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:

- High structural complexity
- Low metabolic stability
- Low oral bioavailability
- Low membrane permeability; i.e. intracellular targets not amenable
- Low tissue penetration
- Short half-life
- Chemical synthesis often complex and lengthy
- Often accessible only by fermentation or recombinant methods
- High production costs
- Complex quality control and development processes.

The present invention describes now novel, fully synthetic, macrocyclic natural product-like molecules of type **Ia/Ib** (Figure 1), which can be synthesized in a modular approach by connecting suitably protected building blocks **A**, **B**, and **C** to a linear precursor followed by subsequent cyclization.

Building blocks **A** (Figure 2) serve as conformation-inducing templates ("Template") and are based on appropriately substituted and protected divalent phenol or thiophenol derivatives.

Building blocks **B** (Figure 2) are corresponding to appropriately substituted and protected tertiary amins.
Building blocks **B** serve as a conformational modulator ("Modulator") by influencing the conformation of the macrocycle, e.g. through *cis/trans*-isomerization of amides.

In macrocycles of type **Ia/Ib** the building blocks **A** and **B** are connected via the "Bridge" **C** (Figure 2), which can be constituted by one to three appropriately and independently substituted subunits **c1**, **c2** and **c3** derived from suitably substituted and protected precursors, most often from, but not limited to, appropriately substituted and protected amino acid or amine derivatives.

The connection of building block **A** to building block **B** occurs via an ether (X=O) or thioether (X=S) bond and to building block **C** via M-L as detailed below. The sulfur atom of a thioether linkage can easily and selectively be oxidized to the corresponding sulfoxide (S=O) or sulfone ($S(=O)_2$) both of which are therefore a part of the invention (Figure 3).

The functional moiety U connects the bridge **C** with the nitrogen atom of modulator **B**. In most cases this is realized by an amide bond (secondary or tertiary), in which case the moiety U corresponds to a carbonyl group (-C(=O)-). Alternatively, U can be defined as a carbamoyl moiety ($-NR^4-C(=O)-$) which corresponds to a urea moiety (including the N-atom of **B**) as functional connection between **B** and **C**. Similarly a carboxyl group (-O-C(=O)-) as U describes a carbamate linkage between **B** and **C**. In addition, U can represent an oxalyl group (-C(=O)-C(=O)-) or the corresponding acetal ($-C(-OR^{20})_2-C(=O)-$).

Importantly, in case that R^2 of building block **B** constitutes an amine substituent, two alternatives for linking building block **B** with building block **C** is possible: Either the standard link via the heterocyclic nitrogen atom or, alternatively, the exocyclic amine functionality. This is reflected either by formula **Ia** or formula **Ib**, respectively, which are both integral part of this invention sharing equally common technical features.

The connectivity between **C** and **A** is described in a generic way with the functional unit M-L, which corresponds in most cases to a secondary or tertiary amide bond (M-L = $-NR^4-C(=O)-$). Alternative connections of M-L are thioethers ($-CHR^6-S-$) and its oxidation products, i.e. sulfoxides ($-CHR^6-S(=O)-$) or sulfones ($-CHR^6-S(=O)_2-$), as well as olefinic moieties ($-CR^6=CR^{12}-(CHR^3)_q-$) and their reduced forms, the aliphatic groups ($-CHR^6-CHR^{12}-(CHR^3)_q-$).

As already mentioned, the bridge **C** in turn can be constituted by one to three appropriately and independently substituted subunits **c1**, **c2** and **c3**. These subunits **c1** to **c3** are independently connected to each other by the generic groups V and W which can correspond to an amide bond ($-C(=O)NR^4-$), a methylene-heteroatom linkage ($-CHR^3-Z-$), an alkene[1,2]diyl moiety ($-CHR^{12}=CHR^{13}-$), introduced by olefin metathesis, an alkane[1,2]diyl spacer ($-CHR^{12}-CHR^{13}-$), accessible from the metathesis product by hydrogenation, an oxalyl group ($-C(=O)-C(=O)-$) or a disulfide bridge ($-S-S-$).

The spatial orientation of the substituents in macrocycles of type **Ia/Ib** is modulated by the ring size and the stereochemical connectivity within building blocks **A**, **B** and **C**. Both, the macrocyclic backbone and the substituents can contribute to the biological activity of compounds of type **Ia/Ib**.

For most examples the backbone of macrocycles **Ia/Ib** contains an aromatic ether/thioether linkage and one or more tertiary amide bonds; in other cases a secondary amide bond, an aliphatic ether linkage, an ethylidene or an ethylene moiety may be part of the backbone as defined above. Ether linkages in macrocyclic molecules have been shown to be beneficial by favorably influencing physico-chemical and pharmacological properties, such as 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 containing macrocycles show increased proteolytic stability, cell permeability and oral bioavailability compared to the parent molecules with secondary amide bonds (E. Biron, J. Chatterjee, O. Ovadia, D. Langenegger, J. Brueggen, D. Hoyer, H. A. Schmid, R. Jelinek, C. Gilon, A. Hoffmann, H. Kessler, *Angew. Chem. Int. Ed.* **2008**, *47*, 1-6; J. Chatterjee, O. Ovadia, G. Zahn, L. Marinelli, A. Hoffmann, C. Gilon, H. Kessler, *J. Med. Chem.* **2007**, *50*, 5878-5881). For example, the cyclic undecapeptide cyclosporin A (INN: Ciclosporin), which is used as immunosuppressant in organ transplants, contains seven *N*-methylated amino acids and possesses good oral bioavailability when formulated appropriately (P. R. Beauchesne, N. S. C. Chung, K. M. Wasan, *Drug Develop. Ind. Pharm.* **2007**, *33*, 211-220). Peptidyl *cis/trans* isomerization of proline or pipecolic acid containing polypeptides and proteins is a well known process in protein folding events. *In vivo*, this process can be mediated by peptidyl prolyl *cis/trans* isomerases such as the cyclophilins, the FK506-binding proteins and the parvulins (A. Bell, P. Monaghan, A. P. Page, *Int. J. Parasitol.* **2006**, *36*, 261-276).

Besides their role in protein folding and in the immune system, peptidyl prolyl *cis/trans* isomerases have been implicated in cell cycle control (P. E. Shaw, *EMBO Reports* **2002**, *3*, 521-526) and therefore constitute interesting pharmaceutical targets. FK506 and cyclosporin A which bind to the FK506-binding protein and cyclophilins, respectively, are both macrocyclic natural products, with the former one containing a pipecolic acid residue.

For many existing and emerging biological targets it is difficult to find classical small molecule hits as starting points for drug development (J. A. Robinson, S. DeMarco, F. Gombert, K. Moehle, D. Obrecht, *Drug Disc. Today* **2008**, *13*, 944-951). Many of these extra- and intracellular "difficult targets" involve protein-protein interactions, such as receptor tyrosine kinases, growth factor receptors, transcription modulators, chaperones, and others. For several of them macrocyclic natural and synthetic compounds have been described as good starting points for drug discovery programs (e.g. D. Obrecht, J. A. Robinson, F. Bernardini, C. Bisang, S. J. DeMarco, K. Moehle, F. O. Gombert, *Curr. Med. Chem.* **2009**, *16*, 42-65).

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

- Natural product-like structural complexity
- Good solubility
- High metabolic stability
- Improved oral bioavailability
- Improved membrane permeability
- Extra- and intracellular targets amenable
- Improved tissue penetration
- Small molecule-like pharmacokinetics

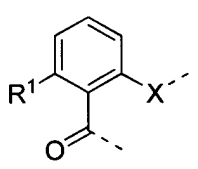
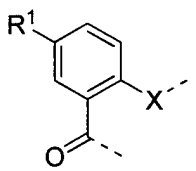
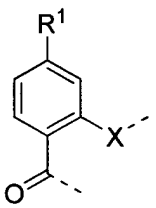
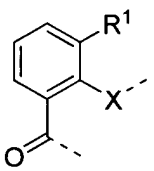
- Modular chemical synthesis
- Synthesis process well suited for parallelization
- Reasonable production costs
- Small molecule-like QC and development processes

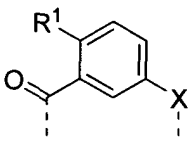
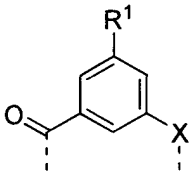
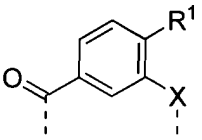
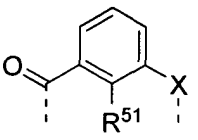
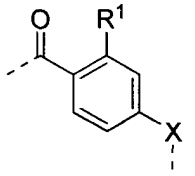
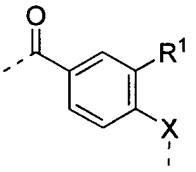
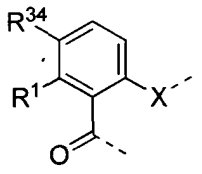
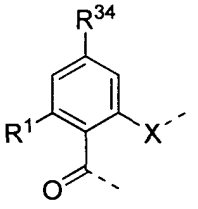
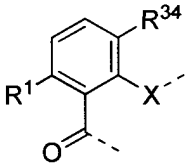
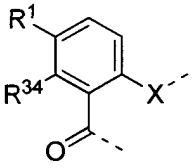
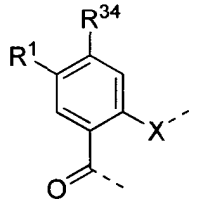
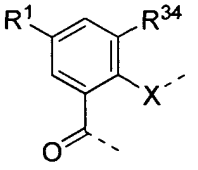
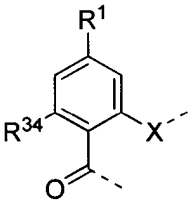
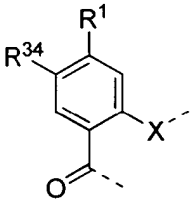
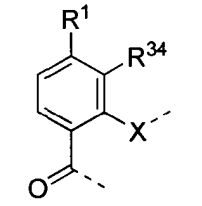
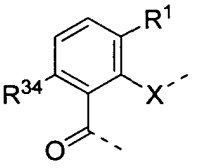
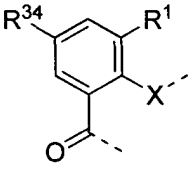
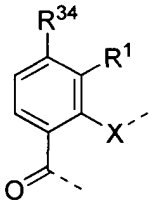
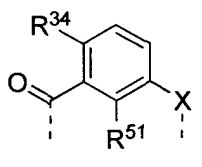
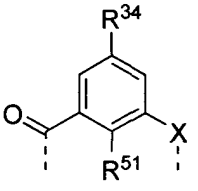
The main embodiment of the current invention of novel and fully synthetic macrocyclic compounds of type **Ia/Ib** according Figure 1 (detailed in Figure 2 and 3) is defined by groups of selected building blocks **A, B** and **C** as shown in Table 1 to 3 and by the appending substituents R^1-R^{53} as detailed below.

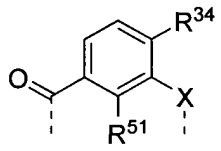
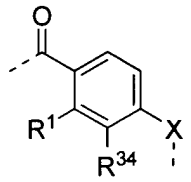
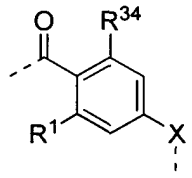
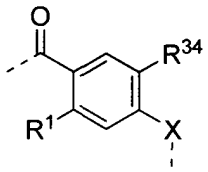
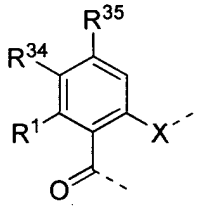
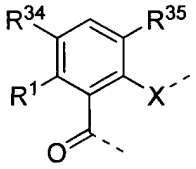
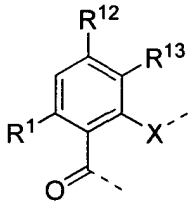
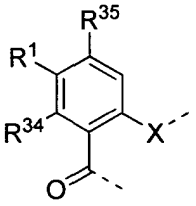
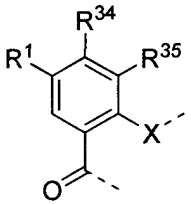
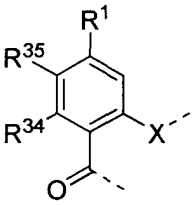
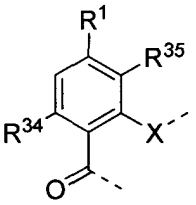
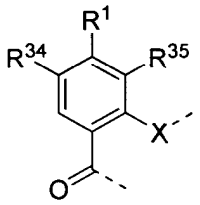
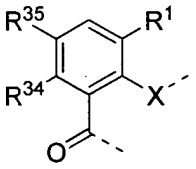
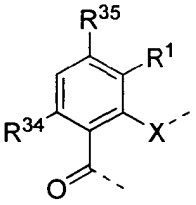
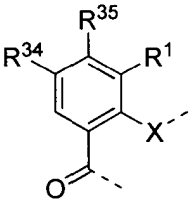
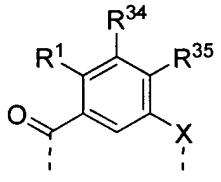
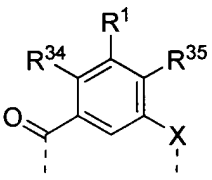
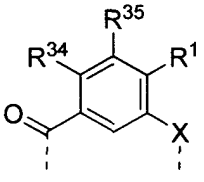
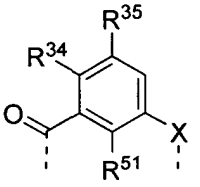
Building block A is a bivalent radical selected from the group of Table 1.

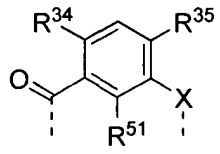
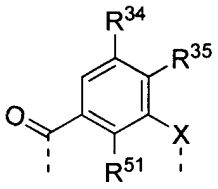
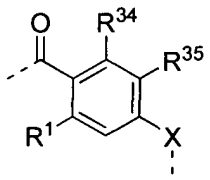
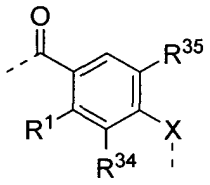
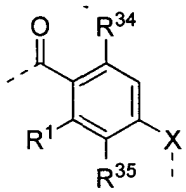
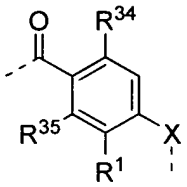
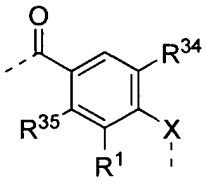
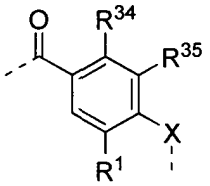
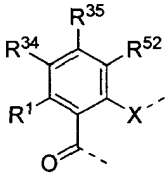
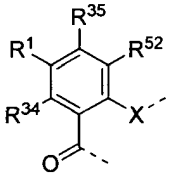
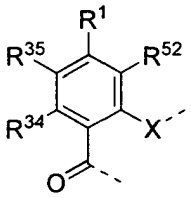
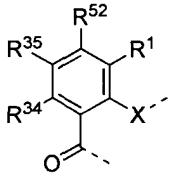
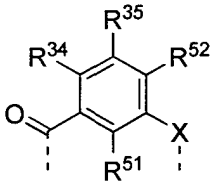
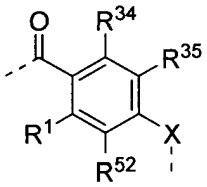
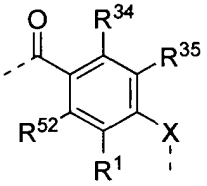
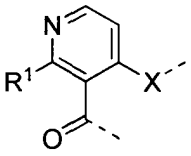
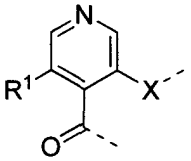
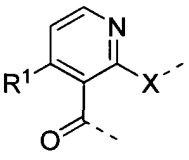
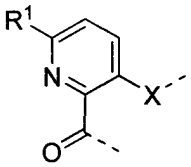
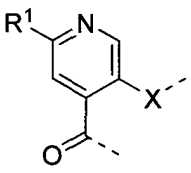
As mentioned hereinabove, building blocks of type **A** act as templates and exert an important conformational constraint on products of type **Ia/Ib**. The structural effects of building blocks of type **A** depend largely on the relative orientation of the attachment vectors of -X- and -L- and on the spatial distance between these groups. Molecular modeling, performed on the prevalent examples wherein -L- is -C(=O)-, clearly indicates that distances (typically between 2.5 and 7.5 Å) and vector arrangements for -X- and -C(=O)- in **A1-A683** vary considerably, thus strongly influencing the conformations of macrocycles of type **Ia/Ib**.

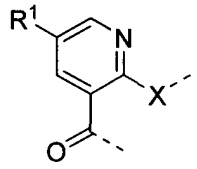
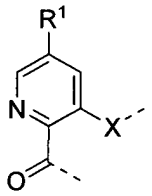
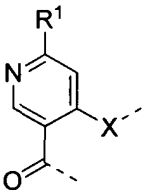
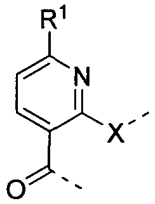
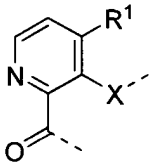
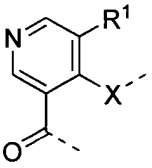
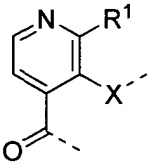
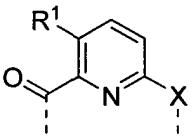
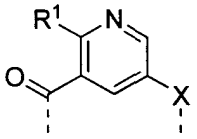
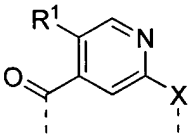
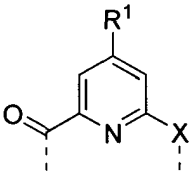
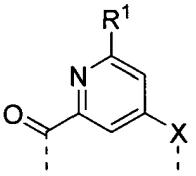
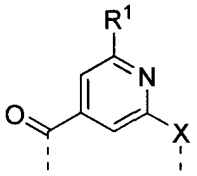
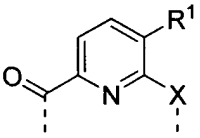
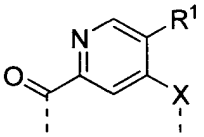
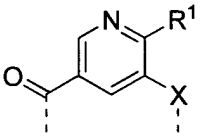
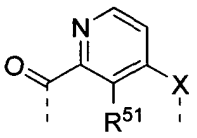
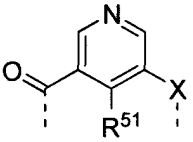
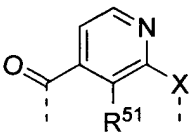
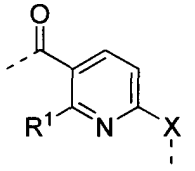
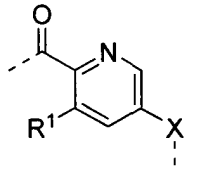
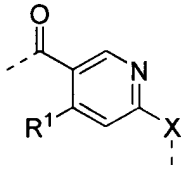
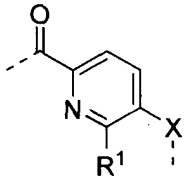
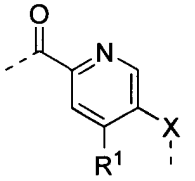
Table 1: Radicals **A1-A683** (*continued on the following pages*)

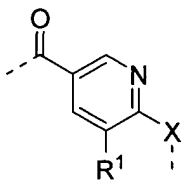
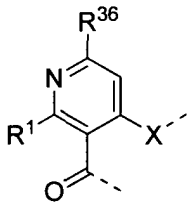
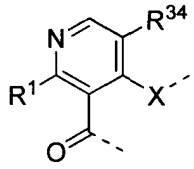
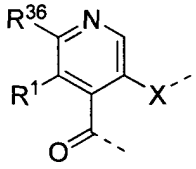
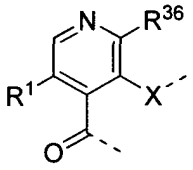
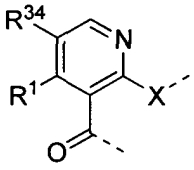
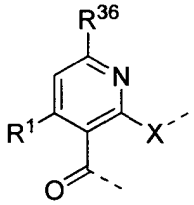
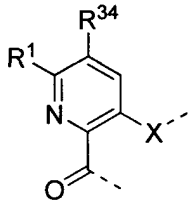
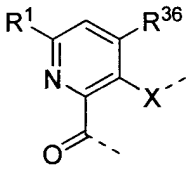
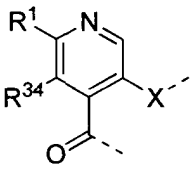
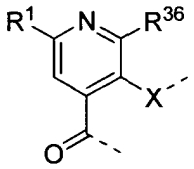
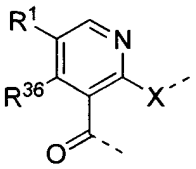
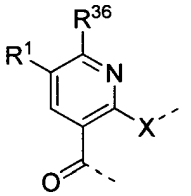
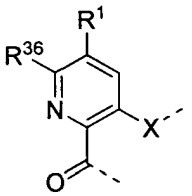
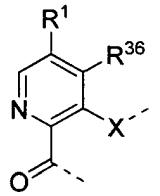
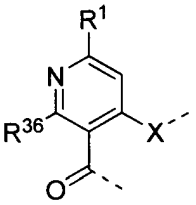
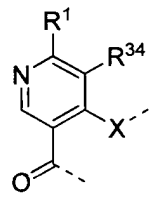
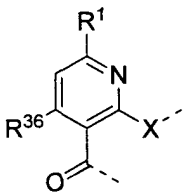
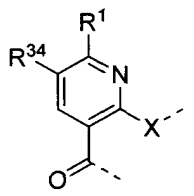
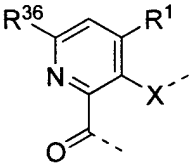
			
A1 (a1)	**A2** (a1)	**A3** (a1)	**A4** (a1)

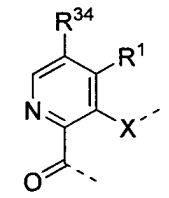
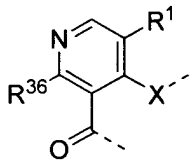
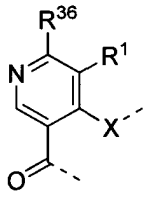
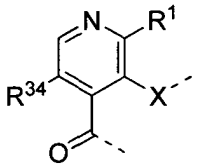
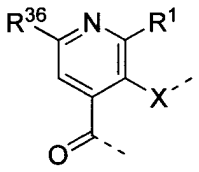
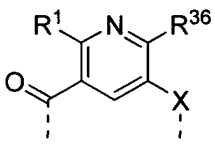
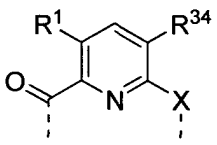
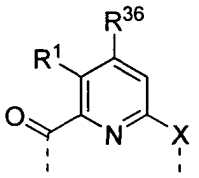
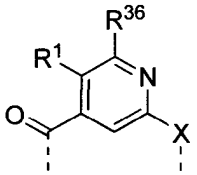
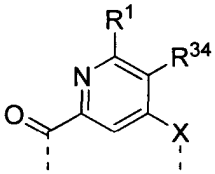
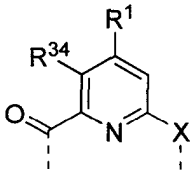
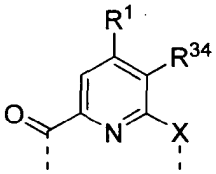
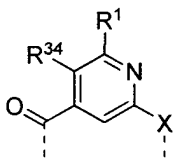
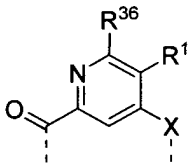
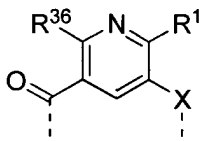
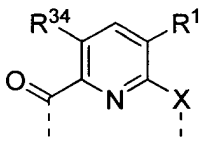
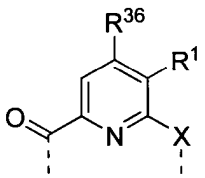
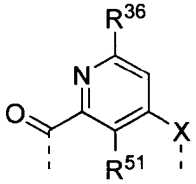
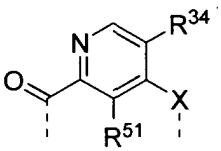
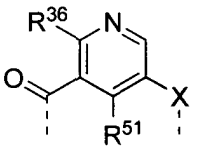
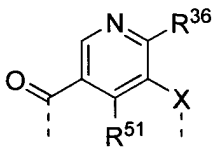
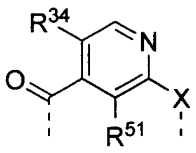
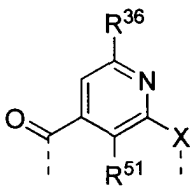
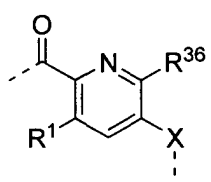
 **A5** (a1)	 **A6** (a1)	 **A7** (a1)	 **A8** (a1)
 **A9** (a1)	 **A10** (a1)	 **A11** (a1)	 **A12** (a1)
 **A13** (a1)	 **A14** (a1)	 **A15** (a1)	 **A16** (a1)
 **A17** (a1)	 **A18** (a1)	 **A19** (a1)	 **A20** (a1)
 **A21** (a1)	 **A22** (a1)	 **A23** (a1)	 **A24** (a1)

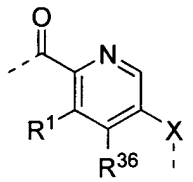
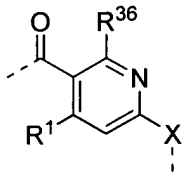
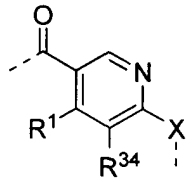
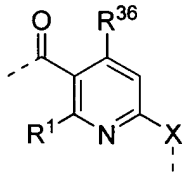
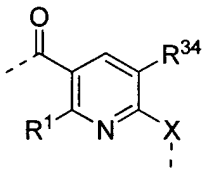
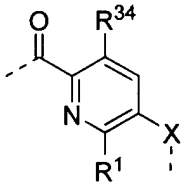
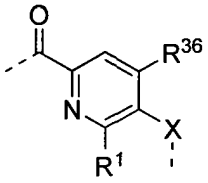
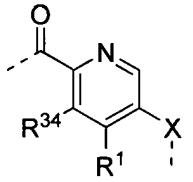
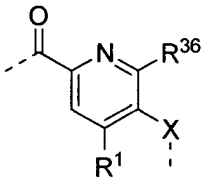
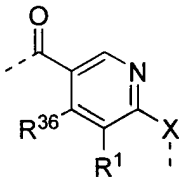
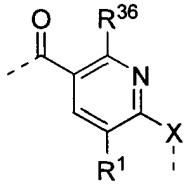
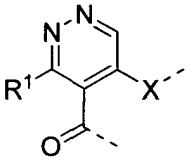
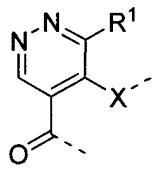
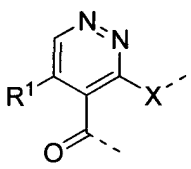
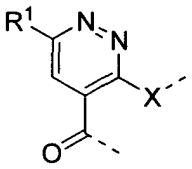
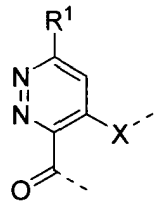
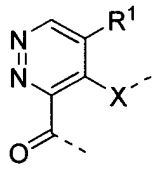
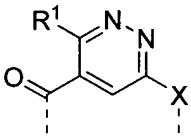
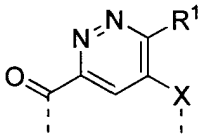
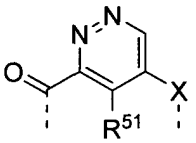
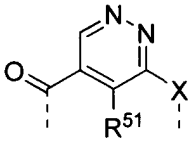
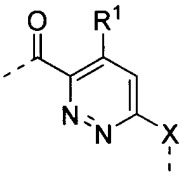
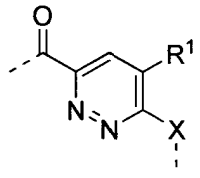
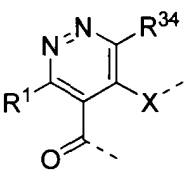
 **A25** (a1)	 **A26** (a1)	 **A27** (a1)	 **A28** (a1)
 **A29** (a1)	 **A30** (a1)	 **A31** (a1)	 **A32** (a1)
 **A33** (a1)	 **A34** (a1)	 **A35** (a1)	 **A36** (a1)
 **A37** (a1)	 **A38** (a1)	 **A39** (a1)	 **A40** (a1)
 **A41** (a1)	 **A42** (a1)	 **A43** (a1)	 **A44** (a1)

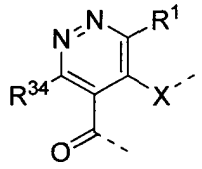
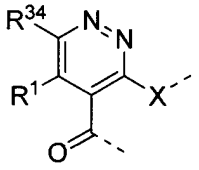
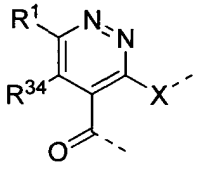
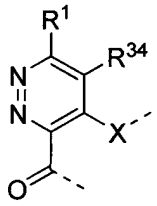
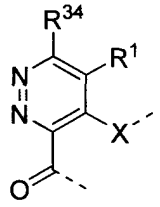
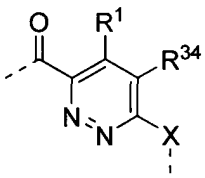
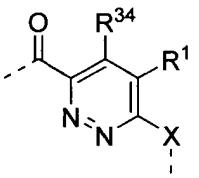
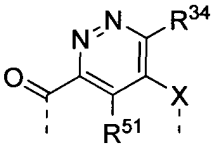
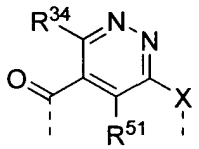
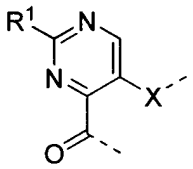
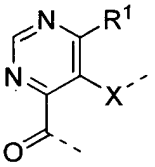
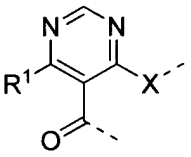
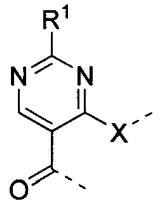
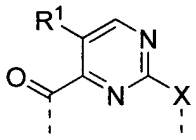
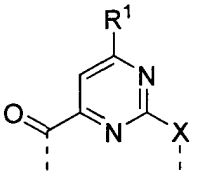
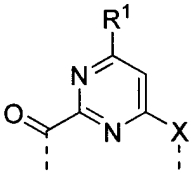
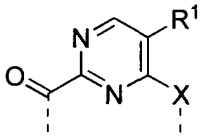
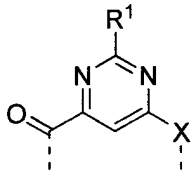
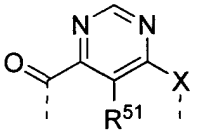
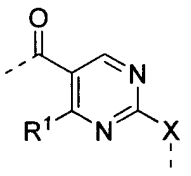
 **A45** (a1)	 **A46** (a1)	 **A47** (a1)	 **A48** (a1)
 **A49** (a1)	 **A50** (a1)	 **A51** (a1)	 **A52** (a1)
 **A53** (a1)	 **A54** (a1)	 **A55** (a1)	 **A56** (a1)
 **A57** (a1)	 **A58** (a1)	 **A59** (a1)	 **A60** (a2)
 **A61** (a2)	 **A62** (a2)	 **A63** (a2)	 **A64** (a2)

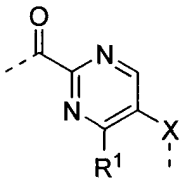
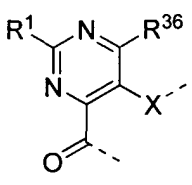
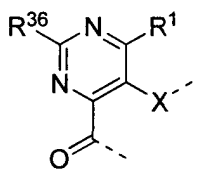
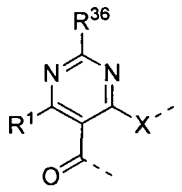
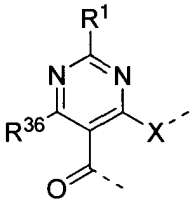
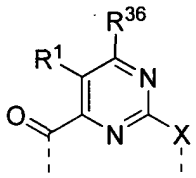
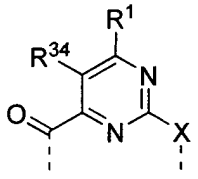
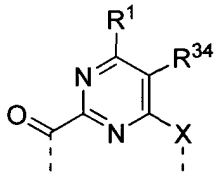
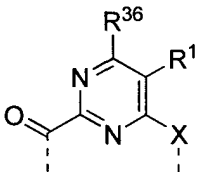
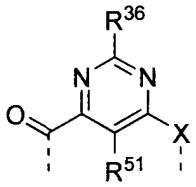
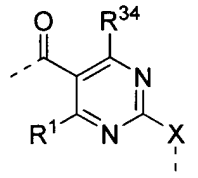
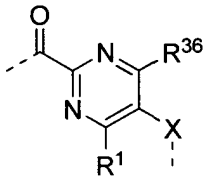
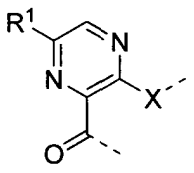
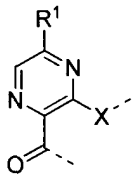
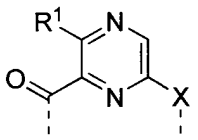
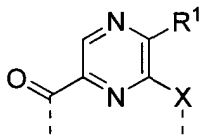
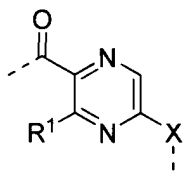
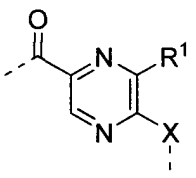
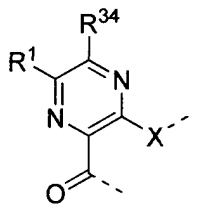
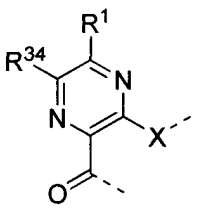
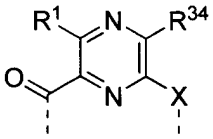
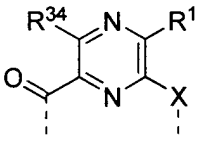
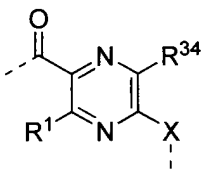
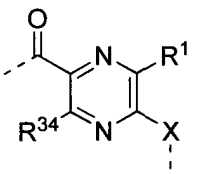
 **A65** (a2)	 **A66** (a2)	 **A67** (a2)	 **A68** (a2)
 **A69** (a2)	 **A70** (a2)	 **A71** (a2)	 **A72** (a2)
 **A73** (a2)	 **A74** (a2)	 **A75** (a2)	 **A76** (a2)
 **A77** (a2)	 **A78** (a2)	 **A79** (a2)	 **A80** (a2)
 **A81** (a2)	 **A82** (a2)	 **A83** (a2)	 **A84** (a2)
 **A85** (a2)	 **A86** (a2)	 **A87** (a2)	 **A88** (a2)

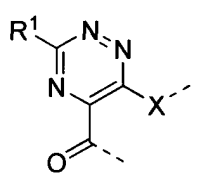
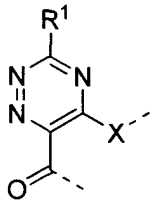
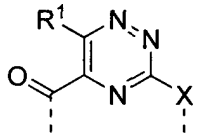
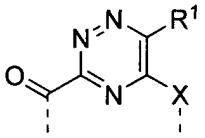
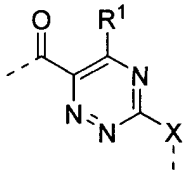
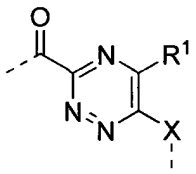
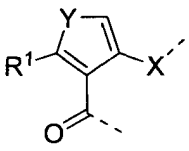
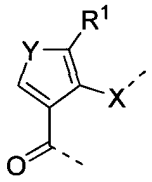
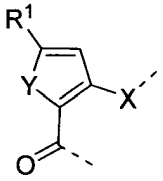
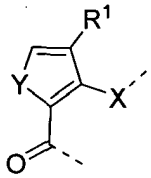
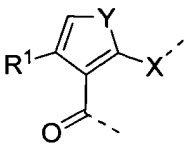
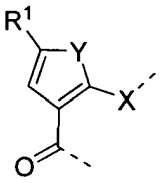
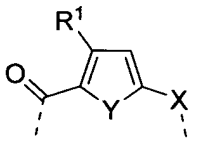
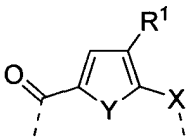
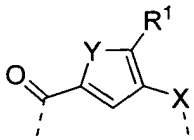
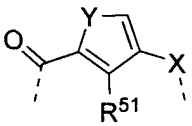
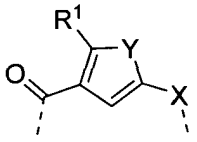
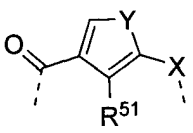
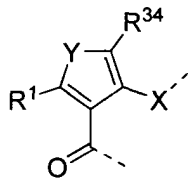
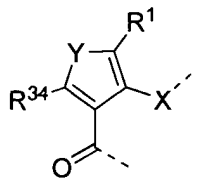
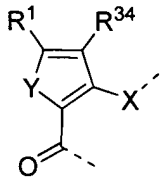
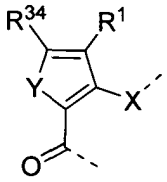
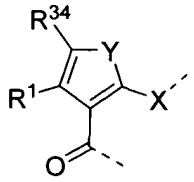
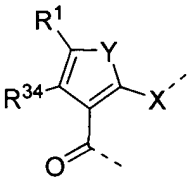
 **A89** (a2)	 **A90** (a2)	 **A91** (a2)	 **A92** (a2)
 **A93** (a2)	 **A94** (a2)	 **A95** (a2)	 **A96** (a2)
 **A97** (a2)	 **A98** (a2)	 **A99** (a2)	 **A100** (a2)
 **A101** (a2)	 **A102** (a2)	 **A103** (a2)	 **A104** (a2)
 **A105** (a2)	 **A106** (a2)	 **A107** (a2)	 **A108** (a2)

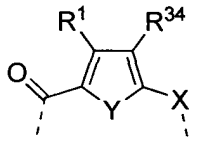
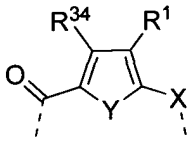
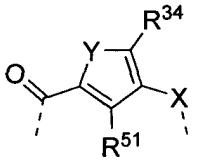
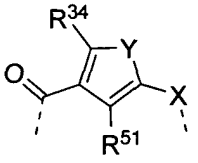
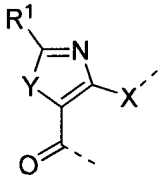
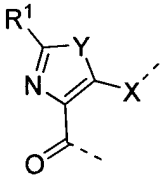
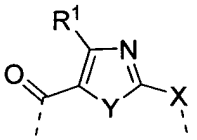
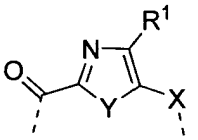
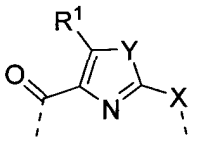
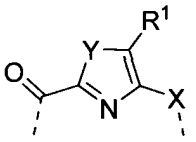
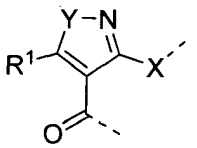
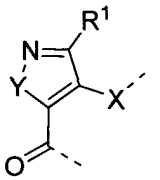
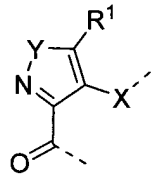
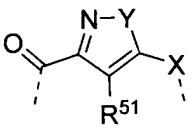
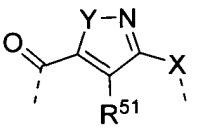
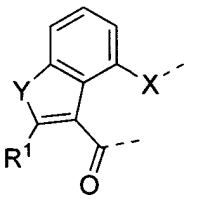
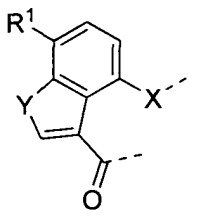
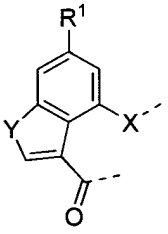
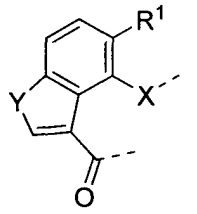
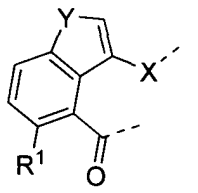
 **A109** (a2)	 **A110** (a2)	 **A111** (a2)	 **A112** (a2)
 **A113** (a2)	 **A114** (a2)	 **A115** (a2)	 **A116** (a2)
 **A117** (a2)	 **A118** (a2)	 **A119** (a2)	 **A120** (a2)
 **A121** (a2)	 **A122** (a2)	 **A123** (a2)	 **A124** (a2)
 **A125** (a2)	 **A126** (a2)	 **A127** (a2)	 **A128** (a2)
 **A129** (a2)	 **A130** (a2)	 **A131** (a2)	 **A132** (a2)

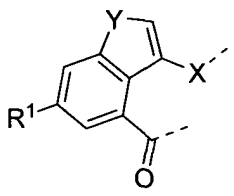
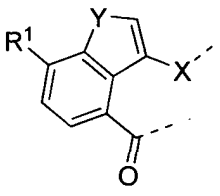
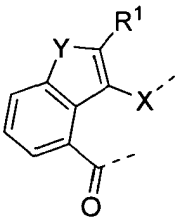
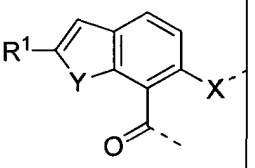
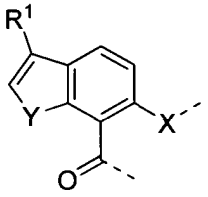
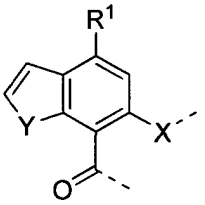
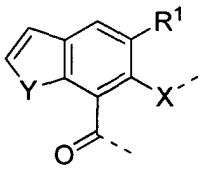
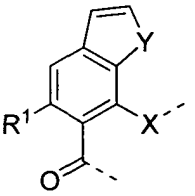
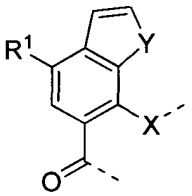
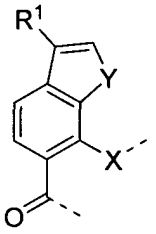
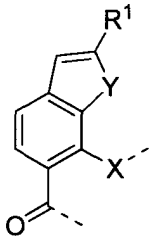
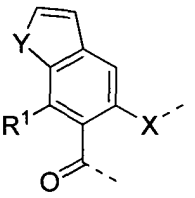
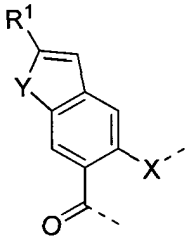
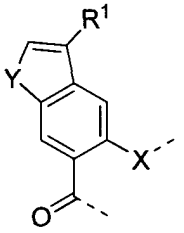
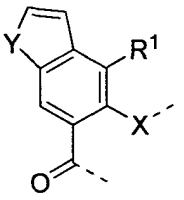
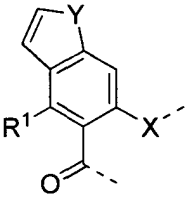
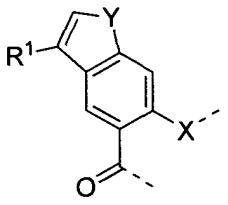
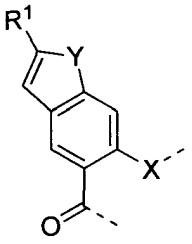
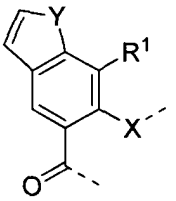
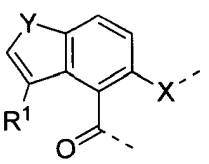
 **A133** (a2)	 **A134** (a2)	 **A135** (a2)	 **A136** (a2)
 **A137** (a2)	 **A138** (a2)	 **A139** (a2)	 **A140** (a2)
 **A141** (a2)	 **A142** (a2)	 **A143** (a2)	 **A144** (a3)
 **A145** (a3)	 **A146** (a3)	 **A147** (a3)	 **A148** (a3)
 **A149** (a3)	 **A150** (a3)	 **A151** (a3)	 **A152** (a3)
 **A153** (a3)	 **A154** (a3)	 **A155** (a3)	 **A156** (a3)

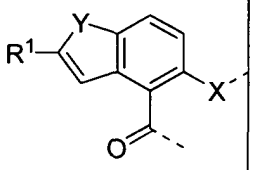
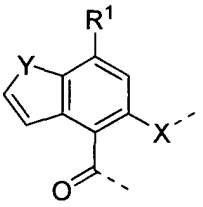
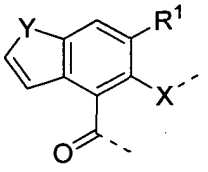
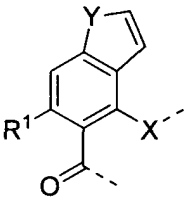
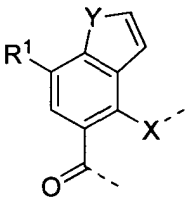
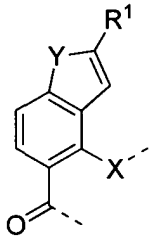
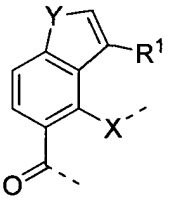
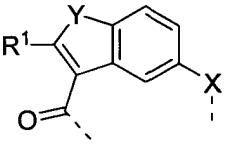
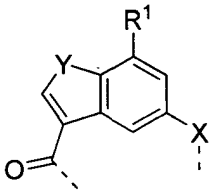
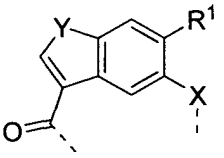
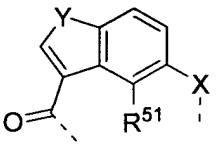
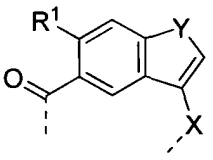
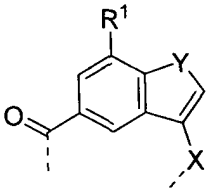
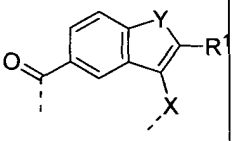
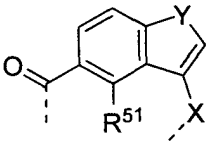
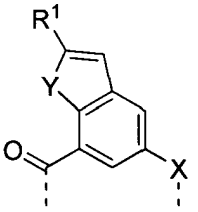
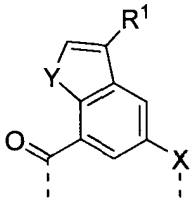
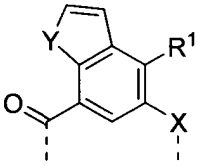
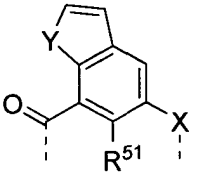
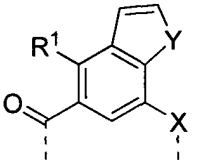
 **A157** (a3)	 **A158** (a3)	 **A159** (a3)	 **A160** (a3)
 **A161** (a3)	 **A162** (a3)	 **A163** (a3)	 **A164** (a3)
 **A165** (a3)	 **A166** (a4)	 **A167** (a4)	 **A168** (a4)
 **A169** (a4)	 **A170** (a4)	 **A171** (a4)	 **A172** (a4)
 **A173** (a4)	 **A174** (a4)	 **A175** (a4)	 **A176** (a4)

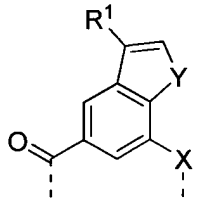
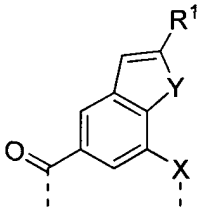
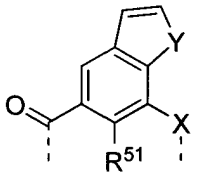
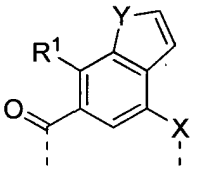
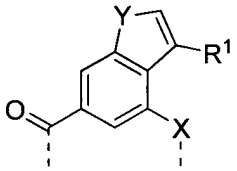
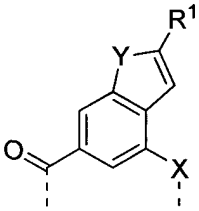
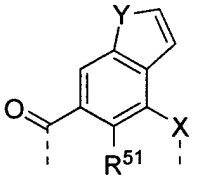
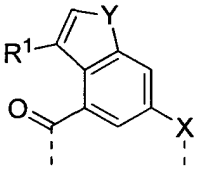
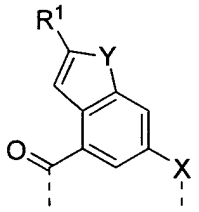
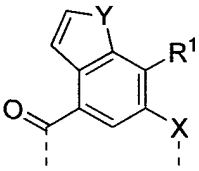
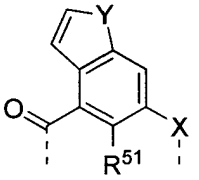
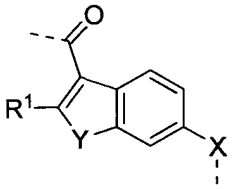
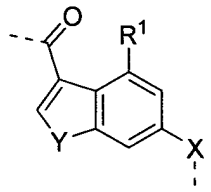
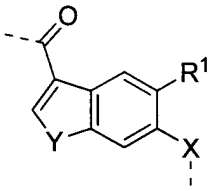
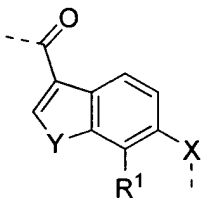
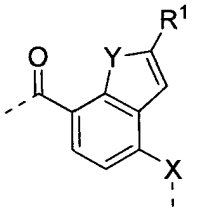
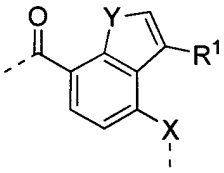
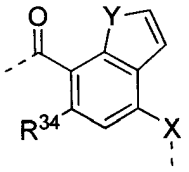
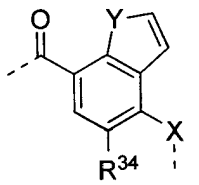
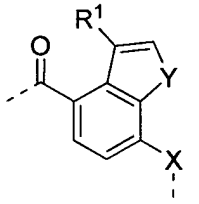
 **A177** (a4)	 **A178** (a4)	 **A179** (a4)	 **A180** (a4)
 **A181** (a4)	 **A182** (a4)	 **A183** (a4)	 **A184** (a4)
 **A185** (a4)	 **A186** (a4)	 **A187** (a4)	 **A188** (a4)
 **A189** (a5)	 **A190** (a5)	 **A191** (a5)	 **A192** (a5)
 **A193** (a5)	 **A194** (a5)	 **A195** (a5)	 **A196** (a5)
 **A197** (a5)	 **A198** (a5)	 **A199** (a5)	 **A200** (a5)

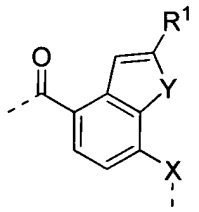
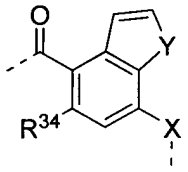
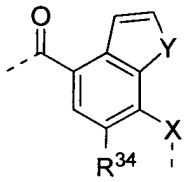
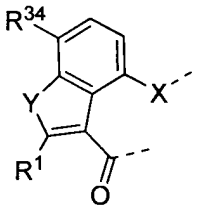
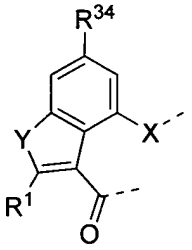
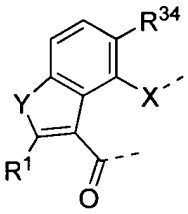
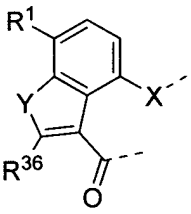
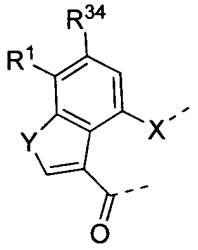
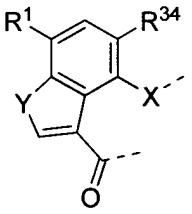
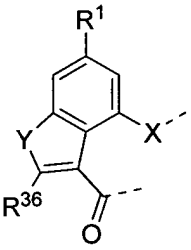
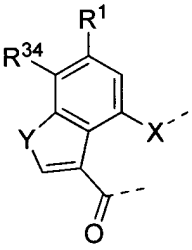
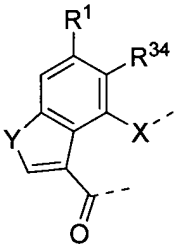
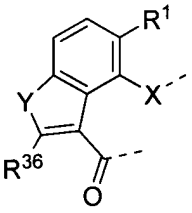
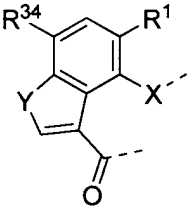
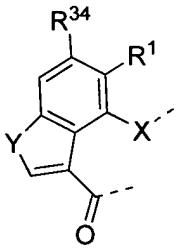
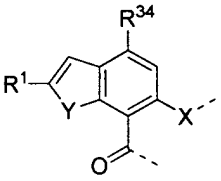
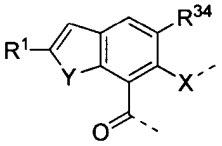
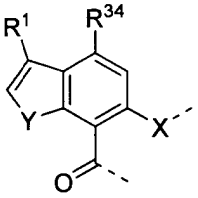
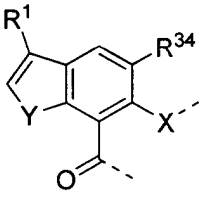
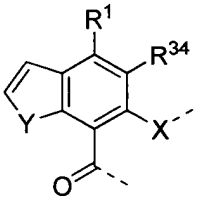
 **A201** (a6)	 **A202** (a6)	 **A203** (a6)	 **A204** (a6)
 **A205** (a6)	 **A206** (a6)	 **A207** (a7)	 **A208** (a7)
 **A209** (a7)	 **A210** (a7)	 **A211** (a7)	 **A212** (a7)
 **A213** (a7)	 **A214** (a7)	 **A215** (a7)	 **A216** (a7)
 **A217** (a7)	 **A218** (a7)	 **A219** (a7)	 **A220** (a7)
 **A221** (a7)	 **A222** (a7)	 **A223** (a7)	 **A224** (a7)

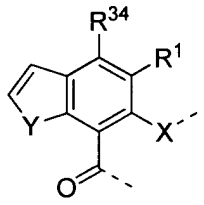
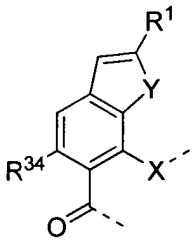
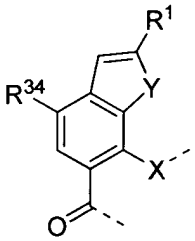
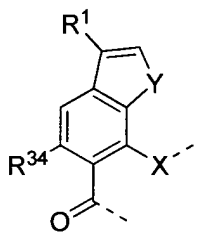
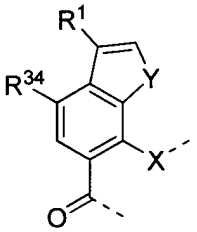
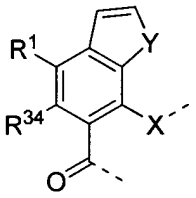
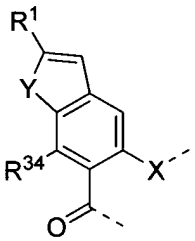
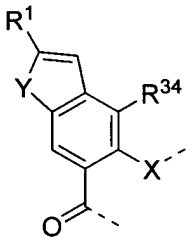
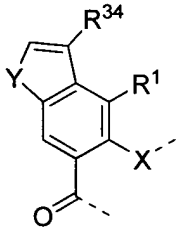
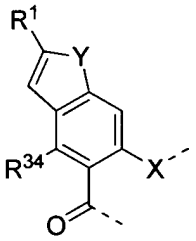
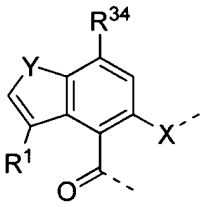
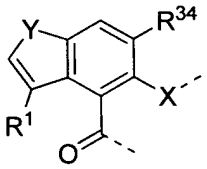
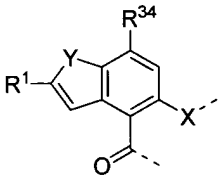
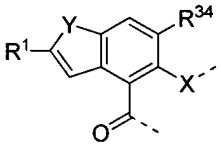
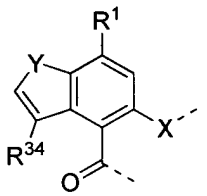
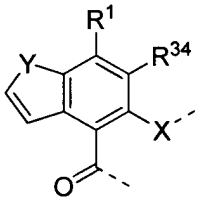
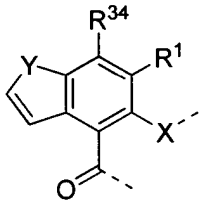
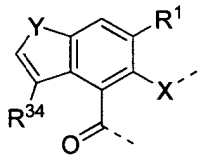
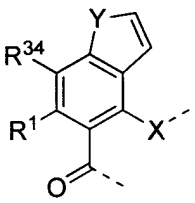
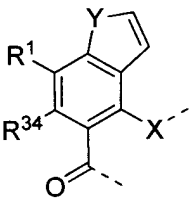
 **A225** (a7)	 **A226** (a7)	 **A227** (a7)	 **A228** (a7)
 **A229** (a8)	 **A230** (a8)	 **A231** (a8)	 **A232** (a8)
 **A233** (a8)	 **A234** (a8)	 **A235** (a9)	 **A236** (a9)
 **A237** (a9)	 **A238** (a9)	 **A239** (a9)	 **A240** (a10)
 **A241** (a10)	 **A242** (a10)	 **A243** (a10)	 **A244** (a10)

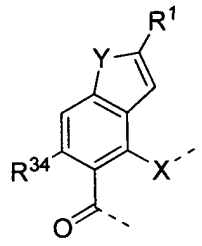
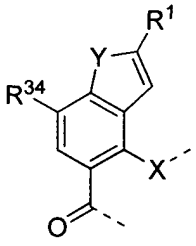
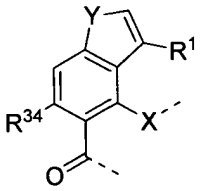
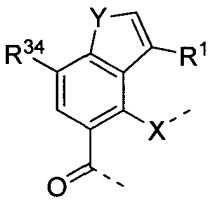
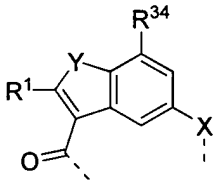
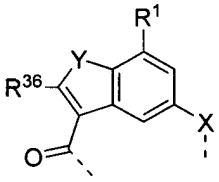
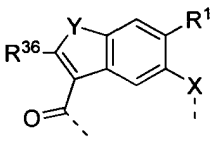
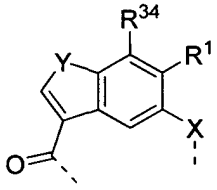
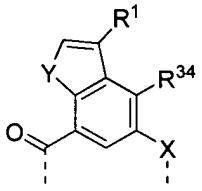
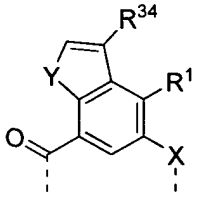
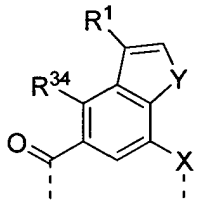
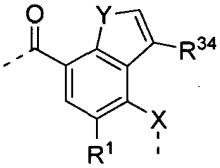
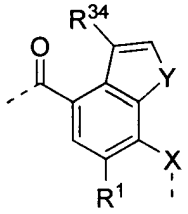
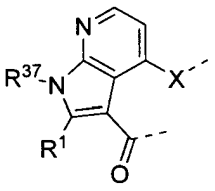
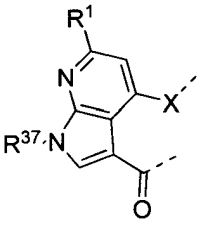
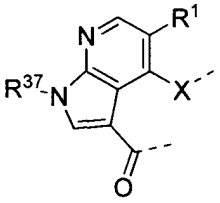
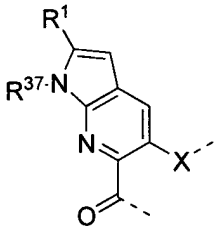
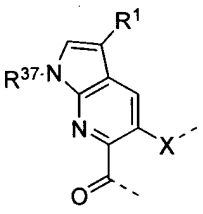
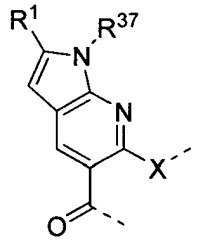
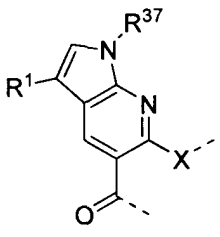
 **A245** (a10)	 **A246** (a10)	 **A247** (a10)	 **A248** (a10)
 **A249** (a10)	 **A250** (a10)	 **A251** (a10)	 **A252** (a10)
 **A253** (a10)	 **A254** (a10)	 **A255** (a10)	 **A256** (a10)
 **A257** (a10)	 **A258** (a10)	 **A259** (a10)	 **A260** (a10)
 **A261** (a10)	 **A262** (a10)	 **A263** (a10)	 **A264** (a10)

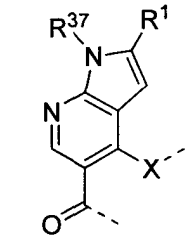
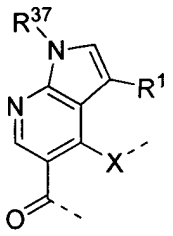
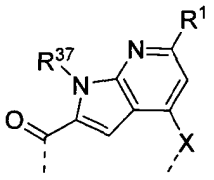
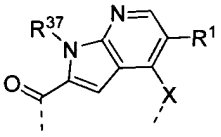
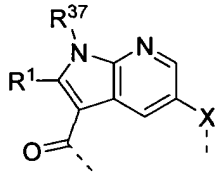
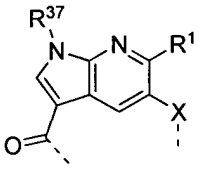
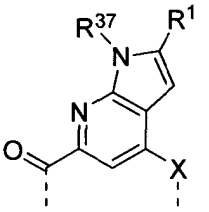
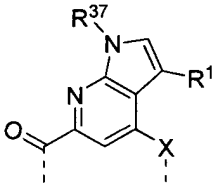
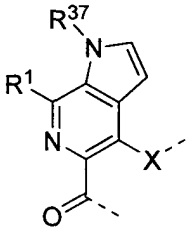
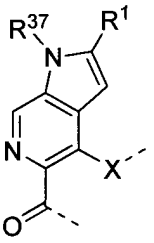
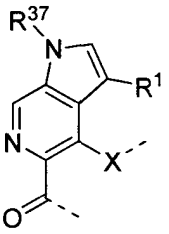
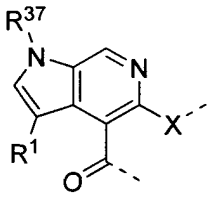
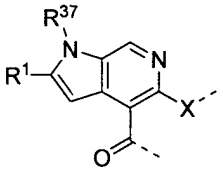
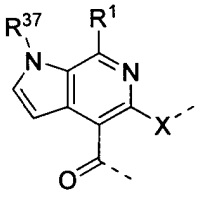
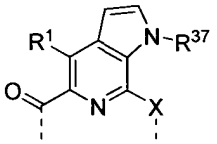
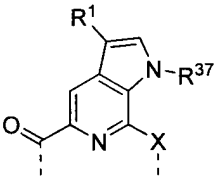
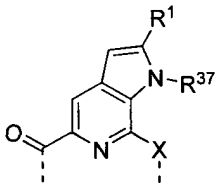
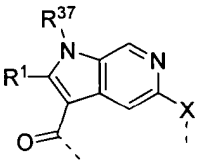
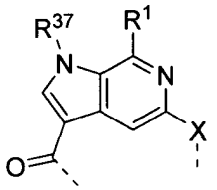
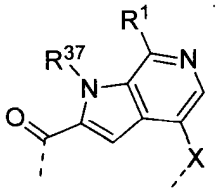
 **A265** (a10)	 **A266** (a10)	 **A267** (a10)	 **A268** (a10)
 **A269** (a10)	 **A270** (a10)	 **A271** (a10)	 **A272** (a10)
 **A273** (a10)	 **A274** (a10)	 **A275** (a10)	 **A276** (a10)
 **A277** (a10)	 **A278** (a10)	 **A279** (a10)	 **A280** (a10)
 **A281** (a10)	 **A282** (a10)	 **A283** (a10)	 **A284** (a10)

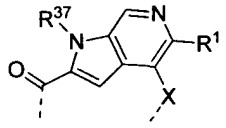
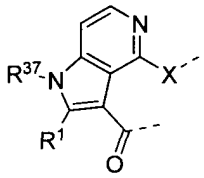
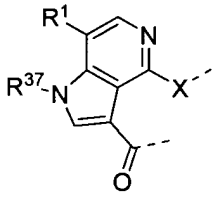
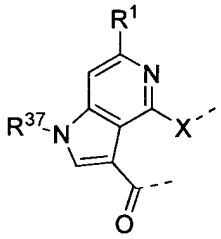
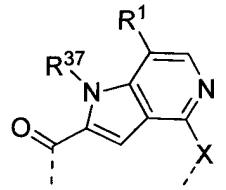
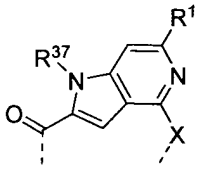
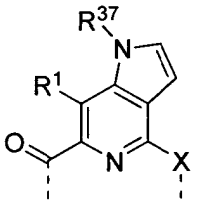
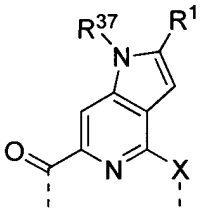
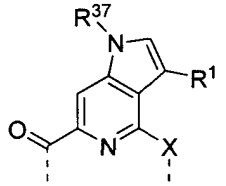
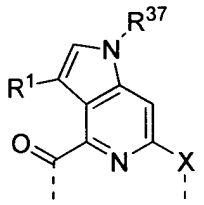
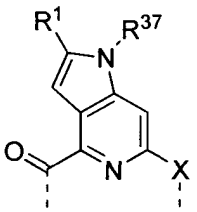
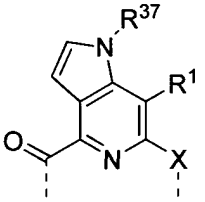
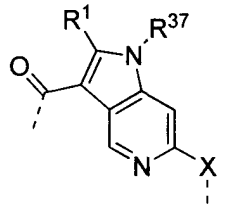
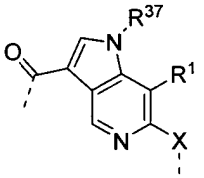
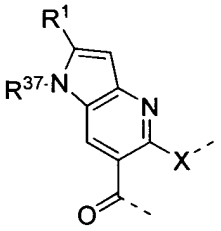
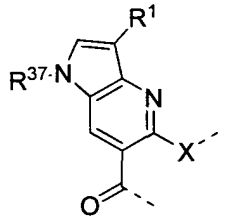
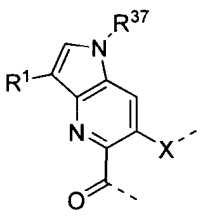
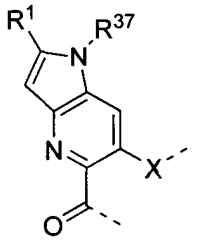
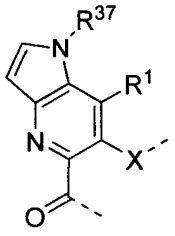
 **A285** (a10)	 **A286** (a10)	 **A287** (a10)	 **A288** (a10)
 **A289** (a10)	 **A290** (a10)	 **A291** (a10)	 **A292** (a10)
 **A293** (a10)	 **A294** (a10)	 **A295** (a10)	 **A296** (a10)
 **A297** (a10)	 **A298** (a10)	 **A299** (a10)	 **A300** (a10)
 **A301** (a10)	 **A302** (a10)	 **A303** (a10)	 **A304** (a10)

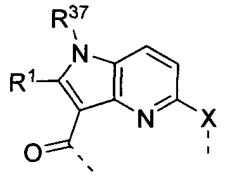
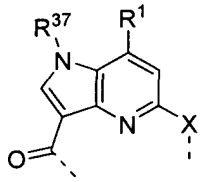
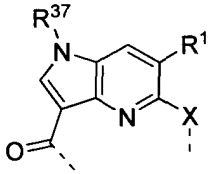
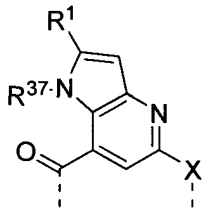
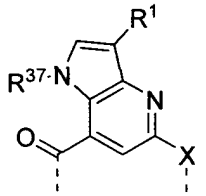
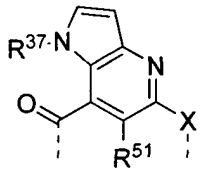
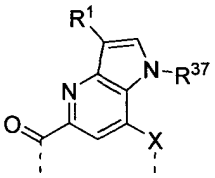
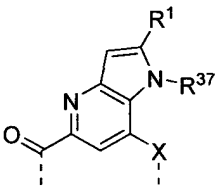
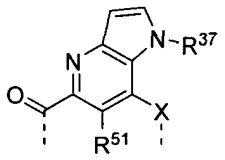
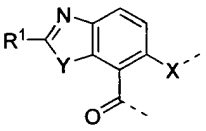
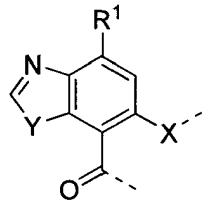
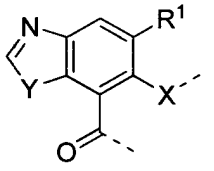
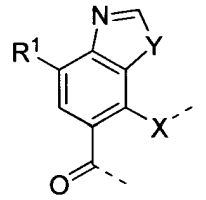
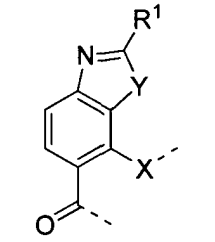
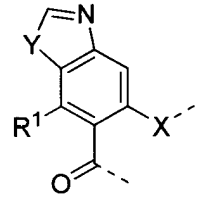
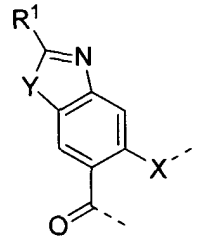
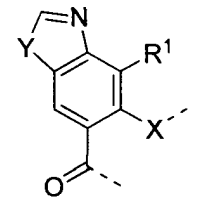
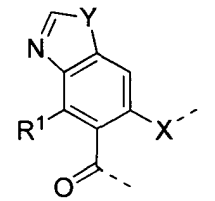
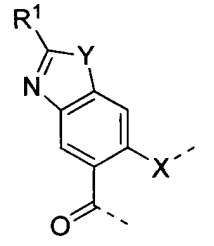
 **A305** (a10)	 **A306** (a10)	 **A307** (a10)	 **A308** (a10)
 **A309** (a10)	 **A310** (a10)	 **A311** (a10)	 **A312** (a10)
 **A313** (a10)	 **A314** (a10)	 **A315** (a10)	 **A316** (a10)
 **A317** (a10)	 **A318** (a10)	 **A319** (a10)	 **A320** (a10)
 **A321** (a10)	 **A322** (a10)	 **A323** (a10)	 **A324** (a10)

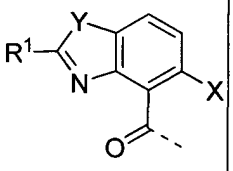
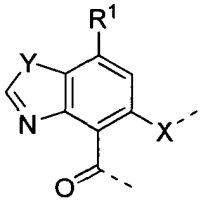
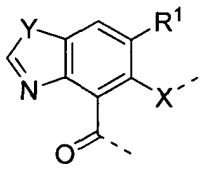
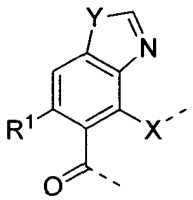
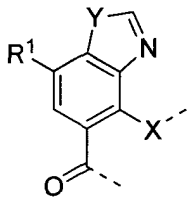
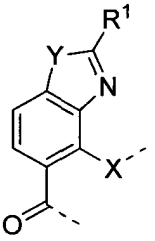
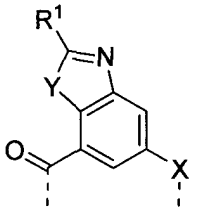
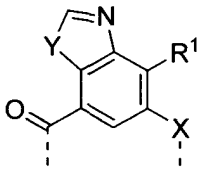
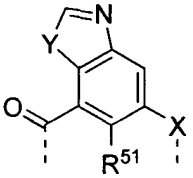
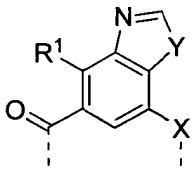
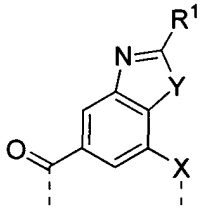
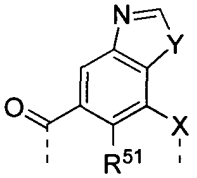
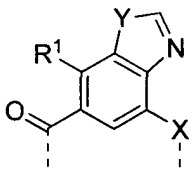
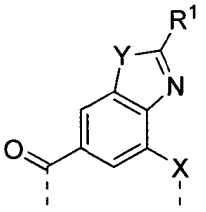
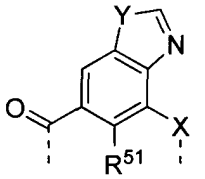
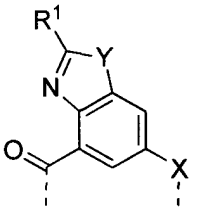
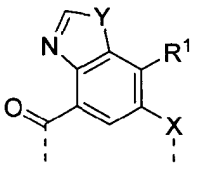
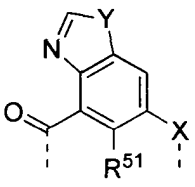
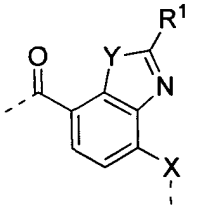
 **A325** (a10)	 **A326** (a10)	 **A327** (a10)	 **A328** (a10)
 **A329** (a10)	 **A330** (a10)	 **A331** (a10)	 **A332** (a10)
 **A333** (a10)	 **A334** (a10)	 **A335** (a10)	 **A336** (a10)
 **A337** (a10)	 **A338** (a10)	 **A339** (a10)	 **A340** (a10)
 **A341** (a10)	 **A342** (a10)	 **A343** (a10)	 **A344** (a10)

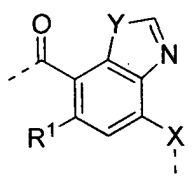
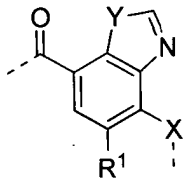
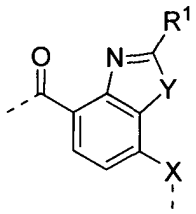
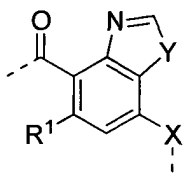
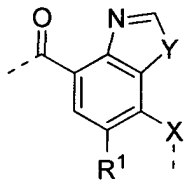
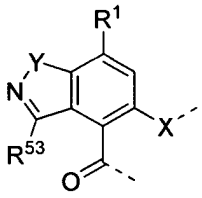
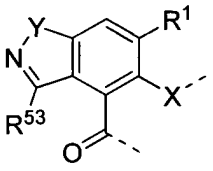
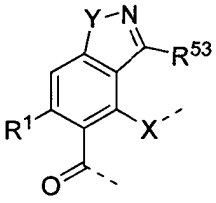
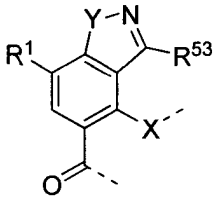
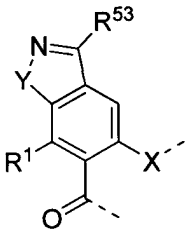
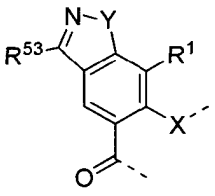
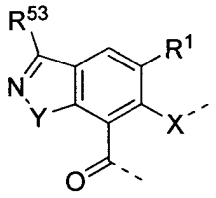
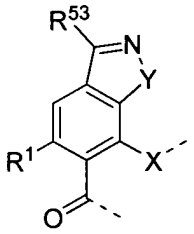
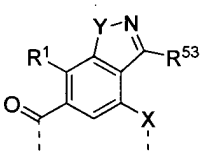
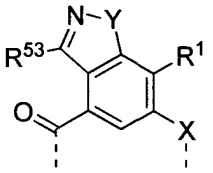
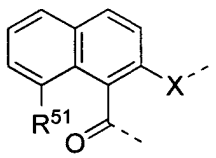
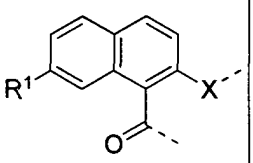
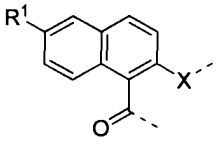
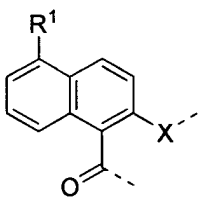
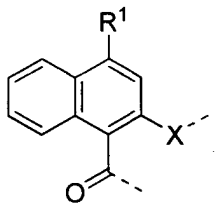
 **A345** (a10)	 **A346** (a10)	 **A347** (a10)	 **A348** (a10)
 **A349** (a10)	 **A350** (a10)	 **A351** (a10)	 **A352** (a10)
 **A353** (a10)	 **A354** (a10)	 **A355** (a10)	 **A356** (a10)
 **A357** (a10)	 **A358** (a11)	 **A359** (a11)	 **A360** (a11)
 **A361** (a11)	 **A362** (a11)	 **A363** (a11)	 **A364** (a11)

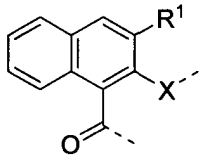
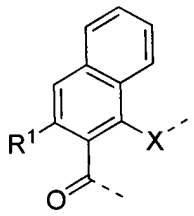
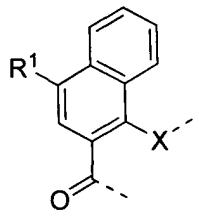
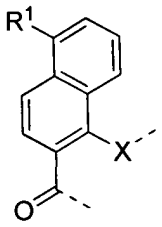
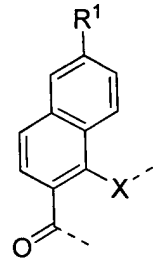
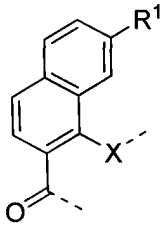
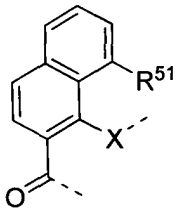
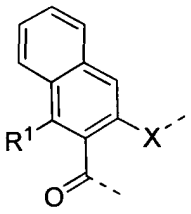
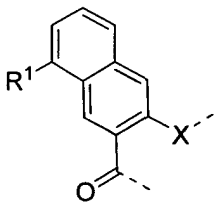
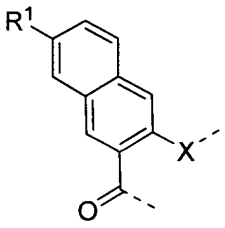
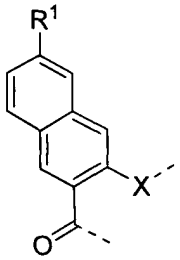
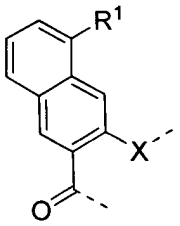
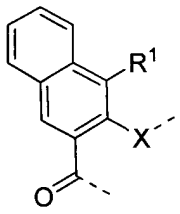
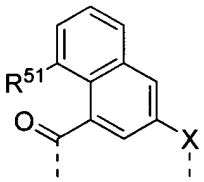
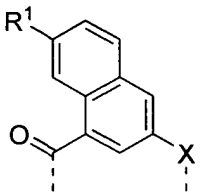
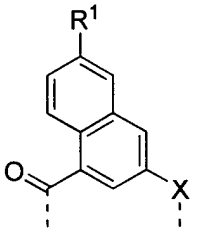
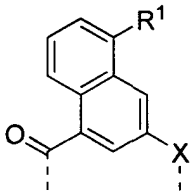
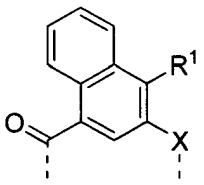
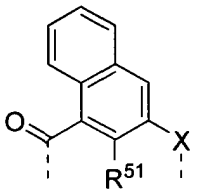
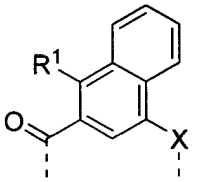
 **A365** (a11)	 **A366** (a11)	 **A367** (a11)	 **A368** (a11)
 **A369** (a11)	 **A370** (a11)	 **A371** (a11)	 **A372** (a11)
 **A373** (a12)	 **A374** (a12)	 **A375** (a12)	 **A376** (a12)
 **A377** (a12)	 **A378** (a12)	 **A379** (a12)	 **A380** (a12)
 **A381** (a12)	 **A382** (a12)	 **A383** (a12)	 **A384** (a12)

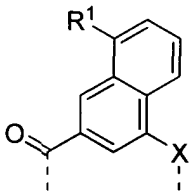
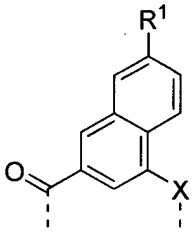
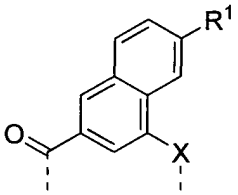
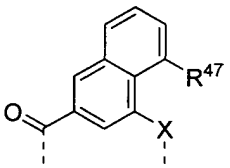
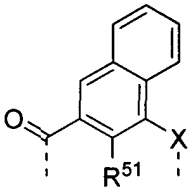
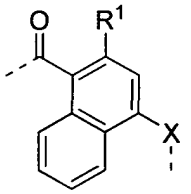
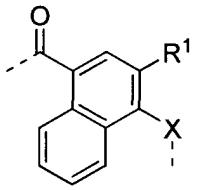
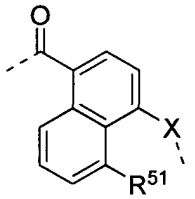
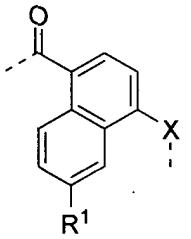
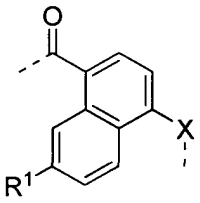
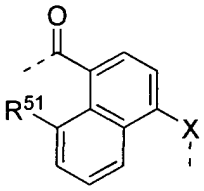
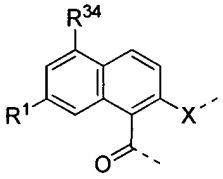
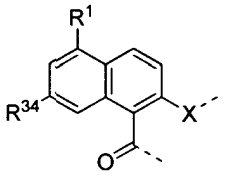
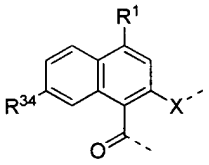
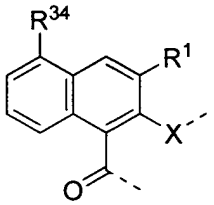
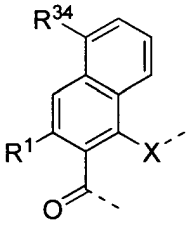
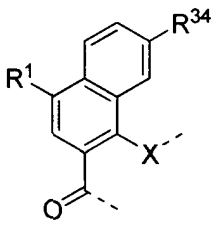
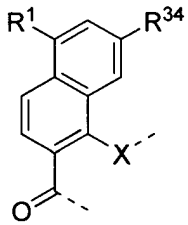
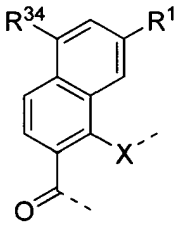
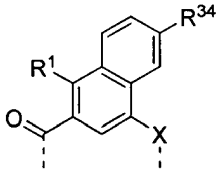
 **A385** (a12)	 **A386** (a13)	 **A387** (a13)	 **A388** (a13)
 **A389** (a13)	 **A390** (a13)	 **A391** (a13)	 **A392** (a13)
 **A393** (a13)	 **A394** (a13)	 **A395** (a13)	 **A396** (a13)
 **A397** (a13)	 **A398** (a13)	 **A399** (a14)	 **A400** (a14)
 **A401** (a14)	 **A402** (a14)	 **A403** (a14)	 **A404** (a14)

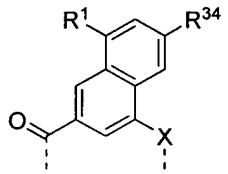
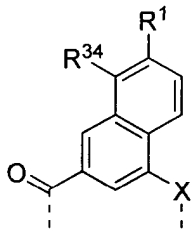
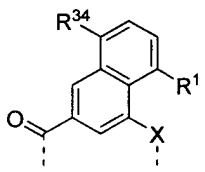
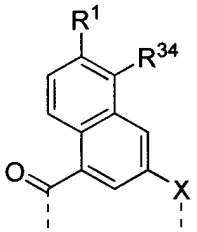
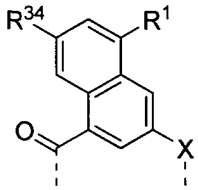
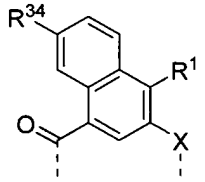
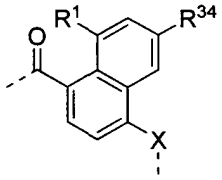
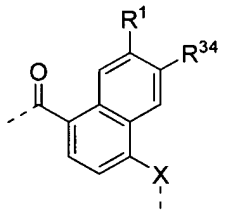
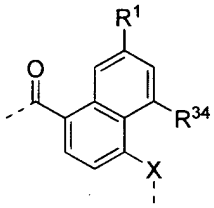
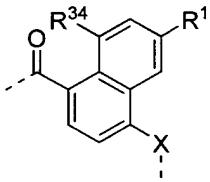
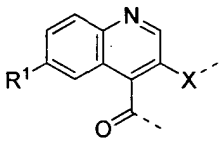
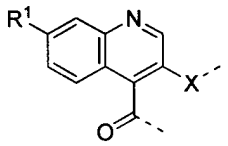
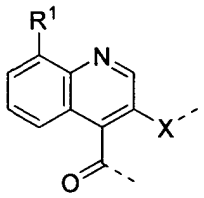
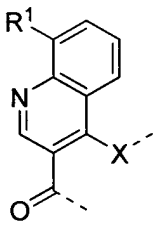
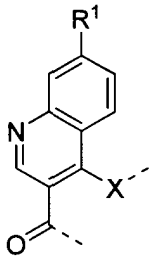
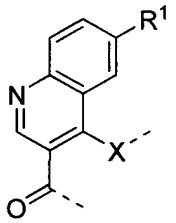
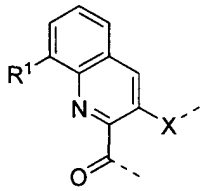
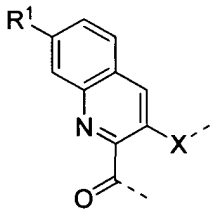
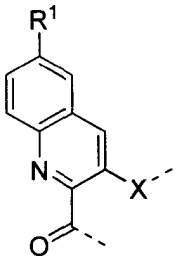
 **A405** (a14)	 **A406** (a14)	 **A407** (a14)	 **A408** (a14)
 **A409** (a14)	 **A410** (a14)	 **A411** (a14)	 **A412** (a14)
 **A413** (a14)	 **A414** (a15)	 **A415** (a15)	 **A416** (a15)
 **A417** (a15)	 **A418** (a15)	 **A419** (a15)	 **A420** (a15)
 **A421** (a15)	 **A422** (a15)	 **A423** (a15)	 **A424** (a15)

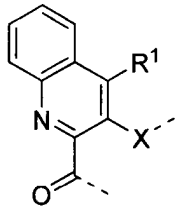
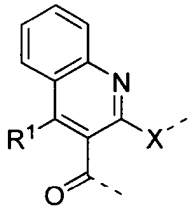
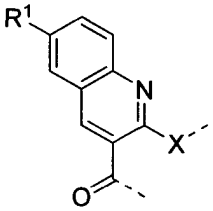
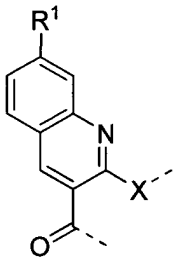
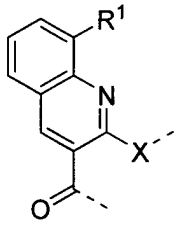
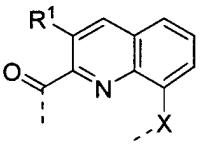
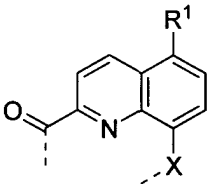
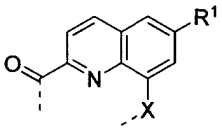
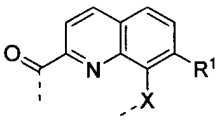
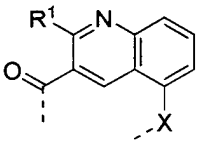
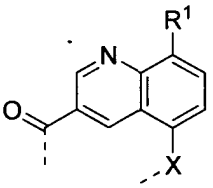
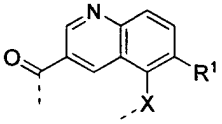
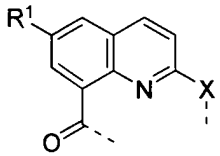
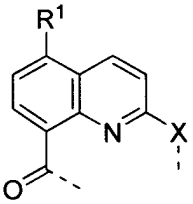
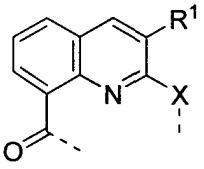
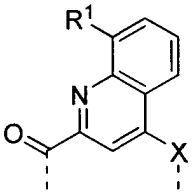
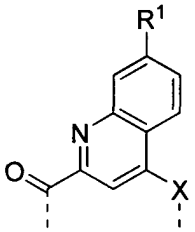
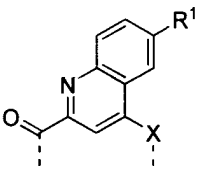
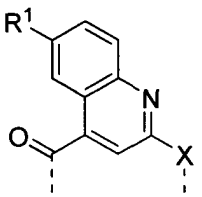
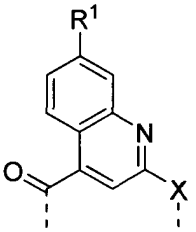
 **A425** (a15)	 **A426** (a15)	 **A427** (a15)	 **A428** (a15)
 **A429** (a15)	 **A430** (a15)	 **A431** (a15)	 **A432** (a15)
 **A433** (a15)	 **A434** (a15)	 **A435** (a15)	 **A436** (a15)
 **A437** (a15)	 **A438** (a15)	 **A439** (a15)	 **A440** (a15)
 **A441** (a15)	 **A442** (a15)	 **A443** (a15)	 **A444** (a15)

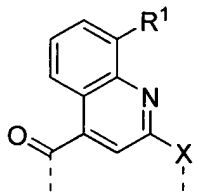
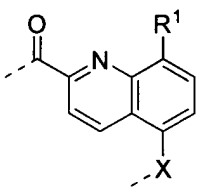
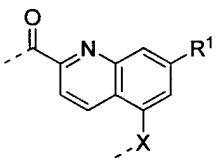
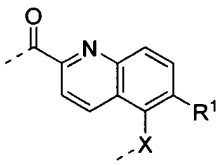
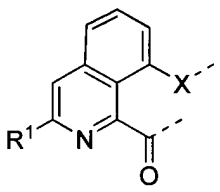
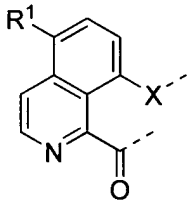
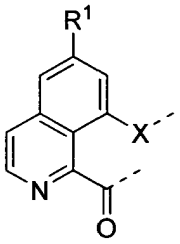
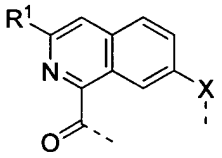
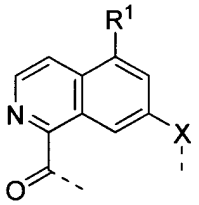
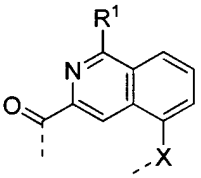
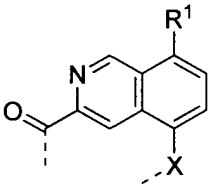
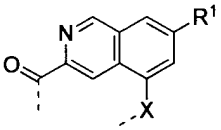
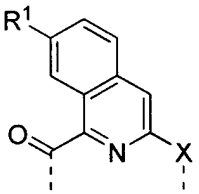
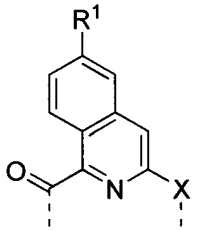
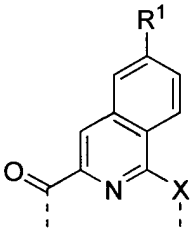
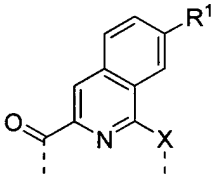
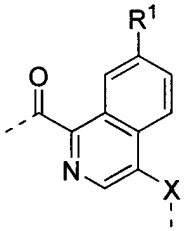
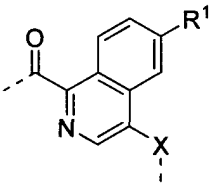
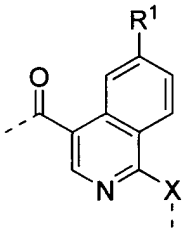
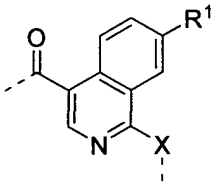
 **A445** (a15)	 **A446** (a15)	 **A447** (a15)	 **A448** (a15)
 **A449** (a15)	 **A450** (a16)	 **A451** (a16)	 **A452** (a16)
 **A453** (a16)	 **A454** (a16)	 **A455** (a16)	 **A456** (a16)
 **A457** (a16)	 **A458** (a16)	 **A459** (a16)	 **A460** (a17)
 **A461** (a17)	 **A462** (a17)	 **A463** (a17)	 **A464** (a17)

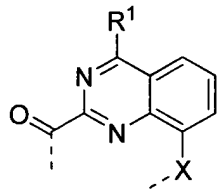
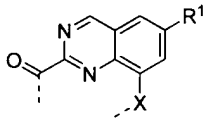
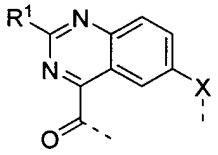
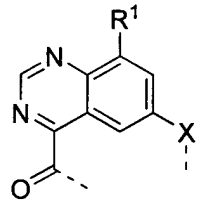
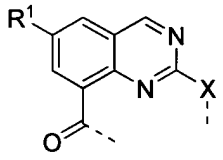
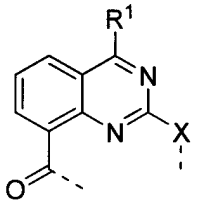
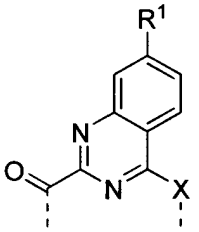
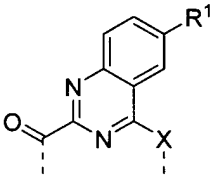
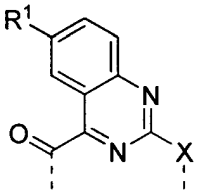
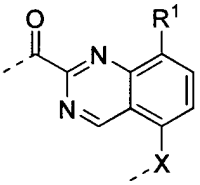
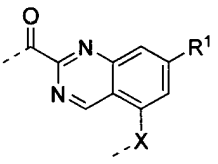
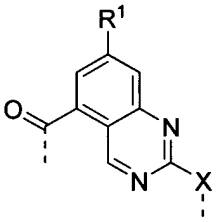
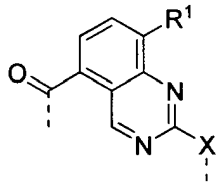
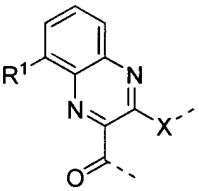
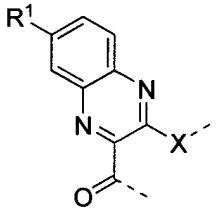
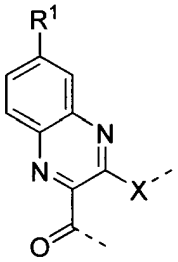
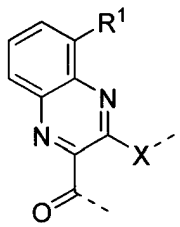
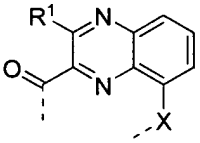
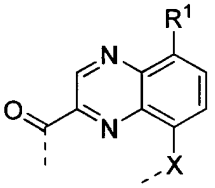
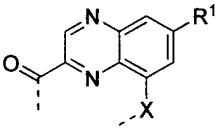
 **A465** (a17)	 **A466** (a17)	 **A467** (a17)	 **A468** (a17)
 **A469** (a17)	 **A470** (a17)	 **A471** (a17)	 **A472** (a17)
 **A473** (a17)	 **A474** (a17)	 **A475** (a17)	 **A476** (a17)
 **A477** (a17)	 **A478** (a17)	 **A479** (a17)	 **A480** (a17)
 **A481** (a17)	 **A482** (a17)	 **A483** (a17)	 **A484** (a17)

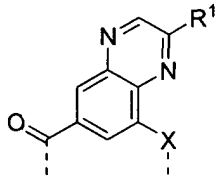
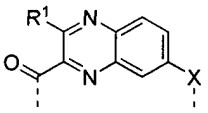
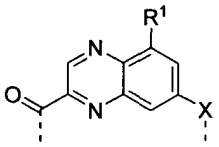
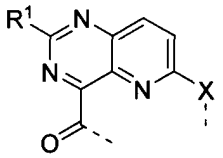
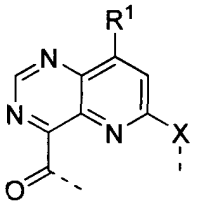
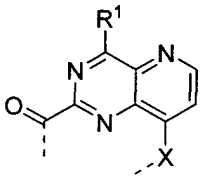
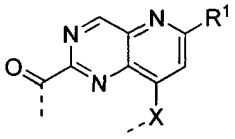
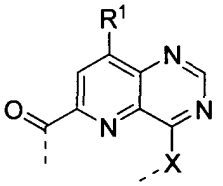
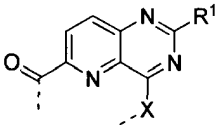
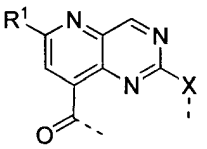
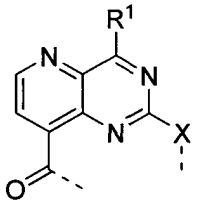
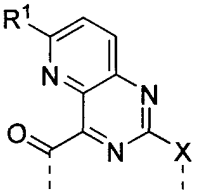
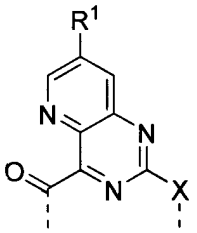
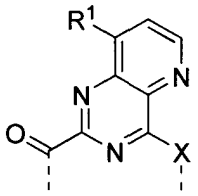
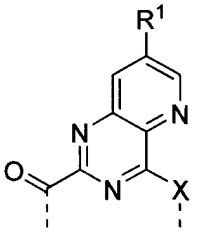
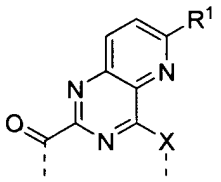
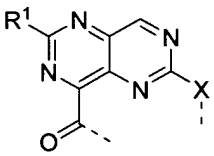
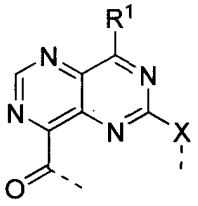
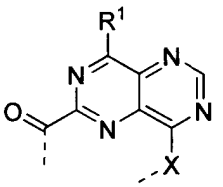
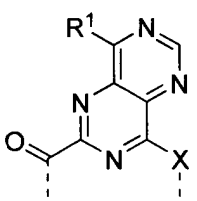
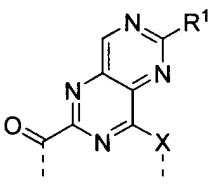
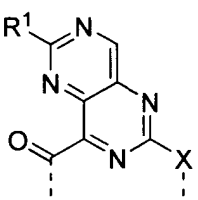
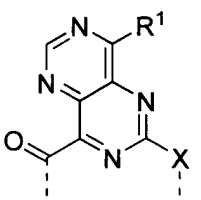
 **A485** (a17)	 **A486** (a17)	 **A487** (a17)	 **A488** (a17)
 **A489** (a17)	 **A490** (a17)	 **A491** (a17)	 **A492** (a17)
 **A493** (a17)	 **A494** (a17)	 **A495** (a17)	 **A496** (a17)
 **A497** (a17)	 **A498** (a17)	 **A499** (a17)	 **A500** (a17)
 **A501** (a17)	 **A502** (a17)	 **A503** (a17)	 **A504** (a17)

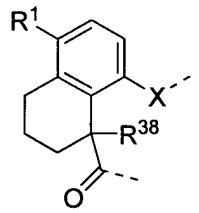
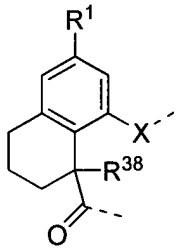
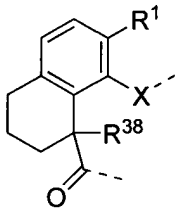
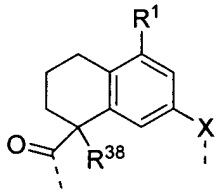
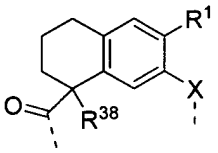
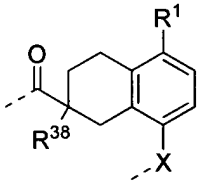
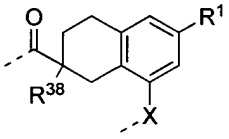
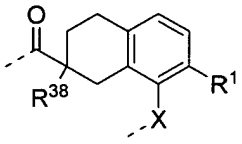
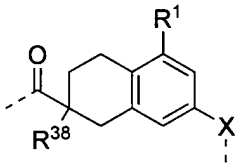
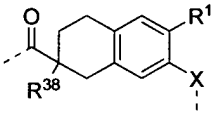
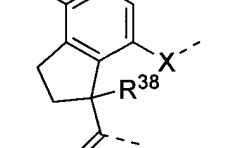
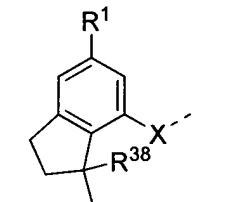
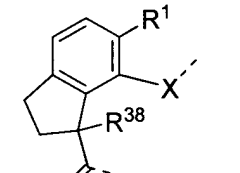
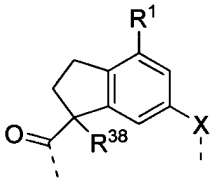
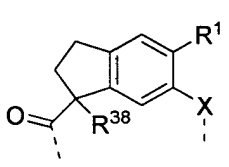
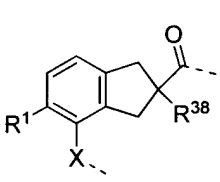
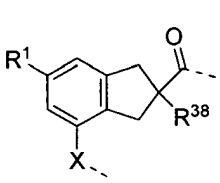
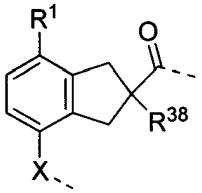
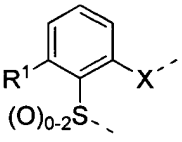
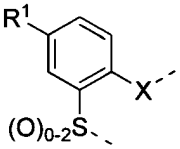
 **A505** (a17)	 **A506** (a17)	 **A507** (a17)	 **A508** (a17)
 **A509** (a17)	 **A510** (a17)	 **A511** (a17)	 **A512** (a17)
 **A513** (a17)	 **A514** (a17)	 **A515** (a17)	 **A516** (a18)
 **A517** (a18)	 **A518** (a18)	 **A519** (a18)	 **A520** (a18)
 **A521** (a18)	 **A522** (a18)	 **A523** (a18)	 **A524** (a18)

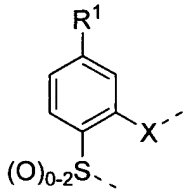
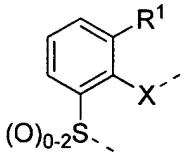
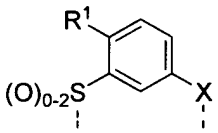
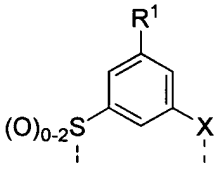
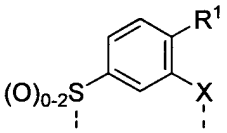
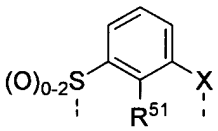
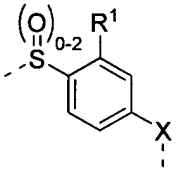
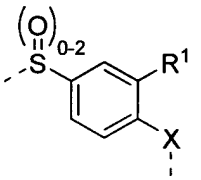
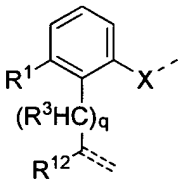
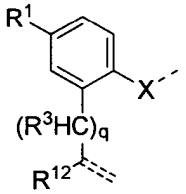
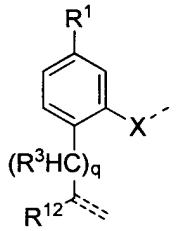
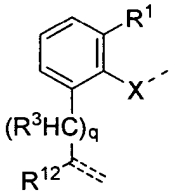
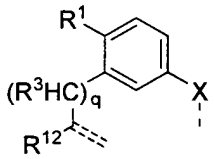
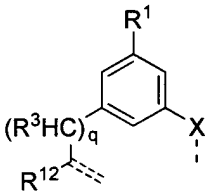
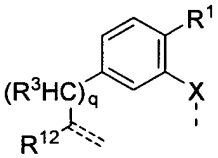
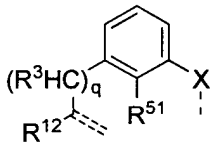
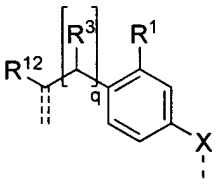
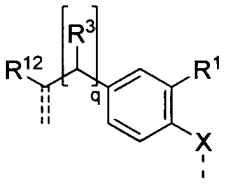
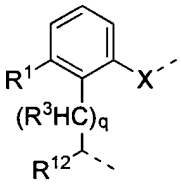
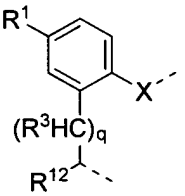
 **A525** (a18)	 **A526** (a18)	 **A527** (a18)	 **A528** (a18)
 **A529** (a18)	 **A530** (a18)	 **A531** (a18)	 **A532** (a18)
 **A533** (a18)	 **A534** (a18)	 **A535** (a18)	 **A536** (a18)
 **A537** (a18)	 **A538** (a18)	 **A539** (a18)	 **A540** (a18)
 **A541** (a18)	 **A542** (a18)	 **A543** (a18)	 **A544** (a18)

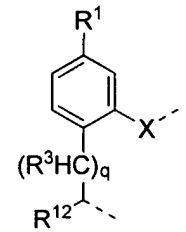
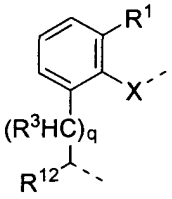
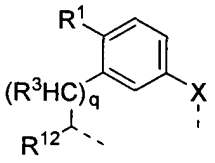
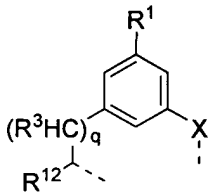
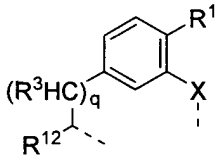
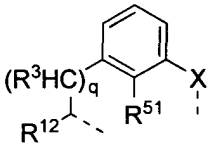
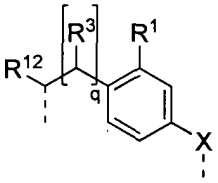
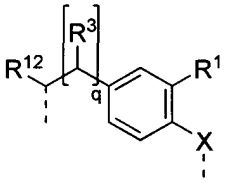
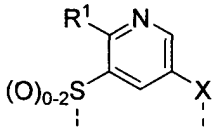
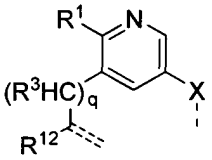
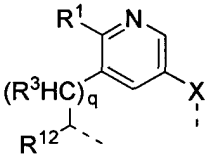
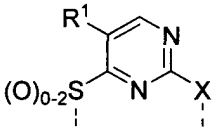
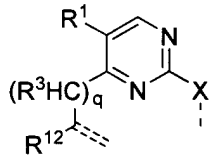
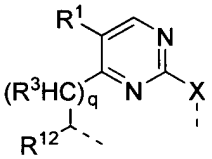
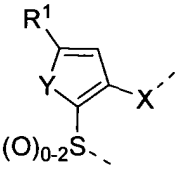
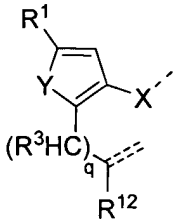
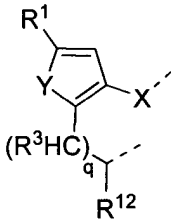
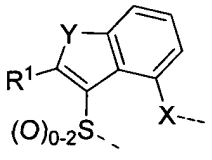
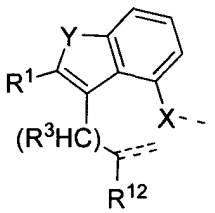
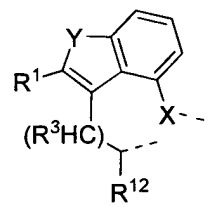
 **A545** (a18)	 **A546** (a18)	 **A547** (a18)	 **A548** (a18)
 **A549** (a19)	 **A550** (a19)	 **A551** (a19)	 **A552** (a19)
 **A553** (a19)	 **A554** (a19)	 **A555** (a19)	 **A556** (a19)
 **A557** (a19)	 **A558** (a19)	 **A559** (a19)	 **A560** (a19)
 **A561** (a19)	 **A562** (a19)	 **A563** (a19)	 **A564** (a19)

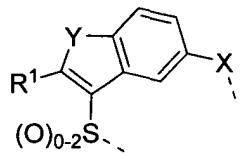
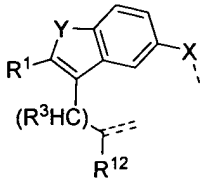
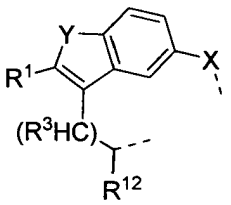
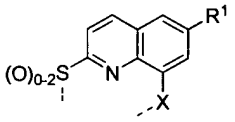
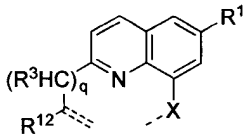
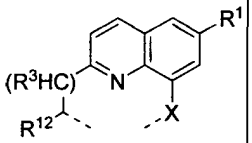
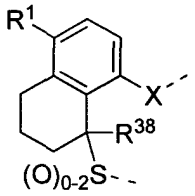
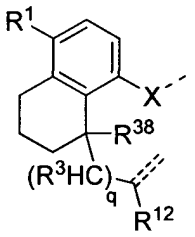
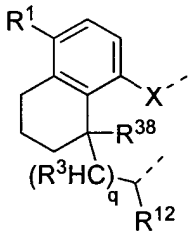
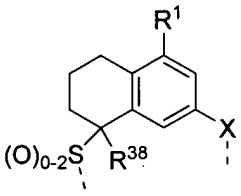
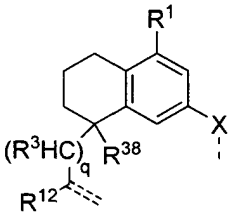
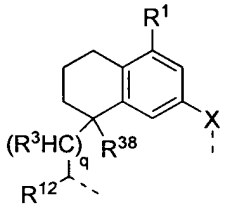
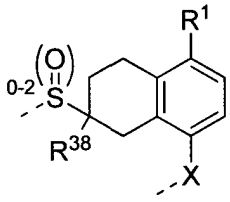
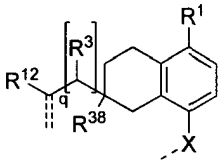
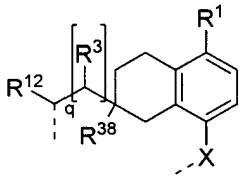
 **A565** (a20)	 **A566** (a20)	 **A567** (a20)	 **A568** (a20)
 **A569** (a20)	 **A570** (a20)	 **A571** (a20)	 **A572** (a20)
 **A573** (a20)	 **A574** (a20)	 **A575** (a20)	 **A576** (a20)
 **A577** (a20)	 **A578** (a21)	 **A579** (a21)	 **A580** (a21)
 **A581** (a21)	 **A582** (a21)	 **A583** (a21)	 **A584** (a21)

 **A585** (a21)	 **A586** (a21)	 **A587** (a21)	 **A588** (a22)
 **A589** (a22)	 **A590** (a22)	 **A591** (a22)	 **A592** (a22)
 **A593** (a22)	 **A594** (a22)	 **A595** (a22)	 **A596** (a22)
 **A597** (a22)	 **A598** (a22)	 **A599** (a22)	 **A600** (a22)
 **A601** (a22)	 **A602** (a23)	 **A603** (a23)	 **A604** (a23)
			

A605 (a23)	**A606** (a23)	**A607** (a23)	**A608** (a23)
			
A609 (a24)	**A610** (a24)	**A611** (a24)	**A612** (a24)
			
A613 (a24)	**A614** (a24)	**A615** (a24)	**A616** (a24)
			
A617 (a24)	**A618** (a24)	**A619** (a25)	**A620** (a25)
			
A621 (a25)	**A622** (a25)	**A623** (a25)	**A624** (a25)
			
A625 (a25)	**A626** (a25)	**A627** (a1)	**A628** (a1)
			

 **A629** (a1)	 **A630** (a1)	 **A631** (a1)	 **A632** (a1)
 **A633** (a1)	 **A634** (a1)	 **A635** (a1)	 **A636** (a1)
 **A637** (a1)	 **A638** (a1)	 **A639** (a1)	 **A640** (a1)
 **A641** (a1)	 **A642** (a1)	 **A643** (a1)	 **A644** (a1)
 **A645** (a1)	 **A646** (a1)	 **A647** (a1)	 **A648** (a1)

 **A649** (a1)	 **A650** (a1)	 **A651** (a1)	 **A652** (a1)
 **A653** (a1)	 **A654** (a1)	 **A655** (a1)	 **A656** (a1)
 **A657** (a2)	 **A658** (a2)	 **A659** (a2)	 **A660** (a4)
 **A661** (a4)	 **A662** (a4)	 **A663** (a7)	 **A664** (a7)
 **A665** (a7)	 **A666** (a10)	 **A667** (a10)	 **A668** (a10)

 **A669** (a10)	 **A670** (a10)	 **A671** (a10)	 **A672** (a18)
 **A673** (a18)	 **A674** (a18)	 **A675** (a24)	 **A676** (a24)
 **A677** (a24)	 **A678** (a24)	 **A679** (a24)	 **A680** (a24)
 **A681** (a24)	 **A682** (a24)	 **A683** (a24)	

Building block B is a bivalent radical selected from the group of Table 2.

B1-B22 are optionally substituted cyclic secondary amines carrying a moiety of type $-CHR^3-LG$, wherein LG is a suitable leaving group that can be replaced by the nucleophilic groups of building blocks **A** forming an ether (-O-) or a thioether

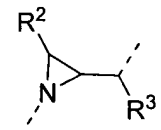
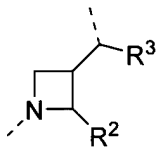
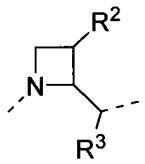
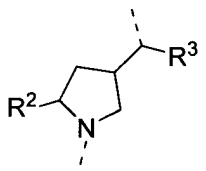
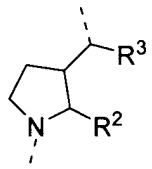
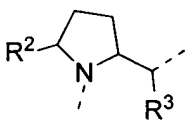
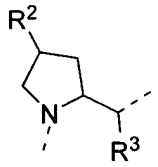
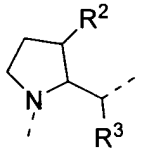
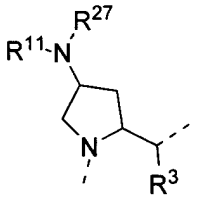
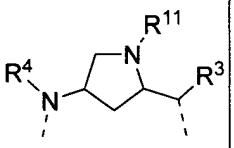
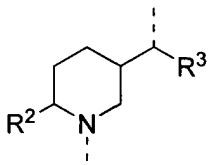
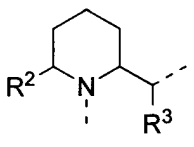
(-S-) linkage (or their oxidized forms) between building blocks of type **A** and **B**.

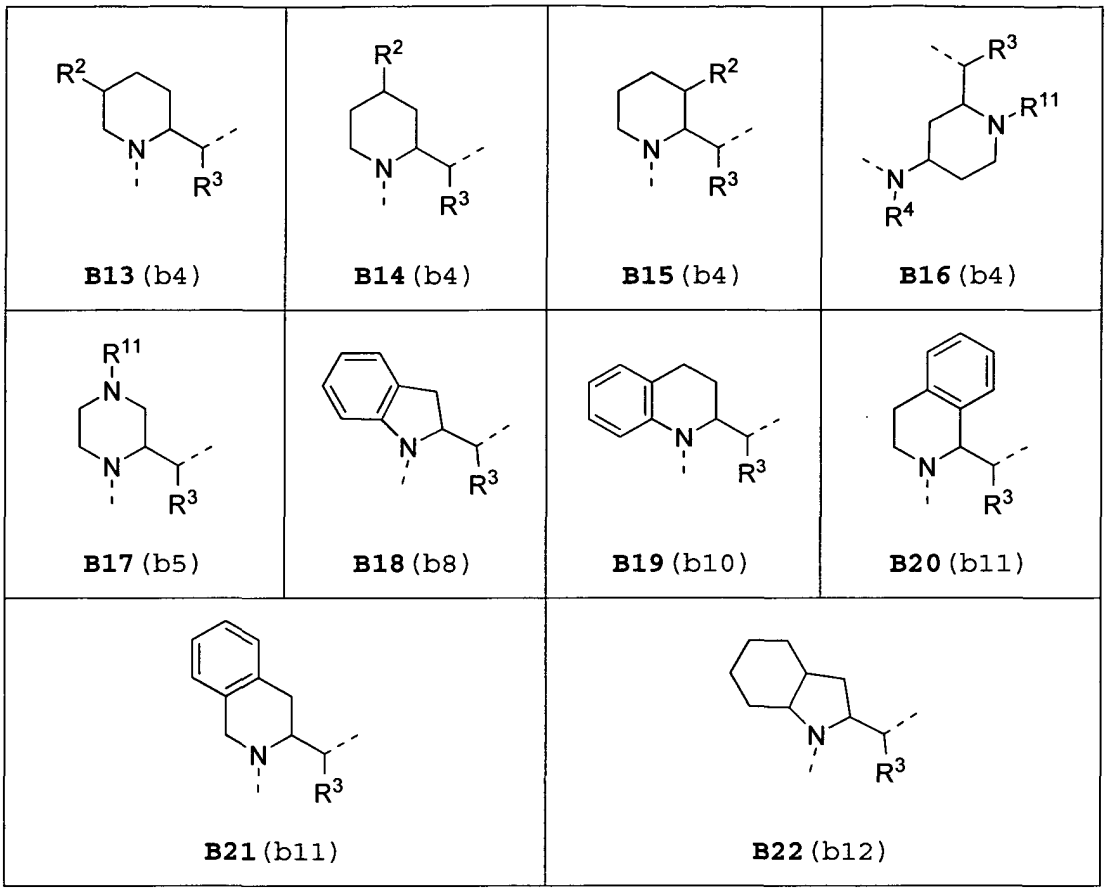
Appropriate LGs are for example -OH being transformed into the active LG *in situ* during a Mitsunobu reactions, or halogens like -Br or -I amenable to S_N reactions.

In most examples of type **Ia/Ib**, the secondary amine nitrogen of building block **B** forms a tertiary amide bond with a carboxyl group of building blocks of type **C**. In case suitable exocyclic amine functionality is present, it can be, instead of the ring-nitrogen, involved in the formation of a secondary or preferably tertiary amide connection. Such an alternative binding mode according formula **Ib** is realized with e.g. **B10**.

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 **Ia/Ib**.

Table 2: Radicals **B1-B22** (*continued on the following page*)

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

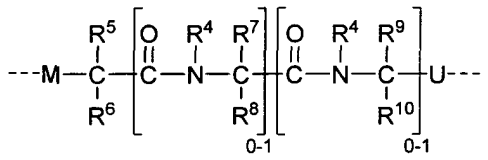
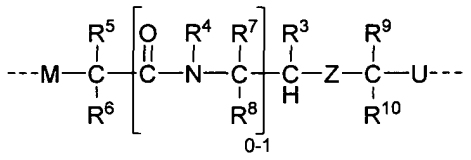
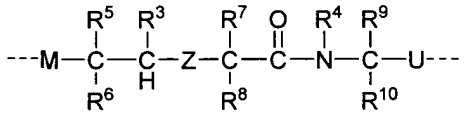
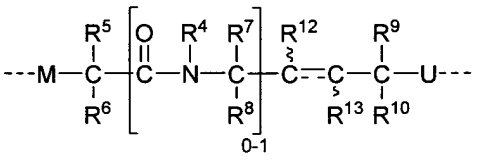
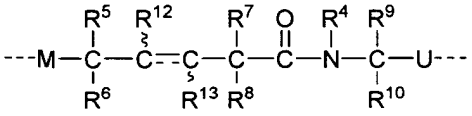
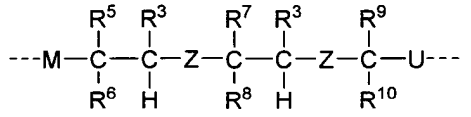
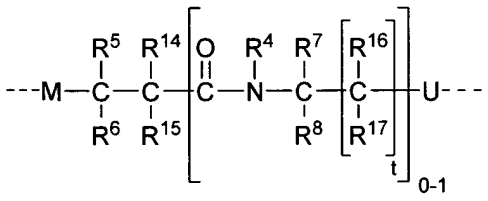
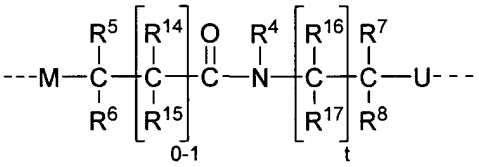
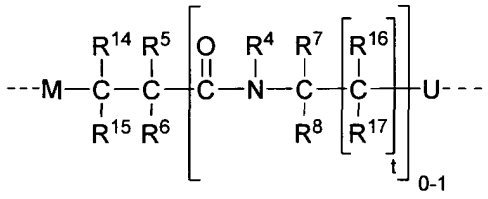
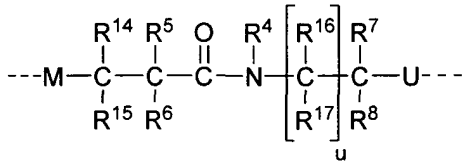


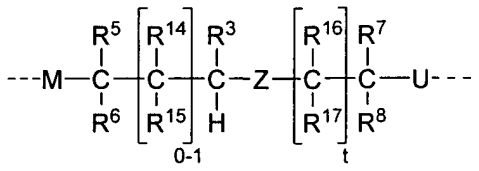
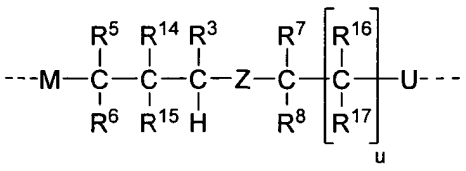
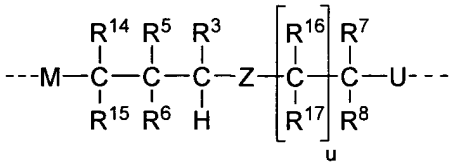
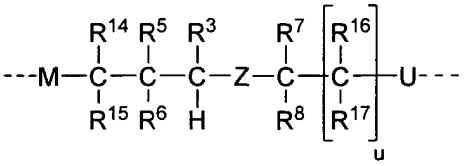
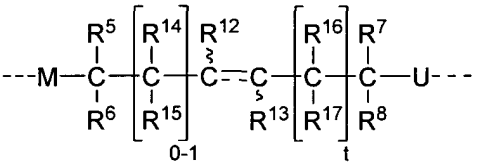
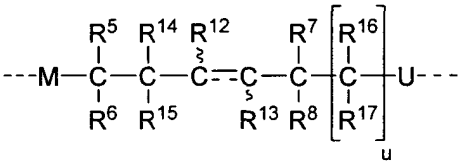
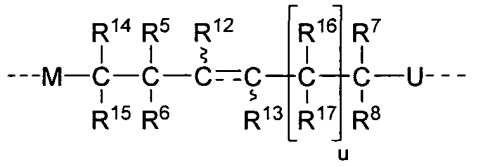
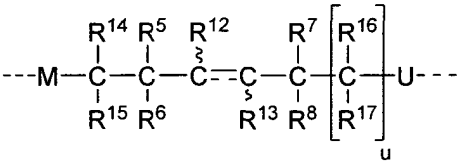
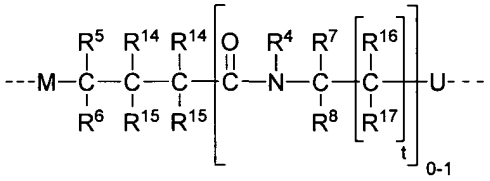
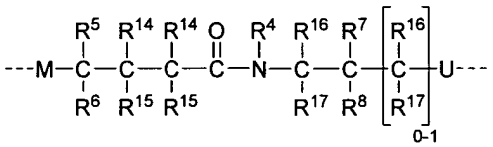
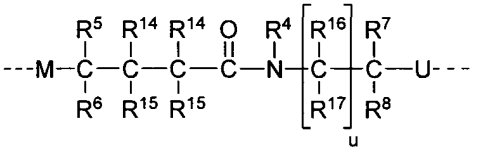
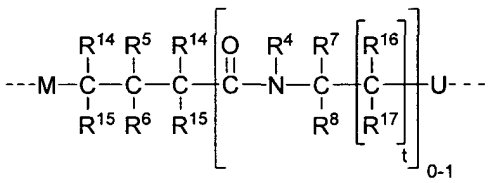
Building block C is a bivalent radical selected from the group of Table 3.

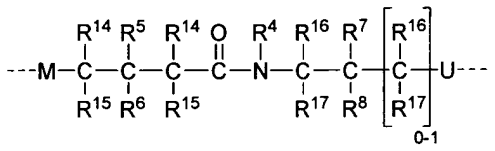
As mentioned before the divalent moiety **C** may consist of one to three subunits **c1** to **c3**. As a consequence it directly influences the ring size of the macrocycle and can be regarded as spacer or linker. This linker ensemble **C** is joined to building block **A** via its *M*-terminus (i.e. *N*-terminus in case of an amino acid) and to building block **B** via its *U*-terminus (i.e. *C*-terminus in case of an amino acid) to form the macrocyclic ring of type **Ia/Ib**. As detailed above linker **C** contributes with the four groups M, U, V and W (cf. Figure 2 and 3) to the backbone of macrocycle **Ia/Ib**. For example, in case M is $-NR^4-$, **C1** represents a linker moiety constituted of one to three α-amino acid derivatives connected along their main chains, while **C7-C10** are equivalent to moieties containing β-amino acids. The

simplest situation in which at least one connection between the subunits **c1** to **c3** is realized by a non-amidic group are **C2-C5**. Finally **C58-C101** depict cases in which longer carbon chains (>3 C-atoms) separate at least one pair of the generic groups M, V, W, U.

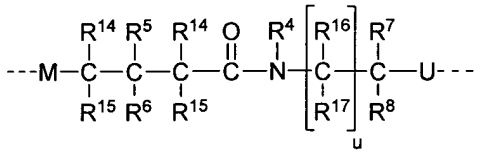
Table 3: Representations of Linker **C** (*continued on the following pages*)

 **C1**	 **C2**
 **C3**	 **C4**
 **C5**	 **C6**
 **C7**	 **C8**
 **C9**	 **C10**

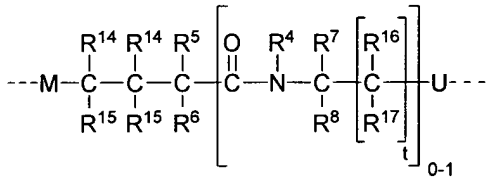
 C11	 C12
 C13	 C14
 C15	 C16
 C17	 C18
 C19	 C20
 C21	 C22



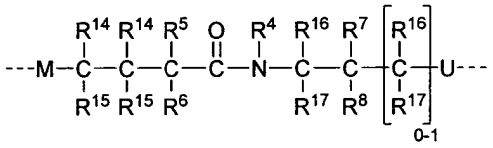
C23



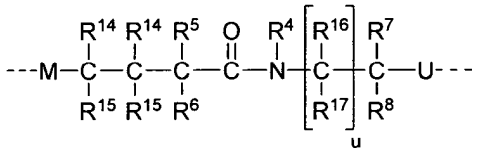
C24



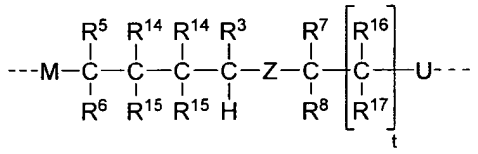
C25



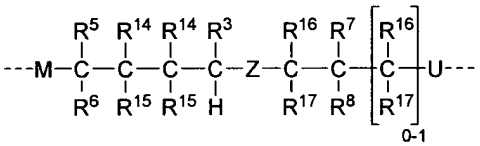
C26



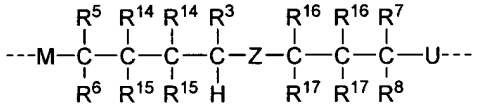
C27



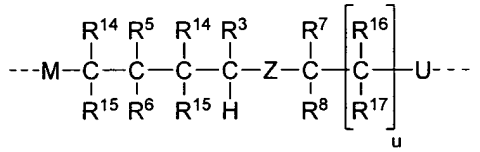
C28



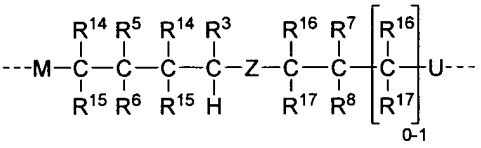
C29



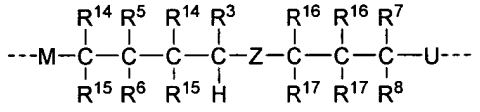
C30



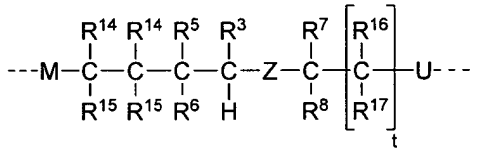
C31



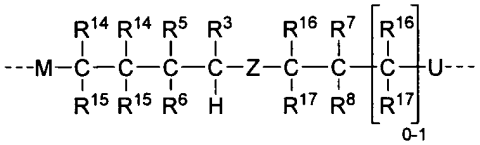
C32

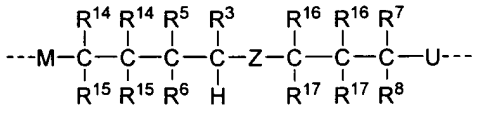


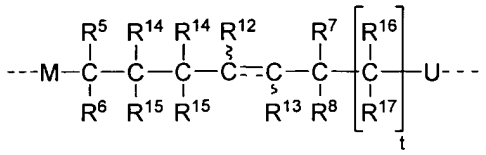
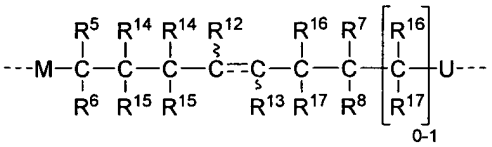
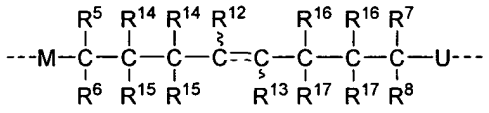
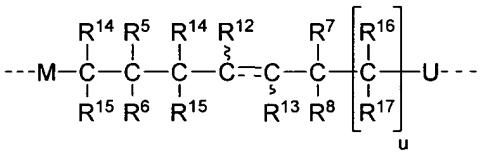
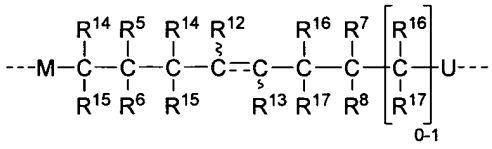
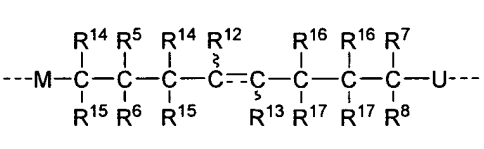
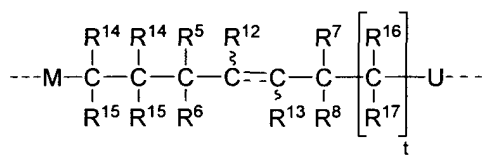
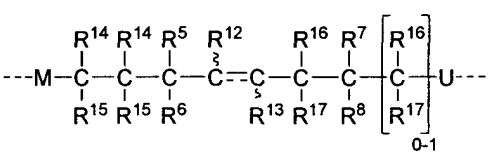
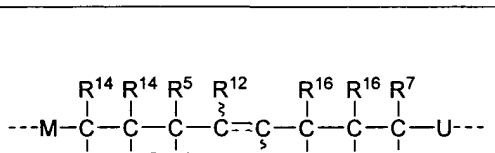
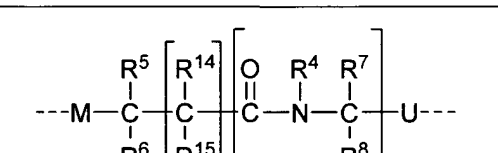
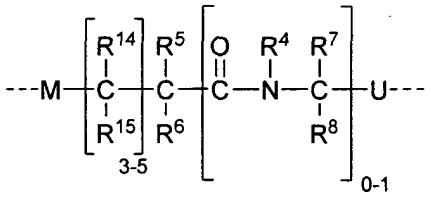
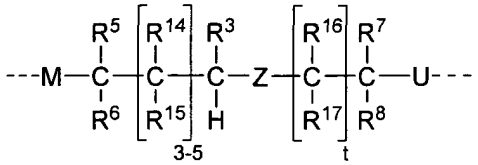
C33

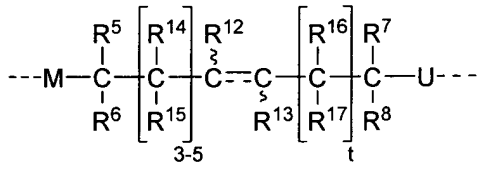


C34

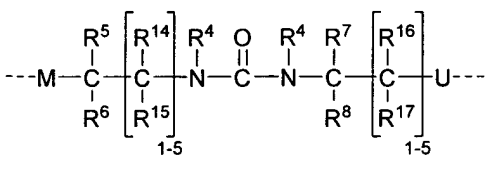




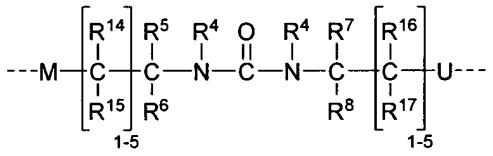
C35	C36
	
C37	C38
	
C39	C40
	
C41	C42
	
C43	C44
	
C45	C46
C47	C48
	



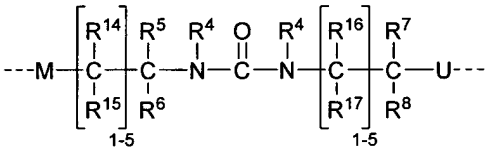
C49



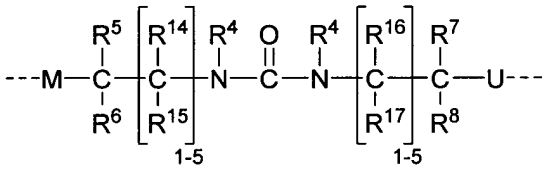
C50



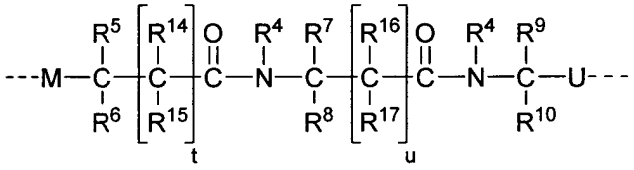
C51



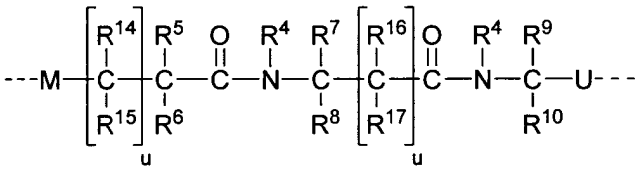
C52



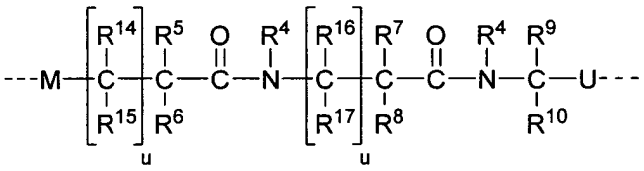
C53



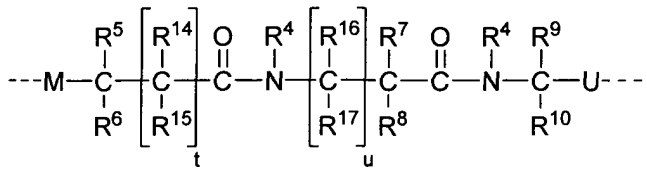
C54



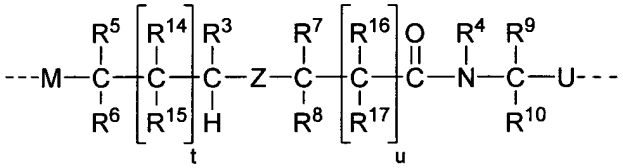
C55



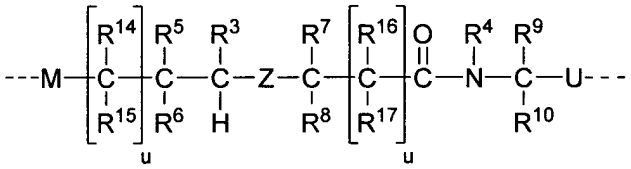
C56



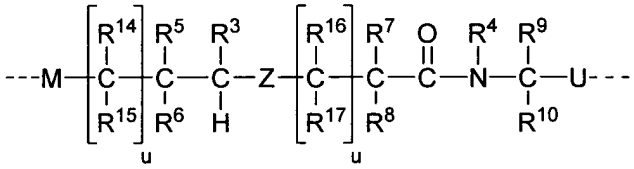
C57



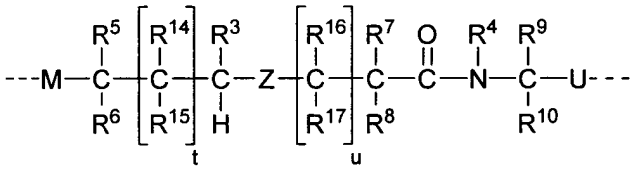
C58



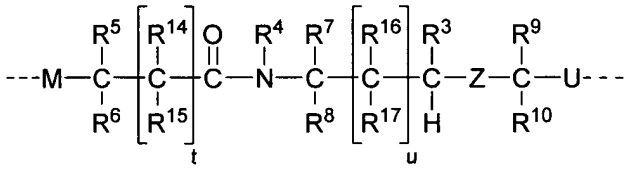
C59



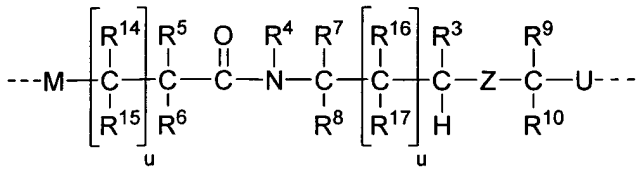
C60



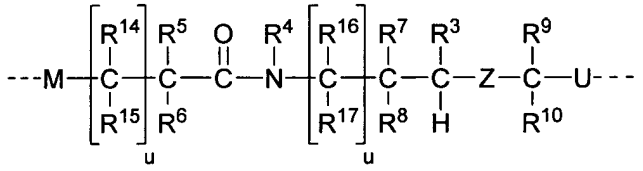
C61



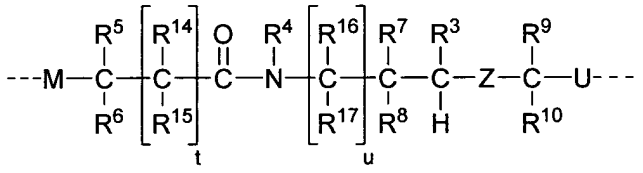
C62



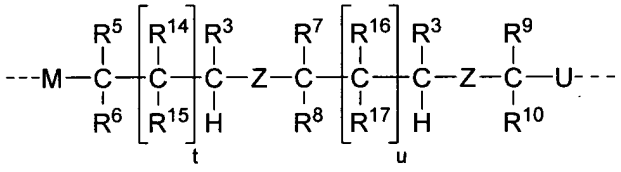
C63



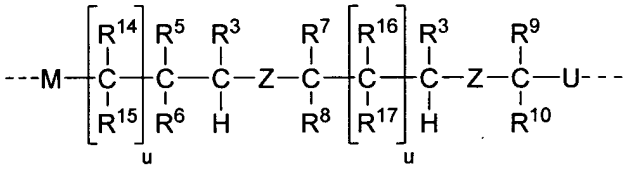
C64



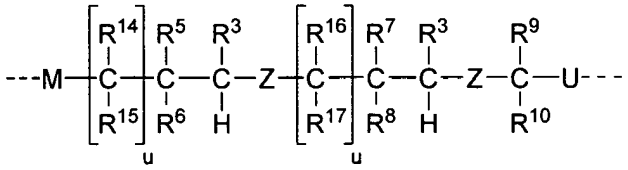
C65



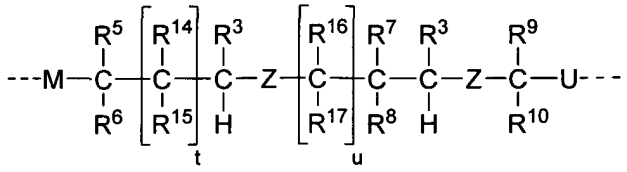
C66



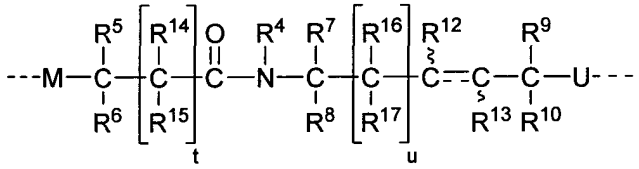
C67



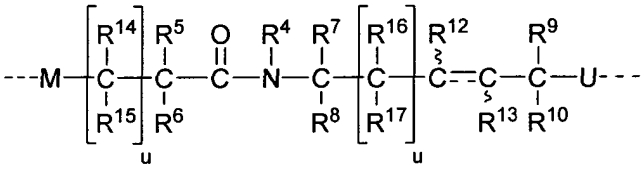
C68



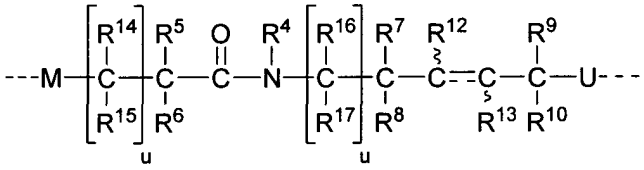
C69



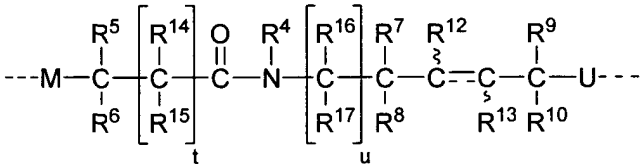
C70



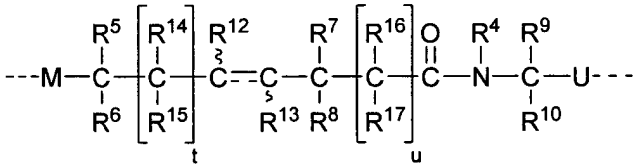
C71



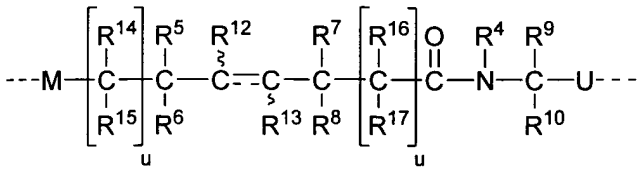
C72



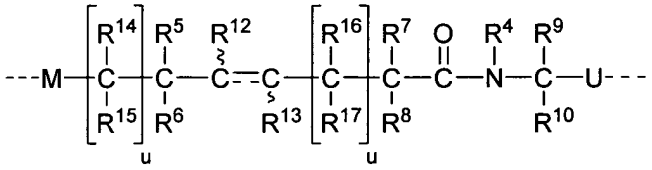
C73



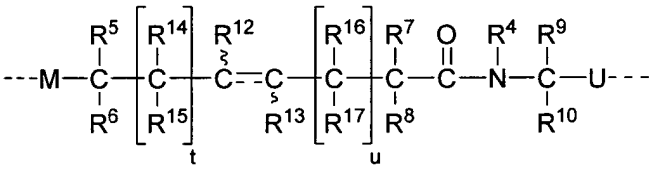
C74



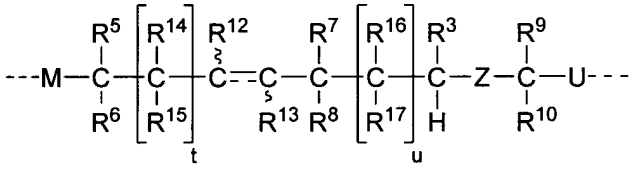
C75



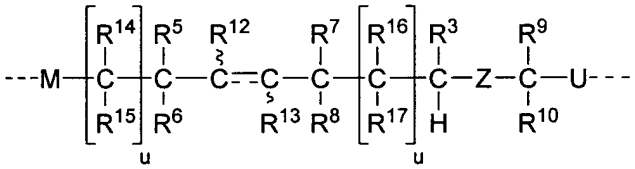
C76



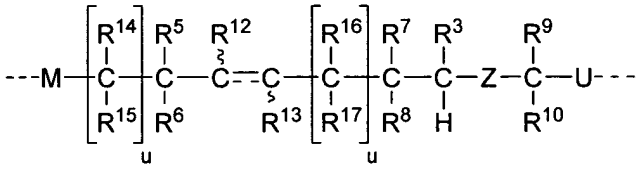
C77



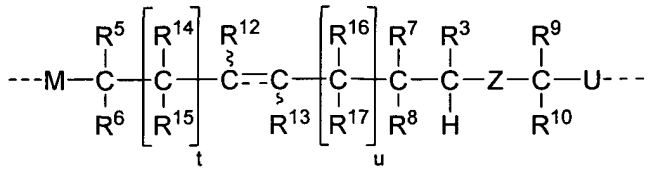
C78



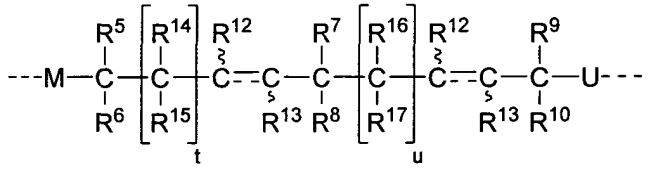
C79



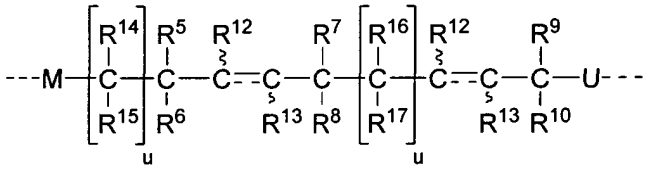
C80



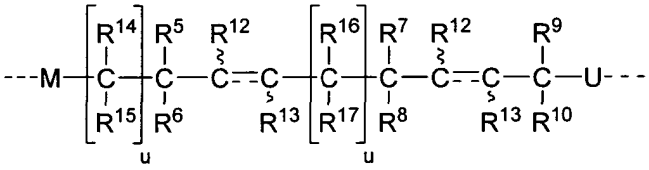
C81



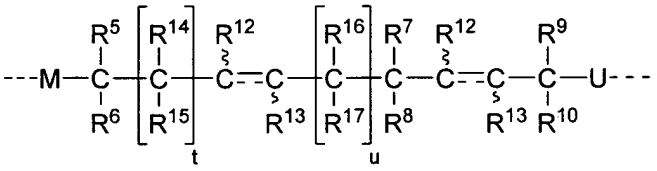
C82



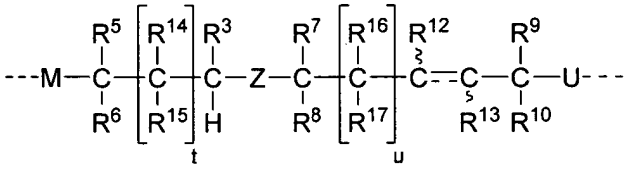
C83



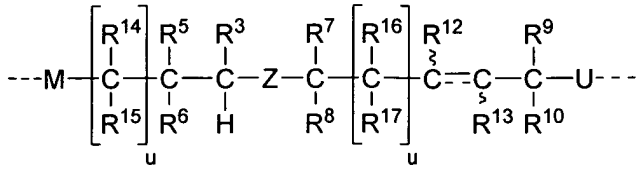
C84



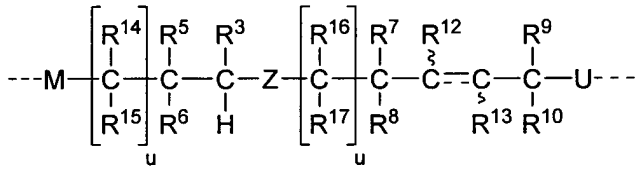
C85



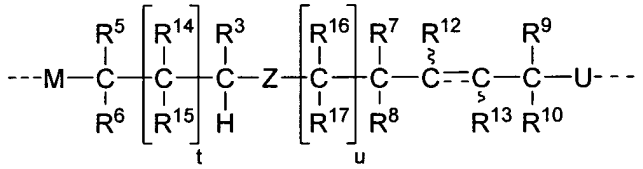
C86



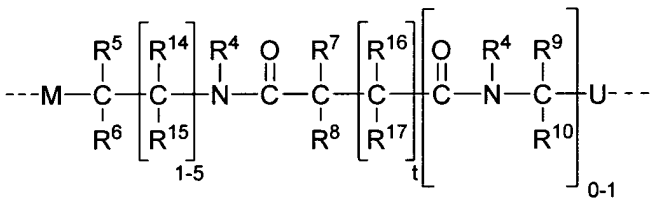
C87



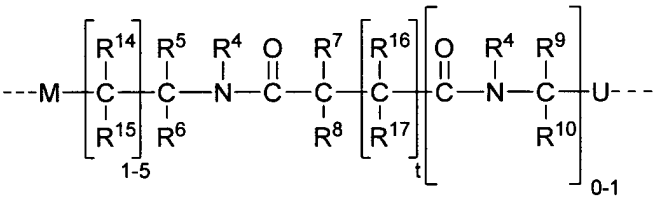
C88



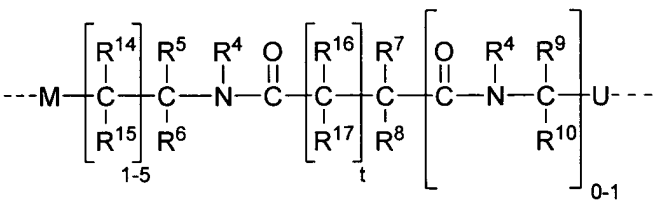
C89



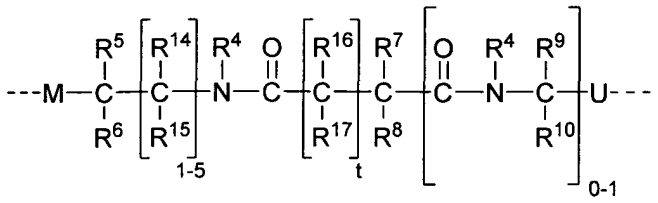
C90



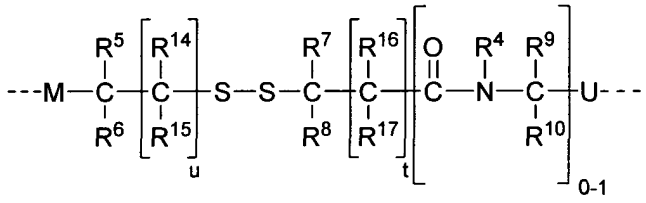
C91



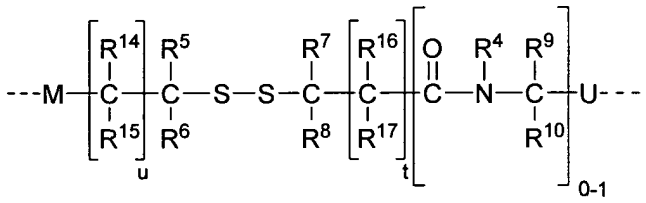
C92



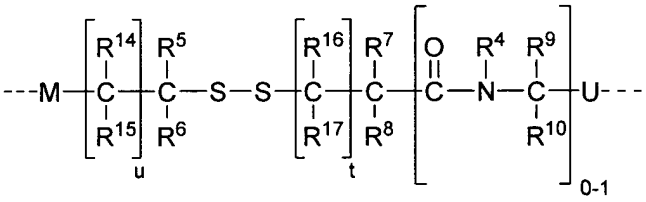
C93



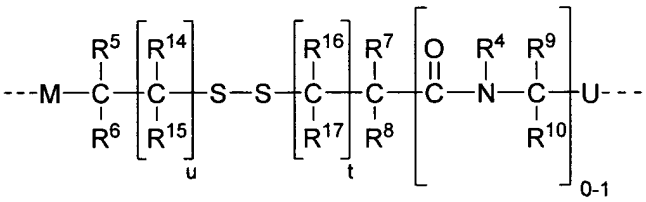
C94



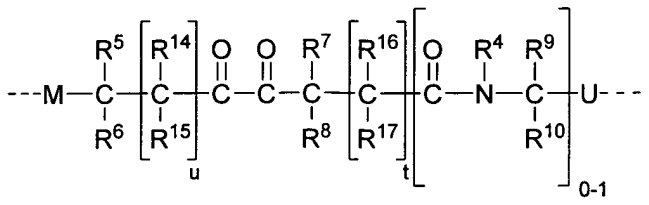
C95



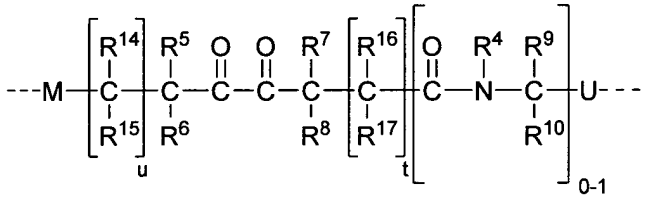
C96



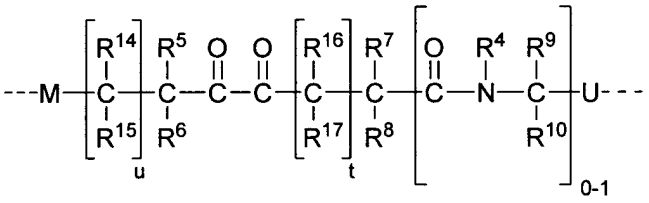
C97



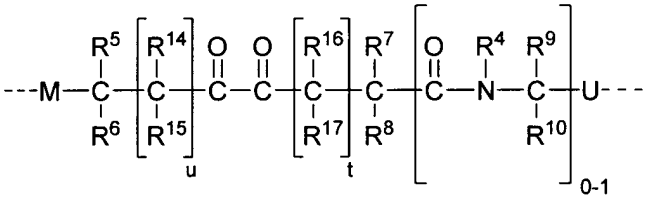
C98



C99



C100



C101

According to the preceding definitions, macrocycles of type **Ia/Ib** contain at least one amide bond or isosteric surrogates thereof. As mentioned in the introduction, tertiary amide containing products generally show various ratios of *cis* and *trans* amide bond conformations in solution; this preference is in contrast to secondary amides that strongly prefer *trans* conformations. The occurrence of *cis* and/or *trans* conformations in macrocyclic natural products containing tertiary amide groups is well documented. In some cases a rapid equilibration

between the *cis* and *trans* amide bonds, a so-called "peptidyl *cis/ trans* isomerization", is observed; whereas in other cases discrete *cis* and *trans* tertiary amide bonds are detected as two stable conformers in solution at room temperature.
Consequently all possible stereoisomers (explicitly including atropisomers), conformers or rotamers of macrocycles **Ia/Ib** are part of this invention.

The substituents mentioned in formulae **Ia** and **Ib**, respectively in the above description of the building blocks **A**, **B** or **C** are defined in detail with the following terms:

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

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

R^3 is H; CF_3; alkyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; or heteroarylalkyl;

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

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

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

R^{11} is H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; a suitable protecting group; $-(CR^{18}R^{19})_rOR^{20}$; $-(CR^{18}R^{19})_rSR^{20}$; $-(CR^{18}R^{19})_rNR^4R^{27}$; $-(CR^{18}R^{19})_rOCONR^4R^{27}$; $-(CR^{18}R^{19})_rOCOOR^{21}$; $-(CR^{18}R^{19})_rNR^4COOR^{21}$; $-(CR^{18}R^{19})_rNR^4CONR^4R^{27}$; $-(CR^{18}R^{19})_rNR^4SO_2R^{23}$; $-(CR^{18}R^{19})_rNR^4SO_2NR^4R^{27}$; $-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{27}$; $-(CR^{18}R^{19})_qCOR^{22}$; $-(CR^{18}R^{19})_qSO_2R^{23}$; $-(CR^{18}R^{19})_qSO_2NR^4R^{27}$; $-(CR^{18}R^{19})_qR^{24}$; $-(CR^{18}R^{19})_sR^{25}$; $-(CR^{18}R^{19})_qR^{26}$; or $-(CR^{18}R^{19})_qR^{31}$;

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

R^{14} and R^{16} are independently defined as H; F; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{18}R^{19})_qOR^{20}$; $-(CR^{18}R^{19})_qNR^4R^{11}$; $-(CR^{18}R^{19})_qNR^4COOR^{21}$; $-(CR^{18}R^{19})_qNR^4COR^{22}$; $-(CR^{18}R^{19})_qNR^4CONR^4R^{11}$;

$-(CR^{18}R^{19})_qNR^4SO_2R^{23}$;$-(CR^{18}R^{19})_qNR^4SO_2NR^4R^{11}$; $-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{11}$; $-(CR^{18}R^{19})_qSO_2NR^4R^{11}$; or $-(CR^{18}R^{19})_qCOR^{22}$;

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

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

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

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

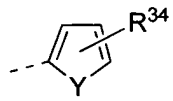
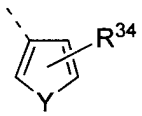
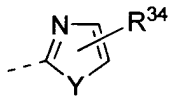
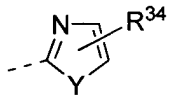
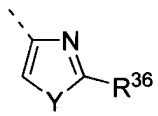
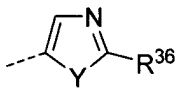
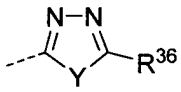
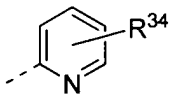
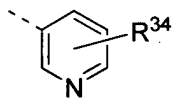
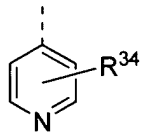
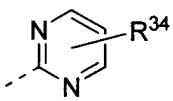
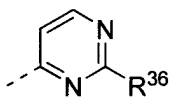
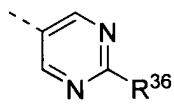
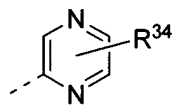
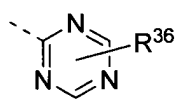
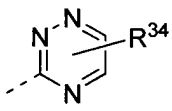
R^{21} is H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; or a suitable *O*-protecting group;

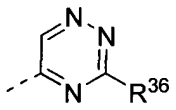
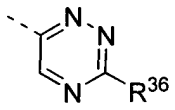
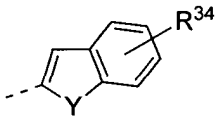
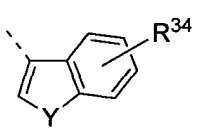
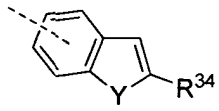
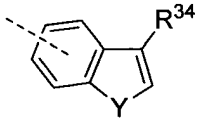
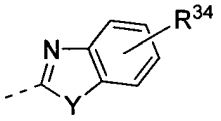
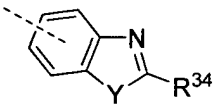
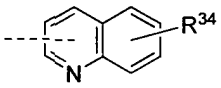
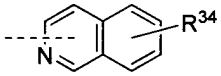
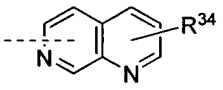
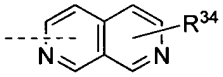
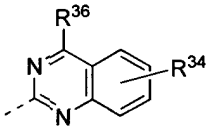
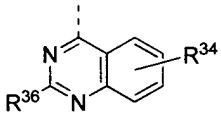
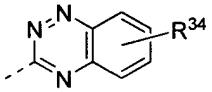
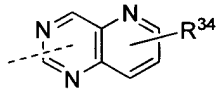
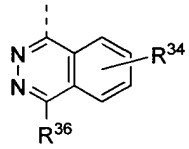
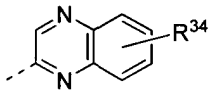
R^{22} is alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{29}R^{30})_sOR^{31}$; $-(CR^{29}R^{30})_sSR^{31}$; $-(CR^{29}R^{30})_sNR^{28}R^{31}$; $-(CR^{29}R^{30})_sOCONR^{28}R^{31}$; $-(CR^{29}R^{30})_sNR^{28}COOR^{21}$; $-(CR^{29}R^{30})_sNR^{28}COR^{31}$;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

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

R^{24} is aryl; heteroaryl; $-C_6H_2R^{34}R^{35}R^{31}$; or a group of one of the formulae **H1-H34** listed in Table 4.

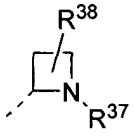
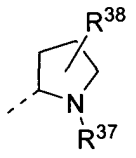
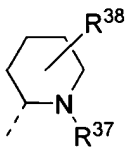
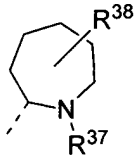
Table 4: Groups of Formulae **H1-H34** (*continued on the following page*)

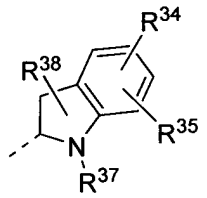
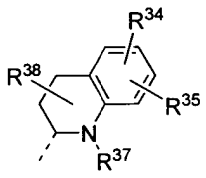
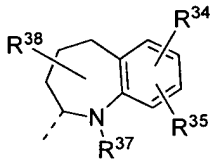
 **H1**	 **H2**	 **H3**	 **H4**
 **H5**	 **H6**	 **H7**	 **H8**
 **H9**	 **H10**	 **H11**	 **H12**
 **H13**	 **H14**	 **H15**	 **H16**

 H17	 H18	 H19	 H20
 H21	 H22	 H23	 H24
 H25	 H26	 H27	 H28
 H29	 H30	 H31	 H32
 H33	 H34		

R^{25} is a group of one of formulae **H35-H41** as shown in Table 5 below.

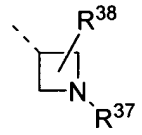
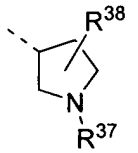
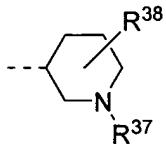
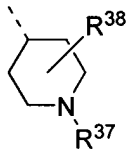
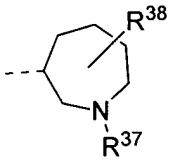
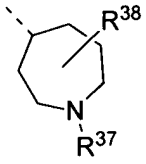
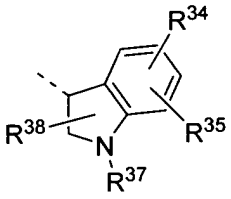
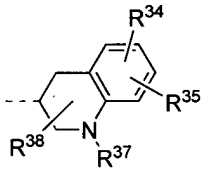
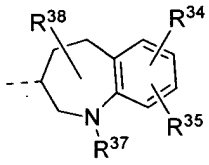
Table 5: Radicals of Formulae **H35-H41**

 H35	 H36	 H37	 H38

		
H39	**H40**	**H41**

R^{26} is a group of one of formulae **H42-H50** as shown in Table 6 below.

