

MACROCYCLIC RIP2-KINASE INHIBITORS

FIELD OF THE INVENTION

5 The present invention relates to macrocyclic compounds and compositions containing said compounds acting as kinase inhibitors, in particular as inhibitors of RIP2-kinase, and/or mutants thereof, for use in the diagnosis, prevention and/or treatment of RIP2-kinase associated diseases. Moreover, the present invention provides methods of using said compounds, for instance as a medicine or diagnostic agent.

BACKGROUND TO THE INVENTION

Protein kinases constitute a large family of structurally related enzymes that are responsible for the control of a wide variety of signal transduction processes in the cell. They have been shown to be key regulators in most cellular functions including proliferation, cell metabolism, cell survival, apoptosis, DNA damage repair, cell motility... Uncontrolled signaling due to defective control of protein phosphorylation has been implicated in a number of diseases, including, for example, cancer, inflammation, allergies, immune diseases, CNS disorders, angiogenesis...

Amongst the families of protein kinases, one particular example is the Receptor-Interacting Serine/Threonine Kinases including RIP2. RIP2 (Receptor-Interacting Protein 2) is also referred to as Card-Containing Ice-Associated Kinase (CARDIAK), CARD3 (C-terminal CAspase-Recruitment Domain 3), Receptor-Interacting Protein Kinase 2 (RIPK2), or Rip-Like Interacting Clarp Kinase (RICK). RIP2 kinase is composed of an N-terminal kinase domain and a C-terminal caspase-recruitment domain (CARD) linked via an intermediate (IM) region (Chin *et al.*, Curr. Med. Chem. **2005** 4 1:35-42). The CARD domain of RIP2 kinase mediates interaction with other CARD-containing proteins, such as the Nucleotide Oligomerization Domain Proteins, NOD1 and NOD2 (Inohara *et al.*, J. Biol. Chem. **2000** 36:27823-31 and Girardin *et al.*, EMBO Rep. **2001** 2:736-742). NOD1 and NOD2 are cytoplasmic receptors which are activated by specific bacterial peptidoglycan motifs and play a key role in innate immune surveillance. Upon intracellular bacterial exposure, NOD1 or NOD2 binds to the protein kinase RIP2 to coordinate NF- κ B (nuclear factor κ B)-mediated cytokine responses. Once associated with NOD1/2, RIP2 undergoes autophosphorylation on Tyr 474 (Y474), and acts as a molecular scaffold to bring together other kinases (TAK1, IKK β involved in NF- κ B and MAPK activation (Strober *et al.*, Nat. Rev. Immunol. **2006** 1:9-20).

Both NOD1/2 and RIP2 are NF- κ B regulated genes, and as such, their activation causes a positive feedback loop in which activation of NOD1/2:RIP2 stimulates further activation and further inflammation. Additionally, NOD1/2 and RIP2 expression are stimulated by a variety of mediators of inflammation, including TNF (Tumor Necrosis Factor) and IFN (Interferon). In addition to NF- κ B pathway activation, the NOD1/2:RIP2 complex stimulates autophagy, bactericidal activity, MHC Class II presentation and MAPK (Mitogen-Activated Protein Kinase)

activation. Overall, this pathway modulates the innate immune system to help tailor the adaptive immune response to eradicate the offending pathogen.

Dysregulation of RIP2-dependent signaling has been linked to autoinflammatory diseases. Patients with loss-of-function NOD2 alleles are prone to the development of Crohn's disease, an inflammatory disorder of the gastrointestinal tract (Lesage *et al.*, *Am. J. Hum. Genet.* **2002** 70:845-857 and Yamamoto *et al.*, *Microbes & Infections* **2009** 12:912-918). Several groups showed that the NOD2/RIPK2 pathway is involved in the pathogenesis of IBD (Negroni *et al.*, *Inflamm. Bowel. Dis.* **2009** 8:1145-1154; Stronati *et al.*, *Digestive and Liver Disease* **2010** 12:848-853; Haile *et al.*, *J. Med. Chem.* **2019** 14:6482-6494; Chen *et al.*, *J. Pathol.* **2020** 250 2:170-182). Negroni showed for the first time an upregulation of both NOD2 and RIPK in colon biopsies from CD patients (Negroni *et al.*, *Inflamm. Bowel Dis.* **2009** 8:1145-1154). Stronati confirmed this finding in a UC pediatric population. Interestingly, beyond RIPK2 and NOD2 upregulations and the subsequent cytokines increase this group also suggested that HD5 and HD6 upregulation (two human defensins, acting as a major component of epithelial innate immune system) could be attributed to NOD2/RIPK2 (Stronati *et al.*, *Digestive and Liver Disease* **2010** 12:848-853). Finally, Haile *et al.* showed that a selective RIPK2 inhibitor could block the spontaneous pro-inflammatory cytokines secretion from UC/CD patient's biopsies. This result underlines that RIPK2 activation in the UC/CD patient's mucosa leads to the pro-inflammatory status of these biopsies (Haile *et al.*, *J. Med. Chem.* **2019** 14:6482-6494). Also, Chen *et al.* studies on links between *Fusobacterium nucleatum* (*F. nucleatum*) and ulcerative colitis shed a new light on RIPK2 role in the epithelial damage. In this paper the authors concluded that, *F. nucleatum* targeted CARD3 through NOD2 to activate the IL-17F/NF- κ B pathway *in-vivo*. Thus, *F. nucleatum* orchestrates a molecular network involving CARD3 and IL-17F to control the UC process (Chen *et al.*, *J. Pathol.* **2020** 250 2:170-182). Another cause of IBD is called IMC (for immune mediated colitis). IMC is a side effect of immune-checkpoint inhibition (ICI). All immune-checkpoint inhibitors (anti-CTLA-4, anti-PD-1 and anti-PD-L1) are at risk for immune-related adverse events. The incidence of IMC ranges from 0.3% to 7% and occur 5 weeks to 10 weeks after the 2nd or 3rd doses of ICI (Som *et al.*, *World J. Clin. Cases* **2019** 4:405-418). Current treatment are oral corticosteroids (mild to moderate stages) and systemic corticosteroids for severe grade. However, about half of IMC patients have a corticosteroid-refractory colitis. Then, anti-TNF α inhibitor treatment is an option. RIPK2 inhibition could be an additional treatment option with a new mechanism of action. Viera *et al.* (Vieira *et al.*, *J. Immunol.* **2012** 10:5116-5122) have first described another indication when they pointed out the role of NOD2/RIPK2 in the development of experimental arthritis. Franca *et al.* (Franca *et al.*, *Scand. J. Rheumatol.* **2016** 45:8-12) confirmed these findings on rheumatoid arthritis (RA) patients. They showed that NOD2/RIPK2 pathway was up-regulated in immune cells of RA patients suggesting that RIPK2 inhibition could be beneficial in this population.

Gain-of-function NOD2 mutations have been genetically linked to other inflammatory diseases, such as Blau Syndrome/Early Onset Sarcoidosis (EOS), a pediatric granulomatous disease characterized by uveitis, dermatitis, and arthritis (Miceli-Richard *et al.*, *Nature Genetics* **2001** 29:19-20 and Becker *et al.*, *Curr. Rheum. Reports* **2005** 7:427-433). Broad genotyping of young patients suffering from allergic rhinitis and atopic dermatitis highlighted common NOD2 polymorphism with Crohn's disease (Kabesh *et al.*, *J. Allergy Clin. Immunol.* **2003** 4:813-7) as probable leading cause of the excessive immune response against skin tissues observed.

Mutations in NOD1 have been associated with asthma (Hysi *et al.*, *Hum. Mol. Genet.* **2005** 14:935-941), and early-onset and extra-intestinal inflammatory bowel disease (McGovern *et al.*, *Hum. Mol. Genet.* **2005** 14:1245-1250). Genetic and functional studies have also suggested a role for RIP2-dependent signaling in a variety of other granulomatous disorders, such as sarcoidosis (Wiken *et al.*, *J. Clin. Immunol.* **2009** 29:78-89) and Wegner's Granulomatosis (Uehara *et al.*, *Diag. Path.* **2009** 4:23).

Metabolic syndrome, a pathology closely related to obesity and overweight, results from a chronic inflammation and is characterized by hypertension, hyperglycemia and lipolysis dysfunction. Activation of the immune system through NOD1 pathway was observed in patients suffering from metabolic syndrome (Zhou *et al.*, *Obesity* **2015** 7:1394-1400). A recent functional study highlighting the impact of RIPK2 inhibitors on lipolysis suggested a role for RIP2-dependent signaling in dysglycemia and lipolysis (Duggan *et al.*, *Scientific reports* **2017** 7:1578).

In cardiac hypertrophy, a complex and multifactorial pathology, inflammation was shown as important hallmark of the disease, notably through the activation of NF- κ B signaling (Yang *et al.*, *PLoS One* **2012** 8:e40196). Knockout studies of RIPK2 on hypertrophic heart mice models subjected suggested a role in the regulation of the inflammation and subsequent tissue fibrosis and hypertrophy (Zhao *et al.*, *Biochem. Biophys. Res. Commun.* **2017** 2:1151-1158).

Beyond immuno-inflammatory diseases, RIPK2 modulation has also been described in several cancers. In triple negative breast cancer (TNBC), RIPK2 high expression has been associated to worse progression-free survival (Singel *et al.*, *Breast Cancer Res.* **2014** 16:R28) as well as a worse overall survival (Jaafar *et al.*, *Biochem. Biophys. Res. Commun.* **2018** 1:115-121). In the first study, authors showed that RIPK2 knockdown increases docetaxel sensitivity and decreases tumor and lung metastasis. Another group studied a new cancer gene cassette on breast cancer patients' chromosome 8 (Inaki *et al.*, *Genome Research* **2014** 24: 1559). They discovered RIPK2 coamplification with other tested oncogenes (such as MYC). In 2016, Mertins *et al.*, studied TNBC biopsies in order to find druggable kinases beyond HER2. It turned-out that RIPK2 was hyper-phosphorylated in basal-like and luminal B breast cancer biopsies suggesting that this pathway could be activated in these type of TNBC (Mertins *et al.*, *Nature* **2016** 7605:55-62).

More recently, phospho-RIPK2 levels as well as NF- κ B activity were shown elevated in biopsies of Inflammatory Breast Cancer (Zare *et al.*, *Cancers* **2018** 10:184). Using 34 head and neck squamous cell carcinoma cell lines, Wu *et al.* showed that RIPK2 knockdown led to cell death, indicating central roles of the protein for cell survival (Wu *et al.*, *Mol. Cell. Proteomics* **2011** 10: 1–14). While others claimed that RIPK2 promotes glioma cell growth by regulating TRAF3 and activating the NF- κ B pathway and p38 signaling (Cai *et al.*, *Oncology Reports* **2018** 39:2915-2923).

Taken together these data strongly support the development of RIPK2 inhibitors in oncology. In 2017, Maloney *et al.* described a new role for RIPK2 in osteosarcoma invasion showing that Gefitinib, via RIPK2 inhibition, prevented progression of pulmonary metastasis (Maloney *et al.*, *J. Am. Col. Surg.* **2017** 4(S1):S150). Moreover, Liu *et al.* discovered that non-canonical NF- κ B plays a pivotal role in non-Hodgkin's lymphoma (Liu *et al.*, *Cell. Biochem. Biophys.* **2015** 72 3:681-5). Finally, using a three-dimensional lymphatic endothelial cell tube formation, Gambino *et al.* identified RIPK2 as a kinase involved in lymphatic vessel remodeling, a key factor for the metastatic spread of cancer (Gambino *et al.*, *Assay Drug. Dev. Technol.* **2017** 15 1:30-43).

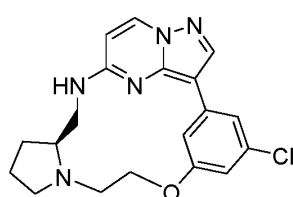
The fact that both loss-of-function polymorphisms and gain-of-function mutations cause inflammatory diseases is likely due to the fact that NOD2 functions a possible function of NOD2 as a rheostat to help maintain normal immunologic homeostasis. Lack of coordination between inflammatory signaling pathways influences the development of inflammatory disorders, and the NOD1/2:RIP2 activation equilibrium is central to this coordination. Treatments for Crohn's disease and sarcoidosis currently rely on broad, non-specific immunologic inhibition (e.g., corticosteroids) or on specific cytokine inhibition (e.g., anti-TNF therapies) with significant costs and side effects. Treatment is less than ideal, however, because not all agents are equally efficacious, the diseases occur over long time frames, and not all agents remain efficacious in the same patient. The RIP2 Y474 autophosphorylation event has been shown to be necessary for effective NOD2 signaling and does not occur in the presence of the most common loss-of-function Crohn's disease-associated NOD2 allele. This autophosphorylation is inhibited by non highly selective kinase inhibitors, Gefitinib and Erlotinib, suggesting that RIP2's tyrosine kinase activity could be targeted specifically in the treatment of inflammatory diseases (Tigno-Aranjuez *et al.*, *Genes Dev* **2010** 1:2666-77). Several clinical cases were reported about Gefitinib or Erlotinib treatment being efficient to clear psoriasis or reduce arthritic symptoms or insulin-resistant type 2 diabetes associated with metabolic syndrome (Brooks, *The Oncologist* **2013** 1:e3-e5). In mouse established models of chronic inflammatory bowel diseases, inhibition of RIP2 activity by the small molecule SB203580 is efficacious to reduce induced-colitis (Hollenbach *et al.*, *JBC*, **2005**, 280: 14981-8). None of these small molecules however, primarily and selectively targets RIP2. It was therefore an object of the present invention to provide a potent, selective, small molecule inhibitor of RIP2 kinase activity which can block specifically RIP2-dependent pro-inflammatory

-5-

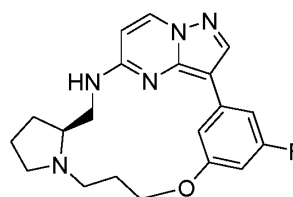
signaling and thereby provides a therapeutic benefit in auto-inflammatory diseases characterized by increased and/or dysregulated RIP2 kinase activity.

We have now found that the macrocyclic compounds and pharmaceutically acceptable compositions according to this invention are useful for the treatment of inflammatory disorders, in particular Crohn's disease, bowel disease, sarcoidosis, psoriasis, atopic dermatitis, allergic rhinitis, rheumatoid arthritis, asthma, insulin-resistant type 2 diabetes, obesity metabolic syndrome, cardiac hypertrophy, ulcerative colitis, lupus, uveitis, Blau syndrome, granulomatous inflammation, in particular Behçet's disease, immune-mediated colitis, multiple sclerosis, and diseases associated with RIP2 kinase activity (i.e. RIP2-kinase associated diseases). Our macrocyclic compounds and pharmaceutically acceptable compositions according to this invention are also useful in oncology, in particular to treat breast cancers (including Inflammatory Breast Cancer), head and neck cancers and gliomas.

In a previously published patent application WO2016/042087 was disclosed a series of macrocyclic pyrazolopyrimidine with nanomolar RIPK2 inhibition, determined by a biochemical assay. Representatives of the series are the two examples O4 and O11.



Example O4



Example O11

SUMMARY OF THE INVENTION

20

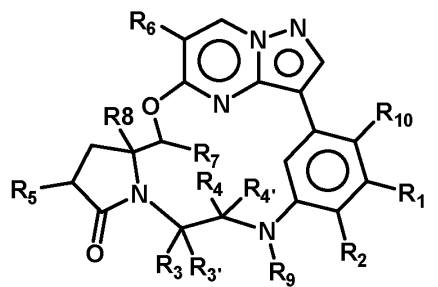
We have surprisingly found a specific combination of several structural modifications of the macrocyclic compounds described herein, such as introduction of substitutions on the pyrrolidine moiety and the replacement of X1=-NH-C₁₋₆alkyl and X2=O-C₁₋₆alkyl by X1= O-C₁₋₆alkyl and X2=-NH-C₁₋₆alkyl (X1 and X2 referring to the Markush formula I described in patent WO2016/042087), which led to drastic improvement of key developability and safety parameters, such as human protein binding, human microsomal metabolic stability and hERG channel inhibition. In more details, as depicted in the Comparative Table between some representative compounds of WO2016/042087 and the compounds of the present invention (see end of experimental part), the compounds described in the present invention display improved human protein binding free fraction (Assay A), a higher metabolic stability (Assay B), and a lower hERG inhibition liability (Assay C). Plasma protein binding, metabolic stability and hERG liability have been recognized in the last 15 years as key developability parameters to optimize in addition to potency and specificity (*Towards Drugs of the Future*, IOS Press, **2009**,

30

-6-

9:53-74). For example, hERG link to cardiotoxicity was recognized as key developability parameter to address, as published by Danker *et al* (Danker *et al*, Front. Pharmacol. **2014**, 5:203).

- 5 Accordingly, in a first aspect, the present invention provides a compound of Formula I or a stereoisomer, tautomer, racemic, salt, hydrate, N-oxide form, or solvate thereof,



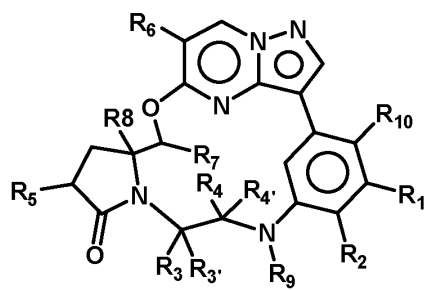
Wherein

- R_1 is selected from -Halo, -O-C₁₋₆alkyl, -Alkynyl, -C₁₋₆alkyl, -C₃₋₆-cycloalkyl, -C(O)-C₁₋₆alkyl, -C(O)-C₁₋₆cycloalkyl, -C(O)-Het₂, -C(O)-NR_aR_b, -Het₁ and -CN; each of said -C₁₋₆alkyl being optionally substituted with one or more substituents selected from -D, -Halo, -O-C₁₋₃alkyl, -C₃₋₆-cycloalkyl, -Ph, -Het₁, -Het₂, and -OH; each of said -Alkynyl being optionally substituted with one substituent selected from -C₁₋₆alkyl, and -CH₂-O-C₁₋₆alkyl;
- R_2 and R_{10} are each independently selected from -H, and -Halo;
- R_3 , R_3' , R_4 , R_4' , R_7 , and R_8 are each independently selected from -H, and -C₁₋₆alkyl; wherein each of said -C₁₋₆alkyl may optionally be substituted with one or more -O-C₁₋₆alkyl; wherein when R_3 and/or R_3' is -C₁₋₆alkyl, then R_4 and R_4' are each -H; wherein when R_4 and/or R_4' is -C₁₋₆alkyl, then R_3 and R_3' are each -H;
- R_5 is selected from -OH, -NR_cR_{c'}, -NHC(O)R_c, -NC(O)R_cR_{c'}, -NC(O)OR_c, -NHS(O₂)R_c, -Halo, -O-C₁₋₆alkyl, -O-C₃₋₅-cycloalkyl, -O-Het₂, -C₁₋₆alkyl, and -CN; each of said -C₁₋₆alkyl being optionally substituted with one or more substituents selected from -D, -OH, -C₁₋₆alkyl, -C₃₋₅-cycloalkyl, -O-C₁₋₆alkyl and -Het₂;
- R_6 is selected from -H, -Halo, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -Het₃; each of said -C₁₋₆alkyl being optionally substituted with one or more substituents selected from -D, and -O-C₁₋₆alkyl;
- R_9 is selected from -H, -C₁₋₆alkyl, -C(O)-C₁₋₆alkyl, and -C(O)-O-C₁₋₆alkyl;
- R_a is selected from -H, and -C₁₋₆alkyl; each of said -C₁₋₆alkyl being optionally substituted with one or more substituents selected from -D, and -C₁₋₆alkyl;
- R_b is selected from -H, -C₁₋₆alkyl, and -O-C₁₋₆alkyl; each of said -C₁₋₆alkyl being optionally substituted with one or more substituents selected from -D, -C₁₋₆alkyl, and -C₃₋₅-cycloalkyl;
- R_c and $R_{c'}$ are each independently selected from -H, and -C₁₋₆alkyl; each of said -C₁₋₆alkyl being optionally substituted with one or more substituents selected from -D, and -C₁₋₆alkyl;
- Het₁ and Het₃ are each independently selected from a 5 or 6-membered aromatic heterocycle

-7-

having from 1 to 3 heteroatoms selected from O, N and S, wherein each of said Het₁ or Het₃ is optionally substituted with from 1 to 3 -C₁₋₆alkyl; each of said -C₁₋₆alkyl being optionally substituted with one or more substituents selected from -D, -halo, -O-C₁₋₃alkyl, and -OH;

- 5 Het₂ is selected from a 4 to 6-membered saturated heterocycle having from 1 to 3 heteroatoms selected from O and N; wherein each of said Het₂ is optionally substituted with from 1 to 3 -C₁₋₆alkyl; each of said -C₁₋₆alkyl being optionally substituted with one or more substituents selected from -D, -halo, -O-C₁₋₃alkyl, and -OH.
- 10 Alternatively, in a first aspect, the present invention provides a compound of Formula I or a stereoisomer, tautomer, racemic, salt, hydrate, N-oxide form, or solvate thereof,



Wherein

- R₁ is selected from -Halo, -O-C₁₋₆alkyl, -Alkynyl, -C₁₋₆alkyl, -C₃₋₆-cycloalkyl, -C(O)-C₁₋₆alkyl, -C(O)-C₁₋₆cycloalkyl, -C(O)-Het₂, -C(O)-NR_aR_b, -Het₁ and -CN; each of said -C₁₋₆alkyl being optionally substituted with one or more substituents selected from -D, -Halo, -O-C₁₋₃alkyl, -C₃₋₆-cycloalkyl, -Ph, -Het₁, -Het₂, and -OH; each of said -Alkynyl being optionally substituted with one substituent selected from -C₁₋₆alkyl, and -CH₂-O-C₁₋₆alkyl;
- 15 R₂ and R₁₀ are each independently selected from -H, and -Halo;
- 20 R₃, R_{3'}, R₄, R_{4'}, R₇, and R₈ are each independently selected from -H, and -C₁₋₆alkyl; wherein each of said -C₁₋₆alkyl may optionally be substituted with one or more -O-C₁₋₆alkyl; wherein when R₃ and/or R_{3'} is -C₁₋₆alkyl, then R₄ and R_{4'} are each -H; wherein when R₄ and/or R_{4'} is -C₁₋₆alkyl, then R₃ and R_{3'} are each -H;
- 25 R₅ is selected from -OH, -NR_cR_{c'}, -NHC(O)R_c, -NC(O)R_cR_{c'}, -NC(O)OR_c, -NHS(O₂)R_c, -Halo, -O-C₁₋₆alkyl, -O-C₃₋₅-cycloalkyl, -O-Het₂, -C₁₋₆alkyl, and -CN; each of said -C₁₋₆alkyl being optionally substituted with one or more substituents selected from -D, -OH, -C₁₋₆alkyl, -C₃₋₅-cycloalkyl, -O-C₁₋₆alkyl and -Het₂;
- R₆ is selected from -H, -Halo, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -O-Het₄, and -Het₃; each of said -C₁₋₆alkyl being optionally substituted with one or more substituents selected from -D, and -O-C₁₋₆alkyl;
- 30 R₉ is selected from -H, -C₁₋₆alkyl, -C(O)-C₁₋₆alkyl, and -C(O)-O-C₁₋₆alkyl;
- R_a is selected from -H, and -C₁₋₆alkyl; each of said -C₁₋₆alkyl being optionally substituted with one or more substituents selected from -D, and -C₁₋₆alkyl;

-8-

- R_b is selected from $-H$, $-C_{1-6}alkyl$, and $-O-C_{1-6}alkyl$; each of said $-C_{1-6}alkyl$ being optionally substituted with one or more substituents selected from $-D$, $-C_{1-6}alkyl$, and $-C_{3-5}cycloalkyl$; R_c and $R_{c'}$ are each independently selected from $-H$, and $-C_{1-6}alkyl$; each of said $-C_{1-6}alkyl$ being optionally substituted with one or more substituents selected from $-D$, and $-C_{1-6}alkyl$;
- 5 Het_1 and Het_3 are each independently selected from a 5 or 6-membered aromatic heterocycle having from 1 to 3 heteroatoms selected from O, N and S, wherein each of said Het_1 or Het_3 is optionally substituted with from 1 to 3 $-C_{1-6}alkyl$; each of said $-C_{1-6}alkyl$ being optionally substituted with one or more substituents selected from $-D$, $-halo$, $-O-C_{1-3}alkyl$, and $-OH$;
- 10 Het_2 is selected from a 4 to 6-membered saturated heterocycle having from 1 to 3 heteroatoms selected from O and N; wherein each of said Het_2 is optionally substituted with from 1 to 3 $-C_{1-6}alkyl$; each of said $-C_{1-6}alkyl$ being optionally substituted with one or more substituents selected from $-D$, $-halo$, $-O-C_{1-3}alkyl$, and $-OH$
- Het_4 is selected from a 4 to 10-membered saturated heterocycle having from 1 to 3
- 15 heteroatoms selected from O and N; wherein each of said Het_4 is optionally substituted with from 1 to 3 $-C_{1-6}alkyl$; each of said $-C_{1-6}alkyl$ being optionally substituted with one or more substituents selected from $-D$, $-halo$, $-O-C_{1-3}alkyl$, and $-OH$.
- In a specific embodiment, the present invention provides a compound of Formula I or a
- 20 stereoisomer, tautomer, racemic, salt, hydrate, N-oxide form, or solvate thereof, wherein
- R_1 is selected from $-Halo$, $-O-C_{1-6}alkyl$, $-Alkynyl$, $-C_{1-6}alkyl$, $-C_{3-6}cycloalkyl$, $-C(O)-C_{1-6}alkyl$, $-C(O)-C_{1-6}cycloalkyl$, $-C(O)-Het_2$, $-C(O)-NR_aR_b$, $-Het_1$ and $-CN$; each of said $-C_{1-6}alkyl$ being optionally substituted with one or more substituents selected from $-D$, $-Halo$, $-O-C_{1-3}alkyl$, $-C_{3-6}cycloalkyl$, $-Ph$, $-Het_1$, $-Het_2$, and $-OH$;
- 25 R_2 and R_{10} are each independently selected from $-H$, and $-Halo$;
- R_3 , $R_{3'}$, R_4 , $R_{4'}$, R_7 , and R_8 are each independently selected from $-H$, and $-C_{1-6}alkyl$; wherein each of said $-C_{1-6}alkyl$ may optionally be substituted with one or more $-O-C_{1-6}alkyl$; wherein when R_3 and/or $R_{3'}$ is $-C_{1-6}alkyl$, then R_4 and $R_{4'}$ are each $-H$; wherein when R_4 and/or $R_{4'}$ is $-C_{1-6}alkyl$, then R_3 and $R_{3'}$ are each $-H$;
- 30 R_5 is selected from $-OH$, $-NR_cR_{c'}$, $-NHC(O)R_c$, $-Halo$, $-O-C_{1-6}alkyl$, $-O-C_{3-5}cycloalkyl$, $-O-Het_2$, $-C_{1-6}alkyl$, and $-CN$; each of said $-C_{1-6}alkyl$ being optionally substituted with one or more substituents selected from $-D$, $-OH$, $-C_{1-6}alkyl$, $-C_{3-5}cycloalkyl$, $-O-C_{1-6}alkyl$ and $-Het_2$;
- R_6 is selected from $-H$, $-Halo$, $-C_{1-6}alkyl$, $-O-C_{1-6}alkyl$, $-O-Het_4$, and $-Het_3$; each of said $-C_{1-6}alkyl$ being optionally substituted with one or more substituents selected from $-D$, and $-O-C_{1-6}alkyl$;
- 35 R_9 is selected from $-H$, $-C_{1-6}alkyl$, $-C(O)-C_{1-6}alkyl$, and $-C(O)-O-C_{1-6}alkyl$;
- R_a is selected from $-H$, and $-C_{1-6}alkyl$;
- R_b is selected from $-H$, $-C_{1-6}alkyl$, and $-O-C_{1-6}alkyl$;
- R_c and $R_{c'}$ are each independently selected from $-H$, and $-C_{1-6}alkyl$;

-9-

- Het₁ and Het₃ are each independently selected from a 5 or 6-membered aromatic heterocycle having from 1 to 3 heteroatoms selected from O and N, wherein each of said Het₁ and Het₃ is optionally substituted with from 1 to 3 -C₁₋₆alkyl;
- Het₂ is selected from a 4 to 6-membered saturated heterocycle having from 1 to 3 O atoms
- 5 Het₄ is selected from a 4 to 10-membered saturated heterocycle having from 1 to 3 heteroatoms selected from O and N; wherein each of said Het₄ is optionally substituted with from 1 to 3 -C₁₋₆alkyl; each of said -C₁₋₆alkyl being optionally substituted with one or more substituents selected from -D, -halo, -O-C₁₋₃alkyl, and -OH.
- 10 In another specific embodiment, the present invention provides a compound of Formula I or a stereoisomer, tautomer, racemic, salt, hydrate, N-oxide form, or solvate thereof, wherein
- R₁ is selected from -Halo, -O-C₁₋₆alkyl, -Alkynyl, -C₁₋₆alkyl, -C₃₋₆-cycloalkyl, -C(O)-C₁₋₆alkyl, -C(O)-C₁₋₆cycloalkyl, -C(O)-Het₂, -C(O)-NR_aR_b, -Het₁ and -CN; each of said -C₁₋₆alkyl being optionally substituted with one or more substituents selected from -D, -Halo, -O-C₁₋₃alkyl, -C₃₋₆-cycloalkyl, -Ph, -Het₁, -Het₂, and -OH;
- 15 R₂ and R₁₀ are each independently selected from -H, and -Halo;
- R₃, R_{3'}, R₄, R_{4'}, R₇, and R₈ are each -H;
- R₅ is selected from -OH, -Halo, -O-C₁₋₆alkyl, -O-C₃₋₅-cycloalkyl, and -C₁₋₆alkyl; each of said -C₁₋₆alkyl being optionally substituted with one or more substituents selected from -D, -OH, -C₁₋₆alkyl, -C₃₋₅-cycloalkyl, and -O-C₁₋₆alkyl;
- 20 R₆ is selected from -H, -Halo, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -O-Het₄, and -Het₃; each of said -C₁₋₆alkyl being optionally substituted with one or more -O-C₁₋₆alkyl;
- R₉ is selected from -H, -C₁₋₆alkyl, -C(O)-C₁₋₆alkyl, and -C(O)-O-C₁₋₆alkyl;
- R_a is selected from -H, and -C₁₋₆alkyl;
- 25 R_b is selected from -H, -C₁₋₆alkyl, and -O-C₁₋₆alkyl; each of said -C₁₋₆alkyl being optionally substituted with one or more ;
- Het₁ and Het₃ are each independently selected from a 5 or 6-membered aromatic heterocycle having from 1 to 3 heteroatoms selected from O and N, wherein each of said Het₁ and Het₃ is optionally substituted with from 1 to 3 -C₁₋₆alkyl;
- 30 Het₂ is selected from a 4 to 6-membered saturated heterocycle having from 1 to 3 O atoms
- Het₄ is selected from a 4 to 10-membered saturated heterocycle having from 1 to 3 heteroatoms selected from O and N; wherein each of said Het₄ is optionally substituted with from 1 to 3 -C₁₋₆alkyl; each of said -C₁₋₆alkyl being optionally substituted with one or more substituents selected from -D, -halo, -O-C₁₋₃alkyl, and -OH.
- 35 In yet a further specific embodiment, the present invention provides a compound of Formula I or a stereoisomer, tautomer, racemic, salt, hydrate, N-oxide form, or solvate thereof, wherein
- R₁ is selected from -Halo, -O-C₁₋₆alkyl, -Alkynyl, -C₁₋₆alkyl, -C₃₋₆-cycloalkyl, -C(O)-C₁₋₆alkyl, -C(O)-NR_aR_b, -Het₁ and -CN; each of said -C₁₋₆alkyl being optionally substituted with one

-10-

or more substituents selected from -D, -Halo, and -O-C₁₋₃alkyl;

R₂ is selected from -H, and -Halo;

R₁₀ is -H;

R₃, R_{3'}, R₄, R_{4'}, R₇, and R₈ are each -H

- 5 R₅ is selected from -OH, -Halo, -O-C₁₋₆alkyl, -O-C₃₋₅-cycloalkyl, and -C₁₋₆alkyl; each of said -C₁₋₆alkyl being optionally substituted with one or more substituents selected from -D, -OH, -C₁₋₆alkyl, -C₃₋₅-cycloalkyl, and -O-C₁₋₆alkyl;

R₆ is selected from -H, -Halo, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -O-Het₄, and -Het₃; each of said -C₁₋₆alkyl being optionally substituted with one or more -O-C₁₋₆alkyl;

- 10 R₉ is -H;

R_a is selected from -H, and -C₁₋₆alkyl;

R_b is selected from -H, -C₁₋₆alkyl, and -O-C₁₋₆alkyl;

Het₁ is a 5-membered aromatic heterocycle having from 1 to 3 heteroatoms selected from O and N, wherein said Het₁ is optionally substituted with from 1 to 3 -C₁₋₆alkyl

- 15 Het₄ is selected from a 4 to 10-membered saturated heterocycle having from 1 to 3 heteroatoms selected from O and N; wherein each of said Het₄ is optionally substituted with from 1 to 3 -C₁₋₆alkyl; each of said -C₁₋₆alkyl being optionally substituted with one or more substituents selected from -D, -halo, -O-C₁₋₃alkyl, and -OH.

- 20 In a more specific embodiment, the present invention provides a selected from any of the tables disclosed herein.

In another specific embodiment, in the compounds of the present invention, the carbon atom bearing the R₈ substituent may be in the S-configuration.

25

In a further specific embodiment, in the compounds of the present invention, the carbon atom bearing the R₅ substituent may be in the R-configuration.

- 30 The present invention further provides a pharmaceutical composition comprising a compound according to this invention.

In a further aspect, the present invention provides a compound or a composition according to this invention, for use as a medicine.

- 35 In a particular embodiment, the present invention provides a compound or composition according to this invention for use in the diagnosis, prevention and/or treatment of a RIP2-kinase associated disease. Said RIP2-kinase associated disease may in particular be an inflammatory disorder, in particular selected from the list comprising: Crohn's disease, bowel disease, sarcoidosis, psoriasis, atopic dermatitis, allergic rhinitis, rheumatoid arthritis, asthma,

-11-

insulin-resistant type 2 diabetes, obesity metabolic syndrome, cardiac hypertrophy, ulcerative colitis, lupus, uveitis, Blau syndrome, granulomatous inflammation, Behçet's disease, immune-mediated colitis, and multiple sclerosis. Alternatively, said RIP2-kinase associated disease may be cancer, more in particular selected from breast cancers (including Inflammatory Breast Cancer), head and neck cancers and gliomas.

Furthermore, the present invention provides the use of a compound or composition according to this invention, suitable for inhibiting the activity of a kinase; in particular a RIP2 kinase; or for the diagnosis, prevention and/or treatment of a RIP2-kinase associated disease.

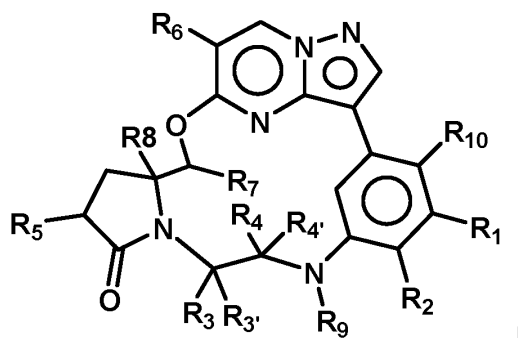
Finally, the present invention provides a method for prevention and/or treatment of a RIP2-kinase associated disease; said method comprising administering to a subject in need thereof a compound or a composition according to the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention will now be further described. In the following passages, different aspects of the invention are defined in more detail. Each aspect so defined may be combined with any other aspect or aspects unless clearly indicated to the contrary. In particular, any feature indicated as being preferred or advantageous may be combined with any other feature or features indicated as being preferred or advantageous.

Unless a context dictates otherwise, asterisks are used herein to indicate the point at which a mono- or bivalent radical depicted is connected to the structure to which it relates and of which the radical forms part.

As already mentioned hereinbefore, in a first aspect the present invention provides a compound of Formula I or a stereoisomer, tautomer, racemic, salt, hydrate, N-oxide form, or solvate thereof,



Wherein

- R_1 is selected from -Halo, -O- C_{1-6} alkyl, -Alkynyl, - C_{1-6} alkyl, -C(O)- C_{1-6} alkyl, -C(O)- C_{1-6} cycloalkyl, -C(O)-Het₂, -C(O)-NR_aR_b, -Het₁ and -CN; each of said - C_{1-6} alkyl being optionally substituted with one or more substituents selected from -D, -Halo, -O- C_{1-3} alkyl, -C₃₋₆-cycloalkyl, -Ph, -Het₁, -Het₂, and -OH; each of said -Alkynyl being optionally substituted with one substituent selected from - C_{1-6} alkyl, and -CH₂-O- C_{1-6} alkyl;
- R_2 and R_{10} are each independently selected from -H, and -Halo;
- R_3 , R_3' , R_4 , R_4' , R_7 , and R_8 are each independently selected from -H, and - C_{1-6} alkyl; wherein each of said - C_{1-6} alkyl may optionally be substituted with one or more -O- C_{1-6} alkyl;
- wherein when R_3 and/or R_3' is - C_{1-6} alkyl, then R_4 and R_4' are each -H;
- wherein when R_4 and/or R_4' is - C_{1-6} alkyl, then R_3 and R_3' are each -H;
- R_5 is selected from -OH, -NR_cR_{c'}, -NHC(O)R_c, -NC(O)R_cR_{c'}, -NC(O)OR_c, -NHS(O₂)R_c, -Halo, -O- C_{1-6} alkyl, -O-C₃₋₅-cycloalkyl, -O-Het₂, - C_{1-6} alkyl, and -CN; each of said - C_{1-6} alkyl being optionally substituted with one or more substituents selected from -D, -OH, - C_{1-6} alkyl, -C₃₋₅-cycloalkyl, -O- C_{1-6} alkyl and -Het₂;
- R_6 is selected from -H, -Halo, - C_{1-6} alkyl, -O- C_{1-6} alkyl, -O-Het₄, and -Het₃; each of said - C_{1-6} alkyl being optionally substituted with one or more substituents selected from -D, and -O- C_{1-6} alkyl;
- R_9 is selected from -H, - C_{1-6} alkyl, -C(O)- C_{1-6} alkyl, and -C(O)-O- C_{1-6} alkyl;
- R_a is selected from -H, and - C_{1-6} alkyl; each of said - C_{1-6} alkyl being optionally substituted with one or more substituents selected from -D, and - C_{1-6} alkyl;
- R_b is selected from -H, - C_{1-6} alkyl, and -O- C_{1-6} alkyl; each of said - C_{1-6} alkyl being optionally substituted with one or more substituents selected from -D, - C_{1-6} alkyl, and -C₃₋₅-cycloalkyl;
- R_c and R_c' are each independently selected from -H, and - C_{1-6} alkyl; each of said - C_{1-6} alkyl being optionally substituted with one or more substituents selected from -D, and - C_{1-6} alkyl;
- Het₁ and Het₃ are each independently selected from a 5 or 6-membered aromatic heterocycle having from 1 to 3 heteroatoms selected from O, N and S, wherein each of said Het₁ or Het₃ is optionally substituted with from 1 to 3 - C_{1-6} alkyl; each of said - C_{1-6} alkyl being optionally substituted with one or more substituents selected from -D, -halo, -O- C_{1-3} alkyl, and -OH;
- Het₂ is selected from a 4 to 6-membered saturated heterocycle having from 1 to 3 heteroatoms selected from O and N; wherein each of said Het₂ is optionally substituted with from 1 to 3 - C_{1-6} alkyl; each of said - C_{1-6} alkyl being optionally substituted with one or more substituents selected from -D, -halo, -O- C_{1-3} alkyl, and -OH;
- Het₄ is selected from a 4 to 10-membered saturated heterocycle having from 1 to 3 heteroatoms selected from O and N; wherein each of said Het₄ is optionally substituted with from 1 to 3 - C_{1-6} alkyl; each of said - C_{1-6} alkyl being optionally substituted with one or more substituents selected from -D, -halo, -O- C_{1-3} alkyl, and -OH.

In any of the herein disclosed embodiments, R_6 may alternatively be selected from -H, -Halo, - C_{1-6} alkyl, -O- C_{1-6} alkyl, and -Het₃; each of said - C_{1-6} alkyl being optionally substituted with one or more substituents selected from -D, and -O- C_{1-6} alkyl; in which case Het₄ is absent.

- 5 The term "alkyl" by itself or as part of another substituent refers to fully saturated hydrocarbon radicals. Generally, alkyl groups of this invention comprise from 1 to 6 carbon atoms. Alkyl groups may be linear or branched and may be substituted as indicated herein. When a subscript is used herein following a carbon atom, the subscript refers to the number of carbon atoms that the named group may contain. Thus, for example, C_{1-6} alkyl means an alkyl of one
- 10 to six carbon atoms. Examples of alkyl groups are methyl, ethyl, n-propyl, i-propyl, butyl, and its isomers (e.g. n-butyl, i-butyl and t-butyl); pentyl and its isomers, hexyl and its isomers. C_{1-6} alkyl includes all linear or branched alkyl groups with between 1 and 6 carbon atoms, and thus includes methyl, ethyl, n-propyl, i-propyl, butyl and its isomers (e.g. n-butyl, i-butyl and t-butyl); pentyl and its isomers, hexyl and its isomers.
- 15 The term "optionally substituted alkyl" refers to an alkyl group optionally substituted with one or more substituents (for example 1 to 3 substituents, for example 1, 2 or 3 substituents or 1 to 2 substituents) at any available point of attachment. Non-limiting examples of such substituents include -D, -halo, -OH, primary and secondary amides, -O- C_{1-6} alkyl, heteroaryl, aryl, cycloalkyl, heterocyclyl and the like.
- 20 The term "alkenyl", as used herein, unless otherwise indicated, means straight-chain, cyclic, or branched-chain hydrocarbon radicals containing at least one carbon-carbon double bond. Examples of alkenyl radicals include ethenyl, E- and Z-propenyl, isopropenyl, E- and Z-butenyl, E- and Z-isobutenyl, E- and Z-pentenyl, E- and Z-hexenyl, E,E-, E,Z-, Z,E-, Z,Z-hexadienyl, and the like. An optionally substituted alkenyl refers to an alkenyl having optionally
- 25 one or more substituents (for example 1, 2, 3 or 4), selected from those defined above for substituted alkyl.
- The term "alkynyl", as used herein, unless otherwise indicated, means straight-chain or branched-chain hydrocarbon radicals containing at least one carbon-carbon triple bond. Examples of alkynyl radicals include ethynyl, E- and Z-propynyl, isopropynyl, E- and Z-butylnyl, E- and Z-isobutylnyl, E- and Z-pentylnyl, E, Z-hexynyl, and the like. An optionally substituted
- 30 alkynyl refers to an alkynyl having optionally one or more substituents (for example 1, 2, 3 or 4), selected from those defined above for substituted alkyl.
- The term "cycloalkyl" by itself or as part of another substituent is a cyclic alkyl group, that is to say, a monovalent, saturated, or unsaturated hydrocarbonyl group having a cyclic structure.
- 35 Cycloalkyl includes all saturated or partially saturated (containing 1 or 2 double bonds) hydrocarbon groups having a cyclic structure. Cycloalkyl groups may comprise 3 or more carbon atoms in the ring and generally, according to this invention comprise from 3 to 6 atoms. Examples of cycloalkyl groups include but are not limited to cyclopropyl, cyclobutyl,

cyclopentyl, Cyclohexane.

Where alkyl groups as defined are divalent, i.e., with two single bonds for attachment to two other groups, they are termed "alkylene" groups. Non-limiting examples of alkylene groups includes methylene, ethylene, methylenemethylene, trimethylene, propylene, tetramethylene, ethylethylene, 1,2-dimethylethylene, pentamethylene and hexamethylene.

Generally, alkylene groups of this invention preferably comprise the same number of carbon atoms as their alkyl counterparts. Where an alkylene or cycloalkylene biradical is present, connectivity to the molecular structure of which it forms part may be through a common carbon atom or different carbon atom. To illustrate this applying the asterisk nomenclature of this invention, a C₃ alkylene group may be for example *-CH₂CH₂CH₂*, *-CH(-CH₂CH₃)*, or *-CH₂CH(-CH₃)*.

The term "heterocycle" as used herein by itself or as part of another group refers to aromatic, non-aromatic, fully saturated or partially unsaturated cyclic groups (for example, 3 to 6 membered monocyclic ring systems, or 8-10 membered bicyclic rings) which have at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, 3 or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms. An optionally substituted heterocyclic refers to a heterocyclic having optionally one or more substituents (for example 1 to 4 substituents, or for example 1, 2, 3 or 4), selected from those defined above for substituted alkyl.

Exemplary non-aromatic heterocyclic groups include piperidinyl, azetidyl, imidazolyl, imidazolidinyl, isoxazolyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, piperidyl, succinimidyl, 3H-indolyl, isoindolyl, 2H-pyrrolyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, pyrrolidinyl, 4H-quinolizyl, 4aH-carbazolyl, 2-oxopiperazinyl, piperazinyl, homopiperazinyl, 2-pyrazolyl, 3-pyrazolyl, pyranyl, dihydro-2H-pyranyl, 4H-pyranyl, 3,4-dihydro-2H-pyranyl, oxetanyl, 3-dioxolanyl, 1,3-dioxanyl, 2,5-dioximidazolidinyl, 2,2,4-piperidonyl, 2-oxopiperidinyl, 2-oxopyrrolodiny, 2-oxoazepinyl, indolyl, tetrahydropyranyl, tetrahydrofuranly, tetrahydrothienyl, tetrahydroquinolyl, tetrahydroisoquinolyl, thiomorpholinyl, thiomorpholinyl sulfoxide, thiomorpholinyl sulfone, 1,3-dioxolanyl, 1,4-oxathianyl, 1,4-dithianyl, 1,3,5-trioxanyl, 6H-1,2,5-thiadiazyl, 2H-1,5,2-dithiazyl, 2H-oxocinyl, 1H-pyrrolizyl, tetrahydro-1,1-dioxothieryl, N-formylpiperazinyl, and morpholinyl; in particular pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, dioxolanyl, dioxanyl, morpholinyl, thiomorpholinyl, piperazinyl, thiazolidinyl, tetrahydropyranyl, tetrahydrofuranly,

7-10 Membered heterocyclic groups are also meant to include spiro-groups, which are bicyclic compounds with both rings connected through a single atom, such as for example spiro[4.5]decane, which is a spiro compound consisting of a cyclohexane ring and a cyclopentane ring. Other examples include oxaspiro[3.3]heptan, which is a spiro compound consisting of a C₄ cycloalkyl and an oxetane ring.

The term "aryl" as used herein refers to a polyunsaturated, aromatic hydrocarbonyl group having from 5-10 atoms. Aryl is also intended to include the partially hydrogenated derivatives of the carbocyclic systems enumerated herein. Non-limiting examples of aryl comprise phenyl, biphenyl, biphenylene, 1- or 2-naphthyl, 1-, 2-, or 3-indenyl, 1- 2-, 3-, 4-, or 5-acenaphthylenyl, 1- or 2-pentalenyl, 4- or 5-indanyl, 5-, 6-, 7-, or 8-tetrahydronaphthyl, 1,2,3,4-tetrahydronaphthyl, 1,4-dihydronaphthyl and 1-, 2-, 3-, 4-, or 5-pyrenyl; in particular phenyl.

The aryl ring can optionally be substituted by one or more substituents. An "optionally substituted aryl" refers to an aryl having optionally one or more substituents (for example 1 to 5 substituents, for example 1, 2, 3 or 4) at any available point of attachment, selected from those defined above for substituted alkyl.

Where a carbon atom in an aryl group is replaced with a heteroatom, the resultant ring is referred to herein as a heteroaryl ring, alternatively, such ring structure is also referred to as an aromatic heterocycle.

The term "heteroaryl" or "aromatic heterocycle" as used herein by itself or as part of another group refers but is not limited to 5 to 10 carbon-atom aromatic rings in which one or more carbon atoms can be replaced by oxygen, nitrogen or sulfur atoms. Non-limiting examples of such heteroaryl, include: pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, oxatriazolyl, pyridinyl, pyrimidyl, pyrazinyl, pyridazinyl, oxazinyl, dioxinyl, thiazinyl, triazinyl, imidazo[2,1-b][1,3]thiazolyl, thieno[3,2-b]furanyl, thieno[2,3-d]imidazolyl, tetrazolo[1,5-a]pyridinyl, indolyl, indolizyl, isoindolyl, benzofuranyl, isobenzofuranyl, indazolyl, benzimidazolyl, 1,3-benzoxazolyl, 1,2-benzisoxazolyl, 2,1-benzisoxazolyl, 1,3-benzothiazolyl, benzotriazolyl, 1,3-benzodioxolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, quinoxalinyl, 7-azaindolyl, 6-azaindolyl, 5-azaindolyl, 4-azaindolyl.

An "optionally substituted heteroaryl" refers to a heteroaryl having optionally one or more substituents (for example 1 to 4 substituents, for example 1, 2, 3 or 4), selected from those defined above for substituted alkyl.

The term "halo" or "halogen" as a group or part of a group is generic for fluoro, chloro, bromo, or iodo, as well as any suitable isotope thereof.

The term "oxo" as used herein refers to the group =O.

The term "alkoxy" or "alkyloxy" as used herein refers to a radical having the Formula -OR^b wherein R^b is alkyl. Preferably, alkoxy is C₁-C₁₀ alkoxy, C₁-C₆ alkoxy, or C₁-C₄ alkoxy. Non-limiting examples of suitable alkoxy include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy and hexyloxy. Where the oxygen atom in an alkoxy group is substituted with sulfur, the resultant radical is referred to as thioalkoxy. "Haloalkoxy" is an alkoxy group wherein one or more hydrogen atoms in the alkyl group are

substituted with halogen.

Whenever the term "substituted" is used in the present invention, it is meant to indicate that one or more hydrogens on the atom indicated in the expression using "substituted" is replaced with a selection from the indicated group, provided that the indicated atom's normal valency is not exceeded, and that the substitution results in a chemically stable compound, i.e. a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into a therapeutic and/or diagnostic agent.

Where groups may be optionally substituted, such groups may be substituted once or more, and preferably once, twice or thrice. Substituents may be selected from, those defined above for substituted alkyl.

As used herein the terms such as "alkyl, aryl, or cycloalkyl, each being optionally substituted with" or "alkyl, aryl, or cycloalkyl, optionally substituted with" refers to optionally substituted alkyl, optionally substituted aryl and optionally substituted cycloalkyl.

More generally, from the above, it will be clear to the skilled person that the compounds of the invention may exist in the form of different isomers and/or tautomers, including but not limited to geometrical isomers, conformational isomers, E/Z-isomers, stereochemical isomers (i.e. enantiomers and diastereoisomers) and isomers that correspond to the presence of the same substituents on different positions of the rings present in the compounds of the invention. All such possible isomers, tautomers and mixtures thereof are included within the scope of the invention.

In addition, the invention includes isotopically-labelled compounds and salts, which are identical to compounds of formula (I), but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number most commonly found in nature. Examples of isotopes that can be incorporated into compounds of formula (I) are isotopes of hydrogen, carbon, nitrogen, fluorine, such as ^2H (Deuterium), ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}O and ^{18}F . Such isotopically-labelled compounds of formula (I) are useful in drug and/or substrate tissue distribution assays. For example, ^2H (Deuterium) are particularly useful, when well positioned on the chemical structure, to decrease metabolism, hence improving pharmacokinetic profile of the deuterated analog in animals and humans (Uttamsingh *et al.*, CTP-656 Phase 1 study results). For example, ^{11}C and ^{18}F isotopes are particularly useful in PET (Positron Emission Tomography). PET is useful as a diagnostic or treatment follow-up tool that can be applied in a translational manner in a preclinical and clinical setting. It also has applications in PK determination of compounds, including biodistribution. Isotopically labeled compounds of formula (I) can generally be prepared by carrying out the procedures disclosed below, by substituting a readily available non-isotopically labeled reagent with an isotopically labeled reagent.

Whenever used in the present invention the term "compounds of the invention" or a similar term is meant to include the compounds of general Formula I and any subgroup thereof. This term also refers to the compounds as depicted in Table 1, their derivatives, *N*-oxides, salts, solvates, hydrates, stereoisomeric forms, racemic mixtures, tautomeric forms, optical isomers, analogues, as well as their quaternized nitrogen analogues. The *N*-oxide forms of said compounds are meant to comprise compounds wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide.

As used in the specification and the appended claims, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise. By way of example, "a compound" means one compound or more than one compound.

The terms described above and others used in the specification are well understood to those in the art.

In a particular embodiment, the present invention provides a compound of Formula I or a stereoisomer, tautomer, racemic, salt, hydrate, *N*-oxide form, or solvate thereof; wherein one or more of the following applies:

R_1 is selected from -Halo, -O-C₁₋₆alkyl, -Alkynyl, -C₁₋₆alkyl, -C(O)-C₁₋₆-alkyl, -C(O)-C₁₋₆cycloalkyl, -C(O)-Het₂, -C(O)-NR_aR_b, -Het₁ and -CN; each of said -C₁₋₆alkyl being optionally substituted with one or more substituents selected from -D, -Halo, -O-C₁₋₃alkyl, -C₃₋₆-cycloalkyl, -Ph, -Het₁, -Het₂, and -OH; each of said -Alkynyl being optionally substituted with one substituent selected from -C₁₋₆alkyl, and -CH₂-O-C₁₋₆alkyl;

R_2 and R_{10} are each independently selected from -H, and -Halo;

R_3 , $R_{3'}$, R_4 , $R_{4'}$, R_7 , and R_8 are each independently selected from -H, and -C₁₋₆alkyl; wherein each of said -C₁₋₆alkyl may optionally be substituted with one or more -O-C₁₋₆alkyl; wherein when R_3 and/or $R_{3'}$ is -C₁₋₆alkyl, then R_4 and $R_{4'}$ are each -H; wherein when R_4 and/or $R_{4'}$ is -C₁₋₆alkyl, then R_3 and $R_{3'}$ are each -H;

R_5 is selected from -OH, -NR_cR_{c'}, -NHC(O)R_c, -NC(O)R_cR_{c'}, -NC(O)OR_c, -NHS(O₂)R_c, -Halo, -O-C₁₋₆alkyl, -O-C₃₋₅-cycloalkyl, -O-Het₂, -C₁₋₆alkyl, and -CN; each of said -C₁₋₆alkyl being optionally substituted with one or more substituents selected from -D, -OH, -C₁₋₆alkyl, -C₃₋₅-cycloalkyl, -O-C₁₋₆alkyl and -Het₂;

R_6 is selected from -H, -Halo, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -O-Het₄, and -Het₃; each of said -C₁₋₆alkyl being optionally substituted with one or more substituents selected from -D, and -O-C₁₋₆alkyl;

R_9 is selected from -H, -C₁₋₆alkyl, -C(O)-C₁₋₆alkyl, and -C(O)-O-C₁₋₆alkyl;

R_a is selected from -H, and -C₁₋₆alkyl; each of said -C₁₋₆alkyl being optionally substituted with one or more substituents selected from -D, and -C₁₋₆alkyl;

R_b is selected from -H, -C₁₋₆alkyl, and -O-C₁₋₆alkyl; each of said -C₁₋₆alkyl being optionally substituted with one or more substituents selected from -D, -C₁₋₆alkyl, and -C₃₋₅-cycloalkyl;

R_c and $R_{c'}$ are each independently selected from $-H$, and $-C_{1-6}alkyl$; each of said $-C_{1-6}alkyl$ being optionally substituted with one or more substituents selected from $-D$, and $-C_{1-6}alkyl$;
 Het_1 and Het_3 are each independently selected from a 5 or 6-membered aromatic heterocycle having from 1 to 3 heteroatoms selected from O, N and S, wherein each of said Het_1 or
 5 Het_3 is optionally substituted with from 1 to 3 $-C_{1-6}alkyl$; each of said $-C_{1-6}alkyl$ being optionally substituted with one or more substituents selected from $-D$, $-halo$, $-O-C_{1-3}alkyl$, and $-OH$;
 Het_2 is selected from a 4 to 6-membered saturated heterocycle having from 1 to 3 heteroatoms selected from O and N; wherein each of said Het_2 is optionally substituted with from 1 to 3
 10 $-C_{1-6}alkyl$; each of said $-C_{1-6}alkyl$ being optionally substituted with one or more substituents selected from $-D$, $-halo$, $-O-C_{1-3}alkyl$, and $-OH$
 Het_4 is selected from a 4 to 10-membered saturated heterocycle having from 1 to 3 heteroatoms selected from O and N; wherein each of said Het_4 is optionally substituted with from 1 to 3 $-C_{1-6}alkyl$; each of said $-C_{1-6}alkyl$ being optionally substituted with one or
 15 more substituents selected from $-D$, $-halo$, $-O-C_{1-3}alkyl$, and $-OH$.

In a specific embodiment, the present invention provides a compound of Formula I or a stereoisomer, tautomer, racemic, salt, hydrate, N-oxide form, or solvate thereof, wherein
 R_1 is selected from $-Halo$, $-O-C_{1-6}alkyl$, $-Alkynyl$, $-C_{1-6}alkyl$, $-C(O)-C_{1-6}alkyl$, $-C(O)-C_{1-6}cycloalkyl$, $-C(O)-Het_2$, $-C(O)-NR_aR_b$, $-Het_1$ and $-CN$; each of said $-C_{1-6}alkyl$ being
 20 optionally substituted with one or more substituents selected from $-D$, $-Halo$, $-O-C_{1-3}alkyl$, $-C_{3-6}cycloalkyl$, $-Ph$, $-Het_1$, $-Het_2$, and $-OH$;
 R_2 and R_{10} are each independently selected from $-H$, and $-Halo$;
 R_3 , $R_{3'}$, R_4 , $R_{4'}$, R_7 , and R_8 are each independently selected from $-H$, and $-C_{1-6}alkyl$; wherein
 25 each of said $-C_{1-6}alkyl$ may optionally be substituted with one or more $-O-C_{1-6}alkyl$;
 wherein when R_3 and/or $R_{3'}$ is $-C_{1-6}alkyl$, then R_4 and $R_{4'}$ are each $-H$;
 wherein when R_4 and/or $R_{4'}$ is $-C_{1-6}alkyl$, then R_3 and $R_{3'}$ are each $-H$;
 R_5 is selected from $-OH$, $-NR_cR_{c'}$, $-NHC(O)R_c$, $-Halo$, $-O-C_{1-6}alkyl$, $-O-C_{3-5}cycloalkyl$, $-O-Het_2$, $-C_{1-6}alkyl$, and $-CN$; each of said $-C_{1-6}alkyl$ being optionally substituted with one or more
 30 substituents selected from $-D$, $-OH$, $-C_{1-6}alkyl$, $-C_{3-5}cycloalkyl$, $-O-C_{1-6}alkyl$ and $-Het_2$;
 R_6 is selected from $-H$, $-Halo$, $-C_{1-6}alkyl$, $-O-C_{1-6}alkyl$, $-O-Het_4$, and $-Het_3$; each of said $-C_{1-6}alkyl$ being optionally substituted with one or more substituents selected from $-D$, and $-O-C_{1-6}alkyl$;
 R_9 is selected from $-H$, $-C_{1-6}alkyl$, $-C(O)-C_{1-6}alkyl$, and $-C(O)-O-C_{1-6}alkyl$;
 35 R_a is selected from $-H$, and $-C_{1-6}alkyl$;
 R_b is selected from $-H$, $-C_{1-6}alkyl$, and $-O-C_{1-6}alkyl$;
 R_c and $R_{c'}$ are each independently selected from $-H$, and $-C_{1-6}alkyl$;
 Het_1 and Het_3 are each independently selected from a 5 or 6-membered aromatic heterocycle having from 1 to 3 heteroatoms selected from O and N, wherein each of said Het_1 and Het_3

is optionally substituted with from 1 to 3 $-C_{1-6}$ alkyl;

Het₂ is selected from a 4 to 6-membered saturated heterocycle having from 1 to 3 O atoms

Het₄ is selected from a 4 to 10-membered saturated heterocycle having from 1 to 3 heteroatoms selected from O and N; wherein each of said Het₄ is optionally substituted with from 1 to 3 $-C_{1-6}$ alkyl; each of said $-C_{1-6}$ alkyl being optionally substituted with one or more substituents selected from $-D$, $-halo$, $-O-C_{1-3}$ alkyl, and $-OH$.

In another specific embodiment, the present invention provides a compound of Formula I or a stereoisomer, tautomer, racemic, salt, hydrate, N-oxide form, or solvate thereof, wherein

10 R₁ is selected from $-Halo$, $-O-C_{1-6}$ alkyl, $-Alkynyl$, $-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ cycloalkyl, $-C(O)-Het_2$, $-C(O)-NR_aR_b$, $-Het_1$ and $-CN$; each of said $-C_{1-6}$ alkyl being optionally substituted with one or more substituents selected from $-D$, $-Halo$, $-O-C_{1-3}$ alkyl, $-C_{3-6}$ -cycloalkyl, $-Ph$, $-Het_1$, $-Het_2$, and $-OH$;

R₂ and R₁₀ are each independently selected from $-H$, and $-Halo$;

15 R₃, R_{3'}, R₄, R_{4'}, R₇, and R₈ are each $-H$;

R₅ is selected from $-OH$, $-Halo$, $-O-C_{1-6}$ alkyl, $-O-C_{3-5}$ -cycloalkyl, and $-C_{1-6}$ alkyl; each of said $-C_{1-6}$ alkyl being optionally substituted with one or more substituents selected from $-D$, $-OH$, $-C_{1-6}$ alkyl, $-C_{3-5}$ -cycloalkyl, and $-O-C_{1-6}$ alkyl;

20 R₆ is selected from $-H$, $-Halo$, $-C_{1-6}$ alkyl, $-O-C_{1-6}$ alkyl, $-O-Het_4$, and $-Het_3$; each of said $-C_{1-6}$ alkyl being optionally substituted with one or more $-O-C_{1-6}$ alkyl;

R₉ is selected from $-H$, $-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkyl, and $-C(O)-O-C_{1-6}$ alkyl;

R_a is selected from $-H$, and $-C_{1-6}$ alkyl;

R_b is selected from $-H$, $-C_{1-6}$ alkyl, and $-O-C_{1-6}$ alkyl; each of said $-C_{1-6}$ alkyl being optionally substituted with one or more ;

25 Het₁ and Het₃ are each independently selected from a 5 or 6-membered aromatic heterocycle having from 1 to 3 heteroatoms selected from O and N, wherein each of said Het₁ and Het₃ is optionally substituted with from 1 to 3 $-C_{1-6}$ alkyl;

Het₂ is selected from a 4 to 6-membered saturated heterocycle having from 1 to 3 O atoms;

30 Het₄ is selected from a 4 to 10-membered saturated heterocycle having from 1 to 3 heteroatoms selected from O and N; wherein each of said Het₄ is optionally substituted with from 1 to 3 $-C_{1-6}$ alkyl; each of said $-C_{1-6}$ alkyl being optionally substituted with one or more substituents selected from $-D$, $-halo$, $-O-C_{1-3}$ alkyl, and $-OH$.

In yet a further specific embodiment, the present invention provides a compound of Formula I or a stereoisomer, tautomer, racemic, salt, hydrate, N-oxide form, or solvate thereof, wherein

35 R₁ is selected from $-Halo$, $-O-C_{1-6}$ alkyl, $-Alkynyl$, $-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkyl, $-C(O)-NR_aR_b$, $-Het_1$ and $-CN$; each of said $-C_{1-6}$ alkyl being optionally substituted with one or more substituents selected from $-D$, $-Halo$, and $-O-C_{1-3}$ alkyl;

R₂ is selected from $-H$, and $-Halo$;

-20-

- R₁₀ is -H;
- R₃, R_{3'}, R₄, R_{4'}, R₇, and R₈ are each -H
- R₅ is selected from -OH, -Halo, -O-C₁₋₆alkyl, -O-C₃₋₅-cycloalkyl, and -C₁₋₆alkyl; each of said -C₁₋₆alkyl being optionally substituted with one or more substituents selected from -D, -OH, -
- 5 C₁₋₆alkyl, -C₃₋₅-cycloalkyl, and -O-C₁₋₆alkyl;
- R₆ is selected from -H, -Halo, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -O-Het₄, and -Het₃; each of said -C₁₋₆alkyl being optionally substituted with one or more -O-C₁₋₆alkyl;
- R₉ is -H;
- R_a is selected from -H, and -C₁₋₆alkyl;
- 10 R_b is selected from -H, -C₁₋₆alkyl, and -O-C₁₋₆alkyl;
- Het₁ is a 5-membered aromatic heterocycle having from 1 to 3 heteroatoms selected from O and N, wherein said Het₁ is optionally substituted with from 1 to 3 -C₁₋₆alkyl
- Het₄ is selected from a 4 to 10-membered saturated heterocycle having from 1 to 3 heteroatoms selected from O and N; wherein each of said Het₄ is optionally substituted
- 15 with from 1 to 3 -C₁₋₆alkyl; each of said -C₁₋₆alkyl being optionally substituted with one or more substituents selected from -D, -halo, -O-C₁₋₃alkyl, and -OH.
- In yet a further embodiment, the present invention provides a compound of Formula I or a stereoisomer, tautomer, racemic, salt, hydrate, N-oxide form, or solvate thereof, wherein one
- 20 or more of the following applies:
- R₁ is selected from -Halo, -O-C₁₋₆alkyl, -Alkynyl, -C₁₋₆alkyl, -C(O)-C₁₋₆-alkyl, -C(O)-NR_aR_b, -Het₁ and -CN; each of said -C₁₋₆alkyl being optionally substituted with one or more substituents selected from -D, -Halo, and -O-C₁₋₃alkyl;
- R₂ is selected from -H, and -Halo;
- 25 R₁₀ is -H;
- R₃, R_{3'}, R₄, R_{4'}, R₇, and R₈ are each -H
- R₅ is selected from -OH, -Halo, -O-C₁₋₆alkyl, -O-C₃₋₅-cycloalkyl, and -C₁₋₆alkyl; each of said -C₁₋₆alkyl being optionally substituted with one or more substituents selected from -D, -OH, -C₁₋₆alkyl, -C₃₋₅-cycloalkyl, and -O-C₁₋₆alkyl;
- 30 R₆ is selected from -H, -Halo, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -O-Het₄, and -Het₃; each of said -C₁₋₆alkyl being optionally substituted with one or more -O-C₁₋₆alkyl;
- R₉ is -H;
- R_a is selected from -H, and -C₁₋₆alkyl;
- R_b is selected from -H, -C₁₋₆alkyl, and -O-C₁₋₆alkyl;
- 35 Het₁ is a 5-membered aromatic heterocycle having from 1 to 3 heteroatoms selected from O and N, wherein said Het₁ is optionally substituted with from 1 to 3 -C₁₋₆alkyl
- Het₄ is selected from a 4 to 10-membered saturated heterocycle having from 1 to 3 heteroatoms selected from O and N; wherein each of said Het₄ is optionally substituted with from 1 to 3 -C₁₋₆alkyl; each of said -C₁₋₆alkyl being optionally substituted with one or

more substituents selected from -D, -halo, -O-C₁₋₃alkyl, and -OH.

In a more specific embodiment, the present invention provides a compound selected from any of the tables disclosed herein.

5

The compounds of the present invention can be prepared according to the reaction schemes provided in the examples hereinafter, but those skilled in the art will appreciate that these are only illustrative for the invention and that the compounds of this invention can be prepared by any of several standard synthetic processes commonly used by those skilled in the art of organic chemistry.

10

The present invention further provides a pharmaceutical composition comprising a compound according to this invention.

In a further aspect, the present invention provides a compound or a composition according to this invention, for use as a human or veterinary medicine.

15

In a particular embodiment, the present invention provides a compound or composition according to this invention for use in the diagnosis, prevention and/or treatment of a RIP2-kinase associated disease.

Said RIP2-kinase associated disease may in particular be inflammatory disorders, in particular Crohn's disease, bowel disease, sarcoidosis, psoriasis, atopic dermatitis, allergic rhinitis, rheumatoid arthritis, asthma, insulin-resistant type 2 diabetes, obesity metabolic syndrome, cardiac hypertrophy, ulcerative colitis, lupus, uveitis, Blau syndrome, granulomatous inflammation, Behçet's disease, immune-mediated colitis, and multiple sclerosis.

20

Alternatively, said RIP2-kinase associated disease may be cancer, more in particular selected from breast cancers (including Inflammatory Breast Cancer), head and neck cancers and gliomas.

25

Furthermore, the present invention provides the use of a compound or composition according to this invention, suitable for inhibiting the activity of a kinase; in particular a RIP2 kinase; or for the diagnosis, prevention and/or treatment of a RIP2-kinase associated disease.

Finally, the present invention provides a method for prevention and/or treatment of a RIP2-kinase associated disease; said method comprising administering to a subject in need thereof a compound or a composition according to the present invention.

30

35

METHOD OF TREATMENT

Compounds of formula (I) or (Ia) a stereoisomer, tautomer, racemic, metabolite, pro- or pre-drug, salt, hydrate, N-oxide form, or solvate thereof, are inhibitors of RIP2 kinase activity and are thus believed to be of potential use in the diagnosis, prevention and/or treatment of inflammatory disorders, or cancer.

As used herein, the terms "inflammatory disorder" or "inflammatory disease" can refer to a disorder or disease characterized by aberrant activation of the immune system that leads to or causes pathogenesis of several acute and chronic conditions including, for example, Crohn's disease, bowel disease, Sarcoidosis, psoriasis, rheumatoid arthritis, asthma, ulcerative colitis, lupus, uveitis, Blau syndrome, granulomatous inflammation, in particular Behçet's disease, multiple sclerosis and insulin-resistant type 2 diabetes. An inflammatory disease can include a state in which there is a response to tissue damage, cell injury, an antigen, an infectious disease, and/or some unknown cause. Symptoms of inflammation may include, but are not limited to, cell infiltration and tissue swelling.

As used herein, the term "cancer" can refer to a disorder or disease characterized by abnormal cell growth with the potential to invade or spread to different parts of the body; such as for example breast cancers (including Inflammatory Breast Cancer), head and neck cancers and gliomas.

In the invention, particular preference is given to compounds of Formula I or any subgroup thereof that in the inhibition assay for RIP2 described below inhibit kinase activity with an IC_{50} value of less than 10 μ M, preferably less than 1 μ M, most preferably less than 100 nM.

Said inhibition may be effected *in vitro* and/or *in vivo*, and when effected *in vivo*, is preferably effected in a selective manner, as defined above.

The term "RIP2 kinase-mediated condition" or "disease", as used herein, means any disease or other deleterious condition in which the RIP2 kinase and/or mutants thereof is/are known to play a role. The term "RIP2 kinase-mediated condition" or "disease" also means those diseases or conditions that are alleviated by treatment with a RIP2 kinase inhibitor. Accordingly, another embodiment of the present invention relates to treating or lessening the severity of one or more diseases in which the RIP2 kinase is known to play a role.

For pharmaceutical use, the compounds of the invention may be used as a free acid or base, and/or in the form of a pharmaceutically acceptable acid-addition and/or base-addition salt (e.g. obtained with non-toxic organic or inorganic acid or base), in the form of a hydrate, solvate and/or complex. As used herein and unless otherwise stated, the term "solvate" includes any combination which may be formed by a compound of this invention with a suitable inorganic solvent (e.g. hydrates) or organic solvent, such as but not limited to alcohols, ketones, esters and the like.

The pharmaceutically acceptable salts of the compounds according to the invention, i.e. in the form of water-, oil-soluble, or dispersible products, include the conventional non-toxic salts or the quaternary ammonium salts which are formed, e.g., from inorganic or organic acids or bases.

- 5 Generally, for pharmaceutical use, the compounds of the inventions may be formulated as a pharmaceutical preparation or pharmaceutical composition comprising at least one compound of the invention and at least one pharmaceutically acceptable carrier, diluent or excipient and/or adjuvant, and optionally one or more further pharmaceutically active compounds.

10 By means of non-limiting examples, such a formulation may be in a form suitable for oral administration, for parenteral administration (such as by intravenous, intramuscular or subcutaneous injection or intravenous infusion), for administration by inhalation, by a skin patch, by an implant, by a suppository, etc.. Such suitable administration forms – which may be solid, semi-solid or liquid, depending on the manner of administration – as well as methods and carriers, diluents and excipients for use in the preparation thereof, will be clear to the skilled person.

Some preferred, but non-limiting examples of such preparations include tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments, creams, lotions, soft and hard gelatin capsules, suppositories, eye drops, sterile injectable solutions and sterile packaged powders (which are usually reconstituted prior to use) for administration as a bolus and/or for continuous administration, which may be formulated with carriers, excipients, and diluents that are suitable per se for such formulations. The formulations can optionally contain other pharmaceutically active substances (which may or may not lead to a synergistic effect with the compounds of the invention) and other substances that are commonly used in pharmaceutical formulations. The compositions may also be formulated so as to provide rapid, sustained or delayed release of the active compound(s) contained therein.

For local administration, the compounds may advantageously be used in the form of a spray, ointment or transdermal patch or another suitable form for topical, transdermal and/or intradermal administration.

30

Composition

Compounds of Formula (1) or pharmaceutically acceptable salts thereof may be formulated into pharmaceutical compositions prior to administration to a subject. According to one aspect, the invention provides a pharmaceutical composition comprising a compound of Formula (1) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient. According to another aspect, the invention provides a process for the preparation of a

pharmaceutical composition comprising admixing a compound of Formula (1) or a pharmaceutically acceptable salt thereof, with a pharmaceutically acceptable excipient.

