(CR^{42}R^{43})_sOCONR^7R^{45}$; $-(CR^{42}R^{43})_sNR^7COOR^{36}$; $-(CR^{42}R^{43})_sNR^7COR^{44}$;
 $-(CR^{42}R^{43})_sNR^7CONR^7R^{45}$; $-(CR^{42}R^{43})_sNR^7SO_2R^{38}$; $-(CR^{42}R^{43})_qCOOR^{36}$;
 $-(CR^{42}R^{43})_qCONR^7R^{45}$; $-(CR^{42}R^{43})_lCOR^{38}$; $-(CR^{42}R^{43})_lR^{39}$; $-(CR^{42}R^{43})_uR^{40}$;
 30 $-(CR^{42}R^{43})_lR^{41}$; or $-(CR^{42}R^{43})_lR^{44}$;

- R^{45} is H; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; an *N*-protecting group; $-(CR^{42}R^{43})_rOR^{36}$;
 $-(CR^{42}R^{43})_rNR^7R^{57}$; $-(CR^{42}R^{43})_rOCONR^7R^{57}$; $-(CR^{42}R^{43})_rNR^7CONR^7R^{57}$;
 35 $-(CR^{42}R^{43})_rNR^7COR^{38}$; $-(CR^{42}R^{43})_rNR^7SO_2R^{38}$; $-(CR^{42}R^{43})_qCOOR^{36}$;

$-(\text{CR}^{42}\text{R}^{43})_q\text{COR}^{38}$; $-(\text{CR}^{42}\text{R}^{43})_q\text{R}^{39}$; $-(\text{CR}^{42}\text{R}^{43})_s\text{R}^{40}$; $-(\text{CR}^{42}\text{R}^{43})_q\text{R}^{41}$; or
 $-(\text{CR}^{42}\text{R}^{43})_s\text{R}^{44}$;

- 5 R^{46} is H; F; Cl; CF_3 ; OCF_3 ; OCHF_2 ; NO_2 ; CN; C_{1-6} -alkyl; C_{2-6} -alkenyl; C_{2-6} -alkynyl; cycloalkyl; heterocycloalkyl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl;
 $-(\text{CR}^{42}\text{R}^{43})_q\text{OR}^{36}$; $-(\text{CR}^{42}\text{R}^{43})_q\text{NR}^{7}\text{R}^{57}$; $-(\text{CR}^{42}\text{R}^{43})_q\text{NR}^{7}\text{COR}^{38}$; $-(\text{CR}^{42}\text{R}^{43})_q\text{COOR}^{36}$;
 $-(\text{CR}^{42}\text{R}^{43})_q\text{CONR}^{7}\text{R}^{45}$; $-(\text{CR}^{42}\text{R}^{43})_q\text{SO}_2\text{NR}^{7}\text{R}^{45}$; $-(\text{CR}^{42}\text{R}^{43})_q\text{COR}^{38}$; or $-(\text{CR}^{42}\text{R}^{43})_q\text{R}^{44}$;

- 10 R^{47} is H; C_{1-6} -alkyl; C_{2-6} -alkenyl; C_{2-6} -alkynyl; cycloalkyl; heterocycloalkyl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; or $-\text{NR}^{7}\text{R}^{45}$.

- R^{48} is H; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl;
 aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; an *N*-protecting group; $-(\text{CR}^{42}\text{R}^{43})_r\text{OR}^{45}$;
 $-(\text{CR}^{42}\text{R}^{43})_r\text{SR}^{45}$; $-(\text{CR}^{42}\text{R}^{43})_r\text{NR}^{7}\text{R}^{45}$; $-(\text{CR}^{42}\text{R}^{43})_r\text{CONR}^{7}\text{R}^{45}$;
 15 $-(\text{CR}^{42}\text{R}^{43})_r\text{NR}^{7}\text{COOR}^{36}$; $-(\text{CR}^{42}\text{R}^{43})_r\text{NR}^{7}\text{COR}^{38}$; $-(\text{CR}^{42}\text{R}^{43})_r\text{NR}^{7}\text{CONR}^{7}\text{R}^{45}$;
 $-(\text{CR}^{42}\text{R}^{43})_r\text{NR}^{7}\text{SO}_2\text{R}^{38}$; $-(\text{CR}^{42}\text{R}^{43})_q\text{COOR}^{36}$; $-(\text{CR}^{42}\text{R}^{43})_q\text{CONR}^{7}\text{R}^{45}$;
 $-(\text{CR}^{42}\text{R}^{43})_q\text{COR}^{38}$; or $-(\text{CR}^{42}\text{R}^{43})_s\text{R}^{44}$;

- R^{49} is H; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl;
 20 aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; $-(\text{CR}^{42}\text{R}^{43})_q\text{OR}^{36}$; $-(\text{CR}^{42}\text{R}^{43})_q\text{NR}^{7}\text{R}^{45}$;
 $-(\text{CR}^{42}\text{R}^{43})_q\text{NR}^{7}\text{COR}^{38}$; $-(\text{CR}^{42}\text{R}^{43})_q\text{NR}^{7}\text{SO}_2\text{R}^{38}$; $-(\text{CR}^{42}\text{R}^{43})_q\text{COOR}^{36}$;
 $-(\text{CR}^{42}\text{R}^{43})_q\text{CONR}^{7}\text{R}^{45}$; $-(\text{CR}^{42}\text{R}^{43})_q\text{COR}^{38}$; or $-(\text{CR}^{42}\text{R}^{43})_q\text{R}^{44}$;

- R^{50} is H; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl;
 25 aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; or an *N*-protecting group.

- R^{51} and R^{53} are independently defined as H; F; CF_3 ; C_{1-6} -alkyl; C_{2-6} -alkenyl;
 cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl;
 $-(\text{CR}^{42}\text{R}^{43})_i\text{OR}^{36}$; $-(\text{CR}^{42}\text{R}^{43})_i\text{NR}^{7}\text{R}^{57}$; $-(\text{CR}^{42}\text{R}^{43})_i\text{COOR}^{36}$; or $-(\text{CR}^{42}\text{R}^{43})_i\text{CONR}^{7}\text{R}^{57}$;
 30

R^{54} is H; F; CF_3 ; OCF_3 ; OCHF_2 ; NO_2 ; CN; C_{1-6} -alkyl; C_{2-6} -alkenyl; C_{2-6} -alkynyl;
 cycloalkyl; heterocycloalkyl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; $-\text{OR}^{36}$; $-\text{NR}^{7}\text{R}^{57}$;
 $-\text{NR}^{7}\text{COR}^{38}$; $-\text{NR}^{7}\text{SO}_2\text{R}^{38}$; $-\text{NR}^{7}\text{CONR}^{7}\text{R}^{57}$; $-\text{COR}^{38}$; or $-\text{SO}_2\text{R}^{38}$;

R^{55} is H; CF_3 ; C_{1-6} -alkyl; C_{2-6} -alkenyl; C_{2-6} -alkynyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; $-COOR^{36}$; or $-CONR^7R^{45}$;

- 5 R^{56} is H; F; CF_3 ; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; $-(CR^{42}R^{43})_sOR^{36}$; $-(CR^{42}R^{43})_sNR^7R^{45}$; $-(CR^{42}R^{43})_qCOOR^{36}$; or $-(CR^{42}R^{43})_qCONR^7R^{45}$.

or a stereoisomer of such a compound; or a salt, solvate, clathrate, *N*-oxide, isotopically enriched or enantiomerically enriched version thereof.

10

4. A compound according to any of claims 1, 2, 3 or 4 wherein the **Template A** is selected from

$A_{B1}-A_{C1}$; $A_{B1}-A_{C4}$; $A_{B1}-A_{C19}$; $A_{B2}-A_{C4}$; $A_{B4}-A_{C1}$; $A_{B4}-A_{C4}$; $A_{B4}-A_{C19}$; $A_{B4}-A_{C59}$; $A_{B5}-A_{C51}$; $A_{B5}-A_{C59}$; $A_{B6}-A_{C31}$; $A_{B9}-A_{C6}$; or $A_{B46}-A_{C58}$;

15

and wherein

R^3 and R^4 are independently defined as H; F; CF_3 ; OCF_3 ; $OCHF_2$; CN; or C_{1-6} -alkoxy;

20

R^5 is H; CF_3 ; or C_{1-6} -alkyl;

R^{33} is H; or C_{1-6} -alkyl;

25

R^{46} is H; F; Cl; CF_3 ; OCF_3 ; $OCHF_2$; NO_2 ; CN; C_{1-6} -alkyl; C_{2-6} -alkenyl; C_{2-6} -alkynyl; cycloalkyl; heterocycloalkyl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; or $-(CR^{42}R^{43})_qR^{44}$;

30

R^{47} is H; C_{1-6} -alkyl; C_{2-6} -alkenyl; C_{2-6} -alkynyl; cycloalkyl; heterocycloalkyl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; or $-NR^7R^{45}$;

R^{49} is H; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; or $-(CR^{42}R^{43})_qR^{44}$;

R^{51} and R^{53} are independently defined as H; F; CF_3 ; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; $-(CR^{42}R^{43})_tOR^{36}$; $-(CR^{42}R^{43})_tNR^7R^{57}$; $-(CR^{42}R^{43})_tCOOR^{36}$; or $-(CR^{42}R^{43})_tCONR^7R^{57}$;

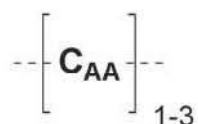
- 5 R^{54} is H; F; CF_3 ; OCF_3 ; $OCHF_2$; NO_2 ; CN; C_{1-6} -alkyl; C_{2-6} -alkenyl; C_{2-6} -alkynyl; cycloalkyl; heterocycloalkyl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; $-OR^{36}$; $-NR^7R^{57}$; $-NR^7COR^{38}$; $-NR^7SO_2R^{38}$; $-NR^7CONR^7R^{57}$; $-COR^{38}$; or $-SO_2R^{38}$;

- 10 R^{55} is H; CF_3 ; C_{1-6} -alkyl; C_{2-6} -alkenyl; C_{2-6} -alkynyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; $-COOR^{36}$; or $-CONR^7R^{45}$;

- R^{56} is H; F; CF_3 ; C_{1-6} -alkyl; C_{2-6} -alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; aryl- C_{1-6} -alkyl; heteroaryl- C_{1-6} -alkyl; $-(CR^{42}R^{43})_sOR^{36}$; $-(CR^{42}R^{43})_sNR^7R^{45}$; $-(CR^{42}R^{43})_qCOOR^{36}$; or $-(CR^{42}R^{43})_qCONR^7R^{45}$;

- 15 or a stereoisomer of such a compound; or a salt, solvate, clathrate, *N*-oxide, isotopically enriched or enantiomerically enriched version thereof.

5. A compound according to any of claim 1 to claim 5 wherein
20 the **Bridge C** is represented by



and wherein

C_{AA} is an amino acid selected from

Ala	L-Alanine;
Arg	L-Arginine;
Asn	L-Asparagine;
Asp	L-Aspartic acid;
Cys	L-Cysteine;
Glu	L-Glutamic acid;
Gln	L-Glutamine;
Gly	Glycine;
His	L-Histidine;

Ile	L-Isoleucine;
Leu	L-Leucine;
Lys	L-Lysine;
Met	L-Methionine;
Phe	L-Phenylalanine;
Pro	L-Proline;
Ser	L-Serine;
Thr	L-Threonine;
Trp	L-Tryptophan;
Tyr	L-Tyrosine;
Val	L-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 -HGlut-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;
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;
Orn	L-Ornithine;
tBuA	L-t-Butylalanine;
Sar	Sarcosine;
Pen	L-Penicillamine;
tBuG	L-tert.-Butylglycine;
4AmPhe	L-para-Aminophenylalanine;
3AmPhe	L-meta-Aminophenylalanine;
2AmPhe	L-ortho-Aminophenylalanine;
Phe(mC(NH ₂)=NH)	L-meta-Amidinophenylalanine;
Phe(pC(NH ₂)=NH)	L-para-Amidinophenylalanine;
Phe(mNHC(NH ₂)=NH)	L-meta-Guanidinophenylalanine;
Phe(pNHC(NH ₂)=NH)	L-para-Guanidinophenylalanine;
2Pal	(2S)-2-Amino-3-(pyridine-2'-yl)-propionic acid;
4Pal	(2S)-2-Amino-3-(pyridine-4'-yl)-propionic acid;
Phg	L-Phenylglycine;
Cha	L-Cyclohexylalanine;
C ₄ al	L-3-Cyclobutylalanine;
C ₅ al	L-3-Cyclopentylalanine;
Nle	L-Norleucine;
2-Nal	L-2-Naphthylalanine;