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

 **H42**	 **H43**	 **H44**	 **H45**
 **H46**	 **H47**	 **H48**	 **H49**
 **H50**			

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

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

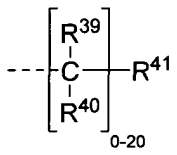
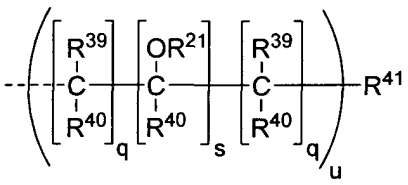
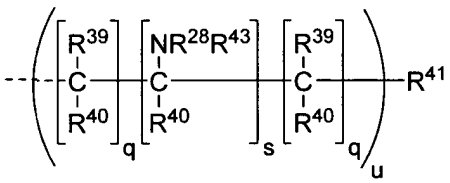
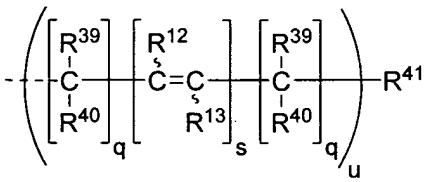
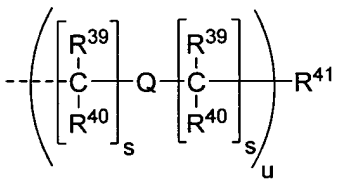
R^{29} is H; F; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{32}R^{33})_sOR^{31}$; $-(CR^{32}R^{33})_sSR^{31}$; $-(CR^{32}R^{33})_sNR^{28}R^{31}$; $-(CR^{32}R^{33})_sOCONR^{28}R^{31}$; $-(CR^{32}R^{33})_sOCOOR^{21}$; $-(CR^{32}R^{33})_sNR^{28}COOR^{21}$;

$-(CR^{32}R^{33})_sNR^{28}COR^{31}$; $-(CR^{32}R^{33})_sNR^{28}CONR^{28}R^{31}$; $-(CR^{32}R^{33})_sNR^{28}SO_2R^{23}$; $-(CR^{32}R^{33})_sNR^{28}SO_2NR^{28}R^{31}$; $-(CR^{32}R^{33})_qCOOR^{21}$; $-(CR^{32}R^{33})_qCONR^{28}R^{31}$; $-(CR^{32}R^{33})_qSO_2NR^{28}R^{31}$; $-(CR^{32}R^{33})_qPO(OR^{21})_2$; $-(CR^{32}R^{33})_qCOR^{31}$; $-(CR^{32}R^{33})_qSO_2R^{23}$; or $-(CR^{32}R^{33})_qR^{31}$;

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

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

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

 **H51**	 **H52**
 **H53**	 **H54**
 **H55**	

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

R^{34} and R^{35} are independently defined as H; F; Cl; CF_3; OCF_3; $OCHF_2$; NO_2; CN; alkyl; alkenyl; alkynyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{29}R^{30})_qOR^{31}$; $-(CR^{29}R^{30})_qSR^{31}$; $-(CR^{29}R^{30})_qNR^{28}R^{31}$; $-(CR^{29}R^{30})_qOCONR^{28}R^{31}$; $-(CR^{29}R^{30})_qNR^{28}COOR^{21}$; $-(CR^{29}R^{30})_qNR^{28}COR^{31}$; $-(CR^{29}R^{30})_qNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_qNR^{28}SO_2R^{23}$; $-(CR^{29}R^{30})_qNR^{28}SO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_qSO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOR^{31}$; $-(CR^{29}R^{30})_qSO_2R^{23}$; or $-(CR^{29}R^{30})_qR^{31}$;

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

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

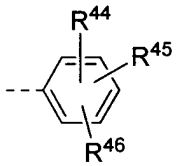
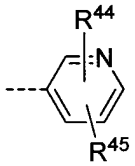
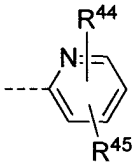
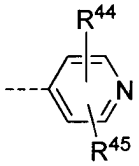
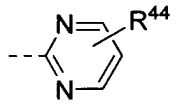
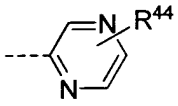
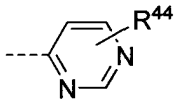
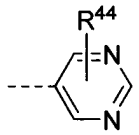
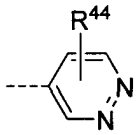
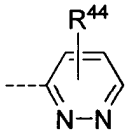
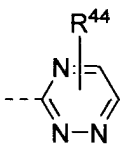
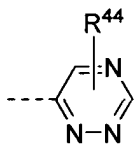
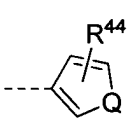
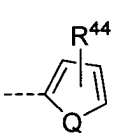
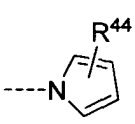
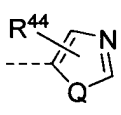
R^{38} is H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{29}R^{30})_qOR^{31}$; $-(CR^{29}R^{30})_qSR^{31}$; $-(CR^{29}R^{30})_qNR^{28}R^{31}$; $-(CR^{29}R^{30})_qNR^{28}COOR^{21}$; $-(CR^{29}R^{30})_qNR^{28}COR^{31}$; $-(CR^{29}R^{30})_qNR^{28}CONR^{28}R^{31}$;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

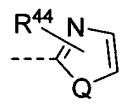
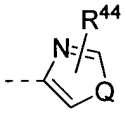
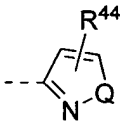
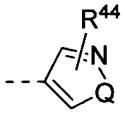
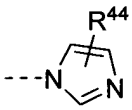
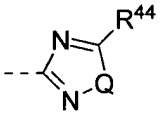
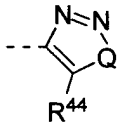
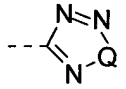
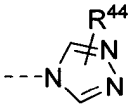
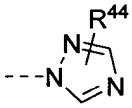
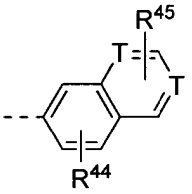
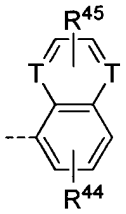
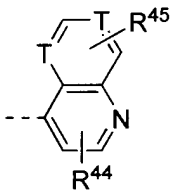
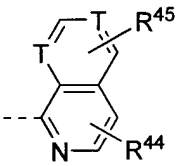
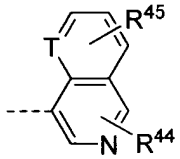
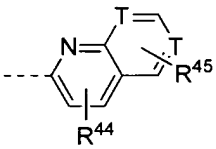
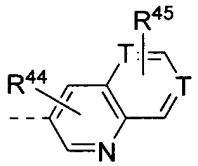
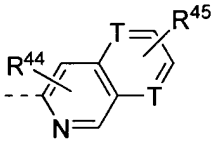
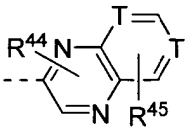
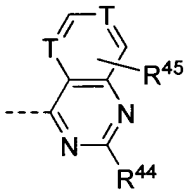
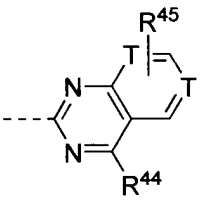
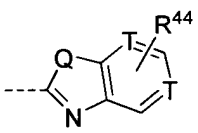
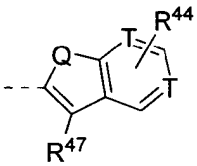
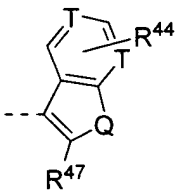
R^{39} is H; F; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{32}R^{33})_uOR^{21}$; $-(CR^{32}R^{33})_uNR^{28}R^{43}$; $-(CR^{32}R^{33})_tCOOR^{21}$; or $-(CR^{32}R^{33})_tCONR^{28}R^{43}$;

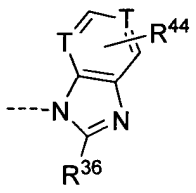
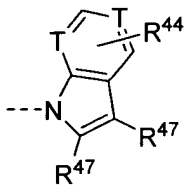
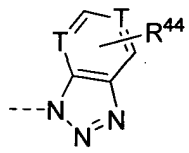
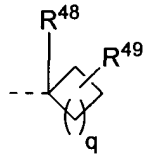
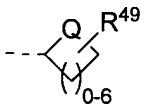
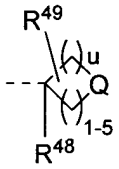
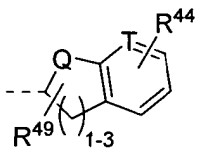
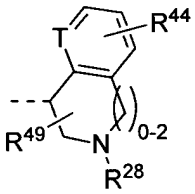
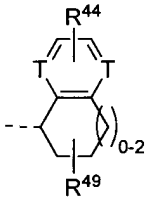
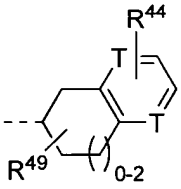
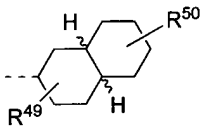
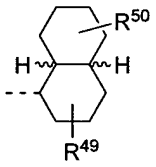
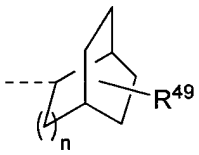
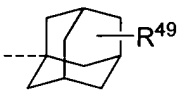
R^{40} is H; F; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{32}R^{33})_uOR^{21}$; $-(CR^{32}R^{33})_uNR^{28}R^{43}$; $-(CR^{32}R^{33})_tCOOR^{21}$; or $-(CR^{32}R^{33})_tCONR^{28}R^{43}$;

R^{41} is H; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-OR^{21}$; $-NR^{28}R^{43}$; $-NR^{28}COR^{23}$; $-NR^{28}COOR^{21}$; $-NR^{28}SO_2R^{23}$; $-NR^{28}CONR^{28}R^{43}$; $-COOR^{21}$; $-CONR^{28}R^{43}$; $-C(=NR^{43})NR^{28}R^{43}$; $-NR^{28}C(=NR^{43})NR^{28}R^{43}$; or a group of one of the formulae **H56-H110** as shown in Table 8 below.

Table 8: 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^{42} is H; alkyl; alkenyl; cycloalkyl; cycloheteroalkyl; aryl; heteroaryl; $-(CR^{23}R^{33})_sOR^{21}$; $-(CR^{23}R^{33})_sNR^4R^{43}$; $-(CR^{23}R^{33})_qCOOR^{21}$; or $-(CR^{23}R^{33})_qCONR^4R^{43}$;

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

R^{44}, R^{45} and R^{46} are independently defined as H; F; CF_3; OCF_3; $OCHF_2$; NO_2; CN; alkyl; alkenyl; alkynyl; cycloalkyl;

heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-OR^{23}$; $-NR^{28}R^{43}$; $-NR^{28}COR^{23}$; $-NR^{28}SO_2R^{23}$; $-NR^{28}CONR^{28}R^{43}$; $-COR^{23}$; or $-SO_2R^{23}$;

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

R^{48} is H; F; CF_3; alkyl; alkenyl; cycloalkyl; cycloheteroalkyl; aryl; heteroaryl; $-(CR^{23}R^{33})_tOR^{21}$; $-(CR^{23}R^{33})_tNR^{28}R^{43}$; $-(CR^{23}R^{33})_tCOOR^{21}$; or $-(CR^{23}R^{33})_tCONR^{21}R^{43}$

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

R^{51} is H; F; Cl; CF_3; OCF_3; or lower alkyl;

R^{52} is H; F; Cl; CF_3; OCF_3; $OCHF_2$; NO_2; CN; lower alkyl; lower alkenyl; lower alkynyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; or lower heteroarylalkyl;

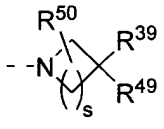
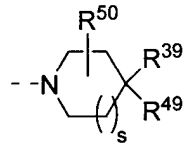
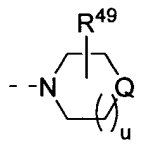
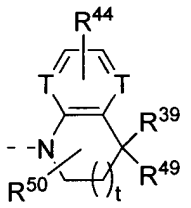
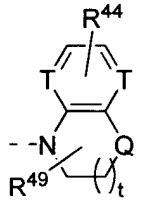
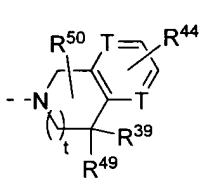
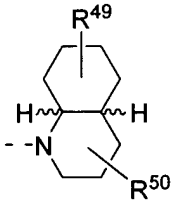
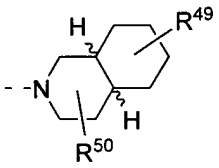
R^{53} is CF_3; OCF_3; CN; lower alkyl; lower cycloalkyl; aryl; lower alkoxy; or aryloxy.

Taken together, the following pairs of said substituents can define cyclic structural elements:

Taken together (R^4 and R^{11}); (R^4 and R^{27}); (R^5 and R^6); (R^5 and R^7); (R^5 and R^9); (R^5 and R^{14}); (R^5 and R^{16}); (R^7 and R^8); (R^7 and R^9); (R^7 and R^{16}); (R^9 and R^{10}); (R^{14} and R^{15}); (R^{16} and R^{17}); (R^{18} and R^{19}); (R^{27} and R^{28}); (R^{28} and R^{31}); (R^{28} and R^{43}); (R^{29} and R^{30}); (R^{32} and R^{33}); (R^{34} and R^{35}); (R^{37} and R^{38}); (R^{39} and R^{40}); (R^{39} and R^{41}); (R^{39} and R^{49}); (R^{42} and R^{43}); (R^{44} and R^{45}); or (R^{44} and R^{46}) can form optionally substituted cycloalkyl or heterocycloalkyl moieties.

In addition, the structural elements $-NR^4R^{11}$; $-NR^{11}R^{27}$; $-NR^{27}R^{28}$; $-NR^{28}R^{31}$ or $-NR^{28}R^{43}$ can form one of the groups of formulae **H111–H118** as shown in Table 9 below.

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

 **H111**	 **H112**	 **H113**	 **H114**
 **H115**	 **H116**	 **H117**	 **H118**

Variable heteroatoms and connector groups in the aforementioned structures are:

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

Y is O; S; or NR^4;

Q is O; S; or NR^{28};

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

The indices in the aforementioned structures are defined as:

q is an integer of 0-4;

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.

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

"Salts" as understood herein are especially, but not limited to, the pharmaceutically acceptable salts of compounds of formula **Ia/Ib**. Such salts are formed, for example, as acid addition salts, preferably with organic or inorganic acids, from compounds of type **Ia/Ib** with a 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, tartaric acid,

citric acid, amino acids, such as glutamic acid or aspartic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, cyclohexanecarboxylic acid, adamantinecarboxylic 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-methyl-benzenesulfonic acid, methylsulfuric acid, ethylsulfuric acid, dodecylsulfuric acid, *N*-cyclohexylsulfamic acid, *N*-methyl-, *N*-ethyl- or *N*-propyl-sulfamic acid, or other organic protonic acids, such as ascorbic acid.

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

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

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

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

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

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

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

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

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

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

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

trialkylamino), arylamino (e.g. monoarylamino, diarylamino, or triarylamino), hydroxy, carboxy, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate.

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

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

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

The 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. 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**.

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, diastereomers.

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 macrocycles of type **Ia/Ib** are part of this invention.

In another embodiment of this invention, the macrocycles of type **Ia/Ib** are defined as above but wherein

M is $-N(R^4)-$

and wherein all possible stereoisomers of such compounds or pharmaceutical acceptable salts thereof are included.

In a preferred embodiment of this invention, the macrocycles of type **Ia/Ib** are defined by groups of selected building blocks **A**, **B** and **C** and substituents R^1-R^{53} as detailed below:

The building block of type **A** is selected from

A1(a1); **A2**(a1); **A3**(a1); **A4**(a1); **A5**(a1); **A6**(a1); **A7**(a1); **A9**(a1); **A10**(a1); **A73**(a2); **A80**(a2); **A170**(a4); **A171**(a4); **A209**(a7); **A210**(a7); **A240**(a10); **A241**(a10); **A242**(a10); **A243**(a10); **A272**(a10); **A530**(a18); **A531**(a18); **A532**(a18); **A533**(a18); **A609**(a24); **A610**(a24); **A611**(a24); **A612**(a24); **A613**(a24); **A614**(a24); **A615**(a24); **A631**(a1); **A632**(a1); **A633**(a1); **A641**(a1); **A642**(a1); **A643**(a1); **A651**(a1); **A652**(a1); or **A653**(a1);

the building block of type **B** is selected from

B4(b3); **B5**(b3); **B6**(b3); **B7**(b3); **B8**(b3); **B9**(b3); **B10**(b3); **B12**(b4); **B13**(b4); **B14**(b4); **B15**(b4); **B16**(b4) or **B17**(b5);

the building block of type **C** is selected from

C1; C2; C3; C4; C5; C6; C7; C8; C9; C10; C11; C12; C13; C14; C15; C16; C17; C18; C19; C20; C21; C25; C26; C27; C28; C29; C30; C34; C35; C36; C37; C38; C39; C43; C44; C45; C46; C47; C48; C49; C50; C51; C52; C53; C54; C55; C56; C57; C58; C59; C60; C61; C62; C63; C64; C65; C66; C67; C68; C69; C70; C71; C72; C73; C74; C75; C76; C77; C78; C79; C80; C81; C86; C87; C88; C89; C90; C91; C92; or **C93;**

and wherein

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

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

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

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

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

R^{11} is H; alkyl; alkenyl; cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; a suitable protecting group; $-(CR^{18}R^{19})_rOR^{20}$; $-(CR^{18}R^{19})_rNR^4R^{27}$; $-(CR^{18}R^{19})_rNR^4COOR^{21}$; $-(CR^{18}R^{19})_rNR^4CONR^4R^{27}$; $-(CR^{18}R^{19})_rNR^4SO_2R^{23}$; $-(CR^{18}R^{19})_rNR^4SO_2NR^4R^{27}$; $-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{27}$; $-(CR^{18}R^{19})_qCOR^{22}$; $-(CR^{18}R^{19})_qSO_2R^{23}$; $-(CR^{18}R^{19})_qSO_2NR^4R^{27}$; $-(CR^{18}R^{19})_qR^{24}$; $-(CR^{18}R^{19})_sR^{25}$; $-(CR^{18}R^{19})_qR^{26}$; or $-(CR^{18}R^{19})_qR^{31}$;

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

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

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

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

R^{19} is H; CF_3; or lower alkyl;

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

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

R^{29} is H; F; CF_3; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{32}R^{33})_sOR^{31}$; $-(CR^{32}R^{33})_sNR^{28}R^{31}$; $-(CR^{32}R^{33})_sNR^{28}COOR^{21}$; $-(CR^{32}R^{33})_sNR^{28}COR^{31}$; $-(CR^{32}R^{33})_sNR^{28}CONR^{28}R^{31}$; $-(CR^{32}R^{33})_sNR^{28}SO_2R^{23}$; $-(CR^{32}R^{33})_qCOOR^{21}$;

$-(CR^{32}R^{33})_qCONR^{28}R^{31}$; $-(CR^{32}R^{33})_qSO_2NR^{28}R^{31}$; $-(CR^{32}R^{33})_qPO(OR^{21})_2$; $-(CR^{32}R^{33})_qCOR^{31}$; $-(CR^{32}R^{33})_qSO_2R^{23}$; or $-(CR^{32}R^{33})_qR^{31}$;

R^{30} and R^{33} are independently defined as H; CF_3; or lower alkyl;

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

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

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

Z is O; S; S(=O); or $S(=O)_2$;

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

In a further preferred embodiment of this invention, the macrocycles of type **Ia/Ib** are defined by groups of selected building blocks **A**, **B** and **C** and substituents R^1-R^{53} as detailed below:

The building block of type **A** is selected from

A1(a1); **A2**(a1); **A3**(a1); **A4**(a1); **A5**(a1); **A6**(a1); **A7**(a1); **A9**(a1); **A10**(a1); **A73**(a2); **A170**(a4); **A209**(a7); **A240**(a10); **A272**(a10); **A532**(a18); **A614**(a24) ; **A631**(a1); **A632**(a1); **A633**(a1); **A641**(a1); **A642**(a1); **A643**(a1); **A651**(a1); **A652**(a1); or **A653**(a1);

the building block of type **B** is selected from

B7(b3); **B8**(b3); **B9**(b3); **B10**(b3); or **B17**(b5);

the building block of type **C** is selected from

C1; **C2**; **C4**; **C7**; **C8**; **C9**; **C10**; **C11**; **C12**; **C13**; **C14**; **C15**; **C16**; **C17**; **C18**; **C19**; **C20**; **C21**; **C25**; **C26**; **C27**; **C28**; **C29**; **C30**; **C34**; **C35**; **C36**; **C37**; **C38**; **C39**; **C43**; **C44**; **C45**; **C46**; **C47**; **C48**; **C49**; **C90**; **C91**; **C92**; or **C93**;

and wherein

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

R^2 is H; CF_3; lower alkyl; lower alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{18}R^{19})_qOR^{20}$; $-(CR^{18}R^{19})_qNR^4R^{11}$;

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

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

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

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

R^{11} is H; alkyl; alkenyl; cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; a suitable protecting group; $-(CR^{18}R^{19})_rOR^{20}$; $-(CR^{18}R^{19})_rNR^4R^{27}$; $-(CR^{18}R^{19})_rNR^4CONR^4R^{27}$; $-(CR^{18}R^{19})_rNR^4SO_2R^{23}$; $-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{27}$; $-(CR^{18}R^{19})_qCOR^{22}$; $-(CR^{18}R^{19})_qR^{24}$; $-(CR^{18}R^{19})_sR^{25}$; $-(CR^{18}R^{19})_qR^{26}$; or $-(CR^{18}R^{19})_qR^{31}$;

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

R^{14} and R^{16} are independently defined as H; F; CF_3; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{18}R^{19})_qOR^{20}$; $-(CR^{18}R^{19})_qNR^4R^{11}$; $-(CR^{18}R^{19})_qNR^4COR^{22}$; $-(CR^{18}R^{19})_qCOOR^{21}$; or $-(CR^{18}R^{19})_qCONR^4R^{11}$;

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

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

R^{19} is H; CF_3; or CH_3;

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

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

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

R^{30} and R^{33} are independently defined as H; CF_3; or CH_3;

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

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

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

Z is O; S or $S(=O)_2$;

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

In a particularly preferred embodiment of this invention, the macrocycles of type **Ia/Ib** are defined by groups of selected building blocks **A**, **B** and **C** and substituents R^1-R^{53} as detailed below:

The building block of type **A** is selected from

A1(a1); **A2**(a1); **A3**(a1); **A4**(a1); **A5**(a1); **A6**(a1); **A7**(a1); **A9**(a1); **A10**(a1); **A73**(a2); **A170**(a4); **A209**(a7); **A240**(a10); **A272**(a10); **A532**(a18); **A614**(a24); **A631**(a1); **A632**(a1); **A633**(a1); **A641**(a1); **A642**(a1); **A643**(a1); **A651**(a1); **A652**(a1); or **A653**(a1).

The building block of type **B** is selected from

B7(b3); **B8**(b3); **B9**(b3); **B10**(b3); or **B17**(b5).

The building block of type **C** is selected from

C1; **C8**; **C9**; **C11**; **C12**; **C15**; **C17**; **C19**; **C20**; **C25**; or **C47**;

and wherein

R^1 is H; F; Cl; Br; CF_3; OCF_3; $OCHF_2$; CN; lower alkyl; lower alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{29}R^{30})_qOR^{20}$; $-(CR^{29}R^{30})_qNR^4R^{11}$; $-(CR^{29}R^{30})_qNR^4COR^{22}$; $-(CR^{29}R^{30})_qNR^4CONR^4R^{11}$; $-(CR^{29}R^{30})_qNR^4SO_2R^{23}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^4R^{11}$; $-(CR^{29}R^{30})_qSO_2NR^4R^{11}$; $-(CR^{29}R^{30})_qCOR^{22}$; $-(CR^{29}R^{30})_qSO_2R^{23}$; $-(CR^{29}R^{30})_qR^{24}$; $-(CR^{29}R^{30})_qR^{25}$; or $-(CR^{29}R^{30})_qR^{26}$;

R^2 is H; CF_3; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{29}R^{30})_qOR^{20}$; $-(CR^{29}R^{30})_qNR^4R^{11}$; $-(CR^{29}R^{30})_qNR^4COR^{22}$; $-(CR^{29}R^{30})_qNR^4CONR^4R^{11}$; $-(CR^{29}R^{30})_qNR^4SO_2R^{23}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^4R^{11}$; $-(CR^{29}R^{30})_qSO_2NR^4R^{11}$; $-(CR^{29}R^{30})_qCOR^{22}$; $-(CR^{29}R^{30})_qSO_2R^{23}$; $-(CR^{29}R^{30})_qR^{24}$; $-(CR^{29}R^{30})_qR^{25}$; or $-(CR^{29}R^{30})_qR^{26}$;

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

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

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

R^{11} is H; alkyl; alkenyl; cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; a suitable protecting group; $-(CR^{18}R^{19})_rOR^{20}$; $-(CR^{18}R^{19})_rNR^4R^{27}$; $-(CR^{18}R^{19})_rNR^4CONR^4R^{27}$; $-(CR^{18}R^{19})_rNR^4SO_2R^{23}$; $-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{27}$; $-(CR^{18}R^{19})_qCOR^{22}$; $-(CR^{18}R^{19})_qR^{24}$; $-(CR^{18}R^{19})_sR^{25}$; $-(CR^{18}R^{19})_qR^{26}$; or $-(CR^{18}R^{19})_qR^{31}$;

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

R^{14} and R^{16} are independently defined as H; F; CF_3; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{29}R^{30})_qOR^{20}$; $-(CR^{29}R^{30})_qNR^4R^{11}$; $-(CR^{29}R^{30})_qNR^4COR^{22}$; $-(CR^{29}R^{30})_qCOOR^{21}$; or $-(CR^{29}R^{30})_qCONR^4R^{11}$;

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

R^{18} is H; F; CF_3; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{29}R^{30})_sOR^{31}$; $-(CR^{29}R^{30})_sNR^{28}R^{31}$; $-(CR^{29}R^{30})_sNR^{28}COR^{31}$; $-(CR^{29}R^{30})_sNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_sNR^{28}SO_2R^{23}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^{28}R^{31}$;

$-(CR^{29}R^{30})_qSO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOR^{31}$; $-(CR^{29}R^{30})_qSO_2R^{23}$; $-(CR^{29}R^{30})_qR^{24}$; $-(CR^{29}R^{30})_qR^{25}$; or $-(CR^{29}R^{30})_qR^{26}$;

R^{19} is H; CF_3; or CH_3;

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

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

R^{24} is aryl; heteroaryl; or $-C_6H_2R^{34}R^{35}R^{31}$;

R^{25} and R^{26} are independently defined as heterocycloalkyl;

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

R^{28} is H; $-(CR^{32}R^{33})_sOR^{21}$; or $-(CR^{32}R^{33})_sNR^{43}R^{42}$;

R^{29} is H; F; CF_3; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower

arylalkyl; lower heteroarylalkyl; $-(CR^{32}R^{33})_sOR^{31}$; $-(CR^{32}R^{33})_sNR^{28}R^{31}$; $-(CR^{32}R^{33})_sNR^{28}COR^{31}$; $-(CR^{32}R^{33})_sNR^{28}CONR^{28}R^{31}$; $-(CR^{32}R^{33})_qCOOR^{21}$; $-(CR^{32}R^{33})_qCONR^{28}R^{31}$; $-(CR^{32}R^{33})_qCOR^{31}$; or $-(CR^{32}R^{33})_qR^{31}$;

R^{30} and R^{33} are independently defined as H; F; CF_3; or CH_3;

R^{31} is H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; or heteroarylalkyl;

R^{32} is H; F; CF_3; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; or lower heteroarylalkyl;

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

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

R^{42} and R^{43} are independently defined as H; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; or a suitable *N*-protecting group;

X is O; S; S(=O); or $S(=O)_2$;

Y is O; S; or NR^4;

Z is O; S or $S(=O)_2$;

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

This particularly preferred embodiment includes all possible stereoisomers (explicitly including atropisomers), conformers and rotamers as well as pharmaceutically acceptable salts, solvates, clathrates, isotopically enriched or enantiomerically enriched versions of above macrocyclic compounds.

In a further particularly preferred embodiment of this invention, the macrocycles of type **Ia/Ib** are defined by groups of selected building blocks **A**, **B** and **C** and substituents R^1-R^{53} as detailed below:

The building block of type **A** is selected from

A2(a1); **A5**(a1); **A9**(a1); **A73**(a2); **A209**(a7); **A272**(a10); **A532**(a18); **A614**(a24); **A641**(a1); or **A651**(a1);

the building block of type **B** is selected from

B7; **B9**; **B10** or **B17**;

the building block of type **C** is selected from

C1; **C8**; **C9**; **C11**; **C15**; **C17**; **C19**; **C20**; **C25**; or **C47**;

and wherein

R^1 is H; F; Cl; Br; CH_3; OCH_3; OH; or aryl;

R^2 is H; CH_3; heterocycloalkyl; aryl; benzyl; heteroaryl; $-OR^{20}$; $-NR^4R^{11}$; $-NR^4COOR^{21}$; $-NR^4COR^{22}$; $-NR^4CONR^4R^{11}$; or $-NR^4SO_2R^{23}$;

R^3 is H;

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

R^5, R^7 and R^9 are independently defined as H; CF_3; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-OR^{20}$; $-NR^4R^{11}$; $-NR^4COR^{22}$; $-NR^4CONR^4R^{11}$; $-NR^4SO_2R^{23}$; $-COOR^{21}$;$-CONR^4R^{11}$; or $-COR^{22}$;

R^6, R^8 and R^{10} are defined as H;

R^{11} is H; alkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{18}R^{19})_rOR^{20}$; $-(CR^{18}R^{19})_rNR^4R^{27}$; $-(CR^{18}R^{19})_qCOOR^{21}$; $-COR^{22}$; $-(CR^{18}R^{19})_qR^{24}$; or $-(CR^{18}R^{19})_qR^{31}$;

R^{12} and R^{13} are defined as H;

R^{14} and R^{16} are independently defined as H; lower alkyl; or lower arylalkyl;

R^{15} and R^{17} are defined as H;

R^{18} and R^{19} are defined as H;

R^{20} is H; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; or $-(CR^{29}R^{30})_qR^{24}$;

R^{21} is H; lower alkyl; lower arylalkyl; or a suitable *O*-protecting group;

R^{22} is lower alkyl; lower alkenyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{29}R^{30})_sOR^{31}$; $-(CR^{29}R^{30})_sNR^{28}R^{31}$; $-(CR^{29}R^{30})_sCOOR^{21}$; $-(CR^{29}R^{30})_tR^{24}$; or $-(CR^{29}R^{30})_tR^{31}$;

R^{23} is H; lower alkyl; aryl; heteroaryl; or $-R^{24}$;

R^{24} is aryl; heteroaryl; or $-C_6H_2R^{34}R^{35}R^{31}$;

R^{27} is H; acetyl; CH_3; or $-(CH_2)_qR^{24}$;

R^{28} is H; $-(CR^{32}R^{33})_sOR^{21}$; or $-(CR^{32}R^{33})_sNR^{43}R^{42}$;

R^{29} is H; lower alkyl; aryl; or heteroaryl;

R^{30}, R^{32} and R^{33} are independently defined as H; CF_3; or CH_3;

R^{31} is H; alkyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; or heteroarylalkyl;

R^{34} and R^{35} are independently defined as H; heterocycloalkyl; $-OR^{31}$; or $-NR^{28}R^{31}$;

R^{38} is H; $-NR^{28}R^{31}$; $-NR^{28}COR^{31}$; or $-NR^{28}COOR^{31}$;

R^{42} and R^{43} are independently defined as H; CH_3; or benzyl;

X is O; S; S(=O); or $S(=O)_2$;

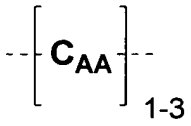
Y is O; S; or NR^4;

Z is O; S or $S(=O)_2$;

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

This further particularly preferred embodiment includes all possible stereoisomers (explicitly including atropisomers), conformers and rotamers as well as pharmaceutically acceptable salts, solvates, clathrates, isotopically enriched or enantiomerically enriched versions of above macrocyclic compounds.

In another preferred embodiment of this invention, the macrocycles of formulae **Ia** and **Ib** as described in the main embodiment can contain as a "Linker" the building block **C** which is represented by the formula



Examples of readily accessible amino acids defining possible subunits C_{AA} of the linker **C** are listed in Table 10 below. Only one stereoisomer of enantiomeric amino acids is cited, usually the L-enantiomer; it is understood that the complementary enantiomer is also part to the embodiment. Also not mentioned explicitly but naturally part of the embodiment are the simple *N*-Methyl derivatives of the listed amino acids.

Table 10: Substances Representing Subunits of "Linkers" **C** (*continued on the following pages*)

Code	Chemical Name
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

Code	Chemical Name
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-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

Code	Chemical Name
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_4al	L-3-Cyclobutylalanine
C_5al	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_2Phe	L-3,4-Dichlorophenylalanine

Code	Chemical Name
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
ACHC	1-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

Code	Chemical Name
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
4AmPyrr2	(2S, 4R)-4-Amino-pyrrolidine-2-carboxylic acid
4PhePyrr1	(2S, 4R)-4-Phenyl-pyrrolidine-2-carboxylic acid
4PhePyrr2	(2S, 4S)-4-Phenyl-pyrrolidine-2-carboxylic acid
5PhePyrr1	(2S, 5R)-5-Phenyl-pyrrolidine-2-carboxylic acid
5PhePyrr2	(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-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

Code	Chemical Name
H-β³-HPhe(pC(NH₂)=NH)-OH	(3S)-3-Amino-4-(4'-amidinophenyl)-butyric acid
H-β³-HPhe(mNHC(NH₂)=NH)-OH	(3S)-3-Amino-4-(3'-guanidinophenyl)-butyric acid
H-β³-HPhe(pNHC(NH₂)=NH)-OH	(3S)-3-Amino-4-(4'-guanidino-phenyl)-butyric acid
H-β³-H2Pal-OH	(3S)-3-Amino-4-(pyridine-2'-yl)-butyric acid
H-β³-H4Pal-OH	(3S)-3-Amino-4-(pyridine-4'-yl)-butyric acid
H-β³-HPhg-OH	(3R)-3-Amino-3-phenyl-propionic acid
H-β³-HCha-OH	(3S)-3-Amino-4-cyclohexyl-butyric acid
H-β³-HC₄al-OH	(3S)-3-Amino-4-cyclobutyl-butyric acid
H-β³-HC₅al-OH	(3S)-3-Amino-4-cyclopentyl-butyric acid
H-β³-HNle-OH	(3S)-3-Amino-heptanoic acid
H-β³-H2Nal-OH	(3S)-3-Amino-4-(2'-naphthyl)-butyric acid
H-β³-H1Nal-OH	(3S)-3-Amino-4-(1'-naphthyl)-butyric acid
H-β³-H4ClPhe-OH	(3S)-3-Amino-4-(4'-chlorophenyl)-butyric acid
H-β³-H3ClPhe-OH	(3S)-3-Amino-4-(3'-chlorophenyl)-butyric acid
H-β³-H2ClPhe-OH	(3S)-3-Amino-4-(2'-chlorophenyl)-butyric acid
H-β³-H3,4Cl₂Phe-OH	(3S)-3-Amino-4-(3',4'-dichlorophenyl)-butyric acid
H-β³-H4FPhe-OH	(3S)-3-Amino-4-(4'-fluorophenyl)-butyric acid
H-β³-H3FPhe-OH	(3S)-3-Amino-4-(3'-fluorophenyl)-butyric acid
H-β³-H2FPhe-OH	(3S)-3-Amino-4-(2'-fluorophenyl)-butyric acid
H-β³-HThi-OH	(3R)-3-Amino-4-(2'-thienyl)-butyric acid
H-β³-HTza-OH	(3R)-3-Amino-4-(2'-thiazolyl)-butyric acid
H-β³-HMso-OH	(3R)-3-Amino-4-methylsulfoxyl-butyric acid
H-β³-HAcLys-OH	(3S)-7-Acetylamino-3-amino-heptanoic acid
H-β³-HDpr-OH	(3R)-3,4-diamino-butyric acid
H-β³-HA₂Bu-OH	(3S)-3,5-Diamino-pentanoic acid
H-β³-HDbu-OH	(3R)-3,4-Diamino-pentanoic acid
H-β³-HAib-OH	Amino-dimethyl acetic acid
H-β³-HCyp-OH	1-Amino-cyclopentane-1-yl-acetic acid

Code	Chemical Name
H-β³-HY(Bzl)-OH	(3S)-3-Amino-4-(4'-benzyloxyphenyl)-butyric acid
H-β³-HH(Bzl)-OH	(3S)-3-Amino-4-(1'-benzylimidazole-4'-yl)-butyric acid
H-β³-HBip-OH	(3S)-3-Amino-4-biphenylyl-butyric acid
H-β³-HS(Bzl)-OH	(3S)-3-Amino-4-(benzyloxy)-butyric acid
H-β³-HT(Bzl)-OH	(3R, 4R)-3-Amino-4-benzyloxy-pentanoic acid
H-β³-HalloT-OH	(3R, 4S)-3-Amino-4-hydroxy-pentanoic acid
H-β³-HLeu3OH-OH	(3R, 4R)-3-Amino-4-hydroxy-5-methyl-hexanoic acid
H-β³-HhAla-OH	(3S)-3-Amino-pentanoic acid
H-β³-HhArg-OH	(3S)-3-Amino-7-guanidino-heptanoic acid
H-β³-HhCys-OH	(3R)-Amino-5-mercapto-pentanoic acid
H-β³-HhGlu-OH	(3S)-3-Amino-heptanedioic acid
H-β³-HhGln-OH	(3S)-3-Amino-6-carbamoyl hexanoic acid
H-β³-HhHis-OH	(3S)-3-Amino-5-(imidazole-4'-yl)-pentanoic acid
H-β³-HhIle-OH	(3S, 5S)-3-Amino-5-methyl-heptanoic acid
H-β³-HhLeu-OH	(3S)-3-Amino-6-methyl-heptanoic acid
H-β³-HhNle-OH	(3S)-3-Amino-octanoic acid
H-β³-DiAoc-OH	(3S)-3,8-Diamino-octanoic acid
H-β³-HhMet-OH	(3S)-3-Amino-6-methylthio-hexanoic acid
H-β³-HhPe-OH	(3S)-3-Amino-5-phenyl-pentanoic acid
H-β³-HhSer-OH	(3S)-3-Amino-5-hydroxy-pentanoic acid
H-β³-HhThr-OH	(3S, 5R)-3-Amino-5-hydroxy-hexanoic acid
H-β³-HhTrp-OH	(3S)-3-Amino-5-(indol-3'-yl)-pentanoic acid
H-β³-HhThr-OH	(3S)-3-Amino-5-(4'-hydroxyphenyl)-pentanoic acid
H-β³-HhCha-OH	(3S)-3-Amino-5-cyclohexyl-pentanoic acid
H-β³-HBpa-OH	(3S)-3-Amino-4-(4'-benzoylphenyl)-butyric acid
H-β³-HOctG-OH	(3S)-3-Amino-undecanoic acid
H-β³-HNle-OH	(3S)-3-Amino-heptanoic acid
H-β³-HTic-OH	(3S)-1,2,3,4-Tetrahydroisoquinoline-3-yl-acetic acid
H-β³-HTiq-OH	(1S)-1,2,3,4-Tetrahydroisoquinoline-1-acetic acid

Code	Chemical Name
H-β^3-HOic-OH	(2S, 3aS, 7aS)-1-Octahydro-1H-indole-2-yl-acetic acid
H-β^3-H4AmPyrr1-OH	(2S, 4S)-4-Amino-pyrrolidine-2-acetic acid
H-β^3-H4AmPyrr2-OH	(2S, 4R)-4-Amino-pyrrolidine-2-acetic acid
H-β^3-H4PhePyrr1-OH	(2S, 4R)-4-Phenyl-pyrrolidine-2-acetic acid
H-β^3-H4PhePyrr2-OH	(2S, 4S)-4-Phenyl-pyrrolidine-2-acetic acid
H-β^3-H5PhePyrr1-OH	(2S, 5R)-5-Phenyl-pyrrolidine-2-acetic acid
H-β^3-H5PhePyrr2-OH	(2S, 5S)-5-Phenyl-pyrrolidine-2-acetic acid
H-β^3-H4Hyp1-OH	(2S, 4S)-4-Hydroxy-pyrrolidine-2-acetic acid
H-β^3-H4Hyp2-OH	(2S, 4R)-4-Hydroxy-pyrrolidine-2-acetic acid
H-β^3-H4Mp1-OH	(2R, 4S)-4-Mercapto-pyrrolidine-2-acetic acid
H-β^3-H4Mp2-OH	(2R, 4R)-4-Mercapto-pyrrolidine-2-acetic acid
H-β^3-HPip-OH	(2S)-Piperidine-2-acetic acid
H-β^3-HPro-OH	(2S)-Pyrrolidine-2-acetic acid
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

Code	Chemical Name
H-γ⁴-DiHPhe(pNHC(NH₂)=NH)-OH	(4R)-4-Amino-5-(4'-guanidino-phenyl)-pentanoic acid
H-γ⁴-DiH2Pal-OH	(4R)-4-Amino-5-(pyridine-4'-yl)-pentanoic acid
H-γ⁴-DiH4Pal-OH	(4R)-4-Amino-5-(pyridine-4'-yl)-pentanoic acid
H-γ⁴-DiHPhg-OH	(4R)-4-Amino-4-phenyl-butyric acid
H-γ⁴-DiHCha-OH	(4R)-4-Amino-5-cyclohexyl-pentanoic acid
H-γ⁴-DiHC₄al-OH	(4R)-4-Amino-5-cyclobutyl-pentanoic acid
H-γ⁴-DiHC₅al-OH	(4R)-4-Amino-5-cyclopentyl-pentanoic acid
H-γ⁴-DiHNle-OH	(4S)-4-Amino-octanoic acid
H-γ⁴-DiH2Nal-OH	(4S)-4-Amino-5-(2'-naphthyl)-pentanoic acid
H-γ⁴-DiH1Nal-OH	(4S)-4-Amino-5-(1'-naphthyl)-pentanoic acid
H-γ⁴-DiH4ClPhe-OH	(4R)-4-Amino-5-(4'-chlorophenyl)-pentanoic acid
H-γ⁴-DiH3ClPhe-OH	(4R)-4-Amino-5-(3'-chlorophenyl)-pentanoic acid
H-γ⁴-DiH2ClPhe-OH	(4R)-4-Amino-5-(2'-chlorophenyl)-pentanoic acid
H-γ⁴-DiH3,4Cl₂Phe-OH	(4R)-4-Amino-5-(3',4'-dichloro-phenyl)-pentanoic acid
H-γ⁴-DiH4FPhe-OH	(4R)-4-Amino-5-(4'-fluorophenyl)-pentanoic acid
H-γ⁴-DiH3FPhe-OH	(4R)-4-Amino-5-(3'-fluorophenyl)-pentanoic acid
H-γ⁴-DiH2FPhe-OH	(4R)-4-Amino-5-(2'-fluorophenyl)-pentanoic acid
H-γ⁴-DiHThi-OH	(4R)-4-Amino-5-(2'-thienyl)-pentanoic acid
H-γ⁴-DiHTza-OH	(4R)-4-Amino-5-(2'-thiazolyl)-pentanoic acid
H-γ⁴-DiHMso-OH	(4R)-4-Amino-5-methylsulfoxyl-pentanoic acid
H-γ⁴-DiHAcLys-OH	(4S)-8-Acetylamino-4-amino-ocatanoic acid
H-γ⁴-DiHDpr-OH	(4R)-4,5-diamino-pentanoic acid
H-γ⁴-DiHA₂Bu-OH	(4R)-4,5-Diamino-hexanoic acid
H-γ⁴-DiHDbu-OH	(4R)-4,5-Diamion-hexanoic acid
H-γ⁴-DiHAib-OH	3-Amino-3,3-dimethyl propionic acid
H-γ⁴-DiHCyp-OH	(1'-Amino-cyclopentane-1'-yl)-3-propionic acid
H-γ⁴-DiHY(Bzl)-OH	(4R)-4-Amino-5-(4'-benzyloxyphenyl)-pentanoic acid

Code	Chemical Name
H-γ^4-DiHH(Bzl)-OH	(4R)-4-Amino-5-(1'-benzylimidazole-4'-yl)-pentanoic acid
H-γ^4-DiHBip-OH	(4R)-4-Amino-5-biphenylyl-pentanoic acid
H-γ^4-DiHS(Bzl)-OH	(4S)-4-Amino-5-(benzyloxy)-pentanoic acid
H-γ^4-DiHT(Bzl)-OH	(4R, 5R)-4-Amino-5-benzyloxy-hexanoic acid
H-γ^4-DiHalloT-OH	(4R, 5S)-4-Amino-5-hydroxy-hexanoic acid
H-γ^4-DiHLeu3OH-OH	(4R, 5R)-4-Amino-5-hydroxy-6-methyl-heptanoic acid
H-γ^4-DiHhAla-OH	(4S)-4-Amino-hexanoic acid
H-γ^4-DiHhArg-OH	(4S)-4-Amino-8-guanidino-octanoic acid
H-γ^4-DiHhCys-OH	(4R)-Amino-6-mercapto-hexanoic acid
H-γ^4-DiHhGlu-OH	(4S)-4-Amino-ocatanedioic acid
H-γ^4-DiHhGln-OH	(4S)-4-Amino-7-carbamoyl-heptanoic acid
H-γ^4-DiHhHis-OH	(4S)-4-Amino-6-(imidazole-4'-yl)-hexanoic acid
H-γ^4-DiHhIle-OH	(4S, 6S)-4-Amino-6-methyl-octanoic acid
H-γ^4-DiHhLeu-OH	(4S)-4-Amino-7-methyl-ocatanoic acid
H-γ^4-DiHhNle-OH	(4S)-4-Amino-nonanoic acid
H-γ^4-DiHhLys-OH	(4S)-4,9-Diamino-nonanoic acid
H-γ^4-DiHhMet-OH	(4R)-4-Amino-7-methylthioheptanoic acid
H-γ^4-DiHhPhe-OH	(4S)-4-Amino-6-phenyl-hexanoic acid
H-γ^4-DiHhSer-OH	(4R)-4-Amino-6-hydroxy-hexanoic acid
H-γ^4-DiHhThr-OH	(4R, 6R)-4-Amino-6-hydroxy-heptanoic acid
H-γ^4-DiHhTrp-OH	(4S)-4-Amino-6-(indol-3'-yl)-hexanoi cacid
H-γ^4-DiHhTyr-OH	(4S)-4-Amino-6-(4'-hydroxyphenyl)-hexanoic acid
H-γ^4-DiHhCha-OH	(4R)-4-Amino-5-cyclohexyl-pentanoic acid
H-γ^4-DihBpa-OH	(4R)-4-Amino-5-(4'-benzoylphenyl)-pentanoic acid
H-γ^4-DiHOctG-OH	(4S)-4-Amino-dodecanoic acid
H-γ^4-DiHNle-OH	(4S)-4-Amino-octanoic acid
H-γ^4-DiHTic-OH	(3R)-1',2',3',4'-Tetrahydroisoquinoline-3'-yl-3-propionic acid
H-γ^4-DiHTiq-OH	(1'R)-1',2',3',4'-Tetrahydroisoquinoline-1'-yl-3-propionic acid
H-γ^4-DiHOic-OH	(2'S, 3'aS, 7'aS)-1'-Octahydro-1H-indole-2'-yl-3-propionic acid

Code	Chemical Name
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_2N-$(CH_2)_3$-$(OCH_2$-$CH_2)_2$-O$(CH_2)_3$]glycine
(Me)G	N-Methylglycine
(Et)G	N-Ethylglycine
(Bu)G	N-Butylglycine
(Pe)G	N-Pentylglycine
(Ip)G	N-Isopropylglycine
(2MePr)G	N-(2-Methylpropyl)glycine
(3MeBu)G	N-(3-Methylbutyl)glycine
(1MePr)G	(1S)-N-(1-Methylpropyl)glycine
(2MeBu)G	(2S)-N-(2-Methylbutyl)glycine
(MthEt)G	N-(Methylthioethyl)glycine
(MthPr)G	N-(Methylthiopropyl)glycine
(Ben)G	N-(Benzyl)glycine

Code	Chemical Name
(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

In a specific preferred embodiment of this invention, the macrocycles of type **Ia/Ib** are selected from the following list:

(2*S*,11*S*,19a*S*)-*N*-[2-(dimethylamino)ethyl]-15-fluoro-7,12-dimethyl-2-{[(1-naphthylamino)carbonyl]amino}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide;

(2*S*,11*S*,19a*S*)-*N*-(2-aminoethyl)-15-fluoro-7,12-dimethyl-2-{[2-(1-naphthyl)acetyl]amino}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriaza-cyclopentadecine-11-carboxamide;

(2*S*,11*S*,19a*S*)-*N*-(2-{[amino(imino)methyl]amino}ethyl)-15-fluoro-7,12-dimethyl-2-{[2-(1-naphthyl)acetyl]amino}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide;

(2*S*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-2-{[2-(1-naphthyl)-acetyl]amino}-5,8,13-trioxo-*N*-[2-(2-pyridinylamino)ethyl]-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide;

(2*S*,11*S*,19a*S*)-*N*-[2-(dimethylamino)ethyl]-15-fluoro-7,12-dimethyl-2-{[2-(1-naphthyl)ethyl]amino}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide;

(2*S*,11*S*,19a*S*)-*N*-[2-(acetylamino)ethyl]-15-fluoro-7,12-dimethyl-2-[2-(1-naphthyl)acetyl]amino-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide;

(2*S*,11*S*,19a*S*)-*N*-[2-(dimethylamino)ethyl]-15-fluoro-7,12-dimethyl-2-{[2-(2-naphthyl)acetyl]amino}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide;

(2*S*,11*S*,19a*S*)-*N*-[2-(dimethylamino)ethyl]-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2-(2-[3-(trifluoromethyl)phenyl]-acetylamino)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide;

(2*S*,11*S*,19a*S*)-*N*-[2-(dimethylamino)ethyl]-15-fluoro-2-[2-(3-methoxyphenyl)acetyl]amino-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide;

(2*S*,11*S*,19a*S*)-*N*-[3-(dimethylamino)propyl]-15-fluoro-7,12-dimethyl-2-[2-(1-naphthyl)acetyl]amino-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*]-[1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide;

(2*S*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-2-[2-(1-naphthyl)-acetyl]amino-5,8,13-trioxo-*N*-(3-pyridinylmethyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]-benzoxatriazacyclopentadecine-11-carboxamide;

N-[(4*S*,6*S*,10*S*)-14-methyl-6-[2-(2-naphthyl)acetyl]amino-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]decanamide;

N-[(4*S*,6*S*,10*S*)-14-methyl-10-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]-2-(2-naphthyl)acetamide;

N-[(4*S*,6*S*,10*S*)-14-methyl-6-[2-(2-naphthyl)acetyl]amino-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2-(1-naphthyl)acetamide;

N-[(4*S*,6*S*,10*S*)-14-methyl-9,15-dioxo-10-[(3-toluidinocarbonyl)-amino]-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]-2-(2-naphthyl)acetamide;

N-[(4*S*,6*S*,10*S*)-10-([3-(dimethylamino)anilino]carbonylamino)-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]-2-(2-naphthyl)acetamide;

N-[(4S,6S,10S)-6-({[3-(dimethylamino)anilino]carbonyl}amino)-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2-(2-naphthyl)acetamide;

N-[(4*S*,6*S*,10*S*)-14-methyl-9,15-dioxo-6-[(3-phenylpropanoyl)-amino]-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]decanamide;

N-[(4*S*,6*S*,10*S*)-14-methyl-6-[(3-morpholinobenzoyl)amino]-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]decanamide;

N-[(4S,6S,10S)-6-({[3-(dimethylamino)anilino]carbonyl}amino)-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]decanamide;

N-[(4S,6S,10S)-6-({[3-(dimethylamino)anilino]carbonyl}amino)-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2-(1-naphthyl)acetamide;

N-[(4*S*,6*S*,10*S*)-6-{[(3-methoxyanilino)carbonyl]amino}-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2-(2-naphthyl)acetamide;

N-[(4*S*,6*S*,10*S*)-14-methyl-9,15-dioxo-6-{[2-(3-phenoxyphenyl)-acetyl]amino}-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]decanamide;

N-[(4*S*,6*S*,10*S*)-14-methyl-6-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-6-phenylhexanamide;

N-[(4*S*,6*S*,10*S*)-14-methyl-6-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-5-phenoxypentanamide;

(*E*)-*N*-[(4*S*,6*S*,10*S*)-14-methyl-6-[2-(2-naphthyl)acetyl]amino-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-3-decenamide;

N-[(4*S*,6*S*,10*S*)-14-methyl-6-{[2-(1-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]decanamide;

6-(benzyloxy)-*N*-[(4*S*,6*S*,10*S*)-14-methyl-6-[2-(2-naphthyl)-acetyl]amino-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]-icosa-1(20),16,18-trien-10-yl]hexanamide;

2-[1,1'-biphenyl]-4-yl-*N*-[(4*S*,6*S*,10*S*)-14-methyl-6-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo-[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]acetamide;

N-[(4*S*,6*S*,10*S*)-14-methyl-6-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-3,3-diphenylpropanamide;

6-(benzyloxy)-*N*-[(4*S*,6*S*,10*S*)-14-methyl-9,15-dioxo-10-[(6-phenylhexanoyl)amino]-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]-icosa-1(20),16,18-trien-6-yl]hexanamide;

2-[1,1'-biphenyl]-3-yl-*N*-[(4*S*,6*S*,10*S*)-6-([3-(dimethylamino)-anilino]carbonylamino)-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-acetamide;

2-[1,1'-biphenyl]-4-yl-*N*-[(4*S*,6*S*,10*S*)-6-([3-(dimethylamino)-anilino]carbonylamino)-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-acetamide;

N-[(4*S*,6*S*,10*S*)-10-[([1,1'-biphenyl]-4-ylsulfonyl)amino]-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]-2-(2-naphthyl)acetamide;

N-[(4*S*,6*S*,10*S*)-6-{[(3-fluoroanilino)carbonyl]amino}-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2-(2-naphthyl)acetamide;

N-[(4*S*,6*S*,10*S*)-6-({[4-(dimethylamino)anilino]carbonyl}amino)-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2-(2-naphthyl)acetamide;

phenyl *N*-[(4*S*,6*S*,10*S*)-14-methyl-10-{[2-(2-naphthyl)acetyl]-amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]carbamate;

N-[(4*S*,6*S*,10*S*)-14-methyl-9,15-dioxo-6-[2-(7-quinolinyl)acetyl]-amino-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2-(2-naphthyl)acetamide;

N-[(4*S*,6*S*,10*S*)-14-methyl-9,15-dioxo-6-{[2-(3-phenoxyphenyl)-acetyl]amino}-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2-(2-naphthyl)acetamide;

N-[(4*S*,6*S*,10*S*)-14-methyl-10-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]decanamide;

N-[(4*S*,6*S*,10*S*)-14-methyl-10-{[2-(1-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]decanamide;

N-[(4*S*,6*S*,10*S*)-14-methyl-10-{[2-(1-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]hexanamide;

2-[1,1'-biphenyl]-4-yl-*N*-[(4*S*,6*S*,10*S*)-14-methyl-10-{[2-(1-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo-[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]acetamide;

N-[(4*S*,6*S*,10*S*)-10-[(2-[1,1'-biphenyl]-4-ylacetyl)amino]-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]-2,2-diphenylacetamide;

N-[(4*S*,6*S*,10*S*)-6-[(2-[1,1'-biphenyl]-4-ylacetyl)amino]-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2,2-diphenylacetamide;

N-[(4*S*,6*S*,10*S*)-6-[(2,2-diphenylacetyl)amino]-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]decanamide;

N-[(4*S*,6*S*,10*S*)-14-methyl-10-{[2-(1-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]-2,2-diphenylacetamide;

N-[(4*S*,6*S*,10*S*)-6-[(3,3-diphenylpropanoyl)amino]-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]decanamide;

2-[1,1'-biphenyl]-4-yl-*N*-[(4*S*,6*S*,10*S*)-10-[(2-[1,1'-biphenyl]-4-ylacetyl)amino]-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo-[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]acetamide;

N-[(4*S*,6*S*,10*S*)-6-({[3-(dimethylamino)anilino]carbonyl}amino)-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-3,3-dimethylbutanamide;

N-[(4*S*,6*S*,10*S*)-6-({[3-(dimethylamino)anilino]carbonyl}amino)-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2-(2-naphthyl)acetamide;

benzyl *N*-[(4*S*,6*S*,10*S*)-6-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]carbamate;

N-[(4*S*,6*S*,10*S*)-6-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]decanamide;

(4*S*,6*R*,15*S*)-11,16-dimethyl-*N*-(2-naphthylmethyl)-9,12,17-trioxo-6-{[3-(4-pyridinyl)propanoyl]amino}-2-thia-8,11,16-triaza-tricyclo[16.3.1.$0^{4,8}$]docosa-1(22),18,20-triene-15-carboxamide;

tert-butyl *N*-[(4*S*,6*R*,15*S*)-11,16-dimethyl-15-{[(2-naphthyl-methyl)amino]carbonyl}-9,12,17-trioxo-2-thia-8,11,16-triaza-tricyclo[16.3.1.$0^{4,8}$]docosa-1(22),18,20-trien-6-yl]carbamate;

(4*S*,6*R*,15*S*)-11,16-dimethyl-*N*-(2-naphthylmethyl)-9,12,17-trioxo-6-(pentanoylamino)-2-thia-8,11,16-triazatricyclo[16.3.1.$0^{4,8}$]-docosa-1(22),18,20-triene-15-carboxamide;

(4*S*,6*R*,15*S*)-6-(acetylamino)-11,16-dimethyl-*N*-(2-naphthyl-methyl)-9,12,17-trioxo-2-thia-8,11,16-triazatricyclo-[16.3.1.$0^{4,8}$]docosa-1(22),18,20-triene-15-carboxamide;

(2*S*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-2-(1-naphthoylamino)-*N*-(2-naphthylmethyl)-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriaza-cyclopentadecine-11-carboxamide;

(2*S*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-2-[2-(2-naphthyl)acetyl]-amino-*N*-(1-naphthylmethyl)-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxa-triazacyclopentadecine-11-carboxamide;

(2*S*,11*S*,19a*S*)-2-[(3-chlorobenzoyl)amino]-15-fluoro-7,12-dimethyl-*N*-(1-naphthylmethyl)-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide.

In another specific preferred embodiment of this invention, the macrocycles of type **Ia/Ib** are selected from the following list:

(2*S*,11*S*,19a*S*)-2-(acetylamino)-15-fluoro-*N*-[2-(1H-indol-3-yl)ethyl]-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide;

(2*S*,11*S*,19a*S*)-N-[2-(dimethylamino)ethyl]-15-fluoro-2-{[2-(1H-indol-3-yl)acetyl]amino}-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*]-[1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide;

(2*S*,11*S*,19a*S*)-15-fluoro-2-{[2-(1H-indol-3-yl)acetyl]amino}-*N*-[2-(1H-indol-3-yl)ethyl]-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*]-[1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide;

(2*S*,11*S*,19a*S*)-2-{[2-(dimethylamino)acetyl]amino}-15-fluoro-*N*-[2-(1H-indol-3-yl)ethyl]-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*]-[1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide;

tert-butyl *N*-[(2*S*,11*S*,19a*S*)-15-fluoro-11-({[2-(1H-indol-3-yl)ethyl]amino}carbonyl)-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*]-[1,4,7,12]benzoxatriazacyclopentadecin-2-yl]carbamate;

(2*S*,11*S*,19a*S*)-*N*-[2-(dimethylamino)ethyl]-15-fluoro-7,12-dimethyl-2-{[2-(1-naphthyl)acetyl]amino}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*]-[1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide;

benzyl *N*-[(4*S*,6*S*,10*S*)-14-methyl-6-{[2-(2-naphthyl)acetyl]-amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]carbamate;

benzyl *N*-[(4*S*,6*S*,13*S*)-6-{[2-(1H-indol-3-yl)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo-[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate;
N-[(4*S*,6*S*,13*S*)-6-{[2-(1*H*-indol-3-yl)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo-[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]decanamide.

Synthesis of the Building Blocks

Readily available examples of amino acids representing subunits of the Bridge **C** are detailed to the level of fully-defined structures in Table 10. 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**.

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**).

Synthesis of Template A Building Blocks

A) General Transformations

The majority of the building blocks of type **A** are based on readily available substances carrying a carboxylic acid group and either an aromatic or heteroaromatic hydroxy (Ar/Hetar-OH) or thiol moiety (Ar/Hetar-SH). The -COOH group may be attached to the same ring as the -OH/-SH group or to an annelated ring which in turn may be aromatic or partially unsaturated. In one subset of building blocks the -COOH group is replaced by a sulfanyl group (-SH) leading to sulfanyl phenols (mercapto phenols) and sulfanyl thiophenols (mercapto thiophenols) as building blocks. Yet another small subset carries instead of the -COOH an alkenyl group ($-(CHR^3)_q-CR^{12}=CH_2$; q=0-4).

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

Selected examples of general scope for transformations introducing a sulfanyl group (-SH), i.e. Ar/Hetar-X → Ar/Hetar-SH (X= OH, F, Cl, Br, I, N_2^+), are the following 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 P_2S_5 (K. Hirai et al., *Heterocycles* **1994**, *38*, 277-280).

T-III: As an alternative to phenols, halogen-substituted (esp. with F or Cl) aromatic ring systems might serve as precursors. In case the halogen is in a position activated by an electron withdrawing group in *ortho*- or *para*-position the -SH moiety or a protected 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 ($-N_2^+$) is 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 benzothioic *S*-acid (N. Sawada et al., *Tetrahedron Lett.* **2006**, *47*, 6595-6597), or Pd-catalyzed substitution with KS-Si(*i*-Pr)$_3$ followed by desilylation of the introduced -SSi(*i*-Pr)$_3$ group (A. M. Rane et al., *Tetrahedron Lett.* **1994**, *35*, 3225-3226).

The thus introduced -SH moieties constitute a thia-bridge -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 (-S(=O)-; i.e. sulfoxide) and sulfonyl (-S(=O)$_2$-; i.e. sulfone) moieties. Suitable oxidation methods are:

T-VI: The selective oxidation of a thioether (-S-) to a sulfoxide (-S(=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 chlorotrimethyl-silane showed high selectivity, too (Y.-J. Chen et al., *Tetrahedron Lett.* **2000**, 41, 5233-5236).

T-VII: Stronger oxidants directly transfer the sulfanyl (-S-) into the sulfonyl group ($-S(=O)_2-$). 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).

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

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

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

H-III: The substitution of halogen atoms (esp. Br and I), which not activated for an S_NAr, can be achieved by transition metal-catalyzed C-O-couplings. Predominant are Pd-catalysts (K.W. Anderson et al., *J. Am. Chem. Soc.* **2006**, *128*, 10694-10695; B.J. Gallon et al., *Angew. Chem., Int. Ed.* **2007**, *46*, 7251-7254), but also others 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).

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

C-I: The oxidation of functional groups like hydroxymethyl ($-CH_2-OH$) or aldehyde ($-C(=O)H$) is achieved under mild conditions (G.V.M. Sharma et al., *Synth. Commun.* **2000**, *30*, 397-406; C. Wiles et al., *Tetrahedron Lett.* **2006**, *47*, 5261-5264). Also methyl groups on benzene rings can be oxidized; however, as harsh reaction conditions are usually required, its applicability is limited. In contrast, the 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, 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 cyanoformate)(A. Lepretre et al., *Tetrahedron* **2000**, *56*, 265-274).

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

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

Applied to commercially available starting materials these general transformations offer a tool box for accessing a huge

variety of Templates **A**. Additional literature examples are cited below within the sections on specific derivatives.

B) Specific Transformations

Selected transformations of broad applicability leading to specific building block categories of hydroxy-aryl or hydroxy-heteroaryl derivatives are described below:

A1-A59 and **A627-A656** Phenyl Derivatives

A plethora of hydroxy benzoic acids with diverse substitution patterns are commercially available and can be directly utilized for constructing the macrocyclic backbone. Even not so common tetrasubstituted hydroxy benzoic acids (**A53-A59**) can be constructed by processes relying on the general procedures mentioned above, e.g. carboxylation of pentasubstituted phenol derivatives (K. Sung, R.J. Lagow, *J. Mater. Chem.* **1996**, *6*, 917-918; E. Marzi, M. Schlosser, *Tetrahedron* **2005**, 61, 3393-3402; K.C. Nicolaou et al., *Angew. Chem., Int. Ed.* **1999**, *38*, 3334-3339). Alternative approaches to tetrasubstituted hydroxy benzoic acids involve, for example, the oxidation of benzaldehydes followed by the introduction of substituents into the remaining free positions (K.C. Nicolaou et al., *Chem. Eur. J.* **2000**, 6, 3095-3115).

In the sulfanyl thiophenol (mercapto thiophenol) series **A627-A636** simpler derivatives are commercially available. The synthesis of more advanced ones can be achieved by subjecting suitable precursors to the general procedures T-I to T-V. Once incorporated in the macrocycle **Ia/Ib** the thioether (sulfanyl group; -S-) can be easily and selectively oxidized to the sulfoxide or sulfone by applying the general procedures T-VI and T-VII. Therefore **A627-A636** should also be regarded as building blocks for inserting a sulfinyl (-S(=O)-) or sulfonyl ($-S(=O)_2-$) group into macrocycle **Ia/Ib**.

A C=C-double bond connectivity between Template **A** und Bridge **C** is conveniently introduced by metathesis or ring closing metathesis reactions. The corresponding building blocks **A** are

based on phenol/thiophenol derivatives carrying a vinyl or alkenyl substituent ($-(CHR^3)_q-CR^{12}=CH_2$; q=0-4). A number of vinyl (q=0) or allyl (q=1) analogs are commercially available. Depending on the length q of the methylene tether, different approaches are feasible. Vinyl (q=0) and allyl (q=1) can be easily obtained by cross coupling reactions of the corresponding halo-substituted (Cl, Br, I) phenols/thiophenols, e.g. by Heck, Suzuki or Stille reaction (L. Joucla et al., *Tetrahedron Lett.* **2008**, *49*, 4738-4741; B. Soederberg et al., *J. Org. Chem.* **1997**, *62*, 5838-5845; Y. Yamamoto et al., *Chem. Lett.* **2006**, 35, 704-705). Very versatile is the mild Negishi coupling which is not only useful for introducing vinyl (T. Yamamoto, T. Yamakawa, *J. Org. Chem.* **2009**, 74, 3603-3605) or allyl substituents (F. Kneisel et al., *Synthesis* **2005**, 2625-2629) but is also suitable for longer side chains with terminal olefin group (q=2-4; e.g. N. Kurono, *Tetrahedron* **1999**, *55*, 6097-6108). Additional approaches involve, e.g.: a) the synthesis of *ortho*-allyl phenols by Claisen rearrangement (W.A.L. Otterlo et al., *Tetrahedron* **2005**, *61*, 7746-7755) or b) the chain elongation of benzaldehydes or phenyl acetaldehydes by addition of vinyl or allyl Grignard reagents followed by reduction of the thus obtained secondary alcohols to the corresponding methylene compounds with trimethylsilane/TFA (B. Dahl et al., *Tetrahedron Lett.* **2004**, *45*, 9599-9602).

Double bonds in the macrocyclic backbone can be easily hydrogenated and should therefore be regarded as building blocks for introducing optionally substituted methylene linkers ($-(CHR^3)_q-CR^{12}-$) as well.

A60-A143 and **A657-A659** Pyridine Derivatives

As with the previous class of compounds, also for pyridines a large number of substances is commercially available and can be incorporated into the macrocycle directly or easily transferred into suitably substituted pyridines by the general methods mentioned above. Selected literature examples are available for transformations of type C-III (M. Shimano et al. *Tetrahedron*

Lett. **1998**, *39*; 4363-4366), H-II (L. Carpino et al., *J. Org. Chem.* **2004**, *69*; 54-61), C-I (T.R. Kelly, F. Lang, *Tetrahedron Lett.* **1995**, *36*, 5319-5322), or C-IV (J.L. LaMattina, R.L. Taylor, *J. Org. Chem.* **1981**, *46*, 4179-4182). For the related sulfanyl/sulfinyl/sulfonyl pyridines **A657** and alkenyl/alkyl pyridines **A658/A659** compare the section about the corresponding phenyl derivatives above.

A144-A165 Pyridazine Derivatives

In analogy to general transformation C-I, readily available, methyl pyridazines can be oxidized to the corresponding 3- or 4-carboxylic acids (M. Morishita et al., *Chem. Pharm. Bull.* **1994**, *42*, 371-372; M. Winn et al., *J. Med. Chem.* **1993**, *36*, 2676-2688). Of equally broad scope is the hydrolysis of the corresponding nitriles under chemical (G. Heinisch, D. Lassnigg, *Arch. Pharm. (Weinheim, Ger.)* **1987**, 320, 1222-1226) or enzymatic conditions (nitrilase from *Rhodococcus sp.*: N. Klempier et al., *Tetrahedron Lett.* **1991**, *32*, 341-344).

In addition, the pyridazine core can be built up from β-keto-esters which are subjected to a Staudinger reaction followed by an aza-Wittig-cyclization of the intermediate azide (S.V. Galiullina et al., *Russ. J. Org. Chem.* **2007**, *43*, 607-614; M. Guillaume et al., *Synthesis* **1995**, *8*, 920-922). In another approach β-ketoesters are cyclocondensed with the monohydrazone of α,β-diketones (E.E. Schweizer, K.-J. Lee, *J. Org. Chem.* **1982**, *47*, 2768-2773).

A166-A188 and **A660-A662** Pyrimidine Derivatives

As for pyridines, a large number of suitable building blocks are commercially available and can be directly used or easily transferred into the targeted compounds by the standard procedures mentioned above, including transformations of type C-I (Y. Honma et al., *Chem. Pharm. Bull.* **1982**, *30*, 4314-4324), or C-IV (I.V. Oleinik, O.A. Zagulyaeva, *Chem. Heterocycl. Compd.* **1993**, *29*, 427-431). In addition, the pyrimidine 2-carboxylic acid core can be constructed by cyclocondensation of oxalates with malonamidine derivatives (G.A. Howard et al., *J. Chem. Soc.*

1944, 476-477). Different substitution patterns are accessible by reacting malonates with amidines (M. Otsuka et al., *Chem. Pharm. Bull.* **1985**, *33*, 515-519).

For the related sulfanyl/sulfinyl/sulfonyl pyrimidines **A660** and alkenyl/alkyl pyrimidines **A661/A662** compare the section about the corresponding phenyl derivatives above.

A189-A200 Pyrazine Derivatives

Pyrazine carboxylic acids are easily obtained by cyclo-condensation of α,β-diaminopropionic acid with α,β-dicarbonyl derivatives (J. Bostroem et al., *Bioorg. Med. Chem.* **2007**, *15*, 4077-4084). Selected standard protocol examples are cited for C-I (J.R. Young et al., *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1723-1728), for C-III (N. Ple et al., *Tetrahedron* **1998**, *54*, 9701-9710), and for C-II (A.P. Krapcho et al., *J. Heterocycl. Chem.* **1997**, *34*, 27-32). Highly chemoselective oxidations of type C-I can also be achieved by biotransformation with *Pseudomonas putida* (A. Kiener, *Angew. Chem.* **1992**, *104*, 748-749).

A201-A206 Triazine Derivatives

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

A207-A228 and **A663-A665** Derivatives of Furan, Thiophene and Pyrrole

Furan-3-carboxylic acids of type **A207/208** can be synthesized from 2-carbonyl-3-oxo-butanoates by bromination and subsequent cyclization (A. Becker, *Helv. Chim. Acta* **1949**, *32*, 1114-1122; R. Richter, *Helv. Chim. Acta* **1949**, *32*, 1123-1136). The analogous thiophenes **A207/208** can be prepared from 3-methoxycarbonyl-tetrahydrothiophene-4-one by oxidation (M.R. Banks et al., *J. Chem. Res. (M)* **1984**, 369-389) or by condensation with aldehydes

and subsequent isomerization (R. Jaunin, *Helv. Chim. Acta* **1980**, 63, 1542-1553). Pyrroles **A207/208** can be obtained from suitably substituted *N*-protected 3-amino-acrylates by treatment with 2-chloro-acetyl chloride followed by cyclization (E. Benary, R. Konrad, *Chem. Ber.* **1923**, *56*, 44-52).

Furans **A209/210** are accessible in multi-step reactions starting from methylenephosphoranes and aldehydes (H.H. Wasserman, G.M. Lee, *Tetrahedron Lett.* **1994**, *35*, 9783-9786). Thiophenes **A209/210** can be prepared from 2-mercaptoacetate and acetylene carboxylates (H. Fiesselmann, G. Pfeiffer, *Chem. Ber.* **1954**, *87*, 848-856).

The pyrroles **A209/210** are obtained by condensing β-alanine esters with 2,3-dioxo-pent-4-enoates (H.H. Wasserman et al., *Tetrahedron Lett.* **1989**, *30*, 1721-1724) or by reacting 3-oxo-propanoates with glycine esters (A. Treibs, A. Ohorodnik, *Liebigs Ann. Chem.* **1958**, *611*, 139-149).

Furan carboxylic acids of type **A211/212** can be synthesized from diazomalonates and suitably substituted alkynes in a two-step-procedure catalyzed by Rh(II)-acetate (P. Müller, C. Gränicher, *Helv. Chim. Acta* **1993**, *76*, 521-534). The corresponding thiophenes **A211-214** are accessible by carboxylation method C-III (J. Sicé, *J. Am. Chem. Soc.* **1953**, *75*, 3697-3700), which is also applied for the synthesis of furans **A213/214** (D.G. Manly, E.D. Amstutz, *J. Org. Chem.* **1956**, *21*, 516-519).

Pyrroles **A211/212** can be prepared from suitably substituted 2-chloroethylidene-malonates by a tandem Staudinger reaction/ aza-Wittig protocol (F.-P. Montforts et al., *Liebigs Ann. Chem.* **1990**, 1037-1043). Pyrroles **A213/214** can be obtained from *N*-protected glutamate, which is transformed into the didehydro derivative and cyclized in the presence of $LiCuMe_2$ (M.M. Paz, F.J. Sardina, *J. Org. Chem.* **1993**, *58*, 6990-6995).

Thiophenes **A215/216** are available from 3-bromo-thiophenes in a multi-step sequence involving general reactions T-IV and C-II (E.C. Taylor, D.E. Vogel, *J. Org. Chem.* **1985**, *50*, 1002-1004).

Pyrroles **A215/216** can be prepared from amino-oxoacetate and oxalyl chloride, alcoholysis of the isocyanate and reaction with (3-bromoacetonyl)triphenylphosphonium bromide (J.P. Bazureau et al., *Tetrahedron Lett.* **1988**, *29*, 1921-1922), or from *N*-Pfp-protected 3-oxo-prolinates (F.-A. Marcotte, W.D. Lubell, *Org. Lett.* **2002**, *4*, 2601-2603).

Furans **A217/218** can be obtained from acetylene carboxylates by reaction with ethoxyvinylidene-tetracarbonyl-ferrocene complexes (Atiq-ur-Rehman et al., *J. Am. Chem. Soc.* **1993**, *115*, 9848-9849). Thiophenes **A217/218** are accessible from formylsuccinates by cyclization in the presence of methanol, hydrogen chloride and hydrogen sulfide (S. Mitra et al., *J. Chem. Soc.* **1939**, 1116-1117), or from 2,4-dibromothiophenes by carboxylation of type C-II (D. Spinelli et al., *J. Chem. Res. (M)* **1993**, *8*, 1873-1890). Pyrroles **A217/218** (keto-tautomer) can be obtained from suitably substituted aminomethylene succinates by base-induced cyclization (C.A. Grob, P. Ankli, *Helv. Chim. Acta* **1949**, *32*, 2023-2038).

For the related sulfanyl/sulfinyl/sulfonyl analogs **A663** and alkenyl/alkyl analogs **A664/A665** compare the section about the corresponding phenyl derivatives above.

A229-A234 Oxazole, Thiazole and Imidazole Derivatives

Oxazoles of type **A229** are obtained by reaction of acetyl isocyanates and diazoacetate followed by cyclization (O. Tsuge et al., *Tetrahedron* **1973**, *29*, 1983-1990), whereas the thiazoles **A229** can be synthesized from bromomalonates and thioamides (F.A.J. Kerdesky et al., *J. Med. Chem.* **1991**, *34*, 2158-2165), and the imidazoles **A229** from aminomalonate and acetimidates (M.S. Poonian, E.F. Nowoswiat, *J. Org. Chem.* **1980**, *45*, 203-208).

The oxazoles and thiazoles of type **A230** are accessible by cyclizing monoethyl acetamidomalonate in the presence of trifluoroacetic anhydride (J. Morgan et al., *J. Chem. Soc., Perkin Trans. 1*, **1997**, *5*, 613-620) or phosphorus pentasulfide (A.G. Long, A. Tulley, *J. Chem. Soc.* **1964**, 1190-1192). The imidazoles **A230** can be obtained from aminomalonate by reaction

with trimethylorthoformate and subsequent cyclization (R.S. Hosmane, B.B. Lim, *Tetrahedron Lett.* **1985**, *26*, 1915-1918).

Oxazoles of type **A231** might be accessed from hydroxyacetaldehyde dimer (C.M. Shafer, T.F. Molinski, *J. Org. Chem.* **1998**, *63*, 551-555), and the corresponding thiazoles **A231** from β-ketoesters (P.-F. Zhang, Z.-C. Chen, *Synth. Comm.* **2001**, *31*, 415-420). Imidazoles **A231** can be prepared from *N*-protected glycines in a multi-step reaction sequence (G. van Lommen et al., *Bioorg. Med. Chem. Lett.* **2005**, *15*, 497-500; J. Singh et al., *Tetrahedron Lett.* **1993**, *34*, 211-214).

Oxazoles of type **A232** can be synthesized from diazoacetates by rhodium-catalyzed reaction with cyanoformate (G. Shi et al., *J. Fluorine Chem.* **1991**, *52*, 149-157). Oxazoles of type **A233** can be obtained by heating acetylene carboxylates with diazoacetates (R. Huisgen, H. Blaschke, *Chem. Ber.* **1965**, *98*, 2985-2997).

Thiazoles **A233** are available from suitably substituted cysteine esters by reaction with diphosgene followed by bromination/elimination (G. Serra et al., *Heterocycles* **1995**, *41*, 2701-2711).

Oxazoles **A234** can be obtained from suitably substituted hydroxyacetonitriles and oxalyl chloride (K. van Aken, G. Hoornaert, *J. Chem. Soc., Chem. Comm.* **1992**, *12*, 895-896), and the thiazoles **A234** from 2-mercaptoacetate and cyanoformate (G. Satzinger, *Liebigs Ann. Chem.* **1978**, 473-511).

A235-A239 Isoxazole, Isothiazole and Pyrazole Derivatives

Isoxazoles and pyrazoles of type **A235** can be synthesized from (2-methoxymethylene)-malonates by reaction with hydroxylamine (K. Bowden et al., *J. Chem. Soc. C* **1968**, 172-185) or hydrazine (T.M. Willson et al., *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1047-1050).

The isothiazoles **A236** can be obtained from suitably substituted *O*-toluenesulfonyloxyiminoacetates by reacting with thioglycollates (B. Rezessy et al., *Tetrahedron Lett.* **1992**, *33*, 6523-6526); and the corresponding pyrazoles **A236** can be prepared either from suitably substituted 2-oxopropionates and hydrazinoacetates (R.N. Comber et al., *Carbohyd. Res.* **1992**, *216*,

441-452) or from 3-oxopropionates by 2-diazotation and subsequent cyclization (F.J.L. Herrera, C.U. Baelo, *Carbohyd. Res.* **1985**, *143*, 161-174).

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

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

A240-A357 and **A666-A671** Benzofuran, Benzothiophene and Indole Derivatives

Benzothiophenes **A240** can be prepared in a multi-step sequence transforming 2-hydroxy-benzaldehydes into the 3-isopropoxy-2,3-dihydrobenzothiophen-2-ones and carboxylating the 3-position (A.V. Kalinin et al., *J. Org. Chem.* **2003**, *68*, 5992-5999). A possible route to benzofurans of type **A241-A243** involves condensation of suitably substituted cyclohexane-1,3-diones and 3-bromo-2-oxo-propionic acid followed by Pd-catalyzed dehydrogenation (G. Kneen, P.J. Maddocks, *Synth. Comm.* **1986**, *16*, 1635-1640). Indoles **A244-A247** can be obtained from 2-bromo-3-nitro-benzoates by a Stille coupling to the corresponding 1-ethoxy-styrene and subsequent Pd-catalyzed cyclization in the presence of CO (R.W. Clawson et al., *Tetrahedron* **2006**, *62*, 10829-10834).

Benzofurans of type **A248-A251** can be synthesized from suitably substituted 2,6-dihydroxy-benzoates by treatment with 2-chloro-ketones (F.H. Curd, A. Robertson, *J. Chem. Soc.* **1933**, 714-720). The corresponding indoles **A250/251** might be accessible from 6-hydroxy-3-methyl-2-nitro-benzoic acid in a multi-step reaction sequence consisting of hydrogenation, cyclization, diazotization and hydroxylation (H.D. Hollis Showalter et al., *J. Org. Chem.* **1996**, *61*, 1155-1158). Benzothiophenes **A250/251** could be obtained from 2-(thiophen-3-yl-)acetaldehydes by reaction with propargyl alcohol followed by iodo-cyclization, oxidation and hydroxylation H-IV (J.P. Waldo et al., *J. Org. Chem.* **2008**, *73*, 6679-6685).

The benzothiophenes of type **A252-A255** are accessible from 3-methyl-thiophene-2-carboxylates (J.W. Terpstra, A.M. van Leusen, *J. Org. Chem.* **1986**, *51*, 230-238). Indoles **A252-A255** can be synthesized from methyl 2-methoxy-4-methyl-benzoates by bromination, nitration, reaction with dimethylformamide followed by reductive cyclization (P.L. Beaulieu et al., *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4987-4993).

Possible precursors of benzofurans **A256-A259** and **A264-A267** are suitably substituted 2,4-dihydroxy-benzoates that might be alkylated in the 4-position with bromoacetaldehyde dialkyl acetals followed by cyclization (M. Dixit et al., *Synlett* **2006**, *10*, 1497-1502). Indoles of type **A256-A259** and **A264-A267** can be obtained from suitably substituted 5-hydroxy-indoles via diethyl carbamates which undergo anionic Fries rearrangement (E.J. Griffen et al., *J. Org. Chem.* **1995**, *60*, 1484-1485). The benzothiophenes of type **A260** and **A263** are accessible from 4,6-dibromo-benzene-1,3-carbaldehyde by treatment with methoxide and 2-mercaptoacetate followed by cyclization, decarboxylation, demethylation and oxidation of the aldehyde to the acid (A.E. Jakobs et al., *Tetrahedron* **1994**, *50*, 9315-9324).

Benzofurans of type **A268-A271** can be synthesized from the corresponding 4-hydroxy-benzofurans by carboxylation (T. Reichstein, R. Hirt, *Helv. Chim. Acta* **1933**, *16*, 121-129) or by reacting 5-carbomethoxy-6-hydroxy-salicylaldehydes with bromo-

acetates followed by saponification and cyclization (R.T. Foster, A. Robertson, *J. Chem. Soc.* **1948**, 115-116). Preparation of the corresponding benzothiophenes **A268-A271** can start from a suitably substituted 4-oxo-tetrahydrobenzothiophene which is subjected to acylation and subsequent aromatization (P.P. Yadav et al., *Bioorg. Med. Chem.* **2005**, *13*, 1497-1505). Similarly indoles **A268-A271** can be prepared from 4-oxo-tetrahydroindoles, or alternatively by Claisen rearrangement of the allyl ether of 4-amino-salicylic acid followed by cleavage of the double bond and cyclization (T. Kakigami et al., *Chem. Pharm. Bull.* **1988**, *46*, 42-52). Benzofurans of type **A272-A275** can be synthesized from *O*-protected 4-hydroxy-salicylaldehydes by reaction with diazoacetate followed by dehydration (M. E. Dudley et al., *Synthesis* **2006**, 1711-1714). Benzothiophenes **A272-A275** are accessible from 5-bromo-benzothiophene by Friedel-Crafts acylation as key step (S. Mitsumori et al., *J. Med. Chem.* **2003**, *46*, 2446-2455), and the corresponding indoles **A272-A275** by Nenitzescu reaction of para-benzoquinones with substituted 2-aminoacrylates (E.A. Steck et al., *J. Org. Chem.* **1959**, *24*, 1750-1752). Benzofurans of type **A276-A279** can be obtained from 3-acetyl-4-hydroxy-benzoates by bromination and subsequent base-induced cyclization (G. Doria et al., *Farmaco* **1980**, *35*, 674-680).

Benzothiophenes **A276-A279** can be prepared from 4-fluorobenzoates and thioglycolate by intramolecular Friedel-Crafts acylation (D.L. Gernert et al., *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2759-2764).

Benzofurans and benzothiophenes of type **A284-A287** can be synthesized from suitably substituted 3-furaldehydes or 3-formyl-thiophenes by cyclocondensation with succinates (D. Simoni et al., *J. Med. Chem.* **2006**, *49*, 3143-3152). Indoles of type **A284** and **A287** are accessible from 3-methoxy-4-amino-benzoates by a reaction sequence consisting of iodination, Sonogashira coupling and cyclization (J. Ezquerra et al., *J. Org. Chem.* **1996**, *61*, 5804-5812). Benzofurans and benzothiophenes of type **A288-A291** can be obtained from suitably

substituted 2-furaldehydes (D. Simoni et al., *J. Med. Chem.* **2006**, *49*, 3143-3152). Indoles **A288-A291** are available by cyclo-condensation of pyrrole-2-carbaldehydes and diethyl succinate (C. Fuganti, S. Serra, *J. Chem. Res. (M)* **1998**, *10*, 2769-2782).

Indoles of type **A292-A295** can be prepared from *N*-protected furo[3,2-*b*]pyrrole-5-carboxylates by decarboxylation and subsequent Diels-Alder reaction (A. Krutosikova, M. Hanes, *Collect. Czech. Chem. Comm.* **1992**, *57*, 1487-1494).

Benzofurans of type **A296-A299** can be obtained from suitably substituted (*p*-acetoxyphenoxy)acetyl chlorides by reacting with cyanide followed by $ZnCl_2$-mediated cyclization with 1,3-dihydroxy-benzene (L. Crombie et al., *J. Chem. Soc., Perkin Trans. 1*, **1987**, 2783-2786). The corresponding benzothiophenes **A296-A299** can be synthesized from suitably substituted 3-bromothiophenols (S. Mitsumori et al., *J. Med. Chem.* **2003**, *46*, 2446-2455). Indoles **A296-A299** are accessible from *O*-protected 6-hydroxyindoles (M. Fedouloff et al., *Bioorg. Med. Chem.* **2001**, *9*, 2119-2128).

Benzofurans **A300-A303** can be obtained from suitably substituted 3-acetyl-furans via the silylenol ether (A. Benitez et al., *J. Org. Chem.* **1996**, *61*, 1487-1492).

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

The indoles **A304-A307** can be obtained by Diels-Alder reaction of the silylenolate of *N*-protected 2-acetylpyrrole with propio-

nate followed by air oxidation (M. Ohno et al., *Heterocycles* **1991**, *32*, 1199-1202).

The mentioned synthetic routes are also feasible for preparing the more highly substituted derivatives **A308-A357**.

For the related sulfanyl/sulfinyl/sulfonyl and alkenyl/alkyl analogs **A666-A671** compare the section about the corresponding phenyl derivatives above.

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

Pyrrolopyridines **A365/366** can be synthesized from 7-azaindoles via pyridine-*N*-oxides (X. Wang et al., *J. Org. Chem.* **2006**, *71*, 4021-4023) by a carboxylation reaction of type C-II (A. L'Heureux et al., *Tetrahedron Lett.* **2004**, *45*, 2317-2320). Pyrrolopyridines of type **A367/368** can be obtained from suitably substituted 4-chloro-3-formyl-pyridines by treatment with azidoacetate and subsequent Hemetsberger-Knittel reaction (P.J. Roy et al., *Synthesis* **2005**, 2751-2757).

Pyrrolopyridines of type **A369/370** are accessible from the corresponding 5-chloro-pyrrolopyridine by formylation in a Duff reaction, oxidation and hydrolysis (R.H. Bahekar et al., *Bioorg. Med. Chem.* **2007**, *15*, 6782-6795). The synthesis of pyrrolopyridines **A371/372** can start from 4-chloro-7-azaindole and proceed via the *N*-oxide (T. Storz et al., *Synthesis* **2008**, 201-214).

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

Pyrrolopyridines of type **A379** can be obtained from suitably substituted 4-iodo-3-nitro-pyridines involving Sonogashira coupling and $TiCl_4$-mediated cyclization as key reactions (T. Sakamoto et al., *Chem. Pharm. Bull.* **1986**, *34*, 2362-2368). Pyrrolopyridines of type **A382/383** can be prepared from 2-methoxy-4-iodo-5-aminopyridines by Sonogashira coupling with TMS-acetylene, CuI-mediated cyclization, formylation and oxidation (D. Mazeas et al., *Heterocycles* **1999**, *50*, 1065-1080).

Pyrrolopyridines of type **A384/385** are accessible from suitably substituted 4-methoxy-pyrrole-2-carbaldehydes by reductive amination with 3,3-diethoxy-2-amino-propionate and subsequent cyclization (S.K. Singh et al., *Heterocycles* **1997**, *44*, 379-392).

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

Pyrrolopyridines **A387/388** are accessible from *N*-alkylated 2-formyl-pyrroles via 2-pyrrylacryl azides (J.S. New et al., *J. Med. Chem.* **1989**, *32*, 1147-1156). Pyrrolopyridines of type **A389/390** can be obtained from 2-methoxy-3-formyl-pyridines by reaction with azidoacetate and subsequent Hemetsberger-Knittel reaction (P.J. Roy et al., *Synthesis* **2005**, 2751-2757).

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

Pyrrolopyridines of type **A406/407** can be obtained from 2-(6-methoxy-3-nitro-2-pyridyl)acetates by Knoevenagel condensation with formaldehyde followed by Pd-catalyzed cyclization in the presence of hydrogen and CO (B.C.G. Soederberg et al., *Synthesis* **2008**, *6*, 903-912).

Pyrrolopyridines **A410** and **A413** can be synthesized from suitably substituted 2-chloro-3-nicotinonitriles by Sonogashira coupling with TMS-acetylene and subsequent cyclization as key steps (T. Sakamoto et al., *Chem. Pharm. Bull.* **1986**, *34*, 2362-2368). Alternatively, their preparation can be achieved by reacting 3-nitro-pyridines with vinylmagnesium bromide (Z. Zhang et al., *J. Org. Chem.* **2002**, *67*, 2345-2347). Pyrrolopyridines **A408** and **A412** are available from 2-alkynyl-3-amino-pyridines by CuI-catalyzed cyclization (A.M. Palmer et al., *Bioorg. Med. Chem.* **2008**, *16*, 1511-1530).

A414-A449 Derivatives of Benzoxazole, Benzothiazole and Benzimidazole

Benzoxazoles **A415/416** can be prepared from *N*-acylated 3-chloro-4-anisidines via benzyne-formation and carboxylation (D.R. Reavill, S.K. Richardson, *Synth. Comm.* **1990**, *20*, 1423-1436). The corresponding benzimidazoles **A415/416** are accessible from 2-amino-3-halo-benzoates by acylation of the amine, nitration and reductive cyclization (K. Kubo et al., *J. Med. Chem.* **1993**, *36*, 1772-1784).

Benzimidazoles of type **A417-A419** can be obtained from the corresponding 4-acetamido-2-methoxy-benzoates by chlorination in 5-position, nitration in 3-position and reductive cyclization (S. Bolgunas et al., *J. Med. Chem.* **2006**, *49*, 4762-4766).

Benzimidazoles **A420-A422** are accessible from the corresponding 5-methoxy-6-methyl-benzimidazoles by oxidations of type C-I (B.D. Palmer et al., *J. Med. Chem.* **1999**, *42*, 2373-2382). Benzoxazoles of type **A423-A425** can be obtained by condensing 4-methylene-2-oxazolin-5-ones and 4-triphenylphosphoranylidene-3-oxobutanoates, followed by aromatization (F. Clerici et al., *Tetrahedron* **1991**, *47*, 8907-8916). The synthesis of the corresponding benzimidazoles **A423-A425** is possible starting from 4-amino-2-hydroxy-5-nitrobenzoates by acylation, reduction of the nitro group and cyclization (A. Tanaka et al., *Chem. Pharm. Bull.* **1994**, *42*, 560-569). Benzoxazoles of type **A426-A428** can be synthesized starting from 2,5-dihydroxybenzoate (D. Diez-Martin et al., *Tetrahedron* **1992**, *48*, 7899-7939).

Benzimidazoles **A429-A431** are accessible from *O*-protected 3,4-diamino-2-hydroxy-benzoates by acylation and subsequent cyclization (Y. Hirokawa et al., *Chem. Pharm. Bull.* **2002**, *50*, 941-959; A. Viger, P.B. Dervan, *Bioorg. Med. Chem.* **2006**, *14*, 8539-8549). Benzothiazoles of type **A438-A440** can be synthesized by heating suitably substituted 4-amino-3-methoxy-benzoates with thiocyanate in the presence of copper(II)-salts and subsequent 2-desamination (I.A. Ismail et al., *J. Org. Chem.* **1980**, *45*, 2243-2246). Benzimidazoles **A441-A443** can be prepared by a multi-step sequence from 8-aminoquinolines via the corresponding 5,6-dihydro-4*H*-imidazoquinolines (R.C. Elderfield, F.J. Kreysa, *J. Am. Chem. Soc.* **1948**, *70*, 44-48). Benzimidazoles **A444** and **A447** can be obtained by reaction of suitably substituted 3-amino-4-methoxy-benzoates with nitriles followed by NaOCl-induced cyclization (J. Regan et al., *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2737-2742).

A450-A459 Derivatives of Benzisoxazole, Benzisothiazole and Indazole

Benzisoxazoles **A456** and **A459** can be synthesized starting from 2,6-dihydroxy-3-formyl-4-methyl-benzoates by reaction with hydroxylamine followed by thermal cyclization (D.H.R. Barton et al., *J. Chem. Soc. C* **1971**, 2166-2174); this method also is suitable for benzisoxazoles of types **A450-A455** and **A457/458**.

The preparation of indazoles **A457** has been described as reaction between 3-amino-2-methoxy-4-methylbenzoate and iso-amylnitrite (S. Bolgunas et al., *J. Med. Chem.* **2006**, *49*, 4762-4766).

A460-A515 Naphthalene Derivatives

A large number of suitably substituted naphthalene derivatives is commercially available. In addition, naphthalenes **A460-A465** and **A496-A499** can be obtained from the corresponding 2-hydroxy-naphthalenes via lithiation and carboxylation (cf. C-III) (K. Takahashi et al., *Tetrahedron* **1994**, *50*, 1327-1340). Higher substituted analogs can be prepared in a multi-step sequence from suitably substituted 2-bromotoluenes via 2-tetralone-1-carboxylates (F.C. Goerth et al., *Eur. J. Org. Chem.* **2000**, 2605-2612).

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

The naphthalenes **A484-A489** and **A504-A507** can easily be built up by condensation of succinic esters with either benzaldehydes (A.M. El-Abbady et al., *J. Org. Chem.* **1961**, *26*, 4871-4873; M. Kitamura et al., *Angew. Chem. Int. Ed.* **1999**, *38*, 1229-1232) or with benzophenones (F.G. Baddar et al., *J. Chem. Soc.* **1955**, 1714-1718).

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

A516-A548 and **A672-A674** Quinoline Derivatives

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

Quinolines **A522-A524** are easily accessible from 2-amino-benzaldehydes via a modified Friedländer synthesis (D.L. Boger, J.-H. Chen, *J. Org. Chem.* **1995**, *60*, 7369-7371). Similarly, quinoline derivatives **A527-A529** can be obtained from 2-amino-benzaldehydes by condensation with malonic acid (J. Tröger, C. Cohaus, *J. Prakt. Chem.* **1927**, *117*, 97-116).

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

Quinolines of type **A530-A533** can be constructed from 2-anisidines by reacting with 2-oxosuccinic esters followed by thermal cyclization (L. Musajo, M. Minchilli, *Chem. Ber.* **1941**, *74*, 1839-1843). Syntheses of quinolines **A534-A536** and **A537-A539** can be achieved via the corresponding halogen substituted analogs followed by carboxylation of type C-II (F. Cottet et al., *Eur. J. Org. Chem.* **2003**, *8*, 1559-1568).

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

Derivatives of type **A546-A548** can be obtained in a multi-step reaction starting with 3-chloroanilines (A.M. Spivey, F.H.S. Curd, *J. Chem. Soc.* **1949**, 2656-2662).

For the related sulfanyl/sulfinyl/sulfonyl quinolines **A672** and alkenyl/alkyl quinolines **A673/A674** compare the section about the corresponding phenyl derivatives above.

A549-A564 Isoquinoline Derivatives

Isoquinolines of type **A549-A553** with a carboxyl in 1-position can be prepared from benzaldehydes in a multi-step sequence consisting of transformation into aminoethanes, reaction with oxalic ester, cyclization, and aromatization (M. Keizo et al.,

Chem. Pharm. Bull. **1982**, *30*, 4170-4174; S. Naoki et al., *Chem. Pharm. Bull.* **1989**, *37*, 1493-1499).

Isoquinoline-3-carboxylates **A554-A556** are accessible from hydroxy-phenylalanines by Bischler-Napieralski reaction and subsequent aromatization, or alternatively from 2-methyl benzaldehydes by reacting with azidoacetate, thermal cyclization and aromatization (Y. Fukuda et al., *J. Med. Chem.* **1999**, *42*, 1448-1458; T. R. Burke et al., *Heterocycles* **1992**, *34*, 757-764).

Compounds of type **A557/558** can be synthesized by reaction of 2-aminobenzoic acids and 5-chloro-3-carboxy-1,2,4-pyrazines in the presence of amylnitrite (A.M. d'A. Rocha Gonsalves, T.M.V.D. Pinho e Melo, *Tetrahedron* **1992**, *48*, 6821-6826), whereas isoquinolines **A559/560** can be prepared from 2-formylbenzoic acids via isothiochromenone (D.J. Dijksman, G.T. Newbold, *J. Chem. Soc.* **1951**, 1213-1217).

Access to isoquinolines **A561/562** is feasible by transformation of isoquinolines into the corresponding Reissert compounds, nitration in 4-position and hydrolysis (M. Sugiura et al., *Chem. Pharm. Bull.* **1992**, *40*, 2262-2266).

Isoquinolines of type **A563/564** are accessible from (2-methoxycarbonyl-phenyl)acetic acids by reaction with methyl formate followed by cyclization and amination (H.E. Ungnade et al., *J. Org. Chem.* **1945**, *10*, 533-536).

A565-A577 Quinazoline Derivatives

The most general routes to quinazolines use appropriately substituted phenyl derivatives onto which the pyrimido ring is cyclized, e.g. the cyclocondensation of 2-amino benzamides with oxalates (M. Suesse et al., *Helv. Chim. Acta* **1986**, *69*, 1017-1024), of *ortho*-carbonyl substituted phenyl oxalamic acid esters with ammonium formate (S. Ferrini et al., *Org. Lett.* **2007**, 9, 69-72), of 2-amino benzonitriles with carbonylformimidate or chloroformamidine (A. McKillop et al., *Tetrahedron Lett.* **1982**, *23*, 3357-3360; N. Harris et al., *J. Med. Chem.* **1990**, *33*, 434-444), or of *ortho*-oxalyl anilides with ammonia (M.T. Bogert, F.P. Nabenhauer, *J. Am. Chem. Soc.* **1924**, *46*, 1702-1707).

A578-A587 Quinoxaline Derivatives

The synthesis of quinoxalines **A578-581** via their 2-carbaldehydes is well-documented (E. Lippmann et al., *Zeitschr. Chem.* **1990**, 30, 251-252). Representative structures of type **A582-587** are available by cyclocondensation of α,β-dicarbonyl derivatives or β-ketoesters with appropriately substituted *ortho*-phenylendiamines (S. Grivas et al., *Acta Chem. Scand.* **1993**, 47, 521-528; A. Zychilinski, I. Ugi, *Heterocycles* **1998**, 49, 29-32; D. Zhou et al., *Bioorg. Med. Chem.* **2008**, 16, 6707-6723). In addition, it is possible to introduce a carboxyl group into the 2-position of the quinoxaline ring by biotransformation with *Arthrobacter nicotianae* (T. Yoshida et al., *Biosci. Biotech. Biochem.* **2002**, 66, 2388-2394).

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

The bicyclic cores **A588-A601** can be accessed by annelating suitably substituted pyridines. Feasible starting materials for these cyclocondensation reactions include pyridine-2,3-dicarboxylic acids (A. Tikad et al., *Synlett* **2006**, *12*, 1938-1942), 3-aminopyridine-2-carboxylates (M. Hayakawa et al., *Bioorg. Med. Chem.* **2006**, *14*, 6847-6858) or 3-aminopyridine-2-nitriles (J.B. Smaill et al., *J. Med. Chem.* **2000**, *43*, 1380-1397).

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

Access to the pyrimidopyrimidine group can be achieved via the well-known 4,6-dichloro (G. Rewcastle et al., *J. Med. Chem.* **1997**, *40;* 12, 1820-1826) or 2,4,6,8-tetrachloro derivatives (J. Northen et al., *J. Chem. Soc., Perkin Trans. 1*, **2002**, 108-115) utilizing the general methods described above.

A609-A618 and **A675-A683** Tetraline Derivatives

A large number of reaction sequences towards tetralines occur via 1- or 2-tetralones as key intermediates. Their carbonyl groups are elaborated into carboxyl moieties by the action of trimethylsilyl cyanide (TMSCN) or diethyl cyanophosphonate (DECNP) and subsequent hydrolysis (M. Meyer et al., *J. Med. Chem.* **1997**, *40*, 1049-1062; F. Berardi et al., *J. Med. Chem.*

2004, *47*, 2308-2317). These tetralones in turn are synthesized by an intramolecular Friedel-Crafts acylation of cyclization precursors derived from phenylacetonitriles and 2-phenyl malonates (R.S. Natekar, S. D. Samant, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2002**, 41, 187-190; L. Gong, H. Parnes, *J. Labelled Compd. Radiopharm.* **1996**, 38, 425-434). Alternatively, the intramolecular cyclization can be achieved by a Buchner reaction (A. Cheung et al., *Bioorg. Med. Chem. Lett.* **2003**, *13*, 133-138).

The synthesis of enantiomerically pure analogs is described by D. Obrecht et al., *Helv. Chim. Acta* **1995**, *78*, 1567-1587.

For the related sulfanyl/sulfinyl/sulfonyl and alkenyl/alkyl tetralines **A675-A683** compare the section about the corresponding phenyl derivatives above.

A619-A626 Indane Derivatives

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

Indane derivatives of types **A624-A626** with a carboxyl group in 2-position can be obtained from readily accessible indan-1-ones by treatment of the corresponding enolate with dimethyl carbonate, subsequent hydrogenation of the carbonyl group and final hydrolysis (T. Tanaka et al., *Chem. Pharm. Bull.* **1994**, *42*, 1756-1759; U. Hacksell et al. *J. Med. Chem.* **1981**, *24*, 429-434). Alternatively the indane ring system can be built up starting from *ortho*-xylenes by NBS bromination of both methyl groups, followed by alkylative spirocyclization with the enolate of barbituric acid and finally decarboxylative ring cleavage to indan-2-caboxylic acids (G.A. Kraus et al., *J. Org. Chem.* **2002**, *67*, 5857-5859).

Synthesis of Modulator B Building Blocks

The Modulator **B** moieties of macrocycle **Ia/Ib** are derived from appropriately substituted 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 R^3 can be introduced by standard nucleophilic addition of organometallic reagents to carbonyl or carboxyl derivatives. For **B18-B21**, carrying no additional C-substituent on their ring system, such precursors are commercially available. Similarly, in the case of **B9**, **B10**, **B16** and **B17** the diversification of the substitution pattern can be easily achieved by standard transformations of the commercial analogs with free amine functionalities (i.e. $-NH_2 \rightarrow -NR^{11}R^{27}$ in the case of **B9** and $-NH \rightarrow -NR^{11}$ for **B10**, **B16** and **B17**).

B1 Aziridine Derivatives

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

B2-B3 Azetidine Derivatives

The standard approach to hydroxymethyl azetidines subjects easily accessible *O*-protected glycidols successively to epoxide-ring opening with azide, transformation of the thus obtained alcohol group into a suitable leaving group (e.g. tosylate or sulfate), and reduction of the azide to amine with concomitant intramolecular cyclization (F. Hosono et al.,

Tetrahedron **1994**, *50*, 13335-13346; D.-G. Liu, G.-Q. Lin, *Tetrahedron Lett.* **1999**, 40, 337-340).

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

The synthetic pathways to pyrrolidine and piperidine building blocks **B** rely on the same strategy, and 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-Freytag reaction (M. E. Wolff, *Chem. Rev.* **1963**, *63*, 55-64). Alternatively, amines carrying two substituents, each with an alkene or alkyne bond, can be subjected to a ring closing metathesis (RCM) reaction (Y. Coquerel, J. Rodriguez, *Eur. J. Org. Chem.* **2008**, 1125-1132) and subsequent reduction of the 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 Ia/Ib

General procedures for the synthesis of libraries of macrocyclic compounds of general structure **Ia/Ib** 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 **Ia/Ib**.

The macrocyclic compounds of the invention are obtained by cyclization of suitable linear precursors which are derived from optionally substituted bifunctional phenols or thiophenols **A** ("Template"), substituted amino alcohols **B** ("Modulator"), and one to three building blocks forming "Bridge" **C**.

Phenol or thiophenol building blocks **A** comprise optionally substituted hydroxyaryl, hydroxyheteroaryl, mercaptoaryl, and mercapto-heteroaryl carboxylic acids, mercaptophenols, hydroxy-mercapto-heteroaryl compounds, alkenyl phenols or alkenyl thiophenols.

Variable substituents are introduced by pre- or postcyclative derivatization of one or more orthogonally protected attachment points (e.g. amino groups, carboxyl groups, hydroxyl groups) on **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 the invention can be prepared either in solution or on solid support.

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

- Macrolactamization between **C** and **B**;
- Macrolactamization between **A** and **C**;
- Macrolactamization between any two subunits of Bridge **C**;
- Arylether or arylthioether formation between **A** and **B**;
- Arylthioether formation between **A** and **C**;
- Ring closing metathesis (RCM) reaction between any two subunits of **C**; or
- Ring closure metathesis reaction between **A** and **C**.

SW-1: Synthesis workflow for the preparation of side-chain protected macrocycles Ia/Ib by macrolactamization in solution

Macrocycles of structure **Ia/Ib** with orthogonally protected exocyclic functional groups (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. Within this workflow SW-1 the generic group M is NR^4 or CHR^6; and both V and W are $CONR^4$.

a1) Condensation of an appropriately protected hydroxy- or mercapto-aryl/heteroaryl carboxylic acid PG^1–**A**–OH and a suitable *C*-terminally and side-chain protected **C**-subunit building block H–NR^4–**c1**–CO–OPG^2 to form PG^1–**A**–NR^4–**c1**–CO–OPG^2; the related compounds PG^1–**A**–CHR^6–**c1**–CO–OPG^2 are obtained if a mercaptophenol or hydroxy-mercapto heteroaryl compound is used as **A** building block and connected to a *C*-terminally and side-chain protected compound LG–CHR^6–**c1**–CO–OPG^2 by *S*-alkylation (LG represents a leaving group like halide, alkyl- or aryl-sulfonate).

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**–**A**–M–**c1**–CO–OPG^2;

d1) Cleavage of the "main chain" protective groups affording the free amino acid H–**B**–**A**–M–**c1**–CO–OH, which is either subjected to (i) immediate macrocyclization (step e1) or (ii) chain elongation by one (steps f1-i1) or (iii) two additional **C**-subunits followed my macrocyclization (steps j1-o1).

(i) Direct macrolactamization

e1) Intramolecular amide coupling to *cyclo*(**B**–**A**–M–**c1**–CO–) as macrocyclic product.

(ii) Chain elongation by one additional **C**-subunit and subsequent macrolactamization

f1) *N*-Reprotection of the product of step d1;

g1) Coupling with a second suitably *C*-protected amino acid to PG^3-**B**-**A**-M-**c1**-V-**c2**-CO-OPG^2;

h1) Cleavage of the "main chain" protective groups;

i1) Macrolactamization to the side-chain protected macrocycle *cyclo*(**B**-**A**-M-**c1**-V-**c2**-CO-).

(iii) Chain elongation by two additional **C**-subunits and subsequent macrolactamization

j1) *N*-Protection of the product obtained in step d1;

k1) Coupling with a second suitably *C*-protected amino acid;

l1) Cleavage of the *C*-terminal protective group or cleavage of *N*- and *C*-terminal protective groups followed by reprotection of the *N*-terminus;

m1) Coupling with a third suitably *C*-protected amino acid yielding PG^3-**B**-**A**-M-**c1**-V-**c2**-W-**c3**-CO-;

n1) Cleavage of the "main chain" protective groups;

o1) Macrolactamization to the side-chain protected macrocycle *cyclo*(**B**-**A**-M-**c1**-V-**c2**-W-**c3**-CO-).

In addition to the steps described above, the free carboxylic acid functionality of the *N*-reprotected product of step f1, or of a linear precursor (cf. steps a1, g1, k1, m1) after selective deprotection 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.

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

As an alternative to SW-1 the protected cyclization precursor PG^3-**B**-**A**-M-**c1**-CO-OPG^2 (wherein M is NR^4) can also be synthesized by an inverted order of reaction steps:

a2) Arylether or arylthioether formation between a hydroxyl or mercapto-aryl/heteroaryl ester H–**A**–OPG^4 and a suitably protected amino alcohol PG^3–**B**–OH to afford PG^3–**B**–**A**–OPG^4;

b2) Deprotection of the carboxylic acid group to PG^3–**B**–**A**–OH;

c2) Condensation with a *C*-terminally and side-chain protected building block H–M–**c1**–CO–OPG^2 to PG^3–**B**–**A**–M–**c1**–CO–OPG^2.

Possible subsequent steps are as described in SW-1.

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

As an alternative to SW-1(ii) macrocycles of type *cyclo*(**B**–**A**–M–**c1**–V–**c2**–CO–) can be synthesized by interconnecting the **C**-subunits (i.e. by formation of the V moiety) as last and macrocyclization step:

a3) Synthesis of PG^1–**A**–M–**c1**–CO–OPG^2 as described above (cf. a1);

b3) Deprotection to H–**A**–M–**c1**–CO–OPG^2 (cf. b1);

c3) *N*-acylation of aminoalcohol H–**B**–OH with a suitably *N*-terminally protected amino acid PG^5–NR^4–**c2**–CO–OH to afford amidoalcohol PG^5–NR^4–**c2**–CO–**B**–OH (cf. a1);

d3) Arylether or arylthioether bond formation between the products of steps b3 and c3 to PG^5–NR^4–**c2**–CO–**B**–**A**–M–**c1**–CO–OPG^2 (cf. c1);

e3) Cleavage of the "main chain" protective groups to give the cyclization precursor H–NR^4–**c2**–CO–**B**–**A**–M–**c1**–CO–OH (cf. d1);

f3) Macrolactamization to the side-chain protected macrocycle *cyclo*(**c2**–CO–**B**–**A**–M–**c1**–V–) i.e. *cyclo*(**B**–**A**–M–**c1**–V–**c2**–CO–) wherein M is NR^4 and V is CONR^4 (cf. e1 and i1).

Similar to SW-1(iii) a third **C**-subunit could be introduced by subjecting H–**B**–OH to two successive *N*-acylation, *N*-deprotection sequences affording PG^5–NR^4–**c2**–W–**c3**–CO–**B**–OH. Subsequent ether or thioether formation and main chain deprotection (cf. d3 and e3) yield H–NR^4–**c2**–W–**c3**–CO–**B**–**A**–M–**c1**–CO–OH which is finally cyclized

to macrolactam *cyclo*(**B**–**A**–M–**c1**–V–**c2**–W–**c3**–CO–) wherein M is NR^4 and both V and W are $CONR^4$.

General procedures for synthetic steps utilized in SW-1 to SW-3

In all general procedures below M represents NR^4 or CHR^6.

Amidation reactions (steps a1, g1, k1, m1, c2)

An appropriately protected (preferably as acetyloxy or acetylmercapto) and optionally substituted aryl/heteroaryl carboxylic acid (PG^1–**A**–OH) is converted into the corresponding acid chloride and then condensed with a suitably protected amino acid ester H–NR^4–**c1**–CO–OPG^2 in the presence of an auxiliary base (e.g. *i*-Pr_2NEt, Et_3N, pyridine, collidine) in solvents like CH_2Cl_2, $CHCl_3$, THF to afford PG^1–**A**–NR^4–**c1**–CO–OPG^2. Alternatively this product can be obtained by amide coupling of an acyloxy or acylmercapto aryl/heteroaryl carboxylic acid (PG^1–**A**–OH) with an amino acid ester H–NR^4–**c1**–CO–OPG^2 in the presence of a coupling reagent (e.g. benzotriazole derivatives like HBTU, HCTU, PyBOP; their aza analogs like HATU; or carbodiimides like EDC). Hydroxyaryl or heteroaryl carboxylic acids H–**A**–OH do not necessarily require protection of the phenolic OH-group and can directly be coupled with the H–NR^4–**c1**–CO–OPG^2 to the free phenol derivative H–**A**–NR^4–**c1**–CO–OPG^2 in the presence of a coupling reagent.

Deprotection of aromatic hydroxy or mercapto groups (step b1)

Deacylation of PG^1–**A**–NR^4–**c1**–CO–OPG^2 to the corresponding free hydroxyl or mercapto aryl/heteroaryl amide H–**A**–NR^4–**c1**–CO–OPG^2 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, a2)

Alkylation of the phenol or thiophenol H–**A**–M–**c1**–CO–OPG^2 with a suitably *N*-protected amino alcohol PG^3–**B**–OH to the ether or thioether PG^3–**B**–**A**–M–**c1**–CO–OPG^2 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, CH_2Cl_2, $CHCl_3$ or THF at 0°C to room temperature. As a variation, the reaction is induced with CMBP in toluene at temperatures of 20-110°C.

In an alternative approach, the alcohol PG^3–**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 H–**A**–M–**c1**–CO–OPG^2 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 PG^3–**B**–**A**–M–**c1**–CO–OPG^2.

Cleavage of the main chain protective groups (steps d1, h1, l1)

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. $Pd(PPh_3)_4$) in the presence of 1,3-dimethyl barbituric acid in solvents like CH_2Cl_2 or EtOAc or mixtures thereof.

N-Reprotection (steps f1, j1, l1)

N-Reprotection is achieved by applying standard amino acid protection protocols with chloroformates or *N*-hydroxy-succinimidyl carbonates in solvents like dioxane, and if required in the presence of a base such as aqueous Na_2CO_3.

Macrolactamization (steps e1, i1, o1)

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*-Pr_2NEt) 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; or 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).

SW-4: Synthesis workflow for the preparation of side-chain protected macrocycles Ia/Ib by ring-closing metathesis in solution

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. RCM of the examples was accomplished either between subunits of Bridge **C** or between Template **A** and Bridge **C**:

(i) RCM between subunits of Bridge **C**

a4) Coupling of an optionally substituted alkenyl amine building block $H\text{-}NR^4\text{-}\mathbf{c1}\text{-}CR^{12}=CH_2$ with the carboxylic acid

derivatives PG^1-**A**-OH or H-**A**-OH to afford PG^1-**A**-NR^4-**c1**-$CR^{12}=CH_2$ or H-**A**-NR^4-**c1**-$CR^{12}=CH_2$;

b4) If required release of the aryl/heteroaryl hydroxyl or mercapto group;

c4) *N*-acylation of the aminoalcohol H-**B**-OH with an optionally substituted alkenyl carboxylic acid as second **C**-subunit to afford the amido alcohol $H_2C=CR^{13}$-**c2**-CO-**B**-OH;

d4) Arylether or arylthioether formation to the cyclization precursor $H_2C=CR^{13}$-**c2**-CO-**B**-**A**-NR^4-**c1**-$CR^{12}=CH_2$;

e4) Ring-closing metathesis to *cyclo*(CR^{13}-**c2**-CO-**B**-**A**-NR^4-**c1**-CR^{12}=) i.e. *cyclo*(**B**-**A**-NR^4-**c1**-$CR^{12}=CR^{13}$-**c2**-CO-).

(ii)RCM between Template **A** and Bridge **C**

a5) Identical to step c4 as described above;

b5) Arylether formation with an alkenyl-substituted phenol H-**A**-CH_2 to the cyclization precursor $H_2C=CR^{12}$-**c1**-CO-**B**-**A**-CH_2;

c5) Ring-closing metathesis to *cyclo*(**B**-**A**-CR^{12}-**c1**-CO-).

Optionally the olefinic double bonds of the macrocycles obtained in step e4 or step c5 can be hydrogenated to the *cyclo*(**B**-**A**-NR^4-**c1**-CHR^{12}-CHR^{13}-**c2**-CO-) or *cyclo*(**B**-**A**-CHR^{12}-**c1**-CO-).

In analogy to SW-1(ii)/(iii) it is also feasible to prepare olefinic macrocycles with extended Bridges **C** such as *cyclo*(**B**-**A**-NR^4-**c1**-$CR^{12}=CR^{13}$-**c2**-W-**c3**-CO-), *cyclo*(**B**-**A**=CR^{12}-**c1**-V-**c2**-CO-) or *cyclo*(**B**-**A**=CR^{12}-**c1**-V-**c2**-W-**c3**-CO-) and subsequently the respective hydrogenated analogs.

General procedures for synthetic steps utilized in SW-4

Apart from the RCM all steps are conducted in analogy to the transformations described for SW-1 to SW-3.

Ring-closing metathesis (steps e4 and c5)

The ring-closing metathesis is conveniently performed in solvents like CH_2Cl_2 or toluene at temperatures of 20-100°C in the presence of indenylidene-ruthenium complexes such as di-

chloro-(3-phenyl-1*H*-inden-1-ylidene)bis(tricyclohexyl-phosphine)-ruthenium(II); [1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]-dichloro-(3-phenyl-1*H*-inden-1-ylidene(tricyclohexylphosphine)-ruthenium(II); or [1,3-bis(2,4,6-trimethylphenyl)-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).

SW-5: Synthesis workflow for derivatizations of attachment points in solution

The macrocyclic compounds obtained according to SW-1 to SW-4 can be further modified by transformations involving attachment points 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-hetero-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:

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.

General procedures for synthetic steps utilized in SW-5

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. Koncienski, *Protecting Groups*, 3rd ed., Georg Thieme Verlag **2005**).

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 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 Pd catalyst (e.g. Buchwald couplings).

(ii) Carboxyl group derivatizations like

- Amidation with amines in the presence of a coupling reagent;
- Esterification with alcohols.

(iii) Alcoholic hydroxyl group derivatizations as

- Alkylation to alkyl ethers with alkyl halides or alkylsulfonates;
- 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;
- 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 or Negishi coupling reactions etc.

SW-6: Synthesis workflow for derivatizations of attachment points on solid phase

As an alternative to SW-5, macrocyclic compounds **Ia/Ib** 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 by:

a7) Attachment of the macrocyclic amine to an appropriately functionalized solid support by reductive amination;

b7) Acylation, carbamoylation, oxycarbonylation or sulfonylation of the secondary amine functionality generated in the previous step a7;

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;

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;

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.

General procedures for synthetic steps utilized in SW-6

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^{R}), or of polyacrylamide (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**). 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 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 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 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-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-methoxy-phenoxy)butyryl NovaGel; a PEG PS resin).

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

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

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 methanol, or $NaBH(OAc)_3$ 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 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-5) are applied for their deprotection and derivatization.

Release from the resin (step f7)

The final products are detached from the solid support by acids dissolved in organic solvents and/or H_2O. The use of TFA in dichloromethane, of TFA in dichloromethane in the presence of a scavenger such as H_2O or dimethyl sulfide, or of TFA/H_2O and

TFA/H_2O/dimethylsulfide has been described (cf. references cited for the functionalized solid support).

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.

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.

SW-7: Synthesis workflow for the preparation of side-chain protected macrocycles Ia/Ib on solid support

Macrocyclic compounds of general formula **Ia/Ib** with highly variable side chain motifs in Bridge **C** can advantageously be prepared in a parallel array synthesis on solid support with an appropriately protected precursor comprising building blocks **A** and **B** as starting material. After its immobilization the precursor is coupled with one to three subunits of Bridge **C** and macrocyclizd to the product which is finally cleaved from the resin:

a9) Condensation (cf. SW-2) of a suitable hydroxy or mercapto aryl/heteroaryl carboxylic acid ester H–**A**–OPG^4 with an appropriately *N*-protected amino alcohol PG^3–**B**–OH, which is substituted with an orthogonally protected primary amino group;

b9) Removal of the protective group from the primary amine;

c9) Attachment to the solid support in a reductive alkylation step (cf. SW-6, a7) providing the polymer-supported PG^3–**B**–**A**–OPG^4 carrying a free secondary side chain amino group;

d9) Acylation, carbamoylation, oxycarbonylation or sulfonylation of the secondary amine (cf. SW-6, b7);

e9) Cleavage of the "main chain" amine protecting group to H–**B**–**A**–OPG^4 which is then condensed with either (i) one **C**-subunit or (ii) two **C**-subunits:

(i) Synthesis of a macrocycle **Ia/Ib** with a Bridge **C** consisting of two subunits

f9) Coupling of H–**B**–**A**–OPG^4 with an appropriately protected **C**-subunit PG^5–NR^4–**c2**–CO–OH to PG^5–NR^4–**c2**–CO–**B**–**A**–OPG^4;

g9) Cleavage of the main chain acid protective group PG^4 affording PG^5–NR^4–**c2**–CO–**B**–**A**–OH;

h9) Coupling of PG^5–NR^4–**c2**–CO–**B**–**A**–OH with a suitably protected **C**-subunit H–NR^4–**c1**–CO–OPG^2 to PG^5–NR^4–**c2**–CO–**B**–**A**–NR^4–**c1**–CO–OPG^2;

i9) Removal of the carboxylic acid protective group PG^2;

j9) Removal of the amine protective group PG^5;

k9) Macrolactamization of the linear cyclization precursor on solid support to afford *cyclo*(**B**–**A**–M–**c1**–V–**c2**–CO–) wherein M is NR^4 and V is CONR^4;

l9) Detachment of the final product.

(ii) Synthesis of a macrocycle **I** with a Bridge **C** consisting of three subunits

f10) Coupling of H–**B**–**A**–OPG^4 with an appropriately protected **C**-subunit PG^5–NR^4–**c3**–CO–OH to PG^5–NR^4–**c3**–CO–**B**–**A**–OPG^4;

g10) Removal of the amine protective group PG^5;

h10) Coupling with the second **C**-subunit PG^5–NR^4–**c2**–CO–OH to PG^5–NR^4–**c2**–CO–NR^4–**c3**–CO–**B**–**A**–OPG^4;

i10) Cleavage of the main chain acid protective group PG^4;

j10) Coupling with the suitably protected third **C**-subunit H–NR^4–**c1**–CO–OPG^2 to PG^5–NR^4–**c2**–CO–NR^4–**c3**–CO–**B**–**A**–NR^4–**c1**–CO–OPG^2;

k10) Removal of the carboxylic acid protective group PG^2;

l10) Removal of the amine protective group PG^5;

m10) Macrolactamization of the linear cyclization precursor on solid support to afford *cyclo*(**B**–**A**–M–**c1**–V–**c2**–W–**c3**–CO–) wherein M is NR^4 and both V and W are CONR^4;

n10) Detachment of the final product.

Related examples for macrocyclizations (step k9 or m10) on solid support are published by C. Cabrele et al., *J. Org. Chem.* **1999**, *64*, 4353-4361.

In an alternative approach an equivalent of the product of step d9 can be obtained by reductive alkylation of the product from step b9 with a bifunctional linker such as (4-(4-formyl-3,5-dimethoxy)phenoxy)butyric acid in solution, subsequent derivatization of the resulting secondary amine and coupling to a suitable polymeric support such as aminomethyl polystyrene.

In another variation solid phase chemistry and solution chemistry can be combined. In some instances it proved advantageous to synthesize the linear cyclization precursor on solid support (product of steps j9 or l10), then to release it and to conduct the macrolactamization in solution with soluble coupling reagents as described above (cf. SW-1) or with polymer-supported coupling reagents such as *N*-cyclohexyl-carbodiimide-*N'*-methylpolystyrene or *N*-alkyl-2-chloro pyridinium triflate resin (S. Crosignani et al, *Org. Lett.* **2004**, *6*, 4579-4582).

Further viable alternatives for the synthesis of macrocycles **Ia/Ib** on solid support could involve

- Macrolactamization in other positions, e.g. between the Modulator **B** and Bridge **C** corresponding to an adaptation of SW-1 to solid phase chemistry; or
- Alternative macrocyclizations modes, e.g. similar to the RCM route of SW-4.

Properties and usefulness

The macrocycles of type **Ia/Ib** of the present invention interact with specific biological targets. In particular, they show agonistic or antagonistic activity on the motilin receptor (MR receptor), on the serotonin receptor of subtype 5-HT_{2B} (5-HT_{2B} receptor), on the prostaglandin F2α receptor (FP receptor), on the purinoreceptor $P2Y_1$, on the voltage-gated potassium channel $K_v1.3$, or on the canonical (β-catenin-dependent) Wnt pathway. Accordingly, these compounds are useful for the treatment of motility disorders of the gastrointestinal tract such as functional dyspepsia, diabetic gastroparesis or constipation type irritable bowl syndrome; of CNS related diseases like migraine, schizophrenia, psychosis, depression or Alzheimer disease; of ocular hypertension such as associated with glaucoma and of preterm labour; of CNS inflammatory disorders like multiple sclerosis; of thromboembolic disorders; of cell proliferation disorders, especially various cancer types; or of bone and cartilage-related disorders.

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

When used to treat or prevent the diseases mentioned above the macrocycles can be administered singly, as mixtures of several macrocycles, or in combination with other pharmaceutically active agents. The macrocycles can be administered per se or as pharmaceutical compositions.

Pharmaceutical compositions comprising macrocycles of the invention may be manufactured by means of conventional mixing, dissolving, granulating, coated tablet-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes. Pharmaceutical compositions may be formulated in

conventional manner using one or more physiologically acceptable carriers, diluents, excipients or auxiliaries which facilitate processing of the active macrocycles into preparations which can be used pharmaceutically. Proper formulation depends upon the method of administration chosen.

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

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

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

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

For oral administration, the compounds can be readily formulated per se or by combining the active macrocycles of the invention with pharmaceutically acceptable carriers well known in the art. Such carriers enable the macrocycles of type **Ia/Ib** to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions etc., for oral ingestion by a patient to be treated. For oral formulations such as, for example, powders, capsules and tablets, suitable excipients include fillers such as sugars, (e.g. lactose, sucrose, mannitol or sorbitol) or such as cellulose preparations (e.g. maize starch, wheat starch, rice starch, potato starch,

gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl cellulose, sodium carboxymethylcellulose); and/or granulating agents; and/or binding agents such as polyvinylpyrrolidone (PVP). If desired, desintegrating agents may be added, such as cross-linked polyvinylpyrrolidones, agar, or alginic acid or a salt thereof, such as sodium alginate. Solid dosage forms may be sugar-coated or enteric-coated using standard techniques.

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

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

For administration by inhalation, the macrocycles of the invention are conveniently delivered in form of an aerosol spray from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g. hydrofluoroalkanes (HFA) such as HFA 134a (1,1,1,2,-tetrafluoroethane); carbon dioxide or another suitable gas. In the case of a pressurized aerosol the dose unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the macrocycles of the invention and a suitable powder base such as lactose or starch.

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

In addition to the formulations described 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 **Ia/Ib** 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.

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 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 procedures in cell cultures or experimental animals, e.g., by determining the LD_{50} (the dose lethal to 50% of the population) or the LD_{100} (the dose lethal to 100% of the population). The dose ratio between toxic and therapeutic effect is the therapeutic index. Compounds which exhibit high therapeutic indices are preferred. The data obtained from cell culture assays and animal studies can be used in formulating a dosage range that is not toxic for use in humans. The dosage of the macrocycles of the invention lies preferably within a range

of circulating concentrations that include the effective dose with little or no toxicity. The dosage may vary within the range depending upon the dosage form and the route of administration. The exact formulation, route of administration and dose can be chosen by the individual physician in view of the patient's condition (cf. E. Fingl et al. 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 **Ia/Ib**, except that one or more atoms are replaced by an atom having an atomic mass number or mass different from the atomic mass number or mass usually found in nature, e.g. compounds enriched in ^{2}H (D), ^{3}H, ^{11}C, ^{14}C, ^{125}I etc. These isotopic analogs and their pharmaceutical salts and formulations are considered useful agents in 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.

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

DIC: *N,N'*-diisopropylcarbodiimide

DMF: dimethylformamide

DMSO: dimethyl sulfoxide

DPPA: diphenyl phosphoryl azide

DVB: divinylbenzene

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

equiv.: equivalent

Et: ethyl

Et_3N: triethylamine

Et_2O: diethyl ether

EtOAc: ethyl acetate

FC: flash chromatography

FDPP: pentafluorophenyl diphenylphosphinate

Fmoc: 9-fluorenylmethoxycarbonyl

FmocOSu: 9-fluorenylmethoxycarbonyl-N-hydroxysuccinimide

h: hour(s)

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

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

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

HL: high loading

HOAt: 1-hydroxy-7-azabenzotriazole

$HOBt.H_2O$: 1-hydroxybenzotriazole hydrate

HMPA: hexamethylphosphoramide

i.v.: in vacuo

m: multiplet (spectral)

MeCN: acetonitrile

MeOH: methanol

Me: methyl

NMP: 1-methyl-2-pyrrolidinone

NS: 4-nitrobenzenesulfonyl

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

PEG PS resin: polyethyleneglycol coated polystyrene resin

PG: protective group

Ph: phenyl

PPh_3: triphenylphosphine

prep.: preparative

i-Pr: isopropyl

i-Pr_2NEt: *N*-ethyl-*N,N*-diisopropylamine

PyBOP: (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate

PyBroP: Bromotripyrrolidinophosphonium hexafluorophosphate

q: quartet (spectral)

quant.: quantitative

rt: *room temperature*

sat.: saturated

soln: solution

t: triplet (spectral)

TBAF: tetrabutylammonium fluoride

Teoc: 2-(trimethylsilyl)ethoxycarbonyl

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

TFA: trifluoroacetic acid

THF: tetrahydrofuran

tlc: thin layer chromatography

TMAD: tetramethylazodicarboxamide

T3P: propanphosphonic acid cyclic anhydride

p-TsOH: p-toluenesulfonic acid

General Methods

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

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

I. Analytical HPLC-MS and HPLC methods:

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

UV wave length 220 nm, 254 nm

MS: Electrospray Ionization

Volume of injection: 5 µL

Method 1a and 1b

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

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

Column oven temperature: 45°C

Gradient:

Time [min.]	Flow [µl/min]	%A	%B
0	500	97	3
0.1	500	97	3
3	500	3	97
3.6	500	3	97
3.7	500	97	3
4.3	500	97	3

MS scan range: 100 - 800 Da; centroid mode (**Method 1a**)

300 - 2000 Da; centroid mode (**Method 1b**)

scan time: 1 sec

Method 2

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

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

Column oven temperature: 45°C

Gradient:

Time [min.]	Flow [µl/min]	%A	%B
0	800	97	3
0.1	800	97	3
2.2	800	3	97
2.5	800	3	97
2.55	1000	97	3
2.75	1000	97	3
2.8	800	97	3

MS scan range: 100 - 2000 Da; centroid mode

scan time: 1 sec

Method 3: cf. Method 2;

Mobile Phases: A: 1 mM ammonium bicarbonate pH 10; B: MeCN

Method 4a-4b

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

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

Column oven temperature: 45°C

Gradient:

Time [min.]	Flow [µl/min]	%A	%B
0	800	97	3
0.1	800	97	3
2.7	800	3	97
3	800	3	97
3.05	1000	97	3
3.25	1000	97	3
3.3	800	97	3

MS scan range: 100 - 2000 Da; centroid mode (**Method 4a**)
350 - 2000 Da; profile mode (**Method 4b**)

scan time: 1 sec

Method 5a-5b: cf. Method 4a-4b;

Mobile Phases: A: 1 mM ammonium bicarbonate pH 10; B: MeCN

Method 6-7:

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

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

Column oven temperature: 55°C

Gradient:

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

MS scan range: 100 - 1650 Da; centroid mode (**Method 6**)
100 - 1650 Da; profile mode (**Method 7**)

scan time: 0.5 sec

Method 8: cf. Method 7;

Mobile Phases: A: 1 mM ammonium bicarbonate pH 10; B: MeCN

Method 9a-9c:

Column: Acquity UPLC BEH C18 1.7 µm, 2.1x100 mm (cod. 186002350 - Waters AG)

Mobile Phases: A: 0.1% TFA in Water/MeCN 95/5 (v/v); B: 0.085% TFA in MeCN

Column oven temperature: 55°C

Gradient:

Time [min.]	Flow [µl/min]	%A	%B
0	700	99	1
0.2	700	99	1
2.5	700	3	97
2.85	700	3	97
2.86	700	99	1
3.20	700	99	1

MS scan range: 100 - 800 Da; profile mode (**Method 9a**)

100 - 1200 Da; profile mode (**Method 9b**)

200 - 1400 Da; profile mode (**Method 9c**)

scan time: 1 sec

Method 10a-10d:

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

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

Gradient:

Time [min]	Flow [µl/min]	%A	%B
0	1300	97	3
0.5	1300	97	3
2.95	1300	3	97
3.15	1300	3	97
3.17	1300	97	3
3.2	1300	97	3

MS scan range:

95 - 1800 Da; centroid mode; Voltage: 40 V (Method **10a**)

95 - 1800 Da; profile mode; Voltage: 40 V (Method **10b**)

95 - 1800 Da; centroid mode; Voltage: 20 V (Method **10c**)

95 - 1800 Da; centroid mode; Voltage: 80 V (Method **10d**)

Methods 11a-11c: cf. Methods 10a-10c;

Mobile Phases: A: 1 mM ammonium bicarbonate pH 10; B: MeCN

Method 12:

Column: AtlantisT3 3 µm, 2x50 mm (Waters AG)

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

Gradient:

Time [min]	**Flow [µl/min]**	**%A**	**%B**
0	800	97	3
0.1	800	97	3
2.9	800	3	97
3.2	800	3	97
3.22	800	97	3
3.3	800	97	3

MS scan range: 90 - 800 Da; centroid mode; Voltage: 40 V

Method 13:

Column: Ascentis Express C18 2.1 µm, 3x50 mm (Supelco Inc.)

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

Gradient:

Time [min]	**Flow [µl/min]**	**%A**	**%B**
0	1400	97	3
0.5	1400	97	3
1.95	1400	3	97
2.15	1400	3	97
2.18	1400	97	3
2.3	1400	97	3

MS scan range: 100 - 1650 Da; centroid mode; Voltage: 40 V

General **Analytical HPLC** (x% CH_3CN):

R_t in min (purity at 220 nm in %)

Column: Develosil RPAq 5 µM, 4.6 x 50 mm (Phenomenex Inc.)

Flow rate: 1.5 ml/min

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

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

5.0-6.2 min (100% CH_3CN)

Details: see individual experiment below.

II. Preparative HPLC methods:

1. Reverse Phase *- Acidic conditions*

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

Mobile phases:

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

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

2. Reverse Phase *- Basic conditions*

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

Mobile phases:

A: 10 mM Ammonium Bicarbonate pH 10/Acetonitrile 95/5 v/v

B: Acetonitrile

3. Normal Phase

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

Mobile phases: ***A***: Hexane

B: Ethylacetate

C: Methanol

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

Specific Examples

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. Koncienski, *Protecting Groups*, 3rd ed., Georg Thieme Verlag **2005**; and M. Goodman (ed.), *Methods of Organic Chemistry (Houben-Weyl)*, Vol E22a, Synthesis of Peptides and Peptidomimetics, Georg Thieme Verlag **2004**.

Starting materials

Template A building blocks (Scheme 1):

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

3-Acetoxybenzoic acid (**3**) and 4-acetoxybenzoic acid (**4**) are commercially available.

5-Hydroxy nicotinic acid (**5**) is commercially available; its conversion into **6** is described below.

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

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

3-Mercaptobenzoic acid (**11**) is commercially available; for its conversion into **12** see below.

Ethyl 3-hydroxybenzoate (**142**) and 3-mercaptophenol (**143**) are commercially available.

3-Hydroxythiophene-2-carboxylic acid (**144**) is commercially available; for its conversion into **145** see below.

5-Hydroxy-1,2-dimethyl-1-*H*-indole-3-carboxylic acid (**146**) is commercially available; its conversion into **147** is shown below.

3-Methoxybenzyl bromide (**148**) is commercially available; for conversion into **149** see below.

Methyl 5-bromosalicyclic acid (**151**) was prepared according to the method of T. Esumi et al. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2621-2625.

Modulator B building blocks (Scheme 2)

Commercially available are:

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

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

(*S*)-tert-Butyl 3-(hydroxymethyl)piperazine-1-carboxylate hydrochloride (**21**·HCl); and

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

(2*S*,4*S*)-Allyl 2-(hydroxymethyl)-4-((2-(trimethylsilyl)ethoxy)-carbonylamino)pyrrolidine-1-carboxylate (**16**) was prepared from amino alcohol **13** in three steps by 1) alloc protection of the secondary amino group with allyloxycarbonyl-N-hydroxy-succinimide (AllocOSu) in CH_2Cl_2, 2) cleavage of the Boc group with dioxane-HCl, and 3) Teoc protection of the primary amino group with 2-(trimethylsilyl)ethyl 4-nitrophenyl carbonate (Teoc-ONp) in CH_2Cl_2 in the presence of Et_3N) applying standard conditions.

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

(2*S*,4*R*)-Allyl 2-(hydroxymethyl)-4-((2-(trimethylsilyl)ethoxy)-carbonylamino)pyrrolidine-1-carboxylate (**20**) was prepared from

amino alcohol hydrochloride **17**·HCl, applying the same transformations as described for **16** with the exception of the Alloc protection step which was performed with allyl chloroformate in CH_2Cl_2 in the presence of aq. $NaHCO_3$ soln.

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

(*S*)-1-Allyl 4-tert-butyl 2-(hydroxymethyl)piperazine-1,4-dicarboxylate (**22**) was prepared from amino alcohol hydrochloride **21**·HCl, applying allyl chloroformate in CH_2Cl_2 in the presence of aq. $NaHCO_3$ soln.

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

(2*S*,4*R*)-2-(Trimethylsilyl)ethyl 4-(tert-butoxycarbonylamino)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (**152**)

152 was obtained by Teoc protection of the secondary amino group of **17** with 2-(trimethylsilyl)ethyl 4-nitrophenyl carbonate (Teoc-ONp) in CH_2Cl_2 in the presence of Et_3N applying standard conditions.

Data of **152**: $C_{16}H_{32}N_2O_5Si$ (360.5). ^{1}H-NMR (DMSO-d_6): 7.03 (br. s, 1 H), 4.71 (m, 1 H), 4.07-4.01 (m, 3 H), 3.76 (m, 1 H), 3.45-3.35 (br. m, 3 H), 3.11 (m, 1 H), 2.00 (m, 1 H), 1.75 (m, 1 H), 1.36 (s, 9 H), 0.91 (t, J = 7.8, 2 H), 0.00 (s, 9 H).

(2*S*,4*S*)-Allyl 2-(hydroxymethyl)-4-phenoxypyrrolidine-1-carboxylate (**156**)

BH_3-$S(CH_3)_2$ (5.47 mL, 57.7 mmol) was added to a soln of (2*S*,4*S*)-1-(tert-butoxycarbonyl)-4-phenoxypyrrolidine-2-carboxylic acid

(**153**, 8.87 g, 28.9 mmol) in THF (170 mL). The mixture was heated to 50°C for 2 h, cooled to 0°C and treated with H_2O (100 mL), followed by an aqueous workup (CH_2Cl_2, H_2O; Na_2SO_4). FC (hexane/EtOAc) afforded **154** (8.46 g, quant. yield).

Cleavage of the Boc protective group with HCl-dioxane and introduction of the alloc protective group with allyl chloroformate in CH_2Cl_2 in the presence of sat. aq. $NaHCO_3$ soln afforded **156**.

Data of **156**: $C_{15}H_{19}NO_4$ (277.3). LC-MS (method 4a): R_t = 1.89 (91), 278 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 7.30 (t, J = 7.9, 2 H), 6.97-6.91 (m, 3 H), 5.93 (m, 1 H), 5.29 (br. d, J = 17.5, 1 H), 5.19 (br. d, J = 10.5, 1 H), 5.01 (br. m, 1 H), 4.75 (br. m, 1 H), 4.53 (br. m, 2 H), 3.86 (br. m, 1 H), 3.78 (dd, J = 5.2, 12.1, 1 H), 3.67 (br. m, 1 H), 3.39-3.30 (br. m, 2 H), 2.24 (br. m, 2 H).

(2*S*,4*S*)-Allyl 4-(4-bromobenzyloxy)-2-(hydroxymethyl) pyrrolidine-1-carboxylate (**161**)

To a suspension of NaH (dispersion, 60% in oil; 3.8 g; 95 mmol) in dry THF (53 mL) was slowly added at 0°C a soln of (2*S*,4*S*)-1-(tert-butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid (**157**; 10.0 g, 43 mmol) in THF (83 mL). The mixture was stirred for 15 min, followed by the addition of NaI (7.8 g, 52 mmol). 4-Bromobenzyl bromide (13 g, 52 mmol) in THF (32 mL) was slowly added and the mixture was stirred at rt for 15 h. The mixture was distributed between EtOAc and 0.2 M aq. HCl soln. The organic layer was separated, dried (Na_2SO_4), concentrated and purified by FC (hexane/EtOAc/MeOH gradient) to give **158** (17.3 g, 99%). The acid **158** was reduced with BH_3-$S(CH_3)_2$ in THF, applying the procedure described for the synthesis of **154**.

Cleavage of the Boc protective group with HCl-dioxane and introduction of the alloc protective group with allyl chloroformate in CH_2Cl_2 in the presence of sat. aq. $NaHCO_3$ soln applying standard conditions afforded **161**.

Data of **161**: $C_{16}H_{20}BrNO_4$ (370.2). LC-MS (method 10a): R_t = 2.05 (94), 370/372 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 7.55 (d, J = 8.4, 2

H), 7.28 (d, J = 8.4, 2 H), 5.92 (m, 1 H), 5.28 (br. d, J ca. 17.2, 1 H), 5.18 (br. qd, J ca. 1.5, 10.5, 1 H), 4.73 (q-like m, 1 H), 4.58-4.42 (m, 4 H), 4.12 (br. m, 1 H), 3.78 (br. m, 1 H), 3.61-3.55 (m, 2 H), 3.43-3.29 (m, 2 H), 2.19 (m, 1 H), 2.03 (m, 1 H).

(2*S*,4*S*)-Allyl 4-benzyl-2-(hydroxymethyl)pyrrolidine-1-carboxylate (**165**) was prepared from (2*S*,4*S*)-4-benzyl-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (**162**) applying conditions as described for the synthesis of **156**.

Data of **165**: $C_{16}H_{21}NO_3$ (275.3). LC-MS (method 10a): R_t = 1.93 (91), 276 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 7.29 (t, J = 7.3, 2 H), 7.21 (d, J = 7.4, 3 H), 5.90 (m, 1 H), 5.24 (br. d, J ca. 16.8, 1 H), 5.16 (dd, J = 1.2, 10.5, 1 H), 4.69 (br. s, 1 H), 4.47 (br. s, 2 H), 3.71 (br. m, 1 H), 3.59-3.53 (m, 3 H), 2.85 (m, 1 H), 2.65 (d, J = 7.2, 2 H); 2.27 (m, 1 H), 2.03 (m, 1 H), 1.57 (m, 1 H).

(2S,4R)-tert-butyl 2-(hydroxymethyl)-4-((2-(trimethylsilyl)-ethoxy)carbonylamino)pyrrolidine-1-carboxylate (**167**) was obtained from the protected amino alcohol **20** by cleavage of the alloc group ($Pd(PPh_3)_4$, pyrrolidine in CH_2Cl_2/EtOAc) and introduction of a Boc group (Boc_2O, CH_2Cl_2, 1 M aq. NaOH).

Data of **167**: $C_{16}H_{32}NO_5Si$ (360.5). FI-MS: 361 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 7.21 (d, J = 6.9, 1 H), 4.72 (br. m, 1 H), 4.15-3.98 (m, 3 H), 3.75 (br. m, 1 H), 3.40-3.31 (m, 3 H), 3.06 (dd, J = 6.6, 10.6, 1 H), 2.05 (br. m, 1 H), 1.78 (br. m, 1 H), 1.36 (s, 9 H), 0.89 (t, J = 8.3, 2 H), 0.00 (s, 9 H).

Building blocks for subunits of Bridge C (Scheme 3):

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

A mixture of Boc-L-Glu(OAll)-OH (**23**; 33 g, 115 mmol) and $NaHCO_3$ (27 g, 322 mmol) in DMF (500 mL) was stirred for 1 h at rt followed by slow addition of benzyl bromide (35 mL, 299 mmol)

in DMF (15 mL). Stirring was continued for 16 h followed by aqueous workup (Et_2O, sat. aq. $NaHCO_3$ soln, sat aq. NaCl soln) and purification by FC (CH_2Cl_2/MeOH 100:0 to 98:2) to give the corresponding benzyl ester (34.4 g, 79%), which was dissolved in dioxane (40 mL) and treated with 4M HCl-dioxane (400 mL) for 1 h. The volatiles were evaporated. The residue was crystallized from Et_2O to afford **24**·HCl (23.8 g, 83%).

4-Nitrobenzenesulfonyl chloride (39 g, 178 mmol) was added at 0°C to a soln of **24**·HCl (46.5 g, 148 mmol) and pyridine (42 mL, 519 mmol) in CH_2Cl_2 (700 mL). The mixture was stirred for 15 h followed by aqueous workup (CH_2Cl_2, 1 M aq. HCl soln) and purification of the crude by FC (hexane/EtOAc 80:20 to 75:25) to yield **25** (55.54 g, 81%).

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

A soln of **26** (17.4 g, 37 mmol) in dry, degassed CH_3CN (270 mL) was treated with thiophenol (6.7 mL, 66 mmol) and Cs_2CO_3 (39 g, 121 mmol) at rt for 16 h. The mixture was filtered and the residue was washed with Et_2O. The filtrate was carefully concentrated (bath temperature 20°C) and immediately purified by FC (hexane/EtOAc 80:20 to 50:50). The combined product fractions were carefully concentrated, immediately treated with 4M HCl-dioxane (20 mL) for 5 min and concentrated to give **27**·HCl (8.62 g, 72%).

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

(*R*)-5-Allyl 1-benzyl 2-(methylamino)pentanedioate hydrochloride (**29**·HCl) was prepared from Boc-D-Glu(OAll)OH (**28**) applying the

methods described above for the synthesis of the enantiomer (**27**·HCl).

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

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

Cbz-L-Ser-OH (**30**) was converted into amino acid **31** by β-lactone formation and opening with $HNCH_3Si(CH_3)_3$ (J. Kim et al., *Inorg. Chem.* **1998**, *37*, 3835-3841), following literature procedures (J.K. Kretsinger, J.P. Schneider, *J. Am. Chem. Soc.* **2003**, *125*, 7907-7913; E.S. Ratemi, J.C. Vederas, *Tetrahedron Lett.* **1994**, *35*, 7605-7608).

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

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

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

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

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

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

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

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

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

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

Cbz-L-Dab-OH (**37**) was converted into the allylester-pTsOH salt **38**·pTsOH (T.M. Kamenecka, S.J. Danishefsky, l.c.)

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

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

Data of **40**·HCl: $C_{16}H_{22}N_2O_4$·HCl (306.3, free base). Flow injection MS (ESI, positive modus): 307 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 8.97 (br. s, NH_2^+), 7.92 (d, J = 7.8, NH), 7.40-7.25 (m, 5 arom. H), 5.88 (m, 1 H), 5.32 (d, J = 17.2, 1 H), 5.22 (d, J = 10.5, 1 H), 5.05 (s, 2 H), 4.60 (d, J = 5.2, 2 H), 4.22 (m, 1 H), 2.94 (m, 2 H), 2.50 (s, 3 H, superimposed by DMSO-d signal), 2.10 (m, 1 H), 2.00 (m, 1 H).

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

Cbz-L-Orn-OH (**41**) was converted into the allylester-pTsOH salt **42**·pTsOH (T.M. Kamenecka and S.J. Danishefsky, l.c.).

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

The allyl ester group was then cleaved applying the conditions described for the treatment of **39**. The saponification of the resulting trifluoroacetamido acid was performed according to the procedure of Chu-Biao Xue et al. *J. Med. Chem.* **2001**, *44*, 2636-2660, with the exception that 2 equiv. of LiOH were used.

The resulting amino acid (3.80 g, containing LiCl ca. 9 mmol) was treated at rt with allyl alcohol (100 mL) and thionyl chloride (3.0 mL, 41 mmol). The mixture was heated for 2 h at 70°C. Stirring was continued at rt for 17 h. The volatiles were evaporated; and the resulting solid was washed with CH_2Cl_2 to afford **44**·HCl (3.62 g, ca. 75% w/w; yield 83%, used without further purification).

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

Sarcosine allyl ester (**46**) was prepared as p-TsOH salt (T.M. Kamenecka and S.J. Danishefsky, l.c.).

2-((Allyloxycarbonyl)(methyl)amino)acetic acid (**47**) and 3-((Allyloxycarbonyl)(methyl)amino)propanoic acid (**49**) were prepared according to the method of M. Mori et al., *Chem. Pharm. Bull.* **2000**, *48*, 716-728.

(*S*)-2-(Benzyloxycarbonylamino)pent-4-enoic acid (**51**) was prepared from (*S*)-allylglycine by *N*-protection (CBzOSu, dioxane, aq. Na_2CO_3) in analogy to the procedure of D.R. Ijzendoorn et al., *Org. Lett* **2006**, *8*, 239-242.

Methyl 1-aminocyclopentanecarboxylate hydrochloride (**169**·HCl) was obtained by treatment of 1-aminocyclopentanecarboxylic acid (**168**) with MeOH and $SOCl_2$ as described by L.V. Adriaenssens et al., *J. Org. Chem.* **2007**, *72*, 10287-10290, for the synthesis β-aminoacid methylesters hydrochlorides.

(*S*)-Methyl 3-amino-4-(naphthalen-2-yl)butanoate hydrochloride (**171**·HCl) was obtained by treatment of (*S*)-3-amino-4-(naphthalen-2-yl)butanoic acid hydrochloride (**170**·HCl) with MeOH and $SOCl_2$ (L.V. Adriaenssens et al., l.c.).

(*S*)-Benzyl 3-(2-(allyloxy)-2-oxoethoxy)-2-(methylamino)propanoate hydrochloride (**178**·HCl)

Boc-Ser-OH (**172**; 4.0 g, 19.5 mmol) was converted into the allyl ether **173** according to the procedure of M.P. Glenn et al. *J. Med. Chem.* **2002**, *45* (2), 371-381. The crude product **173** was converted into the benzyl ester **174** (4.95 g, 76% over the two steps) applying the procedure described for the synthesis of **24** with the exception that 1.7 equivalents of benzyl bromide were used and the volatiles were evaporated prior to aqueous workup. Ag_2O (9.64 g, 41.6 mmol), acetic acid (0.79 mL, 13.9 mmol) and methyliodide (17.3 mL, 277 mmol) were successively added to a soln of **174** (4.65 g, 13.9 mmol) in DMF (60 mL). The suspension was stirred for 24 h, filtered through a pad of celite and distributed between Et_2O and sat. aq. $NaHCO_3$ soln. The organic layer was separated, washed (H_2O, sat. aq. NaCl soln), dried (Na_2SO_4), filtered and concentrated. FC (hexane/acetone 100:0 to 90:10) yielded **175** (4.37 g used without further purification).

At rt, *N*-methylmorpholine-*N*-oxide (0.84 g, 7.2 mmol) and osmium tetroxide (2.5% w/w in tert butanol; 3.47 mL, 0.27 mmol) were added to a soln of **175** (1.93 g, ca. 4 mmol) in acetone (60 mL) and H_2O (15 mL). The mixture was stirred for 18 h. Celite (20 g) and $Na_2S_2O_3$ (5 g) were added and stirring was continued for 45 min. The mixture was filtered through celite. The residue was washed with acetone. The filtrate was concentrated and evaporated with toluene. FC (hexane/EtOAc 50:50 to 100:0) afforded **176** (1.3 g, 60%).

A soln of **176** (2.63 g, 6.86 mmol) in THF (50 mL) and H_2O (50 mL) was treated with $NaIO_4$ (2.93 g, 13.7 mmol) and stirred at rt for 1.5 h. The mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), filtered and concentrated. The product (2.45 g) thus obtained was dissolved in CH_2Cl_2 (25 mL). CH_3CN (25 mL) and H_2O (40 mL) were added. $NaIO_4$ (2.93 g, 13.7 mmol) and ruthenium(III)-chloride hydrate (77 mg, 0.34 mmol) were added. The mixture was vigorously stirred for 2 h and distributed between CH_2Cl_2 and H_2O. The organic layer was separated, washed (sat. aq. NaCl soln), dried (Na_2SO_4), filtered and concentrated. A soln of the product (2.29 g) in dry DMF (33 mL) was treated with $NaHCO_3$ (1.05 g, 12.5 mmol) and allyl bromide (1.05 mL, 12.5 mmol). The mixture was stirred for 3 d followed by an aqueous workup (Et_2O, H_2O, sat. aq. NaCl soln; Na_2SO_4) to afford **177** (2.37 g, 85%).

At -10°C, TFA (24 mL) was added to a soln of **177** (2.4 g, 5.9 mmol) in CH_2Cl_2 (24 mL). The soln was stirred for 1.5 h at this temperature, poured onto sat. aq. $NaHCO_3$ soln and extracted with CH_2Cl_2. The organic layer was separated, dried (Na_2SO_4), filtered and concentrated (bath temperature 30°C) to give 1.7 g of a light brown oil, which was dissolved in CH_2Cl_2 (20 mL) and treated with 4M HCl-dioxane (7.3 mL). The volatiles were evaporated to afford **178**·HCl (2.13 g, quant.).

Data of **178**·HCl: $C_{16}H_{21}NO_5$·HCl (307.3, free base). LC-MS (method 5a): R_t = 1.99 (86), 308 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 9.58 (br. s, NH_2^+), 7.46-7.33 (m, 5 H), 5.92 (m, 1 H), 5.32 (qd, J = 1.6, 17.2, 1 H), 5.28 (s, 2 H), 5.23 (qd, J = 1.4, 10.5, 1 H), 4.62

(d, J = 5.5, 2 H), 4.45 (t-like s, 1 H), 4.26 (s, 2 H), 4.18-4.04 (m, 2 H), 2.63 (s, 3 H).

(*S*)-Allyl 2-(benzyloxycarbonylamino)-6-(methylamino)hexanoate hydrochloride (**182**·HCl)

The amino ester **182**·HCl was prepared from Cbz-L-Lys-OH (**179**) applying the methods described for the synthesis of **44**·HCl.

An analytical sample of **182**·HCl was purified by prep. HPLC (method 1).

Data of **182**·HCl: $C_{18}H_{26}N_2O_4$·HCl (334.4, free base). LC-MS (method 10a): R_t = 1.39 (98), 335 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 8.34 (br. s, NH_2^+), 7.77 (d, J = 7.8, 1 H), 7.29 (m, 5 H), 5.90 (m, 1 H), 5.31 (dd, J = 1.6, 17.2, 1 H), 5.22 (dd, J = 1.4, 10.5, 1 H), 5.07 (d, J = 12.5, 1 H), 5.01 (d, J = 12.5, 1 H), 4.59 (d, J = 5.3, 2 H), 4.05 (m, 1 H), 2.94-2.73 (m, 2 H), 2.54 (s, 3 H), 1.75-1.30 (several m, 6 H).

(*S*)-Allyl 6-bromo-2-(tert-butoxycarbonylamino)hexanoate **(185)**

At 0°C, allyl bromide (3.9 mL, 45 mmol) was slowly added to a soln of Boc-L-6-hydroxynorleucine (**183**; 8.55 g, 34.6 mmol) and $NaHCO_3$ (7.26 g, 86.4 mmol) in DMF (120 mL). The mixture was stirred for 4 h at 0°C to rt, followed by the addition of more $NaHCO_3$ (7.26 g, 86.4 mmol) and allyl bromide (3.9 mL, 45 mmol). Stirring was continued for 18 h. The mixture was distributed between EtOAc and aq. NaCl soln. The organic phase was separated, washed (diluted aq. NaCl soln, H_2O, sat. aq. NaCl soln), dried (Na_2SO_4), filtered and concentrated. FC (hexane/EtOAc 2:1 to 1:2) afforded **184** (9.17 g, 92%).

The alcohol **184** was converted into the bromide **185** following the procedure described for the synthesis of (2*S*)-2[(benzyloxycarbonyl)amino]-6-bromohexanoic acid methyl ester (R. Bambal and R.P. Hanzlik, *J. Org. Chem.* **1994**, *59*, 729-732).

Data of **185**: $C_{14}H_{24}BrNO_4$ (350.2). LC-MS (method 10c): R_t = 2.30 (91), 352/350 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 7.29 (d, J = 7.8, 1 H), 5.89 (m, 1 H), 5.32 (dd, J = 1.6, 17.2, 1 H), 5.21 (dd, J = 1.3, 10.5, 1 H), 4.59-4.55 (m, 2 H), 3.94 (m, 1 H), 3.51 (t, J

= 6.6, 2 H), 1.83-1.57 (2 m, 4 H), 1.47-1.33 (m, 2 H), 1.38 (s, 9 H).

Synthesis of (*S*)-allyl 5-amino-2-hydroxypentanoate (**190**)

(2*S*)-2-amino-5-phthalimidopentanoic acid hydrochloride (**187**·HCl; 17.3 g, 65%) was obtained from L-ornithine hydrochloride (**186**·HCl; 15 g, 89 mmol) and *N*-carbethoxy-phthalimide (CEP; 19.5 g, 89 mmol; M.J. Bunegar et al., *Org. Process Res. Dev.* **1998**, *2*, 334-336); **187**·HCl was isolated by diluting the mixture with H_2O and 3 M aq. HCl soln until all precipitate was dissolved. The aq. soln was washed twice with EtOAc and concentrated to ca. 20% of its volume. A precipitate was formed which was collected, washed with cold H_2O and Et_2O and dried i.v.

H_2SO_4 (95%w/w; 3.4 mL, 60 mmol) was added at 0°C to a soln of **187**·HCl (4.5 g, 15 mmol) in H_2O (40 mL). The mixture was carefully warmed until all starting material was dissolved. $NaNO_2$ (4.2 g, 60 mmol) in H_2O (20 mL) was added at rt over 2 h. The mixture was stirred for 16 h. The precipitate formed was collected, washed with cold H_2O (10 mL) and dried i.v. to give **188** (3.37 g) which was used without further purification.

KOH (6.21 g, 111 mmol) was added to a soln of **188** (7.28 g, 28 mmol) in H_2O (100 mL). The mixture was stirred for 3 h at rt, acidified with 1 M aq. HCl soln to pH ca. 1 and heated to reflux for 1 h. The mixture was extracted with EtOAc. The aqueous phase was concentrated and dried i.v. to give crude **189** (11.5 g) which was dissolved in allyl alcohol (122 mL). $SOCl_2$ (8.07 mL, 111 mmol) was added at 0°C. The mixture was heated to 70°C for 2.5 h. The mixture was concentrated to afford **190**·HCl (13.17 g, ca. 80%; containing ca. 50% w/w KCl)

Data of **190**·HCl: $C_8H_{15}NO_3$·HCl (173.2, free base). FIA-MS: 174 ($[M+H]^+$). ^{1}H-NMR (D_2O): 5.89 (m, 1 H), 5.36-5.10 (m, 2 H), ca. 4.6 (m, 2 H, partially superimposed by HDO signal), 4.30 (m, 1 H), 2.94 (t-like m, 2 H), 1.88-1.63 (m, 4 H).

Synthesis of the A-C fragment H–**A**–M–**c1**–CO–OPG^2

Procedure A

A.1: Acid chloride formation

Oxalyl chloride (3.5-5.0 equiv.) was added to a mixture of the acetoxyaryl carboxylic acid (Ac–**A**–OH) and dry Et_2O or CH_2Cl_2. The resulting mixture was stirred at rt for 15 min followed by the addition of a few drops (ca 50-100 µL) of dry DMF. Stirring was continued for 16 h. The mixture was filtered. The filtrate was concentrated and the residue dried i.v. to afford the crude acetoxyaryl carboxylic acid chloride (Ac–**A**–Cl), which was immediately used in the next step.

A.2: Amide coupling

A mixture of the amino ester salt (H–NR^4–**c1**–CO–OAll·HX), the crude acetoxyaryl carboxylic acid chloride (Ac–**A**–Cl, 1.1-1.5 equiv.) and dry CH_2Cl_2 or THF was cooled to 0°C. An auxiliary base (*sym*-collidine or *i*-Pr_2NEt; 3.0 equiv.) was added dropwise. The mixture was stirred at rt for 16 h. The mixture was distributed between EtOAc and 1 M aq. HCl soln. The organic phase was washed (1 M aq. HCl soln, then sat. aq. $NaHCO_3$ soln or sat aq. NaCl soln), dried (Na_2SO_4), filtered and concentrated. FC (hexane/EtOAc gradients) gave the acetoxyaryl amide (Ac–**A**–NR^4–**c1**–CO–OAll).

A.3: Deacetylation

A soln of acetoxyarylamide (Ac–**A**–NR^4–**c1**–CO–OAll) in dry THF was treated at 0°C with 3-dimethylaminopropylamine (3.0-4.5 equiv.). The soln was stirred at rt for 1-5 h. The mixture was distributed between EtOAc and ice-cold 0.1 M or 1 M aq. HCl soln. The organic phase was washed (0.1 or 1 M aq. HCl soln, sat. aq. NaCl soln), dried (Na_2SO_4), filtered and concentrated to afford the hydroxyaryl amide (H–**A**–NR^4–**c1**–CO–OAll).

Synthesis of the linear cyclization precursor H–**B**–**A**–M–**c1**–CO–OH

Procedure B

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

A mixture of the hydroxyaryl amide (H–**A**–M–**c1**–CO–OAll; M = NR^4, CHR^6) and PPh_3 (1.5 equiv.) was dried i.v. for 15 min. Under argon a soln of alcohol (HO–**B**–Alloc, 1.2 equiv.) in dry benzene was added and the resulting soln was cooled to 0°C. A soln of DEAD (40% in toluene, 1.2 equiv.) in benzene was slowly added (by syringe pump). The mixture was stirred at rt for 18 h and concentrated. FC (hexane/EtOAc gradients) gave the protected amino acid Alloc–**B**–**A**–M–**c1**–CO–OAll used in the next step without further purification.

B.1.2: Mitsunobu aryl ether synthesis using CMBP

A soln of the hydroxyaryl amide (H–**A**–M–**c1**–CO–OAll; M= NR^4, CHR^6), the alcohol (HO–**B**–Alloc, 1.2-1.3 equiv.) and CMBP (2 equiv.) was heated in dry toluene at reflux for 1-4 h. The soln was concentrated. FC (hexane/EtOAc gradients) afforded the protected amino acid (Alloc–**B**–**A**–M–**c1**–CO–OAll).

B.2: Cleavage of the allyl/alloc protective groups

$Pd(PPh_3)_4$ (0.05-0.1 equiv.) was added to a mixture of the protected amino acid (Alloc–**B**–**A**–M–**c1**–CO–OAll) and 1,3-dimethylbarbituric acid (2.5 equiv.) in degassed EtOAc/CH_2Cl_2 (ca. 1:1). The resulting soln was stirred at rt for 1-3 h and concentrated. FC (EtOAc, CH_2Cl_2/EtOH, or CH_2Cl_2/MeOH gradients) afforded the free amino acid (H–**B**–**A**–M–**c1**–CO–OH).

Synthesis of the cyclization precursor H–**B**–**A**–M–**c1**–V–**c2**–CO–OH

Procedure C

C.1: Allyl carbamate formation

At 0°C allylchloroformate (1.1 equiv.) was slowly added to a mixture of amino acid (H–**B**–**A**–M–**c1**–CO–OH) and Na_2CO_3 (1.5-3 equiv.) in dioxane/H_2O 1:1. The mixture was stirred at rt for 15 h. The mixture was diluted with EtOAc and treated with 1 M

aq. HCl soln until pH ca. 2 was reached. The organic phase was separated, washed (sat. aq. NaCl soln), dried (Na_2SO_4), filtered, concentrated and dried i.v. to afford the alloc protected amino acid (Alloc-**B**-**A**-M-**c1**-CO-OH).

C.2: Amide coupling

i-Pr_2NEt (5.0 equiv.) was slowly added to a mixture of the alloc protected amino acid (Alloc-**B**-**A**-M-**c1**-CO-OH), the amino acid ester salt (H-NR^4-**c2**-CO-OAll·p-TsOH, 1.2 equiv.), HOAt (1.5 equiv.) and HATU (1.5 equiv.) in DMF. The mixture was stirred at rt for 20 h followed by distribution between EtOAc and ice-cold 0.5 M aq. HCl soln. The organic phase was washed (0.5 M aq. HCl soln, H_2O, sat. aq. $NaHCO_3$ soln, sat. aq. NaCl soln), dried (Na_2SO_4), filtered and concentrated. FC (hexane/EtOAc gradients) afforded the protected amino acid (Alloc-**B**-**A**-M-**c1**-V-**c2**-CO-OAll; V= $CONR^4$).

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

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

Synthesis of the C-B fragment PG^5-NR^4-**c2**-CO-**B**-OH

Procedure D

Synthesis in two steps, via amidoester and subsequent saponification

i-Pr_2NEt (5.0 equiv.) was slowly added to a mixture of the *N*-protected amino acid (Alloc-NR^4-**c2**-CO-OH, 2.2 equiv.), the aminoalcohol hydrochloride HO-**B**-H·HCl, Cl-HOBt (0.25 equiv.) and HCTU (2.5 equiv.) in DMF. The resulting soln was stirred at rt for 17 h, followed by distribution between EtOAc and sat. aq. Na_2CO_3 soln. The organic phase was washed (1 M aq. HCl

soln, sat. aq. NaCl soln), dried (Na_2SO_4), filtered and concentrated. FC (hexane/EtOAc or CH_2Cl_2/MeOH gradients) afforded the corresponding amidoester, which was dissolved in THF/H_2O 4:1 and treated with lithium hydroxide monohydrate (3.0 equiv.) for 2 h at rt. The mixture was concentrated to about 50% of the original volume, diluted with EtOAc and extracted with 1 M aq. NaOH soln. The organic phase was washed (H_2O, sat. aq. NaCl soln), dried (Na_2SO_4), filtered and concentrated to afford the amidoalcohol (HO–**B**–CO–**c2**–NR^4–Alloc).

Synthesis of cyclization precursor H–NR^4–**c2**–CO–**B**–**A**–M–**c1**–CO–OH

Procedure E

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

A mixture of the hydroxyaryl amide (H–**A**–M–**c1**–CO–OAll) and PPh_3 (1.5-4.5 equiv.) was dissolved in benzene. The soln was concentrated and the residue was dried *i.v.* for 15-30 min. Under argon, a soln of alcohol HO–**B**–CO–**c2**–NR^4–Alloc (1.2-2.3 equiv.) in dry and degassed benzene was added and the resulting mixture was cooled to 0°C. A soln of DEAD (40% in toluene, 1.2-4.5 equiv.) was slowly added. The mixture was stirred at rt for 18 h. In case of incomplete consumption of the hydroxyaryl amide as indicated by tlc control, additional triphenylphosphine (1.0-1.3 equiv.) and DEAD (40% in toluene, 1.0 equiv.) and alcohol (1.0 equiv.) were added and stirring was continued for 18 h. The mixture was concentrated. FC (hexane/EtOAc, CH_2Cl_2/EtOH, or CH_2Cl_2/MeOH gradients) afforded Alloc–NR^4–**c2**–CO–**B**–**A**–M–**c1**–CO–OAll used in the next step without further purification.

E.1.2: Mitsunobu aryl ether synthesis using CMBP

CMBP (2-3 equiv.) was added to a mixture of the hydroxyaryl amide (H–**A**–M–**c1**–CO–OAll) and the alcohol (HO–**B**–CO–**c2**–NR^4–Alloc, 1.2-2.2 equiv.) in dry toluene. The mixture was heated at reflux for 16 h and concentrated.

FC (hexane/EtOAc gradients) afforded the protected amino acid (Alloc-NR^4-**c2**-CO-**B**-**A**-M-**c1**-CO-OAll).

E.2: Cleavage of the allyl/alloc protective groups

$Pd(PPh_3)_4$ (0.05-0.1 equiv.) was added to a mixture of the protected amino acid (Alloc-NR^4-**c2**-CO-**B**-**A**-M-**c1**-CO-OAll) and 1,3-dimethylbarbituric acid (2.4 equiv.) in degassed EtOAc/CH_2Cl_2 1:1. The resulting soln was stirred at rt for 1-3 h and concentrated. FC (EtOAc, CH_2Cl_2/EtOH, or CH_2Cl_2/MeOH gradients) afforded the free amino acid (H-NR^4-**c2**-CO-**B**-**A**-M-**c1**-CO-OH).