Pharmaceutical compositions may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Such a unit may contain, for example, 0.1mg, 0.5mg, or 1mg to 50mg, 100mg, 200mg, 250mg, 500mg, 750mg or 1g of a compound of the present invention, depending on the disease being treated, the route of administration and the age, weight and condition of the subject, or pharmaceutical compositions may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. In other embodiments, the unit dosage compositions are those containing a daily dose or sub-dose as described herein, or an appropriate fraction thereof, of an active ingredient. Furthermore, such pharmaceutical compositions may be prepared by any of the methods well-known to one skilled in the art.

A therapeutically effective amount of a compound of Formula (1) will depend upon a number of factors including, for example, the age and weight of the intended recipient, the precise condition requiring treatment and its severity, the nature of the formulation, and the route of administration, and will ultimately be at the discretion of the attendant prescribing the medication. However, a therapeutically effective amount of a compound of formula (1) for the treatment of diseases described in the present invention will generally be in the range of 0.1 to 100mg/kg body weight of recipient per day and more usually in the range of 1 to 10mg/kg body weight per day. Thus, for a 70 kg adult mammal, the actual amount per day would usually be from 70 to 700mg and this amount may be given in a single dose per day or in a number of sub-doses per day as such as two, three, four, five or six doses per day. Or the dosing can be done intermittently, such as once every other day, once a week or once a month. A therapeutically effective amount of a pharmaceutically acceptable salt or solvate, etc., may be determined as a proportion of the therapeutically effective amount of the compound of Formula (1) *per se*. It is envisaged that similar dosages would be appropriate for treatment of the other diseases referred to above.

The pharmaceutical compositions of the invention may contain one or more compounds of Formula (1) or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical compositions may contain more than one compound of the invention. For example, in some embodiments, the pharmaceutical compositions may contain two or more compounds of Formula (1) or a pharmaceutically acceptable salt thereof. In addition, the pharmaceutical compositions may optionally further comprise one or more additional active pharmaceutical ingredients (APIs).

As used herein, "pharmaceutically acceptable excipient" means a pharmaceutically acceptable material, composition or vehicle involved in giving form or consistency to the pharmaceutical composition. Each excipient may be compatible with the other ingredients of the pharmaceutical composition when commingled such that interactions which would

substantially reduce the efficacy of the compound of the invention when administered to a subject and interactions which would result in pharmaceutical compositions that are not pharmaceutically acceptable are avoided.

The invention will now be illustrated by means of the following synthetic and biological examples, which do not limit the scope of the invention in any way.

ABBREVIATIONS

The following abbreviations are employed herein:

- Ph = phenyl
- Ac = Acetate
- 10 Bn = benzyl
- t-Bu = tertiary butyl
- n-Bu = linear butyl
- Me = methyl
- Et = ethyl
- 15 Pr = propyl
- iPr = isopropyl
- Bu = Butyl
- TMS = trimethylsilyl
- TBS = tert-butyldimethylsilyl
- 20 THF = tetrahydrofuran
- DMF = dimethyl formamide
- AA = acetic acid
- TFA = trifluoroacetic acid
- i-Pr₂NEt or DIPEA = diisopropylethylamine
- 25 TEA = triethylamine
- DMAP = 4-dimethylaminopyridine
- Pd/C = palladium on carbon
- KOH = potassium hydroxide
- NaOH = sodium hydroxide
- 30 LiOH = lithium hydroxide
- Ar = argon
- N₂ = nitrogen
- EDC = 3-ethyl-3'-(dimethylamino)propyl-carbodiimide hydrochloride (or 1-[(3-(dimethyl)amino)propyl]-3-ethylcarbodiimide hydrochloride)
- 35 HOBT = 1-hydroxybenzotriazole hydrate
- DIC = 1,3-dipropylcarbodiimide
- BOP = (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate
- PyBOP = benzotriazol-1-yloxy-tripyrrolidino phosphonium hexafluorophosphate

-26-

HATU = 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid

hexafluorophosphate

LiHMDS = lithium bis(trimethylsilyl)amide

LAH = Lithium Aluminium Hydride

5 Boc = tert-butoxycarbonyl

Cbz = Carboxybenzyl

LDA = lithium diisopropylamide

NBS = N-bromosuccinimide

ACN = Acetonitrile

10 min = minute(s)

h or hr = hour(s)

L = liter

mL = milliliter

μL = microliter

15 g = gram(s)

mg = milligram(s)

mol = moles

mmol = millimole(s)

meq = milliequivalent

20 rt = room temperature

RT = retention time

sat or sat'd = saturated

aq. = aqueous

TLC = thin layer chromatography

25 HPLC = high performance liquid chromatography

LC/MS = high performance liquid chromatography/mass spectrometry

MS or Mass Spec = mass spectrometry

NMR = nuclear magnetic resonance

mp = melting point

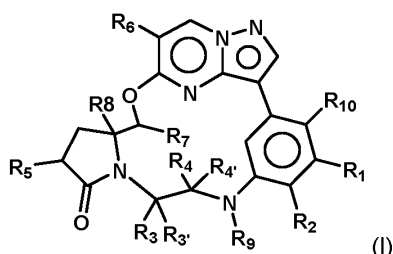
30

EXAMPLES

The compounds of the present invention may be synthesized by many methods available to those skilled in the art of organic chemistry (Maffrand, J.P. *et al.*, *Heterocycles*, 16(1):35-37 (1981)). General synthetic schemes for preparing compounds of the present invention are described below. These schemes are illustrative and are not meant to limit the possible techniques one skilled in the art may use to prepare the compounds disclosed herein. Different methods to prepare the compounds of the present invention will be evident to those skilled in the art. Additionally, the various steps in the synthesis may be performed in an alternate sequence in order to give the desired compound or compounds.

General schemes:

As indicated herein before, the present invention in general provides compounds according to formula I.



5 Examples of compounds of the present invention prepared by methods described in the general schemes are given in the intermediates and examples section set out hereinafter. Preparation of homochiral examples may be carried out by techniques known to one skilled in the art. For example, homochiral compounds may be prepared by separation of racemic products by chiral phase preparative HPLC or preparative SFC. Alternatively, the example
10 compounds may be prepared by methods known to give enantiomerically enriched products. These include, but are not limited to, the incorporation of chiral auxiliary functionalities into racemic intermediates which serve to control the diastereoselectivity of transformations, providing enantio-enriched products upon cleavage of the chiral auxiliary.

The compounds of the present invention can be prepared in a number of ways known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or by variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. The reactions are performed in a solvent or solvent mixture appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention.

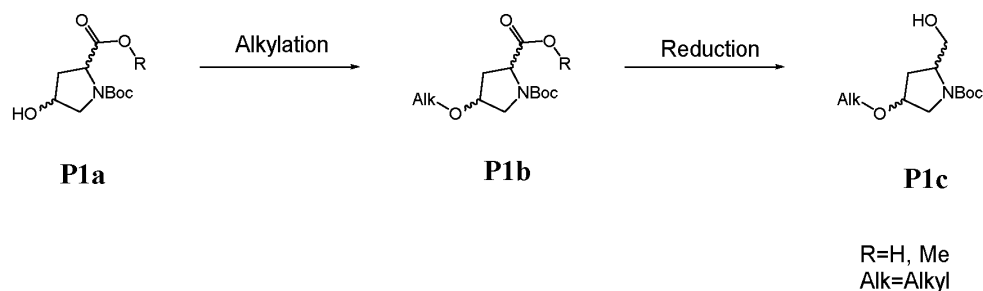
25 It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. An authoritative account describing the many alternatives to the trained practitioner is Greene *et al.* (*Protective Groups in Organic Synthesis*, 4th Edition, Wiley-Interscience (2006)).

30 Compounds of this invention with the formula (I) can be prepared by the methods illustrated in the following schemes.

-28-

As shown in Scheme 1a, Compound **P1a** (commercially available) can undergo alkylation reaction either using silver oxide or sodium hydride to afford compound **P1b**. The expected compound **P1c** can be obtained by reduction of the acid or ester moiety in presence of a reductive agent (such as LAH, Sodium borohydride or $\text{BH}_3\cdot\text{SMe}_2$).

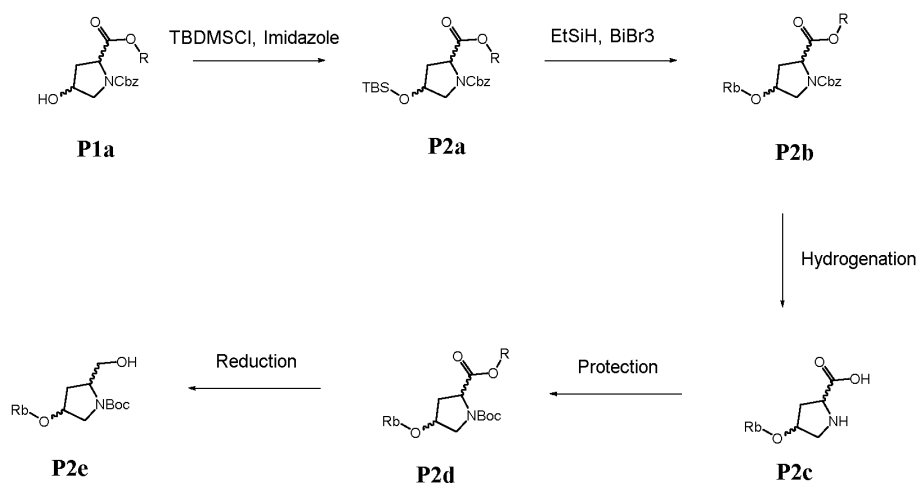
5 Scheme 1a



As shown in Scheme 1b, Compound **P1a** (commercially available) can undergo silylation reaction in presence of weak base (such as Imidazole) to afford compound **P2a**. The ether **P2b** can be obtained by reaction with an aldehyde or a ketone in presence of BiBr_3 and Triethylsilane. The sequential hydrogenation in presence of Pd/C, Boc protection and ester reduction in presence of Borohydride reagent can afford the expected compound **P2e**.

10

Scheme 1b

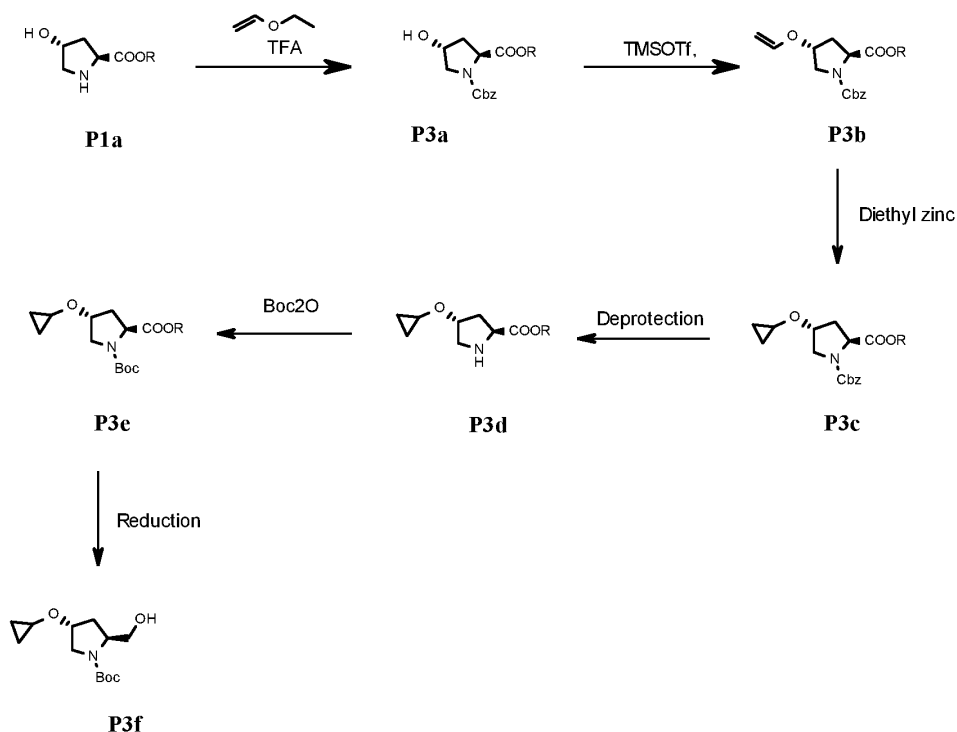


As shown in Scheme 1c, Compound **P1a** (commercially available) can undergo a reaction in presence of TMSOTf to afford the enolate **P3b**. The cyclopropanation can be achieved in presence of Diethyl Zinc afforded **P3c**. 2-step transprotection can be achieved by sequential deprotection of Cbz in presence of Palladium on charcoal, followed by Boc_2O reaction to obtain **P3e**. A final reduction in presence of Borohydride reagent can afford the expected compound **P3f**.

20

-29-

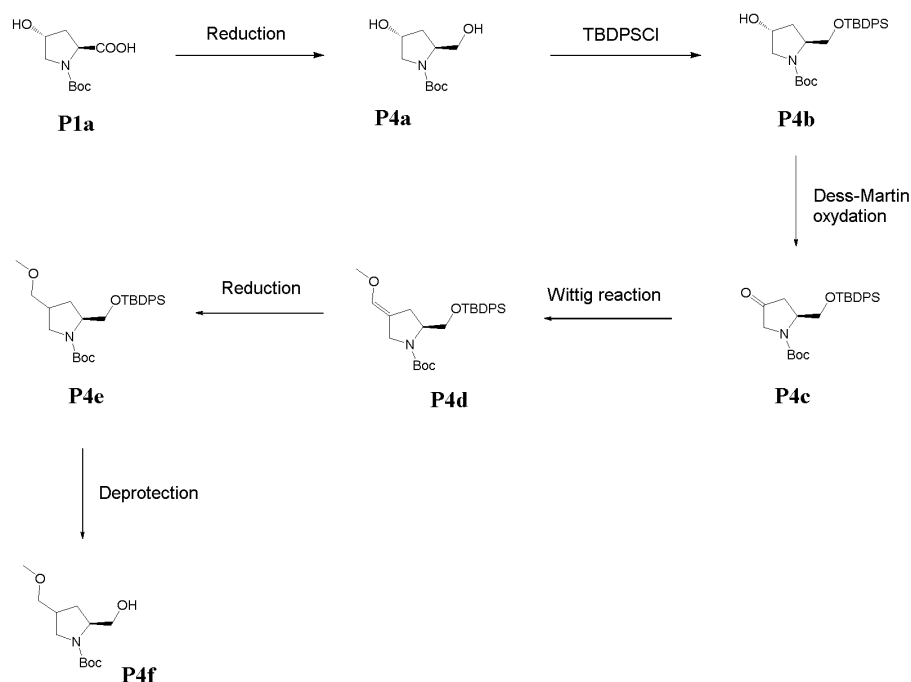
Scheme 1c



As shown in Scheme 1d, Compound **P1a** (commercially available) can undergo reduction reaction in presence of a borane reagent (such as $\text{BH}_3 \cdot \text{SMe}_2$) to afford compound **P4a**. The primary alcohol can be protected in presence of TBDPSCI, followed by a Dess-Martin oxidation to afford the ketone **P4c**. The enolate **P4d** can be obtained by Wittig reaction, followed by a reduction of the double bond by hydrogenation. The expected compound **P4f** can be obtained by deprotection of the silyl group, for example in presence of a fluorine-containing reagent.

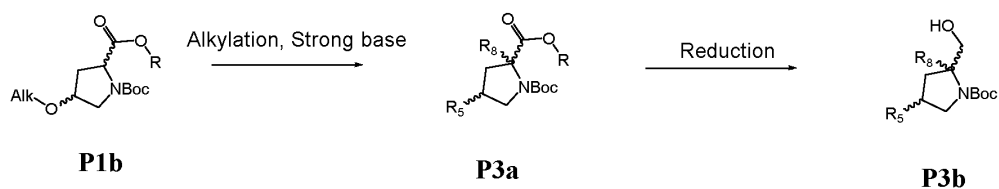
-30-

Scheme 1d



As shown in Scheme 1e, Compound **P1b** can undergo alkylation reaction in presence of strong base (such as LDA) to afford compound **P2a**. The reduction of the ester moiety in presence of Sodium borohydride can afford the expected compound **P2b**.

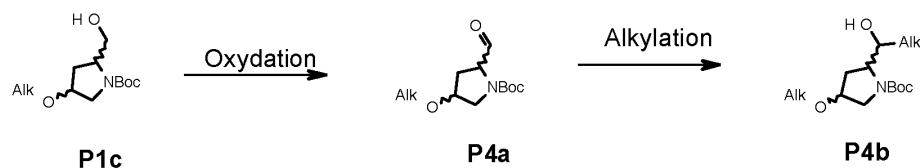
Scheme 1e



10

As shown in Scheme 1f, Compound **P1c** can undergo oxidation under Swern conditions followed by strong alkylating agent (such as alkylmagnesium bromide) to afford the Pyrrolidine **P4b**.

Scheme 1f



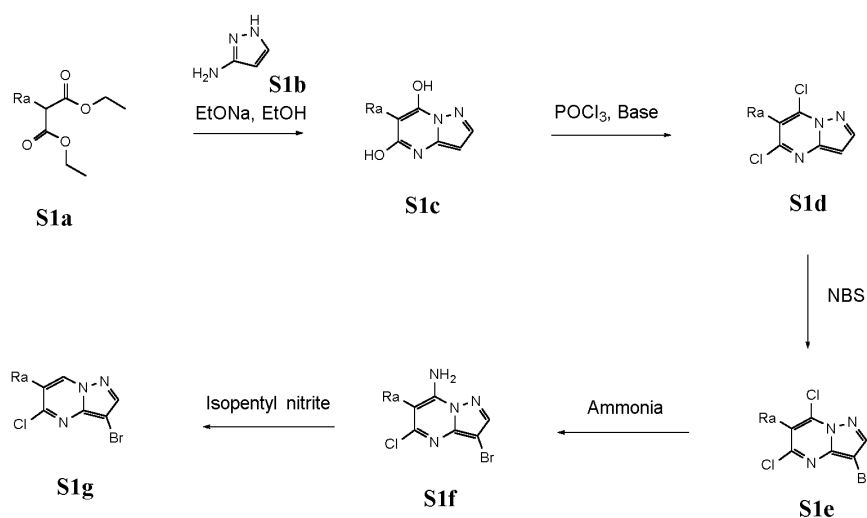
15

-31-

As shown in Scheme 2a, Compound **S1a** can undergo cyclization reaction in presence of amino-pyrazole **S1b**. The intermediate **S1c** can be sequential treated by Phosphorous oxychloride followed by N-bromosuccinimide to give the intermediate **S1e**. An aromatic nucleophilic substitution can be achieved in presence of Ammonia to afford compound **S1f**.

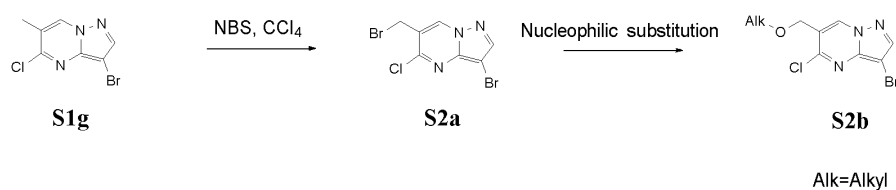
- 5 The scaffold **S1g** is obtained by diazotation reaction in presence of isopentyl nitrite, followed by elimination in a one-pot reaction.

Scheme 2a



- 10 As shown in Scheme 2b, Compound **S1g** can undergo a bromination in presence of N-bromosuccinimide to afford compound **S2a**. The expected compound **S2b** can be obtained by alkylation of the scaffold by Sodium alcoholates.

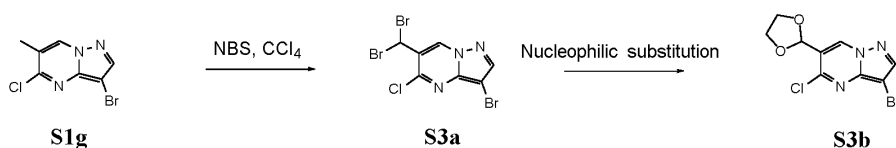
Scheme 2b



15

As shown in Scheme 2c, Compound **S1g** can undergo a bromination in presence of N-bromosuccinimide to afford compound **S3a**. The expected compound **S3b** can be obtained by alkylation of the scaffold by Sodium alcoholates.

Scheme 2c

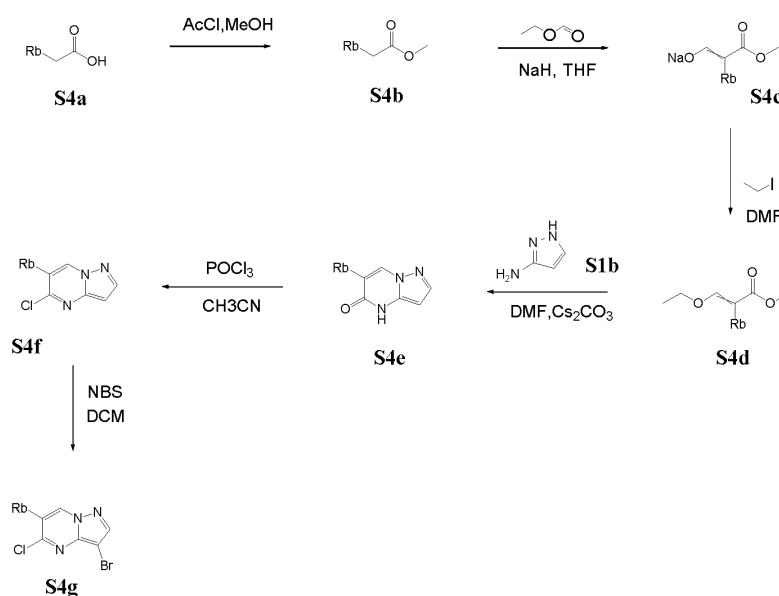


20

-32-

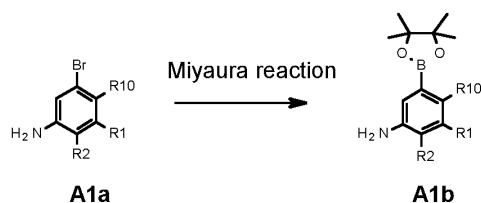
As shown in Scheme 2d, Compound **S4a** can undergo esterification in presence of MeOH and Acetyl Chloride, followed by reaction with Ethyl formate in presence of a strong base. Intermediate **S4c** was converted to the enol ester **S4d**. The subsequent cyclization reaction can be achieved in presence of amino-pyrazole **S1b**. The intermediate **S4e** can be sequential treated by Phosphorous oxychloride followed by N-bromosuccinimide to afford the expected compound **S4g**.

Scheme 2d



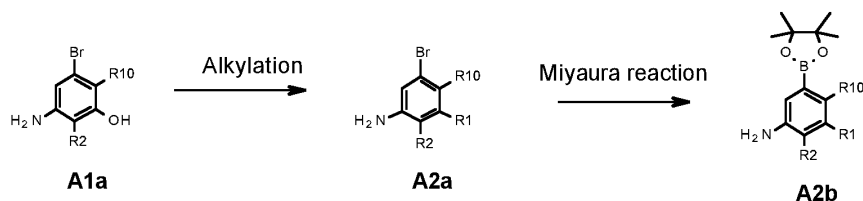
As shown in Scheme 3a, Compound **A1a** can undergo Miyaura borylation reaction to afford **A1b**.

Scheme 3a



As shown in Scheme 3b, Compound **A1a** can undergo alkylation in presence of alkyl halide to afford the intermediate **A2a**. The aniline **A2b** can be obtained by Miyaura borylation reaction.

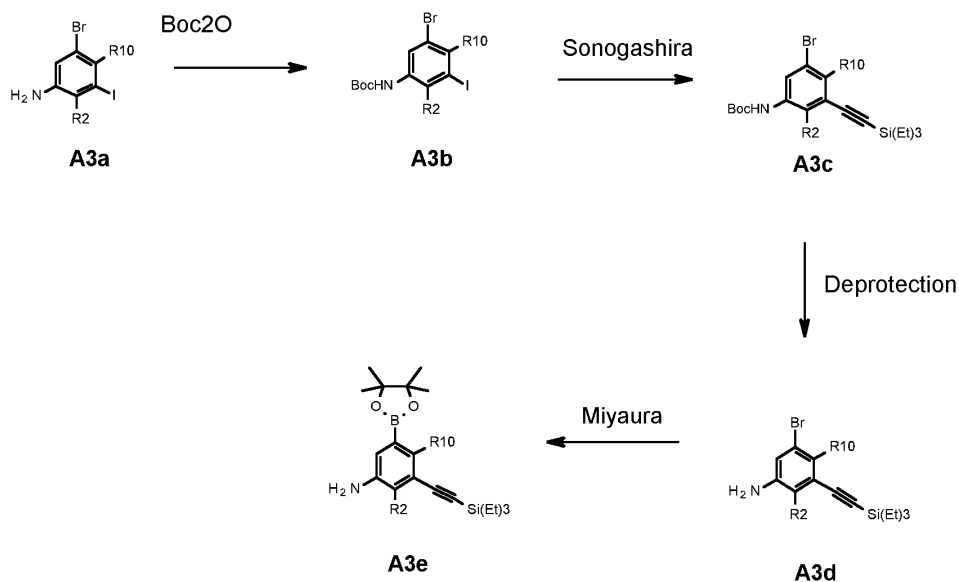
Scheme 3b



-33-

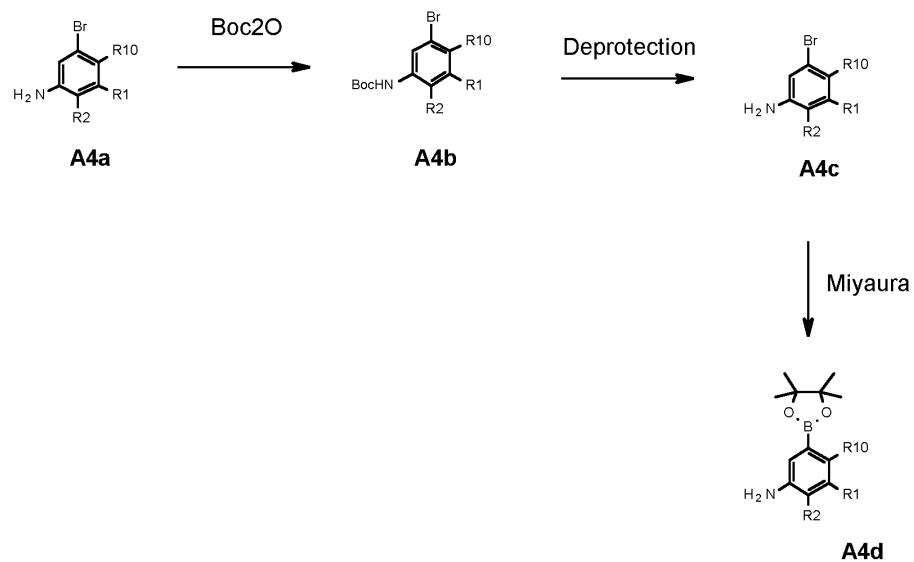
As shown in Scheme 3c, Compound **A3a** can undergo Bocylation, followed by a Sonogashira to obtain intermediate **A3c**. The Bromide can be converted to the free aniline **A3d** using strong acid (such as HCl), which can undergo Miyaura borylation reaction to afford **A3e**.

Scheme 3c



As shown in Scheme 3d, Compound **A4a** can undergo Bocylation, followed by Boc deprotection (purification process) to afford intermediate **A4c**. The compound **A4d** can be obtained by Miyaura borylation reaction.

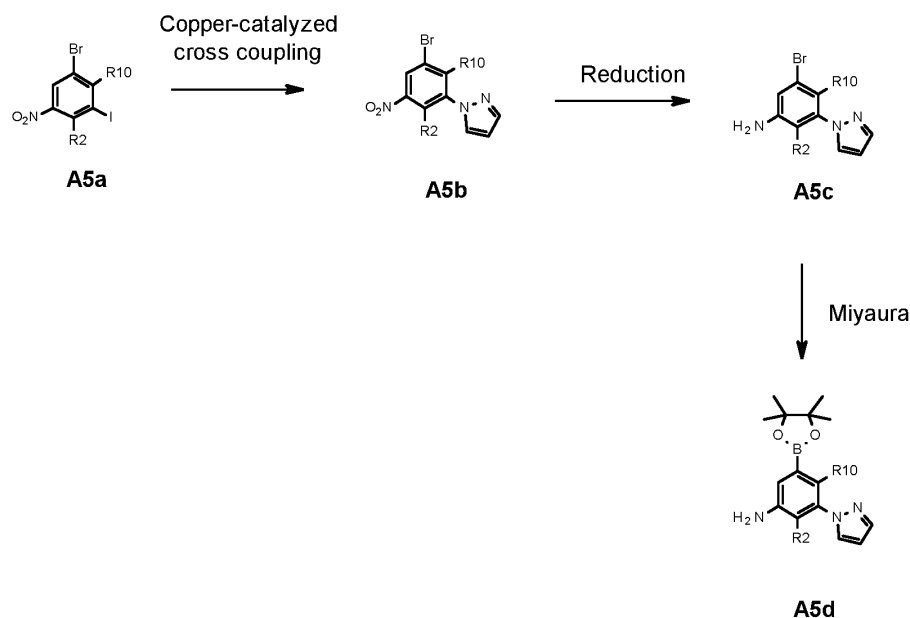
10 Scheme 3d



-34-

As shown in Scheme 3e, Compound **A5a** can undergo Copper-catalyzed cross-coupling reaction followed by nitro reduction (for example using Iron and Ammonium Chloride) to afford intermediate **A5c**. The compound **A5d** can be obtained by Miyaura borylation reaction.

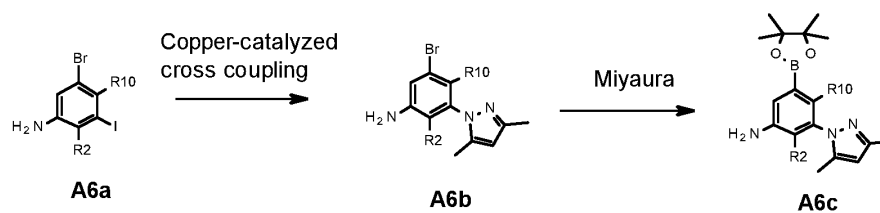
Scheme 3e



5

As shown in Scheme 3f, Compound **A6a** can undergo Copper-catalyzed cross-coupling reaction followed by Miyaura borylation reaction to afford the boronate **A6c**.

Scheme 3f



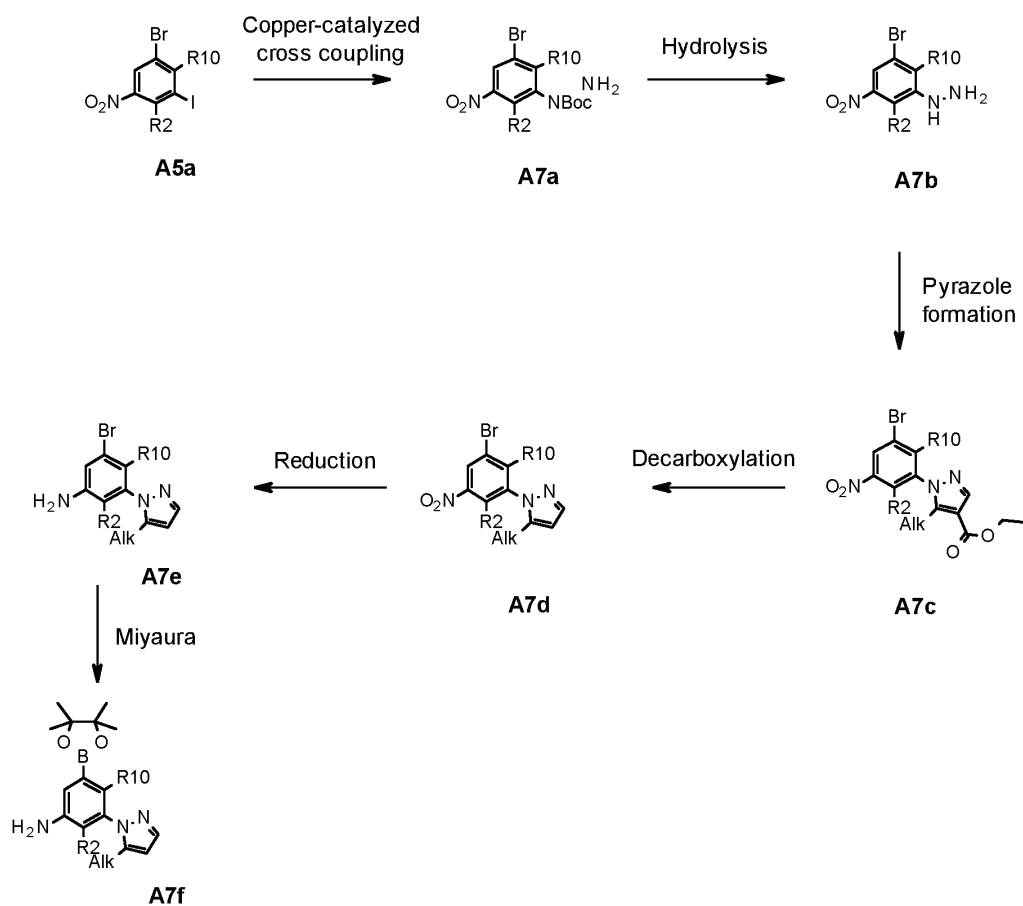
10

As shown in Scheme 3g, Compound **A5a** can undergo Copper-catalyzed cross-coupling reaction followed by Boc hydrolysis to afford the boronate **A6c**. The hydrazine derivative can be converted to the pyrazole **A7c**. The intermediate can be decarboxylated in presence of strong acid, followed by nitro reduction in presence using Iron and Ammonium chloride to afford **A7e**. The boronate **A7f** can be obtained by Miyaura borylation reaction.

15

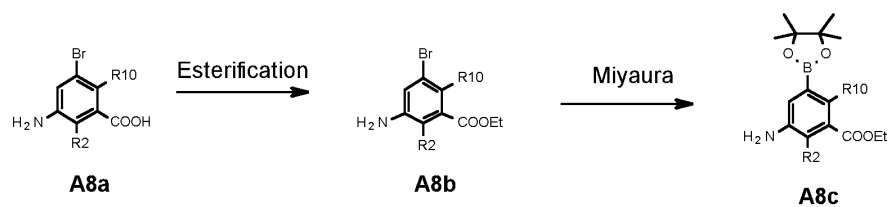
-35-

Scheme 3g



- 5 As shown in Scheme 3h, Compound **A8a** can undergo esterification followed by Miyaura borylation reaction to afford the boronate **A8c**.

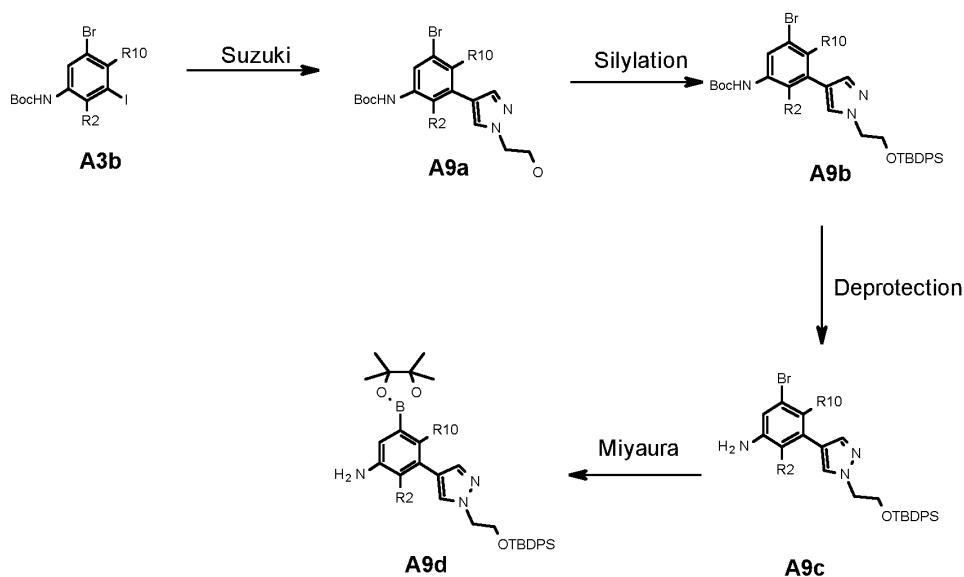
Scheme 3h



-36-

As shown in Scheme 3i, Compound **A3a** can undergo Suzuki coupling followed by a silylation protection by TBDPS to obtain intermediate **A9c**. The compound can be converted to a free aniline using strong acid (for example HCl) followed by Miyaura borylation reaction to afford the boronate **A9d**.

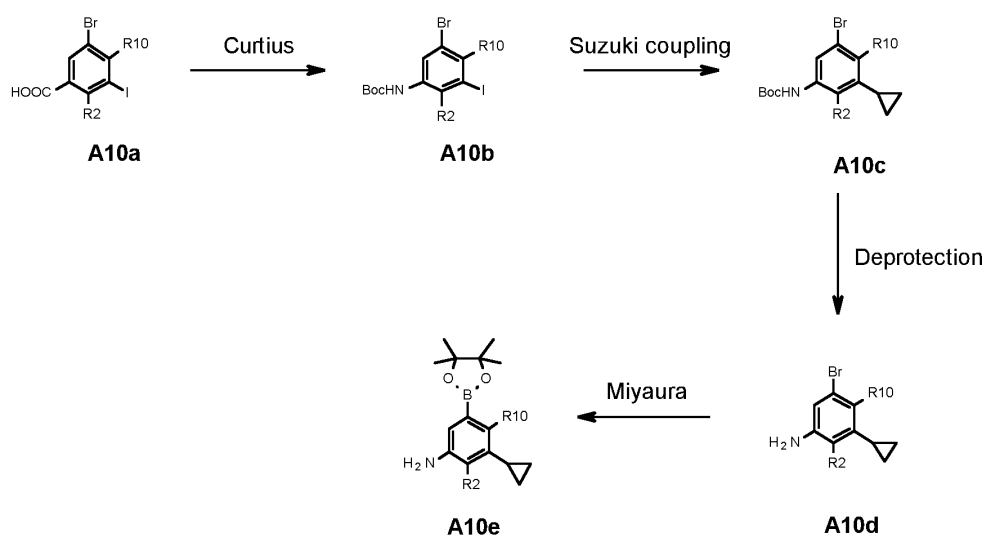
5 Scheme 3i



As shown in Scheme 3j, Compound **A10a** can undergo Curtius reaction followed by a Suzuki coupling to obtain intermediate **A10c**. The compound can be converted to a free aniline using strong acid (for example HCl) followed by Miyaura borylation reaction to afford the boronate **A10e**.

10

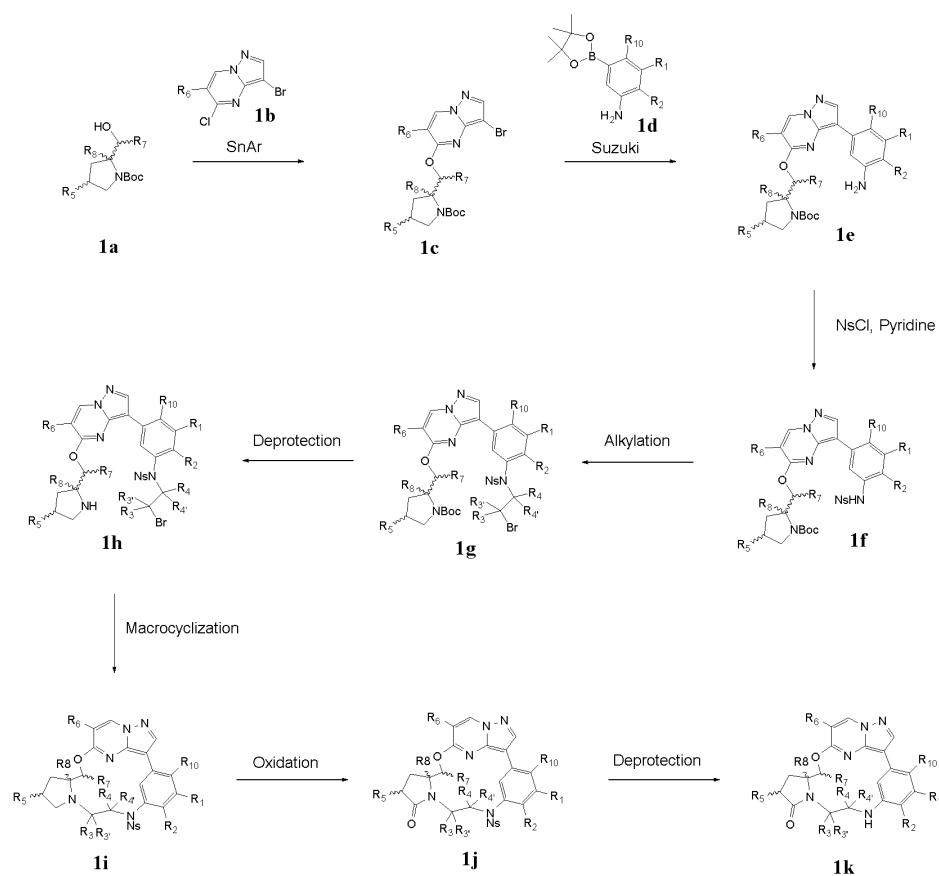
Scheme 3j



-37-

As shown in Scheme 1, Compound **1a**, accounting for intermediates such as **P1c** or **P2b**, can undergo aromatic nucleophilic substitution by reaction with **1b**. The Boronic ester **1d**, prepared from its corresponding Bromophenyl by Borylation, can be introduced by transition metal catalyzed cross coupling to afford **1e**. Sequential Nosyl protection of the aniline, its alkylation and deprotection of the Boc group can lead to the amine **1h**. Macrocyclization can be performed using Finkelstein conditions to give **1i**, which can be followed by oxidation in presence of iodine to afford **1j**. Nosyl deprotection can provide final compound **1k**.

Scheme 1:



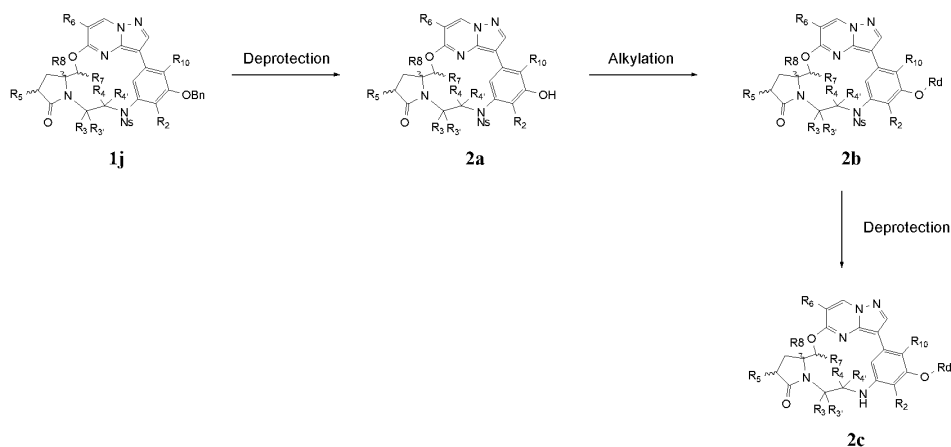
10

As shown in Scheme 2, compound **1j**, containing $\text{R}_1=\text{OBn}$, can be deprotected in presence of TFA and Anisole to afford the phenol **2a**. Subsequent and sequential alkylation and deprotection of the Nosyl provides final compound **2c**.

15

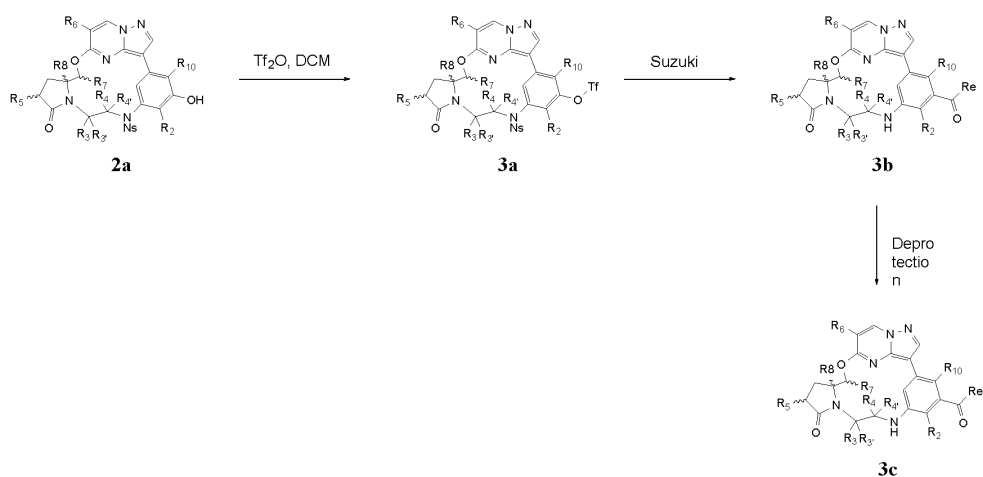
-38-

Scheme 2



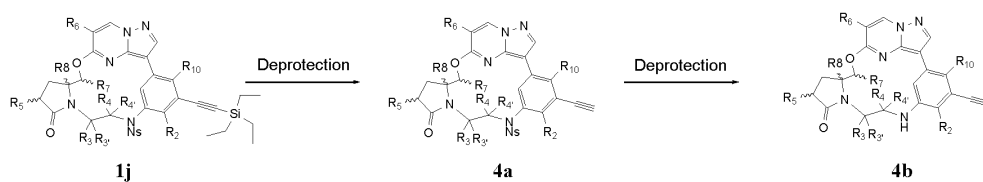
As shown in Scheme 3, the phenol **2a** can be converted to the triflate **3a**. Acyl moieties were introduced by transition metal catalyzed cross coupling to afford **3b**. Subsequent deprotection of the Nosyl provides final compound **3c**.

Scheme 3



As shown in Scheme 4, the final compound **4b** could be obtained by sequential deprotection of the Nosyl group then by removal of the silyl moiety in presence of Methanol and a base from the compound **1j**.

Scheme 4

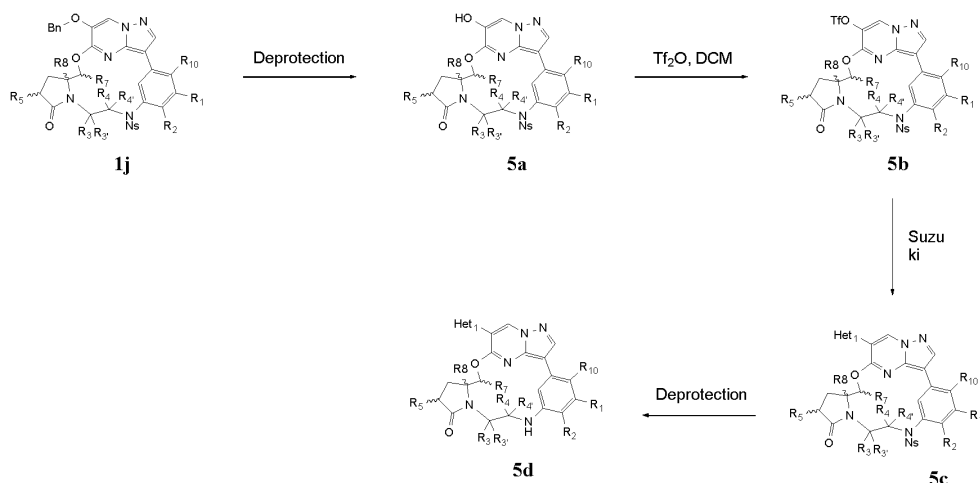


-39-

As shown in Scheme 5, compound **1j**, containing $R_6=OBn$, can undergo a deprotection of the benzylic moiety in presence of TFA and Anisole to afford the phenol **5a**. Following the formation of a triflate in presence of Triflate anhydride and Pyridine, a saturated heterocycle was introduced by a transition metal catalyzed cross coupling to afford the compound **5c**. The

5 Nosyl group was removed in presence of Thiophenol to afford the final compound **5d**.

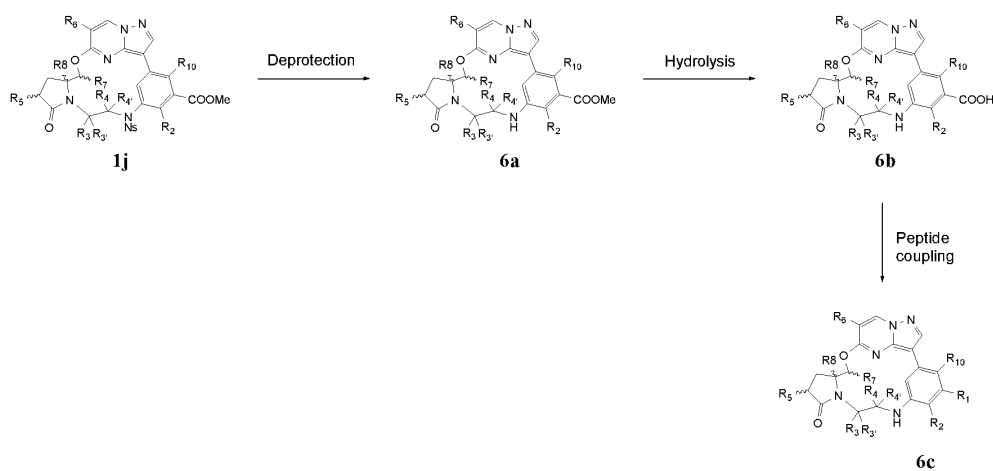
Scheme 5



As shown in Scheme 6, compound **1j**, containing $R_1=COOMe$, can undergo hydrolysis to the compound **6a**. Following a saponification in presence of a base to the compound **6b**, a peptidic coupling can afford the final compound **6c**.

10

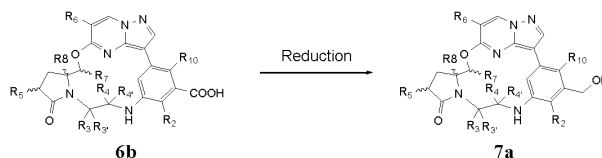
Scheme 6



-40-

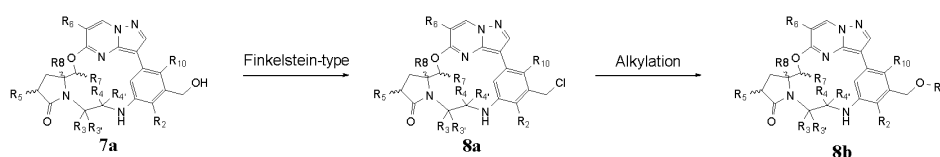
As shown in Scheme 7, compound **6b** can undergo reduction in presence of Borane dimethyl sulfide to afford the final compound **7a**.

Scheme 7



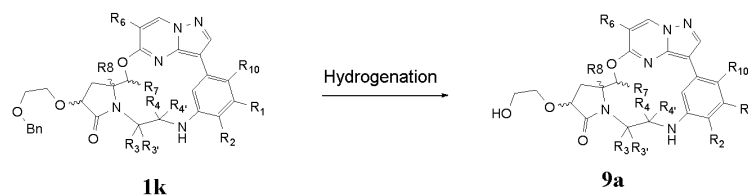
- 5 As shown in Scheme 8, compound **7a** can undergo chlorination in presence of Thionyl chloride to give compound **8a**. The final compound **8b** is obtained by alkylation of alcoholates.

Scheme 8



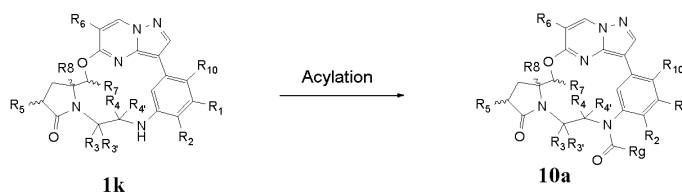
- 10 As shown in Scheme 9, compound **1k**, containing $R_5 = \text{OCH}_2\text{CH}_2\text{OBn}$, can undergo hydrogenation in presence of Palladium on charcoal to afford the final compound **9a**.

Scheme 9



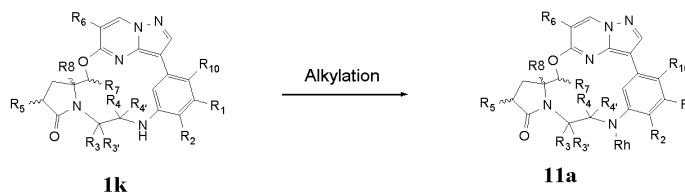
As shown in Scheme 10, compound **1k** can undergo acylation reaction to afford the final compound **10a**.

- 15 Scheme 10



As shown in Scheme 11, compound **1k** can undergo alkylation reaction to afford the final compound **11a**.

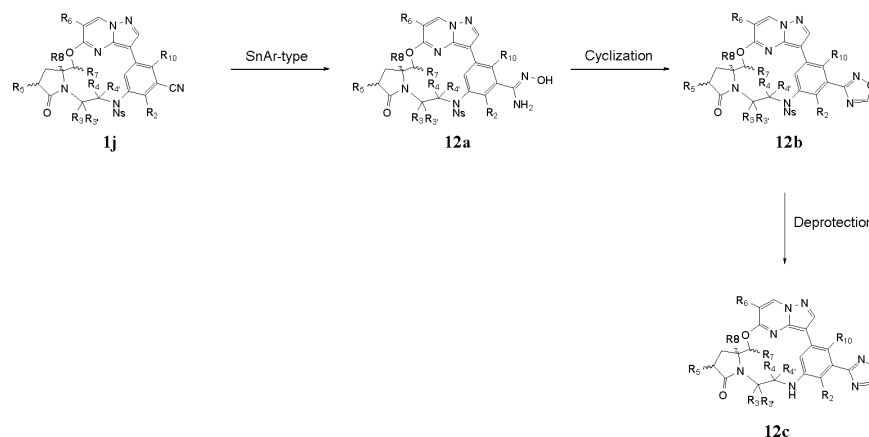
Scheme 11



-41-

As shown in Scheme 12, compound **1j** can be converted to compound **12a** in presence of hydroxylamine. The formation of the heterocycle is achieved in presence of Triethyl orthoformate to give **12b**. A deprotection of the Nosyl group afford the final compound **12c**.

Scheme 12

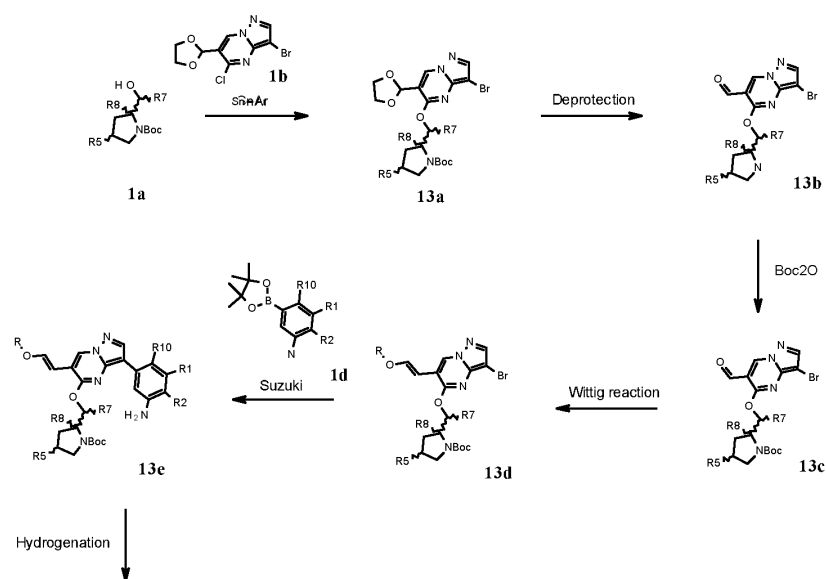


5

As shown in Scheme 13, compound **1a** can undergo aromatic nucleophilic substitution by reaction with **1b** to afford **13a**. The alkene **13d** can be obtained by sequential deprotection of the acetal moiety, protection of the amine with Boc group and a Wittig reaction. The Boronic ester **1d** can be introduced by transition metal catalyzed cross coupling to afford **13e**.

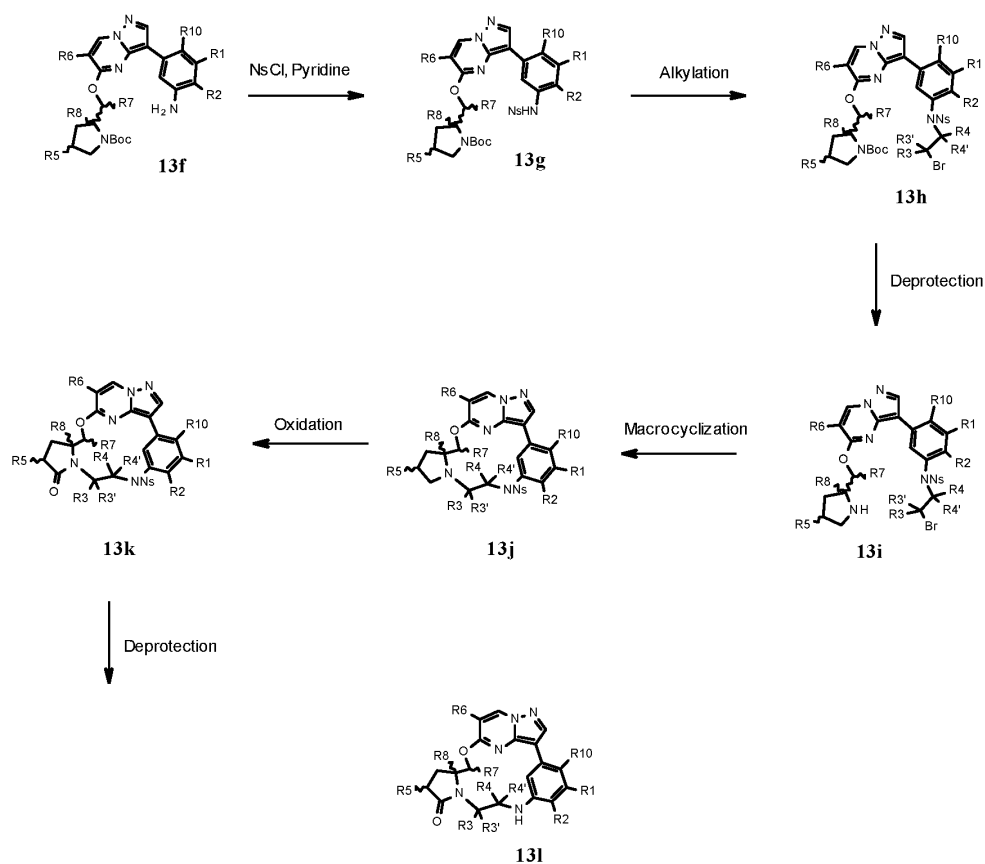
Sequential Nosyl protection of the aniline, its alkylation and deprotection of the Boc group led to the amine **13i**. Macrocyclization was performed using Finkelstein conditions to give **13j**, which followed by oxidation in presence of iodine to afford **13k**. Nosyl deprotection provides final compound **13l**.

Scheme 13



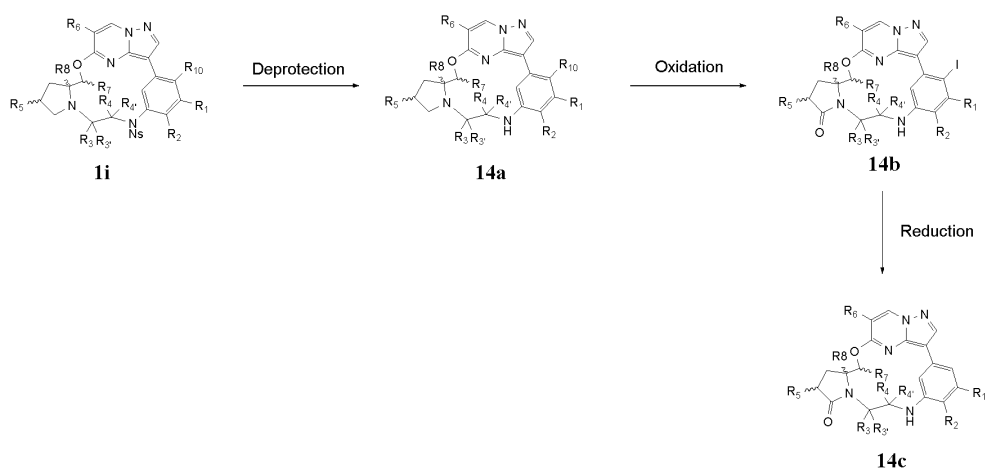
15

-42-



As shown in Scheme 14, compound **1i** can undergo deprotection of the Nosyl group, followed by oxidation in presence of Iodine and finally a reduction of the extra Iodine present in the structure to afford the final compound **14c**.

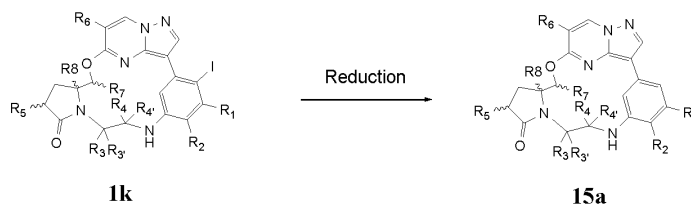
Scheme 14:



-43-

As shown in Scheme 15, compound **1k** can undergo a reduction of the extra iodine (present in the structure as a consequence to oxidation in presence of Iodine) in presence of Iridium catalyst to afford the final compound **15a**.

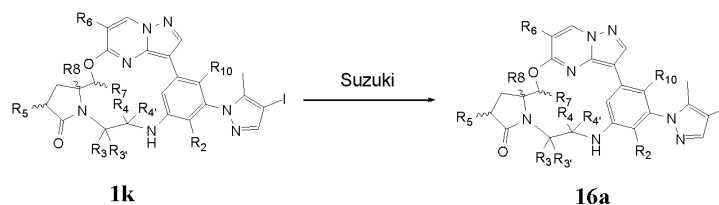
Scheme 15



5

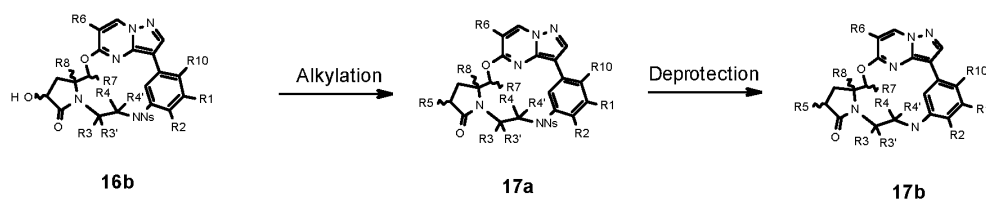
As shown in Scheme 16, compound **1k** can undergo a Suzuki coupling in presence of a boronic ester to afford the final compound **16a**.

Scheme 16



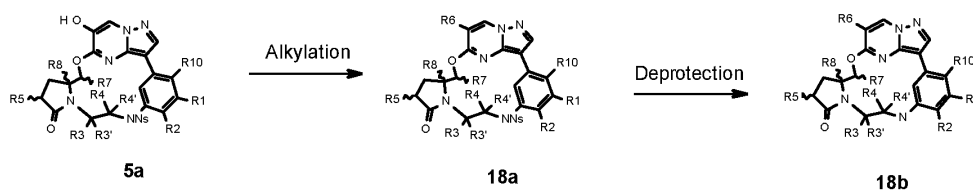
10 As shown in Scheme 17, compound **16b** can undergo alkylation in presence of an alkyl halide followed by nosyl deprotection using a sulfur derivative (for example Methylbenzenethiol) to afford the final compound **17b**.

Scheme 17



15 As shown in Scheme 18, compound **5a** can undergo alkylation in presence of an alkyl halide and a mild base (for ex. Cesium carbonate), followed by Nosyl deprotection using a sulfur derivative (for example Methylbenzenethiol) to afford the final compound **18b**.

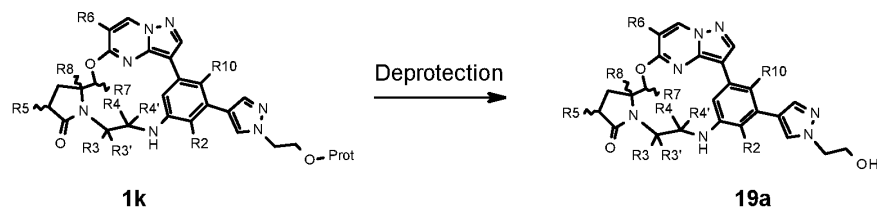
Scheme 18



-44-

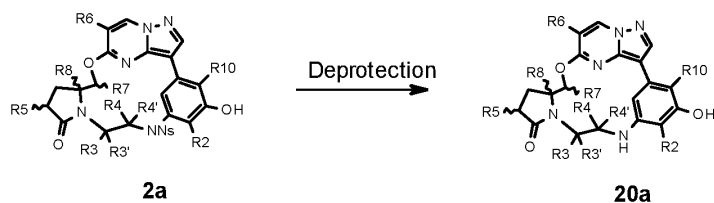
As shown in Scheme 19, compound **1k** can undergo deprotection, such as silyl TBDPS removal, in presence of TBAF to afford the final compound **19a**.

Scheme 19



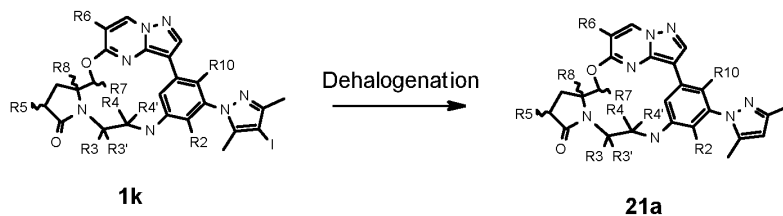
- 5 As shown in Scheme 20, compound **2a** can undergo Nosyl deprotection using a sulfur derivative (for example Methylbenzenethiol) to afford the final compound **20a**.

Scheme 20



- 10 As shown in Scheme 21, compound **1k** can undergo dehalogenation in presence of Iridium-based catalyst to afford the final compound **21a**.

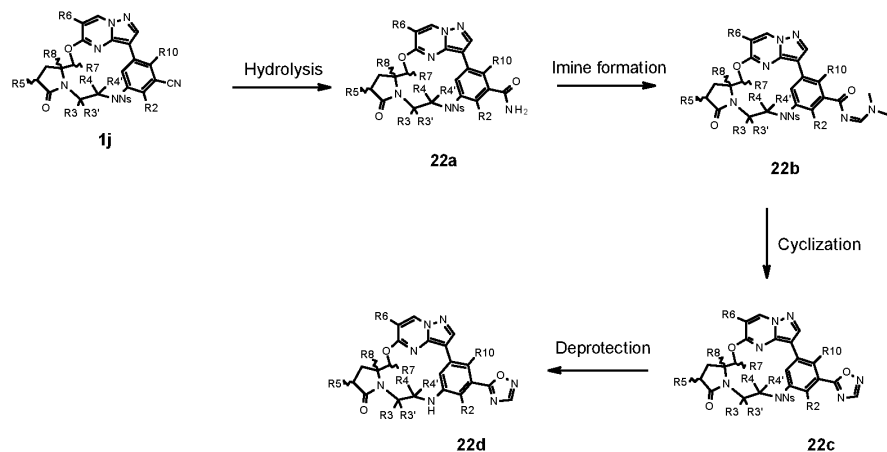
Scheme 21



- 15 As shown in Scheme 22, compound **1j** can undergo hydrolysis in presence of Sodium hydroxide, followed by the imine formation using Dimethoxy-N,N-dimethylmethanamine directly followed by a cyclization in presence of Hydroxylamine to afford the intermediate **22c**. The final compound **22d** can be obtained by Nosyl deprotection using a sulfur derivative (for example 4-Methylbenzenethiol).

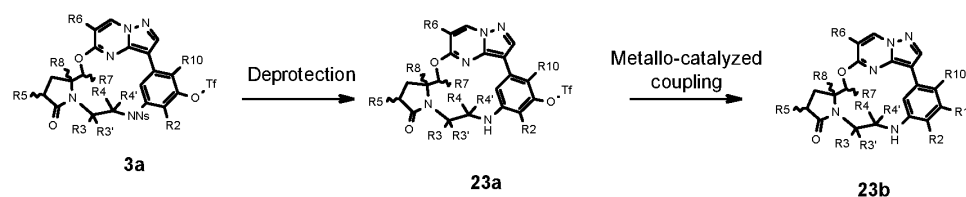
-45-

Scheme 22



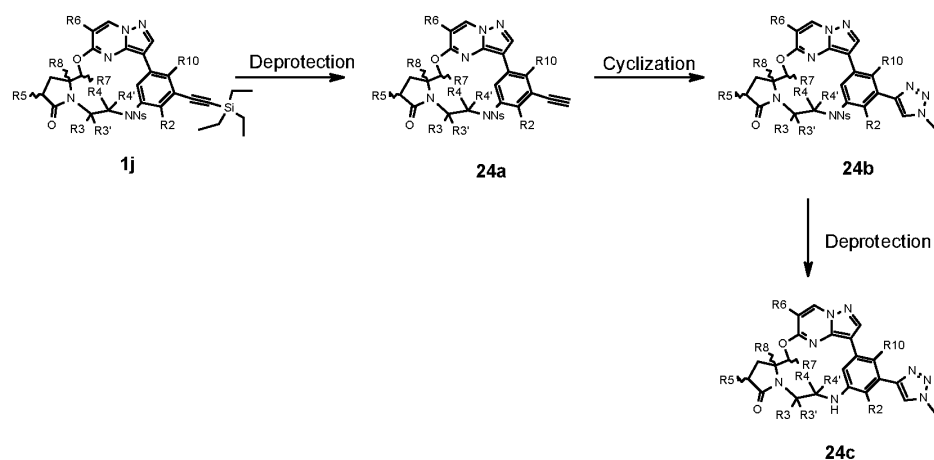
As shown in Scheme 23, compound **3a** can undergo Nosyl deprotection using a sulfur derivative (for example 4-Methylbenzenethiol) followed by a transition metal catalyzed cross coupling (such as a Stille coupling) to afford the final compound **23b**.

Scheme 23



As shown in Scheme 24, compound **3a** can undergo silyl deprotection using a fluoride-containing reagent (for example TBAF), followed by a click reaction using an alkyl halide and Sodium azide to afford intermediate **24b**. The final compound **24c** could be obtained by Nosyl deprotection using a sulfur derivative (for example 4-Methylbenzenethiol).

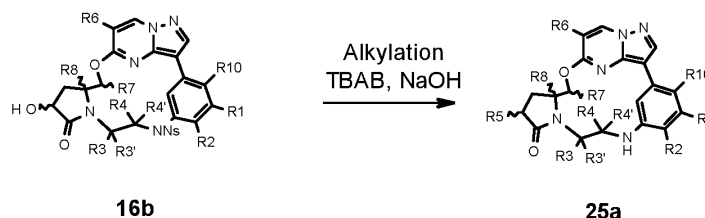
Scheme 24



-46-

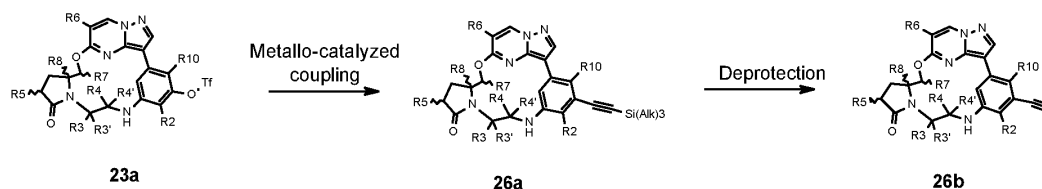
As shown in Scheme 25, compound **16b** can undergo ether formation by reaction with alkyl halide and TBAB to afford the final compound **25a**.

Scheme 25



- 5 As shown in Scheme 26, compound **16b** can undergo a transition metal catalyzed cross coupling (such as Sonogashira coupling) followed by alkyne deprotection in presence of a mild base (such as Potassium carbonate) in alcohol to afford the final compound **26b**.