1-Nal	L-1-Naphthylalanine;
4ClPhe	L-4-Chlorophenylalanine;
3ClPhe	L-3-Chlorophenylalanine;
2ClPhe	L-2-Chlorophenylalanine;
3,4Cl ₂ Phe	L-3,4-Dichlorophenylalanine;
4FPhe	L-4-Fluorophenylalanine;
3FPhe	L-3-Fluorophenylalanine;
2FPhe	L-2-Fluorophenylalanine;
Thi	L-β-2-Thienylalanine;
Tza	L-2-Thiazolylalanine;
Mso	L-Methionine sulfoxide;
AcLys	N-Acetyllysine;
Dap	2,3-Diaminopropionic acid;
Dab	2,4-Diaminobutyric acid;
Dbu	(2S)-2,3-Diamino-butyric acid;
Abu	γ-Aminobutyric acid (GABA);
Aha	ε-Aminohexanoic acid;
Aib	α-Aminoisobutyric acid;
ACC	1-Amino cyclopropane carboxylic acid;
ACBC	1-Amino cyclobutane carboxylic acid;
ACPC	1-Amino cyclopentane carboxylic acid;
1-ACHC	1-Amino cyclohexane carboxylic acid;
2-ACHC	2-Amino cyclohexane carboxylic acid;
3-ACHC	3-Amino cyclohexane carboxylic acid;
4-ACHC	4-Amino cyclohexane carboxylic acid;
Y(Bzl)	L-O-Benzyltyrosine;
H(Bzl)	(3S)-2-Amino-3-(1'-benzylimidazole-4'-yl)-propionic acid;
Bip	L-(4-phenyl)phenylalanine;
S(Bzl)	L-O-Benzylserine;
T(Bzl)	L-O-Benzylthreonine;
alloT	(2S, 3S)-2-Amino-3-hydroxy-butyric acid;
Leu3OH	(2S, 3R)-2-Amino-3-hydroxy-4-methyl-pentanoic acid;
hAla	L-Homo-alanine;

hArg	L-Homo-arginine;
hCys	L-Homo-cysteine;
hGlu	L-Homo-glutamic acid;
hGln	L-Homo-glutamine;
hHis	L-Homo-histidine;
hIle	L-Homo-isoleucine;
hLeu	L-Homo-leucine;
hNle	L-Homo-norleucine;
hLys	L-Homo-lysine;
hMet	L-Homo-Methionine;
hPhe	L-Homo-phenylalanine;
hSer	L-Homo-serine;
hThr	L-Homo-threonine;
hTrp	L-Homo-tryptophan;
hTyr	L-Homo-tyrosine;
hVal	L-Homo-valine;
hCha	L-Homo-cyclohexylalanine;
Bpa	L-4-Benzoylphenylalanine;
OctG	L-Octylglycine;
Tic	(3S)-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid;
Tiq	(1S)-1,2,3,4-Tetrahydroisoquinoline-1-carboxylic acid;
Oic	(2S, 3aS, 7aS)-1-Octahydro-1H-indole-2-carboxylic acid;
4AmPyr1	(2S, 4S)-4-Amino-pyrrolidine-2-carboxylic acid;
4AmPyr2	(2S, 4R)-4-Amino-pyrrolidine-2-carboxylic acid;
4PhePyr1	(2S, 4R)-4-Phenyl-pyrrolidine-2-carboxylic acid;
4PhePyr2	(2S, 4S)-4-Phenyl-pyrrolidine-2-carboxylic acid;
5PhePyr1	(2S, 5R)-5-Phenyl-pyrrolidine-2-carboxylic acid;
5PhePyr2	(2S, 5S)-5-Phenyl-pyrrolidine-2-carboxylic acid;
4Hyp1	(4S)-L-Hydroxyproline;
4Hyp2	(4R)-L-Hydroxyproline;
4Mp1	(4S)-L-Mercaptoproline;
4Mp2	(4R)-L-Mercaptoproline;

Pip	L-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 -HiBuA-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 -HiBuG-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;
H- β^3 -H2ClPhe-OH	(3S)-3-Amino-4-(2'-chlorophenyl)-butyric acid;
H- β^3 -H3,4Cl ₂ Phe-OH	(3S)-3-Amino-4-(3',4'-dichlorophenyl)-butyric acid;
H- β^3 -H4FPhe-OH	(3S)-3-Amino-4-(4'-fluorophenyl)-butyric acid;
H- β^3 -H3FPhe-OH	(3S)-3-Amino-4-(3'-fluorophenyl)-butyric acid;
H- β^3 -H2FPhe-OH	(3S)-3-Amino-4-(2'-fluorophenyl)-butyric acid;
H- β^3 -HThi-OH	(3R)-3-Amino-4-(2'-thienyl)-butyric acid;
H- β^3 -HTza-OH	(3R)-3-Amino-4-(2'-thiazolyl)-butyric acid;
H- β^3 -HMso-OH	(3R)-3-Amino-4-methylsulfoxyl-butyric acid;

H- β^3 -HAcLys-OH	(3S)-7-Acetylamino-3-amino-heptanoic acid;
H- β^3 -HDpr-OH	(3R)-3,4-diamino-butyric acid;
H- β^3 -HA ₂ Bu-OH	(3S)-3,5-Diamino-pentanoic acid;
H- β^3 -HDbu-OH	(3R)-3,4-Diamino-pentanoic acid;
H- β^3 -HAib-OH	Amino-dimethyl acetic acid;
H- β^3 -HCyp-OH	1-Amino-cyclopentane-1-yl-acetic acid;
H- β^3 -HY(Bzl)-OH	(3S)-3-Amino-4-(4'-benzyloxyphenyl)-butyric acid;
H- β^3 -HH(Bzl)-OH	(3S)-3-Amino-4-(1'-benzylimidazole-4'-yl)-butyric acid;
H- β^3 -HBip-OH	(3S)-3-Amino-4-biphenyl-butyl-butyric acid;
H- β^3 -HS(Bzl)-OH	(3S)-3-Amino-4-(benzyloxy)-butyric acid;
H- β^3 -HT(Bzl)-OH	(3R, 4R)-3-Amino-4-benzyloxy-pentanoic acid;
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 -H4AmPyr1-OH	(2S, 4S)-4-Amino-pyrrolidine-2-acetic acid;
H- β^3 -H4AmPyr2-OH	(2S, 4R)-4-Amino-pyrrolidine-2-acetic acid;
H- β^3 -H4PhePyr1-OH	(2S, 4R)-4-Phenyl-pyrrolidine-2-acetic acid;
H- β^3 -H4PhePyr2-OH	(2S, 4S)-4-Phenyl-pyrrolidine-2-acetic acid;
H- β^3 -H5PhePyr1-OH	(2S, 5R)-5-Phenyl-pyrrolidine-2-acetic acid;
H- β^3 -H5PhePyr2-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;
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 ₄ al-OH	(4R)-4-Amino-5-cyclobutyl-pentanoic acid;
H- γ^4 -DiHC ₅ al-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 ₂ Phe-OH	(4R)-4-Amino-5-(3',4'-dichloro-phenyl)-pentanoic acid;
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-octanoic acid;
H- γ^4 -DiHDpr-OH	(4R)-4,5-diamino-pentanoic acid;
H- γ^4 -DiHA ₂ Bu-OH	(4R)-4,5-Diamino-hexanoic acid;
H- γ^4 -DiHDbu-OH	(4R)-4,5-Diamino-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-biphenyl-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-ocitanoic acid;
H- γ^4 -DiHhNle-OH	(4S)-4-Amino-nonanoic acid;
H- γ^4 -DiHhLys-OH	(4S)-4,9-Diamino-nonanoic acid;
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)-hexanoic acid;
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 -DiH4AmPyr1-OH	(2'R, 4'S)-4'-Amino-pyrrolidine-2'-yl-3-propionic acid;
H- γ^4 -DiH4AmPyr2-OH	(2'R, 4'R)-4'-Amino-pyrrolidine-2'-yl-3-propionic acid;
H- γ^4 -DiH4PhePyr1-OH	(2'R, 4'R)-4'-Phenyl-pyrrolidine-2'-yl-3-propionic acid;
H- γ^4 -DiH4PhePyr2-OH	(2'R, 4'S)-4'-Phenyl-pyrrolidine-2'-yl-3-propionic acid;
H- γ^4 -DiH5PhePyr1-OH	(2'S, 5'R)-5'-Phenyl-pyrrolidine-2'-yl-3-propionic acid;
H- γ^4 -DiH5PhePyr2-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;

	acid;
H-γ ⁴ -DiH4Mp1-OH	(2'R, 4'S)-4'-Mercapto-pyrrolidine-2'-yl-3-propionic acid;
	acid;
H-γ ⁴ -DiH4Mp2-OH	(2'R, 4'R)-4'-Mercapto-pyrrolidine-2'-yl-3-propionic acid;
	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;
(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;
(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;
Nip	(S)-Nipecotic acid/ (S)-3-Piperidinecarboxylic acid;
INip	Isonipecotic acid/ 4-Piperidinecarboxylic acid;
PCA	(S)-2-Piperazinecarboxylic acid; or
(S)betaPro	(S)- β -Proline/ (S)-Pyrrolidine-3-carboxylic acid.

or a respective stereoisomer or *N*-methyl derivative.

6. A compound according to any of claims 1 to 6 selected from:

benzyl *N*-[(12*R*,16*S*,18*S*)-16-[(*tert*-butoxycarbonyl)amino]-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0^{2,7}.0^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]carbamate;
tert-butyl *N*-[(12*R*,16*S*,18*S*)-12-amino-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0^{2,7}.0^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-16-yl]carbamate;
benzyl *N*-[(12*R*,16*S*,18*S*)-16-amino-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0^{2,7}.0^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]carbamate;
tert-butyl *N*-[(12*R*,16*S*,18*S*)-12-{[2-(1-naphthyl)acetyl]amino}-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0^{2,7}.0^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-16-yl]carbamate;
N-[(12*R*,16*S*,18*S*)-16-amino-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0^{2,7}.0^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]-2-(1-naphthyl)acetamide;
methyl *N*-[(12*R*,16*S*,18*S*)-12-{[2-(1-naphthyl)acetyl]amino}-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0^{2,7}.0^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-16-yl]carbamate;
N-[(12*R*,16*S*,18*S*)-8,13-dioxo-16-{[2-(1-pyrrolidinyl)acetyl]amino}-20-oxa-9,14-diazatetracyclo[19.3.1.0^{2,7}.0^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]-2-(1-naphthyl)acetamide;
N-[(12*R*,16*S*,18*S*)-16-(dimethylamino)-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0^{2,7}.0^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]-2-(1-naphthyl)acetamide;

(12*R*,16*S*,18*S*)-12,16-diamino-20-oxa-9,14-diazatetracyclo[19.3.1.0^{2,7}.0^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaene-8,13-dione;
benzyl *N*-[(12*R*,16*S*,18*S*)-16-{[2-(2-naphthyl)acetyl]amino}-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0^{2,7}.0^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]carbamate;
N-[(12*R*,16*S*,18*S*)-12-amino-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0^{2,7}.0^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-16-yl]-2-(2-naphthyl)acetamide;
2-(dimethylamino)-*N*-[(12*R*,16*S*,18*S*)-16-{[2-(2-naphthyl)acetyl]amino}-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0^{2,7}.0^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]acetamide;
3-methyl-*N*-[(12*R*,16*S*,18*S*)-16-{[2-(2-naphthyl)acetyl]amino}-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0^{2,7}.0^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]butanamide;
benzyl *N*-[(12*R*,16*S*,18*S*)-8,13-dioxo-16-[(phenoxycarbonyl)amino]-20-oxa-9,14-diazatetracyclo[19.3.1.0^{2,7}.0^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]carbamate;
benzyl *N*-[(10*S*,12*S*,16*S*)-12-[(*tert*-butoxycarbonyl)amino]-20-methyl-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0^{2,7}.0^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]carbamate;
tert-butyl *N*-[(10*S*,12*S*,16*S*)-16-amino-20-methyl-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0^{2,7}.0^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-12-yl]carbamate;
benzyl *N*-[(10*S*,12*S*,16*S*)-12-amino-20-methyl-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0^{2,7}.0^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]carbamate;
benzyl *N*-[(10*S*,12*S*,16*S*)-20-methyl-12-{[2-(2-naphthyl)acetyl]amino}-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0^{2,7}.0^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]carbamate;
N-[(10*S*,12*S*,16*S*)-16-amino-20-methyl-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0^{2,7}.0^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-12-yl]-2-(2-naphthyl)acetamide;
2-(dimethylamino)-*N*-[(10*S*,12*S*,16*S*)-20-methyl-12-{[2-(2-naphthyl)acetyl]amino}-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0^{2,7}.0^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]acetamide;
N-[(10*S*,12*S*,16*S*)-16-[(cyclopropylsulfonyl)amino]-20-methyl-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0^{2,7}.0^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-12-yl]-2-(2-naphthyl)acetamide;

N-[(10*S*,12*S*,16*S*)-20-methyl-16-[[[(methylamino)carbonyl]amino]-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0^{2,7}.0^{10,14}]hexacos-1(26),2,4,6,22,24-hexaen-12-yl]-2-(2-naphthyl)acetamide;