Synthesis of macrocyclic compounds *cyclo*(**B**-**A**-M-**c1**-CO-) **and** *cyclo*(**B**-**A**-M-**c1**-V-**c2**-CO-)

Procedure F

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

F.1.1: T3P mediated lactam formation

A soln of the precursor (H-**B**-**A**-M-**c1**-CO-OH, H-**B**-**A**-M-**c1**-V-**c2**-CO-OH or H-NR^4-**c2**-CO-**B**-**A**-M-**c1**-CO-OH) in dry CH_2Cl_2 was added within 2 h by syringe pump to a soln of T3P (50% in EtOAc, 2 equiv.) and *i*-Pr_2NEt (4 equiv.) in dry CH_2Cl_2. The soln was stirred at rt for 20 h, extracted with sat. aq. Na_2CO_3 soln and with H_2O, dried (Na_2SO_4), filtered and then concentrated. FC (hexane/EtOAc/MeOH or CH_2Cl_2/MeOH gradients) afforded macrocycle *cyclo*(**B**-**A**-M-**c1**-CO-) or *cyclo*(**B**-**A**-M-**c1**-V-**c2**-CO-) wherein V is NR^4.

F.1.2: FDPP mediated lactam formation

A soln of the precursor (H-**B**-**A**-M-**c1**-CO-OH, H-**B**-**A**-M-**c1**-V-**c2**-CO-OH or H-NR^4-**c2**-CO-**B**-**A**-M-**c1**-CO-OH) in dry DMF was added within 2 h to a soln of FDPP (2.0 equiv.) in dry DMF. The soln was stirred at rt for 20 h. The volatiles were evaporated and the residue taken up in EtOAc and washed (sat. aq. $NaHCO_3$ soln, H_2O, sat. aq. NaCl soln). The organic phase was dried (Na_2SO_4), filtered and concentrated. FC (hexane/EtOAc/MeOH or CH_2Cl_2/MeOH

gradients) afforded the macrocycle *cyclo*(**B**–**A**–M–**c1**–CO–) or *cyclo*(**B**–**A**–M–**c1**–V–**c2**–CO– wherein V is NR^4.

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

Deprotection reactions

Procedure H

A soln of a macrocyclic benzyl ester or benzyl ether in MeOH or MeOH/THF (ca 100 mL per g of starting material) was hydrogenolyzed for 2 h at rt and at normal pressure in the presence of palladium hydroxide on activated charcoal (moistened with 50% H_2O; 0.5 g per g of starting material). The mixture was filtered through a pad of celite. The residue was washed (MeOH, MeOH/CH_2Cl_2 1:1, THF). The combined filtrate and washings were concentrated to obtain a macrocyclic acid or alcohol.

Procedure I

I.1: Teoc deprotection with dioxane-HCl

A soln of a macrocyclic Teoc-amine (1.5 mmol) in dioxane (18 mL) was treated with 4M HCl in dioxane (18 mL) and stirred at rt for 4-16 h. The mixture was treated with Et_2O and filtered. The solid was washed with Et_2O and dried i.v. to give the macrocyclic amine hydrochloride.

I.2: Teoc deprotection with TBAF in THF

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

Procedure J

A soln of a macrocyclic Boc-amine in dioxane (10 mL per g of starting material) was treated with 4M HCl in dioxane (20 mL

per g of starting material) and stirred at rt for 2 h. The mixture was filtered. The solid was washed with Et_2O and dried i.v. to give the macrocyclic amine hydrochloride.

Procedure K

K.1: A soln of a macrocyclic benzylcarbamate (0.9 mmol) in MeOH (52 mL) was hydrogenolyzed for 4 h at rt and at normal pressure in the presence of palladium hydroxide on activated charcoal (moistened with 50% H_2O; 0.3 g). The mixture was filtered through a pad of celite. The residue was washed (MeOH). The combined filtrate and washings were concentrated to obtain the macrocyclic amine.

K.2: A soln of a macrocyclic benzylcarbamate (0.16 mmol) in MeOH (2 mL) was treated with NH_3 soln (7 M in MeOH; 4 equiv.) and hydrogenolyzed for 3 h at rt and at normal pressure in the presence of 5% palladium on activated charcoal (moistened with 50% H_2O; 32 mg). The mixture was filtered through a pad of celite. The residue was washed (MeOH). The combined filtrate and washings were concentrated to give the macrocyclic amine.

K.3: A soln of the macrocyclic benzylamine (0.7 mmol) in acetic acid (11 mL) was hydrogenolyzed for 15 h at rt and at normal pressure in the presence of palladium hydroxide on activated charcoal (moistened with 50% H_2O; 0.14 g). The mixture was filtered through a pad of celite. The residue was washed (MeOH). The combined filtrate and washings were concentrated to obtain the macrocyclic amine.

Acylation, carbamoylation, sulfonylation, and alkylation reactions

Procedure L

L.1: Amide coupling of a macrocyclic amine with

L.1.1: carboxylic acid anhydrides or acylchlorides

At 0°C a soln of an amino macrocycle (free amine or hydrochloride; 0.09 mmol) in CH_2Cl_2 (1 mL) was successively treated with pyridine (10 equiv.) and the carboxylic acid anhydride (1.05-5 equiv.) or a carboxylic acid chloride (1.05-

2.0 equiv.). The soln was stirred at rt for 15 h. After the addition of MeOH (0.1 mL) the soln was stirred for 10 min and concentrated. The resulting crude product was co-evaporated with toluene and purified by chromatography (FC, normal phase or reverse phase prep. HPLC) to give an *N*-acylamino macrocycle.

L.1.2: carboxylic acid and polymer-supported carbodiimide

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

L.1.3: carboxylic acid and HATU

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

L.2: Amide coupling of a macrocyclic carboxylic acid with an amine and HATU

A soln of a macrocyclic carboxylic acid (0.78 mmol), an amine (2.0 equiv.), HATU (2.0 equiv.), HOAt (2.0 equiv.) in DMF (6 mL) was treated with *i*-Pr_2NEt (4.0 equiv.). The mixture was stirred for 15 h at rt. The solvent was removed. The residue was distributed between $CHCl_3$ and sat. aq. $NaHCO_3$ soln. The organic phase was washed (H_2O), dried (Na_2SO_4), filtered and

concentrated. Purification of the crude product by chromatography (FC, normal phase or reverse phase prep. HPLC) afforded a macrocyclic amide.

L.3: Sulfonamide formation with sulfonyl chlorides

At 0°C a soln of an amino macrocycle (0.24 mmol) in CH_2Cl_2 (1 mL) was successively treated with triethylamine (2.0 equiv.) and the sulfonyl chloride (1.0 equiv.). The mixture was stirred at 0°C to rt for 0.5–16 h, followed by an aqueous workup ($CHCl_3$, sat. aq. Na_2CO_3 soln; Na_2SO_4). The crude product was purified by chromatography (FC, normal phase or reverse phase prep. HPLC) to afford the macrocyclic sulfonamide.

L.4: Urea formation with isocyanates or equivalents of isocyanates

A soln of an amino macrocycle (0.1 mmol) in CH_2Cl_2 was treated at rt with an isocyanate (1.1 equiv.) or with a succinimidyl carbamate (1.1 equiv.) and *i*-Pr_2NEt (3 equiv.). Aqueous workup (CH_2Cl_2, sat. aq. Na_2CO_3 soln; Na_2SO_4) and purification by chromatography (FC, normal phase or reverse phase prep. HPLC) afforded the targeted urea.

***N*-Alkylation by reductive amination**

Procedure M

M.1: *N,N*-Diethylamino macrocycles by reductive amination

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

M.2: Synthesis of secondary amines by reductive amination

Activated molecular sieve powder (3 Å; 1 mg per mg of starting material) was added at rt to a soln of an amino macrocycle (0.8 mmol) and an aldehyde (1.1 equiv.) in THF (3.5 mL). The suspension was stirred for 4 h at rt, followed by the addition

of acetic acid (1.1 equiv.) and $NaBH(OAc)_3$ (2.0 equiv.). The mixture was stirred for 18 h and filtered. Aqueous workup of the filtrate (CH_2Cl_2, sat. aq. Na_2CO_3 soln; Na_2SO_4) and purification of the crude product by chromatography (FC, normal phase or reverse phase prep. HPLC) afforded the alkylamino macrocycle.

M.3: Synthesis of tertiary amines by *N*-methylation of secondary amines

At 0°C formaldehyde soln (36.5% in H_2O; 5 equiv.) and $NaBH(OAc)_3$ (2.5 equiv.) were added to a soln of the macrocyclic amine (0.16 mmol) in THF (3 mL). The mixture was stirred at rt for 3 h followed by aqueous workup (CH_2Cl_2, sat. aq. Na_2CO_3 soln; Na_2SO_4). Purification of the crude product by chromatography (FC, normal phase or reverse phase prep. HPLC) afforded the desired *N*-methyl-*N*-alkylamino macrocycle.

If the HCl salt of the macrocyclic amine was used, the transformation was carried out in the presence of 2 equiv. of *i*-Pr_2NEt.

M.4: Synthesis of tertiary amines by debenzylation/ *N*-methylation

A soln of a tert. benzylamine (0.1 mmol) in MeOH (2.0 mL) / acetic acid (0.5 mL) was hydrogenolyzed for 2 h at rt and normal pressure in the presence of palladium hydroxide on activated charcoal (moistened with 50% H_2O; 20 mg). Aq. formaldehyde soln (36.5% in H_2O; 10 equiv.) was added and hydrogenation was continued for 1 h.

The mixture was filtered through a pad of celite. The residue was washed (MeOH). The combined filtrate and washings were concentrated followed by aqueous workup ($CHCl_3$, sat. aq. Na_2CO_3 soln; Na_2SO_4). The crude product was purified by chromatography (FC, normal phase or reverse phase prep. HPLC) to afford a tertiary methylamino macrocycle.

M.5: Synthesis of tertiary amines by reductive amination of secondary amines

i-Pr_2NEt (2 equiv.) was added at 0°C to a mixture of the macrocyclic amine (0.15 mmol) and DCE (1.0 mL). The aldehyde

(1.2 equiv.) was added. The mixture was stirred for 0.5 h, followed by the addition of $NaBH(OAc)_3$ (3 equiv.). Stirring was continued at rt for 15 h. After aqueous workup ($CHCl_3$, 1 M aq. Na_2CO_3 soln; Na_2SO_4) the crude product was purified by chromatography (FC, normal phase or reverse phase prep. HPLC) to afford the macrocyclic tertiary amine.

Miscellaneous transformations

Procedure N: Methylester cleavage

A soln of the methylester (57 μMol) in THF (1.5 mL) and MeOH (0.5 mL) was treated with H_2O (0.5 mL) and lithium hydroxide monohydrate (3 equiv.) for 2 h at rt. The mixture was acidified by addition of aq. 1 M HCl and concentrated. The crude product was purified by chromatography (FC, normal phase or reverse phase prep. HPLC).

Procedure O: Conversion of macrocyclic primary amines into piperazines by *N*-alkylation

A mixture of the amino macrocycle (1.4 mmol) and *N*-benzyl-2-chloro-*N*-(2-chloroethyl)ethanamine (1.5 equiv.) in ethanol (15 mL) was treated with $NaHCO_3$ (4 equiv.) and heated to reflux for 3 h. Aqueous workup (EtOAc, half-sat. aq. $NaHCO_3$ soln; Na_2SO_4) and chromatography (FC, normal phase or reverse phase prep. HPLC) afforded the *N*-benzylpiperazino macrocycle.

Procedure P: Suzuki couplings

A soln of Na_2CO_3 (3.0 equiv.) in H_2O (1.6 mL) was added to a mixture of the macrocyclic arylbromide (0.25 mmol), the boronic acid (2.0 equiv.) and $Pd(PPh_3)_4$ (0.1 equiv.) in DME (5.2 mL). The mixture was heated to reflux for 1 h, followed by aqueous workup (EtOAc, sat. aq. Na_2CO_3 soln; Na_2SO_4). Purification of the crude product by chromatography (FC, normal phase or reverse phase prep. HPLC) afforded the biaryl-substituted macrocyclic product.

Procedure Q: *O*-Alkylation of macrocyclic alcohols

At 0°C NaH (60% in oil, 2 equiv.) was added portionwise to a soln of the macrocyclic alcohol (0.38 mmol) and the alkylhalide (1.1 equiv.) in THF (3.7 mL)/DMF (1.3 mL). The mixture was stirred at rt for 2 h, treated with 1 M aq. HCl soln and extracted with EtOAc. The organic phase was dried (Na_2SO_4), filtered and concentrated. Purification of the crude product by chromatography (FC, normal phase or reverse phase prep. HPLC) afforded the macrocyclic alkyl ether.

Procedures R and S: *Vide infra* "Transformations on solid support"

Synthesis of the A-B fragments PG^3-B-A-OH and PG^3-B-A=CH_2

1. Synthesis of 3-(((2*S*,4*S*)-1-(allyloxycarbonyl)-4-(tert-butoxycarbonylamino)pyrrolidin-2-yl)methoxy)benzoic acid (**192**) (Scheme 4)

A soln of ethyl 3-hydroxybenzoate (**142**; 3.1 g, 18.6 mmol), alcohol **14** (5.66 g, 18.8 mmol) and CMBP (9.0 g, 37.3 mmol) in toluene (60 mL) was heated to reflux for 2 h. Evaporation of the volatiles and FC (hexane/EtOAc) gave **191** (7.3 g, 87%).

A soln of ester **191** (4.3 g, 9.5 mmol) in THF/MeOH/H_2O (3:1:1; 55 mL) was cooled to 0°C, treated with $LiOH \cdot H_2O$ (801 mg, 19.1 mmol) and stirred at 0°C to rt for 16 h. The mixture was treated with 1 M aq. NaH_2PO_4 soln (100 mL) and repeatedly extracted with CH_2Cl_2. The combined organic layer was dried (Na_2SO_4), filtered and concentrated to yield **192** (3.86 g, 96%).

Data of **192**: $C_{21}H_{28}N_2O_7$ (420.5). LC-MS (method 10c): R_t = 1.97 (97), 421 ($[M+H]^+$).

2. Synthesis of (2*S*,4*S*)-4-(4-bromobenzyloxy)-2-((3-(but-3-enyl)phenoxy)methyl)pyrrolidine (**194**)

2.1 Synthesis of 3-(But-3-enyl)phenol (**149**) (Scheme 1)

3-Methoxybenzyl bromide (**148**; 3.3 g, 16.3 mmol) was converted into 1-(but-3-enyl)-3-methoxybenzene (2.3 g, 86%) according to the procedure of A.B. Smith et al., *Org. Lett.* **2005**, 7, 315-318, describing the synthesis of (3-but-enyl-phenoxy)-*tert*-butyl dimethylsilane.

At 0°C, BBr_3 (0.775 mL, 7.9 mmol) was slowly added to a soln of 1-(but-3-enyl)-3-methoxybenzene (1.36 g, 8.4 mmol) in dry CH_2Cl_2 (48 mL). Stirring at 0°C was continued for 3 h, then 1 M aq. $NaHCO_3$ soln (20 mL) was added and stirring continued for 30 min. The mixture was diluted with CH_2Cl_2 (100 mL) and 1 M aq. $NaHCO_3$ soln (100 mL). The organic layer was separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried (Na_2SO_4), filtered and concentrated. FC (hexane/EtOAc 98:2 to 80:20) afforded **149** (896 mg, 72%).

Data of **149**: $C_{10}H_{12}O$ (148.2). ^{1}H-NMR (DMSO-d_6): 9.21 (s, OH), 7.04 (t, J = 7.5, 1 H), 6.76-6.55 (m, 3 H), 5.82 (m, 1 H), 5.06-4.93 (m, 2 H), 2.59 (t, J = 7.7, 2 H), 2.30 (q-like m, 1 H).

2.2 Synthesis of amine **194** (Scheme 4)

A mixture of phenol **149** (1.095 g, 7.3 mmol), alcohol **161** (2.28 g, 6.16 mmol) and PPh_3 (2.42 g, 9.24 mmol) was dissolved in $CHCl_3$ (46 mL) and degassed. ADDP (2.33 g, 9.24 mmol) was added and the mixture was stirred for 20 h at rt. The mixture was diluted with CH_2Cl_2, washed with sat. aq. $NaHCO_3$ soln, dried (Na_2SO_4), filtered and concentrated. FC (hexane/EtOAc gradient) afforded **193** (2.94 g, 95%).

To a degassed soln of **193** (200 mg, 0.4 mmol) in CH_2Cl_2/EtOAc (1:1, 5.2 mL) were added $Pd(PPh_3)_4$ (2.5 mg) and 1,3-dimethylbarbituric acid (125 mg, 0.8 mmol). The mixture was stirred for 45 min at rt followed by an aqueous workup (CH_2Cl_2, sat. aq. Na_2CO_3 soln; Na_2SO_4) and FC (EtOAc/MeOH gradient) to yield **194** (160 mg, 96%).

Data of **194**: $C_{22}H_{26}BrNO_2$ (416.3). LC-MS (method 10a): R_t = 2.00 (82), 416/418 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 7.51 (d, J = 8.3, 2 H), 7.28 (d, J = 8.4, 2 H), 7.17 (t, J = 7.8, 1 H), 6.79-6.70

(m, 3 H), 5.83 (m, 1 H), 5.03 (qd, J = 1.7, 17.2, 1 H), 4.96 (d-like m, J ca. 10.2, 1 H), 4.42 (s, 2 H), 4.11 (m, 1 H), 3.91 (d, J = 6.3, 2 H), 3.45 (m, 1 H), 2.97 (d, J = 4.3, 2 H), 2.63 (t, J ca. 7.7, 2 H), 2.31 (q-like m, 2 H), 2.15 (m, 1 H), 1.66 (m, 1 H).

3. Synthesis of 5-bromo-2-(((2*S*,4*R*)-4-(tert-butoxycarbonyl-amino)-1-((2-(trimethylsilyl)ethoxy)carbonyl)pyrrolidin-2-yl)-methoxy)benzoic acid (**196**) (Scheme 4)

At 0°C DEAD (40% in toluene; 3.5 mL, 7.6 mmol) was slowly added to a mixture of phenol **151** (1.76 g, 7.6 mmol), alcohol **152** (1.83 g, 5.1 mmol) and PPh_3 (2.0 g, 7.6 mmol) in benzene (50 mL). The mixture was stirred at rt for 16 h, followed by evaporation of the volatiles and FC (hexane/EtOAc 2:1) to yield **195** (2.78 g, 95%).

A soln of ester **195** (2.6 g, 4.5 mmol) in THF (20 mL) was treated with 2M aq. LiOH soln (22.5 mL, 45 mmol). The mixture was heated to 50°C for 15 h. The organic solvent was evaporated. The remaining aqueous phase was acidified with 3 M aq. HCl soln and extracted with EtOAc. The organic phase was dried (Na_2SO_4), filtered and concentrated to give **196** (2.44 g, 96%).

Data of **196**: $C_{23}H_{35}BrN_2O_7Si$ (559.5). LC-MS (method 10a): R_t = 2.49 (98), 559/561 ($[M+H]^+$).

4. Synthesis of 3-(((2S,4S)-1-(allyloxycarbonyl)-4-(4-bromobenzyloxy)pyrrolidin-2-yl)methoxy)benzoic acid (**198**) (Scheme 4)

TMAD (5.0 g, 28 mmol) in degassed benzene (100 mL) was slowly added at 0°C to a soln of ethyl 3-hydroxybenzoate (**142**; 4.7 g, 28 mmol), alcohol **161** (6.92 g, 19 mmol) and PPh_3 (7.4 g, 28 mmol) in benzene (300 mL). The resulting suspension was diluted with benzene (100 mL) and stirred at rt for 20 h. Et_2O was added and the mixture was filtered. The filtrate was concentrated and purified by FC (hexane/EtOAc 75:25 to 70:30) to afford **197** (6.24 g, 64%).

A soln of **197** (883 mg, 1.7 mmol) in THF (5 mL) was treated with 2 M aq. LiOH soln (3 mL, 6 mmol) and MeOH (2.5 mL) for 2 h at rt. The volatiles were partially evaporated. The remaining soln was acidified with 1 M aq. HCl soln and extracted with EtOAc. The organic phase was dried (Na_2SO_4), filtered and concentrated to yield **198** (770 mg, 92%).

Data of **198**: $C_{23}H_{24}BrNO_6$ (490.3). LC-MS (method 10a): R_t = 2.30 (98), 492/490 ($[M+H]^+$).

Synthesis of the A-C fragments H-A-M-c1-CO-OPG^2 and H-A-M-c1-CR^{12}=CH$_2$

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

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

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

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

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

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

presence of DMF (50 µL) afforded 2-acetoxy-5-fluoro benzoyl chloride (**52**).

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

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

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

Following procedure **A** (steps **A.1-A.3**), the reaction of 3-acetoxybenzoic acid (**3**, 6.0 g, 33 mmol) and oxalylchloride (14 mL, 164 mmol) in dry Et_2O (216 mL) in the presence of DMF (50 µL) afforded 3-acetoxybenzoyl chloride (**57**, 7.0 g, quant.).

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

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

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

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

Following procedure **A** (steps **A.1-A.3**), the reaction of 3-acetoxybenzoic acid (**3**, 5.82 g, 32.3 mmol) and oxalylchloride

(11.1 mL, 129 mmol) in dry Et_2O (210 mL) in the presence of DMF (50 μL) afforded 3-acetoxybenzoyl chloride (**57**, 6.5 g, 100%).
Reaction of **57** (6.5 g, 32.3 mmol) with (*R*)-allyl 2-(benzyloxycarbonylamino)-3-(methylamino)propanoate hydrochloride (**36**·HCl, 8.5 g, 26 mmol) in CH_2Cl_2 (220 mL) in the presence of 2,4,6-collidine (10.3 mL, 77.6 mmol) yielded **60** (10.73 g, 92%).
Acetate **60** (15.46 g, 34 mmol) was treated with 3-dimethylamino-1-propylamine (12.8 mL, 102 mmol) in THF (140 mL) to afford phenol **61** (12.92 g, 92%).
Data of **61**: $C_{22}H_{24}N_2O_6$ (412.4). LC-MS (method 2): R_t = 1.77 (98), 413 ($[M+H]^+$).

5. Synthesis of (*S*)-allyl 2-(benzyloxycarbonylamino)-4-(3-hydroxy-*N*-methylbenzamido)butanoate (**63**) (Scheme 4)
Following procedure **A** (steps **A.1-A.3**), the reaction of 3-acetoxybenzoic acid (**3**, 7.65 g, 43 mmol) and oxalylchloride (18.2 mL, 213 mmol) in dry CH_2Cl_2 (140 mL) in the presence of DMF (300 μL) afforded after 3 h at rt 3-acetoxybenzoyl chloride (**57**).
Reaction of **57** with (*S*)-allyl 2-(benzyloxycarbonylamino)-5-(methylamino)butanoate hydrochloride (**40**·HCl, 8.7 g, 28 mmol) in THF (140 mL) in the presence of *i*-Pr_2NEt (15 mL, 85 mmol) yielded **62** (8.1g, 61%).
Acetate **62** (4.85 g, 10 mmol) was treated with 3-dimethylamino-1-propylamine (3.8 mL, 31 mmol) in THF (90 mL) to afford phenol **63** (4.23 g, 95%).
Data of **63**: $C_{23}H_{26}N_2O_6$ (426.5). LC-MS: (method 6): R_t = 1.06 (99), 427 ($[M+H]^+$).

6. Synthesis of (*S*)-allyl 2-(benzyloxycarbonylamino)-5-(3-hydroxy-*N*-methylbenzamido)pentanoate (**65**) (Scheme 4)
Following procedure **A** (steps **A.1-A.3**), the reaction of 3-acetoxybenzoic acid (**3**, 10 g, 58 mmol) and oxalylchloride (19

mL, 218 mmol) in dry CH_2Cl_2 (450 mL) in the presence of DMF (500 µL) afforded 3-acetoxybenzoyl chloride (**57**).

Reaction of **57** with (S)-allyl 2-(benzyloxycarbonylamino)-5-(methylamino)pentanoate hydrochloride (**44**·HCl, 17.3 g, 48 mmol) in THF (200 mL) in the presence of *i*-Pr_2NEt (25 mL, 145 mmol) yielded **64** (12.08 g, 51%), which was treated with 3-dimethylamino-1-propylamine (9.3 mL, 75 mmol) in THF (240 mL) to afford after aqueous workup (EtOAc, 1 M aq. HCl soln, sat. aq. $NaHCO_3$ soln, sat. aq. NaCl soln) phenol **65** (10.84 g, 98%).

Data of **65**: $C_{24}H_{28}N_2O_6$ (440.5). LC-MS (method 6): R_t = 1.15 (91), 441 ($[M+H]^+$).

7. Synthesis of (*S*)-5-allyl 1-benzyl 2-(4-hydroxy-*N*-methylbenzamido)pentanedioate (**68**) (Scheme 4)

Following procedure **A** (steps **A.1-A.3**), the reaction of 4-acetoxybenzoic acid (**4**, 10.7 g, 59.5 mmol) and oxalylchloride (17.7 mL, 206 mmol) in dry CH_2Cl_2 (350 mL) in the presence of DMF (50 µL) afforded 4-acetoxybenzoyl chloride (**66**).

Reaction of **66** with (*S*)-5-allyl 1-benzyl 2-(methylamino)pentanedioate hydrochloride (**27**·HCl, 15.0 g, 46 mmol) in THF (250 mL) in the presence of *i*-Pr_2NEt (23.3 mL, 137 mmol) yielded **67** (16.24 g, 78%).

Treatment of **67** (15.2 g, 33.5 mmol) with 3-dimethylamino-1-propylamine (12.6 mL, 101 mmol) in THF (140 mL) afforded phenol **68** (14.86 g, quant.).

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

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

A mixture of 5-hydroxy nicotinic acid (**5**, 3.5 g, 25.1 mmol) and acetic anhydride (23 mL, 243 mmol) was heated at 95°C for 45 min and cooled to rt. The mixture was filtered. The solid was washed (H_2O, Et_2O) and dried i.v. to give 5-acetoxynicotinic acid (**6**; 3.76 g, 82%) (cf. Scheme 1)

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

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

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

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

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

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

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

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

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

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

Following procedure **A** (steps **A.1-A.3**), the reaction of 3-acetoxybenzoic acid (**3**, 23.7 g, 132 mmol) and oxalylchloride (45.3 mL, 527 mmol) in dry Et_2O (800 mL) in the presence of DMF (100 µL) afforded 3-acetoxybenzoyl chloride (**57**).

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

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

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

12. Synthesis of (*S*)-5-allyl-1-benzyl 2-(3-mercapto-*N*-methylbenzamido)pentanedioate (**80**) (Scheme 4)

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

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

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

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

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

13. Synthesis of (*S*)-allyl 2-(benzyloxycarbonylamino)-4-(5-fluoro-2-hydroxybenzamido) butanoate (**199**) (Scheme 4)

Following procedure **A** (step **A.1**), the reaction of 2-acetoxy-5-fluoro benzoic acid (**2**; 10.5 g, 53.1 mmol) and oxalyl chloride

(15.8 mL, 184 mmol) in dry CH_2Cl_2 (460 mL) in the presence of DMF (0.2 mL) afforded 2-acetoxy-5-fluoro benzoyl chloride (**52**). (*S*)-Allyl-4-amino-2-(benzyloxycarbonylamino) butanoate toluene-4-sulfonate (**38**·pTsOH; 19.0 g, 40.9 mmol) and THF (230 mL) were added. The mixture was cooled to 0°C and *i*-Pr_2NEt (21 mL, 123 mmol) was added dropwise. The mixture was stirred at rt for 2 h. 3-Dimethylaminopropylamine (15.5 mL, 123 mmol) was added. The mixture was stirred at rt for 2 h followed by aqueous workup (CH_2Cl_2, 1 M aq. NaH_2PO_4 soln). The organic layer was separated, dried (Na_2SO_4), filtered and concentrated. FC (hexane/EtOAc) afforded **199** (15.5 g, 88%).

Data of **199**: $C_{22}H_{23}FN_2O_6$ (430.4). LC-MS (method 10a): R_t = 2.14 (90), 431 ($[M+H]^+$).

14. Synthesis of (*S*)-allyl 2-(benzyloxycarbonylamino)-5-(3-hydroxybenzamido) pentanoate (**200**) (Scheme 4)

Following procedure **A** (step **A.1**), the reaction of 3-acetoxy benzoic acid (**3**, 4.2 g, 23.3 mmol) and oxalyl chloride (7.5 mL, 87.6 mmol) in dry CH_2Cl_2 (160 mL) in the presence of DMF (0.1 mL) afforded after 2 h at rt 3-acetoxybenzoyl chloride (**57**). (*S*)-Allyl-5-amino-2-(benzyloxycarbonylamino)pentanoate toluene-4-sulfonate (**42**·pTsOH; 9.3 g, 19.5 mmol) and THF (70 mL) were added. The mixture was cooled to 0°C and *i*-Pr_2NEt (10.0 mL, 58.4 mmol) was added within 5 min. The mixture was stirred at rt for 2 h followed by the addition of 3-dimethylamino-propylamine (7.4 mL, 58.4 mmol). Stirring was continued for 2 h. The mixture was distributed between EtOAc and 1 M aq. HCl soln. The organic layer was separated, washed (H_2O, sat. aq. $NaHCO_3$ soln, sat. aq. NaCl soln), dried (Na_2SO_4), filtered and concentrated. FC (EtOAc/hexane) afforded **200** (5.83 g, 70%).

Data of **200**: $C_{23}H_{26}N_2O_6$ (426.5). LC-MS (method 4b): R_t = 1.96 (97), 427 ($[M+H]^+$).

15. Synthesis of (*S*)-allyl 2-(benzyloxycarbonylamino)-5-(5-fluoro-2-hydroxy-N-methylbenzamido) pentanoate (**202**) (Scheme 4)

Following procedure **A** (steps **A.1**-**A.3**) the reaction of 2-acetoxy-5-fluoro benzoic acid (**2**; 5.6 g, 28.6 mmol) and oxalyl chloride (9.2 mL, 107 mmol) in dry CH_2Cl_2 (220 mL) in the presence of DMF (0.05 mL) afforded after 6 h at rt 2-acetoxy-5-fluoro benzoyl chloride (**52**).

Reaction of the acid chloride **52** with (*S*)-allyl-2-(benzyloxycarbonylamino)-5-(methylamino)pentanoate hydrochloride (**44**·HCl; 8.5 g, 23.8 mmol) in THF (130 mL) in the presence of *i*-Pr_2NEt (12.2 mL, 71.5 mmol) yielded **201** (4.86 g, 41%).

Acetate **201** was treated with 3-dimethylaminopropylamine (3.64 mL, 29.1 mmol) in THF (45 mL) to afford after aqueous workup (EtOAc, 1 M aq. HCl soln, sat. aq. NaCl soln) the phenol **202** (4.08 g, 92%).

Data of **202**: $C_{24}H_{27}FN_2O_6$ (458.5). LC-MS (method 4b): R_t = 2.08 (83), 459 ($[M+H]^+$).

16. Synthesis of 5-allyl 1-benzyl (2*S*)-2-[[(3-hydroxy-2-thienyl)carbonyl](methyl)amino]pentanedioate (**205**) (Scheme 4)

At 0°C acetic anhydride (6.5 mL, 69.4 mmol) was added to a soln of 3-hydroxythiophene-2-carboxylic acid (**144**; 2.0 g, 13.9 mmol) in 2 M aq. NaOH (34.7 mL, 69.4 mmol). The mixture was stirred for 5 h, acidified with 1 M aq. HCl soln and extracted with EtOAc. The organic layer was separated, dried (Na_2SO_4), filtered and concentrated to give 3-acetoxythiophene-2-carboxylic acid (**145**; 1.74 g, 67%) (cf. Scheme 1).

Following procedure **A** (steps **A.1**-**A.3**) the reaction of **145** (1.74 g, 9.3 mmol) and oxalyl chloride (8.0 mL, 93 mmol) in dry CH_2Cl_2 (130 mL) in the presence of DMF (0.05 mL) afforded after 2.5 h at rt 2-(chlorocarbonyl)thiophen-3-yl acetate (**203**).

Reaction of the acid chloride **203** with (*S*)-5-allyl-1-benzyl-2-(methylamino) pentanedioate hydrochloride (**27**·HCl; 2.80 g, 8.5 mmol) in THF (95 mL) in the presence of *i*-Pr_2NEt (4.4 mL, 25.6 mmol) yielded after aqueous workup (EtOAc, 1 M aq. HCl soln, H_2O, sat. aq. NaCl soln) the crude acetate **204** (3.56 g), which was treated with 3-dimethylaminopropylamine (1.95 mL, 15.5 mmol) in THF (87 mL) to afford after aqueous workup (EtOAc, 1 M

aq. HCl soln, sat. aq. NaCl soln) and after FC (CH_2Cl_2) phenol **205** (1.65 g, 42%).

Data of **205**: $C_{21}H_{23}NO_6S$ (417.5). LC-MS (method 7): R_t = 1.43 (93), 418 ($[M+H]^+$).

17. Synthesis of (*S*)-allyl 2-(benzyloxycarbonylamino)-6-(5-hydroxy-*N*-methylnicotinamido)hexanoate (**207**) (Scheme 4)

Following procedure **A** (step **A.1**), the reaction of 5-acetoxynicotinic acid (**6**, 41 g, 226 mmol, synthesized as described above, cf. phenol **71**) and oxalyl chloride (71.8 mL, 849 mmol) in $CHCl_3$ (1660 mL) in the presence of DMF (0.26 mL) afforded after 1.5 h at rt 5-acetoxy-nicotinoyl chloride (**69**). At 0°C a suspension of the acid chloride **69** in CH_2Cl_2 (100 mL) was added over 10 min to a mixture of (*S*)-allyl-2-(benzyloxycarbonylamino)-6-(methylamino)hexanoate hydrochloride (**182**·HCl; 70.0 g, 189 mmol) in CH_2Cl_2 (260 mL) and 1 M aq. Na_2CO_3 soln (360 mL). The mixture was stirred at rt for 2 h. The organic layer was separated; the aqueous layer was extracted twice with CH_2Cl_2 (250 mL). The combined organic layer was dried (Na_2SO_4), filtered and concentrated. FC (hexane/EtOAc/MeOH gradient) afforded **206** (33.5 g, 36%).

Following procedure **A** (step **A.3**), acetate **206** was treated with 3-dimethylaminopropylamine (25.4 mL, 202 mmol) in THF (330 mL) to afford after 2 h at rt and aqueous workup (EtOAc, 1 M aq. NaH_2PO_4 soln) **207** (29.1 g, 95%).

Data of **207**: $C_{24}H_{29}N_3O_6$ (455.5). LC-MS (method 4a): R_t = 1.77 (96), 456 ($[M+H]^+$).

18. Synthesis of 5-allyl 1-benzyl (2*S*)-2-[[(5-hydroxy-1,2-dimethyl-1*H*-indol-3-yl)carbonyl](methyl)amino]pentanedioate (**210**) (Scheme 4)

Pyridine (6.3 mL, 78 mmol) was added to a suspension of 5-hydroxy-1,2-dimethyl-1*H*-indole-3-carboxylic acid (**146**; 4.0 g, 19 mmol) in EtOAc (40 mL). Acetic anhydride (3.7 mL, 39 mmol) was added. The mixture was stirred at rt for 3 h followed by distribution between CH_2Cl_2 and 1 M aq. HCl soln. The organic

layer was separated, dried (Na_2SO_4), filtered and concentrated. FC (CH_2Cl_2/MeOH 100:0 to 97:3). The product was suspended in Et_2O, filtered and dried i.v. to afford 5-acetoxy-1,2-dimethyl-1*H*-indole-3-carboxylic acid (**147**; 3.62 g, 75%) (cf. Scheme 1).

Following procedure **A** (step **A.1**), the reaction of **147** (3.6 g, 15 mmol) and oxalyl chloride (3.1 mL, 37 mmol) in dry CH_2Cl_3 (90 mL) afforded after 2 h at rt 3-(chlorocarbonyl)-1,2-dimethyl-1H-indol-5-yl acetate (**208**).

At 0°C (*S*)-5-allyl-1-benzyl-2-(methylamino) pentanedioate hydrochloride (**27**·HCl; 4.0 g 12 mmol) was added portionwise to a mixture of the acid chloride **208** and *i*-Pr_2NEt (8.4 mL, 49 mmol) in CH_2Cl_2 (43 mL). The mixture was stirred for 2 h at rt followed by distribution between EtOAc and 1 M aq. HCl soln. The organic layer was separated, washed (sat. aq. $NaHCO_3$ soln, sat. aq. NaCl soln), dried (Na_2SO_4), filtered and concentrated. FC (CH_2Cl_2/MeOH 100:0 to 97:3) afforded **209** (6.34 g, 99%).

Treatment of **209** with 3-dimethylaminopropylamine (6.8 mL, 54 mmol) in THF (70 mL) at rt for 16 h afforded after aqueous workup (EtOAc, 1 M aq. HCl soln, sat. aq. $NaHCO_3$ soln, sat. aq. NaCl soln) **210** (5.40 g, 93%).

Data of **210**: $C_{27}H_{30}N_2O_6$ (478.5). LC-MS (method 4b): R_t = 2.20 (95), 479 ($[M+H]^+$).

19. Synthesis of (*S*)-allyl 2-(*tert.*-butoxycarbonylamino)-5-(3-mercapto-*N*-methylbenzamido) pentanoate (**212**) (Scheme 4)

Following procedure **A** (steps **A.1**-**A.3**) the reaction of 3-(acetylthio)benzoic acid (**12**, 10.0 g, 51 mmol; synthesized as described above, cf. thiophenol **80**) and oxalyl chloride (16.0 mL, 192 mmol) in dry CH_2Cl_2 (380 mL) in the presence of DMF (0.1 mL) afforded after 3.5 h at rt 3-(acetylthio)benzoyl chloride (**78**).

Reaction of the acid chloride **78** with (*S*)-allyl-2-(benzyloxycarbonylamino)-5-(methylamino) pentanoate hydrochloride (**44**·HCl; 15.2 g, 43 mmol) in THF (175 mL) in the presence of *i*-Pr_2NEt (22 mL, 128 mmol) yielded after aqueous workup (EtOAc, 1 M aq. HCl soln) and FC (hexane/EtOAc) **211** (12.31 g,

57%). Treatment of **211** (8.0 g, 16 mmol) with 3-dimethylaminopropylamine (6.1 mL, 48 mmol) in THF (135 mL) afforded after 1 h and aqueous workup (EtOAc, 1 M aq. HCl soln) **212** (7.49 g, quant. yield; used without further purification).

Data of **212**: $C_{24}H_{28}N_2O_5S$ (456.5). LC-MS (method 10a): R_t = 2.12 (83), 457 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 7.83-7.74 (m, 1 H), 7.39-7.28 (m, 8 H), 7.08 (m, 1 H), 5.89 (m, 1 H), 5.61 (s, 1 H), 5.31 (d, J = 17.0, 1 H), 5.21 (td, J = 1.4, 10.5, 1 H), 5.05 (s, 2 H), 4.58 (br. s, 2 H), 4.12, 4.04 (2 br. m, 1 H), 3.49, 3.38 (2 br. m, 1 H), 3.18 (br. m, 1 H), 2.89, 2.81 (2 br. s, 3 H), 1.80-1.40 (br. m, 4 H).

20. Synthesis of (*S*)-allyl 2-(benzyloxycarbonylamino)-6-(3-hydroxyphenylthio)hexanoate (**213**) (Scheme 4)

A mixture of **185** (4.97 g, 14.2 mmol) and $NaHCO_3$ (3.57 g, 42.6 mmol) was suspended in degassed anhydrous DMF (85 mL). At 0°C a soln of 3-mercaptophenol (**143**; 2.17 mL, 21.3 mmol) in DMF (5 mL) was added dropwise. The mixture was stirred for 6 h at rt. The mixture was distributed between EtOAc and aq. NaCl soln. The organic phase was separated, washed (H_2O, NaCl soln), dried (Na_2SO_4), filtered and concentrated to yield after FC (hexane/EtOAc 3:1) **213** (5.6 g, quant. yield).

Data of **213**: $C_{20}H_{29}NO_5S$ (395.5). LC-MS (method 10c): R_t = 2.24 (95), 396 ($[M+H]^+$).

Synthesis of the C-B fragments PG^5–NR^4–c2–CO–B–OH and H_2C=CR^{12}–c2–CO–B–OH

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

A soln of (2-((allyloxycarbonyl)(methyl)amino)acetic acid (**47**, 8.0 g, 46 mmol) and aminoalcohol **13** (11.0 g, 51 mmol) in DMF (120 mL) was cooled to 0°C. 2,4,6-Collidine (11 mL, 82 mmol) was added followed by HATU (22 g, 58 mmol). The mixture was

stirred for 1 h at 0°C then for 16 h at rt followed by distribution between EtOAc and sat. aq. Na_2CO_3 soln. The organic phase was washed (1 M aq. HCl soln, sat. aq. NaCl soln), dried (Na_2SO_4), filtered and concentrated. FC (EtOAc/MeOH 100:0 to 95:5) afforded amidoalcohol **81** (14.7 g, 86%).

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

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

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

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

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

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

mL) and H_2O (245 mL) to yield after FC (EtOAc) amidoalcohol **84**; 22.8g, 79%).

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

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

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

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

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

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

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

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

Synthesis of Mitsunobu product **87**

To a soln of **54** (350 mg, 0.82 mmol), **16** (590 mg, 1,7 mmol) and PPh_3 (1069 mg, 4.08 mmol) in dry degassed $CHCl_3$ (11 mL) was added ADDP (1028 mg, 4.08 mmol) in one portion at 0°C, under an N_2 atmosphere. The resulting mixture was stirred for 16 h at rt. The mixture was filtered and the slurry washed further with Et_2O. The combined filtrates were concentrated *in vacuo*. The crude residue was purified by FC (CH_2Cl_2/EtOH 100:0 to 99:1) to afford **87** (1.05 g containing residual triphenylphosphine oxide), which was used in the next step without further purification.

Synthesis of amino acid **88**

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

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

Synthesis of macrolactam **Ex.1**

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

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

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

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

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

Data of **Ex.2**: $C_{30}H_{36}FN_3O_7$ (569.6) LC-MS (method 7): R_t = 1.35 (62), 570 ($[M+H]^+$); 1.39 (15), 570 ($[M+H]^+$).

^{1}H-NMR (DMSO-d_6): complex spectrum, several isomers; 7.46-7.30 (m, 5 H), 7.27-7.06 (m, 2 H), 6.98-6.67 (4 dd, 1 H), 5.54-5.06 (m, 3 H), 4.68-3.48 (m, 6 H), 3.05-1.98 (m 10 H; s at 2.82, 2.69, 2.64), 1.44-1.41 (3 s, 9 H).

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

Synthesis of Mitsunobu product **89**

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

Synthesis of amino acid **90**

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

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

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

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

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

Synthesis of acid **Ex.4**

According to procedure **H**, ester **Ex.3** (2.0 g, 3.1 mmol) was hydrogenolyzed in MeOH (120 mL)/THF (40 mL) in the presence of catalyst (1 g) for 2 h to afford **Ex.4** (1.68 g, 97%).

Data of **Ex.4**: $C_{26}H_{35}FN_4O_8$ (550.6). HPLC (5% CH_3CN): R_t = 3.60 (86). LC-MS: (method 9c): R_t = 1.53; 551 ($[M+H]^+$), 451 ($[M+H-Boc]^+$).

Synthesis of amine **Ex.5**:

According to procedure **J**, ester **Ex.3** (100 mg, 0.16 mmol) in dioxane (3 mL) was treated with 4M HCl-dioxane (3 mL) to afford **Ex.5**·HCl (100 mg, quant.).

Data of **Ex.5**·HCl: $C_{28}H_{33}FN_4O_6$·HCl (540.6, free base). LC-MS: (method 9c): R_t = 1.44, 541 ($[M+H]^+$).

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

Synthesis of Mitsunobu product **91**

Following procedure **E.1.1** the reaction of phenol **54** (8.0 g, 19 mmol), alcohol **82** (16.0 g, 43 mmol), DEAD (40% in toluene, 38 mL, 84 mmol), and PPh_3 (22 g, 84 mmol) in dry benzene (260 mL)

afforded after FC the protected amino acid **91** (33.5 g, contaminated with triphenylphosphine oxide) which was used in the next step without further purification).

Synthesis of amino acid **92**

Following procedure **E.2**, the reaction of **91** (33.5 g, contaminated with triphenylphosphine oxide), 1,3-dimethyl-barbituric acid (16 g, 102 mmol) and $Pd(PPh_3)_4$ (0.2 g) in EtOAc/CH_2Cl_2 (45:55, 340 mL) yielded after 3 h and after FC (CH_2Cl_2/EtOH 100:0 to 70:30 then CH_2Cl_2/MeOH 90:10 to 70:30) amino acid **92** (4.8 g, 39% over two steps based on phenol **54**).

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

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

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

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

Synthesis of acid **Ex.57**

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

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

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

Synthesis of Mitsunobu product **93**

Following procedure **E.1.1**, the reaction of phenol **56** (6.6 g, 15 mmol), alcohol **81** (13 g, 35 mmol), DEAD (40% in toluene, 32 mL, 69 mmol), and PPh_3 (18 g, 69 mmol) in dry benzene (220 mL) afforded after FC (CH_2Cl_2/MeOH 100:0 to 94:6) the protected amino acid **93** (34.5 g, crude product used in the next step without further purification).

Synthesis of amino acid **94**

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

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

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

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

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

3.16 (t, J = 9.1, 1 H), 3.13 (s, 2.55 H, NCH_3 of major isomer), 3.03 (s, 0.45 H, NCH_3 of minor isomer), 2.98 (s, 2.55 H, NCH_3 of major isomer), 2.87 (0.45 H, NCH_3 of minor isomer), 2.64-2.41 (m, 2 H), 2.27-2.09 (m, 1 H), 1.98-1.83 (m, 2 H), 1.79-1.66 (m, 2 H), 1.45 (s, 7.65 H, Boc, major isomer), 1.35 (s, 1.35 H, Boc, minor isomer).

Synthesis of acid **Ex.86**

According to procedure **H**, ester **Ex.85** (2.0 g, 3.1 mmol) was hydrogenolyzed in MeOH (120 mL) / THF (40 mL) in the presence of the catalyst (1 g) for 2 h to afford, after washing of the filtration residue with warm (50°C) MeOH/TFH 3:1, acid **Ex.86** (1.67 g, 97%).

Data of **Ex.86**: $C_{26}H_{35}FN_4O_8$ (550.6). LC-MS: (method 3): R_t = 1.10 (83), 551 ($[M+H]^+$); 1.17 (15), 551 ($[M+H]^+$).

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

Synthesis of Mitsunobu product **95**

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

Synthesis of amino acid **96**

Following procedure **E.2**, the reaction of **95** (16.0 g, 20 mmol), 1,3-dimethylbarbituric acid (8 g, 49 mmol) and $Pd(PPh_3)_4$ (0.1 g) in EtOAc/CH_2Cl_2 (55:45, 220 mL) yielded after 3 h and after FC (CH_2Cl_2/EtOH 100:0 to 70:30 then CH_2Cl_2/MeOH 90:10 to 70:30) amino acid **96** (11 g, 81%).

Data of **96**: $C_{33}H_{43}FN_4O_9$ (658.7). LC-MS (method 2): R_t = 1.63 (97), 659 ($[M+H]^+$).

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

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

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

Synthesis of acid **Ex.105**

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

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

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

Synthesis of Mitsunobu product **97**

A mixture of the phenol **54** (6.42 g, 14.9 mmol), alcohol **22** (4.04 g, 13.5 mmol), and PPh_3 (9.73 g, 37.1 mmol) was dried i.v. for 15 min. and dissolved in dry, degassed chloroform (130 mL). The soln was cooled to 0°C. A soln of ADDP (9.36 g, 37.1 mmol) in chloroform (20 mL) was slowly added. The mixture was stirred at rt for 3 h followed by the addition of more **22** (4.04 g, 13.5 mmol) and PPh_3 (5.97 g, 22.8 mmol) in chloroform (20 mL). Again, the mixture was cooled to 0°C; and a soln of ADDP (5.74 g, 22.7 mmol) in chloroform (20 mL) was slowly added. The soln was stirred at rt for 16 h and concentrated. The residue was suspended in Et_2O and filtered. The solid was washed with Et_2O. The combined filtrate and washings were concentrated. FC (CH_2Cl_2/EtOAc 10:1) gave **97** (7.73 g, 73%).

Synthesis of amino acid **98**

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

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

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

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

Synthesis of the protected diamide **100**

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

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

Synthesis of the deprotected amino acid **101**

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

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

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

According to procedure **F.1.1**, amino acid **101** (3.44 g, 5.2 mmol) in dry CH_2Cl_2 (50 mL) was treated with T3P (50% in EtOAc, 6.2

mL, 10 mmol) and *i*-Pr_2NEt (3.6 mL, 21 mmol) in dry CH_2Cl_2 (470 mL) to give after FC (CH_2Cl_2/MeOH 95:5) macrolactam **Ex.115** (2.95 g, 90%).

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

Synthesis of acid **Ex.116**

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

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

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

Synthesis of Mitsunobu product **102**

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

Synthesis of amino acid **103**

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

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

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

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

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

Synthesis of acid **Ex.133**

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

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

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

Synthesis of Mitsunobu product **104**

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

Synthesis of amino acid **105**

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

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

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

According to procedure **F.1.1**, amino acid **105** (2.4 g, 3.6 mmol) in dry CH_2Cl_2 (40 mL) was treated with T3P (50% in EtOAc, 4.2 mL, 7.1 mmol) and *i*-Pr_2NEt (2.4 mL, 14.2 mmol) in dry CH_2Cl_2 (300 mL) to give after FC (CH_2Cl_2/MeOH 95:5) macrolactam **Ex.142** (1.92 g, 82%).

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

Synthesis of acid **Ex.143**

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

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

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

Synthesis of Mitsunobu product **106**

Following procedure **B.1.2**, the reaction of phenol **63** (4.2 g, 9.8 mmol), alcohol **16** (4.4 g, 13 mmol), and CMBP (4.8 g, 20 mmol) in dry toluene (120 mL) afforded after 4 h and FC

(hexane/EtOAc 50:50) the protected amino acid **106** (6.37 g, 86%).

Synthesis of amino acid **107**

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

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

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

According to procedure **F.1.2**, amino acid **107** (310 mg, 0.49 mmol) in dry DMF (5 mL) was treated with FDPP (379 mg, 0.99 mmol) in dry DMF (500 mL) to afford after FC (hexane/EtOAc/MeOH 50:50:0 to 0:95:5) macrolactam **Ex.164** (131 mg, 43%).

Data of **Ex.164**: $C_{31}H_{42}N_4O_7Si$ (610.8). LC-MS: (method 7): R_t = 1.34 (98), 611 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 7.42-7.27 (m, 8 H), 6.98 (dd, J = 1.4, 8.2, 1 H), 6.91 (d, J = 7.5, 1 H), 6.84 (s, 1 H), 4.98 (s, 2 H), 4.50 (d, J = 11.9, 1 H), 4.35-4.15 (m, 3 H), 4.06-3.96 (m, 4 H), 3.21 (m, 1 H), 3.10-2.95 (m, 2 H), 2.87 (s, 3 H), 2.30-1.80 (m, 4 H), 0.91 (t, J = 8.3, 2 H), 0.00 (s, 9 H).

Synthesis of amine **Ex.165**

At 0°C a soln of TBAF in THF (1 M, 3.9 mL, 3.9 mmol) was added to a soln of **Ex.164** (1.2 g, 1.96 mmol) in THF (42 mL). The soln was stirred at 0°C to rt for 15 h, followed by the addition of TBAF in THF (1 M, 1.18 mL, 1.18 mmol). Stirring was continued for 2 h. The soln was distributed between CH_2Cl_2 and H_2O. The aqueous phase was repeatedly extracted with CH_2Cl_2. The combined organic phase was dried (Na_2SO_4), filtered and concentrated. FC (CH_2Cl_2/MeOH 100:0 to 90:10) afforded **Ex.165** (0.76 g, 83%).

Data of **Ex.165**: $C_{25}H_{30}N_4O_5$ (466.52). LC-MS: (method 4a): R_t = 1.49 (99), 467 ($[M+H]^+$).

Core 11a: Synthesis of Ex.181 and Ex.182 (Scheme 15)

Synthesis of Mitsunobu product **108**

Following procedure **B.1.2**, the reaction of phenol **65** (10.7 g, 24 mmol), alcohol **16** (10.0 g, 29 mmol), and CMBP (12.0 g, 49 mmol) in dry toluene (362 mL) afforded after FC (hexane/EtOAc 50:50 to 70:30) the protected amino acid **108** (14.55 g, 78%).

Synthesis of amino acid **109**

Following procedure **B.2**, the reaction of **108** (14.50 g, 19 mmol), 1,3-dimethylbarbituric acid (7.0 g, 47.0 mmol) and $Pd(PPh_3)_4$ (0.1 g) in EtOAc/CH_2Cl_2 (55:45, 203 mL) yielded after 3 h and after FC (CH_2Cl_2/MeOH 99:1 to 90:10) amino acid **109** (11.26 g, 92%).

Data of **109**: $C_{32}H_{46}N_4O_8Si$ (642.8). LC-MS: (method 6): R_t = 1.13 (94), 643 ($[M+H]^+$).

Synthesis of the protected macrolactam **Ex.181**

According to procedure **F.1.1**, amino acid **109** (4.0 g, 6.2 mmol) in dry CH_2Cl_2 (100 mL) was treated with T3P (50% in EtOAc, 7.4 mL, 12.4 mmol) and *i*-Pr_2NEt (4.3 mL, 24.8 mmol) in dry CH_2Cl_2 (560 mL). Prior to aqueous workup, the CH_2Cl_2 was replaced by EtOAc. FC (hexane/EtOAc 50:50 to 0:100) afforded the macrolactam **Ex.181** (2.11 g, 54%).

Data of **Ex.181**: $C_{32}H_{44}N_4O_7Si$ (624.8). LC-MS (method 7): R_t = 1.37 (99), 625 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 7.46 (d, J = 8.0, 1 H), 7.42 (d, J = 7.2, 1 H), 7.34-7.23 (m, 6 H), 7.06 (d, J = 8.2, 1 H), 6.82 (d, J = 7.4, 1 H), 6.78 (s, 1 H), 5.02-4.86 (m, 3 H), 4.13 (t, J = 8.5, 1 H), 4.06-3.67 (m, 7 H), 3.05 (br. m, 1 H), 2.88 (br. m, 1 H), 2.88 (s, 3 H), 2.15 (m, 2 H), 1.51 (br. m, 2 H), 1.33 (br. m, 1 H), 1.12 (br. m, 1 H), 0.91 (t-like m, J ca. 8.4, 2 H), 0.00 (s, 9 H).

Synthesis of amine **Ex.182**

According to procedure **I.2**, carbamate **Ex.181** (844 mg, 1.3 mmol) in THF (34 mL) was treated with TBAF soln (4.1 mL) to afford after FC (CH_2Cl_2/MeOH 90:10) amine **Ex.182** (620 mg, 95%)

Data of **Ex.182**: $C_{26}H_{32}N_4O_5$ (480.5). LC-MS: (method 2): R_t = 1.35 (99), 481 ($[M+H]^+$).

Core 11b: Synthesis of Ex.560 and Ex.561 (Scheme 15)

Synthesis of Mitsunobu product **214**

Following procedure **B.1.2**, the reaction of phenol **65** (2.60 g, 5.9 mmol), alcohol **156** (1.96 g, 7.08 mmol) and CMBP (2.85 g, 11.8 mmol) in toluene (84 mL) afforded after 3 h and after FC (hexane/EtOAc gradient) **214** (3.85 g, 93%).

Synthesis of amino acid **215**

Following procedure **B.2**, the reaction of **214** (3.8 g, 5.4 mmol), 1,3-dimethylbarbituric acid (2.12 g, 13.6 mmol) and $Pd(PPh_3)_4$ (31 mg) in EtOAc/CH_2Cl_2 (1:1, 50 mL) afforded after 20 h at rt, evaporation of the volatiles and repeated washing (EtOAc) the solid **215** (3.04 g, 97%).

Data of **215**: $C_{32}H_{37}N_3O_7$ (575.6). LC-MS: (method 4a): R_t = 1.81 (84), 576 ($[M+H]^+$).

Synthesis of macrolactam **Ex.560**

FDPP (1.73 g, 4.5 mmol) was added to a suspension of amino acid **215** (1.51 g, 2.62 mmol) in dry DMF (460 mL). The mixture was stirred at rt for 20 h and concentrated. FC (hexane/EtOAc gradient) afforded **Ex.560** (0.92 g, 63%).

Data of **Ex.560**: $C_{32}H_{35}N_3O_6$ (557.6). LC-MS: (method 4b): R_t = 2.29 (95), 558 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 7.48 (d, J = 7.8, 1 H), 7.37-7.26 (m, 8 H), 7.06-6.94 (m, 4 H), 6.85-6.76 (m, 2 H), 5.01 (s, 2 H), 4.94-4.82 (m, 2 H), 4.39 (t-like m, 1 H), 4.14-4.04 (m, 2 H), 3.95 (q-like m, 1 H), 3.10 (m, 1 H), 3.00-2.82 (m, 2 H), 2.91 (s, 3 H), 2.58 (m, 1 H), 2.19 (td, J = 6.4, 13.3, 1 H), 1.65-1.50 (m, 2 H), 1.38 (m, 1 H), 1.17 (m, 1 H).

Synthesis of amine **Ex.561**

A soln of the benzyl carbamate **Ex.560** (0.87 g, 1.55 mmol) in MeOH (25 mL) was hydrogenolyzed in the presence of 10% palladium on activated charcoal (185 mg) at rt and normal pressure for 4 h. The mixture was filtered through a pad of celite. The filtrate was concentrated. FC (CH_2Cl_2/MeOH 80:20) afforded **Ex.561** (0.65 g, 99%).

Data of **Ex.561**: $C_{24}H_{29}N_3O_4$ (423.5). LC-MS: (method 4a): R_t = 1.56 (98), 424 ($[M+H]^+$).

Core 11c: Synthesis of Ex.567 and Ex.568 (Scheme 15)

Synthesis of Mitsunobu product **216**

Following procedure **B.1.2**, the reaction of phenol **65** (3.0 g, 6.8 mmol), alcohol **161** (3.0 g, 8.2 mmol) and CMBP (3.8 g, 16 mmol) in toluene (76 mL) afforded after 1.5 h and after FC (hexane/EtOAc/MeOH gradient) **216** (3.88 g, 71%).

Synthesis of amino acid **217**

Following procedure **B.2**, the reaction of **216** (25.4 g, 32 mmol), 1,3-dimethylbarbituric acid (13 g, 80 mmol) and $Pd(PPh_3)_4$ (1.9 g) in EtOAc/CH_2Cl_2 (50:50, 410 mL) afforded after 20 h at rt, filtration and washing (CH_2Cl_2) the solid **217** (18.05 g, 84%).

Data of **217**: $C_{33}H_{38}BrN_3O_7$ (668.6). LC-MS: (method 10a): R_t = 1.75 (88), 668/670 ($[M+H]^+$).

Synthesis of macrolactam **Ex.567**

According to procedure **F.1.1**, a mixture of **217** (1.95 g, 2.9 mmol) and *i*-Pr_2NEt (2 mL, 12 mmol) in CH_2Cl_2 (85 mL) was treated with T3P (50% in EtOAc, 4.3 mL, 7.3 mmol) in CH_2Cl_2 (440 mL). After stirring at rt for 20 h, evaporation of the volatiles, aqueous workup (CH_2Cl_2, sat. aq. $NaHCO_3$ soln; Na_2SO_4) and FC (hexane/EtOAc 25:75) **Ex.567** (1.1 g, 57%) was obtained.

Data of **Ex.567**: $C_{33}H_{36}BrN_3O_6$ (650.5). LC-MS: (method 10b): R_t = 2.33 (96), 652/650 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 7.56 (d, *J* = 8.4, 2 H), 7.42 (d, *J* = 7.8, 1 H), 7.34-7.27 (m, 8 H), 6.90 (dd, *J* =

1.9, 10.1, 1 H), 6.84 (d, J = 7.5, 1 H), 6.78 (s, 1 H), 5.00 (s, 2 H), 4.81 (d, J = 12.7, 1 H), 4.48 (d, J = 12.2, 1 H), 4.43 (d, J = 12.2, 1 H), 4.27 (t-like m, 1 H), 4.07-3.89 (m, 4 H), 3.07 (m, 1 H), 2.93 (m, 1 H), 2.93 (s, 3 H), 2.70 (dd, J = 7.3, 10.3, 1 H), 2.30 (m, 1 H), 2.10 (m, 1 H), 1.65-1.50 (m, 2 H), 1.36 (m, 1 H), 1.17 (m, 1 H).

Synthesis of amine **Ex.568**

A soln of **Ex.567** (1.5 g, 2.3 mmol) in MeOH (31 mL) was treated with NH_3 (7 M in MeOH; 1 mL, 7 mmol) and hydrogenolyzed at rt and normal pressure in the presence of 5% palladium on activated charcoal (moistened with 50% H_2O; 400 mg) for 15 h. The mixture was filtered through a pad of celite. The filtrate was concentrated, dissolved in CH_2Cl_2, washed (sat. aq. $NaHCO_3$ soln), filtered and concentrated to afford **Ex.568** (0.98 g, 97%).

Data of **Ex.568**: $C_{25}H_{31}N_3O_4$ (437.5). LC-MS: (method 10a): R_t = 1.41 (96), 438 ($[M+H]^+$).

Core 11d: Synthesis of Ex.586 and Ex.587 (Scheme 15)

Synthesis of Mitsunobu product **218**

Following procedure **B.1.2**, the reaction of the phenol **65** (0.94 g, 2.1 mmol), alcohol **165** (0.705 g, 2.5 mmol) and CMBP (1.03 g, 4.27 mmol) in toluene (22 mL) afforded after 1.5 h and after FC (hexane/EtOAc 1:1) **218** (1.2 g, 80%).

Synthesis of amino acid **219**

Following procedure **B.2**, the reaction of **218** (1.19 g, 1.17 mmol), 1,3-dimethylbarbituric acid (0.64 g, 4.1 mmol) and $Pd(PPh_3)_4$ (0.1 g) in EtOAc/CH_2Cl_2 (55:45, 29 mL) afforded after 2 h and after FC (EtOAc, then CH_2Cl_2/MeOH 100:0 to 80:20) **219** (0.88 g, 89%).

Data of **219**: $C_{33}H_{39}N_3O_6$ (573.7). LC-MS: (method 10a): R_t = 1.67 (87), 574 ($[M+H]^+$).

Synthesis of macrolactam **Ex.586**

According to procedure **F.1.1**, a mixture of **219** (0.87 g, 1.5 mmol) in CH_2Cl_2 (30 mL) was treated with T3P (50% in EtOAc, 2.7 mL, 4.5 mmol) and *i*-Pr_2NEt (1.0 mL, 6 mmol) in CH_2Cl_2 (300 mL). After stirring at rt for 0.5 h, aqueous workup (CH_2Cl_2, sat. aq. Na_2CO_3 soln; Na_2SO_4) and FC (hexane/EtOAc 25:75), **Ex.586** (0.313 g, 37%) was obtained.

Data of **Ex.586**: $C_{33}H_{37}N_3O_5$ (555.6). LC-MS: (method 10b): R_t = 2.22 (96), 556 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 7.43 (d, J = 8.1, 1 H), 7.39-7.18 (m, 11 H), 6.86-6.79 (m, 3 H), 4.95-4.85 (m, 3 H), 4.14 (br. t, J = 8.4, 1 H), 3.91 (d, J = 11.3, 1 H), 3.76 (br. q, J = 7.2, 1 H), 3.55 (t-like m, 1 H), 3.08 (m, 1 H), 2.93 (m, 1 H), 2.91 (s, 3 H), 2.67 (d, J = 6.5, 2 H), 2.37 (t, J = 10.4, 1 H), 2.25 (m, 1 H), 2.01-1.93 (m, 2 H), 1.65-1.50 (m, 2 H), 1.32 (m, 1 H), 1.15 (m, 1 H).

Synthesis of amine **Ex.587**

According to procedure **K**, the benzyl carbamate **Ex.586** (279 mg, 0.5 mmol) was hydrogenolyzed in MeOH (17 mL) in the presence of the catalyst (56 mg) for 3 h to afford **Ex.587** (203 mg, 96%).

Data of **Ex.587**: $C_{25}H_{31}N_3O_3$ (421.5). LC-MS (method 10a): R_t = 1.47 (99), 422 ($[M+H]^+$).

Core 12: Linear synthesis of Ex.196 and Ex.197 (Scheme 16)

Synthesis of Mitsunobu product **110**

Following procedure **B.1.1**, the reaction of phenol **59** (5.22 g, 12.6 mmol), alcohol **16** (5.2 g, 15.2 mmol), PPh_3 (5.0 g, 19 mmol) in dry benzene (124 mL) and DEAD (40% in toluene, 7.0 mL, 15.2 mmol) in dry benzene (36 mL) afforded after FC (hexane/EtOAc 60:40 to 40:60) the protected amino acid **110** (8.3 g, 88%, contaminated with triphenylphosphine oxide, used in the next stop without further purification).

Synthesis of amino acid **111**

Following procedure **B.2**, the reaction of **110** (4.15 g, 5.62 mmol), 1,3-dimethylbarbituric acid (2.19 g, 14.0 mmol) and $Pd(PPh_3)_4$ (0.71 g) in EtOAc/CH_2Cl_2 1:1 (60 mL) yielded after 1 h and after FC (CH_2Cl_2/EtOH 95:5 to 90:10 then CH_2Cl_2/MeOH 90:10 to 70:30) amino acid **111** (2.75 g, 80%).

Data of **111**: $C_{30}H_{42}N_4O_8Si$ (614.8). HPLC (10% CH_3CN): R_t = 3.82 (99). LC-MS (method 9a): R_t = 1.81, 615 ($[M+H]^+$).

Synthesis of the alloc protected amino acid **112**

Following procedure **C.1**, the reaction of amino acid **111** (1.5 g, 2.4 mmol), allyl chloroformate (0.29 mL, 2.68 mmol) and Na_2CO_3 (0.72 g, 6.83 mmol) in dioxane (40 mL) and H_2O (40 mL) gave acid **112** (1.7 g, 100%).

Synthesis of the protected amino acid **113**

Following procedure **C.2**, the acid **112** (1.7 g, 2.4 mmol) was reacted with sarcosine allylester p-toluenesufonate (**46**·p-TsOH, 0.88 g, 2.9 mmol), HOAt (0.5 g, 3.6 mmol), HATU (1.4 g, 3.6 mmol) and *i*-Pr_2NEt (2.1 mL, 12 mmol) in DMF (25 mL) to afford the protected amino acid **113** (1.51 g, 75%).

Data of **113**: $C_{40}H_{55}N_5O_{11}Si$ (809.9). HPLC (40% CH_3CN): R_t = 4.43 (91). LC-MS (method 9c): R_t = 2.51, 810 ($[M+H]^+$).

Deprotection to amino acid **114**

Following procedure **C.3**, the reaction of the protected amino acid **113** (1.5 g, 1.85 mmol), 1,3-dimethylbarbituric acid (0.72 g, 4.6 mmol) and $Pd(PPh_3)_4$ (0.23 g) in EtOAc/CH_2Cl_2 (1:1, 25 mL) yielded amino acid **114** (1.05 g, 83%).

Data of **114**: $C_{33}H_{47}N_5O_9Si$ (685.8). HPLC (10% CH_3CN): R_t = 3.85 (95). LC-MS (method 9c): R_t = 1.78, 686 ($[M+H]^+$).

Synthesis of the protected macrolactam **Ex.196**

According to procedure **F.1.2**, amino acid **114** (1.0 g, 1.46 mmol) in dry DMF (20 mL) was treated with FDPP (1.12 g, 2.92 mmol) in

dry DMF (130 mL) to yield after FC (EtOAc) the macrolactam **Ex.196** (0.61 g, 63%).

Data of **Ex.196**: $C_{33}H_{45}N_5O_8Si$ (667.8). LC-MS (method 1a): R_t = 2.66 (100), 668 ($[M+H]^+$). LC-MS (method 9c): R_t = 2.12, 668 ($[M+H]^+$), 640. ^{1}H-NMR ($CDCl_3$): 7.34-7.26 (m, 6 H), 7.17 (d, J = 7.6, 1 H), 7.02 (s, 1 H), 6.91 (d, J = 9.5, 1 H), 5.49 (d, J = 9.5, 2 H), 5.10 (m, 1 H), 5.06 (s, 2 H), 4.39-4.13 (m, 5 H), 4.00-3.95 (m, 2 H), 3.65 (m, 1 H), 3.36 (br. s, 2 H), 3.14 (m, 2 H), 3.09 (s, 3 H), 2.74 (s, 3 H), 2.45 (m, 1 H), 2.08 (m, 1 H), 0.98 (m, 2 H), 0.00 (s, 9 H). ^{1}H-NMR (DMSO-d_6): 7.98 (d, J = 9.9, 1 H), 7.52 (d, J = 7.9, 1 H), 7.36-7.27 (m, 6 H), 7.18 (s, 1 H), 7.06 (dd, J = 1.8, 8.1, 1 H), 6.83 (d, J = 7.5, 1 H), 5.12 (d, J = 12.5, 1 H), 5.04 (d, J = 12.5, 1 H), 4.87 (d, J = 8.8, 1 H), 4.25-3.89 (m, 8 H), 3.71-3.66 (m, 2 H), 3.20 (m, 1 H), 3.02 (m, 1 H), 2.97 (s, 3 H), 2.65 (s, 3 H), 2.20 (m, 1 H), 2.09 (m, 1 H), 0.92 (t, J = 8.2, 2 H), 0.00 (s, 9 H).

Synthesis of amine **Ex.197**

According to procedure **I.1**, carbamate **Ex.196** (120 mg, 0.18 mmol) in dioxane (3 mL) was treated with 4M HCl-dioxane (3 mL) to afford **Ex.197**·HCl (59 mg, 58%).

Data of **Ex.197**·HCl: $C_{27}H_{33}N_5O_6$·HCl (523.5, free base). HPLC (5% CH_3CN): R_t = 3.05 (83). LC-MS (method 9c): R_t = 1.12, 524 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 8.53 (br. s, NH_3^+), 8.03 (d, J = 9.9, 1 H), 7.41-7.31 (m, 7 H), 7.15 (m, 1 H), 6.85 (d, J = 7.5, 1 H), 5.14 (d, J = 12.5, 1 H), 5.04 (d, J = 12.5, 1 H), 4.86 (dd, J ca. 2.2, 11.0, 1 H), 4.42-4.13 (m, 2 H), 4.05 (t, J = 8.5, 1 H), 3.96 (d, J = 17.8, 1 H), 3.85-3.75 (m, 2 H), 3.65 (br. m, 1 H), ca. 3.3-3.1 (m, 3 H, partially superimposed by the H_2O signal), 2.97 (s, 3 H), 2.67 (s, 3 H), 2.42 (m, 1 H), 2.18 (br. q, J ca. 11.1, 1 H).

Core 12: Convergent synthesis of Ex.197 and Ex.198 (Scheme 17)

Synthesis of Mitsunobu product **115**

Following procedure **E.1.1**, phenol **59** (4.6 g, 11 mmol) was treated for 40 h with alcohol **81** (5.0 g, 13 mmol), DEAD (40% in toluene, 6.1 mL, 13 mmol) and PPh_3 (4.4 g, 17 mmol) in dry benzene (150 mL). After 2h and after 18 h, additional PPh_3 (1.82 g, 6.9 mmol), alcohol **81** (2.04 g, 5.5 mmol) in benzene (50 mL), and DEAD (40% in toluene, 2.55 mL, 5.6 mmol) in benzene (13 mL) were added. FC (hexane/EtOAc 50:50 to 90:10) afforded the protected amino acid **115.1** (2.5 g, 29%).

Following procedure **E.1.2**, the reaction of phenol **59** (2.9 g, 7.0 mmol), alcohol **81**, (5.7 g, 15 mmol) and CMBP (5.1 g, 21 mmol) in dry toluene (121 mL) afforded after FC (hexane/EtOAc 20:80 to 90:10) the protected amino acid **115.2** (2.92 g, 54%).

Synthesis of amino acid **116**

Following procedure **E.2**, the reaction of **115.1** (3.17 g, 4.14 mmol), 1,3-dimethylbarbituric acid (1.62 g, 10.3 mmol) and $Pd(PPh_3)_4$ (0.53 g) in EtOAc/CH_2Cl_2 (1:1, 46 mL) yielded after 1 h and after FC (CH_2Cl_2/MeOH 90:10 to 70:30) the amino acid **116.1** (1.86 g, 70%).

Data of **116.1**: $C_{32}H_{43}N_5O_9$ (641.7). HPLC (5% CH_3CN): R_t = 3.65 (100). LC-MS (method 9c): R_t = 1.60, 642 ($[M+H]^+$).

Following procedure **E.2**, the reaction of **115.2** (2.9 g, 3.8 mmol), 1,3-dimethylbarbituric acid (1.5 g, 9.5 mmol) and $Pd(PPh_3)_4$ (0.48 g) in EtOAc/CH_2Cl_2 (1:1, 46 mL) yielded after 1 h and after FC (CH_2Cl_2/MeOH 90:10 to 70:30) the amino acid **116.2** (2.0 g, 83%).

Data of **116.2**: $C_{32}H_{43}N_5O_9$ (641.7). HPLC (5% CH_3CN): R_t = 3.73 (98). LC-MS (method 9c): R_t = 1.61, 642 ($[M+H]^+$).

Synthesis of the protected macrolactam **Ex.198**

According to procedure **F.1.1**, the amino acid **116.1** (1.0 g, 1.6 mmol) in dry CH_2Cl_2 (200 mL) was treated with T3P (50% in EtOAc, 1.8 mL, 3.1 mmol) and *i*-Pr_2NEt (1.1 mL, 6.2 mmol) in dry

CH_2Cl_2 (1400 mL) to afford after FC (EtOAc/MeOH 95:5 to 80:20) the macrolactam **Ex.198** (containing 15% of the epimer **Ex.231**; 0.38 g, 39%).

Data of **Ex.198**: $C_{32}H_{41}N_5O_8$ (623.7). LC-MS: (method 2): R_t = 1.78 (84), 624 ($[M+H]^+$); 1.82 (15). LC-MS (method 9c): R_t = 1.87, 624 ($[M+H]^+$).

^{1}H-NMR ($CDCl_3$): 7.42-7.25 (m, 7 H), 7.07 (s, 1 H), 7.00 (d, J = 8.2, 1 H), 5.59 (d, J = 9.5, 1 H), 5.38 (br. d, J ca. 7.9, 1 H), 5.18 (dd, J = 2.5, 12.2, 1 H), 5.13 (s, 2 H), 4.43-4.01 (m, 5 H), 3.73 (m, 1 H), 3.47 (d, J = 17.7, 1 H), 3.33 (d, J = 17.7, 1 H), 3.20-3.11 (m, 2 H), 3.17 (s, 3 H), 2.81 (s, 3 H), 2.50 (m, 1 H), 2.15 (m, 1 H), 1.51 (s, Boc, major isomer), 1.45 (s, Boc, minor isomer); ^{1}H-NMR (DMSO-d_6): 7.97 (d, J = 10.3, 1 H), 7.41-7.30 (m, 7 H), 7.18 (s, 1 H), 7.09 (d, J = 8.2, 1 H), 6.85 (J = 7.6, 1 H), 5.12 (d, J = 12.5, 1 H), 5.05 (d, J = 12.6, 1 H), 4.89 (J = 9.6, 1 H), 4.30-3.55 (m, 6 H), 3.40 (2 H, superimposed by H_2O signal), 3.25-3.00 (m, 2 H), 2.99 (s, 3 H), 2.65 (s, 3 H), 2.22 (m, 1 H), 2.05 (br. q, 1 H), 1.41, (s, 9 H).

According to procedure **F.1.1**, amino acid **116.2** (0.85 g, 1.3 mmol) in dry CH_2Cl_2 (170 mL) was treated with T3P (50% in EtOAc, 1.56 mL, 2.6 mmol) and *i*-Pr_2NEt (0.91 mL, 5.3 mmol) in dry CH_2Cl_2 (1190 mL) to afford after FC (EtOAc/MeOH 95:5 to 80:20) the macrolactam **Ex.198** and its epimer **Ex.231** (ca 1:1 mixture; 0.61 g, 73%).

Data of the mixture **Ex.198/Ex.231**: $C_{32}H_{41}N_5O_8$ (623.7). LC-MS: (method 2): R_t = 1.78 (44), 624 ($[M+H]^+$); 1.82 (56), 624 ($[M+H]^+$). ^{1}H-NMR ($CDCl_3$): complex spectrum, mixture of epimers, 7.41-7.20 (m, 6 H), 7.07-6.92 (m, 3 H) 5.8-4.8 (several m, 5 H), 4.3-3.0 (several m, 10 H), 3.16 (s, NCH_3), 2.81 (s, NCH_3), 2.58-2.45 (m, 1 H), 2.19-2.03 (m, 1 H), 1.51, 1.41 (2 s, 9 H)

Synthesis of amine **Ex.197**

According to procedure **J**, carbamate **Ex.198/Ex.231** (ca. 85:15, 749 mg, 1.2 mmol) in dioxane (7.5 mL) was treated with 4M HCl-dioxane (15 mL) to afford **Ex.197**·HCl/**Ex.232**·HCl (607 mg, 90%).

Data of **Ex.197**·HCl/**Ex.232**·HCl: $C_{27}H_{33}N_5O_6$·HCl (523.5, free base). LC-MS (method 2): R_t = 1.26 (75), 1.33 (14); 524 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6), major component **Ex.197**·HCl: spectrum identical with the one described above for compound **Ex.197**·HCl (cf. Scheme 16).

According to procedure **J**, carbamate **Ex.198/Ex.231** (ca. 1:1, 1.32 g, 2.12 mmol) in dioxane (13 mL) was treated with 4M HCl-dioxane (26 mL) to afford after separation of the isomers by preparative RP-HPLC (method 1) **Ex.197**·TFA (460 mg, 34%) and **Ex.232**·TFA (470 mg, 35%).

Data of **Ex.197**·TFA: $C_{27}H_{33}N_5O_6$·$C_2HF_3O_2$ (523.5, free base). LC-MS (method 2): R_t = 1.25 (99), 524 ($[M+H]^+$). LC-MS (method 7): R_t = 0.74 (97), 524 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 8.34 (br. s, NH_3^+), 8.07 (d, J = 9.9, 1 H), 7.43-7.33 (m, 6 H), 7.20 (s, 1 H), 7.10 (dd, J = 1.5, 8.2, 1 H), 6.87 (d, J = 7.4, 1 H), 5.17 (d, J = 12.5, 1 H), 5.05 (d, J = 12.5, 1 H), 4.87 (br. dd, 1 H), 4.27-4.16 (m, 2 H), 4.06 (t, J = 8.6, 1 H), 4.01-3.91 (m, 2 H), 3.82 (t-like dd, J ca. 8.1, 1 H), 3.70 (br. m, 1 H), 3.35-3.20 (m, 3 H), 2.98 (s, 3 H), 2.70 (s, 3 H), 2.49 (m, 1 H), 2.18 (br. q, J ca. 11.0, 1 H).

Data of **Ex.232**·TFA: See below; Core 14.

Core 13: Synthesis of Ex.215 and Ex.216 (Scheme 18)

Synthesis of Mitsunobu product **117**

Following procedure **B.1.1**, the reaction of phenol **59** (2.1 g, 5.1 mmol), alcohol **20** (2.1 g, 6.1 mmol), PPh_3 (2.0 g, 7.6 mmol) in dry benzene (50 mL) and DEAD (40% in toluene, 2.8 mL, 6.1 mmol) in dry benzene (14 mL) afforded, after further addition of PPh_3 (0.84 g, 3.2 mmol), alcohol **20** (0.88 g, 2.6 mmol) in benzene (21 mL) and DEAD (40% in toluene, 1.2 mL, 2.6 mmol) in

benzene (6 mL) and after FC (hexane/EtOAc 50:50) the protected amino acid **117** (3.8 g, 100%).

Synthesis of amino acid **118**

Following procedure **B.2**, the reaction of **117** (7.63 g, 10.3 mmol), 1,3-dimethylbarbituric acid (4.03 g, 25.8 mmol) and $Pd(PPh_3)_4$ (1.31 g) in $EtOAc/CH_2Cl_2$ (1:1, 110 mL) yielded after 1 h and after FC (CH_2Cl_2/MeOH 95:5 to 70:30) amino acid **118** (3.48 g, 60%).

Data of **118**: $C_{30}H_{42}N_4O_8Si$ (614.8). HPLC (10% CH_3CN): R_t = 3.88 (100). LC-MS (method 9a): R_t = 1.80, 615 ($[M+H]^+$).

Synthesis of the alloc protected amino acid **119**

Following procedure **C.1**, the reaction of amino acid **118** (3.36 g, 5.5 mmol), allyl chloroformate (0.64 mL, 6.0 mmol) and Na_2CO_3 (0.87 g, 8.2 mmol) in dioxane (51 mL) and H_2O (51 mL) gave acid **119** (3.51 g, 92%).

Synthesis of the protected amino acid **120**

Following procedure **C.2**, acid **119** (3.47 g, 5.0 mmol) was reacted with sarcosine allylester p-toluenesufonate (**46**·p-TsOH, 1.8 g, 6.0 mmol), HOAt (1.0 g, 7.4 mmol), HATU (2.8 g, 7.4 mmol) and *i*-Pr_2NEt (4.2 mL, 25 mmol) in DMF (108 mL) to afford the protected amino acid **120** (3.52 g, 88%).

Data of **120**: $C_{40}H_{55}N_5O_{11}Si$ (809.9). LC-MS: (method 4b): R_t = 2.51 (95), 810 ($[M+H]^+$)

Deprotection to amino acid **121**

Following procedure **C.3**, the reaction of the protected amino acid **120** (3.49 g, 4.31 mmol), 1,3-dimethylbarbituric acid (1.68 g, 10.8 mmol) and $Pd(PPh_3)_4$ (0.55 g) in $EtOAc/CH_2Cl_2$ (1:1; 50 mL) yielded amino acid **121** (2.72 g,92%).

Data of **121**: $C_{33}H_{47}N_5O_9Si$ (685.8). LC-MS: (method 4b): R_t = 1.84 (94), 686 ($[M+H]^+$)

Synthesis of the protected macrolactam **Ex.215**

According to procedure **F.1.2**, amino acid **121** (1.33 g, 1.94 mmol) in dry DMF (27 mL) was treated with FDPP (1.49 g, 3.88 mmol) in dry DMF (164 mL) to yield after FC (EtOAc/MeOH 95:5) macrolactam **Ex.215** (0.89 g, 68%).

Data of **Ex.215**: $C_{33}H_{45}N_5O_8Si$ (667.8). LC-MS: (method 1b): R_t = 2.60 (99), 668 ($[M+H]^+$). LC-MS: (method 9c): R_t = 2.14, 668 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 7.94 (d, J = 9.8, 1 H), 7.39-7.27 (m, 7 H), 7.11 (s, 1 H), 6.97 (dd, J = 1.5, 8.2, 1 H), 6.82 (d, J = 7.5, 1 H), 5.05 (s, 2 H), 4.83 (br. d, 1 H), 4.25 (br. m, 1 H), 4.17-3.96 (m, 5 H), 3.73 (br. q, J ca. 16.8, 2 H), 3.47 (m, 1 H), 3.33 (m, 1 H), 3.19 (m, 2 H), 2.96 (s, 3 H), 2.67 (s, 3 H), 2.20 (m, 1 H), 2.00 (m, 1 H), 0.91 (t, J = 8.4, 2 H), 0.00 (s, 9 H).

Synthesis of amine **Ex.216**

According to procedure **I.1**, carbamate **Ex.215** (881 mg, 1.3 mmol) in dioxane (16 mL) was treated with 4M HCl-dioxane (16 mL) to afford **Ex.216**·HCl (666 mg, 90%).

Data of **Ex.216**·HCl: $C_{27}H_{33}N_5O_6$·HCl (523.5, free base). HPLC (5% CH_3CN): R_t = 3.11 (91). LC-MS (method 9c): R_t = 1.19, 524 ($[M+H]^+$).

Core 14: Synthesis of Ex.231 and Ex.232 (Scheme 19)

Synthesis of Mitsunobu product **122**

A mixture of phenol **61** (4.6 g, 11.2 mmol) and PPh_3 (5.27 g, 20.1 mmol) was dissolved in benzene. The soln was concentrated and the residue was dried i.v. for 20 min. A soln of the alcohol **81**, (7.46 g, 20.1 mmol) in dry, degassed benzene (120 mL) was added. The resulting mixture was cooled to 0°C. DEAD (40% in toluene, 11.5 mL, 25.1 mmol)

in benzene (10 mL) was slowly added. The soln was stirred at rt for 16 h. More PPh_3 (1.46 g, 5.6 mmol), alcohol **81** (1.04 g, 2.8 mmol) and at 0°C, a soln of DEAD (40% in toluene, 2.6 mL, 5.7 mmol) in benzene (2 mL) were added and stirring at rt was

continued for 7 h. More PPh_3 (1.46 g, 5.6 mmol), alcohol **81** (1.04 g, 2.8 mmol), and at 0°C, a soln of DEAD (40% in toluene, 2.6 mL, 5.7 mmol) in benzene (2 mL) were added. Stirring at rt was continued for 16 h. The mixture was concentrated. FC (hexane/EtOAc 30:70 to 0:100) afforded **122** (12.8 g, contaminated with ca. 40% triphenylphosphine oxide, yield ca. 90%), which was used in the next step without further purification.

Synthesis of amino acid **123**

Following procedure **E.2**, the reaction of the protected amino acid **122** (contaminated with ca. 40% of triphenylphosphine oxide, 12.8 g, ca. 10 mmol), 1,3-dimethylbarbituric acid (3.91 g, 25.1 mmol) and $Pd(PPh_3)_4$ (1.27 g) in $EtOAc/CH_2Cl_2$ (1:1, 120 mL) yielded after 1 h and after FC (CH_2Cl_2/MeOH 100:0 to 70:30 then $CHCl_3$/MeOH 70:30) the amino acid **123** (2.80 g, 44%).

Data of **123**: $C_{32}H_{43}N_5O_9$ (641.7). LC-MS: (method 2): R_t = 1.56 (94), 642 ($[M+H]^+$).

Synthesis of the protected macrolactam **Ex.231**

According to procedure **F.1.2**, amino acid **123** (3.29 g, 5.13 mmol) in dry DMF (150 mL) was added within 4 h at 60°C to FDPP (3.94 g, 10.3 mmol) in dry DMF (4980 mL) to afford after 16 h at 60°C and after FC (EtOAc/MeOH 100:0 to 95:5) macrolactam **Ex.231** (containing ca. 15% of its epimer **Ex.198**; 2.5 g, 78%).

Data of **Ex.231**: $C_{32}H_{41}N_5O_8$ (623.7). LC-MS: (method 2): R_t = 1.78 (12), 1.82 (83), 624 ($[M+H]^+$). LC-MS: (method 7): R_t = 1.16 (18), 624 ($[M+H]^+$); 1.18 (80), 624 ($[M+H]^+$). ^{1}H-NMR ($CDCl_3$): complex spectrum, two epimers; 7.38-7.22 (m, 6 H), 7.06-6.90 (m, 3 H), 5.80-4.80 (several m, 4 H), 5.08, 5.12 (2 s, 2 H), 4.43-2.80 (several br. m, 15 H), 2.51 (m, 1 H), 2.19-2.03 (m, 1 H), 1.50, 1.42 (2 s, 9 H).

Synthesis of amine **Ex.232**

According to procedure **J**, carbamate **Ex.231** (containing 15% of the epimer **Ex.198**; 1.42 g, 2.3 mmol) in dioxane (30 mL) was

treated with 4M HCl-dioxane (45 mL) to afford after preparative RP-HPLC (method 1) **Ex.232**·TFA (1.10 g, 71%) and **Ex.197**·TFA (0.27 g, 17%).

Data of **Ex.232**·TFA: $C_{27}H_{33}N_5O_6 \cdot C_2HF_3O_2$ (523.5, free base). LC-MS (method 2): R_t = 1.32 (99), 524 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): complex spectrum, mixture of isomers; 8.40 (br. s), 8.20 (br. s), 7.84 (d, J = 7.1), 7.50-6.80 (several m), 5.25-3.40 (several m, partially superimposed by the H_2O signal), 3.30-2.80 (m), 3.04 (s, NCH_3), 2.98 (s, NCH_3), 2.67 (s, NCH_3), 2.64 (s, NCH_3), 2.6-1.9 (several m).

Data of **Ex.197**·TFA: See above; Core 12.

Core 15 and Core 16:

Synthesis of Ex.238 and Ex.239 (Scheme 20)

Synthesis of Mitsunobu product **124**

Following procedure **E.1.1**, phenol **77** (1.63 g, 8.5 mmol), alcohol **85** (5.72 g, 12.8 mmol) and PPh_3 (4.02 g, 15.3 mmol) in dry benzene (80 mL) were treated with DEAD (40% in toluene, 8.79 mL, 19.2 mmol) for 20 h. Purification by FC(hexane/EtOAc 20:80 to 100:0) then (hexane/EtOAc 50:50 to 20:80) afforded the protected amino acid **124** (1.96 g, 37%).

Synthesis of the macrocycle **Ex.238**

Dichloro-[1,3-bis(mesityl)-2-imidazoldinylidene]-(3-phenyl-1*H*-inden-1-ylidene)(tricyclohexylphosphine)ruthenium (II) (Umicore M2 catalyst; 88 mg) was added to a soln of **124** (1160 mg, 1.29 mmol) in dry, degassed CH_2Cl_2 (170 mL). The soln was stirred in a sealed tube at 40°C for 68 h, followed by 45 h at rt. During this period further equal portions of catalyst (in total 350 mg) were added after 20 h, 28 h, 44 h, and 52 h. The soln was concentrated. FC (hexane/EtOAc 70:30 to 0:100) gave **Ex.238** (350 mg, 46%, mixture of two isomers, ratio > 9:1, acceptable for the use in the next step). An analytical sample (69 mg) was further purified by preparative RP-HPLC (method 2) to afford pure **Ex.238** (major isomer; 45 mg).

Data of **Ex.238** (major isomer): $C_{32}H_{40}N_4O_7$ (592.6). LC-MS: (method 4a): R_t = 2.23 (92), 593 ($[M+H]^+$). ^{1}H-NMR ($CDCl_3$): 7.62-7.31 (m, 6 H), 7.07 (d, J = 7.6, 1 H), 6.99 (dd, J = 2.0, 7.9, 1 H), 6.85 (s, 1 H), 5.69-5.61 (m, 2 H), 5.48 (d, J = 8.2, 1 H), 5.21 (m, 1 H), 5.10 (s, 2 H), 4.76 (d, J = 10.1, 1 H), 4.54 (dt, J = 3.5, 7.9, 1 H), 4.41-4.25 (m, 2 H), 4.13 (d, J = 10.7, 1 H), 3.97 (m, 1 H), 3.62 (m, 2 H), 3.48 (m, 1 H), 3.10 (s, 3 H), 2.73 (m, 1 H), 2.60-2.45 (m, 2 H), 2.02 (m, 1 H), 1.46 (s, 9 H).

Synthesis of amine **Ex.239**

A soln of **Ex.238** (430 mg, 0.73 mmol) in MeOH/THF 1:3, 36 mL) was hydrogenated for 3.5 h at rt under normal pressure in the presence of palladium hydroxide on activated charcoal (moistened with 50% H_2O; 215 mg). The mixture was filtered through a pad of celite. The filtrate was concentrated to give **Ex.239** (355 mg, quant.; used in the next step without further purification).

An analytical sample (68 mg) was purified by preparative RP-HPLC (method 2) to afford pure **Ex.239** (37 mg).

Data of **Ex.239**: $C_{24}H_{36}N_4O_5$ (460.6): LC-MS (method 7): R_t = 0.88 (97), 461 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 7.36 (t, J = 7.8, 1 H), 7.25 (d, J = 6.1, 1 H), 7.03 (dd, J = 1.6, 8.2, 1 H), 6.88-6.65 (m, 2 H), 4.51 (d, J = 8.3, 1 H), 4.18 (t, J = 10.3, 2 H), 4.09 (br. s, 1 H), 3.96 (br. m, 2 H), 3.19-2.72 (m, 3 H), 2.92 (s, 3 H), 2.34 (m, 2 H), 2.05 (br. q, 1 H), 1.82 (m, 1 H), 1.60-0.85 (m, 5 H), 1.40 (s, 9 H), 0.82 (m, 1 H).

Core 17: Synthesis of Ex.248 and Ex.249 (Scheme 21)

Synthesis of Mitsunobu product **125**

Following procedure **E.1.1**, phenol **68** (6.0 g, 14.6 mmol), alcohol **82** (9.75 g, 26.2 mmol), and PPh_3 (6.88 g, 26.2 mmol) were treated in dry benzene (160 mL) with DEAD (40% in toluene, 15 mL, 32.8 mmol) for 40 h. After 18 h and after 25 h, more PPh_3 (1.27 g, 4.8 mmol) and DEAD (40% in toluene, 2.23 mL, 4.9

mmol) in benzene (2 mL) were added. FC (hexane/EtOAc 30:70 to 20:80) afforded the protected amino acid **125** (16.85 g, contaminated with ca. 40% triphenylphosphine oxide, yield ca. 85%), which was used in the next step without further purification.

Synthesis of amino acid **126**

Following procedure **E.2**, the reaction of **125** (16.8 g, contaminated with ca. 40% of triphenylphosphine oxide, ca. 12 mmol), 1,3-dimethylbarbituric acid (4.80 g, 30.8 mmol) and $Pd(PPh_3)_4$ (1.56 g) in EtOAc/CH_2Cl_2 (1:1, 170 mL) yielded after 1 h and after FC (CH_2Cl_2/MeOH 0:100 to 70:30, then $CHCl_3$/MeOH 70:30) amino acid **126** (4.15 g, ca. 52%).

Data of **126**: $C_{33}H_{44}N_4O_9$ (640.7). HPLC (10% CH_3CN): R_t = 3.67 (69). LC-MS (method 9c): R_t = 1.75, 641 ($[M+H]^+$).

Synthesis of the protected macrolactam **Ex.248**

According to procedure **F.1.1**, amino acid **126** (4.55 g, 7.1 mmol) in dry CH_2Cl_2 (120 mL) was added within 3 h to T3P (50% in EtOAc, 8.37 ml, 14.2 mmol) and *i*-Pr_2NEt (4.83 ml, 28.4 mmol) in dry CH_2Cl_2 (6660 mL). Prior to aqueous workup, CH_2Cl_2 was replaced with EtOAc. FC (CH_2Cl_2/MeOH 100:0 to 95:5) yielded macrolactam **Ex.248** (2.38 g, 54%).

Data of **Ex.248**: $C_{33}H_{42}N_4O_8$ (622.7). LC-MS: (method 2): R_t = 1.83 (100), 623 ($[M+H]^+$). LC-MS: (method 9c): R_t = 1.97, 623 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 7.45-7.34 (m, 5 H), 7.15-6.78 (m, 5 H), 5.25 (s, 2 H), 5.08 (d, J = 12.8, 1 H), 4.62 (d, J = 13.5, 2 H), 4.29 (m, 1 H), 4.09 (d, J = 7.3, 1 H), 3.89 (d, J = 12.4, 1 H), 3.54 (br. t, 1 H), 3.27 (m, 1 H), 3.07 (s, 3 H), 2.80 (m, 1 H), 2.71 (s, 3 H), 2.28-2.06 (m, 4 H), 1.94 (m, 1 H), 1.71 (m, 1 H), 1.39 (s, 9 H).

Synthesis of acid **Ex.249**

According to procedure **H**, the ester **Ex.248** (2.16 g, 3.5 mmol) was hydrogenolyzed in MeOH (130 mL)/THF (40 mL) in the presence

of the catalyst (1.09 g) for 2.5 h to afford the acid **Ex.249** (1.83 g, 99%).

Data of **Ex.249**: $C_{26}H_{36}N_4O_8$ (532.6). LC-MS: (method 2): R_t = 1.42 (95), 533 ($[M+H]^+$).

Core 18: Synthesis of Ex.272, Ex.273, and Ex.274 (Scheme 22)

Synthesis of Mitsunobu product **127**

Following procedure **E.1.1**, the reaction of phenol **71** (6.47 g, 15,7 mmol), alcohol **81** (10.5 g, 28.2 mmol), DEAD (40% in toluene, 26 mL, 56.3 mmol), and PPh_3 (14.8 g, 56.3 mmol) in dry benzene (380 mL) afforded after 2 h at rt and after aqueous workup (EtOAc, sat. aq. Na_2CO_3 soln, sat. aq. NaCl soln), drying (Na_2SO_4), concentration of the organic layer and FC (hexane/EtOAc 30:70, 0:100, then CH_2Cl_2/MeOH 90:10) the protected amino acid **127** (12.0 g, 99%).

Synthesis of amino acid **128**

Following procedure **E.2**, the reaction of **127** (12.0 g, 16 mmol), 1,3-dimethylbarbituric acid (5.9 g, 38.0 mmol) and $Pd(PPh_3)_4$ (0.9 g) in EtOAc/CH_2Cl_2 (55:45, 275 mL) yielded after 2 h and after FC (EtOAc, then CH_2Cl_2/MeOH 90:10 to 60:40) amino acid **128** (9.05 g, 90%).

Data of **128**: $C_{31}H_{42}N_6O_9$ (642.7). LC-MS: (method 7): R_t = 0.90 (94), 643 ($[M+H]^+$).

Synthesis of the protected macrolactam **Ex.272**

According to procedure **F.1.1**, amino acid **128** (5.04 g, 7.8 mmol) in dry CH_2Cl_2 (100 mL) was treated with T3P (50% in EtOAc, 9.2 mL, 16 mmol) and *i*-Pr_2NEt (5.4 mL, 31 mmol) in dry CH_2Cl_2 (700 mL) to afford after FC (CH_2Cl_2/MeOH 39:1 to 19:1) the epimeric macrolactams **Ex.272** (1.90 g, 38%).

Data of **Ex.272**: $C_{31}H_{40}N_6O_8$ (624.7). LC-MS: (method 2): R_t = 1.61 (99), 625 ($[M+H]^+$). LC-MS: (method 7): R_t = 1.01 (99), 625 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 8.47 (d, J = 2.6, 1 H), 8.12 (s, 1 H), 7.95 (d, J = 9.6, 1 H), 7.61 (s, 1 H), 7.40-7.29 (m, 6 H),

5.10 (d, J = 12.6, 1 H), 5.04 (d, J = 12.6, 1 H), 4.98 (br. d, J = 10.7, 1 H), 4.16 (br. d, J = 11.8, 1 H), 4.10-3.90 (m, 4 H), 3.71 (br. t, J ca. 8.4, 1 H), 3.65-3.40 (m, 2 H), 3.23 (br. dd, J = 11.1, 15.2, 1 H), 3.04 (s, 3 H), 2.92 (t, J = 9.6, 1 H), 2.66 (s, 3 H), 2.12 (m, 1 H), 2.09 (br. q, 1 H), 1.42 (s, 9 H).

Synthesis of amine **Ex.273**

According to procedure **J**, carbamate **Ex.272** (3.12 g, 5 mmol) in dioxane (31 mL) was treated with 4M HCl-dioxane (62 mL) to afford **Ex.273**·2HCl (2.9 g, 97%)

Data of **Ex.273**·2HCl: $C_{26}H_{32}N_6O_6$·2HCl (524.5, free base). LC-MS (method 2): R_t = 1.31 (92), 525 ($[M+H]^+$).

Synthesis of amine **Ex.274**

According to procedure **K**, carbamate **Ex.272** (200 mg, 0.32 mmol) was hydrogenolyzed in MeOH (20 mL) in the presence of the catalyst (100 mg) to afford **Ex.274** (154 mg, 97%).

Data of **Ex.274**: $C_{23}H_{34}N_6O_6$. (490.5). LC-MS (method 2): R_t = 1.26 (98), (491 ($[M+H]^+$).

Core 19: Synthesis of Ex.297 and Ex.298 (Scheme 23)

Synthesis of Mitsunobu product **129**

Following procedure **E.1.2**, the reaction of phenol **75** (4.58 g, 9.9 mmol), alcohol **81** (5.5 g, 15 mmol), and CMBP (4.8 g, 20 mmol) in dry toluene (24 mL) afforded after FC (hexane/EtOAc 1:3) the protected amino acid **129** (5.54 g, 68%).

Synthesis of amino acid **130**

Following procedure **E.2**, the reaction of **129** (5.53 g, 6.8 mmol), 1,3-dimethylbarbituric acid (2.5 g, 16 mmol) and $Pd(PPh_3)_4$ (0.39 g) in EtOAc/CH_2Cl_2 55:45 (118 mL) yielded after 2 h and after FC (CH_2Cl_2/MeOH 95:5 to 70:30) amino acid **130** (1.45 g, 85%).

Data of **130**: $C_{36}H_{45}N_5O_9$ (691.7). LC-MS (method 7): R_t = 1.09 (96), 692 ($[M+H]^+$).

Synthesis of the protected macrolactam **Ex.297**

According to procedure **F.1.1**, amino acid **130** (2.57 g, 3.7 mmol) in dry CH_2Cl_2 (40 mL) was treated with T3P (50% in EtOAc, 4.4 mL, 7.4 mmol) and *i*-Pr_2NEt (2.5 mL, 14.9 mmol) in dry CH_2Cl_2 (330 mL) to give after FC (CH_2Cl_2/MeOH 99:1 to 90:10) macrolactam **Ex.297** (2.5 g, contaminated with ca. 20% *i*-Pr_2NEt; yield 80%).

Data of **Ex.297**: $C_{36}H_{43}N_5O_8$ (673.7). LC-MS: (method 7): R_t = 1.18 (93), 674 ($[M+H]^+$).

Aqueous workup (EtOAc, 1 M aq. NaH_2PO_4 soln) of an analytical sample (100 mg) afforded pure **Ex.297** (81 mg).

LC-MS: (method 2): R_t = 2.20 (93), 674 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): complex spectrum, several isomers, 8.51 (d, *J* = 8.5, 0.2 H), 8.47 (d, *J* = 8.7, 0.1 H), 8.40 (d, *J* = 8.5, 0.55 H), 8.32 (d, *J* = 8.5, 0.15 H), 7.68-7.10 (several m, 10 H), 5.96 (br. s, 0.3 H), 5.90 (br. s, 0.3 H), 5.4-5.0 (m, 2.4 H), 4.8-3.8 (several m, 8 H), 3.3-2.5 (several m and s, 8 H), 2.5-1.6 (several m, 4 H), 1.42, 1.41, 1.36, 1.26 (4 s, Boc).

Synthesis of acid **Ex.298**

According to procedure **H**, the ester **Ex.297** (2.0 g, contaminated with ca. 20% *i*-Pr_2NEt 2.4 mmol) was hydrogenolyzed in MeOH (200 mL) in the presence of catalyst (1 g) for 3 h.

The crude product was suspended in Et_2O (20 mL) stirred for 20 min, filtered, washed (Et_2O) and dried to afford **Ex.298** (1.63 g, contaminated with 15% *i*-Pr_2NEt, quant. yield).

Aqueous workup (CH_2Cl_2, 1 M aq. NaH_2PO_4 soln) of an analytical sample (200 mg) afforded pure **Ex.298** (135 mg).

Data of **Ex.298**: $C_{29}H_{37}N_5O_8$ (583.6). LC-MS: (method 4a): R_t = 1.78 (86), 584 ($[M+H]^+$).

Core 20: Synthesis of Ex.311 (Scheme 24)

Synthesis of Mitsunobu product **131**

A soln of phenol **72** (200 mg, 0.34 mmol), alcohol **16** (178 mg, 0.52 mmol) and PPh_3 (180 mg, 0.69 mmol) in benzene (5 mL) was degassed. At 0°C, DEAD (40% in toluene, 0.32 mL, 0.69 mmol) was added. The mixture was stirred at rt for 15 h. Additional alcohol **16** (178 mg, 0.52 mmol) and PPh_3 (180 mg, 0.69 mmol) were added. DEAD (40% in toluene, 0.32 mL, 0.69 mmol) was added at 0°C. The mixture was stirred for 20 h and concentrated. FC (CH_2Cl_2/EtOAc 100:0 to 80:20) afforded **131** (containing ca. 20% of diethyl hydrazine-1,2-dicarboxylate; used without further purification).

Synthesis of amino acid **132**

Following procedure **B.2**, the reaction of **131** (250 mg, ca. 80%, 0.22 mmol), 1.3-dimethylbarbituric acid (107 mg, 0.69 mmol) and $Pd(PPh_3)_4$ (16 mg) in EtOAc/CH_2Cl_2 (55:45, 4.8 mL) yielded after 3 h and after FC (EtOAc/MeOH 100:0 to 90:10, then CH_2Cl_2/MeOH 90:10 to 80:20) **132** (177 mg, yield over the two steps: 73%).

Data of **132**: $C_{39}H_{57}N_5O_{10}Si$ (784.0): LC-MS: (method 7): R_t = 1.31, 784.2 ($[M+H]^+$).

Synthesis of the alloc protected amino acid **133**

Following procedure **C.1**, the reaction of **132** (150 mg, 0.19 mmol), allyl chloroformate (23 µL, 0.21 mmol) and Na_2CO_3 (61 mg, 0.57 mmol) in dioxane (1.5 mL) and H_2O (1.5 mL) gave, after 2 h at 0°C, acid **133** (154 mg, 92%).

Synthesis of the protected amino acid **134**

Following procedure **C.2**, acid **133** (140 mg, 0.16 mmol) was reacted with sarcosine allylester p-toluenesulfonate (**46**·pTsOH, 58 mg, 0.194 mmol), HOAt (33 mg, 0.24 mmol), HATU (92 mg, 0.24 mmol) and *i*-Pr_2NEt (0.138 mL, 0.81 mmol) in DMF (2.4 mL) to afford the protected amino acid **134** (106 mg, 67%).

Data of **134**: $C_{49}H_{70}N_6O_{13}Si$ (979.2). LC-MS: (method 7): R_t = 1.68, 979.3 ($[M+H]^+$).

Synthesis of amino acid **135**

Following procedure **C.3**, the reaction of the protected amino acid **134** (100 mg, 0.10 mmol), 1.3-dimethylbarbituric acid (38 mg, 0.25 mmol) and $Pd(PPh_3)_4$ (6 mg) in EtOAc/CH_2Cl_2 (45:55, 1.9 mL) yielded after 16 h and after FC (EtOAc, then CH_2Cl_2/MeOH 90:10) **135** (70 mg, 80%).

Data of **135**: $C_{42}H_{62}N_6O_{11}Si$ (855.1). LC-MS: (method 7): R_t = 1.30, 855.5 ($[M+H]^+$).

Synthesis of the protected macrolactam **Ex.311**

According to procedure **F.1.1**, a soln of the amino acid **135** (60 mg, 0.07 mmol) in dry CH_2Cl_2 (2 mL), was added within 2 h to T3P (50% in EtOAc; 84 µL, 0.14 mmol) and *i*-Pr_2NEt (48 µL, 0.28 mmol) in CH_2Cl_2 (5 mL). Then sat. aq. $NaHCO_3$ soln was added and the mixture was extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4), filtered and concentrated. FC (EtOAc) afforded **Ex.311** (26 mg, 44%).

Data of **Ex.311**: ($C_{42}H_{60}N_6O_{10}Si$ (837.0). LC-MS: (method 7): R_t = 1.51 (90), 837.4 ($[M+H]^+$). ^{1}H-NMR ($CDCl_3$): 7.26 (s, 5 H), 7.09 (t, J = 8.4, 1 H), 6.78 (d-like m, 1 H), 6.61 (d, J = 7.4, 1 H), 5.50-4.90 (several br. m, 5 H), 4.90-3.80 (several br. m, 8 H), 3.69 (br. t, J ca. 8.5, 1 H), 3.6-2.3 (several br. m, 14 H), 2.12 (m, 1 H), 1.61 (m, 1 H), 1.38 (s, 9 H), 1.24 (s, 2 H), 0.93 (br. t, J ca. 8.0, 2 H), 0.00, -0.03 (2 s, 9 H).

Core 21: Synthesis of Ex.312 - Ex.315 (Scheme 25)

Synthesis of Mitsunobu product **136**

Alcohol **82** (217 mg, 0.58 mmol) and CMBP (212 mg, 0.88 mmol) were dissolved in dry degassed toluene (7 mL) and heated at 100°C for 30 min. A soln of **80** (250 mg, 0.58 mmol) in toluene (2 mL) was added dropwise. Stirring at 100°C was continued for

1 h. The volatiles were evaporated. FC (hexane/EtOAc 2:1 to 1:1) yielded **136** (290 mg, 63%).

Synthesis of amino acid **137**

Following procedure **E.2** the reaction of **136** (250 mg, 0.32 mmol), 1,3-dimethylbarbituric acid (120 mg, 0.77 mmol) and $Pd(PPh_3)_4$ (18 mg) in EtOAc/CH_2Cl_2 (45:55, 5.5 mL) yielded after 0.5 h and after FC (CH_2Cl_2/MeOH 95:5 to 70:30) amino acid **137** (164 mg, 78%).

Data of **137**: $C_{33}H_{44}N_4O_8S$ (656.8). LC-MS (method 7): R_t = 1.15 (95), 657 ($[M+H]^+$).

Synthesis of the protected macrolactam **Ex.312**

According to procedure **F.1.1**, a soln of the amino acid **137** (100 mg, 0.15 mmol) in dry CH_2Cl_2 (2 mL) was added over 2 h to T3P (50% in EtOAc, 0.18 mL, 0.31 mmol) and *i*-Pr_2NEt (0.1 mL, 0.61 mmol) in dry CH_2Cl_2 (13 mL). Stirring at rt was continued for 1 h, followed by aqueous workup (EtOAc, sat. aq. $NaHCO_3$ soln, Na_2SO_4) and FC (EtOAc) to afford **Ex.312** (56 mg, 57%).

Data of **Ex.312**: $C_{33}H_{42}N_4O_7S$ (638.7). LC-MS (method 7): R_t = 1.33 (95), 639 ($[M+H]^+$). ^{1}H-NMR ($CDCl_3$): 7.37-7.23 (m, 8 H), 6.92 (br. s, 1 H), 5.25 (m, 2 H), 5.17 (s, 1 H), 4.88 (d, J = 16.2, 1 H), 4.62 (br. m, 1 H), 4.46 (br. t-like m, 1 H), 4.31 (br. m, 1 H), 4.17 (dd, J = 4.1, 14.2, 1 H), 3.72 (dd, J = 4.8, 10.7, 1 H), 3.50 (m, 1 H), 3.30-2.80 (several m, 2 H), 3.14 (s, 3 H), 3.01 (s, 3 H), 2.60-1.90 (several m, 6 H), 1.46 (s, 9 H).

Synthesis of sulfone **Ex.313**

m-CPBA (70% w/w; 10 mg, 41 µmol) was added at 0°C to a soln of **Ex.312** (20 mg, 31 µmol) in CH_2Cl_2 (0.5 mL). The mixture was stirred for 15 min followed by the addition of m-CPBA (9 mg, 37 µmol). The mixture was allowed to warm to rt over 1 h, diluted with CH_2Cl_2 and washed with aq. $Na_2S_2O_3$ soln and with aq. $NaHCO_3$ soln. The organic phase was dried (Na_2SO_4), filtered and

concentrated. FC (EtOAc/MeOH 100:0 to 90:10) afforded **Ex.313** (8 mg, 38%).

Data of **Ex.313**: $C_{33}H_{42}N_4O_9S$ (670.7). LC-MS (method 6): R_t = 1.24 (95), 671 ($[M+H]^+$). ^{1}H-NMR ($CDCl_3$): 7.89 (td, J = 1.7, 7.3, 1 H), 7.71 (s, 1 H), 7.43-7.28 (m, 7 H), 5.17 (d, J = 12.0, 1 H), 5.10 (d, J = 12.0, 1 H), 5.01 (dd, J = 5.9, 9.1, 1 H), 4.96-4.85 (m, 2 H), 4.71 (d, J = 15.4, 1 H), 4.57 (br. m, 1 H), 4.33 (br. m, 2 H), 3.85 (dd, J = 7.8, 12.3, 1 H), 3.25 (s, 3 H), 3.20 (m, 1 H), 3.10 (m, 1 H), 2,97 (s, 3 H), 2.73-2.54 (m, 2 H), 2.45-2.23 (m, 2 H), 2.17 (m, 1 H), 1.99 (m, 1 H), 1.46 (s, 9 H).

Synthesis of acid **Ex.314**

A soln of the benzyl ester **Ex.312** (1.69 g, 2.6 mmol) in THF/MeOH (3:1; 36 mL) was treated with H_2O (9 mL) and at 0°C $LiOH \cdot H_2O$ (0.22 g, 5.2 mmol) was added. The mixture was stirred for 1 h at 0°C, acidified to pH 5 with 1 M aq. NaH_2PO_4 soln and extracted with $CHCl_3$. The organic layer was dried (Na_2SO_4), filtered and concentrated. The resulting solid was suspended in Et_2O and filtered to give **Ex.314** (1.4 g, 96%).

Data of **Ex.314**: $C_{26}H_{36}N_4O_7S$ (548.6). LC-MS (method 7): R_t = 1.29 (97), 549 ($[M+H]^+$).

Synthesis of acid **Ex.315**

According to procedure **H**, a soln of the benzyl ester **Ex.313** (1.69 g, 2.5 mmol) was hydrogenolyzed in MeOH (65 mL) in the presence the catalyst (1.69 g) for 4 h, filtered through a pad of celite and concentrated to afford **Ex.315** (1.35 g, 92%).

Data of **Ex.315**: $C_{26}H_{36}N_4O_9S$ (580.6). LC-MS (method 4b): R_t = 1.62 (99), 581 ($[M+H]^+$).

Core 22: Synthesis of Ex.342 and Ex.343 (Scheme 26)

Synthesis of Mitsunobu product **220**

At 0°C DEAD (40% in toluene, 33 mL, 71.6 mmol) was slowly added to a soln of phenol **199** (15.42 g, 35.8 mmol), alcohol **14** (12.9

g, 43 mmol) and PPh_3 (18.8 g, 71.6 mmol) in dry benzene (306 mL). The mixture was stirred for 3.5 h at 0°C to rt. H_2O (0.64 mL, 35.8 mmol) was added and stirring continued for 5 min. The mixture was concentrated. The residue was suspended in Et_2O (150 mL) and filtered. The filtrate was concentrated. This washing procedure was repeated twice to afford after concentration of the filtrate and FC (hexane/EtOAc) the protected amino acid **220** (20.3 g, 80%; contaminated with diethyl hydrazine-1,2-dicarboxylate, used without further purification).

Synthesis of amino acid **221**

Following procedure **B.2**, the reaction of **220** (19.86 g, 27.8 mmol), 1,3-dimethylbarbituric acid (10.87 g, 69.6 mmol) and $Pd(PPh_3)_4$ (0.32 g) in EtOAc/CH_2Cl_2 (55:45, 300 mL) yielded after 2 h and evaporation of the volatiles a solid which was filtered and washed with EtOAc to give **221** (13.95 g, 85%).

Data of **221**: $C_{29}H_{37}FN_4O_8$ (588.6). LC-MS (method 10a): R_t = 1.58 (95), 589 ($[M+H]^+$).

Synthesis of the protected macrolactam **Ex.342**

Amino acid **221** (12.58 g, 21.4 mmol) was added in portions to a soln of T3P (50% in EtOAc, 37.8 mL, 64.1 mmol) and *i*-Pr_2NEt (18.3 mL, 106.9 mmol) in dry CH_2Cl_2 (4280 mL). Stirring at rt was continued for 2 h, followed by evaporation of the volatiles. FC (hexane/EtOAc/MeOH gradient) afforded the macrolactam **Ex.342** (9.4 g, contaminated with 10% of the cyclic dimer). Further purification of this material (1.0 g) by FC (hexane/EtOAc/MeOH gradient) afforded pure **Ex.342** (0.81 g).

Data of **Ex.342**: $C_{29}H_{35}FN_4O_7$ (570.6). LC-MS (method 10b): R_t = 2.05 (97), 571 ($[M+H]^+$), 471. ^{1}H-NMR (DMSO-d_6): 8.21 (br. t, 1 H), 7.57 (d, J = 6.7, 1 H), 7.50 (d, J = 8.8, 1 H), 7.40-7.31 (m, 7 H), 7.22 (d, J = 6.6, 1 H), 5.06 (d, J = 12.4, 1 H), 4.99 (d, J = 12.6, 1 H), 4.45-4.40 (m, 2 H), 4.35-4.25 (m, 2 H), 4.13 (m, 1 H), 4.03 (m, 1 H), 3.64 (m, 1 H), 3.30 (m, 2 H,

superimposed by H_2O signal), 2.27 (m, 1 H), 1.99-1.86 (m, 3 H), 1.39 (s, 9 H).

Synthesis of amine **Ex.343**

According to procedure **K**, benzyl carbamate **Ex.342** (5.0 g, 8.7 mmol) was hydrogenolyzed in MeOH (100 mL) in the presence of catalyst (656 mg) for 2 h to afford after filtration, evaporation of the volatiles and FC (CH_2Cl_2/MeOH 95:5 to 80:20) amine **Ex.343** (3.2 g, 84%).

Data of **Ex.343**: $C_{21}H_{29}FN_4O_5$ (436.5). LC-MS (method 10b): R_t = 1.37 (100), 437 ($[M+H]^+$), 381, 337.

Core 23: Synthesis of Ex.363 and Ex.364 (Scheme 27)

Synthesis of the amide **222**

T3P (50% in EtOAc, 6.8 mL, 11.5 mmol) was added to a soln of acid **192** (2.4 g, 5.8 mmol) and amine hydrochloride **178**·HCl (1.8 g, 5.8 mmol) in dry CH_2Cl_2 (65 mL). *i*-Pr_2NEt (4.1 mL, 23.9 mmol) was slowly added; and the mixture was stirred for 5 h at rt. The mixture was distributed between 1 M aq. NaH_2PO_4 soln and CH_2Cl_2. The organic phase was dried (Na_2SO_4), filtered and concentrated. FC (hexane/EtOAc gradient) afforded amide **222** (3.49 g, 93%).

Data of **222**: $C_{37}H_{47}N_3O_{11}$ (709.8). LC-MS (method 10a): R_t = 2.50 (96), 710 ($[M+H]^+$).

Synthesis of amino acid **223**

Following procedure **B.2**, the reaction of **222** (3.45 g, 4.86 mmol), 1,3-dimethylbarbituric acid (1.9 g, 12.1 mmol) and $Pd(PPh_3)_4$ (28 mg) in EtOAc/CH_2Cl_2 (1:1, 60 mL) yielded after 4 h and after FC (CH_2Cl_2/MeOH 90:10 to 70:30) amino acid **223** (2.32 g, 81%).

Data of **223**: $C_{30}H_{39}N_3O_9$ (585.6). LC-MS (method 10a): R_t = 1.62 (97), 586 ($[M+H]^+$).

Synthesis of the protected macrolactam **Ex.363**

According to procedure **F.1.2**, the amino acid **223** (2.3 g, 3.9 mmol) in dry DMF (50 mL) was treated with FDPP (3.15 g, 8.2 mmol) in DMF (700 mL). After completion of the addition, the mixture was concentrated. FC (hexane/EtOAc/MeOH gradient) afforded macrolactam **Ex.363** (1.78 g, 80%).

Data of **Ex.363**: $C_{30}H_{37}N_3O_8$ (567.6). LC-MS (method 10b): R_t = 2.00 (98), 568 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 7.43-7.34 (m, 5 H), 7.27 (t, J = 7.8, 1 H), 7.20 (d, J = 7.2, 1 H), 7.01 (m, 1 H), 6.85 (br. s, 1 H), 6.79 (d, J = 7.4, 1 H), 5.22 (s, 2 H), 5.05 (d, J = 12.5, 1 H), 4.76 (dd, J = 3.7, 9.8, 1 H), 4.08 (t, J = 8.7, 1 H), 3.94-3.80 (m, 4 H), 3.59 (dd, J = 3.7, 12.3, 1 H), 3.26 (br. t, J ca. 8.5, 1 H), 3.15 (d, J = 14.1, 1 H), 2.78 (s, 3 H), 2.22-2.03 (m, 3 H), 1.37 (s, 9 H).

Synthesis of acid **Ex.364**

Ester **Ex.363** (1.5 g, 2.6 mmol) was hydrogenolyzed in MeOH (30 mL) in the presence of 10% palladium on charcoal (moistened with 50% H_2O; 0.34 g) for 4 h, filtered through a pad of celite and concentrated to afford **Ex.364** (1.26 g, 97%).

Data of **Ex.364**: $C_{23}H_{31}N_3O_8$ (477.5). LC-MS (method 10c): R_t = 1.42 (98), 478 ($[M+H]^+$).

Core 24a: Synthesis of Ex.379 and Ex.380 (Scheme 28)

Synthesis of Mitsunobu product **Ex.379**

Following procedure **B.1.2**, the reaction of phenol **200** (4.31 g, 10.1 mmol), alcohol **14** (3.64 g, 12.1 mmol) and CMBP (4.88 g, 20.2 mmol) in dry toluene (180 mL) afforded after 2 h and after FC (hexane/EtOAc/MeOH gradient) the protected amino acid **224** (8.8 g, contaminated with ca. 20% of tributylphosphine oxide; used without any further purification).

Synthesis of amino acid **225**

Following procedure **B.2**, the reaction of **224** (8.8 g), 1,3-dimethylbarbituric acid (3.86 g, 24.7 mmol) and $Pd(PPh_3)_4$ (57

mg) in EtOAc/CH_2Cl_2 (1:1, 88 mL) yielded after 3 h, dilution with EtOAc and centrifugation an orange solid, which was washed (EtOAc) to give **225** (6.02 g, ca. 80% over the two steps).

Data of **225**: $C_{30}H_{40}N_4O_8$ (584.6). LC-MS (method 4a): R_t = 1.70 (90), 585 ($[M+H]^+$). Purity based on ^{1}H-NMR ca. 80%; used without further purification.

Synthesis of macrolactam **Ex.379**

According to procedure **F.1.1**, the amino acid **225** (2.0 g, 3.06 mmol) and *i*-Pr_2NEt (1.0 mL, 5.9 mmol) in dry DMF (20 mL) was treated with T3P (50% in EtOAc; 3.6 mL, 6.1 mmol) and *i*-Pr_2NEt (1.2 mL, 7 mmol) in CH_2Cl_2 (550 mL) to afford after evaporation of the volatiles and FC (hexane/EtOAc/MeOH gradient) **Ex.379** (1.23 g, 71%).

Data of **Ex.379**: $C_{30}H_{38}N_4O_7$ (566.6). LC-MS (method 10c): R_t = 1.94 (98), 567 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 7.98 (d, J = 6.8, 0.5 H), 7.63 (br. t, 0.5 H), 7.56 (d, J = 7.5, 0.5 H), 7.37-7.11 (several m, 8.5 H), 7.00 (d, J = 7.4, 1 H), 6.87 (d, J = 7.4, 0.5 H), 6.82 (s, 0.5 H), 5.03-4.87 (s and m, 3 H), 4.41 (m, 0.5 H), 4.28 (t-like m, 0.5 H), 4.13 (m, 1 H), 3.97-3.65 (m, 3 H), 3.04 (br. d, J ca. 11.1, 1 H), 2.81 (m, 1 H), 2.30 (t, J = 9.5, 1 H), 2.14 (m, 1 H), 1.90 (m, 1 H), 1.66 (m, 2 H), 1.40, 1.34 (2 s, 9 H), 1.40-1.15 (m, 2 H).

Synthesis of amine **Ex.380**

According to procedure **K**, benzyl carbamate **Ex.379** (700 mg, 1.23 mmol) was hydrogenolyzed in MeOH (7.0 mL) in the presence of catalyst (139 mg) for 2 h. After filtration and evaporation of the volatiles, **Ex.380** (550 mg, 100%) was obtained.

Data of **Ex.380**: $C_{22}H_{32}N_4O_5$ (432.5). LC-MS (method 10a): R_t = 1.34 (100), 433 ($[M+H]^+$).

Core 24b: Synthesis of Ex.392 and Ex.393 (Scheme 28)

Synthesis of Mitsunobu product **226**

Following procedure **B.1.2**, the reaction of phenol **200** (2.74 g, 6.4 mmol), alcohol **156** (2.14 g, 7.7 mmol) and CMBP (3.1 g, 12.8 mmol) in dry toluene (96 mL) afforded after 2 h and after FC (hexane/EtOAc gradient) the protected amino acid **226** (3.16 g, 72%).

Synthesis of amino acid **227**

Following procedure **B.2**, the reaction of **226** (2.98 g, 4.35 mmol), 1,3-dimethylbarbituric acid (1.7 g, 10.9 mmol) and $Pd(PPh_3)_4$ (25 mg) in EtOAc/CH_2Cl_2 (1:1, 58 mL) yielded after 4 h, evaporation of the volatiles and repeated washing (EtOAc) of the residue the amino acid **227** (2.42 g, 97%).

Data of **227**: $C_{31}H_{35}N_3O_7$ (561.6). LC-MS (method 10a): R_t = 1.59 (97), 562 ($[M+H]^+$).

Synthesis of macrolactam **Ex.392**

To a soln of HATU (1.24 g, 3.3 mmol), HOAt (0.44 g, 3.2 mmol) and *i*-Pr_2NEt (1.2 mL, 6.5 mmol) in DMF (1600 mL) was added within 2 h via syringe pump a soln of **227** (0.916 g, 1.6 mmol) in DMF (40 mL). The mixture was stirred for 20 h at rt, followed by evaporation of the volatiles. FC (hexane/EtOAc/MeOH gradient) afforded **Ex.392** (0.78 g, 88%).

Data of **Ex.392**: $C_{31}H_{33}N_3O_6$ (543.6). LC-MS (method 10b): R_t = 2.04 (96), 544 ($[M+H]^+$).

Synthesis of amine **Ex.393**

According to procedure **K**, benzyl carbamate **Ex.392** (66 mg, 0.12 mmol) was hydrogenolyzed in MeOH (1.5 mL) in the presence of catalyst (25 mg) for 1 h. After filtration, evaporation of the volatiles and FC (CH_2Cl_2/MeOH 95:5 to 80:20) **Ex.393** (40 mg, 80%) was obtained.

Data of **Ex.393**: $C_{23}H_{27}N_3O_4$ (409.5). LC-MS (method 10a): R_t = 1.34 (99), 410 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 7.93 (d, J = 6.2, 0.67 H), 7.75 (br. s, 0.33 H), 7.37-6.81 (m, 8 H), 6.74 (d, J = 8.0, 1

H), 4.94 (d, J = 13.8, 1 H), 4.86 (m, 1 H), 4.47-4.30 (m, 1 H), 4.25-4.04 (m, 2 H), 3.74 (br. s, 1 H), 3.12 (t-like m, 1 H), 2.80 (m, 1 H), 2.66 (dd, J = 5.7, 11.1, 1 H), 2.50-2.00 (several m, 2 H), 1.80-1.50 (br. m, 3 H), 1.31 (m, 1 H).

Core 24c: Synthesis of Ex.398 (Scheme 28)

Synthesis of the amide **228**

A soln of **198** (750 mg, 1.53 mmol) in CH_2Cl_2 (14 mL) was treated with $SOCl_2$ (0.34 mL, 4.59 mmol) and heated to 45°C for 1 h. The volatiles were evaporated. **190**·HCl (ca. 50%w/w; 1.01 g, 2.4 mmol) and CH_2Cl_2 (14 mL) were added. The mixture was cooled to 0°C. *i*-Pr_2NEt (0.785 mL, 4.5 mmol) was slowly added and stirring was continued for 1 h. The volatiles were evaporated. Aqueous workup (EtOAc, 0.2 M aq. HCl soln) and FC (hexane/EtOAc 1:1) afforded **228** (693 mg, 70%).

Data of **228**: $C_{31}H_{37}BrN_2O_8$ (645.5). LC-MS (method 10a): R_t = 2.32 (95), 647/645 ($[M+H]^+$).

Synthesis of amino acid **229**

Following procedure **B.2**, the reaction of **228** (680 mg, 1.05 mmol), 1,3-dimethylbarbituric acid (395 mg, 2.5 mmol) and $Pd(PPh_3)_4$ (61 mg) in EtOAc/CH_2Cl_2 (9:8, 17 mL) yielded after 2 h, evaporation of the volatiles and washing (EtOAc) **229** (571 mg, quant. yield).

Data of **229**: $C_{24}H_{29}BrN_2O_6$ (521.4). LC-MS (method 10a): R_t = 1.39 (94), 521/523 ($[M+H]^+$).

Synthesis of macrolactam **Ex.398**

A suspension of amino acid **229** (550 mg, 1.06 mmol) in dry CH_2Cl_2 (100 mL) was added over 2 h to a soln of T3P (50% in EtOAc; 1.5 mL, 2.6 mmol) and *i*-Pr_2NEt (0.72 mL, 4.2 mmol) in CH_2Cl_2 (930 mL). The mixture was stirred for 2 h. More T3P 50% in EtOAc; 1.5 mL, 2.6 mmol) and *i*-Pr_2NEt (0.72 mL, 4.2 mmol) in CH_2Cl_2 (30 mL) were added and stirring was continued until completion of the transformation. Evaporation of the solvent,

aqueous workup (EtOAc, 0.1 M aq. HCl soln, sat. aq. $NaHCO_3$ soln; Na_2SO_4) and FC (CH_2Cl_2/MeOH 100:0 to 95:5) afforded **Ex.398** (254 mg, 47%).

Data of **Ex.398**: $C_{24}H_{27}BrN_2O_5$ (503.3). LC-MS (method 10a): R_t = 1.81 (97), 505/503 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 8.16-6.77 (several m, 9 H), 4.96-4.81 (m, 1 H), 4.71 (d, J = 6.9, exchanged upon addition of D_2O, OH), 4.54-3.97 (several m, 6 H), 3.65-3.30 (several m, 2 H), 3.11 (d-like m, 1 H), 2.90-2.60 (several m, 1 H), 2.40-1.50 (several br. m, 6 H).

Core 25: Synthesis of Ex.403 and Ex.404 (Scheme 29)

Synthesis of Mitsunobu product **230**

At rt CMBP (2.44 g, 9.6 mmol) was added to a soln of alcohol **167** (2.31 g, 6.41 mmol) in toluene (100 mL). The mixture was heated to 100°C for 30 min, followed by the addition of a soln of phenol **202** (2.82 g, 6.15 mmol) in toluene (25 mL). The mixture was stirred for 3 h at 100°C and concentrated. FC (hexane/acetone) afforded **230** (3.17 g, 62%).

Data of **230**: $C_{40}H_{57}FN_4O_{10}Si$ (800.9). LC-MS (method 4b): R_t = 2.67 (93), 801 ($[M+H]^+$).

Synthesis of amino ester **231**

At 0°C TBAF (1 M in THF; 15.7 mL, 15.7 mmol) was added to a soln of **230** (3.15 g, 3.96 mmol) in THF (50 mL). The mixture was stirred at 0°C to rt for 3 h. More TBAF soln (15.7 mL) was added and stirring continued for 4 h. The mixture was concentrated and the residue dissolved in CH_2Cl_2, washed (sat. aq. $NaHCO_3$ soln, sat. aq. NaCl soln), dried (Na_2SO_4), filtered and concentrated. FC (CH_2Cl_2/MeOH/conc. aq. NH_3 soln 95:5:0.5 to 90:10:0.5) afforded **231** (2.06 g, 87%).

Synthesis of amino acid **232**

A soln of **231** (2.0 g, 3.05 mmol), 1,3-dimethylbarbituric acid (0.59 g, 3.81 mmol) and $Pd(PPh_3)_4$ (0.35 g) in EtOAc/CH_2Cl_2 (50:50, 35 mL) was stirred at rt for 2 h, concentrated and

purified by FC (CH_2Cl_2/MeOH 100:0 to 90:10, then 70:30) to yield **232** (1.36 g, 72%).

Data of **232**: $C_{31}H_{41}FN_4O_8$ (616.6). LC-MS (method 7): R_t = 1.09 (98), 617 ($[M+H]^+$).

Synthesis of the macrolactam **Ex.403**

According to procedure **F.1.2**, a soln of **232** (1.34 g, 2.17 mmol) in dry DMF (100 mL) was treated with FDPP (1.67 g, 4.35 mmol) in DMF (2070 mL). Purification by FC (hexane/EtOAc/MeOH 60:40:0 to 0:90:10) afforded **Ex.403** (0.934 g, 73%).

Data of **Ex.403**: $C_{31}H_{39}FN_4O_7$ (598.6). LC-MS (method 4b): R_t = 2.16 (100), 599 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 8.69, 8.51 (2 br. s, 1 H), 7.51 (d, J = 7.5, 1 H), 7.40-7.28 (m, 5 H), 7.19-7.04 (m, 3 H), 5.01 (s, 2 H), 4.82, 4.55 (2 br. s, 1 H), 4.20-3.80 (m, 4 H), 3.75-3.26 (m, 4 H, partially superimposed by the H_2O signal), 2.70 (s, 3 H), 2.66 (m, 1 H), 2.22 (m, 1 H), ca. 1.8-1.2 (br. m, 4 H), 1.42, 1.35 (2 s, 9 H).

Synthesis of amine **Ex.404**

According to procedure **K**, benzyl carbamate **Ex.403** (180 mg, 0.30 mmol) was hydrogenolyzed in MeOH (2.0 mL) in the presence of catalyst (34 mg) for 2 h. After filtration and evaporation of the volatiles, **Ex.404** (139 mg, 99%) was obtained.

Data of **Ex.404**: $C_{23}H_{33}FN_4O_5$ (464.5). LC-MS (method 4a): R_t = 1.61 (98), 465 ($[M+H]^+$).

Core 26: Synthesis of Ex.415 and Ex.416 (Scheme 30)

Synthesis of Mitsunobu product **233**

According to procedure **E.1.1**, a mixture of phenol **205** (1.65 g, 3.95 mmol), alcohol **82** (1.75 g, 4.7 mmol) and PPh_3 (3.08 g, 11.7 mmol) in dry benzene (42 mL) was treated at 0°C with DEAD (40% in toluene, 5.4 mL, 11.7 mmol) in benzene (28 mL). After 16 h at rt, additional PPh_3 (1.36 g, 5.2 mmol) and alcohol **82** (0.35 g, 0.94 mmol) in benzene (8.4 mL) were added, followed by DEAD (40% in toluene, 2.4 mL, 5.2 mmol) in benzene (11 mL).

Stirring was continued for 7 h. Evaporation of the volatiles and repeated FC (CH_2Cl_2/MeOH and hexane/EtOAc) afforded **233** (2.27 g, 75%, contaminated with triphenylphosphine oxide; used without further purification).

Synthesis of amino acid **234**

Following procedure **E.2**, the reaction of **233** (2.26 g, 2.93 mmol), 1,3-dimethylbarbituric acid (1.14 g, 7.33 mmol) and $Pd(PPh_3)_4$ (0.37 g) in EtOAc/CH_2Cl_2 (50:50, 32 mL) yielded after 30 min and after FC (EtOAc, then CH_2Cl_2/MeOH 90:10 to 60:40) **234** (1.40 g, 74%).

Data of **234**: $C_{31}H_{42}N_4O_9S$ (646.7). LC-MS (method 4b): R_t = 1.76 (95), 647 ($[M+H]^+$).

Synthesis of the protected macrolactam **Ex.415**

According to procedure **F.1.1**, amino acid **234** (500 mg, 0.77 mmol) in dry CH_2Cl_2 (11 mL) was treated with T3P (50% in EtOAc, 0.92 mL, 1.5 mmol) and *i*-Pr_2NEt (0.53 mL, 3.1 mmol) in CH_2Cl_2 (66 mL). After stirring at rt for 1 h, aqueous workup (EtOAc, sat. aq. $NaHCO_3$ soln) and FC (EtOAc), **Ex.415** (0.34 g, 69%) was obtained.

Data of **Ex.415**: $C_{31}H_{40}N_4O_8S$ (628.7). LC-MS (method 4b): R_t = 2.05 96), 629 ($[M+H]^+$). ^{1}H-NMR ($CDCl_3$): 7.39-7.29 (m, 6 H), 6.74 (d, J = 5.5, 1 H), 5.21 (J = 12.3, 1 H), 5.15 (d, J = 12.3, 1 H), 5.15 (m, 1 H), 5.00 (br. dd, J = 2.7, 10.6, 1 H), 4.40 (br. t, J = 7.4, 1 H), 4.23-4.18 (m, 2 H), 3.98 (br. d, J = 10.2, 1 H), 3.75-3.61 (m, 2 H), 3.45 (br. d, 1 H), 3.06 (s, 3 H), 2.91 (s, 3 H), 2.58-2.06 (m, 7 H), 1.45 (s, 9 H).

Synthesis of acid **Ex.416**

According to procedure **H**, ester **Ex.415** (530 mg, 0.84 mmol) was hydrogenolyzed in MeOH (9 mL)/THF (9 mL) in the presence of catalyst (0.55 g) for 6 h to afford after filtration and washing of the residue with $CHCl_3$ **Ex.416** (494 mg, quant. yield).

Data of **Ex.416**: $C_{24}H_{34}N_4O_8S$ (538.6). LC-MS (method 4b): R_t = 1.61 (92), 539 ($[M+H]^+$).

Core 27: Synthesis of Ex.424 and Ex.425 (Scheme 31)

Synthesis of Mitsunobu product **235**

Following procedure **B.1.2**, the reaction of phenol **207** (12.1 g, 26.5 mmol), alcohol **14** (9.57 g, 31.8 mmol) and CMBP (12.8 g, 53.1 mmol) in dry toluene (354 mL) afforded after FC (hexane/EtOAc 50:50 to 0:100) the protected amino acid **235** (19.2 g, 98%).

Synthesis of amino acid **236**

Following procedure **B.2**, the reaction of **235** (19.1 g, 25.8 mmol), 1,3-dimethylbarbituric acid (10.1 g, 64.7 mmol) and $Pd(PPh_3)_4$ (0.3 g) in EtOAc/CH_2Cl_2 (55:45, 278 mL) yielded after 2 h and after FC (CH_2Cl_2/MeOH 98:2 to 90:10, then 70:30) **236** (14.38 g, 91%).

Data of **236**: $C_{31}H_{43}N_5O_8$ (613.7). LC-MS (method 4a): R_t = 1.65 (95), 614 ($[M+H]^+$).

Synthesis of the protected macrolactam **Ex.424**

According to procedure **F.1.1**, the amino acid **236** (3.37 g, 5.5 mmol) in dry CH_2Cl_2 (50 mL) was treated with T3P (50% in EtOAc; 9.7 mL, 16.5 mmol) and *i*-Pr_2NEt (4.7 mL, 27.6 mmol) in CH_2Cl_2 (1100 mL). Aqueous workup (CH_2Cl_2, 1 M aq. Na_2CO_3 soln) and FC (CH_2Cl_2/MeOH 100:0 to 95:5) yielded **Ex.424** (2.58 g, 79%).

Data of **Ex.424**: $C_{31}H_{41}N_5O_7$ (595.6). LC-MS (method 11a): R_t = 1.87 (95), 596 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 8.39 (d, J = 2.7, 1 H), 8.15 (d, J = 1.5, 1 H), 7.37-7.26 (m, 7 H), 7.20 (d, J = 6.3, 1 H), 4.99 (s, 2 H), 4.65 (d, J = 9.8, 1 H), 4.23-3.93 (m, 5 H), 3.16-2.94 (m, 2 H), 3.14 (t, J ca. 9.0, 1 H), 2.94 (s, 3 H), 2.30 (m, 1 H), 2.04 (br. q, 1 H), 1.67 (m, 1 H), 1.41 (s, 9 H), 1.30-0.93 (m, 5 H).

Synthesis of amine **Ex.425**

According to procedure **K**, benzyl carbamate **Ex.424** (600 mg, 1.0 mmol) was hydrogenolyzed in MeOH (12 mL) in the presence of catalyst (113 mg) for 2 h to afford **Ex.425** (482 mg, quant. yield).

Data of **Ex.425**: $C_{23}H_{35}N_5O_5$ (461.5). LC-MS (method 4a): R_t = 1.32 (99), 462 ($[M+H]^+$).

Core 28: Synthesis of Ex.435, Ex.436 and Ex.437 (Scheme 32)

Synthesis of Mitsunobu product **237**

Tributylphosphine (7.0 mL, 28.2 mmol) was added to a soln of phenol **210** (4.5 g, 9.4 mmol) and alcohol **82** (5.2 g, 14.1 mmol) in dry, degassed benzene (235 mL). The mixture was cooled to 0°C, followed by the slow addition of TMAD (4.85 g, 28.1 mmol) in benzene (40 mL). The soln was stirred for 30 min at 0°C and for 15 h at rt and filtered. The filtrate was concentrated and purified by FC (hexane/EtOAc 40:60 to 25:75) to yield **237** (7.2 g, 92%).

Synthesis of amino acid **238**

Following procedure **B.2**, the reaction of **237** (7.15 g, 8.6 mmol), 1,3-dimethylbarbituric acid (3.35 g, 21.5 mmol) and $Pd(PPh_3)_4$ (0.5 g) in EtOAc/CH_2Cl_2 (45:55, 145 mL) yielded after 16 h and after FC (CH_2Cl_2/MeOH 100:0 to 70:30) **238** (4.80 g, 79%).

Data of **238**: $C_{37}H_{49}N_5O_9$ (707.8). LC-MS (method 10a): R_t = 1.76 (98), 708 ($[M+H]^+$).

Synthesis of the protected macrolactam **Ex.435**

According to procedure **F.1.1**, the amino acid **238** (4.7 g, 6.6 mmol) in dry CH_2Cl_2 (100 mL) was treated with T3P (50% in EtOAc; 9.9 mL, 16.7 mmol) and *i*-Pr_2NEt (4.6 mL, 26.8 mmol) in CH_2Cl_2 (570 mL). Aqueous workup (CH_2Cl_2, sat. aq. $NaHCO_3$ soln) after completion of the addition and FC (EtOAc/CH_3CN 95:5) yielded **Ex.435**(2.7 g, 58%).

Data of **Ex.435**: $C_{37}H_{47}N_5O_8$ (689.8). LC-MS (method 10a): R_t = 2.06 (100), 690 ($[M+H]^+$). ^{1}H-NMR (C_6D_6): 7.34-7.09 (m, 8 H), 6.87 (d, J = 9.0, 1 H), 5.59 (br. d, J ca. 12.7, 1 H), 5.20 (br. d, J ca. 12.7, 1 H), 5.15 (br. d, J ca. 12.6, 1 H), 4.75-4.60 (m, 3 H), 4.20 (br. d, J ca. 7.6, 1 H), 3.88 (br. d, J ca. 9.4, 1 H), 3.73-3.62 (m, 2 H), ca. 3.2 (m, 1 H), 3.08 (s, 3 H), 2.97 (s, 3 H), 2.75 (s, 3 H), 2.72-2.57 (m, 2 H), 2.27 (s, 3 H), 2.27-2.04 (m, 2 H), 1.58 (s, 9 H), 1.54-1.41 (m, 2 H).

Synthesis of acid **Ex.436**

According to procedure **H**, a soln of **Ex.435** (300 mg, 0.43 mmol) in MeOH (18 mL)/THF (6 mL) was hydrogenolyzed in the presence of catalyst (163 mg) to yield **Ex.436** (250 mg, 91%).

Data of **Ex.436**: $C_{30}H_{41}N_5O_8$ (599.6). LC-MS (method 10a): R_t = 1.62 (98), 600 ($[M+H]^+$).

Synthesis of amine **Ex.437**

TFA (1 mL) was added at 0°C to a soln of **Ex.435** (320 mg, 0.46 mmol) in CH_2Cl_2 (3 mL). The soln was allowed to warm to rt over 2 h. The volatiles were evaporated. Residual solvent was removed by co-evaporation (twice) with $CHCl_3$ to afford **Ex.437**·CF_3CO_2H (322 mg, 98%).

Data of **Ex.437**·CF_3CO_2H: $C_{32}H_{39}N_5O_6 \cdot C_2HF_3O_2$ (589.7, free base). LC-MS (method 10a): R_t = 1.48 (97), 590($[M+H]^+$).

Core 29: Synthesis of Ex.447 and Ex.448 (Scheme 33)

Synthesis of bis-olefine **240**

A mixture of **194** (1.515 g, 3.64 mmol), **51** (2.72 g, 5.46 mmol), HATU (2.075 g, 5.46 mmol) and HOAt (743 mg, 5.46 mmol) in DMF (36 mL) was cooled to 0°C. *i*-Pr_2NEt (2.0 mL, 11.7 mmol) was slowly added and the soln was stirred for 2 h. Aqueous workup (EtOAc, 1 M aq. Na_2CO_3 soln; Na_2SO_4) and FC (hexane/EtOAc afforded **240** (1.96 g, 84%).

Data of **240**: $C_{35}H_{39}BrN_2O_5$ (647.6). LC-MS (method 10a): R_t = 2.99 (93), 649/647 ($[M+H]^+$).

Synthesis of macrocycle **Ex.447**

[1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro-(3-phenyl-1*H*-inden-1-ylidene)pyridyl)ruthenium(II) (Umicore M31 catalyst; 10 mg) was added to a degassed soln of **240** (80 mg, 0.124 mmol) in CH_2Cl_2 (15 mL). The soln was stirred at 40°C for 24 h. Evaporation of the solvent and purification by prep. HPLC method 1 afforded **Ex.447** (24 mg, 31%).

Data of **Ex.447**: $C_{33}H_{35}BrN_2O_5$ (619.5). LC-MS (method 10b): R_t = 2.79 (95), 621/619($[M+H]^+$).

Synthesis of amino alcohol **Ex.448**

A soln of **Ex.447** (79 mg, 0.128 mmol) in MeOH (1.5 mL) and THF (0.5 mL) was hydrogenated for 5 h under normal pressure at rt 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 filtrate was concentrated, suspended in CH_2Cl_2 and filtered. The solid was then further purified by prep HPLC method 1 to afford **Ex.448**·CF_3CO_2H (24 mg, 50%).

Data of **Ex.448**·CF_3CO_2H: $C_{18}H_{26}N_2O_3 \cdot C_2HF_3O_2$ (318.4, free base). LC-MS (method 10a): 1.22 (91), 319 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 7.96 (br. s, 3 H), 7.16 (t, J = 7.7, 1 H), 6.78-6.72 (m, 3 H), 5.34 (br. s, 1 H), 4.76 (d, J = 11.1, 1 H), 4.18-4.10 (m, 4 H), 3.84 (dd, J = 6.7, 10.0, 1 H), 2.83 (t-like m, J ca. 9.4, 1 H), 2.70 (m, 1 H), 2.45 (m, 1 H), 2.25 (m, 1 H), 2.07 (m, 1 H), 1.80-0.80 (several br. m, 8 H).

Core 30: Synthesis of Ex.451, Ex.452 and Ex.453 (Scheme 34)

Synthesis of Mitsunobu product **241**

Following procedure **B.1.2**, the reaction of thiophenol **212** (2.0 g, 4.4 mmol), alcohol **161** (1.9 g, 5.3 mmol) and CMBP (1.6 g, 6.6 mmol) in dry toluene (87 mL) afforded after 1 h and after

FC (hexane/Et_2O 30:70 to 0:100, then hexane/EtOAc 50:50 to 30:70) the protected amino acid **241** (2.43 g, crude, used without further purification).

Synthesis of amino acid **242**

Following procedure **B.2**, the reaction of **241** (2.38 g) 1,3-dimethylbarbituric acid (1.1 g, 7.1 mmol) and $Pd(PPh_3)_4$ (0.17 g) in EtOAc/CH_2Cl_2 (55:45, 52 mL) yielded after 2 h and after FC (EtOAc, then CH_2Cl_2/MeOH 100:0 to 80:20) **242** (1.89 g, 64% over the two steps).

Data of **242**: $C_{33}H_{38}BrN_3O_6S$ (684.6). LC-MS (method 10a): R_t = 1.83 (94), 686/684 ($[M+H]^+$).

Synthesis of the protected macrolactam **Ex.451**

According to procedure **F.1.1**, amino acid **242** (1.5 g, 2.2 mmol) in dry CH_2Cl_2 (45 mL) was treated with T3P (50% in EtOAc; 4.5 mL, 7.7 mmol) and *i*-Pr_2NEt (2.6 mL, 15 mmol) in CH_2Cl_2 (1080 mL). After 3 h at rt, aqueous workup (CH_2Cl_2, sat. aq. Na_2CO_3 soln) and FC (hexane/EtOAc/MeOH) yielded **Ex.451** (1.15 g, 79%).

Data of **Ex.451**: $C_{33}H_{36}BrN_3O_5S$ (666.6). LC-MS (method 10b): R_t = 2.33 (96), 668/666 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 7.85 (s, 0.5 H), 7.69 (d, J = 8.0, 0.5 H), 7.57 (d, J = 7.6, 2 H), 7.50 (d, J = 7.9, 0.5 H), 7.39-7.18 (m, 10.5 H), 5.08 (d, J = 12.6, 0.5 H), 4.99 (s, 1 H), 4.96 (d, J = 12.8, 0.5 H), 4.49-4.38 (4 d, 2 H), 4.16 (t-like m, 0.5 H), 4.00-3.65 (m, 3 H), 3.60-3.45 (m, 1 H), 3.12-2.98 (m, 3 H), 2.91, 2.89 (2 s, 3 H), 2.55-2.44 (m, 1 H, superimposed by DMSO-d signal), 2.35-2.15 (br. m, 2 H), 1.70-1.20 (several br. m, 4 H).

Synthesis of the sulfone **Ex.452**

m-CPBA (70%; 462 mg, 1.88 mmol) was added at 0°C to a soln of **Ex.451** (500 mg, 0.75 mmol) in CH_2Cl_2 (12 mL). The mixture was stirred for 15 min at 0°C and for 2 h at rt. The mixture was diluted with CH_2Cl_2, washed (sat. aq. $NaHCO_3$ soln, 10% aq. $Na_2S_2O_3$ soln, sat. aq. $NaHCO_3$ soln), dried (Na_2SO_4), filtered and concentrated to yield **Ex.452** (471 mg, 89%).

Data of **Ex.452**: $C_{33}H_{36}BrN_3O_7S$ (698.6). LC-MS (method 10a): R_t = 2.13 (95), 700/698 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 8.16 (s, 0.75 H), 8.05-7.26 (several m, 13.25 H), 5.01 (d, J = 12.6, 0.75 H), 4.97 (s, 0.5 H), 4.89 (d, J = 12.6, 0.75 H), 4.53 (s, 1.5 H), 4.53-4.10 (m, 2.5 H), 4.10-3.65 (m, 2 H), 3.45 (s, 2 H), 3.25-2.75 (br. m, 3 H), 2.97 (s, 3 H), ca. 2.6 (m, 1 H), 2.35-2.20 (m, 1 H), 1.80-1.30 (m, 4 H).

Synthesis of amine **Ex.453**

NH_3 soln (7 M in MeOH, 0.49 mL, 3.43 mmol) was added to a soln of **Ex.452** (600 mg, 0.86 mmol) in MeOH (13 mL). The soln was hydrogenolyzed at rt under normal pressure for 17 h in the presence of 5% palladium on activated charcoal (moistened with 50% H_2O; 165 mg). The mixture was filtered through a pad of celite and Na_2CO_3. The filtrate was concentrated, dissolved in 1 M aq. HCl soln (15 mL) and washed with EtOAc. Sat. aq. Na_2CO_3 soln was added. The aqueous layer was treated with sat. aq. Na_2CO_3 soln and repeatedly extracted with $CHCl_3$. The combined organic phase was dried (Na_2SO_4), filtered and concentrated to give **Ex.453** (369 mg, 88%).

Data of **Ex.453**: $C_{25}H_{31}N_3O_5S$ (485.6). LC-MS (method 10a): R_t = 1.29 (98), 486 ($[M+H]^+$).

Core 31: Synthesis of Ex.460, Ex.461, Ex.462 and Ex.466

(Scheme 35)

Synthesis of Mitsunobu product **243**

A soln of phenol **213** (770 mg, 1.9 mmol) in dry benzene (10 mL) was added to a soln of PPh_3 (776 mg, 2.9 mmol) and alcohol **161** (865 mg, 2.3 mmol) in benzene (25 mL). The soln was cooled to 0°C. DEAD (40% in toluene, 1.33 mL, 2.9 mmol) was added slowly. The mixture was stirred at rt for 40 h followed by addition of more alcohol **161** (360 mg, 0.97 mmol) in benzene (3 mL), PPh_3 (510 mg, 1.9 mmol) and DEAD (40% in toluene, 0.9 mL, 2 mmol). Stirring was continued for 19 h. The mixture was treated with MeOH (1 mL), pre-adsorbed on silica gel and purified by FC (hexane/EtOAc 80:20 to 75:25) to give **243** (810 mg, 56%).

Synthesis of amino acid **244**

Following procedure **B.2**, the reaction of **243** (949 mg, 1.27 mmol) 1,3-dimethylbarbituric acid (476 mg, 3.0 mmol) and $Pd(PPh_3)_4$ (73 mg) in EtOAc/CH_2Cl_2 (55:45, 22 mL) yielded after 3 h and after FC (EtOAc; CH_2Cl_2/MeOH 95:5 to 75:25) **244** (492 mg, 62%).

Data of **244**: $C_{29}H_{39}BrN_2O_6S$ (623.6). LC-MS (method 10a): R_t = 1.93 (99), 625/623 ($[M+H]^+$).

Synthesis of the protected macrolactam **Ex.460**

According to procedure **F.1.1**, amino acid **244** (491 mg, 0.79 mmol) in dry CH_2Cl_2 (10 mL) was treated with T3P (50% in EtOAc; 0.93 mL, 1.57 mmol) and *i*-Pr_2NEt (0.54 mL, 3.1 mmol) in CH_2Cl_2 (385 mL). After 4 h at rt, aqueous workup (CH_2Cl_2, sat. aq. $NaHCO_3$ soln) and FC (hexane/EtOAc 1:2) yielded **Ex.460** (471 mg, 99%).

Data of **Ex.460**: $C_{29}H_{37}BrN_2O_5S$ (605.6). LC-MS (method 10a): R_t = 2.84 (99), 607/605 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 7.58 (d, J = 8.4, 2 H), 7.46 (d, J = 8.5, 1 H), 7.34 (d, J = 8.4, 2 H), 7.21-7.15 (m, 2 H), 6.82 (d, J = 7.6, 1 H), 6.72 (d, J = 8.2, 1 H), 4.96 (d, J = 9.5, 1 H), 4.53 (s, 2 H), 4.41 (t-like m, 1 H), 4.30-4.10 (m, 3 H), 3.54 (s, 2 H), 3.12 (br. t, J = 12.5, 1 H), 2.78 (t-like m, 1 H), 2.35 (d, J = 13.9, 1 H), 2.11 (m, 1 H), 1.77 (m, 1 H), 1.61-1.32 (m, 5 H), 1.40 (s, 9 H).

Synthesis of sulfone **Ex.461**

m-CPBA (70%; 440 mg, 1.78 mmol) was added at 0°C to a soln of **Ex.460** (432 mg, 0.71 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 15 min at 0°C and for 2 h at rt. The mixture was diluted with CH_2Cl_2, washed (sat. aq. $NaHCO_3$ soln, 10% aq. $Na_2S_2O_3$ soln, sat. aq. $NaHCO_3$ soln), dried (Na_2SO_4), filtered and concentrated to yield **Ex.461** (443 mg, 97%).

Data of **Ex.461**: $C_{29}H_{37}BrN_2O_7S$ (637.6). LC-MS (method 10a): R_t = 2.41 (93), 639/637 ($[M+H]^+$). ^{1}H-NMR ($CDCl_3$): 7.54-7.42 (m, 4 H), 7.28-7.24 (m, 3 H), 7.20 (td, J = 2.6, 6.8, 1 H), 5.16 (d, J =

8.4, 1 H), 4.91 (dd, J = 1.7, 12.8, 1 H), 4.55 (s, 2 H), 4.40 (t-like m, 1 H), 4.31-4.24 (m, 2 H), 4.15-4.04 (m, 2 H), 3.26-3.16 (m, 3 H), 2.35-2.26 (m, 2 H), 1.76-1.65 (m, 2 H) 1.42 (s, 9 H), 1.25-1.13 (m, 2 H), 1.05-0.80 (m, 2 H).

Synthesis of amine **Ex.462**

A soln of **Ex.461** (414 mg, 0.649 mmol) in dioxane (2.0 mL) was treated at rt with 4M HCl-dioxane (4.0 mL) for 2 h. The mixture was concentrated. The remaining solid was washed with Et_2O and dried i.v. to afford **Ex.462**·HCl (325 mg, 87%).

Data of **Ex.462**·HCl: cf. **Table 47b**

Synthesis of amine **Ex.466**

A soln of **Ex.460** (650 mg, 1.073 mmol) in dioxane (3.5 mL) was treated at rt with 4M HCl-dioxane (6.5 mL) for 4 h. The mixture was concentrated. The remaining solid was washed with Et_2O and dried i.v. to afford **Ex.466**·HCl (523 mg, 90%).

Data of **Ex.466**·HCl: cf. **Table 47b**

Core 32: Synthesis of Ex.470 – Ex.475 (Scheme 36)

Synthesis of acid **246**

i-Pr_2NEt (2.2 mL, 12.8 mmol) was added to a mixture of acid **196** (2.4 g, 4.3 mmol), aminoester hydrochloride **169**·HCl (0.925 g, 5.15 mmol), HATU (2.44 g, 6.4 mmol) and HOAt (0.876 g, 6.4 mmol) in DMF (50 mL). The mixture was stirred at rt for 12 h, treated with 1 M aq. HCl soln and extracted with EtOAc. The organic phase was dried (Na_2SO_4), filtered and concentrated. FC (hexane/EtOAc 1:1) afforded **245** (2.42 g, 82%) which was dissolved in THF (34 mL) and treated with 2 M aq. LiOH soln (26.2 mL, 52.4 mmol). The mixture was heated to 60°C for 5 h. The mixture was acidified with 1 M aq. HCl soln and extracted with EtOAc. The organic phase was dried (Na_2SO_4), filtered and concentrated to give **246** (2.3 g 97%).

Data of **246**: $C_{29}H_{44}BrN_3O_8Si$ (670.6). LC-MS (method 10a): R_t = 2.50 (100), 670/672 ($[M+H]^+$).

Synthesis of amino acid **249**

i-Pr_2NEt (1.59 mL, 9.3 mmol) was added to a mixture of acid **246** (2.1 g, 3.1 mmol), aminoester hydrochloride **171**·HCl (1.04 g, 3.7 mmol), HATU (1.41 g, 3.7 mmol) and HOAt (0.50 g, 3.7 mmol) in DMF (53 mL). The mixture was stirred at rt for 48 h, diluted with H_2O (170 mL), acidified with 1 M aq. HCl soln (30 mL) and extracted with EtOAc. The organic phase was dried (Na_2SO_4), filtered and concentrated. FC (hexane/EtOAc 2:1 to 1:1) afforded **247** (2.58 g, 83%)

At 0°C, TBAF (1 M in THF; 8.4 mL, 8.4 mmol) was added to a soln of **247** (2.52 g, 2.8 mmol) in THF (58 mL). The mixture was stirred at 0°C to rt for 15 h, treated with sat. aq. $NaHCO_3$ soln and extracted with EtOAc.

The organic phase was dried (Na_2SO_4), filtered and concentrated. FC (CH_2Cl_2/MeOH 100:0 to 98:2) yielded **248** (1.75 g, 82%), which was dissolved in THF (13 mL) and treated with 2 M aq. LiOH soln (3.45 mL, 6.9 mmol). The mixture was heated to 60°C for 2 h and concentrated. The residue was dissolved in H_2O, acidified with 3 M aq. HCl soln to pH ca. 1 and extracted with EtOAc. The organic phase was dried (Na_2SO_4), filtered and concentrated to give a colorless solid (2.2 g), which was suspended in Et_2O and filtered to afford **249**·HCl (1.69 g, 94%).

Data of **249**·HCl: $C_{37}H_{45}BrN_4O_7$ (737.6, internal salt). LC-MS (method 10d): R_t = 1.92 (97), 737/739 ($[M+H]^+$).

Synthesis of macrolactam **Ex.470**

According to procedure **F.1.1**, amino acid **249** (120 mg, 0.16 mmol) in dry CH_2Cl_2 (20 mL) was treated with T3P (50% in EtOAc; 0.24 mL, 0.41 mmol) and *i*-Pr_2NEt (0.11 mL, 0.65 mmol) in CH_2Cl_2 (140 mL). After 2 h at rt, aqueous workup (CH_2Cl_2, sat. aq. $NaHCO_3$ soln) and FC (hexane/EtOAc 10:90 then CH_2Cl_2/MeOH 90:10) **Ex.470** (80 mg, 68%) was obtained.

Data of **Ex.470**: $C_{37}H_{43}BrN_4O_6$ (719.6). LC-MS (method 10a): R_t = 2.41 (97), 719/721 ($[M+H]^+$). ^{1}H-NMR (DMSO-d_6): 7.89-7.79 (m, 4 H), 7.64 (s, 1 H), 7.57-7.36 (m, 6 H), 7.10-7.06 (m, 2 H), 4.31 (br. d, J ca. 8.9, 1 H), 4.24 (br. t, 1 H), 4.12 (m, 1 H), 4.03

(d, J ca. 7.6, 1 H), 3.95 (m, 1 H), 3.71 (t-like m, 1 H), 3.44-3.30 (m, 3 H), 3.15 (br. t, J ca. 12.7, 1 H), 2.98 (dd, J = 6.7, 13.2, 1 H), 2.37 (m, 1 H), 2.31 (d, J = 13.1, 1 H), 2.05-1.90 (m, 3 H), 1.65-1.37 (m, 5 H), 1.37 (s, 9 H).

Synthesis of the Suzuki product **Ex.471**

A soln of Na_2CO_3 (13 mg, 0.125 mmol) in H_2O (0.225 mL) was added to a suspension of **Ex.470** (30 mg, 0.042 mmol), 2-naphthaleneboronic acid (14 mg, 0.083 mmol) and $Pd(PPh_3)_4$ (5 mg) in DME (1.75 mL). The mixture was heated to reflux for 2 h, diluted with H_2O and extracted with EtOAc. The organic layer was dried (Na_2SO_4), filtered and concentrated. FC (CH_2Cl_2/MeOH) yielded **Ex.471** (20 mg, 62%).

Data of **Ex.471**: cf. **Table 48b**

Synthesis of amine **Ex.474**

A soln of **Ex.471** (15 mg, 0.02 mmol) in dioxane (0.91 mL) was treated with 4M HCl-dioxane (0.66 mL) at rt for 15 h. The volatiles were evaporated to afford **Ex.474**·HCl (14 mg, quant. yield).

Data of **Ex.474**·HCl: cf. **Table 48b**

Synthesis of the Suzuki product **Ex.472**

Ex.472 (20 mg, 62%) was obtained from **Ex.470** (30 mg, 0.042 mmol) and 1*H*-indol-4-ylboronic acid (6.7 mg, 0.42 mmol) by following the conditions described for the synthesis of **Ex.471**.

Data of **Ex.472**: cf. **Table 48b**

Synthesis of amine **Ex.475**

A soln of **Ex.472** (14 mg, 0.02 mmol) in CH_3CN (1.0 mL) and H_2O (0.05 mL) was treated with bismuth(III)-trifluoromethane-sulphonate (12.1 mg, 0.018 mmol) and heated to 75°C for 5 h. The mixture was diluted with EtOAc, washed (sat. aq. Na_2CO_3 soln), dried (Na_2SO_4), filtered and concentrated. FC (CH_2Cl_2/MeOH 95:5 to 90:10) afforded **Ex.475** (10 mg, 83%).

Data of **Ex.475**: cf. **Table 48b**

Synthesis of amine **Ex.473**

A soln of **Ex.470** (15 mg, 0.02 mmol) in dioxane (0.8 mL) was treated with 4M HCl-dioxane (0.7 mL) at rt for 15 h. The volatiles were evaporated to afford **Ex.473**·HCl (13 mg, 92%).

Data of **Ex.473**·HCl: *cf.* **Table 48b**

Transformations on solid support

Core 33: Synthesis of **Ex.476** (Scheme 37)

Synthesis of *N*-methyl-L-alanine allyl ester hydrochloride (**257**·HCl)

4M HCl-dioxane (3.0 mL) was added to a suspension of *N*-methyl L-alanine (**256**, 1.05 g, 10.1 mmol) in CH_2Cl_2 (16 mL). PCl_5 (2.54 g, 12.2 mmol) was added portionwise at 0°C. The mixture was allowed to warm to rt over 15 h. The volatiles were evaporated. The residue was dissolved in CH_2Cl_2 (10 mL) and allyl alcohol (0.83 mL, 12.2 mmol) was added dropwise. The mixture was stirred for 2 h and concentrated to give **257**·HCl (1.80 g, 98%).

Data of **257**·HCl: $C_7H_{13}NO_2$·HCl (143.2, free base). ^{1}H-NMR (DMSO-d_6): 9,79 (br. s, 1 H), 9.40 (br. s, 1 H), 5.94 (m, 1 H), 5.38 (qd, J = 1.6, 17.3, 1 H), 5.28 (qd, J = 1.4, 10.5, 1 H), 4.85 (m, 2 H), 4.41 (q, J ca. 6.8, 1 H), 2.55 (s, 3 H), 1.48 (d, J = 7.2, 3 H).

Synthesis of 9*H*-fluoren-9-ylmethyl (2*S*,4*R*)-4-[(*tert*-butoxycarbonyl)amino]-2-(hydroxymethyl)tetrahydro-1*H*-pyrrole-1-carboxylate (**252**)

252 was obtained by Fmoc protection of the secondary amino group of **17**·HCl with (9H-fluoren-9-yl)methyl 2,5-dioxopyrrolidin-1-yl carbonate (FmocOSu) in dioxane in the presence of aq. $NaHCO_3$ soln under standard conditions.

Data of **252**: $C_{25}H_{30}N_2O_5$ (438.5). LC-MS (method 6): R_t = 1.26 (99), 439([M+H]$^+$).

Synthesis of 9*H*-fluoren-9-ylmethyl (2*S*,4*R*)-2-(3-[(allyloxy)-carbonyl]phenoxymethyl)-4-aminotetrahydro-1*H*-pyrrole-1-carboxylate hydrochloride (**254**·HCl)

Oxalyl chloride (64 mL, 749 mmol) was added to a soln of 3-acetoxybenzoic acid (30 g, 167 mmol) in CH_2Cl_2 (300 mL). Few drops of DMF were added. The soln was stirred for 4 h at rt. The volatiles were evaporated. The residue was dissolved in CH_2Cl_2 (300 mL) and at 0°C allyl alcohol (34 mL, 500 mmol) was added. Triethylamine (23 mL, 167 mmol) was slowly added. The mixture was stirred for 1 h at rt followed by an aqueous workup (CH_2Cl_2, 1 M aq. HCl soln; Na_2SO_4). FC (hexane/EtOAc 17:3) yielded **250** (24.3 g, 65%).

The material was dissolved in THF (485 mL) and treated for 3 h at 0°C to rt with 3-dimethylaminopropylamine (25 mL, 1.8 mmol). The soln was diluted with EtOAc and washed with 0.1 M aq. HCl soln, then with sat. aq. NaCl soln, dried (Na_2SO_4) and concentrated to afford **251** (17.13 g, 85%).

A soln of phenol **251** (3.6 g, 20 mmol), alcohol **252** (11 g, 24 mmol) and PPh_3 (6.4 g, 24 mmol) in benzene (140 mL) was cooled to 0°C. DEAD (40% in toluene, 11 mL, 24 mmol) was slowly added. The mixture was stirred at rt for 16 h. The volatiles were evaporated. FC (CH_2Cl_2/EtOAc) afforded **253** (7.35 g, 61%).

Data of **253**: $C_{35}H_{38}N_2O_7$ (598.7). LC-MS (method 4b): R_t = 2.72 (96), 599 ($[M+H]^+$), 243.

A soln of **253** (4.0 g, 6.68 mmol) in dioxane (11 mL) was treated with 4M HCl-dioxane (65 mL) for 3 h at rt.

