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.

Compounds with structures, which show some similarity to the structures of the macrocyclic compounds of the invention, are known from EP 0 807 639, which describes cyclic polypepttides having gastrointestinal motor stimulating activity, from Marsault et al. (*J. Med. Chem.* **2006**, *49*, *7109-7197*), which describes a novel class of macrocyclic peptidomimetics, which are identified and optimized as potent antagonists to the human motilin receptor (hMOT-R) and from Marsault et al. (*Bioorg. Med. Chem. Lett.* **2007**, *17*, *4187-4190*), which describes novel, potent small molecule receptor antagonists composed of a tripeptide cyclized backbone-to backbone with a nonpeptidic tether and bear new unnatural amino acids containing basic side chains.

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**).

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~~ affecting CNS including migraine, schizophrenia, psychosis, depression or Alzheimer disease; of ocular hypertension such as associated with glaucoma and of preterm labour; ~~of CNS~~ inflammatory disorders ~~like~~ affecting CNS including 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

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 $5HT_{2B}$ ($5\text{-}HT_{2B}$ 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~~ including functional dyspepsia, diabetic gastroparesis or constipation type irritable bowl syndrome; of diseases affecting CNS ~~related diseases like~~ including migraine, schizophrenia, psychosis, depression or Alzheimer disease; of ocular hypertension such as associated with glaucoma and of preterm labour; ~~of CNS~~ inflammatory disorders ~~like~~ affecting CNS including 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.