2-methoxy-*N*-[(10*S*,12*S*,16*S*)-20-methyl-12-[[2-(2-naphthyl)acetyl]amino]-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0^{2,7}.0^{10,14}]hexacos-1(26),2,4,6,22,24-hexaen-16-yl]acetamide;

3-methyl-*N*-[(10*S*,12*S*,16*S*)-20-methyl-12-[[2-(2-naphthyl)acetyl]amino]-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0^{2,7}.0^{10,14}]hexacos-1(26),2,4,6,22,24-hexaen-16-yl]butanamide;

N-[(10*S*,12*S*,16*S*)-20-methyl-15,21-dioxo-16-[(2-phenylacetyl)amino]-8-oxa-14,20-diazatetracyclo[20.3.1.0^{2,7}.0^{10,14}]hexacos-1(26),2,4,6,22,24-hexaen-12-yl]-2-(2-naphthyl)acetamide;

N-[(10*S*,12*S*,16*S*)-20-methyl-12-[[2-(2-naphthyl)acetyl]amino]-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0^{2,7}.0^{10,14}]hexacos-1(26),2,4,6,22,24-hexaen-16-yl]benzamide;

N-[(10*S*,12*S*,16*S*)-20-methyl-12-[[2-(2-naphthyl)acetyl]amino]-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0^{2,7}.0^{10,14}]hexacos-1(26),2,4,6,22,24-hexaen-16-yl]butanamide;

N-[(10*S*,12*S*,16*S*)-20-methyl-12-[[2-(2-naphthyl)acetyl]amino]-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0^{2,7}.0^{10,14}]hexacos-1(26),2,4,6,22,24-hexaen-16-yl]pentanamide;

2-[[[(10*S*,12*S*,16*S*)-16-[[2-(dimethylamino)acetyl]amino]-20-methyl-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0^{2,7}.0^{10,14}]hexacos-1(26),2,4,6,22,24-hexaen-12-yl]amino]acetic acid;

2-(dimethylamino)-*N*-[(10*S*,12*S*,16*S*)-20-methyl-12-[[[(methylamino)carbothioyl]amino]-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0^{2,7}.0^{10,14}]hexacos-1(26),2,4,6,22,24-hexaen-16-yl]acetamide;

2-(dimethylamino)-*N*-[(10*S*,12*S*,16*S*)-20-methyl-15,21-dioxo-12-[[2-(sulfanylacetyl)amino]-8-oxa-14,20-diazatetracyclo[20.3.1.0^{2,7}.0^{10,14}]hexacos-1(26),2,4,6,22,24-hexaen-16-yl]acetamide;

2-(dimethylamino)-*N*-[(10*S*,12*S*,16*S*)-20-methyl-15,21-dioxo-12-[[2-(tritylsulfanyl)acetyl]amino]-8-oxa-14,20-diazatetracyclo[20.3.1.0^{2,7}.0^{10,14}]hexacos-1(26),2,4,6,22,24-hexaen-16-yl]acetamide;

2-(dimethylamino)-*N*-[(10*S*,12*S*,16*S*)-20-methyl-12-[[[(methylamino)carbonyl]amino]-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0^{2,7}.0^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]acetamide;

2-(dimethylamino)-*N*-[(10*S*,12*S*,16*S*)-12-([3-(dimethylamino)anilino]carbonyl)amino]-20-methyl-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0^{2,7}.0^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]acetamide;

2-(dimethylamino)-*N*-[(10*S*,12*S*,16*S*)-20-methyl-12-[(2-naphthylamino)carbonyl]amino]-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0^{2,7}.0^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]acetamide;

2-(dimethylamino)-*N*-[(10*S*,12*S*,16*S*)-20-methyl-12-[(methylsulfonyl)amino]-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0^{2,7}.0^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]acetamide;

N-[(10*S*,12*S*,16*S*)-12-[(benzylsulfonyl)amino]-20-methyl-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0^{2,7}.0^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]-2-(dimethylamino)acetamide;

tert-butyl *N*-[(10*S*,12*S*,16*S*)-16-[[2-(dimethylamino)acetyl]amino]-20-methyl-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0^{2,7}.0^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-12-yl]carbamate;

N-[(10*S*,12*S*,16*S*)-12-amino-20-methyl-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0^{2,7}.0^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]-2-(dimethylamino)acetamide;

ethyl 2-[(10*S*,12*S*,16*S*)-16-[[2-(dimethylamino)acetyl]amino]-20-methyl-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0^{2,7}.0^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-12-yl]amino}acetate;

benzyl (10*R*,15*S*)-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxylate;

(10*R*,15*S*)-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxylic acid;

(10*R*,15*S*)-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide;

(10*R*,15*S*)-4-methoxy-*N*,10,16-trimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide;

(10*R*,15*S*)-4-methoxy-10,16-dimethyl-12,17-dioxo-*N*-phenyl-8-oxa-11,16-diazatricyclo[16.3.1.0^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide;

(10*R*,15*S*)-4-methoxy-10,16-dimethyl-15-(1-pyrrolidinylcarbonyl)-8-oxa-11,16-diazatricyclo[16.3.1.0^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-12,17-dione;

(10*R*,15*S*)-*N*-[2-(dimethylamino)ethyl]-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide;

tert-butyl *N*-[3-({[(10*R*,15*S*)-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0^{2,7}]docosa-1(22),2,4,6,18,20-hexaen-15-yl]carbonyl}amino)propyl]carbamate;

(10*R*,15*S*)-*N*-(3-aminopropyl)-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide;

(10*R*,15*S*)-4-methoxy-10,16-dimethyl-12,17-dioxo-*N*-(3-pyridinylmethyl)-8-oxa-11,16-diazatricyclo[16.3.1.0^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide;

(10*R*,15*S*)-4-methoxy-*N*-(2-methoxyethyl)-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide;

(10*R*,15*S*)-*N*-cyclopropyl-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide;

(10*R*,15*S*)-4-methoxy-10,16-dimethyl-12,17-dioxo-*N*-(2,2,2-trifluoroethyl)-8-oxa-11,16-diazatricyclo[16.3.1.0^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide

(10*R*,15*S*)-*N*-isobutyl-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide;

(10*R*,15*S*)-*N*-(2-hydroxyethyl)-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide;

tert-butyl 2-({[(10*R*,15*S*)-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0^{2,7}]docosa-1(22),2,4,6,18,20-hexaen-15-yl]carbonyl}amino)acetate;

2-({ [(10*R*,15*S*)-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0^{2,7}]docosa-1(22),2,4,6,18,20-hexaen-15-yl]carbonyl}amino)acetic acid;

(10*R*,15*S*)-4-methoxy-10,16-dimethyl-12,17-dioxo-*N*-[(1*S*)-1-phenylethyl]-8-oxa-11,16-diazatricyclo[16.3.1.0^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide;

(10*R*,15*S*)-*N*-[2-(dimethylamino)ethyl]-4-methoxy-*N*,10,16-trimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide;

(10*R*,15*S*)-4-methoxy-10,16-dimethyl-*N*-(1-naphthylmethyl)-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide;

(10*R*,15*S*)-4-methoxy-10,16-dimethyl-*N*-(2-naphthylmethyl)-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide;

(10*R*,15*S*)-15-(hydroxymethyl)-4-methoxy-10,16-dimethyl-8-oxa-11,16-diazatricyclo[16.3.1.0^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-12,17-dione;

(10*R*,15*S*)-4-methoxy-10,16-dimethyl-15-[(3-pyridinyloxy)methyl]-8-oxa-11,16-diazatricyclo[16.3.1.0^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-12,17-dione;

(10*R*,15*S*)-15-(azidomethyl)-4-methoxy-10,16-dimethyl-8-oxa-11,16-diazatricyclo[16.3.1.0^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-12,17-dione;

(10*R*,15*S*)-15-(aminomethyl)-4-methoxy-10,16-dimethyl-8-oxa-11,16-diazatricyclo[16.3.1.0^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-12,17-dione;

N-{[(10*R*,15*S*)-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0^{2,7}]docosa-1(22),2,4,6,18,20-hexaen-15-yl]methyl}-2-phenylacetamide;

[(10*R*,15*S*)-4-methoxy-10,16-dimethyl-12,17-dioxo-8-oxa-11,16-diazatricyclo[16.3.1.0^{2,7}]docosa-1(22),2,4,6,18,20-hexaen-15-yl]methyl *N*-phenylcarbamate;

benzyl (9*S*,14*S*)-9,15-dimethyl-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxylate;

(9*S*,14*S*)-9,15-dimethyl-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxylic acid;

(9*S*,14*S*)-*N*,9,15-trimethyl-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide;

(9*S*,14*S*)-9,15-dimethyl-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide;

(9*S*,14*S*)-9,15-dimethyl-11,16-dioxo-*N*-phenyl-7-oxa-10,15-diazatricyclo[15.3.1.1^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide;

(9*S*,14*S*)-9,15-dimethyl-11,16-dioxo-*N*-phenethyl-7-oxa-10,15-diazatricyclo[15.3.1.1^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide;

(9*S*,14*S*)-9,15-dimethyl-*N*-(1-naphthylmethyl)-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide;

(9*S*,14*S*)-9,15-dimethyl-11,16-dioxo-*N*-(3-pyridinylmethyl)-7-oxa-10,15-diazatricyclo[15.3.1.1^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide;

(9*S*,14*S*)-9,15-dimethyl-11,16-dioxo-*N*-[(1*S*)-1-phenylethyl]-7-oxa-10,15-diazatricyclo[15.3.1.1^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide;

(9*S*,14*S*)-*N*-(2-methoxyethyl)-9,15-dimethyl-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide;
 (9*S*,14*S*)-9,15-dimethyl-11,16-dioxo-*N*-(2,2,2-trifluoroethyl)-7-oxa-10,15-diazatricyclo[15.3.1.1^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide;
 (9*S*,14*S*)-*N*-cyclopropyl-9,15-dimethyl-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide;
 (9*S*,14*S*)-*N*-isobutyl-9,15-dimethyl-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide;
 (9*S*,14*S*)-*N*-(2-hydroxyethyl)-9,15-dimethyl-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide;
tert-butyl 2-({[(9*S*,14*S*)-9,15-dimethyl-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaen-14-yl]carbonyl}amino)acetate;
 2-({[(9*S*,14*S*)-9,15-dimethyl-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaen-14-yl]carbonyl}amino)acetic acid;
 (9*S*,14*S*)-*N*-[2-(dimethylamino)ethyl]-9,15-dimethyl-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide;
 (9*S*,14*S*)-9,15-dimethyl-11,16-dioxo-*N*-[3-(1-pyrrolidinyl)propyl]-7-oxa-10,15-diazatricyclo[15.3.1.1^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide;
 (9*S*,14*S*)-14-(1-azetanylcabonyl)-9,15-dimethyl-7-oxa-10,15-diazatricyclo[15.3.1.1^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-11,16-dione;
 (9*S*,14*S*)-9,15-dimethyl-14-(morpholinocarbonyl)-7-oxa-10,15-diazatricyclo[15.3.1.1^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-11,16-dione;
 (9*S*,14*S*)-9,15-dimethyl-*N*-[(1-methyl-1*H*-imidazol-4-yl)methyl]-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide;
 (9*S*,14*S*)-9,15-dimethyl-*N*-(2-naphthylmethyl)-11,16-dioxo-7-oxa-10,15-diazatricyclo[15.3.1.1^{2,6}]docosa-1(21),2(22),3,5,17,19-hexaene-14-carboxamide;
 benzyl (9*S*,11*R*)-11-[(*tert*-butoxycarbonyl)amino]-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaene-16-carboxylate;
tert-butyl *N*-[(9*S*,11*R*)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]carbamate;

benzyl (9*S*,11*R*)-11-amino-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacos-1(25),2(26),3,5,21,23-hexaene-16-carboxylate;

(9*S*,11*R*)-11-amino-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacos-1(25),2(26),3,5,21,23-hexaene-14,20-dione;

tert-butyl *N*-[(9*S*,11*R*)-16-methyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacos-1(25),2(26),3,5,21,23-hexaen-11-yl]carbamate;

(9*S*,11*R*)-11-amino-16-methyl-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacos-1(25),2(26),3,5,21,23-hexaene-14,20-dione;

N-[(9*S*,11*R*)-16-methyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacos-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(2-naphthyl)acetamide;

tert-butyl *N*-[(9*S*,11*R*)-16-(3-fluorobenzyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacos-1(25),2(26),3,5,21,23-hexaen-11-yl]carbamate;

(9*S*,11*R*)-11-amino-16-(3-fluorobenzyl)-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacos-1(25),2(26),3,5,21,23-hexaene-14,20-dione;

N-[(9*S*,11*R*)-16-methyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacos-1(25),2(26),3,5,21,23-hexaen-11-yl]acetamide;

N-[(9*S*,11*R*)-16-(3-fluorobenzyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacos-1(25),2(26),3,5,21,23-hexaen-11-yl]acetamide;

N-[(9*S*,11*R*)-16-methyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacos-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(1-naphthyl)acetamide;