The volatiles were evaporated to yield **254**·HCl (3.75 g, containing ca. 5% of dioxane, quant. yield).

Data of **254**·HCl: $C_{30}H_{30}N_2O_5$ (498.6, free base). LC-MS (method 4b): R_t = 2.00 (97), 499($[M+H]^+$).

Synthesis of 4-(4-((*N*-((3*R*,5*S*)-1-(((9*H*-fluoren-9-yl)methoxy)-carbonyl)-5-((3-(allyloxycarbonyl)phenoxy)methyl)pyrrolidin-3-yl)benzamido)methyl)-3,5-dimethoxyphenoxy)butanoic acid (**255**)

$NaBH_3CN$ (117 mg, 1.86 mmol) was added to a mixture of **254**·HCl (1.0 g, 1.87 mmol) and 4-(4-formyl-3,5-dimethoxyphenoxy)-

butanoic acid (501 mg, 1.86 mmol) in MeOH (33 mL). The mixture was stirred for 1 h at rt. More 4-(4-formyl-3,5-dimethoxy-phenoxy)butanoic acid (76 mg, 0.28 mmol) and $NaBH_3CN$ (18 mg, 0.28 mmol) were added and stirring was continued for 15 min, followed by evaporation of the volatiles. The residue was dissolved in EtOAc, washed with 1 M aq. HCl soln and concentrated. The residue was dissolved in H_2O (13 mL). Dioxane (20 mL) and $NaHCO_3$ (471 mg, 5.6 mmol) were added. The mixture was cooled to 0°C followed by the addition of benzoyl chloride (0.20 mL, 1.68 mmol). The mixture was stirred for 75 min at 0°C. Aqueous workup (EtOAc, 1 M aq HCl soln; Na_2SO_4) and FC (CH_2Cl_2/MeOH 100:0 to 95:5) gave **255** (930 mg, 58%).

Data of **255**: $C_{50}H_{50}N_2O_{11}$ (854.9). LC-MS (method 4b): R_t = 2.64 (91), 855($[M+H]^+$).

Synthesis of resin **259**

Aminomethyl-PS (0.90 mmol/g; 8.5 g, 7.65 mmol) was swollen in DMF (170 mL) for 30 min and filtered. DMF (85 mL), **255** (6.5 g, 6.89 mmol), *i*-Pr_2NEt (2.6 mL, 15.3 mmol) and HATU (2.91 g, 7.65 mmol) were successively added to the resin and the mixture was shaken for 15 h. The resin was filtered, washed three times with DMF, capped by treatment with acetic anhydride for 30 min (1.4 mL, 15.3 mmol) and *i*-Pr_2NEt (2.6 mL, 15.3 mmol) in DMF (85 mL). The mixture was filtered. The resin was washed three times with DMF, and CH_2Cl_2, twice with MeOH and three times with DMF. The resin was twice treated with 2%(v/v) DBU in DMF (85 mL) for 10 min and filtered. The resin was washed three times with DMF and CH_2Cl_2, twice with MeOH and dried i.v. to afford resin **259** (12.95 g, loading 0.56 mmol/g).

Synthesis of resin **260**

a) First coupling step

Resin **259** (120 mg, 0.067 mmol) was swollen in DMF (1 mL) for 1 h and filtered. DMF (1 mL), Fmoc-3-aminopropanoic acid (Fmoc-Apa-OH; 42 mg, 0.134 mmol), *i*-Pr_2NEt (0.046 mL, 0.269 mmol) and HATU (51 mg, 0.134 mmol) were added. The mixture was shaken for

1 h and filtered. The resin was washed with DMF. The coupling step was repeated. The mixture was filtered and the resin washed three times each with DMF and CH_2Cl_2.

b) First allyl ester cleavage

CH_2Cl_2 (1 mL), phenylsilane (0.08 mL, 0.612 mmol) and $Pd(PPh_3)_4$ (8 mg, 0.007 mmol) were added to the resin. The suspension was shaken for 15 min. The resin was filtered and washed with CH_2Cl_2. The deprotection step was repeated. The resin was filtered and washed three times with CH_2Cl_2 and DMF, twice with MeOH and then three times with DMF.

c) Second coupling step

DMF (1 mL), *N*-methylalanine allylester hydrochloride (**257**·HCl; 18 mg, 0.10 mmol), *i*-Pr_2NEt (0.046 mL, 0.269 mmol) and HATU (51 mg, 0.134 mmol) were added. The mixture was shaken for 3 h and filtered. The mixture was filtered and the resin washed three times each with DMF and CH_2Cl_2.

d) Second allyl ester cleavage was performed applying the conditions described above for the first allyl ester cleavage step.

e) Fmoc cleavage

The resin was twice treated with 2% (v/v) DBU in DMF (1 mL) for 10 min and filtered. The resin was washed five times with DMF, then twice with MeOH and CH_2Cl_2 to afford resin **260**.

Synthesis of the macrocycle **Ex.476**

1. Cyclization on solid support

The resin **260** was treated with DMF (1 mL) and FDPP (52 mg, 0.134 mmol) for 15 h. The mixture was washed five times with DMF. DMF (1 mL) and *i*-Pr_2NEt (0.012 mL, 0.067 mmol) were added to the resin and the mixture was shaken for 15 h. The resin was filtered and washed three times each with DMF and CH_2Cl_2, twice with MeOH and three times with CH_2Cl_2.

A soln of 20% (v/v) TFA in CH_2Cl_2 (1 mL) was added to the resin. The mixture was shaken for 10 min and filtered. The resin was washed with CH_2Cl_2. The cleavage step was repeated. The

combined filtrates and washings were concentrated and dried i.v. Purification by prep. HPLC method 1 afforded **Ex.476** (5 mg, 16%). Data of **Ex.476**: $C_{26}H_{30}N_4O_5$ (478.5). LC-MS (method 10a): R_t = 1.33 (86), 479 ($[M+H]^+$).

^{1}H-NMR (DMSO-d_6): 8.53 (d, J = 6.4, 1 H), 7.85-7.78 (m, 3 H), 7.56-7.44 (m, 3 H), 7.38 (t, J = 7.8, 1 H), 7.06 (d, J ca. 7.4, 1 H), 6.92 (d, J ca. 7.3, 1 H), 6.48 (br. s, 1 H), 4.61 (m, 1 H), 4.41 (m, 1 H), 4.27 (m, 2 H), ca. 3.8 (m, 2 H, superimposed by H_2O signal), 3.49 (br. d, 1 H), 3.28 (m, 1 H), 3.05 (m, 1 H), 2.99 (s, 3 H), 2.85 (m, 1 H), 2.35-2.26 (m, 3 H), 1.26 (d, J = 6.9, 3 H).

2. Cyclization in solution

The resin **260** was treated with 20%(v/v) TFA in CH_2Cl_2 (1 mL) for 10 min and filtered. The resin was washed (CH_2Cl_2) and this cleavage step was repeated.

The combined filtrates and washings were concentrated, dissolved in CH_3CN, again concentrated and dried i.v. Purification by prep. HPLC method 1 afforded **261**·CF_3CO_2H (27 mg, 66%).

Data of **261**·CF_3CO_2H: $C_{26}H_{32}N_4O_6$·CF_3CO_2H (496.5, free base). LC-MS (method 13): R_t = 0.80 (97), 497 ($[M+H]^+$).

FDPP (13 mg, 0.033 mmol) was added to a soln of **261**·CF_3CO_2H (10 mg, 0.016 mmol) in DMF (16 mL). *i*-Pr_2NEt (0.003 mL, 0.016 mmol) was added. The soln was stirred at rt for 15 h and concentrated. Purification of the residue by prep. HPLC method 1 afforded **Ex.476** (7 mg, 88%).

LC-MS (method 10a): R_t = 1.33 (96), 479 ($[M+H]^+$).

General Procedures for the synthesis of final products on solid support

Procedure **R**, exemplified below for **Core 03**, is generally applicable to macrocyclic core structures with an exocyclic carboxyl and amino group.

Procedure **S**, exemplified below for **Core 11a** and **Core 27**, is generally applicable to macrocyclic core structures with two exocyclic amino groups.

Procedure R: Derivatization of a carboxyl group and an amino group

Core 03 (Scheme 38)

Synthesis of the *N*-protected amino acid **Ex.591**

A soln of **Ex.4** (5.59 g, 10.2 mmol) in dioxane (23 mL) was treated with 4M HCl-dioxane (45 mL) for 3 h. Et_2O was added. The mixture was filtered. The solid was washed (Et_2O) and dried i.v. to afford **Ex.590**·HCl (5.46 g; crude, used without further purification).

A soln of **Ex.590**·HCl (5.46 g) in dioxane (130 mL) and H_2O (110 mL) was treated with sat. aq. Na_2CO_3 soln (14.8 mL). Allyl chloroformate (1.18 mL, 11.1 mmol) was added. The mixture was stirred for 1 h, concentrated to ca. 70% of the original volume and acidified with cold 0.5 M HCl soln (200 mL). The mixture was extracted with EtOAc. The organic layer was dried (Na_2SO_4), filtered and concentrated to afford **Ex.591** (5.72 g, quant. yield, contains ca. 5% of dioxane).

Data of **Ex.591**: $C_{25}H_{31}FN_4O_8$ (534.5). LC-MS (method 4b): R_t = 1.58 (91), 535 ($[M+H]^+$).

General procedure for the synthesis of the resins **262**

DFPE polystyrene (1% DVB, 100-200 mesh, loading 0.89 mmol/g; 10 g, 8.9 mmol) was swollen in DCE (100 mL) for 1 h. The resin was filtered. DCE (60 mL), a soln of the amine (5-10 equiv.) in DCE (40 mL) and finally trimethyl orthoformate (50 mL) were added. The resin was shaken for 0.5 h at rt, followed by the addition of sodium triacetoxyborohydride (5-10 equiv.). The mixture was

shaken for 18 h and the resin was filtered. The resin was successively washed with MeOH, three times each with DCE, DMF, 10% *i*-Pr_2NEt in DMF, DMF, CH_2Cl_2, MeOH and dried i.v. to afford resin **262**:

262a (10.8 g, 0.7 mmol/g) was obtained from DFPE polystyrene (1% DVB, 100-200 mesh, loading 0.87 mmol/g; 10 g, 8.7 mmol), *N,N*-dimethylethylenediamine (3.8 g, 43.5 mmol) and $NaBH(OAc)_3$ (9.2 g, 43.5 mmol).

262b (10.94 g, 0.61 mmol/g) was obtained from DFPE polystyrene (1% DVB, 100-200 mesh, loading 0.87 mmol/g; 10 g, 8.7 mmol), 3-pyridinemethylamine (9.4 g, 87 mmol) and $NaBH(OAc)_3$ (18 g, 87 mmol).

262c (21.1 g, 0.83 mmol/g) was obtained from DFPE polystyrene (1% DVB, 100-200 mesh, loading 0.87 mmol/g; 20 g, 17 mmol), isobutylamine (6.4 g, 87 mmol) and $NaBH(OAc)_3$ (18 g, 87 mmol).

262d (11.74 g, 0.77 mmol/g) was obtained from DFPE polystyrene (1% DVB, 100-200 mesh, loading 0.87 mmol/g; 10 g, 8.7 mmol), 2-naphthylmethylamine (6.8 g, 43.5 mmol) and $NaBH(OAc)_3$ (9.2 g, 43.5 mmol).

262e (2.25 g, 0.60 mmol/g) was obtained from DFPE polystyrene (1% DVB, 100-200 mesh, loading 0.89 mmol/g; 2.0 g, 1.78 mmol), 1-naphthylmethylamine (1.4 g, 8.9 mmol) and $NaBH(OAc)_3$ (1.9 g, 8.9 mmol).

Synthesis of resins **265**

1) Immobilization of acid **Ex.591**

A soln of *i*-Pr_2NEt (6 equiv.) in CH_2Cl_2 (0.15 mL) was added to resin **262** (loading 0.82 mmol/g; 100 mg, 0.082 mmol). A soln of carboxylic acid **Ex.591** (0.67 equiv.) in CH_2Cl_2/DMF (1:1; 0.45 mL) and a soln of HATU (3 equiv.) and HOAt (3 equiv.) in DMF (0.4 mL) were added. The mixture was shaken for 16 h and filtered. The resin was washed three times with DMF and CH_2Cl_2.

2) Capping

A soln of *i*-Pr_2NEt (6 equiv.) in CH_2Cl_2 (0.15 mL) was added. Acetic anhydride (6 equiv.) in CH_2Cl_2/DMF (1:1; 0.75 mL) was added. The mixture was shaken for 0.5 h and filtered. The

capping step was repeated. The resin was washed three times with DMF and CH_2Cl_2 to give resin **263**.

3) Cleavage of the Alloc group

The conditions described for the synthesis of resin **141** (see below) were applied.

4) Derivatization

The conditions described for the second derivatization step of resin **141** were applied (see below). In case of an isocyanate/ isocyanate equivalent or a sulfonyl chloride the derivatization step was repeated once.

5) Release of the final products:

The final products of general structure **266** were cleaved from solid support and purified as described for the products of **Core 11a** (see below).

Exception: Resins **265a-b** were treated with 20% TFA in CH_2Cl_2 for 3 x 30 min.

Procedure S: Derivatization of two amino groups

Core 11a (Scheme 39)

Synthesis of amine **Ex.594**

A soln of **Ex.181** (2.0 g, 3.2 mmol) in MeOH (200 mL) was hydrogenolyzed for 3 h at rt under normal pressure in the presence of palladium hydroxide on activated charcoal (15-20% Pd, moistened with 50% H_2O; 400 mg). The mixture was filtered through a pad of celite. The residue was washed (MeOH). The combined filtrate and washings were concentrated and dried i.v. to give the corresponding amine (1.57 g), which was dissolved in CH_2Cl_2 (8 mL) and treated with sat. aq. $NaHCO_3$ soln (2.9 mL) and allyl chloroformate (0.36 mL, 3.43 mmol). The mixture was stirred at rt for 2 h. The organic phase was separated and concentrated. Purification of the residue by FC (EtOAc) afforded allyl carbamate **138**(1.65 g, 92%).

TBAF soln (1 M in THF, 7 mL, 7 mmol) was added at 0°C to a soln of **138** (1.29 g, 2.24 mmol) in THF (53 mL). The soln was stirred at 0°C to rt for 3 h and concentrated. The residue was distributed between CH_2Cl_2 and sat. aq. $NaHCO_3$ soln. The aqueous

phase was separated and extracted with CH_2Cl_2. The combined organic phase was dried (Na_2SO_4), filtered and concentrated. The residue was dissolved in CH_2Cl_2 (10 mL) and treated for 20 min with 25% aq. HCl soln (0.29 mL). The volatiles were evaporated and the residue was dried i.v. to afford **Ex.594**·HCl (1.14 g; contaminated with ca. 15% tetrabutylammonium salt and used without further purification; yield ca. 90%).

Data of **Ex.594**·HCl: $C_{22}H_{30}N_4O_5$·HCl (430.5, free base). LC-MS (method 4a): R_t = 1.22 (92), 431.3 $[M+H]^+$.

Synthesis of resin **140**

DFPE polystyrene (1% DVB, 100-200 mesh, loading 0.89 mmol/g; 200 mg, 0.178 mmol) was swollen in DCE (2 mL) for 1 h. The resin was filtered. A soln of amine hydrochloride **Ex.594**·HCl (ca 85% w/w, 166 mg, 0.303 mmol) in DCE (1.33 mL) and trimethyl orthoformate (0.66 mL, 6.02 mmol) were added. The resin was shaken for 1 h at rt, followed by addition of sodium triacetoxyborohydride (75 mg, 0.356 mmol). The mixture was shaken for 15 h and the resin was filtered. The resin was successively washed three times each with DMF, 10% *i*-Pr_2NEt in DMF, DMF, CH_2Cl_2 and dried i.v. to afford resin **140** (293 mg).

Synthesis of resin **141**

1) First derivatization step

Resin **140** (loading 0.58 mmol/g; 120 mg, 0.07 mmol) was swollen in DMF (1 mL) for 30 min and filtered. The pre-swelling step was repeated. A soln of *i*-Pr_2NEt (8 equiv.) in CH_2Cl_2 (0.15 mL) was added to the resin. A soln of a) the carboxylic acid $R^{III}CO_2H$ (4 equiv.) in CH_2Cl_2/DMF (1:1; 0.45 mL) and a soln of HATU (4 equiv.) in DMF (0.4 mL), or b) the carboxylic acid chloride $R^{III}COCl$ (4 equiv.) in CH_2Cl_2 (0.45 mL) and CH_2Cl_2/DMF (1:1; 0.4 mL), or c) the isocyanate $R^{III}NCO$ or succinimidyl carbamate $R^{III}NHCO_2Su$ (4 equiv.) in CH_2Cl_2/DMF (1:1; 0.85 mL), or d) the sulfonyl chloride $R^{III}SO_2Cl$ (4 equiv.) in CH_2Cl_2/DMF (1:1; 0.85 mL), or e) the chloroformate $R^{III}OCOCl$ (4 equiv.) in CH_2Cl_2 (0.45 mL) and CH_2Cl_2/DMF (1:1; 0.45 mL) 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* and CH_2Cl_2.

2) Cleavage of the Alloc group

Phenylsilane (10 equiv.) in CH_2Cl_2 (0.5 mL), and $Pd(PPh_3)_4$ (0.2 equiv.) in CH_2Cl_2 (0.5 mL), were added to the resin. The mixture was shaken for 15 min and filtered. The resin was washed with CH_2Cl_2 and the deprotection step was repeated.

The resin was filtered, washed three times each with CH_2Cl_2, DMF and twice with MeOH and three times with CH_2Cl_2.

3) Second derivatization step

The carboxylic acids $R^{IV}CO_2H$, the isocyanates $R^{IV}NCO$ or isocyanate equivalents $R^{IV}NCO_2Su$ and the sulfonyl chlorides $R^{IV}SO_2Cl$ were coupled analogously to the first derivatization step, however with two exceptions: a) For couplings of carboxylic PyBOP was used as coupling reagent and b) all couplings were conducted only once.

The resin was filtered, washed three times each with DMF, twice with MeOH and three times with CH_2Cl_2 to afford resin **141**.

Release of the final products

The resin **141** was treated twice with 20% TFA in CH_2Cl_2 (1 mL) for 10 min, filtered and washed three times with CH_2Cl_2. The combined filtrates and washings were concentrated. The residue was treated with CH_3CN, evaporated and dried i.v. Purification of the crude product by normal phase or reversed phase prep. HPLC afforded products of general structure **267**.

Core 27 (Scheme 40)

Synthesis of amine **Ex.593**

A soln of **Ex.424** (19.2 g, 32 mmol) in MeOH (385 mL) was hydrogenolyzed for 2 h at rt under normal pressure in the presence of palladium hydroxide on activated charcoal (15-20% Pd, moistened with 50% H_2O; 4.0 g). The mixture was filtered through a pad of celite. The residue was washed (MeOH). The combined filtrate and washings were concentrated and dried i.v.

to give the corresponding amine (15.5 g), which was dissolved in CH_2Cl_2 (90 mL) and treated with sat. aq. $NaHCO_3$ soln (32 mL) and allyl chloroformate (4.40 mL, 41.5 mmol). The mixture was stirred at rt for 2 h. Additional allyl chloroformate (0.9 mL, 8.5 mmol) was added and stirring was continued for 1 h. The mixture was diluted with sat. aq. $NaHCO_3$ soln and extracted with CH_2Cl_2. The organic phase was separated and concentrated. Purification of the residue by FC (CH_2Cl_2/MeOH 95:5) afforded the allyl carbamate **Ex.592** (15.48 g, 85%).

The material was dissolved in CH_2Cl_2 (73 mL) and treated at 0°C with TFA (73 mL) for 30 min. Stirring was continued at rt for 1 h. The volatiles were evaporated. The residue was treated with sat. aq. Na_2CO_3 soln and repeatedly extracted with $CHCl_3$. The organic phase was dried (Na_2SO_4), filtered and concentrated. The resulting free amine was dissolved in dioxane (147 mL) and treated with 4M HCl-dioxane (29.5 mL). A precipitate was formed. The volatiles were evaporated. The residue was suspended in CH_2Cl_2 and the volatiles were evaporated to afford **Ex.593**·2HCl (14.49 g, 87%).

Data of **Ex.593**·2HCl: $C_{22}H_{31}N_5O_5$·2HCl (445.5, free base). LC-MS (method 10a): R_t = 0.98 (96), 446 ($[M+H]^+$).

Synthesis of resins **269**

Resins **269** was prepared from **Ex.593** by applying the conditions described as for the synthesis of resin **141** from **Ex.594**. The second derivatization step was repeated once if an isocyanate or isocyanate equivalent or sulfonyl chloride was used.

Release of the final products

The final products of general structure **270** were cleaved from solid support and purified as described for the products of **Core 11a** (see above).

Synthesis of final products

Advanced macrocyclic intermediates and final products depicted in **Tables 21a-49a** (Scheme 26) were prepared starting from the suitable precursor macrocyclic acid or macrocyclic amine applying the general procedures (**H-Q, R, S**) described above. Deviations from general procedures are indicated in **Tables 21a-49a.**

Analytical data of these intermediates and final products are depicted in **Tables 21b-49b.**

IUPAC names of all examples are listed in **Tables 20** and **21c-49c.**

The generic macrocyclic ring structures (Cores) related to **Tables 20-49** are depicted in **Scheme 41** in the order of their core numbers.

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.

Detailed description of selected examples

Core 03: Synthesis of selected advanced intermediates and final products (Scheme 42)

Synthesis of amide **Ex.27**

A mixture of **Ex.4** (432 mg, 0.79 mmol), HATU (597 mg, 1.57 mmol) and HOAt (214 mg, 1.57 mmol) was dissolved in DMF (6 mL). *N,N*-Dimethylethylenediamine (173 µL, 1.57 mmol) and *i*-Pr_2NEt (537 µL, 3.14 mmol) were added. The soln was stirred at rt for 15 h and concentrated. The residue was dissolved in $CHCl_3$ and washed with sat. aq. $NaHCO_3$ soln and with H_2O. The organic phase was dried (Na_2SO_4), filtered and concentrated. FC (CH_2Cl_2/MeOH/conc.

aq. NH_3 soln 100:0:0 to 90:10:0.5) afforded **Ex.27** (405 mg, 83%).

Data of **Ex.27**: cf. **Table 21b**

Synthesis of amine **Ex.28**

A soln of **Ex.27** (400 mg, 0.64 mmol) in dioxane (4 mL) was treated at rt with 4M HCl-dioxane (8 mL) for 2 h. The volatiles were evaporated. The residue was dissolved in CH_2Cl_2/MeOH, concentrated and dried i.v. to afford **Ex.28**·HCl (343 mg, 90%).

Data of **Ex.28**: cf. **Table 21b**

Synthesis of amide **Ex.11**

A mixture of **Ex.28**·HCl (75 mg, 0.126 mmol), 1*H*-indole-3-acetic acid (44 mg, 0.253 mmol), HATU (96 mg, 0.253 mmol) and HOAt (34 mg, 0.253 mmol) was dissolved in DMF (2 mL). *i*-Pr_2NEt (87 µL, 0.505 mmol) was added. The soln was stirred at rt for 15 h and concentrated. The residue was dissolved in $CHCl_3$ and washed with sat. aq. $NaHCO_3$ soln and with H_2O. The organic phase was dried (Na_2SO_4), filtered and concentrated. FC (CH_2Cl_2/MeOH/conc. aq. NH_3 soln 100:0:0 to 90:10:1) afforded **Ex.11** (50 mg, 58%).

Data of **Ex.11**: cf. **Table 21b**

^{1}H-NMR (DMSO-d_6): 10.81 (s, 1 H), 8.26 (d, J = 7.4, 1 H), 7.62 (t, J = 5.5, 1 H), 7.46 (d, J = 7.9, 1 H), 7.37-7.15 (m, 4 H), 7.09 (d, J = 2.2, 1 H), 7.04 (t, J = 7.5, 1 H), 6.92 (t, J ca. 7.4, 1 H), 5.08 (d, J ca. 12.5, 1 H), 4.74 (d, J = 8.9, 1 H), 4.37 (d, J = 11.0, 1 H), 4.25 (d, J = 17.7, 1 H), 4.22-4.13 (m, 2 H), 3.97 (d, J = 17.6, 1 H), 3.78 (t, J = 8.3, 1 H), 3.41 (s, 2 H), 3.24 (m, 1 H), 3.15 (m, 1 H), 2.98 (t, J = 9.2, 1 H), 2.88 (s, 3 H), 2.53 (s, 3 H), 2.41-2.27 (m, 4 H), 2.17 (s, 6 H), 2.04 (m, 1 H), 1.83 (t-like m, 2 H), 1.69 (q-like m, 1 H).

Synthesis of amide **Ex.48**

Ex.48 (58 mg, 83%) was obtained from **Ex.28**·HCl (60 mg, 0.101 mmol) and 2-naphthylacetic acid (23 mg, 0.121 mmol) following the procedure described for the synthesis of **Ex.49** (see below).

After purification by FC, the material was submitted to an aqueous extraction ($CHCl_3$, aq. $NaHCO_3$ soln).
Data of **Ex.48**: cf. **Table 21b**

Synthesis of amide **Ex.49**
A mixture of **Ex.28**·HCl (60 mg, 0.101 mmol), 1-naphthylacetic acid (23 mg, 0.121 mmol), and HOBt·H_2O (19 mg, 0.121 mmol) was dissolved in CH_2Cl_2 (1 mL). *N*-Cyclohexyl-carbodiimide-*N'*-methylpolystyrene (1.9 mmol/g; 80 mg, 0.152 mmol) and *i*-Pr_2NEt (52 µL, 0.303 mmol) were added. The mixture was stirred for 15 h at rt. (Polystyrylmethyl)-trimethylammonium bicarbonate (3.5 mmol/g; 87 mg, 0.303 mmol) was added and stirring was continued for 1 h. The mixture was diluted with CH_2Cl_2/MeOH 9:1 (2 mL) and filtered. The polymer was washed with twice with CH_2Cl_2/MeOH 8:2 (5 mL). The combined filtrate and washings were concentrated. Purification of the crude product by FC (CH_2Cl_2/MeOH/conc. aq. NH_3 soln 100:0:0 to 90:10:1) afforded **Ex.49** (58 mg, 83%).
Data of **Ex.49**: cf. **Table 21b**
^{1}H-NMR (DMSO-d_6): 8.45 (d, J = 7.3, 1 H), 8.00-7.87 (m, 2 H), 7.79 (d, J = 8.0, 1 H), 7.62 (t, J = 5.5, 1 H), 7.53-7.25 (m, 6 H), 7.19 (dd, J = 3.0, 8.4, 1 H), 5.10 (d, J = 12.3, 1 H), 4.75 (d, J = 8.9, 1 H), 4.39 (d, J = 10.8, 1 H), 4.27 (d, J = 17.8, 1 H), 4.28-4.08 (m, 2 H), 3.95 (d, J = 17.9, 1 H), 3.83 (m, 1 H), 3.81 (s, 2 H), 3.24 (m, 1 H), 3.16 (m, 1 H), 3.03 (t, J = 9.2, 1 H), 2.87 (s, 3 H), 2.54 (s, 3 H), 2.42-2.27 (m, 4 H), 2.16 (s, 6 H), 2.02 (m, 1 H), 1.84 (t-like m, 2 H), 1.71 (q, J ca. 9.4, 1 H).

Synthesis of amine **Ex.486**
A mixture of activated molecular sieves (powder, 4Å; 120 mg) and **Ex.28** (free base obtained from acid **Ex.591** (Scheme 38) by coupling of *N,N*-dimethylethylenediamine according to Procedure **L.2** and subsequent cleavage of the Alloc group with $Pd(PPh_3)_4$ and morpholine in THF; 60 mg, 0.115 mmol) was suspended in THF

(1 mL). 2-(Naphthalen-1-yl)acetaldehyde (20 mg, 0.115 mmol) in THF (0.25 mL) was added. The mixture was stirred at rt for 4 h. A soln of acetic acid (0.0073 mL, 0.127 mmol) in THF (0.25 mL) was added, followed by $NaBH(OAc)_3$ (49 mg, 0.231 mmol) and stirring was continued for 15 h. Aqueous workup ($CHCl_3$, sat. aq. $NaHCO_3$ soln; Na_2SO_4) and purification by FC (CH_2Cl_2/MeOH/conc. aq. NH_3 soln 98:2:2 to 90:10:2) and by prep. HPLC method 1 afforded **Ex.486**·CF_3CO_2H (6 mg; 6%).

Data of **Ex.486**·CF_3CO_2H: cf. **Table 21b**

Synthesis of amide **Ex.30**

A mixture of **Ex.4** (400 mg, 0.73 mmol), HATU (552 mg, 1.45 mmol), HOAt (198 mg, 1.45 mmol) and tryptamine (233 mg, 1.45 mmol) was dissolved in DMF (6 mL). *i*-Pr_2NEt (497 µL, 2.91 mmol) was added. The soln was stirred at rt for 15 h followed by aqueous workup ($CHCl_3$, sat. aq. $NaHCO_3$ soln, H_2O). The organic phase was dried (Na_2SO_4), filtered and concentrated. FC (CH_2Cl_2/MeOH 100:0 to 95:5) afforded **Ex.30** (410 mg, 81%).

Data of **Ex.30**: cf. **Table 21b**

^{1}H-NMR (DMSO-d_6): 10.80 (s, 1 H), 7.91 (t, J = 5.6, 1 H), 7.56 (d, J = 7.7, 1 H), 7.32 (d, J = 8.0, 1 H), 7.27-7.12 (m, 5 H), 7.06 (t, J = 7.5, 1 H), 6.97 (t, J = 7.4, 1 H), 5.08 (d, J = 12.4, 1 H), 4.75 (d, J = 9.3, 1 H), 4.34 (d, J = 10.9, 1 H), 4.24 (d, J = 17.8, 1 H), 4.10 (t-like m, 1 H), 3.97 (d, J = 17.7, 1 H), 3.86 (m, 1 H), 3.77 (m, 1 H), 3.42-3.30 (m, 2 H), 2.96-2.83 (m, 3 H), 2.89 (s, 3 H), 2.50 (s, 3 H, superimposed by DMSO-d signal), 2.27 (m, 2 H), 2.08 (m, 1 H), 1.84 (t-like m, 2 H), 1.65 (q, J = 10.8, 1 H), 1.34 (s, 9 H).

Synthesis of amine **Ex.55**

A soln of **Ex.30** (380 mg, 0.55 mmol) in dioxane (4 mL) was treated at rt with 4M HCl-dioxane (8 mL) for 4 h. The volatiles were evaporated. The residue was dissolved in dioxane (4 mL) and treated again for 2 h with 4M HCl-dioxane (8 mL). The volatiles were evaporated. The residue was washed with Et_2O and

purified by FC (CH_2Cl_2/MeOH/conc. aq. NH_3 soln 90:10:0 to 90:10:1) to afford **Ex.55** (136 mg, 42%).

Data of **Ex.55**: cf. **Table 21b**

Synthesis of amide **Ex.498**

A mixture of **Ex.5**·HCl (874 mg, 1.52 mmol), 1-naphthylacetic acid (564 mg, 3.03 mmol), HATU (1.15 g, 3.03 mmol) and HOAt (412 mg, 3.03 mmol) was dissolved in DMF (9 mL). *i*-Pr_2NEt (0.778 mL, 4.54 mmol) was added. The soln was stirred at rt for 2 h and concentrated. The residue was dissolved in CH_2Cl_2 and washed with sat. aq. $NaHCO_3$ soln and with H_2O. The organic phase was dried (Na_2SO_4), filtered and concentrated. Purification by FC (EtOAc/MeOH gradient) afforded **Ex.498** contaminated with some *i*-Pr_2NEt which was removed by extraction (CH_2Cl_2, 1 M aq. HCl, sat. aq. $NaHCO_3$ soln) to give **Ex.498** (940 mg, 87%).

Data of **Ex.498**: cf. **Table 21b**

Synthesis of acid **Ex.499**

A soln of **Ex.498** (871 mg, 1.23 mmol) in MeOH (9 mL) was hydrogenolyzed under normal pressure at rt in the presence of palladium hydroxide on activated charcoal (moistened with 50% H_2O; 0.14 g) for 2 h. The mixture was filtered through a pad of celite. The filtrate was concentrated to afford **Ex.499** (732 mg; 96%).

Data of **Ex.499**: cf. **Table 21b**

Synthesis of amide **Ex.488**

A mixture of **Ex.499** (70 mg, 0.11 mmol), HATU (86 mg, 0.23 mmol) and HOAt (31 mg, 0.23 mmol) was suspended in DMF (1 mL). 3-Dimethylaminopropylamine (0.028 mL, 0.23 mol) and *i*-Pr_2NEt (0.039 mL, 0.23 mmol) were added. The mixture was stirred for 3 h and concentrated. Aqueous workup ($CHCl_3$, sat. aq. $NaHCO_3$ soln, H_2O; Na_2SO_4) and purification by prep. HPLC method 2 afforded **Ex.488** (53 mg, 66%).

Data of **Ex.488**: cf. **Table 21b**

Synthesis of amide **Ex.485**

A mixture of **Ex.499** (70 mg, 0.11 mmol), HATU (86 mg, 0.23 mmol) and HOAt (31 mg, 0.23 mmol) was suspended in DMF (1 mL). *N*-(2-Aminoethyl)pyridine-2-amine (31 mg, 0.23 mol) and *i*-Pr_2NEt (0.039 mL, 0.23 mmol) were added. The mixture was stirred for 3 h and concentrated. Aqueous workup ($CHCl_3$, sat. aq. $NaHCO_3$ soln, H_2O; Na_2SO_4) and purification by prep. HPLC method 2 afforded **Ex.485** (50 mg, 60%).

Data of **Ex.485**: cf. **Table 21b**

Synthesis of amide **Ex.500**

A mixture of **Ex.499** (250 mg, 0.40 mmol), HATU (307 mg, 0.81 mmol) and HOAt (110 mg, 0.81 mmol) was suspended in DMF (2.5 mL). *tert.* Butyl-2-aminoethylcarbamate (129 mg, 0.81 mmol) and *i*-Pr_2NEt (0.138 mL, 0.81 mmol) were added. The mixture was stirred for 3 h and concentrated. Aqueous workup ($CHCl_3$, sat. aq. $NaHCO_3$ soln, H_2O; Na_2SO_4) and purification by prep. HPLC method 2 afforded **Ex.500** (227 mg, 74%).

Data of **Ex.500**: cf. **Table 21b**

Synthesis of amine **Ex.483**

4M HCl-dioxane (2 mL) was added to a soln of **Ex.500** (201 mg, 0.26 mmol) in dioxane (2 mL). The mixture was stirred for 2 h at rt and concentrated to afford **Ex.483**·HCl (200 mg, 97%).

Data of **Ex.483**·HCl: cf. **Table 21b**

^{1}H-NMR (DMSO-d_6): 8.46 (d, J = 7.1, 1 H), 8.00-7.78 (several m and br. s, 7 H), 7.52-7.21 (several m, 7 H), 5.15 (d, J = 12.3, 1 H), 4.76 (d, J = 8.8, 1 H), 4.40 (d, J = 10.8, 1 H), 4.28 (d, J = 17.7, 1 H), 4.25-4.12 (m, 3 H), 4.03-3.94 (m, 2 H), 3.81 (m, 1 H), 3.81 (s, 2 H), 3.35 (m, 1 H, superimposed by H_2O signal), 3.01 (m, 1 H), 2.90 (m, 1 H), 2.88 (s, 3 H), 2.56 (s, 3 H), 2.42-2.33 (m, 2 H), 2.10 (m, 1 H), 1.91-1.82 (m, 2 H), 1.70 (m, 1 H).

Synthesis of guanidine **Ex.484**

Triethylamine (0.066 mL) was added to a suspension of **Ex.483**·HCl (110 mg, 0.158 mmol) in $CHCl_3$ (1 mL). 1,3-Di-Boc-(trifluoromethylsulfonyl)-guanidine (65 mg, 0.17 mmol) was added. The mixture was stirred for 22 h at rt, followed by aqueous workup ($CHCl_3$, sat. aq. Na_2CO_3 soln, sat. aq. NaCl soln; Na_2SO_4) and purification by FC (EtOAc/MeOH 100:0 to 80:20) to afford a colorless solid (74 mg) which was dissolved in dioxane (1 mL) and treated with 4M HCl-dioxane (1 mL) for 2 h. More 4M HCl-dioxane (1 mL) was added and stirring was continued for 15 h. The volatiles were evaporated and the residue purified by prep. HPLC (method 1) to afford **Ex.484**·CF_3CO_2H.

Data of **Ex.484**·CF_3CO_2H: cf. **Table 21b**

Synthesis of amide **Ex.487**

At 0°C, pyridine (0.081 mL, 1.0 mmol) and acetic anhydride (0.047 mL, 0.5 mmol) were added to a mixture of **Ex.483**·HCl (70 mg, 0.10 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred for 2 h and concentrated. Purification by prep. HPLC (method 1) afforded **Ex.487** (53 mg, 75%).

Data of **Ex.487**: cf. **Table 21b**

Synthesis of urea **Ex.482**

Ex.482·CF_3CO_2H (11 mg, 25%) was obtained from resin **263a** (0.7 mmol/g; 118 mg, 0.082 mmol) and 1-naphthyl isocyanate (84 mg, 0.498 mmol) according to procedure **R**.

The product was purified by prep. HPLC (method 1).

Data of **Ex.482**·CF_3CO_2H: cf. **Table 21b**

Synthesis of amide **Ex.495**

Ex.495·CF_3CO_2H (11 mg, 24%) was obtained from resin **263a** (0.7 mmol/g; 118 mg, 0.083 mmol) and 3-(trifluoromethyl)phenylacetic acid (102 mg, 0.498 mmol) according to procedure **R**.

The product was purified by prep. HPLC (method 1).

Data of **Ex.495**·CF_3CO_2H: cf. **Table 21b**

Synthesis of amide **Ex.496**

Ex.496·CF_3CO_2H (10 mg, 23%) was obtained from resin **263a** (0.7 mmol/g; 118 mg, 0.083 mmol) and 3-methoxyphenylacetic acid (83 mg, 0.489 mmol) according to procedure **R.**

The product was purified by prep. HPLC (method 1).

Data of **Ex.496**·CF_3CO_2H: cf. **Table 21b**

Synthesis of amide **Ex.497**

Ex.497·CF_3CO_2H (8 mg, 18%) was obtained from the resin **263b** (0.61 mmol/g; 130 mg, 0.079 mmol) and 1-naphthylacetic acid (93 mg, 0.498 mmol) according to procedure **R.**

The product was purified by prep. HPLC (method 1).

Data of **Ex.497**·CF_3CO_2H: cf. **Table 21b**

Synthesis of amide **Ex.501**

Ex.501 (18 mg, 44%) was obtained from resin **263e** (0.602 mmol/g; 130 mg, 0.078 mmol) and 2-naphthylacetic acid (86 mg, 0.498 mmol) according to procedure **R.**

The product was purified by prep. HPLC (method 3).

Data of **Ex.501**: cf. **Table 21b**

Synthesis of amide **Ex.502**

Ex.502 (19 mg, 48%) was obtained from resin **263e** (0.602 mmol/g; 130 mg, 0.078 mmol/g) and 3-chlorobenzoic acid (95 mg, 0.498 mmol) according to procedure **R.**

The product was purified by prep. HPLC (method 3).

Data of **Ex.502**: cf. **Table 21b**

^{1}H-NMR (DMSO-d_6): 8.71 (d, J = 7.1, 1 H), 8.39 (t-like m, 1 H), 8.10 (m, 1 H), 7.95 (m, 1 H), 7.87-7.82 (m, 2 H), 7.75 (d, J ca. 7.8, 1 H), 7.59-7.42 (m, 6 H), 7.29-7.22 (m, 2 H), 6.91 (dd, J = 3.0, 8.4, 1 H), 5.15 (d, J ca. 12.1, 1 H), 4.85-4.70 (m, 2 H), 4.50-4.10 (m, 4 H), 4.03 (d, J = 18.1, 1 H), 3.88 (t, J ca. 8.2, 1 H), 3.08 (t-like m, 1 H), 2.90 (m, 1 H), 2.89 (s, 3 H), 2.57 (s, 3 H), 2.50-2.25 (m, 2 H), 2.10-1.80 (m, 4 H).

Synthesis of amide **Ex.503**

Ex.503 (17 mg, 43%) was obtained from resin **263d** (0.77 mmol/g; 108 mg, 0.083 mmol) and 1-naphthoic acid (85.8 mg, 0.498 mmol) according to procedure **R**.

The product was purified by prep. HPLC (method 3).

Data of **Ex.503**: cf. **Table 21b**

Synthesis of amide **Ex.12**

A mixture of **Ex.55** (68 mg, 0.092 mmol), 1*H*-indole-3-acetic acid (32 mg, 0.184 mmol), HATU (70 mg, 0.184 mmol) and HOAt (25 mg, 0.184 mmol) was dissolved in DMF (2 mL). *i*-Pr_2NEt (63 µL, 0.367 mmol) was added. The soln was stirred at rt for 15 h and concentrated. The residue was dissolved in $CHCl_3$ and washed with sat. aq. $NaHCO_3$ soln and with H_2O. The organic phase was dried (Na_2SO_4), filtered and concentrated. Purification by prep. HPLC, method 1, afforded **Ex.12** (38 mg, 55%).

Data of **Ex.12**: cf. **Table 21b**

^{1}H-NMR (DMSO-d_6): 10.81 (s, 2 H), 8.26 (d, J = 7.2, 1 H), 7.93 (t, J = 5.7, 1 H), 7.57 (d, J = 7.8, 1 H), 7.46 (d, J = 7.7, 1 H), 7.38-6.90 (m, 11 H), 5.10 (d, J = 12.1, 1 H), 4.76 (d, J = 9.3, 1 H), 4.38 (d, J = 10.8, 1 H), 4.26 (d, J = 17.8, 1 H), 4.23-4.11 (m, 2 H), 3.96 (d, J = 18.0, 1 H), 3.78 (t, J = 8.3, 1 H), 3.7-3.25 (m, 3 H), 3.60 (s, 2 H), 3.01-2.81 (m, 2 H), 2.88 (s, 3 H), ca. 2.5 (s, 3 H, superimposed by DMSO-d signal), 2.33 (m, 2 H), 2.06 (m, 1 H), 1.85 (t-like m, 2 H), 1.63 (q, J ca. 10.7, 1 H).

Synthesis of amide **Ex.16**

A mixture of **Ex.55** (68 mg, 0.092 mmol), *N,N*-dimethyl glycine (19 mg, 0.184 mmol), HATU (70 mg, 0.184 mmol) and HOAt (25 mg, 0.184 mmol) was dissolved in DMF (2 mL). *i*-Pr_2NEt (63 µL, 0.367 mmol) was added. The soln was stirred at rt for 15 h and concentrated. The residue was dissolved in $CHCl_3$ and washed with sat. aq. $NaHCO_3$ soln and with H_2O. The organic phase was dried (Na_2SO_4), filtered and concentrated. Purification by prep. HPLC, method 1, afforded **Ex.16**·TFA (40 mg, 55%).

Data of **Ex.16**·TFA: cf. **Table 21b**

^{1}H-NMR (DMSO-d_6): 10.81 (s, 1 H), 9.66 (br. s, NH^+), 8.75 (d, J = 6.9, 1 H), 7.90 (t, J = 5.6, 1 H), 7.56 (d, J = 7.8, 1 H), 7.34-7.14 (m, 5 H), 7.06 (t, J ca. 7.5, 1 H), 6.97 (t, J = 7.4, 1 H), 5.08 (d, J = 12.3, 1 H), 4.78 (d, J = 9.2, 1 H), 4.39 (d, J = 10.7, 1 H), 4.24 (d, J = 17.8, 1 H), 4.24-4.14 (m, 2 H), 4.00 (d, J = 17.8, 1 H), 3.96-3.75 (m, 3 H), 3.45-3.35 (m, 2 H), 3.0-2.67 (m, 3 H), 2.90 (s, 3 H), 2.75 (s, 6 H), 2.50 (s, 3 H, superimposed by DMSO-d signal), 2.5-2.27 (m, 2 H), 2.08 (m, 1 H), 1.85 (t-like m, 2 H), 1.64 (q, J = 10.8, 1 H).

Synthesis of amide **Ex.53**

Pyridine (2 mL) and acetic anhydride (0.14 mL, 1.48 mmol) were added to a soln of **Ex.5**·HCl (95 mg, 0.15 mmol) in dry CH_2Cl_2 (2 mL). The soln was stirred at rt for 20 h. The soln was diluted with EtOAc and washed with 1 M aq. HCl soln, sat. aq. NaCl soln, sat. aq. $NaHCO_3$ soln, and sat. aq. NaCl soln. The organic phase was dried (Na_2SO_4), filtered and concentrated. FC of the crude product afforded **Ex.53** (60 mg, 70%).

Data of **Ex.53**: cf. **Table 21b**

Synthesis of acid **Ex.54**

A soln of **Ex.53** (58 mg, 0.01 mmol) in MeOH (5 mL) was hydrogenolyzed at rt and normal pressure for 2 h in the presence of palladium hydroxide on activated charcoal (moistened with 50% H_2O; 50 mg). The mixture was filtered through a pad of celite. The residue was washed (MeOH). The combined filtrate and washings were concentrated and dried i.v. to yield **Ex.54** (45 mg, 92%).

Data of **Ex.54**: cf. **Table 21b**

Synthesis of amide **Ex.9**

A mixture of **Ex.54** (45 mg, 0.091 mmol), HATU (52 mg, 0.137 mmol) HOAt (19 mg, 0.137 mmol) and tryptamine (22 mg, 0.137 mmol) was dissolved in DMF (1 mL). *i*-Pr_2NEt (47 µL, 0.274 mmol)

was added. The soln was stirred at rt for 20 h followed by aqueous workup ($CHCl_3$, sat. aq. $NaHCO_3$ soln, H_2O). The organic phase was dried (Na_2SO_4), filtered and concentrated. FC (CH_2Cl_2/MeOH 100:0 to 86:14) afforded **Ex.9** (36 mg, 62%).

Data of **Ex.9**: cf. **Table 21b**

^{1}H-NMR (DMSO-d_6): 10.81 (s, 1 H), 8.06 (d, J = 7.0, 1 H), 7.93 (t, J = 5.6, 1 H), 7.56 (d, J = 7.8, 1 H), 7.34-7.14 (m, 5 H), 7.05 (t, J ca. 7.5, 1 H), 6.97 (t, J ca. 7.4, 1 H), 5.09 (d, J = 12.4, 1 H), 4.75 (d, J = 9.1, 1 H), 4.38 (d, J = 10.8, 1 H), 4.26 (d, J = 17.7, 1 H), 4.19-4.10 (m, 2 H), 3.97 (d, J = 17.9, 1 H), 3.78 (t, J = 8.3, 1 H), 3.43-3.30 (m, 2 H), 2.96-2.83 (m, 3 H), 2.89 (s, 3 H), 2.50 (s, 3 H, superimposed by DMSO-d signal), 2.40-2.27 (m, 2 H), 2.08 (m, 1 H), 1.85 (m, 2 H), 1.71 (s, 3 H), 1.62 (q, J ca. 10.6, 1 H).

Core 10: Synthesis of selected advanced intermediates and final products (Scheme 43)

Synthesis of amide **Ex.166**

Pyridine (0.48 mL, 5.9 mmol) and valeroyl chloride (0.141 mL, 1.83 mmol) were added to a mixture of **Ex.165** (345 mg, 0.59 mmol) and CH_2Cl_2 (6.0 mL). The mixture was stirred at 0°C for 1 h followed by the addition of MeOH (0.1 mL). Stirring was continued for 10 min. The volatiles were evaporated. Purification by FC (EtOAc/MeOH 100:0 to 95:5) afforded **Ex.166** (220 mg, 67%).

Data of **Ex.166**: cf. **Table 28b**

Synthesis of amine **Ex.167**

A soln of **Ex.166** (190 mg, 0.345 mmol) in MeOH/THF (3:1; 16 mL) was hydrogenolyzed under normal pressure at rt for 2 h in the presence of palladium hydroxide on activated charcoal (moistened with 50% H_2O; 95 mg). The mixture was filtered through a pad of celite. The filtrate was concentrated to afford **Ex.167** (152 mg, quant. yield).

Data of **Ex.167**: cf. **Table 28b**

Synthesis of amide **Ex.168**

A mixture of **Ex.165** (438 mg, 0.94 mmol), 2-naphthylacetic acid (350 mg, 1.88 mmol), HATU (714 mg, 1.88 mmol) and HOAt (256 mg, 1.88 mmol) was dissolved in DMF (5 mL). *i*-Pr_2NEt (0.65 mL, 3.7 mmol) was added. The soln was stirred at rt for 20 h and concentrated. The residue was dissolved in $CHCl_3$ and washed with sat. aq. $NaHCO_3$ soln. The organic phase was dried (Na_2SO_4), filtered and concentrated. FC (EtOAc) afforded **Ex.168** (404 mg, 68%).

Data of **Ex.168**: cf. **Table 28b**

^{1}H-NMR (DMSO-d_6): 8.45 (d, J = 6.4, 1 H), 7.95-7.83 (m, 3 H), 7.74 (s, 1 H), 7.51-7.41 (m, 4 H), 7.36-7.26 (m, 6 H), 7.03 (dd, J = 1.3, 8.2, 1 H), 6.96 (d, J = 7.5, 1 H), 6.86 (s, 1 H), 4.99 (s, 2 H), 4.55 (d, J = 12.1, 1 H), 4.32 (t-like m, 1 H), 4.24-4.04 (m, 4 H), 3.61 (s, 2 H), ca. 3.2 (m, 1 H), 3.15-2.95 (m, 2 H), 2.89 (s, 3 H), 2.35-2.18 (m, 2 H), 2.06 (m, 1 H), 1.90 (m, 1 H).

Synthesis of amide **Ex.169**

A mixture of **Ex.165** (293 mg, 0.63 mmol), 1-pyrrolidineacetic acid (162 mg, 1.25 mmol), HATU (478 mg, 1.25 mmol) and HOAt (171 mg, 1.25 mmol) was dissolved in DMF (5 mL). *i*-Pr_2NEt (0.43 mL, 2.5 mmol) was added. The soln was stirred at rt for 20 h and concentrated. The residue was dissolved in $CHCl_3$ and washed with sat. aq. $NaHCO_3$ soln. The organic phase was dried (Na_2SO_4), filtered and concentrated. FC (EtOAc, then EtOAc/MeOH 9:1) afforded **Ex.169** (277 mg, 76%).

Data of **Ex.169**: cf. **Table 28b**

Synthesis of amide **Ex.170**

A soln of **Ex.167** (62 mg, 0.15 mmol), 3-(pyridine-4-yl)propanoic acid (27 mg, 0.179 mmol) and HOBt·H_2O (27 mg, 0.179 mmol) in CH_2Cl_2 (1 mL) was treated with *N*-cyclohexyl-carbodiimide-*N'*-methylpolystyrene (1.9 mmol/g; 118 mg, 0.223 mmol) and *i*-Pr_2NEt (0.076 mL, 0.447 mmol). The mixture was stirred for 15 h at rt.

(Polystyrylmethyl)trimethylammonium bicarbonate (3.5 mmol/g; 128 mg, 0.447 mmol) was added and stirring was continued for 1 h. The mixture was diluted with CH_2Cl_2/MeOH 9:1 (2 mL) and filtered. The polymer was washed twice with CH_2Cl_2/MeOH 8:2 (5 mL). The combined filtrate and washings were concentrated. Purification by FC (CH_2Cl_2/MeOH 100:0 to 95:5) afforded **Ex.170** (64 mg, 78%).

Data of **Ex.170**: cf. **Table 28b**

Synthesis of amide **Ex.171**

Pyridine (0.12 mL, 1.5 mmol) and 2-naphthoyl chloride (74 mg, 0.38 mmol) were added to a mixture of **Ex.167** (62 mg, 0.15 mmol) and CH_2Cl_2 (1.0 mL). The mixture was stirred at 0°C for 15 h. More 2-naphthoyl chloride (42 mg, 0.22 mmol) was added. Stirring was continued for 1 h followed by addition of MeOH (0.1 mL). Stirring was continued for 10 min. Aqueous workup ($CHCl_3$, sat. aq. $NaHCO_3$ soln; Na_2SO_4) and purification by prep. HPLC (method 3) afforded **Ex.171** (36 mg, 42%).

Data of **Ex.171**: cf. **Table 28b**

Synthesis of amine **Ex.172**

A soln of **Ex.168** (380 mg, 0.60 mmol) in MeOH/THF (3:1; 32 mL) was hydrogenolyzed under normal pressure at rt for 2 h in the presence of palladium hydroxide on activated charcoal (moistened with 50% H_2O; 190 mg). The mixture was filtered through a pad of celite. The filtrate was concentrated to afford **Ex.172** (292 mg, 97%).

Data of **Ex.172**: cf. **Table 28b**

Synthesis of amine **Ex.173**

A soln of **Ex.169** (257 mg, 0.445 mmol) in MeOH/THF (3:1; 16 mL) was hydrogenolyzed under normal pressure at rt for 2 h in the presence of palladium hydroxide on activated charcoal (moistened with 50% H_2O; 190 mg). The mixture was filtered through a pad of celite. The filtrate was concentrated to afford **Ex.173** (190 mg, 96%).

Data of **Ex.173**: cf. **Table 28b**

Synthesis of amide **Ex.177**

A soln of **Ex.172** (65 mg 0.13 mmol), 1-naphthylacetic acid (29 mg, 0.16 mmol) and HOBt·H_2O (24 mg, 0.16 mmol) in CH_2Cl_2 (1 mL) was treated with *N*-cyclohexyl-carbodiimide-*N'*-methylpolystyrene (1.9 mmol/g; 103 mg, 0.19 mmol) and *i*-Pr_2NEt (0.067 mL, 0.39 mmol). The mixture was stirred for 15 h at rt and filtered. The filtrate was submitted to aqueous workup ($CHCl_3$, sat. aq. $NaHCO_3$ soln; Na_2SO_4). Purification by prep. HPLC (method 3) afforded **Ex.177** (59 mg, 68%).

Data of **Ex.177**: cf. **Table 28b**

^{1}H-NMR (DMSO-d_6): 8.41 (d, J = 6.4, 1 H), 8.34 (d, J = 7.1, 1 H), 8.03 (d, J = 8.2, 1 H), 7.87-7.72 (m, 6 H), 7.49-7.38 (m, 7 H), 7.31 (t, J = 7.8, 1 H), 7.00 (dd, J = 1.5, 8.2, 1 H), 6.94 (d, J = 7.5, 1 H), 6.85 (s, 1 H), 4.53 (t, J = 7.3, 1 H), 4.44 (d, J = 12.8, 1 H), 4.27-3.96 (m, 5 H), 3.96 (d, J = 13.8, 1 H), 3.87 (d, J = 14.9, 1 H), 3.57 (s, 2 H), 3.11 (m, 1 H), 2.94 (m, 1 H), 2.85 (s, 3 H), 2.35-2.20 (m, 2 H), 2.05-1.80 (m, 2 H).

Synthesis of amide **Ex.179**

A soln of **Ex.173** (55 mg 0.12 mmol), 1-naphthylacetic acid (28 mg, 0.15 mmol) and HOBt·H_2O (23 mg, 0.15 mmol) in CH_2Cl_2 (1 mL) was treated with *N*-cyclohexyl-carbodiimide-*N'*-methylpolystyrene (1.9 mmol/g; 98 mg, 0.19 mmol) and *i*-Pr_2NEt (0.064 mL, 0.372 mmol). The mixture was stirred for 15 h at rt. The mixture was filtered. The filtrate was submitted to aqueous workup ($CHCl_3$, sat. aq. $NaHCO_3$ soln; Na_2SO_4). Purification by prep. HPLC (method 3) afforded **Ex.179** (64 mg, 84%).

Data of **Ex.179**: cf. **Table 28b**

Core 11a: Synthesis of selected advanced intermediates and final products (Scheme 44)

Synthesis of amide **Ex.184**

A mixture of **Ex.182** (500 mg, 1.04 mmol), 2-naphthylacetic acid (232 mg, 1.25 mmol), HATU (791 mg, 2.08 mmol) and HOAt (283 mg, 2.08 mmol) was dissolved in DMF (15 mL). *i*-Pr_2NEt (712 µL, 4.16 mmol) was added. The soln was stirred at rt for 20 h and concentrated. The residue was dissolved in $CHCl_3$ and washed with sat. aq. $NaHCO_3$ soln and with H_2O. The organic phase was dried (Na_2SO_4), filtered and concentrated. FC (EtOAc, then CH_2Cl_2/MeOH 95:5) afforded **Ex.184** (637 mg, 94%).

Data of **Ex.184**: cf. **Table 29.1.b**

^{1}H-NMR (DMSO-d_6): 8.41 (d, *J* = 7.0, 1 H), 7.90-7.83 (m, 3 H), 7.77 (s, 1 H), 7.53-7.44 (m, 4 H), 7.32-7.22 (m, 6 H), 7.04 (d, *J* = 8.4, 1 H), 6.86 (d, *J* = 7.4, 1 H), 6.81 (s, 1 H), 5.02-4.90 (m, 3 H), 4.19 (t, *J* ca. 8.6, 1 H), 4.14-3.96 (m, 2 H), 3.83 (t-like m, 2 H), 3.63 (s, 2 H), ca. 3.3 (m, 1 H, superimposed by H_2O signal), 3.05 (m, 1 H), 2.95 (m, 1 H), 2.91 (s, 3 H), 2.27 (m, 1 H), 2.16 (br. q, *J* ca. 11.3, 1 H), 1.54 (m, 2 H), 1.31 (m, 1 H), 1.15 (m, 1 H).

Synthesis of amine **Ex.194**

A soln of **Ex.181** (600 mg, 0.96 mmol) in MeOH (52 mL) was hydrogenolyzed for 4 h at normal pressure and rt in the presence of palladium hydroxide on activated charcoal (moistened with 50% H_2O; 300 mg). The mixture was filtered through a pad of celite. The filtrate was concentrated to afford **Ex.194** (471 mg, 100%).

Data of **Ex.194**: cf. **Table 29.1.b**

Synthesis of amide **Ex.532**

At 0°C tert.-butylacetyl chloride (0.195 mL, 1.39 mmol) was slowly added to a mixture of **Ex.194** (620 mg, 1.26 mmol) and pyridine (0.51 mL, 6.32 mmol) in CH_2Cl_2 (6 mL). The mixture was stirred at rt for 2 h, then tert.-butylacetyl chloride (0.04

mL, 0.32 mmol) was added and stirring was continued for 1 h. Aqueous workup (CH_2Cl_2, sat. aq. Na_2CO_3 soln; Na_2SO_4) and FC (hexane/EtOAc/MeOH gradient) afforded **Ex.532** (679 mg, 91%).
Data of **Ex.532**: cf. **Table 29.1.b**

Synthesis of amine **Ex.533**
At 0°C TFA (3.2 mL) was added to a soln of **Ex.532** (656 mg, 1.11 mmol) in CH_2Cl_2 (3.2 mL). The soln was stirred at 0°C to rt for 1 h. Aqueous workup (CH_3Cl/*i*-PrOH 9:1, aq. Na_2CO_3 soln; Na_2SO_4) afforded **Ex.533** (395 mg, 80%).
Data of **Ex.533**: cf. **Table 29.1.b**

Synthesis of urea **Ex.552**
A soln of **Ex.533** (90 mg, 0.20 mmol) in THF (1 mL) was treated with 2,5-dioxopyrrolidin-1-yl-3-(dimethylamino)phenylcarbamate (62 mg, 0.22 mmol) and *i*-Pr_2NEt (0.069 mL, 0.41 mmol) for 18 h at rt. Aqueous workup ($CHCl_3$, aq. Na_2CO_3 soln; Na_2SO_4) and prep. HPLC (method 3) afforded **Ex.552** (102 mg, 83%).
Data of **Ex.552**: cf. **Table 29.1.b**

Synthesis of urea **Ex.553**
2,5-Dioxopyrrolidin-1-yl-3-(dimethylamino)phenylcarbamate (177 mg, 0.64 mmol) and *i*-Pr_2NEt (0.2 mL, 1.16 mmol) were added to a soln of **Ex.594** (obtained from **Ex.594**·HCl by aqueous extraction (CH_2Cl_2, sat. aq. Na_2CO_3 soln; 250 mg, 0.58 mmol) in THF (2 mL). The mixture was stirred at rt for 18 h. Aqueous workup ($CHCl_3$, sat. aq. Na_2CO_3 soln; Na_2SO_4) and FC (hexane/EtOAc/MeOH gradient) afforded **Ex.553** (313 mg, 91%).
Data of **Ex.553**: $C_{31}H_{40}N_6O_6$ (592.7). LC-MS (method 4a): R_t = 1.47 (99), 593 ($[M+H]^+$).

Synthesis of amine **Ex.554**
$Pd(PPh_3)_4$ (5.6 mg) and 1,3-dimethylbarbituric acid (188 mg, 1.2 mmol) were added to a soln of **Ex.553** (285 mg, 0.48 mmol) in degassed CH_2Cl_2/EtOAc (45:55; 5.1 mL). The mixture was stirred at rt for 2 h. More $Pd(PPh_3)_4$ (5.6 mg) was added and stirring

continued for 1 h. The volatiles were evaporated. FC (CH_2Cl_2/MeOH 90:10 to 50:50) afforded **Ex.554** (234 mg, 93%).

Data of **Ex.554**: $C_{27}H_{36}N_6O_4$ (508.6): LC-MS (method 4a): R_t = 1.20 (96), 509 ($[M+H]^+$).

Synthesis of amide **Ex.508**

A mixture of **Ex.554** (120 mg, 0.236 mmol), 2-naphthylacetic acid (88 mg, 0.47 mmol), HATU (179 mg, 0.47 mmol) and HOAt (64 mg, 0.472 mmol) in DMF (1.8 mL) was treated with *i*-Pr_2NEt (0.162 mmol, 0.94 mmol) and stirred at rt for 16 h. The mixture was concentrated. Aqueous workup (EtOAc, sat. aq. $NaHCO_3$ soln; Na_2SO_4) and FC (hexane/EtOAc/MeOH gradient) gave the product contaminated with a salt of *i*-Pr_2NEt. The material was again extracted (CH_2Cl_2, sat. aq. Na_2CO_3 soln; Na_2SO_4) and purified by FC (CH_2Cl_2/MeOH 100:0 to 95:5) to afford **Ex.508** (89 mg, 57%).

Data of **Ex.508**: cf. **Table 29.1.b**

^{1}H-NMR (DMSO-d_6): 8.48 (d, J = 8.1, 1 H), 8.29 (s, 1 H), 7.83-7.73 (m, 3 H), 7.69 (s, 1 H), 7.45-7.29 (m, 4 H), 7.07-7.01 (m, 2 H), 6.90-6.84 (m, 3 H), 6.69 (d, J ca. 8.5, 1 H), 6.39 (d, J = 7.5, 1 H), 6.34 (dd, J = 2.2, 8.2, 1 H), 4.96 (d, J = 12.8, 1 H), 4.23 (t, J = 8.0, 1 H), 4.10-3.96 (m, 3 H), 3.71 (t-like m, 1 H), 3.61 (s, 2 H), 3.10 (m, 1 H), 2.90 (m, 1 H), 2.90 (s, 3 H), 2.86 (s, 6 H), 2.42-2.27 (m, 2 H), 2.03 (m, 1 H), 1.67-1.46 (m, 2 H), 1.37 (m, 1 H), 1.17 (m, 1 H).

Synthesis of amide **Ex.186**

Ex.186 (11 mg, 41%) was obtained by treatment of resin **140** (0.77 mmol/g; 50 mg, 0.038 mmol) with 2-naphthylacetic acid (65 mg, 0.35 mmol; first coupling step) and with 2-naphthylacetic acid (70 mg, 0.375 mmol; second coupling step) according to procedure **S**.

Data of **Ex.186**: cf. **Table 29.1.b**

^{1}H-NMR (DMSO-d_6): 8.38 (d, J = 7.0, 2 H), 7.91-7.69 (m, 8 H), 7.54-7.27 (m, 7 H), 7.03 (dd, J = 1.5, 8.2, 1 H), 6.86-6.82 (m, 2 H), 4.94 (d, J = 12.7, 1 H), 4.19 (t, J = 8.6, 1 H), 4.11-3.94 (m, 3 H), 3.71 (dd, J = 9.2, 16.5, 1 H), 3.62 (s, 2 H),

3.58 (s, 2 H), 3.08 (m, 1 H), 2.89 (m, 1 H), 2.89 (s, 3 H), 2.5 (m, 1 H, superimposed by DMSO-d signal), 2.30 (m, 1 H), 2.14 (q-like m, 1 H), 1.64-1.49 (m, 2 H), 1.34 (m, 1 H), 1.14 (m, 1 H).

The ^{1}H-NMR spectrum is identical with the spectrum of the sample prepared in soln, cf. **Table 29.1.**

Synthesis of amide **Ex.504**

Ex.504 (10 mg, 26%) was obtained by treatment of resin **140** (0.48 mmol/g; 120 mg, 0.058 mmol) with 2-naphthylacetic acid (108 mg, 0.576 mmol; first coupling step) and with decanoic acid (50 mg, 0.288 mmol; second coupling step) according to procedure **S.**

The product was purified by prep. HPLC (method 1).

Data of **Ex.504**: cf. **Table 29.1.b**

Synthesis of amide **Ex.505**

Ex.505 (7 mg, 33%) was obtained by treatment of resin **140** (0.61 mmol/g; 50 mg, 0.031 mmol) with 2-naphthylacetic acid (114 mg, 0.61 mmol; first coupling step) and with 1-naphthylacetic acid (28 mg, 0.15 mmol; second coupling step) according to procedure **S.**

The product was purified by prep. HPLC (method 3).

Data of **Ex.505**: cf. **Table 29.1.b**

Synthesis of amide **Ex.506**

Ex.506 (10 mg, 45%) was obtained by treatment of resin **140** (0.67 mmol/g; 50 mg, 0.034 mmol) with 2-naphthylacetic acid (63 mg, 0.34 mmol; first coupling step) and with 1-isocyanato-3-methylbenzene (14 mg, 0.10 mmol; second coupling step; THF/DMF 1:1 was used instead of CH_2Cl_2/DMF) according to procedure **S.**

The product was purified by prep. HPLC (method 3).

Data of **Ex.506**: cf. **Table 29.1.b**

Synthesis of amide **Ex.507**

Ex.507 (11 mg, 48%) was obtained by treatment of resin **140** (0.67 mmol/g; 50 mg, 0.034 mmol) with 2-naphthylacetic acid (63 mg, 0.34 mmol; first coupling step) and with 2,5-dioxopyrrolidin-1-yl-3-(dimethylamino)phenylcarbamate (28 mg, 0.10 mmol; second coupling step; THF/DMF 1:1 was used instead of CH_2Cl_2/DMF) according to procedure **S**.

The product was purified by prep. HPLC (method 3).

Data of **Ex.507**: cf. **Table 29.1.b**

Synthesis of amide **Ex.509**

Ex.509 (20 mg, 48%) was obtained by treatment of resin **140** (0.66 mmol/g; 100 mg, 0.066 mmol) with 3-phenylpropanoic acid (80 mg, 0.53 mmol; first coupling step) and with decanoic acid (46 mg, 0.26 mmol; second coupling step) according to procedure **S**.

The product was purified by prep. HPLC (method 3).

Data of **Ex.509**: cf. **Table 29.1.b**

Synthesis of amide **Ex.510**

Ex.510 (11 mg, 20%) was obtained by treatment of resin **140** (0.66 mmol/g; 100 mg, 0.066 mmol) with 3-morpholinobenzoic acid (110 mg, 0.528 mmol; first coupling step) and with decanoic acid (46 mg, 0.26 mmol; second coupling step) according to procedure **S**.

The product was purified by prep. HPLC (method 3).

Data of **Ex.510**: cf. **Table 29.1.b**

Synthesis of amide **Ex.511**

Ex.511·CF_3CO_2H (26 mg, 55%) was obtained by treatment of resin **140** (0.61 mmol/g; 100 mg, 0.061 mmol) with 2,5-dioxopyrrolidin-1-yl-3-(dimethylamino)phenylcarbamate (135 mg, 0.49 mmol; first coupling step) and with decanoic acid (42 mg, 0.24 mmol; second coupling step) according to procedure **S**.

The product was purified by prep. HPLC (method 1).

Data of **Ex.511**·CF_3CO_2H: cf. **Table 29.1.b**

^{1}H-NMR (DMSO-d_6): 8.37 (br. s, 1 H), 8.10 (d, J = 8.3, 1 H), 7.34 (t, J ca. 7.8, 1 H), 7.12-7.03 (m, 3 H), 6.89-6.79 (m, 3 H), 6.55-6.47 (m, 2 H), 4.97 (d, J = 12.5, 1 H), 4.22 (t, J = 8.3, 1 H), 4.08-3.91 (m, 3 H), 3.70 (dd, J = 7.5, 9.7, 1 H), 3.16 (m, 1 H), 2.96 (m, 1 H), 2.92 (s, 9 H), 2.45-2.31 (m, 3 H), 2.04 (t-like m, 3 H), 1.64-1.41 (m, 5 H), 1.19 (br. s, 12 H), 0.83 (t, J = 6.7, 3 H).

Synthesis of amide **Ex.512**

Ex.512·CF_3CO_2H (27 mg, 56%) was obtained by treatment of resin **140** (0.61 mmol/g; 100 mg, 0.061 mmol) with 2,5-dioxopyrrolidin-1-yl-3-(dimethylamino)phenylcarbamate (135 mg, 0.49 mmol; first coupling step) and with 1-naphthylacetic acid (45 mg, 0.24 mmol; second coupling step) according to procedure **S**.
The product was purified by prep. HPLC (method 1).
Data of **Ex.512**·CF_3CO_2H: cf. **Table 29.1.b**

Synthesis of amide **Ex.513**

Ex.513 (10 mg, 25%) was obtained by treatment of resin **140** (0.61 mmol/g; 100 mg, 0.061 mmol) with 1-isocyanato-3-methoxy-benzene (73 mg, 0.49 mmol; first coupling step) and with 2-naphthylacetic acid (45 mg, 0.24 mmol; second coupling step) according to procedure **S**.
The product was purified by prep. HPLC (method 3).
Data of **Ex.513**: cf. **Table 29.1.b**

Synthesis of amide **Ex.514**

Ex.514 (22 mg, 54%) was obtained by treatment of resin **140** (0.61 mmol/g; 100 mg, 0.061 mmol) with 2-(3-methoxyphenyl)-acetic acid (81 mg, 0.49 mmol; first coupling step) and with 2-naphthylacetic acid (45 mg, 0.24 mmol; second coupling step) according to procedure **S**.
The product was purified by prep. HPLC (method 3).
Data of **Ex.514**: cf. **Table 29.1.b**

Synthesis of amide **Ex.515**

Ex.515 (21 mg, 48%) was obtained by treatment of resin **140** (0.61 mmol/g; 100 mg, 0.061 mmol) with 2-(3-phenoxyphenyl)-acetic acid (111 mg, 0.49 mmol; first coupling step) and with decanoic acid (42 mg, 0.24 mmol; second coupling step) according to procedure **S**.

The product was purified by prep. HPLC (method 3).

Data of **Ex.515**: cf. **Table 29.1.b**

Synthesis of amide **Ex.516**

Ex.516 (27 mg, 64%) was obtained by treatment of resin **140** (0.61 mmol/g; 100 mg, 0.061 mmol) with 2-naphthylacetic acid (91 mg, 0.49 mmol; first coupling step) and with 6-phenylhexanoic acid (46 mg, 0.24 mmol; second coupling step) according to procedure **S**.

The product was purified by prep. HPLC (method 3).

Data of **Ex.516**: cf. **Table 29.1.b**

Synthesis of amide **Ex.517**

Ex.517 (24 mg, 57%) was obtained by treatment of resin **140** (0.61 mmol/g; 100 mg, 0.061 mmol) with 2-naphthylacetic acid (91 mg, 0.49 mmol; first coupling step) and with 5-phenoxypentanoic acid (48 mg, 0.24 mmol; second coupling step) according to procedure **S**.

The product was purified by prep. HPLC (method 3).

Data of **Ex.517**: cf. **Table 29.1.b**

Synthesis of amide **Ex.518**

Ex.518 (21 mg, 52%) was obtained by treatment of resin **140** (0.61 mmol/g; 100 mg, 0.061 mmol) with 2-naphthylacetic acid (91 mg, 0.48 mmol; first coupling step) and with (*E*)-dec-3-enoic acid (42 mg, 0.24 mmol; second coupling step) according to procedure **S**.

The product was purified by prep. HPLC (method 3).

Data of **Ex.518**: cf. **Table 29.1.b**

Synthesis of amide **Ex.519**

Ex.519 (24 mg, 59%) was obtained by treatment of resin **140** (0.61 mmol/g; 100 mg, 0.061 mmol) with 1-naphthylacetic acid (91 mg, 0.49 mmol; first coupling step) and with decanoic acid (42 mg, 0.24 mmol; second coupling step) according to procedure **S.**

The product was purified by prep. HPLC (method 3).

Data of **Ex.519**: cf. **Table 29.1.b**

Synthesis of amide **Ex.520**

Ex.520 (22 mg, 59%) was obtained by treatment of resin **140** (0.61 mmol/g; 100 mg, 0.061 mmol) with (*Z*)-hex-3-enoic acid (56 mg, 0.49 mmol; first coupling step) and with 1-naphthylacetic acid (45 mg, 0.24 mmol; second coupling step) according to procedure **S.**

The product was purified by prep. HPLC (method 3).

Data of **Ex.520**: cf. **Table 29.1.b**

Synthesis of amide **Ex.521**

Ex.521 (30 mg, 68%) was obtained by treatment of resin **140** (0.61 mmol/g; 100 mg, 0.061 mmol) with 2-naphthylacetic acid (91 mg, 0.49 mmol; first coupling step) and with 6-(benzyloxy)hexanoic acid (54 mg, 0.24 mmol; second coupling step) according to procedure **S.**

The product was purified by prep. HPLC (method 3).

Data of **Ex.521**: cf. **Table 29.1.b**

Synthesis of amide **Ex.522**

Ex.522 (27 mg, 62%) was obtained by treatment of resin **140** (0.61 mmol/g; 100 mg, 0.061 mmol) with 2-naphthylacetic acid (91 mg, 0.49 mmol; first coupling step) and with 2-(biphenyl-4-yl)acetic acid (52 mg, 0.24 mmol; second coupling step) according to procedure **S.**

The product was purified by prep. HPLC (method 3).

Data of **Ex.522**: cf. **Table 29.1.b**

Synthesis of amide **Ex.523**

Ex.523 (28 mg, 63%) was obtained by treatment of resin **140** (0.61 mmol/g; 100 mg, 0.061 mmol) with 2-naphthylacetic acid (91 mg, 0.49 mmol; first coupling step) and with 3,3-diphenylpropanoic acid (55 mg, 0.24 mmol; second coupling step) according to procedure **S**.

The product was purified by prep. HPLC (method 3).

Data of **Ex.523**: cf. **Table 29.1.b**

Synthesis of amide **Ex.524**

Ex.524 (17 mg, 38%) was obtained by treatment of resin **140** (0.61 mmol/g; 100 mg, 0.061 mmol) with 6-(benzyloxy)hexanoic acid (108 mg, 0.49 mmol; first coupling step) and with 6-phenylhexanoic acid (94 mg, 0.48 mmol; second coupling step repeated twice) according to procedure **S**.

The product was purified by prep. HPLC (method 3).

Data of **Ex.524**: cf. **Table 29.1.b**

Synthesis of amide **Ex.525**

Ex.525 (27 mg, 54%) was obtained by treatment of resin **140** (0.61 mmol/g; 100 mg, 0.061 mmol) with 2,5-dioxopyrrolidin-1-yl-3-(dimethylamino)phenylcarbamate (135 mg, 0.49 mmol; first coupling step) and with 2-(biphenyl-3-yl)acetic acid (52 mg, 0.24 mmol; second coupling step) according to procedure **S**.

The product was purified by prep. HPLC (method 3).

Data of **Ex.525**: cf. **Table 29.1.b**

^{1}H-NMR (DMSO-d_6): 8.39 (d, J = 7.9, 1 H), 8.25 (br. s, 1 H), 7.61 (d, J = 7.0, 2 H), 7.53 (s, 1 H), 7.48-7.42 (m, 3 H), 7.38-7.30 (m, 3 H), 7.22 (d, J = 7.6, 1 H), 7.06-7.02 (m, 2 H), 6.93 (br. s, 1 H), 6.87-6.83 (m, 2 H), 6.70 (d, J = 7.7, 1 H), 6.39-6.37 (m, 2 H), 4.96 (d, J = 12.7, 1 H), 4.23 (t, J = 8.4, 1 H), 4.09-3.96 (m, 3 H), 3.73 (t-like m, 1 H), 3.52 (s, 2 H), 3.07 (m, 1 H), 2.93 (m, 1 H), 2.89 (s, 3 H), 2.86 (s, 6 H), 2.50-2.27 (m, 2 H), 2.01 (m, 1 H), 1.64-1.52 (m, 2 H), 1.35 (m, 1 H), 1.14 (m, 1 H).

Synthesis of amide **Ex.526**

Ex.526 (27 mg, 54%) was obtained by treatment of resin **140** (0.61 mmol/g; 100 mg, 0.061 mmol) with 2,5-dioxopyrrolidin-1-yl-3-(dimethylamino)phenylcarbamate (135 mg, 0.49 mmol; first coupling step) and with 2-(biphenyl-4-yl)acetic acid (52 mg, 0.24 mmol; second coupling step) according to procedure **S**.

The product was purified by prep. HPLC (method 3).

Data of **Ex.526**: cf. **Table 29.1.b**

Synthesis of amide **Ex.527**

Ex.527 (27 mg, 61%) was obtained by treatment of resin **140** (0.61 mmol/g; 100 mg, 0.061 mmol) with 2-naphthylacetic acid (91 mg, 0.48 mmol; first coupling step) and with biphenyl-4-sulfonyl chloride (62 mg, 0.24 mmol; second coupling step) according to procedure **S**.

The product was purified by prep. HPLC (method 3).

Data of **Ex.527**: cf. **Table 29.1.b**

Synthesis of amide **Ex.537**

Ex.537 (25 mg, 63%) was obtained by treatment of resin **140** (0.61 mmol/g; 100 mg, 0.061 mmol) with 1-fluoro-3-isocyanatobenzene (67 mg, 0.49 mmol; first coupling step) and with 2-naphthylacetic acid (45 mg, 0.24 mmol; second coupling step) according to procedure **S**.

The product was purified by prep. HPLC (method 3).

Data of **Ex.537**: cf. **Table 29.1.b**

Synthesis of amide **Ex.538**

Ex.538·CF_3CO_2H (30 mg, 62%) was obtained by treatment of resin **140** (0.61 mmol/g; 100 mg, 0.061 mmol) with 2,5-dioxopyrrolidin-1-yl 4-(dimethylamino)phenylcarbamate (79 mg, 0.49 mmol; first coupling step) and with 2-naphthylacetic acid (45 mg, 0.24 mmol; second coupling step) according to procedure **S**.

The product was purified by prep. HPLC (method 1).

Data of **Ex.538**·CF_3CO_2H: cf. **Table 29.1.b**

Synthesis of amide **Ex.539**

Ex.539 (18 mg, 46%) was obtained by treatment of resin **140** (0.61 mmol/g; 100 mg, 0.061 mmol) with phenylchloroformate (76 mg, 0.49 mmol; first coupling step) and with 2-naphthylacetic acid (45 mg, 0.24 mmol; second coupling step) according to procedure **S.**

The product was purified by prep. HPLC (method 3).

Data of **Ex.539**: cf. **Table 29.1.b**

Synthesis of amide **Ex.540**

Ex.540 (26 mg, 53%) was obtained by treatment of resin **140** (0.61 mmol/g; 100 mg, 0.061 mmol) with 2-(quinolin-7-yl)acetic acid (92 mg, 0.49 mmol; first coupling step) and with 2-naphthylacetic acid (45 mg, 0.24 mmol; second coupling step) according to procedure **S.**

The product was purified by prep. HPLC (method 3).

Data of **Ex.540**: cf. **Table 29.1.b**

Synthesis of amide **Ex.541**

Ex.541 (30 mg, 68%) was obtained by treatment of resin **140** (0.61 mmol/g; 100 mg, 0.061 mmol) with 2-(3-phenoxyphenyl)acetic acid (111 mg, 0.49 mmol; first coupling step) and with 2-naphthylacetic acid (45 mg, 0.24 mmol; second coupling step) according to procedure **S.**

The product was purified by prep. HPLC (method 3).

Data of **Ex.541**: cf. **Table 29.1.b**

Synthesis of amide **Ex.542**

Ex.542 (23 mg, 56%) was obtained by treatment of resin **140** (0.61 mmol/g; 100 mg, 0.061 mmol) with decanoic acid (84 mg, 0.49 mmol; first coupling step) and with 2-naphthylacetic acid (45 mg, 0.24 mmol; second coupling step) according to procedure **S.**

The product was purified by prep. HPLC (method 3).

Data of **Ex.542**: cf. **Table 29.1.b**

Synthesis of amide **Ex.543**

Ex.543 (25 mg, 61%) was obtained by treatment of resin **140** (0.61 mmol/g; 100 mg, 0.061 mmol) with decanoic acid (84 mg, 0.49 mmol; first coupling step) and with 1-naphthylacetic acid (45 mg, 0.24 mmol; second coupling step) according to procedure **S**.

The product was purified by prep. HPLC (method 3).

Data of **Ex.543**: cf. **Table 29.1.b**

Synthesis of amide **Ex.544**

Ex.544 (20 mg, 54%) was obtained by treatment of resin **140** (0.61 mmol/g; 100 mg, 0.061 mmol) with hexanoic acid (57 mg, 0.49 mmol; first coupling step) and with 1-naphthylacetic acid (45 mg, 0.24 mmol; second coupling step) according to procedure **S**.

The product was purified by prep. HPLC (method 3).

Data of **Ex.544**: cf. **Table 29.1.b**

Synthesis of amide **Ex.545**

Ex.545 (28 mg, 65%) was obtained by treatment of resin **140** (0.61 mmol/g; 100 mg, 0.061 mmol) with 2-(biphenyl-4-yl)acetic acid (104 mg, 0.49 mmol; first coupling step) and with 1-naphthylacetic acid (45 mg, 0.24 mmol; second coupling step) according to procedure **S**.

The product was purified by prep. HPLC (method 3).

Data of **Ex.545**: cf. **Table 29.1.b**

Synthesis of amides **Ex.546** and **Ex.551**

Ex.546 (9 mg, 20%) and **Ex.551** (8 mg, 18%) were obtained by treatment of resin **140** (0.61 mmol/g; 100 mg, 0.061 mmol) with 2,2-diphenylacetic acid (104 mg, 0.49 mmol; first coupling step) and with 2-(biphenyl-4-yl)acetic acid (52 mg, 0.24 mmol; second coupling step) according to procedure **S**.

The products were purified by prep. HPLC (method 1).

Data of **Ex.546**: cf. **Table 29.1.b**

Data of **Ex.551**: cf. **Table 29.1.b**

Synthesis of amide **Ex.547**

Ex.547 (29 mg, 65%) was obtained by treatment of resin **140** (0.61 mmol/g; 100 mg, 0.061 mmol) with 2-(biphenyl-4-yl)acetic acid (104 mg, 0.49 mmol; first coupling step) and with 2,2-diphenylacetic acid (52 mg, 0.24 mmol; second coupling step) according to procedure **S**.

The product was purified by prep. HPLC (method 3).

Data of **Ex.547**: cf. **Table 29.1.b**

Synthesis of amide **Ex.548**

Ex.548 (12 mg, 28%) was obtained by treatment of resin **140** (0.61 mmol/g; 100 mg, 0.061 mmol) with 2,2-diphenylacetic acid (104 mg, 0.49 mmol; first coupling step) and with decanoic acid (42 mg, 0.24 mmol; second coupling step) according to procedure **S**.

The product was purified by prep. HPLC (method 1).

Data of **Ex.548**: cf. **Table 29.1.b**

Synthesis of amide **Ex.549**

Ex.549 (10 mg, 23%) was obtained by treatment of resin **140** (0.61 mmol/g; 100 mg, 0.061 mmol) with 2,2-diphenylacetic acid (104 mg, 0.49 mmol; first coupling step) and with 1-naphthylacetic acid (45 mg, 0.24 mmol; second coupling step) according to procedure **S**.

The product was purified by prep. HPLC (method 1).

Data of **Ex.549**: cf. **Table 29.1.b**

Synthesis of amide **Ex.550**

Ex.550 (21 mg, 49%) was obtained by treatment of resin **140** (0.61 mmol/g; 100 mg, 0.061 mmol) with 3,3-diphenylpropanoic acid (110 mg, 0.49 mmol; first coupling step) and with decanoic acid (42 mg, 0.24 mmol; second coupling step) according to procedure **S**.

The product was purified by prep. HPLC (method 3).

Data of **Ex.550**: cf. **Table 29.1.b**

Core 12: Synthesis of selected advanced intermediates and final products (Scheme 45)

Synthesis of amide **Ex.200**

A mixture of **Ex.197**·TFA (60 mg, 0.094 mmol), 1*H*-indole-3-acetic acid (25 mg, 0.14 mmol), HATU (54 mg, 0.14 mmol) and HOAt (19 mg, 0.14 mmol) was dissolved in DMF (1.5 mL). *i*-Pr_2NEt (81 µL, 0.471 mmol) was added. The soln was stirred for 18 h at rt and concentrated. The residue was dissolved in $CHCl_3$ and washed (sat. aq. $NaHCO_3$ soln, H_2O). The organic phase was dried (Na_2SO_4), filtered and concentrated, followed by FC (EtOAc, then CH_2Cl_2/MeOH 95:5) to afford **Ex.200** (50 mg, 78%).

Data of **Ex.200**: cf. **Table 30b**

^{1}H-NMR (DMSO-d_6): 10.86 (s, 1 H), 8.42 (d, J = 7.8, 1 H), 8.01 (d, J = 10.0, 1 H), 7.58 (d, J = 7.8, 1 H), 7.36-7.19 (m, 9 H), 7.07-7.02 (m, 2 H), 6.97 (t, J = 7.1, 1 H), 6.86 (d, J = 7.6, 1 H), 5.08 (s, 2 H), 4.88 (d, J = 8.7, 1 H), 4.30-4.10 (m, 2 H), 4.13 (d, J = 10.9, 1 H), 4.01 (t-like m, 1 H), 3.95 (d, J = 18.0, 1 H), 3.75-3.70 (m, 2 H), 3.56 (s, 2 H), 3.4-3.2 (m, 2 H, partially superimposed by H_2O signal), 3.04 (t, J = 9.9, 1 H), 2.98 (s, 3 H), 2.65 (s, 3 H), 2.27 (m, 1 H), 2.09 (q, J = 11.7, 1 H).

Synthesis of amine **Ex.202**

A soln of **Ex.200** (320 mg, 0.47 mmol) in MeOH (28 mL) was hydrogenolyzed under normal pressure at rt for 4 h in the presence of palladium hydroxide on activated charcoal (moistened with 50% H_2O; 158 mg). The mixture was filtered through a pad of celite. The residue was washed (MeOH). The combined filtrate and washings were concentrated and dried i.v. to yield **Ex.202** (250 mg, 97%).

Data of **Ex.202**: cf. **Table 30b**

Synthesis of amide **Ex.213**

A soln of **Ex.202** (60 mg, 0.11 mmol) in dry CH_2Cl_2 (1 mL) was treated with pyridine (89 µL, 1.1 mmol). Decanoyl chloride (46

µL, 0.22 mmol) was slowly added at 0°C. The mixture was stirred at 0°C to rt for 18 h followed by the addition of MeOH (0.1 mL). Stirring was continued for 10 min. The volatiles were evaporated. The residue was treated three times with toluene and evaporated. Purification by prep. HPLC (method 1) and subsequent FC (EtOAc/MeOH 90:10 to 80:20) afforded **Ex.213** (27 mg, 35%).

Data of **Ex.213**: cf. **Table 30b**

^{1}H-NMR (DMSO-d_6): 10.86 (s, 1 H), 8.53 (d, J = 9.8, 1 H), 8.44 (d, J = 7.7, 1 H), 7.57 (d, J = 7.7, 1 H), 7.35-7.30 (m, 3 H), 7.27 (s, 1 H), 7.19-6.95 (m, 3 H), 6.84 (d, J = 7.5, 1 H), 4.86 (dd, J = 2.4, 11.2, 1 H), 4.60 (q, J = 8.4, 1 H), 4.25 (q-like m, 1 H), 4.14 (d, J = 10.7, 1 H), 4.04-3.82 (m, 3 H), 3.73 (t, J ca. 8.5, 1 H), 3.55 (s, 2 H), 3.24 (d, J = 7.8, 2 H), 3.09 (t, J = 9.5, 1 H), 2.99 (s, 3 H), 2.67 (s, 3 H), 2.26 (m, 1 H), 2.15 (t, J = 7.2, 2 H), 2.09 (m, 1 H), 1.51 (t-like m, 2 H), 1.24 (s, 12 H), 0.85 (t, J = 6.6, 3 H).

Core 21: Synthesis of selected advanced intermediates and final products (Scheme 46)

Synthesis of amide **Ex.316**

A mixture of **Ex.314** (500 mg, 0.91 mmol), HATU (693 mg, 1.82 mmol) and HOAt (248 mg, 1.82 mmol) in DMF (7 mL) was treated with 2-naphthylmethylamine (287 mg, 1.82 mmol) and *i*-Pr_2NEt (0.6 mL, 3.65 mmol) for 15 h. The volatiles were evaporated. Aqueous workup ($CHCl_3$, sat. aq. $NaHCO_3$ soln, H_2O; Na_2SO_4) and FC (CH_2Cl_2/MeOH 97:3 to 95:5) afforded **Ex.316** (542 mg, 86%).

Data of **Ex.316**: cf. **Table 37.2.b**

Synthesis of amide **Ex.317**

A mixture of **Ex.314** (500 mg, 0.91 mmol), HATU (693 mg, 1.82 mmol) and HOAt (248 mg, 1.82 mmol) in DMF (7 mL) was treated with *N,N*-dimethylethylenediamine (0.2 mL, 1.82 mmol) and *i*-

Pr_2NEt (0.6 mL, 3.65 mmol) for 15 h. The volatiles were evaporated. Aqueous workup ($CHCl_3$, sat. aq. $NaHCO_3$ soln, H_2O; Na_2SO_4) and FC (CH_2Cl_2/MeOH 90:10 to 80:20) afforded **317** (406 mg, 72%).

Data of **Ex.317**: cf. **Table 37.2.b**

Synthesis of amine **Ex.318**

A soln of **Ex.316** (500 mg, 0.727 mmol) in dioxane (4.5 mL) was treated with 4M HCl-dioxane (9 mL) at rt for 3 h. The volatiles were evaporated to give **Ex.318**·HCl (479 mg, quantitative yield).

Data of **Ex.318**·HCl: cf. **Table 37.2.b**

Synthesis of amine **Ex.319**

A soln of **Ex.317** (360 mg, 0.582 mmol) in dioxane (3.6 mL) was treated with 4M HCl-dioxane (7.3 mL) at rt for 3 h. The volatiles were evaporated to give **Ex.319**·HCl (391 mg, quant. yield).

Data of **Ex.319**·HCl: cf. **Table 37.2.b**

Synthesis of amide **Ex.320**

A suspension of **Ex.318** (80 mg, 0.128 mmol) in CH_2Cl_2 (1.5 mL) was treated at rt with pyridine (0.10 mL, 1.28 mmol) and acetic anhydride (0.06 mL, 0.64 mmol) for 15 h. MeOH (0.15 mL) was added and stirring was continued for 15 min. The volatiles were evaporated and the residue purified by prep. HPLC (method 1) to afford **Ex.320** (35 mg, 43%).

Data of **Ex.320**: cf. **Table 37.2.b**

Synthesis of amide **Ex.321**

A mixture of **Ex.318** (80 mg, 0.13 mmol), 3-(pyridine-4-yl)propanoic acid (21 mg, 0.14 mmol), HATU (73 mg, 0.19 mmol) and HOAt (26 mg, 0.19 mmol) in DMF (2.2 mL) was treated with *i*-Pr_2NEt (0.11 mL, 0.64 mmol) for 15 h. The volatiles were evaporated. Aqueous workup ($CHCl_3$, sat. aq. $NaHCO_3$ soln, H_2O;

Na_2SO_4) and prep. HPLC (method 1) afforded **Ex.321**·CF_3CO_2H (42 mg, 39%).

Data of **Ex.321**·CF_3CO_2H: cf. **Table 372.2.b**

Synthesis of amide **Ex.322**

Pyridine (0.10 mL, 1.28 mmol) and valeroyl chloride (0.031 mL, 0.256 mmol) were added to a mixture of **Ex.318** (80 mg, 0.13 mmol) and CH_2Cl_2 (1.5 mL). The mixture was stirred at rt for 15 h followed by the addition of MeOH (0.15 mL). Stirring was continued for 10 min. The volatiles were evaporated. Purification by prep. HPLC (method 1) afforded **Ex.322** (43 mg, 49%).

Data of **Ex.322**: cf. **Table 37.2.b**

Synthesis of amide **Ex.326**

A mixture of **Ex.319** (65 mg, 0.11 mmol), 3-(pyridine-4-yl)propanoic acid (33 mg, 0.22 mmol), HATU (84 mg, 0.22 mmol) and HOAt (30 mg, 0.22 mmol) in DMF (1.5 mL) was treated with *i*-Pr_2NEt (0.075 mL, 0.44 mmol) for 15 h. Aqueous workup ($CHCl_3$, sat. aq. $NaHCO_3$ soln, H_2O; Na_2SO_4) and prep. HPLC (method 2) afforded **Ex.326** (42 mg, 39%).

Data of **Ex.326**: cf. **Table 37.2.b**

Core 24a: Synthesis of selected advanced intermediates and final products (Scheme 47)

Synthesis of amide **Ex.382**

i-Pr_2NEt (0.079 mL, 0.462 mmol) was added to a mixture of **Ex.380** (100 mg, 0.231 mmol), 2-naphthylacetic acid (86 mg, 0.462 mmol), HATU (176 mg, 0.462 mmol) and HOAt (63 mg, 0.462 mmol) in DMF (1 mL). The mixture was stirred at rt for 16 h and concentrated. Aqueous workup (CH_2Cl_2, sat. aq. $NaHCO_3$ soln, Na_2SO_4) and FC (hexane/EtOAc/MeOH gradient) and FC (CH_2Cl_2/MeOH) gave **Ex.382** (101 mg, 72%).

Data of **Ex.382**: cf. **Table 40.1.b**

Synthesis of amine **Ex.384**

A soln of **Ex.382** (82 mg, 0.137 mmol) in dioxane (1 mL) was treated with 4M HCl-dioxane (1.0 mL) for 2 h at rt. The volatiles were evaporated. The residue was washed with Et_2O to give **Ex.384**·HCl (70 mg, 96%)

Data of **Ex.384**·HCl: cf. **Table 40.1.b**

Synthesis of amide **Ex.386**

2,5-Dioxopyrrolidin-1-yl-3-(dimethylamino)phenylcarbamate (36 mg, 0.129 mmol) and *i*-Pr_2NEt (0.06 mL, 0.352 mmol) were added to a suspension of **Ex.384**·HCl (63 mg, 0.117 mmol) in THF (1.0 mL). Stirring of the mixture at rt for 16 h followed by aqueous workup (CH_2Cl_2, sat. aq. Na_2CO_3 soln, Na_2SO_4) and FC (hexane/EtOAc/MeOH gradient) gave **Ex.386** (43 mg, 55%).

Data of **Ex.386**: cf. **Table 40.1.b**

Synthesis of amide **Ex.388**

At rt **Ex.379** (93 mg, 0.164 mmol) was treated with 4M HCl-dioxane (3 mL) for 4 h. The volatiles were evaporated to afford **Ex.387**·HCl (86 mg).

i-Pr_2NEt (0.084 mL, 0.49 mmol) was added to a mixture of crude **Ex.387**·HCl (82 mg), 2-naphthylacetic acid (36 mg, 0.196 mmol), HATU (93 mg, 0.245 mmol) and HOAt (33 mg, 0.245 mmol) in DMF (2.4 mL). The mixture was stirred at rt for 20 h and concentrated. Aqueous workup (CH_2Cl_2, 1 M aq. Na_2CO_3 soln, Na_2SO_4) and FC (hexane/EtOAc/MeOH gradient) gave **Ex.388** (64 mg, 61%).

Data of **Ex.388**: cf. **Table 40.1.b**

Synthesis of amide **Ex.389**

i-Pr_2NEt (0.079 mL, 0.462 mmol) was added to a mixture of **Ex.380** (100 mg, 0.231 mmol), decanoic acid (80 mg, 0.462 mmol), HATU (176 mg, 0.462 mmol) and HOAt (63 mg, 0.462 mmol) in DMF (1 mL). The mixture was stirred at rt for 16 h and concentrated. Aqueous workup (CH_2Cl_2, sat. aq. $NaHCO_3$ soln,

Na_2SO_4) and FC (hexane/EtOAc/MeOH gradient) gave **Ex.389** (97 mg, 71%).

Data of **Ex.389**: cf. **Table 40.1.b**

Synthesis of amine **Ex.390**

A soln of **Ex.389** (81 mg, 0.138 mmol) in dioxane (1 mL) was treated with 4M HCl-dioxane (1.0 mL) for 2 h at rt. The volatiles were evaporated. The residue was washed with Et_2O to give **Ex.390**·HCl (76 mg, 91%).

Data of **Ex.390**·HCl: cf. **Table 40.1.b**

Synthesis of amide **Ex.391**

i-Pr_2NEt (0.062 mL, 0.12 mmol) was added to a mixture of **Ex.390**·HCl (63 mg 0.12 mmol), 2-naphthylacetic acid (45 mg, 0.241 mmol), HATU (92 mg, 0.241 mmol) and HOAt (33 mg, 0.241 mmol) in DMF (1 mL). The mixture was stirred at rt for 2 h and concentrated. Aqueous workup (CH_2Cl_2, sat. aq. $NaHCO_3$ soln, Na_2SO_4) and FC (hexane/EtOAc/MeOH gradient) afforded **Ex.391** (56 mg, 70%).

Data of **Ex.391**: cf. **Table 40.1.b**

The generic macrocyclic ring structures (Cores) related to **Tables 20-49** are depicted in **Scheme 41** in the order of their core numbers.

Table 20: Examples of Core 01 and Core 02 (**Ex.1-Ex.2**)

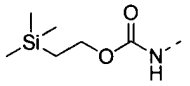
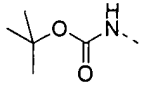
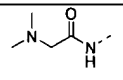
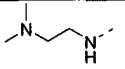
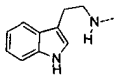
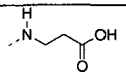
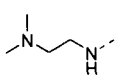
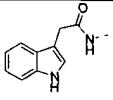
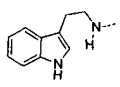
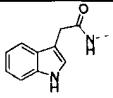
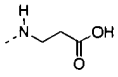
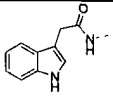
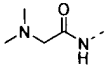
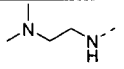
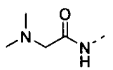
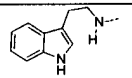
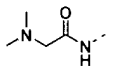
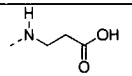
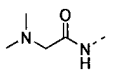
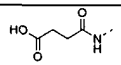
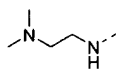
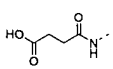
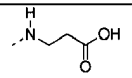
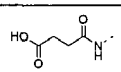
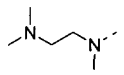
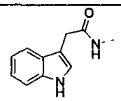
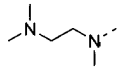
No			IUPAC name
Core 01	R^2	R^{54}	
Ex.1		OCH_2Ph	8-benzyl 2-[2-(trimethylsilyl)ethyl] (2S,8S,16aS)-12-fluoro-9-methyl-5,10-dioxo-2,3,5,6,7,8,9,10,16,16a-decahydro-1*H*-pyrrolo[2,1-*c*][1,4,9]benzoxadiazacyclododecine-2,8-dicarboxylate
Core 02	R^{11}	R^{54}	
Ex.2		OCH_2Ph	9-benzyl 2-(*tert*-butyl) (9S,17aS)-13-fluoro-10-methyl-6,11-dioxo-3,4,6,7,8,9,10,11,17,17a-decahydropyrazino[2,1-*c*][1,4,9]benzoxadiazacyclododecine-2,9(1*H*)-dicarboxylate

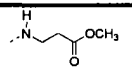
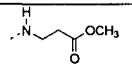
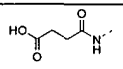
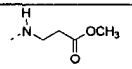
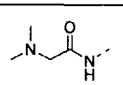
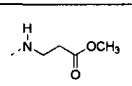
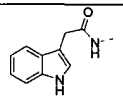
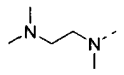
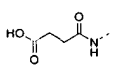
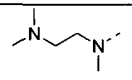
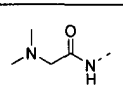
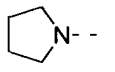
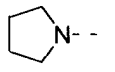
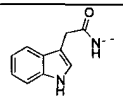
Table 21a: Examples of Core 03 (**Ex.3-Ex.55, Ex.482-Ex.503 and Ex.590-Ex.591**; *continued on the following pages*)

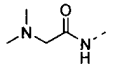
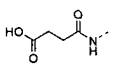
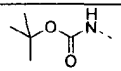
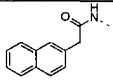
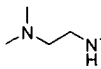
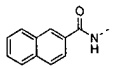
No	R^{54}	R^2	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.3-Ex.5: *cf. experimental description*							
Ex.6	OH		**Ex.52**	H	H_2, $Pd(OH)_2$-C[*)]	Crude product	70%

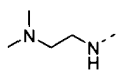
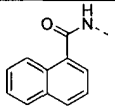
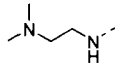
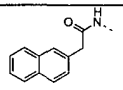
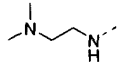
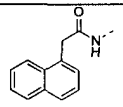
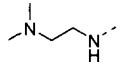
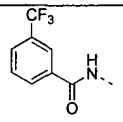
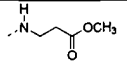
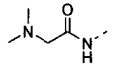
No	R^{54}	R^2	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.7			**Ex.25**	L.1.1	acetic anhydride (5 equiv.)	prep. HPLC, method 1	56%
Ex.8			**Ex.28**	L.1.1	acetic anhydride (10 equiv.)	prep. HPLC, method 1	26% (TFA salt)
Ex.9			**Ex.53**	L.2	tryptamine (1.5 equiv.) HATU (1.5 equiv.) HOAt (1.5 equiv.) *i*-Pr_2NEt (3 equiv.)	FC (CH_2Cl_2/MeOH)	62%
Ex.10			**Ex.31**	N	$LiOH \cdot H_2O$	prep. HPLC, method 1	57%
Ex.11			**Ex.28**	L.1.3	3-indoleacetic acid	FC (CH_2Cl_2/MeOH/aq. NH_3)	58%
Ex.12			**Ex.55**	L.1.3	3-indoleacetic acid	prep. HPLC, method 1	55%
Ex.13			**Ex.34**	N	$LiOH \cdot H_2O$	prep. HPLC, method 1	60%
Ex.14			**Ex.25**	**)	N,N-dimethyl glycine	prep. HPLC, method 1	22% (TFA salt)

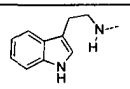
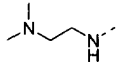
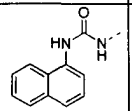
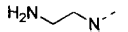
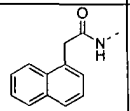
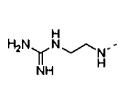
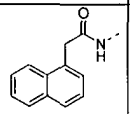
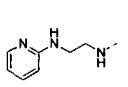
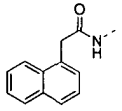
No	R^{54}	R^2	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.15			**Ex.28**	L.1.3	N,N-dimethyl glycine	prep. HPLC, method 1	42% (TFA salt)
Ex.16			**Ex.55**	L.1.3	N,N-dimethyl glycine	prep. HPLC, method 1	56% (TFA salt)
Ex.17			**Ex.33**	N	$LiOH \cdot H_2O$	prep. HPLC, method 1	77% (TFA salt)
Ex.18			**Ex.25**	L.1.1	succinic anhydride (1.05 equiv)	prep. HPLC, method 1	62%
Ex.19			**Ex.28**	L.1.1	succinic anhydride (1.05 equiv) pyridine (49 equiv.)	prep. HPLC, method 1	67% (TFA salt)
Ex.20			**Ex.32**	N	$LiOH \cdot H_2O$	prep. HPLC, method 1	72%
Ex.21			**Ex.23**	L.1.3	3-indoleacetic acid	prep. HPLC, method 1	32%
Ex.22			**Ex.23**	L.1.1	acetic anhydride (10 equiv) pyridine (120 equiv.)	prep. HPLC, method 1	53% (TFA salt)

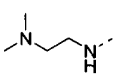
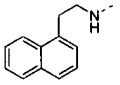
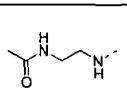
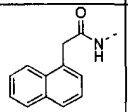
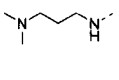
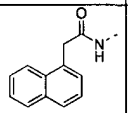
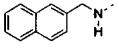
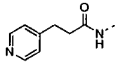
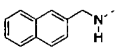
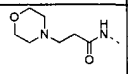
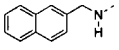
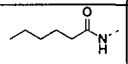
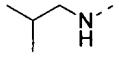
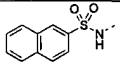
No	R^{54}	R^2	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.23		NH_2	**Ex.29**	J	HCl-dioxane	prep. HPLC, method 1	52% (TFA salt)
Ex.24			**Ex.4**	L.2	methylamine-HCl (10 equiv.), HATU (1.5 equiv.) HOAt (1.5 equiv.) i-Pr_2NEt (13 equiv.)	FC (CH_2Cl_2/MeOH)	89%
Ex.25		NH_2	**Ex.24**	J	HCl-dioxane	crude product	84% (HCl salt)
Ex.26			**Ex.4**	L.2	β-alaninemethylester hydrochloride	FC (CH_2Cl_2/MeOH)	97%
Ex.27			**Ex.4**	L.2	N,N-dimethyl-ethylenediamine	FC (CH_2Cl_2/MeOH/aq. NH_3)	83%
Ex.28		NH_2	**Ex.27**	J	HCl-dioxane	(crude product)	90% (HCl salt)
Ex.29			**Ex.4**	L.2	N,N,N'-trimethyl-ethylenediamine	FC (CH_2Cl_2/MeOH/aq. NH_3)	74%
Ex.30			**Ex.4**	L.2	tryptamine	FC (CH_2Cl_2/MeOH)	81%

No	R^{54}	R^2	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.31			**Ex.51**	L.1.1	acetic anhydride (5 equiv)	prep. HPLC, method 1	72%
Ex.32			**Ex.51**	L.1.1	succinic anhydride (1.05 equiv)	prep. HPLC, method 1	68%
Ex.33			**Ex.51**	L.1.3	N,N-dimethyl glycine	prep. HPLC, method 1	64% (TFA salt)
Ex.34			**Ex.51**	L.1.3	3-indoleacetic acid	prep. HPLC, method 1	24%
Ex.35			**Ex.23**	L.1.1	succinic anhydride (1.05 equiv)	prep. HPLC, method 1	63% (TFA salt)
Ex.36			**Ex.23**	L.1.3	N,N-dimethyl glycine	prep. HPLC, method 1	40% (TFA salt)
Ex.37			**Ex.42**	L.1.1	acetic anhydride (5 equiv)	prep. HPLC, method 1	61%
Ex.38			**Ex.42**	L.1.3	3-indoleacetic acid	prep. HPLC, method 1	43%

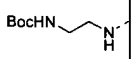
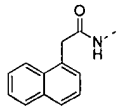
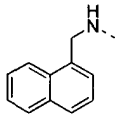
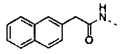
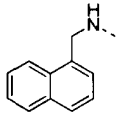
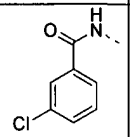
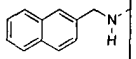
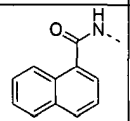
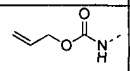
No	R^{54}	R^2	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.39			**Ex.42**	L.1.3	N,N-dimethyl glycine	prep. HPLC, method 1	56% (TFA salt)
Ex.40			**Ex.42**	L.1.1	succinic anhydride (1.05 equiv)	prep. HPLC, method 1	37%
Ex.41			**Ex.4**	L.2	pyrrolidine	FC (CH_2Cl_2/MeOH)	76%
Ex.42		NH_2	**Ex.41**	J	HCl-dioxane	(crude product)	90% (HCl salt)
Ex.43			**Ex.42**	M.1	acetaldehyde	prep. HPLC, method 1	67% (TFA salt)
Ex.44			**Ex.25**	M.1	acetaldehyde	prep. HPLC, method 1	33% (TFA salt)
Ex.45			**Ex.25**	L.1.3	2-naphthylacetic acid	prep. HPLC, method 1	46%
Ex.46			**Ex.28**	L.1.1	2-naphthoyl chloride (3.6 equiv.)	FC (CH_2Cl_2/MeOH/aq. NH_3)	85%

No	R^{54}	R^2	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.47			**Ex.28**	L.1.2	1-naphthoic acid	FC (CH_2Cl_2/MeOH/ aq. NH_3)	85%
Ex.48			**Ex.28**	L.1.2	2-naphthylacetic acid	FC (CH_2Cl_2/MeOH/ aq. NH_3)	83%
Ex.49			**Ex.28**	L.1.2	1-naphthylacetic acid	FC (CH_2Cl_2/MeOH/ aq. NH_3)	83%
Ex.50			**Ex.28**	L.1.1	3-(trifluoromethyl)-benzoyl chloride (4 equiv.)	FC (CH_2Cl_2/MeOH/ aq. NH_3)	24%
Ex.51		NH_2	**Ex.26**	J	HCl-dioxane	crude product	93% (HCl salt)
Ex.52	OCH_2Ph		**Ex.5**	L.1.3	N,N-dimethylglycine (1.7 equiv.) HATU (1.0 equiv.) HOAt (2.0 equiv.) i-Pr_2NEt (4.0 equiv.)	prep. HPLC, method 1	88% (TFA salt)
Ex.53	OCH_2Ph		**Ex.5**	L.1.1	Acetic anhydride (10 equiv.) pyridine/CH_2Cl_2 1:1	FC	70%

No	R^{54}	R^2	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.54	OH		**Ex.54**	H	H_2, $Pd(OH)_2$-C	crude product	92%
Ex.55		NH_2	**Ex.30**	J	HCl-dioxane	FC (CH_2Cl_2/MeOH/aq. NH_3)	42%
Ex.482			**262a**	R	1-naphthyl isocyanate	prep. HPLC, method 1	25% (TFA salt)
Ex.483			**Ex.500**	J	HCl-dioxane	crude product	97% (HCl salt)
Ex.484			**Ex.483**	—	cf. detailed description of examples	prep. HPLC, method 1	18% (TFA salt)
Ex.485			**Ex.499**	L.2	N-(2-amino-ethyl)pyridine-2-amine (2 equiv.) i-Pr_2NEt (2 equiv.)	prep. HPLC, method 2	60%

No	R^{54}	R^2	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.486			**Ex.28**	M.2	2-(naphthalene-1-yl)acetaldehyde	FC(CH_2Cl_2/MeOH/ aq. NH_3), then prep. HPLC, method 1	6% (TFA salt)
Ex.487			**Ex.483**	L.1.1	acetic anhydride (5 equiv.) pyridine (10 equiv)	prep. HPLC, method 1	75%
Ex.488			**Ex.499**	L.2	N,N-dimethylpropylene-diamine (2 equiv.) *i*-Pr_2NEt (2 equiv.)	prep. HPLC, method 2	66%
Ex.489			**262d**	R	3-(pyridin-4-yl)propanoic acid	FC (CH_2Cl_2/EtOAc/ MeOH)	37%
Ex.490			**262d**	R	3-morpholinopropanoic acid hydrochloride	prep. HPLC, method 1	52% (TFA salt)
Ex.491			**262d**	R	hexanoic acid	prep. HPLC, method 3	43%
Ex.492			**262c**	R	naphthalene-2-sulfonyl chloride	prep. HPLC, method 3	24%

No	R^{54}	R^2	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.493			**262c**	R	cyclopropanesulfonyl chloride	prep. HPLC, method 1	35%
Ex.494			**262b**	R	2,5-dioxopyrrolidin-1-yl-4-(methylsulfonyl)-phenylcarbamate	prep. HPLC, method 1	34% (TFA salt)
Ex.495			**262a**	R	3-(trifluoromethyl) phenylacetic acid	prep. HPLC, method 1	24% (TFA salt)
Ex.496			**262a**	R	3-methoxy phenylacetic acid	prep. HPLC, method 1	24% (TFA salt)
Ex.497			**262b**	R	1-naphthylacetic acid	prep. HPLC, method 1	18% (TFA salt)
Ex.498	OCH_2Ph		**Ex.5**	L.1.3	1-naphthylacetic acid (2 equiv.) i-Pr_2NEt (3 equiv.)	FC (EtOAc/MeOH)	87%
Ex.499	OH		**Ex.498**	H	H_2, $Pd(OH)_2$-C	crude product	96%

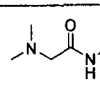
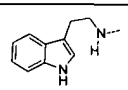
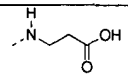
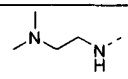
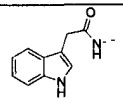
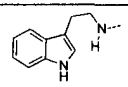
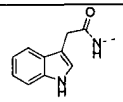
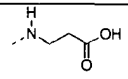
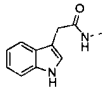
No	R^{54}	R^2	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.500			**Ex.499**	L.2	tert. butyl 2-aminoethylcarbamate (2 equiv.) i-Pr_2NEt (2 equiv.)	FC (CH_2Cl_2/MeOH/aq. NH_3)	74%
Ex.501			**262e**	R	2-naphthylacetic acid	prep. HPLC, method 3	44%
Ex.502			**262e**	R	3-chlorobenzoic acid	prep. HPLC, method 3	48%
Ex.503			**262d**	R	1-naphthoic acid	prep. HPLC, method 3	43%
Ex.590	OH	NH_2	**Ex.4**	***)	HCl-dioxane	crude product	quant. (HCl salt)
Ex.591	OH		**Ex.590**	***)	AllocCl	crude product	95%

*) Prior to debenzylation starting material **Ex.52**·TFA was converted into the free base ($CHCl_3$, aq. Na_2CO_3 soln)

**) The amide coupling was performed at room temperature with *N,N*-dimethyl glycine (2.2 equiv.) in CH_2Cl_2, in the presence of T3P (50% in EtOAc; 2.2 equiv.) and i-Pr_2NEt (3 equiv.).

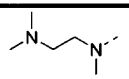
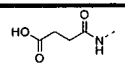
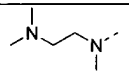
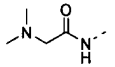
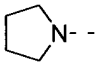
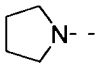
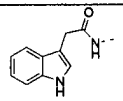
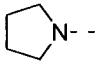
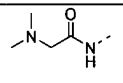
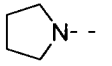
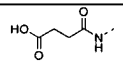
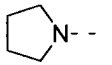
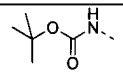
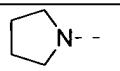
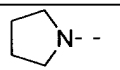
***) cf. detailed description

Table 21b: Examples of Core 03 (**Ex.3-Ex.55, Ex.482-Ex.503 and Ex.590-Ex.591;** *continued on the following pages*)

No	R^{54}	R^2	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.3-Ex.5: *cf. experimental description*							
Ex.6	OH		C25H34FN5O7	535.2	1.05 (99)	536.3	Method 2
Ex.7			C24H32FN5O6	505.2	1.21 (87)	506.3	Method 2
Ex.9			C33H39FN6O6	634.3	2.12 (99)	635.4	Method 1a
Ex.10			C26H34FN5O8	563.2	1.20 (91)	564.2	Method 2
Ex.11			C35H44FN7O6	677.3	1.34 (93)	678.4	Method 2
Ex.12			C41H44FN7O6	749.3	1.73 (92)	750.4	Method 2
Ex.13			C34H39FN6O8	678.3	1.45 (87)	679.3	Method 2
Ex.14			C26H37FN6O6	548.3	1.08 (88)	549.3	Method 2

No	R^{54}	R^2	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.15			C29H44FN7O6	605.3	0.99 (96)	606.4	Method 2
Ex.16			C35H44FN7O6	677.3	1.41 (97)	678.4	Method 2
Ex.17			C28H39FN6O8	606.3	1.09 (94)	607.3	Method 2
Ex.18			C26H34FN5O8	563.2	1.20 (88)	564.3	Method 2
Ex.19			C29H41FN6O8	620.3	1.08 (100)	621.3	Method 2
Ex.20			C28H36FN5O10	621.2	1.18 (91)	622.2	Method 2
Ex.21			C36H46FN7O6	691.4	1.35 (88)	692.4	Method 2
Ex.22			C28H41FN6O6	576.3	1.12 (96)	577.4	Method 2
Ex.23		NH_2	C26H39FN6O5	534.3	0.96 (88)	535.4	Method 2
Ex.24			C27H38FN5O7	563.3	1.54 (93)	564.3	Method 2

No	R^{54}	R^2	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.25		NH_2	C22H30FN5O5	463.2	1.06 (91)	464.2	Method 2
Ex.26			C30H42FN5O9	635.3	1.61 (87)	636.4	Method 2
Ex.27			C30H45FN6O7	620.3	1.53 (92)	621.3	Method 4a
Ex.28		NH_2	C25H37FN6O5	520.3	0.93 (94)	521.3	Method 2
Ex.29			C31H47FN6O7	634.4	1.41 (96)	635.4	Method 2
Ex.30			C36H45FN6O7	692.3	1.79 (99)	693.4	Method 2
Ex.31			C27H36FN5O8	577.3	1.32 (90)	578.3	Method 2
Ex.32			C29H38FN5O10	635.3	1.30 (83)	636.2	Method 2
Ex.33			C29H41FN6O8	620.3	1.18 (100)	621.3	Method 2
Ex.34			C35H41FN6O8	692.3	1.56 (90)	693.3	Method 2

No	R^{54}	R^2	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.35			C30H43FN6O8	634.3	1.10 (94)	635.3	Method 2
Ex.36			C30H46FN7O6	619.4	1.00 (91)	620.3	Method 2
Ex.37			C27H36FN5O6	545.3	1.36 (93)	546.3	Method 2
Ex.38			C35H41FN6O6	660.3	1.60 (94)	661.3	Method 2
Ex.39			C29H41FN6O6	588.3	1.19 (94)	589.3	Method 2
Ex.40			C29H38FN5O8	603.3	1.33 (94)	604.3	Method 2
Ex.41			C30H42FN5O7	603.3	1.67 (90)	604.3	Method 2
Ex.42		NH_2	C25H34FN5O5	503.3	1.17 (92)	504.2	Method 2
Ex.43			C29H42FN5O5	559.3	1.26 (96)	560.3	Method 2
Ex.44			C26H38FN5O5	519.3	1.13 (97)	520.3	Method 2

No	R^{54}	R^2	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.45			C34H38FN5O6	631.3	1.65 (97)	632.2	Method 2
Ex.46			C36H43FN6O6	674.3	1.49 (97)	675.5	Method 2
Ex.47			C36H43FN6O6	674.3	1.43 (96)	675.5	Method 2
Ex.48			C37H45FN6O6	688.3	1.50 (95)	689.5	Method 2
Ex.49			C37H45FN6O6	688.3	1.48 (95)	689.5	Method 2
Ex.50			C33H40F4N6O6	692.3	1.49 (97)	693.5	Method 2
Ex.51		NH_2	C25H34FN5O7	535.2	1.05	536.3	Method 9c
Ex.52	OCH_2Ph		C32H40FN5O7	625.3	1.47	626.3	Method 9c
Ex.53	OCH_2Ph		C30H35FN4O7	582.3	1.65	582.9	Method 9c

No	R^{54}	R^2	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.54	OH		C23H29FN4O7	492.2	1.04	493.1	Method 9c
Ex.55		NH_2	C31H37FN6O5	592.3	1.38	593.0	Method 9c
Ex.482			C36H44FN7O6	689.3	1.43 (91)	690.4	Method 10a
Ex.483			C35H41FN6O6	660.3	1.42 (85)	661.4	Method 10a
Ex.484			C36H43FN8O6	702.3	1.46 (90)	703.3	Method 10a
Ex.485			C40H44FN7O6	737.3	1.79 (93)	738.4	Method 11a
Ex.486			C37H47FN6O5	674.4	1.34 (80)	675.3	Method 10a
Ex.487			C37H43FN6O7	702.3	1.56 (78)	703.4	Method 10a

No	R^{54}	R^2	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.488			C38H47FN6O6	702.4	1.79 (91)	703.5	Method 11a
Ex.489			C40H43FN6O6	722.3	1.52 (97)	723.4	Method 10a
Ex.490			C39H47FN6O7	730.4	1.68 (97)	731.4	Method 4a
Ex.491			C38H46FN5O6	687.3	2.14 (96)	688.4	Method 4a
Ex.492			C35H42FN5O7S	695.3	1.94 (93)	696.4	Method 10a
Ex.493			C28H40FN5O7S	609.3	1.58 (87)	610.3	Method 10a
Ex.494			C35H40FN7O8S	737.3	1.21 (95)	738.3	Method 10a
Ex.495			C34H42F4N6O6	706.3	1.50 (91)	707.4	Method 10a
Ex.496			C34H45FN6O7	668.3	1.31 (93)	669.4	Method 10a

No	R^{54}	R^2	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.497			C39H41FN6O6	708.3	1.47 (87)	709.4	Method 10a
Ex.498	OCH_2Ph		C40H41FN4O7	708.3	2.13 (90)	709.4	Method 10a
Ex.499	OH		C33H35FN4O7	618.3	1.63 (90)	619.2	Method 10a
Ex.500			C40H49FN6O8	760.4	1.90 (95)	761.5	Method 10a
Ex.501			C44H44FN5O6	757.3	2.27 (93)	758.4	Method 4a
Ex.502			C39H39ClFN5O6	727.3	2.22 (95)	728.3	Method 4a
Ex.503			C43H42FN5O6	743.3	2.17 (97)	744.4	Method 4a

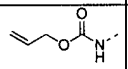
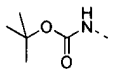
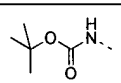
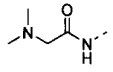
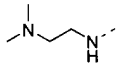
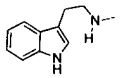
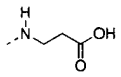
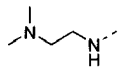
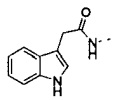
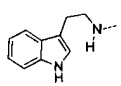
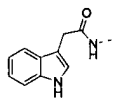
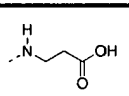
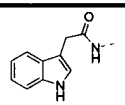
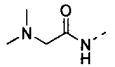
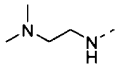
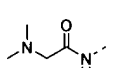
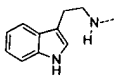
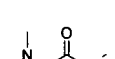
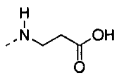
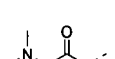
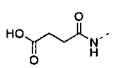
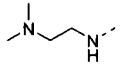
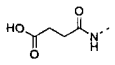
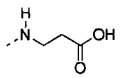
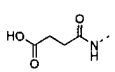
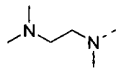
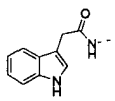
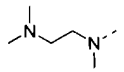
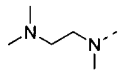
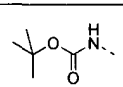
No	R^{54}	R^2	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.590	OH	NH_2	C21H27FN4O6	450.2	1.05 (93)	451.0	Method 4b
Ex.591	OH		C25H31FN4O8	534.2	1.58 (91)	535.2	Method 4b

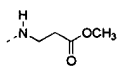
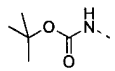
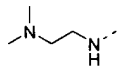
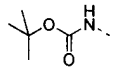
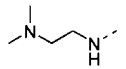
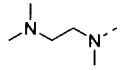
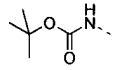
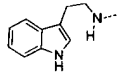
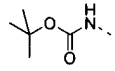
Table 21c: Examples of Core 03 (**Ex.3-Ex.55, Ex.482-Ex.503 and Ex.590-Ex.591**; *continued on the following pages*)

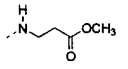
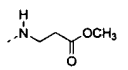
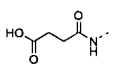
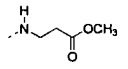
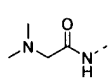
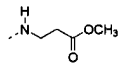
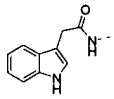
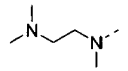
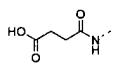
No	R^{54}	R^2	IUPAC name
Ex.3	OCH_2Ph		benzyl (2*S*,11*S*,19a*S*)-2-[(*tert*-butoxycarbonyl)amino]-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxylate
Ex.4	OH		(2*S*,11*S*,19a*S*)-2-[(*tert*-butoxycarbonyl)amino]-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxylic acid
Ex.5	OCH_2Ph	NH_2	benzyl (2*S*,11*S*,19a*S*)-2-amino-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxylate
Ex.6	OH		(2*S*,11*S*,19a*S*)-2-{[2-(dimethylamino)acetyl]amino}-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxylic acid

No	R^{54}	R^2	IUPAC name
Ex.7			(2*S*,11*S*,19a*S*)-2-(acetylamino)-15-fluoro-*N*,7,12-trimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.8			(2*S*,11*S*,19a*S*)-2-(acetylamino)-*N*-[2-(dimethylamino)ethyl]-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.9			(2*S*,11*S*,19a*S*)-2-(acetylamino)-15-fluoro-*N*-[2-(1H-indol-3-yl)ethyl]-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.10			3-({[(2*S*,11*S*,19a*S*)-2-(acetylamino)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-11-yl]carbonyl}amino)propanoic acid
Ex.11			(2*S*,11*S*,19a*S*)-N-[2-(dimethylamino)ethyl]-15-fluoro-2-{[2-(1H-indol-3-yl)acetyl]amino}-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.12			(2*S*,11*S*,19a*S*)-15-fluoro-2-{[2-(1H-indol-3-yl)acetyl]amino}-*N*-[2-(1H-indol-3-yl)ethyl]-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide

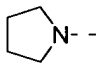
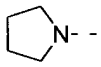
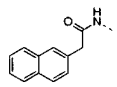
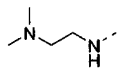
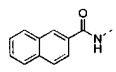
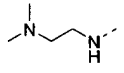
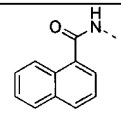
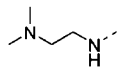
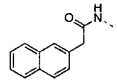
No	R^{54}	R^2	IUPAC name
Ex.13			3-{[((2*S*,11*S*,19a*S*)-15-fluoro-2-{[2-(1H-indol-3-yl)acetyl]amino}-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-11-yl)carbonyl]amino}propanoic acid
Ex.14			(2*S*,11*S*,19a*S*)-2-{[2-(dimethylamino)acetyl]amino}-15-fluoro-*N*,7,12-trimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.15			(2*S*,11*S*,19a*S*)-2-{[2-(dimethylamino)acetyl]amino}-*N*-[2-(dimethylamino)ethyl]-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.16			(2*S*,11*S*,19a*S*)-2-{[2-(dimethylamino)acetyl]amino}-15-fluoro-*N*-[2-(1H-indol-3-yl)ethyl]-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.17			3-{[((2*S*,11*S*,19a*S*)-2-{[2-(dimethylamino)acetyl]amino}-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-11-yl)carbonyl]amino}propanoic acid
Ex.18			4-({(2*S*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-11-[(methylamino)carbonyl]-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-2-yl}amino)-4-oxobutanoic acid

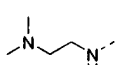
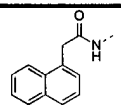
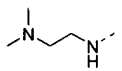
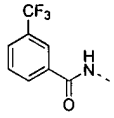
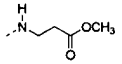
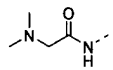
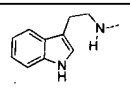
No	R^{54}	R^2	IUPAC name
Ex.19			4-{[(2*S*,11*S*,19a*S*)-11-({[2-(dimethylamino)ethyl]amino}carbonyl)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]amino}-4-oxobutanoic acid
Ex.20			4-[((2*S*,11*S*,19a*S*)-15-fluoro-11-{[(3-hydroxy-3-oxopropyl)amino]carbonyl}-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-2-yl)amino]-4-oxobutanoic acid
Ex.21			(2*S*,11*S*,19a*S*)-N-[2-(dimethylamino)ethyl]-15-fluoro-2-{[2-(1*H*-indol-3-yl)acetyl]amino}-*N*,7,12-trimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.22			(2*S*,11*S*,19a*S*)-2-(acetylamino)-*N*-[2-(dimethylamino)ethyl]-15-fluoro-*N*,7,12-trimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.23		NH_2	(2*S*,11*S*,19a*S*)-2-amino-*N*-[2-(dimethylamino)ethyl]-15-fluoro-*N*,7,12-trimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.24			*tert*-butyl *N*-{(2*S*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-11-[(methylamino)carbonyl]-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-2-yl}carbamate

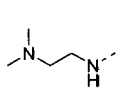
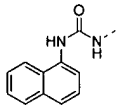
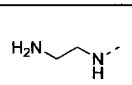
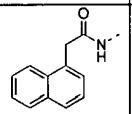
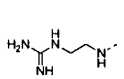
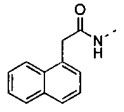
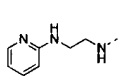
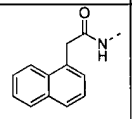
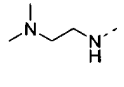
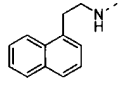
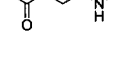
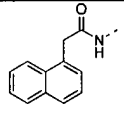
No	R^{54}	R^2	IUPAC name
Ex.25		NH_2	(2*S*,11*S*,19a*S*)-2-amino-15-fluoro-*N*,7,12-trimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.26			methyl 3-[({(2*S*,11*S*,19a*S*)-2-[(*tert*-butoxycarbonyl)amino]-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-11-yl}carbonyl)amino]propanoate
Ex.27			*tert*-butyl N-[(2*S*,11*S*,19a*S*)-11-({[2-(dimethylamino)ethyl]amino}carbonyl)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]carbamate
Ex.28		NH_2	(2*S*,11*S*,19a*S*)-2-amino-*N*-[2-(dimethylamino)ethyl]-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.29			*tert*-butyl *N*-((2*S*,11*S*,19a*S*)-11-{[[2-(dimethylamino)ethyl](methyl)amino]carbonyl}-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-2-yl)carbamate
Ex.30			*tert*-butyl *N*-[(2*S*,11*S*,19a*S*)-15-fluoro-11-({[2-(1H-indol-3-yl)ethyl]amino}carbonyl)-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]carbamate

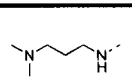
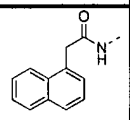
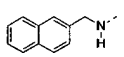
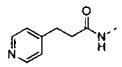
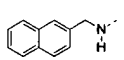
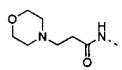
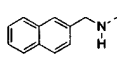
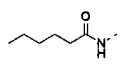
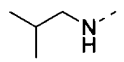
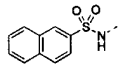
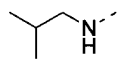
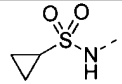
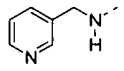
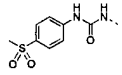
No	R^{54}	R^2	IUPAC name
Ex.31			methyl 3-({[(2*S*,11*S*,19a*S*)-2-(acetylamino)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-11-yl]carbonyl}amino)propanoate
Ex.32			4-[((2*S*,11*S*,19a*S*)-15-fluoro-11-{[(3-methoxy-3-oxopropyl)amino]carbonyl}-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-2-yl)amino]-4-oxobutanoic acid
Ex.33			methyl 3-{[((2*S*,11*S*,19a*S*)-2-{[2-(dimethylamino)acetyl]amino}-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-11-yl)carbonyl]amino}propanoate
Ex.34			methyl 3-{[((2*S*,11*S*,19a*S*)-15-fluoro-2-{[2-(1*H*-indol-3-yl)acetyl]amino}-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-11-yl)carbonyl]amino}propanoate
Ex.35			4-[((2*S*,11*S*,19a*S*)-11-{[[2-(dimethylamino)ethyl](methyl)amino]carbonyl}-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-2-yl)amino]-4-oxobutanoic acid

No	R^{54}	R^2	IUPAC name
Ex.36			(2*S*,11*S*,19a*S*)-2-{[2-(dimethylamino)acetyl]amino}-*N*-[2-(dimethylamino)ethyl]-15-fluoro-*N*,7,12-trimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.37			*N*-[(2*S*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]acetamide
Ex.38			*N*-[(2*S*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]-2-(1H-indol-3-yl)acetamide
Ex.39			*N*-[(2*S*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]-2-(dimethylamino)acetamide
Ex.40			4-{[(2*S*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]amino}-4-oxobutanoic acid
Ex.41			*tert*-butyl *N*-[(2*S*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]carbamate

No	R^{54}	R^2	IUPAC name
Ex.42		NH_2	(2*S*,11*S*,19a*S*)-2-amino-15-fluoro-7,12-dimethyl-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,9,10,11,12,19,19a-decahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-5,8,13-trione
Ex.43			(2*S*,11*S*,19a*S*)-2-(diethylamino)-15-fluoro-7,12-dimethyl-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,9,10,11,12,19,19a-decahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-5,8,13-trione
Ex.44			(2*S*,11*S*,19a*S*)-2-(diethylamino)-15-fluoro-*N*,7,12-trimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.45			(2*S*,11*S*,19a*S*)-15-fluoro-*N*,7,12-trimethyl-2-{[2-(2-naphthyl)acetyl]amino}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1H,5H-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.46			(2*S*,11*S*,19a*S*)-*N*-[2-(dimethylamino)ethyl]-15-fluoro-7,12-dimethyl-2-(2-naphthoylamino)-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.47			(2*S*,11*S*,19a*S*)-*N*-[2-(dimethylamino)ethyl]-15-fluoro-7,12-dimethyl-2-(1-naphthoylamino)-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.48			(2*S*,11*S*,19a*S*)-*N*-[2-(dimethylamino)ethyl]-15-fluoro-7,12-dimethyl-2-{[2-(2-naphthyl)acetyl]amino}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide

No	R^{54}	R^2	IUPAC name
Ex.49			(2*S*,11*S*,19a*S*)-*N*-[2-(dimethylamino)ethyl]-15-fluoro-7,12-dimethyl-2-{[2-(1-naphthyl)acetyl]amino}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.50			(2*S*,11*S*,19a*S*)-*N*-[2-(dimethylamino)ethyl]-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2-{[3-(trifluoromethyl)benzoyl]amino}-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.51		NH_2	methyl 3-({[(2*S*,11*S*,19a*S*)-2-amino-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-11-yl]carbonyl}amino)propanoate
Ex.52	OCH_2Ph		benzyl (2*S*,11*S*,19a*S*)-2-{[2-(dimethylamino)acetyl]amino}-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxylate
Ex.53	OCH_2Ph		benzyl (2*S*,11*S*,19a*S*)-2-(acetylamino)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxylate
Ex.54	OH		(2*S*,11*S*,19a*S*)-2-(acetylamino)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxylic acid
Ex.55		NH_2	(2*S*,11*S*,19a*S*)-2-amino-15-fluoro-*N*-[2-(1H-indol-3-yl)ethyl]-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide

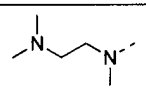
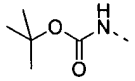
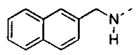
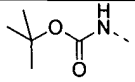
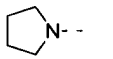
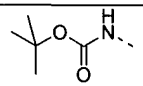
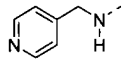
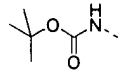
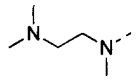
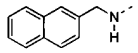
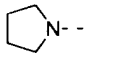
No	R^{54}	R^2	IUPAC name
Ex.482			(2*S*,11*S*,19a*S*)-*N*-[2-(dimethylamino)ethyl]-15-fluoro-7,12-dimethyl-2-{[(1-naphthylamino)carbonyl]amino}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.483			(2*S*,11*S*,19a*S*)-*N*-(2-aminoethyl)-15-fluoro-7,12-dimethyl-2-{[2-(1-naphthyl)acetyl]amino}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.484			(2*S*,11*S*,19a*S*)-*N*-(2-{[amino(imino)methyl]amino}ethyl)-15-fluoro-7,12-dimethyl-2-{[2-(1-naphthyl)acetyl]amino}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.485			(2*S*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-2-{[2-(1-naphthyl)acetyl]amino}-5,8,13-trioxo-*N*-[2-(2-pyridinylamino)ethyl]-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.486			(2*S*,11*S*,19a*S*)-*N*-[2-(dimethylamino)ethyl]-15-fluoro-7,12-dimethyl-2-{[2-(1-naphthyl)ethyl]amino}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.487			(2*S*,11*S*,19a*S*)-*N*-[2-(acetylamino)ethyl]-15-fluoro-7,12-dimethyl-2-{[2-(1-naphthyl)acetyl]amino}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide

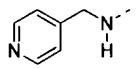
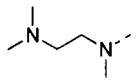
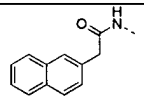
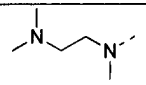
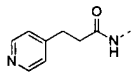
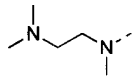
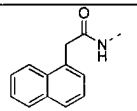
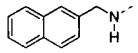
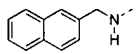
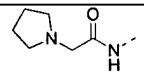
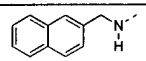
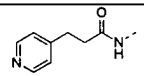
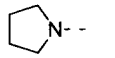
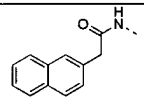
No	R^{54}	R^2	IUPAC name
Ex.488			(2*S*,11*S*,19a*S*)-*N*-[3-(dimethylamino)propyl]-15-fluoro-7,12-dimethyl-2-{[2-(1-naphthyl)acetyl]amino}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.489			(2*S*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-*N*-(2-naphthylmethyl)-5,8,13-trioxo-2-{[3-(4-pyridinyl)propanoyl]amino}-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.490			(2*S*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-2-[(3-morpholinopropanoyl)amino]-*N*-(2-naphthylmethyl)-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.491			(2*S*,11*S*,19a*S*)-15-fluoro-2-(hexanoylamino)-7,12-dimethyl-*N*-(2-naphthylmethyl)-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.492			(2*S*,11*S*,19a*S*)-15-fluoro-*N*-isobutyl-7,12-dimethyl-2-[(2-naphthylsulfonyl)amino]-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.493			(2*S*,11*S*,19a*S*)-2-[(cyclopropylsulfonyl)amino]-15-fluoro-*N*-isobutyl-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.494			(2*S*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-2-({[4-(methylsulfonyl)anilino]carbonyl}amino)-5,8,13-trioxo-*N*-(3-pyridinylmethyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide

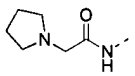
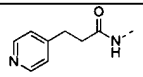
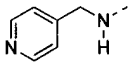
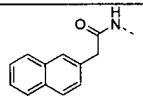
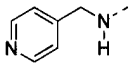
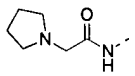
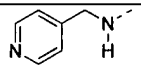
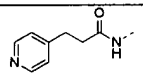
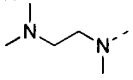
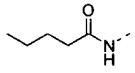
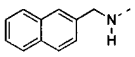
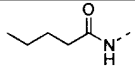
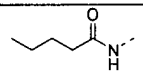
No	R^{54}	R^2	IUPAC name
Ex.495			(2*S*,11*S*,19a*S*)-*N*-[2-(dimethylamino)ethyl]-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2-({2-[3-(trifluoromethyl)phenyl]acetyl}amino)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.496			(2*S*,11*S*,19a*S*)-*N*-[2-(dimethylamino)ethyl]-15-fluoro-2-{[2-(3-methoxyphenyl)acetyl]amino}-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.497			(2*S*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-2-{[2-(1-naphthyl)acetyl]amino}-5,8,13-trioxo-*N*-(3-pyridinylmethyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.498	OCH_2Ph		benzyl (2*S*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-2-{[2-(1-naphthyl)acetyl]amino}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxylate
Ex.499	OH		(2*S*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-2-{[2-(1-naphthyl)acetyl]amino}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxylic acid
Ex.500			*tert*-butyl *N*-(2-{[((2*S*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-2-{[2-(1-naphthyl)acetyl]amino}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-11-yl)carbonyl]amino}ethyl)carbamate

No	R^{54}	R^2	IUPAC name
Ex.501			(2*S*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-2-{[2-(2-naphthyl)acetyl]amino}-*N*-(1-naphthylmethyl)-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.502			(2*S*,11*S*,19a*S*)-2-[(3-chlorobenzoyl)amino]-15-fluoro-7,12-dimethyl-*N*-(1-naphthylmethyl)-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.503			(2*S*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-2-(1-naphthoylamino)-*N*-(2-naphthylmethyl)-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.590	OH	NH_2	(2*S*,11*S*,19a*S*)-2-amino-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxylic acid
Ex.591	OH		(2*S*,11*S*,19a*S*)-2-{[(allyloxy)carbonyl]amino}-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxylic acid

Table 22a: Examples of Core 04 (**Ex.56-Ex.84,** *continued on the following pages*)

No	R^{54}	R^2	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.56-Ex.57: *cf. experimental description*							
Ex.58			**Ex.57**	L.2	N,N,N'-trimetylethylene-diamine	FC (CH_2Cl_2/MeOH/aq. NH_3)	86%
Ex.59			**Ex.57**	L.2	2-naphthylmethylamine	FC (CH_2Cl_2/MeOH)	91%
Ex.60			**Ex.57**	L.2	pyrrolidine	FC (CH_2Cl_2/MeOH)	79%
Ex.61			**Ex.57**	L.2	4-(aminomethyl)-pyridine	FC (CH_2Cl_2/MeOH)	81%
Ex.62		NH_2	**Ex.58**	J	HCl-dioxane	crude product	98% (HCl salt)
Ex.63		NH_2	**Ex.59**	J	HCl-dioxane	crude product	76% (HCl salt)
Ex.64		NH_2	**Ex.60**	J	HCl-dioxane	crude product	94% (HCl salt)

No	R^{54}	R^2	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.65		NH_2	**Ex.61**	J	HCl-dioxane	crude product	91% (HCl salt)
Ex.66			**Ex.62**	L.1.3	2-naphthylacetic acid	prep. HPLC, method 1	67% (TFA salt)
Ex.67			**Ex.62**	L.1.2	3-(pyridine-4-yl)propanoic acid	prep. HPLC, method 2	56%
Ex.68			**Ex.62**	L.1.2	1-naphthylacetic acid (1.5 equiv.)	prep. HPLC, method 1	24% (TFA salt)
Ex.69			**Ex.63**	L.1.1	acetic anhydride (5 equiv.)	prep. HPLC, method 1	75%
Ex.70			**Ex.63**	L.1.3	1-pyrrolidinacetic acid	prep. HPLC, method 1	62% (TFA salt)
Ex.71			**Ex.63**	L.1.2	3-(pyridine-4-yl)propanoic acid	prep. HPLC, method 1	22% (TFA salt)
Ex.72			**Ex.64**	L.1.3	2-naphthylacetic acid	prep. HPLC, method 2	51%

No	R^{54}	R^2	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.73			**Ex.64**	L.1.2	1-pyrrolidinacetic acid (1.7 equiv.)	prep. HPLC, method 1	39% (TFA salt)
Ex.74			**Ex.64**	L.1.2	3-(pyridine-4-yl)propanoic acid	prep. HPLC, method 2	29%
Ex.75			**Ex.65**	L.1.3	2-naphthylacetic acid	prep. HPLC, method 1	37% (TFA salt)
Ex.76			**Ex.65**	L.1.2	1-pyrrolidinacetic acid (1.7 equiv.)	prep. HPLC, method 2	45%
Ex.77			**Ex.65**	L.1.2	3-(pyridine-4-yl)propanoic acid	prep. HPLC, method 2	45%
Ex.78			**Ex.62**	L.1.1	valeroyl chloride (1.6 equiv.)	prep. HPLC, method 1	56%
Ex.79			**Ex.63**	L.1.1	valeroyl chloride (1.6 equiv.)	prep. HPLC, method 1	77%
Ex.80			**Ex.64**	L.1.1	valeroyl chloride (1.3 equiv.)	prep. HPLC, method 1	46%

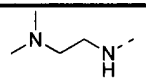
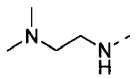
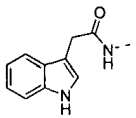
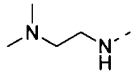
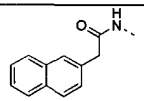
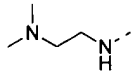
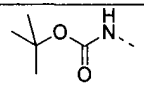
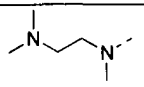
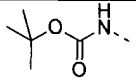
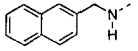
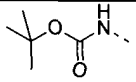
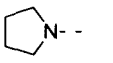
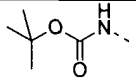
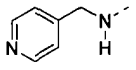
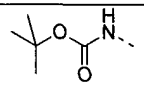
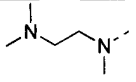
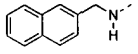
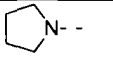
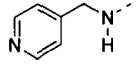
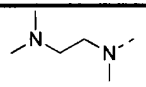
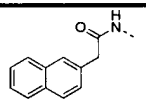
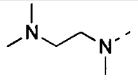
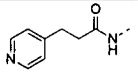
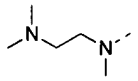
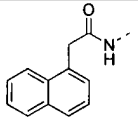
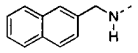
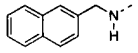
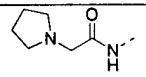
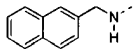
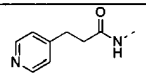
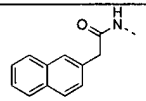
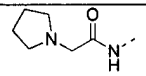
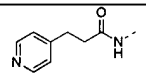
No	R^{54}	R^2	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.81		NH_2	**Ex.84**	J	HCl-dioxane	crude product	99% (HCl salt)
Ex.82			**Ex.81**	L.1.3	3-indoleacetic acid (1.5 equiv.) HATU (1.5 equiv.) HOAt (1.5 equiv.) i-Pr_2NEt (5 equiv.)	prep. HPLC, method 1, then FC (CH_2Cl_2/MeOH/ aq. NH_3)	15%
Ex.83			**Ex.81**	L.1.3	2-naphthylacetic acid (1.2 equiv.)	FC (CH_2Cl_2/MeOH/aq. NH_3), then prep. HPLC, method 1	58%
Ex.84			**Ex.57**	L.2	2-dimethylaminoethyl-amine	FC (CH_2Cl_2/MeOH)	89%

Table 22b: Examples of Core 04 (**Ex.56-Ex.84**; *continued on the following pages*)

No	R^{54}	R^2	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.56-Ex.57: *cf. experimental description*							
Ex.58			C31H47FN6O7	634.4	1.44 (91)	635.5	Method 2
Ex.59			C37H44FN5O7	689.3	1.89 (87)	690.5	Method 2
Ex.60			C30H42FN5O7	603.3	1.67 (84)	604.4	Method 2
Ex.61			C32H41FN6O7	640.3	1.42 (92)	641.4	Method 2
Ex.62		NH_2	C26H39FN6O5	534.3	0.97 (91)	535.4	Method 2
Ex.63		NH_2	C32H36FN5O5	589.3	1.53 (95)	590.4	Method 2
Ex.64		NH_2	C25H34FN5O5	503.3	1.23 (82)	504.3	Method 2
Ex.65		NH_2	C27H33FN6O5	540.3	0.97 (97)	541.4	Method 2

No	R^{54}	R^2	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.66			C38H47FN6O6	702.4	1.51 (97)	703.5	Method 2
Ex.67			C34H46FN7O6	667.4	1.08 (94)	668.5	Method 2
Ex.68			C38H47FN6O6	702.4	1.51 (88)	703.5	Method 2
Ex.69			C34H38FN5O6	631.3	1.66 (90)	632.3	Method 2
Ex.70			C38H45FN6O6	700.3	1.56 (95)	701.5	Method 2
Ex.71			C40H43FN6O6	722.3	1.55 (93)	723.5	Method 2
Ex.72			C37H42FN5O6	671.3	1.73 (87)	672.4	Method 2
Ex.73			C31H43FN6O6	614.3	1.28 (90)	615.4	Method 2
Ex.74			C33H41FN6O6	636.3	1.29 (91)	637.4	Method 2

No	R^{54}	R^2	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.75			C39H41FN6O6	708.3	1.50 (92)	709.4	Method 2
Ex.76			C33H42FN7O6	651.3	1.07 (91)	652.4	Method 2
Ex.77			C35H40FN7O6	673.3	1.07 (90)	674.5	Method 2
Ex.78			C31H47FN6O6	618.4	1.33(98)	619.4	Method 2
Ex.79			C37H44FN5O6	673.3	1.81 (91)	674.4	Method 2
Ex.80			C30H42FN5O6	587.3	1.56 (93)	588.4	Method 2
Ex.81		NH_2	C25H37FN6O5	520.3	1.10 (88)	521.4	Method 2
Ex.82			C35H44FN7O6	677.3	1.36 (93)	678.5	Method 2
Ex.83			C37H45FN6O6	688.3	1.49 (93)	689.5	Method 2

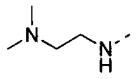
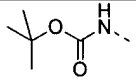
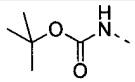
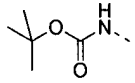
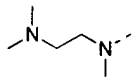
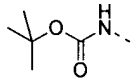
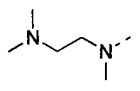
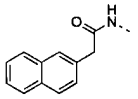
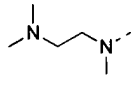
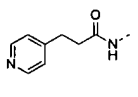
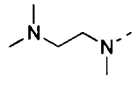
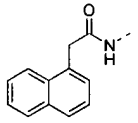
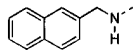
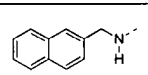
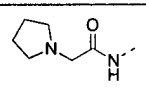
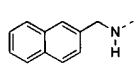
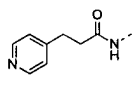
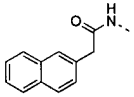
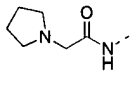
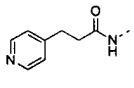
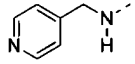
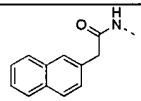
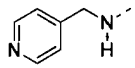
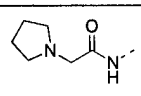
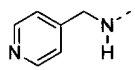
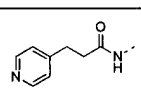
No	R^{54}	R^2	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.84			C30H45FN6O7	620.3	1.38 (87)	621.5	Method 2

Table 22c: Examples of Core 04 (**Ex.56-Ex.84**; *continued on the following pages*)

No	R^{54}	R^2	IUPAC name
Ex.56	OCH_2Ph		benzyl (2*R*,11*S*,19a*S*)-2-[(*tert*-butoxycarbonyl)amino]-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxylate
Ex.57	OH		(2*R*,11*S*,19a*S*)-2-[(*tert*-butoxycarbonyl)amino]-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxylic acid
Ex.58			*tert*-butyl *N*-((2*R*,11*S*,19a*S*)-11-{[[2-(dimethylamino)ethyl](methyl)amino]carbonyl}-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-2-yl)carbamate

No	R^{54}	R^2	IUPAC name
Ex.59			*tert*-butyl *N*-((2*R*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-11-{[(2-naphthylmethyl)amino]carbonyl}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-2-yl)carbamate
Ex.60			*tert*-butyl *N*-[(2*R*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]carbamate
Ex.61			*tert*-butyl *N*-((2*R*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-11-{[(4-pyridinylmethyl)amino]carbonyl}-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-2-yl)carbamate
Ex.62		NH_2	(2*R*,11*S*,19a*S*)-2-amino-*N*-[2-(dimethylamino)ethyl]-15-fluoro-*N*,7,12-trimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.63		NH_2	(2*R*,11*S*,19a*S*)-2-amino-15-fluoro-7,12-dimethyl-*N*-(2-naphthylmethyl)-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.64		NH_2	(2*R*,11*S*,19a*S*)-2-amino-15-fluoro-7,12-dimethyl-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,9,10,11,12,19,19a-decahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-5,8,13-trione
Ex.65		NH_2	(2*R*,11*S*,19a*S*)-2-amino-15-fluoro-7,12-dimethyl-5,8,13-trioxo-*N*-(4-pyridinylmethyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide

No	R^{54}	R^2	IUPAC name
Ex.66			(2*R*,11*S*,19a*S*)-*N*-[2-(dimethylamino)ethyl]-15-fluoro-*N*,7,12-trimethyl-2-{[2-(2-naphthyl)acetyl]amino}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.67			(2*R*,11*S*,19a*S*)-*N*-[2-(dimethylamino)ethyl]-15-fluoro-*N*,7,12-trimethyl-5,8,13-trioxo-2-{[3-(4-pyridinyl)propanoyl]amino}-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.68			(2*R*,11*S*,19a*S*)-*N*-[2-(dimethylamino)ethyl]-15-fluoro-*N*,7,12-trimethyl-2-{[2-(1-naphthyl)acetyl]amino}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.69			(2*R*,11*S*,19a*S*)-2-(acetylamino)-15-fluoro-7,12-dimethyl-*N*-(2-naphthylmethyl)-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.70			(2*R*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-*N*-(2-naphthylmethyl)-5,8,13-trioxo-2-{[2-(1-pyrrolidinyl)acetyl]amino}-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.71			(2*R*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-*N*-(2-naphthylmethyl)-5,8,13-trioxo-2-{[3-(4-pyridinyl)propanoyl]amino}-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide

No	R^{54}	R^2	IUPAC name
Ex.72			*N*-[(2*R*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]-2-(2-naphthyl)acetamide
Ex.73			*N*-[(2*R*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]-2-(1-pyrrolidinyl)acetamide
Ex.74			*N*-[(2*R*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]-3-(4-pyridinyl)propanamide
Ex.75			(2*R*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-2-{[2-(2-naphthyl)acetyl]amino}-5,8,13-trioxo-*N*-(4-pyridinylmethyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.76			(2*R*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-*N*-(4-pyridinylmethyl)-2-{[2-(1-pyrrolidinyl)acetyl]amino}-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.77			(2*R*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-*N*-(4-pyridinylmethyl)-2-{[3-(4-pyridinyl)propanoyl]amino}-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide

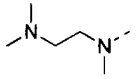
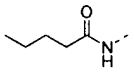
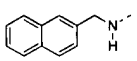
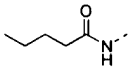
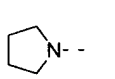
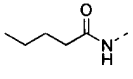
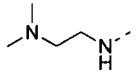
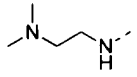
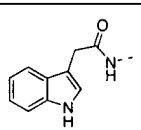
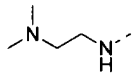
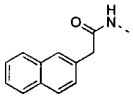
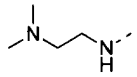
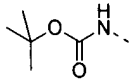
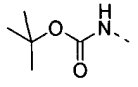
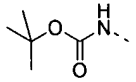
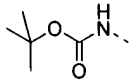
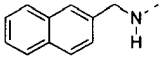
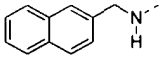
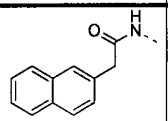
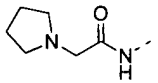
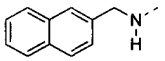
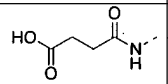
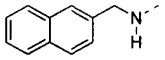
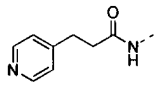
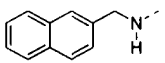
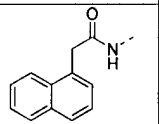
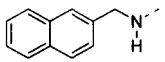
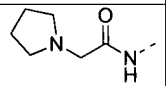
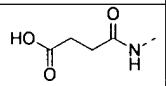
No	R^{54}	R^2	IUPAC name
Ex.78			(2*R*,11*S*,19a*S*)-*N*-[2-(dimethylamino)ethyl]-15-fluoro-*N*,7,12-trimethyl-5,8,13-trioxo-2-(pentanoylamino)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.79			(2*R*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-*N*-(2-naphthylmethyl)-5,8,13-trioxo-2-(pentanoylamino)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.80			*N*-[(2*R*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]pentanamide
Ex.81		NH_2	(2*R*,11*S*,19a*S*)-2-amino-*N*-[2-(dimethylamino)ethyl]-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.82			(2*R*,11*S*,19a*S*)-*N*-[2-(dimethylamino)ethyl]-15-fluoro-2-{[2-(1*H*-indol-3-yl)acetyl]amino}-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.83			(2*R*,11*S*,19a*S*)-*N*-[2-(dimethylamino)ethyl]-15-fluoro-7,12-dimethyl-2-{[2-(2-naphthyl)acetyl]amino}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.84			*tert*-butyl *N*-[(2*R*,11*S*,19a*S*)-11-({[2-(dimethylamino)ethyl]amino}carbonyl)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]carbamate

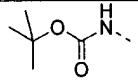
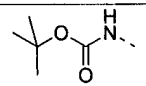
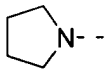
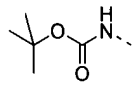
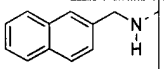
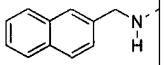
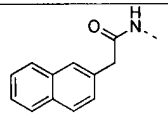
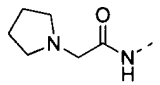
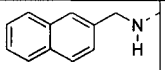
Table 23a: Examples of Core 05 (**Ex.85-Ex.103**; continued on the following pages)

No	R^2	R^{54}	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.85-Ex.86: *cf. experimental description*							
Ex.87			**Ex.86**	L.2	methylamine-hydrochloride (10 equiv.) HATU (1.5 equiv.) HOAt (1.5 equiv.) i-Pr_2NEt (13 equiv.)	FC (CH_2Cl_2/MeOH)	76%
Ex.88			**Ex.86**	L.2	pyrrolidine	FC (CH_2Cl_2/MeOH) then prep. HPLC, method 2	64%
Ex.89			**Ex.86**	L.2	2-naphthylmethylamine	FC (EtOAc/MeOH)	93%
Ex.90	NH_2		**Ex.87**	J	HCl-dioxane	crude product	86% (HCl salt)
Ex.91	NH_2		**Ex.89**	J	HCl-dioxane	crude product	98% (HCl salt)
Ex.92	NH_2		**Ex.88**	J	HCl-dioxane	crude product	94% (HCl salt)

No	R^2	R^{54}	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.93			**Ex.90**	L.1.2	2-naphthylacetic acid	prep. HPLC, method 3	66%
Ex.94			**Ex.91**	L.1.2	1-pyrrolidineacetic acid (1.7 equiv.)	prep. HPLC, method 1	46% (TFA salt)
Ex.95			**Ex.91**	L.1.1	succinic anhydride (1.05 equiv.)	prep. HPLC, method 2	47% ($NH4^+$ salt)
Ex.96			**Ex.91**	L.1.2	3-(pyridine-4-yl)propanoic acid (3.7 equiv.)	FC (CH_2Cl_2/MeOH)	74%
Ex.97			**Ex.91**	L.1.2	1-naphthylacetic acid (1.4 equiv.)	prep. HPLC, method 3	72%
Ex.98			**Ex.92**	L.1.2	1-pyrrolidineacetic acid	prep. HPLC, method 1	68% (TFA salt)
Ex.99			**Ex.92**	L.1.1	succinic anhydride (1.05 equiv.)	prep. HPLC, method 2	40% ($NH4^+$ salt)

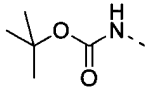
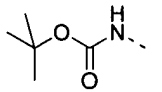
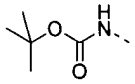
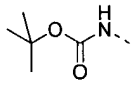
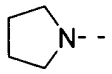
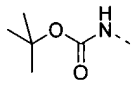
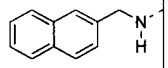
No	R^2	R^{54}	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.100			Ex.92	L.1.2	1-naphthylacetic acid	FC (EtOAc/MeOH)	83%
Ex.101			Ex.92	L.1.1	2-naphthoyl chloride (1.6 equiv.)	FC (EtOAc/MeOH)	84%
Ex.102			Ex.91	L.1.1	decanoyl chloride (4.1 equiv.) pyridine (15 equiv.)	prep. HPLC, method 3	64%
Ex.103			Ex.91	L.1.1	valeroyl chloride (2.0 equiv.)	prep. HPLC, method 3	87%

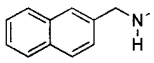
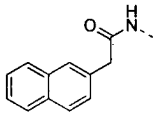
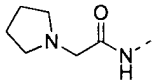
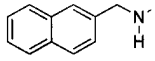
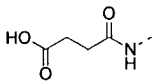
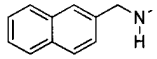
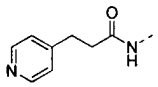
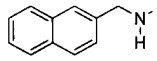
Table 23b: Examples of Core 05 (***Ex.85-Ex.103;*** *continued on the following pages*)

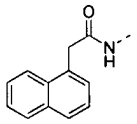
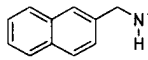
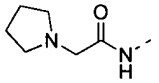
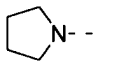
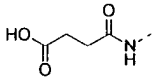
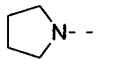
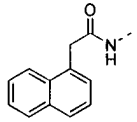
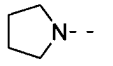
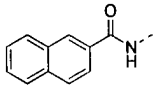
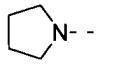
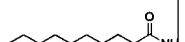
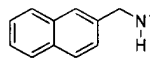
No	R^2	R^{54}	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.85-Ex.86: *cf. experimental description*							
Ex.87			C27H38FN5O7	563.3	1.52 (78)	564.4	Method 2
Ex.88			C30H42FN5O7	603.3	1.59 (64), 1.63 (27)	604.4/604.4	Method 2
Ex.89			C37H44FN5O7	689.3	1.89 (97)	690.5	Method 2
Ex.90	NH_2		C22H30FN5O5	463.2	1.02 (95)	464.3	Method 2
Ex.91	NH_2		C32H36FN5O5	589.3	1.51 (98)	590.4	Method 2
Ex.92	NH_2		C25H34FN5O5	503.3	1.20 (97)	504.3	Method 2
Ex.93			C34H38FN5O6	631.3	1.65 (98)	632.3	Method 2
Ex.94			C38H45FN6O6	700.3	1.55 (100)	701.5	Method 2

No	R^2	R^{54}	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.95			C36H40FN5O8	689.3	1.65 (98)	690.5	Method 2
Ex.96			C40H43FN6O6	722.3	1.51 (96)	723.5	Method 2
Ex.97			C44H44FN5O6	757.3	1.96 (92)	758.5	Method 2
Ex.98			C31H43FN6O6	614.3	1.25 (98)	615.3	Method 2
Ex.99			C29H38FN5O8	603.3	1.34 (100)	604.4	Method 2
Ex.100			C37H42FN5O6	671.3	1.73 (85)	672.4	Method 3
Ex.101			C36H40FN5O6	657.3	1.73 (98)	658.4	Method 2
Ex.102			C42H54FN5O6	743.4	2.16 (95)	744.6	Method 3
Ex.103			C37H44FN5O6	673.3	1.83 (96)	674.5	Method 2

Table 23c: Examples of Core 05 (**Ex.85-Ex.103**; *continued on the following pages*)

No	R^2	R^{54}	IUPAC name
Ex.85		OCH_2Ph	benzyl (2*S*,11*R*,19a*S*)-2-[(*tert*-butoxycarbonyl)amino]-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxylate
Ex.86		OH	(2*S*,11*R*,19a*S*)-2-[(*tert*-butoxycarbonyl)amino]-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxylic acid
Ex.87			*tert*-butyl *N*-{(2*S*,11*R*,19a*S*)-15-fluoro-7,12-dimethyl-11-[(methylamino)carbonyl]-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-2-yl}carbamate
Ex.88			*tert*-butyl *N*-[(2*S*,11*R*,19a*S*)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]carbamate
Ex.89			*tert*-butyl *N*-((2*S*,11*R*,19a*S*)-15-fluoro-7,12-dimethyl-11-{[(2-naphthylmethyl)amino]carbonyl}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-2-yl)carbamate
Ex.90	NH_2		(2*S*,11*R*,19a*S*)-2-amino-15-fluoro-*N*,7,12-trimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide

No	R^2	R^{54}	IUPAC name
Ex.91	NH_2		(2*S*,11*R*,19a*S*)-2-amino-15-fluoro-7,12-dimethyl-*N*-(2-naphthylmethyl)-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.92	NH_2		(2*S*,11*R*,19a*S*)-2-amino-15-fluoro-7,12-dimethyl-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,9,10,11,12,19,19a-decahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-5,8,13-trione
Ex.93			(2*S*,11*R*,19a*S*)-15-fluoro-*N*,7,12-trimethyl-2-{[2-(2-naphthyl)acetyl]amino}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.94			(2*S*,11*R*,19a*S*)-15-fluoro-7,12-dimethyl-*N*-(2-naphthylmethyl)-5,8,13-trioxo-2-{[2-(1-pyrrolidinyl)acetyl]amino}-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.95			4-[((2*S*,11*R*,19a*S*)-15-fluoro-7,12-dimethyl-11-{[(2-naphthylmethyl)amino]carbonyl}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-2-yl)amino]-4-oxobutanoic acid
Ex.96			(2*S*,11*R*,19a*S*)-15-fluoro-7,12-dimethyl-*N*-(2-naphthylmethyl)-5,8,13-trioxo-2-{[3-(4-pyridinyl)propanoyl]amino}-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide

No	R^2	R^{54}	IUPAC name
Ex.97			(2*S*,11*R*,19a*S*)-15-fluoro-7,12-dimethyl-2-{[2-(1-naphthyl)acetyl]amino}-*N*-(2-naphthylmethyl)-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.98			*N*-[(2*S*,11*R*,19a*S*)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]-2-(1-pyrrolidinyl)acetamide
Ex.99			4-{[(2*S*,11*R*,19a*S*)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]amino}-4-oxobutanoic acid
Ex.100			*N*-[(2*S*,11*R*,19a*S*)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]-2-(1-naphthyl)acetamide
Ex.101			*N*-[(2*S*,11*R*,19a*S*)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-11-(1-pyrrolidinylcarbonyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]-2-naphthamide
Ex.102			(2*S*,11*R*,19a*S*)-2-(decanoylamino)-15-fluoro-7,12-dimethyl-*N*-(2-naphthylmethyl)-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide

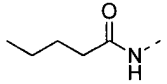
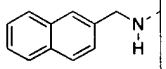
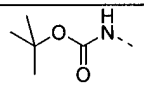
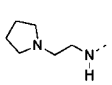
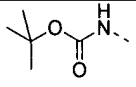
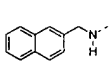
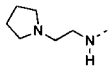
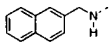
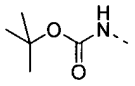
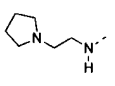
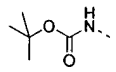
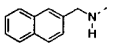
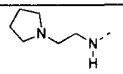
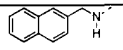
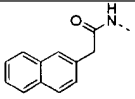
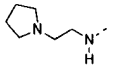
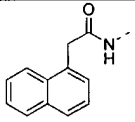
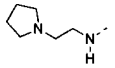
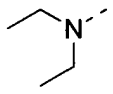
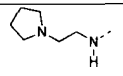
No	R^2	R^{54}	IUPAC name
Ex.103			(2*S*,11*R*,19a*S*)-15-fluoro-7,12-dimethyl-*N*-(2-naphthylmethyl)-5,8,13-trioxo-2-(pentanoylamino)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide

Table 24a: Examples of Core 06 (**Ex.104-Ex.114**; *continued on the following page*)

No	R^2	R^{54}	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.104-Ex.105: *cf. experimental description*							
Ex.106			**Ex.105**	L.2	N-(2-aminoethyl)pyrolidine	FC (CH_2Cl_2/MeOH/aq.NH_3)	78%
Ex.107			**Ex.105**	L.2	2-naphthylmethylamine	FC (CH_2Cl_2/MeOH)	96%
Ex.108	NH_2		**Ex.106**	J	HCl-dioxane	crude product	99% (HCl salt)
Ex.109	NH_2		**Ex.107**	J	HCl-dioxane	crude product	95% (HCl salt)