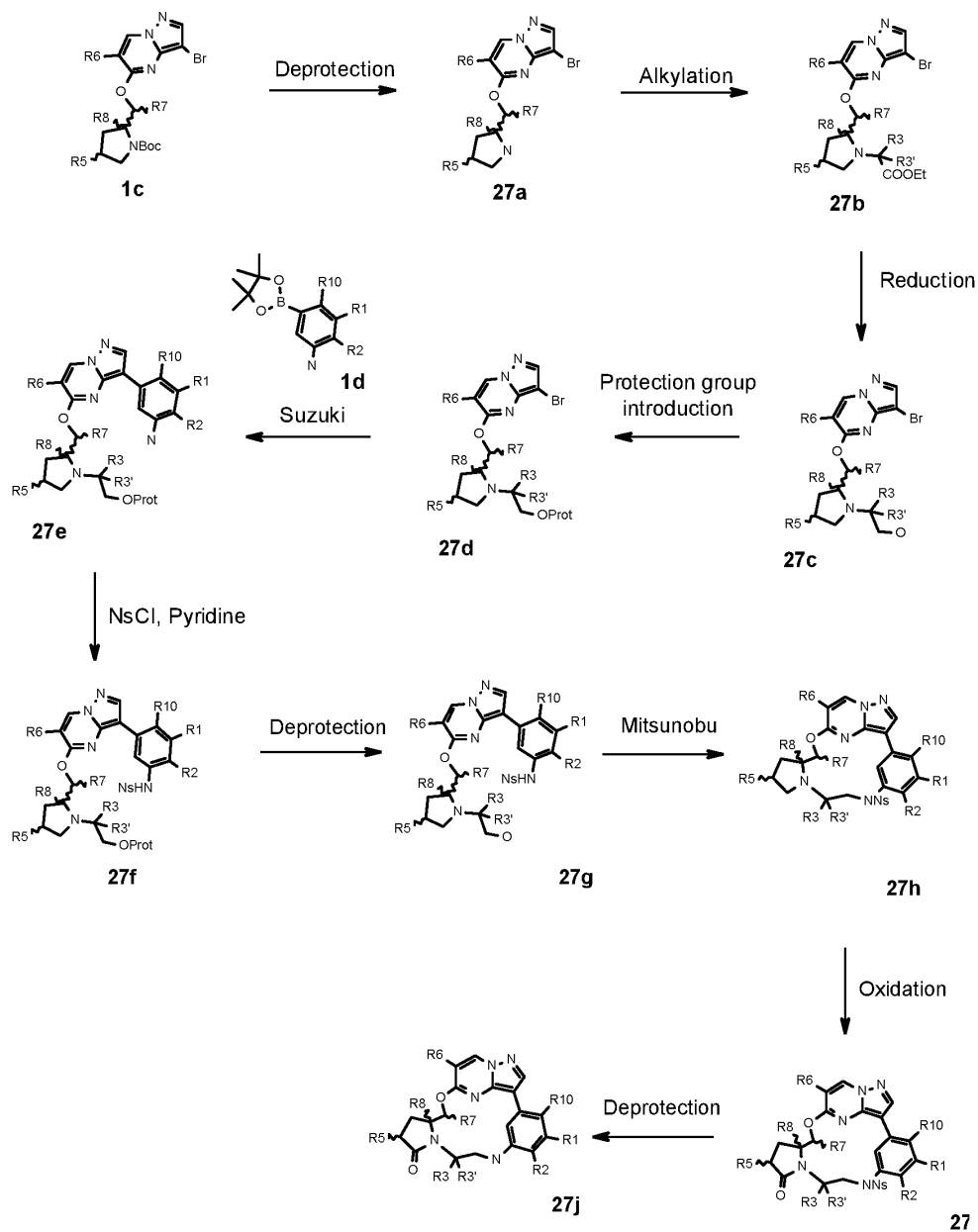
Scheme 26



- 10 As shown in Scheme 27, compound **1c** can undergo amine deprotection using a strong acid (such as HCl), followed by alkylation in presence of alkyl halide to achieve intermediate **27b**. The ester moiety could be reduced to primary alcohol **27c** in presence of a reductive agent (such as Sodium borohydride / Calcium chloride) then a protecting group could be introduced (such as TBDMS) to obtain intermediate **27d**. The compound is then engaged in a Suzuki
- 15 coupling, followed by Nosyl protecting group introduction and the alcohol deprotection (using TBAF in case of silyl protecting group) to obtain **27g**. The macrocyclization could be performed by Mitsunobu reaction, followed by oxidation in presence of Iodine and Nosyl deprotection using a sulfur derivative (for example 4-Methylbenzenethiol) to afford the final compound **27j**.

-47-

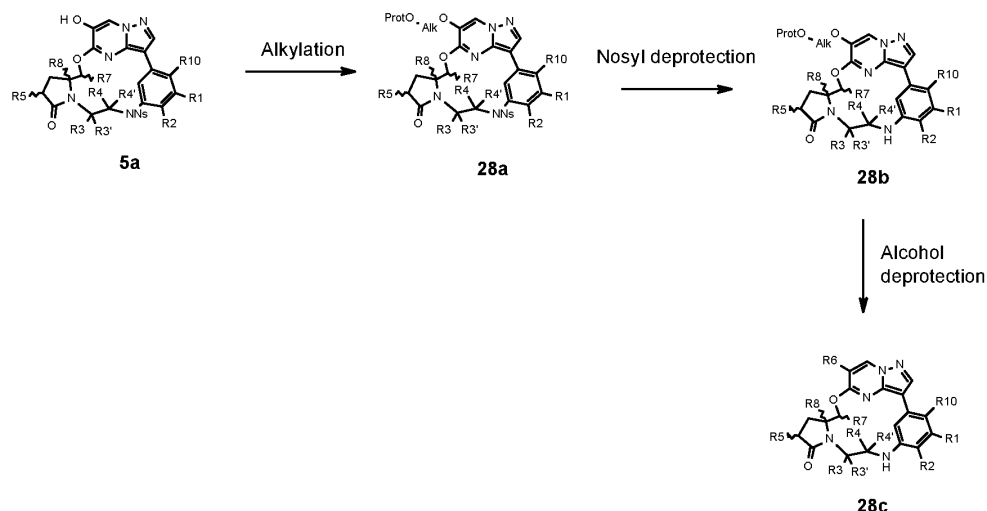
Scheme 27



As shown in Scheme 28, compound **5a** can undergo alkylation using alkyl halide in presence of a mild base (for example Potassium carbonate) followed by nosyl deprotection using a sulfur derivative (for example 4-Methylbenzenethiol) to afford intermediate **28b**. The final compound **28c** could be obtained by alcohol deprotection (for example p-Toluenesulfonic acid in case of THP protecting group).

-48-

Scheme 28



A. Physicochemical properties of the compounds

- 5 Purification of intermediates and final products was carried out via either normal or reverse phase chromatography. Normal phase chromatography was carried out using prepacked SiO₂ cartridges eluting with either gradients of hexanes and EtOAc or DCM and MeOH unless otherwise indicated. Reverse phase preparative HPLC was carried out using a Gilson semi-preparative HPLC system operated by Gilson UNIPOINT software.

10

- Purification method PA:** The purification was carried out on a Phenomenex Luna column (100 mm long x 21.2 mm i.d.; 5 μ m particles) at room temperature, with a constant flow rate of 20.0mL/min. A gradient elution was performed from 32% (25 mM NH₄HCO₃ aqueous solution) / 68% (Acetonitrile-Methanol 1:1) to 4% (25 mM NH₄HCO₃ aqueous solution) / 96% (Acetonitrile-Methanol 1:1) in 20 minutes. The UV detector was set to 226 nm, which corresponds to the wavelength of maximum absorbance observed for the compound.

- Purification method PB:** The purification was carried out on a Phenomenex Gemini C18 column (100 mm long x 30 mm I.D.; 5 μ m particle size) at room temperature, with a flow rate of 30mL/min. A gradient elution was performed from 70% (Water + 25mM Ammonium Bicarbonate) / 5% (Acetonitrile-Methanol 50% mixture) to 27% (Water + 25mM Ammonium Bicarbonate) / 73% (Acetonitrile-Methanol 50% mixture) in 20 minutes; after that, a gradient elution was performed from 27% (Water + 25mM Ammonium Bicarbonate) / 73% (Acetonitrile-Methanol 50% mixture) to 0% (Water + 25mM Ammonium Bicarbonate) / 100% (Acetonitrile-Methanol 50% mixture) in 2 minutes; the resulting composition was held for 5 min; from 0% (Water + 25mM Ammonium Bicarbonate) / 100% (Acetonitrile-Methanol 50% mixture) to 95%

(Water + 25mM Ammonium Bicarbonate) / 5% (Acetonitrile-Methanol 50% mixture) in 2 min, the resulting composition was held for 5 minutes. The standard injection volume was 8mL. Acquisition was set to 254 nm for the UV detector.

Unless otherwise stated, analysis of final products was carried out by LCMS or reverse phase analytical HPLC.

LCMS Method A (MA)

Analytical HPLC was conducted on a X-Select CSH C18 XP column (2.5µm 30 x 4.6 mm id) eluting with 0.1% formic acid in water (solvent A) and 0.1% formic acid in Acetonitrile (solvent B), using the following elution gradient 0-3 minutes: 5% to 100% B, 3-4 minutes 100% B, at a flow rate of 1.8mL/minute at 40°C. The mass spectra (MS) were recorded on a Waters ZQ mass spectrometer (scan 200-900uma) using electrospray positive ionisation [ES+ to give MH⁺ molecular ions] or electrospray negative ionisation [ES- to give (M-H)- molecular ions] modes with a 20V cone voltage.

LCMS Method B (MB)

Analytical HPLC was conducted on a X-Select CSH C18 XP column (2.5µm 30 x 4.6 mm id) eluting with 0.1% ammonia in water (solvent A) and 0.1% ammonia in Acetonitrile (solvent B), using the following elution gradient 0-3 minutes: 5% to 100% B, 3-4 minutes 100% B, at a flow rate of 1.8mL/minute at 40°C. The mass spectra (MS) were recorded on a Waters ZQ mass spectrometer (scan 200-900uma) using electrospray positive ionisation [ES+ to give MH⁺ molecular ions] or electrospray negative ionisation [ES- to give (M-H)- molecular ions] modes with a 20V cone voltage.

LCMS Method C (MC)

Analytical HPLC was conducted on a X-Select CSH C18 XP column (2.5µm 30 x 4.6 mm id) eluting with (NH₄)₂CO₃ aq. 2g/L in water (solvent A) and Acetonitrile (solvent B), using the following elution gradient 0-3 minutes: 5% to 100% B, 3-4 minutes 100% B, at a flow rate of 1.8mL/minute at 40°C. The mass spectra (MS) were recorded on a Waters ZQ mass spectrometer (scan 200-900uma) using electrospray positive ionisation [ES+ to give MH⁺ molecular ions] or electrospray negative ionisation [ES- to give (M-H)- molecular ions] modes with a 20V cone voltage.

LCMS Method D (MD)

In addition to the general procedure LCMS: Analyses were carried out on a YMC pack ODS-AQ C18 column (50 mm long x 4.6 mm i.d.; 3 µm particles) at 35°C, with a flow rate of 2.6mL/min. A gradient elution was performed from 95% (water + 0.1% formic acid) / 5% Acetonitrile to 5% (water + 0.1% formic acid) / 95% Acetonitrile in 4.80 minutes, then the final mobile phase composition was held for an additional 1.00 min. The standard injection volume

was 2 µL. Acquisition ranges were set to 190-400nm for the UV-PDA detector and 100-1400 m/z for the MS detector.

LCMS Method E (ME)

- 5 In addition to the general procedure LCMS: Analyses were carried out on a Phenomenex Kinetex C18 column (50 mm long x 2.1 mm i.d.; 2.6 µm particles) at 35°C, with a flow rate of 0.7mL/min. A gradient elution was performed from 95% (50mM ammonium acetate in water) / 5% Acetonitrile to 5% (50mM ammonium acetate in water) / 95% Acetonitrile in 4.80 minutes, then the final mobile phase composition was held for an additional 1.00 min. The standard
10 injection volume was 2 µL. Acquisition ranges were set to 190-400nm for the UV-PDA detector and 100-1400 m/z for the MS detector.

LCMS Method F (MF)

- Analyses were carried out on a Phenomenex GEMINI C18 column (100 mm long x 4.6 mm
15 i.d.; 5 µm particles) at 25 °C, with a flow rate of 3.014mL/min. A gradient elution was performed as follows: 95% (65mM ammonium acetate in water + Acetonitrile (90:10)) / 5% Acetonitrile for 0.30 min; from the previous composition to 100% Acetonitrile in 4.26 min; the previous composition was held for 0.60 min, and then it went to 95% (65mM ammonium acetate in water + Acetonitrile (90:10)) / 5% Acetonitrile in 1.02 min; the final mobile phase
20 composition was held for an additional 0.57 min. The standard injection volume was 3 µL. Acquisition ranges were set to 200-400 nm for the UV-PDA detector and 100-1000 m/z for the MS detector.

LCMS Method G (MG)

- 25 In addition to the general procedure LCMS: Analyses were carried out on a YMC pack ODS-AQ C18 column (50 mm long x 4.6 mm I.D.; 3 µm particle size) at 35 °C, with a flow rate of 2.6mL/min. A gradient elution was performed using Agilent 1260 from 95% (Water + 0.1% Formic acid)/5% Acetonitrile to 5% (Water + 0.1% Formic acid)/95% Acetonitrile in 4.8 min; the resulting composition was held for 1.0 min; from 5% (Water + 0.1% formic acid)/95%
30 Acetonitrile to 95% (Water + 0.1% formic acid)/5% Acetonitrile in 0.2 min. The standard injection volume was 2 µL. Acquisition ranges were set to 190-400 nm for the UV-PDA detector and 100-1000 m/z for the TOF-MS detector.

LCMS Method H (MH)

- 35 In addition to the general procedure LCMS: Analyses were carried out on a Phenomenex Kinetex C18 column (50 mm long x 2.1 mm i.d.; 1.7 µm particles) at 60°C, with a flow rate of 1.5mL/min. A gradient elution was performed from 90% (water + 0.1% formic acid) / 10% Acetonitrile to 10% (water + 0.1% formic acid) / 90% Acetonitrile in 1.50 minutes, then the final mobile phase composition was held for an additional 0.40 min. The standard injection volume

was 2 μ L. Acquisition ranges were set to 254 nm for the UV-PDA detector and 80-800 m/z for the MS detector.

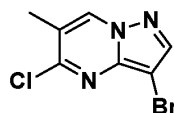
LCMS Method I (MI)

- 5 Analyses were carried out on a Thermo Scientific Accucore C18 (50 mm long x 2.1 mm I.D., 2.6 μ m) at 35 °C, with a flow rate of 1.50mL/min. A gradient elution was performed from 95% (Water + 0.1% Formic acid) / 5% Acetonitrile to 5% (Water + 0.1% Formic acid) / 95% Acetonitrile in 1.30 minutes; the resulting composition was held for 0.5 min; then the final mobile phase composition; from 5% (Water + 0.1% Formic acid) / 95% Acetonitrile to 90%
10 (Water + 0.1% Formic acid) / 10% Acetonitrile in 0.10 minutes. The injection volume was 1 μ L. MS acquisition range and UV detector were set to 100-1000 m/z and 190-400 nm respectively.

LCMS Method K (MK)

- Analytical HPLC was conducted on a Kinetex EVO C18 30*2.1mm,5 μ m eluting with 0.0375%
15 TFA in water (v/v) (solvent A) and 0.01875% TFA in Acetonitrile (v/v) (solvent B), using the following elution gradient 0-1.20 minutes: 5% to 95% B, 1.2-1.55 minutes 95% to 5% B, at a flow rate of 1.5mL/minute at 50°C. The mass spectra (MS) were recorded using ESI ionization source [ES+ to give MH+ molecular ions] modes with a 20V Qarray DC voltage.
- 20 Purification was performed using a Gilson system consisting of a binary pump (333 Model and 334 Model), ASPEC autosampler, column valve selector and UV detector. Data acquisition was performed with Trilution 3.0 software.

Scaffold S1: 3-bromo-5-chloro-6-methylpyrazolo[1,5-a]pyrimidine



Step 1

- To a solution of 1H-pyrazol-5-amine (173 g, 2.09 mol) was added EtONa (343 g, 5.04 mol, 2000mL), followed by diethyl 2-methylpropanedioate (400 g, 2.30 mol, 392mL). The mixture
30 was stirred at 100°C for 12 hours. TLC (petroleum ether/ethyl acetate = 0/1, compound 4, R_f = 0.3) showed that the reaction was completed. The reaction mixture was cooled down to 25°C and filtered to get the light yellow solid. The crude was stirred in EtOH (5 L) for 12 hours, filtered to get a white solid. 7-hydroxy-6-methyl-4H-pyrazolo[1,5-a]pyrimidin-5-one, sodium salt (540 g) was obtained as a white solid.
- 35 The crude material will be used in the next step without further purification.
- ¹H NMR (ppm, 400MHz), MeOD: 7.56 (d, J = 1.8 Hz, 1H), 5.75 (d, J = 2.0 Hz, 1H), 1.95 (s, 3H)

-52-

Step 2

To a solution of POCl_3 (3.15 kg, 20.5 mol, 1.91 L) was added 7-hydroxy-6-methyl-4H-pyrazolo[1,5-a]pyrimidin-5-one, sodium salt (366 g, 2.22 mol). The mixture was stirred at 105°C for 40 hours. The mixture was concentrated to remove most of POCl_3 and the reaction mixture was diluted with ethyl acetate (5000mL), poured into ice water (10000mL) and adjust to pH = 7-8 by addition of saturated NaHCO_3 solution. Then the aqueous phases were extracted with ethyl acetate (2000mL*3), the combined organic layer was washed with Brine (1000mL), dried over sodium sulfate, filtered and concentrated in vacuo. The title compound, 5,7-dichloro-6-methyl-pyrazolo[1,5-a]pyrimidine, (590 g, 2.92 mol, 43.9% yield) was obtained as a black oil.

The crude material will be used in the next step without further purification.

^1H NMR (ppm, 400MHz), CDCl_3 : 8.15 (d, $J = 2.3$ Hz, 1H), 6.69 (d, $J = 2.3$ Hz, 1H), 2.54 (s, 3H)

Step 3

To a solution of 5,7-dichloro-6-methyl-pyrazolo[1,5-a]pyrimidine (290 g, 1.44 mol) in THF (1.5 L) were added Zn (210 g, 3.21 mol), a solution of Ammoniac (35%), (528 g, 5.27 mol, 580mL, 3.67 eq), and a saturated NaCl solution (1.5 L). The reaction mixture was stirred at 25°C for 2 hours. TLC (petroleum ether: ethyl acetate = 3:1) showed that the reaction was completed. The mixture was filtered to remove Zn and then extracted with ethyl acetate (1000mL*3). The combined organic layer was washed with Brine (1000mL), dried over sodium sulfate, filtered and concentrated in vacuo to give the title compound, 5-chloro-6-methyl-pyrazolo[1,5-a]pyrimidine (420 g,) obtained as a yellow solid. The crude material will be used in the next step without further purification.

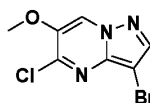
^1H NMR (ppm, 400MHz), CDCl_3 : 8.49 (s, 1H), 8.05 (d, $J = 1.8$ Hz, 1H), 6.63-6.52 (m, 1H), 2.38 (s, 3H)

Step 4

To the solution of 5-chloro-6-methyl-pyrazolo[1,5-a]pyrimidine (400 g, 2.39 mol) in Acetonitrile (2 L) was added N-Bromosuccinimide (480 g, 2.70 mol). The reaction mixture was stirred at 20°C for 0.5 hours. LCMS showed the formation of expected compound. The mixture was poured into water (2000mL), and the solid formed was collected by filtration. The title compound, 3-bromo-5-chloro-6-methyl-pyrazolo[1,5-a]pyrimidine (500 g, 2.03 mol, 85% yield) was obtained as yellow solid. The crude will be used in next step without further purification.

LCMS (MK) RT = 0.837 min, $m/z = 247.9$ ($\text{M}+\text{H}$) $^+$.

Scaffold S2: 3-bromo-5-chloro-6-methoxypyrazolo[1,5-a]pyrimidine



-53-

Step 1:

Dimethyl 2-methoxymalonate (100g, 616.7mmol) was diluted in Ethanol (200mL) and was added to a mixture of 3-aminopyrazole (51.25g, 616.7mmol) and Sodium Ethanolate (370mL) in Ethanol (1.65L).

- 5 The mixture of the reaction was heated at 120°C for 16 hours. Upon complete conversion, monitored by LCMS, the mixture was cooled at 0°C. The resulting violet solid was filtered off and washed with EtOH at 0°C, concentrated, co-evaporated with Acetonitrile and dried under high vacuum.

- 10 To a stirred solution of HCl 1N was added the solid portionwise at 4-5°C. The precipitate was filtered and washed with a minimum of cold water. The beige solid was concentrated in vacuum and co-evaporated with toluene (x3). The beige solid was dried high vacuum and used as such in the next step.

LCMS (MD) RT = 0.405 min, m/z = 182.0 (M+H)⁺.

15 **Step 2:**

To a solution of the title compound from Step 1 (135.8g, 7449.6mmol) and Phosphorous oxychloride (449.8g, 2248.9mmol) was added N,N-diethylaniline (101.71mL, 1049.5mmol) slowly at 0°C. The reaction was heated at 120°C for 4 hrs. After cooling, the excess of Phosphorous oxychloride was removed and the residue was diluted with EtOAc and washed with a saturated solution of NaHCO₃. The organic layer was dried overmgSO₄, filtered and concentrated under vacuo. The product was purified by flash chromatography using as eluents Heptane/ EtOAc (100:0 to 80:20) to afford the title compound as a yellow solid (44.8g, 27% yield).

LCMS (MH) RT = 0.556 min, m/z = 218.1/220.0 (M+H)⁺.

25

Step 3:

The title compound from Step 2 (22.1g, 101.36mmol) was dissolved in Acetonitrile (304mL) and cooled to 0°C. Then, N-Bromosuccinimide (18.04g, 101.36mmol) was added portionwise and the mixture was left stirring at room temperature for 30min. Upon complete conversion, monitored by LCMS, the mixture was diluted with EtOAc and extracted with a saturated solution of NaHCO₃. Organic layer was dried overmgSO₄, filtered and concentrated. The product was purified by flash chromatography using as eluents Heptane/ EtOAc (100:0 to 80:20) to afford the title compound as a yellow solid (23.7g, 78.8%).

LCMS (MH) RT = 0.769 min, m/z = 295.2/299.0 (M+H)⁺.

35

Step 4:

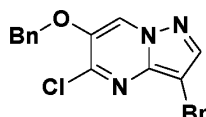
The title compound from Step 3 (20.0g, 67.35mmol) was suspended in EtOH (303mL). Sodium Borohydride (3.06g, 80.8mmol) was added portionwise at 0°C. The reaction mixture was kept at 0°C under continuous stirring. Upon complete conversion, monitored by LCMS, the mixture

-54-

was quenched with water. EtOAc was added and extracted. The organic layer was dried over MgSO_4 , filtered and concentrated to dryness. The crude was purified by flash chromatography on silica gel using as eluent DCM/ MeOH (100:0 to 90:10) afford the expected compound as a yellowish solid.

5 LCMS (MH) RT = 0. 655 min, m/z = 260.2/262.2 (M+H)⁺.

Scaffold S3: 3-Bromo-6-(benzomethyl)-5-chloro-pyrazolo[1,5-a]pyrimidine



10 Step 1

To a solution of 2-(benzyloxy)acetic acid (166 g, 999mmol, 143mL, 1 eq) in MeOH (800mL) was added dropwise Acetyl chloride (117 g, 1.50 mol, 107mL, 1.5 eq) at 10 °C. The mixture was stirred at 20 °C for 1 hr. The mixture was concentrated under vacuum. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate = 10/1 to 5/1) to afford the title compound (170 g, 943mmol, 94.4 % yield) as a colorless oil.

15

¹H NMR: 400 MHz, CDCl_3 : 7.45-7.30 (m, 5H), 4.66 (s, 2H), 4.13 (s, 2H), 3.79 (s, 3H)

Step 2

To a solution of Sodium hydride (33.0 g, 824mmol, 60% purity, 1.1 eq) in THF (675mL) was added Ethyl formate (83.3 g, 1.12 mol, 90.4mL, 1.5 eq). Then the title compound from Step 1 (135 g, 749mmol, 1 eq) in THF (135mL) was added dropwise to the mixture at 0 °C. The mixture was stirred at 25 °C for 3 h. DMF (400mL) and Ethyl iodide (117 g, 749mmol, 59.9mL, 1 eq) were added dropwise to the mixture. The resulting mixture was stirred at 35 °C for 1 h. The mixture was poured into ice water (1500mL), and extracted with Ethyl acetate (1000mL * 3). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure to afford the title compound (185 g, crude) as a yellow oil which was used into next step based on the theoretical 100 % yield without purification.

25

Step 3

To a solution of 3-aminopyrazole (41.0 g, 493mmol, 1 eq), the title compound from Step 2 (175 g, 740mmol, 1.5 eq) in DMF (1000mL) was added Cs_2CO_3 (241 g, 740mmol, 1.5 eq). The mixture was stirred at 110 °C for 10 hr. Upon complete conversion, monitored by LCMS, the mixture was cooled to 20°C and poured into ice water (3000mL), adjusted pH = 5~6 by 2M HCl(700mL), a lot of solid precipitated during this period. The mixture was filtered and the filter cake was washed with water (600mL). The filter cake was triturated with Tert-butyl methyl ether (500mL) to afford the title compound (65.0 g, 269mmol, 54.6 % yield) as a yellow solid.

35

-55-

¹H NMR: DMSO-d₆ 400MHz: 12.40 (s, 1H), 8.33 (s, 1H), 7.66 (d, *J* = 2.1 Hz, 1H), 7.53-7.33 (m, 5H), 5.80 (d, *J* = 1.7 Hz, 1H), 5.05 (s, 2H)

Step 4

- 5 To a solution of the title compound from Step 3 (80.0 g, 332mmol, 1 eq) in Acetonitrile (600mL) was added POCl₃ (127 g, 829mmol, 77.0mL, 2.5 eq) and N, N-Diethylaniline (495mg, 3.32mmol, 530 uL, 0.01 eq). Then the mixture was stirred at 100 °C for 4 hr. Upon complete conversion, monitored by LCMS, the mixture was concentrated under vacuum to remove mostly CH₃CN and POCl₃. Then the mixture was diluted with Ethyl acetate (1000mL) and
- 10 poured into ice water (2000mL), adjusted pH = 7 by potassium carbonate, extracted with ethyl acetate (1000mL * 2). The combined organic layers were washed with Brine (1000mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 10/1 to 5/1) to afford the title compound (66.0 g, 254mmol, 76.6% yield) as a light-yellow solid.
- 15 ¹H NMR: CDCl₃, 400MHz, 8.27 (s, 1H), 8.02 (d, *J* = 2.4 Hz, 1H), 7.58-7.39 (m, 5H), 6.61 (d, *J* = 2.4 Hz, 1H), 5.19 (s, 2H)

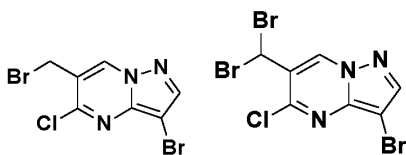
Step 5

- To a solution of the title compound from Step 4 (69.0 g, 266mmol, 1 eq) in Dichloromethane (650mL) was added NBS (47.3 g, 266mmol, 1 eq) slowly. The mixture was stirred at 25 °C for
- 20 2 hr. Upon complete conversion, monitored by LCMS, the mixture was concentrated under reduced pressure. The residue was triturated with a solution of DCM: PE = 1:1(300mL) and filtered. The filter cake was washed with water (1000mL) to afford the expected compound (85.3 g, 252mmol, 94.7% yield) as a light-yellow solid.

¹H NMR: DMSO-d₆, 400MHz, 9.23 (s, 1H), 8.31 (s, 1H), 7.59-7.17 (m, 5H), 5.27 (s, 2H)

25

Scaffold S4 : 3-Bromo-6-(bromomethyl)-5-chloro-pyrazolo[1,5-a]pyrimidine and **Scaffold S5**: 3-bromo-5-chloro-6-(dibromomethyl)pyrazolo[1,5-a]pyrimidine



- To a solution of 3-bromo-5-chloro-6-methyl-pyrazolo[1,5-a]pyrimidine (5.00 g, 20.28mmol) in carbon tetrachloride (100mL) was sequentially added *N*-Bromosuccinimide (36.10 g, 202.84mmol) and 2,2'-azobis(2-methylpropionitrile) (333mg, 2.028mmol). The reaction mixture was stirred at 100°C for 16h.
- 30

- The mixture was filtered and the remaining crude was rising with Dichloromethane. The mixture was diluted with Dichloromethane and washed with saturated aqueous sodium
- 35 bicarbonate solution. The organic phase was dried over anhydrous magnesium sulfate, filtered

-56-

and evaporated under reduced pressure. The residue was purified by silica gel chromatography (eluting gradient 0-5% Heptane/Dichloromethane (9:1)/ethyl acetate) to afford the title compound as a white solid (1.885 g, 28% yield).

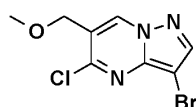
LCMS (MH) RT = 0.797 min, m/z = 325.7 - 327.7 (M+H)⁺.

5

Scaffold S5: 3-bromo-5-chloro-6-(dibromomethyl)pyrazolo[1,5-a]pyrimidine was obtained as a yellowish solid (5.045 g, 61% yield).

LCMS (MH) RT = 0.966 min, m/z = 403.6 - 405.6 (M+H)⁺.

10 **Scaffold S6 :** 3-Bromo-5-chloro-6-(methoxymethyl)pyrazolo[1,5-a]pyrimidine



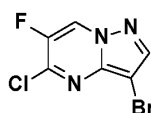
A solution of **Scaffold S4** (1.885 g, 5.793mmol) in Methanol (38mL) was heated in a sealed tube at 100°C for 6h. After cooling, solvent was removed under reduced pressure and the residue was diluted in ethyl acetate. The mixture was washed with saturated aqueous sodium bicarbonate solution and Brine. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting gradient 0-20% Heptane/ethyl acetate) to afford the title compound as a white solid (1.378 g, 86% yield).

15

LCMS (MH) RT = 0.724 min, m/z = 275.9-277.9 (M+H)⁺.

20

Scaffold S7 : 3-Bromo-5-chloro-6-fluoro-pyrazolo[1,5-a]pyrimidine



Step 1

To the mixture of 2-fluoro-malonic acid diethyl ester (10 g, 56.129mmol) in ethanol (170mL), was added 1H-pyrazol-3-ylamine (4.664 g, 56.129mmol) and Sodium ethoxide solution (21wt. % in ethanol) (42mL, 112.258mmol). The reaction mixture was heated at 120°C for 30h. The reaction mixture was concentrated under reduced pressure and co-evaporated with toluene. 1M HCl solution (100mL) was added to the residue. Water was added to the reaction mixture and the precipitate was filtered. The precipitate was suspended in Acetonitrile and evaporated to dryness. The residue was suspended in toluene and evaporated to dryness under reduced pressure to afford the title compound as a light brown solid (6.85 g, 72% yield), which was used without further purifications.

25

30

LCMS (MH) RT = 0.100min, m/z = 170.1 (M+H)⁺.

Step 2

To the mixture of title compound from Step 1 (6.85 g, 40.504mmol) and phosphorus(V) oxychloride (50mL, 263.276mmol) was added slowly diethyl-phenyl-amine (11mL, 56.706mmol) at 0°C. The reaction mixture was warmed to room temperature then heated at 120°C for 3h. After cooling, the reaction mixture was co-evaporated with toluene under reduced pressure. The crude residue was diluted with ethyl acetate and cooled down to 0°C. Saturated aqueous sodium bicarbonate solution was added slowly. The reaction mixture was extracted with ethyl acetate and the combined organic phases were dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The residue was purified by silica gel chromatography (eluting gradient 5-20% Heptane/ethyl acetate) to afford the title compound as a white solid (5.107 g, 61% yield).

LCMS (MH) RT = 0.664min, m/z = 206.0-207.9 (M+H)⁺.

Step 3

To a mixture of the title compound from Step 2 (4.395 g, 21.334mmol) in Acetonitrile (64mL) at 0°C was added portionwise *N*-Bromosuccinimide (3.797 g, 21.334mmol). The reaction mixture was stirred for 30min. A saturated aqueous sodium bicarbonate solution was added and the reaction mixture was extracted with ethyl acetate. The combined organic phases were dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The residue was purified by silica gel chromatography (eluting gradient 5-20% Heptane/ethyl acetate) to afford the title compound as a yellow solid (5.796 g, 95% yield).

LCMS (MH) RT = 0.859min, m/z = 283.9-285.9 (M+H)⁺.

Step 4

The title compound from Step 3 (5.79 g, 20.344mmol) in aqueous Ammonia (100mL) was stirred at room temperature for 16h. The reaction mixture was evaporated under reduced pressure. The residue was diluted with ethyl acetate and a solution aqueous sodium carbonate solution. After separation, the aqueous phase was extracted with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The residue was purified by silica gel chromatography (eluting gradient 10-50% Heptane/ethyl acetate) to afford the title compound as yellowish solid (4.10 g, 76% yield).

LCMS (MH) RT = 0.615 min, m/z = 265-267 (M+H)⁺.

Step 5

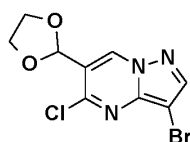
To a solution of the title compound from Step 4 (5.060 g, 19.061mmol) in Dioxane (50mL) was added isopentyl nitrite (5.133mL, 38.122mmol). The reaction mixture was heated at 110°C for 2h. After cooling, the reaction mixture was concentrated under reduced pressure and the crude material was washed with water. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The product was purified by

-58-

silica gel chromatography (eluting gradient 10-20% Heptane/ethyl acetate) to afford the expected compound as a yellow solid (2.158 g, 45 % yield).

LCMS (MH) RT = 0.707 min, m/z = 249.9-251.9 (M+H)⁺.

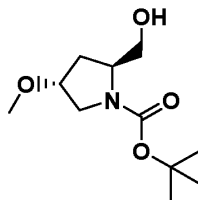
5 **Scaffold S8** : 3-Bromo-5-chloro-6-(dibromomethyl)pyrazolo[1,5-a]pyrimidine



To a solution of **Scaffold S5** (5.00 g, 12.479mmol) in *N,N*-dimethylformamide (38mL) was added ethylene glycol (15.5mL, 249.580mmol) at room temperature. The reaction mixture was stirred at 70°C for 20h. The reaction mixture was diluted with ethyl acetate and washed with saturated aqueous sodium bicarbonate solution. The organic layer was dried with anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting gradient 0-20% Heptane/ethyl acetate) to afford the expected compound as a beige solid (2.89 g, 76 % yield).

15 LCMS (MH) RT = 0.703 min, m/z = 303.9-305.9 (M+H)⁺.

Pyrrolidine P1: tert-butyl (2S,4R)-2-(hydroxymethyl)-4-methoxypyrrolidine-1-carboxylate



20 Step 1

To a solution of (2S,4R)-1-(tert-butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid (8.3g, 35.892mmol) in anhydrous Acetonitrile (500ml) was added Silver (I) Oxide (24.9g, 107.67mmol) followed by Iodomethane (11.2ml, 179.4mmol) cooled at 0°C. The resulting suspension was slowly warmed to ambient temperature and stirred vigorously for 2 days.

25 Upon completion, monitored by LCMS, solid material was removed by filtration and the filtrate was concentrated under vacuum. The residue was purified by flash chromatography eluting with gradient of Heptane/EtOAc (from 10:0 to 5:5) to afford the title product (8.8g, yield: 94%) as a colorless liquid.

LCMS (MH) RT = 0.691 min, m/z = 160.1 (M-56)⁺.

30

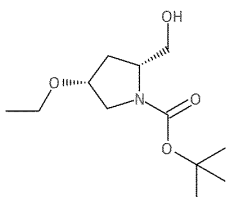
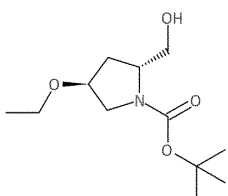
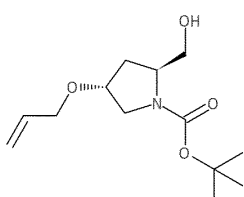
-59-

Step 2

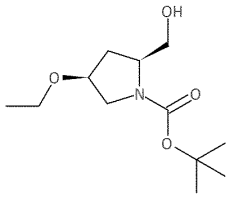
The title compound from Step 1 (8.8 g, 33.938mmol) was dissolved in dry THF and cooled down to 0°C under N₂ atmosphere. Lithium aluminium hydride (2.58 g, 67.876mmol) was added portionwise and stirred for 2 hours. Upon completion, monitored by LCMS, H₂O was added to quenched the reaction, and filtered over a pad of Celite, rinsing with EtOAc. The product was purified by flash chromatography (on silica gel) using DCM/MeOH as eluents (100: to 95:5) to afford the expected compound as a colorless oil (6.2g, 78.99%).

LCMS (MH) RT = 0.518 min, m/z = 132.1 (M-99)⁺.

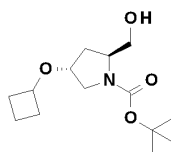
10 Similarly, were prepared the following intermediates:

Intermediate#	Structure	Yield	NMR
P2		93% yield as colorless oil	¹ H NMR (400 MHz, DMSO) 4.69 (1H, t, J = 5.6 Hz), 4.05 - 4.00 (1H, m), 3.79 - 3.70 (1H, m), 3.41 - 3.32 (6H, m), 2.00 - 1.99 (2H, m), 1.40 (9H, s), 1.09 (3H, t, J=7.0 Hz).
P11		49% yield as colorless oil	¹ H NMR (400 MHz, CDCl ₃) 4.01 - 3.92 (3H, m), 3.70 - 3.65 (2H, m), 3.56 - 3.42 (4H, m), 2.21 - 2.12 (1H, m), 1.78 (1H, s), 1.45 (9H, s), 1.18 (3H, t, J=7.2 Hz)
P12		93% yield as colorless oil	¹ H NMR (400 MHz, CDCl ₃) 4.26 (1H, s), 4.05 (1H, dq, J=2.0, 7.2 Hz), 4.00 - 3.95 (1H, m), 3.69 (1H, dd, J=2.7, 11.4 Hz), 3.56 (6H, dd, J=7.0, 11.4 Hz), 3.49 - 3.42 (2H, m), 3.39 (1H, dd, J=4.6, 11.8 Hz), 2.13 - 2.03 (1H, m), 1.70 - 1.66 (1H, m), 1.46 (9H, s), 1.18 (3H, t, J=6.6 Hz).
P13		99% yield as colorless oil	¹ H NMR (400 MHz, CDCl ₃) 5.95 - 5.84 (1H, m), 5.31 - 5.17 (2H, m), 4.13 - 4.06 (1H, m), 4.01 (1H, s), 3.97 (2H, dd, J=1.2, 5.3 Hz), 3.71 (1H, d, J=12.5 Hz), 3.61 (1H, s), 3.57 (1H, dd, J=7.0, 11.4 Hz), 3.40 (1H, dd, J=4.7, 12.2 Hz), 2.18 - 2.04 (1H, m), 1.65 (1H, m), 1.47 (9H, s)

-60-

P14		100% yield as colorless oil	¹ H NMR (400 MHz, CDCl ₃) 4.02 - 3.93 (2H, m), 3.80 - 3.73 (2H, m), 3.56 - 3.42 (4H, m), 2.27 - 2.12 (1H, m), 1.80 (1H, s), 1.46 (9H, s), 1.19 (3H, t, J=7.1 Hz)
-----	---	-----------------------------	---

Pyrrolidine P3: *tert*-butyl (2S,4R)-4-(cyclobutoxy)-2-(hydroxymethyl)pyrrolidine-1-carboxylate



Step 1

- 5 To a suspension of O1-benzyl O2-methyl (2S,4R)-4-hydroxypyrrolidine-1,2-dicarboxylate (5.0 g, 17.90mmol) in Dichloromethane (50mL) was added 1*H*-imidazole (2.438 g, 35.80mmol) and *tert*-butyldimethylsilyl chloride (4.048 g, 26.85mmol). The reaction mixture was stirred at room temperature for 8h and 1*H*-imidazole (2.438 g, 35.80mmol) and *tert*-butyldimethylsilyl chloride (4.048 g, 26.85mmol) were added and the reaction mixture was stirred at room temperature for
- 10 16h. The reaction mixture was diluted with water. The layers were separated and the aqueous layer was extracted with Dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified by silica gel chromatography (eluting gradient 0-20% cyclohexane/ethyl acetate) to afford O1-benzyl O2-methyl (2S,4R)-4-[*tert*-butyl(dimethyl)silyl]oxypyrrolidine-1,2-dicarboxylate
- 15 (6.372 g, 90 % yield) as colorless oil.
LCMS (MA) RT = 3.36 min, m/z = 394.1 (M+H)⁺.

Step 2

- 20 To a suspension of bismuth tribromide (1.423 g, 3.17mmol) in Acetonitrile (25mL) under argon at 0°C was added Triethylsilane (2.54mL, 15.85mmol). The reaction mixture was stirred 10min at 0°C and a suspension of the title compound from Step 1 (4.160 g, 10.57mmol) and cyclobutanone (3.95mL, 52.85mmol) in Acetonitrile (12mL) were added. The reaction mixture was stirred at 0°C for 1h then at room temperature for 1h. The mixture was filtered and washed with ethyl acetate. The filtrate was diluted with water and ethyl acetate. The layers
- 25 were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified by silica gel chromatography (eluting gradient 0-20% cyclohexane/ethyl acetate) to afford the title compound as a pale yellow oil (2.03 g, 55 % yield).
- 30 LCMS (MA) RT = 2.70 min, m/z = 334.1 (M+H)⁺.

-61-

Step 3

To a suspension of the title compound from Step 2 (2.030 g, 6.09mmol) in methanol (35mL) under argon was added 10% Pd/C (200mg). The reaction mixture was stirred under hydrogen atmosphere at room temperature for 6h. The reaction mixture was filtered on Celite pad and washed with methanol and ethyl acetate. The filtrate was evaporated under reduced pressure to afford the title compound as colorless oil (1.205 g, 99 % yield), which was used in the next step without further purification.

¹H NMR (400 MHz, CDCl₃) 4.07 - 3.91 (3H, m), 3.75 - 3.75 (3H, s), 3.15 - 3.10 (1H, m), 3.03 - 2.98 (1H, m), 2.59 (1H, s), 2.26 - 2.17 (3H, m), 2.05-1.85 (3H, m), 1.74 - 1.65 (1H, m), 1.57 - 1.46 (1H, m).

Step 4

To a solution of the title compound from Step 3 (1.205 g, 6.05mmol) in tetrahydrofuran (90mL) was added Triethylamine (2.53mL, 18.15mmol), DMAP (74mg, 0.61mmol) and Boc₂O (3.961 g, 18.15mmol). The reaction mixture was stirred at 70°C for 16h. The reaction mixture was cooled down to room temperature and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (eluting gradient 0-20% cyclohexane/ethyl acetate) to afford the title compound as a light yellow oil (1.460 g, 81 %).

¹H NMR (400 MHz, CDCl₃) 4.44 - 4.32 (1H, m), 4.11 - 4.05 (1H, m), 4.00 - 3.91 (1H, m), 3.75 (3H, m), 3.63 - 3.41 (2H, m), 2.32 - 2.18 (3H, m), 2.09 - 1.92 (3H, m), 1.74 - 1.66 (1H, m), 1.56 - 1.51 (1H, m), 1.48 - 1.41 (9H, m).

Step 5

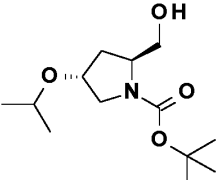
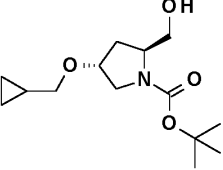
To a suspension of the title compound from Step 4 (1.460 g, 4.88mmol) in a mixture of EtOH/THF 1:1 (44mL) cooled at 0°C were added sodium borohydride (369mg, 9.76mmol) and calcium chloride (542mg, 4.88mmol). The solution was warmed up to room temperature and stirred for 2h at RT. The reaction mixture was quenched by addition of water and aqueous HCl 1M until pH=4. EtOAc was added. The layers were separated. The aqueous layer was extracted with EtOAc (3 x 40mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography using Cyclohexane/EtOAc 100:0 to 50:50 as eluent.

The expected fractions were collected and evaporated under reduced pressure to afford the expected compound as a colorless oil (1.242 g, 4.58mmol, 94 %).

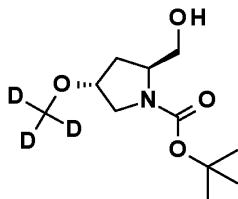
¹H NMR (400 MHz, CDCl₃) , 4.14 - 4.06 (1H, m), 4.00 - 3.90 (2H, m), 3.72 (1H, dd, J=2.4, 11.5 Hz), 3.59 - 3.54 (2H, m), 3.38 (1H, dd, J = 4.6, 12.0 Hz), 2.27 - 2.19 (2H, m), 2.13 - 1.89 (3H, m), 1.75 - 1.64 (2H, m), 1.55 - 1.51 (1H, m), 1.49 (9H, m).

-62-

Similarly, were prepared the following intermediates:

Intermediate#	Structure	Yield	¹ H NMR
P4		97% yield as colorless oil	¹ H NMR (400 MHz, CDCl ₃) 4.13 - 4.05 (2H, m), 3.74 - 3.50 (4H, m), 3.42 (1H, dd, J = 4.7, 12.0 Hz), 2.10 - 2.06 (2H, m), 1.69 - 1.64 (1H, m), 1.48 (9H, s), 1.16 (6H, t, J = 6.1 Hz).
P5		95% yield as colorless oil	¹ H NMR (400 MHz, DMSO) , 4.70 - 4.67 (1H, m), 4.06 - 4.01 (1H, m), 3.79 - 3.70 (1H, m), 3.44 - 3.31 (3H, m), 3.28 - 3.20 (2H, m), 3.17 - 3.12 (1H, m), 2.07 - 1.86 (2H, m), 1.40 (9H, s), 1.02-0.89 (1H, m), 0.44 (2H, d, J = 8.0 Hz), 0.17 - 0.12 (2H, m).

Pyrrolidine P6: tert-butyl (2S,4R)-2-(hydroxymethyl)-4-(trideuteriomethoxy)pyrrolidine-1-carboxylate



5

Step 1

To a solution of 1-(tert-butyl) 2-methyl (2S,4R)-4-hydroxypyrrolidine-1,2-dicarboxylate (3.2 g, 13.046mmol) was dissolved in dry tetrahydrofuran (65mL) at 0°C was added sodium hydride (60% dispersion in mineral oil) (1.044 g, 26.092mmol). The reaction mixture was stirred for 45min. Iodomethane-d₃ (1.624 g, 26.092mmol) was added and the reaction mixture was stirred for 30min. The reaction mixture was quenched at 0°C with water and extracted with ethyl acetate. The combined organic phases were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting gradient 0-50% Heptane/ethyl acetate) to afford the title compound as a white solid (2.6 g, 39% yield).

15

LCMS (MH) RT = 0.736 min, m/z = 163.1 (M+H)⁺-Boc .

Step 2

To the title compound from Step 1 (2.6g, 10.471mmol) was added borane dimethyl sulfide complex solution (2.0 M/THF) (15mL), dropwise at 0°C. The mixture was stirred at room temperature for 16 h. The reaction mixture was carefully quenched with methanol at 0°C. The solvent was removed under reduced pressure. The residue was purified by silica gel

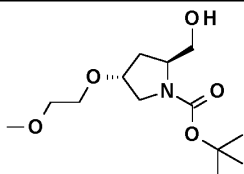
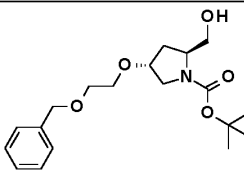
20

-63-

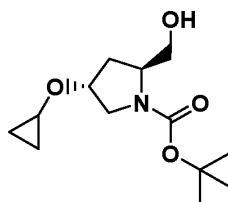
chromatography (eluting gradient 0-40% Heptane/ethyl acetate) to afford the expected compound as a colorless oil (2.2 g, 90% yield).

LCMS (MH) RT = 0.534 min, m/z = 135.1 (M+H)⁺-Boc.

5 Similarly, were prepared the following intermediates:

Intermediate#	Structure	Yield	LCMS
P7		61% yield as yellowish oil	LCMS (MH) RT = 0.545 min, m/z = 220.1 (M+H) ⁺ -55.
P8		83% yield as Pinkish oil	LCMS (MH) RT = 0.876 min, m/z = 296.1 (M+H) ⁺ -55.

Pyrrolidine P9: tert-butyl (2S,4R)-4-cyclopropoxy-2-(hydroxymethyl)pyrrolidine-1-carboxylate



Step 1

- 10 To a suspension Benzyl chloroformate (23.4mL, 166.8mmol) in THF/Water (100mL/50mL) under vigorous stirring was added Potassium carbonate (46.11g, 333.6mmol) then Methyl (2S,4R)-4-hydroxypyrrolidine-2-carboxylate hydrochloride (16.15g, 111.2mmol) carefully. The reaction mixture was stirred at room temperature for 2h. Upon complete conversion, monitored by LCMS, the mixture was acidified with aqueous HCl 1M until pH = 1. The layers were
- 15 separated. The aqueous layer was extracted with EtOAc (3 x 100mL) and the combined organic layer was washed with Brine, dried over anhydrous Sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified on silica gel column using Cyclohexane/EtOAc (100:0 to 0:100) as eluent to afford the title compound as yellow oil (20.58g, 66 % yield).
- 20 LCMS (MA) RT = 1.93 min, m/z = 280.1 (M+H)⁺

-64-

Step 2

Palladium (II) acetate (787mg, 3.50mmol) and 1,10-Phenanthroline (695mg, 3.85mmol) were dissolved in dry Dichloromethane (40mL) under Argon and the resulting solution was stirred 10min at room temperature. Then was added Ethyl vinyl ether (140mL). The solution was degassed by bubbling argon 10 min. The reaction mixture was stirred for 15 min at room temperature and an Argon-atmosphere solution of the title compound from Step 1 (9.79g, 35.05mmol) in dry Dichloromethane (110mL) was added. The reaction mixture was stirred at reflux overnight. Upon complete conversion, monitored by TLC plate, the reaction mixture was cooled down to room temperature and diluted with water (100mL). The aqueous layer was extracted with DCM (3 x 60mL). The combined organic layer was dried over Sodium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography using Cyclohexane/EtOAc (100:0 to 50:50) as eluent to afford the title compound as a pale yellow oil (6.796 g, 64 %).

LCMS (MA) RT = 2.56 min, m/z = 306.1 (M+H)⁺

Step 3

Under argon atmosphere, to a suspension of Diethylzinc in Hexane 1M (86.0mL, 85.53mmol) in DCM (300mL) cooled at 0°C was added dropwise Diiodomethane (6.94mL, 85.53mmol) in DCM (60mL). The reaction mixture was stirred at 0°C for 30min. Then the title compound from Step 2 (8.70g, 28.51mmol) in DCM (100mL) was added dropwise at 0°C. The mixture was warmed to room temperature and stirred overnight at rt. LCMS monitoring highlighted partial conversion and the mixture was further stirred at rt for 10h. The reaction mixture was quenched by addition of saturated aqueous Ammonium chloride solution (150mL). The layers were separated and the aqueous layer was extracted with DCM (3 x 100mL). The combined organic layer was dried over Sodium sulfate and concentrated in vacuo to afford the title compound as a colorless oil (6.69g, 74% yield). The crude was directly engaged in the next step without further purification.

LCMS (MA) RT = 2.55 min, m/z = 320.1 (M+H)⁺

Step 4

Under argon, to a suspension of the title compound from Step 3 (2.83g, 8.88mmol) in Methanol (50mL) was added Palladium on charcoal 10% (275mg). The reaction mixture was stirred under hydrogen atmosphere at room temperature for 4h. Upon complete conversion, monitored by TLC plate, the mixture was filtered on Celite and washed with MeOH and EtOAc. The filtrate was evaporated under reduced pressure to afford the title compound as colorless oil (1.54g, 94 % yield). The crude was directly engaged in the next step without further purification.

¹H NMR (400 MHz, DMSO) δ 4.11 - 4.06 (1H, m), 3.75 (1H, t, J=7.8 Hz), 3.62 (3H, s), 3.28 - 3.23 (1H, m), 2.95 (1H, dd, J=4.7, 11.5 Hz), 2.84 (1H, qd, J=1.3, 11.6 Hz), 2.67 (1H, s), 2.08 -

-65-

2.01 (1H, m), 1.90 - 1.83 (1H, m), 0.48 - 0.41 (4H, m);

Step 5

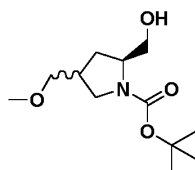
- To a solution of the title compound from Step 4 (1.54g, 8.31mmol) in THF (125mL) were added
 5 Et₃N (3.48mL, 24.94mmol), DMAP (101mg, 0.83mmol) and then Boc₂O (5.44g, 24.94mmol).
 The reaction mixture was stirred at 70°C overnight. After cooling down to room temperature,
 the solvent was evaporated under reduced pressure. The residue was purified by silica gel
 chromatography using Cyclohexane/EtOAc (100:0 to 50:50) as eluent to afford the title
 compound as a light-yellow oil (1.52g, 64% yield).
 10 ¹H NMR (400 MHz, DMSO) δ 4.18 - 4.13 (2H, m), 3.67 (3H, s), 3.45 (2H, dd, J=4.5, 7.5 Hz),
 3.33 - 3.29 (1H, m), 2.39 - 2.28 (1H, m), 2.03 - 1.92 (1H, m), 1.34 (9H, s), 0.50 - 0.43 (4H, m);

Step 6

- To a suspension of the title compound from Step 5 (1.52g, 5.34mmol) in a mixture of
 15 EtOH/THF 1:1 (50mL) cooled at 0°C were added Sodium borohydride (404mg, 10.68mmol)
 and Calcium chloride (593mg, 5.34mmol). The solution was warmed to room temperature and
 stirred for 1h at rt. The reaction mixture was quenched by addition of Water and aqueous HCl
 1M until pH=4. EtOAc was added. The layers were separated and the aqueous layer was
 extracted with EtOAc (3 x 40mL). The combined organic layer was dried over Sodium sulfate
 20 and concentrated in vacuo. The residue was purified by silica gel chromatography using
 Cyclohexane/EtOAc (100:0 to 50:50) as eluent to afford the expected compound as a colorless
 oil (1.30g, 95 % yield).
¹H NMR (400 MHz, DMSO) δ 4.71 (1H, t, J=5.7 Hz), 4.15 - 4.10 (1H, m), 3.73 (1H, s), 3.47 -
 3.43 (3H, m), 3.28 - 3.23 (2H, m), 2.08 - 1.92 (2H, m), 1.40 (9H, s), 0.48 - 0.42 (4H, m).

25

Pyrrolidine P10: tert-butyl (2S)-2-(hydroxymethyl)-4-(methoxymethyl)pyrrolidine-1-carboxylate



Step 1

- To (2S,4R)-1-(tert-butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid (10g, 43.243mmol)
 30 was added Borane-methyl sulfide complex (30mL) at 0°C under nitrogen atmosphere. The
 mixture spontaneously started to heat with effervescence. The mixture was kept stirring for
 16h at room temperature. Methanol was added slowly and dropwise at 0°C until the bubbling
 was stopped and the mixture was concentrated under vacuum to afford the title compound as
 a colorless oil (9.3g, yield: 99%). The crude was used as such in the next step.
 35 LCMS (MH) RT = 0.340 min, m/z = 162.1 (M-56) / 118.2 (M-100)

-66-

Step 2

To a solution of the title compound from Step 1 (9.17g, 42.206mmol) in DMF (130mL) was added Imidazole (5.75g, 84.41mmol) followed by tert-Butylchlorodiphenylsilane (11.93mL, 46.427mmol) at 0°C and stirred for 16h. Upon complete conversion, monitored by LCMS, a solution of saturated NaHCO₃ (200mL) was added and the mixture was extracted with EtOAc (4x100mL). The combined organic layers were dried overmgSO₄, filtered and concentrated under vacuum. The crude was purified on column of silica gel using Heptane/EtOAc (from 100.0 to 40:60) as eluent to afford the expected compound as yellowish gum (3.75g, yield: 19.5%).

LCMS (MH) RT = 1.396 min, m/z = 356.1 (M-100)

Step 3

To a solution of the title compound from Step 2 (3.75g, 8.23mmol) in DCM (40mL) was added Dess-Martin periodinane (6.981g, 16.458mmol) portionwise at room temperature and keep stirring for 16h.

A solution of saturate aqueous solution of NaHCO₃ (100mL) was added and the mixture was extracted with DCM. The combined organic layers were dried overmgSO₄, filtered and concentrated under vacuum. The product was purified on column of silica gel using as eluent Heptane/EtOAc (80:20) to afford the expected compound (3.6g, yield: 96%) as a colorless gum.

LCMS (MH) RT = 1.478 min, m/z = 354.1 (M-100) / 320.0 (M-259)

Step 4

To Methoxymethyl)triphenylphosphonium chloride (5.78g, 16.88mmol) in dry THF (25ml) was added Potassium bis(trimethylsilyl)amide solution 1M in THF (17ml, 16.884mmol) portionwise at -78°C and kept stirring for 30min. To the mixture was added the title compound from Step 3 (3.83g, 8.442mmol) in dry THF (15ml). The resulting mixture was stirred for 1h at the same temperature. Upon complete conversion, monitored by LCMS, a saturated aqueous solution of NaHCO₃ (100mL) was added and extracted with EtOAc (4x50mL). The combined organic layer was dried overmgSO₄, filtered and concentrated under vacuum. The product was purified on column of silica gel using Heptane/EtOAc (93:7) as eluent to afford the expected compound as yellowish viscous oil (3.06g, yield: 75%).

LCMS (MH) RT = 1.650 min, m/z = 382.1 (M-100)

Step 5

To a solution of the title compound from Step 4 (3.03g 6.298mmol) in Ethyl acetate (20mL) was added Palladium on activated carbon wet 10% (0.5g) and purged with hydrogen atmosphere (balloon) and stirred at room temperature for 16h. Upon complete conversion, monitored by LCMS, the mixture was filtered over a pad of Celite rinsing with EtOAc. Solvent

-67-

was removed on the rotavapor. The crude was dried under high vacuum to afford the expected compound as yellow gum (2.95g, yield: 96.83%), which was used as such in the next step.

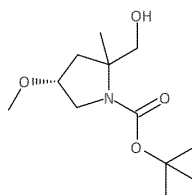
LCMS (MH) RT = 1.645 min, m/z = 384.1 (M-100)

5 Step 6

To the title compound from Step 5 (2.95g, 6.098mmol) in THF (40ml) was added Tetrabutylammonium fluoride, 1M in THF (18.3mL) at room temperature and stirred for 16h. The mixture was diluted with EtOAc (100mL) and washed twice with a saturated aqueous solution of NaHCO₃ (50mL). The organic layer was dried overmgSO₄, filtered and concentrated under vacuum. The crude was purified on column of silica gel using Heptane/EtOAc (80:20) as eluent to afford the expected product as a colorless oil (1.29g, yield: 86%).

LCMS (MH) RT = 0.595 min, m/z = 190.1 (M-56) / 146.1 (M-100)

15 **Pyrrolidine P15:** tert-butyl (4R)-2-(hydroxymethyl)-4-methoxy-2-methylpyrrolidine-1-carboxylate



Step 1

To a solution of (2S,4R)-1-(tert-butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid (8.3g, 35.892mmol) in anhydrous Acetonitrile (500ml) was added Silver (I) Oxide (24.9g, 107.67mmol) followed by Iodomethane (11.2ml, 179.4mmol) cooled at 0°C. The resulting suspension was slowly warmed to ambient temperature and stirred vigorously for 2 days. Upon completion, monitored by LCMS, solid material was removed by filtration and the filtrate was concentrated under vacuum. The residue was purified by flash chromatography eluting with gradient of Heptane/EtOAc (from 10:0 to 5:5) to afford the title product (8.8g, yield: 94%) as a colorless liquid.

LCMS (MH) RT = 0.691 min, m/z = 160.1 (M-56)⁺.

Step 2

30 n-butyllithium 2.5 M in n-hexane (6.94mL, 17.35mmol) was added dropwise at 5° C to a solution of Diisopropylamine (2.44mL, 17.35mmol) in THF (100mL) and stirred for 10 min. Then the mixture was cooled to -35° C and combined with a solution of the title compound from Step 1 (3.00g, 11.57mmol) in THF (100mL). The mixture was stirred at 0° C for 1h and then cooled to -78° C. Methyl iodide (1.080mL, 17.35mmol) was added dropwise and the

-68-

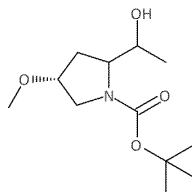
mixture was stirred for 4h at -78°C. Then 10mL sat. ammonium chloride solution was added dropwise and the mixture was heated to rt. Then it was mixed with water and extracted three times with ethyl acetate. The combined organic phase was dried on sodium sulfate, filtered and evaporated under vacuum. The residue was purified by column chromatography using Cyclohexane/EtOAc (80/20) as eluent to afford the title compound as a yellow oil (1.548g, 5.66mmol, 49% yield).

Step 3

To a suspension of the title compound from Step 2 (1.55g, 5.66mmol) in a mixture of EtOH/THF (30mL/30mL) cooled at 0°C were added Sodium borohydride (0.428g, 11.33mmol) and Calcium chloride (0.629g, 5.66mmol). The solution was warmed up to room temperature and stirred for 1h at rt. The reaction mixture was quenched by addition of water and aqueous HCl 1M until pH=4. EtOAc was added and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 60mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography using Cyclohexane/EtOAc (100/0 to 60/40) as eluent to afford the expected product as colorless oil (0.782g, 3.19mmol, 56% yield) as a colorless oil.

¹H NMR (400 MHz, DMSO) 4.77 - 4.68 (1H, m), 3.85 - 3.79 (1H, m), 3.72 - 3.36 (3H, m), 3.31 - 3.23 (1H, m), 3.22 - 3.20 (3H, m), 2.33 - 2.13 (1H, m), 1.77 - 1.65 (1H, m), 1.39 (9H, d, J=3.8 Hz), 1.28 - 1.22 (3H, m).

Pyrrolidine P16: tert-butyl (4R)-2-(1-hydroxyethyl)-4-methoxypyrrolidine-1-carboxylate



Step 1

To a stirred solution of 2M Oxalyl chloride solution in DCM (10mL, 20mmol) in Dichloromethane (100mL) at -78° C was added Dimethyl sulfoxide (2.84mL, 40mmol) dropwise via syringe. The mixture was stirred at -78° C. for 10min and a solution of Pyrrolidine P1 (2.31g, 10mmol) in Dichloromethane (25mL) was added. The mixture was stirred at -78° C. for 15 minutes, and Triethylamine (4.30mL, 40mmol) was added. After 15 minutes, the reaction mixture was allowed to warm to 0° C and stirred at that temperature for 30 minutes. The mixture was washed with water and Brine, dried with sodium sulfate, filtered, and concentrated in vacuo. The crude was purified by column chromatography on silica gel using a Cyclohexane/EtOAc (0-50%) to afford the title compound (Diastereomer mixture) as a colorless oil (2.44g).

-69-

Dia1 : ¹H NMR (400 MHz, CDCl₃) 9.45 (1H, d, J=3.8 Hz), 4.23 - 4.17 (1H, m), 3.98 - 3.93 (1H, m), 3.75 (1H, d, J=12.0 Hz), 3.57 - 3.49 (1H, m), 3.35 (3H, s), 2.29 - 2.19 (1H, m), 2.00 - 1.89 (1H, m), 1.45 (9H, s).

Dia2: ¹H NMR (400 MHz, CDCl₃) 9.57 (1H, d, J=2.7 Hz), 4.32 (1H, t, J=8.1 Hz), 3.98 - 3.93 (1H, m), 3.57 - 3.49 (2H, m), 3.35 (3H, s), 2.29 - 2.19 (1H, m), 2.00 - 1.89 (1H, m), 1.49 (9H, s).

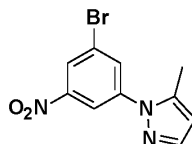
Step 2

To a solution of the title compound from Step 1 (1.63g, 7.10mmol) in anhydrous Diethyl ether (105mL) under nitrogen atmosphere cooled to 0°C was added via syringe Methylmagnesium bromide (3M in Diethyl ether; 5.92mL, 17.77mmol) and the resulting solution stirred for two hours at 0°C. The reaction was quenched with saturated solution of Ammonium chloride and extracted with Diethyl ether. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using Cyclohexane/EtOAc (100/0-50/50) to afford the expected compound (diastereomer mixture) as a colorless oil (150mg, 0.611mmol).

Dia1: ¹H NMR (400 MHz, CDCl₃) , 4.06 - 3.68 (4H, m), 3.32 - 3.31 (4H, m), 2.17 - 2.09 (1H, m), 1.82 - 1.68 (1H, m), 1.50 (9H, s), 1.15 (3H, d, J=6.6 Hz).

Dia2: ¹H NMR (400 MHz, CDCl₃) , 4.06 - 3.68 (4H, m), 3.32 - 3.31 (4H, m), 2.17 - 2.09 (1H, m), 1.82 - 1.68 (1H, m), 1.50 (9H, s), 1.09 (3H, d, J=6.7 Hz).

Intermediate I1 : 1-(3-bromo-5-nitrophenyl)-5-methyl-1H-pyrazole



Step 1

In a sealed tube 1-bromo-3-iodo-5-nitrobenzene (3.0 g, 9.149mmol) was dissolved in DMSO (9mL). *Tert*-butyl carbazate (1.451 g, 10.979mmol), cesium carbonate (4.471 g, 13.723mmol) and copper(I) iodide (174mg, 0.915mmol) were added and the reaction mixture was stirred at 50°C for 4h. Water was added and the mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting gradient 0-15% Heptane/ethyl acetate) to afford *tert*-butyl 1-(3-bromo-5-nitrophenyl)hydrazine-1-carboxylate (1.045g, 34% yield) as a brown sticky solid.

LCMS (MH) RT = 1.044 min, m/z = 275.9-277.9 (M+H)⁺.

-70-

Step 2

The title compound from Step 1 (1.040 g, 3.131mmol) was dissolved in HCl (4M/Dioxane) (10mL). The reaction mixture was stirred at room temperature for 16h. The solvent was removed under reduced pressure to afford the crude (3-bromo-5-nitrophenyl)hydrazine dihydrochloride (950mg, 100% yield) as a brown solid which was used without further purifications.

LCMS (MH) RT = 0.518 min, m/z = 231.9-233.9 (M+H)⁺.

Step 3

To a solution of the title compound from Step 2 (950mg, 3.131mmol) in ethanol (12mL) was added Triethylamine (1.306mL, 9.39mmol) followed by ethyl 2-((dimethylamino)methylene)-3-oxobutanoate (696mg, 3.757mmol) at room temperature. The reaction mixture was heated at 100°C for 2h. After cooling, a saturated aqueous sodium bicarbonate solution was added and the mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The residue was purified by silica gel chromatography (eluting solvent 80/20% Heptane/ethyl acetate) to afford ethyl 1-(3-bromo-5-nitrophenyl)-5-methyl-1H-pyrazole-4-carboxylate (780mg, 75% yield) as an orange solid.

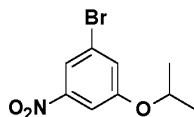
LCMS (MH) RT = 1.026 min, m/z = 353.9-356.0 (M+H)⁺.

Step 4

In a pressure flask, to the title compound from Step 3 (780mg, 2.202mmol) was added acetic acid/HBr (3:1) (7mL) and the mixture was heated at 150°C for 5 days. After cooling, solvent was removed under reduced pressure and the crude residue was diluted with ethyl acetate and washed with a saturated aqueous sodium bicarbonate solution and Brine. The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The residue was purified by silica gel chromatography (eluting eluent 90/10% Heptane/ethyl acetate) to afford the expected compound (300mg, 48% yield) as a brown solid.

LCMS (MH) RT = 0.896 min, m/z = 281.9 - 283.9 (M+H)⁺.

Intermediate I2: 1-bromo-3-nitro-5-(propan-2-yloxy)benzene

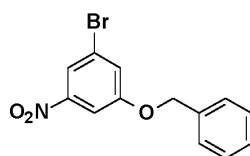


To a solution of 3-bromo-5-nitro-phenol (5.0 g, 22.9mmol) in acetone (100mL) was added portionwise potassium carbonate (4.75 g, 34.4mmol). The reaction mixture was stirred at room temperature for 10min. Then 2-iodopropane (4.0mL, 68.70mmol) was added and the reaction mixture was heated at 70°C for 5h. The reaction mixture was cooled to room temperature. The

-71-

insoluble material was filtered off and washed with acetone. The filtrate was concentrated under reduced pressure to afford the expected compound (6.0 g, 100% yield) as yellow liquid. LCMS (MA) RT = 3.12 min, m/z = 260.1 (M+H)⁺.

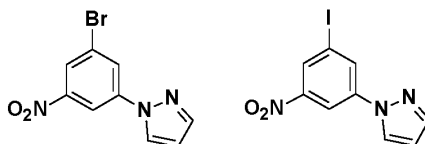
5 **Intermediate I3:** 1-(benzyloxy)-3-bromo-5-nitrobenzene



To a solution of 3-bromo-5-nitro-phenol (20 g, 91.74mmol) in acetone (200mL) was added portionwise potassium carbonate (19.02 g, 137.61mmol). The reaction mixture was stirred at room temperature for 10min. Then Bromomethylbenzene (11.46mL, 96.33mmol) was added and the reaction mixture was heated at 70°C for 2h. The reaction mixture was cooled to room temperature. The insoluble material was filtered off and washed with acetone. The filtrate was concentrated under reduced pressure to afford the expected compound (28.3 g, 100% yield) as a cream solid.

¹H NMR (400 MHz, CDCl₃) 8.01 - 7.99 (1H, m), 7.79 - 7.78 (1H, m), 7.48 - 7.44 (6H, m), 5.16 (2H, s).

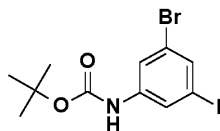
Intermediate I4: Mixture of 1-(3-bromo-5-nitrophenyl)-1H-pyrazole and 1-(3-iodo-5-nitrophenyl)-1H-pyrazole



In a pressure flask, 3-bromo-5-iodonitrobenzene (7.2 g, 21.958mmol), Pyrazole (1.495 g, 21.958mmol), copper(I) iodide (836mg, 4.392mmol), trans-N,N'-dimethylcyclohexane-1,2-diamine (1.249mL, 21.958mmol) and cesium carbonate (21.67 g, 65.67mmol) in DMF (45mL). The reaction mixture was bubbled with a nitrogen stream for 5 min and the mixture was stirred at 50°C for 12h. The reaction mixture was filtered over a pad of Celite and rinsing with ethyl acetate. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting gradient 0-20% Heptane/ethyl acetate) to afford to afford a mixture of the expected compound and 1-(3-iodo-5-nitrophenyl)-1H-pyrazole (3.3 g, 25% yield) as a brown solid.

LCMS (MH) RT = 0.902 min, m/z = 267.9 - 269.9 (M+H)⁺ and RT = 0.942 min, m/z = 315.9 (M+H)⁺.

-72-

Intermediate I5: tert-butyl N-(3-bromo-5-iodophenyl)carbamate

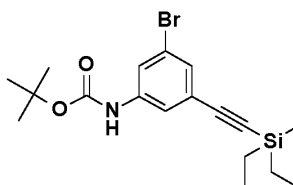
To a stirred solution of 3-bromo-5-iodo-benzoic acid (30 g, 91.77mmol) in dry *tert*-butanol (150mL) and Triethylamine (16.6mL, 119.30mmol) under argon was added
 5 Diphenylphosphoryl azide (21.7mL, 100.95mmol). The reaction mixture was refluxed at 80°C under argon for 16h. The reaction mixture was cooled to room temperature and the solvent were evaporated under reduced pressure. The residue was dissolved in ethyl acetate and successively washed with a 10% Sodium hydroxide solution, water and Brine. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced
 10 pressure. The residue was purified by silica gel chromatography (eluting eluent 90/10% cyclohexane/ethyl acetate) to afford the expected compound (32.2 g, 88% yield) as yellowish amorphous solid.

¹H NMR (400 MHz, DMSO) 9.66 (1H, s), 7.86 (1H, t, J=1.6 Hz), 7.70 (1H, t, J=1.8 Hz), 7.50 (1H, t, J=1.6 Hz), 1.48 - 1.47 (9H, m).

15

Similarly prepared:

Int. n°	structure	name	Intermediate	Analytical data
I6		tert-butyl N-(5-bromo-2-fluoro-3-methoxyphenyl)carbamate	From 5-bromo-2-fluoro-3-methoxybenzoic acid 82% yield as a white solid	LCMS (MA) RT = 3.01 min, m/z = 320-322 (M+H) ⁺ .

Intermediate I7: tert-butyl N-{3-bromo-5-[2-(triethylsilyl)ethynyl]phenyl}carbamate

To a solution of **Intermediate I5** (32.2g, 80.9mmol) in dry tetrahydrofuran (250mL) under Argon was added (triethylsilyl)acetylene (21.74mL, 121.35mmol), Bis(triphenylphosphine) palladium(II) dichloride (2.84 g, 4.045mmol), copper iodide (770mg, 4.045mmol) and Triethylamine (33.83mL, 242.7mmol). The reaction mixture was stirred at room temperature for 2h. The reaction mixture was diluted with water and extracted with ethyl acetate. The
 20 combined organic layers were washed with Brine and dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified by silica gel
 25

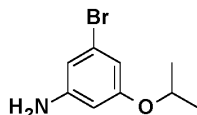
-73-

chromatography (eluting eluent 90/10% cyclohexane/ethyl acetate) to afford the expected compound (27.1 g, 82% yield) as a brown oil.

¹H NMR (400 MHz, CDCl₃) 7.63 (1H, m), 7.45 - 7.37 (1H, m), 7.30 - 7.27 (1H, m), 6.47 - 6.43 (1H, m), 1.54 - 1.53 (9H, m), 1.08 - 1.03 (9H, m), 0.71 - 0.65 (6H, m).