N-[(9*S*,11*R*)-16-methyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacos-1(25),2(26),3,5,21,23-hexaen-11-yl]-*N*-phenylurea;

N-[*(9S,11R)*-16-methyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]benzenesulfonamide;

tert-butyl *N*-[*(9S,11R)*-16-[2-(dimethylamino)acetyl]-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]carbamate;

(9S,11R)-11-amino-16-[2-(dimethylamino)acetyl]-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaene-14,20-dione;

N-[*(9S,11R)*-16-[2-(dimethylamino)acetyl]-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-phenylacetamide;

N-[*(9S,11R)*-16-[2-(dimethylamino)acetyl]-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]cyclopropanesulfonamide;

N-[*(9S,11R)*-16-[2-(dimethylamino)acetyl]-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-*N*-methylurea;

tert-butyl *N*-[*(9S,11R)*-16-(cyclopropylsulfonyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]carbamate;

(9S,11R)-11-amino-16-(cyclopropylsulfonyl)-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaene-14,20-dione;

N-[*(9S,11R)*-16-(cyclopropylsulfonyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]benzamide;

tert-butyl *N*-[*(9S,11R)*-16-[(methylamino)carbonyl]-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]carbamate;

(9S,11R)-11-amino-*N*-methyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaene-16-carboxamide;

(9*S*,11*R*)-11-[(3-fluorobenzoyl)amino]-*N*-methyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacos-1(25),2(26),3,5,21,23-hexaene-16-carboxamide;

allyl *N*-[(13*S*,16*R*)-16-methyl-14-oxo-18-oxa-8-thia-15-azatricyclo[17.3.1.0^{2,7}]tricos-1(23),2,4,6,19,21-hexaen-13-yl]carbamate;

(13*S*,16*R*)-13-amino-16-methyl-18-oxa-8-thia-15-azatricyclo[17.3.1.0^{2,7}]tricos-1(23),2,4,6,19,21-hexaen-14-one;

N-[(13*S*,16*R*)-16-methyl-14-oxo-18-oxa-8-thia-15-azatricyclo[17.3.1.0^{2,7}]tricos-1(23),2,4,6,19,21-hexaen-13-yl]-2-(1-naphthyl)acetamide;

N-[(13*S*,16*R*)-16-methyl-14-oxo-18-oxa-8-thia-15-azatricyclo[17.3.1.0^{2,7}]tricos-1(23),2,4,6,19,21-hexaen-13-yl]-2-(2-naphthyl)acetamide;

N-[(13*S*,16*R*)-16-methyl-14-oxo-18-oxa-8-thia-15-azatricyclo[17.3.1.0^{2,7}]tricos-1(23),2,4,6,19,21-hexaen-13-yl]-2-(1-pyrrolidinyl)acetamide;

N-[(13*S*,16*R*)-16-methyl-14-oxo-18-oxa-8-thia-15-azatricyclo[17.3.1.0^{2,7}]tricos-1(23),2,4,6,19,21-hexaen-13-yl]nicotinamide;

3-methyl-*N*-[(13*S*,16*R*)-16-methyl-14-oxo-18-oxa-8-thia-15-azatricyclo[17.3.1.0^{2,7}]tricos-1(23),2,4,6,19,21-hexaen-13-yl]butanamide;

methyl *N*-[(13*S*,16*R*)-16-methyl-14-oxo-18-oxa-8-thia-15-azatricyclo[17.3.1.0^{2,7}]tricos-1(23),2,4,6,19,21-hexaen-13-yl]carbamate;

N-[(13*S*,16*R*)-16-methyl-14-oxo-18-oxa-8-thia-15-azatricyclo[17.3.1.0^{2,7}]tricos-1(23),2,4,6,19,21-hexaen-13-yl]cyclopropanesulfonamide;

N-[(13*S*,16*R*)-16-methyl-14-oxo-18-oxa-8-thia-15-azatricyclo[17.3.1.0^{2,7}]tricos-1(23),2,4,6,19,21-hexaen-13-yl]benzenesulfonamide;

N-methyl-*N*-[(13*S*,16*R*)-16-methyl-14-oxo-18-oxa-8-thia-15-azatricyclo[17.3.1.0^{2,7}]tricos-1(23),2,4,6,19,21-hexaen-13-yl]urea;

N-[(13*S*,16*R*)-16-methyl-14-oxo-18-oxa-8-thia-15-azatricyclo[17.3.1.0^{2,7}]tricos-1(23),2,4,6,19,21-hexaen-13-yl]-*N*-(3-pyridinyl)urea;

(13*S*,16*R*)-13-(isobutylamino)-16-methyl-18-oxa-8-thia-15-azatricyclo[17.3.1.0^{2,7}]tricos-1(23),2,4,6,19,21-hexaen-14-one;

(13*S*,16*R*)-13-(isopentylamino)-16-methyl-18-oxa-8-thia-15-azatricyclo[17.3.1.0^{2,7}]tricos-1(23),2,4,6,19,21-hexaen-14-one;

allyl *N*-[(13*S*,16*R*)-16-methyl-8,8,14-trioxo-18-oxa-8 λ^6 -thia-15-azatricyclo[17.3.1.0^{2,7}]tricos-1(23),2,4,6,19,21-hexaen-13-yl]carbamate;

(13*S*,16*R*)-13-amino-16-methyl-18-oxa-8 λ^6 -thia-15-azatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaene-8,8,14-trione;

N-[(13*S*,16*R*)-16-methyl-8,8,14-trioxo-18-oxa-8 λ^6 -thia-15-azatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]-2-(1-naphthyl)acetamide;

N-[(13*S*,16*R*)-16-methyl-8,8,14-trioxo-18-oxa-8 λ^6 -thia-15-azatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]-2-(2-naphthyl)acetamide;

N-[(13*S*,16*R*)-16-methyl-8,8,14-trioxo-18-oxa-8 λ^6 -thia-15-azatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]-2-(1-pyrrolidinyl)acetamide;

N-[(13*S*,16*R*)-16-methyl-8,8,14-trioxo-18-oxa-8 λ^6 -thia-15-azatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]nicotinamide;

3-methyl-*N*-[(13*S*,16*R*)-16-methyl-8,8,14-trioxo-18-oxa-8 λ^6 -thia-15-azatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]butanamide;

methyl *N*-[(13*S*,16*R*)-16-methyl-8,8,14-trioxo-18-oxa-8 λ^6 -thia-15-azatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]carbamate;

N-[(13*S*,16*R*)-16-methyl-8,8,14-trioxo-18-oxa-8 λ^6 -thia-15-azatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]cyclopropanesulfonamide;

N-[(13*S*,16*R*)-16-methyl-8,8,14-trioxo-18-oxa-8 λ^6 -thia-15-azatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]benzenesulfonamide;

N-methyl-*N*-[(13*S*,16*R*)-16-methyl-8,8,14-trioxo-18-oxa-8 λ^6 -thia-15-azatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]urea;

N-[(13*S*,16*R*)-16-methyl-8,8,14-trioxo-18-oxa-8 λ^6 -thia-15-azatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]-*N*-(3-pyridinyl)urea;

(13*S*,16*R*)-13-(isobutylamino)-16-methyl-18-oxa-8 λ^6 -thia-15-azatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaene-8,8,14-trione;

(13*S*,16*R*)-13-(isopentylamino)-16-methyl-18-oxa-8 λ^6 -thia-15-azatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaene-8,8,14-trione;

allyl *N*-[(10*R*,13*S*)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]carbamate;

(10*R*,13*S*)-13-amino-10-methyl-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-12-one;

(10*R*,13*S*)-13-(dimethylamino)-10-methyl-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-12-one;
 (10*R*,13*S*)-13-(isobutylamino)-10-methyl-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-12-one;
 (10*R*,13*S*)-13-[(3-fluorobenzyl)amino]-10-methyl-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-12-one;
N-[(10*R*,13*S*)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]acetamide;
 2-methoxy-*N*-[(10*R*,13*S*)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]acetamide;
 2-(dimethylamino)-*N*-[(10*R*,13*S*)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]acetamide;
N-[(10*R*,13*S*)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]nicotinamide;
 3-methyl-*N*-[(10*R*,13*S*)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]butanamide;
tert-butyl *N*-(3-[(10*R*,13*S*)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]amino)-3-oxopropyl)carbamate;
 3-amino-*N*-[(10*R*,13*S*)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]propanamide;
N-[(10*R*,13*S*)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]-2-(1-naphthyl)acetamide;
N-[(10*R*,13*S*)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]-2-(2-naphthyl)acetamide;
 3,3,3-trifluoro-*N*-[(10*R*,13*S*)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]propanamide;
 3-fluoro-*N*-[(10*R*,13*S*)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]benzamide;
N-[(10*R*,13*S*)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]-*N*-(3-pyridinyl)urea
N-methyl-*N*-[(10*R*,13*S*)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]urea;

tert-butyl 3-[[[(10*R*,13*S*)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]amino}carbonyl]amino]propanoate;
 3-[[[(10*R*,13*S*)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]amino}carbonyl]amino]propanoic acid;
N-[(10*R*,13*S*)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]methanesulfonamide;
N-[(10*R*,13*S*)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]cyclopropanesulfonamide;
N-[(10*R*,13*S*)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]benzenesulfonamide;
 methyl *N*-[(10*R*,13*S*)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]carbamate;
 2-methoxyethyl *N*-[(10*R*,13*S*)-10-methyl-12-oxo-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]carbamate;
 allyl *N*-[(10*R*,13*S*)-10-methyl-12,18,18-trioxo-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]carbamate;
 (10*R*,13*S*)-13-amino-10-methyl-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaene-12,18,18-trione;
 (10*R*,13*S*)-13-(dimethylamino)-10-methyl-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaene-12,18,18-trione;
 (10*R*,13*S*)-13-(isobutylamino)-10-methyl-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaene-12,18,18-trione;
 (10*R*,13*S*)-13-[(3-fluorobenzyl)amino]-10-methyl-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaene-12,18,18-trione;
N-[(10*R*,13*S*)-10-methyl-12,18,18-trioxo-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]acetamide;
 2-methoxy-*N*-[(10*R*,13*S*)-10-methyl-12,18,18-trioxo-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]acetamide;
 2-(dimethylamino)-*N*-[(10*R*,13*S*)-10-methyl-12,18,18-trioxo-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]acetamide;
N-[(10*R*,13*S*)-10-methyl-12,18,18-trioxo-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]nicotinamide;

3-methyl-*N*-[(10*R*,13*S*)-10-methyl-12,18,18-trioxo-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]butanamide;

tert-butyl *N*-(3-[(10*R*,13*S*)-10-methyl-12,18,18-trioxo-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]amino)-3-oxopropyl)carbamate;

3-amino-*N*-[(10*R*,13*S*)-10-methyl-12,18,18-trioxo-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]propanamide;

N-[(10*R*,13*S*)-10-methyl-12,18,18-trioxo-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]-2-(1-naphthyl)acetamide;

N-[(10*R*,13*S*)-10-methyl-12,18,18-trioxo-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]-2-(2-naphthyl)acetamide;

3,3,3-trifluoro-*N*-[(10*R*,13*S*)-10-methyl-12,18,18-trioxo-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]propanamide;

3-fluoro-*N*-[(10*R*,13*S*)-10-methyl-12,18,18-trioxo-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]benzamide;

N-[(10*R*,13*S*)-10-methyl-12,18,18-trioxo-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]-*N*-(3-pyridinyl)urea;

N-methyl-*N*'-[(10*R*,13*S*)-10-methyl-12,18,18-trioxo-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]urea;

tert-butyl 3-[(10*R*,13*S*)-10-methyl-12,18,18-trioxo-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]amino}carbonyl)amino]propanoate;

3-[(10*R*,13*S*)-10-methyl-12,18,18-trioxo-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]amino}carbonyl)amino]propanoic acid;

N-[(10*R*,13*S*)-10-methyl-12,18,18-trioxo-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]methanesulfonamide;

N-[(10*R*,13*S*)-10-methyl-12,18,18-trioxo-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]cyclopropanesulfonamide;