No	R^2	R^{54}	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.110			**Ex.108**	L.1.2	2-naphthylacetic acid	prep. HPLC, method 1 and workup ($CHCl_3$/aq. $NaHCO_3$ soln)	51%
Ex.111			**Ex.108**	L.1.2	1-naphthylacetic acid	prep. HPLC, method 1	55% (TFA salt)
Ex.112			**Ex.108**	M.1	acetaldehyde	FC (CH_2Cl_2/MeOH/aq.NH_3)	48%
Ex.113			**Ex.109**	L.1.2	1-naphthylacetic acid (3.7 equiv.)	prep. HPLC, method 3	77%
Ex.114			**Ex.109**	L.1.1	valeroyl chloride (2 equiv.)	prep. HPLC, method 3	84%

Table 24b: Examples of Core 06 (**Ex.104-Ex.114**; *continued on the following page*)

No	R^2	R^{54}	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.104-Ex.105: *cf. experimental description*							
Ex.106			C32H47FN6O7	646.4	1.36 (43), 1.42(27), 1.44 (27)	647.5/647.5 647.5	Method 2
Ex.107			C37H44FN5O7	689.3	1.94 (42)/ 1.98 (50)	690.5/690.5	Method 2
Ex.108	NH_2		C27H39FN6O5	546.3	1.37 (50), 1.44 (38)	547.5/547.5	Method 3
Ex.109	NH_2		C32H36FN5O5	589.3	1.55 (96)	590.3	Method 2
Ex.110			C39H47FN6O6	714.4	1.62 (44), 1.66 (52)	715.4/715.4	Method 2
Ex.111			C39H47FN6O6	714.4	1.51 (46), 1.56 (54)	715.5/715.5	Method 2
Ex.112			C31H47FN6O5	602.4	1.14 (57), 1.18 (39)	603.4/603.5	Method 2

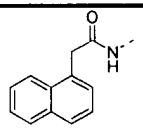
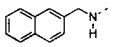
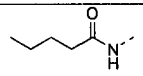
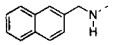
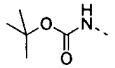
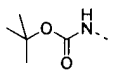
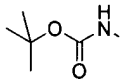
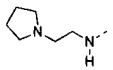
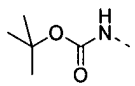
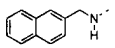
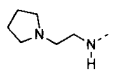
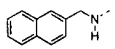
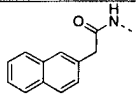
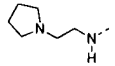
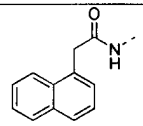
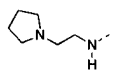
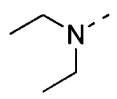
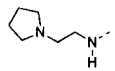
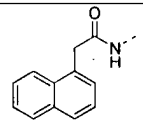
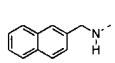
No	R^2	R^{54}	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.113			C44H44FN5O6	757.3	2.15 (52), 2.19 (41)	758.4/758.4	Method 4a
Ex.114			C37H44FN5O6	673.3	2.00 (58), 2.05 (41)	674.4/674.4	Method 4a

Table 24c: Examples of Core 06 (**Ex.104-Ex.114**; *continued on the following page*)

No	R^2	R^{54}	IUPAC name
Ex.104		OCH_2Ph	benzyl (2*R*,11*R*,19a*S*)-2-[(*tert*-butoxycarbonyl)amino]-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxylate
Ex.105		OH	(2*R*,11*R*,19a*S*)-2-[(*tert*-butoxycarbonyl)amino]-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxylic acid
Ex.106			*tert*-butyl *N*-[(2*R*,11*R*,19a*S*)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-11-({[2-(1-pyrrolidinyl)ethyl]amino}carbonyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-2-yl]carbamate

No	R^2	R^{54}	IUPAC name
Ex.107			*tert*-butyl *N*-((2*R*,11*R*,19a*S*)-15-fluoro-7,12-dimethyl-11-{[(2-naphthylmethyl)amino]carbonyl}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecin-2-yl)carbamate
Ex.108	NH_2		(2*R*,11*R*,19a*S*)-2-amino-15-fluoro-7,12-dimethyl-5,8,13-trioxo-*N*-[2-(1-pyrrolidinyl)ethyl]-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.109	NH_2		(2*R*,11*R*,19a*S*)-2-amino-15-fluoro-7,12-dimethyl-*N*-(2-naphthylmethyl)-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.110			(2*R*,11*R*,19a*S*)-15-fluoro-7,12-dimethyl-2-{[2-(2-naphthyl)acetyl]amino}-5,8,13-trioxo-*N*-[2-(1-pyrrolidinyl)ethyl]-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.111			(2*R*,11*R*,19a*S*)-15-fluoro-7,12-dimethyl-2-{[2-(1-naphthyl)acetyl]amino}-5,8,13-trioxo-*N*-[2-(1-pyrrolidinyl)ethyl]-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.112			(2*R*,11*R*,19a*S*)-2-(diethylamino)-15-fluoro-7,12-dimethyl-5,8,13-trioxo-*N*-[2-(1-pyrrolidinyl)ethyl]-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide
Ex.113			(2*R*,11*R*,19a*S*)-15-fluoro-7,12-dimethyl-2-{[2-(1-naphthyl)acetyl]amino}-*N*-(2-naphthylmethyl)-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide

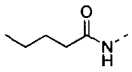
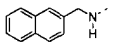
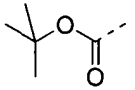
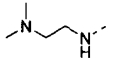
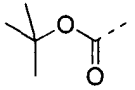
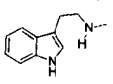
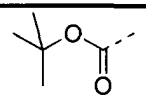
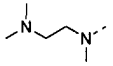
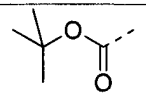
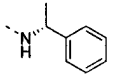
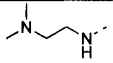
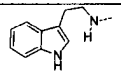
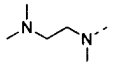
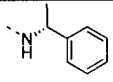
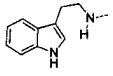
No	R^2	R^{54}	IUPAC name
Ex.114			(2*R*,11*R*,19a*S*)-15-fluoro-7,12-dimethyl-*N*-(2-naphthylmethyl)-5,8,13-trioxo-2-(pentanoylamino)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide

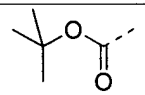
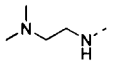
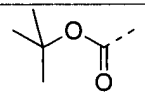
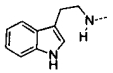
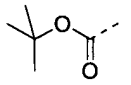
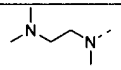
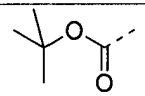
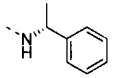
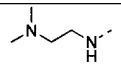
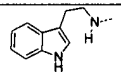
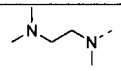
Table 25a: Examples of Core 07 (**Ex.115-Ex.131**; *continued on the following pages*)

No	R^{11}	R^{54}	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.115-Ex.116: *cf. experimental description*							
Ex.117			**Ex.116**	L.2	N,N-dimethyl-ethylenediamine	FC (CH_2Cl_2/MeOH/aq. NH_3)	73%
Ex.118			**Ex.116**	L.2	tryptamine	FC (CH_2Cl_2/MeOH)	98%

No	R^{11}	R^{54}	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.119			**Ex.116**	L.2	N,N,N'-trimethyl-ethylenediamine	FC (CH_2Cl_2/MeOH)	79%
Ex.120			**Ex.116**	L.2	D-(+)-α-methylbenzylamine	prep. HPLC, method 1	70%
Ex.121	H		**Ex.117**	J	HCl-dioxane	crude product	98% (HCl salt)
Ex.122	H		**Ex.118**	J	HCl-dioxane	crude product	98% (HCl salt)
Ex.123	H		**Ex.119**	J	HCl-dioxane THF/CH_2Cl_2 as cosolvent	crude product	quant. (HCl salt)
Ex.124	H		**Ex.120**	J	HCl-dioxane	crude product	95% (HCl salt)
Ex.125			**Ex.122**	L.1.1	acetic anhydride (1.1 equiv.) pyridine/CH_2Cl_2 1:1 (3 mL)	prep. HPLC, method 1	62%

No	R^{11}	R^{54}	Starting material	General Procedure	Reagent	Purification Method	Yield, (isolated salt)
Ex.126			**Ex.121**	L.1.3	N,N-dimethylglycine	prep. HPLC, method 1	39% (TFA salt)
Ex.127			**Ex.121**	L.1.3	3-indoleacetic acid	prep. HPLC, method 1	20% (TFA salt)
Ex.128			**Ex.122**	L.1.3	N,N-dimethylglycine	prep. HPLC, method 1	21% (TFA salt)
Ex.129			**Ex.122**	L.1.3	3-indoleacetic acid	prep. HPLC, method 1	45%
Ex.130			**Ex.123**	L.1.1	acetic anhydride (5 equiv.)	prep. HPLC, method 1	14% (TFA salt)
Ex.131			**Ex.123**	L.1.3	N,N-dimethylglycine	prep. HPLC, method 1	44% (TFA salt)

Table 25b: Examples of Core 07 (**Ex.115-Ex.131**; *continued on the following pages*)

No	R^{11}	R^{54}	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.115-Ex.116: *cf. experimental description*							
Ex.117			C30H45FN6O7	620.3	1.45	621.2	Method 9c
Ex.118			C36H45FN6O7	692.3	1.94	693.1	Method 9c
Ex.119			C31H47FN6O7	634.4	1.48	635.4	Method 9c
Ex.120			C34H44FN5O7	653.3	1.99	653.9	Method 9c
Ex.121	H		C25H37FN6O5	520.3	1.23 (17), 1.29 (80)	521.3/ 521.3	Method 3
Ex.122	H		C31H37FN6O5	592.3	1.40 (89)	593.3	Method 2
Ex.123	H		C26H39FN6O5	534.3	1.32 (96)	535.3	Method 3

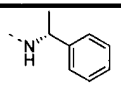
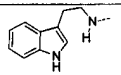
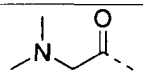
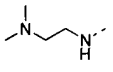
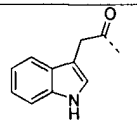
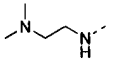
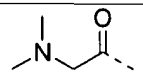
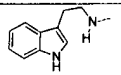
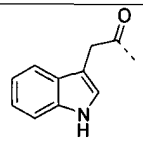
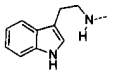
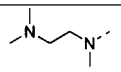
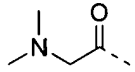
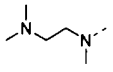
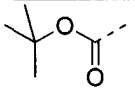
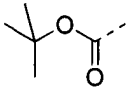
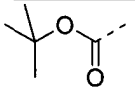
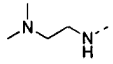
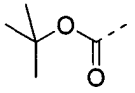
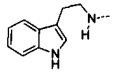
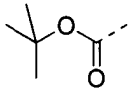
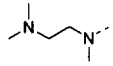
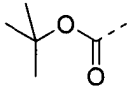
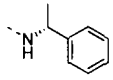
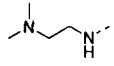
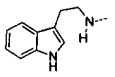
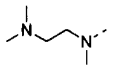
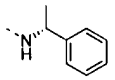
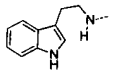
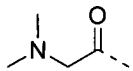
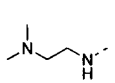
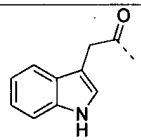
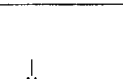
No	R^{11}	R^{54}	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.124	H		C29H36FN5O5	553.3	1.41 (98)	554.3	Method 2
Ex.125			C33H39FN6O6	634.3	1.54 (100)	635.3	Method 2
Ex.126			C29H44FN7O6	605.3	1.37 (83)	606.4	Method 3
Ex.127			C35H44FN7O6	677.3	1.32 (12), 1.38 (84)	678.3/ 678.3	Method 2
Ex.128			C35H44FN7O6	677.3	1.40 (98)	678.4	Method 2
Ex.129			C41H44FN7O6	749.3	1.73 (85)	750.4	Method 2
Ex.130			C28H41FN6O6	576.3	1.10 (98)	577.3	Method 2
Ex.131			C30H46FN7O6	619.4	1.41 (96)	620.4	Method 3

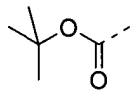
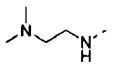
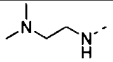
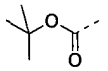
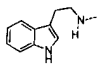
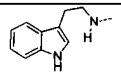
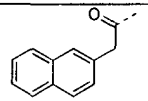
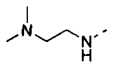
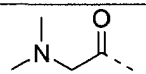
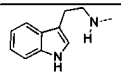
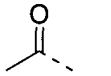
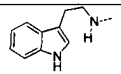
Table 25c: *Examples of Core 07* (**Ex.115-Ex.131**; *continued on the following pages*)

No	R^{11}	R^{54}	IUPAC name
Ex.115		OCH_2Ph	12-benzyl 2-(*tert*-butyl) (12*S*,20a*S*)-16-fluoro-8,13-dimethyl-6,9,14-trioxo-3,4,7,8,9,10,11,12,13,14,20,20a-dodecahydro-6*H*-pyrazino[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-2,12(1*H*)-dicarboxylate
Ex.116		OH	(12*S*,20a*S*)-2-(*tert*-butoxycarbonyl)-16-fluoro-8,13-dimethyl-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6*H*-pyrazino[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxylic acid
Ex.117			*tert*-butyl (12*S*,20a*S*)-12-({[2-(dimethylamino)ethyl]amino}carbonyl)-16-fluoro-8,13-dimethyl-6,9,14-trioxo-3,4,7,8,9,10,11,12,13,14,20,20a-dodecahydro-6*H*-pyrazino[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-2(1*H*)-carboxylate
Ex.118			*tert*-butyl (12*S*,20a*S*)-16-fluoro-12-({[2-(1*H*-indol-3-yl)ethyl]amino}carbonyl)-8,13-dimethyl-6,9,14-trioxo-3,4,7,8,9,10,11,12,13,14,20,20a-dodecahydro-6*H*-pyrazino[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-2(1*H*)-carboxylate
Ex.119			*tert*-butyl (12*S*,20a*S*)-12-{[[2-(dimethylamino)ethyl](methyl)amino]carbonyl}-16-fluoro-8,13-dimethyl-6,9,14-trioxo-3,4,7,8,9,10,11,12,13,14,20,20a-dodecahydro-6*H*-pyrazino[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-2(1*H*)-carboxylate
Ex.120			*tert*-butyl (12*S*,20a*S*)-16-fluoro-8,13-dimethyl-6,9,14-trioxo-12-({[(1*R*)-1-phenylethyl]amino}carbonyl)-3,4,7,8,9,10,11,12,13,14,20,20a-dodecahydro-6*H*-pyrazino[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-2(1*H*)-carboxylate
Ex.121	H		(12*S*,20a*S*)-*N*-[2-(dimethylamino)ethyl]-16-fluoro-8,13-dimethyl-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6*H*-pyrazino[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxamide

No	R^{11}	R^{54}	IUPAC name
Ex.122	H		(12*S*,20a*S*)-16-fluoro-*N*-[2-(1*H*-indol-3-yl)ethyl]-8,13-dimethyl-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6*H*-pyrazino[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxamide
Ex.123	H		(12*S*,20a*S*)-*N*-[2-(dimethylamino)ethyl]-16-fluoro-*N*,8,13-trimethyl-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6*H*-pyrazino[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxamide
Ex.124	H		(12*S*,20a*S*)-16-fluoro-8,13-dimethyl-6,9,14-trioxo-*N*-[(1*R*)-1-phenylethyl]-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-*6*H-pyrazino[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxamide
Ex.125			(12*S*,20a*S*)-2-acetyl-16-fluoro-*N*-[2-(1H-indol-3-yl)ethyl]-8,13-dimethyl-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6*H*-pyrazino[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxamide
Ex.126			(12*S*,20a*S*)-2-[2-(dimethylamino)acetyl]-*N*-[2-(dimethylamino)ethyl]-16-fluoro-8,13-dimethyl-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6*H*-pyrazino[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxamide
Ex.127			(12*S*,20a*S*)-N-[2-(dimethylamino)ethyl]-16-fluoro-2-[2-(1*H*-indol-3-yl)acetyl]-8,13-dimethyl-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6*H*-pyrazino[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxamide

No	R^{11}	R^{54}	IUPAC name
Ex.128			(12*S*,20a*S*)-2-[2-(dimethylamino)acetyl]-16-fluoro-*N*-[2-(1*H*-indol-3-yl)ethyl]-8,13-dimethyl-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6*H*-pyrazino[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxamide
Ex.129			(12*S*,20a*S*)-16-fluoro-2-[2-(1H-indol-3-yl)acetyl]-*N*-[2-(1*H*-indol-3-yl)ethyl]-8,13-dimethyl-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6*H*-pyrazino[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxamide
Ex.130			(12*S*,20a*S*)-2-acetyl-*N*-[2-(dimethylamino)ethyl]-16-fluoro-*N*,8,13-trimethyl-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6*H*-pyrazino[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxamide
Ex.131			(12*S*,20a*S*)-2-[2-(dimethylamino)acetyl]-*N*-[2-(dimethylamino)ethyl]-16-fluoro-*N*,8,13-trimethyl-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6*H*-pyrazino[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxamide

Table 26a: *Examples of Core 08 (**Ex.132-Ex.141**; continued on the following page)*

No	R^{11}	R^{54}	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.132-Ex.133: *cf. experimental description*							
Ex.134			**Ex.133**	L.2	N,N-dimethylethylenediamine	FC (CH_2Cl_2/MeOH/aq. NH_3)	80%
Ex.135	H		**Ex.134**	J	HCl-dioxane	crude product	100% (HCl salt)
Ex.136			**Ex.133**	L.2	tryptamine	FC (CH_2Cl_2/MeOH /aq.NH_3)	89%
Ex.137	H		**Ex.136**	J	HCl-dioxane	crude product	100% (HCl salt)
Ex.138			**Ex.135**	L.1.2	2-naphthylacetic acid	prep. HPLC, method 1	71% (TFA salt)
Ex.139			**Ex.137**	L.1.2	N,N-dimethyl glycine	prep. HPLC, method 1	40% (TFA salt)
Ex.140			**Ex.137**	L.1.1	acetic anhydride (5 equiv.)	prep. HPLC, method 1	50%

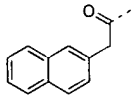
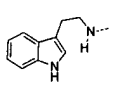
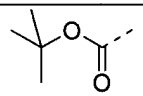
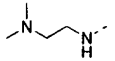
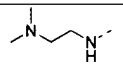
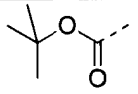
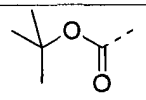
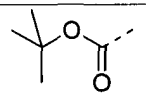
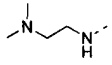
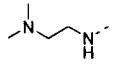
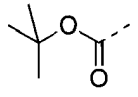
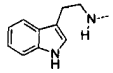
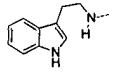
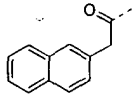
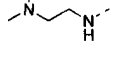
No	R^{11}	R^{54}	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.141			**Ex.137**	L.1.2	2-naphthylacetic acid	prep. HPLC, method 3, then FC (EtOAc/MeOH)	39%

Table 26b: Examples of Core 08 (**Ex.132-Ex.141**; *continued on the following page*)

No	R^{11}	R^{54}	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.132-Ex.133: *cf. experimental description*							
Ex.134			C30H45FN6O7	620.3	1.40 (20), 1.45 (77)	621.5/621.5	Method 2
Ex.135	H		C25H37FN6O5	520.3	0.94 (85)	521.4	Method 2

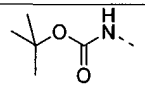
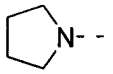
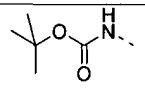
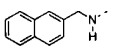
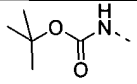
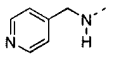
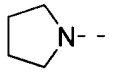
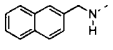
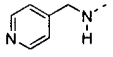
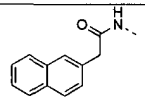
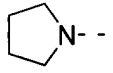
No	R^{11}	R^{54}	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.136			C36H45FN6O7	692.3	1.83 (91)	693.5	Method 2
Ex.137	H		C31H37FN6O5	592.3	1.41 (80)	593.4	Method 2
Ex.138			C37H45FN6O6	688.3	1.46 (15), 1.51 (84)	689.5/ 689.5	Method 2
Ex.139			C35H44FN7O6	677.3	1.43 (92)	678.5	Method 2
Ex.140			C33H39FN6O6	634.3	1.57 (97)	635.5	Method 2
Ex.141			C43H45FN6O6	760.3	1.86 (95)	761.5	Method 2

Table 26c: Examples of Core 08 (**Ex.132-Ex.141**; *continued on the following page*)

No	R^{11}	R^{54}	IUPAC name
Ex.132		OCH_2Ph	12-benzyl 2-(*tert*-butyl) (12*R*,20a*R*)-16-fluoro-8,13-dimethyl-6,9,14-trioxo-3,4,7,8,9,10,11,12,13,14,20,20a-dodecahydro-6*H*-pyrazino[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-2,12(1*H*)-dicarboxylate
Ex.133		OH	(12*R*,20a*R*)-2-(*tert*-butoxycarbonyl)-16-fluoro-8,13-dimethyl-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6*H*-pyrazino[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxylic acid
Ex.134			*tert*-butyl (12*R*,20a*R*)-12-({[2-(dimethylamino)ethyl]amino}carbonyl)-16-fluoro-8,13-dimethyl-6,9,14-trioxo-3,4,7,8,9,10,11,12,13,14,20,20a-dodecahydro-6*H*-pyrazino[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-2(1H)-carboxylate
Ex.135	H		(12*R*,20a*R*)-*N*-[2-(dimethylamino)ethyl]-16-fluoro-8,13-dimethyl-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6*H*-pyrazino[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxamide
Ex.136			*tert*-butyl (12*R*,20a*R*)-16-fluoro-12-({[2-(1*H*-indol-3-yl)ethyl]amino}carbonyl)-8,13-dimethyl-6,9,14-trioxo-3,4,7,8,9,10,11,12,13,14,20,20a-dodecahydro-6H-pyrazino[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-2(1*H*)-carboxylate
Ex.137	H		(12*R*,20a*R*)-16-fluoro-*N*-[2-(1H-indol-3-yl)ethyl]-8,13-dimethyl-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6*H*-pyrazino[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxamide
Ex.138			(12*R*,20a*R*)-*N*-[2-(dimethylamino)ethyl]-16-fluoro-8,13-dimethyl-2-[2-(2-naphthyl)acetyl]-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6*H*-pyrazino[2,1-c][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxamide

No	R^{11}	R^{54}	IUPAC name
Ex.139			(12*R*,20a*R*)-2-[2-(dimethylamino)acetyl]-16-fluoro-*N*-[2-(1*H*-indol-3-yl)ethyl]-8,13-dimethyl-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6*H*-pyrazino[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxamide
Ex.140			(12*R*,20a*R*)-2-acetyl-16-fluoro-*N*-[2-(1*H*-indol-3-yl)ethyl]-8,13-dimethyl-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6*H*-pyrazino[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxamide
Ex.141			(12*R*,20a*R*)-16-fluoro-N-[2-(1*H*-indol-3-yl)ethyl]-8,13-dimethyl-2-[2-(2-naphthyl)acetyl]-6,9,14-trioxo-1,2,3,4,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-6*H*-pyrazino[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-12-carboxamide

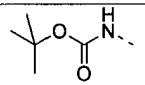
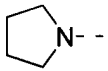
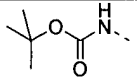
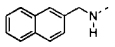
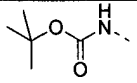
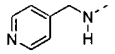
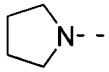
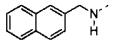
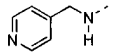
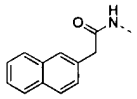
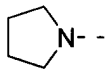
Table 27a: *Examples of Core 09 (**Ex.142-Ex.163**; continued on the following pages)*

No	R^2	R^{54}	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.142-Ex.143: *cf. experimental description*							
Ex.144			**Ex.143**	L.2	pyrrolidine	FC (CH_2Cl_2/MeOH)	91%
Ex.145			**Ex.143**	L.2	2-naphthylmethylamine	FC (CH_2Cl_2/MeOH)	72%
Ex.146			**Ex.143**	L.2	4-(aminomethyl)pyridine	FC (CH_2Cl_2/MeOH)	87%
Ex.147	NH_2		**Ex.144**	J	HCl-dioxane	crude product	100% (HCl salt)
Ex.148	NH_2		**Ex.145**	J	HCl-dioxane	crude product	97% (HCl salt)
Ex.149	NH_2		**Ex.146**	J	HCl-dioxane	crude product	87% (HCl salt)
Ex.150			**Ex.147**	L.1.2	2-naphthylacetic acid	Prep. HPLC, method 3	72%

No	R^2	R^{54}	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.151			**Ex.147**	L.1.1	valeroyl chloride (2.0 equiv.)	Prep. HPLC, method 3	73%
Ex.152			**Ex.147**	L.1.2	1-pyrriolidinacetic acid	Prep. HPLC, method 2	26%
Ex.153			**Ex.148**	L.1.2	2-naphthylacetic acid	Prep. HPLC, method 3	68%
Ex.154			**Ex.148**	L.1.1	valeroyl chloride (2.0 equiv.)	Prep. HPLC, method 3	76%
Ex.155			**Ex.148**	L.1.1	acetic anhydride (5.0 equiv.)	Prep. HPLC, method 3	72%
Ex.156			**Ex.148**	L.1.1	succinic anhydride (1.05 equiv.)	Prep. HPLC, method 2	69% (NH_4^+ salt)
Ex.157			**Ex.149**	L.1.2	2-naphthylacetic acid (1.7 equiv.)	Prep. HPLC, method 2	24%
Ex.158			**Ex.149**	L.1.1	valeroyl chloride (2.0 equiv.)	Prep. HPLC, method 2	42%

No	R^2	R^{54}	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.159			**Ex.149**	L.1.2	1-pyrriolidinacetic acid (2.5 equiv.)	Prep. HPLC, method 2	55%
Ex.160			**Ex.149**	L.1.1	succinic anhydride (1.05 equiv.)	Prep. HPLC, method 2	69% (NH_4^+ salt)
Ex.161			**Ex.147**	L.1.2	3-(pyridine-4-yl)propanoic acid	Prep. HPLC, method 2	53%
Ex.162			**Ex.148**	L.1.2	3-(pyridine-4-yl)propanoic acid	Prep. HPLC, method 2	48%
Ex.163			**Ex.149**	L.1.2	3-(pyridine-4-yl)propanoic acid (1.7 equiv.)	Prep. HPLC, method 2	63%

Table 27b: Examples of Core 09 (**Ex.142-Ex.163**; *continued on the following pages*)

No	R^2	R^{54}	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.142-Ex.143: *cf. experimental description*							
Ex.144			C31H44FN5O7	617.3	1.66 (90)	618.4	Method 2
Ex.145			C38H46FN5O7	703.3	1.90 (90)	704.5	Method 2
Ex.146			C33H43FN6O7	654.3	1.39 (92)	655.5	Method 2
Ex.147	NH_2		C26H36FN5O5	517.3	1.36 (79)	518.4	Method 3
Ex.148	NH_2		C33H38FN5O5	603.3	1.53 (98)	604.4	Method 2
Ex.149	NH_2		C28H35FN6O5	554.3	1.25 (8), 1.31 (85)	555.4	Method 3
Ex.150			C38H44FN5O6	685.3	1.72 (98)	686.5	Method 2

No	R^2	R^{54}	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.151			C31H44FN5O6	601.3	1.55 (98)	602.5	Method 2
Ex.152			C32H45FN6O6	628.3	1.52 (94)	629.5	Method 3
Ex.153			C45H46FN5O6	771.3	1.94 (96)	772.5	Method 2
Ex.154			C38H46FN5O6	687.3	1.82 (97)	688.5	Method 2
Ex.155			C35H40FN5O6	645.3	1.67 (99)	646.4	Method 2
Ex.156			C37H42FN5O8	703.3	1.65 (99)	704.5	Method 2
Ex.157			C40H43FN6O6	722.3	1.48 (94)	723.8	Method 2
Ex.158			C33H43FN6O6	638.3	1.50 (95)	639.5	Method 3

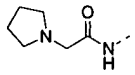
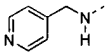
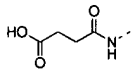
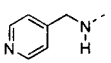
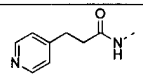
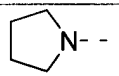
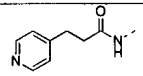
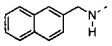
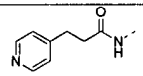
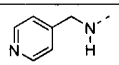
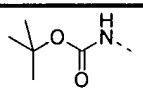
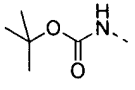
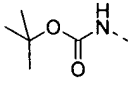
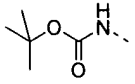
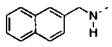
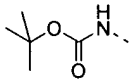
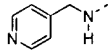
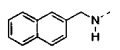
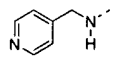
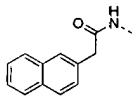
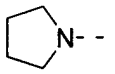
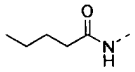
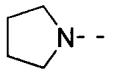
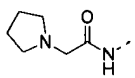
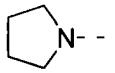
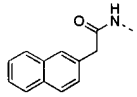
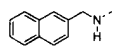
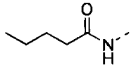
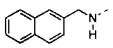
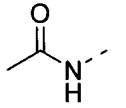
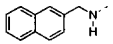
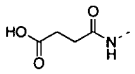
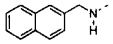
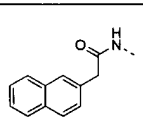
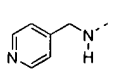
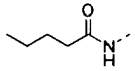
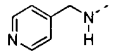
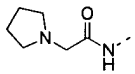
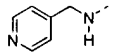
No	R^2	R^{54}	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.159			C34H44FN7O6	665.3	1.47 (96)	666.5	Method 3
Ex.160			C32H39FN6O8	654.3	1.04 (96)	655.4	Method 3
Ex.161			C34H43FN6O6	650.3	1.47 (91)	651.5	Method 3
Ex.162			C41H45FN6O6	736.3	1.55 (96)	737.6	Method 2
Ex.163			C36H42FN7O6	687.3	1.42 (99)	688.5	Method 3

Table 27c: Examples of Core 09 (**Ex.142-Ex.163**; *continued on the following pages*)

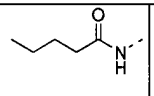
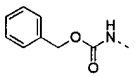
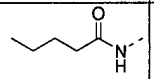
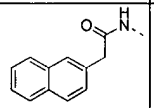
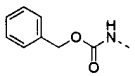
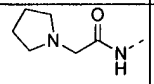
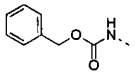
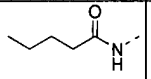
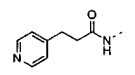
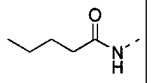
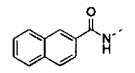
No	R^2	R^{54}	IUPAC name
Ex.142		OCH_2Ph	benzyl (2*R*,12*S*,20a*S*)-2-[(*tert*-butoxycarbonyl)amino]-16-fluoro-8,13-dimethyl-5,9,14-trioxo-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1*H*-pyrrolo[2,1-*c*][1,4,8,13]benzoxatriazacyclohexadecine-12-carboxylate
Ex.143		OH	(2*R*,12*S*,20a*S*)-2-[(*tert*-butoxycarbonyl)amino]-16-fluoro-8,13-dimethyl-5,9,14-trioxo-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1*H*-pyrrolo[2,1-*c*][1,4,8,13]benzoxatriazacyclohexadecine-12-carboxylic acid
Ex.144			*tert*-butyl *N*-[(2*R*,12*S*,20a*S*)-16-fluoro-8,13-dimethyl-5,9,14-trioxo-12-(1-pyrrolidinylcarbonyl)-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1*H*-pyrrolo[2,1-*c*][1,4,8,13]benzoxatriazacyclohexadecin-2-yl]carbamate
Ex.145			*tert*-butyl *N*-((2*R*,12*S*,20a*S*)-16-fluoro-8,13-dimethyl-12-{[(2-naphthylmethyl)amino]carbonyl}-5,9,14-trioxo-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1*H*-pyrrolo[2,1-*c*][1,4,8,13]benzoxatriazacyclohexadecin-2-yl)carbamate
Ex.146			*tert*-butyl *N*-((2*R*,12*S*,20a*S*)-16-fluoro-8,13-dimethyl-5,9,14-trioxo-12-{[(4-pyridinylmethyl)amino]carbonyl}-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1*H*-pyrrolo[2,1-*c*][1,4,8,13]benzoxatriazacyclohexadecin-2-yl)carbamate
Ex.147	NH_2		(2*R*,12*S*,20a*S*)-2-amino-16-fluoro-8,13-dimethyl-12-(1-pyrrolidinylcarbonyl)-2,3,7,8,10,11,12,13,20,20a-decahydro-1*H*-pyrrolo[2,1-*c*][1,4,8,13]benzoxatriazacyclohexadecine-5,9,14(6*H*)-trione

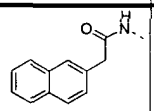
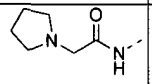
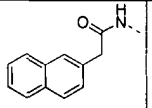
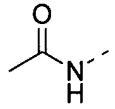
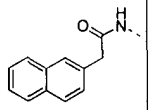
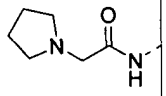
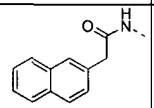
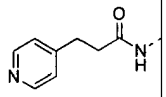
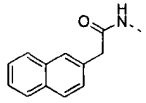
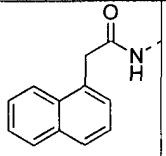
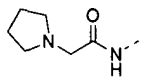
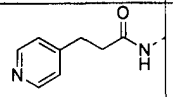
No	R^2	R^{54}	IUPAC name
Ex.148	NH_2		(2*R*,12*S*,20a*S*)-2-amino-16-fluoro-8,13-dimethyl-N-(2-naphthylmethyl)-5,9,14-trioxo-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1*H*-pyrrolo[2,1-*c*][1,4,8,13]benzoxatriazacyclohexadecine-12-carboxamide
Ex.149	NH_2		(2*R*,12*S*,20a*S*)-2-amino-16-fluoro-8,13-dimethyl-5,9,14-trioxo-*N*-(4-pyridinylmethyl)-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1*H*-pyrrolo[2,1-*c*][1,4,8,13]benzoxatriazacyclohexadecine-12-carboxamide
Ex.150			*N*-[(2*R*,12*S*,20a*S*)-16-fluoro-8,13-dimethyl-5,9,14-trioxo-12-(1-pyrrolidinylcarbonyl)-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1*H*-pyrrolo[2,1-*c*][1,4,8,13]benzoxatriazacyclohexadecin-2-yl]-2-(2-naphthyl)acetamide
Ex.151			*N*-[(2*R*,12*S*,20a*S*)-16-fluoro-8,13-dimethyl-5,9,14-trioxo-12-(1-pyrrolidinylcarbonyl)-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1*H*-pyrrolo[2,1-*c*][1,4,8,13]benzoxatriazacyclohexadecin-2-yl]pentanamide
Ex.152			*N*-[(2*R*,12*S*,20a*S*)-16-fluoro-8,13-dimethyl-5,9,14-trioxo-12-(1-pyrrolidinylcarbonyl)-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1*H*-pyrrolo[2,1-*c*][1,4,8,13]benzoxatriazacyclohexadecin-2-yl]-2-(1-pyrrolidinyl)acetamide
Ex.153			(2*R*,12*S*,20a*S*)-16-fluoro-8,13-dimethyl-2-{[2-(2-naphthyl)acetyl]amino}-*N*-(2-naphthylmethyl)-5,9,14-trioxo-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1*H*-pyrrolo[2,1-*c*][1,4,8,13]benzoxatriazacyclohexadecine-12-carboxamide

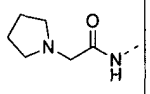
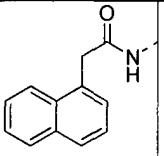
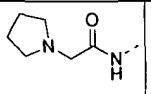
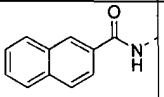
No	R^2	R^{54}	IUPAC name
Ex.154			(2*R*,12*S*,20a*S*)-16-fluoro-8,13-dimethyl-*N*-(2-naphthylmethyl)-5,9,14-trioxo-2-(pentanoylamino)-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1*H*-pyrrolo[2,1-*c*][1,4,8,13]benzoxatriazacyclohexadecine-12-carboxamide
Ex.155			(2*R*,12*S*,20a*S*)-2-(acetylamino)-16-fluoro-8,13-dimethyl-*N*-(2-naphthylmethyl)-5,9,14-trioxo-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1*H*-pyrrolo[2,1-c][1,4,8,13]benzoxatriazacyclohexadecine-12-carboxamide
Ex.156			4-[((2*R*,12*S*,20a*S*)-16-fluoro-8,13-dimethyl-12-{[(2-naphthylmethyl)amino]carbonyl}-5,9,14-trioxo-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1*H*-pyrrolo[2,1-*c*][1,4,8,13]benzoxatriazacyclohexadecin-2-yl)amino]-4-oxobutanoic acid
Ex.157			(2*R*,12*S*,20a*S*)-16-fluoro-8,13-dimethyl-2-{[2-(2-naphthyl)acetyl]amino}-5,9,14-trioxo-*N*-(4-pyridinylmethyl)-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1*H*-pyrrolo[2,1-*c*][1,4,8,13]benzoxatriazacyclohexadecine-12-carboxamide
Ex.158			(2*R*,12*S*,20a*S*)-16-fluoro-8,13-dimethyl-5,9,14-trioxo-2-(pentanoylamino)-*N*-(4-pyridinylmethyl)-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1*H*-pyrrolo[2,1-*c*][1,4,8,13]benzoxatriazacyclohexadecine-12-carboxamide
Ex.159			(2*R*,12*S*,20a*S*)-16-fluoro-8,13-dimethyl-5,9,14-trioxo-*N*-(4-pyridinylmethyl)-2-{[2-(1-pyrrolidinyl)acetyl]amino}-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-*1H*-pyrrolo[2,1-c][1,4,8,13]benzoxatriazacyclohexadecine-12-carboxamide

No	R^2	R^{54}	IUPAC name
Ex.160			4-[((2*R*,12*S*,20a*S*)-16-fluoro-8,13-dimethyl-5,9,14-trioxo-12-{[(4-pyridinylmethyl)amino]carbonyl}-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1*H*-pyrrolo[2,1-*c*][1,4,8,13]benzoxatriazacyclohexadecin-2-yl)amino]-4-oxobutanoic acid
Ex.161			N-[(2*R*,12*S*,20a*S*)-16-fluoro-8,13-dimethyl-5,9,14-trioxo-12-(1-pyrrolidinylcarbonyl)-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1*H*-pyrrolo[2,1-*c*][1,4,8,13]benzoxatriazacyclohexadecin-2-yl]-3-(4-pyridinyl)propanamide
Ex.162			(2*R*,12*S*,20a*S*)-16-fluoro-8,13-dimethyl-*N*-(2-naphthylmethyl)-5,9,14-trioxo-2-{[3-(4-pyridinyl)propanoyl]amino}-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1*H*-pyrrolo[2,1-c][1,4,8,13]benzoxatriazacyclohexadecine-12-carboxamide
Ex.163			(2*R*,12*S*,20a*S*)-16-fluoro-8,13-dimethyl-5,9,14-trioxo-*N*-(4-pyridinylmethyl)-2-{[3-(4-pyridinyl)propanoyl]amino}-2,3,5,6,7,8,9,10,11,12,13,14,20,20a-tetradecahydro-1*H*-pyrrolo[2,1-*c*][1,4,8,13]benzoxatriazacyclohexadecine-12-carboxamide

Table 28a: Examples of Core 10 (**Ex.164-Ex.180**; *continued on the following pages*)

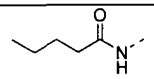
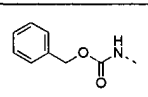
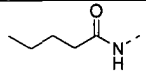
No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.164-Ex.165: *cf. experimental description*							
Ex.166			**Ex.165**	L.1.1	valeroyl chloride (2.0 equiv.)	FC (EtOAc/MeOH)	ca.70%
Ex.167		NH_2	**Ex.166**	K.1	H_2, $Pd(OH)_2$-C	crude product	quant.
Ex.168			**Ex.165**	L.1.3	2-naphthylacetic acid	FC (EtOAc)	68%
Ex.169			**Ex.165**	L.1.3	1-pyrrolidinacetic acid	FC (EtOAc/MeOH)	76%
Ex.170			**Ex.167**	L.1.2	3-(pyridine-4-yl)propanoic acid	FC (CH_2Cl_2/MeOH)	78%
Ex.171			**Ex.167**	L.1.1	2-naphthoyl chloride (2.6 equiv.)	Prep. HPLC, method 3	42%

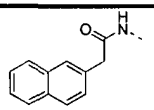
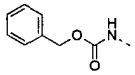
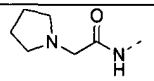
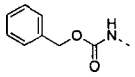
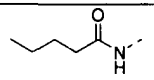
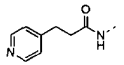
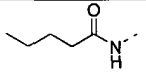
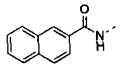
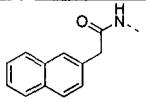
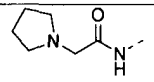
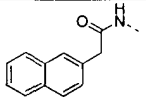
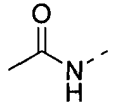
No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.172		NH_2	**Ex.168**	K.1	H_2, $Pd(OH)_2$-C	crude product	97%
Ex.173		NH_2	**Ex.169**	K.1	H_2, $Pd(OH)_2$-C	crude product	96%
Ex.174			**Ex.172**	L.1.1	acetic anhydride (5 equiv.)	Prep. HPLC, method 3	97%
Ex.175			**Ex.172**	L.1.2	1-pyrrolidinacetic acid (2.2 equiv.)	Prep. HPLC, method 3	58%
Ex.176			**Ex.172**	L.1.2	3-(pyridine-4-yl)propanoic acid	Prep. HPLC, method 3	71%
Ex.177			**Ex.172**	L.1.2*)	1-naphthylacetic acid	Prep. HPLC, method 3	68%
Ex.178			**Ex.173**	L.1.2	3-(pyridine-4-yl)propanoic acid	Prep. HPLC, method 2	48%

No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.179			**Ex.173**	L.1.2*)	1-naphthylacetic acid	Prep. HPLC, method 3	84%
Ex.180			**Ex.173**	L.1.1*)	2-naphthoyl chloride (1.5 equiv.)	Prep. HPLC, method 3	78%

*) The treatment with (polystyrylmethyl)trimethylammonium bicarbonate was replaced by an aqueous workup ($CHCl_3$, sat. aq. $NaHCO_3$ soln)

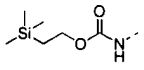
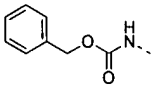
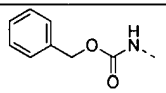
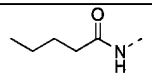
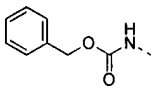
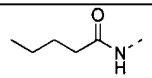
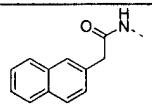
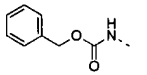
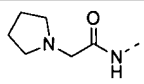
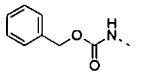
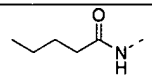
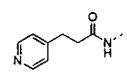
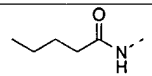
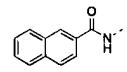
Table 28b: Examples of Core 10 (**Ex.164-Ex.180;** *continued on the following pages*)

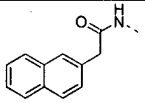
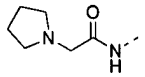
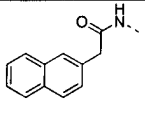
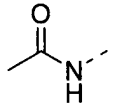
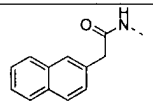
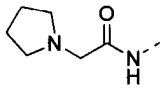
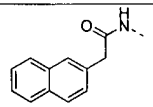
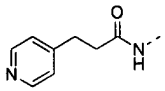
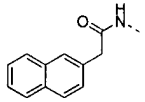
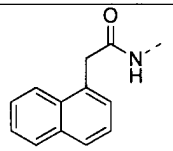
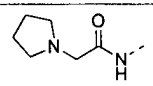
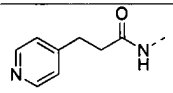
No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.164-Ex.165: *cf. experimental description*							
Ex.166			C30H38N4O6	550.3	1.96 (99)	551.3	Method 4a
Ex.167		NH_2	C22H32N4O4	416.2	1.4 (99)	417.3	Method 4a

No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.168			C37H38N4O6	634.3	2.2 (98)	635.3	Method 4a
Ex.169			C31H39N5O6	577.3	1.57 (99)	578.4	Method 4a
Ex.170			C30H39N5O5	549.3	1.47 (97)	550.4	Method 4a
Ex.171			C33H38N4O5	570.3	2.1 (100)	571.3	Method 4a
Ex.172		NH_2	C29H32N4O4	500.2	1.60 (91)	501.3	Method 4a
Ex.173		NH_2	C23H33N5O4	443.3	1.48 (99)	444.2	Method 5a
Ex.174			C31H34N4O5	542.3	1.82 (99)	543.2	Method 4a

No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.175			C35H41N5O5	611.3	1.69 (96)	612.2	Method 4a
Ex.176			C37H39N5O5	633.3	1.68 (99)	634.3	Method 4a
Ex.177			C41H40N4O5	668.3	2.24 (92)	669.3	Method 4a
Ex.178			C31H40N6O5	576.3	1.07 (98)	577.3	Method 4a
Ex.179			C35H41N5O5	611.3	1.69 (93)	612.3	Method 4a
Ex.180			C34H39N5O5	597.3	1.69 (97)	597.8	Method 4a

Table 28c: Examples of Core 10 (**Ex.164-Ex.180**; *continued on the following pages*)

No	R^2	R^5	IUPAC name
Ex.164			benzyl *N*-[(4*S*,6*S*,10*S*)-13-methyl-9,14-dioxo-6-({[2-(trimethylsilyl)ethoxy]carbonyl}amino)-2-oxa-8,13-diazatricyclo[13.3.1.$0^{4,8}$]nonadeca-1(19),15,17-trien-10-yl]carbamate
Ex.165	NH_2		benzyl *N*-[(4*S*,6*S*,10*S*)-6-amino-13-methyl-9,14-dioxo-2-oxa-8,13-diazatricyclo[13.3.1.$0^{4,8}$]nonadeca-1(19),15,17-trien-10-yl]carbamate
Ex.166			benzyl *N*-[(4*S*,6*S*,10*S*)-13-methyl-9,14-dioxo-6-(pentanoylamino)-2-oxa-8,13-diazatricyclo[13.3.1.$0^{4,8}$]nonadeca-1(19),15,17-trien-10-yl]carbamate
Ex.167		NH_2	*N*-[(4*S*,6*S*,10*S*)-10-amino-13-methyl-9,14-dioxo-2-oxa-8,13-diazatricyclo[13.3.1.$0^{4,8}$]nonadeca-1(19),15,17-trien-6-yl]pentanamide
Ex.168			benzyl *N*-[(4*S*,6*S*,10*S*)-13-methyl-6-{[2-(2-naphthyl)acetyl]amino}-9,14-dioxo-2-oxa-8,13-diazatricyclo[13.3.1.$0^{4,8}$]nonadeca-1(19),15,17-trien-10-yl]carbamate
Ex.169			benzyl *N*-[(4*S*,6*S*,10*S*)-13-methyl-9,14-dioxo-6-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,13-diazatricyclo[13.3.1.$0^{4,8}$]nonadeca-1(19),15,17-trien-10-yl]carbamate
Ex.170			*N*-[(4*S*,6*S*,10*S*)-13-methyl-9,14-dioxo-10-{[3-(4-pyridinyl)propanoyl]amino}-2-oxa-8,13-diazatricyclo[13.3.1.$0^{4,8}$]nonadeca-1(19),15,17-trien-6-yl]pentanamide
Ex.171			*N*-[(4*S*,6*S*,10*S*)-13-methyl-9,14-dioxo-6-(pentanoylamino)-2-oxa-8,13-diazatricyclo[13.3.1.$0^{4,8}$]nonadeca-1(19),15,17-trien-10-yl]-2-naphthamide

No	R^2	R^5	IUPAC name
Ex.172		NH_2	*N*-[(4*S*,6*S*,10*S*)-10-amino-13-methyl-9,14-dioxo-2-oxa-8,13-diazatricyclo[13.3.1.$0^{4,8}$]nonadeca-1(19),15,17-trien-6-yl]-2-(2-naphthyl)acetamide
Ex.173		NH_2	*N*-[(4*S*,6*S*,10*S*)-10-amino-13-methyl-9,14-dioxo-2-oxa-8,13-diazatricyclo[13.3.1.$0^{4,8}$]nonadeca-1(19),15,17-trien-6-yl]-2-(1-pyrrolidinyl)acetamide
Ex.174			*N*-[(4*S*,6*S*,10*S*)-10-(acetylamino)-13-methyl-9,14-dioxo-2-oxa-8,13-diazatricyclo[13.3.1.$0^{4,8}$]nonadeca-1(19),15,17-trien-6-yl]-2-(2-naphthyl)acetamide
Ex.175			*N*-[(4*S*,6*S*,10*S*)-13-methyl-9,14-dioxo-10-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,13-diazatricyclo[13.3.1.$0^{4,8}$]nonadeca-1(19),15,17-trien-6-yl]-2-(2-naphthyl)acetamide
Ex.176			*N*-[(4*S*,6*S*,10*S*)-13-methyl-6-{[2-(2-naphthyl)acetyl]amino}-9,14-dioxo-2-oxa-8,13-diazatricyclo[13.3.1.$0^{4,8}$]nonadeca-1(19),15,17-trien-10-yl]-3-(4-pyridinyl)propanamide
Ex.177			*N*-[(4*S*,6*S*,10*S*)-13-methyl-6-{[2-(2-naphthyl)acetyl]amino}-9,14-dioxo-2-oxa-8,13-diazatricyclo[13.3.1.$0^{4,8}$]nonadeca-1(19),15,17-trien-10-yl]-2-(1-naphthyl)acetamide
Ex.178			*N*-[(4*S*,6*S*,10*S*)-13-methyl-9,14-dioxo-6-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,13-diazatricyclo[13.3.1.$0^{4,8}$]nonadeca-1(19),15,17-trien-10-yl]-3-(4-pyridinyl)propanamide

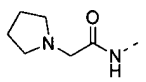
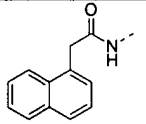
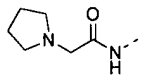
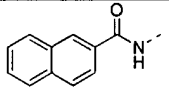
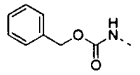
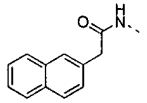
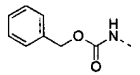
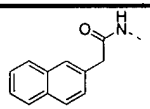
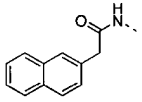
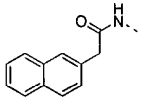
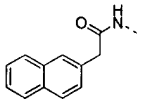
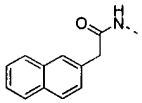
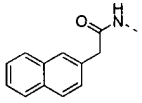
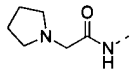
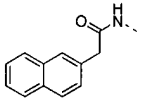
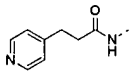
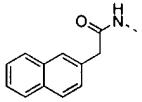
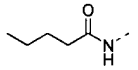
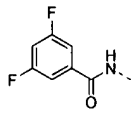
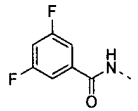
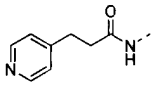
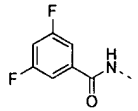
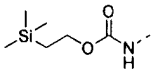
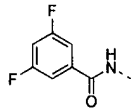
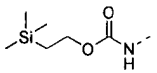
No	R^2	R^5	IUPAC name
Ex.179			*N*-[(4*S*,6*S*,10*S*)-13-methyl-9,14-dioxo-6-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,13-diazatricyclo[13.3.1.$0^{4,8}$]nonadeca-1(19),15,17-trien-10-yl]-2-(1-naphthyl)acetamide
Ex.180			*N*-[(4*S*,6*S*,10*S*)-13-methyl-9,14-dioxo-6-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,13-diazatricyclo[13.3.1.$0^{4,8}$]nonadeca-1(19),15,17-trien-10-yl]-2-naphthamide

Table 29.1.a: Examples of Core 11a (**Ex.181-Ex.195, Ex.504-Ex.559 and Ex.594**; *continued on the following pages*)

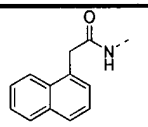
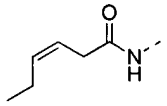
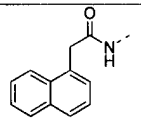
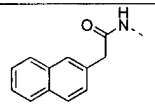
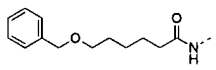
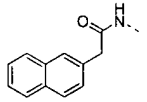
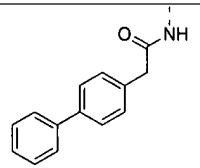
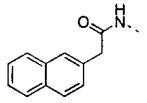
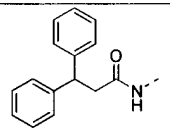
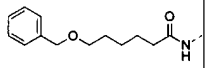
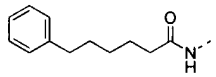
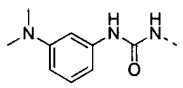
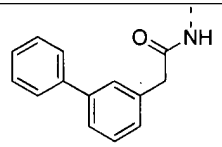
No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.181-Ex.182: *cf. experimental description*							
Ex.183			**Ex.182**	L.1.1	acetic anhydride (5 equiv.)	FC (CH_2Cl_2/MeOH)	75%
Ex.184			**Ex.182**	L.1.3	2-naphthyl-acetic acid (1.2 equiv.)	FC (EtOAc, then CH_2Cl_2/MeOH)	94%

No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.185		NH_2	**Ex.184**	K.1	H_2, $Pd(OH)_2$-C	crude product	99%
Ex.186			**Ex.185**	L.1.3	2-naphthyl-acetic acid (1.2 equiv.)	prep. HPLC, method 3	60%
Ex.186			**Ex.594**	S	2-naphthyl-acetic acid	prep. HPLC, method 3	32%
Ex.187			**Ex.185**	L.1.3	pyrrolidin-1-acetic acid (1.2 equiv.)	prep. HPLC, method 3 then prep. HPLC, method 1	38% (TFA salt)
Ex.188			**Ex.185**	L.1.3	3-(pyridine-4-yl)propanoic acid (1.2 equiv.)	prep. HPLC, method 3 then prep. HPLC, method 1	32% (TFA salt)
Ex.189			**Ex.185**	L.1.1	valeroyl chloride (2 equiv.)	prep. HPLC, method 3	52%

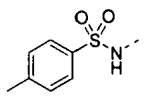
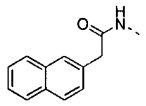
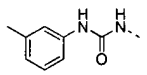
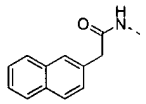
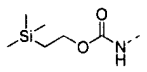
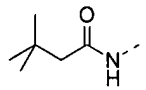
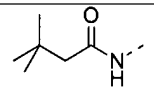
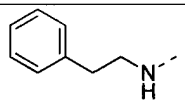
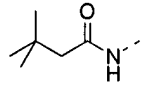
No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.190	NH_2		**Ex.193**	I.2	TBAF (4 equiv.) in THF	crude product, contaminated with TBAF	ca 70%
Ex.191			**Ex.190**	L.1.1	Acetic anhydride (10 equiv.) Pyridine/CH_2Cl_2 1:1 (3 mL)	prep. HPLC, method 3	62%
Ex.192			**Ex.190**	L.1.3	3-(pyridine-4-yl)propanoic acid (1.2 equiv.)	prep. HPLC, method 3	63%
Ex.193			**Ex.194**	L.1.1	3,5-difluoro-benzoyl chloride (2 equiv.)	FC (EtOAc)	85%
Ex.194		NH_2	**Ex.181**	K.1	H_2, $Pd(OH)_2$-C	crude product	quant.

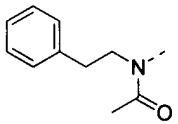
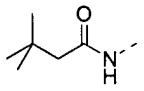
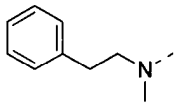
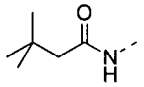
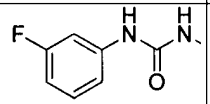
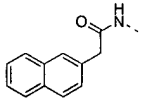
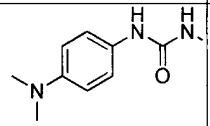
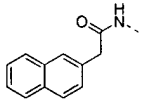
No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.195			**Ex.190**	L.1.1	benzoyl chloride (2 equiv.)	prep. HPLC, method 3	78%
Ex.504		$CH_3(CH_2)_8CONH$	**140**	S	cf. detailed description	prep. HPLC method 1	26%
Ex.505			**140**	S	cf. detailed description	prep. HPLC method 3	33%
Ex.506			**140**	S	cf. detailed description	prep. HPLC method 3	45%
Ex.507			**140**	S	cf. detailed description	prep. HPLC method 3	48%
Ex.508			**Ex.554**	L.1.3	cf. detailed description	prep. HPLC method 3	57%
Ex.509		$CH_3(CH_2)_8CONH$	**140**	S	cf. detailed description	prep. HPLC method 3	48%
Ex.510		$CH_3(CH_2)_8CONH$	**140**	S	cf. detailed description	prep. HPLC method 3	20%

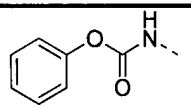
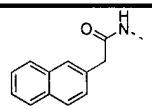
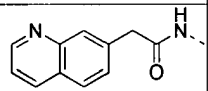
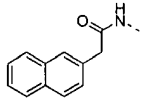
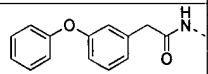
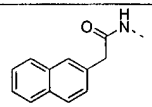
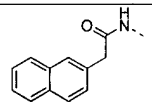
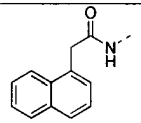
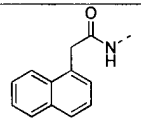
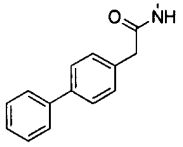
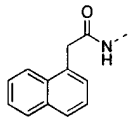
No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.511		$CH_3(CH_2)_8CONH$	**140**	S	cf. detailed description	prep. HPLC method 1	55% (TFA salt)
Ex.512			**140**	S	cf. detailed description	prep. HPLC method 1	56% (TFA salt)
Ex.513			**140**	S	cf. detailed description	prep. HPLC method 3	25%
Ex.514			**140**	S	cf. detailed description	prep. HPLC method 3	54%
Ex.515		$CH_3(CH_2)_8CONH$	**140**	S	cf. detailed description	prep. HPLC method 3	48%
Ex.516			**140**	S	cf. detailed description	prep. HPLC method 3	64%
Ex.517			**140**	S	cf. detailed description	prep. HPLC method 3	57%
Ex.518			**140**	S	cf. detailed description	prep. HPLC method 3	52%

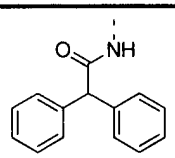
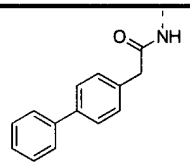
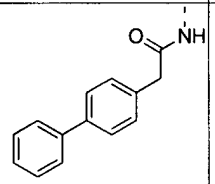
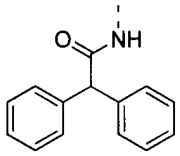
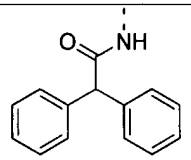
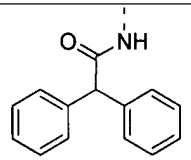
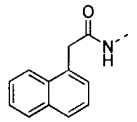
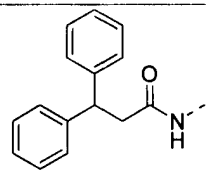
No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.519		$CH_3(CH_2)_8CONH$	**140**	S	cf. detailed description	prep. HPLC method 3	59%
Ex.520			**140**	S	cf. detailed description	prep. HPLC method 3	59%
Ex.521			**140**	S	cf. detailed description	prep. HPLC method 3	68%
Ex.522			**140**	S	cf. detailed description	prep. HPLC method 3	62%
Ex.523			**140**	S	cf. detailed description	prep. HPLC method 3	63%
Ex.524			**140**	S	cf. detailed description	prep. HPLC method 3	38%
Ex.525			**140**	S	cf. detailed description	prep. HPLC method 3	54%

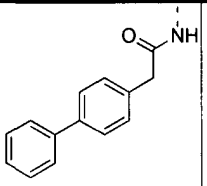
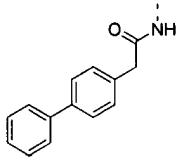
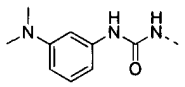
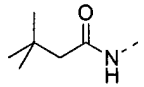
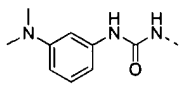
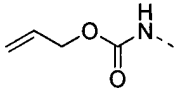
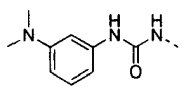
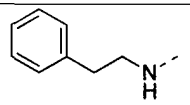
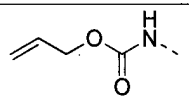
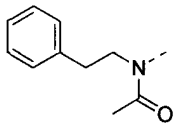
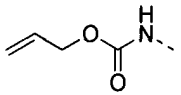
No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.526			**140**	S	cf. detailed description	prep. HPLC method 3	54%
Ex.527			**140**	S	cf. detailed description	prep. HPLC method 3	61%
Ex.528			**140**	S	1. 2-naphthyl-acetic acid 2. methane-sulfonyl chloride	prep. HPLC method 3	45%
Ex.529			**140**	S	1. 2-naphthyl-acetic acid 2. toluene-4-sulfonyl chloride	prep. HPLC method 3	61%

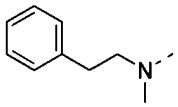
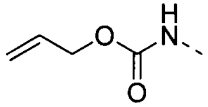
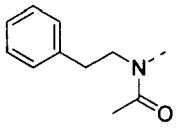
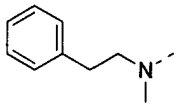
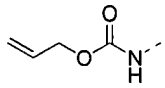
No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.530			**140**	S	1. toluene-4-sulfonyl chloride 2. 2-naphthyl-acetic acid	prep. HPLC method 3	19%
Ex.531			**140**	S	1. 3-methyl-phenyl isocyanate 2. 2-naphthyl-acetic acid	prep. HPLC method 3	44%
Ex.532			**Ex.194**	L.1.1	cf. detailed description	FC (hexane/EtOAc/ MeOH)	91%
Ex.533	NH_2		**Ex.532**	-	cf. detailed description	crude product	80%
Ex.534			**Ex.533**	M.2	2-phenyl-acetaldehyde	prep. HPLC method 3	59%

No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.535			**Ex.558**	L.1.1	3,3-dimethyl-butanoyl chloride (1.1 equiv.) pyridine (5 equiv.)	FC (hexane/EtOAc/ MeOH)	91%
Ex.536			**Ex.559**	L.1.1	3,3-dimethyl-butanoyl chloride (1.1 equiv.) pyridine (5 equiv.)	FC (hexane/EtOAc/ MeOH)	74%
Ex.537			**140**	S	cf. detailed description	prep. HPLC method 3	63%
Ex.538			**140**	S	cf. detailed description	prep. HPLC method 1	62% (TFA salt)

No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.539			**140**	S	cf. detailed description	prep. HPLC method 3	46%
Ex.540			**140**	S	cf. detailed description	prep. HPLC method 3	53%
Ex.541			**140**	S	cf. detailed description	prep. HPLC method 3	68%
Ex.542	$CH_3(CH_2)_8CONH$		**140**	S	cf. detailed description	prep. HPLC method 3	56%
Ex.543	$CH_3(CH_2)_8CONH$		**140**	S	cf. detailed description	prep. HPLC method 3	61%
Ex.544	$CH_3(CH_2)_4CONH$		**140**	S	cf. detailed description	prep. HPLC method 3	54%
Ex.545			**140**	S	cf. detailed description	prep. HPLC method 3	65%

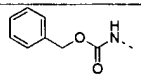
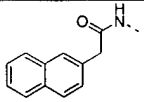
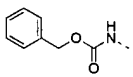
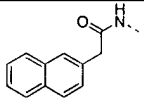
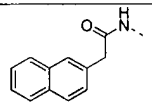
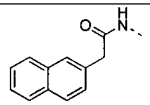
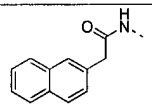
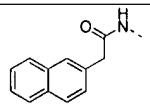
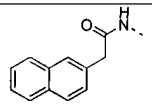
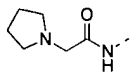
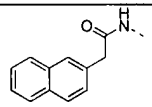
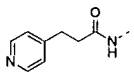
No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.546			**140**	S	cf. detailed description	prep. HPLC method 1	20%
Ex.547			**140**	S	cf. detailed description	prep. HPLC method 3	65%
Ex.548		$CH_3(CH_2)_8CONH$	**140**	S	cf. detailed description	prep. HPLC method 1	28%
Ex.549			**140**	S	cf. detailed description	prep. HPLC method 1	23%
Ex.550		$CH_3(CH_2)_8CONH$	**140**	S	cf. detailed description	prep. HPLC method 3	49%

No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.551			**140**	S	cf. detailed description	prep. HPLC method 1	18%
Ex.552			**Ex.533**	L.4	cf. detailed description	prep. HPLC method 3	83%
Ex.553			**Ex.594**	L.4	cf. detailed description	FC (hexane/EtOAc/ MeOH)	91%
Ex.554		NH_2	**Ex.534**	B.2	cf. detailed description	FC (CH_2Cl_2/MeOH)	93%
Ex.555			**Ex.594**	M.2	2-phenyl-acetaldehyde	prep. HPLC method 3	73%
Ex.556			**Ex.555**	L.1.1	acetic anhydride (5 equiv.) pyridine (10 equiv.)	FC (hexane/EtOAc/ MeOH)	67%

No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.557			**Ex.555**	M.3	aq. formaldehyde soln	FC (hexane/EtOAc/ MeOH)	86%
Ex.558		NH_2	**Ex.556**	B.2	$Pd(PPh_3)_4$, 1,3-dimethyl-barbituric acid	FC (CH_2Cl_2/MeOH/ aq. NH_3)	96%
Ex.559		NH_2	**Ex.556**	B.2	$Pd(PPh_3)_4$, 1,3-dimethyl-barbituric acid	FC (CH_2Cl_2/MeOH/ aq. NH_3)	86%
Ex.594	NH_2		**Ex.181**	*)	1. H_2, $Pd(OH)_2$-C 2. AllocCl 3. TBAF in THF	*)	ca 80% (HCl salt)

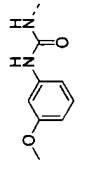
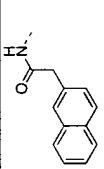
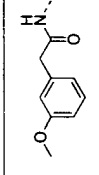
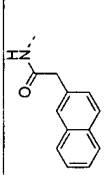
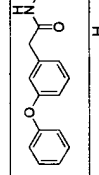
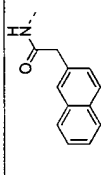
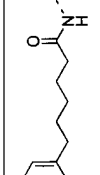
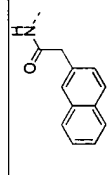
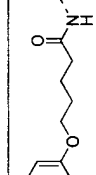
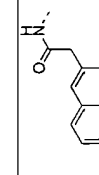
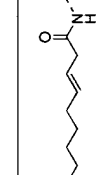
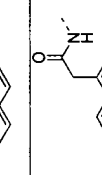
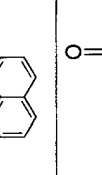
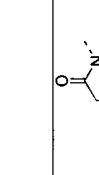
*) cf. detailed description

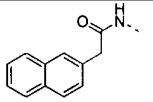
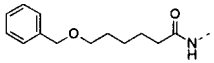
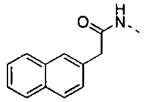
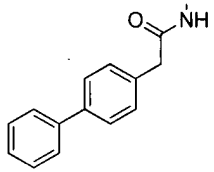
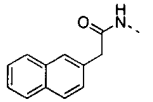
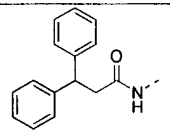
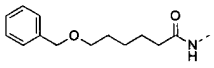
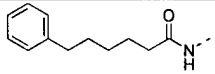
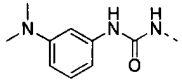
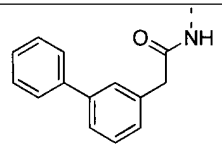
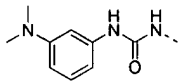
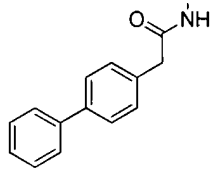
Table 29.1.b: Examples of Core 11a (**Ex.181-Ex.195, Ex.504-Ex.559 and Ex.594**; *continued on the following pages*)

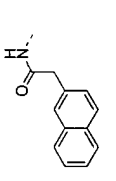
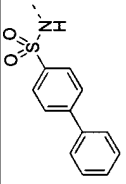
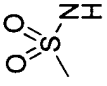
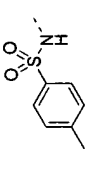
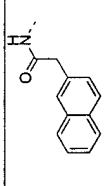
No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.181-Ex.182: *cf. experimental description*							
Ex.183			C28H34N4O6	522.3	1.56 (99)	523.3	Method 2
Ex.184			C38H40N4O6	648.3	1.92 (96)	649.5	Method 2
Ex.185		NH_2	C30H34N4O4	514.3	1.48 (98)	515.4	Method 2
Ex.186			C42H42N4O5	682.3	2.00 (91)	683.5	Method 2
Ex.186			C42H42N4O5	682.3	2.26 (98)	683.3	Method 4a
Ex.187			C36H43N5O5	625.3	1.62 (100)	626.4	Method 2
Ex.188			C38H41N5O5	647.3	1.60 (99)	648.3	Method 2

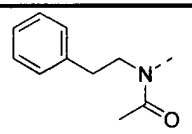
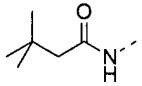
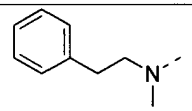
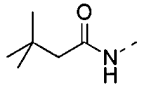
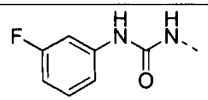
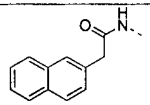
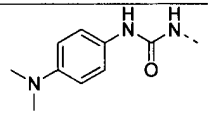
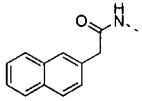
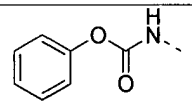
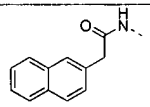
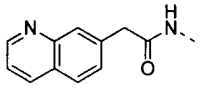
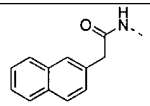
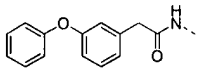
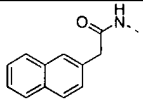
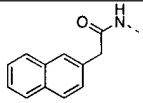
No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.189			C35H42N4O5	598.3	1.88 (85), 1.93 (8)	599.5	Method 2
Ex.190	NH_2		C25H28F2N4O4	486.2	1.42 (98)	487.3	Method 4a
Ex.191			C27H30F2N4O5	528.2	1.69 (99)	529.3	Method 4a
Ex.192			C33H35F2N5O5	619.3	1.50 (99)	620.3	Method 4a
Ex.193			C31H40F2N4O6Si	630.3	2.13 (97)	631.4	Method 2
Ex.194		NH_2	C24H38N4O5Si	490.3	1.62 (99)	491.3	Method 2
Ex.195			C32H32F2N4O5	590.2	1.99 (98)	591.3	Method 4a
Ex.504		$CH_3(CH_2)_8CONH$	C40H52N4O5	668.4	2.54 (99)	669.3	Method 4b

No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.505			C42H42N4O5	682.3	2.23 (95)	683.3	Method 4b
Ex.506			C38H41N5O5	647.3	2.19 (99)	648.3	Method 4a
Ex.507			C39H44N6O5	676.3	1.75 (94)	677.3	Method 4a
Ex.508			C39H44N6O5	676.3	1.72 (94)	677.3	Method 4b
Ex.509		$CH_3(CH_2)_8CONH$	C37H52N4O5	632.4	2.43 (98)	633.3	Method 4b
Ex.510		$CH_3(CH_2)_8CONH$	C39H55N5O6	689.4	2.31 (99)	690.3	Method 4b
Ex.511		$CH_3(CH_2)_8CONH$	C37H54N6O5	662.4	1.96 (99)	663.4	Method 4a
Ex.512			C39H44N6O5	676.3	1.72 (98)	677.3	Method 4a

No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.513			C38H41N5O6	663.3	2.13 (95)	664.3	Method 4a
Ex.514			C39H42N4O6	662.3	2.12 (98)	663.3	Method 4a
Ex.515		$CH_3(CH_2)_8CONH$	C42H54N4O6	710.4	2.60 (97)	711.4	Method 4a
Ex.516			C42H48N4O5	688.4	2.36 (97)	689.4	Method 4a
Ex.517			C41H46N4O6	690.3	2.26 (98)	691.4	Method 4a
Ex.518			C40H50N4O5	666.4	2.36 (92)	667.5	Method 10a
Ex.519		$CH_3(CH_2)_8CONH$	C40H52N4O5	668.4	2.53 (94)	669.4	Method 4a
Ex.520			C36H42N4O5	610.3	2.15 (98)	611.3	Method 4a

No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.521			C43H50N4O6	718.4	2.14 (92)	719.5	Method 10a
Ex.522			C44H44N4O5	708.3	2.35 (98)	709.4	Method 4a
Ex.523			C45H46N4O5	722.4	2.33 (97)	723.4	Method 4a
Ex.524			C43H56N4O6	724.4	2.28 (95)	725.5	Method 10a
Ex.525			C41H46N6O5	702.4	1.63 (97)	703.4	Method 10a
Ex.526			C41H46N6O5	702.4	1.63 (97)	703.4	Method 10a

No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.527			C42H42N4O6S	730.3	2.37 (95)	731.3	Method 4a
Ex.528			C31H36N4O6S	592.2	1.92 (95)	593.2	Method 4a
Ex.529			C37H40N4O6S	668.3	2.18 (96)	669.3	Method 4a
Ex.530			C37H40N4O6S	668.3	2.20 (91)	669.3	Method 4b
Ex.531			C38H41N5O5	647.3	2.19 (98)	648.3	Method 4b
Ex.532			C30H48N4O6Si	588.3	2.27 (99)	589.2	Method 4b
Ex.533	NH_2		C24H36N4O4	444.3	1.36 (99)	445.3	Method 4b
Ex.534			C32H44N4O4	548.3	1.70 (86)	549.4	Method 4a

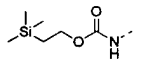
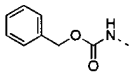
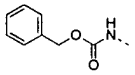
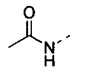
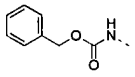
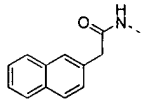
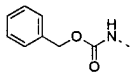
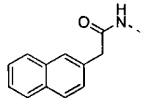
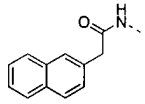
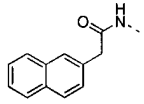
No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.535			C34H46N4O5	590.4	2.06 (95)	591.4	Method 4a
Ex.536			C33H46N4O4	562.4	1.78 (97)	563.4	Method 4a
Ex.537			C37H38FN5O5	651.3	2.18 (92)	652.1	Method 4a
Ex.538			C39H44N6O5	676.3	1.70 (98)	677.3	Method 4a
Ex.539			C37H38N4O6	634.3	2.20 (97)	635.3	Method 4a
Ex.540			C41H41N5O5	683.3	1.49 (98)	684.1	Method 10a
Ex.541			C44H44N4O6	724.3	2.34 (96)	725.4	Method 4a
Ex.542	$CH_3(CH_2)_8CONH$		C40H52N4O5	668.4	2.54 (99)	669.4	Method 4a

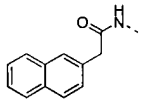
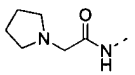
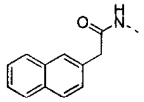
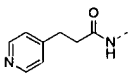
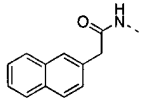
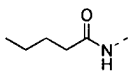
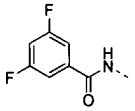
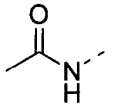
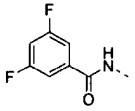
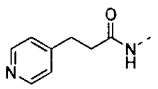
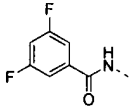
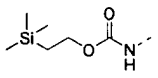
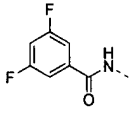
No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.543	$CH_3(CH_2)_8CONH$		C40H52N4O5	668.4	2.54 (95)	669.4	Method 4a
Ex.544	$CH_3(CH_2)_4CONH$		C36H44N4O5	612.3	2.18 (98)	613.3	Method 4a
Ex.545			C44H44N4O5	708.3	2.33 (97)	709.4	Method 4a
Ex.546			C46H46N4O5	734.4	2.30 (99)	735.4	Method 10a
Ex.547			C46H46N4O5	734.4	2.42 (99)	735.4	Method 4a
Ex.548		$CH_3(CH_2)_8CONH$	C42H54N4O5	694.4	2.61 (98)	695.4	Method 4a

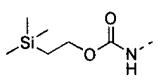
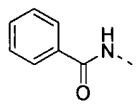
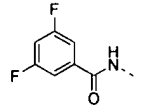
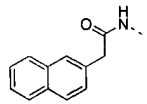
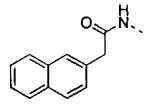
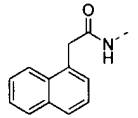
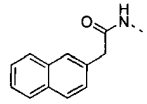
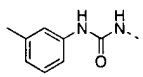
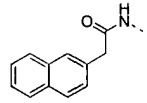
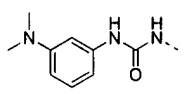
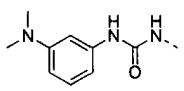
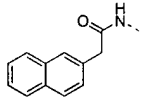
No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.549			C44H44N4O5	708.3	2.34 (97)	709.4	Method 4a
Ex.550		$CH_3(CH_2)_8CONH$	C43H56N4O5	708.4	2.58 (98)	709.5	Method 4a
Ex.551			C46H46N4O5	734.4	2.29 (95)	735.4	Method 10a
Ex.552			C33H46N6O5	606.4	1.54 (99)	607.3	Method 4b
Ex.553			C31H40N6O6	592.3	1.47 (99)	593.3	Method 4a
Ex.554		NH_2	C27H36N6O4	508.3	1.20 (95)	509.2	Method 4a
Ex.555			C30H38N4O5	534.3	1.64 (93)	535.3	Method 4a

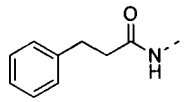
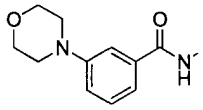
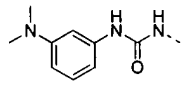
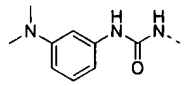
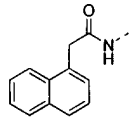
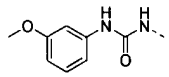
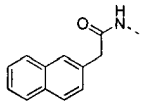
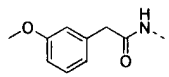
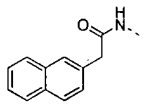
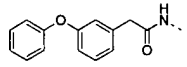
No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.556			C32H40N4O6	576.3	2.00 (93)	577.3	Method 4a
Ex.557			C31H40N4O5	548.3	1.65 (92)	549.4	Method 4a
Ex.558		NH_2	C28H36N4O4	492.3	1.58 (94)	493.2	Method 4a
Ex.559		NH_2	C27H36N4O3	464.3	1.32 (86)	465.3	Method 4a
Ex.594	NH_2		C22H30N4O5	430.2	1.22 (92)	431.3	Method 4a

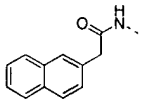
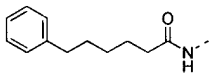
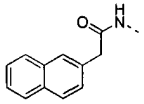
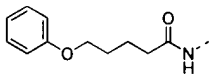
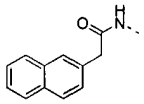
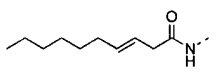
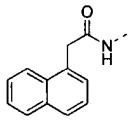
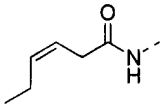
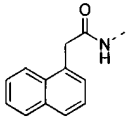
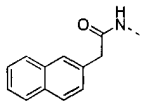
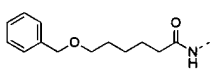
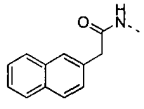
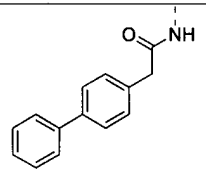
Table 29.1.c: Examples of Core 11a (**Ex.181-Ex.195, Ex.504-Ex.559 and Ex.594**; *continued on the following pages*)

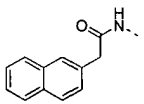
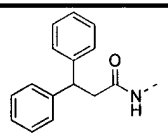
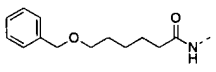
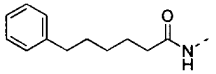
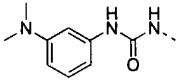
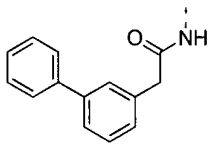
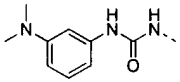
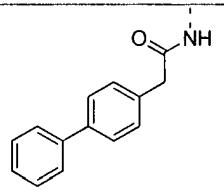
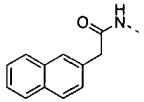
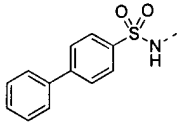
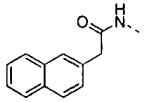
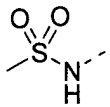
No	R^2	R^5	IUPAC name
Ex.181			benzyl *N*-[(4*S*,6*S*,10*S*)-14-methyl-9,15-dioxo-6-({[2-(trimethylsilyl)ethoxy]carbonyl}amino)-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]carbamate
Ex.182	NH_2		benzyl *N*-[(4*S*,6*S*,10*S*)-6-amino-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]carbamate
Ex.183			benzyl *N*-[(4*S*,6*S*,10*S*)-6-(acetylamino)-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]carbamate
Ex.184			benzyl *N*-[(4*S*,6*S*,10*S*)-14-methyl-6-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]carbamate
Ex.185		NH_2	*N*-[(4*S*,6*S*,10*S*)-10-amino-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]-2-(2-naphthyl)acetamide
Ex.186			*N*-[(4*S*,6*S*,10*S*)-14-methyl-10-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]-2-(2-naphthyl)acetamide

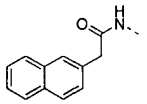
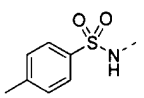
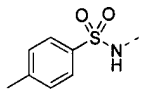
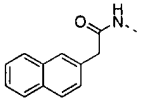
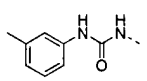
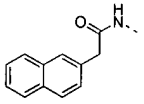
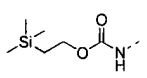
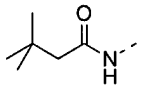
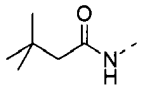
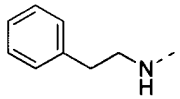
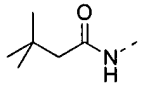
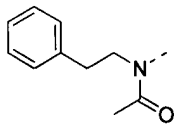
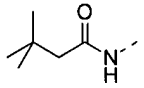
No	R^2	R^5	IUPAC name
Ex.187			*N*-[(4*S*,6*S*,10*S*)-14-methyl-9,15-dioxo-10-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]-2-(2-naphthyl)acetamide
Ex.188			*N*-[(4*S*,6*S*,10*S*)-14-methyl-6-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-3-(4-pyridinyl)propanamide
Ex.189			*N*-[(4*S*,6*S*,10*S*)-14-methyl-6-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]pentanamide
Ex.190	NH_2		*N*-[(4*S*,6*S*,10*S*)-6-amino-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-3,5-difluorobenzamide
Ex.191			*N*-[(4*S*,6*S*,10*S*)-6-(acetylamino)-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-3,5-difluorobenzamide
Ex.192			3,5-difluoro-*N*-[(4*S*,6*S*,10*S*)-14-methyl-9,15-dioxo-6-{[3-(4-pyridinyl)propanoyl]amino}-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]benzamide
Ex.193			2-(trimethylsilyl)ethyl *N*-[(4*S*,6*S*,10*S*)-10-[(3,5-difluorobenzoyl)amino]-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]carbamate

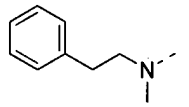
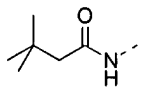
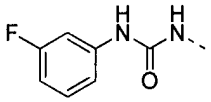
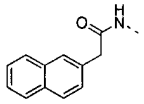
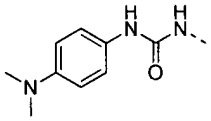
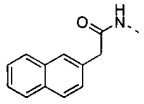
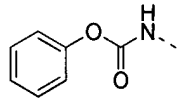
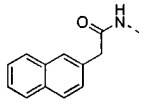
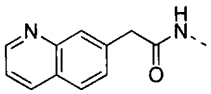
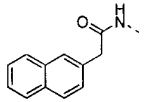
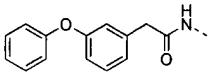
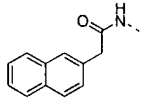
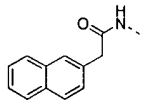
No	R^2	R^5	IUPAC name
Ex.194		NH_2	2-(trimethylsilyl)ethyl *N*-[(4*S*,6*S*,10*S*)-10-amino-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]carbamate
Ex.195			*N*-[(4*S*,6*S*,10*S*)-6-(benzoylamino)-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-3,5-difluorobenzamide
Ex.504		$CH_3(CH_2)_8CONH$	*N*-[(4*S*,6*S*,10*S*)-14-methyl-6-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]decanamide
Ex.505			*N*-[(4*S*,6*S*,10*S*)-14-methyl-6-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2-(1-naphthyl)acetamide
Ex.506			*N*-[(4*S*,6*S*,10*S*)-14-methyl-9,15-dioxo-10-[(3-toluidinocarbonyl)amino]-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]-2-(2-naphthyl)acetamide
Ex.507			*N*-[(4*S*,6*S*,10*S*)-10-({[3-(dimethylamino)anilino]carbonyl}amino)-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]-2-(2-naphthyl)acetamide
Ex.508			*N*-[(4S,6S,10S)-6-({[3-(dimethylamino)anilino]carbonyl}amino)-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2-(2-naphthyl)acetamide

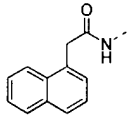
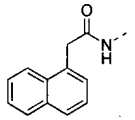
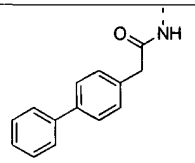
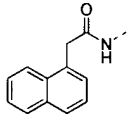
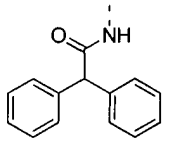
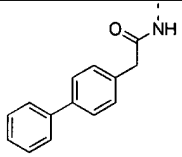
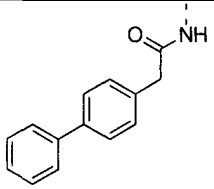
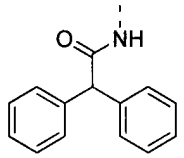
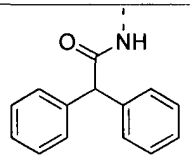
No	R^2	R^5	IUPAC name
Ex.509		$CH_3(CH_2)_8CONH$	*N*-[(4*S*,6*S*,10*S*)-14-methyl-9,15-dioxo-6-[(3-phenylpropanoyl)amino]-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]decanamide
Ex.510		$CH_3(CH_2)_8CONH$	*N*-[(4*S*,6*S*,10*S*)-14-methyl-6-[(3-morpholinobenzoyl)amino]-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]decanamide
Ex.511		$CH_3(CH_2)_8CONH$	*N*-[(4S,6S,10S)-6-({[3-(dimethylamino)anilino]carbonyl}amino)-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]decanamide
Ex.512			*N*-[(4S,6S,10S)-6-({[3-(dimethylamino)anilino]carbonyl}amino)-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2-(1-naphthyl)acetamide
Ex.513			*N*-[(4*S*,6*S*,10*S*)-6-{[(3-methoxyanilino)carbonyl]amino}-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2-(2-naphthyl)acetamide
Ex.514			2-(3-methoxyphenyl)-*N*-[(4*S*,6*S*,10*S*)-14-methyl-10-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]acetamide
Ex.515		$CH_3(CH_2)_8CONH$	*N*-[(4*S*,6*S*,10*S*)-14-methyl-9,15-dioxo-6-{[2-(3-phenoxyphenyl)acetyl]amino}-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]decanamide

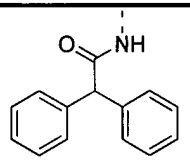
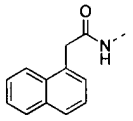
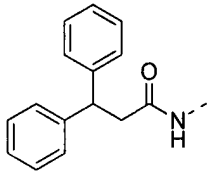
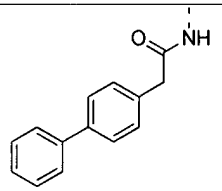
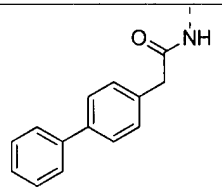
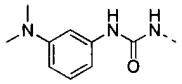
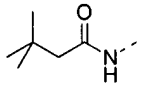
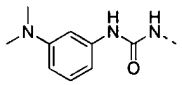
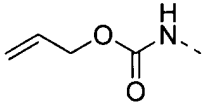
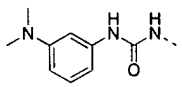
No	R^2	R^5	IUPAC name
Ex.516			*N*-[(4*S*,6*S*,10*S*)-14-methyl-6-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-6-phenylhexanamide
Ex.517			*N*-[(4*S*,6*S*,10*S*)-14-methyl-6-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-5-phenoxypentanamide
Ex.518			(*E*)-*N*-[(4*S*,6*S*,10*S*)-14-methyl-6-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-3-decenamide
Ex.519		$CH_3(CH_2)_8CONH$	*N*-[(4*S*,6*S*,10*S*)-14-methyl-6-{[2-(1-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]decanamide
Ex.520			(*Z*)-*N*-[(4*S*,6*S*,10*S*)-14-methyl-10-{[2-(1-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]-3-hexenamide
Ex.521			6-(benzyloxy)-*N*-[(4*S*,6*S*,10*S*)-14-methyl-6-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]hexanamide
Ex.522			2-[1,1'-biphenyl]-4-yl-*N*-[(4*S*,6*S*,10*S*)-14-methyl-6-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]acetamide

No	R^2	R^5	IUPAC name
Ex.523			*N*-[(4*S*,6*S*,10*S*)-14-methyl-6-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-3,3-diphenylpropanamide
Ex.524			6-(benzyloxy)-*N*-[(4*S*,6*S*,10*S*)-14-methyl-9,15-dioxo-10-[(6-phenylhexanoyl)amino]-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]hexanamide
Ex.525			2-[1,1'-biphenyl]-3-yl-*N*-[(4*S*,6*S*,10*S*)-6-({[3-(dimethylamino)anilino]carbonyl}amino)-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]acetamide
Ex.526			2-[1,1'-biphenyl]-4-yl-*N*-[(4*S*,6*S*,10*S*)-6-({[3-(dimethylamino)anilino]carbonyl}amino)-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]acetamide
Ex.527			*N*-[(4*S*,6*S*,10*S*)-10-[([1,1'-biphenyl]-4-ylsulfonyl)amino]-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]-2-(2-naphthyl)acetamide
Ex.528			*N*-[(4*S*,6*S*,10*S*)-14-methyl-10-[(methylsulfonyl)amino]-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]-2-(2-naphthyl)acetamide

No	R^2	R^5	IUPAC name
Ex.529			*N*-[(4*S*,6*S*,10*S*)-14-methyl-10-{[(4-methylphenyl)sulfonyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]-2-(2-naphthyl)acetamide
Ex.530			*N*-[(4*S*,6*S*,10*S*)-14-methyl-6-{[(4-methylphenyl)sulfonyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2-(2-naphthyl)acetamide
Ex.531			*N*-[(4*S*,6*S*,10*S*)-14-methyl-9,15-dioxo-6-[(3-toluidinocarbonyl)amino]-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2-(2-naphthyl)acetamide
Ex.532			2-(trimethylsilyl)ethyl *N*-[(4*S*,6*S*,10*S*)-10-[(3,3-dimethylbutanoyl)amino]-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]carbamate
Ex.533	NH_2		*N*-[(4*S*,6*S*,10*S*)-6-amino-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-3,3-dimethylbutanamide
Ex.534			3,3-dimethyl-*N*-[(4*S*,6*S*,10*S*)-14-methyl-9,15-dioxo-6-(phenethylamino)-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]butanamide
Ex.535			*N*-[(4*S*,6*S*,10*S*)-6-[acetyl(phenethyl)amino]-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-3,3-dimethylbutanamide

No	R^2	R^5	IUPAC name
Ex.536			3,3-dimethyl-N-[(4*S*,6*S*,10*S*)-14-methyl-6-[methyl(phenethyl)amino]-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]butanamide
Ex.537			*N*-[(4*S*,6*S*,10*S*)-6-{[(3-fluoroanilino)carbonyl]amino}-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2-(2-naphthyl)acetamide
Ex.538			*N*-[(4*S*,6*S*,10*S*)-6-({[4-(dimethylamino)anilino]carbonyl}amino)-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2-(2-naphthyl)acetamide
Ex.539			phenyl *N*-[(4*S*,6*S*,10*S*)-14-methyl-10-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]carbamate
Ex.540			*N*-[(4*S*,6*S*,10*S*)-14-methyl-9,15-dioxo-6-{[2-(7-quinolinyl)acetyl]amino}-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2-(2-naphthyl)acetamide
Ex.541			*N*-[(4*S*,6*S*,10*S*)-14-methyl-9,15-dioxo-6-{[2-(3-phenoxyphenyl)acetyl]amino}-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2-(2-naphthyl)acetamide
Ex.542	$CH_3(CH_2)_8CONH$		*N*-[(4*S*,6*S*,10*S*)-14-methyl-10-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]decanamide

No	R^2	R^5	IUPAC name
Ex.543	$CH_3(CH_2)_8CONH$		*N*-[(4*S*,6*S*,10*S*)-14-methyl-10-{[2-(1-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]decanamide
Ex.544	$CH_3(CH_2)_4CONH$		*N*-[(4*S*,6*S*,10*S*)-14-methyl-10-{[2-(1-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]hexanamide
Ex.545			2-[1,1'-biphenyl]-4-yl-*N*-[(4*S*,6*S*,10*S*)-14-methyl-10-{[2-(1-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]acetamide
Ex.546			*N*-[(4*S*,6*S*,10*S*)-10-[(2-[1,1'-biphenyl]-4-ylacetyl)amino]-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]-2,2-diphenylacetamide
Ex.547			*N*-[(4*S*,6*S*,10*S*)-6-[(2-[1,1'-biphenyl]-4-ylacetyl)amino]-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2,2-diphenylacetamide
Ex.548		$CH_3(CH_2)_8CONH$	*N*-[(4*S*,6*S*,10*S*)-6-[(2,2-diphenylacetyl)amino]-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]decanamide

No	R^2	R^5	IUPAC name
Ex.549			*N*-[(4*S*,6*S*,10*S*)-14-methyl-10-{[2-(1-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]-2,2-diphenylacetamide
Ex.550		$CH_3(CH_2)_8CONH$	*N*-[(4*S*,6*S*,10*S*)-6-[(3,3-diphenylpropanoyl)amino]-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]decanamide
Ex.551			2-[1,1'-biphenyl]-4-yl-*N*-[(4*S*,6*S*,10*S*)-10-[(2-[1,1'-biphenyl]-4-ylacetyl)amino]-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]acetamide
Ex.552			*N*-[(4*S*,6*S*,10*S*)-6-({[3-(dimethylamino)anilino]carbonyl}amino)-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-3,3-dimethylbutanamide
Ex.553			allyl *N*-[(4*S*,6*S*,10*S*)-6-({[3-(dimethylamino)anilino]carbonyl}amino)-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]carbamate
Ex.554		NH_2	*N*-[(4*S*,6*S*,10*S*)-10-amino-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]-*N*'-[3-(dimethylamino)phenyl]urea

No	R^2	R^5	IUPAC name
Ex.555			allyl *N*-[(4*S*,6*S*,10*S*)-14-methyl-9,15-dioxo-6-(phenethylamino)-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]carbamate
Ex.556			allyl *N*-[(4*S*,6*S*,10*S*)-6-[acetyl(phenethyl)amino]-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]carbamate
Ex.557			allyl *N*-[(4*S*,6*S*,10*S*)-14-methyl-6-[methyl(phenethyl)amino]-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]carbamate
Ex.558		NH_2	*N*-[(4*S*,6*S*,10*S*)-10-amino-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]-*N*-phenethylacetamide
Ex.559		NH_2	(4*S*,6*S*,10*S*)-10-amino-14-methyl-6-[methyl(phenethyl)amino]-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-9,15-dione
Ex.594	NH_2		allyl *N*-[(4*S*,6*S*,10*S*)-6-amino-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]carbamate

Table 29.2.a: Examples of Core 11b (**Ex.560-Ex.566**)

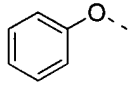
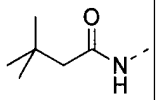
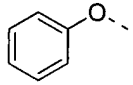
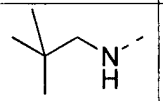
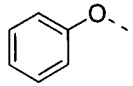
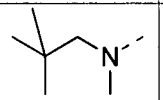
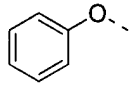
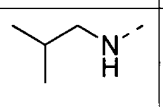
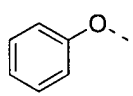
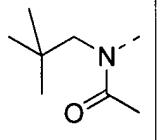
No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.560-Ex.561: *cf. experimental description*							
Ex.562			**Ex.561**	L.1.1	3,3-dimethylbutanoyl chloride (1.5 equiv.) pyridine (5 equiv.)	FC (CH_2Cl_2/MeOH)	85%
Ex.563			**Ex.561**	M.2	Pivalaldehyde (1.0 equiv.)	FC (CH_2Cl_2/MeOH)	30%
Ex.564			**Ex.563**	M.3	aq. formaldehyde soln	FC (CH_2Cl_2/MeOH)	93%
Ex.565			**Ex.561**	M.2	isobutyraldehyde	FC (CH_2Cl_2/MeOH)	63%
Ex.566			**Ex.563**	L.1.1	acetic anhydride (1.2 mL), pyridine (1.1 mL), CH_2Cl_2 (1.2 mL)	crude product	95%

Table 29.2.b: Examples of Core 11b (**Ex.560-Ex.566**)

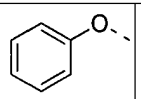
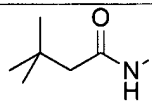
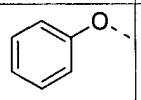
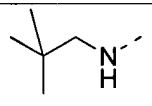
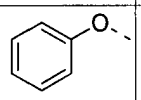
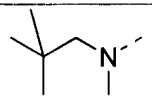
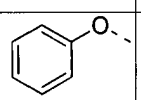
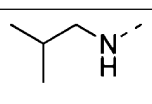
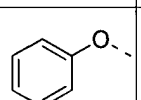
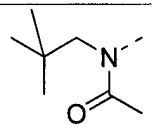
No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.560-Ex.561: *cf. experimental description*							
Ex.562			C30H39N3O5	521.3	2.21 (97)	522.4	Method 4a
Ex.563			C29H39N3O4	493.3	1.80 (98)	494.3	Method 4a
Ex.564			C30H41N3O4	507.3	1.61 (96)	508.2	Method 10b
Ex.565			C28H37N3O4	479.3	1.57 (99)	480.3	Method 10b
Ex.566			C31H41N3O5	535.3	2.07 (94)	536.3	Method 10a

Table 29.2.c: Examples of Core 11b (**Ex.560-Ex.566**)

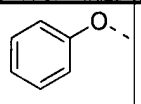
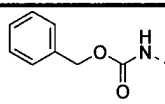
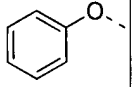
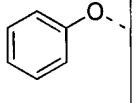
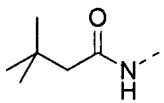
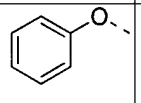
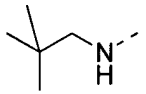
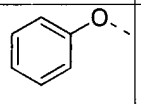
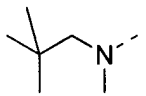
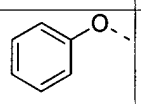
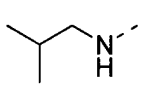
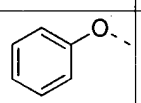
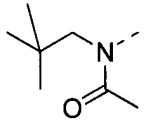
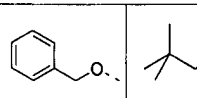
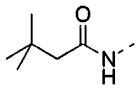
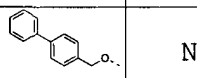
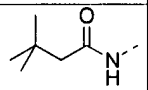
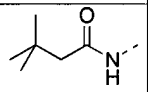
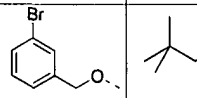
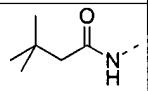
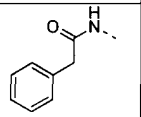
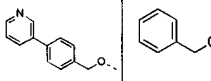
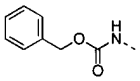
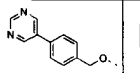
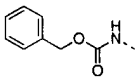
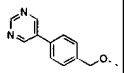
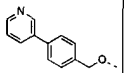
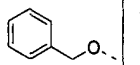
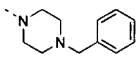
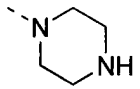
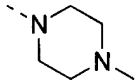
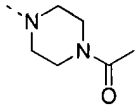
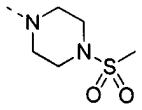
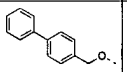
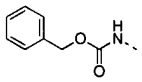
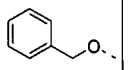
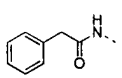
No	R^2	R^5	IUPAC name
Ex.560			benzyl *N*-[(4*S*,6*S*,10*S*)-14-methyl-9,15-dioxo-6-phenoxy-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]carbamate
Ex.561		NH_2	(4*S*,6*S*,10*S*)-10-amino-14-methyl-6-phenoxy-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-9,15-dione
Ex.562			3,3-dimethyl-*N*-[(4*S*,6*S*,10*S*)-14-methyl-9,15-dioxo-6-phenoxy-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]butanamide
Ex.563			(4*S*,6*S*,10*S*)-14-methyl-10-(neopentylamino)-6-phenoxy-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-9,15-dione
Ex.564			(4*S*,6*S*,10*S*)-14-methyl-10-[methyl(neopentyl)amino]-6-phenoxy-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-9,15-dione
Ex.565			(4*S*,6*S*,10*S*)-10-(isobutylamino)-14-methyl-6-phenoxy-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-9,15-dione
Ex.566			*N*-[(4*S*,6*S*,10*S*)-14-methyl-9,15-dioxo-6-phenoxy-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-*N*-neopentylacetamide

Table 29.3.a: Examples of Core 11c (**Ex.567-Ex.585**; *continued on the following pages*)

No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.567-Ex.568: *cf. experimental description*							
Ex.569			**Ex.568**	L.1.1	3,3-dimethylbutanoyl chloride (1.1 equiv.) i-Pr_2NEt (5 equiv.)	FC (hexane/ EtOAc)	76%
Ex.570		NH_2	**Ex.584**	K.2	H_2, 5%Pd-C, NH_3-MeOH	crude product	81% (HCl salt)*)
Ex.571	OH		**Ex.569**	H	H_2, $Pd(OH)_2$-C, MeOH/AcOH 2:1	crude product	93%
Ex.572	OCH_3		**Ex.571**	**)	**)	FC (EtOAc)	38%
Ex.573			**Ex.571**	Q	3-bromobenzyl bromide	FC (hexane/EtOAc)	60%
Ex.574	OH		**Ex.585**	H	H_2, $Pd(OH)_2$-C, MeOH/AcOH 4:1	crude product	100%
Ex.575			**Ex.567**	P	pyridine-3-boronic acid	prep. HPLC method 3	91%

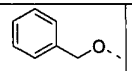
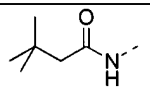
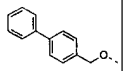
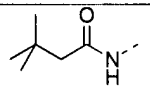
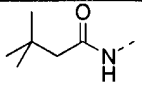
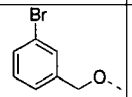
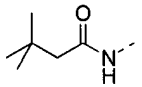
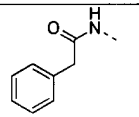
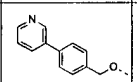
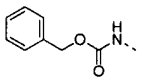
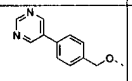
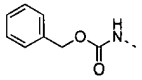
No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.576			**Ex.567**	P	pyrimidine-5-boronic acid	prep. HPLC method 3	86%
Ex.577		NH_2	**Ex.576**	K.2	H_2, 5%Pd-C, NH_3-MeOH	crude product	93%
Ex.578		NH_2	**Ex.575**	K.2	H_2, 5%Pd-C, NH_3-MeOH	crude product	91%
Ex.579			**Ex.568**	O	N-benzyl-2-chloro-N-(2-chloroethyl) ethanamine	FC (hexane/ EtOAc/MeOH)	61%
Ex.580	OH		**Ex579**	K.3	H_2, $Pd(OH)_2$-C, AcOH	FC (CH_2Cl_2/MeOH/ aq.NH_3)	94%
Ex.581	OH		**Ex.580**	M.3	aq. formaldehyde soln	FC (CH_2Cl_2/MeOH/ aq.NH_3)	70%
Ex.582	OH		**Ex.580**	L.1.1	acetyl chloride (1.0 equiv.) triethylamine (2 equiv.) 0°C, 30 min	FC (CH_2Cl_2/MeOH)	75%

No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.583	OH		**Ex.580**	L.3	methanesulfonyl chloride 0°C, 30 min	FC (hexane/ EtOAc/MeOH)	63%
Ex.584			**Ex.567**	P	phenylboronic acid (2 equiv.)	FC (EtOAc/hexane)	75%
Ex.585			**Ex.568**	L.1.1	phenylacetyl chloride (1 equiv.) DIPEA (3 equiv.)	FC (EtOAc)	70%

*) the crude product was converted into the HCl salt

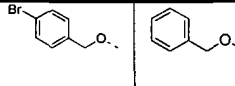
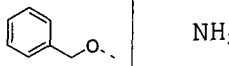
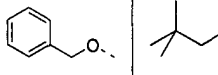
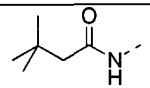
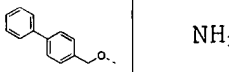
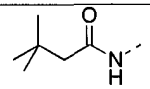
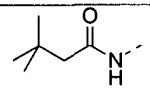
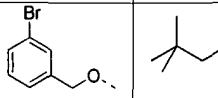
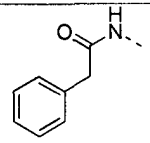
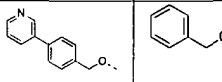
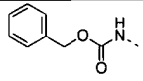
**) dimethyl sulfate, benzyltriethylammonium chloride, toluene, 2 M aq. NaOH

Table 29.3.b: Examples of Core 11c (**Ex.567-Ex.585**; *continued on the following pages*)

No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.567-Ex.568: *cf. experimental description*							
Ex.569			C31H41N3O5	535.3	2.22 (92)	536.4	Method 4a
Ex.570		NH_2	C31H35N3O4	513.3	1.88 (97)	514.3	Method 4a
Ex.571	OH		C24H35N3O5	445.3	1.59 (95)	446.3	Method 4a
Ex.572	OCH_3		C25H37N3O5	459.3	1.62 (96)	460.2	Method 10a
Ex.573			C31H40BrN3O5	613.2	2.33 (93)	616.2	Method 4a
Ex.574	OH		C26H31N3O5	465.2	1.35 (87)	466.3	Method 10a
Ex.575			C38H40N4O6	648.3	1.57 (94)	649.1	Method 10a
Ex.576			C37H39N5O6	649.3	1.90 (98)	650.3	Method 10a

No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.577		NH_2	C29H33N5O4	515.3	1.30 (95)	516.3	Method 10a
Ex.578		NH_2	C30H34N4O4	514.3	1.08 (95)	515.3	Method 10a
Ex.579			C36H44N4O4	596.3	1.61 (97)	597.3	Method 10a
Ex.580	OH		C22H32N4O4	416.2	0.80 (98)	417.2	Method 10a
Ex.581	OH		C23H34N4O4	430.3	0.83 (99)	431.2	Method 10a
Ex.582	OH		C24H34N4O5	458.3	0.82 (97)	459.2	Method 10a
Ex.583	OH		C23H34N4O6S	494.2	0.84 (94)	495.2	Method 10a
Ex.584			C39H41N3O6	647.3	2.46 (65%)	648.3	Method 12
Ex.585			C33H37N3O5	555.3	1.99 (88%)	557.3	Method 10a

Table 29.3.c: *Examples of Core 11c* (**Ex.567-Ex.585**; *continued on the following pages*)

No	R^2	R^5	IUPAC name
Ex.567			benzyl *N*-[(4*S*,6*S*,10*S*)-6-[(4-bromobenzyl)oxy]-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]carbamate
Ex.568		NH_2	(4*S*,6*S*,10*S*)-10-amino-6-(benzyloxy)-14-methyl-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-9,15-dione
Ex.569			*N*-[(4*S*,6*S*,10*S*)-6-(benzyloxy)-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-3,3-dimethylbutanamide
Ex.570		NH_2	(4*S*,6*S*,10*S*)-10-amino-6-([1,1'-biphenyl]-4-ylmethoxy)-14-methyl-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-9,15-dione
Ex.571	OH		*N*-[(4*S*,6*S*,10*S*)-6-hydroxy-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-3,3-dimethylbutanamide
Ex.572	OCH_3		*N*-[(4*S*,6*S*,10*S*)-6-methoxy-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-3,3-dimethylbutanamide
Ex.573			*N*-[(4*S*,6*S*,10*S*)-6-[(3-bromobenzyl)oxy]-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-3,3-dimethylbutanamide
Ex.574	OH		*N*-[(4*S*,6*S*,10*S*)-6-hydroxy-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2-phenylacetamide
Ex.575			benzyl *N*-[(4*S*,6*S*,10*S*)-14-methyl-9,15-dioxo-6-{[4-(3-pyridinyl)benzyl]oxy}-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]carbamate

No	R^2	R^5	IUPAC name
Ex.576			benzyl *N*-[(4*S*,6*S*,10*S*)-14-methyl-9,15-dioxo-6-{[4-(5-pyrimidinyl)benzyl]oxy}-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]carbamate
Ex.577		NH_2	(4*S*,6*S*,10*S*)-10-amino-14-methyl-6-{[4-(5-pyrimidinyl)benzyl]oxy}-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-9,15-dione
Ex.578		NH_2	(4*S*,6*S*,10*S*)-10-amino-14-methyl-6-{[4-(3-pyridinyl)benzyl]oxy}-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-9,15-dione
Ex.579			(4*S*,6*S*,10*S*)-6-(benzyloxy)-10-(4-benzylpiperazino)-14-methyl-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-9,15-dione
Ex.580	OH		(4*S*,6*S*,10*S*)-6-hydroxy-14-methyl-10-piperazino-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-9,15-dione
Ex.581	OH		(4*S*,6*S*,10*S*)-6-hydroxy-14-methyl-10-(4-methylpiperazino)-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-9,15-dione
Ex.582	OH		(4*S*,6*S*,10*S*)-10-(4-acetylpiperazino)-6-hydroxy-14-methyl-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-9,15-dione
Ex.583	OH		(4*S*,6*S*,10*S*)-6-hydroxy-14-methyl-10-[4-(methylsulfonyl)piperazino]-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-9,15-dione
Ex.584			benzyl *N*-[(4*S*,6*S*,10*S*)-6-([1,1'-biphenyl]-4-ylmethoxy)-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]carbamate
Ex.585			*N*-[(4*S*,6*S*,10*S*)-6-(benzyloxy)-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2-phenylacetamide

Table 29.4.a: Examples of Core 11d (**Ex.586-Ex.589**; *continued on the following page*)

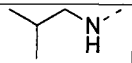
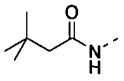
No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.586-Ex.587: *cf. experimental description*							
Ex.588	CH_2Ph		**Ex.587**	M.2	isobutyraldehyde	prep.HPLC, method 3	61%
Ex.589	CH_2Ph		**Ex.587**	L.1.1	3,3-dimethylbutanoyl chloride (1.2 equiv.) pyridine (5 equiv.)	prep.HPLC, method 3	70%

Table 29.4.b: Examples of Core 11d (**Ex.586-Ex.589**)

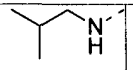
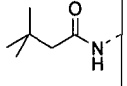
No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.586-Ex.587: *cf. experimental description*							
Ex.588	CH_2Ph		C29H39N3O3	477.3	1.67 (98)	478.3	Method 10a
Ex.589	CH_2Ph		C31H41N3O4	519.3	2.13 (98)	520.3	Method 10a

Table 29.4.c: Examples of Core 11d (**Ex.586-Ex.589**)

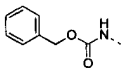
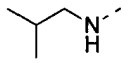
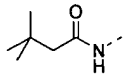
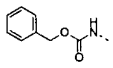
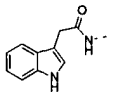
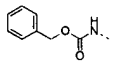
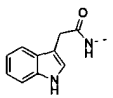
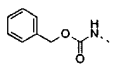
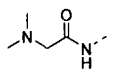
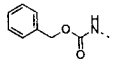
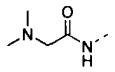
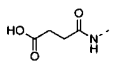
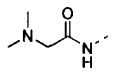
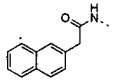
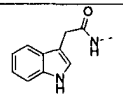
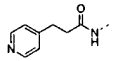
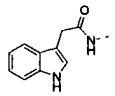
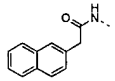
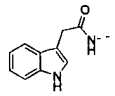
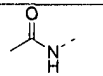
No	R^2	R^5	IUPAC name
Ex.586	CH_2Ph		benzyl *N*-[(4*S*,6*S*,10*S*)-6-benzyl-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]carbamate
Ex.587	CH_2Ph	NH_2	(4*S*,6*S*,10*S*)-10-amino-6-benzyl-14-methyl-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-9,15-dione
Ex.588	CH_2Ph		(4*S*,6*S*,10*S*)-6-benzyl-10-(isobutylamino)-14-methyl-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-9,15-dione
Ex.589	CH_2Ph		*N*-[(4*S*,6*S*,10*S*)-6-benzyl-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-3,3-dimethylbutanamide

Table 30a: *Examples of Core 12* (**Ex.196-Ex.214**; *continued on the following pages*)

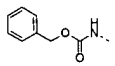
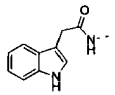
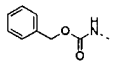
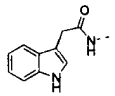
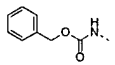
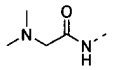
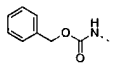
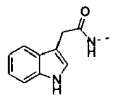
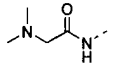
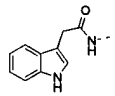
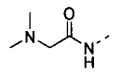
No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.196-Ex.198: *cf. experimental description*							
Ex.199			**Ex.197** ·HCl	L.1.1	acetic anhydride (10 equiv.) pyridine (2 mL)	FC (CH_2Cl_2/MeOH) then prep HPLC, method 1	36%
Ex.200			**Ex.197** ·HCl	L.1.3	3-indoleacetic acid (1.5 equiv.), HATU (1.5 equiv.), HOAt (1.5 equiv), i-Pr_2NEt (5 equiv.)	FC (CH_2Cl_2/MeOH) then prep HPLC, method 1	22%
Ex.200			**Ex.197** ·TFA	L.1.3	3-indoleacetic acid (1.5 equiv.), HATU (1.5 equiv.), HOAt (1.5 equiv), i-Pr_2NEt (5 equiv.)	FC (EtOAc, then CH_2Cl_2/MeOH)	78%
Ex.201			**Ex.197** ·HCl	L.1.3	N,N-dimethyl glycine (1.7 equiv.)	FC (CH_2Cl_2/MeOH) and prep HPLC, method 1	91%*) (TFA salt)

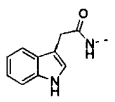
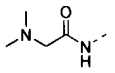
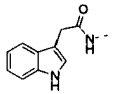
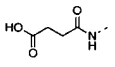
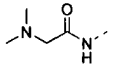
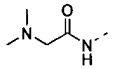
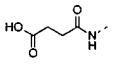
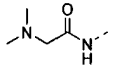
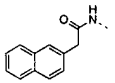
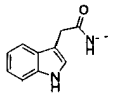
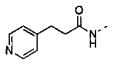
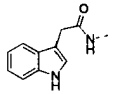
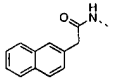
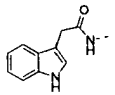
No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.202		NH_2	**Ex.200**	K.1	H_2, $Pd(OH)_2$-C	crude product	97%
Ex.203		NH_2	**Ex.201**	K.1	H_2, $Pd(OH)_2$-C	crude product	99%
Ex.204			**Ex.214**	L.1.3	3-indoleacetic acid (1.2 equiv.), HATU (1.5 equiv.), HOAt (1.5 equiv), i-Pr_2NEt (3 equiv.)	FC (CH_2Cl_2/MeOH)	64%
Ex.205			**Ex.214**	L.1.3	N,N-dimethyl glycine (1.7 equiv.)	prep HPLC, method 1	47% (TFA salt)
Ex.206			**Ex.202**	L.1.3	N,N-dimethyl glycine (1.7 equiv.)	prep HPLC, method 1	39% (TFA salt)
Ex.207			**Ex.202**	L.1.1	succinic anhydride (1.05 equiv.) pyridine (49 equiv.)	prep HPLC, method 2	48%
Ex.208			**Ex.203**	L.1.1	acetic anhydride (10 equiv.) pyridine/CH_2Cl_2 1.1 (3 mL)	prep HPLC, method 2	59%

No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.209			**Ex.203**	L.1.1	succinic anhydride (1.05 equiv.) pyridine (49 equiv.)	prep HPLC, method 2	35%
Ex.210			**Ex.203**	L.1.3	2-naphthylacetic acid (1.2 equiv.)	prep HPLC, method 1	38% (TFA salt)
Ex.211			**Ex.202**	L.1.2	3-(pyridine-4-yl)propanoic acid	prep HPLC, method 1	44% (TFA salt)
Ex.212			**Ex.202**	L.1.3	2-naphthylacetic acid (1.2 equiv.)	prep HPLC, method 1 then FC (EtOAc/MeOH)	53%
Ex.213		$CH_3(CH_2)_8CONH$	**Ex.202**	L.1.1	decanoyl chloride (2 equiv.)	prep HPLC, method 1 then FC (EtOAc/MeOH)	35%
Ex.214		NH_2	**Ex.199**	K.1	H_2, $Pd(OH)_2$-C	crude product	98%

*) An analytical sample was further purified by prep. HPLC (method 1), to afford the TFA salt of the corresponding product

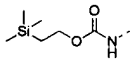
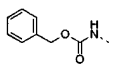
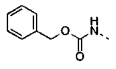
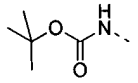
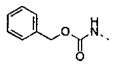
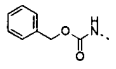
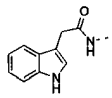
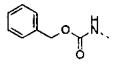
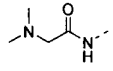
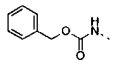
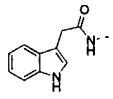
Table 30b: Examples of Core 12 (**Ex.196-Ex.214**; *continued on the following page*)

No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.196-Ex.198: *cf. experimental description*							
Ex.199			C29H35N5O7	565.3	1.92 (100)	566.4	Method 1a
Ex.200			C37H40N6O7	680.3	2.23 (98)	681.4	Method 1a
Ex.200			C37H40N6O7	680.3	1.68 (93)	681.5	Method 2
Ex.201			C31H40N6O7	608.3	1.28 (99)	609.4	Method 2
Ex.202		NH_2	C29H34N6O5	546.3	1.32 (76)	547.4	Method 2
Ex.203		NH_2	C23H34N6O5	474.3	0.77	475.5	Method 9c
Ex.204			C31H36N6O6	588.3	1.49 (87)	589.2	Method 4a
Ex.205			C25H36N6O6	516.3	1.42 (100)	517.3	Method 1a

No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.206			C33H41N7O6	631.3	1.84 (97)	632.4	Method 1a
Ex.207			C33H38N6O8	646.3	1.42 (100)	647.4	Method 2
Ex.208			C25H36N6O6	516.3	0.95 (100)	517.4	Method 2
Ex.209			C27H38N6O8	574.3	1.02 (92)	575.4	Method 3
Ex.210			C35H42N6O6	642.3	1.37 (100)	643.4	Method 2
Ex.211			C37H41N7O6	679.3	1.34 (92)	680.5	Method 2
Ex.212			C41H42N6O6	714.3	1.75 (86)	715.5	Method 2
Ex.213		$CH_3(CH_2)_8CONH$	C39H52N6O6	700.4	1.96 (99)	701.6	Method 2
Ex.214		NH_2	C21H29N5O5	431.2	0.81*)	432.2	Method 9c

*) Analytical HPLC (5% CH_3CN): 2.52 (93)

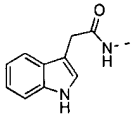
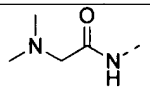
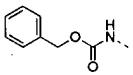
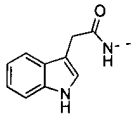
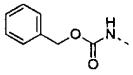
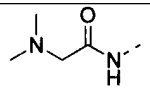
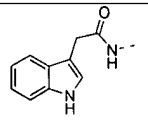
Table 30c: Examples of Core 12 (**Ex.196-Ex.214**; *continued on the following pages*)

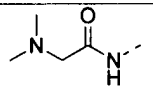
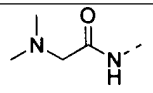
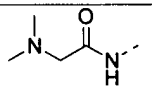
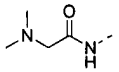
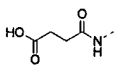
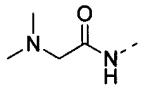
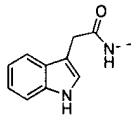
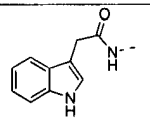
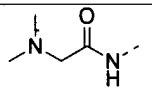
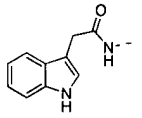
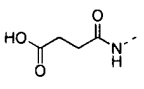
No	R^2	R^5	IUPAC name
Ex.196			benzyl *N*-[(4*S*,6*S*,13*S*)-11,15-dimethyl-9,12,16-trioxo-6-({[2-(trimethylsilyl)ethoxy]carbonyl}amino)-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.197	NH_2		benzyl *N*-[(4*S*,6*S*,13*S*)-6-amino-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.198			benzyl *N*-[(4*S*,6*S*,13*S*)-6-[(*tert*-butoxycarbonyl)amino]-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.199			benzyl *N*-[(4*S*,6*S*,13*S*)-6-(acetylamino)-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.200			benzyl *N*-[(4*S*,6*S*,13*S*)-6-{[2-(1H-indol-3-yl)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.201			benzyl *N*-[(4*S*,6*S*,13*S*)-6-{[2-(dimethylamino)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.202		NH_2	*N*-[(4*S*,6*S*,13*S*)-13-amino-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]-2-(1*H*-indol-3-yl)acetamide

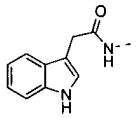
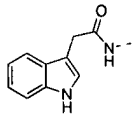
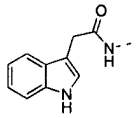
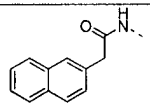
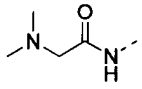
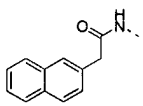
No	R^2	R^5	IUPAC name
Ex.203		NH_2	*N*-[(4*S*,6*S*,13*S*)-13-amino-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]-2-(dimethylamino)acetamide
Ex.204			*N*-[(4*S*,6*S*,13*S*)-6-(acetylamino)-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]-2-(1*H*-indol-3-yl)acetamide
Ex.205			*N*-[(4*S*,6*S*,13*S*)-6-(acetylamino)-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]-2-(dimethylamino)acetamide
Ex.206			2-(dimethylamino)-*N*-[(4*S*,6*S*,13*S*)-6-{[2-(1H-indol-3-yl)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]acetamide
Ex.207			4-{[(4*S*,6*S*,13*S*)-6-{[2-(1*H*-indol-3-yl)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]amino}-4-oxobutanoic acid
Ex.208			*N*-[(4*S*,6*S*,13*S*)-13-(acetylamino)-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]-2-(dimethylamino)acetamide
Ex.209			4-{[(4*S*,6*S*,13*S*)-6-{[2-(dimethylamino)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]amino}-4-oxobutanoic acid

No	R^2	R^5	IUPAC name
Ex.210			2-(dimethylamino)-*N*-[(4*S*,6*S*,13*S*)-11,15-dimethyl-13-{[2-(2-naphthyl)acetyl]amino}-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]acetamide
Ex.211			*N*-[(4*S*,6*S*,13*S*)-6-{[2-(1*H*-indol-3-yl)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]-3-(4-pyridinyl)propanamide
Ex.212			*N*-[(4*S*,6*S*,13*S*)-11,15-dimethyl-13-{[2-(2-naphthyl)acetyl]amino}-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]-2-(1*H*-indol-3-yl)acetamide
Ex.213		$CH_3(CH_2)_8CONH$	*N*-[(4*S*,6*S*,13*S*)-6-{[2-(1*H*-indol-3-yl)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]decanamide
Ex.214		NH_2	*N*-[(4*S*,6*S*,13*S*)-13-amino-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]acetamide

Table 31a: Examples of Core 13 (**Ex.215-Ex.230**; *continued on the following pages*)

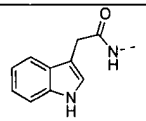
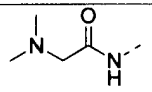
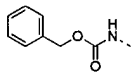
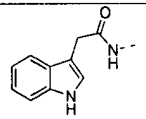
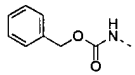
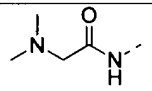
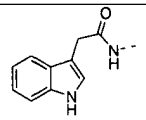
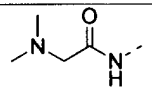
No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.215-Ex.216: *cf. experimental description*							
Ex.217			**Ex.221**	L.1.1	acetic anhydride (10 equiv.) pyridine/CH_2Cl_2 1:1 (2 mL)	prep. HPLC, method 1	41%
Ex.218			**Ex.216** ·HCl	L.1.3	N,N-dimetyl glycine (1.7 equiv.)	FC (CH_2Cl_2/MeOH)	85%*)
Ex.219			**Ex.216** ·HCl	L.1.3	3-indoleacetic acid (1.1 equiv.) HATU (1.5 equiv.) HOAt (1.5 equiv.) i-Pr_2NEt (5 equiv.)	FC (CH_2Cl_2/MeOH)	63%
Ex.220		NH_2	**Ex.218**	K.1	H_2, $Pd(OH)_2$-C	crude product	93%*)
Ex.221		NH_2	**Ex.219**	K.1	H_2, $Pd(OH)_2$-C	crude product	94%*)

No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.222			**Ex.220**	L.1.1	acetic anhydride (5 equiv.)	prep. HPLC, method 1	25% (TFA salt)
Ex.223			**Ex.220**	L.1.3	N,N-dimetyl glycine (1.7 equiv.)	prep. HPLC, method 1	24% (TFA salt)
Ex.224			**Ex.220**	L.1.1	succinic anhydride (1.05 equiv.)	prep. HPLC, method 1	37% (TFA salt)
Ex.225			**Ex.220**	L.1.3	3-indoleacetic acid (1.2 equiv.) HATU (1.5 equiv.) HOAt (1.5 equiv.) i-Pr_2NEt (3 equiv.)	prep. HPLC, method 1	28% (TFA salt)
Ex.226			**Ex.221**	L.1.3	N,N-dimetyl glycine (1.7 equiv.)	prep. HPLC, method 1	45% (TFA salt)
Ex.227			**Ex.221**	L.1.1	succinic anhydride (1.05 equiv.) pyridine (49 equiv.)	prep. HPLC, method 1	49%

No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.228			**Ex.221**	L.1.3	3-indoleacetic acid (1.2 equiv.) HATU (1.5 equiv.) HOAt (1.5 equiv.) i-Pr_2NEt (3 equiv.)	prep. HPLC, method 1	33%
Ex.229			**Ex.221**	L.1.3	2-naphthylacetic acid (1.2 equiv.)	prep. HPLC, method 1	56%
Ex.230			**Ex.220**	L.1.3	2-naphthylacetic acid (1.2 equiv.)	prep. HPLC, method 1	52% (TFA salt)

*) Analytical sample further purified by prep. HPLC, method 1 to afford the TFA salt of the product

Table 31b: Examples of Core 13 (**Ex.215-Ex.230**; *continued on the following pages*)

No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.215-Ex.216: *cf. experimental description*							
Ex.217			C31H36N6O6	588.3	1.82 (94)	589.2	Method 1b
Ex.218			C31H40N6O7	608.3	1.36 (100)	609.2	Method 4b
Ex.219			C37H40N6O7	680.3	1.64 (96)	681.3	Method 2
Ex.220		NH_2	C23H34N6O5	474.3	1.19 (92)	475.2	Method 5b
Ex.221		NH_2	C29H34N6O5	546.3	1.38 (96)	547.2	Method 4b
Ex.222			C25H36N6O6	516.3	1.23 (97)	517.2	Method 5b

No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.223			C27H41N7O6	559.3	1.33 (94)	560.3	Method 5b
Ex.224			C27H38N6O8	574.3	1.04 (100)	575.2	Method 5b
Ex.225			C33H41N7O6	631.3	1.30 (97)	632.3	Method 4b
Ex.226			C33H41N7O6	631.3	1.39 (92)	632.2	Method 4b
Ex.227			C33H38N6O8	646.3	1.49 (94)	647.2	Method 4b
Ex.228			C39H41N7O6	703.3	1.75 (91)	704.3	Method 4b
Ex.229			C41H42N6O6	714.3	1.91 (92)	715.3	Method 4b

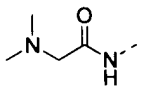
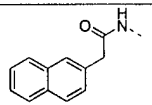
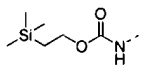
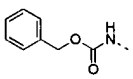
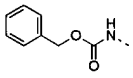
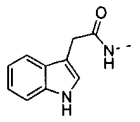
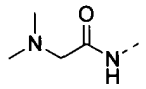
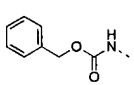
No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.230			C35H42N6O6	642.3	1.50 (100)	643.2	Method 4b

Table 31c: Examples of Core 13 (**Ex.215-Ex.230**; *continued on the following pages*)

No	R^2	R^5	IUPAC name
Ex.215			benzyl *N*-[(4*S*,6*R*,13*S*)-11,15-dimethyl-9,12,16-trioxo-6-({[2-(trimethylsilyl)ethoxy]carbonyl}amino)-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.216	NH_2		benzyl *N*-[(4*S*,6*R*,13*S*)-6-amino-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.217			*N*-[(4*S*,6*R*,13*S*)-13-(acetylamino)-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]-2-(1*H*-indol-3-yl)acetamide
Ex.218			benzyl *N*-[(4*S*,6*R*,13*S*)-6-{[2-(dimethylamino)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate

No	R^2	R^5	IUPAC name
Ex.219			benzyl *N*-[(4*S*,6*R*,13*S*)-6-{[2-(1H-indol-3-yl)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.220		NH_2	*N*-[(4*S*,6*R*,13*S*)-13-amino-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]-2-(dimethylamino)acetamide
Ex.221		NH_2	*N*-[(4*S*,6*R*,13*S*)-13-amino-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]-2-(1*H*-indol-3-yl)acetamide
Ex.222			*N*-[(4*S*,6*R*,13*S*)-13-(acetylamino)-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]-2-(dimethylamino)acetamide
Ex.223			2-(dimethylamino)-*N*-[(4*S*,6*R*,13*S*)-13-{[2-(dimethylamino)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]acetamide
Ex.224			4-{[(4*S*,6*R*,13*S*)-6-{[2-(dimethylamino)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]amino}-4-oxobutanoic acid
Ex.225			2-(dimethylamino)-*N*-[(4*S*,6*R*,13*S*)-13-{[2-(1*H*-indol-3-yl)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]acetamide

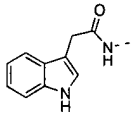
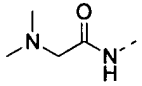
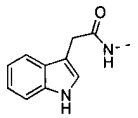
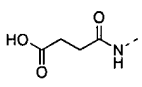
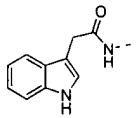
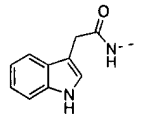
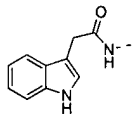
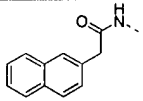
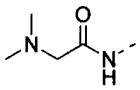
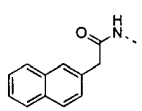
No	R^2	R^5	IUPAC name
Ex.226			2-(dimethylamino)-*N*-[(4*S*,6*R*,13*S*)-6-{[2-(1*H*-indol-3-yl)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]acetamide
Ex.227			4-{[(4*S*,6*R*,13*S*)-6-{[2-(1*H*-indol-3-yl)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]amino}-4-oxobutanoic acid
Ex.228			2-(1*H*-indol-3-yl)-*N*-[(4*S*,6*R*,13*S*)-13-{[2-(1H-indol-3-yl)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]acetamide
Ex.229			*N*-[(4*S*,6*R*,13*S*)-11,15-dimethyl-13-{[2-(2-naphthyl)acetyl]amino}-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]-2-(1*H*-indol-3-yl)acetamide
Ex.230			2-(dimethylamino)-*N*-[(4*S*,6*R*,13*S*)-11,15-dimethyl-13-{[2-(2-naphthyl)acetyl]amino}-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]acetamide

Table 32a: Examples of Core 14 (**Ex.231-Ex.237**)

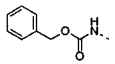
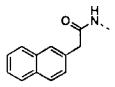
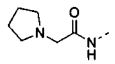
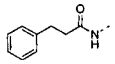
No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.231-Ex.232: *cf. experimental description*							
Ex.233			**Ex.232**·TFA	L.1.3	3-indoleacetic acid (1.5 equiv.) HATU (1.5 equiv.) HOAt (1.5 equiv.) i-Pr_2NEt (5 equiv)	FC (EtOAc, then CH_2Cl_2/MeOH)	68%
Ex.234		NH_2	**Ex.233**	K.1	H_2, $Pd(OH)_2$-C	crude product	99%
Ex.235			**Ex.234**	L.1.3	2-naphthylacetic acid (1.2 equiv.)	prep. HPLC, method 3	68%
Ex.236			**Ex.234**	L.1.3	pyrrolidin-1-acetic acid (1,2 equiv.)	prep. HPLC, method 3	28%
Ex.237			**Ex.234**	L.1.3	3-phenylpropionic acid	prep. HPLC, method 3	66%

Table 32b: Examples of Core 14 (**Ex.231-Ex.237**)

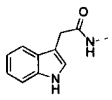
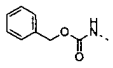
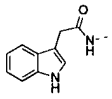
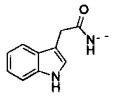
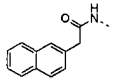
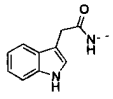
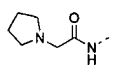
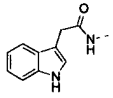
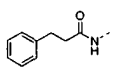
No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.231-Ex.232: *cf. experimental description*							
Ex.233			C37H40N6O7	680.3	1.80 (96)	681.4	Method 2
Ex.234		NH_2	C29H34N6O5	546.3	1.47 (93)	547.3	Method 2
Ex.235			C41H42N6O6	714.3	1.80 (90)	715.4	Method 2
Ex.236			C35H43N7O6	657.3	1.45 (94)	658.4	Method 2
Ex.237			C38H42N6O6	678.3	1.81 (96)	679.4	Method 2

Table 32c: Examples of Core 14 (**Ex.231-Ex.237**)

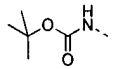
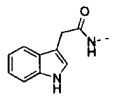
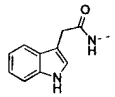
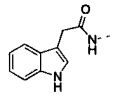
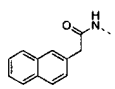
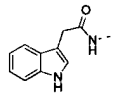
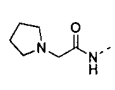
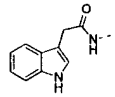
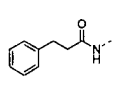
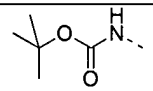
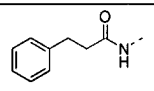
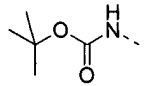
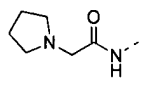
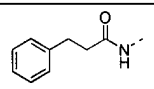
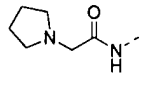
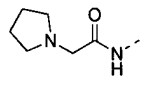
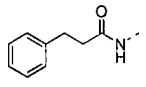
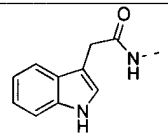
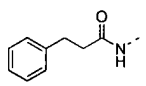
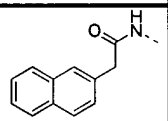
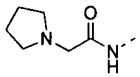
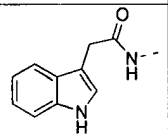
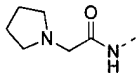
No	R^2	R^5	IUPAC name
Ex.231			benzyl *N*-[(4*S*,6*S*,13*R*)-6-[(*tert*-butoxycarbonyl)amino]-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.232	NH_2		benzyl *N*-[(4*S*,6*S*,13*R*)-6-amino-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.233			benzyl *N*-[(4*S*,6*S*,13*R*)-6-{[2-(1H-indol-3-yl)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.234		NH_2	*N*-[(4*S*,6*S*,13*R*)-13-amino-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]-2-(1*H*-indol-3-yl)acetamide
Ex.235			*N*-[(4*S*,6*S*,13*R*)-11,15-dimethyl-13-{[2-(2-naphthyl)acetyl]amino}-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]-2-(1*H*-indol-3-yl)acetamide
Ex.236			*N*-[(4*S*,6*S*,13*R*)-11,15-dimethyl-9,12,16-trioxo-13-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]-2-(1*H*-indol-3-yl)acetamide
Ex.237			*N*-[(4*S*,6*S*,13*R*)-6-{[2-(1H-indol-3-yl)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]-3-phenylpropanamide

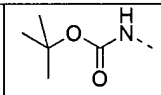
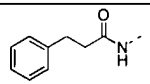
Table 33a: Examples of Core 15 and Core 16 (**Ex.238-Ex.247**; *continued on the following page*)

No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.238-Ex.239: *cf. experimental description*							
Ex.240			**Ex.239**	L.1.3	3-phenylpoanoic acid	FC (EtOAc/MeOH)*)	47%
Ex.241			**Ex.239**	L.1.3	pyrrolidin-1-acetic acid	FC (CH_2Cl_2/MeOH/aq. NH_3)	56%
Ex.242	NH_2		**Ex.240**	J	HCl-dioxane	crude product	quant. (HCl salt)
Ex.243	NH_2		**Ex.241**	J	HCl-dioxane	crude product	quant. (HCl salt)
Ex.244			**Ex.242**	L.1.3	pyrrolidin-1-acetic acid	FC (CH_2Cl_2/MeOH/aq. NH_3)	81%
Ex.245			**Ex.242**	L.1.3	3-indoleacetic acid	FC (CH_2Cl_2/MeOH/aq. NH_3)	59%

No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.246			**Ex.243**	L.1.3	2-naphthylacetic acid	FC (CH_2Cl_2/MeOH/aq. NH_3)	51%
Ex.247			**Ex.243**	L.1.3	3-indoleacetic acid	FC (CH_2Cl_2/MeOH/aq. NH_3)	58%

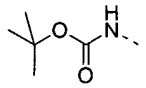
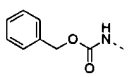
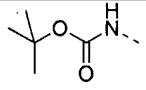
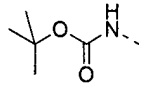
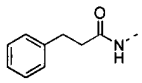
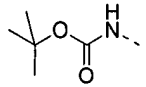
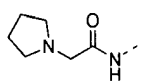
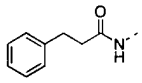
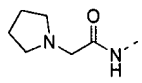
*) An analytical sample was further purified by prep. HPLC, method 2

Table 33b: Examples of Core 15 and Core 16 (**Ex.238-Ex.247**; *continued on the following page*)

No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.238-Ex.239: *cf. experimental description*							
Ex.240			C33H44N4O6	592.3	2.12 (90)	593.3	Method 4a

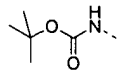
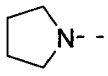
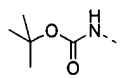
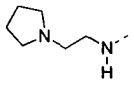
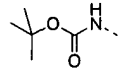
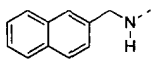
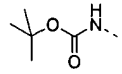
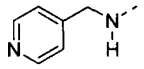
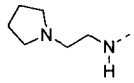
No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.241			C30H45N5O6	571.3	1.58 (91)	572.3	Method 4a
Ex.242	NH_2		C28H36N4O4	492.3	1.53 (88), 1.59 (6)	493.2	Method 4a
Ex.243	NH_2		C25H37N5O4	471.3	1.08 (91)	472.4	Method 4a
Ex.244			C34H45N5O5	603.3	1.63 (93)	604.4	Method 4a
Ex.245			C38H43N5O5	649.3	2.01 (91)	650.3	Method 4a
Ex.246			C37H45N5O5	639.3	1.69 (90)	640.3	Method 4a
Ex.247			C35H44N6O5	628.3	1.52 (94)	629.3	Method 4a

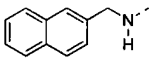
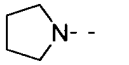
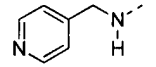
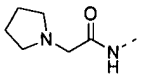
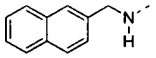
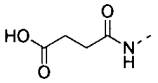
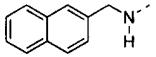
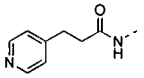
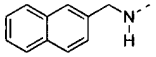
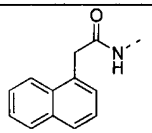
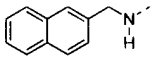
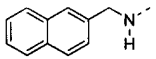
Table 33c: Examples of Core 15 and Core 16 (**Ex.238-Ex.247**; *continued on the following page*)

No	R^2	R^5	IUPAC name
Core 15			
Ex.238			benzyl *N*-[(4*S*,6*S*,10*S*)-6-[(*tert*-butoxycarbonyl)amino]-15-methyl-9,16-dioxo-2-oxa-8,15-diazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),12,17,19-tetraen-10-yl]carbamate
Core 16			
Ex.239		NH_2	*tert*-butyl *N*-[(4*S*,6*S*,10*S*)-10-amino-15-methyl-9,16-dioxo-2-oxa-8,15-diazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]carbamate
Ex.240			*tert*-butyl *N*-[(4*S*,6*S*,10*S*)-15-methyl-9,16-dioxo-10-[(3-phenylpropanoyl)amino]-2-oxa-8,15-diazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]carbamate
Ex.241			*tert*-butyl *N*-[(4*S*,6*S*,10*S*)-15-methyl-9,16-dioxo-10-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,15-diazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]carbamate
Ex.242	NH_2		*N*-[(4*S*,6*S*,10*S*)-6-amino-15-methyl-9,16-dioxo-2-oxa-8,15-diazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-10-yl]-3-phenylpropanamide
Ex.243	NH_2		*N*-[(4*S*,6*S*,10*S*)-6-amino-15-methyl-9,16-dioxo-2-oxa-8,15-diazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-10-yl]-2-(1-pyrrolidinyl)acetamide

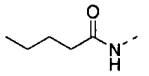
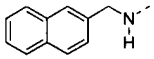
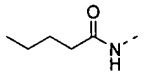
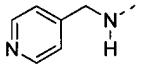
No	R^2	R^5	IUPAC name
Ex.244			*N*-[(4*S*,6*S*,10*S*)-15-methyl-9,16-dioxo-6-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,15-diazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-10-yl]-3-phenylpropanamide
Ex.245			*N*-[(4*S*,6*S*,10*S*)-6-{[2-(1H-indol-3-yl)acetyl]amino}-15-methyl-9,16-dioxo-2-oxa-8,15-diazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-10-yl]-3-phenylpropanamide
Ex.246			*N*-[(4*S*,6*S*,10*S*)-15-methyl-9,16-dioxo-10-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,15-diazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]-2-(2-naphthyl)acetamide
Ex.247			2-(1*H*-indol-3-yl)-*N*-[(4*S*,6*S*,10*S*)-15-methyl-9,16-dioxo-10-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,15-diazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]acetamide

Table 34a: Examples of Core 17 (**Ex.248-Ex.271**; *continued on the following pages*)

No	R^2	R^{54}	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.248-Ex.249: *cf. experimental description*							
Ex.250			**Ex.249**	L.2	pyrrolidine	FC (CH_2Cl_2/MeOH)	81%
Ex.251			**Ex.249**	L.2	N-(2-aminoethyl) pyrrolidine	FC (CH_2Cl_2/MeOH/ aq. NH_3 soln)	88%
Ex.252			**Ex.249**	L.2	2-naphthylmethylamine (1.5 equiv.) HATU (1.5 equiv.) HOAt (1.5 equiv.) i-Pr_2NEt (3 equiv.)	FC (CH_2Cl_2/MeOH)	91%
Ex.253			**Ex.249**	L.2	4-(aminomethyl)-pyridine (1.5 equiv.) HATU (1.5 equiv.) HOAt (1.5 equiv.) i-Pr_2NEt (3 equiv.)	FC (CH_2Cl_2/MeOH) *)	97%
Ex.254	NH_2		**Ex.251**	J	HCl-dioxane	crude product	96% (HCl salt)

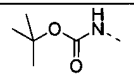
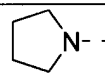
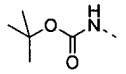
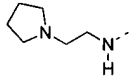
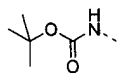
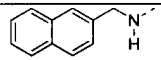
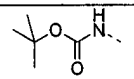
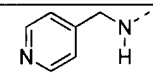
No	R^2	R^{54}	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.255	NH_2		**Ex.252**	J	HCl-dioxane	crude product	100% (HCl salt)
Ex.256	NH_2		**Ex.250**	J	HCl-dioxane	crude product	93% (HCl salt)
Ex.257	NH_2		**Ex.253**	J	HCl-dioxane	crude product	91% (HCl salt)
Ex.258			**Ex.255**	L.1.2	1-pyrrolidinacetic acid (2.7 equiv.) i-Pr_2NEt v(4 equiv.)	FC (CH_2Cl_2/MeOH)	61%
Ex.259			**Ex.255**	L.1.1	succininc anhydride (1.05 equiv.) pyridine (49 equiv.)	prep. HPLC, method 1	15%
Ex.260			**Ex.255**	L.1.2	3-(pyridine-4-yl)propanoic acid	prep. HPLC, method 1	55% (TFA salt)
Ex.261			**Ex.255**	L.1.3	1-naphthylacetic acid (1.2 equiv.)	prep. HPLC, method 1	69%
Ex.262			**Ex.255**	M.1	acetaldehyde	prep. HPLC, method 1	76% (TFA salt)

No	R^2	R^{54}	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.263			**Ex.256**	L.1.1	acetic anhydride (10 equiv.) Pyridine/CH_2Cl_2 1:1 (3 mL)	prep. HPLC, method 1	82%
x.264			**Ex.256**	L.1.3	2-naphthylacetic acid (1.2 equiv.)	prep. HPLC, method 1	61%
Ex.265			**Ex.257**	L.1.3	2-naphthylacetic acid (1.2 equiv.)	prep. HPLC, method 1	59% (TFA salt)
Ex.266			**Ex.257**	L.1.2	1-pyrrolidinacetic acid	prep. HPLC, method 2	71%
Ex.267			**Ex.257**	L.1.1	succininc anhydride (1.5 equiv.) pyridine (49 equiv.)	prep. HPLC, method 1	89% (TFA salt)
Ex.268			**Ex.257**	L.1.3	1-naphthylacetic acid (1.2 equiv.)	prep. HPLC, method 2	45%
Ex.269			**Ex.257**	M.1	acetaldehyde (0.75 mL)	prep. HPLC, method 2	70%

No	R^2	R^{54}	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.270			**Ex.255**	L.1.1	valeroyl chloride (2 equiv.)	prep. HPLC, method 1	77%
Ex.271			**Ex.257**	L.1.1	valeroyl chloride (2 equiv.)	prep. HPLC, method 1	58% (TFA salt)

*) An analytical sample was further purified by prep HPLC, method 1

Table 34b: Examples of Core 17 (**Ex.248-Ex.271**; *continued on the following pages*)

No	R^2	R^{54}	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.248-Ex.249: *cf. experimental description*							
Ex.250			C30H43N5O7	585.4	1.58 (96)	586.4	Method 2
Ex.251			C32H48N6O7	628.4	1.35 (98)	629.5	Method 2
Ex.252			C37H45N5O7	671.3	1.86 (88)	672.4	Method 2
Ex.253			C32H42N6O7	622.3	1.29 (92)	623.4	Method 2

No	R^2	R^{54}	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.254	NH_2		C27H40N6O5	528.3	1.31 (97)	529.5	Method 3
Ex.255	NH_2		C32H37N5O5	571.3	1.45 (94)	572.4	Method 2
Ex.256	NH_2		C25H35N5O5	485.3	1.06 (96)	486.4	Method 2
Ex.257	NH_2		C27H34N6O5	522.3	0.85 (96)	523.3	Method 2
Ex.258			C38H46N6O6	682.4	1.47 (95)	683.5	Method 2
Ex.259			C36H41N5O8	671.3	1.59 (87)	672.4	Method 2
Ex.260			C40H44N6O6	704.3	1.47 (100)	705.5	Method 2
Ex.261			C44H45N5O6	739.3	1.93 (99)	740.5	Method 2
Ex.262			C36H45N5O5	627.3	1.50 (100)	628.5	Method 2

No	R^2	R^{54}	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.263			C27H37N5O6	527.3	1.23 (99)	528.3	Method 2
Ex.264			C37H43N5O6	653.3	1.68 (100)	654.4	Method 2
Ex.265			C39H42N6O6	690.3	1.44 (99)	691.5	Method 2
Ex.266			C33H43N7O6	633.3	0.99 (94)	634.5	Method 2
Ex.267			C31H38N6O8	622.3	1.05 (94)	623.3	Method 2
Ex.268			C39H42N6O6	690.3	1.68 (93)	691.5	Method 3
Ex.269			C31H42N6O5	578.3	0.96 (96)	579.5	Method 2
Ex.270			C37H45N5O6	655.3	1.81 (100)	656.4	Method 2

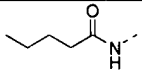
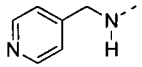
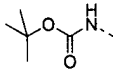
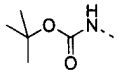
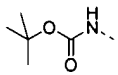
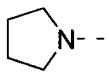
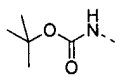
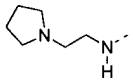
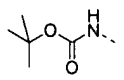
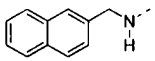
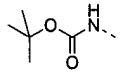
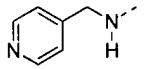
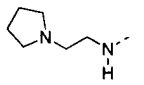
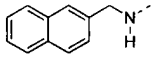
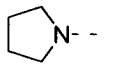
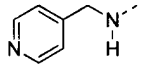
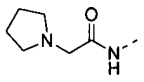
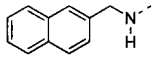
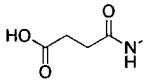
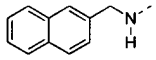
No	R^2	R^{54}	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.271			C32H42N6O6	606.3	1.25 (100)	607.4	Method 2

Table 34c: Examples of Core 17 (**Ex.248-Ex.271**; *continued on the following pages*)

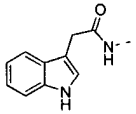
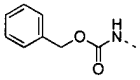
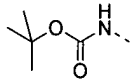
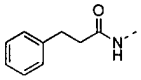
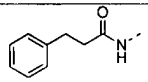
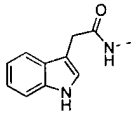
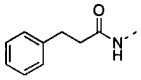
No	R^2	R^{54}	IUPAC name
Ex.248		OCH_2Ph	benzyl (4*S*,6*R*,15*S*)-6-[(*tert*-butoxycarbonyl)amino]-11,16-dimethyl-9,12,17-trioxo-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-triene-15-carboxylate
Ex.249		OH	(4*S*,6*R*,15*S*)-6-[(*tert*-butoxycarbonyl)amino]-11,16-dimethyl-9,12,17-trioxo-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-triene-15-carboxylic acid
Ex.250			*tert*-butyl *N*-[(4*S*,6*R*,15*S*)-11,16-dimethyl-9,12,17-trioxo-15-(1-pyrrolidinylcarbonyl)-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-trien-6-yl]carbamate
Ex.251			*tert*-butyl *N*-[(4*S*,6*R*,15*S*)-11,16-dimethyl-9,12,17-trioxo-15-({[2-(1-pyrrolidinyl)ethyl]amino}carbonyl)-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-trien-6-yl]carbamate

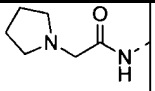
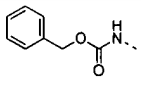
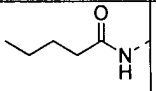
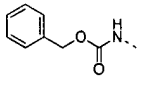
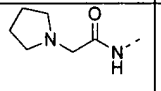
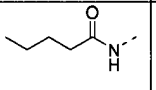
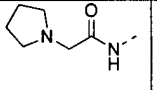
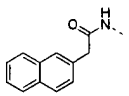
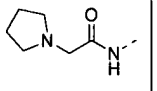
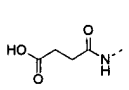
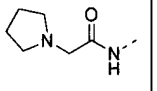
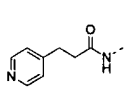
No	R^2	R^{54}	IUPAC name
Ex.252			*tert*-butyl *N*-[(4*S*,6*R*,15*S*)-11,16-dimethyl-15-{[(2-naphthylmethyl)amino]carbonyl}-9,12,17-trioxo-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-trien-6-yl]carbamate
Ex.253			*tert*-butyl *N*-[(4*S*,6*R*,15*S*)-11,16-dimethyl-9,12,17-trioxo-15-{[(4-pyridinylmethyl)amino]carbonyl}-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-trien-6-yl]carbamate
Ex.254	NH_2		(4*S*,6*R*,15*S*)-6-amino-11,16-dimethyl-9,12,17-trioxo-*N*-[2-(1-pyrrolidinyl)ethyl]-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-triene-15-carboxamide
Ex.255	NH_2		(4*S*,6*R*,15*S*)-6-amino-11,16-dimethyl-*N*-(2-naphthylmethyl)-9,12,17-trioxo-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-triene-15-carboxamide
Ex.256	NH_2		(4*S*,6*R*,15*S*)-6-amino-11,16-dimethyl-15-(1-pyrrolidinylcarbonyl)-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-triene-9,12,17-trione
Ex.257	NH_2		(4*S*,6*R*,15*S*)-6-amino-11,16-dimethyl-9,12,17-trioxo-*N*-(4-pyridinylmethyl)-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-triene-15-carboxamide
Ex.258			(4*S*,6*R*,15*S*)-11,16-dimethyl-*N*-(2-naphthylmethyl)-9,12,17-trioxo-6-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-triene-15-carboxamide
Ex.259			4-{[(4*S*,6*R*,15*S*)-11,16-dimethyl-15-{[(2-naphthylmethyl)amino]carbonyl}-9,12,17-trioxo-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-trien-6-yl]amino}-4-oxobutanoic acid

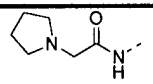
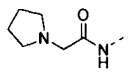
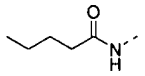
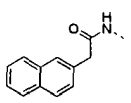
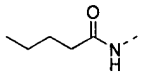
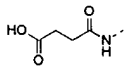
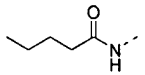
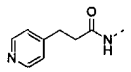
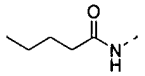
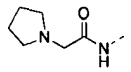
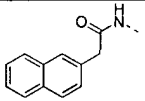
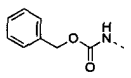
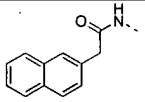
No	R^2	R^{54}	IUPAC name
Ex.260			(4*S*,6*R*,15*S*)-11,16-dimethyl-*N*-(2-naphthylmethyl)-9,12,17-trioxo-6-{[3-(4-pyridinyl)propanoyl]amino}-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-triene-15-carboxamide
Ex.261			(4*S*,6*R*,15*S*)-11,16-dimethyl-6-{[2-(1-naphthyl)acetyl]amino}-*N*-(2-naphthylmethyl)-9,12,17-trioxo-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-triene-15-carboxamide
Ex.262			(4*S*,6*R*,15*S*)-6-(diethylamino)-11,16-dimethyl-*N*-(2-naphthylmethyl)-9,12,17-trioxo-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-triene-15-carboxamide
Ex.263			*N*-[(4*S*,6*R*,15*S*)-11,16-dimethyl-9,12,17-trioxo-15-(1-pyrrolidinylcarbonyl)-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-trien-6-yl]acetamide
Ex.264			*N*-[(4*S*,6*R*,15*S*)-11,16-dimethyl-9,12,17-trioxo-15-(1-pyrrolidinylcarbonyl)-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-trien-6-yl]-2-(2-naphthyl)acetamide
Ex.265			(4*S*,6*R*,15*S*)-11,16-dimethyl-6-{[2-(2-naphthyl)acetyl]amino}-9,12,17-trioxo-*N*-(4-pyridinylmethyl)-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-triene-15-carboxamide
Ex.266			(4*S*,6*R*,15*S*)-11,16-dimethyl-9,12,17-trioxo-N-(4-pyridinylmethyl)-6-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-triene-15-carboxamide

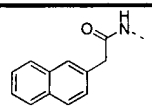
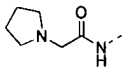
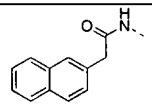
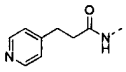
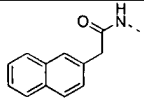
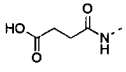
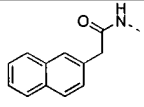
No	R^2	R^{54}	IUPAC name
Ex.267			4-{[(4*S*,6*R*,15*S*)-11,16-dimethyl-9,12,17-trioxo-15-{[(4-pyridinylmethyl)amino]carbonyl}-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-trien-6-yl]amino}-4-oxobutanoic acid
Ex.268			(4*S*,6*R*,15*S*)-11,16-dimethyl-6-{[2-(1-naphthyl)acetyl]amino}-9,12,17-trioxo-*N*-(4-pyridinylmethyl)-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-triene-15-carboxamide
Ex.269			(4*S*,6*R*,15*S*)-6-(diethylamino)-11,16-dimethyl-9,12,17-trioxo-*N*-(4-pyridinylmethyl)-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-triene-15-carboxamide
Ex.270			(4*S*,6*R*,15*S*)-11,16-dimethyl-*N*-(2-naphthylmethyl)-9,12,17-trioxo-6-(pentanoylamino)-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-triene-15-carboxamide
Ex.271			(4*S*,6*R*,15*S*)-11,16-dimethyl-9,12,17-trioxo-6-(pentanoylamino)-*N*-(4-pyridinylmethyl)-2-oxa-8,11,16-triazatricyclo[16.2.2.$0^{4,8}$]docosa-1(20),18,21-triene-15-carboxamide

Table 35a: Examples of Core 18 (**Ex.272-Ex.296;** *continued on the following pages*)

No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.272-Ex.274: *cf. experimental description*							
Ex.275			**Ex.273** (HCl salt)	L.1.3	3-indoleacetic acid (1.1 equiv.) HATU (1.5 equiv.) HOAt (1.5 equiv.) i-Pr_2NEt (5 equiv.)	FC (CH_2Cl_2/MeOH)	53%
Ex.276			**Ex.274**	L.1.3	3-phenylpropanoic acid(1.2 equiv.) HATU (1.5 equiv.) HOAt (1.5 equiv.) i-Pr_2NEt (3 equiv.)	FC (CH_2Cl_2/MeOH)	72%
Ex.277	NH_2		**Ex.276**	J	HCl-dioxane	crude product	quant. (HCl salt)
Ex.278			**Ex.277**	L.1.3	3-indoleacetic acid (1.1 equiv.) HATU (1.5 equiv.) HOAt (1.5 equiv.) i-Pr_2NEt (5 equiv.)	FC (CH_2Cl_2/MeOH)	75%

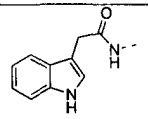
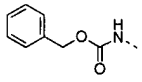
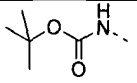
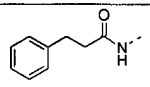
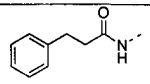
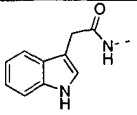
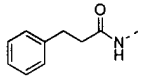
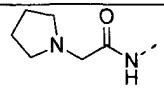
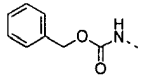
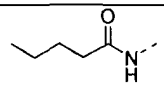
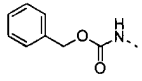
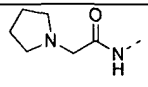
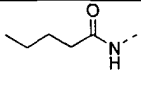
No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.279			**Ex.273** (HCl salt)	L.1.3	pyrrolidine-1-acetic acid (1.2 equiv.)	FC (EtOAc/MeOH)	67%
Ex.280			**Ex.273** (HCl salt)	L.1.1	valeroyl chloride (2 equiv.)	FC (EtOAc/MeOH)	71%
Ex.281		NH_2	**Ex.279**	K.1	H_2, $Pd(OH)_2$-C	crude product	quant.
Ex.282		NH_2	**Ex.280**	K.1	H_2, $Pd(OH)_2$-C	crude product	quant.
Ex.283			**Ex.281**	L.1.3	2-naphthylacetic acid (1.2 equiv.)	Prep. HPLC, method 3	27%
Ex.284			**Ex.281**	L.1.1	succinic anhydride (1.5 equiv.) Pyridine (49 equiv.)	Prep. HPLC, method 2	51%
Ex.285			**Ex.281**	L.1.3	3-(pyridine-4-yl)propanoic acid (1.2 equiv.)	Prep. HPLC, method 2	12%

No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.286			**Ex.281**	L.1.3	pyrrolidine-1-acetic acid (1.2 equiv.)	Prep. HPLC, method 2	16%
Ex.287			**Ex.282**	L.1.3	2-naphthylacetic acid (1.2 equiv.)	FC (CH_2Cl_2/MeOH/ aq. NH_3)	79%
Ex.288			**Ex.282**	L.1.1	succinic anhydride (1.5 equiv.) Pyridine (49 equiv.)	Prep. HPLC, method 2	57%
Ex.289			**Ex.282**	L.1.3	3-(pyridine-4-yl)propanoic acid (1.2 equiv.)	Prep. HPLC, method 3	17%
Ex.290			**Ex.282**	L.1.3	pyrrolidine-1-acetic acid (1.2 equiv.)	FC (CH_2Cl_2/MeOH/ aq. NH_3)	65%
Ex.291			**Ex.273** (HCl salt)	L.1.3	2-naphthylacetic acid (1.2 equiv.)	FC (EtOAc/MeOH)*)	79%
Ex.292		NH_2	**Ex.291**	K.1	H_2, $Pd(OH)_2$-C	FC (EtOAc/MeOH)	69%

No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.293			**Ex.292**	L.1.3	pyrrolidine-1-acetic acid (1.2 equiv.)	Prep. HPLC, method 3	64%
Ex.294			**Ex.292**	L.1.3	3-(pyridine-4-yl)propanoic acid (1.2 equiv.)	Prep. HPLC, method 3	70%
Ex.295			**Ex.292**	L.1.1	succinic anhydride (1.5 equiv.) Pyridine (49 equiv.)	Prep. HPLC, method 2	73%
Ex.296		$CH_3(CH_2)_8$ CONH	**Ex.292**	L.1.1	decanoyl chloride (2 equiv.)	Prep. HPLC, method 3	40%

*) An analytical sample was further purified by prep. HPLC, method 3

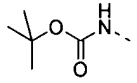
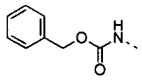
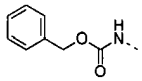
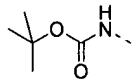
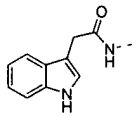
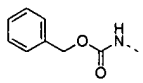
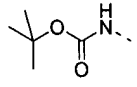
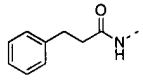
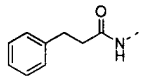
Table 35b: Examples of Core 18 (**Ex.272-Ex.296;** *continued on the following pages*)

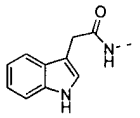
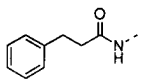
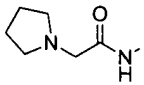
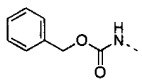
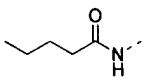
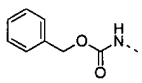
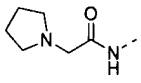
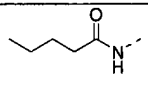
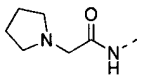
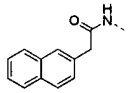
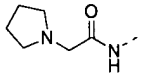
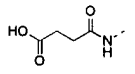
No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.272-Ex.274: *cf. experimental description*							
Ex.275			C36H39N7O7	681.3	1.53 (97)	682.5	Method 2
Ex.276			C32H42N6O7	622.3	1.57 (95)	623.4	Method 2
Ex.277	NH_2		C27H34N6O5	522.3	1.10 (98)	523.4	Method 2
Ex.278			C37H41N7O6	679.3	1.50 (98)	680.5	Method 2
Ex.279			C32H41N7O7	635.3	1.32 (98)	636.3	Method 2
Ex.280			C31H40N6O7	608.3	1.54 (98)	609.3	Method 2
Ex.281		NH_2	C24H35N7O5	501.3	1.32 (98)	502.3	Method 5a
Ex.282		NH_2	C23H34N6O5	474.3	1.24 (94)	475.1	Method 4a

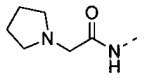
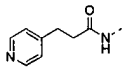
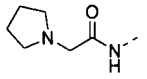
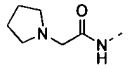
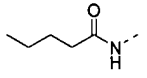
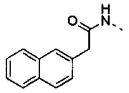
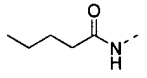
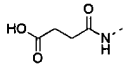
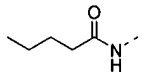
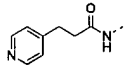
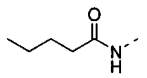
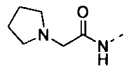
No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.283			C36H43N7O6	669.3	1.42 (95)	670.3	Method 4a
Ex.284			C28H39N7O8	601.3	0.99 (100)	602.2	Method 5a
Ex.285			C32H42N8O6	634.3	1.47 (98)	635.2	Method 5a
Ex.286			C30H44N8O6	612.3	1.55 (99)	613.3	Method 5a
Ex.287			C35H42N6O6	642.3	1.77 (98)	643.3	Method 4a
Ex.288			C27H38N6O8	574.3	1.32 (100)	575.2	Method 4a
Ex.289			C31H41N7O6	607.3	1.25 (95)	608.3	Method 4a
Ex.290			C29H43N7O6	585.3	1.30 (95)	586.4	Method 4a
Ex.291			C38H40N6O7	692.3	1.91 (97)	693.3	Method 4a
Ex.292		NH_2	C30H34N6O5	558.3	1.55 (99)	559.3	Method 4a

No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.293			C36H43N7O6	669.3	1.52 (96)	670.3	Method 4a
Ex.294			C38H41N7O6	691.3	1.46 (97)	692.3	Method 4a
Ex.295			C34H38N6O8	658.3	1.58 (99)	659.2	Method 4a
Ex.296		$CH_3(CH_2)_8CONH$	C40H52N6O6	712.4	2.22 (99)	713.4	Method 4a