5

Intermediate I8: 3-bromo-5-(propan-2-yloxy)aniline

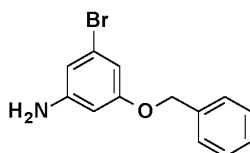


To a solution of **Intermediate I2** (6.0 g, 22.9mmol) in ethanol (140mL) was added portionwise tin (II) chloride dihydrate (20.7 g, 91.6mmol). The reaction mixture was heated under reflux for 2h. The reaction mixture was poured into water. The aqueous phase was basified with 33% NaOH solution and stirred at room temperature for 10min. After extraction with ethyl acetate, the organic phase was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified by silica gel chromatography (eluting gradient 10-40% cyclohexane/ethyl acetate) to afford the expected compound (5.30 g, 100% yield) as a yellowish liquid.

15

LCMS (MA) RT = 2.51 min, m/z = 232.1 (M+H)⁺.

Intermediate I9: 3-(benzyloxy)-5-bromoaniline



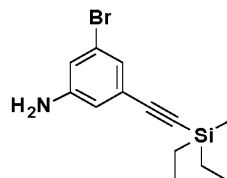
To a solution of **Intermediate I3** (13 g, 42.19mmol) in ethanol (250mL) was added portionwise tin (II) chloride dihydrate (38.08 g, 168.76mmol) and the reaction mixture was heated under reflux for 1h. The reaction mixture was poured into water. The aqueous phase was basified with 33% NaOH solution and stirred at room temperature for 10min. After extraction with ethyl acetate, the organic phase was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified by silica gel chromatography (eluting gradient 10-40% cyclohexane/ethyl acetate) to afford the expected compound (11.35g, 96% yield) as a pale yellow oil.

25

LCMS (MA) RT = 2.93 min, m/z = 280.0 (M+H)⁺.

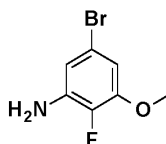
30

-74-

Intermediate I10: 3-bromo-5-[2-(triethylsilyl)ethynyl]aniline

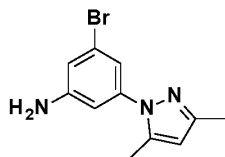
To a solution of **Intermediate I7** (27.10 g, 66.03mmol postulated) in Dichloromethane (300mL) was added trifluoroacetic acid (50mL) at room temperature. The reaction mixture was stirred for 2h at room temperature. Solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (eluting solvent 90/10% cyclohexane/ethyl acetate) to afford the expected compound (18.90 g, 92% yield) as a brown solid.

LCMS (MA) RT = 3.65 min, m/z = 351-353 (M+H)⁺.

Intermediate I11: 5-bromo-2-fluoro-3-methoxyaniline

To a solution of **Intermediate I6** (1.05 g, 3.27mmol) in Dichloromethane (10mL) was added trifluoroacetic acid (2mL, 26.11mmol) and the reaction mixture was stirred at room temperature for 16h. The solvent was evaporated under reduced pressure. The residue was diluted with ethyl acetate and washed with saturated aqueous sodium bicarbonate solution and Brine. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to afford the expected compound (700mg, 97% yield) as a brown solid.

LCMS (MA) RT = 2.27 min, m/z = 220-222 (M+H)⁺.

Intermediate I12: 3-bromo-5-(3,5-dimethyl-1H-pyrazol-1-yl)aniline

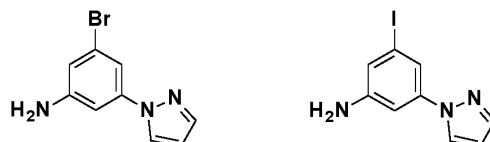
In a pressure flask, 3-bromo-5-iodoaniline hydrochloride (1.2 g, 3.589mmol), 3,5-dimethylpyrazole (345mg, 3.589mmol), copper(I) iodide (410mg, 2.153mmol), DL-Proline (165mg, 1.436mmol), and cesium carbonate (3.508 g, 10.767mmol) in DMSO (12mL) were bubbled with a nitrogen stream for 1min and the mixture was stirred at 150°C for 16h. A saturated aqueous sodium bicarbonate solution was added and the mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel

-75-

chromatography (eluting gradient 0-1.5% Dichloromethane/methanol) to afford the expected compound (220mg, 23% yield) as a brown solid.

LCMS (MH) RT = 0.744 min, m/z = 266-268 (M+H)⁺.

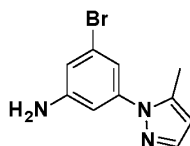
- 5 **Intermediate I13:** Mixture of 3-bromo-5-(1H-pyrazol-1-yl)aniline and 3-iodo-5-(1H-pyrazol-1-yl)aniline



- To a mixture of **Intermediate I4** (3.3 g, 5.659mmol) and ammonium chloride (1.311 g, 24.5mmol) were dissolved in of ethanol/water (4:1) (30mL). Iron powder (3.4 g, 28.295mmol) was added and the reaction mixture was stirred at 50°C for 88h. The reaction mixture was diluted with ethyl acetate and filtered through a Celite pad. The filtrate was washed with a saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting gradient 0-50% Heptane/ethyl acetate) to afford the mixture of the expected compound and 3-iodo-5-(1H-pyrazol-1-yl)aniline (1.8 g, 61% yield) as a brown sticky solid.

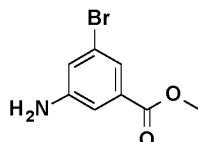
- LCMS (MH) RT = 0.647 min, m/z = 237.9-239.9 (M+H)⁺ and RT = 0.688 min, m/z = 286.0 (M+H)⁺.

- 20 **Intermediate I14:** 3-bromo-5-(5-methyl-1H-pyrazol-1-yl)aniline



- To a stirred solution of **Intermediate I1** (300mg, 1.063mmol) in ethanol/water (5:1) (11mL) was added ammonium chloride (398mg, 7.441mmol) and Iron powder (297mg, 5.315mmol). The reaction mixture was stirred at 50°C for 4h. The reaction mixture was filtered over a Celite pad and rinsing with ethyl acetate. The filtrate was concentrated under reduced pressure. Water was added and the mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting gradient 0-25% Heptane/ethyl acetate) to afford the expected compound (200mg, 75% yield) as a brown solid.
- LCMS (MH) RT = 0.669 min, m/z = 252.0-253.9 (M+H)⁺.

-76-

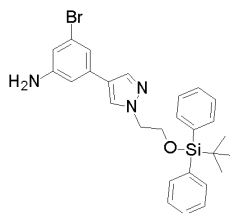
Intermediate I15: methyl 3-amino-5-bromobenzoate

To a solution of 3-amino-5-bromobenzoic acid (5.00 g, 23.144mmol) in methanol (93mL) under nitrogen atmosphere, was added dropwise thionyl chloride (25.184mL, 347.16mmol) at 0°C.

- 5 The reaction mixture was warmed to room temperature then stirred at 70°C for 4h. The solvent was evaporated under reduced pressure then co-evaporated with Heptane. The residue was dried under reduced pressure to afford Methyl 3-amino-5-bromobenzoate (7.85g, 100% yield) as beige solid which was used without further purifications.

LCMS (MH) RT = 0.692 min, m/z = 230-232 (M+H)⁺.

10

Intermediate I16: 3-bromo-5-(1-{2-[(tert-butyldiphenylsilyl)oxy]ethyl}-1H-pyrazol-4-yl)aniline**Step 1**

- To a suspension of **Intermediate I5** (1.50g, 3.77mmol) in Dioxane/Water (48/12mL) were added 2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]ethanol (1.08g, 4.52mmol), Tetrakis(triphenylphosphine)palladium(0) (87mg, 0.07mmol), Xphos (72mg, 0.15mmol) and Potassium phosphate tribasic (2.40g, 11.31mmol). The reaction mixture was degassed by bubbling under argon for 10 min and stirred at 100°C for 1 h. The resulting mixture was allowed to cooled to room temperature. Solvent was evaporated under reduced pressure. The residue was purified by flash chromatography using Cyclohexane/EtOAc (100:0 to 0:100) as eluent. The expected fractions were combined and evaporated under reduced pressure to afford the title compound as a yellow oil (1.63g, quant.).

LCMS (MA) RT = 2.46 min, m/z = 382.1/384.1 (M+H)⁺.

Step 2

- To a solution of the title compound from Step 1 (1.53g, 4.00mmol) in THF (15mL) were added Imidazole (544mg, 8.00mmol) and tert-Butyldiphenylchlorosilane (1.56mL, 6.00mmol). The mixture was stirred at room temperature for 1 h. Upon complete conversion, monitored by LCMS, water and EtOAc were added and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 20mL) and the combined organic layers were dried over anhydrous

-77-

sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using Cyclohexane/EtOAc (100:0 to 50:50) as eluent to afford the title compound as a pale yellow foam (1.91g, 77 %).

LCMS (MA) RT = 3.83 min, m/z = 620.2/622.2 (M+H)⁺.

5

Step 3

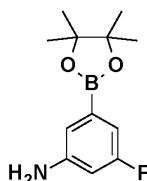
To a solution of the title compound from Step 2 (1.91g, 3.07mmol) in DCM (45mL) was added HCl 4 M in 1,4-Dioxane (2.30mL, 9.22mmol). The mixture was stirred at room temperature for 5 h. LCMS monitoring showed partial conversion, therefore additional HCl 4 M in 1,4-Dioxane (1.50mL, 6.14mmol, 2 eq) was added and the mixture was stirred at room temperature overnight. Upon complete conversion, monitored by LCMS, the mixture was carefully quenched with a saturated solution of NaHCO₃. The layers were separated. The aqueous layer was extracted with DCM (2 x 20mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified on silica gel column using Cyclohexane/EtOAc (100:0 to 60:40) as eluent to afford the title compound as an orange oil (1.39g, 88 % yield).

10

15

LCMS (MA) RT = 3.44 min, m/z = 520.2/522.2 (M+H)⁺.

Aniline A1: 3-Fluoro-5-(tetramethyl-1,3,2-dioxaborolan-2-yl)aniline



20

A mixture of 3-bromo-5-fluoroaniline (21.2 g, 111.61mmol), bis(pinacolato)diboron (28.34 g, 111.61mmol), potassium acetate (32.86 g, 334.83mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (2.45 g, 3.90mmol) in 1,4-Dioxane (120mL) was purged with argon and then heated at 90°C for 16h. The hot reaction mixture was filtered through a Whatmann paper filter. The filtrate was diluted in ethyl acetate and washed with water and Brine. The organic layer was dried over anhydrous sodium sulfate then filtered and evaporated under reduced pressure. The residue was purified by silica gel chromatography (eluting gradient 0-20% pentane/ethyl acetate). The residue was triturated in *n*-Heptane, then filtered and dried to afford the expected compound (11.73 g, 44% yield) as a beige solid.

25

30

LCMS (MA) RT = 2.53 min, m/z = 238.2 (M+H)⁺.

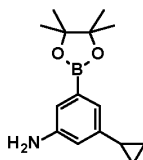
Similarly prepared :

Int.n°	Structure	Name	From intermediates	Analytical data
A2		3-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline	From 3-bromo-5-chloroaniline 79% yield as a beige solid	LCMS (MA) RT = 2.74 min, m/z = 254.1 (M+H) ⁺ .
A3		3-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline	From 3-bromo-5-methoxyaniline 90% yield as a red oil	LCMS (MA) RT = 1.99 min, m/z = 250 (M+H) ⁺ .
A4		3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline	From 3-bromo-5-ethoxyaniline 71% yield as cream crystals	LCMS (MA) RT = 2.30 min, m/z = 264.2 (M+H) ⁺ .
A5		3-isopropoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline	From Intermediate I8 82% yield as a red oil	LCMS (MA) RT = 2.37 min, m/z = 278.2 (M+H) ⁺ .
A6		3-amino-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile	From 3-amino-5-bromo-benzonitrile 84% yield as white solid	LCMS (MA) RT = 2.53 min, m/z = 245.2 (M+H) ⁺ .
A7		3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)aniline	From 3-amino-5-bromobenzotrifluoride 99% yield as brown oil	LCMS (MA) RT = 2.89 min, m/z = 288.1 (M+H) ⁺ .
A8		3-(difluoromethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline	From 3-bromo-5-(difluoromethoxy)aniline 64 % yield as light orange oil	LCMS (MA) RT = 2.64 min, m/z = 286.1 (M+H) ⁺ .

A9		3-benzyloxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline	From Intermediate I9 71% yield as a cream solid	LCMS (MA) RT = 2.70 min, m/z = 326.1 (M+H) ⁺ .
A10		3,4-difluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline	From 3-bromo-4,5-difluoro-aniline 69% yield as a yellow oil	¹ H NMR (400 MHz, DMSO) 6.65 – 6.57 (2H, m), 5.24 (2H, bs), 1.29 – 1.28 (12H, m).
A11		3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(2-triethylsilyl ethynyl)aniline	From Intermediate I10 67% yield as a brown oil	LCMS (MA) RT = 3.67 min, m/z = 358 (M+H) ⁺ .
A12		3-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline	From 3-bromo-5-ethyl-aniline 44% yield as a yellow solid	LCMS (MA) RT = 2.12 min, m/z = 248.2 (M+H) ⁺ .
A13		2-fluoro-3-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline	From Intermediate I11 58% yield as a white solid	LCMS (MA) RT = 2.50 min, m/z = 268.2 (M+H) ⁺ .
A14		2,3-difluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline	From 5-bromo-2,3-difluoro-aniline 40% yield as a white solid	LCMS (MA) RT = 2.85 min, m/z = 256 (M+H) ⁺ .

-80-

A15		3-pyrazol-1-yl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline	From Intermediate I13 90% yield as a brown solid	LCMS (MH) RT = 0.803 min, m/z = 286.1 (M+H) ⁺ .
A16		3-(3,5-dimethylpyrazol-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline	From Intermediate I12 34% yield as a brown sticky solid	LCMS (MI) RT = 0.866 min, m/z = 314.1 (M+H) ⁺ .
A17		3-(5-methylpyrazol-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline	From Intermediate I14 100% yield as black solid	LCMS (MH) RT = 0.819 min, m/z = 300.1 (M+H) ⁺ .
A18		methyl 3-amino-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate	From Intermediate I15 92% yield as beige solid	LCMS (MH) RT = 0.801 min, m/z = 278.1 (M+H) ⁺ .
A19		3-[1-[2-[tert-butyl(diphenyl)silyloxyethyl]pyrazol-4-yl]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline	From Intermediate I16 76% yield as brown oil	LCMS (MA) RT = 3.45 min, m/z = 568.3 (M+H) ⁺ .

Aniline A20: 3-cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

-81-

Step 1

To a stirred solution of 3-Bromo-5-iodo-benzoic acid (20.0g, 61.18mmol) in dry tert-Butanol (100mL) and Triethylamine (11.0mL, 79.53mmol) under Argon was added Diphenyl phosphoryl-azide (14.5mL, 67.30mmol). The reaction mixture was refluxed (80°C) under Argon overnight. The reaction mixture was cooled down to room temperature and the solvent were evaporated in vacuo. The residue was dissolved in ethyl acetate (50mL) and washed successively with a 10% NaOH solution (30mL), water (2x50mL) and Brine. The organic layer was dried over sodium sulfate, filtered and evaporated in vacuo. The crude residue was purified by silica gel chromatography using Cyclohexane/EtOAc (90:10) as eluent to afford the title compound as yellow amorphous solid (16.2g, 67% yield).
LCMS (MA) RT = 3.38 min, m/z = 341.8/343.8 (M+H)⁺.

Step 2

To a suspension of the title compound from Step 1 (3.0g, 7.54mmol) in Toluene/Water (36/6mL) were added Cyclopropylboronic acid (842mg, 9.80mmol), Palladium(II) acetate (85mg, 0.38mmol), Tricyclohexylphosphine (211mg, 0.75mmol) and Potassium phosphate tribasic (4.801g, 22.62mmol). The reaction mixture was degassed by bubbling under argon for 10 min and stirred at 110°C for 39 h. Upon 95% conversion, monitored by LCMS, the mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was purified on silica gel column using Cyclohexane/EtOAc (100:0 to 85:15) as eluent. A second purification on silica gel column was performed using Cyclohexane/EtOAc (100:0 to 90:10) as eluent to afford the title compound as orange oil (1.26g, 53% yield).
LCMS (MA) RT = 3.16-3.22 min, m/z = 312.2/314.1 (M+H)⁺.

Step 3

To a solution of title compound from Step 2 (1.26g, 4.03mmol) in DCM (60mL) was added HCl 4 M in 1,4-Dioxane (5.04mL, 20.15mmol). The mixture was stirred at room temperature for 8h. Upon complete conversion, monitored by LCMS, the mixture was carefully quenched with a saturated solution of NaHCO₃. The layers were separated and the aqueous layer was extracted with DCM (2 x 20mL). The combined organic layer was dried over anhydrous Sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified on silica gel column using Cyclohexane/EtOAc (100:0 to 90:10) as eluent to afford the title compound as orange oil (660mg, 3.11mmol, 77 %).
LCMS (MA) RT = 2.45 min, m/z = 212.0/214.0 (M+H)⁺.

Step 4

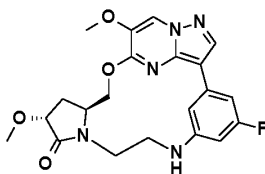
The title compound from Step 3 was further purified by column chromatography using Cyclohexane/EtOAc (100:0 to 85:15) as eluent to afford 483mg of an orange oil.
Under argon atmosphere, to a solution of 3-bromo-5-cyclopropyl-aniline (433mg, 2.04mmol) in

-82-

dry 1,4-Dioxane (12mL) were added Bis(pinacolato)diboron (544mg, 2.14mmol), KOAc (600mg, 6.12mmol) and [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with DCM (42mg, 0.05mmol). The reaction mixture was heated at 90°C for 3h. LCMS monitoring showed 50 % conversion. Additional Bis(pinacolato)diboron (272mg, 1.07mmol), KOAc (300mg, 3.06mmol) and [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with DCM (42mg, 0.05mmol) were added and the reaction was stirred at 90°C for 5 h. Upon complete conversion, monitored by LCMS, the mixture was cooled to rt and the solvent was evaporated under reduced pressure. The residue was diluted with a saturated solution of NaCl and EtOAc and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 20mL) and the combined organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified on silica gel column using Cyclohexane/EtOAc (100:0 to 85:15) as eluent to afford the expected compound as a pale brown foam (251mg, 48% yield).

LCMS (MA) RT = 2.11 min, m/z = 260.2 (M+H)⁺.

Example 1: (12R,14S)-4-fluoro-12,18-dimethoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1².6.0¹⁰.14.0²⁰,²³]pentacosa-1(23),2(25),3,5,17(24),18,21-heptaen-11-one



20 Step 1

To a solution of **Pyrrolidine P1** (2.7 g, 10.29mmol) in dry DMF (50mL) was added Sodium hydride, 60% in mineral oil (0.823 g, 20.57mmol) at 0°C. After 30 min, **Scaffold S2** (2.617 g, 11.31mmol) was added and the mixture was stirred at 4-5 °C for 15min. Monitoring by LCMS showed complete conversion. Water was added dropwise carefully at 4-5°C and the mixture was extracted with EtOAc (4x20mL). The combined organic layers were washed with Brine then dried over Na₂SO₄, filtered and concentrated under vacuum. The product was purified on column of silica gel using Cyclohexane/EtOAc (100-0 to 50-50) as eluent to afford the expected compound (3.498 g, 7.65mmol, 74%) as a light brown oil.

LCMS (MA) RT = 2.76 min, m/z = 459 (M+H)⁺.

30

Step 2

A solution of K₃PO₄ (21.01mmol, 4.46 g) in water (9mL) was added to a solution of the title compound from Step 1 (7mmol, 3.203 g), **Aniline A1** (9.11mmol, 2.159 g) and Xphos (0.28mmol, 229mg) in Dioxane (26mL). The reaction mixture was degassed with argon during 15 min. To the reaction mixture was added Pd(PPh₃)₄ (0.14mmol, 162mg) and the reaction

-83-

was heated at 100°C for 3h. Monitoring by LC/MS showed reaction was complete. The reaction mixture was filtered over Celite then solvent was removed under reduced pressure. The compound was purified by Flash chromatography using a 120g SiO₂ column eluted with Cyclohexane/EtOAc 100/0 to 50/50 to afford the expected compound (3.395 g, 6.96mmol, 99%) as a brown oil.
LCMS (MA) RT = 2.61 min, m/z = 488.2 (M+H)+.

Step 3

To a solution of the title compound from Step 2 (3.524 g, 7.23mmol) in CH₃CN (36mL) were added Pyridine (0.877mL, 10.84mmol) and 2-Nitrobenzenesulfonyl chloride (2.083 g, 9.40mmol). The reaction mixture was heated at 70°C for overnight. Monitoring reaction by LCMS showed complete reaction. The reaction mixture was poured into water. After extraction with EtOAc, the organic phase was dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude was triturated in Diisopropyl ether to the title compound (4.064 g, 6.04mmol, 84%) as a brown oil.
LCMS (MA) RT = 2.95 min, m/z = 673.2 (M+H)+.

Step 4

To a solution of the title compound from Step 3 (0.500g, 0.74mmol) in Acetonitrile (5mL) was added Cesium carbonate (0.727g, 2.23mmol) and 1,2-Dibromoethane (0.961mL, 11.15mmol). The reaction mixture was heated to reflux for 4h. Monitoring of the reaction mixture by LCMS showed the reaction was completed. The solvent was removed, the residue was taken in EtOAc (50mL) extracted with water (50mL) then Brine (2x40mL), the organic layer was dried over anhydrous Na₂SO₄, filtered and dried under vacuum to afford the expected compound (0.598g, 0.74mmol postulated, quantitative yield) as a yellow/orange solid.
LCMS (MA) RT = 3.13 min, m/z = 780 (M+H)+.

Step 5

To a suspension of the title compound from Step 4 (0.598g, 0.77mmol) in DCM (5mL) was added Hydrogen Chloride solution 4M in 1,4-Dioxane (1.918mL, 7.67mmol). The reaction mixture was left stirring overnight. LCMS showed complete reaction. The solvent was removed under reduced pressure to afford the expected compound (0.622g, 0.77mmol postulated, quantitative yield) as a brown solid.
LCMS (MA) RT = 1.97 min, m/z = 679 (M+H)+.

Step 6

To a solution of the title compound from Step 5 (0.622g, 0.87mmol) in CH₃CN (62mL) was added Sodium hydrogenocarbonate (0.365g, 4.34mmol), cesium carbonate (0.849g, 2.61mmol) then Potassium iodide (0.433g, 2.61mmol). The resulting mixture was heated at

-84-

90°C for 4h. Monitoring by LC/MS showed reaction was complete. The reaction mixture was filtered then the solid was purified on silica gel column using DCM/MeOH 100/0 to 98/2 as eluent to afford the expected compound (0.106g, 0.18mmol, 20% yield) as a white solid.
LCMS (MA) RT = 2.29 min, m/z = 599 (M+H)+.

5

Step 7

To a mixture of the title compound from Step 6 (0.106g, 0.18mmol) in THF/H₂O (9mL/3.9mL) was added Sodium bicarbonate (0.298g, 3.54mmol). The reaction mixture was stirred 10 min at room temperature then Iodine (0.674g, 2.66mmol) was added. The reaction mixture was stirred at 60°C for 2h. Monitoring by LC/MS showed reaction was complete. The reaction mixture was quenched by saturated sodium thiosulfate solution then extracted by ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to afford the expected compound (0.118g, 0.18mmol postulated, quantitative yield) as a yellow solid.

10
15 LCMS (MA) RT = 2.49 min, m/z = 613 (M+H)+.

Step 8

The title compound from Step 7 (0.118g, 0.19mmol) and Cesium carbonate (0.126g, 0.39mmol) were dissolved in DMF (2mL). 4-Methylbenzenethiol (0.029g, 0.23mmol) was added and the mixture was stirred at room temperature overnight. Monitoring of the reaction mixture by LCMS showed the reaction was completed. The reaction mixture was filtered to remove cesium carbonate. Solvent was evaporated and the residue was purified by flash column chromatography using (DCM/MeOH 100/0 to 95/5) as eluent. The product fractions were collected and the solvent was evaporated. The residue was purified by flash column chromatography using Cyclohexane/EtOAc (100/0 to 0/100) as eluent to afford the expected product (0.008g, 10% Yield) as a pale yellow powder.

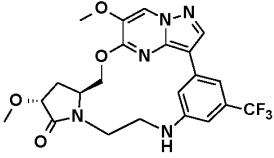
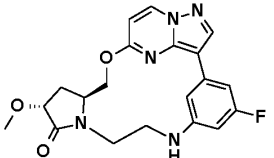
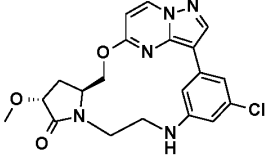
20
25 LCMS (MA) RT = 2.15 min, m/z = 428 (M+H)+.

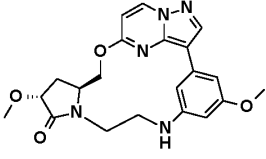
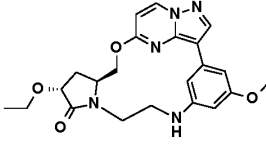
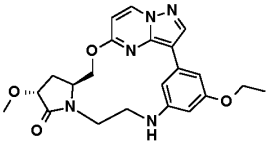
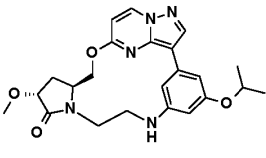
LCMS (MB) RT = 2.22 min, m/z = 428 (M+H)+.

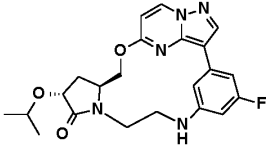
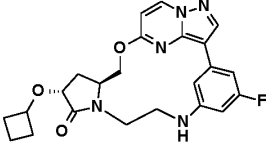
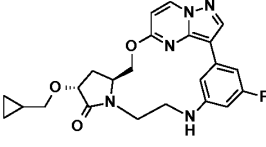
¹H NMR (400 MHz, DMSO) 8.79 (1H, s), 8.40 (1H, s), 7.63 (1H, s), 6.73 (1H, dd, J=1.2, 9.2 Hz), 6.33 (1H, t, J=5.8 Hz), 6.22 – 6.17 (1H, m), 4.96 (1H, d, J=10.4 Hz), 4.49 – 4.46 (1H, m), 4.36 – 4.31 (1H, m), 4.07 – 4.00 (1H, m), 3.90 – 3.89 (3H, m), 3.62 – 3.51 (1H, m), 3.42 – 3.35 (1H, m), 3.33 (3H, s), 3.25 – 3.19 (2H, m), 2.50 – 2.40 (1H, m), 2.00 – 1.91 (1H, m).

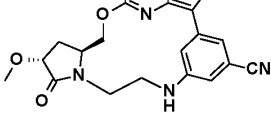
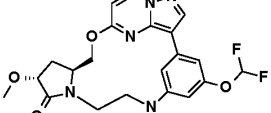
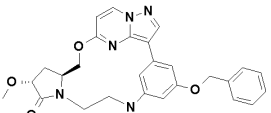
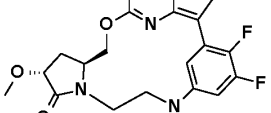
30
35

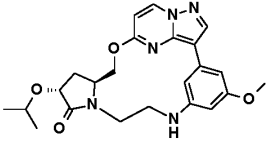
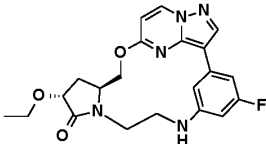
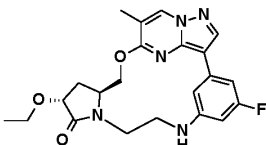
Similarly prepared:

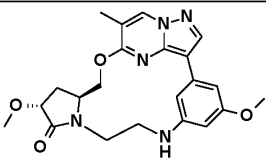
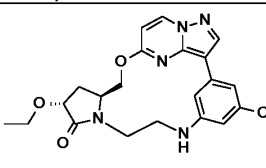
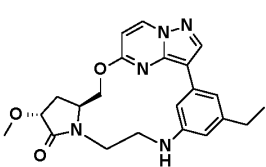
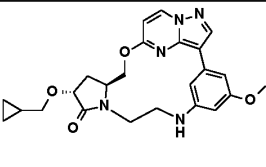
Ex n°	Structure/ Name	From intermediates	Analytical data
2	 (12R,14S)-12,18-dimethoxy-4-(trifluoromethyl)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,¹⁴.0²⁰,²³]pentacosan-1(23),2(25),3,5,17(24),18,21-heptaen-11-one	Scaffold S2 Pyrrolidine P1 Aniline A7 27% yield as a pale yellow solid	LCMS (MA) RT = 2.46 min, m/z = 478 (M+H)⁺ LCMS (MC) RT = 2.40 min, m/z = 478 (M+H)⁺ ¹H NMR (400 MHz, DMSO) 8.81 (1H, s), 8.51 (1H, s), 7.99 – 7.96 (1H, m), 7.17 (1H, s), 6.73 (1H, s), 6.54 (1H, t, J=6.0 Hz), 4.98 – 4.95 (1H, m), 4.60 – 4.40 (1H, m), 4.37 – 4.31 (1H, m), 4.08 – 4.01 (1H, m), 3.90 (3H, s), 3.54 (1H, dd, J=10.3, 13.8 Hz), 3.45 (3H, s), 3.30 – 3.20 (2H, m), 2.45 – 2.35 (1H, m), 1.99 – 1.91 (1H, m), 1.16 – 1.15 (1H, m).
3	 (12R,14S)-4-fluoro-12-methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,¹⁴.0²⁰,²³]pentacosan-1(23),2(25),3,5,17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P1 Aniline A1 58% yield as an off-white crystal	LCMS (MA) RT = 2.21 min, m/z = 398.1 (M+H)⁺ LCMS (MB) RT = 2.21 min, m/z = 398.2 (M+H)⁺ ¹H NMR (400 MHz, DMSO) 8.99 (1H, d, J=7.6 Hz), 8.54 – 8.54 (1H, m), 7.68 (1H, s), 6.77 – 6.73 (1H, m), 6.67 (1H, d, J=7.4 Hz), 6.34 (1H, t, J=5.9 Hz), 6.24 – 6.19 (1H, m), 4.94 (1H, d, J=11.0 Hz), 4.48 – 4.45 (1H, m), 4.37 – 4.31 (1H, m), 3.95 (1H, t, J=10.7 Hz), 3.63 – 3.50 (1H, m), 3.46 (3H, s), 3.39 (1H, s), 3.27 – 3.19 (2H, m), 2.44 (1H, s), 2.01 – 1.92 (1H, m).
4	 (12R,14S)-4-chloro-12-methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,¹⁴.0²⁰,²³]pentacosan-1(23),2(25),3,5,17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P1 Aniline A2 17% Yield as a yellow solid	LCMS (MA) RT = 2.38 min, m/z = 414 (M+H)⁺ LCMS (MC) RT = 2.36 min, m/z = 414 (M+H)⁺ ¹H NMR (400 MHz, DMSO) : 9.00 (1H, d, J=7.4 Hz), 8.58 – 8.56 (1H, m), 7.78 – 7.78 (1H, m), 6.97 (1H, s), 6.67 (1H, d, J=7.4 Hz), 6.48 (1H, t, J=1.7 Hz), 6.38 – 6.34 (1H, m), 4.94 (1H, dd, J=0.9, 10.5 Hz), 4.48 – 4.46 (1H, m), 4.34 (1H, t, J=8.9 Hz), 3.98 – 3.92 (1H, m), 3.65 – 3.50 (1H, m), 3.39 – 3.35 (1H, m), 3.33 (3H, s), 3.27 – 3.19 (2H, m), 2.45 – 2.30 (1H, m), 2.00 – 1.92 (1H, m).

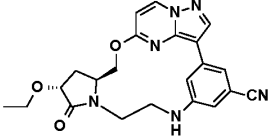
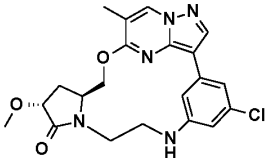
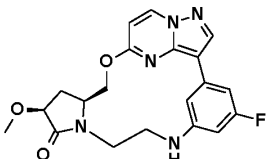
5	 (12R,14S)-4,12-dimethoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]pentacosan-1(23),2(25),3,5,17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P1 Aniline A3 38% yield as a white solid	LCMS (MA) RT = 2.09 min, m/z = 410 (M+H)⁺. LCMS (MC) RT = 2.06 min, m/z = 410 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 8.98 – 8.96 (1H, m), 8.51 (1H, s), 7.49 – 7.46 (1H, m), 6.65 – 6.63 (1H, m), 6.55 (1H, s), 6.06 – 6.02 (2H, m), 4.93 (1H, d, J=10.4 Hz), 4.49 – 4.46 (1H, m), 4.33 (1H, t, J=8.8 Hz), 4.05 – 3.91 (1H, m), 3.73 – 3.72 (3H, m), 3.60 – 3.45 (1H, m), 3.35 – 3.25 (3H), 3.24 – 3.17 (2H, m), 2.45 – 2.35 (1H, m), 2.01 – 1.94 (1H, m), 1.25 – 1.16 (1H, m).
6	 (12R,14S)-12-ethoxy-4-methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]pentacosan-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P2 Aniline A3 50% yield as a cream solid	LCMS (MA) RT = 2.22 min, m/z = 424.2 (M+H)⁺. LCMS (MB) RT = 2.28 min, m/z = 424.3 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 8.98 – 8.95 (1H, m), 8.50 (1H, s), 7.46 (1H, s), 6.65 – 6.62 (1H, m), 6.54 (1H, d, J=1.1 Hz), 6.05 – 6.02 (2H, m), 4.92 (1H, d, J=10.8 Hz), 4.46 – 4.38 (2H, m), 3.98 – 3.82 (2H, m), 3.73 (3H, s), 3.55 (2H, s), 3.59 – 3.32 (1H, m), 3.20 (2H, s), 2.46 – 2.39 (1H, m), 2.01 – 1.92 (1H, m), 1.15 (3H, t, J=7.0 Hz).
7	 (12R,14S)-4-ethoxy-12-methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]pentacosan-1(23),2(25),3,5,17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P1 Aniline A4 11% yield as a yellow solid	LCMS (MA) RT = 2.23 min, m/z = 424 (M+H)⁺. LCMS (MC) RT = 2.22 min, m/z = 424 (M+H)⁺. ¹H NMR (400 MHz, DMSO): 8.98 – 8.95 (1H, m), 8.50 (1H, s), 7.46 (1H, s), 6.65 – 6.62 (1H, m), 6.54 (1H, dd, J=1.2, 1.8 Hz), 6.03 – 6.01 (2H, m), 4.94 – 4.91 (1H, m), 4.46 (1H, s), 4.36 – 4.30 (1H, m), 4.02 – 3.90 (3H, m), 3.45 – 3.45 (4H, m), 3.44 – 3.37 (1H, m), 3.24 – 3.15 (2H, m), 2.35 – 2.27 (1H, m), 2.01 – 1.91 (1H, m), 1.35 – 1.30 (3H, m).
8	 (12R,14S)-12-methoxy-4-(propan-2-yloxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]pentacosan-1(23),2(25),3,5,17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P1 Aniline A5 21% yield as a white solid	LCMS (MA) RT = 2.32 min, m/z = 438.2 (M+H)⁺. LCMS (MC) RT = 2.33 min, m/z = 438.3 (M+H)⁺. ¹H NMR (400 MHz, CDCl₃): 8.53 – 8.51 (1H, m), 8.30 – 8.30 (1H, m), 7.58 (1H, s), 6.67 (1H, s), 6.43 – 6.41 (1H, m), 6.23 – 6.21 (1H, m), 5.08 – 5.05 (2H, m), 4.62 – 4.55 (4H, m), 4.26 – 4.21 (2H, m), 3.92 – 3.86 (2H, m), 3.63 – 3.62 (3H, m), 3.37 (3H, s), 2.63 (2H, dd, J=8.2, 12.9 Hz), 2.22 – 2.14 (3H, m).

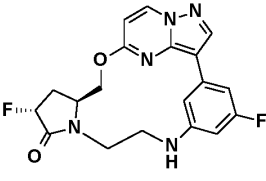
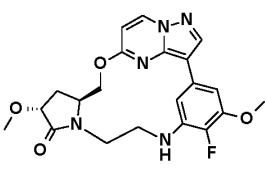
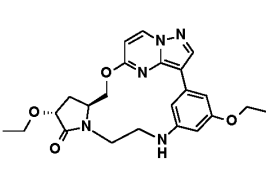
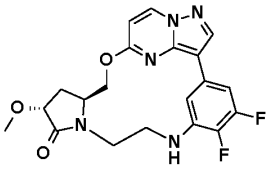
	1(23),2,4,6(25),17(24),18,21-heptaen-11-one		m).
9	 (12R,14S)-4-fluoro-12-(propan-2-yloxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]pentacosan-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P4 Aniline A1 52% yield as a white solid	LCMS (MA) RT = 2.45 min m/z = 426.2 (M+H)⁺. LCMS (MC) RT = 2.45 min m/z = 426.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 8.99 (1H, d, J=7.4 Hz), 8.54 (1H, s), 7.68 (1H, s), 6.77 – 6.73 (1H, m), 6.66 (1H, d, J=7.4 Hz), 6.34 (1H, t, J=5.9 Hz), 6.24 – 6.19 (1H, m), 4.95 – 4.90 (1H, m), 4.52 (1H, t, J=8.6 Hz), 4.43 – 4.47 (1H, m), 4.04 – 3.95 (2H, m), 3.59 – 3.51 (1H, m), 3.42 – 3.37 (1H, m), 3.26 – 3.21 (2H, m), 2.44 – 2.39 (1H, m), 1.97 – 1.89 (1H, m), 1.14 (6H, dd, J=6.2, 8.4 Hz)
10	 (12R,14S)-12-cyclobutoxy-4-fluoro-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]pentacosan-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P3 Aniline A1 36% yield as a white solid	LCMS (MA) RT = 2.55 min, m/z = 438.2 (M+H)⁺. LCMS (MC) RT = 2.55 min, m/z = 438.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 8.99 (1H, d, J=7.4 Hz), 8.54 (1H, s), 7.67 (1H, s), 6.77 – 6.74 (1H, m), 6.67 (1H, d, J=7.6 Hz), 6.34 (1H, t, J=5.7 Hz), 6.23 – 6.19 (1H, m), 4.94 – 4.90 (1H, m), 4.50 – 4.36 (2H, m), 4.29 – 4.22 (1H, m), 3.97 (1H, t, J=10.8 Hz), 3.56 – 3.50 (1H, m), 3.42 – 3.36 (1H, m), 3.26 – 3.19 (2H, m), 2.43 – 2.38 (1H, m), 2.23 – 2.15 (2H, m), 2.00 – 1.81 (3H, m), 1.67 – 1.59 (1H, m), 1.49 – 1.41 (1H, m).
11	 (12R,14S)-12-(cyclopropylmethoxy)-4-fluoro-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]pentacosan-1(23),2(25),3,5,17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P5 Aniline A1 26% yield as a yellow solid	LCMS (MA) RT = 2.50 min, m/z = 438 (M+H)⁺. LCMS (MC) RT = 2.50 min, m/z = 438 (M+H)⁺. ¹H NMR (400 MHz, DMSO) : 8.99 (1H, d, J=7.4 Hz), 8.55 – 8.54 (1H, m), 7.68 – 7.66 (1H, m), 6.77 – 6.73 (1H, m), 6.67 (1H, d, J=7.4 Hz), 6.36 – 6.31 (1H, m), 6.24 – 6.19 (1H, m), 4.94 (1H, d, J=10.8 Hz), 4.47 – 4.41 (2H, m), 4.06 – 3.92 (1H, m), 3.67 – 3.52 (2H, m), 3.45 – 3.35 (2H, m), 3.27 – 3.18 (2H, m), 2.45 – 2.35 (1H, m), 2.00 – 1.99 (1H, m), 1.08 – 0.99 (1H, m), 0.50 – 0.46 (2H, m), 0.22 – 0.18 (2H, m).

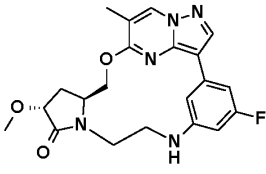
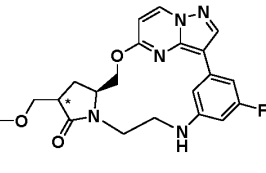
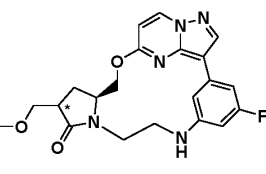
12	 (12R,14S)-12-methoxy-11-oxo-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]pentacosan-1(23),2,4,6(25),17(24),18,21-heptaene-4-carbonitrile	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P1 Aniline A6 22% yield as a beige solid	LCMS (MA) RT = 2.16 min, m/z = 405.1 (M+H)⁺. LCMS (MC) RT = 2.15 min, m/z = 405.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 9.03 – 9.00 (1H, m), 8.63 – 8.62 (1H, m), 8.09 (1H, s), 7.35 (1H, s), 6.78 (1H, dd, J=1.4, 2.2 Hz), 6.69 (1H, d, J=7.4 Hz), 6.56 (1H, t, J=5.7 Hz), 4.94 (1H, d, J=10.6 Hz), 4.48 (1H, d, J=7.8 Hz), 4.37 – 4.31 (1H, m), 3.96 (1H, t, J=10.8 Hz), 3.63 – 3.52 (1H, m), 3.45 (3H, s), 3.33 – 3.32 (3H, m), 2.48 – 2.40 (1H, m), 2.00 – 1.91 (1H, m).
13	 (12R,14S)-4-(difluoromethoxy)-12-methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]pentacosan-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P1 Aniline A8 31% yield as a salmon solid	LCMS (MA) RT = 2.32 min, m/z = 446.1 (M+H)⁺. LCMS (MC) RT = 2.31 min, m/z = 446.1 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 9.01 – 8.97 (1H, m), 8.54 – 8.52 (1H, m), 7.70 (1H, s), 6.74 (1H, s), 6.68 – 6.65 (1H, m), 6.38 – 6.32 (1H, m), 6.23 (1H, s), 4.93 (1H, d, J=11.0 Hz), 4.48 – 4.45 (1H, m), 4.34 (1H, t, J=8.7 Hz), 3.95 (1H, t, J=10.8 Hz), 3.58 – 3.49 (1H, m), 3.43 (3H, s), 3.42 – 3.35 (1H, m), 3.27 – 3.21 (2H, m), 2.46 – 2.40 (1H, m), 2.01 – 1.93 (1H, m).
14	 (12R,14S)-4-(benzyloxy)-12-methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]pentacosan-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P1 Aniline A9 69% yield as a white crystals	LCMS (MA) RT = 2.56 min, m/z = 486.2 (M+H)⁺. LCMS (MC) RT = 2.55 min, m/z = 486.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO) : 8.97 (1H, d, J=7.6 Hz), 8.51 (1H, s), 7.49 – 7.46 (3H, m), 7.43 – 7.38 (2H, m), 7.35 – 7.31 (1H, m), 6.65 – 6.63 (2H, m), 6.12 – 6.10 (1H, m), 6.05 (1H, t, J= 5.6Hz), 5.09 – 5.07 (2H, s), 4.92 (1H, d, J=10.6 Hz), 4.49 – 4.44 (1H, m), 4.33 (1H, t, J=8.9 Hz), 3.97 – 3.90 (1H, m), 3.57 – 3.49 (1H, m), 3.44 (3H, s), 3.44 – 3.37 (1H, m), 3.27 – 3.17 (2H, m), 2.46 – 2.4 (1H, m), 2.01 – 1.93 (1H, m).
15	 (12R,14S)-3,4-difluoro-12-methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]pentacosan-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P1 Aniline A14 17% yield as a white solid	LCMS (MA) RT = 2.32 min, m/z = 416.2 (M+H)⁺. LCMS (MC) RT = 2.31 min, m/z = 416.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 9.06 (1H, d, J=7.6 Hz), 8.41 (1H, d, J=3.6 Hz), 7.57 – 7.55 (1H, m), 6.74 (1H, d, J=7.6 Hz), 6.45 – 6.39 (1H, m), 6.22 (1H, t, J=6.1

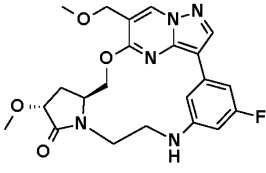
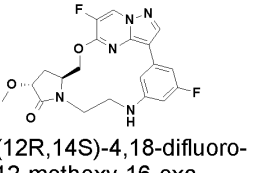
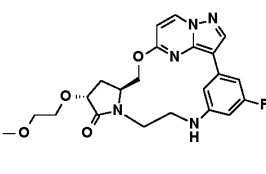
	methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1 ² ,6.0 ¹⁰ ,14.0 ²⁰ ,23]pentaco sa-1(23),2,4,6(25),17(24),18,21-heptaen-11-one		Hz), 4.95 (1H, d, J=11.0 Hz), 4.48 – 4.39 (1H, m), 4.37 – 4.30 (1H,m), 4.00 – 3.90 (1H, m), 3.57 – 3.46 (1H, m), 3.44 (3H, s), 3.35 – 3.28 (1H, m), 3.24 – 3.18 (2H, m), 2.47 – 2.37 (1H, m), 1.98 – 1.88 (1H, m).
16	 (12R,14S)-4-methoxy-12-(propan-2-yloxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentaco sa-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P4 Aniline A3 20% yield as a beige solid	LCMS (MA) RT = 2.33 min, m/z = 438.2 (M+H)⁺. LCMS (MC) RT = 2.33 min, m/z = 438.3 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 8.96 (1H, d, J=7.6 Hz), 8.51 (1H, s), 7.47 (1H, s), 6.63 (1H, d, J=7.5 Hz), 6.56 – 6.54 (1H, m), 6.06 – 6.02 (2H, m), 4.93 – 4.88 (1H, m), 4.53 – 4.42 (2H, m), 4.03 – 3.94 (2H, m), 3.73 (3H, s), 3.64 – 3.48 (1H, m), 3.43 – 3.36 (1H, m), 3.23 – 3.16 (2H, m), 2.43 – 2.38 (1H, m), 1.97 – 1.88 (1H, m), 1.14 (6H, dd, J=6.1, 8.4 Hz).
17	 (12R,14S)-12-ethoxy-4-fluoro-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentaco sa-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P2 Aniline A1 10% yield as a beige solid	LCMS (MA) RT = 2.35 min, m/z = 412.2 (M+H)⁺. LCMS (MC) RT = 2.34 min, m/z = 412.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 9.00 (1H, d, J=7.6 Hz), 8.55 (1H, s), 7.68 – 7.67 (1H, m), 6.77 – 6.74 (1H, m), 6.67 (1H, d, J=7.4 Hz), 6.34 (1H, t, J=5.3 Hz), 6.24 – 6.19 (1H, m), 4.93 (1H, dd, J=1.6, 8.8 Hz), 4.49 – 4.39 (2H, m), 3.99 – 3.83 (2H, m), 3.60 – 3.51 (2H, m), 3.42 – 3.34 (1H, m), 3.26 – 3.16 (2H, m), 2.48 – 2.38 (1H,m), 2.00 – 1.92 (1H, m), 1.15 (3H, t, J=7.0 Hz).
18	 (12R,14S)-12-ethoxy-4-fluoro-18-methyl-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentaco sa-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold S1 Pyrrolidine P2 Aniline A1 45% yield as a white solid	LCMS (MA) RT = 2.50 min, m/z = 426.2 (M+H)⁺. LCMS (MC) RT= 2.49 min, m/z = 426.2 (M+H)⁺. ¹H NMR (400 MHz, CDCl₃) 8.38 (1H, d, J=1.1 Hz), 8.22 (1H, s), 7.73 – 7.70 (1H, m), 6.72 – 6.68 (1H, m), 6.24 – 6.19 (1H, m), 5.14 (1H, d, J=11.2 Hz), 4.55 – 4.50 (1H, m), 4.33 (1H, dd, J=8.2, 9.5 Hz), 4.07 – 3.99 (1H, m), 3.92 – 3.56 (6H, m), 3.31 – 3.24 (1H, m), 2.66 (1H, dd, J=8.0, 12.9 Hz), 2.26 (3H, s), 2.20 -2.10 (1H, m), 1.33 – 1.26 (3H, m).

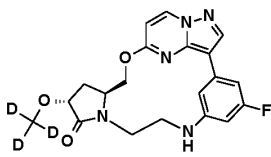
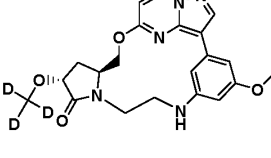
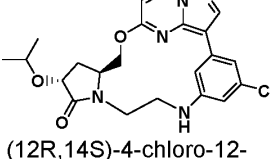
19	 (12R,14S)-4,12-dimethoxy-18-methyl-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0^{1°},¹⁴.0^{2°},²³]pentacosan-1(23),2(25),3,5,17(24),18,21-heptaen-11-one	Scaffold S1 Pyrrolidine P1 Aniline A3 3% yield as a white solid	LCMS (MA) RT = 2.23 min, m/z = 424 (M+H)⁺. LCMS (MC) RT = 2.22 min, m/z = 424 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 8.88 (1H, d, J=1.1 Hz), 8.41 (1H, s), 7.66 – 7.54 (1H, m), 7.46 – 7.45 (1H, m), 6.53 (1H, dd, J=1.2, 2.2 Hz), 6.04 – 6.01 (2H, m), 4.94 (1H, s), 4.35 (1H, dd, J=8.2, 9.3 Hz), 3.99 (1H, t, J=10.8 Hz), 3.72 (3H, s), 3.56 – 3.50 (1H, m), 3.45 – 3.44 (3H, m), 3.24 – 3.19 (2H, m), 2.18 (3H, d, J=1.3 Hz), 2.00 – 1.92 (1H, m), 1.18 (2H, s).
20	 (12R,14S)-4-chloro-12-ethoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0^{1°},¹⁴.0^{2°},²³]pentacosan-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P2 Aniline A2 48% yield as a pale yellow solid	LCMS (MA) RT = 2.50 min, m/z = 428 (M+H)⁺. LCMS (MC) RT = 2.49 min, m/z = 428 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 9.00 (1H, d, J=7.6 Hz), 8.57 (1H, s), 7.78 (1H, s), 6.98 – 6.96 (1H, m), 6.67 (1H, d, J=7.4 Hz), 6.49 – 6.47 (1H, m), 6.38 – 6.33 (1H, m), 4.94 – 4.90 (1H, m), 4.47 – 4.39 (2H, m), 4.05 – 3.82 (2H, m), 3.61 – 3.50 (2H, m), 3.41 – 3.36 (1H, m), 3.25 – 3.20 (2H, m), 2.46 – 2.41 (1H, m), 2.00 – 1.92 (1H, m), 1.15 (3H, t, J=7.2 Hz).
21	 (12R,14S)-4-ethyl-12-methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0^{1°},¹⁴.0^{2°},²³]pentacosan-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P1 Aniline A12 31% yield as a light yellow solid	LCMS (MA) RT = 2.37 min, m/z = 408.2 (M+H)⁺. LCMS (MC) RT = 2.37 min, m/z = 408.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 8.98 – 8.95 (1H, m), 8.47 (1H, s), 7.66 – 7.63 (1H, m), 6.78 (1H, s), 6.64 – 6.62 (1H, m), 6.31 (1H, s), 5.96 (1H, t, J=5.9 Hz), 4.94 – 4.90 (1H, m), 4.47 – 4.44 (1H, m), 4.36 – 4.30 (1H, m), 3.96 – 3.91 (1H, m), 3.55 – 3.47 (1H, m), 3.45 (3H, s), 3.44 – 3.36 (1H, m), 3.24 – 3.15 (2H, m), 2.57 – 2.37 (3H, m), 2.01 – 1.93 (1H, m), 1.22 – 1.17 (3H, m).
22	 (12R,14S)-12-(cyclopropylmethoxy)-4-methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0^{1°},¹⁴.0^{2°},²³]pentacosan-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P5 Aniline A3 46% yield as a yellow solid	LCMS (MA) RT = 2.37 min, m/z = 450 (M+H)⁺. LCMS (MC) RT = 2.37 min, m/z = 450 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 8.98 – 8.95 (1H, m), 8.51 (1H, s), 7.47 – 7.47 (1H, m), 6.65 – 6.62 (1H, m), 6.55 (1H, dd, J=1.2, 2.2 Hz), 6.06 – 6.02 (2H, m), 4.92 (1H, d, J=10.8 Hz), 4.46 – 4.40 (2H, m), 3.94 (1H, t, J=10.6 Hz), 3.73 (3H, s).

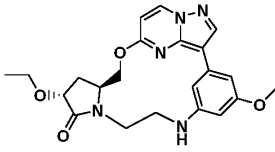
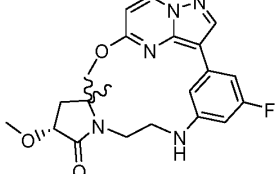
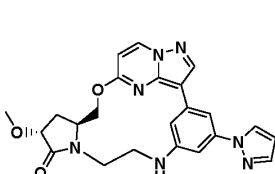
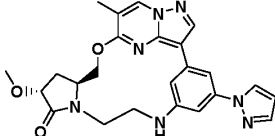
	2.1 ² ,6.0 ^{1°} ,14.0 ^{2°} , ²³]pentaco sa- 1(23),2(25),3,5,17(24),18, 21-heptaen-11-one		s), 3.64 (1H, dd, J=6.9, 10.2 Hz), 3.33 – 3.32 (3H, m), 3.26 – 3.17 (2H, m), 2.45 – 2.30 (1H, m), 2.03 – 1.94 (1H, m), 1.07 – 0.99 (1H, m), 0.50 – 0.46 (2H, m), 0.22 – 0.18 (2H, m).
23	 (12R,14S)-12-ethoxy-11- oxo-16-oxa- 7,10,20,21,24- pentaazapentacyclo[15.5. 2.1 ² ,6.0 ^{1°} ,14.0 ^{2°} , ²³]pentaco sa- 1(23),2,4,6(25),17(24),18, 21-heptaene-4- carbonitrile	Scaffold 3-bromo-5- chloro- pyrazolo[1,5- a]pyrimidine Pyrrolidine P2 Aniline A6 21% yield as a white solid	LCMS (MA) RT = 2.28 min, m/z = 419.2 (M+H) ⁺ . LCMS (MC) RT = 2.28 min, m/z = 419.2 (M+H) ⁺ . ¹ H NMR (400 MHz, DMSO) 9.01 (1H, d, J=7.4 Hz), 8.63 (1H, s), 8.09 (1H, s), 7.35 (1H, s), 6.78 (1H, dd, J=1.3, 2.3 Hz), 6.69 (1H, d, J=7.4 Hz), 6.58 – 6.54 (1H, m), 4.93 (1H, d, J=10.6 Hz), 4.49 – 4.39 (2H, m), 4.00 – 3.83 (2H, m), 3.61 – 3.52 (2H, m), 3.30 – 3.19 (2H, m), 2.48 – 2.38 (1H, m), 2.00 – 1.91 (1H, m), 1.25 – 1.23 (1H, m), 1.17 – 1.12 (3H, m).
24	 (12R,14S)-4-chloro-12- methoxy-18-methyl-16- oxa-7,10,20,21,24- pentaazapentacyclo[15.5. 2.1 ² ,6.0 ^{1°} ,14.0 ^{2°} , ²³]pentaco sa- 1(23),2(25),3,5,17(24),18, 21-heptaen-11-one	Scaffold S1 Pyrrolidine P1 Aniline A2 47% yield as a white solid	LCMS (MA) RT = 2.50 min, m/z = 428 (M+H) ⁺ . LCMS (MC) RT = 2.51 min, m/z = 428 (M+H) ⁺ . ¹ H NMR (400 MHz, DMSO) 8.90 (1H, d, J=1.1 Hz), 8.47 (1H, s), 7.77 – 7.75 (1H, m), 6.95 (1H, t, J=1.5 Hz), 6.47 (1H, t, J=2.1 Hz), 6.34 (1H, t, J=5.9 Hz), 4.95 (1H, d, J=10.4 Hz), 4.47 – 4.45 (1H, m), 4.36 (1H, dd, J=8.4, 9.5 Hz), 4.12 – 3.96 (1H, m), 3.65 – 3.50 (1H, m), 3.45 (3H, s), 3.40 – 3.30 (1H, m), 3.25 – 3.10 (2H, m), 2.45 – 2.40 (1H, m), 2.18 (3H, d, J=1.1 Hz), 2.00 – 1.91 (1H, m).
25	 (12S,14S)-4-fluoro-12- methoxy-16-oxa- 7,10,20,21,24- pentaazapentacyclo[15.5. 2.1 ² ,6.0 ^{1°} ,14.0 ^{2°} , ²³]pentaco sa- 1(23),2(25),3,5,17(24),18, 21-heptaen-11-one	Scaffold 3-bromo-5- chloro- pyrazolo[1,5- a]pyrimidine Pyrrolidine 215918- 39-1 Aniline A1 21% yield as a yellow solid	LCMS (MA) RT = 2.31 min, m/z = 398 (M+H) ⁺ . LCMS (MC) RT = 2.30 min, m/z = 398 (M+H) ⁺ . ¹ H NMR (400 MHz, DMSO) 9.00 (1H, d, J=7.6 Hz), 8.55 (1H, s), 7.69 – 7.68 (1H, m), 6.78 – 6.67 (2H, m), 6.33 (1H, t, J=5.9 Hz), 6.24 – 6.19 (1H, m), 5.10 (1H, d, J=10.8 Hz), 4.47 (1H, t, J=8.0 Hz), 3.88 (1H, t, J=10.4 Hz), 3.79 (1H, d, J=6.1 Hz), 3.64 – 3.55 (1H, m), 3.32 (3H, s), 3.30 – 3.22 (1H, m), 3.19 – 3.16 (2H, m), 2.41 – 2.33 (1H, m), 1.96 (1H, d, J=14.4 Hz).

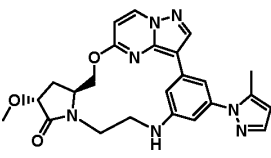
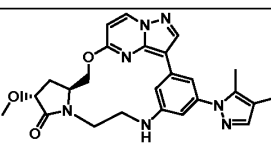
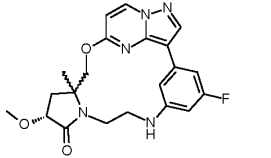
26	 (12R,14S)-4,12-difluoro-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]pentacosan-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine 1138324-48-7 Aniline A1 40% yield as a beige solid	LCMS (MA) RT = 2.27 min m/z = 386.3 (M+H)⁺ LCMS (MC) RT = 2.26 min, m/z = 386.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 9.01 – 8.99 (1H, m), 8.56 – 8.55 (1H, m), 7.68 – 7.66 (1H, m), 6.78 – 6.74 (1H, m), 6.68 (1H, d, J=7.6 Hz), 6.35 (1H, t, J=5.9 Hz), 6.25 – 6.20 (1H, m), 4.98 (1H, d, J=10.8 Hz), 4.60 (1H, s), 4.05 – 3.94 (1H, m), 3.61 – 3.39 (2H, m), 3.30 – 3.24 (2H, m), 2.68 – 2.58 (1H, m), 2.34 – 2.22 (1H, m), 1.42 – 1.41 (1H, m).
27	 (12R,14S)-5-fluoro-4,12-dimethoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]pentacosan-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P1 Aniline A13 32% yield as a yellow solid	LCMS (MA) RT = 2.16 min, m/z = 428.1 (M+H)⁺. LCMS (MC) RT = 2.17 min, m/z = 428.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 8.98 – 8.95 (1H, m), 8.55 (1H, s), 7.63 (1H, d, J=5.1 Hz), 6.76 (1H, dd, J=1.6, 6.9 Hz), 6.65 – 6.63 (1H, m), 5.99 – 5.95 (1H, m), 4.92 (1H, d, J=10.6 Hz), 4.50 – 4.47 (1H, m), 4.36 – 4.30 (1H, m), 3.96 – 3.90 (1H, m), 3.86 (3H, s), 3.62 – 3.52 (1H, m), 3.45 (3H, s), 3.37 – 3.25 (2H, m), 3.21 – 3.14 (1H, m), 2.47 – 2.41 (1H, m), 2.01 – 1.93 (1H, m).
28	 (12R,14S)-4,12-diethoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]pentacosan-1(23),2(25),3,5,17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P2 Aniline A4 39% yield as a yellow solid	LCMS (MA) RT = 2.32 min, m/z = 438 (M+H)⁺. LCMS (MC) RT = 2.33 min, m/z = 438 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 8.97 – 8.95 (1H, m), 8.50 (1H, s), 7.45 (1H, s), 6.65 – 6.62 (1H, m), 6.54 (1H, s), 6.04 – 6.01 (2H, m), 4.92 (1H, d, J=11.0 Hz), 4.46 – 4.38 (2H, m), 4.12 – 3.84 (4H, m), 3.60 – 3.50 (2H, m), 3.19 – 3.16 (4H, m), 2.00 – 1.95 (1H, m), 1.33 (3H, t, J=7.0 Hz), 1.15 (3H, t, J=7.0 Hz).
29	 (12R,14S)-4,5-difluoro-12-methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]pentacosan-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P1 Aniline A10 39% yield as yellow solid	LCMS (MA) RT = 2.40 min, m/z = 416 (M+H)⁺. LCMS (MC) RT = 2.40 min, m/z = 416 (M+H)⁺. ¹H NMR (400 MHz, CDCl₃) 8.51 – 8.48 (1H, m), 8.21 – 8.20 (1H, m), 7.78 – 7.64 (1H, m), 6.74 – 6.67 (1H, m), 6.43 – 6.40 (1H, m), 5.09 – 5.03 (1H, m), 4.56 – 4.43 (2H, m), 4.21 (1H, dd, J=8.2, 9.3 Hz), 3.95 – 3.83 (1H, m), 3.62 – 3.61 (4H, m), 2.96 – 2.95 (2H, m), 2.88

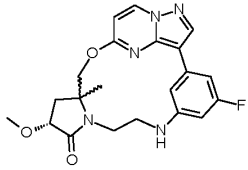
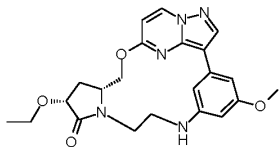
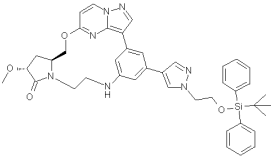
	2.1 ² , 6.0 ^{1°} , 14.0 ^{2°} , ²³]pentaco sa-1(23), 2(25), 3, 5, 17(24), 18, 21-heptaen-11-one		– 2.88 (2H, m), 2.64 (1H, dd, J=8.0, 13.1 Hz).
30	 (12R, 14S)-4-fluoro-12-methoxy-18-methyl-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1.2.1]pentaco sa-1(23), 2(25), 3, 5, 17(24), 18, 21-heptaen-11-one	Scaffold S1 Pyrrolidine P1 Aniline A1 89% yield as white solid	LCMS (MD) RT = 3.134 min, m/z = 412.1 (M+H)⁺. LCMS (ME) RT = 3.502 min, m/z = 412.1 (M+H)⁺. ¹H NMR (400 MHz, DMSO) δ 8.90 (d, J = 1.2 Hz, 1H), 8.44 (s, 1H), 7.66 (s, 1H), 6.73 (d, J = 9.4 Hz, 1H), 6.32 (t, J = 5.8 Hz, 1H), 6.20 (dt, J = 11.8, 2.1 Hz, 1H), 4.96 (d, J = 10.7 Hz, 1H), 4.47 (s, 1H), 4.36 (t, J = 8.9 Hz, 1H), 4.00 (t, J = 10.7 Hz, 1H), 3.55 (dd, J = 12.4, 8.4 Hz, 1H), 3.45 (s, 3H), 3.39 (d, J = 10.3 Hz, 1H), 3.28 – 3.15 (m, 2H), 2.48 – 2.40 (m, 1H), 2.18 (d, J = 0.9 Hz, 3H), 2.02 – 1.89 (m, 1H).
31	 E1-(12R, 14S)-4-fluoro-12-(methoxymethyl)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1.2.1]pentaco sa-1(23), 2(25), 3, 5, 17(24), 18, 21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P10 Aniline A1 71% yield as a white solid	LCMS (MD) RT = 3.115 min, m/z = 412.1 (M+H)⁺. LCMS (ME) RT = 3.500 min, m/z = 412.1 (M+H)⁺. ¹H NMR (400 MHz, DMSO) δ 8.91 (d, J = 1.2 Hz, 1H), 8.54 (s, 1H), 8.45 (s, 1H), 7.78 (s, 1H), 7.72 – 7.69 (m, 1H), 7.34 (s, 1H), 6.96 (t, J = 2.0 Hz, 1H), 6.53 (dd, J = 2.4, 1.8 Hz, 1H), 6.35 (t, J = 5.8 Hz, 1H), 4.98 (d, J = 11.1 Hz, 1H), 4.51 (brs, 1H), 4.37 (t, J = 8.9 Hz, 1H), 4.01 (t, J = 10.8 Hz, 1H), 3.59 (dd, J = 23.1, 9.4 Hz, 1H), 3.46 (s, 3H), 3.41 (d, J = 13.3 Hz, 1H), 3.27 (dd, J = 11.6, 4.9 Hz, 2H), 2.47 (d, J = 8.1 Hz, 1H), 2.19 (s, 3H), 1.97 (dt, J = 11.7, 8.7 Hz, 1H).
32	 E2-(12S, 14S)-4-fluoro-12-(methoxymethyl)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1.2.1]pentaco sa-1(23), 2(25), 3, 5, 17(24), 18, 21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P10 Aniline A1 68% yield as a white solid	LCMS (MD) RT = 3.019 min, m/z = 412.1 (M+H)⁺. LCMS (ME) RT = 3.416 min, m/z = 412.1 (M+H)⁺. ¹H NMR (400 MHz, DMSO) δ 8.99 (d, J = 7.5 Hz, 1H), 8.54 (s, 1H), 7.71 (s, 1H), 6.75 (d, J = 10.2 Hz, 1H), 6.67 (d, J = 7.5 Hz, 1H), 6.32 (t, J = 5.9 Hz, 1H), 6.21 (dt, J = 11.8, 2.1 Hz, 1H), 4.94 (d, J = 10.9 Hz, 1H), 4.41 (s, 1H), 3.99 (t, J = 10.6 Hz, 1H), 3.60 (dd, J = 11.4, 8.9 Hz, 1H), 3.55 (dd, J = 9.5, 3.8 Hz, 1H), 3.49 (dd, J = 9.5, 5.8 Hz, 1H), 3.40 (dt, 1H), 3.25 (s, 3H), 3.18 (dd, J = 14.2, 9.0 Hz, 2H), 2.91 (tdd, J = 9.7, 5.5, 4.0 Hz, 1H), 2.10 (t, J = 10.6 Hz, 2H).

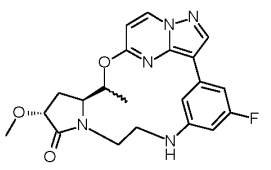
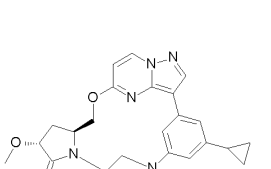
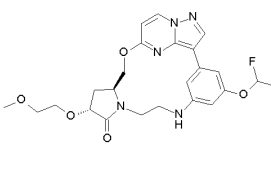
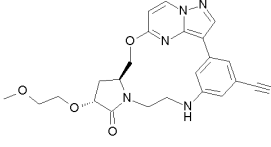
33	 (12R,14S)-4-fluoro-12-methoxy-18-(methoxymethyl)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]heptaen-11-one	Scaffold S6 Pyrrolidine P1 Aniline A1 66% yield as a white solid	LCMS (MD) RT = 3.005 min, m/z = 442.1 (M+H)⁺. LCMS (ME) RT = 3.401 min, m/z = 442.1 (M+H)⁺. 1H NMR (400 MHz, DMSO) δ 8.95 (s, 1H), 8.53 (s, 1H), 7.65 (s, 1H), 6.75 (d, J = 9.3 Hz, 1H), 6.33 (t, J = 5.8 Hz, 1H), 6.21 (dt, J = 11.8, 2.1 Hz, 1H), 4.97 (d, J = 10.7 Hz, 1H), 4.49 (t, J = 7.5 Hz, 1H), 4.45 (d, J = 12.4 Hz, 1H), 4.41 (d, J = 13.0 Hz, 1H), 4.36 (dd, J = 9.4, 8.4 Hz, 1H), 4.00 (t, J = 10.7 Hz, 1H), 3.62 – 3.51 (m, 1H), 3.45 (s, 3H), 3.40 (d, J = 3.9 Hz, 1H), 3.37 (s, 3H), 3.27 – 3.13 (m, 2H), 2.45 (dd, J = 12.7, 8.1 Hz, 1H), 1.95 (dt, J = 11.6, 8.8 Hz, 1H).
34	 (12R,14S)-4,18-difluoro-12-methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]heptaen-11-one	Scaffold S7 Pyrrolidine P1 Aniline A1 13% yield as a white solid	LCMS (MD) RT = 3.016 min, m/z = 416.1 (M+H)⁺. LCMS (MF) RT = 4.828 min, m/z = 416.2 (M+H)⁺. 1H NMR (400 MHz, DMSO) δ 9.51 (d, J = 5.9 Hz, 1H), 8.55 (s, 1H), 7.61 (s, 1H), 6.76 (d, J = 10.1 Hz, 1H), 6.36 (t, J = 5.8 Hz, 1H), 6.23 (dt, J = 11.8, 2.1 Hz, 1H), 4.98 (d, J = 11.1 Hz, 1H), 4.50 (t, J = 8.8 Hz, 1H), 4.35 (t, J = 8.8 Hz, 1H), 4.13 (t, J = 10.7 Hz, 1H), 3.56 (dt, J = 11.8, 7.3 Hz, 1H), 3.45 (s, 3H), 3.39 (d, J = 10.6 Hz, 1H), 3.28 – 3.15 (m, 2H), 2.47 (dd, J = 12.0, 8.0 Hz, 1H), 2.03 – 1.90 (m, 1H).
35	 (12R,14S)-4-fluoro-12-(2-methoxyethoxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P7 Aniline A1 70% yield as a beige solid	LCMS (MD) RT = 2.026 min, m/z = 442.2 (M+H)⁺. LCMS (ME) RT = 3.406 min, m/z = 442.1 (M+H)⁺. 1H NMR (400 MHz, DMSO) δ 8.99 (d, J = 7.5 Hz, 1H), 8.54 (s, 1H), 7.67 (s, 1H), 6.75 (d, J = 9.3 Hz, 1H), 6.67 (d, J = 7.5 Hz, 1H), 6.34 (t, J = 5.8 Hz, 1H), 6.21 (dt, J = 11.8, 2.1 Hz, 1H), 4.94 (d, J = 10.7 Hz, 1H), 4.45 (d, J = 6.0 Hz, 1H), 3.97 (dd, J = 10.7, 9.4 Hz, 1H), 3.95 (t, J = 11.4 Hz, 1H), 3.69 – 3.62 (m, 1H), 3.60 – 3.50 (m, 1H), 3.48 (t, J = 4.8 Hz, 2H), 3.44 – 3.35 (m, 1H), 3.26 (s, 3H), 3.25 – 3.14 (m, 2H), 2.44 (dd, J = 12.7, 8.2 Hz, 2H), 1.98 (dt, J = 12.0, 8.8 Hz, 1H).

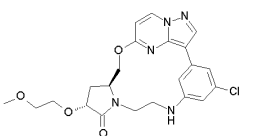
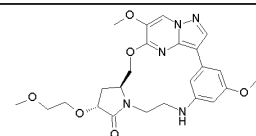
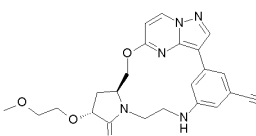
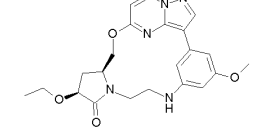
36	 (12R,14S)-4-fluoro-12-(²H₃)methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0.1^{4,20}.2³]pentaco-1(23),2(25),3,5,17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P6 Aniline A1 49% yield as a white solid	LCMS (MD) RT = 2.887 min, m/z = 401.1 (M+H)⁺. LCMS (ME) RT = 3.251 min, m/z = 401.2 (M+H)⁺. 1H NMR (400 MHz, DMSO) δ 8.99 (d, J = 7.5 Hz, 1H), 8.54 (s, 1H), 7.67 (s, 1H), 6.81 – 6.70 (m, 1H), 6.67 (d, J = 7.5 Hz, 1H), 6.34 (t, J = 5.8 Hz, 1H), 6.21 (dt, J = 11.8, 2.1 Hz, 1H), 4.94 (d, J = 10.9 Hz, 1H), 4.48 (t, J = 8.0 Hz, 1H), 4.33 (t, J = 8.8 Hz, 1H), 3.95 (t, J = 10.8 Hz, 1H), 3.55 (dt, J = 11.4, 9.0 Hz, 1H), 3.38 (dd, J = 16.4, 6.9 Hz, 1H), 3.30 – 3.12 (m, 2H), 2.44 (dd, J = 12.7, 8.2 Hz, 1H), 1.96 (dt, J = 11.9, 8.8 Hz, 1H).
37	 (12R,14S)-12-(²H₃)methoxy-4-methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0.1^{4,20}.2³]pentaco-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P6 Aniline A3 12% yield as a beige solid	LCMS (MD) RT = 2.668 min, m/z = 413.1 (M+H)⁺. LCMS (ME) RT = 3.092 min, m/z = 413.2 (M+H)⁺. 1H NMR (400 MHz, DMSO) δ 8.92 (d, J = 7.5 Hz, 1H), 8.46 (s, 1H), 7.43 (s, 1H), 6.60 (d, J = 7.5 Hz, 1H), 6.50 (d, J = 0.7 Hz, 1H), 6.01 (d, J = 5.8 Hz, 1H), 5.99 (t, J = 2.1 Hz, 1H), 4.88 (d, J = 10.8 Hz, 1H), 4.41 (t, J = 9.1 Hz, 1H), 4.29 (t, J = 8.9 Hz, 1H), 3.89 (t, J = 10.7 Hz, 1H), 3.69 (s, 3H), 3.55 – 3.44 (m, 1H), 3.42 – 3.31 (m, 1H), 3.20 – 3.05 (m, 2H), 2.39 (dd, J = 12.7, 8.2 Hz, 1H), 1.93 (dt, J = 11.8, 8.8 Hz, 1H).
38	 (12R,14S)-4-chloro-12-(propan-2-yloxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0.1^{4,20}.2³]pentaco-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P4 Aniline A2 40% yield as a beige solid	LCMS (MA) RT = 2.58 min / MH⁺ = 442.0 LCMS (MB) RT = 2.60 min / MH⁺ = 442.1 1H NMR (400 MHz, DMSO) δ 9.00 (1H, d, J=7.6 Hz), 8.57 (1H, s), 7.78 (1H, s), 6.97 (1H, t, J=1.4 Hz), 6.67 (1H, d, J=7.4 Hz), 6.48 (1H, t, J=2.0 Hz), 6.36 (1H, t, J=6.2 Hz), 4.94 – 4.89 (1H, m), 4.54 – 4.44 (2H, m), 4.04 – 3.94 (2H, m), 3.63 – 3.50 (1H, m), 3.40 – 3.36 (1H, m), 3.25 – 3.19 (2H, m), 2.43 – 2.38 (1H, m), 1.96 – 1.88 (1H, m), 1.14 (6H, dd, J=6.1, 8.4 Hz).