N-[(10*R*,13*S*)-10-methyl-12,18,18-trioxo-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]benzenesulfonamide;

methyl *N*-[(10*R*,13*S*)-10-methyl-12,18,18-trioxo-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]carbamate;
2-methoxyethyl *N*-[(10*R*,13*S*)-10-methyl-12,18,18-trioxo-8-oxa-18 λ^6 -thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricoso-1(23),2,4,6,19,21-hexaen-13-yl]carbamate;
(9*S*,16*S*,19*R*)-16-benzyl-19,20-dimethyl-7-oxa-13,17,20,24-tetraazatetracyclo[20.3.1.1^{2,6}.0^{9,13}]heptacosa-1(26),2(27),3,5,22,24-hexaene-14,18,21-trione;
(9*S*,19*S*)-19-benzyl-20-methyl-7-oxa-13,17,20,24-tetraazatetracyclo[20.3.1.1^{2,6}.0^{9,13}]heptacosa-1(26),2(27),3,5,22,24-hexaene-14,18,21-trione;
(9*S*,19*S*)-19-benzyl-7-oxa-13,17,20,24-tetraazatetracyclo[20.3.1.1^{2,6}.0^{9,13}]heptacosa-1(26),2(27),3,5,22,24-hexaene-14,18,21-trione;
(9*S*,16*R*,19*S*)-19-benzyl-16,17,20-trimethyl-7-oxa-13,17,20,24-tetraazatetracyclo[20.3.1.1^{2,6}.0^{9,13}]heptacosa-1(26),2(27),3,5,22,24-hexaene-14,18,21-trione;
(9*S*,16*R*)-16,17,20-trimethyl-7-oxa-13,17,20,24-tetraazatetracyclo[20.3.1.1^{2,6}.0^{9,13}]heptacosa-1(26),2(27),3,5,22,24-hexaene-14,18,21-trione;
(9*S*,16*R*,19*S*)-19-benzyl-16,17-dimethyl-7-oxa-13,17,20,24-tetraazatetracyclo[20.3.1.1^{2,6}.0^{9,13}]heptacosa-1(26),2(27),3,5,22,24-hexaene-14,18,21-trione;
(9*S*,16*S*)-16-benzyl-21-methyl-7-oxa-13,17,21,25-tetraazatetracyclo[21.3.1.1^{2,6}.0^{9,13}]octacosa-1(27),2(28),3,5,23,25-hexaene-14,18,22-trione;
3-[(9*S*,16*R*,19*S*)-16,17,20-trimethyl-14,18,21-trioxo-7-oxa-13,17,20,24-tetraazatetracyclo[20.3.1.1^{2,6}.0^{9,13}]heptacosa-1(26),2(27),3,5,22,24-hexaen-19-yl]propanoic acid;
(9*S*,16*R*,22*S*)-16,17,20,22,23-pentamethyl-7-oxa-13,17,20,23,27-pentaazatetracyclo[23.3.1.1^{2,6}.0^{9,13}]triaconta-1(29),2(30),3,5,25,27-hexaene-14,18,21,24-tetrone;
(9*S*,16*R*,22*S*)-16,17,22-trimethyl-7-oxa-13,17,20,23,27-pentaazatetracyclo[23.3.1.1^{2,6}.0^{9,13}]triaconta-1(29),2(30),3,5,25,27-hexaene-14,18,21,24-tetrone;

(9*S*,19*R*,22*S*)-16,19,20,22,23-pentamethyl-7-oxa-13,16,20,23,27-pentaazatetracyclo[23.3.1.1^{2,6}.0^{9,13}]triaconta-1(29),2(30),3,5,25,27-hexaene-14,17,21,24-tetrone;

(9*S*,18*S*,22*R*)-16,18,19,22,23-pentamethyl-7-oxa-13,16,19,23,27-pentaazatetracyclo[23.3.1.1^{2,6}.0^{9,13}]triaconta-1(29),2(30),3,5,25,27-hexaene-14,17,20,24-tetrone;

(9*S*,18*S*,21*R*)-18-benzyl-21,22-dimethyl-7-oxa-13,16,19,22,26-pentaazatetracyclo[22.3.1.1^{2,6}.0^{9,13}]nonacosa-1(28),2(29),3,5,24,26-hexaene-14,17,20,23-tetrone;

(9*S*,18*S*,21*R*)-18-benzyl-16,21-dimethyl-7-oxa-13,16,19,22,26-pentaazatetracyclo[22.3.1.1^{2,6}.0^{9,13}]nonacosa-1(28),2(29),3,5,24,26-hexaene-14,17,20,23-tetrone;

(9*S*,18*S*,21*R*)-18-benzyl-16,21,22-trimethyl-7-oxa-13,16,19,22,26-pentaazatetracyclo[22.3.1.1^{2,6}.0^{9,13}]nonacosa-1(28),2(29),3,5,24,26-hexaene-14,17,20,23-tetrone;

3-[(9*S*,16*R*,19*S*,22*S*)-16,17,19,23-tetramethyl-14,18,21,24-tetraoxo-7-oxa-13,17,20,23,27-pentaazatetracyclo[23.3.1.1^{2,6}.0^{9,13}]triaconta-1(29),2(30),3,5,25,27-hexaen-22-yl]propanoic acid;

3-[(9*S*,15*S*,18*R*,21*S*)-18-benzyl-15,22-dimethyl-14,17,20,23-tetraoxo-7-oxa-13,16,19,22,26-pentaazatetracyclo[22.3.1.1^{2,6}.0^{9,13}]nonacosa-1(28),2(29),3,5,24,26-hexaen-21-yl]propanoic acid;

3-[(9*S*,15*R*,18*S*,21*S*)-18-benzyl-15,22-dimethyl-14,17,20,23-tetraoxo-7-oxa-13,16,19,22,26-pentaazatetracyclo[22.3.1.1^{2,6}.0^{9,13}]nonacosa-1(28),2(29),3,5,24,26-hexaen-21-yl]propanoic acid;

(9*S*,16*R*,19*S*,22*R*)-19-(4-aminobutyl)-16,17,22-trimethyl-7-oxa-13,17,20,23,27-pentaazatetracyclo[23.3.1.1^{2,6}.0^{9,13}]triaconta-1(29),2(30),3,5,25,27-hexaene-14,18,21,24-tetrone;

benzyl (10*S*,12*S*)-12-[(*tert*-butoxycarbonyl)amino]-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0^{2,7}.0^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaene-17-carboxylate;

benzyl (10*S*,12*S*)-12-amino-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0^{2,7}.0^{10,14}]hexacosa-1(24),2,4,6,22,25-hexaene-17-carboxylate;

tert-butyl *N*-[(10*S*,12*S*)-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0^{2,7}.0^{10,14}]hexacos-1(24),2,4,6,22,25-hexaen-12-yl]carbamate;

tert-butyl *N*-[(10*S*,12*S*)-17-methyl-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0^{2,7}.0^{10,14}]hexacos-1(24),2,4,6,22,25-hexaen-12-yl]carbamate;

(10*S*,12*S*)-12-amino-17-methyl-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0^{2,7}.0^{10,14}]hexacos-1(24),2,4,6,22,25-hexaene-15,21-dione;

N-[(10*S*,12*S*)-17-methyl-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0^{2,7}.0^{10,14}]hexacos-1(24),2,4,6,22,25-hexaen-12-yl]-2-(1-naphthyl)acetamide;

3-methyl-*N*-[(10*S*,12*S*)-17-methyl-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0^{2,7}.0^{10,14}]hexacos-1(24),2,4,6,22,25-hexaen-12-yl]butanamide;

N-[(10*S*,12*S*)-17-methyl-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0^{2,7}.0^{10,14}]hexacos-1(24),2,4,6,22,25-hexaen-12-yl]-*N*-(3-pyridinyl)urea;

N-[(10*S*,12*S*)-17-methyl-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0^{2,7}.0^{10,14}]hexacos-1(24),2,4,6,22,25-hexaen-12-yl]benzenesulfonamide;

tert-butyl *N*-[(10*S*,12*S*)-17-[2-(dimethylamino)acetyl]-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0^{2,7}.0^{10,14}]hexacos-1(24),2,4,6,22,25-hexaen-12-yl]carbamate;

(10*S*,12*S*)-12-amino-17-[2-(dimethylamino)acetyl]-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0^{2,7}.0^{10,14}]hexacos-1(24),2,4,6,22,25-hexaene-15,21-dione;

N-[(10*S*,12*S*)-17-[2-(dimethylamino)acetyl]-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0^{2,7}.0^{10,14}]hexacos-1(24),2,4,6,22,25-hexaen-12-yl]-2-phenylacetamide;

N-[(10*S*,12*S*)-17-[2-(dimethylamino)acetyl]-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0^{2,7}.0^{10,14}]hexacos-1(24),2,4,6,22,25-hexaen-12-yl]-*N*-methylurea;

N-[(10*S*,12*S*)-17-[2-(dimethylamino)acetyl]-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0^{2,7}.0^{10,14}]hexacos-1(24),2,4,6,22,25-hexaen-12-yl]cyclopropanesulfonamide;

benzyl (10*S*,12*S*)-12-(acetylamino)-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0^{2,7}.0^{10,14}]hexacos-1(24),2,4,6,22,25-hexaene-17-carboxylate;

N-[(10*S*,12*S*)-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0^{2,7}.0^{10,14}]hexacos-1(24),2,4,6,22,25-hexaen-12-yl]acetamide;

N-[(10*S*,12*S*)-17-(3-fluorobenzyl)-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0^{2,7}.0^{10,14}]hexacos-1(24),2,4,6,22,25-hexaen-12-yl]acetamide;

N-[(10*S*,12*S*)-15,21-dioxo-17-[2-(1-pyrrolidinyl)acetyl]-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0^{2,7}.0^{10,14}]hexacos-1(24),2,4,6,22,25-hexaen-12-yl]acetamide;

(10*S*,12*S*)-12-(acetylamino)-15,21-dioxo-*N*-phenyl-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0^{2,7}.0^{10,14}]hexacos-1(24),2,4,6,22,25-hexaene-17-carboxamide;

N-[(10*S*,12*S*)-15,21-dioxo-17-(phenylsulfonyl)-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0^{2,7}.0^{10,14}]hexacos-1(24),2,4,6,22,25-hexaen-12-yl]acetamide;

3-({[(10*S*,12*S*)-12-(acetylamino)-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0^{2,7}.0^{10,14}]hexacos-1(24),2,4,6,22,25-hexaen-17-yl]carbonyl}amino)propanoic acid;

tert-butyl 3-({[(10*S*,12*S*)-12-(acetylamino)-15,21-dioxo-8-oxa-3,14,17,20-tetraazatetracyclo[20.2.2.0^{2,7}.0^{10,14}]hexacos-1(24),2,4,6,22,25-hexaen-17-yl]carbonyl}amino)propanoate;

methyl (8*S*,17*S*,19*S*)-17-[(*tert*-butoxycarbonyl)amino]-24-fluoro-6,14-dioxo-10,21-dioxo-4-thia-7,15-diazatetracyclo[20.3.1.1^{2,5}.0^{15,19}]heptacos-1(26),2,5(27),12,22,24-hexaene-8-carboxylate;

methyl (8*S*,17*S*,19*S*)-17-[(*tert*-butoxycarbonyl)amino]-24-fluoro-6,14-dioxo-10,21-dioxo-4-thia-7,15-diazatetracyclo[20.3.1.1^{2,5}.0^{15,19}]heptacos-1(26),2,5(27),22,24-pentaene-8-carboxylate;

methyl (8*S*,17*S*,19*S*)-17-amino-24-fluoro-6,14-dioxo-10,21-dioxo-4-thia-7,15-diazatetracyclo[20.3.1.1^{2,5}.0^{15,19}]heptacos-1(26),2,5(27),22,24-pentaene-8-carboxylate;

methyl (8*S*,17*S*,19*S*)-24-fluoro-6,14-dioxo-17-[(2-phenylacetyl)amino]-10,21-dioxo-4-thia-7,15-diazatetracyclo[20.3.1.1^{2,5}.0^{15,19}]heptacos-1(26),2,5(27),22,24-pentaene-8-carboxylate;

(8*S*,17*S*,19*S*)-24-fluoro-6,14-dioxo-17-[(2-phenylacetyl)amino]-10,21-dioxo-4-thia-7,15-diazatetracyclo[20.3.1.1^{2,5}.0^{15,19}]heptacos-1(26),2,5(27),22,24-pentaene-8-carboxylic acid;

(8*S*,17*S*,19*S*)-24-fluoro-6,14-dioxo-17-[(2-phenylacetyl)amino]-10,21-dioxo-4-thia-7,15-diazatetracyclo[20.3.1.1^{2,5}.0^{15,19}]heptacos-1(26),2,5(27),22,24-pentaene-8-carboxamide;

(8*S*,17*S*,19*S*)-24-fluoro-*N*-isobutyl-6,14-dioxo-17-[(2-phenylacetyl)amino]-10,21-dioxo-4-thia-7,15-diazatetracyclo[20.3.1.1^{2,5}.0^{15,19}]heptacos-1(26),2,5(27),22,24-pentaene-8-carboxamide;

methyl (8*S*,12*E*,18*S*,20*S*)-18-[(*tert*-butoxycarbonyl)amino]-25-fluoro-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaene-8-carboxylate;

(8*S*,12*E*,18*S*,20*S*)-18-[(*tert*-butoxycarbonyl)amino]-25-fluoro-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaene-8-carboxylic acid;

methyl (8*S*,12*E*,18*S*,20*S*)-18-amino-25-fluoro-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaene-8-carboxylate;

methyl (8*S*,12*E*,18*S*,20*S*)-25-fluoro-18-[2-(2-naphthyl)acetyl]amino-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaene-8-carboxylate;

tert-butyl *N*-[(8*S*,12*E*,18*S*,20*S*)-25-fluoro-8-[(isobutylamino)carbonyl]-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaen-18-yl]carbamate;