Table 35c: Examples of Core 18 (**Ex.272-Ex.296**; *continued on the following pages*)

No	R^2	R^5	IUPAC name
Ex.272			benzyl *N*-[(4*S*,6*S*,13*S*)-6-[(*tert*-butoxycarbonyl)amino]-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.273	NH_2		benzyl *N*-[(4*S*,6*S*,13*S*)-6-amino-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.274		NH_2	*tert*-butyl *N*-[(4*S*,6*S*,13*S*)-13-amino-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]carbamate
Ex.275			benzyl *N*-[(4*S*,6*S*,13*S*)-6-{[2-(1*H*-indol-3-yl)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.276			*tert*-butyl *N*-[(4*S*,6*S*,13*S*)-11,15-dimethyl-9,12,16-trioxo-13-[(3-phenylpropanoyl)amino]-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]carbamate
Ex.277	NH_2		*N*-[(4*S*,6*S*,13*S*)-6-amino-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]-3-phenylpropanamide

No	R^2	R^5	IUPAC name
Ex.278			*N*-[(4*S*,6*S*,13*S*)-6-{[2-(1*H*-indol-3-yl)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]-3-phenylpropanamide
Ex.279			benzyl *N*-[(4*S*,6*S*,13*S*)-11,15-dimethyl-9,12,16-trioxo-6-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.280			benzyl *N*-[(4*S*,6*S*,13*S*)-11,15-dimethyl-9,12,16-trioxo-6-(pentanoylamino)-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.281		NH_2	*N*-[(4*S*,6*S*,13*S*)-13-amino-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]-2-(1-pyrrolidinyl)acetamide
Ex.282		NH_2	*N*-[(4*S*,6*S*,13*S*)-13-amino-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]pentanamide
Ex.283			*N*-[(4*S*,6*S*,13*S*)-11,15-dimethyl-9,12,16-trioxo-6-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]-2-(2-naphthyl)acetamide
Ex.284			4-{[(4*S*,6*S*,13*S*)-11,15-dimethyl-9,12,16-trioxo-6-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]amino}-4-oxobutanoic acid

No	R^2	R^5	IUPAC name
Ex.285			*N*-[(4*S*,6*S*,13*S*)-11,15-dimethyl-9,12,16-trioxo-6-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]-3-(4-pyridinyl)propanamide
Ex.286			*N*-[(4*S*,6*S*,13*S*)-11,15-dimethyl-9,12,16-trioxo-13-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]-2-(1-pyrrolidinyl)acetamide
Ex.287			*N*-[(4*S*,6*S*,13*S*)-11,15-dimethyl-13-{[2-(2-naphthyl)acetyl]amino}-9,12,16-trioxo-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]pentanamide
Ex.288			4-{[(4*S*,6*S*,13*S*)-11,15-dimethyl-9,12,16-trioxo-6-(pentanoylamino)-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]amino}-4-oxobutanoic acid
Ex.289			*N*-[(4*S*,6*S*,13*S*)-11,15-dimethyl-9,12,16-trioxo-13-{[3-(4-pyridinyl)propanoyl]amino}-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]pentanamide
Ex.290			*N*-[(4*S*,6*S*,13*S*)-11,15-dimethyl-9,12,16-trioxo-13-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]pentanamide

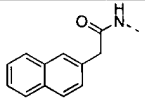
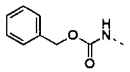
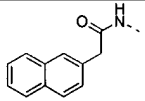
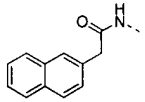
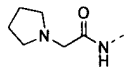
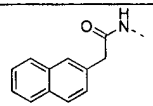
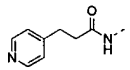
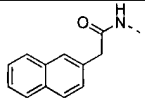
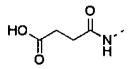
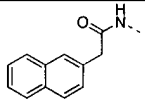
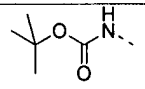
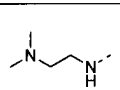
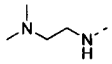
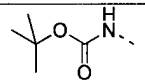
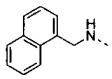
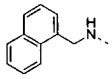
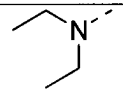
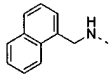
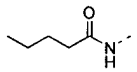
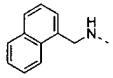
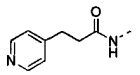
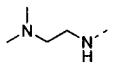
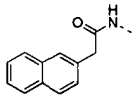
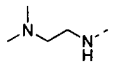
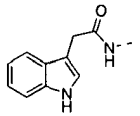
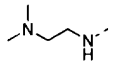
No	R^2	R^5	IUPAC name
Ex.291			benzyl *N*-[(4*S*,6*S*,13*S*)-11,15-dimethyl-6-{[2-(2-naphthyl)acetyl]amino}-9,12,16-trioxo-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate
Ex.292		NH_2	*N*-[(4*S*,6*S*,13*S*)-13-amino-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]-2-(2-naphthyl)acetamide
Ex.293			*N*-[(4*S*,6*S*,13*S*)-11,15-dimethyl-9,12,16-trioxo-13-{[2-(1-pyrrolidinyl)acetyl]amino}-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]-2-(2-naphthyl)acetamide
Ex.294			*N*-[(4*S*,6*S*,13*S*)-11,15-dimethyl-6-{[2-(2-naphthyl)acetyl]amino}-9,12,16-trioxo-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]-3-(4-pyridinyl)propanamide
Ex.295			4-{[(4*S*,6*S*,13*S*)-11,15-dimethyl-6-{[2-(2-naphthyl)acetyl]amino}-9,12,16-trioxo-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]amino}-4-oxobutanoic acid
Ex.296		$CH_3(CH_2)_8CONH$	*N*-[(4*S*,6*S*,13*S*)-11,15-dimethyl-6-{[2-(2-naphthyl)acetyl]amino}-9,12,16-trioxo-2-oxa-8,11,15,19-tetraazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]decanamide

Table 36a: Examples of Core 19 (**Ex.297-Ex.310**; *continued on the following pages*)

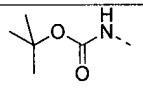
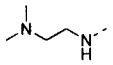
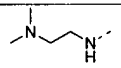
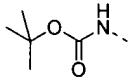
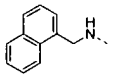
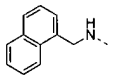
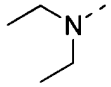
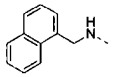
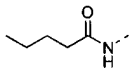
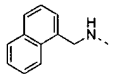
No	R^2	R^{54}	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.297-Ex.298: *cf. experimental description*							
Ex.299			**Ex.298**	L.2	N,N-dimethylethylene-diamine	Flash Chromatography	80%
Ex.300	NH_2		**Ex.299**	J	HCl-dioxane	No purification	quant. (HCl salt)
Ex.301			**Ex.298**	L.2	1-naphthylmethylamine	FC (CH_2Cl_2/MeOH)	75%
Ex.302	NH_2		**Ex.301**	J	HCl-dioxane	Crude product	quant. (HCl salt)
Ex.303			**Ex.302**	M.1	acetaldehyde	Prep. HPLC, method 2	45%
Ex.304			**Ex.302**	L.1.1	valeroyl chloride (5 equiv.)	Prep. HPLC, method 2	22%

No	R^2	R^{54}	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.305			**Ex.302**	L.1.2	3-(pyridine-4-yl)propanoic acid (3.7 equiv.) i-Pr_2NEt (4 equiv.) bicarbonate resin (4equiv.)	FC (CH_2Cl_2/MeOH/ aq. NH_3) then Prep. HPLC, method 3	55%
Ex.306			**Ex.302**	L.1.2	N,N-dimethyl glycine (6.2 equiv.) carbodiimide resin (2.5 equiv.) i-Pr_2NEt (5 equiv.) bicarbonate resin (5 equiv.)	FC (CH_2Cl_2/MeOH)	43%
Ex.307			**Ex.300**	L.1.1	valeroyl chloride (2 equiv.)	Prep. HPLC, method 2	36%

No	R^2	R^{54}	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.308			**Ex.300**	L.1.2	3-(pyridine-4-yl)propanoic acid (1.2 equiv.) i-Pr_2NEt (4 equiv.), bicarbonate resin (4equiv.)	FC (CH_2Cl_2/MeOH)	77%
Ex.309			**Ex.300**	L.1.2*)	2-naphthylacetic acid i-Pr_2NEt (4 equiv.)	Prep. HPLC, method 2	58%
Ex.310			**Ex.300**	L.1.2	3-indoleacetic acid (3.7 equiv.) i-Pr_2NEt (4 equiv.) DMF (0.2 mL) bicarbonate resin (4equiv.)	Prep. HPLC, method 2	28%

*) The treatment with (polystyrylmethyl)trimethylammonium bicarbonate was replaced by an aqueous workup ($CHCl_3$, sat. aq. $NaHCO_3$ soln)

Table 36b: Examples of Core 19 (**Ex.297-Ex.310**; *continued on the following pages*)

No	R^2	R^{54}	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.297-Ex.298: *cf. experimental description*							
Ex.299			C33H47N7O7	653.4	1.62 (97)	654.4	Method 4a
Ex.300	NH_2		C28H39N7O5	553.3	1.11 (64), 1.08 (35)	554.3	Method 4a
Ex.301			C40H46N6O7	722.3	2.19 (89)	723.4	Method 4a
Ex.302	NH_2		C35H38N6O5	622.3	1.70 (79)	623.3	Method 4a
Ex.303			C39H46N6O5	678.4	1.75 (100)	679.4	Method 4a
Ex.304			C40H46N6O6	706.4	2.09 (100)	707.4	Method 4a

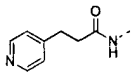
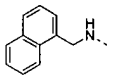
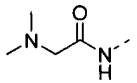
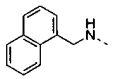
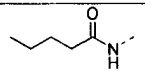
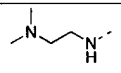
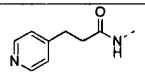
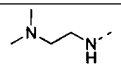
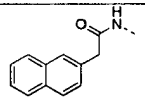
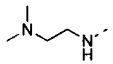
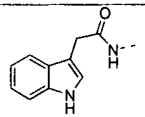
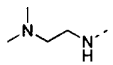
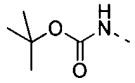
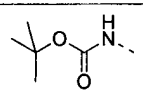
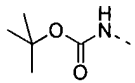
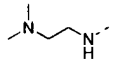
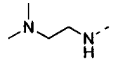
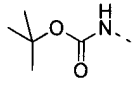
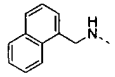
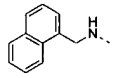
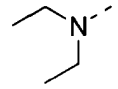
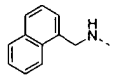
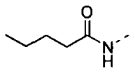
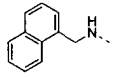
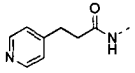
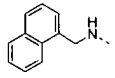
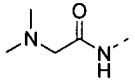
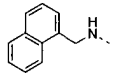
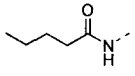
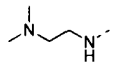
No	R^2	R^{54}	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.305			C43H45N7O6	755.3	1.67 (57), 1.70 (38)	756.4	Method 4a
Ex.306			C39H45N7O6	707.3	1.71 (86)	708.3	Method 4a
Ex.307			C33H47N7O6	637.4	1.50 (638.3)	638.3	Method 4a
Ex.308			C36H46N8O6	686.4	1.57 (92)	687.4	Method 5a
Ex.309			C40H47N7O6	721.4	1.68 (98)	722.4	Method 4a
Ex.310			C38H46N8O6	710.4	1.52 (97)	711.4	Method 4a

Table 36c: Examples of Core 19 (**Ex.297-Ex.310**; *continued on the following pages*)

No	R^2	R^{54}	IUPAC name
Ex.297		OCH_2Ph	benzyl (4*S*,6*S*,15*S*)-6-[(*tert*-butoxycarbonyl)amino]-11,16-dimethyl-9,12,17-trioxo-2-oxa-8,11,16,26-tetraazatetracyclo[16.6.2.$0^{4,8}$.$0^{21,25}$]hexacosa-1(24),18,20,22,25-pentaene-15-carboxylate
Ex.298		OH	(4*S*,6*S*,15*S*)-6-[(*tert*-butoxycarbonyl)amino]-11,16-dimethyl-9,12,17-trioxo-2-oxa-8,11,16,26-tetraazatetracyclo[16.6.2.$0^{4,8}$.$0^{21,25}$]hexacosa-1(24),18,20,22,25-pentaene-15-carboxylic acid
Ex.299			*tert*-butyl *N*-[(4*S*,6*S*,15*S*)-15-({[2-(dimethylamino)ethyl]amino}carbonyl)-11,16-dimethyl-9,12,17-trioxo-2-oxa-8,11,16,26-tetraazatetracyclo[16.6.2.$0^{4,8}$.$0^{21,25}$]hexacosa-1(24),18,20,22,25-pentaen-6-yl]carbamate
Ex.300	NH_2		(4*S*,6*S*,15*S*)-6-amino-*N*-[2-(dimethylamino)ethyl]-11,16-dimethyl-9,12,17-trioxo-2-oxa-8,11,16,26-tetraazatetracyclo[16.6.2.$0^{4,8}$.$0^{21,25}$]hexacosa-1(24),18,20,22,25-pentaene-15-carboxamide
Ex.301			*tert*-butyl *N*-[(4*S*,6*S*,15*S*)-11,16-dimethyl-15-{[(1-naphthylmethyl)amino]carbonyl}-9,12,17-trioxo-2-oxa-8,11,16,26-tetraazatetracyclo[16.6.2.$0^{4,8}$.$0^{21,25}$]hexacosa-1(25),18(26),19,21,23-pentaen-6-yl]carbamate
Ex.302	NH_2		(4*S*,6*S*,15*S*)-6-amino-11,16-dimethyl-*N*-(1-naphthylmethyl)-9,12,17-trioxo-2-oxa-8,11,16,26-tetraazatetracyclo[16.6.2.$0^{4,8}$.$0^{21,25}$]hexacosa-1(25),18(26),19,21,23-pentaene-15-carboxamide

No	R^2	R^{54}	IUPAC name
Ex.303			(4*S*,6*S*,15*S*)-6-(diethylamino)-11,16-dimethyl-*N*-(1-naphthylmethyl)-9,12,17-trioxo-2-oxa-8,11,16,26-tetraazatetracyclo[16.6.2.$0^{4,8}$.$0^{21,25}$]hexacosa-1(25),18(26),19,21,23-pentaene-15-carboxamide
Ex.304			(4*S*,6*S*,15*S*)-11,16-dimethyl-*N*-(1-naphthylmethyl)-9,12,17-trioxo-6-(pentanoylamino)-2-oxa-8,11,16,26-tetraazatetracyclo[16.6.2.$0^{4,8}$.$0^{21,25}$]hexacosa-1(25),18(26),19,21,23-pentaene-15-carboxamide
Ex.305			(4*S*,6*S*,15*S*)-11,16-dimethyl-*N*-(1-naphthylmethyl)-9,12,17-trioxo-6-{[3-(4-pyridinyl)propanoyl]amino}-2-oxa-8,11,16,26-tetraazatetracyclo[16.6.2.$0^{4,8}$.$0^{21,25}$]hexacosa-1(25),18(26),19,21,23-pentaene-15-carboxamide
Ex.306			(4*S*,6*S*,15*S*)-6-{[2-(dimethylamino)acetyl]amino}-11,16-dimethyl-*N*-(1-naphthylmethyl)-9,12,17-trioxo-2-oxa-8,11,16,26-tetraazatetracyclo[16.6.2.$0^{4,8}$.$0^{21,25}$]hexacosa-1(25),18(26),19,21,23-pentaene-15-carboxamide
Ex.307			(4*S*,6*S*,15*S*)-*N*-[2-(dimethylamino)ethyl]-11,16-dimethyl-9,12,17-trioxo-6-(pentanoylamino)-2-oxa-8,11,16,26-tetraazatetracyclo[16.6.2.$0^{4,8}$.$0^{21,25}$]hexacosa-1(25),18(26),19,21,23-pentaene-15-carboxamide

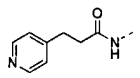
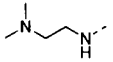
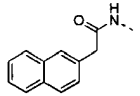
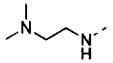
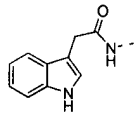
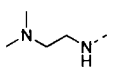
No	R^2	R^{54}	IUPAC name
Ex.308			(4*S*,6*S*,15*S*)-*N*-[2-(dimethylamino)ethyl]-11,16-dimethyl-9,12,17-trioxo-6-{[3-(4-pyridinyl)propanoyl]amino}-2-oxa-8,11,16,26-tetraazatetracyclo[16.6.2.$0^{4,8}$.$0^{21,25}$]hexacosa-1(25),18(26),19,21,23-pentaene-15-carboxamide
Ex.309			(4*S*,6*S*,15*S*)-*N*-[2-(dimethylamino)ethyl]-11,16-dimethyl-6-{[2-(2-naphthyl)acetyl]amino}-9,12,17-trioxo-2-oxa-8,11,16,26-tetraazatetracyclo[16.6.2.$0^{4,8}$.$0^{21,25}$]hexacosa-1(25),18(26),19,21,23-pentaene-15-carboxamide
Ex.310			(4*S*,6*S*,15*S*)-*N*-[2-(dimethylamino)ethyl]-6-{[2-(1*H*-indol-3-yl)acetyl]amino}-11,16-dimethyl-9,12,17-trioxo-2-oxa-8,11,16,26-tetraazatetracyclo[16.6.2.$0^{4,8}$.$0^{21,25}$]hexacosa-1(25),18(26),19,21,23-pentaene-15-carboxamide

Table 37.1.a: Example of Core 20 (**Ex.311**)

No	R^2	R^5	R^{38}	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.311: *cf. experimental description*								

Table 37.1.b: Example of Core 20 (**Ex.311**)

No	R^2	R^5	R^{38}	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.311: *cf. experimental description*								

Table 37.1.c: Example of Core 20 (**Ex.311**)

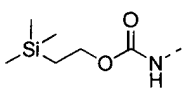
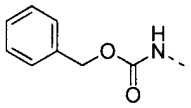
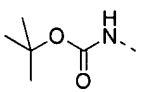
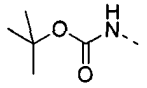
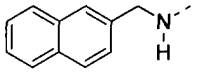
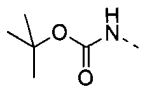
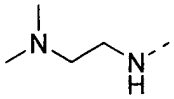
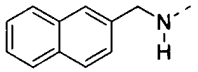
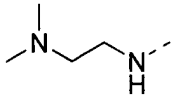
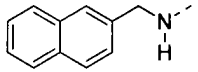
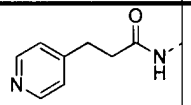
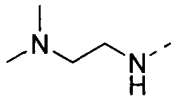
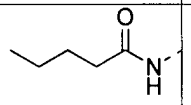
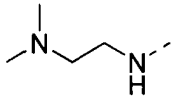
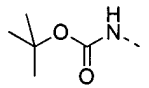
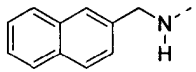
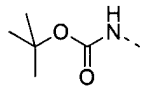
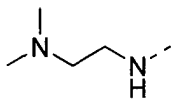
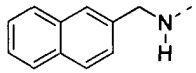
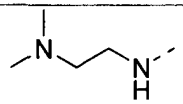
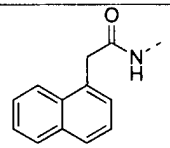
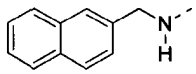
No	R^2	R^5	R^{38}	IUPAC name
Ex.311				benzyl *N*-[(4*S*,6*S*,13*S*,17*S*)-17-[(*tert*-butoxycarbonyl)amino]-11,15-dimethyl-9,12,16-trioxo-6-({[2-(trimethylsilyl)ethoxy]carbonyl}amino)-2-oxa-8,11,15-triazatetracyclo[15.6.2.$0^{4,8}$.$0^{20,24}$]pentacosa-1(24),20,22-trien-13-yl]carbamate

Table 37.2.a: Examples of Core 21 (**Ex.312-Ex.341**; *continued on the following pages*)

No	X	R^2	R^{54}	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.312-Ex.315: *cf. experimental description*								
Ex.316	S			**Ex.314**	L.2	2-naphthylmethyl amine (2 equiv.)	FC (CH_2Cl_2/MeOH)	86%
Ex.317	S			**Ex.314**	L.2	N,N-dimethyl-ethyl amine (2 equiv.)	FC (CH_2Cl_2/MeOH)	72%
Ex.318	S	NH_2		**Ex.316**	J	HCl (4M dioxane)	crude product	quant. (HCl salt)
Ex.319	S	NH_2		**Ex.317**	J	HCl (4M dioxane)	crude product	quant. (HCl salt)
Ex.320	S			**Ex.318**	L.1.1	acetic anhydride (5 equiv.)	prep., HPLC, method 1	43%

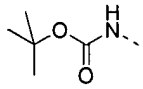
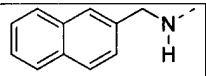
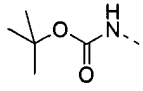
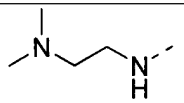
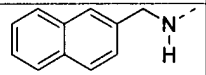
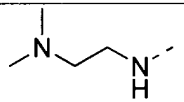
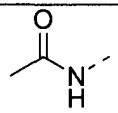
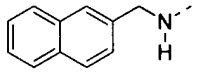
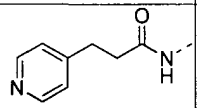
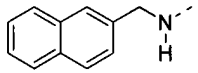
No	X	R^2	R^{54}	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.321	S			**Ex.318**	L.1.3	HATU (1.5 equiv.), HOAt (1.5 equiv.), DIPEA (5 equiv), 3-pyridyl-propanoic acide (1.1 equiv.)	prep. HPLC, method 1	39% (TFA salt)
Ex.322	S			**Ex.318**	L.1.1	pentanoic acid chloride (2 equiv.)	prep. HPLC, method 1	49%
Ex.323	S			**Ex.319**	L.1.3	2-naphthylacetic acid (2 equiv.)	prep. HPLC, method 2	40%
Ex.324	S			**Ex.319**	L.1.3	1-naphthylacetic acid (2 equiv.)	prep. HPLC, method 2	43%
Ex.325	S			**Ex.319**	L.1.1	acetic anhydride (5 equiv.)	prep. HPLC, method 2	73%

No	X	R^2	R^{54}	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.326	S			**Ex.319**	L.1.3	3-pyridinyl-propanoic acid (2 equiv.)	prep. HPLC, method 2	43%
Ex.327	S			**Ex.319**	L.1.1	pentanoyl chloride (4 equiv.)	prep. HPLC, method 2	55%
Ex.328	SO_2			**Ex.315**	L.2	2-naphthyl-methylamine (2 equiv.)	prep. HPLC, method 2	75%
Ex.329	SO_2			**Ex.315**	L.2	N,N-dimethylene-diamine (2 equiv.)	FC (CH2Cl2/MeOH/ aq.NH3)	97%
Ex.330	SO_2	NH_2		**Ex.328**	J	HCl(4M dioxane)	crude product	88% (HCl salt)
Ex.331	SO_2	NH_2		**Ex.329**	J	HCl(4M dioxane)	crude product	75% (HCl salt)
Ex.332	SO_2			**Ex.330**	L.1.2	1-naphthylacetic acid (1.2 equiv.)	prep. HPLC, method 1 then method 3	60%

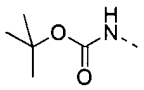
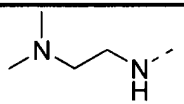
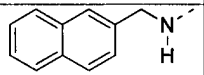
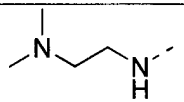
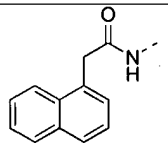
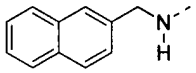
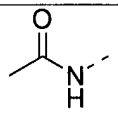
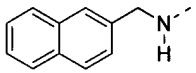
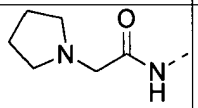
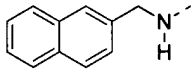
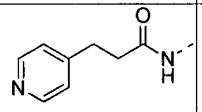
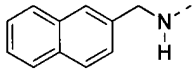
No	X	R^2	R^{54}	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.333	SO_2			**Ex.330**	L.1.1	acetic anhydride (5 equiv).	prep. HPLC, method 2 then method 3	65%
Ex.334	SO_2			**Ex.330**	L.1.2	1-pyrrolidine-acetic acid (1.8 equiv.) HOBt·H_2O (1.8 equiv.)	prep. HPLC, method 2	60%
Ex.335	SO_2			**Ex.330**	L.1.2	4-pyridinyl-propanoic acid (2.5 equiv.) HOBt.H_2O (1.8 equiv.)	prep. HPLC, method 2	67%
Ex.336	SO_2			**Ex.330**	L.1.1	pentanoyl chloride (6 equiv.) pyridine (10 equiv.), Et_3N (5 equiv.)	prep. HPLC, method 1 then method 3	49%

No	X	R^2	R^{54}	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.337	SO_2			**Ex.331**	L.1.3	2-naphthylacetic acid (2 equiv.)	prep. HPLC, method 2	41%
Ex.338	SO_2			**Ex.331**	L.1.3	1-naphthylacetic acid (2 equiv.)	prep. HPLC, method 2	45%
Ex.339	SO_2			**Ex.331**	L.1.1	acetic anhydride (5 equiv.)	prep. HPLC, method 2	30%
Ex.340	SO_2			**Ex.331**	L.1.3	3-pyridinyl-propanoic acid (2 equiv.)	prep. HPLC, method 2	23%
Ex.341	SO_2			**Ex.331**	L.1.1	pentanoyl chloride (4 equiv.)	prep. HPLC, method 2	48%

Table 37.2.b: Examples of Core 21 (**Ex.312-Ex.341**; *continued on the following pages*)

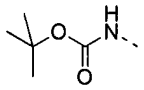
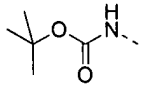
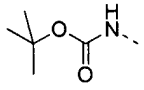
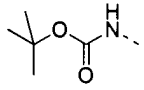
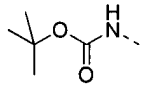
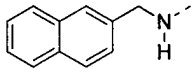
No	X	R^2	R^{54}	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.312-Ex.315: *cf. experimental description*								
Ex.316	S			C37H45N5O6S	687.3	2.20 (95)	688.2	Method 4b
Ex.317	S			C30H46N6O6S	618.3	1.57 (95)	619.2	Method 4b
Ex.318	S	NH_2		C32H37N5O4S	587.3	1.66 (91)	588.0	Method 4b
Ex.319	S	NH_2		C25H38N6O4S	518.3	1.44 (87)	519.2	Method 5b
Ex.320	S			C34H39N5O5S	629.3	1.88 (92)	630.2	Method 4b
Ex.321	S			C40H44N6O5S	720.3	1.56 (93)	721.3	Method 2

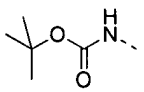
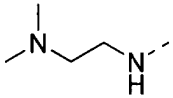
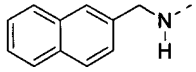
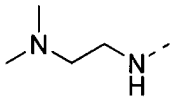
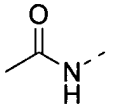
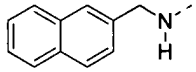
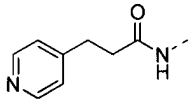
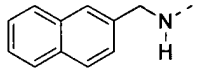
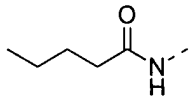
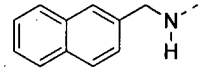
No	X	R^2	R^{54}	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.322	S			C37H45N5O5S	671.3	2.08 (91)	672.3	Method 4b
Ex.323	S			C37H46N6O5S	686.3	1.67 (96)	687.2	Method 4b
Ex.324	S			C37H46N6O5S	686.3	1.66 (96)	687.2	Method 4b
Ex.325	S			C27H40N6O5S	560.3	1.19 (98)	561.2	Method 4b
Ex.326	S			C33H45N7O5S	651.3	1.12 (89)	652.2	Method 4b
Ex.327	S			C30H46N6O5S	602.3	1.46 (97)	603.0	Method 4b
Ex.328	SO_2			C37H45N5O8S	719.3	2.08 (98)	720.2	Method 4b

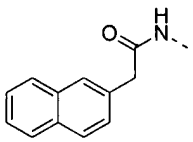
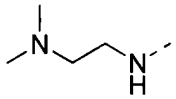
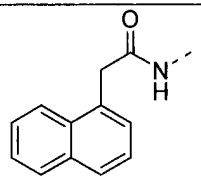
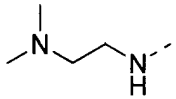
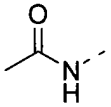
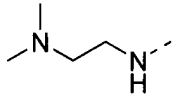
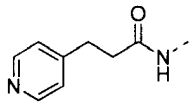
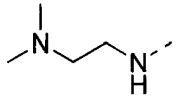
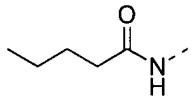
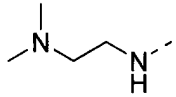
No	X	R^2	R^{54}	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.329	SO_2			C30H46N6O8S	650.3	1.45 (94)	651.2	Method 4b
Ex.330	SO_2	NH_2		C32H37N5O6S	619.3	1.58 (94)	620.0	Method 4b
Ex.331	SO_2	NH_2		C25H38N6O6S	550.3	1.28 (80)	551.2	Method 5a
Ex.332	SO_2			C44H45N5O7S	787.3	2.14 (96)	788.2	Method 4b
Ex.333	SO_2			C34H39N5O7S	661.3	1.78 (95)	661.8	Method 4b
Ex.334	SO_2			C38H46N6O7S	730.3	1.64 (95)	731.2	Method 4b
Ex.335	SO_2			C40H44N6O7S	752.3	1.63 (98)	753.2	Method 4b

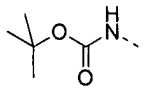
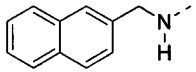
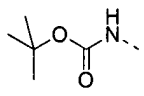
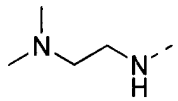
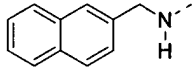
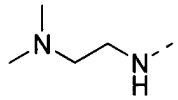
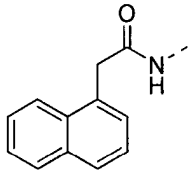
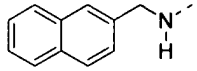
No	X	R^2	R^{54}	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.336	SO_2			C37H45N5O7S	703.3	1.98 (96)	704.2	Method 4b
Ex.337	SO_2			C37H46N6O7S	718.3	1.61 (96)	719.3	Method 4a
Ex.338	SO_2			C37H46N6O7S	718.3	1.59 (96)	719.3	Method 4a
Ex.339	SO_2			C27H40N6O7S	592.3	1.33 (95)	593.3	Method 5a
Ex.340	SO_2			C33H45N7O7S	683.3	1.49 (100)	684.1	Method 5a
Ex.341	SO_2			C30H46N6O7S	634.3	1.61 (91)	635.3	Method 5a

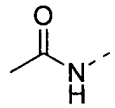
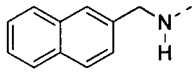
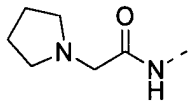
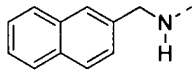
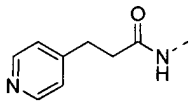
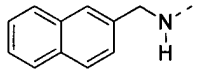
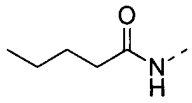
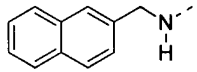
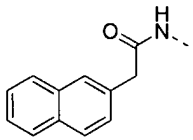
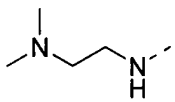
Table 37.2.c: Examples Core 21 (**Ex.312-Ex.341**; *continued on the following pages*)

No	R^2	R^{54}	X	IUPAC name
Ex.312		OCH_2Ph	S	benzyl (4*S*,6*R*,15*S*)-6-[(*tert*-butoxycarbonyl)amino]-11,16-dimethyl-9,12,17-trioxo-2-thia-8,11,16-triazatricyclo[16.3.1.$0^{4,8}$]docosa-1(22),18,20-triene-15-carboxylate
Ex.313		OCH_2Ph	SO_2	benzyl (4*S*,6*R*,15*S*)-6-[(*tert*-butoxycarbonyl)amino]-11,16-dimethyl-2,2,9,12,17-pentaoxo-2λ^6-thia-8,11,16-triazatricyclo[16.3.1.$0^{4,8}$]docosa-1(22),18,20-triene-15-carboxylate
Ex.314		OH	S	(4*S*,6*R*,15*S*)-6-[(*tert*-butoxycarbonyl)amino]-11,16-dimethyl-9,12,17-trioxo-2-thia-8,11,16-triazatricyclo[16.3.1.$0^{4,8}$]docosa-1(22),18,20-triene-15-carboxylic acid
Ex.315		OH	SO_2	(4*S*,6*R*,15*S*)-6-[(*tert*-butoxycarbonyl)amino]-11,16-dimethyl-2,2,9,12,17-pentaoxo-2λ^6-thia-8,11,16-triazatricyclo[16.3.1.$0^{4,8}$]docosa-1(22),18,20-triene-15-carboxylic acid
Ex.316			S	*tert*-butyl *N*-[(4*S*,6*R*,15*S*)-11,16-dimethyl-15-{[(2-naphthylmethyl)amino]carbonyl}-9,12,17-trioxo-2-thia-8,11,16-triazatricyclo[16.3.1.$0^{4,8}$]docosa-1(22),18,20-trien-6-yl]carbamate

No	R^2	R^{54}	X	IUPAC name
Ex.317			S	*tert*-butyl *N*-[(4*S*,6*R*,15*S*)-15-({[2-(dimethylamino)ethyl]amino}carbonyl)-11,16-dimethyl-9,12,17-trioxo-2-thia-8,11,16-triazatricyclo[16.3.1.$0^{4,8}$]docosa-1(22),18,20-trien-6-yl]carbamate
Ex.318	NH_2		S	(4*S*,6*R*,15*S*)-6-amino-11,16-dimethyl-*N*-(2-naphthylmethyl)-9,12,17-trioxo-2-thia-8,11,16-triazatricyclo[16.3.1.$0^{4,8}$]docosa-1(22),18,20-triene-15-carboxamide
Ex.319	NH_2		S	(4*S*,6*R*,15*S*)-6-amino-*N*-[2-(dimethylamino)ethyl]-11,16-dimethyl-9,12,17-trioxo-2-thia-8,11,16-triazatricyclo[16.3.1.$0^{4,8}$]docosa-1(22),18,20-triene-15-carboxamide
Ex.320			S	(4*S*,6*R*,15*S*)-6-(acetylamino)-11,16-dimethyl-*N*-(2-naphthylmethyl)-9,12,17-trioxo-2-thia-8,11,16-triazatricyclo[16.3.1.$0^{4,8}$]docosa-1(22),18,20-triene-15-carboxamide
Ex.321			S	(4*S*,6*R*,15*S*)-11,16-dimethyl-*N*-(2-naphthylmethyl)-9,12,17-trioxo-6-{[3-(4-pyridinyl)propanoyl]amino}-2-thia-8,11,16-triazatricyclo[16.3.1.$0^{4,8}$]docosa-1(22),18,20-triene-15-carboxamide
Ex.322			S	(4*S*,6*R*,15*S*)-11,16-dimethyl-*N*-(2-naphthylmethyl)-9,12,17-trioxo-6-(pentanoylamino)-2-thia-8,11,16-triazatricyclo[16.3.1.$0^{4,8}$]docosa-1(22),18,20-triene-15-carboxamide

No	R^2	R^{54}	X	IUPAC name
Ex.323			S	(4*S*,6*R*,15*S*)-*N*-[2-(dimethylamino)ethyl]-11,16-dimethyl-6-{[2-(2-naphthyl)acetyl]amino}-9,12,17-trioxo-2-thia-8,11,16-triazatricyclo[16.3.1.$0^{4,8}$]docosa-1(22),18,20-triene-15-carboxamide
Ex.324			S	(4*S*,6*R*,15*S*)-*N*-[2-(dimethylamino)ethyl]-11,16-dimethyl-6-{[2-(1-naphthyl)acetyl]amino}-9,12,17-trioxo-2-thia-8,11,16-triazatricyclo[16.3.1.$0^{4,8}$]docosa-1(22),18,20-triene-15-carboxamide
Ex.325			S	(4*S*,6*R*,15*S*)-6-(acetylamino)-*N*-[2-(dimethylamino)ethyl]-11,16-dimethyl-9,12,17-trioxo-2-thia-8,11,16-triazatricyclo[16.3.1.$0^{4,8}$]docosa-1(22),18,20-triene-15-carboxamide
Ex.326			S	(4*S*,6*R*,15*S*)-*N*-[2-(dimethylamino)ethyl]-11,16-dimethyl-9,12,17-trioxo-6-{[3-(4-pyridinyl)propanoyl]amino}-2-thia-8,11,16-triazatricyclo[16.3.1.$0^{4,8}$]docosa-1(22),18,20-triene-15-carboxamide
Ex.327			S	(4*S*,6*R*,15*S*)-*N*-[2-(dimethylamino)ethyl]-11,16-dimethyl-9,12,17-trioxo-6-(pentanoylamino)-2-thia-8,11,16-triazatricyclo[16.3.1.$0^{4,8}$]docosa-1(22),18,20-triene-15-carboxamide

No	R^2	R^{54}	X	IUPAC name
Ex.328			SO_2	*tert*-butyl *N*-[(4*S*,6*R*,15*S*)-11,16-dimethyl-15-{[(2-naphthylmethyl)amino]carbonyl}-2,2,9,12,17-pentaoxo-2λ^6-thia-8,11,16-triazatricyclo[16.3.1.0^{4,8}]docosa-1(22),18,20-trien-6-yl]carbamate
Ex.329			SO_2	*tert*-butyl *N*-[(4*S*,6*R*,15*S*)-15-({[2-(dimethylamino)ethyl]amino}carbonyl)-11,16-dimethyl-2,2,9,12,17-pentaoxo-2λ^6-thia-8,11,16-triazatricyclo[16.3.1.0^{4,8}]docosa-1(22),18,20-trien-6-yl]carbamate
Ex.330	NH_2		SO_2	(4*S*,6*R*,15*S*)-6-amino-11,16-dimethyl-*N*-(2-naphthylmethyl)-2,2,9,12,17-pentaoxo-2λ^6-thia-8,11,16-triazatricyclo[16.3.1.0^{4,8}]docosa-1(22),18,20-triene-15-carboxamide
Ex.331	NH_2		SO_2	(4*S*,6*R*,15*S*)-6-amino-*N*-[2-(dimethylamino)ethyl]-11,16-dimethyl-2,2,9,12,17-pentaoxo-2λ^6-thia-8,11,16-triazatricyclo[16.3.1.0^{4,8}]docosa-1(22),18,20-triene-15-carboxamide
Ex.332			SO_2	(4*S*,6*R*,15*S*)-11,16-dimethyl-6-{[2-(1-naphthyl)acetyl]amino}-N-(2-naphthylmethyl)-2,2,9,12,17-pentaoxo-2λ^6-thia-8,11,16-triazatricyclo[16.3.1.0^{4,8}]docosa-1(22),18,20-triene-15-carboxamide

No	R^2	R^{54}	X	IUPAC name
Ex.333			SO_2	(4*S*,6*R*,15*S*)-6-(acetylamino)-11,16-dimethyl-*N*-(2-naphthylmethyl)-2,2,9,12,17-pentaoxo-2λ^6-thia-8,11,16-triazatricyclo[16.3.1.0^{4,8}]docosa-1(22),18,20-triene-15-carboxamide
Ex.334			SO_2	(4*S*,6*R*,15*S*)-11,16-dimethyl-*N*-(2-naphthylmethyl)-2,2,9,12,17-pentaoxo-6-{[2-(1-pyrrolidinyl)acetyl]amino}-2λ^6-thia-8,11,16-triazatricyclo[16.3.1.0^{4,8}]docosa-1(22),18,20-triene-15-carboxamide
Ex.335			SO_2	(4*S*,6*R*,15*S*)-11,16-dimethyl-*N*-(2-naphthylmethyl)-2,2,9,12,17-pentaoxo-6-{[3-(4-pyridinyl)propanoyl]amino}-2λ^6-thia-8,11,16-triazatricyclo[16.3.1.0^{4,8}]docosa-1(22),18,20-triene-15-carboxamide
Ex.336			SO_2	(4*S*,6*R*,15*S*)-11,16-dimethyl-*N*-(2-naphthylmethyl)-2,2,9,12,17-pentaoxo-6-(pentanoylamino)-2λ^6-thia-8,11,16-triazatricyclo[16.3.1.0^{4,8}]docosa-1(22),18,20-triene-15-carboxamide
Ex.337			SO_2	(4*S*,6*R*,15*S*)-*N*-[2-(dimethylamino)ethyl]-11,16-dimethyl-6-{[2-(2-naphthyl)acetyl]amino}-2,2,9,12,17-pentaoxo-2λ^6-thia-8,11,16-triazatricyclo[16.3.1.0^{4,8}]docosa-1(22),18,20-triene-15-carboxamide

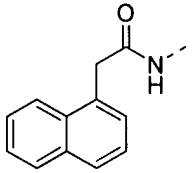
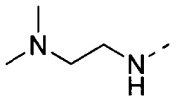
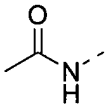
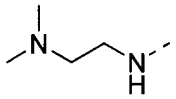
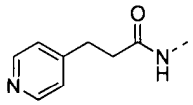
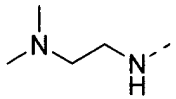
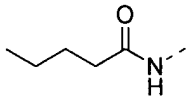
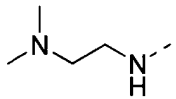
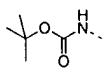
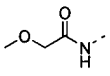
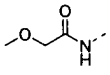
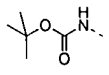
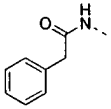
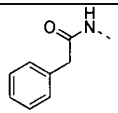
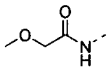
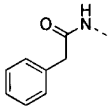
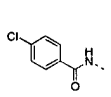
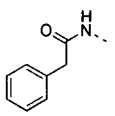
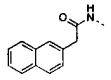
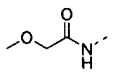
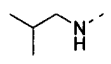
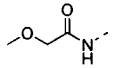
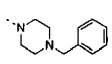
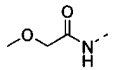
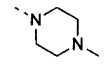
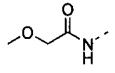
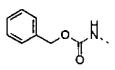
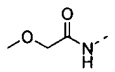
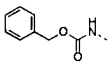
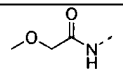
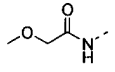
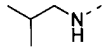
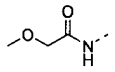
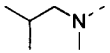
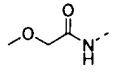
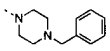
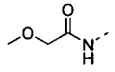
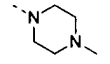
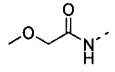
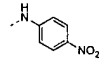
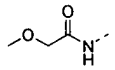
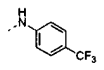
No	R^2	R^{54}	X	IUPAC name
Ex.338			SO_2	(4*S*,6*R*,15*S*)-*N*-[2-(dimethylamino)ethyl]-11,16-dimethyl-6-{[2-(1-naphthyl)acetyl]amino}-2,2,9,12,17-pentaoxo-2λ^6-thia-8,11,16-triazatricyclo[16.3.1.0^{4,8}]docosa-1(22),18,20-triene-15-carboxamide
Ex.339			SO_2	(4*S*,6*R*,15*S*)-6-(acetylamino)-*N*-[2-(dimethylamino)ethyl]-11,16-dimethyl-2,2,9,12,17-pentaoxo-2λ^6-thia-8,11,16-triazatricyclo[16.3.1.0^{4,8}]docosa-1(22),18,20-triene-15-carboxamide
Ex.340			SO_2	(4*S*,6*R*,15*S*)-*N*-[2-(dimethylamino)ethyl]-11,16-dimethyl-2,2,9,12,17-pentaoxo-6-{[3-(4-pyridinyl)propanoyl]amino}-2λ^6-thia-8,11,16-triazatricyclo[16.3.1.0^{4,8}]docosa-1(22),18,20-triene-15-carboxamide
Ex.341			SO_2	(4*S*,6*R*,15*S*)-*N*-[2-(dimethylamino)ethyl]-11,16-dimethyl-2,2,9,12,17-pentaoxo-6-(pentanoylamino)-2λ^6-thia-8,11,16-triazatricyclo[16.3.1.0^{4,8}]docosa-1(22),18,20-triene-15-carboxamide

Table 38a: Examples of Core 22 (**Ex.342-Ex.362**; *continued on the following pages*)

No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.342-Ex.343: *cf. experimental description*							
Ex.344			**Ex.343**	L.1.1	2-methoxyacetyl chloride (1.5 equiv.) pyridine (5 equiv.)	FC (hexane/EtOAc/MeOH)	97%
Ex.345	NH_2		**Ex.344**	J	HCl-dioxane	crude product	76% (HCl salt)
Ex.346			**Ex.343**	L.1.1	phenylacetyl chloride (1.5 equiv.) pyridine (5 equiv.)	FC (hexane/EtOAc/MeOH)	84%
Ex.347	NH_2		**Ex.346**	J	HCl-dioxane	crude product	94% (HCl salt)
Ex.348			**Ex.347**	L.1.1	2-methoxyacetyl chloride (1.5 equiv.) pyridine (5 equiv.)	FC (hexane/EtOAc/MeOH)	97%

No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.349			**Ex.347**	L.1.1	4-chlorobenzoyl chloride (1.5 equiv.) pyridine (5 equiv.)	FC (hexane/EtOAc/MeOH)	77%
Ex.350			**Ex.345**	L.1.3	2-naphthylacetic acid (1.0 equiv.), HATU (1.0 equiv.) HOAt (1.0 equiv.) pyridine (5 equiv.)	FC (hexane/EtOAc/MeOH)	77%
Ex.351			**Ex.345**[*)]	M.2	isobutyraldehyde (1.0 equiv.)	FC (hexane/EtOAc/MeOH)	65%
Ex.352			**Ex.345**	O	N-benzyl-2-chloro-N-(2-chloroethyl)-ethanamine	FC (hexane/EtOAc/MeOH)	52%
Ex.353			**Ex.352**	M.4	H_2, $Pd(OH)_2$-C aq. formaldehyde soln	FC (CH_2Cl_2/MeOH/aq. NH_3)	75%
Ex.354	NH_2		**Ex.342**	J	HCl-dioxane	crude product	93% (HCl salt)

No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.355			**Ex.354**	L.1.1	2-methoxyacetyl chloride (1.5 equiv.) pyridine (5 equiv.)	FC (hexane/EtOAc/MeOH)	86%
Ex.356		NH_2	**Ex.355**	K.1	H_2, $Pd(OH)_2$-C	crude product	94%
Ex.357			**Ex.356**	M.2	isobutyraldehyde (1.0 equiv.)	FC (hexane/EtOAc/MeOH)	73%
Ex.358			**Ex.357**	M.3	aq. formaldehyde soln (2.5 equiv.) $NaBH(OAc)_3$ (3 equiv.)	FC (hexane/EtOAc/MeOH)	78%
Ex.359			**Ex.356**	O	N-benzyl-2-chloro-N-(2-chloroethyl)-ethanamine	FC (EtOAc/MeOH)	52%
Ex.360			**Ex.359**	M.4	H_2, $Pd(OH)_2$-C aq. formaldehyde soln	FC (CH_2Cl_2/MeOH/aq. NH_3)	66%
Ex.361			**Ex.356**	**)	**)	FC (hexane/EtOAc/MeOH)	59%

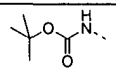
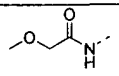
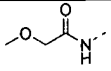
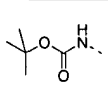
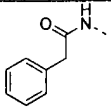
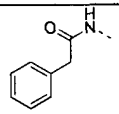
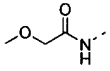
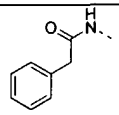
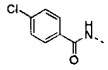
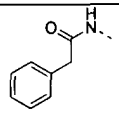
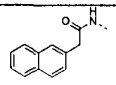
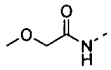
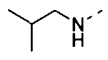
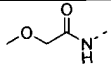
No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.362			**Ex.356**	***)	***)	prep. HPLC method 1	9%

*) Used as free base

) A soln of **Ex.356 (60 mg, 0.15 mmol) in DMSO (0.3 mL) was treated with 1-fluoro-4-nitrobenzene (0.031 mL, 0.3 mmol) and i-Pr_2NEt (0.084 mL, 0.6 mmol) at 50°C for 15 h. Aq. workup (EtOAc, H_2O, 1 M aq. HCl soln; Na_2SO_4) and FC (hexane/EtOAc/MeOH) afforded **Ex.361** (46 mg, 59%).

***) Dioxane (2.0 mL) was added to a mixture of 4-bromobenzotrifluoride (0.05 mL, 0.35 mmol), tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (30 mg), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (18 mg), **Ex.356** (60 mg, 0.15 mmol) and Cs_2CO_3 (115 mg, 0.35 mmol). The mixture was heated to 90°C for 36 h, followed by aq. workup (CH_2Cl_2, aq. Na_2CO_3 soln; Na_2SO_4) and prep. HPLC method 3 afforded **Ex.362** (7 mg, 9%).

Table 38b: Examples of Core 22 (**Ex.342-Ex.362**; *continued on the following page*)

No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.342-Ex.343: *cf. experimental description*							
Ex.344			C24H33FN4O7	508.2	1.66 (99)	509.1	Method 10a
Ex.345	NH_2		C19H25FN4O5	408.2	0.91 (100)	409.2	Method 10a
Ex.346			C29H35FN4O6	554.3	1.92 (99)	555.3	Method 10a
Ex.347	NH_2		C24H27FN4O4	454.2	1.20 (98)	455.2	Method 10a
Ex.348			C27H31FN4O6	526.2	1.50 (97)	527.2	Method 10a
Ex.349			C31H30ClFN4O5	592.2	1.93 (97)	593.2	Method 10a
Ex.350			C31H33FN4O6	576.2	1.72 (97)	577.2	Method 10a
Ex.351			C23H33FN4O5	464.2	1.16 (93)	465.2	Method 10a

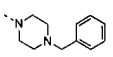
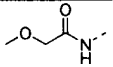
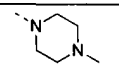
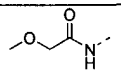
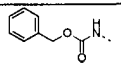
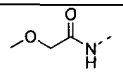
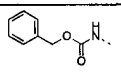
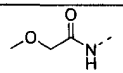
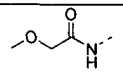
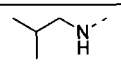
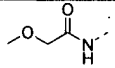
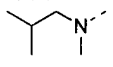
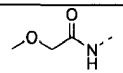
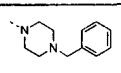
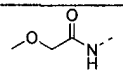
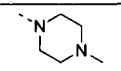
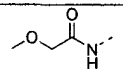
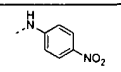
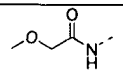
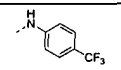
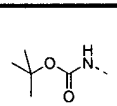
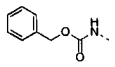
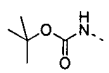
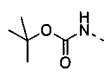
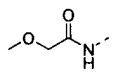
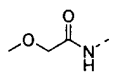
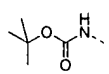
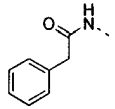
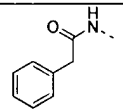
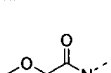
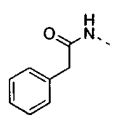
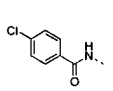
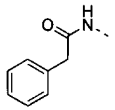
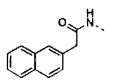
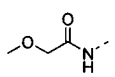
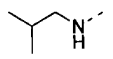
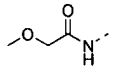
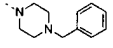
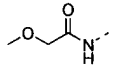
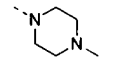
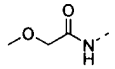
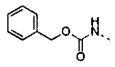
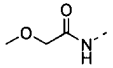
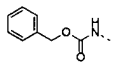
No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.352			C30H38FN5O5	567.3	1.24 (84)	568.3	Method 10a
Ex.353			C24H34FN5O5	491.2	1.01 (88)	492.1	Method 10a
Ex.354	NH_2		C24H27FN4O5	470.2	1.29 (93)	471.2	Method 10a
Ex.355			C27H31FN4O7	542.2	1.60 (95)	543.2	Method 10a
Ex.356		NH_2	C19H25FN4O5	408.2	1.02 (99)	409.2	Method 10a
Ex.357			C23H33FN4O5	464.2	1.15 (96)	465.2	Method 10a
Ex.358			C24H35FN4O5	478.2	1.19 (100)	479.3	Method 10a
Ex.359			C30H38FN5O5	567.3	1.22 (96)	568.3	Method 10a
Ex.360			C24H34FN5O5	491.3	1.04 (96)	492.1	Method 10a
Ex.361			C25H28FN5O7	529.2	1.61 (98)	530.2	Method 10a
Ex.362			C26H28F4N4O5	552.2	1.90 (97)	553.2	Method 10a

Table 38c: Examples of Core 22 (**Ex.342-Ex.362**; *continued on the following pages*)

No	R^2	R^5	IUPAC name
Ex.342			*tert*-butyl *N*-((2*S*,6*S*,16a*S*)-6-{[(benzyloxy)carbonyl]amino}-12-fluoro-5,10-dioxo-2,3,5,6,7,8,9,10,16,16a-decahydro-1*H*-pyrrolo[2,1-*c*][1,4,9]benzoxadiazacyclododecin-2-yl)carbamate
Ex.343		NH_2	*tert*-butyl *N*-[(2*S*,6*S*,16a*S*)-6-amino-12-fluoro-5,10-dioxo-2,3,5,6,7,8,9,10,16,16a-decahydro-1*H*-pyrrolo[2,1-*c*][1,4,9]benzoxadiazacyclododecin-2-yl]carbamate
Ex.344			*tert*-butyl *N*-{(2*S*,6*S*,16a*S*)-12-fluoro-6-[(2-methoxyacetyl)amino]-5,10-dioxo-2,3,5,6,7,8,9,10,16,16a-decahydro-1*H*-pyrrolo[2,1-*c*][1,4,9]benzoxadiazacyclododecin-2-yl}carbamate
Ex.345	NH_2		*N*-[(2*S*,6*S*,16a*S*)-2-amino-12-fluoro-5,10-dioxo-2,3,5,6,7,8,9,10,16,16a-decahydro-1*H*-pyrrolo[2,1-*c*][1,4,9]benzoxadiazacyclododecin-6-yl]-2-methoxyacetamide
Ex.346			*tert*-butyl *N*-{(2*S*,6*S*,16a*S*)-12-fluoro-5,10-dioxo-6-[(2-phenylacetyl)amino]-2,3,5,6,7,8,9,10,16,16a-decahydro-1*H*-pyrrolo[2,1-*c*][1,4,9]benzoxadiazacyclododecin-2-yl}carbamate
Ex.347	NH_2		*N*-[(2*S*,6*S*,16a*S*)-2-amino-12-fluoro-5,10-dioxo-2,3,5,6,7,8,9,10,16,16a-decahydro-1*H*-pyrrolo[2,1-*c*][1,4,9]benzoxadiazacyclododecin-6-yl]-2-phenylacetamide
Ex.348			*N*-{(2*S*,6*S*,16a*S*)-12-fluoro-5,10-dioxo-6-[(2-phenylacetyl)amino]-2,3,5,6,7,8,9,10,16,16a-decahydro-1*H*-pyrrolo[2,1-*c*][1,4,9]benzoxadiazacyclododecin-2-yl}-2-methoxyacetamide

No	R^2	R^5	IUPAC name
Ex.349			*N*-{(2*S*,6*S*,16a*S*)-12-fluoro-5,10-dioxo-6-[(2-phenylacetyl)amino]-2,3,5,6,7,8,9,10,16,16a-decahydro-1*H*-pyrrolo[2,1-*c*][1,4,9]benzoxadiazacyclododecin-2-yl}-4-chlorobenzamide
Ex.350			*N*-((2*S*,6*S*,16a*S*)-12-fluoro-2-{[2-(2-naphthyl)acetyl]amino}-5,10-dioxo-2,3,5,6,7,8,9,10,16,16a-decahydro-1*H*-pyrrolo[2,1-*c*][1,4,9]benzoxadiazacyclododecin-6-yl)-2-methoxyacetamide
Ex.351			*N*-[(2*S*,6*S*,16a*S*)-12-fluoro-2-(isobutylamino)-5,10-dioxo-2,3,5,6,7,8,9,10,16,16a-decahydro-1*H*-pyrrolo[2,1-*c*][1,4,9]benzoxadiazacyclododecin-6-yl]-2-methoxyacetamide
Ex.352			*N*-[(2*S*,6*S*,16a*S*)-2-(4-benzylpiperazino)-12-fluoro-5,10-dioxo-2,3,5,6,7,8,9,10,16,16a-decahydro-1*H*-pyrrolo[2,1-*c*][1,4,9]benzoxadiazacyclododecin-6-yl]-2-methoxyacetamide
Ex.353			*N*-[(2*S*,6*S*,16a*S*)-12-fluoro-2-(4-methylpiperazino)-5,10-dioxo-2,3,5,6,7,8,9,10,16,16a-decahydro-1*H*-pyrrolo[2,1-*c*][1,4,9]benzoxadiazacyclododecin-6-yl]-2-methoxyacetamide
Ex.354	NH_2		benzyl *N*-[(2*S*,6*S*,16a*S*)-2-amino-12-fluoro-5,10-dioxo-2,3,5,6,7,8,9,10,16,16a-decahydro-1*H*-pyrrolo[2,1-*c*][1,4,9]benzoxadiazacyclododecin-6-yl]carbamate
Ex.355			benzyl *N*-{(2*S*,6*S*,16a*S*)-12-fluoro-2-[(2-methoxyacetyl)amino]-5,10-dioxo-2,3,5,6,7,8,9,10,16,16a-decahydro-1*H*-pyrrolo[2,1-*c*][1,4,9]benzoxadiazacyclododecin-6-yl}carbamate

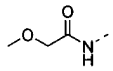
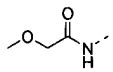
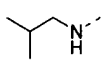
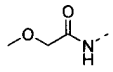
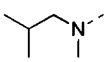
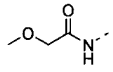
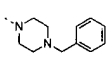
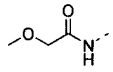
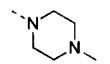
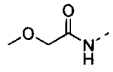
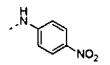
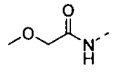
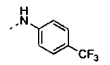
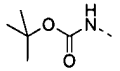
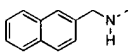
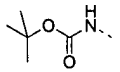
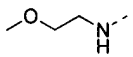
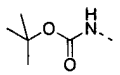
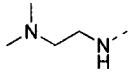
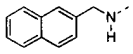
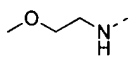
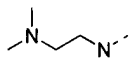
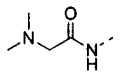
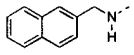
No	R^2	R^5	IUPAC name
Ex.356		NH_2	*N*-[(2*S*,6*S*,16a*S*)-6-amino-12-fluoro-5,10-dioxo-2,3,5,6,7,8,9,10,16,16a-decahydro-1*H*-pyrrolo[2,1-*c*][1,4,9]benzoxadiazacyclododecin-2-yl]-2-methoxyacetamide
Ex.357			*N*-[(2*S*,6*S*,16a*S*)-12-fluoro-6-(isobutylamino)-5,10-dioxo-2,3,5,6,7,8,9,10,16,16a-decahydro-1*H*-pyrrolo[2,1-*c*][1,4,9]benzoxadiazacyclododecin-2-yl]-2-methoxyacetamide
Ex.358			*N*-{(2*S*,6*S*,16a*S*)-12-fluoro-6-[isobutyl(methyl)amino]-5,10-dioxo-2,3,5,6,7,8,9,10,16,16a-decahydro-1*H*-pyrrolo[2,1-*c*][1,4,9]benzoxadiazacyclododecin-2-yl}-2-methoxyacetamide
Ex.359			*N*-[(2*S*,6*S*,16a*S*)-6-(4-benzylpiperazino)-12-fluoro-5,10-dioxo-2,3,5,6,7,8,9,10,16,16a-decahydro-1*H*-pyrrolo[2,1-*c*][1,4,9]benzoxadiazacyclododecin-2-yl]-2-methoxyacetamide
Ex.360			*N*-[(2*S*,6*S*,16a*S*)-12-fluoro-6-(4-methylpiperazino)-5,10-dioxo-2,3,5,6,7,8,9,10,16,16a-decahydro-1*H*-pyrrolo[2,1-*c*][1,4,9]benzoxadiazacyclododecin-2-yl]-2-methoxyacetamide
Ex.361			*N*-[(2*S*,6*S*,16a*S*)-12-fluoro-6-(4-nitroanilino)-5,10-dioxo-2,3,5,6,7,8,9,10,16,16a-decahydro-1*H*-pyrrolo[2,1-*c*][1,4,9]benzoxadiazacyclododecin-2-yl]-2-methoxyacetamide
Ex.362			*N*-{(2*S*,6*S*,16a*S*)-12-fluoro-5,10-dioxo-6-[4-(trifluoromethyl)anilino]-2,3,5,6,7,8,9,10,16,16a-decahydro-1*H*-pyrrolo[2,1-*c*][1,4,9]benzoxadiazacyclododecin-2-yl}-2-methoxyacetamide

Table 39a: Examples of Core 23 (**Ex.363-Ex.378**; continued on the following pages)

No	R^2	R^{54}	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.363-Ex.364: *cf. experimental description*							
Ex.365			**Ex.364**	L.2	2-naphthylmethylmaine	FC (EtOAc/MeOH)	97%
Ex.366			**Ex.364**	L.2	2-methoxyethylamine	FC (EtOAc/MeOH)	100%
Ex.367			**Ex.364**	L.2	N,N-dimethyl-ethylenediamine	FC (CH_2Cl_2/MeOH/ aq. NH_3)	94%
Ex.368	NH_2		**Ex.365**	J	HCl-dioxane	FC (CH_2Cl_2/MeOH/ aq. NH_3)	83%
Ex.369	NH_2		**Ex.366**	J	HCl-dioxane	FC (CH_2Cl_2/MeOH/ aq. NH_3)	94%
Ex.370	NH_2		**Ex.367**	J	HCl-dioxane	FC (CH_2Cl_2/MeOH/ aq. NH_3)	83%
Ex.371			**Ex.368**	L.1.3	N,N-dimethyl glycine (1.2 equiv.) HATU (1.5 equiv.) HOAt (1.5 equiv.) *i*-Pr_2NEt (3 equiv.)	FC (CH_2Cl_2/MeOH)	57%

No	R^2	R^{54}	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.372			**Ex.368**	L.1.3	3-(pyridin-4-yl)propanoic acid (1.2 equiv.) HATU (1.5 equiv.) HOAt (1.5 equiv.) *i*-Pr_2NEt (3 equiv.)	FC (CH_2Cl_2/MeOH)	44%
Ex.373			**Ex.368**	M.2	isobutyraldehyde	FC (CH_2Cl_2/MeOH)	70%
Ex.374			**Ex.370**	L.1.3	2-naphthylacetic acid (1.2 equiv.) HATU (1.5 equiv.) HOAt (1.5 equiv.) *i*-Pr_2NEt (3 equiv.)	FC (CH_2Cl_2/MeOH/ aq. NH_3)	85%
Ex.375			**Ex.370**	L.1.3	1-naphthylacetic acid (1.2 equiv.) HATU (1.5 equiv.) HOAt (1.5 equiv.) *i*-Pr_2NEt (3 equiv.)	FC (CH_2Cl_2/MeOH/ aq. NH_3)	40%
Ex.376			**Ex.369**	M.2	isobutyraldehyde	FC (CH_2Cl_2/MeOH)	48%
Ex.377			**Ex.378**	M.4	H_2, $Pd(OH)_2$; CH_2O	crude product	75%

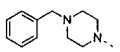
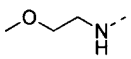
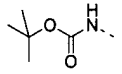
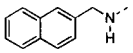
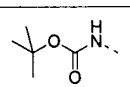
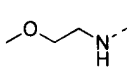
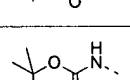
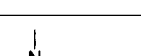
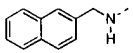
No	R^2	R^{54}	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.378			**Ex.369**	O	N-benzyl-2-chloro-N-(2-chloroethyl)-ethanamine	FC (CH_2Cl_2/MeOH) and prep. HPLC Method 3	43%

Table 39b: Examples of Core 23 (**Ex.363-Ex.378**; *continued on the following pages*)

No	R^2	R^{54}	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.363-Ex.364: *cf. experimental description*							
Ex.365			C34H40N4O7	616.3	2.04 (91)	617.2	Method 10a
Ex.366			C26H38N4O8	534.3	1.53 (100)	535.2	Method 10a
Ex.367			C27H41N5O7	547.3	1.25 (98)	548.3	Method 10a
Ex.368	NH_2		C29H32N4O5	516.2	1.38 (96)	517.2	Method 10a

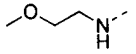
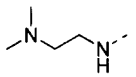
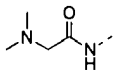
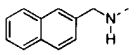
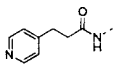
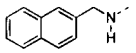
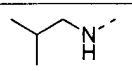
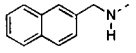
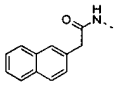
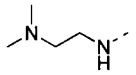
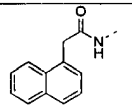
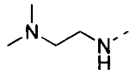
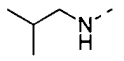
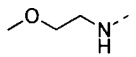
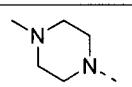
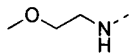
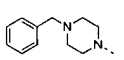
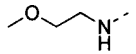
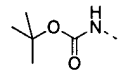
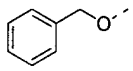
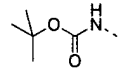
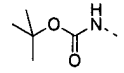
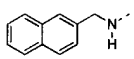
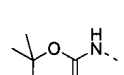
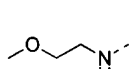
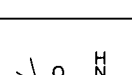
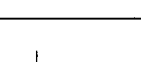
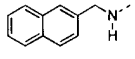
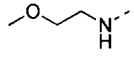
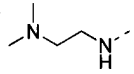
No	R^2	R^{54}	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.369			C21H30N4O6	434.2	0.71 (99)	435.2	Method 10a
Ex.370			C22H33N5O5	447.3	1.02 (99)	448.2	Method 11a
Ex.371			C33H39N5O6	601.2	1.39 (95)	602.3	Method 10a
Ex.372			C37H39N5O6	649.3	1.41 (96)	650.3	Method 10a
Ex.373			C33H40N4O5	572.3	1.54 (94)	573.2	Method 10a
Ex.374			C34H41N5O6	615.3	1.38 (98)	616.3	Method 10a
Ex.375			C34H41N5O6	615.3	1.36 (90)	616.3	Method 10a
Ex.376			C25H38N4O6	490.3	0.99 (97)	491.3	Method 10a
Ex.377			C26H39N5O6	517.3	0.83 (97)	518.3	Method 10a
Ex.378			C32H43N5O6	593.3	1.14 (97)	594.3	Method 10a

Table 39c: Examples of Core 23 (**Ex.363-Ex.378**; *continued on the following pages*)

No	R^2	R^{54}	IUPAC name
Ex.363			benzyl (4*S*,6*S*,13*S*)-6-[(*tert*-butoxycarbonyl)amino]-14-methyl-9,15-dioxo-2,11-dioxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-13-carboxylate
Ex.364		OH	(4*S*,6*S*,13*S*)-6-[(*tert*-butoxycarbonyl)amino]-14-methyl-9,15-dioxo-2,11-dioxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-13-carboxylic acid
Ex.365			*tert*-butyl *N*-[(4*S*,6*S*,13*S*)-14-methyl-13-{[(2-naphthylmethyl)amino]carbonyl}-9,15-dioxo-2,11-dioxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]carbamate
Ex.366			*tert*-butyl *N*-[(4*S*,6*S*,13*S*)-13-{[(2-methoxyethyl)amino]carbonyl}-14-methyl-9,15-dioxo-2,11-dioxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]carbamate
Ex.367			*tert*-butyl *N*-[(4*S*,6*S*,13*S*)-13-({[2-(dimethylamino)ethyl]amino}carbonyl)-14-methyl-9,15-dioxo-2,11-dioxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]carbamate
Ex.368	NH_2		(4*S*,6*S*,13*S*)-6-amino-14-methyl-*N*-(2-naphthylmethyl)-9,15-dioxo-2,11-dioxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-13-carboxamide
Ex.369	NH_2		(4*S*,6*S*,13*S*)-6-amino-*N*-(2-methoxyethyl)-14-methyl-9,15-dioxo-2,11-dioxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-13-carboxamide
Ex.370	NH_2		(4*S*,6*S*,13*S*)-6-amino-*N*-[2-(dimethylamino)ethyl]-14-methyl-9,15-dioxo-2,11-dioxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-13-carboxamide

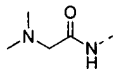
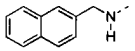
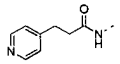
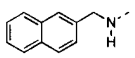
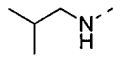
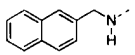
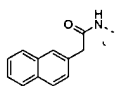
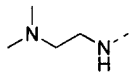
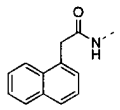
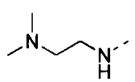
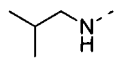
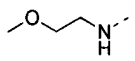
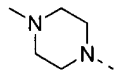
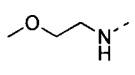
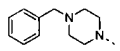
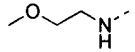
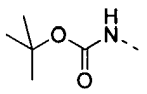
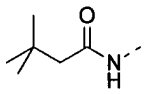
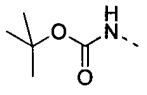
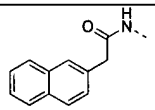
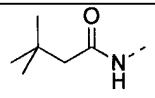
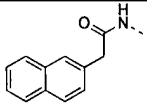
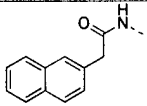
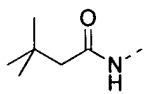
No	R^2	R^{54}	IUPAC name
Ex.371			(4*S*,6*S*,13*S*)-6-{[2-(dimethylamino)acetyl]amino}-14-methyl-*N*-(2-naphthylmethyl)-9,15-dioxo-2,11-dioxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-13-carboxamide
Ex.372			(4*S*,6*S*,13*S*)-14-methyl-*N*-(2-naphthylmethyl)-9,15-dioxo-6-{[3-(4-pyridinyl)propanoyl]amino}-2,11-dioxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-13-carboxamide
Ex.373			(4*S*,6*S*,13*S*)-6-(isobutylamino)-14-methyl-*N*-(2-naphthylmethyl)-9,15-dioxo-2,11-dioxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-13-carboxamide
Ex.374			(4*S*,6*S*,13*S*)-*N*-[2-(dimethylamino)ethyl]-14-methyl-6-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2,11-dioxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-13-carboxamide
Ex.375			(4*S*,6*S*,13*S*)-*N*-[2-(dimethylamino)ethyl]-14-methyl-6-{[2-(1-naphthyl)acetyl]amino}-9,15-dioxo-2,11-dioxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-13-carboxamide
Ex.376			(4*S*,6*S*,13*S*)-6-(isobutylamino)-*N*-(2-methoxyethyl)-14-methyl-9,15-dioxo-2,11-dioxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-13-carboxamide
Ex.377			(4*S*,6*S*,13*S*)-*N*-(2-methoxyethyl)-14-methyl-6-(4-methylpiperazino)-9,15-dioxo-2,11-dioxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-13-carboxamide
Ex.378			(4*S*,6*S*,13*S*)-6-(4-benzylpiperazino)-*N*-(2-methoxyethyl)-14-methyl-9,15-dioxo-2,11-dioxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-13-carboxamide

Table 40.1.a: Examples of Core 24a (**Ex.379-Ex.391**; *continued on the following page*)

No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.379-Ex.380: *cf. experimental description*							
Ex.381			**Ex.380**	L.1.1	3,3-dimethyl-butanoyl chloride (1.5 equiv.) Pyridine (5 equiv.)	FC (hexane/EtOAc/ MeOH)	60%
Ex.382			**Ex.380**	L.1.3	2-naphthylacetic acid i-Pr_2NEt (2 equiv.)	FC(hexane/ EtOAc/MeoH),FC (CH2Cl2/MeOH)	72%
Ex.383	NH_2		**Ex.381**	J	HCl-dioxane	crude product	quant. (HCl salt)
Ex.384	NH_2		**Ex.382**	J	HCl-dioxane	crude product	96% (HCl salt)
Ex.385			**Ex.383**	L.1.3	2-naphthylacetic acid i-Pr_2NEt (3 equiv.)	FC (hexane/EtOAc/ MeOH)	79%

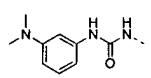
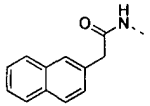
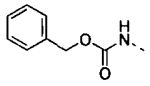
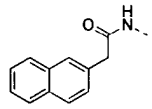
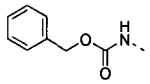
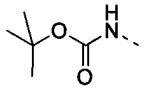
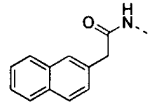
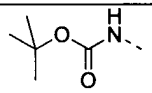
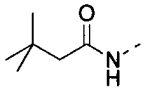
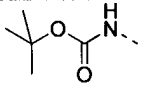
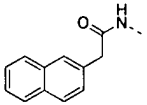
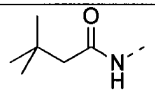
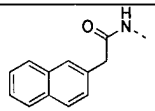
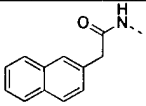
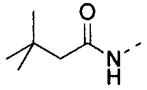
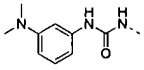
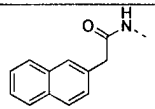
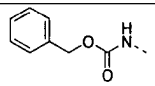
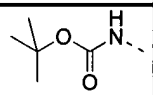
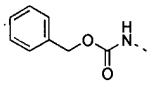
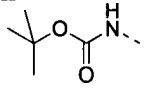
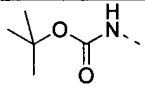
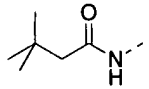
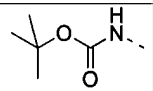
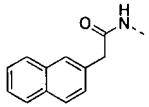
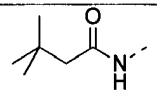
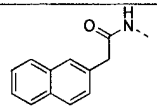
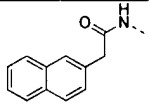
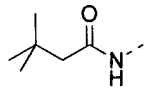
No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.386			**Ex.384**	L.4	2,5-dioxo-pyrrolidin-1-yl-3-(dimethylamino) phenylcarbamate	FC (hexane/EtOAc/ MeOH)	55%
Ex.387	NH_2		**Ex.379**	J	HCl-dioxane	crude product	quant. (HCl salt)
Ex.388			**Ex.387**	L.1.3	2-naphthylacetic acid (1.2 equiv.) HATU (1.5 equiv.) HOAt (1.5 equiv.) i-Pr_2NEt (3 equiv.)	FC (hexane/EtOAc/ MeOH)	63%
Ex.389		$CH_3(CH_2)_8$ CONH	**Ex.380**	L.1.3	decanoic acid i-Pr_2NEt (2 equiv.)	FC (hexane/EtOAc/ MeOH)	71%
Ex.390	NH_2	$CH_3(CH_2)_8$ CONH	**Ex.389**	J	HCl-dioxane	crude product	quant. (HCl salt)
Ex.391		$CH_3(CH_2)_8$ CONH	**Ex.390**	L.1.3	2-naphthylacetic acid i-Pr_2NEt (3 equiv.)	FC (hexane/EtOAc/ MeOH)	70%

Table 40.1.b: Examples of Core 24a (**Ex.379-Ex.391**; *continued on the following page*)

No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.379-Ex.380: *cf. experimental description*							
Ex.381			C28H42N4O6	530.3	1.84 (99)	531.3	Method 10c
Ex.382			C34H40N4O6	600.3	2.01 (99)	601.3	Method 10a
Ex.383	NH_2		C23H34N4O4	430.3	1.15 (98)	431.3	Method 10a
Ex.384	NH_2		C29H32N4O4	500.2	1.39 (93)	501.3	Method 10a
Ex.385			C35H42N4O5	598.3	1.91 (90)	599.2	Method 10a
Ex.386			C38H42N6O5	662.3	1.52 (98)	663.3	Method 10a
Ex.387	NH_2		C25H30N4O5	466.2	1.22 (56)	467.3	Method 10a

No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.388			C37H38N4O6	634.3	1.99 (97)	635.3	Method 10a
Ex.389		$CH_3(CH_2)_8CONH$	C32H50N4O6	586.4	2.38 (87)	587.4	Method 10a
Ex.390	NH_2	$CH_3(CH_2)_8CONH$	C27H42N4O4	486.3	1.69 (91)	487.3	Method 10a
Ex.391		$CH_3(CH_2)_8CONH$	C39H50N4O5	654.4	2.38 (90)	655.4	Method 10a

Table 40.1.c: Examples of Core 24a (**Ex.379-Ex.391**; *continued on the following pages*)

No	R^2	R^5	IUPAC name
Ex.379			benzyl *N*-[(4*S*,6*S*,10*S*)-6-[(*tert*-butoxycarbonyl)amino]-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]carbamate
Ex.380		NH_2	*tert*-butyl *N*-[(4*S*,6*S*,10*S*)-10-amino-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]carbamate
Ex.381			*tert*-butyl *N*-[(4*S*,6*S*,10*S*)-10-[(3,3-dimethylbutanoyl)amino]-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]carbamate
Ex.382			*tert*-butyl *N*-[(4*S*,6*S*,10*S*)-10-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]carbamate
Ex.383	NH_2		N-[(4*S*,6*S*,10*S*)-6-amino-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-3,3-dimethylbutanamide
Ex.384	NH_2		*N*-[(4*S*,6*S*,10*S*)-6-amino-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2-(2-naphthyl)acetamide
Ex.385			3,3-dimethyl-N-[(4*S*,6*S*,10*S*)-6-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]butanamide

No	R^2	R^5	IUPAC name
Ex.386			*N*-[(4*S*,6*S*,10*S*)-6-({[3-(dimethylamino)anilino]carbonyl}amino)-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2-(2-naphthyl)acetamide
Ex.387	NH_2		benzyl *N*-[(4*S*,6*S*,10*S*)-6-amino-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]carbamate
Ex.388			benzyl *N*-[(4*S*,6*S*,10*S*)-6-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]carbamate
Ex.389		$CH_3(CH_2)_8C$ ONH	*tert*-butyl *N*-[(4*S*,6*S*,10*S*)-10-(decanoylamino)-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]carbamate
Ex.390	NH_2	$CH_3(CH_2)_8C$ ONH	*N*-[(4*S*,6*S*,10*S*)-6-amino-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]decanamide
Ex.391		$CH_3(CH_2)_8C$ ONH	*N*-[(4*S*,6*S*,10*S*)-6-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]decanamide

Table 40.2.a: Examples of Core 24b (**Ex.392-Ex.396**)

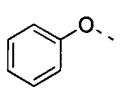
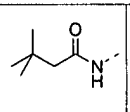
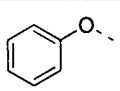
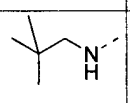
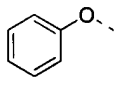
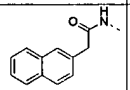
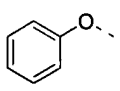
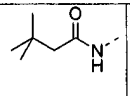
No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.392-Ex.393: *cf. experimental description*							
Ex.394			**Ex.353**	L.1.1	3,3-dimezhylbutanoyl chloride (1.5 equiv.) Pyridine (5 equiv.)	FC (hexane/EtOAc/ MeOH)	68%
Ex.395			**Ex.353**	M.2	pivalaldehyde	FC (hexane/EtOAc/ MeOH)	40%
Ex.396			**Ex.353**	L.1.3	2-naphthylacetic acid i-Pr_2NEt (2 equiv.)	FC (hexane/EtOAc/ MeOH)	37%

Table 40.2.b: Examples of Core 24b (**Ex.392-Ex.396**; *continued on the following page*)

No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.392-Ex.393: *cf. experimental description*							
Ex.394			C29H37N3O5	507.3	1.97 (95)	508.2	Method 10a

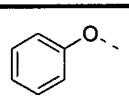
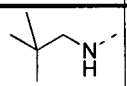
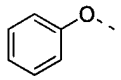
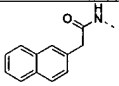
No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.395			C28H37N3O4	479.3	1.62 (99)	480.2	Method 10a
Ex.396			C35H35N3O5	577.3	2.12 (97)	578.0	Method 10a

Table 40.2.c: Examples of Core 24b (**Ex.392-Ex.396**)

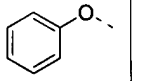
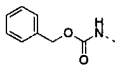
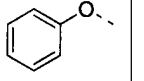
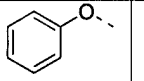
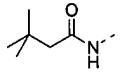
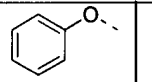
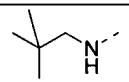
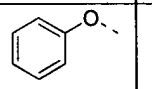
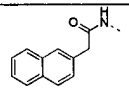
No	R^2	R^5	IUPAC name
Ex.392			benzyl *N*-[(4*S*,6*S*,10*S*)-9,15-dioxo-6-phenoxy-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]carbamate
Ex.393		NH_2	(4*S*,6*S*,10*S*)-10-amino-6-phenoxy-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-9,15-dione
Ex.394			*N*-[(4*S*,6*S*,10*S*)-9,15-dioxo-6-phenoxy-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-3,3-dimethylbutanamide
Ex.395			(4*S*,6*S*,10*S*)-10-(neopentylamino)-6-phenoxy-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-9,15-dione
Ex.396			*N*-[(4*S*,6*S*,10*S*)-9,15-dioxo-6-phenoxy-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2-(2-naphthyl)acetamide

Table 40.3.a: Examples of Core 24c (**Ex.398-Ex.402**)

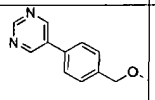
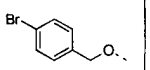
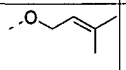
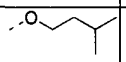
No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.398: *cf. experimental description*							
Ex.399	OH	OH	**Ex.397**	K.1	H_2, $Pd(OH)_2$-C, CH_2Cl_2/MeOH 1:1	FC(CH_2Cl_2/MeOH)	97%
Ex.400		OH	**Ex.397**	P	5-pyrimidineboronic acid (1.3 equiv.)	prep. HPLC, method 1	61%
Ex.401			**Ex.397**	Q	4-bromo-2-methyl-2-butene (2 equiv.)	FC (CH_2Cl_2/MeOH)	52%
Ex.402	OH		**Ex.401**	K.1	H_2, $Pd(OH)_2$-C, MeOH	FC (CH_2Cl_2/MeOH)	51%

Table 40.3.b: Examples of Core 24c (**Ex.398-Ex.402**; *continued on the following page*)

No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.398: *cf. experimental description*							
Ex.399	OH	OH	C17H22N2O5	334.2	0.79 (98)	335.1	Method 10a

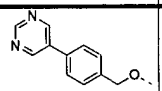
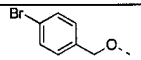
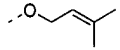
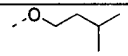
No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.400		OH	C28H30N4O5	502.2	1.40(98)	503.2	Method 10a
Ex.401			C29H35BrN2O5	570.2	2.27 (96)	573.0/571.0	Method 10a
Ex.402	OH		C22H32N2O5	404.2	1.49 (93)	405.2	Method 10a

Table 40.3.c: Examples of Core 24c (**Ex.398-Ex.402**)

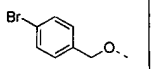
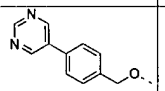
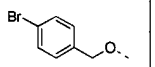
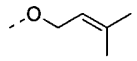
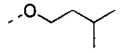
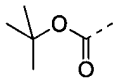
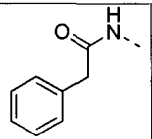
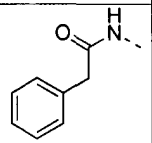
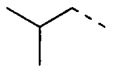
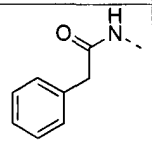
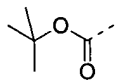
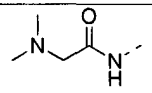
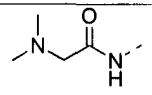
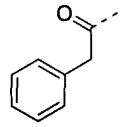
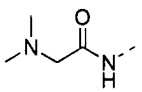
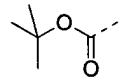
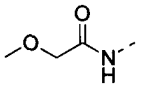
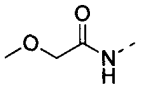
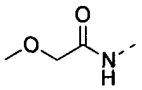
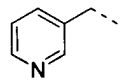
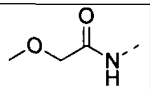
No	R2	R5	IUPAC name
Ex.398		OH	(4*S*,6*S*,10*S*)-6-[(4-bromobenzyl)oxy]-10-hydroxy-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-9,15-dione
Ex.399	OH	OH	(4*S*,6*S*,10*S*)-6,10-dihydroxy-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-9,15-dione
Ex.400		OH	(4*S*,6*S*,10*S*)-10-hydroxy-6-{[4-(5-pyrimidinyl)benzyl]oxy}-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-9,15-dione
Ex.401			(4*S*,6*S*,10*S*)-6-[(4-bromobenzyl)oxy]-10-[(3-methyl-2-butenyl)oxy]-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-9,15-dione
Ex.402	OH		(4*S*,6*S*,10*S*)-6-hydroxy-10-(isopentyloxy)-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-9,15-dione

Table 41a: Examples of Core 25 (**Ex.403-Ex.414;** *continued on the following pages*)

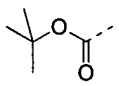
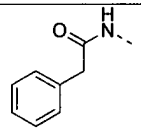
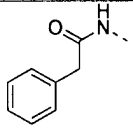
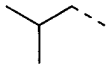
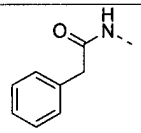
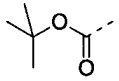
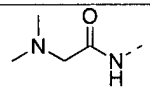
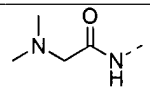
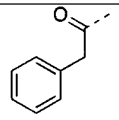
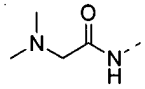
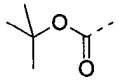
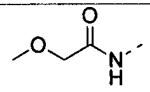
No	R^{11}	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.403-Ex.404: *cf. experimental description*							
Ex.405			**Ex.404**	L.1.3	phenylacetic acid $i\text{-}Pr_2NEt$ (2 equiv.)	FC (hexane/EtOAc)	75%
Ex.406	H		**Ex.405**	J	HCl-dioxane	crude product	88%*)
Ex.407			**Ex.406**	**)	isobutyraldehyde**)	prep. HPLC, method 3	72%
Ex.408			**Ex.404**	L.1.3	N,N-dimethylglycine $i\text{-}Pr_2NEt$ (3 equiv.)	FC (hexane/EtOAc/MeOH)	81%
Ex.409	H		**Ex.408**	J	HCl-dioxane	crude product	94% (HCl salt)

No	R^{11}	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.410			**Ex.409**	L.1.3	phenylacetic acid (1.0 equiv) HATU (1.0 equiv.) HOAt (1.0 equiv.) i-Pr_2NEt (2.0 equiv)	FC (EtOAc, then CH_2Cl_2/MeOH)	46%
Ex.411			**Ex.404**	L.1.1	2-methoxyacetyl chloride (1.5 equiv.) pyridine (5 equiv.)	FC (hexane/EtOAc /MeOH)	84%
Ex.412	H		**Ex.411**	J	HCl-dioxane	crude product	97% (HCl salt)
Ex.413	CH_3		**Ex.412**	M.5	aq. formaldehyde soln (2.5 equiv.)	FC (EtOAc/MeOH)	82%
Ex.414			**Ex.412**	M.5	nicotin aldehyde	FC (EtOAc/MeOH)	77%

*) workup (CH_2Cl_2, aq. Na_2CO_3 soln) to yield the free base

)in analogy to procedure **M.3; isobutyraldehyde (1.2 equiv.), acetic acid (1.2 equiv.), $NaBH(OAc)_3$ (2.5 equiv.) in THF

Table 41b: Examples of Core 25 (**Ex.403-Ex.414**; *continued on the following page*)

No	R^{11}	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.403-Ex.404: *cf. experimental description*							
Ex.405			C31H39FN4O6	582.3	2.06 (93)	583.3	Method 4a
Ex.406	H		C26H31FN4O4	482.2	1.48 (94)	483.3	Method 4a
Ex.407			C30H39FN4O4	538.3	1.45 (97)	539.4	Method 10a
Ex.408			C27H40FN5O6	549.3	1.44 (98)	550.3	Method 10a
Ex.409	H		C22H32FN5O4	449.2	1.27 (98)	450.2	Method 12
Ex.410			C30H38FN5O5	567.3	1.36 (93)	568.3	Method 10a
Ex.411			C26H37FN4O7	536.3	1.66 (97)	537.3	Method 10c

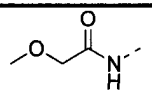
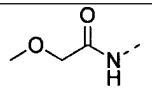
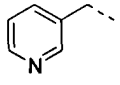
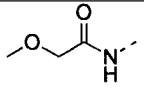
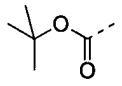
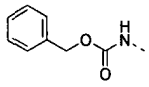
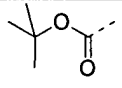
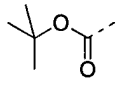
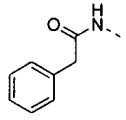
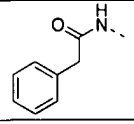
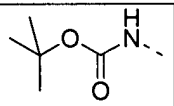
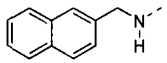
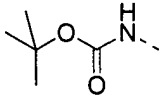
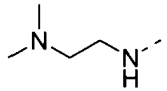
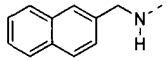
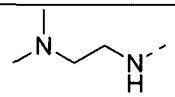
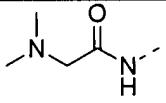
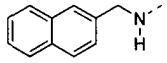
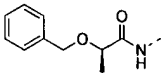
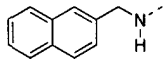
No	R^{11}	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.412	H		C21H29FN4O5	436.2	1.02 (97)	437.2	Method 10a
Ex.413	CH_3		C22H31FN4O5	450.2	1.02 (94)	451.2	Method 10a
Ex.414			C27H34FN5O5	527.3	1.03 (95)	528.2	Method 10a

Table 41c: Examples of Core 25 (**Ex.403-Ex.414**, *continued on the following page*)

No	R^{11}	R^5	IUPAC name
Ex.403			*tert*-butyl (1*S*,15*S*,18*R*)-15-{[(benzyloxy)carbonyl]amino}-7-fluoro-11-methyl-10,16-dioxo-3-oxa-11,17,20-triazatricyclo[16.2.1.$0^{4,9}$]henicosa-4,6,8-triene-20-carboxylate
Ex.404		NH_2	*tert*-butyl (1*S*,15*S*,18*R*)-15-amino-7-fluoro-11-methyl-10,16-dioxo-3-oxa-11,17,20-triazatricyclo[16.2.1.$0^{4,9}$]henicosa-4,6,8-triene-20-carboxylate
Ex.405			*tert*-butyl (1*S*,15*S*,18*R*)-7-fluoro-11-methyl-10,16-dioxo-15-[(2-phenylacetyl)amino]-3-oxa-11,17,20-triazatricyclo[16.2.1.$0^{4,9}$]henicosa-4,6,8-triene-20-carboxylate
Ex.406	H		*N*-[(1*S*,15*S*,18*R*)-7-fluoro-11-methyl-10,16-dioxo-3-oxa-11,17,20-triazatricyclo[16.2.1.$0^{4,9}$]henicosa-4,6,8-trien-15-yl]-2-phenylacetamide

No	R^{11}	R^5	IUPAC name
Ex.407			*N*-[(1*S*,15*S*,18*R*)-7-fluoro-20-isobutyl-11-methyl-10,16-dioxo-3-oxa-11,17,20-triazatricyclo[16.2.1.$0^{4,9}$]henicosa-4,6,8-trien-15-yl]-2-phenylacetamide
Ex.408			*tert*-butyl (1*S*,15*S*,18*R*)-15-{[2-(dimethylamino)acetyl]amino}-7-fluoro-11-methyl-10,16-dioxo-3-oxa-11,17,20-triazatricyclo[16.2.1.$0^{4,9}$]henicosa-4,6,8-triene-20-carboxylate
Ex.409	H		2-(dimethylamino)-*N*-[(1*S*,15*S*,18*R*)-7-fluoro-11-methyl-10,16-dioxo-3-oxa-11,17,20-triazatricyclo[16.2.1.$0^{4,9}$]henicosa-4,6,8-trien-15-yl]acetamide
Ex.410			2-(dimethylamino)-*N*-[(1*S*,15*S*,18*R*)-7-fluoro-11-methyl-10,16-dioxo-20-(2-phenylacetyl)-3-oxa-11,17,20-triazatricyclo[16.2.1.$0^{4,9}$]henicosa-4,6,8-trien-15-yl]acetamide
Ex.411			*tert*-butyl (1*S*,15*S*,18*R*)-7-fluoro-15-[(2-methoxyacetyl)amino]-11-methyl-10,16-dioxo-3-oxa-11,17,20-triazatricyclo[16.2.1.$0^{4,9}$]henicosa-4,6,8-triene-20-carboxylate
Ex.412	H		*N*-[(1*S*,15*S*,18*R*)-7-fluoro-11-methyl-10,16-dioxo-3-oxa-11,17,20-triazatricyclo[16.2.1.$0^{4,9}$]henicosa-4,6,8-trien-15-yl]-2-methoxyacetamide
Ex.413	CH_3		*N*-[(1*S*,15*S*,18*R*)-7-fluoro-11,20-dimethyl-10,16-dioxo-3-oxa-11,17,20-triazatricyclo[16.2.1.$0^{4,9}$]henicosa-4,6,8-trien-15-yl]-2-methoxyacetamide
Ex.414			*N*-[(1*S*,15*S*,18*R*)-7-fluoro-11-methyl-10,16-dioxo-20-(3-pyridinylmethyl)-3-oxa-11,17,20-triazatricyclo[16.2.1.$0^{4,9}$]henicosa-4,6,8-trien-15-yl]-2-methoxyacetamide

Table 42a: Examples of Core 26 (**Ex.415-Ex.423**; *continued on the following page*)

No	R^2	R^{54}	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.415-Ex.416: *cf. experimental description*							
Ex.417			**Ex.416**	L.2	2-naphthyl-methylamine (2 equiv.)	FC (hexane/EtOAc/ MeOH)	96%
Ex.418			**Ex.416**	L.2	2-dimethyl-aminoetylamine (2 equiv.)	FC (CH_2Cl_2/MeOH/ aq.NH_3)	81%
Ex.419	NH_2		**Ex.417**	J	HCl (4M dioxane)	crude product	89% (HCl salt)
Ex.420	NH_2		**Ex.418**	J	HCl (4M dioxane)	crude product	88% (HCl salt)
Ex.421			**Ex.419**	L.1.2	N,N-dimethylglycine (1.8 equiv.)	prep. HPLC, method 1	38% (TFA salt)
Ex.422			**Ex.419**	L.1.3	(R)(+)-2-benzyloxy-propionic acide (2 equiv.)	prep. HPLC, method 1	73%

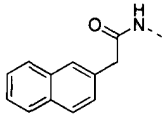
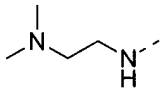
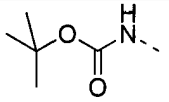
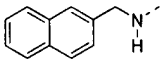
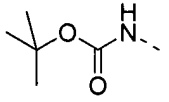
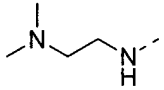
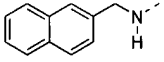
No	R^2	R^{54}	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.423			**Ex.420**	L.1.2	2-naphthylacetic acide ((1.2 equiv.)	prep. HPLC, method 1	36% (TFA salt)

Table 42b: Examples of Core 26 (**Ex.415-Ex.423**; *continued on the following page*)

No	R^2	R^{54}	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.415-Ex.416: *cf. experimental description*							
Ex.417			C35H43N5O7S	677.3	2.08 (89)	678.2	Method 4b
Ex.418			C28H44N6O7S	608.3	1.42 (96)	609.2	Method 4b
Ex.419	NH_2		C30H35N5O5S	577.2	1.61 (84)	578.0	Method 4b

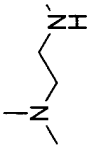
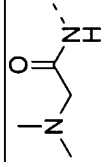
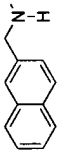
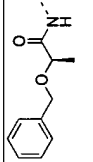
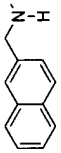
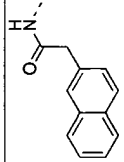
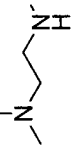
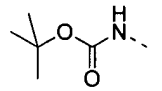
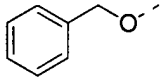
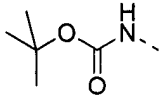
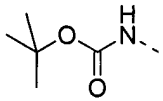
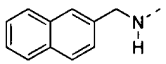
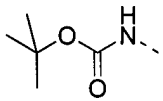
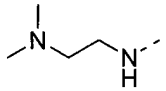
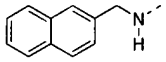
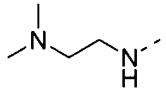
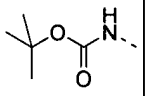
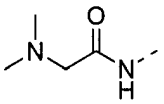
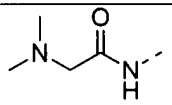
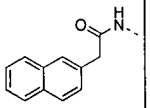
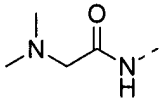
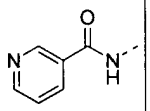
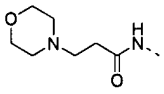
No	R^2	R^{54}	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.420	NH_2		C23H36N6O5S	508.3	1.29 (95)	509.2	Method 5b
Ex.421			C34H42N6O6S	662.3	1.86 (91)	663.2	Method 5b
x.422			C40H45N5O7S	739.3	2.10 (97)	740.2	Method 5b
Ex.423			C35H44N6O6S	676.3	1.85 (97)	677.2	Method 5b

Table 42c: Examples of Core 26 (15-007-01) (**Ex.415-Ex.423**, *continued on the following pages*)

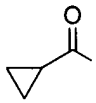
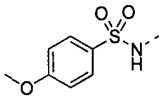
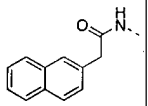
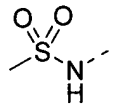
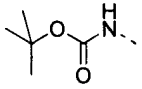
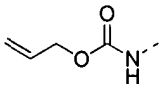
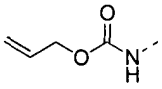
No	R^2	R^{54}	IUPAC name
Ex.415			benzyl (6*S*,15*R*,16a*S*)-15-[(*tert*-butoxycarbonyl)amino]-5,10-dimethyl-4,9,12-trioxo-5,6,7,8,9,10,11,12,15,16,16a,17-dodecahydro-4*H*,14*H*-pyrrolo[2,1-*c*]thieno[2,3-*n*][1,4,7,12]oxatriazacyclopentadecine-6-carboxylate
Ex.416		OH	(6*S*,15*R*,16a*S*)-15-[(*tert*-butoxycarbonyl)amino]-5,10-dimethyl-4,9,12-trioxo-5,6,7,8,9,10,11,12,15,16,16a,17-dodecahydro-4*H*,14*H*-pyrrolo[2,1-*c*]thieno[2,3-*n*][1,4,7,12]oxatriazacyclopentadecine-6-carboxylic acid
Ex.417			*tert*-butyl *N*-((6*S*,15*R*,16a*S*)-5,10-dimethyl-6-{[(2-naphthylmethyl)amino]carbonyl}-4,9,12-trioxo-5,6,7,8,9,10,11,12,15,16,16a,17-dodecahydro-4*H*,14*H*-pyrrolo[2,1-*c*]thieno[2,3-*n*][1,4,7,12]oxatriazacyclopentadecin-15-yl)carbamate
Ex.418			*tert*-butyl *N*-[(6*S*,15*R*,16a*S*)-6-({[2-(dimethylamino)ethyl]amino}carbonyl)-5,10-dimethyl-4,9,12-trioxo-5,6,7,8,9,10,11,12,15,16,16a,17-dodecahydro-4*H*,14*H*-pyrrolo[2,1-*c*]thieno[2,3-*n*][1,4,7,12]oxatriazacyclopentadecin-15-yl]carbamate
Ex.419	NH_2		(6*S*,15*R*,16a*S*)-15-amino-5,10-dimethyl-*N*-(2-naphthylmethyl)-4,9,12-trioxo-5,6,7,8,9,10,11,12,15,16,16a,17-dodecahydro-4*H*,14*H*-pyrrolo[2,1-*c*]thieno[2,3-*n*][1,4,7,12]oxatriazacyclopentadecine-6-carboxamide
Ex.420	NH_2		(6*S*,15*R*,16a*S*)-15-amino-*N*-[2-(dimethylamino)ethyl]-5,10-dimethyl-4,9,12-trioxo-5,6,7,8,9,10,11,12,15,16,16a,17-dodecahydro-4*H*,14*H*-pyrrolo[2,1-*c*]thieno[2,3-*n*][1,4,7,12]oxatriazacyclopentadecine-6-carboxamide

No	R^2	R^{54}	IUPAC name
Ex.421			(6*S*,15*R*,16a*S*)-15-{[2-(dimethylamino)acetyl]amino}-5,10-dimethyl-*N*-(2-naphthylmethyl)-4,9,12-trioxo-5,6,7,8,9,10,11,12,15,16,16a,17-dodecahydro-4*H*,14*H*-pyrrolo[2,1-*c*]thieno[2,3-*n*][1,4,7,12]oxatriazacyclopentadecine-6-carboxamide
Ex.422			(6*S*,15*R*,16a*S*)-15-{[(2R)-2-(benzyloxy)propanoyl]amino}-5,10-dimethyl-*N*-(2-naphthylmethyl)-4,9,12-trioxo-5,6,7,8,9,10,11,12,15,16,16a,17-dodecahydro-4*H*,14*H*-pyrrolo[2,1-*c*]thieno[2,3-*n*][1,4,7,12]oxatriazacyclopentadecine-6-carboxamide
Ex.423			(6*S*,15*R*,16a*S*)-*N*-[2-(dimethylamino)ethyl]-5,10-dimethyl-15-{[2-(2-naphthyl)acetyl]amino}-4,9,12-trioxo-5,6,7,8,9,10,11,12,15,16,16a,17-dodecahydro-4*H*,14*H*-pyrrolo[2,1-*c*]thieno[2,3-*n*][1,4,7,12]oxatriazacyclopentadecine-6-carboxamide

Table 43a: Examples of Core 27 (**Ex.424-Ex.434** and **Ex.592-Ex.593**; *continued on the following pages*)

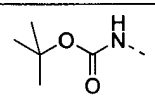
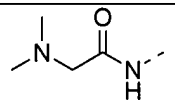
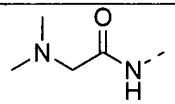
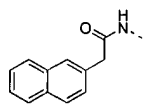
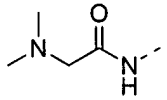
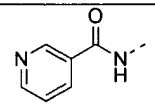
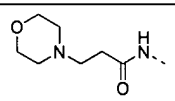
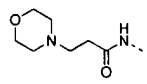
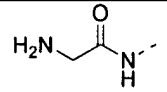
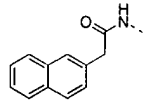
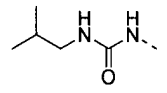
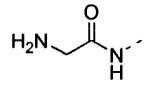
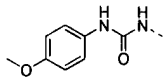
No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.424-Ex.425: *cf. experimental description*							
Ex.426			**Ex.425**	L.1.3	2-dimethylamino carboxylic acid (2 equiv.) i-Pr_2EtN (2 equiv.)	prep. HPLC, Methode 3	75%
Ex.427	NH_2		**Ex.426**	J	HCl (4M dioxane)	crude product	90% (HCl salt)
Ex.428			**Ex.427**		T3P (50% in EtOAc;1.2 quiv.) 2-naphthylacetic acid (1.2 equiv.) i-Pr_2EtN (4 equiv.), CH_2Cl_2, rt, 15 h	prep. HPLC, methode 1	35% (TFA salt)
Ex.429			**268**	S	i) nicotinic acid (2x5 equiv.) ii) 3-morpholino-propanoic acid·HCl (1x5 equiv.)	prep. HPLC, methode1	25% (TFA salt)

No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.430			**268**	S	i) 3-morpholino propanoic acid·HCl (2x5 equiv.) ii) BOC-glycine (1x5 equiv.)	prep. HPLC, methode 1	23% (TFA salt)
Ex.431			**268**	S	i) 2-naphthylacetic acid (2x5 equiv.) ii) N-succinimidyl-N-isobutylcarbamate (1 equiv.)	prep. HPLC, methode 1	37% (TFA salt)
Ex.432			**268**	S	i) BOC-glycine (2x5 equiv.) ii) 4-methoxy-phenylisocyanate (2x5 equiv.)	prep. HPLC, methode 1	53% (TFA salt)

No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.433			**268**	S	i) cyclopropane carboxylic acid (2x5 equiv.) ii) 4-methoxy-benzylsulfonyl chloride (2x5 equiv.)	Prep. HPLC, methode 3	42% (TFA salt)
Ex.434			**268**	S	i) 2-naphthylaceti acid (2x5 equiv.) ii) methanesulfonyl chloride (2x5 equiv.)	Prep. HPLC, Methode 3	48% (TFA salt)
Ex.592			**Ex.424**	*)	1.H2, $Pd(OH)_2$-C 2. AllocCl	FC (CH_2Cl_2/MeOH 95:5)	85%
Ex.593	NH_2		**Ex.592**	*)	1. TFA, CH_2Cl_2 2. HCl-dioxane	crude product	87% (HCl salt)

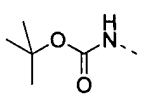
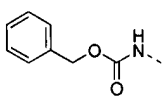
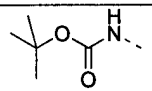
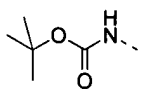
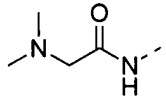
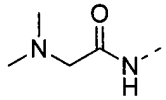
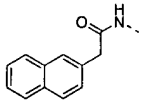
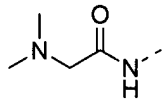
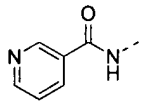
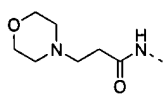
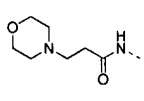
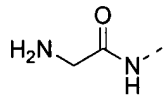
*) cf. detailed description

Table 43b: Examples of Core 27(**Ex.424-Ex.434** and **Ex.592-Ex.593;** *continued on the following page*)

No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.424-Ex.425: *cf. experimental description*							
Ex.426			C27H42N6O6	546.3	1.35	547.4	Method 4a
Ex.427			C22H34N6O4	446.3	1.23	447.3	Method 5a
Ex.428			C34H42N6O5	614.3	1.32 (95)	615.3	Method 10a
Ex.429			C31H41N7O6	607.3	0.78 (96)	608.3	Method 10a
Ex.430			C27H41N7O6	559.3	0.61 (91)	560.2	Method 10a
Ex.431			C35H44N6O5	628.3	1.63 (95)	629.3	Method 10a
Ex.432			C28H37N7O6	567.3	1.09 (98)	568.2	Method 10a

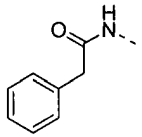
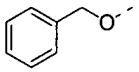
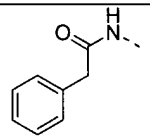
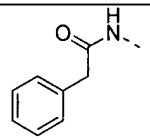
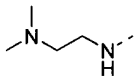
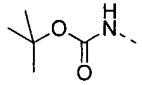
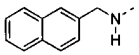
No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.433			C29H37N5O7S	599.2	1.38 (96)	600.2	Method 10a
Ex.434			C31H37N5O6S	607.3	1.49 (90)	608.2	Method 10a
Ex.592			C27H39N5O7	545.2	1.56 (96)	546.2	Method 10a
Ex.593	NH_2		C22H31N5O5	445.2	0.98 (96)	446.1	Method 10a

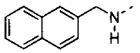
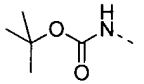
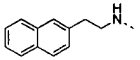
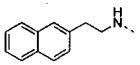
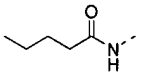
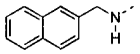
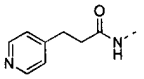
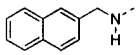
Table 43c: Examples of Core 27 (**Ex.424-Ex.434** and **Ex.592-Ex.593**; *continued on the following page*)

No	R^2	R^5	IUPAC name
Ex.424			benzyl *N*-[(4*S*,6*S*,10*S*)-6-[(*tert*-butoxycarbonyl)amino]-15-methyl-9,16-dioxo-2-oxa-8,15,19-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-10-yl]carbamate
Ex.425		NH_2	*tert*-butyl *N*-[(4*S*,6*S*,10*S*)-10-amino-15-methyl-9,16-dioxo-2-oxa-8,15,19-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]carbamate
Ex.426			*tert*-butyl *N*-[(4*S*,6*S*,10*S*)-10-{[2-(dimethylamino)acetyl]amino}-15-methyl-9,16-dioxo-2-oxa-8,15,19-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]carbamate
Ex.427	NH_2		*N*-[(4*S*,6*S*,10*S*)-6-amino-15-methyl-9,16-dioxo-2-oxa-8,15,19-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-10-yl]-2-(dimethylamino)acetamide
Ex.428			2-(dimethylamino)-*N*-[(4*S*,6*S*,10*S*)-15-methyl-6-{[2-(2-naphthyl)acetyl]amino}-9,16-dioxo-2-oxa-8,15,19-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-10-yl]acetamide
Ex.429			*N*-[(4*S*,6*S*,10*S*)-15-methyl-10-[(3-morpholinopropanoyl)amino]-9,16-dioxo-2-oxa-8,15,19-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]nicotinamide
Ex.430			*N*-[(4*S*,6*S*,10*S*)-10-[(2-aminoacetyl)amino]-15-methyl-9,16-dioxo-2-oxa-8,15,19-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]-3-morpholinopropanamide

No	R^2	R^5	IUPAC name
Ex.431			*N*-[(4*S*,6*S*,10*S*)-10-{[(isobutylamino)carbonyl]amino}-15-methyl-9,16-dioxo-2-oxa-8,15,19-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]-2-(2-naphthyl)acetamide
Ex.432			2-amino-*N*-[(4*S*,6*S*,10*S*)-10-{[(4-methoxyanilino)carbonyl]amino}-15-methyl-9,16-dioxo-2-oxa-8,15,19-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]acetamide
Ex.433			*N*-[(4*S*,6*S*,10*S*)-10-{[(4-methoxyphenyl)sulfonyl]amino}-15-methyl-9,16-dioxo-2-oxa-8,15,19-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]cyclopropanecarboxamide
Ex.434			*N*-[(4*S*,6*S*,10*S*)-15-methyl-10-[(methylsulfonyl)amino]-9,16-dioxo-2-oxa-8,15,19-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]-2-(2-naphthyl)acetamide
Ex.592			allyl *N*-[(4*S*,6*S*,10*S*)-6-[(*tert*-butoxycarbonyl)amino]-15-methyl-9,16-dioxo-2-oxa-8,15,19-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-10-yl]carbamate
Ex.593	NH_2		allyl *N*-[(4*S*,6*S*,10*S*)-6-amino-15-methyl-9,16-dioxo-2-oxa-8,15,19-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-10-yl]carbamate

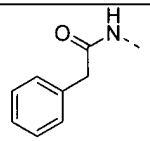
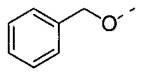
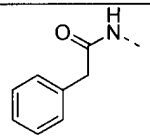
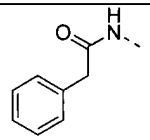
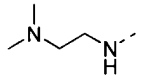
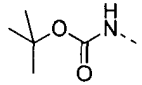
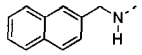
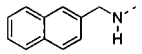
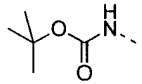
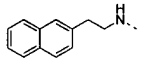
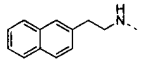
Table 44a: Examples of Core 28 (**Ex.435-Ex.446**; *continued on the following page*)

No	R^2	R^{54}	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.435-Ex.437: *cf. experimental description*							
Ex.438			**Ex.437**	L.1.1	Phenylacetyl-chloride (1.1 equiv.), i-Pr_2NEt (3 equiv.)	FC (EtOAc/MeOH)	75%
Ex.439		OH	**Ex.438**	H	H_2, $Pd(OH)_2$-C	crude product	99%
Ex.440			**Ex.439**	L.2	2-dimethylamino-ethylamine	FC (CH_2Cl_2/MeOH/NH_4OH))	90%
Ex.441			**Ex.436**	L.2	HATU (2.6 equiv.) HOAt (2.6 equiv.) i-Pr_2NEt (5 equiv.) 2-naphthyl-methylamine (2.6 equiv.)	Prep. HPLC, method 3 + size exclusion chromatography	64%

No	R^2	R^{54}	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.442	NH_2		**Ex.441**	*)	TFA, triisopropylsilane *)	crude product	72%
Ex.443			**Ex.436**	L.2	HATU (2.6 equiv.) HOAt (2.6 equiv.) i-Pr_2NEt (8 equiv.) 2-Naphthyl-ethylamine hydrochloride	Prep. HPLC, method 3 + size exclusion chromatography	86%
Ex.444	NH_2		**Ex.443**	*)	TFA, triisopropylsilane *)	prep. HPLC, method 1	43% (TFA salt)
Ex.445			**Ex.442**	L.1.1	Valeroylchloride (4 equiv.)	prep. HPLC, method 3	72%
Ex.446			**Ex.442**	L.1.2	3-(pyridin-4-yl)propanoic acid (1.8 equiv.)	prep. HPLC, method 3	90%

*) A soln of the Boc amine (0.04 mmol) in CH_2Cl_2 (1 mL) was treated at 0°C with triisopropylsilane (3 equiv.) and TFA (0.2 mL). The mixture was stirred for 2.5 h, treated with sat. aq. Na_2CO_3 soln and extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4), filtered and concentrated to afford the corresponding amine.

Table 44b: Examples of Core 28 (**Ex.435-Ex.446**; *continued on the following page*)

No	R^2	R^{54}	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.435-Ex.437: *cf. experimental description*							
Ex.438			C40H45N5O7	707.3	1.93 (97)	708.4	Method 10a
Ex.439		OH	C33H39N5O7	617.3	1.50 (97)	618.3	Method 10a
Ex.440			C37H49N7O6	687.4	1.38 (98)	688.4	Method 10a
Ex.441			C41H50N6O7	738.4	2.08 (98)	739.1	Method 10a
Ex.442	NH_2		C36H42N6O5	638.3	1.50 (94)	639.2	Method 10a
Ex.443			C42H52N6O7	752.4	2.12 (96)	753.1	Method 10a
Ex.444	NH_2		C37H44N6O5	652.3	1.57 (86)	653.3	Methode 10a

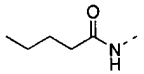
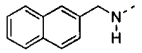
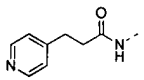
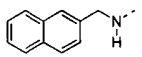
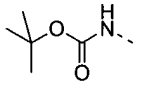
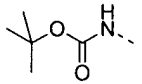
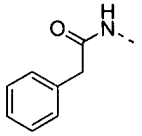
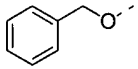
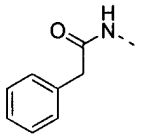
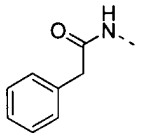
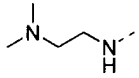
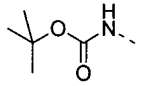
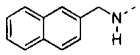
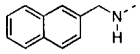
No	R^2	R^{54}	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.445			C41H50N6O6	722.4	2.11 (99)	723.3	Method 4b
Ex.446			C44H49N7O6	771.4	1.73 (99)	772.3	Method 4b

Table 44c: Examples of Core 28 (**Ex.435-Ex.446**; *continued on the following pages*)

No	R^2	R^{54}	IUPAC name
Ex.435			benzyl (4*S*,6*R*,15*S*)-6-[(*tert*-butoxycarbonyl)amino]-11,16,19,20-tetramethyl-9,12,17-trioxo-2-oxa-8,11,16,20-tetraazatetracyclo[16.5.2.$0^{4,8}$.$0^{21,25}$]pentacosa-1(23),18,21,24-tetraene-15-carboxylate
Ex.436		OH	(4*S*,6*R*,15*S*)-6-[(*tert*-butoxycarbonyl)amino]-11,16,19,20-tetramethyl-9,12,17-trioxo-2-oxa-8,11,16,20-tetraazatetracyclo[16.5.2.$0^{4,8}$.$0^{21,25}$]pentacosa-1(23),18,21,24-tetraene-15-carboxylic acid
Ex.437	NH_2		benzyl (4*S*,6*R*,15*S*)-6-amino-11,16,19,20-tetramethyl-9,12,17-trioxo-2-oxa-8,11,16,20-tetraazatetracyclo[16.5.2.$0^{4,8}$.$0^{21,25}$]pentacosa-1(23),18,21,24-tetraene-15-carboxylate

No	R^2	R^{54}	IUPAC name
Ex.438			benzyl (4*S*,6*R*,15*S*)-11,16,19,20-tetramethyl-9,12,17-trioxo-6-[(2-phenylacetyl)amino]-2-oxa-8,11,16,20-tetraazatetracyclo[16.5.2.$0^{4,8}$.$0^{21,25}$]pentacosa-1(23),18,21,24-tetraene-15-carboxylate
Ex.439		OH	(4*S*,6*R*,15*S*)-11,16,19,20-tetramethyl-9,12,17-trioxo-6-[(2-phenylacetyl)amino]-2-oxa-8,11,16,20-tetraazatetracyclo[16.5.2.$0^{4,8}$.$0^{21,25}$]pentacosa-1(23),18,21,24-tetraene-15-carboxylic acid
Ex.440			(4*S*,6*R*,15*S*)-*N*-[2-(dimethylamino)ethyl]-11,16,19,20-tetramethyl-9,12,17-trioxo-6-[(2-phenylacetyl)amino]-2-oxa-8,11,16,20-tetraazatetracyclo[16.5.2.$0^{4,8}$.$0^{21,25}$]pentacosa-1(23),18,21,24-tetraene-15-carboxamide
Ex.441			*tert*-butyl *N*-[(4*S*,6*R*,15*S*)-11,16,19,20-tetramethyl-15-{[(2-naphthylmethyl)amino]carbonyl}-9,12,17-trioxo-2-oxa-8,11,16,20-tetraazatetracyclo[16.5.2.$0^{4,8}$.$0^{21,25}$]pentacosa-1(23),18,21,24-tetraen-6-yl]carbamate
Ex.442	NH_2		(4*S*,6*R*,15*S*)-6-amino-11,16,19,20-tetramethyl-*N*-(2-naphthylmethyl)-9,12,17-trioxo-2-oxa-8,11,16,20-tetraazatetracyclo[16.5.2.$0^{4,8}$.$0^{21,25}$]pentacosa-1(23),18,21,24-tetraene-15-carboxamide

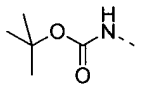
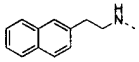
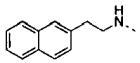
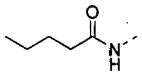
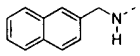
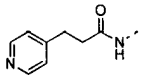
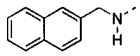
No	R^2	R^{54}	IUPAC name
Ex.443			*tert*-butyl *N*-[(4*S*,6*R*,15*S*)-11,16,19,20-tetramethyl-15-({[2-(2-naphthyl)ethyl]amino}carbonyl)-9,12,17-trioxo-2-oxa-8,11,16,20-tetraazatetracyclo[16.5.2.$0^{4,8}$.$0^{21,25}$]pentacosa-1(23),18,21,24-tetraen-6-yl]carbamate
Ex.444	NH_2		(4*S*,6*R*,15*S*)-6-amino-11,16,19,20-tetramethyl-*N*-[2-(2-naphthyl)ethyl]-9,12,17-trioxo-2-oxa-8,11,16,20-tetraazatetracyclo[16.5.2.$0^{4,8}$.$0^{21,25}$]pentacosa-1(23),18,21,24-tetraene-15-carboxamide
Ex.445			(4*S*,6*R*,15*S*)-11,16,19,20-tetramethyl-*N*-(2-naphthylmethyl)-9,12,17-trioxo-6-(pentanoylamino)-2-oxa-8,11,16,20-tetraazatetracyclo[16.5.2.$0^{4,8}$.$0^{21,25}$]pentacosa-1(23),18,21,24-tetraene-15-carboxamide
Ex.446			(4*S*,6*R*,15*S*)-11,16,19,20-tetramethyl-*N*-(2-naphthylmethyl)-9,12,17-trioxo-6-{[3-(4-pyridinyl)propanoyl]amino}-2-oxa-8,11,16,20-tetraazatetracyclo[16.5.2.$0^{4,8}$.$0^{21,25}$]pentacosa-1(23),18,21,24-tetraene-15-carboxamide

Table 45a: Examples of Core 29 (**Ex.447-Ex.450**)

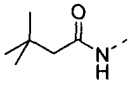
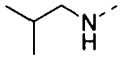
No	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.447-Ex.448: *cf. experimental description*							
Ex.449	OH		**Ex.448**	L.1.1	3,3-dimethylbutanoyl chloride (4.1 equiv.) pyridine (19 equiv.)	FC (CH_2Cl_2/MeOH)	72%
Ex.450	OH		**Ex.448**	M.2	isobutyraldehyde (1.1 equiv.) $NaBH(OAc)_3$ (2.5 equiv.)	prep. HPLC method 1	9% (TFA salt)

Table 45b: Examples of Core 29 (**Ex.447-Ex.450**)

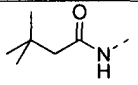
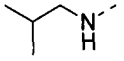
No	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.447-Ex.448: *cf. experimental description*							
Ex.449	OH		C24H36N2O4	416.3	2.01 (91)	417.3	Method 10a
Ex.450	OH		C22H34N2O3	374.3	1.41 (98)	375.2	Method 10a

Table 45c: Examples of Core 29 (**Ex.447-Ex.450**)

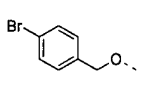
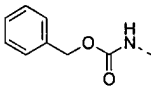
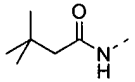
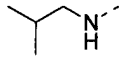
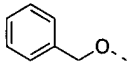
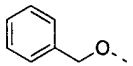
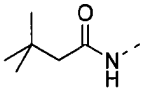
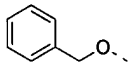
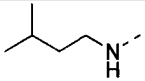
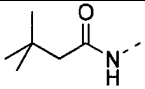
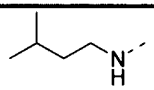
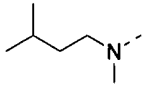
No	R^2	R^5	IUPAC name
Ex.447			1:1 mixture of the 12-*(E)*- and 12-*(Z)*-stereoisomer of benzyl *N*-[(4*S*,6*S*,10*S*)-6-[(4-bromobenzyl)oxy]-9-oxo-2-oxa-8-azatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),12,16,18-tetraen-10-yl]carbamate
Ex.448	OH	NH_2	(4*S*,6*S*,10*S*)-10-amino-6-hydroxy-2-oxa-8-azatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-9-one
Ex.449	OH		*N*-[(4*S*,6*S*,10*S*)-6-hydroxy-9-oxo-2-oxa-8-azatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-3,3-dimethylbutanamide
Ex.450	OH		(4*S*,6*S*,10*S*)-6-hydroxy-10-(isobutylamino)-2-oxa-8-azatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-9-one

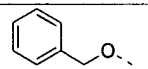
Table 46a: Examples of Core 30 (**Ex.451-Ex.459**; *continued on the following page*)

No	X	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.451-Ex.452 *cf. experimental description*								
Ex.453	SO_2		NH_2	**Ex.452**	K.2	H_2, 5%Pd-C NH_3-MeOH cf. detailed description	crude product	88%
Ex.454	SO_2	HO	NH_2	**Ex.452**	K.1	H_2, $Pd(OH)_2$-C MeOH/AcOH 1:1	FC (CH_2Cl_2/ MeOH/aq.NH_3)	78%
Ex.455	SO_2			**Ex.453**	L.1.1	3,3-dimethyl-butanoyl chloride (1.2 equiv.) pyridine (5 equiv.)	prep. HPLC method 3	83%
Ex.456	SO_2			**Ex.453**	M.2	isovaleraldehyde	prep. HPLC method 3	77%
Ex.457	SO_2	HO		**Ex.455**	H	H_2, $Pd(OH)_2$-C MeOH/AcOH 4:1	crude product	86%

No	X	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.458	SO_2	HO		**Ex.456**	H	H_2, $Pd(OH)_2$-C MeOH/AcOH 4:1	prep. HPLC method 3	19%
Ex.459*)	SO_2	HO		**Ex.456**	H	H_2, $Pd(OH)_2$-C MeOH/AcOH 4:1	prep. HPLC method 3	17%*)

*) obtained as a side product

Table 46b: Examples of Core 30 (**Ex.451-Ex.459**; *continued on the following page*)

No	X	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.451-Ex.452: *cf. experimental description*								
Ex.453	SO_2		NH_2	C25H31N3O5S	485.2	1.29 (98)	486.2	Method 10a
Ex.454	SO_2	HO	NH_2	C18H25N3O5S	395.2	0.70 (100)	396.1	Method 11a

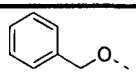
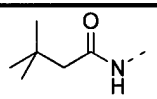
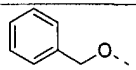
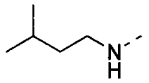
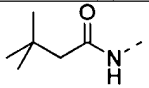
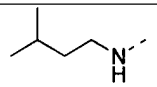
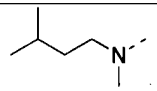
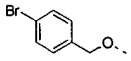
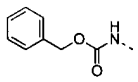
No	X	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.455	SO_2			C31H41N3O6S	583.3	1.90 (95)	584.3	Method 10a
Ex.456	SO_2			C30H41N3O5S	555.3	1.57 (99)	556.2	Method 10a
Ex.457	SO_2	HO		C24H35N3O6S	493.2	1.27 (95)	494.2	Method 10a
Ex.458	SO_2	HO		C23H35N3O5S	465.2	1.03 (95)	466.2	Method 10a
Ex.459	SO_2	HO		C24H37N3O5S	479.2	1.03 (94)	480.2	Method 10a

Table 46c: Examples of Core 30 (**Ex.451-Ex.459**; *continued on the following page*)

No	X	R^2	R^5	IUPAC name
Ex.451	S			benzyl *N*-[(4*S*,6*S*,10*S*)-6-[(4-bromobenzyl)oxy]-14-methyl-9,15-dioxo-2-thia-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]carbamate

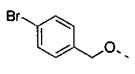
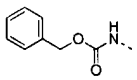
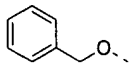
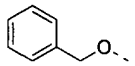
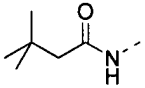
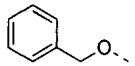
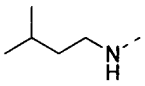
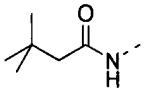
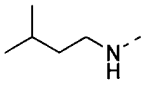
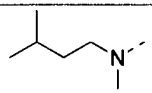
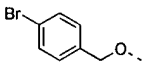
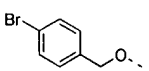
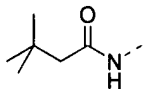
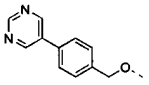
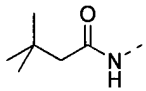
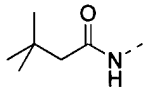
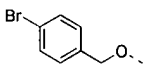
No	X	R^2	R^5	IUPAC name
Ex.452	SO_2			benzyl *N*-[(4*S*,6*S*,10*S*)-6-[(4-bromobenzyl)oxy]-14-methyl-2,2,9,15-tetraoxo-2λ^6-thia-8,14-diazatricyclo[14.3.1.0^{4,8}]icosa-1(20),16,18-trien-10-yl]carbamate
Ex.453	SO_2		NH_2	(4*S*,6*S*,10*S*)-10-amino-6-(benzyloxy)-14-methyl-2λ^6-thia-8,14-diazatricyclo[14.3.1.0^{4,8}]icosa-1(20),16,18-triene-2,2,9,15-tetrone
Ex.454	SO_2	HO	NH_2	(4*S*,6*S*,10*S*)-10-amino-6-hydroxy-14-methyl-2λ^6-thia-8,14-diazatricyclo[14.3.1.0^{4,8}]icosa-1(20),16,18-triene-2,2,9,15-tetrone
Ex.455	SO_2			*N*-[(4*S*,6*S*,10*S*)-6-(benzyloxy)-14-methyl-2,2,9,15-tetraoxo-2λ^6-thia-8,14-diazatricyclo[14.3.1.0^{4,8}]icosa-1(20),16,18-trien-10-yl]-3,3-dimethylbutanamide
Ex.456	SO_2			(4*S*,6*S*,10*S*)-6-(benzyloxy)-10-(isopentylamino)-14-methyl-2λ^6-thia-8,14-diazatricyclo[14.3.1.0^{4,8}]icosa-1(20),16,18-triene-2,2,9,15-tetrone
Ex.457	SO_2	HO		*N*-[(4*S*,6*S*,10*S*)-6-hydroxy-14-methyl-2,2,9,15-tetraoxo-2λ^6-thia-8,14-diazatricyclo[14.3.1.0^{4,8}]icosa-1(20),16,18-trien-10-yl]-3,3-dimethylbutanamide
Ex.458	SO_2	HO		(4*S*,6*S*,10*S*)-6-hydroxy-10-(isopentylamino)-14-methyl-2λ^6-thia-8,14-diazatricyclo[14.3.1.0^{4,8}]icosa-1(20),16,18-triene-2,2,9,15-tetrone
Ex.459	SO_2	HO		(4*S*,6*S*,10*S*)-6-hydroxy-10-[isopentyl(methyl)amino]-14-methyl-2λ^6-thia-8,14-diazatricyclo[14.3.1.0^{4,8}]icosa-1(20),16,18-triene-2,2,9,15-tetrone

Table 47a: Examples of Core 31 (**Ex.460-Ex.469**; *continued on the following page*)

No	L	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.460-Ex.461: *cf. experimental description*								
Ex.462	SO_2		NH_2	**Ex.461**	J	HCl-dioxane	crude product	87% (HCl salt)
Ex.463	SO_2			**Ex.462**	L.1.1	3,3-dimethyl-butanoyl chloride (1.5 equiv.) pyridine (5 equiv.)	FC (hexane/EtOAc)	76%
Ex.464	SO_2			**Ex.463**	P	pyrimidin-5-yl boronic acid	FC (hexane/EtOAc/ MeOH) and FC (CH_2Cl_2/MeOH)	67%
Ex.465	SO_2	OH		**Ex.463**	H	H_2, $Pd(OH)_2$-C	FC (CH_2Cl_2/MeOH/ aq. NH_3)	98%
Ex.466	S		NH_2	**Ex.460**	J	HCl-dioxane	crude product	90% (HCl salt)

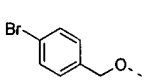
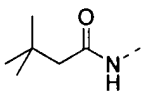
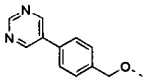
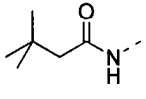
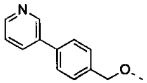
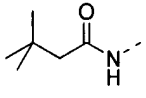
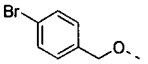
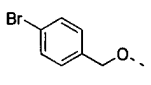
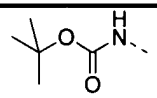
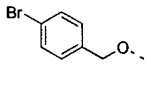
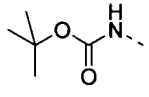
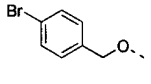
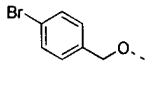
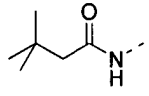
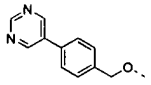
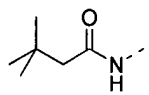
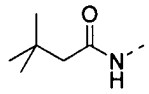
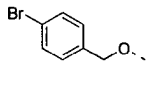
No	L	R^2	R^5	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.467	S			**Ex.466**	L.1.1	3,3-dimethyl-butanoyl chloride (1.5 equiv.) pyridine (5 equiv.)	FC (hexane/EtOAc)	83%
Ex.468	S			**Ex.467**	P	pyrimidin-5-yl boronic acid	FC (hexane/EtOAc/ MeOH)	72%
Ex.469	S			**Ex.467**	P	pyridin-3-yl boronic acid	FC (hexane/EtOAc/ MeOH)	66%

Table 47b: Examples of Core 31 (**Ex.460-Ex.469**; *continued on the following page*)

No	L	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.460-Ex.461: *cf. experimental description*								
Ex.462	SO_2		NH_2	C24H29BrN2O5S	536.1	1.63 (96)	539.1/537.1	Method 10a

No	L	R^2	R^5	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.463	SO_2			C30H39BrN2O6S	634.1	2.33 (99)	635.1/637.1	Method 10a
Ex.464	SO_2			C34H42N4O6S	634.3	1.89 (93)	635.2	Method 10a
Ex.465	SO_2	OH		C23H34N2O6S	466.2	1.47 (97)	467.2	Method 10a
Ex.466	S		NH_2	C24H29BrN2O3S	504.1	1.89 (93)	507.1/505.1	Method 10a
Ex.467	S			C30H39BrN2O4S	602.2	2.75 (96)	605.1/603.1	Method 10a
Ex.468	S			C34H42N4O4S	602.3	2.33 (90)	603.3	Method 10a
Ex.469	S			C35H43N3O4S	601.3	1.92 (98)	602.3	Method 10a

Table 47c: Examples of Core 31 (**Ex.460-Ex.469**; *continued on the following page*)

No	L	R^2	R^5	IUPAC name
Ex.460	S			*tert*-butyl *N*-[(4*S*,6*S*,10*S*)-6-[(4-bromobenzyl)oxy]-9-oxo-2-oxa-15-thia-8-azatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]carbamate
Ex.461	SO_2			*tert*-butyl *N*-[(4*S*,6*S*,10*S*)-6-[(4-bromobenzyl)oxy]-9,15,15-trioxo-2-oxa-15λ^6-thia-8-azatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]carbamate
Ex.462	SO_2		NH_2	(4*S*,6*S*,10*S*)-10-amino-6-[(4-bromobenzyl)oxy]-2-oxa-15λ^6-thia-8-azatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-triene-9,15,15-trione
Ex.463	SO_2			*N*-[(4*S*,6*S*,10*S*)-6-[(4-bromobenzyl)oxy]-9,15,15-trioxo-2-oxa-15λ^6-thia-8-azatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-3,3-dimethylbutanamide
Ex.464	SO_2			3,3-dimethyl-*N*-[(4*S*,6*S*,10*S*)-9,15,15-trioxo-6-{[4-(5-pyrimidinyl)benzyl]oxy}-2-oxa-15λ^6-thia-8-azatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]butanamide
Ex.465	SO_2	OH		*N*-[(4*S*,6*S*,10*S*)-6-hydroxy-9,15,15-trioxo-2-oxa-15λ^6-thia-8-azatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-3,3-dimethylbutanamide
Ex.466	S		NH_2	(4*S*,6*S*,10*S*)-10-amino-6-[(4-bromobenzyl)oxy]-2-oxa-15-thia-8-azatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-9-one

No	L	R^2	R^5	IUPAC name
Ex.467	S			*N*-[(4*S*,6*S*,10*S*)-6-[(4-bromobenzyl)oxy]-9-oxo-2-oxa-15-thia-8-azatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-3,3-dimethylbutanamide
Ex.468	S			3,3-dimethyl-*N*-[(4*S*,6*S*,10*S*)-9-oxo-6-{[4-(5-pyrimidinyl)benzyl]oxy}-2-oxa-15-thia-8-azatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]butanamide
Ex.469	S			3,3-dimethyl-*N*-[(4*S*,6*S*,10*S*)-9-oxo-6-{[4-(3-pyridinyl)benzyl]oxy}-2-oxa-15-thia-8-azatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]butanamide

Table 48a: Examples of Core 32 (**Ex.470-Ex.475**)

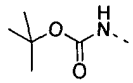
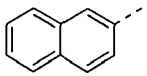
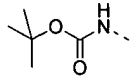
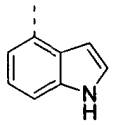
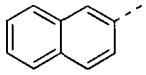
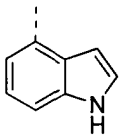
No	R^2	R^1	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.470: *cf. experimental description*							
Ex.471			**Ex.470**	P	cf. experimental description	FC (CH_2Cl_2/MeOH)	62%
Ex.472			**Ex.470**	P	cf. experimental description	FC (CH_2Cl_2/MeOH)	62%
Ex.473	NH_2	(Br)	**Ex.470**	J	cf. experimental description	crude product	92% (HCl salt)
Ex.474	NH_2		**Ex.471**	J	cf. experimental description	crude product	100% (HCl salt)
Ex.475	NH_2		**Ex.474**	---	cf. experimental description	FC (CH_2Cl_2/MeOH)	83%

Table 48b: Examples of Core 32 (**Ex.470-Ex.475**)

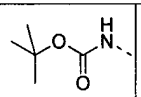
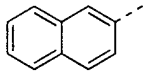
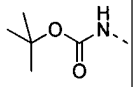
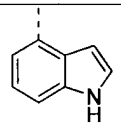
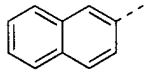
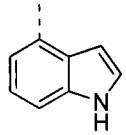
No	R^2	R^1	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.470: *cf. experimental description*							
Ex.471			C47H50N4O6	766.9	2.68 (95)	767.4	Method 10a
Ex.472			C45H49N5O6	755.4	2.37 (92)	756.4	Method 10a
Ex.473	NH_2	(Br)	C32H35BrN4O4	618.2	1.75 (98)	621.1/ 619.1	Method 10a
Ex.474	NH_2		C42H42N4O4	666.3	2.02 (96)	667.3	Method 10a
Ex.475	NH_2		C40H41N5O4	655.3	1.76 (90)	656.3	Method 10a

Table 48c: Examples of Core 32 (**Ex.470-Ex.475**)

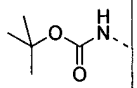
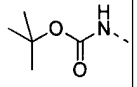
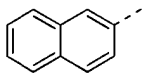
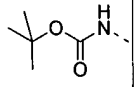
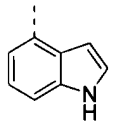
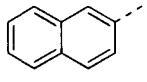
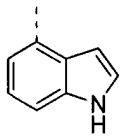
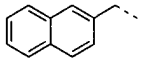
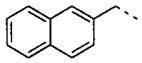
No	R^2	R^1	IUPAC name
Ex.470		(Br)	*tert*-butyl (2*R*,7*S*,18a*S*)-14-bromo-7-(naphthalen-2-ylmethyl)-5,9,12-trioxo-1,2,3,5,6,7,8,9,11,12,18,18a-dodecahydrospiro[benzo[*m*]pyrrolo[2,1-*c*][1,4,8,11]oxatriazacyclotetradecine-10,1'-cyclopentane]-2-ylcarbamate
Ex.471			*tert*-butyl (2*R*,7*S*,18a*S*)-14-(naphthalen-2-yl)-7-(naphthalen-2-ylmethyl)-5,9,12-trioxo-1,2,3,5,6,7,8,9,11,12,18,18a-dodecahydrospiro[benzo[*m*]pyrrolo[2,1-*c*][1,4,8,11]oxatriazacyclotetradecine-10,1'-cyclopentane]-2-ylcarbamate
Ex.472			*tert*-butyl (2*R*,7*S*,18a*S*)-14-(1H-indol-4-yl)-7-(naphthalen-2-ylmethyl)-5,9,12-trioxo-1,2,3,5,6,7,8,9,11,12,18,18a-dodecahydrospiro[benzo[*m*]pyrrolo[2,1-*c*][1,4,8,11]oxatriazacyclotetradecine-10,1'-cyclopentane]-2-ylcarbamate
Ex.473	NH_2	(Br)	(2*R*,7*S*,18a*S*)-2-amino-14-bromo-7-(naphthalen-2-ylmethyl)-2,3,7,8,18,18a-hexahydrospiro[benzo[*m*]pyrrolo[2,1-*c*][1,4,8,11]oxatriazacyclotetradecine-10,1'-cyclopentane]-5,9,12(1*H*,6*H*,11*H*)-trione
Ex.474	NH_2		(2*R*,7*S*,18a*S*)-2-amino-14-(naphthalen-2-yl)-7-(naphthalen-2-ylmethyl)-2,3,7,8,18,18a-hexahydrospiro[benzo[*m*]pyrrolo[2,1-*c*][1,4,8,11]oxatriazacyclotetradecine-10,1'-cyclopentane]-5,9,12(1*H*,6*H*,11*H*)-trione
Ex.475	NH_2		(2*R*,7*S*,18a*S*)-2-amino-14-(1H-indol-4-yl)-7-(naphthalen-2-ylmethyl)-2,3,7,8,18,18a-hexahydrospiro[benzo[*m*]pyrrolo[2,1-*c*][1,4,8,11]oxatriazacyclotetradecine-10,1'-cyclopentane]-5,9,12(1*H*,6*H*,11*H*)-trione

Table 49a: Examples of Core 33*) (**Ex.476-Ex.481**; *continued on the following page*)

No	R^4	R^5	R^7	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.476 *cf. experimental description*								
Ex.477	CH_3	CH_2Ph (*S*)	H	**259**	**)	1. Fmoc-Apa-OH 2. H-MePhe-OAll·pTsOH	Method 2	28%
Ex.478	H	H	H	**259**	**)	1. Fmoc-Apa-OH *i*-Pr_2NEt (6 equiv.) 2. H-Gly-OAll·pTsOH (2 equiv.), *i*-Pr_2NEt (6 equiv.) ***)	Method 2	25%
Ex.479	H	H	 (*S*)	**259**	**)	1. Fmoc-β^3-H2Nal-OH *i*-Pr_2NEt (6 equiv.) 2. H-Gly-OAll·pTsOH (2 equiv.), *i*-Pr_2NEt (6 equiv.) ***)	Method 2	8%

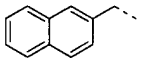
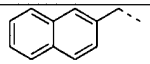
No	R^4	R^5	R^7	Starting material	General Procedure	Reagent	Purification Method	Yield (isolated salt)
Ex.480	CH_3	CH_3 (*S*)	CH_3	**259**	**)	1. Fmoc-β^3-HAla-OH *i*-Pr_2NEt (6 equiv.) 2. H-MeAla-OAll·HCl (2 equiv.), *i*-Pr_2NEt (6 equiv.)	Method 2	40%
Ex.481	CH_3	CH_3 (*S*)	 (*S*)	**259**	**)	1. Fmoc-β^3-H2Nal-OH *i*-Pr_2NEt (6 equiv.) 2. H-MeAla-OAll·HCl (2 equiv.), *i*-Pr_2NEt (6 equiv.)	Method 2	16%

*) R^2 = benzamido (Ph-CO-NH-)

) See details in experimental description of **Ex.476

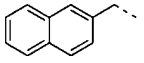
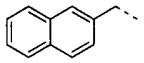
***) Second coupling was repeated once.

Table 49b: Examples of Core 33*) (**Ex.476-Ex.481**)

No	R^4	R^5	R^7	FORMULA	MONOISOTOPIC MASS	Rt (purity at 220nm)	$[M+H]^+$ found	LC-MS-Method
Ex.476: *cf. experimental description*								
Ex.477	CH_3	CH_2Ph (*S*)	H	C32H34N4O5	554.2	1.68 (90)	555.2	Method 10b
Ex.478	H	H	H	C24H26N4O5	450.2	1.29 (95)	451.2	Method 10b
Ex.479	H	H	 (*S*)	C35H34N4O5	590.3	1.88 (94)	591.2	Method 10b
Ex.480	CH_3	CH_3 (*S*)	CH_3 (*S*)	C27H32N4O5	492.2	1.42 (99)	493.0	Method 10b
Ex.481	CH_3	CH_3 (*S*)	 (*S*)	C37H38N4O5	618.3	1.94 (94)	619.2	Method 10b

*) R^2 = benzamido (Ph-CO-NH-)

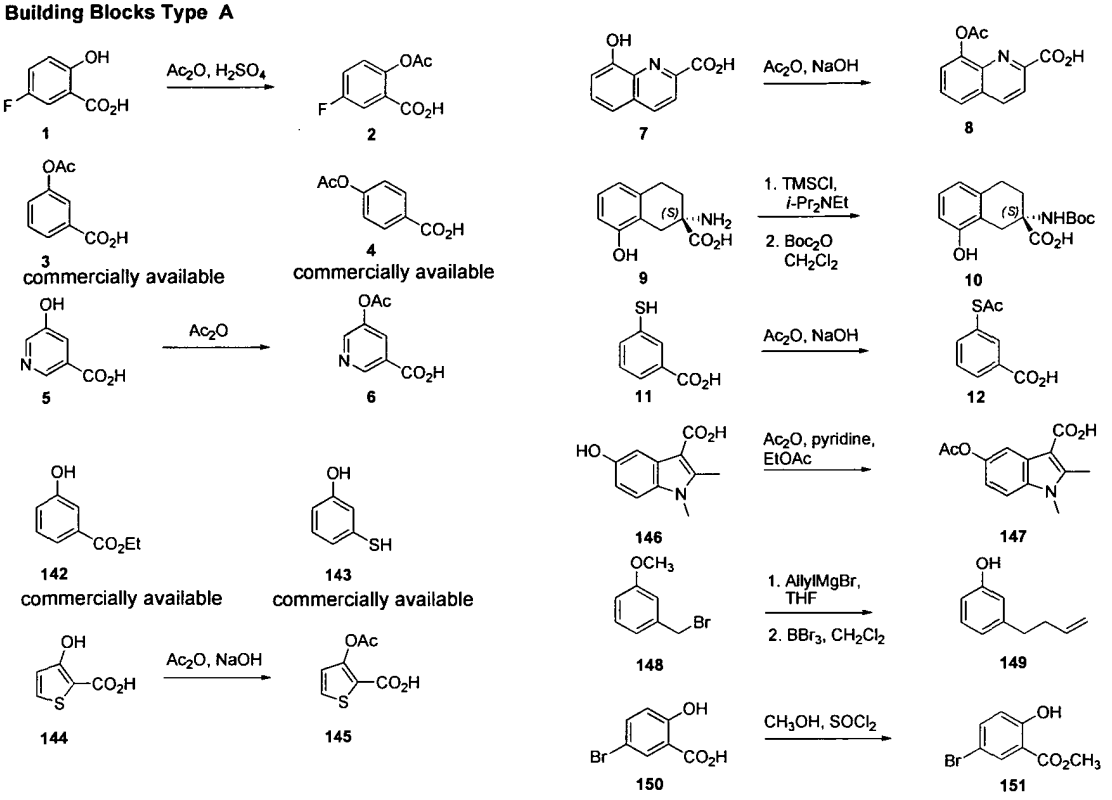
Table 49c: Examples of Core 33*) (**Ex.476-Ex.481**)

No	R^4	R^5	R^7	IUPAC name
Ex.476	CH_3	CH_3 (*S*)	H	*N*-[(4*S*,6*R*,14*S*)-14,15-dimethyl-9,13,16-trioxo-2-oxa-8,12,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]benzamide
Ex.477	CH_3	CH_2Ph (*S*)	H	*N*-[(4*S*,6*R*,14*S*)-14-benzyl-15-methyl-9,13,16-trioxo-2-oxa-8,12,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]benzamide
Ex.478	H	H	H	*N*-[(4*S*,6*R*)-9,13,16-trioxo-2-oxa-8,12,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]benzamide
Ex.479	H	H	 (*S*)	*N*-[(4*S*,6*R*,11*S*)-11-(2-naphthylmethyl)-9,13,16-trioxo-2-oxa-8,12,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]benzamide
Ex.480	CH_3	CH_3 (*S*)	CH_3 (*S*)	*N*-[(4*S*,6*R*,11*S*,14*S*)-11,14,15-trimethyl-9,13,16-trioxo-2-oxa-8,12,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]benzamide
Ex.481	CH_3	CH_3 (*S*)	 (*S*)	*N*-[(4*S*,6*R*,11*S*,14*S*)-14,15-dimethyl-11-(2-naphthylmethyl)-9,13,16-trioxo-2-oxa-8,12,15-triazatricyclo[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-6-yl]benzamide

*) R^2 = benzamido (Ph–CO–NH–)

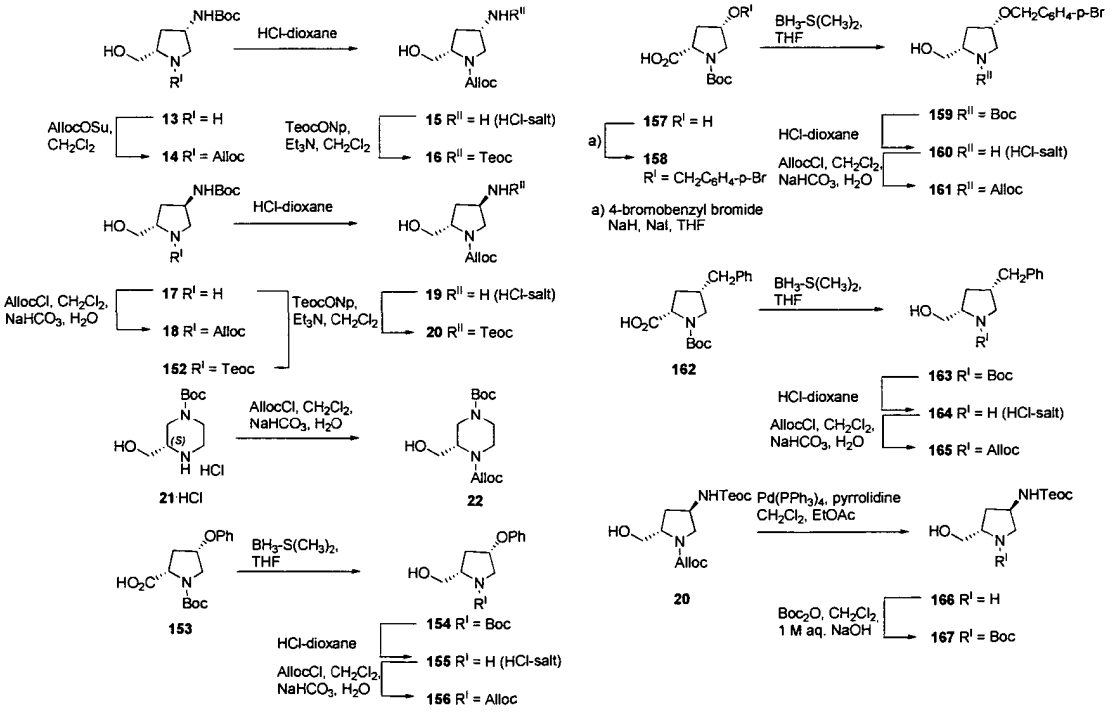
Scheme 1

Building Blocks Type A



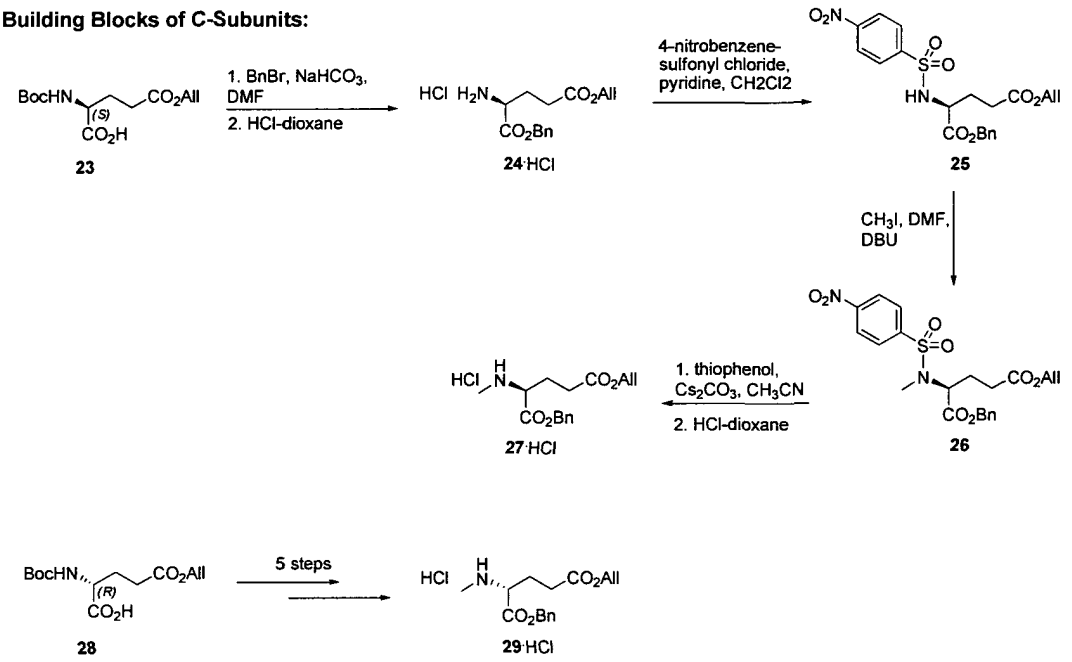
Scheme 2

Building Blocks of Type B



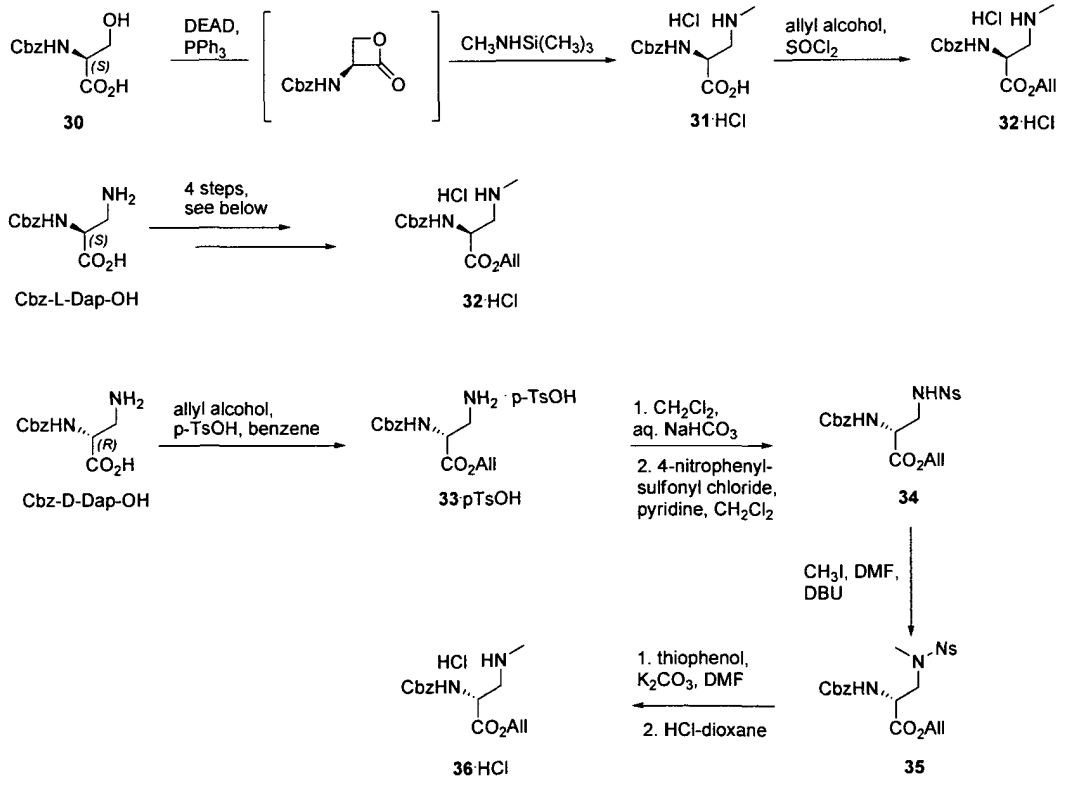
Scheme 3

Building Blocks of C-Subunits:



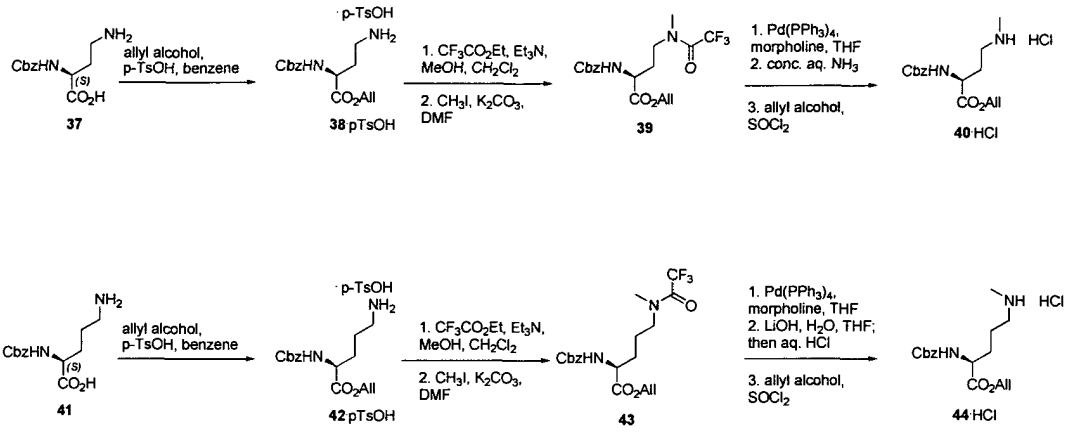
Scheme 3, cont.

Building Blocks of C-Subunits:



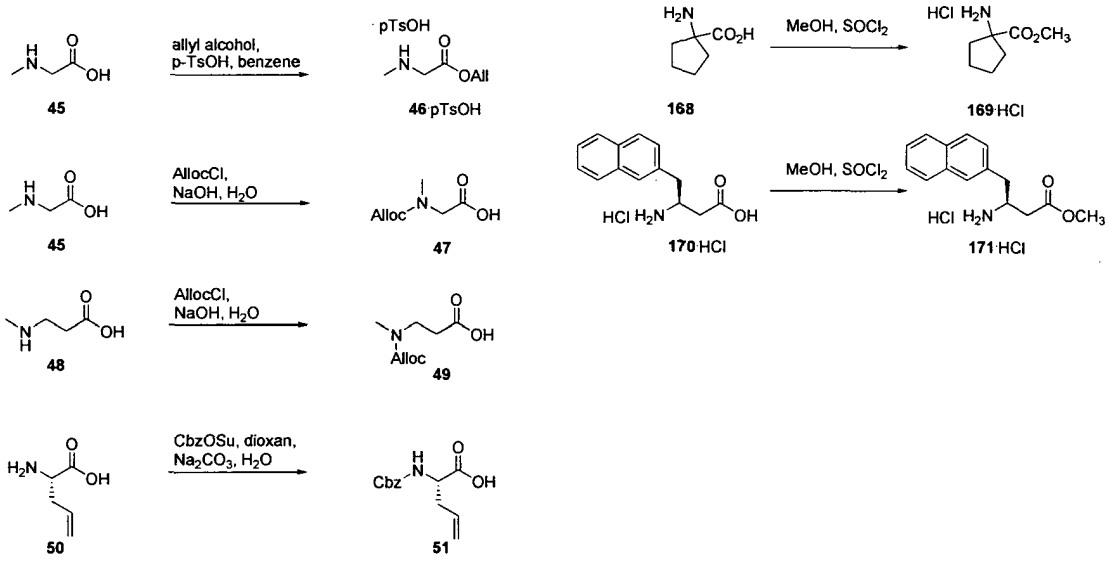
Scheme 3, cont.

Building Blocks of C-Subunits:



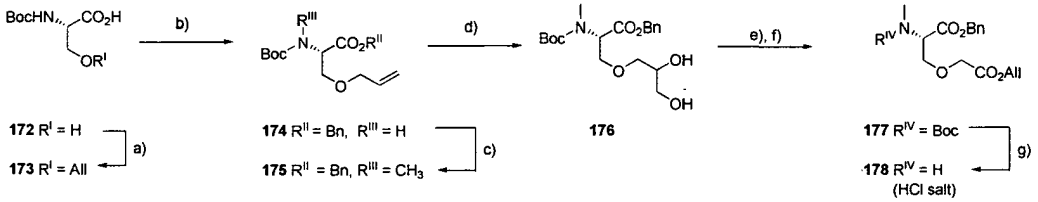
Building Blocks of C-Subunits:

Scheme 3. cont.

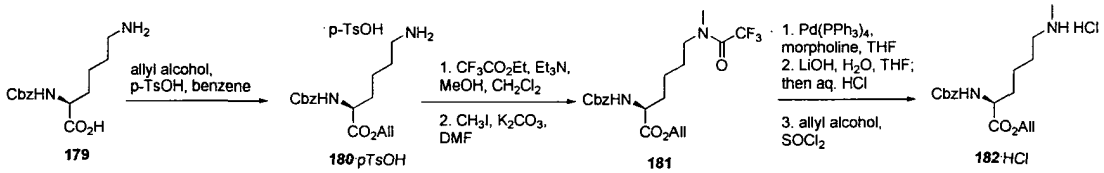


Scheme 3, cont.

Building Blocks of C-Subunits:

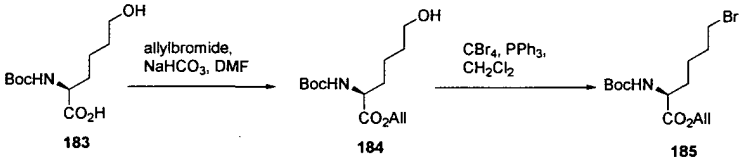


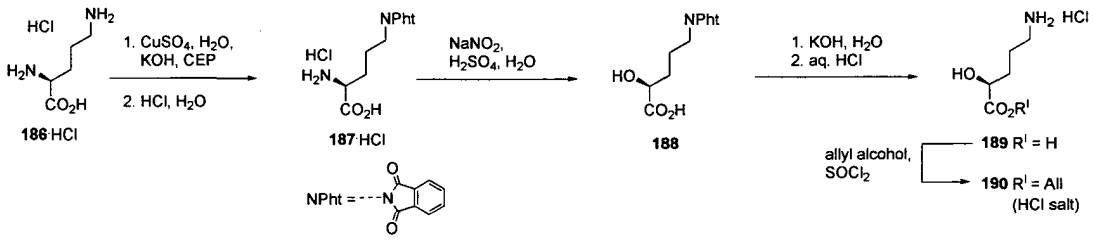
a) NaH, DMF, allyl bromide; b) BnBr, $NaHCO_3$, DMF; c) CH_3I, Ag_2O, DMF, AcOH; d) NMO, OsO_4, acetone, H_2O;
e) 1. $NaIO_4$, THF, H_2O; 2. $NaIO_4$, $RuCl_3$, CH_2Cl_2, CH_3CN, H_2O; f) allyl bromide, $NaHCO_3$, DMF; g) TFA-CH_2Cl_2, then HCl-dioxane



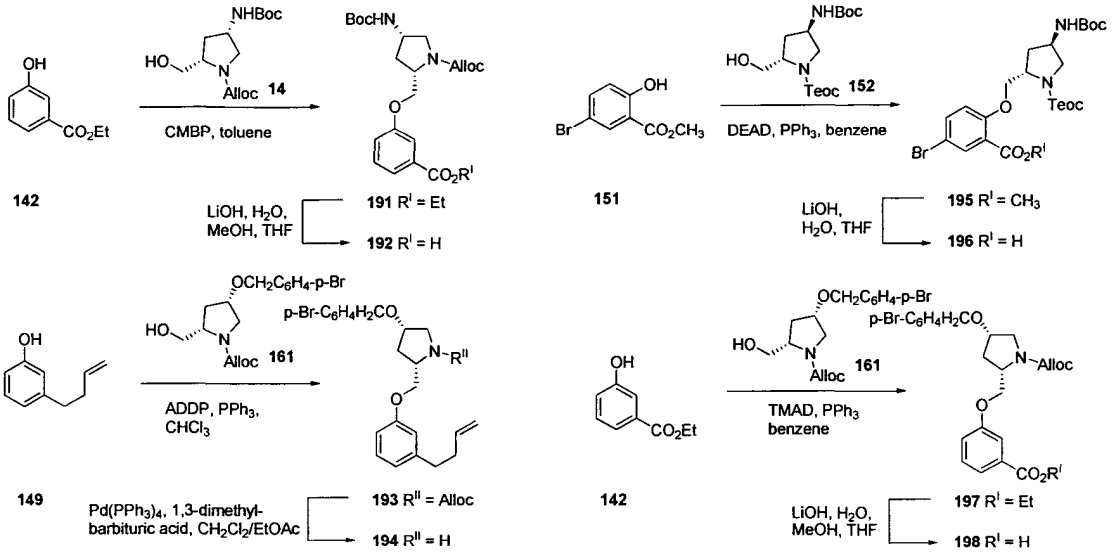
Scheme 3, cont.