39	 (2³Z,2⁴E,5²S,5⁴R)-5⁴-ethoxy-1⁵-methoxy-2⁶-methyl-3-oxa-8-aza-2(3,5)-pyrazolo[1,5-a]96yrimidine-5(2,1)-pyrrolidina-1(1,3)-benzenacyclooctaphan-5⁵-one	Scaffold S1 Pyrrolidine P2 Aniline A3 42% yield as a beige solid	LCMS (MA) RT = 2.43 min / MH⁺ = 438.2 LCMS (MB) RT = 2.45 min / MH⁺ = 438.3 ¹H NMR (400 MHz, DMSO) 8.87 (1H, d, J=1.1 Hz), 8.41 (1H, s), 7.46 (1H, s), 6.53 (1H, dd, J=1.1, 2.1 Hz), 6.04 – 6.01 (2H, m), 4.94 (1H, d, J=11.0 Hz), 4.47 – 4.41 (2H, m), 3.99 (1H, t, J=10.7 Hz), 3.84 (1H, ddd, J=5.9, 8.2, 15.2 Hz), 3.72 (3H, s), 3.60 – 3.52 (2H, m), 3.45 – 3.35 (1H, m), 3.24 – 3.15 (2H, m), 2.49 – 2.43 (1H, m), 2.18 – 2.17 (3H, m), 2.00 – 1.92 (1H, m), 1.15 (3H, t, J=7.0 Hz)
40	 (12R,14S)-12-ethoxy-4-methoxy-18-methyl-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]pentaosa-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P12 Aniline A1 24% yield, as white solid	LCMS (MA) RT = 3.200 min, m/z = 412.1 (M+H)⁺. LCMS (MD): RT = 3.07 min. m/z = 412.1 (M+H)⁺. ¹H NMR (400 MHz, CDCl₃) d 8.49 (d, J = 7.5 Hz, 1H), 8.29 (s, 1H), 8.12 (brs, 1H), 6.67 (d, J = 9.8 Hz, 1H), 6.42 (d, J = 7.5 Hz, 1H), 6.19 (dd, J = 9.1, 2.0 Hz, 1H), 5.70 (d, J = 11.9 Hz, 1H), 4.20 (d, J = 11.9 Hz, 1H), 3.85 (t, J = 7.4 Hz, 1H), 3.82 – 3.61 (m, 3H), 3.56 (s, 3H), 3.51 – 3.36 (m, 1H), 2.37 (d, J = 14.0 Hz, 1H), 2.00 (dd, J = 13.8, 7.2 Hz, 1H), 1.33 (s, 3H), 0.92 – 0.75 (m, 1H).
41	 (12R,14S)-12-methoxy-4-(1H-pyrazol-1-yl)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]pentaosa-1(23),2(25),3,5,17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P1 Aniline A15 35mg, 88% yield as white solid	LCMS (MD) RT = 2.766 min, m/z = 446.1 (M+H)⁺. LCMS (ME) RT = 3.281 min, m/z = 446.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO) d 9.00 (d, J = 7.5 Hz, 1H), 8.63 (s, 1H), 8.45 (d, J = 2.2 Hz, 1H), 7.79 (s, 1H), 7.71 (d, J = 1.5 Hz, 1H), 7.36 (s, 1H), 6.98 (t, J = 2.0 Hz, 1H), 6.68 (d, J = 7.5 Hz, 1H), 6.53 (dd, J = 2.3, 1.9 Hz, 1H), 6.36 (t, J = 5.8 Hz, 1H), 4.96 (d, J = 10.8 Hz, 1H), 4.51 (s, 1H), 4.35 (t, J = 8.9 Hz, 1H), 3.97 (t, J = 10.8 Hz, 1H), 3.66 – 3.51 (m, 1H), 3.46 (s, 3H), 3.44 – 3.38 (m, 1H), 3.31 – 3.18 (m, 2H), 2.45 (dd, J = 12.7, 8.2 Hz, 1H), 1.98 (dt, J = 11.8, 8.8 Hz, 1H).
42	 (12R,14S)-12-methoxy-4-(1H-pyrazol-1-yl)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]pentaosa-1(23),2(25),3,5,17(24),18,21-heptaen-11-one	Scaffold S1 Pyrrolidine P1 Aniline A15 185mg, 81% yield as white solid	LCMS (MD) RT = 2.981 min, m/z = 460.3 (M+H)⁺. LCMS (ME) RT = 4.675 min, m/z = 460.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO) d 8.91

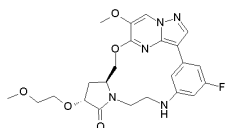
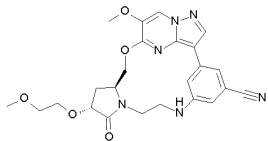
	(12R,14S)-12-methoxy-18-methyl-4-(1H-pyrazol-1-yl)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1 ² ,6.0 ¹⁰ ,14.0 ²⁰ ,23]pentacosan-1(23),2(25),3,5,17(24),18,21-heptaen-11-one		(d, J = 1.2 Hz, 1H), 8.54 (s, 1H), 8.45 (s, 1H), 7.78 (s, 1H), 7.72 – 7.69 (m, 1H), 7.34 (s, 1H), 6.96 (t, J = 2.0 Hz, 1H), 6.53 (dd, J = 2.4, 1.8 Hz, 1H), 6.35 (t, J = 5.8 Hz, 1H), 4.98 (d, J = 11.1 Hz, 1H), 4.51 (brs, 1H), 4.37 (t, J = 8.9 Hz, 1H), 4.01 (t, J = 10.8 Hz, 1H), 3.59 (dd, J = 23.1, 9.4 Hz, 1H), 3.46 (s, 3H), 3.41 (d, J = 13.3 Hz, 1H), 3.27 (dd, J = 11.6, 4.9 Hz, 2H), 2.47 (d, J = 8.1 Hz, 1H), 2.19 (s, 3H), 1.97 (dt, J = 11.7, 8.7 Hz, 1H).
43	 (12R,14S)-12-methoxy-4-(5-methyl-1H-pyrazol-1-yl)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentacosan-1(23),2(25),3,5,17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P1 Aniline A17 29mg, 9% over 3 steps	LCMS (MH) RT = 2.780 min, m/z = 460.2 (M+H)⁺. LCMS (ME) RT = 3.291 min, m/z = 460.2 (M+H)⁺. 1H NMR (400 MHz, DMSO) δ 9.00 (d, J = 7.5 Hz, 1H), 8.59 (s, 1H), 7.87 (s, 1H), 7.52 (d, J = 1.6 Hz, 1H), 7.02 (s, 1H), 6.68 (d, J = 7.5 Hz, 1H), 6.56 (t, J = 1.9 Hz, 1H), 6.35 (t, J = 5.8 Hz, 1H), 6.25 (s, 1H), 4.98 (d, J = 10.8 Hz, 1H), 4.52 (s, 1H), 4.35 (t, J = 8.8 Hz, 1H), 3.97 (t, J = 10.8 Hz, 1H), 3.57 (dd, J = 16.3, 5.8 Hz, 1H), 3.46 (s, 3H), 3.45 – 3.36 (m, 1H), 3.27 (dd, J = 14.3, 8.7 Hz, 2H), 2.46 (dd, J = 12.7, 8.2 Hz, 1H), 2.36 (s, 3H), 1.99 (dt, J = 11.8, 8.8 Hz, 1H).
117	 (12R,14S)-4-(4-iodo-5-methyl-1H-pyrazol-1-yl)-12-methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentacosan-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P1 Aniline A17 180mg, 43% over 3 steps	LCMS (MH) RT = 0.973 min, m/z = 586.2 (M+H)⁺.
85	 E1-(12R,14S)-4-fluoro-12-methoxy-14-methyl-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentacosan-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P15 Aniline A1 6mg obtained after SFC separation as white solid	LCMS (MD) RT = 3.20 min, m/z = 412.1 (M+H)⁺. LCMS(basic) RT = 3.55 min, m/z = 412.1 (M+H)⁺. OR (c:0.1333, DMSO): +1.32° 1H NMR (400 MHz, CDCl₃) δ 8.49 (d, J = 7.5 Hz, 1H), 8.29 (s, 1H), 8.12 (brs, 1H), 6.67 (d, J = 9.8 Hz, 1H), 6.42 (d, J = 7.5 Hz, 1H), 6.19

	pentaazapentacyclo[15.5.2.1 ² ,6.0 ¹⁰ ,4.0 ²⁰ , ²³]pentacos a-1(23),2(25),3,5,17(24),18,21-heptaen-11-one		(dd, J = 9.1, 2.0 Hz, 1H), 5.70 (d, J = 11.9 Hz, 1H), 4.20 (d, J = 11.9 Hz, 1H), 3.85 (t, J = 7.4 Hz, 1H), 3.82-3.61 (m, 3H), 3.56 (s, 3H), 3.51-3.36 (m, 1H), 2.37 (d, J = 14.0 Hz, 1H), 2.00 (dd, J = 13.8, 7.2 Hz, 1H), 1.33 (s, 3H), 0.92 & 0.75 (m, 1H).
86	 E2-(12R,14R)-4-fluoro-12-methoxy-14-methyl-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1 ² ,6.0 ¹⁰ ,4.0 ²⁰ , ²³]pentacos a-1(23),2(25),3,5,17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P15 Aniline A1 6mg obtained after SFC separation as white solid	LCMS (MD) RT = 3.07 min, m/z = 412.2 (M+H) ⁺ . LCMS(basic) RT = 3.45 min, m/z = 412.1 (M+H) ⁺ . OR (c:0.1333, DMSO): +33.9° 1H NMR (400 MHz, CDCl ₃) δ 8.50 (d, J = 7.5 Hz, 1H), 8.30 (s, 1H), 8.06 (brs, 1H), 6.68 (d, J = 9.7 Hz, 1H), 6.43 (d, J = 7.5 Hz, 1H), 6.20 (d, J = 10.9 Hz, 1H), 5.65 (d, J = 10.4 Hz, 1H), 4.13 (t, J = 8.1 Hz, 1H), 3.83 (d, J = 11.7 Hz, 1H), 3.65 (dd, J = 14.3, 6.4 Hz, 1H), 3.61 (s, 3H), 3.42 (d, J = 5.5 Hz, 1H), 2.77 (dd, J = 12.5, 8.0 Hz, 1H), 1.79 (dd, J = 12.2, 8.9 Hz, 2H), 1.40 (s, 3H), 0.90 – 0.74 (m, 2H).
87	 (12R,14R)-12-ethoxy-4-methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1 ² ,6.0 ¹⁰ ,4.0 ²⁰ , ²³]pentacos a-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P11 Aniline A3 75% yield as light salmon solid	LCMS (MA) RT = 2.32 min, m/z = 424.2 (M+H) ⁺ . LCMS(MC) RT = 2.20 min, m/z = 424.4 (M+H) ⁺ . 1H NMR (400 MHz, DMSO) δ 8.97 – 8.95 (1H, m), 8.50 (1H, s), 7.48 – 7.44 (1H, m), 6.65 – 6.62 (1H, m), 6.55 (1H, d, J=0.8 Hz), 6.04 – 6.02 (2H, m), 5.07 (1H, d, J=10.6 Hz), 4.44 (1H, t, J=8.2 Hz), 3.95 – 3.87 (2H, m), 3.77 – 3.69 (4H, m), 3.65 – 3.53 (2H, m), 3.48 – 3.40 (1H, m), 3.34 – 3.09 (2H, m), 2.40 – 2.31 (1H, m), 1.95 (1H, d, J=14.0 Hz), 1.15 (3H, t, J=7.0 Hz)
129	 (12R,14S)-4-(1-{2-[(tert-butyl)diphenylsilyl]oxy}ethyl)-1H-pyrazol-4-yl)-12-methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1 ² ,6.0 ¹⁰ ,14.0 ²⁰ , ²³]penta cosa-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P1 Aniline A19 99% yield as orange foam	LCMS (MA) RT = 2.32 min, m/z = 424.2 (M+H) ⁺ .

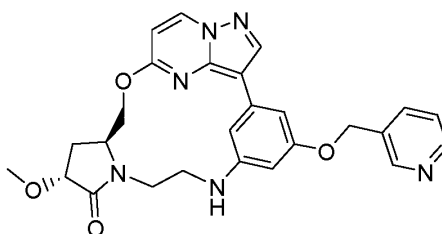
103	 E1-(12R,14S,15R*)-4-fluoro-12-methoxy-15-methyl-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]pentacos a-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P16 Aniline A1 37% yield as green solid	LCMS (MA) RT = 2.22 min, m/z = 412.3 (M+H)⁺. LCMS(MC) RT = 2.21 min, m/z = 412.3 (M+H)⁺. ¹H NMR (400 MHz, CDCl₃) 8.52 (1H, d, J=7.5 Hz), 8.28 (1H, s), 7.70 (1H, s), 6.71 – 6.67 (1H, m), 6.41 (1H, d, J=7.6 Hz), 6.23 (1H, dt, J=11.0, J=2.2 Hz), 5.62 – 5.55 (1H, m), 4.71 – 4.68 (1H, m), 4.18 (1H, t, J=8.8 Hz), 3.88 – 3.80 (1H, m), 3.70 – 3.65 (1H, m), 3.64 (3H, s), 3.62 – 3.56 (2H, m), 3.27 – 3.20 (1H, m), 2.66 – 2.59 (1H, m), 2.09 – 2.00 (1H, m), 1.31 (3H, d, J=6.7 Hz).
108	 (12R,14S)-4-cyclopropyl-12-methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]pentacos a-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P1 Aniline A20 27% yield as pale yellow solid	LCMS (MA) RT = 2.28 min, m/z = 420.4 (M+H)⁺. LCMS (MC) RT = 2.27 min, m/z = 420.4 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 8.96 (1H, d, J=7.4 Hz), 8.49 (1H, s), 7.60 (1H, s), 6.67 – 6.65 (1H, m), 6.63 (1H, d, J=7.4 Hz), 6.18 – 6.16 (1H, m), 5.93 (1H, t, J=5.8 Hz), 4.91 (1H, d, J=10.4 Hz), 4.49 – 4.42 (1H, m), 4.33 (1H, t, J=8.7 Hz), 3.93 (1H, t, J=10.7 Hz), 3.55 – 3.47 (1H, m), 3.45 (3H, s), 3.42 – 3.36 (1H, m), 3.23 – 3.15 (2H, m), 2.46 – 2.41 (1H, m), 2.01 – 1.93 (1H, m), 1.85 – 1.78 (1H, m), 0.92 – 0.87 (2H, m), 0.72 – 0.59 (2H, m).
111	 (12R,14S)-4-(difluoromethoxy)-12-(2-methoxyethoxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]pentacos a-1(23),2(25),3,5,17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P7 Aniline A8 27% yield as pale yellow solid using DL-cysteine instead of 4-Methylbenzenethiol	LCMS (MA) RT = 2.26 min, m/z = 490.2 (M+H)⁺. LCMS (MC) RT = 2.26 min, m/z = 490.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 9.00 (1H, d, J=7.6 Hz), 8.53 (1H, s), 7.70 (1H, s), 7.40 – 6.90 (1H, m), 6.74 – 6.66 (2H, m), 6.36 (1H, t, J=5.8 Hz), 6.23 (1H, t, J=1.9 Hz), 4.95 – 4.91 (1H, m), 4.51 – 4.42 (2H, m), 4.00 – 3.92 (2H, m), 3.67 – 3.61 (1H, m), 3.58 – 3.52 (1H, m), 3.48 (2H, t, J=4.7 Hz), 3.38 (1H, dd, J=7.8, 13.9 Hz), 3.31 (1H, s), 3.26 – 3.26 (5H, m), 2.02 – 1.94 (1H, m);
114	 (12R,14S)-12-(2-methoxyethoxy)-11-oxo-	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P7 Aniline A8 48% yield as Beige solid using DL-cysteine instead of 4-	LCMS (MA) RT = 2.10 min, m/z = 449.3 (M+H)⁺. LCMS (MC) RT = 2.09 min, m/z = 449.3 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 9.02 (1H, d, J=7.6 Hz), 8.63 (1H, s), 8.10 (1H, s), 7.35 (1H, s), 6.79 – 6.78 (1H, m), 6.70 (1H, d, J=7.6

	16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1 ² .6.0 ¹⁰ .4.0 ²⁰ , ²³]pentacos a-1(23),2,4,6(25),17(24),18,21-heptaene-4-carbonitrile	Methylbenzenethiol	Hz), 6.57 (1H, t, J=5.8 Hz), 4.94 (1H, d, J=10.4 Hz), 4.50 - 4.43 (2H, m), 4.00 - 3.93 (2H, m), 3.68 - 3.62 (1H, m), 3.60 - 3.50 (1H, m), 3.48 (2H, t, J=4.7 Hz), 3.31 - 3.23 (3H, m), 3.26 (3H, s), 2.47 - 2.42 (1H, m), 2.01 - 1.93 (1H, m);
116	 (12R,14S)-4-chloro-12-(2-methoxyethoxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1 ² .6.0 ¹⁰ .4.0 ²⁰ , ²³]pentacos a-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P7 Aniline A2 48% yield as Beige solid using DL-cysteine instead of 4-Methylbenzenethiol	LCMS (MA) RT = 2.31 min, m/z = 458.1 (M+H) ⁺ LCMS (MC) RT = 2.28 min, m/z = 458.2 (M+H) ⁺ ¹ H NMR (400 MHz, DMSO) 9.00 - 8.97 (1H, m), 8.57 - 8.56 (1H, m), 7.78 (1H, s), 6.97 - 6.95 (1H, m), 6.68 - 6.65 (1H, m), 6.49 - 6.47 (1H, m), 6.35 (1H, t, J=5.9 Hz), 4.92 (1H, d, J=11.2 Hz), 4.45 (2H, t, J=8.9 Hz), 4.00 - 3.91 (2H, m), 3.68 - 3.61 (1H, m), 3.58 - 3.47 (3H, m), 3.37 - 3.32 (1H, m), 3.25 - 3.21 (5H, m), 2.46 - 2.40 (1H, m), 2.03 - 1.93 (1H, m);
117	 (12R,14S)-4,18-dimethoxy-12-(2-methoxyethoxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1 ² .6.0 ¹⁰ .4.0 ²⁰ , ²³]pentacos a-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold S2 Pyrrolidine P7 Aniline A3 31% yield as yellowish solid using DL-cysteine instead of 4-Methylbenzenethiol	LCMS (MA) RT = 2.03 min, m/z = 484.3 (M+H) ⁺ LCMS (MC) RT = 2.01 min, m/z = 484.3 (M+H) ⁺ ¹ H NMR (400 MHz, DMSO) 8.74 (1H, s), 8.35 (1H, s), 7.42 (1H, s), 6.51 (1H, s), 6.06 - 6.01 (2H, m), 4.93 (1H, d, J=10.6 Hz), 4.44 (2H, t, J=8.8 Hz), 4.05 - 3.91 (2H, m), 3.89 - 3.88 (3H, m), 3.68 - 3.61 (1H, m), 3.50 - 3.46 (3H, m), 3.44 - 3.35 (1H, m), 3.34 (2H, s), 3.27 - 3.26 (6H, m), 2.48 - 2.41 (1H, m), 2.02 - 1.92 (1H, m);
118	 (12R,14S)-4-ethynyl-12-(2-methoxyethoxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1 ² .6.0 ¹⁰ .4.0 ²⁰ , ²³]pentacos a-1(23),2(25),3,5,17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P7 Aniline A11 22% yield as white solid using DL-cysteine instead of 4-Methylbenzenethiol	LCMS (MA) RT = 2.21 min, m/z = 448.2 (M+H) ⁺ LCMS (MC) RT = 2.18 min, m/z = 448.2 (M+H) ⁺ ¹ H NMR (400 MHz, DMSO) 8.99 (1H, d, J=7.4 Hz), 8.57 (1H, s), 7.86 (1H, s), 7.04 (1H, s), 6.66 (1H, d, J=7.6 Hz), 6.56 (1H, s), 6.26 (1H, t, J=5.8 Hz), 4.93 (1H, dd, J=0.9, 10.9 Hz), 4.50 - 4.42 (2H, m), 4.05 - 3.94 (3H, m), 3.68 - 3.61 (1H, m), 3.58 - 3.51 (1H, m), 3.48 (2H, t, J=4.8 Hz), 3.37 (1H, s), 3.31 (1H, s), 3.27 - 3.26 (5H, m), 2.01 - 1.93 (1H, m);
121	 (12S,14S)-12-ethoxy-4-(3-methoxyphenyl)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1 ² .6.0 ¹⁰ .4.0 ²⁰ , ²³]pentacos a-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P14 Aniline A3 27% yield as salmon	LCMS (MA) RT = 2.22 min, m/z = 424.4 (M+H) ⁺ LCMS (MC) RT = 2.21 min, m/z = 424.4 (M+H) ⁺ ¹ H NMR (400 MHz, DMSO) 8.98 - 8.94 (1H, m), 8.50 (1H, s), 7.49 -

-101-

	methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1 ² ,6.0 ^{1°} ,4.0 ^{2°} , ²³]pentacos a-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	solid	7.44 (1H, m), 6.65 - 6.62 (1H, m), 6.55 (1H, s), 6.03 (2H, s), 5.07 (1H, d, J=10.6 Hz), 4.44 (1H, t, J=7.4 Hz), 3.95 - 3.86 (2H, m), 3.74 (4H, m), 3.63 - 3.59 (2H, m), 3.48 - 3.43 (1H, m), 3.27 - 3.11 (2H, m), 2.40 - 2.31 (1H, m), 1.95 (1H, d, J=14.2 Hz), 1.15 (3H, t, J=7.0 Hz);
129	 (12R,14S)-4-fluoro-18-methoxy-12-(2-methoxyethoxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0^{1°},4.0^{2°},²³]pentacos a-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold S2 Pyrrolidine P7 Aniline A1 11mg, 13% yield as Beige solid	LCMS (MA) RT = 2.19 min, m/z = 472.2 (M+H) ⁺ LCMS (MC) RT = 2.13 min, m/z = 472.3 (M+H) ⁺ ¹ H NMR (400 MHz, DMSO) 8.79 (1H, s), 8.40 (1H, s), 7.63 - 7.62 (1H, m), 6.74 - 6.71 (1H, m), 6.33 (1H, t, J=5.8 Hz), 6.20 (1H, d, J=12.3 Hz), 4.96 (1H, d, J=10.7 Hz), 4.49 - 4.43 (2H, m), 4.03 (1H, t, J=11.3 Hz), 3.98 - 3.92 (1H, m), 3.89 (3H, s), 3.67 - 3.62 (1H, m), 3.59 - 3.52 (1H, m), 3.48 (3H, t, J=4.7 Hz), 3.28 - 3.22 (5H, m), 2.46 - 2.42 (1H, m), 2.00 - 1.95 (1H, m).
145	 (12R,14S)-18-methoxy-12-(2-methoxyethoxy)-11-oxo-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0^{1°},4.0^{2°},²³]pentacos a-1(23),2,4,6(25),17(24),18,21-heptaene-4-carbonitrile	Scaffold S2 Pyrrolidine P7 Aniline A6 40mg, 22% yield as Beige solid	LCMS (MA) RT = 2.10 min, m/z = 479.3 (M+H) ⁺ LCMS (MC) RT = 2.08 min, m/z = 479.3 (M+H) ⁺ ¹ H NMR (400 MHz, DMSO) 8.82 (1H, s), 8.49 (1H, s), 8.05 (1H, s), 7.32 (1H, s), 6.77 (1H, s), 6.56 (1H, t, J=5.9 Hz), 4.95 (1H, d, J=9.9 Hz), 4.46 (2H, t, J=8.7 Hz), 3.91 - 3.89 (6H, m), 3.68 - 3.62 (1H, m), 3.57 (1H, s), 3.48 (2H, t, J=4.7 Hz), 3.31 (1H, s), 3.26 (4H, s), 2.48 - 2.42 (1H, m), 1.99 - 1.92 (1H, m).

Example 44: (12R,14S)-12-methoxy-4-(pyridin-3-ylmethoxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0^{1°},4.0^{2°},²³]pentacos a-1(23),2(25),3,5,17(24),18,21-heptaen-11-one



-102-

Following the general synthetic scheme 1, as depicted for the synthesis of Example 1, (12R,14S)-4-(benzyloxy)-12-methoxy-7-(2-nitrobenzenesulfonyl)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.12,6.010,14.020,23]pentacosa-1(23),2,4,6(25),17(24),18,21-heptaen-11-one was obtained as **Intermediate I18** using **Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine, Pyrrolidine P1** and **Aniline A9**.

Step 1

A solution of **Intermediate I18** (1g, 1.491mmol) in TFA (5mL) and Anisole (15mL) was heated at 130°C for 4 hours. LCMS showed complete reaction. The mixture was allowed to cooled to room temperature. The solvent was evaporated under reduced pressure. The gummy residue was triturated with DCM/iPr₂O (1/1). The resulting precipitate was filtered, washed with Diisopropyl ether then pentane and dried to afford the title compound (**Intermediate I19, (12R,14S)-4-hydroxy-12-methoxy-7-(2-nitrobenzenesulfonyl)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.12,6.010, 14.020,23]pentacosa-1(23),2,4,6(25),17(24),18,21-heptaen-11-one**) (0.81g, 93.6% yield) as a cream solid.

LCMS (MA) RT= 2.20min m/z= 581.1 (M+H)⁺.

Step 2

To a solution of the title compound from Step 1 (50mg, 0.0861mmol) under Nitrogen in DMF (3mL) were added 3-(bromomethyl)pyridine, hydrobromide (65mg, 0.258mmol) and Cesium carbonate (168mg, 0.517mmol). The solution was stirred to 80°C for 1H. Monitoring by LCMS showed completed reaction. The crude was evaporated under vacuum. The residue was purified by chromatography on silica eluting with 0%-50% gradient of (3:1 EtOAc: EtOH) / Cyclohexane to afford the expected compound (75mg, 65 % yield) as a yellow glassy solid.

LCMS (MA) RT= 2.02min m/z= 672.1 (M+H)⁺.

Step 3

To a suspension of the title compound from Step 2 (75mg, 0.112mmol) in DMF (5mL) was added cesium carbonate (73mg, 0.224mmol) and 4-methylbenzenethiol (17mg, 0.134mmol). The reaction mixture was stirred at room temperature for 2h, then overnight. The mixture was portioned between water and EtOAc, the organic layer was dried over Na₂SO₄ and evaporated under vacuum. The residue was purified by chromatography on silica eluting with 0%-50% gradient of (3:1 EtOAc: EtOH) / Cyclohexane. The appropriate fractions were evaporated under vacuum and the residue was treated by CH₃CN, a solid cream crystallized, it was filtered, washed with water and dried under vacuum at 60°C to afford the expected product (26mg, 48 % yield) as a cream solid.

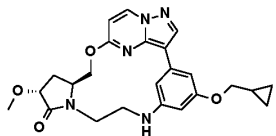
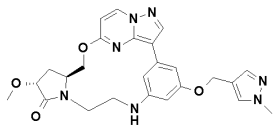
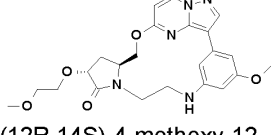
LCMS (MA) RT= 1.67min m/z= 487.1 (M+H)⁺.

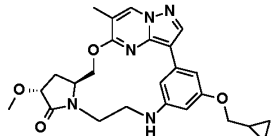
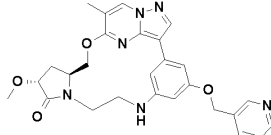
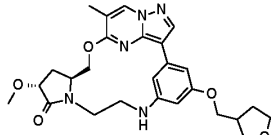
LCMS (MC) RT= 2.10min m/z= 487.1 (M+H)⁺.

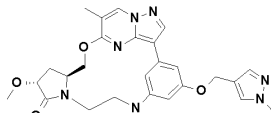
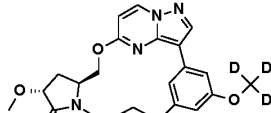
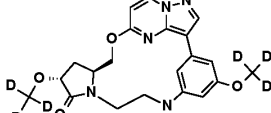
-103-

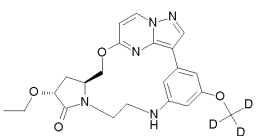
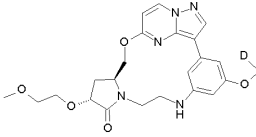
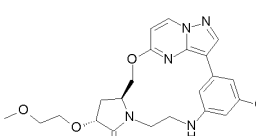
¹H NMR (400 MHz, DMSO) 8.97 (1H, d, J=7.6 Hz), 8.69 (1H, d, J=1.7 Hz), 8.56 – 8.51 (2H, m), 7.90 – 7.86 (1H, m), 7.52 – 7.42 (2H, m), 6.67 – 6.63 (2H, m), 6.13 – 6.05 (2H, m), 5.14 – 5.13 (2H, m), 4.92 (1H, d, J=10.8 Hz), 4.49 – 4.46 (1H, m), 4.36 – 4.30, (1H, m), 3.94 (1H, t, J=10.7Hz), 3.58 – 3.48 (1H, m), 3.44 – 3.36 (1H, m), 3.33 (3H, s), 3.25 – 3.16 (2H, m), 2.46 – 2.40 (1H, m), 2.01 – 1.92 (1H, m)

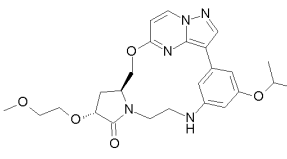
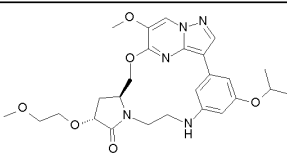
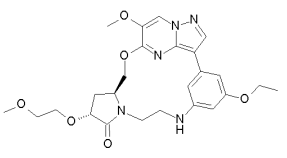
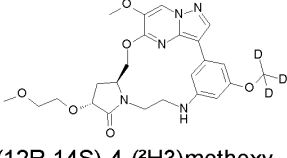
Similarly prepared:

Ex n°	Structure/ Name	From intermediates	Analytical data
45	 (12R,14S)-4-(cyclopropylmethoxy)-12-methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentacosan-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P1 Aniline A9 49% yield as a cream solid	LCMS (MA) RT = 2.38 min, m/z = 450.2 (M+H)⁺. LCMS (MC) RT = 2.38 min, m/z = 450.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO): 8.96 (1H, d, J=7.4 Hz), 8.50 (1H, s), 7.45 (1H, s), 6.63 (1H, d, J=7.4 Hz), 6.55 (1H, s), 6.03 – 5.97 (2H, m), 4.95 – 4.88 (1H, m), 4.48 – 4.44 (1H, m), 4.36 – 4.30 (1H, m), 3.93 (1H, t, J=10.7 Hz), 3.82 – 3.73 (2H, m), 3.64 – 3.49 (2H, m), 3.45 (3H, s), 3.27 – 3.17 (2H, m), 2.47 – 2.41 (1H, m), 2.02 – 1.92 (1H, m), 1.26 – 1.18 (1H, m), 0.61 – 0.54 (2H, m), 0.35 – 0.29 (2H, m).
46	 (12R,14S)-12-methoxy-4-[(1-methyl-1H-pyrazol-4-yl)methoxy]-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentacosan-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P1 Aniline A9 35% yield as a white solid	LCMS (MA) RT = 2.03 min, m/z = 490.3 (M+H)⁺. LCMS (MC) RT = 2.02 min, m/z = 490.3 (M+H)⁺. ¹H NMR (400 MHz, DMSO): 8.98 – 8.95 (1H, m), 8.51 (1H, s), 7.78 (1H, s), 7.51 – 7.50 (2H, m), 6.65 – 6.60 (2H, m), 6.09 – 6.00 (2H, m), 4.93 – 4.90 (3H, m), 4.49 – 4.44 (1H, m), 4.33 (1H, t, J=8.8 Hz), 3.94 (1H, t, J=10.7 Hz), 3.83 (3H, s), 3.57 – 3.38 (3H, m), 3.32 (3H, s), 3.28 – 3.13 (2H, m), 2.47 – 2.40 (1H, m), 2.01 – 1.92 (1H, m).
47	 (12R,14S)-4-methoxy-12-(2-methoxyethoxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentacosan-1(23),2(25),3,5,17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P7 Aniline A9 81% yield as a white solid using K₂CO₃ instead of Cs₂CO₃ in alkylation step	LCMS (MD) RT = 2.72 min, m/z = 454.1 (M+H)⁺. LCMS (ME) RT = 3.20 min, m/z = 454.1 (M+H)⁺. ¹H NMR (400 MHz, DMSO) d 8.96 (d, J = 7.5 Hz, 1H), 8.51 (s, 1H), 7.47 (s, 1H), 6.64 (d, J = 7.5 Hz, 1H), 6.54 (s, 1H), 6.09 – 5.99 (m, 2H), 4.92 (d, J = 10.9 Hz, 1H), 4.54 – 4.38 (m, 2H), 3.95 (ddd, J = 17.7, 11.3, 7.7 Hz, 2H), 3.73 (s, 3H), 3.70

			– 3.60 (m, 1H), 3.59 – 3.50 (m, 1H), 3.48 (t, J = 4.8 Hz, 2H), 3.40 (dd, J = 17.0, 6.9 Hz, 1H), 3.26 (s, 3H), 3.24 – 3.12 (m, 2H), 2.44 (dd, J = 12.7, 8.2 Hz, 1H), 1.98 (dt, J = 11.8, 8.9 Hz, 1H).
48	 (12R,14S)-4-(cyclopropylmethoxy)-12-methoxy-18-methyl-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]pentacos-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold S1 Pyrrolidine P1 Aniline A9 47% yield as a white solid	LCMS (MD) RT = 3.36 min, m/z = 464.2 (M+H)⁺. LCMS (ME) RT = 3.70 min, m/z = 464.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO) δ 8.87 (d, J = 1.2 Hz, 1H), 8.41 (s, 1H), 7.44 (s, 1H), 6.53 (s, 1H), 6.00 (t, J = 2.0 Hz, 1H), 5.98 (d, J = 5.9 Hz, 1H), 4.94 (d, J = 10.7 Hz, 1H), 4.45 (s, 1H), 4.35 (t, J = 8.9 Hz, 1H), 3.98 (t, J = 10.7 Hz, 1H), 3.85 – 3.70 (m, 2H), 3.60 – 3.49 (m, 1H), 3.44 (s, 3H), 3.40 (dd, J = 15.5, 8.4 Hz, 1H), 3.27 – 3.06 (m, 2H), 2.48 – 2.43 (m, 1H), 2.17 (s, 3H), 2.03 – 1.88 (m, 1H), 1.28 – 1.16 (m, 1H), 0.61 – 0.53 (m, 2H), 0.35 – 0.27 (m, 2H).
49	 (12R,14S)-12-methoxy-18-methyl-4-(pyridin-3-ylmethoxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]pentacos-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold S1 Pyrrolidine P1 Aniline A9 62% yield as a white solid	LCMS (MD) RT = 2.33 min, m/z = 501.2 (M+H)⁺. LCMS (ME) RT = 3.54 min, m/z = 501.1 (M+H)⁺. ¹H NMR (400 MHz, DMSO) δ 8.88 (d, J = 1.1 Hz, 1H), 8.69 (d, J = 1.5 Hz, 1H), 8.55 (dd, J = 4.8, 1.7 Hz, 1H), 8.42 (s, 1H), 7.88 (dt, J = 7.8, 1.8 Hz, 1H), 7.49 (s, 1H), 7.44 (ddd, J = 7.8, 4.8, 0.8 Hz, 1H), 6.65 (s, 1H), 6.11 (t, J = 2.1 Hz, 1H), 6.06 (t, J = 5.8 Hz, 1H), 5.13 (s, 2H), 4.95 (d, J = 10.4 Hz, 1H), 4.46 (s, 1H), 4.35 (t, J = 8.9 Hz, 1H), 3.97 (dd, J = 21.8, 11.1 Hz, 1H), 3.53 (dd, J = 11.1, 7.6 Hz, 1H), 3.45 (s, 3H), 3.40 (t, J = 11.9 Hz, 1H), 3.20 (dd, J = 17.1, 10.8 Hz, 2H), 2.48-2.41 (m, 1H), 2.18 (d, J = 0.7 Hz, 3H), 2.05- 1.84 (m, 1H).
50	 (12R,14S)-12-methoxy-18-methyl-4-(oxolan-3-	Scaffold S1 Pyrrolidine P1 Aniline A9 60% yield as a white solid	LCMS (MD) RT = 3.01 min, m/z = 494.2 (M+H)⁺. LCMS (ME) RT = 3.52 min, m/z = 494.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO) δ 8.99 (d, J = 7.5 Hz, 1H), 8.54 (s, 1H), 7.71 (s, 1H), 6.75 (d, J

	ylmethoxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1 ² ,6.0 ¹⁰ ,14.0 ²⁰ , ²³]pentacos-1(23),2,4,6(25),17(24),18,21-heptaen-11-one		= 10.2 Hz, 1H), 6.67 (d, J = 7.5 Hz, 1H), 6.32 (t, J = 5.9 Hz, 1H), 6.21 (dt, J = 11.8, 2.1 Hz, 1H), 4.94 (d, J = 10.9 Hz, 1H), 4.41 (s, 1H), 3.99 (t, J = 10.6 Hz, 1H), 3.60 (dd, J = 11.4, 8.9 Hz, 1H), 3.55 (dd, J = 9.5, 3.8 Hz, 1H), 3.49 (dd, J = 9.5, 5.8 Hz, 1H), 3.40 (dt, 1H), 3.25 (s, 3H), 3.18 (dd, J = 14.2, 9.0 Hz, 2H), 2.91 (tdd, J = 9.7, 5.5, 4.0 Hz, 1H), 2.10 (t, J = 10.6 Hz, 2H).
51	 (12R,14S)-12-methoxy-18-methyl-4-[(1-methyl-1H-pyrazol-4-yl)methoxy]-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,²³]pentacos-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold S1 Pyrrolidine P1 Aniline A9 17% yield as a green solid	LCMS (MD) RT = 2.78 min, m/z = 504.2(M+H) ⁺ . LCMS (MF) RT = 2.71 min, m/z = 504.2 (M+H) ⁺ . ¹ H NMR (400 MHz, DMSO) D 8.88 (d, J = 1.2 Hz, 1H), 8.42 (s, 1H), 7.78 (s, 1H), 7.50 (s, 1H), 7.46 (s, 1H), 6.58 (s, 1H), 6.07 (t, J = 2.0 Hz, 1H), 6.01 (t, J = 5.8 Hz, 1H), 4.95 (d, J = 9.0 Hz, 1H), 4.89 (s, 2H), 4.47 (t, J = 9.5 Hz, 1H), 4.35 (d, J = 6.0 Hz, 1H), 3.99 (t, J = 10.7 Hz, 1H), 3.83 (s, 3H), 3.57 – 3.49 (m, 1H), 3.45 (s, 3H), 3.41 – 3.36 (m, 1H), 3.24 – 3.15 (m, 3H), 2.18 (d, J = 1.0 Hz, 3H), 1.96 (dd, J = 21.6, 8.6 Hz, 1H).
52	 (12R,14S)-4-(²H₃)methoxy-12-methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,²³]pentacos-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P1 Aniline A9 50% yield as a cream solid	LCMS (MA) RT = 2.07min, m/z = 413.2 (M+H) ⁺ . LCMS (MC) RT = 2.08 min, m/z = 412.2 (M+H) ⁺ . ¹ H NMR (400 MHz, DMSO): 8.98 – 8.95 (1H, m), 8.50 (1H, s), 7.47 (1H, s), 6.65 – 6.62 (1H, m), 6.54 (1H, d, J=0.8 Hz), 6.07 – 6.02 (2H, m), 4.96 – 4.89 (1H, m), 4.47 (1H, t, J=8.0 Hz), 4.33 (1H, t, J=8.8 Hz), 3.94 (1H, t, J=10.7 Hz), 3.57 – 3.37 (2H, m), 3.33 (3H, s), 3.27 – 3.16 (2H, m), 2.46 – 2.41 (1H, m), 2.02 – 1.92 (1H, m).
53	 (12R,14S)-4,12-bis(²H₃)methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.	Scaffold S1 Pyrrolidine P6 Aniline A9 20% yield as a white solid	LCMS (MD) RT = 2.66 min, m/z = 416.2 (M+H) ⁺ . LCMS (ME) RT = 3.09 min, m/z = 416.2 (M+H) ⁺ . ¹ H NMR (400 MHz, DMSO) d 8.89 (d, J = 7.5 Hz, 1H), 8.43 (s, 1H), 7.39 (s, 1H), 6.56 (d, J = 7.5 Hz, 1H), 6.47 (dd, J = 1.9, 1.1 Hz, 1H), 5.98 (d, J =

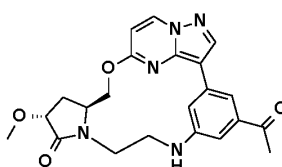
	$1^2,6.0^{10},14.0^{20},^{23}$]pentacos-1(23),2,4,6(25),17(24),18,21-heptaen-11-one		5.9 Hz, 1H), 5.96 (t, J = 2.1 Hz, 1H), 4.85 (d, J = 10.9 Hz, 1H), 4.39 (t, J = 8.8 Hz, 1H), 4.25 (t, J = 8.8 Hz, 1H), 3.86 (t, J = 10.7 Hz, 1H), 3.51 – 3.40 (m, 1H), 3.38 – 3.28 (m, 1H), 3.18 – 3.04 (m, 2H), 2.36 (dd, J = 12.7, 8.2 Hz, 1H), 1.89 (dt, J = 12.0, 8.8 Hz, 1H).
94	 (12R,14S)-12-ethoxy-4-($^2\text{H}_3$)methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.$1^2,6.0^{10},14.0^{20},^{23}$]pentacos-1(23),2(25),3,5,17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P2 Aniline A9 24% yield as a green solid	LCMS (MA) RT = 1.81 min, m/z = 410.4 (M+H) ⁺ . LCMS (MC) RT = 1.80 min, m/z = 410.4 (M+H) ⁺ . ¹ H NMR (400 MHz, DMSO) 8.97 – 8.94 (2H, m), 8.39 – 8.38 (1H, m), 7.97 – 7.95 (1H, m), 7.35 – 7.32 (1H, m), 6.64 – 6.61 (1H, m), 6.35 (1H, s), 5.93 (1H, t, J=2.0 Hz), 4.94 – 4.89 (1H, m), 4.44 – 4.38 (2H, m), 3.98 – 3.82 (2H, m), 3.48 (4H, d, J=10.4 Hz), 3.20 – 3.14 (1H, m), 2.01 – 1.91 (1H, m), 1.17 – 1.04 (4H, m);
95	 (12R,14S)-4-($^2\text{H}_3$)methoxy-12-(2-methoxyethoxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.$1^2,6.0^{10},14.0^{20},^{23}$]pentacos-1(23),2(25),3,5,17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P7 Aniline A9 27% yield as a yellow solid using DL-cysteine instead of 4-Methylbenzenethiol	LCMS (MA) RT = 2.11 min, m/z = 427.5 (M+H) ⁺ . LCMS (MC) RT = 2.10 min, m/z = 427.4 (M+H) ⁺ . ¹ H NMR (400 MHz, DMSO) 8.98 – 8.96 (1H, m), 8.51 – 8.50 (1H, m), 7.46 – 7.45 (1H, m), 6.65 – 6.63 (1H, m), 6.55 (1H, d, J=2.3 Hz), 6.06 – 6.02 (2H, m), 4.95 – 4.90 (1H, m), 4.44 – 4.39 (2H, m), 3.98 – 3.83 (2H, m), 3.60 – 3.49 (2H, m), 3.45 – 3.35 (1H, m), 3.24 – 3.16 (2H, m), 2.45 – 2.35 (1H, m), 2.01 – 1.93 (1H, m), 1.17 – 1.08 (3H, m)
112	 (12R,14S)-4-ethoxy-12-(2-methoxyethoxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.$1^2,6.0^{10},14.0^{20},^{23}$]pentacos-1(23),2(25),3,5,17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P7 Aniline A9 66mg, 68% yield as a white solid using DL-cysteine instead of 4-Methylbenzenethiol	LCMS (MA) RT = 2.17 min, m/z = 468.2 (M+H) ⁺ . LCMS (MC) RT = 2.15 min, m/z = 468.5 (M+H) ⁺ . ¹ H NMR (400 MHz, DMSO) 8.98 – 8.95 (1H, m), 8.51 (1H, s), 7.46 (1H, s), 6.64 (1H, d, J=7.6 Hz), 6.54 (1H, dd, J=1.3, 1.9 Hz), 6.02 (2H, t, J=2.1 Hz), 4.92 (1H, dd, J=1.0, 9.4 Hz), 4.47 – 4.42 (2H, m), 4.01 – 3.93 (4H, m), 3.67 – 3.61 (1H, m), 3.51 (1H, s), 3.48 (2H, t, J=4.8 Hz), 3.30 (2H, s), 3.26 – 3.26 (3H, m), 3.20 – 3.16 (2H, m), 2.03 – 1.94 (1H, m), 1.35 – 1.31 (3H, m);

113	 (12R,14S)-12-(2-methoxyethoxy)-4-(propan-2-yloxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentacos-1(23),2(25),3,5,17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P7 Aniline A9 41mg, 41% yield as a white solid using DL-cysteine instead of 4-Methylbenzenethiol	LCMS (MA) RT = 2.26 min, m/z = 482.5 (M+H)⁺. LCMS (MC) RT = 2.26 min, m/z = 482.5 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 8.98 – 8.95 (1H, m), 8.51 (1H, s), 7.45 – 7.43 (1H, m), 6.65 – 6.62 (1H, m), 6.53 – 6.52 (1H, m), 6.03 – 5.98 (2H, m), 4.94 – 4.91 (1H, m), 4.59 – 4.52 (1H, m), 4.45 (2H, dd, J=8.3, 9.4 Hz), 4.00 – 3.90 (2H, m), 3.67 – 3.61 (1H, m), 3.52 – 3.50 (1H, m), 3.50 – 3.35 (3H, m), 3.31 (1H, s), 3.26 – 3.26 (5H, m), 2.02 – 1.94 (1H, m), 1.27 (6H, t, J=5.6 Hz);
131	 (12R,14S)-18-methoxy-12-(2-methoxyethoxy)-4-(propan-2-yloxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentacos-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold S2 Pyrrolidine P7 Aniline A9 10mg, 26% yield as a Beige solid using K₂CO₃ instead of Cs₂CO₃ at alkylation step	LCMS (MA) RT = 2.23 min, m/z = 512.4 (M+H)⁺. LCMS (MC) RT = 2.22 min, m/z = 512.4 (M+H)⁺. ¹H NMR (400 MHz, CDCl₃) 8.19 (1H, s), 8.14 (1H, s), 7.48 – 7.45 (1H, m), 6.58 (1H, s), 6.07 (1H, t, J=2.0 Hz), 5.13 (1H, d, J=10.8 Hz), 4.61 – 4.50 (2H, m), 4.38 – 4.32 (1H, m), 4.21 – 4.08 (2H, m), 3.96 – 3.94 (6H, m), 3.70 – 3.53 (4H, m), 3.42 – 3.41 (4H, m), 2.73 (1H, dd, J=8.2, 13.1 Hz), 2.24 – 2.17 (1H, m), 1.38 (6H, dd, J=2.3, 6.1 Hz);
140	 (12R,14S)-4-ethoxy-18-methoxy-12-(2-methoxyethoxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentacos-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold S2 Pyrrolidine P7 Aniline A9 10mg, 31% yield as a Beige solid using NaH instead of Cs₂CO₃ at alkylation step	LCMS (MA) RT = 2.15 min, m/z = 498.4 (M+H)⁺. LCMS (MC) RT = 2.13 min, m/z = 498.4 (M+H)⁺. ¹H NMR (400 MHz, CDCl₃) 8.20 – 8.19 (1H, m), 8.14 – 8.13 (1H, m), 7.49 – 7.46 (1H, m), 6.59 (1H, dd, J=1.3, 2.1 Hz), 6.07 (1H, t, J=2.2 Hz), 5.15 – 5.10 (1H, m), 4.54 – 4.49 (1H, m), 4.38 – 4.32 (1H, m), 4.20 – 4.14 (1H, m), 4.09 – 4.03 (3H, m), 3.95 – 3.94 (6H, m), 3.70 – 3.49 (4H, m), 3.42 – 3.42 (3H, m), 3.30 – 3.23 (1H, m), 2.73 (1H, dd, J=8.2, 13.1 Hz), 2.25 – 2.16 (1H, m), 1.44 (3H, t, J=7.0 Hz);
141	 (12R,14S)-4-(²H₃)methoxy-18-methoxy-12-(2-methoxyethoxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentacos-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold S2 Pyrrolidine P7 Aniline A9 9mg, 25% yield as a Light brown solid using NaH instead of Cs₂CO₃ at alkylation step	LCMS (MA) RT = 2.02 min, m/z = 487.4 (M+H)⁺. LCMS (MC) RT = 1.99 min, m/z = 487.4 (M+H)⁺. ¹H NMR (400 MHz, CDCl₃) 8.21 – 8.21 (1H, m), 8.15 – 8.14 (1H, m), 7.50 – 7.47 (1H, m), 6.59 (1H, dd, J=1.2, 2.2 Hz), 6.08

-108-

	7,10,20,21,24-pentaazapentacyclo[15.5.2.1 ² ,6.0 ¹⁰ ,14.0 ²⁰ , ²³]pentacos-1(23),2,4,6(25),17(24),18,21-heptaen-11-one		(1H, t, J=2.2 Hz), 5.13 (1H, d, J=10.8 Hz), 4.52 (1H, t, J=8.8 Hz), 4.35 (1H, dd, J=8.2, 9.5 Hz), 4.21 - 4.13 (2H, m), 3.96 - 3.95 (6H, m), 3.70 - 3.57 (4H, m), 3.42 - 3.42 (3H, m), 3.30 - 3.23 (1H, m), 2.73 (1H, dd, J=8.1, 13.2 Hz), 2.25 - 2.16 (1H, m);
--	---	--	--

Example 54: (12R,14S)-4-acetyl-12-methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,²³]pentacos-1(23),2,4,6(25),17(24),18,21-heptaen-11-one



5

Step 1

To a solution of Triethylamine (0.13mL, 0.956mmol) and **Intermediate I19** (370mg, 0.637mmol) in Dichloromethane (30mL) was added portionwise *N*-phenyl-bis(trifluoromethanesulfonimide) (250mg, 0.701mmol). The reaction mixture was stirred at room temperature for 5h. Water (30mL) was added to the reaction and extracted with Dichloromethane. The combined organic layers were washed with Brine, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified by silica gel chromatography (eluting gradient 0-50% cyclohexane/ethyl acetate) to afford the title compound (430mg, 95% yield) as a yellowish solid.

LCMS (MA) RT = 2.91 min, m/z = 713.2 (M+H)⁺.

Step 2

To a solution of the title compound from Step 1 (100mg, 0.140mmol) in DMF (3.5mL) was added Cesium carbonate (91mg, 0.280mmol) and 4-Methylbenzenethiol (21mg, 0.168mmol). The reaction mixture was stirred at room temperature for 30 min. The mixture was diluted with water (3mL) and EtOAc (3mL) and the two layers were separated. The aqueous layer was extracted three times (3x5mL) with ethyl acetate. The organic layers were combined, washed with Brine (5mL) and dried over sodium sulfate. The crude residue was purified by silica gel chromatography using cyclohexane/ethyl acetate 100:0 to 0:100 as eluent s to afford the title compound (65mg, 88% yield) as a white amorphous solid.

LCMS (MA) RT = 2.62 min, m/z = 528.1 (M+H)⁺.

25

Step 3

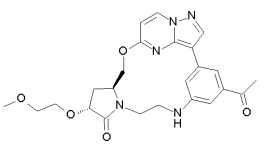
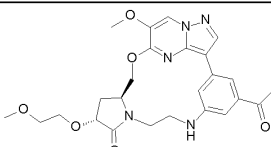
In a microwave vial, the title compound from Step 2 (31mg, 0.059mmol) and LiCl (8mg, 0.177mmol) were dissolved in Dioxane (1mL) and the mixture was degassed with Ar for 10 minutes. Tributyl(1-ethoxyvinyl)stannane (0.024mL, 0.070mmol) and Pd(PPh₃)₄ (7mg, 0.006mmol) were added and the vial containing the resulting transparent solution was sealed and heated to 100°C for 1h. The reaction mixture was partitioned between a 1M solution of HCl (2mL) and Ethyl acetate (2mL). The two layers were separated, the aqueous layer was extracted three times with Ethyl acetate (3x2mL). The combined organic layers were washed with Brine (2mL), dried over sodium sulfate and concentrated in vacuum. The crude residue was purified by silica gel chromatography using cyclohexane/ethyl acetate 50:50 to 0:100 as eluents to afford the expected product (13mg, 52% yield) as a yellowish amorphous solid.

LCMS (MA) RT = 2.00 min, m/z = 422.2 (M+H)⁺.

LCMS (MC) RT = 2.02 min, m/z = 422.3 (M+H)⁺.

¹H NMR (400 MHz, DMSO) 9.00 (1H, d, J=7.6 Hz), 8.63 (1H, s), 8.04 – 8.03 (1H, m), 7.50 (1H, s), 7.05 (1H, dd, J=1.4, 2.4 Hz), 6.67 (1H, d, J=7.4 Hz), 6.37 (1H, s), 4.93 (1H, d, J=10.4 Hz), 4.52 – 4.47 (1H, m), 4.37 – 4.31 (1H, m), 3.95 (1H, t, J=10.8 Hz), 3.46 – 3.45 (4H, m), 3.28 – 3.24 (2H, m), 2.58 – 2.57 (3H, m), 2.44 (1H, dd, J=8.6, 15.4 Hz), 2.05 – 1.92 (1H, m). One proton was overlapped by the water signal.

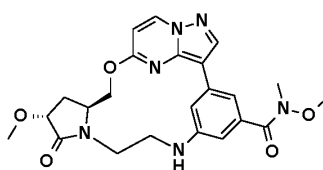
20 Similarly prepared:

Ex n°	Structure/ Name	From intermediates	Analytical data
98	 (12R,14S)-4-acetyl-12-(2-methoxyethoxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]pentacosan-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P7 Aniline A9 64% yield as yellow solid	LCMS (MA) RT = 1.96 min, m/z = 466.4 (M+H)⁺. LCMS (MC) RT = 1.96 min, m/z = 466.4 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 9.00 (1H, d, J=7.4 Hz), 8.64 (1H, s), 8.04 (1H, ls), 7.50 – 7.49 (1H, m), 7.05 – 7.04 (1H, m), 6.68 (1H, d, J=7.6 Hz), 6.37 (1H, t, J=5.9 Hz), 4.95 – 4.91 (1H, m), 4.52 – 4.43 (2H, m), 4.00 – 3.92 (2H, m), 3.68 – 3.62 (1H, m), 3.58 – 3.48 (1H, m), 3.48 (2H, t, J=4.8 Hz), 3.41 – 3.35 (1H, m), 3.29 – 3.23 (2H, m), 3.26 (3H, s), 2.57 (3H, s), 2.47 – 2.42 (1H, m), 2.02 – 1.91 (1H, m).
99	 (12R,14S)-4-acetyl-18-	Scaffold S2 Pyrrolidine P7 Aniline A9 64% yield as yellow solid	LCMS (MA) RT = 1.97 min, m/z = 496.4 (M+H)⁺. LCMS (MC) RT = 1.97 min, m/z = 496.4 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 8.79 (1H, s), 8.49 (1H, s), 7.99 – 7.99 (1H, m), 7.47 (1H, s), 7.03 (1H, t, J=1.9 Hz), 6.36

-110-

	methoxy-12-(2-methoxyethoxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1 ² ,6.0 ¹⁰ ,14.0 ²⁰ ,23]pentacos		(1H, t, J=5.7 Hz), 4.95 (1H, d, J=10.2 Hz), 4.48 – 4.43 (2H, m), 3.91 – 3.90 (6H, m), 3.68 – 3.62 (1H, m), 3.50 – 3.46 (3H, m), 3.27 – 3.26 (6H, m), 2.65 – 2.55 (3H, m); 2.01 – 1.93 (1H, m)
	a-1(23),2(25),3,5,17(24),18,21-heptaen-11-one		

Example 55: (12R,14S)-N,12-dimethoxy-N-methyl-11-oxo-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentacos-1(23),2,4,6(25),17(24),18,21-heptaene-4-carboxamide



5
Following the general synthetic scheme 1, as depicted for the synthesis of Example 1, Methyl (12R,14S)-12-methoxy-11-oxo-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentacos-1(23),2,4,6(25),17(24),18,21-heptaene-4-carboxylate was obtained as **Intermediate I20** using **Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine**, **Pyrrolidine P1** and **Aniline A18**.
10

Step 1

To a solution of **Intermediate I20** (0.32 g, 0.731mmol) in Methanol (15mL), Tetrahydrofuran (15mL) and water (15mL) was added 1N sodium hydroxide solution (3.6mL, 3.657mmol). The
15 reaction mixture was stirred at 50°C for 3h. The reaction mixture was cooled to room temperature, then slightly acidified with a of 1N HCl solution (~pH=4-5) and concentrated under reduced pressure. Water was added to the residue. The resulting precipitate was filtered, washed with water, then pentane and dried to afford the title compound (280mg, 90% yield) as an off-white solid.
20 L36119-1 LCMS (MA) RT = 1.89 min, m/z = 424.1 (M+H)+.

Step 2

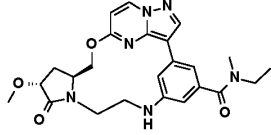
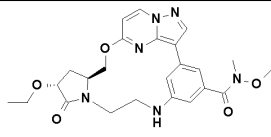
To a solution of the title compound from Step 1 (50mg, 0.118mmol) in *N,N*-dimethylformamide (5mL) were added HATU (67mg, 0.177mmol), *N*-Methoxymethanamine hydrochloride (35mg ,
25 0.354mmol) and Triethylamine (0.08mL, 0.59mmol). The reaction mixture was stirred at room temperature for 1h. The reaction mixture was concentrated under reduced pressure. Water was added to the residue and after extraction with Dichloromethane, the combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC (eluting solvent 90-10%

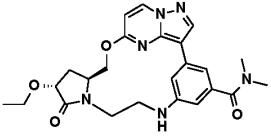
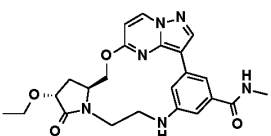
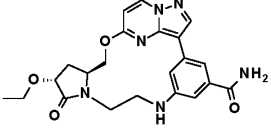
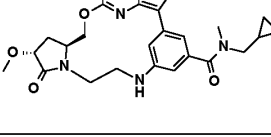
-111-

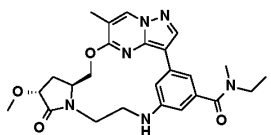
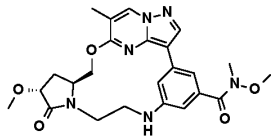
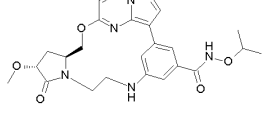
Dichloromethane/methanol). The gummy residue was triturated with Dichloromethane/pentane (1:4). The resulting precipitate was filtered, washed with pentane and dried under reduced pressure to afford the expected product (35mg, 63% yield) as a white solid.

- 5 LCMS (MA) RT = 1.90 min, m/z = 467.1 (M+H)⁺.
 LCMS (MC) RT = 1.89 min, m/z = 467.2 (M+H)⁺.
¹H NMR (400 MHz, DMSO) : 8.99 (1H, d, J=7.4 Hz), 8.55 (1H, s), 7.93 – 7.89 (1H, m), 7.06 (1H, s), 6.67 – 6.62 (2H, m), 6.31 – 6.26 (1H, m), 4.95 (1H, d, J=10.6 Hz), 4.49 (1H, t, J=8.1 Hz), 4.37 – 4.31 (1H, m), 3.95 (1H, t, J=10.7 Hz), 3.61 (3H, s), 3.58 – 3.51 (1H, m), 3.46 (3H, s), 3.44 – 3.36 (1H, m), 3.26 (3H, s), 3.26 – 3.17 (2H, m), 2.47 – 2.42 (1H, m), 2.02 – 1.93 (1H, m).

Similarly prepared:

Ex n°	Structure/ Name	From intermediates	Analytical data
56	 (12R,14S)-N-ethyl-12-methoxy-N-methyl-11-oxo-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]pentacosan-1(23),2,4,6(25),17(24),18,21-heptaene-4-carboxamide	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P1 Aniline A18 76.5% yield as an off-white solid	LCMS (MA) RT = 1.96 min, m/z = 465.1 (M+H)⁺. LCMS (MC) RT = 1.97 min, m/z = 465.1 (M+H)⁺. ¹H NMR (400 MHz, DMSO) : 8.99 (1H, d, J= 7.6Hz), 8.56 (1H, s), 7.87 (1H, brs), 6.88 (1H, s), 6.67 – 6.65 (1H, d, J= 7.4Hz), 6.40 (1H, s), 6.25 (1H, brs), 4.95 (1H, d, J=10.2 Hz), 4.50 (1H, t, J=8.1 Hz), 4.37 – 4.31 (1H, m), 3.96 (1H, t, J=10.8 Hz), 3.60 – 3.51 (1H, m), 3.46 (3H, s), 3.44 – 3.38 (1H, m), 3.30 – 3.21 (2H, m), 2.95 – 2.83 (5H, m), 2.47 2.42 (1H, m), 2.02 – 1.93 (1H, m), 1.14 (3H, t, J= 7.2Hz).
57	 (12R,14S)-12-ethoxy-N-methoxy-N-methyl-11-oxo-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]pentacosan-1(23),2(25),3,5,17(24),18,21-heptaene-4-carboxamide	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P2 Aniline A18 14% yield as an pale yellow solid	LCMS (MA) RT = 2.02 min, m/z = 481 (M+H)⁺. LCMS (MC) RT = 1.96 min, m/z = 481.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO) : 8.99 (1H, d, J=7.6 Hz), 8.55 (1H, s), 7.96 – 7.91 (1H, m), 7.06 (1H, s), 6.68 – 6.62 (2H, m), 6.29 (1H, t, J=6.1 Hz), 4.95 (1H, d, J=10.8 Hz), 4.51 – 4.39 (2H, m), 4.00 – 3.83 (2H, m), 3.33 – 3.32 (4H, m), 3.30 (1H, s), 3.26 – 3.25 (5H, m), 2.45 – 2.40 (1H, m), 2.01 – 1.93 (1H, m), 1.17 – 1.13 (4H, m).

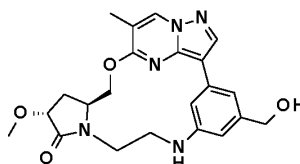
58	 (12R,14S)-12-ethoxy-N,N-dimethyl-11-oxo-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{1°,14}.0^{2°,23}]pentacosan-1(23),2(25),3,5,17(24),18,21-heptaene-4-carboxamide	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P2 Aniline A18 62% yield as a yellow solid	LCMS (MA) RT = 1.98 min, m/z = 465 (M+H)⁺. LCMS (MC) RT = 1.97 min, m/z = 465.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO) : 9.00 – 8.97 (1H, m), 8.55 – 8.55 (1H, m), 7.86 (1H, s), 6.90 (1H, s), 6.66 (1H, d, J=7.6 Hz), 6.44 – 6.42 (1H, m), 6.27 – 6.22 (1H, m), 4.94 (1H, d, J=11.6 Hz), 4.51 – 4.39 (2H, m), 4.00 – 3.83 (2H, m), 3.62 – 3.51 (2H, m), 2.97 (6H, s), 2.70 – 2.69 (2H, m), 2.45 – 2.40 (1H, m), 2.02 – 1.91 (1H, m), 1.18 – 1.10 (4H, m).
59	 (12R,14S)-12-ethoxy-N-methyl-11-oxo-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{1°,14}.0^{2°,23}]pentacosan-1(23),2(25),3,5,17(24),18,21-heptaene-4-carboxamide	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P2 Aniline A18 39% yield as a white solid	LCMS (MA) RT = 1.92 min, m/z = 451 (M+H)⁺. LCMS (MC) RT = 1.91 min, m/z = 451.3 (M+H)⁺. ¹H NMR (400 MHz, DMSO) : 9.00 – 8.98 (1H, m), 8.49 (1H, s), 8.28 (1H, q, J=4.5 Hz), 7.94 – 7.92 (1H, m), 7.36 (1H, s), 6.94 (1H, dd, J=1.4, 2.4 Hz), 6.68 – 6.65 (1H, m), 6.25 (1H, t, J=5.9 Hz), 4.93 (1H, d, J=11.0 Hz), 4.49 – 4.39 (2H, m), 4.00 – 3.83 (2H, m), 3.67 – 3.51 (2H, m), 3.45 – 3.35 (1H, m), 3.25 – 3.15 (2H, m), 2.79 (3H, d, J=4.6 Hz), 2.01 – 1.91 (1H, m), 1.17 – 1.13 (4H, m).
60	 (12R,14S)-12-ethoxy-11-oxo-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{1°,14}.0^{2°,23}]pentacosan-1(23),2(25),3,5,17(24),18,21-heptaene-4-carboxamide	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P2 Aniline A18 68% yield as a yellow solid	LCMS (MA) RT = 1.85 min, m/z = 437 (M+H)⁺. LCMS (MC) RT = 1.83 min, m/z = 437.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO) : 8.99 (1H, d, J=7.4 Hz), 8.50 – 8.50 (1H, m), 7.93 – 7.93 (1H, m), 7.81 – 7.79 (1H, m), 7.42 (1H, s), 7.24 (1H, s), 6.97 (1H, dd, J=1.5, 2.3 Hz), 6.66 (1H, d, J=7.4 Hz), 6.25 – 6.20 (1H, m), 4.94 (1H, d, J=10.4 Hz), 4.51 – 4.39 (2H, m), 4.00 – 3.83 (2H, m), 3.61 – 3.52 (2H, m), 3.29 – 3.20 (1H, m), 2.70 – 2.69 (2H, m), 2.01 – 1.93 (1H, m), 1.18 – 1.10 (4H, m).
61	 (12R,14S)-12-ethoxy-11-oxo-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{1°,14}.0^{2°,23}]pentacosan-1(23),2(25),3,5,17(24),18,21-heptaene-4-carboxamide	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P1 Aniline A18	LCMS (MA) RT = 2.12 min, m/z = 491.2 (M+H)⁺. LCMS (MC) RT = 2.12 min, m/z = 491.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO): 8.98 (1H, d, J= 7.6Hz), 8.56

	(12R,14S)-N-(cyclopropylmethyl)-12-methoxy-N-methyl-11-oxo-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1 ² ,6.0 ¹⁰ ,14.0 ²⁰ ,23]pentaco sa-1(23),2,4,6(25),17(24),18,21-heptaene-4-carboxamide	60% yield as an off-white solid	(1H, s), 7.89 – 7.87 (1H, m), 6.88 (1H, s), 6.65 (1H, d, J=7.4Hz), 6.41 (1H, d, J=0.8 Hz), 6.25 (1H, t, J=5.8 Hz), 4.96 (1H, d, J=11.2 Hz), 4.50 – 4.48 (1H, m), 4.37 – 4.31 (1H, m), 3.95 (1H, t, J=10.7 Hz), 3.59 – 3.51 (1H, m), 3.45 (3H, s), 3.27 – 3.21 (2H, m), 3.04 – 2.98 (3H, m), 2.9 – 2.85 (3H, m), 2.47 – 2.42 (1H, m), 2.02 – 1.93 (1H, m), 1.08 – 0.9 (1H, m), 0.54 – 0.43 (3H, m), 0.34 – 0.26 (1H, m).
62	 (12R,14S)-N-ethyl-12-methoxy-N,18-dimethyl-11-oxo-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1 ² ,6.0 ¹⁰ ,14.0 ²⁰ ,23]pentaco sa-1(23),2(25),3,5,17(24),18,21-heptaene-4-carboxamide	Scaffold S2 Pyrrolidine P1 Aniline A18 5% yield as a white solid	LCMS (MD) RT = 2.668 min, m/z = 479.2 (M+H) ⁺ . LCMS (ME) RT = 3.203 min, m/z = 479.1 (M+H) ⁺ . 1H NMR (400 MHz, DMSO) d 8.90 (d, J = 0.9 Hz, 1H), 8.46 (s, 1H), 7.86 (s, 1H), 6.86 (s, 1H), 6.39 (s, 1H), 6.23 (s, 1H), 4.97 (d, J = 10.5 Hz, 1H), 4.49 (t, J = 8.1 Hz, 1H), 4.36 (t, J = 8.9 Hz, 1H), 4.00 (t, J = 10.7 Hz, 1H), 3.66 – 3.50 (m, 1H), 3.45 (s, 3H), 3.43 (d, J = 3.6 Hz, 1H), 3.38 (dd, J = 13.0, 3.2 Hz, 1H), 3.29 – 3.17 (m, 3H), 2.93 (s, 3H), 2.49 – 2.44 (m, 1H), 2.19 (s, 3H), 1.96 (dt, J = 12.2, 9.1 Hz, 1H), 1.11 (brs, 3H).
63	 (12R,14S)-N,12-dimethoxy-N,18-dimethyl-11-oxo-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1 ² ,6.0 ¹⁰ ,14.0 ²⁰ ,23]pentaco sa-1(23),2,4,6(25),17(24),18,21-heptaene-4-carboxamide	Scaffold S2 Pyrrolidine P1 Aniline A18 37% yield as a white solid	LCMS (MD) RT = 2.401 min, m/z = 481.2 (M+H) ⁺ . LCMS (ME) RT = 3.153 min, m/z = 481.1 (M+H) ⁺ . 1H NMR (400 MHz, DMSO) 8.91 (d, J = 1.2 Hz, 1H), 8.45 (s, 1H), 7.90 (s, 1H), 7.05 (s, 1H), 6.61 (d, J = 1.3 Hz, 1H), 6.27 (t, J = 5.8 Hz, 1H), 4.98 (d, J = 10.8 Hz, 1H), 4.49 (t, J = 9.0 Hz, 1H), 4.36 (t, J = 8.8 Hz, 1H), 4.00 (t, J = 10.8 Hz, 1H), 3.61 (s, 2H), 3.55 (dd, J = 13.0, 7.9 Hz, 2H), 3.45 (s, 2H), 3.40 (dd, J = 18.2, 8.3 Hz, 1H), 3.30 (s, 2H), 3.25 (s, 3H), 3.19 (dd, J = 15.7, 4.7 Hz, 2H), 2.19 (d, J = 1.0 Hz, 3H), 1.96 (dd, J = 21.5, 8.9 Hz, 1H).
107	 (12R,14S)-12-methoxy-	Scaffold 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine Pyrrolidine P1	LCMS (MA) RT = 1.870 min, m/z = 481.3 (M+H) ⁺ . LCMS (MC) RT = 2.84 min, m/z = 481.4 (M+H) ⁺ . 1H NMR (400 MHz, CDCl ₃)

-114-

	11-oxo-N-(propan-2-yloxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1 ² ,6.0 ¹⁰ ,14.0 ²⁰ ,23]pentacos-1(23),2,4,6(25),17(24),18,21-heptaene-4-carboxamide	Aniline A18 88% yield as a beige solid	9.24 – 9.21 (1H, m), 8.52 – 8.48 (1H, m), 8.35 (1H, s), 7.97 (1H, s), 7.26 (1H, m), 6.90 – 6.87 (1H, m), 6.41 – 6.38 (1H, m), 4.99 (1H, d, J=10.6 Hz), 4.54 – 4.20 (4H, m), 3.81 – 3.64 (2H, m), 3.60 (3H, s), 3.56 – 3.44 (2H, m), 3.23 (1H, q, J=7.3 Hz), 2.66 – 2.58 (1H, m), 2.14 – 2.06 (1H, m), 1.40 – 1.33 (6H, m).
--	---	--	--

Example 64: (12R,14S)-4-(hydroxymethyl)-12-methoxy-18-methyl-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentacos-1(23),2,4,6(25),17(24),18,21-heptaen-11-one



5 Following the general synthetic scheme 1, as depicted for the synthesis of Example 1, Methyl (12R,14S)-12-methoxy-18-methyl-11-oxo-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentacos-1(23),2,4,6(25),17(24),18,21-heptaene-4-carboxylate was obtained as **Intermediate I21** using **Scaffold S1**, **Pyrrolidine P1** and **Aniline A18**.