(8*S*,12*E*,18*S*,20*S*)-18-amino-25-fluoro-*N*-isobutyl-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaene-8-carboxamide;

(8*S*,12*E*,18*S*,20*S*)-25-fluoro-*N*-isobutyl-6,15-dioxo-18-[(3-pyridinylcarbonyl)amino]-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaene-8-carboxamide;

tert-butyl *N*-[(8*S*,12*E*,18*S*,20*S*)-8-(anilinocarbonyl)-25-fluoro-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaen-18-yl]carbamate;

(8*S*,12*E*,18*S*,20*S*)-18-amino-25-fluoro-6,15-dioxo-*N*-phenyl-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaene-8-carboxamide;

methyl (8*S*,12*E*,18*S*,20*S*)-25-fluoro-6,15-dioxo-18-[(2-phenylacetyl)amino]-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaene-8-carboxylate;

(8*S*,12*E*,18*S*,20*S*)-25-fluoro-6,15-dioxo-18-[(2-phenylacetyl)amino]-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaene-8-carboxylic acid;

methyl (8*S*,12*E*,18*S*,20*S*)-18-[(3-chlorobenzoyl)amino]-25-fluoro-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaene-8-carboxylate;

(8*S*,12*E*,18*S*,20*S*)-18-[(3-chlorobenzoyl)amino]-25-fluoro-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaene-8-carboxylic acid;

(8*S*,12*E*,18*S*,20*S*)-25-fluoro-*N*-isobutyl-18-[[2-(2-naphthyl)acetyl]amino]-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaene-8-carboxamide;

(8*S*,12*E*,18*S*,20*S*)-25-fluoro-18-[[2-(2-naphthyl)acetyl]amino]-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacos-1(27),2,5(28),12,23,25-hexaene-8-carboxylic acid;

methyl (8*S*,18*S*,20*S*)-18-[(*tert*-butoxycarbonyl)amino]-25-fluoro-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacos-1(27),2,5(28),23,25-pentaene-8-carboxylate;

(8*S*,18*S*,20*S*)-18-[(*tert*-butoxycarbonyl)amino]-25-fluoro-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacos-1(27),2,5(28),23,25-pentaene-8-carboxylic acid;

methyl (8*S*,18*S*,20*S*)-18-amino-25-fluoro-6,15-dioxo-10,22-dioxo-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacos-1(27),2,5(28),23,25-pentaene-8-carboxylate;

methyl (8S,18S,20S)-25-fluoro-18-[[2-(2-naphthyl)acetyl]amino]-6,15-dioxo-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacosa-1(27),2,5(28),23,25-pentaene-8-carboxylate;

tert-butyl *N*-[(8S,18S,20S)-8-(anilinocarbonyl)-25-fluoro-6,15-dioxo-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacosa-1(27),2,5(28),23,25-pentaen-18-yl]carbamate;

(8S,18S,20S)-18-amino-25-fluoro-6,15-dioxo-*N*-phenyl-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacosa-1(27),2,5(28),23,25-pentaene-8-carboxamide;

methyl (8S,18S,20S)-25-fluoro-6,15-dioxo-18-[(2-phenylacetyl)amino]-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacosa-1(27),2,5(28),23,25-pentaene-8-carboxylate;

(8S,18S,20S)-18-[(3-chlorobenzoyl)amino]-25-fluoro-6,15-dioxo-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacosa-1(27),2,5(28),23,25-pentaene-8-carboxylic acid;

methyl (8S,18S,20S)-18-[(3-chlorobenzoyl)amino]-25-fluoro-6,15-dioxo-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacosa-1(27),2,5(28),23,25-pentaene-8-carboxylate;

(8S,18S,20S)-25-fluoro-6,15-dioxo-18-[(2-phenylacetyl)amino]-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacosa-1(27),2,5(28),23,25-pentaene-8-carboxylic acid;

(8S,18S,20S)-25-fluoro-18-[[2-(2-naphthyl)acetyl]amino]-6,15-dioxo-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacosa-1(27),2,5(28),23,25-pentaene-8-carboxylic acid;

tert-butyl *N*-[(8S,18S,20S)-25-fluoro-8-[(isobutylamino)carbonyl]-6,15-dioxo-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacosa-1(27),2,5(28),23,25-pentaen-18-yl]carbamate;

(8S,18S,20S)-18-amino-25-fluoro-*N*-isobutyl-6,15-dioxo-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacosa-1(27),2,5(28),23,25-pentaene-8-carboxamide;

(8S,18S,20S)-25-fluoro-*N*-isobutyl-6,15-dioxo-18-[(3-pyridinylcarbonyl)amino]-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacosa-1(27),2,5(28),23,25-pentaene-8-carboxamide;

tert-butyl *N*-[(8*S*,18*S*,20*S*)-8-[(4-chloroanilino)carbonyl]-25-fluoro-6,15-dioxo-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacosa-1(27),2,5(28),23,25-pentaen-18-yl]carbamate;

(8*S*,18*S*,20*S*)-18-amino-*N*-(4-chlorophenyl)-25-fluoro-6,15-dioxo-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacosa-1(27),2,5(28),23,25-pentaene-8-carboxamide;

tert-butyl *N*-[(8*S*,18*S*,20*S*)-25-fluoro-6,15-dioxo-8-(3-toluidinocarbonyl)-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacosa-1(27),2,5(28),23,25-pentaen-18-yl]carbamate;

(8*S*,18*S*,20*S*)-18-amino-25-fluoro-*N*-(3-methylphenyl)-6,15-dioxo-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacosa-1(27),2,5(28),23,25-pentaene-8-carboxamide;

tert-butyl *N*-[(8*S*,18*S*,20*S*)-8-[(benzylamino)carbonyl]-25-fluoro-6,15-dioxo-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacosa-1(27),2,5(28),23,25-pentaen-18-yl]carbamate;

(8*S*,18*S*,20*S*)-18-amino-*N*-benzyl-25-fluoro-6,15-dioxo-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacosa-1(27),2,5(28),23,25-pentaene-8-carboxamide;

benzyl *N*-[(9*S*,11*S*,15*S*)-11-[(4-bromobenzyl)oxy]-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0^{2,6}.0^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]carbamate;

(9*S*,11*S*,15*S*)-15-amino-11-hydroxy-18,21-dimethyl-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0^{2,6}.0^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraene-14,19-dione;

(9*S*,11*S*,15*S*)-15-amino-11-(benzyloxy)-18,21-dimethyl-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0^{2,6}.0^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraene-14,19-dione;

N-[(9*S*,11*S*,15*S*)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0^{2,6}.0^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]-2-(2-naphthyl)acetamide;

N-[(9*S*,11*S*,15*S*)-11-(benzyloxy)-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0^{2,6}.0^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]acetamide;

N-[(9*S*,11*S*,15*S*)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0^{2,6}.0^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]-2-(1-naphthyl)acetamide;

N-[(9*S*,11*S*,15*S*)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0^{2,6}.0^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]-3-methylbutanamide;

3-fluoro-*N*-[(9*S*,11*S*,15*S*)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0^{2,6}.0^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]benzamide;

N-[(9*S*,11*S*,15*S*)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0^{2,6}.0^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]benzenesulfonamide;

N-[(9*S*,11*S*,15*S*)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0^{2,6}.0^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]methanesulfonamide;

methyl *N*-[(9*S*,11*S*,15*S*)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0^{2,6}.0^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]carbamate;

N-[(9*S*,11*S*,15*S*)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0^{2,6}.0^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]-*N*-methylurea;

N-[(9*S*,11*S*,15*S*)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0^{2,6}.0^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]-*N*-(3-pyridinyl)urea;

N-[(9*S*,11*S*,15*S*)-11-methoxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0^{2,6}.0^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]-2-(2-naphthyl)acetamide;

N-[(9*S*,11*S*,15*S*)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0^{2,6}.0^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]-*N*-(2-naphthyl)urea;

N-[(9*S*,11*S*,15*S*)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0^{2,6}.0^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]-2-phenylacetamide;

N-[(9*S*,11*S*,15*S*)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0^{2,6}.0^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]-3-methoxybenzamide;

N-[(9*S*,11*S*,15*S*)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0^{2,6}.0^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]-2-naphthalenesulfonamide;

3-(4-fluorophenyl)-*N*-[(9*S*,11*S*,15*S*)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0^{2,6}.0^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]propanamide;

N-[(9*S*,11*S*,15*S*)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0^{2,6}.0^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]-2-(1*H*-indol-3-yl)acetamide;

(9*S*,11*S*,15*S*)-11-hydroxy-18,21-dimethyl-15-[[2-(2-naphthyl)ethyl]amino]-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0^{2,6}.0^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraene-14,19-dione;

(9*S*,11*S*,15*S*)-15-[(4-fluorobenzyl)amino]-11-hydroxy-18,21-dimethyl-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0^{2,6}.0^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraene-14,19-dione;

benzyl *N*-[(13*S*,19*S*)-4,8-dimethyl-23-nitro-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1^{2,6}.0^{15,19}]heptacosa-1(24),2(27),3,5,22,25-hexaen-13-yl]carbamate;

benzyl *N*-[(13*R*,19*S*)-4,8-dimethyl-23-nitro-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1^{2,6}.0^{15,19}]heptacosa-1(24),2(27),3,5,22,25-hexaen-13-yl]carbamate;

(13*S*,19*S*)-13-amino-4,8-dimethyl-23-nitro-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1^{2,6}.0^{15,19}]heptacosa-1(24),2(27),3,5,22,25-hexaene-7,14-dione;

benzyl *N*-[(13*S*,19*S*)-23-amino-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1^{2,6}.0^{15,19}]heptacosa-1(24),2(27),3,5,22,25-hexaen-13-yl]carbamate;

benzyl *N*-[(13*S*,19*S*)-23-(acetilamino)-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1^{2,6}.0^{15,19}]heptacosa-1(24),2(27),3,5,22,25-hexaen-13-yl]carbamate;

N-[(13*S*,19*S*)-13-amino-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1^{2,6}.0^{15,19}]heptacosa-1(24),2(27),3,5,22,25-hexaen-23-yl]acetamide;

N-(2-chlorophenyl)-*N*-[(13*S*,19*S*)-4,8-dimethyl-23-nitro-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1^{2,6}.0^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-13-yl]urea;

N-[(13*S*,19*S*)-23-amino-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1^{2,6}.0^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-13-yl]-*N*-(2-chlorophenyl)urea;

N-[(13*S*,19*S*)-13-[(2-chloroanilino)carbonyl]amino]-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1^{2,6}.0^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-23-yl]methanesulfonamide;

N-[(13*S*,19*S*)-4,8-dimethyl-23-nitro-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1^{2,6}.0^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-13-yl]cyclopropanecarboxamide;

N-[(13*S*,19*S*)-23-amino-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1^{2,6}.0^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-13-yl]cyclopropanecarboxamide;

N-[(13*S*,19*S*)-4,8-dimethyl-23-[(methylsulfonyl)amino]-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1^{2,6}.0^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-13-yl]cyclopropanecarboxamide;

N-[(13*S*,19*S*)-13-amino-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1^{2,6}.0^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-23-yl]methanesulfonamide;

benzyl *N*-[(13*S*,19*S*)-4,8-dimethyl-23-[(methylsulfonyl)amino]-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1^{2,6}.0^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-13-yl]carbamate;

benzyl *N*-[(13*S*,19*S*)-4,8-dimethyl-7,14-dioxo-23-(2-pyrimidinylamino)-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1^{2,6}.0^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-13-yl]carbamate;

(13*S*,19*S*)-13-amino-4,8-dimethyl-23-(2-pyrimidinylamino)-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1^{2,6}.0^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaene-7,14-dione;

N-[(13*S*,19*S*)-13-(dimethylamino)-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1^{2,6}.0^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-23-yl]acetamide;

N-[(13*S*,19*S*)-23-(acetylamino)-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1^{2,6}.0^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-13-yl]-2-phenylacetamide;

N-[(13*S*,19*S*)-13-[(3-chlorophenyl)sulfonyl]amino]-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1^{2,6}.0^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-23-yl]acetamide;

N-[(13*S*,19*S*)-13-[(isobutylamino)carbonyl]amino]-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1^{2,6}.0^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-23-yl]acetamide;

N-[(13*S*,19*S*)-4,8-dimethyl-23-[(methylsulfonyl)amino]-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1^{2,6}.0^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-13-yl]-4-fluorobenzamide;

N-[(13*S*,19*S*)-13-[(3-fluorobenzyl)amino]-4,8-dimethyl-7,14-dioxo-21-oxa-3,8,15,27-tetraazatetracyclo[20.2.2.1^{2,6}.0^{15,19}]heptacos-1(24),2(27),3,5,22,25-hexaen-23-yl]methanesulfonamide;

benzyl *N*-[(15*R*,16*aS*)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16*a*,17-octahydro-14*H*-dibenzo[*i,k*]pyrrolo[2,1-*c*][1,4,7]oxadiazacyclododecin-15-yl]carbamate;