Building Blocks of C-Subunits:

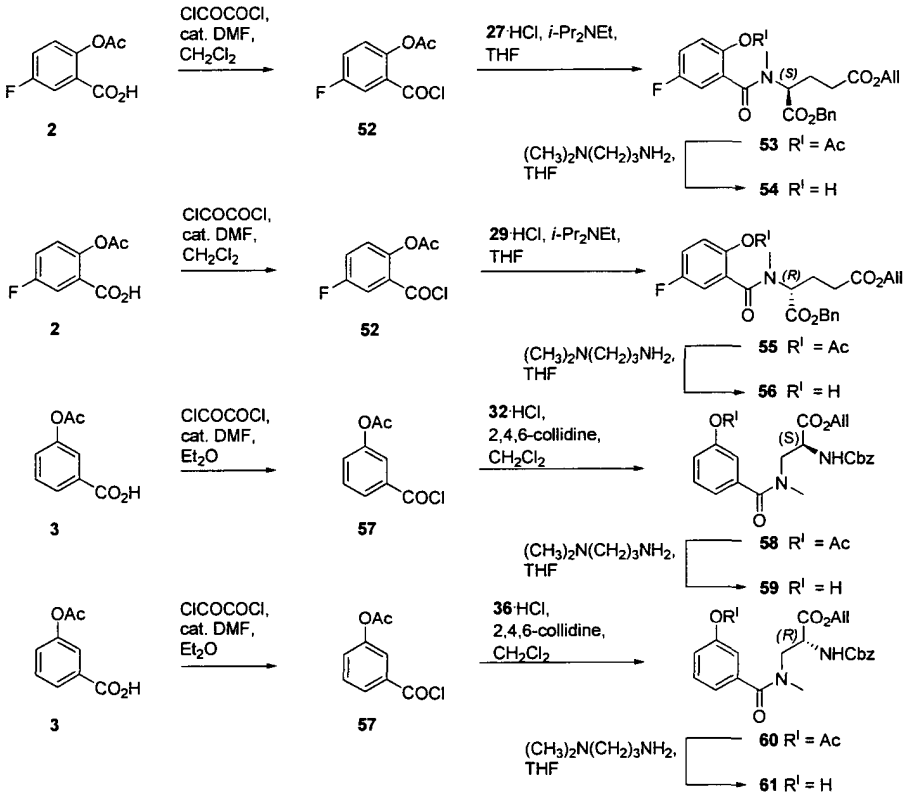




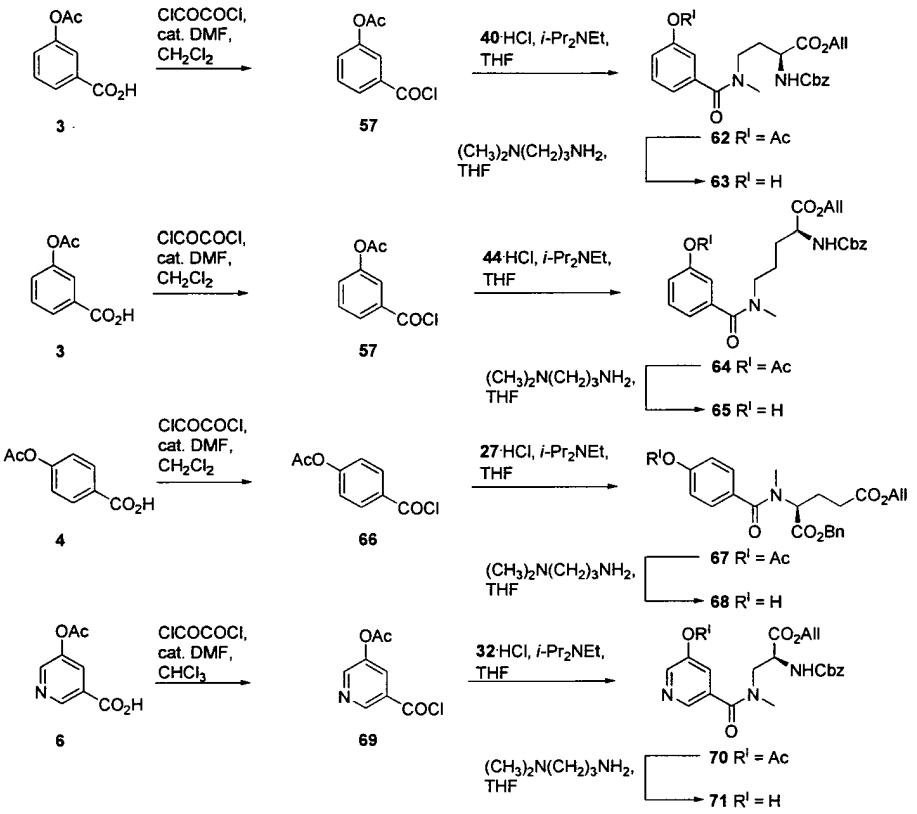
A-B Fragments Scheme 4



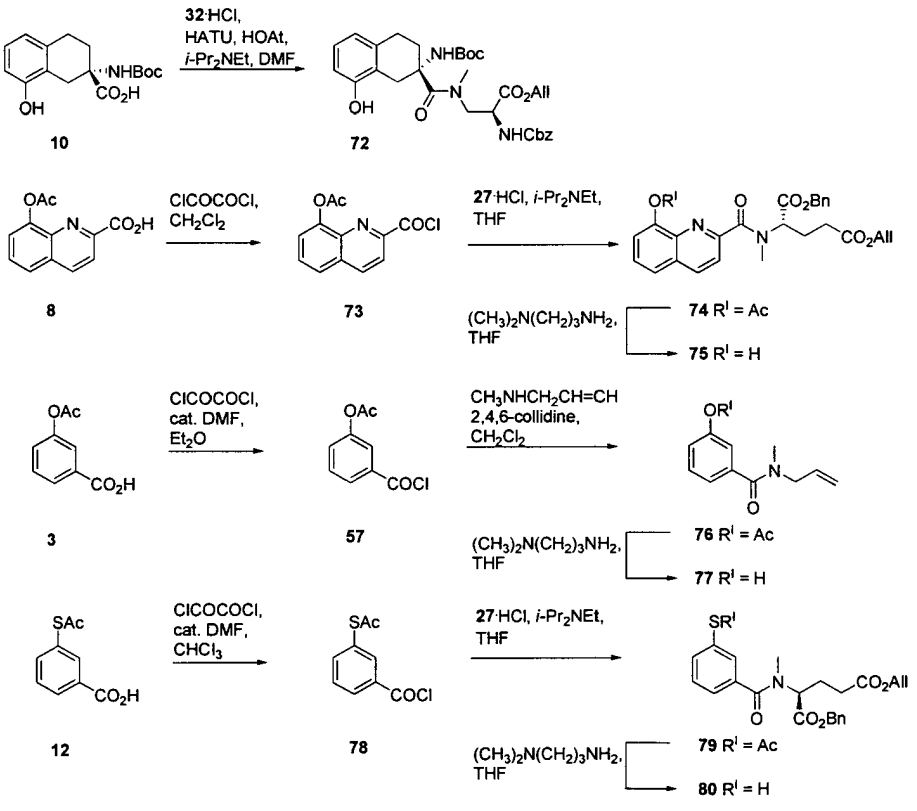
A-C Fragments Scheme 4, cont.



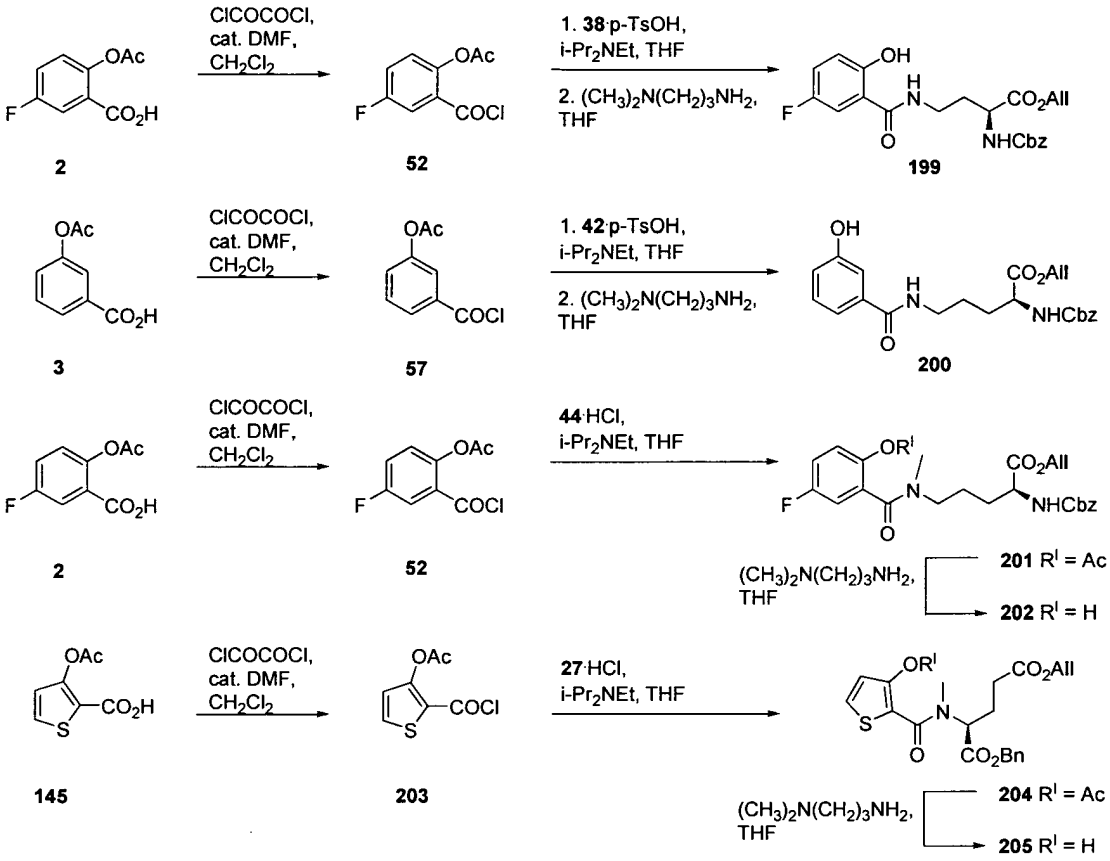
A-C Fragments Scheme 4, cont.



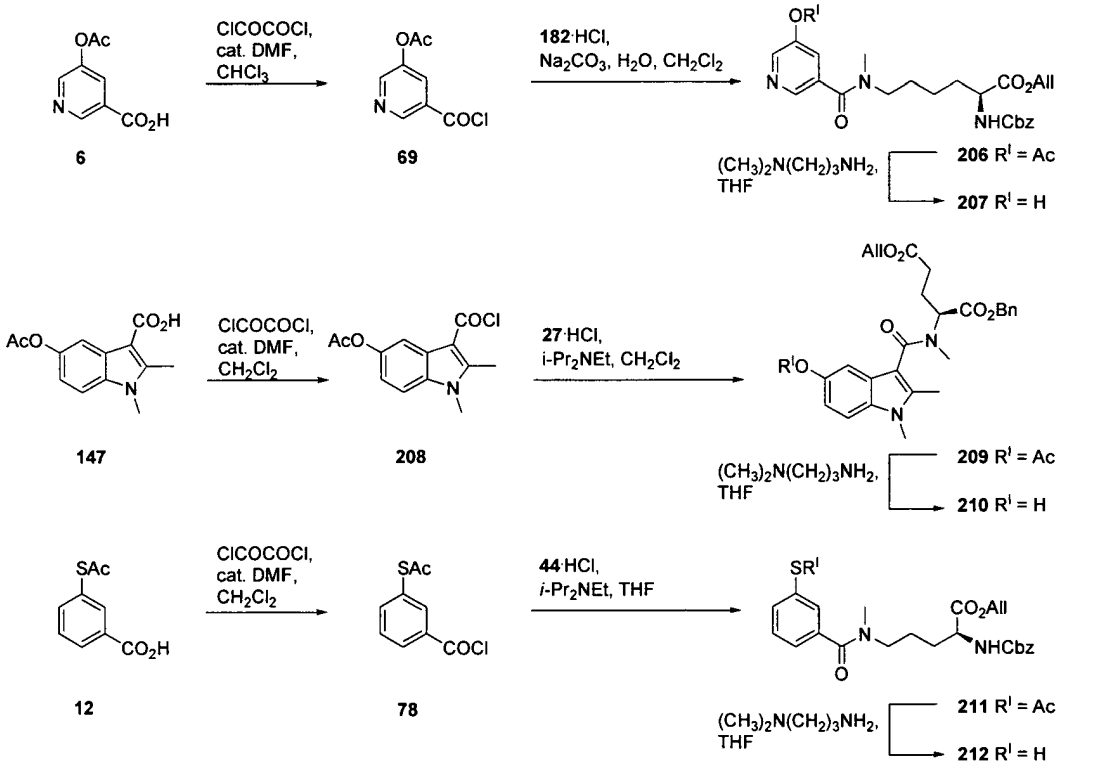
A-C Fragments Scheme 4, cont.



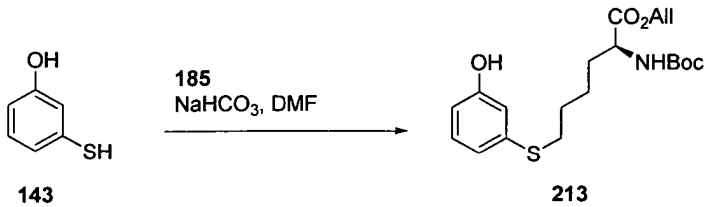
A-C Fragments Scheme 4, cont.



A-C Fragments Scheme 4, cont.

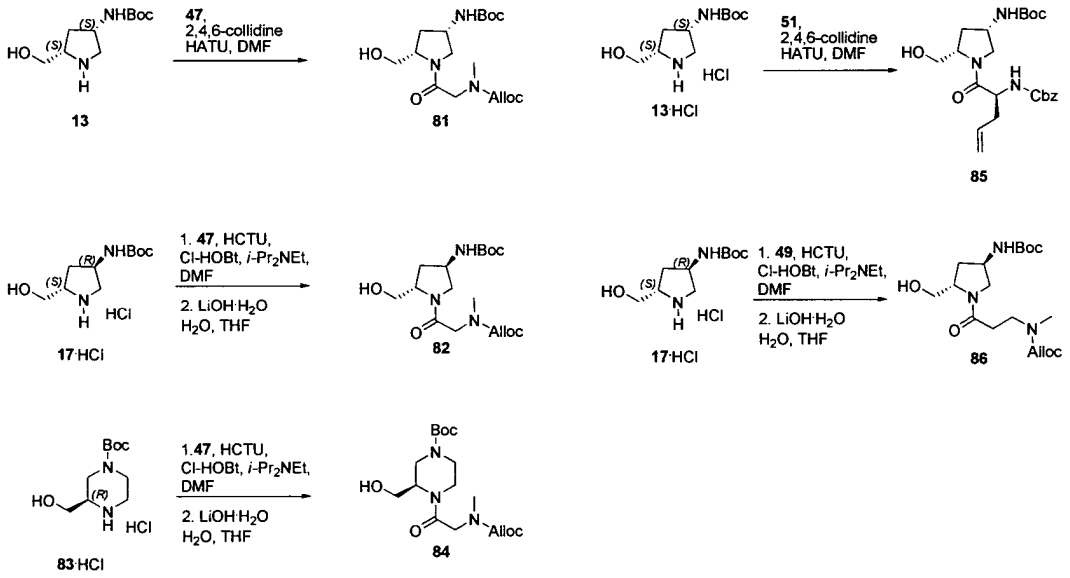


A-C Fragments Scheme 4, cont.

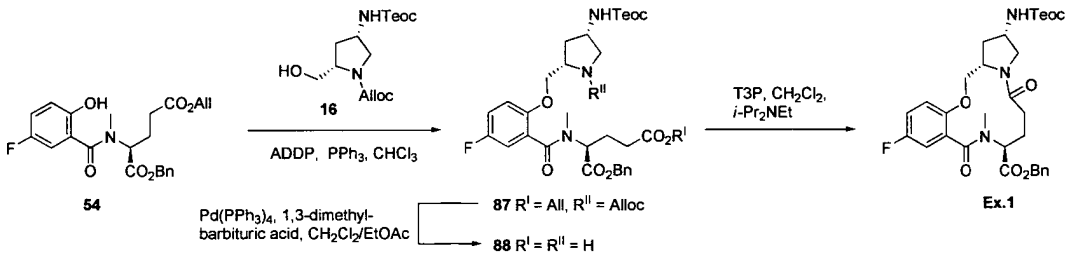


143 213

C-B Fragments Scheme 5



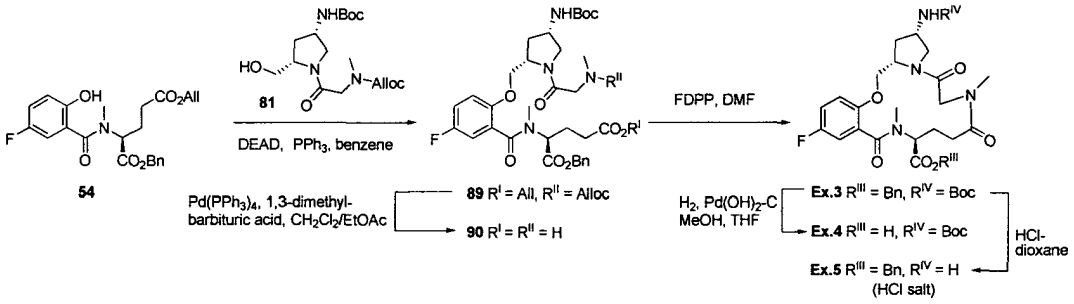
Core 01 Scheme 6



Core 02: cf. Scheme 11

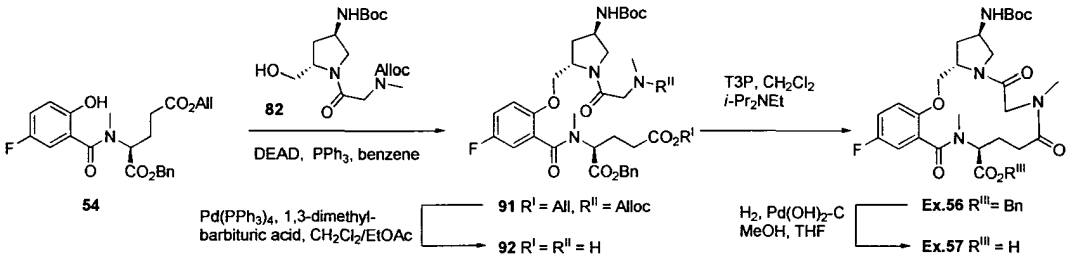
Core 03

Scheme 7



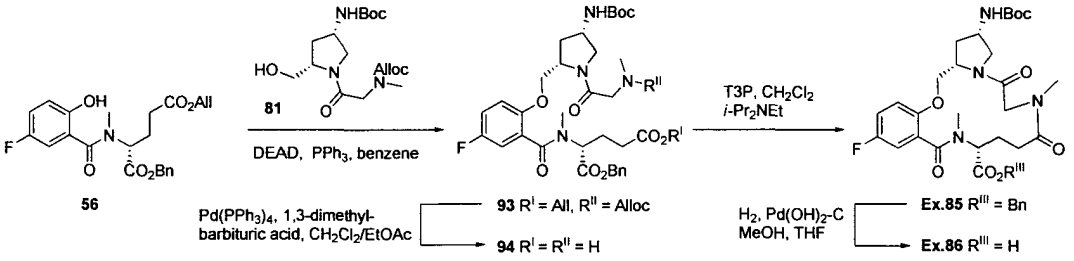
Core 04

Scheme 8



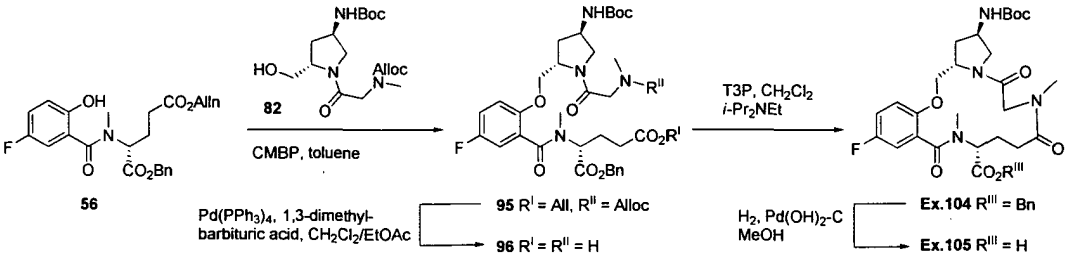
Core 05

Scheme 9



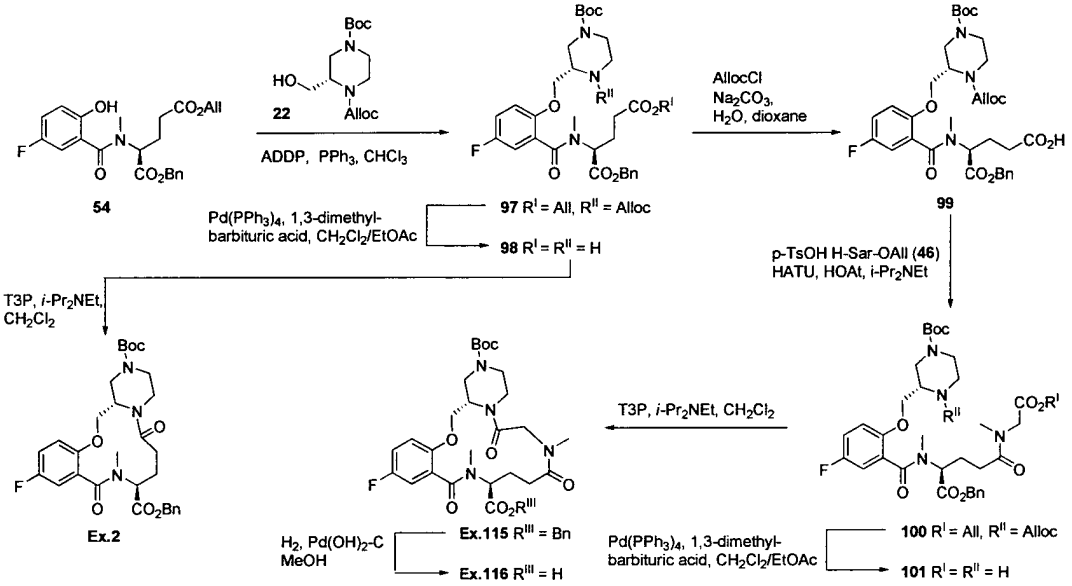
Core 06

Scheme 10



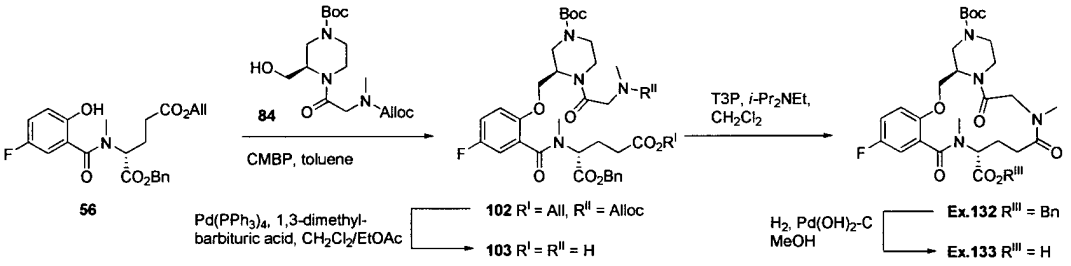
Core 02 and Core 07

Scheme 11



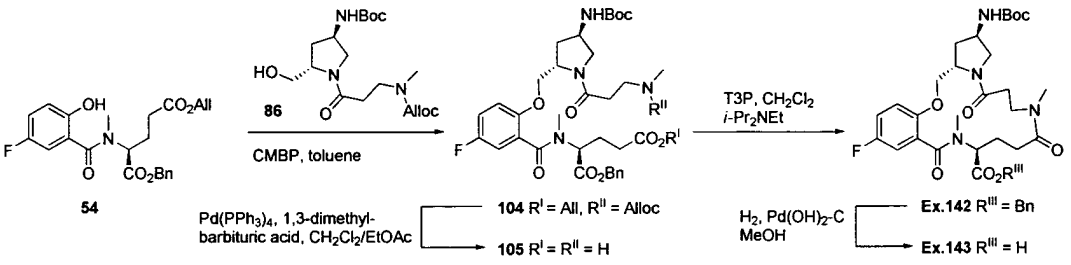
Core 08

Scheme 12



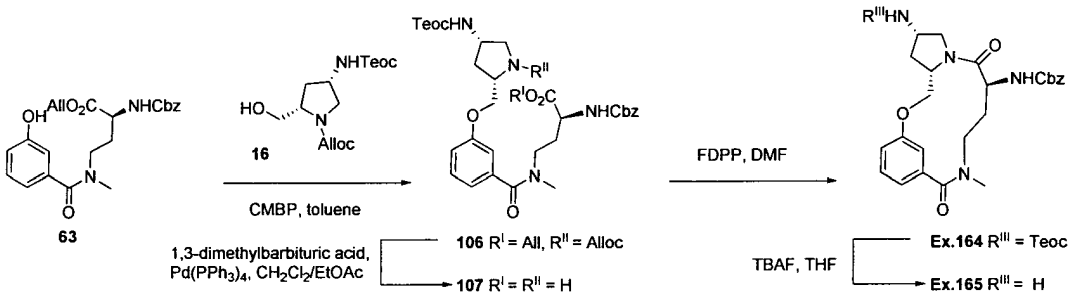
Core 09

Scheme 13



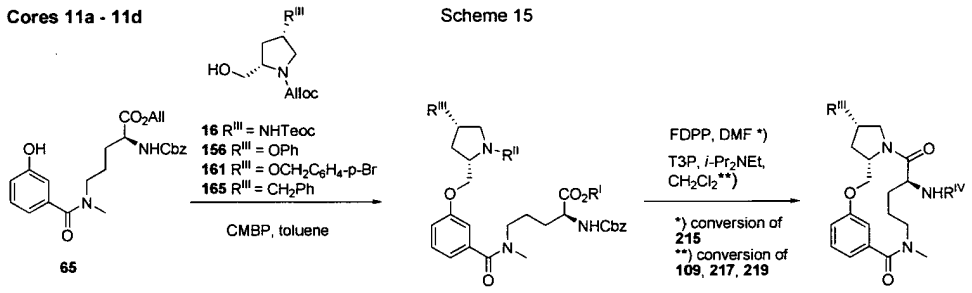
Scheme 14

Core 10



Cores 11a - 11d

Scheme 15



Pd(PPh3)4,1,3-dimethyl-barbituric acid, CH2Cl2/EtOAc → **108** RI = All, RII = Alloc, RIII = NHTeoc; **109** RI = RII = H, RIII = NHTeoc

Pd(PPh3)4,1,3-dimethyl-barbituric acid, CH2Cl2/EtOAc → **214** RI = All, RII = Alloc, RIII = OPh; **215** RI = RII = H, RIII = OPh

Pd(PPh3)4,1,3-dimethyl-barbituric acid, CH2Cl2/EtOAc → **216** RI = All, RII = Alloc, RIII = $OCH_2C_6H_4$-p-Br; **217** RI = RII = H, RIII = $OCH_2C_6H_4$-p-Br

Pd(PPh3)4,1,3-dimethyl-barbituric acid, CH2Cl2/EtOAc → **218** RI = All, RII = Alloc, RIII = CH_2Ph; **219** RI = RII = H, RIII = CH_2Ph

a) → **Ex.181** RIII = NHTeoc, RIV = Cbz; **Ex.182** RIII = NH_2, RIV = Cbz

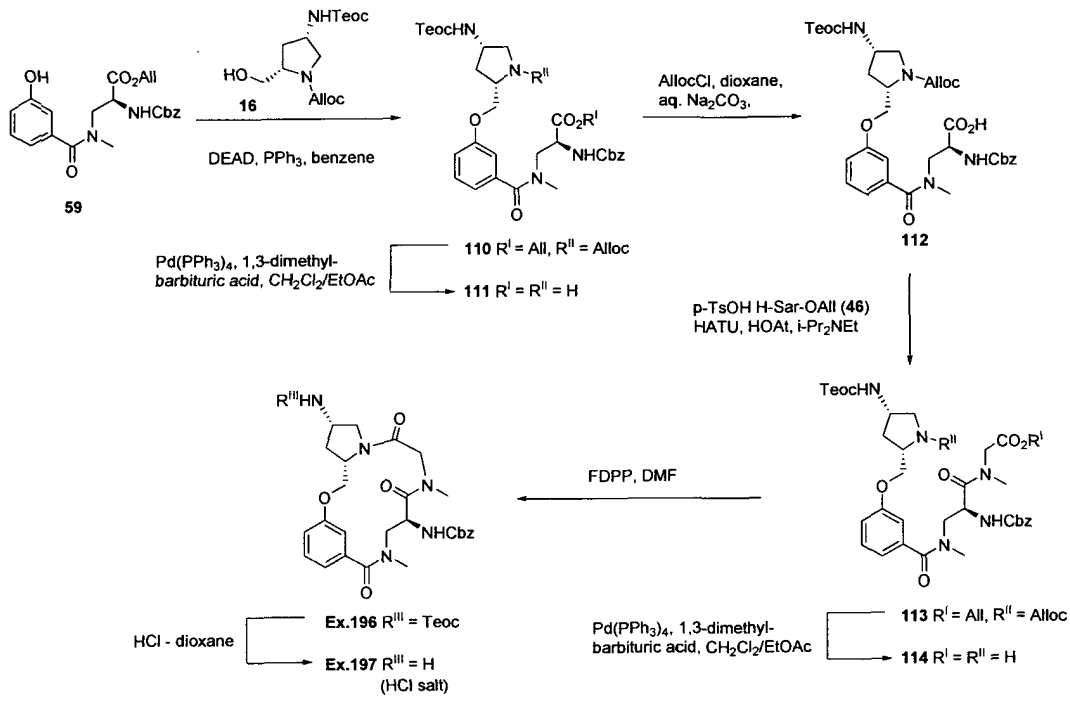
b) → **Ex.560** RIII = OPh, RIV = Cbz; **Ex.561** RIII = OPh, RIV = H

c) → **Ex.567** RIII = $OCH_2C_6H_4$-p-Br, RIV = Cbz; **Ex.568** RIII = $OCH_2C_6H_5$, RIV = H

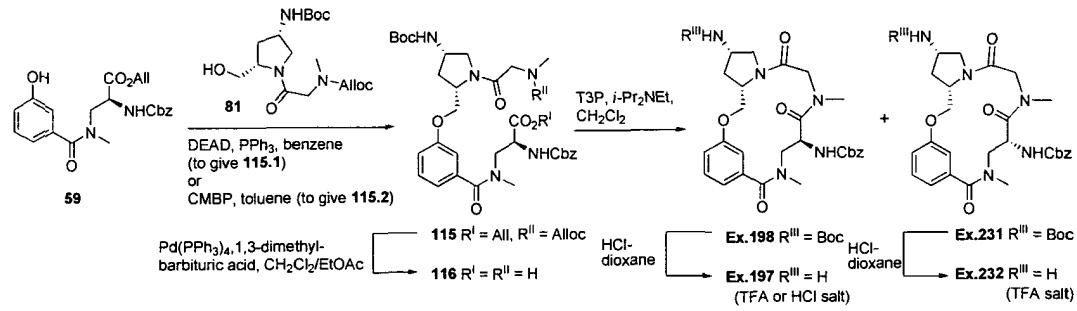
d) → **Ex.586** RIII = CH_2Ph, RIV = Cbz; **Ex.587** RIII = CH_2Ph, RIV = H

a) TBAF, THF
b) H_2, 10% Pd-C, MeOH
c) H_2, 5% Pd-C, NH_3, MeOH
d) H_2, $Pd(OH)_2$-C, MeOH

Core 12 (linear synthesis) Scheme 16

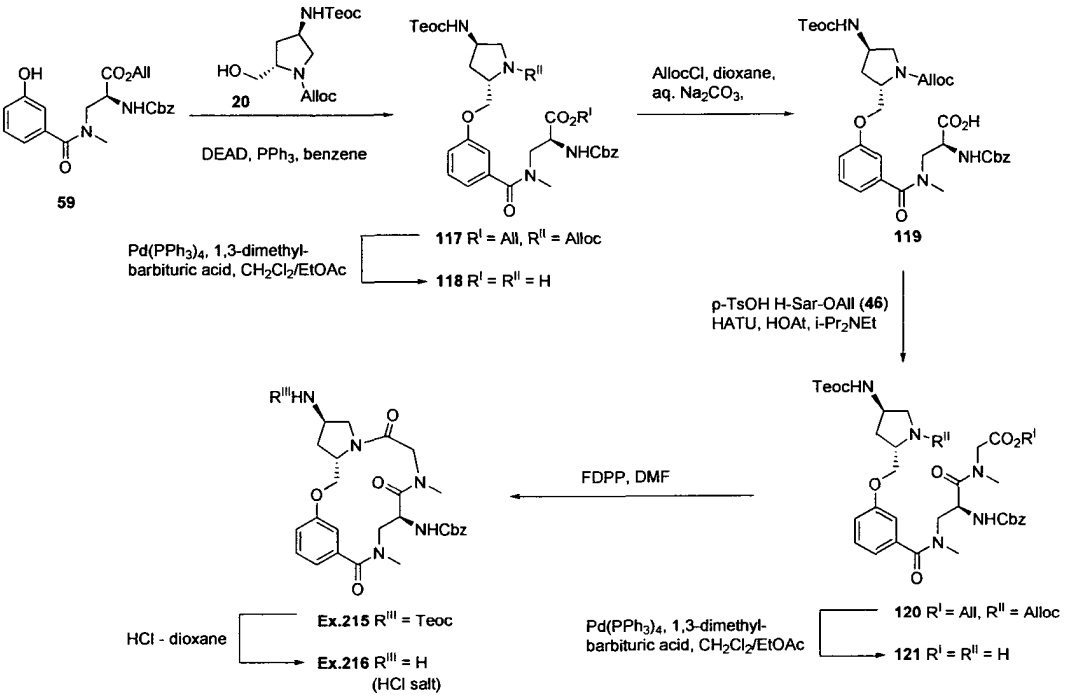


Core 12 (convergent synthesis) Scheme 17



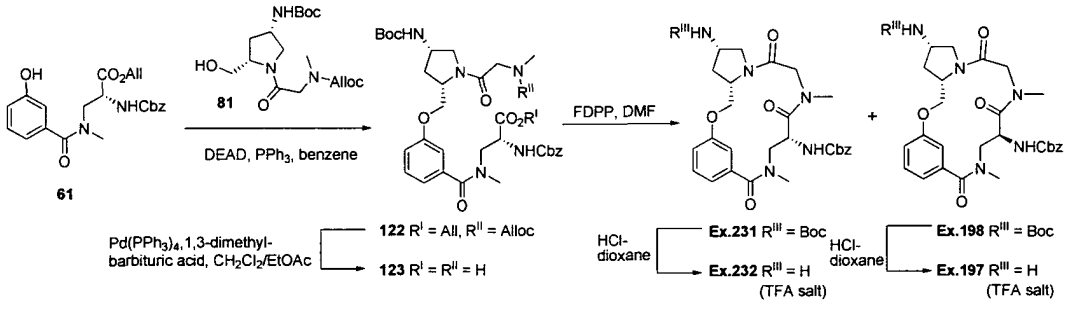
Core 13

Scheme 18



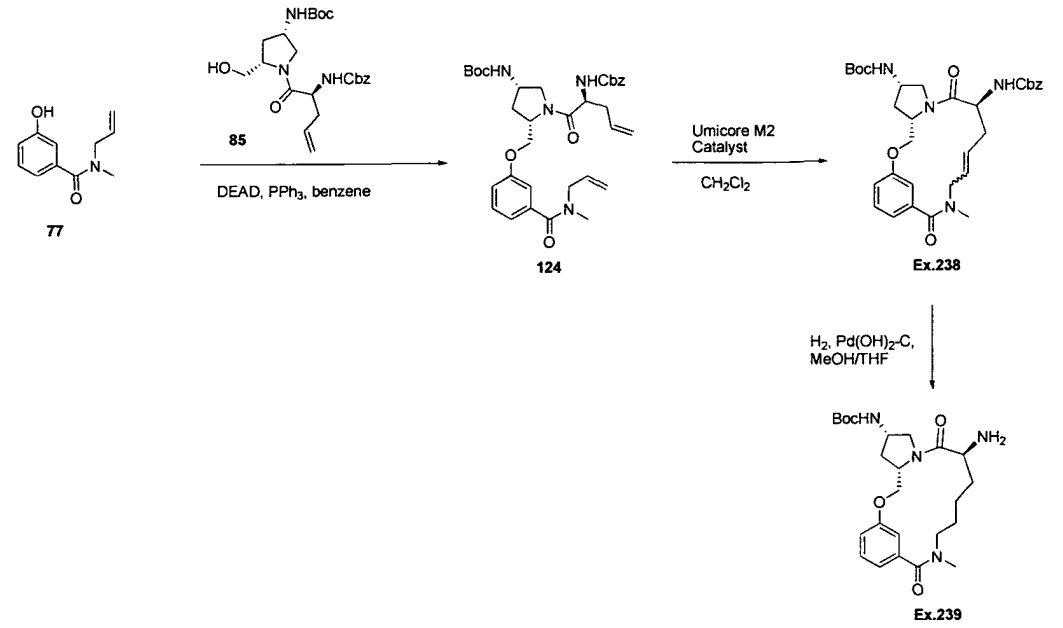
Core 14

Scheme 19



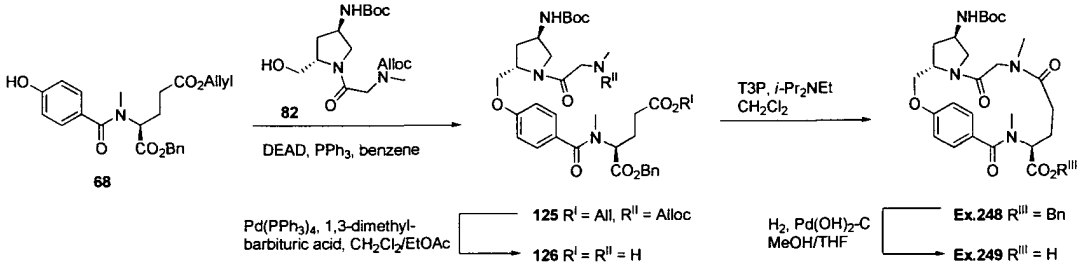
Core 15 and Core 16

Scheme 20



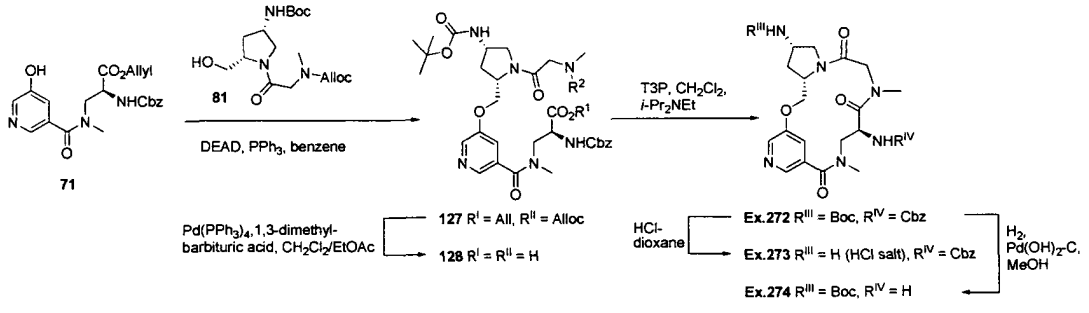
Core 17

Scheme 21

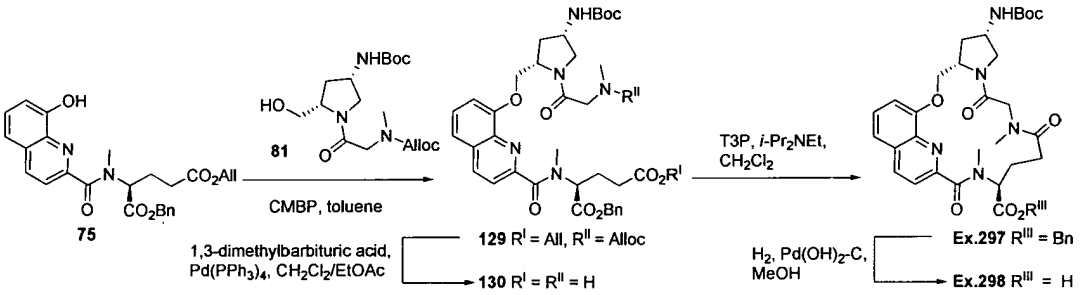


Core 18

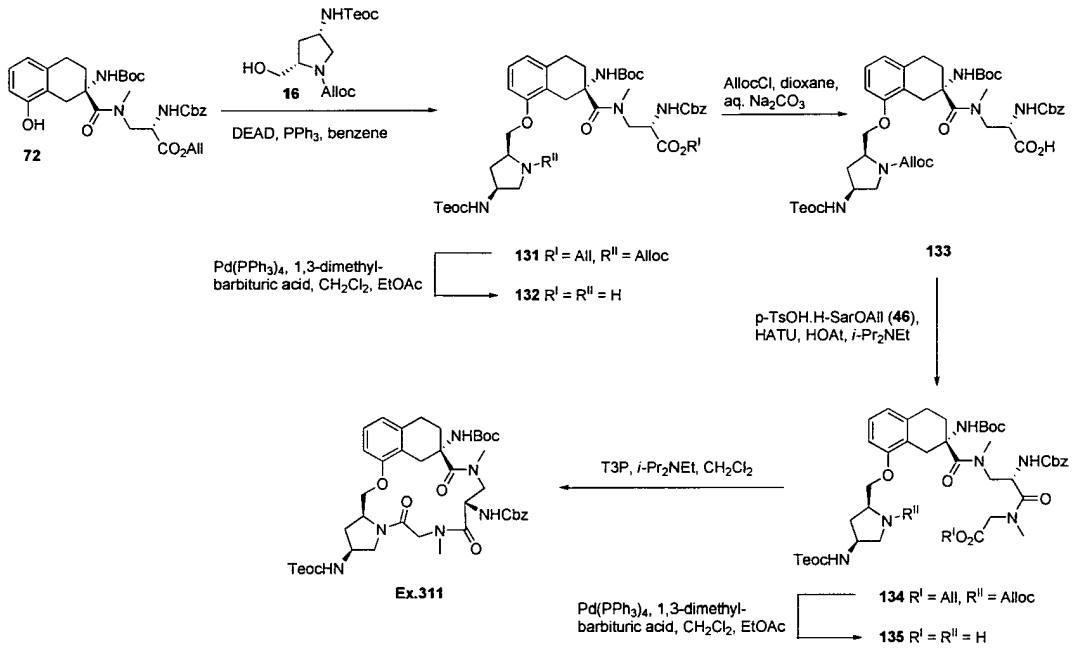
Scheme 22



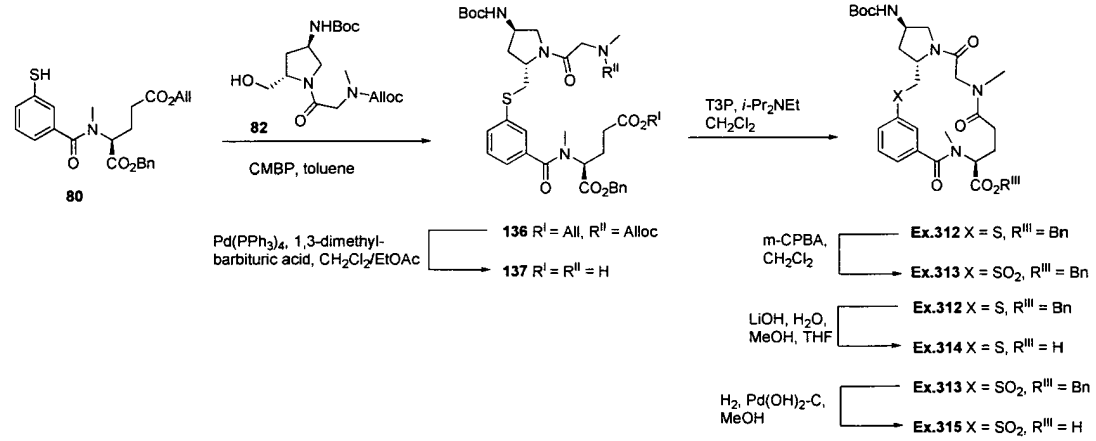
Core 19 Scheme 23



Core 20 Scheme 24

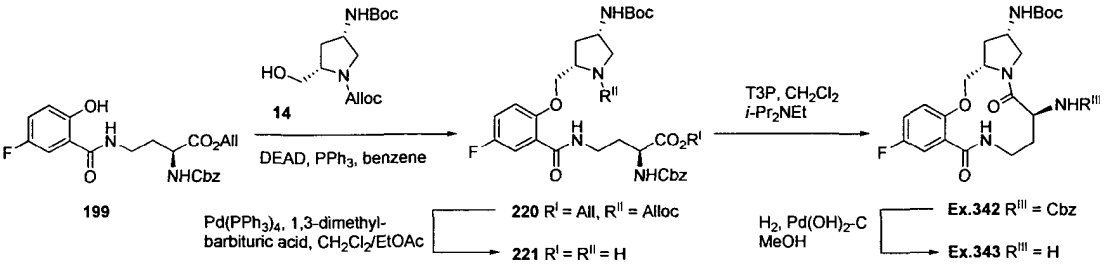


Core 21 Scheme 25



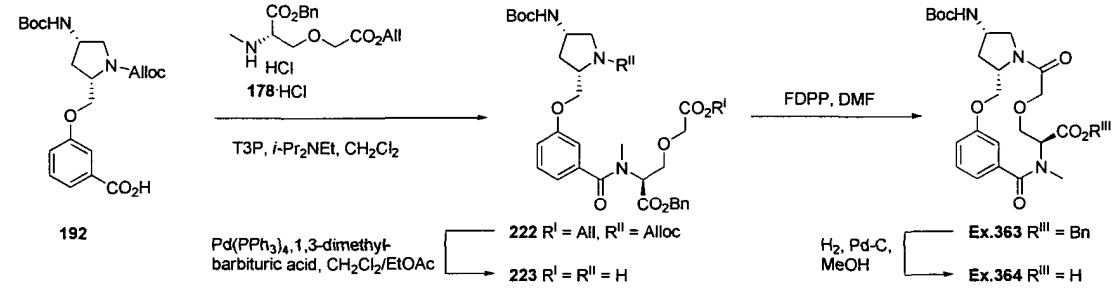
Core 22

Scheme 26



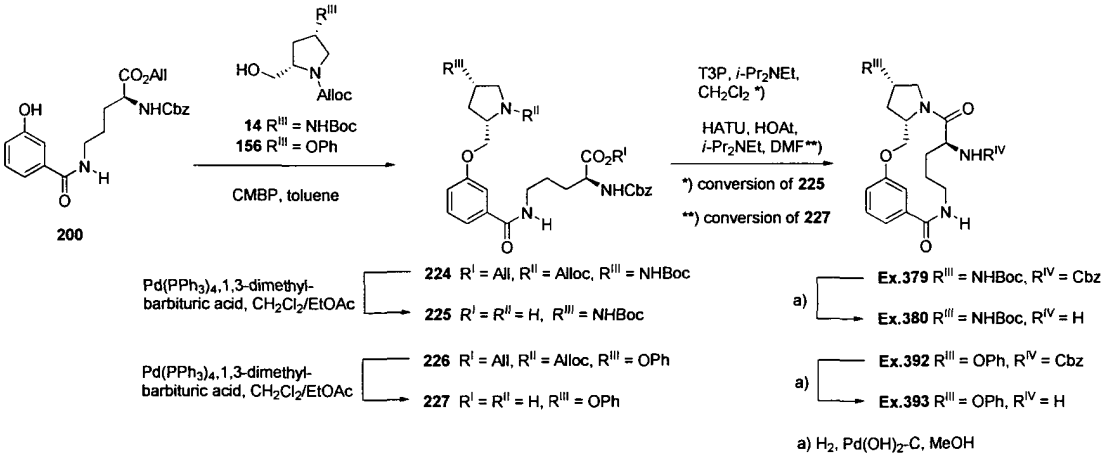
Core 23

Scheme 27

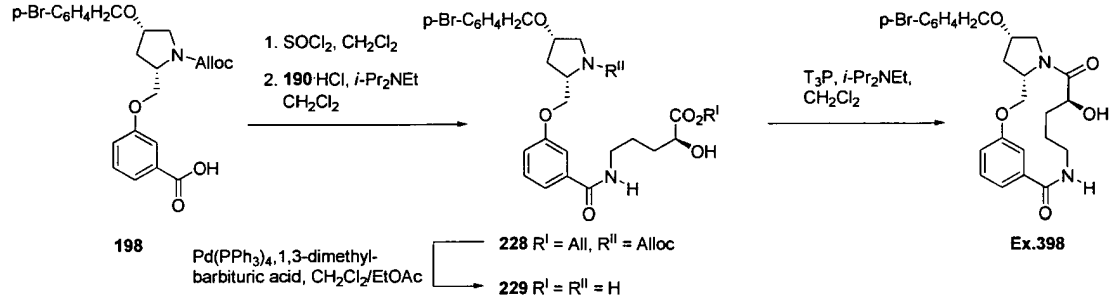


Core 24a/24b

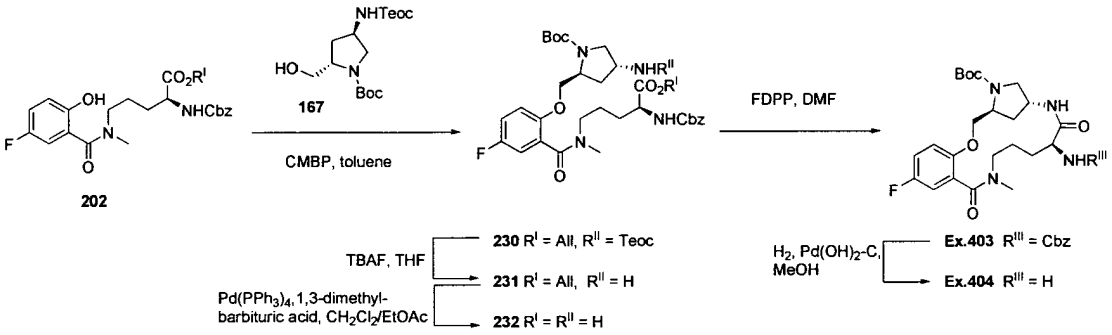
Scheme 28



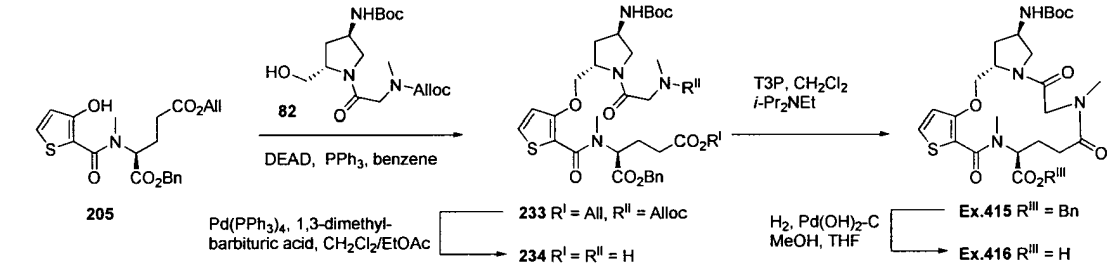
Core 24c Scheme 28, cont.



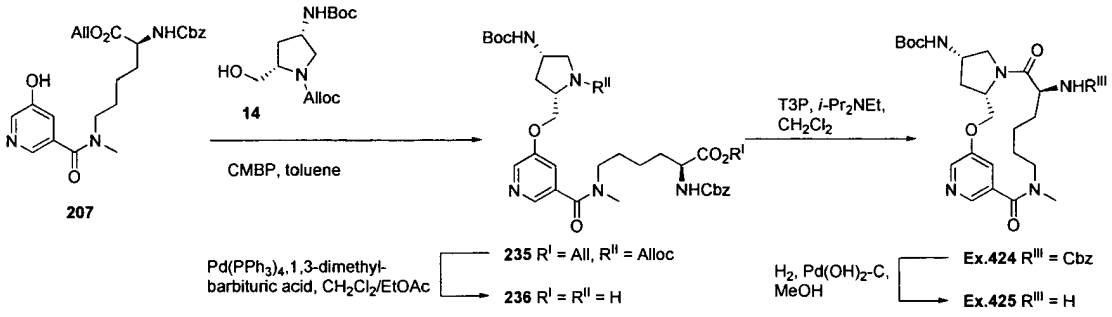
Core 25 Scheme 29



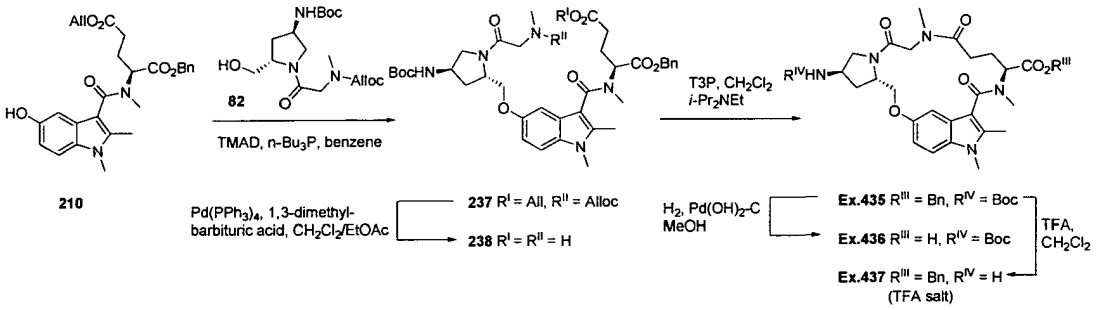
Core 26 Scheme 30



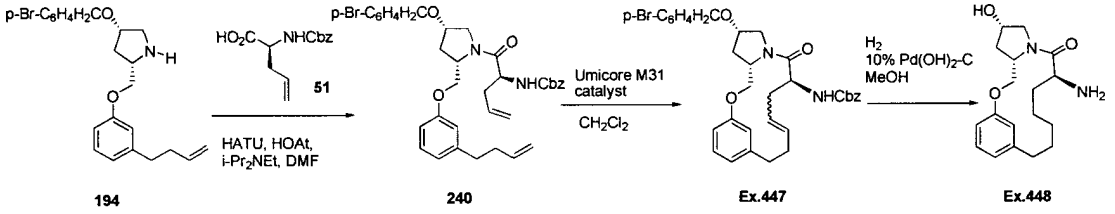
Core 27 Scheme 31



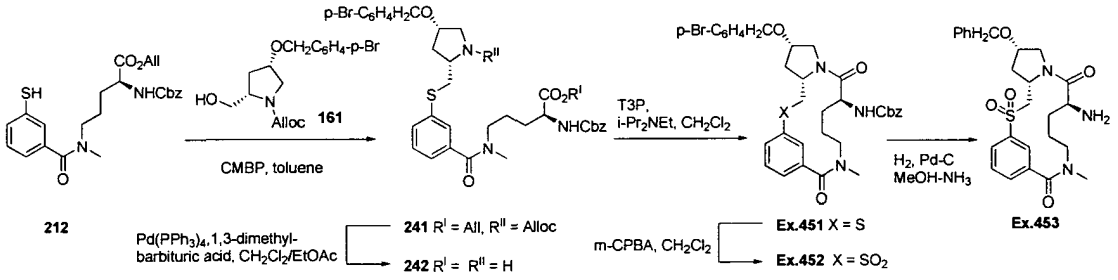
Core 28 Scheme 32



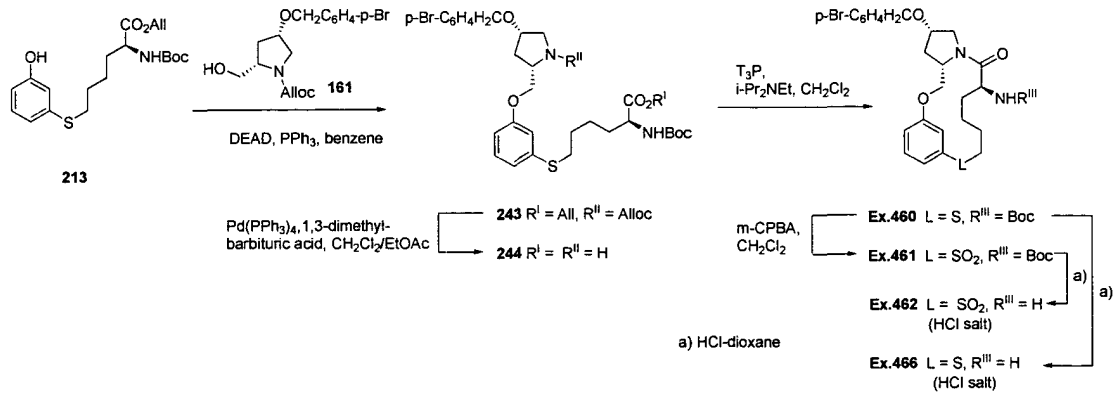
Core 29 Scheme 33



Core 30 Scheme 34

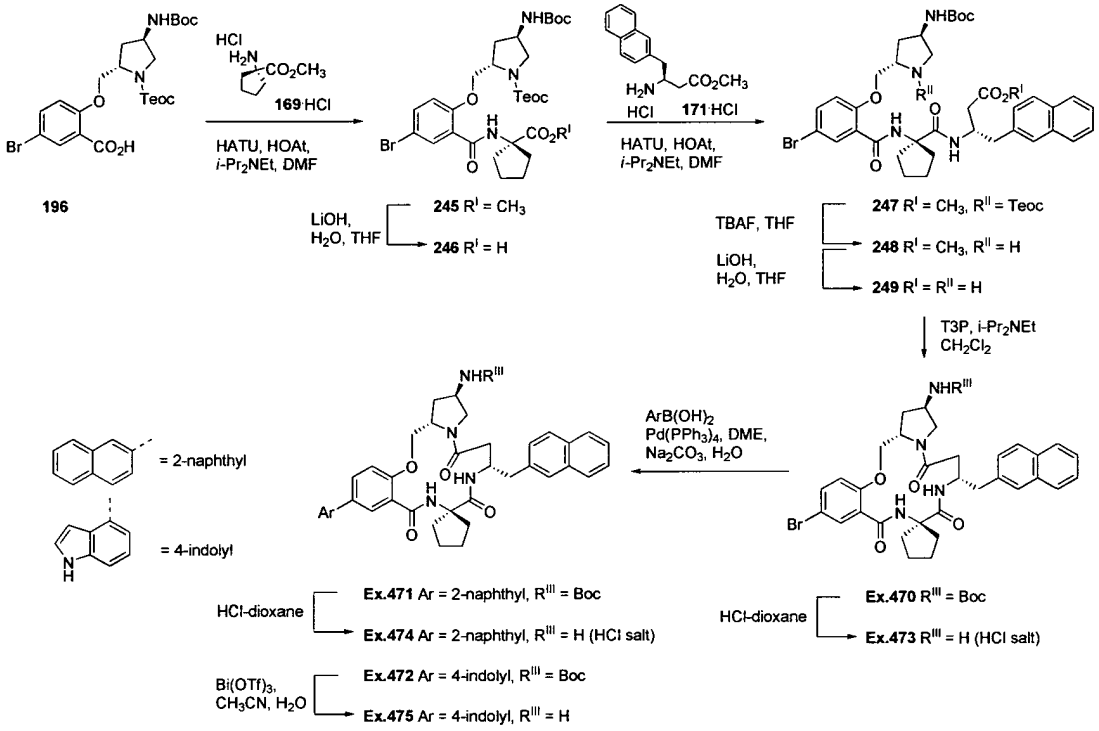


Core 31 Scheme 35



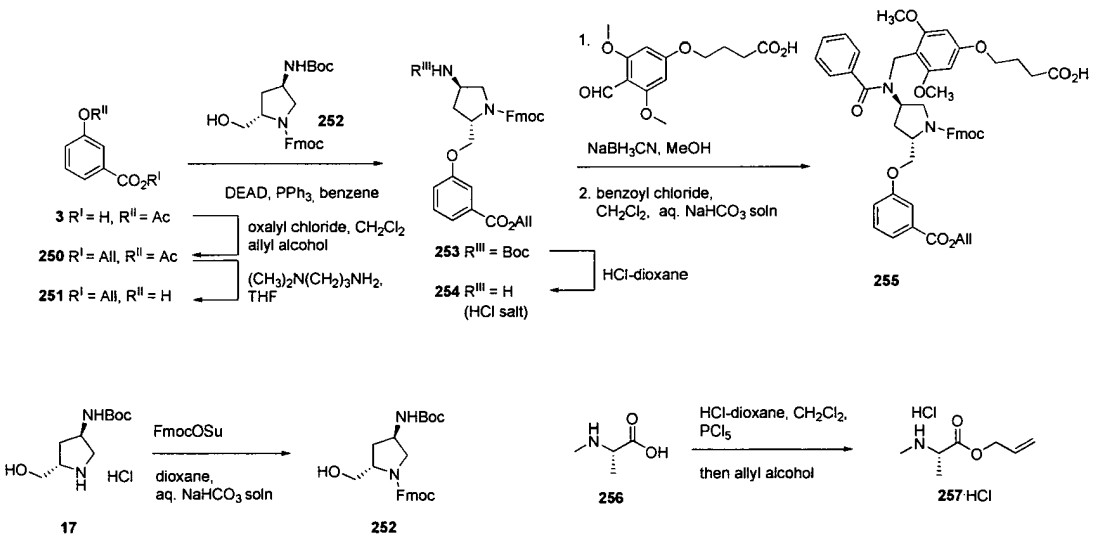
Core 32

Scheme 36



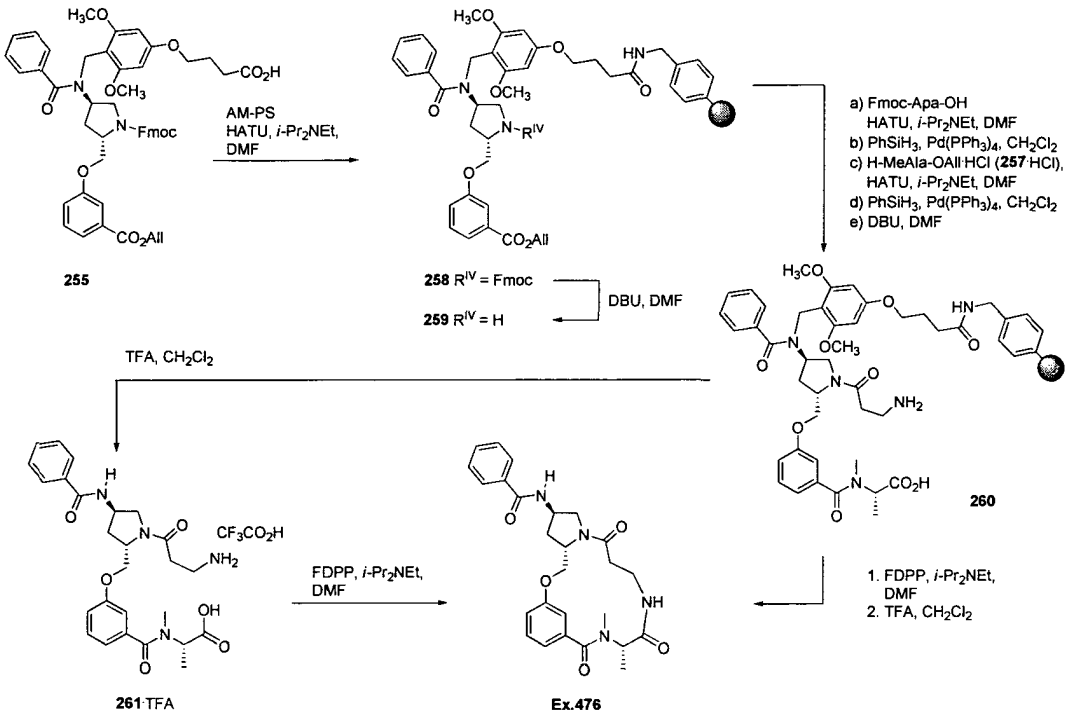
Core 33

Scheme 37



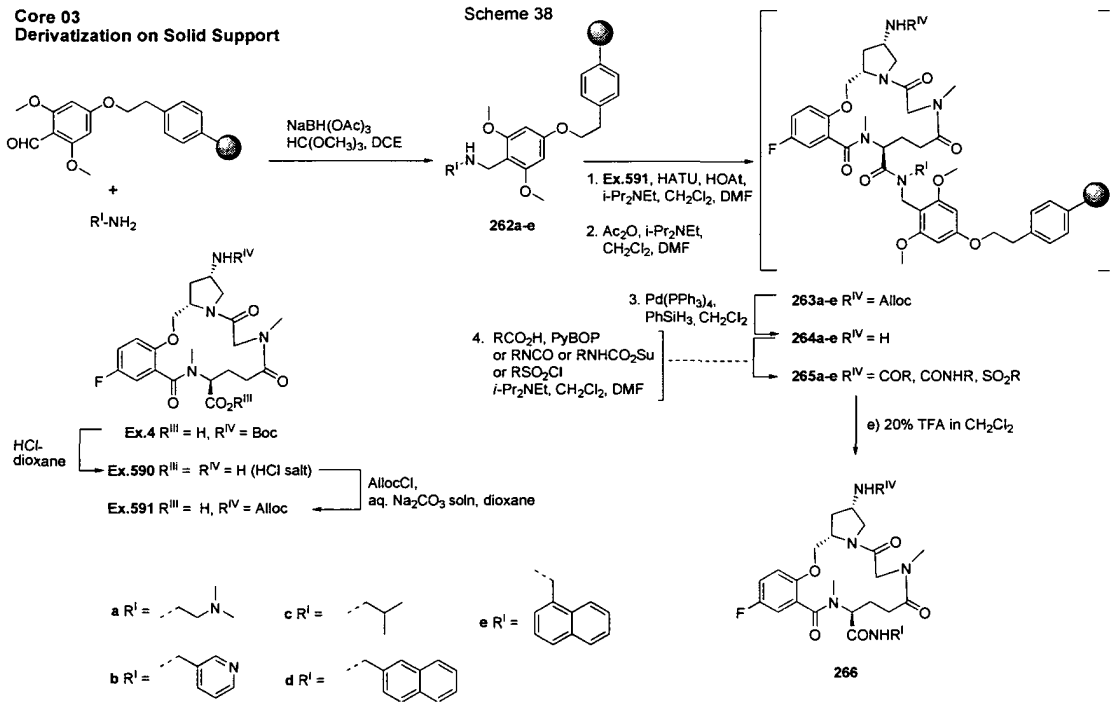
Core 33

Scheme 37, cont.



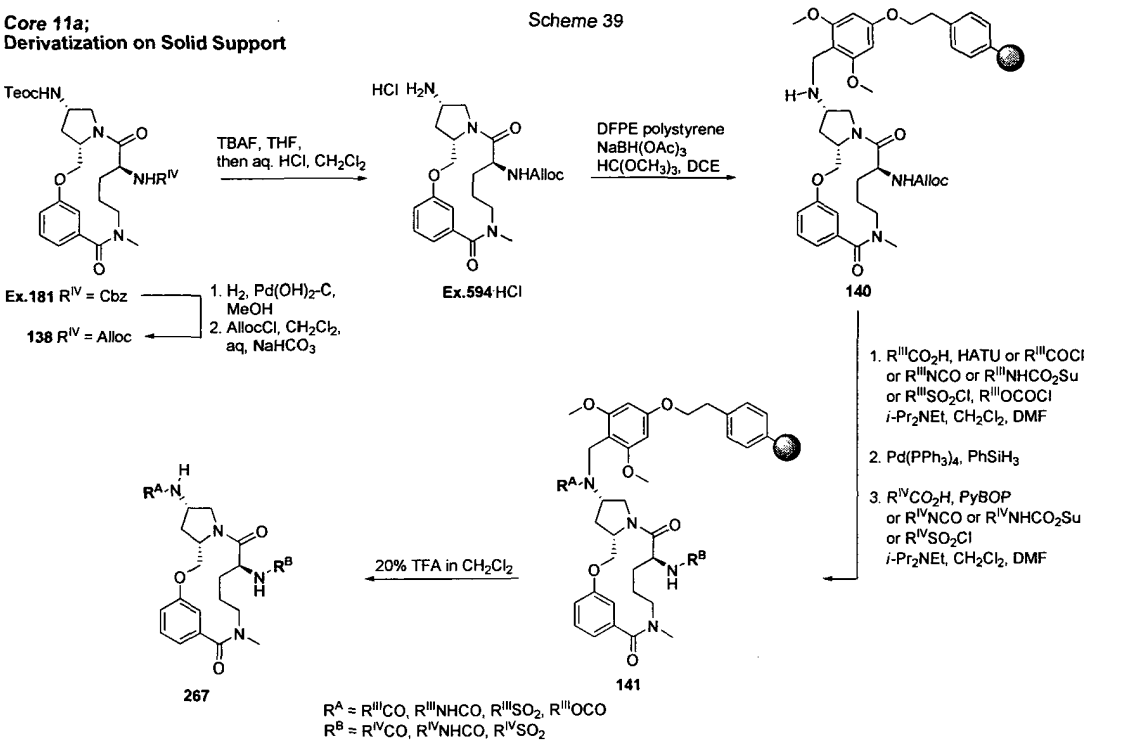
Core 03
Derivatization on Solid Support

Scheme 38



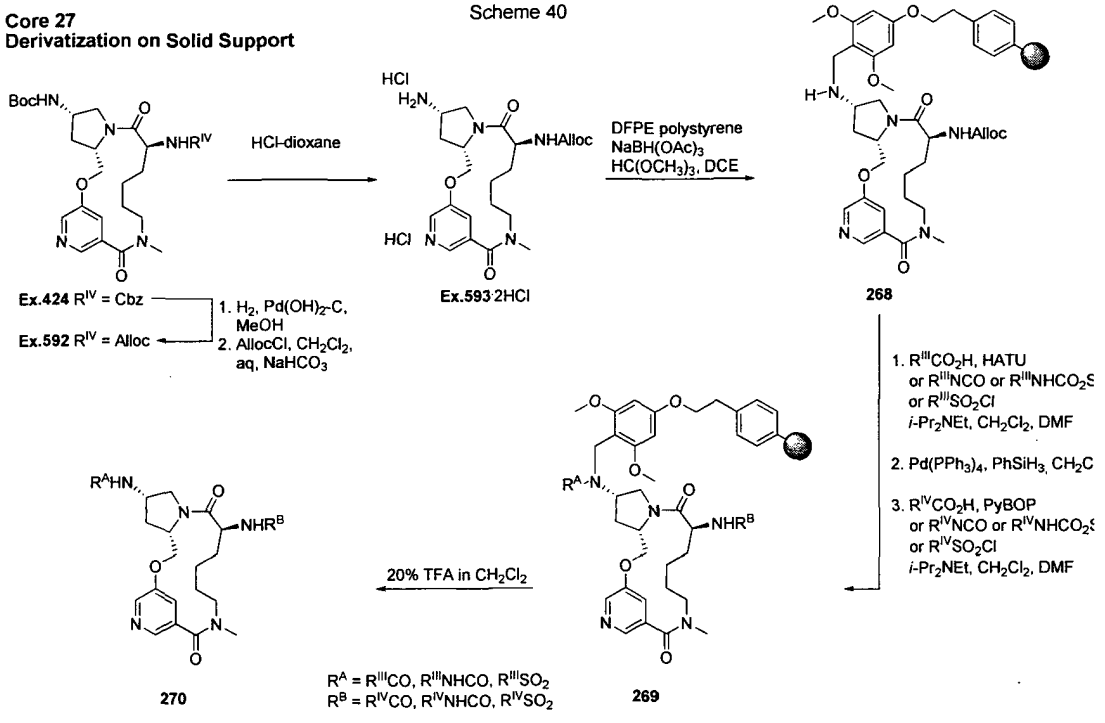
Core 11a;
Derivatization on Solid Support

Scheme 39

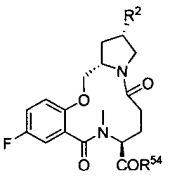


Core 27
Derivatization on Solid Support

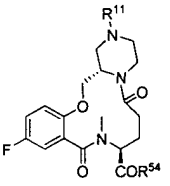
Scheme 40



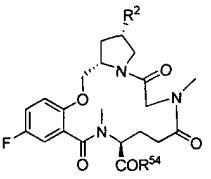
Structures of Examples Scheme 41



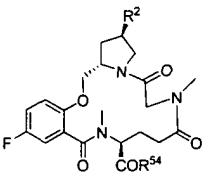
Core 01
Ex.1
definition of R-groups
cf. Table 20



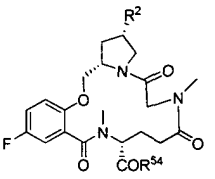
Core 02
Ex.2
definition of R-groups
cf. Table 20



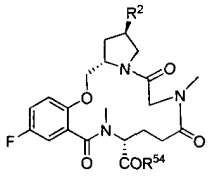
Core 03
Ex.3 - Ex.55
Ex.482 - Ex.503;
Ex.590, Ex.591
definition of R-groups
cf. Table 21



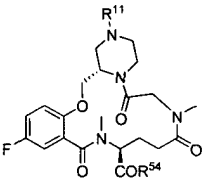
Core 04
Ex.56 - Ex.84
definition of R-groups
cf. Table 22



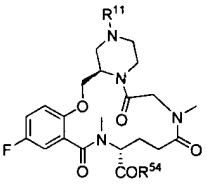
Core 05
Ex.85 - Ex.103
definition of R-groups
cf. Table 23



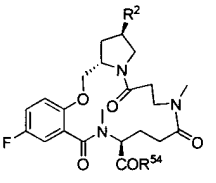
Core 06
Ex.104 - Ex.114
definition of R-groups
cf. Table 24



Core 07
Ex. 115 - Ex. 131
definition of R-groups
cf. Table 25

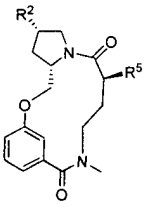


Core 08
Ex.132 - Ex.141
definition of R-groups
cf. Table 26

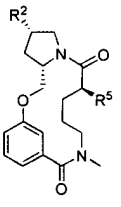


Core 09
Ex.142 - Ex.163
definition of R-groups
cf. Table 27

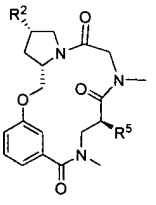
Structures of Examples Scheme 41, cont.



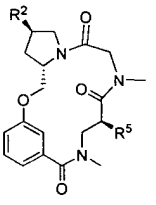
Core 10
Ex.164 - Ex.180
definition of R-groups
cf. Table 28



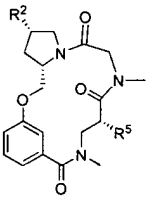
Core 11a
Ex.181 - Ex.195
Ex.504 - Ex.559, Ex.594
Core11b
Ex.560 - Ex.566
Core11c
Ex.567- Ex. 585
Core11d
Ex.586- Ex. 589
definition of R-groups
cf. Tables 29.1 to 29.4



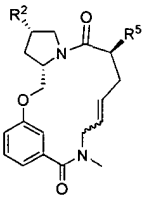
Core 12
Ex.196 - Ex.214
definition of R-groups
cf. Table 30



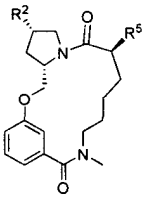
Core 13
Ex.215 - Ex.230
definition of R-groups
cf. Table 31



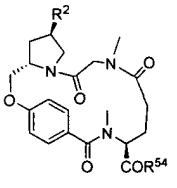
Core 14
Ex.231 - Ex.237
definition of R-groups
cf. Table 32



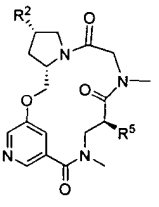
Core 15
Ex. 238
definition of R-groups
cf. Table 33



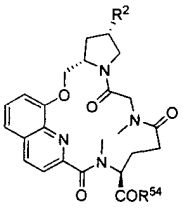
Core 16
Ex.239 - Ex.247
definition of R-groups
cf. Table 33



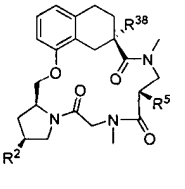
Core 17
Ex.248 - Ex.271
definition of R-groups
cf. Table 34



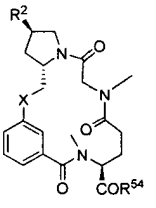
Core 18
Ex.272 - Ex.296
definition of R-groups
cf. Table 35



Core 19
Ex.297 - Ex.310
definition of R-groups
cf. Table 36

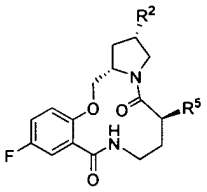


Core 20
Ex.311
definition of R-groups
cf. Table 37.1

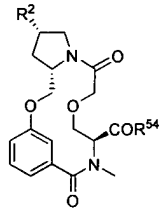


Core 21 (X = S, SO_2)
Ex.312 - Ex.341
definition of R-groups
cf. Table 37.2

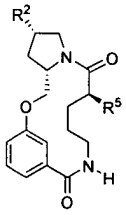
Structures of Examples Scheme 41, cont.



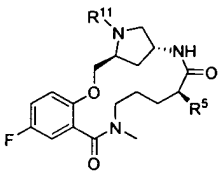
Core 22
Ex.342 - Ex.362
definition of R-groups
cf. Table 38



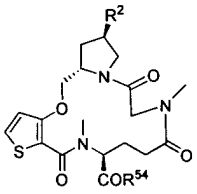
Core 23
Ex.363 - Ex.378
definition of R-groups
cf. Table 39



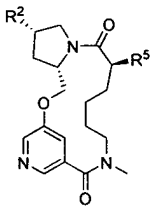
Core 24a
Ex.379 - Ex.391
Core 24b
Ex.392 - Ex.396
Core 24c
Ex.398 - Ex.402
definition of R-groups
cf. Table 40.1 to 40.3



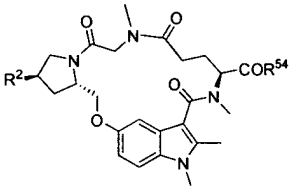
Core 25
Ex. 403 - Ex. 414
definition of R-groups
cf. Table 41



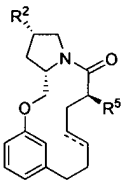
Core 26
Ex.415 - Ex.423
definition of R-groups
cf. Table 42



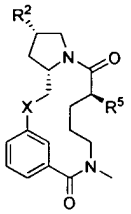
Core 27
Ex.424 - Ex.434,
Ex.592, Ex.593
definition of R-groups
cf. Table 43



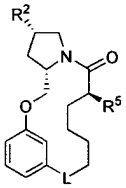
Core 28
Ex.435 - Ex.446
definition of R-groups
cf. Table 44



Core 29
Ex.447 - Ex.450
definition of R-groups
cf. Table 45

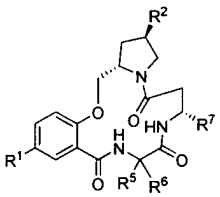


Core 30 (X = S, SO_2)
Ex.451 - Ex.459
definition of R-groups
cf. Table 46

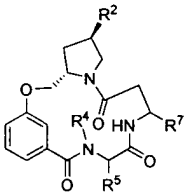


Core 31 (L = S, SO_2)
Ex.460 - Ex.469
definition of R-groups
cf. Table 47

Structures of Examples Scheme 41, cont.

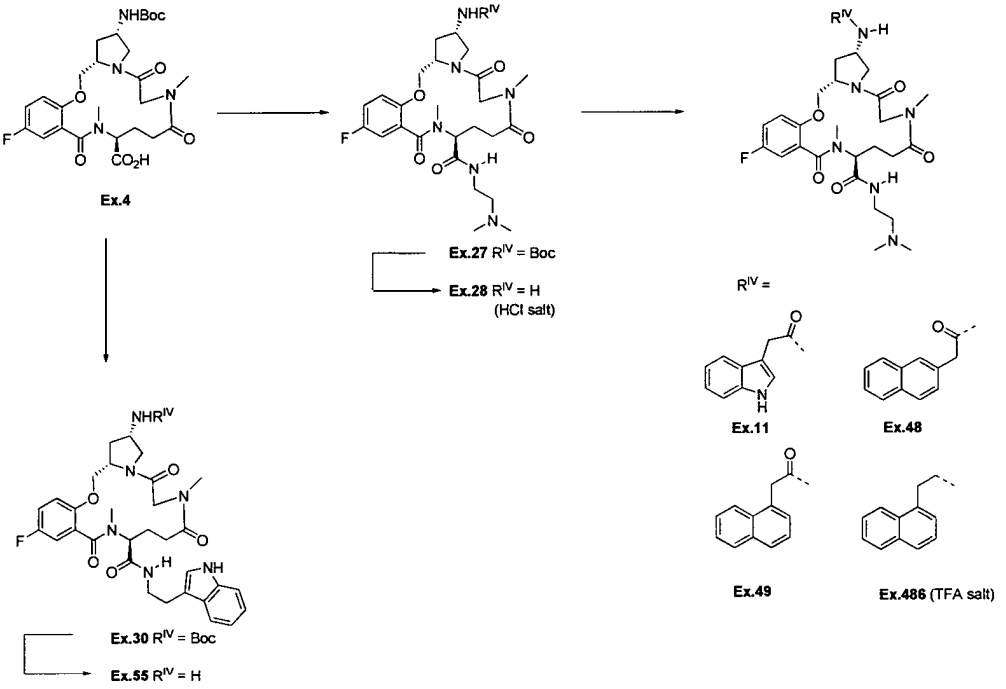


Core 32
Ex.470 - Ex.475
definition of R-groups
cf. Table 48

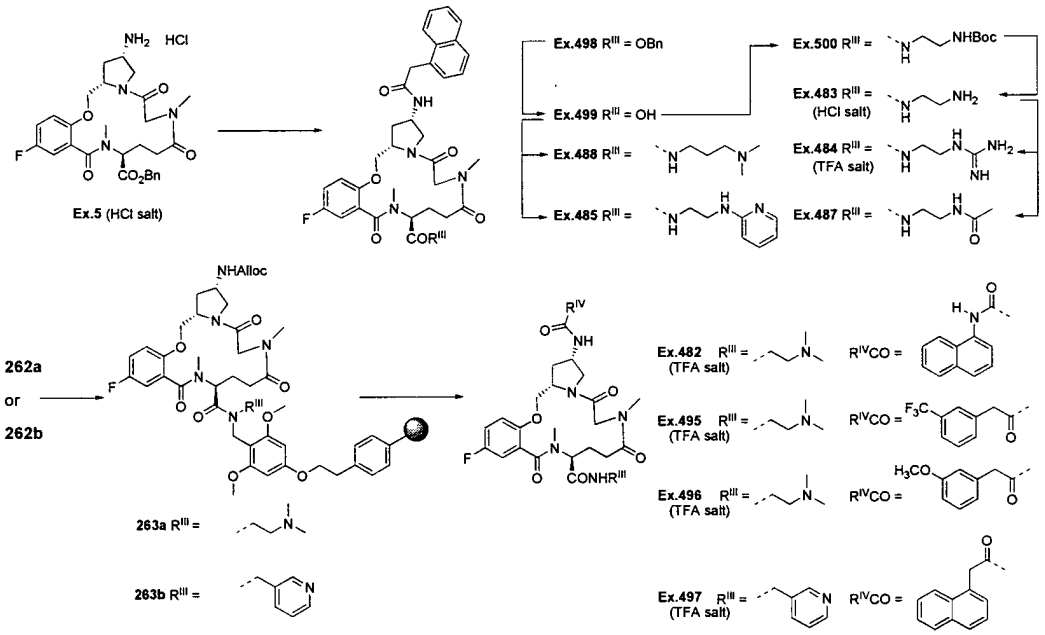


Core 33
Ex.476 - Ex.481
definition of R-groups
cf. Table 49

Core 03; Selected Final Products Scheme 42

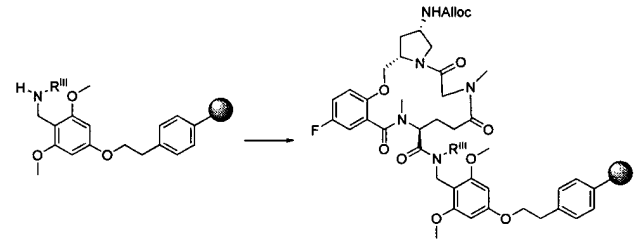


Core 03; Selected Final Products Scheme 42, cont

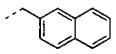


Core 03; Selected Final Products

Scheme 42, cont



262d R^{III} =



262e R^{III} =



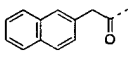
263d

263e

Ex.501 R^{III} =



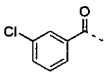
$R^{IV}CO$ =



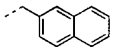
Ex.502 R^{III} =



$R^{IV}CO$ =



Ex.503 R^{III} =

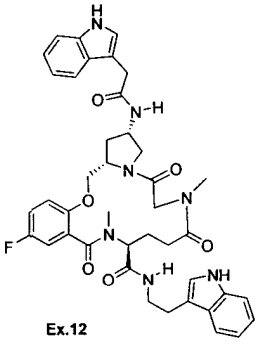


$R^{IV}CO$ =

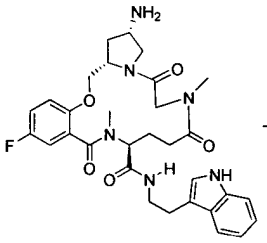


Core 03; Selected Final Products

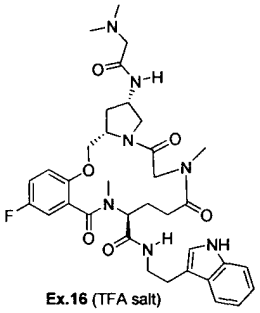
Scheme 42, cont.



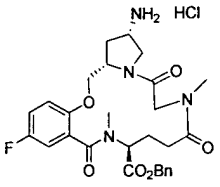
Ex.12



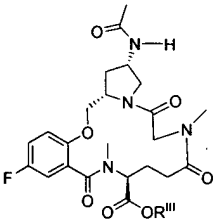
Ex.55



Ex.16 (TFA salt)

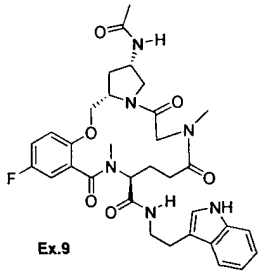


Ex.5 (HCl salt)



Ex.53 R^{III} = Bn

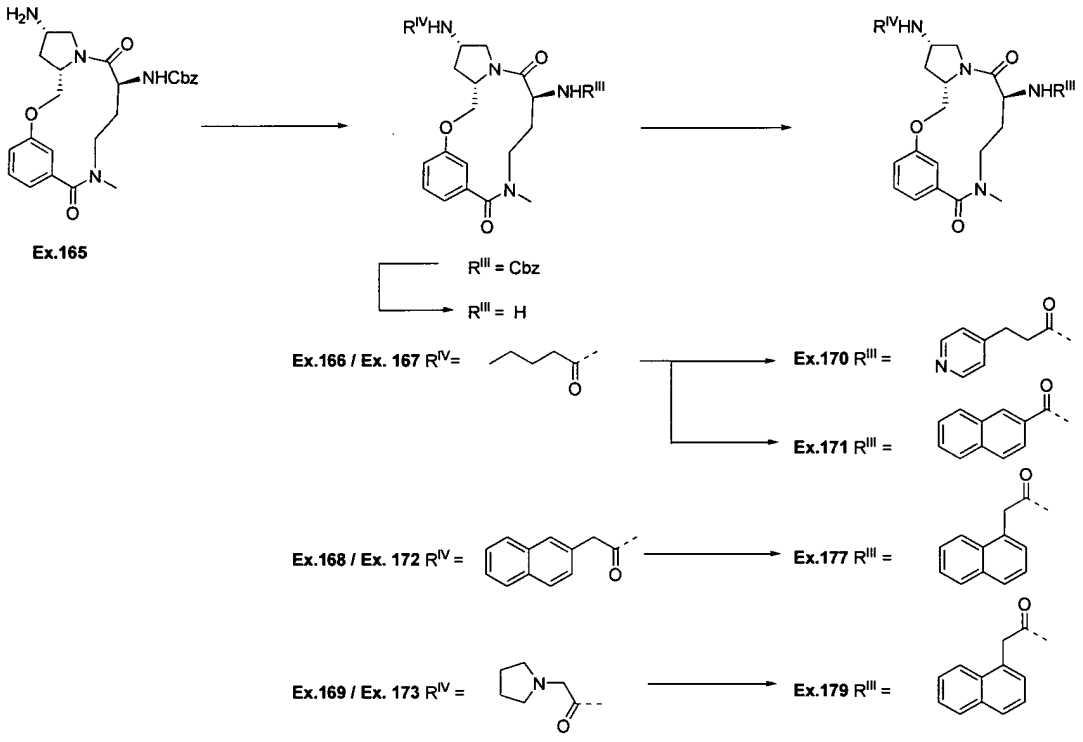
Ex.54 R^{III} = H



Ex.9

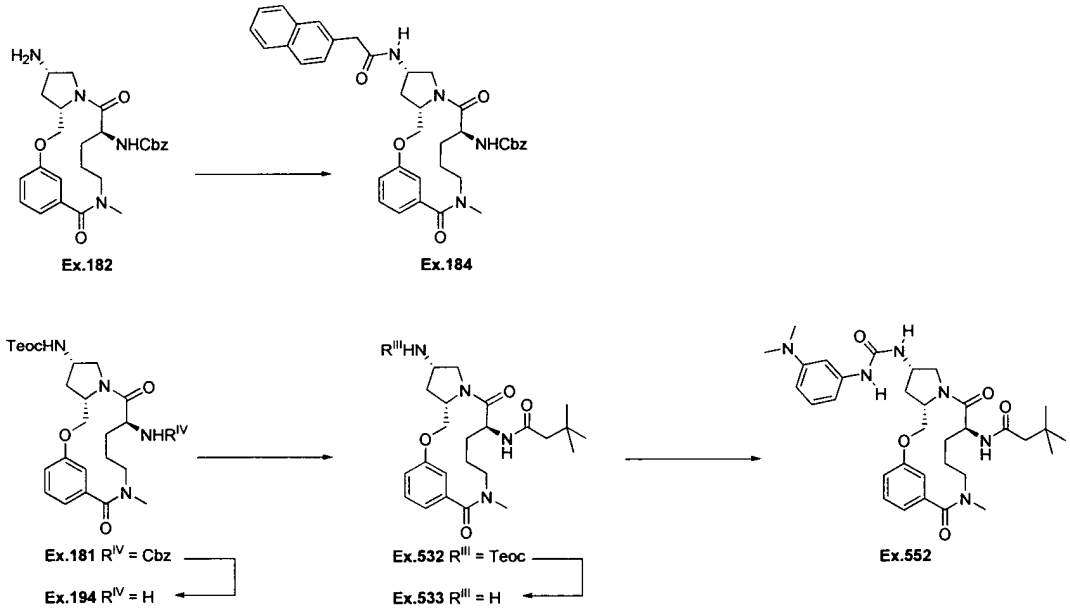
Core 10;
examples

Scheme 43



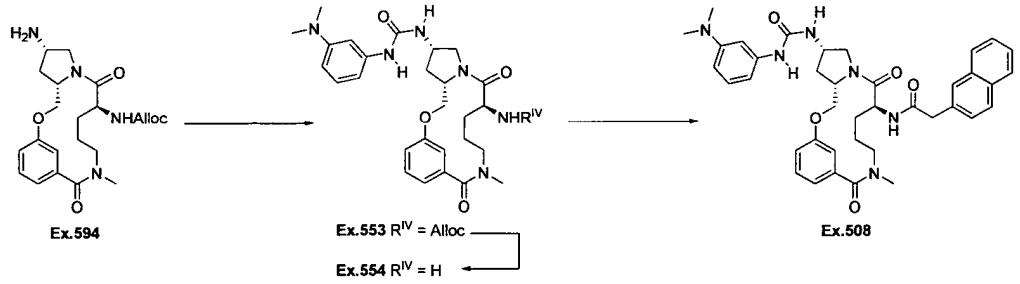
Core 11a;
Selected Examples prepared in solution

Scheme 44



Core 11a;
Selected Examples prepared in solution

Scheme 44, cont.



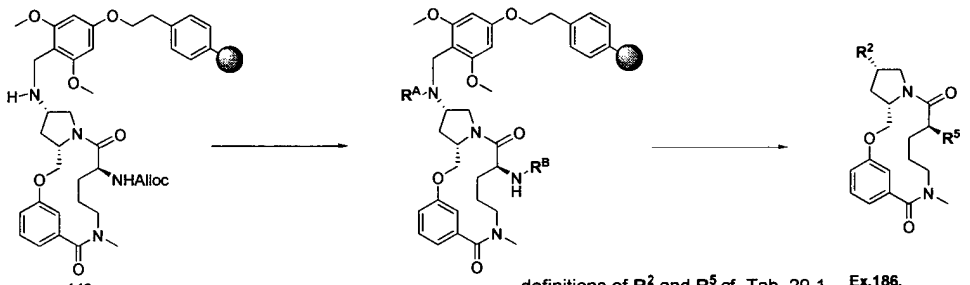
Ex.594

Ex.553 R^{IV} = Alloc

Ex.554 R^{IV} = H

Ex.508

Core 11a;
Selected Examples prepared on solid support



140

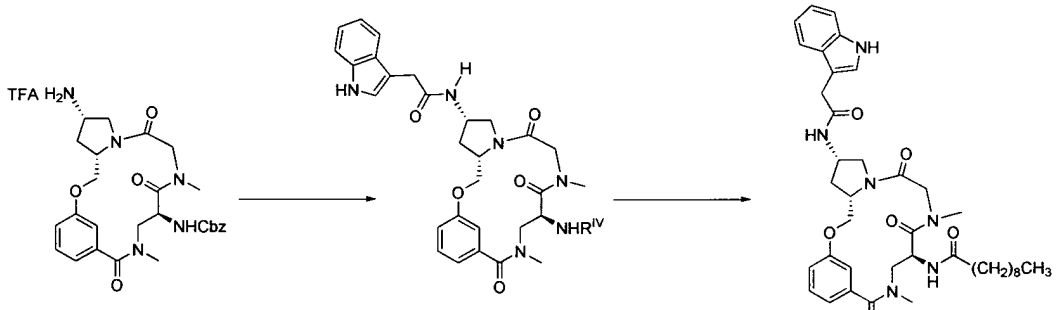
141

definitions of R^2 and R^5 cf. Tab. 29.1
$R^A NH = R^2$; $R^B NH = R^5$

Ex.186, Ex.504-Ex.507 Ex.509-Ex.527 Ex.537-Ex.551

Core 12;
Selected Examples

Scheme 45



Ex.197 (TFA salt)

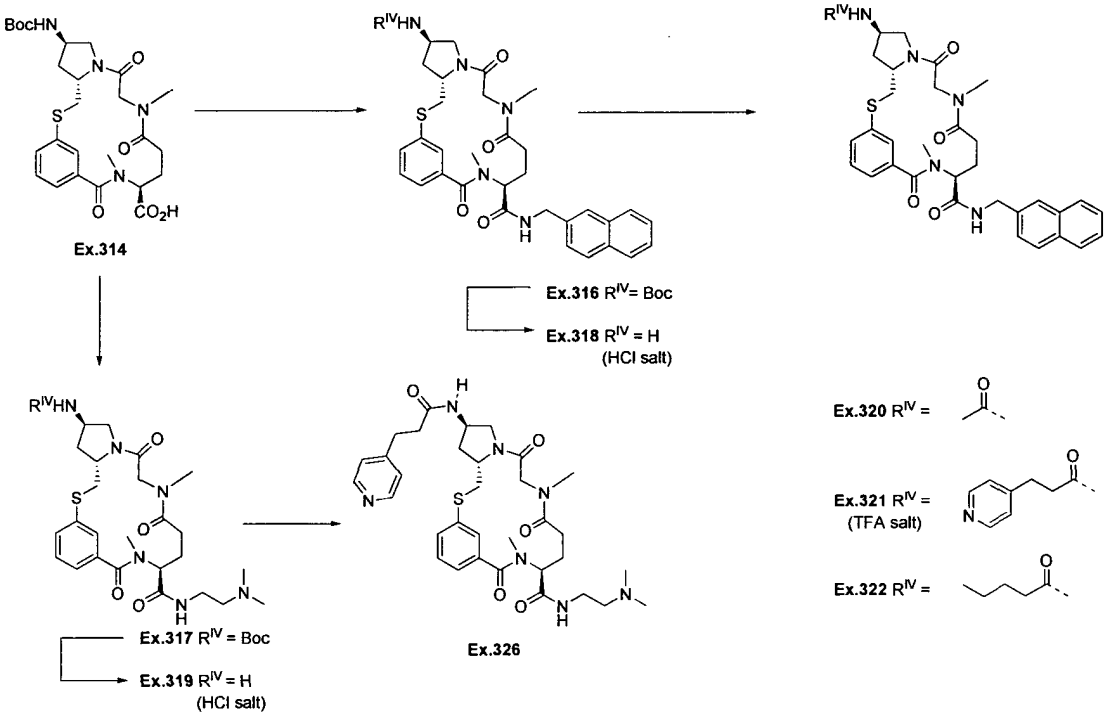
Ex.200 R^{IV} = Cbz

Ex.202 R^{IV} = H

Ex.213

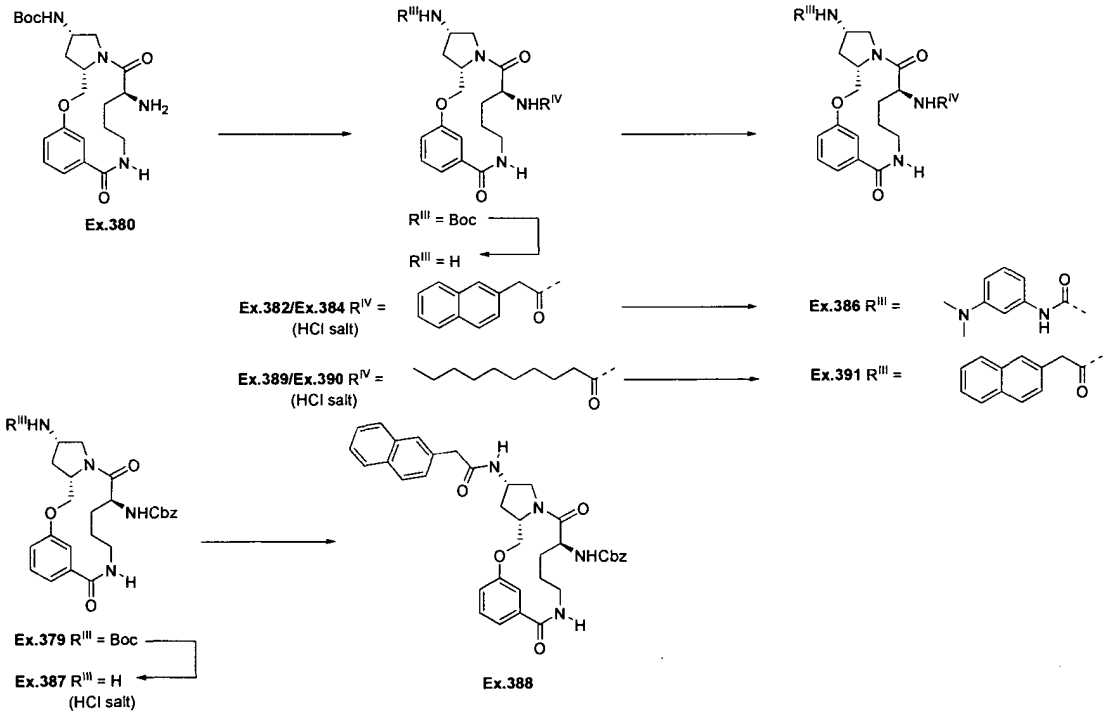
Core 21; Examples

Scheme 46



Core 24a; Selected Examples

Scheme 47



Biological and pharmacological methods

1. Ca^{2+} assays for the GPCRs motilin receptor, prostaglandin F (FP) receptor, 5-hydroxytryptamine 2B ($5\text{-}HT_{2B}$) receptor, and purinoreceptor $P2Y_1$

Assays were performed using 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 forty-five (45) minutes at room temperature. After room temperature incubation, the assay plates were incubated at 37°C 5% CO_2 for 24 hours prior to assaying.

Calcium Dye Loading:

All GPCR assays were performed using Fluo-8 Ca^{2+} dye.

Ca^{2+} dye was prepared at 1 x dye concentration in GPCR assay buffer. After 24 hours of incubation, cells were washed with GPCR assay buffer, 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.

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 seven (7) minutes before antagonist assay.

Using the EC_{80} values determined during the agonist assay, all pre-incubated sample compound and reference antagonist (if applicable) wells were stimulated at the EC_{80} of the reference agonist. As reference ligands for the first three assays their obvious natural ligands motilin, prostaglandin F2α, and serotonin (5-HT, 5-Hydroxytryptamine) were used; and for the $P2Y_1$ assay 2MeSATP (2-methyl-thio-adeno-sine 5'-triphosphate, i.e.(2R,3S,4R)-5-(6-amino-2-methylsulfanyl-purin-9-yl)-3,4-dihydroxy -tetrahydrofuran-2-yl]methyl (hydroxy-phosphonooxy-phosphoryl) hydrogen phosphate) was applied.

After the addition of the reference agonist fluorescence was monitored for 180 sec using FLIPR Tetra.

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 assay are summarized in Table 50.1 to Table 50.4.

2. Assay for the voltage gated ion channel $K_v1.3$

Assays were performed and analyzed with a FLIPR^{TETRA} device as specified above.

Compounds for inhibition of ion channel $K_v1.3$ were assayed in Jurkat cells recombinantly expressing human $K_v1.3$. For high throughput screening a thallium-sensitive, fluorescence-based assay was used. Cells were incubated with the Tl^+ sensitive dye according to the protocol suggested by the manufacturer (FluxOR potassium ion channel assay, Invitrogen AG). Channel activation was carried out as suggested by the supplier by depolarization, accomplished by increasing the extracellular potassium concentration (thallium sulfate containing buffer at concentrations between 10-15 mM Tl^+ and 30 mM K_2SO_4, FluxOR potassium ion channel assay, Invitrogen AG). To identify blockers of this ion channel the cells were incubated with different concentrations of compounds 5 min before increasing the potassium and thallium concentration. The fluorescence signals by increasing potassium were then compared in the absence and presence of compounds. Dose response curves were established by adding different concentrations of compounds and analyzing the signal. As reference $K_v1.3$ blockers margatoxin and quinidine in Cl-free buffer were used as described in the literature.

The results of the $K_v1.3$ assay are depicted in Table 51 below.

3. Assays for the Wnt-pathway

For determining the activity of the test compounds on the Wnt-pathway each substances war subjected to two distinct assays: The first (Wnt/Beta-Catenin) assay screened for inhibitors of the Wnt-pathway while the second (MAPK/MEK/B-raf) was conducted in order to confirm that the test compounds modulate the β-catenin-dependent, canonical Wnt pathway and are not acting via a possibly competing β-catenin-independent, noncanonical Wnt

messaging system. All examples were inactive in this negative control.

Both assays were performed and analyzed with a Tecan Safire^2 fluorescence plate reader.

The results are shown in Table 52 below.

Wnt/Beta-Catenin (APC-/-) - LEF-TCF-bla SW480 - Inhibitor Screen, Constitutively Activated

LEF-TCF-bla SW480 cells are thawed and resuspended in Assay Media (OPTI-MEM, 0.5% dialyzed FBS, 0.1 mM NEAA, 1 mM Sodium Pyruvate, 100 U/mL/100 µg/mL Pen/Strep) to a concentration of 312,500 cells/mL. 4 µL of a 10X serial dilution of ICG-001 (control inhibitor starting concentration, 10,000 nM) or compounds are added to appropriate wells of a TC-Treated assay plate. 32 µL of cell suspension (10,000 cells) is added to the wells. 4 µL of Assay Media is added to all wells to bring the final assay volume to 40 µL. The plate is incubated for 16-24 hours at 37°C/5% CO_2 in a humidified incubator. 8 µL of 1 µM Substrate Loading Solution is added to each well and the plate is incubated for 2 hours at room temperature.

MAPK/MEK/B-raf - AP1-bla A375 - Inhibitor Screen, Constitutively Activated

AP1-bla A375 cells are thawed and resuspended in Assay Media (OPTI-MEM, 0.5% dialyzed FBS, 0.1 mM NEAA, 1 mM Sodium Pyruvate, 100 U/mL/100 µg/mL Pen/Strep) to a concentration of 312,500 cells/mL. 4 µL of a 10X serial dilution of Raf1 Kinase Inhibitor (control inhibitor starting concentration, 10,000 nM) or compounds are added to appropriate wells of a TC-Treated assay plate. 32 µL of cell suspension (10,000 cells) is added to the wells. 4 µL of Assay Media is added to all wells to bring the final assay volume to 40 µL. The plate is incubated for 16-24 hours at 37°C/5% CO_2 in a humidified incubator. 8 µL of 1 µM Substrate Loading Solution is added to each well and the plate is incubated for 2 hours at room temperature.

4. Plasma and metabolic stability assays

Example compounds were dissolved in DMSO/H_2O 90:10 to a final concentration of 10 mM for plasma stability determination and metabolic stability determination.

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 53 below.

Plasma stability assay

Human plasma (3-5 donors, Blutspendedienst SRK, Basel) and CD-1 mouse plasma (mixed gender pool >50 animals, Innovative Research, CA, USA) are both sodium citrate stabilized. The assay is performed in triplicates at 10 µM compound concentration and 37°C. Samples are taken at 0, 15, 60, and 240 minutes and stopped by precipitation with 2 volumes of acetonitrile. The supernatant is collected, evaporated and reconstituted in a 5% acetonitrile solution to be analyzed by HPLC/MS/MS. The resulting peak area counts are expressed in percent of the 0 value and used to determine the endpoint stability in % and the half life T½ in minutes. In order to monitor assay integrity the degradation of propantheline is assayed with every experimental set.

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. Compounds are incubated at 37°C in duplicates and samples are taken after 0, 20 and 60 minutes. After acetonitrile precipitation (2 volumes) and HPLC/MS/MS analysis metabolic turnover is expressed in % of the initial 0 minutes value and half life T½ (min) is calculated. Verapamil for human and propranolol for mouse are used as reference and are assayed with every experimental set.

5. Pharmacokinetic study (PK) analysis

Pharmacokinetic analyses after single intravenous (i.v.) and two different peroral (p.o.) administrations were performed for the test compounds. 240 grams (± 10 gram) male SD rats were catheterized and used in the study. The vehicle, Solutol HS-15/ 0.9% saline (5:95), was added to give a final concentration of 0.33 mg/ml of the compounds for i.v. application, and 0.5 or 2.0 mg/ml for p.o. applications. The volumes used for applications were 3 ml/kg i.v. and 10 ml/kg p.o. resulting in a final dose of 1 mg/kg for the intravenous dose and 5 or 20 mg/kg for the peroral doses.

Blood samples were withdrawn via the catheter at 1) predose, 5, 15, 30, 60, 120, 240, and 480 minutes for the i.v. application and 2) predose, 15, 30, 60, 120, 240, 480 and 720 minutes for the p.o. applications. Plasma was prepared by centrifugation of heparinized whole blood. Plasma samples (~120 µl each time point, Li-Heparin, 20 IE/ml) were stored at -80°C until HPLC-MSMS analysis.

Preparation of the plasma calibration samples:

"Blank" rat plasma from untreated animals was used. Aliquots of plasma of 50 µL each were spiked with Internal Standard (ISTD) and with known amounts test compounds in order to obtain 11 plasma calibration samples in the range 0.25-4000 ng/mL.

Preparation of plasma samples:

To 50 µL of sample from treated animals 20 µL of internal standard were added. After mixing with 200 µL of acetonitrile, 2% HCOOH were added and each sample was vortexed for several seconds. Precipitated material was removed by centrifugation for 10 min (13200 rpm), the supernatant removed and dried under a constant flow of N2 (Porvair, MiniVap). To reconstitute the dried samples, 200 µL of [DMSO/acetonitrile/H_2O, 4/4/2 (v/v/v) + 2% HCOOH] were added and the sample was shaken for at least 5 minutes.

LC-MSMS Analysis of samples:

Reconstituted samples were analysed by HPLC/MSMS on a reverse phase analytical column (BEH C18, 100 x 2.1 mm, 1.7 µm, Waters). Mobile phase A: H_2O/acetonitrile (95:5, v:v) 0.1% formic acid, mobile phase B: Acetonitrile/H2O (95:5, v:v) 0.1% formic acid. Compounds were eluted from the column by using a gradient from 1%B to 60%B in 2.5 min.).

Pharmacokinetic evaluation:

PK analysis was performed on mean values (generally n=3) using WinNonLin software (Version 5.3, Pharsight Corporation). The area under the curve AUC was calculated by the linear trapezoidal rule (linear interpolation, uniform weighting). $AUC_{(t-\infty)}$ was estimated as Ct/b (b: elimination rate constant). $AUC_{(t-\infty)}$ is the sum of $AUC_{(0-t)}$ and $AUC_{(t-\infty)}$. Elimination half-life was calculated by the linear regression on at least three data points during the elimination phase. The time intervals selected for the half-life determinations were evaluated by the correlation coefficient (r^2), which should be at least above 0.85 and ideally above 0.96.

In case of i.v. administration the initial concentration at t_{zero} was determined by extrapolation of the curve through the first two time points. Finally bioavailability after p.o. administration was calculated from the dose normalized $AUC_{(0-\infty)}$ ration after p.o. *versus* i.v. administration.

The results are shown in Table 54 below.

Table 50.1: Motilin Receptor Assay

No	Antagonist activity [% Inhibition at 10 µM]	Antagonist activity IC_{50} [µM]]
Ex.11	79	0.78
Ex.12	95	2.7
Ex.48	29	n.d.
Ex.49	98	0.16
Ex.482	62	1.1
Ex.483	100	0.023
Ex.484	99	0.20
Ex.485	93	0.28
Ex.486	93	0.18
Ex.487	47	n.d.
Ex.488	23	n.d.
Ex.495	26	n.d.
Ex.496	31	n.d.
Ex.497	24	n.d.

Table 50.2: FP Receptor Assay *(continued on the following pages)*

No	Antagonist activity [% Inhibition at 10 µM]	Antagonist activity IC_{50} [µM]
Ex.12	44	n.d.
Ex.184	74	0.52
Ex.186	53	1.2
Ex.200	38	28
Ex.213	78	1.7

No	Antagonist activity [% Inhibition at 10 µM]	Antagonist activity IC_{50} [µM]
Ex.386	85	2.7
Ex.388	99	0.32
Ex.391	93	0.25
Ex.504	62	0.441
Ex.505	47	0.64
Ex.506	55	2.2
Ex.507	51	1.1
Ex.508	93	0.43
Ex.509	54	2.1
Ex.510	42	1.5
Ex.511	99	0.059
Ex.512	97	0.120
Ex.513	95	0.65
Ex.515	32	5.1
Ex.516	97	0.59
Ex.517	98	0.65
Ex.518	80	0.49
Ex.519	n.d.	3.0
Ex.521	81	1.0
Ex.522	95	0.35
Ex.523	92	0.86
Ex.524	85	1.7
Ex.525	99	0.094
Ex.526	99	0.180
Ex.527	73	0.204
Ex.537	75	n.d.
Ex.538	80	n.d.

No	Antagonist activity [% Inhibition at 10 μM]	Antagonist activity IC_{50} [μM]
Ex.539	59	n.d.
Ex.540	43	n.d.
Ex.541	65	n.d.
Ex.542	74	n.d.
Ex.543	82	n.d.
Ex.544	81	n.d.
Ex.545	80	n.d.
Ex.546	37	n.d.
Ex.547	47	n.d.
Ex.548	69	n.d.
Ex.549	62	n.d.
Ex.550	73	n.d.
Ex.551	72	n.d.
Ex.552	71	n.d.

Table 50.3: 5-HT_{2B} Receptor Assay

No	Agonist activity [% activation at 12.5 μM]	Agonist activity EC_{50} [μM]
Ex.9	48	12
Ex.12	36	3.3
Ex.16	45	6.6
Ex.30	48	3.3

Table 50.4: $P2Y_1$ Receptor Assay

No	Antagonist [% Inhibition at 10 µM]	Antagonist activity IC_{50} [µM]
Ex.316	57	n.d.
Ex.321	45	7.5
Ex.320	19	n.d.
Ex.322	60	n.d.

Table 51: $K_{v1,3}$ Ionchannel Assay

No	$K_{v1,3}$ antagonist activity [% Inhibition at 10 µM]	$K_{v1,3}$ antagonist activity IC50 [µM]]
Ex.166	20	n.d.
Ex.168	44	1.69
Ex.170	10	n.d.
Ex.171	12	n.d.
Ex.177	54	3.5

Table 52: Wnt-Pathway Assays

No	TCF/LEF receptor gene activity [% inhibition at 10 µM]	TCF/LEF receptor gene activity IC_{50} [µM]	AP receptor gene activity IC_{50} [µM]
Ex.501	100	1.1	> 50
Ex.502	82	5.5	> 50
Ex.503	68	5.8	> 50

Table 53: Plasma Stability and Metabolic Stability Assays of Selected Examples

(*continued on the following pages*)

	Plasma Stability				Metabolic Stability			
No	**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.9	240	99	240	93	32	20	60	80
Ex.11	240	100	240	100	60	74	60	77
Ex.12	240	99	240	100	17	7	35	33
Ex.16	240	95	240	97	38	31	60	79
Ex.30	240	85	240	100	22	2	60	55
Ex.37	240	77	240	100	60	100	60	100
Ex.43	240	82	240	89	60	100	60	98
Ex.49	240	83	240	96	24	10	60	83
Ex.78	240	65	240	100	60	78	60	100
Ex.91	240	96	240	88	60	91	60	95
Ex.93	240	100	240	100	24	1	29	15
Ex.95	240	100	240	93	60	76	60	94

	Plasma Stability				Metabolic Stability			
No	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.98	240	100	240	78	60	97	60	100
Ex.102	240	65	240	75	23	4	42	39
Ex.103	240	97	240	75	35	22	36	25
Ex.138	240	89	240	78	60	62	60	99
Ex.184	240	66	240	58	15	0	22	0
Ex.200	240	91	240	100	27	12	30	26
Ex.208	240	98	240	90	60	84	60	100
Ex.213	n.d.	n.d.	n.d.	n.d.	16	0	17	4
Ex.230	240	100	240	95	60	61	60	90
Ex.260	240	100	240	100	37	19	60	69
Ex.262	240	100	240	93	21	0	23	4
Ex.264	240	94	240	88	n.d.	n.d.	42	32
Ex.266	240	92	240	74	60	100	60	98
Ex.267	240	75	240	79	60	99	60	100

	Plasma Stability				Metabolic Stability			
No	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.272	240	95	240	92	60	65	60	81
Ex.482	240	100	240	100	22	11	60	84
Ex.483	240	100	240	100	60	55	60	85
Ex.484	240	100	240	90	21	11	60	100
Ex.485	240	100	240	99	14	8	17	11
Ex.486	240	100	240	98	23	13	60	100
Ex.168	240	85	240	99	25	17	26	21
Ex.170	240	92	240	100	60	60	60	86
Ex.167	n.d	n.d.	35	17	60	58	60	65
Ex.505	240	100	240	98	21	9	13	3
Ex.511	240	100	n.d.	n.d.	2	1	14	14
Ex.512	240	86	n.d.	n.d.	17	8	12	10
Ex.525	240	100	n.d.	n.d.	16	13	25	29
Ex.527	109	26	n.d.	n.d.	22	23	20	24

	Plasma Stability				Metabolic Stability			
No	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.533	240	95	240	100	60	59	60	93
Ex.561	240	99	240	100	39	42	60 (56)	79 (53)
Ex.568	240	97	240	89	60	53	60 (60)	60 (57)
Ex.563	240	88	240	81	8	1	12 (31)	4 (32)
Ex.570	240	92	240	100	13	20	60 (60)	69 (76)
Ex.571	240	86	240	89	60	90	60 (60)	74 (88)
Ex.572	240	85	240	100	54	49	60 (60)	54 (92)
Ex.574	240	91	240	95	60	94	60 (60)	93 (92)
Ex.577	240	87	240	101	47	41	27	25
Ex.578	240	100	240	86	52	46	60	55
Ex.580	240	70	(240)	(79)	60	100	n.d.	n.d.
Ex.581	240	70	(210)	(77)	60	98	60	100
Ex.582	240	100	240	96	60	100	60	98
Ex.583	240	91	240	83	60	100	60	95

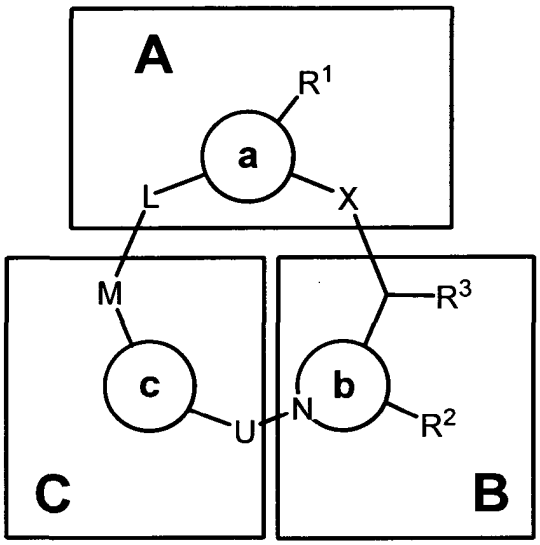
	Plasma Stability				Metabolic Stability			
No	T ½ [min] hum	240 min hum [% remain.]	T ½ [min] mouse/ (rat)	240 min mouse/ (rat) [% remain.]	T ½ [min] hum	60 min hum [% remain.]	T ½ [min] mouse/ (rat)	60 min mouse/ (rat) [% remain.]
Ex.368	240	72	(240)	(100)	60	83	60 (60)	82 (98)
Ex.369	240	85	(240)	(79)	60	100	60 (60)	80 (100)
Ex.372	240	68	(240)	(100)	46	43	60 (60)	73 (72)
Ex.373	240	55	(240)	(100)	12	12	36 (7)	39 (0)
Ex.374	240	57	(240)	(82)	60	61	60 (60)	94 (90)
Ex.376	240	90	(240)	(89)	60	79	60 (60)	91 (78)
Ex.377	240	95	(240)	(100)	60	72	60 (60)	86 (97)
Ex.378	240	48	(240)	(100)	60	65	60 (60)	87 (72)
Ex.403	240	100	240	65	36	37	57	55
Ex.406	240	75	240	89	60	77	60 (60)	94 (96)
Ex.407	240	80	240	98	51	47	60	84

Table 54: PK-Data of Selected Examples

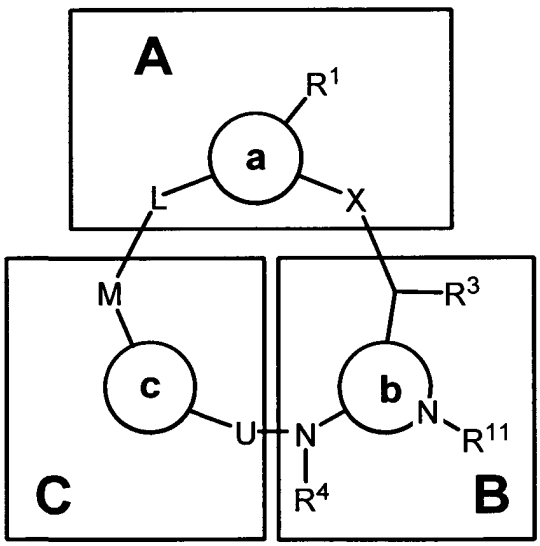
		Ex.561			Ex.568			Ex.571		
	Route	iv	po	po	iv	po	po	iv	po	po
Parameter	mg/kg	1	5	20	1	5	20	1	5	20
R^2		0.997	1.000	0.968	0.979	0.999	0.992	1.000	0.990	0.991
$T_{1/2}$ (terminal)	hr	2.11	3.00	2.71	1.67	1.92	2.07	1.70	2.18	2.30
Tmax	hr	0.08	0.50	0.25	0.08	0.25	0.25	0.08	0.25	0.25
Cmax	ng/mL	183.67	67.00	248.00	194.67	64.33	379.67	643.67	340.33	1516.67
Cmax dose normalized	kg*ng/mL/mg	183.67	13.40	12.40	194.67	12.87	18.98	643.67	68.07	75.83
C_0	ng/mL	240.24			284.59			932.47		
V (terminal)	mL/kg	13831.40			14320.56			7618.59		
$AUC_{(t-\infty)}$ dose normalized	hr*kg*ng/mL/mg	219.89	24.00	36.88	167.93	29.83	36.22	321.32	93.34	87.49
Bioavailability	%		**10.9**	**16.8**		**17.8**	**21.6**		**29.0**	**27.2**

Claims

1. Compounds consisting of a cyclic arrangement of the building blocks **A**, **B** and **C** and represented by the general formulae **Ia** or **Ib**



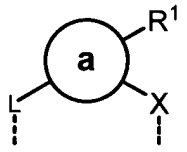
Ia



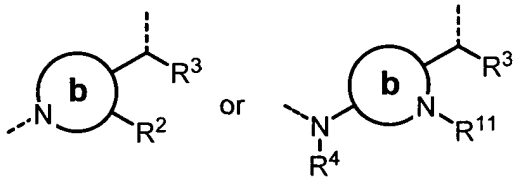
Ib

wherein

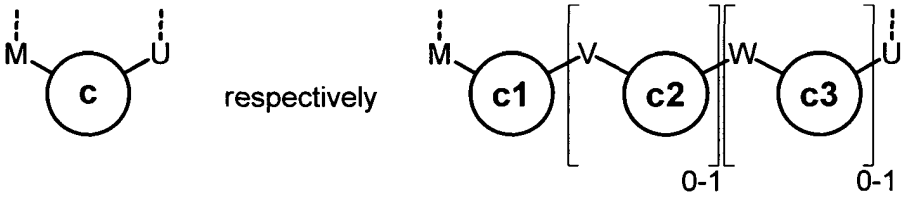
building block A ("Template") is represented by



building block B ("Modulator") is represented by

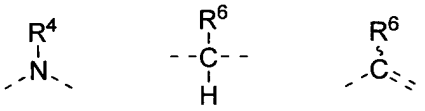


building block C ("Bridge") is represented by



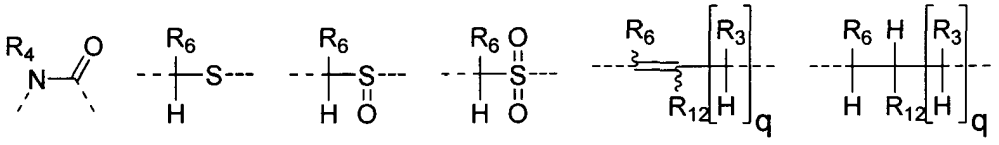
and wherein

M represents a divalent or trivalent radical selected from the group of

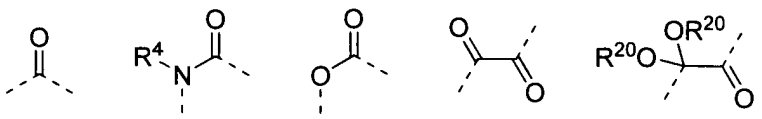


forming an integral part of the

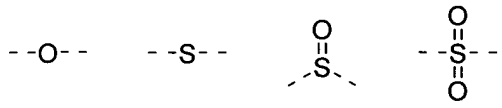
M-L connectivity which in turn represents a divalent radical selected from the group of



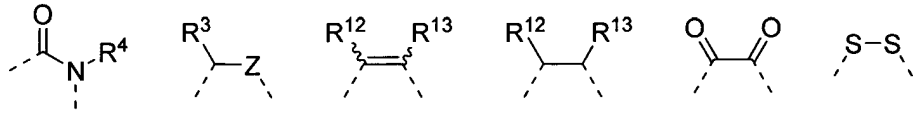
U represents a divalent radical selected from the group of



X represents a divalent radical selected from the group of

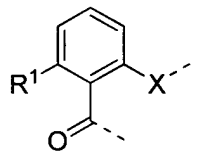
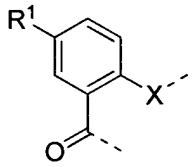
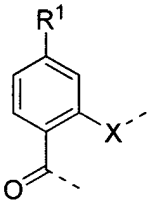
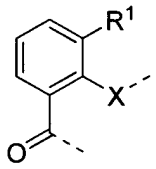
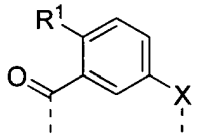
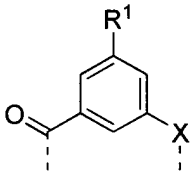
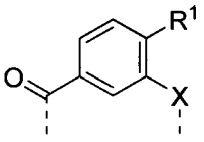
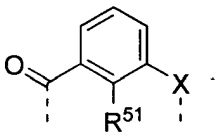
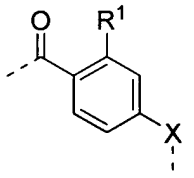
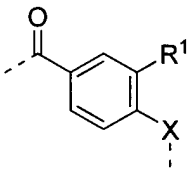
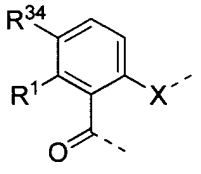
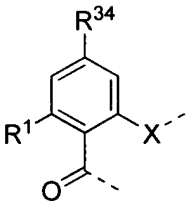


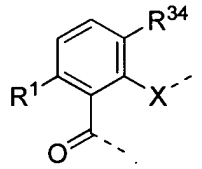
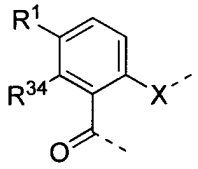
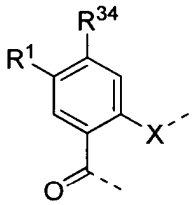
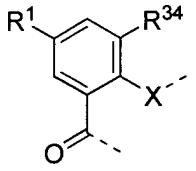
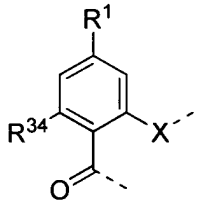
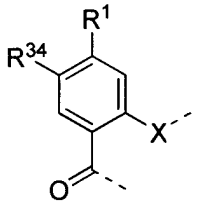
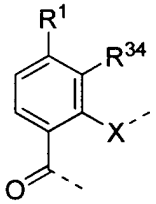
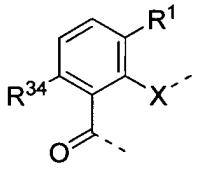
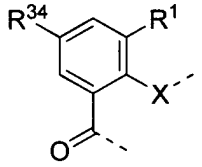
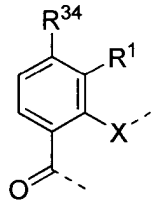
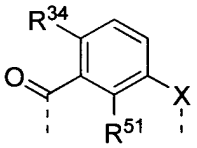
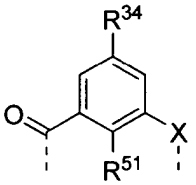
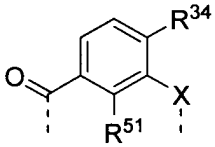
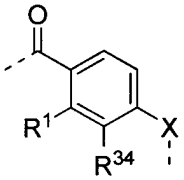
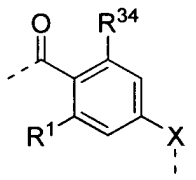
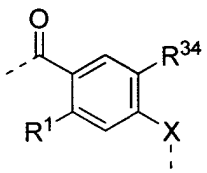
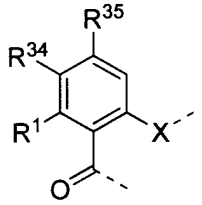
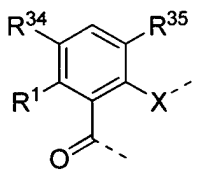
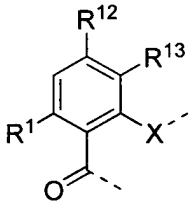
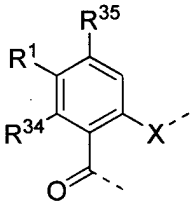
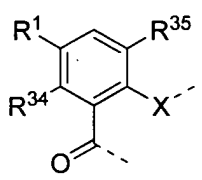
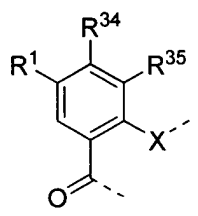
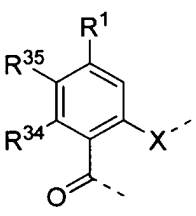
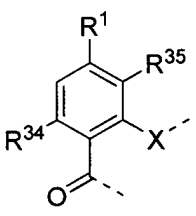
V and W are independently representing a divalent radical selected from the group of

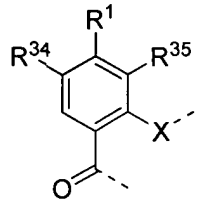
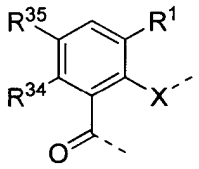
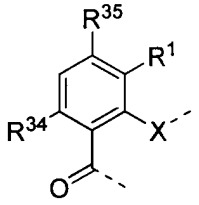
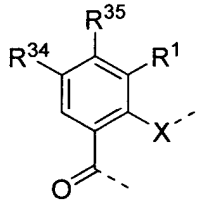
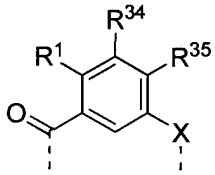
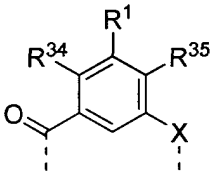
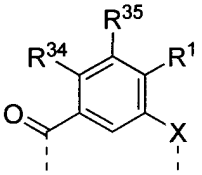
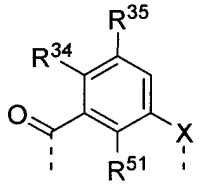
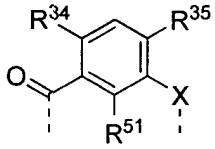
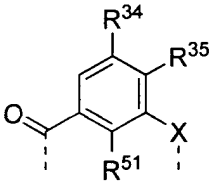
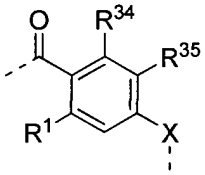
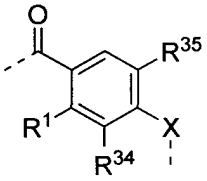
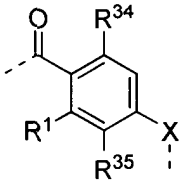
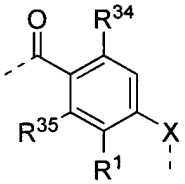
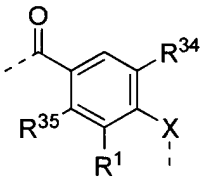
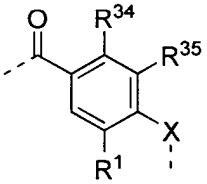
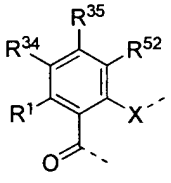
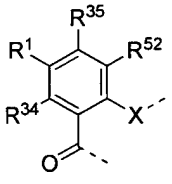
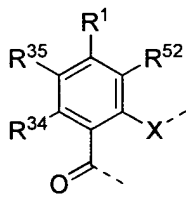
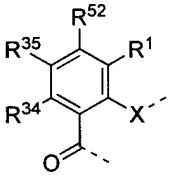


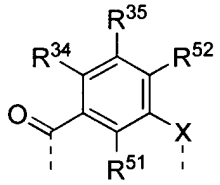
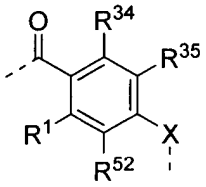
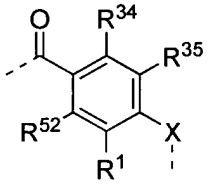
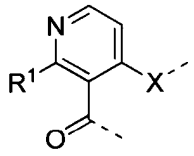
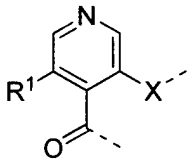
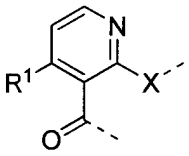
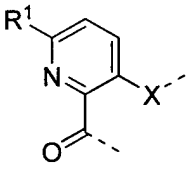
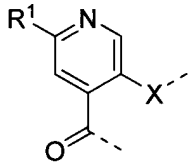
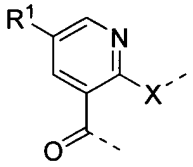
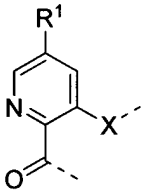
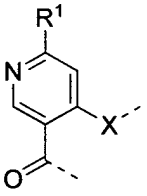
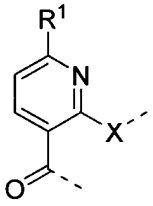
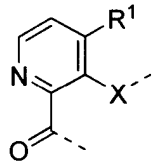
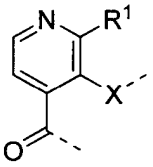
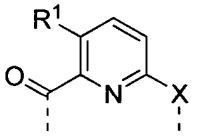
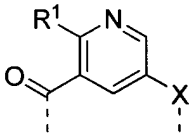
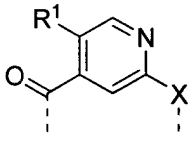
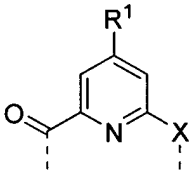
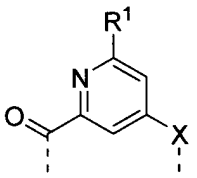
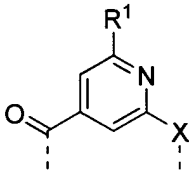
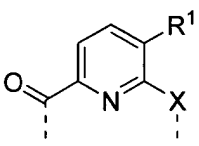
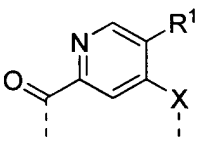
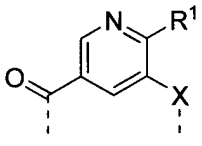
and wherein

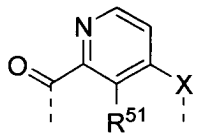
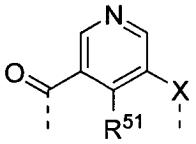
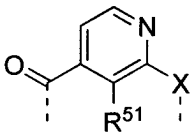
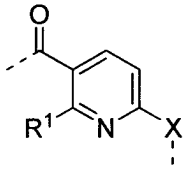
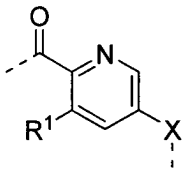
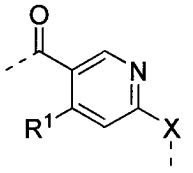
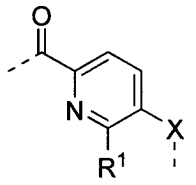
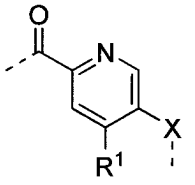
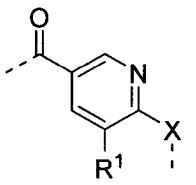
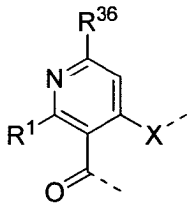
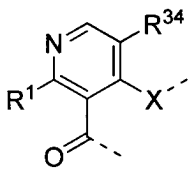
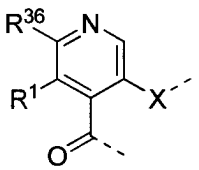
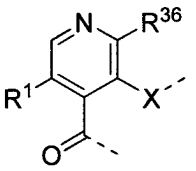
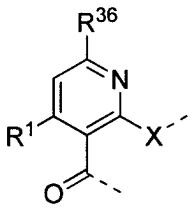
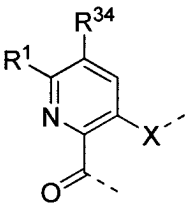
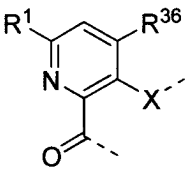
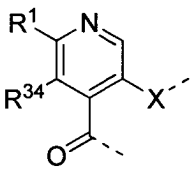
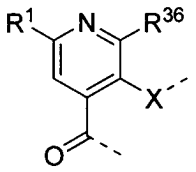
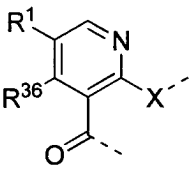
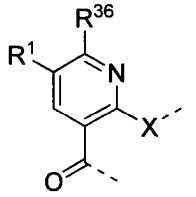
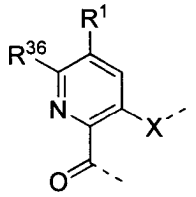
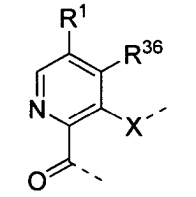
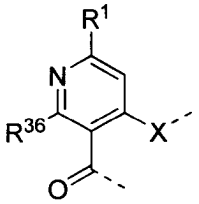
said **building block A** is a bivalent radical selected from the group of

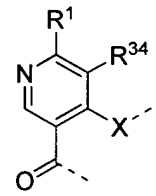
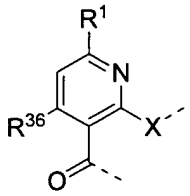
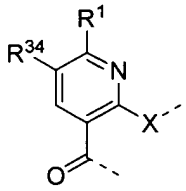
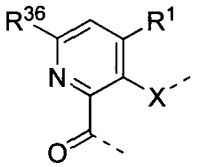
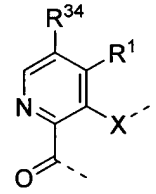
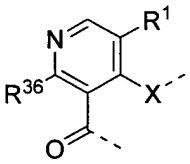
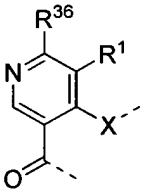
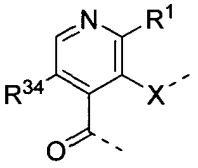
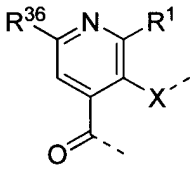
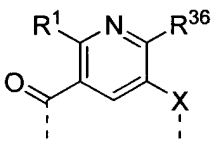
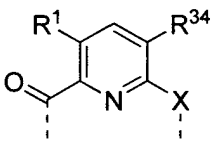
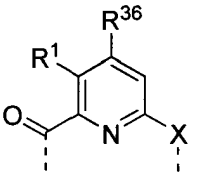
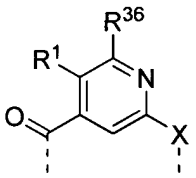
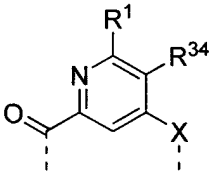
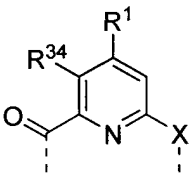
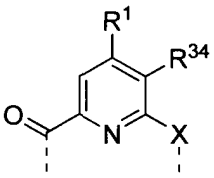
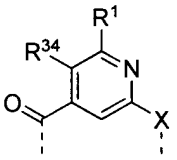
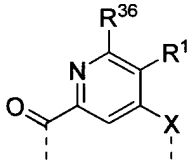
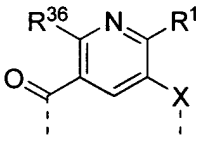
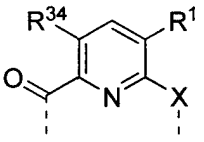
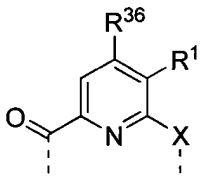
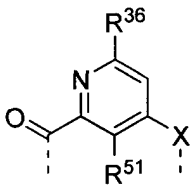
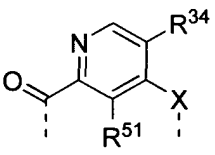
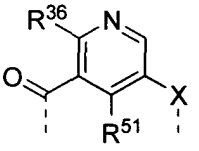
 **A1** (a1)	 **A2** (a1)	 **A3** (a1)	 **A4** (a1)
 **A5** (a1)	 **A6** (a1)	 **A7** (a1)	 **A8** (a1)
 **A9** (a1)	 **A10** (a1)	 **A11** (a1)	 **A12** (a1)

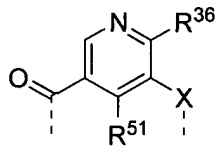
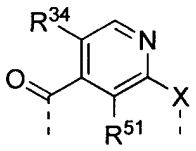
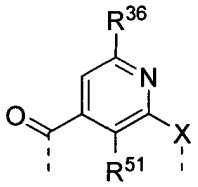
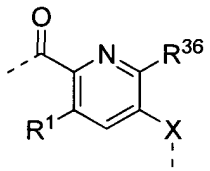
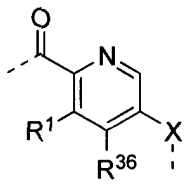
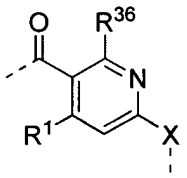
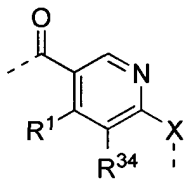
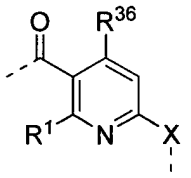
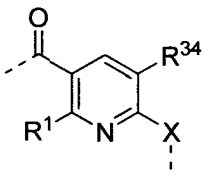
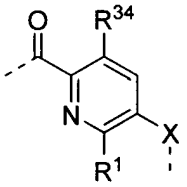
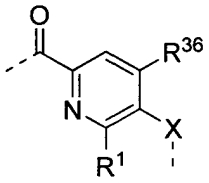
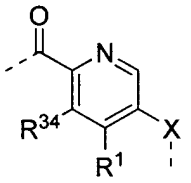
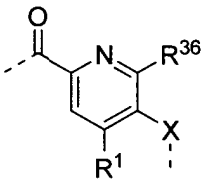
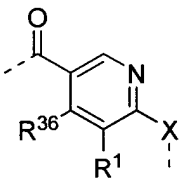
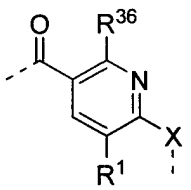
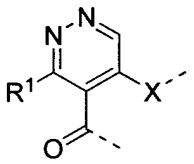
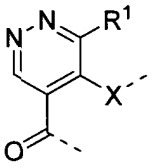
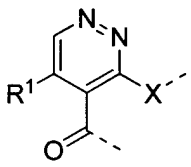
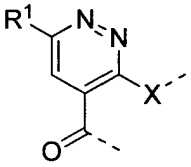
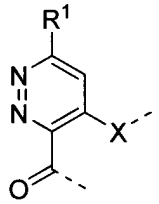
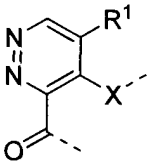
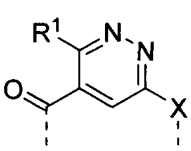
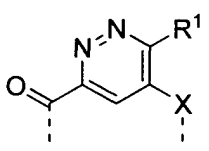
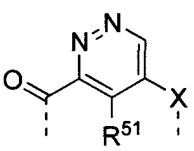
 **A13** (a1)	 **A14** (a1)	 **A15** (a1)	 **A16** (a1)
 **A17** (a1)	 **A18** (a1)	 **A19** (a1)	 **A20** (a1)
 **A21** (a1)	 **A22** (a1)	 **A23** (a1)	 **A24** (a1)
 **A25** (a1)	 **A26** (a1)	 **A27** (a1)	 **A28** (a1)
 **A29** (a1)	 **A30** (a1)	 **A31** (a1)	 **A32** (a1)
			

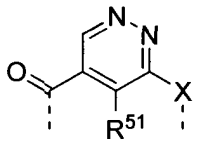
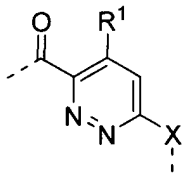
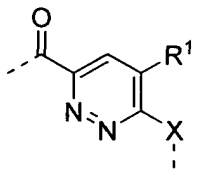
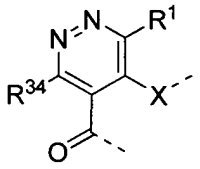
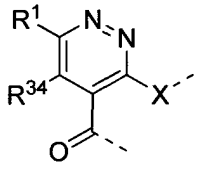
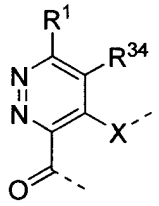
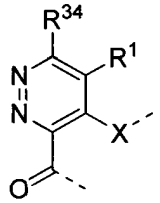
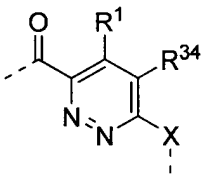
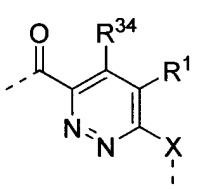
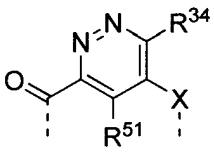
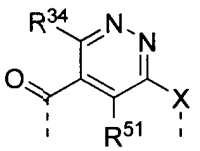
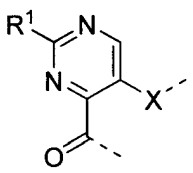
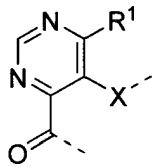
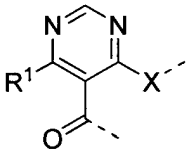
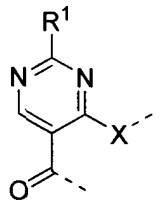
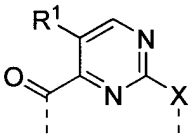
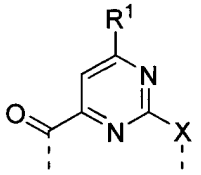
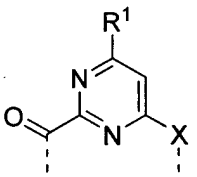
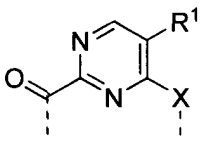
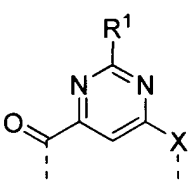
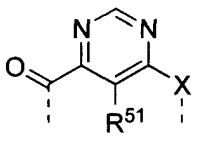
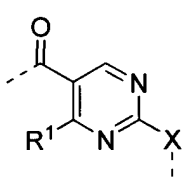
A33 (a1)	**A34** (a1)	**A35** (a1)	**A36** (a1)
 **A37** (a1)	 **A38** (a1)	 **A39** (a1)	 **A40** (a1)
 **A41** (a1)	 **A42** (a1)	 **A43** (a1)	 **A44** (a1)
 **A45** (a1)	 **A46** (a1)	 **A47** (a1)	 **A48** (a1)
 **A49** (a1)	 **A50** (a1)	 **A51** (a1)	 **A52** (a1)
 **A53** (a1)	 **A54** (a1)	 **A55** (a1)	 **A56** (a1)

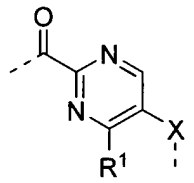
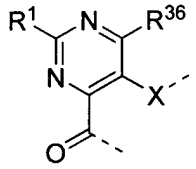
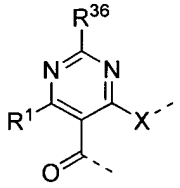
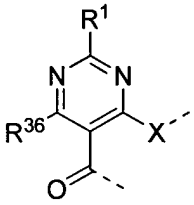
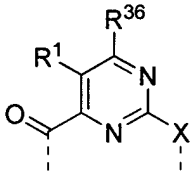
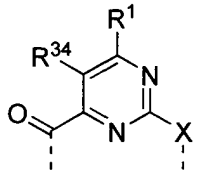
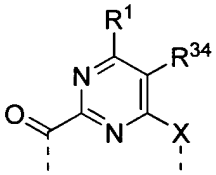
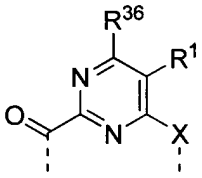
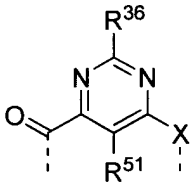
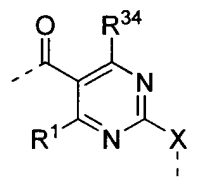
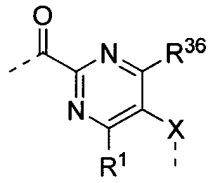
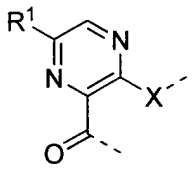
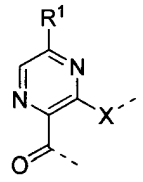
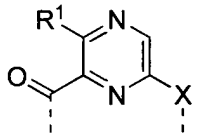
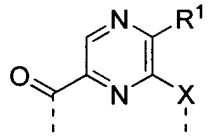
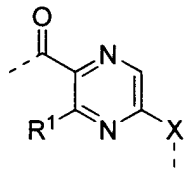
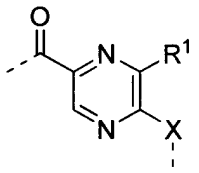
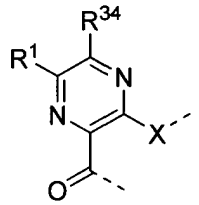
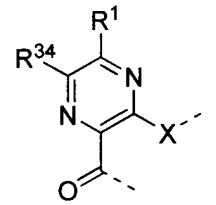
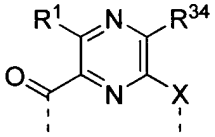
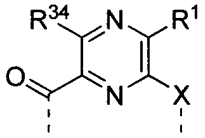
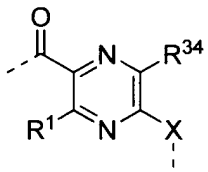
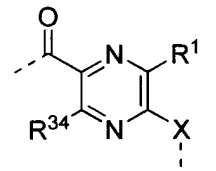
 **A57** (a1)	 **A58** (a1)	 **A59** (a1)	 **A60** (a2)
 **A61** (a2)	 **A62** (a2)	 **A63** (a2)	 **A64** (a2)
 **A65** (a2)	 **A66** (a2)	 **A67** (a2)	 **A68** (a2)
 **A69** (a2)	 **A70** (a2)	 **A71** (a2)	 **A72** (a2)
 **A73** (a2)	 **A74** (a2)	 **A75** (a2)	 **A76** (a2)
 **A77** (a2)	 **A78** (a2)	 **A79** (a2)	 **A80** (a2)

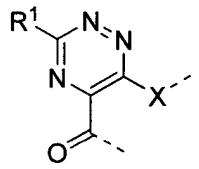
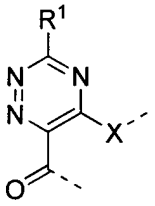
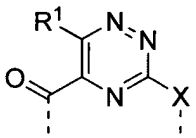
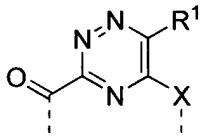
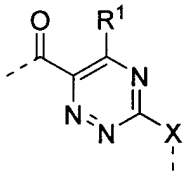
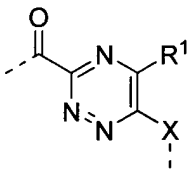
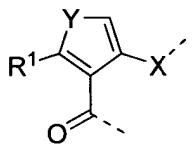
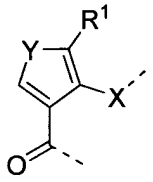
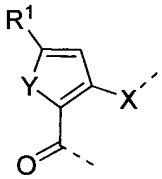
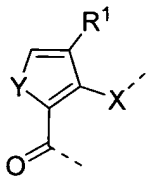
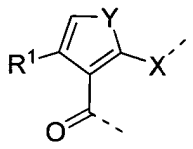
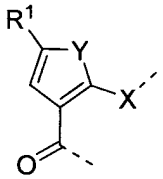
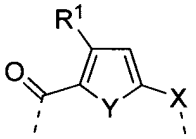
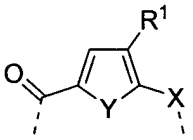
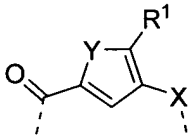
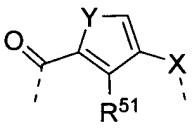
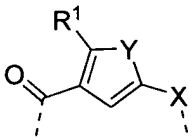
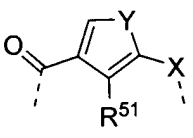
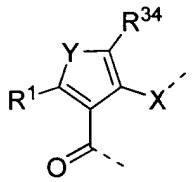
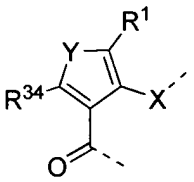
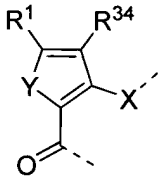
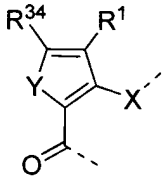
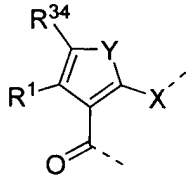
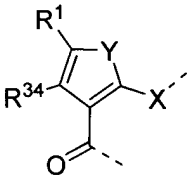
 **A81** (a2)	 **A82** (a2)	 **A83** (a2)	 **A84** (a2)
 **A85** (a2)	 **A86** (a2)	 **A87** (a2)	 **A88** (a2)
 **A89** (a2)	 **A90** (a2)	 **A91** (a2)	 **A92** (a2)
 **A93** (a2)	 **A94** (a2)	 **A95** (a2)	 **A96** (a2)
 **A97** (a2)	 **A98** (a2)	 **A99** (a2)	 **A100** (a2)
 **A101** (a2)	 **A102** (a2)	 **A103** (a2)	 **A104** (a2)

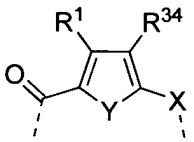
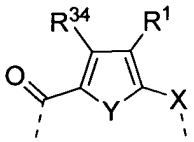
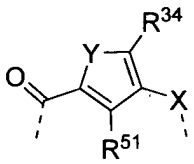
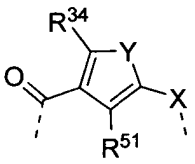
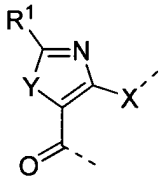
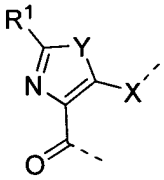
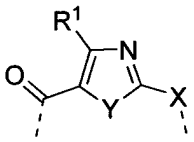
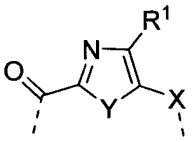
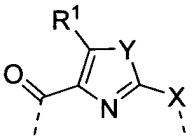
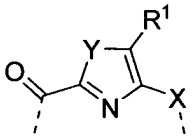
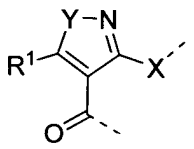
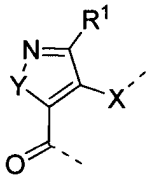
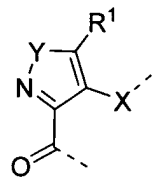
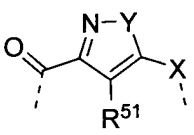
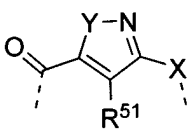
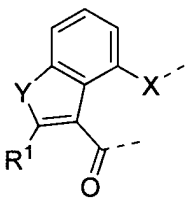
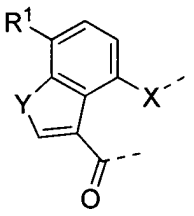
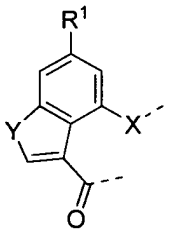
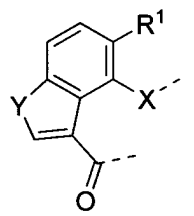
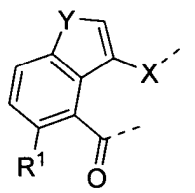
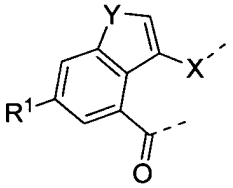
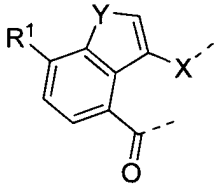
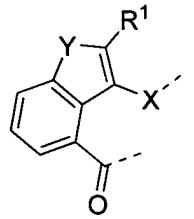
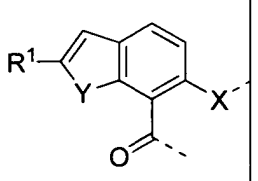
 **A105** (a2)	 **A106** (a2)	 **A107** (a2)	 **A108** (a2)
 **A109** (a2)	 **A110** (a2)	 **A111** (a2)	 **A112** (a2)
 **A113** (a2)	 **A114** (a2)	 **A115** (a2)	 **A116** (a2)
 **A117** (a2)	 **A118** (a2)	 **A119** (a2)	 **A120** (a2)
 **A121** (a2)	 **A122** (a2)	 **A123** (a2)	 **A124** (a2)
 **A125** (a2)	 **A126** (a2)	 **A127** (a2)	 **A128** (a2)

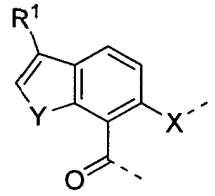
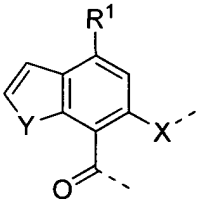
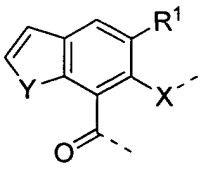
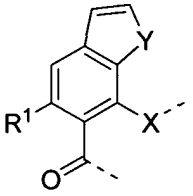
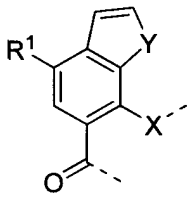
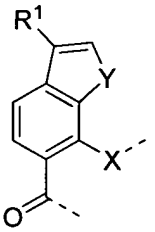
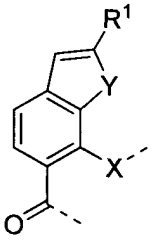
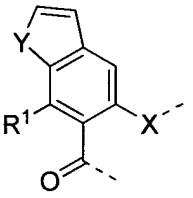
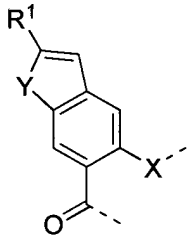
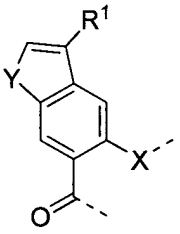
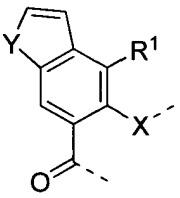
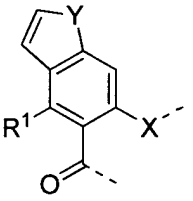
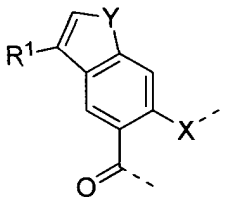
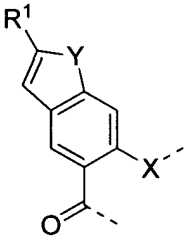
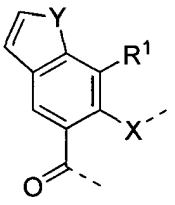
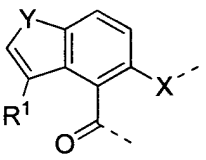
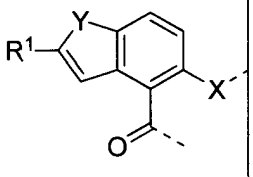
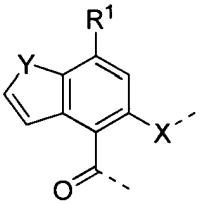
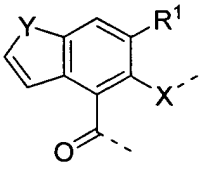
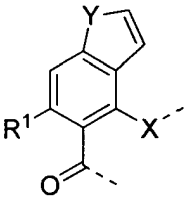
 **A129** (a2)	 **A130** (a2)	 **A131** (a2)	 **A132** (a2)
 **A133** (a2)	 **A134** (a2)	 **A135** (a2)	 **A136** (a2)
 **A137** (a2)	 **A138** (a2)	 **A139** (a2)	 **A140** (a2)
 **A141** (a2)	 **A142** (a2)	 **A143** (a2)	 **A144** (a3)
 **A145** (a3)	 **A146** (a3)	 **A147** (a3)	 **A148** (a3)
 **A149** (a3)	 **A150** (a3)	 **A151** (a3)	 **A152** (a3)

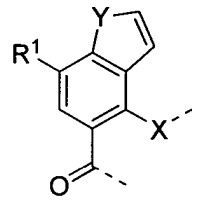
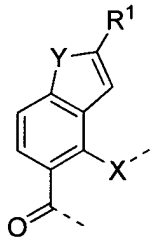
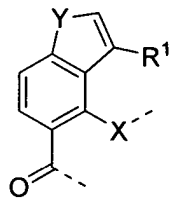
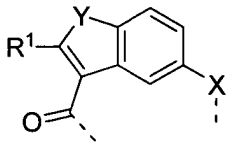
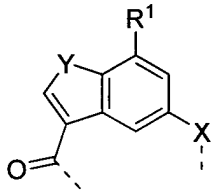
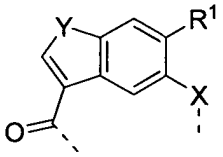
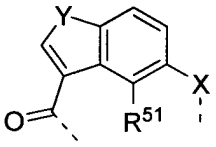
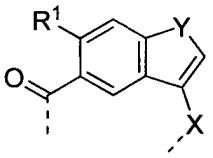
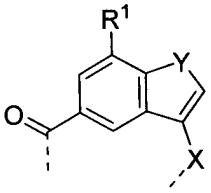
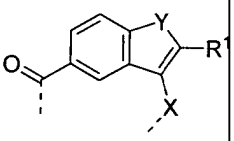
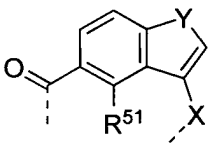
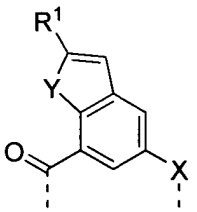
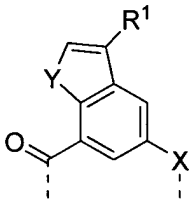
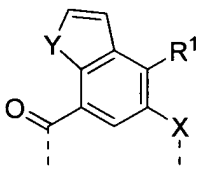
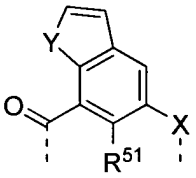
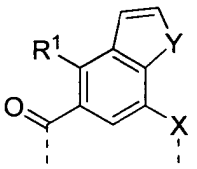
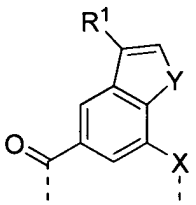
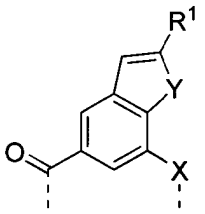
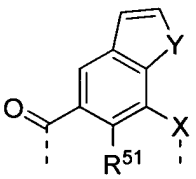
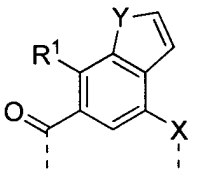
 **A153** (a3)	 **A154** (a3)	 **A155** (a3)	 **A156** (a3)
 **A157** (a3)	 **A158** (a3)	 **A159** (a3)	 **A160** (a3)
 **A161** (a3)	 **A162** (a3)	 **A163** (a3)	 **A164** (a3)
 **A165** (a3)	 **A166** (a4)	 **A167** (a4)	 **A168** (a4)
 **A169** (a4)	 **A170** (a4)	 **A171** (a4)	 **A172** (a4)
 **A173** (a4)	 **A174** (a4)	 **A175** (a4)	 **A176** (a4)

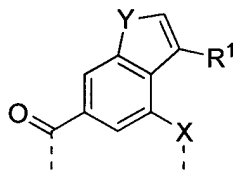
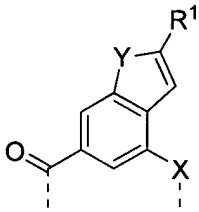
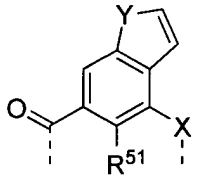
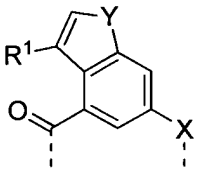
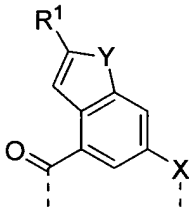
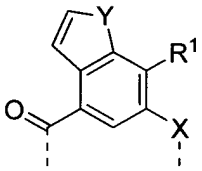
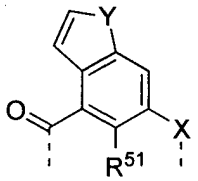
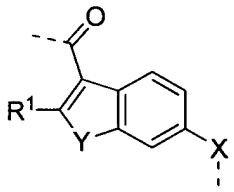
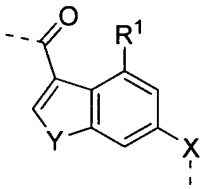
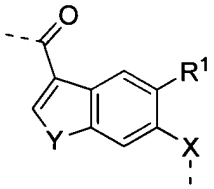
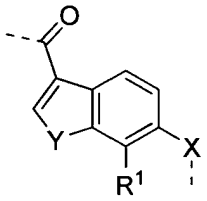
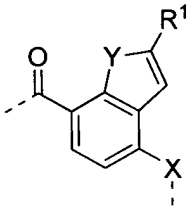
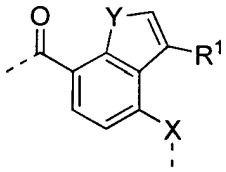
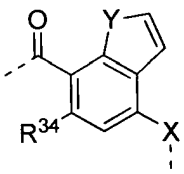
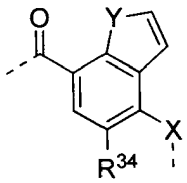
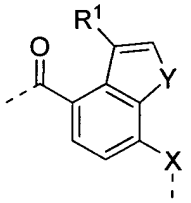
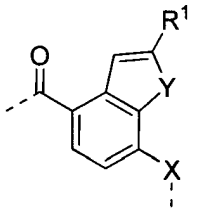
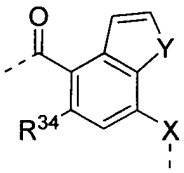
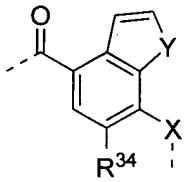
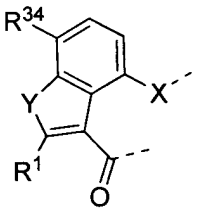
 **A177** (a4)	 **A178** (a4)	 **A179** (a4)	 **A180** (a4)
 **A181** (a4)	 **A182** (a4)	 **A183** (a4)	 **A184** (a4)
 **A185** (a4)	 **A186** (a4)	 **A187** (a4)	 **A188** (a4)
 **A189** (a5)	 **A190** (a5)	 **A191** (a5)	 **A192** (a5)
 **A193** (a5)	 **A194** (a5)	 **A195** (a5)	 **A196** (a5)
 **A197** (a5)	 **A198** (a5)	 **A199** (a5)	 **A200** (a5)

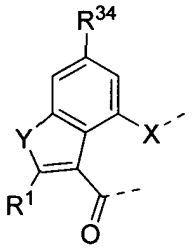
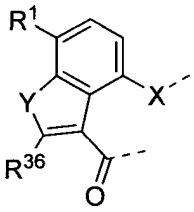
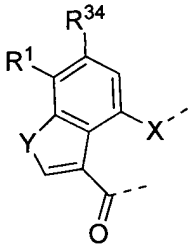
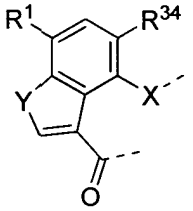
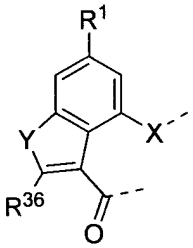
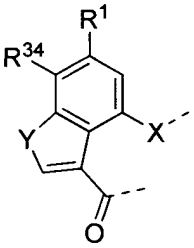
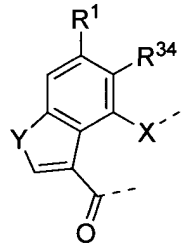
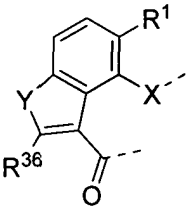
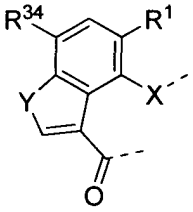
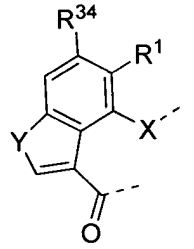
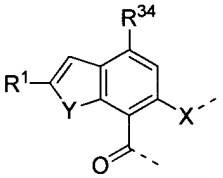
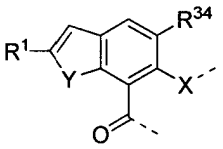
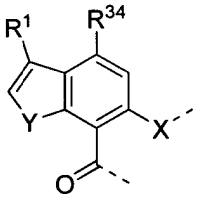
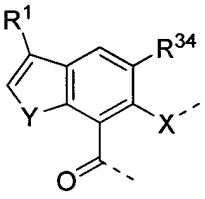
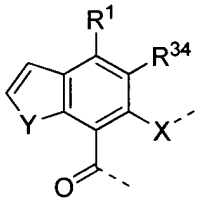
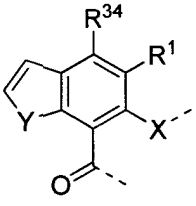
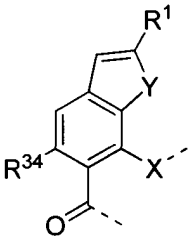
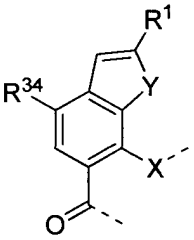
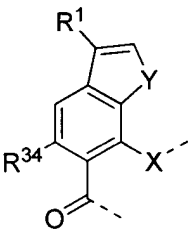
 **A201** (a6)	 **A202** (a6)	 **A203** (a6)	 **A204** (a6)
 **A205** (a6)	 **A206** (a6)	 **A207** (a7)	 **A208** (a7)
 **A209** (a7)	 **A210** (a7)	 **A211** (a7)	 **A212** (a7)
 **A213** (a7)	 **A214** (a7)	 **A215** (a7)	 **A216** (a7)
 **A217** (a7)	 **A218** (a7)	 **A219** (a7)	 **A220** (a7)
 **A221** (a7)	 **A222** (a7)	 **A223** (a7)	 **A224** (a7)