Step 1

Intermediate I21 (50mg, 0.11mmol) was suspended in water (2mL) and hydrochloric acid 37% solution (2mL) was added. The reaction mixture was stirred at room temperature for 16h. The mixture was concentrated under reduced pressure and co-evaporated with Heptane. The crude residue was dried under vacuum to afford the expected compound as pink solid. The crude was used in the next step without further purifications.

LCMS (MH) RT = 0.696 min, m/z = 438.1 (M+H)⁺.

20 Step 2

Borane dimethyl sulfide complex (2M/THF) (1.14mL, 2.11mmol) was added to a stirred solution of the title compound from Step 1 (100mg, 0.211mmol) in dry THF (3mL) under Nitrogen atmosphere at 0°C. The reaction mixture was warmed to ambient temperature and stirred for 1h. The reaction mixture was cooled down to 0°C and quenched with a few drops of methanol. The solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (eluting gradient 0-2.5% Dichloromethane/methanol) to afford the expected product (40mg, 45% yield) as a white solid.

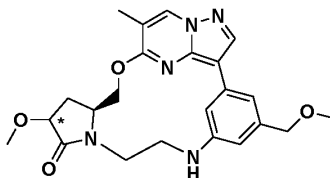
-115-

LCMS (MD) RT = 2.374 min, m/z = 424.1 (M+H)⁺.

LCMS (ME) RT = 2.977 min, m/z = 424.1 (M+H)⁺.

¹H NMR (400 MHz, DMSO) δ 8.88 (d, J = 1.2 Hz, 1H), 8.34 (s, 1H), 7.67 (s, 1H), 6.83 (s, 1H), 6.45 (s, 1H), 6.02 (t, J = 5.9 Hz, 1H), 5.04 (t, J = 5.7 Hz, 1H), 4.94 (d, J = 10.7 Hz, 1H), 4.46 (t, J = 8.5 Hz, 1H), 4.42 (d, J = 5.8 Hz, 2H), 4.36 (d, J = 8.0 Hz, 1H), 3.99 (t, J = 10.7 Hz, 1H), 3.60 - 3.48 (m, 1H), 3.45 (s, 3H), 3.38 (dd, J = 9.6, 3.6 Hz, 1H), 3.25 - 3.12 (m, 2H), 2.46 (dd, J = 12.0, 6.0 Hz, 1H), 2.18 (d, J = 1.0 Hz, 3H), 1.96 (dd, J = 21.4, 8.7 Hz, 1H).

Examples 65 & 66: (12R or S,14S)-12-methoxy-4-(methoxymethyl)-18-methyl-16-oxa-7,10,20,21,24-pentaazapenta cyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]pentacos-1(23),2,4,6(25),17(24),18,21-heptaen-11-one (single unknown isomer 1, single unknown isomer 2)



Step 1

To a stirred solution of **Example 64** (150mg, 0.354mmol) in Dichloromethane (4.5mL) was added Thionyl chloride (0.129mL, 1.170mmol). The reaction was stirred at room temperature for 1h. The solvent was removed under reduced pressure. The residue was diluted with toluene and evaporated to dryness to afford the title compound (160mg) as a beige solid, which was used without further purifications.

LCMS (MD) RT = 0.860 min, m/z = 444.1 (M+H)⁺.

20

Step 2

To a solution of the title compound from Step 1 (160mg, 0.362mmol) in Methanol (6mL) was added Sodium methoxide solution (25 Wt. % in methanol) (1.6mL). The reaction mixture was stirred at 80°C for 3h. A saturated aqueous sodium bicarbonate solution was added and the mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure.

25

Reverse phase purification:

72% [25 mM NH₄HCO₃] - 28% [Acetonitrile:Methanol 1:1] 36% [25mM NH₄HCO₃] - 64% [Acetonitrile:Methanol 1:1]

30

35

-116-

Example 65: Single unknown isomer 1

70 mg, 44.3% yield as a white solid

LCMS (MD) RT = 2857 min, m/z = 438.1 (M+H)⁺.LCMS (ME) RT = 3.349 min, m/z = 438.2 (M+H)⁺.

- 5 ¹H NMR (400 MHz, DMSO) δ 8.88 (dd, J = 12.0, 6.0 Hz, 1H), 8.38 (s, 1H), 7.73 (s, 1H), 6.84 (s, 1H), 6.42 (s, 1H), 6.07 (t, J = 5.8 Hz, 1H), 4.95 (d, J = 10.6 Hz, 1H), 4.48 (t, J = 9.1 Hz, 1H), 4.36 (d, J = 8.0 Hz, 1H), 4.32 (s, 2H), 3.99 (t, J = 10.7 Hz, 1H), 3.60 - 3.48 (m, 1H), 3.45 (s, 3H), 3.43 - 3.35 (m, 1H), 3.29 (s, 3H), 3.27 - 3.16 (m, 2H), 2.48 - 2.42 (m, 1H), 2.18 (s, 3H), 1.96 (dt, J = 12.3, 8.3 Hz, 1H)

10

Example 66: Single unknown isomer 2

8.1mg, 5.1% yield as a white solid .

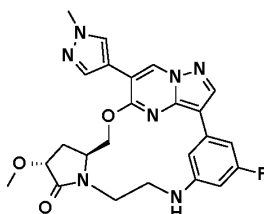
LCMS (MD) RT = 3.007 min, m/z = 438.2 (M+H)⁺.LCMS (ME) RT = 3.390 min, m/z = 438.1 (M+H)⁺.

- 15 ¹H NMR (400 MHz, DMSO) δ 8.88 (d, J = 1.2 Hz, 1H), 8.38 (s, 1H), 7.73 (s, 1H), 6.84 (s, 1H), 6.42 (s, 1H), 6.07 (t, J = 5.8 Hz, 1H), 5.11 (d, J = 10.6 Hz, 1H), 4.50 - 4.40 (m, 1H), 4.33 (s, 2H), 3.93 (t, J = 10.5 Hz, 1H), 3.80 (d, J = 6.4 Hz, 1H), 3.67 - 3.53 (m, 1H), 3.45 (s, 3H), 3.30 (d, J = 3.8 Hz, 4H), 3.24 (dd, J = 11.0, 6.1 Hz, 1H), 3.19 - 3.06 (m, 1H), 2.41 - 2.30 (m, 1H), 2.18 (d, J = 0.7 Hz, 3H), 1.98 (d, J = 14.1 Hz, 1H).

20

Example 67: (12R,14S)-4-fluoro-12-methoxy-18-(1-methyl-1H-pyrazol-4-yl)-16-oxa-

7,10,20,21,24-pentaazapentacyclo[15.5.2.1².6.0¹⁰,14.0²⁰,23]pentacosa-1(23),2(25),3,5,17(24),
18,21-heptaen-11-one



- 25 Following the general synthetic scheme 1, as depicted for the synthesis of Example 1, (12R,14S)-18-(benzyloxy)-4-fluoro-12-methoxy-7-(2-nitrobenzenesulfonyl)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.12,6.010,14.020,23]pentacosa-1(23),2,4,6(25),17(24),18,21-heptaen-11-one was obtained as **Intermediate I22** using **Scaffold S3**, **Pyrrolidine P1** and **Aniline A1**.

30

Step 1

In a sealed tube was added **Intermediate I22** (664mg, 0.964mmol), Anisole (4.212mL, 38.56mmol) and trifluoroacetic acid (4.5mL). The reaction mixture was stirred at 130°C for 16h.

-117-

Solvent was removed under reduced pressure and the product was crystallized in Acetonitrile to afford the title compound (**Intermediate I28**, (12R,14S)-4-fluoro-18-hydroxy-12-methoxy-7-(2-nitrobenzenesulfonyl)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.12,6.0¹⁰,14.0²⁰,23]pentacos-1(23),2,4,6(25),17(24),18,21-heptaen-11-one) (432mg, 75% yield) as a brown solid.

5 LCMS (MH) RT = 0.821 min, m/z = 599 (M+H)⁺.

Step 2

Trifluoromethanesulfonic anhydride (0.061mL, 0.367mmol) was added to a stirred solution of the title compound from Step 1 (200mg, 0.334mmol) and Pyridine (0.079mL, 1.002mmol) in dry Dichloromethane (2mL). The reaction mixture was stirred at room temperature for 1h. An aqueous saturated solution of sodium bicarbonate was added and extracted with ethyl acetate. The combined organic phases were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting gradient 0-2% Dichloromethane/methanol) to afford expected compound (220mg, 90% yield) as a brown solid.

10 15 LCMS (MH) RT = 1.084 min, m/z = 730.9 (M+H)⁺.

Step 3

In a pressure flask, the title compound from Step 2 (100mg, 0.137mmol), 1,5-dimethyl-1H-pyrazole-4-boronic acid, pinacol ester (36mg, 0.164mmol), and Potassium phosphate tribasic (87mg, 0.411mmol) were mixed in Dioxane/water (4:1) (2mL). The reaction mixture was bubbled with a Nitrogen stream for 5min. Then Tetrakis(triphenylphosphine)palladium(0) (9mg, 0.008mmol) and Xphos (8mg, 0.016mmol) were added and the mixture was stirred at 80°C for 2h. Water was added and extracted with ethyl acetate. The combined organic phases were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting gradient 0-2% Dichloromethane/methanol) to afford the expected compound (22mg, 24% yield) as a brown solid.

20 25 30 LCMS (MD) RT = 3.423 min, m/z = 677.1 (M+H)⁺.

Step 4

Thiophenol (0.028mL, 0.273mmol) was added to a stirred solution of the title compound from Step 3 (0.060g, 0.091mmol) and Cesium carbonate (0.089g, 0.273mmol) in DMF (2.0mL) at 0°C. The mixture was stirred at room temperature for 1 hour. Upon complete conversion, monitored by LCMS, an aqueous saturated solution of NaHCO₃ was added and the mixture was extracted with EtOAc. (x3). The combined organic layer was dried overmgSO₄, filtered and concentrated under vacuum. The product was purified by flash chromatography (on silica

35

-118-

gel) using DCM/MeOH as eluents (100:0 to 97:3) to afford the expected product as a white solid (10mg, 23.01%).

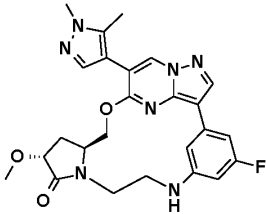
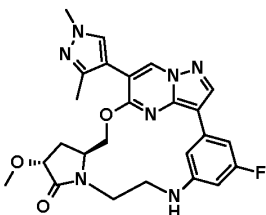
LCMS (MD) RT = 2.977 min, m/z = 478.1(M+H)⁺.

LCMS (ME) RT = 3.551 min, m/z = 478.1 (M+H)⁺.

- 5 ¹H NMR (400 MHz, DMSO) 9.38 (s, 1H), 8.52 (s, 1H), 8.29 (s, 1H), 8.11 (s, 1H), 7.68 (s, 1H), 6.76 (d, J = 9.4 Hz, 1H), 6.34 (t, J = 5.8 Hz, 1H), 6.21 (dt, J = 11.8, 2.1 Hz, 1H), 5.06 (d, J = 10.5 Hz, 1H), 4.53 (brs, 1H), 4.35 (t, J = 8.9 Hz, 1H), 4.08 (t, J = 10.7 Hz, 1H), 3.93 (s, 3H), 3.63 - 3.52 (m, 1H), 3.48 (s, 3H), 3.44 - 3.36 (m, 1H), 3.28 - 3.19 (m, 2H), 2.64 (dd, J = 12.7, 8.2 Hz, 1H), 1.97 (dt, J = 11.9, 9.0 Hz, 1H).

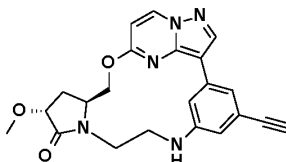
10

Similarly prepared:

Ex n°	Structure/ Name	From intermediates	Analytical data
68	 (12R,14S)-18-(1,5-dimethyl-1H-pyrazol-4-yl)-4-fluoro-12-methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,1⁴.0²⁰,2³]pentacosan-1(23),2(25),3,5,17(24),18,21-heptaen-11-one	1,5-dimethyl-1H-pyrazole-4-boronic acid, pinacol ester 67% yield as a beige solid	LCMS (MG) RT = 3.133 min, m/z = 492.05 (M+H)⁺. LCMS (MD) RT = 4.550 min, m/z = 492.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO) d 8.92 (s, 1H), 8.55 (s, 1H), 7.71 (s, 1H), 7.58 (s, 1H), 6.77 (d, J = 9.4 Hz, 1H), 6.35 (t, J = 5.8 Hz, 1H), 6.22 (dt, J = 11.8, 2.1 Hz, 1H), 4.98 (d, J = 10.4 Hz, 1H), 4.54 (t, J = 9.9 Hz, 1H), 4.32 (t, J = 8.8 Hz, 1H), 3.95 (t, J = 10.7 Hz, 1H), 3.82 (s, 3H), 3.64 - 3.51 (m, 1H), 3.44 (s, 3H), 3.42 - 3.36 (m, 1H), 3.28 - 3.19 (m, 2H), 2.44 (dd, J = 12.6, 8.2 Hz, 1H), 2.32 (s, 3H), 1.97 (dt, J = 12.0, 8.8 Hz, 1H).
69	 (12R,14S)-18-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoro-12-methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,1⁴.0²⁰,2³]pentacosan-1(23),2(25),3,5,17(24),18,21-heptaen-11-one	1,3-dimethyl-1H-pyrazole-4-boronic acid, pinacol ester 62% yield as a beige solid	LCMS (MD) RT = 3.003 min m/z = 492.1 (M+H)⁺ LCMS (ME) RT = 3.590 min m/z = 492.1 (M+H)⁺. ¹H NMR (400 MHz, DMSO) d 8.93 (s, 1H), 8.54 (s, 1H), 7.91 (s, 1H), 7.70 (s, 1H), 6.77 (d, J = 9.3 Hz, 1H), 6.35 (t, J = 5.8 Hz, 1H), 6.22 (dd, J = 11.8, 2.1 Hz, 1H), 4.99 (d, J = 10.4 Hz, 1H), 4.54 (s, 1H), 4.34 (t, J = 8.8 Hz, 1H), 3.97 (t, J = 10.7 Hz, 1H), 3.84 (s, 3H), 3.64 - 3.52 (m, 2H), 3.46 (s, 3H), 3.43 - 3.36 (m, 1H), 3.28 - 3.19 (m, 2H), 2.27 (s, 3H), 1.97 (dd, J = 21.6, 8.8 Hz, 1H).

-119-

Example 70 : (12R,14S)-4-ethynyl-12-methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1².6.0¹⁰.14.0²⁰,²³]pentacosa-1(23),2(25),3,5,17(24),18,21-heptaen-11-one



5 Step 1

To a solution of tert-butyl (2S,4R)-2-(hydroxymethyl)-4-methoxy-pyrrolidine-1-carboxylate (4.674g, 20.21mmol) in dry DMF (65mL) was added sodium hydride, 60% in mineral oil (1.347g, 33.68mmol) at 0°C. After 30 min 3-Bromo-5-chloropyrazolo[1,5-a]pyrimidine (3.915g, 16.84mmol) was added and the mixture was stirred at 0 °C for 1h. Monitoring by LCMS
 10 showed complete reaction. Water was added dropwise carefully at 0°C and the mixture was extracted with EtOAc (4x50mL). The combined organic layer was washed with Brine then dried over Na₂SO₄, filtered and concentrated under vacuum. the residue was purified by flash column chromatography using Cyclohexane/EtOAc (100/0 to 60/40) as eluent to afford the title compound as a yellow oil (3.831g, 53% yield).
 15 LCMS (MA) RT = 2.73 min, m/z = 428 (M+H)⁺.

Step 2

A mixture of the title compound from Step 1 (0.327g, 0.77mmol), **Aniline A11** (0.356g, 0.99mmol), Xphos (0.015g, 0.03mmol), and K₃PO₄ (0.487g, 2.30mmol) were dissolved in 1,4-Dioxane/Water (3mL/1mL) and degassed with Argon during 15min.
 20 Tetrakis(triphenylphosphine)palladium(0) (0.018g, 0.02mmol) was added and the reaction mixture was stirred at 110°C for 3h. Monitoring of the reaction mixture by LCMS showed the reaction was completed. The reaction mixture was cooled down and filtered over Celite then solvent was evaporated. The residue was purified by column chromatography using
 25 Cyclohexane/EtOAc (100/0 to 50/50) as eluent to afford the title compound as a yellow oil (0.272g, 62%yield).
 LCMS (MA) RT = 3.55 min, m/z = 578 (M+H)⁺.

Step 3

To a solution of the title compound from Step 2 (0.272g, 0.47mmol) in Acetonitrile (3.4mL) were added Pyridine (0.057mL, 0.71mmol) and 2-Nitrobenzene-1-sulfonyl chloride (0.136g, 0.61mmol). The reaction mixture was stirred at rt overnight. Monitoring reaction by LCMS showed complete reaction. The solvent was removed under reduced pressure and the residue was poured into water (40mL) and EtOAc (80mL). The aqueous layer was extracted with
 35 EtOAc (3x40mL) and the organic layer was washed with Brine (2x40mL), dried (Na₂SO₄),

-120-

filtered and concentrated under reduced pressure to afford the title compound (0.485g, quantitative yield) as an orange solid.

LCMS (MA) RT = 3.72 min, m/z = 763.3 (M+H)⁺.

5 Step 4

To a solution of the title compound from Step 3 (0.485g, 0.64mmol) in Acetonitrile (4mL) were added Cesium carbonate (0.621g, 1.91mmol) and 1,2-Dibromoethane (0.822mL, 9.54mmol). The reaction mixture was heated to reflux for 4h. Monitoring of the reaction mixture by LCMS showed the reaction was completed. The mixture was taken in EtOAc (50mL) extracted with
10 Water (50mL) then Brine (2x40mL), the organic layer was dried over Na₂SO₄ anh. filtered and dried under vacuum. The residue was purified by column chromatography using Cyclohexane/EtOAc (100/0 to 60/40) as eluent to afford the title compound (0.301g, 54%yield) as a yellow oil.

LCMS (MA) RT = 3.82 min, m/z = 870 (M+H)⁺.

15

Step 5

To a suspension of the title compound from Step 4 (0.301g, 0.35mmol) in DCM (3mL) was added Hydrogen Chloride solution 4M in 1,4-Dioxane (0.865mL, 3.46mmol). The reaction mixture was left stirring overnight. LCMS showed complete reaction. The solvent was removed
20 under reduced pressure to afford the title compound as a yellow oil (0.489g, quantitative yield).
LCMS (MA) Rt = 2.60 min, m/z = 770 (M+H)⁺.

Step 6

To a solution of the title compound from Step 5 (0.489g, 0.35mmol postulated) in Acetonitrile
25 (48mL) were added Sodium hydrogenocarbonate (0.255g, 3.03mmol), Cesium carbonate (0.593g, 1.82mmol) then Potassium iodide (0.302g, 1.82mmol). The resulting mixture was heated at 90°C for 6h. Monitoring by LC/MS showed reaction was complete. The mixture was taken in EtOAc (50mL) washed with Water (50mL) and Brine (2x40mL). The organic layer was dried over Na₂SO₄ anh. filtered and dried under vacuum. The residue was purified on silica gel
30 column chromatography using Cyclohexane/EtOAc (100/0 to 50/50) as eluent to afford the title compound as a white solid (0.067g, 28% yield)solid.

LCMS (MA) RT = 3.31 min m/z = 689 (M+H)⁺.

Step 7

35 To a mixture of the title compound from Step 6 (0.067g, 0.10mmol) in THF/H₂O (5mL/2mL) was added Sodium bicarbonate (0.163g, 1.95mmol). The reaction mixture was stirred 10 min at room temperature then Iodine (0.370g, 1.46mmol) was added. The reaction mixture was stirred at 60°C for 2h. Monitoring by LC/MS showed complete reaction. The reaction mixture was quenched by saturated Sodium thiosulfate solution then extracted by ethyl acetate. The

-121-

organic layer was dried over anhydrous Sodium sulfate, filtered and evaporated under reduced pressure to afford the title compound as a purple solid (**Intermediate I32**, (12R,14S)-12-methoxy-7-(2-nitrobenzenesulfonyl)-4-[2-(triethylsilyl)ethynyl]-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.12,6.010,14.020,23]pentacosa-1(23),2,4,6(25),17(24),18,21-

5 heptaen-11-one, 0.150g, quantitative yield).

LCMS (MA) RT = 3.44 min, m/z = 703 (M+H)⁺.

Step 8

The title compound from Step 7 (150mg, 0.10mmol) and Cesium carbonate (139mg, 10 0.43mmol) were dissolved in *N,N*-Dimethylformamide (8mL). 4-Methylbenzenethiol (32mg, 0.26mmol) was added and the mixture was stirred at room temperature for 2h. The reaction mixture was filtered. Solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography using Dichloromethane/Methanol (100:0 to 98:2) as eluent) to afford the title compound (28mg, 25% yield) as a yellow solid.

15 LCMS (MA) RT = 3.34 min, m/z = 518 (M+H)⁺.

Step 9

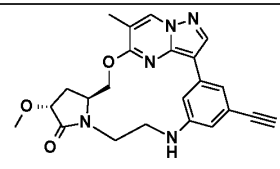
To a solution of the title compound from Step 8 (28mg, 0.05mmol) in Methanol (2mL) at room temperature, was added Potassium carbonate (37mg, 0.27mmol). The reaction mixture was 20 heated at 50°C for 16h. The reaction mixture was poured in water and extracted with Ethyl acetate. The organic layer was washed with Brine, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified by silica gel chromatography using Cyclohexane/EtOAc (100:0 to 80:20) as eluent to afford the expected product (17mg, 0.04mmol) as a beige powder.

25 LCMS (MA) RT = 2.25 min, m/z = 404 (M+H)⁺.

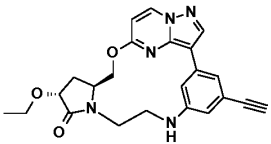
LCMS (MC) RT = 2.25 min, m/z = 404 (M+H)⁺.

¹H NMR (400 MHz, DMSO) 9.00 - 8.97 (1H, m), 8.56 - 8.56 (1H, m), 7.87 - 7.86 (1H, m), 7.04 (1H, s), 6.66 (1H, d, J=7.4 Hz), 6.57 - 6.55 (1H, m), 6.23 (1H, t, J=6.0 Hz), 4.96 - 4.92 (1H, m), 4.50 - 4.45 (1H, m), 4.36 - 4.31 (1H, m), 4.03 (1H, s), 3.95 (1H, t, J=10.8 Hz), 3.58 - 3.52 (1H, 30 m), 3.41 - 3.33 (1H, m), 3.32 - 3.31 (5H, m), 2.48 - 2.41 (1H, m), 2.00 - 1.94 (1H, m).

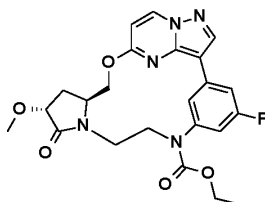
Similarly prepared:

Ex n°	Structure/ Name	From intermediates	Analytical data
71	 (12R,14S)-4-ethynyl-12-	Scaffold S2 Pyrrolidine P1 Aniline A11 16% yield as a beige solid	LCMS (MA) RT = 2.41 min, m/z = 418 (M+H)⁺. LCMS (MC) RT = 2.36 min, m/z = 418 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 8.90 (1H, d, J=1.1 Hz), 8.47 (1H, s), 7.85 (1H, d, J=1.1 Hz), 7.02 (1H, s), 6.56 - 6.54 (1H, m), 6.22 (1H,

-122-

	methoxy-18-methyl-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1 ² ,6.0 ^{1°} ,14.0 ^{2°} , ²³]pentacosan-1(23),2(25),3,5,17(24),18,21-heptaen-11-one		t, J=5.9 Hz), 4.98 - 4.95 (1H, m), 4.47 (1H, s), 4.38 - 4.33 (1H, m), 4.03 - 4.02 (2H, m), 3.54 (1H, dd, J=6.6, 11.0 Hz), 3.45 (3H, s), 3.36 - 3.35 (1H, m), 3.25 - 3.10 (2H, m), 2.45 - 2.40 (1H, m), 2.19 - 2.18 (3H, m), 2.00 - 1.91 (1H, m).
72	 (12R,14S)-12-ethoxy-4-ethynyl-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0^{1°},14.0^{2°},²³]pentacosan-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloropyrazolo[1,5-a]pyrimidine Pyrrolidine P2 Aniline A11 26% yield as a white solid	LCMS (MA) RT = 2.50 min, m/z=418.3 (M+H)⁺. LCMS (MC) RT = 2.47 min, m/z = 418.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 8.99 (1H, d, J=7.4 Hz), 8.56 (1H, s), 7.86 (1H, s), 7.04 (1H, s), 6.66 (1H, d, J=7.6 Hz), 6.57 - 6.55 (1H, m), 6.27 - 6.22 (1H, m), 4.96 - 4.90 (1H, m), 4.47 - 4.39 (2H, m), 4.04 (1H, s), 3.99 - 3.82 (2H, m), 3.61 - 3.49 (3H, m), 3.25 - 3.18 (2H, m), 2.46 - 2.41 (1H, m), 2.01 - 1.92 (1H, m), 1.15 (3H, t, J=7.0 Hz).

Example 73: Ethyl (12R,14S)-4-fluoro-12-methoxy-11-oxo-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0^{1°},14.0^{2°},²³]pentacosan-1(23),2,4,6(25),17(24),18,21-heptaene-7-carboxylate



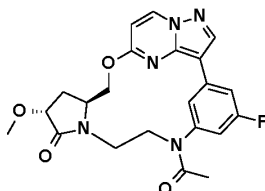
5

To a solution of **Example 3** (50mg, 0.13mmol) in Tetrahydrofuran (3mL) was added Triethylamine (53 μ L, 0.38mmol) and Ethyl chloroformate (36 μ L, 0.38mmol) dropwise. The solution was stirred at room temperature for 36h. Solvent was removed under reduced pressure. The residue was purified by preparative HPLC (Column XSELECT C18 19*100mm 5 μ m, [(NH₄)₂CO₃ aq 2 g/L / Acetonitrile] 45%B to 55%B in 7min - 19mL/min R.T) to afford the expected product (33mg, 56% yield) as a light yellow solid.

LCMS (MA) RT = 2.47 min, m/z = 470.2 (M+H)⁺.
LCMS (MC) RT = 2.47 min, m/z = 470.3 (M+H)⁺.
¹H NMR (400 MHz, DMSO) 9.02 (1H, d, J=7.4 Hz), 8.77 - 8.76 (1H, m), 8.54 (1H, s), 7.53 - 7.48 (1H, m), 7.37 - 7.31 (1H, m), 6.70 (1H, d, J=7.4 Hz), 5.06 (1H, d, J=11.2 Hz), 4.61 (1H, t, J=8.6 Hz), 4.37 - 4.17 (4H, m), 4.09 - 3.94 (2H, m), 3.63 - 3.52 (1H, m), 3.46 (3H, s), 3.41 (1H, d, J=12.2 Hz), 2.46 - 2.39 (1H, m), 2.00 - 1.88 (1H, m), 1.30 (3H, t, J=7.3 Hz).

-123-

Example 74: (12R,14S)-7-acetyl-4-fluoro-12-methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1².6.0¹⁰,¹⁴.0²⁰,²³]pentacosa-1(23),2,4,6(25),17(24),18,21-heptaen-11-one



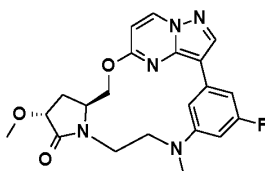
- 5 To a solution of **Example 3** (50mg, 0.13mmol) in Tetrahydrofuran (3mL) was added Triethylamine (70 μ L, 0.50mmol) and acetyl chloride (20 μ L, 0.28mmol) dropwise. The reaction mixture was stirred at room temperature for 48h. Solvent was removed under reduced pressure. The residue was purified by preparative HPLC. (Column XSELECT PHENYL-HEXYL 19*100mm 5 μ m [(NH₄)₂CO₃ aq. 2 g/L / Acetonitrile] 35%B to 45%B in 7min 19mL/min
- 10 R.T) to afford the expected product (40mg, 72% yield) as a white solid.

LCMS (MA) RT = 2.12 min, m/z = 440.2 (M+H)⁺.

LCMS (MC) RT = 2.13 min, m/z = 440.3 (M+H)⁺.

- ¹H NMR (400 MHz, DMSO) 9.03 (1H, d, J=7.6 Hz), 8.78 (1H, s), 8.62 (1H, s), 7.59 (1H, d, J=10.2 Hz), 7.25 (1H, s), 6.71 (1H, d, J=7.4 Hz), 5.06 (1H, d, J=10.6 Hz), 4.68 - 4.63 (1H, m),
- 15 4.33 (2H, t, J=8.9 Hz), 4.20 - 4.14 (1H, m), 3.98 (1H, t, J=10.9 Hz), 3.44 (3H, s), 3.35 (2H, s), 2.39 (1H, dd, J=8.1, 12.6 Hz), 2.20 (3H, s), 1.94 - 1.86 (1H, m).

Example 75: (12R,14S)-4-fluoro-12-methoxy-7-methyl-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1².6.0¹⁰,¹⁴.0²⁰,²³]pentacosa-1(23),2(25),3,5,17(24),18,21-heptaen-11-one



- To a solution of **Example 3** (50mg, 0.13mmol) in *N,N*-Dimethylformamide (5mL) under argon atmosphere was added sodium hydride, (60% dispersion in mineral oil) (10mg, 0.25mmol) at room temperature. After 30 min Iodomethane (0.117mL, 1.89mmol) was added and the
- 25 reaction mixture was stirred at room temperature for 2h. Additional sodium hydride (60% dispersion in mineral oil) (10mg, 0.25mmol) and Iodomethane (0.117mL, 1.89mmol) were successively added after 2h, 18h, 20h, 24h, 40h, 44h until total conversion of starting material. Water and ethyl acetate were added to the reaction mixture. After extraction with Ethyl acetate (3x 30ml), the combined organic phase was dried over anhydrous sodium sulfate, filtered and
- 30 concentrated under reduced pressure. Water and ethyl acetate were added to the reaction

-124-

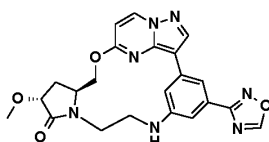
mixture. After extraction with ethyl acetate, the combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (Column XSELECT C18 19*100mm 5 μ m [(NH₄)₂CO₃ aq 2 g/L / Acetonitrile] 45%B to 50%B in 7min 19mL/min R.T) to afford the expected product (15mg, 29% yield) as a white solid.

LCMS (MA) RT = 2.42 min, m/z = 412 (M+H)⁺.

LCMS (MC) RT = 2.41 min, m/z = 412 (M+H)⁺.

¹H NMR (400 MHz, DMSO) 9.00 (1H, d, J=7.4 Hz), 8.56 (1H, s), 7.78 (1H, s), 6.83 (1H, d, J=9.9 Hz), 6.67 (1H, d, J=7.4 Hz), 6.33 (1H, d, J=12.9 Hz), 4.95 (1H, d, J=10.2 Hz), 4.49 - 4.46 (1H, m), 4.35 (1H, t, J=8.7 Hz), 3.96 (1H, t, J=10.5 Hz), 3.73 (2H, dd, J=12.6, 21.2 Hz), 3.46 (3H, s), 3.03 - 3.01 (3H, m), 2.00 - 1.91 (1H, m), 1.25 - 1.23 (2H, m), 0.87 - 0.83 (1H, m)

Example 76: (12R,14S)-12-methoxy-4-(1,2,4-oxadiazol-3-yl)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1².6.0¹⁰.14.0²⁰.23]pentacosa-1(23),2(25),3,5,17(24),18,21-heptaen-11-one



Following the general synthetic scheme 1, as depicted for the synthesis of Example 1,

(12R,14S)-12-methoxy-7-(2-nitrobenzenesulfonyl)-11-oxo-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.12.6.010.14.020.23]pentacosa-1(23),2(25),3,5,17(24),18,21-

heptaene-4-carbonitrile was obtained as **Intermediate I23** using **Scaffold 3-bromo-5-chloropyrazolo[1,5-a]pyrimidine**, **Pyrrolidine P1** and **Aniline A6**.

LCMS (MA) RT = 2.38 min, m/z = 590.2 (M+H)⁺.

Step 1

To a solution of **Intermediate I23** (589mg, 1mmol) in Ethanol/Water mixture (10mL/4mL) was added Sodium carbonate (318mg, 3mmol) and Hydroxylamine hydrochloride (271mg, 3.9mmol). The reaction mixture was stirred and heated to 65°C for 2h. The reaction mixture was cooled down and a precipitate appeared. The resulting precipitate was filtered and rinsed with cold diethyl ether then dried under reduced pressure to afford the title compound (520mg, 83% yield) as a yellow solid.

LCMS (MA) RT = 1.75 min, m/z = 623.2 (M+H)⁺.

Step 2

To a stirred solution of the title compound from Step 1 (520mg, 0.83mmol) in Tetrahydrofuran (5mL) was added Triethyl orthoformate (0.415mL, 2.5mmol). The mixture was cooled 0°C.

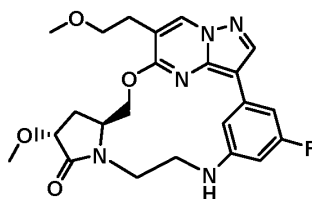
-125-

- Boron trifluoride ethyl etherate (0.123mL, 1mmol) was then added dropwise and the reaction mixture was stirred at ambient temperature for 16h. Additional Ethanol (5mL) and Triethyl orthoformate (0.415mL, 2.5mmol) were added and the mixture was heated to reflux for 24h. The reaction mixture was cooled down and the precipitate was filtered off and dried under reduced pressure. The residue was triturated with diethyl ether and dried to afford the title compound (454mg, 87% yield) as a cream solid.
- LCMS (MA) RT = 2.44 min, m/z = 633.1 (M+H)⁺.

Step3

- To the title compound from Step 2 (0.454g, 0.72mmol) in DMF (3mL) was added Cesium carbonate (469mg, 1.44mmol) and 4-Methylbenzenethiol (107mg, 0.86mmol), the reaction mixture was stirred at rt for 1h. Monitoring of the reaction mixture by LCMS showed the reaction was completed. The reaction mixture was adsorbed on silica and evaporated to dryness. The residue was purified by chromatography using DCM/MeOH (98/2 to 85/15) as eluent. The expected fractions were combined and evaporated under reduced pressure. The residue was triturated in MeOH, filtered and dried under vacuum to afford the expected product (99mg, 31%) as a cream solid.
- LCMS (MA) RT = 2.12 min, m/z = 448.1 (M+H)⁺.
- LCMS (MC) RT = 2.18 min, m/z = 448 (M+H)⁺.
- ¹H NMR (400 MHz, DMSO) 9.69 - 9.68 (1H, m), 9.02 - 8.99 (1H, m), 8.61 - 8.59 (1H, m), 7.99 (1H, s), 7.54 (1H, s), 7.20 (1H, s), 6.68 (1H, d, J=7.6 Hz), 6.49 (1H, t, J=6.0Hz), 4.96 (1H, d, J=11.2 Hz), 4.50 - 4.31 (2H, m), 3.96 (1H, t, J=10.6 Hz), 3.61 - 3.52 (1H, m), 3.46 (3H, s), 3.43 - 3.36 (1H, m), 3.32 - 3.25 (2H, m), 2.48 - 2.41 (1H, m), 2.02- 1.94 (1H, m);

- Example 77:** (12R,14S)-4-fluoro-12-methoxy-18-(2-methoxyethyl)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentacosa-1(23),2(25),3,5,17(24),18,21-heptaen-11-one



Step 1

- Pyrrolidine P1** (0.720 g, 3.113mmol) in 16mL of dry DMF (5mL/mmol) was added sodium hydride, 60% in mineral oil (C, 0.373 g, 9.339mmol), at 0°C, after 30 min **Scaffold S8** (1.043 g, 3.424mmol) was added and the mixture was stirred at 4-5°C for 15 min. Upon complete conversion, monitored by TLC, EtOAc was added and the mixture was quenched carefully by dropwise water at 0°C. Then, it was extracted with EtOAc (x3) and the combined organic

-126-

layers were dried over MgSO_4 , filtered and concentrated under vacuum. The product was purified by flash chromatography on silica gel using Heptane/EtOAc (100:0 to 60:40) as eluents to afford the expected compound as a yellow oil (2.253 g, 54.9% yield).

LCMS (MI) RT = 0.884 min, m/z = 499-401 (M+H)⁺-Boc.

5

Step 2

To a solution of the title compound from Step 1 (2.253 g, 4.512mmol) in Dichloromethane (7mL) was added Trifluoroacetic acid (7mL). The reaction mixture was stirred at room temperature for 16h. The solvent was evaporated under reduced pressure the title compound

10 (2.804 g, 100% yield) as a dark orange oil which was used without further purification.

LCMS (MI) RT = 0.303 min, m/z = 355-357 (M+H)⁺.

Step 3

To a solution of the title compound from Step 2 (2.804 g, 4.512mmol) in Dichloromethane (14mL) was added di-*tert*-butyl Dicarboxylate (2.954 g, 13.536mmol) followed by Triethylamine (1.887mL, 13.536mmol) at 0°C. The reaction mixture was stirred at room temperature for 1h. Solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (eluting solvent 70-30% Heptane/ethyl acetate) to afford the title compound

15 (1.332g, 65% yield) as a yellow solid.

20 LCMS (MH) RT = 0.987 min, m/z = 355-357 (M+H)⁺-Boc.

Step 4

To a solution of methoxymethyltriphenylphosphonium chloride (2.579 g, 7.524mmol) in dry THF (14mL) was added potassium bis(trimethylsilyl)amide solution (1M/THF) (12.54mL, 12.540mmol) in one portion at -78°C. The reaction mixture was stirred at -78°C for 1h. The title compound from Step 3 (1.142 g, 2.508mmol) in dry THF (9mL) was added dropwise and the reaction mixture was stirred at -78°C for 2h. Methyl-*tert*-butyl-ether and saturated aqueous sodium bicarbonate solution were added and the reaction mixture was warmed to room temperature. The reaction mixture was heated up to 60°C and stirred for 16h. The phases

25 were separated and the aqueous phase was extracted with MTBE. The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting gradient 0-30% Heptane/ethyl acetate) to afford the title compound (314mg, 26% yield) as a yellow sticky solid.

30 LCMS (MH) RT = 1.216 min, m/z = 483-485 (M+H)⁺.

Step 5

The title compound from Step 4 (0.300 g, 0.621mmol), **Aniline A1** (0.191 g, 0.807mmol), Potassium phosphate tribasic (0.264 g, 1.242mmol) and Xphos (0.030 g, 0.062mmol) were

-127-

mixed in Dioxane/water (4:1) (7mL/mmol) (4.30mL) and the mixture was bubbled with nitrogen for 5 min. Then, Tetrakis (triphenylphosphine)palladium(0) (C, 0.036 g, 0.031mmol) was added and the mixture was stirred at 90°C in a pressure flask for 16 hours. Water was added and the mixture was extracted with EtOAc (x2). The combined organic layers were dried over MgSO_4 ,
5 filtered and concentrated under vacuum giving the crude which was purified by flash chromatography on silica gel using Heptane/EtOAc (100:0 to 40:60) as eluents to afford the title compound (0.168 g, 52.68% yield) as a yellow solid.
LCMS (MH) RT = 1.107 min, m/z = 514.2 (M+H)⁺.

10 Step 6

To a solution of the title compound from Step 5 (168mg, 0.327mmol) in Ethyl acetate (33mL) under nitrogen atmosphere was added Pd/C 10% (67mg). The reaction mixture was stirred at room temperature under hydrogen atmosphere for 16h. Additional Palladium/C 10% (67mg)
15 was added and the reaction mixture was stirred at room temperature under hydrogen atmosphere for 16h. The reaction was filtered over Celite pad and washed with Dichloromethane/Methanol (4:1) mixture. The filtrate was concentrated under reduced pressure to afford the title compound (143mg, 85% yield) as an orange sticky solid, which was used in the next step without further purification.
LCMS (MH) RT = 1.029 min, m/z = 516.2 (M+H)⁺.

20

Step 7

A solution of the title compound from Step 6 (0.143 g, 0.277mmol) and Pyridine (0.066mL, 0.831mmol) in DCM (1.4mL, 5mL/mmol) was cooled to 0°C. Then, 2-nitrobenzenesulfonyl chloride (0.068 g, 0.305mmol) was added portionwise and the mixture was allowed to stir at
25 room temperature for 16 h. A solution of NaHCO_3 10% was added and the mixture was extracted with DCM (x2). The combined organic layers were dried over MgSO_4 , filtered and concentrated under vacuum. The product was purified by flash chromatography on silica gel using Heptane/EtOAc (100:0 to 20:80) as eluents to afford the title compound (0.136g, 70.1% yield) as a yellow solid.
30 LCMS (MH) RT = 1.173 min, m/z = 701.1 (M+H)⁺.

Step 8

1,2-Dibromoethane (0.364mL, 1.940mmol) was added to a stirred solution of the title compound from Step 7 (0.136 g, 0.194mmol) and Cesium carbonate (0.316 g, 0.970mmol) in
35 1.65mL of DMA (8.5mL/mmol). The mixture was stirred at 50°C for 16 hours. Water was added and the mixture was extracted with EtOAc (x2). The combined organic layers were dried over MgSO_4 , filtered and concentrated under vacuum affording the crude which was purified by flash chromatography on silica gel using Heptane/EtOAc (100:0 to 50:50) as eluents to afford the title compound (0.100 g, 63.8% yield) as a colorless sticky solid.

-128-

LCMS (MH) RT = 1.281 min, m/z = 707.0 - 708.9 (M+H)+-Boc.

Step 9

5 The title compound from Step 8 (0.100 g, 0.124mmol) was dissolved in Hydrochloric acid [4M] in Dioxane (2mL) and the resulting mixture was stirred at rt for 16 hours. The mixture was concentrated under vacuum co-evaporated with Heptane to afford the title compound (0.090 g) as an orange sticky solid. The crude was used in the next step without purification.

LCMS (MH) RT = 0.959 min, m/z = 707-709 (M+H)⁺.

10 Step 10

The title compound from Step 9 (0.087 g, 0.117mmol) in 12mL of Acetonitrile, Sodium hydrogen carbonate (0.098 g, 1.170mmol) and Potassium iodide (0.058 g, 0.351mmol) were added and the mixture was stirred at 90°C for 16 hours. Further Sodium hydrogen carbonate (0.098 g, 1.170mmol) and Potassium iodide (0.058 g, 0.351mmol) were added and the mixture
15 was stirred at 90°C for 16 hours. EtOAc and water were added and the product was extracted with EtOAc (x3). The combined organic layer was dried over MgSO₄, filtered and concentrated under vacuum affording the title compound (0.069 g) as a cream solid. The crude was used in the next step without purification.

LCMS (MI) RT = 0.803 min, m/z = 627.2 (M+H)⁺.

20

Step 11

To a mixture of the title compound from Step 10 (0.066 g, 0.105mmol) in THF:H₂O (2.5:1) (1.00mL) was added Sodium bicarbonate (0.176 g, 2.100mmol). The reaction mixture was stirred 10 min at room temperature. Then, Iodine (0.400 g, 1.575mmol) was added and stirred
25 at rt for 1 h. The mixture was diluted with EtOAc and washed with Sodium thiosulfate 10% aqueous solution. The aqueous phase was extracted with EtOAc (x3) and the combined organic layer was dried overmgSO₄, filtered and concentrated under vacuum. Finally, the product was purified on silica gel column chromatography using DCM/EtOAc (100:0 to 40:60) as eluents to afford the title compound (0.025 g, 37.2% yield) as a white solid.

30 LCMS (MH) RT = 1.041 min, m/z = 641.0 (M+H)⁺.

Step 12

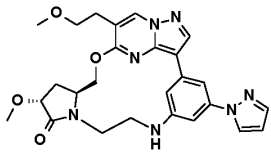
Thiophenol (0.013mL, 0.117mmol) was added to a suspension of the title compound from Step 11 (0.025 g, 0.039mmol) and Cesium carbonate (0.038 g, 0.117mmol) in 0.50mL of DMF at
35 0°C. The mixture was stirred at rt for 1 hour. EtOAc and water were added and the mixture was extracted with EtOAc (x2). The combined organic layers were dried overmgSO₄, filtered and concentrated under vacuum yielding the crude which was purified by flash chromatography on silica gel using Heptane/EtOAc (100:0 to 40:60) as eluents to afford the expected product (0.004 g, 22.52% yield) as a beige solid.

-129-

LCMS (MD) RT = 3.081 min, m/z = 456.2 (M+H)⁺.LCMS (MF) RT = 4.575 min, m/z = 456.2 (M+H)⁺.

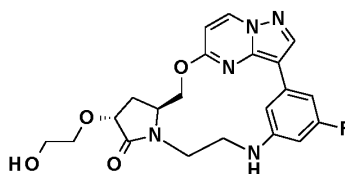
¹H NMR (400 MHz, DMSO) d 8.88 (s, 1H), 8.48 (s, 1H), 7.65 (s, 1H), 6.74 (d, J = 9.4 Hz, 1H), 6.32 (t, J = 5.8 Hz, 1H), 6.20 (dt, J = 11.8, 2.0 Hz, 1H), 4.98 (d, J = 10.5 Hz, 1H), 4.49 (t, J = 9.9 Hz, 1H), 4.36 (t, J = 8.9 Hz, 1H), 4.00 (t, J = 10.7 Hz, 1H), 3.60 (t, J = 6.5 Hz, 2H), 3.55 (dd, J = 11.9, 7.2 Hz, 1H), 3.45 (s, 3H), 3.42 – 3.34 (m, 1H), 3.28 (s, 3H), 3.26 – 3.16 (m, 2H), 2.83 (t, J = 6.5 Hz, 2H), 2.48 – 2.42 (m, 1H), 1.96 (dt, J = 11.7, 8.8 Hz, 1H).

Similarly prepared:

Ex n°	Structure/ Name	From intermediates	Analytical data
78	 (12R,14S)-12-methoxy-18-(2-methoxyethyl)-4-(1H-pyrazol-1-yl)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,²³]pentacos-1(23),2(25),3,5,17(24),18,21-heptaen-11-one	Scaffold S8 Pyrrolidine P1 Aniline A15 45% yield as a beige solid	LCMS (MD) RT = 2.938 min, m/z = 504.2 (M+H)⁺. LCMS (MF) RT = 4.533 min, m/z = 504.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO) d 8.89 (s, 1H), 8.56 (s, 1H), 8.45 (d, J = 2.3 Hz, 1H), 7.76 (s, 1H), 7.71 (d, J = 1.5 Hz, 1H), 7.35 (s, 1H), 6.97 (t, J = 2.0 Hz, 1H), 6.58 – 6.46 (m, 1H), 6.35 (t, J = 5.8 Hz, 1H), 4.99 (d, J = 10.4 Hz, 1H), 4.51 (brs, 1H), 4.37 (t, J = 8.9 Hz, 1H), 4.09 – 3.92 (m, 1H), 3.61 (t, J = 6.5 Hz, 2H), 3.56 (d, J = 13.1 Hz, 1H), 3.46 (s, 3H), 3.44 – 3.36 (m, 1H), 3.33 (s, 3H), 3.26 (d, J = 6.1 Hz, 2H), 2.84 (t, J = 6.5 Hz, 2H), 2.49 – 2.41 (m, 2H).

10

Example 79: (12R,14S)-4-fluoro-12-(2-hydroxyethoxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,²³]pentacos-1(23),2(25),3,5,17(24),18,21-heptaen-11-one



Following the general synthetic scheme 1, as depicted for the synthesis of Example 1, (12R,14S)-12-[2-(benzyloxy)ethoxy]-4-fluoro-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,²³]pentacos-1(23),2,4,6(25),17(24),18,21-heptaen-11-one was obtained as **Intermediate I24** using **Scaffold 3-bromo-5-chloropyrazolo[1,5-a]pyrimidine**, **Pyrrolidine P8** and **Aniline A1**.

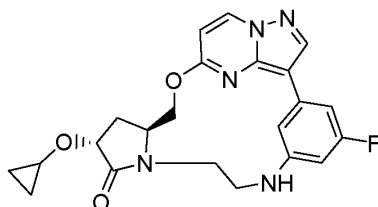
20

-130-

Step 1

- To a solution of **Intermediate I24** (100mg, 0.193mmol) in Ethyl acetate (2mL) under nitrogen atmosphere was added 10% Palladium/C (20mg). The reaction mixture was stirred at room temperature under hydrogen atmosphere for 16h. Additional palladium/C 10% (67mg) was added and the reaction mixture was stirred at room temperature under hydrogen atmosphere for 16h. The crude was filtered off over a Celite pad rinsing with ethyl acetate, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting gradient 0-2% Dichloromethane/methanol) to afford the expected product (40mg, 48.49% yield) as a white solid.
- LCMS (MG) RT = 2.813 min, m/z = 428.1 (M+H)⁺.
 LCMS (MF) RT = 4.652 min, m/z = 428.1 (M+H)⁺.
¹H NMR (400 MHz, DMSO) δ 8.98 (d, J = 7.5 Hz, 1H), 8.53 (s, 1H), 7.67 (s, 1H), 6.79 - 6.70 (m, 1H), 6.66 (d, J = 7.5 Hz, 1H), 6.33 (t, J = 5.8 Hz, 1H), 6.21 (dt, J = 11.8, 2.1 Hz, 1H), 4.93 (d, J = 10.9 Hz, 1H), 4.71 (t, J = 5.5 Hz, 1H), 4.56 - 4.36 (m, 2H), 3.95 (t, J = 10.8 Hz, 1H), 3.82 (dt, J = 9.6, 4.7 Hz, 1H), 3.62 - 3.47 (m, 4H), 3.45 - 3.34 (m, 1H), 3.27 - 3.12 (m, 2H), 2.44 (dd, J = 12.7, 8.2 Hz, 1H), 2.05 - 1.90 (m, 1H).

- Example 80:** (12R,14S)-12-cyclopropoxy-4-fluoro-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1².6.0¹⁰.14.0²⁰,²³]pentacos-1(23),2(25),3,5,17(24),18,21-heptaen-11-one



Step 1

- To a solution of **Pyrrolidine P9** (0.500 g, 1.943mmol) in dry DMF (10mL) was added Sodium hydride, 60% in mineral oil (0.233 g, 5.829mmol), at 0°C. After 30min stirring, 3-bromo-5-chloropyrazolo[1,5-a]pyrimidine (0.903 g, 3.886mmol) was added and the mixture was stirred at 4-5°C for 30 min. Water was added dropwise carefully at 4-5°C and the mixture was extracted with EtOAc (x4). The combined organic layers were dried over mgSO₄, filtered and concentrated under vacuum. The product was purified on column of silica gel using as eluent Heptane/EtOAc (from 100:0 to 85:15) to afford the title compound (0.471g, yield: 53.47%) as yellowish gum.
- LCMS (MH) RT = 1.142 min, m/z = 353.0 (M-100)

-131-

Step 2

In a pressure flask the title compound from Step 1 (0.450 g, 0.993mmol), **Aniline A1** (0.283 g, 1.192mmol), and K_3PO_4 (0.632 g, 2.979mmol) were mixed in Dioxane/ H_2O (4:1) (6mL), and the reaction mixture was bubbled with a Nitrogen stream for 5 min.

5 Tetrakis(triphenylphosphine)palladium(0) (0.070 g, 0.060mmol) and Xphos (0.057 g, 0.119mmol) were added and the mixture was stirred at 80°C for 16 hours. Upon complete conversion, monitored by LCMS, water was added and extracted with EtOAc (x3). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography (on silica gel) using DCM/MeOH as eluents (100:0 to 97:3) to afford the title compound (0.291g, 61% yield) as a brown solid.

10 LCMS (MH) RT = 1.082 min, m/z = 484.1 (M+H)⁺.

Step 3

A solution of the title compound from Step 2 (0.293g, 0.606mmol) and Pyridine (0.13mL, 1.82mmol) in DCM (3mL) was cooled down to 0°C, then 2-Nitrobenzenesulfonyl chloride (0.15 g, 0.67mmol) was added dropwise and the mixture was allowed to stir at room temperature for 16h. An aqueous solution of $NaHCO_3$ (10%) was added and the mixture was extracted with DCM (x3). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography (on silica gel) using DCM/MeOH as eluents (100:0 to 96:4) to afford the title compound (0.370 g, 91.3% yield) as a brown gum.

20 LCMS (MH) RT = 1.215 min, m/z = 569.0 (M+H)⁺.

Step 4

25 The title compound from Step 3 (0.360 g, 0.538mmol) was dissolved in DMA (18mL, 33mL/mmol). Then Cesium carbonate (0.876 g, 2.69mmol) and 1,2-Dibromoethane (0.464mL, 5.380mmol) were added and stirred at 50°C for 16 hours. Upon complete conversion, monitored by LCMS, water was added and extracted with EtOAc (x3). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude

30 was purified by flash chromatography using DCM/MeOH as eluents (100:0 to 98:2) to afford the title compound (0.380 g, 91.06% yield) as a brown solid.

LCMS (MH) RT = 1.342 min, m/z = 675.0/677.0 (M-100).

Step 5

35 The title compound from Step 4 (0.357 g, 0.460mmol) was cooled down to 0°C. DCM/TFA 1:1 (4mL) was added and stirred from 0°C to rt for 16 hours. The reaction mixture was concentrated under reduced pressure to afford the title compound as crude brown sticky solid (0.320 g), was used as such in the next step without further purification.

LCMS (MH) RT = 0.901 min, m/z = 675.0/677.0 (M+H)⁺.

-132-

Step 6

To a solution of the title compound from Step 5 (crude, 0.36g, 0.46mmol) in Acetonitrile (138mL), Sodium hydrogen carbonate (0.386 g, 4.600mmol) and Potassium iodide (0.076 g, 0.460mmol) were added and the mixture was stirred at 90°C for 16 hours. Water was added and extracted with EtOAc (x3). The combined organic phases were dried over MgSO_4 , filtered and concentrated under reduced pressure. The crude was purified by flash chromatography (on silica gel) using DCM/MeOH as eluents (100:0 to 98:2) to afford the title compound (0.202 g, 73.8% yield) as a yellow solid.

LCMS (MH) RT = 1.047 min, m/z = 595.0 (M+H)⁺.

10

Step 7

To the mixture of the title compound from Step 6 (0.125 g, 0.210mmol) in DMF (5mL) was added Cesium carbonate (0.205 g, 0.630mmol). The mixture was cooled in a bath of ice/water, and then, Thiophenol (0.065mL, 0.630mmol) was added. The mixture was stirred at room temperature for 30 minutes. The mixture was diluted with EtOAc, water was added and the mixture was extracted with EtOAc (x4). The combined organic layers were dried over MgSO_4 , filtered and concentrated under vacuum. The crude was purified by flash chromatography on silica gel, using as eluents DCM/MeOH (from 100:0 to 97.5:2.5), to afford the title compound (0.068 g, 79.08% yield) as yellowish solid.

LCMS (MH) RT = 0.710 min, m/z = 410.1 (M+H)⁺.

Step 8

To a solution of the title compound from Step 7 (0.058 g, 0.142mmol) in THF:H₂O (9:1) (8.5mL) was added Sodium bicarbonate (0.179 g, 2.130mmol). The reaction mixture was stirred 10 min at room temperature. Then, Iodine (0.252 g, 0.994mmol) was added and stirred at room temperature. LCMS showed the partial conversion. The mixture was heated at 50°C and stirred for 6h. The mixture was diluted with EtOAc, water was added and the mixture was extracted with EtOAc (x4). The combined organic layers were dried over MgSO_4 , filtered and concentrated under vacuum. The crude was purified by flash chromatography on silica gel, using as eluents DCM/MeOH (from 100:0 to 90:10) to afford the title compound (0.019 g) contaminated with di-iodo derivative as yellowish solid.

LCMS (MH) RT = 0.710 min, m/z = 410.1 (M+H)⁺.

Step 9

A vial equipped with a magnetic stir bar was charged with the title compound from Step 8 (0.005g, 0.009mmol) and $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbpy})]\text{PF}_6$ (0.001g, 0.0009mmol). Acetonitrile (0.2mL) was added to the vial followed by DIPEA (0.006g, 0.036mmol) followed by Tris(trimethylsilyl)silane (0.006g, 0.018mmol). The mixture was stirred keeping the vial open to air and then illuminated with a 42W blue LED strip for 45min. The temperature near the

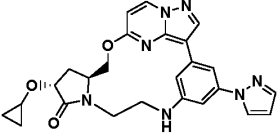
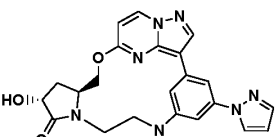
surface of the vial was 40°C. Upon completion, monitored by LCMS, solvent was removed under reduced pressure and the crude was purified on column of silica gel using DCM/MeOH (98:2) as eluents to afford the expected product (4.2mg, 55%) as white solid.

LCMS (MD) RT = 3.250 min, m/z = 424.1 (M+H)⁺.

- 5 ¹H NMR (400 MHz, CDCl₃): 8.51 (d, J = 7.5 Hz, 1H), 8.26 (s, 1H), 7.69 (s, 1H), 6.69 (d, J = 9.6 Hz, 1H), 6.41 (d, J = 7.5 Hz, 1H), 6.24 (d, J = 10.8 Hz, 1H), 5.06 (d, J = 11.0 Hz, 1H), 3.91 - 3.83 (m, 1H), 3.81 (dd, J = 6.1, 3.0 Hz, 1H), 3.76 (t, J = 10.8 Hz, 1H), 3.63 - 3.50 (m, 3H), 3.26 (t, J = 11.5 Hz, 1H), 2.61 (dd, J = 13.1, 8.1 Hz, 1H), 2.14 (dd, J = 21.9, 9.0 Hz, 2H), 0.90 - 0.81 (m, 1H), 0.80 - 0.73 (m, 1H), 0.70 - 0.63 (m, 1H), 0.60 - 0.48 (m, 2H).

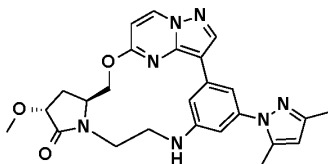
10

Similarly prepared:

Ex n°	Structure/ Name	From intermediates	Analytical data
81	 (12R,14S)-12-cyclopropoxy-4-(1H-pyrazol-1-yl)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]pentacos-1(23),2(25),3,5,17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloropyrazolo[1,5-a]pyrimidine Pyrrolidine P9 Aniline A15 5.1mg, 47% yield	LCMS (MD) RT = 3.092 min, m/z = 472.2 (M+H)⁺. LCMS (ME) RT = 3.472 min, m/z = 472.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO) d 9.00 (d, J = 7.5 Hz, 1H), 8.63 (s, 1H), 8.45 (d, J = 2.4 Hz, 1H), 7.79 (s, 1H), 7.71 (d, J = 1.6 Hz, 1H), 7.36 (s, 1H), 6.98 (t, J = 1.9 Hz, 1H), 6.67 (d, J = 7.5 Hz, 1H), 6.56 - 6.50 (m, 1H), 6.36 (t, J = 5.8 Hz, 1H), 4.95 (d, J = 10.8 Hz, 1H), 4.57 - 4.48 (m, 1H), 4.02 (t, J = 10.8 Hz, 1H), 3.74 (ddd, J = 9.2, 6.0, 3.0 Hz, 1H), 3.58 (dd, J = 21.6, 10.0 Hz, 2H), 3.49 - 3.37 (m, 2H), 3.30 - 3.21 (m, 1H), 2.49 - 2.40 (m, 1H), 2.05 - 1.92 (m, 1H), 0.68 - 0.55 (m, 2H), 0.51 (dd, J = 12.0, 4.0 Hz, 2H).
82	 (12R,14S)-12-hydroxy-4-(1H-pyrazol-1-yl)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]pentacos-1(23),2(25),3,5,17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloropyrazolo[1,5-a]pyrimidine Pyrrolidine P9 Aniline A15 4.7mg, 47% yield	LCMS (MD) RT = 2.452 min, m/z = 432.1 (M+H)⁺. LCMS (ME) RT = 2.947 min, m/z=432.1 (M+H)⁺. ¹H NMR (400 MHz, DMSO) d 9.00 (d, J = 7.5 Hz, 1H), 8.63 (s, 1H), 8.45 (d, J = 2.2 Hz, 1H), 7.81 (d, J = 1.5 Hz, 1H), 7.71 (d, J = 1.5 Hz, 1H), 7.36 (s, 1H), 6.98 (t, J = 2.0 Hz, 1H), 6.68 (d, J = 7.5 Hz, 1H), 6.58 - 6.50 (m, 1H), 6.35 (t, J = 5.8 Hz, 1H), 5.61 (brs, 1H), 4.95 (d, J = 11.0 Hz, 1H), 4.48 (t, J = 9.0 Hz, 2H), 3.98 (t, J = 10.8 Hz, 1H), 3.58 (dt, J = 12.6, 8.6 Hz, 1H), 3.50 - 3.40 (m, 1H), 3.28 - 3.17 (m, 2H), 2.39 (dd, J = 12.5, 8.2 Hz, 1H), 2.00 - 1.85 (m, 1H).

-134-

Example 83: (12R,14S)-4-(3,5-dimethyl-1H-pyrazol-1-yl)-12-methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1².6.0¹⁰,14.0²⁰,23]pentacosa-1(23),2(25),3,5,17(24),18,21-heptaen-11-one



5 Following the general synthetic scheme 1, as depicted for the synthesis of Example 1, (12R,14S)-4-(4-iodo-3,5-dimethyl-1H-pyrazol-1-yl)-12-methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1².6.0¹⁰,14.0²⁰,23]pentacosa-1(23),2,4,6(25),17(24),18,21-heptaen-11-one was obtained as **Intermediate I25** using **Scaffold 3-bromo-5-chloropyrazolo[1,5-a]pyrimidine**, **Pyrrolidine P1** and **Aniline A16**.

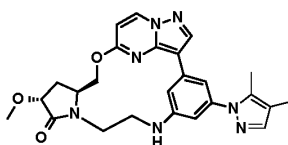
10

Step 1

To a solution of **Intermediate I25** (93mg, 0.155mmol) in Acetonitrile (4mL), was added *N,N*-Diisopropylethylamine (0.379mL, 2.17mmol) followed by Tris(trimethylsilyl)silane (0.385mL, 1.240mmol) and (Ir[dF(CF₃)ppy]₂(dtbpy))PF₆ (18mg, 0.016mmol). The reaction mixture was stirred keeping the vial open to air and then illuminated with a 42 W blue LED strip for 2h. The mixture was diluted with Ethyl acetate, water was added and the reaction mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting gradient 0-2% Dichloromethane/methanol) to afford the expected product (55mg, 75% yield) as a beige solid.

LCMS (MD) RT = 2.881 min, m/z = 474.2 (M+H)⁺.
 LCMS (ME) RT = 3.361 min, m/z = 474.2 (M+H)⁺.
¹H NMR (400 MHz, DMSO) δ 8.91 (d, J = 7.5 Hz, 1H), 8.50 (s, 1H), 7.75 (s, 1H), 6.89 (s, 1H), 6.58 (d, J = 7.5 Hz, 1H), 6.46 (t, J = 2.0 Hz, 1H), 6.22 (t, J = 5.8 Hz, 1H), 5.95 (s, 1H), 4.88 (d, J = 10.9 Hz, 1H), 4.26 (t, J = 8.9 Hz, 1H), 3.88 (t, J = 10.7 Hz, 1H), 3.48 (dt, J = 12.7, 8.9 Hz, 1H), 3.35 - 3.29 (m, 1H), 3.24 (s, 3H), 3.21 (s, 1H), 3.20 - 3.11 (m, 2H), 2.36 (dd, J = 12.6, 8.2 Hz, 1H), 2.23 (s, 3H), 2.09 (s, 3H), 1.89 (dt, J = 12.1, 8.9 Hz, 1H).

Example 84: (12R,14S)-4-(4,5-dimethyl-1H-pyrazol-1-yl)-12-methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1².6.0¹⁰,14.0²⁰,23]pentacosa-1(23),2(25),3,5,17(24),18,21-heptaen-11-one



-135-

Step 1

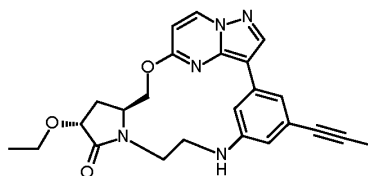
Intermediate I17 (60mg, 0.102mmol), Methylboronic acid (18mg, 0.306mmol), Potassium phosphate tribasic (65mg, 0.306mmol) were mixed in Dioxane/water (4:1) (1.8mL). The reaction mixture was bubbled with nitrogen for 5min and [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (5mg, 0.006mmol) was added. The reaction mixture was stirred at 80°C in a pressure flask for 6h. Water was added and the mixture was extracted with Ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (Purification method PB) 70% [25mM NH₄HCO₃] - 30% [Acetonitrile: MeOH 1:1] 27% [25mM NH₄HCO₃] - 73% [Acetonitrile: MeOH 1:1] to afford the expected product (26mg, 53% yield) as a white solid.

LCMS (MD) RT = 3.093 min, m/z = 474.2 (M+H)⁺.

LCMS (ME) RT = 3.450 min, m/z = 474.2 (M+H)⁺.

¹H NMR (400 MHz, DMSO) δ 9.00 (d, J = 7.5 Hz, 1H), 8.58 (s, 1H), 7.85 (s, 1H), 7.40 (s, 1H), 6.98 (s, 1H), 6.68 (d, J = 7.5 Hz, 1H), 6.53 (t, J = 1.9 Hz, 1H), 6.34 (t, J = 5.9 Hz, 1H), 4.97 (d, J = 10.8 Hz, 1H), 4.52 (t, J = 8.5 Hz, 1H), 4.35 (t, J = 8.9 Hz, 1H), 3.57 (dd, J = 16.4, 5.9 Hz, 1H), 3.46 (s, 3H), 3.44 – 3.38 (m, 1H), 3.30 – 3.16 (m, 2H), 2.47 – 2.39 (m, 2H), 2.26 (s, 3H), 2.02 (s, 3H), 1.97 (dd, J = 12.5, 9.0 Hz, 1H)

Example 88: (12R,14S)-12-methoxy-4-(prop-1-yn-1-yl)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentacos-1(23),2,4,6(25),17(24),18,21-heptaen-11-one



Step 1

In a microwave vial (5mL), **Example 20** (205mg, 0.5mmol) was suspended in Acetonitrile (5mL). At room temperature, were added Xphos (50mg, 0.1mmol) and Cesium carbonate (490mg, 1.5mmol). The resulting mixture was degassed by bubbling Argon for 10 min before addition of Bis(acetonitrile)dichloropalladium(II) (15mg, 0.05mmol). The reaction mixture was stirred 10 min at room temperature. Then, Trimethyl(propargyl)silane (0.375mL, 2.5mmol) was added. The reaction vessel was sealed and heated for 5hr under microwave irradiation using Biotage Initiator at 120°C. Monitoring by LCMS showed the reaction was completed. The reaction mixture was adsorbed on silica and purified by silica gel column chromatography using DCM/MeOH (100/0 to 9/1) as eluent. The expected fractions were combined and evaporated under reduced pressure. The residue was recrystallized in EtOH twice. The expected

-136-

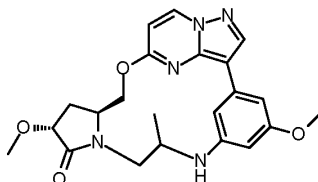
product was obtained as a cream-colored solid (35mg, 0.08mmol, 17%).

LCMS (MA) RT = 2.28 min, m/z = 418.4 (M+H)⁺.

LCMS (MC) RT = 2.28 min, m/z = 418.4 (M+H)⁺.

¹H NMR (400 MHz, DMSO) 9.00 - 8.96 (1H, m), 8.55 - 8.53 (1H, m), 7.79 - 7.76 (1H, m), 6.96 (1H, s), 6.67 - 6.63 (1H, m), 6.49 - 6.47 (1H, m), 6.18 - 6.17 (1H, m), 4.94 (1H, t, J=10.3 Hz), 4.46 (1H, s), 4.33 (1H, t, J=8.7 Hz), 3.94 (1H, t, J=10.6 Hz), 3.54 (1H, d, J=18.3 Hz), 3.35 - 3.32 (6H, m), 2.46 - 2.40 (1H, m), 2.05 - 2.01 (4H, m)

Example 89: (12R,14S)-4,12-dimethoxy-8-methyl-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentacos-1(23),2,4,6(25),17(24),18,21-heptaen-11-one



Step 1

To a suspension Sodium hydride, 60% in oil (3.2g, 80.0mmol) in dry THF (25mL) was added at 0°C a solution of Pyrrolidine P1 (9.25 g, 40.0mmol) in THF (25mL). After 30 min, 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine (9.3g, 40.01mmol) was added and the mixture was stirred at 0°C for 15 min, and then at rt for 4h. The mixture was carefully diluted with water and EtOAc (250ml) was added. The layers were separated. The aqueous layer was extracted with EtOAc (2x100mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to afford the title compound as a yellow (17g, 39.79mmol, 99 %).

LCMS (MA) RT = 2.84 min, m/z = 429.1 (M+H)⁺.

Step 2

To a suspension of the title compound from Step 1 (3.33 g, 7.79mmol) in Acetonitrile (10mL) was added HCl in 1,4-Dioxane 4M (9.75mL, 38.9mmol). The mixture was stirred at room temperature for 1h. The solvent was evaporated under reduced pressure to afford the title compound as a yellow foam (2.83g), which was directly engaged in the next step without further purification.

LCMS (MA) RT = 1.29 min, m/z = 329.1 (M+H)⁺.

Step 3

To a solution of the title compound from Step 2 (363mg, 1mmol) in DCM (20mL) was added Triethylamine (0.418mL, 3mmol). The resulting mixture was stirred at room temperature for

-137-

- 15min then 2-(tert-Butyldimethylsilyloxy)propanal was added (375mg, 1.2mmol). After further stirring for 15 min was added Sodium triacetoxyborohydride (318mg, 1.5mmol). The reaction mixture was left stirring at room temperature for 3hr. Monitoring of the reaction mixture by LCMS showed the reaction was completed. The reaction mixture was diluted in DCM (50ml) and water was added. The water layer was extracted with DCM. The combined organic layers were washed with saturated Brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude was purified by flash chromatography using Cyclohexane/EtOAc (100/0 to 6/4) as eluent to afford the title compound as a colorless oil (0.39g, 79%).
- 10 LCMS (MA) RT = 2.20 min, m/z = 421.1 (M+H)⁺.

Step 4

- To a solution of the title compound from Step 3 (3.06g, 6.12mmol) in Dioxane/water (30/7mL) was added **Aniline A3** (1.98g, 7.96mmol), Tetrakis(triphenylphosphine)palladium(0) (139mg, 0.12mmol), Xphos (114mg, 0.24mmol) and Potassium phosphate tribasic (3.9g, 18.36mmol).
- 15 The reaction mixture was degassed by bubbling under argon for 15 min and stirred at 90°C for 4h. Upon complete conversion, monitored by LCMS, the mixture was allowed to cooled to room temperature and was diluted with water and EtOAc. Layers were separated and the water layer was extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography using Cyclohexane/EtOAc-EtOH (3:1) (100:0 to 6:4) as eluent to afford the title compound as a yellow oil (3.21g, 97%).
- 20 LCMS (MA) RT = 2.04 min, m/z = 542.4 (M+H)⁺.

25 Step 5

- To a solution of the title compound from Step 4 (3.21g, 5.9mmol) in Acetonitrile (45mL) was added Pyridine (0.62mL, 7.7mmol) and 2-nitrobenzenesulfonyl chloride (1.44 g, 6.5mmol) portionwise. The reaction mixture was stirred at room temperature for 2h. Upon complete conversion, monitored by LCMS, the solvent was evaporated under reduced pressure. The crude was purified by flash chromatography using Cyclohexane/EtOAc-EtOH (3:1) (100:0 to 6:4) as eluent to afford the title compound as a yellow foam (3.8g, 88%).
- 30 LCMS (MA) RT = 2.49 min, m/z = 727.3 (M+H)⁺.

Step 6

- 35 To a solution of the title compound from Step 5 (3.8g, 5.23mmol) in THF (100mL) was added a solution of TBAF (5.75mL, 5.75mmol). The reaction mixture was stirred at room temperature for 72h. Upon complete conversion, monitored by LCMS, the solvent was evaporated under reduced pressure. The crude was purified by flash chromatography using DCM/MeOH (100/0 to 9/1) as eluent to afford the title compound as a yellow foam (3.62g, 100%).

-138-

LCMS (MA) RT = 1.78 min, m/z = 613.3 (M+H)⁺.