(15*R*,16*aS*)-15-amino-10-methyl-10,11,15,16,16*a*,17-hexahydro-14*H*-dibenzo[*i,k*]pyrrolo[2,1-*c*][1,4,7]oxadiazacyclododecine-9,12-dione;

(15*R*,16*aS*)-15-(dimethylamino)-10-methyl-10,11,15,16,16*a*,17-hexahydro-14*H*-dibenzo[*i,k*]pyrrolo[2,1-*c*][1,4,7]oxadiazacyclododecine-9,12-dione;

N-[(15*R*,16*aS*)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16*a*,17-octahydro-14*H*-dibenzo[*i,k*]pyrrolo[2,1-*c*][1,4,7]oxadiazacyclododecin-15-yl]acetamide;

N-[(15*R*,16*aS*)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16*a*,17-octahydro-14*H*-dibenzo[*i,k*]pyrrolo[2,1-*c*][1,4,7]oxadiazacyclododecin-15-yl]-3-methylbutanamide;

N-[(15*R*,16*aS*)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16*a*,17-octahydro-14*H*-dibenzo[*i,k*]pyrrolo[2,1-*c*][1,4,7]oxadiazacyclododecin-15-yl]-2-(2-naphthyl)acetamide;

N-[(15*R*,16*aS*)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16*a*,17-octahydro-14*H*-dibenzo[*i,k*]pyrrolo[2,1-*c*][1,4,7]oxadiazacyclododecin-15-yl]-2-(1-naphthyl)acetamide;

N-[(15*R*,16*aS*)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16*a*,17-octahydro-14*H*-dibenzo[*i,k*]pyrrolo[2,1-*c*][1,4,7]oxadiazacyclododecin-15-yl]-2-(dimethylamino)acetamide;

tert-butyl *N*-(3-[(15*R*,16*aS*)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16*a*,17-octahydro-14*H*-dibenzo[*i,k*]pyrrolo[2,1-*c*][1,4,7]oxadiazacyclododecin-15-yl]amino-3-oxopropyl)carbamate;

N-[(15*R*,16*aS*)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16*a*,17-octahydro-14*H*-dibenzo[*i,k*]pyrrolo[2,1-*c*][1,4,7]oxadiazacyclododecin-15-yl]-3-aminopropanamide;

N-[(15*R*,16*aS*)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16*a*,17-octahydro-14*H*-dibenzo[*i,k*]pyrrolo[2,1-*c*][1,4,7]oxadiazacyclododecin-15-yl]-3-fluorobenzamide;

N-[(15*R*,16*aS*)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16*a*,17-octahydro-14*H*-dibenzo[*i,k*]pyrrolo[2,1-*c*][1,4,7]oxadiazacyclododecin-15-yl]isonicotinamide;

N-[(15*R*,16*aS*)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16*a*,17-octahydro-14*H*-dibenzo[*i,k*]pyrrolo[2,1-*c*][1,4,7]oxadiazacyclododecin-15-yl]-*N*-methylurea;

N-[(15*R*,16*aS*)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16*a*,17-octahydro-14*H*-dibenzo[*i,k*]pyrrolo[2,1-*c*][1,4,7]oxadiazacyclododecin-15-yl]-*N*-(3-pyridinyl)urea;

2-methoxyethyl *N*-[(15*R*,16*aS*)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16*a*,17-octahydro-14*H*-dibenzo[*i,k*]pyrrolo[2,1-*c*][1,4,7]oxadiazacyclododecin-15-yl]carbamate;

tert-butyl 3-[(3-[(15*R*,16*aS*)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16*a*,17-octahydro-14*H*-dibenzo[*i,k*]pyrrolo[2,1-*c*][1,4,7]oxadiazacyclododecin-15-yl]amino)carbonyl)amino]propanoate;

3-[(3-[(15*R*,16*aS*)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16*a*,17-octahydro-14*H*-dibenzo[*i,k*]pyrrolo[2,1-*c*][1,4,7]oxadiazacyclododecin-15-yl]amino)carbonyl)amino]propanoic acid;

N-[(15*R*,16*aS*)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16*a*,17-octahydro-14*H*-dibenzo[*i,k*]pyrrolo[2,1-*c*][1,4,7]oxadiazacyclododecin-15-yl]methanesulfonamide;

N-[(15*R*,16*aS*)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16*a*,17-octahydro-14*H*-dibenzo[*i,k*]pyrrolo[2,1-*c*][1,4,7]oxadiazacyclododecin-15-yl]benzenesulfonamide;

(15*R*,16*aS*)-15-[(3-fluorobenzyl)amino]-10-methyl-10,11,15,16,16*a*,17-hexahydro-14*H*-dibenzo[*i,k*]pyrrolo[2,1-*c*][1,4,7]oxadiazacyclododecine-9,12-dione;

(15*R*,16*aS*)-15-(isobutylamino)-10-methyl-10,11,15,16,16*a*,17-hexahydro-14*H*-dibenzo[*i,k*]pyrrolo[2,1-*c*][1,4,7]oxadiazacyclododecine-9,12-dione;

N,N,N,N'-[(15*R*,16*aS*)-10-methyl-9,12-dioxo-9,10,11,12,15,16,16*a*,17-octahydro-14*H*-dibenzo[*i,k*]pyrrolo[2,1-*c*][1,4,7]oxadiazacyclododecin-15-yl]-*N,N,N,N*'-tetramethylguanidine;

benzyl (16*S*,18*S*)-16-[(*tert*-butoxycarbonyl)amino]-7,13-dioxo-4-(trifluoromethyl)-5,20-dioxa-3,8,11,14-tetraazatetracyclo[19.3.1.0^{2,6}.0^{14,18}]pentacosa-1(25),2(6),3,21,23-pentaene-11-carboxylate;

tert-butyl *N*-[(16*S*,18*S*)-7,13-dioxo-4-(trifluoromethyl)-5,20-dioxa-3,8,11,14-tetraazatetracyclo[19.3.1.0^{2,6}.0^{14,18}]pentacosa-1(25),2(6),3,21,23-pentaen-16-yl]carbamate;

benzyl (16*S*,18*S*)-16-amino-7,13-dioxo-4-(trifluoromethyl)-5,20-dioxa-3,8,11,14-tetraazatetracyclo[19.3.1.0^{2,6}.0^{14,18}]pentacosa-1(25),2(6),3,21,23-pentaene-11-carboxylate;

allyl *N*-[(12*R*,16*S*,18*S*)-16-[(*tert*-butoxycarbonyl)amino]-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0^{2,7}.0^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]carbamate;

allyl *N*-[(12*R*,16*S*,18*S*)-16-amino-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0^{2,7}.0^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]carbamate;
2-(1*H*-imidazol-1-yl)-*N*-[(12*R*,16*S*,18*S*)-12-[[2-(1-naphthyl)acetyl]amino]-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0^{2,7}.0^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-16-yl]acetamide;

N-[(12*R*,16*S*,18*S*)-8,13-dioxo-16-[[3-pyridinylamino)carbonyl]amino]-20-oxa-9,14-diazatetracyclo[19.3.1.0^{2,7}.0^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]-2-(1-naphthyl)acetamide;

2-(3-chlorophenyl)-*N*-[(12*R*,16*S*,18*S*)-8,13-dioxo-16-[[2-(1-pyrrolidinyl)acetyl]amino]-20-oxa-9,14-diazatetracyclo[19.3.1.0^{2,7}.0^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]acetamide;

2-cyclohexyl-*N*-[(12*R*,16*S*,18*S*)-8,13-dioxo-16-[[2-(1-pyrrolidinyl)acetyl]amino]-20-oxa-9,14-diazatetracyclo[19.3.1.0^{2,7}.0^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]acetamide;

N-[(12*R*,16*S*,18*S*)-12-[[1-naphthylamino)carbonyl]amino]-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0^{2,7}.0^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-16-yl]-2-(1-pyrrolidinyl)acetamide;

N-[(12*R*,16*S*,18*S*)-12-[(benzylsulfonyl)amino]-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0^{2,7}.0^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-16-yl]-2-(1-pyrrolidinyl)acetamide;

benzyl *N*-[(12*R*,16*S*,18*S*)-8,13-dioxo-16-[[2-(1-pyrrolidinyl)acetyl]amino]-20-oxa-9,14-diazatetracyclo[19.3.1.0^{2,7}.0^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]carbamate;

N-[(12*R*,16*S*,18*S*)-12-amino-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0^{2,7}.0^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-16-yl]-2-(1-pyrrolidinyl)acetamide;

N-[(12*R*,16*S*,18*S*)-12-[[2-(1-naphthyl)ethyl]amino]-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0^{2,7}.0^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-16-yl]-2-(1-pyrrolidinyl)acetamide;

N-[(9*S*,11*R*)-16-(3-fluorobenzyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(1-naphthyl)acetamide;

N-[(9*S*,11*R*)-16-(3-fluorobenzyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(2-naphthyl)acetamide;

N-[(9*S*,11*R*)-16-(3-fluorobenzyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-*N*-(2-naphthyl)urea;

N-[(9*S*,11*R*)-16-(3-fluorobenzyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-naphthalenesulfonamide;

N-[(9*S*,11*R*)-16-(3-fluorobenzyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-3-(2-naphthyl)propanamide;

N-[(9*S*,11*R*)-16-(3-fluorobenzyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-3-phenylpropanamide;

2-(dimethylamino)-*N*-[(9*S*,11*R*)-16-(3-fluorobenzyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]acetamide;

benzyl (9*S*,11*R*)-11-[[2-(2-naphthyl)acetyl]amino]-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaene-16-carboxylate;

N-[(9*S*,11*R*)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(2-naphthyl)acetamide;

N-[(9*S*,11*R*)-16-(3-fluorobenzoyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(2-naphthyl)acetamide;

N-[(9*S*,11*R*)-16-benzyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(2-naphthyl)acetamide;

N-[(9*S*,11*R*)-14,20-dioxo-16-phenethyl-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(2-naphthyl)acetamide;

N-[(9*S*,11*R*)-14,20-dioxo-16-(3-phenylpropyl)-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(2-naphthyl)acetamide;

N-[(9*S*,11*R*)-16-isopentyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(2-naphthyl)acetamide;

N-[(9*S*,11*R*)-16-isobutyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(2-naphthyl)acetamide;

2-(dimethylamino)ethyl (9*S*,11*R*)-11-[[2-(2-naphthyl)acetyl]amino]-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaene-16-carboxylate;

N-[(9*S*,11*R*)-16-[2-(dimethylamino)ethyl]-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(2-naphthyl)acetamide; or

3,3-dimethyl-*N*-[(9*S*,11*R*)-16-methyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]butanamide.

7. A compound according to any of claims 1 to 7 selected from:

- tert*-butyl *N*-[(12*R*,16*S*,18*S*)-12-amino-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0^{2,7}.0^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-16-yl]carbamate;

- N*-[(12*R*,16*S*,18*S*)-8,13-dioxo-16-[[2-(1-pyrrolidinyl)acetyl]amino]-20-oxa-9,14-diazatetracyclo[19.3.1.0^{2,7}.0^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]-2-(1-naphthyl)acetamide;
- benzyl *N*-[(12*R*,16*S*,18*S*)-8,13-dioxo-16-[(phenoxycarbonyl)amino]-20-oxa-9,14-diazatetracyclo[19.3.1.0^{2,7}.0^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]carbamate;
- 5 benzyl *N*-[(10*S*,12*S*,16*S*)-20-methyl-12-[[2-(2-naphthyl)acetyl]amino]-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0^{2,7}.0^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]carbamate;
- 10 2-(dimethylamino)-*N*-[(10*S*,12*S*,16*S*)-20-methyl-12-[[2-(2-naphthyl)acetyl]amino]-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0^{2,7}.0^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]acetamide;
- N*-[(10*S*,12*S*,16*S*)-16-[(cyclopropylsulfonyl)amino]-20-methyl-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0^{2,7}.0^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-12-yl]-2-
- 15 (2-naphthyl)acetamide;
- 3-methyl-*N*-[(10*S*,12*S*,16*S*)-20-methyl-12-[[2-(2-naphthyl)acetyl]amino]-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0^{2,7}.0^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]butanamide;
- N*-[(10*S*,12*S*,16*S*)-20-methyl-15,21-dioxo-16-[(2-phenylacetyl)amino]-8-oxa-14,20-diazatetracyclo[20.3.1.0^{2,7}.0^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-12-yl]-2-(2-
- 20 naphthyl)acetamide;
- N*-[(10*S*,12*S*,16*S*)-20-methyl-12-[[2-(2-naphthyl)acetyl]amino]-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0^{2,7}.0^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]benzamide;
- 25 *N*-[(10*S*,12*S*,16*S*)-20-methyl-12-[[2-(2-naphthyl)acetyl]amino]-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0^{2,7}.0^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-yl]butanamide;
- N*-[(10*S*,12*S*,16*S*)-20-methyl-12-[[2-(2-naphthyl)acetyl]amino]-15,21-dioxo-8-oxa-14,20-diazatetracyclo[20.3.1.0^{2,7}.0^{10,14}]hexacosa-1(26),2,4,6,22,24-hexaen-16-
- 30 yl]pentanamide;
- (10*R*,15*S*)-4-methoxy-10,16-dimethyl-12,17-dioxo-*N*-(3-pyridinylmethyl)-8-oxa-11,16-diazatricyclo[16.3.1.0^{2,7}]docosa-1(22),2,4,6,18,20-hexaene-15-carboxamide;
- tert*-butyl *N*-[(9*S*,11*R*)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-
- 35 yl]carbamate;