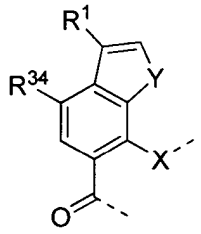
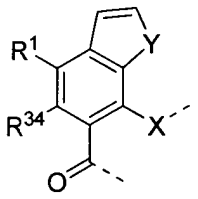
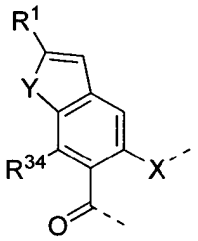
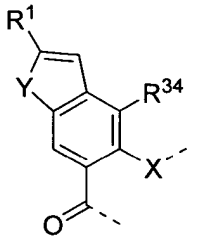
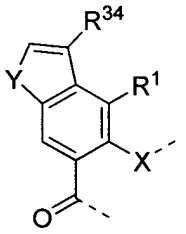
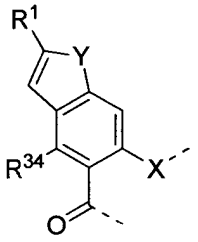
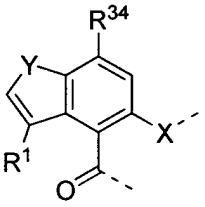
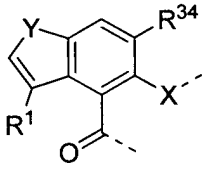
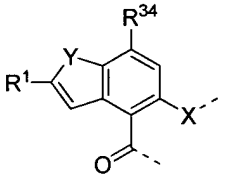
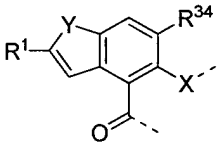
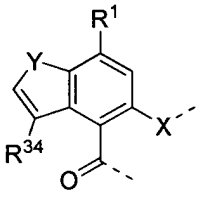
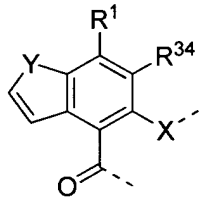
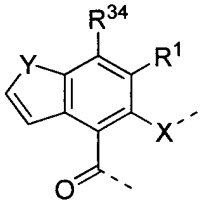
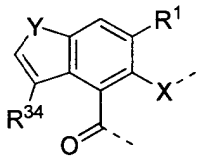
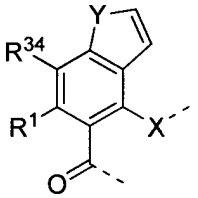
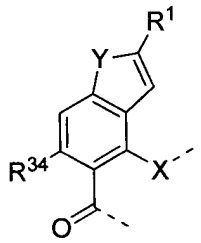
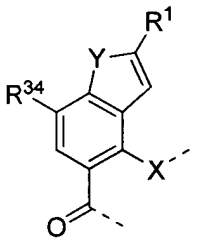
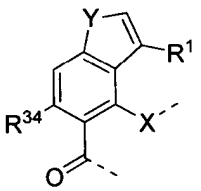
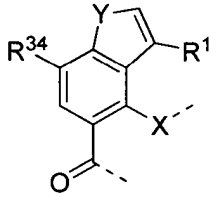
 **A225** (a7)	 **A226** (a7)	 **A227** (a7)	 **A228** (a7)
 **A229** (a8)	 **A230** (a8)	 **A231** (a8)	 **A232** (a8)
 **A233** (a8)	 **A234** (a8)	 **A235** (a9)	 **A236** (a9)
 **A237** (a9)	 **A238** (a9)	 **A239** (a9)	 **A240** (a10)
 **A241** (a10)	 **A242** (a10)	 **A243** (a10)	 **A244** (a10)
 **A245** (a10)	 **A246** (a10)	 **A247** (a10)	 **A248** (a10)

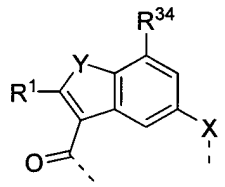
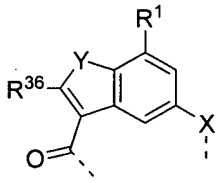
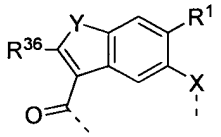
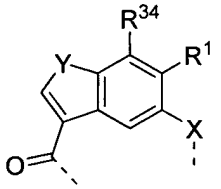
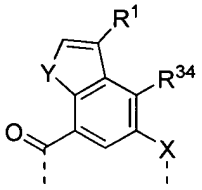
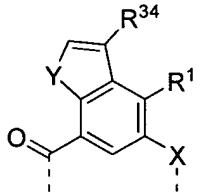
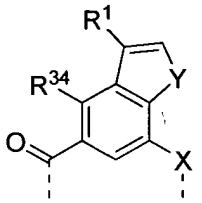
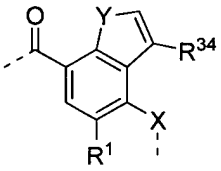
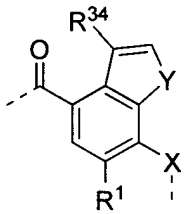
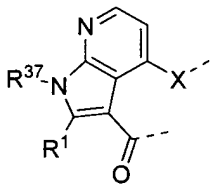
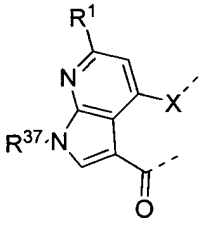
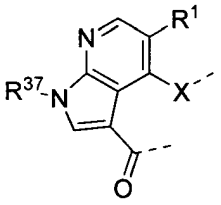
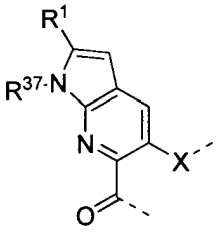
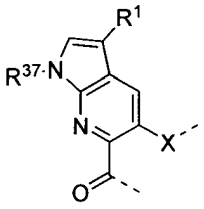
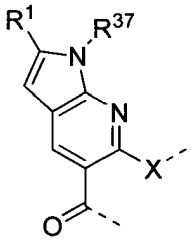
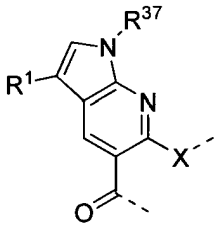
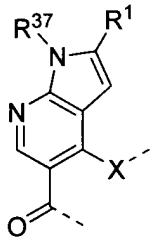
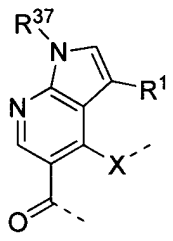
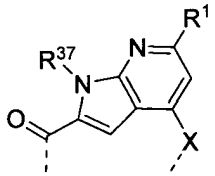
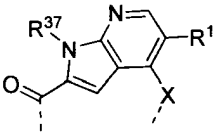
 **A249** (a10)	 **A250** (a10)	 **A251** (a10)	 **A252** (a10)
 **A253** (a10)	 **A254** (a10)	 **A255** (a10)	 **A256** (a10)
 **A257** (a10)	 **A258** (a10)	 **A259** (a10)	 **A260** (a10)
 **A261** (a10)	 **A262** (a10)	 **A263** (a10)	 **A264** (a10)
 **A265** (a10)	 **A266** (a10)	 **A267** (a10)	 **A268** (a10)

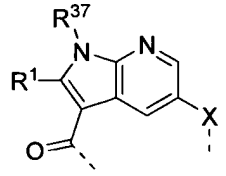
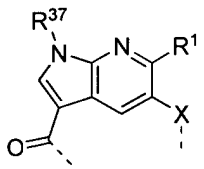
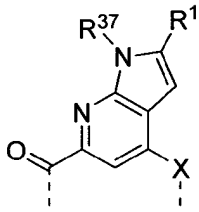
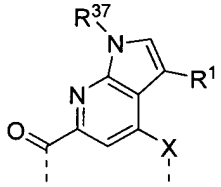
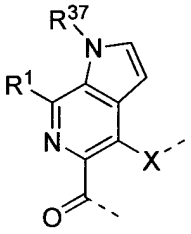
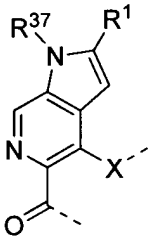
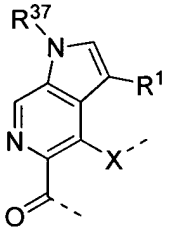
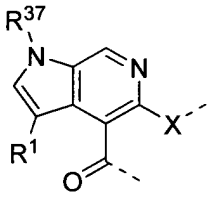
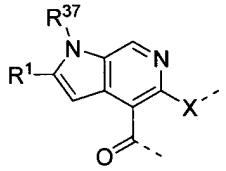
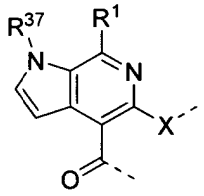
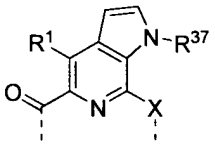
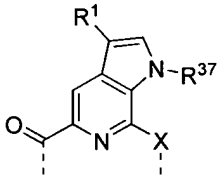
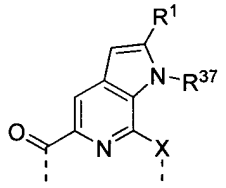
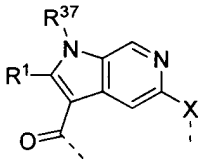
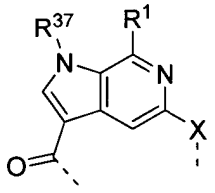
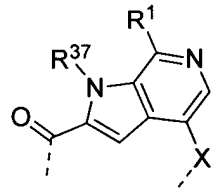
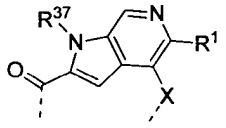
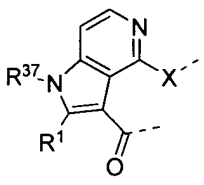
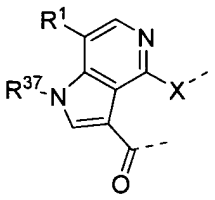
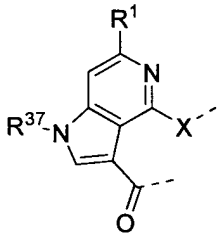
 **A269** (a10)	 **A270** (a10)	 **A271** (a10)	 **A272** (a10)
 **A273** (a10)	 **A274** (a10)	 **A275** (a10)	 **A276** (a10)
 **A277** (a10)	 **A278** (a10)	 **A279** (a10)	 **A280** (a10)
 **A281** (a10)	 **A282** (a10)	 **A283** (a10)	 **A284** (a10)
 **A285** (a10)	 **A286** (a10)	 **A287** (a10)	 **A288** (a10)

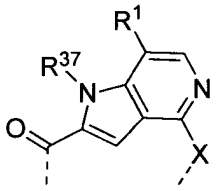
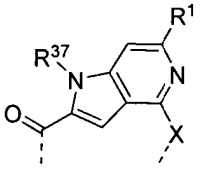
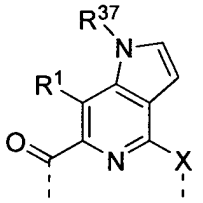
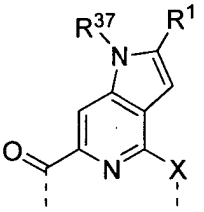
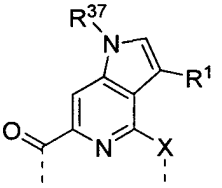
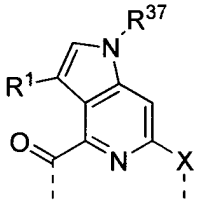
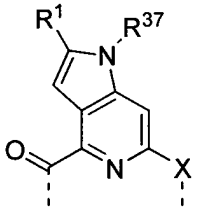
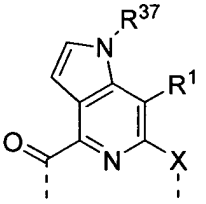
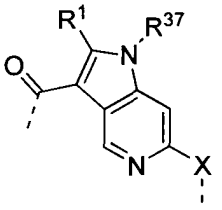
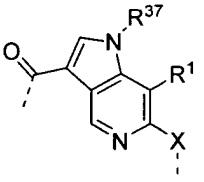
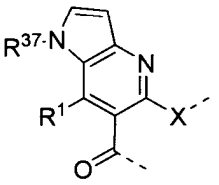
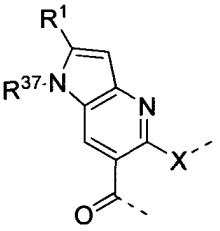
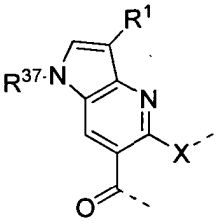
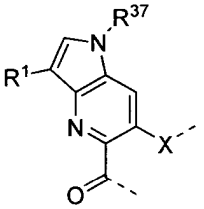
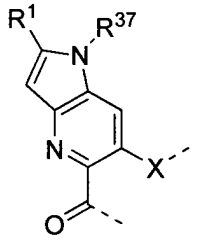
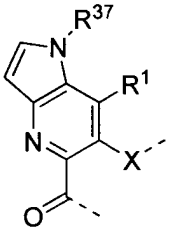
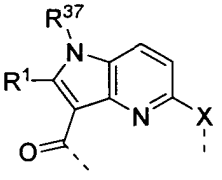
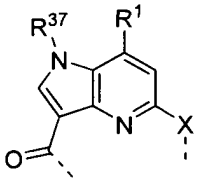
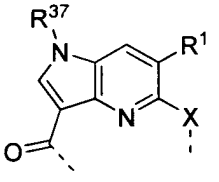
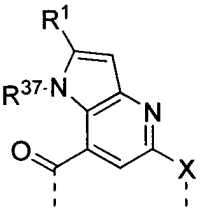
 **A289** (a10)	 **A290** (a10)	 **A291** (a10)	 **A292** (a10)
 **A293** (a10)	 **A294** (a10)	 **A295** (a10)	 **A296** (a10)
 **A297** (a10)	 **A298** (a10)	 **A299** (a10)	 **A300** (a10)
 **A301** (a10)	 **A302** (a10)	 **A303** (a10)	 **A304** (a10)
 **A305** (a10)	 **A306** (a10)	 **A307** (a10)	 **A308** (a10)

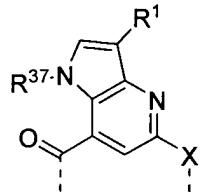
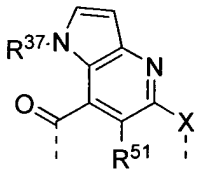
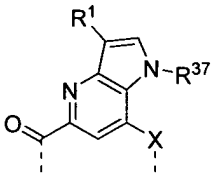
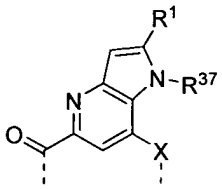
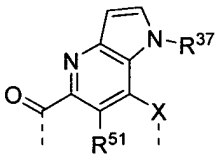
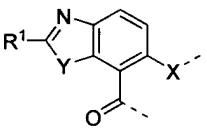
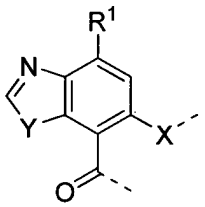
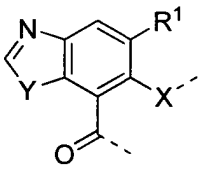
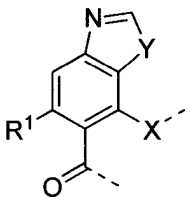
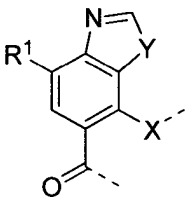
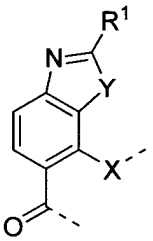
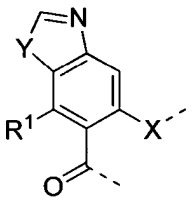
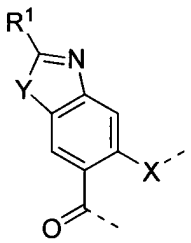
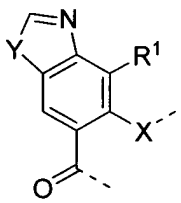
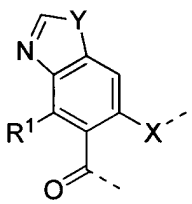
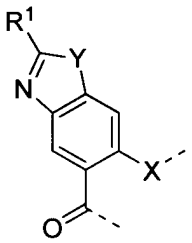
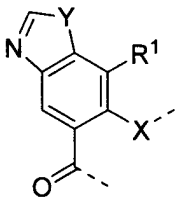
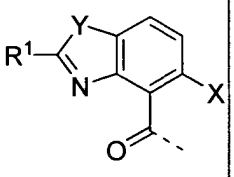
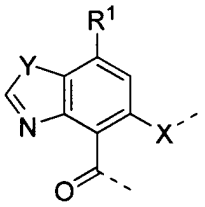
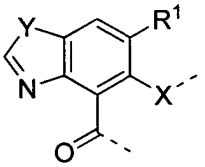
 **A309** (a10)	 **A310** (a10)	 **A311** (a10)	 **A312** (a10)
 **A313** (a10)	 **A314** (a10)	 **A315** (a10)	 **A316** (a10)
 **A317** (a10)	 **A318** (a10)	 **A319** (a10)	 **A320** (a10)
 **A321** (a10)	 **A322** (a10)	 **A323** (a10)	 **A324** (a10)
 **A325** (a10)	 **A326** (a10)	 **A327** (a10)	 **A328** (a10)

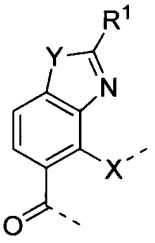
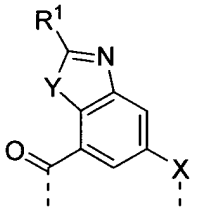
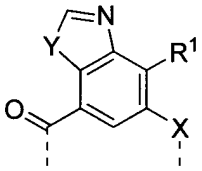
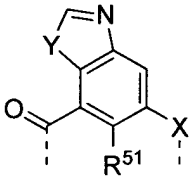
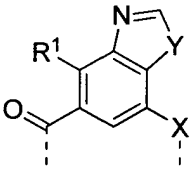
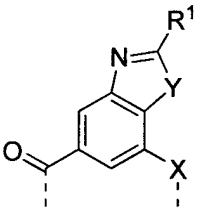
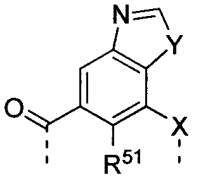
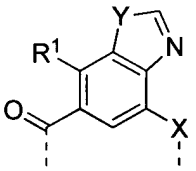
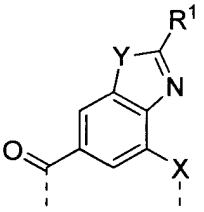
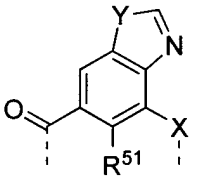
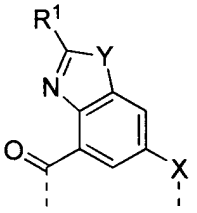
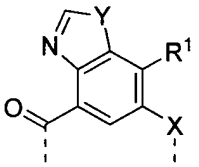
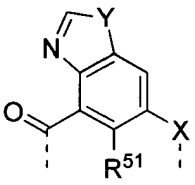
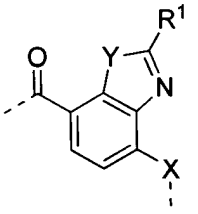
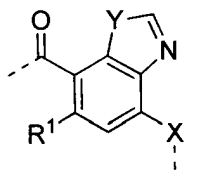
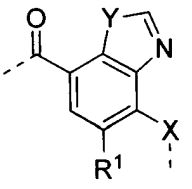
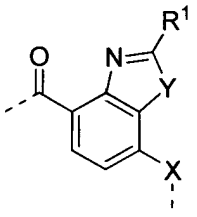
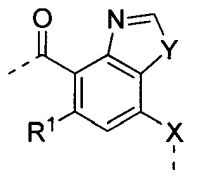
 **A329** (a10)	 **A330** (a10)	 **A331** (a10)	 **A332** (a10)
 **A333** (a10)	 **A334** (a10)	 **A335** (a10)	 **A336** (a10)
 **A337** (a10)	 **A338** (a10)	 **A339** (a10)	 **A340** (a10)
 **A341** (a10)	 **A342** (a10)	 **A343** (a10)	 **A344** (a10)
 **A345** (a10)	 **A346** (a10)	 **A347** (a10)	 **A348** (a10)

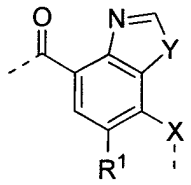
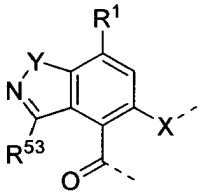
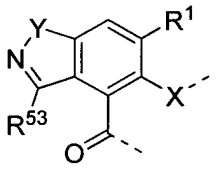
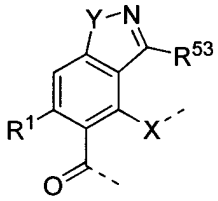
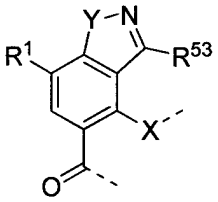
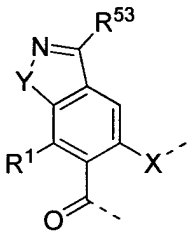
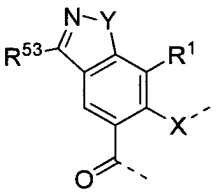
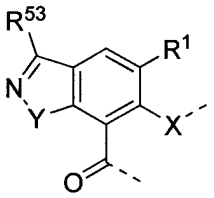
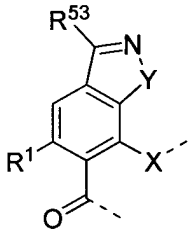
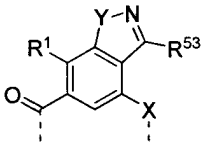
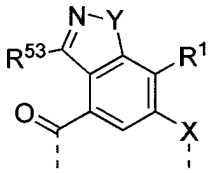
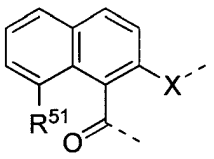
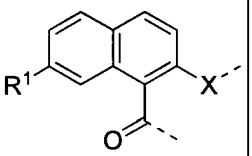
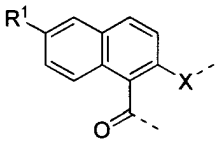
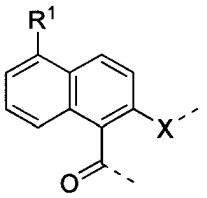
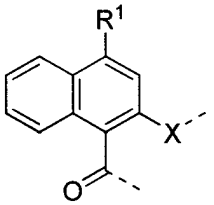
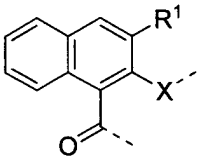
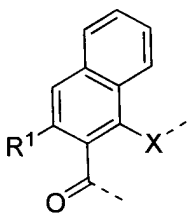
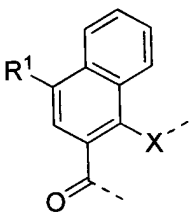
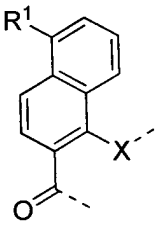
 **A349** (a10)	 **A350** (a10)	 **A351** (a10)	 **A352** (a10)
 **A353** (a10)	 **A354** (a10)	 **A355** (a10)	 **A356** (a10)
 **A357** (a10)	 **A358** (a11)	 **A359** (a11)	 **A360** (a11)
 **A361** (a11)	 **A362** (a11)	 **A363** (a11)	 **A364** (a11)
 **A365** (a11)	 **A366** (a11)	 **A367** (a11)	 **A368** (a11)

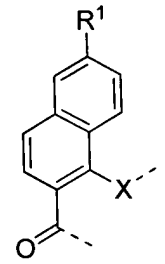
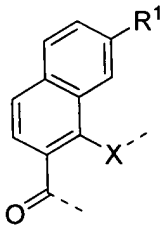
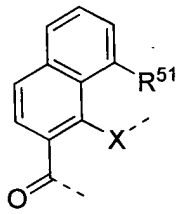
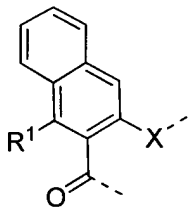
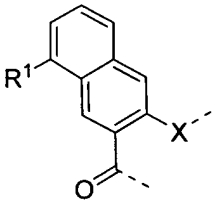
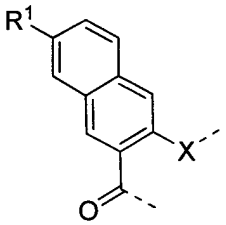
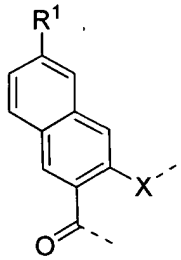
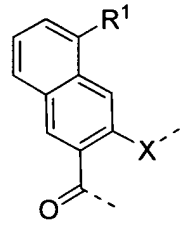
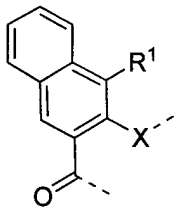
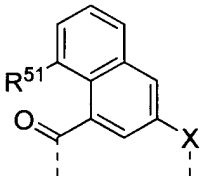
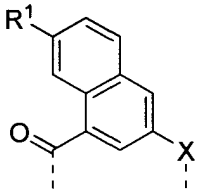
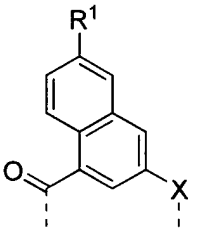
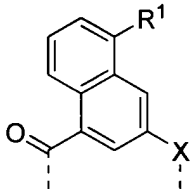
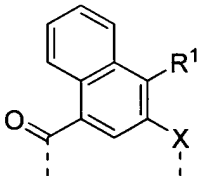
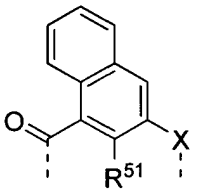
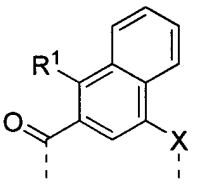
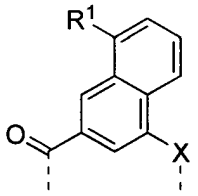
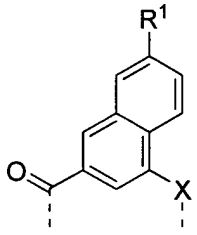
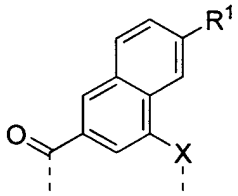
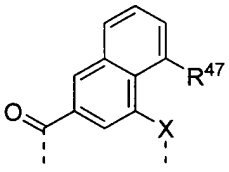
 **A369** (a11)	 **A370** (a11)	 **A371** (a11)	 **A372** (a11)
 **A373** (a12)	 **A374** (a12)	 **A375** (a12)	 **A376** (a12)
 **A377** (a12)	 **A378** (a12)	 **A379** (a12)	 **A380** (a12)
 **A381** (a12)	 **A382** (a12)	 **A383** (a12)	 **A384** (a12)
 **A385** (a12)	 **A386** (a13)	 **A387** (a13)	 **A388** (a13)

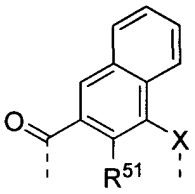
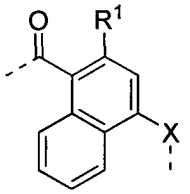
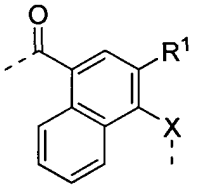
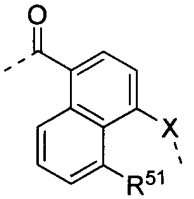
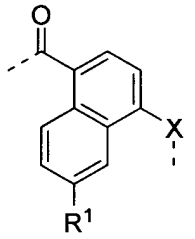
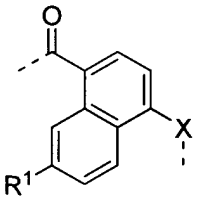
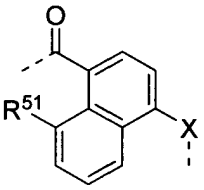
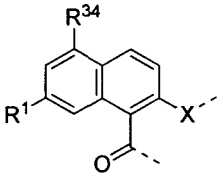
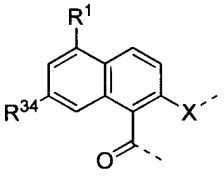
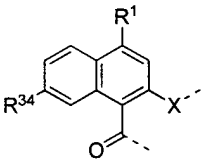
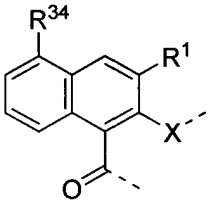
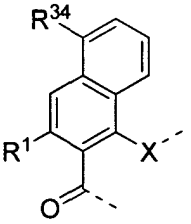
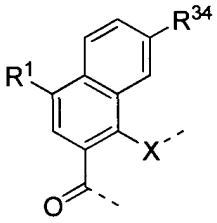
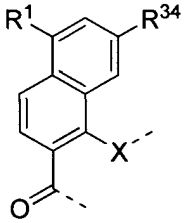
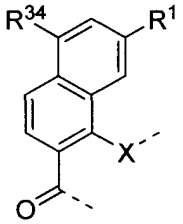
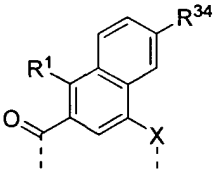
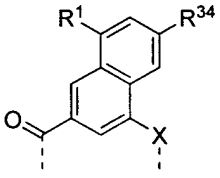
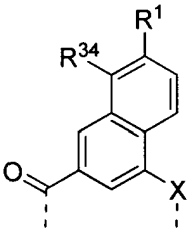
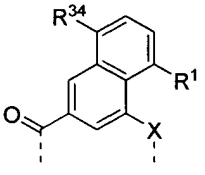
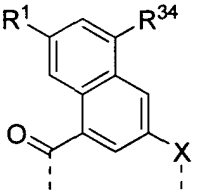
 **A389** (a13)	 **A390** (a13)	 **A391** (a13)	 **A392** (a13)
 **A393** (a13)	 **A394** (a13)	 **A395** (a13)	 **A396** (a13)
 **A397** (a13)	 **A398** (a13)	 **A399** (a14)	 **A400** (a14)
 **A401** (a14)	 **A402** (a14)	 **A403** (a14)	 **A404** (a14)
 **A405** (a14)	 **A406** (a14)	 **A407** (a14)	 **A408** (a14)

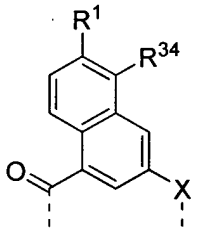
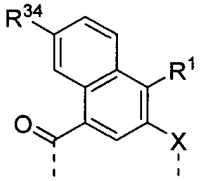
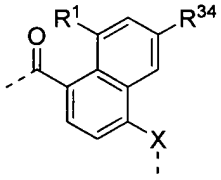
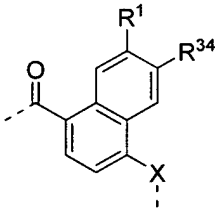
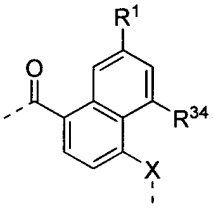
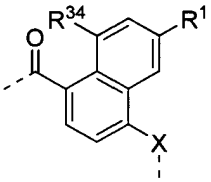
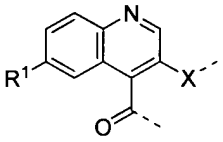
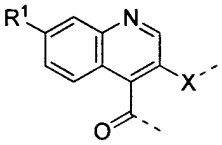
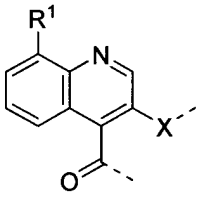
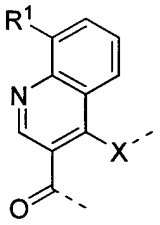
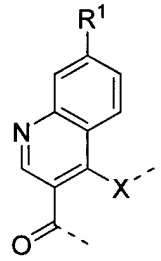
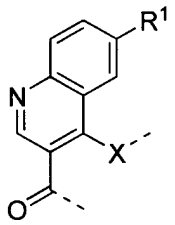
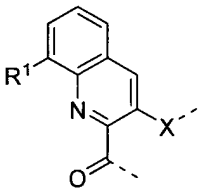
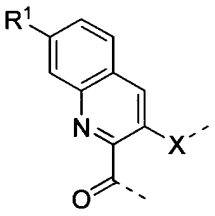
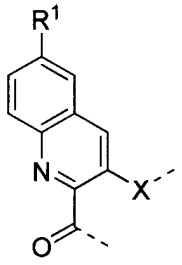
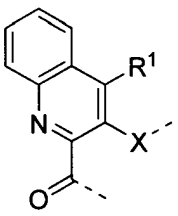
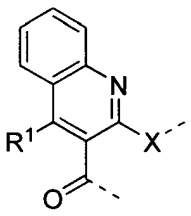
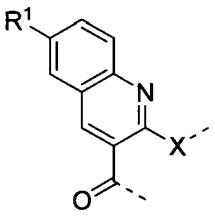
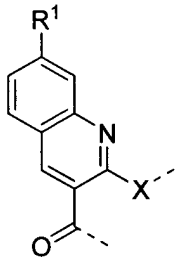
 **A409** (a14)	 **A410** (a14)	 **A411** (a14)	 **A412** (a14)
 **A413** (a14)	 **A414** (a15)	 **A415** (a15)	 **A416** (a15)
 **A417** (a15)	 **A418** (a15)	 **A419** (a15)	 **A420** (a15)
 **A421** (a15)	 **A422** (a15)	 **A423** (a15)	 **A424** (a15)
 **A425** (a15)	 **A426** (a15)	 **A427** (a15)	 **A428** (a15)

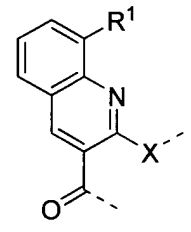
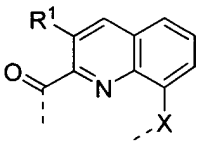
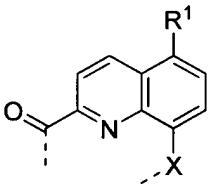
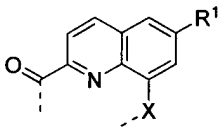
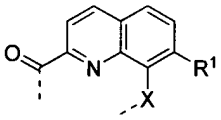
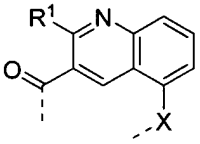
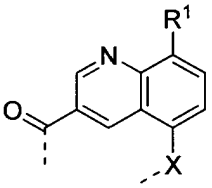
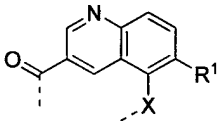
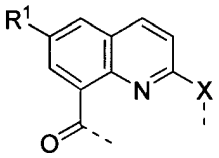
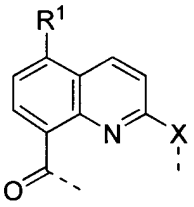
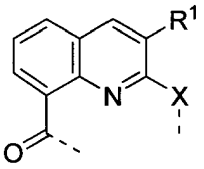
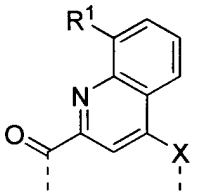
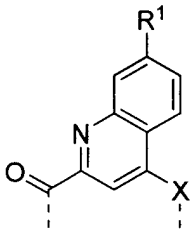
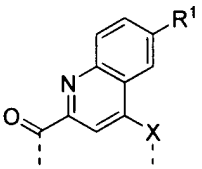
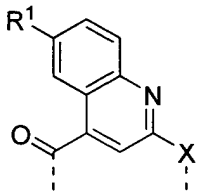
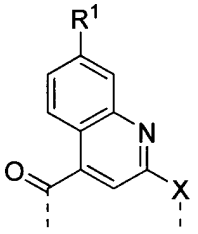
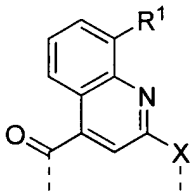
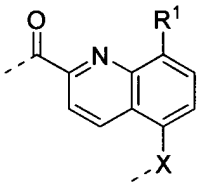
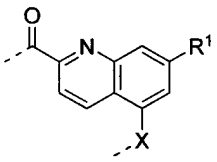
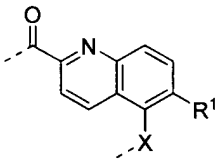
 **A429** (a15)	 **A430** (a15)	 **A431** (a15)	 **A432** (a15)
 **A433** (a15)	 **A434** (a15)	 **A435** (a15)	 **A436** (a15)
 **A437** (a15)	 **A438** (a15)	 **A439** (a15)	 **A440** (a15)
 **A441** (a15)	 **A442** (a15)	 **A443** (a15)	 **A444** (a15)
 **A445** (a15)	 **A446** (a15)	 **A447** (a15)	 **A448** (a15)

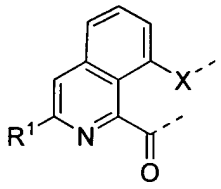
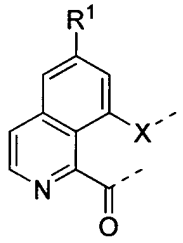
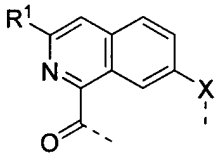
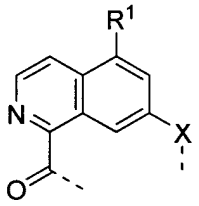
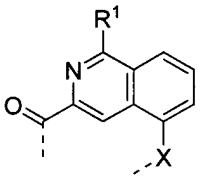
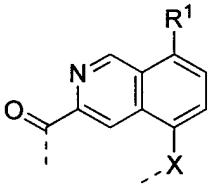
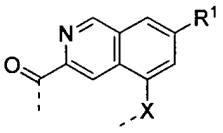
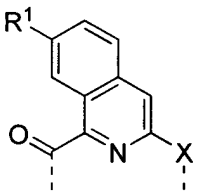
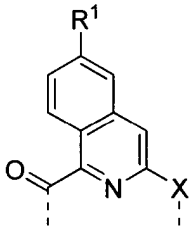
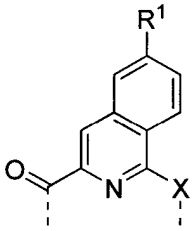
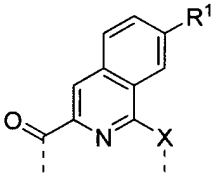
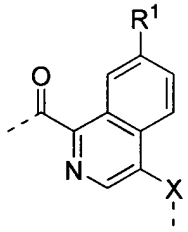
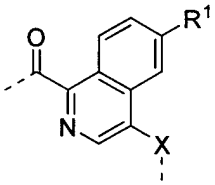
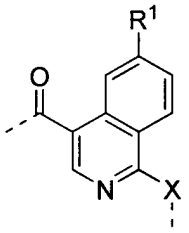
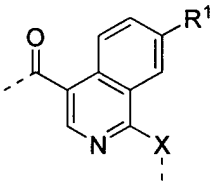
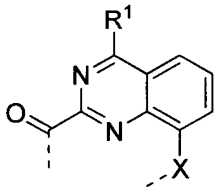
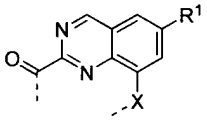
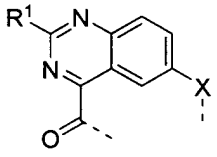
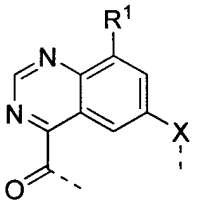
 **A449** (a15)	 **A450** (a16)	 **A451** (a16)	 **A452** (a16)
 **A453** (a16)	 **A454** (a16)	 **A455** (a16)	 **A456** (a16)
 **A457** (a16)	 **A458** (a16)	 **A459** (a16)	 **A460** (a17)
 **A461** (a17)	 **A462** (a17)	 **A463** (a17)	 **A464** (a17)
 **A465** (a17)	 **A466** (a17)	 **A467** (a17)	 **A468** (a17)

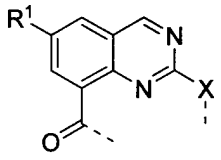
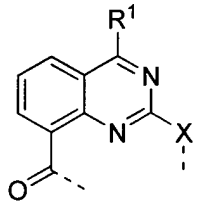
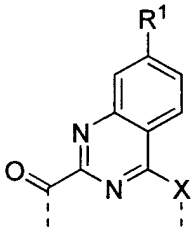
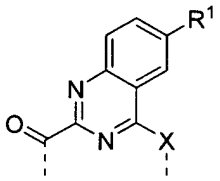
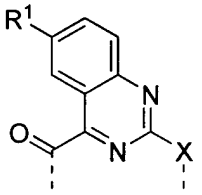
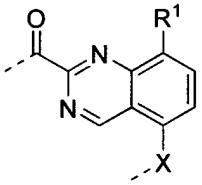
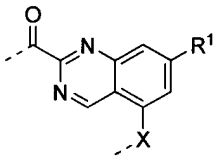
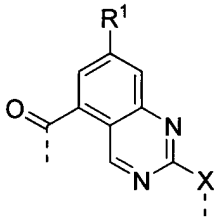
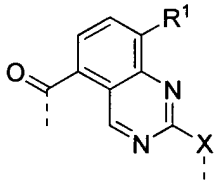
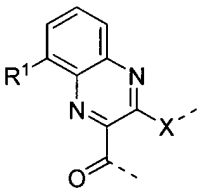
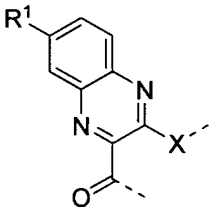
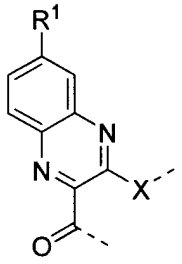
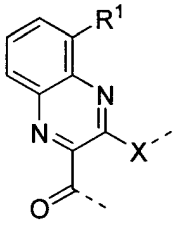
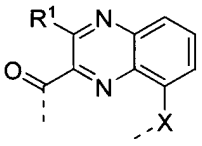
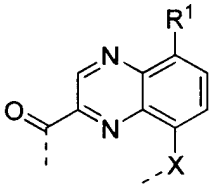
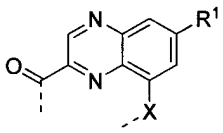
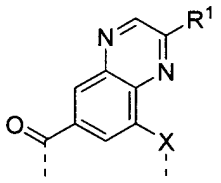
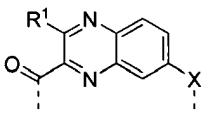
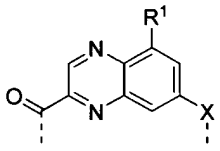
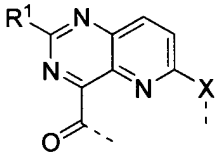
 **A469** (a17)	 **A470** (a17)	 **A471** (a17)	 **A472** (a17)
 **A473** (a17)	 **A474** (a17)	 **A475** (a17)	 **A476** (a17)
 **A477** (a17)	 **A478** (a17)	 **A479** (a17)	 **A480** (a17)
 **A481** (a17)	 **A482** (a17)	 **A483** (a17)	 **A484** (a17)
 **A485** (a17)	 **A486** (a17)	 **A487** (a17)	 **A488** (a17)

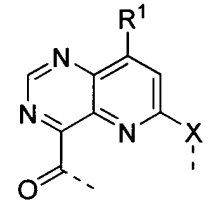
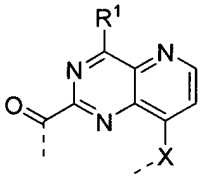
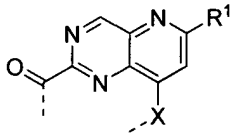
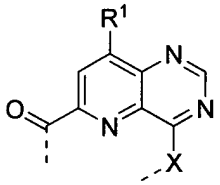
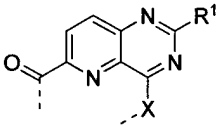
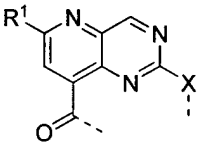
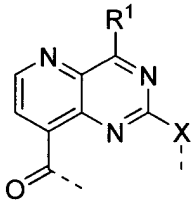
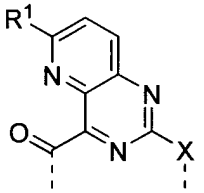
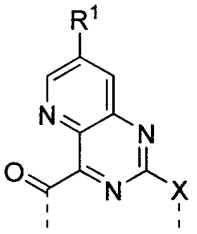
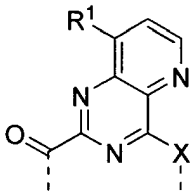
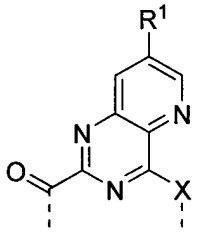
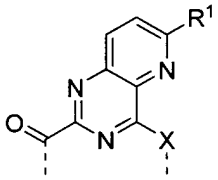
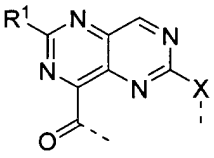
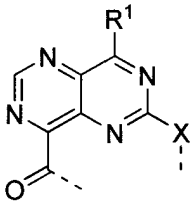
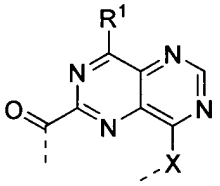
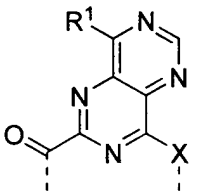
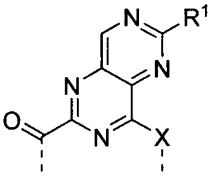
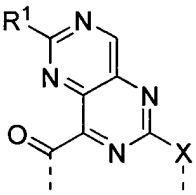
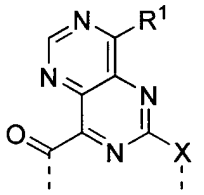
 **A489** (a17)	 **A490** (a17)	 **A491** (a17)	 **A492** (a17)
 **A493** (a17)	 **A494** (a17)	 **A495** (a17)	 **A496** (a17)
 **A497** (a17)	 **A498** (a17)	 **A499** (a17)	 **A500** (a17)
 **A501** (a17)	 **A502** (a17)	 **A503** (a17)	 **A504** (a17)
 **A505** (a17)	 **A506** (a17)	 **A507** (a17)	 **A508** (a17)

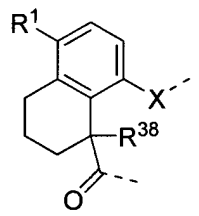
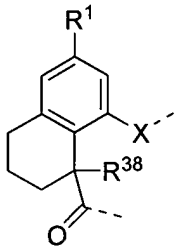
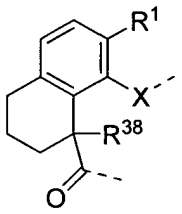
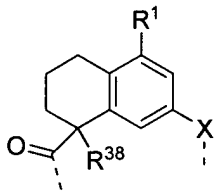
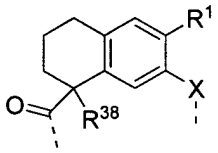
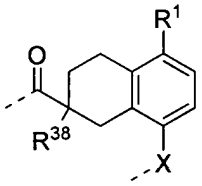
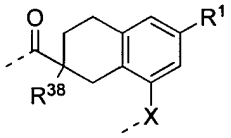
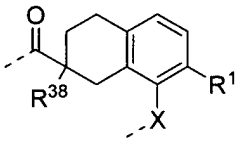
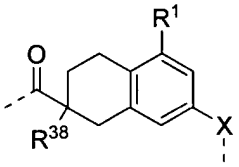
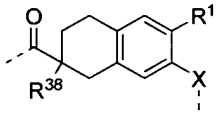
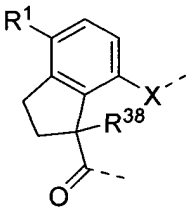
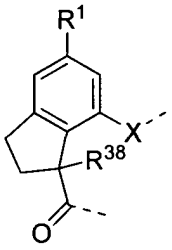
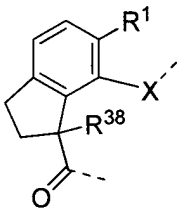
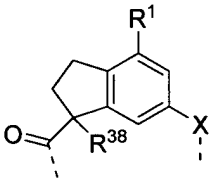
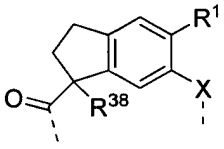
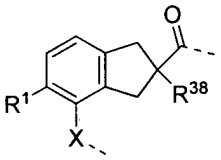
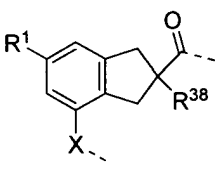
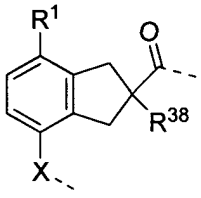
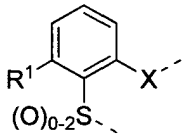
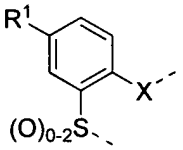
 **A509** (a17)	 **A510** (a17)	 **A511** (a17)	 **A512** (a17)
 **A513** (a17)	 **A514** (a17)	 **A515** (a17)	 **A516** (a18)
 **A517** (a18)	 **A518** (a18)	 **A519** (a18)	 **A520** (a18)
 **A521** (a18)	 **A522** (a18)	 **A523** (a18)	 **A524** (a18)
 **A525** (a18)	 **A526** (a18)	 **A527** (a18)	 **A528** (a18)

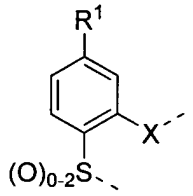
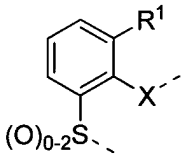
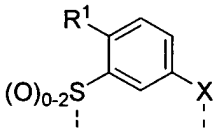
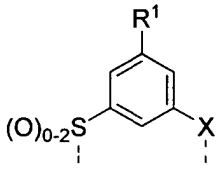
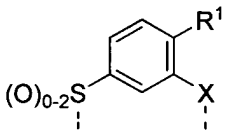
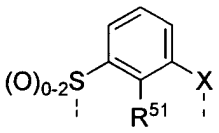
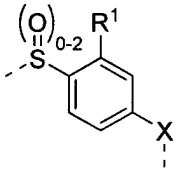
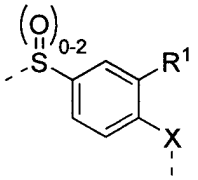
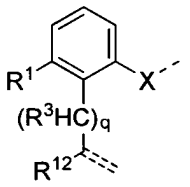
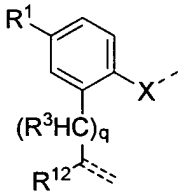
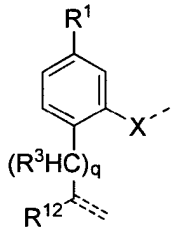
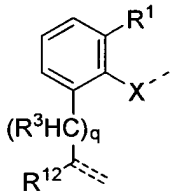
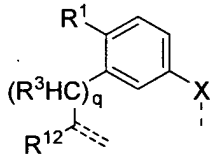
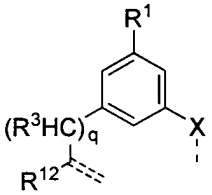
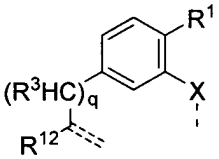
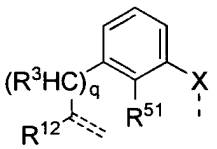
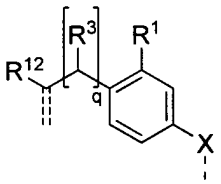
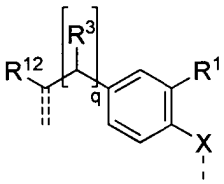
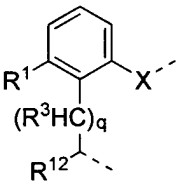
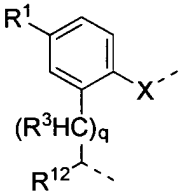
 **A529** (a18)	 **A530** (a18)	 **A531** (a18)	 **A532** (a18)
 **A533** (a18)	 **A534** (a18)	 **A535** (a18)	 **A536** (a18)
 **A537** (a18)	 **A538** (a18)	 **A539** (a18)	 **A540** (a18)
 **A541** (a18)	 **A542** (a18)	 **A543** (a18)	 **A544** (a18)
 **A545** (a18)	 **A546** (a18)	 **A547** (a18)	 **A548** (a18)

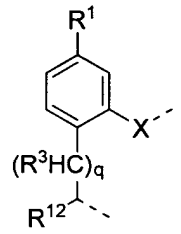
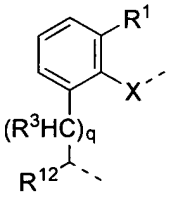
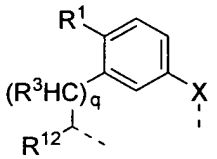
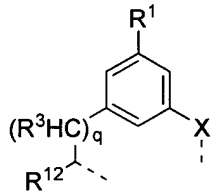
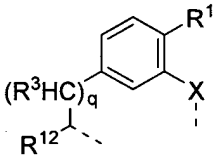
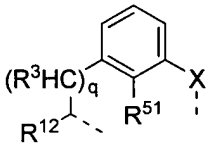
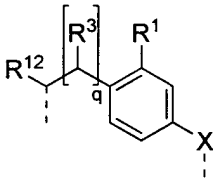
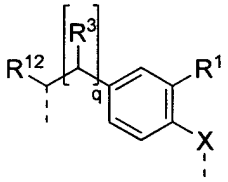
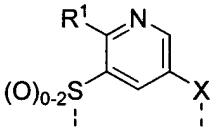
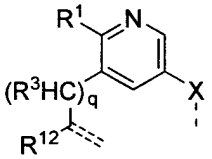
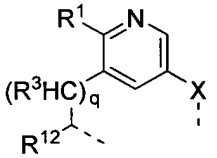
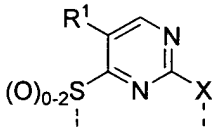
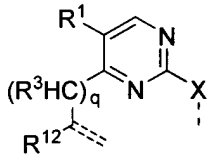
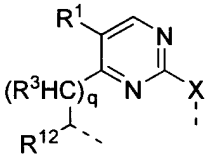
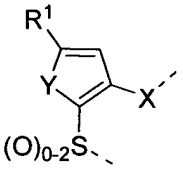
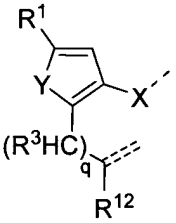
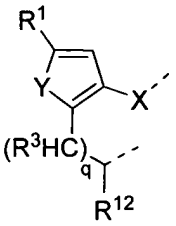
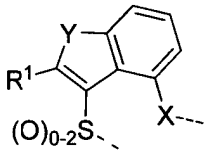
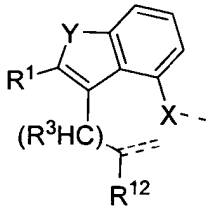
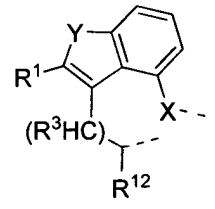
 **A549** (a19)	 **A550** (a19)	 **A551** (a19)	 **A552** (a19)
 **A553** (a19)	 **A554** (a19)	 **A555** (a19)	 **A556** (a19)
 **A557** (a19)	 **A558** (a19)	 **A559** (a19)	 **A560** (a19)
 **A561** (a19)	 **A562** (a19)	 **A563** (a19)	 **A564** (a19)
 **A565** (a20)	 **A566** (a20)	 **A567** (a20)	 **A568** (a20)

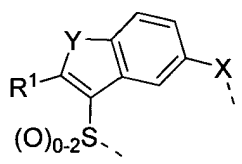
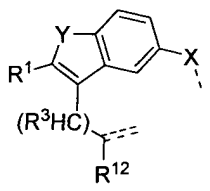
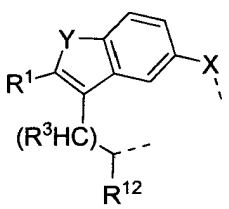
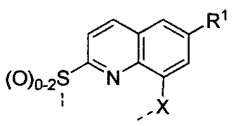
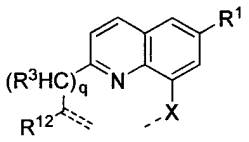
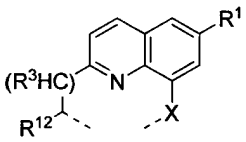
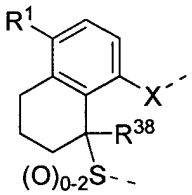
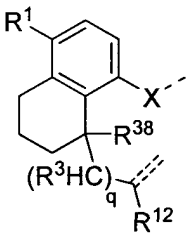
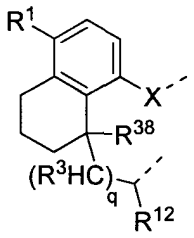
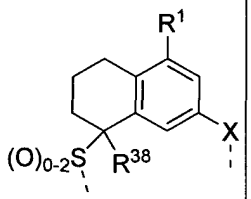
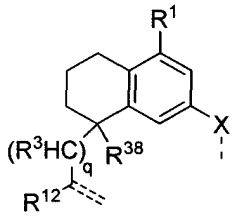
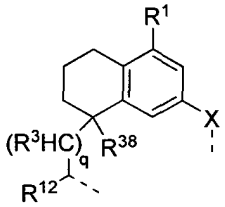
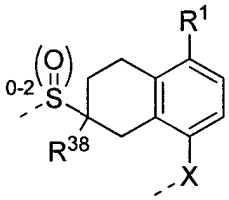
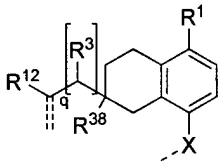
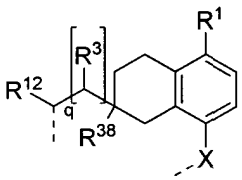
 **A569** (a20)	 **A570** (a20)	 **A571** (a20)	 **A572** (a20)
 **A573** (a20)	 **A574** (a20)	 **A575** (a20)	 **A576** (a20)
 **A577** (a20)	 **A578** (a21)	 **A579** (a21)	 **A580** (a21)
 **A581** (a21)	 **A582** (a21)	 **A583** (a21)	 **A584** (a21)
 **A585** (a21)	 **A586** (a21)	 **A587** (a21)	 **A588** (a22)

 **A589** (a22)	 **A590** (a22)	 **A591** (a22)	 **A592** (a22)
 **A593** (a22)	 **A594** (a22)	 **A595** (a22)	 **A596** (a22)
 **A597** (a22)	 **A598** (a22)	 **A599** (a22)	 **A600** (a22)
 **A601** (a22)	 **A602** (a23)	 **A603** (a23)	 **A604** (a23)
 **A605** (a23)	 **A606** (a23)	 **A607** (a23)	 **A608** (a23)

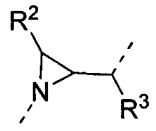
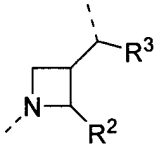
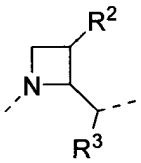
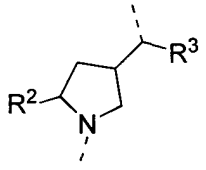
 **A609** (a24)	 **A610** (a24)	 **A611** (a24)	 **A612** (a24)
 **A613** (a24)	 **A614** (a24)	 **A615** (a24)	 **A616** (a24)
 **A617** (a24)	 **A618** (a24)	 **A619** (a25)	 **A620** (a25)
 **A621** (a25)	 **A622** (a25)	 **A623** (a25)	 **A624** (a25)
 **A625** (a25)	 **A626** (a25)	 **A627** (a1)	 **A628** (a1)

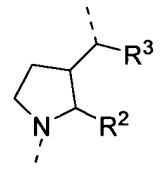
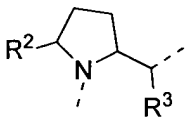
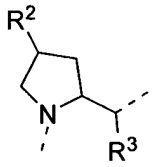
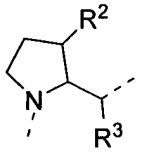
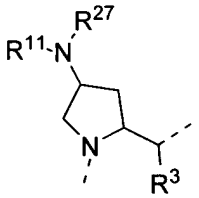
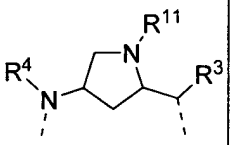
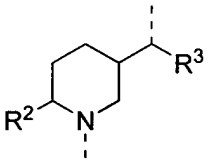
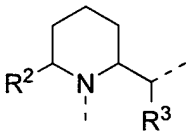
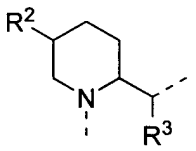
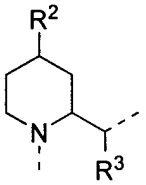
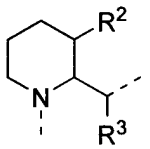
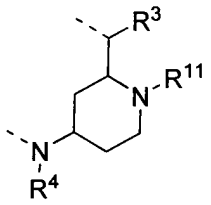
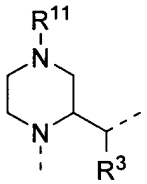
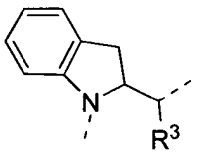
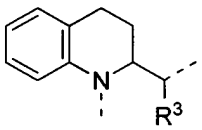
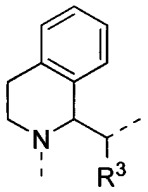
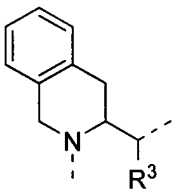
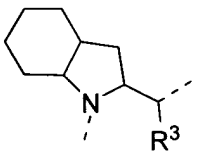
 **A629** (a1)	 **A630** (a1)	 **A631** (a1)	 **A632** (a1)
 **A633** (a1)	 **A634** (a1)	 **A635** (a1)	 **A636** (a1)
 **A637** (a1)	 **A638** (a1)	 **A639** (a1)	 **A640** (a1)
 **A641** (a1)	 **A642** (a1)	 **A643** (a1)	 **A644** (a1)
 **A645** (a1)	 **A646** (a1)	 **A647** (a1)	 **A648** (a1)

 **A649** (a1)	 **A650** (a1)	 **A651** (a1)	 **A652** (a1)
 **A653** (a1)	 **A654** (a1)	 **A655** (a1)	 **A656** (a1)
 **A657** (a2)	 **A658** (a2)	 **A659** (a2)	 **A660** (a4)
 **A661** (a4)	 **A662** (a4)	 **A663** (a7)	 **A664** (a7)
 **A665** (a7)	 **A666** (a10)	 **A667** (a10)	 **A668** (a10)

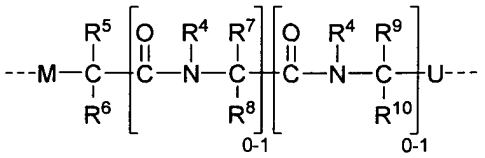
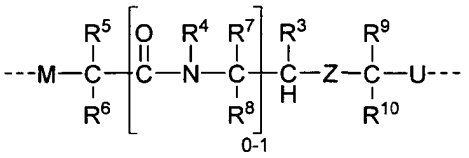
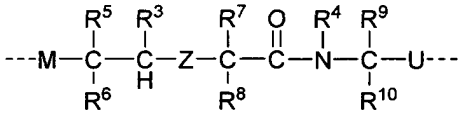
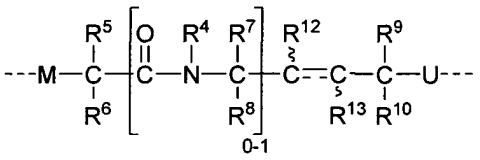
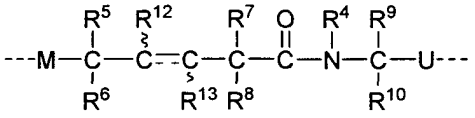
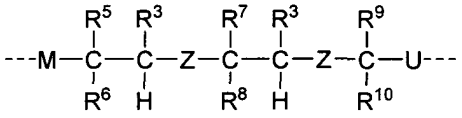
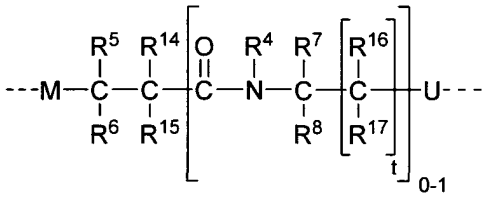
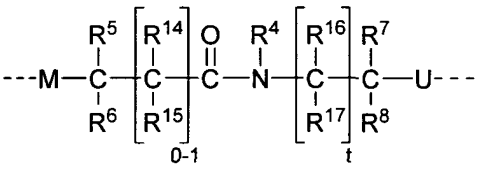
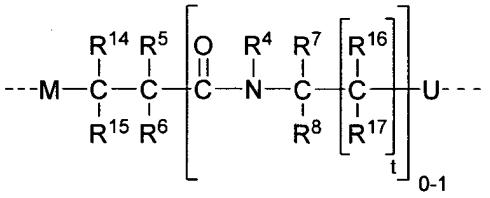
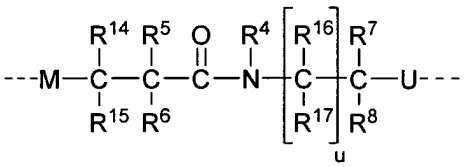
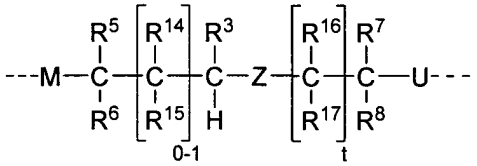
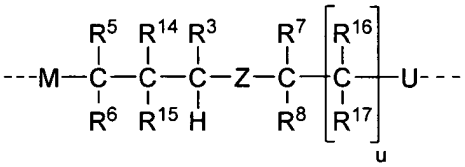
 **A669** (a10)	 **A670** (a10)	 **A671** (a10)	 **A672** (a18)
 **A673** (a18)	 **A674** (a18)	 **A675** (a24)	 **A676** (a24)
 **A677** (a24)	 **A678** (a24)	 **A679** (a24)	 **A680** (a24)
 **A681** (a24)	 **A682** (a24)	 **A683** (a24)	

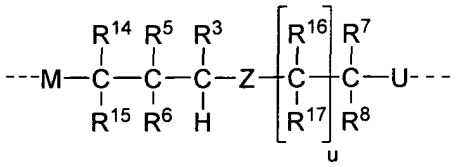
building block B is a bivalent radical selected from the group of

 **B1** (b1)	 **B2** (b2)	 **B3** (b2)	 **B4** (b3)

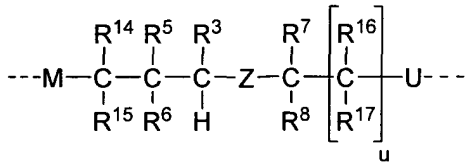
 **B5** (b3)	 **B6** (b3)	 **B7** (b3)	 **B8** (b3)
 **B9** (b3)	 **B10** (b3)	 **B11** (b4)	 **B12** (b4)
 **B13** (b4)	 **B14** (b4)	 **B15** (b4)	 **B16** (b4)
 **B17** (b5)	 **B18** (b8)	 **B19** (b10)	 **B20** (b11)
 **B21** (b11)		 **B22** (b12)	

building block C is a bivalent radical selected from the group of

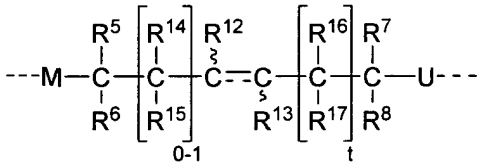
 C1	 C2
 C3	 C4
 C5	 C6
 C7	 C8
 C9	 C10
 C11	 C12



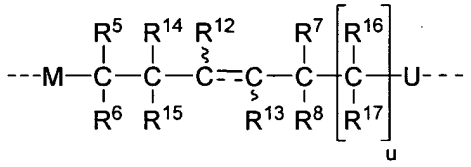
C13



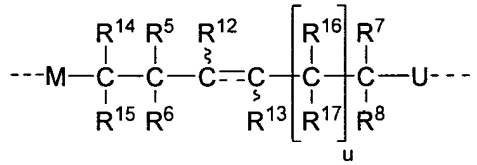
C14



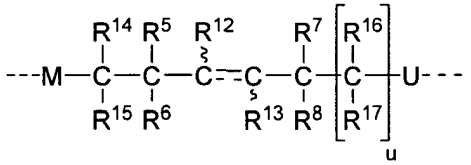
C15



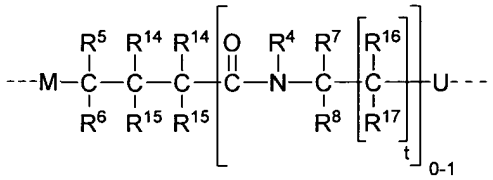
C16



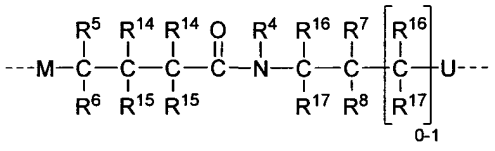
C17



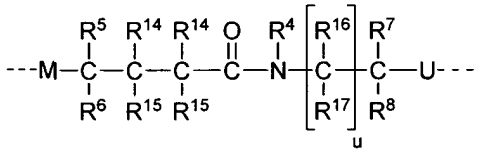
C18



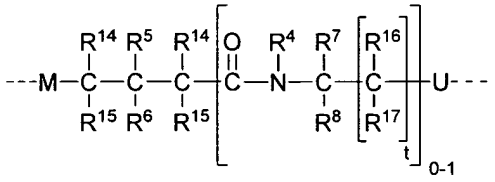
C19



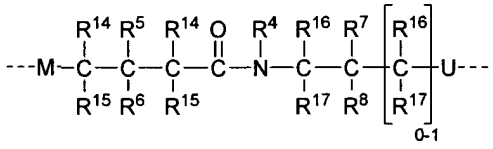
C20



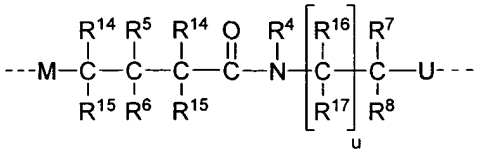
C21



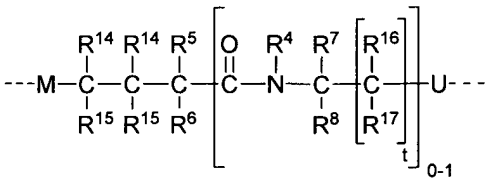
C22



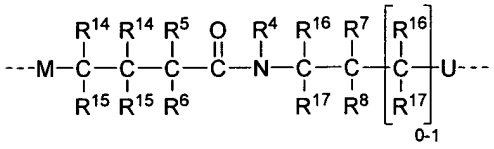
C23



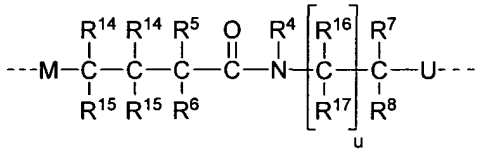
C24



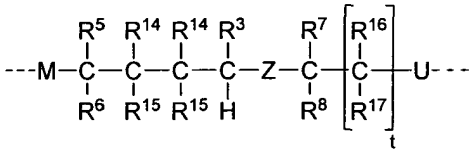
C25



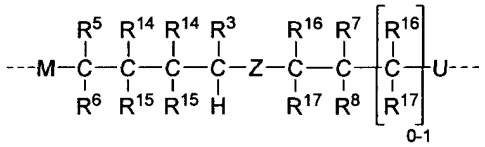
C26



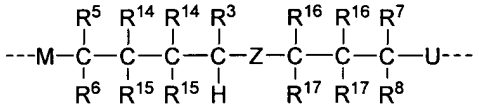
C27



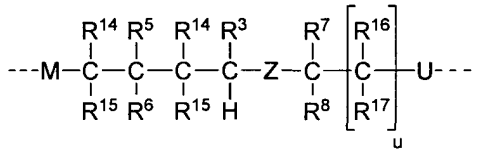
C28



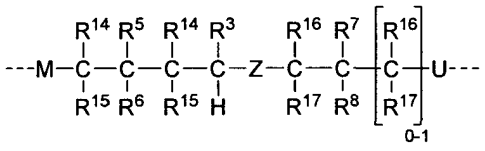
C29



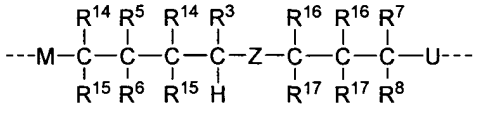
C30



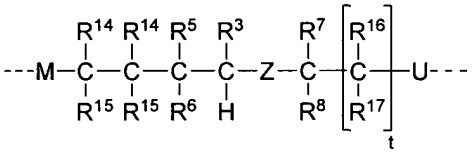
C31



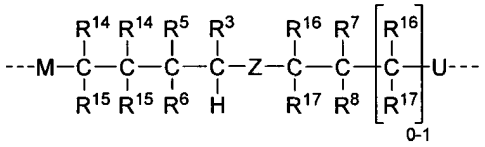
C32



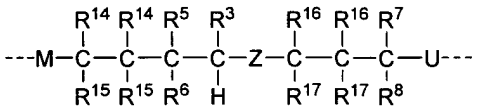
C33



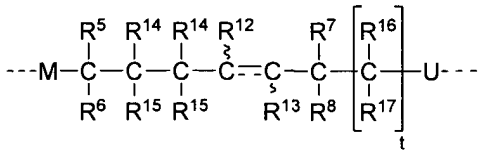
C34

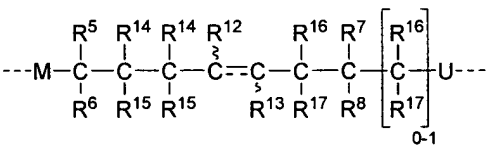


C35

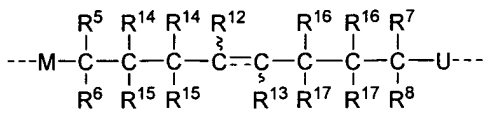


C36

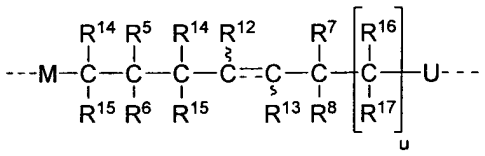




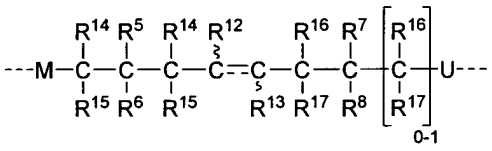
C37



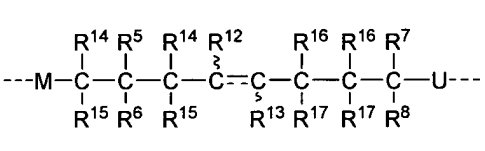
C38



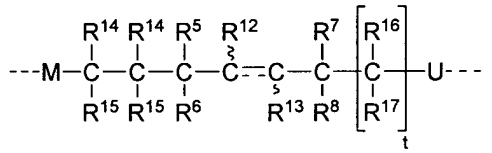
C39



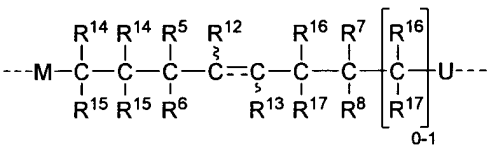
C40



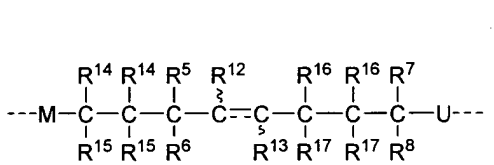
C41



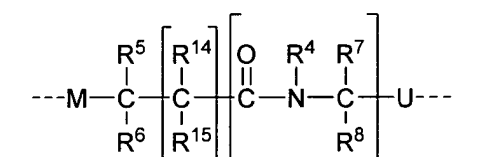
C42



C43



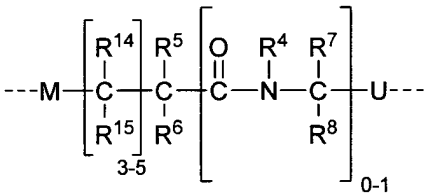
C44



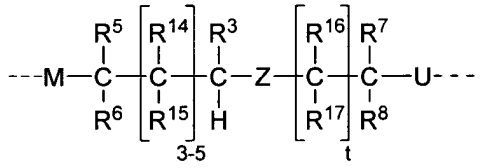
C45

C46

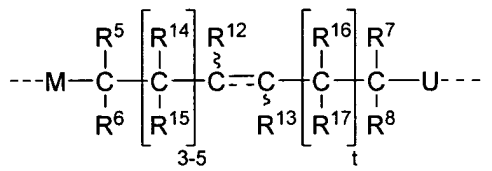
C47



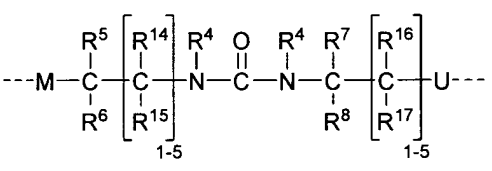
C48

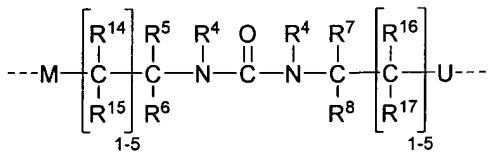


C49

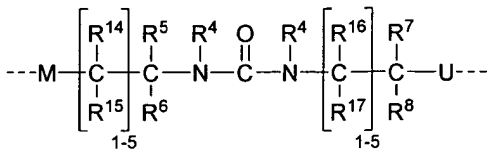


C50

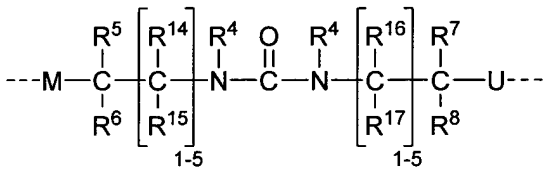




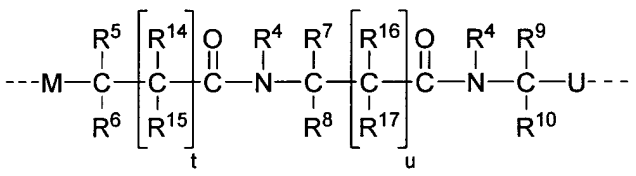
C51



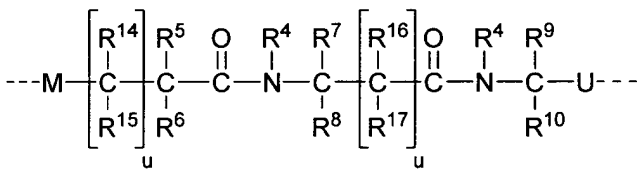
C52



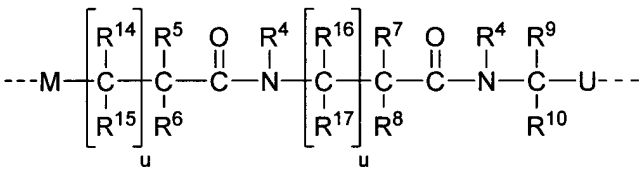
C53



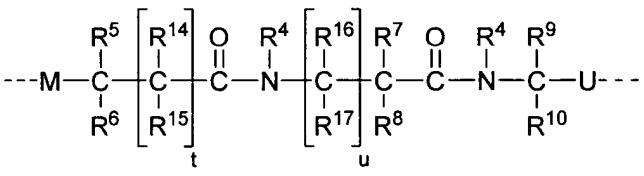
C54



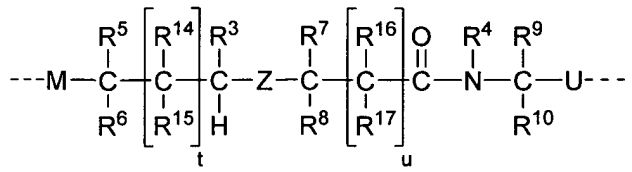
C55



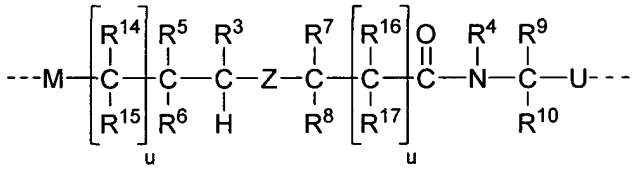
C56



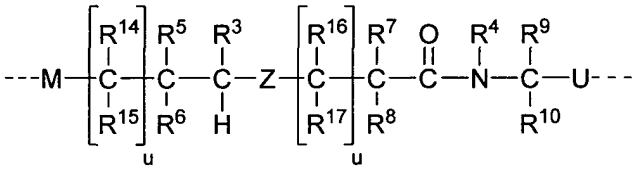
C57



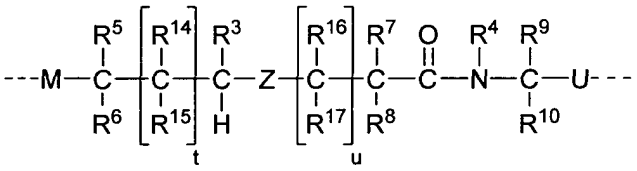
C58



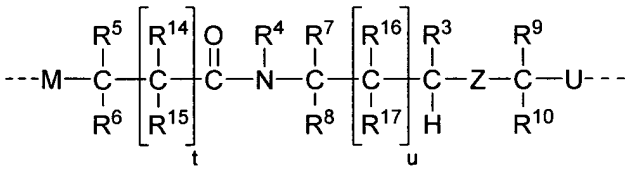
C59



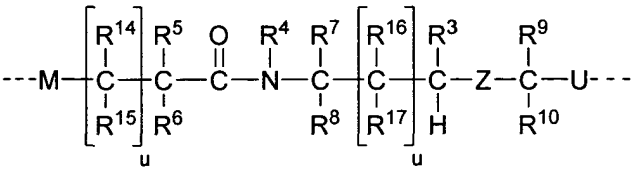
C60



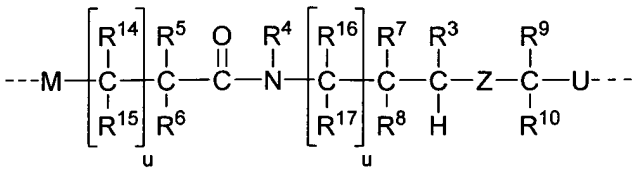
C61



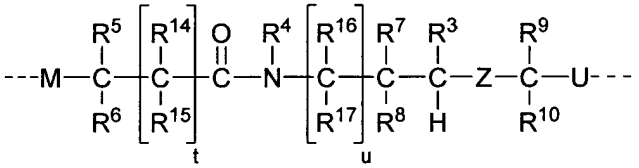
C62



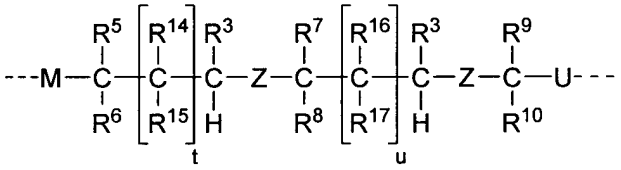
C63



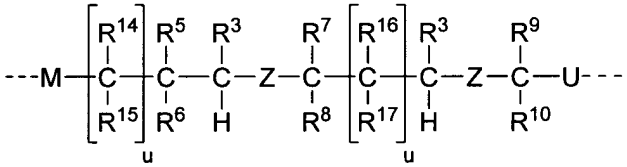
C64



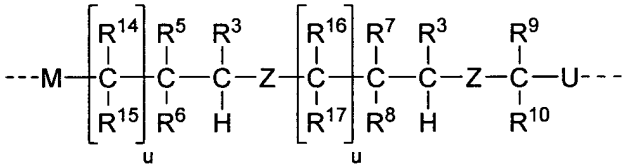
C65



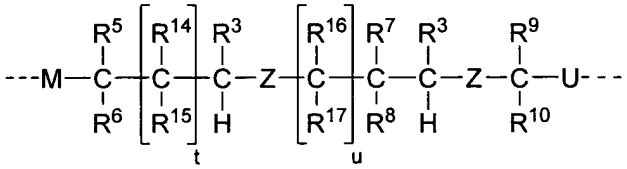
C66



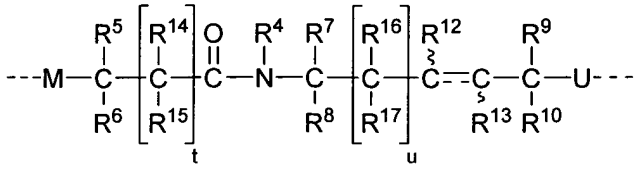
C67



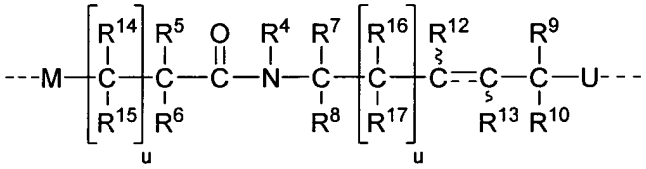
C68



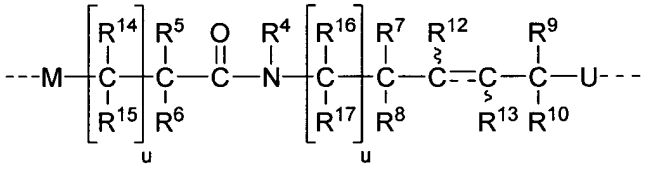
C69



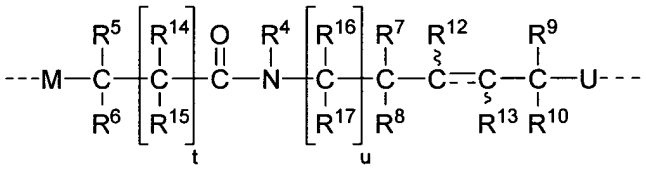
C70



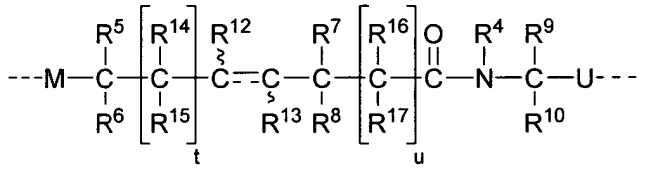
C71



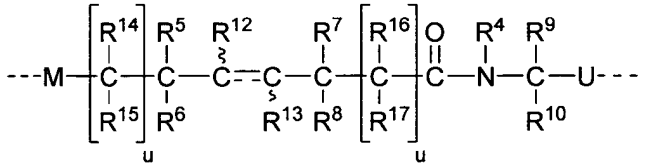
C72



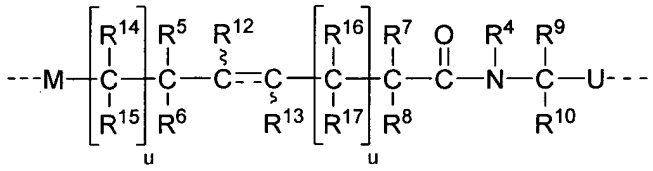
C73



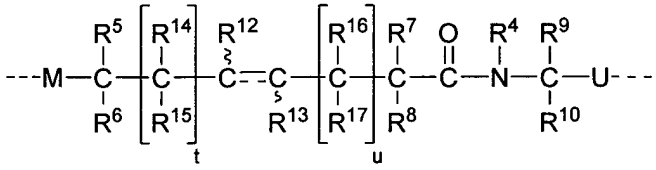
C74



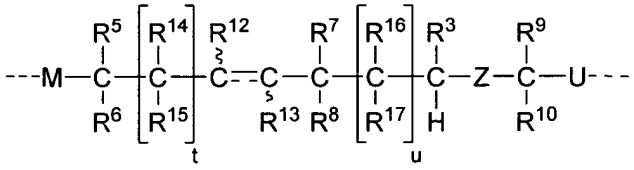
C75



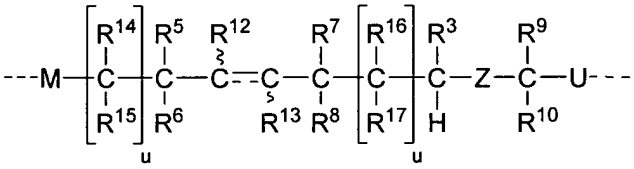
C76



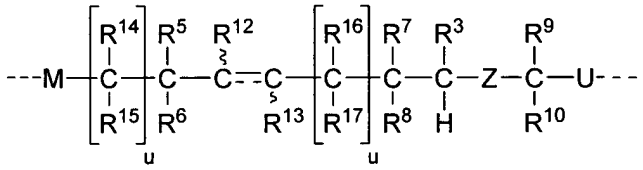
C77



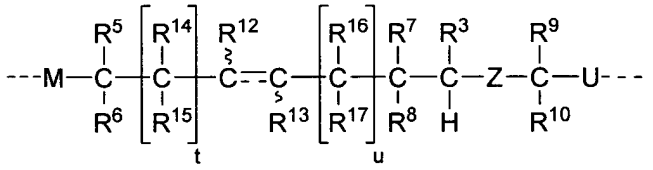
C78



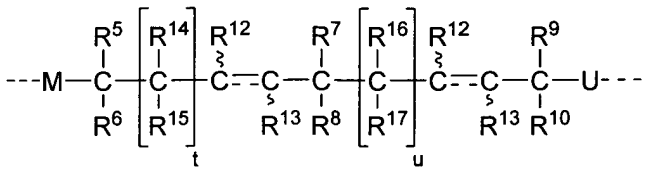
C79



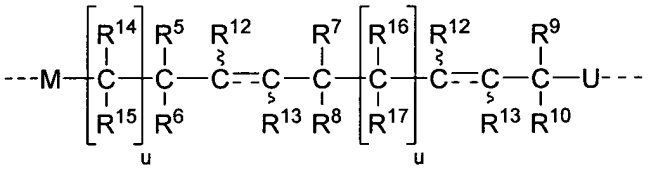
C80



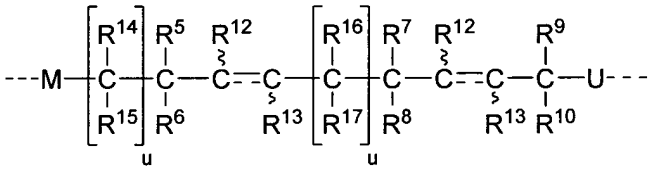
C81



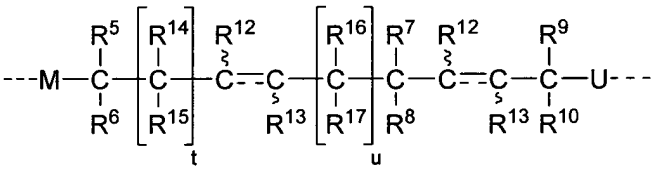
C82



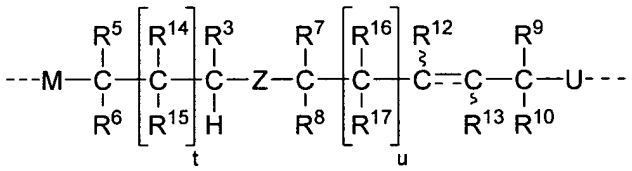
C83



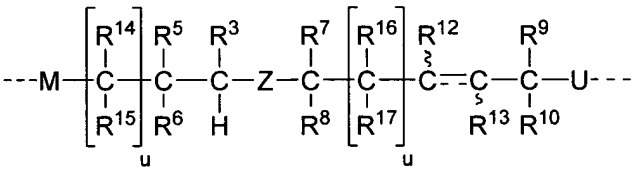
C84



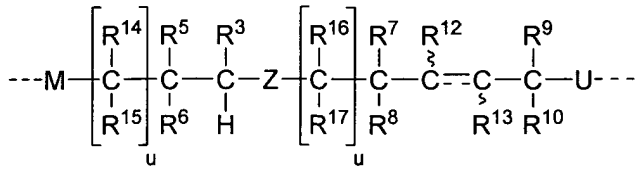
C85



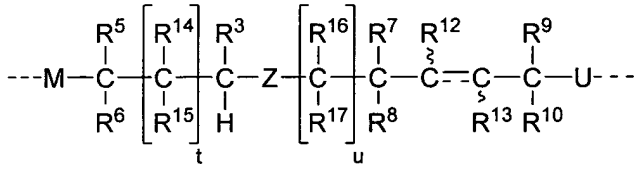
C86



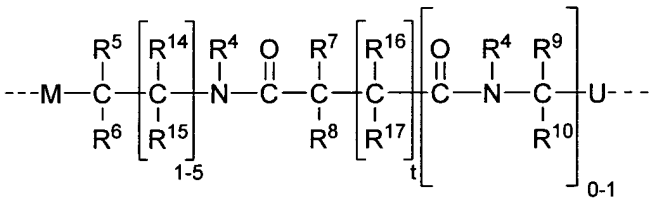
C87



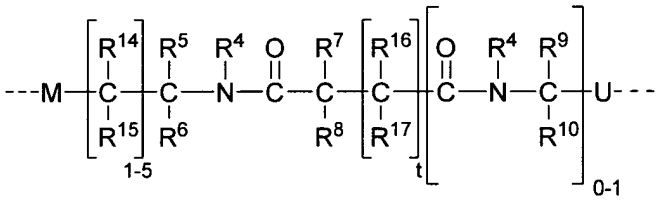
C88



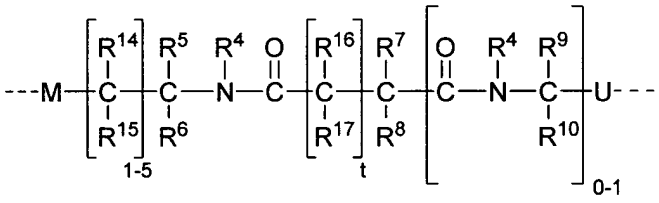
C89



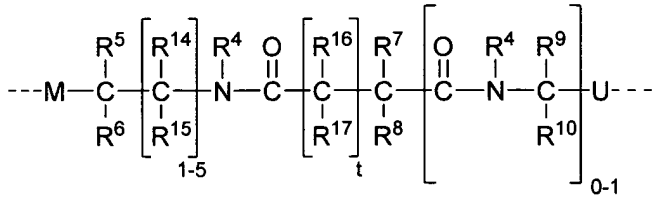
C90



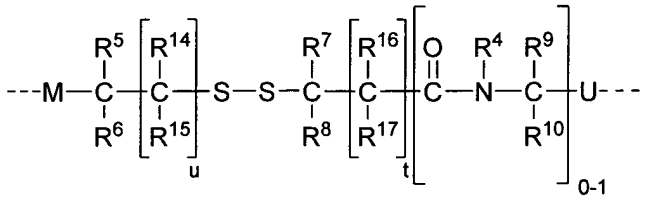
C91



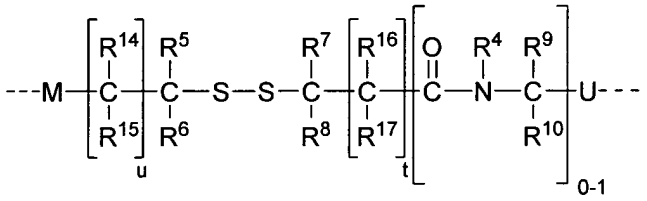
C92



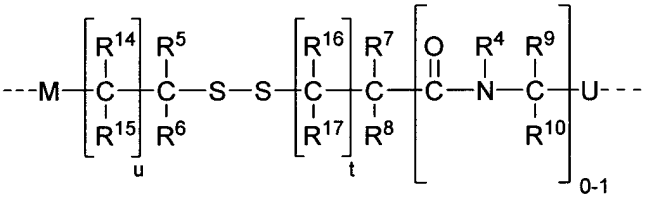
C93



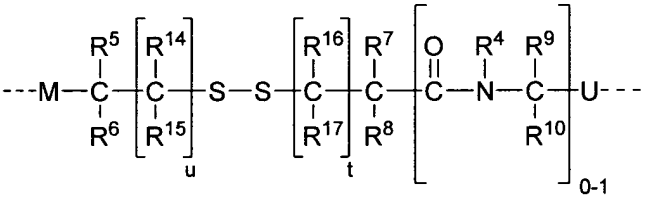
C94



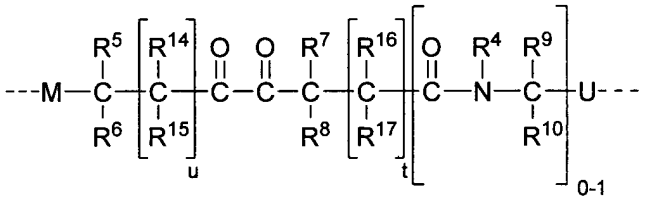
C95



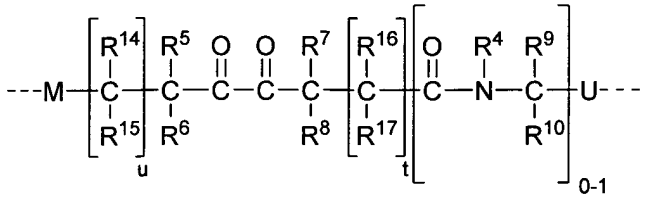
C96



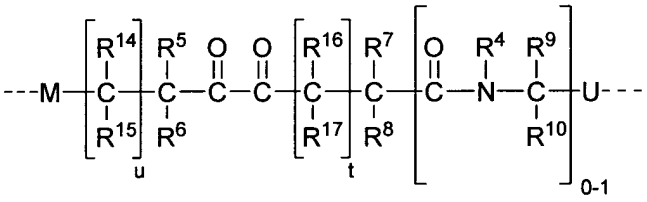
C97



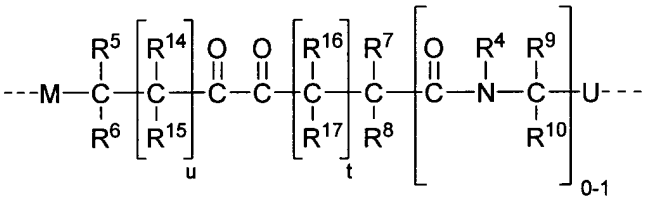
C98



C99



C100



C101

and wherein further

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

R^2 is H; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl;

$-(CR^{18}R^{19})_qOR^{20}$; $-(CR^{18}R^{19})_qSR^{20}$; $-(CR^{18}R^{19})_qNR^4R^{11}$; $-(CR^{18}R^{19})_qOCONR^4R^{11}$; $-(CR^{18}R^{19})_qOCOOR^{21}$; $-(CR^{18}R^{19})_qNR^4COOR^{21}$; $-(CR^{18}R^{19})_qNR^4COR^{22}$; $-(CR^{18}R^{19})_qNR^4CONR^4R^{11}$; $-(CR^{18}R^{19})_qNR^4SO_2R^{23}$; $-(CR^{18}R^{19})_qNR^4SO_2NR^4R^{11}$; $-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{11}$; $-(CR^{18}R^{19})_qSO_2NR^4R^{11}$; $-(CR^{18}R^{19})_qPO(OR^{21})_2$; $-(CR^{18}R^{19})_qCOR^{22}$; $-(CR^{18}R^{19})_qSO_2R^{23}$; $-(CR^{18}R^{19})_qR^{24}$; $-(CR^{18}R^{19})_qR^{25}$; or $-(CR^{18}R^{19})_qR^{26}$;

R^3 is H; CF_3; alkyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; or heteroarylalkyl;

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

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

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

R^{11} is H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; a suitable protecting group; $-(CR^{18}R^{19})_rOR^{20}$; $-(CR^{18}R^{19})_rSR^{20}$; $-(CR^{18}R^{19})_rNR^4R^{27}$; $-(CR^{18}R^{19})_rOCONR^4R^{27}$; $-(CR^{18}R^{19})_rOCOOR^{21}$; $-(CR^{18}R^{19})_rNR^4COOR^{21}$; $-(CR^{18}R^{19})_rNR^4CONR^4R^{27}$; $-(CR^{18}R^{19})_rNR^4SO_2R^{23}$; $-(CR^{18}R^{19})_rNR^4SO_2NR^4R^{27}$;

$-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{27}$; $-(CR^{18}R^{19})_qCOR^{22}$; $-(CR^{18}R^{19})_qSO_2R^{23}$; $-(CR^{18}R^{19})_qSO_2NR^4R^{27}$; $-(CR^{18}R^{19})_qR^{24}$; $-(CR^{18}R^{19})_sR^{25}$; $-(CR^{18}R^{19})_qR^{26}$; or $-(CR^{18}R^{19})_qR^{31}$;

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

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

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

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

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

R^{20} is H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{29}R^{30})_rOR^{31}$; $-(CR^{29}R^{30})_rSR^{31}$; $-(CR^{29}R^{30})_rNR^{28}R^{31}$; $-(CR^{29}R^{30})_rOCONR^{28}R^{31}$; $-(CR^{29}R^{30})_rNR^{28}COOR^{21}$; $-(CR^{29}R^{30})_rNR^{28}COR^{31}$; $-(CR^{29}R^{30})_rNR^{28}CONR^{28}R^{31}$;

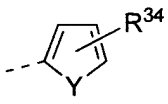
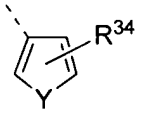
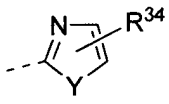
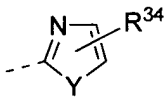
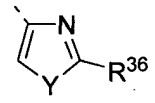
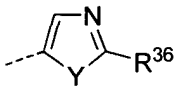
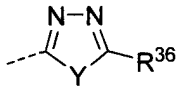
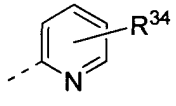
$-(CR^{29}R^{30})_rNR^{28}SO_2R^{23}$;$-(CR^{29}R^{30})_rNR^{28}SO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_qSO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOR^{31}$; $-(CR^{29}R^{30})_qSO_2R^{23}$; $-(CR^{29}R^{30})_qR^{24}$; $-(CR^{29}R^{30})_qR^{25}$; $-(CR^{29}R^{30})_qR^{26}$; or $-(CR^{29}R^{30})_qR^{31}$;

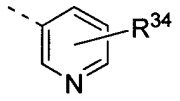
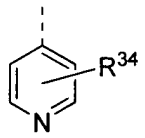
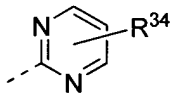
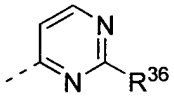
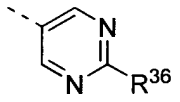
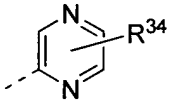
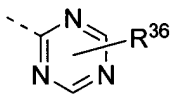
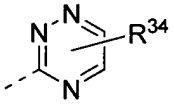
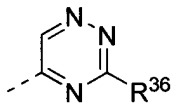
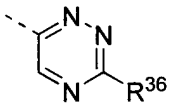
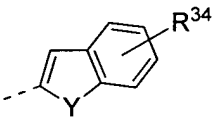
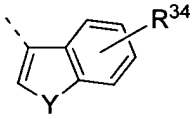
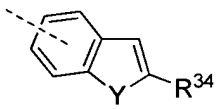
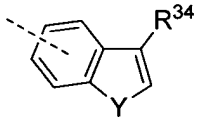
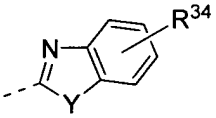
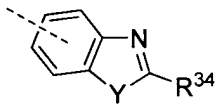
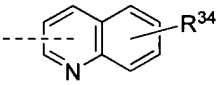
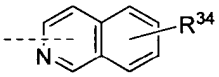
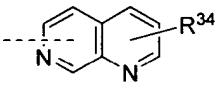
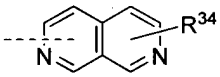
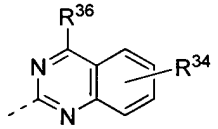
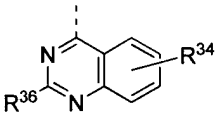
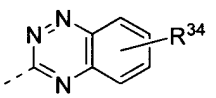
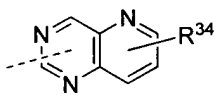
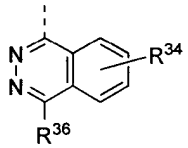
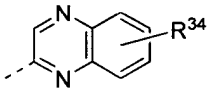
R^{21} is H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; or a suitable *O*-protecting group;

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

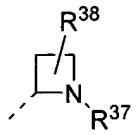
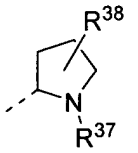
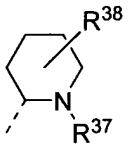
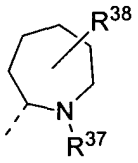
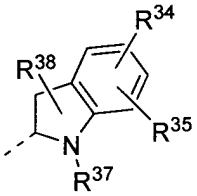
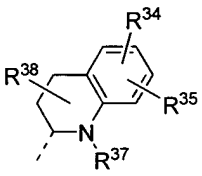
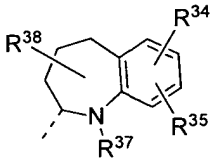
R^{23} is H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; or $-(CR^{32}R^{33})_tR^{24}$;

R^{24} is aryl; heteroaryl; $-C_6H_2R^{34}R^{35}R^{31}$; or a group of one of the formulae

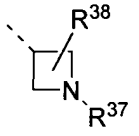
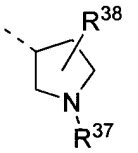
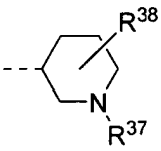
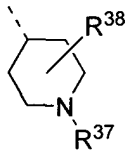
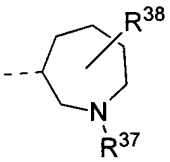
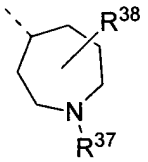
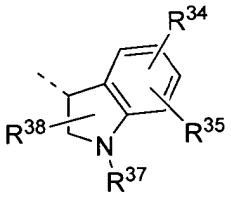
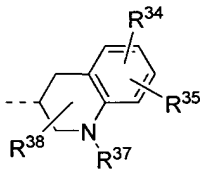
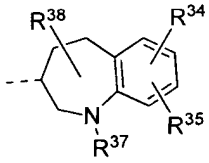
 **H1**	 **H2**	 **H3**	 **H4**
 **H5**	 **H6**	 **H7**	 **H8**

 H9	 H10	 H11	 H12
 H13	 H14	 H15	 H16
 H17	 H18	 H19	 H20
 H21	 H22	 H23	 H24
 H25	 H26	 H27	 H28
 H29	 H30	 H31	 H32
 H33		 H34	

R^{25} is a group of one of the formulae

 H35	 H36	 H37	 H38
 H39	 H40	 H41	

R^{26} is a group of one of the formulae

 H42	 H43	 H44	 H45
 H46	 H47	 H48	 H49
 H50			

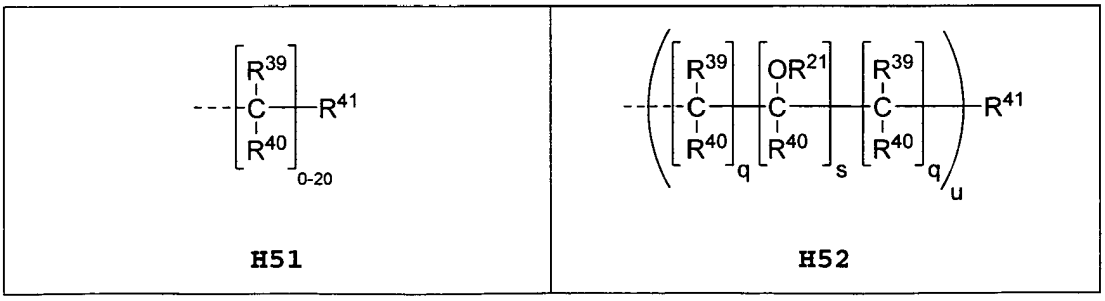
R^{27} is H; alkyl; lower alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; a suitable protecting group; or $-(CR^{29}R^{30})_qR^{24}$;

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

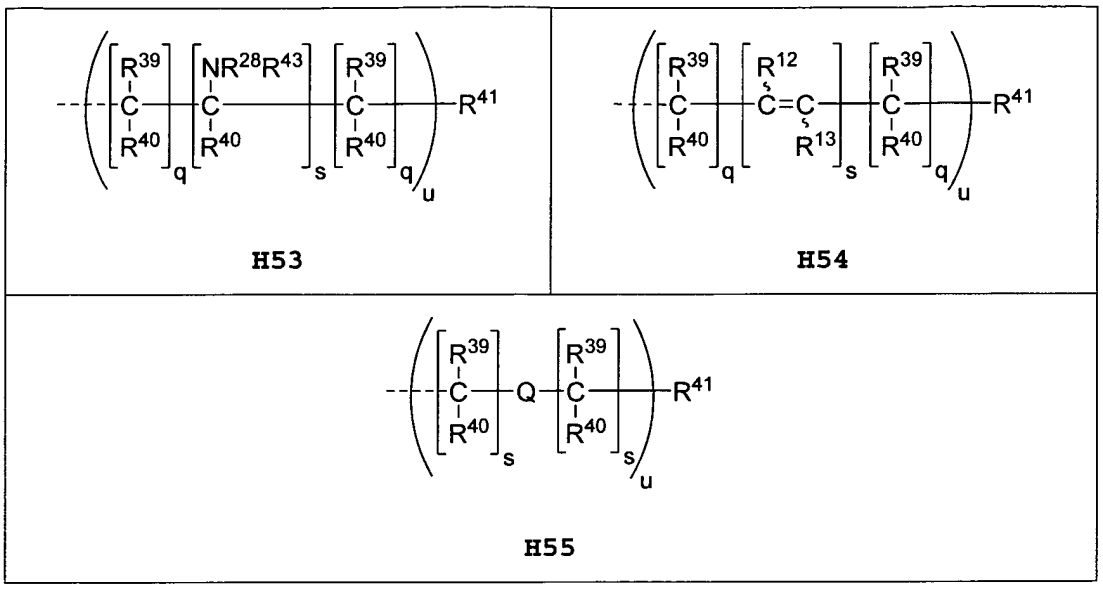
R^{29} is H; F; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{32}R^{33})_sOR^{31}$; $-(CR^{32}R^{33})_sSR^{31}$; $-(CR^{32}R^{33})_sNR^{28}R^{31}$; $-(CR^{32}R^{33})_sOCONR^{28}R^{31}$; $-(CR^{32}R^{33})_sOCOOR^{21}$; $-(CR^{32}R^{33})_sNR^{28}COOR^{21}$;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

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

R^{31} is H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; or a group of one of the formulae



H51 **H52**



H53 H54

H55

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

R^{34} and R^{35} are independently defined as H; F; Cl; CF_3; OCF_3; $OCHF_2$; NO_2; CN; alkyl; alkenyl; alkynyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{29}R^{30})_qOR^{31}$; $-(CR^{29}R^{30})_qSR^{31}$; $-(CR^{29}R^{30})_qNR^{28}R^{31}$; $-(CR^{29}R^{30})_qOCONR^{28}R^{31}$; $-(CR^{29}R^{30})_qNR^{28}COOR^{21}$; $-(CR^{29}R^{30})_qNR^{28}COR^{31}$; $-(CR^{29}R^{30})_qNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_qNR^{28}SO_2R^{23}$; $-(CR^{29}R^{30})_qNR^{28}SO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_qSO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOR^{31}$; $-(CR^{29}R^{30})_qSO_2R^{23}$; or $-(CR^{29}R^{30})_qR^{31}$;

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

R^{37} is H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; a suitable *N*-protecting group; $-(CR^{29}R^{30})_rOR^{31}$; $-(CR^{29}R^{30})_rSR^{31}$; $-(CR^{29}R^{30})_rNR^{28}R^{31}$; $-(CR^{29}R^{30})_rOCONR^{28}R^{31}$; $-(CR^{29}R^{30})_rNR^{28}COOR^{21}$; $-(CR^{29}R^{30})_rNR^{28}COR^{31}$; $-(CR^{29}R^{30})_rNR^{28}CONR^{28}R^{31}$; $-(CR^{29}R^{30})_rNR^{28}SO_2R^{23}$;

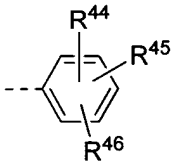
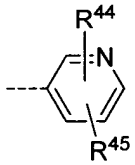
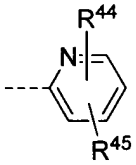
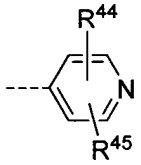
$-(CR^{29}R^{30})_rNR^{28}SO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_rSO_2NR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOR^{31}$; $-(CR^{29}R^{30})_qSO_2R^{23}$; or $-(CR^{29}R^{30})_qR^{31}$;

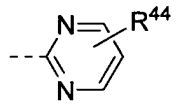
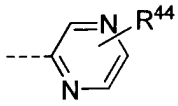
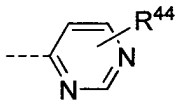
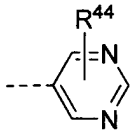
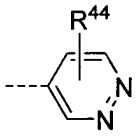
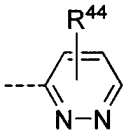
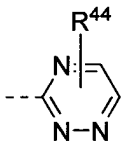
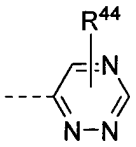
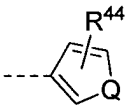
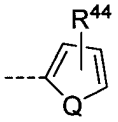
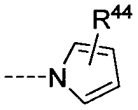
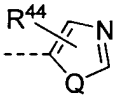
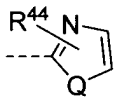
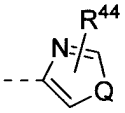
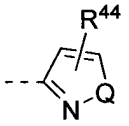
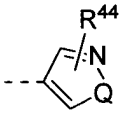
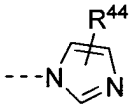
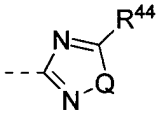
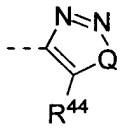
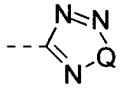
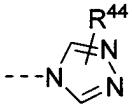
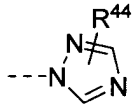
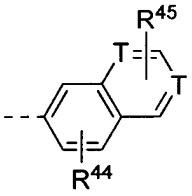
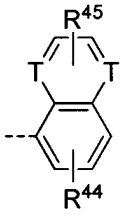
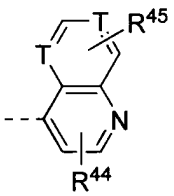
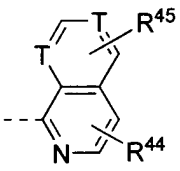
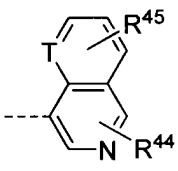
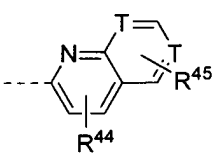
R^{38} is H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{29}R^{30})_qOR^{31}$; $-(CR^{29}R^{30})_qSR^{31}$; $-(CR^{29}R^{30})_qNR^{28}R^{31}$; $-(CR^{29}R^{30})_qNR^{28}COOR^{21}$; $-(CR^{29}R^{30})_qNR^{28}COR^{31}$; $-(CR^{29}R^{30})_qNR^{28}CONR^{28}R^{31}$;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

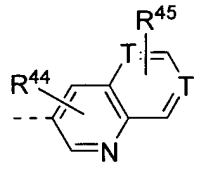
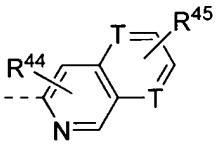
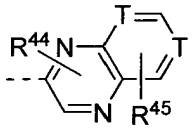
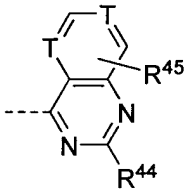
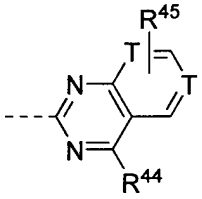
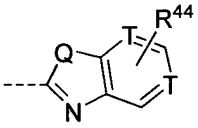
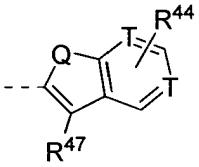
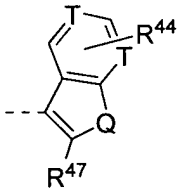
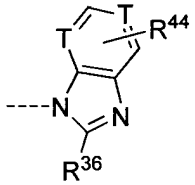
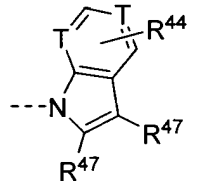
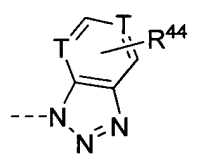
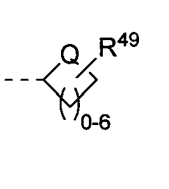
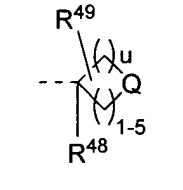
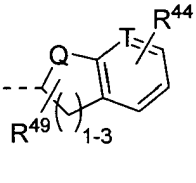
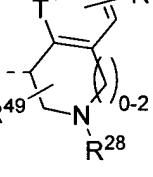
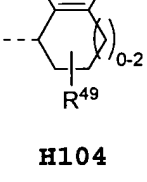
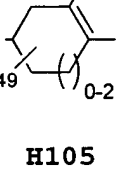
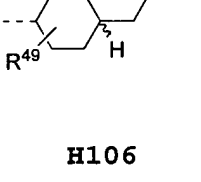
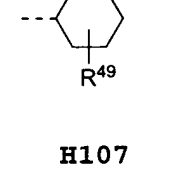
R^{39} is H; F; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-(CR^{32}R^{33})_uOR^{21}$; $-(CR^{32}R^{33})_uNR^{28}R^{43}$; $-(CR^{32}R^{33})_tCOOR^{21}$; or $-(CR^{32}R^{33})_tCONR^{28}R^{43}$;

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

R^{41} is H; CF_3; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; $-OR^{21}$; $-NR^{28}R^{43}$; $-NR^{28}COR^{23}$; $-NR^{28}COOR^{21}$; $-NR^{28}SO_2R^{23}$; $-NR^{28}CONR^{28}R^{43}$; $-COOR^{21}$; $-CONR^{28}R^{43}$; $-C(=NR^{43})NR^{28}R^{43}$; $-NR^{28}C(=NR^{43})NR^{28}R^{43}$; 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

R^{42} is H; alkyl; alkenyl; cycloalkyl; cycloheteroalkyl; aryl; heteroaryl; $-(CR^{23}R^{33})_sOR^{21}$; $-(CR^{23}R^{33})_sNR^4R^{43}$; $-(CR^{23}R^{33})_qCOOR^{21}$; or $-(CR^{23}R^{33})_qCONR^4R^{43}$;

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

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

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

R^{48} is H; F; CF_3; alkyl; alkenyl; cycloalkyl; cycloheteroalkyl; aryl; heteroaryl; $-(CR^{23}R^{33})_tOR^{21}$; $-(CR^{23}R^{33})_tNR^{28}R^{43}$; $-(CR^{23}R^{33})_tCOOR^{21}$; or $-(CR^{23}R^{33})_tCONR^{21}R^{43}$;

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

R^{51} is H; F; Cl; CF_3; OCF_3; or lower alkyl;

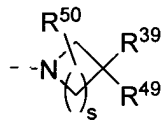
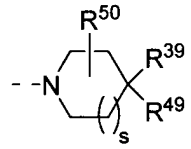
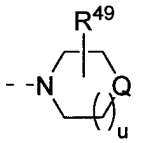
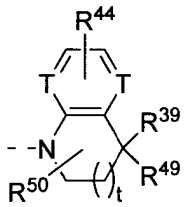
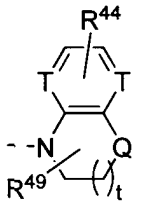
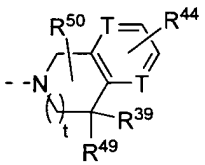
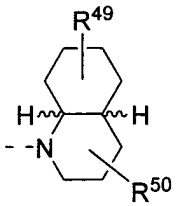
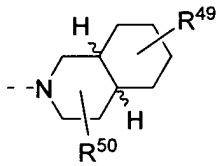
R^{52} is H; F; Cl; CF_3; OCF_3; $OCHF_2$; NO_2; CN; lower alkyl; lower alkenyl; lower alkynyl; lower cycloalkyl; lower

heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; or lower heteroarylalkyl;

R^{53} is CF_3; OCF_3; CN; lower alkyl; lower cycloalkyl; aryl; lower alkoxy; or aryloxy;

taken together (R^4 and R^{11}); (R^4 and R^{27}); (R^5 and R^6); (R^5 and R^7); (R^5 and R^9); (R^5 and R^{14}); (R^5 and R^{16}); (R^7 and R^8); (R^7 and R^9); (R^7 and R^{16}); (R^9 and R^{10}); (R^{14} and R^{15}); (R^{16} and R^{17}); (R^{18} and R^{19}); (R^{27} and R^{28}); (R^{28} and R^{31}); (R^{28} and R^{43}); (R^{29} and R^{30}); (R^{32} and R^{33}); (R^{34} and R^{35}); (R^{37} and R^{38}); (R^{39} and R^{40}); (R^{39} and R^{41}); (R^{39} and R^{49}); (R^{42} and R^{43}); (R^{44} and R^{45}); or (R^{44} and R^{46}) can form optionally substituted cycloalkyl or heterocycloalkyl moieties;

in addition, the structural elements $-NR^4R^{11}$; $-NR^{11}R^{27}$; $-NR^{27}R^{28}$; $-NR^{28}R^{31}$ or $-NR^{28}R^{43}$ can form one of the groups of the formulae

 **H111**	 **H112**	 **H113**	 **H114**
 **H115**	 **H116**	 **H117**	 **H118**

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

Y is O; S; or NR^4;

Q is O; S; or NR^{28};

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

q is an integer of 0-4;
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;

and all possible stereoisomers of such compounds;
or salts, solvates, clathrates, *N*-oxides, isotopically enriched or enantiomerically enriched versions thereof.

2. Compounds according to claim 1 wherein

the building block of type **A** is selected from **A1** to **A626**;
the building block of type **B** is selected from **B1** to **B21**;
the building block of type **C** is selected from **C1** to **C101**;
and wherein
M is $-N(R^4)-$;
and all possible stereoisomers of such compounds;
or pharmaceutical acceptable salts thereof.

3. Compounds according to claim 1 or 2 wherein

the building block of type **A** is selected from
A1(a1); **A2**(a1); **A3**(a1); **A4**(a1); **A5**(a1); **A6**(a1); **A7**(a1); **A9**(a1); **A10**(a1); **A73**(a2); **A80**(a2); **A170**(a4); **A171**(a4); **A209**(a7); **A210**(a7); **A240**(a10); **A241**(a10); **A242**(a10); **A243**(a10); **A272**(a10); **A530**(a18); **A531**(a18); **A532**(a18); **A533**(a18); **A609**(a24); **A610**(a24); **A611**(a24); **A612**(a24); **A613**(a24); **A614**(a24); **A615**(a24); **A631**(a1); **A632**(a1); **A633**(a1); **A641**(a1); **A642**(a1); **A643**(a1); **A651**(a1); **A652**(a1); or **A653**(a1);

the building block of type **B** is selected from

B4(b3); **B5**(b3); **B6**(b3); **B7**(b3); **B8**(b3); **B9**(b3); **B10**(b3); **B12**(b4); **B13**(b4); **B14**(b4); **B15**(b4); **B16**(b4) or **B17**(b5);

the building block of type **C** is selected from

C1; C2; C3; C4; C5; C6; C7; C8; C9; C10; C11; C12; C13; C14; C15; C16; C17; C18; C19; C20; C21; C25; C26; C27; C28; C29; C30; C34; C35; C36; C37; C38; C39; C43; C44; C45; C46; C47; C48; C49; C50; C51; C52; C53; C54; C55; C56; C57; C58; C59; C60; C61; C62; C63; C64; C65; C66; C67; C68; C69; C70; C71; C72; C73; C74; C75; C76; C77; C78; C79; C80; C81; C86; C87; C88; C89; C90; C91; C92; or **C93;**

and wherein

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

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

$-(CR^{18}R^{19})_qCOR^{22}$; $-(CR^{18}R^{19})_qSO_2R^{23}$; $-(CR^{18}R^{19})_qR^{24}$; $-(CR^{18}R^{19})_qR^{25}$; or $-(CR^{18}R^{19})_qR^{26}$;

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

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

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

R^{11} is H; alkyl; alkenyl; cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; a suitable protecting group; $-(CR^{18}R^{19})_rOR^{20}$; $-(CR^{18}R^{19})_rNR^4R^{27}$; $-(CR^{18}R^{19})_rNR^4COOR^{21}$; $-(CR^{18}R^{19})_rNR^4CONR^4R^{27}$; $-(CR^{18}R^{19})_rNR^4SO_2R^{23}$; $-(CR^{18}R^{19})_rNR^4SO_2NR^4R^{27}$; $-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{27}$; $-(CR^{18}R^{19})_qCOR^{22}$; $-(CR^{18}R^{19})_qSO_2R^{23}$; $-(CR^{18}R^{19})_qSO_2NR^4R^{27}$; $-(CR^{18}R^{19})_qR^{24}$; $-(CR^{18}R^{19})_sR^{25}$; $-(CR^{18}R^{19})_qR^{26}$; or $-(CR^{18}R^{19})_qR^{31}$;

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

R^{14} and R^{16} are independently defined as H; F; CF_3; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{18}R^{19})_qOR^{20}$; $-(CR^{18}R^{19})_qNR^4R^{11}$; $-(CR^{18}R^{19})_qNR^4COOR^{21}$;

$-(CR^{18}R^{19})_qNR^4COR^{22}$; $-(CR^{18}R^{19})_qNR^4CONR^4R^{11}$; $-(CR^{18}R^{19})_qNR^4SO_2R^{23}$; $-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{11}$; or $-(CR^{18}R^{19})_qCOR^{22}$;

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

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

R^{19} is H; CF_3; or lower alkyl;

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

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

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

R^{30} and R^{33} are independently defined as H; CF_3; or lower alkyl;

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

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

R^{38} is H; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{29}R^{30})_qOR^{31}$; $-(CR^{29}R^{30})_qNR^{28}R^{31}$; $-(CR^{29}R^{30})_qNR^{28}COOR^{21}$; $-(CR^{29}R^{30})_qNR^{28}COR^{31}$; $-(CR^{29}R^{30})_qNR^{28}CONR^{28}R^{31}$;

$-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^{28}R^{31}$; $-(CR^{29}R^{30})_qCOR^{31}$; or $-(CR^{29}R^{30})_qR^{31}$;

Z is O; S; S(=O); or $S(=O)_2$;

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

4. Compounds according to claim 1 or 2 wherein

the building block of type **A** is selected from

A1(a1); **A2**(a1); **A3**(a1); **A4**(a1); **A5**(a1); **A6**(a1); **A7**(a1); **A9**(a1); **A10**(a1); **A73**(a2); **A170**(a4); **A209**(a7); **A240**(a10); **A272**(a10); **A532**(a18); **A614**(a24) ; **A631**(a1); **A632**(a1); **A633**(a1); **A641**(a1); **A642**(a1); **A643**(a1); **A651**(a1); **A652**(a1); or **A653**(a1);

the building block of type **B** is selected from

B7(b3); **B8**(b3); **B9**(b3); **B10**(b3); or **B17**(b5);

the building block of type **C** is selected from

C1; **C2**; **C4**; **C7**; **C8**; **C9**; **C10**; **C11**; **C12**; **C13**; **C14**; **C15**; **C16**; **C17**; **C18**; **C19**; **C20**; **C21**; **C25**; **C26**; **C27**; **C28**; **C29**; **C30**; **C34**; **C35**; **C36**; **C37**; **C38**; **C39**; **C43**; **C44**; **C45**; **C46**; **C47**; **C48**; **C49**; **C90**; **C91**; **C92**; or **C93**;

and wherein

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

$-(CR^{18}R^{19})_qSO_2NR^4R^{11}$; $-(CR^{18}R^{19})_qCOR^{22}$; $-(CR^{18}R^{19})_qSO_2R^{23}$; $-(CR^{18}R^{19})_qR^{24}$; $-(CR^{18}R^{19})_qR^{25}$; or $-(CR^{18}R^{19})_qR^{26}$;

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

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

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

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

R^{11} is H; alkyl; alkenyl; cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; a suitable protecting group; $-(CR^{18}R^{19})_rOR^{20}$; $-(CR^{18}R^{19})_rNR^4R^{27}$; $-(CR^{18}R^{19})_rNR^4CONR^4R^{27}$; $-(CR^{18}R^{19})_rNR^4SO_2R^{23}$; $-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{27}$; $-(CR^{18}R^{19})_qCOR^{22}$; $-(CR^{18}R^{19})_qR^{24}$; $-(CR^{18}R^{19})_sR^{25}$; $-(CR^{18}R^{19})_qR^{26}$; or $-(CR^{18}R^{19})_qR^{31}$;

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

R^{14} and R^{16} are independently defined as H; F; CF_3; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{18}R^{19})_qOR^{20}$; $-(CR^{18}R^{19})_qNR^4R^{11}$; $-(CR^{18}R^{19})_qNR^4COR^{22}$; $-(CR^{18}R^{19})_qCOOR^{21}$; or $-(CR^{18}R^{19})_qCONR^4R^{11}$;

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

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

R^{19} is H; CF_3; or CH_3;

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

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

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

R^{30} and R^{33} are independently defined as H; CF_3; or CH_3;

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

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

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

Z is O; S or $S(=O)_2$;

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

5. Compounds according to claim 1 or 2 wherein

the building block of type **A** is selected from
A1(a1); **A2**(a1); **A3**(a1); **A4**(a1); **A5**(a1); **A6**(a1); **A7**(a1); **A9**(a1); **A10**(a1); **A73**(a2); **A170**(a4); **A209**(a7); **A240**(a10); **A272**(a10); **A532**(a18); **A614**(a24); **A631**(a1); **A632**(a1); **A633**(a1); **A641**(a1); **A642**(a1); **A643**(a1); **A651**(a1); **A652**(a1); or **A653**(a1);

the building block of type **B** is selected from
B7(b3); **B8**(b3); **B9**(b3); **B10**(b3); or **B17**(b5);

the building block of type **C** is selected from
C1; **C8**; **C9**; **C11**; **C12**; **C15**; **C17**; **C19**; **C20**; **C25**; or **C47**;

and wherein

R^1 is H; F; Cl; Br; CF_3; OCF_3; $OCHF_2$; CN; lower alkyl; lower alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{29}R^{30})_qOR^{20}$; $-(CR^{29}R^{30})_qNR^4R^{11}$; $-(CR^{29}R^{30})_qNR^4COR^{22}$; $-(CR^{29}R^{30})_qNR^4CONR^4R^{11}$; $-(CR^{29}R^{30})_qNR^4SO_2R^{23}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^4R^{11}$; $-(CR^{29}R^{30})_qSO_2NR^4R^{11}$; $-(CR^{29}R^{30})_qCOR^{22}$; $-(CR^{29}R^{30})_qSO_2R^{23}$; $-(CR^{29}R^{30})_qR^{24}$; $-(CR^{29}R^{30})_qR^{25}$; or $-(CR^{29}R^{30})_qR^{26}$;

R^2 is H; CF_3; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{29}R^{30})_qOR^{20}$; $-(CR^{29}R^{30})_qNR^4R^{11}$; $-(CR^{29}R^{30})_qNR^4COR^{22}$; $-(CR^{29}R^{30})_qNR^4CONR^4R^{11}$; $-(CR^{29}R^{30})_qNR^4SO_2R^{23}$; $-(CR^{29}R^{30})_qCOOR^{21}$; $-(CR^{29}R^{30})_qCONR^4R^{11}$;

$-(CR^{29}R^{30})_qSO_2NR^4R^{11}$; $-(CR^{29}R^{30})_qCOR^{22}$; $-(CR^{29}R^{30})_qSO_2R^{23}$; $-(CR^{29}R^{30})_qR^{24}$; $-(CR^{29}R^{30})_qR^{25}$; or $-(CR^{29}R^{30})_qR^{26}$;

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

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

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

R^{11} is H; alkyl; alkenyl; cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; a suitable protecting group; $-(CR^{18}R^{19})_rOR^{20}$; $-(CR^{18}R^{19})_rNR^4R^{27}$; $-(CR^{18}R^{19})_rNR^4CONR^4R^{27}$; $-(CR^{18}R^{19})_rNR^4SO_2R^{23}$; $-(CR^{18}R^{19})_qCOOR^{21}$; $-(CR^{18}R^{19})_qCONR^4R^{27}$; $-(CR^{18}R^{19})_qCOR^{22}$; $-(CR^{18}R^{19})_qR^{24}$; $-(CR^{18}R^{19})_sR^{25}$; $-(CR^{18}R^{19})_qR^{26}$; or $-(CR^{18}R^{19})_qR^{31}$;

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

R^{14} and R^{16} are independently defined as H; F; CF_3; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{29}R^{30})_qOR^{20}$; $-(CR^{29}R^{30})_qNR^4R^{11}$; $-(CR^{29}R^{30})_qNR^4COR^{22}$; $-(CR^{29}R^{30})_qCOOR^{21}$; or $-(CR^{29}R^{30})_qCONR^4R^{11}$;

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

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

R^{19} is H; CF_3; or CH_3;

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

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

R^{24} is aryl; heteroaryl; or $-C_6H_2R^{34}R^{35}R^{31}$;

R^{25} and R^{26} are independently defined as heterocycloalkyl;

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

R^{28} is H; $-(CR^{32}R^{33})_sOR^{21}$; or $-(CR^{32}R^{33})_sNR^{43}R^{42}$;

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

R^{30} and R^{33} are independently defined as H; F; CF_3; or CH_3;

R^{31} is H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; or heteroarylalkyl;

R^{32} is H; F; CF_3; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; or lower heteroarylalkyl;

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

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

R^{42} and R^{43} are independently defined as H; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; or a suitable *N*-protecting group;

X is O; S; S(=O); or $S(=O)_2$;

Y is O; S; or NR^4;

Z is O; S or $S(=O)_2$;

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

or pharmaceutically acceptable salts, solvates, clathrates, isotopically enriched or enantiomerically enriched versions thereof.

6. Compounds according to claim 1 or 2 wherein

the building block of type **A** is selected from
A2(a1); **A5**(a1); **A9**(a1); **A73**(a2); **A209**(a7); **A272**(a10); **A532**(a18); **A614**(a24); **A641**(a1); or **A651**(a1);

the building block of type **B** is selected from
B7; **B9**; **B10** or **B17**;

the building block of type **C** is selected from
C1; **C8**; **C9**; **C11**; **C15**; **C17**; **C19**; **C20**; **C25**; or **C47**;

and wherein

R^1 is H; F; Cl; Br; CH_3; OCH_3; OH; or aryl;

R^2 is H; CH_3; heterocycloalkyl; aryl; benzyl; heteroaryl; $-OR^{20}$; $-NR^4R^{11}$; $-NR^4COOR^{21}$; $-NR^4COR^{22}$; $-NR^4CONR^4R^{11}$; or $-NR^4SO_2R^{23}$;

R^3 is H;

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

R^5, R^7 and R^9 are independently defined as H; CF_3; lower alkyl; lower alkenyl; lower cycloalkyl; lower heterocycloalkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-OR^{20}$; $-NR^4R^{11}$; $-NR^4COR^{22}$; $-NR^4CONR^4R^{11}$; $-NR^4SO_2R^{23}$; $-COOR^{21}$;$-CONR^4R^{11}$; or $-COR^{22}$;

R^6, R^8 and R^{10} are defined as H;

R^{11} is H; alkyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{18}R^{19})_rOR^{20}$; $-(CR^{18}R^{19})_rNR^4R^{27}$; $-(CR^{18}R^{19})_qCOOR^{21}$; $-COR^{22}$; $-(CR^{18}R^{19})_qR^{24}$; or $-(CR^{18}R^{19})_qR^{31}$;

R^{12} and R^{13} are defined as H;

R^{14} and R^{16} are independently defined as H; lower alkyl; or lower arylalkyl;

R^{15} and R^{17} are defined as H;

R^{18} and R^{19} are defined as H;

R^{20} is H; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; or $-(CR^{29}R^{30})_qR^{24}$;

R^{21} is H; lower alkyl; lower arylalkyl; or a suitable *O*-protecting group;

R^{22} is lower alkyl; lower alkenyl; aryl; heteroaryl; lower arylalkyl; lower heteroarylalkyl; $-(CR^{29}R^{30})_sOR^{31}$; $-(CR^{29}R^{30})_sNR^{28}R^{31}$; $-(CR^{29}R^{30})_sCOOR^{21}$; $-(CR^{29}R^{30})_tR^{24}$; or $-(CR^{29}R^{30})_tR^{31}$;

R^{23} is H; lower alkyl; aryl; heteroaryl; or $-R^{24}$;

R^{24} is aryl; heteroaryl; or $-C_6H_2R^{34}R^{35}R^{31}$;

R^{27} is H; acetyl; CH_3; or $-(CH_2)_qR^{24}$;

R^{28} is H; $-(CR^{32}R^{33})_sOR^{21}$; or $-(CR^{32}R^{33})_sNR^{43}R^{42}$;

R^{29} is H; lower alkyl; aryl; or heteroaryl;

R^{30}, R^{32} and R^{33} are independently defined as H; CF_3; or CH_3;

R^{31} is H; alkyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; arylalkyl; or heteroarylalkyl;

R^{34} and R^{35} are independently defined as H; heterocycloalkyl; $-OR^{31}$; or $-NR^{28}R^{31}$;

R^{38} is H; $-NR^{28}R^{31}$; $-NR^{28}COR^{31}$; or $-NR^{28}COOR^{31}$;

R^{42} and R^{43} are independently defined as H; CH_3; or benzyl;

X is O; S; S(=O); or $S(=O)_2$;

Y is O; S; or NR^4;

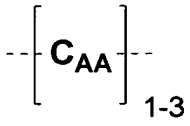
Z is O; S or $S(=O)_2$;

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

or pharmaceutically acceptable salts, solvates, clathrates, isotopically enriched or enantiomerically enriched versions thereof.

7. Compounds according to claim 4 wherein

the building block of type **C** is represented by



and wherein

C_{AA} is an amino acid or its complemetary enatiomer selected from the list of

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-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;
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_4al	L-3-Cyclobutylalanine;
C_5al	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_2Phe	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;
ACHC	1-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;
4AmPyrr2	(2S, 4R)-4-Amino-pyrrolidine-2-carboxylic acid;
4PhePyrr1	(2S, 4R)-4-Phenyl-pyrrolidine-2-carboxylic acid;
4PhePyrr2	(2S, 4S)-4-Phenyl-pyrrolidine-2-carboxylic acid;
5PhePyrr1	(2S, 5R)-5-Phenyl-pyrrolidine-2-carboxylic acid;
5PhePyrr2	(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-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-β³-HtBuG-OH (3R)-3-Amino-4,4-dimethyl-pentanoic acid;

H-β³-H4AmPhe-OH (3S)-3-Amino-4-(4'-aminophenyl)-butyric acid;

H-β³-H3AmPhe-OH (3S)-3-Amino-4-(3'-aminophenyl)-butyric acid;

H-β³-H2AmPhe-OH (3S)-3-Amino-4-(2'-aminophenyl)-butyric acid;

H-β³-HPhe(mC(NH_2)=NH)-OH (3S)-3-Amino-4-(3'-amidinophenyl)-butyric acid;

H-β³-HPhe(pC(NH_2)=NH)-OH (3S)-3-Amino-4-(4'-amidinophenyl)-butyric acid;

H-β³-HPhe(mNHC(NH_2)=NH)-OH (3S)-3-Amino-4-(3'-guanidinophenyl)-butyric acid;

H-β³-HPhe(pNHC(NH_2)=NH)-OH (3S)-3-Amino-4-(4'-guanidino-phenyl)-butyric acid;

H-β³-H2Pal-OH (3S)-3-Amino-4-(pyridine-2'-yl)-butyric acid;

H-β³-H4Pal-OH (3S)-3-Amino-4-(pyridine-4'-yl)-butyric acid;

H-β³-HPhg-OH (3R)-3-Amino-3-phenyl-propionic acid;

H-β³-HCha-OH (3S)-3-Amino-4-cyclohexyl-butyric acid;

H-β³-HC_4al-OH (3S)-3-Amino-4-cyclobutyl-butyric acid;

H-β³-HC_5al-OH (3S)-3-Amino-4-cyclopentyl-butyric acid;

H-β³-HNle-OH (3S)-3-Amino-heptanoic acid;

H-β³-H2Nal-OH (3S)-3-Amino-4-(2'-naphthyl)-butyric acid;

H-β³-H1Nal-OH (3S)-3-Amino-4-(1'-naphthyl)-butyric acid;

H-β³-H4ClPhe-OH (3S)-3-Amino-4-(4'-chlorophenyl)-butyric acid;

H-β³-H3ClPhe-OH (3S)-3-Amino-4-(3'-chlorophenyl)-butyric acid;

H-β³-H2ClPhe-OH (3S)-3-Amino-4-(2'-chlorophenyl)-butyric acid;

H-β³-H3,4Cl_2Phe-OH (3S)-3-Amino-4-(3',4'-dichlorophenyl)-butyric acid;

H-β³-H4FPhe-OH (3S)-3-Amino-4-(4'-fluorophenyl)-butyric acid;

H-β³-H3FPhe-OH (3S)-3-Amino-4-(3'-fluorophenyl)-butyric acid;

H-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-biphenylyl-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-β³-HhMet-OH	(3S)-3-Amino-6-methylthio-hexanoic acid;
H-β³-HhPe-OH	(3S)-3-Amino-5-phenyl-pentanoic acid;
H-β³-HhSer-OH	(3S)-3-Amino-5-hydroxy-pentanoic acid;
H-β³-HhThr-OH	(3S, 5R)-3-Amino-5-hydroxy-hexanoic acid;
H-β³-HhTrp-OH	(3S)-3-Amino-5-(indol-3'-yl)-pentanoic acid;
H-β³-HhThr-OH	(3S)-3-Amino-5-(4'-hydroxyphenyl)-pentanoic acid;
H-β³-HhCha-OH	(3S)-3-Amino-5-cyclohexyl-pentanoic acid;
H-β³-HBpa-OH	(3S)-3-Amino-4-(4'-benzoylphenyl)-butyric acid;
H-β³-HOctG-OH	(3S)-3-Amino-undecanoic acid;
H-β³-HNle-OH	(3S)-3-Amino-heptanoic acid;
H-β³-HTic-OH	(3S)-1,2,3,4-Tetrahydroisoquinoline-3-yl-acetic acid;
H-β³-HTiq-OH	(1S)-1,2,3,4-Tetrahydroisoquinoline-1-acetic acid;
H-β³-HOic-OH	(2S, 3aS, 7aS)-1-Octahydro-1H-indole-2-yl-acetic acid;
H-β³-H4AmPyrr1-OH	(2S, 4S)-4-Amino-pyrrolidine-2-acetic acid;
H-β³-H4AmPyrr2-OH	(2S, 4R)-4-Amino-pyrrolidine-2-acetic acid;
H-β³-H4PhePyrr1-OH	(2S, 4R)-4-Phenyl-pyrrolidine-2-acetic acid;
H-β³-H4PhePyrr2-OH	(2S, 4S)-4-Phenyl-pyrrolidine-2-acetic acid;
H-β³-H5PhePyrr1-OH	(2S, 5R)-5-Phenyl-pyrrolidine-2-acetic acid;
H-β³-H5PhePyrr2-OH	(2S, 5S)-5-Phenyl-pyrrolidine-2-acetic acid;
H-β³-H4Hyp1-OH	(2S, 4S)-4-Hydroxy-pyrrolidine-2-acetic acid;
H-β³-H4Hyp2-OH	(2S, 4R)-4-Hydroxy-pyrrolidine-2-acetic acid;
H-β³-H4Mp1-OH	(2R, 4S)-4-Mercapto-pyrrolidine-2-acetic acid;
H-β³-H4Mp2-OH	(2R, 4R)-4-Mercapto-pyrrolidine-2-acetic acid;
H-β³-HPip-OH	(2S)-Piperidine-2-acetic acid;
H-β³-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_4al-OH	(4R)-4-Amino-5-cyclobutyl-pentanoic acid;
H-γ^4-DiHC_5al-OH	(4R)-4-Amino-5-cyclopentyl-pentanoic acid;
H-γ^4-DiHNle-OH	(4S)-4-Amino-octanoic acid;
H-γ^4-DiH2Nal-OH	(4S)-4-Amino-5-(2'-naphthyl)-pentanoic acid;
H-γ^4-DiH1Nal-OH	(4S)-4-Amino-5-(1'-naphthyl)-pentanoic acid;
H-γ^4-DiH4ClPhe-OH	(4R)-4-Amino-5-(4'-chlorophenyl)-pentanoic acid;

H-γ^4-DiH3ClPhe-OH	(4R)-4-Amino-5-(3'-chlorophenyl)-pentanoic acid;
H-γ^4-DiH2ClPhe-OH	(4R)-4-Amino-5-(2'-chlorophenyl)-pentanoic acid;
H-γ^4-DiH3,4Cl_2Phe-OH	(4R)-4-Amino-5-(3',4'-dichloro-phenyl)-pentanoic acid
H-γ^4-DiH4FPhe-OH	(4R)-4-Amino-5-(4'-fluorophenyl)-pentanoic acid;
H-γ^4-DiH3FPhe-OH	(4R)-4-Amino-5-(3'-fluorophenyl)-pentanoic acid;
H-γ^4-DiH2FPhe-OH	(4R)-4-Amino-5-(2'-fluorophenyl)-pentanoic acid;
H-γ^4-DiHThi-OH	(4R)-4-Amino-5-(2'-thienyl)-pentanoic acid;
H-γ^4-DiHTza-OH	(4R)-4-Amino-5-(2'- thiazolyl)-pentanoic acid;
H-γ^4-DiHMso-OH	(4R)-4-Amino-5-methylsulfoxyl-pentanoic acid;
H-γ^4-DiHAcLys-OH	(4S)-8-Acetylamino-4-amino-ocatanoic acid;
H-γ^4-DiHDpr-OH	(4R)-4,5-diamino-pentanoic acid;
H-γ^4-DiHA_2Bu-OH	(4R)-4,5-Diamino-hexanoic acid;
H-γ^4-DiHDbu-OH	(4R)-4,5-Diamion-hexanoic acid;
H-γ^4-DiHAib-OH	3-Amino-3,3-dimethyl propionic acid;
H-γ^4-DiHCyp-OH	(1'-Amino-cyclopentane-1'-yl)-3-propionic acid;
H-γ^4-DiHY(Bzl)-OH	(4R)-4-Amino-5-(4'-benzyloxyphenyl)-pentanoic acid;
H-γ^4-DiHH(Bzl)-OH	(4R)-4-Amino-5-(1'-benzylimidazole-4'-yl)-pentanoic acid;
H-γ^4-DiHBip-OH	(4R)-4-Amino-5-biphenylyl-pentanoic acid;
H-γ^4-DiHS(Bzl)-OH	(4S)-4-Amino-5-(benzyloxy)-pentanoic acid;
H-γ^4-DiHT(Bzl)-OH	(4R, 5R)-4-Amino-5-benzyloxy-hexanoic acid;
H-γ^4-DiHalloT-OH	(4R, 5S)-4-Amino-5-hydroxy-hexanoic acid;
H-γ^4-DiHLeu3OH-OH	(4R, 5R)-4-Amino-5-hydroxy-6-methyl-heptanoic acid;
H-γ^4-DiHhAla-OH	(4S)-4-Amino-hexanoic acid;
H-γ^4-DiHhArg-OH	(4S)-4-Amino-8-guanidino-octanoic acid;
H-γ^4-DiHhCys-OH	(4R)-Amino-6-mercapto-hexanoic acid;

H-γ^4-DiHhGlu-OH	(4S)-4-Amino-ocatanedioic acid;
H-γ^4-DiHhGln-OH	(4S)-4-Amino-7-carbamoyl-heptanoic acid;
H-γ^4-DiHhHis-OH	(4S)-4-Amino-6-(imidazole-4'-yl)-hexanoic acid;
H-γ^4-DiHhIle-OH	(4S, 6S)-4-Amino-6-methyl-octanoic acid;
H-γ^4-DiHhLeu-OH	(4S)-4-Amino-7-methyl-ocatanoic acid;
H-γ^4-DiHhNle-OH	(4S)-4-Amino-nonanoic acid;
H-γ^4-DiHhLys-OH	(4S)-4,9-Diamino-nonanoic acid;
H-γ^4-DiHhMet-OH	(4R)-4-Amino-7-methylthioheptanoic acid;
H-γ^4-DiHhPhe-OH	(4S)-4-Amino-6-phenyl-hexanoic acid;
H-γ^4-DiHhSer-OH	(4R)-4-Amino-6-hydroxy-hexanoic acid;
H-γ^4-DiHhThr-OH	(4R, 6R)-4-Amino-6-hydroxy-heptanoic acid;
H-γ^4-DiHhTrp-OH	(4S)-4-Amino-6-(indol-3'-yl)-hexanoi cacid;
H-γ^4-DiHhTyr-OH	(4S)-4-Amino-6-(4'-hydroxyphenyl)-hexanoic acid;
H-γ^4-DiHhCha-OH	(4R)-4-Amino-5-cyclohexyl-pentanoic acid;
H-γ^4-DihBpa-OH	(4R)-4-Amino-5-(4'-benzoylphenyl)-pentanoic acid;
H-γ^4-DiHOctG-OH	(4S)-4-Amino-dodecanoic acid;
H-γ^4-DiHNle-OH	(4S)-4-Amino-octanoic acid;
H-γ^4-DiHTic-OH	(3R)-1',2',3',4'-Tetrahydroisoquinoline-3'-yl-3-propionic acid;
H-γ^4-DiHTiq-OH	(1'R)-1',2',3',4'-Tetrahydroisoquinoline-1'-yl-3-propionic acid;
H-γ^4-DiHOic-OH	(2'S, 3'aS, 7'aS)-1'-Octahydro-1H-indole-2'-yl-3-propionic acid;
H-γ^4-DiH4AmPyrr1-OH	(2'R, 4'S)-4'-Amino-pyrrolidine-2'-yl-3-propionic acid;
H-γ^4-DiH4AmPyrr2-OH	(2'R, 4'R)-4'-Amino-pyrrolidine-2'-yl-3-propionic acid;
H-γ^4-DiH4PhePyrr1-OH	(2'R, 4'R)-4'-Phenyl-pyrrolidine-2'-yl-3-propionic acid;
H-γ^4-DiH4PhePyrr2-OH	(2'R, 4'S)-4'-Phenyl-pyrrolidine-2'-yl-3-propionic acid
H-γ^4-DiH5PhePyrr1-OH	(2'S, 5'R)-5'-Phenyl-pyrrolidine-2'-yl-3-propionic acid;

H-γ^4-DiH5PhePyrr2-OH	(2'S, 5'S)-5'-Phenyl-pyrrolidine-2'-yl-3-propionic acid
H-γ^4-DiH4Hyp1-OH	(2'R, 4'S)-4'-Hydroxy-pyrrolidine-2'-yl-2-propionic acid;
H-γ^4-DiH4Hyp2-OH	(2'R, 4'R)-4'-Hydroxy-pyrrolidine-2'-yl-3-propionic acid;
H-γ^4-DiH4Mp1-OH	(2'R, 4'S)-4'-Mercapto-pyrrolidine-2'-yl-3-propionic acid;
H-γ^4-DiH4Mp2-OH	(2'R, 4'R)-4'-Mercapto-pyrrolidine-2'-yl-3-propionic acid;
H-γ^4-DiHPip-OH	(2'S)-Piperidine-2'-yl-3-propionic acid;
H-γ^4-DiHPro-OH	(2'S)-Pyrrolidine-2'-yl-3-propionic acid;
(AEt)G	N-(2-Aminoethyl)glycine;
(APr)G	N-(3-Amino-n-propyl)glycine;
(ABu)G	N-(4-Amino-n-butyl)glycine;
(APe)G	N-(5-Amino-n-pentyl)glycine;
(GuEt)G	N-(2-Guanidinoethyl)glycine;
(GuPr)G	N-(3-Guanidino-n-propyl)glycine;
(GuBu)G	N-(4-Guanidino-n-butyl)glycine;
(GuPe)G	N-(5-Guanidino-n-pentyl)glycine;
(PEG_3-NH_2)G	N-[H_2N-$(CH_2)_3$-$(OCH_2$-$CH_2)_2$-O$(CH_2)_3$]glycine;
(Me)G	N-Methylglycine;
(Et)G	N-Ethylglycine;
(Bu)G	N-Butylglycine;
(Pe)G	N-Pentylglycine;
(Ip)G	N-Isopropylglycine;
(2MePr)G	N-(2-Methylpropyl)glycine;
(3MeBu)G	N-(3-Methylbutyl)glycine;
(1MePr)G	(1S)-N-(1-Methylpropyl)glycine;
(2MeBu)G	(2S)-N-(2-Methylbutyl)glycine;
(MthEt)G	N-(Methylthioethyl)glycine;
(MthPr)G	N-(Methylthiopropyl)glycine;
(Ben)G	N-(Benzyl)glycine;
(PhEt)G	N-(2-Phenylethyl)glycine;
(HphMe)G	N-([4'-hydroxyphenyl]methyl)glycine;
(HphEt)G	N-(2-[4'-hydroxyphenyl]ethyl)glycine

(ImMe)G N-(Imidazol-5-yl-methyl)glycine;
(ImEt)G N-(2-(Imidazol-5'-yl)ethyl)glycine;
(InMe)G N-(Indol-2-yl-methyl)glycine;
(InEt)G N-(2-(Indol-2'-yl)ethyl)glycine;
(CboMe)G N-(Carboxymethyl)glycine;
(CboEt)G N-(2-Carboxyethyl)glycine;
(CboPr)G N-(3-Carboxypropyl)glycine;
(CbaMe)G N-(Carbamoylmethyl)glycine;
(CbaEt)G N-(2-Carbamoylethyl)glycine;
(CbaPr)G N-(3-Carbamoylpropyl)glycine;
(HyEt)G N-(2-Hydroxyethyl)glycine;
(HyPr)G (2R)-N-(2-Hydroxypropyl)glycine; or
(Mcet)G N-(2-Mercaptoethyl)glycine.

8. Compounds according to claim 1, selected from:

(2*S*,11*S*,19a*S*)-*N*-[2-(dimethylamino)ethyl]-15-fluoro-7,12-dimethyl-2-{[(1-naphthylamino)carbonyl]amino}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide;
(2*S*,11*S*,19a*S*)-*N*-(2-aminoethyl)-15-fluoro-7,12-dimethyl-2-{[2-(1-naphthyl)acetyl]amino}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide;
(2*S*,11*S*,19a*S*)-*N*-(2-{[amino(imino)methyl]amino}ethyl)-15-fluoro-7,12-dimethyl-2-{[2-(1-naphthyl)acetyl]amino}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide;
(2*S*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-2-{[2-(1-naphthyl)-acetyl]amino}-5,8,13-trioxo-*N*-[2-(2-pyridinylamino)ethyl]-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide;
(2*S*,11*S*,19a*S*)-*N*-[2-(dimethylamino)ethyl]-15-fluoro-7,12-dimethyl-2-{[2-(1-naphthyl)ethyl]amino}-5,8,13-trioxo-

2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide;

(2*S*,11*S*,19a*S*)-*N*-[2-(acetylamino)ethyl]-15-fluoro-7,12-dimethyl-2-[2-(1-naphthyl)acetyl]amino-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide;

(2*S*,11*S*,19a*S*)-*N*-[2-(dimethylamino)ethyl]-15-fluoro-7,12-dimethyl-2-{[2-(2-naphthyl)acetyl]amino}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide;

(2*S*,11*S*,19a*S*)-*N*-[2-(dimethylamino)ethyl]-15-fluoro-7,12-dimethyl-5,8,13-trioxo-2-(2-[3-(trifluoromethyl)phenyl]-acetylamino)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide;

(2*S*,11*S*,19a*S*)-*N*-[2-(dimethylamino)ethyl]-15-fluoro-2-[2-(3-methoxyphenyl)acetyl]amino-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide;

(2*S*,11*S*,19a*S*)-*N*-[3-(dimethylamino)propyl]-15-fluoro-7,12-dimethyl-2-[2-(1-naphthyl)acetyl]amino-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*]-[1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide;

(2*S*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-2-[2-(1-naphthyl)-acetyl]amino-5,8,13-trioxo-*N*-(3-pyridinylmethyl)-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]-benzoxatriazacyclopentadecine-11-carboxamide;

N-[(4*S*,6*S*,10*S*)-14-methyl-6-[2-(2-naphthyl)acetyl]amino-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]decanamide;

N-[(4*S*,6*S*,10*S*)-14-methyl-10-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]-2-(2-naphthyl)acetamide;

N-[(4*S*,6*S*,10*S*)-14-methyl-6-[2-(2-naphthyl)acetyl]amino-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2-(1-naphthyl)acetamide;

N-[(4*S*,6*S*,10*S*)-14-methyl-9,15-dioxo-10-[(3-toluidinocarbonyl)-amino]-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]-2-(2-naphthyl)acetamide;

N-[(4*S*,6*S*,10*S*)-10-([3-(dimethylamino)anilino]carbonylamino)-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]-2-(2-naphthyl)acetamide;

N-[(4S,6S,10S)-6-({[3-(dimethylamino)anilino]carbonyl}amino)-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2-(2-naphthyl)acetamide;

N-[(4*S*,6*S*,10*S*)-14-methyl-9,15-dioxo-6-[(3-phenylpropanoyl)-amino]-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]decanamide;

N-[(4*S*,6*S*,10*S*)-14-methyl-6-[(3-morpholinobenzoyl)amino]-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]decanamide;

N-[(4S,6S,10S)-6-({[3-(dimethylamino)anilino]carbonyl}amino)-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]decanamide;

N-[(4S,6S,10S)-6-({[3-(dimethylamino)anilino]carbonyl}amino)-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2-(1-naphthyl)acetamide;

N-[(4*S*,6*S*,10*S*)-6-{[(3-methoxyanilino)carbonyl]amino}-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2-(2-naphthyl)acetamide;

N-[(4*S*,6*S*,10*S*)-14-methyl-9,15-dioxo-6-{[2-(3-phenoxyphenyl)-acetyl]amino}-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]decanamide;

N-[(4*S*,6*S*,10*S*)-14-methyl-6-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-6-phenylhexanamide;

N-[(4*S*,6*S*,10*S*)-14-methyl-6-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-5-phenoxypentanamide;

(*E*)-*N*-[(4*S*,6*S*,10*S*)-14-methyl-6-[2-(2-naphthyl)acetyl]amino-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-3-decenamide;

N-[(4*S*,6*S*,10*S*)-14-methyl-6-{[2-(1-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]decanamide;

6-(benzyloxy)-*N*-[(4*S*,6*S*,10*S*)-14-methyl-6-[2-(2-naphthyl)-acetyl]amino-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]-icosa-1(20),16,18-trien-10-yl]hexanamide;

2-[1,1'-biphenyl]-4-yl-*N*-[(4*S*,6*S*,10*S*)-14-methyl-6-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo-[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]acetamide;

N-[(4*S*,6*S*,10*S*)-14-methyl-6-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-3,3-diphenylpropanamide;

6-(benzyloxy)-*N*-[(4*S*,6*S*,10*S*)-14-methyl-9,15-dioxo-10-[(6-phenylhexanoyl)amino]-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]-icosa-1(20),16,18-trien-6-yl]hexanamide;

2-[1,1'-biphenyl]-3-yl-*N*-[(4*S*,6*S*,10*S*)-6-([3-(dimethylamino)-anilino]carbonylamino)-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-acetamide;

2-[1,1'-biphenyl]-4-yl-*N*-[(4*S*,6*S*,10*S*)-6-([3-(dimethylamino)-anilino]carbonylamino)-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-acetamide;

N-[(4*S*,6*S*,10*S*)-10-[([1,1'-biphenyl]-4-ylsulfonyl)amino]-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]-2-(2-naphthyl)acetamide;

N-[(4*S*,6*S*,10*S*)-6-{[(3-fluoroanilino)carbonyl]amino}-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2-(2-naphthyl)acetamide;

N-[(4*S*,6*S*,10*S*)-6-({[4-(dimethylamino)anilino]carbonyl}amino)-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2-(2-naphthyl)acetamide;

phenyl *N*-[(4*S*,6*S*,10*S*)-14-methyl-10-{[2-(2-naphthyl)acetyl]-amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]carbamate;

N-[(4*S*,6*S*,10*S*)-14-methyl-9,15-dioxo-6-[2-(7-quinolinyl)acetyl]-amino-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2-(2-naphthyl)acetamide;

N-[(4*S*,6*S*,10*S*)-14-methyl-9,15-dioxo-6-{[2-(3-phenoxyphenyl)-acetyl]amino}-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2-(2-naphthyl)acetamide;

N-[(4*S*,6*S*,10*S*)-14-methyl-10-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]decanamide;

N-[(4*S*,6*S*,10*S*)-14-methyl-10-{[2-(1-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]decanamide;

N-[(4*S*,6*S*,10*S*)-14-methyl-10-{[2-(1-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]hexanamide;

2-[1,1'-biphenyl]-4-yl-*N*-[(4*S*,6*S*,10*S*)-14-methyl-10-{[2-(1-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo-[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]acetamide;

N-[(4*S*,6*S*,10*S*)-10-[(2-[1,1'-biphenyl]-4-ylacetyl)amino]-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]-2,2-diphenylacetamide;

N-[(4*S*,6*S*,10*S*)-6-[(2-[1,1'-biphenyl]-4-ylacetyl)amino]-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2,2-diphenylacetamide;

N-[(4*S*,6*S*,10*S*)-6-[(2,2-diphenylacetyl)amino]-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]decanamide;

N-[(4*S*,6*S*,10*S*)-14-methyl-10-{[2-(1-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]-2,2-diphenylacetamide;

N-[(4*S*,6*S*,10*S*)-6-[(3,3-diphenylpropanoyl)amino]-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]decanamide;

2-[1,1'-biphenyl]-4-yl-*N*-[(4*S*,6*S*,10*S*)-10-[(2-[1,1'-biphenyl]-4-ylacetyl)amino]-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo-[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-6-yl]acetamide;

N-[(4*S*,6*S*,10*S*)-6-({[3-(dimethylamino)anilino]carbonyl}amino)-14-methyl-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-3,3-dimethylbutanamide;

N-[(4*S*,6*S*,10*S*)-6-({[3-(dimethylamino)anilino]carbonyl}amino)-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]-2-(2-naphthyl)acetamide;

benzyl *N*-[(4*S*,6*S*,10*S*)-6-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]carbamate;

N-[(4*S*,6*S*,10*S*)-6-{[2-(2-naphthyl)acetyl]amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]decanamide;

(4*S*,6*R*,15*S*)-11,16-dimethyl-*N*-(2-naphthylmethyl)-9,12,17-trioxo-6-{[3-(4-pyridinyl)propanoyl]amino}-2-thia-8,11,16-triazatricyclo[16.3.1.$0^{4,8}$]docosa-1(22),18,20-triene-15-carboxamide;

tert-butyl *N*-[(4*S*,6*R*,15*S*)-11,16-dimethyl-15-{[(2-naphthylmethyl)amino]carbonyl}-9,12,17-trioxo-2-thia-8,11,16-triazatricyclo[16.3.1.$0^{4,8}$]docosa-1(22),18,20-trien-6-yl]carbamate;

(4*S*,6*R*,15*S*)-11,16-dimethyl-*N*-(2-naphthylmethyl)-9,12,17-trioxo-6-(pentanoylamino)-2-thia-8,11,16-triazatricyclo[16.3.1.$0^{4,8}$]-docosa-1(22),18,20-triene-15-carboxamide;

(4*S*,6*R*,15*S*)-6-(acetylamino)-11,16-dimethyl-*N*-(2-naphthylmethyl)-9,12,17-trioxo-2-thia-8,11,16-triazatricyclo-[16.3.1.$0^{4,8}$]docosa-1(22),18,20-triene-15-carboxamide;

(2*S*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-2-(1-naphthoylamino)-*N*-(2-naphthylmethyl)-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide;

(2*S*,11*S*,19a*S*)-15-fluoro-7,12-dimethyl-2-[2-(2-naphthyl)acetyl]-amino-*N*-(1-naphthylmethyl)-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide;

(2*S*,11*S*,19a*S*)-2-[(3-chlorobenzoyl)amino]-15-fluoro-7,12-dimethyl-*N*-(1-naphthylmethyl)-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide.

9. Compounds according to claim 2, selected from:

(2*S*,11*S*,19a*S*)-2-(acetylamino)-15-fluoro-*N*-[2-(1H-indol-3-yl)ethyl]-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide;

(2*S*,11*S*,19a*S*)-N-[2-(dimethylamino)ethyl]-15-fluoro-2-{[2-(1H-indol-3-yl)acetyl]amino}-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*]-[1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide;

(2*S*,11*S*,19a*S*)-15-fluoro-2-{[2-(1H-indol-3-yl)acetyl]amino}-*N*-[2-(1H-indol-3-yl)ethyl]-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*]-[1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide;

(2*S*,11*S*,19a*S*)-2-{[2-(dimethylamino)acetyl]amino}-15-fluoro-*N*-[2-(1H-indol-3-yl)ethyl]-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*]-[1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide;

tert-butyl *N*-[(2*S*,11*S*,19a*S*)-15-fluoro-11-({[2-(1H-indol-3-yl)ethyl]amino}carbonyl)-7,12-dimethyl-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*]-[1,4,7,12]benzoxatriazacyclopentadecin-2-yl]carbamate;

(2*S*,11*S*,19a*S*)-*N*-[2-(dimethylamino)ethyl]-15-fluoro-7,12-dimethyl-2-{[2-(1-naphthyl)acetyl]amino}-5,8,13-trioxo-2,3,6,7,8,9,10,11,12,13,19,19a-dodecahydro-1*H*,5*H*-pyrrolo[2,1-*c*]-[1,4,7,12]benzoxatriazacyclopentadecine-11-carboxamide;

benzyl *N*-[(4*S*,6*S*,10*S*)-14-methyl-6-{[2-(2-naphthyl)acetyl]-amino}-9,15-dioxo-2-oxa-8,14-diazatricyclo[14.3.1.$0^{4,8}$]icosa-1(20),16,18-trien-10-yl]carbamate;

benzyl *N*-[(4*S*,6*S*,13*S*)-6-{[2-(1H-indol-3-yl)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo-[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]carbamate;

N-[(4*S*,6*S*,13*S*)-6-{[2-(1*H*-indol-3-yl)acetyl]amino}-11,15-dimethyl-9,12,16-trioxo-2-oxa-8,11,15-triazatricyclo-[15.3.1.$0^{4,8}$]henicosa-1(21),17,19-trien-13-yl]decanamide.

10. Compounds according to any one of claims 1-9 for use as therapeutically active substances.

11. Compounds according to claim 10 for use as therapeutically active substances having agonistic or antagonistic activity on the motilin receptor (MR receptor), on the serotonin receptor of subtype 5-HT_{2B} (5-HT_{2B} receptor), on the prostaglandin F2α receptor (FP receptor), on the purinoreceptor $P2Y_1$, on the voltage-gated potassium channel $K_v1.3$; or on the canonical (β-catenin-dependent) Wnt pathway.

12. A pharmaceutical composition containing a compound or a mixture of compounds according to any one of claims 1-9 and at least one therapeutically inert excipient.

13. A composition according to claim 12 containing a compound or a mixture of compounds according to any one of claims 1-9, having agonistic or antagonistic activity on the motilin receptor (MR receptor), on the serotonin receptor of subtype 5-HT_{2B} (5-HT_{2B} receptor), on the prostaglandin F2α receptor (FP receptor), on the purinoreceptor $P2Y_1$, on the voltage-gated potassium channel $K_v1.3$; or on the canonical (β-catenin-dependent) Wnt pathway.

14. A composition according to claim 12 or 13 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. The use of compounds according to any one of claims 1-9, having agonistic or antagonistic activity on the motilin receptor (MR receptor), on the serotonin receptor of subtype 5-HT_{2B} (5-HT_{2B} receptor), on the prostaglandin F2α receptor (FP receptor), on the purinoreceptor $P2Y_1$, on the voltage-gated potassium channel $K_v1.3$; or on the canonical (β-catenin-dependent) Wnt pathway, for the manufacture of a medicament.

16. The use of compounds according to any one of claims 1-9 for the manufacture of a medicament, wherein said medicament is intended for the treatment of motility disorders of the gastrointestinal tract such as functional dyspepsia, diabetic gastroparesis or constipation type irritable bowl syndrome; of CNS related diseases like migraine, schizophrenia, psychosis, depression or Alzheimer disease; of ocular hypertension such as associated with glaucoma and of preterm labour; of CNS inflammatory disorders like multiple sclerosis; of thromboembolic disorders; of cell proliferation disorders, especially various cancer types; or of bone and cartilage-related disorders.

17. The use of compounds according to anyone of claims 1-9 for pharmaceutical lead finding.