Step 7

A solution of the title compound from Step 6 (3.31g, 5.4mmol) in THF (30mL) and a solution of DIAD (3.18mL, 16.2mmol) in Toluene (30mL) were added dropwise (over 1hr) and simultaneously to a solution of Triphenylphosphine (4.25g, 16.2mmol) in Toluene (300mL) heated at 90°C. The reaction mixture was heated at 90°C for 1h. Upon complete conversion, monitored by LCMS, solvents were removed under reduced pressure and the crude was purified by column chromatography using DCM/MeOH (100/0 to 9/1) as eluent. The purification was repeated using Cyclohexane/ EtOAc-EtOH (3:1) (100/0 to 3/7) as eluent to afford the title compound as a cream foam (700mg, 22% yield).

LCMS (MA) RT = 2.05 min, m/z = 595.2 (M+H)⁺.

Step 8

To a solution of the title compound from Step 7 (700mg, 1.17mmol) in Acetonitrile/water (60mL/20mL) was added Sodium bicarbonate (0.98g, 11.7mmol). The reaction mixture was stirred 30min at 45°C, then Iodine (1.9 g, 8.77mmol) was added. The reaction mixture was stirred at 45°C for 3h. Upon complete conversion, monitored by LCMS, the reaction mixture was quenched by a saturated Sodium thiosulfate solution (100mL). To the mixture was added DCM (200mL), which was extracted with water (100mL) and Brine (100mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The crude was purified by column chromatography using DCM/MeOH (100/0 to 9/1) as eluent to afford the title compound as a cream solid (0.5g, 70% yield).

LCMS (MA) RT = 2.50 min, m/z = 609.2 (M+H)⁺.

Step 9

To a suspension of the title compound from Step 8 (0.5g, 0.82mmol) in THF/Acetonitrile (40mL/4mL) was added Cesium carbonate (0.53g, 1.64mmol) and 4-Methylbenzenethiol (0.12g, 0.98mmol). The reaction mixture was stirred at room temperature overnight. The mixture was filtered and evaporated under reduced pressure. The crude was purified by flash chromatography using DCM/MeOH (100:0 to 90:10) as eluent. The expected fractions were combined and evaporated under reduced pressure. The residue was triturated in Diethylether/Acetonitrile (98/2) to afford the expected product as a cream solid (0.18g, 52% yield).

LCMS (MA) RT = 2.09 min, m/z = 424.4 (M+H)⁺.

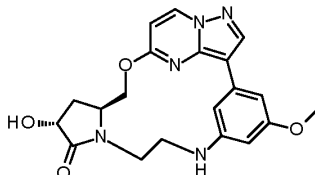
LCMS (MC) RT = 2.90 min, m/z = 424.4 (M+H)⁺.

¹H NMR (400 MHz, DMSO) 8.99 - 8.95 (1H, m), 8.60 - 8.60 (1H, m), 7.98 (1H, s), 6.65 (1H, d, J=7.7 Hz), 6.61 - 6.59 (1H, m), 6.14 - 6.10 (1H, m), 6.03 (1H, t, J=2.1 Hz), 5.30 - 5.25 (1H, m), 4.39 - 4.33 (1H, m), 4.23 - 4.19 (1H, m), 4.08 (1H, t, J=11.4 Hz), 3.75 (1H, d, J=12.6 Hz), 3.63 - 3.55 (1H, m), 3.45 - 3.44 (6H, m), 2.47 - 2.41 (1H, m), 2.02 - 1.94 (1H, m), 1.28 (3H, d, J=6.8

-139-

Hz), 1.15 - 1.12 (1H, m)

Example 90: (12R,14S)-12-hydroxy-4-methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0^{1°},14.0^{2°},23]pentacosa-1(23),2,4,6(25),17(24),18,21-heptaen-11-one



5 Following the general synthetic scheme 1, as depicted for the synthesis of Example 1, (12R,14S)-4-methoxy-7-(2-nitrobenzenesulfonyl)-12-(prop-2-en-1-yloxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.12,6.010,14.020,23]pentacosa-1(23),2,4,6(25),17(24),18,21-heptaene was obtained as **Intermediate I26** using **Scaffold 3-bromo-5-chloropyrazolo[1,5-a]pyrimidine**, **Pyrrolidine P13** and **Aniline A3**.
 10 LCMS (MA) RT = 2.29 min, m/z = 607.2 (M+H)⁺.

Step 1

Under argon, to a suspension of **Intermediate I26** (315mg, 0.52mmol) in EtOH/TFA
 15 (4.5/0.4mL) was added Tetrakis(triphenylphosphine)palladium(0) (120mg, 0.10mmol). The reaction mixture was stirred at 80°C for 14 h. Upon complete conversion, monitored by LCMS, the reaction mixture was cooled to room temperature and was carefully quenched with a saturated solution of NaHCO₃. An emulsion was observed so the mixture was filtered and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 15mL) and the
 20 combined organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified on silica gel column using Cyclohexane/(EtOAc/EtOH 3:1) (100:0 to 50:50) as eluent to afford the title compound as an orange foam (184mg, 62% yield).
 LCMS (MA) RT = 1.80 min, m/z = 567.1 (M+H)⁺.

25

Step 2

To a suspension of the title compound from Step 1 (1.38g, 2.44mmol) in THF/H₂O (80/16mL) was added Sodium bicarbonate (4.100 g, 48.80mmol). The reaction mixture was stirred 10 min at room temperature and then Iodine (9.29g, 36.60mmol) was added. The reaction mixture
 30 was stirred at 60°C for 1 h. Upon complete conversion, monitored by LCMS, the reaction mixture was cooled to room temperature, quenched with a saturated solution of sodium thiosulfate and diluted with ethyl acetate. The layers were separated. The aqueous layer was extracted with EtOAc (2 x 25mL) and the combined organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to afford the title compound

-140-

(**Intermediate I27**, (12R,14S)-12-hydroxy-4-methoxy-7-(2-nitrobenzenesulfonyl)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.12,6.0¹⁰,14.0²⁰,23]pentacos-1(23),2,4,6(25),17(24),18,21-heptaen-11-one) as a beige solid (1.679g). The compound was directly engaged in the next step without further purification.

5 LCMS (MA) RT = 2.27 min, m/z = 581.1 (M+H)⁺.

Step 3

To a suspension of the title compound from Step 2 (100mg, 0.17mmol) in DMF (1.5mL) were added Cesium carbonate (110mg, 0.34mmol) and 4-Methylbenzenethiol (25mg, 0.20mmol).

10 The reaction was stirred at rt for 30 min. Upon complete conversion, monitored by LCMS, the mixture was diluted with water and ethyl acetate. The layers were separated. The aqueous layer was extracted with EtOAc (2 x 15mL) and the combined organic layer was dried over anhydrous Sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified on silica gel column using DCM/MeOH (100:0 to 95:5) as eluent. The compound was

15 triturated into acetonitrile, filtered and dried under reduced pressure to afford the expected product as a pale beige solid (26mg, 38% yield).

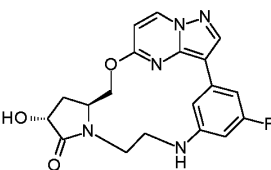
LCMS (MA) RT = 1.79 min, m/z = 396.4 (M+H)⁺.

LCMS (MC) RT = 1.78 min, m/z = 396.4 (M+H)⁺.

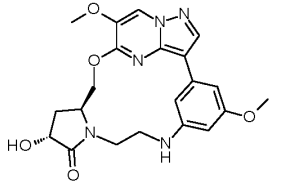
¹H NMR (400 MHz, DMSO) 8.96 (1H, d, J=7.6 Hz), 8.51 (1H, s), 7.48 (1H, s), 6.64 (1H, d, J=7.4 Hz), 6.55 - 6.54 (1H, m), 6.05 - 6.02 (2H, m), 5.59 (1H, d, J=5.7 Hz), 4.92 - 4.89 (1H, m), 4.50 - 4.42 (2H, m), 3.96 (1H, t, J=10.8 Hz), 3.73 (3H, s), 3.57 - 3.49 (1H, m), 3.44 - 3.37 (1H, m), 3.26 - 3.16 (2H, m), 2.40 - 2.33 (1H, m), 1.96 - 1.88 (1H, m)

20

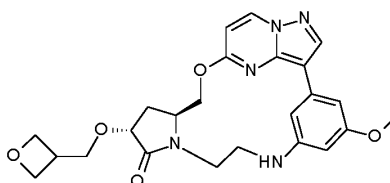
Similarly prepared:

Ex n°	Structure/ Name	From intermediates	Analytical data
104	 (12R,14S)-4-fluoro-12-hydroxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.12,6.0¹⁰,14.0²⁰,23]pentacos-1(23),2(25),3,5,17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloropyrazolo[1,5-a]pyrimidine Pyrrolidine P13 Aniline A1 7mg, 10% yield as white solid	LCMS (MA) RT = 1.92 min, m/z = 384.3 (M+H)⁺. LCMS (MC) RT = 1.91 min, m/z = 384.3 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 8.99 (1H, d, J=7.6 Hz), 8.54 (1H, s), 7.68 (1H, s), 6.75 (1H, d, J=9.3 Hz), 6.68 (1H, d, J=7.4 Hz), 6.33 (1H, t, J=6.3 Hz), 6.24 - 6.19 (1H, m), 4.91 (1H, s), 4.51 - 4.44 (2H, m), 3.97 (1H, t, J=10.6 Hz), 3.53 (1H, s), 3.45 - 3.35 (1H, m), 3.22 (2H, s), 2.40 - 2.32 (2H, m), 1.93 - 1.88 (1H, m);

-141-

143	 (12R,14S)-12-hydroxy-4,18-dimethoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]pentacosan-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold S2 Pyrrolidine P13 Aniline A3 9mg, 53% yield as white solid	LCMS (MA) RT = 1.86 min, m/z = 426.2 (M+H)⁺. LCMS (MC) RT = 1.87 min, m/z = 426.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 8.76 (1H, s), 8.36 (1H, s), 7.44 (1H, brs), 6.53 - 6.51 (1H, m), 6.04 - 6.01 (2H, m), 5.60 (1H, d, J=5.9 Hz), 4.92 (1H, d, J=10.1 Hz), 4.51 - 4.42 (2H, m), 4.04 (1H, t, J=10.6 Hz), 3.89 (3H, s), 3.72 (3H, s), 3.57 - 3.49 (1H, m), 3.44 - 3.37 (1H, m), 3.24 - 3.16 (2H, m), 2.40 - 2.33 (1H, m), 1.95 - 1.87 (1H, m).
-------------------	--	---	--

Example 91: (12R,14S)-4-fluoro-12-(oxetan-3-ylmethoxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]pentacosan-1(23),2(25),3,5,17(24),18,21-heptaen-11-one

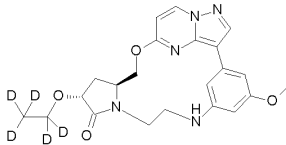
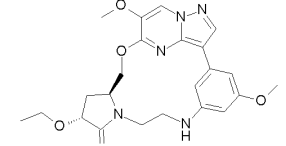
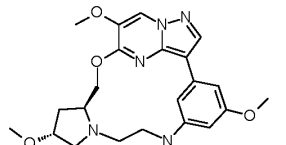


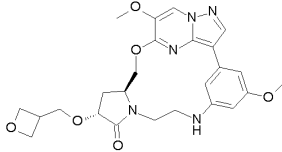
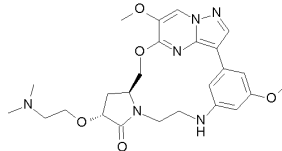
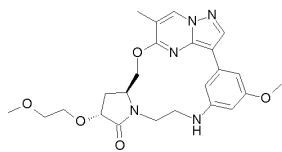
- 5
- Step 1
- To a solution of **Intermediate I27** (0.10g, 0.18mmol) and 3-Bromomethyloxetane (0.032g, 0.21mmol) in dry DMF (2mL) was added Potassium tert-butoxide (0.024g, 0.21mmol) at 0°C and the mixture was stirred at 0°C for 2h. Upon complete conversion, monitored by LCMS,
- 10 Water was added dropwise carefully at 0°C. The resulting mixture was extracted with EtOAc (2x10mL). The combined organic layers were washed with Brine, dried over Na₂SO₄, filtered and concentrated under vacuum to afford the title compound as a yellow oil (0.030g, 27% yield).
- LCMS (MA) RT = 2.51 min, m/z = 639.1 (M+H)⁺.
- 15
- Step 2
- The title compound from Step 1 (0.03g, 0.05mmol) and Cesium carbonate (0.031g, 0.09mmol) were dissolved in DMF (1.1mL). 4-Methylbenzenethiol (0.007g, 0.06mmol) was added and the mixture was stirred at rt overnight. Upon complete conversion, monitored by LCMS, the
- 20 reaction mixture was filtered. Solvent was evaporated and the residue was purified by flash column chromatography using Cyclohexane/EtOAc (100/0 to 0/100) as eluent to afford the expected product as a white solid (0.011g, 52% Yield).
- LCMS (MA) RT = 2.12 min, m/z = 454.2 (M+H)⁺.
LCMS (MC) RT = 2.11 min, m/z = 454.2 (M+H)⁺.

-142-

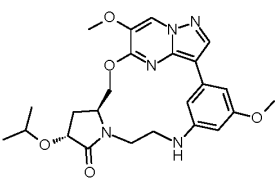
¹H NMR (400 MHz, CDCl₃) 8.55 - 8.52 (1H, m), 8.31 - 8.30 (1H, m), 7.72 - 7.71 (1H, m), 6.74 - 6.69 (1H, m), 6.46 - 6.43 (1H, m), 6.26 - 6.21 (1H, m), 5.11 (1H, t, J=6.9 Hz), 4.87 - 4.82 (1H, m), 4.53 - 4.49 (3H, m), 4.34 - 4.29 (2H, m), 3.93 - 3.57 (6H, m), 3.36 - 3.25 (1H, m), 2.64 (1H, dd, J=8.0, 12.9 Hz), 2.07 - 2.07 (1H, m), 1.30 - 1.26 (2H, m);

5 Similarly prepared:

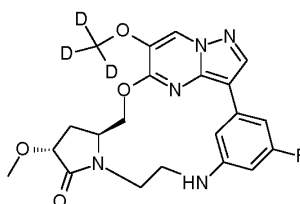
Ex n°	Structure/ Name	From intermediates	Analytical data
110	 (12R,14S)-12-(²H₅)ethoxy-4-methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentacos-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold 3-bromo-5-chloropyrazolo[1,5-a]pyrimidine Pyrrolidine P13 Aniline A3 48mg, 53% yield using Sodium Hydride instead of tBuOK at alkylation step	LCMS (MA) RT = 2.13 min, m/z = 429.2 (M+H)⁺. LCMS (MC) RT = 2.11 min, m/z = 429.3 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 8.97 (1H, d, J=7.6 Hz), 8.51 (1H, s), 7.47 (1H, s), 6.64 (1H, d, J=7.6 Hz), 6.55 - 6.54 (1H, m), 6.06 - 6.02 (2H, m), 4.94 - 4.90 (1H, m), 4.48 - 4.38 (2H, m), 3.94 (1H, t, J=10.6 Hz), 3.73 (3H, s), 3.55 - 3.49 (1H, m), 3.44 - 3.40 (1H, m), 3.24 - 3.16 (2H, m), 2.46 - 2.40 (1H, m), 2.00 - 1.92 (1H, m).
132	 (12R,14S)-12-ethoxy-4,18-dimethoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentacos-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold S2 Pyrrolidine P13 Aniline A3 18mg, 51% yield as Pale yellow solid using Sodium Hydride instead of tBuOK at alkylation step	LCMS (MA) RT = 2.10 min, m/z = 454.3 (M+H)⁺. LCMS (MC) RT = 2.09 min, m/z = 454.3 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 8.76 (1H, s), 8.36 (1H, s), 7.43 - 7.42 (1H, m), 6.52 (1H, dd, J=1.2, 2.0 Hz), 6.06 - 6.01 (2H, m), 4.92 (1H, s), 4.45 - 4.39 (2H, m), 4.06 - 4.00 (1H, m), 3.89 - 3.88 (4H, m), 3.72 (3H, s), 3.61 - 3.49 (2H, m), 3.43 - 3.36 (1H, m), 3.23 - 3.16 (2H, m), 2.44 (1H, dd, J=8.4, 12.8 Hz), 1.99 - 1.91 (1H, m), 1.15 (3H, t, J=7.0 Hz).
133	 (12R,14S)-4,12,18-trimethoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentacos-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold S2 Pyrrolidine P13 Aniline A3 12mg, 42% yield as Pale yellow solid using Sodium Hydride instead of tBuOK at alkylation step	LCMS (MA) RT = 1.98 min, m/z = 440.3 (M+H)⁺. LCMS (MC) RT = 1.97 min, m/z = 440.4 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 8.76 (1H, s), 8.36 (1H, s), 7.42 (1H, brs), 6.52 (1H, dd, J=1.2, 2.2 Hz), 6.05 - 6.01 (2H, m), 4.94 (1H, d, J=11.0 Hz), 4.50 - 4.43 (1H, m), 4.36 - 4.30 (1H, m), 4.02 (1H, t, J=10.9 Hz), 3.89 (3H, s), 3.72 (3H, s), 3.57 - 3.49 (1H, m), 3.44 (3H, s), 3.41 - 3.37 (1H, m), 3.23 - 3.15 (2H, m), 2.47 -

			2.41 (1H, m), 1.99 - 1.91 (1H, m).
134	 (12R,14S)-4,18-dimethoxy-12-(oxetan-3-ylmethoxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6.0}^{10,14.0}^{20,23}]pentacosan-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold S2 Pyrrolidine P13 Aniline A3 12mg, 37% yield as Pale yellow solid using Sodium Hydride instead of tBuOK at alkylation step	LCMS (MA) RT = 2.10 min, m/z = 454.3 (M+H)⁺. LCMS (MC) RT = 2.09 min, m/z = 454.3 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 8.76 (1H, s), 8.36 (1H, s), 7.42 (1H, brs), 6.52 (1H, dd, J=1.3, 2.1 Hz), 6.06 - 6.01 (2H, m), 4.97 - 4.92 (1H, m), 4.64 (2H, dd, J=5.9, 7.8 Hz), 4.51 - 4.44 (2H, m), 4.35 - 4.30 (2H, m), 4.09 - 4.00 (2H, m), 3.89 (3H, s), 3.77 - 3.74 (1H, m), 3.72 (3H, s), 3.58 - 3.49 (1H, m), 3.44 - 3.36 (1H, m), 3.24 - 3.14 (3H, m), 2.48 - 2.42 (1H, m), 2.02 - 1.93 (1H, m).
135	 (12R,14S)-12-[2-(dimethylamino)ethoxy]-4,18-dimethoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6.0}^{10,14.0}^{20,23}]pentacosan-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold S2 Pyrrolidine P13 Aniline A3 6mg, 19% yield as Beige solid using Sodium Hydride instead of tBuOK at alkylation step	LCMS (MA) RT = 1.49 min, m/z = 497.4 (M+H)⁺. LCMS (MC) RT = 1.49 min, m/z = 497.4 (M+H)⁺. ¹H NMR (400 MHz, CDCl₃) 8.22 (1H, s), 8.15 (1H, s), 7.49 (1H, s), 6.60 (1H, dd, J=1.3, 2.1 Hz), 6.09 (1H, t, J=2.2 Hz), 5.14 (1H, d, J=11.0 Hz), 4.56 - 4.50 (1H, m), 4.35 - 4.30 (1H, m), 4.26 - 4.20 (1H, m), 4.14 (1H, t, J=5.8 Hz), 3.96 (3H, s), 3.92 - 3.86 (1H, m), 3.87 - 3.82 (1H, m), 3.84 (3H, s), 3.67 - 3.50 (3H, m), 3.32 - 3.24 (1H, m), 2.81 - 2.70 (2H, m), 2.48 (6H, s), 2.27 - 2.17 (1H, m).
115	 (12R,14S)-4-methoxy-12-(2-methoxyethoxy)-18-methyl-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6.0}^{10,14.0}^{20,23}]pentacosan-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold S1 Pyrrolidine P13 Aniline A3 11mg, 24% yield as Beige solid using Sodium Hydride instead of tBuOK at alkylation step	LCMS (MA) RT = 2.15 min, m/z = 468.4 (M+H)⁺. LCMS (MC) RT = 2.15 min, m/z = 468.4 (M+H)⁺. ¹H NMR (400 MHz, DMSO): 8.88 - 8.87 (1H, m), 8.41 - 8.40 (1H, m), 7.46 (1H, s), 6.53 (1H, d, J=0.8 Hz), 6.06 - 6.01 (2H, m), 4.94 (1H, d, J=10.6 Hz), 4.51 - 4.44 (2H, m), 4.02 - 3.91 (2H, m), 3.72 (3H, s), 3.69 - 3.62 (1H, m), 3.58 - 3.30 (5H, m), 3.26 (3H, s), 3.23 - 3.15 (1H, m), 2.51 - 2.44 (1H, m), 2.19 - 2.17 (3H, m), 2.02 - 1.93 (1H, m);

-144-

147	 (12R,14S)-4,18-dimethoxy-12-(propan-2-yloxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]pentacosa-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold S2 Pyrrolidine P13 Aniline A3 13mg, 12% yield as Light yellow solid using Sodium Hydride instead of tBuOK at alkylation step LCMS (MA) RT = 2.24 min, m/z = 468.4 (M+H)⁺. LCMS (MC) RT = 2.20 min, m/z = 468.4 (M+H)⁺. ¹H NMR (400 MHz, CDCl₃) 8.21 (1H, s), 8.16 - 8.13 (1H, m), 7.72 - 7.55 (1H, m), 7.49 (2H, s), 6.59 (1H, t, J=1.6 Hz), 6.09 - 6.07 (1H, m), 5.13 (1H, d, J=10.8 Hz), 4.51 (1H, t, J=9.2 Hz), 4.35 (1H, dd, J=8.1, 9.8 Hz), 4.17 - 4.15 (1H, m), 4.10 - 4.03 (1H, m), 3.95 (3H, s), 3.94 - 3.85 (1H, m), 3.84 (3H, s), 3.63 - 3.53 (1H, m), 3.30 - 3.23 (1H, m), 2.72 - 2.66 (1H, m), 2.19 - 2.08 (1H, m);
-----	--	--

Example 92: (12R,14S)-4-fluoro-18-(²H₃)methoxy-12-methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6}.0^{10,14}.0^{20,23}]pentacosa-1(23),2(25),3,5,17(24),18,21-heptaen-11-one



5

Step 1

To a suspension of **Intermediate I28** (0.064g, 0.11mmol) in DMF (3.3mL) were added Cesium carbonate (0.105g, 0.32mmol) and Iodo(²H₃)methane (0.046g, 0.32mmol). The reaction mixture was stirred at 70°C for 2h. Upon complete conversion, monitored by LCMS, the reaction mixture was allowed to cooled to room temperature. The solution was concentrated under reduced pressure and then diluted with water and EtOAc. The layers were separated. The aqueous layer was extracted with EtOAc (3 x 20mL) and the combined organic layer was washed with Brine, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to afford the title compound as yellow solid (0.202g).

LCMS (MA) RT = 2.55 min, m/z = 616.2 (M+H)⁺.

15

Step 2

The title compound from Step 1 (0.066g, 0.11mmol) and Cesium carbonate (0.070g, 0.21mmol) were dissolved in DMF (2.4mL). 4-Methylbenzenethiol (0.016g, 0.13mmol) was added and the mixture was stirred at rt overnight. Upon complete conversion, monitored by LCMS, the reaction mixture was filtered, solvent was evaporated to dryness. The residue was

20

-145-

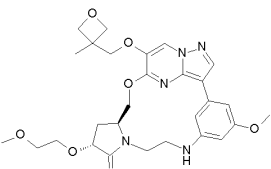
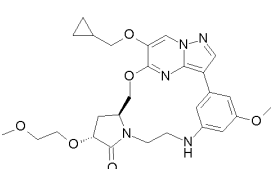
purified by flash column chromatography using Cyclohexane/EtOAc (100/0 to 20/80) as eluent to afford the expected product as a white solid (25mg, 54% Yield).

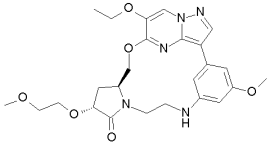
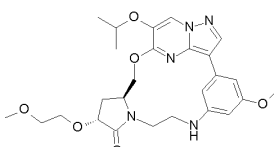
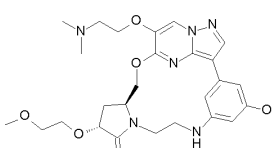
LCMS (MA) RT = 2.23 min, m/z = 431.2 (M+H)⁺.

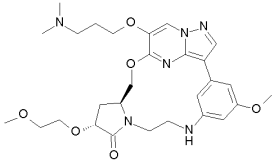
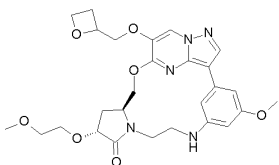
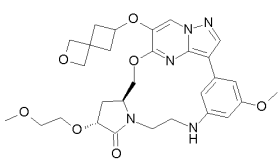
LCMS (MC) RT = 2.14 min, m/z = 431.3 (M+H)⁺.

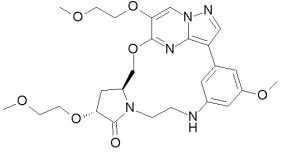
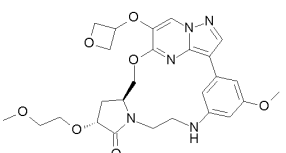
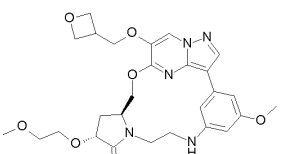
- 5 ¹H NMR (400 MHz, DMSO) 8.79 – 8.78 (1H, m), 8.40 – 8.39 (1H, m), 7.63 – 7.62 (1H, m), 6.72 (1H, d, J=9.9 Hz), 6.40 – 6.25 (1H, m), 6.22 – 6.17 (1H, m), 4.95 (1H, d, J=10.1 Hz), 4.48 (1H, s), 4.33 (1H, t, J=8.9 Hz), 4.03 (1H, t, J=10.7 Hz), 3.59 – 3.51 (1H, m), 3.41 – 3.36 (1H, m), 3.33 (3H, s), 3.31 (1H, s), 3.23 – 3.16 (2H, m), 1.99 – 1.91 (1H, m);

10 Similarly prepared:

Ex n°	Structure/ Name	From intermediates	Analytical data
122	 (12R,14S)-4-methoxy-12-(2-methoxyethoxy)-18-[(3-methyloxetan-3-yl)methoxy]-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0^{1°},¹⁴.0^{2°},²³]pentacos-1(23),2(25),3,5,17(24),18,21-heptaen-11-one	Scaffold S3 Pyrrolidine P7 Aniline A3 35mg, 69% yield	LCMS (MA) RT = 2.14 min, m/z = 554 (M+H)⁺. LCMS (MC) RT = 2.36 min, m/z = 554 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 8.87 (1H, s), 8.37 (1H, s), 7.41 (1H, t, J=4.5 Hz), 6.52 (1H, dd, J=1.1, 2.1 Hz), 6.06 - 6.02 (2H, m), 4.96 - 4.93 (1H, m), 4.54 - 4.46 (4H, m), 4.35 (2H, d, J=5.9 Hz), 4.23 (1H, d, J=9.5 Hz), 4.16 - 4.03 (2H, m), 3.97 - 3.92 (1H, m), 3.73 - 3.72 (4H, m), 3.47 (3H, t, J=4.8 Hz), 3.31 (2H, s), 3.26 (3H, s), 3.25 - 3.10 (2H, m), 2.05 - 1.85 (1H, m), 1.41 (3H, s);
123	 (12R,14S)-18-(cyclopropylmethoxy)-4-methoxy-12-(2-methoxyethoxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0^{1°},¹⁴.0^{2°},²³]pentacos-1(23),2(25),3,5,17(24),18,21-heptaen-11-one	Scaffold S3 Pyrrolidine P7 Aniline A3 35mg, 69% yield using K₂CO₃ instead of Cs₂CO₃ at alkylation step	LCMS (MA) RT = 2.36 min, m/z = 524 (M+H)⁺. LCMS (MC) RT = 2.32 min, m/z = 524 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 8.70 (1H, s), 8.35 (1H, s), 7.43 (1H, s), 6.52 - 6.51 (1H, m), 6.06 - 6.01 (2H, m), 4.94 - 4.91 (1H, m), 4.50 - 4.44 (2H, m), 4.10 - 4.04 (1H, m), 3.98 - 3.86 (3H, m), 3.72 - 3.72 (4H, m), 3.48 (2H, t, J=4.7 Hz), 3.30 (2H, s), 3.25 (3H, s), 3.24 - 3.10 (2H, m), 2.10 - 1.80 (1H, m), 1.29 - 1.24 (2H, m), 0.65 - 0.61 (2H, m), 0.38 - 0.34 (2H, m);

124	 (12R,14S)-18-ethoxy-4-methoxy-12-(2-methoxyethoxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentacos-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold S3 Pyrrolidine P7 Aniline A3 28mg, 28% yield using K₂CO₃ instead of Cs₂CO₃ at alkylation step	LCMS (MA) RT = 2.13 min, m/z = 498.3 (M+H)⁺. LCMS (MC) RT = 2.14 min, m/z = 498.4 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 8.75 (1H, s), 8.36 (1H, s), 7.42 (1H, s), 6.53 - 6.51 (1H, m), 6.06 - 6.01 (2H, m), 4.92 (1H, d, J=10.4 Hz), 4.52 - 4.43 (2H, m), 4.17 - 4.09 (2H, m), 4.04 (1H, t, J=10.6 Hz), 3.96 - 3.90 (1H, m), 3.72 (3H, s), 3.68 - 3.62 (1H, m), 3.58 - 3.51 (1H, m), 3.48 (2H, t, J=4.8 Hz), 3.42 - 3.36 (1H, m), 3.26 (3H, s), 3.22 - 3.16 (2H, m), 2.49 - 2.42 (1H, m), 2.01 - 1.93 (1H, m), 1.39 (3H, t, J=6.9 Hz).
125	 (12R,14S)-4-methoxy-12-(2-methoxyethoxy)-18-(propan-2-yloxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentacos-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold S3 Pyrrolidine P7 Aniline A3 54mg, 53% yield using K₂CO₃ instead of Cs₂CO₃ at alkylation step	LCMS (MA) RT = 2.26 min, m/z = 512.4 (M+H)⁺. LCMS (MC) RT = 2.26min, m/z = 512.4 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 8.83 (1H, s), 8.37 (1H, s), 7.42 (1H, brs), 6.52 (1H, dd, J=1.1, 2.1 Hz), 6.06 - 6.01 (2H, m), 4.92 (1H, d, J=10.4 Hz), 4.62 (1H, sept, J=6.03 Hz), 4.51 - 4.44 (2H, m), 4.03 (1H, t, J=10.6 Hz), 3.96 - 3.90 (1H, m), 3.72 (3H, s), 3.68 - 3.63 (1H, m), 3.58 - 3.52 (1H, m), 3.50 - 3.46 (2H, m), 3.42 - 3.37 (1H, m), 3.27 (3H, s), 3.23 - 3.16 (2H, m), 2.47 - 2.42 (1H, m), 2.01 - 1.93 (1H, m), 1.33 (6H, dd, J=6.1, 7.4 Hz).
126	 (12R,14S)-18-[2-(dimethylamino)ethoxy]-4-methoxy-12-(2-methoxyethoxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentacos-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold S3 Pyrrolidine P7 Aniline A3 4mg, 4% yield as white solid using K₂CO₃ instead of Cs₂CO₃ at alkylation step	LCMS (MA) RT = 1.40 min, m/z = 541.4 (M+H)⁺. LCMS (MC) RT = 2.01min, m/z = 541.4 (M+H)⁺. ¹H NMR (400 MHz, CDCl₃) 8.22 - 8.21 (2H, m), 7.49 (1H, brs), 6.59 (1H, dd, J=1.3, 2.1 Hz), 6.08 (1H, t, J=2.2 Hz), 5.11 (1H, d, J=11.0 Hz), 4.53 - 4.48 (1H, m), 4.36 (1H, dd, J=8.2, 9.5 Hz), 4.24 - 4.20 (1H, m), 4.14 (2H, t, J=5.7 Hz), 3.90 - 3.84 (2H, m), 3.84 (3H, s), 3.83 - 3.80 (1H, m), 3.70 - 3.52 (4H, m), 3.42 (3H, s), 3.31 - 3.22 (1H, m), 2.86 - 2.81 (2H, m), 2.70 (1H, dd, J=8.3, 13.2 Hz), 2.40 (6H, s),

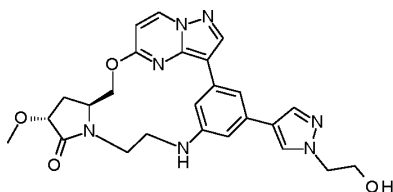
127	 (12R,14S)-18-[3-(dimethylamino)propoxy]-4-methoxy-12-(2-methoxyethoxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentacosan-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold S3 Pyrrolidine P7 Aniline A3 17mg, 15% yield as Beige solid using K₂CO₃ instead of Cs₂CO₃ at alkylation step	2.24 - 2.16 (1H, m). LCMS (MA) RT = 1.46 min, m/z = 555.3 (M+H)⁺. LCMS (MC) RT = 2.06min, m/z = 555.4 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 8.76 (1H, s), 8.35 (1H, s), 7.41 (1H, brs), 6.53 - 6.50 (1H, m), 6.06 - 6.01 (2H, m), 4.95 - 4.91 (1H, m), 4.52 - 4.44 (2H, t, J=8.8 Hz), 4.11 (2H, t, J=6.2 Hz), 4.04 (1H, t, J=11.0 Hz), 3.97 - 3.91 (1H, m), 3.72 (3H, s), 3.68 - 3.62 (1H, m), 3.58 - 3.51 (1H, m), 3.48 (2H, t, J=4.8 Hz), 3.44 - 3.37 (1H, m), 3.26 (3H, s), 3.23 - 3.16 (2H, m), 2.48 - 2.34 (3H, m), 2.16 (6H, s), 1.99 - 1.87 (3H, m).
130	 (12R,14S)-4-methoxy-12-(2-methoxyethoxy)-18-(oxetan-2-ylmethoxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentacosan-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold S3 Pyrrolidine P7 Aniline A3 15mg, 43% yield as Off-white solid using K₂CO₃ instead of Cs₂CO₃ at alkylation step	LCMS (MA) RT = 1.99 min, m/z = 540.3 (M+H)⁺. LCMS (MC) RT = 2.01min, m/z = 540.3 (M+H)⁺. ¹H NMR (400 MHz, CDCl₃) 8.36 (1H, s), 8.22 (1H, s), 7.50 (1H, d, J=0.4 Hz), 6.59 (1H, dd, J=1.3, 2.1 Hz), 6.09 (1H, t, J=2.2 Hz), 5.25 - 5.11 (2H, m), 4.80 - 4.66 (2H, m), 4.54 - 4.49 (1H, m), 4.37 (1H, dd, J=8.3, 9.6 Hz), 4.27 - 4.18 (3H, m), 3.85 - 3.84 (6H, m), 3.70 - 3.53 (4H, m), 3.42 (3H, s), 3.31 - 3.24 (1H, m), 2.90 - 2.67 (3H, m), 2.25 - 2.16 (1H, m);
136	 (12R,14S)-4-methoxy-12-(2-methoxyethoxy)-18-{2-oxaspiro[3.3]heptan-6-yloxy}-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentacosan-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold S3 Pyrrolidine P7 Aniline A3 20mg, 23% yield as Beige solid using K₂CO₃ instead of Cs₂CO₃ at alkylation step	LCMS (MA) RT = 2.07 min, m/z = 566.4 (M+H)⁺. LCMS (MC) RT = 2.06min, m/z = 566.4 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 8.58 (1H, s), 8.37 (1H, s), 7.40 (1H, s), 6.52 (1H, s), 6.06 - 6.01 (2H, m), 4.89 (1H, s), 4.66 - 4.63 (3H, m), 4.57 (2H, s), 4.46 (2H, t, J=8.7 Hz), 4.05 - 3.90 (2H, m), 3.72 (3H, s), 3.65 (1H, td, J=5.1, 10.2 Hz), 3.52 - 3.46 (3H, m), 3.44 - 3.38 (1H, m), 3.26 (3H, s), 3.20 - 3.15 (2H, m), 2.89 - 2.83 (2H, m), 2.48 - 2.41 (1H, m), 2.35 - 2.25 (2H, m), 1.98 - 1.91 (1H, m);

137	 (12R,14S)-4-methoxy-12,18-bis(2-methoxyethoxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentacosan-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold S3 Pyrrolidine P7 Aniline A3 30mg, 29% yield as Pale yellow solid using K₂CO₃ instead of Cs₂CO₃ at alkylation step	LCMS (MA) RT = 2.05 min, m/z = 528.3 (M+H)⁺. LCMS (MC) RT = 2.04min, m/z = 528.4 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 8.78 (1H, s), 8.36 (1H, s), 7.42 (1H, brs), 6.53 - 6.51 (1H, m), 6.06 - 6.01 (2H, m), 4.93 (1H, d, J=10.2 Hz), 4.52 - 4.44 (2H, m), 4.24 - 4.19 (2H, m), 4.05 (1H, t, J=10.6 Hz), 3.96 - 3.88 (1H, m), 3.72 (3H, s), 3.72 - 3.70 (2H, m), 3.68 - 3.62 (1H, m), 3.58 - 3.51 (1H, m), 3.48 (2H, t, J=4.8 Hz), 3.43 - 3.36 (1H, m), 3.34 (3H, s), 3.26 (3H, s), 3.24 - 3.16 (2H, m), 2.48 - 2.43 (1H, m), 2.02 - 1.93 (1H, m).
138	 (12R,14S)-4-methoxy-12-(2-methoxyethoxy)-18-(oxetan-3-yloxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentacosan-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold S3 Pyrrolidine P7 Aniline A3 8mg, 8% yield as Pale yellow solid using K₂CO₃ instead of Cs₂CO₃ at alkylation step	LCMS (MA) RT = 1.96 min, m/z = 526.3 (M+H)⁺. LCMS (MC) RT = 1.94min, m/z = 526.3 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 8.59 (1H, s), 8.39 (1H, s), 7.41 (1H, brs), 6.53 - 6.51 (1H, m), 6.06 (1H, t, J=5.5 Hz), 6.02 (1H, t, J=2.1 Hz), 5.37 - 5.31 (1H, m), 5.00 - 4.92 (3H, m), 4.68 - 4.61 (2H, m), 4.50 - 4.44 (2H, m), 4.07 (1H, t, J=10.7 Hz), 3.96 - 3.91 (1H, m), 3.72 (3H, s), 3.69 - 3.63 (1H, m), 3.58 - 3.51 (1H, m), 3.48 (2H, t, J=4.7 Hz), 3.43 - 3.36 (1H, m), 3.27 (3H, s), 3.24 - 3.15 (2H, m), 2.48 - 2.44 (1H, m), 2.02 - 1.94 (1H, m).
144	 (12R,14S)-4-methoxy-12-(2-methoxyethoxy)-18-(oxetan-3-ylmethoxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentacosan-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold S3 Pyrrolidine P7 Aniline A3 24mg, 22% yield as Pale yellow solid using K₂CO₃ instead of Cs₂CO₃ at alkylation step	LCMS (MA) RT = 2.02 min, m/z = 540.2 (M+H)⁺. LCMS (MC) RT = 2.03min, m/z = 540.3 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 8.85 (1H, s), 8.38 (1H, s), 7.41 (1H, brs), 6.52 (1H, dd, J=1.1, 2.1 Hz), 6.07 - 6.01 (2H, m), 4.93 (1H, d, J=10.8 Hz), 4.75 (2H, dd, J=6.1, 7.8 Hz), 4.49 - 4.47 (2H, m), 4.44 (2H, t, J=6.0 Hz), 4.35 - 4.31 (2H, m), 4.05 (1H, t, J=10.6 Hz), 3.96 - 3.90 (1H, m), 3.72 (3H, s), 3.68 - 3.62 (1H, m), 3.58 - 3.51 (1H, m), 3.47 (2H, t, J=4.8 Hz), 3.45 - 3.36 (2H, m).

-149-

			m), 3.26 (3H, s), 3.23 - 3.16 (2H, m), 2.47 - 2.41 (1H, m), 2.01 - 1.92 (1H, m).
--	--	--	--

Example 93: (12R,14S)-4-[1-(2-hydroxyethyl)-1H-pyrazol-4-yl]-12-methoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1².6.0^{1°},14.0^{2°},²³]pentacos-1(23),2,4,6(25),17(24),18,21-heptaen-11-one



5

Step 1

To a suspension of **Intermediate 129** (170mg, 0.23mmol) in THF (1.2mL) was added TBAF in THF 1 M (0.25mL, 0.25mmol). The reaction was stirred at rt for 1 h. Upon complete conversion, monitored by LCMS, the solvent was evaporated under reduced pressure. The residue was purified on silica gel column chromatography using DCM/MeOH (100:0 to 90:10) as eluent. The expected fractions were combined and evaporated under reduced pressure. The resulting solid was triturated into acetonitrile, filtered and dried under vacuum to afford the expected product as a pale pink solid (80mg, 98%).

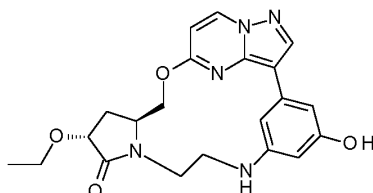
LCMS (MA) RT = 1.75 min, m/z = 490.4 (M+H)⁺.

15 LCMS (MC) RT = 1.76 min, m/z = 490.4 (M+H)⁺.

¹H NMR (400 MHz, DMSO) 8.98 (1H, d, J=7.4 Hz), 8.59 (1H, s), 8.07 (1H, s), 7.82 (1H, s), 7.70 (1H, ls), 7.19 – 7.18 (1H, m), 6.65 (1H, d, J=7.6 Hz), 6.64 – 6.63 (1H, m), 6.03 (1H, t, J=5.9 Hz), 4.97 – 4.93 (1H, m), 4.95 (1H, t, J=5.3 Hz), 4.51 – 4.50 (1H, m), 4.34 (1H, t, J=9.0 Hz), 4.17 (2H, t, J=5.6 Hz), 3.95 (1H, t, J=10.9 Hz), 3.78 (2H, q, J=5.5 Hz), 3.59 – 3.51 (1H, m), 3.45 (3H, s), 3.44 – 3.39 (1H, m), 3.27 – 3.20 (2H, m), 2.47 – 2.41 (1H, m), 2.02 – 1.94 (1H, m).

Example 96 : (12R,14S)-12-ethoxy-4-hydroxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1².6.0^{1°},14.0^{2°},²³]pentacos-1(23),2(25),3,5,17(24),18,21-heptaen-11-one

25



-150-

Following the general synthetic scheme 1, as depicted for the synthesis of **Example 1**, (12R,14S)-4-(benzyloxy)-12-ethoxy-7-(2-nitrobenzenesulfonyl)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.12,6.0¹⁰,14.0²⁰,23]pentacosa-1(23),2,4,6(25),17(24),18,21-heptaen-11-one was obtained as **Intermediate I30** using **Scaffold 3-bromo-5-chloropyrazolo[1,5-a]pyrimidine**, **Pyrrolidine P2** and **Aniline A9**.
 LCMS (MA) RT = 2.87 min, m/z = 685.3 (M+H)⁺.

Step 1

To a solution of **Intermediate I30** (2.38g, 3.47mmol) in TFA (43mL) was added Anisole (15.19mL, 138.9mmol). The reaction mixture was stirred at 130°C for 2h. Upon complete conversion, monitored by LCMS, the mixture was allowed to cooled at room temperature and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography using Cyclohexane/EtOAc (100/0 to 0/100) as eluent to afford the title compound as a brown solid (1.96g, 95% Yield).

Step 2

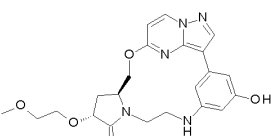
The title compound from Step 1 (0.20g, 0.34mmol) and Cesium carbonate (0.219g, 0.67mmol) were dissolved in DMF (7.4mL). 4-Methylbenzenethiol (0.050g, 0.40mmol) was added and the mixture was stirred at rt overnight. Upon complete conversion, monitored by LCMS, the reaction mixture was filtered and mother liquor was concentrated to dryness. The residue was purified by flash column chromatography using Cyclohexane/EtOAc (100/0 to 20/80) as eluent to afford the expected product as a green solid (33mg, 24% yield).

LCMS (MA) RT = 1.81 min, m/z = 410.4 (M+H)⁺.

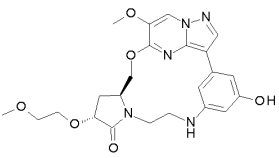
LCMS (MC) RT = 1.80 min, m/z = 410.4 (M+H)⁺.

¹H NMR (400 MHz, DMSO) 8.97 – 8.94 (2H, m), 8.39 – 8.38 (1H, m), 7.97 – 7.95 (1H, m), 7.35 – 7.32 (1H, m), 6.64 – 6.61 (1H, m), 6.35 (1H, s), 5.93 (1H, t, J=2.0 Hz), 4.94 – 4.89 (1H, m), 4.44 – 4.38 (2H, m), 3.98 – 3.82 (2H, m), 3.48 (4H, d, J=10.4 Hz), 3.20 – 3.14 (1H, m), 2.01 – 1.91 (1H, m), 1.17 – 1.04 (4H, m);

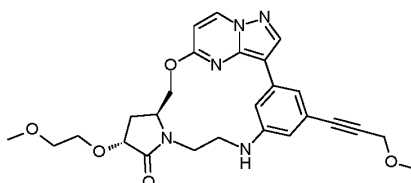
Similarly prepared:

Ex n°	Structure/ Name	From intermediates	Analytical data
97	 (12R,14S)-4-hydroxy-12-(2-methoxyethoxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentacosa-	Scaffold 3-bromo-5-chloropyrazolo[1,5-a]pyrimidine Pyrrolidine P7 Aniline A9 5.1mg, 47% yield	LCMS (MA) RT = 1.81 min, m/z = 440.2 (M+H)⁺. LCMS (MC) RT = 1.74 min, m/z = 440.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 8.97 - 8.95 (2H, m), 8.38 (1H, s), 7.34 - 7.32 (1H, m), 6.63 (1H, d, J=7.6 Hz), 6.35 (1H, s), 5.95 - 5.92 (2H, m), 4.90 (1H, s), 4.47 - 4.42 (2H, m), 3.99 - 3.90 (2H, m), 3.67 -

-151-

	1(23),2(25),3,5,17(24),18,21-heptaen-11-one		3.61 (1H, m), 3.49 - 3.46 (3H, m), 3.44 - 3.40 (1H, m), 3.3 - 3.25 (3H, m), 3.25 - 3.00 (2H, m), 2.45 - 2.35 (1H, m), 2.02 - 1.94 (1H, m)
128	 (12R,14S)-4-hydroxy-18-methoxy-12-(2-methoxyethoxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6.0}^{10,14.0}^{20,23}]pentacos-1(23),2,4,6(25),17(24),18,21-heptaen-11-one	Scaffold S2 Pyrrolidine P7 Aniline A9 10mg, 56% yield as Beige solid	LCMS (MA) RT = 1.78 min, m/z = 470.2 (M+H)⁺. LCMS (MC) RT = 1.81 min, m/z = 470.2 (M+H)⁺. ¹H NMR (400 MHz, DMSO) 8.94 (1H, s), 8.75 (1H, s), 8.24 (1H, s), 7.28 - 7.27 (1H, m), 6.33 (1H, s), 5.94 - 5.90 (2H, m), 4.96 - 4.91 (1H, m), 4.44 (2H, t, J=8.7 Hz), 4.04 - 3.92 (2H, m), 3.89 - 3.87 (3H, m), 3.68 - 3.61 (1H, m), 3.48 (3H, t, J=4.7 Hz), 3.44 - 3.39 (1H, m), 3.26 (3H, s), 3.16 - 3.12 (2H, m), 2.44 (1H, dd, J=8.2, 13.4 Hz), 2.00 - 1.92 (1H, m).

Example 100: (12R,14S)-12-(2-methoxyethoxy)-4-(3-methoxyprop-1-yn-1-yl)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6.0}^{10,14.0}^{20,23}]pentacos-1(23),2,4,6(25),17(24),18,21-heptaen-11-one



5

Following the general synthetic scheme 1, as depicted for the synthesis of Example 1, (12R,14S)-4-(benzyloxy)-12-(2-methoxyethoxy)-7-(2-nitrobenzenesulfonyl)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1^{2,6.0}^{10,14.0}^{20,23}]pentacos-1(23),2,4,6(25),17(24),18,21-heptaen-11-one was obtained as **Intermediate I31** using **Scaffold 3-bromo-5-chloropyrazolo[1,5-a]pyrimidine**, **Pyrrolidine P7** and **Aniline A9**.
LCMS (MA) RT = 2.75 min, m/z = 715.4 (M+H)⁺.

10

Step 1

To a suspension of **Intermediate I31** (296mg, 0.41mmol) in TFA (6mL) was added Anisole (1.78mL, 16.4mmol). The reaction mixture was stirred at 130°C overnight. Upon complete conversion, monitored by LCMS, the reaction mixture was cooled to room temperature. The solvent was evaporated under reduced pressure. The residue was purified on silica gel column chromatography using DCM/MeOH (100:0 to 95:5) as eluent to afford the title compound as a beige solid (250mg, 97% yield).

15

LCMS (MA) RT = 2.15 min, m/z = 625.3 (M+H)⁺.

20

-152-

Step 2

To a suspension of the title compound from Step 1 (250mg, 0.4mmol) in DCM (20mL) was added Triethylamine (0.085mL, 0.6mmol). N-phenyl-bis(trifluoromethanesulfonimide) (157mg, 0.44mmol) was added portionwise to the slurry. The reaction mixture was stirred at rt overnight. Upon complete conversion, monitored by LCMS, the reaction mixture was diluted with water and the layers were separated. The aqueous layer was extracted with DCM (2 x 15mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to afford the title compound as a beige foam (450mg). The crude was directly engaged in the next step without further purification.

LCMS (MA) RT = 2.73 min, m/z = 757.3 (M+H)⁺.

Step 3

To a suspension of the title compound from Step 2 (303mg, 0.4mmol) in DMF (3.5mL) were added Cesium carbonate (260mg, 0.8mmol) and then 4-Methylbenzenethiol (60mg, 0.48mmol). The reaction was stirred at rt overnight. Upon complete conversion, monitored by LCMS, the reaction mixture was adsorbed on silica and evaporated to dryness. The residue was purified by silica gel column chromatography using DCM/MeOH (100/0 to 9/1) as eluent to afford the title compound as a white solid (**Intermediate I33**, (12R,14S)-12-(2-methoxyethoxy)-11-oxo-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.12,6.010,14.020,23]pentacos-1(23),2,4,6(25),17(24),18,21-heptaen-4-yltrifluoromethanesulfonate, 150mg, 66% yield). LCMS (MA) RT = 2.54 min, m/z = 572.2 (M+H)⁺.

Step 4

In a sealed tube, to a suspension of the title compound from Step 3 (0.050g, 0.09mmol) in dry 1,4-Dioxane (1.5mL), was added Lithium chloride (0.011g, 0.26mmol). The mixture was degassed by bubbling argon for 10 min. Tributyl(vinyl)stannane (0.038g, 0.10mmol) and Pd(PPh₃)₄ (0.010g, 0.01mmol) were added and the reaction was stirred at 100°C with a sand bath for 2h. Upon complete conversion, monitored by LCMS, the reaction mixture was cooled down and filtered over Celite then solvent was evaporated. The residue was purified by column chromatography using Cyclohexane/EtOAc (100/0 to 0/100) as eluent to afford the expected product as a white solid (17mg, 40% yield).

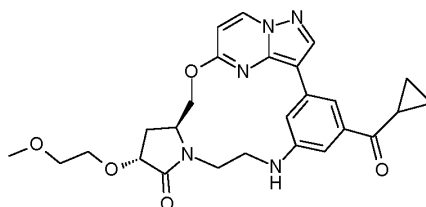
LCMS (MA) RT = 2.22 min, m/z = 492.4 (M+H)⁺.

LCMS (MC) RT = 2.21 min, m/z = 492.4 (M+H)⁺.

¹H NMR (400 MHz, DMSO) 9.00 - 8.98 (1H, m), 8.57 (1H, s), 7.85 (1H, s), 7.03 (1H, d, J=1.3 Hz), 6.66 (1H, d, J=7.4 Hz), 6.54 (1H, dd, J=1.5, 2.3 Hz), 6.26 - 6.22 (1H, m), 4.93 (1H, d, J=11.0 Hz), 4.45 (2H, dd, J=8.3, 9.4 Hz), 4.32 (2H, s), 4.00 - 3.92 (2H, m), 3.68 - 3.62 (1H, m), 3.55 - 3.50 (1H, m), 3.48 (2H, t, J=4.7 Hz), 3.45 - 3.35 (3H, m), 3.26 - 3.26 (4H, m), 2.50 - 2.40 (1H, m), 2.02 - 1.96 (1H, m), 1.15 (1H, t, J=1.0 Hz), 0.88 (1H, t, J=7.3 Hz);

-153-

Example 101: (12R,14S)-4-cyclopropanecarbonyl-12-(2-methoxyethoxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1².6.0¹⁰,14.0²⁰,23]pentacos-1(23),2,4,6(25),17(24),18,21-heptaen-11-one



5 Step 1

Into a sealed tube, to a suspension under argon of **Intermediate I33** (64mg, 0.11mmol) in dry Toluene (0.22mL) were added Cyclopropane-methanol (10μL, 0.13mmol), Acetone (40μL, 0.55mmol) and TMP (37μL, 0.22mmol). The mixture was degassed by bubbling argon for 10 min and then Triphos (8mg, 0.01mmol) and Ni(OTf)₂ (4mg, 0.01mmol) were added. The tube was sealed and heated at 140°C with a sand bath pre-heated at 140°C. The reaction was stirred at 140°C for 48h. Upon complete conversion of the starting material, monitored by LCMS, the layers were separated. The aqueous layer was extracted with EtOAc (2 x 10mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The reaction was restarted in the same conditions over the crude. The mixture was warmed to 140°C overnight. Upon completion, monitored by LCMS, the reaction was cooled at rt and the mixture was diluted with water and ethyl acetate. The layers were separated. The aqueous layer was extracted with EtOAc (2 x 10mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified by preparative HPLC: Column Waters XSELECT C18 19*100mm, 5μm, A: (NH₄)₂CO₃aq. 2 g/L, B: ACN, 19ml/min, rt, 40% B to 45% B in 7 min. The residue (~15mg) was purified a second time by Preparative TLC 0.5mm using Cyclohexane/(EtOAc/EtOH 3:1) 1:1 as eluent to afford the expected product as a pale yellow solid (11mg, 16 %).

LCMS (MA) RT = 2.15 min, m/z = 492.4 (M+H)⁺.

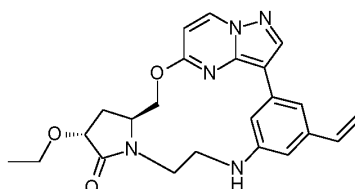
LCMS (MC) RT = 2.15 min, m/z = 492.4 (M+H)⁺.

¹H NMR (400 MHz, CDCl₃) 8.54 (1H, d, J=7.4 Hz), 8.42 (1H, s), 8.10 (1H, ls), 7.62 - 7.60 (1H, m), 7.16 - 7.14 (1H, m), 6.45 (1H, d, J=7.4 Hz), 5.13 - 5.07 (1H, m), 4.54 - 4.47 (1H, m), 4.40 - 4.34 (1H, m), 4.35 - 4.31 (1H, m), 4.27 - 4.21 (1H, m), 3.90 - 3.56 (6H, m), 3.43 (3H, s), 3.33 - 3.27 (1H, m), 2.74 - 2.62 (2H, m), 2.28 - 2.21 (1H, m), 1.30 - 1.25 (2H, m), 1.10 - 1.05 (2H, m)

30

-154-

Example 102: (12R,14S)-4-ethenyl-12-ethoxy-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1².6.0¹⁰,14.0²⁰,23]pentacosa-1(23),2,4,6(25),17(24),18,21-heptaen-11-one



5 Step 1

To a solution of **Intermediate 130** (2.38g, 3.47mmol) in TFA (43mL) was added Anisole (15.168mL, 138.86mmol). The reaction mixture was stirred at 130°C for 2h. Upon complete conversion, monitored by LCMS, the mixture was allowed to cooled at room temperature and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography using Cyclohexane/EtOAc (100/0 to 0/100) as eluent to afford the title compound as a brown solid (1.96g, 95% yield).
10 LCMS (MA) RT = 2.35 min, m/z = 595.2 (M+H)⁺.

Step 2

15 To a suspension of the title compound from Step 1 (250mg, 0.42mmol) in DCM (20mL) were added Triethylamine (0.09mL, 0.63mmol), then N-Phenylbis(Trifluoromethanesulfonimide) (165mg, 0.46mmol) portionwise. Upon complete conversion, monitored by LCMS, the reaction mixture was diluted with water. The layers were separated. The aqueous layer was extracted with DCM (2 x 15mL). The combined organic layer was dried over anhydrous sodium sulfate,
20 filtered and evaporated under reduced pressure to afford the title compound as a grey foam (430mg), which was directly engaged in the next step without further purification.
LCMS (MA) RT = 2.86 min, m/z = 727.1 (M+H)⁺.

Step 3

25 To a suspension of the title compound from Step 2 (305mg, 0.42mmol) in DMF (3.4mL) were added Cesium carbonate (274mg, 0.84mmol) and then 4-Methylbenzenethiol (62mg, 0.50mmol). The reaction was stirred at rt for 45 min. Upon complete conversion, monitored by LCMS, the mixture was diluted with water and ethyl acetate. The layers were separated. The aqueous layer was extracted with EtOAc (2 x 15mL). The combined organic layers were dried
30 over anhydrous Sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified on silica gel column using DCM/MeOH (100:0 to 95:5) as eluent to afford the title compound as a white solid (169mg, 74% yield).
LCMS (MA) RT = 2.69 min, m/z = 542.1 (M+H)⁺.

-155-

Step 4

Into a sealed tube, to a suspension of the title compound from Step 3 (100mg, 0.18mmol) in dry 1,4-Dioxane (3mL) was added Lithium chloride (23mg, 0.55mmol) and the mixture was degassed by bubbling Argon for 10 min. Tributyl(vinyl)stannane (65μL, 0.22mmol) and Pd(PPh₃)₄ (21mg, 0.02mmol) were added and the reaction was stirred at 100°C with a sand bath for 3 h. Upon complete conversion, monitored by LCMS, the mixture was cooled to rt. The mixture was diluted with water and ethyl acetate and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 15mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified by preparative HPLC: Column Waters XSelect C18 19*100mm, 5μm, [(NH₄)₂CO₃ aq 2g/L / ACN], 19ml/min, rt, 40% B to 60% B in 7 min to afford the expected product as a beige solid (71mg, 55 % yield).

LCMS (MA) RT = 2.36 min, m/z = 420.2(M+H)⁺.

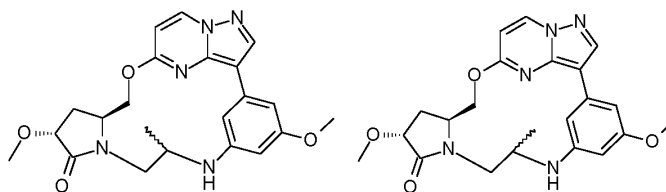
LCMS (MC) RT = 2.35 min, m/z = 420.2 (M+H)⁺.

¹H NMR (400 MHz, DMSO) 8.98 (1H, d, J=7.6 Hz), 8.56 (1H, s), 7.76 (1H, ls), 7.08 - 7.07 (1H, m), 6.68 - 6.61 (2H, m), 6.53 - 6.52 (1H, m), 6.09 (1H, t, J=5.9 Hz), 5.79 (1H, dd, J=1.1, 17.7 Hz), 5.22 (1H, dd, J=1.1, 10.8 Hz), 4.93 (1H, d, J=10.6 Hz), 4.48 - 4.39 (2H, m), 3.95 (1H, t, J=10.9 Hz), 3.91 - 3.83 (1H, m), 3.61 - 3.49 (2H, m), 3.43 - 3.36 (1H, m), 3.26 - 3.18 (2H, m), 2.44 (1H, dd, J=8.1, 12.4 Hz), 2.01 - 1.93 (1H, m), 1.15 (3H, t, J=7.0 Hz).

20

Example 105 and 106: E1-(8R*,12R,14S)-4,12-dimethoxy-8-methyl-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1².6.0^{1°},14.0^{2°},23]pentacosa-1(23),2,4,6(25),17(24),18,21-heptaen-11-one / E2-(8R*,12R,14S)-4,12-dimethoxy-8-methyl-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1².6.0^{1°},14.0^{2°},23]pentacosa-1(23),2,4,6(25),17(24),18,21-heptaen-11-one

25



Step 1

To a suspension Sodium hydride, 60% in oil (3.2g, 80.0mmol) in dry THF (25mL) was added at 0°C a solution of **Pyrrolidine P1** (9.25 g, 40.0mmol) in THF (25mL). After 30 min, 3-bromo-5-chloro-pyrazolo[1,5-a]pyrimidine (9.3g, 40.01mmol) was added and the mixture was stirred at 0°C for 15 min, and then at rt for 4h. The mixture was carefully diluted with water and EtOAc (250ml) was added. The layers were separated. The aqueous layer was extracted with EtOAc (2x100mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to afford the title compound as a yellow oil (17g, 99 %

30

-156-

yield).

LCMS (MA) RT = 2.84 min, m/z = 429.1 (M+H)⁺.

Step 2

- 5 To a suspension of title compound from Step 1 (3.33g, 7.79mmol) in Acetonitrile (10mL) was added HCl in 1,4-Dioxane 4M (9.75mL, 38.9mmol). The mixture was stirred at room temperature for 1h. The solvent was evaporated under reduced pressure to afford the title compound as a yellow foam (2.83g, quant.). The crude was used in the next step without further purification.
- 10 LCMS (MA) RT = 1.29 min, m/z = 329.1 (M+H)⁺.

Step 3

- To a solution of the title compound from Step 2 (2.46g, 6.76mmol) in DCM (60mL) was added Triethylamine (2.83mL, 20.28mmol) it was left stirring for 5min then was added 2-(tert-Butyldimethylsilyloxy)propanal (2.54g, 8.11mmol). After 15min Sodium triacetoxyborohydride (2.15g, 10.14mmol) was added. The reaction mixture was left stirring at rt for 3hr. Upon complete conversion, monitored by LCMS, the reaction mixture was diluted in DCM (60mL), and water solution was extracted with Dichloromethane. The organic layer was washed with saturated Brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using Cyclohexane/EtOAc (100/0 to 6/4) as eluent to afford the title compound as a colorless oil (2.66g, 78% yield).
- 15
- 20
- LCMS (MA) RT = 2.37 min, m/z = 501.2 (M+H)⁺.

25 Step 4

- To a solution of the title compound from Step 3 (3.06g, 6.12mmol) in Dioxane/Water (30/7mL) was added **Aniline A3** (1.98g, 7.96mmol), Tetrakis(triphenylphosphine)palladium(0) (139mg, 0.12mmol), Xphos (114mg, 0.24mmol) and Potassium phosphate tribasic (3.9g, 18.36mmol). The reaction mixture was degassed by bubbling under argon for 15 min and stirred at 90°C for 4h. Upon complete conversion, monitored by LCMS, the mixture was allowed to cooled to room temperature and was diluted with water and EtOAc. Layers were separated. The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using Cyclohexane/EtOAc-EtOH (3:1) (100:0 to 6:4) as eluent to afford the title compound as a yellow oil (3.21g, 97% yield).
- 30
- 35
- LCMS (MA) RT = 2.04 min, m/z = 542.4 (M+H)⁺.

-157-

Step 5

To a solution of the title compound from Step 4 (3.21g, 5.9mmol) in Acetonitrile (45mL) was added Pyridine (0.62mL, 7.7mmol) then 2-nitrobenzenesulfonyl chloride (1.44 g, 6.5mmol) portionwise. The reaction mixture was stirred at room temperature for 2h. Upon complete conversion, monitored by LCMS, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography using Cyclohexane/EtOAc-EtOH (3:1) (100:0 to 6:4) as eluent to afford the title compound as a yellow foam (3.8g, 88% yield). LCMS (MA) RT = 2.49 min, m/z = 727.3 (M+H)⁺.

Step 6

To a solution of the title compound from Step 5 (3.8g, 5.23mmol) in THF (100mL) was added a solution of TBAF (5.75mL, 5.75mmol). The reaction mixture was stirred at room temperature for 72h. Upon complete conversion, monitored by LCMS, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography using DCM/MeOH (100/0 to 9/1) as eluent to afford the title compound as a yellow foam (3.62g, contain traces of TBAF). LCMS (MA) RT = 1.78 min, m/z = 613.3 (M+H)⁺.

Step 7

A solution of the title compound from Step 6 (3.31g, 5.4mmol) in THF (30mL) and a solution of DIAD (3.18mL, 16.2mmol) in Toluene (30mL) were added slowly dropwise (over 1hr) simultaneously to a solution of Triphenylphosphine (4.25g, 16.2mmol) in Toluene (300mL) heated at 90°C. The reaction mixture was heated at 90°C for 1h. Upon complete conversion, monitored by LCMS, solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography using DCM/MeOH (100/0 to 9/1) as eluent. A second flash chromatography was performed using Cyclohexane/ EtOAc-EtOH (3:1) (100/0 to 3/7) as eluent to afford the title compound as a cream foam (700mg, 1.17mmol, 22%yield). LCMS (MA) RT = 2.05 min, m/z = 595.2 (M+H)⁺.

Step 8

To a solution of the title compound from Step 7 (700mg, 1.17mmol) in Acetonitrile/Water (60mL/20mL) was added Sodium bicarbonate (0.983g, 11.7mmol). The reaction mixture was stirred 30min at 45°C and then Iodine (1.9 g, 8.77mmol) was added. The reaction mixture was stirred at 45°C for 3h. Upon complete conversion, monitored by LCMS, the reaction mixture was quenched by saturated Sodium thiosulfate solution (100mL). The mixture was mixed with DCM (200mL) extracted with water (100mL) and Brine (100mL). The organic layer were combined, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using DCM/MeOH (100/0 to 9/1) as eluent to afford the title compound as a cream solid (0.5g, 0.82mmol, 70%).

-158-

LCMS (MA) RT = 2.50/2.58 min, m/z = 609.2 (M+H)⁺.

Step 9

- To a suspension of the title compound from Step 8 (0.5g, 0.82mmol) in THF/Acetonitrile (40mL/4mL) was added Cesium carbonate (0.534g, 1.64mmol) and 4-Methylbenzenethiol (0.122g, 0.98mmol). The reaction mixture was stirred at room temperature overnight. The mixture was filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using DCM/MeOH (100:0 to 90:10) as eluent to afford the title compound as a cream solid (0.18g, 52% yield).
- LCMS (MA) RT = 2.90 min, m/z = 424.4 (M+H)⁺.

Step 10

- The mixture of 2 diastereoisomers obtained on Step 9 was separated by chiral preparative HPLC using the following conditions : Column Daicel IA 19×250mm, 5μm (C7/IPA) (75/25) +0.1%DEA 19ml/min, RT 30min

Example 105 as E1-(8R*,12R,14S)-4,12-dimethoxy-8-methyl-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1².6.0^{1°},14.0^{2°},23]pentacosa-1(23),2,4,6(25),17(24),18,21-heptaen-11-one (10mg, 5.8% yield) as white solid

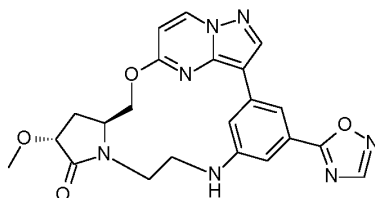
- LCMS (MA) RT = 2.10 min, m/z = 424.3 (M+H)⁺.
LCMS (MC) RT = 2.11 min, m/z = 424.3 (M+H)⁺.
Chiral HPLC Method RT = 11.838 min, ee 99.5%
¹H NMR (400 MHz, CDCl₃) 8.53 - 8.50 (1H, m), 8.33 - 8.31 (1H, m), 7.57 (1H, s), 6.62 - 6.61 (1H, m), 6.43 - 6.39 (1H, m), 6.12 - 6.11 (1H, m), 5.12 (1H, d, J=11.0 Hz), 4.52 (1H, d, J=9.9 Hz), 4.25 (1H, dd, J=8.3, 9.8 Hz), 3.85 - 3.84 (6H, m), 3.66 - 3.60 (5H, m), 2.68 (1H, dd, J=7.7, 12.8 Hz), 2.13 - 2.06 (1H, m), 1.37 (3H, d, J=5.7 Hz).

Example 106 as E2-(8R*,12R,14S)-4,12-dimethoxy-8-methyl-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1².6.0^{1°},14.0^{2°},23]pentacosa-1(23),2,4,6(25),17(24),18,21-heptaen-

- 11-one (25mg, 14.7% yield) as white solid
LCMS (MA) RT = 2.17 min, m/z = 424.2 (M+H)⁺.
LCMS (MC) RT = 2.11 min, m/z = 424.2 (M+H)⁺.
Chiral HPLC Method RT = 15.825 min, ee 99.5%
¹H NMR (400 MHz, CDCl₃) 8.53 - 8.50 (1H, m), 8.37 (1H, s), 8.10 (1H, s), 6.65 (1H, s), 6.44 - 6.41 (1H, m), 6.16 - 6.14 (1H, m), 5.46 - 5.43 (1H, m), 4.43 - 4.38 (1H, m), 4.24 (1H, dd, J=7.3, 10.2 Hz), 3.93 - 3.80 (6H, m), 3.72 - 3.62 (5H, m), 2.65 (1H, dd, J=7.4, 12.3 Hz), 2.20 - 2.12 (1H, m), 1.48 - 1.45 (3H, d, J=6.8 Hz).

-159-

Example 109: (12R,14S)-12-methoxy-4-(1,2,4-oxadiazol-5-yl)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1².6.0¹⁰;14.0²⁰,²³]pentacosa-1(23),2(25),3,5,17(24),18,21-heptaen-11-one



5 Step 1

To a solution of **Intermediate I23** (1.10g, 1.87mmol) in Methanol (17.6mL) was added Sodium hydroxide solution 1M (2.052mL, 2.05mmol) and Hydrogen peroxide solution 30% (0.212mL, 2.05mmol). The reaction mixture was stirred at 40°C for 1h. Upon complete conversion, monitored by LCMS, solvent was removed under reduced pressure. The crude was diluted with Water (20mL) and EtOAc (20mL). The aqueous layer was extracted with EtOAc (2x10mL) and the combined organic layer was washed with Brine (2x20mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography using DCM/MeOH (100/0 to 95/5) as eluant to afford the title compound as a yellow solid (0.19g, 17% yield).

15 LCMS (MA) RT = 2.02 min, m/z = 608.1 (M+H)⁺.

Step 2

To a stirred solution of the title compound from Step 1 (0.19g, 0.32mmol) in 1,4-Dioxane (1.3mL) was added Dimethoxy-N,N-dimethylmethanamine (0.05mL, 0.38mmol). The reaction mixture was stirred at 50°C for 2 h. Upon complete conversion, monitored by LCMS, the reaction mixture was concentrated under vacuum to afford the title compound as a yellow solid (0.168g, 80% Yield). The crude was directly engaged in the next step without further purification.

LCMS (MA) RT = 2.10 min, m/z = 663.2 (M+H)⁺.

25

Step 3

To a stirred solution of the title compound from Step 2 (0.168g, 0.25mmol) in ethanol (5mL) was added Hydroxylamine hydrochloride (0.021g, 0.30mmol). The reaction mixture was stirred at 90°C for 4 days, then solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography using Cyclohexane/EtOAc (100/0 to 0/100) as eluent to afford the title compound as a white solid (0.105g, 65% yield).

LCMS (MA) RT = 2.43 min, m/z = 633.2 (M+H)⁺.

30

-160-

Step 4

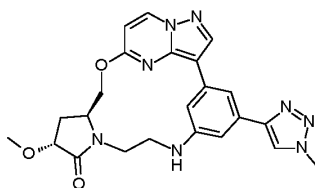
The title compound from Step 3 (0.105g, 0.17mmol) and Cesium carbonate (0.108g, 0.33mmol) were dissolved in DMF (3.7mL). 4-Methylbenzenethiol (0.025g, 0.20mmol) was added and the mixture was stirred at rt overnight. Upon complete conversion, monitored by LCMS, the reaction mixture was filtered and the solvent was evaporated under vacuum. The residue was purified by flash column chromatography using Cyclohexane/EtOAc (100/0 to 0/100) as eluent to afford the expected product as a white solid (36mg, 48% yield).

LCMS (MA) RT = 2.87 min, m/z = 448.4 (M+H)⁺.

LCMS (MC) RT = 2.05 min, m/z = 448.4 (M+H)⁺.

- 10 ¹H NMR (400 MHz, DMSO) 9.09 (1H, s), 9.04 - 9.01 (1H, m), 8.68 (1H, s), 8.10 (1H, s), 7.63 (1H, s), 7.26 (1H, s), 6.70 (1H, d, J=7.6 Hz), 6.65 - 6.55 (1H, m), 4.97 (1H, d, J=10.8 Hz), 4.51 - 4.49 (1H, m), 4.35 (1H, t, J=8.7 Hz), 4.05 - 3.94 (1H, m), 3.59 - 3.53 (1H, m), 3.40 - 3.37 (1H, m), 3.33 - 3.29 (6H, m), 2.01 - 1.93 (1H, m);

- 15 **Example 119:** (12R,14S)-12-methoxy-4-(1-methyl-1H-1,2,3-triazol-4-yl)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1².6.0¹⁰.14.0²⁰,²³]pentacosa-1(23),2,4,6(25),17(24),18,21-heptaen-11-one



Step 1

- 20 To a solution of **Intermediate 132** (0.50g, 0.71mmol) in THF (3.5mL) was added Tetrabutylammonium fluoride 1M in THF (0.780mL, 0.78mmol) dropwise at room temperature. The resulting reaction mixture was stirred 16 hours at room temperature. Upon complete conversion, monitored by LCMS, the reaction mixture was poured into ice water and stirred for 20 min. The aqueous phase was extracted with EtOAc (2 x 15mL) and the combined organic phase was washed with saturated Brine (15mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography on silica gel column using Cyclohexane/EtOAc (30/70) as eluent to afford the title compound as a light brown solid (0.151 g, 36% yield).