- tert*-butyl *N*-[(9*S*,11*R*)-16-methyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]carbamate;
- N*-[(9*S*,11*R*)-16-methyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(2-naphthyl)acetamide;
- N*-[(9*S*,11*R*)-16-(3-fluorobenzyl)-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]acetamide;
- N*-[(9*S*,11*R*)-16-methyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]-2-(1-naphthyl)acetamide;
- N*-[(9*S*,11*R*)-16-methyl-14,20-dioxo-7-oxa-13,16,19,23-tetraazatetracyclo[19.3.1.1^{2,6}.0^{9,13}]hexacosa-1(25),2(26),3,5,21,23-hexaen-11-yl]benzenesulfonamide;
- (13*S*,16*R*)-13-amino-16-methyl-18-oxa-8-thia-15-azatricyclo[17.3.1.0^{2,7}]tricos-1(23),2,4,6,19,21-hexaen-14-one;
- N*-[(13*S*,16*R*)-16-methyl-14-oxo-18-oxa-8-thia-15-azatricyclo[17.3.1.0^{2,7}]tricos-1(23),2,4,6,19,21-hexaen-13-yl]-2-(1-pyrrolidinyl)acetamide;
- (10*R*,13*S*)-13-amino-10-methyl-8-oxa-18-thia-11,21-diazatricyclo[17.3.1.0^{2,7}]tricos-1(23),2,4,6,19,21-hexaen-12-one;
- (8*S*,18*S*,20*S*)-18-amino-25-fluoro-6,15-dioxo-*N*-phenyl-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacosa-1(27),2,5(28),23,25-pentaene-8-carboxamide;
- (8*S*,18*S*,20*S*)-18-amino-*N*-(4-chlorophenyl)-25-fluoro-6,15-dioxo-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacosa-1(27),2,5(28),23,25-pentaene-8-carboxamide;
- (8*S*,18*S*,20*S*)-18-amino-25-fluoro-*N*-(3-methylphenyl)-6,15-dioxo-10,22-dioxa-4-thia-7,16-diazatetracyclo[21.3.1.1^{2,5}.0^{16,20}]octacosa-1(27),2,5(28),23,25-pentaene-8-carboxamide;
- N*-[(9*S*,11*S*,15*S*)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0^{2,6}.0^{9,13}]tricos-1(22),2(6),4,20(23)-tetraen-15-yl]-2-(2-naphthyl)acetamide;

- N*-[(9*S*,11*S*,15*S*)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0^{2,6}.0^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]-2-(1-naphthyl)acetamide;
- 5 *N*-[(9*S*,11*S*,15*S*)-11-methoxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0^{2,6}.0^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]-2-(2-naphthyl)acetamide;
- N*-[(9*S*,11*S*,15*S*)-11-hydroxy-18,21-dimethyl-14,19-dioxo-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0^{2,6}.0^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraen-15-yl]-*N'*-(2-naphthyl)urea;
- 10 (9*S*,11*S*,15*S*)-11-hydroxy-18,21-dimethyl-15-[[2-(2-naphthyl)ethyl]amino]-7-oxa-3-thia-13,18,21,22-tetraazatetracyclo[18.2.1.0^{2,6}.0^{9,13}]tricoso-1(22),2(6),4,20(23)-tetraene-14,19-dione;
- 2-(1*H*-imidazol-1-yl)-*N*-[(12*R*,16*S*,18*S*)-12-[[2-(1-naphthyl)acetyl]amino]-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0^{2,7}.0^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-16-yl]acetamide;
- 15 *N*-[(12*R*,16*S*,18*S*)-8,13-dioxo-16-[[3-(pyridinylamino)carbonyl]amino]-20-oxa-9,14-diazatetracyclo[19.3.1.0^{2,7}.0^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]-2-(1-naphthyl)acetamide;
- 2-(3-chlorophenyl)-*N*-[(12*R*,16*S*,18*S*)-8,13-dioxo-16-[[2-(1-pyrrolidinyl)acetyl]amino]-20-oxa-9,14-diazatetracyclo[19.3.1.0^{2,7}.0^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]acetamide;
- 20 2-cyclohexyl-*N*-[(12*R*,16*S*,18*S*)-8,13-dioxo-16-[[2-(1-pyrrolidinyl)acetyl]amino]-20-oxa-9,14-diazatetracyclo[19.3.1.0^{2,7}.0^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-12-yl]acetamide; or
- 25 *N*-[(12*R*,16*S*,18*S*)-12-[[1-(naphthylamino)carbonyl]amino]-8,13-dioxo-20-oxa-9,14-diazatetracyclo[19.3.1.0^{2,7}.0^{14,18}]pentacosa-1(25),2,4,6,21,23-hexaen-16-yl]-2-(1-pyrrolidinyl)acetamide.
8. A compound according to any one of claims 1 to 8 for use as a therapeutically
- 30 active substance.
9. A compound according to claim 9 for use as a therapeutically active substance having i) inhibitory activity on endothelin converting enzyme of subtype 1 (ECE-1), ii) inhibitory activity on the cysteine protease cathepsin S (CatS), iii)
- 35 antagonistic activity on the oxytocin (OT) receptor), iv) antagonistic activity on the

thyrotropin-releasing hormone (TRH) receptor), v) agonistic activity on the bombesin 3 (BB3) receptor, vi) antagonistic activity on the leukotriene B4 (LTB4) receptor, and/or vii) antimicrobial activity against at least one bacterial strain, in particular *Staphylococcus aureus* or *Streptococcus pneumoniae*.

5

10. A pharmaceutical composition comprising a compound or a mixture of compounds according to any one of claims 1 to 8, or pharmaceutically acceptable salt(s) thereof, and at least one therapeutically inert excipient.

10 11. A pharmaceutical composition according to claim 11 suitable for oral, topical, transdermal, injection, buccal, transmucosal, pulmonary or inhalation administration, particularly in form of tablets, dragees, capsules, solutions, liquids, gels, plaster, creams, ointments, syrup, slurries, suspensions, spray, nebulizer or suppositories.

15 12. The use of a compound according to any one of claims 1 to 8 for the manufacture of a medicament, having i) inhibitory activity on endothelin converting enzyme of subtype 1 (ECE-1), ii) inhibitory activity on the cysteine protease cathepsin S (CatS), iii) antagonistic activity on the oxytocin (OT) receptor, iv) antagonistic activity on the thyrotropin-releasing hormone (TRH) receptor, v) agonistic activity on
20 the bombesin 3 (BB3) receptor, vi) antagonistic activity on the leukotriene B4 (LTB4) receptor, and/or vii) antimicrobial activity against at least one bacterial strain, in particular *Staphylococcus aureus* or *Streptococcus pneumoniae*.

25 13. The use of a compound according to any one of claims 1 to 8 for the manufacture of a medicament for the prevention or treatment of i) diseases resulting from abnormally high plasma or tissue levels of the potent vasoconstrictive peptide endothelin-1 (ET-1), like systemic and pulmonary hypertension, cerebral vasospasm and stroke, asthma, cardiac and renal failure, atherosclerosis, preeclampsia, benign prostatic hyperplasia, and carcinogenesis; ii) a wide range of diseases related to
30 Cathepsin S, including neuropathic hyperalgesia, obesity, and in particular diseases of the immune system, like rheumatoid arthritis (RA), multiple sclerosis (MS), myasthenia gravis, transplant rejection, diabetes, Sjögrens syndrome, Grave's disease, systemic lupus erythematosus, osteoarthritis, psoriasis, idiopathic thrombocytopenic purpura, allergic rhinitis, asthma, atherosclerosis, and chronic
35 obstructive pulmonary disease (COPD); iii) diseases and conditions associated to an

overexpression of oxytocin (OT), like preterm delivery; iv) diseases related to a dysfunction in the homeostatic system of the thyrotropin-releasing hormone (TRH), such as infantile spasms, generalized and refractory partial seizures, edematous and destructive forms of acute pancreatitis, and certain inflammatory disorders (e.g. autoimmune diseases, inflammatory bowel diseases, cancer-related fatigue or depression, and Alzheimer's disease); v) diseases related to a dysfunction of the bombesin 3 (BB3) receptor, like obesity and impairment of glucose metabolism, disorders of lung development, pulmonary diseases, CNS disorders and carcinogenesis; vi) diseases potentially treatable by blockade of the leukotriene B4 (LTB4) receptor, especially inflammatory and allergic diseases like asthma, acute respiratory distress syndrome (ARDS), acute lung injury (ALI), chronic obstructive pulmonary disease (COPD), rheumatoid arthritis (RA) and inflammatory bowel disease (IBD), allergic rhinitis, atopic dermatitis, allergic conjunctivitis, obliterative bronchiolitis after lung transplantation, or interstitial lung diseases; and/or vii) a wide range of infections caused by microorganisms, in particular strains of *Staphylococcus aureus* or *Streptococcus pneumoniae*, comprising infections related to: a) respiratory diseases like cystic fibrosis, emphysema, asthma or pneumonia, b) skin or soft tissue diseases such as surgical wounds, traumatic wounds, burn wounds or herpes, smallpox, rubella or measles, c) gastrointestinal diseases including epidemic diarrhea, necrotizing enterocolitis, typhilitis or gastroenteritis or pancreatitis, d) eye diseases such as keratitis and endophthalmitis, e) ear diseases, e.g. otitis, f) CNS diseases including brain abscess and meningitis or encephalitis, g) bone diseases such as osteochondritis and osteomyelitis, h) cardiovascular diseases like endocarditis and pericarditis, or i) genitourinary diseases such as epididymitis, prostatitis and urethritis.

25

14. A compound according to any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, for the prevention or treatment of i) diseases resulting from abnormally high plasma or tissue levels of the potent vasoconstrictive peptide endothelin-1 (ET-1), like systemic and pulmonary hypertension, cerebral vasospasm and stroke, asthma, cardiac and renal failure, atherosclerosis, preeclampsia, benign prostatic hyperplasia, and carcinogenesis; ii) a wide range of diseases related to Cathepsin S, including neuropathic hyperalgesia, obesity, and in particular diseases of the immune system, like rheumatoid arthritis (RA), multiple sclerosis (MS), myasthenia gravis, transplant rejection, diabetes, Sjögren's syndrome, Grave's disease, systemic lupus erythematosus, osteoarthritis, psoriasis, idiopathic

35

thrombocytopenic purpura, allergic rhinitis, asthma, atherosclerosis, and chronic obstructive pulmonary disease (COPD); iii) diseases and conditions associated to an overexpression of oxytocin (OT), like preterm delivery; iv) diseases related to a dysfunction in the homeostatic system of the thyrotropin-releasing hormone (TRH),
5 such as infantile spasms, generalized and refractory partial seizures, edematous and destructive forms of acute pancreatitis, and certain inflammatory disorders (e.g. autoimmune diseases, inflammatory bowel diseases, cancer-related fatigue or depression, and Alzheimer's disease); v) diseases related to a dysfunction of the bombesin 3 (BB3) receptor, like obesity and impairment of glucose metabolism,
10 disorders of lung development, pulmonary diseases, CNS disorders and carcinogenesis; vi) diseases potentially treatable by blockade of the leukotriene B4 (LTB4) receptor, especially inflammatory and allergic diseases like asthma, acute respiratory distress syndrome (ARDS), acute lung injury (ALI), chronic obstructive pulmonary disease (COPD), rheumatoid arthritis (RA) and inflammatory bowel
15 disease (IBD), allergic rhinitis, atopic dermatitis, allergic conjunctivitis, obliterative bronchiolitis after lung transplantation, or interstitial lung diseases; and/or vii) a wide range of infections caused by microorganisms, in particular strains of *Staphylococcus aureus* or *Streptococcus pneumoniae*, comprising infections related to: a) respiratory diseases like cystic fibrosis, emphysema, asthma or pneumonia, b) skin or soft tissue
20 diseases such as surgical wounds, traumatic wounds, burn wounds or herpes, smallpox, rubella or measles, c) gastrointestinal diseases including epidemic diarrhea, necrotizing enterocolitis, typhilitis or gastroenteritis or pancreatitis, d) eye diseases such as keratitis and endophthalmitis, e) ear diseases, e.g. otitis, f) CNS diseases including brain abscess and meningitis or encephalitis, g) bone diseases such as
25 osteochondritis and osteomyelitis, h) cardiovascular diseases like endocarditis and pericarditis, or i) genitourinary diseases such as epididymitis, prostatitis and urethritis.

15. The use of a compound according to any one of claims 1 to 8 for pharmaceutical lead finding.