LCMS (MA) RT = 2.46 min, m/z = 404.4 (M+H)⁺.

30

Step 2

To a solution of the title compound from Step 1 (0.05g, 0.08mmol) in Water (0.18mL) and tert-Butanol (0.05mL) were added Methyl iodide (6μL, 0.10mmol), Sodium azide (6mg, 0.09mmol), CuI (3mg, 0.02mmol) and Sodium L-ascorbate (3mg, 0.02mmol). The reaction mixture was

-161-

stirred and heated to 75°C overnight. LCMS showed the reaction was incomplete, therefore further Methyl iodide (6uL, 0.10mmol), Sodium azide (6mg, 0.09mmol), CuI (3mg, 0.02mmol) and Sodium L-ascorbate (3mg, 0.02mmol) in Water (0.18mL) and tert-Butanol (0.05mL) were added. The reaction mixture was stirred and heated at 75°C for 24h. Upon 75% conversion, monitored by LCMS, the mixture was then diluted with Dichloromethane and filtered off. The aqueous layer was extracted with Dichloromethane and the combined organic layer was washed with Brine, dried over Sodium sulfate, filtered and evaporated under vacuum to afford the title compound as a solid (36mg, 66% yield). The crude was directly engaged in the next step without further purification.

LCMS (MA) RT = 2.16 min, m/z = 646.4 (M+H)⁺.

Step 3

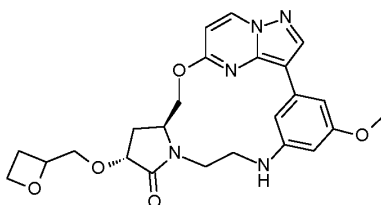
The title compound from Step 2 (36mg, 0.06mmol) and Cesium carbonate (0.04g, 0.11mmol) were suspended in N,N-Dimethylformamide (1mL). 4-Methylbenzenethiol (0.01g, 0.07mmol) was added and the mixture was stirred at room temperature for 2 hours. Upon complete conversion, monitored by LCMS, the reaction mixture was poured into Water then diluted with Ethyl acetate. The suspension was filtered off and the organic layer was washed with Brine, dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel column using DCM /MeOH (95/5) as eluent to afford the expected product as an off-white solid (20mg, 78% yield).

LCMS (MA) RT = 1.80 min, m/z = 461.4 (M+H)⁺.

LCMS (MC) RT = 1.80 min, m/z = 461.4 (M+H)⁺.

¹H NMR (400 MHz, CDCl₃) 8.54 - 8.51 (1H, m), 8.42 (1H, s), 7.90 (1H, s), 7.79 (1H, s), 7.46 (1H, s), 7.02 (1H, s), 6.44 - 6.41 (1H, m), 5.11 (1H, d, J=10.8 Hz), 4.54 (1H, t, J=8.3 Hz), 4.19 - 4.18 (4H, m), 3.91 - 3.72 (2H, m), 3.65 (4H, s), 3.37 - 3.29 (1H, m), 2.66 (1H, dd, J=8.3, 13.2 Hz), 2.19 - 2.11 (1H, m), 1.29 - 1.27 (1H, m);

Example 120: (12R,14S)-4-methoxy-12-(oxetan-2-ylmethoxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentacosa-1(23),2,4,6(25),17(24),18,21-heptaen-11-one



-162-

Step 1

Into a sealed tube, to a suspension of **Intermediate I27** (400mg, 0.69mmol) in dry THF (0.8mL) were added n-Tetrabutylammonium bromide (78mg, 0.24mmol) and aqueous Sodium hydroxide solution 32%w (1.30mL, 10.35mmol). The mixture was stirred for 30 min and 2-
 5 (Bromomethyl)oxetane (520mg, 3.45mmol) was added. The reaction was stirred at 80°C for 2 h. Upon complete conversion, monitored by LCMS, the reaction was stopped and cooled to rt. The mixture was diluted with Ethyl acetate and Water. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 15mL). The combined organic layer was dried
 10 over anhydrous Sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified by preparative HPLC: Column Waters XSELECT C18 19*100mm, 5µm, A: (NH₄)₂CO₃ aq. 2 g/L, B: CAN 19ml/min, rt 30% B to 45% B in 7 min. The expected fractions were collected and evaporated under reduced pressure. A second purification was performed by preparative TLC 0.25mm using DCM/MeOH (9:1) as eluent. The compound was scratched and silica was dissolved with DCM/MeOH 8:2. The suspension was filtered and the solvent
 15 was evaporated under reduced pressure to afford the expected product as a beige solid (7mg, 0.02mmol, 2 %).

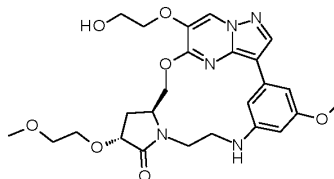
LCMS (MA) RT = 1.99 min, m/z = 466.4 (M+H)⁺.

LCMS (MC) RT = 1.99 min, m/z = 466.4 (M+H)⁺.

¹H NMR (400 MHz, CDCl₃) 8.51 (1H, d, J=7.4 Hz), 8.32 (1H, s), 7.55 (1H, ls), 6.61 - 6.59 (1H, m), 6.41 (1H, d, J=7.6 Hz), 6.11 - 6.09 (1H, m), 5.12 - 5.07 (1H, m), 5.07 - 5.00 (1H, m), 4.74 -
 20 4.68 (1H, m), 4.65 - 4.59 (1H, m), 4.52 - 4.44 (2H, m), 4.20 (1H, dd, J=3.2, 11.2 Hz), 3.93 (1H, dd, J=6.6, 11.3 Hz), 3.89 - 3.81 (1H, m), 3.84 (3H, s), 3.77 - 3.71 (1H, m), 3.67 - 3.60 (1H, m), 3.60 - 3.52 (1H, m), 3.32 - 3.24 (1H, m), 2.76 - 2.63 (2H, m), 2.58 - 2.50 (1H, m), 2.24 - 2.17 (1H, m) ;

25

Example 139: (12R,14S)-18-(2-hydroxyethoxy)-4-methoxy-12-(2-methoxyethoxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentacosa-1(23),2,4,6(25),17(24),18,21-heptaen-11-one



30 Following the general synthetic scheme 1, as depicted for the synthesis of Example 1, (12R,14S)-18-(benzyloxy)-4-methoxy-12-(2-methoxyethoxy)-7-(2-nitrobenzenesulfonyl)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.12,6.010,14.020,23]pentacosa-1(23),2(25),3,5,17(24),18,21-heptaen-11-one was obtained as **Intermediate I34** using **Scaffold S3**, **Pyrrolidine P7** and **Aniline A3**.

-163-

Step 1

To a solution of **Intermediate 134** (5.46g, 7.34mmol) in TFA (92mL) was added Anisole (32.06mL, 7.34mmol). The reaction mixture was stirred at 110°C overnight. Upon complete conversion, monitored by LCMS, the mixture was allowed to cooled at room temperature and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography using DCM/MeOH (100/0 to 95/5) as eluent to afford the title compound as a brown solid (4.66g, 97% Yield).

LCMS (MA) RT = 2.30 min, m/z = 655.2 (M+H)⁺.

Step 2

To a suspension of the title compound from Step 1 in DMF (2mL) was added Potassium carbonate (63mg, 0.46mmol) and 2-(2-Bromoethoxy)oxane (0.028mL, 0.18mmol). The reaction mixture was stirred at 80°C for 60 min. The reaction mixture was filtered and concentrate under reduce pression to afford the title compound as a light brown solid (120mg, 100% yield).

The crude was directly engaged in the next step without further purification.

LCMS (MA) RT = 2.66 min, m/z = 783.3 (M+H)⁺.

Step 3

The title compound from Step 2 (0.12g, 0.15mmol) and Cesium carbonate (0.10g, 0.31mmol) were suspended in N,N-Dimethylformamide (1mL). 4-Methylbenzenethiol (0.023g, 0.18mmol) was added and the mixture was stirred at room temperature for 2 hours. Upon complete conversion, monitored by LCMS, the reaction mixture was poured into water then diluted with Ethyl acetate. The suspension was filtered. The organic layer was washed with Brine, dried over Sodium sulfate, filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography using DCM/MeOH (95/5) as eluent to afford to afford the title compound as a beige solid (70mg, 76% yield).

LCMS (MA) RT = 1.99 min, m/z = 466.4 (M+H)⁺.

Step 4

To a solution of the title compound from Step 3 (0.067g, 0.11mmol) in MeOH (1.3mL) and Water (0.2mL) was added p-Toluenesulfonic acid monohydrate (0.107g, 0.56mmol) and the reaction mixture was stirred at 65°C for 16h. Upon complete conversion, monitored by LCMS, the reaction mixture was dissolved in Ethyl acetate then a saturated aqueous solution of Sodium hydrogen carbonate was added. After separation, the aqueous layer was extracted with Ethyl acetate (2x). The combined organic layer was washed with Brine, dried over Sodium sulfate, filtered and evaporated under reduced pressure to afford the expected product as a light yellow solid (31mg, 54% yield).

LCMS (MA) RT = 1.81 min, m/z = 514.4 (M+H)⁺.

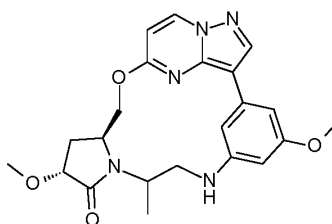
LCMS (MC) RT = 1.80 min, m/z = 514.3 (M+H)⁺.

-164-

¹H NMR (400 MHz, DMSO) 8.77 (1H, s), 8.36 - 8.35 (1H, m), 7.43 - 7.43 (1H, m), 6.52 (1H, d, J=0.8 Hz), 6.07 - 6.01 (2H, m), 4.99 - 4.92 (2H, m), 4.46 (2H, t, J=8.8 Hz), 4.13 - 3.90 (4H, m), 3.77 (2H, s), 3.72 (2H, s), 3.65 (1H, s), 3.58 - 3.51 (1H, m), 3.48 (2H, t, J=4.8 Hz), 3.43 - 3.36 (1H, m), 3.27 - 3.26 (6H, m), 2.46 (1H, dd, J=7.5, 12.9 Hz), 2.00 - 1.96 (1H, m);

5

Example 142: (12R,14S)-4,12-dimethoxy-9-methyl-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1².6.0^{1°},14.0^{2°},23]pentacosa-1(23),2(25),3,5,17(24),18,21-heptaen-11-one



10 Step 1

To a solution of **Pyrrolidine P1** (5.97g, 25.81mmol) in dry DMF (83mL) was added Sodium hydride, 60% in Mineral oil (1.72g, 43.02mmol) at 0°C. After 30 min 3-Bromo-5-chloropyrazolo[1,5-a]pyrimidine (5.00g, 21.51mmol) was added and the mixture was stirred at rt for 1h. Upon complete conversion, monitored by LCMS, Water was carefully added dropwise

15

at 0°C and the mixture was extracted with EtOAc (3x50mL). The combined organic layers were washed with Brine, dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by flash chromatography using Cyclohexane/EtOAc (100/0 to 60/40) as eluent to afford the title compound as an orange oil (5.55g, 60% yield).

LCMS (MA) RT = 2.72 min, m/z = 427.1/429.1 (M+H)⁺.

20

Step 2

To a suspension of the title compound from Step 1 (5.55g, 12.99mmol) in Acetonitrile (130mL) was added Hydrogen Chloride solution 4M in 1,4-Dioxane (16.24mL, 64.97mmol). The reaction mixture was stirred overnight. Upon complete conversion, monitored by LCMS, the solvent was removed under reduced pressure to afford the title compound as a yellow solid (4.84g, quantitative yield). The crude was directly engaged in the next step without further purification.

25

LCMS (MA) RT = 1.17 min, m/z = 327.2/329.2 (M+H)⁺.

30 Step 3

To a solution of the title compound from Step 2 (4.72g, 14.44mmol) in Acetonitrile (114mL) was added Potassium carbonate (5.99g, 43.32mmol) and Ethyl 2-bromopropanoate (5.23g, 28.88mmol). The reaction mixture was stirred at 50°C overnight. Upon complete conversion,

-165-

monitored by LCMS, aqueous 1N NaOH solution was added and the reaction mixture was stirred for 10 minutes. Water and Ethyl acetate were added to the mixture and extracted with Ethyl acetate. The organic layer was dried over anhydrous Sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography using
5 Cyclohexane/EtOAc (100/0 to 70/30) as eluent to afford the title compound as a yellow oil (4.729g, 77% yield).

LCMS (MA) RT = 1.72/1.83min, m/z = 427.1/429.1 (M+H)⁺.

Step 4

10 To a suspension of the title compound from Step 3 (4.73g, 11.07mmol) in a mixture of EtOH/THF (60mL/60mL) cooled at 0°C were added Sodium borohydride (1.26g, 33.20mmol) and Calcium chloride (1.84g, 16.60mmol). The solution was allowed to reach room temperature and stirred for 4h at rt. The reaction mixture was quenched by addition of Water and aqueous HCl 1M until pH=4. EtOAc was added and the layers were separated. The
15 aqueous layer was extracted with EtOAc. The combined organic layer was dried over Sodium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography using Cyclohexane/AE (100/0 to 0/100) as eluent to afford the title compound as a yellow oil (1.23g, 29% yield).

LCMS (MA) RT = 1.21/1.24min, m/z = 385.3/385.3 (M+H)⁺.

20

Step 5

To a solution of the title compound from Step 4 (1.23g, 3.20mmol) in DMF (18mL) was added imidazole (0.653g, 9.59mmol) and tert-Butyldimethylsilyl chloride (1.44g, 9.59mmol). The reaction mixture was stirred at room temperature overnight. Upon complete conversion,
25 monitored by LCMS, an aqueous saturated solution of NaHCO₃ was added and the mixture was extracted with Ethyl acetate. The combined organic layer was dried over anhydrous Sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by Flash chromatography using Cyclohexane/EtOAc (100/0 to 70/30) as eluent to afford the title compound as a yellow oil (1.279g, 80% Yield).

30 LCMS (MA) RT = 2.20/2.25min, m/z = 499.2/501.2 (M+H)⁺.

Step 6

A mixture of the title compound from Step 5 (1.18g, 2.36mmol), **Aniline A3** (0.76g, 3.07mmol), Xphos (0.045g, 0.09mmol), and K₃PO₄ (1.50g, 7.08mmol) were dissolved in 1,4-
35 Dioxane/Water (15mL/5mL) and degassed with Argon during 15min. Tetrakis(triphenylphosphine)palladium(0) (0.055g, 0.05mmol) was added and the reaction mixture was stirred at 110°C for 1h. Upon complete conversion, monitored by LCMS, the reaction mixture was cooled down and filtered over Celite then solvent was evaporated. The

-166-

residue was purified by column chromatography using Cyclohexane/EtOAc (100/0 to 40/60) as eluent to afford the title compound as a yellow oil (1.33g, quantitative yield).

LCMS (MA) RT = 2.00/2.04min, m/z = 542.5 (M+H)⁺.

5 Step 7

To a solution of the title compound from Step 6 (1.28g, 2.36mmol) in Acetonitrile (33mL) were added Pyridine (0.29mL, 3.54mmol) and 2-Nitrobenzene-1-sulfonyl chloride (0.68g, 3.07mmol). The reaction mixture was stirred at rt overnight. Upon complete conversion, monitored by LCMS, the solvent was removed under reduced pressure and the residue was
10 poured into water (40mL) and EtOAc (80mL). The aqueous layer was extracted with EtOAc (3x40mL) and the organic layer was washed with Brine (2x40mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound as a red solid (1.88g, quantitative yield). The crude was directly engaged in the next step without further purification. LCMS (MA) RT = 2.38min, m/z = 727.5 (M+H)⁺.

15

Step 8

To a solution of the title compound from Step 7 (1.73g, 2.37mmol) in THF (21mL) was added Tetrabutylammonium fluoride 1M in THF (4.749mL, 4.75mmol) at room temperature. The resulting reaction mixture was stirred at rt for 2h. Upon complete conversion, monitored by
20 LCMS, the reaction mixture was diluted with saturated Ammonium chloride solution and extracted with Ethyl acetate twice. The combined organic layer was dried over anhydrous Sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography using DCM/MeOH (100/0 to 95/5) as eluent to afford the title compound as a brown solid (1.653g, quantitative yield).

25 LCMS (MA) RT = 1.80min, m/z = 613.3 (M+H)⁺.

Step 9

A solution of the title compound from Step 8 (1.45g, 2.37mmol) in Me-THF (71ml) and DIAD (1.399ml, 7.12mmol) in Toluene (71ml) were simultaneously added dropwise to a solution of
30 Triphenylphosphine (1.87g, 7.12mmol) in Toluene (237ml) at 90°C for 1.5h. Upon complete conversion, monitored by LCMS, solvent was removed under reduced pressure. The residue was purified by column chromatography using Cyclohexane/EtOAc (100/0 to 50/50). The desired fractions were collected and evaporated. The residue was triturated in Diethylether to afford the title compound as a yellow oil (1.52g, 37% yield).

35 LCMS (MA) RT = 2.76min, m/z = 595.4 (M+H)⁺.

Step 10

To a mixture of the title compound from Step 9 (1.41g, 2.37mmol) in THF/H₂O (185mL/49mL) was added Sodium bicarbonate (3.99g, 47.49mmol) and Iodine (9.04g, 35.62mmol). The

-167-

reaction mixture was stirred at 60°C for 1h. Upon complete conversion, monitored by LCMS, the reaction mixture was quenched by saturated Sodium thiosulfate solution then extracted by Ethyl acetate. The organic layer was dried over anhydrous Sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified by column chromatography using Cyclohexane/EtOAc (100/0 to 30/70) as eluent to afford the title compound as a yellow solid (0.539g, 37% yield).

LCMS (MA) RT = 2.62min, m/z = 609.3 (M+H)⁺.

Step 11

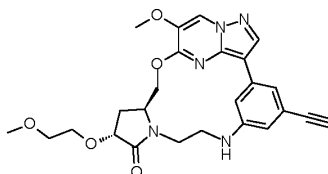
- To a solution of the title compound from Step 10 (0.54g, 0.89mmol) in DMF (20mL) were added Lithium hydroxide (0.127g, 5.31mmol) and DL-cysteine (0.13g, 1.06mmol) and the mixture was stirred at rt overnight. Upon complete conversion, monitored by LCMS, Water was added and the resulting mixture was extracted by Ethyl acetate. The organic layer sequentially washed with a saturated Sodium bicarbonate solution and saturated Brine, dried over Na₂SO₄, filtered and concentrated to dryness. The crude was triturated in Acetonitrile to afford the expected product as a white solid (0.201g, 54% yield).

LCMS (MA) RT = 2.10min, m/z = 424.4 (M+H)⁺.

LCMS (MC) RT = 2.10min, m/z = 424.4 (M+H)⁺.

- ¹H NMR (400 MHz, DMSO) 8.97 (1H, dd, J=7.6, 9.7 Hz), 8.60 (0.63H, s), 8.47 (0.37H, s), 7.99 (0.63H, s), 7.22 (0.37H, s), 6.67 - 6.60 (1.63H, m), 6.48 (0.37H, dd, J=1.0, 2.2 Hz), 6.21 (0.37H, t, J=5.8 Hz), 6.14 - 6.02 (1.63H, m), 5.28 (0.63H, d, J=11.6 Hz), 4.87 - 4.83 (0.37H, m), 4.52 - 4.47 (0.37H, m), 4.36 (0.63H, dd, J=7.3, 10.2 Hz), 4.21 (1H, t, J=8.6 Hz), 4.12 - 3.98 (1.37H, m), 3.73 - 3.72 (4H, m), 3.64 - 3.55 (0.63H, m), 3.45 - 3.41 (4H, m), 2.47 - 2.30 (1H, m), 2.03 - 1.95 (1H, m), 1.45 (1.11H, d, J=6.8 Hz), 1.28 (1.89H, d, J=6.8 Hz);

Example 146: (12R,14S)-4-ethynyl-18-methoxy-12-(2-methoxyethoxy)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.1²,6.0¹⁰,14.0²⁰,23]pentacosa-1(23),2,4,6(25),17(24),18,21-heptaen-11-one



- Following the general synthetic scheme 1, as depicted for the synthesis of Example 1, (12R,14S)-4-(benzyloxy)-18-methoxy-12-(2-methoxyethoxy)-7-(2-nitrobenzenesulfonyl)-16-oxa-7,10,20,21,24-pentaazapentacyclo[15.5.2.12,6.010,14.020,23]pentacosa-1(23),2(25),3,5,17(24),18,21-heptaen-11-one was obtained as **Intermediate I35** using **Scaffold S2**, **Pyrrolidine P7** and **Aniline A9**.
- LCMS (MA) RT = 2.77 min, m/z = 745.3 (M+H)⁺.

-168-

Step 1

To a solution of **Intermediate 135** (80mg, 0.107mmol) in TFA (1mL) was added Anisole (0.5mL, 4.30mmol). The reaction mixture was stirred at 130°C for 40 min. Upon complete conversion, monitored by LCMS, the mixture was allowed to cooled at room temperature and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography using DCM/Methanol (100/0 to 98/2) as eluent to afford the title compound as a pale brown solid (65mg, 93% Yield).

LCMS (MA) RT = 2.20 min, m/z = 655.2 (M+H)⁺.

10 Step 2

To a solution of Triethylamine (0.02mL, 0.148mmol) and the title compound from Step 1 (65mg, 0.099mmol) in Dichloromethane (5mL) was added portionwise N-Phenyl-bis(trifluoromethanesulfonimide) (39mg, 0.109mmol), and the reaction mixture was stirred at room temperature for 5h. Upon complete conversion, monitored by LCMS, Water (5mL) was added to the reaction solution. Thereafter, the reaction solution was extracted with Dichloromethane (3x 5mL), the combined organic layer was washed with Brine (10mL), dried over anhydrous Sodium sulfate, and concentrated under reduced pressure to afford the title compound as a yellowish amorphous solid (80mg, postulated, qt.). The crude was directly engaged in the next step further without purification.

LCMS (MA) RT = 2.77 min, m/z = 787.2 (M+H)⁺.

Step 3

To a solution of the title compound from Step 2 (80mg, 0.099mmol postulated) in DMF (1mL) were added Cesium carbonate (64mg, 0.148mmol) and then 4-Methylbenzenethiol (15mg, 0.119mmol). The reaction was stirred at rt for 45 min. Upon complete conversion, monitored by LCMS, the mixture was diluted with Water (3mL) and Ethyl acetate (3mL). The layers were separated. The aqueous layer was extracted with EtOAc (2 x 3mL) and the combined organic layer was dried over anhydrous Sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified on silica gel column chromatography using DCM/MeOH (100:0 to 97.5:2.5) as eluent to afford the title compound as a yellowish amorphous solid (40mg, 67% Yield over two steps).

LCMS (MA) RT = 2.54 min, m/z = 602.3 (M+H)⁺.

Step 4

In a microwave reactor, a solution of the title compound from Step 3 (15mg, 0.025mmol) in dry Acetonitrile/DMF (1.4:0.15mL) was degassed by bubbling argon for 10 min. Then, were added cesium carbonate (24mg, 0.075mmol), bis(acetonitrile)dichloropalladium(II) (0.6mg, 0.0025mmol), Xphos (2.4mg, 0.005mmol) and Triethylsilylacetylene (0.022mL, 0.125mmol). The reaction mixture was stirred at 100°C under microwave irradiation for 1h. LCMS showed

-169-

full conversion with main formation of the expected compound.

The reaction was repeated with the title compound from Step 3 (15mg, 0.025mmol) using similar conditions, but microwave irradiation was maintained for 3h. Both reaction mixtures were combined, filtrated over Celite and concentrated in vacuo. To afford the title compound as a dark brown amorphous solid (34mg, qt. postulated). The crude was directly engaged in the next step without further purification.

LCMS (MA) RT = 3.29 min, m/z = 592.4 (M+H)⁺.

Step 5

To a solution of title compound from Step 4 (34mg, 0.050mmol postulated) in Methanol (1mL) was added Potassium carbonate (34mg, 0.250mmol). The reaction mixture was stirred at 50°C 3h. Upon complete conversion, monitored by LCMS, the reaction mixture was cooled down to room temperature then quenched with Water (2mL) and diluted with Ethyl acetate (2mL). The two layers were separated and the aqueous layer was extracted three times with Ethyl acetate (3x3mL). The combined organic layer was washed with Brine (3mL), dried over Sodium sulfate, filtered and concentrated in vacuo. The crude residue was purified by preparative TLC using Ethyl acetate/Methanol (95:5). The expected fraction was scratched, extracted with Dichloromethane/Methanol 9:1, filtered off and concentrated in vacuo to afford the expected product as a brownish amorphous solid (4mg, 17% over two steps).

LCMS (MA) RT = 2.26 min, m/z = 478.2(M+H)⁺.

LCMS (MC) RT = 2.16 min, m/z = 478.3 (M+H)⁺.

¹H NMR (400 MHz, CDCl₃) 8.24 - 8.17 (2H, m), 7.86 - 7.86 (1H, m), 7.15 - 7.13 (1H, m), 6.67 (1H, s), 5.12 (1H, d, J=10.6 Hz), 4.53 - 4.48 (1H, m), 4.36 (1H, t, J=8.7 Hz), 4.21 - 4.13 (1H, m), 3.96 (3H, s), 3.93 - 3.79 (3H, m), 3.69 - 3.55 (5H, m), 3.43 - 3.41 (3H, m), 3.29 - 3.23 (1H, m), 3.06 (1H, s), 2.76 - 2.70 (1H, m), 2.26 - 2.18 (1H, m).

RIPK2 AlphaLISA® Assay (Amplified Luminescent Proximity Homogeneous Assay)

30

A non-specific kinase inhibitor (CZC-8004 Cayman #916603-07-1) bound to an acceptor bead (#6772001 PerkinElmer) was mixed to the recombinant hRIPK2 protein (kinase domain aa 1-299-His-tagged – Life Technologies PR7829A) and a Ni²⁺-tagged donor beads (#AS101D PerkinElmer). In the presence of an inhibitor, the compound beads displacement from hRIPK2 was followed by signal loss. In a 384-well ProxiPlate® (Perkin Elmer, 6008280) add:

2 µL RIPK2 inhibitor (in DMSO 0.8%).

2 µL human recombinant RIPK2 (10nM diluted in AlphaLISA buffer 1X).

4 µL Mix of donor Compound-beads 1/1000 and acceptor Ni²⁺-beads 1/1000 in AlphaLISA buffer 1X.

-170-

Homogenize using a microtiter plate shaker and incubate for 2h at 23 °C.

Read using EnVision®-Alpha Reader (PerkinElmer) according to manufacturer specifications.

- + indicates an IC₅₀ between 100nM and 1uM, ++ indicates an IC₅₀ of between 10 nM and 100nM, and +++ indicates an IC₅₀ < 10nM; ND = Not determined

Ex ID	Activity	Ex ID	Activity	Ex ID	Activity	Ex ID	Activity
1	+++	41	+++	81	+++	121	+++
2	+++	42	+++	82	+++	122	+++
3	+++	43	+++	83	+++	123	+++
4	+++	44	++	84	+++	124	+++
5	+++	45	+	85	+	125	+++
6	+++	46	++	86	+++	126	+++
7	+++	47	+++	87	+	127	+++
8	+++	48	+	88	+++	128	+++
9	+++	49	++	89	+++	129	+++
10	+++	50	++	90	+++	130	+++
11	+++	51	+	91	+++	131	+++
12	+++	52	+++	92	+++	132	+++
13	+++	53	+++	93	+	133	+++
14	++	54	+++	94	+++	134	+++
15	++	55	+++	95	+++	135	+++
16	+++	56	+++	96	+++	136	+++
17	+++	57	+++	97	+++	137	+++
18	+++	58	+++	98	+++	138	+++
19	+++	59	+++	99	+++	139	+++
20	+++	60	+++	100	++	140	+++
21	++	61	+	101	+	141	+++
22	+++	62	+++	102	+++	142	++
23	+++	63	+++	103	++	143	+++
24	+++	64	++	104	+++	144	+++
25	+++	65	+++	105	+++	145	+++
26	+++	66	+++	106	++	146	+++
27	+++	67	+++	107	++	147	+++
28	+++	68	+++	108	+		
29	+++	69	+++	109	+++		
30	+++	70	+++	110	+++		

-171-

31	+++		71	+++		111	+++			
32	+++		72	+++		112	+++			
33	+++		73	++		113	++			
34	+++		74	++		114	+++			
35	+++		75	++		115	+++			
36	+++		76	+++		116	+++			
37	+++		77	+++		117	+++			
38	+++		78	+++		118	+++			
39	+++		79	+++		119	++			
40	+++		80	+++		120	+++			

Comparative table between representative compounds from WO2016/042087 and representative compounds from present patent application properties

Example ID	Assay A	Assay B	Assay C
Example O4 of WO2016042087	+	+	++
Example O11 of WO2016042087	+	+	+
Example 1	ND	+++	+++
Example 55	ND	+++	+++
Example 67	ND	+++	+++
Example 3	+++	++	+++
Example 54	+++	++	+++
Example 79	+++	+++	++

- 5 Human protein binding free fraction data legend: + indicates F% below 0.1%, ++ indicates F% of between 0.1-1%, and +++ indicates F% above 1%; ND = Not determined
- Human Clint data legend: + indicates hCl above 18ug/min/mg prot, ++ indicates hCl between 6-18ug/min/mg prot, and +++ indicates hCl equal or below 5ug/min/mg prot; ND = Not determined
- 10 hERG q-patch inhibition data legend: + indicates an IC50 below 1uM, ++ indicates an IC50 of between 1-10uM, and +++ indicates an IC50 above 10uM; ND = Not determined

Human Clint protocol: Pooled liver microsomes (Sekisui Xenotech) were diluted at 0.5mg/mL in 50 mM phosphate buffer, pH 7.4 then pre-incubated with 0.5 μ M OD945 for 7 min at 37°C.

- 15 The reactions were initiated by adding prewarmed cofactor (0.44 mM NADPH). Aliquots of samples were taken at 0, 5, 10, 20 and 45 min and the reactions stopped by addition of cold acetonitrile containing an internal standard. Samples were centrifuged at 3000g for 10 min at 4°C and then supernatants were analyzed by LC/MS/MS for the amount of parent compound remaining.

-172-

Human protein binding protocol: Compound was added to plasma or brain homogenate and incubated at 2 µM at 37°C in the RED plate (Thermo n°96009, cut-off 8000Da) against PBS buffer. After 4h, aliquots of plasma and buffer side were transferred to a well containing acetonitrile with an internal standard. After protein precipitation, samples were centrifuged and
5 supernatant was injected in LC/MS/MS. Standards were prepared in the same matrix and treated as samples.

A fraction unbound ($f_{u_{plasma}}$) was determined for each plasma sample as follows:

$$f_{u_{plasma}} (\%) = \frac{C_{buffer}}{C_{plasma}} \times 100\%$$

10 hERG q-patch assay protocol: The potential for test compound to inhibit the hERG potassium channel was determined using the Charles River ChanTest® hERG-HEK stably transfected cell line on the Sophion Qube automated electrophysiology platform. The assay was performed at room temperature and recordings of the hERG tail current from a population of cells were made using multi-hole QChips.

15

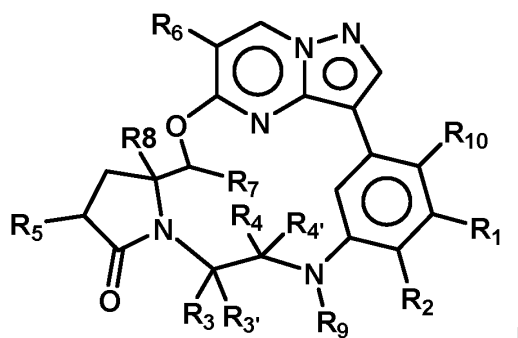
REFERENCES

- Becker *et al.*, Curr. Rheum. Reports **2005** 7:427-433
- Brooks, The Oncologist **2013** 1:e3-e5
- Cai *et al.*, Oncology Reports **2018** 39:2915-2923
- Chen *et al.*, J. Pathol. **2020** 250 2:170-182
- Chin *et al.*, Curr. Med. Chem. **2005** 4 1:35-42
- Duggan *et al.*, Scientific reports **2017** 7:1578
- Franca *et al.*, Scand. J. Rheumatol. **2016** 45:8-12
- Gambino *et al.*, Assay Drug. Dev. Technol. **2017** 15 1:30-43
- Girardin *et al.*, EMBO Rep. **2001** 2:736-742
- Haile *et al.*, J. Med. Chem. **2019** 14:6482-6494
- Hollenbach *et al.*, JBC, **2005**, 280: 14981-8
- Hysi *et al.*, Hum. Mol. Genet. **2005** 14:935-941
- Inaki *et al.*, Genome Research **2014** 24: 1559
- Inohara *et al.*, J Biol Chem **2000** 36:27823-31
- Jaafar *et al.*, Biochem. Biophys. Res. Commun. **2018** 1:115-121
- Kabesh *et al.*, J. Allergy Clin. Immunol. **2003** 4:813-7
- Lesage *et al.*, Am. J. Hum. Genet. **2002** 70:845-857
- Liu *et al.*, Cell. Biochem. Biophys. **2015** 72 3:681-5
- Maloney *et al.*, JACS **2017** 4(S1):S150
- McGovern *et al.*, Hum. Mol. Genet. **2005** 14:1245-1250
- Mertins *et al.*, Nature **2016** 7605:55-62
- Miceli-Richard *et al.*, Nature Genetics **2001** 29:19-20
- Negroni *et al.*, Inflamm. Bowel Dis. **2009** 8:1145-1154
- Singel *et al.*, Breast Cancer Res. **2014** 16:R28
- Som *et al.*, World J. Clin. Cases **2019** 4:405-418
- Strober *et al.*, Nat. Rev. Immunol. **2006** 1:9-20
- Stronati *et al.*, Digestive and Liver Disease **2010** 12:848-853
- Tigino-Aranjuez *et al.*, Genes Dev. **2010** 1:2666-77
- Uehara *et al.*, Diag. Path. **2009** 4:23
- Vieira *et al.*, J. Immunol. **2012** 10:5116-5122
- Wiken *et al.*, J. Clin. Immunol. **2009** 29:78-89
- Wu *et al.*, Mol. Cell. Proteomics **2011** 10: 1-14
- Yamamoto *et al.*, Microbes & Infections **2009** 12:912-918
- Yang *et al.*, PLoS One **2012** 8:e40196
- Zare *et al.*, Cancers **2018** 10:184
- Zhao *et al.*, Biochem. Biophys. Res. Commun. **2017** 2:1151-1158
- Zhou *et al.*, Obesity **2015** 7:1394-1400

-174-

CLAIMS

1. A compound of Formula I or a stereoisomer, tautomer, racemic, salt, hydrate, N-oxide form, or solvate thereof,



- 5 Wherein
- R_1 is selected from -Halo, -O- C_{1-6} alkyl, -Alkynyl, - C_{1-6} alkyl, - C_{3-6} -cycloalkyl, -C(O)- C_{1-6} -alkyl, -C(O)- C_{1-6} cycloalkyl, -C(O)-Het₂, -C(O)-NR_aR_b, -Het₁ and -CN; each of said - C_{1-6} alkyl being optionally substituted with one or more substituents selected from -D, -Halo, -O- C_{1-3} alkyl, - C_{3-6} -cycloalkyl, -Ph, -Het₁, -Het₂, and -OH; each of said -Alkynyl being optionally
- 10 substituted with one substituent selected from - C_{1-6} alkyl, and -CH₂-O- C_{1-6} alkyl;
- R_2 and R_{10} are each independently selected from -H, and -Halo;
- R_3 , R_3' , R_4 , R_4' , R_7 , and R_8 are each independently selected from -H, and - C_{1-6} alkyl; wherein each of said - C_{1-6} alkyl may optionally be substituted with one or more -O- C_{1-6} alkyl; wherein when R_3 and/or R_3' is - C_{1-6} alkyl, then R_4 and R_4' are each -H;
- 15 wherein when R_4 and/or R_4' is - C_{1-6} alkyl, then R_3 and R_3' are each -H;
- R_5 is selected from -OH, -NR_cR_{c'}, -NHC(O)R_c, -NC(O)R_cR_{c'}, -NC(O)OR_c, -NHS(O₂)R_c, -Halo, -O- C_{1-6} alkyl, -O- C_{3-5} -cycloalkyl, -O-Het₂, - C_{1-6} alkyl, and -CN; each of said - C_{1-6} alkyl being optionally substituted with one or more substituents selected from -D, -OH, - C_{1-6} alkyl, - C_{3-5} -cycloalkyl, -O- C_{1-6} alkyl and -Het₂;
- 20 R_6 is selected from -H, -Halo, - C_{1-6} alkyl, -O- C_{1-6} alkyl, -O-Het₄, and -Het₃; each of said - C_{1-6} alkyl being optionally substituted with one or more substituents selected from -D, and -O- C_{1-6} alkyl;
- R_9 is selected from -H, - C_{1-6} alkyl, -C(O)- C_{1-6} alkyl, and -C(O)-O- C_{1-6} alkyl;
- R_a is selected from -H, and - C_{1-6} alkyl; each of said - C_{1-6} alkyl being optionally substituted with
- 25 one or more substituents selected from -D, and - C_{1-6} alkyl;
- R_b is selected from -H, - C_{1-6} alkyl, and -O- C_{1-6} alkyl; each of said - C_{1-6} alkyl being optionally substituted with one or more substituents selected from -D, - C_{1-6} alkyl, and - C_{3-5} -cycloalkyl;
- R_c and $R_{c'}$ are each independently selected from -H, and - C_{1-6} alkyl; each of said - C_{1-6} alkyl being optionally substituted with one or more substituents selected from -D, and - C_{1-6} alkyl;
- 30 Het₁ and Het₃ are each independently selected from a 5 or 6-membered aromatic heterocycle having from 1 to 3 heteroatoms selected from O, N and S, wherein each of said Het₁ or

-175-

Het₃ is optionally substituted with from 1 to 3 -C₁₋₆alkyl; each of said -C₁₋₆alkyl being optionally substituted with one or more substituents selected from -D, -halo, -O-C₁₋₃alkyl, and -OH;

5 Het₂ is selected from a 4 to 6-membered saturated heterocycle having from 1 to 3 heteroatoms selected from O and N; wherein each of said Het₂ is optionally substituted with from 1 to 3 -C₁₋₆alkyl; each of said -C₁₋₆alkyl being optionally substituted with one or more substituents selected from -D, -halo, -O-C₁₋₃alkyl, and -OH

10 Het₄ is selected from a 4 to 10-membered saturated heterocycle having from 1 to 3 heteroatoms selected from O and N; wherein each of said Het₄ is optionally substituted with from 1 to 3 -C₁₋₆alkyl; each of said -C₁₋₆alkyl being optionally substituted with one or more substituents selected from -D, -halo, -O-C₁₋₃alkyl, and -OH.

2. A compound according to claim 1 wherein;

15 R₁ is selected from -Halo, -O-C₁₋₆alkyl, -Alkynyl, -C₁₋₆alkyl, -C₃₋₆-cycloalkyl, -C(O)-C₁₋₆alkyl, -C(O)-C₁₋₆cycloalkyl, -C(O)-Het₂, -C(O)-NR_aR_b, -Het₁ and -CN; each of said -C₁₋₆alkyl being optionally substituted with one or more substituents selected from -D, -Halo, -O-C₁₋₃alkyl, -C₃₋₆-cycloalkyl, -Ph, -Het₁, -Het₂, and -OH;

R₂ and R₁₀ are each independently selected from -H, and -Halo;

20 R₃, R_{3'}, R₄, R_{4'}, R₇, and R₈ are each independently selected from -H, and -C₁₋₆alkyl; wherein each of said -C₁₋₆alkyl may optionally be substituted with one or more -O-C₁₋₆alkyl; wherein when R₃ and/or R_{3'} is -C₁₋₆alkyl, then R₄ and R_{4'} are each -H; wherein when R₄ and/or R_{4'} is -C₁₋₆alkyl, then R₃ and R_{3'} are each -H;

25 R₅ is selected from -OH, -NR_cR_{c'}, -NHC(O)R_c, -Halo, -O-C₁₋₆alkyl, -O-C₃₋₅-cycloalkyl, -O-Het₂, -C₁₋₆alkyl, and -CN; each of said -C₁₋₆alkyl being optionally substituted with one or more substituents selected from -D, -OH, -C₁₋₆alkyl, -C₃₋₅-cycloalkyl, -O-C₁₋₆alkyl and -Het₂;

R₆ is selected from -H, -Halo, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -O-Het₄, and -Het₃; each of said -C₁₋₆alkyl being optionally substituted with one or more substituents selected from -D, and -O-C₁₋₆alkyl;

R₉ is selected from -H, -C₁₋₆alkyl, -C(O)-C₁₋₆alkyl, and -C(O)-O-C₁₋₆alkyl;

R_a is selected from -H, and -C₁₋₆alkyl;

30 R_b is selected from -H, -C₁₋₆alkyl, and -O-C₁₋₆alkyl;

R_c and R_{c'} are each independently selected from -H, and -C₁₋₆alkyl;

Het₁ and Het₃ are each independently selected from a 5 or 6-membered aromatic heterocycle having from 1 to 3 heteroatoms selected from O and N, wherein each of said Het₁ and Het₃ is optionally substituted with from 1 to 3 -C₁₋₆alkyl;

35 Het₂ is selected from a 4 to 6-membered saturated heterocycle having from 1 to 3 O atoms

Het₄ is selected from a 4 to 10-membered saturated heterocycle having from 1 to 3 heteroatoms selected from O and N; wherein each of said Het₄ is optionally substituted with from 1 to 3 -C₁₋₆alkyl; each of said -C₁₋₆alkyl being optionally substituted with one or more substituents selected from -D, -halo, -O-C₁₋₃alkyl, and -OH.

-176-

3. A compound according to claim 1 wherein;

- R_1 is selected from -Halo, -O- C_{1-6} alkyl, -Alkynyl, - C_{1-6} alkyl, - C_{3-6} -cycloalkyl, -C(O)- C_{1-6} alkyl, -C(O)- C_{1-6} cycloalkyl, -C(O)-Het₂, -C(O)-NR_aR_b, -Het₁ and -CN; each of said - C_{1-6} alkyl being optionally substituted with one or more substituents selected from -D, -Halo, -O- C_{1-3} alkyl, - C_{3-6} -cycloalkyl, -Ph, -Het₁, -Het₂, and -OH;
- R_2 and R_{10} are each independently selected from -H, and -Halo;
- R_3 , R_3' , R_4 , R_4' , R_7 , and R_8 are each -H;
- R_5 is selected from -OH, -Halo, -O- C_{1-6} alkyl, -O- C_{3-5} -cycloalkyl, and - C_{1-6} alkyl; each of said - C_{1-6} alkyl being optionally substituted with one or more substituents selected from -D, -OH, - C_{1-6} alkyl, - C_{3-5} -cycloalkyl, and -O- C_{1-6} alkyl;
- R_6 is selected from -H, -Halo, - C_{1-6} alkyl, -O- C_{1-6} alkyl, -O-Het₄, and -Het₃; each of said - C_{1-6} alkyl being optionally substituted with one or more -O- C_{1-6} alkyl;
- R_9 is selected from -H, - C_{1-6} alkyl, -C(O)- C_{1-6} alkyl, and -C(O)-O- C_{1-6} alkyl;
- R_a is selected from -H, and - C_{1-6} alkyl;
- R_b is selected from -H, - C_{1-6} alkyl, and -O- C_{1-6} alkyl; each of said - C_{1-6} alkyl being optionally substituted with one or more;
- Het₁ and Het₃ are each independently selected from a 5 or 6-membered aromatic heterocycle having from 1 to 3 heteroatoms selected from O and N, wherein each of said Het₁ and Het₃ is optionally substituted with from 1 to 3 - C_{1-6} alkyl;
- Het₂ is selected from a 4 to 6-membered saturated heterocycle having from 1 to 3 O atoms
- Het₄ is selected from a 4 to 10-membered saturated heterocycle having from 1 to 3 heteroatoms selected from O and N; wherein each of said Het₄ is optionally substituted with from 1 to 3 - C_{1-6} alkyl; each of said - C_{1-6} alkyl being optionally substituted with one or more substituents selected from -D, -halo, -O- C_{1-3} alkyl, and -OH.

25 .

4. A compound according to anyone of claims 1 to 3 wherein;

- R_1 is selected from -Halo, -O- C_{1-6} alkyl, -Alkynyl, - C_{1-6} alkyl, - C_{3-6} -cycloalkyl, -C(O)- C_{1-6} alkyl, -C(O)-NR_aR_b, -Het₁ and -CN; each of said - C_{1-6} alkyl being optionally substituted with one or more substituents selected from -D, -Halo, and -O- C_{1-3} alkyl;
- R_2 is selected from -H, and -Halo;
- R_{10} is -H;
- R_3 , R_3' , R_4 , R_4' , R_7 , and R_8 are each -H
- R_5 is selected from -OH, -Halo, -O- C_{1-6} alkyl, -O- C_{3-5} -cycloalkyl, and - C_{1-6} alkyl; each of said - C_{1-6} alkyl being optionally substituted with one or more substituents selected from -D, -OH, - C_{1-6} alkyl, - C_{3-5} -cycloalkyl, and -O- C_{1-6} alkyl;
- R_6 is selected from -H, -Halo, - C_{1-6} alkyl, -O- C_{1-6} alkyl, -O-Het₄, and -Het₃; each of said - C_{1-6} alkyl being optionally substituted with one or more -O- C_{1-6} alkyl;
- R_9 is -H;
- R_a is selected from -H, and - C_{1-6} alkyl;

-177-

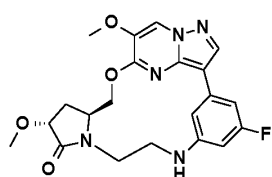
R_b is selected from $-H$, $-C_{1-6}alkyl$, and $-O-C_{1-6}alkyl$;

Het₁ is a 5-membered aromatic heterocycle having from 1 to 3 heteroatoms selected from O and N, wherein said Het₁ is optionally substituted with from 1 to 3 $-C_{1-6}alkyl$

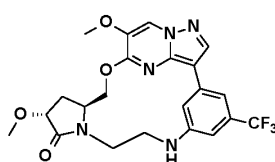
Het₄ is selected from a 4 to 10-membered saturated heterocycle having from 1 to 3 heteroatoms selected from O and N; wherein each of said Het₄ is optionally substituted with from 1 to 3 $-C_{1-6}alkyl$; each of said $-C_{1-6}alkyl$ being optionally substituted with one or more substituents selected from $-D$, $-halo$, $-O-C_{1-3}alkyl$, and $-OH$.

5. A compound according to claim 1 and being selected from the list comprising:

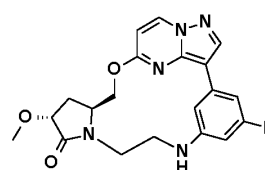
10



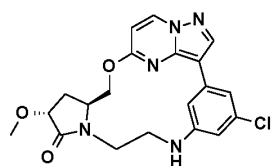
Example 1



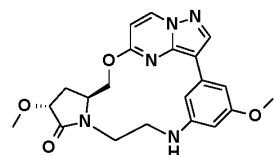
Example 2



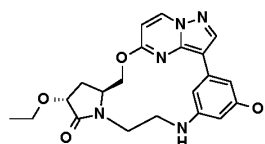
Example 3



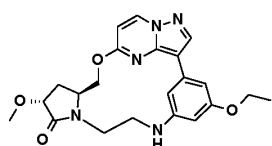
Example 4



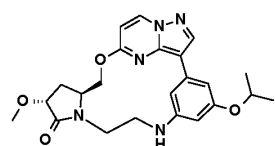
Example 5



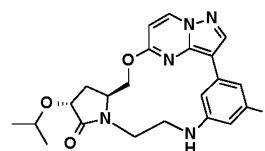
Example 6



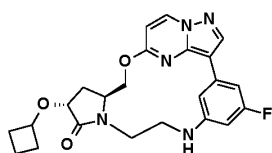
Example 7



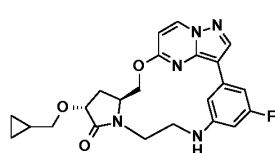
Example 8



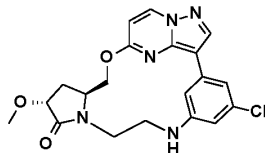
Example 9



Example 10

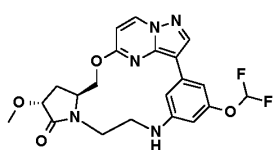


Example 11

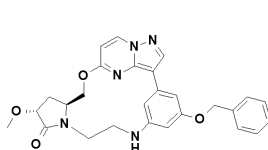


Example 12

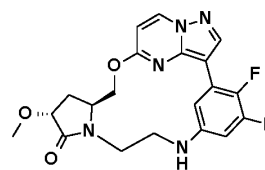
-178-



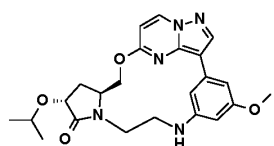
Example 13



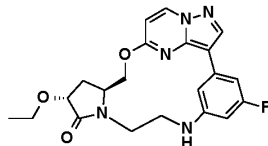
Example 14



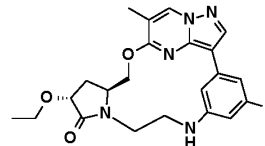
Example 15



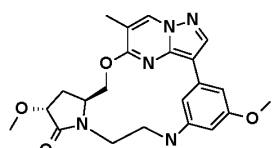
Example 16



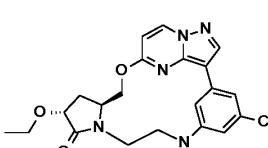
Example 17



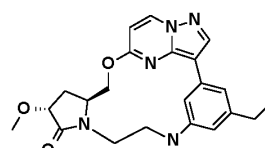
Example 18



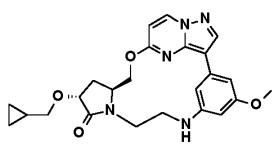
Example 19



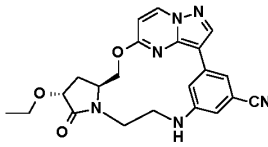
Example 20



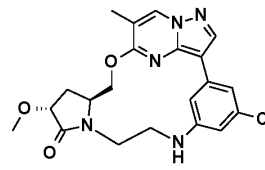
Example 21



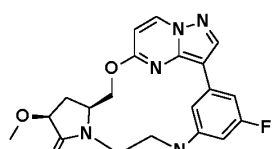
Example 22



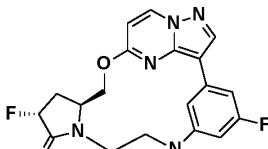
Example 23



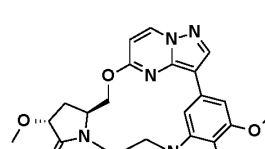
Example 24



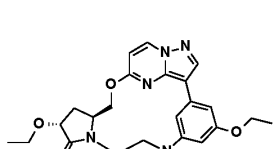
Example 25



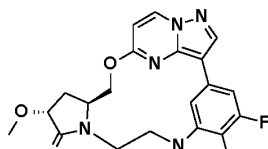
Example 26



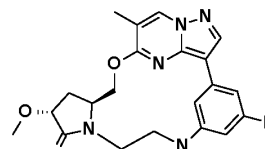
Example 27



Example 28

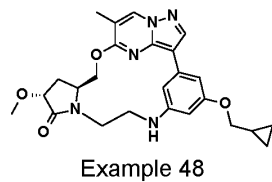
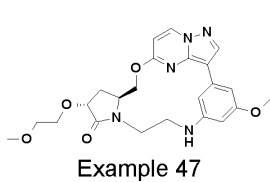
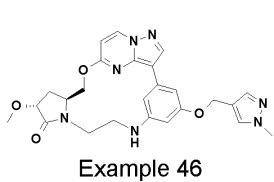
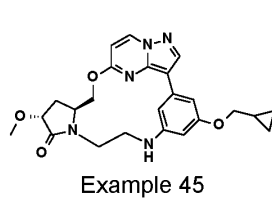
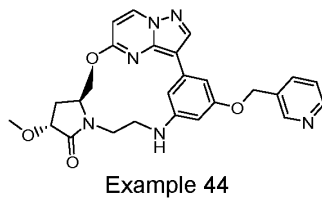
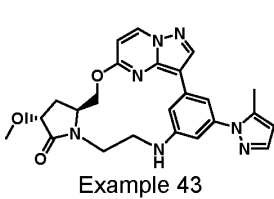
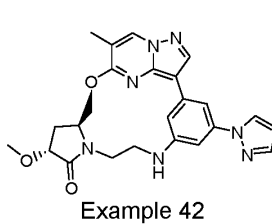
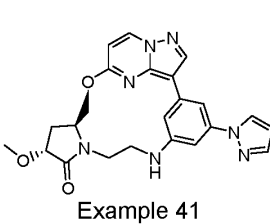
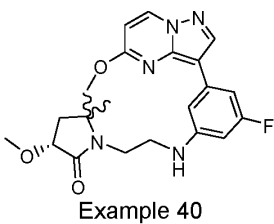
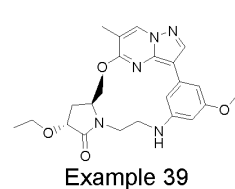
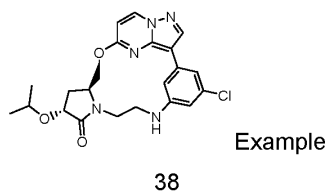
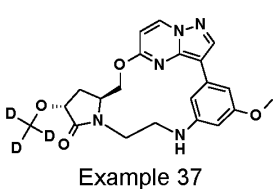
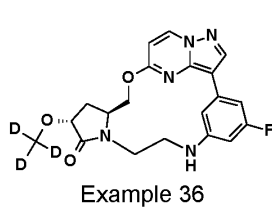
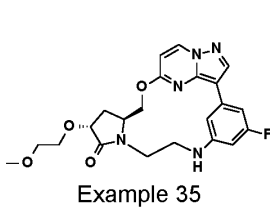
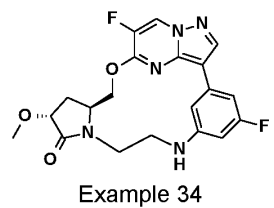
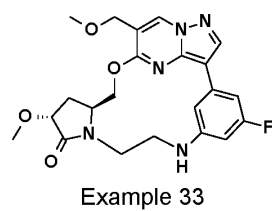
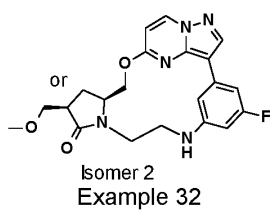
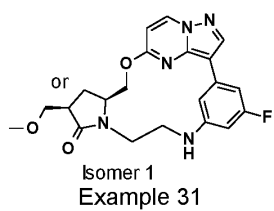


Example 29

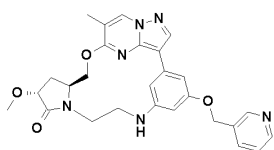


Example 30

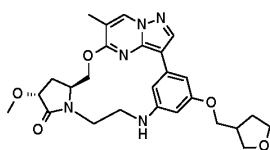
-179-



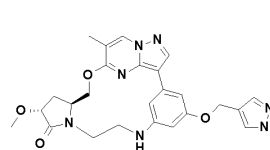
-180-



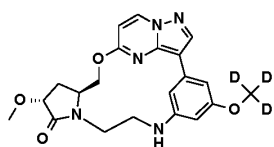
Example 49



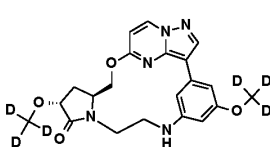
Example 50



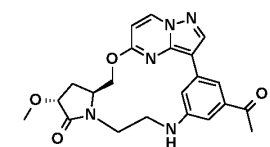
Example 51



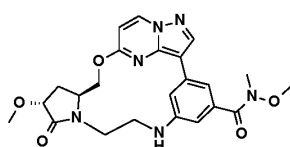
Example 52



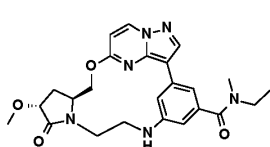
Example 53



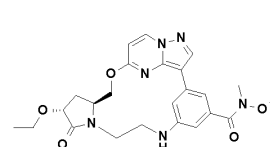
Example 54



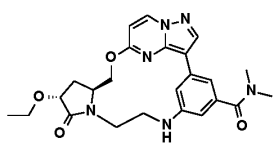
Example 55



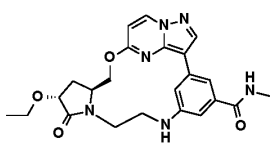
Example 56



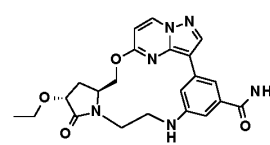
Example 57



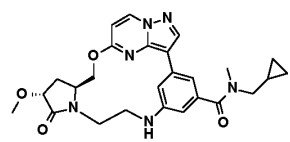
Example 58



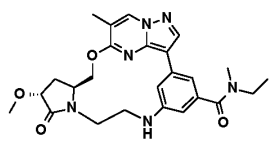
Example 59



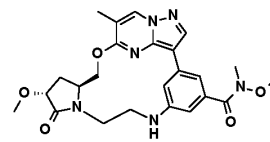
Example 60



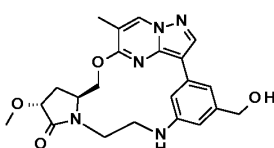
Example 61



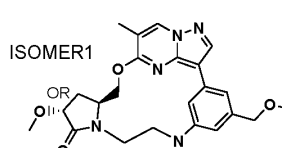
Example 62



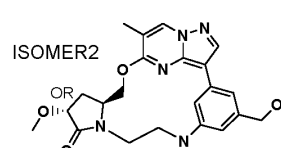
Example 63



Example 64

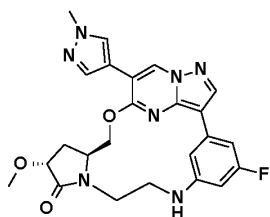


Example 65

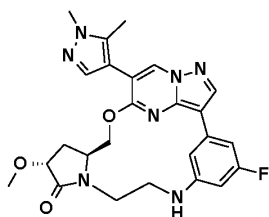


Example 66

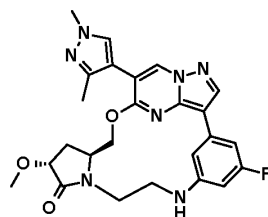
-181-



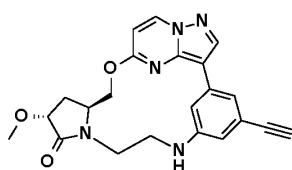
Example 67



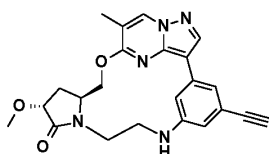
Example 68



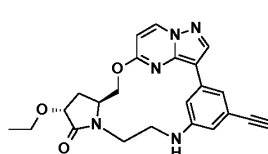
Example 69



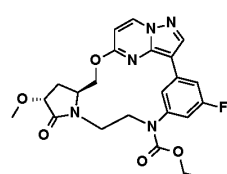
Example 70



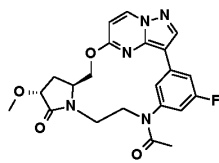
Example 71



Example 72

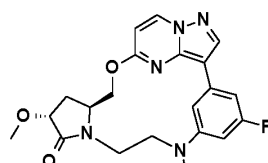


Example 73

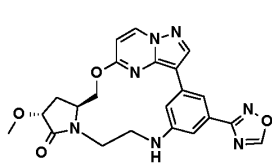


74

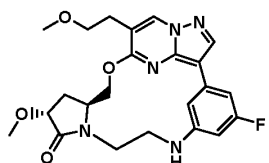
Example



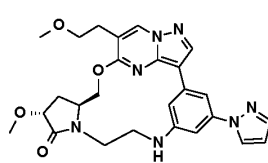
Example 75



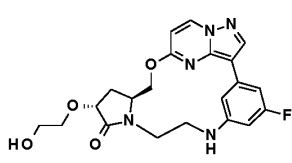
Example 76



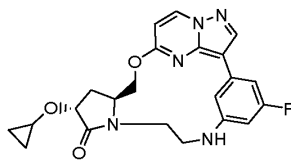
Example 77



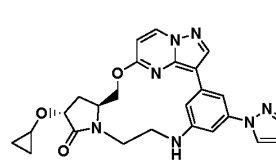
Example 78



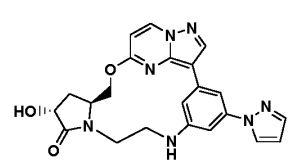
Example 79



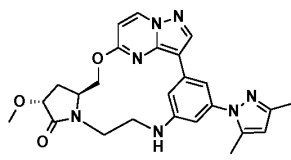
Example 80



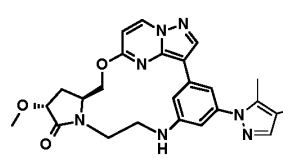
Example 81



Example 82

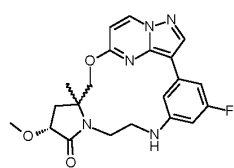


Example 83

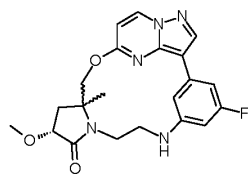


Example 84

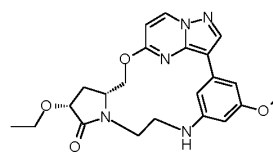
-182-



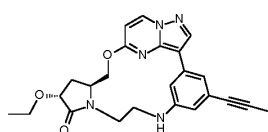
Example 85



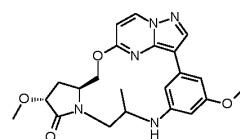
Example 86



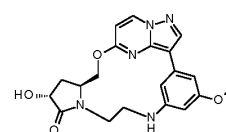
Example 87



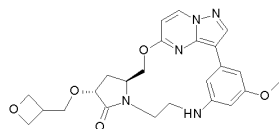
Example 88



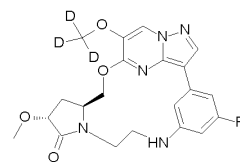
Example 89



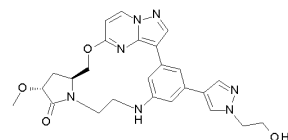
Example 90



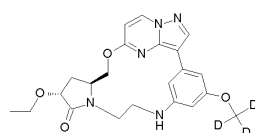
Example 91



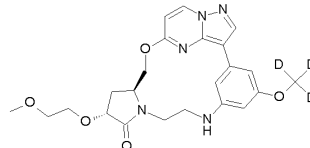
Example 92



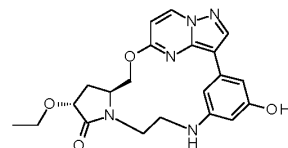
Example 93



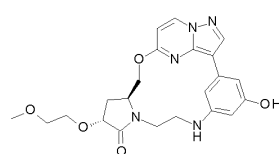
Example 94



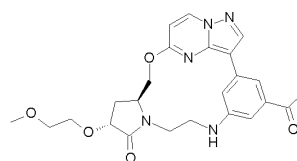
Example 95



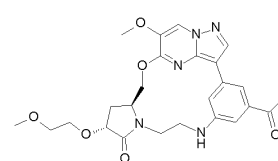
Example 96



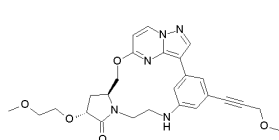
Example 97



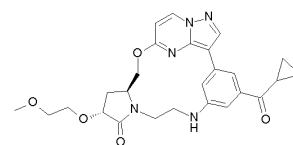
Example 98



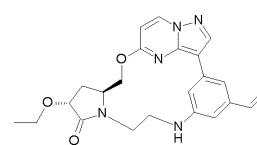
Example 99



Example 100

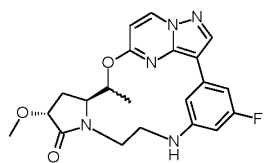


Example 101

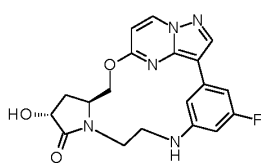


Example 102

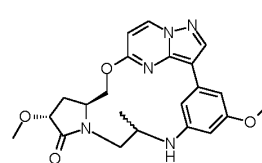
-183-



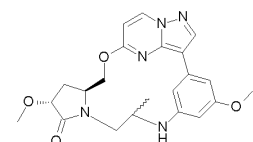
Example 103



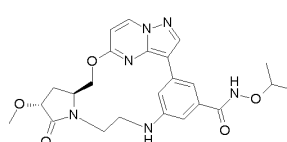
Example 104



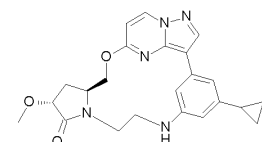
Example 105



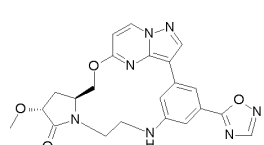
Example 106



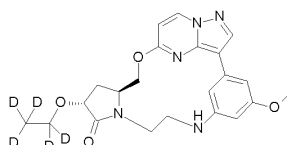
Example 107



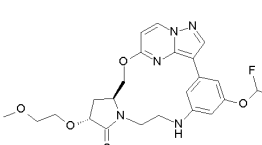
Example 108



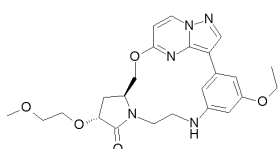
Example 109



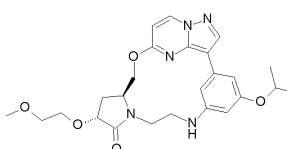
Example 110



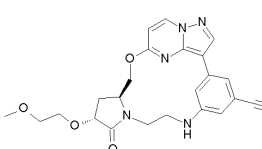
Example 111



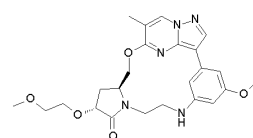
Example 112



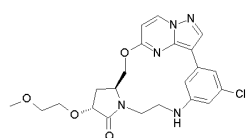
Example 113



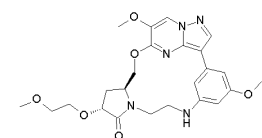
Example 114



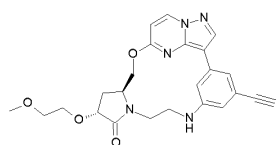
Example 115



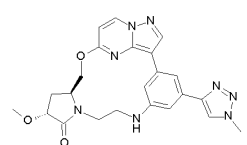
Example 116



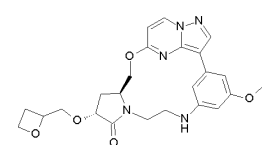
Example 117



Example 118

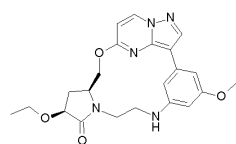


Example 119

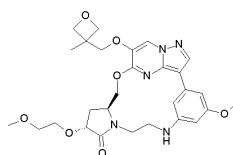


Example 120

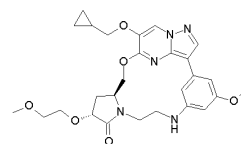
-184-



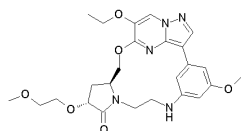
Example 121



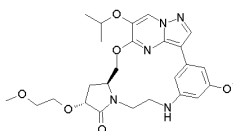
Example 122



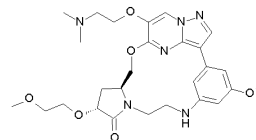
Example 123



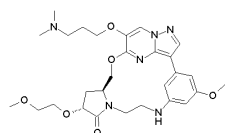
Example 124



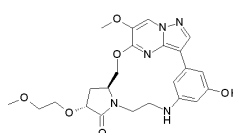
Example 125



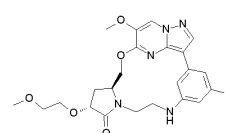
Example 126



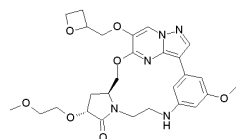
Example 127



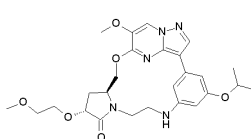
Example 128



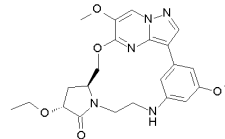
Example 129



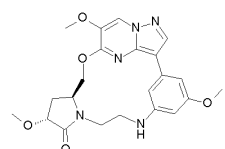
Example 130



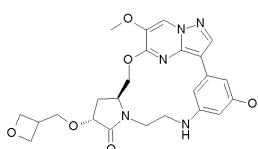
Example 131



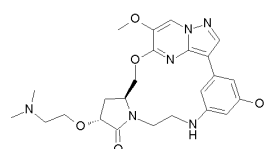
Example 132



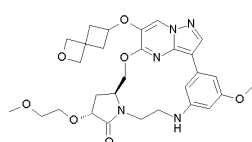
Example 133



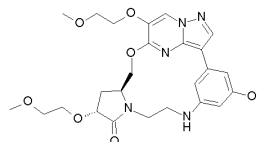
Example 134



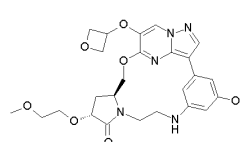
Example 135



Example 136

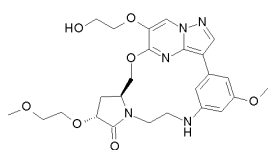


Example 137

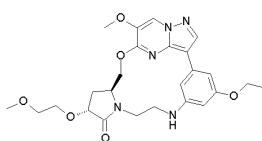


Example 138

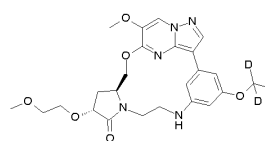
-185-



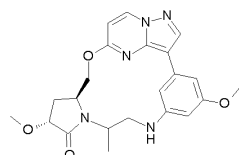
Example 139



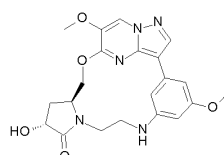
Example 140



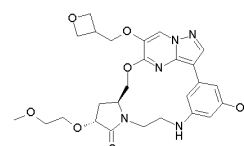
Example 141



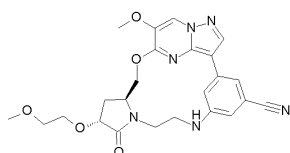
Example 142



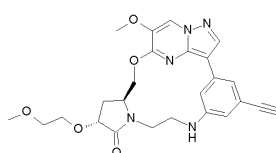
Example 143



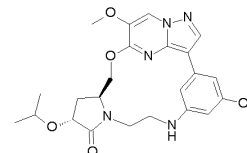
Example 144



Example 145



Example 146



Example 147

6. A compound according to anyone of claims 1 to 4; wherein the carbon atom bearing the R_8 substituent is in the S-configuration.
- 5 7. A compound according to anyone of claims 1 to 4; wherein the carbon atom bearing the R_5 substituent is in the R-configuration.
8. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 7.
- 10 9. A compound as defined in anyone of claims 1 to 7, or a composition according to claim 8 for use as a human or veterinary medicine.
- 10 10. A compound as defined in anyone of claims 1 to 7, or a composition according to claim 8 for use in the diagnosis, prevention and/or treatment of a RIP2-kinase associated disease.
- 15 11. A compound as defined in anyone of claims 1 to 7, or a composition according to claim 8 for use in the diagnosis, prevention and/or treatment of a RIP2-kinase associated disease; wherein the RIP2-kinase associated disease is an inflammatory disorders, in particular selected from the list comprising: Crohn's disease, bowel disease, sarcoidosis, psoriasis,
- 20

-186-

atopic dermatitis, allergic rhinitis, rheumatoid arthritis, asthma, insulin-resistant type 2 diabetes, obesity metabolic syndrome, cardiac hypertrophy, ulcerative colitis, lupus, uveitis, Blau syndrome, granulomatous inflammation, Behçet's disease, immune-mediated colitis, and multiple sclerosis.

5

12. A compound as defined in anyone of claims 1 to 7, or a composition according to claim 8 for use in the diagnosis, prevention and/or treatment of a RIP2-kinase associated disease; wherein the RIP2-kinase associated disease is cancer, more in particular selected from breast cancers (including Inflammatory Breast Cancer), head and neck cancers and gliomas.

10

13. Use of a compound as defined in anyone of claims 1 to 7, or a composition as defined in claim 8, suitable for inhibiting the activity of a kinase; in particular a RIP2 kinase.

14. Use of a compound as defined in anyone of claims 1 to 7 or a composition as defined in claim 8, for the diagnosis, prevention and/or treatment of a RIP2-kinase associated disease.

15

15. A method for the prevention and/or treatment of a RIP2-kinase associated disease; said method comprising administering to a subject in need thereof a compound as defined in anyone of claims 1 to 7 or a composition as defined in claim 8.

20